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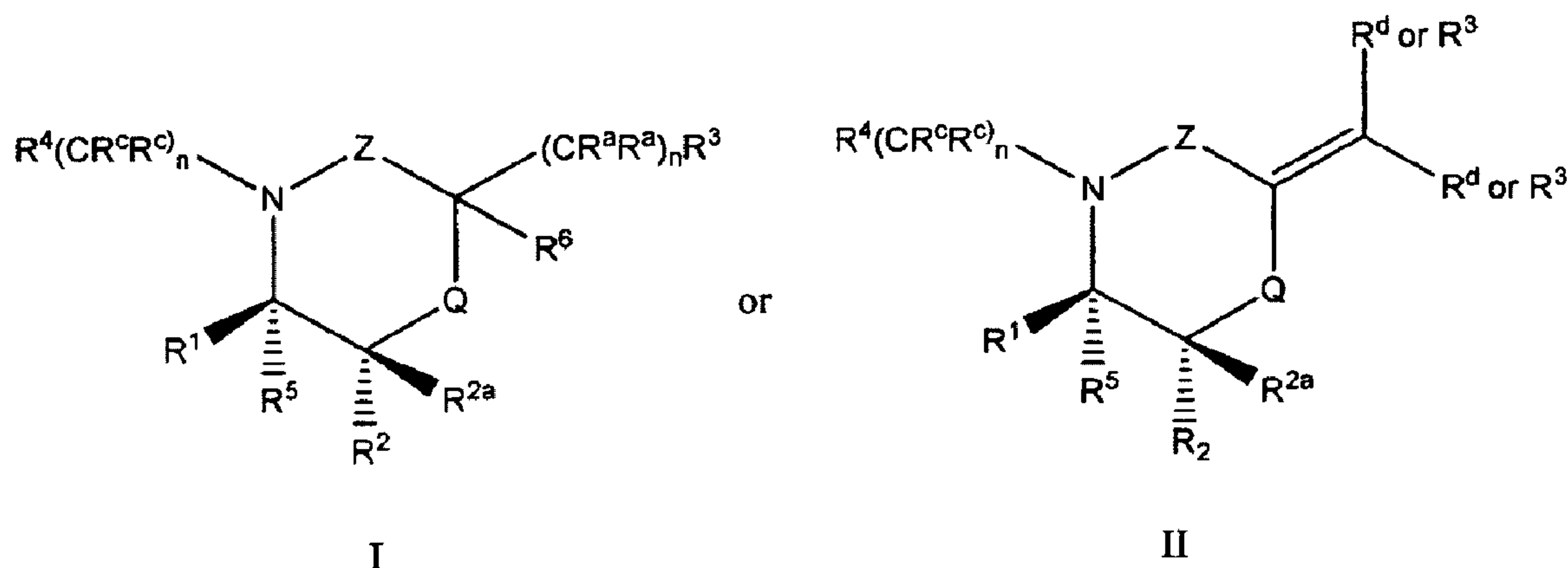
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(54) Titre : HETEROCYCLES UTILISES COMME INHIBITEURS DE MDM2 DANS LE TRAITEMENT DU CANCER
(54) Title: HETEROCYCLIC COMPOUNDS AS MDM2 INHIBITORS FOR THE TREATMENT OF CANCER



(57) **Abrégé/Abstract:**

The present invention provides MDM2 inhibitor compounds of Formula I or II, or the pharmaceutically acceptable salts thereof, wherein the variables are defined above, which compounds are useful as therapeutic agents, particularly for the treatment of cancers. The present invention also relates to pharmaceutical compositions that contain an MDM2 inhibitor.

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HETEROCYCLIC COMPOUNDS AS MDM2 INHIBITORS FOR THE TREATMENT OF CANCER

FIELD OF THE INVENTION

5 The present invention relates to compounds that are MDM2 inhibitors that are useful as therapeutic agents, particularly for the treatment of cancers. The invention also relates to pharmaceutical compositions that contain a MDM2 inhibitor.

BACKGROUND OF THE INVENTION

10 p53 is a tumor suppressor and transcription factor that responds to cellular stress by activating the transcription of numerous genes involved in cell cycle arrest, apoptosis, senescence, and DNA repair. Unlike normal cells, which have infrequent cause for p53 activation, tumor cells are under constant cellular stress from various insults including hypoxia and pro-apoptotic oncogene activation. Thus, there is a strong selective
15 advantage for inactivation of the p53 pathway in tumors, and it has been proposed that eliminating p53 function may be a prerequisite for tumor survival. In support of this notion, three groups of investigators have used mouse models to demonstrate that absence of p53 function is a continuous requirement for the maintenance of established tumors. When the investigators restored p53 function to tumors with inactivated p53, the
20 tumors regressed.

 p53 is inactivated by mutation and/or loss in 50% of solid tumors and 10% of liquid tumors. Other key members of the p53 pathway are also genetically or epigenetically altered in cancer. MDM2, an oncoprotein, inhibits p53 function, and it is activated by gene amplification at incidence rates that are reported to be as high as 10%.
25 MDM2, in turn, is inhibited by another tumor suppressor, p14ARF. It has been suggested that alterations downstream of p53 may be responsible for at least partially inactivating the p53 pathway in p53^{WT} tumors (p53 wildtype). In support of this concept, some p53^{WT} tumors appear to exhibit reduced apoptotic capacity, although their capacity to undergo cell cycle arrest remains intact. One cancer treatment strategy involves the use of small
30 molecules that bind MDM2 and neutralize its interaction with p53. MDM2 inhibits p53 activity by three mechanisms: 1) acting as an E3 ubiquitin ligase to promote p53

The present invention relates to compounds capable of inhibiting the interaction
10 between p53 and MDM2 and activating p53 downstream effector genes. As such,
compounds of the present invention would be useful in the treatment of cancers, bacterial
infections, viral infections, ulcers and inflammation. In particular, the compounds of the
present invention are useful to treat solid tumors such as: breast, colon, lung and prostate
tumors; and liquid tumors such as lymphomas and leukemias. As used herein, MDM2
15 means a human MDM2 protein and p53 means a human p53 protein. It is noted that
human MDM2 can also be referred to as HDM2 or hMDM2.

In embodiment 1, the present invention provides compounds of Formula I or II, or
20 pharmaceutically acceptable salts thereof,



wherein:

Q is O, S, -S(=O)-, -S(=O)₂-, or -NR^e;

5

Z is -C(=O)- or -S(=O)₂-;

- 10 R¹ is a 5 to 10 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -OH, -NO₂, -NHC(=O)C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, -(CH₂)_nC(=O)R^f, -(CH₂)_nC(=O)NR^fR^f, -CN, -NR^gR^g or A,
- 15 or R¹ and R⁵ together with the carbon atom to which they are attached can form a 3 to 6 membered cycloalkyl or heterocycloalkyl group, optionally containing a -(C=O)- group, which heterocycloalkyl group can contain from one to two heteroatoms independently selected from O, N or S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected
- 20 from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, -(CH₂)_nC(=O)R^f, -(CH₂)_nC(=O)NR^fR^f or -CN, and substituents on two adjacent carbons atoms of the cycloalkyl or heterocycloalkyl group can join together to form a five or six membered ring, including the two carbon atoms, fused to the cycloalkyl or heterocycloalkyl group,
- 25 or when R¹ is substituted with -NR^gR^g, then R^g and R^g together with the nitrogen atom to which they are attached can form a 3 to 6 membered heterocycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from O, N or S, and the heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected
- 30 from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F or -CN;

each A is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from

O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

- 5 R² is a 5 to 10 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -OH, -NO₂, -NHC(=O)C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃,
 10 -OCHF₂, -OCH₂F, -(CH₂)_nC(=O)R^f, -(CH₂)_nC(=O)NR^fR^f, -CN, -NR^gR^g or B,
 or when R² is substituted with -NR^gR^g, then R^g and R^g together with the nitrogen atom to which they are attached can form a 3 to 6 membered heterocycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from O, N or S, and the heterocycloalkyl group can be
 15 unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

- each B is independently a 5 or 6 membered aryl or heteroaryl group, which
 20 heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl groups group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

- 25 R^{2a} is hydrogen or -C₁₋₃alkyl;

- R³ is hydrogen, -C₁₋₆alkyl, -C(=O)OR^f, -C(=O)C₁₋₆alkyl, -S(=O)₂R^f, -S(=O)R^f, -OR^f, -C(=O)NR^fN(R^f)₂, -C(=O)NR^fS(=O)₂R^f, -S(=O)₂NR^fC(=O)R^f, -S(=O)₂NR^fR^f, -N(R^f)C(=O)NR^fR^f, -NR^fC(=O)₂R^f, -C(=O)NR^fR^f, -NR^fS(=O)₂R^f, -CN, -NR^fR^f,
 30 -C(=O)NOH, -NR^fC(=O)OR^f, -NR^fC(=O)R^f, -C₁₋₆alkyl substituted with from 1 to 3 hydroxyl groups, -C₁₋₆alkenyl, or a 5 or 6 membered aryl or heteroaryl group, which

heteroaryl group can contain from one to four heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN, and any C₁₋₆alkyl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -OH, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

R⁴ is hydrogen, -C₁₋₆alkyl, -C₂₋₆alkenyl, -CF₃, -CH₂F, -CHF₂, -S(=O)₂R^f, -SR^f, -S(=O)R^f, -S(=O)₂NR^fR^f, -NR^fS(=O)₂NR^fR^f, -C(=O)NR^fR^f, -NR^fS(=O)₂R^f, -C(=O)₂R^f, -OR^f, a 3 to 7 membered cycloalkyl or heterocycloalkyl, optionally containing a -(C=O)- group, or a 5 to 6 membered aryl or heteroaryl group, which heterocycloalkyl or heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the cycloalkyl, heterocycloalkyl, aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl -OH, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN, and the -C₁₋₆alkyl or -C₂₋₆alkenyl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -NR^fR^f, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

R⁵ is hydrogen or -C₁₋₆alkyl;

R⁶ is hydrogen, -C₁₋₆alkyl, -(CH₂)_nNR^fR^f, or -(CH₂)_nC(=O)NR^fR^f;

each R^a is independently hydrogen, halo or -C₁₋₆alkyl, or two R^a groups that are attached to the same carbon atom can form an (=O) group or a 3 to 6 membered cycloalkyl or heterocycloalkyl group, or an R^a group and R⁶ along with the atoms to which they are attached can form a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can contain from one to two heteroatoms independently selected from O, N or S, and the cycloalkyl or heterocycloalkyl group can

be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

- 5 each R^c is independently hydrogen, -C₁₋₆alkyl, -C₁₋₆alkyl-CF₃, -CF₃, a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can contain from one to two heteroatoms independently selected from O, N or S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl,
10 -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

- or two R^c groups that are attached to the same or adjacent carbon atoms can together with the carbon atom or atoms to which they are attached form or a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can
15 contain from one to two heteroatoms independently selected from O, N or S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

- 20 each R^d is independently hydrogen or -C₁₋₆alkyl;

each R^e is independently hydrogen or -C₁₋₆alkyl;

- each R^f is independently hydrogen, -CN, -C₁₋₆alkyl, -C₁₋₆alkyl-CN,
25 -C₁₋₆alkyl-CF₃, hydroxyC₁₋₆alkyl, -C₁₋₆alkylNR^eR^e, or a 5 to 6 membered aryl, -C₁₋₆alkylaryl, heteroaryl, or -C₁₋₆alkylheteroaryl, or a 3 to 9 membered cycloalkyl -C₁₋₆alkylcycloalkyl, heterocycloalkyl or -C₁₋₆alkylheterocycloalkyl group, which heteroaryl, alkylheteroaryl, heterocycloalkyl, or alkylheterocycloalkyl group can contain from one to three heteroatoms independently selected from O, N or S, and the alkyl, aryl, alkylaryl,
30 heteroaryl, alkylheteroaryl, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, or

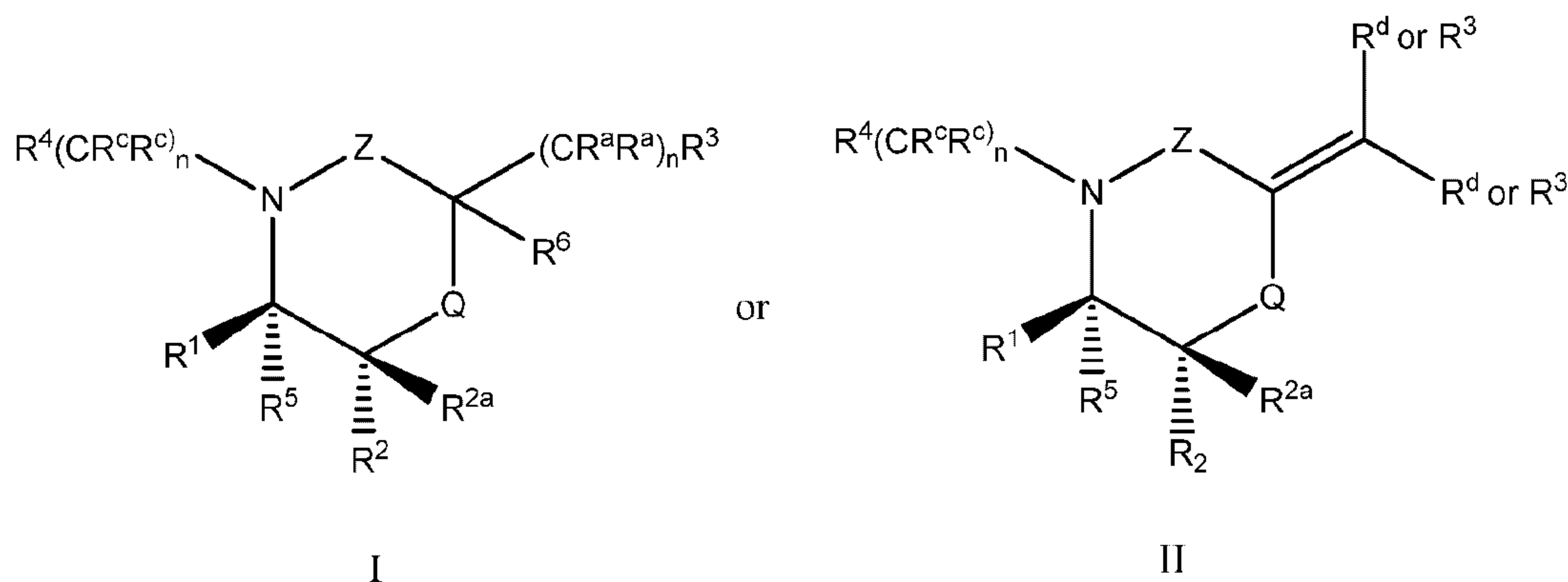
alkylheterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

or when R^f and R^f are part of an NR^fR^f or CR^fR^f moiety in a group, then R^f and R^f together with the nitrogen or carbon atom to which they are attached can form a 3 to 7 membered heterocycloalkyl or cycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from O, N or S, and the heterocycloalkyl or cycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

each R^g is independently hydrogen, or -C₁₋₆alkyl; and

each n is independently 0, 1, 2, 3 or 4, provided that the compound is not 2-((2*R*,5*R*,6*R*)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((1*S*,2*S*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid; 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*S*,2*S*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid; 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*R*,2*R*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid; or 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*R*,2*R*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid.

In embodiment 1A, the present invention provides compounds of Formula I or II, or pharmaceutically acceptable salts thereof,



wherein:

5 Q is O, S, -S(=O)-, -S(=O)₂-, or -NR^e;

Z is -C(=O)- or -S(=O)₂-;

10

R¹ is a 5 to 10 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -OH, -NO₂,

15 -NHC(=O)C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃,
-OCHF₂, -OCH₂F, -(CH₂)_nC(=O)R^f, -(CH₂)_nC(=O)NR^fR^f, -CN, -NR^gR^g or A,

or R¹ and R⁵ together with the carbon atom to which they are attached can form a 3 to 6 membered cycloalkyl or heterocycloalkyl group, optionally containing a -(C=O)- group, which heterocycloalkyl group can contain from one to two heteroatoms

independently selected from O, N or S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, -(CH₂)_nC(=O)R^f, -(CH₂)_nC(=O)NR^fR^f or -CN, and substituents on two adjacent carbons atoms of the cycloalkyl or heterocycloalkyl group can join together to form a five or six membered ring, including the two carbon atoms, fused to the cycloalkyl or heterocycloalkyl group,

or when R^1 is substituted with $-NR^gR^g$, then R^g and R^g together with the nitrogen atom to which they are attached can form a 3 to 6 membered heterocycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from O, N or S, and the heterocycloalkyl group can be
 5 unsubstituted or substituted with from one to three substituents independently selected from halo, $-C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$ or $-CN$;

each A is independently a 5 or 6 membered aryl or heteroaryl group, which
 10 heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, $-C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, or $-CN$;

15 R^2 is a 5 to 10 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, $-C_{1-6}$ alkyl, $-OH$, $-NO_2$, $-NHC(=O)C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$,
 20 $-OCHF_2$, $-OCH_2F$, $-(CH_2)_nC(=O)R^f$, $-(CH_2)_nC(=O)NR^fR^f$, $-CN$, $-NR^gR^g$ or B,

or when R^2 is substituted with $-NR^gR^g$, then R^g and R^g together with the nitrogen atom to which they are attached can form a 3 to 6 membered heterocycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from O, N or S, and the heterocycloalkyl group can be
 25 unsubstituted or substituted with from one to three substituents independently selected from halo, $-C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, or $-CN$;

each B is independently a 5 or 6 membered aryl or heteroaryl group, which
 30 heteroaryl group can contain from one to three heteroatoms independently selected from

O, N or S, and the aryl or heteroaryl groups group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

5 R^{2a} is hydrogen or -C₁₋₃alkyl;

R³ is hydrogen, -C₁₋₆alkyl, -C(=O)OR^f, -C(=O)C₁₋₆alkyl, -S(=O)₂R^f, -S(=O)R^f, -OR^f, -C(=O)NR^fN(R^f)₂, -C(=O)NR^fS(=O)₂R^f, -S(=O)₂NR^fC(=O)R^f, -S(=O)₂NR^fR^f, -N(R^f)C(=O)NR^fR^f, -NR^fC(=O)₂R^f, -C(=O)NR^fR^f, -NR^fS(=O)₂R^f, -CN, -NR^fR^f,
 10 -C(=O)NOH, -C₁₋₆alkenyl, or a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to four heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN, and any C₁₋₆alkyl
 15 group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -OH, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

R⁴ is hydrogen, -C₁₋₆alkyl, -C₂₋₆alkenyl, -CF₃, -CH₂F, -CHF₂, -S(=O)₂R^f, -SR^f,
 20 -S(=O)R^f, -S(=O)₂NR^fR^f, -NR^fS(=O)₂NR^fR^f, -C(=O)NR^fR^f, -NR^fS(=O)₂R^f, -C(=O)₂R^f, -OR^f, a 3 to 7 membered cycloalkyl or heterocycloalkyl, optionally containing a -(C=O)- group, or a 5 to 6 membered aryl or heteroaryl group, which heterocycloalkyl or heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the cycloalkyl, heterocycloalkyl, aryl or heteroaryl group can be
 25 unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl -OH, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN, and the -C₁₋₆alkyl or -C₂₋₆alkenyl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -NR^fR^f, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F,
 30 or -CN;

R^5 is hydrogen or $-C_{1-6}$ alkyl;

R^6 is hydrogen, $-C_{1-6}$ alkyl, $-(CH_2)_nNR^fR^f$, or $-(CH_2)_nC(=O)NR^fR^f$;

5 each R^a is independently hydrogen, halo or $-C_{1-6}$ alkyl, or two R^a groups that are attached to the same carbon atom can form an $(=O)$ group or a 3 to 6 membered cycloalkyl or heterocycloalkyl group, or an R^a group and R^6 along with the atoms to which they are attached can form a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can contain from one to two heteroatoms
 10 independently selected from O, N or S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, $-C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, or $-CN$;

15 each R^c is independently hydrogen, $-C_{1-6}$ alkyl, a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can contain from one to two heteroatoms independently selected from O, N or S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, C_{1-6} alkyl, $-S(=O)_2C_{1-6}$ alkyl,
 20 $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, or $-CN$;

or two R^c groups that are attached to the same or adjacent carbon atoms can together with the carbon atom or atoms to which they are attached form or a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can
 25 contain from one to two heteroatoms independently selected from O, N or S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, $-C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, or $-CN$;

30 each R^d is independently hydrogen or $-C_{1-6}$ alkyl;

each R^e is independently hydrogen or -C₁₋₆alkyl;

each R^f is independently hydrogen, -C₁₋₆alkyl, hydroxyC₁₋₆alkyl,
 -C₁₋₆alkylNR^eR^e, or a 5 to 6 membered aryl, -C₁₋₆alkylaryl, heteroaryl, or
 5 -C₁₋₆alkylheteroaryl, or a 3 to 7 membered cycloalkyl, -C₁₋₆alkylcycloalkyl,
 heterocycloalkyl or -C₁₋₆alkylheterocycloalkyl group, which heteroaryl, alkylheteroaryl,
 heterocycloalkyl, or alkylheterocycloalkyl group can contain from one to three
 heteroatoms independently selected from O, N or S, and the aryl, alkylaryl, heteroaryl,
 alkylheteroaryl, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, or alkylheterocycloalkyl
 10 group can be unsubstituted or substituted with from one to three substituents
 independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl,
 -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

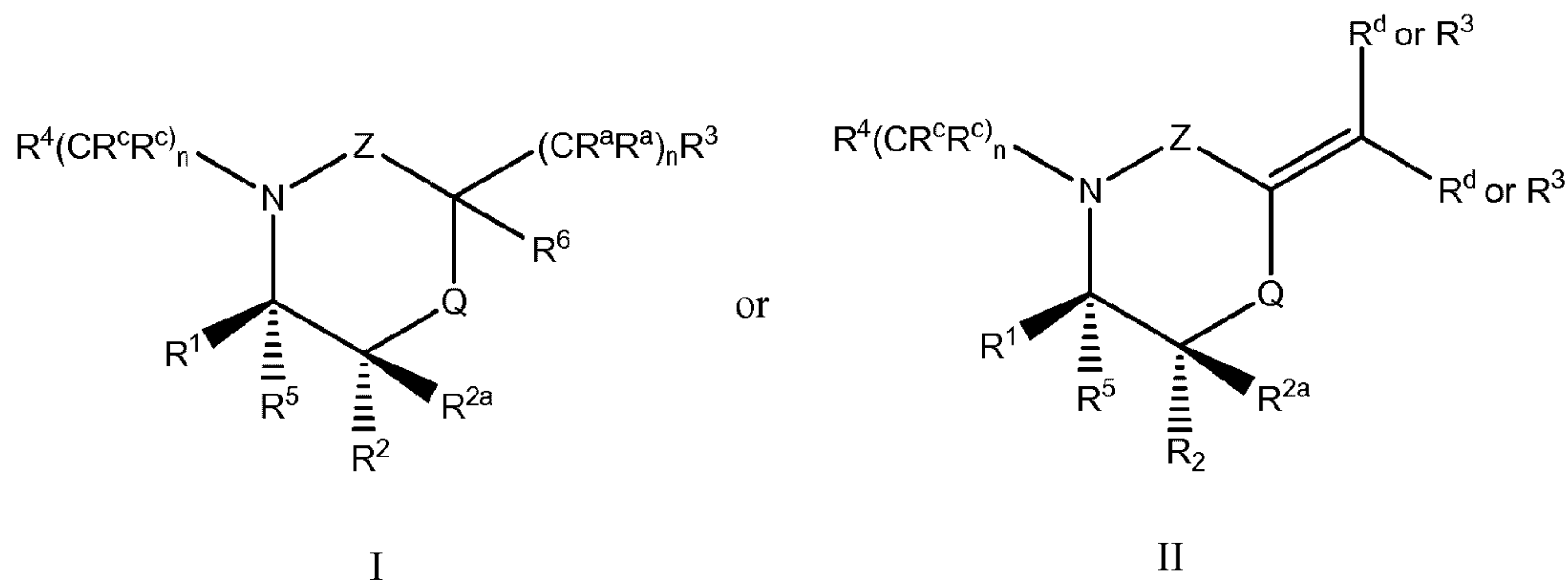
or when R^f and R^f are part of an NR^fR^f or CR^fR^f moiety in a group, then R^f and R^f
 together with the nitrogen or carbon atom to which they are attached can form a 3 to 7
 15 membered heterocycloalkyl or cycloalkyl group, which heterocycloalkyl group can
 contain from one to two additional heteroatoms independently selected from O, N or S,
 and the heterocycloalkyl or cycloalkyl group can be unsubstituted or substituted with
 from one to three substituents independently selected from halo, -C₁₋₆alkyl,
 -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

20

each R^g is independently hydrogen, or -C₁₋₆alkyl; and

each n is independently 0, 1, 2, 3 or 4, provided that the compound is not
 2-((2*R*,5*R*,6*R*)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((1*S*,2*S*)-2-
 25 (isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid; 2-((2*S*,5*R*,6*R*)-6-(3-
 chlorophenyl)-5-(4-chlorophenyl)-4-((1*S*,2*S*)-2-(isopropylsulfonyl)cyclopentyl)-3-
 oxomorpholin-2-yl)acetic acid; 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-
 ((1*R*,2*R*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid; or 2-
 ((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*R*,2*R*)-2-
 30 (isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid.

In embodiment 1a, the present invention provides compounds of Formula I or II, or pharmaceutically acceptable salts thereof,



wherein:

Q is O, S, -S(=O)-, -S(=O)₂-, or -NR^e;

Z is -C(=O)- or -S(=O)₂-;

15 R^1 is a 5 to 10 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, $-C_{1-6}$ alkyl, $-OH$, $-NO_2$, $-NHC(=O)C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$,
20 $-OCHF_2$, $-OCH_2F$, $-(CH_2)_nC(=O)R^f$, $-(CH_2)_nC(=O)NR^fR^f$, $-CN$, $-NR^gR^g$ or A,
or R^1 and R^5 together with the carbon atom to which they are attached can form a 3 to 6 membered cycloalkyl or heterocycloalkyl group, optionally containing a $-(C=O)-$ group, which heterocycloalkyl group can contain from one to two heteroatoms independently selected from O, N or S, and the cycloalkyl or heterocycloalkyl group can
25 be unsubstituted or substituted with from one to three substituents independently selected from halo, $-C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$,

-OCHF₂, -OCH₂F, -(CH₂)_nC(=O)R^f, -(CH₂)_nC(=O)NR^fR^f or -CN, and substituents on two adjacent carbon atoms of the cycloalkyl or heterocycloalkyl group can join together to form a five or six membered ring, including the two carbon atoms, fused to the cycloalkyl or heterocycloalkyl group,

- 5 or when R¹ is substituted with -NR^gR^g, then R^g and R^g together with the nitrogen atom to which they are attached can form a 3 to 6 membered heterocycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from O, N or S, and the heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected
- 10 from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F or -CN;

- each A is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from
- 15 O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

- R² is a 5 to 10 membered aryl or heteroaryl group, which heteroaryl group can
- 20 contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -OH, -NO₂, -NHC(=O)C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, -(CH₂)_nC(=O)R^f, -(CH₂)_nC(=O)NR^fR^f, -CN, -NR^gR^g or B,
- 25 or when R² is substituted with -NR^gR^g, then R^g and R^g together with the nitrogen atom to which they are attached can form a 3 to 6 membered heterocycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from O, N or S, and the heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected
- 30 from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

each B is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl groups group can be unsubstituted or substituted
 5 with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

R^{2a} is hydrogen or -C₁₋₃alkyl;

10 R³ is hydrogen, -C₁₋₆alkyl, -C(=O)OR^f, -C(=O)C₁₋₆alkyl, -S(=O)₂R^f, -S(=O)R^f, -OR^f, -C(=O)NR^fN(R^f)₂, -C(=O)NR^fS(=O)₂R^f, -S(=O)₂NR^fC(=O)R^f, -S(=O)₂NR^fR^f, -N(R^f)C(=O)NR^fR^f, -NR^fC(=O)₂R^f, -C(=O)NR^fR^f, -NR^fS(=O)₂R^f, -CN, -NR^fR^f, or a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to four heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group
 15 can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN, and any C₁₋₆alkyl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -OH, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

20 R⁴ is hydrogen, -C₁₋₆alkyl, -C₂₋₆alkenyl, -CF₃, -CH₂F, -CHF₂, -S(=O)₂R^f, -SR^f, -S(=O)R^f, -S(=O)₂NR^fR^f, -NR^fS(=O)₂NR^fR^f, -C(=O)NR^fR^f, -NR^fS(=O)₂R^f, -C(=O)₂R^f, -OR^f, a 3 to 7 membered cycloalkyl or heterocycloalkyl, optionally containing a -(C=O)-group, or a 5 to 6 membered aryl or heteroaryl group, which heterocycloalkyl or
 25 heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the cycloalkyl, heterocycloalkyl, aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl -OH, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN, and the -C₁₋₆alkyl or -C₂₋₆alkenyl group can be unsubstituted
 30 or substituted with from one to three substituents independently selected from halo,

-NR^fR^f, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

R⁵ is hydrogen or -C₁₋₆alkyl;

5

R⁶ is hydrogen, -C₁₋₆alkyl, -(CH₂)_nNR^fR^f, or -(CH₂)_nC(=O)NR^fR^f;

each R^a is independently hydrogen, halo or -C₁₋₆alkyl, or two R^a groups that are attached to the same carbon atom can form an (=O) group or a 3 to 6 membered
 10 cycloalkyl or heterocycloalkyl group, or an R^a group and R⁶ along with the atoms to which they are attached can form a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can contain from one to two heteroatoms independently selected from O, N or S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected
 15 from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

each R^c is independently hydrogen, -C₁₋₆alkyl, a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can contain from one to two
 20 heteroatoms independently selected from O, N or S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

25 or two R^c groups that are attached to the same or adjacent carbon atoms can together with the carbon atom or atoms to which they are attached form or a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can contain from one to two heteroatoms independently selected from O, N or S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to
 30 three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

each R^d is independently hydrogen or -C₁₋₆alkyl;

each R^e is independently hydrogen or -C₁₋₆alkyl;

5

each R^f is independently hydrogen, -C₁₋₆alkyl or a 5 to 6 membered aryl, -C₁₋₆alkylaryl, heteroaryl, or -C₁₋₆alkylheteroaryl, or a 3 to 7 membered cycloalkyl -C₁₋₆alkylcycloalkyl, heterocycloalkyl or -C₁₋₆alkylheterocycloalkyl group, which heteroaryl alkylheteroaryl, heterocycloalkyl, or alkylheterocycloalkyl group can contain
 10 from one to three heteroatoms independently selected from O, N or S, and the aryl, alkylaryl, heteroaryl, alkylheteroaryl, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, or alkylheterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;
 15 or when R^f and R^f are part of an NR^fR^f or CR^fR^f moiety in a group, then R^f and R^f together with the nitrogen or carbon atom to which they are attached can form a 3 to 7 membered heterocycloalkyl or cycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from O, N or S, and the heterocycloalkyl or cycloalkyl group can be unsubstituted or substituted with
 20 from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

each R^g is independently hydrogen, or -C₁₋₆alkyl; and

25

each n is independently 0, 1, 2, 3 or 4, provided that the compound is not 2-((2*R*,5*R*,6*R*)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((1*S*,2*S*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid; 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*S*,2*S*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid; 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*R*,2*R*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid; or 2-
 30

((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*R*,2*R*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid.

In embodiment 2, the present invention provides compounds in accordance with
 5 embodiment 1, 1A or 1a, or pharmaceutically acceptable salts thereof, wherein:

Q is O;

Z is -C(=O)-;

10

R¹ is a 5 to 10 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, -CN, or A;
 15

each A is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from
 20 one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

R² is a 5 to 10 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the
 25 aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -SO₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, -CN, or B;

each B is independently a 5 or 6 membered aryl or heteroaryl group, which
 30 heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl,

-S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

R³ is hydrogen, -C₁₋₆alkyl, -C(=O)OR^f, -C(=O)C₁₋₆alkyl, -S(=O)₂R^f, -S(=O)R^f,
 -OR^f, -C(=O)NR^fN(R^f)₂, -C(=O)NR^fS(=O)₂R^f, -S(=O)₂NR^fC(=O)R^f, -S(=O)₂NR^fR^f,
 5 -N(R^f)C(=O)NR^fR^f, -NR^fC(=O)₂R^f, -C(=O)NR^fR^f, -NR^fS(=O)₂R^f, -CN, -NR^fR^f, or a 5 or
 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to
 four heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group
 can be unsubstituted or substituted with from one to three substituents independently
 selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃,
 10 -OCF₃, -OCHF₂, -OCH₂F, or -CN, and any C₁₋₆alkyl group can be unsubstituted or
 substituted with from one to three substituents independently selected from halo, -OH,
 -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

R⁴ is hydrogen, -C₁₋₆alkyl, -C₂₋₆alkenyl, -CF₃, -CH₂F, -CHF₂, -S(=O)₂R^f, -SR^f,
 15 -S(=O)R^f, -S(=O)₂NR^fR^f, -NR^fS(=O)₂NR^fR^f, -C(=O)NR^fR^f, -NR^fS(=O)₂R^f, -C(=O)₂R^f,
 -OR^f, a 3 to 7 membered cycloalkyl or heterocycloalkyl, optionally containing a -(C=O)-
 group, or a 5 to 6 membered aryl or heteroaryl group, which heterocycloalkyl or
 heteroaryl group can contain from one to three heteroatoms independently selected from
 O, N or S, and the cycloalkyl, heterocycloalkyl, aryl or heteroaryl group can be
 20 unsubstituted or substituted with from one to three substituents independently selected
 from halo, -C₁₋₆alkyl -OH, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃,
 -OCHF₂, -OCH₂F, or -CN, and the -C₁₋₆alkyl or -C₂₋₆alkenyl group can be unsubstituted
 or substituted with from one to three substituents independently selected from halo, -
 NR^fR^f, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F,
 25 or -CN;

R⁶ is hydrogen or -C₁₋₆alkyl;

each R^a is independently hydrogen or -C₁₋₆alkyl; and

30

each R^c is independently hydrogen or -C₁₋₆alkyl.

In embodiment 3, the present invention provides compounds in accordance with embodiment 1, 1A or 1a, or pharmaceutically acceptable salts thereof, wherein:

5 Q is O;

Z is -C(=O)-;

10 R¹ is a 5 to 10 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, -CN, or A;

15 each A is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

20 R² is a 5 to 10 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, -C₁₋₆alkyl, -SO₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, 25 -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, -CN, or B;

each B is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group group can be unsubstituted or substituted with 30 from one to three substituents independently selected from halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, or -CN;

R^3 is hydrogen, $-C(=O)OH$, $-C(=O)OC_{1-6}alkyl$, $-S(=O)_2C_{1-6}alkyl$, $-S(=O)C_{1-6}alkyl$, $-OH$, or a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to four heteroatoms independently selected from O, N or S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, $-C_{1-6}alkyl$, $-S(=O)_2C_{1-6}alkyl$, $-S(=O)C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, or $-CN$;

R^4 is hydrogen, $-C_{1-6}alkyl$, $-C_{2-6}alkenyl$, $-CF_3$, $-CH_2F$, $-CHF_2$, $-S(=O)_2C_{1-6}alkyl$, $-S(=O)C_{1-6}alkyl$, $-C(=O)C_{1-6}alkyl$, $-OR^f$, $-S(=O)_2R^f$, $-S(=O)R^f$, $-NR^fS(=O)_2R^f$, a 3 to 6 membered cycloalkyl or heterocycloalkyl, or a 5 to 6 membered aryl or heteroaryl group, which heterocycloalkyl or heteroaryl group can contain from one to three heteroatoms independently selected from O, N or S, and the cycloalkyl, heterocycloalkyl, aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from halo, $-C_{1-6}alkyl$, $-S(=O)_2C_{1-6}alkyl$, $-S(=O)C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, or $-CN$;

R^6 is hydrogen or $-C_{1-6}alkyl$;

each R^a is independently hydrogen or $-C_{1-6}alkyl$; and

each R^c is independently hydrogen or $-C_{1-6}alkyl$.

In embodiment 4, the present invention provides compounds in accordance with embodiment 1, 1A or 1a, or pharmaceutically acceptable salts thereof, wherein Q is O.

In embodiment 5, the present invention provides compounds in accordance with embodiment 1, 1A or 1a, or pharmaceutically acceptable salts thereof, wherein Z is $-C(=O)-$.

In embodiment 6, the present invention provides compounds in accordance with any one of embodiments 1A, 1a or 1 to 3, or pharmaceutically acceptable salts thereof, wherein $-(CR^aR^a)_n-$ is $-CH_2-$.

5 In embodiment 7, the present invention provides compounds in accordance with any one of embodiments 1A, 1a or 1 to 3, or pharmaceutically acceptable salts thereof, wherein R^3 is $-CO_2R^f$ or tetrazolyl.

10 In embodiment 8, the present invention provides compounds in accordance with any one of embodiments 1A, 1a or 1 to 3, or pharmaceutically acceptable salts thereof, wherein R^3 is $-CO_2H$ or tetrazolyl.

In embodiment 9, the present invention provides compounds in accordance with any one of embodiments 1A, 1a or 1 to 3, or pharmaceutically acceptable salts thereof, 15 wherein $-(CR^aR^a)_n-$ is $-CH_2-$ and R^3 is $-CO_2H$ or tetrazolyl.

In embodiment 10, the present invention provides compounds in accordance with any one of embodiments 1A, 1a or 1 to 9, or pharmaceutically acceptable salts thereof, wherein $-(CR^cR^c)_n-$ is absent, $-CH_2-$, $-CH(CH_2CH_3)-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, 20 $-CH(CH_3)-$, $-CH(CH_2CH_3)CH_2-$, $-CH(CHCH_3CH_3)CH_2-$, or $-C(CCH_3CH_3CH_3)CH_2-$.

In embodiment 11, the present invention provides compounds in accordance with embodiment 10, or pharmaceutically acceptable salts thereof, wherein $-(CR^cR^c)_n-$ is absent. 25

In embodiment 12, the present invention provides compounds in accordance with embodiment 10, or pharmaceutically acceptable salts thereof, wherein $-(CR^cR^c)_n-$ is $-CH_2-$.

30 In embodiment 13, the present invention provides compounds in accordance with embodiment 10, or pharmaceutically acceptable salts thereof, wherein $-(CR^cR^c)_n-$ is

-CH(CH₂CH₃)-.

In embodiment 14, the present invention provides compounds in accordance with embodiment 10, or pharmaceutically acceptable salts thereof, wherein -(CR^cR^c)_n- is
5 -CH(CH₃)-.

In embodiment 15, the present invention provides compounds in accordance with embodiment 10, or pharmaceutically acceptable salts thereof, wherein -(CR^cR^c)_n- is
10 -CH(CH₂CH₃)CH₂-.

In embodiment 16, the present invention provides compounds in accordance with any one of embodiments 1A, 1a or 1 to 15, or pharmaceutically acceptable salts thereof, wherein R⁴ is hydrogen, cyclopropyl, -C(=O)₂C₁₋₆alkyl, cyclopentyl, cyclobutyl, cyclohexyl, phenyl, oxazolyl, -CF₃, -C₁₋₆alkyl, -C₂₋₆alkenyl, -S(=O)₂C₁₋₆alkyl, -OH,
15 -S(=O)₂phenyl, or -N(phenyl)S(=O)₂-cyclopropyl.

In embodiment 17, the present invention provides compounds in accordance with embodiment 16, or pharmaceutically acceptable salts thereof, wherein R⁴ is cyclopropyl.

20 In embodiment 18, the present invention provides compounds in accordance with embodiment 16, or pharmaceutically acceptable salts thereof, wherein R⁴ is -C(=O)₂C₁₋₆alkyl.

In embodiment 19, the present invention provides compounds in accordance with
25 embodiment 16, or pharmaceutically acceptable salts thereof, wherein R⁴ is -C₁₋₆alkyl.

In embodiment 20, the present invention provides compounds in accordance with embodiment 16, or pharmaceutically acceptable salts thereof, wherein R⁴ is
30 -S(=O)₂C₁₋₆alkyl.

In embodiment 21, the present invention provides compounds in accordance with embodiment 16, or pharmaceutically acceptable salts thereof, wherein R⁴ is -OH.

In embodiment 22, the present invention provides compounds in accordance with
5 embodiment 16, or pharmaceutically acceptable salts thereof, wherein R⁴ is
-S(=O)₂phenyl.

In embodiment 23, the present invention provides compounds in accordance with
embodiment 16, or pharmaceutically acceptable salts thereof, wherein R⁴ is
10 -N(phenyl)S(=O)₂-cyclopropyl.

In embodiment 24, the present invention provides compounds in accordance with
any one of embodiments 1A, 1a or 1 to 9, or pharmaceutically acceptable salts thereof,
wherein R⁴(CR^cR^c)_n- is hydrogen, -CH₂-cyclopropyl, -CH(CH₂CH₃)CH₂S(=O)₂C₁₋₆alkyl,
15 -CH₂-cyclopentyl, -CH₂-cyclobutyl, -CH₂-cyclohexyl, cyclopropyl, cyclobutyl,
cyclohexyl or -C₁₋₆alkyl.

In embodiment 25, the present invention provides compounds in accordance with
any one of embodiments 1A, 1a or 1 to 24, or pharmaceutically acceptable salts thereof,
20 wherein R¹ is substituted phenyl, indolyl, substituted benzimidazolyl, benzthiazolyl,
substituted pyridyl, or substituted thiophenyl.

In embodiment 26, the present invention provides compounds in accordance with
embodiment 25, or pharmaceutically acceptable salts thereof, wherein R¹ is
25 4-chlorophenyl.

In embodiment 27, the present invention provides compounds in accordance with
embodiment 25, or pharmaceutically acceptable salts thereof, wherein R¹ is
30 3-chlorophenyl.

In embodiment 28, the present invention provides compounds in accordance with any one of embodiments 1A, 1a or 1 to 27, or pharmaceutically acceptable salts thereof, wherein R² is substituted phenyl or substituted pyridyl.

5 In embodiment 29, the present invention provides compounds in accordance with embodiment 28, or pharmaceutically acceptable salts thereof, wherein R² is 3-chlorophenyl.

10 In embodiment 30, the present invention provides compounds in accordance with any one of embodiments 1A, 1a or 1 to 29, or pharmaceutically acceptable salts thereof, wherein R⁶ is hydrogen or -CH₃.

15 In embodiment 31, the present invention provides compounds in accordance with embodiment 30, or pharmaceutically acceptable salts thereof, wherein R⁶ is hydrogen.

In embodiment 32, the present invention provides compounds in accordance with any one of embodiments 1A, 1a or 1 to 31, or pharmaceutically acceptable salts thereof, wherein R⁵ is hydrogen or -CH₃.

20 In embodiment 33, the present invention provides compounds in accordance with embodiment 32, or pharmaceutically acceptable salts thereof, wherein R⁵ is hydrogen.

25 In embodiment 34, the present invention provides compounds in accordance with any one of embodiments 1A, 1a or 1 to 33, or pharmaceutically acceptable salts thereof, wherein R^d is hydrogen.

In embodiment 35, the present invention provides compounds in accordance with embodiment 1A, 1a or 1, or pharmaceutically acceptable salts thereof, wherein:

30 Q is O;

Z is -C(=O)-;

-(CR^aR^a)_n- is -CH₂-;

R³ is -C(=O)₂H or tetrazolyl;

5

-(CR^cR^c)_n- is absent, -CH₂-, -CH(CH₂CH₃)-, -CH₂CH₂-,
-CH₂CH₂CH₂-, -CH(CH₃)-, -CH(CH₂CH₃)CH₂-, -CH(CHCH₃CH₃)CH₂-, or
-C(CCH₃CH₃CH₃)CH₂-;

10

R⁴ is hydrogen, cyclopropyl, -C(=O)₂C₁₋₆alkyl, cyclopentyl, cyclobutyl,
cyclohexyl, phenyl, oxazolyl, -CF₃, -C₁₋₆alkyl, -C₂₋₆alkenyl, -S(=O)₂C₁₋₆alkyl,
-OH, -S(=O)₂phenyl, or -N(phenyl)S(=O)₂-cyclopropyl;

15

R¹ is substituted phenyl, indolyl, substituted benzimidazolyl, benzthiazolyl,
substituted pyridyl, or substituted thiophenyl; and

R² is substituted phenyl or substituted pyridyl.

20

In embodiment 36, the present invention provides compounds, or
pharmaceutically acceptable salts thereof, selected from:

2-((2R,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-5-(1H-indol-2-yl)-3-
oxomorpholin-2-yl)acetic acid;

2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-5-(1H-indol-2-yl)-3-
oxomorpholin-2-yl)acetic acid;

25

2-((2R,5R,6S)-5-(benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-
oxomorpholin-2-yl)acetic acid;

2-((2S,5R,6S)-5-(benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-
oxomorpholin-2-yl)acetic acid;

30

2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-5-(1-methyl-1H-
benzo[d]imidazol-2-yl)-3-oxomorpholin-2-yl)acetic acid;

- 2-((2R,5S,6S)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-5-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-5-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 5 2-((2S,5S,6S)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-5-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(5-chloropyridin-2-yl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(5-chloropyridin-2-yl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 10 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-(3,3,3-trifluoropropyl)morpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-cyclobutyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-cyclobutyl-3-oxomorpholin-2-yl)acetic acid;
- 20 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-cyclopentyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-cyclopentyl-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-cyclohexyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-cyclohexyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((R)-1-cyclohexylethyl)-3-oxomorpholin-2-yl)acetic acid;
- 30

- 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-cyclohexylethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((R)-1-cyclobutylethyl)-3-oxomorpholin-2-yl)acetic acid;
- 5 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((R)-1-cyclobutylethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-cyclobutylethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-cyclobutylethyl)-3-oxomorpholin-2-yl)acetic acid;
- 10 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((R)-1-phenylethyl)morpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((R)-1-phenylethyl)morpholin-2-yl)acetic acid;
- 15 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((S)-1-phenylethyl)morpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((S)-1-phenylethyl)morpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopentylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 20 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopentylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-4-((R)-1-(*tert*-butoxy)-1-oxobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2S,5R,6R)-4-((S)-1-(*tert*-butoxy)-1-oxobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-4-((S)-1-(*tert*-butoxy)-1-oxobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-4-((R)-1-(*tert*-butoxy)-1-oxobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 30 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;

- 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-isobutyl-3-oxomorpholin-2-yl)acetic acid;
2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-isobutyl-3-oxomorpholin-2-yl)acetic acid;
5 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclobutylmethyl)-3-oxomorpholin-2-yl)acetic acid;
2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclobutylmethyl)-3-oxomorpholin-2-yl)acetic acid;
10 2-((2S,5R,6R)-4-butyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclohexylmethyl)-3-oxomorpholin-2-yl)acetic acid;
2-((2S,5R,6R)-4-benzyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
15 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(oxazol-2-ylmethyl)-3-oxomorpholin-2-yl)acetic acid;
2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-ethyl-3-oxomorpholin-2-yl)acetic acid;
20 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-ethyl-3-oxomorpholin-2-yl)acetic acid;
2-((2R,5R,6R)-4-allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
2-((2S,5R,6R)-4-allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
25 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-propylmorpholin-2-yl)acetic acid;
2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-propylmorpholin-2-yl)acetic acid;
30 (2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-2-((tetrazol-5-yl)methyl)morpholin-3-one;

- (2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-2-((tetrazol-5-yl)methyl)morpholin-3-one;
- (Z)-2-((5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-ylidene)acetic acid;
- 5 (E)-2-((5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-ylidene)acetic acid
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-(pentan-3-yl)morpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-5-(4-chloro-2-fluorophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 10 2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-phenylmorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-5-(4-fluorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(4-(trifluoromethyl)phenyl)morpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-5-(4-ethylphenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(4-(trifluoromethoxy)phenyl)morpholin-2-yl)acetic acid;
- 20 2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(p-tolyl)morpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(p-tolyl)morpholin-2-yl)acetic acid;
- 25 2-((2R,5R,6R)-5-(4-chloro-2-fluorophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-phenylmorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-5-(4-fluorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 30

- 2-((2R,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(4-(trifluoromethoxy)phenyl)morpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-5-(4-isopropylphenyl)-3-oxomorpholin-2-yl)acetic acid;
- 5 2-((2R,5R,6R)-5-(4-bromophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-5-(4-bromophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5S,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(thiophen-2-yl)morpholin-2-yl)acetic acid;
- 10 2-((2S,5S,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(thiophen-2-yl)morpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(6-chloropyridin-3-yl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(6-chloropyridin-3-yl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-5-(6-methoxypyridin-3-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-5-(6-methoxypyridin-3-yl)-3-oxomorpholin-2-yl)acetic acid;
- 20 2-((2R,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-5-(4-methoxyphenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-5-(4-methoxyphenyl)-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2R,5R,6R)-5-(4-chloro-3-fluorophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-5-(4-chloro-3-fluorophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-5-(2-bromo-4-chlorophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 30

- 2-((2S,5R,6R)-5-(2-bromo-4-chlorophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(6-(trifluoromethyl)pyridin-3-yl)morpholin-2-yl)acetic acid;
- 5 2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(6-(trifluoromethyl)pyridin-3-yl)morpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chloro-5-fluorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chloro-5-fluorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 10 2-((2R,5R,6R)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-6-(3-fluorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-6-(3-fluorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2R,5R,6R)-5-(4-chlorophenyl)-6-(5-chloropyridin-3-yl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-5-(4-chlorophenyl)-6-(5-chloropyridin-3-yl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-6-(3-methoxyphenyl)-3-oxomorpholin-2-yl)acetic acid;
- 20 2-((2S,5R,6R)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-6-(3-methoxyphenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-5-(4-chlorophenyl)-6-(2-chloropyridin-4-yl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2S,5R,6R)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-6-(5-methoxypyridin-3-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-6-(3,5-dichlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chloro-4-fluorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 30 2-((2S,5R,6R)-6-(3-chloro-4-fluorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;

- 2-((2S,5R,6R)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-6-(3-(trifluoromethoxy)phenyl)morpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-6-(3,5-difluorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 5 2-((2S,5R,6R)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-6-(3,5-difluorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-5-(4-chlorophenyl)-6-(3-cyano-5-fluorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-5-(4-chlorophenyl)-6-(3-cyano-5-fluorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 10 2-((2R,5R,6R)-6-(5-chloro-2-fluorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(5-chloro-2-fluorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2R,5R,6R)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-6-(m-tolyl)morpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-6-(m-tolyl)morpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-bromo-5-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 20 2-((2S,5R,6R)-6-(3-bromo-5-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chloro-5-(1H-pyrazol-4-yl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2S,5R,6R)-6-(3-chloro-5-(1H-pyrazol-4-yl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chloro-5-(pyrimidin-5-yl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chloro-5-(pyrimidin-5-yl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
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- 2-((2R,5R,6R)-6-(3-chloro-5-(methylsulfonyl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chloro-5-(methylsulfonyl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid;
- 5 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(ethylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(ethylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-hydroxybutan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 10 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-hydroxybutan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((S)-1-(phenylsulfonyl)butan-2-yl)morpholin-2-yl)acetic acid;
- 15 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((S)-1-(phenylsulfonyl)butan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(isopropylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(isopropylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 20 2-((2R,5R,6R)-4-((S)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-4-((S)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((S)-1-(*tert*-pentylsulfonyl)butan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((S)-1-(*tert*-pentylsulfonyl)butan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chloro-5-fluorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(isopropylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 30

- 2-((2S,5R,6R)-6-(3-chloro-5-fluorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(isopropylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((3S,5S)-5-hydroxyhexan-3-yl)-3-oxomorpholin-2-yl)acetic acid;
- 5 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((3S,5R)-5-hydroxyhexan-3-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((S)-1-(N-phenylcyclopropanesulfonamido)butan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((S)-1-(N-phenylcyclopropanesulfonamido)butan-2-yl)morpholin-2-yl)acetic acid;
- 10 2-((2R,5R,6R)-4-((S)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-4-((S)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-5-methyl-3-oxomorpholin-2-yl)acetic acid; or
- 2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-5-methyl-3-oxomorpholin-2-yl)acetic acid.

20 In embodiment 37, the present invention provides compounds, or pharmaceutically acceptable salts thereof, selected from:

- 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(N-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(N-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(N-(4-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(N-(4-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 30 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-((2-chlorophenyl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;

- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-((2-chlorophenyl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(cyclopentylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 5 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(cyclopentylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(cyclobutylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(cyclobutylsulfonyl)butan-10 2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(neopentylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(neopentylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2*R*,5*R*,6*R*)-5-(4-chlorophenyl)-6-(3,5-dichlorophenyl)-4-((*S*)-1-(isopropylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-5-(4-chlorophenyl)-6-(3,5-dichlorophenyl)-4-((*S*)-1-(isopropylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-5-(4-chlorophenyl)-6-(3,5-dichlorophenyl)-4-((*S*)-1-(*tert*-20 butylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-5-(4-chlorophenyl)-6-(3,5-dichlorophenyl)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- methyl 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate;
- 25 methyl 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate;
- (2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-(2-hydroxyethyl)morpholin-3-one;
- (2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-(2-hydroxyethyl)morpholin-3-one;
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- (2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-(2-methoxyethyl)morpholin-3-one;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 5 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(isopropylsulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-
- 10 (isopropylsulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid (Isomer 2);
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-methylcyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-methylcyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-
- 20 chlorophenyl)-5-methyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-5-methyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)-3-methylbutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)-3-methylbutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*R*)-1-(*tert*-butylsulfonyl)-3-methylbutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*R*)-1-(*tert*-butylsulfonyl)-3-methylbutan-2-yl)-6-(3-chlorophenyl)-5-(4-
- 30 chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;

- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)-3,3-dimethylbutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)-3,3-dimethylbutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 5 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)methylsulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)methylsulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)propan-2-ylsulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 10 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)propan-2-ylsulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)-1-methylcyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)-1-methylcyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(3-fluoropyridin-2-yl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(3-fluoropyridin-2-yl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 20 *N*-((*S*)-2-((2*S*,5*R*,6*R*)-2-allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholino)butyl)-*N*-(pyridin-2-yl)cyclopropanesulfonamide;
- N*-((*S*)-2-((2*R*,5*R*,6*R*)-2-allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholino)butyl)-*N*-(pyridin-2-yl)cyclopropanesulfonamide;
- 25 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((*S*)-1-(*N*-(pyridin-2-yl)cyclopropanesulfonamido)butan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((*S*)-1-(*N*-(pyridin-2-yl)cyclopropanesulfonamido)butan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-5-(4-chloro-3-fluorophenyl)-6-(3-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
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- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-5-(4-chloro-3-fluorophenyl)-6-(3-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(oxetan-3-ylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 5 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(oxetan-3-ylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((*S*)-1-((tetrahydro-2*H*-pyran-4-yl)sulfonyl)butan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((*S*)-1-((tetrahydro-2*H*-pyran-4-yl)sulfonyl)butan-2-yl)morpholin-2-yl)acetic acid;
- 10 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(3-fluoropyridin-2-yl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(3-fluoropyridin-2-yl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-((cyclopropylmethyl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-((cyclopropylmethyl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-3-methyl-1-(*N*-phenylcyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 20 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*R*)-3-methyl-1-(*N*-phenylcyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)pentan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)pentan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)-3-methylbutan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 30 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)-3-methylbutan-2-yl)-3-oxomorpholin-2-yl)acetic acid;

- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)propan-2-ylsulfonamido)-3-methylbutan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)propan-2-ylsulfonamido)-3-methylbutan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)-2-methylpropan-2-ylsulfonamido)-3-methylbutan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)-2-methylpropan-2-ylsulfonamido)-3-methylbutan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((*S*)-1-(pyridin-2-ylsulfonyl)butan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((*S*)-1-(pyridin-2-ylsulfonyl)butan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2,4-difluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2,4-difluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-cyanophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-cyanophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(((*S*)-2-methylpyrrolidin-1-yl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(((*S*)-2-methylpyrrolidin-1-yl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(((*R*)-2-methylpyrrolidin-1-yl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(((*R*)-2-methylpyrrolidin-1-yl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;

- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(cyclopropylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(cyclopropylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 5 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N,N*-dimethylsulfamoyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N,N*-dimethylsulfamoyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*S*,6*R*)-6-(3-chlorophenyl)-5-(5-chlorothiophen-2-yl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 10 2-((2*S*,5*S*,6*R*)-6-(3-chlorophenyl)-5-(5-chlorothiophen-2-yl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*S*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(5-chlorothiophen-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2*S*,5*S*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(5-chlorothiophen-2-yl)-3-oxomorpholin-2-yl)acetic acid ;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)pentan-3-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)pentan-3-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 20 (5*R*,6*R*)-4-((*S*)-1-(*tert*-butylthio)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)morpholin-3-one;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetamide;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetamide;
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- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-methylacetamide;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-methylacetamide;
- 5 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-hydroxyacetamide;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-hydroxyacetamide;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N,N*-dimethylacetamide;
- 10 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N,N*-dimethylacetamide;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-(2-hydroxyethyl)acetamide;
- 15 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-(2-hydroxyethyl)acetamide;
- (2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-(2-morpholino-2-oxoethyl)morpholin-3-one;
- (2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-(2-morpholino-2-oxoethyl)morpholin-3-one;
- 20 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-(methylsulfonyl)acetamide;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-(methylsulfonyl)acetamide;
- 25 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)-*N*-(methylsulfonyl)acetamide;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)-*N*-(methylsulfonyl)acetamide;
- 30 (methylsulfonyl)acetamide;

- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetamide;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetamide;
- 5 *N*-((*S*)-2-((2*R*,5*R*,6*R*)-2-((1*H*-tetrazol-5-yl)methyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholino)butyl)-*N*-methylcyclopropanesulfonamide;
- N*-((*S*)-2-((2*S*,5*R*,6*R*)-2-((1*H*-tetrazol-5-yl)methyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholino)butyl)-*N*-methylcyclopropanesulfonamide;
- (2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-(3-hydroxy-2-oxopropyl)morpholin-3-one;
- 10 (2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-(3-hydroxy-2-oxopropyl)morpholin-3-one;
- methyl 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-((2-(dimethylamino)ethyl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetate;
- 15 methyl 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-((2-(dimethylamino)ethyl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetate;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-((2-(dimethylamino)ethyl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-((2-(dimethylamino)ethyl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 20 2-((2*R*,5*R*,6*R*)-4-((1*S*,2*S*)-2-(*tert*-butylsulfonyl)cyclohexyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2,6-difluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2,6-difluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- (*R*)-2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)propanoic acid;

- (*S*)-2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)propanoic acid;
- (*R*)-2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)propanoic acid;
- (*S*)-2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)propanoic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetamide;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetamide ;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)-*N*-(isopropylsulfonyl)acetamide;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)-*N*-(isopropylsulfonyl)acetamide;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetamide;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetamide;
- 3-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)propanoic acid;
- 3-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido) butan-2-yl) -3-oxomorpholin-2-yl)propanoic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-chlorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid; or
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-chlorophenyl)cyclopropanesulfonamido)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid.

In embodiment 38, the present invention provides compounds, or pharmaceutically acceptable salts thereof, selected from:

- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)-4,4,4-trifluorobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)-4,4,4-trifluorobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*R*)-1-(*tert*-butylsulfonyl)-4,4,4-trifluorobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*R*)-1-(*tert*-butylsulfonyl)-4,4,4-trifluorobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclobutylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclobutylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*R*)-2-(*tert*-butylsulfonyl)-1-cyclobutylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*R*)-2-(*tert*-butylsulfonyl)-1-cyclobutylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((*R*)-1,1,1-trifluoro-3-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)propan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((*R*)-1,1,1-trifluoro-3-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)propan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((*S*)-1,1,1-trifluoro-3-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)propan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((*S*)-1,1,1-trifluoro-3-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)propan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2,5-difluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetic acid
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2,5-difluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetic acid;

- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((*S*)-4,4,4-trifluoro-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((*S*)-4,4,4-trifluoro-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)morpholin-2-yl)acetic acid;
- 5 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((*R*)-4,4,4-trifluoro-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((*R*)-4,4,4-trifluoro-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)morpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-((*S*)-*sec*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 10 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-((*R*)-*sec*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-((*S*)-*sec*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-((*R*)-*sec*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(((*R*)-3-methylbutan-2-yl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(((*S*)-3-methylbutan-2-yl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 20 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(((*R*)-3-methylbutan-2-yl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(((*S*)-3-methylbutan-2-yl)sulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(pyridin-4-ylsulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(pyridin-4-ylsulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-((2-hydroxy-2-methylpropyl)sulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 30

- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-((2-hydroxy-2-methylpropyl)sulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-2-((2-cyanopropan-2-yl)sulfonyl)-1-cyclopropylethyl)-3-oxomorpholin-2-yl)acetic acid;
- 5 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-2-((2-cyanopropan-2-yl)sulfonyl)-1-cyclopropylethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*N*-(*tert*-butyl)sulfamoyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*N*-(*tert*-butyl)sulfamoyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 10 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)sulfamoyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)sulfamoyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(((*S*)-2-methylpyrrolidin-1-yl)sulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(((*S*)-2-methylpyrrolidin-1-yl)sulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-((5-fluoroindolin-1-yl)sulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 20 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-((5-fluoroindolin-1-yl)sulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*N*-(*tert*-butyl)-*N*-methylsulfamoyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*N*-(*tert*-butyl)-*N*-methylsulfamoyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(morpholinosulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(morpholinosulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 30 (morpholinosulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;

- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(((*R*)-2-methylpyrrolidin-1-yl)sulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(((*R*)-2-methylpyrrolidin-1-yl)sulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 5 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-((2,2-dimethylpyrrolidin-1-yl)sulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-((2,2-dimethylpyrrolidin-1-yl)sulfonyl)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-5-(4-chloro-3-fluorophenyl)-6-(3-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 10 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-5-(4-chloro-3-fluorophenyl)-6-(3-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)-3-methylbutan-2-yl)-5-(4-chloro-3-fluorophenyl)-6-(3-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)-3-methylbutan-2-yl)-5-(4-chloro-3-fluorophenyl)-6-(3-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*R*)-1-(*tert*-butylsulfonyl)-3-methylbutan-2-yl)-5-(4-chloro-3-fluorophenyl)-6-(3-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*R*)-1-(*tert*-butylsulfonyl)-3-methylbutan-2-yl)-5-(4-chloro-3-fluorophenyl)-6-(3-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 20 2-((2*R*,5*R*,6*R*)-5-(4-chloro-3-fluorophenyl)-6-(3-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-5-(4-chloro-3-fluorophenyl)-6-(3-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-5-(4-chloro-2-fluorophenyl)-6-(3-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-5-(4-chloro-2-fluorophenyl)-6-(3-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-5-(4-chlorophenyl)-6-
- 30 (3,4-dichlorophenyl)-3-oxomorpholin-2-yl)acetic acid;

- 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-5-(4-chlorophenyl)-6-(3,4-dichlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chloro-4-fluorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 5 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chloro-4-fluorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(4-bromo-3-chlorophenyl)-4-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(4-bromo-3-chlorophenyl)-4-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-10 5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chloro-4-cyanophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chloro-4-cyanophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chloro-2-fluorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chloro-2-fluorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chloro-4-methylphenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 20 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-6-(3-chloro-4-methoxyphenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-6-(3-chloro-4-methoxyphenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 30 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)butan-2-yl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;

- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxo-2-(2,2,2-trifluoroethyl)morpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxo-2-(2,2,2-trifluoroethyl)morpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(((*S*)-2-methylpyrrolidin-1-yl)sulfonyl)ethyl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(((*S*)-2-methylpyrrolidin-1-yl)sulfonyl)ethyl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)-4,4,4-trifluorobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)-4,4,4-trifluorobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)-4,4,4-trifluorobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-ethyl-3-oxomorpholin-2-yl)acetic acid;

- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)-4,4,4-trifluorobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-ethyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-cyanoacetamide;
- 5 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-cyanoacetamide;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-(2,2,2-trifluoroethyl)acetamide;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-(2,2,2-trifluoroethyl)acetamide;
- 10 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-(cyanomethyl)acetamide;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-(cyanomethyl)acetamide;
- 15 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-phenylacetamide;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-phenylacetamide;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-(2-fluorophenyl)acetamide;
- 20 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-(2-fluorophenyl)acetamide;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-(pyridin-2-yl)acetamide;
- 25 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)-*N*-(pyridin-2-yl)acetamide;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetamide;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetamide;
- 30 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetamide;

- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2,6-difluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetamide;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2,6-difluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetamide;
- 5 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-phenylcyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetamide;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-phenylcyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)acetamide;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)-4,4,4-trifluorobutan-2-yl)-6-(3-chlorophenyl)-
- 10 5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetamide;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)-4,4,4-trifluorobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetamide;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)-*N*-
- 15 methylacetamide;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)-*N*-methylacetamide;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)-*N*,*N*-
- 20 dimethylacetamide;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)-*N*,*N*-dimethylacetamide;
- 25 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)-*N*-(pyridin-2-yl)acetamide;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-cyclopropyl-2-(*N*-(2-fluorophenyl)cyclopropanesulfonamido)ethyl)-3-oxomorpholin-2-yl)-*N*-(pyridin-2-
- 30 yl)acetamide;

- (2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-(2-hydroxyethyl)morpholin-3-one;
- (2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-(2-hydroxyethyl)morpholin-3-one;
- 5 (2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-((*R*)-2,3-dihydroxypropyl)morpholin-3-one;
- (2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-((*S*)-2,3-dihydroxypropyl)morpholin-3-one;
- (2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-((*R*)-2,3-dihydroxypropyl)morpholin-3-one;
- 10 (2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-((*S*)-2,3-dihydroxypropyl)morpholin-3-one;
- 3-(((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)methyl)-1,1-diethylurea;
- 15 3-(((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)methyl)-1,1-diethylurea;
- tert*-butyl (((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)methyl)carbamate;
- tert*-butyl (((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)methyl)carbamate;
- 20 (2*R*,5*R*,6*R*)-2-(aminomethyl)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)morpholin-3-one;
- and (2*S*,5*R*,6*R*)-2-(aminomethyl)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)morpholin-3-one;
- 25 *N*-(((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)methyl)acetamide;
- N*-(((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)methyl)acetamide;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetonitrile;
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- (2*R*,5*R*,6*R*)-2-((1*H*-tetrazol-5-yl)methyl)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)morpholin-3-one;
- (2*S*,5*R*,6*R*)-2-((1*H*-tetrazol-5-yl)methyl)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)morpholin-3-one;
- 5 (2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-(isoxazol-5-ylmethyl)morpholin-3-one;
- (2*R*,5*R*,6*R*)-2-((1*H*-1,2,3-triazol-5-yl)methyl)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)morpholin-3-one;
- (2*S*,5*R*,6*R*)-2-((1*H*-1,2,3-triazol-5-yl)methyl)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)morpholin-3-one;
- 10 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetonitrile;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetonitrile;
- 15 (2*R*,5*R*,6*R*)-2-((1*H*-1,2,4-triazol-5-yl)methyl)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)morpholin-3-one;
- (2*S*,5*R*,6*R*)-2-((1*H*-1,2,4-triazol-5-yl)methyl)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)morpholin-3-one;
- (2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-((3-methyl-1*H*-1,2,4-triazol-5-yl)methyl)morpholin-3-one;
- 20 (2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-((3-methyl-1*H*-1,2,4-triazol-5-yl)methyl)morpholin-3-one;
- N*-((*S*)-2-((2*R*,3*R*,6*R*)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-((3-methyl-1*H*-1,2,4-triazol-5-yl)methyl)-5-oxomorpholino)-2-cyclopropylethyl)-*N*-(2-fluorophenyl)cyclopropanesulfonamide;
- 25 *N*-((*S*)-2-((2*S*,3*R*,6*R*)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-((3-methyl-1*H*-1,2,4-triazol-5-yl)methyl)-5-oxomorpholino)-2-cyclopropylethyl)-*N*-(2-fluorophenyl)cyclopropanesulfonamide;
- N*-((*S*)-2-((2*R*,5*R*,6*R*)-2-((1*H*-1,2,3-triazol-5-yl)methyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholino)-2-cyclopropylethyl)-*N*-(2-fluorophenyl)cyclopropanesulfonamide;
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- N*-((*S*)-2-((2*S*,5*R*,6*R*)-2-((1*H*-1,2,3-triazol-5-yl)methyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholino)-2-cyclopropylethyl)-*N*-(2-fluorophenyl)cyclopropanesulfonamide;
- 5 *N*-((*S*)-2-((2*R*,5*R*,6*R*)-2-((1*H*-1,2,4-triazol-5-yl)methyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholino)-2-cyclopropylethyl)-*N*-(2-fluorophenyl)cyclopropanesulfonamide;
- N*-((*S*)-2-((2*S*,5*R*,6*R*)-2-((1*H*-1,2,4-triazol-5-yl)methyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholino)-2-cyclopropylethyl)-*N*-(2-fluorophenyl)cyclopropanesulfonamide;
- 10 *N*-((*S*)-2-((2*R*,5*R*,6*R*)-2-((1*H*-tetrazol-5-yl)methyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholino)-2-cyclopropylethyl)-*N*-(2-fluorophenyl)cyclopropanesulfonamide;
- N*-((*S*)-2-((2*S*,5*R*,6*R*)-2-((1*H*-tetrazol-5-yl)methyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholino)-2-cyclopropylethyl)-*N*-(2-fluorophenyl)cyclopropanesulfonamide;
- 15 (2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-((1-methyl-1*H*-tetrazol-5-yl)methyl)morpholin-3-one;
- (2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-((2-methyl-2*H*-tetrazol-5-yl)methyl)morpholin-3-one;
- 20 (2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-((1-methyl-1*H*-imidazol-2-yl)methyl)morpholin-3-one;
- N*-((*S*)-2-((2*R*,3*R*,6*R*)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)-5-oxomorpholino)-2-cyclopropylethyl)-*N*-(2-fluorophenyl)cyclopropanesulfonamide;
- 25 *N*-((*S*)-2-((2*S*,3*R*,6*R*)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)-5-oxomorpholino)-2-cyclopropylethyl)-*N*-(2-fluorophenyl)cyclopropanesulfonamide;
- N*-((*S*)-2-((2*R*,3*R*,6*R*)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-((1-methyl-1*H*-tetrazol-5-yl)methyl)-5-oxomorpholino)-2-cyclopropylethyl)-*N*-(2-fluorophenyl)cyclopropanesulfonamide;
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- N*-((*S*)-2-((2*S*,3*R*,6*R*)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-((1-methyl-1*H*-tetrazol-5-yl)methyl)-5-oxomorpholino)-2-cyclopropylethyl)-*N*-(2-fluorophenyl)cyclopropanesulfonamide;
- 5 *N*-((*S*)-2-((2*R*,3*R*,6*R*)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-((2-methyl-2*H*-tetrazol-5-yl)methyl)-5-oxomorpholino)-2-cyclopropylethyl)-*N*-(2-fluorophenyl)cyclopropanesulfonamide;
- N*-((*S*)-2-((2*R*,3*R*,6*R*)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-((2-methyl-2*H*-tetrazol-5-yl)methyl)-5-oxomorpholino)-2-cyclopropylethyl)-*N*-(2-fluorophenyl)cyclopropanesulfonamide;
- 10 *N*-((*S*)-2-((2*R*,3*R*,6*S*)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-5-oxo-6-(sulfamoylmethyl)morpholino)-2-cyclopropylethyl)-*N*-(2-fluorophenyl)cyclopropanesulfonamide;
- N*-((*S*)-2-((2*S*,3*R*,6*S*)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-5-oxo-6-(sulfamoylmethyl)morpholino)-2-cyclopropylethyl)-*N*-(2-
- 15 fluorophenyl)cyclopropanesulfonamide;
- 2-((2*R*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-5-(4-chloro-3-fluorophenyl)-6-(3-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-5-(4-chloro-3-fluorophenyl)-6-(3-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)acetic acid;
- 20 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((2*S*,3*S*)-2-(isopropylsulfonyl)pentan-3-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((2*S*,3*S*)-2-(isopropylsulfonyl)pentan-3-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((2*R*,3*S*)-2-
- 25 (isopropylsulfonyl)pentan-3-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((2*R*,3*S*)-2-(isopropylsulfonyl)pentan-3-yl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*S*,2*S*)-1-cyclopropyl-2-(isopropylsulfonyl)propyl)-3-oxomorpholin-2-yl)acetic acid;
- 30 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*S*,2*S*)-1-cyclopropyl-2-(isopropylsulfonyl)propyl)-3-oxomorpholin-2-yl)acetic acid;

- 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*S*,2*R*)-1-cyclopropyl-2-(isopropylsulfonyl)propyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*S*,2*R*)-1-cyclopropyl-2-(isopropylsulfonyl)propyl)-3-oxomorpholin-2-yl)acetic acid;
- 5 2-((2*R*,5*R*,6*R*)-4-((2*S*,3*S*)-2-(*tert*-butylsulfonyl)pentan-3-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((2*S*,3*S*)-2-(*tert*-butylsulfonyl)pentan-3-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((2*R*,3*S*)-2-(*tert*-butylsulfonyl)pentan-3-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 10 2-((2*S*,5*R*,6*R*)-4-((2*R*,3*S*)-2-(*tert*-butylsulfonyl)pentan-3-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((2*S*,3*R*)-2-(*tert*-butylsulfonyl)pentan-3-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 15 2-((2*S*,5*R*,6*R*)-4-((2*S*,3*R*)-2-(*tert*-butylsulfonyl)pentan-3-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*R*,5*R*,6*R*)-4-((2*R*,3*R*)-2-(*tert*-butylsulfonyl)pentan-3-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((2*R*,3*R*)-2-(*tert*-butylsulfonyl)pentan-3-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 20 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-5-(4-chloro-3-fluorophenyl)-6-(3-chloro-5-fluorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)propan-2-yl)-5-(4-chloro-3-fluorophenyl)-6-(3-chloro-5-fluorophenyl)-3-oxomorpholin-2-yl)acetic acid;
- 25 2-((2*R*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-5-(4-chloro-3-fluorophenyl)-6-(3-chloro-5-fluorophenyl)-3-oxomorpholin-2-yl)acetic acid; or
- 2-((2*S*,5*R*,6*R*)-4-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-5-(4-chloro-3-fluorophenyl)-6-(3-chloro-5-fluorophenyl)-3-oxomorpholin-2-yl)acetic acid.

In embodiment 39, the present invention provides pharmaceutical compositions comprising a compound of any one of embodiments 1A, 1a or 1 to 38, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

5 In embodiment 40, the present invention provides methods of treating cancer in a subject in need thereof, the methods comprising administering to the subject an effective dosage amount of a compound according to any one of embodiments 1A, 1a or 1 to 38, or a pharmaceutically acceptable salt thereof.

10 In embodiment 41, the present invention provides methods of treating cancer in accordance with embodiment 40, wherein the cancer is selected from bladder, breast, colon, rectum, kidney, liver, small cell lung cancer, non-small-cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, skin, acute lymphocytic leukemia, chronic myelogenous leukemia, acute lymphoblastic leukemia, B-
15 cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, Burkett's lymphoma, acute and chronic myelogenous leukemia, melanoma, endometrial cancer, head and neck cancer, glioblastoma, or osteosarcoma.

DETAILED DESCRIPTION OF THE INVENTION

20 The present invention provides compounds of Formula I or II, as defined above, or pharmaceutically acceptable salts thereof. The present invention also provides pharmaceutical compositions comprising a compound of Formula I or II, or pharmaceutically acceptable salts thereof, and methods of treating diseases and/or conditions, such as diabetes, using compounds of Formula I or II, or pharmaceutically
25 acceptable salts thereof.

The term "alkyl" means a straight or branched chain hydrocarbon. Representative examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, sec-butyl, pentyl and hexyl. Typical alkyl groups are alkyl groups having from 1 to 8 carbon atoms, which groups are commonly represented as C₁₋₈alkyl.

substituted pyridyl or substituted thiophenyl is substituted with from one to three substituents independently selected from the group consisting of halo, $-C_{1-6}alkyl$, $-OH$, $-NO_2$, $-NHC(=O)C_{1-6}alkyl$, $-S(=O)_2C_{1-6}alkyl$, $-S(=O)C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-(CH_2)_nC(=O)R^f$, $-(CH_2)_nC(=O)NR^fR^f$, $-CN$, $-NR^gR^g$ and A,

- 5 when R^1 is substituted with $-NR^gR^g$, then R^g and R^g together with the nitrogen atom to which they are attached can form a 3 to 6 membered heterocycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from the group consisting of O, N and S, and the heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the
- 10 group consisting of halo, $-C_{1-6}alkyl$, $-S(=O)_2C_{1-6}alkyl$, $-S(=O)C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$ and $-CN$;

each A is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from the group consisting of O, N and S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one

15 to three substituents independently selected from the group consisting of halo, $-C_{1-6}alkyl$, $-S(=O)_2C_{1-6}alkyl$, $-S(=O)C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$;

R^2 is substituted phenyl or substituted pyridyl, wherein the substituted phenyl or substituted pyridyl is substituted with from one to three substituents independently selected from the group consisting of halo, $-C_{1-6}alkyl$, $-OH$, $-NO_2$, $-NHC(=O)C_{1-6}alkyl$, $-S(=O)_2C_{1-6}alkyl$,

20 $-S(=O)C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-(CH_2)_nC(=O)R^f$, $-(CH_2)_nC(=O)NR^fR^f$, $-CN$, $-NR^gR^g$ and B,

when R^2 is substituted with $-NR^gR^g$, then R^g and R^g together with the nitrogen atom to which they are attached can form a 3 to 6 membered heterocycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently

25 selected from the group consisting of O, N and S, and the heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, $-C_{1-6}alkyl$, $-S(=O)_2C_{1-6}alkyl$, $-S(=O)C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$;

each B is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from the group consisting of O, N and S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one

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to three substituents independently selected from the group consisting of halo, $-C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$;

R^{2a} is hydrogen or $-C_{1-3}$ alkyl;

R^3 is C_{1-6} alkyl substituted with from one to three substituents independently selected from the group consisting of halo, $-OH$, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$; $-C(=O)OR^f$, $-C(=O)C_{1-6}$ alkyl, $-S(=O)_2R^f$, $-S(=O)R^f$, $-OR^f$, $-C(=O)NR^fN(R^f)_2$, $-C(=O)NR^fS(=O)_2R^f$, $-S(=O)_2NR^fC(=O)R^f$, $-S(=O)_2NR^fR^f$, $-N(R^f)C(=O)NR^fR^f$, $-NR^fC(=O)_2R^f$, $-C(=O)NR^fR^f$, $-NR^fS(=O)_2R^f$, $-CN$, $-NR^fR^f$, $-C(=O)NOH$, $-NR^fC(=O)OR^f$, $-NR^fC(=O)R^f$, or a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to four heteroatoms independently selected from the group consisting of O, N and S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, $-C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$;

R^4 is hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-CF_3$, $-CH_2F$, $-CHF_2$, $-S(=O)_2R^f$, $-SR^f$, $-S(=O)R^f$, $-S(=O)_2NR^fR^f$, $-NR^fS(=O)_2NR^fR^f$, $-C(=O)NR^fR^f$, $-NR^fS(=O)_2R^f$, $-C(=O)_2R^f$, $-OR^f$, a 3 to 7 membered cycloalkyl or heterocycloalkyl, optionally containing a $-(C=O)-$ group, or a 5 to 6 membered aryl or heteroaryl group, which heterocycloalkyl or heteroaryl group can contain from one to three heteroatoms independently selected from the group consisting of O, N and S, and the cycloalkyl, heterocycloalkyl, aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, $-C_{1-6}$ alkyl, $-OH$, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$, and the $-C_{1-6}$ alkyl or $-C_{2-6}$ alkenyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, $-NR^fR^f$, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$;

R^5 is hydrogen or $-C_{1-6}$ alkyl;

R^6 is hydrogen, $-C_{1-6}$ alkyl, $-(CH_2)_nNR^fR^f$, or $-(CH_2)_nC(=O)NR^fR^f$;

each R^a is independently hydrogen, halo or $-C_{1-6}$ alkyl, or two R^a groups that are attached to the same carbon atom can form an $(=O)$ group or a 3 to 6 membered cycloalkyl or heterocycloalkyl group, or an R^a group and R^6 along with the atoms to which they are attached can form a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can

contain from one to two heteroatoms independently selected from the group consisting of O, N and S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

- 5 each R^c is independently hydrogen, -C₁₋₆alkyl, -C₁₋₆alkyl-CF₃, -CF₃, a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can contain from one to two heteroatoms independently selected from the group consisting of O, N and S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl,
10 -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

- or two R^c groups that are attached to the same or adjacent carbon atoms can together with the carbon atom or atoms to which they are attached form a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can contain from one to two heteroatoms independently selected from the group consisting of O, N and S, and the cycloalkyl or
15 heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

each R^d is independently hydrogen or -C₁₋₆alkyl;

each R^e is independently hydrogen or -C₁₋₆alkyl;

- 20 each R^f is independently hydrogen, -CN, -C₁₋₆alkyl, -C₁₋₆alkyl-CN, -C₁₋₆alkyl-CF₃, hydroxyC₁₋₆alkyl, -C₁₋₆alkylNR^eR^e, or a 5 to 6 membered aryl, -C₁₋₆alkylaryl, heteroaryl, or -C₁₋₆alkylheteroaryl, or a 3 to 9 membered cycloalkyl, -C₁₋₆alkylcycloalkyl, heterocycloalkyl or -C₁₋₆alkylheterocycloalkyl group, which heteroaryl, alkylheteroaryl, heterocycloalkyl, or alkylheterocycloalkyl group can contain from one to three heteroatoms independently selected
25 from the group consisting of O, N and S, and the alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, or alkylheterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

or when R^f and R^f are part of an NR^fR^f or CR^fR^f moiety in a group, then R^f and R^f together with the nitrogen or carbon atom to which they are attached can form a 3 to 7 membered heterocycloalkyl or cycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from the group consisting of O, N and S, and the
 5 heterocycloalkyl or cycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, $-C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$;

each R^g is independently hydrogen, or $-C_{1-6}$ alkyl; and

each n is independently 0, 1, 2, 3 or 4, provided that the compound is not 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*S*,2*S*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid; 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*S*,2*S*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid; 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*R*,2*R*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid; or 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*R*,2*R*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid.
 10
 15

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of Formula I or II, as defined above, or pharmaceutically acceptable salts thereof. The present invention also provides pharmaceutical compositions comprising a compound of Formula I or II, or pharmaceutically acceptable salts
 20 thereof, and methods of treating diseases and/or conditions, such as diabetes, using compounds of Formula I or II, or pharmaceutically acceptable salts thereof.

The term "alkyl" means a straight or branched chain hydrocarbon. Representative examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, sec-butyl, pentyl and hexyl. Typical alkyl groups are alkyl groups having from 1 to 8 carbon atoms,
 25 which groups are commonly represented as C_{1-8} alkyl.

The term "alkoxy" means an alkyl group bonded to an oxygen atom. Representative examples of alkoxy groups include methoxy, ethoxy, tert-butoxy, propoxy and isobutoxy. Common alkoxy groups are C₁₋₈alkoxy.

The term "halogen" or "halo" means chlorine, fluorine, bromine or iodine.

5 The term "alkenyl" means a branched or straight chain hydrocarbon having one or more carbon-carbon double bonds. Representative examples alkenyl groups include ethenyl, propenyl, allyl, butenyl and 4-methylbutenyl. Common alkenyl groups are C₂₋₈alkenyl.

10 The term "alkynyl" means a branched or straight chain hydrocarbon having one or more carbon-carbon triple bonds. Representative examples of alkynyl groups include ethynyl, propynyl (propargyl) and butynyl. Common alkynyl groups are C₂₋₈ alkynyl.

15 The term "cycloalkyl" means a cyclic, nonaromatic hydrocarbon. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A cycloalkyl group can contain one or more double bond. Examples of cycloalkyl groups that contain double bonds include cyclopentenyl, cyclohexenyl, cyclohexadienyl and cyclobutadienyl. Common cycloalkyl groups are C₃₋₈ cycloalkyl groups. A cycloalkyl group can also be a bicyclic group comprising a cycloalkyl ring fused to an aryl or heteroaryl ring. An example of such a fused bicyclic group is tetrahydronaphthalene.

20 The term "perfluoroalkyl" means an alkyl group in which all of the hydrogen atoms have been replaced with fluorine atoms. Common perfluoroalkyl groups are C₁₋₈perfluoroalkyl. An example of a common perfluoroalkyl group is -CF₃.

25 The term "acyl" means a group derived from an organic acid by removal of the hydroxy group (-OH). For example, the acyl group CH₃C(=O)- is formed by the removal of the hydroxy group from CH₃C(=O)OH.

The term "aryl" means a cyclic, aromatic hydrocarbon. Examples of aryl groups include phenyl and naphthyl. Common aryl groups are six to thirteen membered rings.

The term "heteroatom" as used herein means an oxygen, nitrogen or sulfur atom.

30 The term "heteroaryl" means a cyclic, aromatic hydrocarbon in which one or more carbon atoms of an aryl group have been replaced with a heteroatom. If the heteroaryl group contains more than one heteroatom, the heteroatoms may be the same or different.

Examples of heteroaryl groups include pyridyl, pyrimidinyl, imidazolyl, thienyl, furyl, pyrazinyl, pyrrolyl, indolyl, triazolyl, pyridazinyl, indazolyl, purinyl, quinoliziny, isoquinolyl, quinolyl, naphthyridinyl, quinoxaliny, isothiazolyl and benzo[b]thienyl.

Common heteroaryl groups are five to thirteen membered rings that contain from 1 to 4
5 heteroatoms. Heteroaryl groups that are five and six membered rings that contain 1 to 3 heteroatoms are particularly common.

The term "heterocycloalkyl" means a cycloalkyl group in which one or more of the carbon atoms has been replaced with a heteroatom. If the heterocycloalkyl group contains more than one heteroatom, the heteroatoms may be the same or different.

10 Examples of heterocycloalkyl groups include tetrahydrofuryl, morpholinyl, piperazinyl, piperidinyl and pyrrolidinyl. It is also possible for the heterocycloalkyl group to have one or more double bonds, but is not aromatic. Examples of heterocycloalkyl groups containing double bonds include dihydrofuran. Common heterocycloalkyl groups are three to ten membered rings containing from 1 to 4 heteroatoms. Heterocycloalkyl groups
15 that are five and six membered rings that contain 1 to 2 heteroatoms are particularly common. A heterocycloalkyl group can also be a bicyclic group comprising a heterocycloalkyl ring fused to an aryl or heteroaryl ring. Examples of such fused bicyclic ring include tetrahydroquinoline or tetrahydroisoquinoline.

It is also noted that the cyclic ring groups, i.e., aryl, heteroaryl, cycloalkyl, and
20 heterocycloalkyl, can comprise more than one ring. For example, the naphthyl group is a fused bicyclic ring system. It is also intended that the present invention include ring groups that have bridging atoms, or ring groups that have a spiro orientation.

Representative examples of five to six membered aromatic rings, optionally having one or two heteroatoms, are phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl,
25 imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridiazinyl, pyrimidinyl, and pyrazinyl.

Representative examples of partially saturated, fully saturated or fully unsaturated five to eight membered rings, optionally having one to three heteroatoms, are cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and phenyl. Further exemplary five
30 membered rings are furyl, thienyl, pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, oxazolyl, thiazolyl, imidazolyl, 2H-imidazolyl, 2-imidazoliny,

imidazolidinyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 3H-1,2-oxathiolyl, 1,2,3-oxadizaolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4oxadiazolyl, 1,2,3-triazolyl, 1,2,4-trizaolyl, 1,3,4-thiadiazolyl, 3H-1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 5H-1,2,5-oxathiazolyl, and 1,3-oxathiolyl.

Further exemplary six membered rings are 2H-pyranyl, 4H-pyranyl, pyridinyl, piperidinyl, 1,2-dioxinyl, 1,3-dioxinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyndazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-trithianyl, 4H-1,2-oxazinyl, 2H-1,3-oxazinyl, 6H-1,3-oxazinyl, 6H-1,2-oxazinyl, 1,4-oxazinyl, 2H-1,2-oxazinyl, 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-(3-oxathiazinyl, and 1,4,2-oxadiazinyl.

Further exemplary seven membered rings are azepinyl, oxepinyl, thiepinyl and 1,2,4-triazepinyl.

Further exemplary eight membered rings are cyclooctyl, cyclooctenyl and cyclooctadienyl.

Exemplary bicyclic rings consisting of two fused partially saturated, fully saturated or fully unsaturated five and/or six membered rings, optionally having one to four heteroatoms, are indolizinyl, indolyl, isoindolyl, indolinyl, cyclopenta(b)pyridinyl, pyrano(3,4-b)pyrrolyl, benzofuryl, isobenzofuryl, benzo(b)thienyl, benzo(c)thienyl, 1H-indazolyl, indoxazinyl, benzoxazolyl, anthranilyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, indenyl, isoindenyl, naphthyl, tetralinyl, decalinyl, 2H-1-benzopyranyl, pyrido(3,4-b)pyridinyl, pyrido(3,2-b)pyridinyl, pyrido(4,3-b)-pyridinyl, 2H-1,3-benzoxazinyl, 2H-1,4-benzoxazinyl, 1H-2,3-benzoxazinyl, 4H-3,1-benzoxazinyl, 2H-1,2-benzoxazinyl and 4H-1,4-benzoxazinyl.

A cyclic ring group may be bonded to another group in more than one way. If no particular bonding arrangement is specified, then all possible arrangements are intended. For example, the term "pyridyl" includes 2-, 3-, or 4-pyridyl, and the term "thienyl" includes 2-, or 3-thienyl.

The term "substituted" means that a hydrogen atom on a molecule or group is replaced with a group or atom. Typical substituents include: halogen, C₁₋₈alkyl, hydroxyl, C₁₋₈alkoxy, -NR^xR^x, nitro, cyano, halo or perhaloC₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, -SR^x, -S(=O)₂R^x, -C(=O)OR^x, -C(=O)R^x, wherein each R^x is independently hydrogen or C₁₋₈ alkyl. It is noted that when the substituent is -NR^xR^x, the R^x groups may be joined together with the nitrogen atom to form a ring.

The term "oxo", when used as a substituent, means the =O group, which is typically attached to a carbon atom.

A group or atom that replaces a hydrogen atom is also called a substituent.

Any particular molecule or group can have one or more substituent depending on the number of hydrogen atoms that can be replaced.

The symbol "-" represents a covalent bond and can also be used in a radical group to indicate the point of attachment to another group. In chemical structures, the symbol is commonly used to represent a methyl group in a molecule.

The term "comprising" is meant to be open ended, including the indicated component but not excluding other elements.

A group or atom that replaces a hydrogen atom is also called a substituent.

Any particular molecule or group can have one or more substituent depending on the number of hydrogen atoms that can be replaced.

The symbol "-" represents a covalent bond and can also be used in a radical group to indicate the point of attachment to another group. In chemical structures, the symbol is commonly used to represent a methyl group in a molecule.

The term "therapeutically effective amount" means an amount of a compound that ameliorates, attenuates or eliminates one or more symptom of a particular disease or condition, or prevents or delays the onset of one or more symptom of a particular disease or condition.

The terms "patient" and "subject" may be used interchangeably and mean animals, such as dogs, cats, cows, horses, sheep and humans. Particular patients are mammals. The term patient includes males and females.

The term "pharmaceutically acceptable" means that the referenced substance, such as a compound of Formula I or II, or a salt of a compound of Formula I or II, or a

formulation containing a compound of Formula I or II, or a particular excipient, are suitable for administration to a patient.

The terms "treating", "treat" or "treatment" and the like include preventative (e.g., prophylactic) and palliative treatment.

5 The term "excipient" means any pharmaceutically acceptable additive, carrier, diluent, adjuvant, or other ingredient, other than the active pharmaceutical ingredient (API), which is typically included for formulation and/or administration to a patient.

10 The compounds of the present invention are administered to a patient in a therapeutically effective amount. The compounds can be administered alone or as part of a pharmaceutically acceptable composition or formulation. In addition, the compounds or compositions can be administered all at once, as for example, by a bolus injection, multiple times, such as by a series of tablets, or delivered substantially uniformly over a period of time, as for example, using transdermal delivery. It is also noted that the dose of the compound can be varied over time.

15 In addition, the compounds of the present invention can be administered alone, in combination with other compounds of the present invention, or with other pharmaceutically active compounds. The other pharmaceutically active compounds can be intended to treat the same disease or condition as the compounds of the present invention or a different disease or condition. If the patient is to receive or is receiving multiple pharmaceutically active compounds, the compounds can be administered simultaneously, or sequentially. For example, in the case of tablets, the active compounds may be found in one tablet or in separate tablets, which can be administered at once or sequentially in any order. In addition, it should be recognized that the compositions may be different forms. For example, one or more compound may be delivered via a tablet, 20 while another is administered via injection or orally as a syrup. All combinations, delivery methods and administration sequences are contemplated.

The term "cancer" means a physiological condition in mammals that is characterized by unregulated cell growth. General classes of cancers include carcinomas, lymphomas, sarcomas, and blastomas.

30 The compounds of the present invention can be used to treat cancer. The methods of treating a cancer comprise administering to a patient in need thereof a therapeutically

effective amount of a compound of Formula I or II, or a pharmaceutically acceptable salt thereof.

The compounds of the present invention can be used to treat tumors. The methods of treating a tumor comprise administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I or II, or a pharmaceutically acceptable salt thereof.

The invention also concerns the use of a compound of the present invention in the manufacture of a medicament for the treatment of a condition such as a cancer.

Cancers which may be treated with compounds of the present invention include, without limitation, carcinomas such as cancer of the bladder, breast, colon, rectum, kidney, liver, lung (small cell lung cancer, and non-small-cell lung cancer), esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage (including leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma); hematopoietic tumors of myeloid lineage (including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia); tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, e.g., soft tissue and bone); tumors of the central and peripheral nervous system (including astrocytoma, neuroblastoma, glioma and schwannomas); and other tumors (including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratoanthoma, thyroid follicular cancer and Kaposi's sarcoma). Other cancers that can be treated with a compound of the present invention include endometrial cancer, head and neck cancer, glioblastoma, malignant ascites, and hematopoietic cancers.

Particular cancers that can be treated by the compounds of the present invention include soft tissue sarcomas, bone cancers such as osteosarcoma, breast tumors, bladder cancer, Li-Fraumeni syndrome, brain tumors, rhabdomyosarcoma, adrenocortical carcinoma, colorectal cancer, non-small cell lung cancer, and acute myelogenous leukemia (AML).

In a particular embodiment of the invention that relates to the treatment of cancers, the cancer is identified as p53wildtype (p53^{WT}). In another particular embodiment, the cancer is identified as p53^{WT} and CDKN2A mutant. In another aspect, the present invention provides a diagnostic for determining which patients should be administered a compound of the present invention. For example, a sample of a patient's cancer cells may be taken and analyzed to determine the status of the cancer cells with respect to p53 and/or CDKN2A. In one aspect, a patient having a cancer that is p53^{WT} will be selected for treatment over patients having a cancer that is mutated with respect to p53. In another aspect, a patient having a cancer that is both p53^{WT} and has a mutant CDKN2A protein is selected over a patient that does not have these characteristics. The taking of a cancer cells for analyses is well known to those skilled in the art. The term "p53^{WT}" means a protein encoded by genomic DNA sequence no. NC_000017 version 9 (7512445..7531642)(GenBank); a protein encoded by cDNA sequence no. NM_000546 (GenBank); or a protein having the GenBank sequence no. NP_000537.3. The term "CDKN2A mutant" means a CDKN2A protein that is not wildtype. The term "CDKN2A wildtype" means a protein encoded by genomic DNA sequence no. 9:21957751-21984490 (Ensembl ID); a protein encoded by cDNA sequence no. NM_000077 (GenBank) or NM_058195 (GenBank) or; or a protein having the GenBank sequence no. NP_000068 or NP_478102.

The compounds of the present invention can also be used to treat hyperproliferative disorders such as thyroid hyperplasia (especially Grave's disease), and cysts (such as hypervascularity of ovarian stroma, characteristic of polycystic ovarian syndrome (Stein- Leventhal syndrome)).

The compounds of the present invention can also be used to treat the following diseases or conditions: asthma, chronic obstructive pulmonary disease (COPD), emphysema, psoriasis, contact dermatitis, conjunctivitis, allergic rhinitis, systemic lupus erythematosus (SLE), ulcerative colitis, Crohn's disease, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, Alzheimer's disease, atherosclerosis and Huntington's disease.

The compounds of the present invention can also be used to treat inflammatory diseases, hypoxia, ulcers, viral infections, bacterial infections, and bacterial sepsis.

The compounds of Formula I, or the pharmaceutically acceptable salts thereof, may also be administered in combination with one or more additional pharmaceutically active compounds/agents. In a particular embodiment, the additional pharmaceutically active agent is an agent that can be used to treat a cancer. For example, an additional
5 pharmaceutically active agent can be selected from antineoplastic agents, anti-angiogenic agents, chemotherapeutic agents and peptidal cancer therapy agents. In yet another embodiment, the antineoplastic agents are selected from antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents, kinase inhibitors, miscellaneous agents and combinations thereof. It is noted that
10 the additional pharmaceutically active compounds/agents may be a traditional small organic chemical molecules or can be macromolecules such as a proteins, antibodies, peptibodies, DNA, RNA or fragments of such macromolecules.

Examples of specific pharmaceutically active agents that can be used in the treatment of cancers and that can be used in combination with one or more compound of
15 the present invention include: methotrexate; tamoxifen; fluorouracil; 5-fluorouracil; hydroxyurea; mercaptopurine; cisplatin; carboplatin; daunorubicin; doxorubicin; etoposide; vinblastine; vincristine; paclitaxel; thioguanine; idarubicin; dactinomycin; imatinib; gemcitabine; altretamine; asparaginase; bleomycin; capecitabine; carmustine; cladisat. aq. NaCl solution; cyclophosphamide; cytarabine; decarazine; docetaxel;
20 idarubicin; ifosfamide; irinotecan; fludarabine; mitomycin; mitoxane; mitoxantrone; topotecan; vinorelbine; adriamycin; mithramycin; imiquimod; alemtuzumab; exemestane; bevacizumab; cetuximab; azacitidine; clofarabine; decitabine; dasatinib; dexrazoxane; docetaxel; epirubicin; oxaliplatin; erlotinib; raloxifene; fulvestrant; letrozole; gefitinib; gemtuzumab; trastuzumab; gefitinib; ixabepilone; lapatinib; lenalidomide; aminolevulinic
25 acid; temozolomide; nelarabine; sorafenib; nilotinib; pegaspargase; pemetrexed; rituximab; dasatinib; thalidomide; bexarotene; temsirolimus; bortezomib; vorinostat; capecitabine; zoledronic acid; anastrozole; sunitinib; aprepitant and nelarabine, or a pharmaceutically acceptable salt thereof.

Additional pharmaceutically active agents that can be used in the treatment of
30 cancers and that can be used in combination with one or more compound of the present invention include: vascular endothelial growth factor (VEGF) inhibitors, hepatocyte

growth factor/scatter factor (HGF/SF) inhibitors, angiopoietin 1 and/or 2 inhibitors, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) agonists, recombinant human apo2 ligand (TRAIL), insulin-like growth factor 1 receptor (IGFR-1) inhibitors, cFMS inhibitors, HER 2 inhibitors, c-met inhibitors, aurora kinase inhibitors, CDK 4
5 and/or 6 inhibitors, and B-raf inhibitors.

Further additional pharmaceutically active agents that can be used in the treatment of cancers and that can be used in combination with one or more compound of the present invention include antibody drug conjugates (ADCs) whereby an antibody that binds to a protein, preferably on a cancer cell, is conjugated using a linker with a chemical
10 compound that is detrimental to the cancer cell. Examples of chemical compounds that are detrimental to a cancer cell include maytansinoids derivatives and auristatin derivatives.

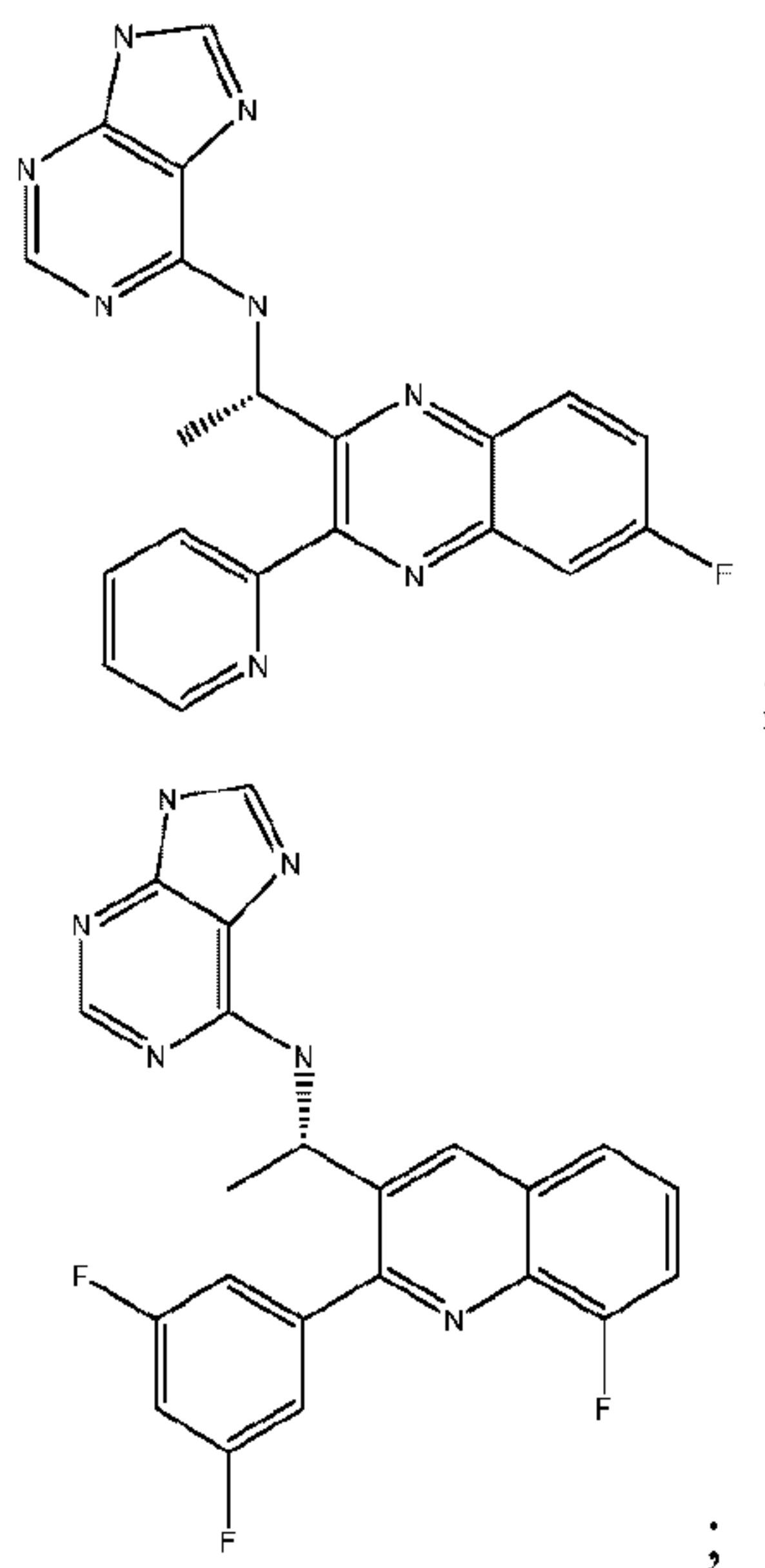
Still further additional pharmaceutically active agents that can be used in the treatment of cancers and that can be used in combination with one or more compound of
15 the present invention include: epoetin alfa; darbepoetin alfa; panitumumab; pegfilgrastim; palifermin; filgrastim; denosumab; anacetim; AMG 102; AMG 319; AMG 386; AMG 479 (Ganitumab); AMG 511, AMG 900, AMG 655 (Conatumumab); AMG 745; AMG 951; and AMG 706 (Motesanib), or a pharmaceutically acceptable salt thereof.

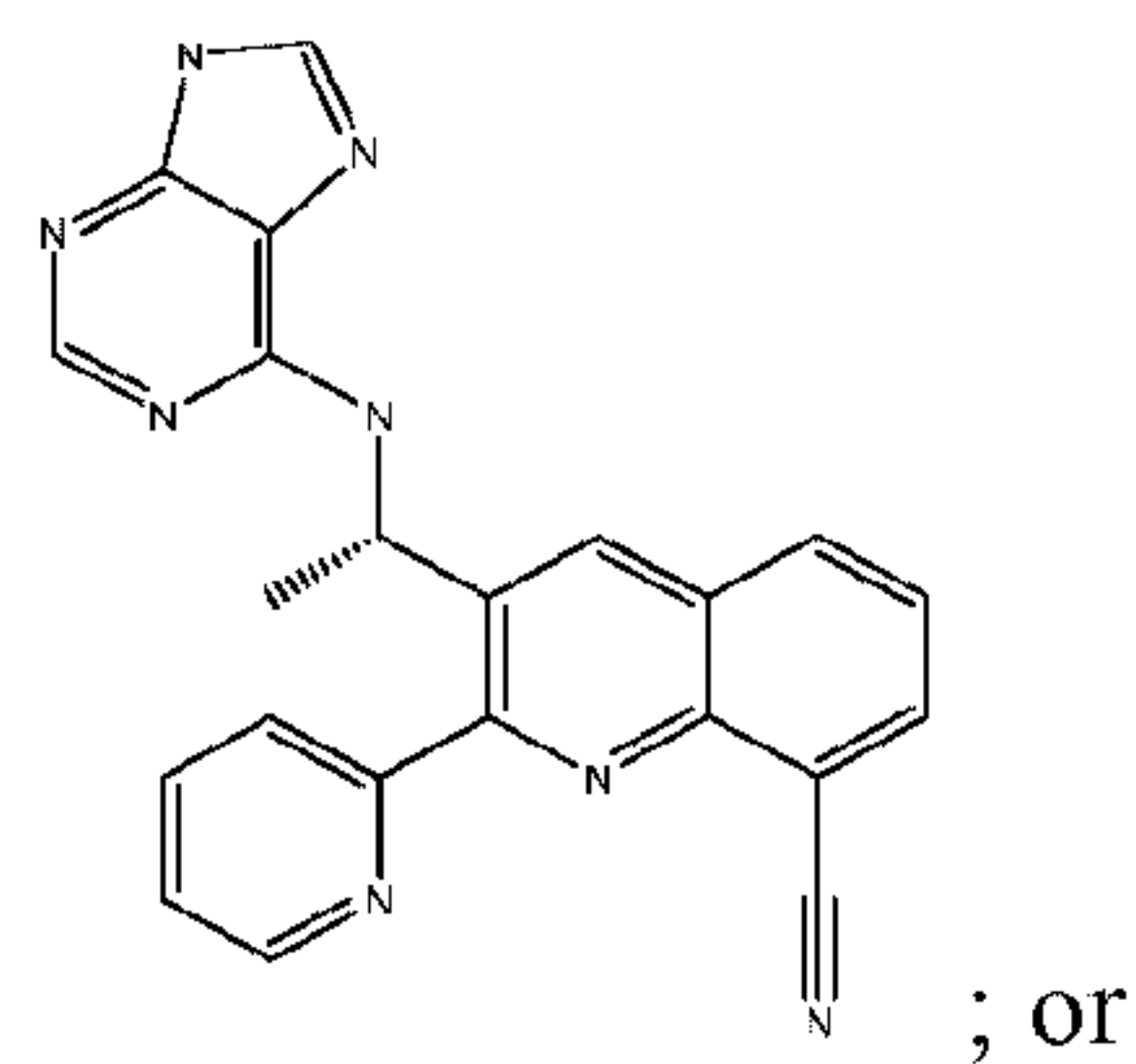
In another aspect, the present invention relates to the use of the compounds of the
20 present invention in combination with one or more pharmaceutical agent that is an inhibitor of a protein in the phosphatidylinositol 3-kinase (PI3K) pathway. Combinations of compounds of the present invention along with inhibitors of proteins in the PI3K pathway have shown synergy in cancer cell growth assays, including enhanced apoptosis and cell killing. Examples of proteins in the PI3K pathway include PI3K, mTOR and
25 PKB (also known as Akt). The PI3K protein exists in several isoforms including α , β , δ , or γ . It is contemplated that a PI3K inhibitor that can be used in combination with a compound of the present invention can be selective for one or more isoform. By selective it is meant that the compounds inhibit one or more isoform more than other isoforms. Selectivity is a concept well known to those in the art and can be measured
30 with well known activity in vitro or cell-based assays. Preferred selectivity includes greater than 2 fold, preferably 10 fold, or more preferably 100 fold greater selectivity for

one or more isoform over the other isoforms. In one aspect, the PI3K inhibitors that can be used in combination with compounds of the present invention is a PI3K α selective inhibitor. In another aspect the compound is a PI3K δ selective inhibitor.

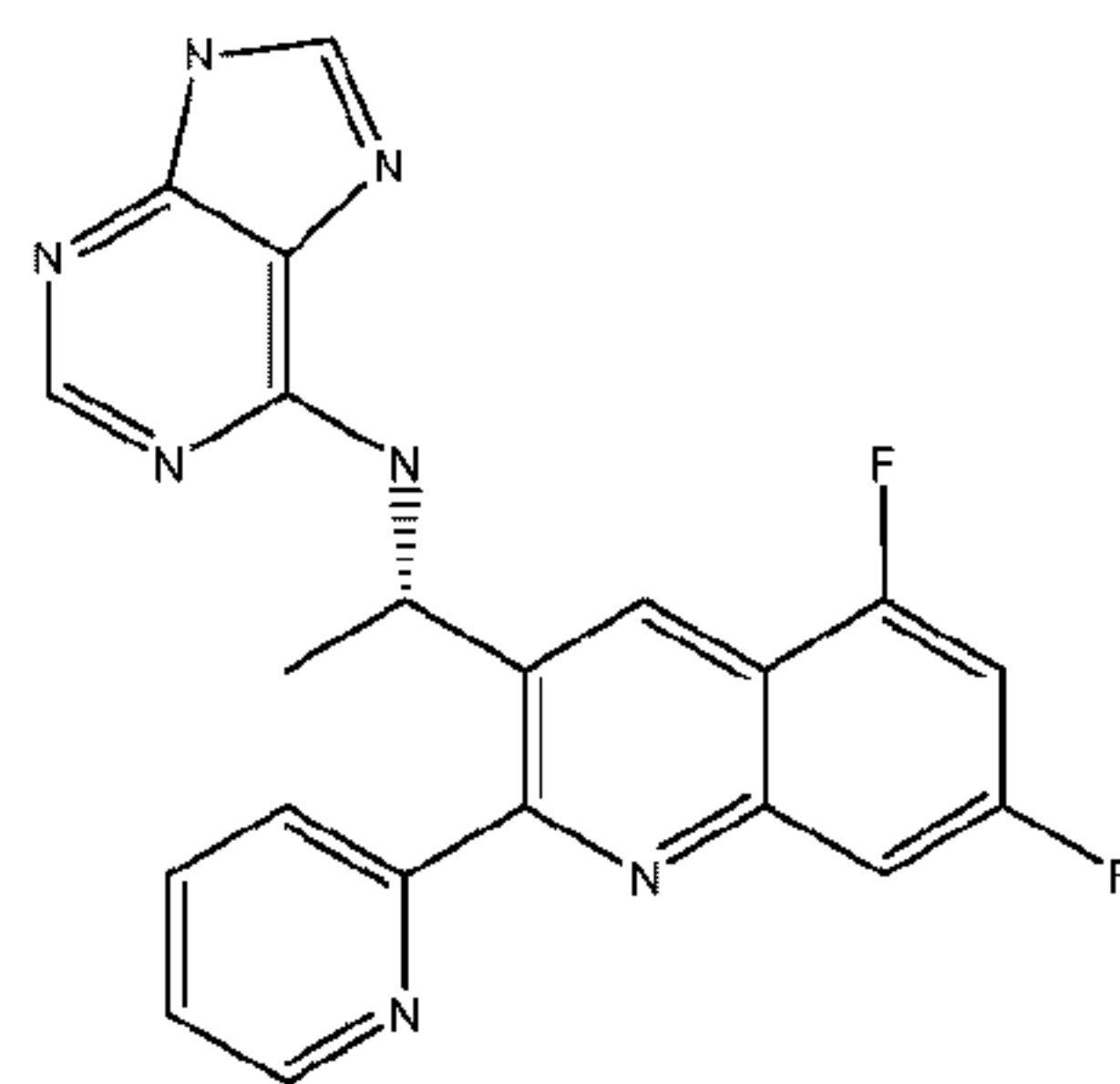
Examples of PI3K inhibitors that can be used in combination with one or more
 5 compounds of the present invention include those disclosed in the following: PCT
 published application no. WO2010/151791; PCT published application no.
 WO2010/151737;
 PCT published application no. WO2010/151735; PCT published application no.
 WO2010151740; PCT published application no. WO2008/118455; PCT published
 10 application no. WO2008/118454; PCT published application no. WO2008/118468; U.S.
 published application no. US20100331293; U.S. published application no.
 US20100331306; U.S. published application no. US20090023761; U.S. published
 application no. US20090030002; U.S. published application no. US20090137581;
 U.S. published application no. US2009/0054405; U.S. published application no. U.S.
 15 2009/0163489; U.S. published application no. US 2010/0273764; U.S. published
 application no. U.S. 2011/0092504; or PCT published application no. WO2010/108074.

Preferred PI3K inhibitors for use in combination with compounds of the present
 invention include:





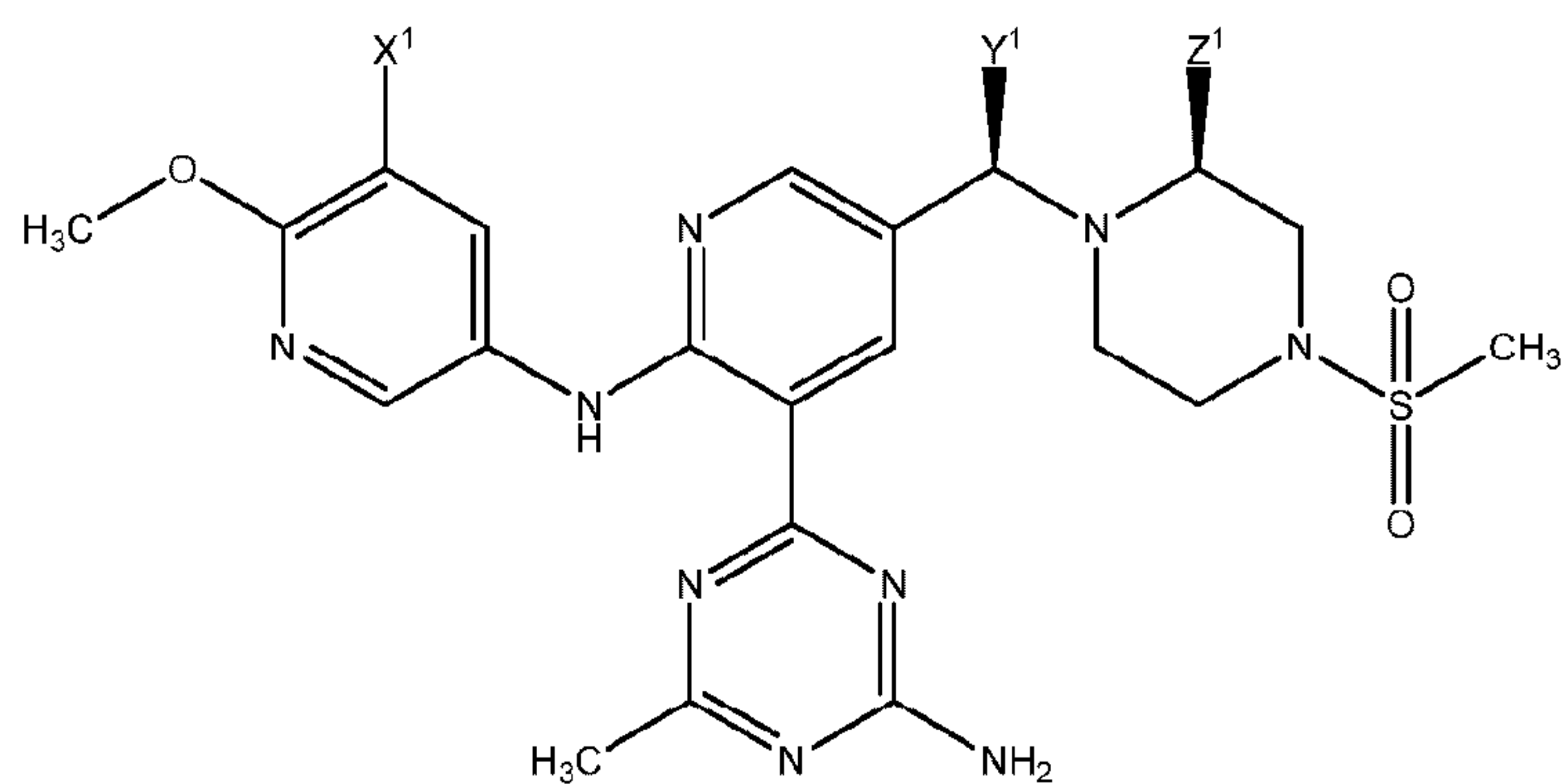
; or



5

, or a pharmaceutically acceptable salt thereof.

Also preferred is a compound of Formula IIa below, or a pharmaceutically acceptable salt thereof,



IIa

10 wherein X¹ is fluorine or hydrogen; Y¹ is hydrogen or methyl; and Z¹ is hydrogen or methyl.

Compounds that inhibit both PI3K and mTOR (dual inhibitors) are known. In still another aspect, the present invention provides the use of dual PI3K and mTOR inhibitors for use in combination with a compound of the present invention.

mTOR is a protein in the PI3K pathway. It is another aspect of the present invention to use an mTOR inhibitor in combination with one or more compounds of the present invention. mTOR inhibitors that can be used in combination with compounds of the present invention include those disclosed in the following documents: PCT published
5 application no. WO2010/132598 or PCT published application no. WO2010/096314.

PKB (Akt) is also a protein in the PI3K pathway. It is another aspect of the present invention to use an mTOR inhibitor in combination with one or more compounds of the present invention. PKB inhibitors that can be used in combination with compounds of the present invention include those disclosed in the following documents: U.S. patent
10 no. 7,354,944; U.S. patent no. 7,700,636; U.S. patent no. 7,919,514; U.S. patent no. 7,514,566; U.S. patent application publication no. US 2009/0270445 A1; U.S. patent no. 7,919,504; U.S. patent no. 7,897,619; or PCT published application no. WO 2010/083246 A1.

The compounds of the present invention can be used in combination with CDK4
15 and/or 6 inhibitors. CDK 4 and/or 6 inhibitors that can be used in combination with compounds of the present invention include those disclosed in the following documents: PCT published application no. WO 2009/085185 or U.S. patent application publication no. US2011/0097305.

The compounds of the present invention can also be used in combination with
20 pharmaceutically active agents that treat nausea. Examples of agents that can be used to treat nausea include: dronabinol; granisetron; metoclopramide; ondansetron; and prochlorperazine; or a pharmaceutically acceptable salt thereof.

In addition, the compounds of the present invention can be used in combination with other agents that can be used to treat cancer such as acemannan; aclarubicin;
25 aldesleukin; alitretinoin; amifostine; amrubicin; amsacrine; anagrelide; arglabin; arsenic trioxide; BAM 002 (Novelos); bicalutamide; broxuridine; celmoleukin; cetorelix; cladribine; clotrimazole; DA 3030 (Dong-A); daclizumab; denileukin diftitox; deslorelin; dilazep; docosanol; doxercalciferol; doxifluridine; bromocriptine; cytarabine; HIT diclofenac; interferon alfa; tretinoin; edelfosine; edrecolomab; eflornithine; emitefur;
30 epirubicin; epoetin beta; etoposide phosphate; exisulind; fadrozole; finasteride; fludarabine phosphate; formestane; fotemustine; gallium nitrate; gemtuzumab zogamycin;

gimeracil/oteracil/tegafur combination; glycopine; goserelin; heptaplatin; human chorionic gonadotropin; human fetal alpha fetoprotein; ibandronic acid; interferon alfa; interferon alfa natural; interferon alfa-2; interferon alfa-2a; interferon alfa-2b; interferon alfa-N1; interferon alfa-n3; interferon alfacon-1; interferon alpha natural; interferon beta; 5 interferon beta-1a; interferon beta-1b; interferon gamma natural; interferon gamma-1a; interferon gamma-1b; interleukin-1 beta; iobenguane; irsogladine; lanreotide; LC 9018 (Yakult); leflunomide; lenograstim; lentinan sulfate; letrozole; leukocyte alpha interferon; leuprorelin; levamisole + fluorouracil; liarozole; lobaplatin; lonidamine; lovastatin; masoprocol; melarsoprol; metoclopramide; mifepristone; miltefosine; mirimostim; 10 mismatched double stranded RNA; mitoguazone; mitolactol; mitoxantrone; molgramostim; nafarelin; naloxone + pentazocine; nartograstim; nedaplatin; nilutamide; noscapine; novel erythropoiesis stimulating protein; NSC 631570 octreotide; oprelvekin; osaterone; paclitaxel; pamidronic acid; peginterferon alfa-2b; pentosan polysulfate sodium; pentostatin; picibanil; pirarubicin; rabbit antithymocyte polyclonal antibody; 15 polyethylene glycol interferon alfa-2a; porfimer sodium; raltitrexed; rasburicase; rhenium Re 186 etidronate; RII retinamide; romurtide; samarium (153 Sm) lexidronam; sargramostim; sizofiran; sobuzoxane; sonermin; strontium-89 chloride; suramin; tasonermin; tazarotene; tegafur; temoporfin; teniposide; tetrachlorodecaoxide; thymalfasin; thyrotropin alfa; toremifene; tositumomab-iodine 131; treosulfan; tretinoin; 20 trilostane; trimetrexate; triptorelin; tumor necrosis factor alpha natural; ubenimex; bladder cancer vaccine; Maruyama vaccine; melanoma lysate vaccine; valrubicin; verteporfin; virulizin; zinostatin stimalamer; abarelix; AE 941 (Aeterna); ambamustine; antisense oligonucleotide; bcl-2 (Genta); APC 8015 (Dendreon); dexaminoglutethimide; diaziquone; EL 532 (Elan); EM 800 (Endorecherche); eniluracil; etanidazole; fenretinide; 25 filgrastim SD01 (Amgen); galocitabine; gastrin 17 immunogen; HLA-B7 gene therapy (Vical); granulocyte macrophage colony stimulating factor; histamine dihydrochloride; ibritumomab tiuxetan; ilomastat; IM 862 (Cytran); interleukin-2; iproxifene; LDI 200 (Milkhaus); leridistim; lintuzumab; CA 125 monoclonal antibody(MAb) (Biomira); cancer MAb (Japan Pharmaceutical Development); HER-2 and Fc MAb (Medarex); 30 idiotypic 105AD7 MAb (CRC Technology); idiotypic CEA MAb (Trilex); LYM-1-iodine 131 MAb (Techniclone); polymorphic epithelial mucin-yttrium 90 MAb

(Antisoma); marimastat; menogaril; mitumomab; motexafin gadolinium; MX 6 (Galderma); nolatrexed; P 30 protein; pegvisomant; porfiromycin; prinomastat; RL 0903 (Shire); rubitecan; satraplatin; sodium phenylacetate; sparfosic acid; SRL 172 (SR Pharma); SU 5416 (Pfizer); TA 077 (Tanabe); tetrathiomolybdate; thaliblastine; 5 thrombopoietin; tin ethyl etiopurpurin; tirapazamine; cancer vaccine (Biomira); melanoma vaccine (New York University); melanoma vaccine (Sloan Kettering Institute); melanoma oncolysate vaccine (New York Medical College); viral melanoma cell lysates vaccine (Royal Newcastle Hospital); or valspodar. It is noted that the agents recited above may also be administered as pharmaceutically acceptable salts when 10 appropriate.

The compounds of the present invention may also be used in combination with radiation therapy, hormone therapy, surgery and immunotherapy, which therapies are well known to those skilled in the art.

Since one aspect of the present invention contemplates the treatment of the 15 disease/conditions with a combination of pharmaceutically active compounds that may be administered separately, the invention further relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of the present invention, and a second pharmaceutical compound. The kit comprises a container for containing the separate compositions such 20 as a divided bottle or a divided foil packet. Additional examples of containers include syringes, boxes and bags. Typically, the kit comprises directions for the use of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the 25 individual components of the combination is desired by the prescribing physician or veterinarian.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a 30 sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The

recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses
5 between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, e.g., in the form of
10 numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday,
... etc ... Second Week, Monday, Tuesday, ... " etc. Other variations of memory aids
15 will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of a compound of the present invention can consist of one tablet or capsule, while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this and aid in correct administration of the active agents.

20 In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is
25 a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

The compounds of the present invention and other pharmaceutically active compounds, if desired, can be administered to a patient either orally, rectally,
30 parenterally, (for example, intravenously, intramuscularly, or subcutaneously) intracisternally, intravaginally, intraperitoneally, intravesically, locally (for example,

powders, ointments or drops), or as a buccal or nasal spray. All methods that are used by those skilled in the art to administer a pharmaceutically active agent are contemplated.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Microorganism contamination can be prevented by adding various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Prolonged absorption of injectable pharmaceutical compositions can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (e) solution retarders, as for example, paraffin; (f) absorption accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols,

sodium lauryl sulfate, or mixtures thereof. In the case of capsules, and tablets, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be used as fillers in soft and hard filled gelatin capsules using such excipients as lactose or milk sugar, as well as high
5 molecular weight polyethylene glycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may also contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a
10 delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active
15 compounds, the liquid dosage form may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame seed oil,
20 glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. Suspensions, in addition to the active compound, may contain suspending agents,
25 as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administration are preferable suppositories, which can be prepared by mixing the compounds of the present invention with suitable non-irritating
30 excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax,

which are solid at ordinary room temperature, but liquid at body temperature, and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of the present invention include ointments, powders, sprays and inhalants. The active compound or fit compounds are admixed under sterile condition with a physiologically acceptable carrier, and any
5 preservatives, buffers, or propellants that may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The compounds of the present invention can be administered to a patient at
10 dosage levels in the range of about 0.1 to about 3,000 mg per day. For a normal adult human having a body weight of about 70 kg, a dosage in the range of about 0.01 to about 100 mg per kilogram body weight is typically sufficient. The specific dosage and dosage range that can be used depends on a number of factors, including the requirements of the patient, the severity of the condition or disease being treated, and the pharmacological
15 activity of the compound being administered. The determination of dosage ranges and optimal dosages for a particular patient is within the ordinary skill in the art.

The compounds of the present invention can be administered as pharmaceutically acceptable salts, esters, amides or prodrugs. The term "salts" refers to inorganic and organic salts of compounds of the present invention. The salts can be prepared in situ
20 during the final isolation and purification of a compound, or by separately reacting a purified compound in its free base or acid form with a suitable organic or inorganic base or acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate,
25 tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. The salts may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine,
30 trimethylamine, triethylamine, ethylamine, and the like. See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J Pharm Sci, 66: 1-19 (1977).

Examples of pharmaceutically acceptable esters of the compounds of the present invention include C₁-C₈ alkyl esters. Acceptable esters also include C₅-C₇ cycloalkyl esters, as well as arylalkyl esters such as benzyl. C₁-C₄ alkyl esters are commonly used. Esters of compounds of the present invention may be prepared according to methods that are well known in the art.

Examples of pharmaceutically acceptable amides of the compounds of the present invention include amides derived from ammonia, primary C₁-C₈ alkyl amines, and secondary C₁-C₈ dialkyl amines. In the case of secondary amines, the amine may also be in the form of a 5 or 6 membered heterocycloalkyl group containing at least one nitrogen atom. Amides derived from ammonia, C₁-C₃ primary alkyl amines and C₁-C₂ dialkyl secondary amines are commonly used. Amides of the compounds of the present invention may be prepared according to methods well known to those skilled in the art.

The term "prodrug" means compounds that are transformed in vivo to yield a compound of the present invention. The transformation may occur by various mechanisms, such as through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Prodrugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

To illustrate, if the compound of the invention contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C₁-C₈ alkyl, (C₂-C₁₂)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)ethyl having from 5 to 10 carbon atoms, alkoxy-carbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxy-carbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxy-carbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxy-carbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxy-carbonyl)aminomethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁-C₂)alkylamino(C₂-C₃)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di(C₁-C₂)alkylcarbamoyl-(C₁-C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂₋₃)alkyl.

Similarly, if a compound of the present invention comprises an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-C₆)alkoxycarbonyloxymethyl, N-(C₁-
5 C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁-C₆)alkanoyl, α -amino(C₁-C₄)alkanoyl, arylacyl and α -aminoacyl, or α -aminoacyl- α -aminoacyl, where each α -aminoacyl group is independently selected from the naturally occurring L-amino acids, -P(O)(OH)₂, -P(O)(O(C₁-C₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

10 The compounds of the present invention may contain asymmetric or chiral centers, and therefore, exist in different stereoisomeric forms. It is contemplated that all stereoisomeric forms of the compounds as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention contemplates all geometric and positional isomers. For example, if the compound
15 contains a double bond, both the cis and trans forms (designated as Z and E, respectively), as well as mixtures, are contemplated.

Mixture of stereoisomers, such as diastereomeric mixtures, can be separated into their individual stereochemical components on the basis of their physical chemical differences by known methods such as chromatography and/or fractional crystallization.
20 Enantiomers can also be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., an alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some compounds may be atropisomers (e.g., substituted biaryls).

25 The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water (hydrate), ethanol, and the like. The present invention contemplates and encompasses both the solvated and unsolvated forms.

It is also possible that compounds of the present invention may exist in different
30 tautomeric forms. All tautomers of compounds of the present invention are contemplated. For example, all of the tautomeric forms of the tetrazole moiety are included in this

invention. Also, for example, all keto-enol or imine-enamine forms of the compounds are included in this invention.

Those skilled in the art will recognize that the compound names and structures contained herein may be based on a particular tautomer of a compound. While the name
5 or structure for only a particular tautomer may be used, it is intended that all tautomers are encompassed by the present invention, unless stated otherwise.

It is also intended that the present invention encompass compounds that are synthesized in vitro using laboratory techniques, such as those well known to synthetic chemists; or synthesized using in vivo techniques, such as through metabolism,
10 fermentation, digestion, and the like. It is also contemplated that the compounds of the present invention may be synthesized using a combination of in vitro and in vivo techniques.

The present invention also includes isotopically-labelled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an
15 atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{16}O , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl . In one aspect, the present invention relates to compounds wherein one
20 or more hydrogen atom is replaced with deuterium (^2H) atoms.

Compounds of the present invention that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or
25 substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detection. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.
30 Isotopically labelled compounds of this invention can generally be prepared by

substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

The compounds of the present invention may exist in various solid states including crystalline states and as an amorphous state. The different crystalline states, also called polymorphs, and the amorphous states of the present compounds are contemplated as part of this invention.

In synthesizing compounds of the present invention, it may be desirable to use certain leaving groups. The term "leaving groups" ("LG") generally refer to groups that are displaceable by a nucleophile. Such leaving groups are known in the art. Examples of leaving groups include, but are not limited to, halides (e.g., I, Br, F, Cl), sulfonates (e.g., mesylate, tosylate), sulfides (e.g., SCH₃), N-hydroxysuccinimide, N-hydroxybenzotriazole, and the like. Examples of nucleophiles include, but are not limited to, amines, thiols, alcohols, Grignard reagents, anionic species (e.g., alkoxides, amides, carbanions) and the like.

All patents, published patent applications and other publications recited herein are hereby incorporated by reference.

The examples presented below illustrate specific embodiments of the present invention. These examples are meant to be representative and are not intended to limit the scope of the claims in any manner. Unless otherwise noted, when a percent is used herein with respect to a solid, the percent is by weight with respect to the referenced solid composition. When a percent is used herein with respect to a liquid, the percent is by volume with respect to the referenced solution.

