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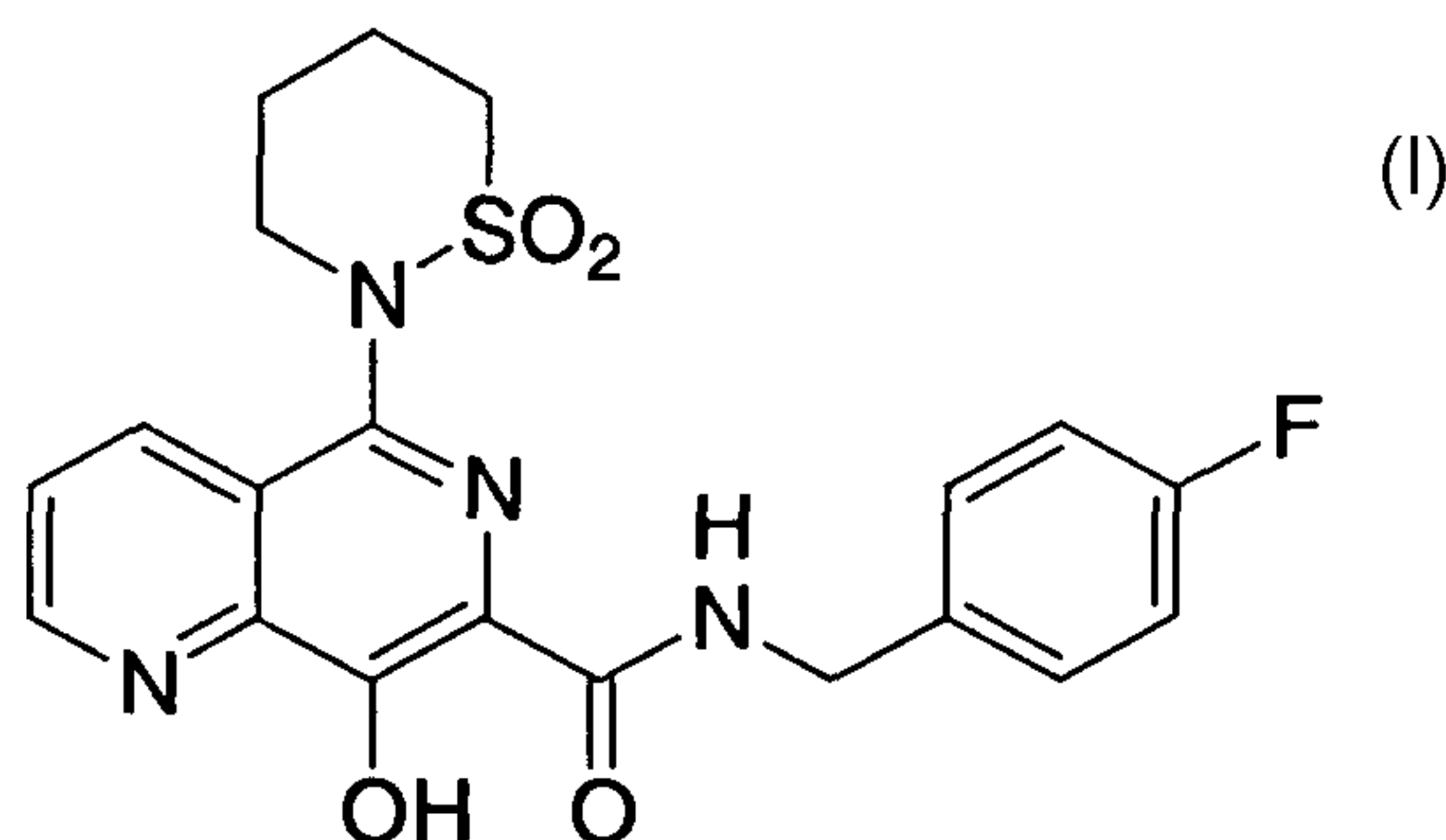
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(54) Titre : SEL DE SODIUM D'UN INHIBITEUR DE L'INTEGRASE DU VIH

(54) Title: SODIUM SALT OF AN HIV INTEGRASE INHIBITOR



**Compound A**

(57) **Abrégé/Abstract:**

A sodium salt of Compound A is disclosed, wherein Compound A is of formula: (I) Compound ACompound A is an HIV integrase inhibitor useful for preventing or treating HIV infection, for delaying the onset of AIDS, and for treating AIDS.

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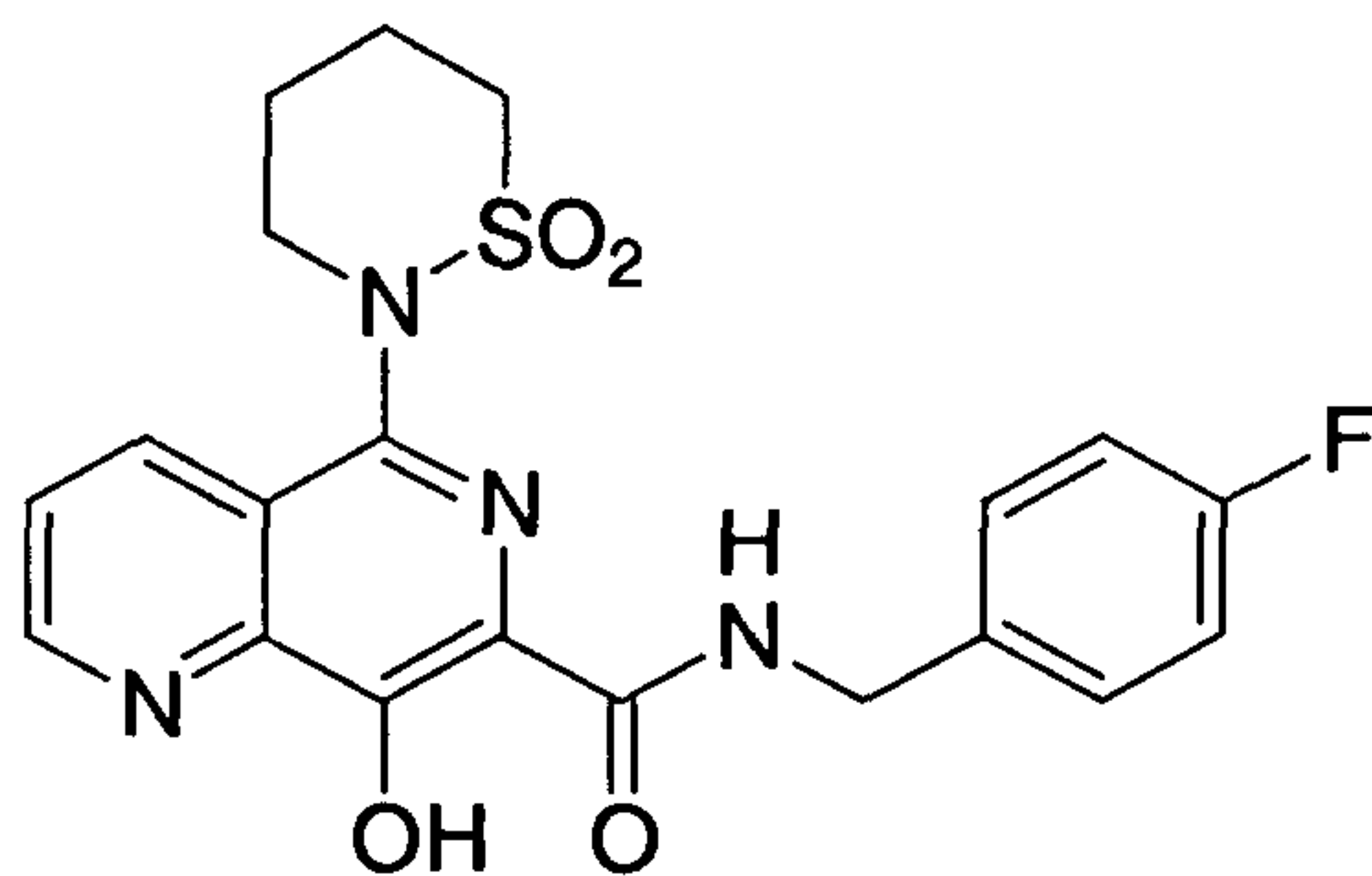
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(54) Title: SODIUM SALT OF AN HIV INTEGRASE INHIBITOR



