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(54) **METHOD FOR THE TREATMENT OF A CONDITION REMEDIABLE BY ADMINISTRATION OF A SELECTIVE ANDROGEN RECEPTOR MODULATOR**

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(57) **ABSTRACT**

Selective androgen receptor modulators (SARMs) having antagonist activity in hormone-dependent tumors while exhibiting no activity or agonist activity against other non-tumor tissues containing the androgen receptor as well as methods for identifying, designing and using SARMs are provided.

8 Claims, No Drawings

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METHOD FOR THE TREATMENT OF A CONDITION REMEDIABLE BY ADMINISTRATION OF A SELECTIVE ANDROGEN RECEPTOR MODULATOR

INTRODUCTION

This application claims priority from U.S. Provisional Application Ser. No. 60/214,392, filed Jun. 28, 2000, from U.S. Provisional Application Ser. No. 60/233,519, filed Sep. 19, 2000, from U.S. Provisional Application Ser. No. 60/284,617, filed Apr. 18, 2001, from U.S. Provisional Application Ser. No. 60/284,438, filed Apr. 18, 2001, and from U.S. Provisional Application Ser. No. 60/284,730, filed Apr. 18, 2001, each of which are incorporated herein by reference in their entirety.

FIELD OF INVENTION

Selective androgen receptor modulators (SARMs) have now been identified which exhibit antagonistic activity against hormone-dependent tumors while exhibiting no activity or more preferably agonist activity against other nontumor tissues containing the androgen receptor. The present invention relates to methods for using these SARMs in the treatment of conditions remediable by administration of an androgen receptor modulator. The present invention also relates to methods for designing and identifying new SARMs that exhibit antagonistic activity against hormone-dependent tumors while exhibiting no activity, or more preferably agonist activity, against other nontumor tissues containing the androgen receptor. This invention also relates to structure coordinates of an androgen receptor ligand binding domain or ligand binding domain complex and method of using these structure coordinates for designing and selecting new SARMs that modulate androgen receptors.

BACKGROUND OF THE INVENTION

The androgen receptor (AR) is a member of the steroid nuclear-receptor superfamily of ligand-dependent transcription factors and is widely distributed among reproductive and nonreproductive tissues, including the prostate and seminal vesicles, male and female genitalia, skin, testis, ovary, cartilage, sebaceous glands, hair follicles, sweat glands, cardiac muscle, skeletal and smooth muscle, gastrointestinal vesicular cells, thyroid follicular cells, adrenal cortex, liver, pineal, and numerous brain cortical and subcortical regions, including spinal motor neurons (Negro-Vilar, A. JCE&M 1999 54(10):3459–62). As with the other members of the steroid receptor family, AR has several functional domains including a DNA binding domain (DBD), and a 261 residue ligand-binding domain (LBD) (Mw=30,245 Da) that contains the androgen binding site, and is responsible for switching on the androgen function. The cDNA and amino acid sequences of human and rat androgen receptors have been described (Proc. Natl. Acad. Sci. U.S.A. 1988 85: 7211–7215).

AR is an important target in multiple areas of drug discovery and patient therapy. In Oncology, for example, inhibitors (antagonists or partial antagonists) of the androgen receptor function are useful for the treatment of androgen dependent prostate cancer while agonists or partial agonists of the AR are applicable to the treatment of breast cancer. For metabolic and endocrine diseases disorders, for example, agonists or partial agonists of the androgen receptor function are useful for the treatment of age-related diseases and conditions of cachexia in several disease states

including, but not limited to, AIDS. Functional AR has also been identified in various bone cells and androgen administration has beneficial effects on skeletal development and maintenance in men and women.

Progress of androgen therapy has been limited by the inability to separate desirable androgenic activities from undesirable or dose limiting side effects. However, recent advances in the development of selective estrogen receptor modulators (SERMs), with a great degree of tissue selectivity in targeting the estrogen receptor while eliminating undesired side effects, has resulted in the suggestion of SARMs, selective androgen receptor modulators (Negro-Vilar, A. JCE&M 1999 54(10):3459–62; Reid et al. Investigational New Drugs 1999 17:271–284).

U.S. Pat. No. 6,017,924 discloses non-steroidal compounds characterized as high affinity, high specificity agonists, partial agonists (i.e. partial activators and/or tissue-specific activators) and antagonists for androgen receptors based upon a "cis-trans" or "co-transfection" assays. Non-steroidal compounds characterized as high affinity, high specificity agonists, partial agonists (i.e. partial activators and/or tissue-specific activators) and antagonists for androgen receptors via the "cis-trans" or "co-transfection" assays are also described in WO 01/16108, WO 01/16133, and WO 01/16139. This co-transfection assay (Evans et al. Science 1988 240:889–95) is suggested to provide a method for identifying functional agonists and partial agonists which mimic, or antagonists which inhibit, the effect of native hormones, and quantifying their activity for responsive intracellular receptor proteins.

In addition, hydroxyflutamide, a known AR antagonist in most tissues, has been suggested to function as a selective AR modulator (SARM) for effects on IL-6 production by osteoblasts (Hofbauer et al. J. Bone Miner. Res. 1999 14:1330–1337).

Hydroxyflutamide and Casodex, both known to be full AR antagonists in most tissues, have been shown, in AR-transfected PC3 cells, to activate MAP kinases Erk-1 and Erk-2 in an AR dependent fashion similar to DHT (Peterziel et. al. *Oncogene* 18, 6322–6329 (1999)).

The compound LGD2226, a non-steroidal AR agonist, has also been characterized as a selective androgen receptor modulator for use in the treatment of androgen-related diseases such as osteoporosis, male hormone replacement, male and female sexual dysfunction and cachexia (SCRIP—World Pharmaceutical New FILED 12 May 2000; WO 01/16108; WO 01/16133; and WO 01/16139).

The compound LG120907, a non-steroidal AR antagonist, has been shown, in rats, to have reduced antagonist effects on the hypothalamic axis and on libido (reproductive rate) as compared to other clinically used AR antagonists, such as Casodex. As such, LG120907 has been characterized as a selective androgen receptor modulator for the treatment of prostate cancer (Wang et. al. *Poster* # P3-126, *Endocrine Society* 80th *Annual Meeting* (1998), Hamann et. al. *Presentation* # *S*39-2, *Endocrine Society* 80th *Annual Meeting* (1998)).

Recent reports exploring the nogenotropic effects of sex steroid hormones such as DHT and E2 on the AR and ER, clearly show that both receptors regulate functions not specifically involved with transcriptional events (Kousteni et. al., *Cell* 104, 719–730 (2001)). The antiapoptic effects of ER and AR have been shown to be inducible by ligands that have no effects on transcription. It has also been shown that ligands that have effects on transcription can have no anti-apoptotic effect.

SARMs exhibiting a difference-in-kind of the modulation effected in tumors containing the androgen receptor relative to the modulation effected in other, nontumor tissues containing the androgen receptor (especially, antagonist activity in tumors versus agonist activity in other, nonmalignant tissues containing the androgen receptor), have heretofore been neither disclosed nor suggested. The present invention provides SARMs, and methods for identifying and designing such SARMs, which exhibit antagonist activity in hormone-dependent tumors while exhibiting no activity, or more preferably agonist activity, against other nontumor tissues containing the androgen receptor. As described below, these SARMs can be employed, for example, to treat hormone-dependent tumors such as prostate cancer in patients by both inhibiting the growth of the tumor while mitigating side effects such as muscle wasting/cachexia, loss of libido, osteoporosis and gynecomastia. The term "patient" as used herein denotes an animal, preferably a mammal such as a dog, cat, or, most preferably, a human.

SUMMARY OF THE INVENTION

An object of the present invention is to provide methods for identifying SARMs having antagonist activity against hormone-dependent tumors while exhibiting no activity, or more preferably agonist activity, against other nontumor tissues containing the androgen receptor. In one embodiment, antagonist activity in hormone-dependent tumors is ascertained via screening for inhibition of growth, either in vitro or in vivo, in hormone-dependent tumor cell lines. In this embodiment, the activity of a potential SARM is also assessed in a normal, nontumor cell line. Alternatively, an animal model bearing a hormone-dependent tumor can be used to assess the antagonist activity of a potential SARM against the tumor as well as its activity in nontumor tissues in the animal.

Another object of the present invention is to provide methods for designing SARMs having antagonist activity in hormone-dependent tumors while exhibiting no activity, or more preferably agonist activity, against other nontumor tissues containing the androgen receptor by using information about the AR crystal structure and the estrogen receptor (ER) crystal structure with estradiol, tamoxifen or raloxifen.

Another object of the present invention is to provide molecule or molecular complexes comprising all or any part of a ligand binding site defined by structure coordinates of an androgen-receptor ligand binding domain (AR-LBD) amino acids V685, L700, L701, S702, S703, L704, N705, E706, L707, G708, E709, Q711, A735, I737, Q738, Y739, S740, W741, M742, G743, L744, M745, V746, F747, A748, M749, G750, R752, Y763, F764, A765, L768, F770, M780, M787, I869, L873, H874, F876, T877, F878, M894, M895, A896, E897, I898, I899, S900, V901, Q902, V903, P904, K905, I906 and L907 according to Table A as provided herein, or a mutant or homologue of said molecule or molecular complex for use in identifying SARMs.

Another object of the present invention is to provide machine-readable data storage media comprising a data storage material encoded with machine readable data, wherein the data is defined by the structure coordinates of an AR-LBD with an AR-LBD ligand or ligand complex according to Table A or a homologue of said complex, wherein said homologue comprises backbone atoms that have a root mean square deviation from the backbone atoms of the complex of not more than 3.0 Å.

Another object of the present invention is to provide a binding site in AR-LBD for an AR modulator in which a portion of said ligand is in van der Walls contact or hydrogen bonding contact with any portion or all of residues V685, L700, L701, S702, S703, L704, N705, E706, L707, G708, E709, Q711, A735, I737, Q738, Y739, S740, W741, M742, G743, L744, M745, V746, F747, A748, M749, G750, R752, Y763, F764, A765, L768, F770, M780, M787, I869, L873, H874, F876, T877, F878, L880, L881, V889, F891, P892, E893, M894, M895, A896, E897, I898, I899, S900, V901, Q902, V903, P904, K905, I906 or L907 of AR-LBD according to Table A. In a preferred embodiment, the binding site is a homologue or mutant with 25%–95% identity to residues V685, L700, L701, S702, S703, L704, N705, E706, L707, G708, E709, Q711, A735, I737, Q738, Y739, S740, W741, M742, G743, L744, M745, V746, F747, A748, M749, G750, R752, Y763, F764, A765, L768, F770, M780, M787, I869, L873, H874, F876, T877, F878, L880, L881, V889, F891, P892, E893, M894, M895, A896, E897, I898, I899, S900, V901, Q902, V903, P904, K905, I906 or L907 of AR-LBD according to Table A as provided herein.

Another object of the present invention is to provide SARMs having antagonist activity in hormone-dependent tumors while exhibiting no activity, or more preferably agonist activity, against other nontumor tissues containing the androgen receptor, as well as pharmaceutical compositions comprising at least one such SARM and a pharmaceutically acceptable carrier. In a preferred embodiment, the SARM is identified or designed in accordance with a method of the present invention.

Another object of the present invention is to provide a method for inhibiting the growth of hormone-dependent tumor cells comprising contacting the tumor cells with a SARM having antagonist activity in hormone-dependent tumors while exhibiting no activity, or more preferably agonist activity against other nontumor tissues containing the androgen receptor.

Unless otherwise indicated, SARMs of the present invention having antagonist activity against hormone-dependent tumors while exhibiting no activity, more preferably agonist activity against other nontumor tissues containing the androgen receptor are contemplated as further exhibiting, in all embodiments of the invention, agonist, antagonist or no activity against normal prostate tissue.

Yet another object of the present invention is to provide methods for using these SARMs in the treatment of conditions remediable by administration of an androgen receptor modulator as described herein including, but not limited to, hirsutism, acne, seborrhea, Alzheimer's disease, androgenic alopecia, hypogonadism, hyperpilosity, benign prostate hypertrophia, adenomas and neoplasias of the prostate (such as advanced metastatic prostate cancer), treatment of benign or malignant tumor cells containing the androgen receptor such as is the case for breast, brain, skin, ovarian, bladder, lymphatic, liver and kidney cancers, pancreatic cancers, modulation of VEGF expression and the applications therein for use as antiangiogenic agents, osteoporosis, suppressing spermatogenesis, libido, cachexia, endometriosis, polycystic ovary syndrome, anorexia, androgen dependent age-related diseases and conditions, such as androgen supplement for age-related decreased testosterone levels in men, male menopause, male hormone replacement, male and female sexual dysfunction, and inhibition of muscular atrophy in ambulatory patients. Particularly preferred, is the use of SARMs for the treatment of hormone-dependent tumors, particularly early stage prostate cancers, and for chemoprevention of hormone-dependent cancer, particularly prostate cancers.

All documents referred to herein, including but not limited to U.S. patent applications, are incorporated herein by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

Selective androgen receptor modulators (SARMs) have now been identified with antagonist activity against hormone-dependent tumors while exhibiting no activity, or more preferably agonist activity against other (i.e., one or more) nontumor tissues containing the androgen receptor. SARMs of the present invention exhibiting antagonist activity against hormone-dependent tumors and no activity against other nontumor tissues containing the androgen receptor may also be referred to as specific androgen receptor modulators.

For purposes of the present invention by "nontumor", noncancerous" or "nonmalignant" androgen receptor containing tissues it is meant to include, but is not limited to, seminal vesicles, male and female genitalia, skin, testis, ovary, cartilage, sebaceous glands, hair follicles, sweat glands, muscle such as cardiac muscle, skeletal and smooth muscle, gastrointestinal vesicular cells, thyroid follicular cells, adrenal cortex, liver, pineal, bone, stromal cells, kidney tubules, urinary bladder and numerous brain cortical and subcortical regions, including spinal motor neurons.

Unless otherwise indicated, SARMs of the present invention having antagonist activity against hormone-dependent tumors while exhibiting no activity, or more preferably agonist activity, against other nontumor tissues containing the androgen receptor are contemplated as further exhibiting, in all embodiments of the invention, agonist, antagonist or no activity against normal prostate tissue.

As used herein, the phrase "no activity or agonist activity" preferably denotes compounds with an activation effect (greater than 5%) in vivo as compared to control animals on the weights of the ventral prostate, seminal vesicles, levator ani and/or luteinizing hormone serum levels, and most preferably activity which maintains average normal bone density, average normal muscle mass, average normal reproductive function, and/or average normal libido seen in ugonadal warm-blooded male mammals, preferably human males. "No activity or agonist activity" of SARMS of the present invention is preferably exhibited at the same amount or range of amounts that exhibit antagonist activity against hormone-dependent tumors. When administered to a patient, this amount or range of amounts, wherein the SARM exhibits antagonist activity against hormone-dependent tumors while exhibiting no activity or more preferably agonist activity against other nontumor containing tissues, is the preferred therapeutically useful range. As will be understood by those of skill in the art upon reading this disclosure, SARMs of the present invention, when used in amounts outside the preferred therapeutically useful range, may exhibit the same antagonist activity against hormone-dependent tumors and no activity or agonist activity against nontumor containing tissues or may no longer exhibit the same specificity or selectivity. For example, SARMs of the present invention, when used in amounts exceeding the preferred therapeutically useful range may exhibit some antagonist activity in nontumor containing tissues.

The present invention relates to SARMs with these dual activities, methods for identifying these SARMs, pharmaceutical compositions comprising these SARMs, and methods of using these SARMs in the treatment of androgen receptor mediated diseases and disorders.

For example, SARMs of the present invention are useful in selectively inhibiting the growth of hormone-dependent tumors while preferably activating androgen receptor activity in other nontumor, meaning noncancerous or nonmalignant, androgen receptor containing tissues. Accordingly, the SARMs of the present invention are useful in treating tumors including, but not limited to, androgen receptor containing tumors such as prostate, breast, brain, skin, ovarian, bladder, lymphatic, liver and kidney cancers, and pancreatic cancers, while mitigating or eliminating unwanted side effects associated with inhibition of androgen receptor activity in other nontumor androgen receptor containing tissues. Some of the potential unwanted side effects which result from antagonizing the normal function of androgens such as dihydrotestosterone (DHT) seen, for example, with current antiandrogen therapy in the treatment of prostate cancer include, but are not limited to, muscle wasting/cachexia, loss of libido, osteoporosis and gynecomastia.

An additional preferred use of such SARMs is in the area of chemoprevention, particularly as it pertains to prostate cancer. SARMs of the present invention can be administered after radical prostectomy during the period of "watchful waiting" to decrease the incidence of reoccurrence of metastatic prostate cancer.

In addition, these SARMs are useful in the treatment of androgen dependent age-related diseases and conditions including, without limitation, cachexia and osteoporosis. Such agents provide an orally bioavailable androgen replacement therapy that does not suffer from the increased risk of prostate cancer seen with traditional androgen agonists.

The SARMs of the present invention are also expected to be useful in treating other conditions remediable by administration of an androgen receptor modulator such as hirsutism, acne, seborrhea, Alzheimer's disease, androgenic alopecia, hypogonadism, hyperpilosity, benign prostate hypertrophia, modulation of VEGF expression and the applications therein for use as antiangiogenic agents, suppressing spermatogenesis, libido, endometriosis, polycystic ovary syndrome, anorexia, and androgen dependent age-related diseases and conditions, such as androgen supplement for age-related decreased testosterone levels in men, male menopause, male hormone replacement, male and female sexual dysfunction, and inhibition of muscular atrophy in ambulatory patients.

Various methods for identifying SARMs having antagonist activity against hormone-dependent tumors while exhibiting no activity, or more preferably agonist activity against other nontumor tissues containing the androgen receptor can be used. In one embodiment, antagonist activity in hormone-dependent tumors is ascertained via screening for inhibition of growth, either in vitro or in vivo, in hormone-dependent tumor cell lines. Examples of hormone-dependent tumor cell lines which can be used for screening potential SARMs include, but are not limited to, human breast tumor cell line MDA MB453, human breast tumor cell line ZR-75-1, murine breast line Shionogi, rat prostate adenocarcinoma line Dunning R-3327, human prostate tumor cell line MDA PCa 2a and PCa 2b, human prostate cell line LNCap, human prostate tumor cell line CWR22, human prostate tumor cell line LuCaP 35 and LuCaP 23.12, human prostate cell line LAPC-4 and LAPC-9, human prostate tumor cell line PC-295, human prostate tumor cell line PC-310, and human osteosarcoma cell line MG-63. These experimental human and murine prostate and breast cell lines and the tumor model systems derived therein are well accepted by those of skill in the art as indicative of the pharmacology of human hormone-dependent tumors, such as prostate cancer. Examples of the relationship of such models to the human disease state can be found in, but are

not limited to, the following references and the references contained therein, Jacques et. al. *Endocrinology* 140, 416–421 (1999); Yeap et. al. *Endocrinology* 140, 3282–3291 (1999), Sharma et. al. *Oncogene* 18, 5349–5355 (1999), Isaacs, J. T. *Urol. Oncol.* 2, 115–116 (1996), Bentei et. al. *In Vitro Cell Dev. Biol.* 35, 655–662 (1999), Suzuki et. al. *J. Steroid Biochem. Mol. Biol.* 37, 559–567 (1990), Peehl, D. M. *Urol. Oncol.* 2, 100–102 (1996), Wytske et. al. *Urol. Oncol.* 2, 122–125 (1996), Leland, C. W. K. *Urol. Oncol.* 2, 126–128 (1996), Buhler et. al. *The Prostate* 43, 63–70 (2000), Navone et. al. *Clin. Cancer Res.* 6, 1190–1197 (2000), Etreby et. al. *The Prostate* 42, 99–106 (2000), Jongsma et. al. *Cancer Res.* 60, 741–748 (2000), Jongsma et. al. *Amer. J. Path.* 154, 543–551 (1999), Ye et. al. *Clin. Cancer Res.* 5, 2171–2177 (1999), Navone et. al. *Clin. Cancer Res.* 3, 2493–2500 (1997), Klein et. al. *Nature Medicine* 3, 402–408 (1997), Chen et. al. *Cancer Res.* 58, 2777–2783 (1998), and Craft et. al. *Cancer Res.* 59, 5030–5036 (1999).

In this embodiment, the agonist or antagonist activity of a potential SARM is also measured in a normal, nontumor cell line. Examples of normal, nontumor cells lines useful in this method include, but are not limited to, primary rat prostate epithelial and stromal cells, murine muscle cell line C2C12, primary guinea pig smooth muscle cells, primary smooth-muscle cells from immature (I-PSMC) or adult (A-PSMC) rat penis, primary rabbit smooth muscle cell line, prostatic smooth muscle cell line PS-1, prostatic smooth muscle cell line PSMC1, mouse bone cell cultures and osteoblasts cells and primary rat seminal vesicle lines SVC-1 and SCV-2. Such cell lines are described in the following exemplary references and the references contained therein: Nemeth et. al. *J. Andrology* 19, 718–724 (1998), Zhuang et. al. *J. Steroid Biochem. Mol. Biol.* 41, 693–696 (1992), Zhang et. al. *Prostate* 30, 117–129 (1997), Ricciardelli et. al. *J. Endocrinol.* 140, 373–383 (1994), Gonzalez-Cadavid et. al. *Mol. Cell. Endocrinol.* 90, 219–229 (1993), Sadeghi-Nejad et. al. *Int. J. Impotence Res.* 10, 165–169 (1998), Gerdes et. al. *Endocrinology* 139, 3569–3577 (1998), Sarah et. al. *J. Cell. Physiol.* 185, 416–424 (2000), Chen et. al., *FEBS Letters* 491, 91–93 (2001) and Tajana et. al. *EMBO J.* 3, 637–644 (1984).

Alternatively, the agonist and antagonist effects of SARMs are measured in nontumor tissues via a series of in vivo rat models in which surrogate endpoints are measured in tissues including, but not limited to, the prostate, seminal vesicle, and levitor ani muscle, as well as the hypothalmic axis via measurement of plasma luteinizing hormone (LH) levels. Several surrogate endpoint in vivo assays can also be utilized to examine the effects of agents on the AR pathway. These assays involve measuring the effects of agents on normal androgen dependent tissues and functions, such as, but not limited to, prostate, seminal vesicle, levator ani muscle, bone, libido, fertility and hypothalamus (measurement of blood LH levels). These assays are widely recognized as having a direct correlation to the effects of the agents on the AR pathways in humans. Some examples of such surrogate endpoint in vivo assays can be found in, but are not limited to, the following references and the references contained therein: Ashby et. al. *J. Appl. Tox.* 20, 35–47 (2000), Yamada et. al. *Tox. Sciences* 53, 289–296 (2000), Hamann et. al. *J. Med. Chem.* 41, 623–639 (1998), Furr et. al. *Eur. Urol* 29, 83–95 (1996), Broulik et. al. *Bone* 20, 473–475 (1997), Wang et. al. *Poster # P3-126, Endocrine Society* 80th *Annual Meeting* (1998), Hamann et. al. *Presentation # S39-2, Endocrine Society* 80th *Annual Meeting* (1998), Maucher et. al. *J. Cancer Res. Clin. Oncol.* 119, 669–674(1993),and Risek et al. Presentation #P1-497, Endocrine Society 83rd Annual Meeting (2001).

Animal models bearing a hormone-dependent tumor can also be used to assess the antagonist activity of a potential SARM against the tumor and the agonist or antagonist activity against AR containing normal nontumor tissues in the animal. For example, the above surrogate endpoint in vivo assays can be run using a rat bearing an androgen-dependent rat prostate tumor, such as the Dunning R-3327. In this manner, effects of a SARM on a rat androgen-dependent prostate tumor can be determined while simultaneously examining the effects of the SARM agent on AR containing normal nontumor tissues such as, but not limited to, prostate, seminal vesicle, and levitor ani muscle as well as effects on the hypothalmic axis via measurements of plasma LH levels. In a similar fashion, immune compromised nude rats bearing human androgen-dependent prostate tumors can be employed. In this manner, effects of a SARM on a human androgen-dependent prostate tumor can be determined while simultaneously examining the effects of the SARM agent on normal tissues such as, but not limited to, prostate, seminal vesicle, and levitor ani muscle as well as effects on the hypothalmic axis via measurements of plasma LH levels. In addition, in vivo rat assays can be employed to determine the effect of SARMs on libido and reproduction.

SARMs having antagonist activity in hormone-induced tumors and no activity, or more preferably agonist activity, in other nontumor tissues can also be designed using information about the AR crystal structure and the estrogen receptor (ER) crystal structure with estradiol, tamoxifen or raloxifen. The crystal structure of the androgen receptor ligand binding domain (AR-LBD) has been determined to 2.0 Å resolution and is described in U.S. patent application Ser. No. 09/687,609, filed Oct. 13, 2000 and corresponding PCT/US00/28495, Matias et al., *J. Biol. Chem.* 275, 26164–26171 (2000) and Sack et. al., *Proc. Natl. Acad. Sci. USA* 98, 4904–4909 (2001), herein incorporated by reference. The crystal structure of ER is disclosed, for example, in WO 99/50658, herein incorporated by reference. Using these crystal structures, structure-based or rational drug design techniques can be used to design, select, and synthesize chemical entities, including the inhibitory and stimulatory SARMs of the present invention.

One particularly useful drug design technique enabled by this invention is iterative drug design. Iterative drug design is a method for optimizing associations between a protein and a compound by determining and evaluating the three-dimensional structures of successive sets of protein/ligand complexes. Those of skill in the art will understand upon this disclosure that association of natural ligands or substrates with the binding pockets of their corresponding receptors or enzymes is the basis of many biological mechanisms of action. The term "binding pocket" as used herein, refers to a region of a molecule or molecular complex, that, as a result of its shape, favorably associates with another chemical entity or compound, i.e. ligand. Similarly, many drugs exert their biological effects through association with the binding pockets of receptors and enzymes. Such associations may occur with all or any parts of the binding pockets. An understanding of such associations will help lead to the design of drugs having more favorable associations with their target receptor or enzyme, and thus, improved biological effects. Therefore, this information is valuable in designing potential SARMs of this invention.

The term "associating with" refers to a condition of proximity between chemical entities or compounds, or por-

tions thereof, i.e. ligands. The association may be non-covalent, wherein the juxtaposition is energetically favored by hydrogen bonding or van der Waals or electrostatic interactions, or it may be covalent.

In iterative drug design, crystals of a series of protein/ligand complexes are obtained. The three-dimensional structures of each complex are then solved. Such an approach provides insight into the association between the proteins and ligands of each complex. This is accomplished by selecting compounds with inhibitory activity, obtaining crystals of this new protein/ligand complex, solving the three dimensional structure of the complex, and comparing the associations between the new protein/ligand complex and previously solved protein/ligand complexes. By observing how changes in the compound effect the protein/ligand associations, these associations may be optimized.

In some cases, iterative drug design is carried out by forming successive protein/ligand complexes and then crystallizing each new complex. Alternatively, a pre-formed protein crystal is soaked in the presence of an inhibitor, thereby forming a protein/ligand complex and obviating the need to crystallize each individual protein/ligand complex.

As used herein, the term "soaked" refers to a process in which the crystal is transferred to a solution containing the compound of interest.

The present invention also provides for computational methods using three-dimensional models of the androgen and/or estrogen receptors that are based on crystals of AR-LBD/AR-LBD ligand complex and/or the ER-LBD/ER-LBD ligand complex. Generally, the computational method of designing receptor ligands determines which amino acid or amino acids of the receptor ligand binding domain interact with at least one chemical moiety of the ligand. A ligand is then docked into the binding site of the receptor LBD using the three dimensional model of a crystallized protein comprising the AR-LBD or ER-LBD. The orientation of the ligand in the binding site is then optimized (vide infra) and is then used to design at least one chemical modification of a chemical moiety of the ligand that produces a second chemical moiety of the ligand structure that either decreases or increases an interaction between the interacting amino acid(s) from the receptor LDB and the second chemical moiety compared to the interaction between the interacting amino acid and the corresponding chemical moiety on the natural hormones.

The computational methods of the present invention are for designing SARMs using such crystal and three-dimensional structural information to generate synthetic ligands that modulate the conformational changes of the androgen receptor's LBD and/or the estrogen receptor's LBD. These computational methods are particularly useful in designing SARMs to the androgen receptor, wherein the SARM has an extended moiety that prevents any one of a number of ligand-induced molecular events that alter the receptor's influence on the regulation of gene expression, such as preventing the normal coordination of the activation domain observed for a naturally occurring ligand or other ligands that mimic the naturally occurring ligand, such as an agonist. Based upon the structures of the ER-LBD complexed with agonist or antagonist (Shiau, et al. Cell 1998 95:927–937; Pike et al. EMBO J. 1999 18(17): 4608–4618) and the structures of AR-LDB coupled with DHT or other ligands (described in U.S. patent application Ser. No. 09/687,609, filed Oct. 13, 2000 and corresponding PCT/US00/28495, incorporated herein in their entirety and Table A as provided herein) it can be determined how to modify chemical compounds so that they specifically interact with AR-LBD amino acids in the binding site. In particular, the above extended moiety can be directed towards helix-12 of the AR structure in such a fashion as to influence the position of this helix as was seen in the structure of ER complexed with tamoxifen or raloxifen and differing from the position of helix-12 seen in the crystal structure of AR bound with DHT or R1881, a synthetic analog of DHT that is a more potent agonist (Matias, et al., *J. Biol. Chem.* 275, 26164–26171 (2000)), and the crystal structure of ER bound with estradiol. Residues on helix-12 that may be affected or in contact with a ligand in the AR-LBD binding site include M894, M895, A896, E897, I898, I899, S900, V901, Q902, V903, P904, K905, I906 and L907. The present invention also relates to the three-dimensional crystal structure as defined by the structure coordinates listed in Table A. The crystal structure of the invention preferably contains at least 25%, more preferably at least 50%, more preferably at least 75%, more preferably at least 90%, more preferably at least 95%, more preferably at least 99%, and most preferably all of the coordinates listed in Table A. More preferably, molecule or molecular complexes are provided comprising all or any part of the ligand binding site defined by structure coordinates of AR-LBD amino acids V685, L700, L701, S702, S703, L704, N705, E706, L707, G708, E709, Q711, A735, I737, Q738, Y739, S740, W741, M742, G743, L744, M745, V746, F747, A748, M749, G750, R752, Y763, F764, A765, L768, F770, M780, M787, I869, L873, H874, F876, T877, F878, M894, M895, A896, E897, I898, I899, S900, V901, Q902, V903, P904, K905, I906 and L907 according to Table A as provided herein, or a mutant or homologue of said molecule or molecular complex. Most preferred are molecules or molecular complexes comprising all or any part of the ligand binding site defined by structure coordinates of AR-LBD amino acids N705, W741, Q711, R752, F764, T877, M895 and I898, according to Table A, or a mutant or homologue of said molecule or molecular complex.

The term "complex" or "molecular complex" as used herein means AR-LBD or a mutant or homologue of AR-LBD in a covalent or non-covalent association with a chemical entity or ligand.

For purposes of the present invention, by "at least a portion of" it is meant all or any part of the ligand binding site defined by these structure coordinates.

By "mutant or homologue" as used herein it is meant a molecule or molecular complex having a similar structure and/or sequences to AR-LBD. By "similar structure" it is meant a mutant or homologue having a binding pocket that has a root mean square deviation from the backbone atoms of said AR-LBD amino acids of not more than 1.5 Angstroms. By "similar sequence" it is meant a mutant or homologue having 30%, or more preferably 75%, identity with AR-LBD.

The term "root mean square deviation" means the square root of the arithmetic mean of the squares of the deviations from the mean. It is a way to express the deviation or variation from a trend or object. For purposes of this invention, the "root mean square deviation" defines the variation in the backbone of a protein or protein complex from the relevant portion of the backbone of the AR portion of the complex as defined by the structure coordinates described herein.

Once the structure coordinates of a protein crystal have been determined they are useful in solving the structures of other crystals.

Thus, in accordance with the present invention, the structure coordinates of an androgen receptor/ligand complex, and portions thereof is stored in a machine-readable storage medium. Such data may be used for a variety of purposes, such as drug discovery and x-ray crystallographic analysis or protein crystal.

Accordingly, in one embodiment of this invention is provided a machine-readable data storage medium comprising a data storage material encoded with the structure coordinates set forth in Table A. One embodiment utilizes System 10 as disclosed in WO 98/11134, the disclosure of which is incorporated herein by reference in its entirety.

The structure coordinates set forth in Table A can also be used to aid in obtaining structural information about another crystallized molecule or molecular complex. This may be achieved by any of a number of well-known techniques, including molecular replacement.

The structure coordinates set forth in Table A can also be used for determining at least a portion of the three-dimensional structure of molecules or molecular complexes which contain at least some structurally similar features to AR. In particular, structural information about another crystallized molecule or molecular complex may be obtained. This may be achieved by any of a number of well-known techniques, including molecular replacement.

Therefore, in another embodiment this invention provides a method of utilizing molecular replacement to obtain structural information about a crystallized molecule or molecular complex whose structure is unknown comprising the steps of:

a) generating an X-ray diffraction pattern from said crystallized molecule or molecular complex;
b) applying at least a portion of the structure coordinates set forth in Table A to the X-ray diffraction pattern to generate a three-dimensional electron density map of the molecule or molecular complex whose structure is unknown; and
c) using all or a portion of the structure coordinates set forth in Table A to generate homology models of AR-LBD or any other nuclear hormone receptor ligand binding domain.

Preferably, the crystallized molecule or molecular complex is obtained by soaking a crystal of this invention in a solution.

By using molecular replacement, all or part of the structure coordinates of the AR-LBD/AR-LBD ligand complex provided by this invention or molecular complex whose structure is unknown more quickly and efficiently than attempting to determine such information ab initio.

Molecular replacement provides an accurate estimation of the phases for an unknown structure. Phases are a factor in equations used to solve crystal structures that can not be determined directly. Obtaining accurate values for the phases, by methods other than molecular replacement, is a time-consuming process that involves iterative cycles of approximations and refinements and greatly hinders the solution of crystal structures. However, when the crystal structure of a protein containing at least a homologous portion has been solved, the phases from the known structure provide a satisfactory estimate of the phases for the unknown structure.

Thus, this method involves generating a preliminary model of a molecule or molecular complex whose structure coordinates are unknown, by orienting and positioning the relevant portion of the AR-LBD/AR-LBD ligand complex according to Table A within the unit cell of the crystal of the unknown molecule or molecular complex so as best to account for the observed X-ray diffraction pattern of the crystal of the molecule or molecular complex whose structure is unknown. Phases can then be calculated from this model and combined with the observed X-ray diffraction pattern amplitudes to generate an electron density map of the structure whose coordinates are unknown. This, in turn, can be subjected to any well-known model building and structure refinement techniques to provide a final, accurate structure of the unknown crystallized molecule or molecular complex [E. Lattman, "Use of the Rotation and Translation Functions", in Meth. Enzymol., 115, pp. 55–77 (1985); M. G. Rossmann, ed., "The Molecular Replacement Method", Int. Sci. Rev. Set., No. 13, Gordon & Breach, New York (1972)].

The structure of any portion of any crystallized molecule or molecular complex, or mutant, homologue or orphan receptor that is sufficiently homologous to any portion of the AR-LBD/AR-LBD ligand complex can be solved by this method. Along with the aforementioned AR, there also exist a number of receptors for which the activating or deactivating ligands may not be characterized. These proteins are classified as nuclear hormone receptors due to strong sequence homology to AR, and are known as orphan receptors.

The structure coordinates are also particularly useful to solve the structure of crystals of AR-LBD/AR-LBD ligand co-complexed with a variety of chemical entities. This approach enables the determination of the optimal sites for interaction between chemical entities, including interaction of candidate AR inhibitors with the complex. For example, high resolution X-ray diffraction data collected from crystals exposed to different types of solvent allows the determination of where each type of solvent molecule resides. Small molecules that bind tightly to these sites can then be designed and synthesized and tested for their AR inhibition activity.

All of the complexes referred to above may be studied using well-known X-ray diffraction techniques and may be refined versus 1.5–3 Å resolution X-ray data to an R value of about 0.20 or less using computer software, such as X-PLOR [Yale University, 1992, distributed by Molecular Simulations, Inc.; see, e.g., Blundell & Johnson, supra; Meth. Enzymol., vol. 114 & 115, H. W. Wyckoff et al., eds., Academic Press (1985)]. This information may thus be used to optimize known AR agonists, partial agonists, antagonists, partial antagonists and SARMS, and more importantly, to design new AR agonists/antagonists.

Accordingly, the present invention is also directed to a binding site in AR-LBD for an AR-LBD ligand in which a portion of AR-LBD ligand is in van der Walls contact or hydrogen bonding contact with at least one of the following residues: V685, L700, L701, S702, S703, L704, N705, E706, L707, G708, E709, Q711, A735, I737, Q738, Y739, S740, W741, M742, G743, L744, M745, V746, F747, A748, M749, G750, R752, Y763, F764, A765, L768, F770, M780, M787, I869, L873, H874, F876, T877, F878, L880, L881, V889, F891, P892, E893, M894, M895, A896, E897, I898, I899, S900, V901, Q902, V903, P904, K905, I906, or L907 of AR-LBD according to Table A. For purposes of this invention, by AR-LBD binding site it is also meant to include mutants or homologues thereof In a preferred embodiment, the mutants or homologues have at least 25% identity, more preferably 50% identity, more preferably 75% identity, and most preferably 95% identity to residues V685, L700, L701, S702, S703, L704, N705, E706, L707, G708, E709, Q711, A735, I737, Q738, Y739, S740, W741, M742, G743, L744, M745, V746, F747, A748, M749, G750, R752, Y763, F764, A765, L768, F770, M780, M787, I869, L873,

H874, F876, T877, F878, L880, L881, V889, F891, P892, E893, M894, M895, A896, E897, I898, I899, S900, V901, Q902, V903, P904, K905, I906, or L907 of AR-LBD binding sites according to Table A.

The present invention is also directed to a machine-readable data storage medium, comprising a data storage material encoded with machine readable data, wherein the data is defined by the structure coordinates of an AR-LBD/AR-LBD ligand according to Table A or a homologue of said complex, wherein said homologue comprises backbone atoms that have a root mean square deviation from the backbone atoms of the complex of not more than 3.0 Å. Preferably, the machine-readable data storage medium, according to the invention, is wherein said molecule or molecular complex is defined by the set of structure coordinates for AR-LBD/AR-LBD ligand according to Table A, or a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 2.0 Å. In a preferred embodiment the machine-readable data storage medium comprises a data storage material encoded with a first set of machine readable data comprising a Fourier transform of at least a portion of the structural coordinates for an AR-LBD/AR-LBD ligand according to Table A; which, when combined with a second set of machine readable data comprising an X-ray diffraction pattern of a molecule or molecular complex of unknown structure, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data, said first set of data and said second set of data.

The present invention also provides for computational methods using three dimensional models of the androgen receptor that are based on crystals of AR-LBD/AR-LBD ligand complex. Generally, the computational method of designing an androgen receptor ligand determines which amino acid or amino acids of the AR-LBD interact with a chemical moiety (at least one) of the ligand using a three dimensional model of a crystallized protein comprising the AR-LBD with a bound ligand, and selecting a chemical modification (at least one) of the chemical moiety to produce a second chemical moiety with a structure that either decreases or increases an interaction between the interacting amino acid and the second chemical moiety compared to the interaction between the interacting amino acid and the corresponding chemical moiety on the natural hormone. In a preferred embodiments, the method for identifying a compound that modulates androgen receptor activity comprises any combination of the following steps:

a. modeling test compounds that fit spatially into the AR-LBD as defined by structure coordinates according to Table A, or using a three-dimensional structural model of AR-LBD, mutant AR-LBD or AR-LBD homologue or portion thereof;

b. using the AR-LBD structure coordinates or ligand binding site as set forth herein to identify structural and chemical features;

c. employing identified structural or chemical features to design or select compounds as potential SARMs;

d. employing the three-dimensional structural model or the ligand binding site to design or select compounds as potential SARMs;

e. synthesizing the potential SARMs;

f. screening the potential SARMs in an assay characterized by binding of a test compound to the AR-LBD; and

g. modifying or replacing one or more amino acids from AR-LBD selected from the group consisting of V685, L700, L701, S702, S703, L704, N705, E706, L707, G708, E709, Q711, A735, I737, Q738, Y739, S740, W741, M742, G743, L744, M745, V746, F747, A748, M749, G750, R752, Y763, F764, A765, L768, F770, M780, M787, I869, L873, H874, F876, T877, F878, L880, L881, V889, F891, P892, E893, M894, M895, A896, E897, I898, I899, S900, V901, Q902, V903, P904, K905, I906 or L907 of AR-LBD according to Table A.

The computational methods of the present invention are for designing androgen receptor synthetic ligands using such crystal and three dimensional structural information to generate synthetic ligands that modulate the conformational changes of the androgen receptor's LBD. These computational methods are particularly useful in designing an agonist, partial agonist, antagonist or partial antagonist or SARM to the androgen receptor, wherein the agonist, partial agonist, antagonist or partial antagonist or SARM has an extended moiety that prevents any one of a number of ligand-induced molecular events that alter the receptor's influence on the regulation of gene expression, such as preventing the normal coordination of the activation domain observed for a naturally occurring ligand or other ligands that mimic the naturally occurring ligand, such as an agonist. As described herein, synthetic ligands of the androgen receptor will be useful in modulating androgen receptor activity in a variety of medical conditions.

It is also possible to design an extended chemical moiety that is directed towards helix-3 or helix-11 that stabilize or disrupt critical ligand-receptor interactions (Humm et al. Arch. Pharm. (Weinheim) 1990 323:83–87; Poujol, et al. J. Biol. Chem. 2000 275(31):24022–24031). The structure of AR-LBD complexed with DHT shows that the 17α-hydroxyl group of androgens (DHT) forms critical hydrogen bonds with Thr-877 and Asn-705 of the AR-LBD (Sack et al. Proc. Natl Acad. Sci. (USA) 98(9):4904–4909 (2001)). Experiments show that when Asn-705 is mutated to alanine (N705A), that nonsteroidal antiandrogens have low antagonistic properties compared to wild type AR. Asn-705 thus plays a crucial role in the anchoring of nonsteroidal antiandrogens and design of chemical moieties directed at Ans-705 and Thr-877 can also be used for development of a SARM. As described herein, synthetic ligands of the androgen receptor will be useful in inhibiting androgen receptor activity in hormone-induced tumors and activating androgen receptors in other androgen receptor containing nontumor tissues.

The location of the secondary structure (SS) elements for three dimensional structures of ER-LDB and AR-LBD are depicted below. The amino acid sequence alignment shown is based upon a structural superposition of the AR-LBD and the ER-LDB. Sequence numbering is for the AR-LBD. H (or G) indicates that a particular amino acid is in a helix, E (or B) indicates a particular amino acid is in a beta strand. The AR-LDB amino acids extend from Ile-672 through His-917 (SEQ ID NO:1) and the ER-LBD amino acids extend from Ser-305 through Arg-548 (SEQ ID NO:2). Helix numbering is indicated below sequence and structure definitions.

```
                        680                 700                 720                 740
                         |         |         |         |         |         |         |
AR      ---------IFLNVLEAIEPGVVCAGHDNAQPDSFAALLSSLNELGERQLVHVVKWAKALPGFRNLHVDDQMAVIQYSWMG
ER      SLALSLTADQMVSALLDAEPPILYSE------FSEASMMGLLTNLADRELVHMINWAKRVPGFVDLTLHDQVHLLECAWLE
SS AR          -HHHHHHHH----------------HHHHHHHHHHHHHHHHHHHHHHHG---GGG--HHHHHHHHHHHHHHH
SS ER   -------HHHHHHHHHHH---------------HHHHHHHHHHHHHHHHHHHHHHHG---GGG--HHHHHHHHHHHHHHH
                   |                                   |                                 |
                 Helix-1                             Helix-3                           Helix-4

                        760                 780                 800                 820
                 |         |         |         |         |         |         |         |
AR      LMVFAMGWRSFTNVNSRMLYFAPDLVFNEYRMHKSR-MYSQCVRMRHLSQEFGWLQITPQEFLCMKALLLFSIIPVDGLKN
ER      ILMIGLVWRSM--EHPGKLLFAPNLLLDRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVCLKSIILLNSG-------
SS AR   HHHHHHHHHHHHH----EE-B--BEE-HHHEH-------HHHHHHHHHHHHH----HHHHHHHHHHGG-EEE------
SS ER   HHHHHHHHHG--------EE-B--B-EEGGGGGG---HHHHHHHHHHHHHHHHHH---HHHHHHHHHHHHHH---------
         |                                 |                 |                 |
       Helix-5                         Helix-6           Helix-7           Helix-8

                        840                 860                 880
                 |         |         |         |         |         |         |
AR      Q---------KFFDELRMNYIKELDRIIA--CAAAAA-ASCSRRFYQLTKLLDSVQPIARELHQFTFDLLIKSHMVSVDFP
ER      -VYTFTLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLAQLLLILSHIRHMSNKGMEHLYSMKCKN---VVPLY
SS AR   H---------HHHHHHHHHHHHHHH-------------HHHHHHHHHHHHHHHHHHHHHHHHHHHHHHH-HHHH-----
SS ER   -GGG--HHHHHHHHHHHHHHHHHHHHHHHHH----HHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHH----------
                         |                                   |
                       Helix-9                            Helix-10/11

             900
              |         |
AR      EMMAEIISVQVPKILSGKVKPIYFH
ER      DLLLEMLD-AHR-------------
SS AR   HHHHHHHH-HHHHH---EEE----
SS ER   HHHHHHHH-HH--------------
             |
          Helix-12
```

Various computer programs are available that use crystallography data such as available for AR and ER and enable the rational design of SARMs of the present invention. Software programs such as ICM (version 2.7 or higher; Molsoft LLC, La Jolla, Calif.) or SYBYL® (Tripos Inc. St Louis, Mo.) can be used with the atomic coordinates from AR and ER crystals to generate three-dimensional models and/or determine the structures involved in ligand binding. Other molecular visualization programs such as INSIGHT II® (Pharmacopeia/Molecular Simulations, Inc., San Diego, Calif.) and GRASP (Columbia University, New York, N.Y.) allow for further manipulation and the ability to introduce new structures. In addition, a number computer modeling systems are available in which the sequence of the AR-LBD and the AR-LBD structure can be entered. The computer system then generates the structural details of the site in which a potential AR modulator binds so that complementary structural details of the potential modulators can be determined. Design in these modeling systems is generally based upon the compound being capable of physically and structurally associating with AR-LBD. In addition, the compound must be able to assume a conformation that allows it to associate with AR-LBD. Some modeling systems estimate the potential inhibitory or binding effect of a potential AR modulator prior to actual synthesis and testing.

Methods for screening chemical entities or fragments for their ability to associate with AR and ER are also well known. Often these methods begin by visual inspection of the active site on the computer screen. Selected fragments or chemical entities are then positioned with the AR-LBD or ER-LBD. Docking is accomplished using software, followed by optimization of the ligand in the receptor binding site by global optimization procedures or molecular dynamics and minimization protocols with standard molecular mechanic forcefields such as CHARMM and AMBER. Examples of computer programs which assist in molecular docking and the selection of chemical fragments or chemical entities useful in the present invention include, but are not limited to, GRID (Goodford, P. J. J. Med. Chem. 1985 28:849–857), AUTODOCK (Goodsell, D. S. and Olsen, A. J. Proteins, Structure, Functions, and Genetics 1990 8:195–202), and DOCK (Kunts et al. J. Mol. Biol. 1982 161:269–288) and ICM (Molsoft LLC, La Jolla Calif., ICM 2.7 Program manual, Abagan et al. 1994 J. Mol. Biol. 235:983–1002, Totrov et al. 1997 Proteins Suppl. 1:215–220).

Upon selection of preferred chemical entities or fragments, their relationship to each other and AR or ER can be visualized and the entities or fragments can be assembled into a single potential modulator. Programs useful in assembling the individual chemical entities include, but are not limited to CAVEAT (Bartlett et al. Molecular Recognition in Chemical and Biological Problems Special Publication, Royal Chem. Soc. 78, 182–196 (1989)) and 3D Database systems (Martin, Y. C. J. Med. Chem. 1992 35:2145–2154).

Alternatively, compounds can be designed de novo using either an empty active site or optionally including some portion of a known inhibitor. Methods of this type of design include, but are not limited to LUDI (Bohm H-J, J. Comp. Aid. Molec. Design 1992 6:61–78) and LeapFrog™(Tripos Associates, St. Louis. Mo.).

Numerous protocols have been developed to score the designed and docked chemical entities in the receptor binding sites. Programs useful in scoring the chemical entities in protein binding sites include, but are not limited to DOCK (Kunts et al. J. Mol. Biol. 1982 161:269–288, ICM (Molsoft LLC, La Jolla Calif., Totrov et al. 1997 Proteins Suppl. 1:215–220, Schapira et al. 2000 Proc. Natl. Acad. Sci USA 97(3):1008–1013) and SYBYL® (Tripos Inc. St Louis, Mo.

Once a computationally designed ligand (CDL) is synthesized, it can be tested using assays such as those described herein to establish its activity as an antagonist in

hormone-dependent tumors and to assess its activity in other nonmalignant AR containing tissues. A CDL, which acts as an antagonist in hormone-dependent tumors and exhibits no activity, or more preferably partial agonist or agonist activity, in other nontumor AR containing tissues is a SARM in accordance with this invention. After such testing, the CDLs can be further refined by generating LBD crystals with a CDL bound to the LBD. The structure of the CDL can then be further refined using established chemical modification methods for three-dimensional models to improve the activity or affinity of the CDL and make second generation CDLs with improved properties, such as that of a "super SARM", meaning a compound having superior agonist activity while maintaining antagonist activity in selected tissues.

In a particularly preferred embodiment of the present invention, SARMs having the following activity levels are contemplated. Such SARMs are preferred in the methods and compositions of the present invention, and exhibit antagonist activity levels described in the following section (i) and/or (ii), and no activity, or more preferably agonist activity levels described in the following sections (iii) and/or (iv):

(i) an IC_{50} of about 1 μM or less, more preferably 0.5 μM or less, most preferable 0.1 μM or less relative, to the maximal signal induction obtained for DHT, for the inhibition of at least one hormone-dependent tumor cell line, preferably a prostate tumor cell line or another hormone-dependent tumor cell line predictive of activity in a prostate tumor cell line, such as those described above in connection with screening for SARMs of the present invention and in Examples 3, 4, and 6 below; and/or

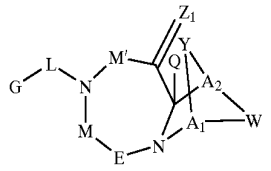
(ii) inhibition of hormone dependent tumor growth in vivo in a model such as described above and in Examples 10, 11, 12 or 13 below; and preferably;

(iii) at least 30% activation at 1 μM as compared to DHT, more preferably an EC_{50} of about 0.5 μM or less, most preferably an EC_{50} of about 0.1 μM or less, in normal AR-responsive tissue;

(iv) and/or more than 20%, preferably more than 40%, more preferably more than 70%, more preferably more than 90% of an activation effect, in vivo as compared to control animals on the weights of the ventral prostate, seminal vesicles, levator ani and/or luteinizing hormone serum levels as described above and in Example 8. Preferred SARMs of the present invention also act to maintain average normal bone density, average normal muscle mass, average normal reproductive function, and average normal libido seen in ugonadal warm-blooded male mammals, preferably human males. In a preferred embodiment, SARMs of the present invention exhibit antagonist activity against hormone-dependent tumors, while exhibiting no activity or agonist activity against at the same amount or range of amounts. When administered to a patient, this amount or range of amounts is the preferred therapeutically useful range. As will be understood by those of skill in the art upon reading this disclosure, SARMs of the present invention, when used in amounts outside the preferred therapeutically useful range, may exhibit the same antagonist activity against hormone-dependent tumors and no activity or agonist activity against nontumor containing tissues or may no longer exhibit the same specificity or selectivity. For example, SARMs of the present invention, when used in amounts exceeding the preferred therapeutically useful range may exhibit some antagonist activity in nontumor containing tissues.