¹H-NMR spectra were typically acquired on a Bruker Avance III 500 spectrometer system (Bruker, Billerica, MA) operating at a ¹H frequency of 500.13 MHz, equipped with a Bruker 5 mm PABBI probe with a z-axis gradient; or on a Bruker Avance II or Avance III 400 spectrometer operating at a ¹H frequency of 400.23 MHz, equipped with a Bruker 5 mm PABBO probe with a z-axis gradient. Samples were typically dissolved in 500 μL of either DMSO-d₆ or CD₃OD for NMR analysis. ¹H chemical shifts are referenced to the residual solvent signals from DMSO-d₆ at δ 2.50 and CD₃OD at δ 3.30.

Significant peaks are tabulated and typically include: number of protons, multiplicity (s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; br s, broad singlet) and coupling constant(s) in Hertz.

Electron Ionization (EI) mass spectra were typically recorded on an Agilent
 5 Technologies 6140 Quadrupole LC/MS mass spectrometer. Mass spectrometry results are reported as the ratio of mass over charge, sometimes followed by the relative abundance of each ion (in parentheses). Starting materials in the Examples below are typically either available from commercial sources such as Sigma-Aldrich, St. Louis, MO, or via literature procedures.

10

The following abbreviations may be used herein:

~	about
+ve or pos. ion	positive ion
Δ	heat
Ac	acetyl
Ac ₂ O	acetic anhydride
aq	aqueous
AcOH	acetic acid
Bn	benzyl
Boc	tert-butyloxycarbonyl
BSA	bovine serum albumin
Bu	butyl
Bz	benzoyl
Calcd or Calc'd	calculated
Conc.	concentrated
CSA	camphor-10-sulfonic acid
d	day(s)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DEA	diethylamine
Dess-Martin periodinane; Dess-Martin reagent	1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1 <i>H</i>)-one
DIEA or DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
DTT	dithiothreitol
DVB	divinylbenzene
EDC	N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide
ee or e.e.	enantiomeric excess
eq	equivalent
ESI or ES	electrospray ionization
Et	ethyl
Et ₂ O	diethyl ether
Et ₃ N	triethylamine
EtOAc	ethyl acetate
EtOH	ethyl alcohol
g	gram(s)
h	hour(s)
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU	O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluorophosphate
Hex	hexanes
HMPA	hexamethylphosphoramide
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	hydroxybenzotriazole
HPLC	high pressure liquid chromatography

IPA or iPrOH	isopropyl alcohol
Jones reagent	solution of chromium(IV)oxide and sulfuric acid in water
KHMDS	potassium hexamethyldisilazide
KOAc	potassium acetate
LCMS, LC-MS or LC/MS	liquid chromatography mass spectrometry
LDA	lithium diisopropylamide
LHMDS or LiHMDS	lithium hexamethyldisilazide
L-Selectride [®]	lithium tri- <i>sec</i> -butylborohydride (Sigma-Aldrich, St. Louis)
M	molar (mol L ⁻¹)
mCPBA	m-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeI	iodomethane
MeOH	methyl alcohol
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
M	mole(s)
MS	mass spectrometry
MsCl	methanesulfonyl chloride
MTBE or MtBE	methyl tert-butyl ether
m/z	mass-to-charge ratio
NaHMDS	sodium hexamethyldisilazide
NaOtBu	sodium tert-butoxide
NBS	N-bromosuccinimide
nBuLi	n-butyl lithium
NMO	N-methylmorpholine-N-oxide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
N-Selectride [®]	sodium tri- <i>sec</i> -butylborohydride (Sigma-Aldrich, St.

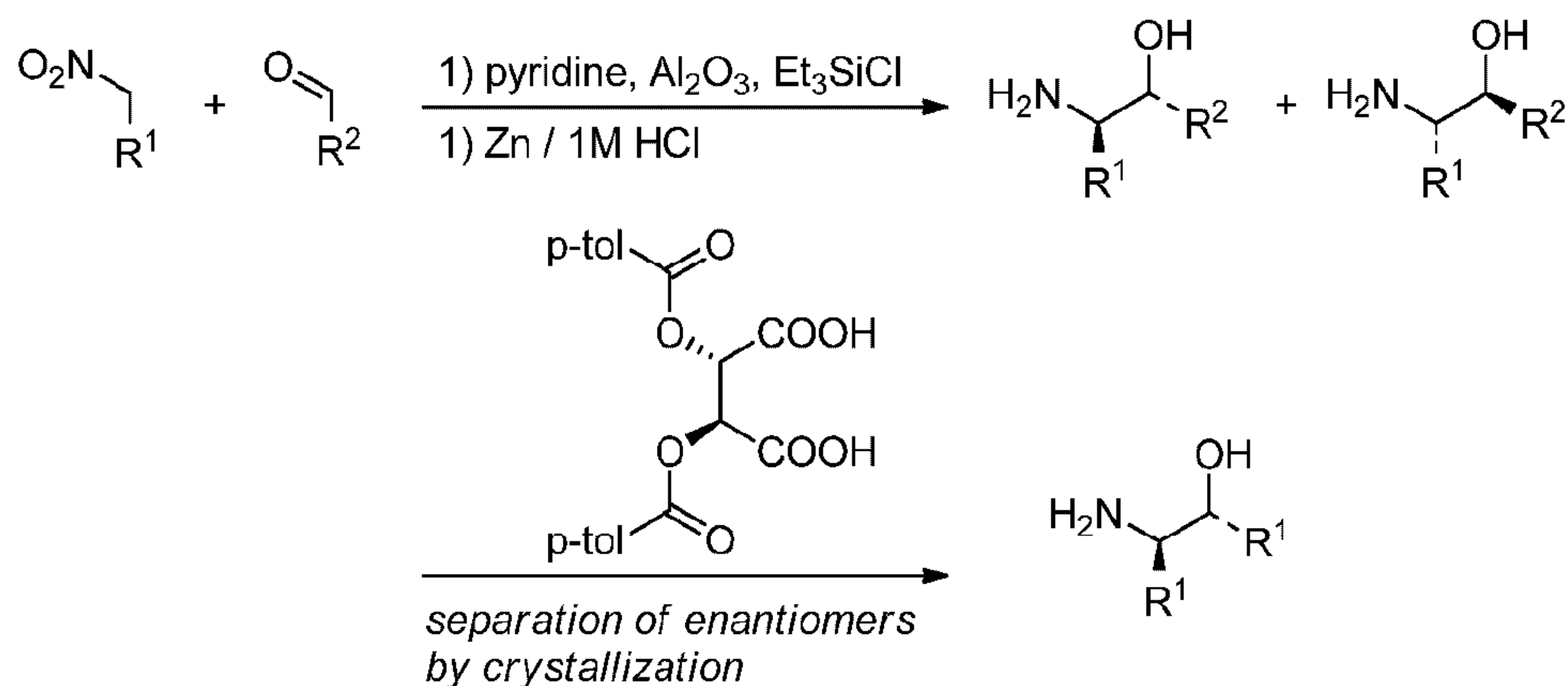
	Louis)
PBS	phosphate buffered saline
PMB	paramethoxybenzyl
Pr	propyl
ppm	parts per million
PTFE	polytetrafluoroethylene
p-tol	para-toluoyl
rac	racemic
RP-HPLC or RPHPLC	reversed phase high pressure liquid chromatography
RT or rt or r.t.	room temperature
sat. or sat'd or satd	saturated
SFC	supercritical fluid chromatography
TBAF	tetrabutylammonium fluoride
TBDMS	tert-butyldimethylsilyl
TBDMS-Cl	tert-butyldimethylsilyl chloride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
tert or t	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl or trimethylsilane
TPAP	tetrapropylammonium perruthenate
t_R	retention time
tBuOH	tert-butyl alcohol
v/v	volume per volume

EXAMPLES

General Synthetic Schemes

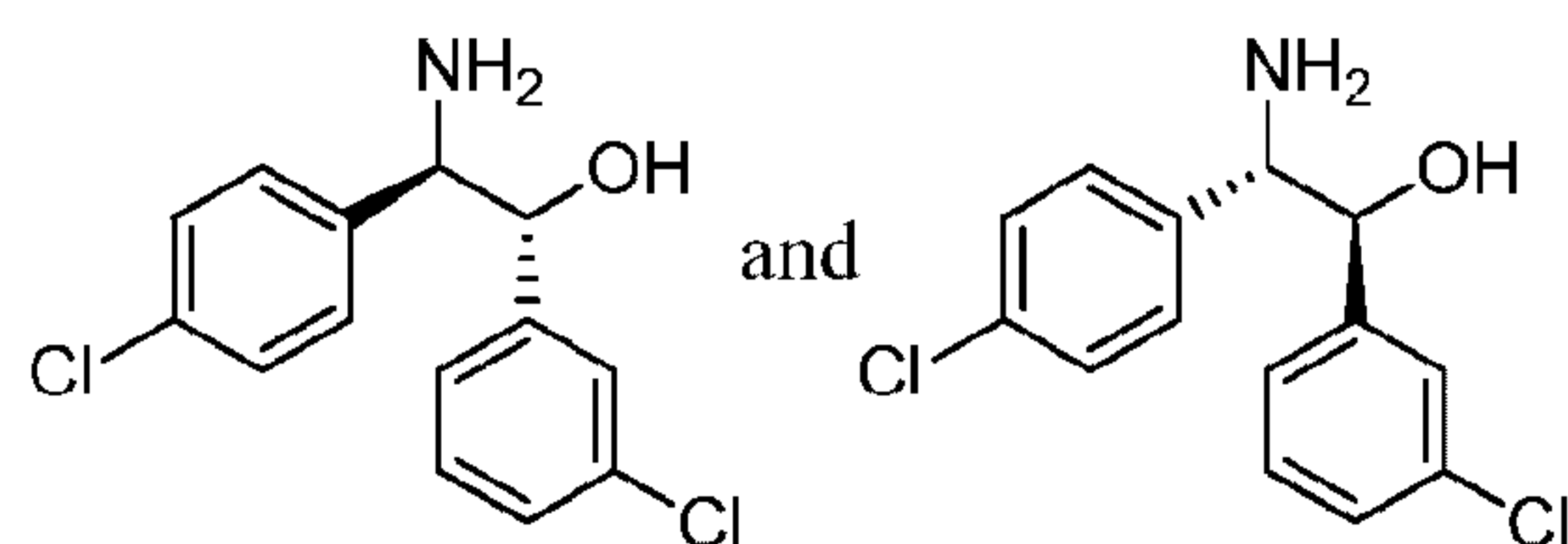
Compounds of the present invention generally can be prepared beginning with commercially available starting materials and using synthetic techniques known to those of skill in the art. Outlined below are some reaction schemes suitable for preparing compounds of the present invention. Further exemplification is found in the specific examples provided.

General Procedure 1

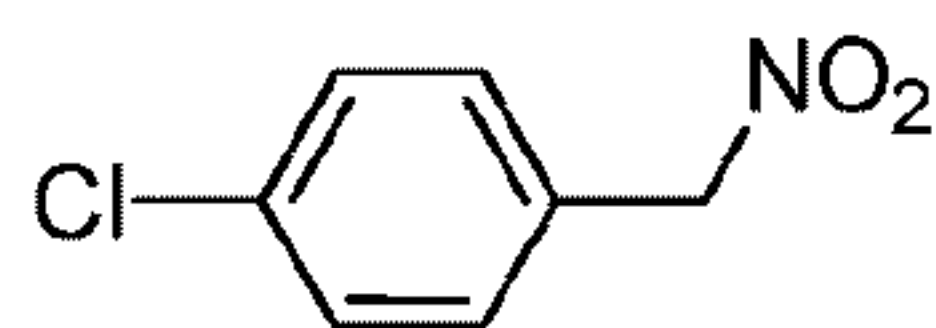


Intermediate A1

(1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol and (1S,2S)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol



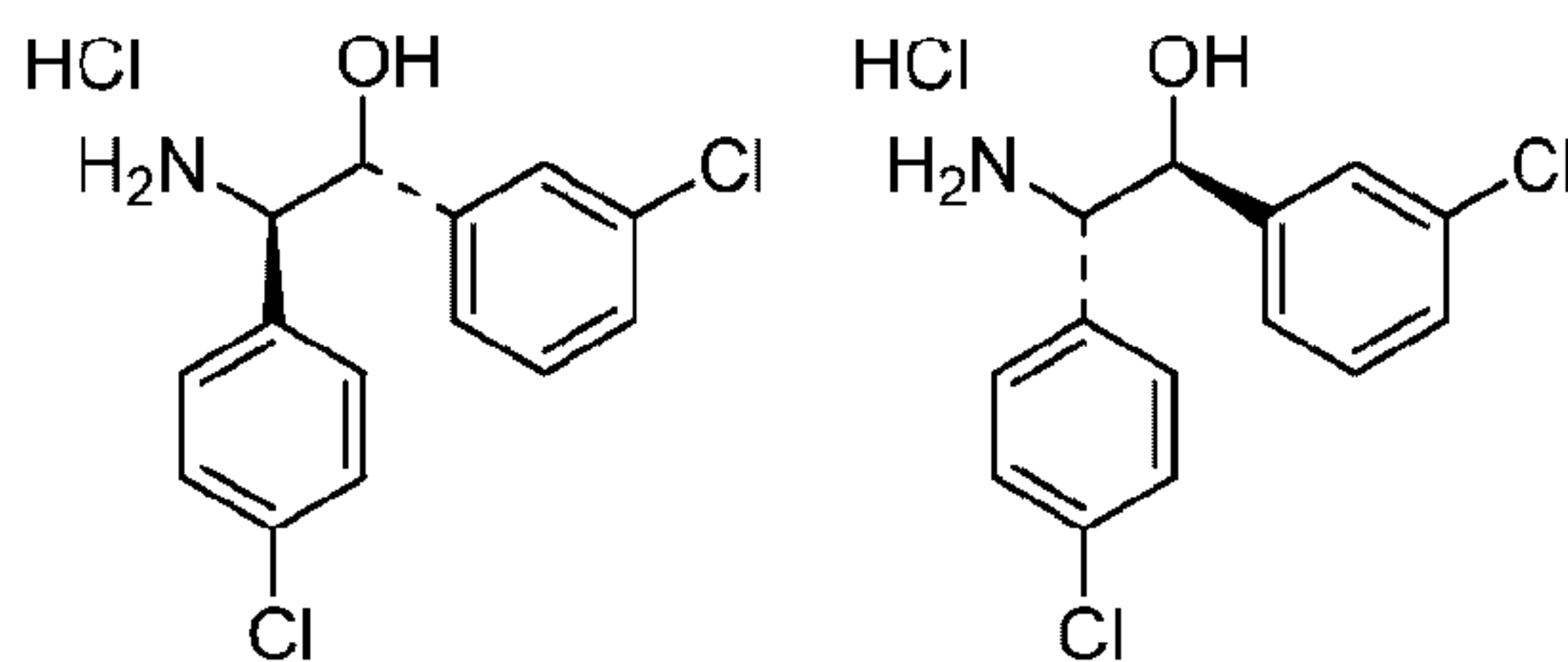
Step A. 1-Chloro-4-(nitromethyl)benzene



A suspension of AgNO_2 (392 g) in diethylether (1.6 L) was cooled to 0 °C and a solution of 4-chlorobenzylbromide (395 g, 1.92 mol) in diethylether (1.6 L) was added dropwise over 1 h (temperature maintained below 3 °C during addition). The reaction mixture was stirred for 16 h at 0 °C in the dark. Then the mixture was filtered and the solids were washed with diethylether (3x). The combined filtrates were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: 0 to 10% EtOAc in heptane; gradient elution) to give the title compound.

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Step B. (1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol hydrochloride and (1S,2S)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol hydrochloride



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To a flask containing 3-chlorobenzaldehyde (135 mL, 168 g, 1.19 mol) was added 1-chloro-4-(nitromethyl)-benzene (205 g, 1.19 mol, Step A), alumina (135 g), pyridine (96 mL, 1.19 mol) and chlorotriethylsilane (200 mL, 180 g, 1.19 mol). The flask was covered in aluminum foil and spun for 16 h in the dark at room temperature on a rotary evaporator. The resulting thick paste was then filtered and washed with isopropanol. The filtrate was divided into two equal portions and used in the next step. Procedure for each portion: To each solution was added 1 M HCl (7 L, 7 mol) and then Zn powder (800 g, 12.3 mol) was added in several portions. The reaction mixture was stirred until the observed exothermic reaction (to 35°C) was complete (90 mins). Then the mixture was cooled to 0 °C and basified with 30% NaOH to a pH of about 10. The suspension was filtered through a pad of Celite[®] (J.T. Baker, Phillipsberg, NJ, diatomaceous earth) and washed with DCM. The filtrate was transferred to a separatory funnel and the layers

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were separated. The aqueous layer was extracted with DCM. The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in MTBE (1.5 L) and cooled to 0 °C. Then 4 N HCl in dioxane (375 mL, 1.5 mol) was added dropwise. The solid was collected by filtration.

5 The solid was purified by crystallization from dioxane/ethanol to give a racemic mixture of the title compounds.

Step C. (1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol and (1S,2S)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol

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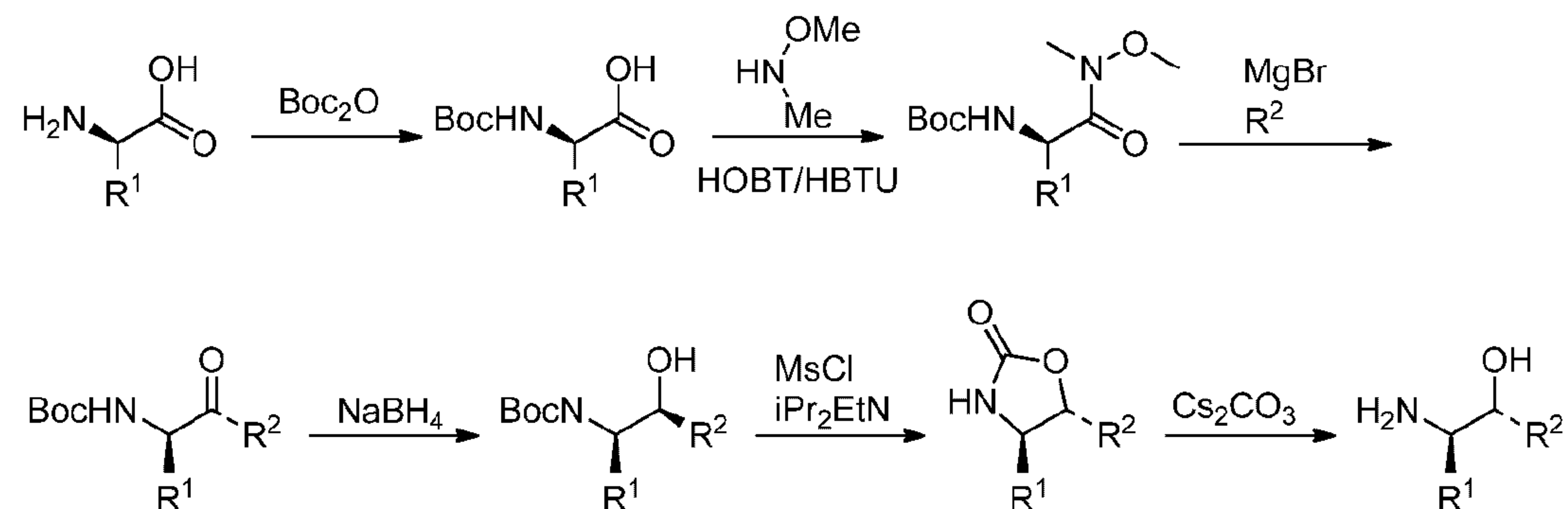
To a racemic mixture of (1R,2R)-2-amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol hydrochloride and (1S,2S)-2-amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol hydrochloride (65.5 g, 0.205 mol, Step B) in EtOAc (500 mL) was added 2 N aq. NaOH (500 mL, 1 mol). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give a racemic mixture of the title compounds as a white solid. Mass Spectrum (ESI) m/z = 282.0 (M+H).

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Alternatively, Intermediate A1 can also be prepared by the following General Procedure

20 2:

General Procedure 2



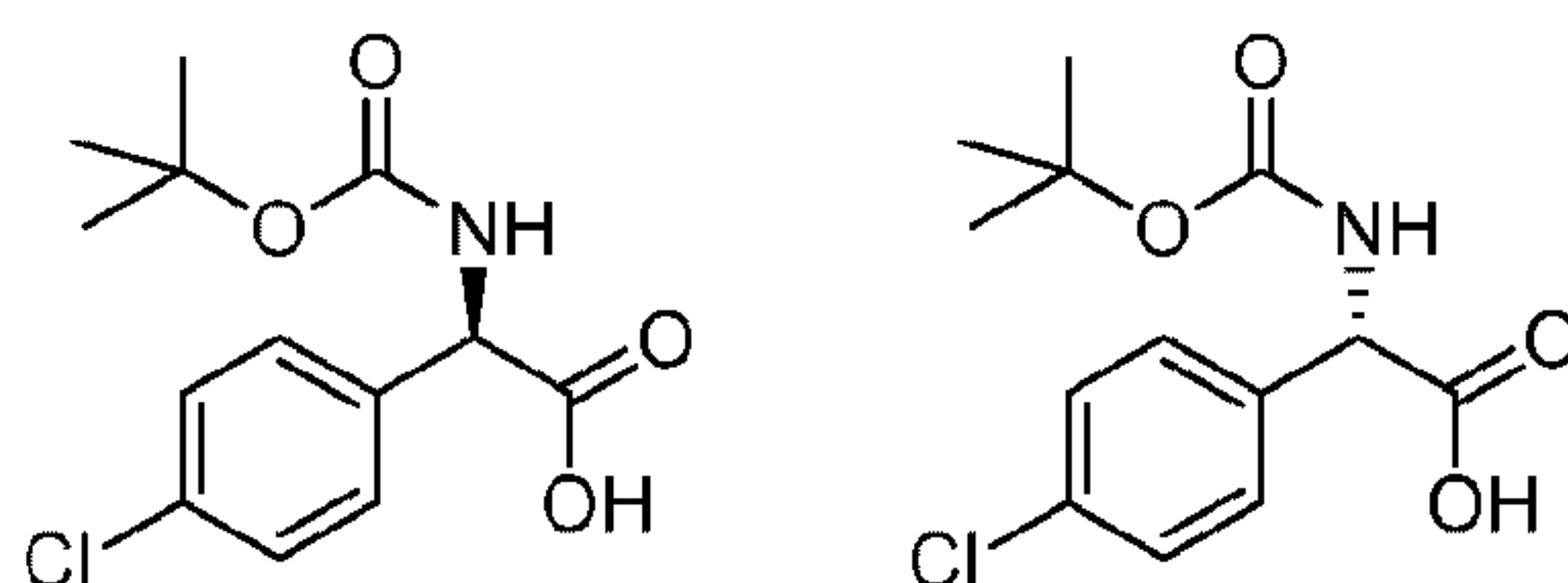
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Intermediate A1

(1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol and (1S,2S)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol

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Step A. (R)-2-((tert-Butoxycarbonyl)amino)-2-(4-chlorophenyl)acetic acid and (S)-2-((tert-Butoxycarbonyl)amino)-2-(4-chlorophenyl)acetic acid



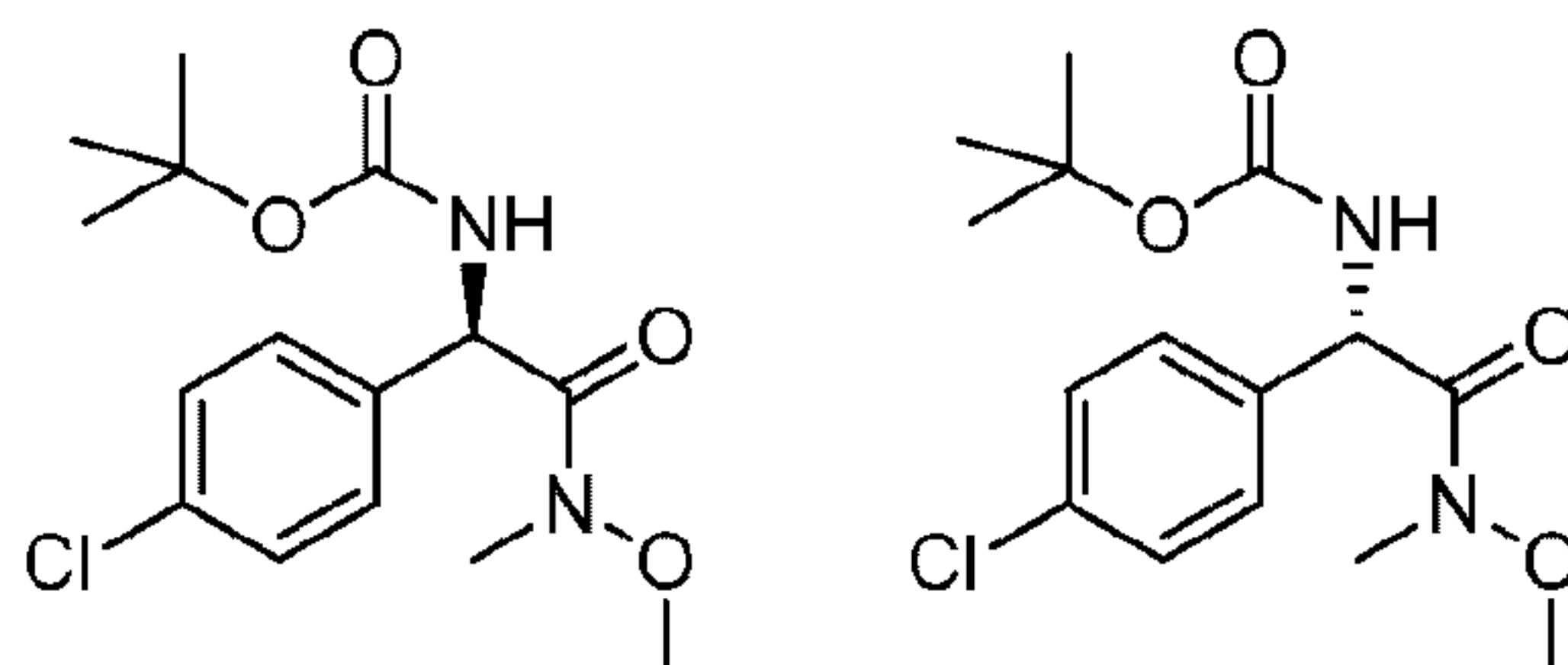
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To a stirred solution of racemic 2-amino-2-(4-chlorophenyl)acetic acid (20 g, 108 mmol) in dioxane:water (200 mL:100 mL) at 0 °C was added sodium hydroxide (1N aqueous solution, 100 mL, 100 mmol). The reaction was stirred for 5 minutes and then di-tert-butyl dicarbonate (35 g, 162 mmol) and sodium hydrogen carbonate (9.08 g, 108 mmol) were added in one portion. The reaction was stirred at r.t. for 24 hours. After this time the reaction was evaporated under a vacuum and then acidified to a pH of about 4 with saturated aqueous KHSO₄ solution. The separated organic layer was extracted with EtOAc (300 mL), dried over MgSO₄, filtered and the filtrate was evaporated under reduced pressure to give the title compound. Mass Spectrum (ESI) m/z = 229.9 (M-*t*Bu+H).

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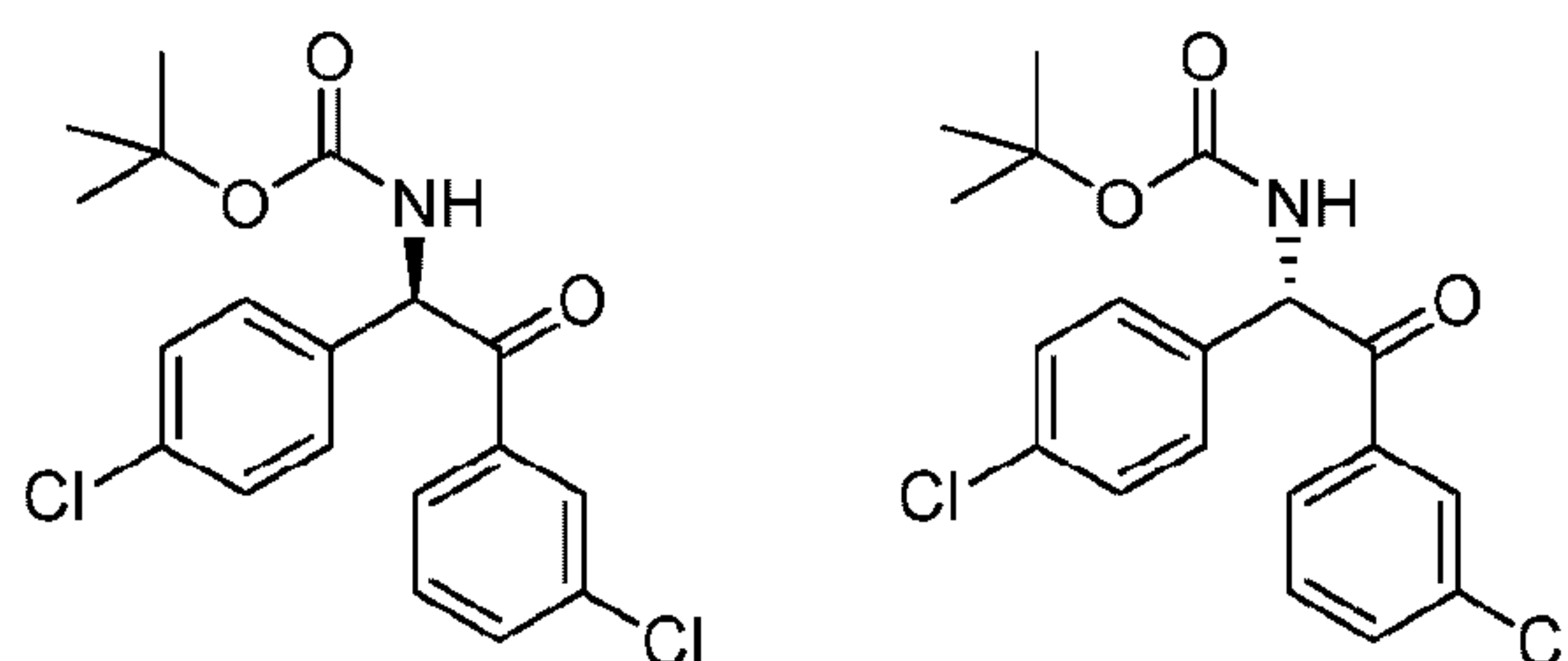
Step B. (R)-tert-Butyl 1-(4-chlorophenyl)-2-(methoxy(methyl)amino)-2-oxoethylcarbamate and (S)-tert-Butyl 1-(4-chlorophenyl)-2-(methoxy(methyl)amino)-2-oxoethylcarbamate

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To a stirred solution of 2-((tert-butoxycarbonyl)amino)-2-(4-chlorophenyl)acetic acid (14 g, 49 mmol, Step A), HBTU (19 g, 49 mmol), HOBT (7.5 g, 49 mmol) and DIEA (8.5 mL, 49 mmol) at 0 °C in DCM (200 mL) was added a solution of N,O-dimethylhydroxylamine hydrochloride (4.8 g, 49 mmol) and DIEA (8.5 mL, 49 mmol) in DCM (40 mL) dropwise over 10 minutes. The reaction was allowed to warm to r.t. overnight. After this time the solvent was evaporated under a vacuum and the resulting oil was dissolved in EtOAc (400 mL) and NH₄Cl (100 mL, sat. aq. solution). The separated organic layer was washed with NaCl (saturated aqueous solution, 100 mL), dried over MgSO₄, filtered and evaporated under a vacuum. Column chromatography on silica gel (80 g, hexanes / EtOAc, 1:0 to 1:1, gradient elution) gave the title compound as a white solid. Mass Spectrum (ESI) m/z = 351.1 (M+23).

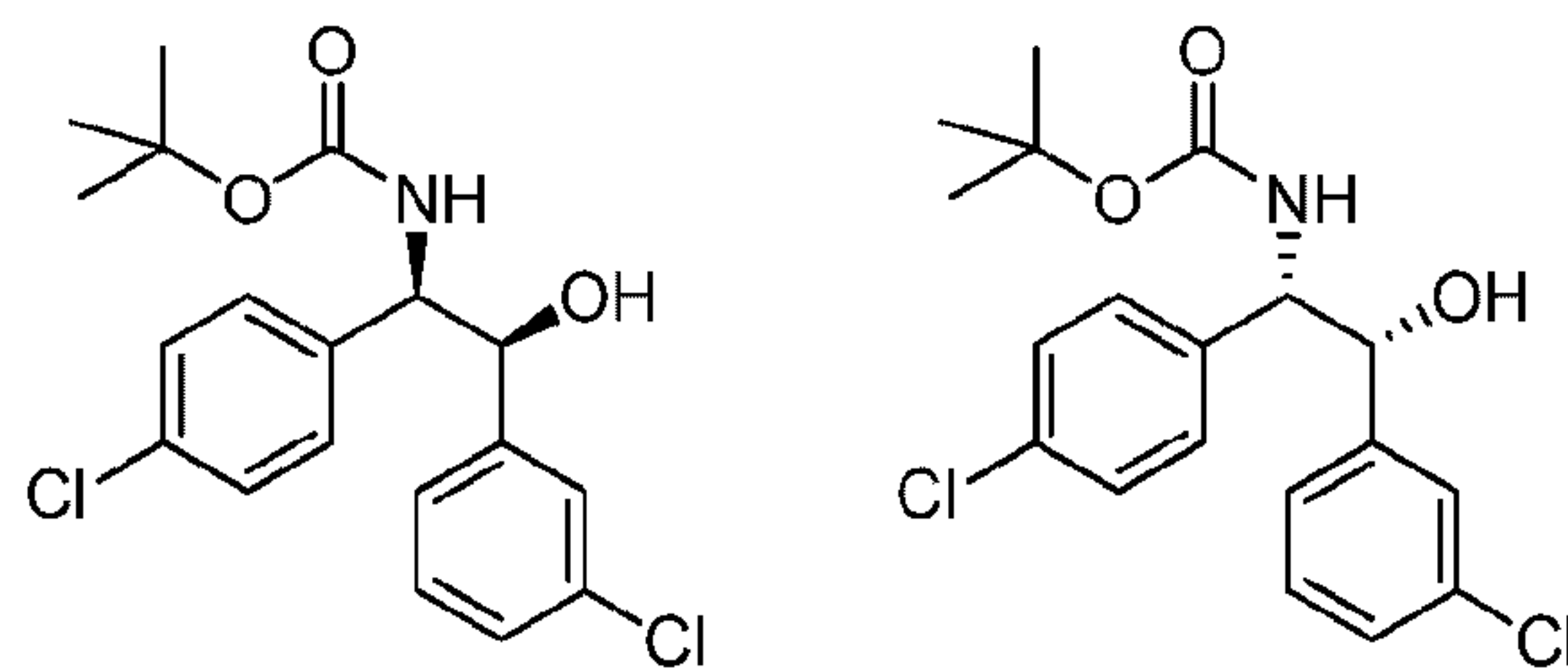
Step C. (R)-tert-Butyl (2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-oxoethyl)carbamate and (S)-tert-Butyl (2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-oxoethyl)carbamate



To a stirred solution of tert-butyl 1-(4-chlorophenyl)-2-(methoxy(methyl)amino)-2-oxoethylcarbamate (3.2 g, 10 mmol, Step B) in THF (50 mL) at -10 °C was added (3-chlorophenyl)magnesium bromide (49 mL, 24 mmol, 0.5 M in THF) dropwise over 5 minutes. The reaction was stirred at r.t. for 6 hours and then it was quenched by the addition of a saturated aqueous solution of NH₄Cl (40 mL). The mixture was then

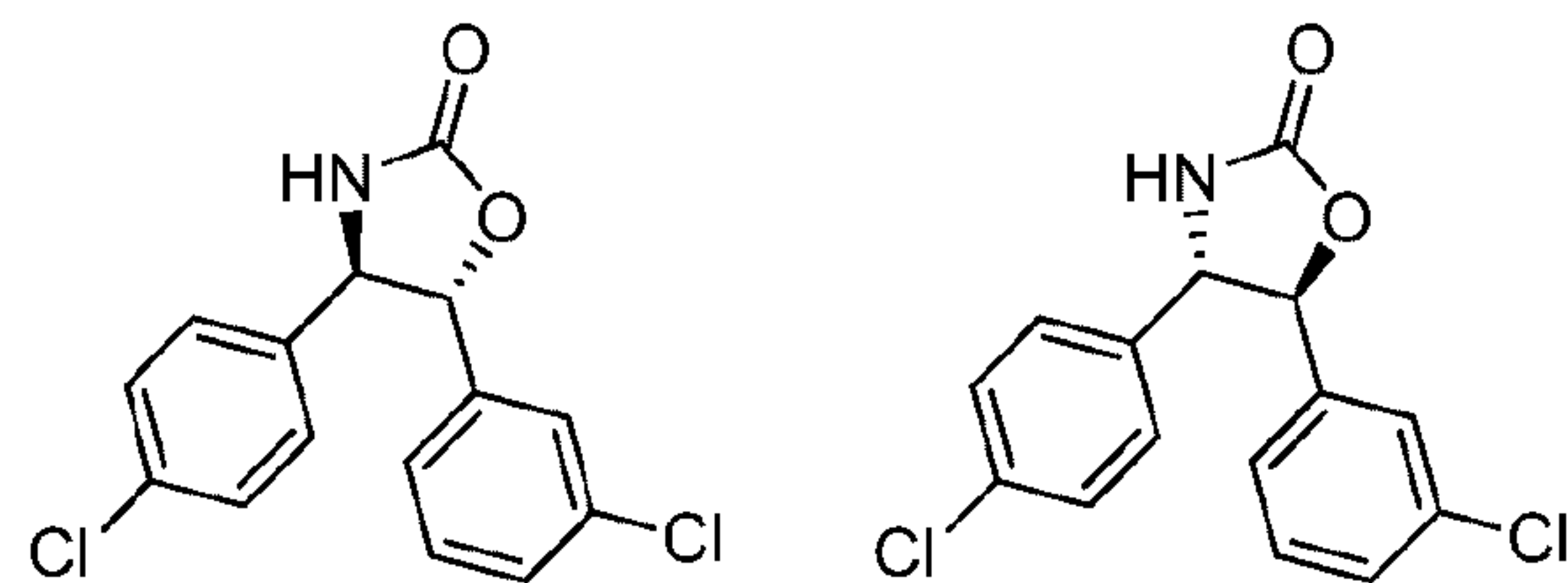
partitioned between EtOAc (200 mL) and water (50 mL). The separated aqueous layer was extracted with EtOAc (100 mL) and the combined organic extracts were washed with NaCl (50 mL, saturated aqueous solution), dried over MgSO₄, filtered and the filtrate was evaporated under a vacuum. Column chromatography on silica gel (80 g, hexanes / EtOAc 1:0 to 2:1, gradient elution) gave a racemic mixture of the title compounds as a white solid.

Step D. tert-Butyl ((1R,2S)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-hydroxyethyl)carbamate and tert-Butyl ((1S,2R)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-hydroxyethyl)carbamate



To a stirred solution of tert-butyl (2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-oxoethyl)carbamate (8.2 g, 22 mmol, Step C) in THF (100 mL) at 0 °C was added a suspension of sodium borohydride (0.82 g, 22 mmol) in THF (30 mL). The reaction was allowed to warm to r.t. for 3 hours. After this time the reaction was treated with EtOAc (300 mL) and NaHCO₃ (50 mL, sat. aq. solution). The separated organic layer was washed with NaCl (saturated aqueous solution, 50 mL), dried over MgSO₄, filtered and the filtrate was evaporated under a vacuum to give a mixture of the title compounds as a white solid.

Step E. (4R,5R)-5-(3-Chlorophenyl)-4-(4-chlorophenyl)oxazolidin-2-one and (4S,5S)-5-(3-Chlorophenyl)-4-(4-chlorophenyl)oxazolidin-2-one



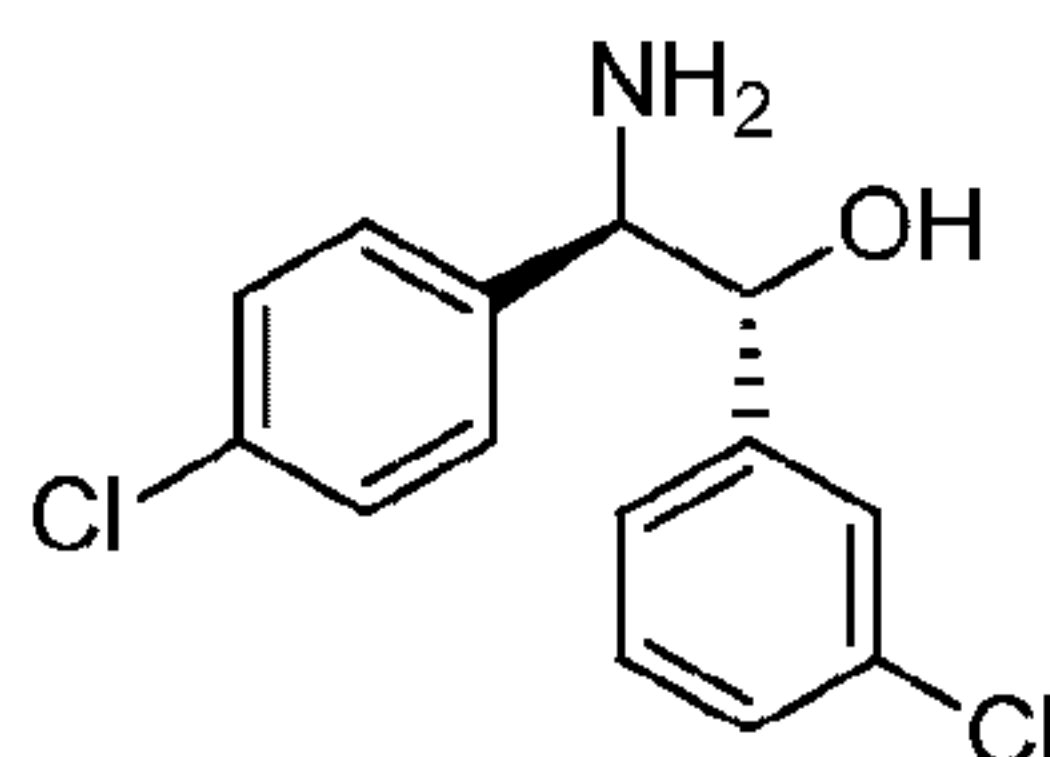
To a stirred solution of tert-butyl ((1R,2S)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-hydroxyethyl)carbamate and tert-butyl ((1S,2R)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-hydroxyethyl)carbamate (2.5 g, 6.54 mmol, Step D) in DCM (25 mL) at r.t. was added methane sulfonyl chloride (1.01 mL, 13.08 mmol) and DIEA (4.56 mL, 26.16 mmol) and the reaction was heated at 80 °C for 48 hours. After this time the reaction was cooled to r.t. and diluted with DCM (80 mL). The organic layer was washed with NaHCO₃ (saturated aqueous solution, 30 mL), NaCl (saturated aqueous solution, 30 mL), dried over MgSO₄, filtered and evaporated in vacuo. Column chromatography (40 g SiO₂, hexanes / EtOAc, 1:0 to 1:1, gradient elution) gave the title compounds as a white solid.

Step F. (1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol and (1S,2S)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol

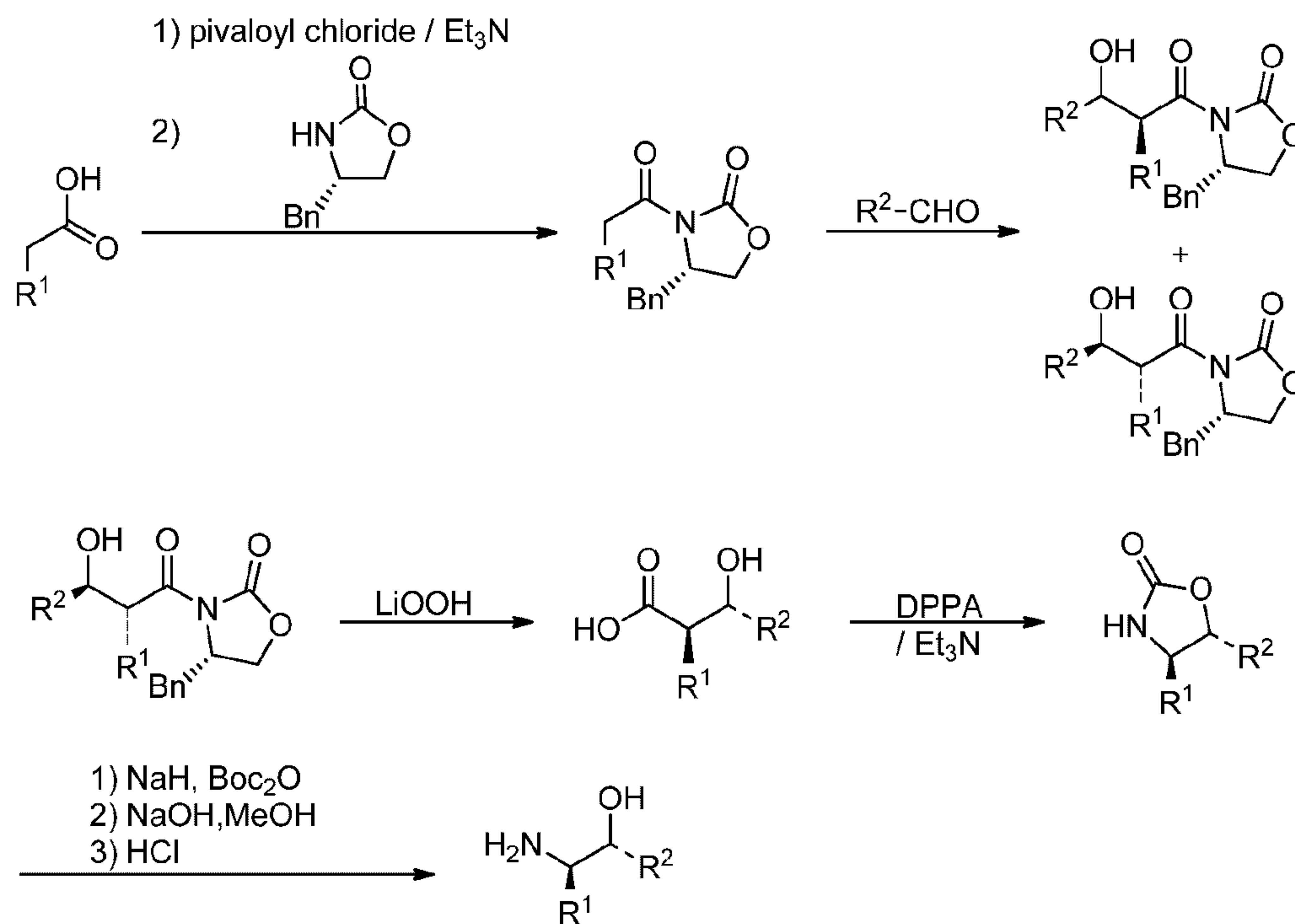
(4R,5R)-5-(3-chlorophenyl)-4-(4-chlorophenyl)oxazolidin-2-one and (4S,5S)-5-(3-chlorophenyl)-4-(4-chlorophenyl)oxazolidin-2-one (400 mg, 1.30 mmol, Step E) in water (10 mL) and acetone (10 mL) was treated with Cs₂CO₃ (4.23 g, 12.98 mmol) in a microwave vessel. The reaction was heated in a microwave reactor for 50 minutes to 200 °C. After this time the reaction mixture was concentrated and diluted with DCM (40 mL) and water (20 mL). The layers were separated and the organic layer was dried over MgSO₄, filtered and the filtrate was concentrated in vacuo. Column chromatography (12g SiO₂, EtOAc / hexanes, 1:0 to 1:1, gradient elution) gave the title compounds as a white solid. Mass Spectrum (ESI) m/z = 282.0 (M+H).

Intermediate A2

(1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol



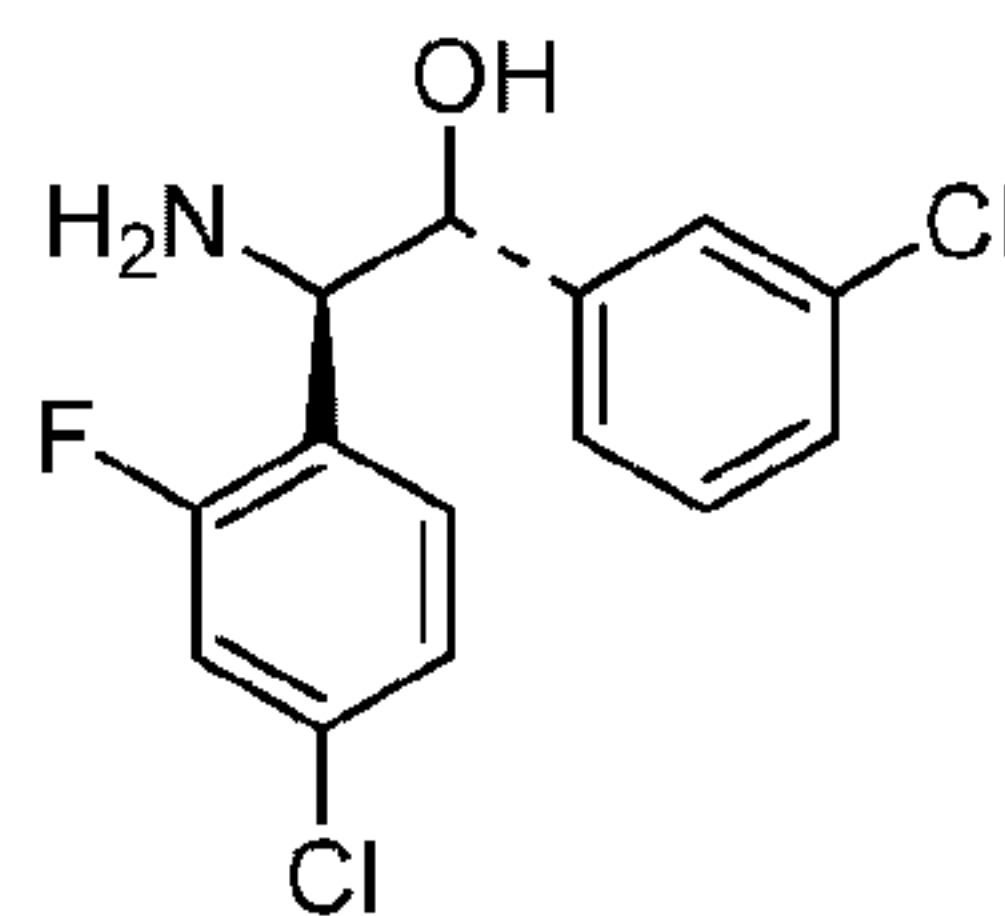
- A racemic mixture of (1R,2R)-2-amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol and (1S,2S)-2-amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol (57g, 0.2 mol; Intermediate A1) was dissolved in ethanol (2.65L) and (+)-di-p-toluoyl-D-tartaric acid (68.4 g, 0.169 mol) was added. The mixture was heated to reflux and water was added until the solution became clear (175 mL). The mixture was seeded with seeding crystals (ee 95%) and allowed to cool to rt over a period of 16 h. The mixture was filtered and the solid was washed with ethanol and dried to give the salt, ee. 75%. This salt was recrystallized twice from 12.5:1 EtOH / water (36 mL/gram of salt) using seed crystals to initialize crystallization to provide the salt with 97.6% ee. The salt was dissolved in 1:1 EtOAc / 2 N aq. NaOH. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to give the title compound with 97.8% ee. Enantiomeric excess was determined by HPLC using a Chiralpak[®] AD-H column (Chiral Technologies, Inc., West Chester, PA) and eluting with 5% IPA/hexanes.
- $R_t = 20.1$ min. $[\alpha]_D^{23.5} = +92.7^\circ$ (c = 0.385, in MeOH).
- (1S,2S)-2-amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol: $R_t = 21.7$ min.

General Procedure 3

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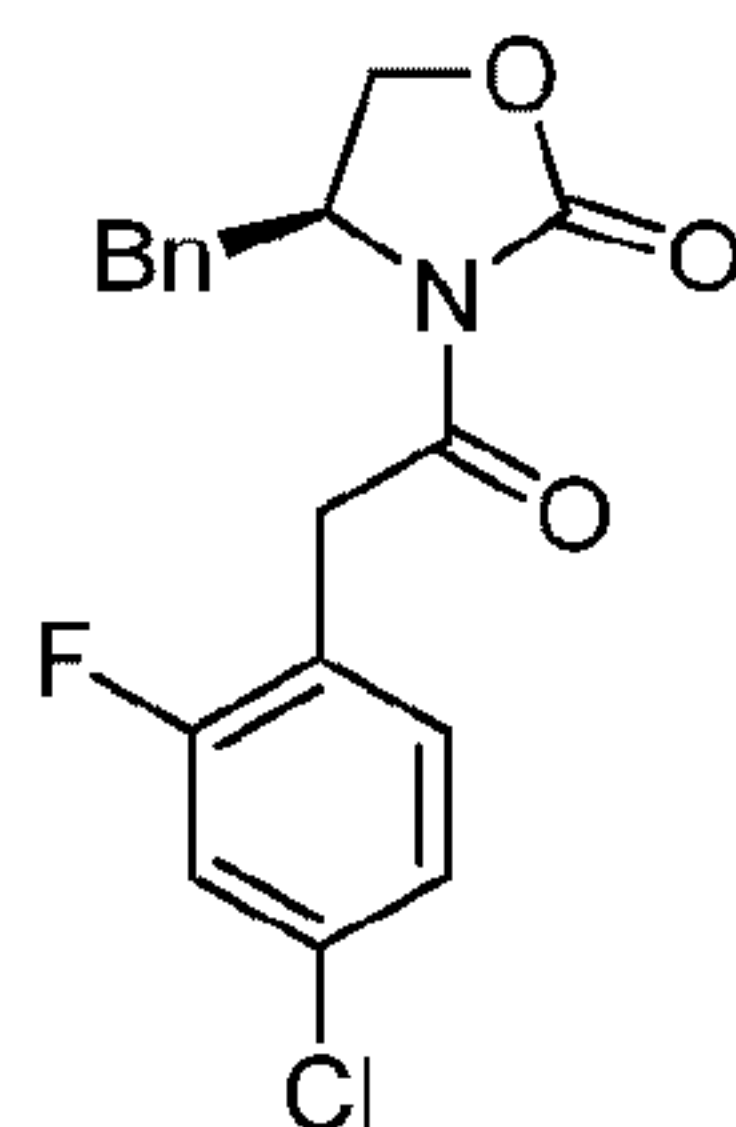
Intermediate B1

(1R,2R)-2-Amino-2-(4-chloro-2-fluorophenyl)-1-(3-chlorophenyl)ethanol



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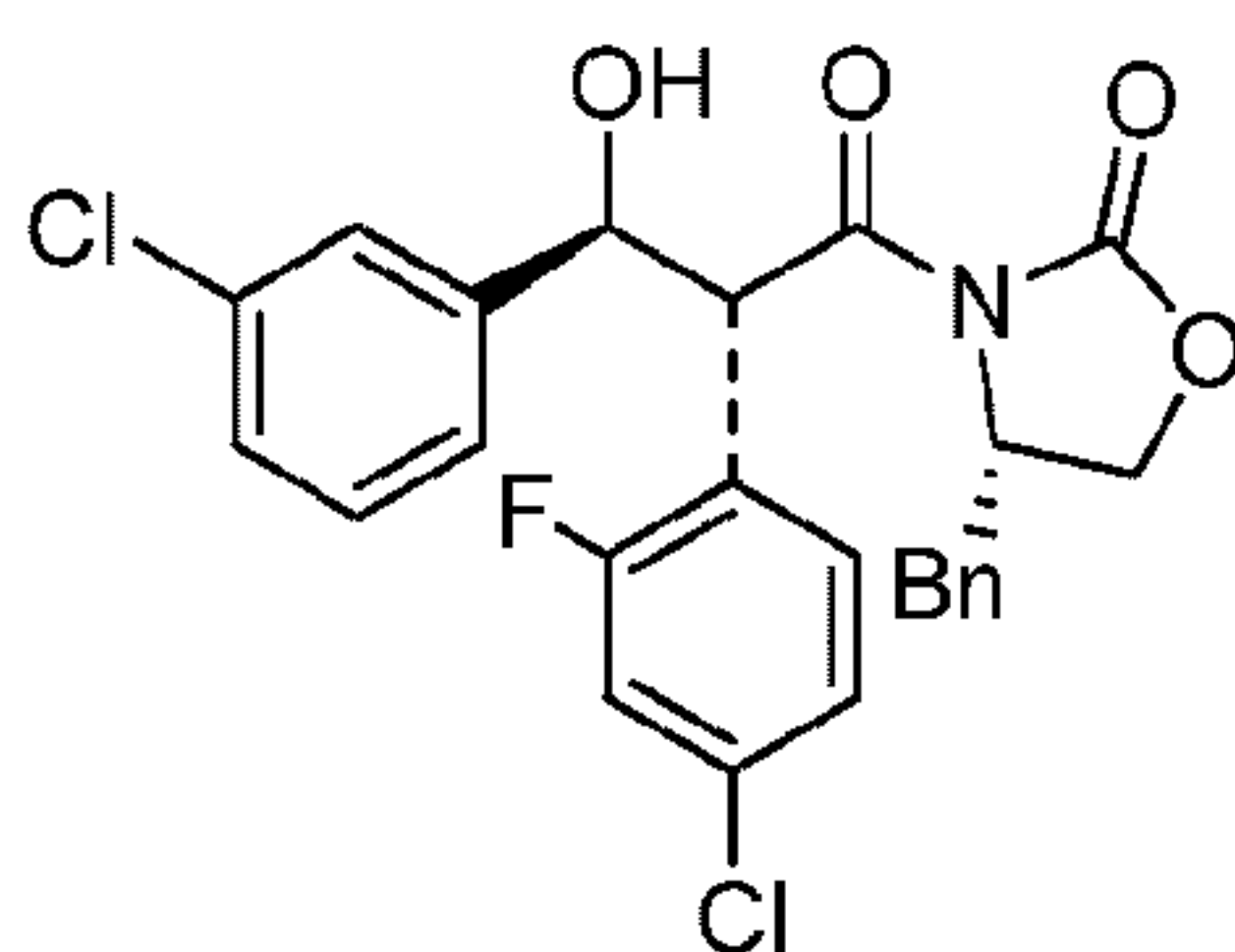
Step A. (S)-4-Benzyl-3-(2-(4-chloro-2-fluorophenyl)acetyl)oxazolidin-2-one



(S)-4-Benzylloxazolidin-2-one (4.68 g, 26.4 mmol), 2-(4-chloro-2-fluorophenyl)acetic acid (7.47 g, 39.6 mmol), and triethylamine (11.04 mL, 79 mmol) were dissolved in 50 mL of toluene and the mixture was heated to 80 °C. Then pivaloyl chloride (4.9 mL, 39.6 mmol) in 10 mL of toluene was added while the internal temp was maintained between 80 °C and 85 °C. The reaction mixture was heated to reflux for 18 h, cooled to room temperature and was washed with 2 N hydrochloric acid, 5% aqueous sodium carbonate, and brine. The organic layer was concentrated and the crude product was triturated with hexane. The title compound was filtered off as a white solid.

¹H NMR (400 MHz, CDCl₃) δ ppm 2.77 - 2.86 (m, 1 H) 3.31 (dd, *J*=13.30, 3.13 Hz, 1 H) 4.21 - 4.37 (m, 4 H) 4.66 - 4.74 (m, 1 H) 7.13 - 7.23 (m, 5 H) 7.28 - 7.37 (m, 3 H).

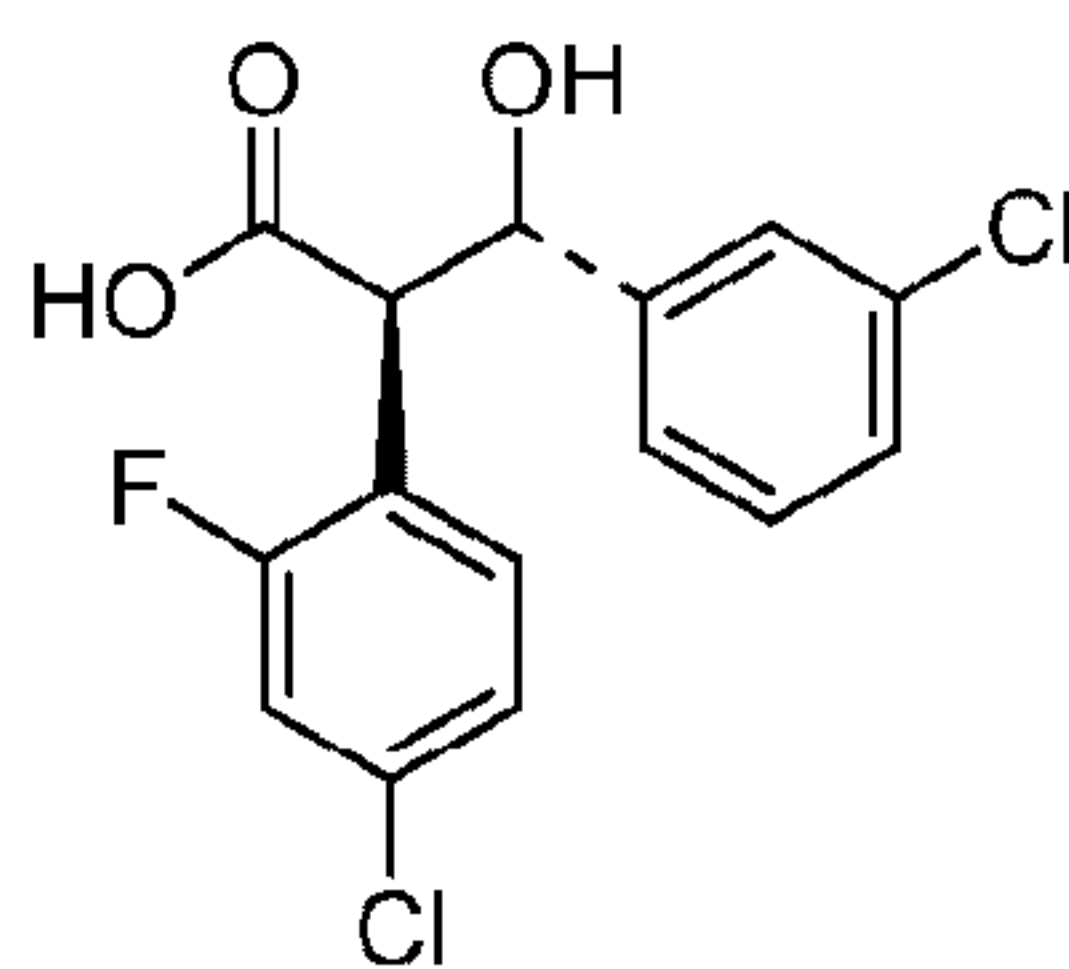
Step B. (S)-4-Benzyl-3-((2R,3S)-2-(4-chloro-2-fluorophenyl)-3-(3-chlorophenyl)-3-hydroxypropanoyl)oxazolidin-2-one



To a stirred solution of (S)-4-benzyl-3-(2-(4-chloro-2-fluorophenyl)acetyl)oxazolidin-2-one (12 g, 35 mmol, Step A), 3-chlorobenzaldehyde (7.8 g, 55 mmol), chlorotrimethylsilane (11 g, 104 mmol) and magnesium chloride (0.66 g, 6.9 mmol) in 80 mL of EtOAc under nitrogen, was added dropwise a solution of

triethylamine (14 g, 138 mmol) in 20 mL of EtOAc. The reaction mixture was stirred overnight and then 200 mL of sat. aq. NH_4Cl solution and 100 mL of EtOAc were added. The organic layer was washed with brine, dried over MgSO_4 and concentrated. Next, the crude product was dissolved in 100 mL of DCM, and 15 mL of 4N HCl/dioxane, diluted to 50 mL with DCM, was added dropwise. After the removal of the silyl group was complete (less than 2h), the reaction mixture was quenched by portionwise addition of 200 mL of a sat. aq. NaHCO_3 solution. The organic layer was separated, washed with brine, dried over MgSO_4 , filtered and the filtrate was concentrated *in vacuo* to give the crude product. Purification via silica gel chromatography employing a gradient of ethyl acetate in hexane yielded the desired product in the slower-eluting fraction. ^1H NMR (400 MHz, CDCl_3) δ ppm 2.81 (dd, $J=13.50$, 9.00 Hz, 1 H) 3.27 (dd, $J=13.60$, 3.42 Hz, 1 H) 3.36 (d, $J=6.46$ Hz, 1 H) 4.13 (d, $J=7.04$ Hz, 1 H) 4.65 - 4.73 (m, 1 H) 5.19 - 5.26 (m, 1 H) 5.65 (d, $J=8.02$ Hz, 1 H) 6.96 (dd, $J=9.78$, 2.15 Hz, 1 H), 7.00 - 7.04 (m, 11H). Mass Spectrum (ESI) m/z = 470.0 (M-18).

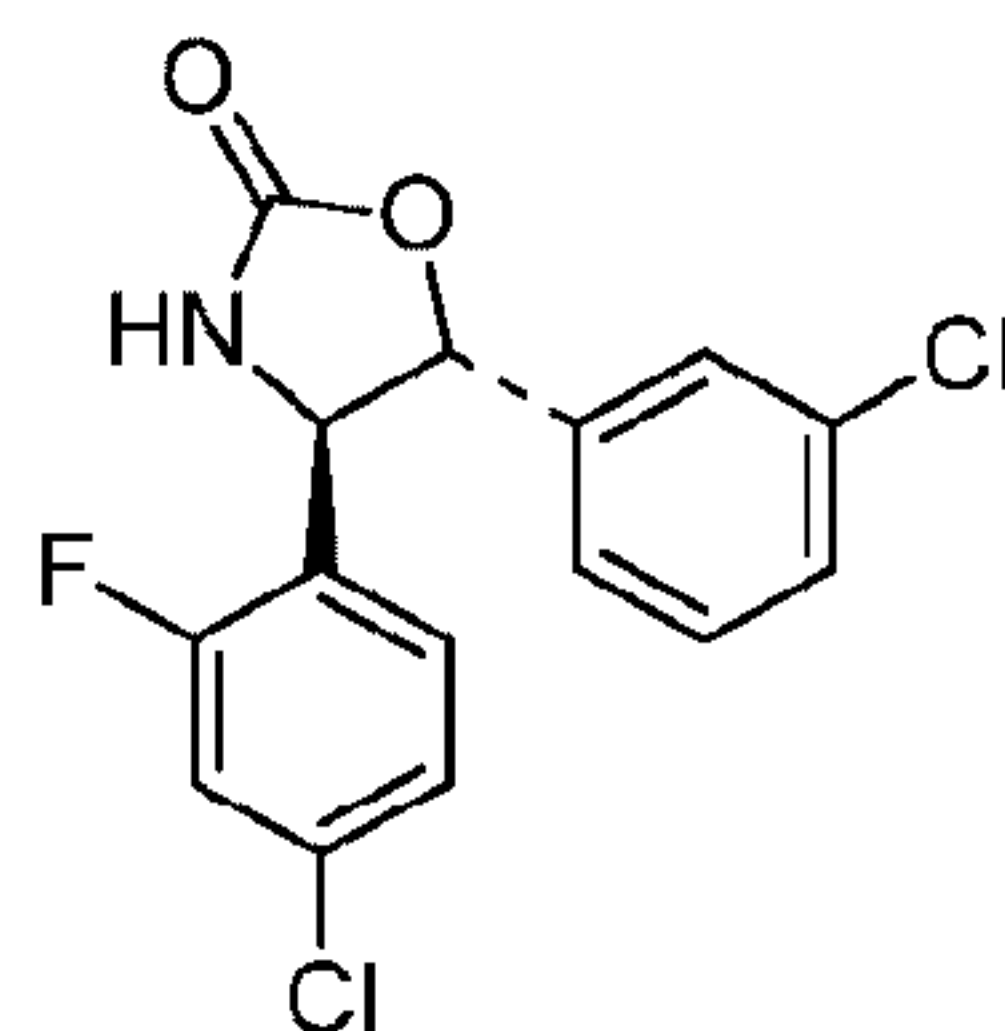
Step C. (2R,3S)-2-(4-Chloro-2-fluorophenyl)-3-(3-chlorophenyl)-3-hydroxypropanoic acid



(S)-4-Benzyl-3-((2R,3S)-2-(4-chloro-2-fluorophenyl)-3-(3-chlorophenyl)-3-hydroxypropanoyl)oxazolidin-2-one (7.19g, 15 mmol, Step B) and hydrogen peroxide (8.6g, 88 mmol) were combined in 125 mL of THF and cooled in an ice bath. A solution of LiOH (0.71g, 15 mmol) in 10 mL of water was added dropwise over 10 minutes. After 25 minutes the reaction mixture was removed from the ice bath, concentrated and redissolved in 200 mL of DCM and 200 mL of a citric acid/sodium sulfite solution. The organic layer was separated and the aqueous phase was extracted with 200 mL of DCM. The combined organic layers were dried over MgSO_4 , filtered and the filtrate was

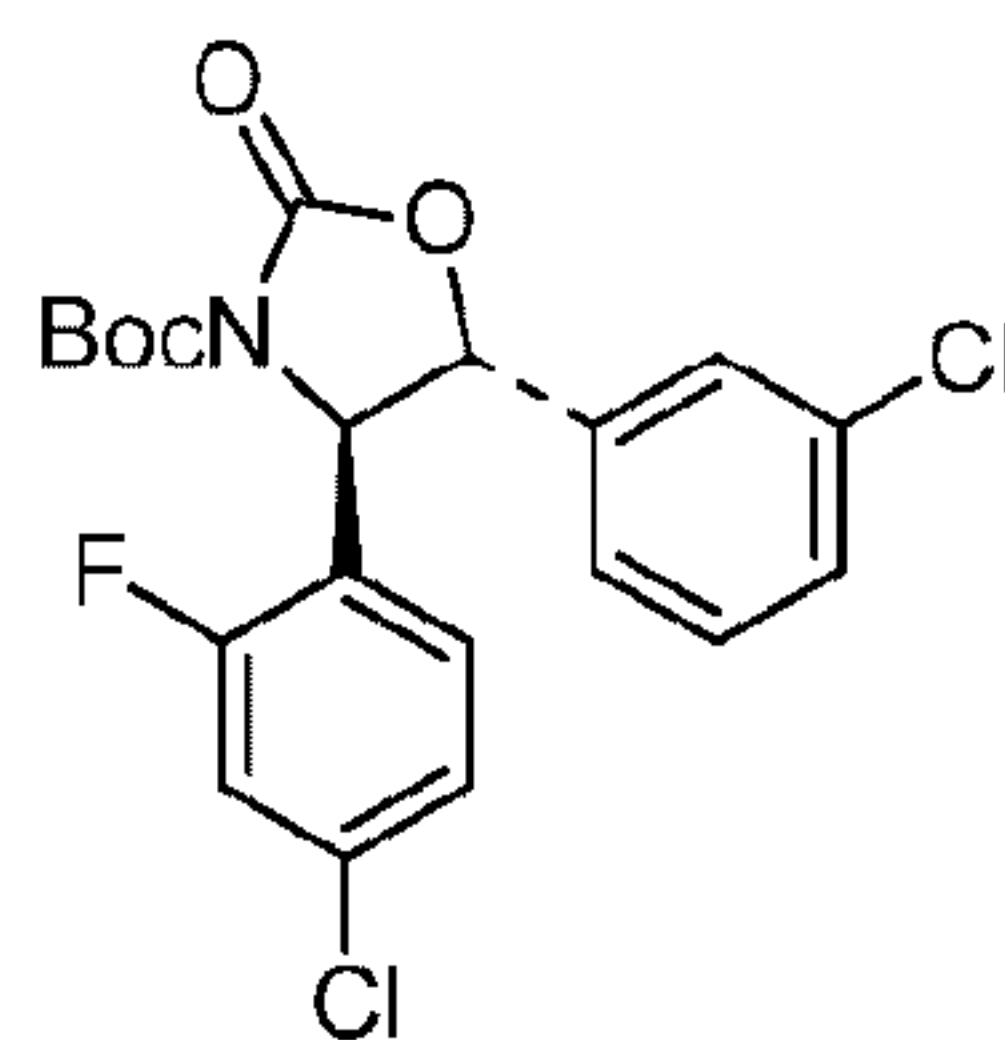
concentrated. The crude product was purified by chromatography on silica gel (gradient ranging from 0 to 40% ethyl acetate in hexane, 0.1% v/v AcOH in all solvents). ¹H NMR (400 MHz, CDCl₃) δ ppm 4.20 (d, *J*=9.19 Hz, 1 H) 5.18 (d, *J*=9.00 Hz, 1 H) 6.95 – 7.00 (m, 2 H) 7.04 (dd, *J*=8.41, 1.96 Hz, 1 H) 7.10 – 7.24 (m, 4 H). Mass Spectrum (ESI) *m/z* = 346.0 (M+18).

Step D. (4R,5R)-4-(4-Chloro-2-fluorophenyl)-5-(3-chlorophenyl)oxazolidin-2-one



To a solution of (2R,3S)-2-(4-chloro-2-fluorophenyl)-3-(3-chlorophenyl)-3-hydroxypropanoic acid (1.24g, 3.8 mmol, Step C) in 50 mL of toluene was added triethylamine (0.42 g, 4.1 mmol). The reaction mixture was heated to 40 °C in an oil bath, after which DPPA (diphenylphosphoryl azide, 1.1 g, 4.1 mmol) was added. The reaction was then heated to 85 °C overnight to give the product which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ ppm 5.04 (d, *J*=5.7 Hz, 1 H) 5.32 (d, *J*=5.7 Hz, 1 H) 5.89 (s, 1 H) 7.18 (dd, *J*=10.1, 2.1 Hz, 2 H) 7.21 - 7.26 (m, 1 H) 7.36 (s, 1 H) 7.38 - 7.41 (m, 3 H) 7.42 - 7.50 (m, 2 H) 7.46 (t, *J*=8.1 Hz, 5 H). Mass Spectrum (ESI) *m/z* = 326.0 (M+1).

Step E. (4R,5R)-*tert*-Butyl 4-(4-chloro-2-fluorophenyl)-5-(3-chlorophenyl)-2-oxooxazolidine-3-carboxylate

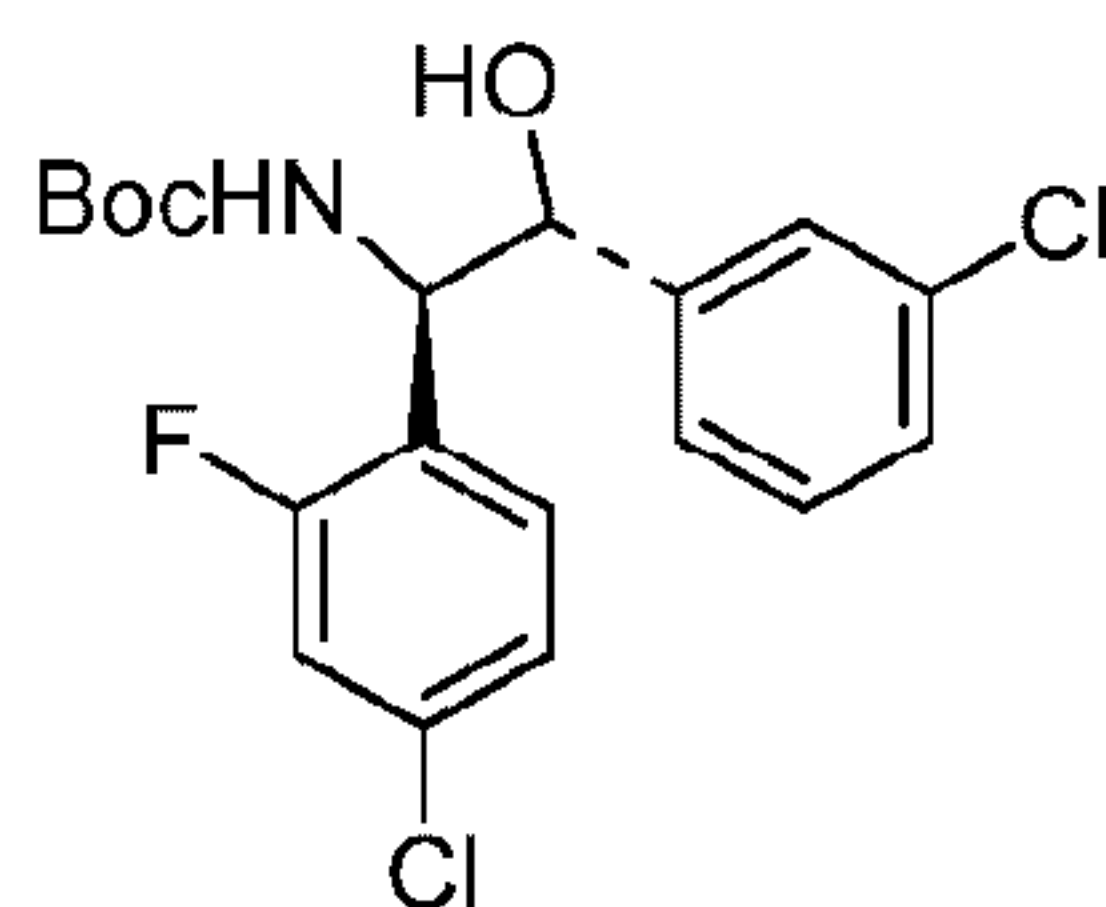


To (4R,5R)-4-(4-chloro-2-fluorophenyl)-5-(3-chlorophenyl)oxazolidin-2-one (0.38g, 1.2 mmol, Step D) was added 8 mL of THF followed by sodium hydride (60% dispersion in mineral oil, 0.23g, 5.9 mmol). The reaction mixture was stirred for one hour at room temperature, then di-tert-butyl dicarbonate (0.31g, 1.4 mmol) was added. After
 5 the reaction mixture was stirred at room temperature for an additional hour, the mixture was quenched with 20% aq. citric acid solution. The organic layers were extracted with EtOAc and the combined organic layers were dried over MgSO₄, filtered and the filtrate was concentrated under reduced pressure.

Mass Spectrum (ESI) $m/z = 450.0$ (M+23).

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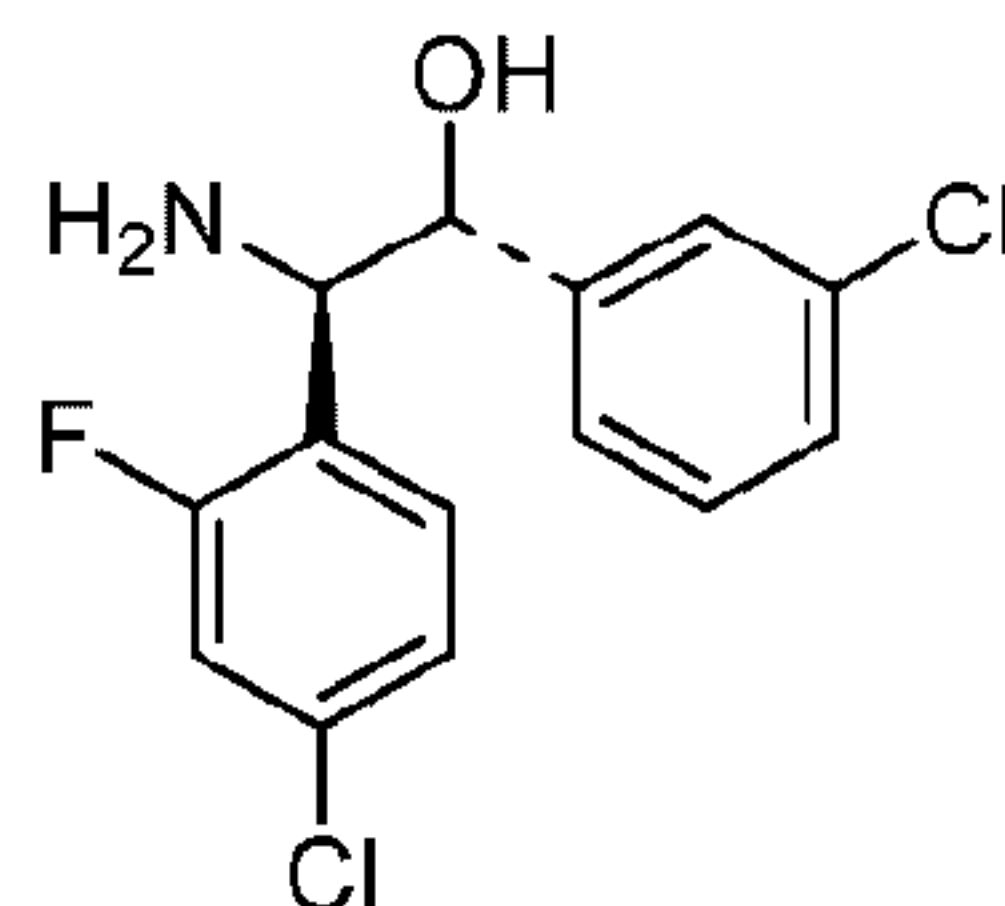
Step F. *tert*-Butyl ((1R,2R)-1-(4-chloro-2-fluorophenyl)-2-(3-chlorophenyl)-2-hydroxyethyl)carbamate



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To (4R,5R)-*tert*-butyl 4-(4-chloro-2-fluorophenyl)-5-(3-chlorophenyl)-2-oxooxazolidine-3-carboxylate (0.38g, 1.2 mmol) from Step E above was added 10 mL MeOH followed by NaOH (0.23g, 5.9 mmol, dissolved in 5 mL of H₂O) and the reaction was left to stir at room temperature for 2 hours. The reaction mixture was transferred to a separatory funnel, the mixture was extracted with DCM (3 x 100 mL), the organic
 20 layers were combined, dried over MgSO₄, filtered and the filtrate was concentrated under reduced pressure to give the title compound which was used in the next step without further purification.

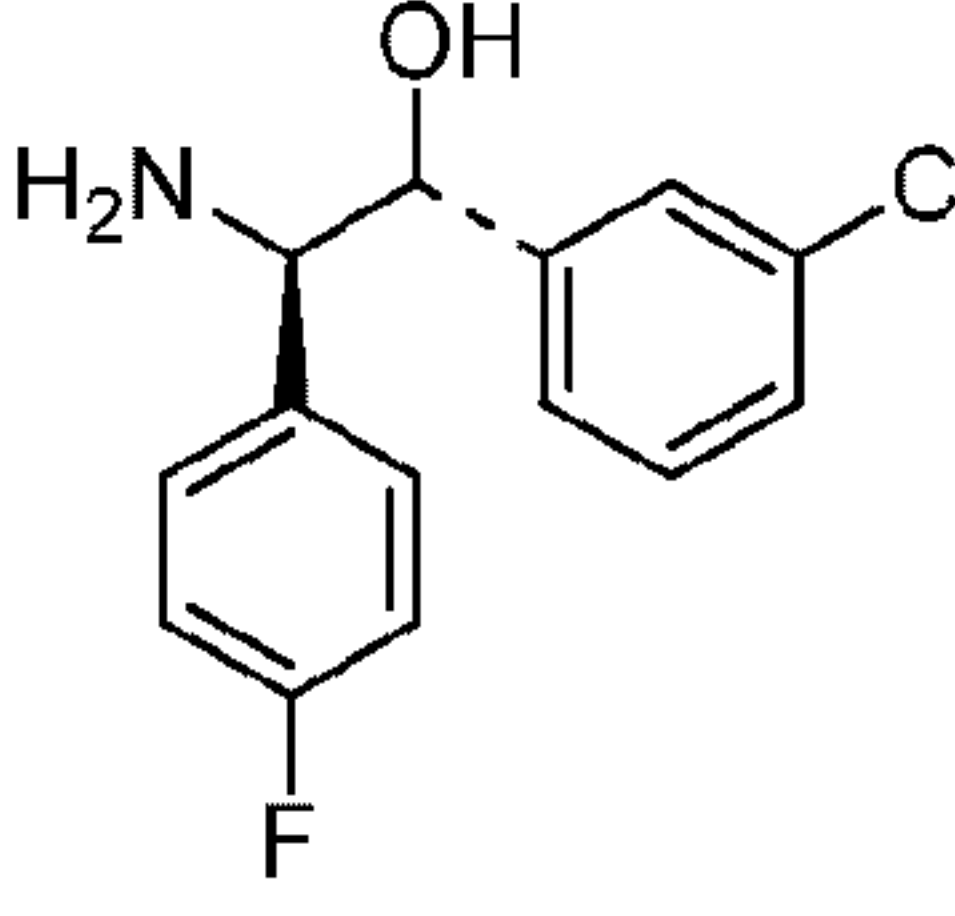
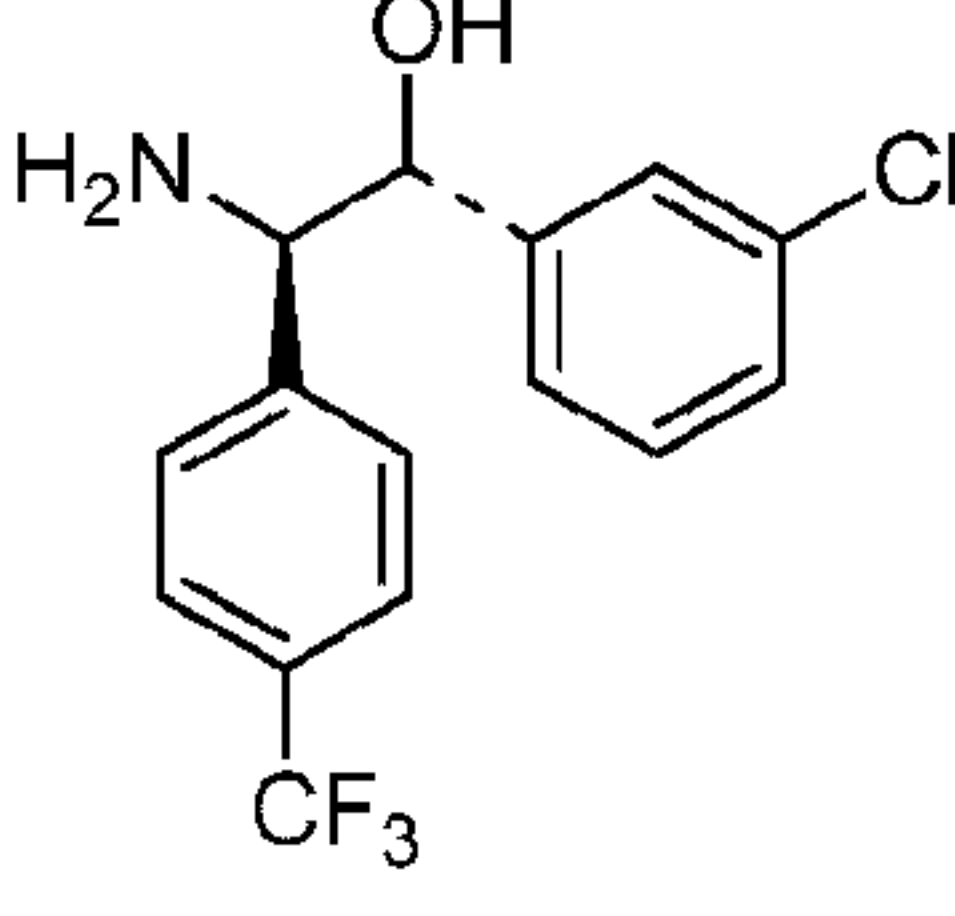
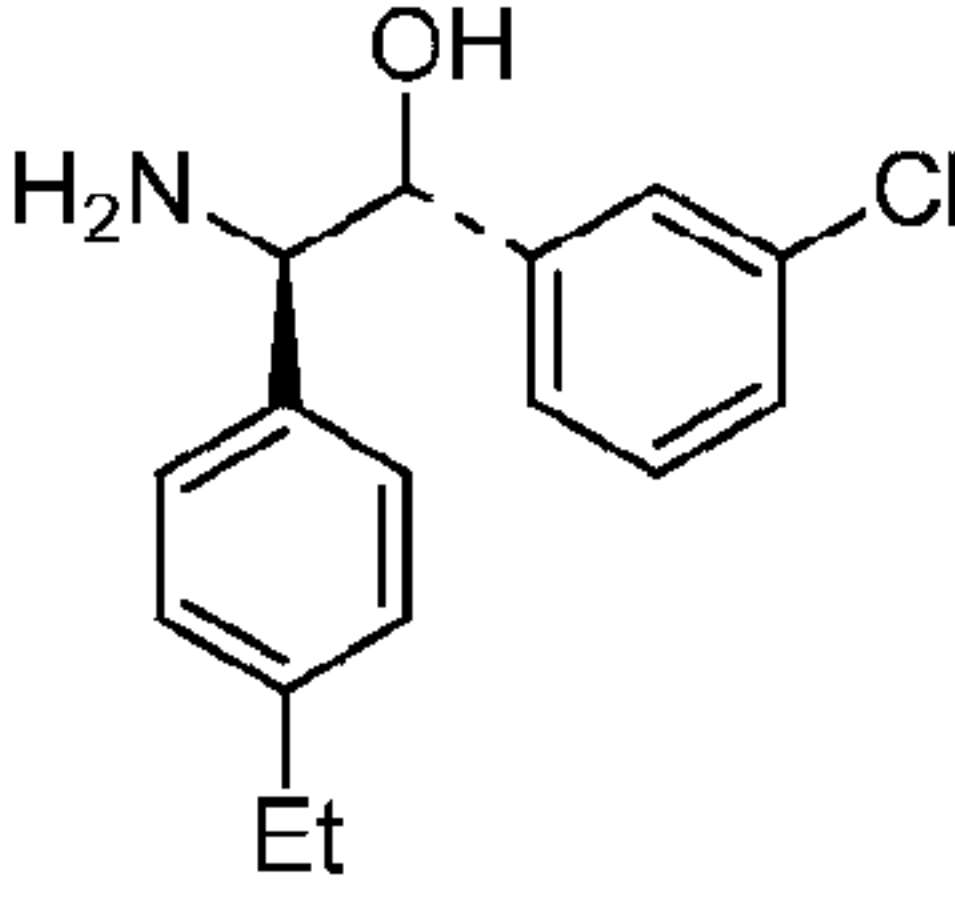
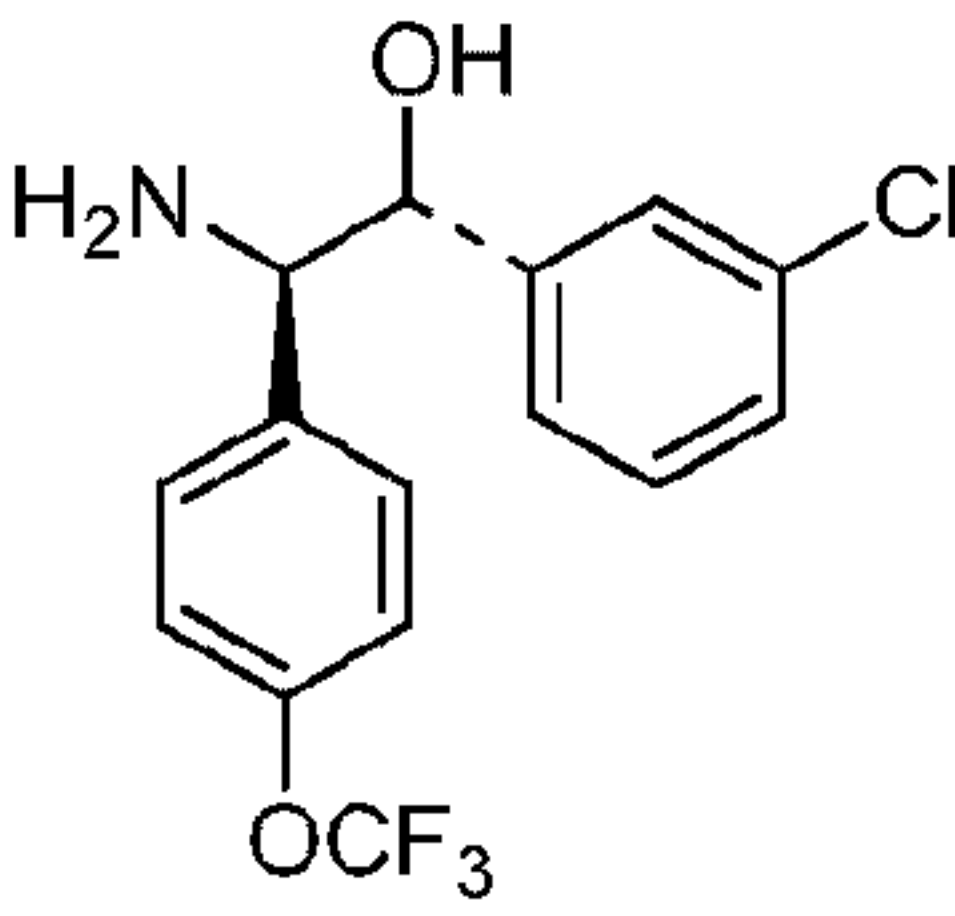
Step G. (1R,2R)-2-Amino-2-(4-chloro-2-fluorophenyl)-1-(3-chlorophenyl)ethanol



tert-Butyl (1R,2R)-1-(4-chloro-2-fluorophenyl)-2-(3-chlorophenyl)-2-hydroxyethylcarbamate (0.165 g, 0.41 mmol) from Step E above was dissolved in 6 mL of 4.0 M HCl in dioxane. The reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure. To the residue was added saturated aq. sodium bicarbonate solution followed by EtOAc. The mixture was filtered through an unbuffered 5 mL Chem ElutTM cartridge (Agilent technologies, Santa Clara, CA) and washed with ethyl acetate. Concentration of the organic filtrate under reduced pressure gave the title compound as a white solid. Mass Spectrum (ESI) $m/z = 300.1$ (M+1).

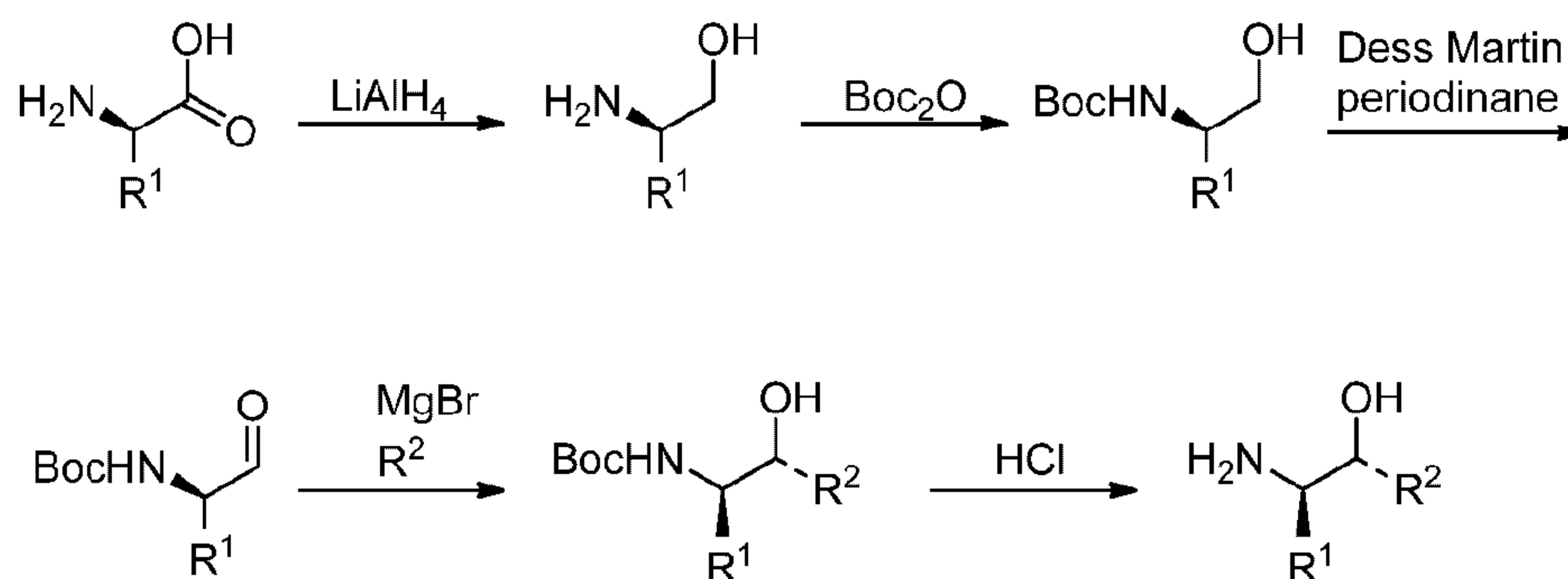
The following intermediates B2 – B8 were also prepared by a procedure analogous to the one described above, substituting 2-(4-chloro-2-fluorophenyl)acetic acid in Step A for the appropriate carboxylic acid:

Intermediate	Structure	Name	Characterization
B2		(1R,2R)-2-Amino-1-(3-chlorophenyl)-2-phenylethanol	MS 248.1 (M+1). ¹ H NMR (400 MHz, CDCl ₃) δ ppm 2.74 (3 H, br. s.), 3.97 (1 H, d, $J=6.8$ Hz), 4.65 (1 H, d, $J=6.6$ Hz), 6.99 (1 H, d, $J=7.6$ Hz), 7.10 - 7.33 (8 H, m).

B3		(1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(4-fluorophenyl)ethanol	MS 266.0 (M+1). ¹ H NMR (400 MHz, <i>CDCl</i> ₃) δ ppm 2.60 (3 H, br. s.), 3.98 (1 H, d, <i>J</i> =6.6 Hz), 4.60 (1 H, d, <i>J</i> =6.6 Hz) 6.93 - 7.00 (3 H, m), 7.12 - 7.29 (5 H, m).
B4		(1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(4-(trifluoromethyl)phenyl)ethanol	MS 316.0 (M+1). ¹ H NMR (400 MHz, <i>DMSO D</i> ₆) δ ppm 2.11 (3 H, br. s.), 4.58 (1 H, d, <i>J</i> =4.6 Hz), 5.64 (1 H, br. s.) 7.07 - 7.11 (1 H, m), 7.18 - 7.24 (3 H, m), 7.43 (2 H, d, <i>J</i> =8.1 Hz), 7.56 (2 H, d, <i>J</i> =8.3 Hz).
B5		(1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(4-ethylphenyl)ethanol	MS 276.1 (M+1). ¹ H NMR (400 MHz, <i>CDCl</i> ₃) δ ppm 1.37 (3 H, t, <i>J</i> =7.6 Hz), 2.77 (2 H, q, <i>J</i> =7.6 Hz), 3.62 (3 H, br. s.), 4.17 (1 H, d, <i>J</i> =6.8 Hz), 4.86 (1 H, d, <i>J</i> =6.8 Hz) 7.16 (1 H, d, <i>J</i> =7.3 Hz), 7.25 - 7.55 (7 H, m).
B6		(1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(4-(trifluoromethoxy)phenyl)ethanol	MS 332.0 (M+1). ¹ H NMR (400 MHz, <i>CDCl</i> ₃) δ ppm 2.84 (3 H, br. s.), 3.99 (1 H, d, <i>J</i> =6.4 Hz), 4.60 (1 H, d, <i>J</i> =6.6 Hz) 6.95 (1 H, d, <i>J</i> =7.3), 7.10 - 7.40 (7 H, m).

B7		(1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(<i>p</i> -tolyl) ethanol	MS 262.1 (M+1). ¹ H NMR (400 MHz, <i>DMSO-D</i> ₆) δ ppm 1.98 (2 H, br. s.), 2.22 (3 H, s.), 3.81 (1 H, d, <i>J</i> =6.8 Hz), 4.47 (1 H, d, <i>J</i> =6.3 Hz) 5.56 (1 H, br. s.), 6.96 - 7.06 (5 H, m), 7.13 - 7.20 (3 H, m).
B8		(1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(4-isopropylphenyl) ethanol	MS 290.0 (M+1). ¹ H NMR (400 MHz, <i>CDCl</i> ₃) δ ppm 1.23 (6 H, d, <i>J</i> =6.8 Hz), 2.88 (1 H, m), 4.00 (1 H, d, <i>J</i> =6.6 Hz), 4.68 (1 H, d, <i>J</i> =6.6 Hz), 7.04 (1 H, d, <i>J</i> =7.1 Hz), 7.10 - 7.39 (7 H, m).

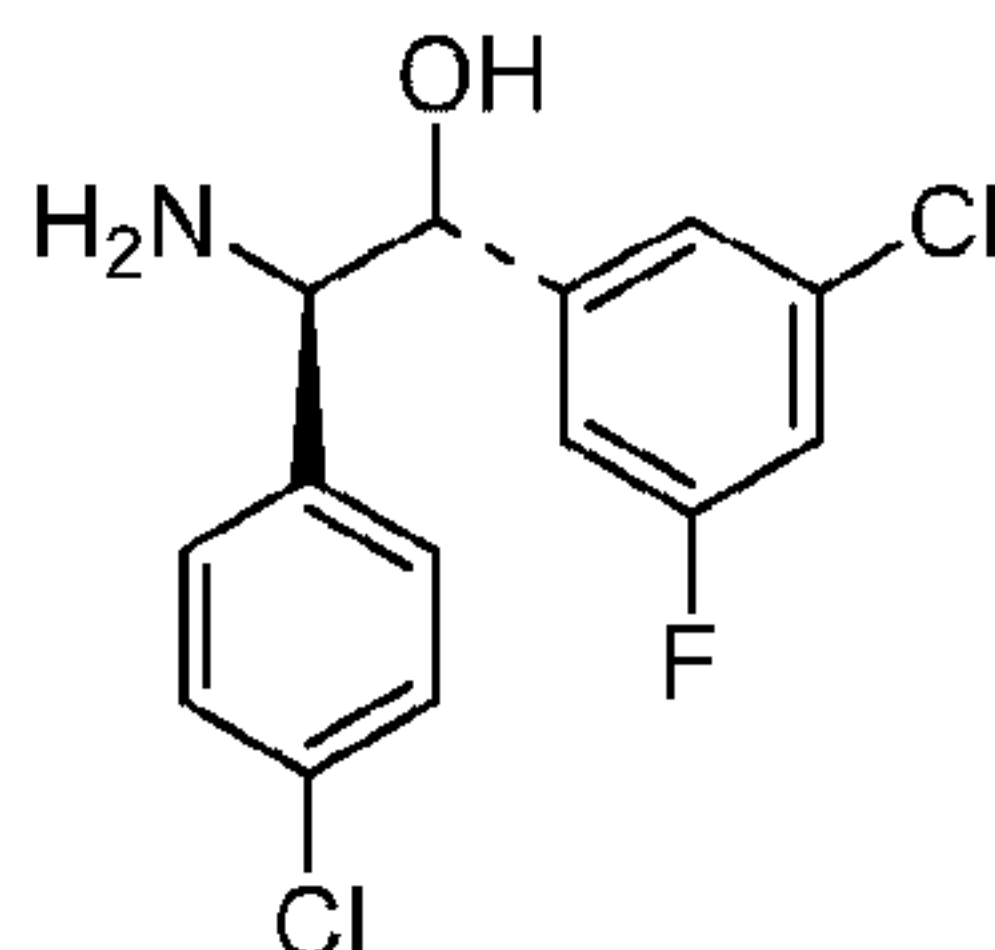
General Procedure 4



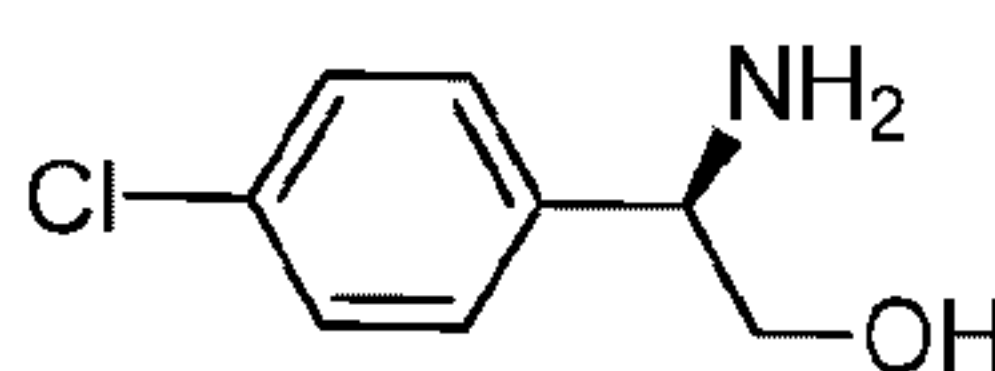
5

Intermediate C1

(1R,2R)-2-Amino-1-(3-chloro-5-fluorophenyl)-2-(4-chlorophenyl)ethanol



Step A. (R)-2-Amino-2-(4-chlorophenyl)ethanol

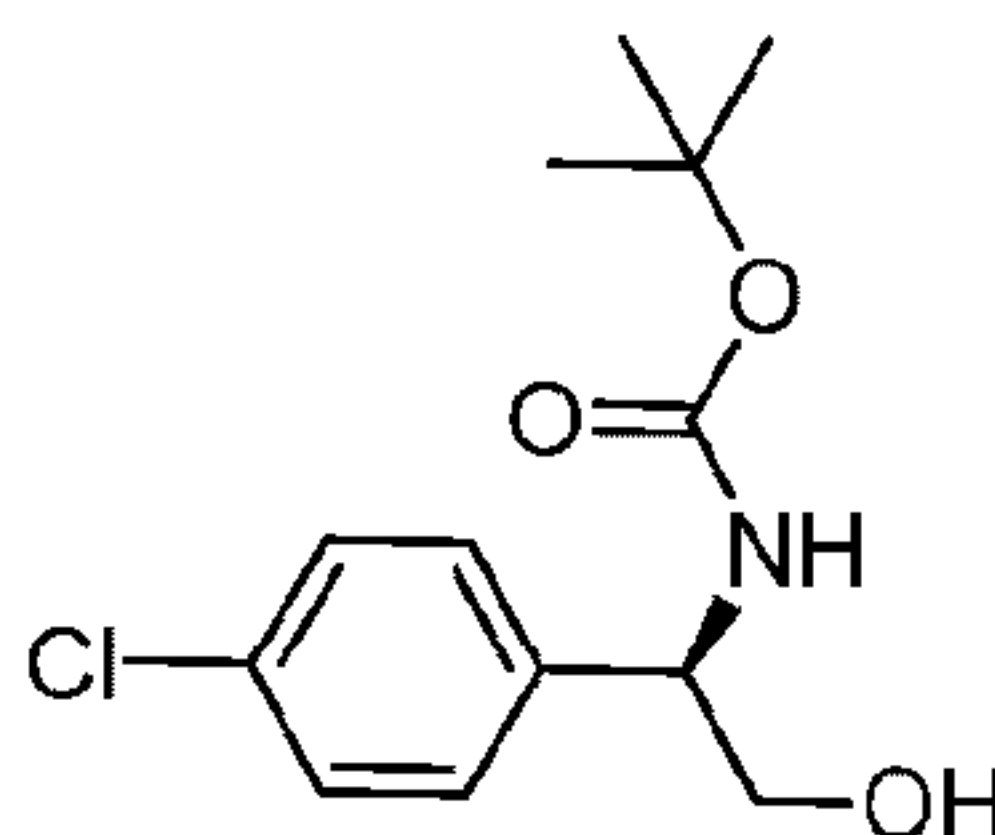


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A solution of 1.0M LiAlH₄ in THF was diluted with 460 mL anhydrous THF and was heated to 75 °C under a nitrogen atmosphere. (R)-2-Amino-2-(4-chlorophenyl)acetic acid (25.0 g, 135 mmol; Asta Tech, Inc., Bristol, PA) was added in several portions. The reaction mixture was heated to reflux for about 3 hours, cooled to room temperature and quenched by adding water (8.0 mL), aq. 15% NaOH (8.0 mL) and water (25.6 mL), successively. The mixture was stirred vigorously for 30 minutes. The solids were filtered off, rinsed with THF and the combined organics were concentrated *in vacuo* to provide the desired product as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.59 (br. s., 2 H) 2.48 (br. s., 1 H) 3.53 (dd, *J*=10.56, 8.02 Hz, 1 H) 3.69 - 3.78 (m, 1 H) 4.05 (br. s., 1 H) 7.29 (m, 2 H) 7.31 - 7.35 (m, 2 H). Mass Spectrum (CI⁺) *m/z* = 172.0 (M+1).

15

Step B. (R)-*tert*-Butyl 1-(4-chlorophenyl)-2-hydroxyethylcarbamate



20

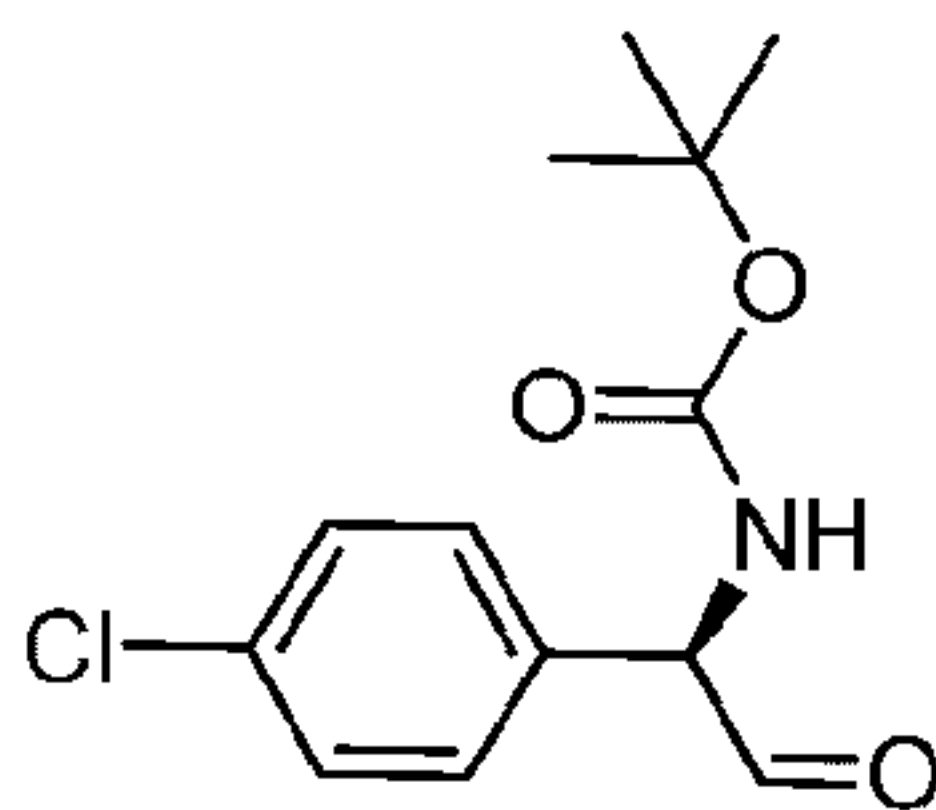
A solution of di-*tert*-butyl dicarbonate (36.6 g, 168 mmol) in DCM (50 mL) was added dropwise to a solution of (R)-2-amino-2-(4-chlorophenyl)ethanol (23.01 g, 134

mmol, Step A) in DCM (200 mL) at 0 °C. After the addition was completed, the ice bath was removed and the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated *in vacuo* and the crude material was triturated with 10% DCM / hexane (850 mL) to provide the title compound as a white powder.

- 5 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.36 (s, 9 H) 3.41 - 3.52 (m, 2 H) 4.43 - 4.56 (m, 1 H) 4.75 - 4.84 (m, 1 H) 7.24 (d, *J*=8.02 Hz, 1 H) 7.27 - 7.32 (m, 2 H) 7.33 - 7.39 (m, 2 H). Mass Spectrum (CI+) *m/e* = 565.0 (2M⁺ + 23).

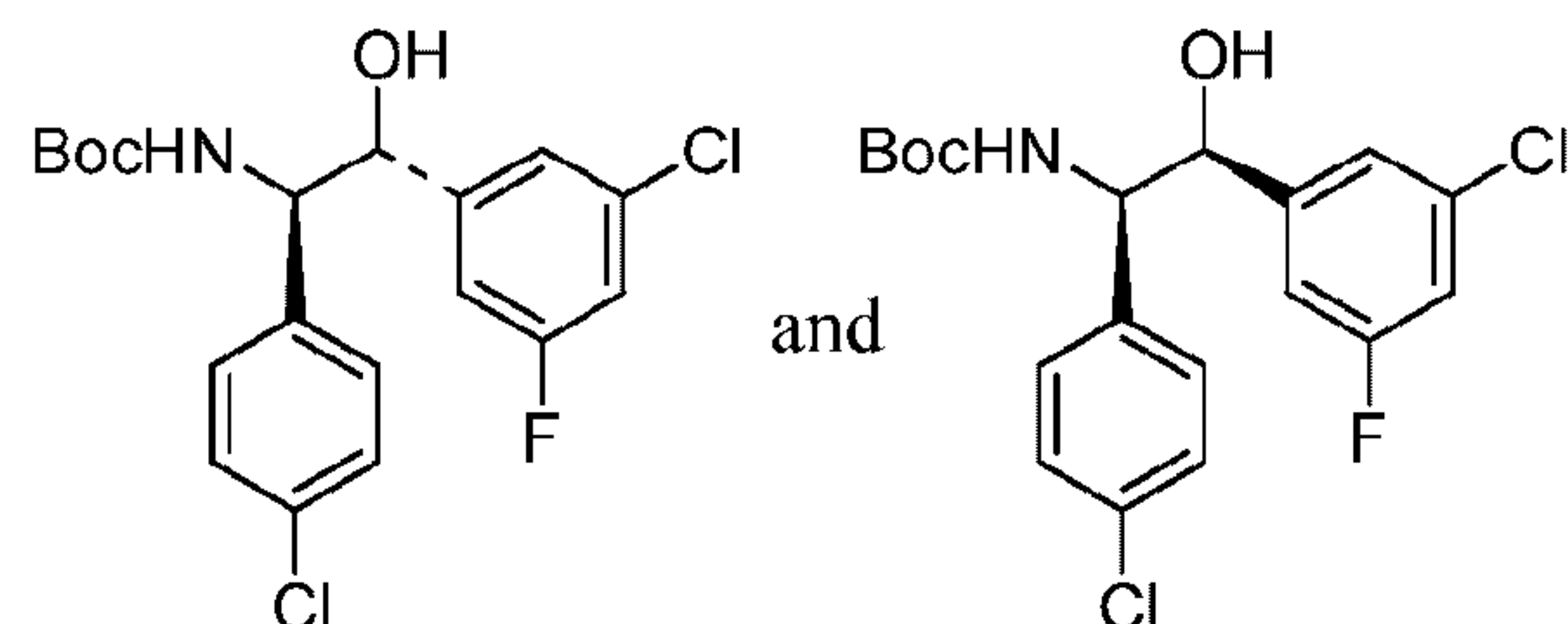
Step C. (R)-*tert*-Butyl 1-(4-chlorophenyl)-2-oxoethylcarbamate

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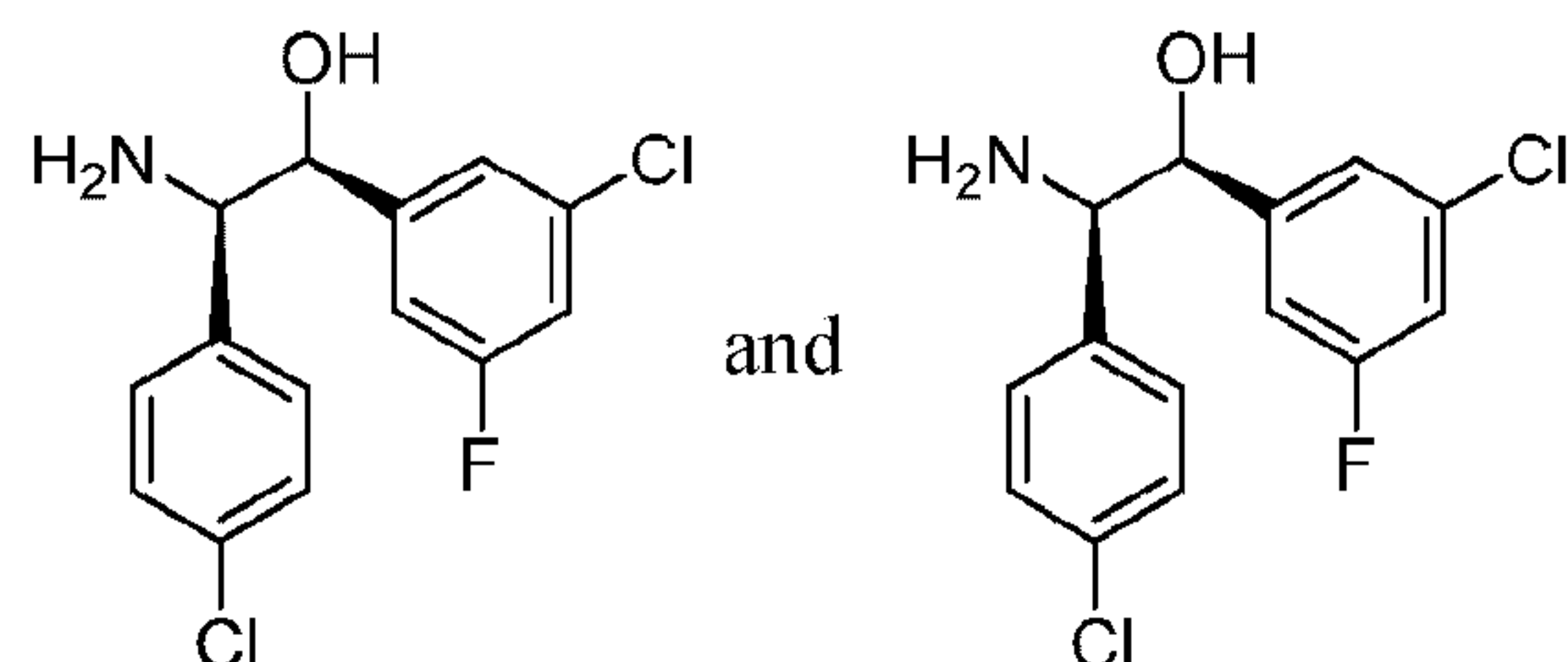
- 1,1,1,-Tris(acetoxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)one ("Dess Martin periodinane") (17.42 g, 41.1 mmol) was added in several portions to a stirred suspension of (R)-*tert*-butyl 1-(4-chlorophenyl)-2-hydroxyethylcarbamate (5.58 g, 20.53 mmol) in wet DCM (40 mL DCM/ 40 μL water) at room temperature. The reaction was stirred for 2 hours, diluted with diethyl ether (40 mL) and quenched by adding a solution of Na₂S₂O₃ (10eq) in sat. aq. NaHCO₃ solution (80 mL) at rt. The mixture was stirred vigorously for 10 minutes and the layers were separated. The aqueous layer was extracted with ether (40mL). The organics were pooled, washed with sat. aq. NaHCO₃ solution and brine, dried over MgSO₄, filtered and the filtrate was concentrated. The crude material was used in the next step without further purification.
- 20

- Step D. *tert*-Butyl (1R,2R)-2-(3-chloro-5-fluorophenyl)-1-(4-chlorophenyl)-2-hydroxyethylcarbamate and *tert*-Butyl (1R,2S)-2-(3-chloro-5-fluorophenyl)-1-(4-chlorophenyl)-2-hydroxyethylcarbamate
- 25



A 500 mL 3-neck flask was charged with a magnetic stirring bar, magnesium (2.163 g, 89 mmol), a crystal of iodine and anhydrous ethyl ether (100 mL). The flask was equipped with an addition funnel and a reflux condensor. The addition funnel was charged with a solution of 1-bromo-3-chloro-5-fluorobenzene (18.64 g, 89 mmol) in anhydrous ether. 15 mL of this solution was added dropwise into the flask under vigorous stirring. Then the reaction mixture was heated to reflux for about 5 minutes until the color of the iodine was no longer visible. The heating source was removed and the remainder of the 1-bromo-3-chloro-5-fluorobenzene solution was added dropwise at a rate to maintain gentle reflux. After the addition had completed, the reaction mixture was maintained at reflux temperature for another 30 min. The reaction mixture turned light brown during the heating. The oil-bath was removed and, without cooling, a solution of (R)-tert-butyl 1-(4-chlorophenyl)-2-oxoethylcarbamate (4.80 g, 17.80 mmol) in anhydrous ethyl ether (66 mL) was added over a period of 30 min. The reaction was stirred for 2 more hours at rt. The reaction mixture was poured into 200 mL of a cold sat. aq. NH_4Cl solution. The two layers were separated and the aqueous layer was extracted with more ethyl acetate (2 x 100 mL). The combined organic layers were washed with water and then brine, dried over Na_2SO_4 , filtered and the filtrate was concentrated. The residue was washed with 100 mL hexanes, filtered and dried to provide the title compounds as a mixture of two diastereomers (anti : syn = 10 : 1 by NMR). The crude material was used in the next step without further purification.