(I)

Compound A

(57) Abstract: A sodium salt of Compound A is disclosed, wherein Compound A is of formula: (I) Compound A is an HIV integrase inhibitor useful for preventing or treating HIV infection, for delaying the onset of AIDS, and for treating AIDS.

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## SODIUM SALT OF AN HIV INTEGRASE INHIBITOR

### FIELD OF THE INVENTION

The present invention is directed to a pharmaceutically acceptable sodium salt of an HIV integrase inhibitor, Compound A as defined below. The present invention is also directed processes for preparing a sodium salt of Compound A, pharmaceutical compositions containing the salt, and methods for using the salt.

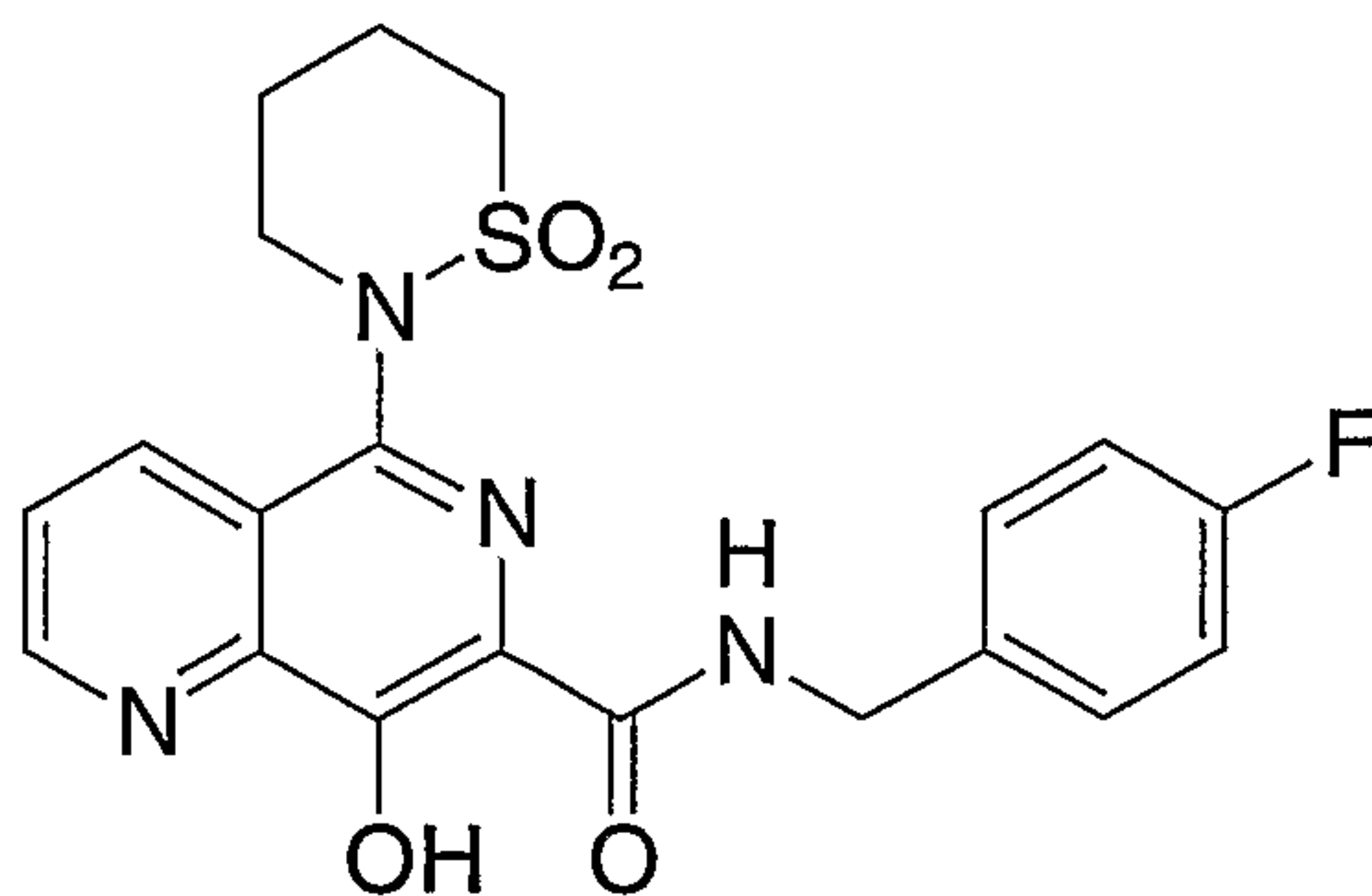
### BACKGROUND OF THE INVENTION

The HIV retrovirus is the causative agent for AIDS. The HIV-1 retrovirus primarily uses the CD4 receptor (a 58 kDa transmembrane protein) to gain entry into cells, through high-affinity interactions between the viral envelope glycoprotein (gp 120) and a specific region of the CD4 molecule found in T-lymphocytes and CD4 (+) T-helper cells (Lasky L.A. et al., *Cell* 1987, 50: 975-985). HIV infection is characterized by an asymptomatic period immediately following infection that is devoid of clinical manifestations in the patient. Progressive HIV-induced destruction of the immune system then leads to increased susceptibility to opportunistic infections, which eventually produces a syndrome called ARC (AIDS-related complex) characterized by symptoms such as persistent generalized lymphadenopathy, fever, and weight loss, followed itself by full blown AIDS.

After entry of the retrovirus into a cell, viral RNA is converted into DNA, which is then integrated into the host cell DNA. Integration of viral DNA is an essential step in the viral life cycle. Integration is believed to be mediated by integrase, a 32 kDa enzyme, in three steps: assembly of a stable nucleoprotein complex with viral DNA sequences; cleavage of two nucleotides from the 3' termini of the linear proviral DNA; and covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site. The fourth step in the process, repair synthesis of the resultant gap, may be accomplished by cellular enzymes.

The compound 5-(1,1-dioxido-1,2-thiazinan-2-yl)-N-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide (hereinafter designated herein as "Compound A") is a potent HIV integrase inhibitor. The structure of Compound A is as follows:





Compound A

Compound A and structurally related HIV integrase inhibitors are  
5 described in WO 02/30930.