The present invention is also directed to a selective androgen receptor modulator (SARM), which includes any compound that is an antagonist in hormone-induced tumors and inactive, or more preferably an agonist, in other AR containing nontumor tissues. In a preferred embodiment, the SARM is identified via screening assays as set forth herein or designed in accordance with the computational processes described herein. Compounds, which are small molecules, especially compounds other than peptides or steroids, are preferred. Without limitation to a particular chemotype, compounds selected from the following formulae Ia or Ib are preferred as SARMs of the present invention, especially particular compounds of these formulae set forth in the Examples herein. Compounds of the formula Ia are described further (as compounds of the "formula I") in U.S. Provisional Patent Application Ser. No. 60/214,392, filed Jun. 28, 2000, U.S. Provisional Patent Application Ser. No. 60/284,617, filed Apr. 18, 2001, and U.S. patent application Ser. No. 09/885,798, entitled "Fused Cyclic Modulators of Nuclear Hormone Receptor Function", by Salvati et al., filed Jun. 20, 2001; compounds of the formula Ib are described further (as compounds of the "formula I") in U.S. Provisional Patent Application Ser. No. 60/233,519, filed Sep. 19, 2000, U.S. Provisional Patent Application Ser. No. 60/284,730, filed Apr. 18, 2001, and U.S. patent application Ser. No. 09/885,381, entitled "Fused Heterocyclic Succinimide Compounds and Analogs Thereof, Modulators of Nuclear Hormone receptor Function", by Salvati et al., filed Jun. 20, 2001, all of which applications are incorporated herein by reference in their entirety. Formula Ia is as follows:

(Ia)



where the symbols have the following meanings unless otherwise indicated, and are, for each occurrence, independently selected:

G is an aryl or heterocyclo (e.g., heteroaryl) group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions, preferably with hydrogen, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, halo, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, arylalkyl or substituted arylalkyl, heterocycloalkyl or substituted heterocycloalkyl, CN, $R^1OC{=}O$, $R^1C{=}O$, $R^1C{=}S$, $R^1HNC{=}O$, $R^1R^2NC{=}O$, $HOCR^3R^{3'}$, nitro, R^1OCH_2, R^1O, NH_2, NR^4R^5, SR^1, $S{=}OR^1$, SO_2R^1, SO_2OR^1, $SO_2NR^1R^{1'}$, $(R^1O)(R^{1'}O)P{=}O$, $(R^1)(R^{1'})P{=}O$, or $(R^{1'})(NHR^1)P{=}O$;

E is $C{=}Z_2$, $CR^7R^{7'}$(e.g. CHR^7), SO_2, $P{=}OR^2$, or $P{=}OOR^2$;

Z_1 is O, S, NH, or NR^6;

Z_2 is O, S, NH, or NR^6;

A_1 is CR^7 or N;

A_2 is CR^7 or N;

Y is J-J'-J" where J is $(CR^7R^{7'})n$ and n=0–3, J' is a bond or O, S, S=O, SO_2, NH, NR^6, C=O, OC=O, $NR^1C{=}O$, $CR^7R^{7'}$, $C{=}CR^8R^{8'}$, $R^2P{=}O$, $OPOOR^2$, OPO_2, OSO_2, C=N, NHNH, $NHNR^6$, NR^6NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo or aryl or substituted aryl, and J" is $(CR^7R^{7'})n$ and n=0–3, where Y is not a bond;

W is $CR^7R^{7'}$—$CR^7R^{7'}$, CR^8=$CR^{8'}$, $CR^7R^{7'}$—C=O, NR^9—$CR^7R^{7'}$, N=CR^8, N=N, NR^9—$NR^{9'}$, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl;

Q is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, R^1OC=O, R^4C=O, R^5R^6NC=O, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, C=OSR^1, SO_2R^1 or NR^4R^5;

M is a bond, O, $CR^7R^{7'}$ or NR^{10}, and M' is a bond or NR^{10}, with the proviso that at least one of M or M' must be a bond;

L is a bond, $(CR^7R^{7'})n$, NH, NR^5 or $N(CR^7R^{7'})n$, where n=0–3;

R^1 and $R^{1'}$ are each independently H, alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^2 is alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^3 and $R^{3'}$ are each independently H, alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, hydroxylamine, hydroxamide, alkoxy or substituted alkoxy, amino, NR^1R^2, thiol, alkylthio or substituted alkylthio;

R^4 is H, alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, R^1C=O, R^1NHC=O, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^5 is alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, R^1C=O, R^1NHC=O, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^6 is alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, R^1C=O, R^1NHC=O, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^7 and $R^{7'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, OR^1, nitro, hydroxylamine, hydroxylamide, amino, NHR^4, NR^2R^5, NOR^1, thiol, alkylthio or substituted alkylthio, R^1C=O, R^1OC=O, R^1NHC=O, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC$=O, C=OSR^1, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

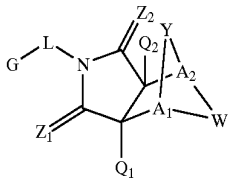
R^8 and $R^{8'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, NOR^1, alkylthio or substituted alkylthio, C=OSR^1, R^1OC=O, R^1C=O, R^1NHC=O, $R^1R^{1'}NC$=O, SO_2OR^1, S=OR^1, SO_2R^1, $PO_3R^1R^{1'}$, or $SO_2NR^1R^{1'}$;

R^9 and $R^{9'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, R^1C=O, R^1OC=O, R^1NHC=O, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$; and

R^{10} is H, alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, R^1C=O, R^1OC=O, $R^1R^{1'}NC$=O, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$.

Formula Ib is as follows:

(Ib)



where the symbols have the following meanings unless otherwise indicated, and are, for each occurrence, independently selected:

G is an aryl or heterocyclo (e.g., heteroaryl) group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions, preferably with hydrogen, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, halo, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, arylalkyl or substituted arylalkyl, heterocycloalkyl or substituted heterocycloalkyl, CN, R^1OC=O, R^1C=O, R^1C=S, R^1HNC=O, R^1R^2NC=O, $HOCR^3R^{3'}$, nitro, R^1OCH_2, R^1O, NH_2,

NR^4R^5, SR^1, $S{=}OR^1$, SO_2R^1, SO_2OR^1, $SO_2NR^1R^{1'}$, $(R^1O)(R^{1'}O)P{=}O$, oxo, $(R^1)(R^{1'})P{=}O$, or $(R^1)(NHR^1)P{=}O$;

Z, is O, S, NH, or NR^6;

Z_2 is O, S, NH, or NR^6;

A_1 is CR^7 or N;

A_2 is CR^7 or N;

Y is J-J'-J" where J is $(CR^7R^{7'})n$ and n=0–3, J' is a bond or O, S, S=O, SO_2, NH, NR^7, C=O, OC=O, $NR^1C{=}O$, $CR^7R^{7'}$, $C{=}CR^8R^{8'}$, $R^2P{=}O$, $R^2P{=}S$, $R^2OP{=}O$, $R^2NHP{=}O$, $OP{=}OOR^2$, $OP{=}ONHR^2$, $OP{=}OR^2$, OSO_2, $C{=}NR^7$, NHNH, $NHNR^6$, NR^6NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo or aryl or substituted aryl, and J" is $(CR^7R^{7'})n$ and n=0–3, where Y is not a bond;

W is $CR^7R^{7'}{-}CR^7R^{7'}$, $CR^8{=}CR^{8'}$, $CR^7R^{7'}{-}C{=}O$, $NR^9{-}CR^7R^{7'}$, $N{=}CR^8$, N=N, $NR^9{-}NR^{9'}$, $S{-}CR^7R^{7'}$, $SO{-}CR^7R^{7'}$, $SO_2{-}CR^7R^{7'}$, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein when W is not $NR^9{-}CR^7R^{7'}$, $N{=}CR^8$, N=N, $NR^9{-}NR^{9'}$, $S{-}CR^7R^{7'}$, $SO{-}CR^7R^{7'}$, $SO_2{-}CR^7R^{7'}$, or heterocyclo or substituted heterocyclo, then J' must be O, S, S=O, SO_2, NH, NR^7, OC=O, $NR^1C{=}O$, $OP{=}OOR^2$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, or N=N;

Q_1 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., substituted heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 or NR^4R^5;

Q_2 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 or NR^4R^5;

L is a bond, $(CR^7R^{7'})n$, NH, NR^5, NH $(CR^7R^{7'})n$, or NR^5 $(CR^7R^{7'})n$, where n=0–3;

R^1 and $R^{1'}$ are each independently H, alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^2 is alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^3 and $R^{3'}$ are each independently H, alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, hydroxylamine, hydroxamide, alkoxy or substituted alkoxy, amnino, NR^1R^2, thiol, alkylthio or substituted alkylthio;

R^4 is H, alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^5 is alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^6 is alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^7 and $R^{7'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, OR^1, nitro, hydroxylamine, hydroxylamide, amino, NHR^4, NR^2R^5, NOR^1, thiol, alkylthio or substituted alkylthio, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$, or wherein A_1 or A_2 contains a group R^7 and W contains a group R^7, said R7 groups of A_1 or A_2 and W together form a heterocyclic ring;

R^8 and $R^{8'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, NOR^1, alkylthio or substituted alkylthio, $C{=}OSR^1$, $R^1OC{=}O$, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, SO_2OR^1, $S{=}OR^1$, SO_2R^1, $PO_3R^1R^{1'}$, or $SO_2NR^1R^{1'}$; and

R^9 and $R^{9'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$.

The present invention is further directed to methods of using SARMs to inhibit the growth of hormone-induced

tumors. Hormone-induced tumors can be treated by administering to a patient an effective amount of a SARM with antagonist activity in hormone-induced tumors and no activity, or more preferably agonist activity, in other nontumor AR containing tissues. By "effective amount" it is meant an amount or concentration of SARM that inhibits the growth of hormone-induced tumor cells in the patient. In a preferred embodiment, "effective amount" also refers to an amount or concentration, which induces agonist activity in nontumor AR containing tissues. Such amounts or concentrations can be determined routinely by those of ordinary skill in the art, for example, based upon cell based assays such as described herein or through other art-recognized means.

SARMs of the present invention can be administered alone or simultaneously or sequentially with radiation and/or one or more active agents, such as chemotherapeutic agents. Examples of classes of anti-cancer and cytotoxic agents useful in combination with the present compounds include but are not limited to: alkylating agents such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes; antimetabolites such as folate antagonists, purine analogues, and pyrimidine analogues; antibiotics such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; enzymes such as L-asparaginase; farnesyl-protein transferase inhibitors; 5α reductase inhibitors; inhibitors of 17β-hydroxy steroid dehydrogenase type 3; hormonal agents such as glucocorticoids, estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone antagonists, octreotide acetate; microtubule-disruptor agents, such as ecteinascidins or their analogs and derivatives; microtubule-stabilizing agents such as taxanes, for example, paclitaxel (Taxol®), docetaxel (Taxotere®), and their analogs, and epothilones, such as epothilones A–F and their analogs; plant-derived products, such as vinca alkaloids, epipodophyllotoxins, taxanes; and topiosomerase inhibitors; prenyl-protein transferase inhibitors; and miscellaneous agents such as hydroxyurea, procarbazine, mitotane, hexamethylmelamine, platinum coordination complexes such as cisplatin and carboplatin; and other agents used as anti-cancer and cytotoxic agents such as biological response modifiers, growth factors; immune modulators and monoclonal antibodies. The compounds of the invention may also be used in conjunction with radiation therapy.

Representative examples of these classes of anti-cancer and cytotoxic agents include but are not limited to mechlorethamine hydrochloride, cyclophosphamide, chlorambucil, melphalan, ifosfamide, busulfan, carmustin, lomustine, semustine, streptozocin, thiotepa, dacarbazine, methotrexate, thioguanine, mercaptopurine, fludarabine, pentastatin, cladribin, cytarabine, fluorouracil, doxorubicin hydrochloride, daunorubicin, idarubicin, bleomycin sulfate, mitomycin C, actinomycin D, safracins, saframycins, quinocarcins, discodermolides, vincristine, vinblastine, vinorelbine tartrate, etoposide, etoposide phosphate, teniposide, paclitaxel, tamoxifen, estramustine, estramustine phosphate sodium, flutamide, buserelin, leuprolide, pteridines, diyneses, levamisole, aflacon, interferon, interleukins, aldesleukin, filgrastim, sargramostim, rituximab, BCG, tretinoin, irinotecan hydrochloride, betamethosone, gemcitabine hydrochloride, altretamine, and topoteca and any analogs or derivatives thereof.

Preferred member of these classes include, but are not limited to, paclitaxel, cisplatin, carboplatin, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, mitomycin C, ecteinascidin 743, or porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine and leurosine.

Examples of anticancer and other cytotoxic agents include the following: epothilone derivatives as found in German Patent No. 4138042.8; WO 97/19086, WO 30 98/22461, WO 98/25929, WO 98/38192, WO 99/01124, WO 99/02224, WO 99/02514, WO 99/03848, WO 99/07692, WO 99/27890, WO 99/28324, WO 99/43653, WO 99/54330, WO 99/54318, WO 99/54319, WO 99/65913, WO 99/67252, WO 99/67253 and WO 00/00485; cyclin dependent kinase inhibitors as found in WO 99/24416 (see also U.S. Pat. No. 6,040,321); and prenyl-protein transferase inhibitors as found in WO 97/30992 and WO 98/54966; and agents such as those described generically and specifically in U.S. Pat. No. 6,011,029 (the compounds of which U.S. patent can be employed together with any NHR modulators (including, but not limited to, those of present invention) such as AR modulators, ER modulators, with LHRH modulators, or with surgical castration, especially in the treatment of cancer).

The combinations of the present invention can also be formulated or co-administered with other therapeutic agents that are selected for their particular usefulness in administering therapies associated with the aforementioned conditions. For example, the compounds of the invention may be formulated with agents to prevent nausea, hypersensitivity and gastric irritation, such as antiemetics, and H_1 and H_2 antihistaminics.

SARMs of the present invention, for example, compounds identified as SARMs by the methods disclosed herein, which are active when given orally can be formulated as liquids, for example, syrups, suspensions or emulsions, tablets, capsules and lozenges. A liquid composition will generally comprise a suspension or solution of the compound in a suitable liquid carrier(s), for example, ethanol, glycerin, sorbitol, non-aqueous solvent such as polyethylene glycol, oils or water, with a suspending agent, preservative, surfactant, wetting agent, flavoring or coloring agent. Alternatively, a liquid formulation can be prepared from a reconstitutable powder. For example, a powder containing active compound, suspending agent, sucrose and a sweetener can be reconstituted with water to form a suspension; and a syrup can be prepared from a powder containing active ingredient, sucrose and a sweetener. A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s), such as those routinely used for preparing solid compositions. Examples of such carriers include magnesium stearate, starch, lactose, sucrose, microcrystalline cellulose, and binders, for example, polyvinylpyrrolidone. The tablet can also be provided with a color film coating, or color included as part of the carrier(s). In addition, active compound can be formulated in a controlled release dosage form as a tablet comprising a hydrophilic or hydrophobic matrix. A composition in the form of a capsule can be prepared, for example, using routine encapsulation procedures, such as by incorporation of active compound and excipients into a hard gelatin capsule. Other examples of capsule preparation include, for example, filling a hard gelatin capsule with a semi-solid matrix of active compound and high molecular weight polyethylene glycol; or filling a soft gelatin capsule with a solution of active compound in polyethylene glycol or a suspension in edible oil, for example liquid paraffin or fractionated coconut oil.

SARMs of the present invention, for example, compounds identified by the methods disclosed herein, which are active when given parenterally, can be formulated, for example, for any suitable mode of parenteral administration, such as for intramuscular or intravenous administration. A typical composition for intra-muscular administration will comprise a suspension or solution of active ingredient in an oil, for example arachis oil or sesame oil. A typical composition for intravenous administration will comprise a sterile isotonic aqueous solution containing, for example, active ingredient, dextrose, sodium chloride, a co-solvent, for example polyethylene glycol and, optionally, a chelating agent, for example ethylenediaminetetracetic acid and an anti-oxidant, for example, sodium metabisulphite. Alternatively, the solution can be freeze dried and then reconstituted with a suitable solvent just prior to administration.

SARMs of the present invention, for example, compounds identified as SARMs by the methods disclosed herein, which are active on rectal administration, can be formulated as suppositories. A typical suppository formulation will generally comprise active ingredient with a binding and/or lubricating agent such as a gelatin or cocoa butter or other low melting vegetable or synthetic wax or fat.

SARMs of the present invention, for example, compounds identified as SARMs by the methods disclosed herein, which are active on topical administration, can be formulated, for example, as transdermal compositions. Such compositions include, for example, a backing, active compound reservoir, a control membrane, liner and contact adhesive.

The typical daily dose of SARM varies according to the activity of the SARM, the individual needs, the condition to be treated and the route of administration. Exemplary suitable doses are in the general range of from 0.001 to 10 mg/kg bodyweight of the recipient per day.

The following nonlimiting examples are provided to further illustrate the present invention.

EXAMPLES

Example 1

Exemplary SARMs of the Present Invention

Exemplary SARMS of the present invention are depicted in Table 1. The absolute configuration for the following compounds was not determined. For simplicity in nomenclature, compound [3aR-(3aα,4β,7β,7aα)]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile is designated herein as having an "R" configuration and compound [3aS-(3aα,4β,7β,7aα)]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile is designated herein as having an "S" configuration. Enantiomerically pure products derived from [3aR-(3aα,4β,7β,7aα]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile are designated herein as having an "R" configuration and enantiomerically pure products derived from compound [3aS-(3aα,4β,7β,7aα)]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile are designated herein as having an "S" configuration. For simplicity in nomenclature, compound [3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile is designated herein as having an "S" configuration and compound [3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile is designated herein as having an "R" configuration. Enantiomerically pure products derived from [3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile are designated herein as having an "S" configuration and enantiomerically pure products derived from [3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile are designated herein as having an "R" configuration. Enantiomerically pure products derived from [3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)-benzonitrile are designated herein as having a "R" configuration and enantiomerically pure products derived from [3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimethyl-ethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile are designated herein as having an "S" configuration.

The chromatography techniques used to determine the compound retention times of Table 1 are as follows: LCMS=YMC S5 ODS column, 4.6×50 mm eluting with 10–90% MeOH/H2O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm; LC=YMC S5 ODS column, 4.6×50 mm eluting with 10–90% MeOH/H2O over 4 minutes containing 0.2% phosphoric acid; 4 mL/min, monitoring at 220 nm. The molecular mass of the compounds listed in Table 1, where provided, were determined by MS(ES) by the formula m/z.

TABLE 1

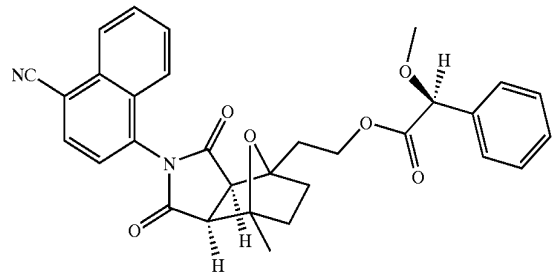
Cmp #	Structure	Compound Name	Retention Time Min./Molecular Mass	Proc. of Ex.
1		(αR)-α-Methoxybenzeneacetic acid, 2-[(3aα,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-y]ethyl ester.	3.28 & 3.74 LC Atrop Isomers 547.26 $[M + Na]^+$	2f, 2j

TABLE 1-continued

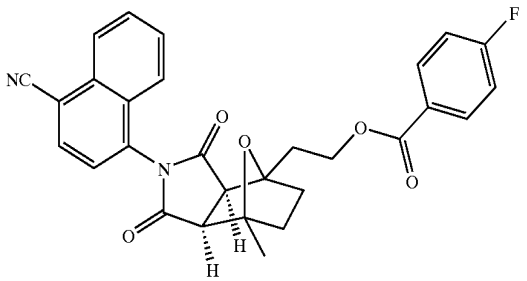
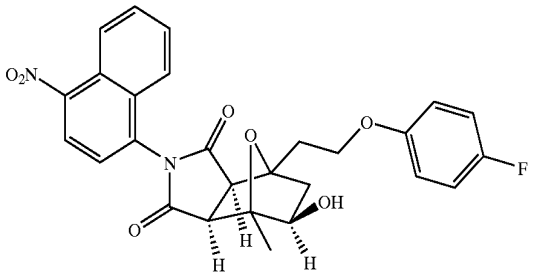
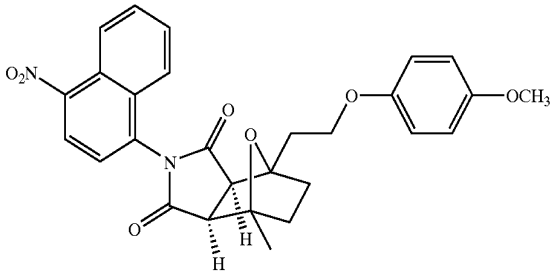
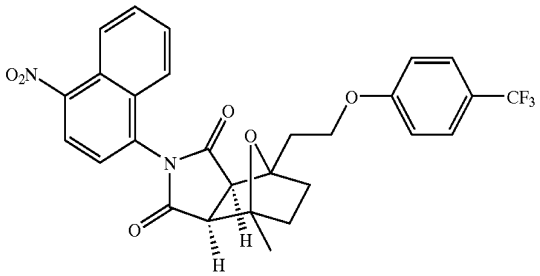
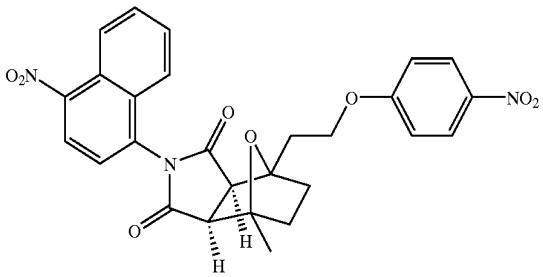
Cmp #	Structure	Compound Name	Retention Time Min./Molecular Mass	Proc. of Ex.
2		4-Fluorobenzoic acid, 2-[(3aα,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-y]ethyl ester.	3.64 & 3.77 LC Atrop Isomers 499.8 $[M + Na]^+$	2f, 2j
3		(3aα,4β,7β,7aα)-7-[2-(4-Fluorophenoxy)ethyl]-hexahydro-5-hydroxy-4-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.53 LC 505.2 $[M - H]^-$	2k
4		(3aα,4β,7β,7aα)-Hexahydro-4-[2-(4-methoxyphenoxy)ethyl]-7-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.42 & 3.55 LC Atrop Isomers 503.21 $[M + Na]^+$	2f, 2j
5		(3aα,4β,7β,7aα)-Hexahydro-4-methyl-2-(4-nitro-1-naphthalenyl)-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.81 & 3.93 LC Atrop Isomers 563.12 $[M + Na]^+$	2f, 2j
6		(3aα,4β,7β,7aα)-Hexahydro-4-methyl-2-(4-nitro-1-naphthalenyl)-7-[2-(4-nitrophenoxy)ethyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.48 & 3.61 LC Atrop Isomers 540.17 $[M + Na]^+$	2f, 2j

TABLE 1-continued

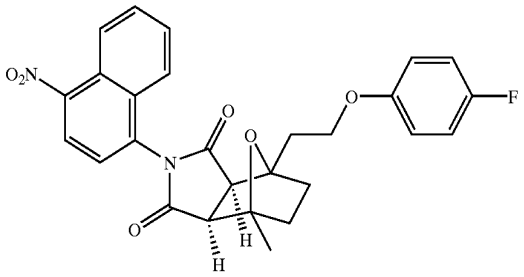
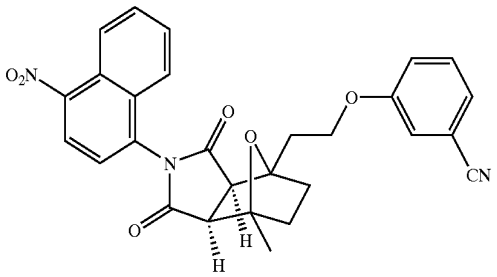
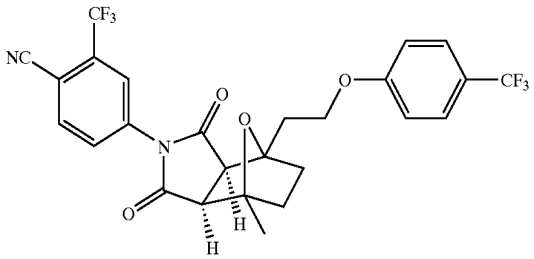
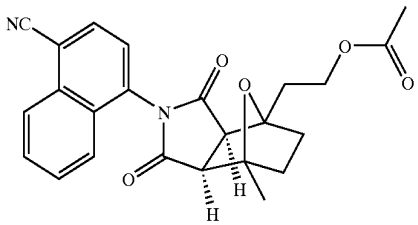
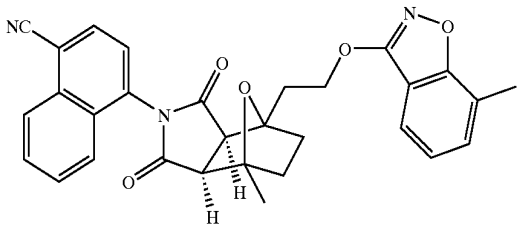
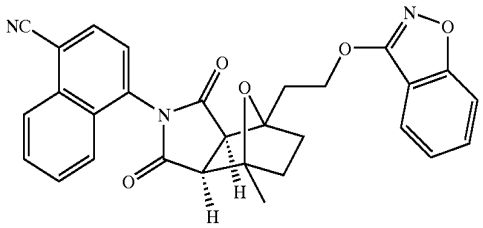
Cmp #	Structure	Compound Name	Retention Time Min./Molecular Mass	Proc. of Ex.
7		(3aα,4β,7β,7aα)-4-[2-(4-Fluorophenoxy)ethyl]-hexahydro-7-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.48 & 3.61 LC Atrop Isomers 491.46 $[M + H]^+$	2f, 2j
8		(3aα,4β,7β,7aα)-4-[Octahydro-7-methyl-2-(4-nitro-1-naphthalenyl)-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]benzonitrile.	3.63 LC 498.12 $[M + H]^+$	2f, 2j
9		(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phen-oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzo-nitrile.	3.93 LC	2f, 2j
10		(3aα,4β,7β,7aα)-4-[2-(Acetyloxy)ethyl]-2-(4-cyano-1-naphthalenyl)hexahydro-7-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.84 & 3.03 LC Atrop Isomers	2f, 2j
11		(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-7-[2-[(7-methyl-1,2-benzisoxazol-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.79 & 3.92 LC Atrop Isomers	2r
12		(3aα,4β,7β,7aα)-4-[4-[2-(1,2-Benzisoxazol-3-yloxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.55 & 3.70 LC Atrop Isomers	2r

TABLE 1-continued

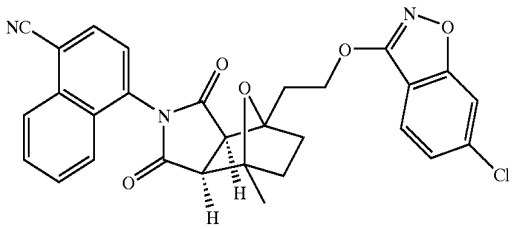
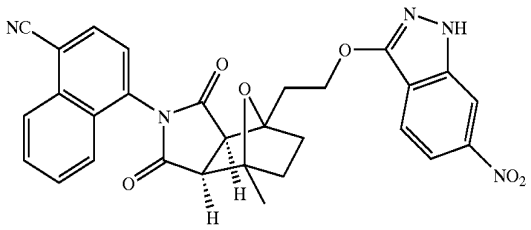
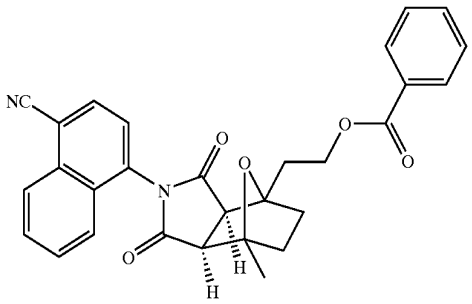
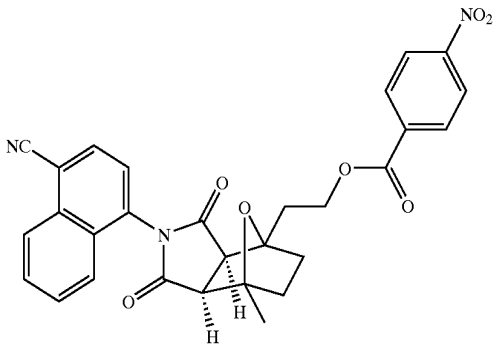
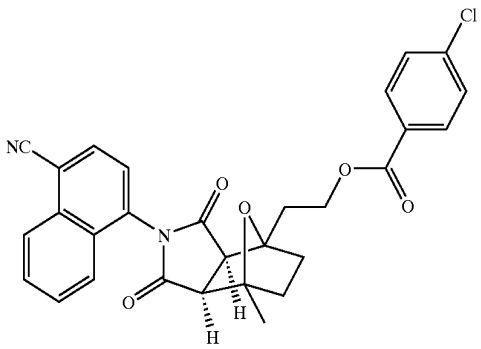
Cmp #	Structure	Compound Name	Retention Time Min./Molecular Mass	Proc. of Ex.
13		(3aα,4β,7β,7aα)-4-[4-[2-[(6-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.89 & 4.02 LC Atrop Isomers 528.0 $[M + H]^+$	2r
14		(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-7-[2-[(6-nitro-1H-indazol-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.60 & 3.74 LC Atrop Isomers 536.0 $[M - H]^-$	2s
15		(3aα,4β,7β,7aα)-4-[2-(Benzoyloxy)ethyl]-2-(4-cyano-1-naphthalenyl)hexahydro-7-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.51 & 3.66 LC Atrop Isomers	2f, 2j
16		(3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)-4-[2-[(4-nitrobenzoyl)oxy]ethyl] hexahydro-7-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.52 & 3.67 LC Atrop Isomers	2f, 2j
17		4-Chlorobenzoic acid, 2-[(3aα,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl ester.	3.79 & 3.83 LC Atrop Isomers	2f, 2j

TABLE 1-continued

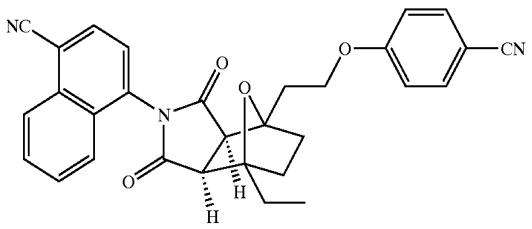
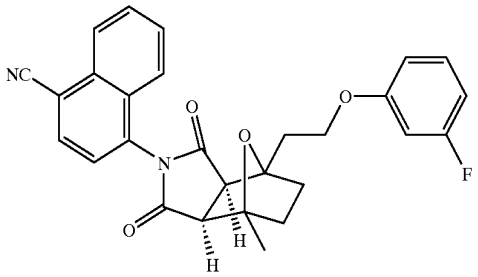
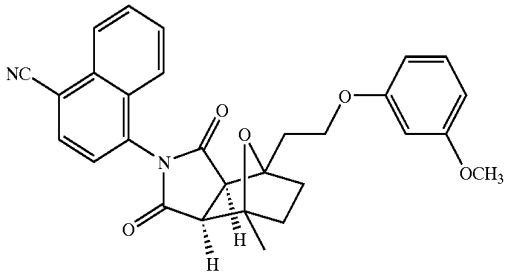
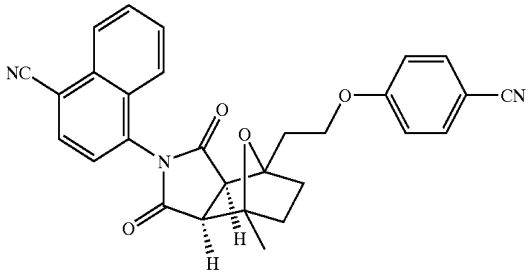
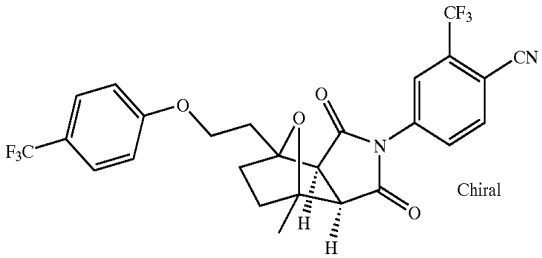
Cmp #	Structure	Compound Name	Retention Time Min./Molecular Mass	Proc. of Ex.
18		(3aα,4β,7β,7aα)-4-[4-[2-(4-Cyanophenoxy)ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.65 LC 492.16 $[M + H]^+$	2v
19		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Fluorophenoxy)ethyl]-octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.80 LC 471.65 $[M + H]^+$	2n, 2o
20		[3aR-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(3-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.73 LC 483.65 $[M + H]^+$	2n, 2o
21		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Cyanophenoxy)ethyl]-octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.80 LC	2n, 2o
22		[3aR-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile, faster eluting antipode.	3.93 LC	2i

TABLE 1-continued

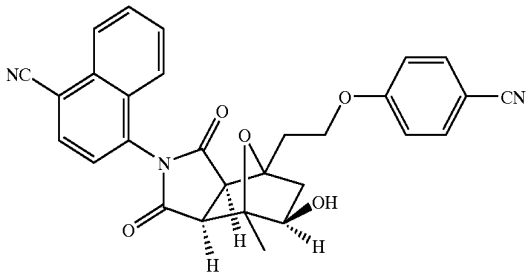
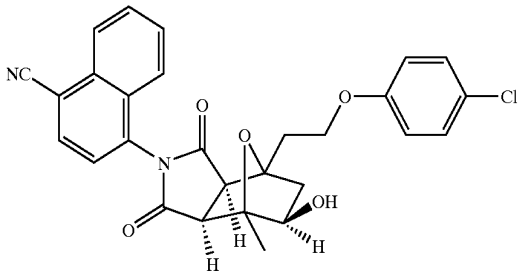
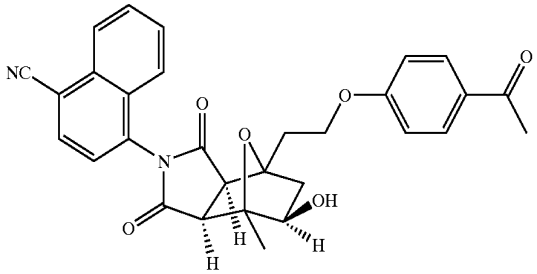
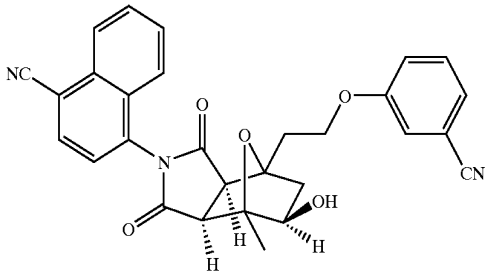
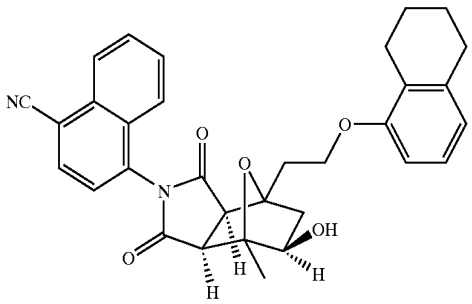
Cmp #	Structure	Compound Name	Retention Time Min./Molecular Mass	Proc. of Ex.
23		[3aR-(3aα,4β,5β,7β,7aα]-4-[7-[2-(4-Cyanophenoxy)ethyl]-octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.07 LC 494.09 $[M + H]^+$	2p, 2q
24		[3aR-(3aα,4β,5β,7β,7aα]-4-[7-[2-(4-Chlorophenoxy)ethyl]-octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.51 LC 503.08 $[M + H]^+$	2p, 2q
25		[3aR-(3aα,4β,5β,7β,7aα]-4-[7-[2-(4-Acetylphenoxy)ethyl]-octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.05 LC 511.13 $[M + H]^+$	2p, 2q
26		[3aR-(3aα,4β,5β,7β,7aα]-4-[7-[2-(3-Cyanophenoxy)ethyl]-octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.85 LC 494.13 $[M + H]^+$	2p, 2q
27		[3aR-(3aα,4β,5β,7β,7aα]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[(5,6,7,8-tetrahydro-1-naphthalenyl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.85 LC 523.17 $[M + H]^+$	2p, 2q

TABLE 1-continued

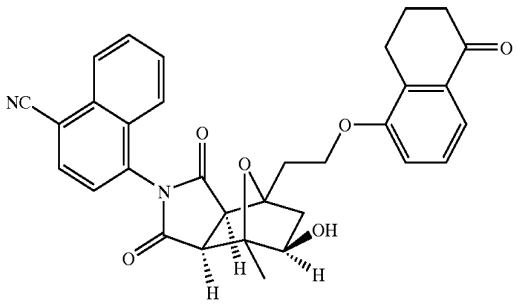
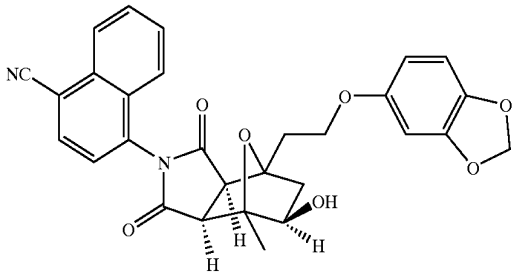
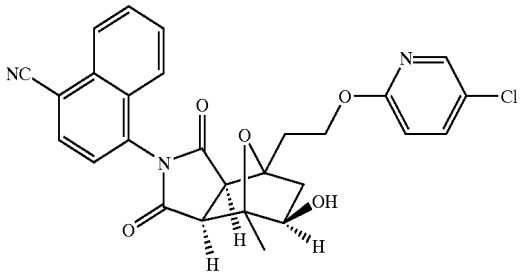
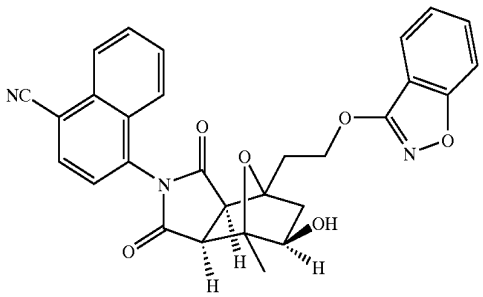
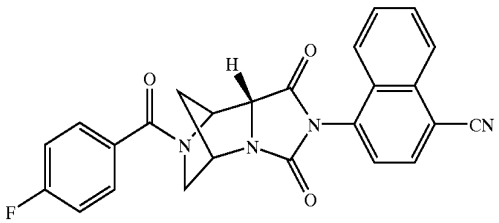
Cmp #	Structure	Compound Name	Retention Time Min./Molecular Mass	Proc. of Ex.
28		[3aR-(3aα,4β,5β,7β,7aα]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.29 LC 537.13 $[M + H]^+$	2p, 2q
29		[3aR-(3aα,4β,5β,7β,7aα]-4-[7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]oxtahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.22 LC 571.2 $[M - H + OAc]^-$	2p, 2q
30		[3aR-(3aα,4β,5β,7β,7aα]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]-octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.37 LC 504.0 $[M + H]^+$	2p, 2q
31		[3aR-(3aα,4β,5β,7β,7aα]-4-[7-[2-(1,2-Benzisoxazol-3-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.29 LC 510.4 $[M + H]^+$	2p, 2q
32		[5S-(5α,8α,8aα)]-2-(4-Cyano-1-naphthalenyl)-7-(4-fluorobenzoyl) tetrahydro-5,8-methanoimidazo[1,5-a]pyrazine-1,3(2H,5H)-dione.	2.76 LC 441.09 $[M + H]^+$	2d

TABLE 1-continued

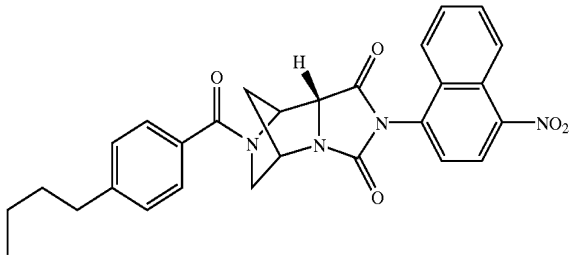
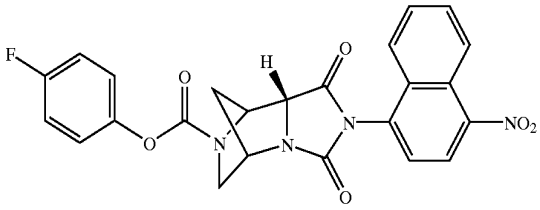
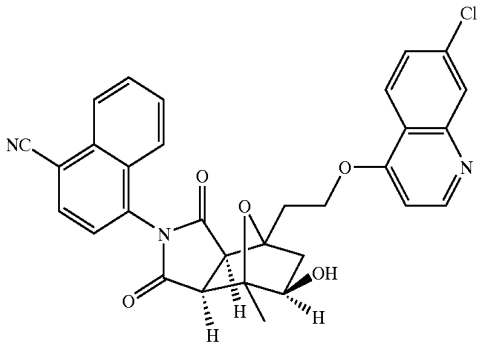
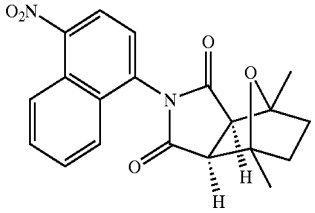
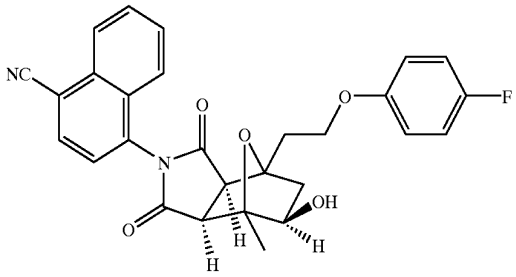
Cmp #	Structure	Compound Name	Retention Time Min./Molecular Mass	Proc. of Ex.
33		[5S-(5α,8α,8aα)]-7-(4-Butylbenzoyl)tetrahydro-2-(4-nitro-1-naphthalenyl)-5,8-methanoimidazo[1,5-a]pyrazine-1,3(2H,5H)-dione.	3.69 LC 499.45 [M + H]+	2d
34		[5S-(5α,8α,8aα)]-Hexahydro-2-(4-nitro-1-naphthalenyl)-1,3-dioxo-5,8-methanoimidazo[1,5-a]pyrazine-7(8H)-carboxylic acid, 4-fluorophenyl ester.	3.21 LC 477.38 [M + H]+	2d
35		[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-[(7-Chloro-4-quinolinyl)oxy]ethyl]-octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1).	2.53 LC 554.27 [M + H]+	2p, 2q
36		(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.04 LCMS	2e
37		[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-(4-Fluorophenoxy)ethyl]-octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.27 LC 487.11 [M + H]+	2p, 2q

TABLE 1-continued

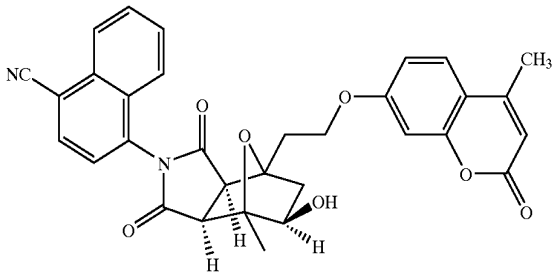
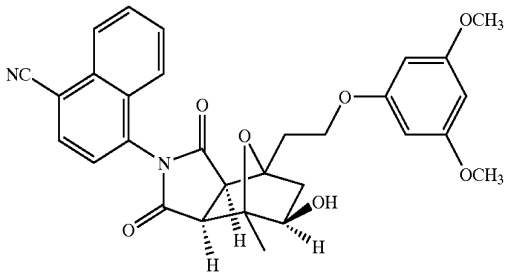
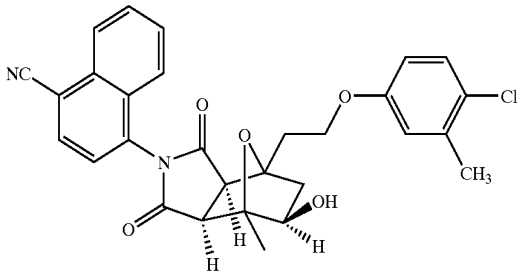
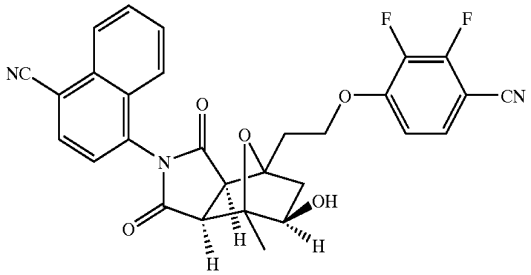
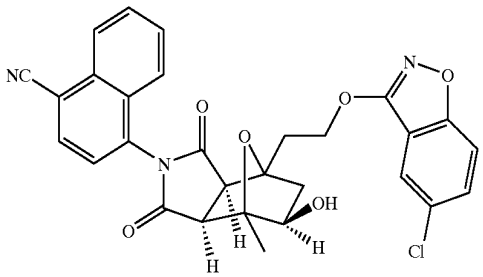
Cmp #	Structure	Compound Name	Retention Time Min./Molecular Mass	Proc. of Ex.
38		[3aR-(3aα,4β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(4-methyl-2-oxo-2H-1-benzopyran-7-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.15 LC 551.15 $[M + H]^+$	2p, 2q
39		[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-(3,5-Dimethoxyphenoxy)-ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.26 LC 529.12 $[M + H]^+$	2p, 2q
40		[3aR-(3aα,4β,7β,7aα)]-]-4-[7-[2-(4-Chloro-3-methylphenoxy)ethyl]-octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.68 LC 517.33 $[M + H]^+$	2p, 2q
41		[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-(4-Cyano-2,3-difluorophenoxy)ethyl] octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.23 LC 530.13 $[M + H]^+$	2p, 2q
42		[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.57 LC 602.0 $[M - H + OAc]^-$	2p, 2q

TABLE 1-continued

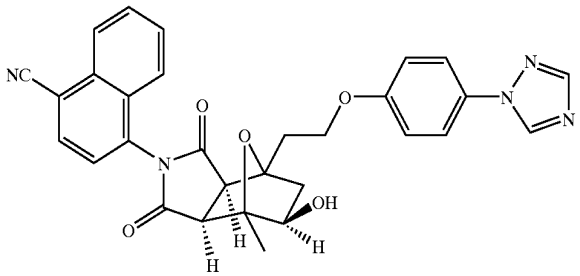
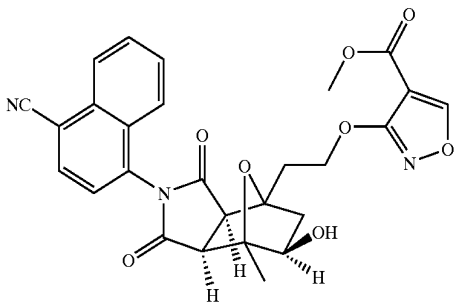
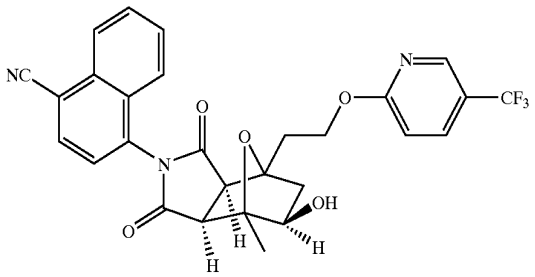
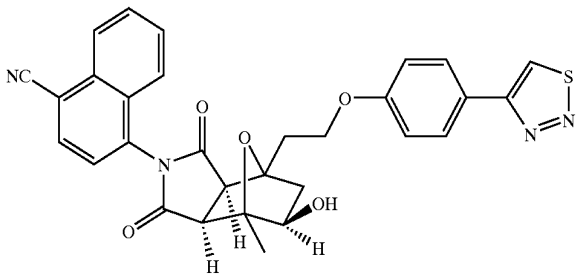
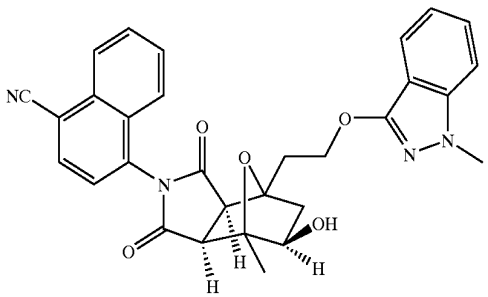
Cmp #	Structure	Compound Name	Retention Time Min./Molecular Mass	Proc. of Ex.
43		[3aR-(3aα,4β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[4-(1H-1,2,4-triazol-1-yl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	2.93 LC 536.30 $[M + H]^+$	2p, 2q
44		[3aR-(3aα,4β,7β,7aα)]-3-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-6-hydroxy-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]-5-isoxazolecarboxylic acid, methyl ester.	2.90 LC 518.27 $[M + H]^+$	2p, 2q
46		[3aR-(3α,4β,5β, 7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[5-(trifluoromethyl)-2-pyridinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.45 LC 538.23 $[M + H]^+$	2p, 2q
47		[3aR-(3α,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[4-(1,2,3-thiadiazol-5-yl)phenoxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.20 LC 553.25 $[M + H]^+$	2p, 2q
48		[3aR-(3α,4β,5β,7β,7aα)[-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(1-methyl-1H-indazol-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.33 LC	2p, 2q

TABLE 1-continued

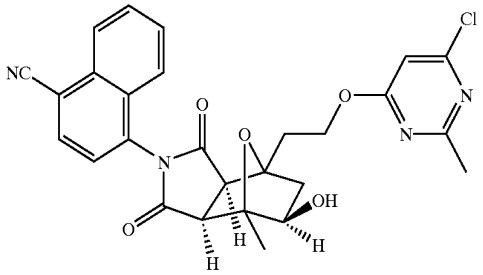
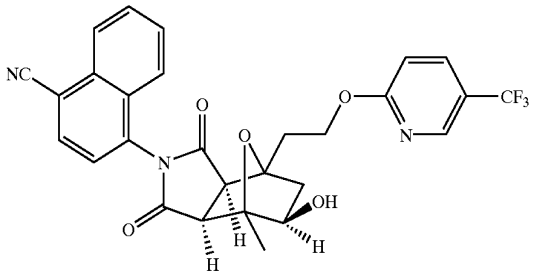
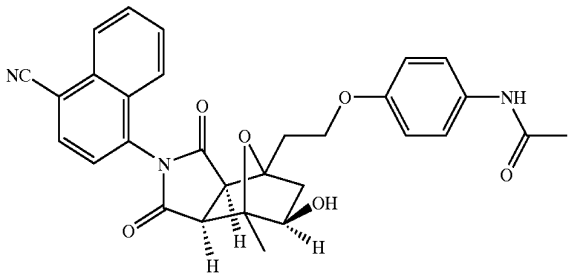
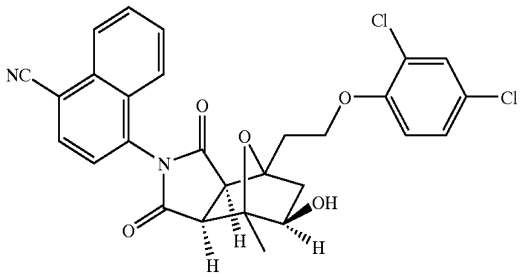
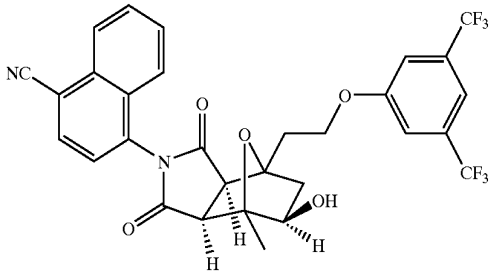
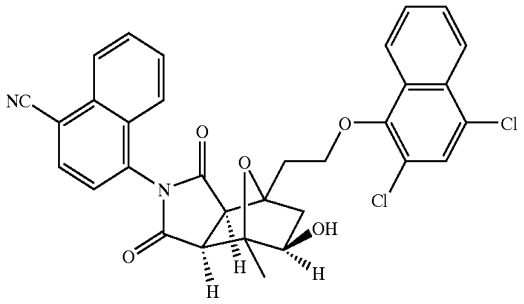
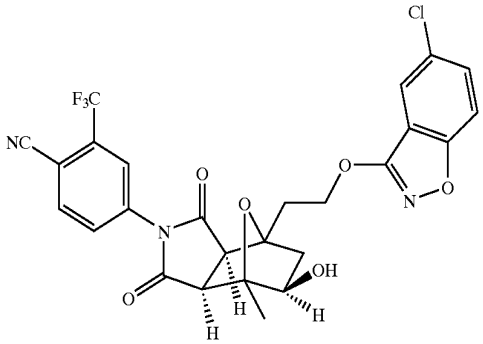
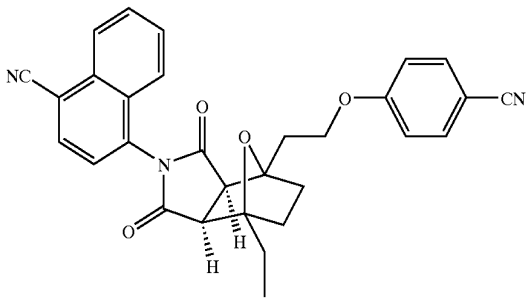
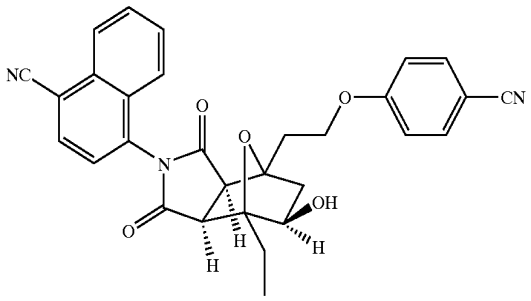
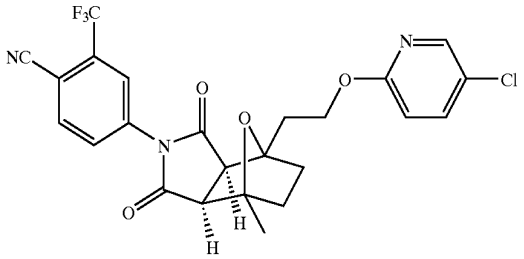
Cmp #	Structure	Compound Name	Retention Time Min./Molecular Mass	Proc. of Ex.
49		[3aR-(3α,4β,5β,7β,7aα)]-4-[7-[2-[(6-Chloro-2-methyl-4-pyrimidinyl)oxy]ethyl] octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.02 LC	2p, 2q
50		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[5-(trifluoromethyl)-2-pyridinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.46 LC 538.24 $[M + H]^+$	2p, 2q
60		[3aR-(3aα,4β,5β,7β,7aα)]-N[4-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-7H-isoindol-7-yl]ethoxy]phenyl]acet-amide	2.747 LC 526.28 $[M + H]^+$	2p, 2q
61		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(2,4-Dichlorophenoxy)ethyl] octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.71 LC 537.17 $[M + H]^+$	2p, 2q
62		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[3,5-Bis(trifluoromethyl)-phenoxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.89 LC 605.25 $[M + H]^+$	2p, 2q

TABLE 1-continued

Cmp #	Structure	Compound Name	Retention Time Min./Molecular Mass	Proc. of Ex.
63		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5,7-Dichloro-8-quinolinyl)oxy]ethyl]-octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalene carbonitrile, trifluoroacetate (1:1)	3.70 LC 588.26 $[M + H]^+$	2p, 2q
64		[3aS-(3aα,4β,5β,7β,7aα)]-4-7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl) benzonitrile	3.563 LC 562.08 $[M + H]^+$	2a(i)
65		(3aα,4β,7β,7aα)-4-[4-[2-(4-Cyanophenoxy)ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.65 LC 562.08 $[M + H]^+$	2v
66		(3aα,4β,5β,7β,7aα)-4-[7-[2-(4-Cyanophenoxy)ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.15 LC 508.14 $[M + H]^+$	2c(i)
67		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]-octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzo-nitrile	3.37 LC 522.08 $[M + H]^+$	2a(i)

The in vitro activity of these exemplary SARMs was examined in the MDA MB-453 breast tumor line reporter assay, the Shionogi mouse breast tumor line proliferation assay and C2C12 muscle cell reporter assay. Both the IC_{50} (antagonist mode, in the presence of DHT) and the EC_{50} (agonist mode, in the absence of DHT) relative to the maximal signal obtained by DHT were determined. In addition, for the reporter assays, % activation (absence of DHT) and % inhibition (presence of DHT) at a set drug concentration relative to DHT were determined. For the Shionogi proliferation assay, the % proliferation (absence of DHT) and % inhibition (presence of DHT) of proliferation at a set drug concentration relative to DHT were also determined. Unless indicated in the above Table, compounds were presented as a racemic mixture. While differing in some degree in their level of activity, all the exemplary compounds in the above Table demonstrated a SARM profile in accordance with the present invention.