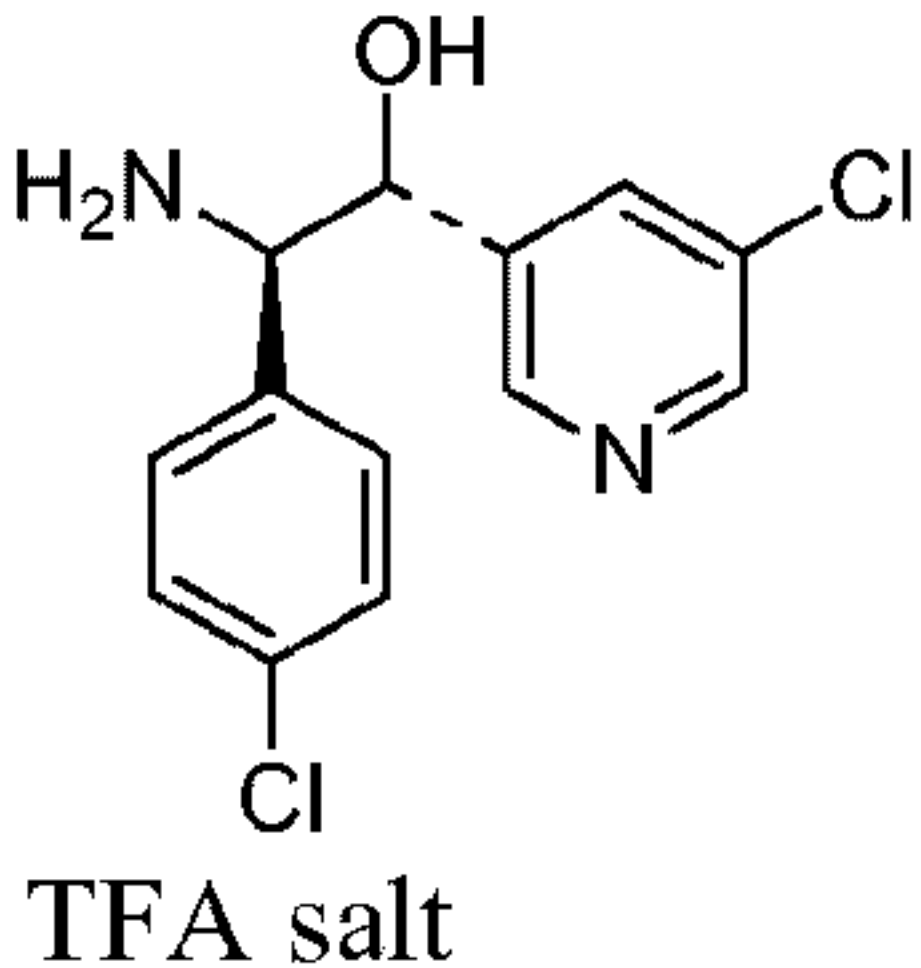
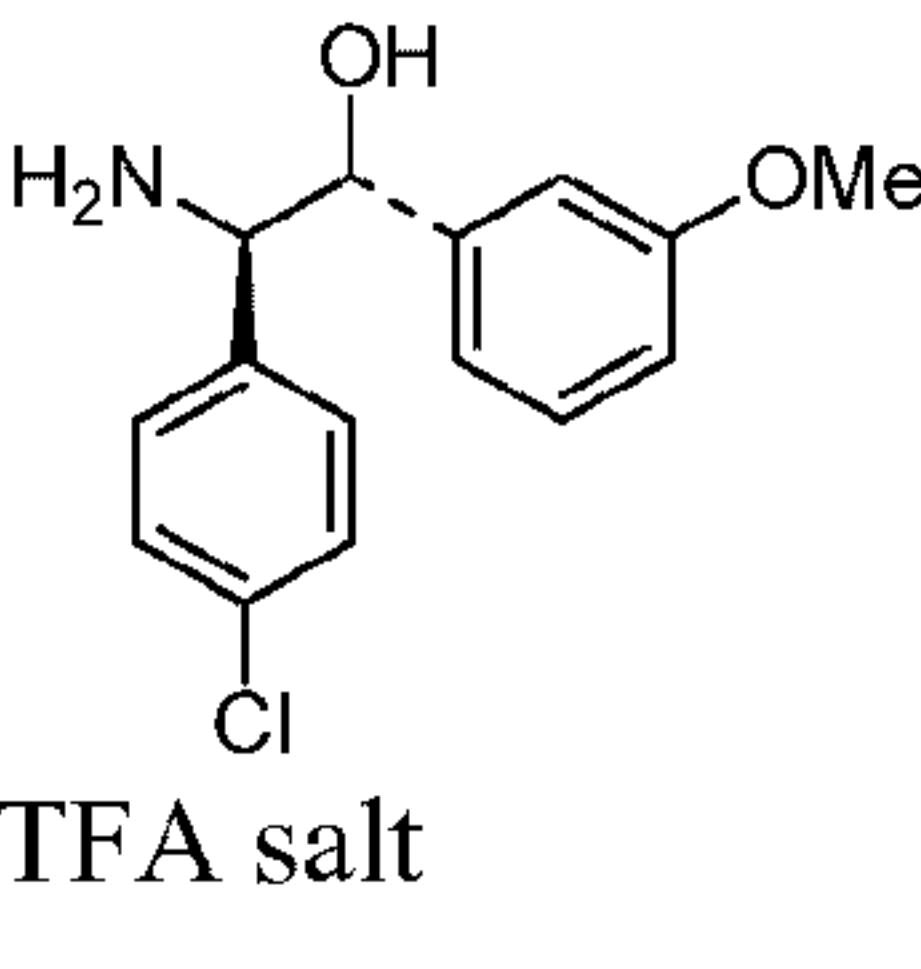
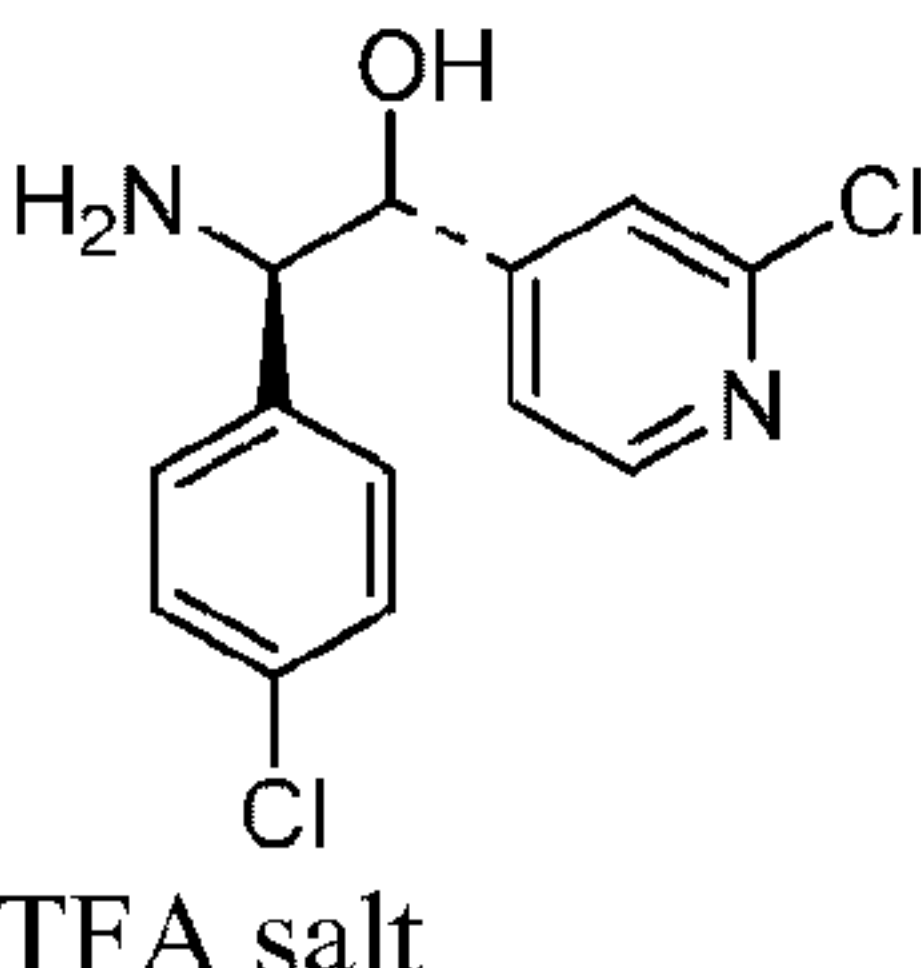
Step E. (1R,2R)-2-Amino-1-(3-chloro-5-fluorophenyl)-2-(4-chlorophenyl)ethanol and (1S,2R)-2-Amino-1-(3-chloro-5-fluorophenyl)-2-(4-chlorophenyl)ethanol

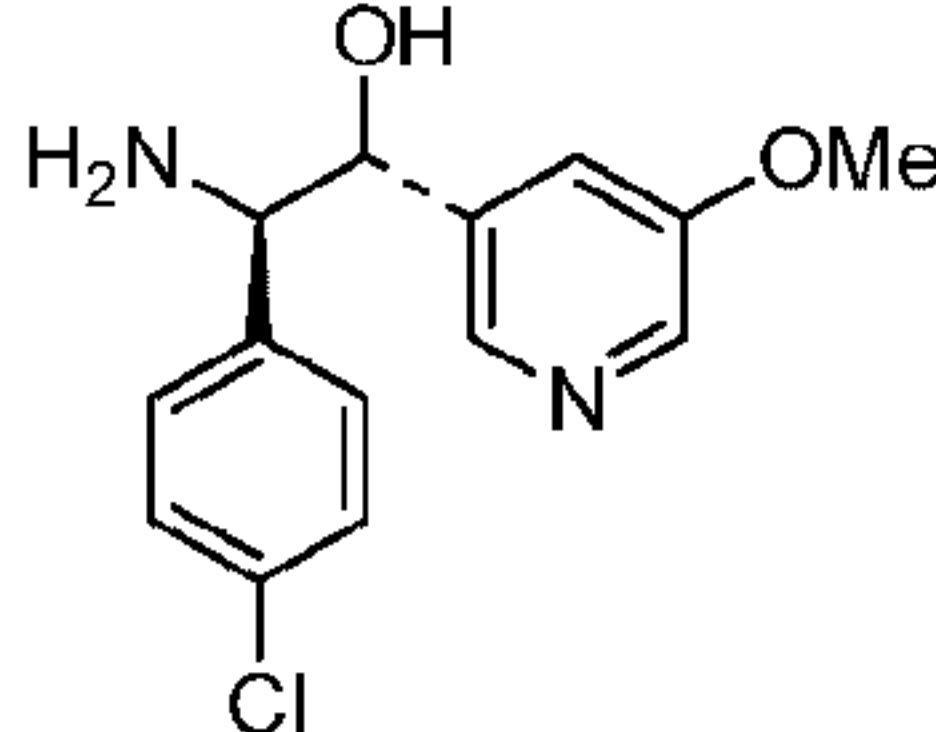
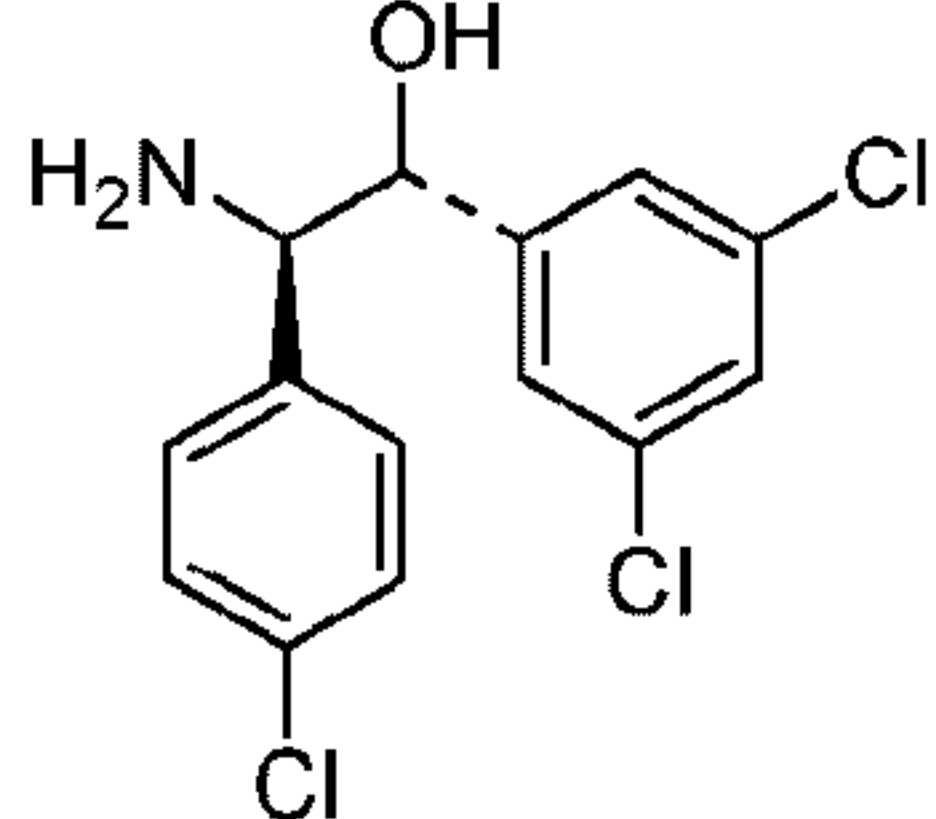
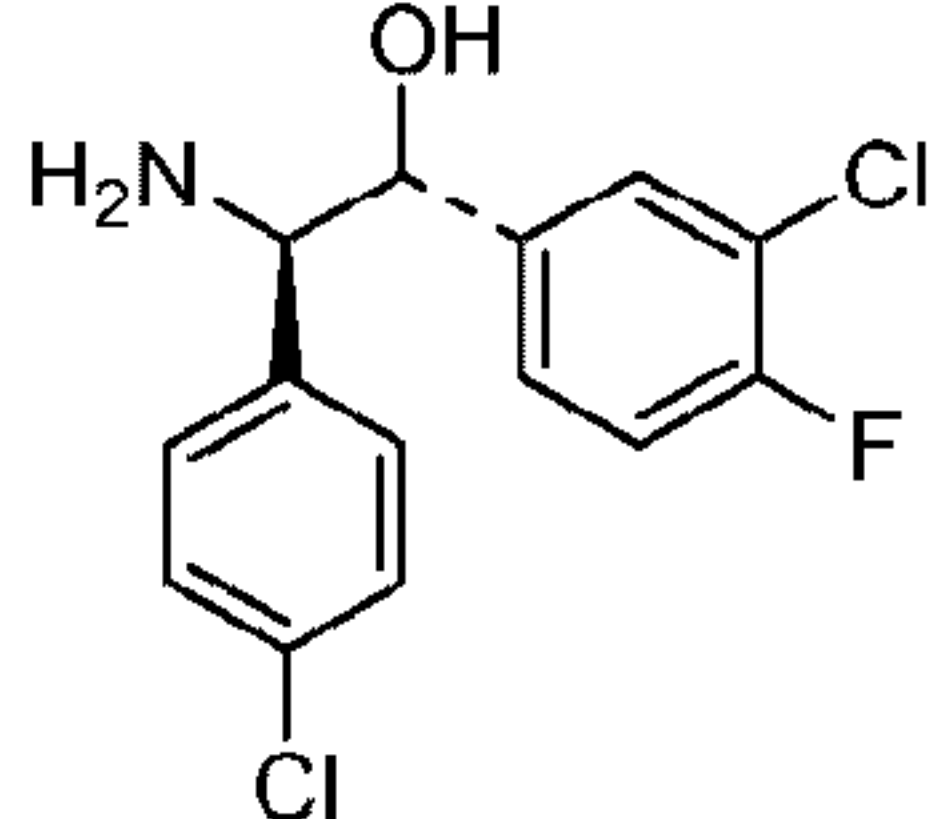


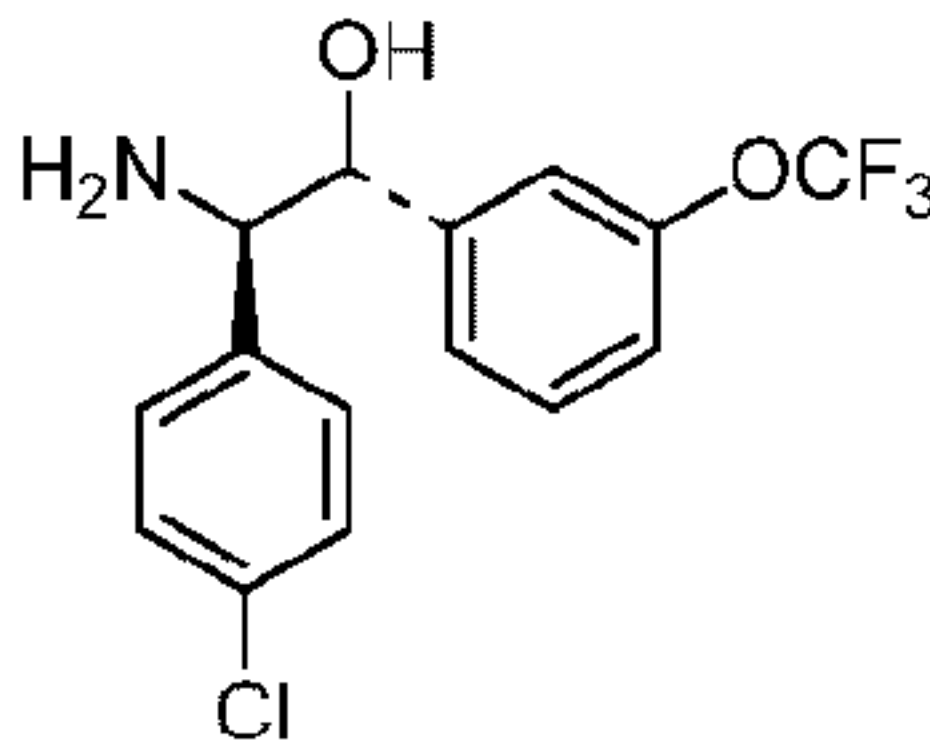
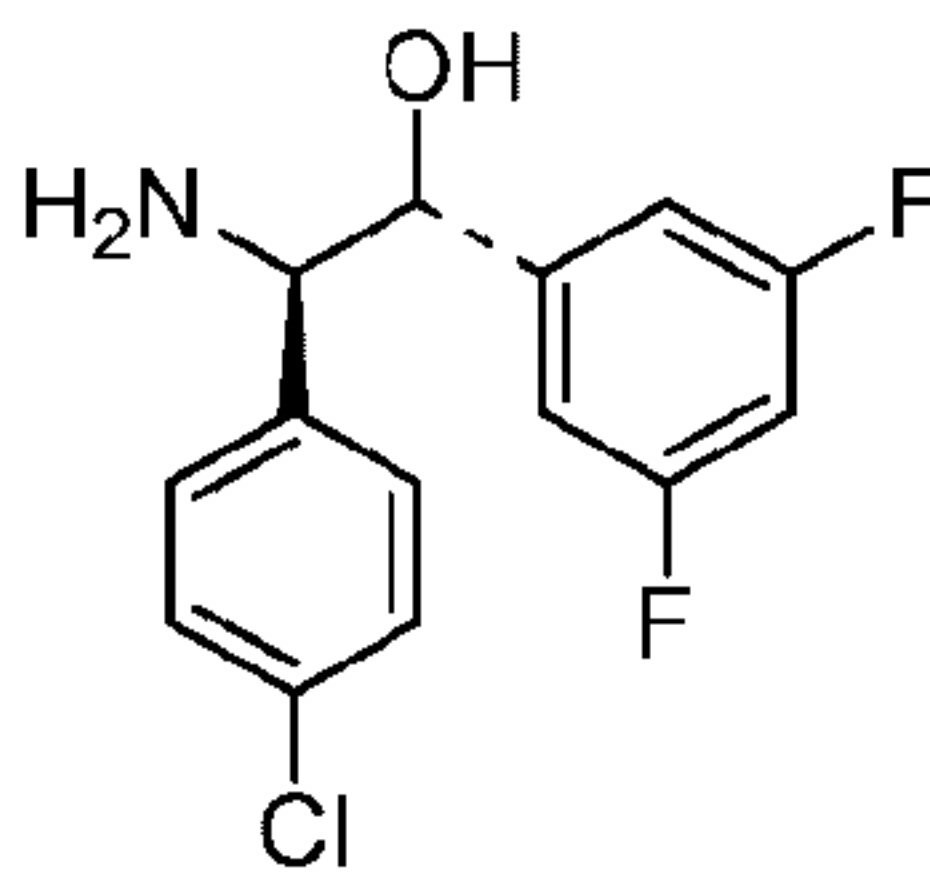
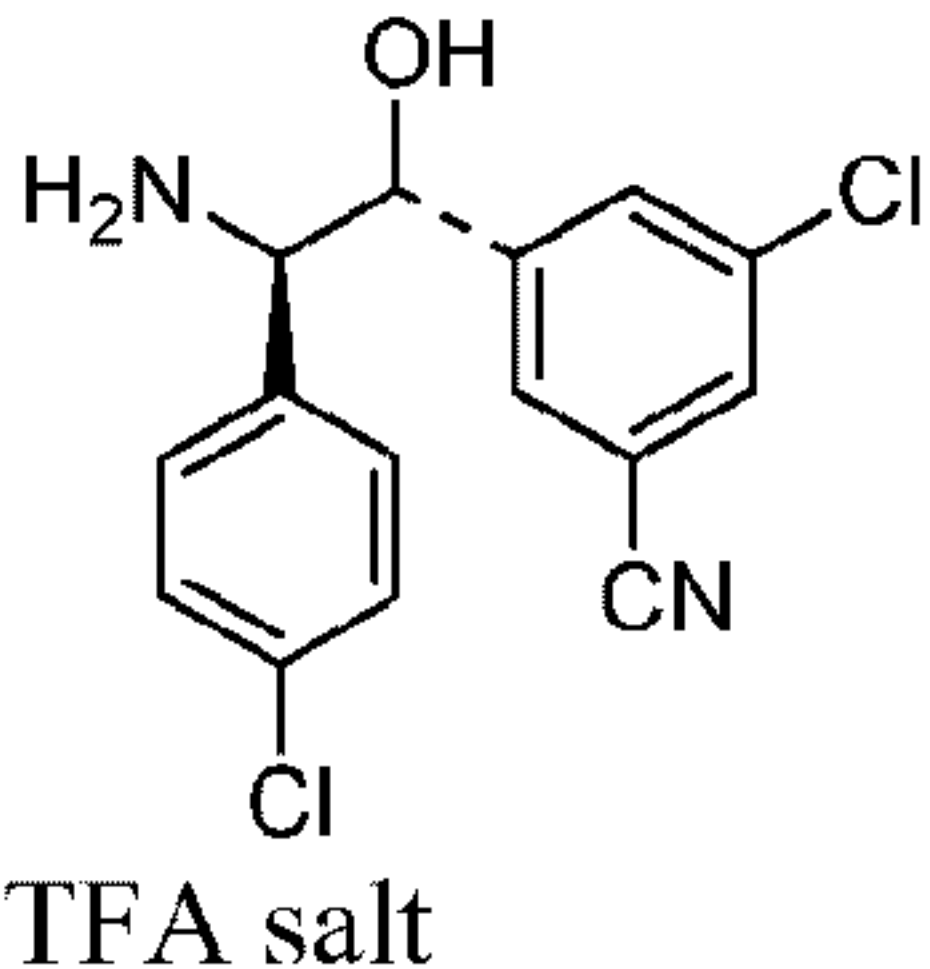
- The material obtained in general procedure 4, Step D (3.0 g, 7.49 mmol) was treated with 20mL 4N HCl in dioxane at room temperature for 2 hours. The solvent was evaporated. The residue was triturated with ethyl ether, filtered, washed with ether and dried under vacuum. The crude material was purified by preparative HPLC (Gemini™ 10 μ m 250 x 30 mm C₁₈ column 110A, Phenomenex, Torrance, CA; 10 to 19% MeCN/water with 0.1%TFA) to give the title compounds as a mixture of two diastereomers (anti : syn = 18 : 1 by NMR).
- ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 4.51 (d, *J*=7.83 Hz, 1 H) 4.85 (dd, *J*=8.22, 3.91 Hz, 1 H) 6.70 (d, *J*=3.91 Hz, 1 H) 7.05 - 7.11 (m, 1 H) 7.16 (s, 1 H) 7.30 (dt, *J*=8.75, 2.08 Hz, 1 H) 7.39 (d, *J*=8.61 Hz, 2 H) 7.44 (d, *J*=8.61 Hz, 2 H) 8.47 (br. s., 3 H). $[\alpha]_D = +96^\circ$ (*c* = 0.11, MeOH, 23.4 °C).

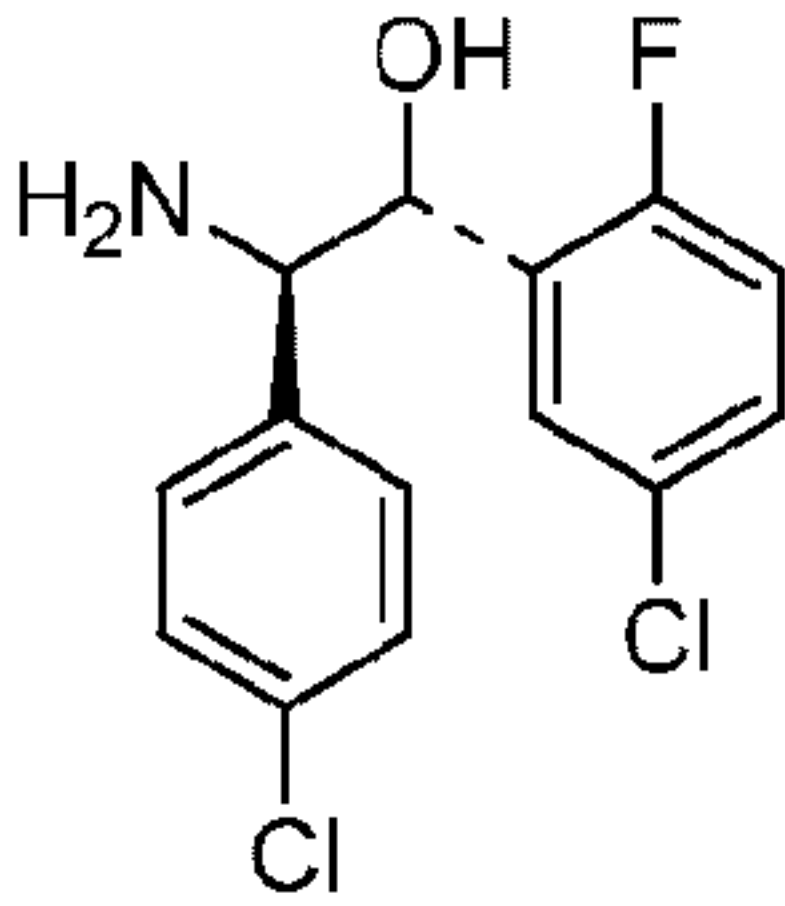
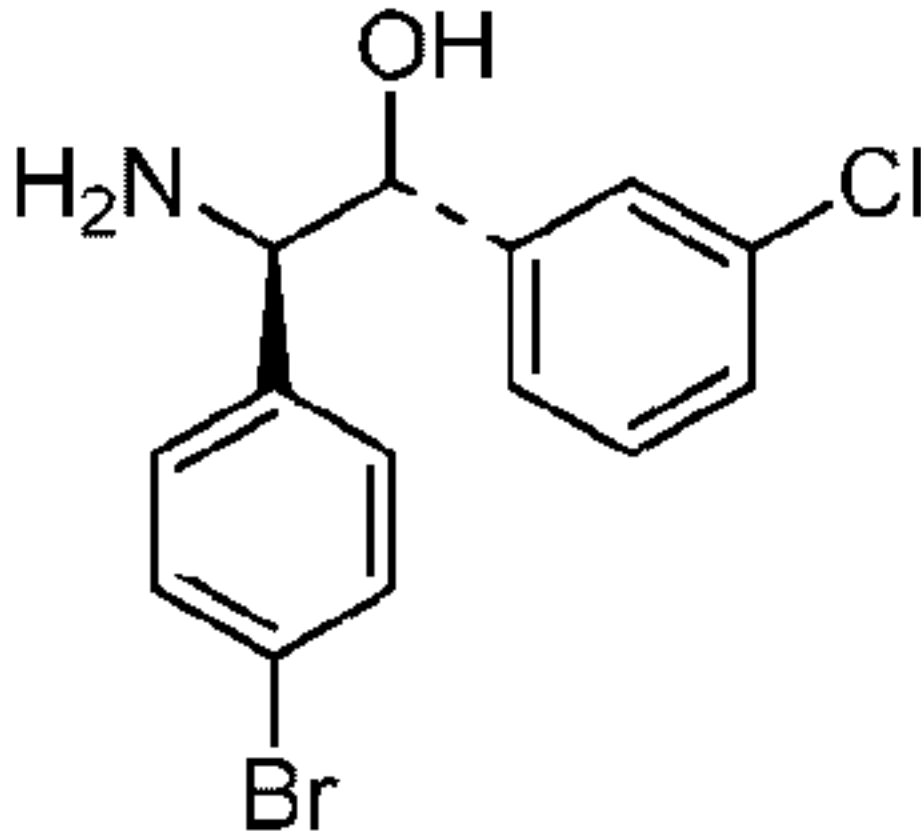
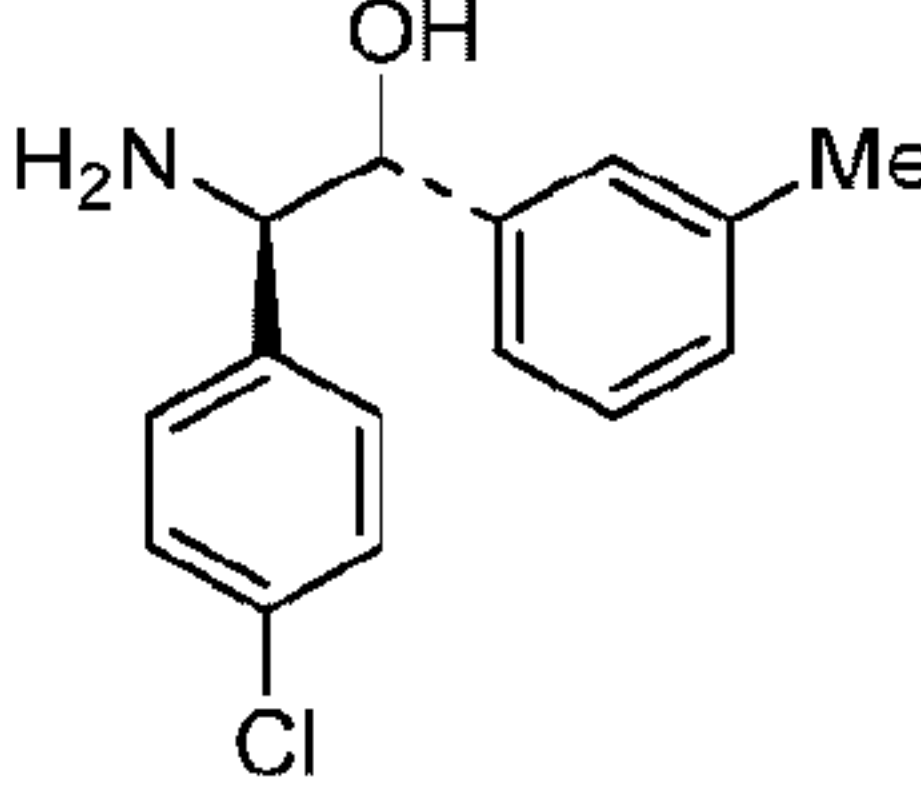
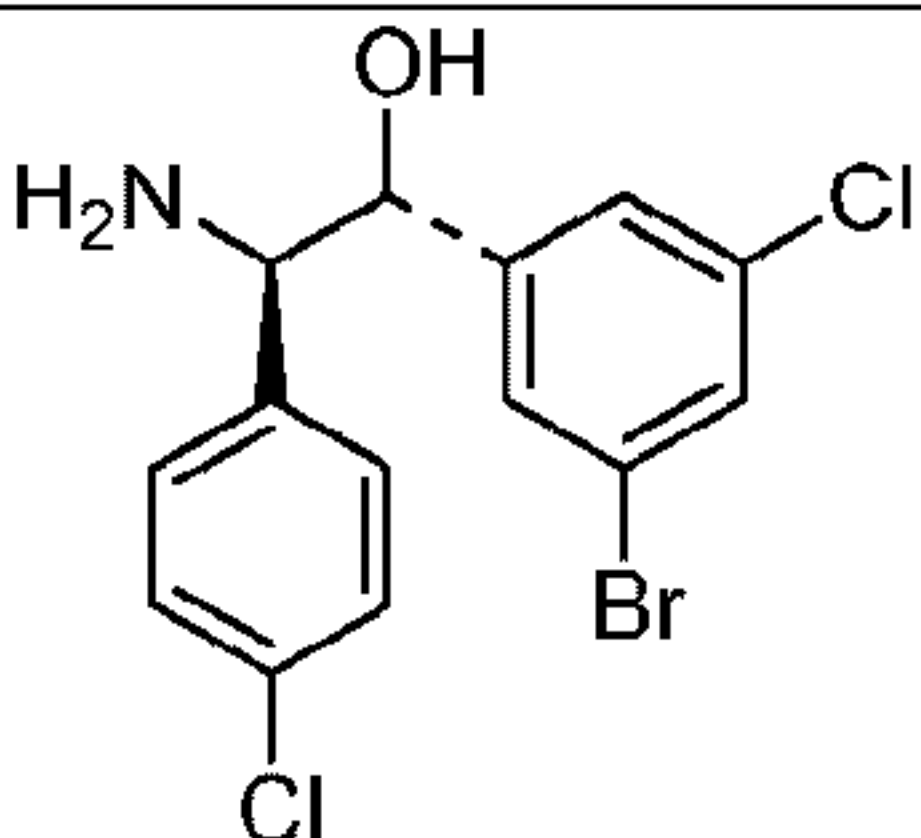
- The following intermediates C2 – C15 were also prepared by a procedure analogous to the one described above, substituting the Grignard reagent prepared from 1-bromo-3-chloro-5-fluorobenzene in Step D for the appropriate Grignard reagent that was either commercially available or was prepared from the appropriate halide as described in Step D.

Intermediate	Structure	Name	Characterization
C2	TFA salt	(1R,2R)-2-Amino-2-(4-chlorophenyl)-1-(3-fluorophenyl) ethanol	MS 266.0 (M+1). ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 4.45 (d, <i>J</i> =8.80 Hz, 1 H) 4.83 (dd, <i>J</i> =9.00, 3.52 Hz, 1 H) 6.61 (d, <i>J</i> =3.72 Hz, 1 H) 6.94 (d, <i>J</i> =7.63 Hz, 1 H) 7.00 - 7.11 (m, 2 H) 7.22 - 7.30 (m, 1 H)

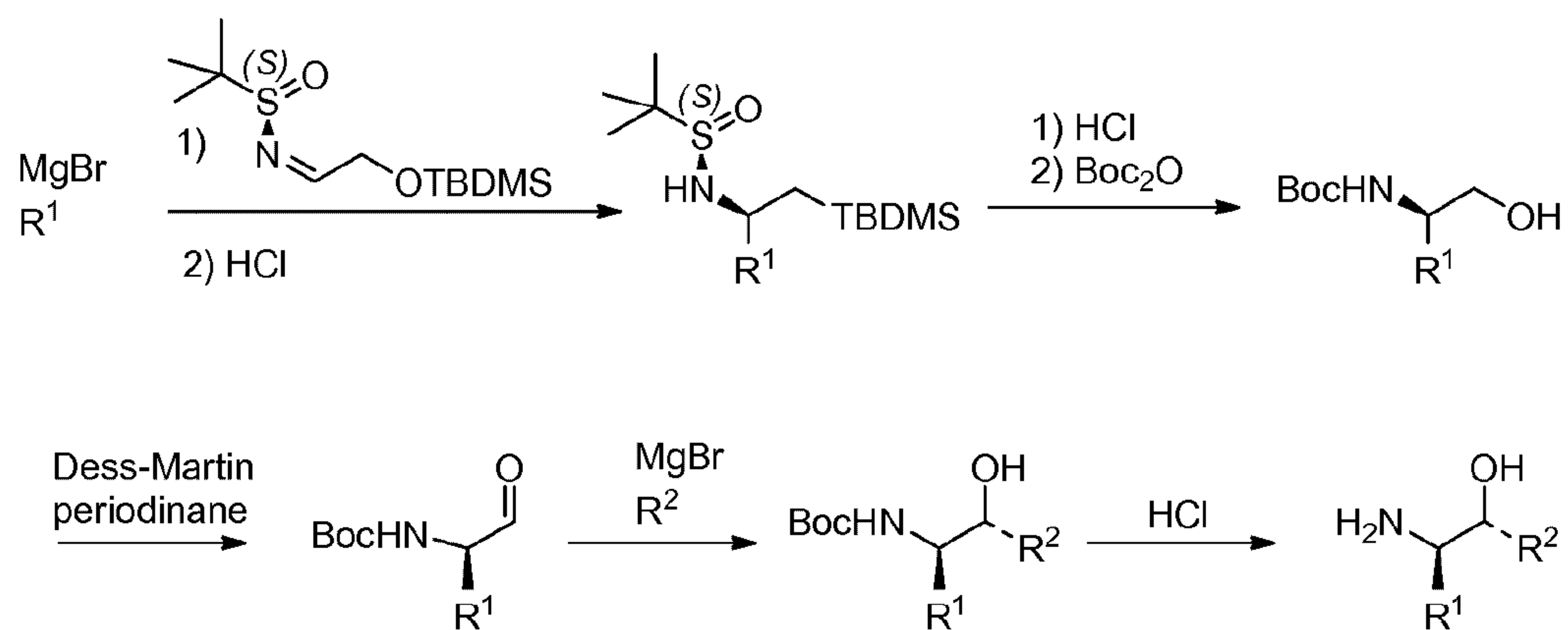
			7.33 (m, $J=8.61$ Hz, 2 H) 7.39 (m, $J=8.41$ Hz, 2 H) 8.48 (br. s., 3 H). $[\alpha]_D = +79^\circ$ (c = 0.252g/100mL, MeOH, 25.1 °C).
C3	 TFA salt	(1R,2R)-2-Amino-2-(4-chlorophenyl)-1-(5-chloropyridin-3-yl) ethanol	MS 283.0 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 4.59 (dd, $J=7.63$, 4.89 Hz, 1 H) 4.94 (d, $J=8.61$ Hz, 1 H) 6.75 (br. s., 1 H) 7.37 - 7.41 (m, 2 H) 7.41 - 7.46 (m, 2 H) 7.85 (t, $J=1.96$ Hz, 1 H) 8.26 (d, $J=1.76$ Hz, 1 H) 8.48 (d, $J=2.35$ Hz, 1 H) 8.55 (br. s., 3 H). $[\alpha]_D = +89^\circ$ (c = 0.133g/100mL, MeOH, 22.4 °C).
C4	 TFA salt	(1R,2R)-2-Amino-2-(4-chlorophenyl)-1-(3-methoxyphenyl) ethanol	MS 278.0 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 3.66 (s, 3 H) 4.39 (d, $J=5.67$ Hz, 1 H) 4.80 (dd, $J=9.19$, 3.52 Hz, 1 H) 6.47 (d, $J=3.72$ Hz, 1 H) 6.68 (d, $J=7.63$ Hz, 1 H) 6.72 - 6.79 (m, 2 H) 7.12 (t, $J=7.73$ Hz, 1 H) 7.31 - 7.41 (m, 4 H) 8.53 (br. s., 3 H). $[\alpha]_D = +124^\circ$ (c = 0.148g/100mL, MeOH, 24.0 °C).
C5	 TFA salt	(1R,2R)-2-Amino-2-(4-chlorophenyl)-1-(2-chloropyridin-4-yl) ethanol	MS 283.0 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.50 (3 H, br. s.), 8.30 (1 H, d, $J=5.1$ Hz), 7.37 - 7.49 (5 H, m), 7.22 (1 H, dd, $J=5.1$, 1.2 Hz), 6.81 (1 H, br. s.), 4.88 (1 H, d, $J=7.8$ Hz), 4.54 (1 H, br.

			s.). $[\alpha]_D = +93^\circ$ (c = 0.134g/100mL, MeOH, 24.0 °C).
C6	 TFA salt	(1R,2R)-2-Amino-2-(4-chlorophenyl)-1-(5-methoxypyridin-3-yl) ethanol	MS 279.1 (M+1). MS 279.1 (M+1). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.79 (s, 3 H) 4.56 (dd, $J=8.41$, 5.28 Hz, 1 H) 4.90 (d, $J=8.80$ Hz, 1 H) 6.68 (br. s., 1 H) 7.32 - 7.35 (m, 1 H) 7.35 - 7.39 (m, 2 H) 7.39 - 7.44 (m, 2 H) 7.92 (d, $J=1.57$ Hz, 1 H) 8.17 (d, $J=2.74$ Hz, 1 H) 8.54 (br. s., 3 H). $[\alpha]_D = +84^\circ$ (c = 0.149g/100mL, MeOH, 23.6°C). MS 279.1 (M+1)
C7	 HCl salt	((1R,2R)-2-Amino-2-(4-chlorophenyl)-1-(3,5-dichlorophenyl) ethanol	MS 316 (M+1). MS 316.0 (M+1). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 4.51 (d, $J=8.02$ Hz, 1 H) 4.90 (dd, $J=8.12$, 4.01 Hz, 1 H) 6.71 (d, $J=4.11$ Hz, 1 H) 7.25 (d, $J=1.96$ Hz, 2 H) 7.43 (s, 4 H) 7.47 (t, $J=1.96$ Hz, 1 H) 8.58 (br. s., 3 H). MS 316 (M+1) $[\alpha]_D = +105^\circ$ (c = 0.252g/100mL, MeOH, 23.2 °C).
C8	 TFA salt	(1R,2R)-2-Amino-1-(3-chloro-4-fluorophenyl)-2-(4-chlorophenyl) ethanol	MS 300.0 (M+1). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 4.43 - 4.51 (m, 1 H) 4.80 - 4.86 (m, 1 H) 6.63 (d, $J=3.52$ Hz, 1 H) 7.14 (ddd, $J=8.61$, 4.69, 2.15

			Hz, 1 H) 7.26 - 7.31 (m, 1 H) 7.33 - 7.37 (m, 2 H) 7.40 - 7.44 (m, 2 H) 7.46 (dd, $J=7.24, 1.96$ Hz, 1 H) 8.47 (br. s., 3 H). $[\alpha]_D = +88^\circ$ (c = 0.151g/100mL, MeOH, 23.8°C).
C9		(1R,2R)-2-Amino-2-(4-chlorophenyl)-1-(3-(trifluoromethoxy)phenyl) ethanol	MS 332.0 (M+1). ^1H NMR (400 MHz, CHLOROFORM- d) δ ppm 3.00 (br. s., 2 H) 4.06 (d, $J=7.04$ Hz, 1 H) 4.71 (d, $J=7.43$ Hz, 1 H) 7.05 - 7.18 (m, 6 H) 7.28 - 7.33 (m, 3 H).
C10		(1R,2R)-2-Amino-2-(4-chlorophenyl)-1-(3,5-difluorophenyl) ethanol	MS 284.0 (M+1). ^1H NMR (400 MHz, CHLOROFORM- d) δ ppm 2.47 (br. s., 3 H) 3.94 (d, $J=6.46$ Hz, 1 H) 4.59 (d, $J=6.65$ Hz, 1 H) 6.66 - 6.76 (m, 3 H) 7.11 - 7.17 (m, 2 H) 7.25 - 7.31 (m, 2 H).
C11		3-((1R,2R)-2-Amino-2-(4-chlorophenyl)-1-hydroxyethyl)-5-chlorobenzonitrile	MS 307.0 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 4.77 (dd, $J=8.51, 4.99$ Hz, 1 H) 4.86 (t, $J=5.09$ Hz, 1 H) 5.63 (d, $J=5.48$ Hz, 1 H) 7.19 (d, $J=8.80$ Hz, 1 H) 7.30 - 7.37 (m, 4 H) 7.46 - 7.52 (m, 1 H) 7.52 - 7.57 (m, 1 H) 7.58 - 7.64 (m, 2 H). $[\alpha]_D = +58^\circ$ (c = 0.228g/100mL, MeOH, 22.4°C).

C12		(1R,2R)-2-Amino-1-(5-chloro-2-fluorophenyl)-2-(4-chlorophenyl)ethanol	MS 300.0 (M+1). ¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ ppm 2.79 (br. s., 3 H) 4.14 (d, <i>J</i> =5.67 Hz, 1 H) 4.98 (d, <i>J</i> =5.67 Hz, 1 H) 6.87 (dd, <i>J</i> =9.39, 8.80 Hz, 1 H) 7.19 (ddd, <i>J</i> =6.55, 4.40, 2.15 Hz, 1 H) 7.21 - 7.25 (m, 2 H) 7.26 - 7.29 (m, 2 H) 7.50 (dd, <i>J</i> =6.06, 2.74 Hz, 1 H).
C13		(1R,2R)-2-Amino-2-(4-bromophenyl)-1-(3-chlorophenyl)ethanol	MS 328.0 (M+1). ¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ ppm 4.27 (d, <i>J</i> =10.17 Hz, 1 H) 4.93 (d, <i>J</i> =9.98 Hz, 1 H) 6.77 (d, <i>J</i> =7.63 Hz, 1 H) 6.99 (m, <i>J</i> =8.61 Hz, 2 H) 7.07 - 7.13 (m, 2 H) 7.19 - 7.23 (m, 1 H) 7.38 (m, <i>J</i> =8.41 Hz, 2 H).
C14		(1R,2R)-2-Amino-2-(4-chlorophenyl)-1-(m-tolyl)ethanol	MS 262.1 (M+1). ¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ ppm 2.30 (s, 3 H) 2.58 (br. s., 3 H) 4.08 (d, <i>J</i> =6.46 Hz, 1 H) 4.63 (d, <i>J</i> =6.65 Hz, 1 H) 6.95 (d, <i>J</i> =7.63 Hz, 1 H) 7.04 (d, <i>J</i> =7.04 Hz, 2 H) 7.12 - 7.20 (m, 3 H) 7.22 - 7.26 (m, 2 H).
C15		(1R,2R)-2-Amino-1-(3-bromo-5-chlorophenyl)-2-(4-chlorophenyl)ethanol	MS 360.0 (M+1). ¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ ppm 1.60 (br. s., 2 H) 3.99 (d, <i>J</i> =6.46 Hz, 1 H) 4.59 (d, <i>J</i> =6.46 Hz, 1 H) 7.11 (s, 1 H) 7.16 (d,

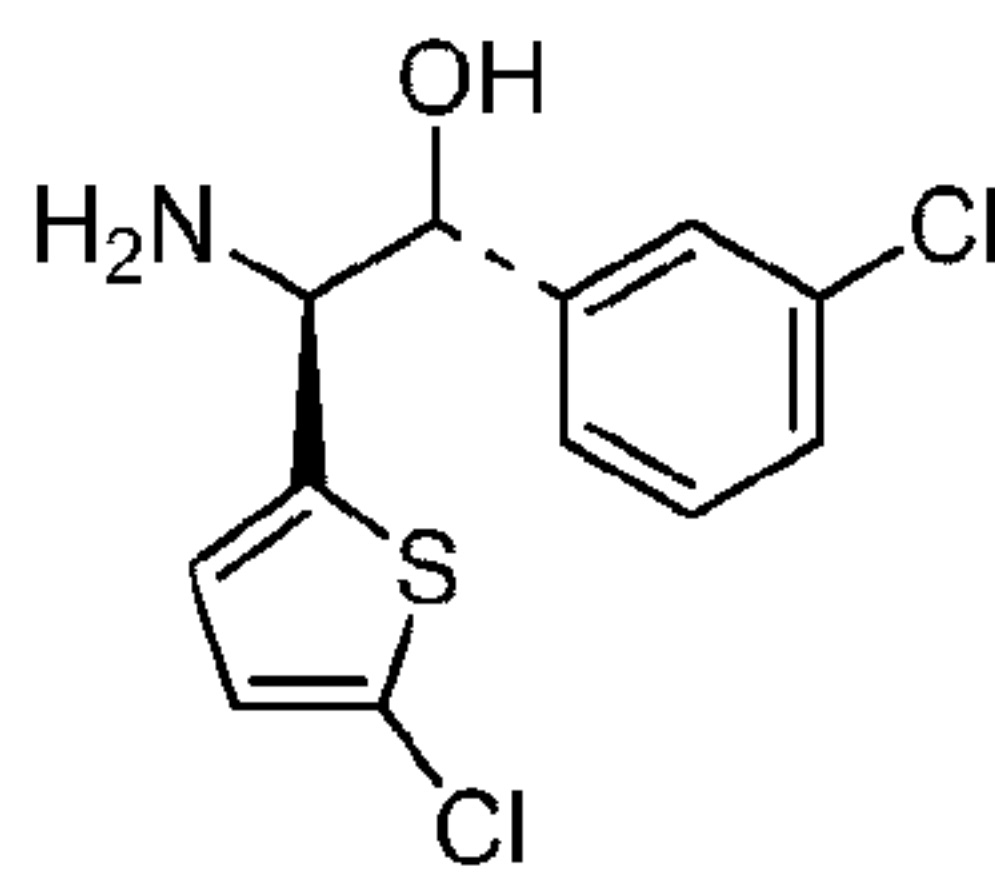
			$J=8.22$ Hz, 2 H) 7.22 (s, 1 H) 7.28 - 7.32 (m, 3 H) 7.38 (t, $J=1.66$ Hz, 1 H).
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General Procedure 5

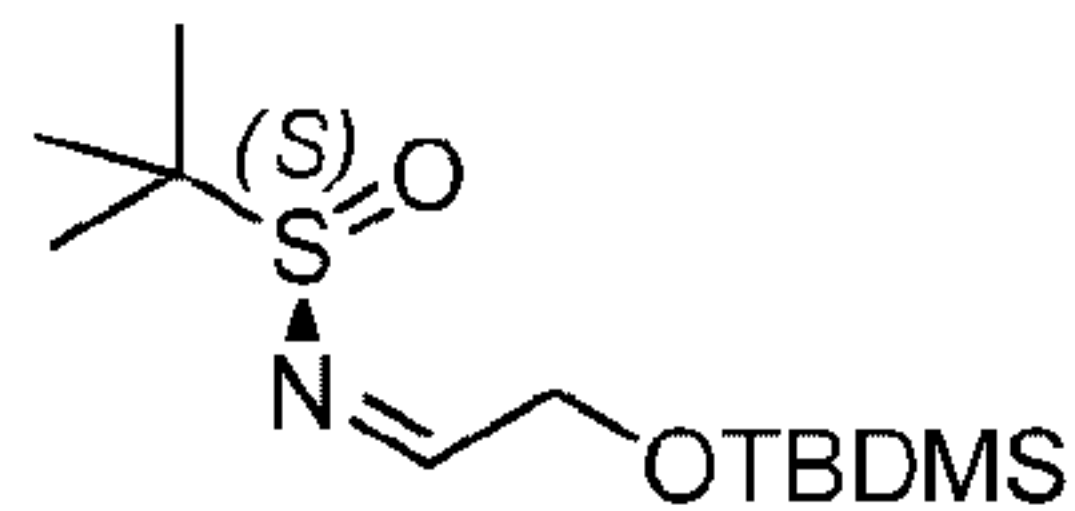
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Intermediate D1

(1R,2S)-2-Amino-1-(3-chlorophenyl)-2-(5-chlorothiophen-2-yl)ethanol

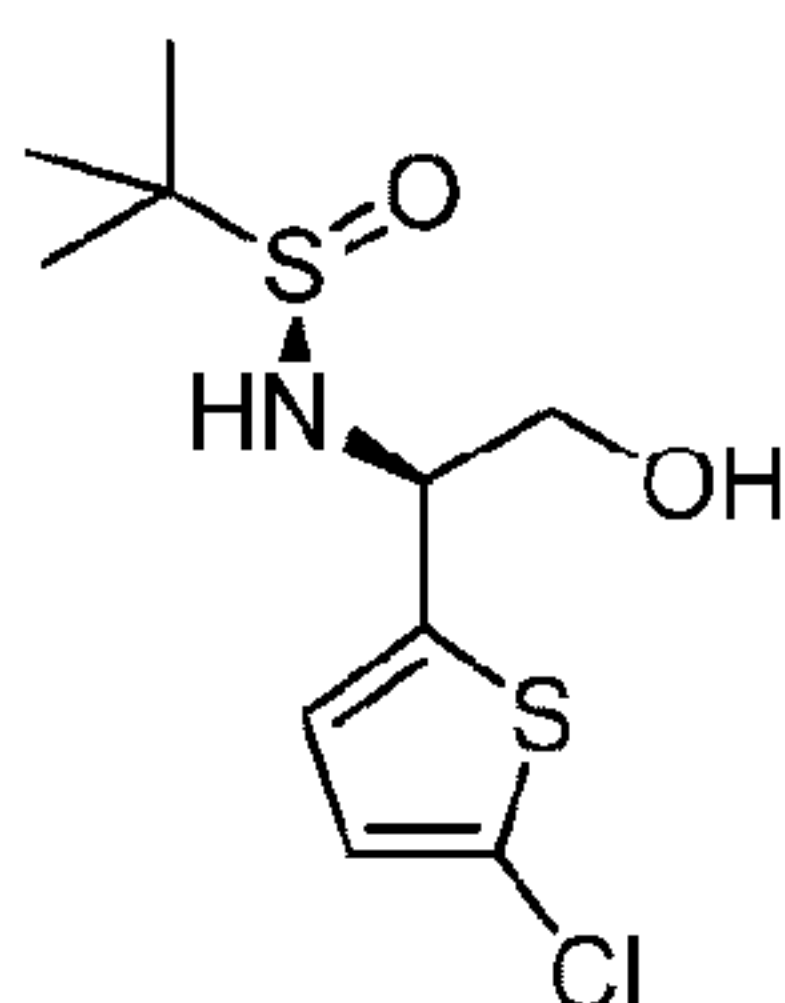


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Step A. (S)-N-(2-(*tert*-Butyldimethylsilyloxy)ethylidene)-2-methylpropane-2-sulfinamide

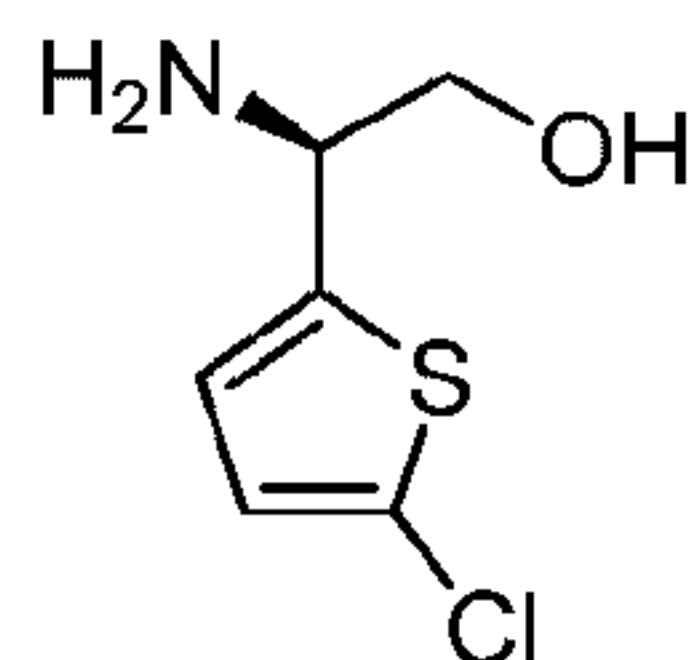
Copper(II) sulfate (30.3 g, 190 mmol) was added to a mixture of (tert-butyltrimethylsilyloxy)acetaldehyde (16.55 g, 95 mmol) and (S)-(-)-2-methyl-2-propanesulfonamide (9.59 g, 79 mmol) in DCM (150 mL). The mixture was stirred at room temperature for 17 h. The mixture was filtered through a pad of Celite[®] (J.T. Baker, Phillipsberg, NJ, diatomaceous earth) followed by a rinse with 500 mL of DCM. The filtrate was concentrated and the crude product was purified by chromatography on silica gel (eluent: 0 to 30% EtOAc in hexane, gradient) to afford the title compound. Mass Spectrum (CI+) m/z = 278.1 (M+1).

10 Step B. (S)-N-((S)-2-(tert-Butyltrimethylsilyloxy)-1-(5-chlorothiophen-2-yl)ethyl)-2-methylpropane-2-sulfonamide



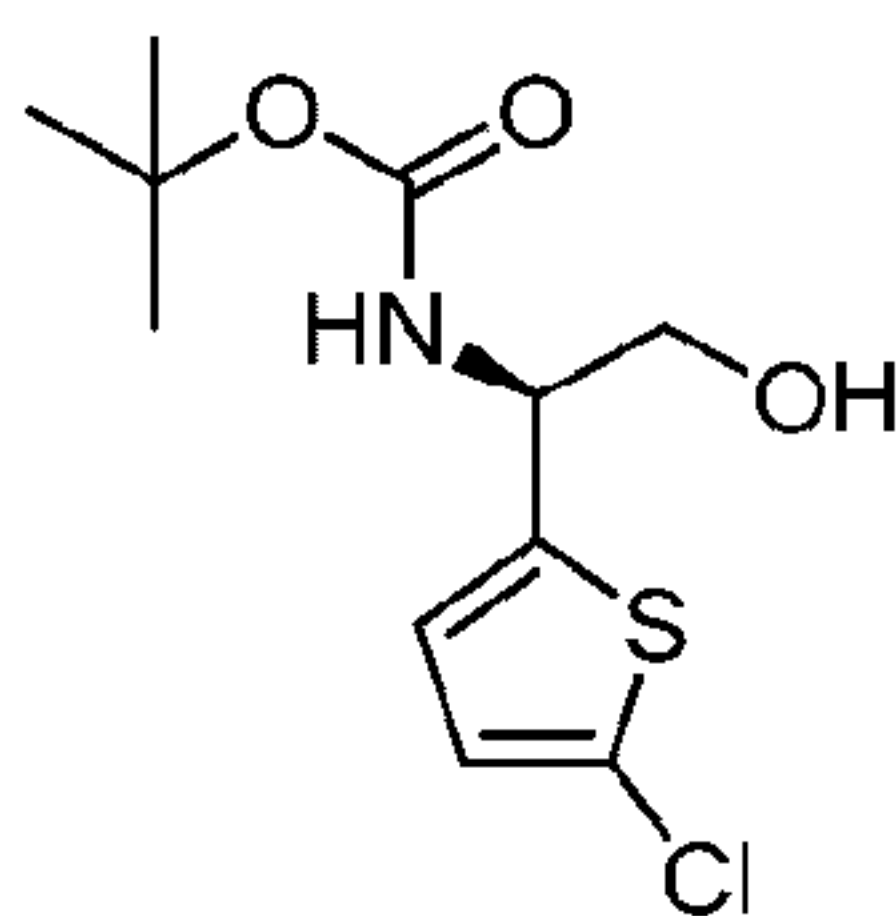
15 To a solution of (S)-N-(2-(tert-butyltrimethylsilyloxy)ethylidene)-2-methylpropane-2-sulfonamide (6.02 g, 21.69 mmol) in DCM (120 mL) at -78 °C was added a 0.5M solution of 5-chloro-2-thienylmagnesium bromide in THF (87 mL, 43.4 mmol) over a period of 30 min via syringe. After 10 minutes at -78 °C, the reaction mixture was warmed to 0 °C. The reaction mixture was stirred at 0 °C for 3 h., then
 20 quenched by addition of 30 mL of a sat. aq. NH₄Cl solution and extracted with EtOAc. The combined organics were washed with 100 mL of brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (linear gradient 0 to 70% EtOAc w/0.1% AcOH : hexane) to give the title compound.
 1H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.02 (s, 6 H) 0.85 (s, 9 H) 1.12 (s, 9 H) 3.31 (s, 1
 25 H) 3.62 - 3.89 (m, 2 H) 4.31 - 4.53 (m, 1 H) 5.73 (d, J =7.83 Hz, 1 H) 6.98 (s, 2 H). Mass Spectrum (CI+) m/z = 419.0 (M+23).

Step C. (S)-2-Amino-2-(5-chlorothiophen-2-yl)ethanol hydrochloride.



- 5 To a solution of (S)-N-((S)-2-(tert-butyldimethylsilyloxy)-1-(5-chlorothiophen-2-yl)ethyl)-2-methylpropane-2-sulfonamide (4.60 g, 11.61 mmol) in MeOH (20 mL) at 0 °C was slowly added a 4.0M solution of HCl in 1,4-dioxane (14.5 mL, 58.1 mmol). After 45 min at 0 °C the reaction mixture was concentrated *in vacuo* to afford the title compound.
- ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.04 - 3.09 (m, 2 H) 3.13 (d, *J*=4.30 Hz, 1 H) 3.88
- 10 (d, *J*=5.09 Hz, 1 H) 6.38 (d, *J*=3.52 Hz, 1 H) 6.50 (d, *J*=3.91 Hz, 1 H) 7.99 (br. s., 2 H).

Step D. (S)-*tert*-Butyl 1-(5-chlorothiophen-2-yl)-2-hydroxyethylcarbamate



15

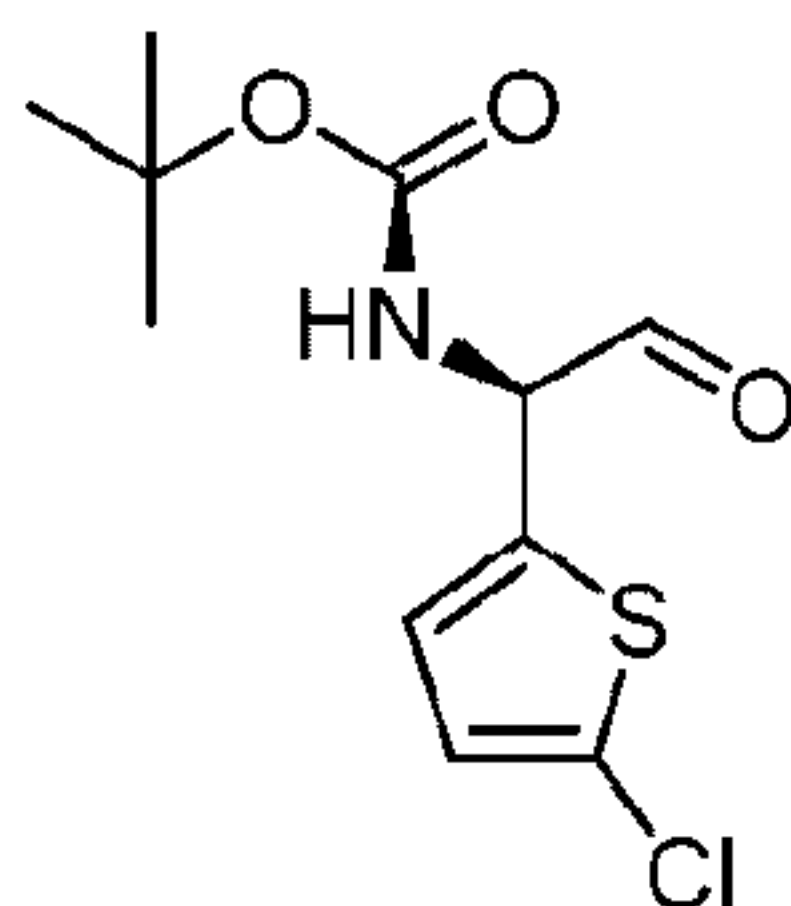
- A solution of di-*tert*-butyl dicarbonate (3.05 g, 13.96 mmol) in DCM (10 mL) was added over a period of 30 min to a solution of (S)-2-amino-2-(5-chlorothiophen-2-yl)ethanol hydrochloride (2.48 g, 13.96 mmol) and triethylamine (3.89 mL, 27.9 mmol) in dry DCM (50 mL). The ice bath was removed after addition went to completion and
- 20 the mixture was stirred at rt for 3 h. The mixture was washed with water, concentrated *in vacuo* and the crude product was purified by chromatography on silica gel (0 to 100% EtOAc in hexane, gradient elution) to afford the title compound along with a small amount of (S)-*tert*-butyl 2-(tert-butoxycarbonyloxy)-1-(5-chlorothiophen-2-yl)ethylcarbamate. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.46 (s, 9 H) 1.92 (br. s., 1 H)

3.89 (dd, $J=8.61, 4.30$ Hz, 2 H) 4.94 (br. s., 1 H) 5.18 (br. s., 1 H) 6.76 - 6.82 (m, 2 H).

Mass Spectrum (CI+) $m/z = 300.0$ (M+23).

Step E. (S)-*tert*-Butyl 1-(5-chlorothiophen-2-yl)-2-oxoethylcarbamate

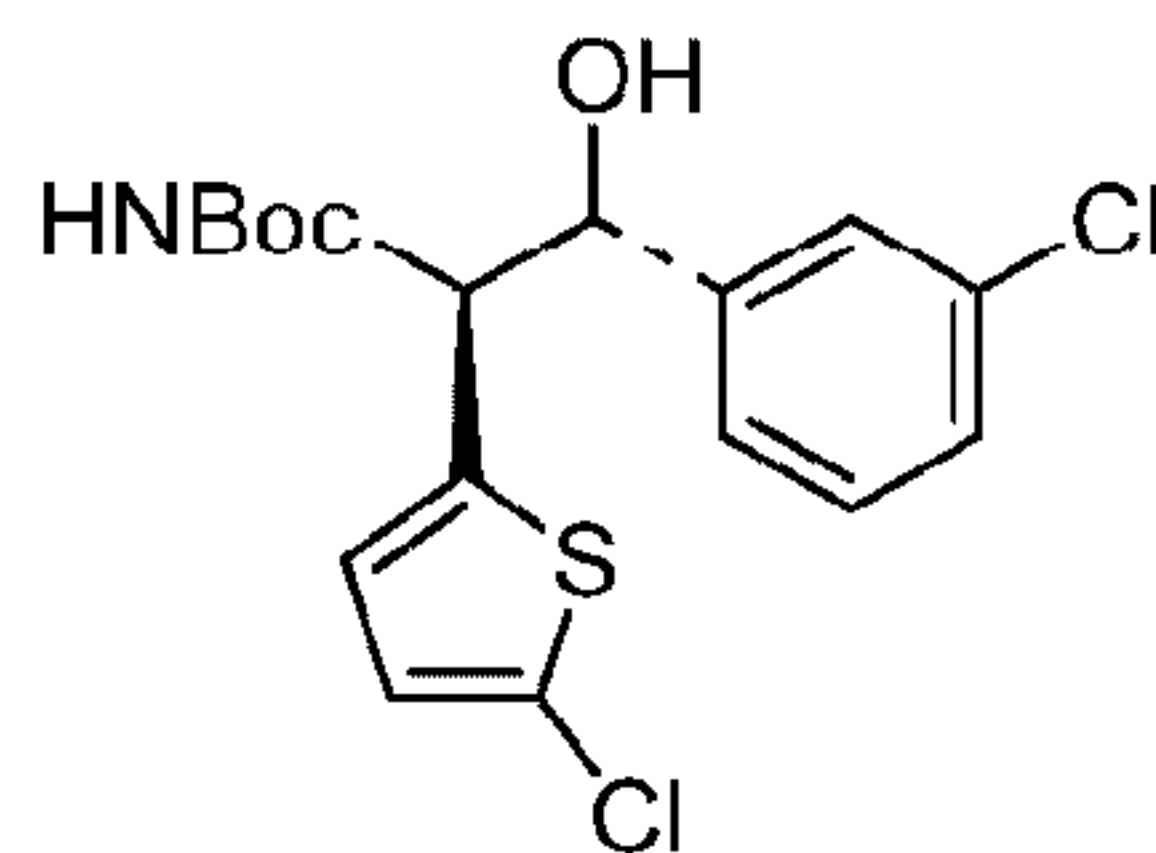
5



Dess-Martin periodinane (7.39 g, 17.42 mmol) was added to a solution of (S)-*tert*-butyl 1-(5-chlorothiophen-2-yl)-2-hydroxyethylcarbamate (2.420 g, 8.71 mmol) in wet
 10 (1 μ L water/1 mL DCM) DCM (18 mL) at rt. The reaction mixture was stirred at rt for 1.5 hours. The reaction mixture was diluted with diethyl ether (20 mL) and a solution of $\text{Na}_2\text{S}_2\text{O}_3$ (10 equiv) in saturated aqueous NaHCO_3 (40 mL) was added. The mixture was stirred vigorously for 10 minutes and the layers were separated. The aqueous layer was extracted with diethyl ether. The organics were combined, washed with sat. aq. NaHCO_3
 15 solution, water, and brine, dried over MgSO_4 , filtered and the filtrate was concentrated to provide the title compound which was used without further purification.

Step F. *tert*-Butyl (1S,2R)-2-(3-chlorophenyl)-1-(5-chlorothiophen-2-yl)-2-hydroxyethylcarbamate

20



The (S)-*tert*-butyl 1-(5-chlorothiophen-2-yl)-2-oxoethylcarbamate (2.170g, 7.87 mmol) dissolved in THF (40 mL) was added to 3-chlorophenylmagnesium bromide, 0.5M in THF (79 mL, 39.3 mmol) via syringe over 15 minutes at room temperature with

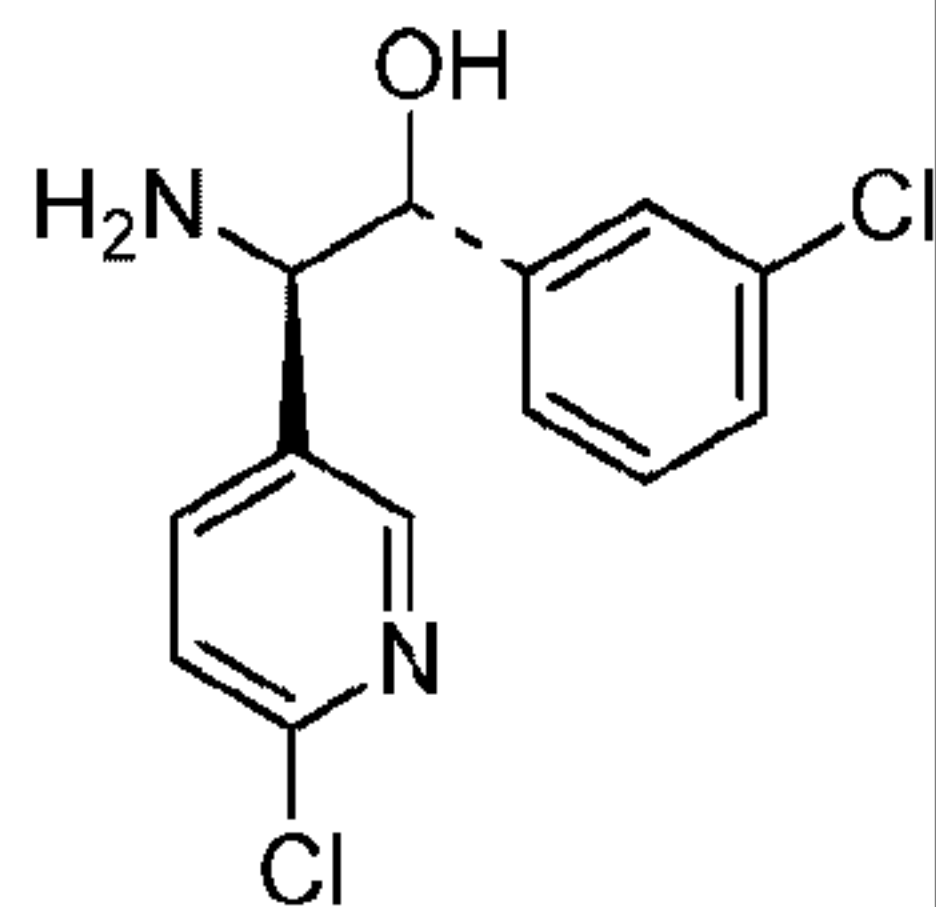
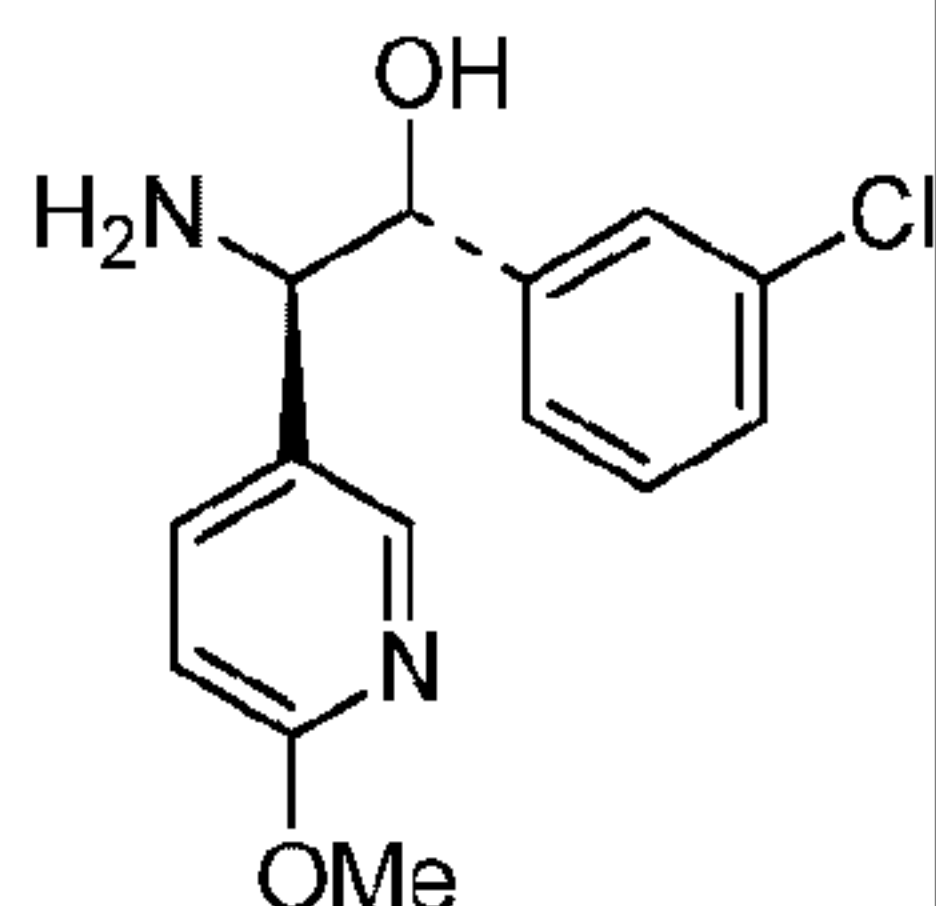
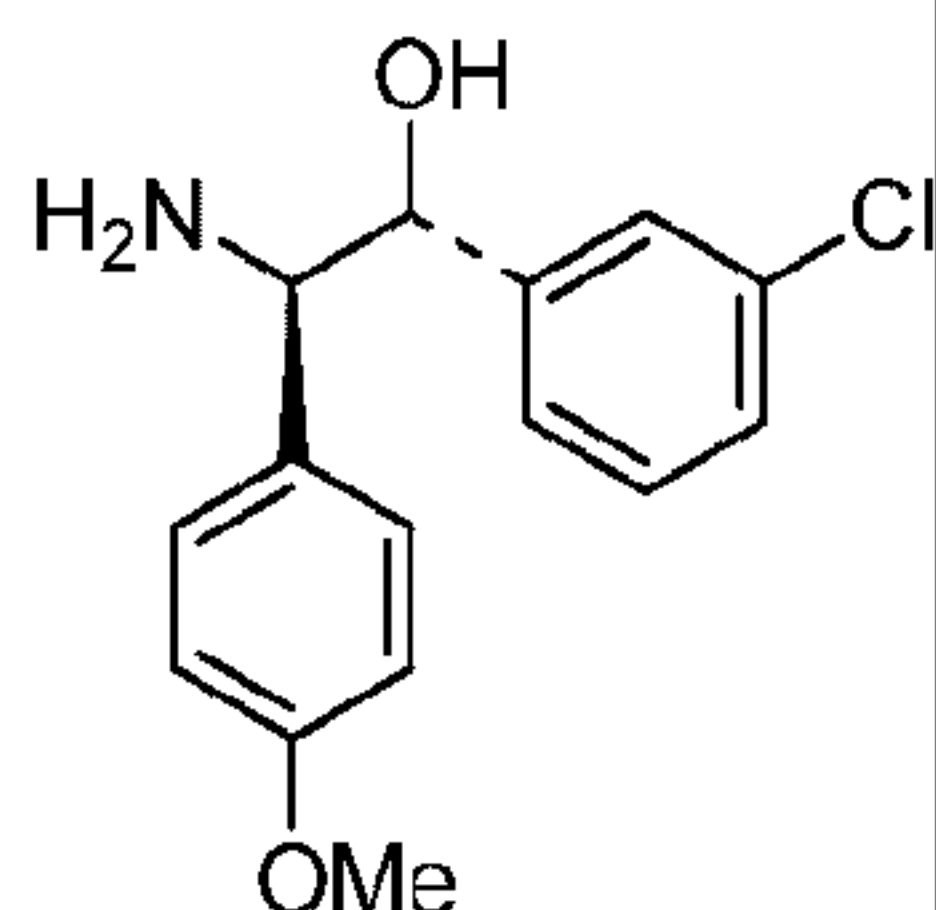
stirring. After the addition was completed, the reaction mixture was stirred at rt for 2 hours and then quenched by addition of a sat. aq. NH_4Cl solution at 0 °C. The aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine, dried with MgSO_4 , filtered and concentrated *in vacuo* to provide crude material. The product was purified via chromatography on silica gel (0 to 80% EtOAc w/ 0.1% AcOH in hexane, gradient elution) and via prep HPLC chromatography (50 to 95% gradient MeCN in water, with 0.1% TFA) to afford the title compound.

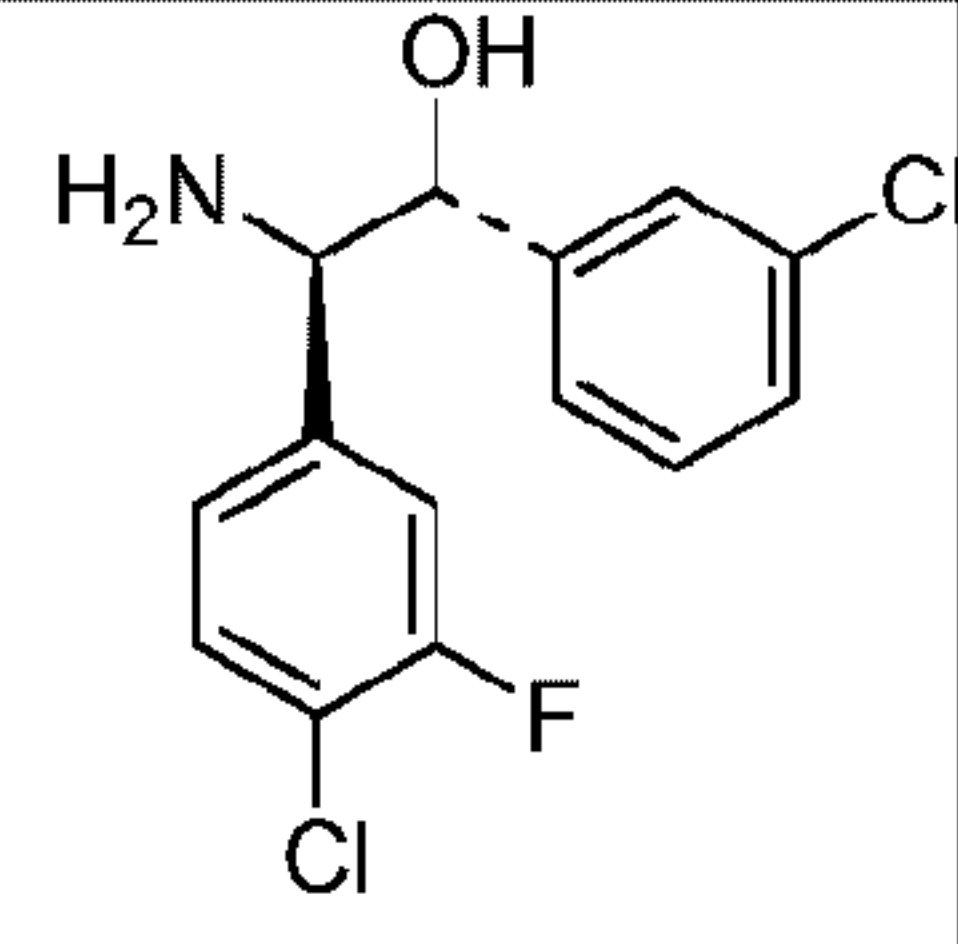
^1H NMR (400 MHz, CDCl_3) δ ppm 1.33 (br. s., 9 H) 4.97 (d, $J=3.3$ Hz, 1 H) 5.03 (br. s., 1 H) 5.33 (br. s., 1 H) 6.71 - 6.75 (m, 1 H) 6.75 - 6.80 (m, 1 H) 7.17 - 7.24 (m, 1 H) 7.24 - 7.31 (m, 2 H) 7.39 (s, 1 H). Mass Spectrum (CI+) m/z = 410.0 (M+23).

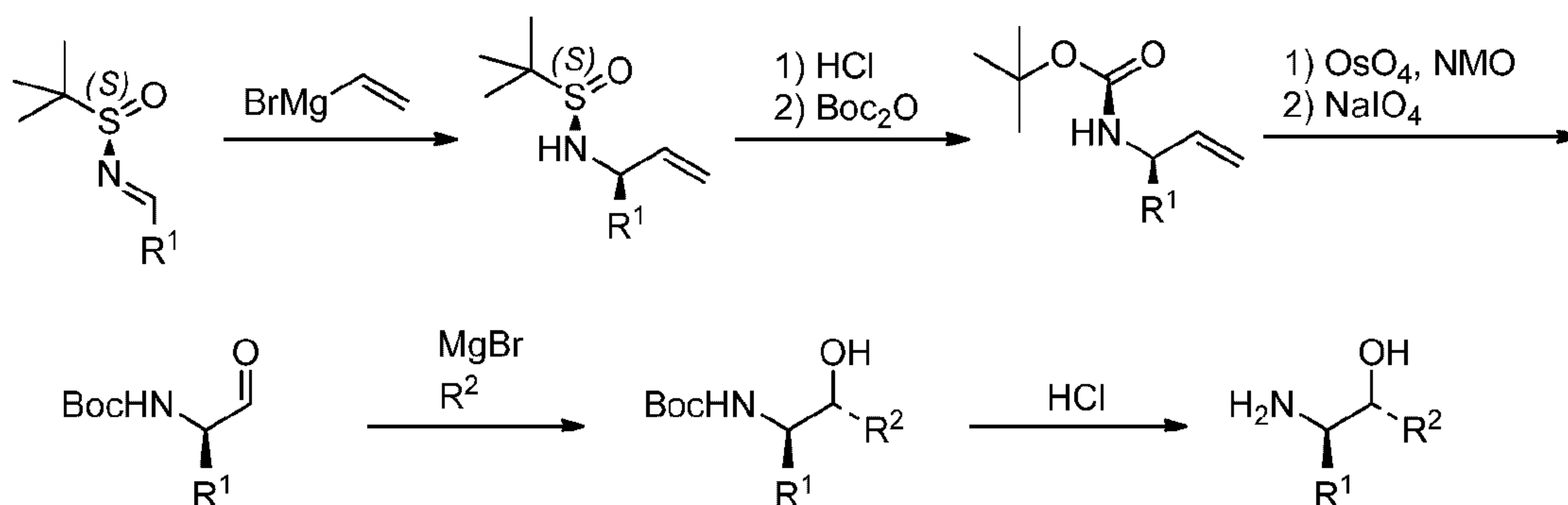
Step G. (1R,2S)-2-Amino-1-(3-chlorophenyl)-2-(5-chlorothiophen-2-yl)ethanol

tert-Butyl (1S,2R)-2-(3-chlorophenyl)-1-(5-chlorothiophen-2-yl)-2-hydroxyethylcarbamate (0.32g, 0.824 mmol) was dissolved in 40 mL HCl (4.0 M in dioxane). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. To the residue was added saturated aq. sodium bicarbonate solution followed by EtOAc. The layers were separated, the aq. layer was extracted with more EtOAc and the combined organic layers were dried over MgSO_4 , filtered and the filtrate was concentrated under reduced pressure. ^1H NMR (400 MHz, CDCl_3) δ ppm 3.61 - 3.68 (m, 1 H) 3.75 - 3.81 (m, 2 H) 4.19 (d, $J=6.06$ Hz, 1 H) 4.65 (d, $J=6.06$ Hz, 1 H) 6.52 (d, $J=3.91$ Hz, 1 H) 6.70 (d, $J=3.72$ Hz, 1 H) 7.11 (d, $J=6.46$ Hz, 1 H) 7.19 - 7.26 (m, 2 H) 7.33 (s, 1 H). Mass Spectrum (CI+) m/z = 288.0 (M+1).

The following intermediates D2 to D5 were also prepared by a procedure analogous to the one described above, substituting 5-chloro-2-thienylmagnesium bromide in Step A for the appropriate Grignard reagent that was either commercially available or was prepared from the appropriate halide as described in Step D.

Intermediate	Structure	Name	Characterization
D2		(1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(6-chloropyridin-3-yl)ethanol	¹ H NMR (400 MHz, CDCl ₃) δ ppm 2.60 (3 H, br. s.), 3.98 (1 H, d, <i>J</i> =6.6 Hz), 4.60 (1 H, d, <i>J</i> =6.6 Hz) 6.93 - 7.00 (3 H, m), 7.12 - 7.29 (5 H, m). Mass Spectrum (CI+) <i>m/z</i> = 283.0 (M+1).
D3		(1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(6-methoxypyridin-3-yl)ethanol	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 3.79 (s, 3 H) 4.46 (dd, <i>J</i> =9.00, 5.09 Hz, 1 H) 4.88 (d, <i>J</i> =9.19 Hz, 1 H) 6.63 (br. s., 1 H) 6.78 - 6.85 (m, 1 H) 7.11 - 7.18 (m, 1 H) 7.21 - 7.32 (m, 2 H) 7.35 (s, 1 H) 7.73 (dd, <i>J</i> =8.71, 2.45 Hz, 1 H) 8.04 (d, <i>J</i> =2.15 Hz, 1 H) 8.45 (br. s., 3 H) (TFA salt). Mass Spectrum (CI+) <i>m/z</i> = 279.1 (M+1)
D4		(1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(4-methoxyphenyl)ethanol	¹ H NMR (400 MHz, CDCl ₃) δ ppm 3.79 (s, 3 H) 3.91 (d, <i>J</i> =6.46 Hz, 1 H) 4.59 (d, <i>J</i> =6.65 Hz, 1 H) 6.76 - 6.88 (m, 2 H) 6.98 (d, <i>J</i> =7.24 Hz, 1 H) 7.03 - 7.33 (m, 5 H). Mass Spectrum (CI+) <i>m/z</i> = 278.0 (M+1).

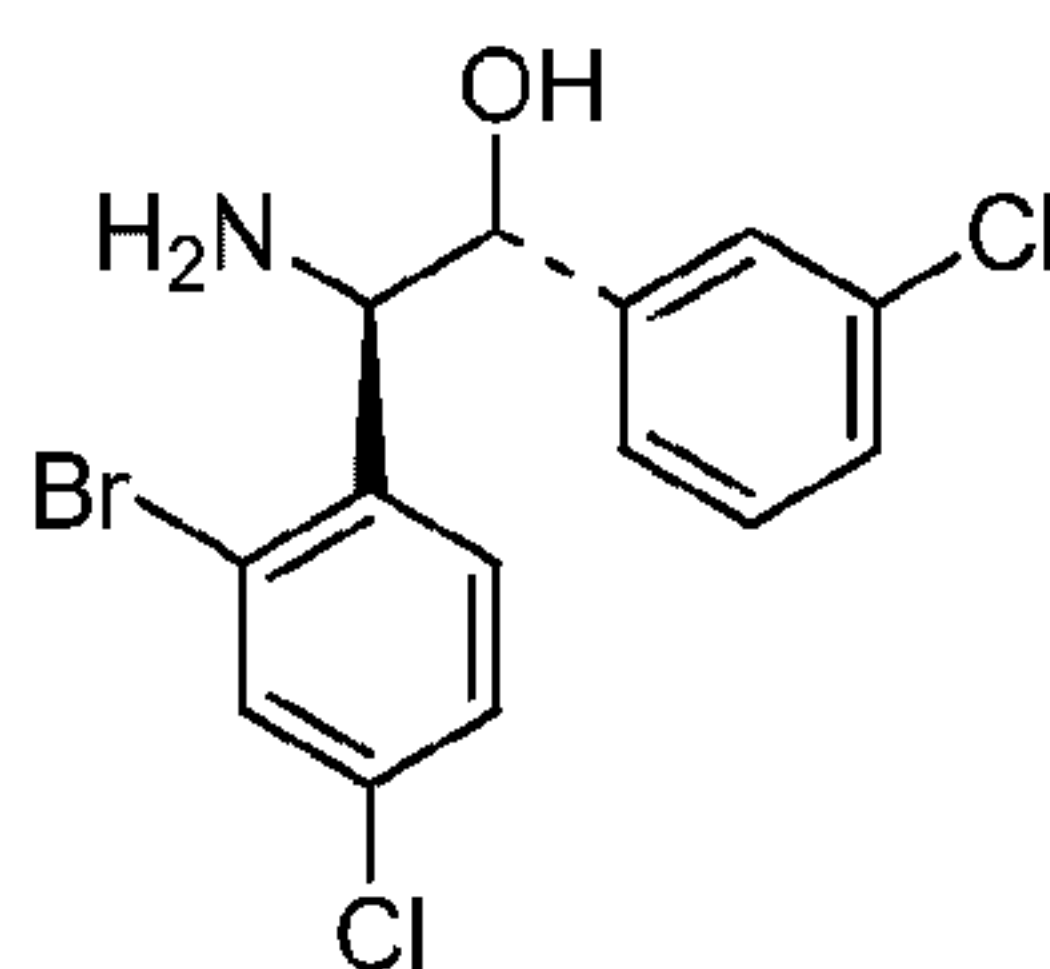
D5		(1R,2R)-2-Amino-2-(4-chloro-3-fluorophenyl)-1-(3-chlorophenyl)ethanol	Mass Spectrum (CI+) m/z = 300.0 (M+1).
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General Procedure 6

5

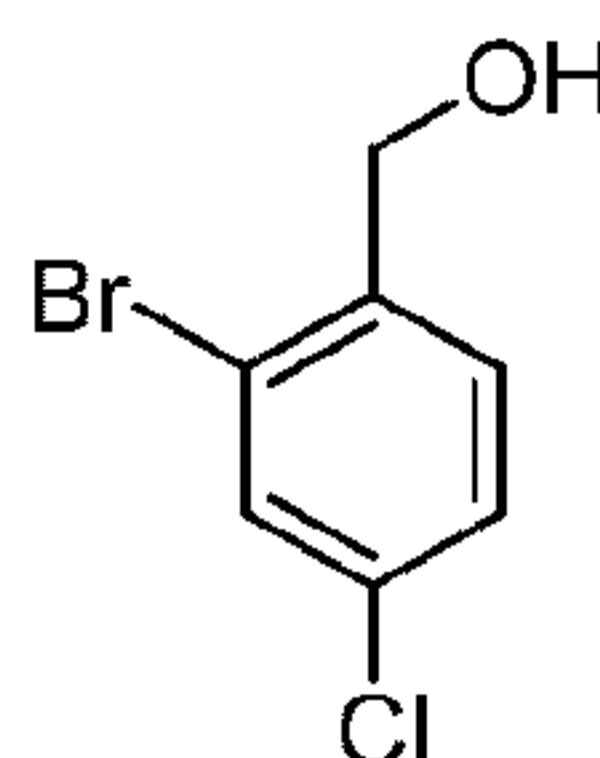
Intermediate E1

(1R,2R)-2-Amino-2-(2-bromo-4-chlorophenyl)-1-(3-chlorophenyl)ethanol



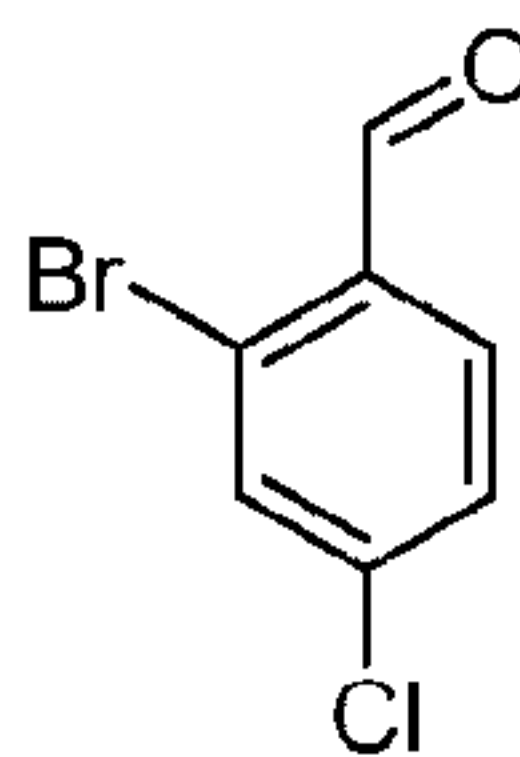
10

Step A. (2-Bromo-4-chlorophenyl)methanol



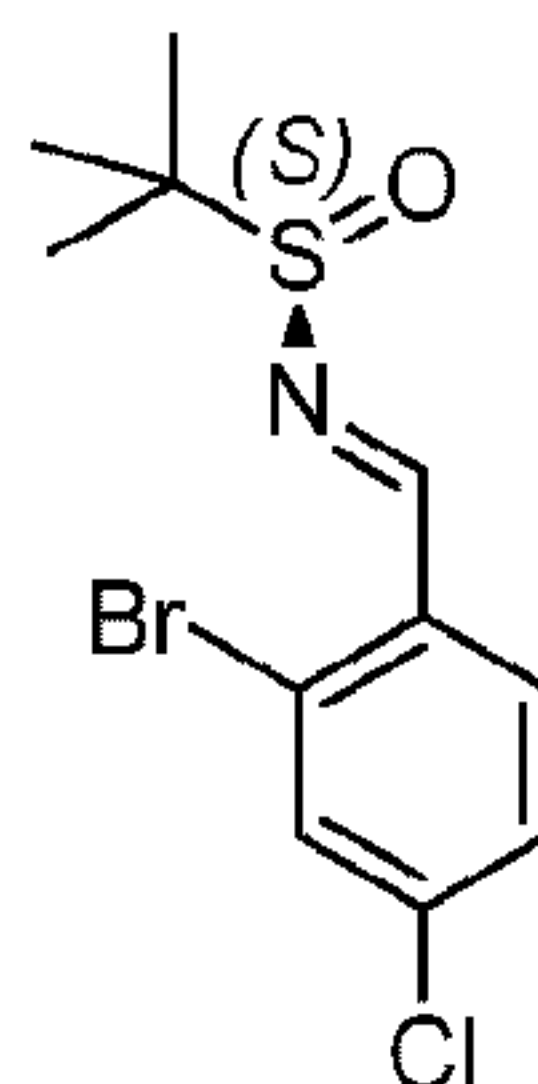
To a solution of 2-bromo-4-chlorobenzoic acid (25.2 g, 107 mmol) in THF (100 mL) at 0 °C was added borane tetrahydrofuran complex, 1.0M in THF (214 mL, 214 mmol). The reaction mixture was stirred at 0 °C for 9 h. The reaction was quenched by adding 1M aq. NaOH solution at 0 °C with stirring. The mixture was concentrated and then extracted with DCM. The combined DCM fractions were washed with 100 mL of brine, dried over Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (220g silica gel, linear gradient 0 to 50% EtOAc : hexane) to give the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.96 (s, 1 H), 4.72 (s, 2 H), 7.33 (dd, *J*=8.22, 2.15 Hz, 1 H), 7.44 (d, *J*=8.22 Hz, 1 H), 7.57 (d, *J*=2.15 Hz, 1 H).

Step B. 2-Bromo-4-chlorobenzaldehyde



To a solution of (2-bromo-4-chlorophenyl)methanol (10.33 g, 46.6 mmol) in CHCl₃ (100 mL) was added manganese (IV) oxide (40.5 g, 466 mmol) with stirring. The reaction mixture was heated to reflux for 4 h under N₂. Then the reaction mixture was filtered and concentrated *in vacuo*. The crude was purified by flash chromatography on silica gel (220g silica gel, linear gradient 0 to 50% EtOAc : hexane) to give the title compound as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.43 (ddd, *J*=8.36, 1.91, 0.88 Hz, 1 H) 7.69 (d, *J*=1.96 Hz, 1 H) 7.87 (d, *J*=8.22 Hz, 1 H) 10.31 (d, *J*=0.78 Hz, 1 H).

Step C. (R)-N-(2-Bromo-4-chlorobenzylidene)-2-methylpropane-2-sulfinamide

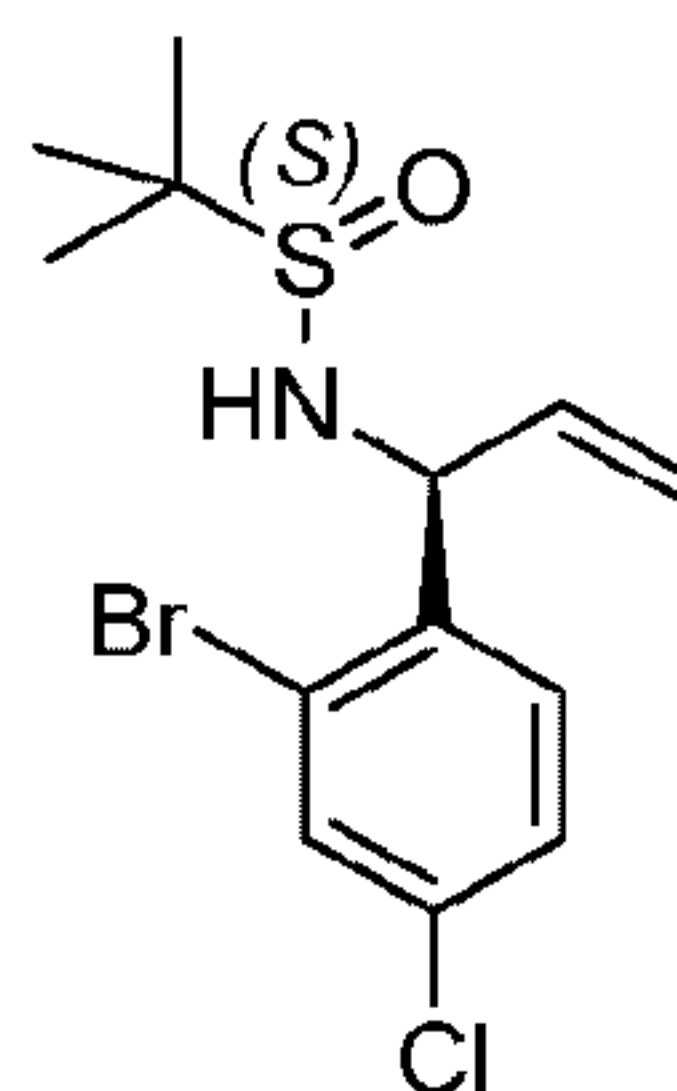


2-Bromo-4-chlorobenzaldehyde (8.72g, 39.8 mmol) and (R)-(+)-*t*-butylsulfinamide (4.38g, 36.1 mmol) were dissolved in 100 mL of THF and titanium (IV) isopropoxide (22.6g, 80.0 mmol) was added dropwise. The reaction mixture was stirred at 65 °C for 17 hours. Then 120 mL of brine was added and the mixture was stirred vigorously for 20 minutes and filtered through a pad of Celite[®] (J.T. Baker, Phillipsberg, NJ, diatomaceous earth), washing with additional EtOAc. After filtration the layers were separated and the organic layer was dried over MgSO₄, filtered and the filtrate was concentrated. The resulting material was purified by chromatography on silica gel (220g silica gel, linear gradient 0 to 60% EtOAc : hexane) to give the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.28 (s, 9 H) 7.39 (ddd, *J*=8.46, 2.01, 0.68 Hz, 1 H) 7.68 (d, *J*=2.15 Hz, 1 H) 8.00 (d, *J*=8.61 Hz, 1 H) 8.91 - 8.94 (m, 1 H). Mass Spectrum (ESI) *m/z* = 322.0 (*M*+1), 645.2 (2*M*+1).

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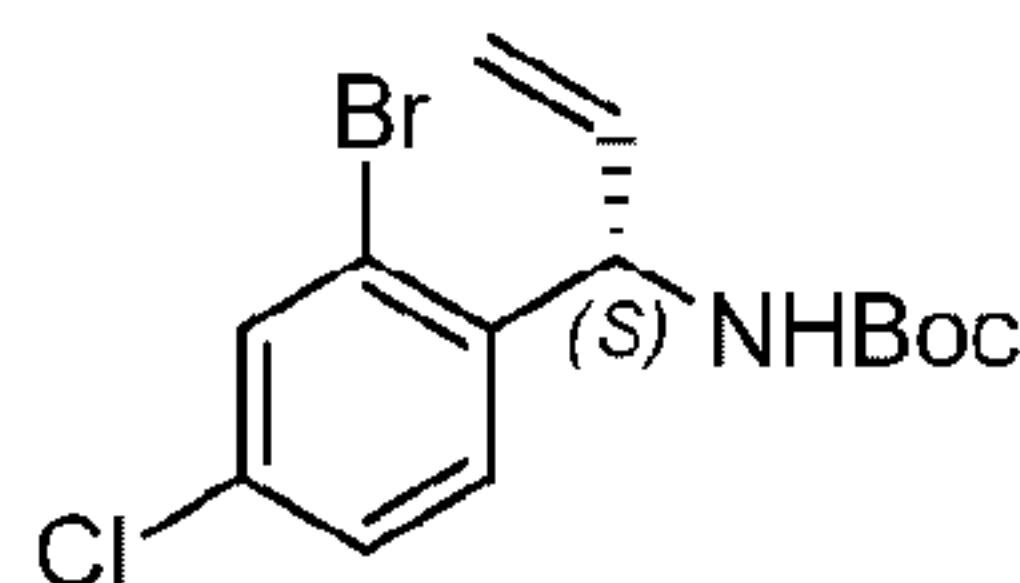
Step D. (S)-N-((S)-1-(2-Bromo-4-chlorophenyl)allyl)-2-methylpropane-2-sulfinamide



20

A solution of (S)-N-(2-bromo-4-chlorobenzylidene)-2-methylpropane-2-sulfinamide (5.85 g, 18.13 mmol) in DCM (50 mL) was cooled to -78 °C and vinylmagnesium bromide (1.0 M in THF, 36.3 mL, 36.3 mmol) was added dropwise over

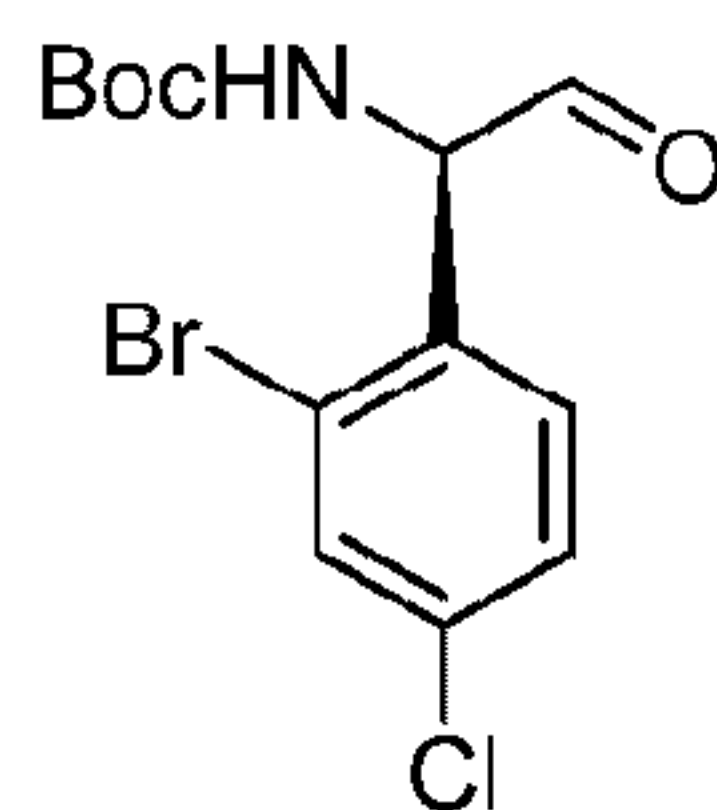
- a period of 25 minutes. The reaction mixture was stirred at -78 °C for 5 h, then 40 mL of sat. aq. NH₄Cl solution was added at -78 °C. The reaction mixture was removed from the cooling bath and allowed to come to rt. The reaction mixture was concentrated under reduced pressure. Water and EtOAc was added and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and the filtrate was concentrated. The residue was purified by chromatography on silica gel (220g silica gel column, RediSep® Rf, Teledyne Isco, Lincoln, NE; eluent: ethyl acetate / DCM = 0:1 to 1:1, gradient elution over 50min, maintaining 1:1 over 10 min; flow rate 100 mL/min) to give the title compound.
- ¹H NMR (400 MHz, CDCl₃) δ ppm 1.23 (s, 9 H) 3.52 (d, *J*=3.91 Hz, 1 H) 5.21 - 5.34 (m, 2 H) 5.44 (dd, *J*=5.87, 4.50 Hz, 1 H) 6.00 (ddd, *J*=16.92, 10.47, 6.26 Hz, 1 H) 7.29 - 7.39 (m, 2 H) 7.59 (d, *J*=1.96 Hz, 1 H) Mass Spectrum (ESI) *m/z* = 352.0 (M+1), 703.0 (2M+1).
- Step E. (S)-*tert*-Butyl 1-(2-bromo-4-chlorophenyl)allylcarbamate



- A 4.0M solution of hydrogen chloride in dioxane (11.4 mL, 45.5 mmol) was added to a solution of (S)-N-((S)-1-(2-bromo-4-chlorophenyl)allyl)-2-methylpropane-2-sulfonamide (4.56 g, 13.00 mmol) in MeOH (12 mL). The mixture was stirred at rt for 30 minutes and concentrated under reduced pressure. The residue was triturated with ether and filtered. The filter cake was washed with ether and dried *in vacuo* to give (S)-1-(2-bromo-4-chlorophenyl)prop-2-en-1-amine as the hydrochloride salt.
- Di-*t*-butyl dicarbonate (3.05 g, 13.99 mmol) was added dropwise to a stirred solution of triethylamine (3.54 mL, 25.4 mmol) and the product from above in DCM (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes and then at rt for 18 h. The reaction mixture was diluted with DCM and washed with water. The combined organic layers were concentrated *in vacuo*. The residue was absorbed onto a plug of silica gel and

purified by chromatography on silica gel (120 g silica gel column, RediSep®
 Rf, Teledyne Isco, Lincoln, NE; eluent: ethyl acetate in hexane 0% to 40%, gradient
 elution) to give the title compound as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm
 1.43 (br. s., 9 H) 4.96 (br. s., 1 H) 5.08 - 5.19 (m, 1 H) 5.19 - 5.29 (m, 1 H) 5.58 (br. s., 1
 5 H) 5.86 - 6.06 (m, 1 H) 7.16 - 7.34 (m, 2 H) 7.59 (d, *J*=1.96 Hz, 1 H). Mass Spectrum
 (ESI) *m/z* = 695.0 (2*M*+1).

Step F. (R)-*tert*-Butyl (1-(2-bromo-4-chlorophenyl)-2-oxoethyl)carbamate

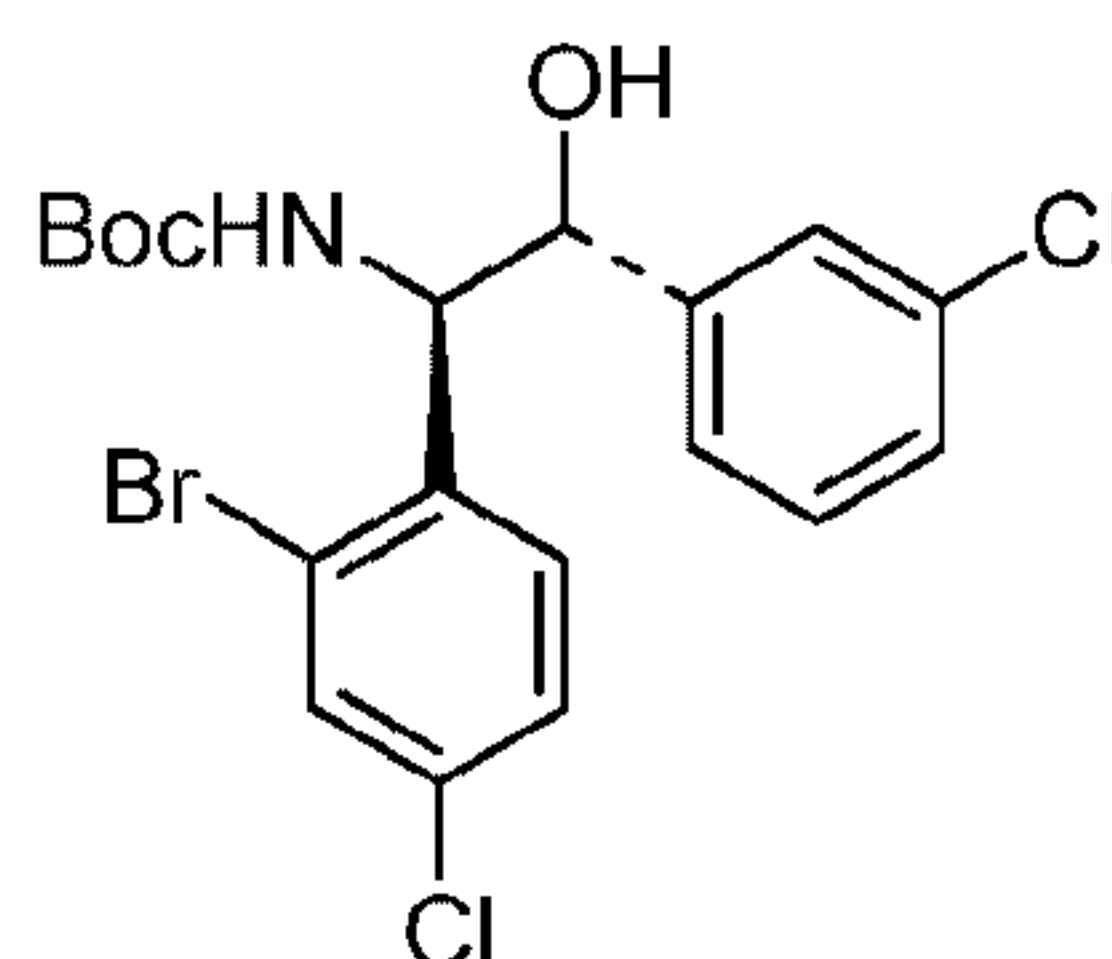


10

Osmium tetroxide (4 wt. % in water, 8.20 mL, 158 mmol) was added dropwise to
 a mixture of (S)-*tert*-butyl 1-(2-bromo-4-chlorophenyl)allylcarbamate (4.06 g, 11.71
 mmol) and 4-methylmorpholine 4-oxide hydrate (3.17 g, 23.42 mmol) in 120 mL of 2:1
 15 t-BuOH (80 mL) and water (40.0 mL). The reaction mixture was stirred overnight at
 room temperature, quenched with 30 mL of sat. aq. sodium thiosulfate solution and
 extracted with 4 x 80 mL of CHCl₃. The combined CHCl₃ extracts were dried over
 MgSO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by
 chromatography on silica gel (120 g silica gel column, RediSep® Rf, Teledyne Isco,
 20 Lincoln, NE; eluent: ethyl acetate / hexanes 0% to 100%, gradient elution over 40min,
 maintaining 100% over 10 min; flow rate 80 mL/min) to give the diol, *tert*-butyl ((1*R*)-1-
 (2-bromo-4-chlorophenyl)-2,3-dihydroxypropyl)carbamate. This material was dissolved
 in a mixture of Et₂O (70.0 mL) and water (35 mL), then sodium periodate (4.59 g, 21.44
 mmol) was added. The reaction mixture was stirred at rt for 3 hours, diluted with ether
 25 (50 mL) and was quenched with 40 mL of sat. aq. Na₂S₂O₃ solution. The layers were
 separated and the aqueous layer was extracted with 3 x 60 mL of ether. The combined
 organic layers were washed with brine, then were dried over MgSO₄, filtered and the
 filtrate was concentrated to give the title compound. ¹H NMR (500 MHz, CDCl₃) δ ppm

1.44 (br. s., 9 H) 5.77 (d, $J=5.38$ Hz, 1 H) 5.90 (br. s., 1 H) 7.22 (d, $J=8.31$ Hz, 1 H) 7.35 (dd, $J=8.31, 1.96$ Hz, 1 H) 7.66 (d, $J=1.71$ Hz, 1 H) 9.58 (br. s., 1 H).

Step G: *tert*-Butyl ((1R,2R)-1-(2-bromo-4-chlorophenyl)-2-(3-chlorophenyl)-2-hydroxyethyl)carbamate



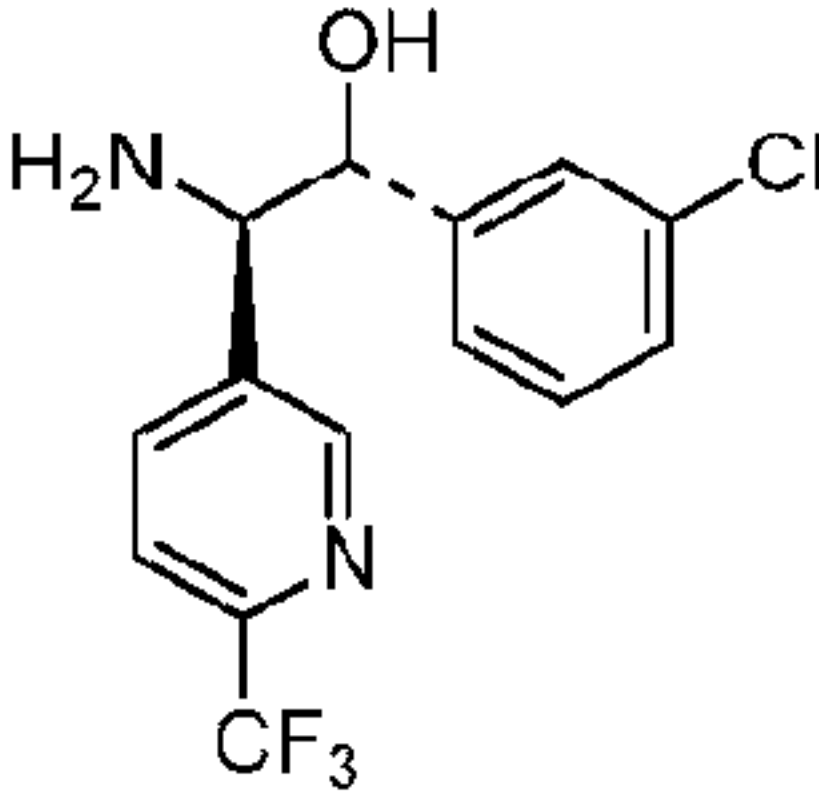
A solution of (R)-*tert*-butyl 1-(2-bromo-4-chlorophenyl)-2-oxoethylcarbamate (3.74 g, 10.73 mmol; general procedure 6, step F) in 40 mL of THF was added to a 0.5M solution of 3-chlorophenylmagnesium bromide in THF (107 mL, 53.6 mmol) dropwise over a period of 40 minutes at room temperature. The reaction mixture was then stirred at room temperature for another 1.5 hours and quenched with 40 mL of sat. aq. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with 3 x 100 mL of EtOAc. The combined organic layers were washed with sat. aq. NaCl solution, then were dried over MgSO_4 , filtered and the filtrate was concentrated. The residue was purified by chromatography on silica gel (120 g silica gel column, RediSep® Rf, Teledyne Isco, Lincoln, NE; eluent: ethyl acetate / hexanes 0% to 100%, gradient elution) to give the title compound as a white crystalline solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.31 (s, 9 H) 4.92 (br. s., 1 H) 5.20 (br. s., 1 H) 7.20 - 7.35 (m, 2 H) 7.39 (d, $J=8.22$ Hz, 2 H) 7.45 - 7.57 (m, 2 H) 7.62 (d, $J=2.15$ Hz, 1 H).

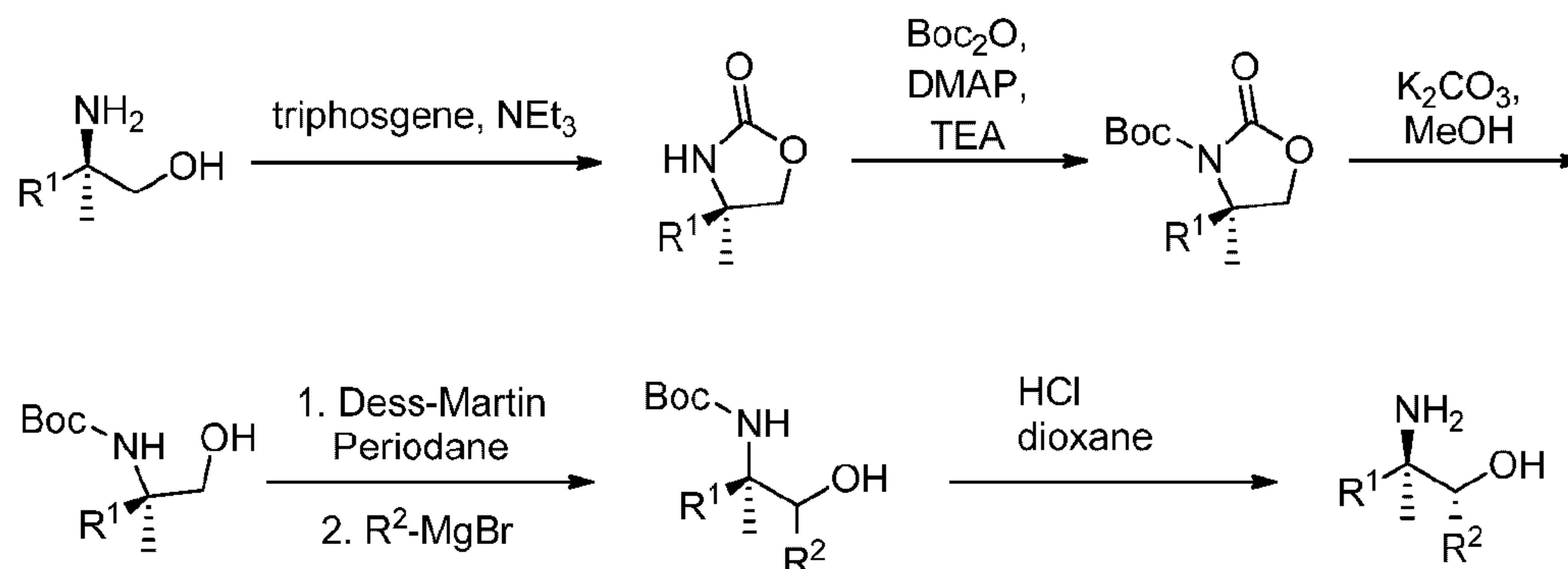
Step H. (1R,2R)-2-Amino-2-(2-bromo-4-chlorophenyl)-1-(3-chlorophenyl)ethanol hydrochloride

A solution of 4.0M HCl in 1,4-dioxane (12.68 mL, 50.7 mmol) was added to *tert*-butyl (1R,2R)-1-(2-bromo-4-chlorophenyl)-2-(3-chlorophenyl)-2-hydroxyethylcarbamate

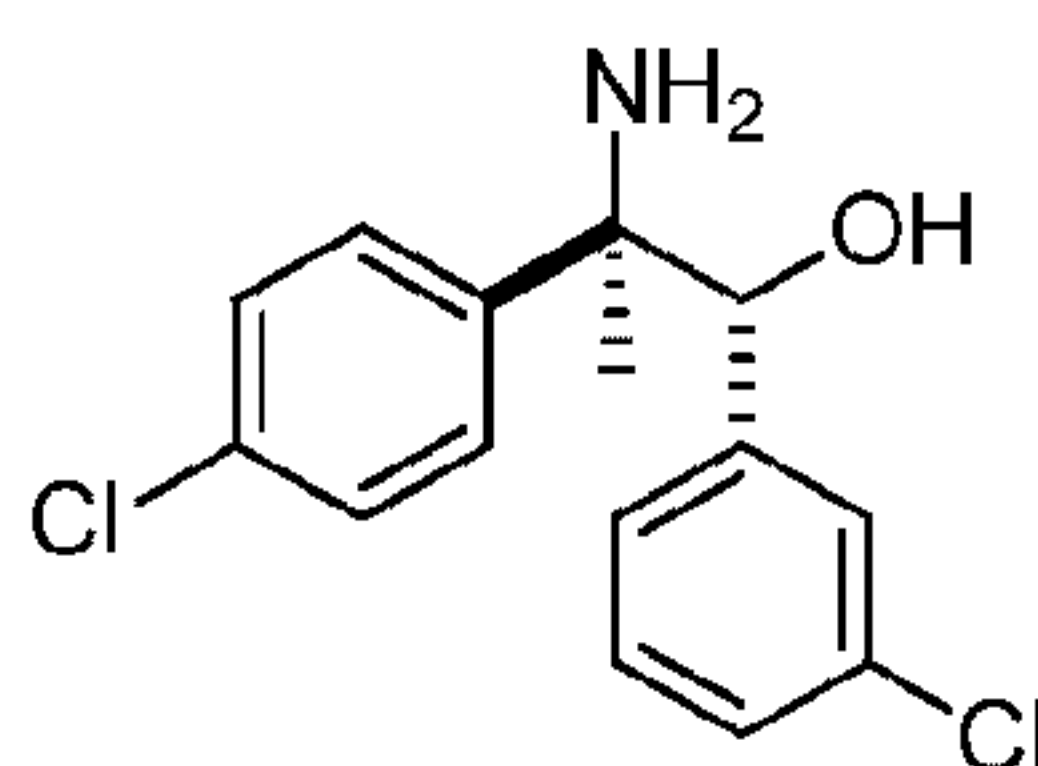
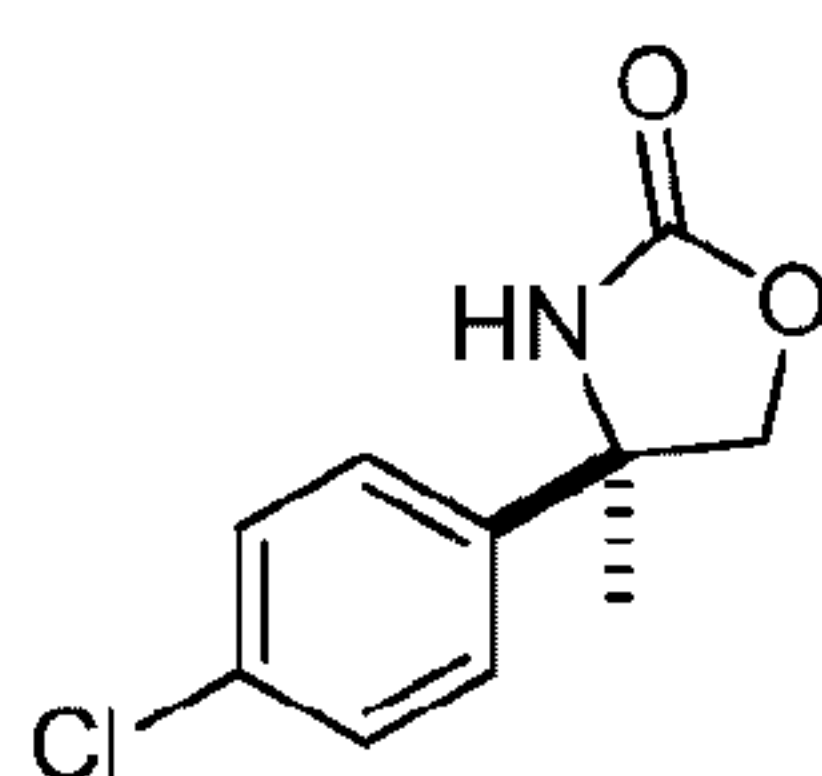
(2.34 g, 5.07 mmol, Step G) in DCM (20 mL) and the reaction mixture was stirred at rt for 1.5 h and concentrated *in vacuo* to afford a semi-solid that was triturated with ether. The solids were separated by filtration to afford the title compound. The product was used in the next step without further purification. Mass Spectrum (ESI) m/z = 360.0 (M+1).

The following intermediate E2 was prepared by a procedure analogous to the one described above.

Intermediate	Structure	Name	Characterization
E2		(1R,2R)-2-amino-1-(3-chlorophenyl)-2-(6-(trifluoromethyl)pyridin-3-yl) ethanol	^1H NMR (500 MHz, CD_3OD) δ ppm 4.68 (d, J =7.83 Hz, 1 H) 5.02 (d, J =7.83 Hz, 1 H) 7.16 - 7.22 (m, 1 H) 7.27 - 7.30 (m, 2 H) 7.40 (s, 1 H) 7.86 (d, J =8.07 Hz, 1 H) 8.11 (dd, J =8.19, 2.08 Hz, 1 H) 8.61 (d, J =1.71 Hz, 1 H). Mass Spectrum (ESI) m/z = 317.0 (M+1).

General Procedure 7**5 Intermediate F1**

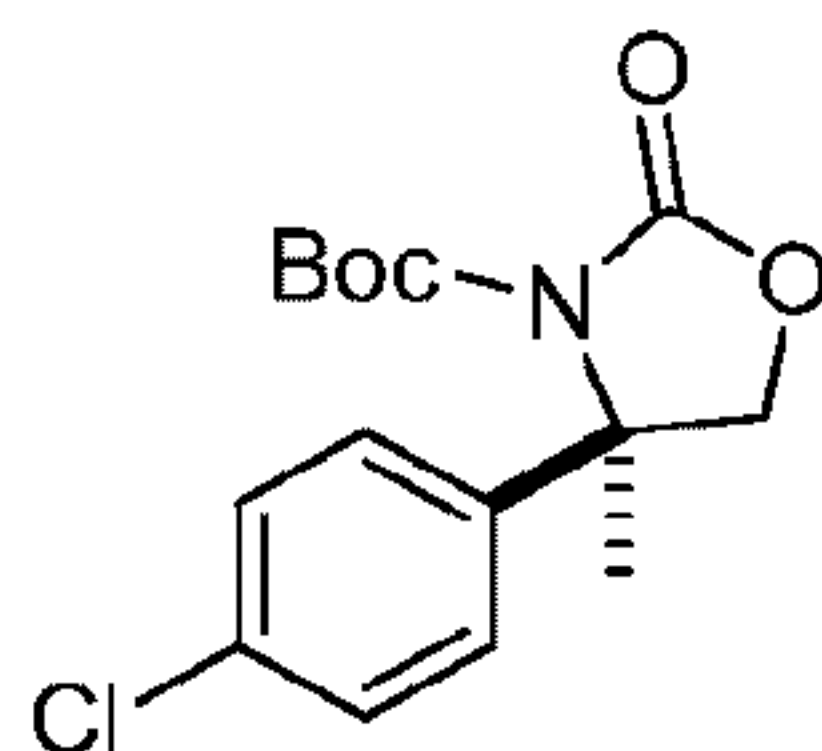
(1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)propan-1-ol

**10 Step A. (R)-4-(4-Chlorophenyl)-4-methyloxazolidin-2-one**

To a 100-mL round-bottomed flask equipped with an addition funnel was added (2R)-2-amino-2-(4-chlorophenyl)propan-1-ol HCl salt (5 g, 22.51 mmol) and triethylamine (9.4 mL, 67.5 mmol) in CH₂Cl₂ (45.0 mL) at 0 °C. To this mixture a solution of triphosgene (1.670 mL, 11.26 mmol) in DCM (20 mL) was added dropwise over a period of 1 h at 0 °C. The reaction was stirred for an additional 2 h at 0 °C. The reaction was then allowed to stir at rt overnight. After this period, the reaction was

quenched with a saturated sodium bicarbonate solution (30 mL) and allowed to stir for 1 hour. The crude biphasic mixture was then separated. The aqueous layer was washed with DCM (3 x 30 mL). The organic extract was dried over MgSO₄. The solution was filtered and concentrated in vacuo to give the crude material as a light-yellow oil. The crude material was purified by chromatography on silica gel, eluting with isocratic 3 step gradient of 10% to 30% acetone in hexanes, to provide the title compound as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.40 (t, *J* = 2.50 Hz, 1H), 7.37 (t, *J* = 2.50 Hz, 2H), 7.34 (t, *J* = 2.35 Hz, 2H), 7.31 (t, *J* = 2.20 Hz, 1H), 5.77 - 5.97 (m, 1H), 4.38 (d, *J* = 8.41 Hz, 1H), 4.31 (d, *J* = 8.61 Hz, 1H), 1.76 (s, 3H). Mass Spectrum (ESI) *m/z* = 212.2 [M]⁺.

Step B. (R)-tert-Butyl 4-(4-chlorophenyl)-4-methyl-2-oxooxazolidine-3-carboxylate

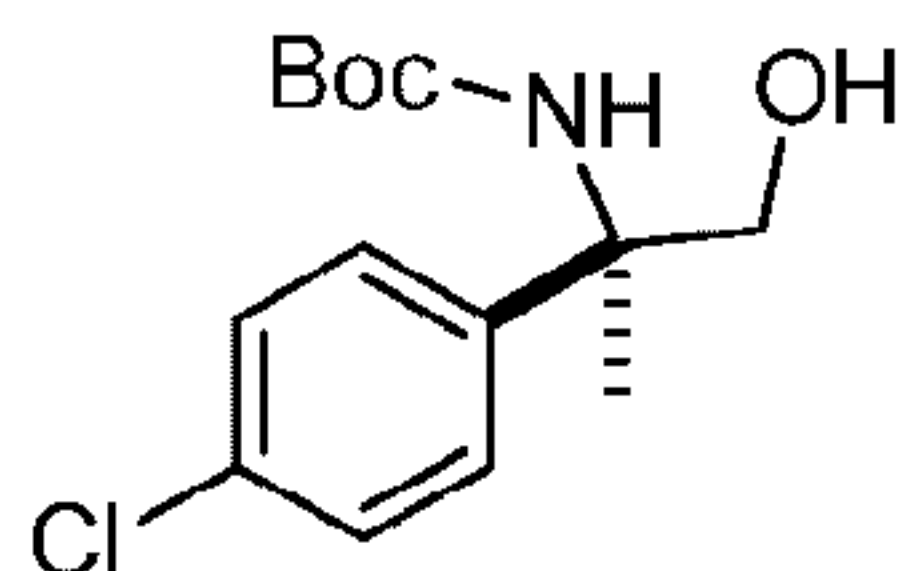


15

To a 100-mL round-bottomed flask was added (R)-4-(4-chlorophenyl)-4-methyloxazolidin-2-one (4.6 g, 21.73 mmol, Step A), DMAP (0.266 g, 2.173 mmol) and triethylamine (4.53 mL, 32.6 mmol) in THF (43.5 mL). To this solution at 0 °C, di-tert-butyl dicarbonate (6.98 mL, 32.6 mmol) was added. The reaction was allowed to stir at room temperature overnight. The reaction mixture was diluted with saturated sodium bicarbonate (30 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried over MgSO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was absorbed onto a plug of silica gel and purified by chromatography on a silica gel column (120 g, RediSep® Rf, Teledyne Isco, Lincoln, NE), eluting with a gradient of 0% to 30% acetone in hexanes, to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.28 - 7.35 (m, 2H), 7.21 - 7.28 (m, 2H), 4.10 (s, 2H), 1.89 (s, 3H), 1.21 (s, 9H). Mass Spectrum (ESI) *m/z* = 256.2 [M - tBu]⁺.

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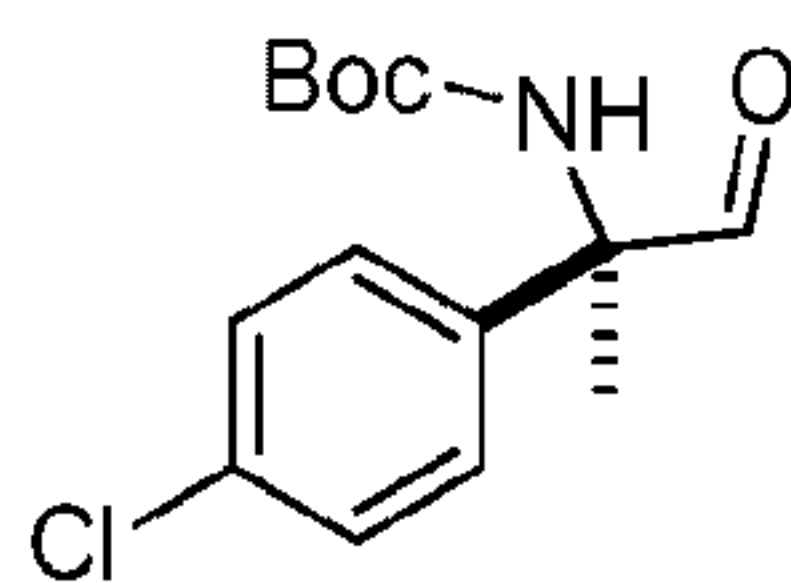
Step C: (R)-*tert*-Butyl (2-(4-chlorophenyl)-1-hydroxypropan-2-yl)carbamate



- 5 To a 250-mL round-bottomed flask was added (R)-*tert*-butyl 4-(4-chlorophenyl)-4-methyl-2-oxooxazolidine-3-carboxylate (5.7 g, 18.28 mmol, Step B) and potassium carbonate (2.76 g, 45.7 mmol) in methanol (73 mL). The reaction was stirred at this temperature overnight. The reaction mixture was diluted with dichloromethane (80 mL) and extracted with brine (3 x 30 mL). The organic extract was washed with water (30
- 10 mL) and dried over MgSO₄. The solution was filtered and concentrated in vacuo to give the crude material as a light yellow solid. The crude material was absorbed onto a plug of silica gel and purified by chromatography on a silica gel column (120 g, RediSep[®] Rf, Teledyne Isco, Lincoln, NE), eluting with a gradient of 5% to 35% acetone in hexanes, to provide the title compound as white solid.
- 15 ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, *J* = 0.78 Hz, 4H), 5.13 - 5.26 (m, 1H), 3.85 - 3.97 (m, 1H), 3.73 (s, 1H), 1.60 (s, 3H), 1.43 (br. s., 9H). Mass Spectrum (ESI) *m/z* = 308.2 [M + Na]⁺.

Step D: (R)-*tert*-Butyl (2-(4-chlorophenyl)-1-oxopropan-2-yl)carbamate

20



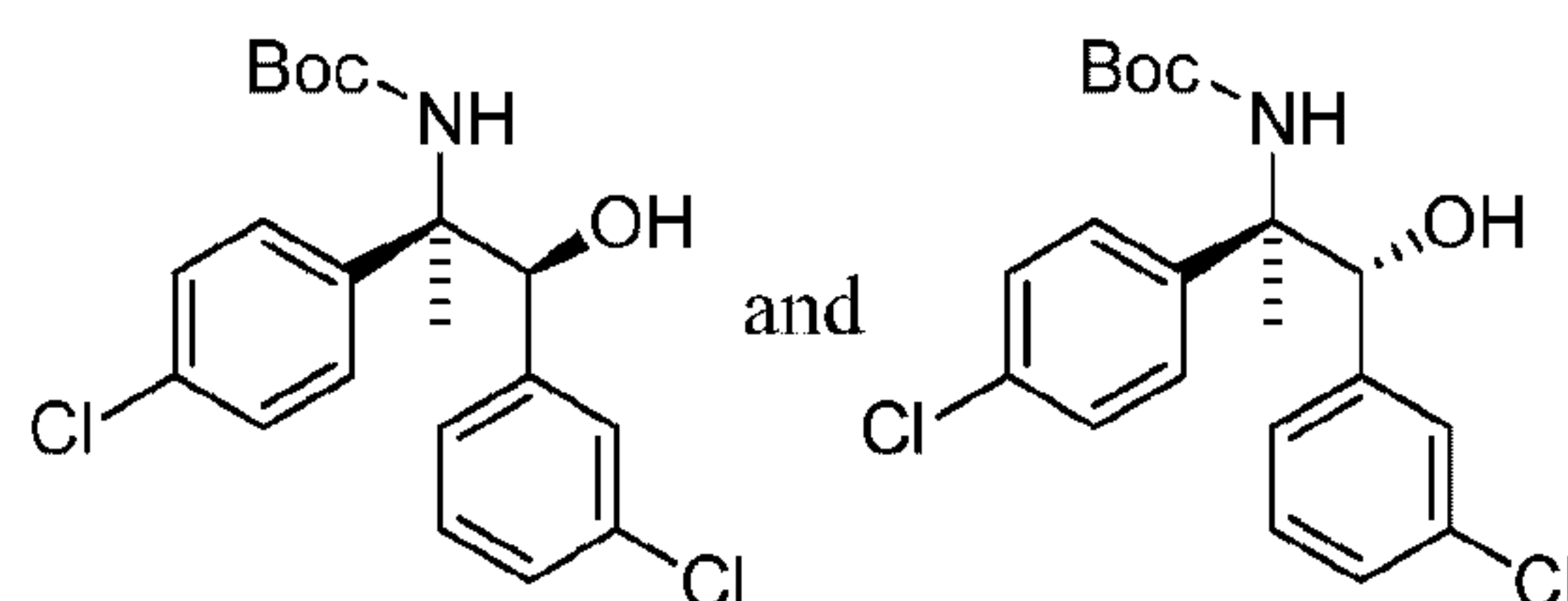
- Dess-martin periodinane (13.36 g, 31.5 mmol) was added to a suspension of (R)-*tert*-butyl (2-(4-chlorophenyl)-1-hydroxypropan-2-yl)carbamate (4.5 g, 15.75 mmol,
- 25 Step C) in wet DCM (1 μL water/ 1 mL DCM) at rt. The mixture was stirred at 25 °C for 2 h. After this time the reaction mixture was diluted with ether (40 mL) and a solution of Na₂S₂O₃ (10 equiv) in saturated aq. NaHCO₃ solution (40 mL) was added. The mixture

was stirred vigorously for 10 minutes and the layers were separated. The aq. layer was extracted with diethyl ether. The organics were pooled, dried over MgSO_4 , filtered and concentrated in vacuo to provide an off-white solid. The product was used in the following step without further purification.

- 5 (Note: The reaction requires the use of wet DCM. This is prepared by stirring vigorously 1 μL water/ 1mL DCM until no water droplets are observed. The resulting aldehyde is prone to the formation of hemiacetals so avoid the use of ethanol-stabilized diethyl ether). ^1H NMR (400 MHz, CDCl_3) δ 9.28 (s, 1H), 7.29 - 7.42 (m, 4H), 5.60 - 5.85 (m, 1H), 1.82 (s, 3H), 1.42 (d, J = 8.80 Hz, 9H). Mass Spectrum (ESI) m/z = 306.1 $[\text{M} + \text{Na}]^+$.

10

Step E. *tert*-Butyl ((1S,2R)-1-(3-chlorophenyl)-2-(4-chlorophenyl)-1-hydroxypropan-2-yl)carbamate and *tert*-Butyl ((1R,2R)-1-(3-chlorophenyl)-2-(4-chlorophenyl)-1-hydroxypropan-2-yl)carbamate

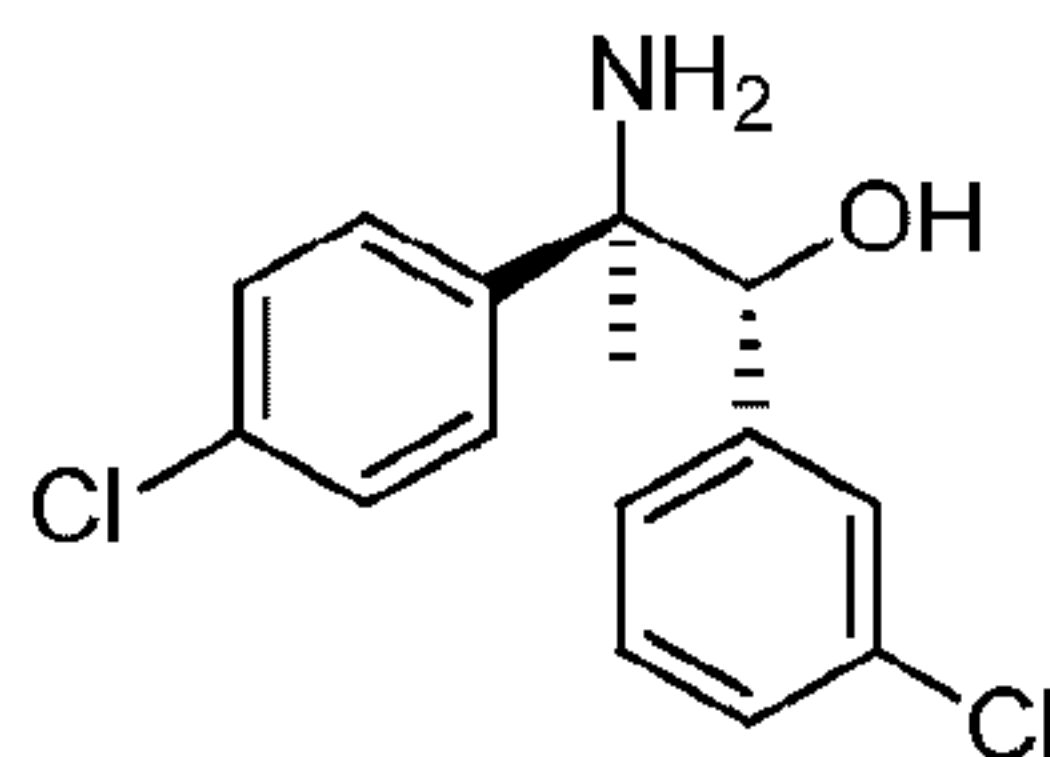


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- To a solution of (3-chlorophenyl)magnesium bromide (1M, 40 mmols) in diethyl ether was added a solution of (R)-*tert*-butyl (2-(4-chlorophenyl)-1-oxopropan-2-yl)carbamate (5.66 g, 19.95 mmol, Step D) in Et_2O (20 mL). After stirring overnight, the reaction mixture was quenched by addition of sat. aq. NH_4Cl solution (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were pooled and dried over MgSO_4 . The solution was filtered and concentrated. The crude material was absorbed onto a plug of silica gel and purified by chromatography on a silica gel column (330 g, RediSep® Rf, Teledyne Isco, Lincoln, NE), eluting with a gradient of 0 % to 40 % EtOAc in hexane, to provide the title compounds as a 3:1 mixture of isomers. Mass Spectrum (ESI) m/z = 418.2 $[\text{M} + \text{Na}]^+$.