#### SUMMARY OF THE INVENTION

The present invention is directed to a pharmaceutically acceptable  
alkali metal salt of an HIV integrase inhibitor. More particularly, the present  
10 invention includes a sodium salt of Compound A. An embodiment of the present  
invention is a crystalline sodium salt of Compound A. The sodium salt of Compound  
A exhibits superior oral absorption and improved pharmacokinetics in animal models  
compared to crystalline Compound A per se.

The present invention also includes processes for preparing the sodium  
15 salt of Compound A and methods of using the Compound A salt for inhibiting HIV  
integrase, for preventing or treating HIV infection, and for treating or delaying the  
onset of AIDS.

The foregoing embodiments and other embodiments, aspects and  
features of the present invention are either further described in or will be apparent  
20 from the ensuing description, examples, and appended claims.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a pharmaceutically acceptable  
sodium salt of Compound A, pharmaceutical compositions containing the salt, and  
25 methods of making and using the salt. The Compound A sodium salt and  
pharmaceutical compositions of the present invention are useful for inhibiting  
HIV integrase, preventing infection by HIV, treating infection by HIV, delaying  
the onset of AIDS, and treating AIDS, in adults, children or infants. Delaying the

onset of AIDS, treating AIDS, or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC, both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the sodium salt and pharmaceutical compositions thereof of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery. The salts of the invention can also be used in "salvage" therapy; i.e., the sodium salt of Compound A can be used to treat HIV infection, AIDS, or ARC in HIV-positive subjects whose viral load achieved undetectable levels via conventional therapies (e.g., therapies employing known protease inhibitors in combination with one or more known reverse transcriptase inhibitors), and then rebounded due to the emergence of HIV mutants resistant to the known inhibitors.

Compound A is an inhibitor of HIV integrase. Compound A has been tested in an integrase inhibition assay in which strand transfer is catalyzed by recombinant integrase, and has been found to be a potent inhibitor. The strand transfer assay is described in Example 193 of WO 02/30930. Compound A has also been found to be active in an assay for the inhibition of acute HIV infection of T-lymphoid cells conducted in accordance with Vacca et al., *Proc. Natl. Acad. Sci. USA* 1994, 91: 4096-4100.

The crystalline sodium salt of Compound A has exhibited superior oral bioavailability and improved pharmacokinetics (e.g., improved  $C_{max}$  and AUC) in rats and dogs relative to amorphous and crystalline Compound A.

An embodiment of the present invention is a crystalline monosodium sodium salt of Compound A. Still another embodiment is the crystalline monosodium salt, characterized by crystallographic d-spacings of 12.6, 5.0, and 4.6 angstroms. Another embodiment of the present invention is a crystalline monosodium salt of Compound A characterized by crystallographic d-spacings of 12.6, 5.0, 4.8, 4.6, 3.9, and 3.5 angstroms. Still another embodiment of the present invention is a crystalline monosodium salt of Compound A characterized by crystallographic d-spacings of 12.6, 5.9, 5.0, 4.9, 4.8, 4.6, 4.5, 4.3, 3.9, 3.7, 3.5, 3.2, 3.1, and 2.9 angstroms. Yet another embodiment of the present invention is a crystalline monosodium salt of Compound A characterized by crystallographic d-spacings of 12.63, 5.94, 5.05, 4.94, 4.81, 4.61, 4.54, 4.34, 3.88, 3.73, 3.49, 3.45, 3.22, 3.15, 3.12, and 2.86 angstroms. In an aspect of each of the four preceding embodiments, the Na



crystalline salt of Compound A is further characterized by a differential scanning calorimetry curve, at a heating rate of 10°C/min in an open cup under flowing nitrogen, exhibiting an endotherm with a peak temperature of about 348°C and an associated heat of fusion of about 45 J/gm followed by an exotherm with a peak  
5 temperature of about 352°C and an associated heat of fusion of about 45 J/gm.

The crystallographic d-spacings set forth in the foregoing embodiments can be determined from the XRPD pattern of the crystalline Compound A monosodium salt.

The present invention includes pharmaceutical compositions  
10 comprising a sodium salt of Compound A as originally defined above or as set forth in any of the foregoing embodiments or aspects and a pharmaceutically acceptable carrier.

The present invention also includes pharmaceutical compositions which comprise the product made by combining a sodium salt of Compound A as  
15 originally defined above or as set forth in any of the foregoing embodiments or aspects and a pharmaceutically acceptable carrier.

Other embodiments of the present invention include the following:

(a) A method of preventing or treating HIV infection in a subject in need thereof, which comprises administering to the subject a therapeutically effective  
20 amount of a sodium salt of Compound A.

(b) A method of delaying the onset of AIDS in a subject in need thereof, which comprises administering to the subject a therapeutically effective amount of a sodium salt of Compound A.

(c) A method of treating AIDS in a subject in need thereof, which  
25 comprises administering to the subject a therapeutically effective amount of a sodium salt of Compound A.

(d) A method of inhibiting HIV integrase in a subject in need thereof, which comprises administering to the subject a therapeutically effective amount of a sodium salt of Compound A.

(e) A method of preventing or treating HIV infection in a subject in need thereof, which comprises administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a sodium salt of Compound A and a pharmaceutically acceptable carrier.  
30

(f) A method of delaying the onset of AIDS in a subject in need  
35 thereof, which comprises administering to the subject a pharmaceutical composition

comprising a therapeutically effective amount of a sodium salt of Compound A and a pharmaceutically acceptable carrier.

(g) A method of treating AIDS in a subject in need thereof, which comprises administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a sodium salt of Compound A and a pharmaceutically acceptable carrier.

(h) A method of inhibiting HIV integrase in a subject in need thereof, which comprises administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a sodium salt of Compound A and a pharmaceutically acceptable carrier.

(i) The method of (a) or (b) or (c) or (d), wherein the sodium salt of Compound A is administered in combination with a therapeutically effective amount of at least one AIDS treatment agent selected from the group consisting of AIDS antiviral agents, immunomodulators, and anti-infective agents.

(j) The method of (a) or (b) or (c) or (d), wherein the sodium salt of Compound A is administered in combination with a therapeutically effective amount of at least one antiviral agent selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors.

Additional embodiments of the invention include the methods set forth in (a)-(j) above, wherein the sodium salt of Compound A employed therein is a Compound A sodium salt as set forth in any one of the embodiments or aspects described above.

The present invention also includes a process for preparing a sodium salt of Compound A, which comprises dissolving Compound A in a solvent and treating the resulting solution with NaOH to form the sodium salt. A suitable solvent for dissolution of Compound A is a ketone such as a di(C<sub>1-3</sub> alkyl) ketone. In one embodiment, the solvent is acetone. The solution of Compound A can be formed by adding Compound A to the solvent and then heating the mixture to effect dissolution.

Treatment with NaOH typically involves addition of an aqueous solution of NaOH to the solution containing Compound A. NaOH can be added to the Compound A solution in any proportion with respect to Compound A which results in the formation of at least some of the desired sodium salt. However, NaOH is typically added in a proportion which, under the treatment conditions employed (e.g., temperature, degree of agitation), will permit conversion of at least a major



portion (and more often substantially all to all) of Compound A to the desired salt. Accordingly, NaOH is typically added in an amount of from about 0.9 to about 5 equivalents per equivalent of Compound A, and is more typically added in an amount of from about 1 to about 2 equivalents per equivalent of Compound A. In one  
5 embodiment, Compound A is dissolved in a solvent and treated with from about 1.0 to about 1.3 equivalents of NaOH per equivalent of Compound A.