Specifically, all exemplary SARMs tested exhibited an IC_{50} of less than 0.8 μM and an EC_{50} of greater than 5 μM in the MDA MB-453 breast tumor line reporter assay. Similar results were observed in the Shionogi mouse breast tumor line proliferation assay for a number of the SARMs tested. Specifically, several of the compounds exhibited an IC_{50} of less than 0.8 μM and an EC_{50} of greater than 5 μM. In contrast, in the C2C12 muscle cell reporter assay a number of the compounds tested exhibited an IC_{50} of 3 μM or greater and a particularly preferred subset of the compounds tested exhibited an EC_{50} of less than 0.8 μM or an agonist activity of greater than 25%. Preferred exemplary SARMs of Table 1, which were tested, include Compounds, 3, 7, 11, 13, 19, 23, 24, 25, 30, 31 and 67.

In addition, the effects of SARMS of Table 1 were compared with full AR antagonists in a Mature Rat Prostate Weight Assay (MRPW, Example 9). To compare the effect of AR full antagonists with SARM Compounds 7, 9, and 36 on ventral prostate (VP), seminal vesicles (SV), levator ani (LA), and Leutinizing hormone (LH) serum levels, mature male rats (n=5) were dosed orally for fourteen consecutive days followed by analysis of organ weights and serum. Compared with the full AR antagonists, in particular, the Compound 2e (prepared in Example 2 below) and Casodex (a known AR antagonist) which showed significant inhibitory effects, SARM Compounds 9 and 36 showed only a modest inhibitory effect on VP, SV, and LA weights at the highest dose (100 mg/kg or "mpk"). Compound 7, also exhibiting only modest inhibition fuirther showed (in contrast with Compounds 9 and 36) a reverse dose response, being even less potent as an inhibitor of VP, SV and LA weights at 100 mpk. The serum LH levels were very similar to the intact controls suggesting very weak, if any, activity of these SARMs at the hypothalamus-pituitary axis.

In vivo agonist activities of the SARM Compounds 7 and 9 of the present invention were also examined in the Rat Levator Ani Muscle Model (Example 8) using a preventative schedule of drug administration. In this animal model, sexually mature (6–8 weeks old) male Sprague-Dawley rats were used. The rats were castrated and broken up into treatment groups and treated with test materials beginning three days following surgery. Potential SARM effects of Compounds 7 and 9 were compared to testosterone via a dose-response study comparing testosterone proprionate (0.3 mg/kg–3 mg/kg) to these SARMs. Both SARMs were tested at 90 mg/kg via oral delivery. Compound 7 increased the levator ani wet weight by 27% compared to the vehicle-treated castrated control while having no effect on the prostate wet weight. Compound 9 was ineffective on both the levator ani muscle and prostate.

Compounds 7 and 9 (which are racemic) were also compared with Casodex in the CWR-22 prostate carcinoma model in nude mice (n=8). All three compounds were administered orally for 14 consecutive days. Both Compounds 7 and 9 exhibited inhibition similar to Casodex (150 mg/kg) when dosed at 75 rnpk. The two antipodes of Compound 9 were then separated into Compound 22 (shown in Table 1) and its mirror image Compound 22' (not shown in Table 1). Both compounds were tested in vivo in the immature wet prostate weight assay. Compound 22 showed little activity in the normal tissues while the full antagonist enantiomer Compound 22' showed clear activity and a dose response. This is unexpected given the stronger binding affinity and antagonist activity (in MID-453) of Compound 5 22. Testing of both compounds in the CWR22 human prostate xenograft model showed the opposite activity profile: Compound 22 was as potent as Casodex (150 mg/kg) at a 19 mg/kg dose while Compound 22' showed no significant activity at the maximum dose tested (75 mpk).

The in vivo data obtained mirrored the in vitro data, showing that the compounds were antagonists to the two AR dependent tumor cell lines while being agonists towards the normal muscle cell line.

Example 2

Chemical Synthesis of SARMs

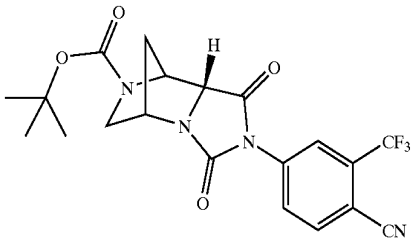
Exemplary chemical syntheses of SARMs of the present invention are included in the following Examples 2a–2d(i). As will be understood by those of skill in the art upon reading this disclosure, other methods than those set forth herein can also be used in the synthesis of these exemplary SARMs.

The following abbreviations are used herein:

DBU=1,8-diazabicyclo[5.4.0]undec-7-ene
4-DMAP=4-dimethylaminopyridine
ee=enantiomeric excess
DMF=dimethylformamide
EtOAc=ethyl acetate
Me=methyl
RT=retention time
TFA=trifluoroacetic acid
THF=tetrahydrofuran
TLC=thin layer chromatography
pTSA=para-toluenesulfonic acid
t-Bu=tert-butyl
Ph=phenyl
Pd/C=palladium on activated charcoal
Ts=tosyl
TBS=tert-butyldimethylsilane
TEA=triethylamine
n-Bu=n-butyl
rt=room temperature
LC=liquid chromatography
Et=ethyl
MS=molecular sieves
MS(ES)=Electro-Spray Mass Spectrometry
DEAD=diethyl azodicarboxylate
WSDCC=water soluble dicarbonyldiimide 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride
TBAF-tetrabutylammonium floride
DBAD-Di-tert-butylazodicarboxylate
ADDP-1,1-[azodicarbonyl]dipiperdine

Example 2a

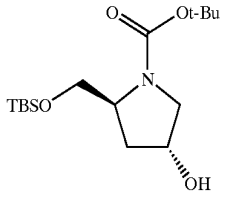
Production of [5S-(5α,8α,8aα)]-2-[4-Cyano-3-(trifluoromethyl)phenyl]hexahydro-1,3-dioxo-5,8-methanoimidazo[1,5-a]pyrazine-7(8H)-carboxylic acid, 1,1-dimethylethyl ester (2a)



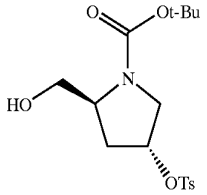
To a solution of 4-isocyanato-2-(trifluoromethyl)-benzonitrile (1.0 mmol) in toluene (4 mL) with activated 4 Å MS (0.300 g) was added (1S-exo)-2,5-diazabicyclo[2.2.1] heptane-2,6-dicarboxylic acid, 2-(1,1-dimethylethyl) 6-methyl ester (2a(1)) (0.220 g, 0.856 mmol) in toluene (6 mL). After 10 h at 25° C., DBU (0.166 mL, 1.11 mmol) was added and the reaction was heated at 81° C. for 2 h. The reaction was then cooled to 25° C. and poured into 1 N HCl (50 mL). The solution was then extracted with methylene chloride (3×30 mL) and the combined organics were dried over anhydrous sodium sulfate. The resulting crude material was purified by flash chromatography on SiO_2 eluting with acetone/chloroform (0–2–4–8% acetone) to give 2a (0.155 g, 42%) MS (ES): m/z 437.09 $[M+H]^+$. HPLC RT=3.280 min (100%) (YMC S5 ODS column, 4.6×50 mm; 10–90% MeOH/H_2O gradient, +0.1% TFA; 4 mL/min, 220 nM detection). HPLC RT=3.133 min (100%) (YMC S5 ODS column, 4.6×50 mm; 10–90% MeOH/H_2O gradient, +0.1% TFA; 4 mL/min, 220 nM detection); as white foam.

The starting compound, 2a(1), was made by the following procedure:

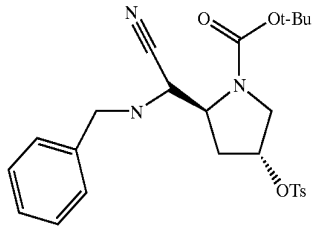
N-(tert-butoxycarbonyl)-L-4-hydroxyproline (10.0 g, 43.3 mmol) was dissolved in THF and cooled to 0° C. Borane/THF (1.0 M solution, 86.6 mL) was then added over a 15 min period. The reaction was then warmed to 25° C. followed by heating to reflux for 16 h. The reaction flask was then removed from the heat source and anhydrous methanol (35 mL) was added slowly. After cooling to 25° C., the solvent was removed in vacuo and the resulting crude diol intermediate was taken on directly. The crude diol (1.81 g, 8.34 mmol) was dissolved in methylene chloride (50 mL), 2,6-lutidine (1.46 mL, 12.51 mmol) was added and the mixture was cooled to −78° C. tert-Butyl dimethylsilyltrifluoro-methansulfonate (1.92 mL, 8.34 mmol) was then added. After 2 h, the mixture was poured into 1 N HCl (100 mL), extracted with methylene chloride (2×100 mL) and the organics were dried over anhydrous sodium sulfate. The resulting crude alcohol was purified by flash chromatography on SiO_2 eluting with acetone in chloroform (0–5–10% acetone) to give 1.011 g (37% for 2-steps) of (2S-trans)-4-hydroxy-2-[[[(1,1-dimethylethyl) dimethylsilyl]oxy]methyl]-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester (2a(2)) as a clear oil:



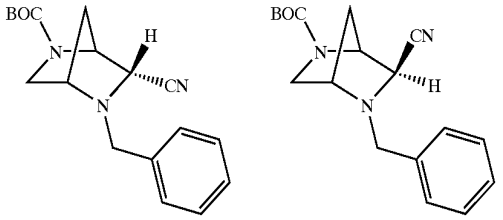
2a(2) (3.41 g, 10.3 mmol) was dissolved in anhydrous pyridine (30.0 mL) and cooled to 0° C. p-Toluenesulfonylchloride (5.89 g, 30.9 mmol) was then added in portions over a 10 minute period. The flask was then placed in a refrigerator at 4° C. for 48 h. The resulting solution was poured into 1 N HCl (300 mL), extracted with methylene chloride (3×200 mL) and the organics were dried over anhydrous sodium sulfate. The crude tosylate intermediate was dissolved in THF (50 mL), to which was added H_2O (0.5 mL) followed by pTSA-H_2O (1.03 mmol). Once the reaction was complete as determined by TLC, the mixture was poured into saturated aqueous $NaHCO_3$ (150 mL) and extracted with methylene chloride (3×50 mL). The combined organics were dried over sodium sulfate. The crude alcohol was purified by flash chromatography on SiO_2 eluting with acetone/chloroform (0–5–10% acetone) to give 2.71 g (71% for 2-steps) of (2S-trans)-2-hydroxymethyl-4-[[(4-methylphenyl)sulfonyl]oxy]-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester (2a(3)) as a clear oil:



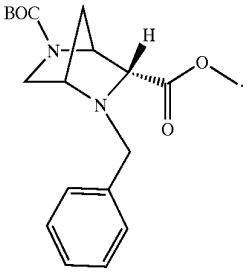
To a solution of oxalyl chloride (2.0 M soln in CH_2Cl_2, 2.82 mL) in CH_2Cl_2 (40 mL) at −78° C. was added anhydrous dimethylsulfoxide (0.462 mL, 6.51 mmol). The mixture was allowed to stand for 15 min, after which a solution of 2a(3) (1.61 g, 4.34 mmol) in CH_2Cl_2 (10 mL) was slowly added. After an additional 30 min, triethylamine (1.81 mL, 13.02 mmol) was added and the reaction was slowly warmed to 0° C. The reaction was then quenched with H_2O (25 mL) and diluted with CH_2Cl_2 (100 mL). The mixture was then washed sequentially with 1 N HCl (1×100 mL), saturated aqueous $NaHCO_3$ (50 mL), and water (2×50 mL). The organics were dried over anhydrous sodium sulfate and the volatile organics removed in vacuo. The crude aldehyde intermediate (1.60 g, 4.34 mmol) was dissolved in THF (25 mL) and diethyl cyanophosphonate (90%, 0.95 mL, 5.64 mmol) was added followed by benzyl amine (1.23 mL, 11.3 mmol). After 2 h, the reaction was complete, as observed by TLC and the volatile organics were removed in vacuo. The crude reaction mixture was purified by flash chromatography on SiO_2 eluting with acetone/chloroform (0–2–3% acetone) to give 1.48 g (70%) of (2S-trans)-2-[cyano [(phenylmethyl)amino]methyl]-4-[[(4-methylphenyl)-sulfonyl]oxy]-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester (2a(4))as a white solid. 2a(4) (structure below) was determined to be a ~1:1 mixture of diastereomers by NMR spectroscopy.



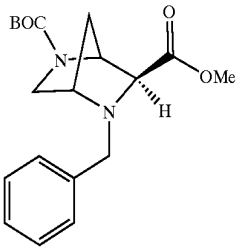
2a(4) (1.48 g, 3.05 mmol) was dissolved in dichloroethane (25 mL) and diisopropyl ethylamine (1.45 mL) was added. The mixture was heated to 100° C. in a sealed tube for 18 h. The volatiles were then removed in vacuo and the resulting crude material was purified by flash chromatography on SiO_2 eluting with acetone/chloroform (0–2–3% acetone), to yield a mixture of (1S-endo)-6-cyano-5-(phenylmethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylic acid, 1,1-dimethylethyl ester (2a(5A)) (0.591 g, 62%) and (1S-exo)-6-cyano-5-(phenylmethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylic acid, 1,1-dimethylethyl ester (2a(5B)) (0.370 g, 38%) as clear oils. Structural assignments for these compounds were made after NOE, COESY and DEPT NMR experiments:



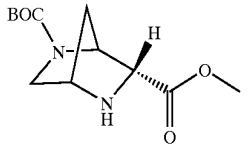
(2a(5A) (0.400 g, 1.28 mmol) was dissolved in NaOMe (0.5 M, 12.8 mL) and heated to 60° C. for 5 h. The reaction was cooled to 0° C. and 3 N HCl (4.0 mL) was added slowly. After 2h at 0° C. the reaction was poured into saturated aqueous $NaHCO_3$ (50 mL). The mixture was extracted with CH_2Cl_2 (3×50 mL) and the combined organics were dried over anhydrous sodium sulfate. The crude ester was purified by flash chromatography on SiO_2 eluting with chloroform/acetone (0–2–4% acetone) to give 0.320 g (0.92 mmol, 72%) of (1-S-endo)-5-(phenylmethyl)-2,5-diazabicyclo[2.2.1]heptane-2,6-dicarboxylic acid, 2-(1,1-dimethylethyl) 6-methyl ester (2a(6A)) as a clear oil:



2a(5B) (0.400 g, 1.28 mmol) was dissolved in NaOMe (0.5 M, 12.8 mL) and heated to 60° C. for 5 h. The reaction was cooled to 0° C. and 3 N HCl (4.0 mL) was added slowly. After 2 h at 0° C. the reaction was poured into saturated aqueous $NaHCO_3$ (50 mL). The mixture was extracted with CH_2Cl_2 (3×50 mL) and the combined organics were dried over anhydrous sodium sulfate. The crude ester was purified by flash chromatography on SiO_2 eluting with chloroform/acetone (0–2–4% acetone) to give 0.290 g (0.85 mmol, 66%) of (1S-exo)-5-phenylmethyl)-2,5-diazabicyclo[2.2.1]heptane-2,6-dicarboxylic acid, 2-(1,1-dimethylethyl) 6-methyl ester (2a(6B)) as a clear oil:

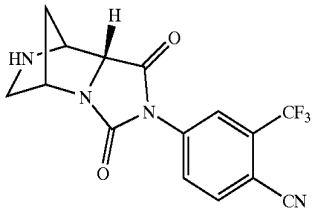


2a(6A) (0.280 g, 0.81 mmol) was dissolved in absolute EtOH (10.0 mL) and Pd/C (10% Pd, 0.080 g) was added. An atmosphere of H_2 was introduced via a balloon and the reaction was stirred at 25° C. for 20 h. The Pd was removed by filtration through celite followed by rinsing with EtOAc. The volatiles were removed in vacuo to give 2a(1) (0.205 g, 99%) as viscous yellow oil. This compound was taken on directly without purification. MS(ES)=m/z 257.18 $[M+H]^+$. HPLC RT=1.223 min (95%) (YMC S5 ODS column, 4.6×50 mm; 10–90% MeOH/H_2O gradient, +0.1% TFA; 4 mL/min, 220 nM detection):



Example 2b

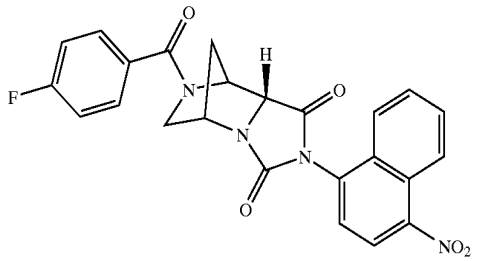
Production of 5S-(5α,8α,8aα)-4-(Hexahydro-1,3-dioxo-5,8-methanoimidazo[1,5-a]pyrazin-2(3H)-yl)-2-(trifluoromethyl)benzonitrile (2b)



2a (0.115 g, 0.264 mmol) was dissolved in anhydrous methylene chloride (3 mL) and anhydrous TFA (1.0 mL) was added at 25° C. After 1 h, the reaction was concentrated in vacuo and the resulting residue was dissolved in methylene chloride and poured into saturated aq $NaHCO_3$. This solution was then extracted with methylene chloride (3×10 mL) and the combined organics dried over anhydrous sodium sulfate. This gave 0.089 g (97%) of free 2b as a yellow solid. MS (ES): m/z 359.09 $[M+Na]^+$. HPLC RT=1.477 min (100%) (YMC S5 ODS column, 4.6×50 mm; 10–90% MeOH/H_2O gradient, +0.1% TFA; 4 mL/min, 220 nM detection).

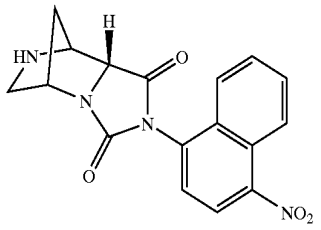
Example 2c

Production of [5S-(5α,8α,8aα)]-7-(4-Fluorobenzoyl)tetrahydro-2-(4-nitro-1-naphthalenyl)-5,8-methanoimidazo[1,5-a]pyrazine-1,3(2H,5H)-dione (2c)



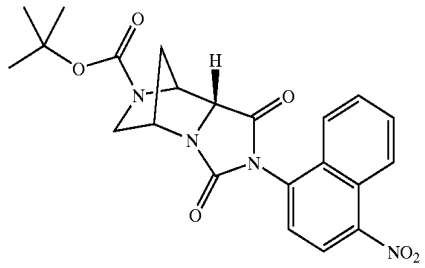
[5S-(5α,8α,8aα)]-Tetrahydro-2-(4-nitro-1-naphthalenyl)-5,8 methanoimidazo[1,5-a]pyrazine-1,3(2H,5H)-dione (2c(1)) (0.077 g, 0.228 mmol) was dissolved in methylene chloride (2.0 mL) and TEA (0.127 mL, 0.912 mmol) and 4-DMAP (0.001 g) were added. The reaction was cooled to 0° C. and 4-fluorobenzoylchloride (0.040 mL, 0.342 mmol) was added. The reaction was then slowly warmed to 25° C. After 3 h, the reaction was diluted with methylene chloride (50 mL) and then washed successively with 1N HCl and sat aq $NaHCO_3$ then and dried over anhydrous sodium sulfate. The crude material was purified by preparative TLC on silica eluting with 5% acetone in chloroform to give 0.022 g of 2c as a yellow solid. HPLC: 100% at 2.960 min (retention time) (YMC S5 ODS column 4.6×50 mm, 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 461.07 $[M+H]^+$. The starting material was made as described following.

[5S-(5α,8α,8aα)]-Tetrahydro-2-(4-nitro-1-naphthalenyl)-5,8 methanoimidazo[1,5-a]pyrazine-1,3(2H,5H)-dione (2c(1))



[5S-(5α,8α,8aα)]Hexahydro-2-(4-nitro-1-naphthalenyl)-1,3-dioxo-5,8-methanoimidazo[1,5-a]pyrazine-7(8H)-carboxylic acid, 1,1-dimethylethyl ester (2c(2)) (0.160 g, 0.37 mmol) was dissolved in methylene chloride (5.0 mL) and TFA (1.5 mL) was added at 25° C. After 1.5 h, the reaction was concentrated in vacuo and redissolved in methylene chloride. This solution was washed with sat aq $NaHCO_3$. The aqueous layer was extracted with methylene chloride (3×25 mL). The combined organics were then dried over anhydrous sodium sulfate. Concentration in vacuo gave 0.115 g of 2c(1) as a yellow solid. HPLC: 93% at 1.747 min (retention time) (YMC S5 ODS column 4.6×50 mm, 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 369.07 $[M+MeOH]^+$.

[5S-(5(5α,8α,8aα)]Hexahydro-2-(4-nitro-1-naphthalenyl)-1,3-dioxo-5,8-methanoimidazo[1,5-a]pyrazine-7(8H)-carboxylic acid, 1,1-dimethylethyl ester (2c(2))



2a(1) (0.220 g, 0.856 mmol) was added to a suspension of freshly activated 4 Å molecular sieves (0.300 g) in dry toluene (10.0 mL). To this mixture was added 4-nitronaphthal-1-isocyanate (0.214 g, 1.0 mmol). After stirring at 25° C. for 14 h, DBU (0.166 mL, 1.11 mmol) was added and the reaction was heated at 80° C. for 2 h. After 2 h, the reaction was cooled to 25° C. and then poured into 1 N HCl (50 mL). This solution was extracted with methylene chloride (3×30 mL) and the combined organics were dried over anhydrous sodium sulfate. The crude material was purified by flash chromatography on silica eluting with 0–2–6% acetone in chloroform to give 0.211 g of 2c(2) as a yellow foam. HPLC: 95% at 3.130 min (retention time) (YMC S5 ODS column 4.6×50 mm, 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 439.19 $[M+H]^+$.

Example 2d

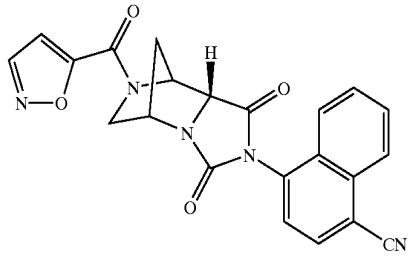
Production of [5S-(5α,8α,8aα)]-2-(4-Cyano-1-naphthalenyl)tetrahydro-7-(5-isoxazolylcarbonyl)-5,8-methanoimidazo[1,5-a]pyrazine-1,3(2H,5H)-dione (2dLibSyn1), [5S-(5α,8α,8aα)]-2-(4-Cyano-1-naphthalenyl)hexahydro-1,3-dioxo-5,8-methanoimidazo[1,5-a]pyrazine-7(8H)-carboxylic acid, 4-fluorophenyl ester (2dLibSyn2), [5S-(5α,8α,8aα)]-2-(4-Cyano-1-naphthalenyl)tetrahydro-7-[(1-methyl-1H-imidazol-4-yl)sulfonyl]-5,8-methanoimidazo[1,5-a]pyrazine-1,3(2H,5H)-dione (2dLibSyn3) & [5S-(5α,8α,8aα)]-2-(4-Cyano-1-naphthalenyl)-N-(4-fluorophenyl)hexahydro-1,3-dioxo-5,8-methanoimidazo[1,5-a]pyrazine-7(8H)-carboxamide (2dLibSyn4)

Solution Phase Library Synthesis

The below procedure is a general approach to the synthesis of SARMs of the present invention in a solution phase library format. A more detailed description of individual compounds made via this combinatorial approach follows. A series of free amine starting materials analogous to 2c(1) (0.05 mmol, prepared as described above) were dissolved in dichloromethane (1.5 mL) in a polystyrene tube with a coarse frit. N,N-(Diisopropyl)aminomethyl polystyrene (3.49 mmol/g, 60 mg) was then added to each reaction vessel followed by addition of the desired acid chloride, isocyanate, chloroformate or sulfonyl chloride (0.10 mmol) in 0.5 mL dichloroethane by automated synthesizer. The reaction vessels were shaken at 25° C. for 24 h and then Tris-(2-Aminoethyl)amine Polystyrene HL (200–400 mesh, 3.3 mmol/g, 75 mg) was added to each reaction vessel and the vessels shaken again for 18 h at 25° C. The liquid from each tube was drained into pretared 2.5 ml STR tubes and

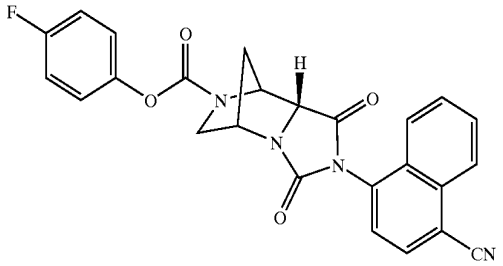
the resin was rinsed with dichloromethane (3×0.25 mL). The pretared tubes were then concentrated and analyzed by analytical HPLC and LC-MS. HPLC: (Phenomenex Prime 5μ C-18 column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 n).

[5S-(5α,8α,8aα)]-2-(4-Cyano-1-naphthalenyl) tetrahydro-7-(5-isoxazolylcarbonyl)-5,8-methanoimidazo[1,5-a]pyrazine-1,3(2H,5H)-dione (2dLibSyn1)



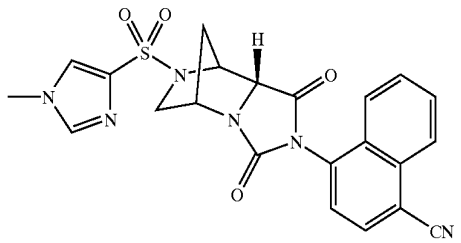
[5S-(5α,8α,8aα)]-4-(Hexahydro-1,3-dioxo-5,8-methanoimidazo[1,5-a]pyrazin-2(3H)-yl)-1-naphthalenecarbonitrile (2d(1)) (0.030 g, 0.094 mmol) was dissolved in dichloromethane (2.0 mL) in a polystyrene tube with a coarse frit. N,N-(Diisopropyl)aminomethyl polystyrene (3.49 mmol/g, 65 mg) was then added to each reaction vessel followed by addition of isoxazolacid chloride (0.025 g, 0.19 mmol) The tube was shaken at 25° C. for 24 h and then Tris-(2-Aminoethyl)amine Polystyrene HL (200–400 mesh, 3.3 mmol/g, 75 mg) was added to the reaction vessel and it was shaken again for 18 h at 25° C. The liquid was drained into pretared 2.5 ml STR tube and the resin was rinsed with dichloromethane (3×0.25 mL). Concentration in vacuo gave the crude 2dLibSyn1 (0.058 g) was a yellow solid. No purification was necessary. HPLC: 100% at 2.237 min (retention time) (YMC S5 ODS column 4.6×50 mm, 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 414.11 $[M+H]^+$.

[5S-(5α,8α,8aα)]-2-(4-Cyano-1-naphthalenyl) hexahydro-1,3-dioxo-5,8-methanoimidazo[1,5-a] pyrazine-7(8H)-carboxylic acid, 4-fluorophenyl ester (2dLibSyn2)



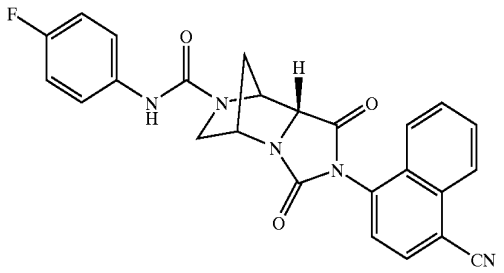
2d(1) (0.030 g, 0.094 mmol) was dissolved in dichloromethane (2.0 mL) in a polystyrene tube with a coarse frit. N,N-(Diisopropyl)aminomethyl polystyrene (3.49 mmol/g, 65 mg) was then added to each reaction vessel followed by addition of 4-fluorophenylchloroformate (0.033 g, 0.19 mmol) The tube was shaken at 25° C. for 24 h and then Tris-(2-aminoethyl)amine Polystyrene HL (200–400 mesh, 3.3 mmol/g, 75 mg) was added to the reaction vessel and it was shaken again for 18 h at 25° C. The liquid was drained into a pretared 2.5 ml STR tube and the resin was rinsed with dichloromethane (3×0.25 mL). Concentration in vacuo gave crude 2dLibSyn2 (0.053 g) as a yellow solid. No purification was necessary. HPLC: 93% at 2.987 min (retention time) (YMC S5 ODS column 4.6×50 mm, 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 457.07 $[M+H]^+$.

[5S-(5α,8α,8aα)]-2-(4-Cyano-1-naphthalenyl) tetrahydro-7-[(1-methyl-1H-imidazol-4-yl)sulfonyl]-5,8-methanoimidazo[1,5-a]pyrazine-1,3(2H,5H)-dione (2dLibSyn3)



2d(1) (0.030 g, 0.094 mmol) was dissolved in dichloromethane (2.0 mL) in a polystyrene tube with a coarse frit. N,N-(Diisopropyl)aminomethyl polystyrene (3.49 mmol/g, 65 mg) was then added to each reaction vessel followed by addition of imidazolesulfonylchloride (0.034 g, 0.19 mmol). The tube was shaken at 25° C. for 24 h and then Tris-(2-aminoethyl)amine Polystyrene HL (200–400 mesh, 3.3 mmol/g, 75 mg) was added to the reaction vessel and it was shaken again for 18 h at 25° C. The liquid was drained into a pretared 2.5 ml STR tube and the resin was rinsed with dichloromethane (3×0.25 mL). Concentration in vacuo gave the crude 2dLibSyn3 (0.043 g) as a yellow solid. No purification was necessary. HPLC: 70% at 1.603 min (retention time) (YMC S5 ODS column 4.6×50 mm, 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 463.07 $[M+H]^+$.

[5S-(5α,8α,8aα)]-2-(4-Cyano-1-naphthalenyl)-N-(4-fluorophenyl)hexahydro-1,3-dioxo-5,8-methanoimidazo[1,5-a]pyrazine-7(8H)-carboxamide (2dLibSyn4)

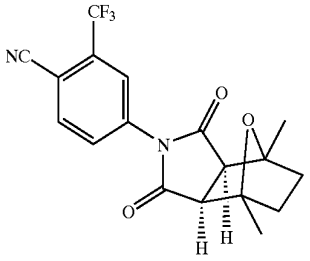


2d(1) (0.030 g, 0.094 mmol) was dissolved in dichloromethane (2.0 mL) in a polystyrene tube with a coarse frit. N,N-(Diisopropyl)aminomethyl polystyrene (3.49 mmol/g, 65 mg) was then added to each reaction vessel followed by addition of 4-fluorophenylisocyanate (0.026 g, 0.19 mmol). The tube was shaken at 25° C. for 24 h and then Tris-(2-aminoethyl)amine Polystyrene HL (200–400 mesh, 3.3

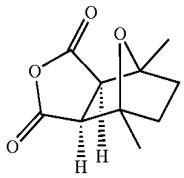
mmol/g, 75 mg) was added to the reaction vessel and it was shaken again for 18 h at 25° C. The liquid was drained into a pretared 2.5 ml STR tube and the resin was rinsed with dichloromethane (3×0.25 mL). Concentration in vacuo gave the crude 2dLibSyn4 (0.058 g) as a yellow solid. No purification was necessary. HPLC: 100% at 2.890 min (retention time) (YMC S5 ODS column 4.6×50 mm, 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 456.4 $[M+H]^+$.

Example 2e

Production of (3aα,4β,7β,7aα)-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (2e)



(3aα,4β,7β,7aα)-Hexahydro-4,7-epoxyisobenzofuran-1,3-dione (2e(1))



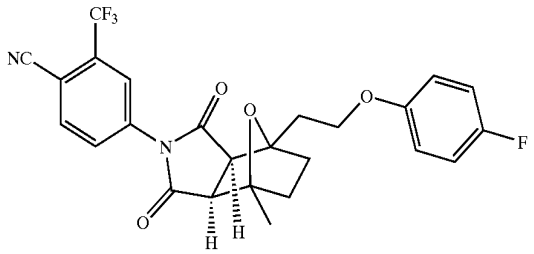
Freshly distilled dimethyl furan (1.60 mL, 15.3 mmol) was dissolved in CH_2Cl_2 (2.0 mL) and maleic anhydride (1.0 g, 10.2 mmol) was added. The reaction was stirred at 25° C. for 16 h and was then concentrated in vacuo to give a yellow solid. This solid was dissolved in ethyl acetate (30 mL) and Pd/C (10% Pd, 0.200 g) was added. Hydrogen was then introduced by a balloon and the reaction stirred for 24 h. The Pd was removed by filtration through celite rinsing with EtOAc followed by concentration in vacuo to give 2e(1) (1.69 g) as a white solid. 2-Dimensional NOE experiments confirmed the structural assignment to be that of 2e(1).

(3aα,4β,7β,7aα)-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (2e)

A solution of 2e(1) (640 mg, 3.44 mmol, 1.07 eq) and TsOH (10 mg, cat amount) in toluene (5 mL) was heated in a sealed tube for 2 days. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 50% EtOAc/hexanes gave 400 mg (1.10 mmol, 34%) of 2e as a white solid. HPLC: 99% at 3.04 min (retention time) (YMC S5 ODS column 4.6×50 mm, 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ESI): m/z 382.2 $[M+NH_4]^+$.

Example 2f

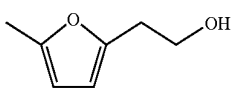
Production of (3aα,4β,7β,7aα)-4-[4-[2-(4-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl) benzonitrile (2f)



DEAD (0.06 mL, 0.380 mmol, 1.5 eq) was added to a solution of triphenylphosphine (100 mg, 0.380 mmol, 1.5 eq) in THF (1.3 mL) at room temperature under an inert atmosphere. After stirring for 10 mins, 4-fluorophenol (43 mg, 0.380 mmol, 1.5 eq) was added in one portion. The reaction mixture was stirred for 5 mins, (3aα,4β,7β,7aα)-4-[octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (2f(1)) (100 mg, 0.254 mmol, 1 eq) was added and stirring was continued for 3.5 h. Purification by flash chromatography on silica gel eluting with 50% EtOAc/Hexanes followed by preparative chromatography [HPLC: 11.93 min (retention time) (YMC S5 ODS column 20×100 mm, 0–100% aqueous methanol over 10 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm)] gave 72 mg (58%) of 2f as a solid. HPLC: 99% at 3.74 min (retention time) (YMC S5 ODS column 4.6×50 mm, 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ESI): m/z 487.1 $[M-H]^-$.

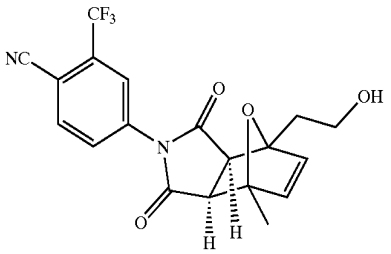
The starting compound, 2f(1), was made by the following procedure:

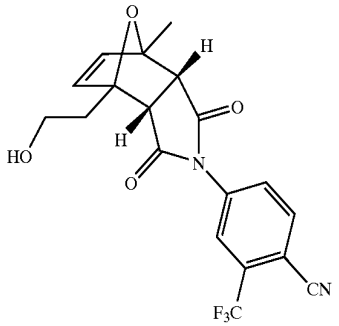
A solution of n-BuLi (83 mL, 133.0 mmol, 1.2 eq, 1.6 M in hexanes) was added to a stirred solution of 2-methylfuran (10 mL, 110.8 mmol, 1 eq) in THF (85 mL) at 0° C. under inert atmosphere. The reaction mixture was stirred for 4 h at room temperature then cooled to 0° C. Ethylene oxide (8.3 mL, 166.3 mmol, 1.5 eq) was added dropwise and the reaction mixture was allowed to warm to room temperature overnight. After quenching with saturated aqueous NH_4Cl, the resulting layers were separated and the aqueous layer was extracted with Et_2O (2×). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Distillation at atmospheric pressure (170–185° C.) gave 10.13 g (80.3 mmol, 72%) of 5-methyl-2-furanethanol (2f(2)) as a light yellow oil:



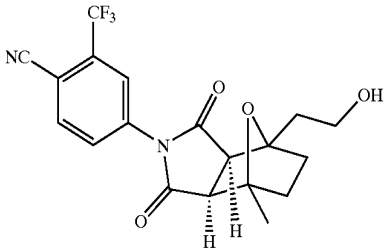
A solution of 2f(2) (252 mg, 2 mmol, 1 eq) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-3-trifluoromethylben-

zonitrile (798 mg, 3 mmol, 1.5 eq) in CH_2Cl_2 (10 mL) was stirred at room temperature for 2 days. The reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 65% EtOAc/hexanes gave 217 mg of pure (3aα,4β,7β,7aα)-4-[1,3,3a,4,7,7a-hexahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (2f(3A)), 73 mg of pure (3aα,4α,7α,7aα)-4-[1,3,3a,4,7,7a-hexahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (2f(3B)) and 310 mg of a mixture of both 2f(3A) and 2f(3B). All three fractions were isolated as white solids with a total isolated yield of 600 mg (1.53 mmol, 76.5%). 2f(3A): HPLC 90% at 2.56 min (retention time) (YMC S5 ODS column 4.6×50 mm, 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). 2f(3B): HPLC 90% at 2.56 min (retention time) (YMC S5 ODS column 4.6×50 mm, 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).



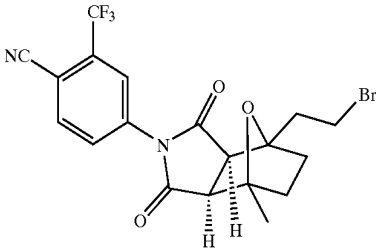


A solution of 2f(3A) (0.2 g, 0.51 mmol, 1 eq) and 10% Pd/C (43 mg, cat.) in EtOH (12 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The reaction mixture was filtered through celite and concentrated under reduced pressure to give 0.2 g (0.51 mmol, 100%) of 2f(1)as a white solid. HPLC: 95% at 2.59 min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm), MS (ESI): m/z 394.97 $[M+H]^+$:



Example 2g

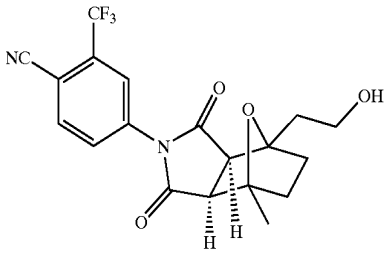
Production of (3aα,4β,7β,7aα)-4-[4-(2-Bromoethyl] octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (2g)



A solution of 2f(1)(495 mg, 1.26 mmol, 1 eq) and pyridine (0.1 ml, 1.26 mmol, 1 eq) in CH_2Cl_2 (2 ml) was added to a solution of Ph_3PBr_2 (636 mg, 1.51 mmol, 1.2 eq) in CH_2Cl_2 (2 ml) at 0° C. The reaction mixture was stirred at room temperature for 3 hr, then the solvent was removed under reduced pressure. The resulting residue was washed 2× with 10 ml portions of EtOAc-hexane (6:4) and the combined washings were purified by flash chromatography on silica gel eluting with 60% EtOAc/hexane to give 390 mg (0.85 mmol, 67.7%) of 2 g as a white solid. HPLC: 99% at 3.51 min (retention time) (YMC S5 ODS column 4.6×50 mm, 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 456.7 $[M-H]^-$.

Example 2h

Production of (3aα,4β,7β,7aα)-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrue (2h)



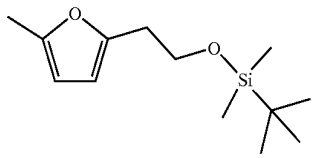
(3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl) dimethylsilyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (2h(1)) (0.031 g, 0.061 mmol) was dissolved in THF (0.5 mL) and transferred to a polypropylene container followed by cooling to 0° C. HF.pyridine (~47% HF, 0.1 mL) was then added. After 15 min, the reaction was complete as determined by LC and was poured into cold sat aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with 1 N HCl (1×20 mL) and dried over anhydrous Na_2SO_4. 2h was isolated as a yellow oil. No purification was necessary

HPLC: 95% at 2.59 min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 394.97 $[M+H]^+$.

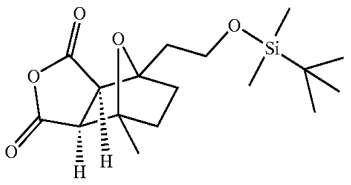
The starting material, 2h(1), was made by the following procedure.

To a solution of 5-methyl-2-furanethanol 2f(2) (2.00 g, 15.9 mmol) in DMF (50 mL) was added imidazole (1.62 g,

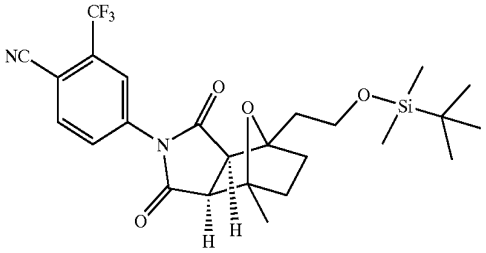
23.9 mmol), followed by tert-butyldimethylsilyl chloride (2.63 g, 17.5 mmol). After 2 h at 25° C., the reaction was poured into diethyl ether (300 mL) and washed with water (1×100 mL), 1N HCl (1×100 mL), water (1×100 mL), brine (1×50 mL) and dried over anhydrous $MgSO_4$. Crude 2-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-5-methylfuran (2h(2)) was analyzed by LCMS and NMR and determined to be pure enough to be carried on directly to the next step. HPLC: 100% at 4.347 min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm):



2h(2) (4.0 g, 18.9 mmol) and maleic anhydride (1.42 g, 14.51 mmol) were dissolved in dichloroethane (10 mL) and stirred at 25° C. for 60 hours. The volatiles were then removed in vacuo and the resulting orange oil was dissolved in absolute ethanol (50 mL) and Pd/C (10% Pd, 1.00 g) was added. Hydrogen was then introduced via a balloon. After 3 h, the reaction was filtered through celite rinsing with EtOAc and concentrated in vacuo. The crude anhydride was purified by rapid flash chromatography in SiO_2 eluting with acetone/chloroform (0–2–4% acetone) to give 1.30 g of (3aα,4β,7β,7aα)-4-[2-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]ethyl] hexahydro-7-methyl-4,7-epoxy-1H-isobenzofuran-1,3(2H)-dione (2h(3)) as a clear oil, in addition to 3.00 g of the starting 2-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-5-methylfuran. Characterization by proton NMR spectroscopy showed only the exo isomer. 1H NMR, 400 MHz, CDCl3, 3.83 (2 H, t, J=6.0 Hz), 3.22 (1 H, d, J=8.2 Hz), 3.06 (1 H, d, J=8.2 Hz), 1.70–2.25 (6 H, m), 1.55 (3 H, s), 0.82 (9 H, s), 0.00 (6 H, s):

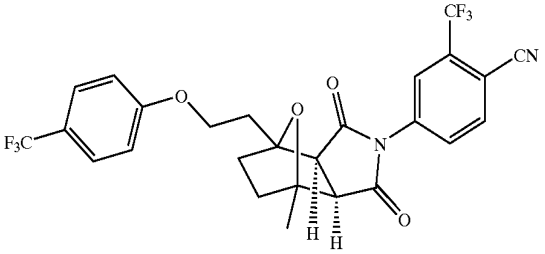


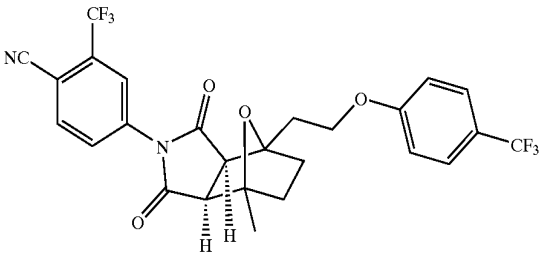
2h(3) (0.250 g, 0.8 mmol) and 4-amino-2-trifluoromethylbenzonitrile (0.124 g, 0.668 mmol) were suspended in dry toluene (2.0 mL) in a sealed tube. $MgSO_4$ (0.200 g) and triethylamine (0.5 mL) were then added and the tube was sealed and placed in a oil bath at 125° C. After 40 h, the reaction was cooled to 25° C., filtered and concentrated in vacuo. The crude material was purified by flash chromatography on SiO_2 eluting with CH_2Cl_2 to give 0.111 g of 2h(1) as a yellow solid. HPLC: 92% at 4.203 min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 531.1 $[M+Na]^+$:



Example 2i

Production of [3aR-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl) phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (2iA), faster eluting antipode and [3aS-(3aα, 4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl) phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (2iB), slower eluting enantiomer

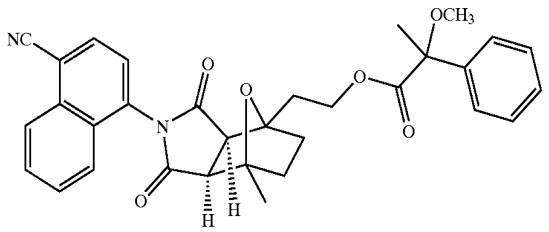




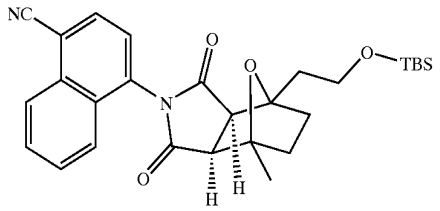
The racemic compound, synthesized as described for 2f, was separated into the individual antipodes by chiral normal phase liquid chromatography. A Chiralpak AD column (50×500 mm) was used eluting with 85% hexanes/7.5% methanol/7.5% ethanol, @ 50 mL/min. UV detection at 220 nm was used. The faster eluting isomer isomer 2iA (retention time=55.86 min) was found to have 95.8% ee ($[\alpha]_D^{25}$=−53.02°, C=3.134 mg/cc in CH_2Cl_2) and the slower eluting isomer 2iB (retention time=62.86 min) was 86% ee ($[\alpha]_D^{25}$=+48.74°, C=2.242 mg/cc in CH_2Cl_2) by analytical chiral normal phase chromatography.

Example 2j

Production of (αR)-α-Methoxybenzeneacetic acid, 2-[(3aα,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl) octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-y]ethyl ester (2j)



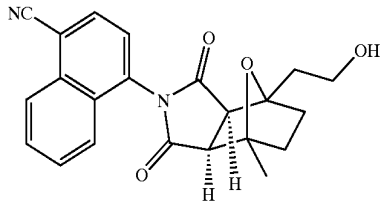
(3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl) dimethylsilyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2j(1))



A solution of 4-amino-1-naphthalenecarbonitrile (19.2 g, 114 mmol) and maleic anhydride (14.0 g, 113 mmol) in AcOH (230 mL) was heated at 115° C. for 12 h. After cooling to rt, the reaction mixture was concentrated under reduced pressure then diluted with CH_2Cl_2 (2.5 L). The organic layer was washed 3× with H_2O (3 L), 1× with sat. aq Na_2CO_3 (1 L) and 1× with brine (1 L), dried over $MgSO_4$ and concentrated to ~200 mL under reduced pressure. Purification by flash chromatography on cation exchange resin (60 g, CUBX13M6 from United Chemical Technologies) eluting with CH_2Cl_2 gave 25.0 g (88%) of 4-(2,5-Dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile as a yellow solid. HPLC 96% at 2.48 min (Phenomenex-prime S5-C18 column 4.6×50 mm, 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 249.25 $[M+H]^+$.

4-(2,5-Dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (1.00 g, 4.03 mmol) was suspended in benzene (6.0 mL) in a sealed tube and 2h(2) (1.11 g, 5.24 mmol) was added. The reaction was heated at 60° C. for 16 h and then cooled to 25° C. The benzene was removed in vacuo to give a yellow solid. The solid was dissolved in ethyl acetate (40 mL) and Pd/C (10% Pd, 0.300 g) was added. Hydrogen was then introduced via a balloon. After 4 h, the reaction was filtered through celite rinsing with ethyl acetate. Concentration in vacuo gave a pale yellow solid. Which was purified by flash chromatography on silica gel eluting with acetone/chloroform (0%–1.5%–3% acetone) to give 2j(1) (1.53 g) as a yellow foam. HPLC: 86% at 4.173 min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

(3aα,4β,7β,7aα)-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2j (2))



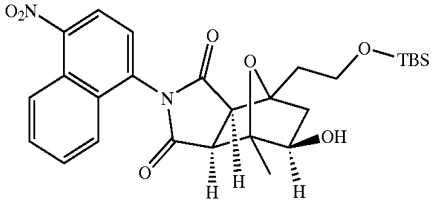
2j(1) (1.37 g, 2.97 mmol) was dissolved in THF (8.0 mL) and transferred to a polypropylene bottle and cooled to 0° C. HF.Pyridine (2.0 mL) was then added. After 20 min, the reaction was carefully poured into cold sat. aq sodium bicarbonate and extracted with methylene chloride (3×30 mL). The organics were then washed with 1 N HCl and dried over anhydrous sodium sulfate. Concentration in vacuo gave the 2j(2) (0.99 g) as a yellow foam which was not purified further. HPLC: 96% at 2.443 and 2.597 (atropisomers) min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 399.02 $[M+Na]^+$.