25

Step F. (1R,2R)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)propan-1-ol

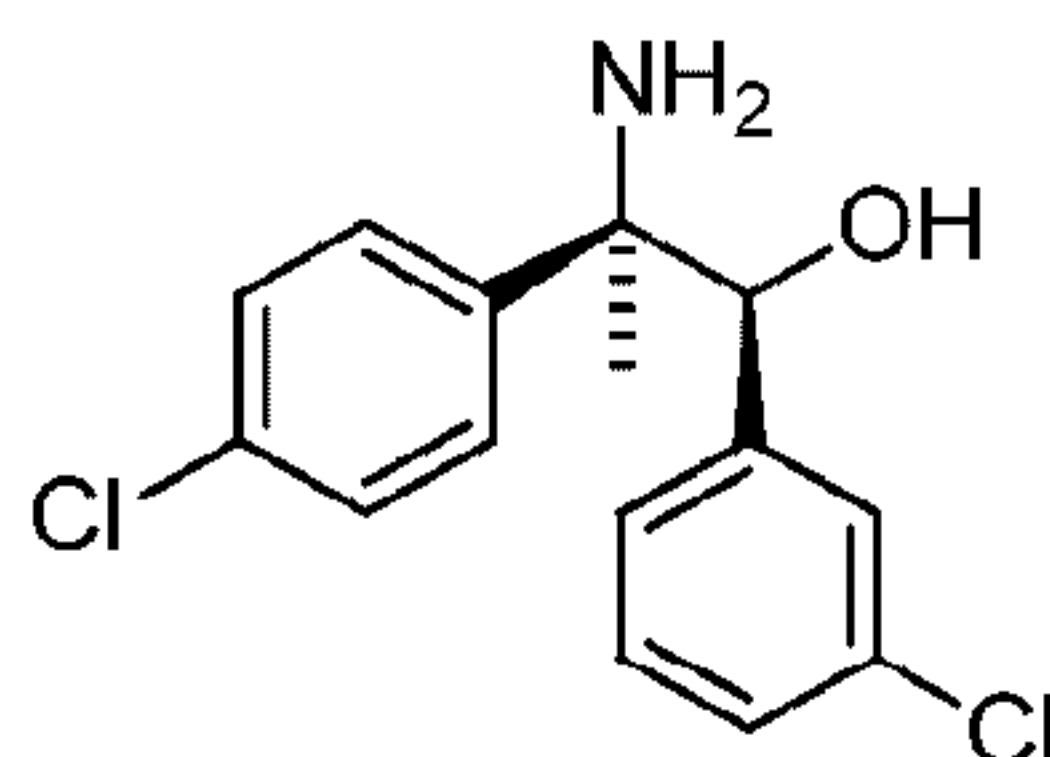


The mixture of *tert*-butyl ((1*S*,2*R*)-1-(3-chlorophenyl)-2-(4-chlorophenyl)-1-hydroxypropan-2-yl)carbamate and *tert*-butyl ((1*R*,2*R*)-1-(3-chlorophenyl)-2-(4-chlorophenyl)-1-hydroxypropan-2-yl)carbamate (3.0 g, 7.57 mmol, Step E) was treated with a 4.0M solution of HCl in 1,4-dioxane (34.1 mL, 136 mmol) at rt for 2 h. The crude mixture was basified with a saturated solution of sodium bicarbonate. The biphasic solution was separated and the aqueous layer was washed with dichloromethane (3 x 30 mL). The combined organic layers were dried over MgSO₄, filtered and the filtrate was concentrated. The residue was absorbed onto a plug of silica gel and purified by chromatography on silica gel column (120 g, RediSep® Rf, Teledyne Isco, Lincoln, NE), eluting with isocratic 70/25/5 DCM/Acetone/MeOH with 0.1 % of triethylamine to provide the title compound as the first (faster) eluting isomer. ¹H NMR (400 MHz, CDCl₃) δ 7.21 - 7.25 (m, 3H), 7.11 - 7.16 (m, 1H), 7.03 - 7.10 (m, 2H), 6.79 (d, *J* = 7.63 Hz, 1H), 4.61 (s, 1H), 2.07 (s, 2H), 1.18 (s, 3H). Mass Spectrum (ESI) *m/z* = 296.2 [*M*]⁺.

Further elution provided:

Intermediate F2

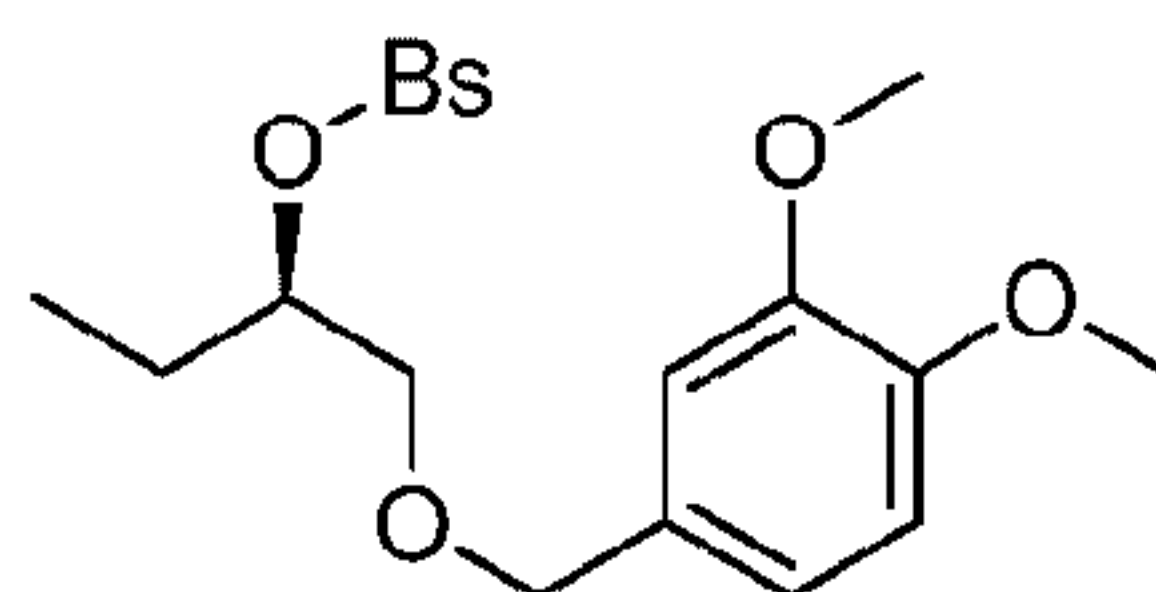
(1*S*,2*R*)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)propan-1-ol



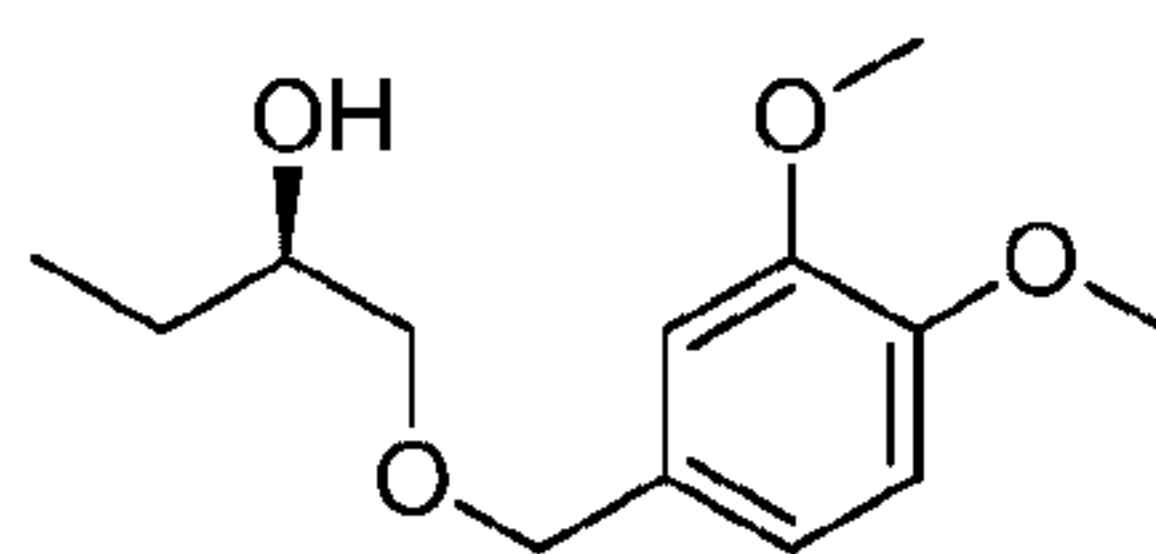
^1H NMR (400 MHz, CDCl_3) δ 7.10 - 7.18 (m, 2H), 7.02 - 7.09 (m, 2H), 6.97 (d, $J = 15.65$ Hz, 1H), 6.87 (t, $J = 1.86$ Hz, 1H), 6.64 (d, $J = 7.83$ Hz, 1H), 4.54 (s, 1H), 2.01 - 2.10 (m, 2H), 1.46 (s, 3H). Mass Spectrum (ESI) $m/z = 296.2$ $[\text{M}]^+$.

5 Intermediate G

(R)-1-((3,4-Dimethoxybenzyl)oxy)butan-2-yl 4-bromobenzenesulfonate



10 Step A. (R)-1-((3,4-Dimethoxybenzyl)oxy)butan-2-ol

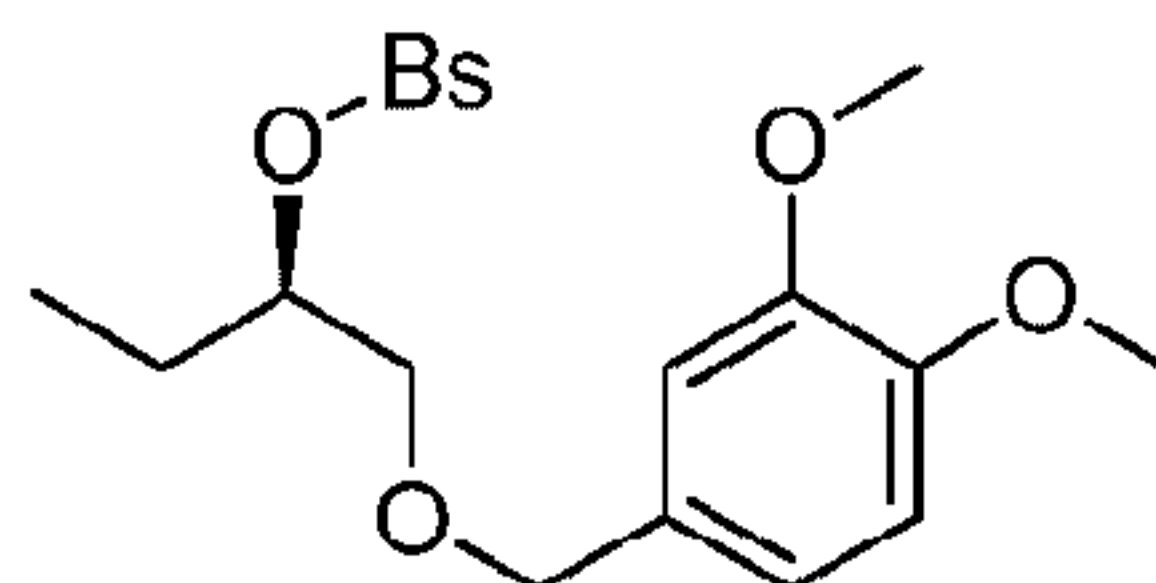


Over a period of 30 min, to a suspension of sodium hydride (60% dispersion in mineral oil, 8.91 g, 223 mmol) in DMF (300 mL) at 60 °C was added dropwise a solution of 3,4-dimethoxybenzyl alcohol (29.4 mL, 202 mmol) in DMF (100 mL). The reaction was stirred at 60 °C for 0.5 h until H_2 evolution ceased. The reaction was cooled to 45 °C, and then (R)-2-ethyloxirane (17.61 mL, 202 mmol) was added dropwise. The reaction was allowed to stir at 45 °C overnight. The reaction mixture was diluted with sat aq. NaHCO_3 solution (300 mL) and extracted with diethyl ether (3 x 300 mL). The organic extract was washed with water (3 x 300 mL) and dried over MgSO_4 . The solution was filtered and concentrated under reduced pressure. The residue was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (330 g, RediSep® Rf, Teledyne Isco, Lincoln, NE), eluting with a gradient of 10 % to 40% acetone in hexanes, to provide the title compound as an off-white oil. ^1H NMR (400 MHz, CDCl_3) δ 6.81 - 6.93 (m, 3H), 4.51 (s, 2H), 3.91 (d, $J = 1.00$ Hz, 6H), 3.69 - 3.82

(m, 1H), 3.52 (dd, $J = 3.03, 9.49$ Hz, 1H), 3.33 (dd, $J = 8.02, 9.39$ Hz, 1H), 1.44 - 1.58 (m, 2H), 0.98 (t, $J = 7.53$ Hz, 3H). MS (ESI) 263.2 $[M + Na]^+$.

Step B. (R)-1-((3,4-Dimethoxybenzyl)oxy)butan-2-yl 4-bromobenzenesulfonate

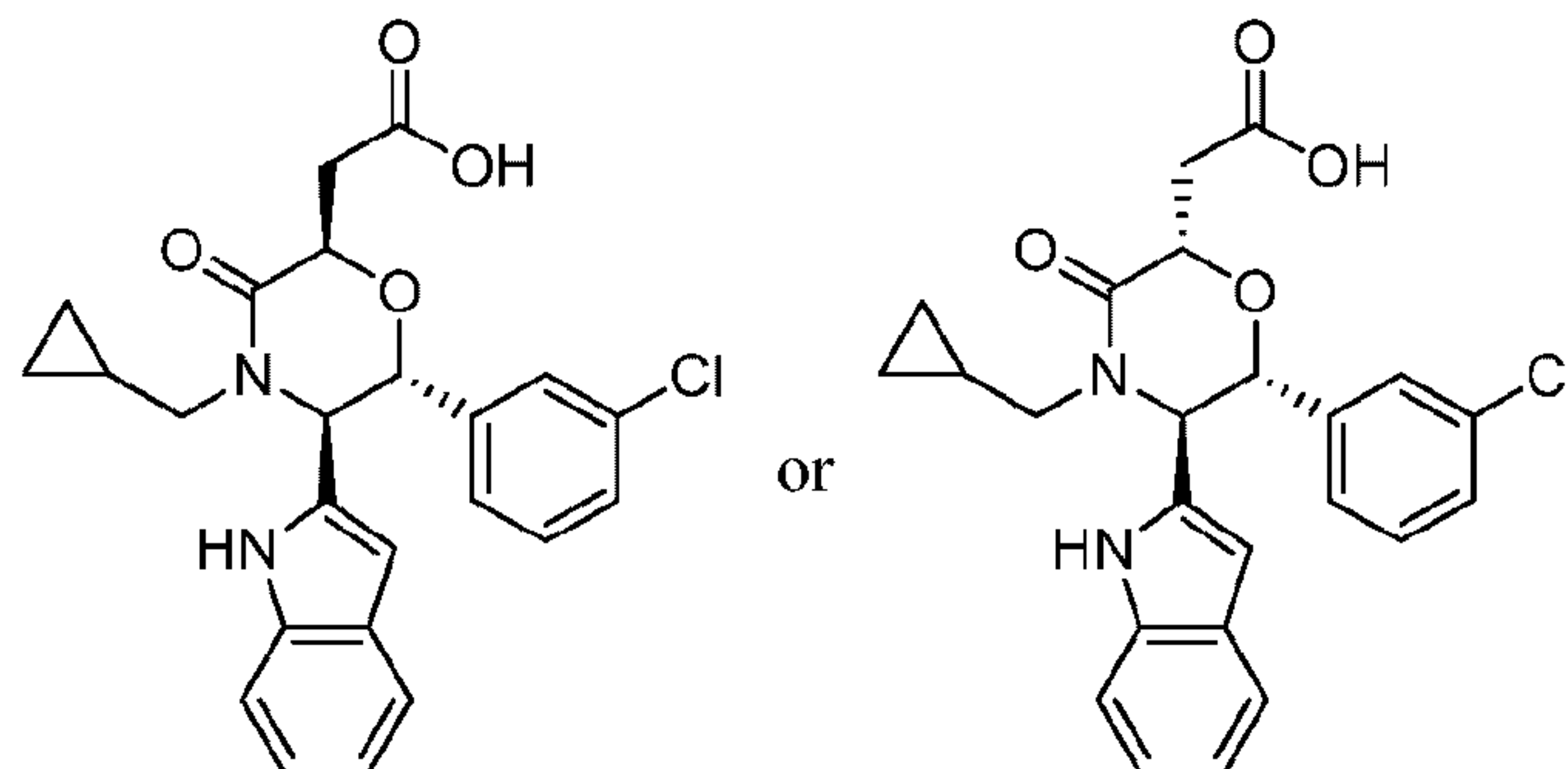
5



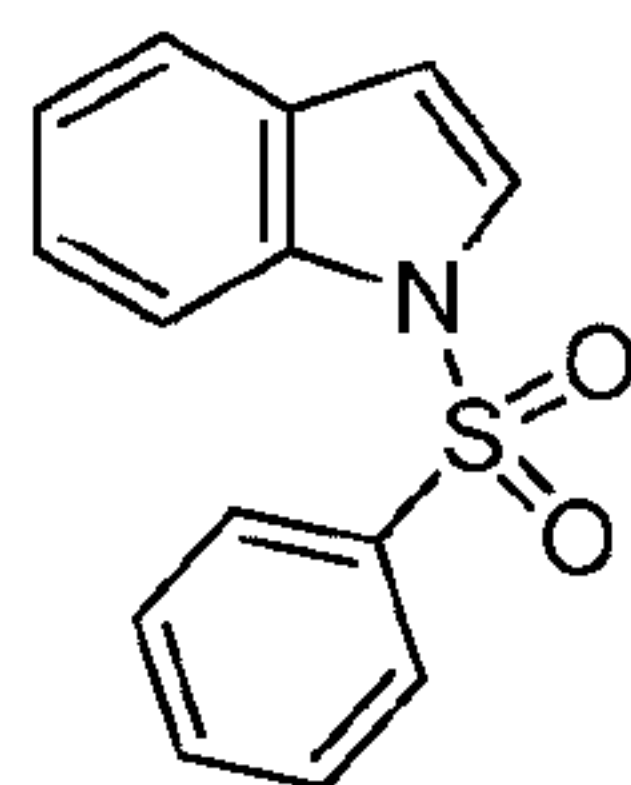
To DMAP (14.54 g, 119 mmol) and (R)-1-((3,4-dimethoxybenzyl)oxy)butan-2-ol (13.0 g, 54.1 mmol) in CH_2Cl_2 (180 mL) was added 4-bromobenzene-1-sulfonyl chloride (20.74 g, 81 mmol). The reaction was stirred at room temperature overnight. The crude material was partitioned between ethyl acetate (50 mL) and saturated sodium bicarbonate (100 mL). The organics were sequestered and the aqueous was extracted further with ethyl acetate (50 mL). The organics were combined and washed with 0.1 M HCl (2 x 50 mL). The organics were then washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (330 g, RediSep® Rf, Teledyne Isco, Lincoln, NE), eluting with a 3 step gradient of 10% to 30% acetone in hexanes which afforded the title compound. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, $J = 8.56$ Hz, 2H), 7.59 (d, $J = 8.31$ Hz, 2H), 6.66 - 6.89 (m, 3H), 4.67 (quin, $J = 5.62$ Hz, 1H), 4.25 - 4.45 (m, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.42 - 3.58 (m, 2H), 1.64 - 1.82 (m, 2H), 0.88 (t, $J = 7.46$ Hz, 3H). MS (ESI) 481.0 $[M + Na]^+$.

EXAMPLE 1

2-((2R,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(1H-indol-2-yl)-3-oxomorpholin-2-yl)acetic acid or 2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(1H-indol-2-yl)-3-oxomorpholin-2-yl)acetic acid



Step A. 1-(Phenylsulfonyl)-1H-indole

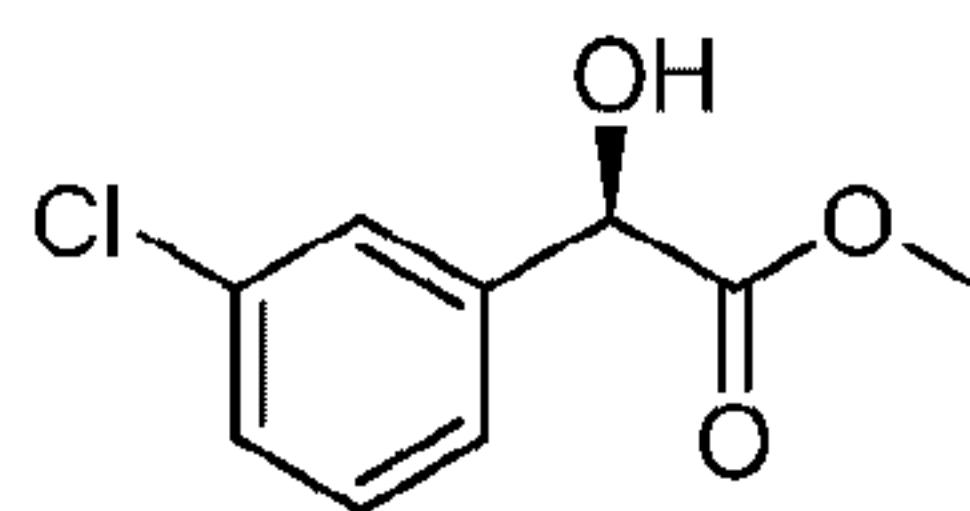


5

Indole (10.00 g, 85 mmol) was added slowly to a suspension of NaH (60% in mineral oil, 4.27 g, 107 mmol) in anhydrous DMF (213 mL) at 0 °C under argon. After 20 minutes the ice bath was removed. After 1 hour the reaction mixture was recooled to 0 °C, benzenesulfonyl chloride (12.1 mL, 94 mmol) was added slowly and the reaction mixture was allowed to warm to rt. After 16 hours the reaction mixture was poured into ice-cold water (500 mL) and extracted with diethyl ether (3 x 300 mL). The organics were pooled, washed with brine, dried over MgSO₄, filtered and the filtrate was concentrated to provide an off-white solid. Purification by chromatography on silica gel (300 g silica gel column, RediSep® Rf, Teledyne Isco, Lincoln, NE; eluent: ethyl acetate in hexane 0% to 10%, gradient elution) provided the title compound as a white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.70 (d, *J* = 3.6 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.46 (m, 2H), 7.55 (m, 2H), 7.60 (d, *J* = 3.6 Hz, 1H), 7.90 (m, 2H), 8.03 (d, *J* = 8.3 Hz, 1H).

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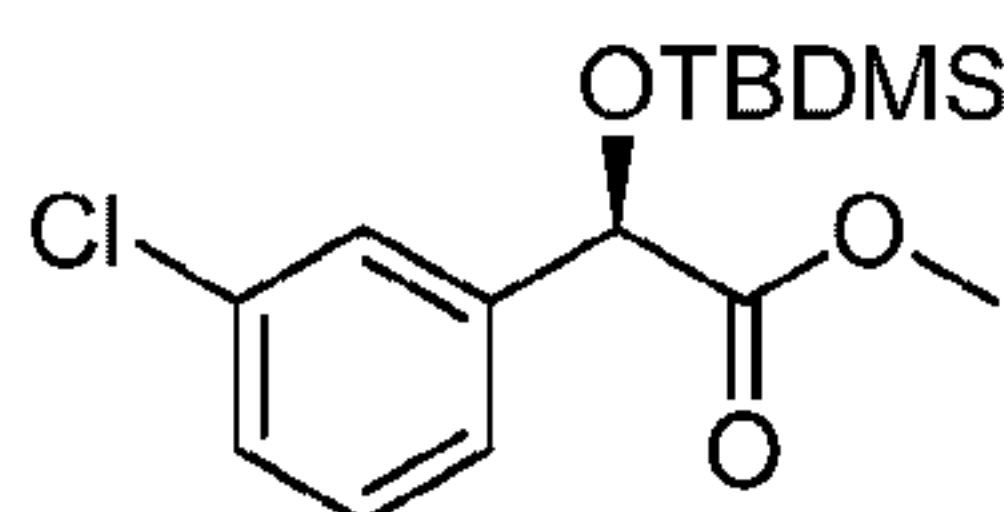
Step B. (R)-Methyl 2-(3-chlorophenyl)-2-hydroxyacetate



Sulfuric acid (1.43 mL, 26.8 mmol) was added to a solution of (R)-2-(3-chlorophenyl)-2-hydroxyacetic acid (50.00 g, 268 mmol) in MeOH (536 mL) at rt. The reaction mixture was heated to reflux for 5 hours. Most of the MeOH was removed in vacuo and the remaining solution was partitioned between EtOAc (200 mL) and sat. aq. NaHCO₃ solution (300 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 200 mL). The organics were pooled, washed with brine, dried over MgSO₄, filtered and the filtrate was concentrated to provide a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ ppm 3.74 (s, 3H), 5.11 (s, 1H), 7.26 (m, 3 H), 7.45 (s, 1H).

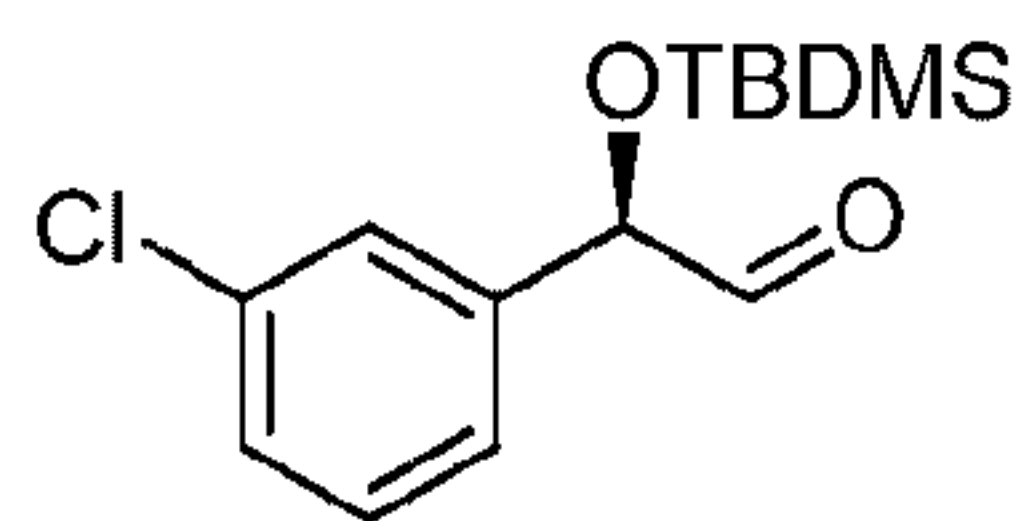
Step C. (R)-Methyl 2-(*tert*-butyldimethylsilyloxy)-2-(3-chlorophenyl)acetate



TBDMS-Cl (59.8 g, 397 mmol) was added to a solution of (R)-methyl 2-(3-chlorophenyl)-2-hydroxyacetate (53.10 g, 265 mmol; Example 1, step B) and imidazole (45.0 g, 662 mmol) in anhydrous DMF (265 mL) at rt under argon. After 9 hours the reaction mixture was poured into water (1 L) and extracted with Et₂O (3 x 500 mL). The organics were pooled, washed with brine, dried over MgSO₄, filtered and the filtrate was concentrated to provide a colorless liquid. Purification by chromatography on silica gel (2 stacked 330 g silica gel columns, RediSep® Rf, Teledyne Isco, Lincoln, NE; eluent: ethyl acetate in hexane 0% to 25%, gradient elution) provided the title compound as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.03 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 3.68 (s, 3H), 5.08 (s, 1H), 7.24 (m, 2H), 7.34 (m, 1H), 7.46 (m, 1H).

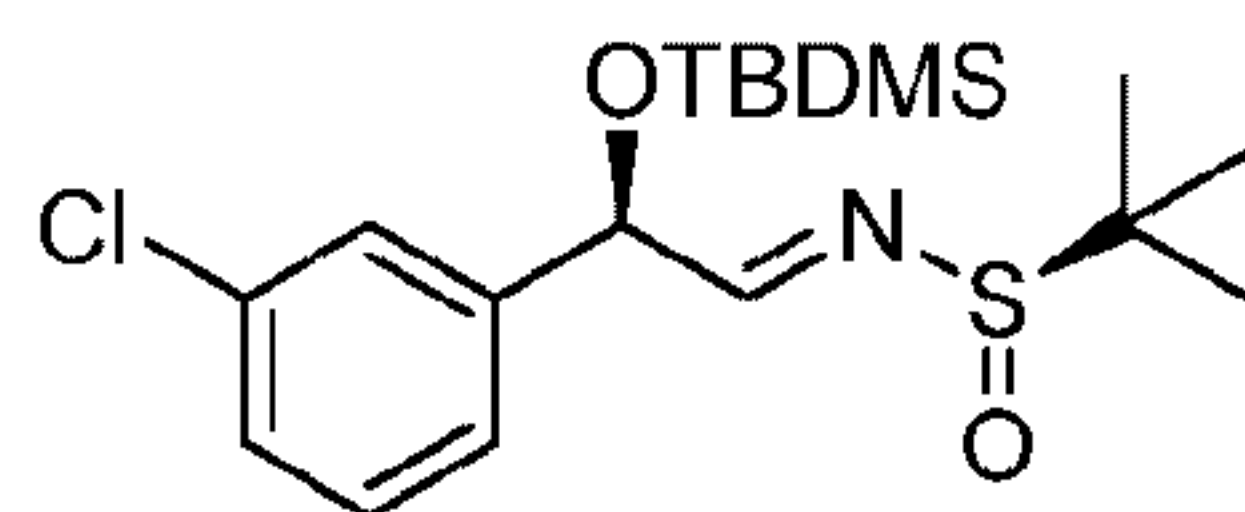
Step D. (R)-2-(*tert*-Butyldimethylsilyloxy)-2-(3-chlorophenyl)acetaldehyde



DIBAL-H (1.5 M in toluene, Aldrich) (249 mL, 374 mmol) was added dropwise
 5 over 1.5 hours to a solution of (R)-methyl 2-(*tert*-butyldimethylsilyloxy)-2-(3-chlorophenyl)acetate (78.50 g, 249 mmol, Step C) in anhydrous diethyl ether (499 mL) at -78 °C under argon. After 1 hour the reaction was quenched by the addition of methanol (45 mL). The reaction mixture was poured into a sat. aq. solution of potassium sodium tartrate (Rochelle salt) and stirred at rt overnight. The layers were separated and the
 10 aqueous layer was extracted with diethyl ether (2 x 500 mL). The organics were pooled, washed with brine, dried (MgSO₄), filtered and the filtrate was concentrated in vacuo to provide a colorless liquid. Purification by chromatography on silica gel (2 stacked 330g silica gel columns, RediSep® Rf, Teledyne Isco, Lincoln, NE; eluent: ethyl acetate in hexane 0% to 25%, gradient elution) provided the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.07 (s, 3H), 0.14 (s, 3H), 0.96 (s, 9H), 4.98 (d, *J* = 2.2 Hz, 1H), 7.31 (m, 3H), 7.41 (m, 1H), 9.51 (d, *J* = 2.1 Hz, 1H).

Step E. (R)-N-((R)-2-(*tert*-Butyldimethylsilyloxy)-2-(3-chlorophenyl)ethylidene)-2-methylpropane-2-sulfinamide

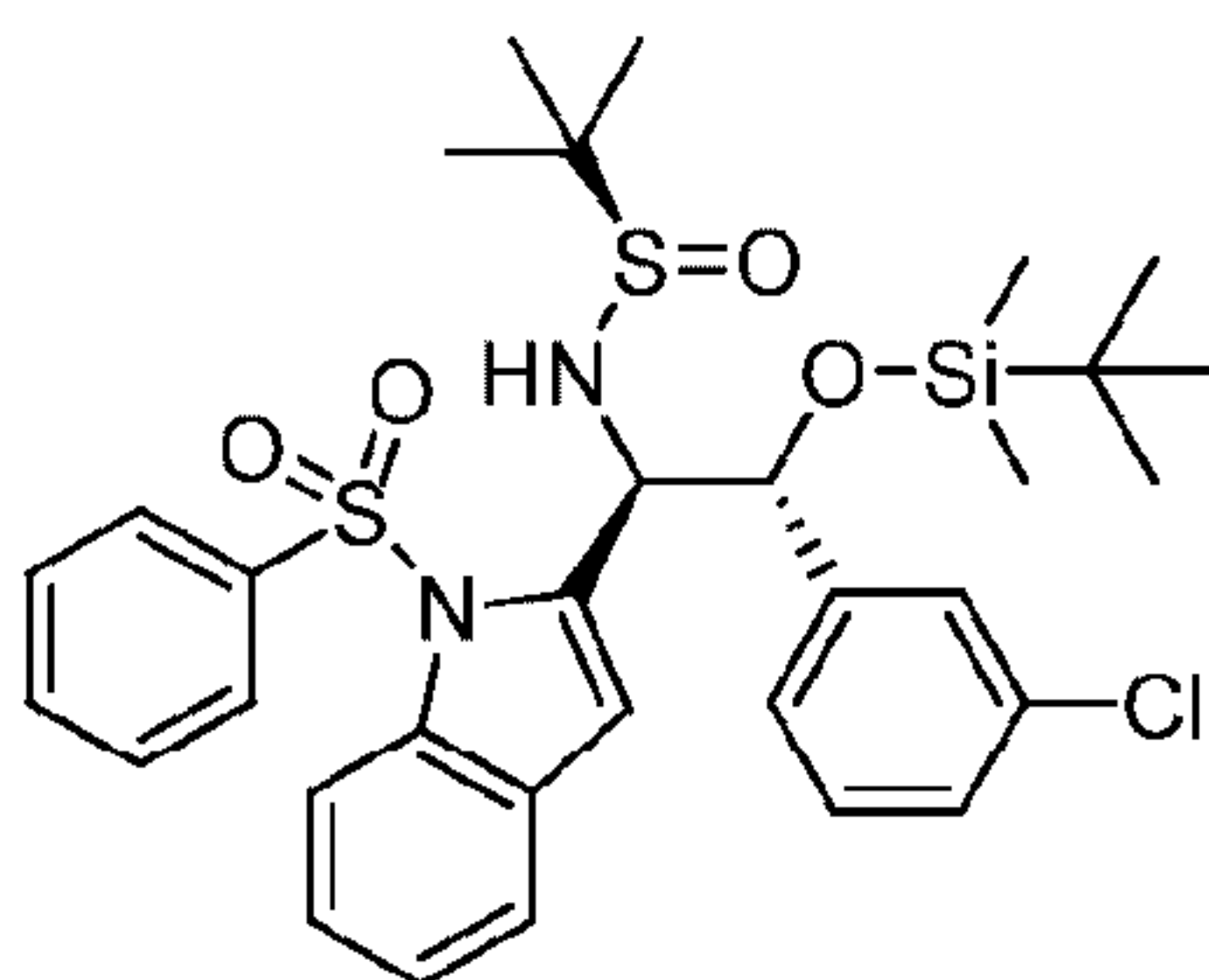
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Copper(II)sulfate (14.64 g, 92 mmol) was added to a solution of (R)-2-(*tert*-butyldimethylsilyloxy)-2-(3-chlorophenyl)acetaldehyde (11.88 g, 41.7 mmol, Step D)
 25 and (R)-2-methylpropane-2-sulfinamide (5.56 g, 45.9 mmol) in anhydrous dichloromethane (83 mL) at rt. After 68 hours the reaction mixture was filtered through a pad of Celite® (J.T. Baker, Phillipsberg, NJ, diatomaceous earth), washed with DCM and

the combined filtrates were concentrated in vacuo to provide an orange oil. Purification by chromatography on silica gel (330 g silica gel column, RediSep® Rf, Teledyne Isco, Lincoln, NE; eluent: ethyl acetate in hexane 0% to 25%, gradient elution) provided the title compound as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ ppm 0.05 (s, 3H), 0.11 (s, 3H), 0.93 (s, 9H), 1.23 (s, 9H), 5.44 (d, *J* = 5.1 Hz, 1H), 7.30 (m, 3H), 7.42 (m, 1H), 7.93 (d, *J* = 5.4 Hz, 1H).

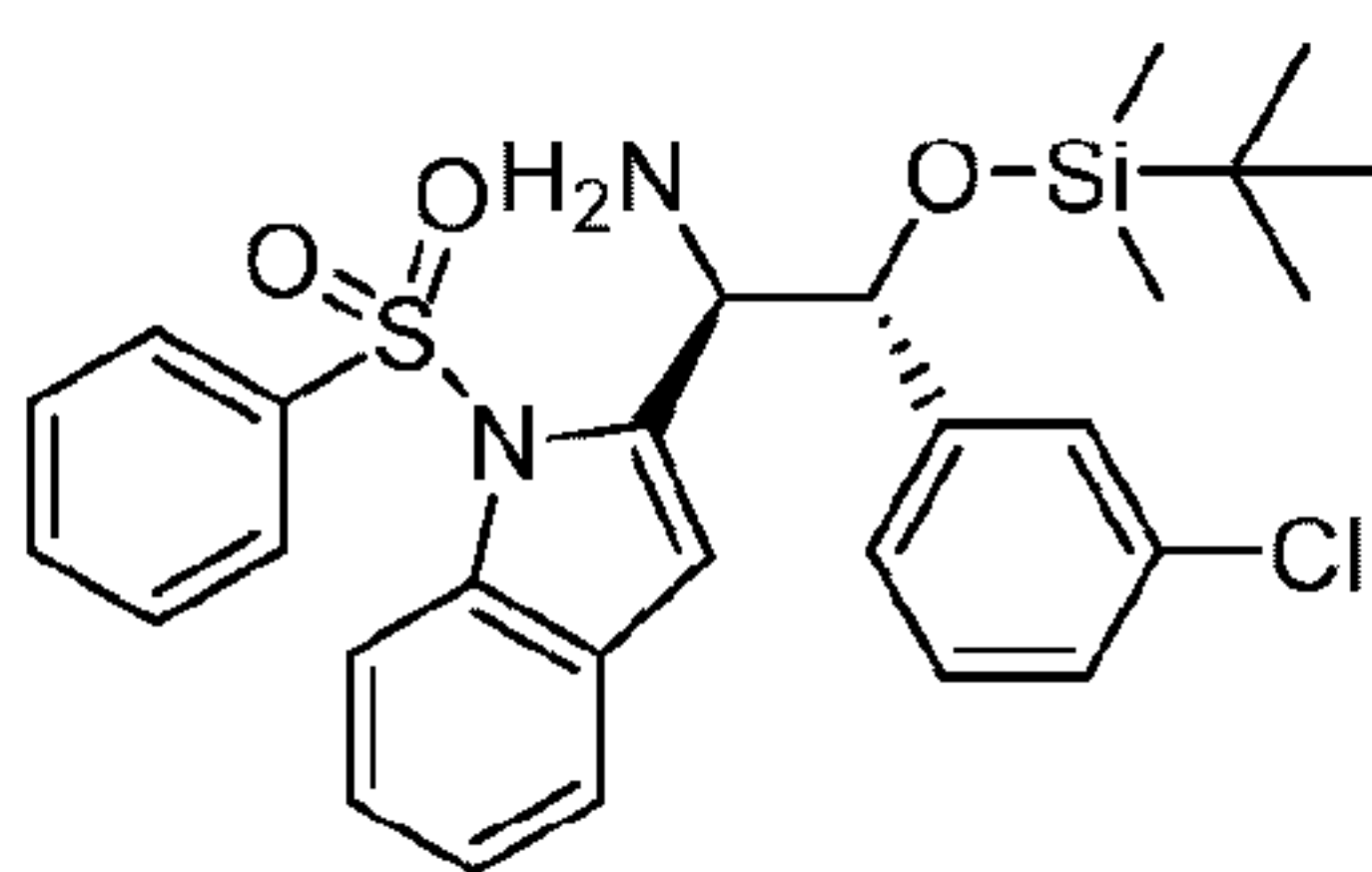
Step F. (R)-N-((1R,2R)-2-(*tert*-Butyldimethylsilyloxy)-2-(3-chlorophenyl)-1-(1-(phenylsulfonyl)-1H-indol-2-yl)ethyl)-2-methylpropane-2-sulfinamide



n-BuLi (2.5 M in hexanes) (8.02 mL, 20.04 mmol) was added over 30 minutes to a solution of 1-(phenylsulfonyl)-1H-indole (5.50 g, 21.38 mmol, Step A) in anhydrous THF (25 mL) at -78 °C under argon. The reaction mixture was slowly warmed to 0 °C over a period of 1.5 hours. This solution was added via cannula to a solution of (R)-N-((R)-2-(*tert*-butyldimethylsilyloxy)-2-(3-chlorophenyl)ethylidene)-2-methylpropane-2-sulfinamide (5.18 g, 13.36 mmol, Step E) in anhydrous THF (25 mL) at -78 °C under argon. The reaction mixture was allowed to warm to rt as the bath warmed. After 14 hours the reaction was quenched by the addition of sat. aq. NH₄Cl solution and the layers were separated. The aqueous layer was extracted with EtOAc (3x) and the organics were pooled, washed with brine, dried (MgSO₄), filtered and the filtrate was concentrated to provide a brown oil. Purification by chromatography on silica gel (330 g silica gel column, RediSep® Rf, Teledyne Isco, Lincoln, NE; eluent: ethyl acetate in hexane 10% to 35%, gradient elution) provided the title compound as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ ppm -0.53 (s, 3H), -0.29 (s, 3H), 0.81 (s, 9H), 1.10 (s, 9H), 4.09 (d, *J* =

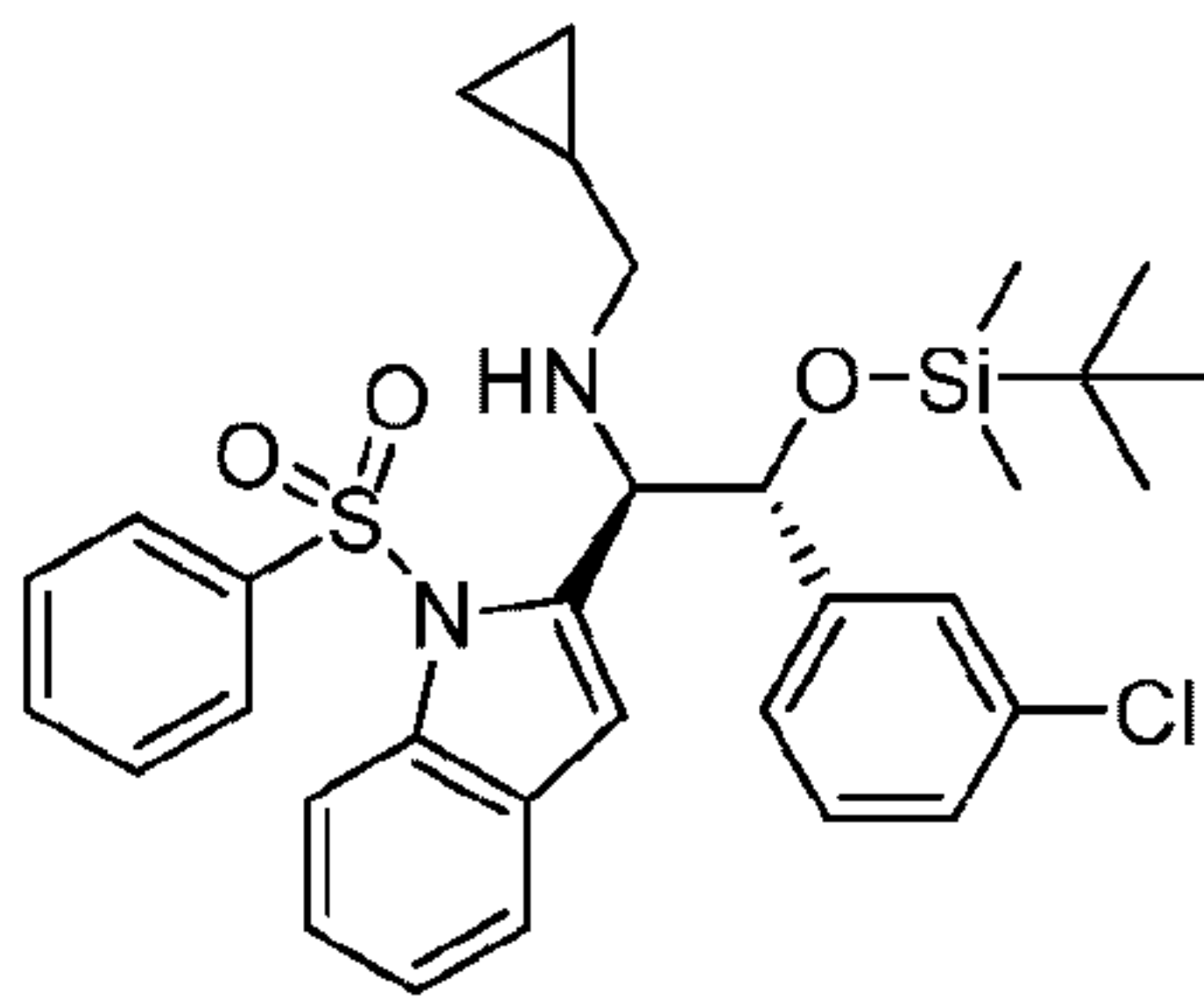
5.9 Hz, 1H), 5.40 (s, 1H), 5.41 (d, $J = 6.4$ Hz, 1H), 6.70 (s, 1H), 7.25 (m, 1H), 7.30-7.40 (m, 5H), 7.43-7.52 (m, 3H), 7.61 (m, 1H), 7.79 (m, 2H), 8.19 (d, $J = 8.0$ Hz, 1H). Mass spectrum (ESI) m/z 645.2 $[M + H]^+$.

- 5 Step G. (1R,2R)-2-(*tert*-Butyldimethylsilyloxy)-2-(3-chlorophenyl)-1-(1-(phenylsulfonyl)-1H-indol-2-yl)ethanamine



- 10 4M HCl in dioxane (10.38 mL, 41.5 mmol) was added to a solution of (R)-N-((1R,2R)-2-(*tert*-butyldimethylsilyloxy)-2-(3-chlorophenyl)-1-(1-(phenylsulfonyl)-1H-indol-2-yl)ethyl)-2-methylpropane-2-sulfinamide (5.36 g, 8.31 mmol) in MeOH (83 mL) at rt. After 45 minutes the reaction mixture was diluted with water (200 mL), adjusted to a pH of about 8 with sat. aq. NaHCO₃ solution and extracted with EtOAc (3 x 150 mL).
- 15 The organics were pooled, washed with brine, dried over MgSO₄, filtered and the filtrate was concentrated in vacuo to provide the crude title compound as an oil, which was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ ppm -0.54 (s, 3H), -0.31 (s, 3H), 0.77 (s, 9H), 4.72 (s, 1H), 5.42 (s, 1H), 6.72 (s, 1H), 7.23 (m, 1H), 7.26-7.36 (m, 5H), 7.43 (m, 1H), 7.47 (m, 1H), 7.54 (d, $J = 7.6$ Hz, 1H), 7.63 (m, 1H), 7.66 (m, 2H),
- 20 8.17 (d, $J = 8.4$ Hz, 1H). Mass spectrum (ESI) m/z 541.2 $[M + H]^+$.

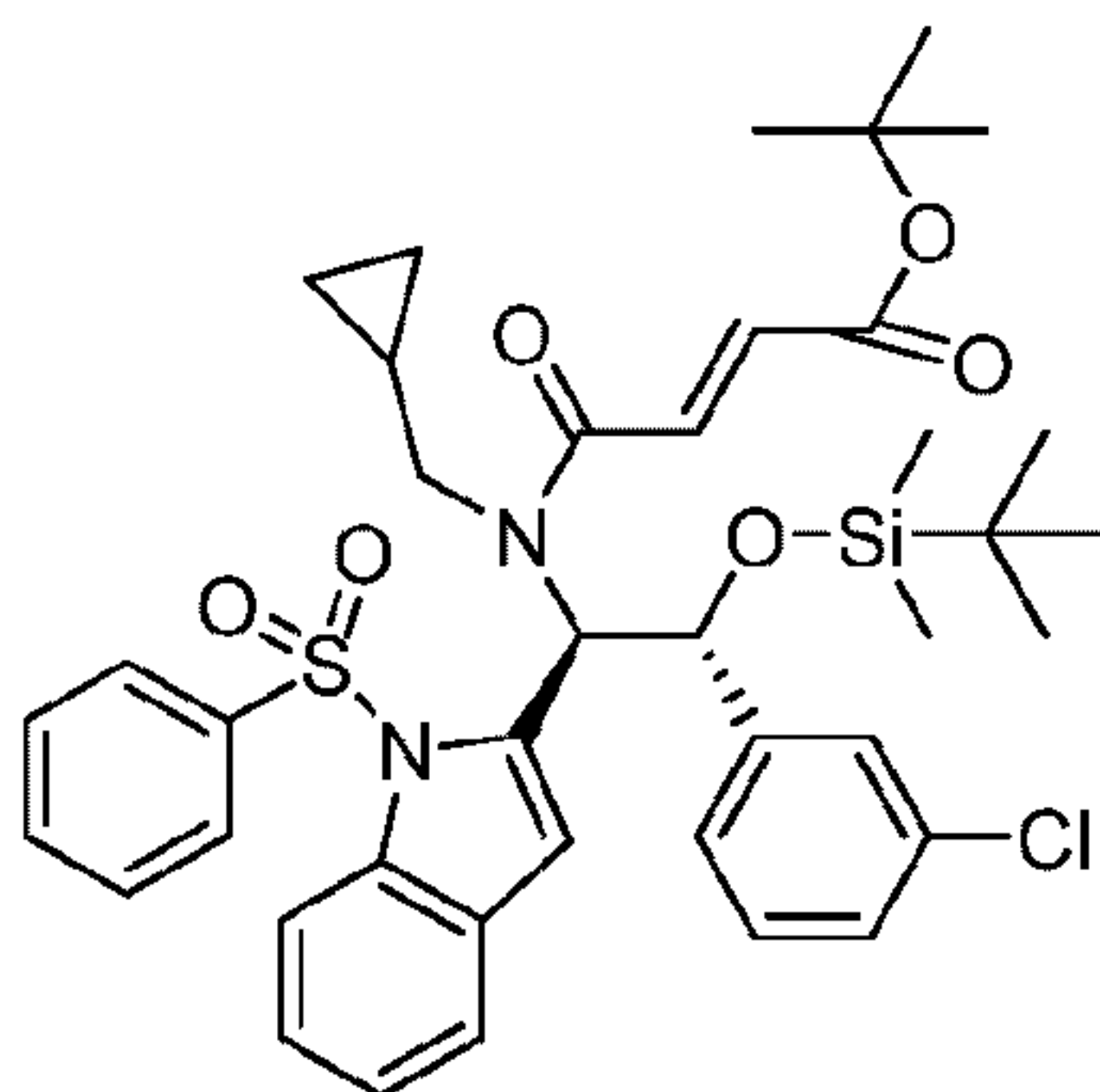
Step H. (1R,2R)-2-(*tert*-Butyldimethylsilyloxy)-2-(3-chlorophenyl)-N-(cyclopropylmethyl)-1-(1-(phenylsulfonyl)-1H-indol-2-yl)ethanamine



Cyclopropanecarbaldehyde (0.456 mL, 6.10 mmol) was added to a solution of (1R,2R)-2-(*tert*-butyldimethylsilyloxy)-2-(3-chlorophenyl)-1-(1-(phenylsulfonyl)-1H-indol-2-yl)ethanamine (3.00 g, 5.54 mmol) in MeOH (27.7 mL) at rt. After 1 h sodium borohydride (0.252 g, 6.65 mmol) was added and the reaction mixture was stirred for 15 minutes before it was quenched with sat. aq. NH₄Cl solution. Water (50 mL) was added and the mixture was extracted with EtOAc (2x). The organics were pooled, washed with brine, dried over MgSO₄, filtered and the filtrate was concentrated to provide a yellow oil. Purification by chromatography on silica gel (330 g silica gel column, RediSep® Rf, Teledyne Isco, Lincoln, NE; eluent: ethyl acetate in hexane 0% to 20%, gradient elution) provided the title compound as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ ppm -0.50 (s, 3H), -0.34 (s, 3H), -0.14 (m, 2H), 0.29 (m, 2H), 0.67 (m, 1H), 0.79 (s, 9H), 1.96 (dd, *J* = 6.3 and 11.7 Hz, 1H), 2.12 (dd, *J* = 6.9 and 11.8 Hz, 1H), 4.52 (s, 1H), 5.23 (s, 1H), 6.72 (s, 1H), 7.24-7.31 (m, 4H), 7.35 (m, 2H), 7.45-7.52 (m, 3H), 7.65 (m, 3H), 8.20 (d, *J* = 8.3 Hz, 1H). Mass spectrum (ESI) *m/z* 595.2 [M + H]⁺.

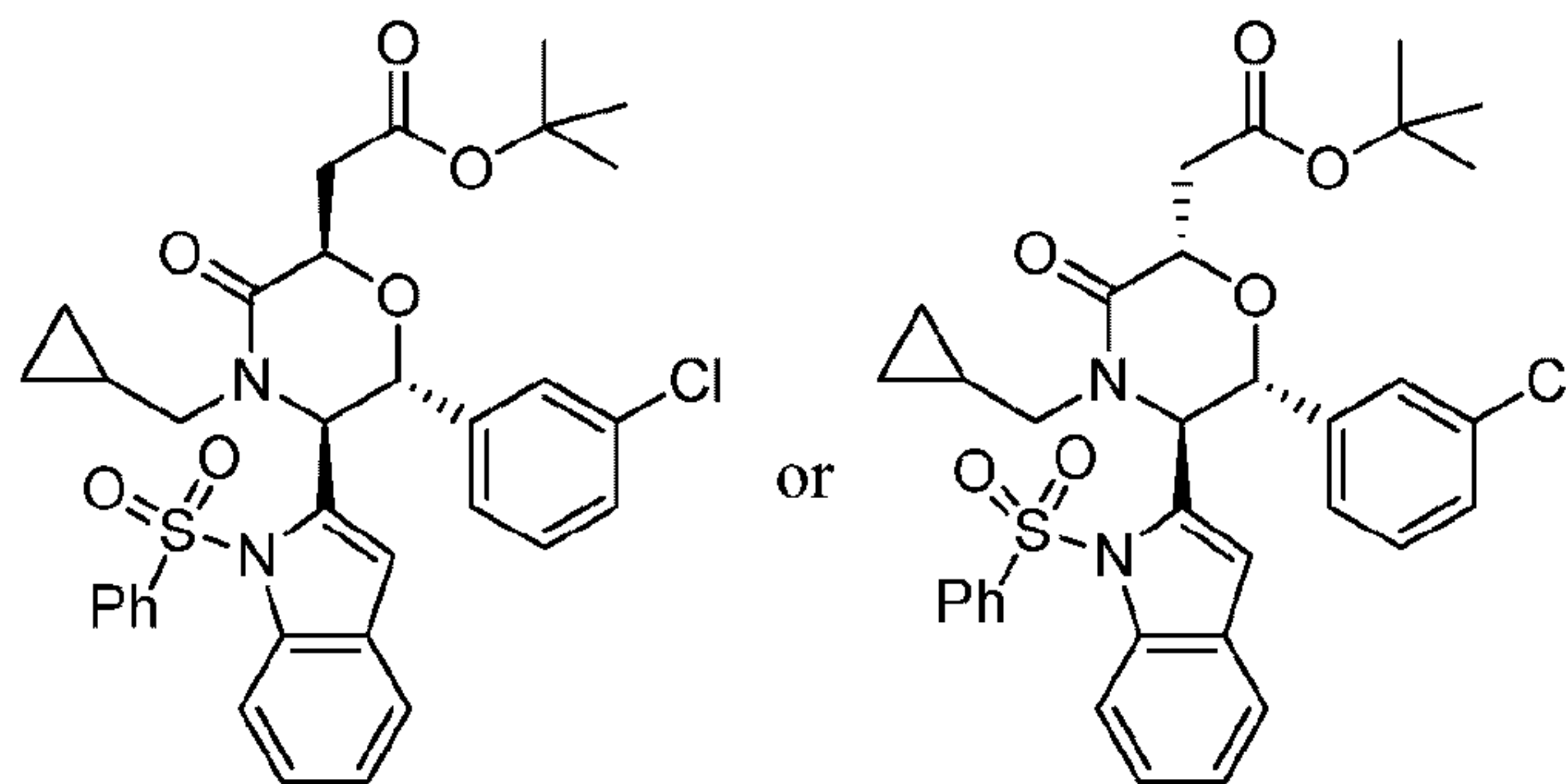
Step I. (E)-*tert*-butyl 4-(((1R,2R)-2-(*tert*-butyldimethylsilyloxy)-2-(3-chlorophenyl)-1-(1-(phenylsulfonyl)-1H-indol-2-yl)ethyl)(cyclopropylmethyl)amino)-4-oxobut-2-enoate

20



One drop of DMF was added to a solution of (E)-4-*tert*-butoxy-4-oxobut-2-enoic acid (1.952 g, 11.34 mmol) and oxalyl chloride (1.588 mL, 18.14 mmol) in DCM (23 mL) at rt. After 2 hours the reaction mixture was concentrated in vacuo, diluted with DCM and concentrated in vacuo again (this was repeated twice) to provide a brown oil. This oil was dissolved in DCM (20 mL) and added to a solution of (1R,2R)-2-(*tert*-butyldimethylsilyloxy)-2-(3-chlorophenyl)-N-(cyclopropylmethyl)-1-(1-(phenylsulfonyl)-1H-indol-2-yl)ethanamine (2.70 g, 4.54 mmol, Step H) in DCM (20 mL) at rt. DIPEA (2.97 mL, 17.01 mmol) was then added to the reaction mixture. After 2 hours the reaction mixture was diluted with water and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organics were pooled, washed with brine, dried over MgSO₄, filtered and the filtrate was concentrated in vacuo to provide a dark brown oil. Purification by chromatography on silica gel (330 g silica gel column, RediSep® Rf, Teledyne Isco, Lincoln, NE; eluent: ethyl acetate in hexane 10% to 35%, gradient elution) provided the title compound as an off-white foam. Mass spectrum (ESI) m/z 749.2 [M + H]⁺.

Step J. *tert*-Butyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(1-(phenylsulfonyl)-1H-indol-2-yl)morpholin-2-yl)acetate or *tert*-Butyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(1-(phenylsulfonyl)-1H-indol-2-yl)morpholin-2-yl)acetate

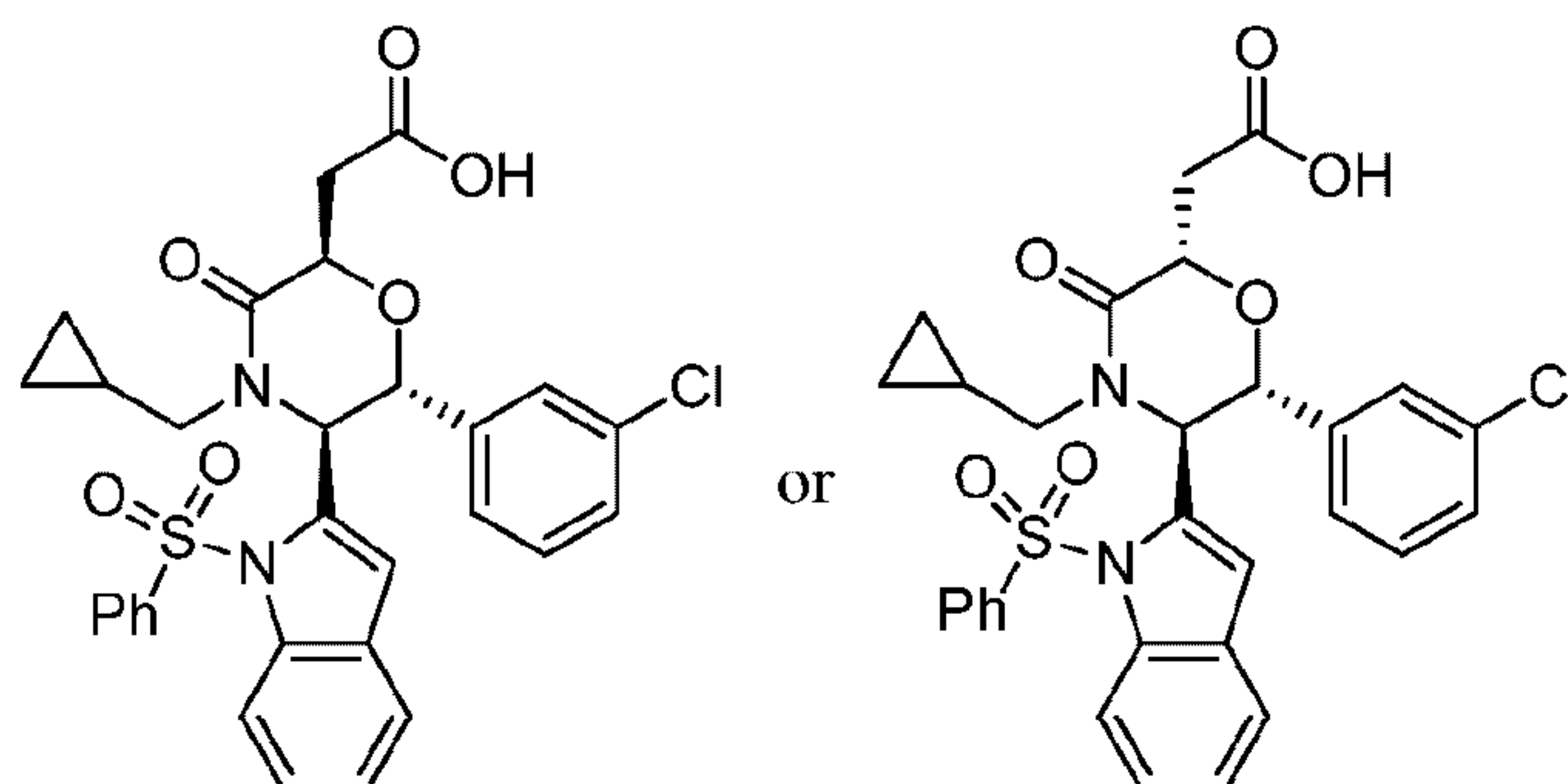


TBAF (1 M in THF) (3.83 mL, 3.83 mmol) was added to a solution of (E)-*tert*-butyl 4-(((1R,2R)-2-(*tert*-butyldimethylsilyloxy)-2-(3-chlorophenyl)-1-(1-(phenylsulfonyl)-1H-indol-2-yl)ethyl)(cyclopropylmethyl)amino)-4-oxobut-2-enoate (2.61 g, 3.48 mmol, Step I) in THF (34.8 mL) at rt. After 1 h the reaction mixture was diluted with sat. aq. NH₄Cl solution and the layers were separated. The aqueous layer was extracted with EtOAc (2x) and the organics were pooled, washed with brine, dried (MgSO₄), filtered and concentrated in vacuo to provide a yellow oil. NMR indicated an approximate 3.3:1 mixture of isomers. Purification by chromatography on silica gel (330 g silica gel column, RediSep® Rf, Teledyne Isco, Lincoln, NE; eluent: 2.5% MTBE / 20% hexanes in DCM) provided one of the title compounds as the first eluting, major isomer. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.16 (m, 1H), 0.24 (m, 1H), 0.55 (m, 1H), 0.66 (m, 1H), 1.01 (m, 1H), 1.43 (s, 9H), 2.35 (dd, *J* = 7.6 and 14.3 Hz, 1H), 2.65 (dd, *J* = 8.8 and 16.0 Hz, 1H), 3.00 (dd, *J* = 3.3 and 16.0 Hz, 1H), 4.03 (dd, *J* = 6.9 and 14.1 Hz, 1H), 4.33 (dd, *J* = 3.3 and 8.8 Hz, 1H), 5.26 (s, 1H), 5.95 (s, 1H), 6.75 (s, 1H), 7.32 (m, 1H), 7.35-7.44 (m, 5H), 7.56 (m, 3H), 7.65 (m, 3H), 8.19 (d, *J* = 8.0 Hz, 1H). Mass spectrum (ESI) *m/z* 657.2 [M + Na]⁺.

Further elution provided another one of the title compounds as the second eluting, minor isomer. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.00 (m, 1H), 0.12 (m, 1H), 0.28 (m, 1H), 0.36 (m, 1H), 0.82 (m, 1H), 1.36 (s, 9H), 2.45 (m, 1H), 2.68 (m, 1H), 2.85 (m, 1H), 3.47 (m, 1H), 4.74 (m, 1H), 5.02 (m, 1H), 5.90 (m, 1H), 6.76 (bs, 1H), 7.10-7.22 (m, 8H), 7.25-7.45 (m, 4H), 7.85 (m, 1H). Mass spectrum (ESI) *m/z* 657.2 [M + Na]⁺.

Step K. 2-((2R,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(1-(phenylsulfonyl)-1H-indol-2-yl)morpholin-2-yl)acetic acid or 2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(1-(phenylsulfonyl)-1H-indol-2-yl)morpholin-2-yl)acetic acid

5



TFA (5.00 mL, 64.9 mmol) was added to a solution of *tert*-butyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(1-(phenylsulfonyl)-1H-indol-2-yl)morpholin-2-yl)acetate or *tert*-butyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(1-(phenylsulfonyl)-1H-indol-2-yl)morpholin-2-yl)acetate (1.19 g, 1.874 mmol, Step J; first eluting, major isomer) in DCM (15.00 mL) at rt. After 2 hours the reaction mixture was concentrated in vacuo, a few mL of hexanes were added and the solvent was removed under reduced pressure on a rotary evaporator. This procedure was repeated twice to provide one of the title compounds as a foam. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.17 (m, 1H), 0.27 (m, 1H), 0.60 (m, 1H), 0.70 (m, 1H), 1.03 (m, 1H), 2.41 (dd, *J* = 7.7 and 14.1 Hz, 1H), 2.90 (dd, *J* = 6.6 and 16.6 Hz, 1H), 3.08 (dd, *J* = 5.4 and 16.4 Hz, 1H), 4.06 (dd, *J* = 6.8 and 14.0 Hz, 1H), 4.30 (t, *J* = 5.9 Hz, 1H), 5.29 (s, 1H), 5.99 (s, 1H), 6.71 (s, 1H), 7.34 (m, 1H), 7.36-7.44 (m, 5H), 7.49 (s, 1H), 7.56-7.66 (m, 5H), 8.19 (dd, *J* = 0.7 and 8.4 Hz, 1H). Mass spectrum (ESI) *m/z* 579.2 [*M* + H]⁺.

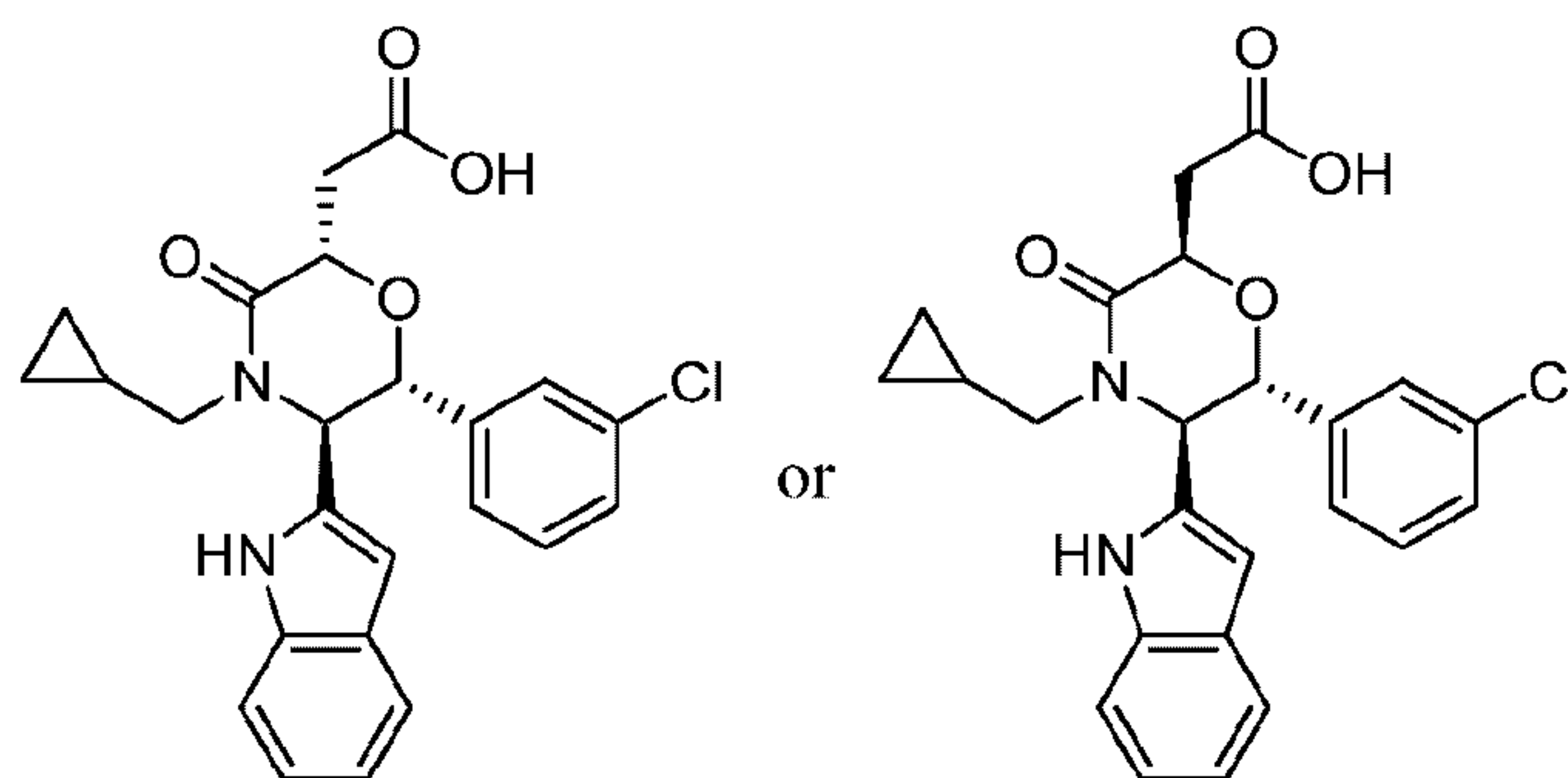
Step L. 2-((2R,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(1H-indol-2-yl)-3-oxomorpholin-2-yl)acetic acid or 2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(1H-indol-2-yl)-3-oxomorpholin-2-yl)acetic acid

A solution of 2-((2R,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(1-(phenylsulfonyl)-1H-indol-2-yl)morpholin-2-yl)acetic acid or 2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(1-(phenylsulfonyl)-1H-indol-2-yl)morpholin-2-yl)acetic acid (1.09 g, 1.882 mmol, Step K) in TBAF (18.82 mL, 18.82 mmol; 1M in THF) was heated to reflux. After 1.5 hours the reaction mixture was cooled to rt, diluted with sat. aq. NH₄Cl solution and the layers were separated. The aqueous layer was extracted with EtOAc (2x) and the organics were pooled, washed with brine, dried over MgSO₄, filtered and the filtrate was concentrated in vacuo to provide a yellow oil. Purification by chromatography on silica gel (120 g silica gel column, RediSep® Rf, Teledyne Isco, Lincoln, NE; eluent: 0 to 5% MeOH/DCM with 0.5% AcOH as additive; gradient elution) provided one of the title compounds as an off-white foam. ¹H NMR (500 MHz, CDCl₃) δ ppm 0.02 (m, 1H), 0.23 (m, 1H), 0.37 (m, 1H), 0.52 (m, 1H), 0.96 (m, 1H), 2.36 (dd, *J* = 8.0 and 14.1 Hz, 1H), 2.65 (dd, *J* = 3.9 and 18.1 Hz, 1H), 3.20 (dd, *J* = 4.2 and 18.1 Hz, 1H), 3.81 (m, 1H), 3.88 (dd, *J* = 6.3 and 14.2 Hz, 1H), 4.96 (s, 1H), 5.12 (s, 1H), 6.22 (d, *J* = 1.5 Hz, 1H), 6.87 (dt, *J* = 1.0 and 7.6 Hz, 1H), 6.96 (dt, *J* = 1.2 and 7.7 Hz, 1H), 7.15-7.23 (m, 4H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.41 (bs, 1H), 10.13 (s, 1H). Mass spectrum (ESI) *m/z* 439.2 [M + H]⁺.

20

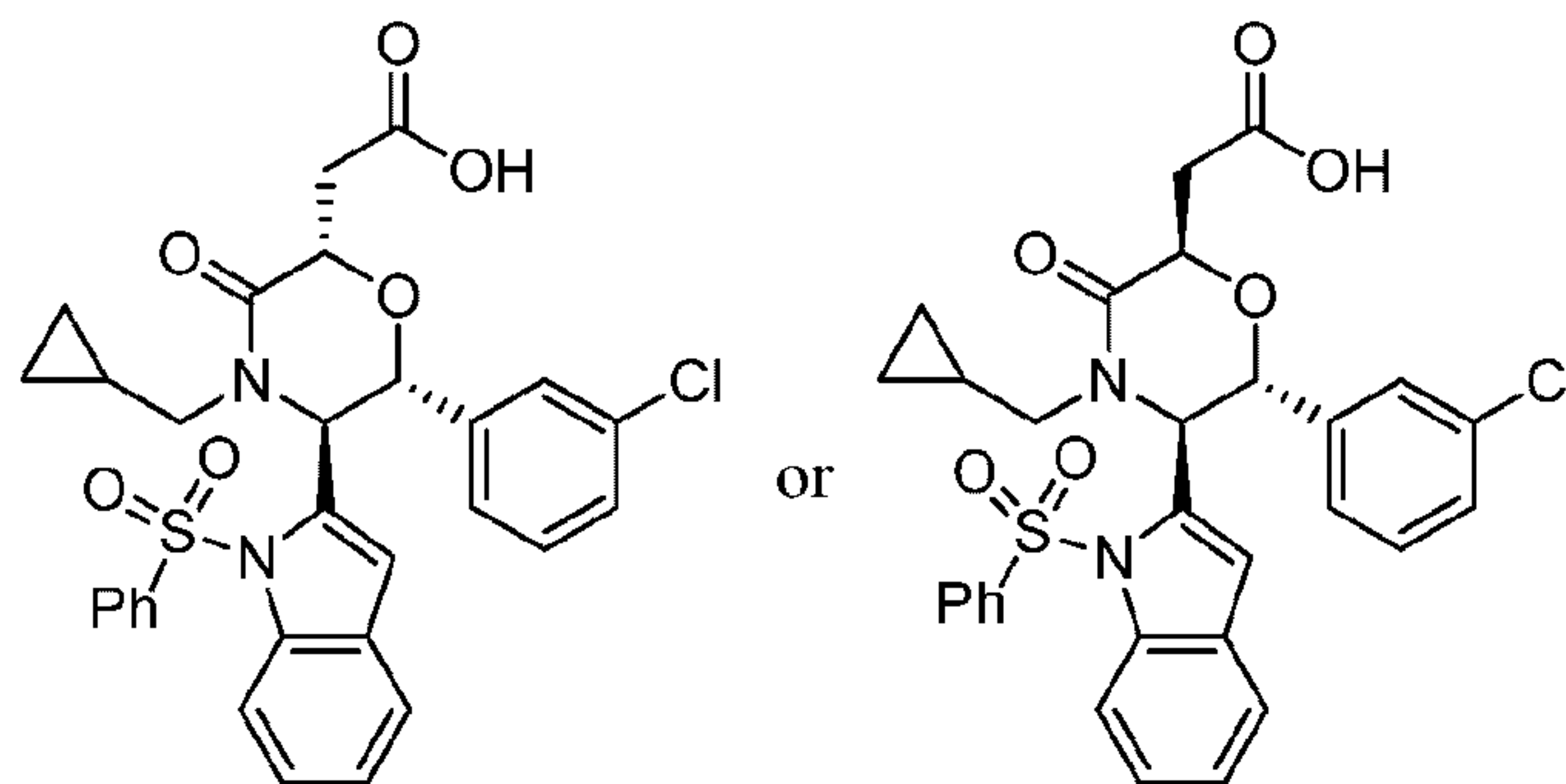
EXAMPLE 2

2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(1H-indol-2-yl)-3-oxomorpholin-2-yl)acetic acid or 2-((2R,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(1H-indol-2-yl)-3-oxomorpholin-2-yl)acetic acid



25

Step A. 2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(1-(phenylsulfonyl)-1H-indol-2-yl)morpholin-2-yl)acetic acid or 2-((2R,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(1-(phenylsulfonyl)-1H-indol-2-yl)morpholin-2-yl)acetic acid



TFA (1.00 mL, 12.98 mmol) was added to a solution of *tert*-butyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(1-(phenylsulfonyl)-1H-indol-2-yl)morpholin-2-yl)acetate or *tert*-butyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(1-(phenylsulfonyl)-1H-indol-2-yl)morpholin-2-yl)acetate (0.254 g, 0.399 mmol; Example 1, step J; second eluting, minor isomer) in DCM (3 mL) at rt. After 2 h the reaction mixture was concentrated in vacuo, a few mL of hexanes were added and the solvent was removed under reduced pressure on a rotary evaporator. This procedure was repeated twice to provide the title compound as a foam. Mass spectrum (ESI) m/z 579.2 $[M + H]^+$.

Step B. 2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(1H-indol-2-yl)-3-oxomorpholin-2-yl)acetic acid or 2-((2R,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(1H-indol-2-yl)-3-oxomorpholin-2-yl)acetic acid

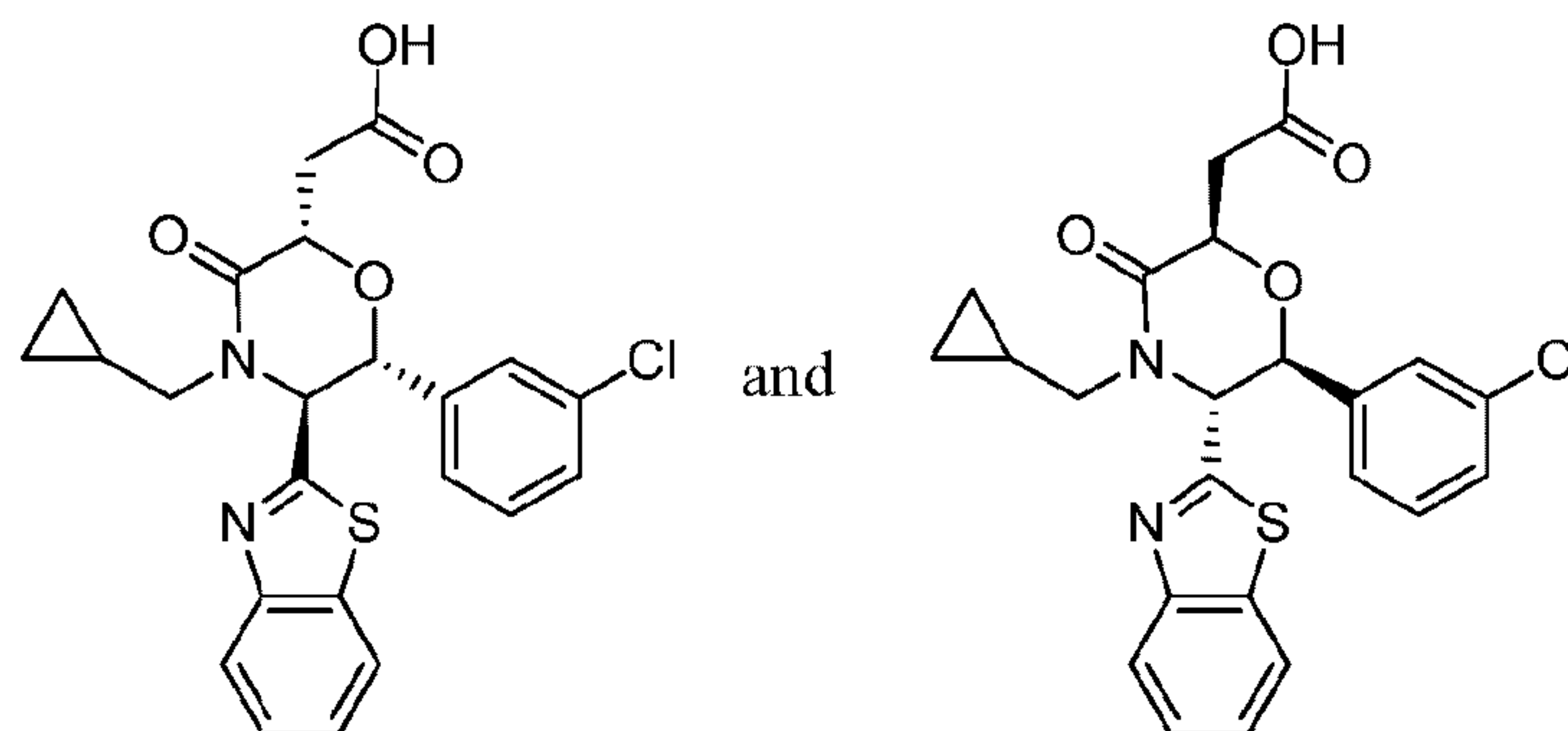
TBAF (1 M solution in THF) (3.99 mL, 3.99 mmol) was added to a solution of 2-((2S,5R,6R)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(1-(phenylsulfonyl)-1H-indol-2-yl)morpholin-2-yl)acetic acid or 2-((2R,5R,6R)-6-(3-chlorophenyl)-4-

(cyclopropylmethyl)-3-oxo-5-(1-(phenylsulfonyl)-1H-indol-2-yl)morpholin-2-yl)acetic acid (0.231 g, 0.399 mmol; Example 2, Step A) in THF (3.0 mL) at rt. The reaction mixture was heated to reflux. After 1.5 h the reaction mixture was cooled to rt, diluted with sat. aq. NH₄Cl and extracted with EtOAc (3x). The organics were pooled, washed with brine, dried over MgSO₄, filtered and the filtrate was concentrated to provide a yellow oil. Purification by chromatography on silica gel (24 g silica gel column, RediSep® Rf, Teledyne Isco, Lincoln, NE; eluent: 0 to 5% MeOH/DCM with 0.5% AcOH as additive; gradient elution) provided the title compound as an off-white foam.

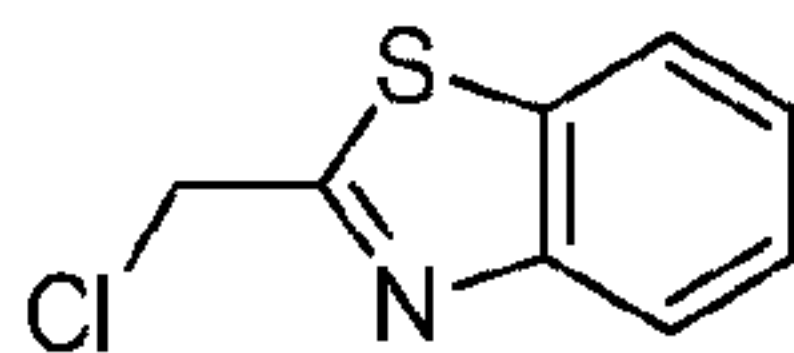
¹H NMR (400 MHz, CDCl₃) δ ppm 0.02 (m, 1H), 0.16 (m, 1H), 0.44 (m, 1H), 0.52 (m, 1H), 1.00 (m, 1H), 2.27 (dd, *J* = 7.8 and 14.0 Hz, 1H), 3.03 (dd, *J* = 6.5 and 16.8 Hz, 1H), 3.33 (dd, *J* = 5.1 and 16.8 Hz, 1H), 3.92 (dd, *J* = 6.4 and 14.1 Hz, 1H), 4.89 (m, 1H), 4.94 (d, *J* = 9.8 Hz, 1H), 4.99 (d, *J* = 9.8 Hz, 1H), 6.13 (d, *J* = 1.4 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 7.09 (m, 1H), 7.18-7.25 (m, 3H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 9.52 (bs, 1H). Mass spectrum (ESI) *m/z* 439.2 [M + H]⁺.

EXAMPLE 3

2-((2S,5S,6R)-5-(Benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid and 2-((2R,5R,6S)-5-(Benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid



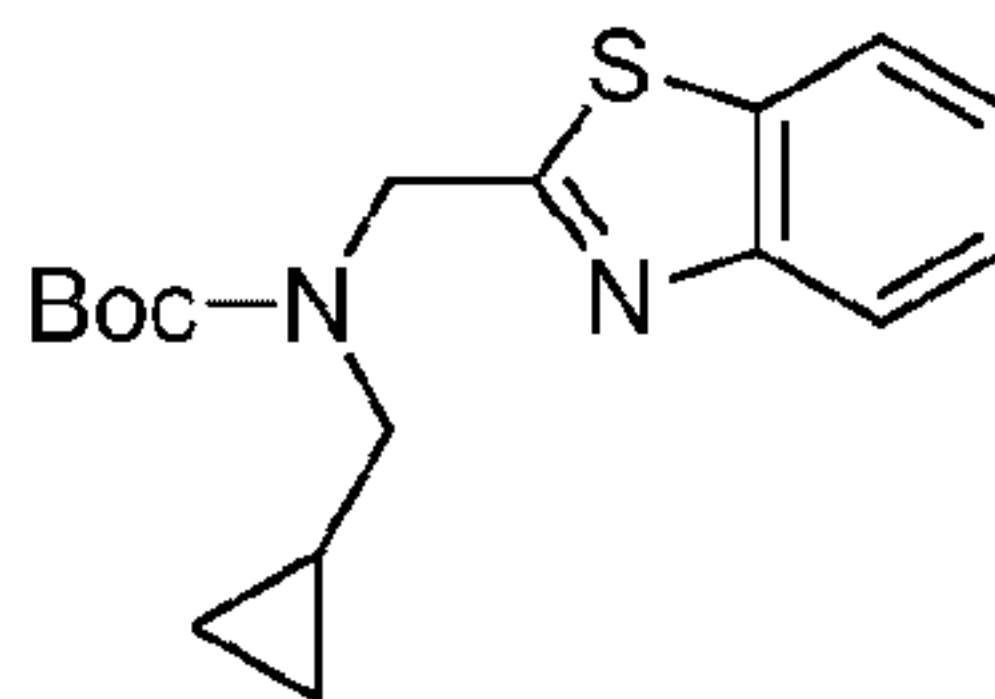
Step A. 2-(Chloromethyl)benzo[d]thiazole



A solution of 2-aminothiophenol (2.29 g, 18.33 mmol) in 2-chloro-1,1,1-
 triethoxyethane (7.00 mL, 36.7 mmol) was heated to 65°C for 2 hours. The reaction
 5 mixture was diluted with sat. NaHCO₃/brine and extracted with ethyl acetate. The
 organics were washed with water, dried over MgSO₄, filtered and the filtrate was
 concentrated under reduced pressure. Purification of the residue by flash chromatography
 on silica gel (eluent: 0 to 10% EtOAc/hexane, gradient elution) provided the title
 compound. Mass Spectrum (ESI) m/z = 168 (M+1).

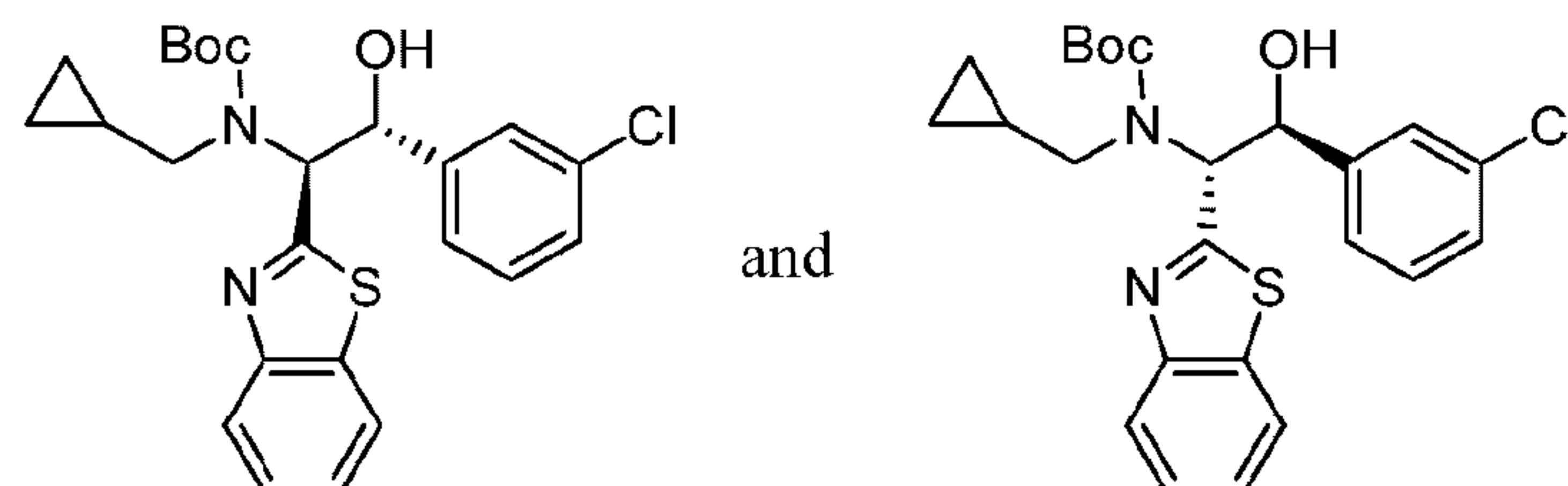
10

Step B. *tert*-Butyl benzo[d]thiazol-2-ylmethyl(cyclopropylmethyl)carbamate



15 To a solution of cyclopropylmethanamine (0.820 mL, 19.75 mmol) and caesium
 carbonate (19.80 g, 60.8 mmol) in DMF (76 mL) was added slowly 2-
 (chloromethyl)benzo[d]thiazole (2.79 g, 15.19 mmol; Example 3, Step A). When the
 reaction was judged complete by LCMS, di-*tert*-butyl dicarbonate (7.63 g, 34.9 mmol)
 was added. The reaction mixture was stirred at ambient temperature overnight, then
 20 diluted with sat. aq. NaHCO₃/brine solution and extracted with ethyl acetate. The
 organics were washed with sat. NaCl solution, then dried over MgSO₄, filtered and the
 filtrate was concentrated under reduced pressure. Purification of the residue by flash
 chromatography on silica gel (eluent: 0 to 20% EtOAc/hexane, gradient elution) provided
 the title compound. Mass Spectrum (ESI) m/z = 219 (M+1-Boc), 263 (M+1-*t*butyl), 319
 25 (M+1), 341 (M+Na).

Step C. *tert*-Butyl ((1*S*,2*R*)-1-(benzo[d]thiazol-2-yl)-2-(3-chlorophenyl)-2-hydroxyethyl)(cyclopropylmethyl)carbamate and *tert*-Butyl ((1*R*,2*S*)-1-(benzo[d]thiazol-2-yl)-2-(3-chlorophenyl)-2-hydroxyethyl)(cyclopropylmethyl)carbamate



5

To a solution of *tert*-butyl benzo[d]thiazol-2-ylmethyl(cyclopropylmethyl)carbamate (3.15g, 9.89 mmol; Example 3, Step B) and methyl 3-chlorobenzoate (1.375 mL, 9.89 mmol) in anhydrous THF (19.78 mL) was added LiHMDS, 1M in THF (24.73 mL, 24.73 mmol). The reaction was monitored by LCMS, with additions of LiHMDS reagent until ketone formation was complete. The reaction mixture was cooled to 0°C, neutralized with NaHCO₃ and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in 30 mL of EtOH, cooled to 0 °C and reduced with sodium borohydride (0.748 g, 19.78 mmol). Still at 0 °C, the reaction mixture was quenched carefully with about 5mL of sat'd aq. NaHCO₃ solution and concentrated under reduced pressure to remove the ethanol. The mixture was extracted with EtOAc and washed with brine. The combined organics were dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure.

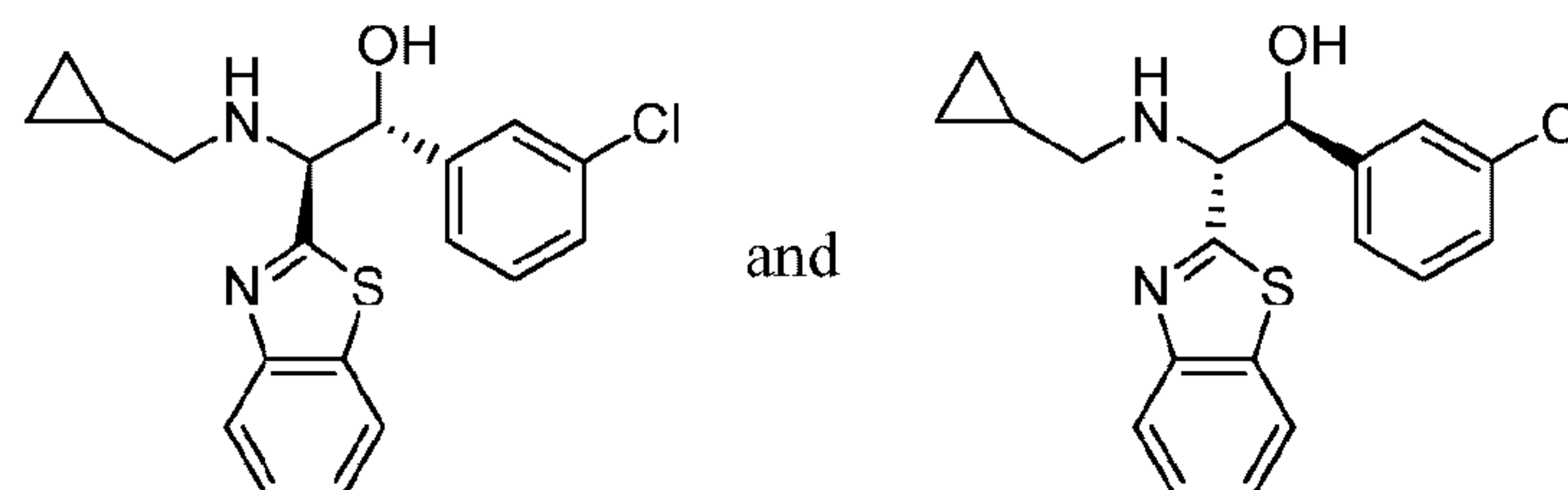
Purification of the residue by flash chromatography on silica gel (eluent: 10 to 20% EtOAc/hexanes, gradient elution) provided the title compounds as the faster eluting, major product peak.

¹H NMR (400 MHz, CDCl₃) δ ppm -0.07 (br. s., 1 H), 0.08 (br. s., 1 H), 0.26 (br. s., 2 H), 0.67 (br. s., 1 H), 1.47 (br. s., 9 H), 2.91 (br. s., 1 H), 3.15 (br. s., 1 H), 5.51 (br. s., 1 H), 5.71 (d, *J*=4.89 Hz, 1 H), 7.21 - 7.31 (m, 2 H), 7.39 (br. s., 1 H), 7.41 - 7.49 (m, 1 H), 7.49 - 7.60 (m, 2 H), 7.90 (d, *J*=8.02 Hz, 1 H), 8.08 (d, *J*=8.22 Hz, 1 H). Mass Spectrum (ESI) *m/z* = 403 (*M*+1-*t*butyl), 459 (*M*+1), 481 (*M* + Na).

25

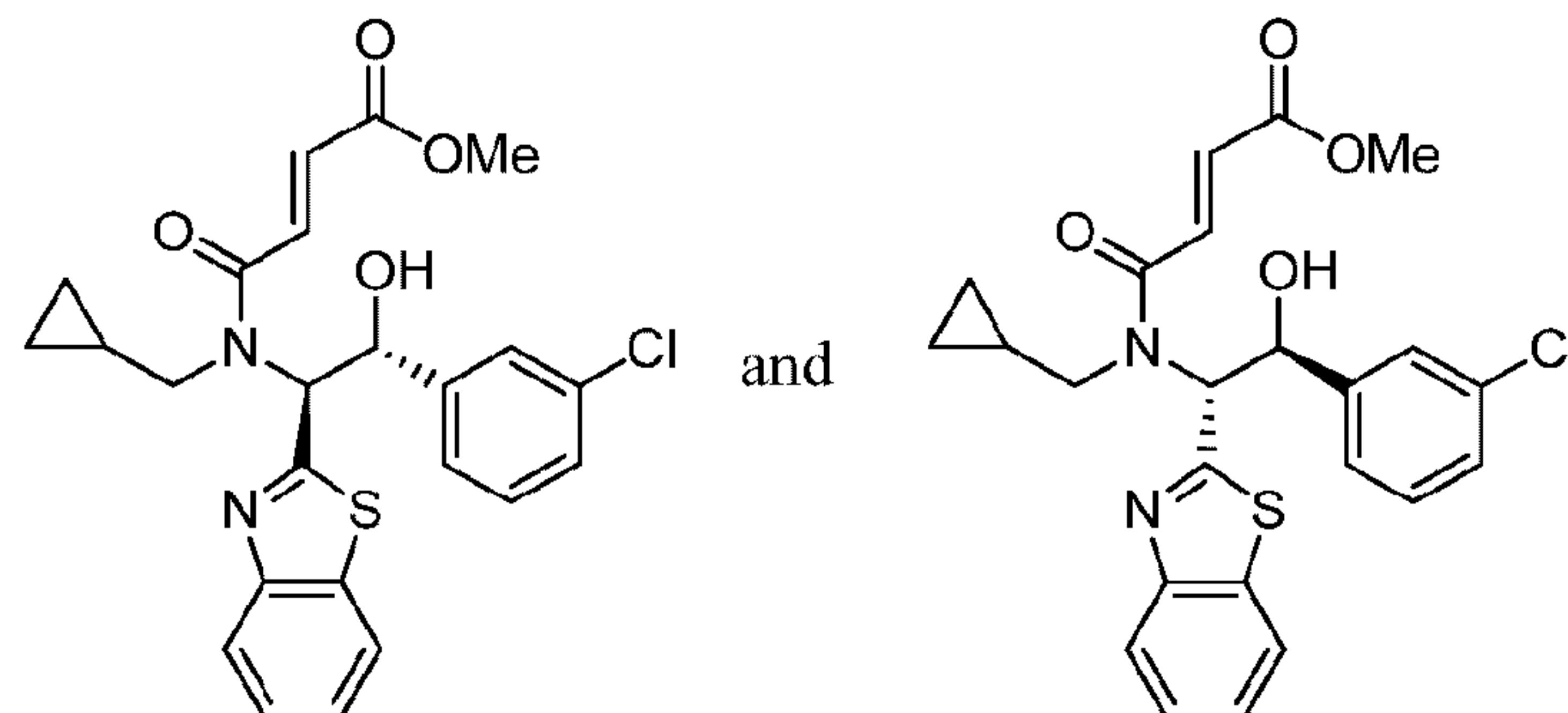
Step D. (1R,2S)-2-(Benzo[d]thiazol-2-yl)-1-(3-chlorophenyl)-2-
 ((cyclopropylmethyl)amino)ethanol and (1S,2R)-2-(Benzo[d]thiazol-2-yl)-1-(3-
 chlorophenyl)-2-((cyclopropylmethyl)amino)ethanol

5



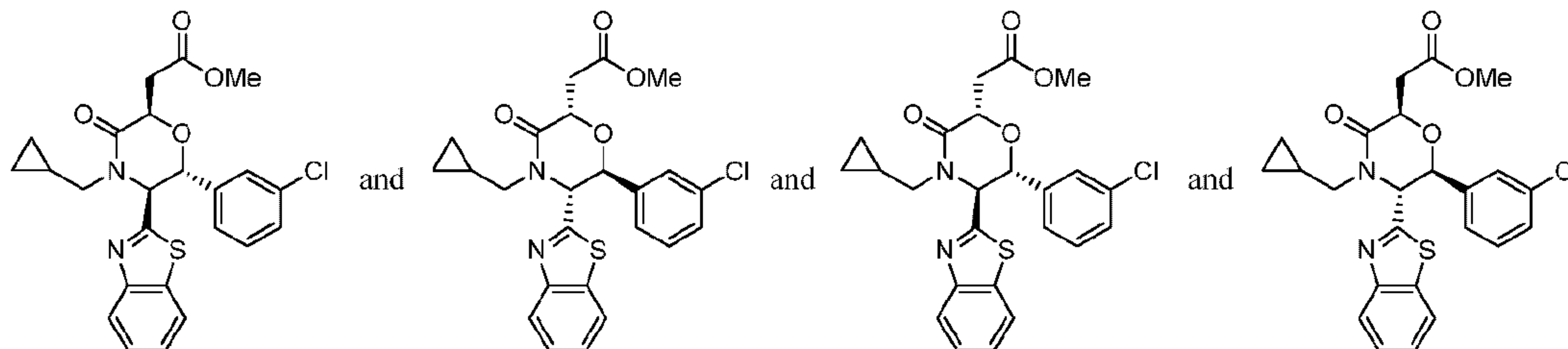
The racemic mixture of *tert*-butyl ((1S,2R)-1-(benzo[d]thiazol-2-yl)-2-(3-
 chlorophenyl)-2-hydroxyethyl)(cyclopropylmethyl)carbamate and *tert*-butyl ((1R,2S)-1-
 10 (benzo[d]thiazol-2-yl)-2-(3-chlorophenyl)-2-hydroxyethyl)(cyclopropylmethyl)carbamate
 (875 mg, 1.906 mmol; Example 3, Step C) was dissolved in a solution of 4N HCl in
 dioxane (10 mL, 40.0 mmol). The reaction mixture was stirred for 1h at ambient
 temperature and then concentrated under reduced pressure. The residue was diluted in
 EtOAc and washed with NaHCO₃ to neutralize. Purification of the residue by flash
 15 chromatography on silica gel (eluent: 0 to 100% EtOAc/hexane, gradient elution)
 provided the title compound as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.00 -
 0.20 (m, 2 H), 0.40 - 0.57 (m, 2 H), 0.89 - 1.03 (m, 1 H), 2.50 (dd, *J*=12.13, 7.24 Hz, 1
 H), 2.64 (dd, *J*=12.13, 6.46 Hz, 1 H), 4.19 (d, *J*=7.43 Hz, 1 H), 4.70 (s, 1 H), 4.98 (d,
J=7.43 Hz, 1 H), 7.03 - 7.11 (m, 1 H), 7.15 (t, *J*=7.73 Hz, 1 H), 7.20 - 7.25 (m, 1 H), 7.27
 20 - 7.30 (m, 1 H), 7.35 - 7.43 (m, 2 H), 7.49 (ddd, *J*=8.22, 7.14, 1.27 Hz, 1 H), 7.82 (d,
J=8.02 Hz, 1 H), 8.00 (d, *J*=8.22 Hz, 1 H). Mass Spectrum (ESI) *m/z* = 359 (M+1).

Step E. (E)-Methyl 4-(((1S,2R)-1-(benzo[d]thiazol-2-yl)-2-(3-chlorophenyl)-2-
 hydroxyethyl) (cyclopropylmethyl)amino)-4-oxobut-2-enoate and (E)-Methyl 4-
 25 (((1R,2S)-1-(benzo[d]thiazol-2-yl)-2-(3-chlorophenyl)-2-hydroxyethyl)
 (cyclopropylmethyl)amino)-4-oxobut-2-enoate



To a solution of the racemic mixture of (1R,2S)-2-(benzo[d]thiazol-2-yl)-1-(3-chlorophenyl)-2-((cyclopropylmethyl)amino)ethanol and (1S,2R)-2-(benzo[d]thiazol-2-yl)-1-(3-chlorophenyl)-2-((cyclopropylmethyl)amino)ethanol (310 mg, 0.864 mmol; Example 3, Step D) and triethylamine (0.60 mL, 4.32 mmol) in DMF (4 mL) was added monomethyl fumarate (112 mg, 0.864 mmol) followed by HATU (328 mg, 0.864 mmol). The reaction was monitored by LCMS, adding additional reagents until complete. Purification of the filtered reaction mixture was done by preparatory RP-HPLC (Sunfire™ Prep C₁₈ OBD 10 μm column; Waters, Milford, MA; eluent: 55 to 75% acetonitrile, water, 0.1%TFA, gradient elution). The pooled fractions were neutralized by addition of sat. aq. NaHCO₃ solution, concentrated under reduced pressure, and extracted with DCM. Then the combined organic layers were dried (Na₂SO₄), filtered and the filtrate was concentrated under reduced pressure to provide the title compounds as a yellow oil.

Step F. Methyl 2-((2R,5S,6R)-5-(benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and Methyl 2-((2S,5R,6S)-5-(benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and Methyl 2-((2S,5S,6R)-5-(benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and Methyl 2-((2R,5R,6S)-5-(benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate



To a solution of (E)-methyl 4-(((1S,2R)-1-(benzo[d]thiazol-2-yl)-2-(3-chlorophenyl)-2-hydroxyethyl) (cyclopropylmethyl)amino)-4-oxobut-2-enoate and (E)-
 5 methyl 4-(((1R,2S)-1-(benzo[d]thiazol-2-yl)-2-(3-chlorophenyl)-2-hydroxyethyl) (cyclopropylmethyl)amino)-4-oxobut-2-enoate (203 mg, 0.43 mmol; Example 3, step E) in DMSO (2.1 mL) at ambient temperature was added caesium carbonate (281 mg, 0.86 mmol). The reaction was stirred for 2 h. It was diluted with sat. aq. NaHCO₃ solution and extracted with DCM. The combined organic layers were washed with water, dried over
 10 MgSO₄, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by preparatory RP-HPLC (eluent: 50% acetonitrile, water, 0.1%TFA, isocratic) provided the title compounds in two separately eluting fractions as racemic mixtures. The pooled HPLC fractions were neutralized by sat. aq. NaHCO₃ solution, concentrated under reduced pressure, and extracted with DCM. The combined organic
 15 layers were dried (Na₂SO₄), filtered and the filtrate was concentrated under reduced pressure to provide the title compounds.

Methyl 2-((2R,5S,6R)-5-(benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and methyl 2-((2S,5R,6S)-5-(benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate (first two eluting compounds). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.24 (dq, *J*=10.42, 4.81 Hz, 1 H), 0.46 (dq, *J*=9.78, 4.83 Hz, 1 H), 0.52 - 0.67 (m, 1 H), 0.70 - 0.82 (m, 1 H), 1.16 (dddd, *J*=9.63, 6.41, 4.70, 3.52 Hz, 1 H), 2.66 (dd, *J*=14.28, 7.83 Hz, 1 H), 2.91 (dd, *J*=16.24, 9.39 Hz, 1 H), 3.20 (dd, *J*=16.24, 3.52 Hz, 1 H), 3.74 (s, 3 H), 4.20
 20 (dd, *J*=14.28, 6.46 Hz, 1 H), 4.55 (dd, *J*=9.39, 3.52 Hz, 1 H), 5.38 (s, 1 H), 5.73 (d, *J*=1.37 Hz, 1 H), 7.34 - 7.61 (m, 5 H), 7.66 (s, 1 H), 7.88 - 7.99 (m, 1 H), 7.99 - 8.07 (m, 1 H). Mass Spectrum (ESI) *m/z* = 471 (M+1), 493 (M+Na).

Methyl 2-((2S,5S,6R)-5-(benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and methyl 2-((2R,5R,6S)-5-(benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate (later two eluting compounds) Mass Spectrum (ESI) $m/z = 471$ (M+1), 493 (M+Na).

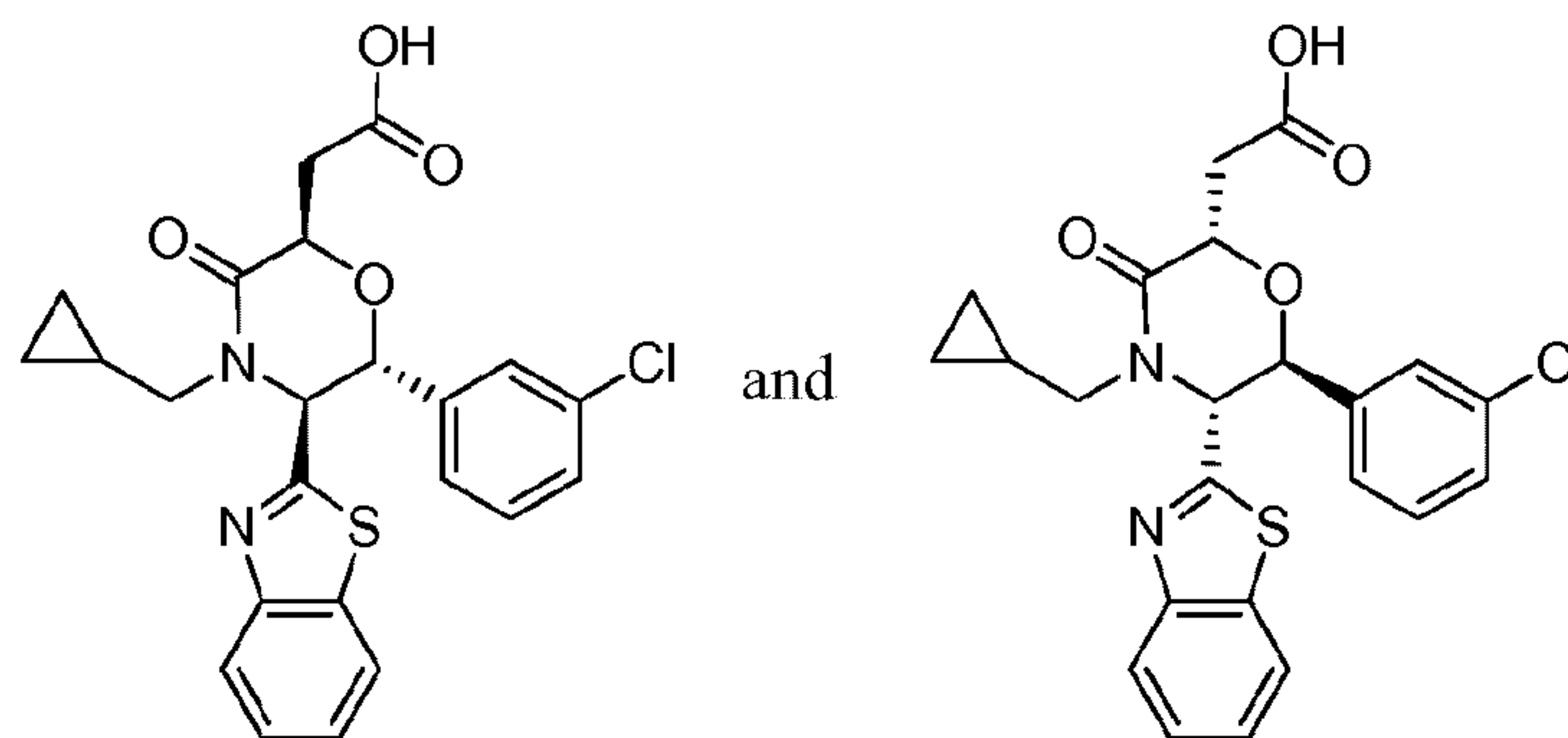
Step G. 2-((2S,5S,6R)-5-(Benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid and 2-((2R,5R,6S)-5-(Benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

To a solution of the racemic mixture of methyl 2-((2R,5S,6R)-5-(benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and methyl 2-((2S,5R,6S)-5-(benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate (20 mg, 0.042 mmol; first eluting compounds from Example 3, Step F) in dioxane (425 μ L) at ambient temperature was added 1M aq. LiOH solution (425 μ L, 0.425 mmol). The reaction mixture was stirred for 1 h, acidified with acetic acid (28.1 mg, 0.467 mmol) and concentrated under reduced pressure. Purification of the residue by preparatory RP-HPLC (SunfireTM Prep C₁₈ OBD 10 μ m column; Waters, Milford, MA; eluent: 40 to 60% acetonitrile, water, 0.1%TFA, gradient elution) gave the title compounds as the first eluting set of compounds (Note: Racemization occurred at C2 during treatment with base). The pooled fractions were neutralized with sat. aq. NaHCO₃ solution, concentrated under reduced pressure, acidified (1N aq. HCl), and extracted (3 x DCM). Then the combined organic layers were dried (Na₂SO₄), filtered and the filtrate was concentrated under reduced pressure. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.09 - 0.22 (m, 1 H), 0.24 - 0.48 (m, 2 H), 0.48 - 0.63 (m, 1 H), 0.95 - 1.07 (m, 1 H), 2.98 (dd, J=14.18, 7.34 Hz, 1 H), 3.06 - 3.19 (m, 1 H), 3.19 - 3.30 (m, 1 H), 3.80 (dd, J=14.09, 6.65 Hz, 1 H), 5.28 (dd, J=7.83, 4.69 Hz, 1 H), 5.41 (d, J=2.93 Hz, 1 H), 5.53 (d, J=2.74 Hz, 1 H), 7.01 - 7.20 (m, 3 H), 7.24 (s, 1 H), 7.33 - 7.51 (m, 2 H), 7.80 - 7.94 (m, 2 H); Mass Spectrum (ESI) $m/z = 457$ (M+1).

Further elution provided:

EXAMPLE 4

2-((2R,5S,6R)-5-(Benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid and 2-((2S,5R,6S)-5-(Benzo[d]thiazol-2-yl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid



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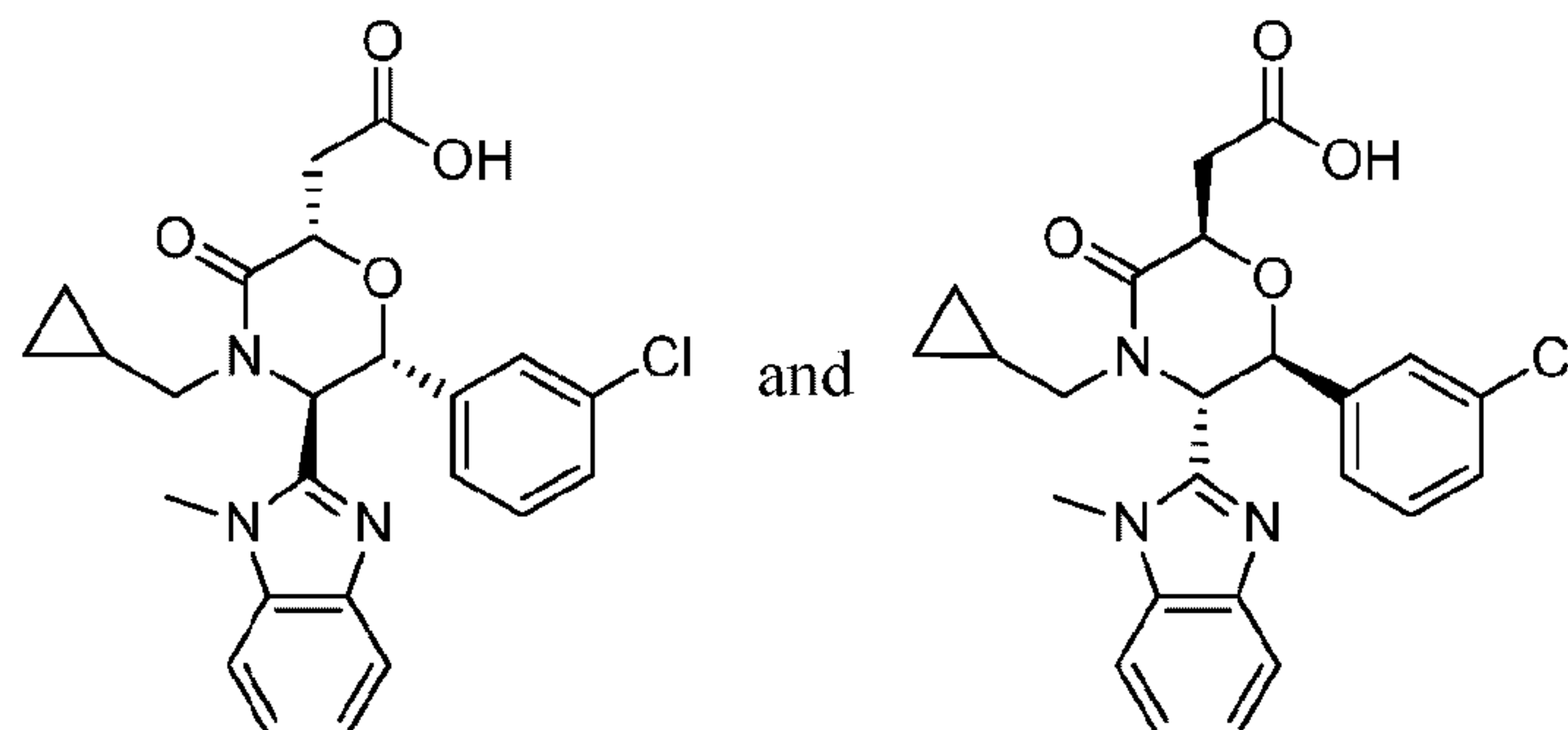
The title compounds were obtained from Example 3, Step G as the later eluting set of compounds (Note: Racemization occurred at C2 during treatment with base). The pooled fractions were neutralized with sat. aq. NaHCO₃ solution, concentrated under reduced pressure, acidified (1N aq. HCl), and extracted (3 x DCM). Then the combined organic layers were dried (Na₂SO₄), filtered and the filtrate was concentrated under reduced pressure. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.22 - 0.33 (m, 1 H), 0.48 (td, J=9.73, 4.60 Hz, 1 H), 0.58 - 0.68 (m, 1 H), 0.74 - 0.84 (m, 1 H), 1.12 - 1.24 (m, 1 H), 2.02 (s, 1 H), 2.72 (dd, J=14.28, 7.82 Hz, 1 H), 2.94 (dd, J=16.33, 6.94 Hz, 1 H), 3.25 (dd, J=16.33, 5.77 Hz, 1 H), 4.20 (dd, J=14.38, 6.55 Hz, 1 H), 4.45 (t, J=6.46 Hz, 1 H), 5.39 (s, 1 H), 5.76 (d, J=0.98 Hz, 1 H), 7.37 - 7.44 (m, 2 H), 7.44 - 7.52 (m, 2 H), 7.55 (ddd, J=8.22, 7.14, 1.27 Hz, 1 H), 7.65 (s, 1 H), 7.95 (d, J=7.43 Hz, 1 H), 8.04 (d, J=7.63 Hz, 1 H); Mass Spectrum (ESI) m/z = 457 (M+1).

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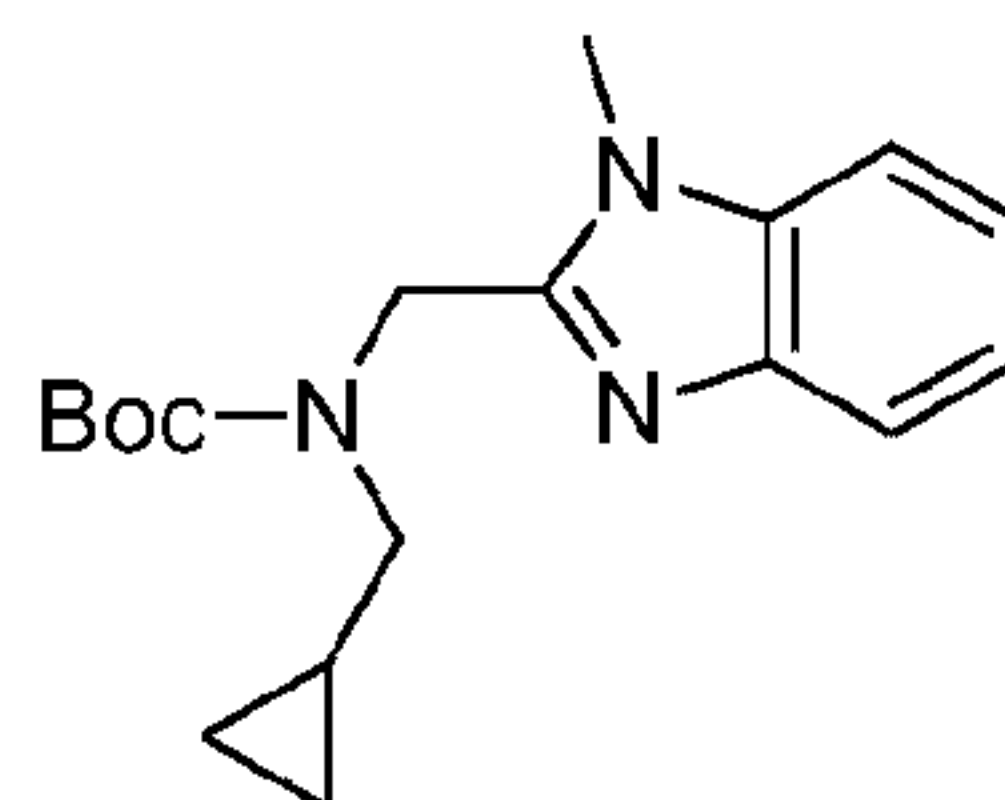
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EXAMPLE 5

2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-oxomorpholin-2-yl)acetic acid and 2-((2R,5S,6S)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-oxomorpholin-2-yl)acetic acid



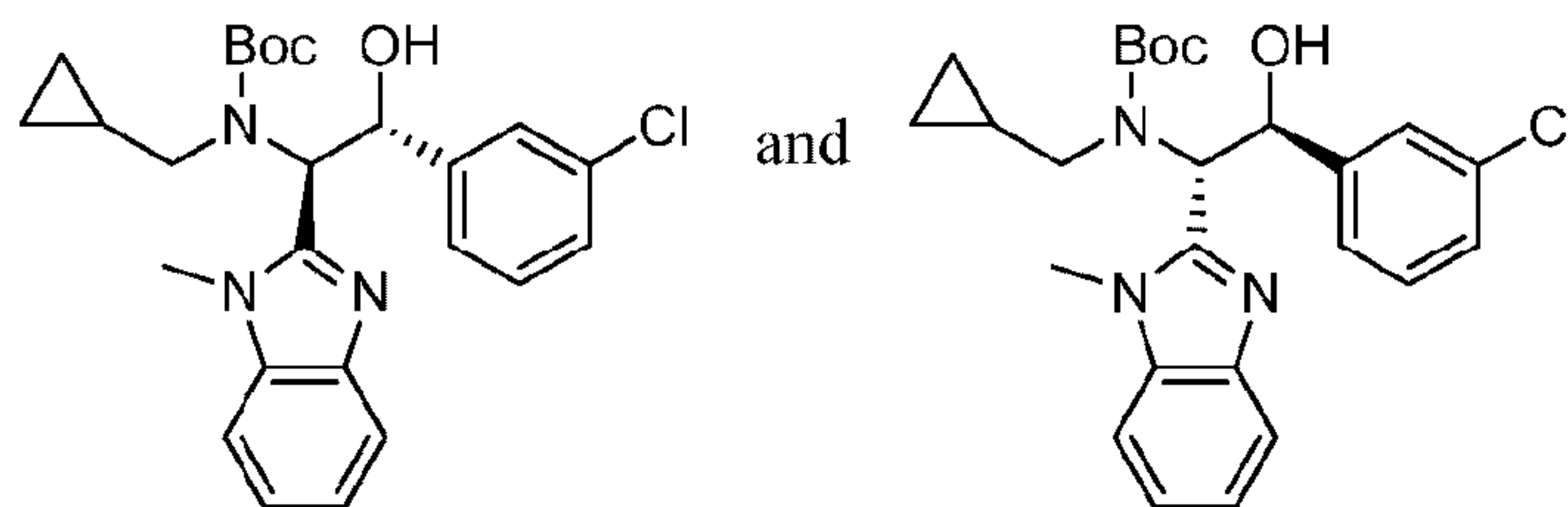
Step A. *tert*-Butyl cyclopropylmethyl((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)carbamate



To a mixture of [1-methyl-1H-benzo[d]imidazole-2-carbaldehyde (1.78 g, 11.11 mmol) and cyclopropylmethanamine (0.790 g, 11.11 mmol) was added a 2 mL of anhydrous acetonitrile and the solvent was removed under reduced pressure on a rotary evaporator. This procedure was repeated several times until a chalky solid was obtained. This was then dissolved in 100 mL of DCM, cooled to 0 °C, and NaBH(OAc)₃ (3.53 g, 16.67 mmol) was added in one portion. After 30 min, the mixture was re-cooled to 0 °C and then triethylamine (4.65 mL, 33.3 mmol) and di-*tert*-butyl dicarbonate (2.91 g, 13.34 mmol) were added. The reaction mixture was allowed to warm to ambient temperature overnight, at which time it was quenched by addition of 100 mL of water and extracted

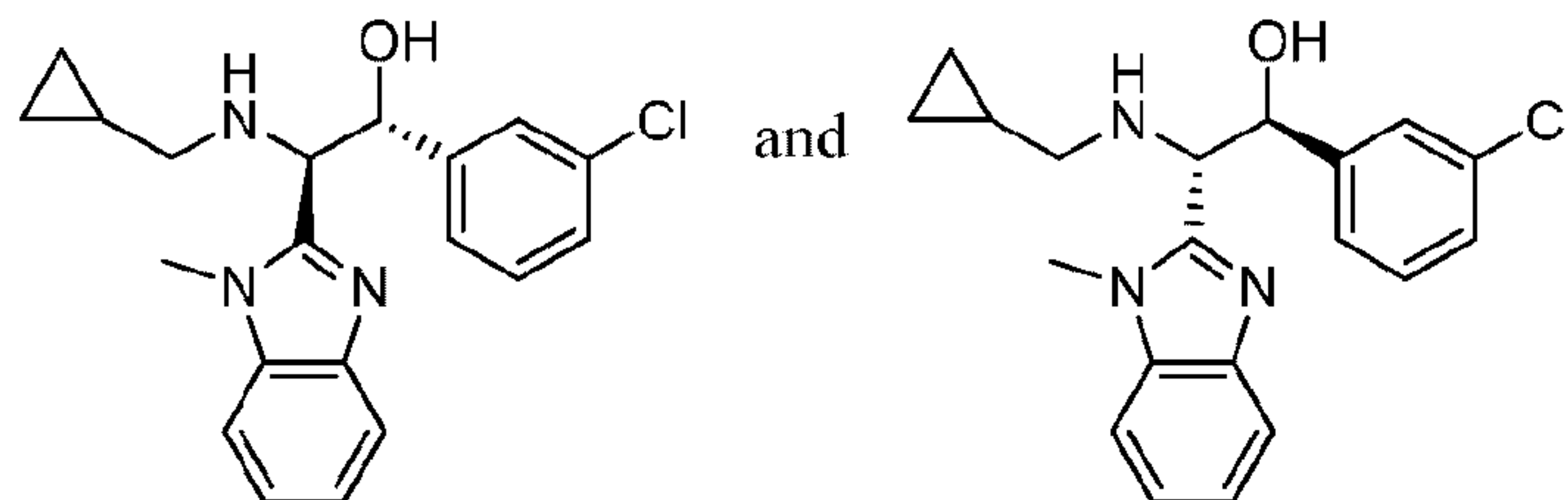
with DCM (100mL×2). The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was suspended in acetonitrile and filtered to remove insoluble impurities. The filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (eluent: 0 to 25% EtOAc/hexane) provided the title compound. Mass Spectrum (ESI) $m/z = 316$ (M+1).

Step B. *tert*-Butyl ((1R,2R)-2-(3-chlorophenyl)-2-hydroxy-1-(1-methyl-1H-benzo[d]imidazol-2-yl)ethyl)(cyclopropylmethyl)carbamate and *tert*-Butyl ((1S,2S)-2-(3-chlorophenyl)-2-hydroxy-1-(1-methyl-1H-benzo[d]imidazol-2-yl)ethyl)(cyclopropylmethyl)carbamate



The title compound was prepared from *tert*-butyl cyclopropylmethyl((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)carbamate (Example 5, Step A) and methyl 3-chlorobenzoate by a procedure similar to the one described in Example 3, Step C. Purification of the residue by flash chromatography on silica gel (eluent: 10 to 20% EtOAc/Hexane) provided the title compounds as a racemic mixture as the faster eluting major stereoisomers. Mass Spectrum (ESI) $m/z = 456$ (M+1).

Step C. (1R,2R)-1-(3-Chlorophenyl)-2-((cyclopropylmethyl)amino)-2-(1-methyl-1H-benzo[d]imidazol-2-yl)ethanol and (1S,2S)-1-(3-Chlorophenyl)-2-((cyclopropylmethyl)amino)-2-(1-methyl-1H-benzo[d]imidazol-2-yl)ethanol

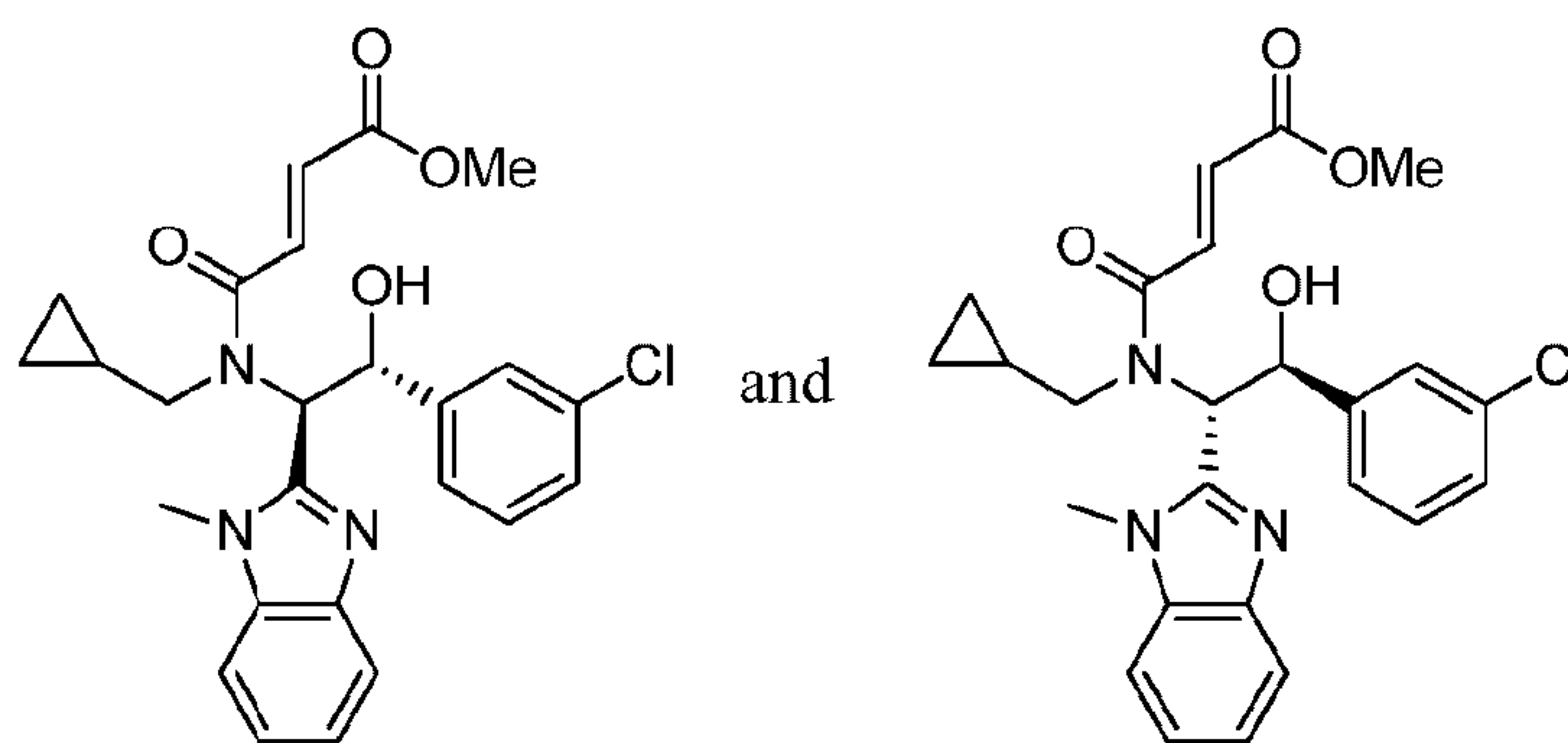


The title compounds were prepared from *tert*-Butyl ((1*R*,2*R*)-2-(3-chlorophenyl)-2-hydroxy-1-(1-methyl-1*H*-benzo[d]imidazol-2-yl)ethyl)(cyclopropylmethyl)carbamate and *tert*-Butyl ((1*S*,2*S*)-2-(3-chlorophenyl)-2-hydroxy-1-(1-methyl-1*H*-benzo[d]imidazol-2-yl)ethyl)(cyclopropylmethyl)carbamate (Example 5, Step B) by a procedure analogous to the one described in Example 3, Step D. The crude material was carried forward without further purification to the next step. Mass Spectrum (ESI) m/z = 356 ($M+1$).

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Step D. (E)-Methyl 4-(((1*R*,2*R*)-2-(3-chlorophenyl)-2-hydroxy-1-(1-methyl-1*H*-benzo[d]imidazol-2-yl)ethyl)(cyclopropylmethyl)amino)-4-oxobut-2-enoate and (E)-Methyl 4-(((1*S*,2*S*)-2-(3-chlorophenyl)-2-hydroxy-1-(1-methyl-1*H*-benzo[d]imidazol-2-yl)ethyl)(cyclopropylmethyl)amino)-4-oxobut-2-enoate

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The title compound was prepared from (1*R*,2*R*)-1-(3-chlorophenyl)-2-((cyclopropylmethyl)amino)-2-(1-methyl-1*H*-benzo[d]imidazol-2-yl)ethanol and (1*S*,2*S*)-1-(3-chlorophenyl)-2-((cyclopropylmethyl)amino)-2-(1-methyl-1*H*-benzo[d]imidazol-2-yl)ethanol (Example 5, Step C) by a procedure analogous to the one described in Example 3, Step E. When complete, the reaction mixture was diluted with diethyl ether,

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rinsed with NaHCO₃/brine, washed with water, dried over MgSO₄, filtered and eluted through a small SiO₂ plug. The filtrate was concentrated under reduced pressure to provide crude product which was carried forward without further purification to the next step. Mass Spectrum (ESI) m/z = 468 (M+1), 490 (M+Na).