The treatment of the Compound A solution with NaOH can be conducted at any temperature at which Compound A is soluble in the chosen solvent. Typically, the treatment step is conducted at a temperature in the range of from about  
10 10 to about 80 °C, and more typically at a temperature in the range of from about 20 to about 80 °C.

Following the addition of NaOH, the solution can be aged for a period of time to permit intimate mixing of NaOH and Compound A. As used herein, the term "aging" and variants thereof (e.g., "aged") mean allowing the reactants (i.e.,  
15 NaOH and Compound A) to stay in contact for a time and under conditions effective for completion of the reaction. The Compound A solution is optionally agitated (e.g., stirred) during NaOH addition and optionally also during any subsequent aging. At the completion of the treatment step, the desired sodium salt can be recovered by filtration, optionally after cooling or concentrating (e.g., by evaporative removal of  
20 solvent by the application of heat and/or vacuum) the treated solution.

The present invention also includes a process for preparing a sodium salt of Compound A, which comprises dissolving a monoethanolate of Compound A in a solvent and treating the resulting solution with NaOH to form the sodium salt. A suitable solvent for dissolution of the Compound A monoethanolate is an alcohol such  
25 as a C<sub>1</sub>-3 alkyl alcohol, optionally in admixture with water as a co-solvent. In one embodiment, the solvent is methanol or ethanol. In an aspect of this embodiment the solvent is ethanol. In another aspect, the solvent is ethanol with a minor amount of water as co-solvent. The solution of the Compound A monoethanolate can be formed by adding the monoethanolate to the solvent and then heating the mixture to effect  
30 dissolution. The treatment of the solution with NaOH can be conducted as described above.

The present invention also includes a process for preparing a sodium salt of Compound A, which comprises dissolving Compound A in an aprotic solvent selected from the group consisting of N-methyl pyrrolidinone (NMP),  
35 N,N-dimethylacetamide, N-ethyl pyrrolidinone, and N,N-dimethylformamide, and



treating the resulting solution with NaOH to form the sodium salt. Treatment with NaOH can involve mixing an aqueous solution of NaOH with the solution containing Compound A, but in a preferred embodiment, treatment with NaOH comprises mixing a solution of NaOH in ethanol and water with the solution of Compound A.

- 5 The relative amounts of NaOH and Compound A employed in this process are as described earlier. Aging of the solution and recovery of the Na salt of Compound A can be conducted as described earlier as well. In a preferred embodiment, Compound A is dissolved in NMP and the Compound A solution is treated with an ethanol-water solution of NaOH. The use of the NMP-EtOH system is characterized by improved  
10 filterability of the resulting crystalline Na salt, relative to the EtOH-water system described in the preceding paragraph.

Embodiments of the processes for preparing a sodium salt of Compound A include any of the preparative processes described above, wherein the sodium salt is crystalline. In each of these embodiments, the Compound A solution  
15 can optionally also be seeded with a crystalline Na salt of Compound A before, during or subsequent to the addition of NaOH to promote crystal formation. An aspect of each of these embodiments is the preparation of a crystalline monosodium salt of Compound A which is characterized by crystallographic d-spacings of 12.6, 5.0, and 4.6 angstroms. Another aspect of each of these embodiments is the preparation of a  
20 crystalline monosodium salt of Compound A which is characterized by crystallographic d-spacings of 12.6, 5.0, 4.8, 4.6, 3.9, and 3.5 angstroms. Still another aspect of each of these embodiments is the preparation of a crystalline monosodium salt of Compound A characterized by crystallographic d-spacings of 12.6, 5.9, 5.0, 4.9, 4.8, 4.6, 4.5, 4.3, 3.9, 3.7, 3.5, 3.2, 3.1, and 2.9 angstroms. Yet another aspect of  
25 each of these embodiments is the preparation of a crystalline monosodium salt of Compound A which is characterized by crystallographic d-spacings of 12.63, 5.94, 5.05, 4.94, 4.81, 4.61, 4.54, 4.34, 3.88, 3.73, 3.49, 3.45, 3.22, 3.15, 3.12, and 2.86 angstroms. Further aspects of each of these embodiments include the preparation of a crystalline sodium salt as in any of the three preceding aspects, wherein the Na salt is  
30 further characterized by a differential scanning calorimetry curve, at a heating rate of 10°C/min in an open cup under flowing nitrogen, exhibiting an endotherm with a peak temperature of about 348°C and an associated heat of fusion of about 45 J/gm followed by an exotherm with a peak temperature of about 352°C and an associated heat of fusion of about 45 J/gm.



As noted above, the present invention includes pharmaceutical compositions useful for inhibiting HIV integrase, comprising an effective amount of a sodium salt of Compound A and a pharmaceutically acceptable carrier.

Pharmaceutical compositions useful for preventing or treating infection by HIV, for  
5 delaying the onset of AIDS, or for treating AIDS, are also encompassed by the present invention, as well as a method of inhibiting HIV integrase, and a method of preventing or treating infection by HIV, or delaying the onset of AIDS, or treating AIDS. An aspect of the present invention is a pharmaceutical composition comprising a therapeutically effective amount of a sodium salt of Compound A in  
10 combination with a therapeutically effective amount of an agent useful for treating HIV infection and/or AIDS (alternatively referred to as an HIV/AIDS treatment agent) selected from:

- (1) an HIV/AIDS antiviral agent,
- (2) an anti-infective agent, and
- 15 (3) an immunomodulator.

The present invention also includes the use of a sodium salt of Compound A as described above as a medicament for (a) inhibiting HIV integrase, (b) preventing or treating infection by HIV, (c) delaying the onset of AIDS, or (d) treating AIDS. The present invention further includes the use of a sodium salt of Compound  
20 A as described above in the preparation of a medicament for (a) inhibiting HIV integrase, (b) preventing or treating infection by HIV, (c) delaying the onset of AIDS, or (d) treating AIDS.

The present invention also includes the use of a sodium salt of Compound A of the present invention as described above in combination with one or  
25 more HIV/AIDS treatment agents selected from an HIV/AIDS antiviral agent, an anti-infective agent, and an immunomodulator for use as a medicament for (a) inhibiting HIV integrase, (b) preventing or treating infection by HIV, (c) delaying the onset of AIDS, or (d) treating AIDS, said medicament comprising an effective amount of the sodium salt of Compound A and an effective amount of the one or more treatment  
30 agents.

The present invention further includes the use of a sodium salt of Compound A of the present invention as described above in combination with one or more HIV/AIDS treatment agents selected from an HIV/AIDS antiviral agent, an anti-infective agent, and an immunomodulator for the manufacture of a medicament for (a)  
35 inhibiting HIV integrase, (b) preventing or treating infection by HIV, (c) delaying the



onset of AIDS, or (d) treating AIDS, said medicament comprising an effective amount of the sodium salt of Compound A and an effective amount of the one or more treatment agents.