(αR)-α-Methoxybenzeneacetic acid, 2-[(3aα,4β,7β, 7aα-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-y]ethyl ester (2j)

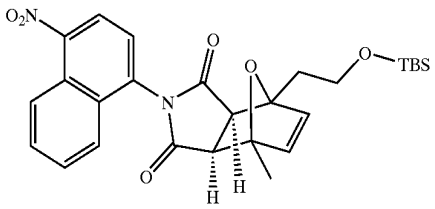
2j(2) (0.200 g, 0.575 mmol) was added to a solution of WSDCC (0.138 g, 0.719 mmol) and (R)-mandelic acid (0.096 g, 0.575 mmol) in dichloromethane (6.0 mL). 4-DMAP (0.005 g) was then added and the reaction stirred at 25° C. for 4 h. The mixture was then diluted with dichloromethane and washed with 1 N HCl (2×10 mL), once with sodium bicarbonate (10 mL) and dried over anhydrous sodium sulfate. Concentration in vacuo gave 2j (0.220 g) as a yellow solid which was not purified further. HPLC: 100% at 3.283 min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 547.26 $[M+Na]^+$.

Example 2k

Production of (3aα,4β,7β,7aα)-7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]hexahydro-5-hydroxy4-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (2k)



(3aα,4β,7β,7aα)-4-[2-[[(1,1-Dimethylethyl) dimethylsilyl]oxy]ethyl]-3a, 4,7,7a-tetrahydro-7-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (2k(1))



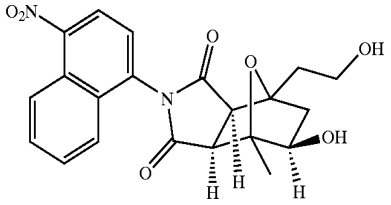
A solution of 2h(2) (455 mg, 1.894 mmol) and 1-[4-nitronaphthalene]-1H-pyrrole-2,5-dione (254 mg, 0.947 mmol) in benzene (2 mL) was heated at 60° C. overnight. 1-[4-nitronaphthalene]-1H-pyrrole-2,5-dione was made as described in 2j(1). The reaction mixture was concentrated under reduced pressure to give crude 2h(2) as a brown solid, which was used directly in the next step without further purification.

(3aα,4β,5β,7β,7aα)-7-[2-[[(1,1-Dimethylethyl) dimethylsilyl]oxy]ethyl]hexahydro-5-hydroxy-4-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1-isoindole-1,3(2H)-dione (2k)

BH_3.THF (0.95 mL, 0.95 mmol, 1M solution in THF) was added to a solution of crude 2k(1) (0.95 mmol) in THF (2 mL) at 0° C. After 2k(1) was consumed, the reaction mixture was concentrated under reduced pressure. The resulting residue was then dissolved in toluene (2 mL), Me_3NO (71 mg, 2.84 mmol) was added and the mixture was heated to reflux overnight. The reaction mixture was then cooled to rt, added to H_2O and extracted with EtOAc (3×). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on SiO_2 eluting with a mixture of 75% EtOAc/30% hexanes, gave 130.2 mg (26%) of 2k as a brown solid. HPLC: 94% at 3.92 min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 527.5 $[M+H]^+$.

Example 2l

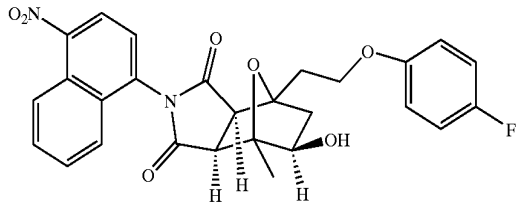
Production of (3aα,4β,5β,7β,7aα)-Hexahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (2l)



A mixture of TBAF (0.3 mL, 0.296 mmol, 1 M solution in THF) and HF (0.3 mL, 50% in H_2O) in CH_3CN (6 mL) was added to a solution of 2k (104 mg, 0.197 mmol) in THF (2 mL) at 0° C. The reaction mixture was stirred overnight at rt. After the starting material was consumed, as was evident by TLC, H_2O and EtOAc were added and the layers were separated. The aqueous layer was extracted with EtOAc (1×) and the combined organic layers were washed with H_2O (1×) and brine (1×), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography on SiO_2 eluting with 5% MeOH/CH_2Cl_2 gave 61.2 mg (75%) of 2l as a yellow solid. HPLC: 99% at 2.47 min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 411.2 $[M-H]^-$.

Example 2m

Production of (3aα,4β,5β,7β,7aα)-7-[2-(4-Fluorophenoxy)ethyl]hexahydro-5-hydroxy-4-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (2m)



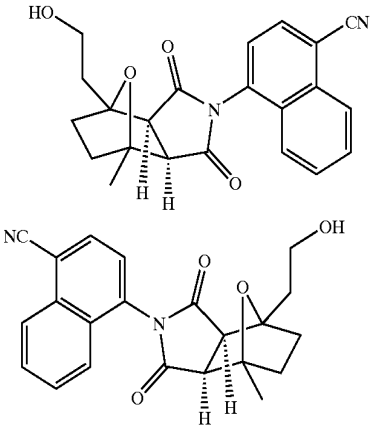
DBAD (37.7 mg, 0.164 mmol, 1.5 eq) was added to a solution of PPh_3 (43 mg, 0.164 mmol, 1.5 eq) in THF (1 mL). After stirring for 10 mins, 4-fluorophenol (18.3 mg, 0.164 mmol, 1.5 eq) was added and the reaction mixture was stirred for a further 5 mins. A solution of 2l (45 mg, 0.109 mmol, 1 eq) in THF (1 mL) was added and the mixture was stirred at rt overnight. HPLC showed the crude reaction mixture to contain mostly starting diol (2l), so this mixture was added to a preformed mixture as before of PPh_3 (86 mg, 3 eq), DBAD (75.4 mg, 3 eq) and phenol (36.6 mg, 3 eq) in THF (4 mL) at rt. Stirring was continued until all of 2l was consumed as was evident by HPLC. The reaction was concentrated under reduced pressure. Purification by preparative chromatography [HPLC at 15.2 min (retention time) (YMC S5 ODS A column 20×100 mm, 10–90% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm)] gave 25.0 mg (45%) of 2m as a light yellow solid. HPLC: 99% at 3.53 min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 505.2 $[M-H]^-$.

DBAD (37.7 mg, 0.164 mmol) was added to a solution of PPh_3 (43 mg, 0.164 mmol) in THF (1 mL). After stirring for 10 mins, 4-fluorophenol (18.3 mg, 0.164 mmol) was added and the reaction mixture was stirred for a further 5 min. A solution of compound 2l (45 mg, 0.109 mmol) in THF (1 mL) was added and the mixture was stirred at rt overnight. HPLC showed the crude reaction mixture to contain mostly starting diol (compound 2l), so this mixture was added to a preformed mixture as before of PPh_3 (86 mg), DBAD (75.4 mg) and phenol (36.6 mg) in THF (4 mL) at rt. Stirring was continued until all of 2l was consumed. The reaction was then concentrated under reduced pressure. Purification by preparative chromatography [HPLC at 15.2 min (retention time) (YMC S5 ODS A column 20×100 mm, 10–90% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm)] gave 25.0 mg (45%) of 2m as a light yellow solid. HPLC: 99% at 3.53 min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with

10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 505.2 $[M-H]^-$.

Example 2n

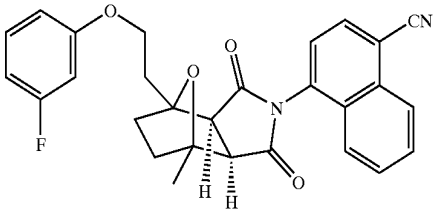
Production of [3aR-(3aα,4β,7β,7aα)]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2nA) & [3aS-(3aα,4β,7β,7aα)]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2nB)



Racemic 2j(2) was separated into its enantiomers by preparative chiral HPLC (CHIRALPAK AD 5×50 cm column; eluting with 20% MeOH/EtOH (1:1) in heptane (isocratic) at 50 mL/min, @ 220 nm) to give the faster eluting compound 2nA (Chiral HPLC: 13.54 min; CHIRALPAK AD 4.6×250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min) and the slower eluting compound 2nB (Chiral HPLC: 14.99 min; CHIRALPAK AD 4.6×250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min). The absolute conformation for compounds 2nA and 2nB have not been established. For simplicity in nomenclature, we have designated compound 2nA as having an "R" configuration and compound 2nB as having a "S" configuration. Enantiomerically pure products derived from 2nA will be designated as having a "R" configuration and enantiomerically pure products derived from 2nB will be designated as having a "S" configuration.

Example 2o

Production of [3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2oA) & [3aS-(-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2oB)



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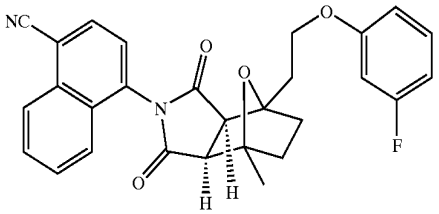
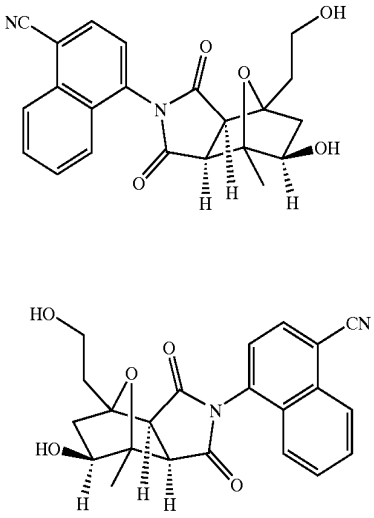


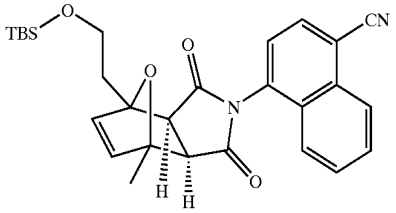
To a solution of triphenylphosphine (0.0524 g, 0.20 mmol) in THF (2.0 mL) was added DBAD (0.046 g, 0.2 mmol). After 10 min, 3-fluorophenol (0.018 mL, 0.2 mmol) was added. After 10 additional minutes, enantiomerically pure 2nA (0.050 g, 0.133 mmol) was added. After 3 h at 25° C., the reaction was concentrated in vacuo and purified by preparative HPLC (YMC S5 ODS 20×100 mm, 10–90% aqueous methanol over 15 minutes containing 0.2% TFA, 20 mL/min, monitoring at 220 nm) to give 0.031 g of compound 2oA as a white solid. This process was repeated with enantiomerically pure compound 2nB to yield 2oB. 2oA: HPLC: 100% at 3.80 min (retention time) (YMC S5 ODS column 4.6×50 mm, 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 471.65 $[M+H]^+$, $[\alpha]_D^{25}$=−47.371 (c=4.412 mg/cc, CH_2Cl_2). 2oB: HPLC: 100% at 3.80 min (retention time) (YMC S5 ODS column 4.6×50 mm, 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 471.65 $[M+H]^+$, $[\alpha]_D^{25}$=+24.3 (c=4.165 mg/cc, CH_2Cl_2).

Example 2p

Production of [3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2pA) & [3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2pB)

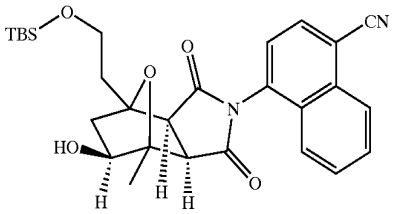


(3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl) dimethylsilyl]oxy]ethyl]-1,3,4,7,7a-hexahydro-1,3-dioxo4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2p(1))



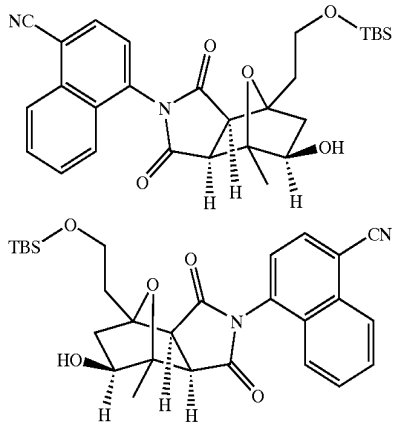
4-(2,5-Dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (18.3 g, 68.7 mmol) was added to a solution of 2h(2) (26.6 g, 110.6 mmol) in benzene (75 mL) and heated to 60° C. overnight. After cooling to rt, the reaction mixture was concentrated under reduced pressure. The residue was treated with MeOH (250 mL) with stirring at 0° C. for 10 min. The resulting solid was filtered, washed with cold MeOH (2×10 mL) and dried to give 26.7 g (79.5%) of 2p(1) as a yellow solid. HPLC analysis of the above solid revealed it to be 95% pure (HPLC conditions: 95% at 2.48 min (Phenomenex-prime S5-C18 column, 4.6×50 mm, 10%–90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm)). The filtrate was then concentrated under reduced pressure and the resulting solid was chromatographed, eluting with 3% acetone/$CHCl_3$, to give an additional 4.36 g of 2p(1) (13%), giving a total final yield of 92.5%.

(3aα,4β,5β,7β,7aα)-4-[7-[2-[[(1,1-Dimethylethyl) dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2p(2))



A mixture of 2p(1) (10 g, 20.46 mmol) and $RhCl(PPh_3)_3$ (0.947 mg, 1.02 mmol) was evacuated and filled with argon (3×). THF (200 mL) was added and once all particulates had dissolved, catecholborane (4.4 mL, 40.93 mmol) was slowly added dropwise. When the formation of product ceased, as was determined by HPLC, the reaction mixture was cooled to 0° C. and quenched with phosphate buffer (330 mL, pH 7.2) then EtOH (130 mL) and H_2O_2 (300 mL, 30% aq sol) were added. Once boronate was consumed, the mixture was extracted with CH_2Cl_2 (3×) and the combined organic layers were washed with 1N NaOH, 10% aq $NaHSO_3$ (1:1, 1×) and brine (1×). The combined washes was extracted with CH_2Cl_2 (1×) and the combined organic layers were dried over Na_2SO_4. Purification by flash chromatography on silica gel eluting with 10% to 30% acetone/$CHCl_3$ gradient over 25 min gave 7.1 g (68%) of 2p(2) as a light yellow solid. HPLC conditions: 98% at 3.82 min (Phenomenex-prime S5-C18 column 4.6×50 mm, 10%–90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm).

[3aS-(3aα,4β,5β,7β,7aα)]4-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2p(3A)) and [3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1Dimethylethyl) dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2p(3B))



The racemic compound 2p(2) was separated into the individual enantiomers by chiral normal phase liquid chromatography. A Chiralpak OD column (50×500 mm) was used, eluting with 13% EtOH/hexanes over 99 min at 50 mL/min detecting at 220 mn. The faster eluting isomer 2p(3A) had a retention time=45 min and the slower eluting isomer 2p(3B) had a retention time=66 min.

[3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2pA) and [3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (2pB)

2p(3A) (0.84 g, 2.14 mmol) was dissolved in 2% 12 N HCl/EtOH (20 mL), stirred for 5 minutes and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 5–10% MeOH/CH_2Cl_2 gave 0.57 g (88%) of 2pA. 2pA which came from the faster eluting isomer (2p(3A)) was found to be 99.7% ee by analytical chiral normal phase chromatography. HPLC conditions: 99.7% at 2.17 min (Chiralcel OJ 44.6×250 mm, 10 micron, 40° C., isocratic 80% Heptane/20% EtOH/MeOH (1:1), 1.0 mL/min., detection at 288 nm).

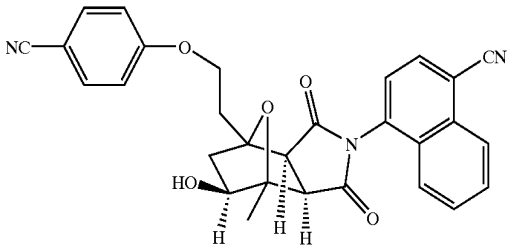
2p(3B) (0.86 g, 2.19 mmol) was dissolved in 2% 12N HCl/EtOH (20 mL), stirred for 5 minutes and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 5–10% MeOH/CH_2Cl_2 gave 0.60 g (90%) of 2pB. 2pB which came from the slower eluting isomer (2p(3B)) was found to have 87.1% ee by analytical chiral normal phase chromatography. HPLC conditions: 87.1% at 18.4 min (Chiralcel OJ 44.6×250 mm, 10 micron, 40° C., isocratic 80% heptane/20% EtOH/MeOH (1:1), 1.0 mL/min., detection at 288 nm).

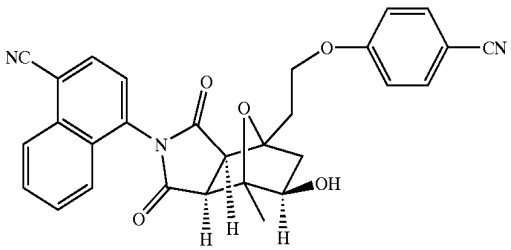
The absolute conformation for compounds 2pA and 2pB has not been determined. For simplicity in nomenclature, we have designated compound 2pA as having an "S" configuration and compound 2pB as having a "R" configuration. Enantiomerically pure products derived from compound

2pA will be designated as having a "S" configuration and enantiomerically pure products derived from compound 2pB will be designated as having a "R" configuration

Example 2q

Production of [3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(4-Cyanophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2qA) and [3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(4-Cyanophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (2qB)



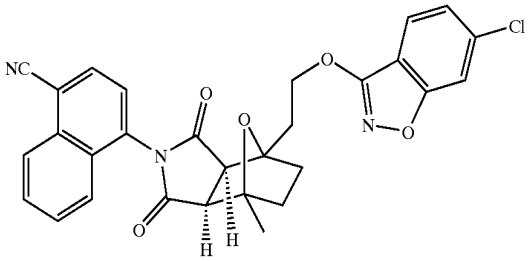


DBAD (26 mg, 0.115 mmol) was added to a solution of PPh_3 (30 mg, 0.115 mmol) in THF (0.65 mL). After stirring for 10 min, 4-cyanophenol (13.6 mg, 0.115 mmol) was added and the reaction mixture was stirred for a further 5 min. Compound 2pA (30 mg, 0.076 mmol) was added and the mixture was stirred at rt for 1 h. The reaction was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 30% acetone/70% $CHCl_3$ gave 23.1 mg (0.047 mmol, 61.7%) of compound 2qA. HPLC conditions: 95% at 3.06 min (YMC S5 ODS 4.6×50 mm, 10%–90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 494.09 $[M+H]^+$. $[\alpha]_D$=53.30°, C=4.5 mg/cc in THF, (589 nm)

DBAD (26 mg, 0.115 mmol) was added to a solution of PPh_3 (30 mg, 0.115 mmol) in THF (0.65 mL). After stirring for 10 min, 4-cyanophenol (13.6 mg, 0.115 mmol) was added and the reaction mixture was stirred for a further 5 min. Compound 2pB (30 mg, 0.076 mmol) was added and the mixture was stirred at rt for 1 h. The reaction was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 30% acetone/70% $CHCl_3$ gave 20.3 mg (0.041 mmol, 54.2%) of compound 2qB. HPLC conditions: 90% at 3.07 min (YMC S5 ODS 4.6×50 mm, 10%–90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 494.09 $[M+H]^+$. $[\alpha]_D$=−42.87°, C=6.6 mg/cc in THF, @ 589 nm)

Example 2r

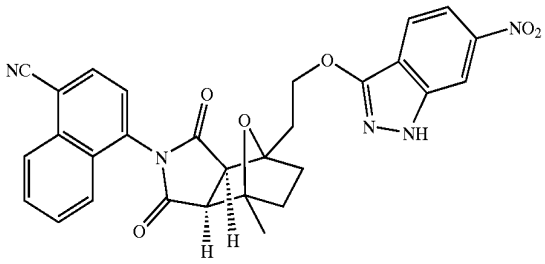
Production of (3aα,4β,7β,7aα)-4-[4-[2-[(6-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2r)



To a solution of PPh_3 (52 mg, 0.20 mmol) in 0.5 mL THF was added DBAD (46 mg, 0.20 mmol) as one solid portion. The resulting mixture was stirred for 10 min before 6-chloro-3-hydroxy-1,2-benzisoxazole (34 mg, 0.20 mmol) was added. Stirring was continued for 10 min before a solution of 2j(2) (50 mg, 0.13 mmol) in 0.5 mL THF was introduced via canula. The resulting mixture was stirred at ambient temperature for 24 h, concentrated and purified by preparative reverse phase HPLC (YMC S5 ODS 20×100 mm column; eluting with 30–100% aqueous MeOH containing 0.1% TFA over 10 min at 20 mL/min) to yield a white solid. The obtained solids were dissolved in CH_2Cl_2, washed with sat. $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated to yield 50 mg (71%) of 2r as a colorless oil. HPLC: 26% at 3.89 min and 74% at 4.02 min (mixture of atropisomers, retention time) (YMC S5 ODS column 4.6×50 mm Ballistic, 10–90% aqueous methanol over 4 minutes containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 528.4 $[M+H]^+$.

Example 2s

Production of (3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-7-[2-[(6-nitro-1H-indazol-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2s)

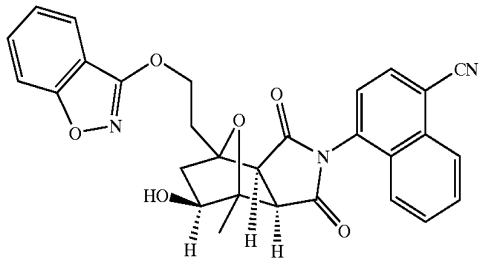


To a solution of 2j(2) (50 mg, 0.13 mmol) in toluene (1 mL) was added ADDP (50 mg, 0.20 mmol), 6-nitro-3-indazolinone (36 mg, 0.20 mmol) and n-Bu_3P (50 μL, 0.2 mmol). The resulting mixture was heated to 80° C. for 24 h, concentrated and purified by a combination of preparative reverse phase HPLC (YMC S5 ODS 20×100 mm column; eluting with 30–100% aqueous MeOH containing 0.1% TFA over 10 min at 20 mL/min) and flash chromatography (silica gel, 25% acetone in $CHCl_3$) to give 17 mg (25%) of 2s as a yellow solid. HPLC: 24% at 3.60 min and 76% at 3.74 min (mixture of atropisomers, retention time) (YMC S5 ODS

column 4.6×50 mm Ballistic, 10–90% aqueous methanol over 4 minutes containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 537.6 $[M+H]^+$.

Example 2t

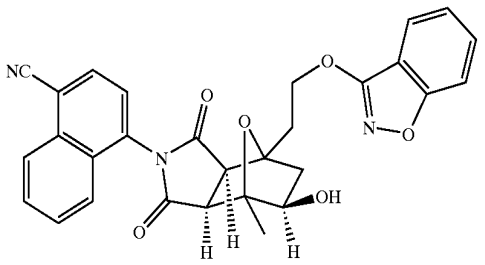
Production of [3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(1,2-Benzisoxazol-3-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2t)



PPh_3 (47 mg, 0.18 mmol), DBAD (41 mg, 0.18 mmol), 3-hydroxy-1,2-benzisoxazole (24 mg, 0.18 mmol) and compound 2pA (35 mg, 0.09 mmol) were reacted according to the procedure given for 2r. Purification was achieved by reverse phase HPLC (YMC S5 ODS 20×100 mm column; eluting with 30–100% aqueous MeOH containing 0.1% TFA over 10 min at 20 mL/min) to yield a white solid. The obtained solids were dissolved in CH_2Cl_2, washed with sat. $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated furnishing 29 mg (64%) of 2t as a colorless oil. HPLC: 96% at 3.29 min (mixture of atropisomers, retention time) (YMC S5 ODS column 4.6×50 mm Ballistic, 0–100% aqueous methanol over 4 minutes containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 510.2 $[M+H]^+$.

Example 2u

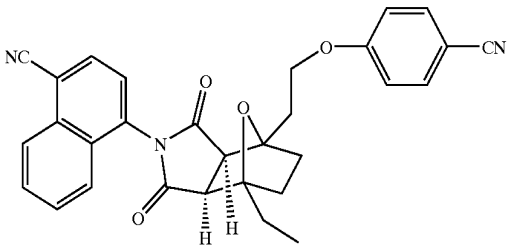
Production of [3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(1,2-Benzisoxazol-3-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2u)



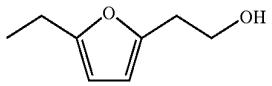
PPh_3 (47 mg, 0.18 mmol), DBAD (41 mg, 0.18 mmol), 3-hydroxy-1,2-benzisoxazole (24 mg, 0.18 mmol) and 2pB (35 mg, 0.09 mmol) were reacted according to the procedure given for 2r. Purification was achieved by reverse phase HPLC (YMC S5 ODS 20×100 mm column; eluting with 30–100% aqueous MeOH containing 0.1% TFA over 10 min at 20 mL/min) to yield a white solid. The obtained solids were dissolved in CH_2Cl_2, washed with sat. $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated furnishing 23 mg (51%) of 2u as a colorless oil. HPLC: 95% at 3.29 min (mixture of atropisomers, retention time) (YMC S5 ODS column 4.6×50 mm Ballistic, 0–100% aqueous methanol over 4 minutes containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 510.4 $[M+H]^+$.

Example 2v

Production of (3aα,4β,7β,7aα)-4-[4-[2-(4-Cyanophenoxy)ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (2v)

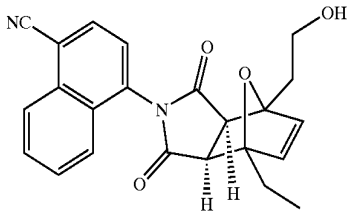


2-Ethyl-5-(2-hydroxyethyl)furan (2v(1))



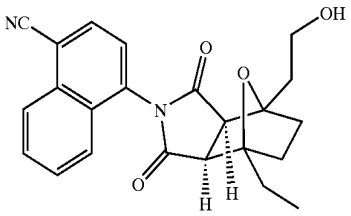
n-BuLi (2.5 M in hexane, 4.4 mL, 11 mmol) was added to a solution of 2-ethylfuran (1.05 mL, 10 mmol) in THF (10 mL) at −25° C. The solution was warmed to rt and stirred for 3 h. Ethylene oxide (0.75 mL) was added at −78° C. The reaction was stirred for 0.5 h at −15° C. and overnight at rt. Aqueous sat. NH_4Cl was added and the mixture was extracted with ether (3×). The combined extracts were washed with water (1×) and brine (1×) and dried over Na_2SO_4. Purification by flash chromatography on silica gel eluting with 30% EtOAc/70% hexane gave 1.12 g (8.02 mmol, 80.2%) of 2v(1) as a yellow oil.

(3aα,4β,7β,7aα)-4-[4-Ethyl-1,3,3a,4,7,7a-hexahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2v(2))



A solution of 2v(1) (280 mg, 2.00 mmol) and the 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (496 mg, 2.00 mmol) in benzene (2 mL) was stirred at 60° C. for 2 h. The reaction mixture was concentrated under reduced pressure. The yellow solid, 2v(2), was used directly in the next step.

(3aα,4β,7β,7aα)-4-[4-Ethyloctahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2v(3))



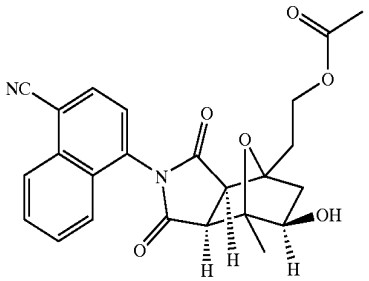
A mixture of 2v(2) (764 mg, 1.97 mmol) and 10% Pd/C (115 mg, cat.) in EtOAc (36 mL) was stirred under a hydrogen atmosphere at rt for 2 h. The reaction mixture was filtered through celite and concentrated under reduced pressure to give 779 mg of crude 2v(3). Purification of this crude product by flash chromatography on silica gel eluting with 70% EtOAc/30% hexane gave 235 mg (0.6 mmol, 30.1%) of 2v(3). HPLC conditions: 99% at 2.84 min (YMC S5 ODS 4.6×50 mm, 10%–90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 391.12 $[M+H]^+$.

(3aα,4β,7β,7aα)-4-[4-[2-(4-Cyanophenoxy)ethyl]-7-ethyloetahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2v)

DBAD (44.2 mg, 0.192 mmol) was added to a solution of PPh_3 (50.4 mg, 0.192 mmol) in THF (1 mL). After stirring for 10 mins, 4-cyanophenol (23 mg, 0.192 mmol) was added and the reaction mixture was stirred for an additional 5 mins. 2v(3) (50 mg, 0.128 mmol) was added and the mixture was stirred at rt for 2 h. The reaction was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 40% EtOAc/60% hexane gave 43 mg (0.087 mmol, 68.4%) of compound 2v as a white solid. HPLC conditions: 99% at 3.65 min (YMC S5 ODS 4.6×50 mm, 10%–90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 492.16 $[M+H]^+$.

Example 2w

Production of [3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(Acetyloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2wA) and [3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile(2wB)



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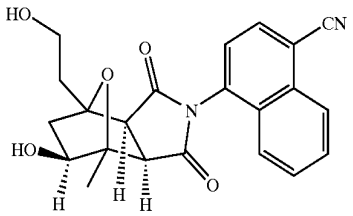


A racemic mixture of compounds 2pA and 2pB (1.90 gram) were dissolved in 100 mL of anhydrous THF in a 2 L flask. Anhydrous tert-butyl-methyl ether (900 mL) and vinyl acetate (40 mL) were transferred into the flask with stirring and lipase (20 g, type II, crude, from porcine pancreas; Sigma, Cat# L3126) was added. The reaction mixture was stirred for 21 hr at rt at which point an additional 5 grams of the lipase and 20 mL of vinyl acetate were added. The reaction was stirred at rt for an additional 19 h, stored at 4° C. without stirring for 36 h and then stirred at rt for another 22 h (until the desired % ee was apparent by chiral HPLC). To monitor the reaction, 200 uL of the mixture was withdrawn and centrifuged. The supernatant (100 uL) was dried under nitrogen and the resulting residue was dissolved in 100 uL of EtOH and subjected to HPLC analysis:

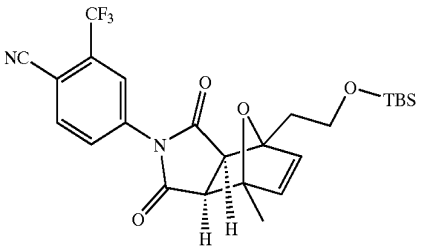
1) Reverse phase HPLC: Column, YMC-ODS AQ 150×4.6; flow rate, 1.2 mL/min; sample size, 10 uL solvent A,: 1 mM HCl in water; solvent B, MeCN; monitored at 300 nm Gradient: Time(min) 0 8 8.5 9.5 10 12 B% 30 60 85 85 30 30

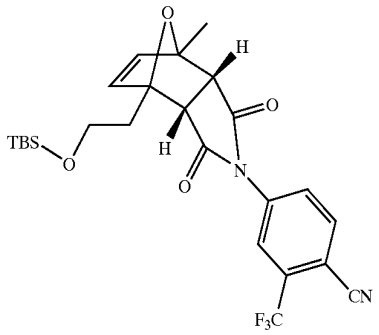
2) Chiral-HPLC: Column, CHIRALCEL OJ 4.6×250 mm mobile phase, Hexane/MeOH/EtOH (8:1:1) flow rate, 1 mL/min; sample size, 20 uL monitored at both 220 and 300 nm performed at 25° C. & 40° C. (for ee % determination of reaction mixture)

The enzyme was removed by filtration and filtrate was concentrated under vacuum. The resulting mixture was dissolved in $CHCl_3$ and adsorbed onto silica gel (63–200 microns). These solids were applied to a VLC funnel (3 cm I.D., VLC is vacuum liquid chromatography using glass funnels having 24/40 joints at the bottom) containing a 5 cm bed height of silica gel (25–40 microns) and a step gradient was carried out. The gradient was 100% $CHCl_3$ in the first 3 fractions, followed by $CHCl_3$-1% MeOH (3 fractions), $CHCl_3$-2% MeOH (3 fractions), $CHCl_3$-3% MeOH (3 fractions), $CHCl_3$-4% MeOH (3 fractions), and finally with $CHCl_3$-5% MeOH (3 fractions). The volume of the fractions was 100 mL until reaching $CHCl_3$-3% MeOH and from that point on it was 200 mL. 2wA elutes in the last two fractions of 100% $CHCl_3$ and until the first fraction of $CHCl_3$-2% MeOH. 2wB elutes starting with the second fraction of $CHCl_3$-2% MeOH, and continues to the first fraction of $CHCl_3$-5% MeOH. The crude compound 2wB contained a small amount of a colored impurity which was removed by a Sephadex column [LH-20 swollen in $CHCl_3$-MeOH (2:1), column (2.5 cm I.D. & 90 cm long) to yield 632 mg of compound 2wB. Compound 2wA: HPLC conditions: 98% at 7.2 min (method 1), chiral HPLC conditions: 29.0 min @ 25° C. (method 2). Compound 2wB: HPLC conditions: 98% at 4.6 min (method 1), chiral HPLC conditions: 96% ee at 25.7 min @ 25° C) & 19.8 min @ 40° C.) (method 2).

Example 2x

Production of (3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,3a,4,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile & (3aα,4α,7α,7aα)-4-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,3a,4,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (2xA & 2xB)

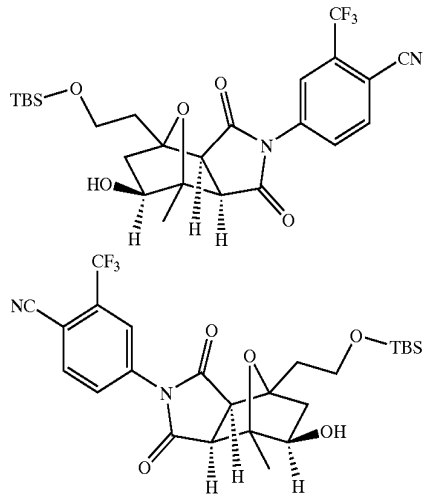




Compound 2h(2) (2.00 g, 8.50 mmol) and 4-(2,5-Dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethyl- benzonitrile (1.50 g, 5.60 mmol) were mixed in benzene (5.0 mL) and heated at 60 ° C. for 14 h, then cooled to 25° C. The solvent was removed at 40° C. under vacuum for 1 h to give the crude material which was purified by flash chromatography on SiO_2 eluting with 0.5% EtOAc/CH_2Cl_2 to give 2.0 g of compound 2xA and 1.3 g of compound 2xB, both as light brown solids. Compound 2xA: HPLC: 95% at 4.200 min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 507.1 $[M+H]^+$. Compound 2xB: HPLC: 95% at 4.20 min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 507.1 $[M+H]^+$.

Example 2y

Production of [3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl] octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile & [3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (2yA & 2yB)



Compound 2xA (1.40 g, 2.77 mmol) and $RhCl(PPh_3)_3$ (0.128 g, 0.14 mmol) were mixed in a flask. The flask was then evacuated and filled with argon three times, followed by the syringe addition of THF (3.0 mL). Once all particulates were dissolved, catecholborane (0.59 mL, 5.54 mmol) was added dropwise. The reaction mixture was stirred at 25° C. under argon for 30 min, then cooled to 0° C. Phosphate buffer (pH=7, 20 mL) was added, followed by EtOH (10 mL), 30% H_2O_2/H_2O (2 mL). The reaction mixture was stirred at 0° C. for 3 h, then extracted with dichloromethane (3×25 mL). The combined organic layers were washed with 1 N NaOH (25 mL), 10% Na_2SO_3 (25 mL) and brine (25 mL). The crude material was then concentrated and purified by flash chromatography on SiO_2 eluting with 2% EtOAc/CH_2Cl_2 to 10% EtOAc/CH_2Cl_2 to give 0.63 g of a racemic mixture of compounds 2yA & 2yB as a light yellow solid. HPLC: 99% at 3.867 min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 525.1 [M+H]

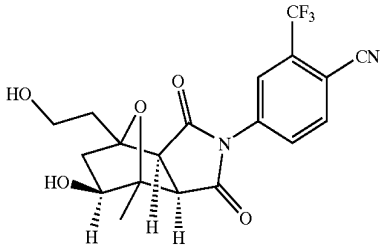
The racemic mixture of compounds 2yA & 2yB was separated by normal phase preparative chiral HPLC using a Chiracel OD column (5 cm×50 cm), eluting with 13% solvent B (EtOH) in solvent A (Hexane), flow rate: 50 mL/min. Compound 2yA eluted from 34 min to 38 min and compound 2yB eluted from 44 min to 49 min. Enantiomeric excess was determined by chiral HPLC. Compound 2yA: >99% ee (12.576 min (retention time) (Chiralcel OJ column 4.6×250 mm eluting with isocratic 85% heptane/15%

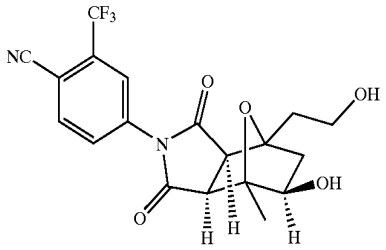
MeOH/ethanol (1:1), 1 mL/min, monitoring at 220 nm, 40° C.). Compound 2yB: 99% ee (18.133 min (retention time) (Chiralcel OJ column 4.6×250 mm eluting with isocratic 85% heptane/15% MeOH/ethanol (1:1), 1 mL/min, monitoring at 220 nm, 40° C.).

The absolute configuration for compounds 2yA & 2yB were not established. For simplicity in nomenclature, compound 2yA is designated herein as having an "R" configuration and compound 2yB as having an "S" configuration. Enantiomerically pure products derived from compound 2yA are designated herein as having a "R" configuration and enantiomerically pure products derived from compound 2yB are designated herein as having an "S" configuration.

Example 2z

Production of [3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile & [3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (2zA & 2zB)



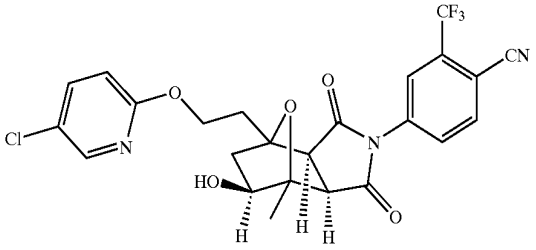


Compound 2yA (180 mg, 0.34 mmol) was dissolved in 2% HCl/EtOH (5.0 mL). After 30 min, saturated $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane (20 mL×3), washed with brine and dried over Na_2SO_4 to give 135 mg of compound 2zA as a white solid. HPLC: 99% at 2.257 min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): mn/z 411.1 $[M+H]^+$.

The above procedure was repeated with compound 2yB to yield the desired diol compound 2zB in similar yield.

Example 2a(i)

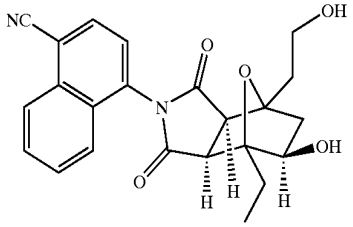
Production of [3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (2a(i))



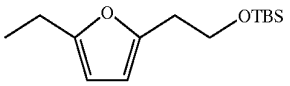
Triphenylphosphine (0.026 g, 0.098 mmol) and DBAD (0.023 g, 0.098 mmol) were mixed in THF (0.5 mL). After allowing the previous mixture to react for 15 min, 2-hydroxy-6-chloropyrimidine (0.016 g, 0.100 mmol) was added, the mixture was allowed to stir for 10 min and compound 2zA (0.020 g, 0.049 mmol) was added. The reaction mixture was stirred at 25° C. for 2 h and then the crude material was purified by preparative TLC, eluting with 10% acetone/$CHCl_3$, to give 0.014 g of compound 2a(i) as a light brown solid. HPLC: 100% at 3.370 min (retention time) (YMC S5 ODS column 4.6×50 mm eluting with 10–90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 mn), MS (ES): m/z 522.08 $[M+H]^+$.

Example 2b(i)

Production of (3aα,4β,5β,7β,7aα)-4-[4-Ethyloctahydro-5-hydroxy-7-(2-hydroxyethyl)-1,3-dioxo4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2b(i)C)



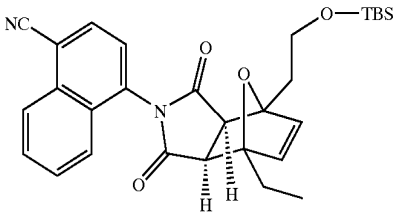
tert-Butyl-[2-(5-ethyl-furan-2-yl)-ethoxy]-dimethyl-silane (2b(i)A)



Imidazole (255 mg, 3.75 mmol) and TBSCl (414 mg, 2.75 mmol) were added to the solution of (2v(1)) (350 mg, 2.5 mmol) in DMF (4 mL). The mixture was stirred at rt for 15 hr and then 100 mg (0.66 mmol) of additional TBSCl was added to drive the reaction to completion. After stirring for an additional hour, the reaction mixture was diluted with

diethylether (100 mL) and washed with water (20 mL), 1 N HCl (20 mL), water (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give 509 mg of compound 2b(i)A (80.3%) as a yellow oil.

(3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl) dimethylsilyl]oxy]ethyl]-4-ethyl-1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2b(i)B)



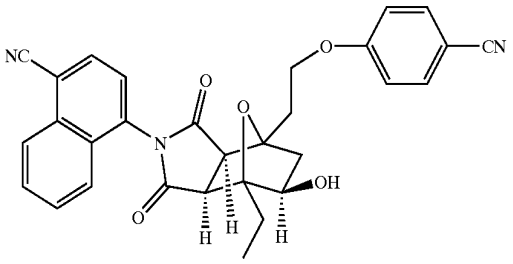
A solution of compound 2b(i)A (509 mg, 2.00 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (498 mg, 2.00 mmol) in benzene (2 mL) was heated at 60° C. for 18 h. The reaction mixture was concentrated under reduced pressure to give 992 mg (99%) of crude compound 2b(i)B, which was used directly in the next step without further purification.

(3aα,4β,5β,7β,7aα)-4-[4-Ethyloctahydro-5-hydroxy-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2b(i)C)

A mixture of compound 2b(i)B (992 mg, 1.98 mmol) and $RhCl_2(PPh_3)_3$ (183 mg, 0.198 mmol) was evacuated and filled with argon (3×). THF (20 mL) was added and once all particulates had dissolved, catecholborane (0.42 mL, 3.96 mmol) was slowly added dropwise. When the formation of product ceased, as was determined by HPLC, the reaction mixture was cooled to 0° C. and quenched with phosphate buffer (34 mL, pH 7.2) followed by the addition of EtOH (19 mL) and H_2O_2 (2.9 mL, 30% aq sol). After 2 h, additional phosphate buffer (6.8 mL, pH 7.2), EtOH (3.8 mL) and H_2O_2 (0.6 mL) were added. The reaction mixture was stirred at rt for 3 h. Once the boronate intermediate was consumed, the mixture was extracted with CH_2Cl_2 (300 mL) and the combined organic layers were washed with 1N NaOH, 10% aq $NaHSO_3$ and brine. The combined organic layers were dried over Na_2SO_4. Purification by flash chromatography on silica gel eluting with 10% $MeOH/CH_2Cl_2$ gave 75 mg (9.3%) of compound 2b(i)C as a gray solid. HPLC conditions: 97% at 2.43 min (Phenomenex-prime S5-C18 column 4.6×50 mm, 10%–90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 407.18 $[M+H]^+$.

Example 2c(i)

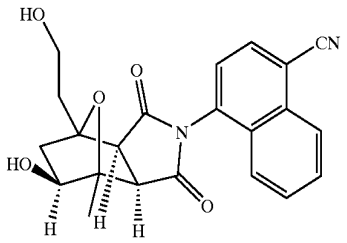
Production of (3aα,4β,5β,7β,7aα)-4-[7-[2-(4-Cyanophenoxy)ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2c(i))



DBAD (39.6 mg, 0.172 mmol) was added to a solution of PPh_3 (45.1 mg, 0.172 mmol) in THF (0.8 mL). After stirring for 10 min, 4-cyanophenol (20.5 mg, 0.172 mmol) was added and the reaction mixture was stirred for an additional 5 min Compound 2b(i)C (25.0 mg, 0.062 mmol) was added and the mixture was stirred at rt for 2 h. The reaction was concentrated under reduced pressure. Purification by Prep TLC eluting with 10% acetone/$CHCl_3$ gave 18.1 mg (0.036 mmol, 57.6%) of compound 2c(i). HPLC conditions: 96% at 3.15 min (YMC S5 ODS 4.6×50 mm, 10%–90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 508.14 $[M+H]^+$.

Example 2d(i)

Production of (3aα,4β,5β,7β,7aα)-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (2d(i))



Compounds (2j(1)) and (2j(2)) were converted to compound 2d(i) by biotransformation.

Microbial Hydroxylation of Compound 2j(1)

Step 1: Reaction

One frozen vial (approximately 2 ml) of *Streptomyces griseus* ATCC 10137 was added to a 500 ml flask containing 100 ml of transformation medium. The transformation medium was prepared as follows: to a 2 liter plastic beaker, 20 g of dextrose, 5.0 g of yeast extract, 5.0 g of soybean meal, 5.0 g of sodium chloride, 5.0 g of potassium phosphate, diabasic and one liter of deionized water were added and the mixture was stirred at room temperature for 3 to 30 min. The pH of the mixture was then adjusted to 7.0 with 1 N HCl or 1 N NaOH. The resulting mixture was dispensed into 500 ml flask (100 ml per flask). The flasks were covered with Bio/Wrap and autoclaved at 121° C. for 15 min. and cooled down to room temperature before use.

The culture was incubated at 28° C. and 250 rpm for 3 days. One ml of the resulting culture was added to a 500 ml flask containing 100 ml of the transformation medium and the flask was incubated at 28° C. and 250 rpm for 24 hours. Ten ml of the resulting culture was transferred to a 50 ml flask, to which 1 mg of compound 2j(1) in 0.2 ml ethanol was added. The flask was incubated at 28° C. and 250 rpm for 23 hours and the reaction culture was extracted with EtOAc (10 ml). The EtOAc extract was dried under N_2 and the residue was dissolved in 1 ml of MeOH (reaction extract). HPLC analysis showed that peak area ratio of compound 2d(i) to compound 2j(1) in the reaction culture was about 1.1/1.

Step 2: Product Analysis

HPLC

10 μl of the reaction extract was injected into HPLC column (YMC ODS-AQ C-18 column, 150×6.0 mm i.d.). The column was eluted with 1 mM HCl in water/CH_3CN at 1.2 ml/min flow rate: 30 to 60% CH_3CN over 8 min, 60 to 85% CH_3CN over 0.5 min, 85% CH_3CN for 1 min, 85 to 30% CH_3CN over 0.5 min. The eluents were monitored at 300 nm. Two major peaks with about 1 to 1 area ratio were observed, which had same UV spectra as those of compounds 2d(i) and (2j(1)), and had retention times of 4.55 min and 7.23 min, respectively, matching the retention times of authentic samples of compound 2d(i)(4.53 min) and compound (2j(1)) (7.2 min).

LC/MS

The reaction extract: two major UV peaks. Peak 1, Tr 4.68 min: 391 $[M+H]^+$, 343, 319, 303, 289 Peak 2, Tr 5.35 min: 375 $[M+H]^+$, 345

Authentic Samples

Compound 2d(i), Tr 4.82 min: 391 $[M+H]^+$, 343, 319, 289

Compound (2j(1)), Tr 5.48 min: 375 $[M+H]^+$, 345

As will be understood by those of skill in the art upon reading this disclosure, additional SARMs for use in the present invention can also be identified in accordance with the methods described herein. For example, a test compound suspected of having selective androgen receptor modulating activity can be screened for antagonist activity in a hormone-dependent tumor cell line such as a human or mouse breast tumor cell line and screened for agonist activity in another nontumor androgen receptor containing cell line such as a muscle, prostate or seminal vesicle cell line as described in the assays below. These screening assays can be performed routinely in accordance with the teachings provided herein.

Example 3

AR Binding Assay

For the whole cell binding assay, human LNCaP cells (T877A mutant AR) or MDA 453 (wild type AR) in 96-well microtiter plates containing RPMI 1640 or DMEM supplemented with 10% charcoal stripped CA-FBS (Cocaleco Biologicals), respectively, were incubated at 37° C. to remove any endogenous ligand that might be complexed with the receptor in the cells. After 48 hours, either a saturation analysis to determine the Kd for tritiated dihydrotestosterone, $[^3H]$-DHT, or a competitive binding assay to evaluate the ability of test compounds to compete with $[^3H]$-DHT were performed. For the saturation analysis, media (RPMI 1640 or DMEM −0.2% CA-FBS) containing $[^3H]$-DHT (in concentrations ranging from 0.1 nM to 16 nM) in the absence (total binding) or presence (non-specific binding) of a 500-fold molar excess of unlabeled DHT were added to the cells. After 4 hours at 37° C., an aliquot of the total binding media at each concentration of $[^3H]$-DHT was removed to estimate the amount of free $[^3H]$-DHT. The remaining media was removed, cells were washed three times with PBS and harvested onto UniFilter GF/B plates (Packard), Microscint (Packard) was added and plates counted in a Top-Counter (Packard) to evaluate the amount of bound $[^3H]$-DHT.

For the saturation analysis, the difference between the total binding and the non-specific binding was defined as specific binding. The specific binding was evaluated by Scatchard analysis to determine the K_d for $[^3H]$-DHT. See e.g. D. Rodbard, Mathematics and statistics of ligand assays: an illustrated guide: In: J. Langon and J. J. Clapp, eds., Ligand Assay, Masson Publishing U.S.A., Inc., New York, pp. 45–99, (1981), the disclosure of which is herein incorporated by reference.

For the competition studies, media containing 1 nM $[^3H]$-DHT and a test compound in concentrations ranging from 10^{-10} to 10^{-5} M were added to the cells. Two replicates were used for each sample. After 4 hours at 37° C., cells were washed, harvested and counted as described above. The data was plotted as the amount of $[^3H]$-DHT (% of control in the absence of test compound) remaining over the range of the dose response curve for a given compound. The concentration of test compound that inhibited 50% of the amount of $[^3H]$-DHT bound in the absence of competing ligand was quantified (IC_{50}) after log-logit transformation. The K_I values were determined by application of the Cheng-Prusoff equation to the IC_{50} values, where:

$$K_I = \frac{IC_{50}}{\left(1 + \left(^3H\text{-}DHT\right)/K_d \text{ for } ^3H\text{-}DHT\right)}.$$

After correcting for non-specific binding, IC_{50} values were determined. The IC_{50} is defined as the concentration of competing ligand needed to reduce specific binding by 50%. The K_ds for $[^3H]$-DHT for MDA 453 and LNCaP were 0.7 and 0.2 nM respectively.

Example 4

Human Prostate Cell Proliferation Assay

The effects of test compound on proliferation of human prostate cancer cell lines was also examined. For that, MDA PCa2b cells, a cell line derived from the metastasis of a patient that failed castration (Navone et al., Clin. Cancer Res., 3, 2493–500 (1997)), were incubated with or without the test compounds for 72 hours and the amount of $[^3H]$-thymidine incorporated into DNA was quantified as a way to assess number of cells and therefore proliferation. The MDA PCa2b cell line was maintained in BRFF-HPCl media (Biological Research Faculty & Facility Inc., MD.) supplemented with 10% FBS. For the assay, cells were plated in Biocoated 96-well microplates and incubated at 37° C. in 10% FBS (charcoal-stripped)/BRFF-BMZERO (without androgens). After 24 hours, the cells were treated in the absence (blank) or presence of 1 nM DHT (control) or with test compounds (sample) in concentrations ranging from 10^{-10} to 10^{-5}M. Duplicates were used for each sample. The compound dilutions were performed on a Biomek 2000 laboratory work station. Seventy two hours later 0.44 uCi. of $[^3H]$-Thymidine (Amersham) was added per well and incubated for another 24 h followed by trypsinization, harvesting of the cells onto GF/B filters. Micro-scint PS were added to the filters before counting them on a Beckman TopCount.

The % Inhibition was calculated as:

$$\% \text{ Inhibition}=100\times(1-[\text{average}_{control}-\text{average}_{blank}/\text{average}_{sample}-\text{average}_{blank}])$$

Data was plotted and the concentration of compound that inhibited 50% of the [^{3}H]-Thymidine incorporation was quantified (IC_{50}).