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Step E. 2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-oxomorpholin-2-yl)acetic acid and 2-((2R,5S,6S)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-5-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-oxomorpholin-2-yl)acetic acid

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To a solution of (E)-methyl 4-(((1R,2R)-2-(3-chlorophenyl)-2-hydroxy-1-(1-methyl-1H-benzo[d]imidazol-2-yl)ethyl)(cyclopropylmethyl)amino)-4-oxobut-2-enoate and (E)-methyl 4-(((1S,2S)-2-(3-chlorophenyl)-2-hydroxy-1-(1-methyl-1H-benzo[d]imidazol-2-yl)ethyl)(cyclopropylmethyl)amino)-4-oxobut-2-enoate (323 mg, 0.690 mmol; Example 5, Step D) in dioxane (3.5 mL) was added aq. 1M LiOH solution (2071 µL, 2.07 mmol). The reaction was stirred until LCMS analysis indicated complete consumption of starting material and a single product peak was apparent. The reaction mixture was neutralized with AcOH and the solvents were removed. Purification of the residue by preparatory RP-HPLC (SunfireTM Prep C₁₈ OBD 10 µm column; Waters, Milford, MA; eluent: 35 to 55% acetonitrile, water, 0.1%TFA, gradient elution) followed by lyophilization provided mixed fractions in which both cyclized and uncyclized acid products were observed. The combined fractions were dissolved in dioxane (3451 µL) and a 55% NaH suspension in mineral oil (90 mg, 2.071 mmol) was added. After 30 minutes at ambient temperature, the reaction was neutralized by addition of AcOH and the mixture was concentrated under reduced pressure. Purification of the residue by preparatory RP-HPLC (SunfireTM Prep C₁₈ OBD 10 µm column; Waters, Milford, MA; eluent: 26% acetonitrile, water, 0.1%TFA, isocratic elution) provided the title compounds as the faster eluting, major products, which were white solids after lyophilization. ¹H NMR (400 MHz, CDCl₃) δ ppm -0.27 to -0.20 (m, 1 H), -0.03 (dq, J=9.83, 5.14 Hz, 1 H), 0.33 - 0.50 (m, 2 H), 0.72 - 0.81 (m, 1 H), 2.34 - 2.43 (m, 1 H), 3.05 - 3.16 (m, 1 H), 3.16 - 3.27 (m, 4 H), 4.16 (dd, J=14.97, 6.16 Hz, 1 H), 4.93 (t, J=4.89 Hz, 1 H), 5.40 (q,

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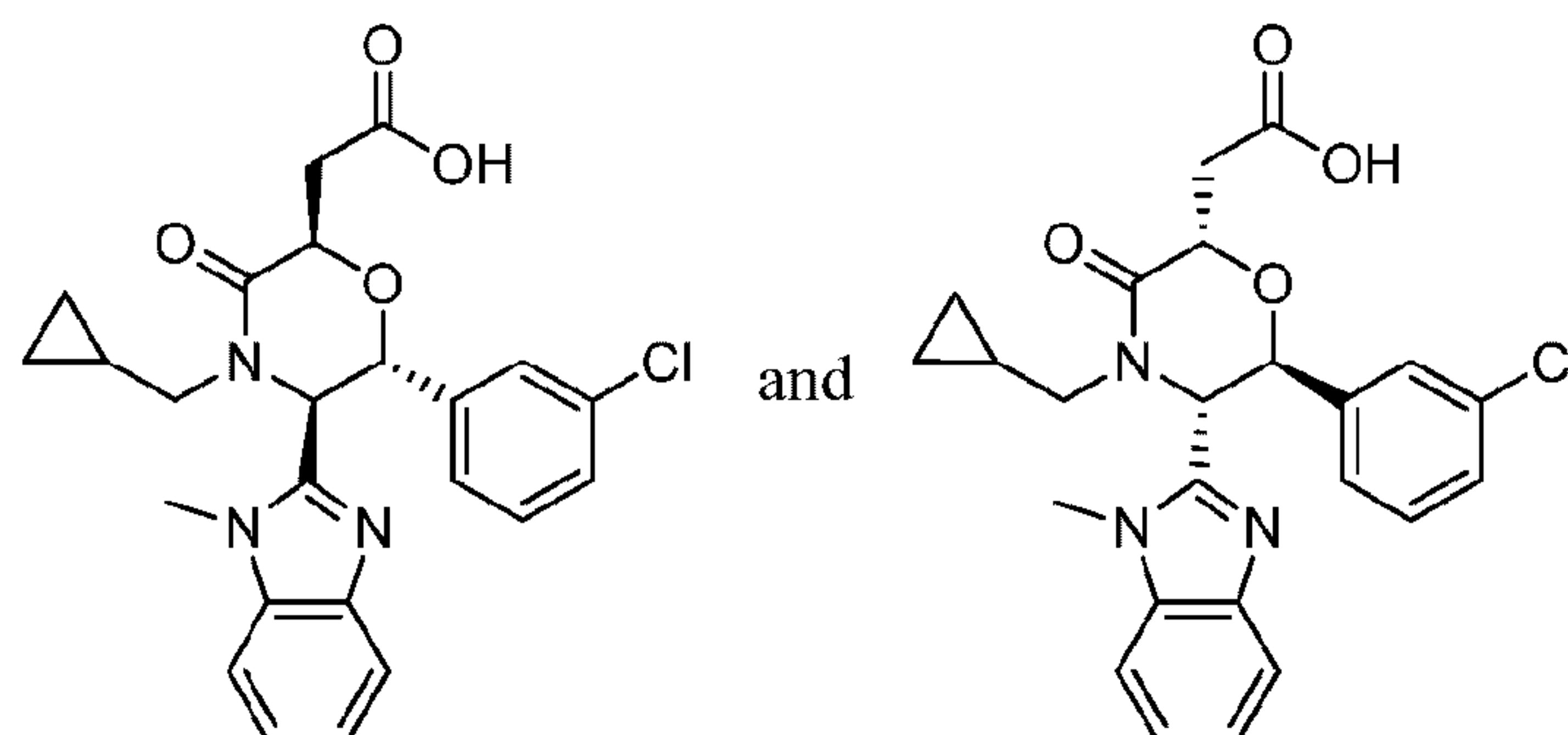
$J=9.52$ Hz, 2 H), 6.77 - 6.83 (m, 1 H), 7.07 - 7.18 (m, 2 H), 7.26 - 7.31 (m, 1 H), 7.34 - 7.39 (m, 1 H), 7.46 - 7.54 (m, 2 H), 7.93 - 7.99 (m, 1 H). Mass Spectrum (ESI) $m/z = 454$ (M+1).

5 Further elution provided:

EXAMPLE 6

2-((2R,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-oxomorpholin-2-yl)acetic acid and 2-((2S,5S,6S)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-oxomorpholin-2-yl)acetic acid

10 oxomorpholin-2-yl)acetic acid



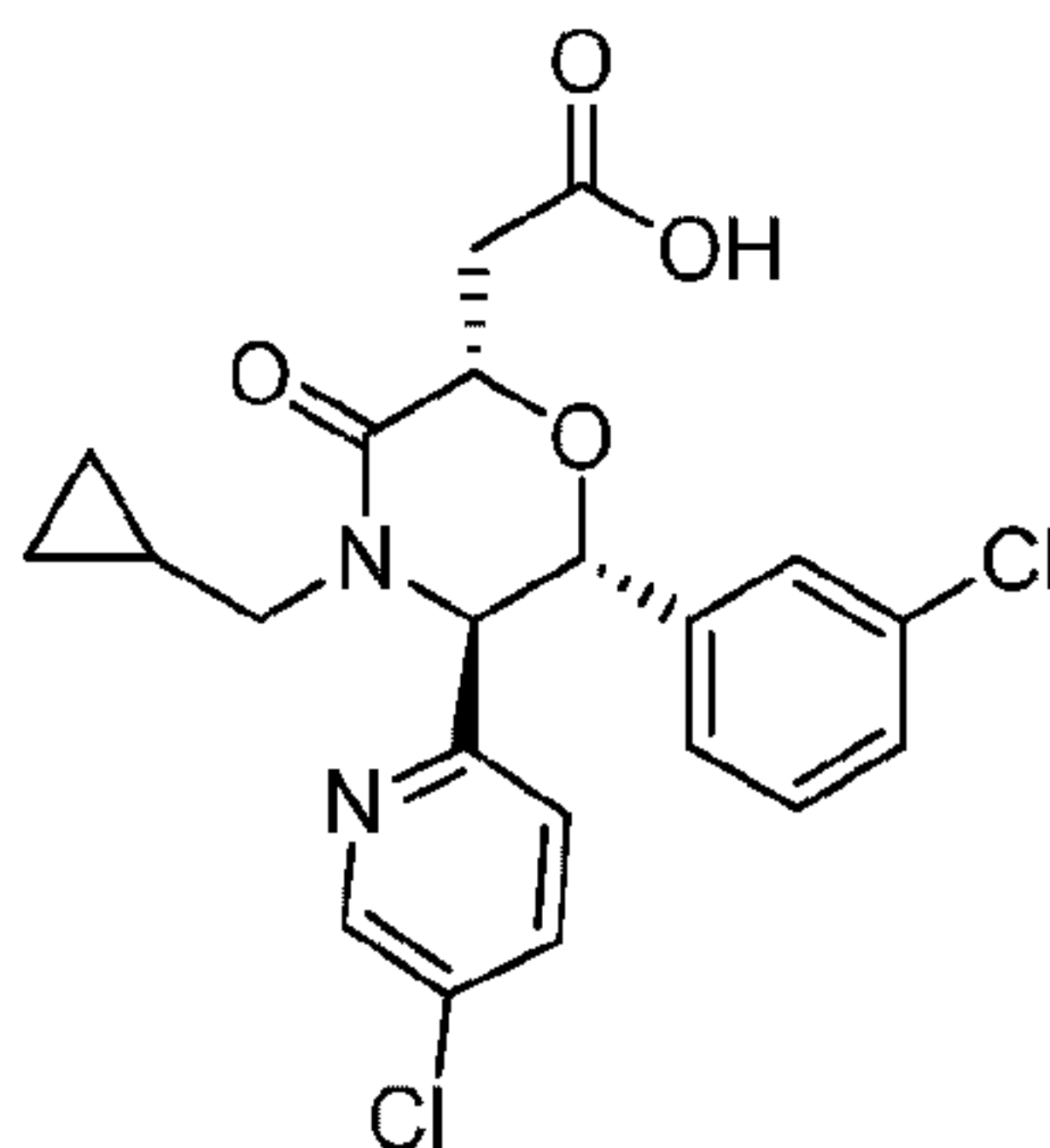
The title compounds were obtained from Example 5, Step E as the later eluting set

15 of compounds (minor products). ^1H NMR (400 MHz, CDCl_3) δ ppm -0.26 to -0.14 (m, 1 H), 0.03 (dq, $J=9.68, 4.99$ Hz, 1 H), 0.33 - 0.54 (m, 2 H), 0.71 - 0.85 (m, 1 H), 2.37 (dd, $J=14.77, 7.73$ Hz, 1 H), 3.05 - 3.32 (m, 5 H), 4.21 (dd, $J=14.77, 6.16$ Hz, 1 H), 4.92 (t, $J=4.79$ Hz, 1 H), 5.33 - 5.44 (m, 2 H), 6.76 (d, $J=7.83$ Hz, 1 H), 7.10 (t, $J=7.83$ Hz, 1 H), 7.18 (t, $J=1.76$ Hz, 1 H), 7.28 - 7.38 (m, 2 H), 7.44 - 7.55 (m, 2 H), 7.98 (dd, $J=6.55, 2.25$

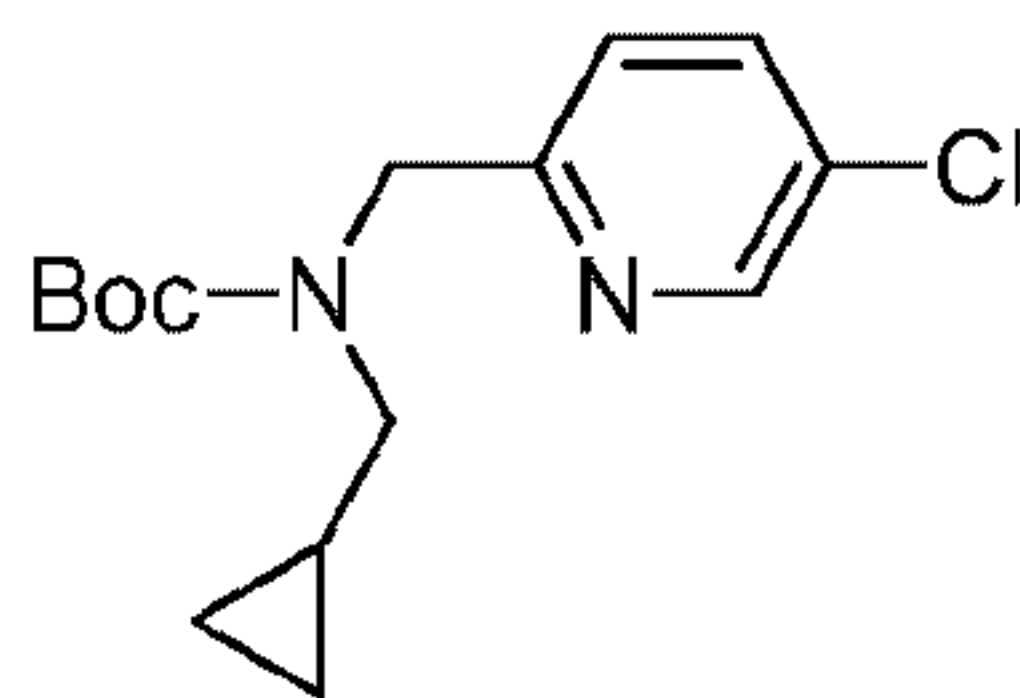
20 Hz, 1 H). Mass Spectrum (ESI) $m/z = 454$ (M+1).

EXAMPLE 7

2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(5-chloropyridin-2-yl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid



Step A. *tert*-Butyl ((5-chloropyridin-2-yl)methyl)(cyclopropylmethyl)carbamate



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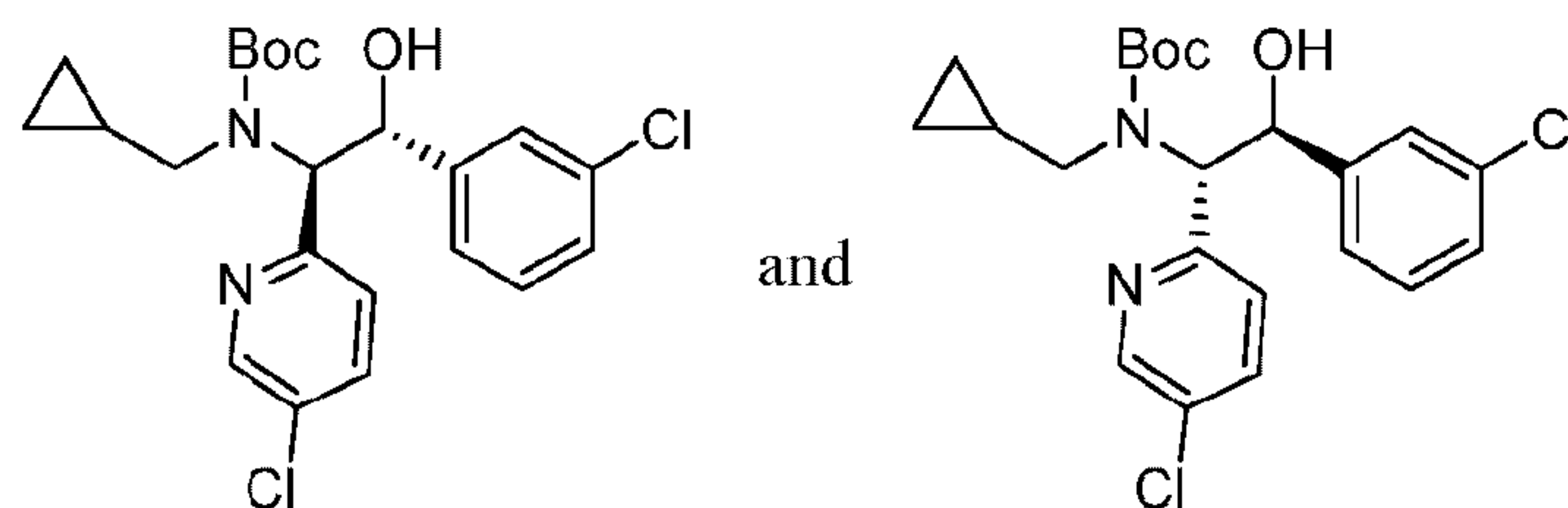
The title compound was prepared from 5-chloropicolinaldehyde, cyclopropylmethanamine, and di-*tert*-butyl dicarbonate as described in Example 5, Step A. Purification of the residue by flash chromatography on silica gel (eluent: 0 to 25% EtOAc/Hexane, gradient elution) provided the title compound as a yellow oil.

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¹H NMR (400 MHz, CDCl₃) δ ppm 0.17 (br. s., 2 H) 0.25 - 0.55 (m, 2 H) 0.94 (br. s., 1 H) 1.08 - 1.78 (m, 9 H) 3.07-3.37 (m, 2 H) 4.62 (br. s., 2 H) 7.23 (br. s., 1 H) 7.63 (d, *J*=7.04 Hz, 1 H) 8.48 (br. s., 1 H). Mass Spectrum (ESI) *m/z* = 197 (*M*+*H*-Boc), 241 (*M*+*H*-*t*butyl), 297 (*M*+1), 319 (*M*+Na).

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Step B. *tert*-Butyl (1R,2R)-(2-(3-chlorophenyl)-1-(5-chloropyridin-2-yl)-2-hydroxyethyl)(cyclopropylmethyl)carbamate and *tert*-Butyl (1S,2S)-(2-(3-chlorophenyl)-1-(5-chloropyridin-2-yl)-2-hydroxyethyl)(cyclopropylmethyl)carbamate



The title compound was prepared from *tert*-butyl ((5-chloropyridin-2-yl)methyl)(cyclopropylmethyl)carbamate (Example 7, Step A) and methyl 3-chlorobenzoate as described in Example 3, Step C. Purification of the residue by flash chromatography on silica gel (eluent: 7 to 10% EtOAc/hexane, solvents purged with NH₃ gas; gradient elution) provided the title compounds as a racemic mixture. Individual stereoisomers were separated by chiral HPLC over several runs (flowrate: 100 mL/min on a Chiralcel AD-H 10 cm I.D. × 50 cm, 20μm column (Daicel Chemical Industries LTD), using 15% isopropyl alcohol/hexane as the eluent) to give *tert*-butyl ((1R,2R)-2-(3-chlorophenyl)-1-(5-chloropyridin-2-yl)-2-hydroxyethyl)(cyclopropylmethyl)carbamate (*t_R* = 16-20 min) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ ppm -0.67 to -0.32 (m, 1 H) -0.31 to -0.07 (m, 1 H) 0.00 (br. s., 2 H) 0.24 - 0.50 (m, 1 H) 1.19 (br. s., 9 H) 2.59 - 3.16 (m, 2 H) 4.88 - 5.16 (m, 1 H) 5.36 (d, *J*=4.70 Hz, 1 H) 5.54 - 6.03 (m, 1 H) 6.90 - 7.34 (m, 5 H) 7.46 (dd, *J*=8.41, 2.54 Hz, 1 H) 8.33 (d, 1 H). Mass Spectrum (ESI) *m/z* = 437 (*M*+H) and 459 (*M*+Na), *t_R* = 6.09 min on Chiralpak[®] AD-H analytical HPLC column, Daicel Chemical Industries LTD, 15% iPrOH/hexanes, isocratic elution.

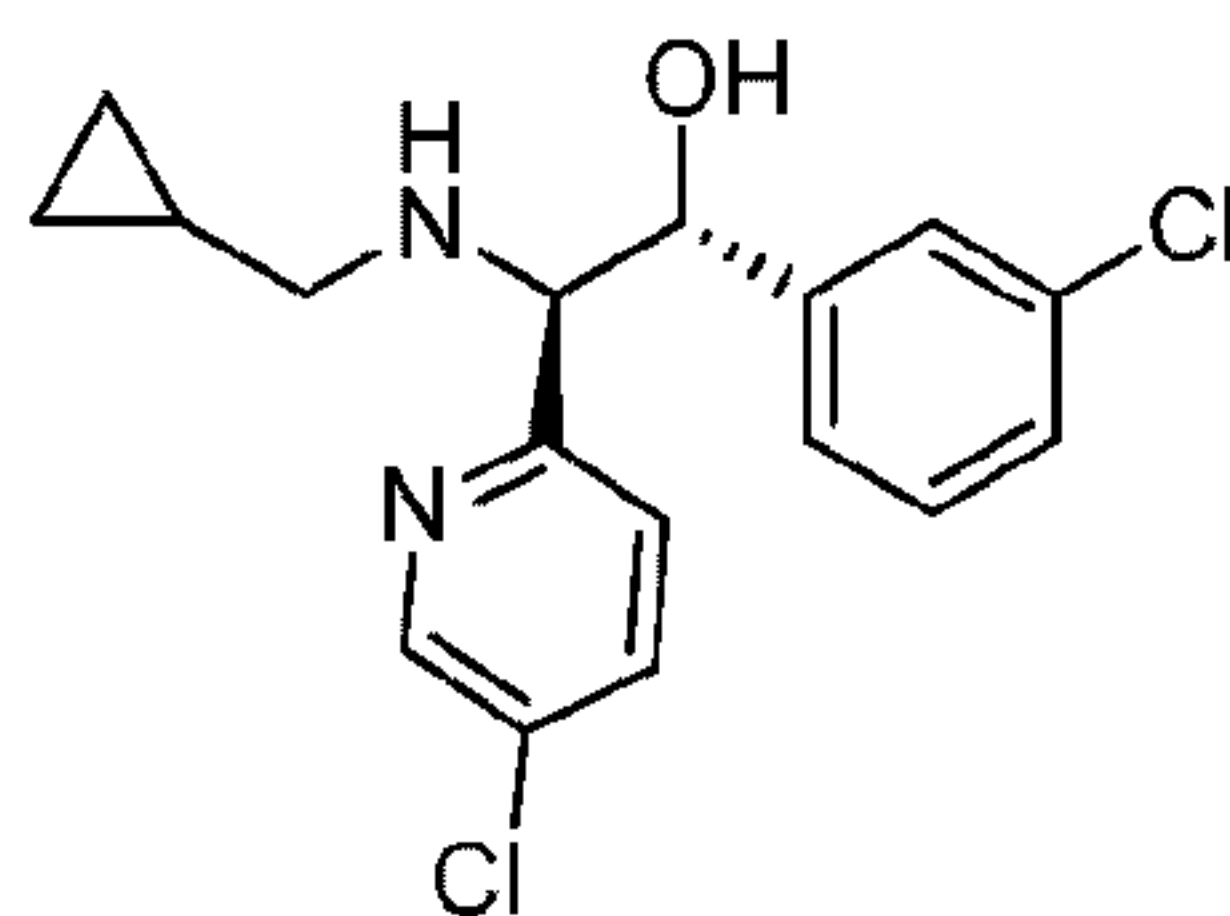
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Further elution using 50% iPrOH/hexanes yielded the other enantiomer, *tert*-butyl (1S,2S)-(2-(3-chlorophenyl)-1-(5-chloropyridin-2-yl)-2-hydroxyethyl)(cyclopropylmethyl)carbamate.

Mass Spectrum (ESI) *m/z* = 381 (*M*+1-*t*butyl), 437 (*M*+Na), *t_R* = 17.5 min on AD-H analytical HPLC column, Daicel Chemical Industries LTD, 15% iPrOH/hexanes, isocratic elution.

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Step D. (1R,2R)-1-(3-Chlorophenyl)-2-(5-chloropyridin-2-yl)-2-((cyclopropylmethyl)amino)ethanol



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The title compound was prepared from *tert*-butyl (1R,2R)-(2-(3-chlorophenyl)-1-(5-chloropyridin-2-yl)-2-hydroxyethyl)(cyclopropylmethyl)carbamate (Example 7, Step C) as described in Example 3, Step D, except that the reaction was run at 50° C for 1.5h. The product was used without further purification in the next step. Mass Spectrum (ESI) $m/z = 337$ (M+1).

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Step E. 2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(5-chloropyridin-2-yl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

To a solution of monomethyl fumarate (42.4 mg, 0.326 mmol) and 3 equiv. triethylamine (0.123 mL, 0.890 mmol) in anhydrous DMF (1 mL) was added HATU (118 mg, 0.311 mmol). The solution was stirred for 10 minutes at ambient temperature, then it was added slowly to a vigorously stirring solution of (1R,2R)-1-(3-chlorophenyl)-2-(5-chloropyridin-2-yl)-2-(cyclopropylmethylamino)ethanol (100 mg, 0.297 mmol; Example 7, Step D) in anhydrous DMF (2 mL). The reaction was monitored by LCMS until it was judged complete, (additional activated ester was added if required). The reaction mixture was cooled to 0° C and a 55% NaH suspension in mineral oil (39 mg, 0.890 mmol) was added. The crude product was filtered. Purification of the filtrate by preparatory RP-HPLC (SunfireTM Prep C₁₈ OBD 10 μ m column, Waters, Milford, MA; eluent: 40-70% acetonitrile, water, 0.1%TFA, gradient elution) provided a cyclized ester mixture. This material was dissolved in dioxane (2 mL) and a solution of 1M LiOH in water (0.89 mL, 0.89 mmol) was added. The reaction mixture was stirred at ambient temperature overnight, then filtered. Purification of the residue by preparatory RP-HPLC (SunfireTM

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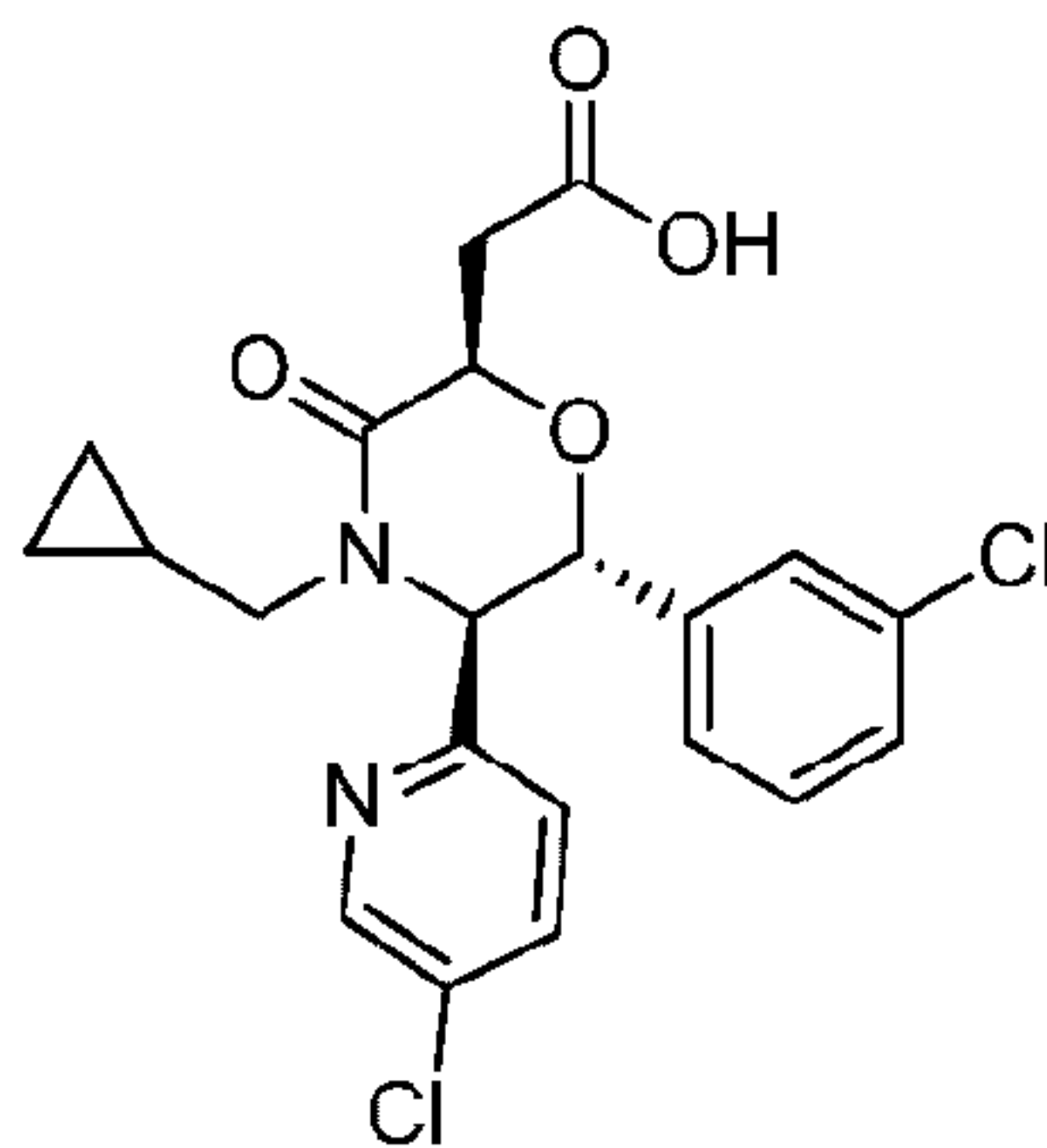
Prep C₁₈ OBD 10 μ m column, Waters, Milford, MA; eluent: 40-70% acetonitrile, water, 0.1%TFA, gradient elution over 30 min) provided the title compound as the first eluting compound. ¹H NMR (400 MHz, CDCl₃) δ ppm -0.06 - 0.12 (m, 2 H) 0.34 - 0.54 (m, 2 H) 0.73 - 0.89 (m, 1 H) 2.28 (dd, *J*=14.38, 7.14 Hz, 1 H) 3.01 - 3.22 (m, 2 H) 3.93 (dd, *J*=14.48, 6.85 Hz, 1 H) 4.80 (t, *J*=5.38 Hz, 1 H) 4.86 - 4.99 (m, 2 H) 6.78 (d, *J*=7.63 Hz, 1 H) 6.87 (d, *J*=8.41 Hz, 1 H) 7.06 - 7.17 (m, 2 H) 7.20 - 7.26 (m, 1 H) 7.58 (dd, *J*=8.22, 2.35 Hz, 1 H) 8.61 (d, *J*=2.35 Hz, 1 H). Mass Spectrum (ESI) *m/z* = 435 (M+1).

Further elution provided:

10

EXAMPLE 8

2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(5-chloropyridin-2-yl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid



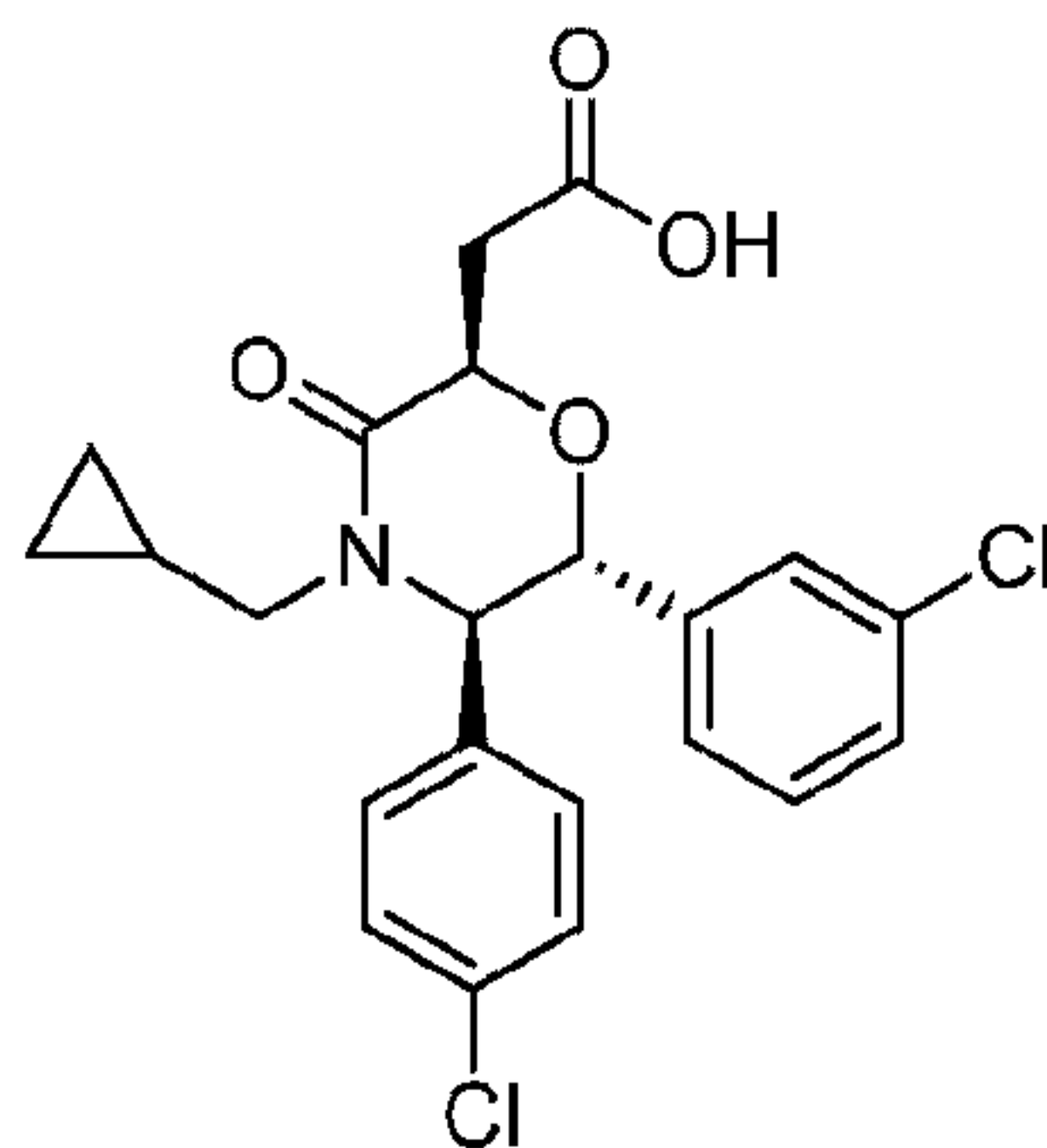
15

The title compound was obtained from Example 7, Step E as the later eluting compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.20 (dq, *J*=9.85, 4.87 Hz, 1 H), 0.32 (dq, *J*=9.66, 4.80 Hz, 1 H), 0.49 - 0.63 (m, 1 H), 0.63 - 0.76 (m, 1 H), 0.98 - 1.16 (m, 1 H), 2.49 (dd, *J*=14.18, 7.73 Hz, 1 H), 2.85 - 3.00 (m, 1 H), 3.00 - 3.15 (m, 1 H), 4.12 (dd, *J*=14.09, 6.65 Hz, 1 H), 4.38 (dd, *J*=6.65, 5.09 Hz, 1 H), 5.17 (d, *J*=1.57 Hz, 1 H), 5.32 (d, *J*=1.96 Hz, 1 H), 7.30 - 7.43 (m, 4 H), 7.58 (s, 1 H), 7.73 (dd, *J*=8.41, 2.54 Hz, 1 H), 8.57 (d, *J*=1.96 Hz, 1 H). Mass Spectrum (ESI) *m/z* = 435 (M+1).

20

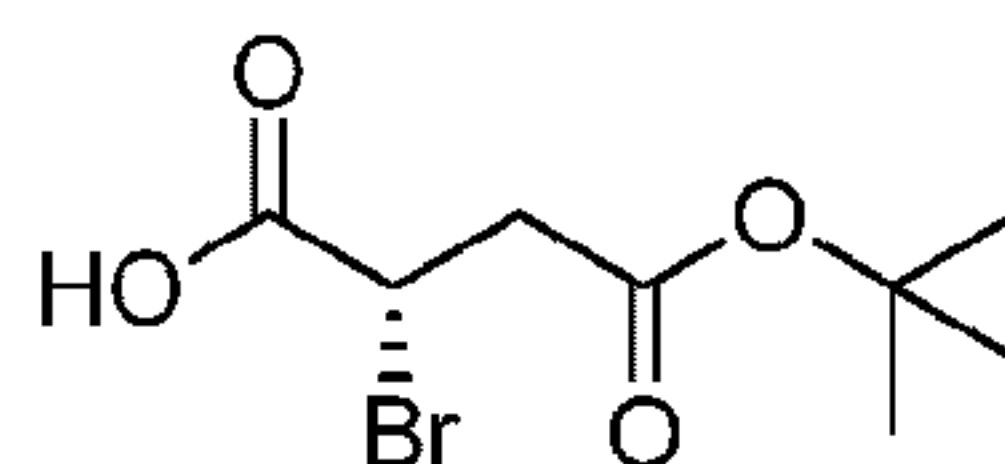
EXAMPLE 9

2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid



5

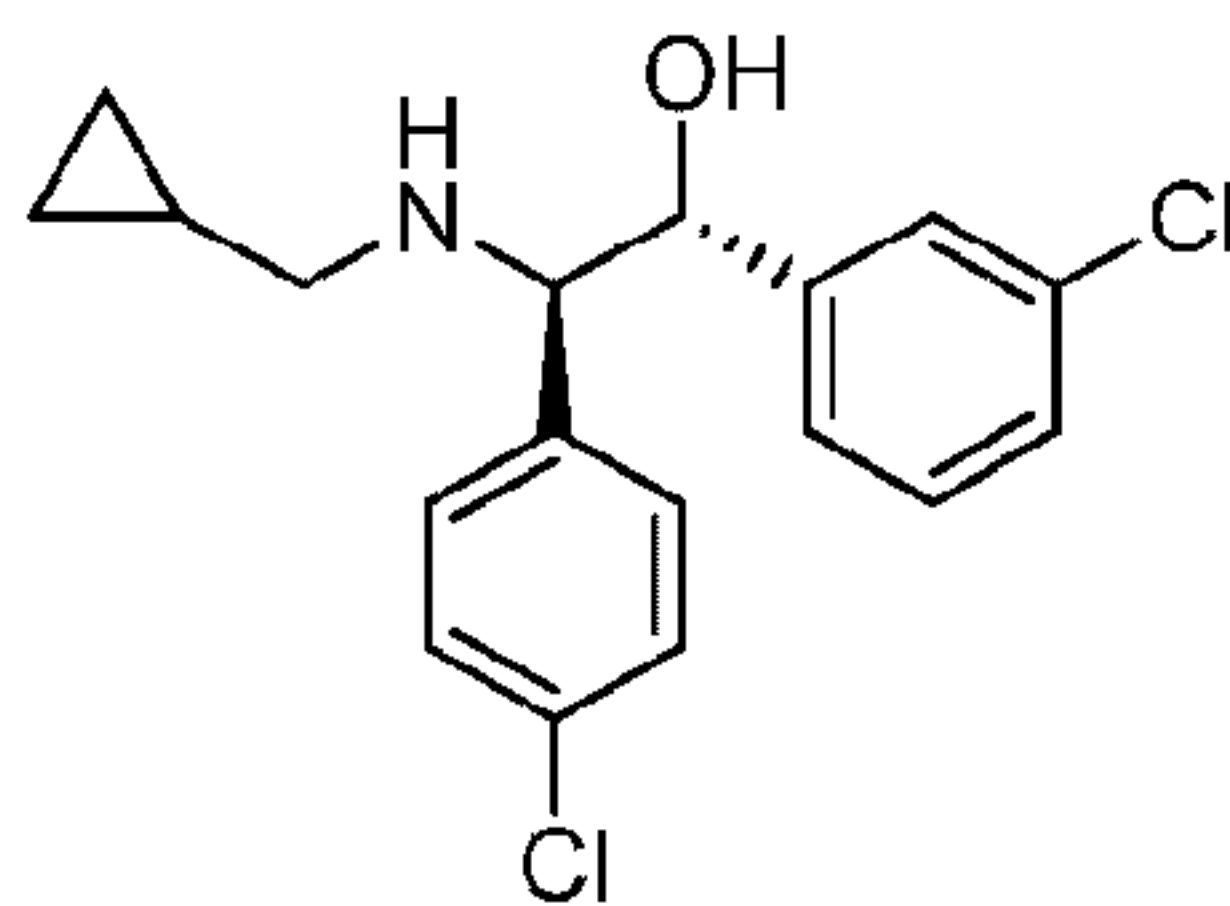
Step A. (S)-2-bromo-4-*tert*-butoxy-4-oxobutanoic acid



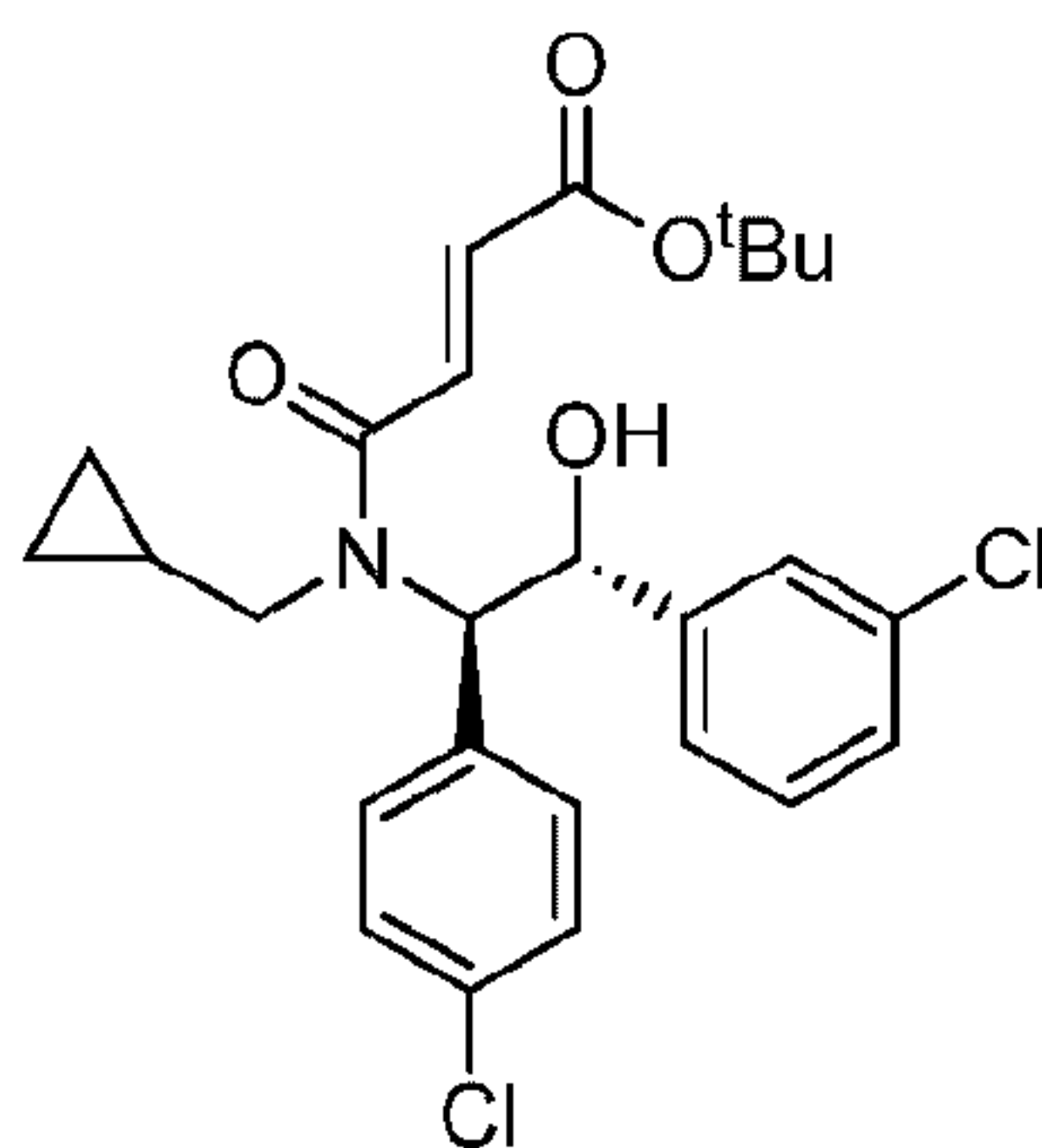
10

To a solution of sodium bromide (10.1 g, 97.8 mmol) in 0.75 M aq. HBr (50 mL, 37.5 mmol) at -15 °C was added sodium nitrite (2.37 g, 34.4 mmol). The reaction mixture color turned yellowish brown then light blue. Then (S)-2-amino-4-*tert*-butoxy-4-oxobutanoic acid (5.0 g, 26.4 mmol) was added. The slurry was stirred at -15 °C for 30 min. A gummy white solid formed. The mixture was extracted with pre-cooled EtOAc (0 °C) (3x). The organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to give a colorless oil. The residue was purified by flash chromatography on silica gel (eluent: 0 to 100% EtOAc in hexanes) to give the title compound (4.07 g, 61%).

20 Step B. (1R,2R)-1-(3-Chlorophenyl)-2-(4-chlorophenyl)-2-(cyclopropylmethylamino)ethanol



- To a solution of (1R,2R)-2-amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol (890 mg, 2681 μmol ; Intermediate A2) in EtOH (25 mL) was added
- 5 cyclopropanecarboxaldehyde (200 μl , 2681 μmol). The reaction mixture was stirred at rt for 1 h then sodium borohydride (162 mg, 4290 μmol) was added. The cloudy reaction mixture was stirred at rt for 10 min. Then the reaction mixture was quenched with 1 M aq. HCl. Evolution of gas was observed and the cloudy reaction mixture became clear. The reaction mixture was concentrated under reduced pressure. The residue was diluted
- 10 with sat. aq. Na_2CO_3 solution and extracted with DCM (2 x). The organic layers were combined, dried over Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel {eluent: 0 to 50% [10% (2 M NH_3 in MeOH) in DCM]/DCM} to give the title compound.
- 15 Step C. (E)-*tert*-Butyl 4-(((1R,2R)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-hydroxyethyl)(cyclopropylmethyl)amino)-4-oxobut-2-enoate



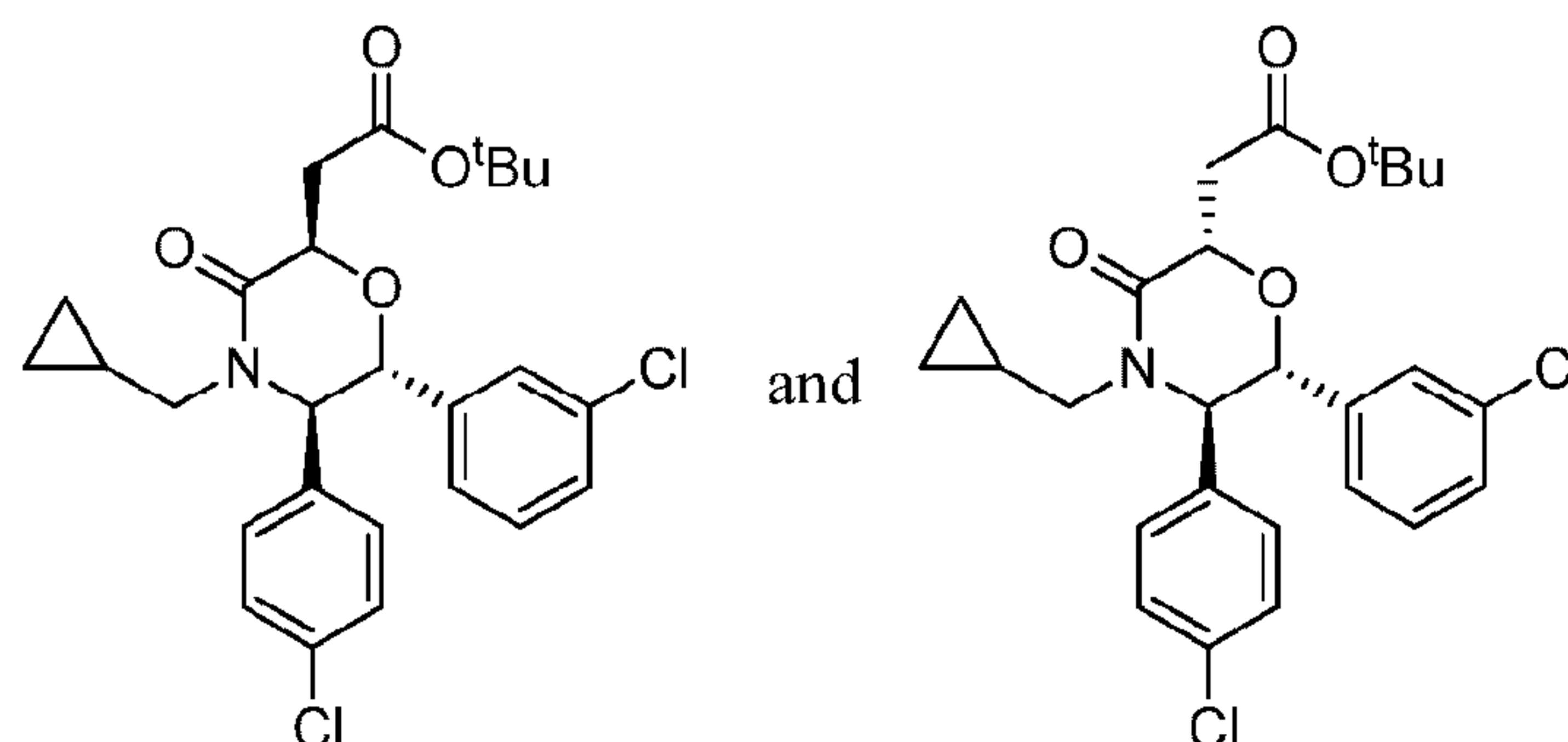
- 20 To a solution of (S)-2-bromo-4-*tert*-butoxy-4-oxobutanoic acid (35 mg, 140 μmol ; Example 9, Step A) in DCM (1 mL) at rt was added DIEA (49 μl , 280 μmol), 1H-benzo[d][1,2,3]triazol-1-ol hydrate (21 mg, 140 μmol) and EDC hydrochloride (27

mg, 140 μ mol). The reaction mixture was stirred at rt for 30 min, then (1R,2R)-1-(3-chlorophenyl)-2-(4-chlorophenyl)-2-(cyclopropylmethylamino)ethanol (47 mg, 140 μ mol; Example 9, step B) in DCM (1 mL) was added. The reaction mixture was stirred at 0 °C for 2 h. Then the reaction mixture was warmed to rt and stirred at rt for 16 h.

5 More DIEA (49 μ l, 280 μ mol) was added and the reaction mixture was stirred at rt for 24 h. The reaction mixture was concentrated under reduced pressure to 1 mL and diluted with EtOAc. The mixture was washed with 1 M HCl, sat. aq. NaHCO₃ solution, and brine. The organic layer was dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel

10 (eluent: 25-100% EtOAc in hexanes, gradient elution) to give the title compound.

Step D. *tert*-Butyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and *tert*-Butyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate



15

To a solution of (E)-*tert*-butyl 4-(((1R,2R)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-hydroxyethyl)(cyclopropylmethyl)amino)-4-oxobut-2-enoate (20 mg, 41 μ mol; Example 9, step C) in THF (1 mL) at rt was added a dispersion of 60% sodium

20 hydride in mineral oil (2.4 mg, 61 μ mol). Evolution of gas was observed and the reaction mixture turned light yellow in color. The reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with sat. NH₄Cl solution and evolution of gas was observed. The reaction mixture was diluted with DCM and the layers were separated. The organic layer was washed with brine, dried over Na₂SO₄, filtered and the filtrate was

25 concentrated under reduced pressure. Purification by flash chromatography on silica gel

(eluent: 30% MTBE in hexanes) provided *tert*-butyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate as the first eluting isomer and *tert*-butyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate as the second eluting isomer.

5

Step E. 2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

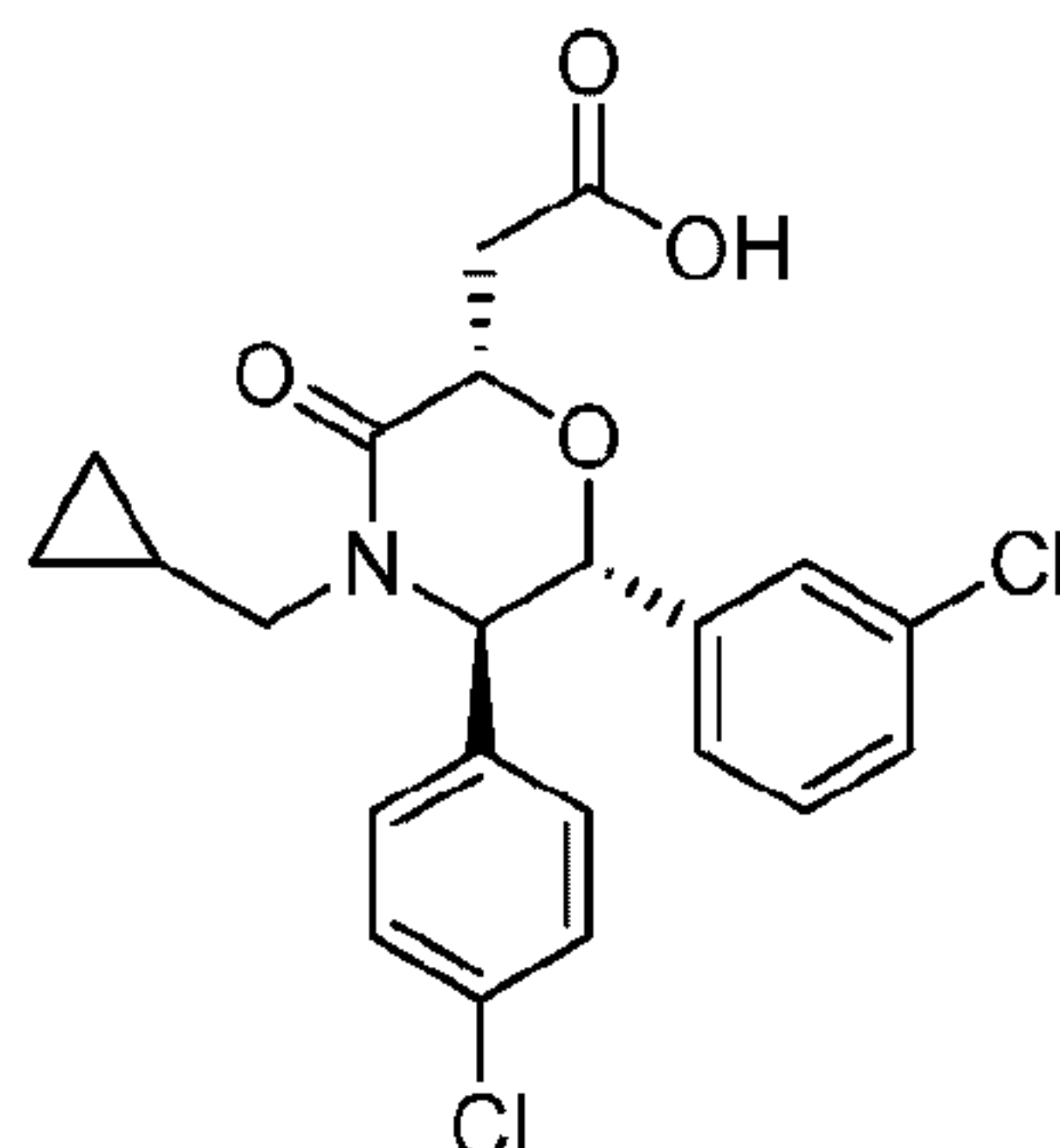
To a solution of *tert*-butyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate (68 mg, 139 μ mol; Example 9, Step D, faster eluting isomer) in DCM (1.5 mL) was added TFA (214 μ L, 2.8 μ mol). The reaction mixture was stirred at rt for 60 min and then concentrated under reduced pressure. The residue was purified by reverse phase preparatory HPLC (GeminiTM Prep C₁₈ 5 μ m column; Phenomenex, Torrance, CA; eluent: 0 to 100% MeCN in water, 0.1% TFA, gradient elution over 20 minutes) to give the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.15 – 0.21 (m, 1 H), 0.23 – 0.29 (m, 1 H), 0.54 – 0.61 (m, 1 H), 0.62 – 0.74 (m, 1 H), 0.96 – 1.10 (m, 1 H), 2.45 (dd, *J*=14.18, 7.73 Hz, 1 H), 3.04 (dd, *J*=16.2, 7.24 Hz, 1 H), 3.15 (dd, *J*=16.24, 4.89 Hz, 1 H), 4.08 (dd, *J*=14.18, 6.55 Hz, 1 H), 4.55 – 4.62 (m, 1 H), 4.90 (d, *J*=3.72 Hz, 1 H), 5.05 (d, *J*=3.91 Hz, 1 H), 7.08 – 7.21 (m, 3 H), 7.29 – 7.39 (m, 4 H), 7.44 (s, 1 H), 8.94 (brs, 1 H). Mass Spectrum (ESI) *m/z* = 434(M+1).

20

EXAMPLE 10

2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

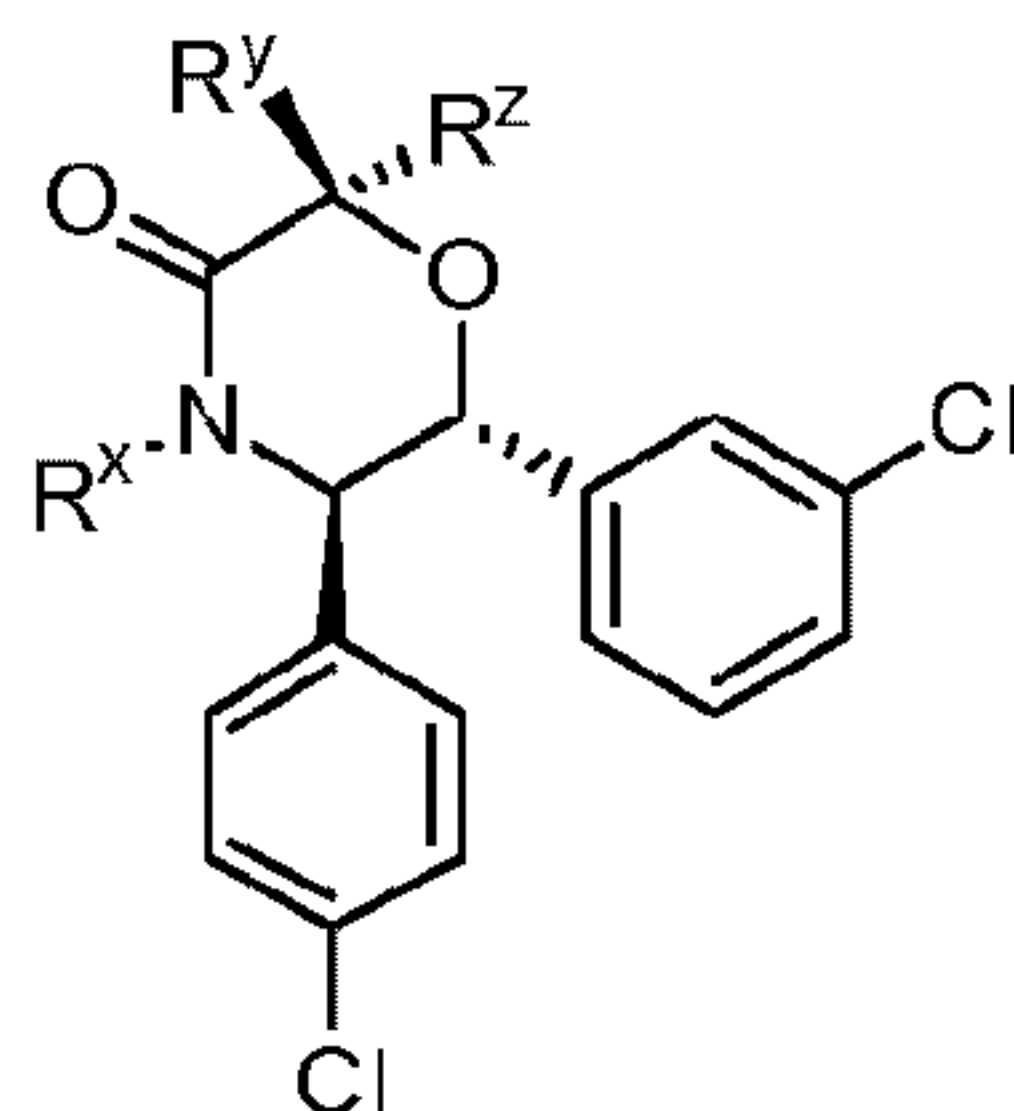
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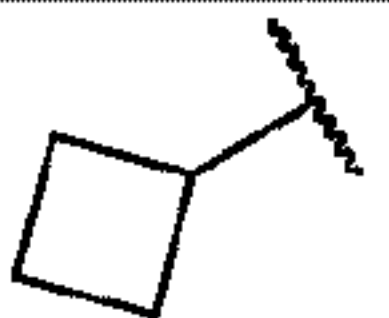
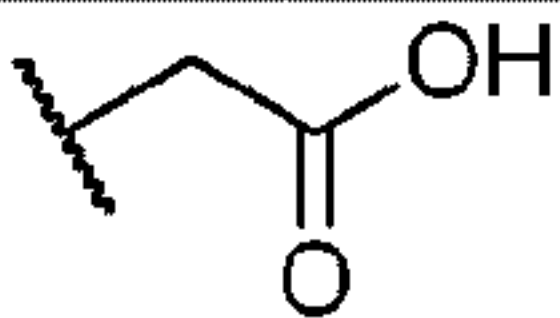
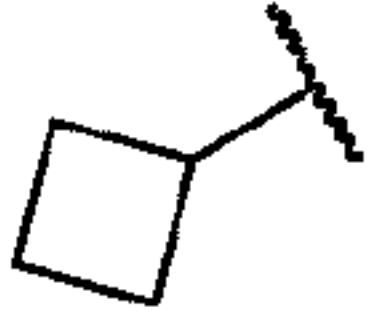
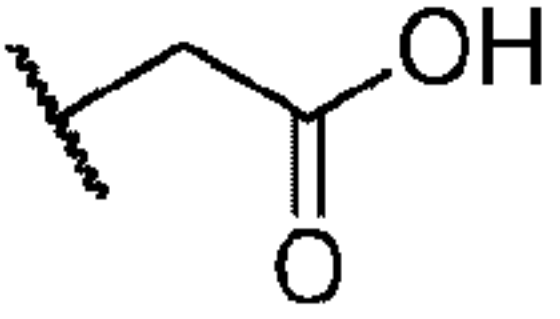
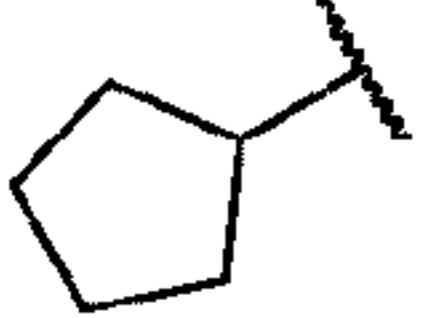
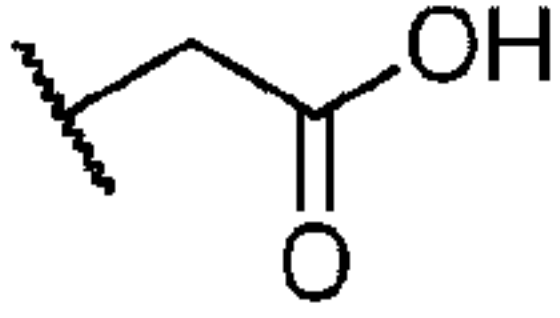
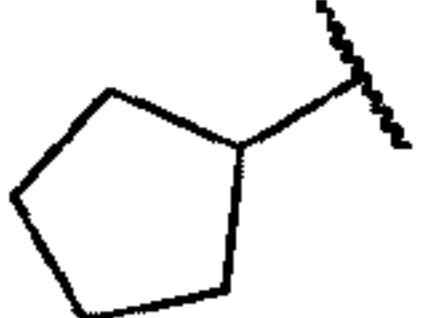
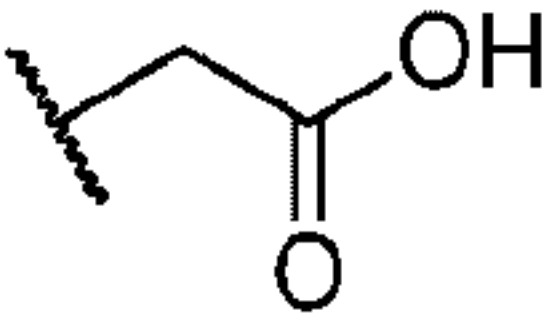
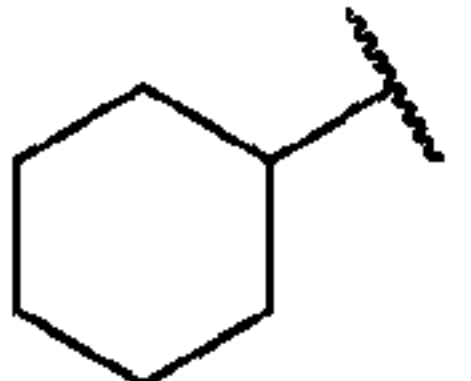
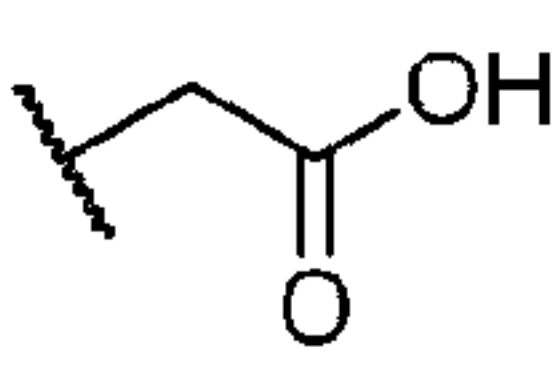
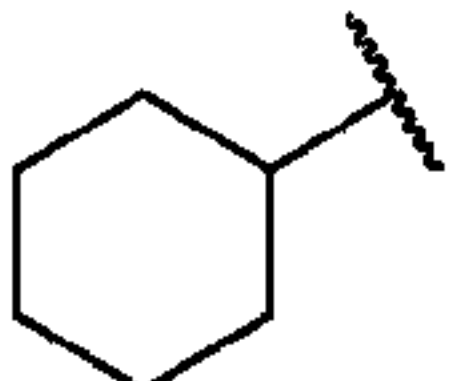
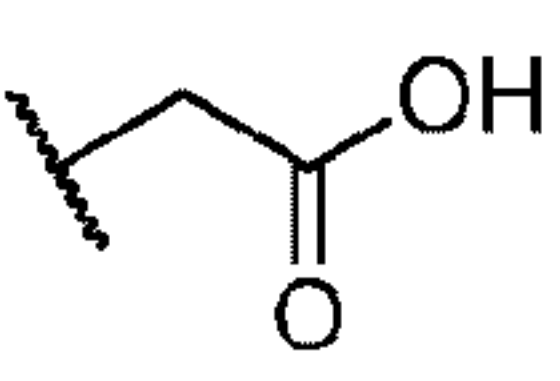
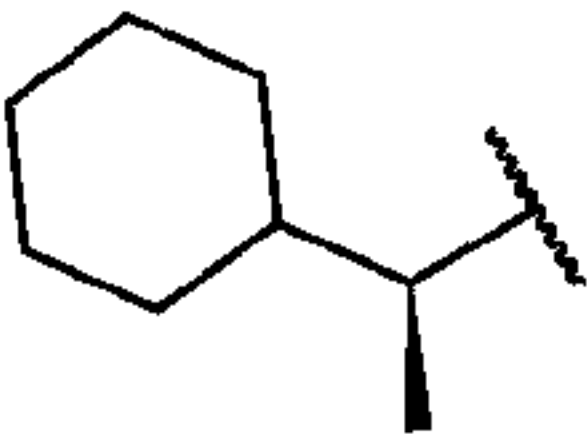
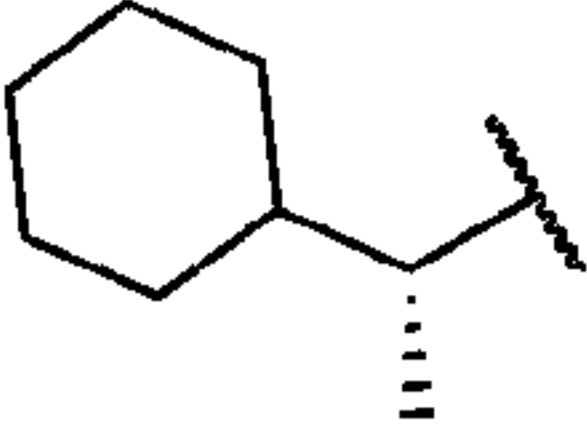
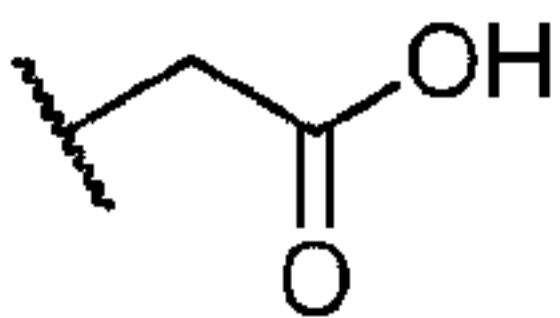
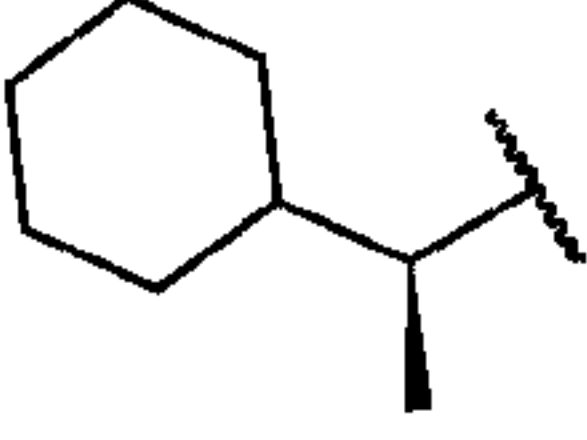
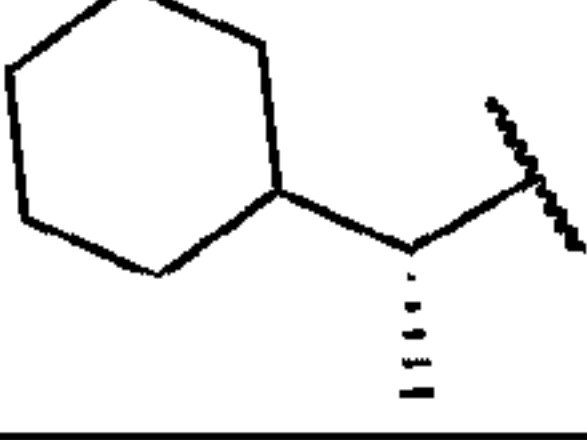
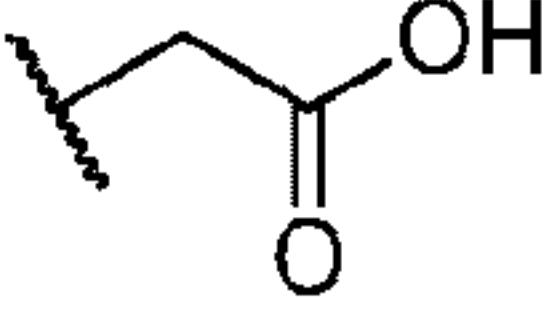
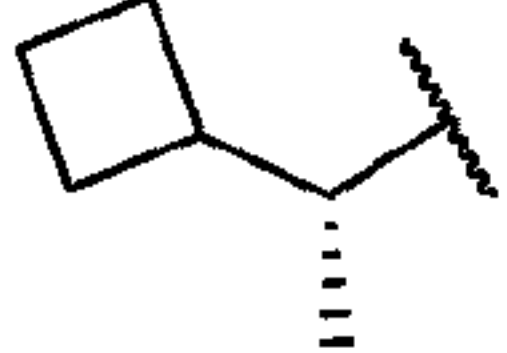
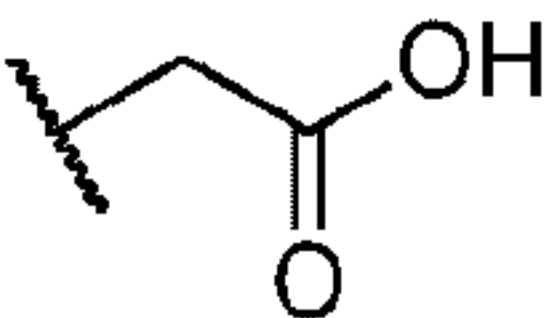
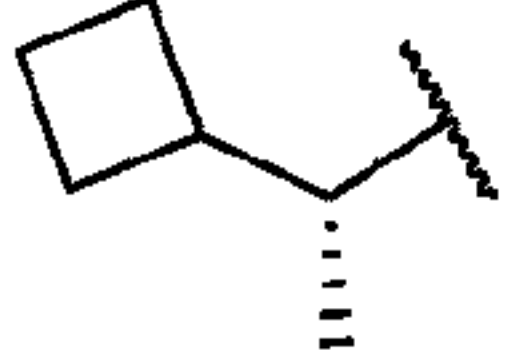
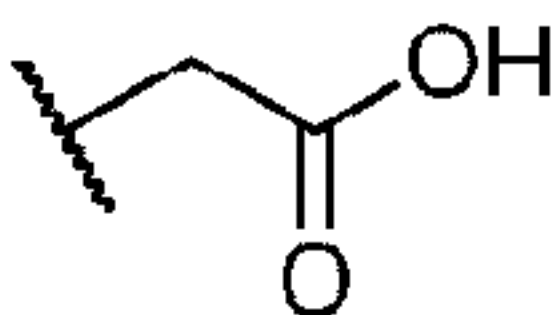
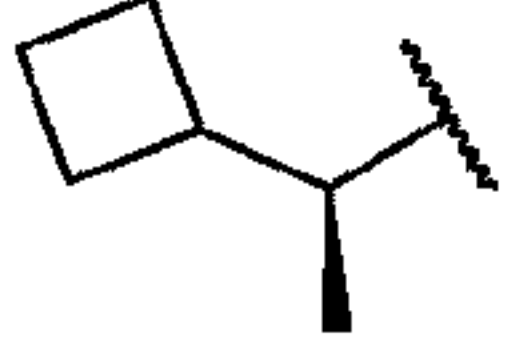
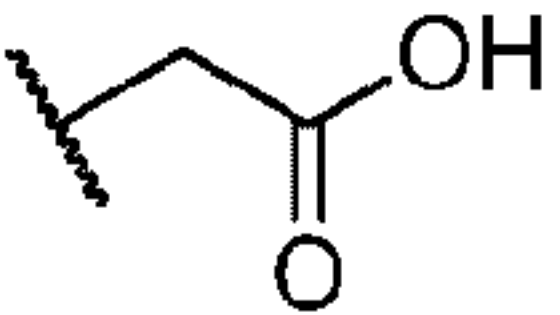
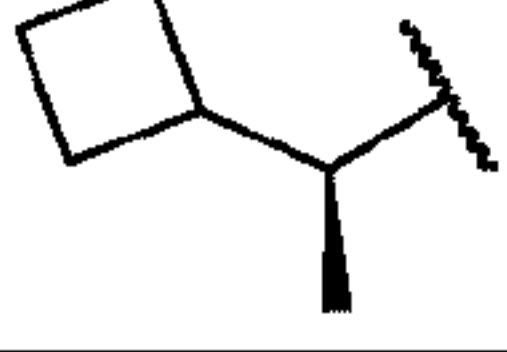
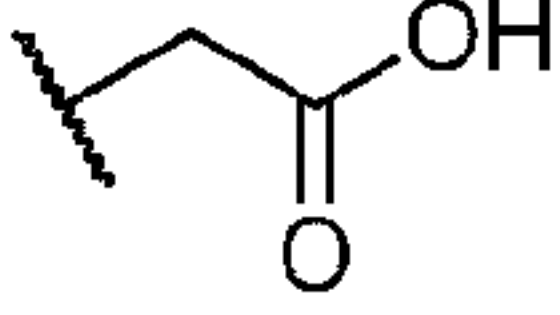
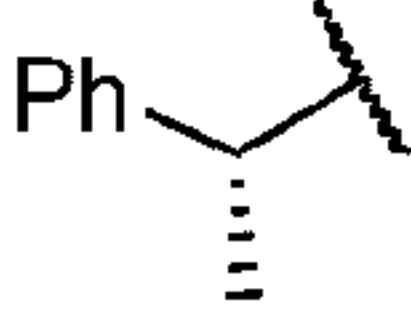
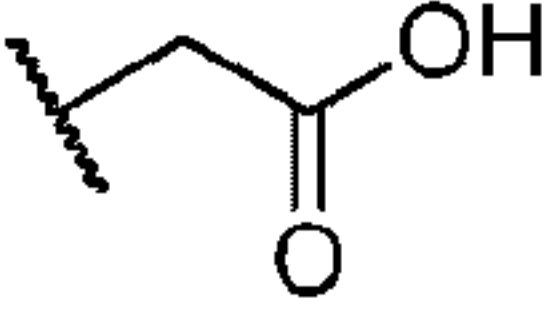
The title compound was prepared from *tert*-butyl 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate (Example 9, Step D, slower eluting isomer) as described in Example 9, Step E.

¹H NMR (400 MHz, CDCl₃) δ ppm -0.03 - 0.09 (m, 2 H) 0.38 - 0.53 (m, 2 H) 0.80 - 0.92 (m, 1 H) 2.32 (dd, *J*=14.28, 7.43 Hz, 1 H) 3.08 - 3.20 (m, 2 H) 4.01 (dd, *J*=14.18, 6.55 Hz, 1 H) 4.60 (d, *J*=9.6 Hz, 1 H) 4.73 - 4.81 (m, 2 H) 6.71 (d, *J*=7.83 Hz, 1 H) 6.91 (d, *J*=8.41 Hz, 2 H) 7.07 - 7.16 (m, 2 H) 7.21 - 7.31 (m, 3 H). Mass Spectrum (ESI) *m/z* = 434(*M*+1).

Examples 11 to 29 were also prepared from (1*R*,2*R*)-2-amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol (890 mg, 2681 μmol; Intermediate A2) by a procedure analogous to the one described in Example 9, replacing cyclopropanecarboxaldehyde and sodiumborohydride in Step B with the reagents designated in the table below.



Example	R ^x	R ^y	R ^z	Reagents used
11		H		3,3,3-trifluoropropanal, NaB(OAc) ₃ H

12		H		cyclobutanone, NaBH ₃ CN
13			H	cyclobutanone, NaBH ₃ CN
14		H		cyclopentanone, NaBH ₃ CN
15			H	cyclopentanone, NaBH ₃ CN
16		H		cyclohexanone, NaBH ₃ CN
17			H	cyclohexanone, NaBH ₃ CN
18	 or 	H		1-cyclohexylethanone, NaBH ₃ CN
19	 or 		H	1-cyclohexylethanone, NaBH ₃ CN
20			H	1-cyclobutylethanone, NaBH ₃ CN
21		H		1-cyclobutylethanone, NaBH ₃ CN
22			H	1-cyclobutylethanone, NaBH ₃ CN
23		H		1-cyclobutylethanone, NaBH ₃ CN
24			H	acetophenone, NaBH ₃ CN

25		H		acetophenone, NaBH ₃ CN
26			H	acetophenone, NaBH ₃ CN
27		H		acetophenone, NaBH ₃ CN
28			H	cyclopentanecarbaldehyde, NaBH ₄
29		H		cyclopentanecarbaldehyde, NaBH ₄

EXAMPLE 11

2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-(3,3,3-trifluoropropyl)morpholin-2-yl)acetic acid

5

¹H NMR (500 MHz, CDCl₃) δ ppm 2.26 - 2.38 (m, 1 H), 2.40 - 2.54 (m, 1 H), 2.77 - 2.87 (m, 1 H), 3.06 - 3.13 (m, 1 H), 3.14 - 3.21 (m, 1 H), 3.96 (ddd, *J* = 14.18, 8.44, 5.50 Hz, 1 H), 4.58 - 4.61 (m, 1 H), 4.61 - 4.65 (m, 1 H), 4.73 (t, *J* = 4.89 Hz, 1 H), 6.73 (dt, *J* = 7.83, 1.22 Hz, 1 H), 6.93 (d, *J* = 8.31 Hz, 2 H), 7.06 (t, *J* = 1.83 Hz, 1 H), 7.12 (t, *J* = 7.83 Hz, 1 H), 7.24 (ddd, *J* = 8.07, 2.20, 0.98 Hz, 1 H), 7.28 - 7.34 (m, 2 H); MS (ESI) *m/z* = 476.1 [M+H]⁺.

10

EXAMPLE 12

2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-cyclobutyl-3-oxomorpholin-2-yl)acetic acid

15

¹H NMR (500 MHz, CDCl₃) δ ppm 1.40 - 1.47 (m, 2 H), 1.59 - 1.67 (m, 1 H), 2.16 (t, *J* = 9.54 Hz, 1 H), 2.22 - 2.29 (m, 1 H), 2.31 - 2.37 (m, 1 H), 2.99 - 3.08 (m, 1 H), 3.09 - 3.18 (m, 1 H), 3.72 - 3.83 (m, 1 H), 4.42 (d, *J* = 9.54 Hz, 1 H), 4.61 - 4.70 (m, 2 H), 6.71 (d, *J* = 7.58 Hz, 1 H), 6.83 (d, *J* = 8.31 Hz, 2 H), 7.11 (s, 1 H), 7.14 (t, *J* = 7.95 Hz, 1 H), 7.24 - 7.27 (m, 3 H); MS (ESI) *m/z* = 434.2 [M+H]⁺.

20

EXAMPLE 13

2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-cyclobutyl-3-oxomorpholin-2-yl)acetic acid

5 ¹H NMR (500 MHz, CDCl₃) δ ppm 1.54 - 1.62 (m, 1 H), 1.63 - 1.68 (m, 1 H), 1.69 - 1.75 (m, 1 H), 1.98 - 2.06 (m, 1 H), 2.25 (quin, *J* = 10.09 Hz, 1 H), 2.31 - 2.39 (m, 1 H), 2.89 (dd, *J* = 16.26, 7.46 Hz, 1 H), 3.14 (dd, *J* = 16.26, 5.26 Hz, 1 H), 4.25 - 4.35 (m, 1 H), 4.49 (dd, *J* = 7.46, 5.26 Hz, 1 H), 4.81 (d, *J* = 3.67 Hz, 1 H), 4.94 (d, *J* = 3.67 Hz, 1 H), 7.08 (d, *J* = 8.56 Hz, 2 H), 7.12 (d, *J* = 7.58 Hz, 1 H), 7.28 - 7.32 (m, 1 H), 7.32 - 7.38
10 (m, 4 H); MS (ESI) *m/z* = 434.1 [M+H]⁺.

EXAMPLE 14

2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-cyclopentyl-3-oxomorpholin-2-yl)acetic acid

15

¹H NMR (500 MHz, CDCl₃) δ ppm 1.31 - 1.34 (m, 1 H), 1.37 - 1.46 (m, 2 H), 1.67 - 1.74 (m, 1 H), 1.75 - 1.83 (m, 2 H), 1.94 - 2.04 (m, 1 H), 2.06 - 2.17 (m, 1 H), 2.99 - 3.07 (m, 1 H), 3.08 - 3.18 (m, 1 H), 3.25 (t, *J* = 8.60 Hz, 1 H), 4.52 - 4.60 (m, 2 H), 4.67 (t, *J* = 5.38 Hz, 1 H), 6.71 (d, *J* = 7.58 Hz, 1 H), 6.94 (d, *J* = 8.31 Hz, 2 H), 7.09 (s, 1 H), 7.12 (t, *J* = 7.83 Hz, 1 H), 7.24 (dt, *J* = 8.07, 0.98 Hz, 1 H), 7.28 (d, *J* = 6.85 Hz, 2 H); MS (ESI) *m/z* = 448.2 [M+H]⁺.
20

EXAMPLE 15

2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-cyclopentyl-3-oxomorpholin-2-yl)acetic acid

25

¹H NMR (500 MHz, CDCl₃) δ ppm 1.45 - 1.54 (m, 2 H), 1.67 - 1.84 (m, 5 H), 1.89 - 2.00 (m, 1 H), 2.91 (dd, *J* = 16.14, 6.85 Hz, 1 H), 3.14 (dd, *J* = 16.14, 5.62 Hz, 1 H), 3.84 - 3.94 (m, 1 H), 4.39 (t, *J* = 6.24 Hz, 1 H), 4.83 - 4.93 (m, 2 H), 7.19 (d, *J* = 8.31 Hz, 3 H), 7.30 - 7.34 (m, 1 H), 7.34 - 7.42 (m, 4 H); MS (ESI) *m/z* = 448.1 [M+H]⁺.
30

EXAMPLE 16

2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-cyclohexyl-3-oxomorpholin-2-yl)acetic acid

5 ¹H NMR (400 MHz, CDCl₃) δ ppm 0.83 - 1.00 (m, 1 H), 1.00 - 1.16 (m, 1 H), 1.29 - 1.37 (m, 1 H), 1.38 - 1.52 (m, 1 H), 1.53 - 1.63 (m, 1 H), 1.63 - 1.73 (m, 2 H), 1.74 - 1.84 (m, 1 H), 1.95 - 2.15 (m, 2 H), 2.96 - 3.09 (m, 1 H), 3.09 - 3.16 (m, 1 H), 3.16 - 3.32 (m, 1 H), 4.50 - 4.56 (m, 1 H), 4.56 - 4.63 (m, 1 H), 4.65 - 4.75 (m, 1 H), 6.72 (d, *J* = 7.63 Hz, 1 H), 6.95 (d, *J* = 8.41 Hz, 1 H), 7.00 (d, *J* = 8.41 Hz, 1 H), 7.08 (br. s., 1 H), 7.12 (dd, *J* = 7.80 Hz, 1 H), 7.24 (d, *J* = 8.22 Hz, 1 H), 7.26 - 7.32 (m, 2 H); MS (ESI) *m/z* = 462.2 [M+H]⁺.

EXAMPLE 17

15 2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-cyclohexyl-3-oxomorpholin-2-yl)acetic acid

¹H NMR (500 MHz, CDCl₃) δ ppm 0.96 - 1.06 (m, 1 H), 1.18 - 1.24 (m, 2 H), 1.39 - 1.50 (m, 1 H), 1.54 - 1.62 (m, 2 H), 1.64 - 1.70 (m, 1 H), 1.72 - 1.76 (m, 1 H), 1.77 - 1.84 (m, 2 H), 2.92 (dd, *J* = 16.26, 7.21 Hz, 1 H), 3.19 (dd, *J* = 16.14, 5.38 Hz, 1 H), 3.98 (ddd, *J* = 11.25, 7.83, 3.67 Hz, 1 H), 4.41 (dd, *J* = 7.09, 5.38 Hz, 1 H), 4.83 (s, 1 H), 4.92 (d, *J* = 1.47 Hz, 1 H), 7.25 (d, *J* = 8.31 Hz, 2 H), 7.27 - 7.30 (m, 1 H), 7.33 - 7.36 (m, 2 H), 7.38 (d, *J* = 8.31 Hz, 2 H), 7.41 (s, 1 H); MS (ESI) *m/z* = 462.1 [M+H]⁺.

EXAMPLE 18

25 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((R)-1-cyclohexylethyl)-3-oxomorpholin-2-yl)acetic acid or 2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-cyclohexylethyl)-3-oxomorpholin-2-yl)acetic acid

30 ¹H NMR (500 MHz, CDCl₃) δ ppm 0.54 - 0.66 (m, 1 H), 0.85 - 0.95 (m, 1 H), 1.03 - 1.13 (m, 1 H), 1.14 - 1.20 (m, 1 H), 1.23 (d, *J* = 6.60 Hz, 3 H), 1.24 - 1.27 (m, 1 H), 1.62 - 1.71 (m, 3 H), 1.80 (d, *J* = 12.72 Hz, 1 H), 1.95 (d, *J* = 11.49 Hz, 1 H), 2.07 - 2.14 (m, 1

H), 2.45 - 2.57 (m, 1 H), 2.93 (dd, $J = 16.38, 5.87$ Hz, 1 H), 3.20 (dd, $J = 16.38, 5.62$ Hz, 1 H), 4.42 (d, $J = 9.78$ Hz, 1 H), 4.60 (d, $J = 9.54$ Hz, 1 H), 4.75 (t, $J = 5.75$ Hz, 1 H), 6.68 (d, $J = 7.82$ Hz, 1 H), 6.99 (d, $J = 8.31$ Hz, 2 H), 7.04 (s, 1 H), 7.10 (t, $J = 7.90$ Hz, 1 H), 7.22 (dd, $J = 7.83, 1.22$ Hz, 1 H), 7.29 (d, $J = 8.31$ Hz, 2 H); MS (ESI) $m/z = 490.1$ [M+H]⁺.

EXAMPLE 19

2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-cyclohexylethyl)-3-oxomorpholin-2-yl)acetic acid or 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((R)-1-cyclohexylethyl)-3-oxomorpholin-2-yl)acetic acid

¹H NMR (500 MHz, CDCl₃) δ ppm 0.66 - 0.73 (m, 1 H), 0.92 - 0.98 (m, 1 H), 1.07 - 1.15 (m, 2 H), 1.24 (d, $J = 6.85$ Hz, 3 H), 1.66 (m, 4 H), 1.77 (m, 2 H), 1.92 - 2.00 (m, 1 H), 2.75 - 2.83 (m, 1 H), 3.04 (dd, $J = 15.89, 7.09$ Hz, 1 H), 3.21 (dd, $J = 16.02, 5.50$ Hz, 1 H), 4.58 (d, $J = 6.36$ Hz, 1 H), 4.76 - 4.83 (m, 2 H), 6.93 (d, $J = 7.58$ Hz, 1 H), 7.15 (d, $J = 8.07$ Hz, 2 H), 7.19 (t, $J = 7.80$ Hz, 1 H), 7.24 (s, 1 H), 7.25 - 7.29 (m, 1 H), 7.34 (d, $J = 8.07$ Hz, 2 H); MS (ESI) $m/z = 490.1$ [M+H]⁺.

EXAMPLE 20

2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((R)-1-cyclobutylethyl)-3-oxomorpholin-2-yl)acetic acid

¹H NMR (500 MHz, CDCl₃) δ ppm 1.11 (d, $J = 6.85$ Hz, 3 H), 1.48 - 1.56 (m, 1 H), 1.68 - 1.80 (m, 4 H), 1.82 - 1.93 (m, 1 H), 2.45 - 2.58 (m, 1 H), 2.98 (dd, $J = 16.14, 7.58$ Hz, 1 H), 3.16 (dd, $J = 16.14, 5.14$ Hz, 1 H), 3.69 - 3.85 (m, 1 H), 4.56 (dd, $J = 6.97, 5.26$ Hz, 1 H), 4.74 (d, $J = 3.42$ Hz, 1 H), 4.79 (d, $J = 3.42$ Hz, 1 H), 7.11 (d, $J = 7.58$ Hz, 1 H), 7.22 (d, $J = 8.31$ Hz, 2 H), 7.24 - 7.28 (m, 1 H), 7.28 - 7.31 (m, 1 H), 7.32 (s, 1 H), 7.36 (d, $J = 8.31$ Hz, 2 H); MS (ESI) $m/z = 462.2$ [M+H]⁺.

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EXAMPLE 21

2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((R)-1-cyclobutylethyl)-3-oxomorpholin-2-yl)acetic acid

5 ¹H NMR (500 MHz, CDCl₃) δ ppm 1.11 (d, *J* = 6.85 Hz, 3 H), 1.42 - 1.48 (m, 1 H), 1.71 - 1.79 (m, 2 H), 1.80 - 1.87 (m, 1 H), 1.88 - 1.97 (m, 1 H), 1.99 - 2.07 (m, 1 H), 2.81 (m, 1 H), 2.95 (dd, *J* = 16.02, 4.77 Hz, 1 H), 3.10 - 3.22 (m, 2 H), 4.47 - 4.53 (m, 1 H), 4.54 - 4.60 (m, 1 H), 4.69 (dd, *J* = 6.97, 4.77 Hz, 1 H), 6.67 (d, *J* = 7.83 Hz, 1 H), 7.00 (d, *J* = 8.31 Hz, 2 H), 7.05 (dd, *J* = 1.70 Hz, 1 H), 7.11 (t, *J* = 7.80 Hz, 1 H), 7.21 - 7.26 (m, 1 H), 7.32 (d, *J* = 8.56 Hz, 2 H); MS (ESI) *m/z* = 462.2 [M+H]⁺.
10

EXAMPLE 22

2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-cyclobutylethyl)-3-oxomorpholin-2-yl)acetic acid

15 ¹H NMR (500 MHz, CDCl₃) δ ppm 0.84 (d, *J* = 7.09 Hz, 3 H), 1.52 - 1.58 (m, 1 H), 1.59 - 1.65 (m, 1 H), 1.69 - 1.75 (m, 1 H), 1.79 - 1.86 (m, 2 H), 1.96 - 2.06 (m, 1 H), 2.61 - 2.73 (m, 1 H), 2.92 (dd, *J* = 16.14, 6.11 Hz, 1 H), 3.20 (dd, *J* = 16.14, 6.36 Hz, 1 H), 4.21 - 4.34 (m, 1 H), 4.48 (t, *J* = 6.24 Hz, 1 H), 4.76 (s, 1 H), 4.85 (d, *J* = 1.22 Hz, 1 H), 7.25 (d, *J* = 8.56 Hz, 3 H), 7.32 - 7.37 (m, 2 H), 7.37 - 7.42 (m, 3 H); MS (ESI) *m/z* = 462.2 [M+H]⁺.
20

EXAMPLE 23

2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-cyclobutylethyl)-3-oxomorpholin-2-yl)acetic acid

25 ¹H NMR (500 MHz, CDCl₃) δ ppm 0.78 (d, *J* = 6.85 Hz, 3 H), 1.44 - 1.52 (m, 1 H), 1.54 - 1.63 (m, 1 H), 1.66 - 1.74 (m, 1 H), 1.75 - 1.84 (m, 1 H), 1.87 - 2.01 (m, 2 H), 2.57 - 2.65 (m, 1 H), 2.96 (dd, *J* = 16.26, 5.75 Hz, 1 H), 3.15 (dd, *J* = 16.38, 5.87 Hz, 1 H), 3.87 - 3.98 (m, 1 H), 4.35 (d, *J* = 9.29 Hz, 1 H), 4.60 (d, *J* = 9.29 Hz, 1 H), 4.74 (t, *J* = 5.62 Hz, 1 H), 6.70 (d, *J* = 7.83 Hz, 1 H), 7.00 (d, *J* = 8.31 Hz, 2 H), 7.04 (t, *J* = 1.70 Hz, 1 H),
30

7.11 (t, $J = 7.80$ Hz, 1 H), 7.21 - 7.25 (m, 1 H), 7.28 (d, $J = 8.31$ Hz, 2 H); MS (ESI) $m/z = 462.2$ $[M+H]^+$.

EXAMPLE 24

5 2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((R)-1-phenylethyl)morpholin-2-yl)acetic acid

^1H NMR (400 MHz, CDCl_3) δ ppm 1.71 (d, $J = 6.85$ Hz, 3 H), 2.94 (dd, $J = 15.45, 7.24$ Hz, 1 H), 3.14 (dd, $J = 16.53, 5.38$ Hz, 1 H), 4.44 - 4.54 (m, 1 H), 4.80 (s, 2 H), 4.89 -
10 4.99 (m, 1 H), 6.93 (d, $J = 7.43$ Hz, 1 H), 7.01 (d, $J = 8.22$ Hz, 2 H), 7.11 - 7.22 (m, 7 H), 7.23 - 7.27 (m, 3 H); MS (ESI) $m/z = 484.1$ $[M+H]^+$.

EXAMPLE 25

15 2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((R)-1-phenylethyl)morpholin-2-yl)acetic acid

^1H NMR (400 MHz, CDCl_3) δ ppm 1.64 (d, $J = 7.04$ Hz, 3 H), 2.97 (dd, $J = 16.43, 5.28$ Hz, 1 H), 3.13 (dd, $J = 16.43, 5.87$ Hz, 1 H), 4.59 - 4.71 (m, 2 H), 4.81 (t, $J = 5.50$ Hz, 1 H), 5.10 - 5.18 (m, 1 H), 6.65 (d, $J = 7.83$ Hz, 1 H), 6.76 (d, $J = 8.41$ Hz, 2 H), 6.99 -
20 7.14 (m, 6 H), 7.14 - 7.19 (m, 3 H), 7.21 (d, $J = 8.02$ Hz, 1 H); MS (ESI) $m/z = 484.1$ $[M+H]^+$.

EXAMPLE 26

25 2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((S)-1-phenylethyl)morpholin-2-yl)acetic acid

^1H NMR (500 MHz, CDCl_3) δ ppm 1.16 (d, $J = 7.24$ Hz, 3 H), 2.96 (dd, $J = 16.24, 7.24$ Hz, 1 H), 3.26 (dd, $J = 15.85, 4.89$ Hz, 1 H), 4.51 (t, $J = 6.16$ Hz, 1 H), 4.55 (s, 1 H), 4.65 (s, 1 H), 6.05 - 6.17 (m, 1 H), 6.75 (d, $J = 7.83$ Hz, 1 H), 6.87 (s, 1 H), 7.07 - 7.14 (m, 1
30 H), 7.15 - 7.23 (m, 3 H), 7.23 - 7.27 (m, 2 H), 7.39 (d, $J = 8.41$ Hz, 2 H), 7.41 - 7.47 (m, 3 H); MS (ESI) $m/z = 484.1$ $[M+H]^+$.

EXAMPLE 27

2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-((S)-1-phenylethyl)morpholin-2-yl)acetic acid

5

¹H NMR (500 MHz, CDCl₃) δ ppm 1.21 (d, *J* = 7.06 Hz, 3 H), 2.98 - 3.10 (m, 1 H), 3.13 - 3.24 (m, 1 H), 4.26 (d, *J* = 8.61 Hz, 1 H), 4.62 (d, *J* = 8.80 Hz, 1 H), 4.82 (br. s., 1 H), 5.54 (d, *J* = 6.65 Hz, 1 H), 6.59 (d, *J* = 7.24 Hz, 1 H), 6.68 (d, *J* = 7.82 Hz, 2 H), 6.91 (br. s., 1 H), 7.01 (t, *J* = 7.70 Hz, 1 H), 7.07 (d, *J* = 6.26 Hz, 2 H), 7.15 (d, *J* = 7.82 Hz, 3 H), 7.22 - 7.27 (m, 3 H); MS (ESI) *m/z* = 484.1 [M+H]⁺.

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EXAMPLE 28

2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopentylmethyl)-3-oxomorpholin-2-yl)acetic acid

15

¹H NMR (400 MHz, CDCl₃) δ ppm 1.07 - 1.14 (m, 1 H), 1.20 - 1.27 (m, 1 H), 1.53 - 1.73 (m, 6 H), 2.12 - 2.22 (m, 1 H), 2.52 (dd, *J* = 13.7, 6.1 Hz, 1 H), 3.02 (dd, *J* = 16.4, 8.8 Hz, 1 H), 3.18 (dd, *J* = 16.2, 5.1 Hz, 1 H), 4.04 (dd, *J* = 13.7, 9.3 Hz, 1 H), 4.75 - 4.78 (m, 1 H), 4.79 (d, *J* = 5.4 Hz, 1 H), 4.84 (d, *J* = 5.5 Hz, 1 H), 6.99 - 7.07 (m, 4 H), 7.22 - 7.36 (m, 5 H). Mass Spectrum (ESI) *m/z* = 462(M+1).

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EXAMPLE 29

2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopentylmethyl)-3-oxomorpholin-2-yl)acetic acid

25

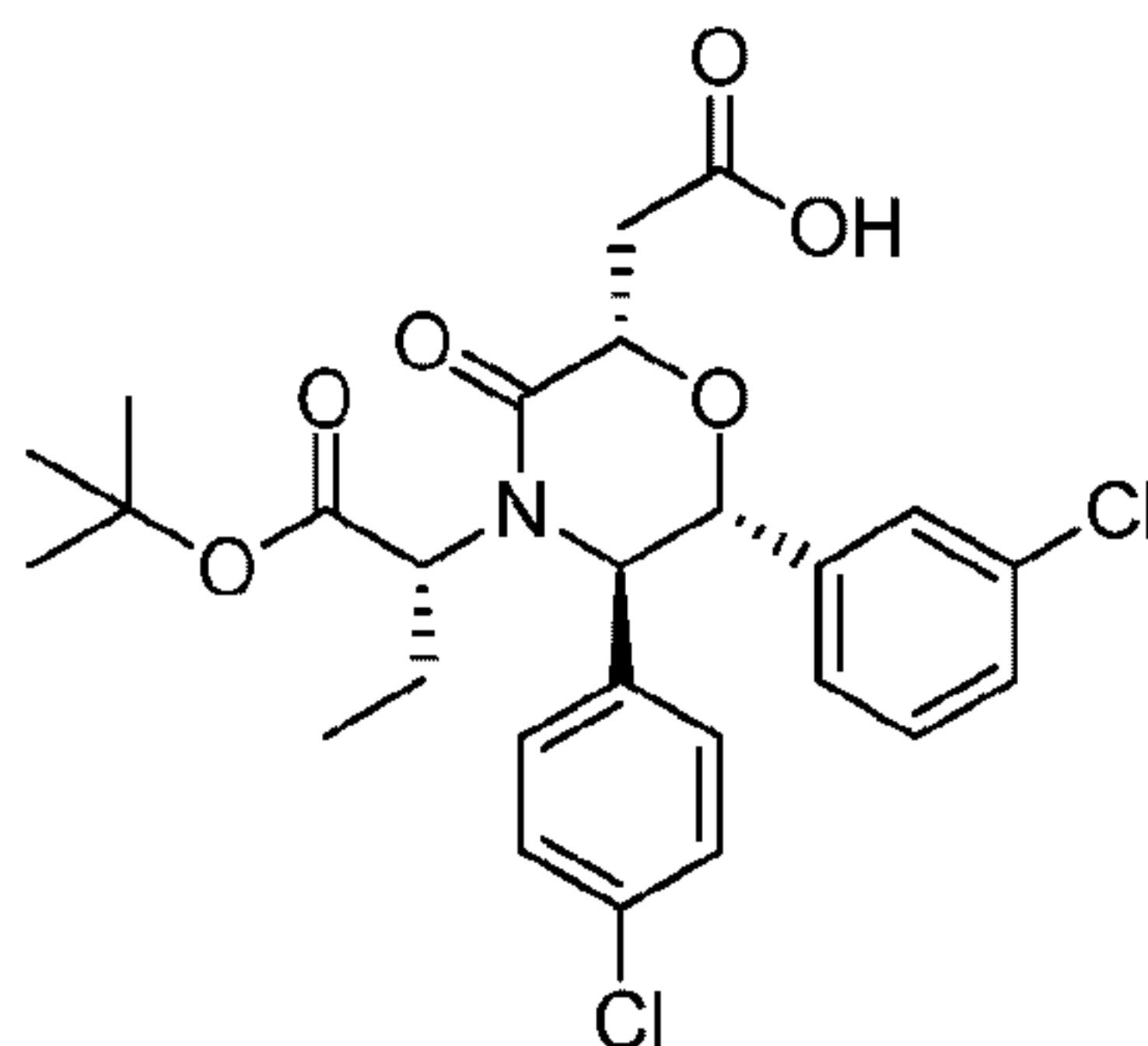
¹H NMR (400 MHz, CDCl₃) δ ppm 0.96 - 1.05 (m, 1 H), 1.10 - 1.16 (m, 1 H), 1.48 - 1.75 (m, 6 H), 2.04 - 2.13 (m, 1 H), 2.38 (dd, *J* = 13.7, 6.8 Hz, 1 H), 3.08 (dd, *J* = 16.7, 5.3 Hz, 1 H), 3.18 (dd, *J* = 16.8, 5.6 Hz, 1 H), 4.04 (dd, *J* = 13.9, 8.5 Hz, 1 H), 4.58 (d, *J* = 9.6 Hz, 1 H), 4.62 (d, *J* = 9.6 Hz, 1 H), 4.76 - 4.79 (m, 1 H), 6.19 (brs, 1 H), 6.70 (d, *J* = 7.8 Hz, 1 H), 6.90 (d, *J* = 8.4 Hz, 2 H), 7.07 - 7.08 (m, 1 H), 7.12 (t, *J* = 8.0 Hz, 1 H), 7.24 - 7.30 (m, 3 H). Mass Spectrum (ESI) *m/z* = 462(M+1).

30

EXAMPLE 30

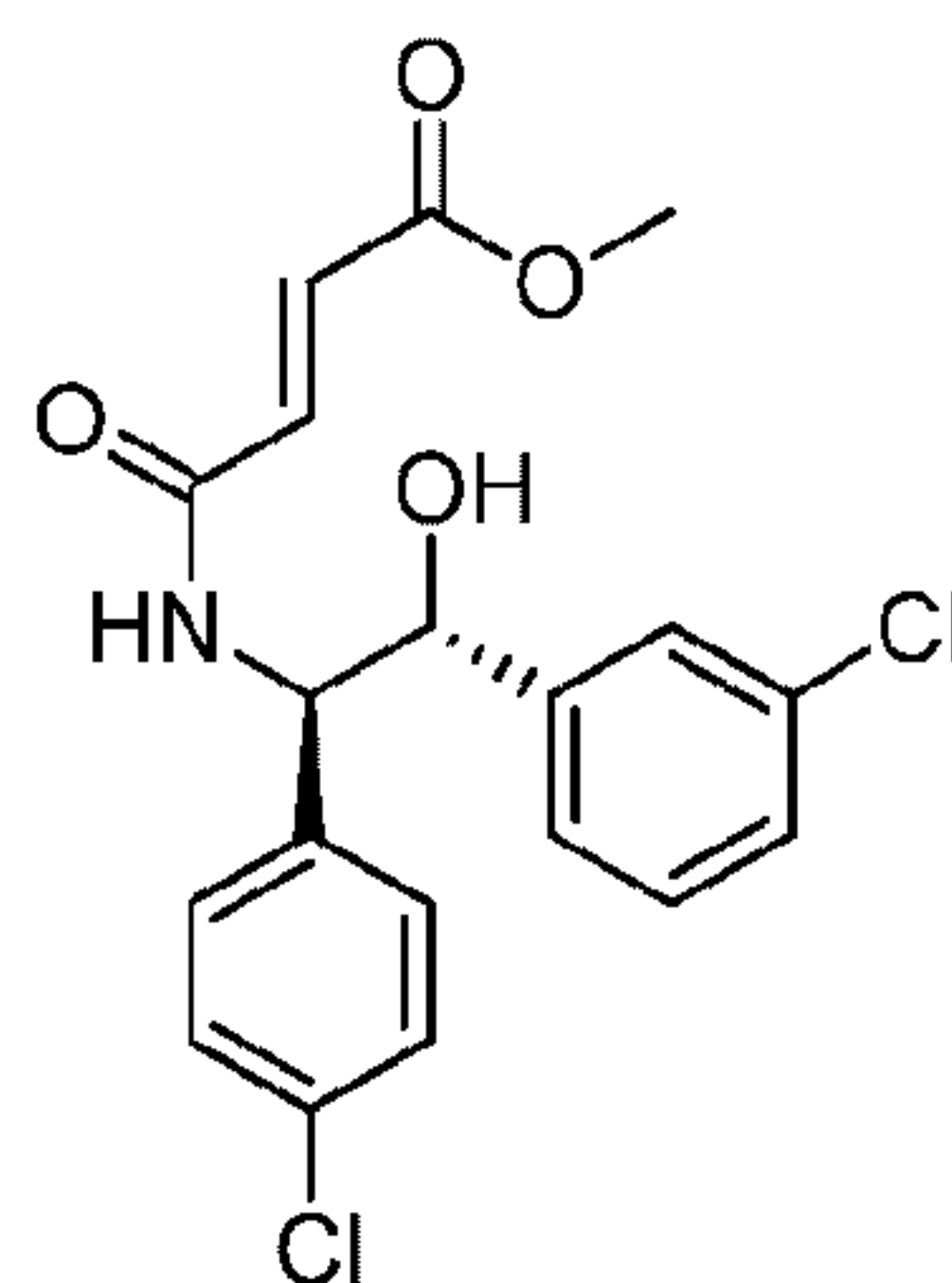
2-((2S,5R,6R)-4-((R)-1-(*tert*-butoxy)-1-oxobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid

5



Step A. (E)-Methyl 4-((1R,2R)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-hydroxyethylamino)-4-oxobut-2-enoate

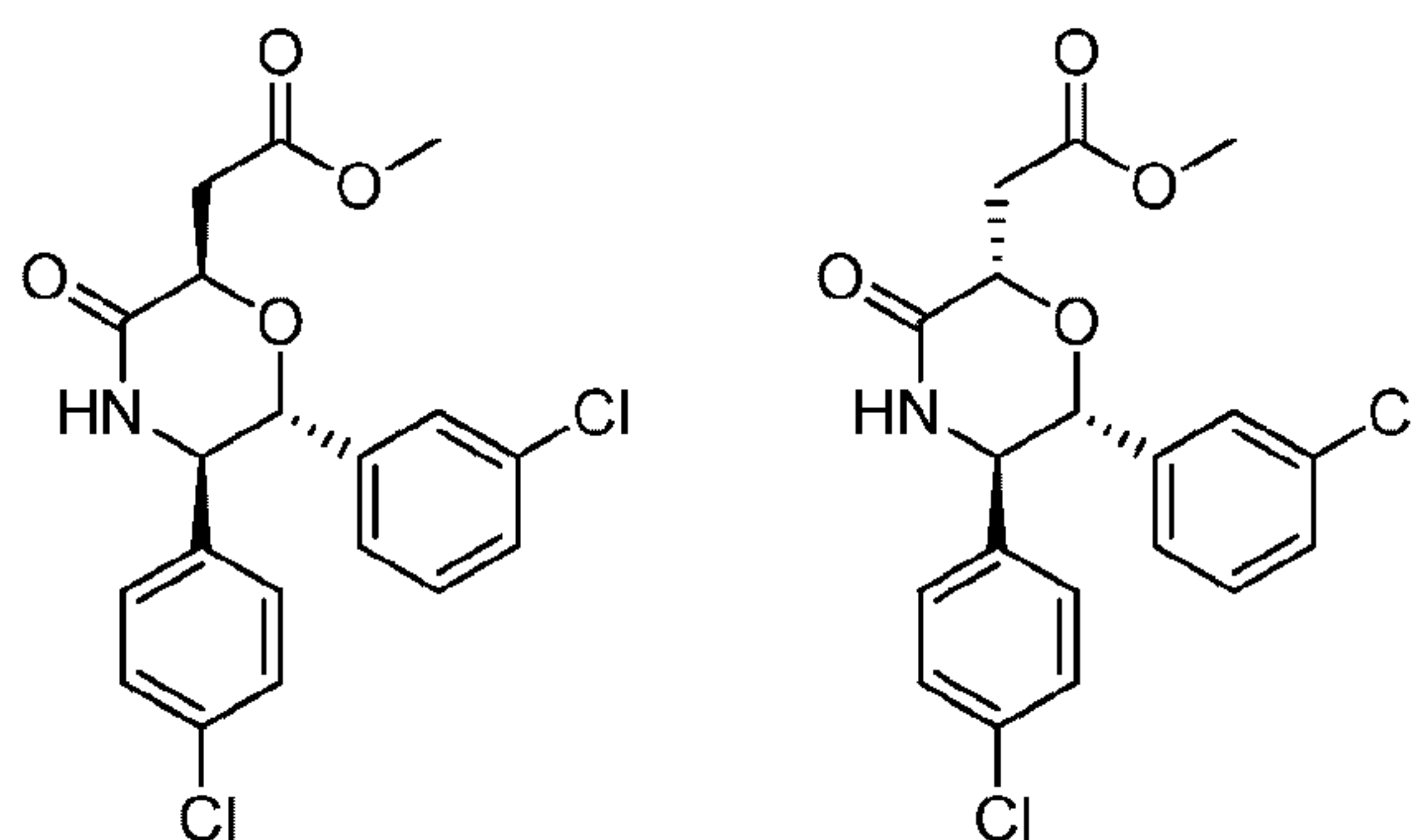
10



To a solution of (E)-4-methoxy-4-oxobut-2-enoic acid (91 mg, 0.702 mmol) in DCM (7 mL) at 0 °C was added 1H-benzo[d][1,2,3]triazol-1-ol hydrate (107 mg, 0.702 mmol) and DCC (145 mg, 0.702 mmol). The reaction mixture was stirred at 0 °C for 60 min then a solution of (1R,2R)-2-amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol (198 mg, 0.702 mmol; Intermediate A2) in DCM (7 mL) was added. The reaction mixture was stirred at 0 °C for 2 h and then warmed to rt for 2 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on

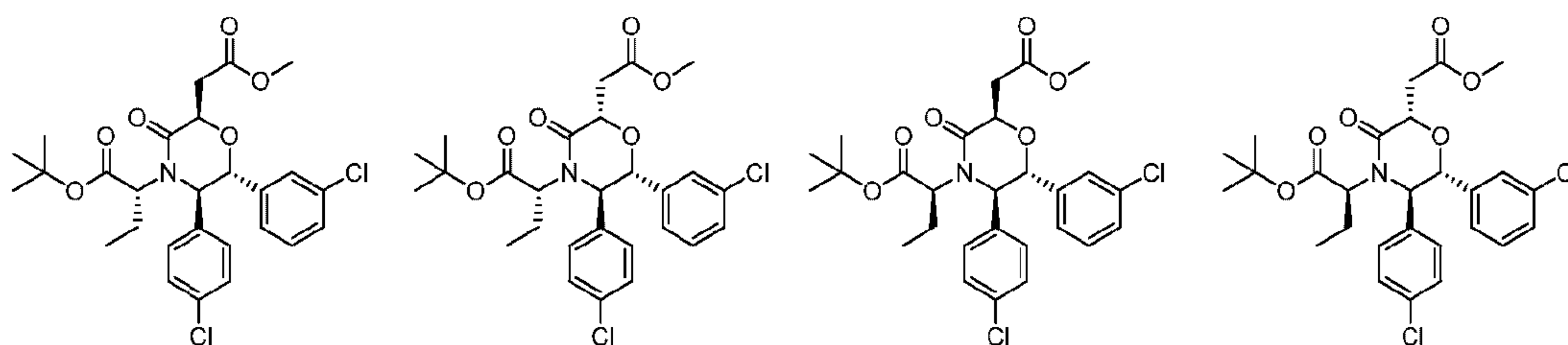
silica gel (eluent: 0 to 100% EtOAc in hexanes) to give the title compound as a colorless film.

Step B. Methyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate and Methyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate



To a solution of (E)-methyl 4-((1R,2R)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-hydroxyethylamino)-4-oxobut-2-enoate (220 mg, 0.558 mmol; Example 28, Step A) in THF (6 mL) was added a dispersion of 60% sodium hydride in mineral oil (33 mg, 0.837 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was quenched with sat. NH_4Cl solution and extracted with DCM. The organic layer was dried over Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 0 to 50% EtOAc in hexanes) to give the title compounds as a mixture of two diastereomers (129 mg, 57% yield).

Step C. (R)-*tert*-Butyl 2-((2R,3R,6R)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-(2-methoxy-2-oxoethyl)-5-oxomorpholino)butanoate and (R)-*tert*-Butyl 2-((2R,3R,6S)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-(2-methoxy-2-oxoethyl)-5-oxomorpholino)butanoate and (S)-*tert*-Butyl 2-((2R,3R,6R)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-(2-methoxy-2-oxoethyl)-5-oxomorpholino)butanoate and (S)-*tert*-Butyl 2-((2R,3R,6S)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-(2-methoxy-2-oxoethyl)-5-oxomorpholino)butanoate



To a solution of methyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate and methyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate (129 mg, 0.327 mmol; Example 28, Step B) in DMF (3 mL) at 0 °C was added a dispersion of 60% sodium hydride in mineral oil (31.4 mg, 1.309 mmol). The reaction mixture was stirred at rt for 20 min and then cooled to 0 °C. *tert*-Butyl 2-bromobutanoate (304 µL, 1.636 mmol) was added and the reaction mixture was warmed to rt and stirred at rt for 4 h. The reaction mixture was quenched with sat. aq. NH₄Cl solution and extracted with DCM (3 x). The organic layers were combined, dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was diluted with EtOAc and washed with 1 M LiCl solution (3 x). The organic layer was dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 0 to 50% DCM in hexanes and then 30% EtOAc in hexanes) to give the title compounds as a mixture of four diastereomers.

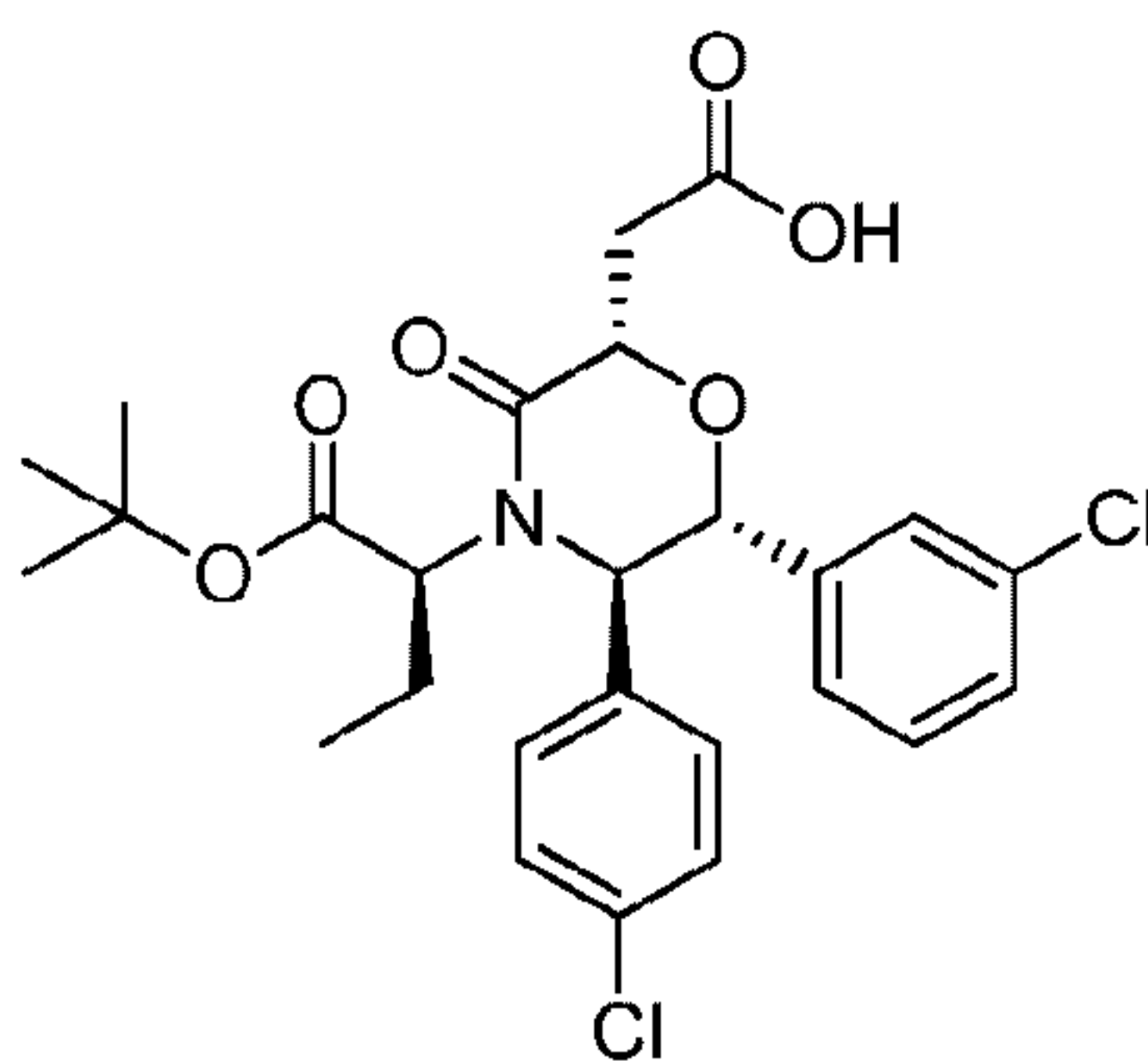
Step D. 2-((2R,5R,6R)-4-((R)-1-*tert*-Butoxy-1-oxobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid and 2-((2S,5R,6R)-4-((R)-1-*tert*-Butoxy-1-oxobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid and 2-((2R,5R,6R)-4-((S)-1-*tert*-Butoxy-1-oxobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid and 2-((2S,5R,6R)-4-((S)-1-*tert*-Butoxy-1-oxobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid

To a mixture of (R)-*tert*-butyl 2-((2R,3R,6R)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-(2-methoxy-2-oxoethyl)-5-oxomorpholino)butanoate, (R)-*tert*-butyl 2-((2R,3R,6S)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-(2-methoxy-2-oxoethyl)-5-oxomorpholino)butanoate, (S)-*tert*-butyl 2-((2R,3R,6R)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-(2-methoxy-2-oxoethyl)-5-oxomorpholino)butanoate, and (S)-*tert*-butyl 2-((2R,3R,6S)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-6-(2-methoxy-2-oxoethyl)-5-oxomorpholino)butanoate (100 mg, 0.186 mmol; Example 28, Step C) in water and THF (1:1, 3 mL total) at rt was added 3 M aq. LiOH solution (311 μ L, 0.932 mmol). The reaction mixture was stirred at rt for 4 h and diluted with EtOAc. The aqueous layer was acidified with 1 M HCl and extracted with EtOAc (3 x). The organic layers were combined, dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. Purification by chiral SFC (flowrate: 24 mL/min on a Lux Cellulose-2 21 x 250 mm column, Phenomenex, Torrance, CA; using methanol (0.2%DEA)/CO₂ as the eluent) provided the title compound as the first eluting isomer that was then further purified by flash chromatography on silica gel (eluent: 7:3:0.1 EtOAc:Hex:AcOH) to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.99 (t, *J*=7.53 Hz, 3 H) 1.46 (s, 9 H) 1.95 - 2.08 (m, 2 H) 3.13 - 3.20 (m, 3 H) 4.63 - 4.75 (m, 3 H) 6.70 (d, *J*=7.63 Hz, 1 H) 7.02 - 7.15 (m, 4 H) 7.21 - 7.23 (m, 1 H) 7.27 (d, *J*=8.6 Hz, 2 H). Mass Spectrum (ESI) *m/z* = 466 (M-58+1).

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EXAMPLE 31

2-((2S,5R,6R)-4-((S)-1-(*tert*-Butoxy)-1-oxobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid

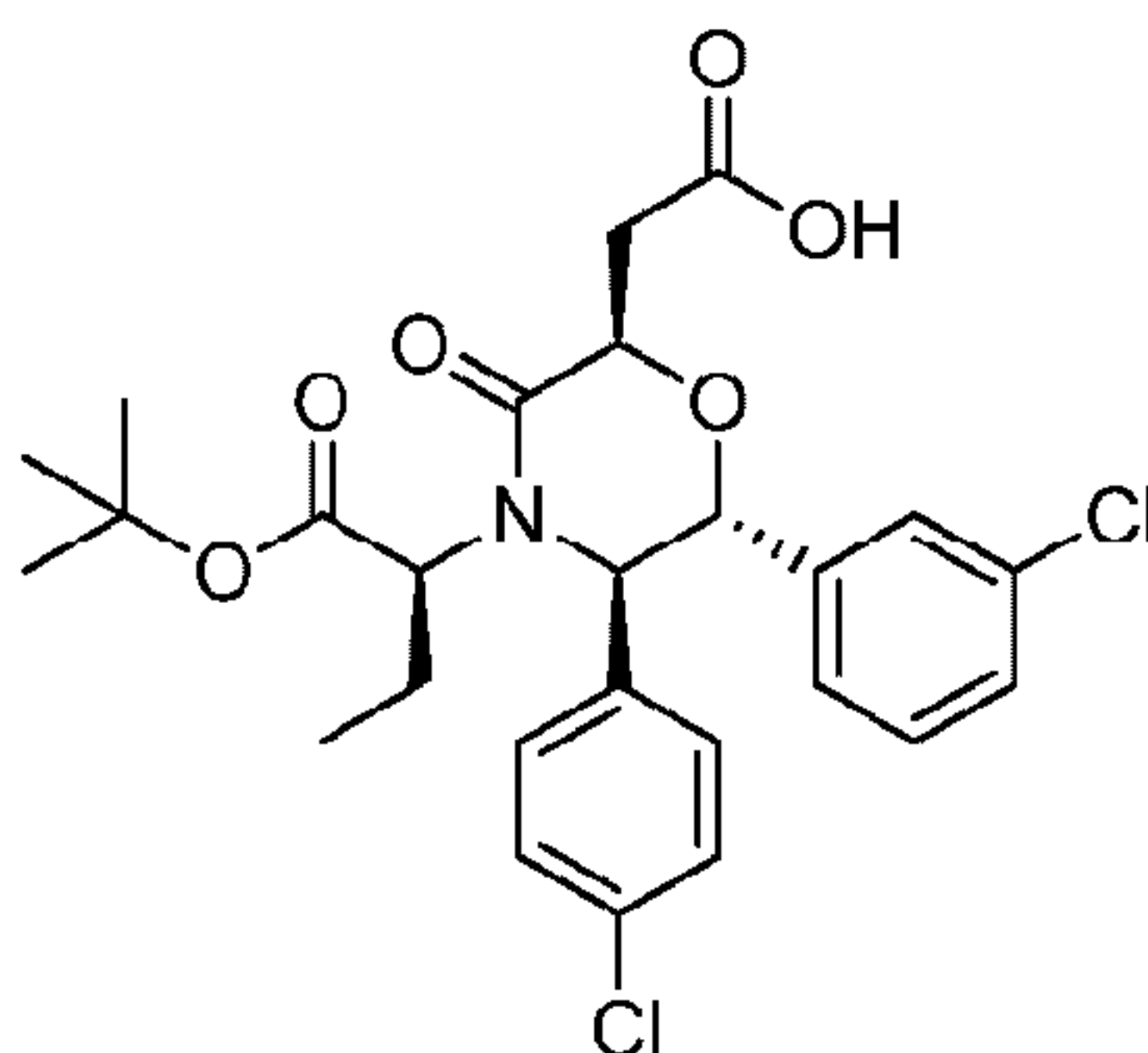


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The second eluting isomer from Example 28, Step D was further purified by flash chromatography on silica gel (eluent: 7:3:0.1 EtOAc:Hex:AcOH) to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.67 (t, *J*=7.53 Hz, 3 H) 1.49 (s, 9 H) 1.63 - 1.75 (m, 1 H) 2.26 (dt, *J*=14.38, 7.48 Hz, 1 H) 2.83 (dd, *J*=16.33, 6.55 Hz, 1 H) 3.12 (dd, *J*=7.73, 5.18 Hz, 1 H) 3.27 (dd, *J*=16.33, 5.97 Hz, 1 H) 4.63 (d, *J*=9.78 Hz, 1 H) 4.76 (d, *J*=9.78 Hz, 1 H) 4.86 (t, *J*=6.26 Hz, 1 H) 6.72 (d, *J*=7.6 Hz, 1 H) 7.03 (d, *J*=8.41 Hz, 1 H) 7.08 - 7.12 (m, 2 H) 7.21 - 7.24 (m, 1 H) 7.30 (d, *J*=8.61 Hz, 3 H). Mass Spectrum (ESI) *m/z* = 466 (*M*-58+1).

EXAMPLE 32

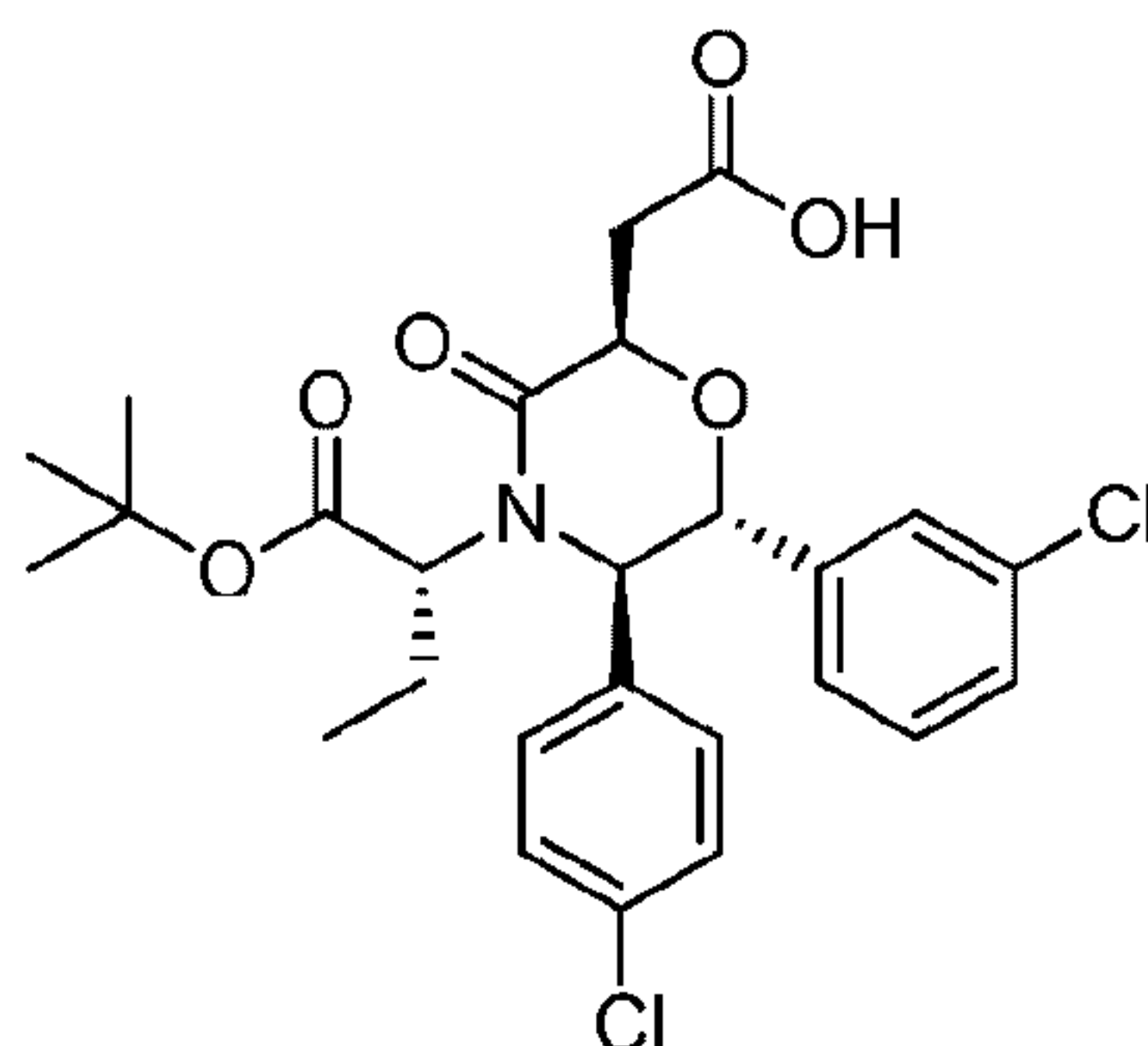
2-((2R,5R,6R)-4-((S)-1-(*tert*-Butoxy)-1-oxobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid



The third eluting isomer from Example 28, Step D was further purified by flash chromatography on silica gel (eluent: EtOAc / Hex / AcOH = 7:3:0.1) to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.69 (t, *J*=7.53 Hz, 3 H) 1.42 (s, 9 H) 1.63 - 1.70 (m, 1 H) 2.14 - 2.24 (m, 1 H) 3.07 (d, *J*=6.06 Hz, 2 H) 3.45 (dd, *J*=8.12, 4.99 Hz, 1 H) 4.65 (t, *J*=6.16 Hz, 1 H) 4.82 (d, *J*=5.48 Hz, 1 H) 4.97 (d, *J*=5.48 Hz, 1 H) 7.10 - 7.15 (m, 1 H) 7.18 - 7.25 (m, 3 H) 7.28 - 7.30 (m, 1 H) 7.34 (d, *J*=8.41 Hz, 2 H) 7.37 (brs, 1 H). Mass Spectrum (ESI) *m/z* = 466 (*M*-58+1).