5 For the uses described above, a sodium salt of Compound A of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

10 The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a sodium salt of Compound A mean providing the salt to the individual in need of treatment. When a salt of the invention is provided in combination with one or more other active agents (e.g., AIDS antivirals), "administration" and its variants are each understood to include concurrent and sequential provision of the salt and other agents.

15 As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

20 The expression "pharmaceutically acceptable" means that the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term "subject," (alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

25 The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated. For the purpose of  
30 prevention of a given disease or condition, a therapeutically effective amount can alternatively be referred to as a prophylactic amount of the active compound or agent.

The pharmaceutical compositions of the present invention may be in the form of orally-administrable capsules, suspensions or tablets, or as nasal sprays,

sterile injectible preparations, for example, as sterile injectible aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

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

The injectible solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

A Compound A sodium salt of this invention can be administered orally to humans on an active ingredient basis in a dosage range of 0.01 to 1000 mg/kg body weight per day in a single dose or in divided doses. One preferred dosage range is 0.1 to 200 mg/kg body weight per day orally in a single dose or in divided doses. Another preferred dosage range is 0.5 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions are preferably provided in the form of tablets containing 1 to 1000 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient for the symptomatic



adjustment of the dosage to the patient to be treated. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The present invention is also directed to combinations of a sodium salt of Compound A of the present invention with one or more agents useful in the treatment of HIV infection and/or AIDS. For example, a Compound A salt of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the HIV/AIDS antivirals, immunomodulators, antiinfectives, or vaccines, such as those in Table 1 as follows:

TABLE 1 - HIV/AIDS ANTIVIRALS, IMMUNOMODULATORS, ANTIINFECTIVES, AND OTHER TREATMENTS

<u>ANTIVIRALS</u>		
<u>Drug Name</u>	<u>Manufacturer</u> (Tradename and/or Location)	<u>Indication</u>
Amprenavir 141 W94 GW 141	Glaxo Wellcome (AGENERASE®)	HIV infection, AIDS, ARC (protease inhibitor)
Abacavir GW 1592 1592U89	Glaxo Wellcome (ZIAGEN®)	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil	Gilead Sciences	HIV infection

AL-721	Ethigen (Los Angeles, CA)	ARC, PGL, HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV, in combination w/Retrovir
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which neutralizes pH labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
BMS-232623 (CGP-73547)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus immune globin	MedImmune	CMV retinitis
Cytovene Ganciclovir	Syntex	sight threatening CMV peripheral CMV retinitis
Delavirdine	Pharmacia-Upjohn (RESCRIPTOR®)	HIV infection, AIDS, ARC (nonnucleoside reverse transcriptase inhibitor)
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC Dideoxycytidine	Hoffman-La Roche (HIVID®)	HIV infection, AIDS, ARC



ddI Dideoxyinosine	Bristol-Myers Squibb (VIDEX®)	HIV infection, AIDS, ARC; combination with AZT/d4T
mozenavir (DMP-450)	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Efavirenz (DMP 266)	DuPont (SUSTIVA®) Merck (STOCRIN®)	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
Famciclovir	Smith Kline	herpes zoster, herpes simplex
FTC	Emory University	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
HBV097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Alameda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck (CRIXIVAN®)	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	Glaxo Wellcome (EPIVIR®)	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection

Nelfinavir	Agouron (VIRACEPT®)	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boeheringer Ingleheim (VIRAMUNE®)	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate PNU-140690	Astra Pharm. Products, Inc Pharmacia Upjohn	CMV retinitis, HIV infection, other CMV infections HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston TX)	HIV infection, AIDS, ARC
Ritonavir (ABT-538)	Abbott (RITONAVIR®)	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche (FORTOVASE®)	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy- thymidine	Bristol-Myers Squibb (ZERIT®)	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	genital HSV & CMV infections



Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-La Roche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome (RETROVIR®)	HIV infection, AIDS, ARC, Kaposi's sarcoma in combination with other therapies (reverse transcriptase inhibitor)
Lopinavir (ABT-378)	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Lopinavir + ritonavir (ABT-378/r); Kaletra	Abbott (KALETRA®)	HIV infection, AIDS, ARC (protease inhibitor)
JE2147/AG1776	Agouron	HIV infection, AIDS, ARC (protease inhibitor)
T-20	Trimeris	HIV infection, AIDS, ARC (fusion inhibitor)
T-1249	Trimeris	HIV infection, AIDS, ARC (fusion inhibitor)
atazanavir (BMS 232632); Zrivada	Bristol-Myers-Squibb (ZRIVADA®)	HIV infection, AIDS, ARC (protease inhibitor)
PRO 542	Progenics	HIV infection, AIDS, ARC (attachment inhibitor)
PRO 140	Progenics	HIV infection, AIDS, ARC (CCR5 co-receptor inhibitor)
TAK-779	Takeda	HIV infection, AIDS, ARC (injectable CCR5 receptor antagonist)
DPC 681 & DPC 684	DuPont	HIV infection, AIDS, ARC (protease inhibitors)
DPC 961 & DPC 083	DuPont	HIV infection AIDS, ARC (nonnucleoside reverse transcriptase inhibitors)
abacavir + lamivudine + zidovudine	GlaxoSmithKline (TRIZIVIR®)	HIV infection, AIDS, ARC (reverse transcriptase inhibitors)

tipranavir (PNU-140690)	Boehringer Ingelheim	HIV infection, AIDS, ARC (protease inhibitor)
tenofovir	Gilead (VIREAD®)	HIV infection, AIDS, ARC (nucleotide reverse transcriptase inhibitor)
TMC-120 & TMC-125	Tibotec	HIV infections, AIDS, ARC (non-nucleoside reverse transcriptase inhibitors)
TMC-126	Tibotec	HIV infection, AIDS, ARC (protease inhibitor)

### IMMUNO-MODULATORS

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
FP-21399	Fuki ImmunoPharm	blocks HIV fusion with CD4+ cells
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoeschst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT



IL-2 Interleukin-2	Hoffman-La Roche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin intravenous (human)	Cutter Biological (Berkeley, CA)	pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine- Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
Remune	Immune Response Corp.	immunotherapeutic
rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma, AIDS, ARC, in combination w/AZT
SK&F106528 Soluble T4	Smith Kline	HIV infection
Thymopentin	Immunobiology Research Institute	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon
etanercept	Immunex Corp (ENBREL®)	rheumatoid arthritis

infliximab	Centocor (REMICADE®)	rheumatoid arthritis and Crohn's disease
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### ANTI-INFECTIVES

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		antibacterial
Trimethoprim/sulfa		antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine isethionate for inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc	cryptosporidia diarrhea
Intraconazole-R51211	Janssen Pharm.	histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP

5

### OTHER

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Daunorubicin	NeXstar, Sequus	Karposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Leukotriene B4 Receptor Antagonist	-	HIV infection



Megestrol Acetate	Bristol-Myers Squibb	treatment of anorexia assoc. w/AIDS
Soluble CD4 Protein and Derivatives	-	HIV infection
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	diarrhea and malabsorption, related to AIDS

It will be understood that the scope of combinations of a Compound A salt of this invention with HIV/AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in Table 1 above, but includes in principle any combination with any pharmaceutical composition useful for the treatment of HIV infection and/or AIDS. When employed in combination with a salt of the invention, the HIV/AIDS antivirals and other agents are typically employed in their conventional dosage ranges and regimens as reported in the art, including the dosages described in the Physicians' Desk Reference, 54<sup>th</sup> edition, Medical Economics Company, 2000.