Example 5

C2C12 Mouse Myoblast Transactivation Assay

Two functional transactivation assays were developed to assess the efficacy of androgen agonists in a muscle cell background using a luciferase reporter. The first assay (ARTA Stable 1) uses a cell line, Stable 1 (clone #72), which stably expresses the full length rat androgen receptor but requires the transient transfection of an enhancer/reporter. This cell line was derived from C2C12 mouse myoblast cells. The second assay (ARTA Stable 2) uses a cell line, Stable 2 (clone #133), derived from Stable 1, which stably expresses both rAR and the enhancer/luciferase reporter. These assays and cell lines

The enhancer/reporter construct used in this system is pGL3/2XDR-1/luciferase. 2XDR-1 was reported to be an AR specific response element in CV-1 cells, Brown et. al. The Journal of Biological Chemistry 272, 8227–8235, (1997). It was developed by random mutagenesis of an AR/GR consensus enhancer sequence.

For the ARTA Stable 1 assay, Stable 1 cells are plated in 96 well format at 6,000 cells/well in high glucose DMEM without phenol red (Gibco BRL, Cat. No.: 21063-029) containing 10% charcoal and dextran treated FBS (HyClone Cat. No.: SH30068.02), 50 mM HEPES Buffer (Gibco BRL, Cat. No.: 15630-080), 1×MEM Na Pyruvate (Gibco BRL, Cat. No.: 11360-070), 0.5×Antibiotic-Antimycotic, and 800 ug/ml Geneticin (Gibco BRL, Cat. No.: 10131-035). Forty-eight hours later, cells are transfected with pGL3/2XDR-1/luciferase using LipofectAMINE Plus™ Reagent (Gibco BRL, Cat. No.: 10964-013). Specifically, 5 ng/well pGL3/2XDR-1/luciferase DNA and 50 ng/well Salmon Sperm DNA (as carrier) are diluted with 5 μl/well Opti-MEM media (Gibco BRL, Cat. No.: 31985-070). To this, 0.5 μl/well Plus reagent is added. This mixture is incubated for 15 minutes at room temperature. In a separate vessel, 0.385 ul/well LipofectAMINE reagent is diluted with 5 μl well Opti-MEM. The DNA mixture is then combined with the LipofectAMINE mixture and incubated for an additional 15 minutes at room temperature. During this time, the media from the cells is removed and replaced with 60 μl/well of Opti-MEM. To this is added 10 μl/well of the DNA/LipofectAMINE transfection mixture. The cells are incubated for 4 hours. Following the incubation, the transfection mixture is removed from the cells and replaced with 90 ul of high glucose DMEM without phenol red (Gibco BRL, Cat. No.: 21063-029) containing 10% charcoal and dextran treated FBS (HyClone Cat. No.: SH30068.02), 50 mM HEPES Buffer (Gibco BRL, Cat. No.: 15630-080), 1×MEM Na Pyruvate (Gibco BRL, Cat. No.: 11360-070), 0.5× Antibiotic-Antimycotic, and 800 μg/ml Geneticin (Gibco BRL, Cat. No.: 10131-035). Test compounds, 10 μl/well at an appropriate drug dilution, are then placed in each well. Twenty-four hours later, the Steady-Glo™ Luciferase Assay System is used to detect activity according to the manufacturer's instructions (Promega, Cat. No.: E2520).

For the ARTA stable 2 assay, Stable 2 cells are plated in 96 well format at 6,000 cells/well in high glucose DMEM without phenol red (Gibco BRL, Cat. No.: 21063-029) containing 10% charcoal and dextran treated FBS (HyClone Cat. No.: SH30068.02), 50 mM HEPES Buffer (Gibco BRL, Cat. No.: 15630-080), 1×MEM Na Pyruvate (Gibco BRL, Cat. No.: 11360-070), 0.5× Antibiotic-Antimycotic, 800 μg/ml Geneticin (Gibco BRL, Cat. No.: 10131-035) and 800 μg/ml Hygromycin β (Gibco BRL, Cat. No.: 10687-010). Forty-eight hours later, the media on the cells is removed and replaced with 90 μl fresh. Test compounds, 10 μl/well at an appropriate drug dilution, are then placed in each well. Twenty-four hours later, the Steady-GloTM Luciferase Assay System is used to detect activity according to the manufacturer's instructions (Promega, Cat. No.: E2520). See U.S. patent application Ser. No. 09/885,831 (unassigned), entitled "Cell Lines and Cell-Based Assays for Identification of Androgen Receptor Modulators", filed Jun. 20, 2001, by Jacek Ostrowski et al., which patent application is incorporated herein by reference by its entirety.

Example 6

Murine Breast Cell Proliferation Assay

The ability of test compounds to modulate the function of the AR was determined by testing said compounds in a proliferation assay using the androgen responsive murine breast cell line derived form the Shionogi tumor (Hiraoka et al., Cancer Res., 47, 6560–6564 (1987)). Stable AR dependent clones of the parental Shionogi line were established by passing tumor fragments under the general procedures originally described in Tetuo, et. al. (Cancer Research 25, 1168–1175 (1965)). From the above procedure, one stable line, SC114, was isolated, characterized and utilized for the testing of example compounds. SC114 cells were incubated with or without the test compounds for 72 hours and the amount of [3H]-thymidine incorporated into DNA was quantified as a surrogate endpoint to assess the number of cells and therefore the proliferation rate as described in Suzuki et. al. (J. Steroid Biochem. Mol. Biol. 37, 559–567 (1990)). The SC114 cell line was maintained in MEM containing 10^{-8} M testosterone and 2% DCC-treated FCS. For the assay, cells were plated in 96-well microplates in the maintenance media and incubated at 37° C. On the following day, the medium was changed to serum free medium [Ham's F-12:MEM (1;1, v/v) containing 0.1% BSA] with (antagonist mode) or without (agonist mode) 10^{-8} M testosterone and the test compounds of the present invention in concentrations ranging from 10^{-10} to 10^{-5} M. Duplicates were used for each sample. The compound dilutions were performed on a Biomek 2000 laboratory work station. Seventy two hours later 0.44 uCi. of [3H]-Thymidine (Amersham) was added per well and incubated for another 2 hr followed by trypsinization, and harvesting of the cells onto GF/B filters. Micro-scint PS were added to the filters before counting them on a Beckman TopCount.

For the antagonist mode, the % Inhibition was calculated as:

$$\% \text{ Inhibition}=100\times(1-[\text{average}_{sample}-\text{average}_{blank}/\text{average}_{control}-\text{average}_{blank}])$$

Data was plotted and the concentration of compound that inhibited 50% of the [^{3}H]-Thymidine incorporation was quantified (IC_{50}).

For the agonist mode, % Control was referred as the effect of the tested compound compared to the maximal effect observed with the natural hormone, in this case DHT, and was calculated as:

$$\% \text{ Control}=100\times(\text{average}_{sample}-\text{average}_{blank})/(\text{average}_{control}-\text{average}_{blank})$$

Data was plotted and the concentration of compound that inhibited 50% of the [^{3}H]-Thymidine incorporation was quantified (EC_{50}).

Example 7

Wet Prostate Weight Assay AR Antagonist Assay

The activity of test compounds as AR antagonists was investigated in an immature male rat model, a standard, recognized test of antiandrogen activity of a given compound (Hershberger et al. Proc. Soc. Expt. Biol. Med., 83, 175 (1953); Walsh. P. C. and Gittes, R. F., Endocrinology, 86, 624 (1970); and Furr et al., J. Endocrinol., 113, R7–9 (1987)). The basis of this assay is the fact that male sexual accessory organs, such as the prostate and seminal vesicles, play an important role in reproductive function. These glands are stimulated to grow and are maintained in size and secretory function by the continued presence of serum testosterone (T), which is the major serum androgen (>95%) produced by the Leydig cells in the testis under the control of the pituitary luteinizing hormone (LH) and follicle stimulating hormone (FSH). Testosterone is converted to the more active form, dihydrotestosterone, (DHT), within the prostate by 5α-reductase. Adrenal androgens also contribute about 20% of total DHT in the rat prostate, compared to 40% of that in 65-year-old men (Labrie et al. Clin. Invest. Med., 16, 475–492 (1993)). However, this is not a major pathway, since in both animals and humans castration leads to almost complete involution of the prostate and seminal vesicles without concomitant adrenalectomy. Therefore, under normal conditions, the adrenals do not support significant growth of prostate tissues (Luke, M. C. and Coffey, D. S. "The Physiology of Reproduction" ed. By E. Knobil and J. D. Neill, 1, 1435–1487 (1994)). Since the male sex organs are the tissues most responsive to modulation of the androgen activity, this model is used to determine the androgen dependent growth of the sex accessory organs in immature castrated rats.

Male immature rats (19–20 days old Sprague-Dawley, Harlan Sprague-Dawley) were castrated under metofane anesthesia. Five days after surgery these castrated rats (60–70 g, 23–25 day-old) were dosed for 3 days. Animals were dosed sub-cutaneously (s.c.) 1 mg/kg with Testosterone Proprionate (TP) in arachis oil vehicle and test compounds (compounds of the present invention) were administered orally by gavage (p.o.) in dissolved/suspensions of 80% PEG 400 and 20% Tween 80 (PEGTW). Animals were dosed (v/w) at 0.5 ml of vehicle /100 g body weight. Experimental groups were as follows:

1. Control vehicle
2. Testosterone Propionate (TP) (3 mg/rat/day, subcutaneous)
3. TP plus Casodex (administered p.o. in PEGTW, QD), a recognized antiandrogen, as a reference compound.
4. To assess antagonist activity, a test compound was administered (p.o. in PEGTW, QD) with TP (s.c. as administered in group 2) in a range of doses.
5. To assess agonist activity, a test compound was administered alone (p.o. in PEGTW, QD) in a range of doses.

At the end of the 3-day treatment, the animals were sacrificed, and the ventral prostate weighed. To compare data from different experiments, weights of the sexual organs were first standardized as mg per 100 g of body weight, and the increase in organ weight induced by TP was considered as the maximum increase (100%). ANOVA followed by one-tailed Student or Fischer's exact test was used for statistical analysis.

The gain and loss of sexual organ weight reflect the changes of the cell number (DNA content) and cell mass (protein content), depending upon the serum androgen concentration (Okuda et al., J. Urol., 145, 188–191 (1991)). Therefore, measurement of organ wet weight is sufficient to indicate the bioactivity of androgens and androgen antagonists. In immature castrated rats, replacement of exogenous androgens increases seminal vesicles (SV) and the ventral prostate (VP) in a dose dependent manner.

The maximum increase in organ weight was 4 to 5-fold when dosing 3 mg/rat/day of testosterone (T) or 1 mg/rat/day of testosterone propionate (TP) for 3 days. The EC_{50} of T and TP were about 1 mg and 0.03 mg, respectively. The increase in the weight of the VP and SV also correlated with the increase in the serum T and DHT concentration. Although administration of T showed 5-times higher serum concentrations of T and DHT at 2 hours after subcutaneous injection than that of TP, thereafter, these high levels declined very rapidly. In contrast, the serum concentrations of T and DHT in TP-treated animals were fairly consistent during the 24 hours, and therefore, TP showed about 10–30-fold higher potency than free T.

In this immature castrated rat model, a known AR antagonist (Casodex) was also administered simultaneously with 0.1 mg of TP (ED_{80}), inhibiting the testosterone-mediated increase in the weights of the VP and SV in a dose dependent manner. The antagonist effects were similar when dosing orally or subcutaneously. SARMs of the invention also exhibited AR antagonist activity by suppressing the testosterone-mediated increase in the weights of VP and SV.

Example 8

Levator Ani & Wet Prostate Weight Assay AR Agonist Assay

The activity of test compounds as AR agonists was investigated in an immature male rat model, a recognized test of anabolic effects in muscle and sustaining effects in sex organs for a given compound (Hershberger et al., *Proc. Soc. Expt. Biol. Med.,* 83, 175 (1953); Beyler et al., *J. Amer. Med. Women's Ass.,* 23, 708 (1968); Fukuda et al., *Nago Dai. Yak. Ken. Nem.* 14, 84 (1966)). The basis of this assay lies in the well-defined action of androgenic agents on the maintenance and growth of muscle tissues and sexual accessory organs in animals and man. Androgenic steroids, such as testosterone (T), have been well characterized for their ability to maintain muscle mass. Treatment of animals or humans after castrations with an exogenous source of T results in a reversal of muscular atrophy. The effects of T on muscular atrophy in the rat levator ani muscle have been well characterized (Masuoka et al., *Am. J. Anat.* 119, 263 (1966); Gori et al., *Boll.—Soc. Ital. Biol. Sper.* 42, 1596 (1966); Gori et al., *Boll.—Soc. Ital. Biol. Sper.* 42, 1600 (1966); Boris et al., *Steroids* 15, 61 (1970)). As described in Example 6, the effects of androgens on maintenance of male sexual accessory organs, such as the prostate and seminal vesicles, is well described. Castration results in rapid involution and atrophy of the prostate and seminal vesicles. This effect can be reversed by exogenous addition of androgens. Since both the levator ani muscle and the male sex organs are the tissues most responsive to the effects of androgenic agents, this model is used to determine the androgen dependent reversal of atrophy in the levator ani muscle and the sex accessory organs in immature castrated rats.

Sexually mature rats (200–250 g, 6–8 weeks-old, Sprague-Dawley, Harlan) were acquired castrated from the vendor (Taconic). The rats were divided into groups and treated daily for 7 to 14 days with one of the following:

1. Control vehicle
2. Testosterone Propionate (TP) (3 mg/rat/day, subcutaneous)

3. TP plus Casodex (administered p.o. in PEGTW, QD), a recognized antiandrogen, as a reference compound.
4. To assess antagonist activity, a test compound was administered (p.o. in PEGTW, QD) with TP (s.c. as administered in group 2) in a range of doses.
5. To assess agonist activity, a test compound was administered alone (p.o. in PEGTW, QD) in a range of doses.

At the end of the 7–14-day treatment, the animals were sacrificed by carbon dioxide, and the levator ani, seminal vesicle and ventral prostate weighed. To compare data from different experiments, the levator ani muscle and sexual organ weights were first standardized as mg per 100 g of body weight, and the increase in organ weight induced by TP was considered as the maximum increase (100%). Superanova (one factor) was used for statistical analysis.

The gain and loss of sexual organ weight reflect the changes of the cell number (DNA content) and cell mass (protein content), depending upon the serum androgen concentration (Okuda et al., *J. Urol.,* 145, 188–191 (1991)). Therefore, measurement of organ wet weight is sufficient to indicate the bioactivity of androgens and androgen antagonist. In immature castrated rats, replacement of exogenous androgens increases levator ani, seminal vesicles (SV) and prostate in a dose dependent manner.

The maximum increase in organ weight was 4- to 5-fold when dosing 3 mg/rat/day of testosterone (T) or 1 mg/rat/day of testosterone propionate (TP) for 3 days. The EC_{50} of T and TP were about 1 mg and 0.03 mg, respectively. The increase in the weight of the VP and SV also correlated with the increase in the serum T and DHT concentration. Although administration of T showed 5-times higher serum concentrations of T and DHT at 2 hours after subcutaneous injection than that of TP, thereafter, these high levels declined very rapidly. In contrast, the serum concentrations of T and DHT in TP-treated animals were fairly consistent during the 24 hours, and therefore, TP showed about 10–30-fold higher potency than free T.

Example 9

Mature Rat Prostate Weight Assay

The activity of test compounds was also investigated in a mature male rat model, which is a variation of the Levator ani and wet prostate weight assay described in Example 7. The in vivo assays of Examples 6 and 7 are recognized assays for determining the anabolic effects in muscle and sustaining effects in sex organs for a given compound (Hershberger et al., *Proc. Soc. Expt. Biol. Med.,* 83, 175 (1953); Beyler et al., *J. Amer. Med. Women's Ass.* 23, 708 (1968); Fukuda et al., *Nago Dai. Yak. Ken. Nem.* 14, 84 (1966)). The basis of this assay lies in the well-defined action of androgenic agents on the maintenance and growth of muscle tissues and sexual accessory organs in animals and man.

The male sexual accessory organs, such as the prostate and seminal vesicles, play an important role in reproductive function. These glands are stimulated to grow and are maintained in size and secretory function by the continued presence of serum testosterone (T), which is the major serum androgen (>95%) produced by the Leydig cells in the testis under the control of the pituitary luteinizing hormone (LH) and follicle stimulating hormone (FSH). Testosterone is converted to the more active form, dihydrotestosterone, (DHT), within the prostate by 5α-reductase. Adrenal androgens also contribute about 20% of total DHT in the rat prostate, compared to 40% of that in 65-year-old men (Labrie et. al. *Clin. Invest. Med.,* 45, 475–492 (1993)). However, this is not a major pathway, since in both animals and humans, castration leads to almost complete involution of the prostate and seminal vesicles without concomitant adrenalectomy. Therefore, under normal conditions, the adrenals do not support significant growth of prostate tissues (Luke, M. C. and Coffey, D. S. "The Physiology of Reproduction" ed. By E. Knobil and J. D. Neill, 1, 1435–1487 (1994)). Since the male sex organs and the levator ani are the tissues most responsive to modulation of the androgen activity, this model is used to determine the activity of compounds that modulate the androgen receptor pathway in mature rats.

Along with its mitogenic activity on tissues such as prostate, seminal vesicle and muscle, testosterone also serves as a negative regulator for its own biosynthesis. Testosterone production in the Leydig cells of the testis is controlled by the level of circulating LH released from the pituitary gland. LH levels are themselves controlled by the level of LHRH produced in the hypothalmic region. Testosterone levels in the blood serve to inhibit the secretion of LHRH and subsequently reduce levels of LH and ultimately the levels of circulating testosterone levels. By measuring blood levels of LH as they are effected by test compounds, it is possible to determine the level of agonist or antagonist activity of said compounds at the hypothalamic axis of this endocrine cycle.

Matched sets of Harlan Sprague-Dawley rats (40–42 days old, 180–220 g), were dosed orally by gavage (p.o.) with the test compounds in dissolved/suspensions of 80% PEG 400 and 20% Tween 20 (PEGTW] for 14 days. Two control groups, one intact and one castrated were dosed orally only with the PEGTW vehicle. Animals were dosed (v/w) at 0.5 ml of vehicle /100 g body weight. Experimental groups were as follows:

1. Intact vehicle (p.o., PEGTW, QD)
2. Control vehicle (p.o., PEGTW, QD)
3. Biacalutamide (Casodex, a recognized antiandrogen, as a reference compound) or a test compound, p.o. in PEGTW QD. (in a range of doses). At the end of the 14-day treatment, the animals were sacrificed, and the ventral prostate, the seminal vesicles, and the levator ani were removed surgically and weighed. To compare data from different experiments, the organs weights were first standardized as mg per 100 g of body weight, and expressed as a percentage of the value of the respective organ in the intact group.

Rat luteinizing hormone (rLH) is quantitatively determined with the Biotrak [^{125}I] kit (Amersham Pharmacia Biotek), following the manufacturer directions. The assay is based on the competition by the LH present in the serum of the binding of [^{125}I] rLH to an Amerlex-M bead/antibody suspension. The radioactivity that remains after incubation with the serum and subsequent washes is extrapolated into a standard curve to obtain a reading in ng/ml.

The gain and loss of sexual organ and levator ani weight reflect the changes of the cell number (DNA content) and cell mass (protein content), depending upon the serum androgen concentration (Okuda et al.,*J. Urol.,* 145, 188–191 (1991)). Therefore, measurement of organ wet weight is sufficient to indicate the bioactivity of androgens and androgen antagonist. In the mature rats assay, active agonist agents will have no effect or will increase the weight of one or more of the androgen responsive organs (levator ani, prostate, seminal vesicle) and will have no effect or a suppressive effect on LH secretion. Compounds with antagonist activity will decrease the weight of one or more

of the androgen responsive organs (levator ani, prostate, seminal vesicle) and will have no effect or a reduced suppressive effect on LH secretion.

Example 10

MDA PCa2b Human Prostate Zenograft Assay

For in vivo antitumor testing, MDA-PCa-2b human prostate tumors were maintained in Balb/c nu/nu nude mice. Tumors were propagated as subcutaneous transplants in adult male nude mice (4–6 weeks old) using tumor fragments obtained from donor mice. Tumor passage occurred every 5–6 weeks.

For antitumor efficacy trial, the required number of animals needed to detect a meaningful response were pooled at the start of the experiment and each was given a subcutaneous implant of a tumor fragment (~50 mg) with a 13-gauge trocar. Tumors were allowed to grow to approximately 100–200 mg (tumors outside the range were excluded) and animals were evenly distributed to various treatment and control groups. Treatment of each animal was based on individual body weight. Treated animals were checked daily for treatment related toxicity/mortality. Each group of animals was weighed before the initiation of treatment (Wt1) and then again following the last treatment dose (Wt2). The difference in body weight (Wt2−Wt1) provides a measure of treatment-related toxicity.

Tumor response was determined by measurement of tumors with a caliper twice a week, until the tumors reach a predetermined "target" size of 0.5 gm. Tumor weights (mg) were estimated from the formula:

$$\text{Tumor weight}=(\text{length}\times\text{width2})\div 2$$

Tumor response end-point was expressed in terms of tumor growth inhibition (% T/C), defined as the ratio of median tumor weights of the treated tumors (T) to that of the control group (C).

To estimate tumor cell kill, the tumor volume doubling time was first calculated with the formula:

$$\text{TVDT}=\text{Median time (days) for control tumors to reach target size}-\text{Median time (days) for control tumors to reach half the target size } s$$

and, Log cell kill was then calculated with the formula

$$\text{Log cell kill}=(T-C)\div(3.32\times TVDT)$$

Statistical evaluations of data were performed using Gehan's generalized Wilcoxon test.

Example 11

CWR22 Human Prostate Zenograft Assay

In vivo antitumor testing was also performed with CWR22 human prostate tumors maintained in Balb/c nu/nu nude mice. Tumors were propagated as subcutaneous transplants in adult male nude mice (4–6 weeks old) using tumor fragments obtained from donor mice. Tumor passage occurred every 5–6 weeks.

For antitumor efficacy trial, the required number of animals needed to detect a meaningful response were pooled at the start of the experiment and each was given a subcutaneous implant of a tumor fragment (~50 mg) with a 13-gauge trocar. Tumors were allowed to grow to approximately 100–200 mg (tumors outside the range were excluded) and animals were evenly distributed to various treatment and control groups. Treatment of each animal was based on individual body weight. Treated animals were checked daily for treatment related toxicity/mortality. Each group of animals was weighed before the initiation of treatment (Wt1) and then again following the last treatment dose (Wt2). The difference in body weight (Wt2−Wt1) provides a measure of treatment-related toxicity.

Tumor response was determined by measurement of tumors with a caliper twice a week, until the tumors reach a predetermined "target" size of 0.5 gm. Tumor weights (mg) were estimated from the formula: Tumor weight=(length×width2)÷2

Tumor response end-point was expressed in terms of tumor growth inhibition (% T/C), defined as the ratio of median tumor weights of the treated tumors (T) to that of the control group (C).

To estimate tumor cell kill, the tumor volume doubling time was first calculated with the formula:

$$\text{TVDT}=\text{Median time (days) for control tumors to reach target size}-\text{Median time (days) for control tumors to reach half the target size } s$$

Log cell kill was calculated with the formula:

$$\text{Log cell kill}=(T-C)\div(3.32\times TVDT)$$

Statistical evaluations of data were performed using Gehan's generalized Wilcoxon test.

Example 12

Dunning R3327H Rat Prostate Tumor Assay

Dunning R3327H prostate tumor is a spontaneously derived, well differentiated androgen responsive adenocarcinoma of the prostate (Smolev et al. *Cancer Treat Rep.* 61, 273–287 (1977)). The growth of the R3327H subline has been selected for its highly androgen-dependent and reproducible growth in intact male rats. Therefore, this model and other sublines of this tumor have been widely used to evaluate in vivo antitumor activities of antiandrogens such as flutamide and bacilutamide/Casodex (Maucher A., and von Angerer, *J. Cancer Res. Clin,. Oncol.* 119, 669–674 (1993), Furr B. J. A. *Euro. URL.* 18(suppl. 3), 2–9 (1990), Shain S. A. and Huot R I. *J. Steriod Biochem.* 31, 711–718 (1988)). For this assay, Dunning tumor pieces (about 4×4 mm) are transplanted subcutaneously to the flank of mature male Copenhagen rats (6–7 weeks old, Harlan-Sprague Dawley, Indianapolis, Md.). About 6 weeks after the implantation, the animals with tumors of measurable size (about 80–120 mm^2) are randomized into treatment groups (8–10 rats/group) and the treatments are initiated. One group of the rats are castrated to serve as the negative control of tumor growth. Animals are treated daily with test compounds, standard antiandrogens such as bacilutamide or vehicle (control) for an average of 10 to 14 weeks. Test compounds are dissolved in a vehicle of (2.5 ml/kg of body weight) 10% polyethylene glycol and 0.05% Tween-80 in 1% carboxymethyl cellulose, PEG/CMC, (Sigma, St. Louis, Mo.). Typical experiments include three groups of three escalating doses for each standard or test compound (in a range of 300–3 mg/kg).

Tumors in the vehicle group the control group tumors reach a size of 1500 to 2500 mm^3. In contrast, the castrated animal group typically shows tumor stasis over the 14 weeks of observation. Animals treated orally with 20 mg/kg of bicalutamide or flutamide are expected to show 40% reduc-

tion in tumor volumes compared to controls after 14 weeks of treatment. The size of tumors are measured weekly by vernier caliper (Froboz, Switzerland), taking perpendicular measurements of length and width. Tumor volumes are measured in mm^3 using the formula: Length×Width×Height=Volume. Statistical differences between treatment groups and control are evaluated using multiple ANOVA analysis followed by one tail non-parametric Student t test.

Example 13

Dunning R3327H Rat Prostate Tumor and Wet Prostate Weight Assay

Dunning tumor pieces (about 4×4 mm), as described in Example 11, are transplanted subcutaneously to the flank of mature male Copenhagen rats (6–7 weeks old, Harlan-Sprague Dawley, Indianapolis, Md.). About 6 weeks after the implantation, the animals with tumors of measurable size (about 80–120 mm^2) are randomized into treatment groups (8–10 rats/group) and the treatments are initiated. One group of the rats are castrated to serve as the negative control of tumor growth. Animals are treated daily with test compounds, standard antiandrogens such as bacilutamide or vehicle (control) for an average of 10 to 14 weeks. Test compounds are dissolved in a vehicle of (2.5 ml/kg of body weight) 10% polyethylene glycol and 0.05% Tween-80 in 1% carboxymethyl cellulose, PEG/CMC, (Sigma, St Louis, Mo.). Typical therapeutic experiments would include three groups of three escalating doses for each standard or test compound (in a range of 300–3 mg/kg).

Tumors in the vehicle group the control group tumors reach a size of 1500 to 2500 mm^3. In contrast, the castrated animal group typically shows tumor stasis over the 14 weeks of observation. Animals treated orally with 20 mg/kg of bicalutamide or flutamide are expected to show 40% reduction in tumor volumes compared to control after 14 weeks of treatment. The size of tumors are measured weekly by vernier caliper (Froboz, Switzerland), taking perpendicular measurements of length and width. Tumor volumes are measured in mm^3 using the formula: Length×Width×Height=Volume. Statistical differences between treatment groups and control are evaluated using multiple ANOVA analysis followed by one tail non-parametric Student t test.

At the end of the treatment, the animals were sacrificed, and the ventral prostate, the seminal vesicles, and the levator ani were removed surgically and weighed. To compare data from different experiments, the organs weights were first standardized as mg per 100 g of body weight, and expressed as a percentage of the value of the respective organ in the intact group.

Rat luteinizing hormone (rLH) can be quantitatively determined in these animals with the Biotrak [^{125}I] kit (Amersham Pharmacia Biotek), following the manufacturer directions. The assay is based on the competition by the LH present in the serum of the binding of [^{125}I] rLH to an Amerlex-M bead/antibody suspension. The radioactivity that remains after incubation with the serum and subsequent washes is extrapolated into a standard curve to obtain a reading in ng/ml.

The gain and loss of sexual organ and levator ani weight reflect the changes of the cell number (DNA content) and cell mass (protein content), depending upon the serum androgen concentration (Okuda et al., J. Urol., 145, 188–191 (1991)). Therefore, measurement of organ wet weight is sufficient to indicate the bioactivity of androgens and androgen antagonist. In this rat assay, active agonist agents will have no effect or will increase the weight of one or more of the androgen responsive organs (levator ani, prostate, seminal vesicle) and will have no effect or a suppressive effect on LH secretion. Compounds with antagonist activity will decrease the weight of one or more of the androgen responsive organs (levator ani, prostate, seminal vesicle) and will have no effect or a reduced suppressive effect on LH secretion.

TABLE A

ATOM	1	CB	ILE	672	15.585	25.993	23.410	1.00	31.24
ATOM	2	CG2	ILE	672	14.852	27.128	24.154	1.00	30.88
ATOM	3	CG1	ILE	672	16.008	24.898	24.385	1.00	31.15
ATOM	4	CD1	ILE	672	16.804	25.398	25.547	1.00	31.82
ATOM	5	C	ILE	672	15.338	24.127	21.758	1.00	30.41
ATOM	6	O	ILE	672	16.366	24.192	21.075	1.00	30.37
ATOM	7	N	ILE	672	13.327	25.032	22.857	1.00	31.02
ATOM	8	CA	ILE	672	14.670	25.387	22.310	1.00	30.84
ATOM	9	N	PHE	673	14.730	22.987	22.058	1.00	29.49
ATOM	10	CA	PHE	673	15.233	21.694	21.628	1.00	28.89
ATOM	11	CB	PHE	673	14.309	20.587	22.143	1.00	28.59
ATOM	12	CG	PHE	673	14.827	19.211	21.890	1.00	28.37
ATOM	13	CD1	PHE	673	15.903	18.721	22.616	1.00	28.33
ATOM	14	CD2	PHE	673	14.259	18.412	20.900	1.00	27.95
ATOM	15	CE1	PHE	673	16.411	17.447	22.358	1.00	28.35
ATOM	16	CE2	PHE	673	14.753	17.151	20.634	1.00	27.76
ATOM	17	CZ	PHE	673	15.831	16.665	21.361	1.00	28.28
ATOM	18	C	PHE	673	15.368	21.591	20.108	1.00	28.44
ATOM	19	O	PHE	673	16.387	21.137	19.594	1.00	28.30
ATOM	20	N	LEU	674	14.334	22.000	19.387	1.00	28.13
ATOM	21	CA	LEU	674	14.393	21.950	17.940	1.00	27.74
ATOM	22	CB	LEU	674	13.033	22.315	17.337	1.00	28.50
ATOM	23	CG	LEU	674	12.094	21.110	17.212	1.00	29.52
ATOM	24	CD1	LEU	674	12.732	20.084	16.273	1.00	29.84
ATOM	25	CD2	LEU	674	11.846	20.487	18.590	1.00	29.46
ATOM	26	C	LEU	674	15.472	22.876	17.402	1.00	27.02
ATOM	27	O	LEU	674	16.174	22.529	16.452	1.00	26.73
ATOM	28	N	ASN	675	15.605	24.048	18.017	1.00	26.63
ATOM	29	CA	ASN	675	16.595	25.031	17.592	1.00	26.23
ATOM	30	CB	ASN	675	16.584	26.238	18.547	1.00	26.53
ATOM	31	CG	ASN	675	15.229	26.955	18.575	1.00	26.69
ATOM	32	OD1	ASN	675	14.771	27.475	17.568	1.00	25.27
ATOM	33	ND2	ASN	675	14.587	26.973	19.740	1.00	28.17

TABLE A-continued

ATOM	34	C	ASN	675	17.971	24.371	17.578	1.00	25.92
ATOM	35	O	ASN	675	18.716	24.475	16.599	1.00	25.60
ATOM	36	N	VAL	676	18.284	23.666	18.663	1.00	25.22
ATOM	37	CA	VAL	676	19.561	22.979	18.800	1.00	24.86
ATOM	38	CB	VAL	676	19.667	22.306	20.180	1.00	24.40
ATOM	39	CG1	VAL	676	20.987	21.567	20.300	1.00	23.97
ATOM	40	CG2	VAL	676	19.525	23.354	21.271	1.00	24.34
ATOM	41	C	VAL	676	19.777	21.920	17.715	1.00	24.78
ATOM	42	O	VAL	676	20.857	21.835	17.123	1.00	23.74
ATOM	43	N	LEU	677	18.742	21.115	17.471	1.00	24.81
ATOM	44	CA	LEU	677	18.804	20.055	16.471	1.00	25.01
ATOM	45	CB	LEU	677	17.540	19.181	16.561	1.00	24.69
ATOM	46	CG	LEU	677	17.645	17.937	17.468	1.00	25.09
ATOM	47	CD1	LEU	677	18.155	18.298	18.847	1.00	24.53
ATOM	48	CD2	LEU	677	16.287	17.270	17.570	1.00	24.88
ATOM	49	C	LEU	677	19.018	20.560	15.037	1.00	24.85
ATOM	50	O	LEU	677	19.770	19.967	14.274	1.00	24.74
ATOM	51	N	GLU	678	18.362	21.655	14.675	1.00	25.51
ATOM	52	CA	GLU	678	18.504	22.232	13.334	1.00	25.67
ATOM	53	CB	GLU	678	17.413	23.284	13.103	1.00	27.59
ATOM	54	CG	GLU	678	17.732	24.340	12.046	1.00	30.04
ATOM	55	CD	GLU	678	16.621	25.379	11.918	1.00	32.44
ATOM	56	OE1	GLU	678	16.830	26.423	11.237	1.00	33.09
ATOM	57	OE2	GLU	678	15.534	25.140	12.505	1.00	33.23
ATOM	58	C	GLU	678	19.874	22.873	13.187	1.00	24.83
ATOM	59	O	GLU	678	20.541	22.715	12.171	1.00	24.31
ATOM	60	N	ALA	679	20.286	23.591	14.224	1.00	24.77
ATOM	61	CA	ALA	679	21.571	24.273	14.244	1.00	24.70
ATOM	62	CB	ALA	679	21.703	25.072	15.515	1.00	24.21
ATOM	63	C	ALA	679	22.744	23.315	14.125	1.00	25.17
ATOM	64	O	ALA	679	23.752	23.637	13.499	1.00	25.65
ATOM	65	N	ILE	680	22.623	22.137	14.722	1.00	25.38
ATOM	66	CA	ILE	680	23.716	21.172	14.676	1.00	25.89
ATOM	67	CB	ILE	680	23.829	20.417	15.999	1.00	25.44
ATOM	68	CG2	ILE	680	23.886	21.427	17.143	1.00	24.98
ATOM	69	CG1	ILE	680	22.649	19.439	16.135	1.00	24.49
ATOM	70	CD1	ILE	680	22.583	18.702	17.442	1.00	24.31
ATOM	71	C	ILE	680	23.620	20.140	13.563	1.00	26.38
ATOM	72	O	ILE	680	24.482	19.270	13.472	1.00	26.49
ATOM	73	N	GLU	681	22.586	20.227	12.728	1.00	26.84
ATOM	74	CA	GLU	681	22.414	19.262	11.641	1.00	28.06
ATOM	75	CB	GLU	681	21.074	19.473	10.946	1.00	28.71
ATOM	76	CG	GLU	681	20.790	18.472	9.850	1.00	29.82
ATOM	77	CD	GLU	681	20.527	17.083	10.393	1.00	31.25
ATOM	78	OE1	GLU	681	20.168	16.187	9.588	1.00	32.01
ATOM	79	OE2	GLU	681	20.677	16.887	11.623	1.00	31.32
ATOM	80	C	GLU	681	23.533	19.348	10.605	1.00	28.62
ATOM	81	O	GLU	681	23.755	20.398	9.993	1.00	29.09
ATOM	82	N	PRO	682	24.247	18.235	10.384	1.00	28.78
ATOM	83	CD	PRO	682	24.071	16.919	11.017	1.00	28.67
ATOM	84	CA	PRO	682	25.348	18.198	9.420	1.00	28.68
ATOM	85	CB	PRO	682	25.864	16.764	9.533	1.00	28.60
ATOM	86	CG	PRO	682	25.440	16.337	10.882	1.00	28.67
ATOM	87	C	PRO	682	24.886	18.505	8.004	1.00	28.93
ATOM	88	O	PRO	682	23.765	18.165	7.620	1.00	29.17
ATOM	89	N	GLY	683	25.760	19.141	7.233	1.00	28.83
ATOM	90	CA	GLY	683	25.438	19.454	5.855	1.00	28.82
ATOM	91	C	GLY	683	25.843	18.296	4.951	1.00	29.01
ATOM	92	O	GLY	683	26.077	17.187	5.421	1.00	28.29
ATOM	93	N	VAL	684	25.935	18.569	3.652	1.00	29.33
ATOM	94	CA	VAL	684	26.293	17.569	2.648	1.00	29.92
ATOM	95	CB	VAL	684	26.276	18.182	1.223	1.00	30.47
ATOM	96	CG1	VAL	684	26.393	17.069	0.166	1.00	30.24
ATOM	97	CG2	VAL	684	25.004	19.006	1.025	1.00	29.99
ATOM	98	C	VAL	684	27.666	16.933	2.855	1.00	29.77
ATOM	99	O	VAL	684	28.602	17.578	3.308	1.00	29.87
ATOM	100	N	VAL	685	27.768	15.657	2.512	1.00	29.69
ATOM	101	CA	VAL	685	29.014	14.922	2.631	1.00	29.84
ATOM	102	CB	VAL	685	28.973	13.936	3.834	1.00	29.89
ATOM	103	CG1	VAL	685	30.357	13.368	4.084	1.00	29.18
ATOM	104	CG2	VAL	685	28.441	14.642	5.088	1.00	29.80
ATOM	105	C	VAL	685	29.207	14.130	1.333	1.00	30.42
ATOM	106	O	VAL	685	28.378	13.291	0.975	1.00	30.40
ATOM	107	N	CYS	686	30.287	14.408	0.615	1.00	30.75
ATOM	108	CA	CYS	686	30.551	13.698	−0.624	1.00	31.29
ATOM	109	CB	CYS	686	31.219	14.636	−1.630	1.00	31.47
ATOM	110	SG	CYS	686	30.172	16.063	−2.105	1.00	33.49
ATOM	111	C	CYS	686	31.415	12.459	−0.366	1.00	31.56
ATOM	112	O	CYS	686	32.266	12.458	0.523	1.00	31.13

TABLE A-continued

ATOM	113	N	ALA	687	31.180	11.405	−1.147	1.00	31.88
ATOM	114	CA	ALA	687	31.905	10.157	−0.987	1.00	32.66
ATOM	115	CB	ALA	687	31.072	8.989	−1.531	1.00	32.89
ATOM	116	C	ALA	687	33.275	10.160	−1.636	1.00	33.22
ATOM	117	O	ALA	687	34.138	9.365	−1.259	1.00	33.23
ATOM	118	N	GLY	688	33.476	11.051	−2.602	1.00	33.83
ATOM	119	CA	GLY	688	34.752	11.123	−3.287	1.00	34.36
ATOM	120	C	GLY	688	34.838	10.039	−4.345	1.00	35.22
ATOM	121	O	GLY	688	35.925	9.648	−4.776	1.00	35.29
ATOM	122	N	HIS	689	33.681	9.540	−4.762	1.00	35.46
ATOM	123	CA	HIS	689	33.639	8.497	−5.773	1.00	36.39
ATOM	124	CB	HIS	689	32.328	7.713	−5.650	1.00	36.01
ATOM	125	CG	HIS	689	32.136	6.683	−6.716	1.00	35.72
ATOM	126	CD2	HIS	689	32.433	5.361	−6.742	1.00	35.47
ATOM	127	ND1	HIS	689	31.590	6.977	−7.946	1.00	35.68
ATOM	128	CE1	HIS	689	31.557	5.882	−8.684	1.00	35.61
ATOM	129	NE2	HIS	689	32.063	4.887	−7.976	1.00	35.45
ATOM	130	C	HIS	689	33.776	9.088	−7.176	1.00	37.25
ATOM	131	O	HIS	689	33.125	10.078	−7.512	1.00	36.54
ATOM	132	N	ASP	690	34.643	8.492	−7.988	1.00	38.49
ATOM	133	CA	ASP	690	34.832	8.967	−9.353	1.00	40.16
ATOM	134	CB	ASP	690	36.285	8.755	−9.803	1.00	40.96
ATOM	135	CG	ASP	690	36.766	7.342	−9.580	1.00	42.31
ATOM	136	OD1	ASP	690	37.918	7.030	−9.977	1.00	42.84
ATOM	137	OD2	ASP	690	35.994	6.541	−9.004	1.00	43.23
ATOM	138	C	ASP	690	33.870	8.242	−10.293	1.00	40.81
ATOM	139	O	ASP	690	33.928	7.020	−10.434	1.00	41.00
ATOM	140	N	ASN	691	32.972	8.997	−10.919	1.00	41.55
ATOM	141	CA	ASN	691	31.992	8.419	−11.838	1.00	42.66
ATOM	142	CB	ASN	691	30.917	9.450	−12.195	1.00	42.57
ATOM	143	CG	ASN	691	30.002	9.782	−11.031	1.00	42.88
ATOM	144	OD1	ASN	691	29.206	10.721	−11.115	1.00	43.45
ATOM	145	ND2	ASN	691	30.096	9.014	−9.946	1.00	42.16
ATOM	146	C	ASN	691	32.620	7.894	−13.132	1.00	43.34
ATOM	147	O	ASN	691	31.931	7.304	−13.962	1.00	43.67
ATOM	148	N	ASN	692	33.918	8.120	−13.307	1.00	43.99
ATOM	149	CA	ASN	692	34.626	7.661	−14.499	1.00	44.50
ATOM	150	CB	ASN	692	36.045	8.233	−14.521	1.00	44.96
ATOM	151	CG	ASN	692	36.163	9.552	−13.757	1.00	45.75
ATOM	152	OD1	ASN	692	35.869	9.625	−12.558	1.00	45.86
ATOM	153	ND2	ASN	692	36.604	10.598	−14.449	1.00	45.86
ATOM	154	C	ASN	692	34.703	6.138	−14.431	1.00	44.51
ATOM	155	O	ASN	692	35.016	5.467	−15.415	1.00	44.65
ATOM	156	N	GLN	693	34.401	5.620	−13.247	1.00	44.30
ATOM	157	CA	GLN	693	34.432	4.195	−12.933	1.00	44.20
ATOM	158	CB	GLN	693	34.091	4.004	−11.452	1.00	44.34
ATOM	159	CG	GLN	693	34.453	2.664	−10.864	1.00	44.63
ATOM	160	CD	GLN	693	35.935	2.552	−10.548	1.00	44.93
ATOM	161	OE1	GLN	693	36.544	3.501	−10.055	1.00	44.97
ATOM	162	NE2	GLN	693	36.518	1.383	−10.813	1.00	44.61
ATOM	163	C	GLN	693	33.469	3.362	−13.765	1.00	43.84
ATOM	164	O	GLN	693	32.271	3.634	−13.802	1.00	44.50
ATOM	165	N	PRO	694	33.976	2.324	−14.439	1.00	43.36
ATOM	166	CD	PRO	694	35.372	1.893	−14.620	1.00	43.36
ATOM	167	CA	PRO	694	33.069	1.503	−15.238	1.00	43.02
ATOM	168	CB	PRO	694	34.021	0.607	−16.027	1.00	43.07
ATOM	169	CG	PRO	694	35.200	0.484	−15.122	1.00	43.30
ATOM	170	C	PRO	694	32.111	0.717	−14.338	1.00	42.75
ATOM	171	O	PRO	694	31.333	−0.121	−14.816	1.00	43.47
ATOM	172	N	ASP	695	32.174	0.993	−13.036	1.00	41.47
ATOM	173	CA	ASP	695	31.309	0.342	−12.056	1.00	40.30
ATOM	174	CB	ASP	695	29.858	0.406	−12.521	1.00	40.36
ATOM	175	CG	ASP	695	28.998	1.238	−11.610	1.00	40.64
ATOM	176	OD1	ASP	695	27.988	1.793	−12.085	1.00	40.36
ATOM	177	OD2	ASP	695	29.329	1.329	−10.411	1.00	41.36
ATOM	178	C	ASP	695	31.701	−1.103	−11.772	1.00	39.59
ATOM	179	O	ASP	695	32.158	−1.829	−12.661	1.00	39.66
ATOM	180	N	SER	696	31.519	−1.511	−10.523	1.00	37.97
ATOM	181	CA	SER	696	31.870	−2.854	−10.093	1.00	36.83
ATOM	182	CB	SER	696	33.334	−3.141	−10.409	1.00	36.85
ATOM	183	OG	SER	696	34.170	−2.172	−9.803	1.00	36.78
ATOM	184	C	SER	696	31.658	−2.985	−8.595	1.00	35.83
ATOM	185	O	SER	696	31.175	−2.063	−7.938	1.00	35.84
ATOM	186	N	PHE	697	32.034	−4.135	−8.058	1.00	34.43
ATOM	187	CA	PHE	697	31.886	−4.376	−6.639	1.00	33.31
ATOM	188	CB	PHE	697	31.970	−5.872	−6.353	1.00	32.81
ATOM	189	CG	PHE	697	31.755	−6.225	−4.910	1.00	32.02
ATOM	190	CD1	PHE	697	30.601	−5.839	−4.253	1.00	31.59
ATOM	191	CD2	PHE	697	32.712	−6.939	−4.207	1.00	31.69

TABLE A-continued

ATOM	192	CE1	PHE	697	30.411	−6.162	−2.913	1.00	31.45
ATOM	193	CE2	PHE	697	32.522	−7.264	−2.871	1.00	31.30
ATOM	194	CZ	PHE	697	31.375	−6.875	−2.227	1.00	30.74
ATOM	195	C	PHE	697	32.959	−3.634	−5.849	1.00	32.77
ATOM	196	O	PHE	697	32.663	−2.997	−4.846	1.00	32.24
ATOM	197	N	ALA	698	34.199	−3.701	−6.326	1.00	32.43
ATOM	198	CA	ALA	698	35.333	−3.059	−5.659	1.00	32.06
ATOM	199	CB	ALA	698	36.628	−3.462	−6.351	1.00	32.14
ATOM	200	C	ALA	698	35.252	−1.533	−5.562	1.00	31.78
ATOM	201	O	ALA	698	35.503	−0.958	−4.506	1.00	31.59
ATOM	202	N	ALA	699	34.903	−0.883	−6.663	1.00	31.20
ATOM	203	CA	ALA	699	34.799	0.569	−6.692	1.00	30.50
ATOM	204	CB	ALA	699	34.627	1.035	−8.125	1.00	30.71
ATOM	205	C	ALA	699	33.658	1.117	−5.837	1.00	30.14
ATOM	206	O	ALA	699	33.793	2.161	−5.192	1.00	29.89
ATOM	207	N	LEU	700	32.525	0.425	−5.856	1.00	29.56
ATOM	208	CA	LEU	700	31.353	0.846	−5.092	1.00	29.08
ATOM	209	CB	LEU	700	30.166	−0.054	−5.431	1.00	29.19
ATOM	210	CG	LEU	700	29.075	0.521	−6.332	1.00	30.19
ATOM	211	CD1	LEU	700	29.649	1.531	−7.321	1.00	29.81
ATOM	212	CD2	LEU	700	28.377	−0.636	−7.053	1.00	30.55
ATOM	213	C	LEU	700	31.600	0.817	−3.587	1.00	28.70
ATOM	214	O	LEU	700	31.687	1.858	−2.939	1.00	28.63
ATOM	215	N	LEU	701	31.718	−0.387	−3.045	1.00	28.11
ATOM	216	CA	LEU	701	31.944	−0.580	−1.624	1.00	28.02
ATOM	217	CB	LEU	701	32.126	−2.068	−1.325	1.00	26.80
ATOM	218	CG	LEU	701	30.785	−2.788	−1.243	1.00	26.52
ATOM	219	CD1	LEU	701	29.977	−2.199	−0.085	1.00	25.48
ATOM	220	CD2	LEU	701	30.028	−2.659	−2.562	1.00	25.47
ATOM	221	C	LEU	701	33.126	0.200	−1.079	1.00	28.03
ATOM	222	O	LEU	701	33.065	0.744	0.023	1.00	27.83
ATOM	223	N	SER	702	34.200	0.250	−1.857	1.00	28.39
ATOM	224	CA	SER	702	35.397	0.965	−1.446	1.00	28.48
ATOM	225	CB	SER	702	36.508	0.793	−2.478	1.00	28.93
ATOM	226	OG	SER	702	37.745	1.184	−1.922	1.00	30.72
ATOM	227	C	SER	702	35.078	2.440	−1.266	1.00	27.81
ATOM	228	O	SER	702	35.585	3.072	−0.345	1.00	28.06
ATOM	229	N	SER	703	34.233	2.984	−2.140	1.00	27.29
ATOM	230	CA	SER	703	33.850	4.388	−2.040	1.00	26.12
ATOM	231	CB	SER	703	33.349	4.916	−3.385	1.00	26.33
ATOM	232	OG	SER	703	31.941	5.056	−3.376	1.00	28.04
ATOM	233	C	SER	703	32.762	4.510	−0.981	1.00	25.38
ATOM	234	O	SER	703	32.637	5.543	−0.333	1.00	25.43
ATOM	235	N	LEU	704	31.975	3.453	−0.791	1.00	24.62
ATOM	236	CA	LEU	704	30.945	3.492	0.247	1.00	23.83
ATOM	237	CB	LEU	704	29.987	2.306	0.122	1.00	23.34
ATOM	238	CG	LEU	704	28.843	2.445	−0.888	1.00	22.81
ATOM	239	CD1	LEU	704	27.962	1.199	−0.844	1.00	22.05
ATOM	240	CD2	LEU	704	28.010	3.673	−0.530	1.00	22.63
ATOM	241	C	LEU	704	31.629	3.473	1.614	1.00	23.67
ATOM	242	O	LEU	704	31.212	4.171	2.537	1.00	23.27
ATOM	243	N	ASN	705	32.681	2.663	1.728	1.00	23.68
ATOM	244	CA	ASN	705	33.454	2.556	2.959	1.00	23.54
ATOM	245	CB	ASN	705	34.597	1.546	2.808	1.00	22.57
ATOM	246	CG	ASN	705	34.135	0.107	2.920	1.00	22.79
ATOM	247	OD1	ASN	705	34.865	−0.826	2.553	1.00	22.63
ATOM	248	ND2	ASN	705	32.932	−0.089	3.447	1.00	21.75
ATOM	249	C	ASN	705	34.051	3.920	3.248	1.00	23.95
ATOM	250	O	ASN	705	34.095	4.355	4.395	1.00	24.17
ATOM	251	N	GLU	706	34.513	4.599	2.204	1.00	24.44
ATOM	252	CA	GLU	706	35.110	5.907	2.402	1.00	25.29
ATOM	253	CB	GLU	706	35.729	6.452	1.118	1.00	26.16
ATOM	254	CG	GLU	706	36.404	7.788	1.340	1.00	27.89
ATOM	255	CD	GLU	706	37.478	7.726	2.428	1.00	29.25
ATOM	256	OE1	GLU	706	37.936	8.799	2.881	1.00	29.77
ATOM	257	OE2	GLU	706	37.868	6.604	2.831	1.00	30.55
ATOM	258	C	GLU	706	34.063	6.874	2.884	1.00	25.01
ATOM	259	O	GLU	706	34.352	7.747	3.694	1.00	25.76
ATOM	260	N	LEU	707	32.842	6.714	2.385	1.00	24.51
ATOM	261	CA	LEU	707	31.749	7.585	2.778	1.00	24.01
ATOM	262	CB	LEU	707	30.511	7.333	1.912	1.00	23.04
ATOM	263	CG	LEU	707	29.345	8.281	2.195	1.00	22.39
ATOM	264	CD1	LEU	707	29.746	9.740	1.906	1.00	21.36
ATOM	265	CD2	LEU	707	28.168	7.883	1.343	1.00	22.62
ATOM	266	C	LEU	707	31.382	7.379	4.230	1.00	24.28
ATOM	267	O	LEU	707	31.075	8.333	4.941	1.00	24.68
ATOM	268	N	GLY	708	31.414	6.126	4.666	1.00	24.48
ATOM	269	CA	GLY	708	31.052	5.818	6.033	1.00	24.27
ATOM	270	C	GLY	708	31.987	6.483	7.013	1.00	24.28