EXAMPLE 33

2-((2R,5R,6R)-4-((R)-1-(*tert*-Butoxy)-1-oxobutan-2-yl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid



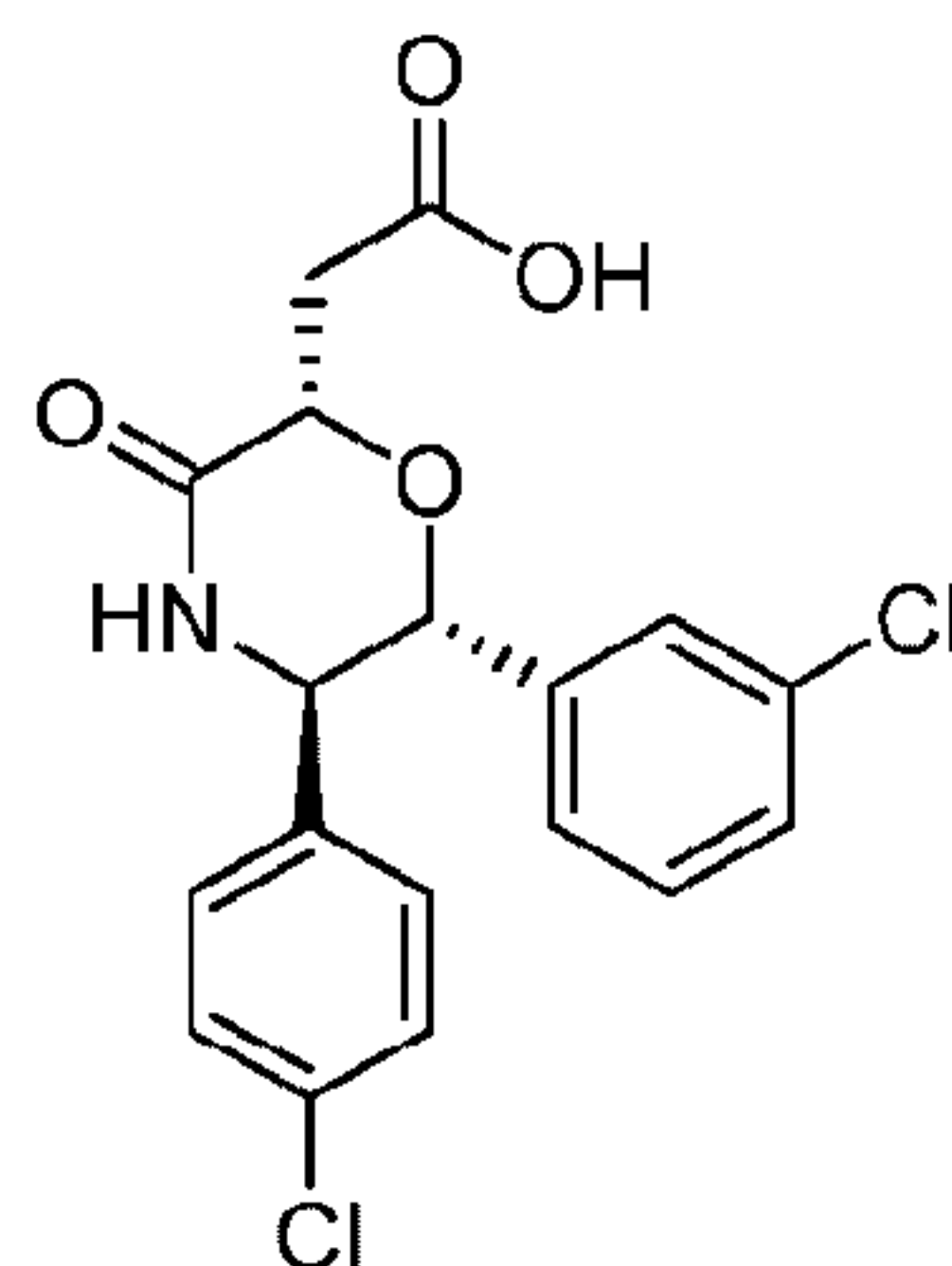
5

The fourth eluting isomer from Example 28, Step D was further purified by flash chromatography on silica gel (eluent: EtOAc / Hex / AcOH = 7:3:0.1) to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.96 (t, *J*=7.43 Hz, 3 H) 1.46 (s, 9 H)

10 1.84 - 2.02 (m, 2 H) 3.04 (dd, *J*=16.0, 8.0 Hz, 1 H) 3.14 (dd, *J*=16.0, 5.3 Hz, 1 H) 3.47 (t, *J*=7.14 Hz, 1 H) 4.76 (d, *J*=7.04 Hz, 1 H) 4.82 - 4.90 (m, 2 H) 6.90 (d, *J*=7.63 Hz, 1 H) 7.12 - 7.25 (m, 5 H) 7.30 (d, *J*=8.41 Hz, 2 H). Mass Spectrum (ESI) *m/z* = 466 (M-58+1).

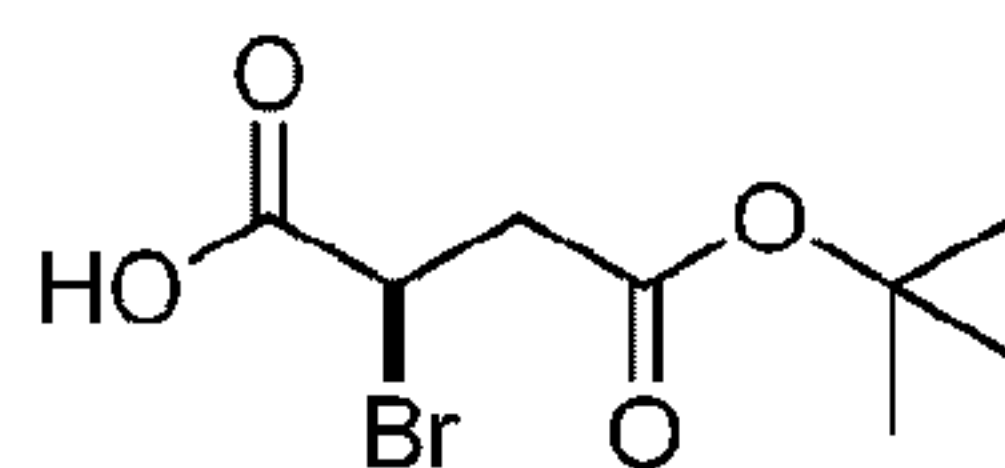
EXAMPLE 34

15 2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid



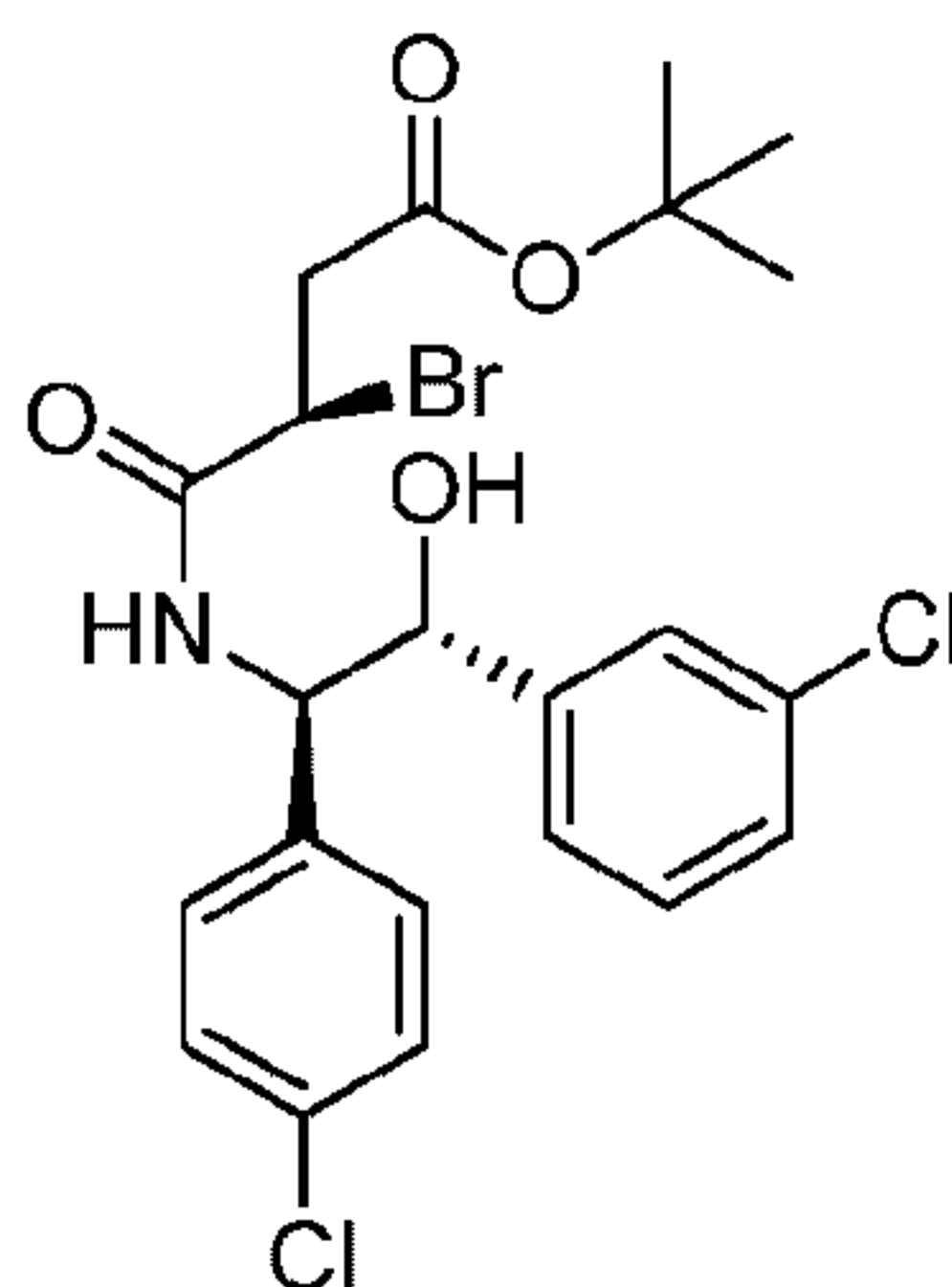
Step A. (R)-2-Bromo-4-*tert*-butoxy-4-oxobutanoic acid

20



The title compound was prepared from (R)-2-amino-4-*tert*-butoxy-4-oxobutanoic acid (Bachem Americas, Inc., Torrance, CA) using the procedures described in Example 9, Step A.

Step B. (R)-*tert*-Butyl 3-bromo-4-((1R,2R)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-hydroxyethylamino)-4-oxobutanoate

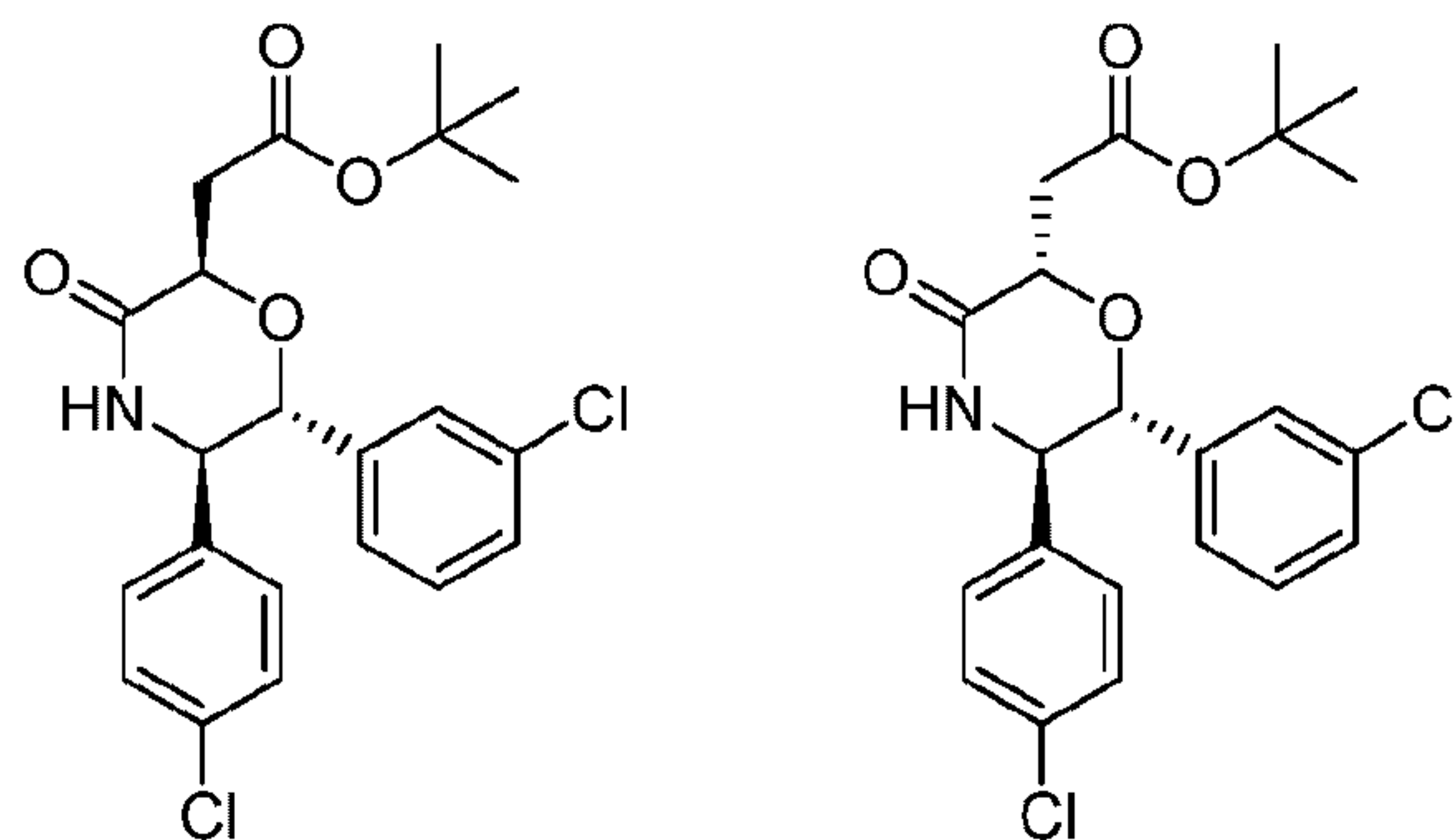


10

To a solution of (R)-2-bromo-4-*tert*-butoxy-4-oxobutanoic acid (0.806 g, 3.19 mmol; Example 34, Step A) in DCM (30 mL) at 0 °C was added 1-hydroxybenzotriazole hydrate (0.488 g, 3.19 mmol) and DCC (0.657 g, 3.19 mmol). The reaction mixture was stirred at 0 °C for 60 min, then ((1R,2R)-2-amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol and (1S,2S)-2-amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol (899 mg, 3.19 mmol; Intermediate A2) in DCM (10 mL) was added. The reaction mixture was stirred at 0 °C for 2 h. Then the reaction mixture was warmed to rt and stirred at rt for 16 h. The reaction mixture was concentrated to 5 mL and filtered. The filtrate was concentrated under reduced pressure. Purification by flash chromatography on silica gel (eluent: 25 to 100% EtOAc in hexanes) provided the title compound as the second eluting isomer.

20

Step C. *tert*-Butyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate and *tert*-Butyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate



5

To a solution of (R)-*tert*-butyl 3-bromo-4-((1R,2R)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-hydroxyethylamino)-4-oxobutanoate (352 mg, 681 μ mol; Example 34, Step B) in DMF (7 mL) at 0 °C was added a dispersion of 60% sodium hydride in mineral oil (33 mg, 817 μ mol). Evolution of gas was observed and the reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched with water. Evolution of gas was observed. The reaction mixture was diluted with EtOAc and the layers were separated. The organic layer was washed with 1 M LiCl and brine. The organic layer was dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure.

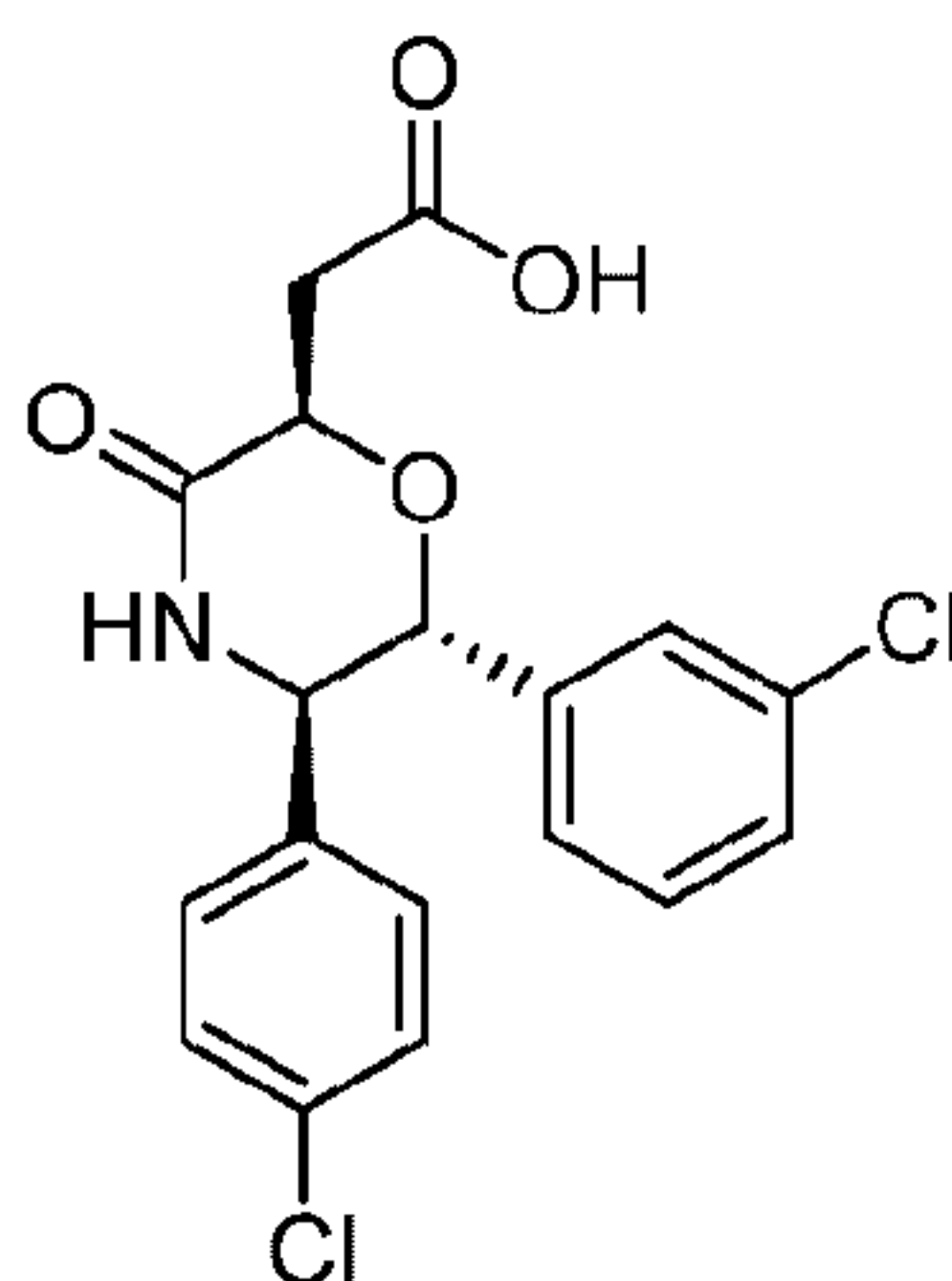
The residue was purified by flash chromatography on silica gel (eluent: 0 to 50% EtOAc in hexanes) to give a residue. The residue was dissolved in THF (1.5 mL) and a dispersion of 60% sodium hydride in mineral oil (26 mg, 639 μ mol) was added at rt. The reaction mixture was stirred at rt for 30 min. The reaction mixture was quenched with water and diluted with EtOAc. The layers were separated and the organic layer was washed with brine. The organic layer was dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. Purification by flash chromatography on silica gel (eluent: 5% MTBE in DCM) (2x) provided *tert*-butyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate as the first eluting diastereomer and *tert*-butyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate as the second eluting diastereomer.

Step D. 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid

- 5 To *tert*-butyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate (26 mg, 60 μ mol; Example 34, Step C, first eluting isomer) in DCM (2 mL) at rt was added TFA (0.5 mL). The reaction mixture was stirred at rt for 90 min. The reaction mixture was concentrated under reduced pressure and the residue was purified by reverse phase preparatory HPLC (GeminiTM Prep C₁₈, 5 μ m column;
- 10 Phenomenex, Torrance, CA; eluent: 0 to 100% MeCN in water, 0.1% TFA, gradient elution over 20 minutes) to give the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 3.09 - 3.25 (m, 2 H) 4.53 (d, *J*=9.4 Hz, 1 H) 4.65 (d, *J*=9.2 Hz, 1 H) 4.77 (t, *J*=4.9 Hz, 1 H) 6.74 (dt, *J*=7.8, 1.37 Hz, 1 H) 6.89 - 6.96 (m, 2 H) 7.09 (t, *J*=1.9 Hz, 1 H) 7.15 (t, *J*=7.8 Hz, 1 H) 7.25 - 7.30 (m, 3 H) 7.98 (br. s, 1 H) 10.53 (br. s, 1 H). Mass Spectrum
- 15 (ESI) *m/z* = 380 (*M*+1).

EXAMPLE 35

2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid



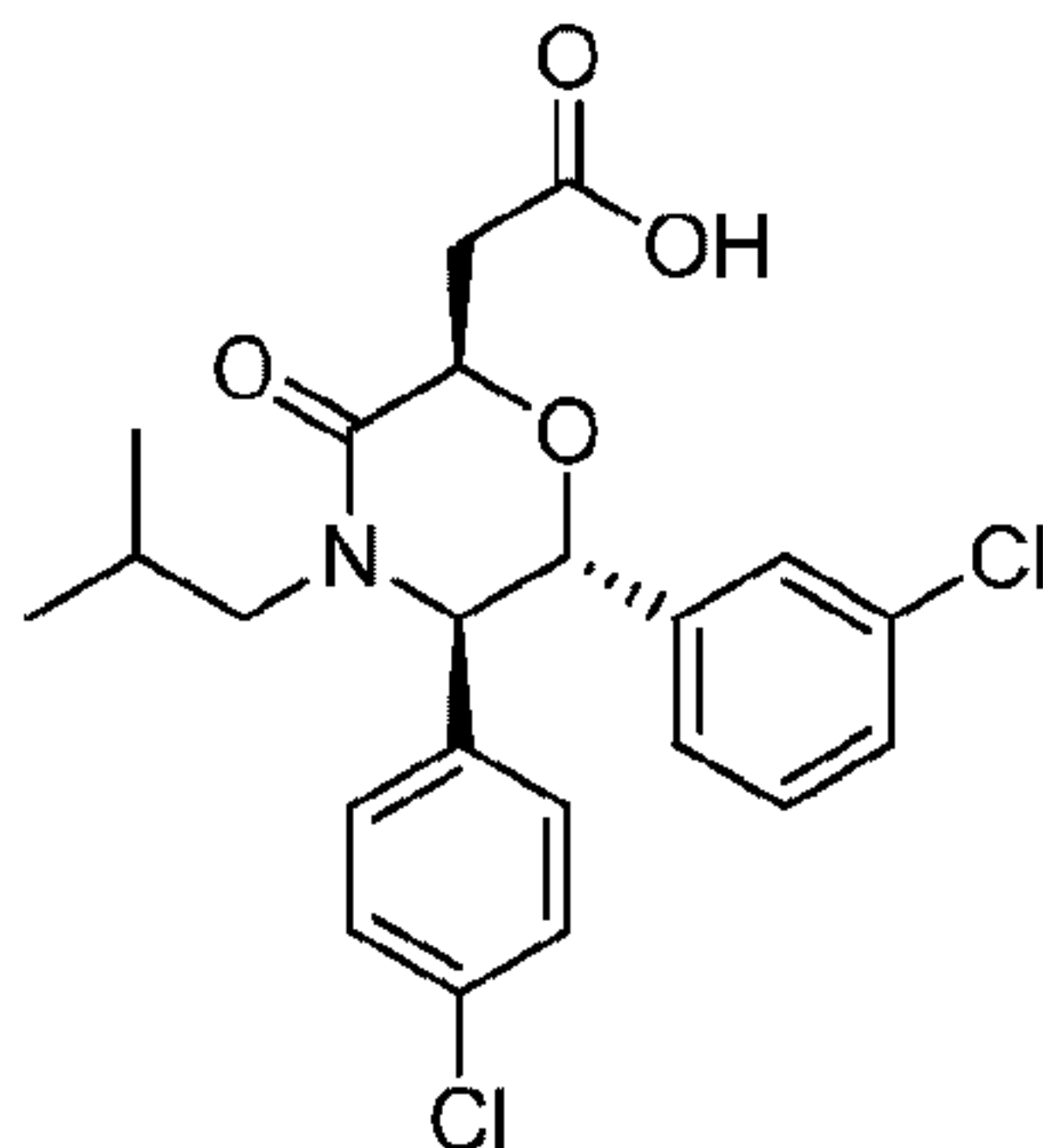
20

- Using *tert*-butyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate (Example 34, Step C; second eluting diastereomer) in the previous procedure provided the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 3.06
- 25 - 3.19 (m, 2 H) 4.65 - 4.74 (m, 2 H) 4.96 - 5.02 (m, 1 H) 6.80 (dt, *J*=7.78, 1.39 Hz, 1 H)

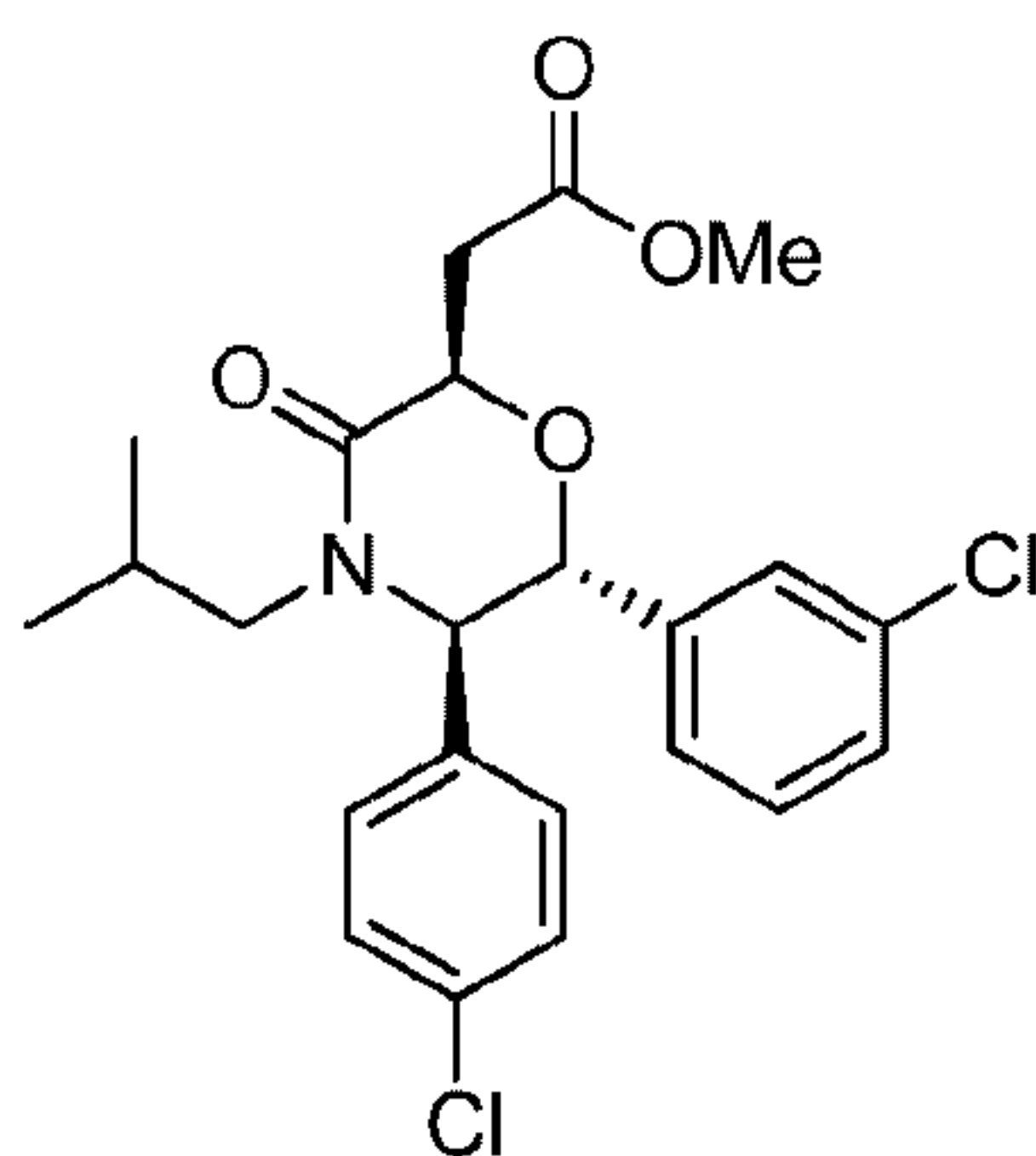
6.94 - 7.00 (m, 2 H) 7.13 - 7.20 (m, 2 H) 7.25 - 7.32 (m, 3 H) 8.06 (br. s, 1 H) 9.87 (br. s, 1 H). Mass Spectrum (ESI) $m/z = 380$ (M+1).

EXAMPLE 36

5 2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-isobutyl-3-oxomorpholin-2-yl)acetic acid



Step A. Methyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-isobutyl-3-oxomorpholin-2-yl)acetate



The title compound was prepared from methyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate and methyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate (Example 30, Step B) by a procedure similar to the one described in Example 30, Step C, replacing sodium hydride and tert-butyl 2-bromobutanoate with isobutyl bromide and Cs_2CO_3 . The mixture of stereoisomers obtained was separated by reversed phase preparatory HPLC (SunfireTM

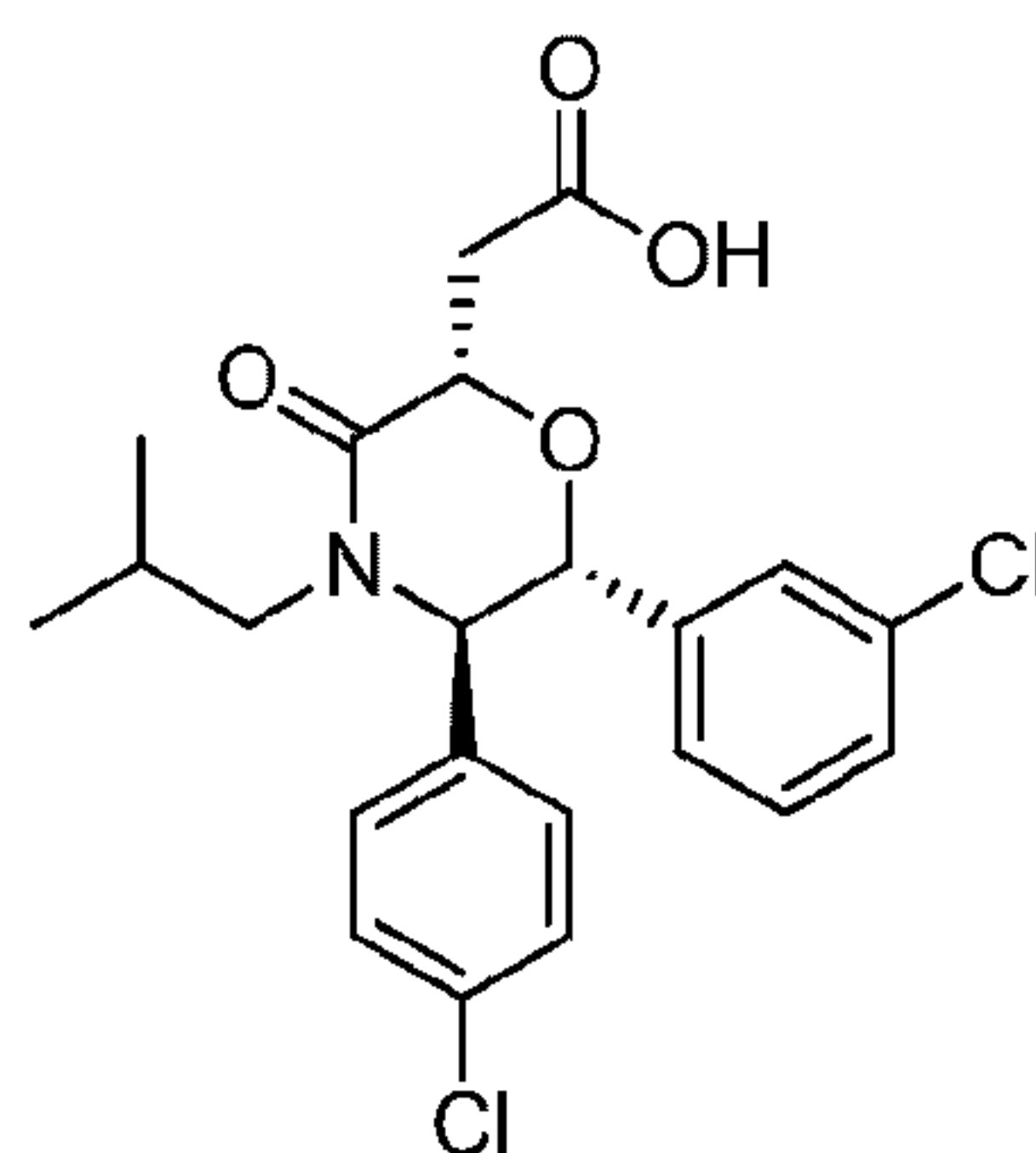
Prep C₁₈ OBD 10 μ m column; Waters, Milford, MA; eluent: acetonitrile, water, 0.1% TFA, gradient elution) to provide the title compound as the first eluting isomer.

Step B. 2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-isobutyl-3-oxomorpholin-2-yl)acetic acid

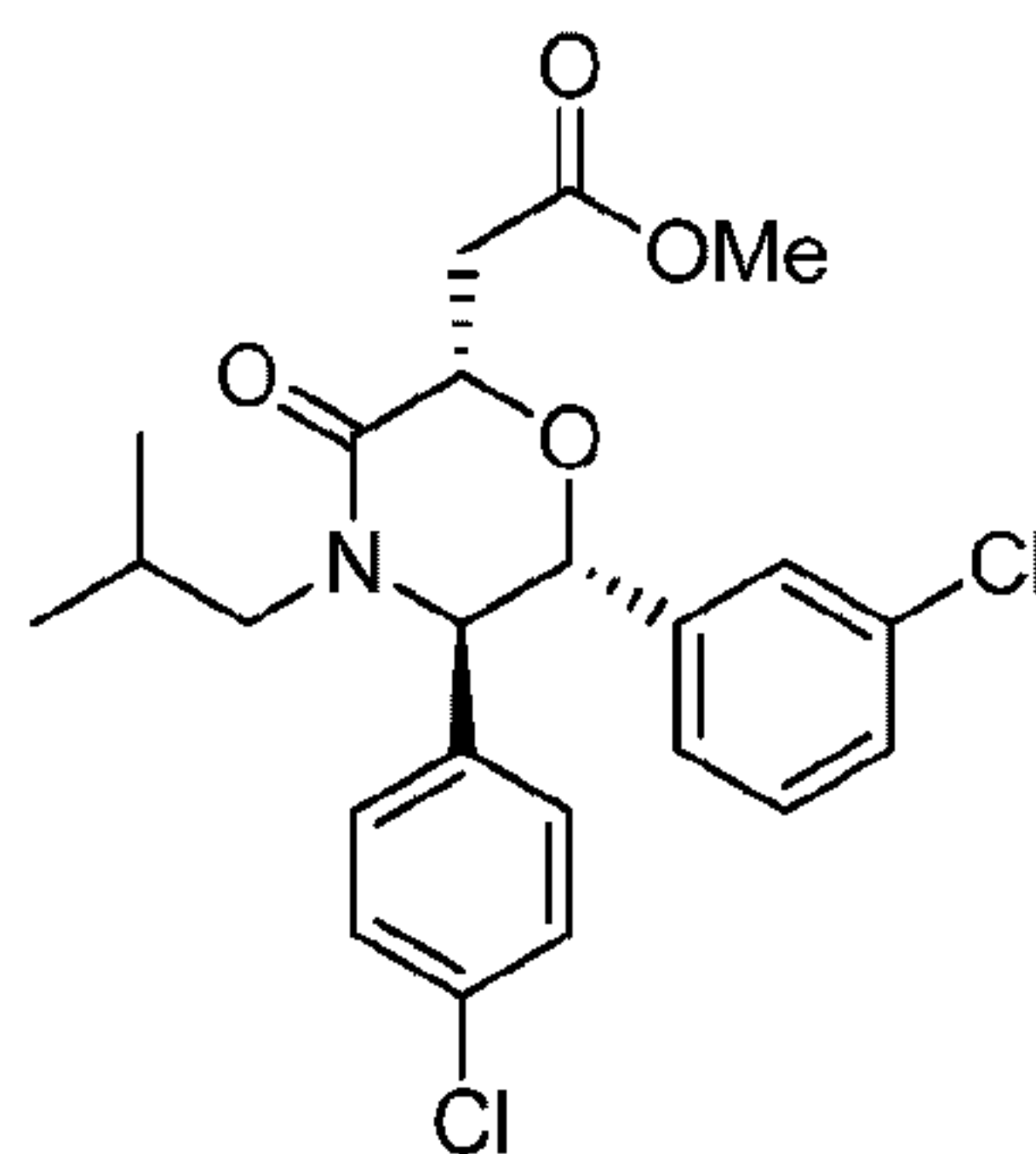
To a solution of methyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-isobutyl-3-oxomorpholin-2-yl)acetate (5.3 mg, 0.012 mmol; Example 36, Step B) in THF (0.26 mL) was added a 1N solution of lithium hydroxide in water (7.41 mg in 0.177 mL). The mixture was stirred at room temperature for 4.5 hours, then acidified to about pH 4 using 1 N HCl, and then concentrated in vacuo. The residue was taken up in EtOAc and the organics were washed with water, dried over MgSO₄, filtered and the filtrate was concentrated to give the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.76 (ddd, *J*=18.10, 6.60, 3.18 Hz, 6 H), 1.82 (dt, *J*=6.17, 3.39 Hz, 1 H) 2.13 - 2.30 (m, 1 H) 2.81 - 3.06 (m, 2 H) 3.68 - 3.88 (m, 1 H) 4.41 - 4.68 (m, 1 H) 4.70 - 4.89 (m, 2 H) 6.86 (d, *J*=7.09 Hz, 1 H) 6.94 - 7.03 (m, 2 H) 7.04 - 7.16 (m, 1 H) 7.16 - 7.38 (m, 5 H). Mass Spectrum (ESI) *m/z* = 436 (M+1).

EXAMPLE 37

2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-isobutyl-3-oxomorpholin-2-yl)acetic acid



Step A. Methyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-isobutyl-3-oxomorpholin-2-yl)acetate



5

The title compound was obtained as the second eluting isomer in Example 36, Step A.

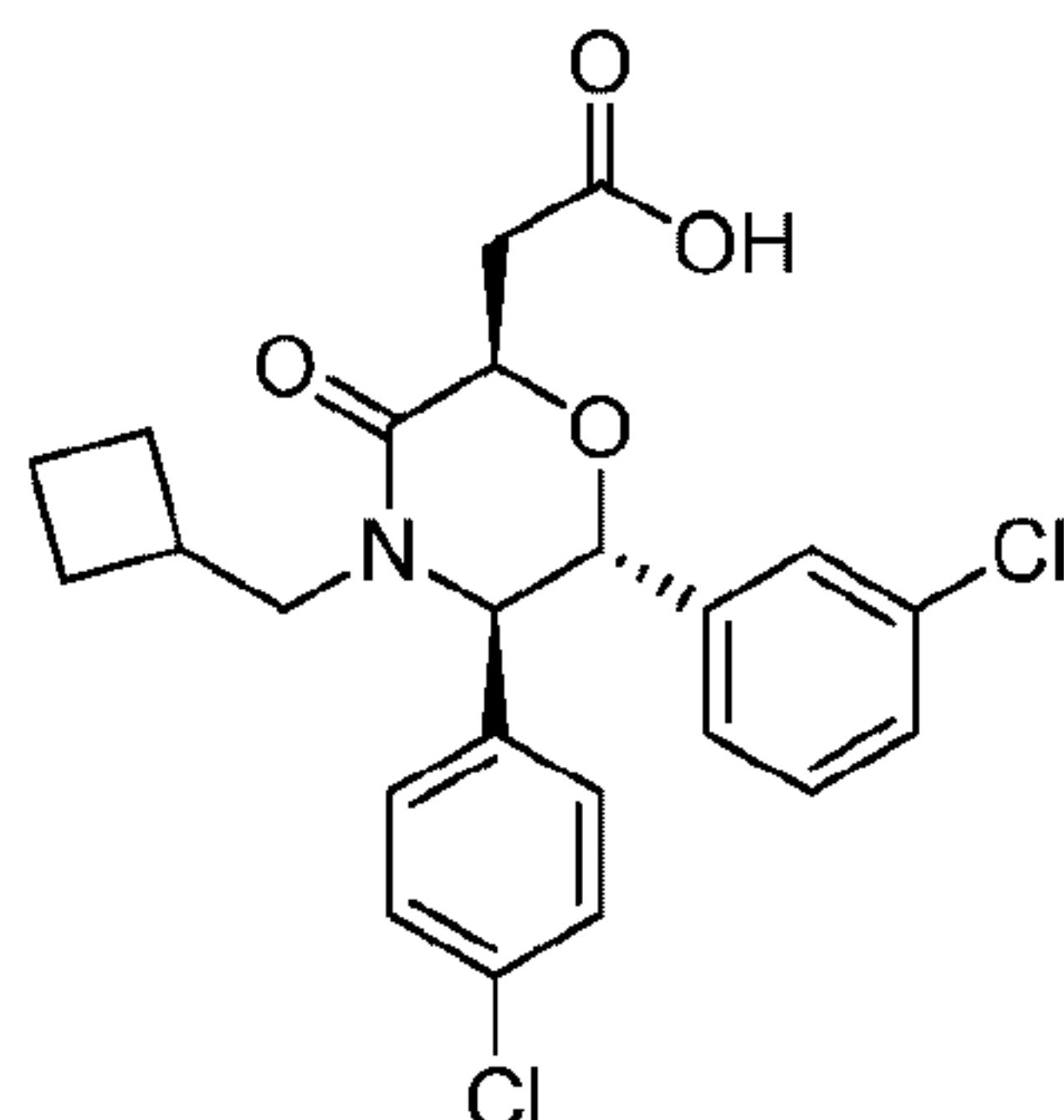
Step B. 2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-isobutyl-3-oxomorpholin-2-yl)acetic acid

The title compound was obtained from methyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-isobutyl-3-oxomorpholin-2-yl)acetate (Example 37, Step A) by a procedure analogous to the one described in Example 36, Step B. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.79 (d, *J*= 8 Hz, 3H), 0.86 (d, *J*= 8 Hz, 3H), 1.82 – 1.90 (m, 1 H), 2.23 (dd, *J*=12, 8 Hz, 1H), 2.98 (dd, *J*=16, 4 Hz, 1H), 3.19 (dd, *J*=16, 4 Hz, 1H), 3.88 (dd, *J*=16, 8 Hz, 1H), 4.54 (d, *J*=8 Hz, 1 H), 4.58 (d, *J*=8 Hz, 1 H), 4.79 (t, *J*=6 Hz, 1 H), 6.69 (d, *J*=8 Hz, 1H), 6.89 (d, *J*= 8 Hz, 2H), 7.08 – 7.12 (m, 2H), 7.22 - 7.29 (m, 3 H). Mass Spectrum (ESI) *m/z* = 436 (M+1).

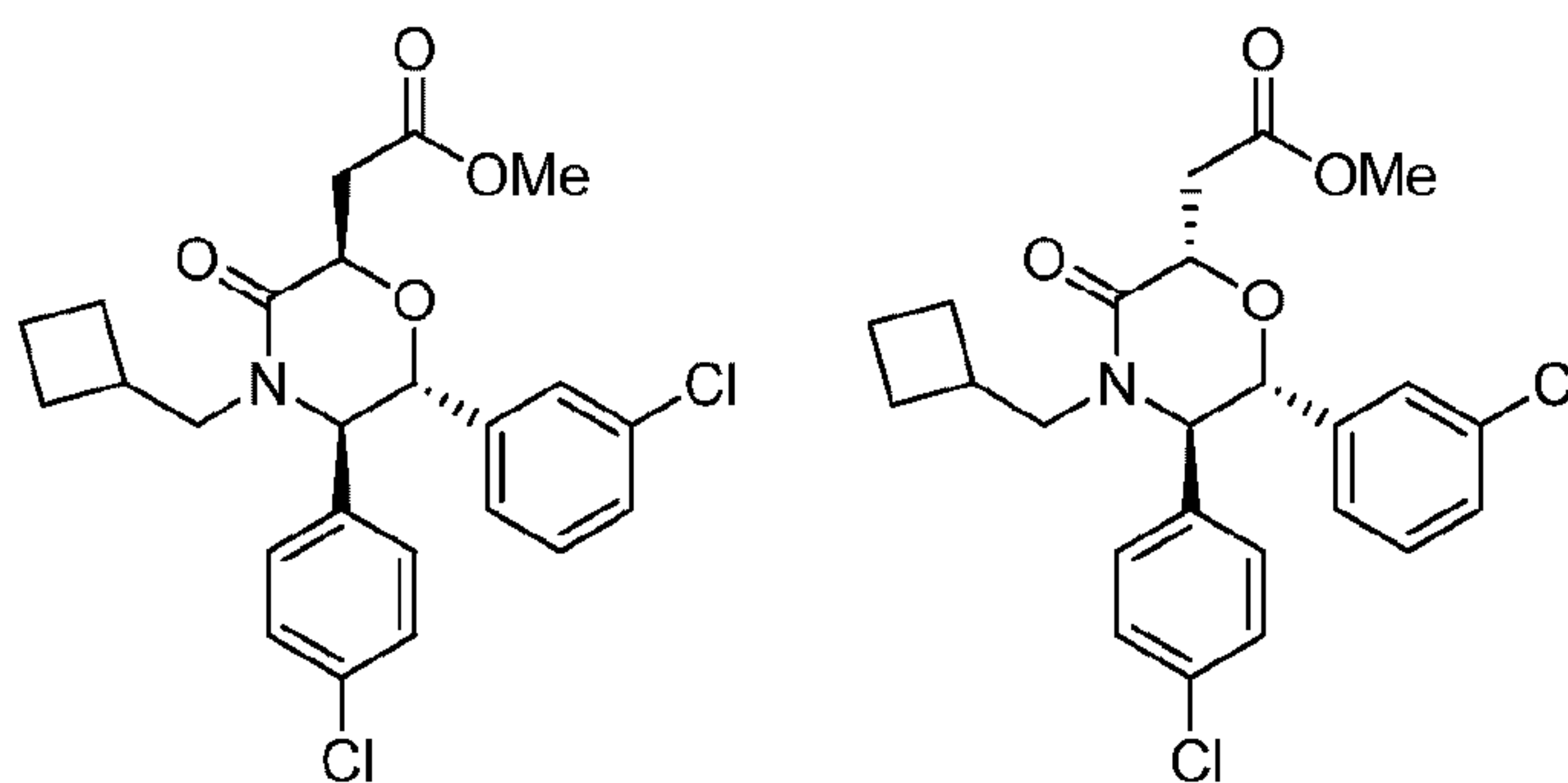
20

EXAMPLE 38

2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclobutylmethyl)-3-oxomorpholin-2-yl)acetic acid



Step A. Methyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclobutylmethyl)-3-oxomorpholin-2-yl)acetate and Methyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclobutylmethyl)-3-oxomorpholin-2-yl)acetate



The title compounds were prepared as a mixture of stereoisomers from methyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate and methyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate (Example 30, Step B) by a procedure analogous to the one described in Example 30, Step C, replacing sodium hydride and tert-butyl 2-bromobutanoate with bromomethyl cyclobutane and Cs₂CO₃.

15

Step B. 2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclobutylmethyl)-3-oxomorpholin-2-yl)acetic acid

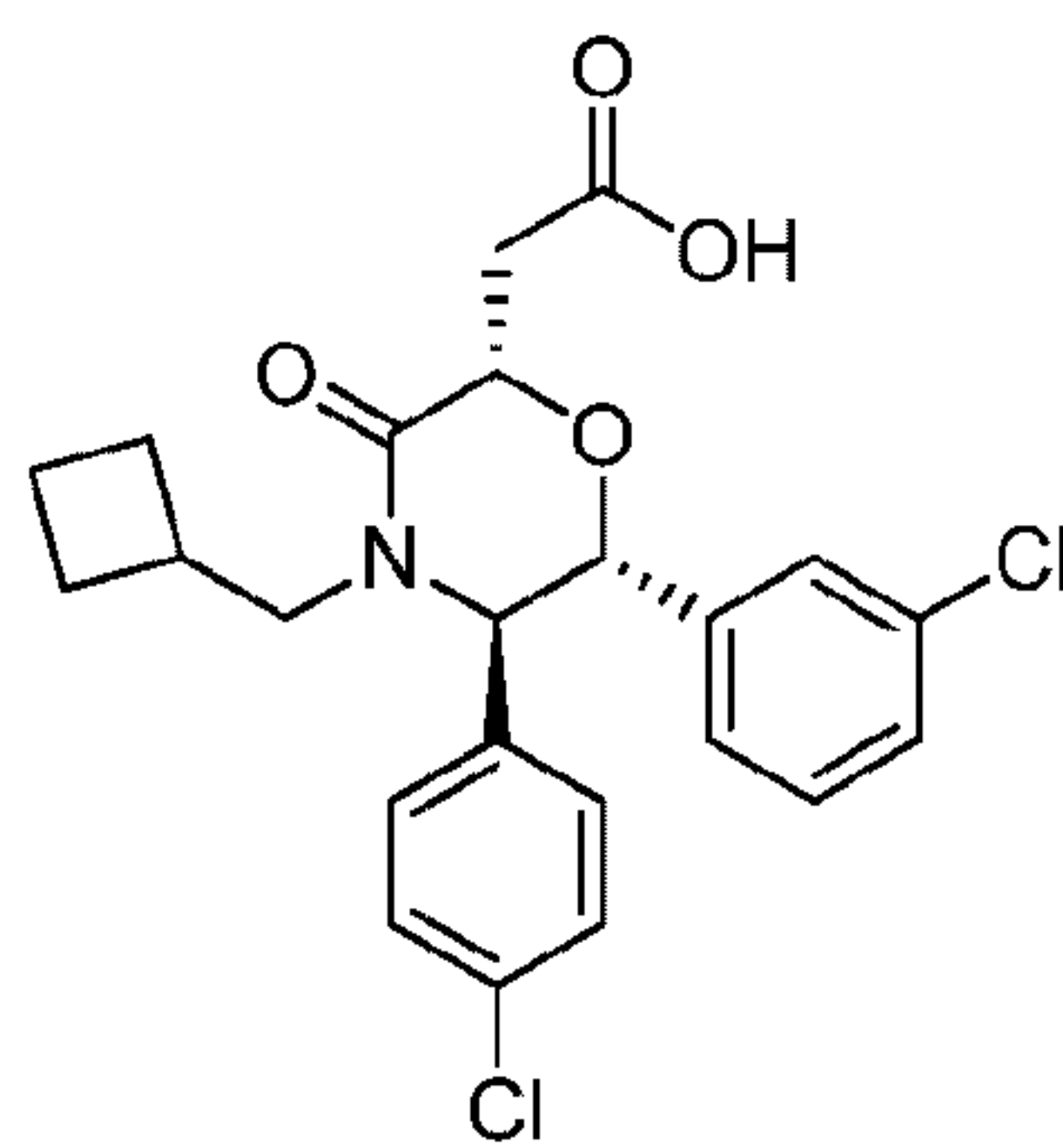
The title compound was obtained from methyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclobutylmethyl)-3-oxomorpholin-2-yl)acetate and methyl 2-

20

((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclobutylmethyl)-3-oxomorpholin-2-yl)acetate (Example 38, Step A) by a procedure similar to the one described in Example 36, Step B. Individual stereoisomers were separated by chiral HPLC (250 x 30 mm Chiralpak® IC column (Chiral Technologies, Inc., West Chester, PA, USA) with 46 g/min isopropylamine + (20 µM NH₃) + 84 g/min CO₂ on a Thar 350 SFC (Thar Technologies, Inc., Pittsburg, PA)) to give the title compound as the first eluting isomer. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.84 - 0.94 (m, 1 H), 1.50 - 1.96 (m, 2 H), 2.02 - 2.15 (m, 1 H), 2.59 - 2.68 (m, 1 H), 2.94 (dd, *J*= 16.1, 6.7 Hz, 1 H), 3.00 (dd, *J*=16.0, 6.8 Hz, 1 H), 3.16 (dd, *J*=16.0, 6.0 Hz, 1 H), 4.04 (dd, *J*=13.9, 8.5 Hz, 1 H), 4.58 (d, *J*=9.6 Hz, 1 H), 3.39 - 3.51 (m, 1 H), 4.12 - 4.18 (m, 1 H), 4.55 (t, *J*=6.5 Hz, 1 H), 4.75 (d, *J*=4.1 Hz, 1H), 4.83 (d, *J*=4.1 Hz, 1H), 7.05 - 7.13 (m, 3 H), 7.27 - 7.36 (m, 5 H), 9.43 (brs, 1 H). Mass Spectrum (ESI) *m/z* = 448 (M+1).

EXAMPLE 39

2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclobutylmethyl)-3-oxomorpholin-2-yl)acetic acid



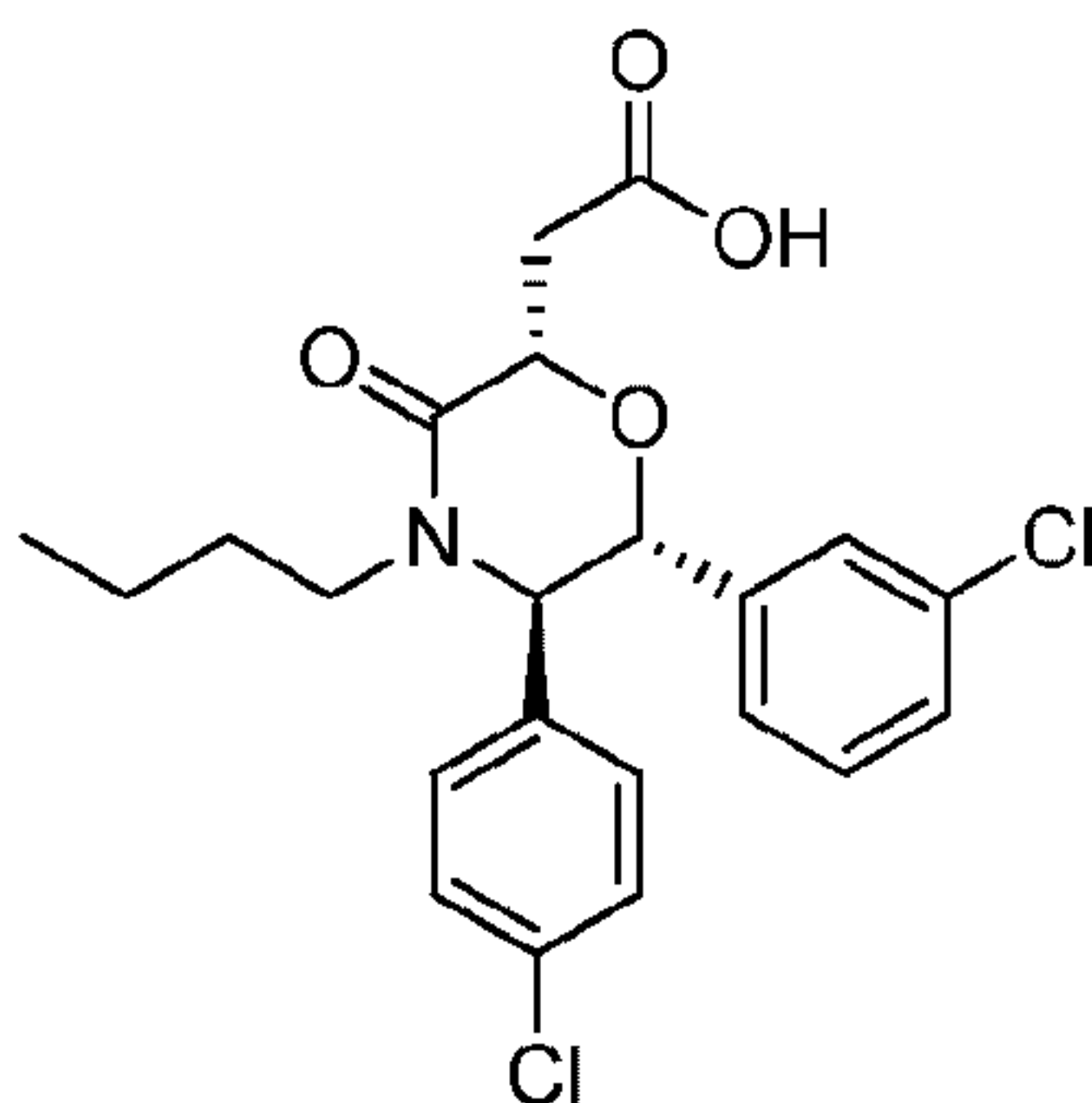
The title compound was obtained as the second eluting isomer from Example 38, Step B.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.50 - 1.66 (m, 2 H), 1.73 - 1.88 (m, 2 H), 1.96 (brs, 1 H), 2.42 - 2.51 (m, 2 H), 2.81 - 2.86 (m, 2 H), 3.10 - 3.16 (m, 1 H), 4.10 - 4.13 (m, 1 H), 4.46 (d, *J*=9.4 Hz, 1 H), 4.53 (d, *J*=9.4 Hz, 1 H), 4.81 (brs, 1 H), 6.63 (d, *J*=7.6 Hz,

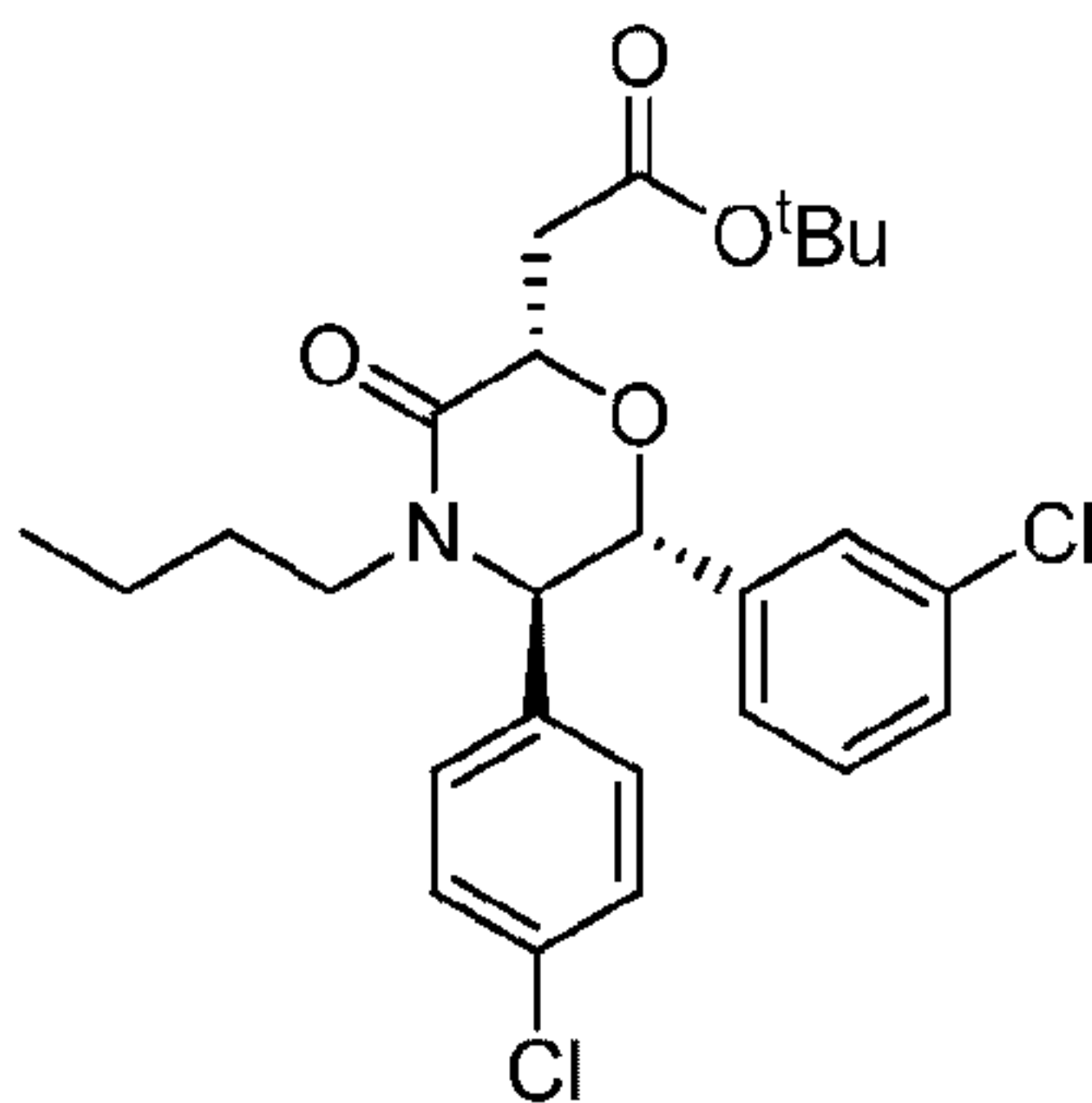
1H), 6.89 (d, $J=8.4$ Hz, 1H), 7.07 (t, $J=7.8$ Hz, 1H), 7.11 (brs, 1 H), 7.07 - 7.08 (m, 1 H), 7.20 - 7.23 (m, 1H), 7.26 - 7.28 (m, 3 H). Mass Spectrum (ESI) $m/z = 448$ (M+1).

EXAMPLE 40

- 5 2-((2S,5R,6R)-4-Butyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid



- 10 Step A. *tert*-Butyl 2-((2S,5R,6R)-4-butyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate



- 15 To a stirring solution of *tert*-butyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate (75.0 mg, 0.172 mmol; Example 34, Step C) dissolved in 430 μ L of DMF was added caesium carbonate (280 mg, 0.859 mmol) at rt. The reaction was stirred at rt for another 15 min and was then treated with 1-iodobutane (157 μ L, 1.375 mmol). After being stirred at rt for 14 h, the reaction was quenched with
20 sat. aq. NaHCO_3 solution and extracted with EtOAc (2X). The combined organic layers

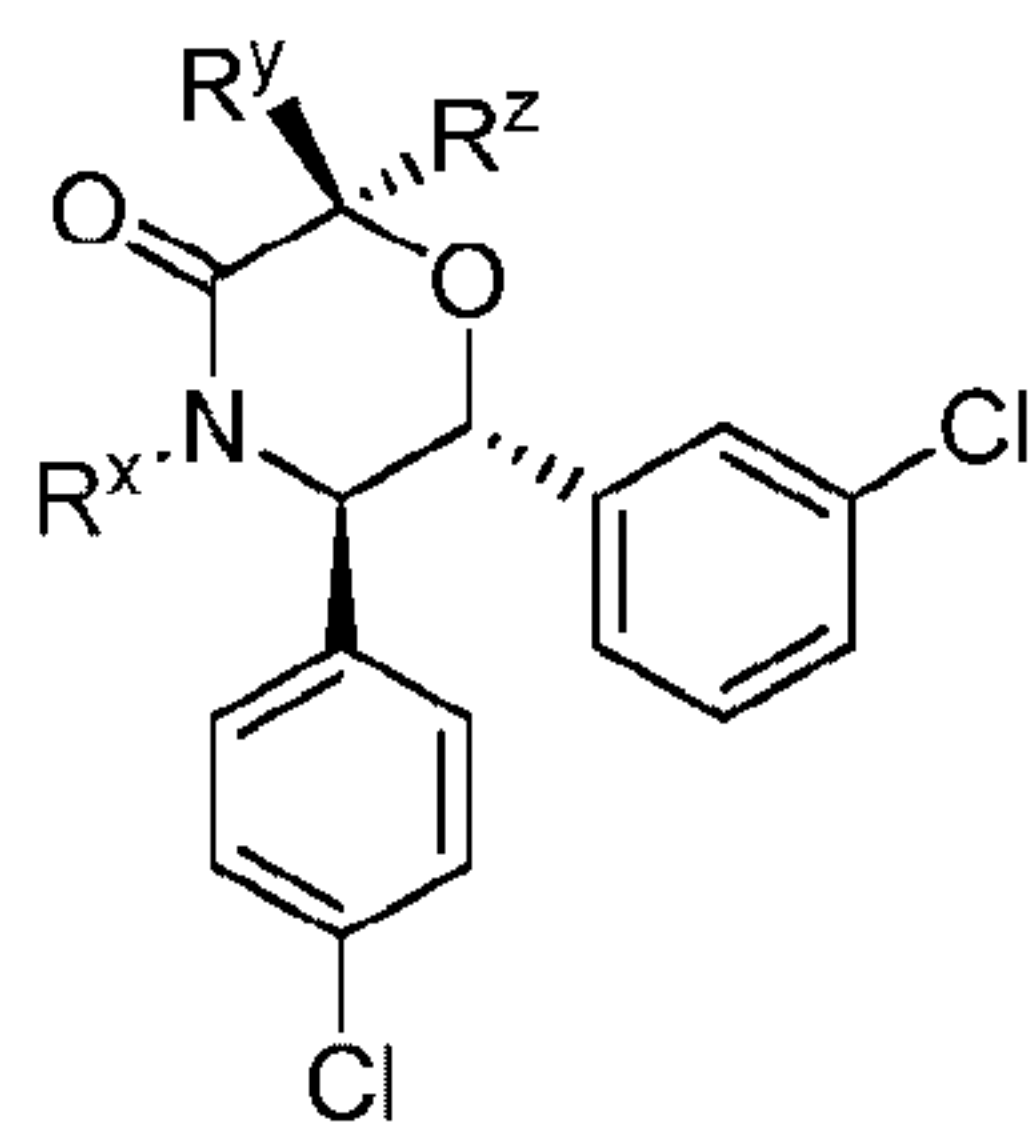
were washed with sat. aq. NaCl solution, dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (eluent: 0 to 40% EtOAc in hexanes, gradient elution) provided the title compound as a colorless solid.

5

Step B. 2-((2S,5R,6R)-4-Butyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid

To a stirring solution of *tert*-butyl 2-((2S,5R,6R)-4-butyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate (45.0 mg, 0.091 mmol; Example 40, Step A) dissolved in 920 µL of dichloromethane at rt was added 2,2,2-trifluoroacetic acid (305 µL, 0.091 mmol). After being stirred at rt for 4 h, the reaction was quenched (water) and extracted with EtOAc (2X). The combined organic layers were washed with sat. aq. NaCl solution, dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by silica gel prep. plate (5% MeOH/DCM) provided the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.82 (t, J = 1.00 Hz, 3 H), 1.10 - 1.25 (m, 2 H), 1.36 - 1.48 (m, 2 H), 2.47 (ddd, J = 13.99, 8.31, 6.06 Hz, 1 H), 2.98 - 3.10 (m, 1 H), 3.10 - 3.21 (m, 1 H), 3.86 - 3.98 (m, 1 H), 4.50 - 4.57 (m, 1 H), 4.58 - 4.64 (m, 1 H), 4.76 (t, J = 5.38 Hz, 1 H), 6.70 (d, J = 7.63 Hz, 1 H), 6.92 (d, J = 8.41 Hz, 2 H), 7.08 (m, 1 H), 7.09 - 7.13 (m, 1 H), 7.20 - 7.25 (m, 1 H), 7.28 (d, J = 8.41 Hz, 2 H). MS (ESI) m/z = 436.1 [M+1].

EXAMPLES 41 – 49 were also prepared from *tert*-butyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate (Example 34, Step C) by a procedure analogous to the one described in Example 40, replacing 1-iodobutane in Step A with the appropriate reagent.



Example	R ^x	R ^y	R ^z	Reagent used in step A
41		H		(iodomethyl)cyclohexane
42		H		benzylbromide
43		H		2-chloromethyloxazole
44	Et		H	iodoethane
45	Et	H		iodoethane
46			H	allylbromide
47		H		allylbromide
48			H	1-bromopropane
49		H		1-bromopropane

EXAMPLE 41

5 2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclohexylmethyl)-3-oxomorpholin-2-yl)acetic acid

¹H NMR (500 MHz, CDCl₃) δ ppm 0.79 - 0.90 (m, 2 H), 1.10 - 1.26 (m, 3 H), 1.51 (d, *J* = 13.94 Hz, 1 H), 1.57 (ddd, *J* = 11.07, 6.42, 3.06 Hz, 1 H), 1.65 (m, 3 H), 1.70 - 1.76 (m, 10 1 H), 2.24 (dd, *J* = 13.94, 6.36 Hz, 1 H), 3.00 (dd, *J* = 16.26, 5.26 Hz, 1 H), 3.19 (dd, *J* =

16.26, 6.24 Hz, 1 H), 3.90 (dd, $J = 13.94, 8.31$ Hz, 1 H), 4.49 - 4.55 (m, 1 H), 4.56 - 4.61 (m, 1 H), 4.76 (t, $J = 5.87$ Hz, 1H), 6.69 (d, $J = 7.83$ Hz, 1 H), 6.90 (d, $J = 8.31$ Hz, 2 H), 7.09 (s, 1 H), 7.12 (t, $J = 7.83$ Hz, 1 H), 7.23 - 7.26 (m, 1 H), 7.29 (d, $J = 8.56$ Hz, 2 H). MS (ESI) $m/z = 476.1$ $[M+H]^+$.

5

EXAMPLE 42

2-((2S,5R,6R)-4-Benzyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid

10 ^1H NMR (400 MHz, CDCl_3) δ ppm 3.08 - 3.18 (m, 1 H), 3.20 - 3.29 (m, 1 H), 3.50 (d, $J = 14.67$ Hz, 1 H), 4.36 (d, $J = 9.78$ Hz, 1 H), 4.66 (d, $J = 9.78$ Hz, 1 H), 4.86 (t, $J = 5.48$ Hz, 1 H), 5.48 (d, $J = 14.67$ Hz, 1 H), 6.63 (d, $J = 7.82$ Hz, 1 H), 6.80 (d, $J = 8.41$ Hz, 2 H), 6.98 (t, $J = 1.76$ Hz, 1 H), 6.99 - 7.02 (m, 2 H), 7.05 (dd, $J = 7.92$ Hz, 1 H), 7.18 (ddd, $J = 8.02, 1.96, 0.98$ Hz, 1 H), 7.26 (d, $J = 5.09$ Hz, 2 H), 7.27 - 7.30 (m, 3 H). MS
15 (ESI) $m/z = 492.1$ $[M+\text{Na}]$.

EXAMPLE 43

2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(oxazol-2-ylmethyl)-3-oxomorpholin-2-yl)acetic acid

20

^1H NMR (400 MHz, CDCl_3) δ ppm 3.03 - 3.13 (m, 1 H), 3.15 - 3.24 (m, 1 H), 3.94 (d, $J = 16.04$ Hz, 1 H), 4.69 - 4.78 (m, 2 H), 4.88 (t, $J = 5.38$ Hz, 1 H), 5.13 (d, $J = 16.04$ Hz, 1 H), 6.72 (d, $J = 7.63$ Hz, 1 H), 6.92 (d, $J = 8.22$ Hz, 2 H), 7.03 (s, 1 H), 7.05 - 7.09 (m, 1 H), 7.10 (s, 1 H), 7.18 - 7.22 (m, 1 H), 7.25 (d, $J = 8.41$ Hz, 2 H), 7.56 (s, 1 H). MS (ESI)
25 $m/z = 483.1$ $[M+\text{Na}]$.

EXAMPLE 44

2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-ethyl-3-oxomorpholin-2-yl)acetic acid

30

¹H NMR (400 MHz, CDCl₃) δ ppm 1.15 (t, *J*=6.97 Hz, 3 H) 2.79 (dd, *J*=13.69, 6.85 Hz, 1 H) 2.90 - 3.09 (m, 1 H) 3.09 - 3.20 (m, 1 H) 3.99 (dd, *J*=13.69, 7.09 Hz, 1 H) 4.56 - 4.71 (m, 1 H) 4.77 (d, *J*=4.65 Hz, 1 H) 4.87 (d, *J*=4.65 Hz, 1 H) 7.03 (d, *J*=7.09 Hz, 1 H) 7.12 (d, *J*=8.07 Hz, 2 H) 7.20 - 7.39 (m, 5 H) 7.66 (br. s., 1 H). Mass Spectrum (ESI) *m/z* = 408 (M+1).

EXAMPLE 45

2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-ethyl-3-oxomorpholin-2-yl)acetic acid

¹H NMR (400 MHz, CDCl₃) δ ppm 1.03 (t, *J*=7.09 Hz, 3 H) 2.68 (dq, *J*=13.88, 6.79 Hz, 1 H) 3.06 - 3.27 (m, 2 H) 3.86 - 4.02 (m, 1 H) 4.54 - 4.72 (m, 2 H) 4.78 (t, *J*=4.65 Hz, 1 H) 6.64 - 6.79 (m, 1 H) 6.95 (d, *J*=8.31 Hz, 2 H) 7.03 - 7.17 (m, 2 H) 7.20 - 7.36 (m, 3 H) 10.33 (br. s., 1 H). Mass Spectrum (ESI) *m/z* = 408 (M+1).

EXAMPLE 46

2-((2R,5R,6R)-4-Allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid

¹H NMR (400 MHz, CDCl₃) δ ppm 2.90 - 3.12 (m, 3 H) 4.54 (t, *J*=5.87 Hz, 1 H) 4.63 - 4.75 (m, 2 H) 4.80 (d, *J*=4.40 Hz, 1 H) 4.99 (d, *J*=16.87 Hz, 1 H) 5.20 (d, *J*=10.03 Hz, 1 H) 5.63 - 5.75 (m, 1 H) 6.94 (d, *J*=7.58 Hz, 1 H) 7.01 (d, *J*=8.31 Hz, 2 H) 7.12 - 7.32 (m, 5 H) 9.15 (br. s., 1 H). Mass Spectrum (ESI) *m/z* = 420 (M+1).

EXAMPLE 47

2-((2S,5R,6R)-4-Allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetic acid

¹H NMR (400 MHz, CDCl₃) δ ppm 3.02 - 3.23 (m, 3 H) 4.55 - 4.75 (m, 3 H) 4.82 (t, *J*=4.77 Hz, 1 H) 4.93 (d, *J*=20 Hz, 1 H) 5.17 (d, *J*=10.27 Hz, 1 H) 5.58 - 5.79 (m, 1 H)

6.64 - 6.80 (m, 1 H) 6.92 (d, $J=8.31$ Hz, 2 H) 7.02 - 7.18 (m, 2 H) 7.20 - 7.37 (m, 3 H) 10.11 (br. s., 1 H). Mass Spectrum (ESI) $m/z = 420$ (M+1).

EXAMPLE 48

5 2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-propylmorpholin-2-yl)acetic acid

^1H NMR (400 MHz, CDCl_3) δ ppm 0.78 (t, $J=7.34$ Hz, 3 H) 1.43 - 1.56 (m, 2 H) 2.54 (ddd, $J=13.84, 8.85, 5.48$ Hz, 1 H) 2.90 (dd, $J=16.04, 7.24$ Hz, 1 H) 3.08 (dd, $J=16.24, 5.48$ Hz, 1 H) 3.83 (ddd, $J=13.55, 9.34, 7.04$ Hz, 1 H) 4.56 (dd, $J=6.94, 5.77$ Hz, 1 H) 4.67 (d, $J=4.89$ Hz, 1 H) 4.77 (d, $J=4.89$ Hz, 1 H) 6.93 - 7.04 (m, 3 H) 7.15 - 7.29 (m, 5 H). Mass Spectrum (ESI) $m/z = 422$ (M+1).

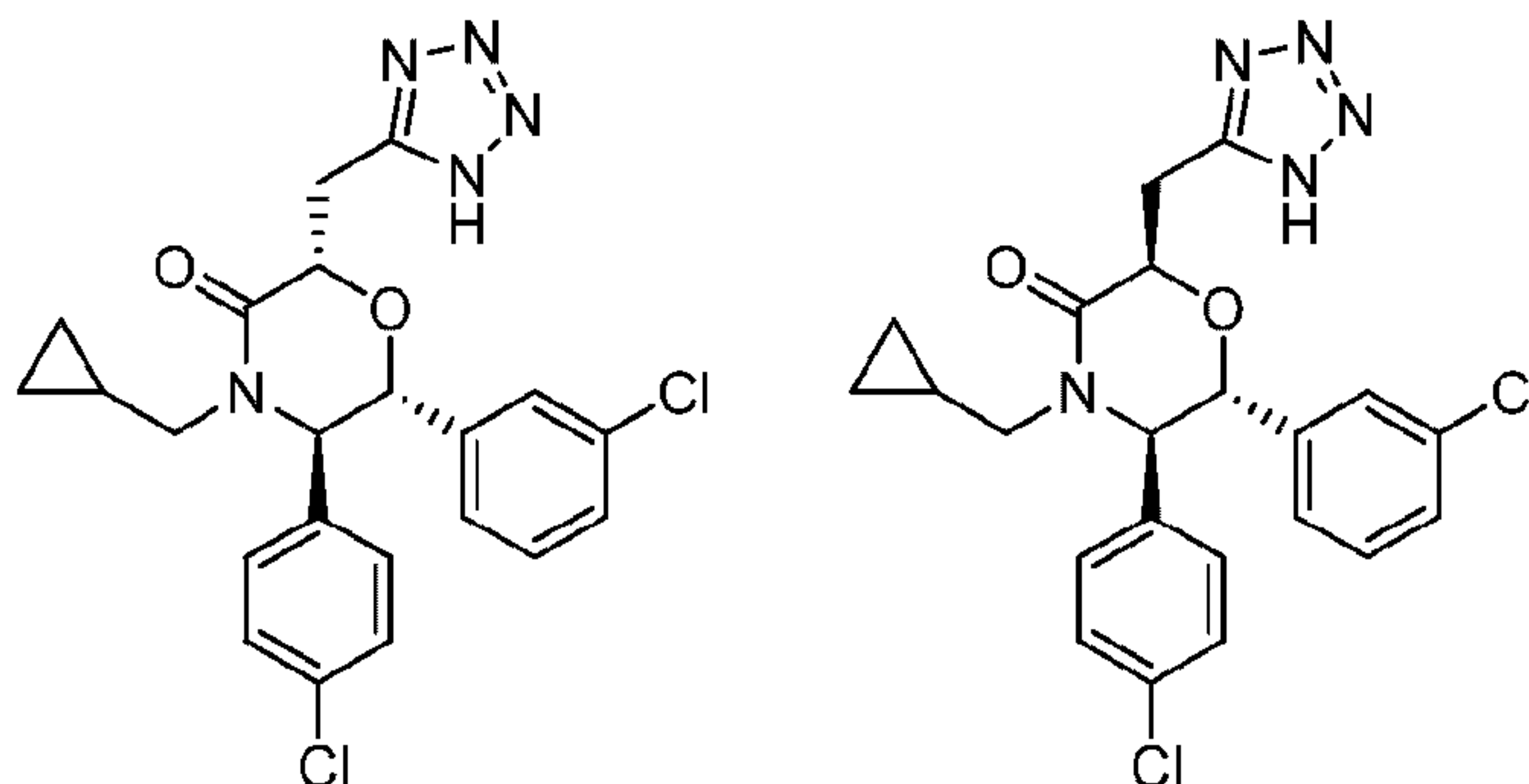
EXAMPLE 49

15 2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-propylmorpholin-2-yl)acetic acid

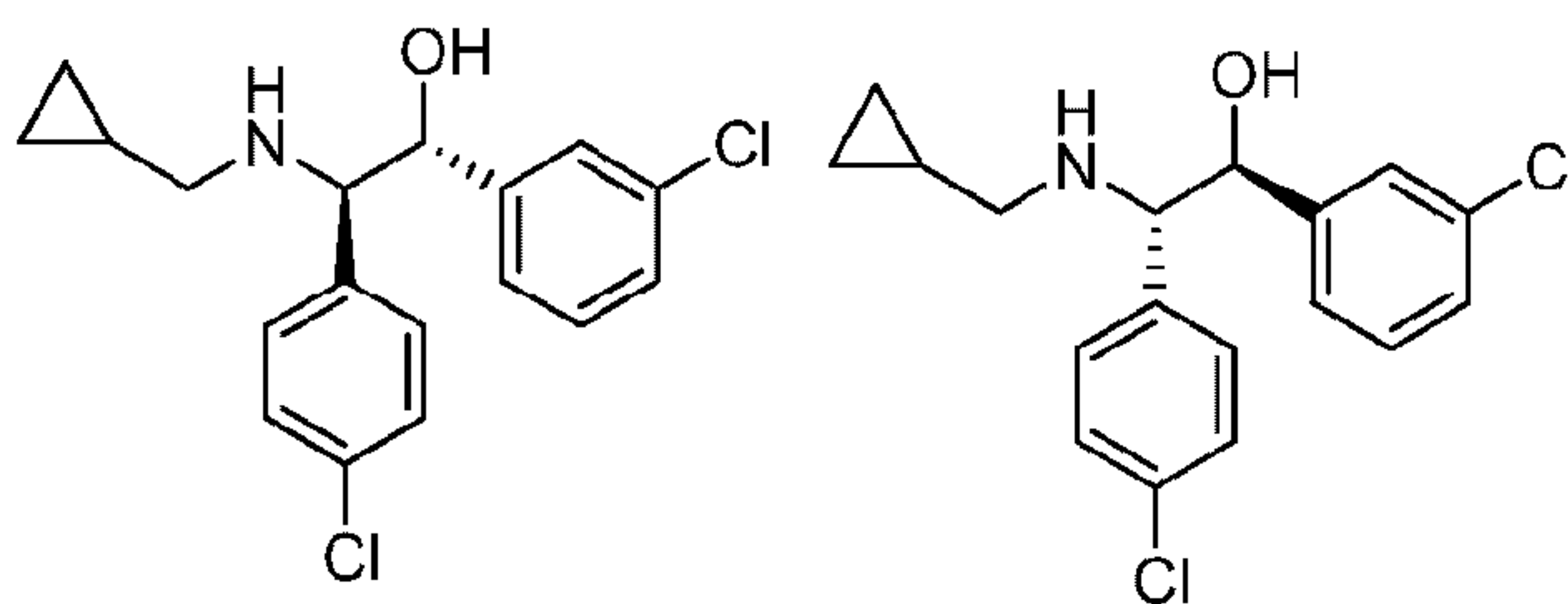
^1H NMR (400 MHz, CDCl_3) δ ppm 0.71 (t, $J=7.34$ Hz, 3 H) 1.28 - 1.47 (m, 2 H) 2.39 (ddd, $J=13.79, 8.90, 5.28$ Hz, 1 H) 3.03 (qd, $J=16.82, 5.28$ Hz, 2 H) 3.80 (ddd, $J=13.74, 9.15, 6.85$ Hz, 1 H) 4.44 - 4.57 (m, 2 H) 4.68 (t, $J=5.38$ Hz, 1 H) 6.63 (d, $J=7.63$ Hz, 1 H) 6.84 (d, $J=8.41$ Hz, 2 H) 6.94 - 7.10 (m, 2 H) 7.10 - 7.31 (m, 3 H). Mass Spectrum (ESI) $m/z = 422$ (M+1).

EXAMPLE 50

25 (2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-2-((tetrazol-5-yl)methyl)morpholin-3-one and (2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-2-((tetrazol-5-yl)methyl)morpholin-3-one



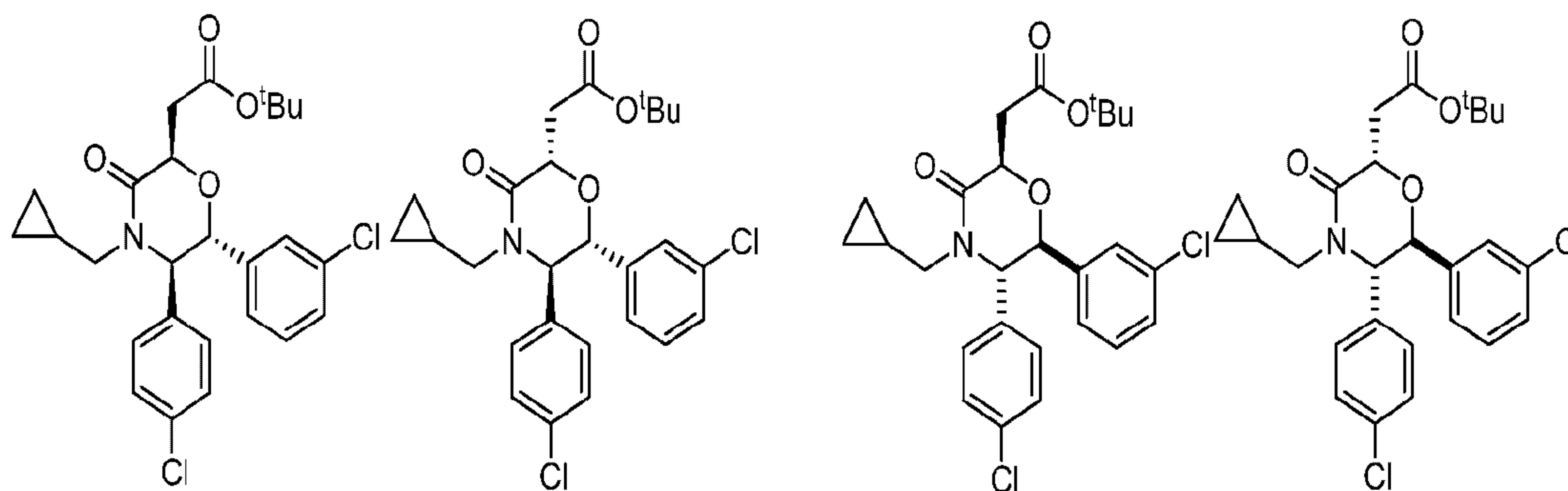
Step A. (1R,2R)-1-(3-Chlorophenyl)-2-(4-chlorophenyl)-2-
 (cyclopropylmethylamino)ethanol and (1S,2S)-1-(3-Chlorophenyl)-2-(4-chlorophenyl)-2-
 5 (cyclopropylmethylamino)ethanol



The title compounds were prepared from the racemic mixture of (1R,2R)-2-
 10 amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol and (1S,2S)-2-amino-1-(3-
 chlorophenyl)-2-(4-chlorophenyl)ethanol (Intermediate A1) using a procedure analogous
 to the one described in Example 9, Step B.

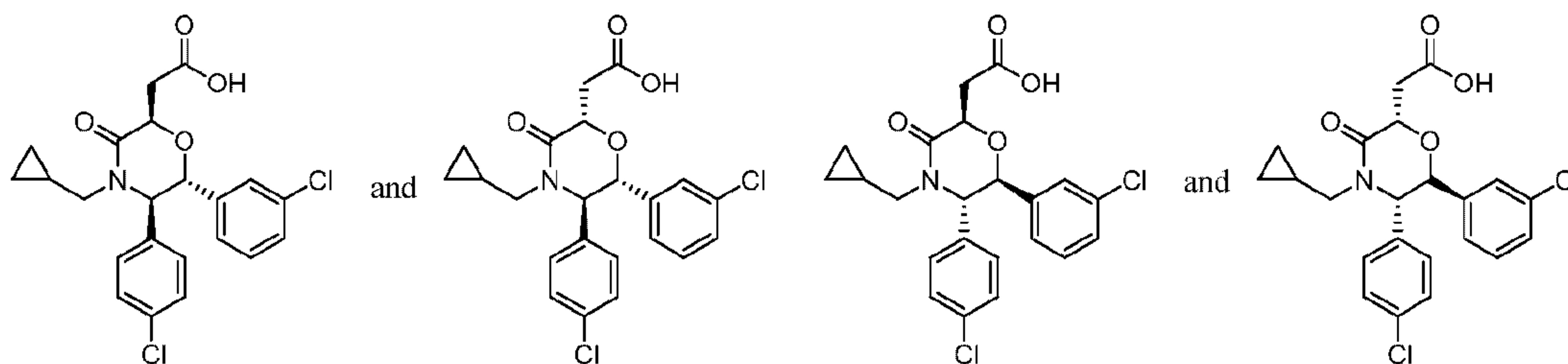
Step B. *tert*-Butyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-
 15 (cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and *tert*-Butyl 2-((2S,5R,6R)-6-(3-
 chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate
 and *tert*-Butyl 2-((2R,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-
 (cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and *tert*-Butyl 2-((2S,5S,6S)-6-(3-
 chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate

20



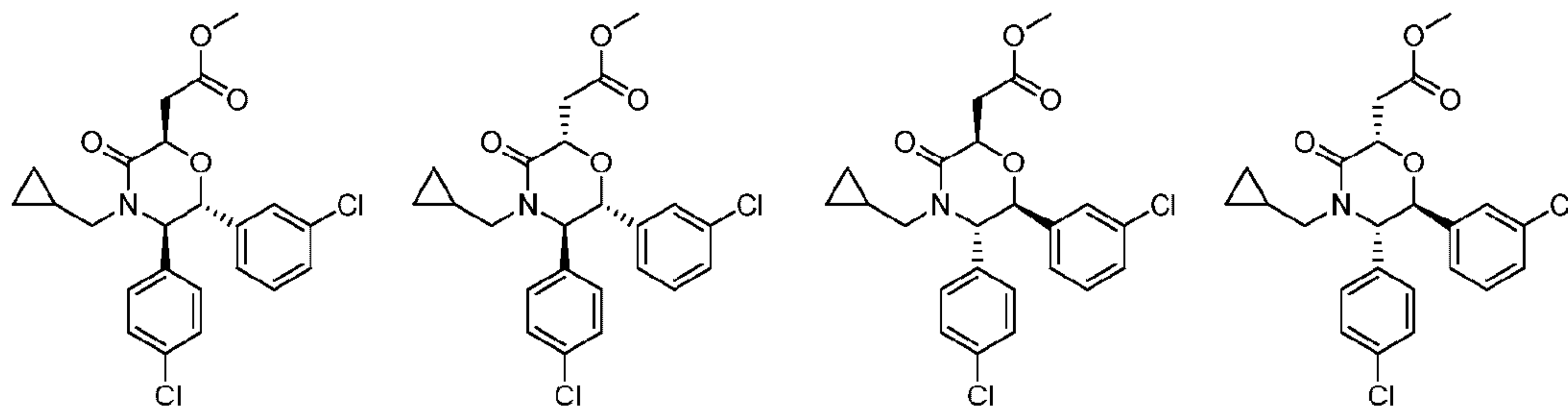
To a solution of (1R,2R)-1-(3-chlorophenyl)-2-(4-chlorophenyl)-2-(cyclopropylmethylamino)ethanol and (1S,2S)-1-(3-chlorophenyl)-2-(4-chlorophenyl)-2-(cyclopropylmethylamino)ethanol (82 mg, 0.244 mmol; Example 50, Step A) in THF (2 mL) at rt was added a dispersion of 60% sodium hydride in mineral oil (10 mg, 268 μ mol). Evolution of gas was observed and the reaction mixture turned light yellow in color. The reaction mixture was stirred at rt for 0.5 h. Then a solution of (S)-4-tert-butyl-1-methyl-2-bromosuccinate (65 mg, 0.244 mmol; Example 9, Step A) in THF (1 mL) was added dropwise over 5 min. The orange slurry was stirred at rt overnight. The mixture was quenched with water and extracted with EtOAc (3x). The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel (4 g column; eluent: 0 to 25% EtOAc in hexanes) to provide the title compounds

Step C. 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid and 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid and 2-((2R,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid and 2-((2S,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid



The title compounds were prepared from *tert*-Butyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate
 5 and *tert*-Butyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and *tert*-Butyl 2-((2R,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and *tert*-Butyl 2-((2S,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate (Example 46, step B) by a procedure
 10 analogous to the one described in Example 9, Step E.

Step D. Methyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and methyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate
 15 and methyl 2-((2S,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and methyl 2-((2R,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate

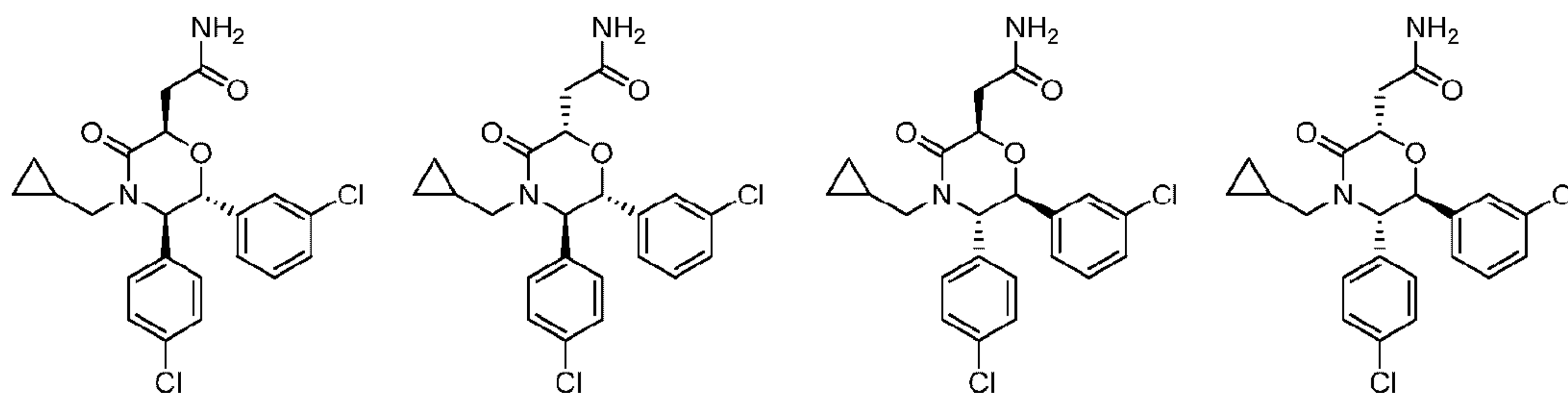


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To a solution of 2-((2S,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid and 2-((2R,5S,6S)-6-(3-

chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid and 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid and 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid (81 mg, 187 μ mol; Example 50, Step C) in 1 mL of MeOH and 2 mL of DCM at 0 °C was added (trimethylsilyl)diazomethane (2.0 M in diethyl ether (187 μ l, 373 μ mol)) dropwise. Evolution of gas was observed. The yellow reaction mixture was stirred at 0 °C for 15 min. The reaction mixture was warmed to rt and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 0 to 20% EtOAc in hexanes, gradient elution) to give the title compounds as a mixture of stereoisomers.

Step E. 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetamide and 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetamide and 2-((2R,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetamide and 2-((2S,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetamide

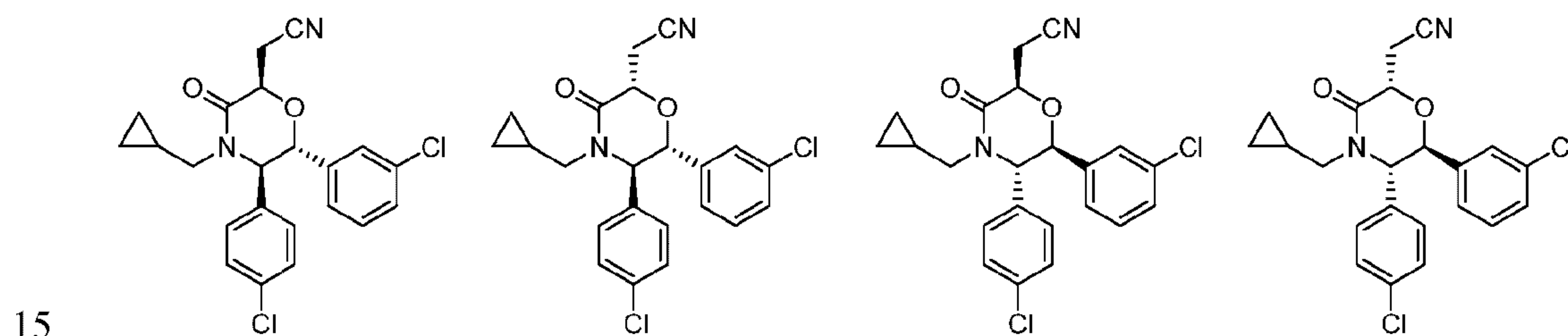


20

To a solution of methyl 2-((2S,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and methyl 2-((2R,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and methyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and methyl 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate (56 mg, 125 μ mol; Example 50, Step D) in 2M NH₃ in MeOH (1 mL) was added sodium

cyanide (0.61 mg, 12 μ mol). The reaction mixture was capped and heated to 50 °C for 7 h. The reaction mixture was cooled to rt and saturated with NH₃ (g) for 1 min. The reaction mixture was capped and heated to 50 °C for 16 h. Again, the reaction mixture was cooled to rt and saturated with NH₃ (g) for 1 min. This process was repeated (3x).
 5 Then the reaction was concentrated under reduced pressure and the crude product was used without further purification.

Step F. 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetonitrile and 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetonitrile and 2-
 10 ((2R,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetonitrile and 2-((2S,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetonitrile



To a solution of 2-((2S,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetamide and 2-((2R,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetamide and 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetamide and 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetamide (54 mg, 125 μ mol; Example 50, Step E) in THF (1 mL) at 0 °C was added triethylamine (87 μ l, 623 μ mol) followed by trifluoroacetic acid anhydride (44 μ l, 312 μ mol). The light orange reaction mixture was stirred at 0 °C for 90 min. The reaction mixture was quenched with 10% aq. citric acid solution and extracted with EtOAc (2 x). The organic layers were combined and washed with brine. The organic layers were dried

over Na₂SO₄ and concentrated under reduced pressure. The crude residue was used without further purification.

Step G. (2S,5R,6R)-2-((2H-Tetrazol-5-yl)methyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)morpholin-3-one and (2R,5R,6R)-2-((2H-Tetrazol-5-yl)methyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)morpholin-3-one

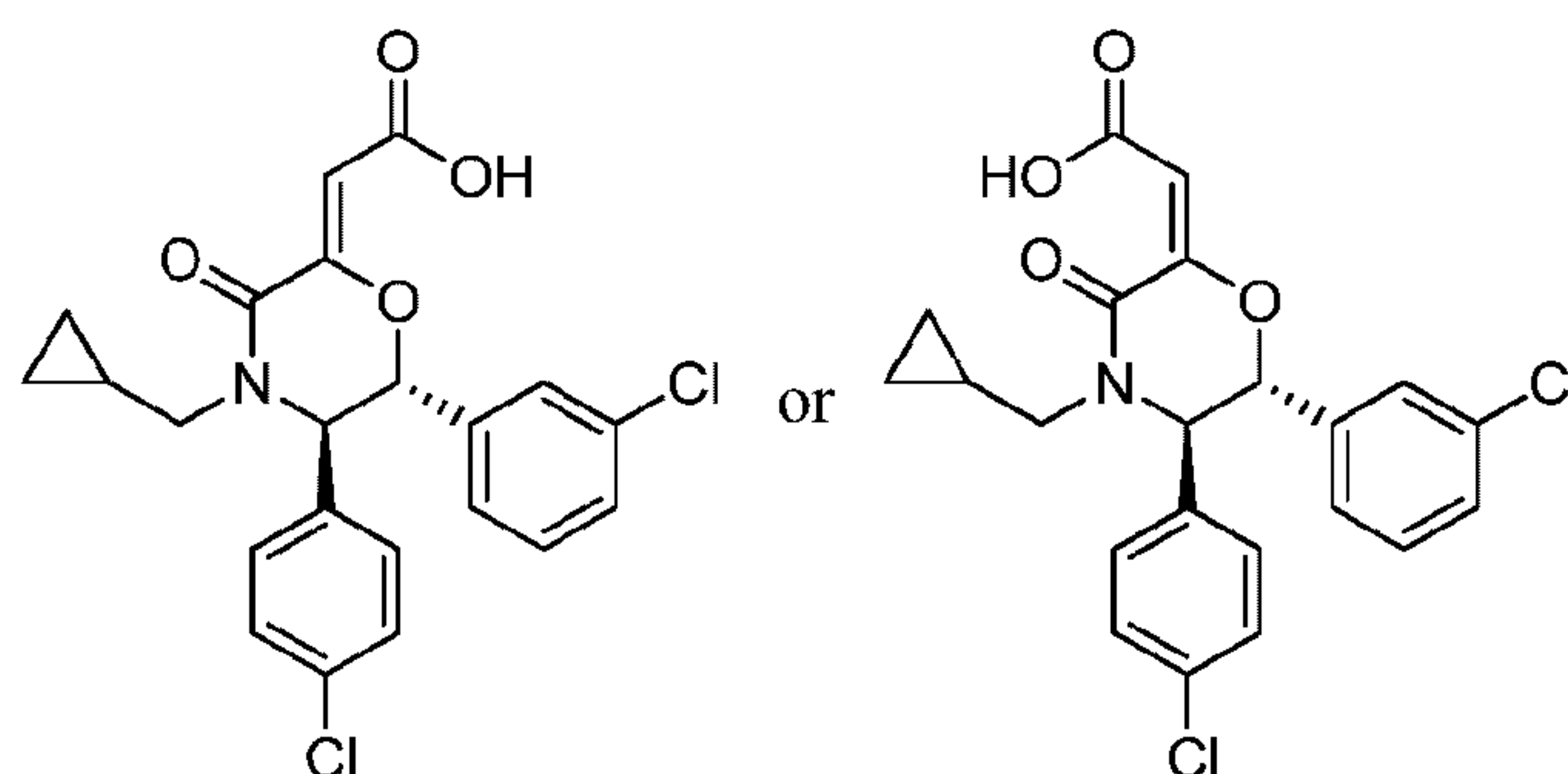
To a solution of 2-((2R,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetonitrile and 2-((2S,5S,6S)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetonitrile and 2-((2S,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetonitrile and 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetonitrile (21 mg, 51 μmol; Example 50, Step F) in dioxane (1 mL) at rt was added azidotributyltin (139 μl, 506 μmol). The reaction mixture was heated to 100 °C for 2 d, cooled to rt and diluted with 3 mL of 10 % aq. citric acid solution. The reaction mixture was stirred at rt for 10 min then extracted with EtOAc (3 x). The organic layers were combined, dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase preparatory HPLC (Gemini™ Prep C₁₈ 5 μm column; Phenomenex, Torrance, CA; eluent: (0 to 100% MeCN + 0.1% TFA) in (water + 0.1% TFA), gradient elution over 20 minutes). The residue was then purified on silica gel (eluent: EtOAc / hexanes / AcOH 7 : 3 : 0.1). Individual stereoisomers were separated by chiral SFC (flow rate: 12 mL/min; 250 x 30 mm Chiralpak® AD-H column (Chiral Technologies, Inc., West Chester, PA, USA) using methanol (0.2%DEA)/CO₂ as the eluent on a Thar 350 SFC, Thar Technologies, Inc., Pittsburg, PA). The enantiopure material obtained was then further purified by flash chromatography on silica gel (eluent: EtOAc / hexanes / AcOH 7 : 3 : 0.1) to give the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm -0.07 to -0.01 (m, 1 H), 0.00 - 0.10 (m, 1 H), 0.37 - 0.54 (m, 2 H), 0.69 - 0.80 (m, 1 H), 2.35 (dd, *J*=14.18, 7.34 Hz, 1 H), 3.61 - 3.77 (m, 2 H), 3.93 (dd, *J*=14.18, 6.75 Hz, 1 H), 4.61 (d, *J*=9.8 Hz, 1 H), 4.69 - 4.73 (m, 2 H), 6.76 (d, *J*=7.83 Hz, 1 H),

6.89 (d, $J=8.41$ Hz, 2 H), 7.09 (s, 1 H), 7.15 (t, $J=7.83$ Hz, 1 H), 7.24 - 7.33 (m, 3 H).

Mass Spectrum (ESI) $m/z = 458(M+1)$.

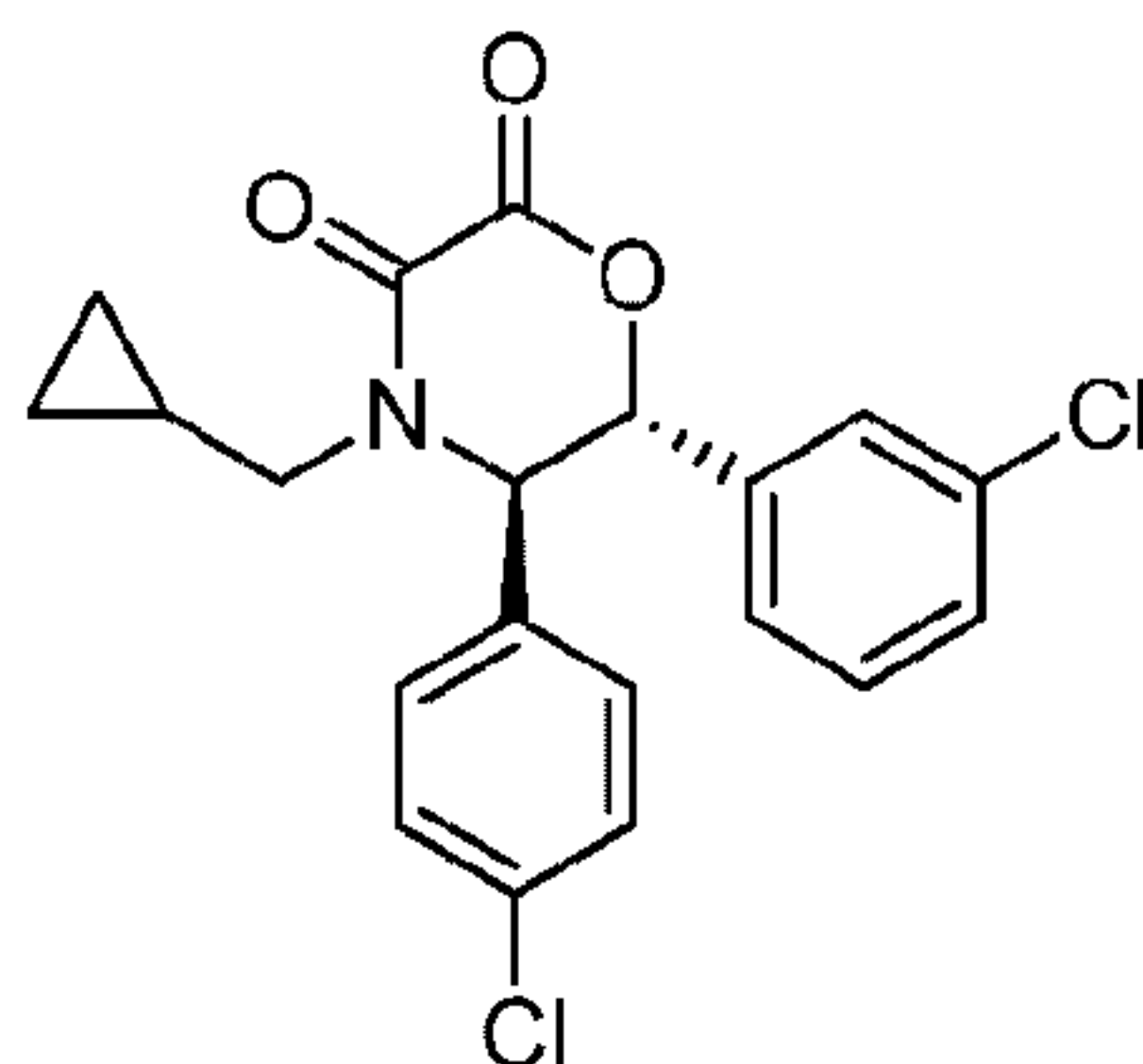
EXAMPLE 51

- 5 (Z)-2-((5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-ylidene)acetic acid or (E)-2-((5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-ylidene)acetic acid (Isomer 1)



10

Step A. (5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)morpholine-2,3-dione



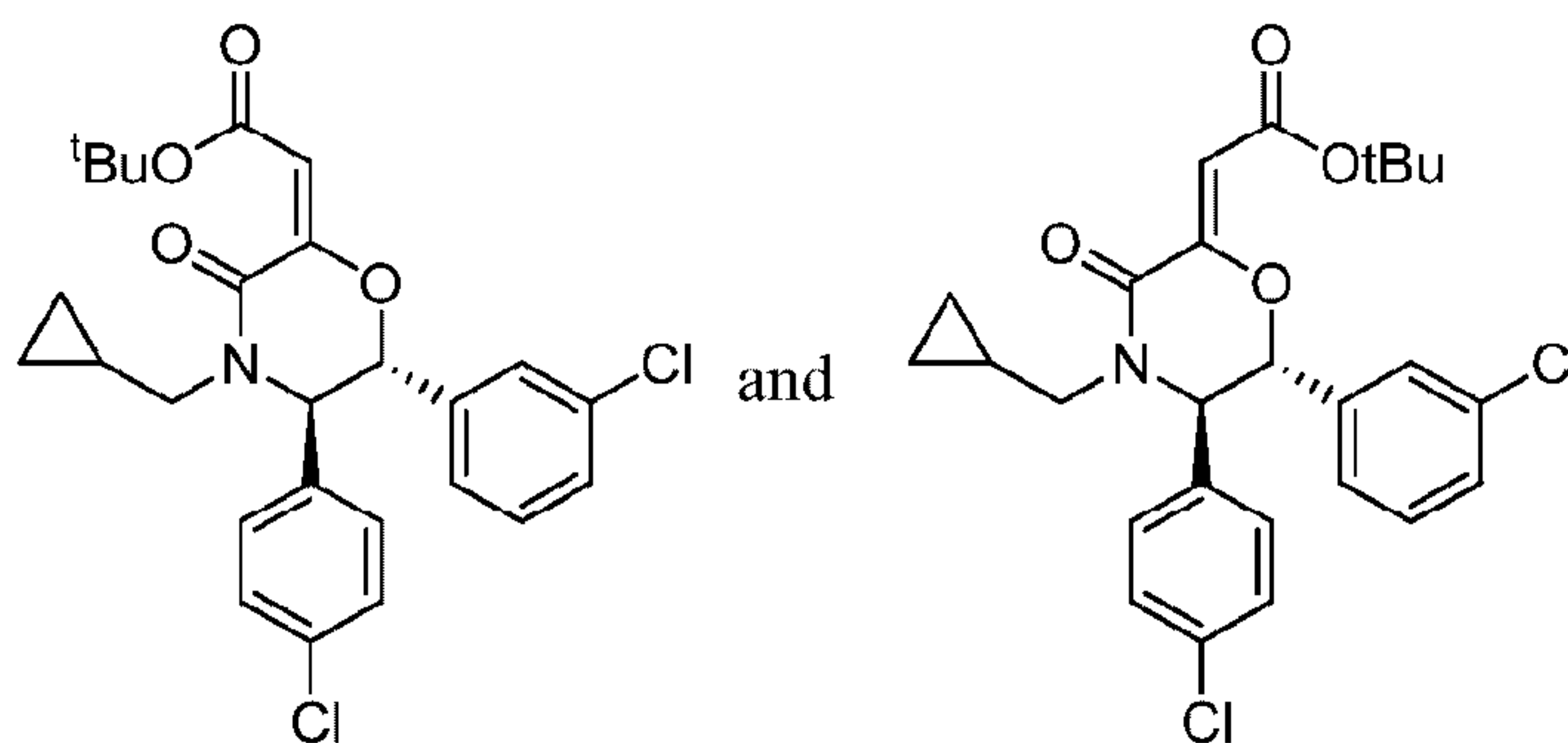
15

(1R,2R)-1-(3-chlorophenyl)-2-(4-chlorophenyl)-2-(cyclopropylmethylamino)ethanol (146 mg, 434 μmol ; Example 9 step B) was dissolved in benzene (8684 μl , 434 μmol) then oxalyl chloride (110 μl , 1303 μmol) was added, followed by pyridine (106 μl , 1303 μmol). The reaction was stirred for 2 h. Then the reaction mixture was concentrated under reduced pressure. The residue was dissolved in DMF/MeOH and purified by reverse phase preparatory HPLC (GeminiTM Prep C18 5 μm column; Phenomenex, Torrance, CA; eluent: (0 to 100%

20

MeCN in water, both containing 0.1% TFA, gradient elution over 20 minutes). The fractions containing the desired product were combined and concentrated to afford the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃) δ -0.07 (dt, *J* = 9.68, 4.94 Hz, 0 H), 0.01 (dq, *J* = 9.56, 4.77 Hz, 0 H), 0.15 - 0.24 (m, 1 H), 0.32 (s, 1 H), 0.53 (ddd, *J* = 12.23, 7.43, 4.60 Hz, 0 H), 2.59 (dd, *J* = 14.18, 7.53 Hz, 0 H), 5.01 (d, *J* = 3.91 Hz, 1 H), 5.49 (d, *J* = 3.72 Hz, 1 H), 6.98 - 7.12 (m, 3 H), 7.18 - 7.39 (m, 5 H). Mass Spectrum (ESI) *m/z* = 390.1 (*M*+1).

Step B. (*E*)-*tert*-Butyl 2-((5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-ylidene)acetate and (*Z*)-*tert*-Butyl 2-((5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-ylidene)acetate



15 (5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)morpholine-2,3-dione (50 mg, 129 μ mol; Example 51, step A) was dissolved in 1 mL of DCM, then (tert-butoxycarbonylmethylene)triphenylphosphorane (68 mg, 181 μ mol) was added. After
20 2 d the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (eluent: linear gradient of 5% to 100% EtOAc / hexanes). The fractions containing the desired product were combined and concentrated to afford a mixture of the title compounds.

Step C. (Z)-2-((5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-ylidene)acetic acid or (E)-2-((5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-ylidene)acetic acid (Isomer 1)

5

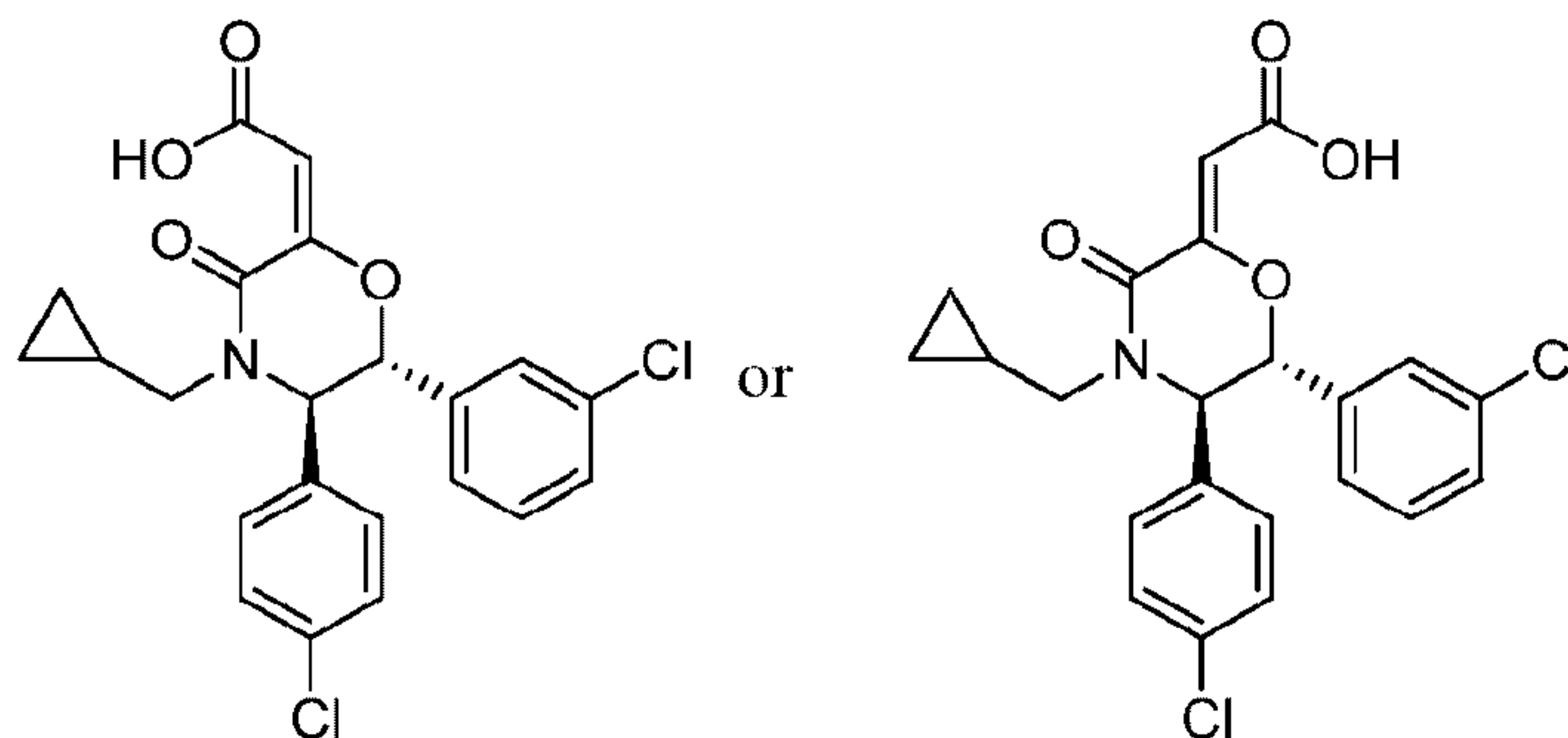
To a solution of (E) and (Z)-tert-butyl 2-((5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-ylidene)acetate (10 mg, 20 μ mol; Example 51, Step B) in 1 mL of DCM was added 0.5 mL of TFA. After 2 h the reaction mixture was concentrated. The residue was dissolved in DMF and
10 purified by reverse phase preparatory HPLC (GeminiTM Prep C₁₈ 5 μ m column; Phenomenex, Torrance, CA; eluent: (0 to 100% MeCN in water, both containing 0.1% TFA, gradient elution over 20 minutes). The fractions containing the desired product were combined and concentrated to afford one of the title compounds as the first eluting isomer. ¹H NMR (400 MHz, CDCl₃) δ -0.08 - 0.03 (m, 1 H), 0.04 - 0.15
15 (m, 1 H), 0.24 - 0.33 (m, 1 H), 0.38 - 0.48 (m, 1 H), 0.60 - 0.72 (m, 1 H), 2.54 (dd, *J* = 14.28, 7.63 Hz, 1 H), 3.85 (dd, *J* = 14.09, 7.24 Hz, 1 H), 5.06 (d, *J* = 3.52 Hz, 1 H), 5.33 (d, *J* = 3.33 Hz, 1 H), 6.33 (s, 1 H), 7.03 - 7.39 (m, 8 H). Mass Spectrum (ESI) *m/z* = 432.1 (M+1).

20

EXAMPLE 52

(E)-2-((5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-ylidene)acetic acid or (Z)-2-((5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-ylidene)acetic acid (Isomer 2)

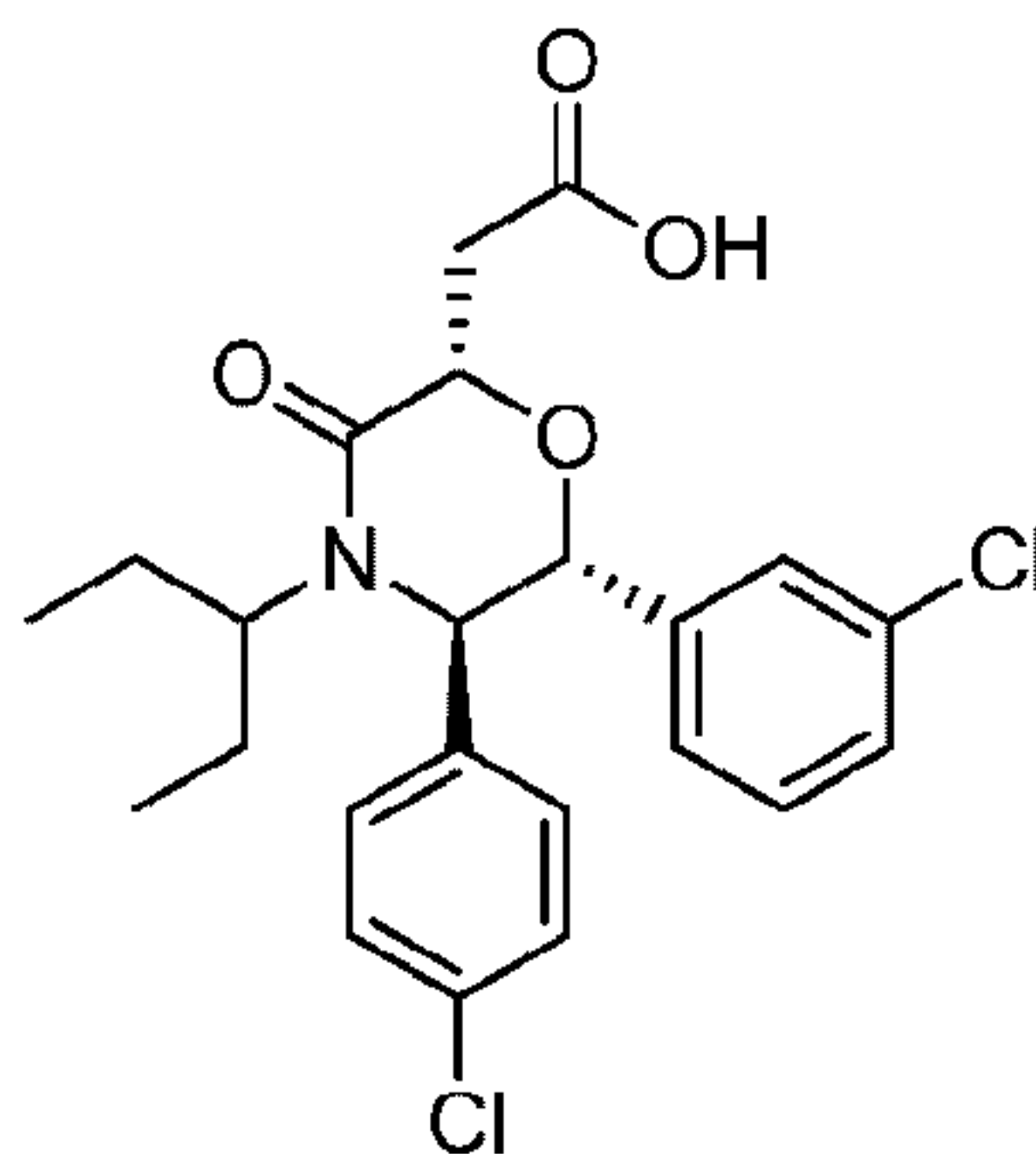
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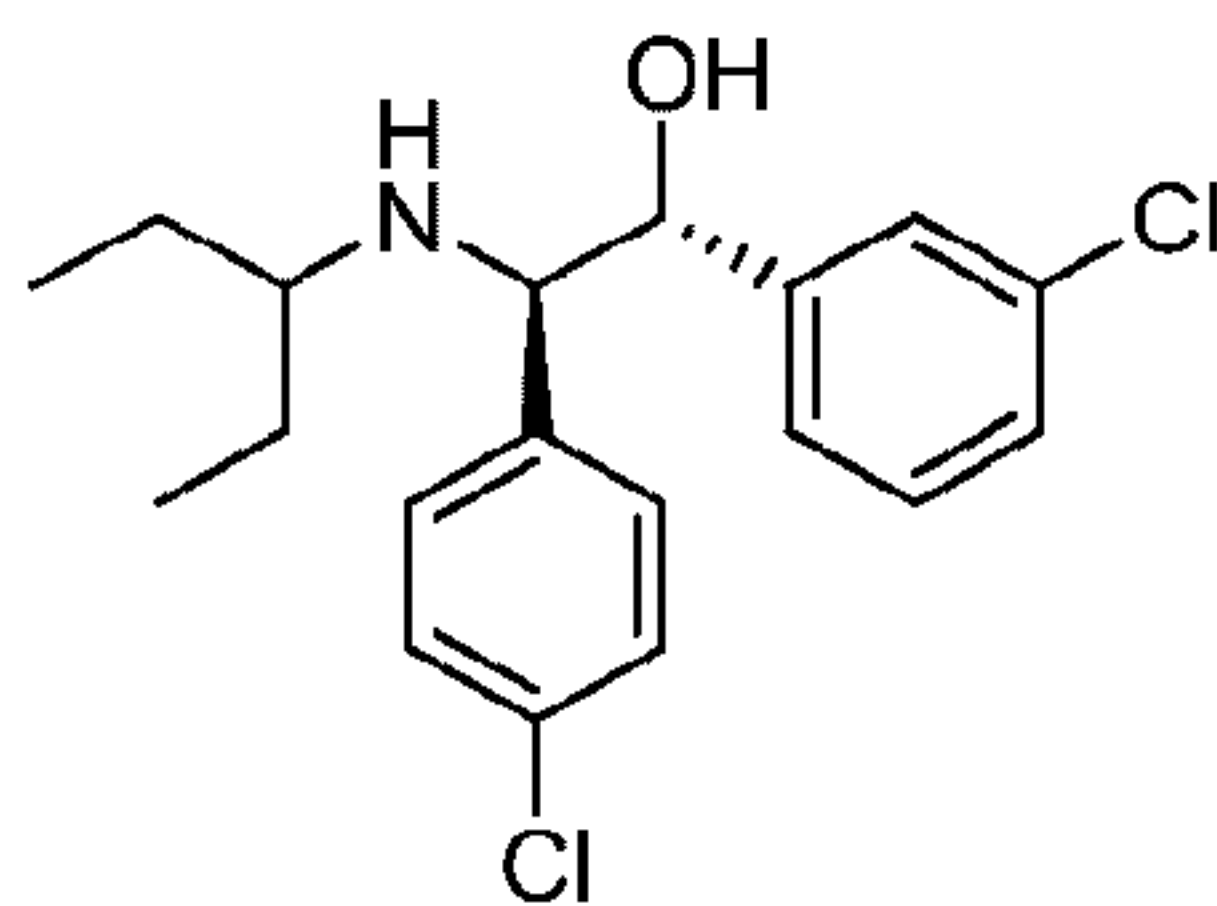
One of the title compounds was obtained as the second (slower) eluting isomer from Example 51, Step C. ¹H NMR (400 MHz, CDCl₃) δ -0.13 - 0.07 (m, 2 H), 0.20 - 0.44 (m, 2 H), 0.57 - 0.77 (m, 1 H), 2.48 (dd, *J* = 14.08, 7.63 Hz, 1 H), 3.78 (dd, *J* = 14.18, 6.75 Hz, 1 H), 4.85 (s, 1 H), 4.98 (d, *J* = 5.28 Hz, 1 H), 5.98 (s, 1 H), 6.81 - 6.98 (m, 2 H), 7.04 - 7.32 (m, 6 H). Mass Spectrum (ESI) *m/z* = 432.1 (*M*+1).

EXAMPLE 53

2-((2*S*,5*R*,6*R*)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-(pentan-3-yl)morpholin-2-yl)acetic acid



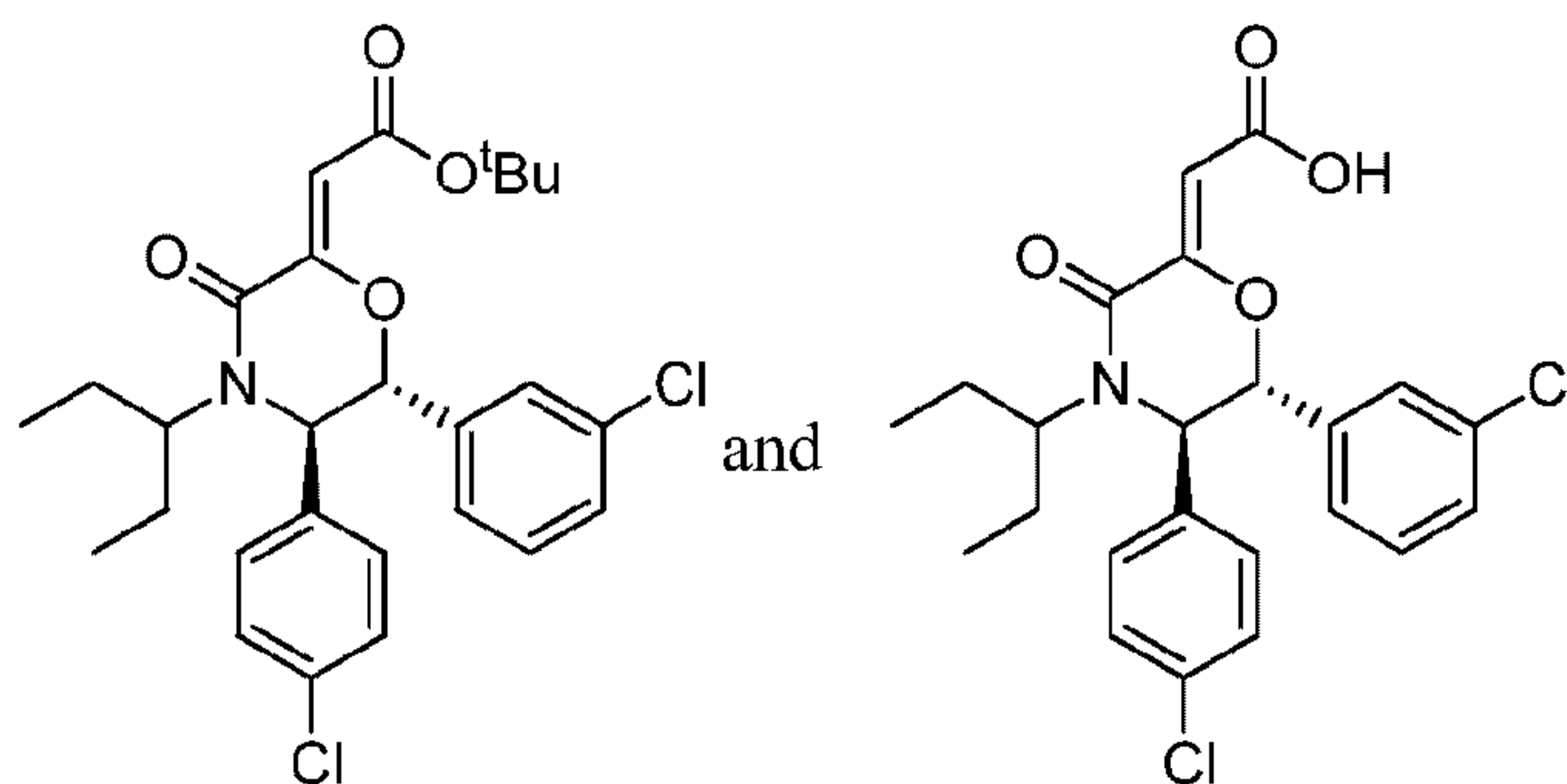
Step A. (1*R*,2*R*)-1-(3-Chlorophenyl)-2-(4-chlorophenyl)-2-(pentan-3-ylamino)ethanol



The title compound was prepared as described in Example 9, Step B, substituting cyclopropanecarboxaldehyde with pentan-3-one.

5

Step B. *tert*-Butyl 2-((5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-(pentan-3-yl)morpholin-2-ylidene)acetate and (Z)-2-((5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-(pentan-3-yl)morpholin-2-ylidene)acetic acid



10

The title compound was obtained from (1R,2R)-1-(3-chlorophenyl)-2-(4-chlorophenyl)-2-(pentan-3-ylamino)ethanol (Example 53, Step A) by a procedure analogous to the one described in Example 51, Step A. Purification by chromatography on silica gel (eluent: 5 to 95% EtOAc in hexanes, gradient elution) provided a mixture of the title compounds. Mass Spectrum (ESI) $m/z = 504$ ($M+1$, t butyl ester) and $m/z = 448$ ($M+1$, acid).