The dosage ranges for a compound of the invention in these combinations are the same as those set forth above just before Table 1.

One suitable combination is a sodium salt of Compound A of the present invention and a nucleoside inhibitor of HIV reverse transcriptase such as AZT, 3TC, ddC, or ddI. Another suitable combination is a Compound A salt of the present invention and a non-nucleoside inhibitor of HIV reverse transcriptase, such as efavirenz, and optionally a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI.

Still another suitable combination is any one of the combinations in the preceding paragraph, further comprising an HIV protease inhibitor such as indinavir, nelfinavir, ritonavir, saquinavir, amprenavir, or abacavir. An aspect of this combination is the combination wherein the HIV protease is the sulfate salt of indinavir. Another aspect of this combination is the combination in which the protease inhibitor is selected from nelfinavir and ritonavir. Still another aspect of this combination is the combination in which the inhibitor of HIV protease is saquinavir, which is typically administered in a dosage of 600 or 1200 mg tid.

Other suitable combinations include a compound of the present invention with the following (1) efavirenz, optionally with AZT and/or 3TC and/or ddI and/or ddC, and optionally with indinavir; (2) any of AZT and/or ddI and/or ddC

and/or 3TC, and optionally with indinavir; (3) d4T and 3TC and/or AZT; (4) AZT and 3TC; and (5) AZT and d4T.

In the above-described combinations, a Compound A sodium salt of the present invention and other active agents may be administered together or  
5 separately. In addition, the administration of one agent may be prior to, concurrent with, or subsequent to the administration of other agent(s). These combinations may have unexpected or synergistic effects on limiting the spread and degree of infection of HIV.

10 Abbreviations used herein include the following:

AIDS = acquired immunodeficiency syndrome

ARC = AIDS related complex

Bn = benzyl

DMF = N,N-dimethylformamide

15 DSC = differential scanning calorimetry

DIPA = diisopropylamine

EDTA = ethylenediamine tetraacetic acid

EtOH = ethanol

g = gram(s)

20 h = hour(s)

HIV = human immunodeficiency virus

HPLC = high-performance liquid chromatography

IPAc = isopropyl acetate

Me = methyl

25 MeCN = acetonitrile

MeOH = methanol

min = minute(s)

Ms = mesyl (methanesulfonyl)

MTBE = methyl t-butyl ether

30 NMP = N-methyl pyrrolidinone

NMR = nuclear magnetic resonance

TEA = triethylamine

THF = tetrahydrofuran

XRPD = x-ray powder diffraction

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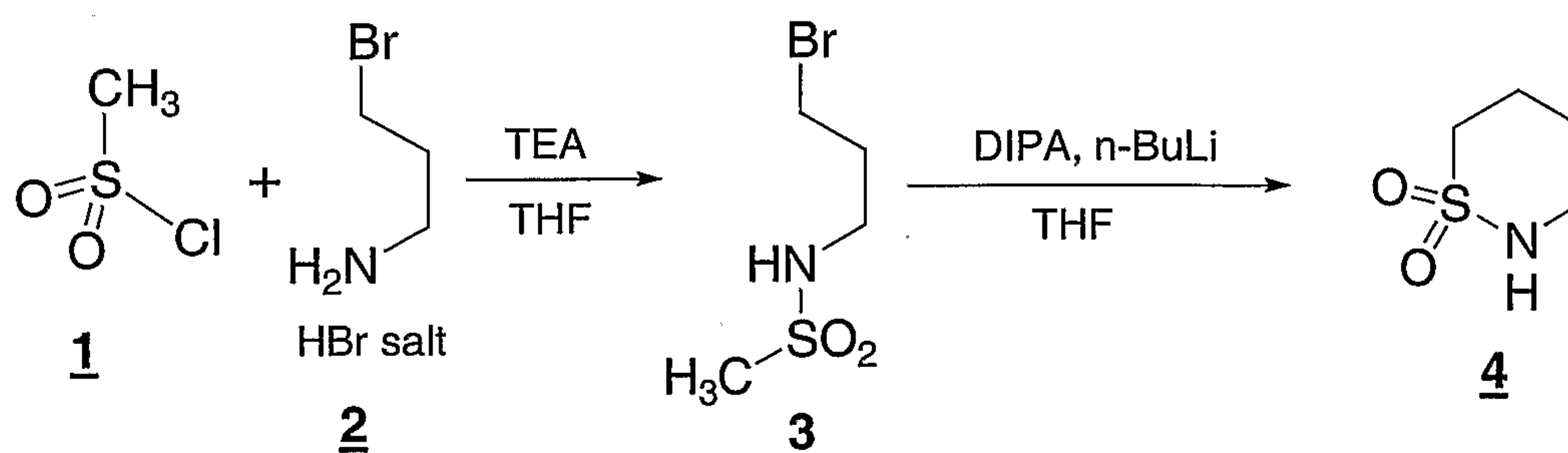


The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention.

5

## EXAMPLE 1

## Preparation of 1,4-Butanesultam



	Weight	FW	Moles	Equiv.	Density	Volume
MsCl ( <u>1</u> )	2.36 Kg	114.55	20.6	1.03	1.480	1.59 L
3-bromopropyl-amine ( <u>2</u> ) HBr salt	4.40 Kg	220	20.0	1.00		
TEA	4.07 Kg	101.19	40.2	2.01	0.726	5.60 L
THF					43 + 4 + 8 = 55 L	
DIPA	481 g	101.19	4.75	0.25	0.722	666 mL
1,10-Phenanthroline	4.11 g	180.21				
n-BuLi, 1.6 M in hexane						

10 The 3-bromopropylamine-HBr salt (2) and THF (43 L) were placed in a 72 L round-bottomed-flask under N<sub>2</sub> and the resulting slurry was cooled to 0 °C. Two dropping funnels were fitted to the flask. One was charged with the TEA and the other with a solution of the MsCl (1) and THF (4L). The contents of the addition funnels were added at roughly the same rate (the TEA was added slightly faster than

15 the MsCl) while maintaining an internal reaction temperature below 10 °C. The addition required 2 h. The resulting white suspension was warmed to 23 °C and aged for 1 h. The suspended solids (a mixture of TEA-HBr and TEA-HCl) were removed