TABLE A-continued

ATOM	271	O	GLY	708	31.557	6.976	8.043	1.00	24.53
ATOM	272	N	GLU	709	33.271	6.488	6.688	1.00	24.50
ATOM	273	CA	GLU	709	34.278	7.094	7.548	1.00	25.04
ATOM	274	CB	GLU	709	35.676	6.727	7.037	1.00	26.02
ATOM	275	CG	GLU	709	36.846	7.291	7.830	1.00	28.27
ATOM	276	CD	GLU	709	36.963	6.712	9.238	1.00	30.06
ATOM	277	OE1	GLU	709	36.142	7.085	10.116	1.00	30.97
ATOM	278	OE2	GLU	709	37.882	5.884	9.466	1.00	30.27
ATOM	279	C	GLU	709	34.083	8.613	7.571	1.00	24.49
ATOM	280	O	GLU	709	34.176	9.240	8.624	1.00	24.26
ATOM	281	N	ARG	710	33.792	9.198	6.414	1.00	23.72
ATOM	282	CA	ARG	710	33.581	10.639	6.342	1.00	23.54
ATOM	283	CB	ARG	710	33.426	11.097	4.885	1.00	23.22
ATOM	284	CG	ARG	710	34.715	10.999	4.073	1.00	23.82
ATOM	285	CD	ARG	710	34.524	11.398	2.626	1.00	24.53
ATOM	286	NE	ARG	710	35.807	11.550	1.952	1.00	25.26
ATOM	287	CZ	ARG	710	35.967	12.064	0.737	1.00	25.57
ATOM	288	NH1	ARG	710	34.920	12.481	0.036	1.00	25.76
ATOM	289	NH2	ARG	710	37.183	12.180	0.226	1.00	26.08
ATOM	290	C	ARG	710	32.365	11.065	7.152	1.00	23.53
ATOM	291	O	ARG	710	32.404	12.074	7.867	1.00	23.75
ATOM	292	N	GLN	711	31.286	10.294	7.052	1.00	23.34
ATOM	293	CA	GLN	711	30.081	10.627	7.786	1.00	23.12
ATOM	294	CB	GLN	711	28.893	9.819	7.274	1.00	22.95
ATOM	295	CG	GLN	711	28.250	10.414	6.037	1.00	22.79
ATOM	296	CD	GLN	711	26.952	9.724	5.655	1.00	23.04
ATOM	297	OE1	GLN	711	26.165	9.329	6.519	1.00	23.05
ATOM	298	NE2	GLN	711	26.715	9.587	4.356	1.00	22.64
ATOM	299	C	GLN	711	30.285	10.400	9.273	1.00	23.07
ATOM	300	O	GLN	711	29.672	11.072	10.092	1.00	22.74
ATOM	301	N	LEU	712	31.159	9.458	9.617	1.00	23.12
ATOM	302	CA	LEU	712	31.459	9.179	11.018	1.00	22.87
ATOM	303	CB	LEU	712	32.475	8.046	11.131	1.00	22.35
ATOM	304	CG	LEU	712	33.072	7.933	12.536	1.00	22.63
ATOM	305	CD1	LEU	712	31.940	7.890	13.580	1.00	22.01
ATOM	306	CD2	LEU	712	33.969	6.701	12.615	1.00	22.12
ATOM	307	C	LEU	712	32.029	10.452	11.651	1.00	23.01
ATOM	308	O	LEU	712	31.681	10.822	12.784	1.00	22.93
ATOM	309	N	VAL	713	32.907	11.119	10.907	1.00	22.87
ATOM	310	CA	VAL	713	33.498	12.362	11.374	1.00	22.95
ATOM	311	CB	VAL	713	34.344	13.042	10.255	1.00	23.84
ATOM	312	CG1	VAL	713	34.691	14.487	10.648	1.00	22.62
ATOM	313	CG2	VAL	713	35.613	12.226	9.988	1.00	23.07
ATOM	314	C	VAL	713	32.384	13.319	11.796	1.00	22.67
ATOM	315	O	VAL	713	32.475	13.957	12.847	1.00	22.99
ATOM	316	N	HIS	714	31.333	13.404	10.981	1.00	22.28
ATOM	317	CA	HIS	714	30.211	14.302	11.266	1.00	22.20
ATOM	318	CB	HIS	714	29.444	14.647	9.980	1.00	22.70
ATOM	319	CG	HIS	714	30.235	15.456	9.001	1.00	22.67
ATOM	320	CD2	HIS	714	30.626	16.751	9.026	1.00	22.73
ATOM	321	ND1	HIS	714	30.735	14.928	7.830	1.00	23.24
ATOM	322	CE1	HIS	714	31.401	15.863	7.175	1.00	22.99
ATOM	323	NE2	HIS	714	31.350	16.979	7.880	1.00	23.40
ATOM	324	C	HIS	714	29.215	13.816	12.310	1.00	21.81
ATOM	325	O	HIS	714	28.598	14.627	12.994	1.00	22.68
ATOM	326	N	VAL	715	29.031	12.509	12.429	1.00	21.29
ATOM	327	CA	VAL	715	28.099	11.992	13.423	1.00	20.49
ATOM	328	CB	VAL	715	27.785	10.476	13.188	1.00	20.64
ATOM	329	CG1	VAL	715	27.000	9.897	14.361	1.00	20.52
ATOM	330	CG2	VAL	715	26.960	10.318	11.921	1.00	19.86
ATOM	331	C	VAL	715	28.697	12.211	14.808	1.00	20.28
ATOM	332	O	VAL	715	27.975	12.476	15.759	1.00	20.31
ATOM	333	N	VAL	716	30.020	12.119	14.917	1.00	19.96
ATOM	334	CA	VAL	716	30.680	12.331	16.203	1.00	19.21
ATOM	335	CB	VAL	716	32.214	12.047	16.125	1.00	18.74
ATOM	336	CG1	VAL	716	32.889	12.440	17.427	1.00	17.72
ATOM	337	CG2	VAL	716	32.457	10.566	15.849	1.00	18.72
ATOM	338	C	VAL	716	30.463	13.766	16.693	1.00	19.14
ATOM	339	O	VAL	716	30.008	13.976	17.806	1.00	19.96
ATOM	340	N	LYS	717	30.788	14.748	15.865	1.00	18.52
ATOM	341	CA	LYS	717	30.620	16.139	16.256	1.00	18.43
ATOM	342	CB	LYS	717	31.233	17.074	15.181	1.00	19.20
ATOM	343	CG	LYS	717	32.760	17.074	15.191	1.00	20.49
ATOM	344	CD	LYS	717	33.397	17.385	13.835	1.00	22.01
ATOM	345	CE	LYS	717	33.242	18.841	13.423	1.00	23.42
ATOM	346	NZ	LYS	717	34.179	19.195	12.301	1.00	23.88
ATOM	347	C	LYS	717	29.149	16.462	16.484	1.00	17.83
ATOM	348	O	LYS	717	28.809	17.280	17.330	1.00	18.37
ATOM	349	N	TRP	718	28.276	15.806	15.733	1.00	17.26

TABLE A-continued

ATOM	350	CA	TRP	718	26.844	16.032	15.863	1.00	16.62
ATOM	351	CB	TRP	718	26.096	15.283	14.747	1.00	15.39
ATOM	352	CG	TRP	718	24.636	15.139	14.991	1.00	13.87
ATOM	353	CD2	TRP	718	23.955	13.949	15.416	1.00	13.60
ATOM	354	CE2	TRP	718	22.583	14.272	15.530	1.00	13.27
ATOM	355	CE3	TRP	718	24.373	12.639	15.710	1.00	12.87
ATOM	356	CD1	TRP	718	23.683	16.105	14.871	1.00	13.87
ATOM	357	NE1	TRP	718	22.444	15.594	15.191	1.00	13.38
ATOM	358	CZ2	TRP	718	21.622	13.334	15.929	1.00	12.65
ATOM	359	CZ3	TRP	718	23.417	11.705	16.106	1.00	12.99
ATOM	360	CH2	TRP	718	22.054	12.060	16.212	1.00	12.90
ATOM	361	C	TRP	718	26.378	15.565	17.243	1.00	16.98
ATOM	362	O	TRP	718	25.760	16.319	18.012	1.00	15.96
ATOM	363	N	ALA	719	26.692	14.312	17.549	1.00	17.83
ATOM	364	CA	ALA	719	26.326	13.721	18.819	1.00	18.17
ATOM	365	CB	ALA	719	26.835	12.287	18.887	1.00	18.35
ATOM	366	C	ALA	719	26.891	14.534	19.978	1.00	18.72
ATOM	367	O	ALA	719	26.148	14.907	20.886	1.00	18.90
ATOM	368	N	LYS	720	28.195	14.822	19.933	1.00	19.47
ATOM	369	CA	LYS	720	28.870	15.570	21.003	1.00	20.52
ATOM	370	CB	LYS	720	30.358	15.793	20.663	1.00	21.24
ATOM	371	CG	LYS	720	31.257	14.541	20.709	1.00	21.82
ATOM	372	CD	LYS	720	31.657	14.170	22.135	1.00	22.50
ATOM	373	CE	LYS	720	32.458	12.850	22.217	1.00	23.14
ATOM	374	NZ	LYS	720	33.777	12.847	21.507	1.00	22.87
ATOM	375	C	LYS	720	28.215	16.912	21.316	1.00	20.70
ATOM	376	O	LYS	720	28.338	17.418	22.429	1.00	21.08
ATOM	377	N	ALA	721	27.520	17.487	20.338	1.00	20.77
ATOM	378	CA	ALA	721	26.844	18.760	20.549	1.00	20.21
ATOM	379	CB	ALA	721	26.944	19.614	19.300	1.00	20.14
ATOM	380	C	ALA	721	25.378	18.592	20.944	1.00	20.23
ATOM	381	O	ALA	721	24.664	19.582	21.088	1.00	20.39
ATOM	382	N	LEU	722	24.925	17.352	21.116	1.00	20.40
ATOM	383	CA	LEU	722	23.536	17.103	21.497	1.00	21.36
ATOM	384	CB	LEU	722	23.166	15.627	21.282	1.00	21.25
ATOM	385	CG	LEU	722	22.682	15.273	19.866	1.00	21.90
ATOM	386	CD1	LEU	722	22.656	13.756	19.658	1.00	20.78
ATOM	387	CD2	LEU	722	21.312	15.893	19.632	1.00	21.16
ATOM	388	C	LEU	722	23.228	17.497	22.944	1.00	22.09
ATOM	389	O	LEU	722	24.085	17.429	23.826	1.00	22.42
ATOM	390	N	PRO	723	21.996	17.941	23.202	1.00	22.76
ATOM	391	CD	PRO	723	20.936	18.384	22.273	1.00	22.83
ATOM	392	CA	PRO	723	21.688	18.318	24.586	1.00	23.30
ATOM	393	CB	PRO	723	20.256	18.860	24.490	1.00	23.27
ATOM	394	CG	PRO	723	20.207	19.447	23.086	1.00	22.63
ATOM	395	C	PRO	723	21.787	17.131	25.539	1.00	23.84
ATOM	396	O	PRO	723	21.100	16.132	25.360	1.00	23.75
ATOM	397	N	GLY	724	22.658	17.236	26.537	1.00	24.31
ATOM	398	CA	GLY	724	22.788	16.172	27.524	1.00	24.68
ATOM	399	C	GLY	724	23.653	14.966	27.180	1.00	25.55
ATOM	400	O	GLY	724	23.896	14.114	28.040	1.00	25.10
ATOM	401	N	PHE	725	24.113	14.876	25.935	1.00	25.87
ATOM	402	CA	PHE	725	24.950	13.757	25.535	1.00	26.37
ATOM	403	CB	PHE	725	25.373	13.898	24.077	1.00	25.67
ATOM	404	CG	PHE	725	26.116	12.706	23.560	1.00	25.20
ATOM	405	CD1	PHE	725	25.428	11.572	23.140	1.00	24.92
ATOM	406	CD2	PHE	725	27.505	12.689	23.546	1.00	24.47
ATOM	407	CE1	PHE	725	26.117	10.429	22.712	1.00	24.76
ATOM	408	CE2	PHE	725	28.198	11.554	23.121	1.00	24.71
ATOM	409	CZ	PHE	725	27.498	10.422	22.704	1.00	24.40
ATOM	410	C	PHE	725	26.202	13.693	26.412	1.00	27.46
ATOM	411	O	PHE	725	26.593	12.622	26.880	1.00	27.31
ATOM	412	N	ARG	726	26.830	14.851	26.618	1.00	28.62
ATOM	413	CA	ARG	726	28.039	14.951	27.430	1.00	29.72
ATOM	414	CB	ARG	726	28.557	16.389	27.416	1.00	30.89
ATOM	415	CG	ARG	726	29.272	16.781	26.134	1.00	32.52
ATOM	416	CD	ARG	726	30.536	15.963	25.976	1.00	34.40
ATOM	417	NE	ARG	726	31.176	15.731	27.271	1.00	35.49
ATOM	418	CZ	ARG	726	32.382	15.196	27.428	1.00	36.20
ATOM	419	NH1	ARG	726	32.878	15.024	28.649	1.00	36.46
ATOM	420	NH2	ARG	726	33.098	14.846	26.365	1.00	36.56
ATOM	421	C	ARG	726	27.855	14.480	28.879	1.00	29.93
ATOM	422	O	ARG	726	28.825	14.378	29.636	1.00	29.51
ATOM	423	N	ASN	727	26.613	14.212	29.274	1.00	29.89
ATOM	424	CA	ASN	727	26.374	13.717	30.616	1.00	30.24
ATOM	425	CB	ASN	727	24.891	13.782	30.968	1.00	30.69
ATOM	426	CG	ASN	727	24.511	15.087	31.645	1.00	31.99
ATOM	427	OD1	ASN	727	23.357	15.539	31.562	1.00	32.19
ATOM	428	ND2	ASN	727	25.479	15.699	32.339	1.00	32.26

TABLE A-continued

ATOM	429	C	ASN	727	26.856	12.279	30.644	1.00	30.26
ATOM	430	O	ASN	727	27.412	11.835	31.632	1.00	30.96
ATOM	431	N	LEU	728	26.659	11.562	29.541	1.00	30.22
ATOM	432	CA	LEU	728	27.080	10.167	29.444	1.00	30.16
ATOM	433	CB	LEU	728	26.884	9.629	28.020	1.00	29.53
ATOM	434	CG	LEU	728	25.469	9.476	27.448	1.00	29.44
ATOM	435	CD1	LEU	728	25.558	9.204	25.960	1.00	29.24
ATOM	436	CD2	LEU	728	24.738	8.351	28.144	1.00	29.16
ATOM	437	C	LEU	728	28.545	10.049	29.800	1.00	30.48
ATOM	438	O	LEU	728	29.315	10.995	29.624	1.00	30.21
ATOM	439	N	HIS	729	28.925	8.884	30.302	1.00	30.85
ATOM	440	CA	HIS	729	30.310	8.638	30.643	1.00	31.47
ATOM	441	CB	HIS	729	30.453	7.268	31.327	1.00	31.98
ATOM	442	CG	HIS	729	31.872	6.884	31.611	1.00	32.66
ATOM	443	CD2	HIS	729	32.844	6.406	30.796	1.00	32.89
ATOM	444	ND1	HIS	729	32.461	7.060	32.845	1.00	33.17
ATOM	445	CE1	HIS	729	33.735	6.713	32.777	1.00	33.16
ATOM	446	NE2	HIS	729	33.994	6.314	31.545	1.00	33.32
ATOM	447	C	HIS	729	31.105	8.650	29.326	1.00	31.63
ATOM	448	O	HIS	729	30.583	8.279	28.273	1.00	31.40
ATOM	449	N	VAL	730	32.359	9.078	29.400	1.00	31.76
ATOM	450	CA	VAL	730	33.250	9.133	28.250	1.00	32.24
ATOM	451	CB	VAL	730	34.731	9.282	28.713	1.00	32.50
ATOM	452	CG1	VAL	730	35.658	9.405	27.508	1.00	32.05
ATOM	453	CG2	VAL	730	34.872	10.489	29.632	1.00	32.57
ATOM	454	C	VAL	730	33.161	7.860	27.408	1.00	33.08
ATOM	455	O	VAL	730	33.019	7.919	26.181	1.00	33.09
ATOM	456	N	ASP	731	33.268	6.715	28.085	1.00	33.39
ATOM	457	CA	ASP	731	33.246	5.400	27.449	1.00	33.76
ATOM	458	CB	ASP	731	33.558	4.322	28.491	1.00	34.69
ATOM	459	CG	ASP	731	34.969	4.433	29.033	1.00	36.10
ATOM	460	OD1	ASP	731	35.190	4.055	30.214	1.00	36.28
ATOM	461	OD2	ASP	731	35.856	4.892	28.270	1.00	36.30
ATOM	462	C	ASP	731	31.946	5.054	26.738	1.00	33.23
ATOM	463	O	ASP	731	31.971	4.444	25.674	1.00	33.20
ATOM	464	N	ASP	732	30.822	5.428	27.344	1.00	32.63
ATOM	465	CA	ASP	732	29.502	5.172	26.784	1.00	31.98
ATOM	466	CB	ASP	732	28.418	5.345	27.861	1.00	32.27
ATOM	467	CG	ASP	732	28.566	4.358	29.018	1.00	32.72
ATOM	468	OD1	ASP	732	29.043	3.223	28.783	1.00	33.04
ATOM	469	OD2	ASP	732	28.185	4.711	30.159	1.00	32.04
ATOM	470	C	ASP	732	29.203	6.107	25.606	1.00	31.68
ATOM	471	O	ASP	732	28.410	5.768	24.722	1.00	31.75
ATOM	472	N	GLN	733	29.826	7.285	25.604	1.00	30.91
ATOM	473	CA	GLN	733	29.631	8.249	24.526	1.00	30.18
ATOM	474	CB	GLN	733	30.481	9.514	24.740	1.00	30.21
ATOM	475	CG	GLN	733	30.198	10.316	25.996	1.00	31.08
ATOM	476	CD	GLN	733	31.070	11.577	26.086	1.00	32.11
ATOM	477	OE1	GLN	733	32.282	11.528	25.855	1.00	33.33
ATOM	478	NE2	GLN	733	30.458	12.699	26.429	1.00	31.97
ATOM	479	C	GLN	733	30.049	7.610	23.202	1.00	29.54
ATOM	480	O	GLN	733	29.263	7.553	22.258	1.00	28.86
ATOM	481	N	MET	734	31.287	7.124	23.146	1.00	29.26
ATOM	482	CA	MET	734	31.818	6.505	21.929	1.00	29.62
ATOM	483	CB	MET	734	33.347	6.432	21.993	1.00	31.24
ATOM	484	CG	MET	734	34.044	7.704	21.512	1.00	34.06
ATOM	485	SD	MET	734	33.906	8.000	19.707	1.00	37.92
ATOM	486	CE	MET	734	35.327	7.026	19.055	1.00	36.58
ATOM	487	C	MET	734	31.253	5.124	21.588	1.00	28.35
ATOM	488	O	MET	734	31.280	4.722	20.428	1.00	28.45
ATOM	489	N	ALA	735	30.765	4.398	22.589	1.00	26.73
ATOM	490	CA	ALA	735	30.181	3.081	22.347	1.00	26.10
ATOM	491	CB	ALA	735	30.003	2.310	23.669	1.00	26.35
ATOM	492	C	ALA	735	28.825	3.298	21.676	1.00	24.76
ATOM	493	O	ALA	735	28.531	2.705	20.653	1.00	24.32
ATOM	494	N	VAL	736	28.012	4.160	22.272	1.00	24.18
ATOM	495	CA	VAL	736	26.704	4.487	21.734	1.00	23.42
ATOM	496	CB	VAL	736	26.022	5.579	22.592	1.00	23.57
ATOM	497	CG1	VAL	736	25.268	6.570	21.713	1.00	23.51
ATOM	498	CG2	VAL	736	25.071	4.932	23.573	1.00	23.24
ATOM	499	C	VAL	736	26.895	4.985	20.301	1.00	23.21
ATOM	500	O	VAL	736	26.228	4.516	19.375	1.00	23.40
ATOM	501	N	ILE	737	27.827	5.917	20.129	1.00	22.03
ATOM	502	CA	ILE	737	28.117	6.479	18.816	1.00	21.62
ATOM	503	CB	ILE	737	29.228	7.550	18.883	1.00	20.18
ATOM	504	CG2	ILE	737	29.787	7.795	17.510	1.00	20.01
ATOM	505	CG1	ILE	737	28.685	8.855	19.468	1.00	19.45
ATOM	506	CD1	ILE	737	29.770	9.894	19.681	1.00	18.31
ATOM	507	C	ILE	737	28.550	5.428	17.795	1.00	22.21

TABLE A-continued

ATOM	508	O	ILE	737	28.040	5.403	16.678	1.00	22.12
ATOM	509	N	GLN	738	29.502	4.576	18.161	1.00	22.07
ATOM	510	CA	GLN	738	29.949	3.572	17.225	1.00	22.29
ATOM	511	CB	GLN	738	31.255	2.943	17.701	1.00	23.58
ATOM	512	CG	GLN	738	32.411	3.940	17.806	1.00	23.70
ATOM	513	CD	GLN	738	33.698	3.287	18.280	1.00	23.85
ATOM	514	OE1	GLN	738	33.682	2.436	19.165	1.00	24.48
ATOM	515	NE2	GLN	738	34.819	3.695	17.702	1.00	23.64
ATOM	516	C	GLN	738	28.891	2.499	16.970	1.00	21.96
ATOM	517	O	GLN	738	28.771	2.037	15.838	1.00	22.01
ATOM	518	N	TYR	739	28.112	2.125	17.990	1.00	20.77
ATOM	519	CA	TYR	739	27.073	1.115	17.800	1.00	19.98
ATOM	520	CB	TYR	739	26.468	0.627	19.120	1.00	20.07
ATOM	521	CG	TYR	739	27.407	0.014	20.133	1.00	20.08
ATOM	522	CD1	TYR	739	28.400	−0.886	19.754	1.00	20.37
ATOM	523	CE1	TYR	739	29.221	−1.484	20.703	1.00	21.09
ATOM	524	CD2	TYR	739	27.254	0.295	21.485	1.00	19.66
ATOM	525	CE2	TYR	739	28.065	−0.301	22.444	1.00	20.66
ATOM	526	CZ	TYR	739	29.050	−1.182	22.049	1.00	20.98
ATOM	527	OH	TYR	739	29.902	−1.706	22.998	1.00	22.42
ATOM	528	C	TYR	739	25.897	1.621	16.964	1.00	19.75
ATOM	529	O	TYR	739	25.249	0.845	16.250	1.00	19.75
ATOM	530	N	SER	740	25.592	2.910	17.063	1.00	18.92
ATOM	531	CA	SER	740	24.450	3.432	16.316	1.00	18.02
ATOM	532	CB	SER	740	23.648	4.420	17.181	1.00	18.07
ATOM	533	OG	SER	740	24.292	5.666	17.302	1.00	18.74
ATOM	534	C	SER	740	24.831	4.069	14.984	1.00	16.97
ATOM	535	O	SER	740	23.969	4.442	14.198	1.00	16.64
ATOM	536	N	TRP	741	26.129	4.150	14.741	1.00	16.05
ATOM	537	CA	TRP	741	26.689	4.725	13.529	1.00	16.05
ATOM	538	CB	TRP	741	28.189	4.350	13.492	1.00	17.09
ATOM	539	CG	TRP	741	29.006	4.764	12.306	1.00	19.02
ATOM	540	CD2	TRP	741	30.294	4.238	11.932	1.00	20.22
ATOM	541	CE2	TRP	741	30.662	4.848	10.713	1.00	20.50
ATOM	542	CE3	TRP	741	31.170	3.302	12.512	1.00	20.91
ATOM	543	CD1	TRP	741	28.667	5.657	11.335	1.00	19.78
ATOM	544	NE1	TRP	741	29.657	5.711	10.368	1.00	20.54
ATOM	545	CZ2	TRP	741	31.864	4.554	10.057	1.00	22.12
ATOM	546	CZ3	TRP	741	32.363	3.006	11.865	1.00	21.59
ATOM	547	CH2	TRP	741	32.702	3.632	10.643	1.00	22.46
ATOM	548	C	TRP	741	25.911	4.300	12.257	1.00	15.45
ATOM	549	O	TRP	741	25.401	5.150	11.526	1.00	14.12
ATOM	550	N	MET	742	25.791	2.998	12.020	1.00	15.44
ATOM	551	CA	MET	742	25.090	2.466	10.845	1.00	15.95
ATOM	552	CB	MET	742	25.100	0.932	10.863	1.00	16.16
ATOM	553	CG	MET	742	24.447	0.326	9.646	1.00	16.45
ATOM	554	SD	MET	742	25.477	0.591	8.187	1.00	17.11
ATOM	555	CE	MET	742	26.513	−0.885	8.352	1.00	16.44
ATOM	556	C	MET	742	23.635	2.924	10.665	1.00	16.26
ATOM	557	O	MET	742	23.259	3.451	9.597	1.00	16.31
ATOM	558	N	GLY	743	22.826	2.683	11.698	1.00	16.23
ATOM	559	CA	GLY	743	21.422	3.049	11.682	1.00	15.96
ATOM	560	C	GLY	743	21.210	4.531	11.437	1.00	16.26
ATOM	561	O	GLY	743	20.346	4.935	10.645	1.00	16.71
ATOM	562	N	LEU	744	21.990	5.351	12.123	1.00	15.86
ATOM	563	CA	LEU	744	21.888	6.791	11.952	1.00	15.37
ATOM	564	CB	LEU	744	22.935	7.512	12.805	1.00	14.98
ATOM	565	CG	LEU	744	22.689	7.629	14.308	1.00	15.65
ATOM	566	CD1	LEU	744	23.916	8.274	14.960	1.00	16.45
ATOM	567	CD2	LEU	744	21.447	8.482	14.581	1.00	14.77
ATOM	568	C	LEU	744	22.100	7.146	10.483	1.00	15.33
ATOM	569	O	LEU	744	21.350	7.939	9.918	1.00	14.53
ATOM	570	N	MET	745	23.121	6.551	9.874	1.00	15.35
ATOM	571	CA	MET	745	23.420	6.819	8.474	1.00	16.27
ATOM	572	CB	MET	745	24.723	6.138	8.046	1.00	17.33
ATOM	573	CG	MET	745	25.987	6.659	8.711	1.00	19.23
ATOM	574	SD	MET	745	27.427	6.326	7.658	1.00	22.31
ATOM	575	CE	MET	745	27.320	4.566	7.432	1.00	20.16
ATOM	576	C	MET	745	22.297	6.350	7.540	1.00	16.24
ATOM	577	O	MET	745	21.939	7.060	6.596	1.00	16.31
ATOM	578	N	VAL	746	21.755	5.156	7.804	1.00	15.42
ATOM	579	CA	VAL	746	20.685	4.615	6.981	1.00	14.36
ATOM	580	CB	VAL	746	20.250	3.215	7.462	1.00	13.88
ATOM	581	CG1	VAL	746	18.936	2.830	6.808	1.00	13.61
ATOM	582	CG2	VAL	746	21.310	2.198	7.121	1.00	13.23
ATOM	583	C	VAL	746	19.474	5.532	7.025	1.00	14.30
ATOM	584	O	VAL	746	18.894	5.835	5.998	1.00	14.06
ATOM	585	N	PHE	747	19.102	5.959	8.229	1.00	14.31
ATOM	586	CA	PHE	747	17.953	6.831	8.433	1.00	14.49

TABLE A-continued

ATOM	587	CB	PHE	747	17.748	7.074	9.923	1.00	13.20
ATOM	588	CG	PHE	747	16.425	7.677	10.263	1.00	12.24
ATOM	589	CD1	PHE	747	15.247	6.951	10.089	1.00	11.83
ATOM	590	CD2	PHE	747	16.348	8.954	10.802	1.00	12.05
ATOM	591	CE1	PHE	747	14.017	7.491	10.450	1.00	11.38
ATOM	592	CE2	PHE	747	15.120	9.498	11.168	1.00	11.97
ATOM	593	CZ	PHE	747	13.951	8.765	10.991	1.00	10.82
ATOM	594	C	PHE	747	18.094	8.180	7.715	1.00	15.24
ATOM	595	O	PHE	747	17.192	8.590	6.994	1.00	15.13
ATOM	596	N	ALA	748	19.211	8.870	7.930	1.00	15.97
ATOM	597	CA	ALA	748	19.445	10.154	7.274	1.00	17.37
ATOM	598	CB	ALA	748	20.765	10.746	7.728	1.00	15.48
ATOM	599	C	ALA	748	19.460	9.940	5.758	1.00	18.41
ATOM	600	O	ALA	748	18.875	10.702	4.998	1.00	19.17
ATOM	601	N	MET	749	20.120	8.882	5.323	1.00	19.85
ATOM	602	CA	MET	749	20.190	8.612	3.909	1.00	21.36
ATOM	603	CB	MET	749	21.056	7.388	3.661	1.00	20.95
ATOM	604	CG	MET	749	21.368	7.151	2.206	1.00	23.14
ATOM	605	SD	MET	749	20.021	6.300	1.350	1.00	24.54
ATOM	606	CE	MET	749	20.381	4.591	1.837	1.00	23.82
ATOM	607	C	MET	749	18.762	8.415	3.395	1.00	22.45
ATOM	608	O	MET	749	18.405	8.880	2.305	1.00	21.89
ATOM	609	N	GLY	750	17.938	7.740	4.193	1.00	23.36
ATOM	610	CA	GLY	750	16.562	7.522	3.787	1.00	23.69
ATOM	611	C	GLY	750	15.934	8.874	3.507	1.00	24.41
ATOM	612	O	GLY	750	15.329	9.091	2.451	1.00	23.64
ATOM	613	N	TRP	751	16.097	9.793	4.461	1.00	25.13
ATOM	614	CA	TRP	751	15.559	11.144	4.342	1.00	25.53
ATOM	615	CB	TRP	751	15.937	11.957	5.570	1.00	25.52
ATOM	616	CG	TRP	751	15.490	13.393	5.533	1.00	24.81
ATOM	617	CD2	TRP	751	14.156	13.886	5.715	1.00	24.48
ATOM	618	CE2	TRP	751	14.223	15.295	5.669	1.00	24.36
ATOM	619	CE3	TRP	751	12.911	13.273	5.913	1.00	24.15
ATOM	620	CD1	TRP	751	16.283	14.488	5.380	1.00	24.77
ATOM	621	NE1	TRP	751	15.532	15.635	5.464	1.00	24.45
ATOM	622	CZ2	TRP	751	13.096	16.104	5.816	1.00	24.20
ATOM	623	CZ3	TRP	751	11.794	14.072	6.058	1.00	24.68
ATOM	624	CH2	TRP	751	11.893	15.481	6.009	1.00	24.71
ATOM	625	C	TRP	751	16.068	11.846	3.085	1.00	26.37
ATOM	626	O	TRP	751	15.279	12.381	2.308	1.00	26.71
ATOM	627	N	ARG	752	17.384	11.850	2.890	1.00	27.04
ATOM	628	CA	ARG	752	17.963	12.478	1.713	1.00	27.72
ATOM	629	CB	ARG	752	19.476	12.286	1.672	1.00	26.90
ATOM	630	CG	ARG	752	20.229	13.200	2.598	1.00	25.98
ATOM	631	CD	ARG	752	21.661	13.368	2.123	1.00	25.78
ATOM	632	NE	ARG	752	22.336	12.086	1.971	1.00	24.53
ATOM	633	CZ	ARG	752	22.620	11.278	2.986	1.00	24.29
ATOM	634	NH1	ARG	752	22.286	11.628	4.222	1.00	23.93
ATOM	635	NH2	ARG	752	23.237	10.127	2.764	1.00	23.51
ATOM	636	C	ARG	752	17.373	11.933	0.427	1.00	28.66
ATOM	637	O	ARG	752	17.107	12.694	−0.508	1.00	29.23
ATOM	638	N	SER	753	17.169	10.620	0.367	1.00	29.64
ATOM	639	CA	SER	753	16.612	10.015	−0.836	1.00	30.86
ATOM	640	CB	SER	753	16.626	8.485	−0.739	1.00	30.75
ATOM	641	OG	SER	753	17.950	7.982	−0.831	1.00	30.65
ATOM	642	C	SER	753	15.196	10.508	−1.049	1.00	31.73
ATOM	643	O	SER	753	14.681	10.498	−2.162	1.00	31.89
ATOM	644	N	PHE	754	14.578	10.951	0.034	1.00	33.09
ATOM	645	CA	PHE	754	13.220	11.457	−0.006	1.00	34.65
ATOM	646	CB	PHE	754	12.604	11.394	1.391	1.00	34.66
ATOM	647	CG	PHE	754	11.246	12.019	1.478	1.00	35.49
ATOM	648	CD1	PHE	754	10.165	11.463	0.799	1.00	35.64
ATOM	649	CD2	PHE	754	11.051	13.185	2.209	1.00	35.56
ATOM	650	CE1	PHE	754	8.913	12.061	0.845	1.00	35.75
ATOM	651	CE2	PHE	754	9.802	13.792	2.264	1.00	35.98
ATOM	652	CZ	PHE	754	8.732	13.232	1.581	1.00	36.01
ATOM	653	C	PHE	754	13.154	12.899	−0.519	1.00	35.79
ATOM	654	O	PHE	754	12.448	13.193	−1.481	1.00	35.70
ATOM	655	N	THR	755	13.896	13.789	0.133	1.00	37.07
ATOM	656	CA	THR	755	13.904	15.204	−0.219	1.00	38.07
ATOM	657	CB	THR	755	14.561	16.051	0.890	1.00	37.76
ATOM	658	OG1	THR	755	15.981	15.846	0.877	1.00	38.00
ATOM	659	CG2	THR	755	14.019	15.656	2.243	1.00	37.83
ATOM	660	C	THR	755	14.626	15.516	−1.521	1.00	38.94
ATOM	661	O	THR	755	14.855	16.684	−1.834	1.00	39.37
ATOM	662	N	ASN	756	14.995	14.487	−2.275	1.00	39.70
ATOM	663	CA	ASN	756	15.693	14.712	−3.533	1.00	40.27
ATOM	664	CB	ASN	756	17.194	14.427	−3.369	1.00	40.38
ATOM	665	CG	ASN	756	17.888	15.424	−2.434	1.00	40.95

TABLE A-continued

ATOM	666	OD1	ASN	756	17.610	15.469	−1.237	1.00	41.37
ATOM	667	ND2	ASN	756	18.792	16.229	−2.986	1.00	41.31
ATOM	668	C	ASN	756	15.128	13.904	−4.702	1.00	40.62
ATOM	669	O	ASN	756	14.494	14.460	−5.599	1.00	40.90
ATOM	670	N	VAL	757	15.337	12.594	−4.687	1.00	41.04
ATOM	671	CA	VAL	757	14.869	11.743	−5.776	1.00	41.30
ATOM	672	CB	VAL	757	15.939	10.680	−6.104	1.00	41.48
ATOM	673	CG1	VAL	757	17.218	11.363	−6.562	1.00	41.53
ATOM	674	CG2	VAL	757	16.226	9.835	−4.878	1.00	41.39
ATOM	675	C	VAL	757	13.529	11.051	−5.518	1.00	41.34
ATOM	676	O	VAL	757	13.206	10.046	−6.154	1.00	41.09
ATOM	677	N	ASN	758	12.747	11.597	−4.593	1.00	41.49
ATOM	678	CA	ASN	758	11.455	11.012	−4.246	1.00	41.40
ATOM	679	CB	ASN	758	10.433	11.290	−5.346	1.00	41.86
ATOM	680	CG	ASN	758	9.848	12.682	−5.251	1.00	42.34
ATOM	681	OD1	ASN	758	9.032	12.968	−4.370	1.00	42.45
ATOM	682	ND2	ASN	758	10.269	13.561	−6.153	1.00	42.55
ATOM	683	C	ASN	758	11.548	9.511	−3.993	1.00	41.14
ATOM	684	O	ASN	758	10.546	8.794	−4.062	1.00	41.19
ATOM	685	N	SER	759	12.760	9.043	−3.716	1.00	40.61
ATOM	686	CA	SER	759	13.003	7.639	−3.418	1.00	40.58
ATOM	687	CB	SER	759	11.925	7.113	−2.462	1.00	40.93
ATOM	688	OG	SER	759	11.878	7.895	−1.277	1.00	41.37
ATOM	689	C	SER	759	13.114	6.704	−4.616	1.00	40.19
ATOM	690	O	SER	759	13.004	5.490	−4.459	1.00	40.32
ATOM	691	N	ARG	760	13.320	7.255	−5.809	1.00	39.83
ATOM	692	CA	ARG	760	13.482	6.412	−6.996	1.00	39.13
ATOM	693	CB	ARG	760	13.278	7.220	−8.289	1.00	40.09
ATOM	694	CG	ARG	760	13.929	6.590	−9.533	1.00	41.59
ATOM	695	CD	ARG	760	13.150	6.877	−10.827	1.00	42.76
ATOM	696	NE	ARG	760	13.856	6.452	−12.047	1.00	44.10
ATOM	697	CZ	ARG	760	14.317	5.221	−12.290	1.00	44.02
ATOM	698	NH1	ARG	760	14.169	4.244	−11.402	1.00	44.29
ATOM	699	NH2	ARG	760	14.926	4.966	−13.437	1.00	44.11
ATOM	700	C	ARG	760	14.897	5.843	−6.951	1.00	37.86
ATOM	701	O	ARG	760	15.200	4.841	−7.603	1.00	37.94
ATOM	702	N	MET	761	15.760	6.489	−6.169	1.00	36.18
ATOM	703	CA	MET	761	17.144	6.040	−6.030	1.00	34.54
ATOM	704	CB	MET	761	18.026	6.693	−7.095	1.00	34.81
ATOM	705	CG	MET	761	17.649	6.378	−8.531	1.00	35.67
ATOM	706	SD	MET	761	18.836	7.089	−9.710	1.00	35.66
ATOM	707	CE	MET	761	18.291	8.796	−9.734	1.00	35.50
ATOM	708	C	MET	761	17.727	6.352	−4.652	1.00	32.75
ATOM	709	O	MET	761	17.347	7.329	−4.009	1.00	32.64
ATOM	710	N	LEU	762	18.661	5.521	−4.211	1.00	30.58
ATOM	711	CA	LEU	762	19.309	5.728	−2.924	1.00	28.84
ATOM	712	CB	LEU	762	19.967	4.435	−2.457	1.00	28.33
ATOM	713	CG	LEU	762	19.019	3.248	−2.303	1.00	28.15
ATOM	714	CD1	LEU	762	19.810	2.045	−1.847	1.00	28.12
ATOM	715	CD2	LEU	762	17.924	3.575	−1.308	1.00	27.94
ATOM	716	C	LEU	762	20.356	6.838	−3.040	1.00	27.76
ATOM	717	O	LEU	762	21.341	6.713	−3.779	1.00	27.12
ATOM	718	N	TYR	763	20.135	7.921	−2.302	1.00	26.72
ATOM	719	CA	TYR	763	21.041	9.071	−2.318	1.00	26.03
ATOM	720	CB	TYR	763	20.224	10.355	−2.181	1.00	26.73
ATOM	721	CG	TYR	763	20.832	11.570	−2.836	1.00	28.00
ATOM	722	CD1	TYR	763	20.532	11.894	−4.159	1.00	28.78
ATOM	723	CE1	TYR	763	21.064	13.037	−4.764	1.00	29.17
ATOM	724	CD2	TYR	763	21.686	12.414	−2.131	1.00	28.81
ATOM	725	CE2	TYR	763	22.226	13.561	−2.729	1.00	29.70
ATOM	726	CZ	TYR	763	21.907	13.865	−4.045	1.00	29.56
ATOM	727	OH	TYR	763	22.410	15.005	−4.629	1.00	30.24
ATOM	728	C	TYR	763	22.074	9.000	−1.180	1.00	25.05
ATOM	729	O	TYR	763	21.886	9.607	−0.130	1.00	24.70
ATOM	730	N	PHE	764	23.154	8.253	−1.386	1.00	23.85
ATOM	731	CA	PHE	764	24.176	8.138	−0.363	1.00	23.36
ATOM	732	CB	PHE	764	25.167	7.026	−0.687	1.00	22.20
ATOM	733	CG	PHE	764	24.592	5.665	−0.577	1.00	20.93
ATOM	734	CD1	PHE	764	24.141	4.997	−1.703	1.00	21.03
ATOM	735	CD2	PHE	764	24.484	5.049	0.654	1.00	20.64
ATOM	736	CE1	PHE	764	23.590	3.728	−1.600	1.00	21.11
ATOM	737	CE2	PHE	764	23.936	3.785	0.765	1.00	20.71
ATOM	738	CZ	PHE	764	23.489	3.123	−0.360	1.00	20.65
ATOM	739	C	PHE	764	24.921	9.442	−0.246	1.00	23.54
ATOM	740	O	PHE	764	25.270	9.866	0.848	1.00	23.77
ATOM	741	N	ALA	765	25.154	10.067	−1.394	1.00	23.97
ATOM	742	CA	ALA	765	25.854	11.346	−1.488	1.00	24.26
ATOM	743	CB	ALA	765	27.346	11.142	−1.219	1.00	24.01
ATOM	744	C	ALA	765	25.627	11.880	−2.909	1.00	24.66

TABLE A-continued

ATOM	745	O	ALA	765	25.211	11.130	−3.789	1.00	24.88
ATOM	746	N	PRO	766	25.888	13.178	−3.153	1.00	25.03
ATOM	747	CD	PRO	766	26.345	14.222	−2.220	1.00	25.22
ATOM	748	CA	PRO	766	25.687	13.740	−4.496	1.00	25.14
ATOM	749	CB	PRO	766	26.159	15.190	−4.335	1.00	25.71
ATOM	750	CG	PRO	766	25.841	15.485	−2.888	1.00	25.20
ATOM	751	C	PRO	766	26.485	12.980	−5.554	1.00	25.17
ATOM	752	O	PRO	766	25.984	12.693	−6.651	1.00	25.08
ATOM	753	N	ASP	767	27.721	12.634	−5.208	1.00	25.17
ATOM	754	CA	ASP	767	28.600	11.898	−6.117	1.00	25.59
ATOM	755	CB	ASP	767	30.058	12.292	−5.858	1.00	25.95
ATOM	756	CG	ASP	767	30.531	11.898	−4.470	1.00	27.34
ATOM	757	OD1	ASP	767	29.780	12.093	−3.487	1.00	26.89
ATOM	758	OD2	ASP	767	31.668	11.400	−4.355	1.00	29.03
ATOM	759	C	ASP	767	28.457	10.374	−6.012	1.00	25.16
ATOM	760	O	ASP	767	29.215	9.644	−6.636	1.00	25.56
ATOM	761	N	LEU	768	27.507	9.891	−5.214	1.00	24.75
ATOM	762	CA	LEU	768	27.298	8.453	−5.076	1.00	24.23
ATOM	763	CB	LEU	768	28.070	7.909	−3.870	1.00	23.92
ATOM	764	CG	LEU	768	28.183	6.378	−3.771	1.00	23.88
ATOM	765	CD1	LEU	768	28.910	5.819	−4.974	1.00	23.45
ATOM	766	CD2	LEU	768	28.943	6.011	−2.523	1.00	24.21
ATOM	767	C	LEU	768	25.808	8.129	−4.944	1.00	24.57
ATOM	768	O	LEU	768	25.285	7.931	−3.846	1.00	24.30
ATOM	769	N	VAL	769	25.133	8.081	−6.088	1.00	24.78
ATOM	770	CA	VAL	769	23.702	7.802	−6.149	1.00	24.65
ATOM	771	CB	VAL	769	22.998	8.807	−7.089	1.00	24.73
ATOM	772	CG1	VAL	769	21.480	8.621	−7.031	1.00	24.37
ATOM	773	CG2	VAL	769	23.398	10.245	−6.700	1.00	24.01
ATOM	774	C	VAL	769	23.560	6.391	−6.698	1.00	24.90
ATOM	775	O	VAL	769	24.156	6.061	−7.717	1.00	25.44
ATOM	776	N	PHE	770	22.794	5.554	−6.007	1.00	24.72
ATOM	777	CA	PHE	770	22.615	4.180	−6.434	1.00	24.40
ATOM	778	CB	PHE	770	22.631	3.224	−5.243	1.00	24.46
ATOM	779	CG	PHE	770	23.994	2.714	−4.867	1.00	23.68
ATOM	780	CD1	PHE	770	25.125	3.522	−4.993	1.00	22.58
ATOM	781	CD2	PHE	770	24.128	1.452	−4.294	1.00	23.29
ATOM	782	CE1	PHE	770	26.363	3.087	−4.552	1.00	22.46
ATOM	783	CE2	PHE	770	25.370	1.003	−3.841	1.00	23.62
ATOM	784	CZ	PHE	770	26.497	1.833	−3.974	1.00	23.15
ATOM	785	C	PHE	770	21.323	3.959	−7.167	1.00	24.70
ATOM	786	O	PHE	770	20.237	4.104	−6.593	1.00	24.80
ATOM	787	N	ASN	771	21.449	3.604	−8.438	1.00	24.57
ATOM	788	CA	ASN	771	20.298	3.288	−9.259	1.00	24.55
ATOM	789	CB	ASN	771	20.531	3.729	−10.699	1.00	24.45
ATOM	790	CG	ASN	771	21.892	3.329	−11.216	1.00	24.66
ATOM	791	OD1	ASN	771	22.551	2.424	−10.678	1.00	24.49
ATOM	792	ND2	ASN	771	22.321	3.991	−12.277	1.00	24.40
ATOM	793	C	ASN	771	20.195	1.770	−9.175	1.00	24.68
ATOM	794	O	ASN	771	21.009	1.131	−8.510	1.00	24.39
ATOM	795	N	GLU	772	19.211	1.185	−9.842	1.00	25.37
ATOM	796	CA	GLU	772	19.052	−0.263	−9.790	1.00	25.97
ATOM	797	CB	GLU	772	17.885	−0.698	−10.673	1.00	26.94
ATOM	798	CG	GLU	772	16.519	−0.461	−10.013	1.00	28.24
ATOM	799	CD	GLU	772	15.988	−1.704	−9.306	1.00	29.05
ATOM	800	OE1	GLU	772	15.347	−1.562	−8.235	1.00	29.60
ATOM	801	OE2	GLU	772	16.203	−2.819	−9.835	1.00	29.05
ATOM	802	C	GLU	772	20.318	−0.987	−10.190	1.00	26.14
ATOM	803	O	GLU	772	20.737	−1.934	−9.518	1.00	26.09
ATOM	804	N	TYR	773	20.948	−0.530	−11.270	1.00	25.97
ATOM	805	CA	TYR	773	22.166	−1.170	−11.734	1.00	25.56
ATOM	806	CB	TYR	773	22.734	−0.445	−12.944	1.00	26.25
ATOM	807	CG	TYR	773	24.033	−1.034	−13.428	1.00	25.78
ATOM	808	CD1	TYR	773	24.073	−2.281	−14.040	1.00	25.69
ATOM	809	CE1	TYR	773	25.282	−2.830	−14.469	1.00	26.68
ATOM	810	CD2	TYR	773	25.228	−0.344	−13.256	1.00	26.64
ATOM	811	CE2	TYR	773	26.448	−0.876	−13.683	1.00	26.53
ATOM	812	CZ	TYR	773	26.469	−2.113	−14.286	1.00	26.86
ATOM	813	OH	TYR	773	27.676	−2.624	−14.705	1.00	26.83
ATOM	814	C	TYR	773	23.222	−1.234	−10.648	1.00	25.39
ATOM	815	O	TYR	773	23.823	−2.286	−10.420	1.00	25.85
ATOM	816	N	ARG	774	23.468	−0.117	−9.975	1.00	24.83
ATOM	817	CA	ARG	774	24.467	−0.129	−8.913	1.00	24.13
ATOM	818	CB	ARG	774	24.806	1.293	−8.493	1.00	23.53
ATOM	819	CG	ARG	774	25.745	1.963	−9.465	1.00	23.97
ATOM	820	CD	ARG	774	25.760	3.472	−9.277	1.00	24.07
ATOM	821	NE	ARG	774	26.915	4.069	−9.934	1.00	24.01
ATOM	822	CZ	ARG	774	27.280	5.332	−9.778	1.00	23.94
ATOM	823	NH1	ARG	774	26.576	6.124	−8.989	1.00	24.20

TABLE A-continued

ATOM	824	NH2	ARG	774	28.350	5.797	−10.405	1.00	24.95
ATOM	825	C	ARG	774	24.016	−0.965	−7.714	1.00	23.78
ATOM	826	O	ARG	774	24.836	−1.553	−7.027	1.00	23.53
ATOM	827	N	MET	775	22.714	−1.019	−7.470	1.00	23.55
ATOM	828	CA	MET	775	22.189	−1.818	−6.375	1.00	24.24
ATOM	829	CB	MET	775	20.680	−1.654	−6.298	1.00	23.35
ATOM	830	CG	MET	775	20.279	−0.409	−5.602	1.00	22.56
ATOM	831	SD	MET	775	18.562	−0.102	−5.803	1.00	23.81
ATOM	832	CE	MET	775	18.596	1.595	−6.444	1.00	23.32
ATOM	833	C	MET	775	22.544	−3.302	−6.556	1.00	25.19
ATOM	834	O	MET	775	22.837	−4.011	−5.589	1.00	24.45
ATOM	835	N	HIS	776	22.530	−3.757	−7.806	1.00	26.18
ATOM	836	CA	HIS	776	22.845	−5.141	−8.119	1.00	26.92
ATOM	837	CB	HIS	776	22.313	−5.505	−9.510	1.00	27.27
ATOM	838	CG	HIS	776	22.615	−6.914	−9.913	1.00	28.49
ATOM	839	CD2	HIS	776	21.882	−8.049	−9.798	1.00	28.49
ATOM	840	ND1	HIS	776	23.841	−7.299	−10.415	1.00	28.47
ATOM	841	CE1	HIS	776	23.851	−8.611	−10.586	1.00	28.94
ATOM	842	NE2	HIS	776	22.675	−9.089	−10.219	1.00	29.04
ATOM	843	C	HIS	776	24.344	−5.376	−8.070	1.00	27.70
ATOM	844	O	HIS	776	24.818	−6.350	−7.481	1.00	28.14
ATOM	845	N	LYS	777	25.086	−4.474	−8.699	1.00	28.16
ATOM	846	CA	LYS	777	26.536	−4.555	−8.760	1.00	28.25
ATOM	847	CB	LYS	777	27.050	−3.468	−9.702	1.00	28.87
ATOM	848	CG	LYS	777	26.568	−3.632	−11.138	1.00	29.22
ATOM	849	CD	LYS	777	27.637	−4.263	−12.030	1.00	29.26
ATOM	850	CE	LYS	777	28.063	−5.643	−11.572	1.00	29.02
ATOM	851	NZ	LYS	777	29.216	−6.132	−12.387	1.00	29.65
ATOM	852	C	LYS	777	27.234	−4.440	−7.398	1.00	28.38
ATOM	853	O	LYS	777	28.306	−5.006	−7.196	1.00	28.33
ATOM	854	N	SER	778	26.638	−3.701	−6.468	1.00	28.47
ATOM	855	CA	SER	778	27.227	−3.542	−5.143	1.00	28.59
ATOM	856	CB	SER	778	26.574	−2.369	−4.408	1.00	28.41
ATOM	857	OG	SER	778	25.199	−2.621	−4.172	1.00	27.42
ATOM	858	C	SER	778	27.043	−4.820	−4.323	1.00	29.24
ATOM	859	O	SER	778	27.756	−5.039	−3.352	1.00	29.39
ATOM	860	N	ARG	779	26.078	−5.645	−4.733	1.00	29.69
ATOM	861	CA	ARG	779	25.739	−6.904	−4.081	1.00	30.16
ATOM	862	CB	ARG	779	26.998	−7.730	−3.817	1.00	30.77
ATOM	863	CG	ARG	779	27.686	−8.208	−5.085	1.00	30.83
ATOM	864	CD	ARG	779	28.959	−8.974	−4.796	1.00	31.77
ATOM	865	NE	ARG	779	29.699	−9.207	−6.030	1.00	33.22
ATOM	866	CZ	ARG	779	30.984	−9.547	−6.096	1.00	33.96
ATOM	867	NH1	ARG	779	31.700	−9.705	−4.987	1.00	33.90
ATOM	868	NH2	ARG	779	31.562	−9.699	−7.283	1.00	34.13
ATOM	869	C	ARG	779	24.942	−6.698	−2.790	1.00	30.89
ATOM	870	O	ARG	779	24.962	−7.541	−1.886	1.00	30.62
ATOM	871	N	MET	780	24.232	−5.570	−2.729	1.00	31.21
ATOM	872	CA	MET	780	23.384	−5.221	−1.592	1.00	31.28
ATOM	873	CB	MET	780	23.948	−4.017	−0.832	1.00	32.57
ATOM	874	CG	MET	780	25.288	−4.215	−0.172	1.00	34.02
ATOM	875	SD	MET	780	25.814	−2.649	0.565	1.00	37.00
ATOM	876	CE	MET	780	26.603	−1.893	−0.815	1.00	34.95
ATOM	877	C	MET	780	22.010	−4.839	−2.137	1.00	30.81
ATOM	878	O	MET	780	21.414	−3.841	−1.718	1.00	31.05
ATOM	879	N	TYR	781	21.497	−5.621	−3.074	1.00	29.92
ATOM	880	CA	TYR	781	20.208	−5.283	−3.651	1.00	29.23
ATOM	881	CB	TYR	781	19.920	−6.156	−4.882	1.00	28.90
ATOM	882	CG	TYR	781	18.721	−5.689	−5.670	1.00	28.52
ATOM	883	CD1	TYR	781	18.851	−4.762	−6.701	1.00	28.60
ATOM	884	CE1	TYR	781	17.726	−4.311	−7.408	1.00	28.68
ATOM	885	CD2	TYR	781	17.443	−6.152	−5.359	1.00	28.60
ATOM	886	CE2	TYR	781	16.318	−5.706	−6.051	1.00	28.33
ATOM	887	CZ	TYR	781	16.461	−4.791	−7.071	1.00	28.53
ATOM	888	OH	TYR	781	15.337	−4.364	−7.748	1.00	28.76
ATOM	889	C	TYR	781	19.087	−5.407	−2.620	1.00	28.96
ATOM	890	O	TYR	781	18.246	−4.513	−2.513	1.00	28.45
ATOM	891	N	SER	782	19.068	−6.504	−1.862	1.00	28.78
ATOM	892	CA	SER	782	18.030	−6.678	−0.835	1.00	28.74
ATOM	893	CB	SER	782	18.209	−8.004	−0.100	1.00	29.02
ATOM	894	OG	SER	782	18.036	−9.090	−0.987	1.00	30.66
ATOM	895	C	SER	782	18.044	−5.531	0.187	1.00	27.95
ATOM	896	O	SER	782	17.045	−4.839	0.363	1.00	28.09
ATOM	897	N	GLN	783	19.170	−5.325	0.855	1.00	27.40
ATOM	898	CA	GLN	783	19.249	−4.244	1.836	1.00	27.42
ATOM	899	CB	GLN	783	20.669	−4.113	2.397	1.00	27.83
ATOM	900	CG	GLN	783	21.268	−5.393	2.978	1.00	28.33
ATOM	901	CD	GLN	783	21.844	−6.302	1.919	1.00	29.14
ATOM	902	OE1	GLN	783	22.658	−7.184	2.215	1.00	29.90