15

Step C. 2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-(pentan-3-yl)morpholin-2-yl)acetic acid

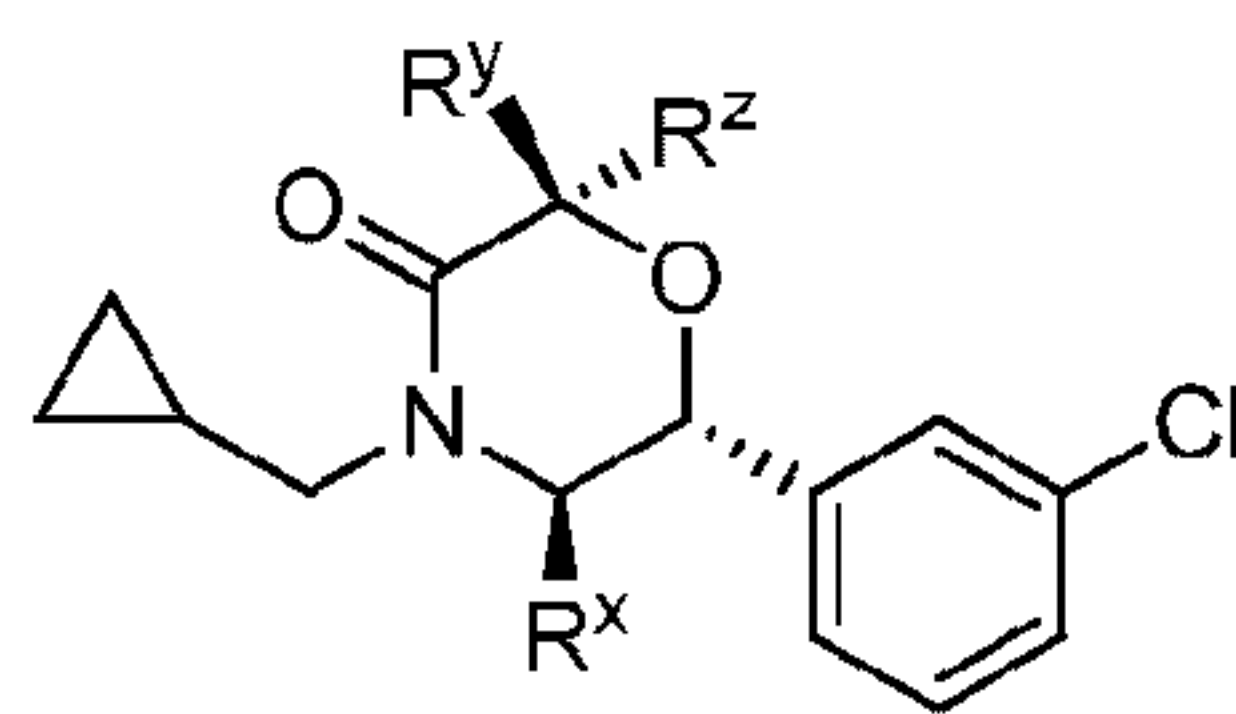
20

To a solution of 620 mg (1.23 mmol) of *tert*-butyl 2-((5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxo-4-(pentan-3-yl)morpholin-2-ylidene)acetate in 10mL of methanol was added 70mg of PtO₂. The reaction vessel was purged with hydrogen (g) and the reaction mixture was stirred under an atmosphere of H₂. After 24h the reaction mixture was filtered through a 0.45 μm PTFE membrane and then concentrated under reduced pressure. To the residue was added 3 mL DCM followed by 1.0 mL TFA. The reaction was then stirred at room temperature for one hour and concentrated under reduced pressure. The residue was purified by HPLC (Gemini™ Prep C₁₈ 5 μm column; Phenomenex, Torrance, CA; 5 to 95% CH₃CN (0.1% TFA) : H₂O (0.1% TFA) gradient) to give the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.66 (t, *J*=7.53 Hz, 3 H) 0.88 - 0.97 (m, 3 H) 1.36 - 1.46 (m, 1 H) 1.57 - 1.66 (m, 1 H) 1.75 - 1.92 (m, 2 H) 2.94 - 3.03 (m, 2 H) 3.19 (dd, *J*=16.14, 6.94 Hz, 1 H) 4.46 (d, *J*=9.59 Hz, 1 H) 4.66 (d, *J*=9.59 Hz, 1 H) 4.74 (dd, *J*=6.85, 4.70 Hz, 1 H) 6.70 (d, *J*=7.63 Hz, 1 H) 7.01 - 7.15 (m, 4 H) 7.23 - 7.34 (m, 3 H). Mass Spectrum (ESI) *m/z* = 450 (M+1).

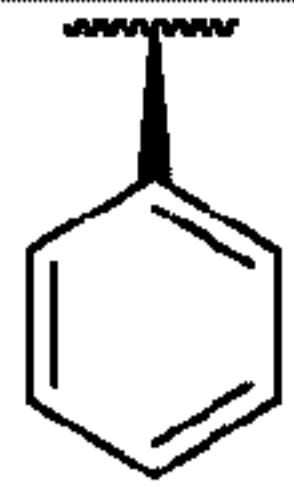
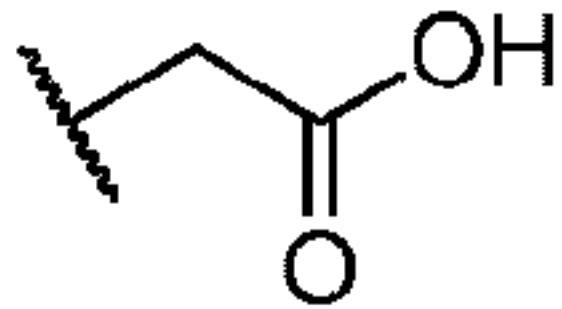
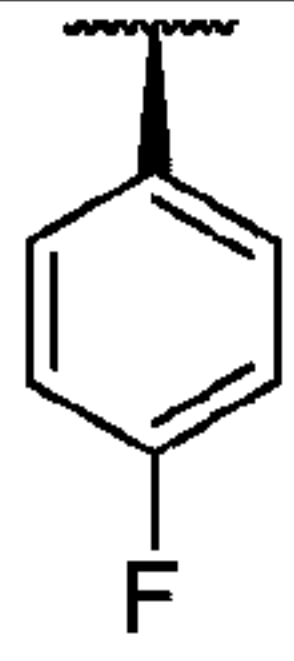
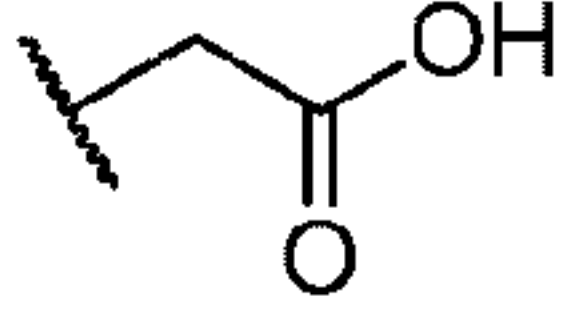
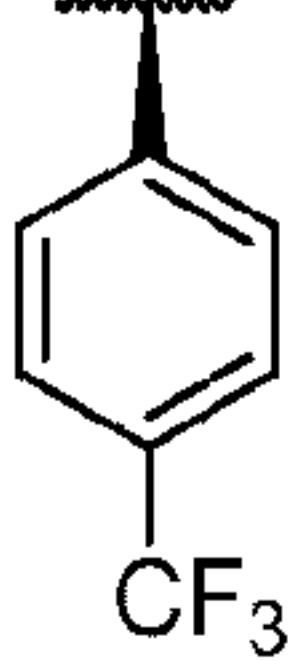
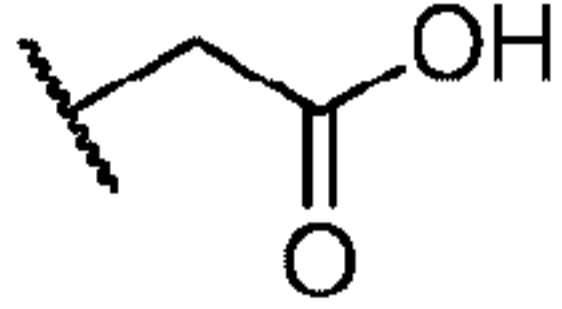
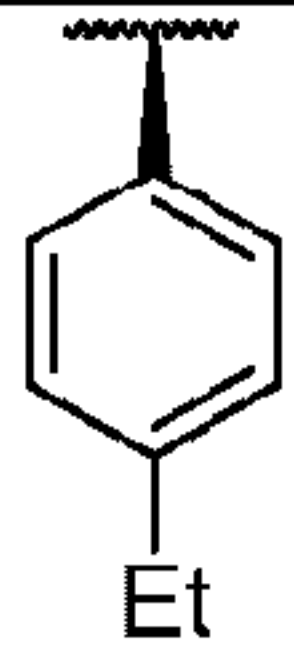
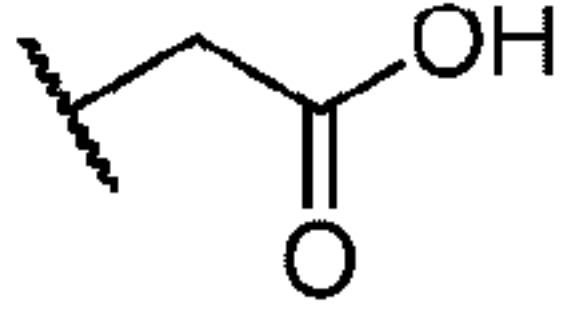
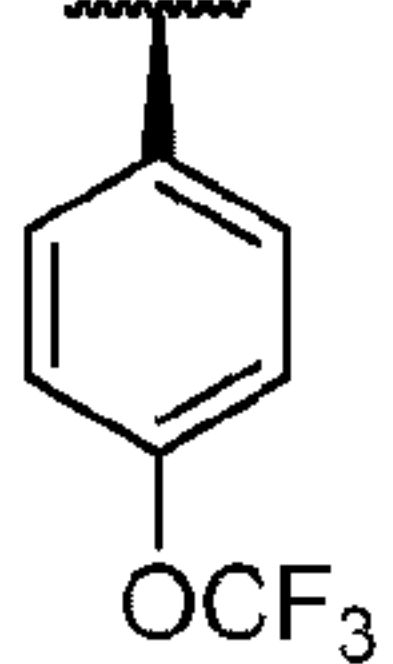
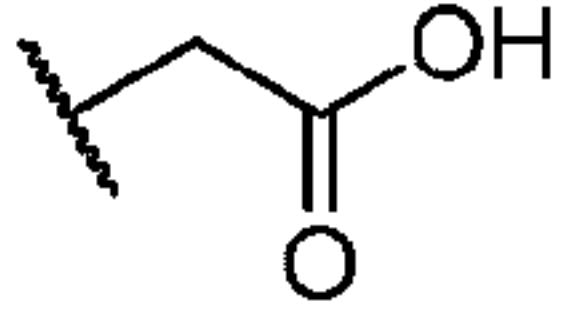
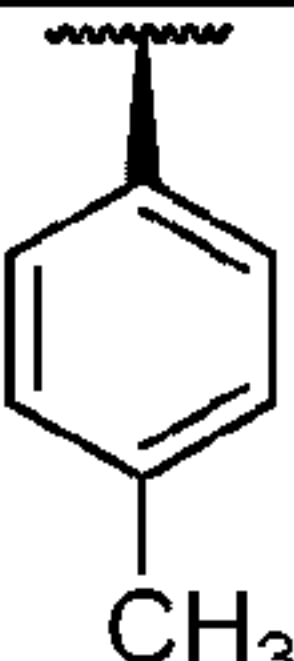
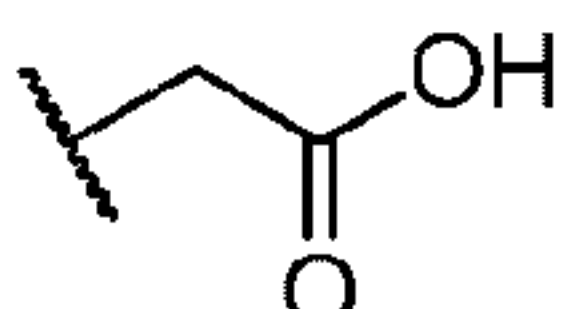
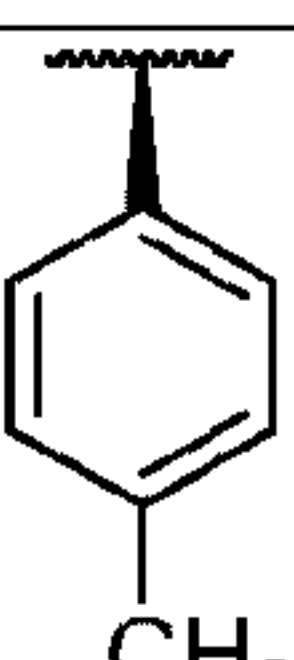
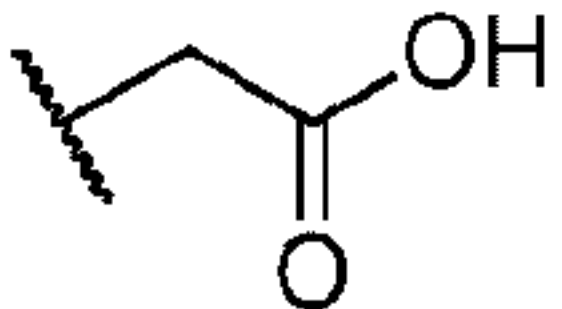
15

Examples 54 to 61 were also prepared by a procedure analogous to the one described in Example 9, Step B and Example 53, replacing (1R,2R)-2-amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol (Intermediate A2) with the designated intermediates.

20



Example	R ^x	R ^y	R ^z	Intermediate used
54		H		B1

55		H		B2
56		H		B3
57		H		B4
58		H		B5
59		H		B6
60		H		B7
61			H	B7

EXAMPLE 54

2-((2S,5R,6R)-5-(4-Chloro-2-fluorophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

5

¹H NMR (400 MHz, CDCl₃) δ ppm 0.03 - 0.09 (m, 2 H) 0.47 (dd, *J*=17.85, 8.07 Hz, 2 H) 0.85 (t, *J*=7.34 Hz, 1 H) 2.34 (dd, *J*=14.67, 7.34 Hz, 1 H) 3.06 - 3.20 (m, 2 H) 3.98 (dd,

$J=14.43$, 6.60 Hz, 1 H) 4.70 (d, $J=9.78$ Hz, 1 H) 4.75 (t, $J=5.14$ Hz, 1 H) 5.10 (d, $J=9.29$ Hz, 1 H) 6.83 (d, $J=7.82$ Hz, 1 H) 7.00 (dd, $J=9.78$, 1.96 Hz, 1 H) 7.06 - 7.19 (m, 4 H) 7.25 (s, 1 H) 7.27 (s, 1 H). Mass Spectrum (CI^+) $m/z = 452.0$ (M+1), 926.2 (2M+23).

5

EXAMPLE 55

2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-phenylmorpholin-2-yl)acetic acid

^1H NMR (400 MHz, CDCl_3) δ ppm -0.06 - 0.11 (m, 2 H) 0.34 - 0.53 (m, 2 H) 0.87 (d, $J=7.34$ Hz, 1 H) 1.04 - 1.21 (m, 1 H) 1.06 - 1.21 (m, 1 H) 1.21 - 1.30 (m, 1 H) 1.36 (t, $J=6.85$ Hz, 2 H) 1.59 (d, $J=10.27$ Hz, 1 H) 1.76 (d, $J=7.34$ Hz, 1 H) 2.28 - 2.40 (m, 1 H) 3.06 (dd, $J=16.38$, 5.14 Hz, 2 H) 3.11 - 3.24 (m, 2 H) 3.98 (dd, $J=14.18$, 6.36 Hz, 1 H) 4.60 - 4.77 (m, 2 H) 4.79 (t, $J=5.38$ Hz, 1 H) 6.72 (d, $J=7.83$ Hz, 1 H) 6.96 (d, $J=7.83$ Hz, 2 H) 7.02 (s, 1 H) 7.09 (t, $J=7.83$ Hz, 1 H) 7.21 (d, $J=7.82$ Hz, 1 H) 7.25 - 7.34 (m, 4 H) 7.74 (br. s., 1 H). Mass Spectrum (CI^+) $m/z = 400.1$ (M+1), 823.3 (2M+23).

15

EXAMPLE 56

2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(4-fluorophenyl)-3-oxomorpholin-2-yl)acetic acid

^1H NMR (400 MHz, CDCl_3) δ ppm -0.07 - 0.06 (m, 2 H) 0.34 - 0.48 (m, 2 H) 0.79 - 0.89 (m, 1 H) 1.13 (t, $J=7.09$ Hz, 1 H) 1.24 (d, $J=7.34$ Hz, 1 H) 2.28 (dd, $J=14.18$, 7.34 Hz, 1 H) 2.93 - 3.03 (m, 1 H) 3.07 - 3.16 (m, 1 H) 3.96 (dd, $J=14.18$, 6.36 Hz, 1 H) 4.59 (d, $J=9.78$ Hz, 1 H) 4.72 (d, $J=9.29$ Hz, 1 H) 4.79 (t, $J=5.38$ Hz, 1 H) 6.69 (d, $J=7.83$ Hz, 1 H) 6.89 - 7.02 (m, 4 H) 7.03 - 7.11 (m, 2 H) 7.20 (d, 1 H). Mass Spectrum (CI^+) $m/z = 418.1$ (M+1), 859.2 (2M+23).

25

EXAMPLE 57

2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(4-(trifluoromethyl)phenyl)morpholin-2-yl)acetic acid

30

1H NMR (400 MHz, CDCl₃) δ ppm -0.03 (br. s., 2 H) 0.32 - 0.47 (m, 2 H) 0.79 - 0.94 (m, 2 H) 2.21 (dd, $J=12.47$, 7.09 Hz, 1 H) 2.89 (dd, $J=13.69$, 1.96 Hz, 1 H) 2.98 - 3.13 (m, 1 H) 3.94 - 4.05 (m, 1 H) 4.13 (q, 1 H) 4.61 (d, $J=10.27$ Hz, 1 H) 4.79 (d, $J=9.78$ Hz, 1 H) 4.89 (br. s., 1 H) 6.64 (d, $J=7.34$ Hz, 1 H) 7.00 - 7.13 (m, 3 H) 7.19 (d, $J=7.83$ Hz, 1 H) 7.53 (d, $J=7.83$ Hz, 2 H). Mass Spectrum (CI⁺) m/z = 468.1 (M+1), 959.3 (2M+23).

EXAMPLE 58

2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(4-ethylphenyl)-3-oxomorpholin-2-yl)acetic acid

10

¹H NMR (400 MHz, CDCl₃) δ ppm -0.05 - 0.11 (m, 2 H) 0.31 - 0.50 (m, 2 H) 0.82 - 0.93 (m, 1 H) 1.14 (t, $J=7.34$ Hz, 1 H) 1.19 - 1.26 (m, 3 H) 2.34 (dd, $J=14.18$, 7.34 Hz, 1 H) 2.63 (q, $J=7.83$ Hz, 2 H) 2.82 (q, $J=7.34$ Hz, 1 H) 2.94 (dd, $J=16.14$, 5.38 Hz, 1 H) 3.14 (dd, $J=16.14$, 5.87 Hz, 1 H) 3.96 (dd, $J=13.94$, 6.60 Hz, 1 H) 4.59 - 4.72 (m, 2 H) 4.81 (t, $J=5.62$ Hz, 1 H) 6.74 (d, $J=7.34$ Hz, 1 H) 6.86 (d, $J=7.82$ Hz, 2 H) 6.99 (s, 1 H) 7.07 - 7.13 (m, 2 H) 7.19 (d, 1 H). Mass Spectrum (CI⁺) m/z = 428.2 (M+1), 879.3 (2M+23).

15

EXAMPLE 59

2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(4-(trifluoromethoxy)phenyl)morpholin-2-yl)acetic acid

20

¹H NMR (400 MHz, CDCl₃) δ ppm -0.03 - 0.06 (m, 2 H) 0.35 - 0.51 (m, 2 H) 0.86 (dd, $J=13.69$, 6.85 Hz, 1 H) 1.16 (t, $J=7.34$ Hz, 2 H) 2.31 (dd, $J=14.18$, 7.34 Hz, 1 H) 2.83 (q, $J=7.01$ Hz, 1 H) 2.93 (dd, $J=16.14$, 5.87 Hz, 1 H) 3.06 - 3.18 (m, 1 H) 3.98 (dd, $J=14.18$, 6.36 Hz, 1 H) 4.59 (d, $J=9.78$ Hz, 1 H) 4.76 (d, $J=9.78$ Hz, 1 H) 4.82 (t, $J=5.62$ Hz, 1 H) 6.69 (d, $J=7.83$ Hz, 1 H) 7.00 (d, $J=8.80$ Hz, 2 H) 7.03 - 7.07 (m, 1 H) 7.05 - 7.10 (m, 1 H) 7.14 (d, $J=7.82$ Hz, 2 H) 7.22 (d, 1 H). Mass Spectrum (CI⁺) m/z = 484.1 (M+1), 991.2 (2M+23).

25

30

EXAMPLE 60

2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(p-tolyl)morpholin-2-yl)acetic acid

- 5 ¹H NMR (400 MHz, CDCl₃) δ ppm -0.08 - 0.11 (m, 2 H) 0.31 - 0.51 (m, 2 H) 0.78 - 0.94 (m, 1 H) 1.13 (t, *J*=7.34 Hz, 1 H) 1.21 - 1.32 (m, 1 H) 2.26 - 2.41 (m, 4 H) 2.81 (q, *J*=7.34 Hz, 1 H) 2.96 (dd, *J*=16.14, 5.38 Hz, 1 H) 3.14 (dd, *J*=16.14, 5.87 Hz, 1 H) 3.96 (dd, *J*=14.18, 6.36 Hz, 1 H) 4.58 - 4.74 (m, 2 H) 4.80 (t, *J*=5.38 Hz, 1 H) 6.72 (d, *J*=7.83 Hz, 1 H) 6.84 (d, *J*=7.82 Hz, 2 H) 6.98 - 7.13 (m, 2 H) 7.16 - 7.24 (m, 1 H). Mass
10 Spectrum (Cl⁺) *m/z* = 414.1 (M+1), 851.2 (2M+23).

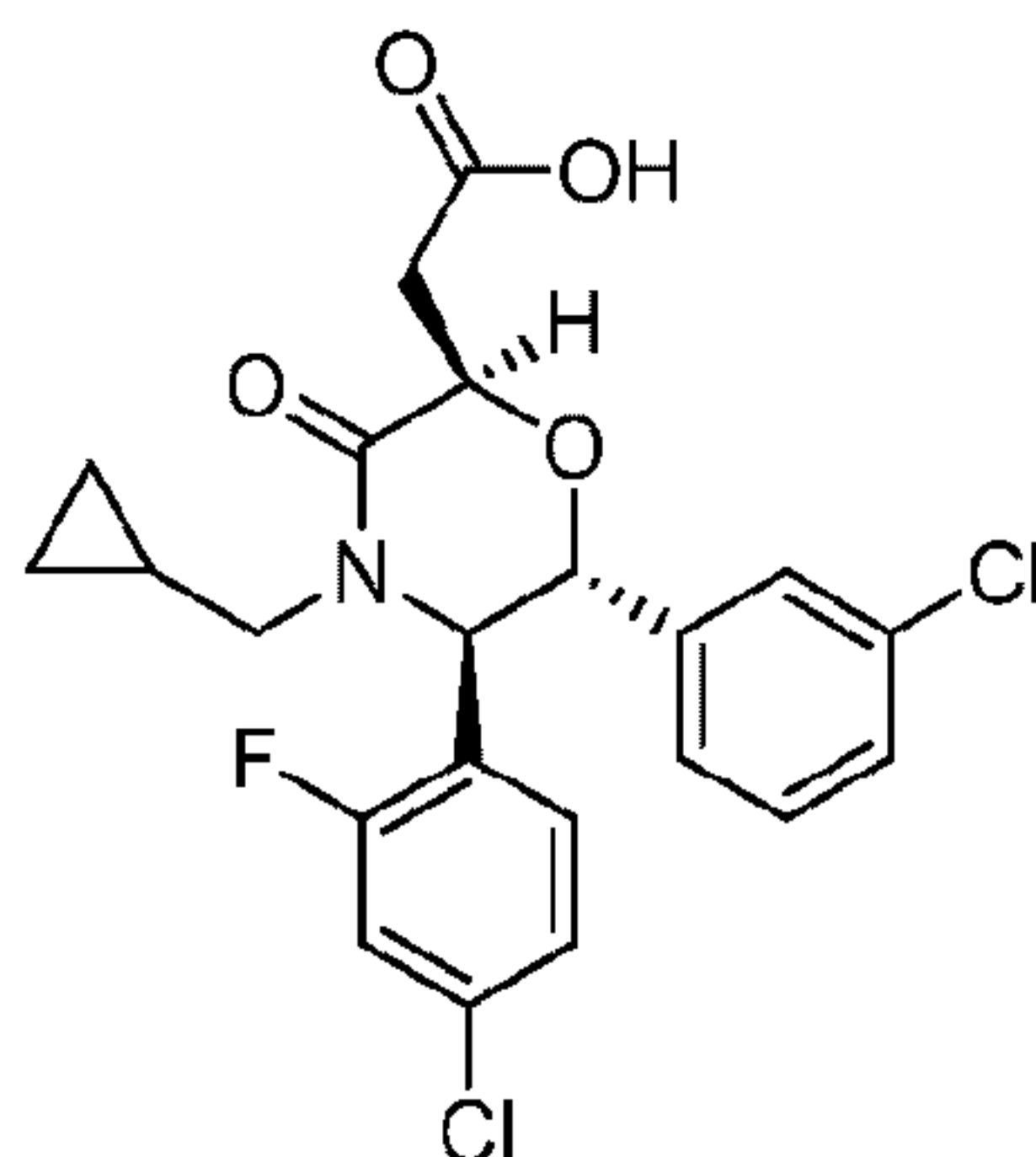
EXAMPLE 61

2-((2R,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(p-tolyl)morpholin-2-yl)acetic acid

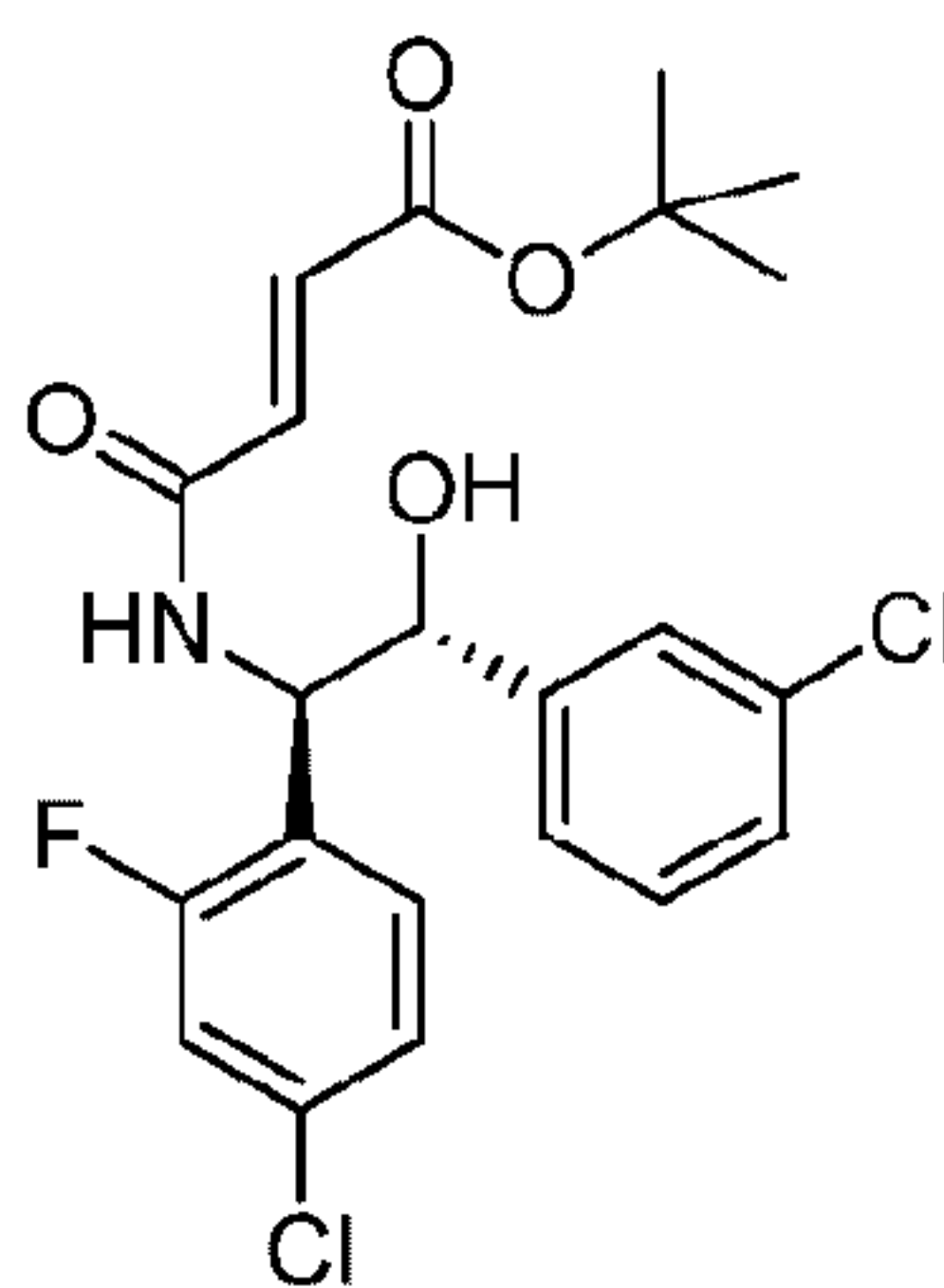
- 15 ¹H NMR (400 MHz, CDCl₃) δ ppm 0.08 (s, 1 H) 0.13 (br. s., 1 H) 0.42 (br. s., 1 H) 0.52 (br. s., 1 H) 0.56 (d, *J*=6.36 Hz, 1 H) 0.71 (d, *J*=6.36 Hz, 1 H) 0.81 - 1.02 (m, 2 H) 1.11 (t, *J*=7.34 Hz, 1 H) 1.27 (s, 3 H) 2.24 - 2.38 (m, 4 H) 2.69 - 2.78 (m, 1 H) 2.79 - 2.87 (m, 1 H) 3.05 (br. s., 1 H) 4.02 (br. s., 1 H) 4.76 (d, *J*=3.42 Hz, 1 H) 4.83 (br. s., 2 H) 6.96
20 (br. s., 2 H) 7.02 - 7.25 (m, 5 H) 7.25 - 7.33 (m, 4 H). Mass Spectrum (Cl⁺) *m/z* = 414.1 (M+1), 851.2 (2M+23).

EXAMPLE 62

- 25 2-((2R,5R,6R)-5-(4-Chloro-2-fluorophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid



Step A. (E)-tert-Butyl 4-(((1R,2R)-1-(4-chloro-2-fluorophenyl)-2-(3-chlorophenyl)-2-hydroxyethyl)amino)-4-oxobut-2-enoate

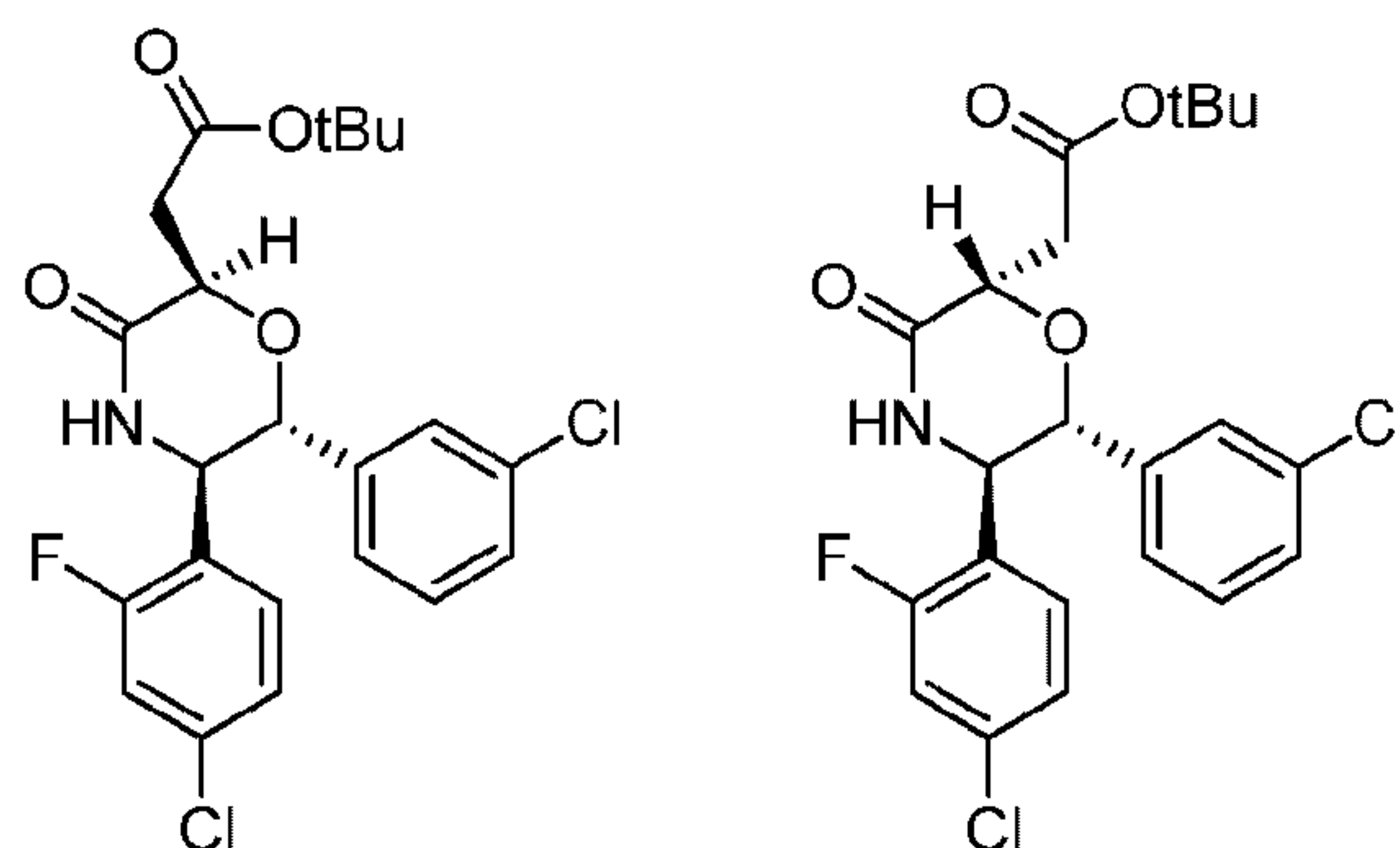


5

To (E)-4-tert-butoxy-4-oxobut-2-enoic acid (0.90g, 0.525 mmol; AMRI, Albany, NY) and HBTU (0.2g, 0.525 mmol) was added dry DMF (858uL) followed by DIEA (0.12 g, 0.913 mmol). The reaction mixture was stirred at rt for about 20 min. after which
 10 (1R,2R)-2-amino-2-(4-chloro-2-fluorophenyl)-1-(3-chlorophenyl)ethanol (0.137g, 0.456 mmol, Intermediate B1) was added. The reaction mixture was stirred at rt for 22h. The mixture was diluted with EtOAc, washed with water, then saturated aq. NaHCO₃ solution. The organic layers were extracted with EtOAc, combined, dried over MgSO₄, filtered and the filtrate was concentrated under reduced pressure. The crude residue was
 15 purified by chromatography on silica gel (eluent: 5 to 95% EtOAc : hexanes, gradient elution). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.13 - 1.21 (m, 6 H) 1.13 - 1.21 (m, 2 H) 1.34 - 1.46 (m, 12 H) 1.95 (s, 1 H) 4.03 (d, *J*=7.34 Hz, 1 H) 4.89 (d, *J*=4.40 Hz, 1 H) 5.35 (dd, *J*=8.31, 4.40 Hz, 1 H) 6.47 - 6.57 (m, 1 H) 6.71 - 6.80 (m, 1 H) 6.92 (s, 1 H) 6.93 -

6.96 (m, 1 H) 6.97 (s, 1 H) 6.98 - 7.04 (m, 2 H) 7.04 - 7.09 (m, 2 H) 7.13 (d, $J=6.36$ Hz, 2 H) 7.25 (s, 1 H). Mass Spectrum (CI^+) $m/z = 454.1$ ($\text{M}+1$), 909.2 ($2\text{M}+1$).

Step B. tert-Butyl 2-((2R,5R,6R)-5-(4-chloro-2-fluorophenyl)-6-(3-chlorophenyl)-3-oxomorpholin-2-yl)acetate and tert-Butyl 2-((2S,5R,6R)-5-(4-chloro-2-fluorophenyl)-6-(3-chlorophenyl)-3-oxomorpholin-2-yl)acetate



A solution of (E)-tert-butyl 4-((1R,2R)-1-(4-chloro-2-fluorophenyl)-2-(3-chlorophenyl)-2-hydroxyethylamino)-4-oxobut-2-enoate (0.73g, 0.161 mmol) in dry THF (2 mL) was cooled to 0 °C in an ice/water bath. To the cooled solution was added sodium hydride (60% in mineral oil, 0.02g, 0.482 mmol). The reaction mixture was stirred at 0 °C for 2h. The reaction mixture was quenched with saturated aq. NH_4Cl solution; after which EtOAc was added. The organic layer was extracted with EtOAc, dried over MgSO_4 , then concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (eluent: 5 to 95% EtOAc : hexanes, gradient elution). Mass Spectrum (CI^+) $m/z = 454.1$ ($\text{M}+1$), 909.2 ($2\text{M}+1$), 931.2 ($2\text{M}+23$).

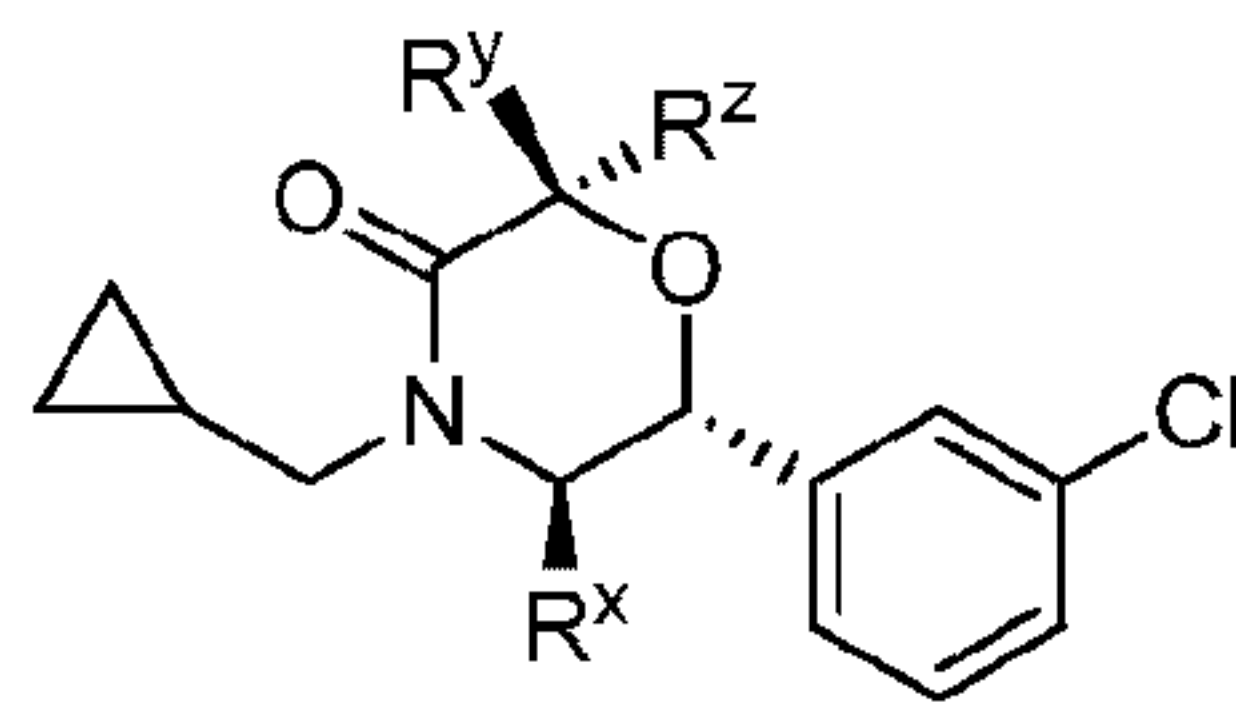
Step C. 2-((2R,5R,6R)-5-(4-Chloro-2-fluorophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

To a mixture of tert-butyl 2-((2R,5R,6R)-5-(4-chloro-2-fluorophenyl)-6-(3-chlorophenyl)-3-oxomorpholin-2-yl)acetate and tert-butyl 2-((2S,5R,6R)-5-(4-chloro-2-fluorophenyl)-6-(3-chlorophenyl)-3-oxomorpholin-2-yl)acetate (0.054g, 0.120 mmol;

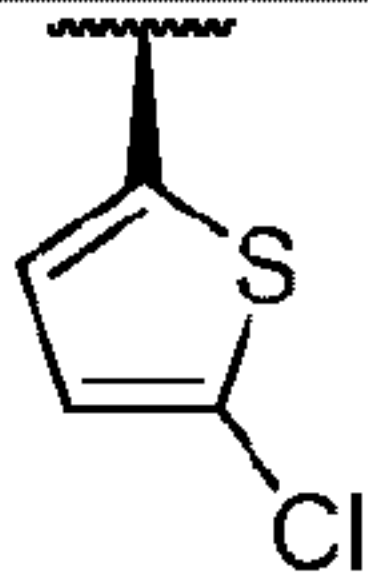
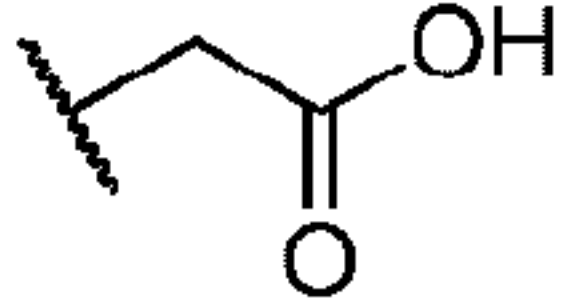
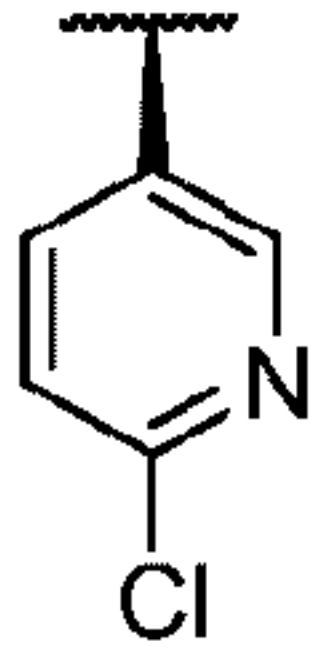
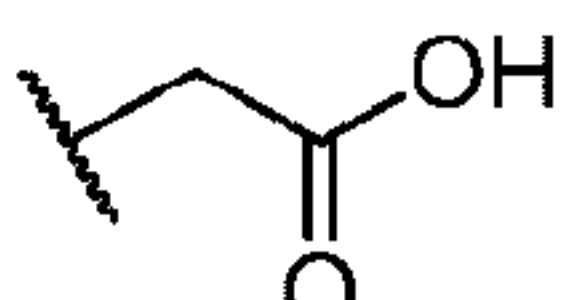
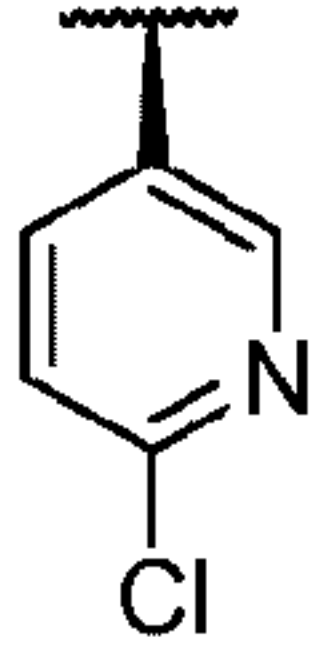
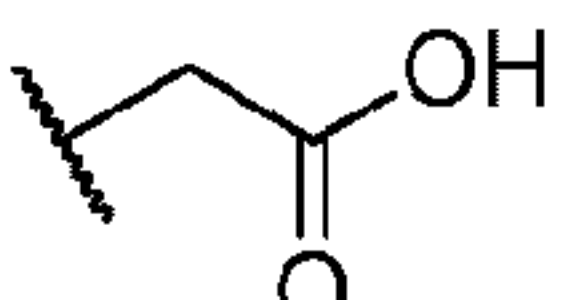
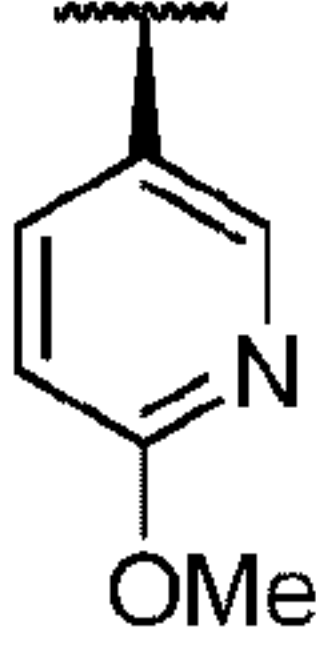
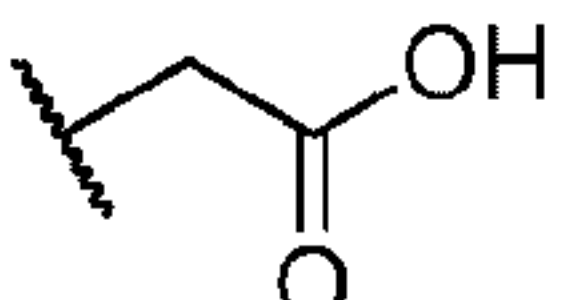
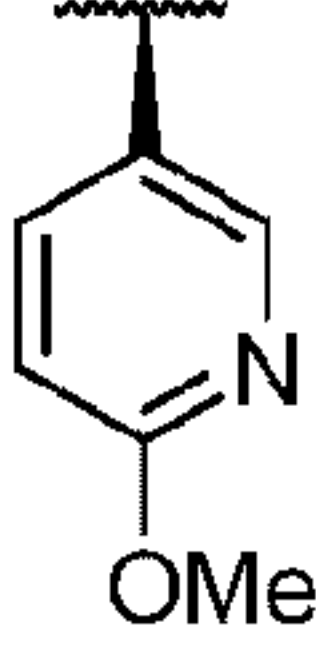
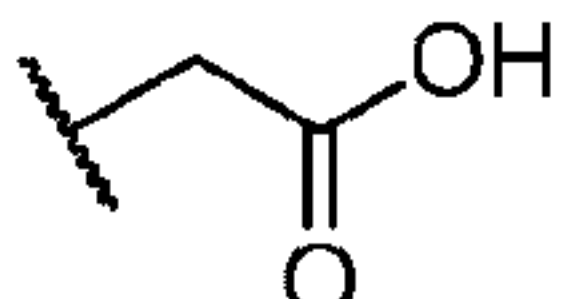
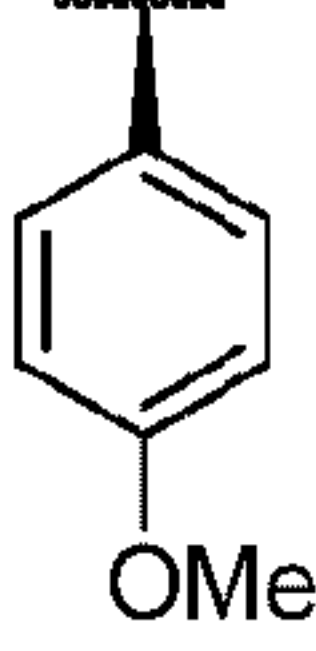
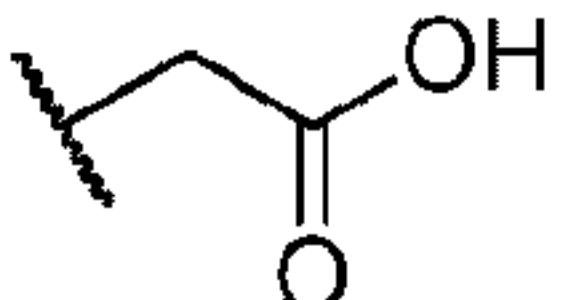
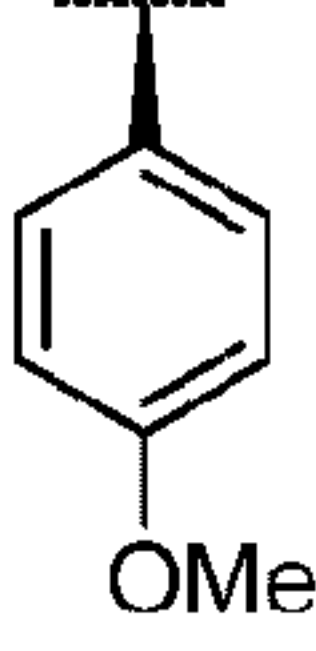
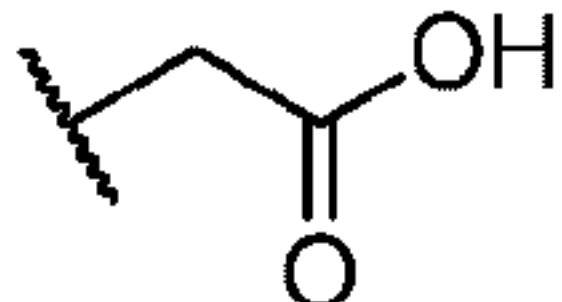
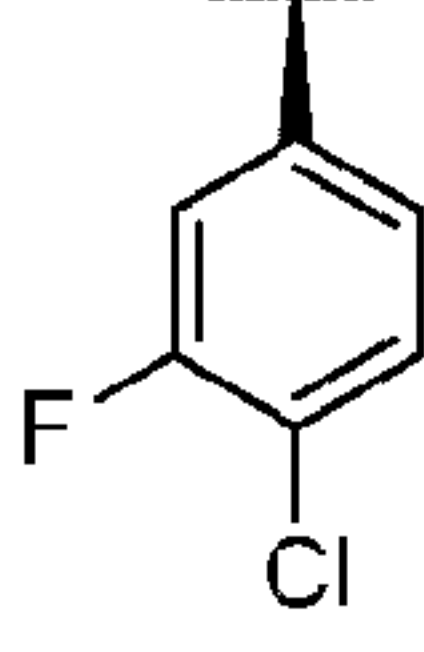
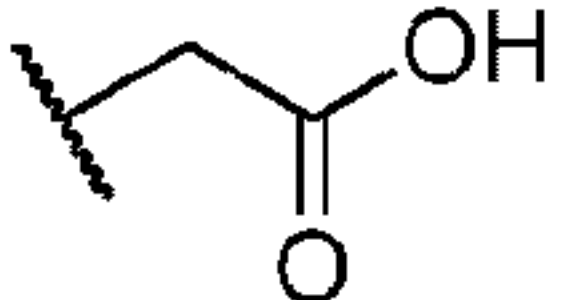
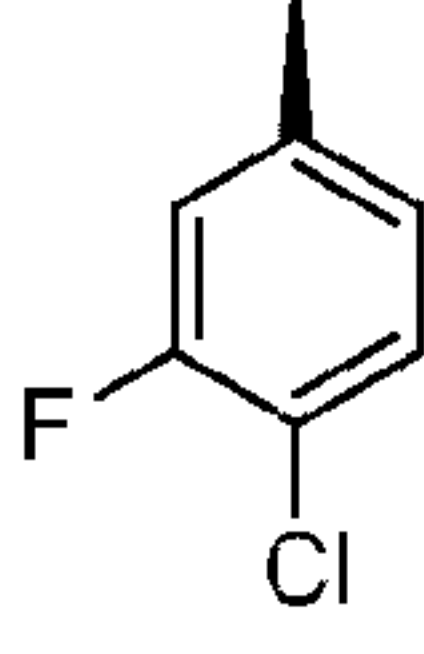
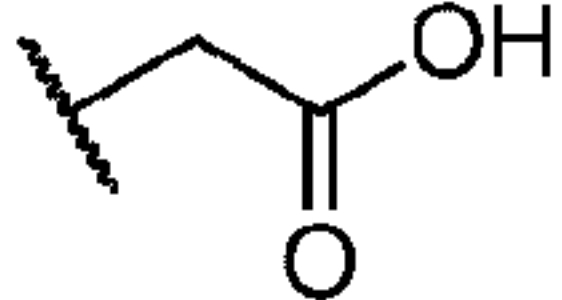
Example 62, Step B) in 3 mL of dry DMF was added caesium carbonate (0.195g, 0.595 mmol). The mixture was stirred at room temperature for approximately 10 minutes, then (bromomethyl)cyclopropane (0.128 g, 0.951 mmol, Oakwood Products, Inc., West Columbia, SC) was added. The reaction mixture was stirred at rt for 22 h. The reaction mixture was diluted with EtOAc and the combined organics were washed with water, saturated aq. NaHCO₃ solution and concentrated under reduced pressure.

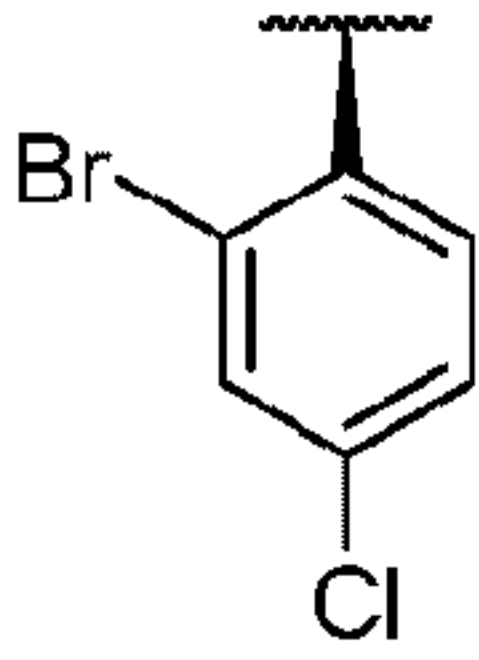
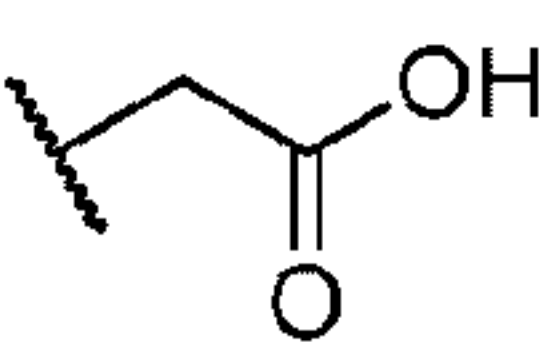
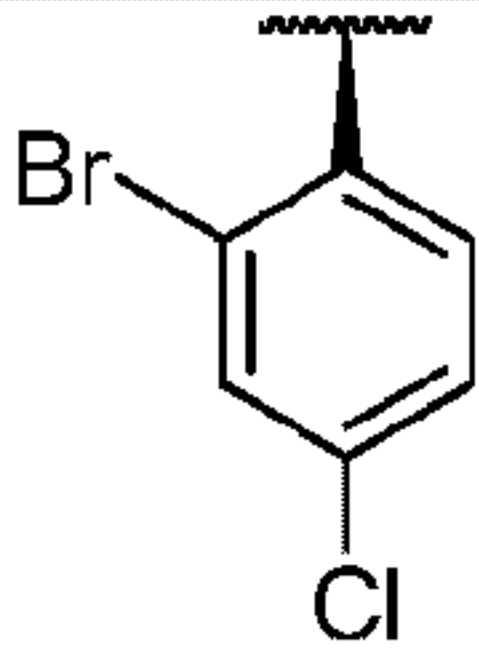
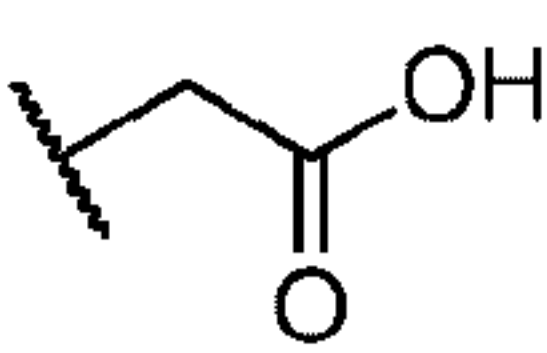
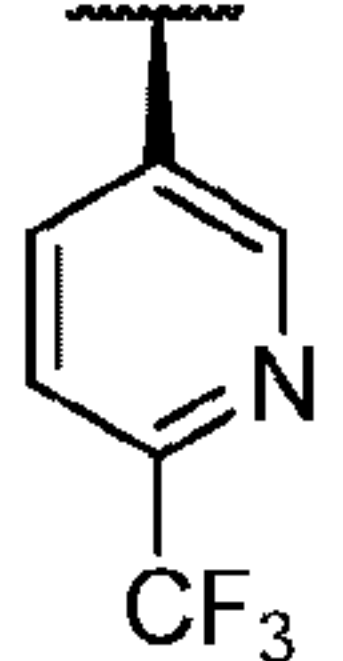
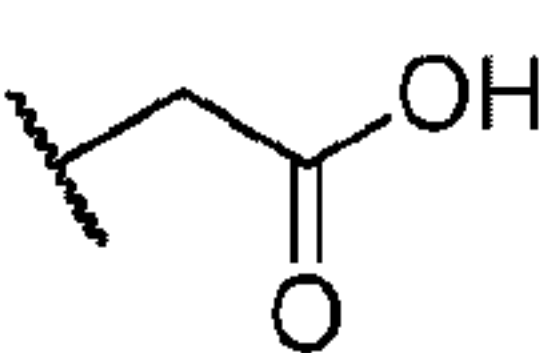
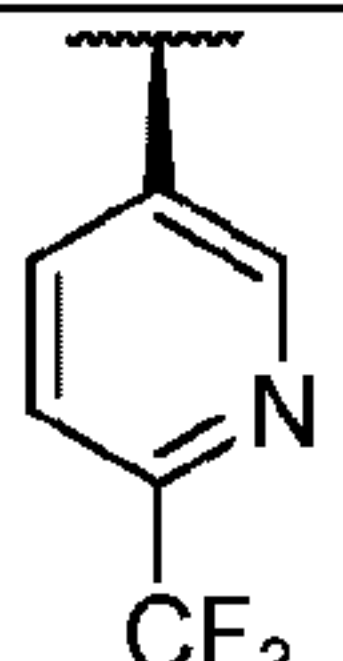
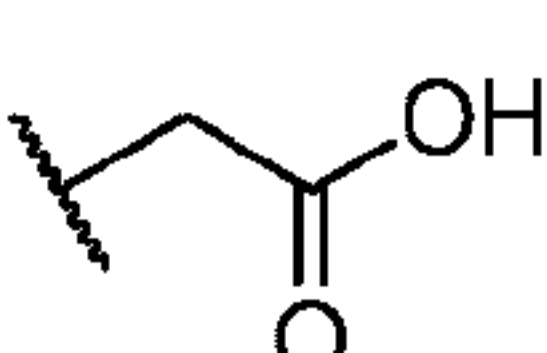
To the crude diastereomeric mixture of tert-butyl 2-((2R,5R,6R)-5-(4-chloro-2-fluorophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and tert-butyl 2-((2S,5R,6R)-5-(4-chloro-2-fluorophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate thus obtained was added 2 mL DCM followed by 1.0 mL trifluoroacetic acid (0.014g, 0.120 mmol). The mixture was stirred at rt for 2 hours and then concentrated under reduced pressure. The residue was purified by SFC (Method: 250 x 21.2 mm IC-H column w/ 20 g/min MeOH (0.2%DEA) + 60 g/min CO₂ on a Thar 80 SFC. Outlet pressure 100 bar; Temp. 20 °C; Wavelength 220 nm). The title compound was obtained as the first eluting stereoisomer. The pooled fractions containing the title compound were concentrated, then diluted with toluene and concentrated followed by repeating this procedure with ethanol in order to azeotrope off diethylamine employed as co-solvent during SFC. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.13 - 0.38 (m, 2 H) 0.55 - 0.79 (m, 2 H) 1.07 (br. s., 1 H) 2.43 (dd, *J*=14.28, 7.63 Hz, 1 H) 2.76 (br. s., 1 H) 2.85 - 3.00 (m, 2 H) 3.03 (s, 1 H) 3.11 (dd, *J*=16.24, 5.67 Hz, 1 H) 4.11 (dd, *J*=14.18, 6.75 Hz, 1 H) 4.43 (t, *J*=6.16 Hz, 1 H) 4.98 (d, *J*=1.76 Hz, 2 H) 5.49 (d, *J*=2.15 Hz, 1 H) 7.15 (dd, *J*=10.17, 1.57 Hz, 1 H) 7.32 - 7.39 (m, 3 H) 7.55 (s, 1 H). Mass Spectrum (Cl⁺) *m/z* =453.1 (M+1), 927.3 (2M+23).

Examples 63 to 82 were also prepared by procedures similar to the one described in Example 62, replacing (1R,2R)-2-amino-2-(4-chloro-2-fluorophenyl)-1-(3-chlorophenyl)ethanol (Intermediate B1) in Step A with the designated intermediates.



Example	R ^x	R ^y	R ^z	Intermediate used
63			H	B2
64			H	B3
65			H	B6
66			H	B8
67			H	C13
68		H		C13
69			H	D1

70		H		D1
71		H		D2
72			H	D2
73			H	D3
74		H		D3
75			H	D4
76		H		D4
77			H	D5
78		H		D5

79			H	E1
80		H		E1
81			H	E2
82		H		E2

EXAMPLE 63

2-((2R,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-phenylmorpholin-2-yl)acetic acid

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¹H NMR (400 MHz, CDCl₃) δ ppm 0.03 - 0.21 (m, 2 H) 0.38 - 0.60 (m, 2 H) 0.89 - 1.04 (m, 1 H) 2.33 (dd, *J*=14.18, 7.73 Hz, 1 H) 2.85 (dd, *J*=16.04, 7.43 Hz, 1 H) 3.07 (dd, *J*=16.04, 5.48 Hz, 1 H) 4.00 (dd, *J*=14.18, 6.55 Hz, 2 H) 4.47 (dd, *J*=7.24, 5.67 Hz, 2 H) 4.82 (d, *J*=3.72 Hz, 1 H) 4.95 (d, *J*=3.91 Hz, 1 H) 7.03 - 7.13 (m, 3 H) 7.14 - 7.27 (m, 3 H) 7.35 (s, 1 H). Mass Spectrum (CI⁺) *m/z* = 400.1 (M+1), 823.2 (2M+23).

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EXAMPLE 64

2-((2R,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(4-fluorophenyl)-3-oxomorpholin-2-yl)acetic acid

5 ¹H NMR (400 MHz, CDCl₃) δ ppm 0.17 - 0.33 (m, 2 H) 0.53 - 0.73 (m, 2 H) 1.01 - 1.14 (m, 1 H) 2.46 (dd, *J*=13.82, 7.70 Hz, 1 H) 2.94 (dd, *J*=16.14, 6.11 Hz, 2 H) 3.17 (dd, *J*=16.14, 6.85 Hz, 2 H) 4.09 (dd, *J*=13.45, 7.34 Hz, 1 H) 4.44 - 4.51 (m, 1 H) 4.90 (br. s., 1 H) 4.89 - 4.90 (m, 1 H) 5.06 (d, *J*=3.42 Hz, 1 H) 5.00 - 5.10 (m, 1 H) 7.06 - 7.14 (m, 2 H) 7.28 - 7.40 (m, 2 H) 7.48 (s, 1 H). Mass Spectrum (CI⁺) *m/z* = 418.1 (M+1), 859.2
10 (2M+23).

EXAMPLE 65

2-((2R,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(4-(trifluoromethoxy)phenyl)morpholin-2-yl)acetic acid

15 ¹H NMR (400 MHz, CDCl₃) δ ppm 0.15 - 0.36 (m, 2 H) 0.48 - 0.76 (m, 2 H) 1.00 - 1.17 (m, 1 H) 2.45 (dd, *J*=14.18, 7.53 Hz, 1 H) 2.88 - 3.00 (m, 2 H) 3.03 (s, 1 H) 3.15 (dd, *J*=16.24, 6.06 Hz, 1 H) 4.10 (dd, *J*=13.99, 6.75 Hz, 1 H) 4.47 (t, *J*=6.36 Hz, 1 H) 4.92 (d, *J*=2.93 Hz, 1 H) 5.11 (d, *J*=3.33 Hz, 2 H) 7.20 - 7.28 (m, 3 H) 7.30 - 7.41 (m, 2 H) 7.48
20 (s, 1 H). Mass Spectrum (CI⁺) *m/z* = 484.1 (M+1), 991.3 (2M+23).

EXAMPLE 66

2-((2R,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(4-isopropylphenyl)-3-oxomorpholin-2-yl)acetic acid

25 ¹H NMR (400 MHz, CDCl₃) δ ppm -0.08 - 0.14 (m, 2 H) 0.28 - 0.55 (m, 2 H) 0.77 - 0.95 (m, 1 H) 1.06 (d, *J*=7.04 Hz, 6 H) 2.27 (dd, *J*=14.09, 7.83 Hz, 1 H) 2.67 - 2.85 (m, 2 H) 2.99 (dd, *J*=16.14, 5.77 Hz, 1 H) 3.89 (dd, *J*=14.08, 6.65 Hz, 1 H) 4.35 (t, *J*=6.46 Hz, 1 H) 4.71 (d, *J*=3.52 Hz, 1 H) 4.83 (d, *J*=3.52 Hz, 1 H) 6.88 (d, *J*=8.02 Hz, 2 H) 7.00 - 7.06
30 (m, 3 H) 7.06 - 7.17 (m, 3 H) 7.20 (s, 1 H). Mass Spectrum (CI⁺) *m/z* = 442.1 (M+1), 907.3 (2M+23).

EXAMPLE 67

2-((2R,5R,6R)-5-(4-Bromophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

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First eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.05 - 0.23 (m, 2 H) 0.40 - 0.65 (m, 2 H) 0.93 (d, *J*=7.24 Hz, 1 H) 0.96 (br. s., 1 H) 1.27 (t, *J*=6.85 Hz, 1 H) 2.26 - 2.39 (m, 1 H) 2.87 (d, *J*=14.09 Hz, 1 H) 3.08 (d, *J*=11.54 Hz, 1 H) 4.05 (dd, *J*=13.79, 5.97 Hz, 1 H) 4.13 (q, *J*=7.17 Hz, 1 H) 4.65 (br. s., 1 H) 4.84 (br. s., 1 H) 4.93 (br. s., 1 H) 7.04 (t, *J*=7.63 Hz, 2 H) 7.06 - 7.13 (m, 1 H) 7.18 - 7.25 (m, 1 H) 7.39 (br. s., 1 H) 7.47 (d, 2 H). Mass Spectrum (CI⁺) *m/z* = 478.0 (M+1), 977.1 (2M+23).

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EXAMPLE 68

15 2-((2S,5R,6R)-5-(4-Bromophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

Second eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.00 (d, *J*=4.30 Hz, 2 H) 0.35 - 0.51 (m, 2 H) 0.77 - 0.86 (m, 1 H) 1.19 - 1.29 (m, 2 H) 2.29 (dd, *J*=14.18, 7.53 Hz, 1 H) 3.00 - 3.22 (m, 2 H) 3.97 (dd, *J*=14.18, 6.55 Hz, 1 H) 4.57 (d, *J*=9.59 Hz, 1 H) 4.69 - 4.78 (m, 2 H) 6.68 (d, *J*=7.63 Hz, 1 H) 6.81 (d, *J*=8.41 Hz, 2 H) 7.01 - 7.15 (m, 2 H) 7.21 (dd, *J*=8.02, 0.98 Hz, 1 H) 7.39 (d, *J*=8.41 Hz, 2 H) 10.47 (br. s., 1 H). Mass Spectrum (CI⁺) *m/z* = 478.0 (M+1), 977.1 (2M+23).

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EXAMPLE 69

2-((2R,5S,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(thiophen-2-yl)morpholin-2-yl)acetic acid

First eluting isomer using chiral SFC separation as described in Example 62.

30 ¹H NMR (400 MHz, CDCl₃) δ ppm 0.03 - 0.28 (m, 2 H) 0.38 - 0.62 (m, 2 H) 0.94 (br. s., 1 H) 1.16 - 1.32 (m, 1 H) 2.58 (dd, *J*=14.38, 7.53 Hz, 1 H) 3.00 - 3.23 (m, 1 H) 3.92 -

4.12 (m, 1 H) 4.62 - 4.78 (m, 2 H) 4.93 (d, $J=9.59$ Hz, 1 H) 6.45 (d, $J=3.72$ Hz, 1 H) 6.70 (d, $J=3.72$ Hz, 1 H) 6.84 - 6.96 (m, 1 H) 7.12 - 7.23 (m, 2 H) 7.30 (d, 1 H). Mass Spectrum (Cl^+) $m/e = 440.0$ ($M+1$), 903.0 ($2M+23$).

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EXAMPLE 70

2-((2S,5S,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(thiophen-2-yl)morpholin-2-yl)acetic acid

Second eluting isomer using chiral SFC separation as described in Example 62.

10 ^1H NMR (400 MHz, CDCl_3) δ ppm 0.06 - 0.23 (m, $J=19.76$, 9.15, 4.72, 4.72 Hz, 2 H) 0.41 - 0.59 (m, 2 H) 0.84 - 1.00 (m, 1 H) 1.26 (s, 1 H) 2.57 (dd, $J=14.38$, 7.53 Hz, 1 H) 3.13 (d, $J=4.89$ Hz, 2 H) 4.02 (dd, $J=14.28$, 6.65 Hz, 1 H) 4.63 - 4.77 (m, 2 H) 4.93 (d, $J=9.39$ Hz, 1 H) 6.45 (d, $J=3.72$ Hz, 1 H) 6.70 (d, $J=3.72$ Hz, 1 H) 6.92 (d, $J=7.82$ Hz, 1 H) 7.10 - 7.23 (m, 2 H) 8.54 (br. s., 1 H). Mass Spectrum (Cl^+) $m/e = 440.0$ ($M+1$),
15 903.1 ($2M+23$).

EXAMPLE 71

2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(6-chloropyridin-3-yl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

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First eluting isomer using chiral SFC separation as described in Example 62.

^1H NMR (400 MHz, CDCl_3) δ ppm -0.01 (br. s., 2 H) 0.32 - 0.53 (m, 2 H) 0.74 - 0.87 (m, 1 H) 2.26 (dd, $J=14.18$, 7.34 Hz, 1 H) 2.81 (q, $J=7.17$ Hz, 2 H) 2.88 (d, $J=6.26$ Hz, 1 H) 3.08 (d, $J=15.26$ Hz, 1 H) 3.97 (dd, $J=14.08$, 6.26 Hz, 1 H) 4.59 (d, $J=9.59$ Hz, 1 H) 4.83
25 (d, $J=9.19$ Hz, 1 H) 6.69 (d, $J=7.63$ Hz, 1 H) 7.11 (t, $J=7.83$ Hz, 1 H) 7.19 (s, 1 H) 7.24 (d, $J=8.22$ Hz, 1 H) 7.30 (d, $J=8.02$ Hz, 1 H) 7.39 (dd, $J=8.02$, 1.56 Hz, 1 H) 7.92 (s, 1 H). Mass Spectrum (Cl^+) $m/z = 435.1$ ($M+1$), 871.1 ($2M+1$).

EXAMPLE 72

30 2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(6-chloropyridin-3-yl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

Second eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.11 - 0.32 (m, 2 H) 0.48 - 0.74 (m, 2 H) 0.78 - 0.97 (m, 3 H) 1.02 (br. s., 2 H) 1.16 (t, *J*=7.04 Hz, 2 H) 2.39 (dd, *J*=8.22, 2.54 Hz, 1 H) 2.83 - 3.08 (m, 3 H) 3.91 - 4.13 (m, 2 H) 4.49 (br. s., 2 H) 4.92 (br. s., 1 H) 5.08 (br. s., 1 H) 7.21 (d, 1 H) 7.29 - 7.35 (m, 2 H) 7.39 (br. s., 1 H) 7.49 (br. s., 1 H) 7.73 (br. s., 1 H) 8.25 (br. s., 1 H). Mass Spectrum (CI⁺) *m/z* = 435.1 (M+1), 871.2 (2M+1).

EXAMPLE 73

2-((2R,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(6-methoxypyridin-3-yl)-3-oxomorpholin-2-yl)acetic acid

First eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.16 - 0.38 (m, 2 H) 0.54 - 0.80 (m, 2 H) 1.03 - 1.17 (m, 1 H) 2.51 (dd, *J*=13.99, 7.73 Hz, 1 H) 3.05 (dd, *J*=13.79, 5.97 Hz, 2 H) 4.01 - 4.11 (m, 3 H) 4.37 (t, *J*=5.67 Hz, 1 H) 4.92 (d, *J*=2.35 Hz, 1 H) 5.10 (d, *J*=2.35 Hz, 1 H) 6.92 (d, *J*=8.61 Hz, 1 H) 7.25 - 7.32 (m, 5 H) 7.33 - 7.43 (m, 2 H) 7.53 (s, 1 H) 7.73 (dd, *J*=8.71, 2.45 Hz, 1 H) 8.17 (d, *J*=2.15 Hz, 1 H). Mass Spectrum (CI⁺) *m/z* = 431.1 (M+1).

EXAMPLE 74

2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(6-methoxypyridin-3-yl)-3-oxomorpholin-2-yl)acetic acid

Second eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.07 (q, *J*=4.24 Hz, 2 H) 0.49 (dd, *J*=15.65, 8.22 Hz, 2 H) 0.80 - 0.93 (m, 1 H) 2.41 (dd, *J*=14.28, 7.24 Hz, 1 H) 3.04 - 3.24 (m, 2 H) 3.90 - 4.01 (m, 4 H) 4.62 (d, *J*=9.78 Hz, 1 H) 4.71 - 4.88 (m, 2 H) 6.80 (t, *J*=8.41 Hz, 2 H) 7.09 - 7.20 (m, 2 H) 7.25 - 7.27 (m, 1 H) 7.28 (dd, *J*=2.15, 1.17 Hz, 1 H) 7.39 (dd, *J*=8.71, 2.45 Hz, 1 H) 7.72 (d, *J*=2.35 Hz, 1 H). Mass Spectrum (CI⁺) *m/z* = 431.1 (M+1), 861.3 (2M+1).

EXAMPLE 75

2-((2R,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(4-methoxyphenyl)-3-oxomorpholin-2-yl)acetic acid

5 First eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.16 - 0.34 (m, 2 H) 0.55 - 0.72 (m, 2 H) 1.05 - 1.11 (m, 1 H) 2.48 (dd, *J*=13.89, 7.83 Hz, 1 H) 2.93 (dd, *J*=15.85, 5.48 Hz, 1 H) 3.19 (dd, *J*=15.94, 7.34 Hz, 1 H) 3.83 (s, 3 H) 4.07 (dd, *J*=14.48, 6.65 Hz, 1 H) 4.47 - 4.53 (m, 1 H) 4.89 (d, *J*=3.91 Hz, 1 H) 4.99 (d, *J*=3.72 Hz, 1 H) 6.92 (d, *J*=8.80 Hz, 2 H) 7.09 (d, *J*=8.61 Hz, 2 H) 7.19 (d, *J*=7.43 Hz, 1 H) 7.29 - 7.38 (m, 3 H) 7.45 (s, 1 H). Mass Spectrum (CI⁺) *m/z* = 430.1 (M+1), 883.3 (2M+23).

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EXAMPLE 76

2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-5-(4-methoxyphenyl)-3-oxomorpholin-2-yl)acetic acid

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Second eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm -0.04 - 0.13 (m, 2 H) 0.33 - 0.53 (m, 2 H) 0.81 - 0.94 (m, 1 H) 2.37 (dd, *J*=14.18, 7.53 Hz, 1 H) 3.04 - 3.23 (m, *J*=16.95, 16.95, 16.58, 5.48 Hz, 2 H) 3.80 (s, 3 H) 3.97 (dd, *J*=14.18, 6.55 Hz, 1 H) 4.59 - 4.72 (m, 2 H) 4.76 (t, *J*=5.48 Hz, 1 H) 6.73 (d, *J*=7.63 Hz, 1 H) 6.78 - 6.84 (m, 2 H) 6.85 - 6.91 (m, 2 H) 7.06 (t, *J*=1.76 Hz, 1 H) 7.10 (t, *J*=7.83 Hz, 1 H) 7.22 (ddd, 1 H). Mass Spectrum (CI⁺) *m/z* = 430.1 (M+1), 883.3 (2M+23).

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EXAMPLE 77

2-((2R,5R,6R)-5-(4-Chloro-3-fluorophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

First eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm -0.10 - 0.07 (m, 2 H) 0.28 - 0.49 (m, 2 H) 0.76 - 0.87 (m, 1 H) 2.15 (dd, *J*=14.09, 7.63 Hz, 1 H) 2.67 (q, *J*=7.17 Hz, 3 H) 3.89 (dd, *J*=14.18,

30

6.55 Hz, 1 H) 4.47 (dd, $J=7.83$, 4.50 Hz, 1 H) 4.67 - 4.80 (m, 2 H) 6.73 (d, $J=8.22$ Hz, 1 H) 6.87 - 6.94 (m, 2 H) 7.03 (t, $J=7.83$ Hz, 1 H) 7.11 (s, 1 H) 7.20 (t, $J=7.73$ Hz, 1 H) 8.24 (br. s., 1 H). Mass Spectrum (CI^+) $m/z = 452.0$ ($M+1$), 928.2 ($2M+23$).

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EXAMPLE 78

2-((2S,5R,6R)-5-(4-chloro-3-fluorophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

Second eluting isomer using chiral SFC separation as described in Example 62.

10 ^1H NMR (400 MHz, CDCl_3) δ ppm -0.01 (d, $J=4.30$ Hz, 2 H) 0.34 - 0.53 (m, 2 H) 0.71 - 0.91 (m, 1 H) 2.26 (dd, $J=14.18$, 7.53 Hz, 1 H) 2.97 (d, $J=4.50$ Hz, 2 H) 3.99 (dd, $J=14.28$, 6.46 Hz, 1 H) 4.56 (d, $J=9.59$ Hz, 1 H) 4.67 - 4.83 (m, 2 H) 6.68 (dd, $J=17.90$, 7.92 Hz, 2 H) 6.80 (dd, $J=9.19$, 1.37 Hz, 1 H) 7.06 - 7.15 (m, 2 H) 7.20 - 7.25 (m, 1 H) 7.28 (t, $J=7.83$ Hz, 1 H) 9.00 (br. s., 1 H). Mass Spectrum (CI^+) $m/z = 452.0$ ($M+1$), 928.2
15 ($2M+23$).

EXAMPLE 79

2-((2R,5R,6R)-5-(2-Bromo-4-chlorophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

20

First eluting isomer using chiral SFC separation as described in Example 62.

^1H NMR (400 MHz, CDCl_3) δ ppm 0.21 (dt, $J=9.63$, 4.87 Hz, 1 H) 0.33 (dd, $J=9.10$, 4.60 Hz, 1 H) 0.52 - 0.68 (m, 1 H) 0.68 - 0.84 (m, 1 H) 1.00 - 1.17 (m, 1 H) 2.33 (dd, $J=14.08$, 8.02 Hz, 1 H) 2.84 - 3.02 (m, 1 H) 3.02 - 3.21 (m, 1 H) 4.04 - 4.26 (m, 1 H) 4.38 (br. s., 1
25 H) 5.02 (s, 1 H) 5.71 (br. s., 1 H) 7.21 - 7.50 (m, 4 H) 7.55 - 7.72 (m, 2 H) 9.43 (br. s., 1 H). Mass Spectrum (CI^+) $m/z = 514.0$ ($M+1$).

EXAMPLE 80

2-((2S,5R,6R)-5-(2-Bromo-4-chlorophenyl)-6-(3-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid
30

Second eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm ppm -0.07 - 0.16 (m, 2 H) 0.28 - 0.54 (m, 2 H) 0.69 - 0.92 (m, 1 H) 2.27 (dd, *J*=14.18, 6.94 Hz, 1 H) 3.07 (d, *J*=4.89 Hz, 2 H) 3.73 - 3.86 (m, 1 H) 4.51 - 4.68 (m, 1 H) 4.74 (t, *J*=4.21 Hz, 1 H) 5.26 (br. s., 1 H) 6.67 (d, *J*=7.63 Hz, 1 H) 6.97 - 7.13 (m, 2 H) 7.17 - 7.26 (m, 2 H) 7.32 (br. s., 1 H) 7.41 (br. s., 1 H) 9.04 (br. s., 1 H). Mass Spectrum (CI⁺) *m/z* = 514.0 (M+1).

EXAMPLE 81

2-((2R,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(6-(trifluoromethyl)pyridin-3-yl)morpholin-2-yl)acetic acid

First eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.11 - 0.31 (m, 2 H) 0.49 - 0.74 (m, 2 H) 0.96 - 1.08 (m, 1 H) 2.29 - 2.45 (m, 1 H) 2.99 (br. s., 2 H) 4.07 (d, *J*=10.17 Hz, 1 H) 4.09 - 4.18 (m, 1 H) 4.42 (br. s., 1 H) 4.93 (br. s., 1 H) 5.23 (br. s., 1 H) 7.30 - 7.39 (m, 2 H) 7.52 (br. s., 1 H) 7.76 (br. s., 2 H) 7.95 (d, *J*=4.89 Hz, 1 H) 8.62 (br. s., 1 H). Mass Spectrum (CI⁺) *m/z* = 469.1 (M+1), 959.2 (2M+23).

EXAMPLE 82

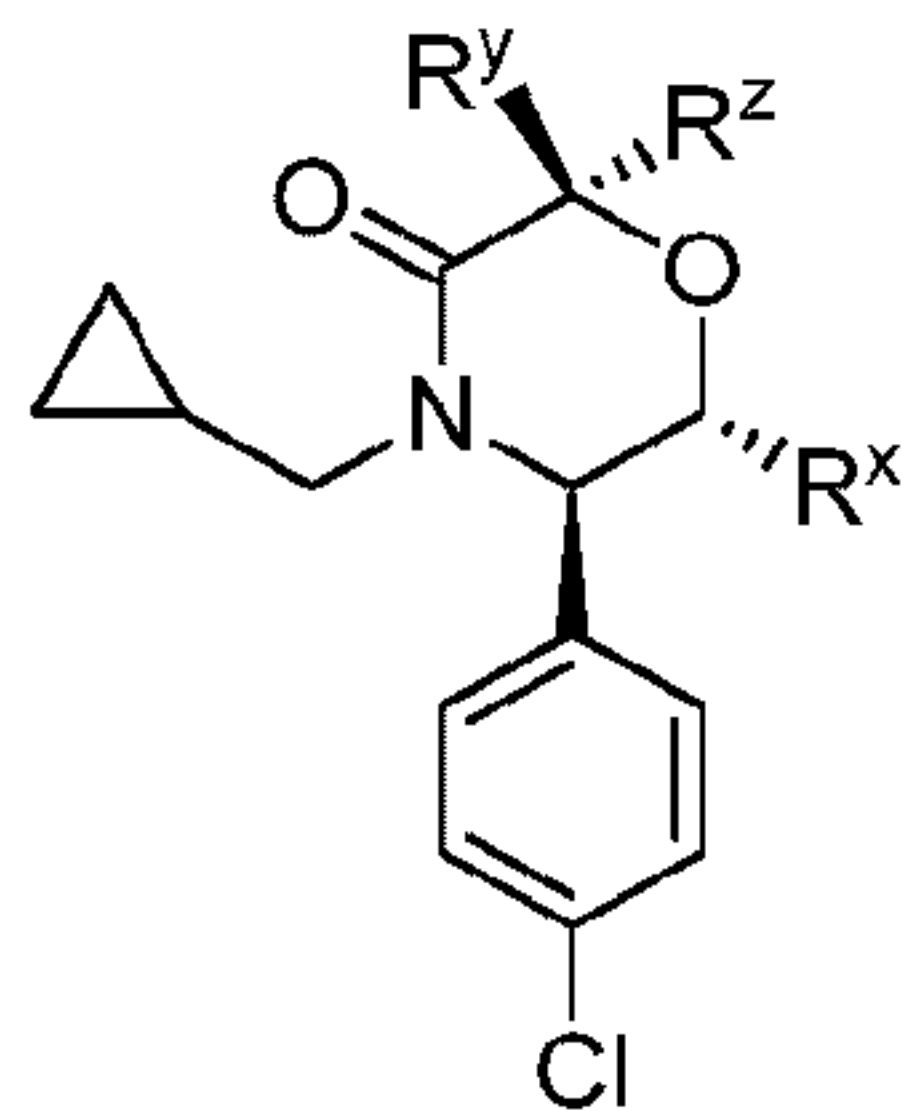
2-((2S,5R,6R)-6-(3-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-5-(6-(trifluoromethyl)pyridin-3-yl)morpholin-2-yl)acetic acid

Second eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm -0.04 (br. s., 2 H) 0.33 - 0.49 (m, 2 H) 0.75 - 0.83 (m, 1 H) 2.18 - 2.30 (m, 1 H) 2.89 - 3.14 (m, 2 H) 3.96 (d, *J*=9.98 Hz, 1 H) 4.64 (br. s., 1 H) 4.91 (d, *J*=9.19 Hz, 2 H) 6.68 (d, *J*=6.46 Hz, 1 H) 7.02 - 7.14 (m, 2 H) 7.22 (d, *J*=7.24 Hz, 2 H) 7.63 (br. s., 2 H) 8.25 (br. s., 1 H). Mass Spectrum (CI⁺) *m/z* = 469.1 (M+1), 959.2 (2M+23).

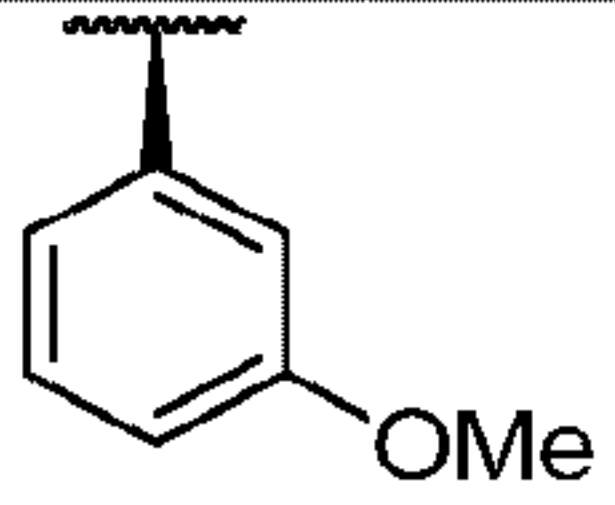
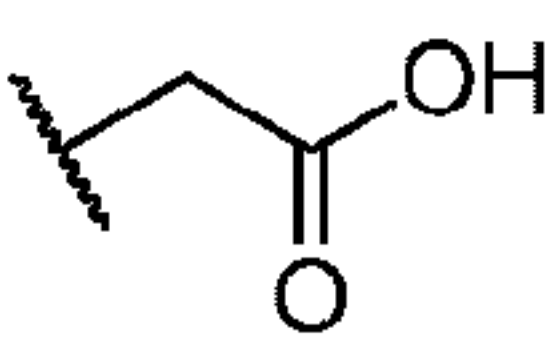
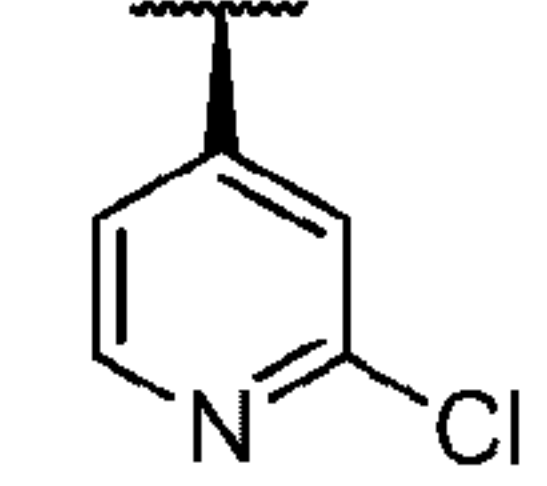
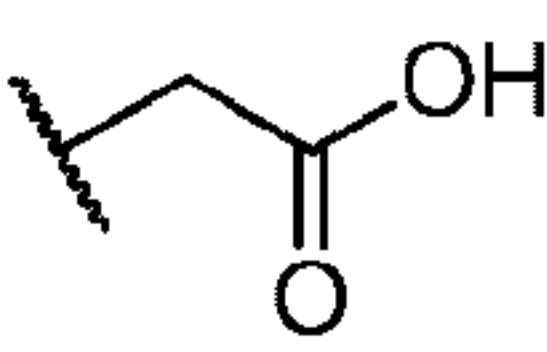
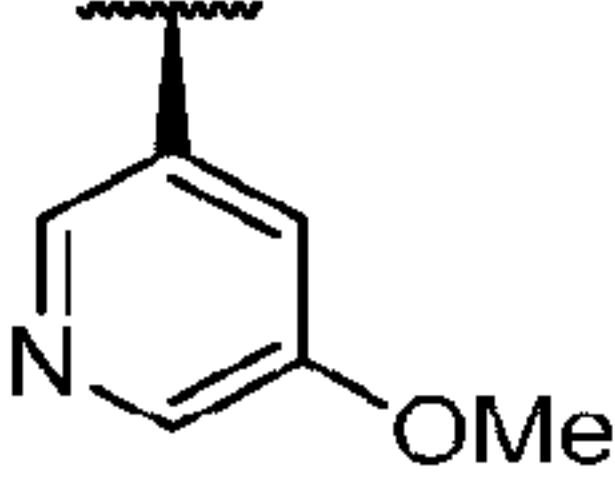
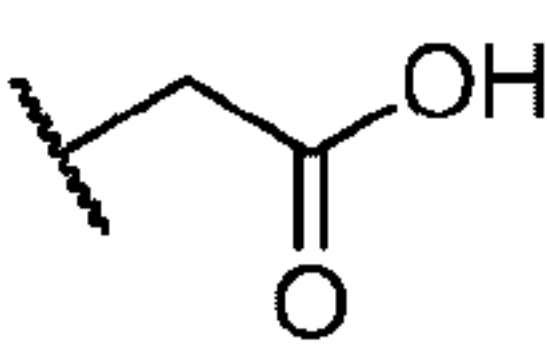
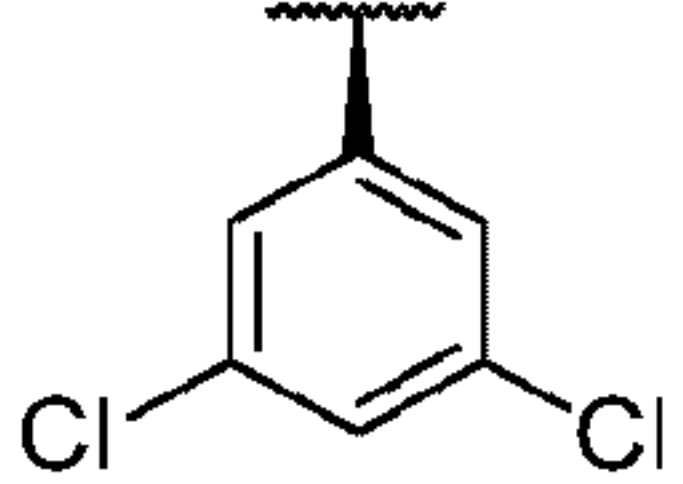
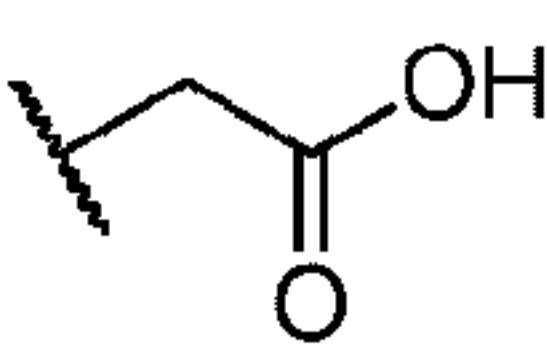
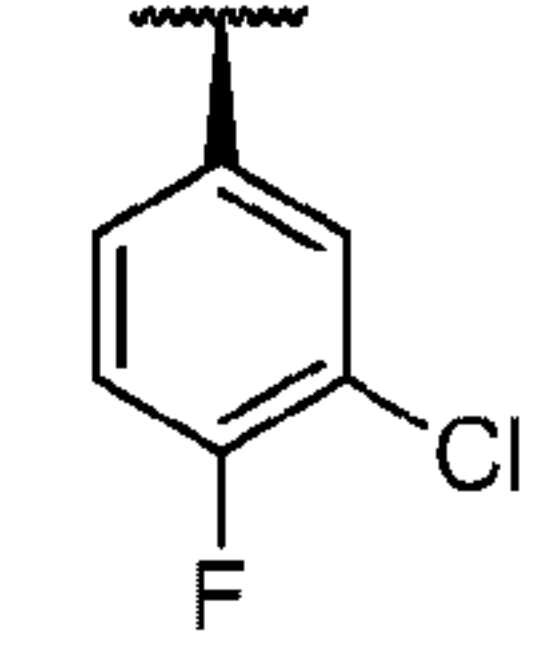
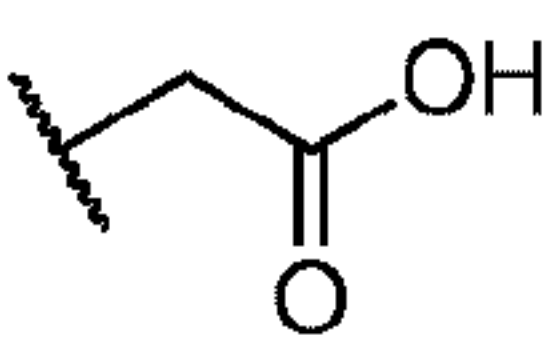
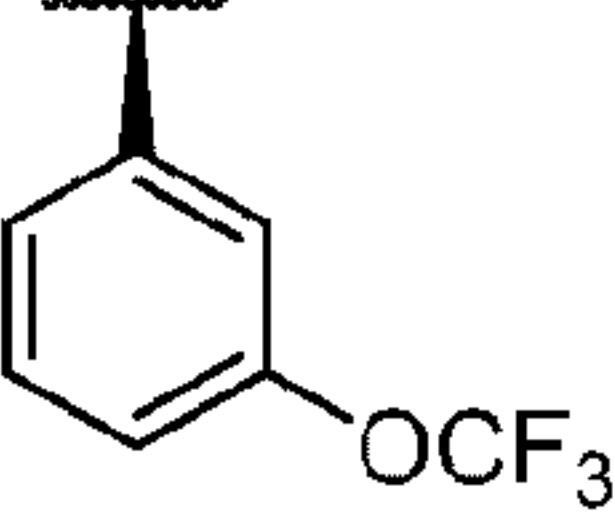
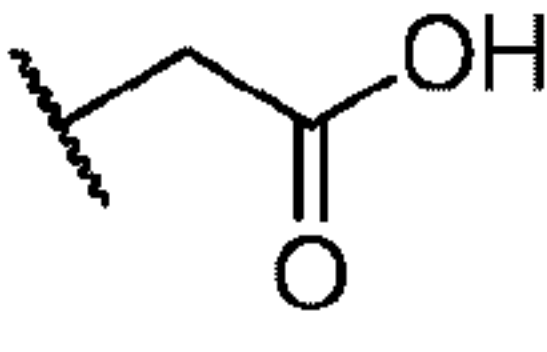
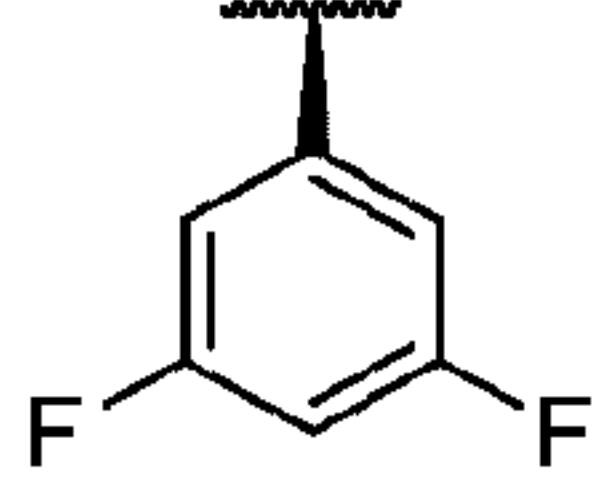
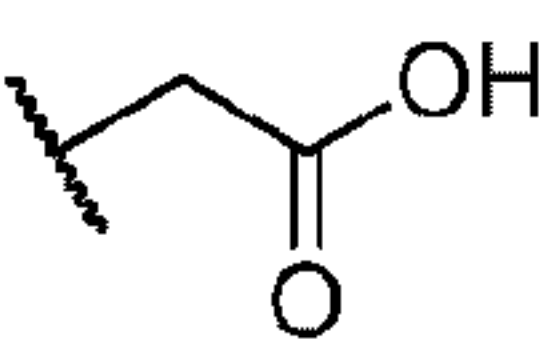
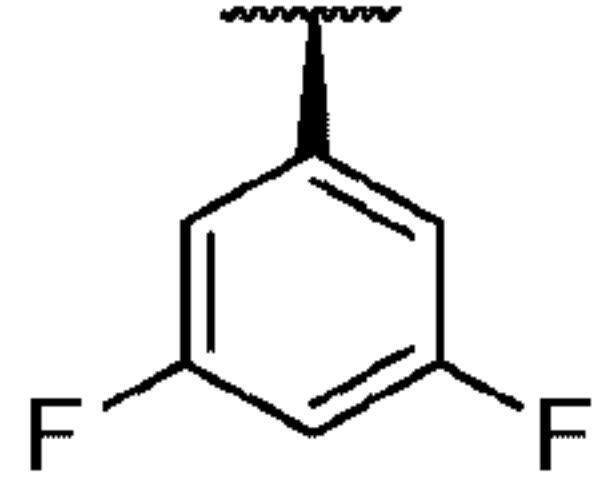
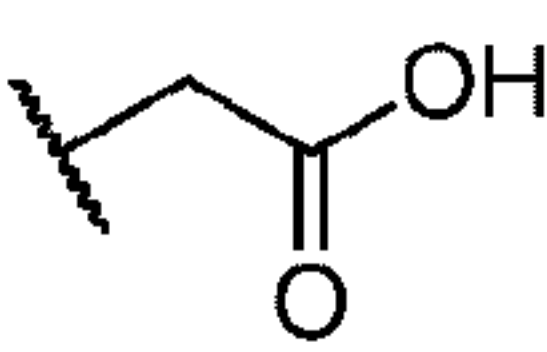
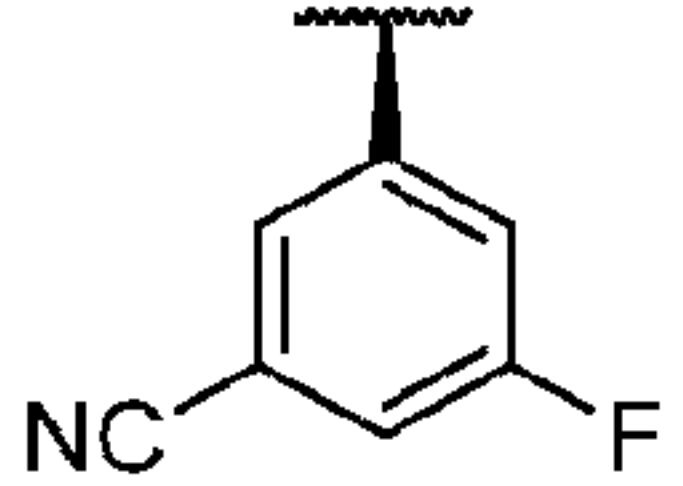
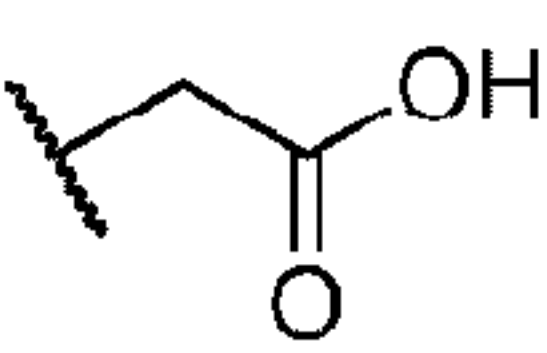
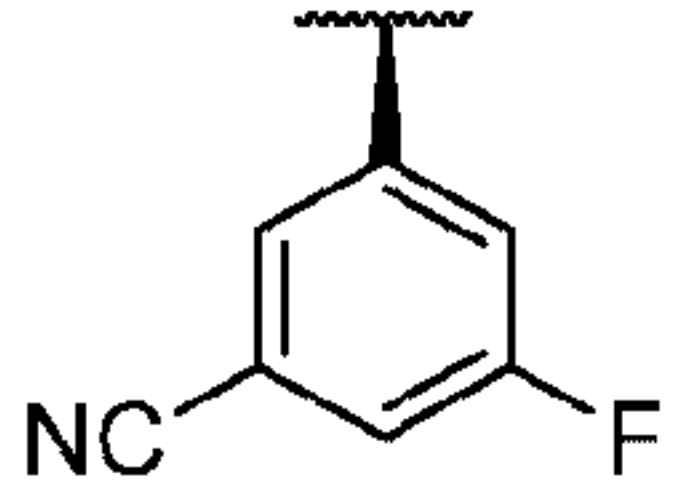
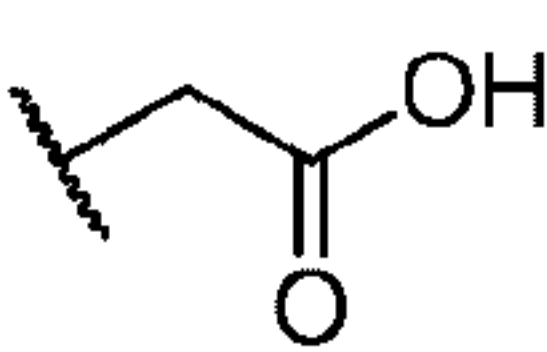
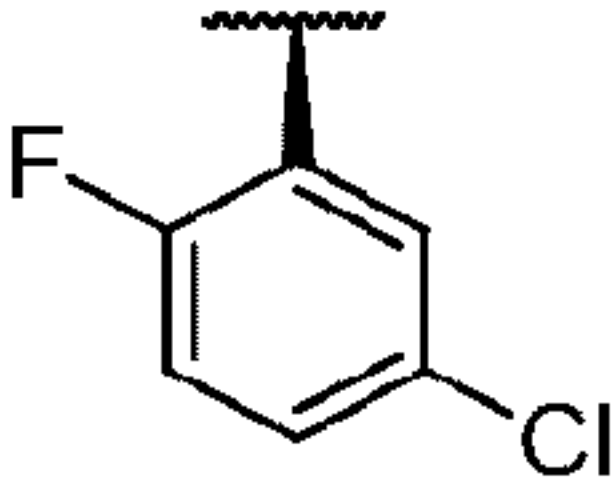
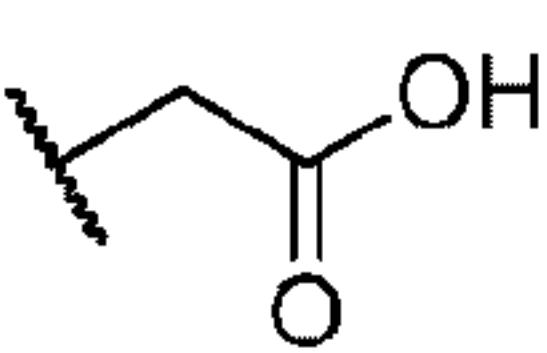
Examples 83 to 105 were also prepared by a procedure analogous to the one described in Example 9, Step B and Example 53, replacing (1R,2R)-2-amino-1-(3-

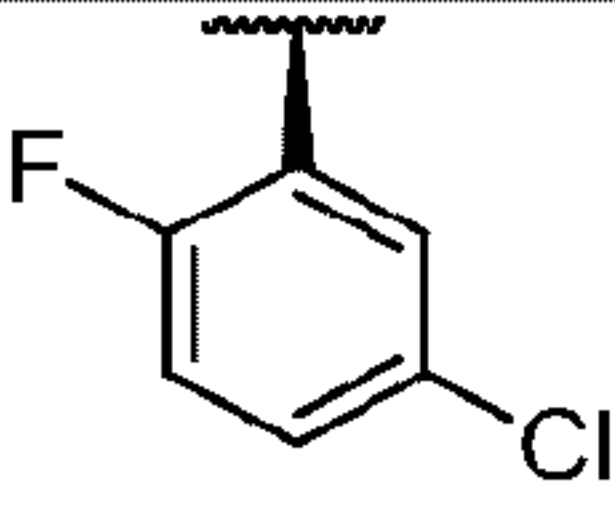
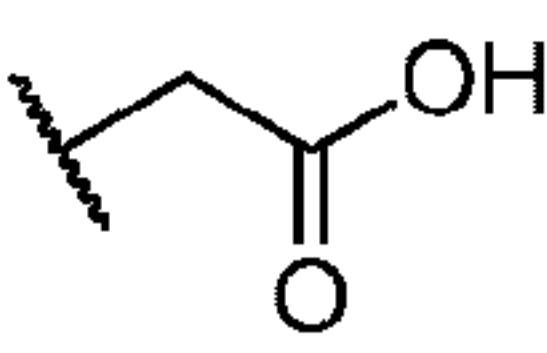
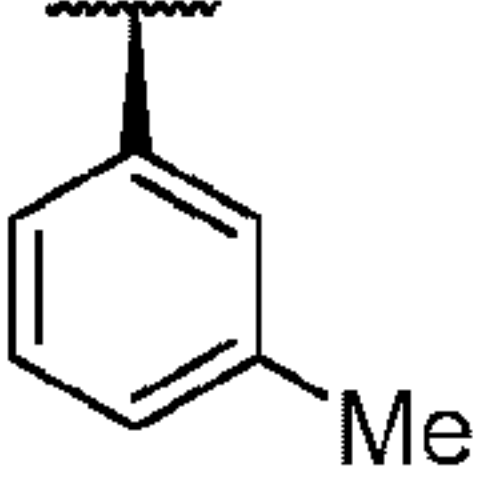
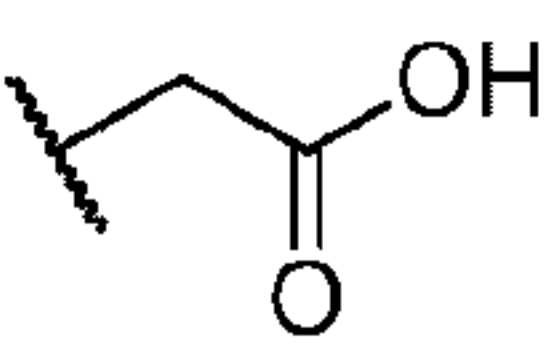
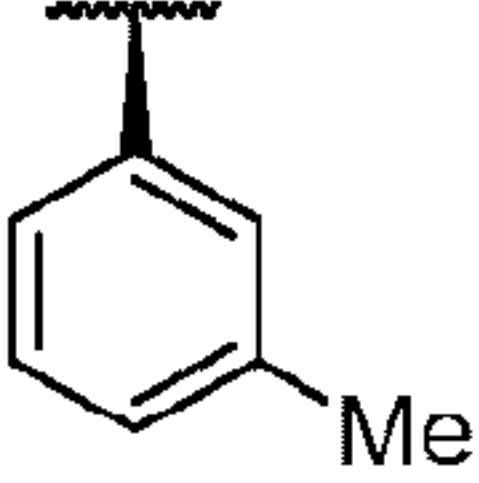
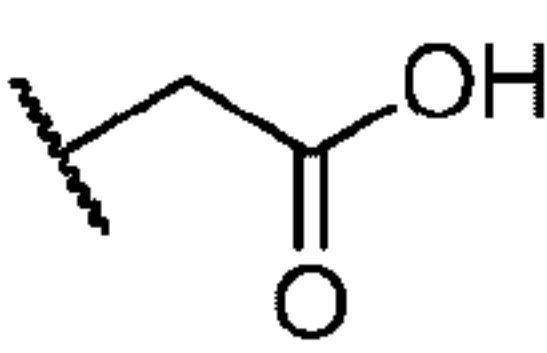
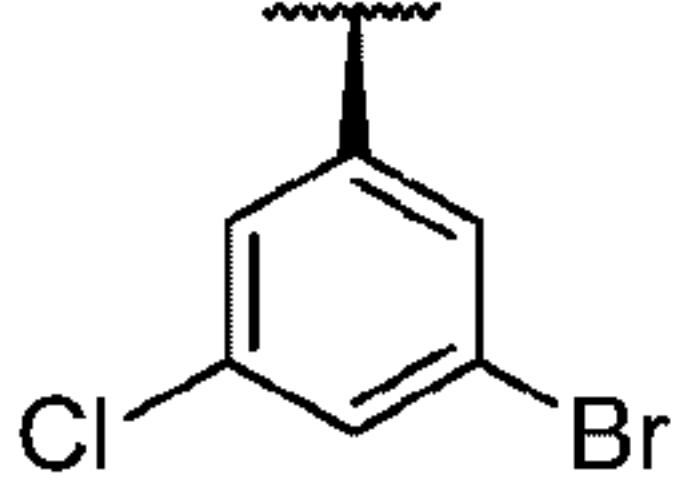
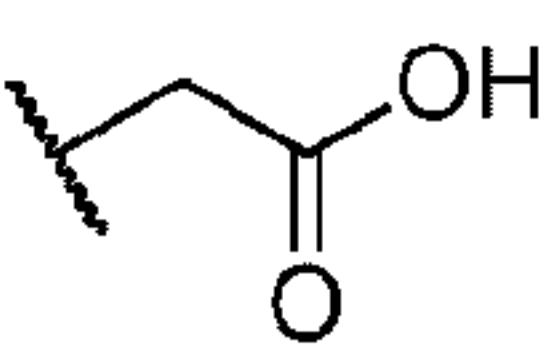
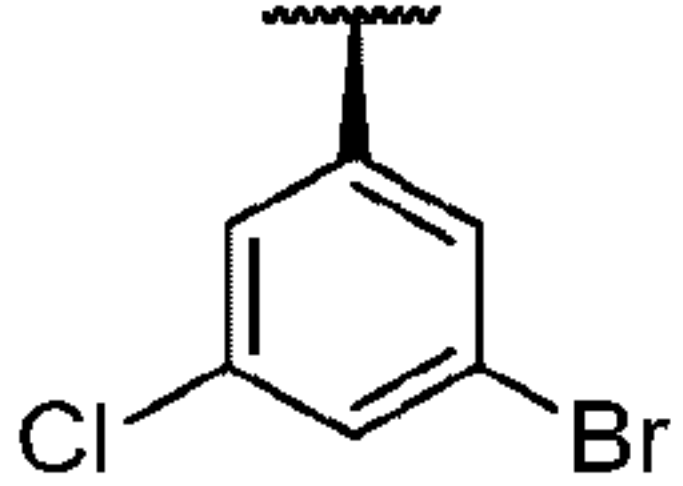
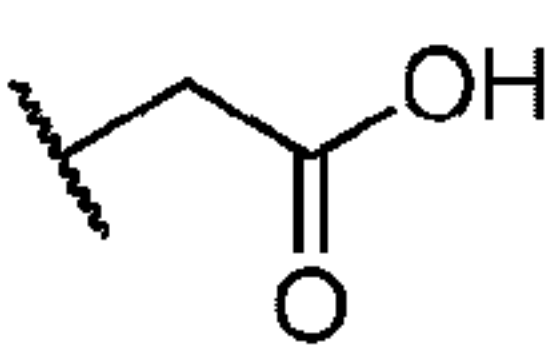
chlorophenyl)-2-(4-chlorophenyl)ethanol (Intermediate A2) with the designated intermediates.



5

Example	R^x	R^y	R^z	Intermediate used
83			H	C1
84		H		C1
85			H	C2
86		H		C2
87			H	C3
88		H		C3
89			H	C4

90		H		C4
91		H		C5
92		H		C6
93		H		C7
94		H		C8
95		H		C9
96			H	C10
97		H		C10
98			H	C11
99		H		C11
100			H	C12

101		H		C12
102			H	C14
103		H		C14
104			H	C15
105		H		C15

EXAMPLE 83

2-((2R,5R,6R)-6-(3-Chloro-5-fluorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

5

First eluting isomer using chiral SFC separation as described in Example 62.

^1H NMR (400 MHz, CDCl_3) δ ppm 0.13 - 0.30 (m, 2 H) 0.58 (d, $J=8.22$ Hz, 1 H) 0.67 (d, $J=4.30$ Hz, 1 H) 0.96 - 1.08 (m, 1 H) 2.41 (dd, $J=13.99$, 7.53 Hz, 1 H) 2.95 - 3.04 (m, 1 H) 3.09 - 3.21 (m, 1 H) 4.09 (dd, $J=13.89$, 6.85 Hz, 1 H) 4.57 (br. s., 1 H) 4.88 (d, $J=3.33$ Hz, 1 H) 5.00 (d, $J=3.52$ Hz, 1 H) 6.28 - 6.38 (m, 1 H) 7.00 (d, $J=8.61$ Hz, 1 H) 7.07 - 7.17 (m, 3 H) 7.20 (s, 1 H) 7.38 (d, $J=8.22$ Hz, 2 H). Mass Spectrum (CI^+) m/z = 451.0 ($\text{M}+1$), 927.1 ($2\text{M}+23$).

10

EXAMPLE 84

2-((2S,5R,6R)-6-(3-Chloro-5-fluorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

5 Second eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.00 (d, *J*=3.91 Hz, 2 H) 0.43 (dd, *J*=15.06, 8.22 Hz, 2 H) 0.73 - 0.88 (m, 1 H) 1.20 - 1.25 (m, 1 H) 2.29 (dd, *J*=14.18, 7.53 Hz, 1 H) 3.12 (br. s., 2 H) 3.95 (dd, *J*=14.18, 6.36 Hz, 1 H) 4.57 (d, *J*=9.59 Hz, 1 H) 4.65 - 4.80 (m, 2 H) 6.54 (d, *J*=8.61 Hz, 1 H) 6.71 (s, 1 H) 6.90 (d, *J*=8.41 Hz, 2 H) 6.97 (dt, *J*=8.36, 1.98 Hz, 1 H) 7.28 (d, *J*=8.41 Hz, 2 H) 8.71 (br. s., 1 H). Mass Spectrum (CI⁺) *m/z* = 451.0 (M+1), 927.1 (2M+23).

EXAMPLE 85

15 2-((2R,5R,6R)-5-(4-Chlorophenyl)-4-(cyclopropylmethyl)-6-(3-fluorophenyl)-3-oxomorpholin-2-yl)acetic acid

First eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.12 - 0.28 (m, 2 H) 0.54 (dd, *J*=8.12, 4.21 Hz, 1 H) 0.60 - 0.68 (m, 1 H) 1.01 (br. s., 1 H) 2.44 (dd, *J*=14.09, 7.63 Hz, 1 H) 2.96 - 3.05 (m, 1 H) 3.08 - 3.18 (m, 1 H) 4.06 (dd, *J*=13.99, 6.16 Hz, 1 H) 4.61 (d, *J*=7.63 Hz, 1 H) 4.90 (d, *J*=3.91 Hz, 1 H) 5.03 (d, *J*=3.91 Hz, 1 H) 7.07 (d, *J*=7.63 Hz, 2 H) 7.12 (d, *J*=8.02 Hz, 3 H) 7.32 - 7.39 (m, 3 H) 7.66 (br. s., 1 H). Mass Spectrum (CI⁺) *m/z* = 418.1 (M+1), 859.2 (2M+23).

25 EXAMPLE 86

2-((2S,5R,6R)-5-(4-Chlorophenyl)-4-(cyclopropylmethyl)-6-(3-fluorophenyl)-3-oxomorpholin-2-yl)acetic acid

Second eluting isomer using chiral SFC separation as described in Example 62.

30 ¹H NMR (400 MHz, CDCl₃) δ ppm 0.00 (d, *J*=4.11 Hz, 2 H) 0.42 (dd, *J*=14.67, 8.02 Hz, 2 H) 0.77 - 0.89 (m, 1 H) 1.21 - 1.25 (m, 1 H) 2.29 (dd, *J*=14.18, 7.53 Hz, 1 H) 3.12 (t,

$J=4.40$ Hz, 2 H) 3.96 (dd, $J=14.09$, 6.46 Hz, 1 H) 4.60 (d, $J=9.59$ Hz, 1 H) 4.71 - 4.80 (m, 2 H) 6.60 (d, $J=7.63$ Hz, 1 H) 6.78 (d, $J=9.39$ Hz, 1 H) 6.88 (d, $J=8.22$ Hz, 2 H) 6.93 (td, $J=8.41$, 2.54 Hz, 1 H) 7.13 (td, $J=7.92$, 6.06 Hz, 1 H) 7.25 (s, 1 H) 8.76 (br. s., 1 H). Mass Spectrum (Cl^+) $m/z = 418.1$ (M+1), 859.2 (2M+23).

5

EXAMPLE 87

2-((2R,5R,6R)-5-(4-Chlorophenyl)-6-(5-chloropyridin-3-yl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

10 First eluting isomer using chiral SFC separation as described in Example 62.

^1H NMR (400 MHz, CDCl_3) δ ppm ppm -0.10 - 0.10 (m, 2 H) 0.30 - 0.49 (m, 2 H) 0.62 - 0.83 (m, 4 H) 2.24 (dd, $J=14.18$, 7.53 Hz, 1 H) 2.81 - 3.09 (m, 2 H) 3.89 (dd, $J=14.38$, 6.94 Hz, 1 H) 4.47 - 4.62 (m, 1 H) 4.55 (br. s., 1 H) 4.74 - 4.91 (m, 2 H) 4.75 - 4.92 (m, 2 H) 4.93 - 4.94 (m, 0 H) 6.93 (d, $J=8.22$ Hz, 2 H) 7.22 (d, $J=8.22$ Hz, 2 H) 7.72 (s, 1 H)

15 8.27 (br. s., 1 H) 8.45 (br. s., 1 H). Mass Spectrum (Cl^+) $m/z = 435.1$ (M+1), 891.1 (2M+23).

EXAMPLE 88

2-((2S,5R,6R)-5-(4-Chlorophenyl)-6-(5-chloropyridin-3-yl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

20

Second eluting isomer using chiral SFC separation as described in Example 62.

^1H NMR (400 MHz, CDCl_3) δ ppm 0.35 - 0.56 (m, 2 H) 0.83 (dd, $J=10.96$, 7.24 Hz, 2 H) 1.25 (s, 2 H) 2.33 (dd, $J=14.18$, 7.53 Hz, 1 H) 3.05 - 3.30 (m, 2 H) 4.00 (dd, $J=14.09$, 6.46 Hz, 1 H) 4.70 - 4.79 (m, 1 H) 4.80 - 4.88 (m, 2 H) 6.98 (d, $J=8.22$ Hz, 2 H) 7.36 (d, $J=8.02$ Hz, 2 H) 7.51 (s, 1 H) 8.23 (br. s., 1 H) 8.62 (br. s., 1 H) 10.09 (br. s., 1 H). Mass Spectrum (Cl^+) $m/z = 435.1$ (M+1), 891.1 (2M+23).

25

EXAMPLE 89

2-((2R,5R,6R)-5-(4-Chlorophenyl)-4-(cyclopropylmethyl)-6-(3-methoxyphenyl)-3-oxomorpholin-2-yl)acetic acid

30

First eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm -0.05 - 0.11 (m, 2 H) 0.30 - 0.51 (m, 2 H) 0.67 - 0.77 (m, 1 H) 0.81 - 0.91 (m, 1 H) 1.00 (t, *J*=7.24 Hz, 1 H) 1.05 - 1.17 (m, 3 H) 2.25 (dd, *J*=14.08, 7.83 Hz, 1 H) 2.67 (d, *J*=7.43 Hz, 1 H) 2.75 (dd, *J*=15.85, 7.04 Hz, 1 H) 2.95 (dd, *J*=15.65, 5.87 Hz, 1 H) 3.62 (s, 3 H) 3.91 (dd, *J*=14.09, 6.46 Hz, 1 H) 4.38 (t, *J*=6.46 Hz, 1 H) 4.72 (d, *J*=3.52 Hz, 1 H) 4.91 (d, *J*=3.52 Hz, 1 H) 6.72 (dd, *J*=8.12, 2.05 Hz, 1 H) 6.75 - 6.81 (m, 2 H) 6.99 (d, *J*=8.61 Hz, 2 H) 7.06 - 7.14 (m, 2 H) 7.19 (d, 2 H). Mass Spectrum (CI⁺) *m/z* = 430.1 (M+1), 883.3 (2M+23).

10

EXAMPLE 90

2-((2S,5R,6R)-5-(4-Chlorophenyl)-4-(cyclopropylmethyl)-6-(3-methoxyphenyl)-3-oxomorpholin-2-yl)acetic acid

15 Second eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.00 (d, *J*=4.11 Hz, 2 H) 0.41 (dd, *J*=16.43, 8.22 Hz, 2 H) 0.81 - 0.86 (m, 1 H) 1.22 (d, 1 H) 2.26 (dd, *J*=14.09, 7.63 Hz, 1 H) 2.82 - 2.90 (m, 1 H) 2.97 - 3.06 (m, 1 H) 3.08 - 3.17 (m, 1 H) 3.67 (s, 3 H) 3.97 (dd, *J*=14.18, 6.36 Hz, 1 H) 4.55 (d, *J*=9.59 Hz, 1 H) 4.70 - 4.81 (m, 2 H) 6.46 - 6.54 (m, 2 H) 6.76 (dd, *J*=8.12, 2.25 Hz, 1 H) 6.88 (d, *J*=8.41 Hz, 2 H) 7.09 (t, *J*=7.92 Hz, 1 H) 7.21 (s, 1 H). Mass Spectrum (CI⁺) *m/z* =430.1 (M+1), 883.3 (2M+23).

20

EXAMPLE 91

2-((2S,5R,6R)-5-(4-Chlorophenyl)-6-(2-chloropyridin-4-yl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

25

Second eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm -0.03 - 0.08 (m, 2 H) 0.37 - 0.56 (m, 2 H) 0.77 - 0.90 (m, 1 H) 2.31 (dd, *J*=14.18, 7.53 Hz, 1 H) 3.17 (dd, *J*=5.09, 2.93 Hz, 2 H) 4.00 (dd, *J*=14.28, 6.46 Hz, 1 H) 4.63 - 4.73 (m, 2 H) 4.78 (t, *J*=5.18 Hz, 1 H) 6.66 (dd, *J*=5.18, 1.27 Hz, 1 H) 6.96 (d, *J*=8.22 Hz, 2 H) 7.05 (s, 1 H) 7.35 (d, *J*=8.02 Hz, 2 H) 8.26 (d,

30

$J=5.09$ Hz, 1 H) 8.59 (br. s., 1 H). Mass Spectrum (CI^+) $m/z = 435.1$ ($M+1$), 893.2 ($2M+23$).

EXAMPLE 92

5 2-((2S,5R,6R)-5-(4-Chlorophenyl)-4-(cyclopropylmethyl)-6-(5-methoxypyridin-3-yl)-3-oxomorpholin-2-yl)acetic acid

First eluting isomer using chiral SFC separation as described in Example 62.

^1H NMR (400 MHz, CDCl_3) δ ppm -0.01 (br. s., 2 H) 0.46 (br. s., 2 H) 0.77 - 0.90 (m, 1
10 H) 1.18 - 1.31 (m, 2 H) 2.36 (d, $J=7.04$ Hz, 1 H) 3.04 - 3.25 (m, 2 H) 3.98 (br. s., 1 H)
4.77 - 4.91 (m, 2 H) 4.96 (d, $J=7.83$ Hz, 1 H) 6.96 - 7.16 (m, 3 H) 7.39 (d, $J=7.43$ Hz, 2
H) 8.31 - 8.45 (m, 1 H). Mass Spectrum (CI^+) $m/z = 431.2$ ($M+1$), 863.2 ($2M+1$).

EXAMPLE 93

15 2-((2S,5R,6R)-5-(4-Chlorophenyl)-4-(cyclopropylmethyl)-6-(3,5-dichlorophenyl)-3-oxomorpholin-2-yl)acetic acid

Second eluting isomer using chiral SFC separation as described in Example 62.

^1H NMR (400 MHz, CDCl_3) δ ppm 0.04 (ddd, $J=3.23, 1.47, 1.17$ Hz, 2 H) 0.38 - 0.53
20 (m, 2 H) 0.78 - 0.90 (m, 1 H) 2.31 (dd, $J=14.18, 7.53$ Hz, 1 H) 3.04 - 3.14 (m, 1 H) 3.14 -
3.23 (m, 1 H) 4.01 (dd, $J=14.18, 6.55$ Hz, 1 H) 4.57 (d, $J=9.59$ Hz, 1 H) 4.68 - 4.80 (m, 2
H) 6.83 (d, $J=1.96$ Hz, 2 H) 6.89 - 6.97 (m, 2 H) 7.22 - 7.29 (m, 2 H) 7.32 (d, $J=8.61$ Hz,
2 H). Mass Spectrum (CI^+) $m/z = 468.1$ ($M+1$), 961.0 ($2M+23$).

25 EXAMPLE 94

2-((2S,5R,6R)-6-(3-Chloro-4-fluorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

Second eluting isomer using chiral SFC separation as described in Example 62.

30 ^1H NMR (400 MHz, CDCl_3) δ ppm 0.00 (d, $J=2.35$ Hz, 2 H) 0.43 (dd, $J=16.24, 8.02$ Hz,
2 H) 0.83 (br. s., 1 H) 2.28 (dd, $J=13.89, 7.24$ Hz, 1 H) 3.10 (br. s., 2 H) 3.93 - 4.03 (m, 1

H) 4.57 (d, $J=9.59$ Hz, 1 H) 4.70 (d, $J=9.59$ Hz, 2 H) 4.74 (d, $J=2.74$ Hz, 2 H) 6.62 - 6.72 (m, 1 H) 6.84 - 7.00 (m, 3 H) 7.14 (d, $J=6.06$ Hz, 1 H) 7.21 - 7.33 (m, 1 H). Mass Spectrum (CI^+) $m/z = 452.0$ ($M+1$), 925.2 ($2M+23$).

5

EXAMPLE 95

2-((2S,5R,6R)-5-(4-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-6-(3-(trifluoromethoxy)phenyl)morpholin-2-yl)acetic acid

Second eluting isomer using chiral SFC separation as described in Example 62.

10 ^1H NMR (400 MHz, CDCl_3) δ ppm 0.02 (d, $J=3.33$ Hz, 2 H) 0.37 - 0.52 (m, 2 H) 0.79 - 0.90 (m, 1 H) 1.19 - 1.28 (m, 1 H) 2.30 (dd, $J=14.09$, 7.63 Hz, 1 H) 3.03 - 3.20 (m, 2 H) 4.00 (dd, $J=14.18$, 6.36 Hz, 1 H) 4.60 - 4.69 (m, 1 H) 4.70 - 4.75 (m, 1 H) 4.79 (br. s., 1 H) 6.78 (s, 1 H) 6.89 (d, $J=8.41$ Hz, 2 H) 6.94 (d, $J=7.82$ Hz, 1 H) 7.12 (d, $J=8.22$ Hz, 1 H) 7.23 - 7.26 (m, 2 H) 7.27 (s, 1 H). Mass Spectrum (CI^+) $m/z = 483.1$ ($M+1$), 991.2
15 ($2M+23$).

EXAMPLE 96

2-((2R,5R,6R)-5-(4-Chlorophenyl)-4-(cyclopropylmethyl)-6-(3,5-difluorophenyl)-3-oxomorpholin-2-yl)acetic acid

20

First eluting isomer using chiral SFC separation as described in Example 62.

^1H NMR (400 MHz, CDCl_3) δ ppm -0.04 - 0.12 (m, 2 H) 0.30 - 0.51 (m, 2 H) 0.80 - 0.88 (m, 2 H) 2.22 (dd, $J=14.18$, 7.73 Hz, 1 H) 2.76 (dd, $J=16.24$, 7.24 Hz, 1 H) 2.96 (dd, $J=16.24$, 5.28 Hz, 1 H) 3.86 - 3.93 (m, 1 H) 4.34 (dd, $J=7.14$, 5.38 Hz, 1 H) 4.69 (d, $J=3.72$ Hz, 1 H) 4.82 (d, $J=3.52$ Hz, 1 H) 6.59 - 6.67 (m, 1 H) 6.76 (d, $J=6.06$ Hz, 2 H) 6.95 (d, $J=8.41$ Hz, 2 H) 7.19 (d, 2 H). Mass Spectrum (CI^+) $m/z = 436.1$ ($M+1$), 895.2
25 ($2M+23$).

EXAMPLE 97

30 2-((2S,5R,6R)-5-(4-Chlorophenyl)-4-(cyclopropylmethyl)-6-(3,5-difluorophenyl)-3-oxomorpholin-2-yl)acetic acid

Second eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.00 (br. s., 2 H) 0.42 (dd, *J*=19.56, 8.22 Hz, 2 H)
0.80 - 0.90 (m, 2 H) 2.27 (dd, *J*=13.79, 7.34 Hz, 1 H) 2.97 - 3.15 (m, 2 H) 3.97 (dd,
5 *J*=13.79, 5.77 Hz, 1 H) 4.57 - 4.66 (m, 1 H) 4.71 (d, *J*=9.39 Hz, 1 H) 4.81 (br. s., 1 H)
6.50 (d, *J*=5.87 Hz, 2 H) 6.69 (t, *J*=8.61 Hz, 1 H) 6.94 (d, *J*=7.83 Hz, 2 H) 7.28 (d, 1 H)
7.30 (s, 1 H). Mass Spectrum (CI⁺) *m/z* = 436.1 (M+1), 895.2 (2M+23).

EXAMPLE 98

10 2-((2R,5R,6R)-5-(4-Chlorophenyl)-6-(3-cyano-5-fluorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

First eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm -0.05 - 0.11 (m, 2 H) 0.35 - 0.53 (m, 2 H) 0.76 - 0.88
15 (m, 1 H) 2.24 (dd, *J*=14.28, 7.63 Hz, 1 H) 2.86 (dd, *J*=16.53, 8.12 Hz, 1 H) 2.93 - 3.06
(m, 1 H) 3.90 (dd, *J*=14.28, 6.65 Hz, 1 H) 4.50 (dd, *J*=8.12, 4.01 Hz, 1 H) 4.76 (q, *J*=4.89
Hz, 2 H) 6.93 (d, *J*=8.22 Hz, 2 H) 7.10 (s, 1 H) 7.22 (d, *J*=8.41 Hz, 2 H) 7.34 (d, *J*=15.45
Hz, 2 H) 7.46 (s, 1 H). Mass Spectrum (CI⁺) *m/z* = 459.1 (M+1), 941.0 (2M+23).

EXAMPLE 99

20 2-((2S,5R,6R)-5-(4-Chlorophenyl)-6-(3-cyano-5-fluorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

Second eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm -0.02 - 0.03 (m, 2 H) 0.36 - 0.52 (m, 2 H) 0.76 - 0.88
25 (m, 1 H) 2.30 (dd, *J*=14.28, 7.63 Hz, 1 H) 3.16 (dd, *J*=9.19, 5.09 Hz, 2 H) 3.53 (s, 1 H)
3.93 - 4.03 (m, 2 H) 4.63 - 4.74 (m, 2 H) 4.77 (t, *J*=4.79 Hz, 1 H) 6.88 - 6.95 (m, 2 H)
7.09 - 7.16 (m, 2 H) 7.32 (d, *J*=8.41 Hz, 2 H) 7.52 (t, *J*=1.76 Hz, 1 H). Mass Spectrum
(CI⁺) *m/z* = 459.1 (M+1), 941.1 (2M+23).