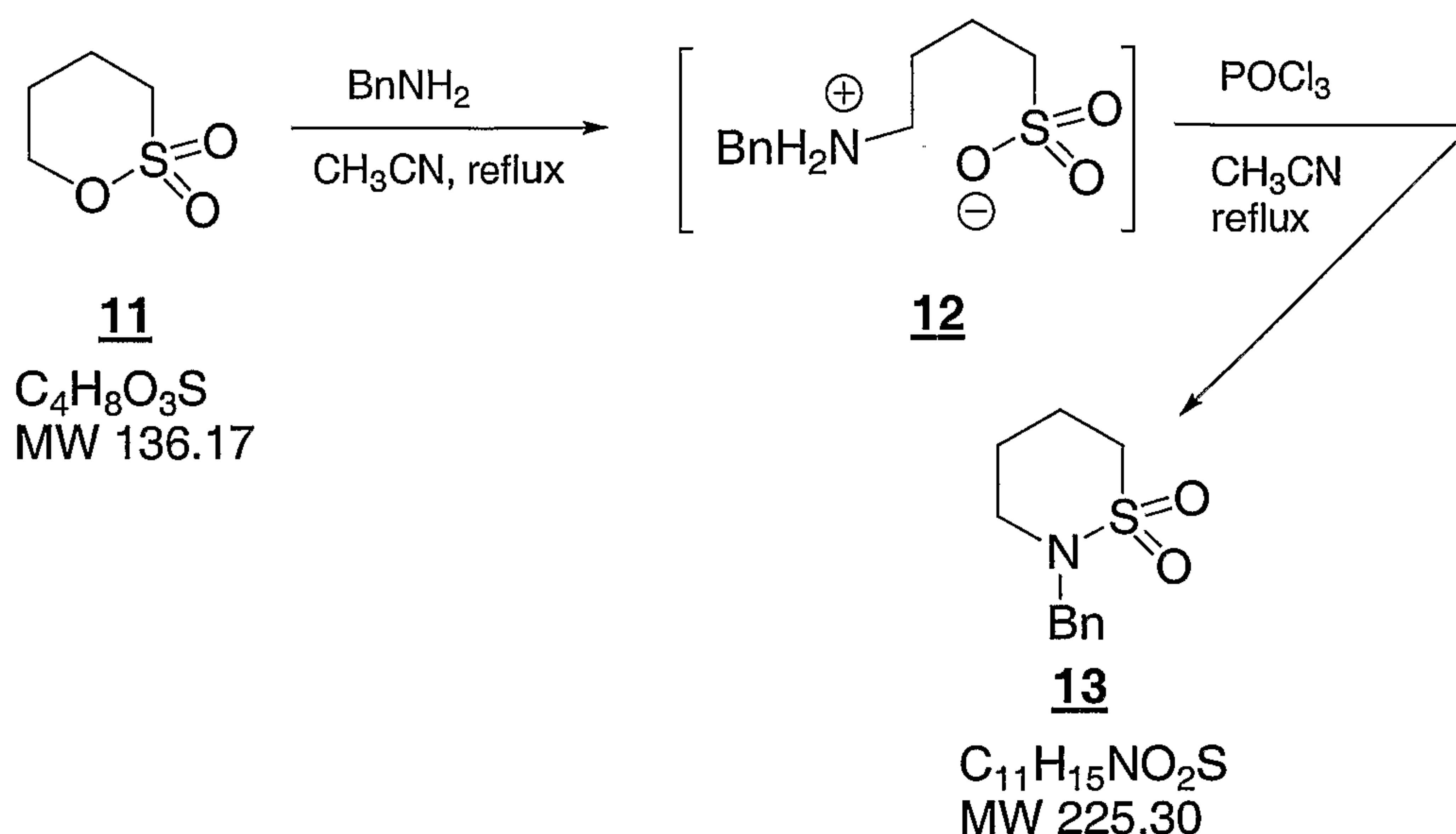
by filtration through a dry frit. The cake was washed with THF (8L). The combined filtrate and cake-rinse, a THF solution of 3, was collected in a 100 L round-bottomed-flask under N<sub>2</sub>. To the solution of 3 was added the 1,10-phenanthroline and the DIPA and the resulting solution was cooled to -30 °C. The *n*-BuLi was added over about 4  
5 h maintaining the internal temperature below -20 °C. After 1.25 eq of the *n*-BuLi was added the reaction mixture became deep brown and the color remained as the addition was completed. The reaction mixture was warmed to 0 °C over 3 h. A small aliquot was removed, and partitioned between saturated NH<sub>4</sub>Cl and EtOAc. The EtOAc was evaporated and the residue examined by <sup>1</sup>H NMR to confirm consumption of 3 and  
10 conversion to 4. To the reaction mixture at 0 °C was added saturated aqueous NH<sub>4</sub>Cl (12 L, the first 1 L slowly, a heat kick to 6 °C was observed) and then brine (12 L). The phases were partitioned and the aqueous phase was extracted with EtOAc (20 L). The organic phases were combined, washed with brine (4 L) and then concentrated under vacuum to about 12 L. The solvent was switched to EtOAc (20 L used)  
15 maintaining a volume of 12 L. After the solvent switch, a yellow slurry resulted. *n*-Heptane (20 L) was added with stirring and the slurry was cooled to 5 °C. After a 1h age the solids were collected on a frit and rinsed with cold (5 °C) 3:5 EtOAc/*n*-heptane. The wet cake was dried for 24 h under a stream of dry N<sub>2</sub> to provide 1.44 Kg (53% from 2) of sultam 4 as a crystalline yellow solid.  
20 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 mHz) δ 4.36 (br s, 1H), 3.45 (m, 2H), 3.10 (m, 2H), 2.24 (m, 2H), 1.64 (m, 2H).