TABLE A-continued

ATOM	903	NE2	GLN	783	21.426	−6.099	0.672	1.00	28.96
ATOM	904	C	GLN	783	18.840	−2.924	1.177	1.00	26.96
ATOM	905	O	GLN	783	18.124	−2.114	1.781	1.00	26.53
ATOM	906	N	CYS	784	19.290	−2.719	−0.064	1.00	26.46
ATOM	907	CA	CYS	784	18.963	−1.506	−0.808	1.00	26.18
ATOM	908	CB	CYS	784	19.695	−1.488	−2.159	1.00	27.17
ATOM	909	SG	CYS	784	21.458	−1.025	−2.047	1.00	28.41
ATOM	910	C	CYS	784	17.452	−1.389	−1.002	1.00	25.21
ATOM	911	O	CYS	784	16.901	−0.290	−0.952	1.00	24.95
ATOM	912	N	VAL	785	16.789	−2.524	−1.210	1.00	24.67
ATOM	913	CA	VAL	785	15.330	−2.554	−1.351	1.00	24.38
ATOM	914	CB	VAL	785	14.821	−3.960	−1.738	1.00	24.36
ATOM	915	CG1	VAL	785	13.455	−4.230	−1.081	1.00	24.20
ATOM	916	CG2	VAL	785	14.705	−4.055	−3.247	1.00	23.60
ATOM	917	C	VAL	785	14.698	−2.157	−0.021	1.00	23.98
ATOM	918	O	VAL	785	13.705	−1.441	0.020	1.00	23.63
ATOM	919	N	ARG	786	15.280	−2.646	1.067	1.00	24.16
ATOM	920	CA	ARG	786	14.808	−2.304	2.411	1.00	24.19
ATOM	921	CB	ARG	786	15.667	−3.016	3.465	1.00	24.76
ATOM	922	CG	ARG	786	15.663	−4.537	3.386	1.00	25.63
ATOM	923	CD	ARG	786	14.617	−5.109	4.314	1.00	26.26
ATOM	924	NE	ARG	786	15.149	−6.186	5.141	1.00	26.47
ATOM	925	CZ	ARG	786	14.769	−6.414	6.396	1.00	26.71
ATOM	926	NH1	ARG	786	13.861	−5.637	6.970	1.00	26.62
ATOM	927	NH2	ARG	786	15.283	−7.426	7.074	1.00	26.60
ATOM	928	C	ARG	786	14.934	−0.783	2.613	1.00	23.52
ATOM	929	O	ARG	786	14.015	−0.128	3.087	1.00	23.13
ATOM	930	N	MET	787	16.079	−0.227	2.236	1.00	23.46
ATOM	931	CA	MET	787	16.326	1.201	2.404	1.00	24.21
ATOM	932	CB	MET	787	17.799	1.506	2.153	1.00	24.32
ATOM	933	CG	MET	787	18.695	0.872	3.191	1.00	25.11
ATOM	934	SD	MET	787	20.411	1.249	2.977	1.00	26.06
ATOM	935	CE	MET	787	20.960	−0.200	2.082	1.00	25.69
ATOM	936	C	MET	787	15.443	2.082	1.535	1.00	24.88
ATOM	937	O	MET	787	14.947	3.113	1.999	1.00	24.39
ATOM	938	N	ARG	788	15.260	1.675	0.278	1.00	25.61
ATOM	939	CA	ARG	788	14.399	2.394	−0.651	1.00	26.64
ATOM	940	CB	ARG	788	14.361	1.661	−2.003	1.00	27.51
ATOM	941	CG	ARG	788	13.561	2.371	−3.089	1.00	28.69
ATOM	942	CD	ARG	788	14.374	2.537	−4.378	1.00	29.41
ATOM	943	NE	ARG	788	14.059	1.556	−5.419	1.00	29.78
ATOM	944	CZ	ARG	788	14.634	1.548	−6.626	1.00	31.03
ATOM	945	NH1	ARG	788	15.549	2.465	−6.935	1.00	30.51
ATOM	946	NH2	ARG	788	14.298	0.631	−7.532	1.00	30.16
ATOM	947	C	ARG	788	13.016	2.401	0.007	1.00	26.84
ATOM	948	O	ARG	788	12.328	3.418	0.047	1.00	26.40
ATOM	949	N	HIS	789	12.632	1.251	0.545	1.00	27.75
ATOM	950	CA	HIS	789	11.359	1.104	1.233	1.00	29.39
ATOM	951	CB	HIS	789	11.238	−0.300	1.811	1.00	30.70
ATOM	952	CG	HIS	789	9.968	−0.996	1.447	1.00	32.08
ATOM	953	CD2	HIS	789	8.916	−1.387	2.205	1.00	32.40
ATOM	954	ND1	HIS	789	9.685	−1.396	0.157	1.00	32.78
ATOM	955	CE1	HIS	789	8.513	−2.009	0.139	1.00	33.40
ATOM	956	NE2	HIS	789	8.026	−2.017	1.369	1.00	33.45
ATOM	957	C	HIS	789	11.275	2.120	2.373	1.00	29.90
ATOM	958	O	HIS	789	10.274	2.829	2.513	1.00	29.93
ATOM	959	N	LEU	790	12.328	2.173	3.192	1.00	30.02
ATOM	960	CA	LEU	790	12.390	3.115	4.307	1.00	30.13
ATOM	961	CB	LEU	790	13.775	3.071	4.956	1.00	30.30
ATOM	962	CG	LEU	790	14.142	4.222	5.896	1.00	30.27
ATOM	963	CD1	LEU	790	13.147	4.322	7.029	1.00	30.03
ATOM	964	CD2	LEU	790	15.536	3.978	6.445	1.00	31.35
ATOM	965	C	LEU	790	12.107	4.533	3.836	1.00	30.25
ATOM	966	O	LEU	790	11.194	5.189	4.325	1.00	30.14
ATOM	967	N	SER	791	12.911	5.000	2.890	1.00	30.62
ATOM	968	CA	SER	791	12.759	6.334	2.338	1.00	31.31
ATOM	969	CB	SER	791	13.661	6.504	1.123	1.00	31.61
ATOM	970	OG	SER	791	13.224	5.654	0.082	1.00	32.91
ATOM	971	C	SER	791	11.318	6.603	1.920	1.00	31.63
ATOM	972	O	SER	791	10.747	7.626	2.290	1.00	32.03
ATOM	973	N	GLN	792	10.734	5.696	1.138	1.00	31.71
ATOM	974	CA	GLN	792	9.354	5.873	0.687	1.00	31.71
ATOM	975	CB	GLN	792	8.909	4.666	−0.150	1.00	31.94
ATOM	976	CG	GLN	792	9.637	4.593	−1.492	1.00	32.57
ATOM	977	CD	GLN	792	9.418	3.282	−2.223	1.00	33.30
ATOM	978	OE1	GLN	792	8.385	3.073	−2.860	1.00	33.62
ATOM	979	NE2	GLN	792	10.394	2.384	−2.128	1.00	33.08
ATOM	980	C	GLN	792	8.417	6.107	1.870	1.00	31.60
ATOM	981	O	GLN	792	7.459	6.881	1.766	1.00	31.38

TABLE A-continued

ATOM	982	N	GLU	793	8.706	5.455	2.997	1.00	31.29
ATOM	983	CA	GLU	793	7.913	5.629	4.216	1.00	30.78
ATOM	984	CB	GLU	793	8.490	4.782	5.353	1.00	31.16
ATOM	985	CG	GLU	793	8.422	3.301	5.099	1.00	31.63
ATOM	986	CD	GLU	793	7.024	2.753	5.256	1.00	32.41
ATOM	987	OE1	GLU	793	6.056	3.549	5.178	1.00	32.89
ATOM	988	OE2	GLU	793	6.892	1.523	5.447	1.00	32.77
ATOM	989	C	GLU	793	7.927	7.101	4.630	1.00	30.41
ATOM	990	O	GLU	793	6.959	7.609	5.202	1.00	30.34
ATOM	991	N	PHE	794	9.032	7.787	4.355	1.00	29.94
ATOM	992	CA	PHE	794	9.119	9.195	4.703	1.00	29.89
ATOM	993	CB	PHE	794	10.498	9.762	4.367	1.00	29.61
ATOM	994	CG	PHE	794	11.586	9.331	5.316	1.00	29.83
ATOM	995	CD1	PHE	794	11.472	9.567	6.683	1.00	29.77
ATOM	996	CD2	PHE	794	12.722	8.684	4.848	1.00	29.90
ATOM	997	CE1	PHE	794	12.466	9.161	7.561	1.00	29.72
ATOM	998	CE2	PHE	794	13.722	8.274	5.726	1.00	30.02
ATOM	999	CZ	PHE	794	13.592	8.513	7.083	1.00	29.58
ATOM	1000	C	PHE	794	8.057	9.943	3.922	1.00	30.47
ATOM	1001	O	PHE	794	7.721	11.075	4.248	1.00	30.71
ATOM	1002	N	GLY	795	7.532	9.296	2.883	1.00	31.23
ATOM	1003	CA	GLY	795	6.513	9.910	2.053	1.00	31.91
ATOM	1004	C	GLY	795	5.101	9.482	2.410	1.00	32.71
ATOM	1005	O	GLY	795	4.219	10.322	2.557	1.00	32.69
ATOM	1006	N	TRP	796	4.875	8.181	2.557	1.00	33.17
ATOM	1007	CA	TRP	796	3.539	7.701	2.897	1.00	34.04
ATOM	1008	CB	TRP	796	3.490	6.176	2.820	1.00	33.54
ATOM	1009	CG	TRP	796	3.880	5.642	1.484	1.00	33.47
ATOM	1010	CD2	TRP	796	4.706	4.499	1.223	1.00	33.26
ATOM	1011	CE2	TRP	796	4.779	4.347	−0.183	1.00	32.92
ATOM	1012	CE3	TRP	796	5.391	3.587	2.039	1.00	33.53
ATOM	1013	CD1	TRP	796	3.497	6.125	0.259	1.00	33.23
ATOM	1014	NE1	TRP	796	4.033	5.351	−0.743	1.00	32.89
ATOM	1015	CZ2	TRP	796	5.509	3.320	−0.793	1.00	32.88
ATOM	1016	CZ3	TRP	796	6.124	2.556	1.426	1.00	33.73
ATOM	1017	CH2	TRP	796	6.172	2.438	0.022	1.00	33.34
ATOM	1018	C	TRP	796	3.079	8.168	4.283	1.00	34.95
ATOM	1019	O	TRP	796	1.883	8.130	4.596	1.00	35.51
ATOM	1020	N	LEU	797	4.026	8.620	5.105	1.00	35.59
ATOM	1021	CA	LEU	797	3.712	9.097	6.451	1.00	35.60
ATOM	1022	CB	LEU	797	4.672	8.487	7.466	1.00	35.55
ATOM	1023	CG	LEU	797	4.539	6.978	7.667	1.00	35.46
ATOM	1024	CD1	LEU	797	5.745	6.465	8.443	1.00	35.46
ATOM	1025	CD2	LEU	797	3.232	6.671	8.390	1.00	35.11
ATOM	1026	C	LEU	797	3.794	10.610	6.545	1.00	35.92
ATOM	1027	O	LEU	797	3.574	11.182	7.612	1.00	36.29
ATOM	1028	N	GLN	798	4.103	11.257	5.427	1.00	36.20
ATOM	1029	CA	GLN	798	4.224	12.711	5.397	1.00	36.28
ATOM	1030	CB	GLN	798	2.830	13.377	5.366	1.00	37.02
ATOM	1031	CG	GLN	798	2.233	13.503	3.939	1.00	38.04
ATOM	1032	CD	GLN	798	0.757	13.919	3.908	1.00	38.46
ATOM	1033	OE1	GLN	798	−0.113	13.231	4.458	1.00	39.04
ATOM	1034	NE2	GLN	798	0.472	15.036	3.247	1.00	38.17
ATOM	1035	C	GLN	798	5.033	13.185	6.598	1.00	35.87
ATOM	1036	O	GLN	798	4.637	14.099	7.321	1.00	36.50
ATOM	1037	N	ILE	799	6.179	12.543	6.794	1.00	35.08
ATOM	1038	CA	ILE	799	7.084	12.869	7.885	1.00	34.09
ATOM	1039	CB	ILE	799	8.205	11.824	7.982	1.00	33.96
ATOM	1040	CG2	ILE	799	9.294	12.288	8.934	1.00	33.52
ATOM	1041	CG1	ILE	799	7.598	10.504	8.439	1.00	34.19
ATOM	1042	CD1	ILE	799	8.575	9.407	8.549	1.00	35.01
ATOM	1043	C	ILE	799	7.691	14.247	7.694	1.00	33.51
ATOM	1044	O	ILE	799	8.244	14.547	6.645	1.00	33.24
ATOM	1045	N	THR	800	7.587	15.074	8.728	1.00	33.31
ATOM	1046	CA	THR	800	8.102	16.436	8.700	1.00	33.05
ATOM	1047	CB	THR	800	7.351	17.341	9.717	1.00	33.44
ATOM	1048	OG1	THR	800	7.803	17.043	11.048	1.00	33.14
ATOM	1049	CG2	THR	800	5.840	17.113	9.636	1.00	32.47
ATOM	1050	C	THR	800	9.582	16.515	9.050	1.00	33.21
ATOM	1051	O	THR	800	10.166	15.577	9.599	1.00	33.40
ATOM	1052	N	PRO	801	10.214	17.644	8.719	1.00	33.07
ATOM	1053	CD	PRO	801	9.726	18.642	7.748	1.00	33.01
ATOM	1054	CA	PRO	801	11.630	17.858	9.007	1.00	32.90
ATOM	1055	CB	PRO	801	11.891	19.229	8.386	1.00	32.72
ATOM	1056	CG	PRO	801	11.012	19.196	7.189	1.00	32.68
ATOM	1057	C	PRO	801	11.886	17.841	10.521	1.00	32.91
ATOM	1058	O	PRO	801	12.899	17.314	10.995	1.00	33.12
ATOM	1059	N	GLN	802	10.967	18.426	11.281	1.00	32.37
ATOM	1060	CA	GLN	802	11.117	18.458	12.729	1.00	31.71

TABLE A-continued

ATOM	1061	CB	GLN	802	10.090	19.425	13.340	1.00	32.11
ATOM	1062	CG	GLN	802	10.276	20.925	12.948	1.00	32.69
ATOM	1063	CD	GLN	802	9.954	21.244	11.464	1.00	33.21
ATOM	1064	OE1	GLN	802	8.898	20.871	10.943	1.00	33.11
ATOM	1065	NE2	GLN	802	10.865	21.956	10.798	1.00	33.53
ATOM	1066	C	GLN	802	10.987	17.045	13.338	1.00	31.06
ATOM	1067	O	GLN	802	11.680	16.711	14.305	1.00	31.17
ATOM	1068	N	GLU	803	10.109	16.217	12.775	1.00	29.88
ATOM	1069	CA	GLU	803	9.935	14.849	13.269	1.00	28.79
ATOM	1070	CB	GLU	803	8.750	14.154	12.587	1.00	29.29
ATOM	1071	CG	GLU	803	7.378	14.677	12.936	1.00	30.44
ATOM	1072	CD	GLU	803	6.286	13.977	12.145	1.00	30.78
ATOM	1073	OE1	GLU	803	6.277	14.099	10.905	1.00	29.94
ATOM	1074	OE2	GLU	803	5.440	13.295	12.766	1.00	32.29
ATOM	1075	C	GLU	803	11.198	14.058	12.940	1.00	27.63
ATOM	1076	O	GLU	803	11.743	13.358	13.783	1.00	27.67
ATOM	1077	N	PHE	804	11.644	14.167	11.694	1.00	25.86
ATOM	1078	CA	PHE	804	12.835	13.472	11.252	1.00	24.53
ATOM	1079	CB	PHE	804	13.176	13.850	9.803	1.00	23.88
ATOM	1080	CG	PHE	804	14.603	13.578	9.439	1.00	23.21
ATOM	1081	CD1	PHE	804	15.098	12.280	9.449	1.00	22.70
ATOM	1082	CD2	PHE	804	15.475	14.625	9.164	1.00	23.07
ATOM	1083	CE1	PHE	804	16.436	12.031	9.199	1.00	22.58
ATOM	1084	CE2	PHE	804	16.823	14.384	8.909	1.00	22.21
ATOM	1085	CZ	PHE	804	17.303	13.091	8.929	1.00	22.63
ATOM	1086	C	PHE	804	14.044	13.755	12.146	1.00	23.92
ATOM	1087	O	PHE	804	14.797	12.841	12.480	1.00	23.49
ATOM	1088	N	LEU	805	14.242	15.013	12.517	1.00	23.43
ATOM	1089	CA	LEU	805	15.377	15.360	13.362	1.00	23.07
ATOM	1090	CB	LEU	805	15.572	16.881	13.432	1.00	22.40
ATOM	1091	CG	LEU	805	15.862	17.582	12.100	1.00	22.11
ATOM	1092	CD1	LEU	805	16.020	19.075	12.339	1.00	22.35
ATOM	1093	CD2	LEU	805	17.104	17.007	11.441	1.00	21.68
ATOM	1094	C	LEU	805	15.240	14.791	14.761	1.00	23.01
ATOM	1095	O	LEU	805	16.231	14.404	15.358	1.00	23.29
ATOM	1096	N	CYS	806	14.028	14.731	15.301	1.00	23.32
ATOM	1097	CA	CYS	806	13.872	14.151	16.638	1.00	23.74
ATOM	1098	CB	CYS	806	12.469	14.379	17.179	1.00	24.34
ATOM	1099	SG	CYS	806	12.141	16.076	17.527	1.00	30.40
ATOM	1100	C	CYS	806	14.145	12.649	16.605	1.00	22.67
ATOM	1101	O	CYS	806	14.877	12.117	17.447	1.00	22.58
ATOM	1102	N	MET	807	13.543	11.971	15.637	1.00	21.64
ATOM	1103	CA	MET	807	13.724	10.532	15.503	1.00	21.18
ATOM	1104	CB	MET	807	12.919	9.991	14.313	1.00	22.00
ATOM	1105	CG	MET	807	11.403	10.114	14.463	1.00	23.29
ATOM	1106	SD	MET	807	10.507	9.386	13.019	1.00	25.08
ATOM	1107	CE	MET	807	10.295	10.783	12.018	1.00	24.91
ATOM	1108	C	MET	807	15.204	10.193	15.330	1.00	19.80
ATOM	1109	O	MET	807	15.698	9.267	15.950	1.00	19.29
ATOM	1110	N	LYS	808	15.900	10.950	14.488	1.00	18.78
ATOM	1111	CA	LYS	808	17.321	10.730	14.250	1.00	18.18
ATOM	1112	CB	LYS	808	17.877	11.789	13.284	1.00	17.70
ATOM	1113	CG	LYS	808	19.376	11.652	13.044	1.00	18.55
ATOM	1114	CD	LYS	808	19.775	11.948	11.583	1.00	18.83
ATOM	1115	CE	LYS	808	19.711	13.425	11.271	1.00	17.98
ATOM	1116	NZ	LYS	808	20.547	14.166	12.258	1.00	18.71
ATOM	1117	C	LYS	808	18.063	10.786	15.588	1.00	17.76
ATOM	1118	O	LYS	808	18.823	9.880	15.921	1.00	16.45
ATOM	1119	N	ALA	809	17.829	11.853	16.347	1.00	17.98
ATOM	1120	CA	ALA	809	18.443	12.011	17.661	1.00	18.61
ATOM	1121	CB	ALA	809	17.950	13.283	18.321	1.00	18.30
ATOM	1122	C	ALA	809	18.105	10.786	18.532	1.00	18.88
ATOM	1123	O	ALA	809	18.986	10.210	19.167	1.00	18.79
ATOM	1124	N	LEU	810	16.842	10.369	18.533	1.00	19.30
ATOM	1125	CA	LEU	810	16.432	9.204	19.321	1.00	19.68
ATOM	1126	CB	LEU	810	14.917	9.033	19.242	1.00	19.80
ATOM	1127	CG	LEU	810	14.250	8.133	20.290	1.00	21.07
ATOM	1128	CD1	LEU	810	14.607	8.601	21.706	1.00	21.00
ATOM	1129	CD2	LEU	810	12.736	8.168	20.094	1.00	20.91
ATOM	1130	C	LEU	810	17.137	7.924	18.837	1.00	19.90
ATOM	1131	O	LEU	810	17.497	7.051	19.631	1.00	19.94
ATOM	1132	N	LEU	811	17.347	7.824	17.530	1.00	20.06
ATOM	1133	CA	LEU	811	18.010	6.665	16.949	1.00	20.23
ATOM	1134	CB	LEU	811	18.125	6.825	15.424	1.00	19.95
ATOM	1135	CG	LEU	811	17.498	5.720	14.561	1.00	20.82
ATOM	1136	CD1	LEU	811	17.661	6.059	13.079	1.00	20.39
ATOM	1137	CD2	LEU	811	18.139	4.380	14.874	1.00	20.09
ATOM	1138	C	LEU	811	19.407	6.447	17.555	1.00	20.02
ATOM	1139	O	LEU	811	19.889	5.326	17.622	1.00	20.87

TABLE A-continued

ATOM	1140	N	LEU	812	20.060	7.513	17.992	1.00	19.93
ATOM	1141	CA	LEU	812	21.389	7.380	18.581	1.00	19.94
ATOM	1142	CB	LEU	812	22.041	8.753	18.753	1.00	19.93
ATOM	1143	CG	LEU	812	23.309	8.740	19.607	1.00	19.48
ATOM	1144	CD1	LEU	812	24.523	8.421	18.748	1.00	19.57
ATOM	1145	CD2	LEU	812	23.467	10.068	20.272	1.00	19.85
ATOM	1146	C	LEU	812	21.355	6.692	19.940	1.00	19.79
ATOM	1147	O	LEU	812	22.383	6.237	20.414	1.00	19.89
ATOM	1148	N	PHE	813	20.182	6.638	20.564	1.00	20.27
ATOM	1149	CA	PHE	813	20.025	6.011	21.872	1.00	20.89
ATOM	1150	CB	PHE	813	19.334	6.988	22.830	1.00	21.71
ATOM	1151	CG	PHE	813	20.049	8.309	22.964	1.00	22.53
ATOM	1152	CD1	PHE	813	21.296	8.381	23.575	1.00	22.94
ATOM	1153	CD2	PHE	813	19.483	9.475	22.452	1.00	22.60
ATOM	1154	CE1	PHE	813	21.974	9.600	23.676	1.00	23.67
ATOM	1155	CE2	PHE	813	20.143	10.698	22.543	1.00	23.12
ATOM	1156	CZ	PHE	813	21.392	10.764	23.156	1.00	24.01
ATOM	1157	C	PHE	813	19.233	4.706	21.814	1.00	21.29
ATOM	1158	O	PHE	813	18.573	4.327	22.780	1.00	20.70
ATOM	1159	N	SER	814	19.304	4.013	20.680	1.00	22.24
ATOM	1160	CA	SER	814	18.571	2.762	20.526	1.00	22.82
ATOM	1161	CB	SER	814	17.604	2.870	19.352	1.00	23.27
ATOM	1162	OG	SER	814	16.529	3.731	19.689	1.00	25.04
ATOM	1163	C	SER	814	19.402	1.502	20.387	1.00	22.78
ATOM	1164	O	SER	814	18.901	0.486	19.933	1.00	23.31
ATOM	1165	N	ILE	815	20.664	1.554	20.792	1.00	23.17
ATOM	1166	CA	ILE	815	21.519	0.388	20.715	1.00	24.25
ATOM	1167	CB	ILE	815	22.260	0.339	19.361	1.00	25.14
ATOM	1168	CG2	ILE	815	22.988	1.640	19.099	1.00	25.51
ATOM	1169	CG1	ILE	815	23.222	−0.849	19.343	1.00	26.20
ATOM	1170	CD1	ILE	815	22.524	−2.177	19.315	1.00	26.03
ATOM	1171	C	ILE	815	22.500	0.376	21.888	1.00	24.71
ATOM	1172	O	ILE	815	23.306	1.292	22.065	1.00	24.79
ATOM	1173	N	ILE	816	22.417	−0.671	22.700	1.00	25.36
ATOM	1174	CA	ILE	816	23.263	−0.784	23.887	1.00	26.22
ATOM	1175	CB	ILE	816	22.595	−0.092	25.081	1.00	25.90
ATOM	1176	CG2	ILE	816	22.537	1.422	24.853	1.00	25.91
ATOM	1177	CG1	ILE	816	21.202	−0.690	25.282	1.00	25.62
ATOM	1178	CD1	ILE	816	20.460	−0.144	26.481	1.00	26.47
ATOM	1179	C	ILE	816	23.570	−2.220	24.328	1.00	26.59
ATOM	1180	O	ILE	816	22.807	−3.142	24.048	1.00	26.12
ATOM	1181	N	PRO	817	24.694	−2.413	25.041	1.00	27.17
ATOM	1182	CD	PRO	817	25.758	−1.427	25.304	1.00	27.29
ATOM	1183	CA	PRO	817	25.085	−3.742	25.525	1.00	27.80
ATOM	1184	CB	PRO	817	26.384	−3.474	26.284	1.00	27.15
ATOM	1185	CG	PRO	817	26.958	−2.313	25.557	1.00	27.61
ATOM	1186	C	PRO	817	24.010	−4.324	26.435	1.00	28.43
ATOM	1187	O	PRO	817	23.380	−3.600	27.212	1.00	27.45
ATOM	1188	N	VAL	818	23.808	−5.634	26.312	1.00	29.98
ATOM	1189	CA	VAL	818	22.833	−6.380	27.108	1.00	31.48
ATOM	1190	CB	VAL	818	22.947	−7.891	26.825	1.00	31.98
ATOM	1191	CG1	VAL	818	24.335	−8.377	27.215	1.00	33.11
ATOM	1192	CG2	VAL	818	21.879	−8.665	27.590	1.00	32.85
ATOM	1193	C	VAL	818	23.032	−6.163	28.609	1.00	32.15
ATOM	1194	O	VAL	818	22.069	−6.152	29.364	1.00	32.43
ATOM	1195	N	ASP	819	24.276	−5.997	29.046	1.00	33.13
ATOM	1196	CA	ASP	819	24.536	−5.786	30.466	1.00	34.13
ATOM	1197	CB	ASP	819	25.707	−6.662	30.932	1.00	35.28
ATOM	1198	CG	ASP	819	27.024	−6.302	30.258	1.00	36.52
ATOM	1199	OD1	ASP	819	27.991	−7.091	30.403	1.00	37.48
ATOM	1200	OD2	ASP	819	27.097	−5.242	29.591	1.00	37.03
ATOM	1201	C	ASP	819	24.798	−4.315	30.798	1.00	34.30
ATOM	1202	O	ASP	819	25.668	−3.989	31.610	1.00	33.84
ATOM	1203	N	GLY	820	24.026	−3.440	30.150	1.00	34.60
ATOM	1204	CA	GLY	820	24.125	−2.005	30.361	1.00	34.11
ATOM	1205	C	GLY	820	25.477	−1.375	30.121	1.00	33.97
ATOM	1206	O	GLY	820	26.474	−2.068	29.945	1.00	33.92
ATOM	1207	N	LEU	821	25.493	−0.042	30.133	1.00	34.32
ATOM	1208	CA	LEU	821	26.693	0.768	29.925	1.00	34.47
ATOM	1209	CB	LEU	821	26.330	2.053	29.191	1.00	34.92
ATOM	1210	CG	LEU	821	25.887	2.042	27.733	1.00	35.26
ATOM	1211	CD1	LEU	821	25.251	3.398	27.420	1.00	35.53
ATOM	1212	CD2	LEU	821	27.080	1.769	26.819	1.00	34.91
ATOM	1213	C	LEU	821	27.348	1.154	31.242	1.00	34.74
ATOM	1214	O	LEU	821	26.836	0.841	32.313	1.00	34.48
ATOM	1215	N	LYS	822	28.476	1.855	31.148	1.00	35.36
ATOM	1216	CA	LYS	822	29.211	2.316	32.325	1.00	36.27
ATOM	1217	CB	LYS	822	30.384	3.204	31.903	1.00	36.87
ATOM	1218	CG	LYS	822	31.286	2.590	30.856	1.00	37.44

TABLE A-continued

ATOM	1219	CD	LYS	822	31.934	1.317	31.361	1.00	38.01
ATOM	1220	CE	LYS	822	32.921	0.770	30.343	1.00	38.61
ATOM	1221	NZ	LYS	822	34.065	1.699	30.117	1.00	39.07
ATOM	1222	C	LYS	822	28.296	3.112	33.263	1.00	36.51
ATOM	1223	O	LYS	822	28.440	3.056	34.480	1.00	36.71
ATOM	1224	N	ASN	823	27.359	3.859	32.690	1.00	36.69
ATOM	1225	CA	ASN	823	26.424	4.644	33.483	1.00	36.49
ATOM	1226	CB	ASN	823	26.893	6.098	33.529	1.00	37.62
ATOM	1227	CG	ASN	823	28.271	6.239	34.150	1.00	39.08
ATOM	1228	OD1	ASN	823	29.251	5.668	33.658	1.00	39.96
ATOM	1229	ND2	ASN	823	28.356	7.000	35.244	1.00	39.54
ATOM	1230	C	ASN	823	25.009	4.550	32.908	1.00	35.90
ATOM	1231	O	ASN	823	24.470	5.523	32.380	1.00	35.84
ATOM	1232	N	GLN	824	24.410	3.371	33.026	1.00	35.27
ATOM	1233	CA	GLN	824	23.064	3.128	32.512	1.00	34.89
ATOM	1234	CB	GLN	824	22.544	1.759	32.968	1.00	35.03
ATOM	1235	CG	GLN	824	22.418	0.736	31.853	1.00	35.35
ATOM	1236	CD	GLN	824	21.877	1.332	30.573	1.00	36.02
ATOM	1237	OE1	GLN	824	20.725	1.789	30.507	1.00	36.30
ATOM	1238	NE2	GLN	824	22.713	1.341	29.538	1.00	36.24
ATOM	1239	C	GLN	824	22.016	4.159	32.879	1.00	34.22
ATOM	1240	O	GLN	824	21.240	4.589	32.029	1.00	34.41
ATOM	1241	N	LYS	825	21.980	4.534	34.150	1.00	33.69
ATOM	1242	CA	LYS	825	20.989	5.478	34.645	1.00	33.20
ATOM	1243	CB	LYS	825	21.240	5.765	36.120	1.00	33.85
ATOM	1244	CG	LYS	825	20.044	6.323	36.860	1.00	34.71
ATOM	1245	CD	LYS	825	18.931	5.304	36.990	1.00	35.57
ATOM	1246	CE	LYS	825	17.744	5.903	37.732	1.00	36.43
ATOM	1247	NZ	LYS	825	18.151	6.447	39.063	1.00	37.01
ATOM	1248	C	LYS	825	20.929	6.788	33.870	1.00	32.38
ATOM	1249	O	LYS	825	19.857	7.329	33.656	1.00	32.60
ATOM	1250	N	PHE	826	22.077	7.299	33.453	1.00	31.31
ATOM	1251	CA	PHE	826	22.094	8.543	32.709	1.00	30.15
ATOM	1252	CB	PHE	826	23.496	9.152	32.709	1.00	30.44
ATOM	1253	CG	PHE	826	24.003	9.506	34.076	1.00	31.16
ATOM	1254	CD1	PHE	826	25.088	10.364	34.226	1.00	32.02
ATOM	1255	CD2	PHE	826	23.415	8.973	35.219	1.00	31.65
ATOM	1256	CE1	PHE	826	25.579	10.682	35.496	1.00	31.86
ATOM	1257	CE2	PHE	826	23.900	9.285	36.490	1.00	31.49
ATOM	1258	CZ	PHE	826	24.983	10.140	36.624	1.00	31.58
ATOM	1259	C	PHE	826	21.618	8.307	31.283	1.00	28.87
ATOM	1260	O	PHE	826	20.921	9.142	30.720	1.00	28.43
ATOM	1261	N	PHE	827	21.989	7.166	30.708	1.00	27.44
ATOM	1262	CA	PHE	827	21.568	6.833	29.354	1.00	26.53
ATOM	1263	CB	PHE	827	22.122	5.476	28.935	1.00	25.44
ATOM	1264	CG	PHE	827	21.708	5.061	27.556	1.00	24.15
ATOM	1265	CD1	PHE	827	22.592	5.157	26.493	1.00	23.63
ATOM	1266	CD2	PHE	827	20.425	4.599	27.312	1.00	23.97
ATOM	1267	CE1	PHE	827	22.202	4.800	25.203	1.00	23.50
ATOM	1268	CE2	PHE	827	20.026	4.241	26.016	1.00	23.68
ATOM	1269	CZ	PHE	827	20.913	4.342	24.968	1.00	22.72
ATOM	1270	C	PHE	827	20.045	6.788	29.340	1.00	26.44
ATOM	1271	O	PHE	827	19.406	7.407	28.492	1.00	26.04
ATOM	1272	N	ASP	828	19.475	6.052	30.296	1.00	26.33
ATOM	1273	CA	ASP	828	18.022	5.931	30.436	1.00	26.22
ATOM	1274	CB	ASP	828	17.669	5.082	31.654	1.00	27.34
ATOM	1275	CG	ASP	828	18.195	3.673	31.567	1.00	28.47
ATOM	1276	OD1	ASP	828	18.511	3.119	32.644	1.00	29.17
ATOM	1277	OD2	ASP	828	18.281	3.117	30.448	1.00	28.69
ATOM	1278	C	ASP	828	17.332	7.288	30.601	1.00	25.75
ATOM	1279	O	ASP	828	16.266	7.506	30.052	1.00	25.47
ATOM	1280	N	GLU	829	17.915	8.191	31.382	1.00	25.59
ATOM	1281	CA	GLU	829	17.292	9.494	31.559	1.00	26.44
ATOM	1282	CB	GLU	829	18.006	10.303	32.650	1.00	28.25
ATOM	1283	CG	GLU	829	17.415	11.696	32.898	1.00	30.25
ATOM	1284	CD	GLU	829	18.210	12.499	33.925	1.00	32.25
ATOM	1285	OE1	GLU	829	19.432	12.719	33.717	1.00	33.52
ATOM	1286	OE2	GLU	829	17.618	12.918	34.946	1.00	33.33
ATOM	1287	C	GLU	829	17.343	10.233	30.223	1.00	25.94
ATOM	1288	O	GLU	829	16.342	10.797	29.777	1.00	25.19
ATOM	1289	N	LEU	830	18.506	10.208	29.575	1.00	25.30
ATOM	1290	CA	LEU	830	18.645	10.859	28.282	1.00	25.23
ATOM	1291	CB	LEU	830	20.072	10.736	27.761	1.00	26.02
ATOM	1292	CG	LEU	830	20.940	11.959	28.038	1.00	27.07
ATOM	1293	CD1	LEU	830	21.096	12.139	29.555	1.00	28.25
ATOM	1294	CD2	LEU	830	22.298	11.793	27.362	1.00	27.32
ATOM	1295	C	LEU	830	17.678	10.249	27.279	1.00	25.12
ATOM	1296	O	LEU	830	16.943	10.966	26.606	1.00	24.67
ATOM	1297	N	ARG	831	17.668	8.922	27.188	1.00	25.07

TABLE A-continued

ATOM	1298	CA	ARG	831	16.768	8.253	26.261	1.00	25.48
ATOM	1299	CB	ARG	831	16.913	6.732	26.358	1.00	25.48
ATOM	1300	CG	ARG	831	15.953	5.993	25.441	1.00	25.24
ATOM	1301	CD	ARG	831	16.261	4.499	25.357	1.00	25.58
ATOM	1302	NE	ARG	831	15.158	3.781	24.719	1.00	25.78
ATOM	1303	CZ	ARG	831	14.822	3.879	23.436	1.00	25.10
ATOM	1304	NH1	ARG	831	15.507	4.661	22.617	1.00	24.95
ATOM	1305	NH2	ARG	831	13.774	3.213	22.982	1.00	25.49
ATOM	1306	C	ARG	831	15.319	8.654	26.526	1.00	25.51
ATOM	1307	O	ARG	831	14.559	8.929	25.590	1.00	25.14
ATOM	1308	N	MET	832	14.948	8.697	27.804	1.00	25.71
ATOM	1309	CA	MET	832	13.591	9.070	28.202	1.00	26.13
ATOM	1310	CB	MET	832	13.393	8.855	29.706	1.00	26.07
ATOM	1311	CG	MET	832	12.280	9.683	30.316	1.00	25.80
ATOM	1312	SD	MET	832	11.876	9.192	32.002	1.00	28.43
ATOM	1313	CE	MET	832	12.867	10.272	32.995	1.00	26.55
ATOM	1314	C	MET	832	13.255	10.518	27.847	1.00	25.99
ATOM	1315	O	MET	832	12.114	10.828	27.518	1.00	26.12
ATOM	1316	N	ASN	833	14.241	11.403	27.916	1.00	26.07
ATOM	1317	CA	ASN	833	13.996	12.800	27.590	1.00	26.18
ATOM	1318	CB	ASN	833	15.129	13.668	28.126	1.00	26.83
ATOM	1319	CG	ASN	833	15.026	13.874	29.625	1.00	27.86
ATOM	1320	OD1	ASN	833	16.004	14.206	30.297	1.00	28.97
ATOM	1321	ND2	ASN	833	13.827	13.682	30.156	1.00	27.93
ATOM	1322	C	ASN	833	13.795	13.021	26.099	1.00	26.03
ATOM	1323	O	ASN	833	12.989	13.856	25.701	1.00	25.96
ATOM	1324	N	TYR	834	14.513	12.267	25.277	1.00	25.89
ATOM	1325	CA	TYR	834	14.375	12.385	23.835	1.00	26.53
ATOM	1326	CB	TYR	834	15.572	11.732	23.142	1.00	25.95
ATOM	1327	CG	TYR	834	16.759	12.670	23.114	1.00	25.75
ATOM	1328	CD1	TYR	834	17.008	13.471	22.004	1.00	25.23
ATOM	1329	CE1	TYR	834	18.028	14.418	22.017	1.00	25.38
ATOM	1330	CD2	TYR	834	17.566	12.839	24.239	1.00	25.31
ATOM	1331	CE2	TYR	834	18.584	13.784	24.260	1.00	24.66
ATOM	1332	CZ	TYR	834	18.813	14.569	23.149	1.00	24.63
ATOM	1333	OH	TYR	834	19.831	15.496	23.153	1.00	24.47
ATOM	1334	C	TYR	834	13.054	11.784	23.364	1.00	27.63
ATOM	1335	O	TYR	834	12.385	12.338	22.493	1.00	27.51
ATOM	1336	N	ILE	835	12.668	10.655	23.948	1.00	28.57
ATOM	1337	CA	ILE	835	11.404	10.044	23.586	1.00	29.73
ATOM	1338	CB	ILE	835	11.131	8.765	24.404	1.00	29.44
ATOM	1339	CG2	ILE	835	9.640	8.458	24.415	1.00	29.00
ATOM	1340	CG1	ILE	835	11.940	7.598	23.828	1.00	29.23
ATOM	1341	CD1	ILE	835	11.798	6.295	24.604	1.00	28.37
ATOM	1342	C	ILE	835	10.294	11.053	23.861	1.00	31.03
ATOM	1343	O	ILE	835	9.354	11.171	23.084	1.00	30.89
ATOM	1344	N	LYS	836	10.410	11.777	24.971	1.00	32.73
ATOM	1345	CA	LYS	836	9.411	12.772	25.335	1.00	34.47
ATOM	1346	CB	LYS	836	9.613	13.246	26.781	1.00	35.12
ATOM	1347	CG	LYS	836	9.220	12.210	27.845	1.00	36.26
ATOM	1348	CD	LYS	836	9.047	12.853	29.226	1.00	36.96
ATOM	1349	CE	LYS	836	8.689	11.822	30.292	1.00	37.93
ATOM	1350	NZ	LYS	836	7.331	11.205	30.106	1.00	38.44
ATOM	1351	C	LYS	836	9.411	13.974	24.401	1.00	35.36
ATOM	1352	O	LYS	836	8.401	14.663	24.288	1.00	35.57
ATOM	1353	N	GLU	837	10.533	14.232	23.730	1.00	36.74
ATOM	1354	CA	GLU	837	10.605	15.360	22.801	1.00	37.88
ATOM	1355	CB	GLU	837	12.056	15.750	22.516	1.00	38.02
ATOM	1356	CG	GLU	837	12.811	16.300	23.720	1.00	38.61
ATOM	1357	CD	GLU	837	12.171	17.552	24.298	1.00	38.88
ATOM	1358	OE1	GLU	837	12.694	18.080	25.301	1.00	38.97
ATOM	1359	OE2	GLU	837	11.145	18.011	23.751	1.00	39.85
ATOM	1360	C	GLU	837	9.902	14.995	21.502	1.00	39.04
ATOM	1361	O	GLU	837	9.248	15.837	20.883	1.00	39.39
ATOM	1362	N	LEU	838	10.035	13.737	21.089	1.00	40.19
ATOM	1363	CA	LEU	838	9.377	13.283	19.873	1.00	41.66
ATOM	1364	CB	LEU	838	9.745	11.840	19.551	1.00	40.92
ATOM	1365	CG	LEU	838	9.059	11.325	18.283	1.00	40.71
ATOM	1366	CD1	LEU	838	9.337	12.287	17.131	1.00	40.13
ATOM	1367	CD2	LEU	838	9.549	9.921	17.961	1.00	40.28
ATOM	1368	C	LEU	838	7.882	13.376	20.098	1.00	43.18
ATOM	1369	O	LEU	838	7.117	13.684	19.187	1.00	43.33
ATOM	1370	N	ASP	839	7.469	13.105	21.329	1.00	45.15
ATOM	1371	CA	ASP	839	6.063	13.176	21.679	1.00	47.48
ATOM	1372	CB	ASP	839	5.852	12.690	23.109	1.00	47.71
ATOM	1373	CG	ASP	839	4.409	12.777	23.538	1.00	48.24
ATOM	1374	CD1	ASP	839	3.575	12.016	22.996	1.00	48.44
ATOM	1375	OD2	ASP	839	4.108	13.617	24.411	1.00	48.69
ATOM	1376	C	ASP	839	5.565	14.617	21.539	1.00	48.74

TABLE A-continued

ATOM	1377	O	ASP	839	4.525	14.866	20.938	1.00	48.83
ATOM	1378	N	ARG	840	6.314	15.566	22.086	1.00	50.51
ATOM	1379	CA	ARG	840	5.922	16.965	21.999	1.00	52.38
ATOM	1380	CB	ARG	840	6.739	17.805	22.985	1.00	52.53
ATOM	1381	CG	ARG	840	6.330	17.586	24.444	1.00	53.33
ATOM	1382	CD	ARG	840	7.033	18.548	25.395	1.00	53.67
ATOM	1383	NE	ARG	840	8.378	18.110	25.759	1.00	53.99
ATOM	1384	CZ	ARG	840	9.318	18.922	26.232	1.00	54.20
ATOM	1385	NH1	ARG	840	9.057	20.214	26.388	1.00	54.27
ATOM	1386	NH2	ARG	840	10.513	18.447	26.558	1.00	54.13
ATOM	1387	C	ARG	840	6.041	17.534	20.585	1.00	53.55
ATOM	1388	O	ARG	840	5.293	18.436	20.211	1.00	53.71
ATOM	1389	N	ILE	841	6.979	17.021	19.796	1.00	54.98
ATOM	1390	CA	ILE	841	7.120	17.511	18.433	1.00	56.52
ATOM	1391	CB	ILE	841	8.440	17.040	17.784	1.00	56.31
ATOM	1392	CG2	ILE	841	8.442	15.540	17.629	1.00	56.61
ATOM	1393	CG1	ILE	841	8.600	17.678	16.405	1.00	56.35
ATOM	1394	CD1	ILE	841	8.600	19.187	16.425	1.00	56.59
ATOM	1395	C	ILE	841	5.927	16.955	17.659	1.00	57.71
ATOM	1396	O	ILE	841	5.593	17.414	16.564	1.00	57.95
ATOM	1397	N	ILE	842	5.285	15.955	18.247	1.00	59.05
ATOM	1398	CA	ILE	842	4.115	15.345	17.644	1.00	60.55
ATOM	1399	CB	ILE	842	3.929	13.899	18.145	1.00	60.34
ATOM	1400	CG2	ILE	842	2.539	13.386	17.786	1.00	60.36
ATOM	1401	CG1	ILE	842	5.014	13.002	17.552	1.00	60.28
ATOM	1402	CD1	ILE	842	4.968	12.899	16.046	1.00	60.36
ATOM	1403	C	ILE	842	2.886	16.173	18.021	1.00	61.84
ATOM	1404	O	ILE	842	2.077	16.521	17.165	1.00	62.01
ATOM	1405	N	ALA	843	2.768	16.503	19.304	1.00	63.28
ATOM	1406	CA	ALA	843	1.636	17.274	19.811	1.00	64.93
ATOM	1407	CB	ALA	843	1.202	16.719	21.168	1.00	64.96
ATOM	1408	C	ALA	843	1.921	18.770	19.931	1.00	66.08
ATOM	1409	O	ALA	843	2.657	19.346	19.125	1.00	66.22
ATOM	1410	N	CYS	844	1.327	19.393	20.946	1.00	67.46
ATOM	1411	CA	CYS	844	1.499	20.825	21.187	1.00	68.93
ATOM	1412	CB	CYS	844	0.818	21.235	22.496	1.00	69.02
ATOM	1413	SG	CYS	844	1.052	22.983	22.913	1.00	69.96
ATOM	1414	C	CYS	844	2.965	21.264	21.224	1.00	69.69
ATOM	1415	O	CYS	844	3.734	20.858	22.103	1.00	69.75
ATOM	1416	N	ALA	845	3.331	22.104	20.260	1.00	70.51
ATOM	1417	CA	ALA	845	4.685	22.631	20.138	1.00	71.20
ATOM	1418	CB	ALA	845	5.697	21.488	20.150	1.00	71.12
ATOM	1419	C	ALA	845	4.805	23.418	18.837	1.00	71.67
ATOM	1420	O	ALA	845	5.173	24.599	18.838	1.00	71.61
ATOM	1421	N	ALA	846	4.473	22.754	17.732	1.00	72.18
ATOM	1422	CA	ALA	846	4.555	23.359	16.411	1.00	72.76
ATOM	1423	CB	ALA	846	5.743	22.785	15.670	1.00	72.64
ATOM	1424	C	ALA	846	3.291	23.178	15.572	1.00	73.29
ATOM	1425	O	ALA	846	2.639	24.157	15.204	1.00	73.45
ATOM	1426	N	LYS	847	2.949	21.925	15.273	1.00	73.74
ATOM	1427	CA	LYS	847	1.780	21.617	14.450	1.00	74.06
ATOM	1428	CB	LYS	847	1.558	20.100	14.383	1.00	74.11
ATOM	1429	CG	LYS	847	2.498	19.384	13.412	1.00	74.21
ATOM	1430	CD	LYS	847	2.359	19.953	12.002	1.00	74.15
ATOM	1431	CE	LYS	847	3.331	19.313	11.026	1.00	74.04
ATOM	1432	NZ	LYS	847	3.206	19.907	9.662	1.00	73.48
ATOM	1433	C	LYS	847	0.478	22.307	14.842	1.00	74.24
ATOM	1434	O	LYS	847	0.203	22.539	16.021	1.00	74.15
ATOM	1435	N	ALA	848	−0.311	22.632	13.820	1.00	74.54
ATOM	1436	CA	ALA	848	−1.600	23.296	13.981	1.00	74.71
ATOM	1437	CB	ALA	848	−1.786	24.350	12.885	1.00	74.65
ATOM	1438	C	ALA	848	−2.755	22.289	13.948	1.00	74.78
ATOM	1439	O	ALA	848	−3.691	22.386	14.746	1.00	75.01
ATOM	1440	N	PRO	849	−2.715	21.318	13.016	1.00	74.70
ATOM	1441	CD	PRO	849	−1.791	21.178	11.874	1.00	74.87
ATOM	1442	CA	PRO	849	−3.789	20.320	12.936	1.00	74.53
ATOM	1443	CB	PRO	849	−3.627	19.756	11.529	1.00	74.63
ATOM	1444	CG	PRO	849	−2.143	19.803	11.336	1.00	74.79
ATOM	1445	C	PRO	849	−3.632	19.250	14.014	1.00	74.18
ATOM	1446	O	PRO	849	−2.519	18.800	14.286	1.00	74.25
ATOM	1447	N	THR	850	−4.746	18.848	14.621	1.00	73.78
ATOM	1448	CA	THR	850	−4.736	17.840	15.682	1.00	73.31
ATOM	1449	CB	THR	850	−6.180	17.441	16.067	1.00	73.45
ATOM	1450	OG1	THR	850	−6.144	16.387	17.038	1.00	73.57
ATOM	1451	CG2	THR	850	−6.961	16.990	14.832	1.00	73.61
ATOM	1452	C	THR	850	−3.933	16.578	15.329	1.00	72.80
ATOM	1453	O	THR	850	−4.467	15.613	14.771	1.00	72.81
ATOM	1454	N	SER	851	−2.648	16.591	15.675	1.00	71.96
ATOM	1455	CA	SER	851	−1.751	15.471	15.393	1.00	71.07