30

EXAMPLE 100

2-((2R,5R,6R)-6-(5-Chloro-2-fluorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

5 First eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.00 (br. s., 2 H) 0.42 (dd, *J*=14.57, 8.71 Hz, 2 H) 0.78 - 0.96 (m, 2 H) 2.28 (dd, *J*=13.50, 7.43 Hz, 1 H) 2.95 - 3.17 (m, 2 H) 3.99 (dd, *J*=13.79, 5.18 Hz, 1 H) 4.72 - 4.88 (m, 2 H) 4.97 (d, *J*=9.19 Hz, 1 H) 6.72 (t, *J*=8.51 Hz, 1 H) 6.94 (d, *J*=7.24 Hz, 2 H) 7.13 - 7.33 (m, 3 H) 7.51 (br. s., 1 H). Mass Spectrum (CI⁺)
10 m/z = 452.0 (M+1), 927.1 (2M+23).

EXAMPLE 101

2-((2S,5R,6R)-6-(5-Chloro-2-fluorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

15

Second eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.01 (d, *J*=3.72 Hz, 2 H) 0.40 (dd, *J*=17.80, 8.02 Hz, 2 H) 0.79 - 0.88 (m, 1 H) 0.92 (t, *J*=7.24 Hz, 1 H) 1.06 - 1.13 (m, 2 H) 2.21 (dd, *J*=14.09, 7.43 Hz, 1 H) 2.64 (q, *J*=7.11 Hz, 1 H) 2.76 - 2.86 (m, 1 H) 2.88 - 2.96 (m, 1 H) 3.89 (dd, *J*=13.89, 6.65 Hz, 1 H) 3.92 - 4.01 (m, 1 H) 4.51 (br. s., 1 H) 4.73 (d, *J*=5.28 Hz, 1 H) 5.00 (d, *J*=5.09 Hz, 1 H) 6.74 (t, *J*=9.10 Hz, 1 H) 6.94 (d, *J*=8.22 Hz, 2 H) 7.12 - 7.20 (m, 3 H) 7.48 (dd, 1 H). Mass Spectrum (CI⁺) m/z = 452.0 (M+1), 927.1 (2M+23).

20

EXAMPLE 102

25 2-((2R,5R,6R)-5-(4-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-6-(m-tolyl)morpholin-2-yl)acetic acid

First eluting isomer using chiral SFC separation as described in Example 62.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.17 - 0.35 (m, 2 H) 0.48 - 0.75 (m, 2 H) 1.02 - 1.16 (m, 1 H) 2.37 (s, 3 H) 2.43 - 2.53 (m, 1 H) 2.90 (dd, *J*=15.94, 4.99 Hz, 1 H) 3.15 (dd, *J*=16.04, 8.02 Hz, 1 H) 4.02 - 4.15 (m, 1 H) 4.37 (d, *J*=14.08 Hz, 1 H) 4.37 (s, 1 H) 4.90

30

(d, $J=2.35$ Hz, 1 H) 5.13 (d, $J=2.54$ Hz, 1 H) 7.13 - 7.23 (m, 3 H) 7.27 (s, 3 H) 7.31 (br. s., 1 H) 7.34 - 7.42 (m, 1 H). Mass Spectrum (CI^+) $m/z = 414.1$ ($M+1$), 851.2 ($2M+23$).

EXAMPLE 103

5 2-((2S,5R,6R)-5-(4-Chlorophenyl)-4-(cyclopropylmethyl)-3-oxo-6-(m-tolyl)morpholin-2-yl)acetic acid

Second eluting isomer using chiral SFC separation as described in Example 62.

^1H NMR (400 MHz, CDCl_3) δ ppm 0.05 (d, $J=3.72$ Hz, 2 H) 0.38 - 0.54 (m, 2 H) 0.84 -
10 0.94 (m, 1 H) 1.25 - 1.30 (m, 1 H) 2.28 (s, 3 H) 2.31 - 2.42 (m, 1 H) 3.16 (br. s., 2 H)
4.00 (dd, $J=14.18$, 6.36 Hz, 1 H) 4.59 (d, $J=9.39$ Hz, 1 H) 4.79 (br. s., 1 H) 4.84 (d,
 $J=9.59$ Hz, 1 H) 6.73 (d, $J=6.65$ Hz, 1 H) 6.85 (s, 1 H) 6.90 (d, $J=8.41$ Hz, 2 H) 7.06 -
7.12 (m, 2 H) 7.27 (d, $J=3.13$ Hz, 1 H) 9.44 (br. s., 1 H). Mass Spectrum (CI^+) $m/z =$
414.1 ($M+1$), 851.2 ($2M+23$).

15

EXAMPLE 104

2-((2R,5R,6R)-6-(3-Bromo-5-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

20 First eluting isomer using chiral SFC separation as described in Example 62.

^1H NMR (400 MHz, CDCl_3) δ ppm -0.01 (dd, $J=3.03$, 1.66 Hz, 2 H) 0.35 - 0.48 (m, 2 H)
0.73 - 0.88 (m, 1 H) 2.27 (dd, $J=14.28$, 7.43 Hz, 1 H) 3.00 - 3.22 (m, 2 H) 3.97 (dd,
 $J=14.28$, 6.65 Hz, 1 H) 4.53 (d, $J=9.59$ Hz, 1 H) 4.67 (d, $J=9.59$ Hz, 1 H) 4.72 (t, $J=5.18$
Hz, 1 H) 6.83 (t, $J=1.47$ Hz, 1 H) 6.88 (s, 1 H) 6.91 (d, $J=3.13$ Hz, 2 H) 7.29 (d, $J=8.41$
25 Hz, 2 H) 7.38 (t, $J=1.76$ Hz, 1 H) 7.59 (br. s., 1 H). Mass Spectrum (CI^+) $m/z = 514.0$
($M+1$).

EXAMPLE 105

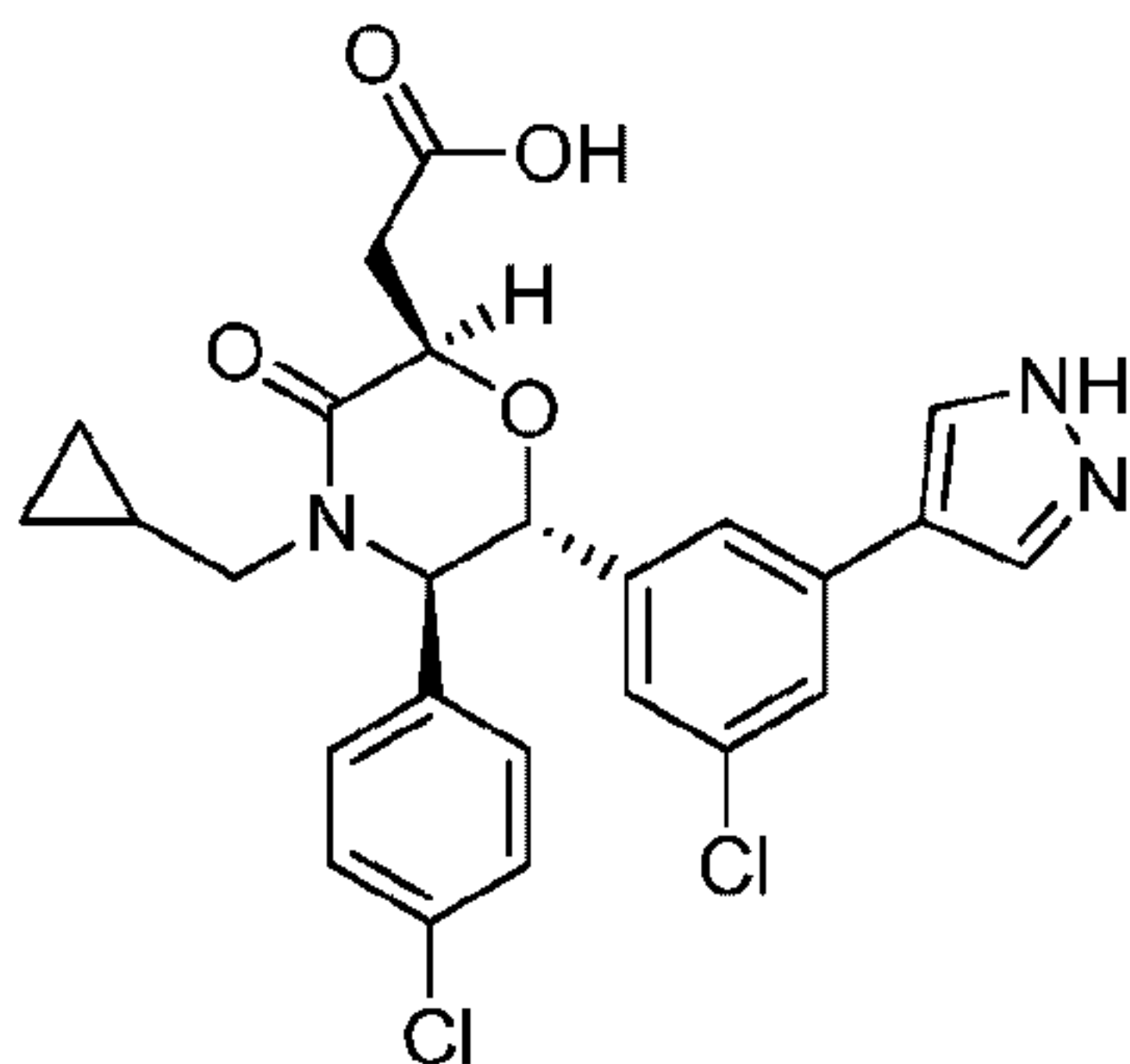
30 2-((2S,5R,6R)-6-(3-Bromo-5-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

Second eluting isomer using chiral SFC separation as described in Example 62.

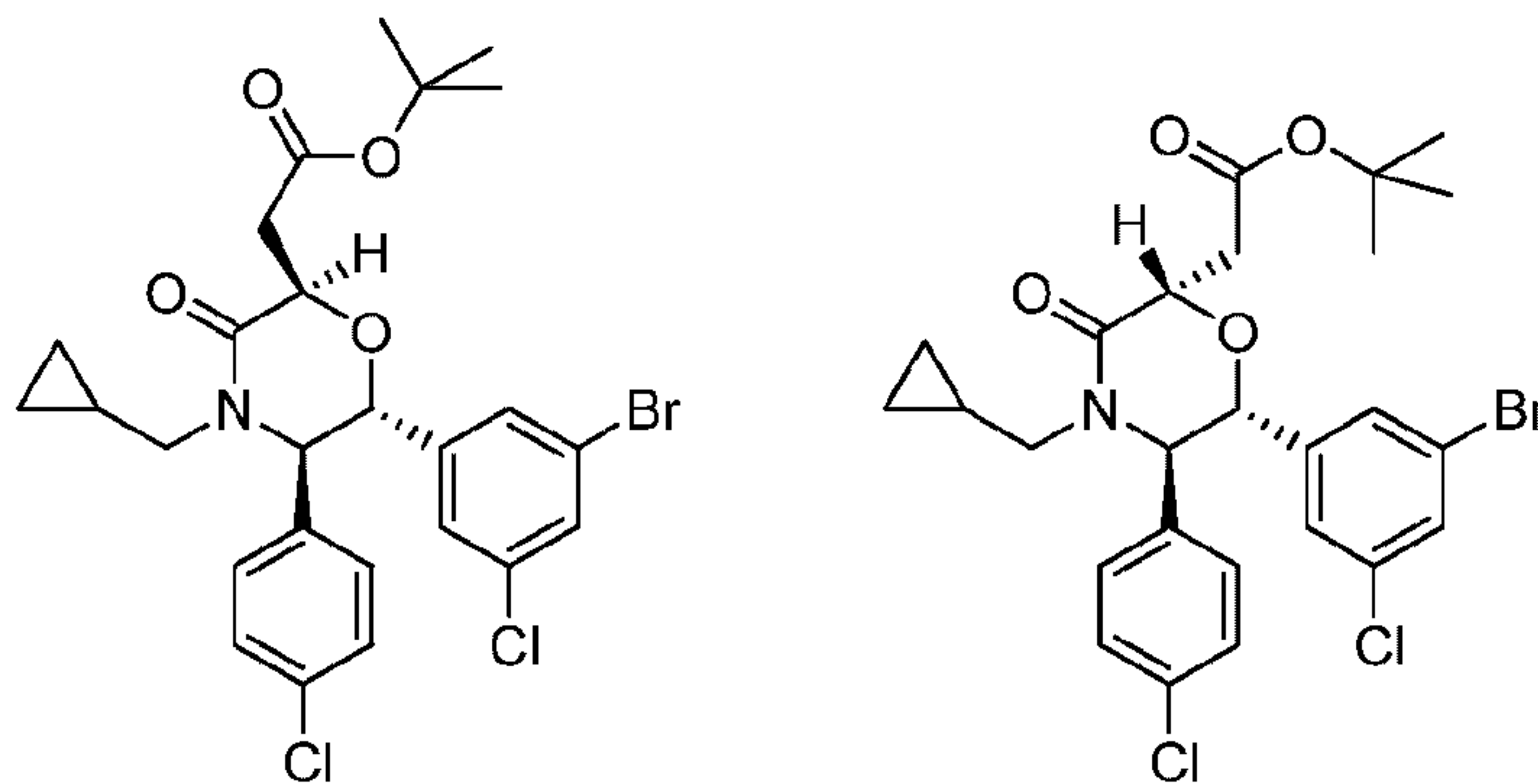
¹H NMR (400 MHz, CDCl₃) δ ppm -0.02 (d, *J*=19.76 Hz, 2 H) 0.24 - 0.51 (m, 2 H) 0.79 (br. s., 1 H) 0.91 - 1.02 (m, 2 H) 1.02 - 1.14 (m, 1 H) 2.02 - 2.22 (m, 1 H) 2.59 - 2.77 (m, 2 H) 2.85 (d, *J*=11.54 Hz, 1 H) 3.78 - 3.97 (m, 1 H) 4.43 (br. s., 1 H) 4.59 - 4.76 (m, 2 H) 5 6.91 (d, *J*=7.24 Hz, 2 H) 7.01 - 7.11 (m, 3 H) 7.11 - 7.22 (m, 3 H). Mass Spectrum (CI⁺) *m/e* = 514.0 (M+1).

EXAMPLE 106

2-((2R,5R,6R)-6-(3-Chloro-5-(1H-pyrazol-4-yl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

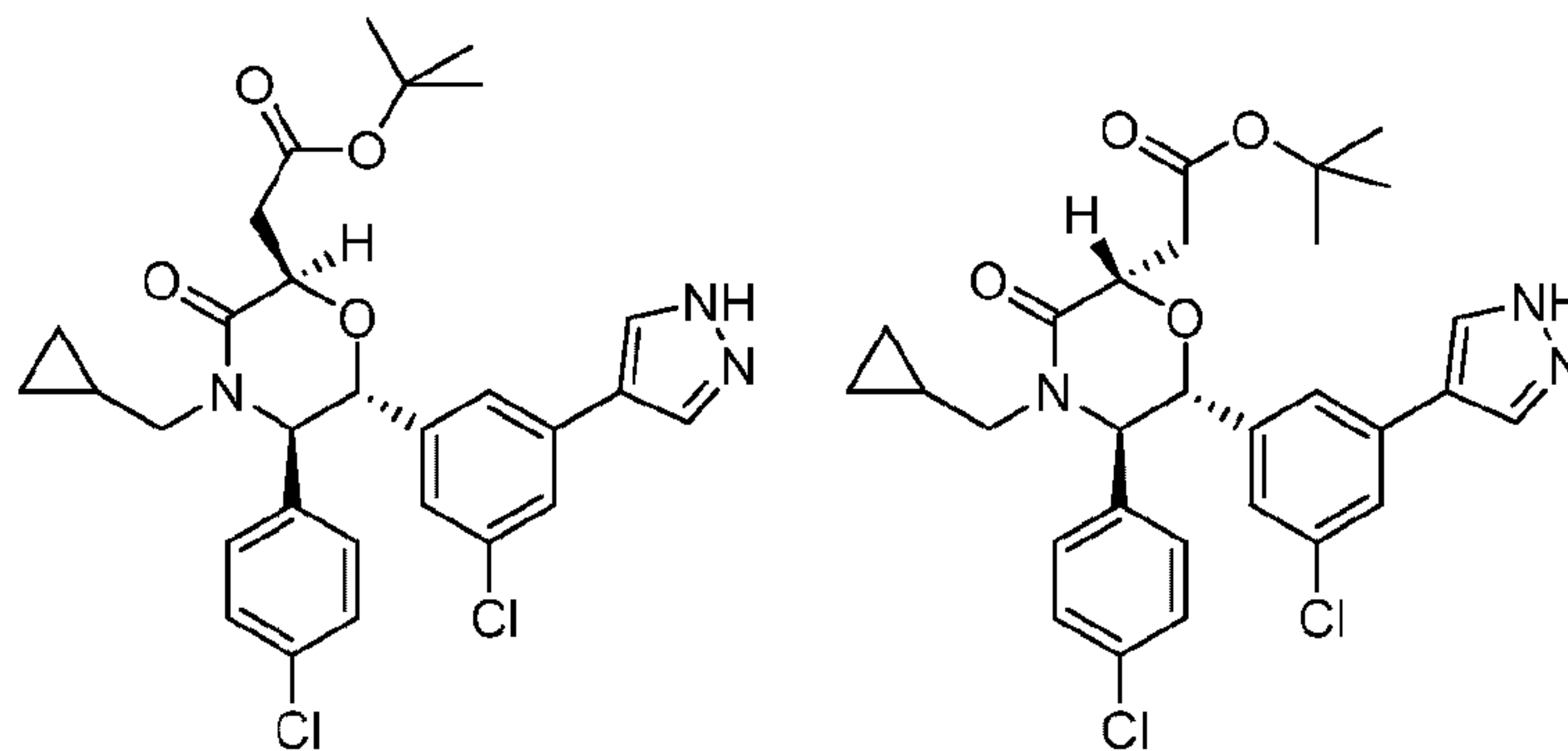


Step A. *tert*-Butyl 2-((2R,5R,6R)-6-(3-bromo-5-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and *tert*-Butyl 2-((2S,5R,6R)-6-(3-bromo-5-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate



The title compound was prepared by a procedure analogous to the one described in Example 9, step A to ttep D, replacing (1R,2R)-2-amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol (Intermediate A2) with (1R,2R)-2-amino-1-(3-bromo-5-chlorophenyl)-2-(4-chlorophenyl) ethanol (Intermediate C15).

Step B. *tert*-Butyl 2-((2R,5R,6R)-6-(3-chloro-5-(1H-pyrazol-4-yl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and *tert*-Butyl 2-((2S,5R,6R)-6-(3-chloro-5-(1H-pyrazol-4-yl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate



A mixture of *tert*-Butyl 2-((2R,5R,6R)-6-(3-bromo-5-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and *tert*-butyl 2-((2S,5R,6R)-6-(3-bromo-5-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate (100 mg, 0.176 mmol, Example 106, Step A), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (155 mg, 0.527 mmol; Acros Organics, Belgium), 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (7.17 mg, 8.78 μ mol; Strem Chemicals, Inc., Newburyport, MA) and sodium carbonate (0.314 mL, 0.878 mmol) in 1 mL of water were mixed in 1 mL of dioxane. The reaction mixture was purged with nitrogen for a few minutes. The mixture was heated to 100°C for 16 hours. After cooling to rt, the reaction mixture was filtered through a Chem ElutTM cartridge (Agilent technologies, Santa Clara, CA), washed with 50 mL of DCM and concentrated *in vacuo*. The crude material was purified by chromatography on silica gel (0 to 100% EtOAc/Hexane, gradient elution) to provide the title compounds as a

mixture of two diastereomers, which was used in the next step without further purification or separation.

Mass Spectrum (ESI) $m/z = 556.2$ (M+1).

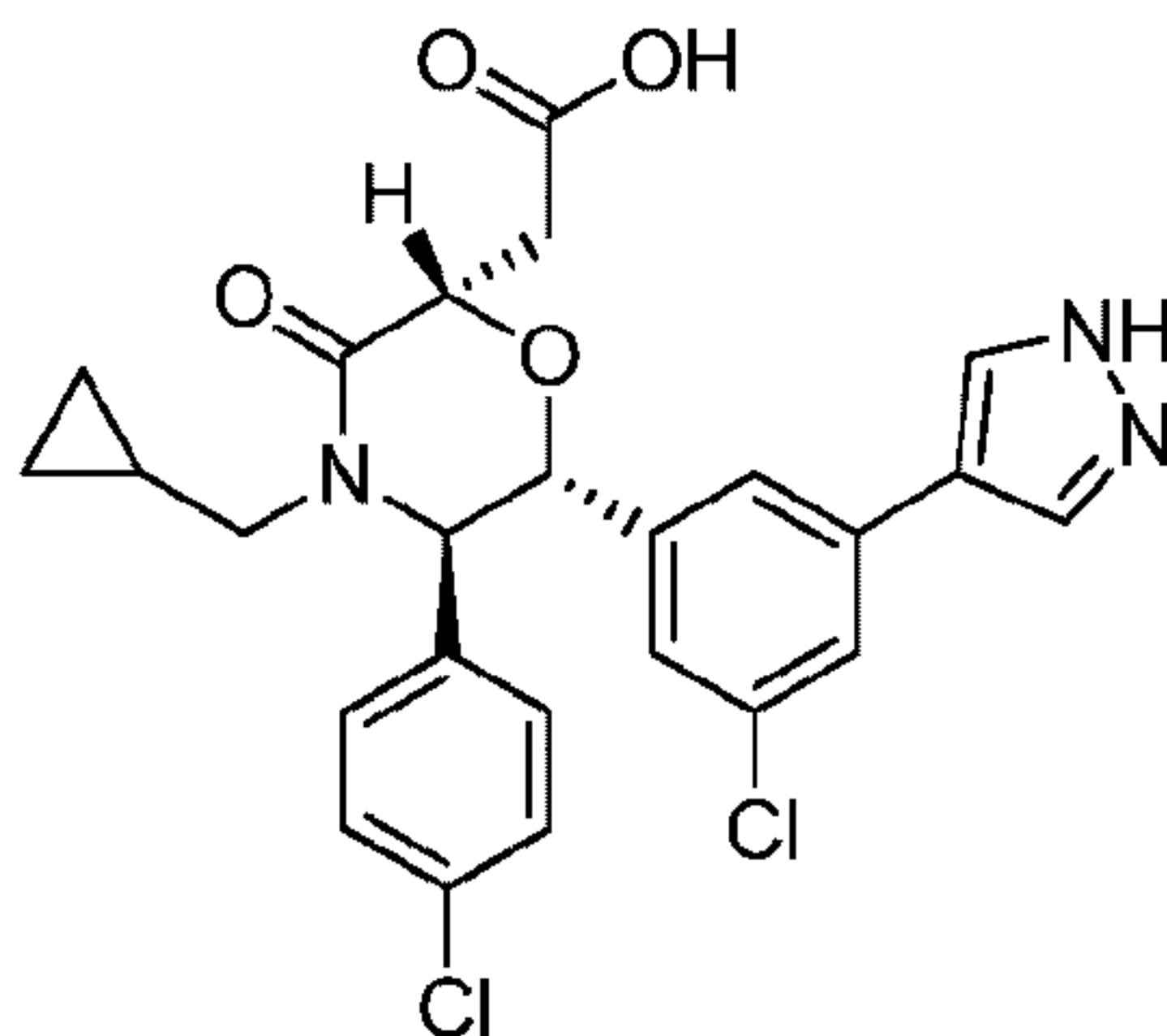
- 5 Step C. 2-((2R,5R,6R)-6-(3-Chloro-5-(1H-pyrazol-4-yl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

A mixture of tert-butyl 2-((2R,5R,6R)-6-(3-chloro-5-(1H-pyrazol-4-yl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and tert-butyl 2-
 10 ((2S,5R,6R)-6-(3-chloro-5-(1H-pyrazol-4-yl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate (59 mg, 0.106 mmol, Example 106, Step B) in 2 mL of DCM was treated with 1 mL of TFA at rt for 2 h. The reaction mixture was evaporated to dryness and purified on a 12 g silica gel column (0 to 100% EtOAc / hexanes, gradient elution) to provide 17mg of white solid as a mixture of two
 15 diastereomers. The mixture was concentrated under reduced pressure. Chiral purification was carried out via SFC using MeOH (0.2%DEA) + 60 g/min CO₂ on a Thar 80 SFC. Outlet pressure 100 bar; Temp. 20°C; Wavelength 220 nm. Toluene followed by ethanol was used to azeotrope off the diethylamine employed as co-solvent during SFC. The title compound was obtained as the first eluting isomer. ¹H NMR (400 MHz, CDCl₃) δ ppm
 20 0.06 - 0.24 (m, 2 H) 0.49 (tt, $J=8.71$, 4.60 Hz, 1 H) 0.59 (tt, $J=8.51$, 4.50 Hz, 1 H) 0.91 - 1.03 (m, 1 H) 1.14 (t, $J=7.24$ Hz, 6 H) 2.33 (dd, $J=14.18$, 7.73 Hz, 1 H) 2.77 (q, $J=7.24$ Hz, 4 H) 2.94 (dd, $J=15.06$, 10.56 Hz, 1 H) 3.10 (dd, $J=15.26$, 3.13 Hz, 1 H) 4.08 (dd, $J=14.09$, 6.46 Hz, 1 H) 4.89 (dd, $J=10.56$, 3.13 Hz, 1 H) 4.92 - 5.01 (m, 2 H) 7.06 - 7.13 (m, 3 H) 7.22 (s, 1 H) 7.29 - 7.35 (m, 3 H) 7.55 (s, 2 H). Mass Spectrum (CI⁺) $m/z =$
 25 500.0 (M+1).

EXAMPLE 107

2-((2S,5R,6R)-6-(3-Chloro-5-(1H-pyrazol-4-yl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid

30

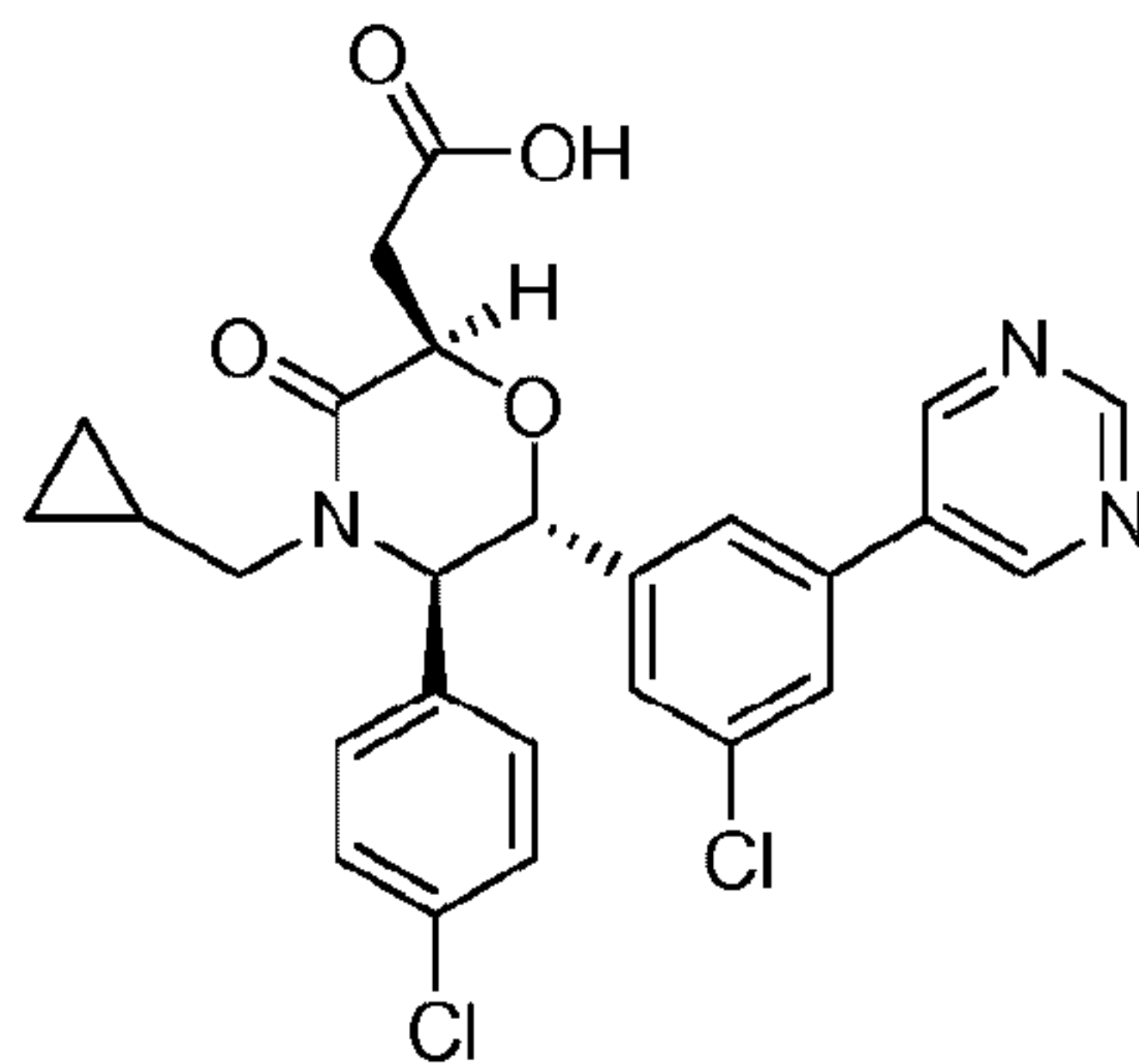


The title compound was obtained as the second eluting isomer from Example 106, Step C. ¹H NMR (400 MHz, CDCl₃) δ ppm -0.02 - 0.07 (m, 2 H) 0.32 - 0.49 (m, 2 H) 0.79 - 0.88 (m, 1 H) 1.22 (t, *J*=7.24 Hz, 6 H) 2.30 (dd, *J*=14.28, 7.63 Hz, 1 H) 2.73 - 2.93 (m, 5 H) 3.24 (dd, *J*=15.85, 3.33 Hz, 1 H) 4.01 (dd, *J*=14.18, 6.36 Hz, 1 H) 4.49 (d, *J*=9.59 Hz, 1 H) 4.68 (d, *J*=9.59 Hz, 1 H) 4.92 (dd, *J*=8.71, 3.42 Hz, 1 H) 6.51 (s, 1 H) 6.86 (s, 1 H) 6.95 (d, *J*=8.22 Hz, 2 H) 7.16 (s, 1 H) 7.30 (s, 2 H) 7.37 (s, 2 H). Mass Spectrum (CI⁺) *m/z* = 500.0 (M+1).

10

EXAMPLE 108

2-((2R,5R,6R)-6-(3-Chloro-5-(pyrimidin-5-yl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid



15

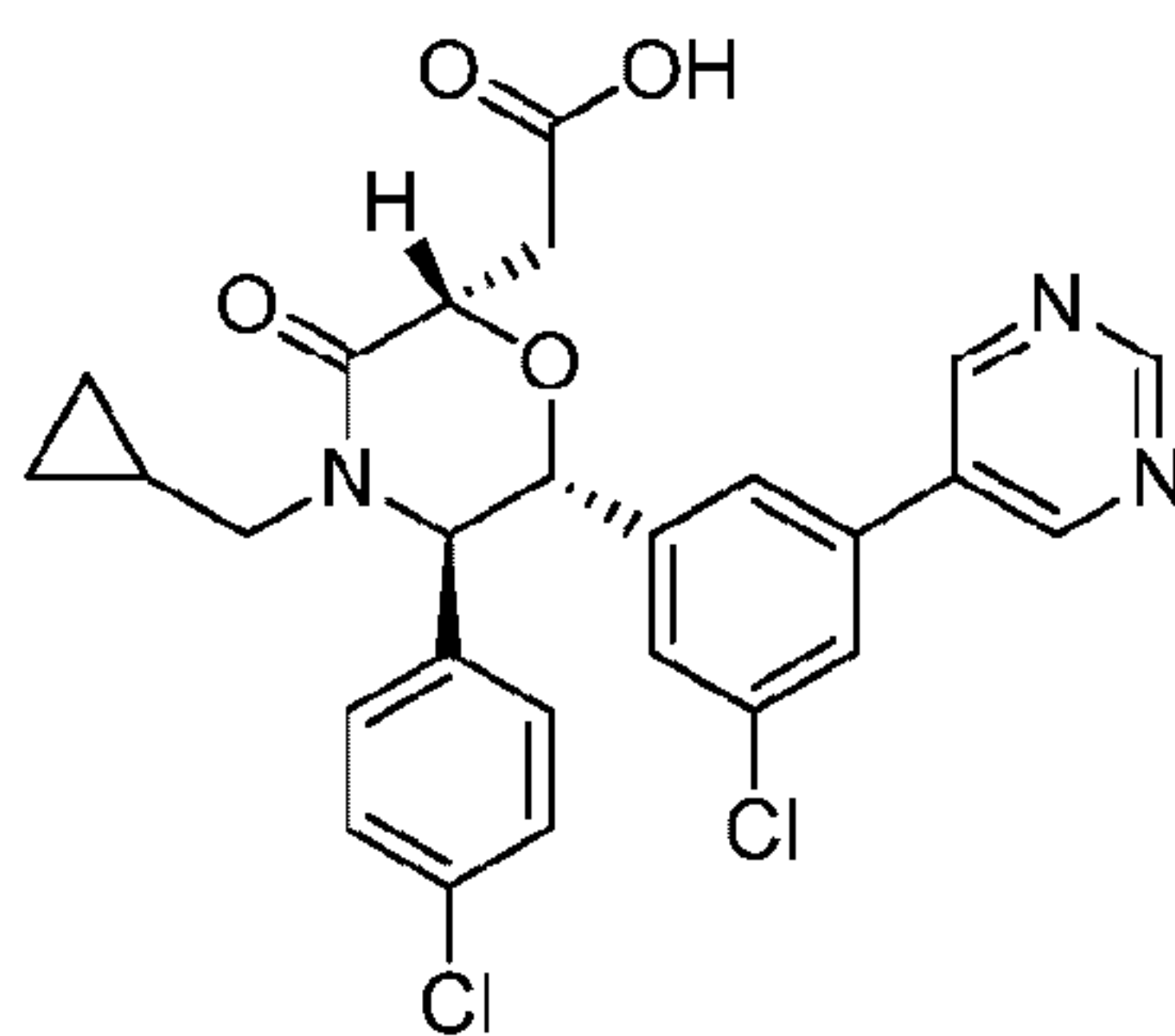
The title compound was obtained by a procedure analogous to the one described in Example 106 Step B and Step C, replacing tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate with pyrimidin-5-ylboronic acid (Combi-Blocks Inc., San Diego, CA), as the first eluting isomer using chiral SFC separation as

20

described in Example 106, Step C. ^1H NMR (400 MHz, CDCl_3) δ ppm 0.13 (dq, $J=9.51$, 4.85 Hz, 1 H) 0.21 (dq, $J=9.44$, 4.68 Hz, 1 H) 0.50 (tt, $J=8.73$, 4.57 Hz, 1 H) 0.56 - 0.65 (m, 1 H) 0.80 - 1.04 (m, 2 H) 1.20 (t, $J=7.34$ Hz, 6 H) 2.34 (dd, $J=14.08$, 7.63 Hz, 1 H) 2.89 (q, $J=7.37$ Hz, 4 H) 3.07 (dd, $J=15.75$, 3.42 Hz, 1 H) 4.08 (dd, $J=14.09$, 6.46 Hz, 1 H) 4.78 (dd, $J=9.10$, 3.42 Hz, 1 H) 5.00 (s, 2 H) 7.15 (d, $J=8.22$ Hz, 2 H) 7.33 - 7.39 (m, 3 H) 7.47 - 7.53 (m, 2 H) 8.89 (s, 2 H) 9.21 (s, 1 H). Mass Spectrum (CI^+) $m/z = 512.0$ (M+1).

EXAMPLE 109

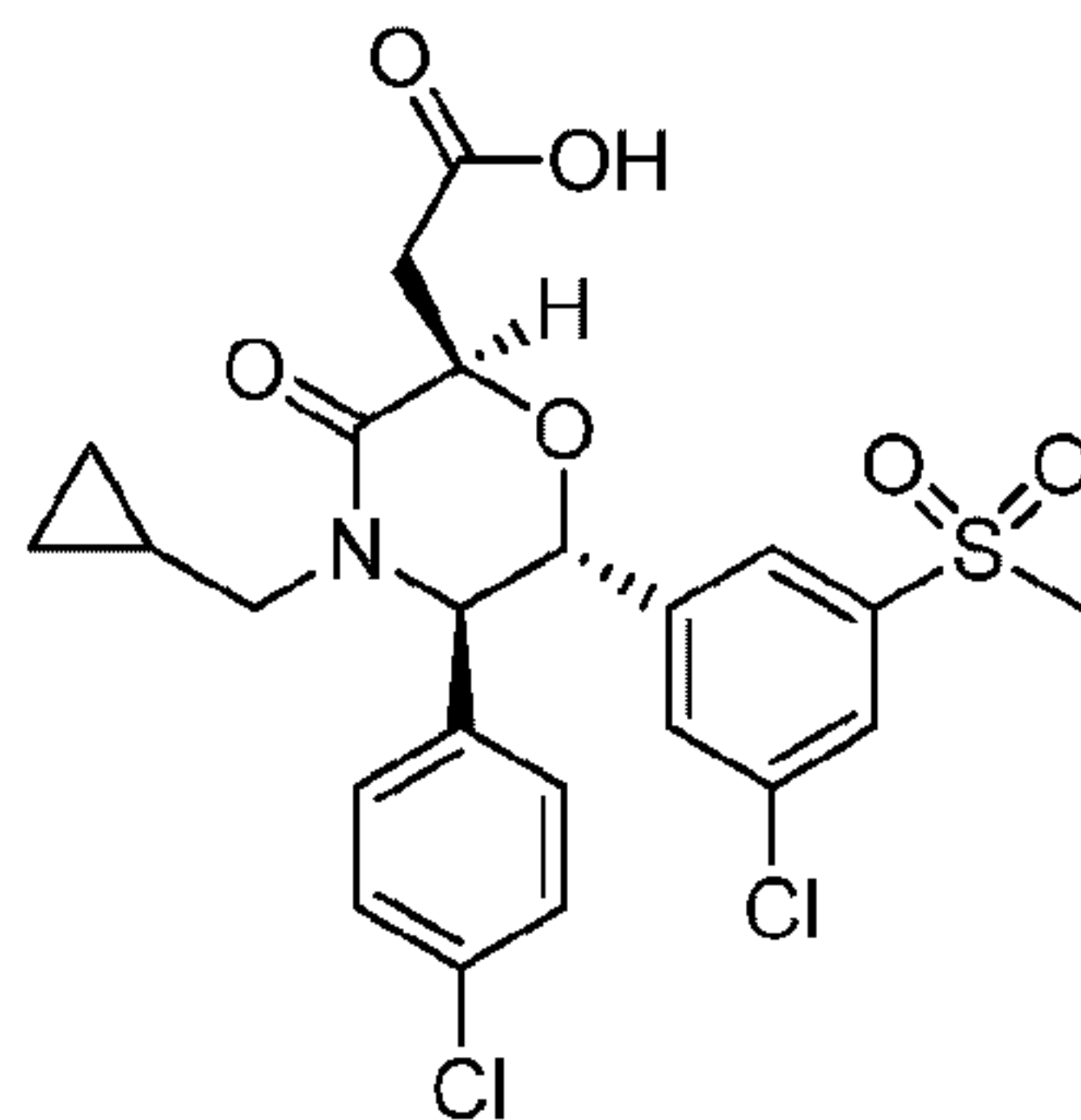
2-((2S,5R,6R)-6-(3-Chloro-5-(pyrimidin-5-yl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid



The title compound was obtained by a procedure analogous to the one described in Example 106 Step B and Step C, replacing tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate with pyrimidin-5-ylboronic acid (Combi-Blocks Inc., San Diego, CA), as the second eluting isomer using chiral SFC separation as described in Example 106, Step C. ^1H NMR (400 MHz, CDCl_3) δ ppm -0.03 - 0.07 (m, 2 H) 0.35 - 0.43 (m, 1 H) 0.43 - 0.51 (m, 1 H) 0.81 - 0.90 (m, 1 H) 1.19 - 1.26 (m, 6 H) 2.31 (dd, $J=14.08$, 7.63 Hz, 1 H) 2.86 (q, $J=7.30$ Hz, 4 H) 3.13 (dd, $J=16.04$, 4.50 Hz, 1 H) 3.49 (q, $J=7.04$ Hz, 1 H) 4.01 (dd, $J=14.28$, 6.26 Hz, 1 H) 4.68 - 4.78 (m, 2 H) 4.87 (dd, $J=6.94$, 4.60 Hz, 1 H) 6.79 (t, $J=1.37$ Hz, 1 H) 6.98 (d, $J=8.41$ Hz, 2 H) 7.25 (t, $J=1.57$ Hz, 1 H) 7.32 (d, $J=8.41$ Hz, 2 H) 7.44 (t, $J=1.86$ Hz, 1 H) 8.69 (s, 2 H) 9.22 (s, 1 H). Mass Spectrum (CI^+) $m/z = 512.0$ (M+1).

EXAMPLE 110

2-((2R,5R,6R)-6-(3-Chloro-5-(methylsulfonyl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid



5

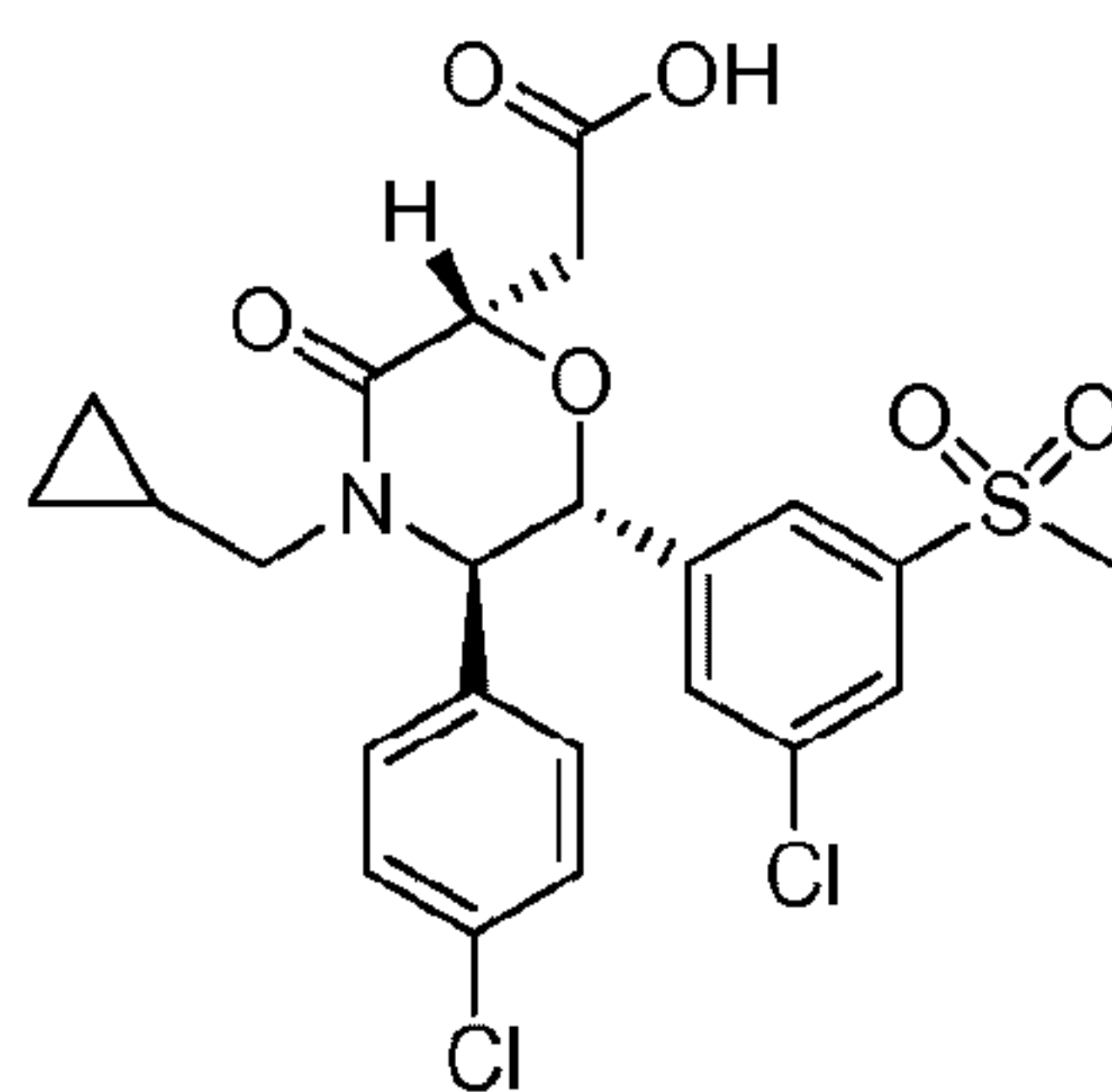
A mixture of *tert*-Butyl 2-((2R,5R,6R)-6-(3-bromo-5-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate and *tert*-butyl 2-((2S,5R,6R)-6-(3-bromo-5-chlorophenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetate (51 mg, 0.090 mmol, Example 106, Step A), copper (I) iodide (4.55 mg, 0.134 mmol) and methanesulphinic acid, sodium salt (36.6 mg, 0.358 mmol) were mixed in DMF. N,N'-dimethylethylenediamine (0.048 mL, 0.448 mmol) was injected. The reaction mixture was purged with nitrogen for 1 minute, then heated to 125°C for 16 hours. After cooling to rt, the reaction mixture was partitioned between EtOAc and water and the layers were separated. The organic layer was washed with brine, dried over MgSO₄, filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by chromatography on silica gel (0 to 100%, EtOAc / hexane, gradient elution) to provide 103 mg of product as a mixture of two diastereomers. Chiral purification was carried out via SFC using MeOH (0.2%DEA) + 60 g/min CO₂ on a Thar 80 SFC. Outlet pressure 100 bar; Temp. 20°C; Wavelength 220 nm. The pooled fractions containing the first eluting isomer were treated with 1 mL TFA/DCM (1:2) at room temperature for 2 hours, concentrated *in vacuo*, and purified by reverse phase HPLC on a 250 x 30 mm 10 μm C₁₈ column (Phenomenex, Torrance, CA; 10 to 90% MeCN/water with 0.1% TFA) to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.11 - 0.29 (m, 2 H) 0.52 - 0.63 (m, 1 H) 0.65 - 0.76 (m, 1 H) 0.94 -

25

1.08 (m, 1 H) 2.37-2.39 (m, $J=13.89$ Hz, 1 H) 2.96 (dd, $J=16.63, 8.02$ Hz, 1 H) 3.04 (s, 3 H) 3.21 (dd, $J=16.53, 4.60$ Hz, 1 H) 4.12 (dd, $J=13.99, 6.55$ Hz, 1 H) 4.60 (dd, $J=7.83, 4.30$ Hz, 1 H) 4.97 (d, $J=4.11$ Hz, 1 H) 5.04 (d, $J=4.11$ Hz, 1 H) 7.12 (d, $J=8.22$ Hz, 2 H) 7.40 (d, $J=8.41$ Hz, 2 H) 7.67 (s, 1 H) 7.76 (s, 1 H) 7.92 (s, 1 H). Mass Spectrum (CI^+)
 5 $m/z = 512.0$ ($\text{M}+1$).

EXAMPLE 111

2-((2S,5R,6R)-6-(3-Chloro-5-(methylsulfonyl)phenyl)-5-(4-chlorophenyl)-4-(cyclopropylmethyl)-3-oxomorpholin-2-yl)acetic acid
 10

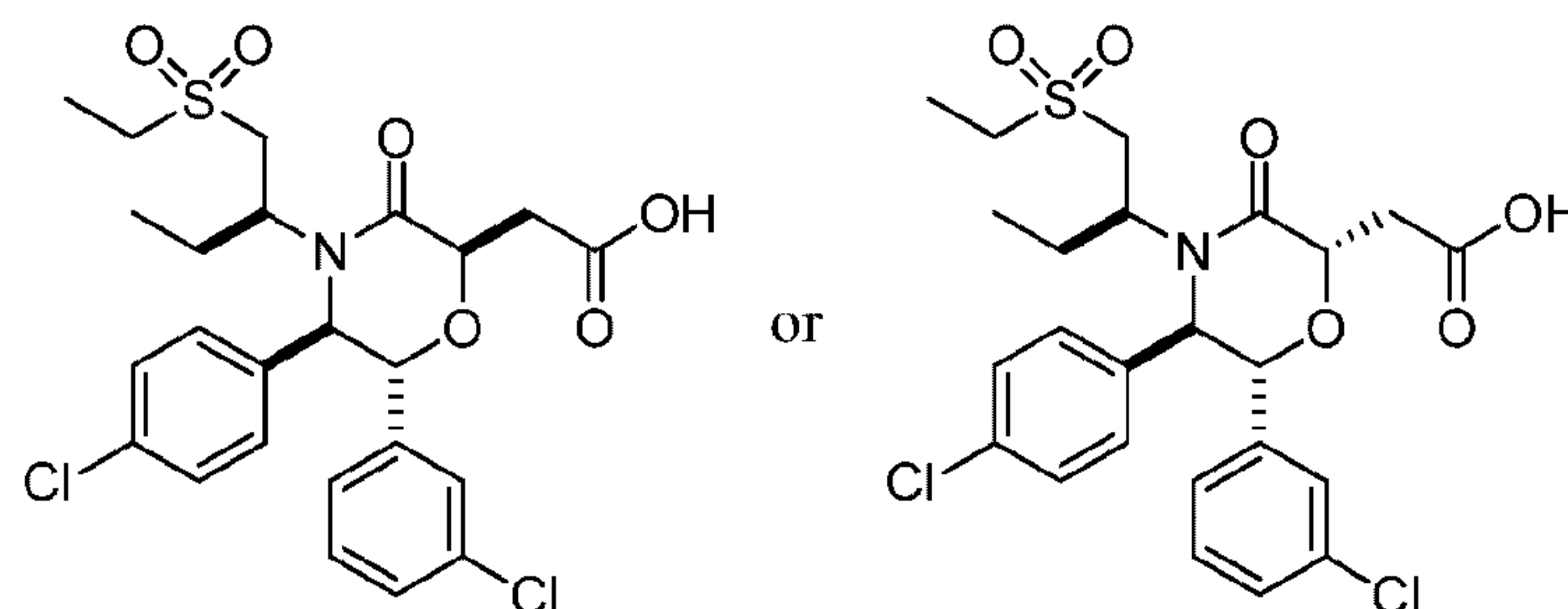


The title compound was obtained in Example 110. The pooled fractions containing the second eluting isomer after chiral SFC separation were treated with 1 mL
 15 TFA/DCM (1:2) at room temperature for 2 hours, concentrated *in vacuo*, and purified by reverse phase HPLC on a 250 x 30 mm 10 μm C_{18} column (Phenomenex, Torrance, CA; 10 to 90% MeCN/water with 0.1% TFA) to provide the title compound. ^1H NMR (400 MHz, CDCl_3) δ ppm -0.01 - 0.08 (m, 2 H) 0.39 - 0.54 (m, 2 H) 0.77 - 0.93 (m, 1 H) 2.34 (dd, $J=14.18, 7.53$ Hz, 1 H) 2.93 (s, 3 H) 3.10 - 3.24 (m, 2 H) 4.02 (dd, $J=14.28, 6.46$ Hz,
 20 1 H) 4.72 (s, 2 H) 4.80 (t, $J=5.28$ Hz, 1 H) 6.94 (d, $J=8.41$ Hz, 2 H) 7.24 - 7.26 (m, 1 H) 7.28 (s, 1 H) 7.33 (d, $J=8.41$ Hz, 2 H) 7.84 (t, $J=1.76$ Hz, 1 H). Mass Spectrum (CI^+) $m/z = 512.0$ ($\text{M}+1$)

EXAMPLE 112

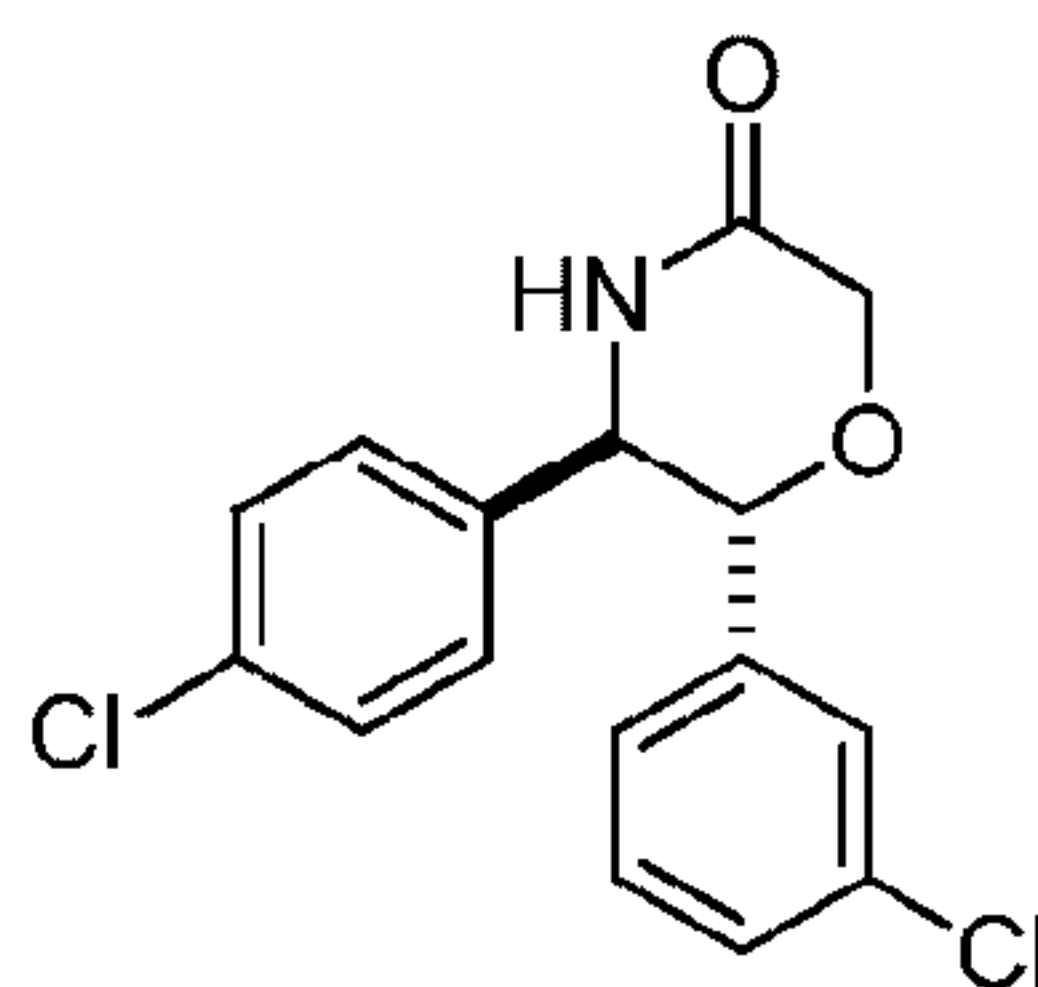
25 2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(ethylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid or 2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-

chlorophenyl)-4-((S)-1-(ethylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid
(Isomer 1)



5

Step A. (5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)morpholin-3-one



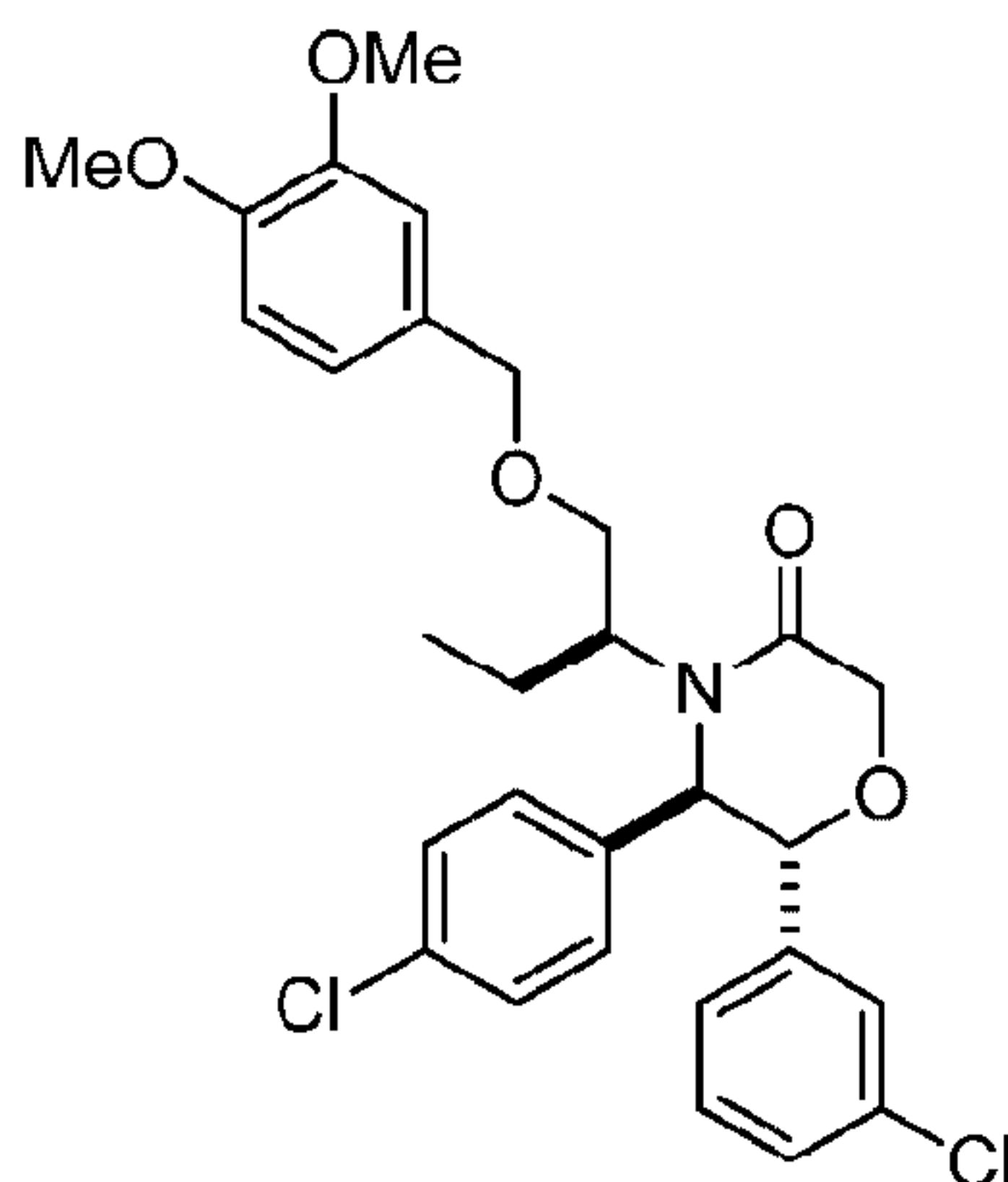
To a solution of (1R,2R)-2-amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)ethanol (0.47 g, 1.666 mmol; Intermediate A2) and triethylamine (0.349 mL, 2.499 mmol) in THF at 0 °C was added chloroacetyl chloride (0.16 mL, 2.0 mmol). The reaction mixture was stirred at 0 °C for 1h. After this time sat aq. NH₄Cl solution and ethyl acetate was added. The layers were separated and the combined organic layers were washed with water (3 x 10 mL) dried over MgSO₄, filtered and the filtrate was concentrated in vacuo to give 2-chloro-N-((1R,2R)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-hydroxyethyl)acetamide as a light yellow oil which was taken to the next step without further purification. MS (ESI) 380.0 [M + Na]⁺.

The product from above was dissolved in THF (15 mL) and treated with several portions of sodium hydride (60% dispersion in mineral oil, 0.167 g, 4.16 mmol) over a period of 5 minutes. The reaction was stirred at rt for 5 h. After this time sat aq. NH₄Cl

solution and ethyl acetate was added. The layers were separated and the combined organic layers were washed with water (3 x 10 mL) dried over MgSO₄, filtered and the filtrate was concentrated in vacuo to give the crude material as a yellow oil. This was absorbed onto a plug of silica gel and purified by chromatography on silica gel, eluting with a gradient of 0% to 30% acetone in hexanes, to provide the title compound as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.47 - 7.54 (m, 1H), 7.46 - 7.54 (m, 1H), 7.34 - 7.42 (m, 2H), 7.29 - 7.32 (m, 2H), 7.26 - 7.29 (m, 1H), 7.13 - 7.25 (m, 1H), 6.98 (d, *J* = 8.41 Hz, 1H), 4.57 - 4.65 (m, 1H), 4.45 (d, *J* = 9.98 Hz, 1H), 4.00 (d, *J* = 5.67 Hz, 2H). Mass Spectrum (ESI) *m/z* = 322.2 (*M*⁺).

10

Step B. (5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-((3,4-dimethoxybenzyl)oxy) butan-2-yl)morpholin-3-one



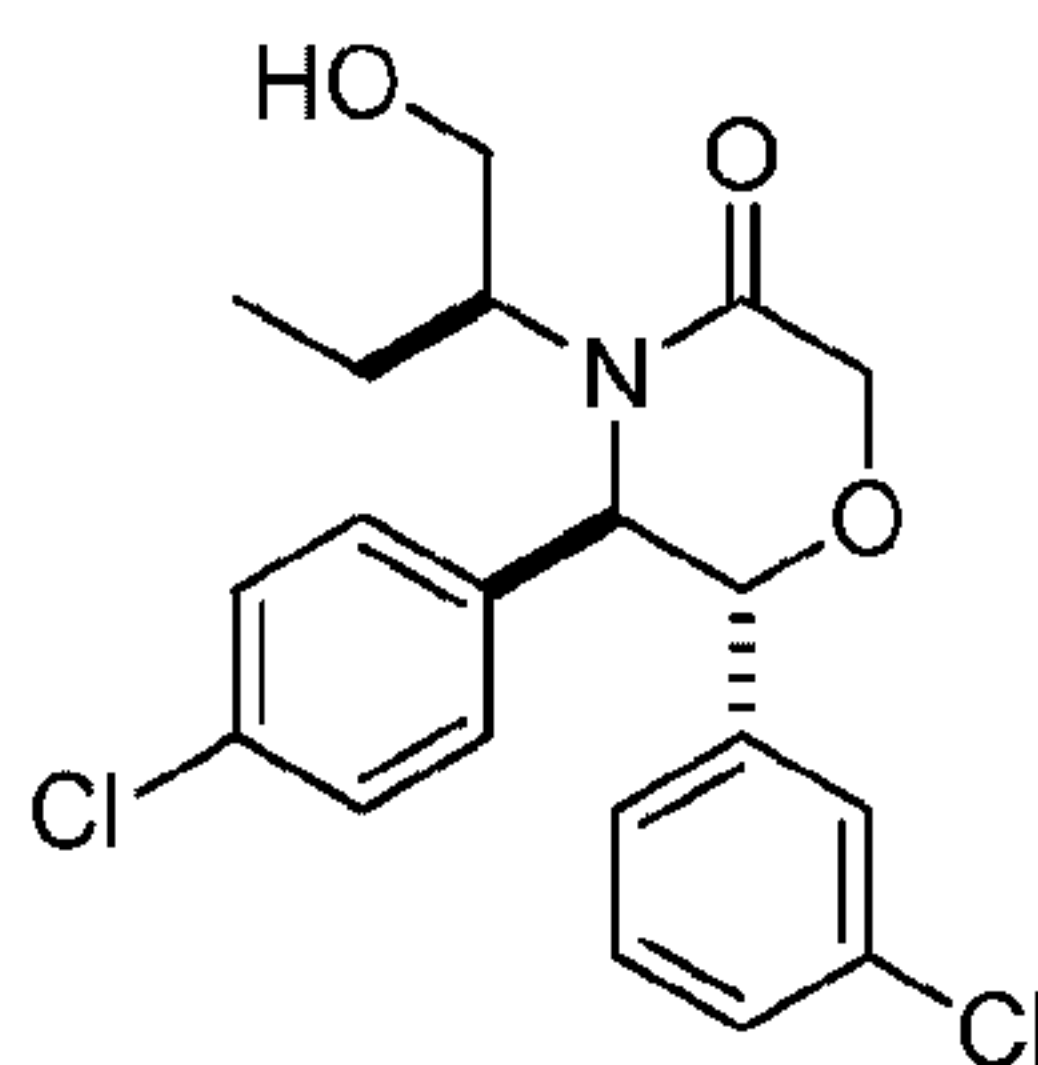
15

A solution of (5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)morpholin-3-one (260 mg, 0.807 mmol, Example 112, Step A), (R)-1-((3,4-dimethoxybenzyl)oxy)butan-2-yl 4-bromobenzenesulfonate (556 mg, 1.210 mmol, Intermediate G), and sodium 2-methylpropan-2-olate (116 mg, 1.210 mmol) in 1,4-dioxane (2 mL) was stirred at 85 °C overnight. After this period the reaction contents were poured into sat. aq. NaHCO₃ solution (10 mL) and brine (10 mL) and extracted with 2.5% MeOH in CH₂Cl₂ (3 x 30 mL). The combined organics were dried over sodium sulfate, filtered and the filtrate was concentrated *in vacuo*. Silica gel chromatography (gradient elution with 10 to 40% acetone in hexanes) afforded the title compound as the second eluting major fraction.

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¹H NMR (400 MHz, CDCl₃) δ 7.29 (s, 3H), 7.21 - 7.25 (m, 1H), 7.18 (t, *J* = 1.66 Hz, 1H), 7.11 (t, *J* = 7.92 Hz, 1H), 7.06 (d, *J* = 8.41 Hz, 1H), 6.78 - 6.92 (m, 3H), 4.77 (d, *J* = 7.83 Hz, 1H), 4.58 (d, *J* = 7.83 Hz, 1H), 4.45 (s, 2H), 3.96 (t, *J* = 9.49 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 1.80 - 1.95 (m, *J* = 7.14, 14.77 Hz, 1H), 1.61 - 1.72 (m, 1H), 0.63 (t, *J* = 7.53 Hz, 3H). Mass Spectrum (ESI) *m/z* = 566.2 [M + Na]⁺.

Step C. (5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-hydroxybutan-2-yl)morpholin-3-one

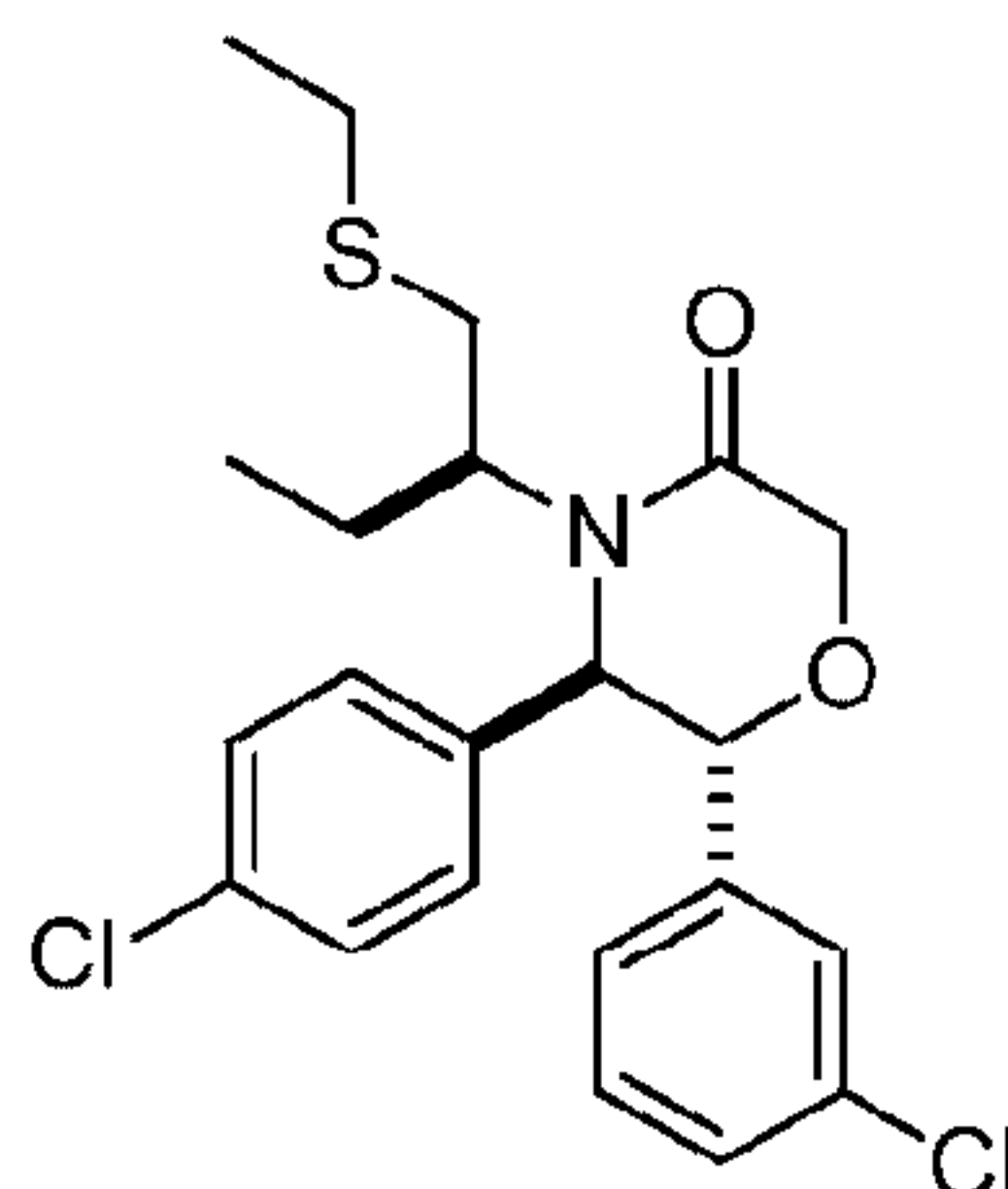


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To a 0 °C solution of (5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-((3,4-dimethoxybenzyl)oxy)butan-2-yl)morpholin-3-one (140 mg, 0.257 mmol; Example 112, Step B) in CH₂Cl₂ (2443 μl) and water (129 μl) was added DDQ (Fluka, Buchs, Switzerland) (70.0 mg, 0.309 mmol). The reaction was stirred at 0 °C. After 2 h the reaction contents were poured into sat. aq. NaHCO₃ solution (50 mL) and CH₂Cl₂ (30 mL). The layers were separated and the aqueous layer was extracted further with CH₂Cl₂ (2 x 20 mL). The combined organics were dried over sodium sulfate, filtered and the filtrate was concentrated *in vacuo*. Silica gel chromatography (gradient elution 10 to 40% acetone in hexanes) afforded the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.22 - 7.26 (m, 2H), 7.17 - 7.21 (m, 1H), 7.01 - 7.13 (m, 4H), 6.75 (d, *J* = 7.83 Hz, 1H), 4.54 (d, *J* = 4.70 Hz, 2H), 4.35 (d, *J* = 2.74 Hz, 2H), 3.53 - 3.62 (m, 2H), 3.41 (q, *J* = 7.04 Hz, 1H), 3.26 - 3.37 (m, 1H), 1.76 - 1.92 (m, 1H), 1.41 (ddd, *J* = 6.06, 7.53, 13.79 Hz, 1H), 1.14 (t, *J* = 6.94 Hz, 1H), 0.62 - 0.70 (m, 3H). Mass Spectrum (ESI) *m/z* = 394.2 [M]⁺.

25

Step D. (5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(ethylthio)butan-2-yl)morpholin-3-one

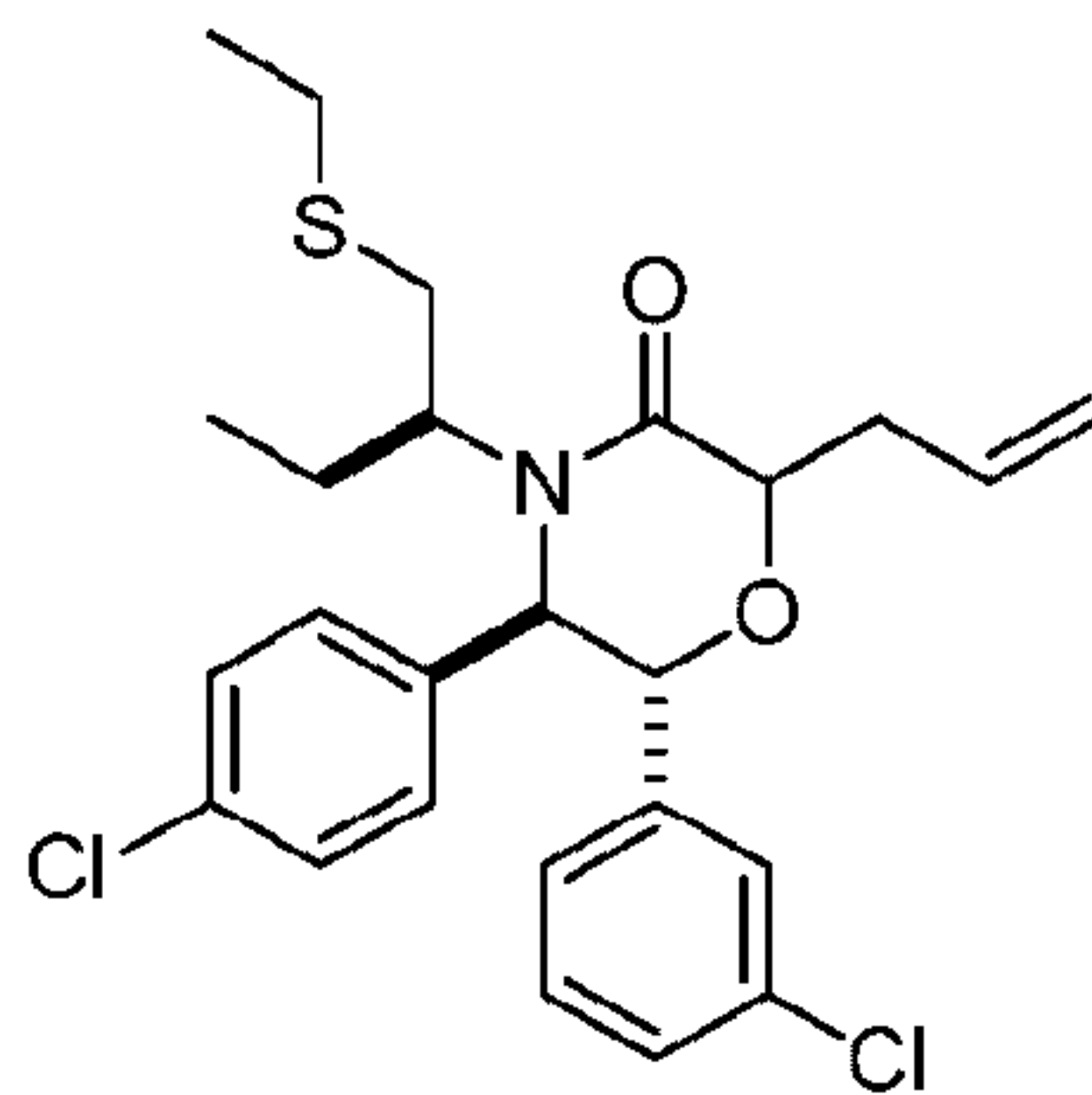


5

To a solution of (5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-hydroxybutan-2-yl)morpholin-3-one (300mg, 0.761 mmol; Example 112, Step C) and ethanethiol (0.225 mL, 3.04 mmol) in 0.2 mL of toluene was added cyanomethylenetriethylphosphorane (TCI America, Portland, OR) (0.735 mL, 3.04 mmol). The resulting solution was stirred at at 110 °C overnight. After this period, the mixture was concentrated, the crude material absorbed onto a plug of silica gel and purified by chromatography on silica gel, eluting with 20% acetone in hexanes to provide the title compound as a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.21 - 7.34 (m, 3H), 7.11 - 7.18 (m, 2H), 7.07 (d, *J* = 8.41 Hz, 2H), 6.79 (d, *J* = 7.83 Hz, 1H), 4.77 (d, *J* = 9.00 Hz, 1H), 4.56 (d, *J* = 9.00 Hz, 1H), 4.44 (q, *J* = 16.43 Hz, 2H), 3.06 - 3.15 (m, 2H), 2.44 - 2.62 (m, 3H), 2.04 (td, *J* = 7.36, 14.43 Hz, 1H), 1.56 - 1.68 (m, 1H), 1.23 - 1.31 (m, 3H), 0.66 (t, *J* = 7.43 Hz, 3H). Mass Spectrum (ESI) *m/z* = 438.2 [M]⁺.

Step E. (5R,6R)-2-Allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(ethylthio)butan-2-yl)morpholin-3-one

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To a 5-mL round-bottomed flask was added (5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(ethylthio)butan-2-yl)morpholin-3-one (40 mg, 0.091 mmol;
 5 Example 112, Step D) and lithium bis(trimethylsilyl)amide (1.0M solution in tetrahydrofuran, 137 μ l, 0.137 mmol) in THF (456 μ l) at -78 °C. The reaction mixture was stirred for 15 minutes. After this period allyl bromide (11.84 μ l, 0.137 mmol) was added at -78 °C. The reaction was allowed to stir for 3 h. After this period it was quenched by addition of a sat. aq. NH_4Cl solution (3 mL), then extracted with diethyl
 10 ether (3 x 10 mL). The combined organic extracts were dried over MgSO_4 . The solution was filtered and concentrated in vacuo to give the crude material as a light yellow oil. The crude material was purified by chromatography on silica gel, eluting with a gradient of 0 % to 20% acetone in hexanes, to provide the title compound as a 2:1 mixture of epimers at C2. Mass Spectrum (ESI) $m/z = 478.0$ $[\text{M}]^+$.

15

Step F. 2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(ethylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid or 2-((2S,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(ethylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid (Isomer 1)

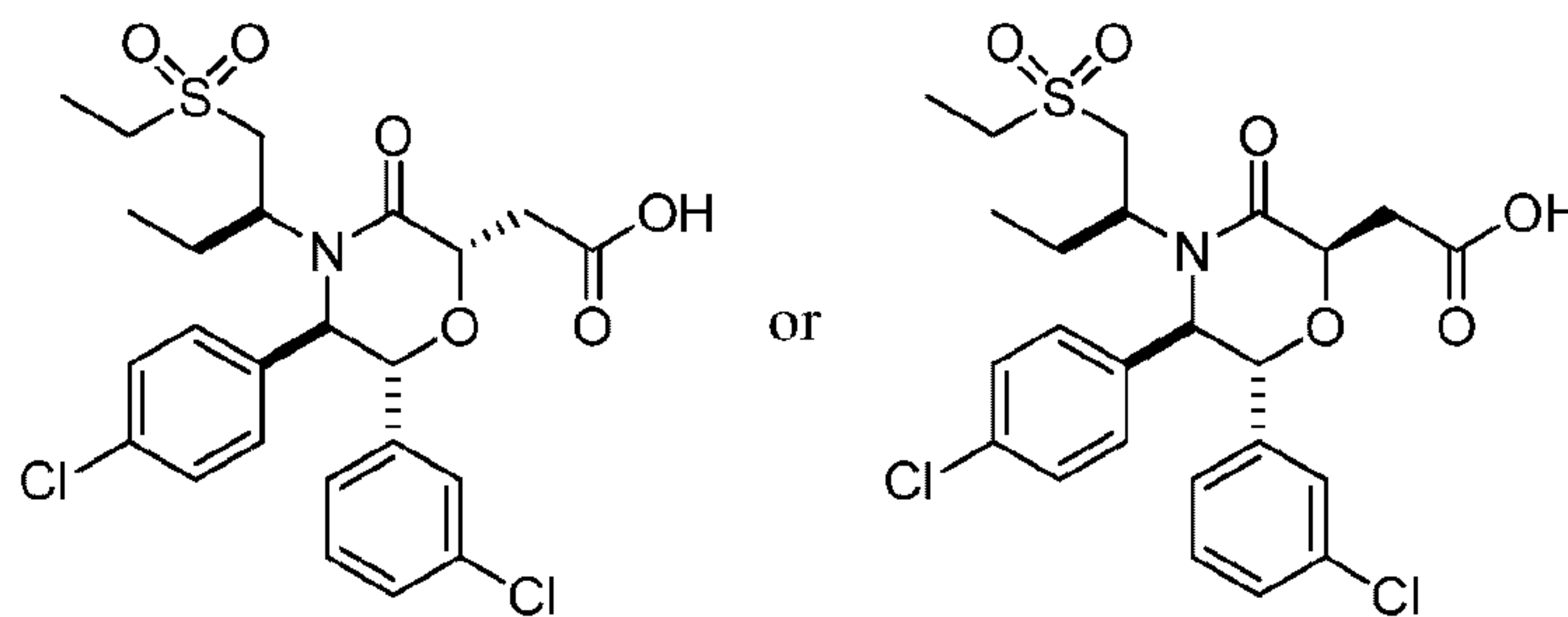
20

To a rapidly stirring solution of (5R,6R)-2-allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-(ethylthio)butan-2-yl)morpholin-3-one (25 mg, 0.052 mmol;
 Example 112, Step E) in a mixture of water (280 μ l), acetonitrile (187 μ l) and CCl_4 (187 μ l) was added sodium periodate (67 mg, 0.31 mmol), followed by ruthenium(III)
 25 chloride hydrate (1.2 mg, 5.2 μ mol). The biphasic mixture was stirred vigorously at rt for 5 h, and then was acidified with 10% citric acid. The mixture was diluted with EtOAc

and filtered through a pad of Celite[®] (diatomaceous earth) to remove. The filtrate was extracted (2 x EtOAc) and the combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure. Purification of the residue by RP-HPLC (Gemini[™] Prep C₁₈ 5 μ m column; Phenomenex, Torrance, CA; 30 to 60% MeCN/H₂O in 30 min) provided one of the title compounds as the faster eluting isomer (*t_R* = 17.51 min). ¹H NMR (400 MHz, CDCl₃) δ 7.33 - 7.38 (m, 2H), 7.25 (td, *J* = 2.15, 3.91 Hz, 4H), 7.14 - 7.21 (m, 1H), 7.02 (d, *J* = 7.63 Hz, 1H), 5.09 (d, *J* = 7.04 Hz, 1H), 4.95 (d, *J* = 7.04 Hz, 1H), 4.79 (t, *J* = 5.87 Hz, 1H), 4.05 (br. s., 1H), 3.44 (br. s., 1H), 3.01 - 3.16 (m, 4H), 2.97 (d, *J* = 12.91 Hz, 1H), 2.14 (ddd, *J* = 7.34, 9.44, 14.13 Hz, 1H), 1.60 (ddd, *J* = 4.21, 7.53, 13.89 Hz, 1H), 1.38 - 1.50 (m, 3H), 0.57 (t, *J* = 7.43 Hz, 3H). Mass Spectrum (ESI) *m/z* = 528.0 [M]⁺.

EXAMPLE 113

2-((2*S*,5*R*,6*R*)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(ethylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid or 2-((2*R*,5*R*,6*R*)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((*S*)-1-(ethylsulfonyl)butan-2-yl)-3-oxomorpholin-2-yl)acetic acid (Isomer 2)



20

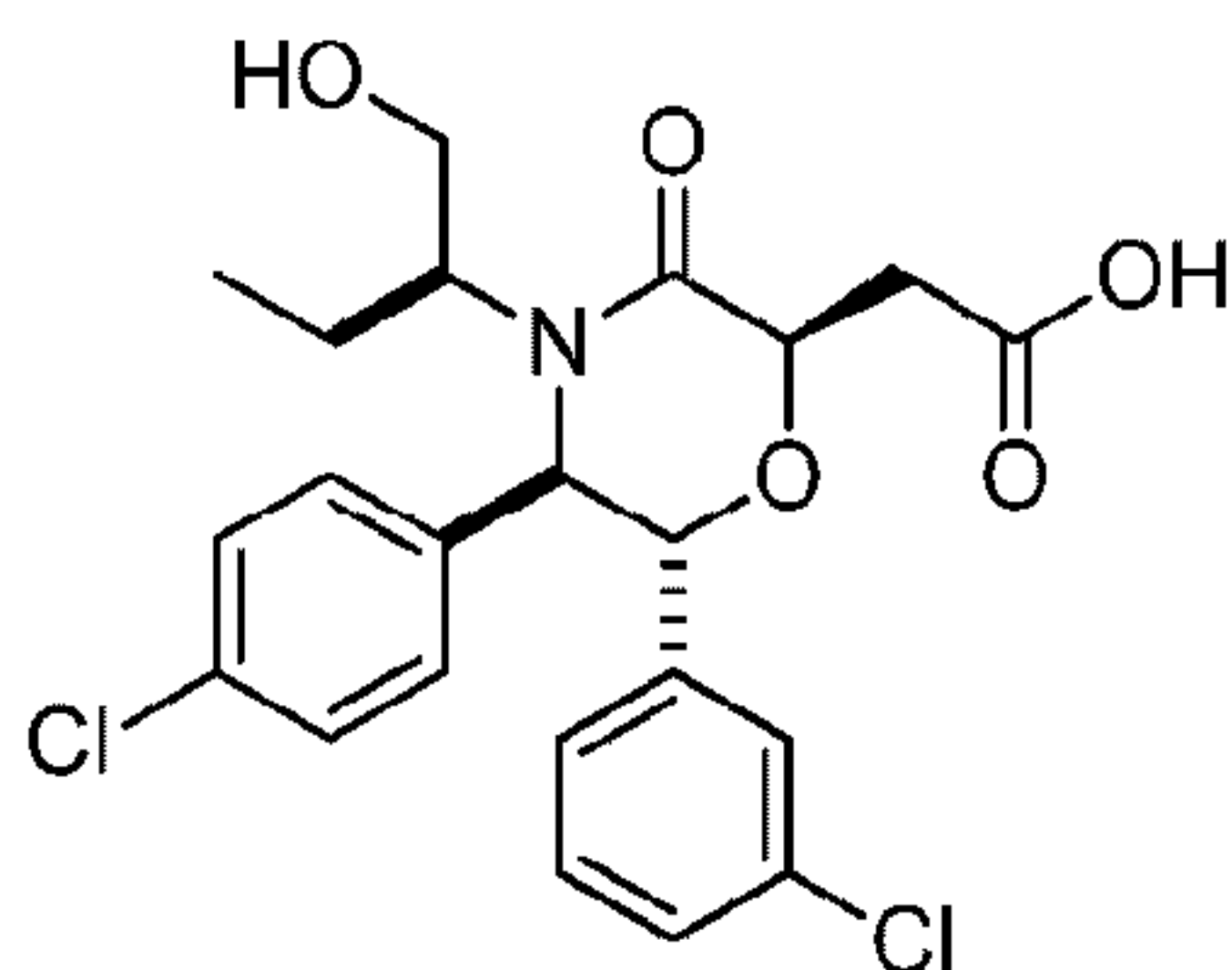
One of the title compounds was obtained as the second (slower) eluting isomer in Example 112, Step F (*t_R* = 18.56 min). ¹H NMR (400 MHz, CDCl₃) δ 7.23 (d, *J* = 7.82 Hz, 9H), 7.13 (d, *J* = 8.02 Hz, 4H), 6.93 - 7.09 (m, 15H), 6.75 (d, *J* = 7.63 Hz, 3H), 4.94 (d, *J* = 9.39 Hz, 3H), 4.56 - 4.71 (m, 7H), 3.09 (d, *J* = 6.46 Hz, 3H), 2.92 - 3.03 (m, 10H), 2.88 - 2.92 (m, 1H), 2.78 - 2.88 (m, 3H), 2.00 - 2.16 (m, 3H), 1.49 - 1.61 (m, 1H), 1.36 (t, *J* = 7.53 Hz, 3H), 0.49 (t, *J* = 7.34 Hz, 3H). Mass Spectrum (ESI) *m/z* = 528.0 [M]⁺.

25

EXAMPLE 114

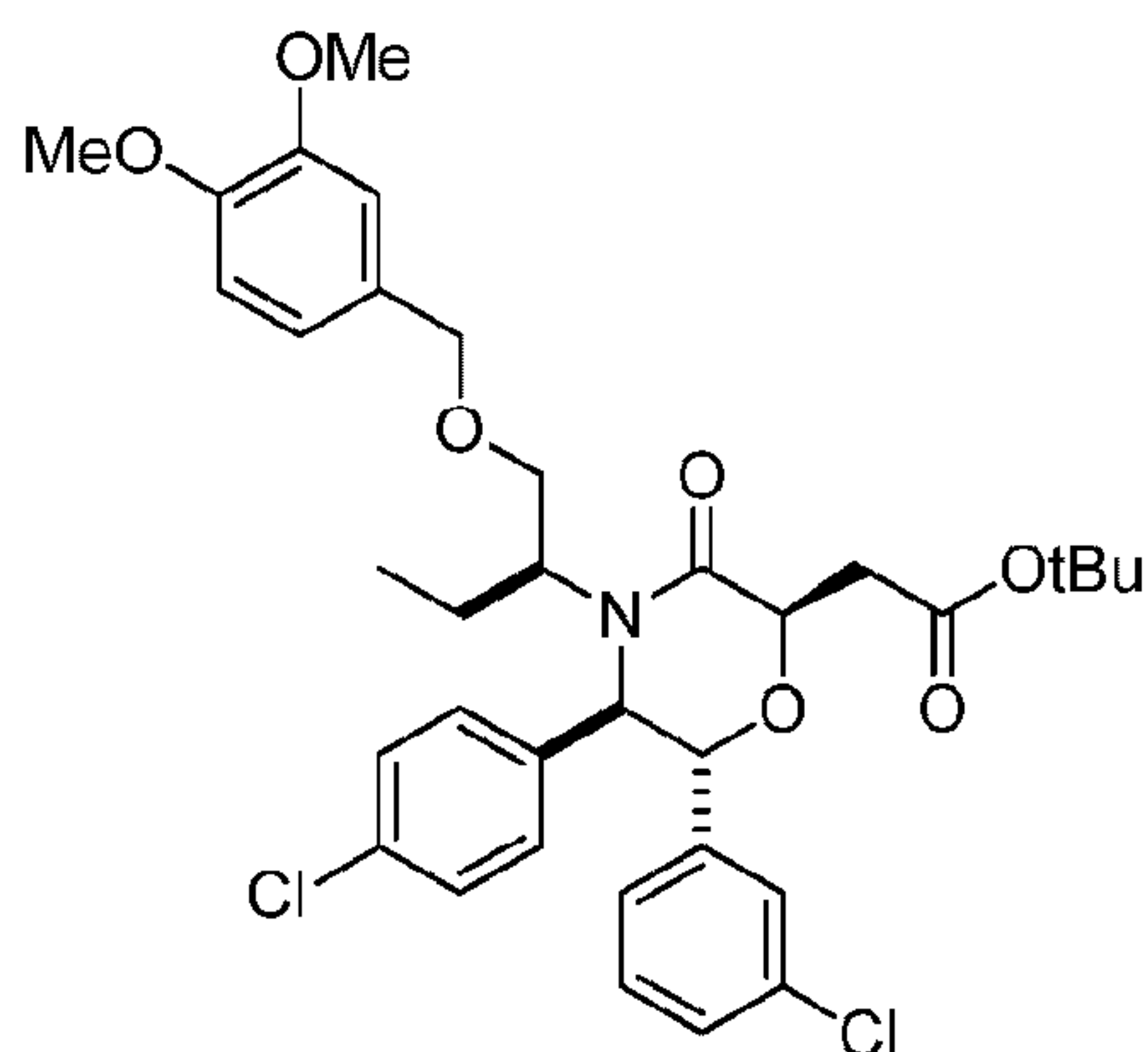
2-((2R,5R,6R)-6-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-hydroxybutan-2-yl)-3-oxomorpholin-2-yl)acetic acid

5



Step A: tert-Butyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-((3,4-dimethoxybenzyl)oxy)butan-2-yl)-3-oxomorpholin-2-yl)acetate

10



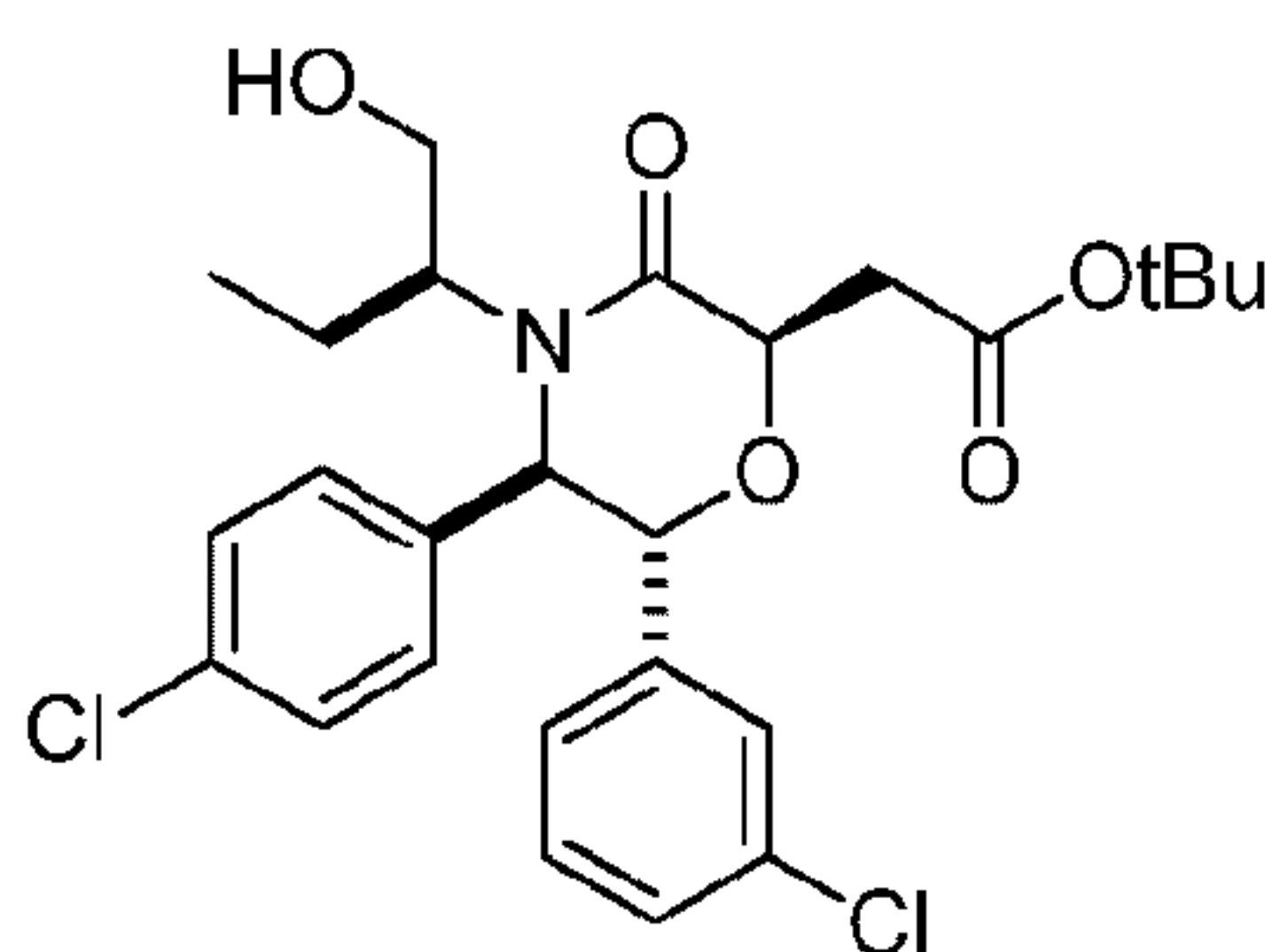
To a solution of tert-butyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-oxomorpholin-2-yl)acetate (0.34 g, 0.779 mmol; Example 32, Step C, second eluting isomer) and (R)-1-((3,4-dimethoxybenzyl)oxy)butan-2-yl 4-bromobenzenesulfonate (0.394 g, 0.857 mmol, Intermediate G) in 2 mL of 1,4-dioxane sodium 2-methylpropan-2-olate (0.082 g, 0.857 mmol) was added. The reaction mixture was stirred at 85 °C overnight. The reaction contents were poured into a mixture of water (50 mL) and brine (10 mL) and extracted against 2.5% MeOH in CH₂Cl₂ (3 x 30 mL). The combined

20

organic extracts were dried over MgSO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient elution 10 to 40% acetone in hexanes) to afford the title compound. Mass Spectrum (ESI) $m/z = 480.2$ $[\text{M} + 2]^+$.

5

Step B. tert-Butyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-hydroxybutan-2-yl)-3-oxomorpholin-2-yl)acetate



10

To a solution of tert-butyl 2-((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-((3,4-dimethoxybenzyl)oxy)butan-2-yl)-3-oxomorpholin-2-yl)acetate (140 mg, 0.213 mmol; Example 114, Step A) in a mixture of CH_2Cl_2 (2019 μl) and water (106 μl) at 0 °C was added DDQ (Fluka, Buchs, Switzerland) (57.9 mg, 0.255 mmol). The

15 reaction was stirred at 0 °C. After 2 h the reaction contents were poured into saturated aq. sodium bicarbonate (50 mL) and CH_2Cl_2 (30 mL). Organics were sequestered and the aqueous was extracted further with CH_2Cl_2 (2 x 20 mL). The combined organics were dried over sodium sulfate, filtered and the filtrate was concentrated *in vacuo*. Silica gel chromatography (gradient elution 10% to 30% acetone in hexanes) afforded the title

20 compound. ^1H NMR (400 MHz, CDCl_3) δ 7.28 (s, 2H), 7.20 - 7.24 (m, 1H), 7.00 - 7.12 (m, 4H), 6.68 (d, $J = 7.63$ Hz, 1H), 4.81 (d, $J = 9.78$ Hz, 1H), 4.61 (d, $J = 9.59$ Hz, 1H), 4.52 (dd, $J = 3.13, 4.11$ Hz, 1H), 4.29 (dd, $J = 10.66, 11.84$ Hz, 1H), 3.53 (dd, $J = 4.11, 12.13$ Hz, 1H), 3.35 (dd, $J = 2.93, 17.02$ Hz, 1H), 2.75 - 2.94 (m, 2H), 1.89 - 2.07 (m, 1H), 1.61 (ddd, $J = 4.11, 7.83, 14.09$ Hz, 1H), 1.55 (s, 9H), 0.58 (t, $J = 7.63$ Hz, 3H).

25 Mass Spectrum (ESI) $m/z = 530.1$ $[\text{M} + \text{Na}]^+$.

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __3__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

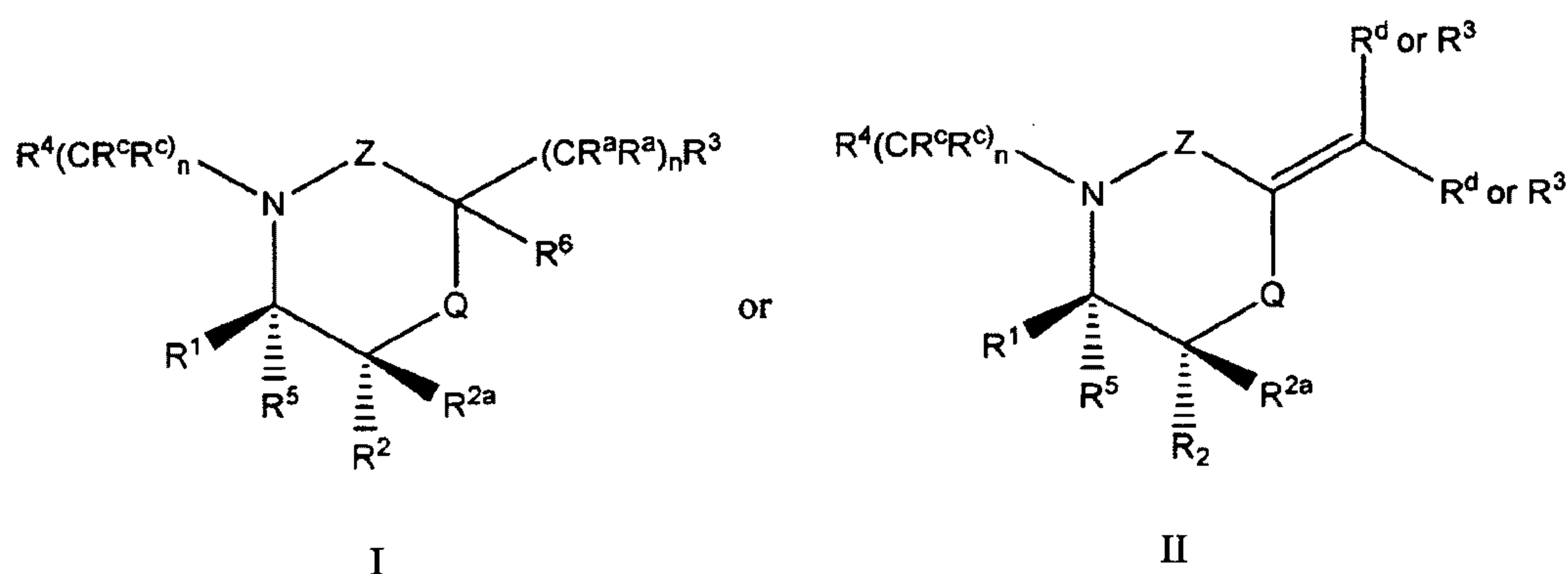
**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __3__

NOTE: For additional volumes please contact the Canadian Patent Office.

CLAIMS:

1. A compound of Formula I or II, or a pharmaceutically acceptable salt thereof,



wherein:

- 5 Q is O, S, -S(=O)-, -S(=O)₂-, or -NR^e;

Z is -C(=O)- or -S(=O)₂-;

R¹ is substituted phenyl, indolyl, substituted benzimidazolyl, benzthiazolyl, substituted pyridyl, or substituted thiophenyl, wherein the substituted phenyl, substituted benzimidazolyl, substituted pyridyl or substituted thiophenyl is substituted with from one to three substituents

- 10 independently selected from the group consisting of halo, -C₁₋₆alkyl, -OH, -NO₂, -NHC(=O)C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, -(CH₂)_nC(=O)R^f, -(CH₂)_nC(=O)NR^fR^f, -CN, -NR^gR^g and A,

when R¹ is substituted with -NR^gR^g, then R^g and R^g together with the nitrogen atom to which they are attached can form a 3 to 6 membered heterocycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from the group consisting of O, N and S, and the heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F and -CN;

- 20 each A is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from the group consisting of O, N and S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one

to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

R² is substituted phenyl or substituted pyridyl, wherein the substituted phenyl or substituted pyridyl is substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -OH, -NO₂, -NHC(=O)C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, -(CH₂)_nC(=O)R^f, -(CH₂)_nC(=O)NR^fR^f, -CN, -NR^gR^g and B,

when R² is substituted with -NR^gR^g, then R^g and R^g together with the nitrogen atom to which they are attached can form a 3 to 6 membered heterocycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from the group consisting of O, N and S, and the heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

each B is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from the group consisting of O, N and S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

R^{2a} is hydrogen or -C₁₋₃alkyl;

R³ is C₁₋₆alkyl substituted with from one to three substituents independently selected from the group consisting of halo, -OH, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN; -C(=O)OR^f, -C(=O)C₁₋₆alkyl, -S(=O)₂R^f, -S(=O)R^f, -OR^f, -C(=O)NR^fN(R^f)₂, -C(=O)NR^fS(=O)₂R^f, -S(=O)₂NR^fC(=O)R^f, -S(=O)₂NR^fR^f, -N(R^f)C(=O)NR^fR^f, -NR^fC(=O)₂R^f, -C(=O)NR^fR^f, -NR^fS(=O)₂R^f, -CN, -NR^fR^f, -C(=O)NOH, -NR^fC(=O)OR^f, -NR^fC(=O)R^f, or a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to four heteroatoms independently selected from the group consisting of O, N and S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

R^4 is hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-CF_3$, $-CH_2F$, $-CHF_2$, $-S(=O)_2R^f$, $-SR^f$, $-S(=O)R^f$, $-S(=O)_2NR^fR^f$, $-NR^fS(=O)_2NR^fR^f$, $-C(=O)NR^fR^f$, $-NR^fS(=O)_2R^f$, $-C(=O)_2R^f$, $-OR^f$, a 3 to 7 membered cycloalkyl or heterocycloalkyl, optionally containing a $-(C=O)-$ group, or a 5 to 6 membered aryl or heteroaryl group, which heterocycloalkyl or heteroaryl group can contain from one to three heteroatoms independently selected from the group consisting of O, N and S, and the cycloalkyl, heterocycloalkyl, aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, $-C_{1-6}$ alkyl, $-OH$, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$, and the $-C_{1-6}$ alkyl or $-C_{2-6}$ alkenyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, $-NR^fR^f$, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$;

R^5 is hydrogen or $-C_{1-6}$ alkyl;

R^6 is hydrogen, $-C_{1-6}$ alkyl, $-(CH_2)_nNR^fR^f$, or $-(CH_2)_nC(=O)NR^fR^f$;

each R^a is independently hydrogen, halo or $-C_{1-6}$ alkyl, or two R^a groups that are attached to the same carbon atom can form an $(=O)$ group or a 3 to 6 membered cycloalkyl or heterocycloalkyl group, or an R^a group and R^6 along with the atoms to which they are attached can form a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can contain from one to two heteroatoms independently selected from the group consisting of O, N and S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, $-C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$;

each R^c is independently hydrogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl- CF_3 , $-CF_3$, a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can contain from one to two heteroatoms independently selected from the group consisting of O, N and S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, C_{1-6} alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$;

or two R^c groups that are attached to the same or adjacent carbon atoms can together with the carbon atom or atoms to which they are attached form a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can contain from one to two heteroatoms independently selected from the group consisting of O, N and S, and the cycloalkyl or

heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

each R^d is independently hydrogen or -C₁₋₆alkyl;

5 each R^e is independently hydrogen or -C₁₋₆alkyl;

each R^f is independently hydrogen, -CN, -C₁₋₆alkyl, -C₁₋₆alkyl-CN, -C₁₋₆alkyl-CF₃, hydroxyC₁₋₆alkyl, -C₁₋₆alkylNR^eR^e, or a 5 to 6 membered aryl, -C₁₋₆alkylaryl, heteroaryl, or -C₁₋₆alkylheteroaryl, or a 3 to 9 membered cycloalkyl, -C₁₋₆alkylcycloalkyl, heterocycloalkyl or -C₁₋₆alkylheterocycloalkyl group, which heteroaryl, alkylheteroaryl, heterocycloalkyl, or

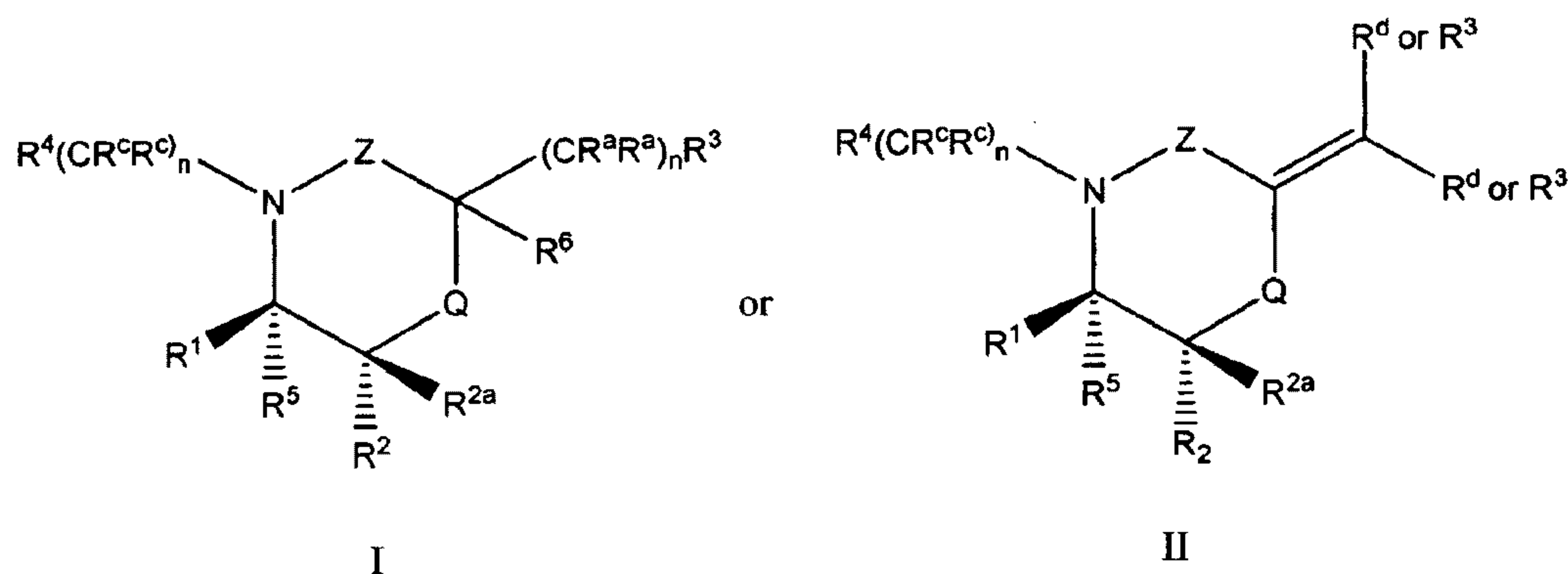
10 alkylheterocycloalkyl group can contain from one to three heteroatoms independently selected from the group consisting of O, N and S, and the alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, or alkylheterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃,
15 -OCHF₂, -OCH₂F, and -CN;

or when R^f and R^f are part of an NR^fR^f or CR^fR^f moiety in a group, then R^f and R^f together with the nitrogen or carbon atom to which they are attached can form a 3 to 7 membered heterocycloalkyl or cycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from the group consisting of O, N and S, and the
20 heterocycloalkyl or cycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

each R^g is independently hydrogen, or -C₁₋₆alkyl; and

each n is independently 0, 1, 2, 3 or 4, provided that the compound is not 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*S*,2*S*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid; 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*S*,2*S*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid; 2-((2*R*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*R*,2*R*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid; or 2-((2*S*,5*R*,6*R*)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((1*R*,2*R*)-2-(isopropylsulfonyl)cyclopentyl)-3-oxomorpholin-2-yl)acetic acid.
30

2. A compound in accordance with claim 1, or a pharmaceutically acceptable salt thereof,



wherein:

Q is O, S, -S(=O)-, -S(=O)₂-, or -NR^e;

5 Z is -C(=O)- or -S(=O)₂-;

R¹ is substituted phenyl, indolyl, substituted benzimidazolyl, benzthiazolyl, substituted pyridyl, or substituted thiophenyl, wherein the substituted phenyl, substituted benzimidazolyl, substituted pyridyl or substituted thiophenyl is substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -OH, -NO₂,

10 -NHC(=O)C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂,
-OCH₂F, -(CH₂)_nC(=O)R^f, -(CH₂)_nC(=O)NR^fR^f, -CN, -NR^gR^g and A,

when R¹ is substituted with -NR^gR^g, then R^g and R^g together with the nitrogen atom to which they are attached can form a 3 to 6 membered heterocycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from the group consisting of O, N and S, and the heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F and -CN;

each A is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl
 20 group can contain from one to three heteroatoms independently selected from the group consisting
 of O, N and S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one
 to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl,
 -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

R^2 is substituted phenyl or substituted pyridyl, wherein the substituted phenyl or substituted pyridyl is substituted with from one to three substituents independently selected from the group consisting of halo, $-C_{1-6}$ alkyl, $-OH$, $-NO_2$, $-NHC(=O)C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-(CH_2)_nC(=O)R^f$,
 5 $-(CH_2)_nC(=O)NR^fR^f$, $-CN$, $-NR^gR^g$ and B,

when R^2 is substituted with $-NR^gR^g$, then R^g and R^g together with the nitrogen atom to which they are attached can form a 3 to 6 membered heterocycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from the group consisting of O, N and S, and the heterocycloalkyl group can be
 10 unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, $-C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$;

each B is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from the group consisting
 15 of O, N and S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, $-C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$;

R^{2a} is hydrogen or $-C_{1-3}$ alkyl;

R^3 is $-C_{1-6}$ alkyl substituted with from one to three substituents independently selected from
 20 the group consisting of halo, $-OH$, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$, $-C(=O)OR^f$, $-C(=O)C_{1-6}$ alkyl, $-S(=O)_2R^f$, $-S(=O)R^f$, $-OR^f$, $-C(=O)NR^fN(R^f)_2$, $-C(=O)NR^fS(=O)_2R^f$, $-S(=O)_2NR^fC(=O)R^f$, $-S(=O)_2NR^fR^f$, $-N(R^f)C(=O)NR^fR^f$, $-NR^fC(=O)_2R^f$, $-C(=O)NR^fR^f$, $-NR^fS(=O)_2R^f$, $-CN$, $-NR^fR^f$, or a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to four heteroatoms independently
 25 selected from the group consisting of O, N and S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, $-C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, $-S(=O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-CN$;

R^4 is hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-CF_3$, $-CH_2F$, $-CHF_2$, $-S(=O)_2R^f$, $-SR^f$, $-S(=O)R^f$,
 30 $-S(=O)_2NR^fR^f$, $-NR^fS(=O)_2NR^fR^f$, $-C(=O)NR^fR^f$, $-NR^fS(=O)_2R^f$, $-C(=O)_2R^f$, $-OR^f$, a 3 to 7 membered cycloalkyl or heterocycloalkyl, optionally containing a $-(C=O)-$ group, or a 5 to 6

membered aryl or heteroaryl group, which heterocycloalkyl or heteroaryl group can contain from one to three heteroatoms independently selected from the group consisting of O, N and S, and the cycloalkyl, heterocycloalkyl, aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -OH, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN, and the -C₁₋₆alkyl or -C₂₋₆alkenyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -NR^fR^f, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

R⁵ is hydrogen or -C₁₋₆alkyl;

R⁶ is hydrogen, -C₁₋₆alkyl, -(CH₂)_nNR^fR^f, or -(CH₂)_nC(=O)NR^fR^f;

each R^a is independently hydrogen, halo or -C₁₋₆alkyl, or two R^a groups that are attached to the same carbon atom can form an (=O) group or a 3 to 6 membered cycloalkyl or heterocycloalkyl group, or an R^a group and R⁶ along with the atoms to which they are attached can form a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can contain from one to two heteroatoms independently selected from the group consisting of O, N and S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

each R^c is independently hydrogen, -C₁₋₆alkyl, a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can contain from one to two heteroatoms independently selected from the group consisting of O, N and S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

or two R^c groups that are attached to the same or adjacent carbon atoms can together with the carbon atom or atoms to which they are attached form a 3 to 6 membered cycloalkyl or heterocycloalkyl group, which heterocycloalkyl group can contain from one to two heteroatoms independently selected from the group consisting of O, N and S, and the cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

each R^d is independently hydrogen or -C₁₋₆alkyl;

each R^e is independently hydrogen or -C₁₋₆alkyl;

each R^f is independently hydrogen, -C₁₋₆alkyl or a 5 to 6 membered aryl, -C₁₋₆alkylaryl, heteroaryl, or -C₁₋₆alkylheteroaryl, or a 3 to 7 membered cycloalkyl, -C₁₋₆alkylcycloalkyl, heterocycloalkyl or -C₁₋₆alkylheterocycloalkyl group, which heteroaryl, alkylheteroaryl, heterocycloalkyl, or alkylheterocycloalkyl group can contain from one to three heteroatoms independently selected from the group consisting of O, N and S, and the alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, or alkylheterocycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

or when R^f and R^f are part of an NR^fR^f or CR^fR^f moiety in a group, then R^f and R^f together with the nitrogen or carbon atom to which they are attached can form a 3 to 7 membered heterocycloalkyl or cycloalkyl group, which heterocycloalkyl group can contain from one to two additional heteroatoms independently selected from the group consisting of O, N and S, and the heterocycloalkyl or cycloalkyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

each R^g is independently hydrogen, or -C₁₋₆alkyl; and

each n is independently 0, 1, 2, 3 or 4.

3. A compound in accordance with claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Q is O;

Z is -C(=O)-;

R¹ is substituted phenyl, indolyl, substituted benzimidazolyl, benzthiazolyl, substituted pyridyl, or substituted thiophenyl, wherein the substituted phenyl, substituted benzimidazolyl, substituted pyridyl or substituted thiophenyl is substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, -CN, and A;

each A is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from the group consisting of O, N and S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl,

5 -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

R² is substituted phenyl or substituted pyridyl, wherein the substituted phenyl or substituted pyridyl is substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -SO₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, -CN, and B;

10 each B is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from the group consisting of O, N and S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

15 R³ is -C₁₋₆alkyl substituted with from one to three substituents independently selected from the group consisting of halo, -OH, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN, -C(=O)OR^f, -C(=O)C₁₋₆alkyl, -S(=O)₂R^f, -S(=O)R^f, -OR^f, -C(=O)NR^fN(R^f)₂, -C(=O)NR^fS(=O)₂R^f, -S(=O)₂NR^fC(=O)R^f, -S(=O)₂NR^fR^f, -N(R^f)C(=O)NR^fR^f, -NR^fC(=O)₂R^f, -C(=O)NR^fR^f, -NR^fS(=O)₂R^f, -CN, -NR^fR^f, or a 5 or 6 membered aryl or
20 heteroaryl group, which heteroaryl group can contain from one to four heteroatoms independently selected from the group consisting of O, N and S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

25 R⁴ is hydrogen, -C₁₋₆alkyl, -C₂₋₆alkenyl, -CF₃, -CH₂F, -CHF₂, -S(=O)₂R^f, -SR^f, -S(=O)R^f, -S(=O)₂NR^fR^f, -NR^fS(=O)₂NR^fR^f, -C(=O)NR^fR^f, -NR^fS(=O)₂R^f, -C(=O)₂R^f, -OR^f, a 3 to 7 membered cycloalkyl or heterocycloalkyl, optionally containing a -(C=O)- group, or a 5 to 6 membered aryl or heteroaryl group, which heterocycloalkyl or heteroaryl group can contain from one to three heteroatoms independently selected from the group consisting of O, N and S, and the
30 cycloalkyl, heterocycloalkyl, aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl,

-OH, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN, and the -C₁₋₆alkyl or -C₂₋₆alkenyl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -NR^fR^f, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

5 R⁶ is hydrogen or -C₁₋₆alkyl;

each R^a is independently hydrogen or -C₁₋₆alkyl; and

each R^c is independently hydrogen or -C₁₋₆alkyl.

4. A compound in accordance with claim 1, or a pharmaceutically acceptable salt thereof, wherein:

10 Q is O;

Z is -C(=O)-;

R¹ is substituted phenyl, indolyl, substituted benzimidazolyl, benzthiazolyl, substituted pyridyl, or substituted thiophenyl, wherein the substituted phenyl, substituted benzimidazolyl, substituted pyridyl or substituted thiophenyl is substituted with from one to three substituents
15 independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, -CN, and A;

each A is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from the group consisting of O, N and S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one
20 to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

R² is substituted phenyl or substituted pyridyl, wherein the substituted phenyl or substituted pyridyl is substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -SO₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃,
25 -OCHF₂, -OCH₂F, -CN, and B;

each B is independently a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to three heteroatoms independently selected from the group consisting of O, N and S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one

to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

R³ is -C(=O)OH, -C(=O)OC₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OH, or a 5 or 6 membered aryl or heteroaryl group, which heteroaryl group can contain from one to four heteroatoms independently selected from the group consisting of O, N and S, and the aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

R⁴ is hydrogen, -C₁₋₆alkyl, -C₂₋₆alkenyl, -CF₃, -CH₂F, -CHF₂, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -C(=O)OC₁₋₆alkyl, -OR^f, -S(=O)₂R^f, -NR^fS(=O)₂R^f, a 3 to 6 membered cycloalkyl or heterocycloalkyl, or a 5 to 6 membered aryl or heteroaryl group, which heterocycloalkyl or heteroaryl group can contain from one to three heteroatoms independently selected from the group consisting of O, N and S, and the cycloalkyl, heterocycloalkyl, aryl or heteroaryl group can be unsubstituted or substituted with from one to three substituents independently selected from the group consisting of halo, -C₁₋₆alkyl, -S(=O)₂C₁₋₆alkyl, -S(=O)C₁₋₆alkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, -OCHF₂, -OCH₂F, and -CN;

R⁶ is hydrogen or -C₁₋₆alkyl;

each R^a is independently hydrogen or -C₁₋₆alkyl; and

each R^c is independently hydrogen or -C₁₋₆alkyl.

5. A compound in accordance with claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is O, or wherein Z is -C(=O)-.

6. A compound in accordance with any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein -(CR^aR^a)_n- is -CH₂-, or wherein R³ is -CO₂R^f or tetrazolyl.

7. A compound in accordance with any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R³ is -CO₂H or tetrazolyl.

8. A compound in accordance with any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein -(CR^aR^a)_n- is -CH₂- and R³ is -CO₂H or tetrazolyl.

9. A compound in accordance with any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein $-(CR^cR^c)_n-$ is absent, $-CH_2-$, $-CH(CH_2CH_3)-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-$, $-CH(CH_2CH_3)CH_2-$, $-CH(CHCH_3CH_3)CH_2-$, or $-C(CCH_3CH_3CH_3)CH_2-$.

5 10. A compound in accordance with claim 9, or a pharmaceutically acceptable salt thereof, wherein $-(CR^cR^c)_n-$ is absent or is selected from the group consisting of $-CH_2-$, $-CH(CH_2CH_3)-$, $-CH(CH_3)-$ and $-CH(CH_2CH_3)CH_2-$.

11. A compound in accordance with any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen, cyclopropyl, $-C(=O)_2C_{1-6}alkyl$, cyclopentyl, 10 cyclobutyl, cyclohexyl, phenyl, oxazolyl, $-CF_3$, $-C_{1-6}alkyl$, $-C_{2-6}alkenyl$, $-S(=O)_2C_{1-6}alkyl$, $-OH$, $-S(=O)_2phenyl$, or $-N(phenyl)S(=O)_2-cyclopropyl$.

12. A compound in accordance with claim 11, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from the group consisting of cyclopropyl, $-C(=O)_2C_{1-6}alkyl$, $-C_{1-6}alkyl$, $-S(=O)_2C_{1-6}alkyl$, $-OH$, $-S(=O)_2phenyl$, and $-N(phenyl)S(=O)_2-cyclopropyl$.

15 13. A compound in accordance with any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein $R^4(CR^cR^c)_n-$ is hydrogen, $-CH_2-cyclopropyl$, $-CH(CH_2CH_3)CH_2S(=O)_2C_{1-6}alkyl$, $-CH_2-cyclopentyl$, $-CH_2-cyclobutyl$, $-CH_2-cyclohexyl$, cyclopropyl, cyclobutyl, cyclohexyl or $-C_{1-6}alkyl$.

14. A compound in accordance with any one of claims 1 to 13, or a pharmaceutically 20 acceptable salt thereof, wherein R^1 is 4-chlorophenyl or 3-chlorophenyl.

15. A compound in accordance with any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein R^2 is 3-chlorophenyl.

16. A compound in accordance with any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^6 is hydrogen or $-CH_3$.

25 17. A compound in accordance with any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen or $-CH_3$.

18. A compound in accordance with any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein R^d is hydrogen.

19. A compound in accordance with claim 1, or a pharmaceutically acceptable salt thereof, wherein:

5 Q is O;

Z is $-C(=O)-$;

$-(CR^aR^a)_n-$ is $-CH_2-$;

R^3 is $-C(=O)_2H$ or tetrazolyl;

10 $-(CR^cR^c)_n-$ is absent, $-CH_2-$, $-CH(CH_2CH_3)-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-$,
 $-CH(CH_2CH_3)CH_2-$, $-CH(CHCH_3CH_3)CH_2-$, or $-C(CCH_3CH_3CH_3)CH_2-$;

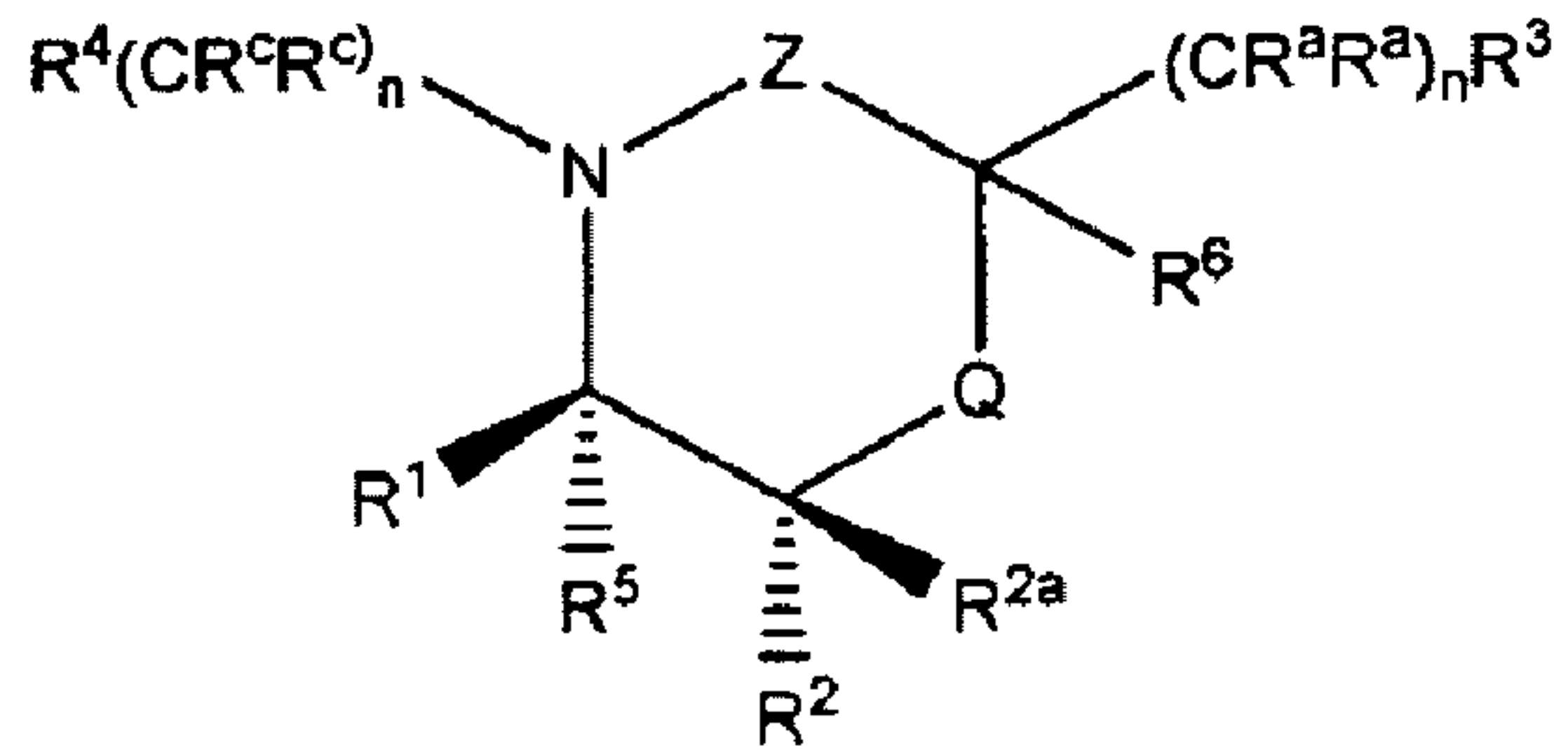
and

R^4 is hydrogen, cyclopropyl, $-C(=O)_2C_{1-6}$ alkyl, cyclopentyl, cyclobutyl, cyclohexyl, phenyl, oxazolyl, $-CF_3$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-S(=O)_2C_{1-6}$ alkyl, $-OH$, $-S(=O)_2$ phenyl, or $-N(phenyl)S(=O)_2$ -cyclopropyl.

15 20. A pharmaceutical composition comprising a compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

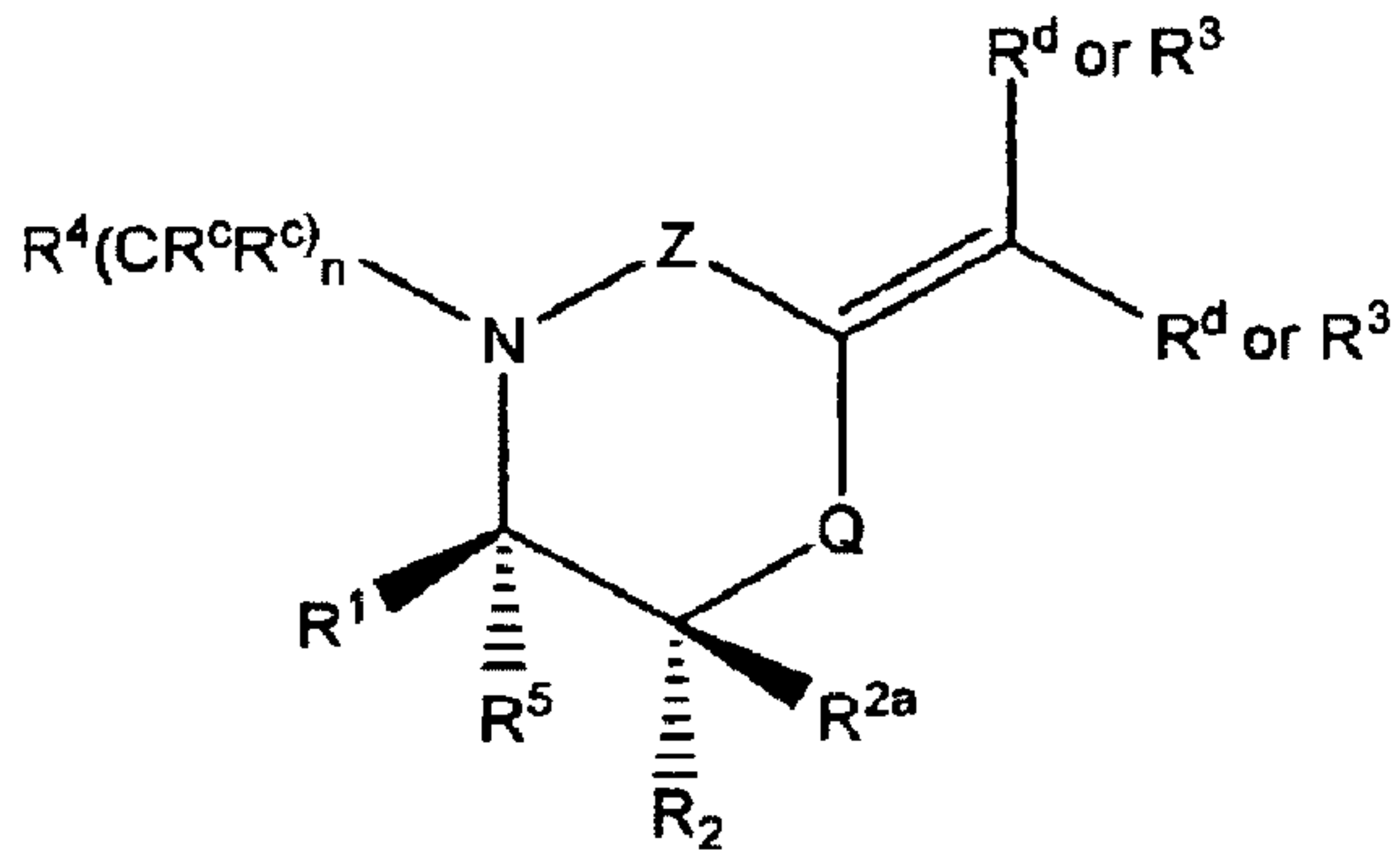
21. Use of a compound according to any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, for treating cancer in a subject in need thereof.

22. The use of claim 21, wherein the cancer is selected from bladder cancer, breast cancer,
 20 colon cancer, rectum cancer, kidney cancer, liver cancer, small cell lung cancer, non-small-cell lung cancer, esophagus cancer, gall-bladder cancer, ovary cancer, pancreas cancer, stomach cancer, cervix cancer, thyroid cancer, prostate cancer, skin cancer, acute lymphocytic leukemia, chronic myelogenous leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma,
 25 Burkett's lymphoma, acute and chronic myelogenous leukemia, melanoma, endometrial cancer, head and neck cancer, glioblastoma, or osteosarcoma.



I

or



II