TABLE A-continued

ATOM	1456	CB	SER	851	−0.664	15.924	14.405	1.00	71.04
ATOM	1457	OG	SER	851	0.243	14.881	14.097	1.00	70.59
ATOM	1458	C	SER	851	−1.099	14.932	16.670	1.00	70.34
ATOM	1459	O	SER	851	−0.015	15.370	17.047	1.00	70.40
ATOM	1460	N	CYS	852	−1.759	13.982	17.333	1.00	69.35
ATOM	1461	CA	CYS	852	−1.225	13.395	18.565	1.00	68.12
ATOM	1462	CB	CYS	852	−1.375	14.384	19.735	1.00	68.59
ATOM	1463	SG	CYS	852	−3.043	15.096	19.978	1.00	69.59
ATOM	1464	C	CYS	852	−1.854	12.050	18.944	1.00	66.82
ATOM	1465	O	CYS	852	−1.848	11.662	20.113	1.00	66.81
ATOM	1466	N	SER	853	−2.382	11.334	17.956	1.00	65.27
ATOM	1467	CA	SER	853	−3.007	10.041	18.211	1.00	63.60
ATOM	1468	CB	SER	853	−4.373	9.970	17.514	1.00	63.93
ATOM	1469	OG	SER	853	−4.272	10.324	16.148	1.00	63.97
ATOM	1470	C	SER	853	−2.134	8.862	17.778	1.00	62.15
ATOM	1471	O	SER	853	−1.316	8.371	18.562	1.00	62.22
ATOM	1472	N	ARG	854	−2.305	8.411	16.537	1.00	60.15
ATOM	1473	CA	ARG	854	−1.532	7.282	16.021	1.00	58.00
ATOM	1474	CB	ARG	854	−2.376	6.455	15.035	1.00	58.75
ATOM	1475	CG	ARG	854	−2.622	7.112	13.680	1.00	59.49
ATOM	1476	CD	ARG	854	−3.460	6.203	12.778	1.00	60.59
ATOM	1477	NE	ARG	854	−3.671	6.744	11.429	1.00	61.32
ATOM	1478	CZ	ARG	854	−4.324	7.873	11.150	1.00	61.65
ATOM	1479	NH1	ARG	854	−4.848	8.611	12.124	1.00	61.58
ATOM	1480	NH2	ARG	854	−4.454	8.267	9.887	1.00	61.67
ATOM	1481	C	ARG	854	−0.241	7.730	15.339	1.00	55.94
ATOM	1482	O	ARG	854	0.411	6.952	14.653	1.00	55.60
ATOM	1483	N	ARG	855	0.129	8.987	15.540	1.00	53.73
ATOM	1484	CA	ARG	855	1.342	9.528	14.946	1.00	51.51
ATOM	1485	CB	ARG	855	1.337	11.051	15.063	1.00	50.74
ATOM	1486	CG	ARG	855	2.404	11.739	14.247	1.00	49.65
ATOM	1487	CD	ARG	855	2.238	11.446	12.760	1.00	48.66
ATOM	1488	NE	ARG	855	3.212	12.183	11.966	1.00	46.95
ATOM	1489	CZ	ARG	855	3.327	12.088	10.650	1.00	46.55
ATOM	1490	NH1	ARG	855	2.526	11.280	9.967	1.00	45.80
ATOM	1491	NH2	ARG	855	4.248	12.802	10.020	1.00	46.32
ATOM	1492	C	ARG	855	2.580	8.955	15.642	1.00	50.40
ATOM	1493	O	ARG	855	3.633	8.777	15.026	1.00	50.15
ATOM	1494	N	PHE	856	2.448	8.669	16.933	1.00	48.68
ATOM	1495	CA	PHE	856	3.554	8.117	17.694	1.00	46.90
ATOM	1496	CB	PHE	856	3.327	8.325	19.196	1.00	47.21
ATOM	1497	CG	PHE	856	4.461	7.836	20.058	1.00	47.24
ATOM	1498	CD1	PHE	856	5.710	8.448	20.004	1.00	47.28
ATOM	1499	CD2	PHE	856	4.278	6.766	20.930	1.00	47.12
ATOM	1500	CE1	PHE	856	6.761	8.000	20.811	1.00	47.48
ATOM	1501	CE2	PHE	856	5.324	6.312	21.743	1.00	47.30
ATOM	1502	CZ	PHE	856	6.566	6.929	21.684	1.00	47.08
ATOM	1503	C	PHE	856	3.705	6.633	17.393	1.00	45.50
ATOM	1504	O	PHE	856	4.825	6.122	17.331	1.00	45.41
ATOM	1505	N	TYR	857	2.584	5.940	17.196	1.00	43.60
ATOM	1506	CA	TYR	857	2.643	4.511	16.910	1.00	41.70
ATOM	1507	CB	TYR	857	1.249	3.880	16.893	1.00	42.01
ATOM	1508	CG	TYR	857	1.271	2.393	16.574	1.00	42.12
ATOM	1509	CD1	TYR	857	1.713	1.462	17.512	1.00	42.35
ATOM	1510	CE1	TYR	857	1.785	0.100	17.206	1.00	42.40
ATOM	1511	CD2	TYR	857	0.895	1.923	15.315	1.00	42.37
ATOM	1512	CE2	TYR	857	0.967	0.562	14.997	1.00	42.18
ATOM	1513	CZ	TYR	857	1.414	−0.341	15.946	1.00	42.56
ATOM	1514	OH	TYR	857	1.516	−1.681	15.629	1.00	42.93
ATOM	1515	C	TYR	857	3.323	4.222	15.582	1.00	40.32
ATOM	1516	O	TYR	857	4.092	3.266	15.478	1.00	40.51
ATOM	1517	N	GLN	858	3.047	5.023	14.558	1.00	38.44
ATOM	1518	CA	GLN	858	3.682	4.764	13.271	1.00	36.90
ATOM	1519	CB	GLN	858	2.888	5.372	12.104	1.00	37.28
ATOM	1520	CG	GLN	858	2.188	6.677	12.379	1.00	37.76
ATOM	1521	CD	GLN	858	0.934	6.820	11.536	1.00	38.54
ATOM	1522	OE1	GLN	858	0.165	5.862	11.391	1.00	38.69
ATOM	1523	NE2	GLN	858	0.712	8.012	10.982	1.00	38.73
ATOM	1524	C	GLN	858	5.134	5.201	13.210	1.00	35.37
ATOM	1525	O	GLN	858	5.949	4.501	12.612	1.00	35.14
ATOM	1526	N	LEU	859	5.471	6.330	13.834	1.00	33.65
ATOM	1527	CA	LEU	859	6.859	6.782	13.826	1.00	32.33
ATOM	1528	CB	LEU	859	6.995	8.191	14.412	1.00	32.33
ATOM	1529	CG	LEU	859	6.425	9.362	13.596	1.00	32.70
ATOM	1530	CD1	LEU	859	6.736	10.688	14.294	1.00	32.82
ATOM	1531	CD2	LEU	859	7.017	9.368	12.210	1.00	32.87
ATOM	1532	C	LEU	859	7.743	5.806	14.607	1.00	31.28
ATOM	1533	O	LEU	859	8.844	5.475	14.174	1.00	30.56
ATOM	1534	N	THR	860	7.264	5.339	15.754	1.00	30.60

TABLE A-continued

ATOM	1535	CA	THR	860	8.043	4.389	16.550	1.00	30.04
ATOM	1536	CB	THR	860	7.398	4.142	17.938	1.00	30.12
ATOM	1537	OG1	THR	860	6.024	3.776	17.777	1.00	30.74
ATOM	1538	CG2	THR	860	7.472	5.403	18.780	1.00	29.71
ATOM	1539	C	THR	860	8.162	3.083	15.764	1.00	29.10
ATOM	1540	O	THR	860	9.114	2.329	15.926	1.00	28.88
ATOM	1541	N	LYS	861	7.191	2.839	14.893	1.00	28.36
ATOM	1542	CA	LYS	861	7.202	1.659	14.039	1.00	27.61
ATOM	1543	CB	LYS	861	5.855	1.517	13.334	1.00	28.44
ATOM	1544	CG	LYS	861	5.025	0.365	13.819	1.00	29.58
ATOM	1545	CD	LYS	861	5.650	−0.948	13.420	1.00	30.16
ATOM	1546	CE	LYS	861	4.869	−2.106	13.998	1.00	30.39
ATOM	1547	NZ	LYS	861	5.567	−3.402	13.771	1.00	31.31
ATOM	1548	C	LYS	861	8.291	1.885	12.991	1.00	26.55
ATOM	1549	O	LYS	861	9.097	1.002	12.680	1.00	26.06
ATOM	1550	N	LEU	862	8.300	3.088	12.439	1.00	25.35
ATOM	1551	CA	LEU	862	9.288	3.421	11.439	1.00	24.93
ATOM	1552	CB	LEU	862	9.030	4.818	10.891	1.00	24.31
ATOM	1553	CG	LEU	862	10.060	5.242	9.855	1.00	24.36
ATOM	1554	CD1	LEU	862	9.948	4.337	8.645	1.00	23.62
ATOM	1555	CD2	LEU	862	9.846	6.687	9.484	1.00	23.25
ATOM	1556	C	LEU	862	10.692	3.332	12.038	1.00	24.54
ATOM	1557	O	LEU	862	11.581	2.748	11.433	1.00	24.21
ATOM	1558	N	LEU	863	10.894	3.901	13.227	1.00	24.64
ATOM	1559	CA	LEU	863	12.216	3.843	13.868	1.00	24.87
ATOM	1560	CB	LEU	863	12.216	4.613	15.188	1.00	24.73
ATOM	1561	CG	LEU	863	12.307	6.129	15.049	1.00	25.00
ATOM	1562	CD1	LEU	863	12.356	6.762	16.428	1.00	24.84
ATOM	1563	CD2	LEU	863	13.554	6.483	14.240	1.00	25.12
ATOM	1564	C	LEU	863	12.689	2.402	14.105	1.00	24.37
ATOM	1565	O	LEU	863	13.837	2.068	13.826	1.00	24.46
ATOM	1566	N	ASP	864	11.815	1.549	14.622	1.00	24.20
ATOM	1567	CA	ASP	864	12.190	0.154	14.835	1.00	24.33
ATOM	1568	CB	ASP	864	11.014	−0.626	15.438	1.00	25.03
ATOM	1569	CG	ASP	864	10.670	−0.189	16.878	1.00	26.02
ATOM	1570	OD1	ASP	864	11.490	0.519	17.518	1.00	25.80
ATOM	1571	OD2	ASP	864	9.578	−0.573	17.367	1.00	25.23
ATOM	1572	C	ASP	864	12.598	−0.511	13.499	1.00	24.21
ATOM	1573	O	ASP	864	13.473	−1.383	13.460	1.00	24.29
ATOM	1574	N	SER	865	11.966	−0.090	12.404	1.00	23.73
ATOM	1575	CA	SER	865	12.237	−0.682	11.098	1.00	23.19
ATOM	1576	CB	SER	865	11.217	−0.194	10.052	1.00	22.65
ATOM	1577	OG	SER	865	11.527	1.099	9.565	1.00	21.98
ATOM	1578	C	SER	865	13.659	−0.432	10.611	1.00	23.12
ATOM	1579	O	SER	865	14.149	−1.138	9.738	1.00	23.62
ATOM	1580	N	VAL	866	14.331	0.562	11.178	1.00	22.48
ATOM	1581	CA	VAL	866	15.708	0.839	10.786	1.00	21.73
ATOM	1582	CB	VAL	866	16.190	2.188	11.345	1.00	20.85
ATOM	1583	CG1	VAL	866	17.665	2.377	11.012	1.00	20.74
ATOM	1584	CG2	VAL	866	15.354	3.317	10.784	1.00	19.44
ATOM	1585	C	VAL	866	16.653	−0.236	11.338	1.00	21.81
ATOM	1586	O	VAL	866	17.656	−0.598	10.723	1.00	22.06
ATOM	1587	N	GLN	867	16.327	−0.744	12.512	1.00	21.74
ATOM	1588	CA	GLN	867	17.178	−1.722	13.153	1.00	21.73
ATOM	1589	CB	GLN	867	16.607	−2.055	14.527	1.00	22.18
ATOM	1590	CG	GLN	867	16.498	−0.829	15.412	1.00	22.59
ATOM	1591	CD	GLN	867	17.837	−0.158	15.638	1.00	22.57
ATOM	1592	OE1	GLN	867	18.826	−0.819	15.953	1.00	23.51
ATOM	1593	NE2	GLN	867	17.873	1.158	15.497	1.00	22.55
ATOM	1594	C	GLN	867	17.481	−2.994	12.372	1.00	21.37
ATOM	1595	O	GLN	867	18.650	−3.330	12.187	1.00	21.44
ATOM	1596	N	PRO	868	16.448	−3.733	11.923	1.00	21.04
ATOM	1597	CD	PRO	868	14.989	−3.550	12.037	1.00	21.82
ATOM	1598	CA	PRO	868	16.770	−4.948	11.175	1.00	20.68
ATOM	1599	CB	PRO	868	15.390	−5.545	10.841	1.00	20.96
ATOM	1600	CG	PRO	868	14.468	−4.383	10.884	1.00	21.59
ATOM	1601	C	PRO	868	17.617	−4.622	9.950	1.00	20.19
ATOM	1602	O	PRO	868	18.479	−5.403	9.551	1.00	20.47
ATOM	1603	N	ILE	869	17.383	−3.455	9.362	1.00	19.77
ATOM	1604	CA	ILE	869	18.175	−3.037	8.216	1.00	18.93
ATOM	1605	CB	ILE	869	17.656	−1.698	7.649	1.00	18.67
ATOM	1606	CG2	ILE	869	18.605	−1.185	6.545	1.00	18.45
ATOM	1607	CG1	ILE	869	16.235	−1.890	7.121	1.00	18.20
ATOM	1608	CD1	ILE	869	15.597	−0.642	6.543	1.00	17.92
ATOM	1609	C	ILE	869	19.641	−2.881	8.665	1.00	18.84
ATOM	1610	O	ILE	869	20.551	−3.408	8.023	1.00	17.81
ATOM	1611	N	ALA	870	19.863	−2.169	9.773	1.00	18.50
ATOM	1612	CA	ALA	870	21.221	−1.964	10.280	1.00	19.01
ATOM	1613	CB	ALA	870	21.207	−1.118	11.563	1.00	17.32

TABLE A-continued

ATOM	1614	C	ALA	870	21.898	−3.305	10.541	1.00	19.42
ATOM	1615	O	ALA	870	23.104	−3.452	10.329	1.00	19.55
ATOM	1616	N	ARG	871	21.116	−4.286	10.981	1.00	20.41
ATOM	1617	CA	ARG	871	21.654	−5.615	11.274	1.00	21.54
ATOM	1618	CB	ARG	871	20.619	−6.462	12.038	1.00	21.89
ATOM	1619	CG	ARG	871	21.042	−7.895	12.307	1.00	23.32
ATOM	1620	CD	ARG	871	22.427	−7.959	12.926	1.00	25.37
ATOM	1621	NE	ARG	871	22.888	−9.331	13.146	1.00	26.95
ATOM	1622	CZ	ARG	871	22.292	−10.205	13.953	1.00	26.98
ATOM	1623	NH1	ARG	871	21.202	−9.854	14.617	1.00	27.28
ATOM	1624	NH2	ARG	871	22.803	−11.420	14.116	1.00	26.87
ATOM	1625	C	ARG	871	22.096	−6.316	9.992	1.00	22.03
ATOM	1626	O	ARG	871	23.135	−6.976	9.970	1.00	22.91
ATOM	1627	N	GLU	872	21.316	−6.171	8.922	1.00	21.94
ATOM	1628	CA	GLU	872	21.683	−6.772	7.647	1.00	21.84
ATOM	1629	CB	GLU	872	20.613	−6.515	6.578	1.00	23.42
ATOM	1630	CG	GLU	872	19.305	−7.281	6.758	1.00	25.54
ATOM	1631	CD	GLU	872	18.418	−7.213	5.518	1.00	27.28
ATOM	1632	OE1	GLU	872	17.294	−7.766	5.553	1.00	28.13
ATOM	1633	OE2	GLU	872	18.845	−6.612	4.503	1.00	27.83
ATOM	1634	C	GLU	872	23.005	−6.198	7.161	1.00	21.22
ATOM	1635	O	GLU	872	23.888	−6.941	6.742	1.00	21.80
ATOM	1636	N	LEU	873	23.140	−4.873	7.222	1.00	20.38
ATOM	1637	CA	LEU	873	24.353	−4.198	6.773	1.00	19.25
ATOM	1638	CB	LEU	873	24.115	−2.677	6.674	1.00	19.83
ATOM	1639	CG	LEU	873	23.051	−2.181	5.675	1.00	19.60
ATOM	1640	CD1	LEU	873	23.053	−0.665	5.635	1.00	20.16
ATOM	1641	CD2	LEU	873	23.330	−2.726	4.279	1.00	19.48
ATOM	1642	C	LEU	873	25.530	−4.489	7.690	1.00	19.03
ATOM	1643	O	LEU	873	26.670	−4.505	7.252	1.00	18.60
ATOM	1644	N	HIS	874	25.264	−4.720	8.972	1.00	18.94
ATOM	1645	CA	HIS	874	26.354	−5.037	9.880	1.00	18.94
ATOM	1646	CB	HIS	874	25.881	−5.078	11.337	1.00	18.69
ATOM	1647	CG	HIS	874	25.715	−3.729	11.956	1.00	17.78
ATOM	1648	CD2	HIS	874	26.460	−2.605	11.855	1.00	17.59
ATOM	1649	ND1	HIS	874	24.703	−3.440	12.843	1.00	17.53
ATOM	1650	CE1	HIS	874	24.835	−2.196	13.267	1.00	17.42
ATOM	1651	NE2	HIS	874	25.894	−1.667	12.685	1.00	17.13
ATOM	1652	C	HIS	874	26.879	−6.396	9.482	1.00	18.68
ATOM	1653	O	HIS	874	28.084	−6.611	9.418	1.00	18.92
ATOM	1654	N	GLN	875	25.971	−7.313	9.202	1.00	19.13
ATOM	1655	CA	GLN	875	26.374	−8.654	8.810	1.00	20.22
ATOM	1656	CB	GLN	875	25.141	−9.518	8.582	1.00	20.38
ATOM	1657	CG	GLN	875	25.441	−10.988	8.502	1.00	21.65
ATOM	1658	CD	GLN	875	26.165	−11.480	9.742	1.00	21.80
ATOM	1659	OE1	GLN	875	27.387	−11.562	9.765	1.00	22.35
ATOM	1660	NE2	GLN	875	25.408	−11.787	10.786	1.00	21.86
ATOM	1661	C	GLN	875	27.226	−8.609	7.536	1.00	20.68
ATOM	1662	O	GLN	875	28.321	−9.185	7.475	1.00	20.84
ATOM	1663	N	PHE	876	26.728	−7.904	6.527	1.00	21.33
ATOM	1664	CA	PHE	876	27.432	−7.778	5.257	1.00	21.58
ATOM	1665	CB	PHE	876	26.563	−7.003	4.258	1.00	22.76
ATOM	1666	CG	PHE	876	27.324	−6.426	3.099	1.00	23.48
ATOM	1667	CD1	PHE	876	27.981	−5.211	3.220	1.00	24.12
ATOM	1668	CD2	PHE	876	27.354	−7.084	1.876	1.00	24.70
ATOM	1669	CE1	PHE	876	28.658	−4.646	2.139	1.00	25.07
ATOM	1670	CE2	PHE	876	28.028	−6.535	0.780	1.00	25.33
ATOM	1671	CZ	PHE	876	28.684	−5.305	0.913	1.00	25.56
ATOM	1672	C	PHE	876	28.782	−7.104	5.404	1.00	21.53
ATOM	1673	O	PHE	876	29.788	−7.616	4.917	1.00	21.91
ATOM	1674	N	THR	877	28.806	−5.952	6.063	1.00	21.43
ATOM	1675	CA	THR	877	30.063	−5.220	6.249	1.00	22.00
ATOM	1676	CB	THR	877	29.824	−3.884	7.014	1.00	20.78
ATOM	1677	CG2	THR	877	31.108	−3.079	7.227	1.00	15.00
ATOM	1678	OG1	THR	877	28.924	−3.062	6.286	1.00	15.00
ATOM	1679	C	THR	877	31.088	−6.071	6.987	1.00	21.87
ATOM	1680	O	THR	877	32.265	−6.025	6.661	1.00	21.92
ATOM	1681	N	PHE	878	30.648	−6.834	7.984	1.00	22.33
ATOM	1682	CA	PHE	878	31.568	−7.694	8.727	1.00	23.05
ATOM	1683	CB	PHE	878	30.867	−8.381	9.899	1.00	22.33
ATOM	1684	CG	PHE	878	31.666	−9.513	10.495	1.00	21.73
ATOM	1685	CD1	PHE	878	32.782	−9.254	11.288	1.00	21.25
ATOM	1686	CD2	PHE	878	31.317	−10.838	10.241	1.00	21.33
ATOM	1687	CE1	PHE	878	33.538	−10.301	11.822	1.00	20.86
ATOM	1688	CE2	PHE	878	32.069	−11.889	10.771	1.00	21.01
ATOM	1689	CZ	PHE	878	33.181	−11.618	11.562	1.00	21.09
ATOM	1690	C	PHE	878	32.092	−8.766	7.775	1.00	23.92
ATOM	1691	O	PHE	878	33.307	−8.936	7.618	1.00	23.91
ATOM	1692	N	ASP	879	31.166	−9.503	7.160	1.00	24.70

TABLE A-continued

ATOM	1693	CA	ASP	879	31.545	−10.540	6.203	1.00	25.62
ATOM	1694	CB	ASP	879	30.318	−11.110	5.483	1.00	26.61
ATOM	1695	CG	ASP	879	29.466	−12.011	6.373	1.00	28.26
ATOM	1696	OD1	ASP	879	29.869	−12.286	7.532	1.00	29.19
ATOM	1697	OD2	ASP	879	28.388	−12.446	5.903	1.00	28.52
ATOM	1698	C	ASP	879	32.485	−9.937	5.161	1.00	25.71
ATOM	1699	O	ASP	879	33.446	−10.586	4.743	1.00	25.95
ATOM	1700	N	LEU	880	32.224	−8.690	4.759	1.00	25.33
ATOM	1701	CA	LEU	880	33.050	−8.038	3.740	1.00	25.14
ATOM	1702	CB	LEU	880	32.420	−6.706	3.288	1.00	24.49
ATOM	1703	CG	LEU	880	33.171	−5.970	2.157	1.00	24.36
ATOM	1704	CD1	LEU	880	33.263	−6.890	0.941	1.00	24.34
ATOM	1705	CD2	LEU	880	32.486	−4.669	1.777	1.00	23.43
ATOM	1706	C	LEU	880	34.494	−7.800	4.174	1.00	24.87
ATOM	1707	O	LEU	880	35.414	−7.954	3.384	1.00	24.35
ATOM	1708	N	LEU	881	34.672	−7.424	5.433	1.00	25.68
ATOM	1709	CA	LEU	881	35.984	−7.151	6.010	1.00	26.42
ATOM	1710	CB	LEU	881	35.823	−6.684	7.459	1.00	26.13
ATOM	1711	CG	LEU	881	37.124	−6.552	8.247	1.00	25.98
ATOM	1712	CD1	LEU	881	37.921	−5.392	7.676	1.00	25.56
ATOM	1713	CD2	LEU	881	36.828	−6.335	9.726	1.00	26.07
ATOM	1714	C	LEU	881	36.905	−8.358	5.988	1.00	27.40
ATOM	1715	O	LEU	881	38.030	−8.284	5.498	1.00	27.41
ATOM	1716	N	ILE	882	36.416	−9.466	6.532	1.00	28.64
ATOM	1717	CA	ILE	882	37.187	−10.694	6.610	1.00	30.19
ATOM	1718	CB	ILE	882	36.353	−11.858	7.171	1.00	29.99
ATOM	1719	CG2	ILE	882	37.279	−13.022	7.499	1.00	30.50
ATOM	1720	CG1	ILE	882	35.594	−11.420	8.431	1.00	29.82
ATOM	1721	CD1	ILE	882	36.488	−10.926	9.537	1.00	28.87
ATOM	1722	C	ILE	882	37.734	−11.143	5.270	1.00	31.79
ATOM	1723	O	ILE	882	38.813	−11.731	5.212	1.00	32.60
ATOM	1724	N	LYS	883	36.997	−10.886	4.192	1.00	33.37
ATOM	1725	CA	LYS	883	37.456	−11.298	2.873	1.00	35.08
ATOM	1726	CB	LYS	883	36.473	−12.298	2.254	1.00	35.22
ATOM	1727	CG	LYS	883	35.030	−12.122	2.676	1.00	35.39
ATOM	1728	CD	LYS	883	34.263	−13.428	2.488	1.00	35.67
ATOM	1729	CE	LYS	883	33.018	−13.508	3.387	1.00	35.63
ATOM	1730	NZ	LYS	883	33.347	−13.507	4.849	1.00	34.49
ATOM	1731	C	LYS	883	37.729	−10.165	1.901	1.00	36.23
ATOM	1732	O	LYS	883	37.951	−10.409	0.720	1.00	36.16
ATOM	1733	N	SER	884	37.735	−8.929	2.394	1.00	38.01
ATOM	1734	CA	SER	884	38.010	−7.781	1.535	1.00	39.99
ATOM	1735	CB	SER	884	37.908	−6.480	2.331	1.00	39.82
ATOM	1736	OG	SER	884	38.779	−6.500	3.445	1.00	40.42
ATOM	1737	C	SER	884	39.421	−7.946	0.991	1.00	41.45
ATOM	1738	O	SER	884	39.857	−7.222	0.100	1.00	41.65
ATOM	1739	N	HIS	885	40.129	−8.916	1.552	1.00	43.33
ATOM	1740	CA	HIS	885	41.485	−9.216	1.146	1.00	45.27
ATOM	1741	CB	HIS	885	42.079	−10.274	2.085	1.00	46.21
ATOM	1742	CG	HIS	885	41.975	−9.918	3.539	1.00	47.51
ATOM	1743	CD2	HIS	885	42.927	−9.619	4.457	1.00	47.92
ATOM	1744	ND1	HIS	885	40.765	−9.800	4.193	1.00	47.61
ATOM	1745	CE1	HIS	885	40.977	−9.443	5.448	1.00	47.80
ATOM	1746	NE2	HIS	885	42.280	−9.326	5.635	1.00	48.03
ATOM	1747	C	HIS	885	41.482	−9.732	−0.291	1.00	46.02
ATOM	1748	O	HIS	885	42.195	−9.210	−1.145	1.00	46.12
ATOM	1749	N	MET	886	40.650	−10.739	−0.545	1.00	46.78
ATOM	1750	CA	MET	886	40.542	−11.377	−1.856	1.00	47.47
ATOM	1751	CB	MET	886	40.210	−12.861	−1.660	1.00	48.40
ATOM	1752	CG	MET	886	40.207	−13.696	−2.934	1.00	49.75
ATOM	1753	SD	MET	886	39.580	−15.376	−2.674	1.00	51.35
ATOM	1754	CE	MET	886	37.809	−15.116	−2.950	1.00	50.99
ATOM	1755	C	MET	886	39.533	−10.762	−2.842	1.00	47.47
ATOM	1756	O	MET	886	39.399	−11.242	−3.966	1.00	47.36
ATOM	1757	N	VAL	887	38.821	−9.713	−2.441	1.00	47.33
ATOM	1758	CA	VAL	887	37.851	−9.109	−3.351	1.00	46.96
ATOM	1759	CB	VAL	887	36.451	−9.054	−2.723	1.00	47.00
ATOM	1760	CG1	VAL	887	35.425	−8.807	−3.799	1.00	47.21
ATOM	1761	CG2	VAL	887	36.149	−10.356	−2.003	1.00	47.16
ATOM	1762	C	VAL	887	38.271	−7.702	−3.772	1.00	46.99
ATOM	1763	O	VAL	887	37.553	−7.017	−4.511	1.00	46.75
ATOM	1764	N	SER	888	39.435	−7.279	−3.283	1.00	46.66
ATOM	1765	CA	SER	888	40.008	−5.982	−3.617	1.00	46.35
ATOM	1766	CB	SER	888	40.275	−5.926	−5.123	1.00	46.40
ATOM	1767	OG	SER	888	41.043	−7.042	−5.542	1.00	45.75
ATOM	1768	C	SER	888	39.180	−4.765	−3.200	1.00	46.54
ATOM	1769	O	SER	888	38.840	−3.922	−4.038	1.00	46.44
ATOM	1770	N	VAL	889	38.876	−4.666	−1.907	1.00	46.50
ATOM	1771	CA	VAL	889	38.104	−3.546	−1.375	1.00	46.35

TABLE A-continued

ATOM	1772	CB	VAL	889	36.750	−4.024	−0.836	1.00	46.08
ATOM	1773	CG1	VAL	889	35.952	−2.849	−0.321	1.00	46.13
ATOM	1774	CG2	VAL	889	35.986	−4.742	−1.925	1.00	46.06
ATOM	1775	C	VAL	889	38.864	−2.854	−0.243	1.00	46.74
ATOM	1776	O	VAL	889	39.218	−3.490	0.751	1.00	46.95
ATOM	1777	N	ASP	890	39.117	−1.554	−0.391	1.00	46.98
ATOM	1778	CA	ASP	890	39.834	−0.804	0.640	1.00	47.18
ATOM	1779	CB	ASP	890	40.261	0.589	0.145	1.00	48.23
ATOM	1780	CG	ASP	890	40.782	0.586	−1.275	1.00	49.20
ATOM	1781	OD1	ASP	890	41.642	−0.261	−1.600	1.00	50.24
ATOM	1782	OD2	ASP	890	40.339	1.452	−2.065	1.00	49.63
ATOM	1783	C	ASP	890	38.946	−0.595	1.863	1.00	46.72
ATOM	1784	O	ASP	890	37.725	−0.488	1.748	1.00	46.63
ATOM	1785	N	PHE	891	39.568	−0.534	3.033	1.00	46.21
ATOM	1786	CA	PHE	891	38.850	−0.284	4.274	1.00	45.79
ATOM	1787	CB	PHE	891	38.739	−1.551	5.129	1.00	44.93
ATOM	1788	CG	PHE	891	37.417	−2.260	5.003	1.00	43.95
ATOM	1789	CD1	PHE	891	37.284	−3.385	4.192	1.00	43.65
ATOM	1790	CD2	PHE	891	36.300	−1.795	5.683	1.00	43.28
ATOM	1791	CE1	PHE	891	36.060	−4.032	4.064	1.00	43.03
ATOM	1792	CE2	PHE	891	35.071	−2.437	5.561	1.00	42.87
ATOM	1793	CZ	PHE	891	34.952	−3.557	4.750	1.00	42.99
ATOM	1794	C	PHE	891	39.647	0.764	5.028	1.00	46.31
ATOM	1795	O	PHE	891	40.804	0.535	5.376	1.00	46.19
ATOM	1796	N	PRO	892	39.056	1.945	5.258	1.00	46.87
ATOM	1797	CD	PRO	892	37.779	2.479	4.761	1.00	47.03
ATOM	1798	CA	PRO	892	39.800	2.973	5.989	1.00	47.86
ATOM	1799	CB	PRO	892	38.777	4.100	6.126	1.00	47.55
ATOM	1800	CG	PRO	892	38.002	3.981	4.856	1.00	47.27
ATOM	1801	C	PRO	892	40.272	2.421	7.337	1.00	48.77
ATOM	1802	O	PRO	892	39.559	1.660	7.994	1.00	48.53
ATOM	1803	N	GLU	893	41.478	2.804	7.737	1.00	49.95
ATOM	1804	CA	GLU	893	42.069	2.330	8.987	1.00	50.96
ATOM	1805	CB	GLU	893	43.278	3.194	9.349	1.00	51.80
ATOM	1806	CG	GLU	893	44.243	2.521	10.314	1.00	53.18
ATOM	1807	CD	GLU	893	44.688	1.145	9.833	1.00	53.98
ATOM	1808	OE1	GLU	893	43.850	0.215	9.823	1.00	54.56
ATOM	1809	OE2	GLU	893	45.874	0.995	9.461	1.00	54.43
ATOM	1810	C	GLU	893	41.108	2.267	10.177	1.00	50.91
ATOM	1811	O	GLU	893	41.006	1.232	10.834	1.00	51.08
ATOM	1812	N	MET	894	40.415	3.368	10.454	1.00	50.86
ATOM	1813	CA	MET	894	39.468	3.418	11.567	1.00	50.94
ATOM	1814	CB	MET	894	38.942	4.846	11.768	1.00	51.97
ATOM	1815	CG	MET	894	39.769	5.723	12.688	1.00	53.43
ATOM	1816	SD	MET	894	39.094	7.410	12.777	1.00	55.12
ATOM	1817	CE	MET	894	40.330	8.326	11.783	1.00	54.74
ATOM	1818	C	MET	894	38.278	2.495	11.337	1.00	50.28
ATOM	1819	O	MET	894	37.617	2.069	12.287	1.00	50.13
ATOM	1820	N	MET	895	38.007	2.204	10.068	1.00	49.44
ATOM	1821	CA	MET	895	36.885	1.351	9.682	1.00	48.35
ATOM	1822	CB	MET	895	36.715	1.388	8.155	1.00	49.15
ATOM	1823	CG	MET	895	35.410	0.824	7.630	1.00	49.68
ATOM	1824	SD	MET	895	34.001	1.826	8.121	1.00	51.13
ATOM	1825	CE	MET	895	34.136	3.188	6.979	1.00	50.63
ATOM	1826	C	MET	895	37.094	−0.089	10.152	1.00	46.87
ATOM	1827	O	MET	895	36.336	−0.597	10.975	1.00	46.59
ATOM	1828	N	ALA	896	38.136	−0.729	9.634	1.00	45.22
ATOM	1829	CA	ALA	896	38.442	−2.113	9.977	1.00	43.83
ATOM	1830	CB	ALA	896	39.706	−2.563	9.247	1.00	43.37
ATOM	1831	C	ALA	896	38.601	−2.324	11.481	1.00	42.67
ATOM	1832	O	ALA	896	38.473	−3.440	11.976	1.00	42.42
ATOM	1833	N	GLU	897	38.872	−1.243	12.200	1.00	41.32
ATOM	1834	CA	GLU	897	39.058	−1.306	13.640	1.00	39.88
ATOM	1835	CB	GLU	897	39.828	−0.058	14.101	1.00	40.74
ATOM	1836	CG	GLU	897	40.690	−0.236	15.353	1.00	41.25
ATOM	1837	CD	GLU	897	41.768	0.849	15.491	1.00	41.90
ATOM	1838	OE1	GLU	897	42.665	0.918	14.619	1.00	41.86
ATOM	1839	OE2	GLU	897	41.723	1.632	16.468	1.00	42.21
ATOM	1840	C	GLU	897	37.685	−1.390	14.313	1.00	38.68
ATOM	1841	O	GLU	897	37.346	−2.397	14.944	1.00	38.45
ATOM	1842	N	ILE	898	36.889	−0.339	14.159	1.00	36.89
ATOM	1843	CA	ILE	898	35.558	−0.308	14.745	1.00	35.29
ATOM	1844	CB	ILE	898	34.799	0.981	14.366	1.00	35.18
ATOM	1845	CG2	ILE	898	33.459	1.003	15.063	1.00	34.79
ATOM	1846	CG1	ILE	898	35.614	2.212	14.782	1.00	35.43
ATOM	1847	CD1	ILE	898	34.990	3.555	14.378	1.00	34.84
ATOM	1848	C	ILE	898	34.728	−1.513	14.307	1.00	33.92
ATOM	1849	O	ILE	898	33.926	−2.034	15.087	1.00	33.92
ATOM	1850	N	ILE	899	34.912	−1.951	13.064	1.00	32.03

TABLE A-continued

ATOM	1851	CA	ILE	899	34.173	−3.108	12.566	1.00	30.47
ATOM	1852	CB	ILE	899	34.485	−3.404	11.099	1.00	30.35
ATOM	1853	CG2	ILE	899	33.746	−4.653	10.663	1.00	29.70
ATOM	1854	CG1	ILE	899	34.090	−2.222	10.221	1.00	30.03
ATOM	1855	CD1	ILE	899	34.481	−2.407	8.775	1.00	29.09
ATOM	1856	C	ILE	899	34.528	−4.370	13.343	1.00	29.56
ATOM	1857	O	ILE	899	33.668	−5.007	13.934	1.00	29.56
ATOM	1858	N	SER	900	35.809	−4.717	13.339	1.00	28.34
ATOM	1859	CA	SER	900	36.283	−5.916	14.007	1.00	27.55
ATOM	1860	CB	SER	900	37.767	−6.124	13.711	1.00	27.86
ATOM	1861	OG	SER	900	38.539	−5.030	14.182	1.00	29.18
ATOM	1862	C	SER	900	36.072	−5.940	15.511	1.00	26.83
ATOM	1863	O	SER	900	35.911	−7.016	16.108	1.00	26.70
ATOM	1864	N	VAL	901	36.066	−4.761	16.122	1.00	25.47
ATOM	1865	CA	VAL	901	35.914	−4.669	17.565	1.00	24.36
ATOM	1866	CB	VAL	901	36.810	−3.539	18.132	1.00	24.53
ATOM	1867	CG1	VAL	901	36.613	−3.401	19.635	1.00	24.63
ATOM	1868	CG2	VAL	901	38.261	−3.838	17.826	1.00	24.17
ATOM	1869	C	VAL	901	34.489	−4.457	18.052	1.00	23.82
ATOM	1870	O	VAL	901	34.056	−5.107	18.998	1.00	23.59
ATOM	1871	N	GLN	902	33.754	−3.565	17.404	1.00	23.25
ATOM	1872	CA	GLN	902	32.396	−3.264	17.836	1.00	23.10
ATOM	1873	CB	GLN	902	32.128	−1.771	17.652	1.00	23.43
ATOM	1874	CG	GLN	902	33.026	−0.856	18.468	1.00	24.40
ATOM	1875	CD	GLN	902	32.724	−0.898	19.960	1.00	25.11
ATOM	1876	OE1	GLN	902	32.836	0.108	20.652	1.00	25.82
ATOM	1877	NE2	GLN	902	32.353	−2.070	20.463	1.00	26.55
ATOM	1878	C	GLN	902	31.285	−4.062	17.150	1.00	22.80
ATOM	1879	O	GLN	902	30.330	−4.488	17.802	1.00	22.81
ATOM	1880	N	VAL	903	31.409	−4.260	15.840	1.00	21.89
ATOM	1881	CA	VAL	903	30.397	−4.985	15.083	1.00	21.01
ATOM	1882	CB	VAL	903	30.753	−4.987	13.568	1.00	20.43
ATOM	1883	CG1	VAL	903	29.811	−5.891	12.783	1.00	20.60
ATOM	1884	CG2	VAL	903	30.625	−3.572	13.033	1.00	19.46
ATOM	1885	C	VAL	903	30.118	−6.404	15.594	1.00	20.85
ATOM	1886	O	VAL	903	28.962	−6.798	15.710	1.00	19.49
ATOM	1887	N	PRO	904	31.172	−7.182	15.925	1.00	21.30
ATOM	1888	CD	PRO	904	32.614	−6.943	15.734	1.00	20.97
ATOM	1889	CA	PRO	904	30.941	−8.545	16.421	1.00	21.34
ATOM	1890	CB	PRO	904	32.356	−9.114	16.548	1.00	20.99
ATOM	1891	CG	PRO	904	33.120	−8.353	15.512	1.00	21.65
ATOM	1892	C	PRO	904	30.175	−8.585	17.750	1.00	22.05
ATOM	1893	O	PRO	904	29.548	−9.600	18.077	1.00	22.76
ATOM	1894	N	LYS	905	30.234	−7.503	18.524	1.00	21.69
ATOM	1895	CA	LYS	905	29.512	−7.464	19.791	1.00	22.05
ATOM	1896	CB	LYS	905	29.823	−6.183	20.577	1.00	22.91
ATOM	1897	CG	LYS	905	31.236	−6.070	21.145	1.00	23.84
ATOM	1898	CD	LYS	905	31.333	−4.835	22.041	1.00	24.82
ATOM	1899	CE	LYS	905	32.692	−4.710	22.736	1.00	25.65
ATOM	1900	NZ	LYS	905	32.716	−3.560	23.693	1.00	25.72
ATOM	1901	C	LYS	905	28.023	−7.491	19.477	1.00	21.85
ATOM	1902	O	LYS	905	27.208	−7.982	20.255	1.00	21.42
ATOM	1903	N	ILE	906	27.675	−6.929	18.330	1.00	21.67
ATOM	1904	CA	ILE	906	26.286	−6.873	17.903	1.00	21.52
ATOM	1905	CB	ILE	906	26.078	−5.742	16.827	1.00	21.27
ATOM	1906	CG2	ILE	906	24.655	−5.766	16.313	1.00	20.46
ATOM	1907	CG1	ILE	906	26.442	−4.380	17.434	1.00	20.69
ATOM	1908	CD1	ILE	906	26.272	−3.193	16.517	1.00	21.16
ATOM	1909	C	ILE	906	25.865	−8.226	17.331	1.00	21.33
ATOM	1910	O	ILE	906	24.902	−8.827	17.800	1.00	21.55
ATOM	1911	N	LEU	907	26.607	−8.715	16.342	1.00	20.88
ATOM	1912	CA	LEU	907	26.274	−9.990	15.717	1.00	21.31
ATOM	1913	CB	LEU	907	27.244	−10.280	14.561	1.00	19.40
ATOM	1914	CG	LEU	907	27.380	−9.060	13.634	1.00	18.63
ATOM	1915	CD1	LEU	907	28.333	−9.370	12.509	1.00	17.46
ATOM	1916	CD2	LEU	907	26.008	−8.646	13.092	1.00	17.25
ATOM	1917	C	LEU	907	26.225	−11.165	16.695	1.00	21.62
ATOM	1918	O	LEU	907	25.360	−12.037	16.563	1.00	22.68
ATOM	1919	N	SER	908	27.118	−11.177	17.685	1.00	21.63
ATOM	1920	CA	SER	908	27.150	−12.266	18.664	1.00	22.10
ATOM	1921	CB	SER	908	28.564	−12.433	19.238	1.00	21.84
ATOM	1922	OG	SER	908	28.952	−11.279	19.949	1.00	22.32
ATOM	1923	C	SER	908	26.146	−12.060	19.802	1.00	22.09
ATOM	1924	O	SER	908	26.086	−12.862	20.740	1.00	22.15
ATOM	1925	N	GLY	909	25.376	−10.976	19.730	1.00	22.11
ATOM	1926	CA	GLY	909	24.361	−10.718	20.743	1.00	22.44
ATOM	1927	C	GLY	909	24.707	−9.946	22.006	1.00	22.41
ATOM	1928	O	GLY	909	23.843	−9.735	22.854	1.00	22.66
ATOM	1929	N	LYS	910	25.950	−9.519	22.152	1.00	22.78

TABLE A-continued

ATOM	1930	CA	LYS	910	26.332	−8.773	23.344	1.00	23.71
ATOM	1931	CB	LYS	910	27.838	−8.650	23.410	1.00	24.13
ATOM	1932	CG	LYS	910	28.521	−9.978	23.588	1.00	25.11
ATOM	1933	CD	LYS	910	30.006	−9.783	23.775	1.00	25.46
ATOM	1934	CE	LYS	910	30.613	−11.053	24.288	1.00	26.49
ATOM	1935	NZ	LYS	910	29.764	−11.585	25.391	1.00	27.68
ATOM	1936	C	LYS	910	25.702	−7.381	23.438	1.00	24.13
ATOM	1937	O	LYS	910	25.442	−6.880	24.540	1.00	23.96
ATOM	1938	N	VAL	911	25.465	−6.769	22.278	1.00	24.03
ATOM	1939	CA	VAL	911	24.869	−5.445	22.182	1.00	24.31
ATOM	1940	CB	VAL	911	25.868	−4.413	21.588	1.00	24.16
ATOM	1941	CG1	VAL	911	26.588	−5.010	20.444	1.00	25.18
ATOM	1942	CG2	VAL	911	25.142	−3.180	21.086	1.00	24.84
ATOM	1943	C	VAL	911	23.672	−5.582	21.272	1.00	24.68
ATOM	1944	O	VAL	911	23.781	−6.139	20.185	1.00	25.01
ATOM	1945	N	LYS	912	22.527	−5.081	21.710	1.00	24.92
ATOM	1946	CA	LYS	912	21.322	−5.192	20.910	1.00	25.57
ATOM	1947	CB	LYS	912	20.429	−6.297	21.470	1.00	26.08
ATOM	1948	CG	LYS	912	21.049	−7.676	21.478	1.00	26.96
ATOM	1949	CD	LYS	912	20.221	−8.591	22.357	1.00	28.27
ATOM	1950	CE	LYS	912	20.096	−7.986	23.747	1.00	28.84
ATOM	1951	NZ	LYS	912	21.426	−7.849	24.424	1.00	28.86
ATOM	1952	C	LYS	912	20.516	−3.903	20.836	1.00	25.87
ATOM	1953	O	LYS	912	20.561	−3.069	21.742	1.00	25.78
ATOM	1954	N	PRO	913	19.763	−3.731	19.742	1.00	26.36
ATOM	1955	CD	PRO	913	19.645	−4.672	18.615	1.00	26.55
ATOM	1956	CA	PRO	913	18.927	−2.550	19.520	1.00	26.76
ATOM	1957	CB	PRO	913	18.356	−2.777	18.118	1.00	26.68
ATOM	1958	CG	PRO	913	19.296	−3.755	17.493	1.00	27.35
ATOM	1959	C	PRO	913	17.808	−2.527	20.549	1.00	27.50
ATOM	1960	O	PRO	913	17.435	−3.571	21.088	1.00	27.19
ATOM	1961	N	ILE	914	17.288	−1.335	20.826	1.00	28.15
ATOM	1962	CA	ILE	914	16.168	−1.190	21.743	1.00	28.95
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ATOM	1965	CG1	ILE	914	17.563	−0.195	23.598	1.00	29.16
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ATOM	1969	N	TYR	915	14.010	−1.879	20.844	1.00	29.76
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ATOM	1971	CB	TYR	915	12.344	−3.133	19.514	1.00	29.35
ATOM	1972	CG	TYR	915	13.194	−3.687	18.405	1.00	29.23
ATOM	1973	CD1	TYR	915	14.242	−4.574	18.667	1.00	29.36
ATOM	1974	CE1	TYR	915	15.055	−5.047	17.641	1.00	29.21
ATOM	1975	CD2	TYR	915	12.981	−3.289	17.092	1.00	29.29
ATOM	1976	CE2	TYR	915	13.785	−3.749	16.064	1.00	29.70
ATOM	1977	CZ	TYR	915	14.818	−4.626	16.340	1.00	29.95
ATOM	1978	OH	TYR	915	15.597	−5.080	15.296	1.00	31.15
ATOM	1979	C	TYR	915	11.641	−1.180	20.861	1.00	29.93
ATOM	1980	O	TYR	915	11.549	−1.412	22.060	1.00	30.36
ATOM	1981	N	PHE	916	10.765	−0.426	20.217	1.00	29.99
ATOM	1982	CA	PHE	916	9.610	0.105	20.917	1.00	30.60
ATOM	1983	CB	PHE	916	9.025	1.319	20.191	1.00	30.23
ATOM	1984	CG	PHE	916	9.744	2.602	20.478	1.00	30.62
ATOM	1985	CD1	PHE	916	9.659	3.192	21.731	1.00	30.55
ATOM	1986	CD2	PHE	916	10.503	3.226	19.494	1.00	30.58
ATOM	1987	CE1	PHE	916	10.315	4.381	22.000	1.00	30.34
ATOM	1988	CE2	PHE	916	11.163	4.417	19.757	1.00	30.86
ATOM	1989	CZ	PHE	916	11.068	4.994	21.010	1.00	30.74
ATOM	1990	C	PHE	916	8.564	−1.014	20.982	1.00	31.09
ATOM	1991	O	PHE	916	7.976	−1.259	22.038	1.00	31.66
ATOM	1992	N	HIS	917	8.345	−1.696	19.858	1.00	31.14
ATOM	1993	CA	HIS	917	7.373	−2.782	19.802	1.00	31.46
ATOM	1994	CB	HIS	917	6.375	−2.579	18.651	1.00	30.70
ATOM	1995	CG	HIS	917	5.843	−1.185	18.534	1.00	29.89
ATOM	1996	CD2	HIS	917	4.695	−0.628	18.984	1.00	29.89
ATOM	1997	ND1	HIS	917	6.514	−0.188	17.863	1.00	29.93
ATOM	1998	CE1	HIS	917	5.800	0.924	17.899	1.00	29.50
ATOM	1999	NE2	HIS	917	4.691	0.683	18.574	1.00	29.71
ATOM	2000	C	HIS	917	8.093	−4.099	19.590	1.00	32.03
ATOM	2001	O	HIS	917	9.218	−4.116	19.102	1.00	33.01
ATOM	2002	N	ALA	918	7.442	−5.201	19.949	1.00	32.62
ATOM	2003	CA	ALA	918	8.025	−6.529	19.777	1.00	32.98
ATOM	2004	CB	ALA	918	7.769	−7.382	21.013	1.00	33.52
ATOM	2005	C	ALA	918	7.421	−7.201	18.551	1.00	33.16
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SEQUENCE LISTING

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Lys Ala Leu Pro Gly Phe Arg Asn Leu His Val Asp Asp Gln Met Ala
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Val Ile Gln Tyr Ser Trp Met Gly Leu Met Val Phe Ala Met Gly Trp
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Arg Ser Phe Thr Asn Val Asn Ser Arg Met Leu Tyr Phe Ala Pro Asp
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Leu Val Phe Asn Glu Tyr Arg Met His Lys Ser Arg Met Tyr Ser Gln
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Cys Val Arg Met Arg His Leu Ser Gln Glu Phe Gly Trp Leu Gln Ile
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Thr Pro Gln Glu Phe Leu Cys Met Lys Ala Leu Leu Leu Phe Ser Ile
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Ile Pro Val Asp Gly Leu Lys Asn Gln Lys Phe Phe Asp Glu Leu Arg
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Asn Trp Ala Lys Arg Val Pro Gly Phe Val Asp Leu Thr Leu His Asp
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Leu Val Trp Arg Ser Met Glu His Pro Gly Lys Leu Leu Phe Ala Pro
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Asn Leu Leu Leu Asp Arg Asn Gln Gly Lys Cys Val Glu Gly Met Val
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Glu Ile Phe Asp Met Leu Leu Ala Thr Ser Ser Arg Phe Arg Met Met
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Asn Leu Gln Gly Glu Glu Phe Val Cys Leu Lys Ser Ile Ile Leu Leu
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Asn Ser Gly Val Tyr Thr Phe Thr Leu Lys Ser Leu Glu Glu Lys Asp
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His Ile His Arg Val Leu Asp Lys Ile Thr Asp Thr Leu Ile His Leu
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Met Ala Lys Ala Gly Leu Thr Leu Gln Gln Gln His Gln Arg Leu Ala
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Gln Leu Leu Leu Ile Leu Ser His Ile Arg His Met Ser Asn Lys Gly
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Asp Leu Leu Leu Glu Met Leu Asp Ala His Arg
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What is claimed is:

1. A method for inhibiting the growth of hormone-dependent tumor cells in a patient in need thereof, comprising administering to said patient a selective androgen receptor modulator compound in an amount effective therefor, wherein:

said selective androgen receptor modulator compound exhibits antagonist activity inhibiting growth of said hormone-dependent tumor; and

wherein said selective androgen receptor modulator compound exhibits no activity or agonist activity against other, nontumor tissues containing the androgen receptor,

wherein said no activity is maintaining at least one of average normal bone density, average normal muscle mass, average normal reproductive function, and average normal libido seen in ugonadal warm-blooded male mammals,

wherein said agonist activity is having an activation effect greater than 5% in vivo as compared to control animals on the weights of at least one of ventral prostate, seminal vesicles, levator ani, and luteinizing hormone serum levels, and

wherein said selective androgen receptor modulator compound binds to an androgen receptor ligand binding domain having the structural coordinates of Table A.

2. The method of claim **1**, wherein said tumor cells are prostate tumor cells and wherein, in addition to exhibiting antagonist activity in said tumor cells and no activity or agonist activity against other, nontumor tissues containing the androgen receptor, said selective androgen receptor modulator compound further exhibits agonist, antagonist or no activity in normal prostate tissue.

3. The method of claim **1**, wherein said selective androgen receptor modulator compound exhibits agonist activity against other, nontumor tissues containing the androgen receptor.

4. The method of claim **1**, wherein said selective androgen receptor modulator compound exhibits no activity against other, nontumor tissues containing the androgen receptor.

5. The method of claim **1**, wherein said hormone-dependent tumor is prostate cancer.

6. The method of claim **1**, wherein said other, nontumor tissue containing the androgen receptor comprises one or more of the following tissues: seminal vesicles, male and female genitalia, skin, testis, ovary, cartilage, sebaceous glands, hair follicles, sweat glands, muscle, gastrointestinal vesicular cells, thyroid follicular cells, adrenal cortex, liver, pineal, bone, stromal cells, kidney tubules, urinary bladder and/or brain cortical and subcortical regions.

7. The method of claim **6**, wherein said other, nontumor tissue containing the androgen receptor comprises one or more of the following tissues: cardiac muscle, skeletal muscle and/or smooth muscle.

8. A method for inhibiting the growth of hormone-dependent tumor cells in a patient in need thereof, comprising administering to said patient a selective androgen receptor modulator compound in an amount effective therefor, wherein:

said selective androgen receptor modulator compound exhibits antagonist activity inhibiting growth of said hormone-dependent tumor;

wherein said selective androgen receptor modulator compound exhibits agonist activity against other, nontumor tissues containing the androgen receptor, and

wherein said selective androgen receptor modulator compound binds to an androgen receptor ligand binding domain having the structural coordinates of Table A.

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