## EXAMPLE 2

### Alternative Preparation of 1,4-Butanesultam

25 Step 1:

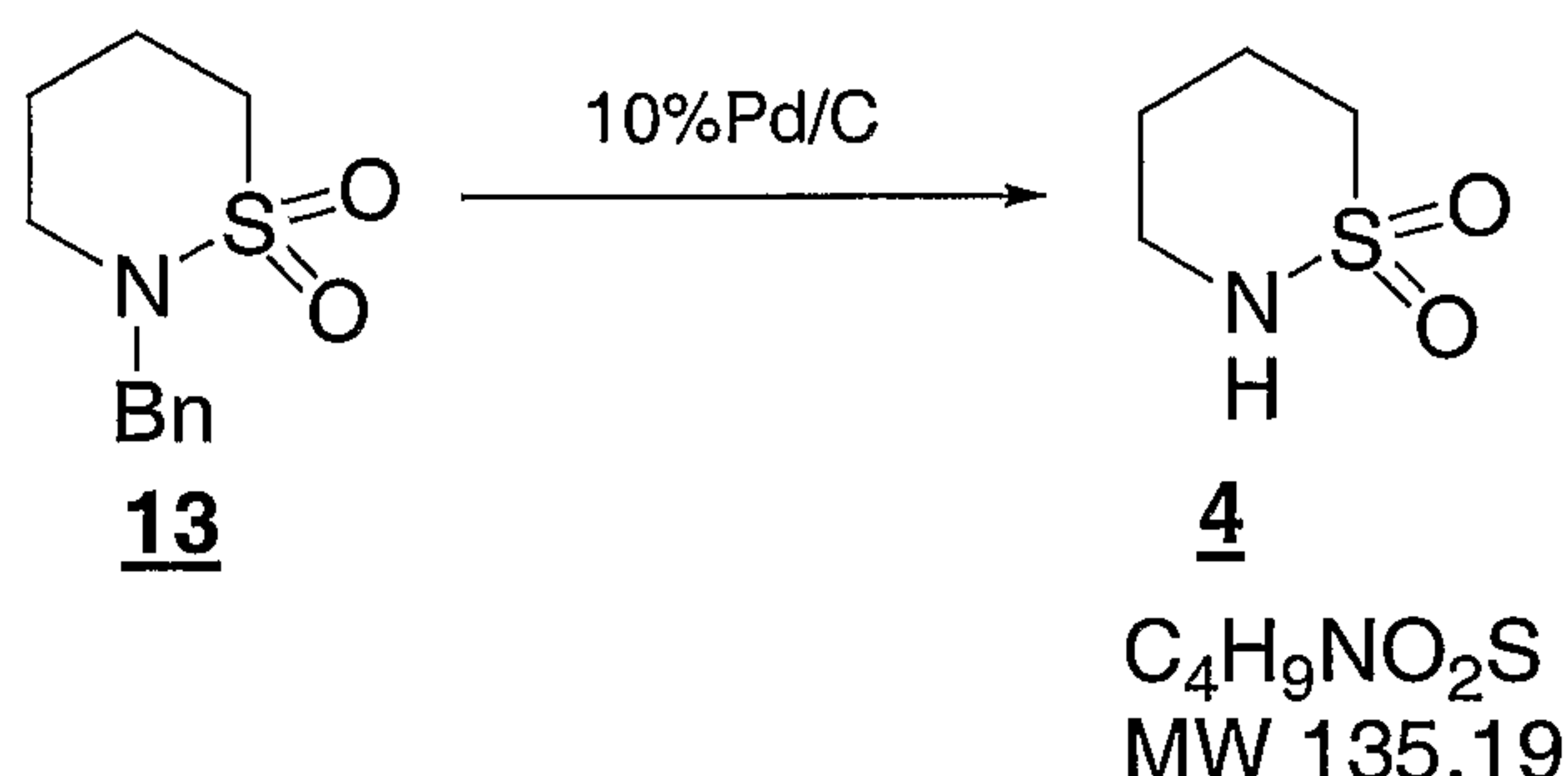




	Materials	MW	Amount	Moles	Equivalent
	1,4-Butane sultone	136.17	68.10 g	0.5000	1
5	Benzylamine	107.16	69.70 g	0.6500	1.3
	Acetonitrile		625 mL		
	Phosphorus oxychloride	153.33	153.33 g	1.000	2

A solution of 1,4-butane sultone **11** (68.10 g, 0.5000 moles) and  
 10 benzylamine (69.70 g, 0.6500 moles) in acetonitrile (625 mL) was refluxed at 82°C  
 for 24 hours, with the reaction monitored by  $^1H$  NMR until conversion of **11** to **12**  
 was >98%. While the resulting slurry was cooled to 50°C, phosphorus oxychloride  
 (153.33 g, 1.000 moles) was slowly added via a dropping funnel. After complete  
 addition, the mixture was refluxed at 82 °C for 8 hours, with the reaction monitored  
 15 by HPLC until conversion was > 98%. The reaction mixture was concentrated to  
 remove acetonitrile, and the residue was cooled to 0-5°C and neutralized with 20%  
 sodium hydroxide to pH = 7. The resulting mixture was extracted with IPAc (3 x 350  
 mL), and the combined extracts were washed with 10% sodium bicarbonate (2 x 100  
 mL) and 25% of brine (100 mL). The resulting clear solution was concentrated and  
 20 solvent switched to methanol (total volume 1000 mL), which was used in the next  
 step of the reaction. For compound **13**:  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$ : 7.38-7.32 (m,  
 5 H), 4.32 (s, 2H), 3.23 (m, 2 H), 3.11 (m, 2 H), 2.22 (m, 2 H), 1.62 (m, 2 H).

Step 2:



	Materials	MW	Amount	Moles	Equivalent
5	<i>N</i> -Benzyl-1,4-buthanesultam	225.30		0.5000	1
	10% Pd/C		12.0 g		10%wt
	1 N HCl (aqueous)		80 mL		
	Solka Flock		20 g		

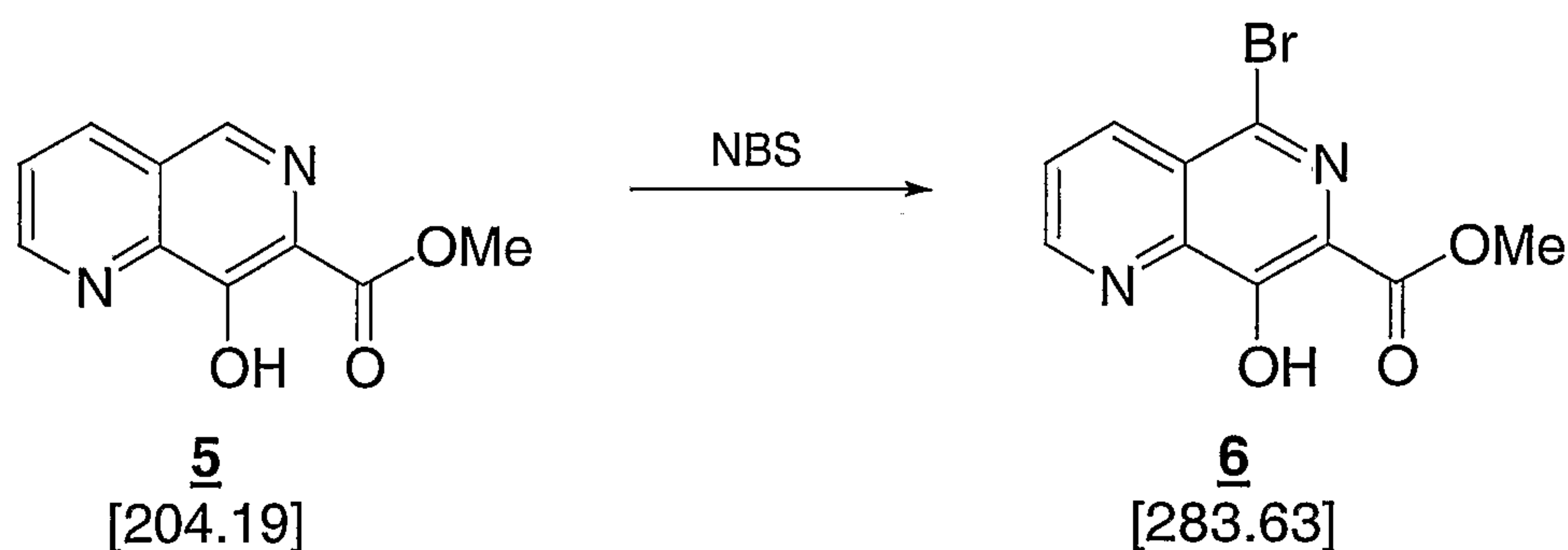
- 10 To a solution of *N*-Benzyl-1,4-buthanesultam **13** (0.5000 moles) in methanol (total volume 1000 mL) and 1 N HCl aqueous (80 mL) was added 10% Pd/C (12.0 g). The resulting slurry was submitted to hydrogenation at 40°C, 45 psi for 24 hours, with the reaction monitored by HPLC until conversion of **13** to **4** was >99%. The reaction mixture was cooled to ambient temperature and filtered by
- 15 passing through a pad of Solka Flock (20 g) and washed with methanol (3 x 100 mL). The combined filtrates were concentrated to remove the methanol, and a crystalline solid was precipitated out during the concentration. To the slurry solution was added heptane/MTBE (3:2, 100 mL). The resulting mixture was cooled to 0 °C, and aged for 0.5 hour. The crystalline solid was filtered off and washed with cold heptane/MTBE
- 20 (3:2, 50 mL), and dried under vacuum with a nitrogen sweep to give 1,4-buthanesultam **4** (49.8 g, 74% overall from **11**).

### EXAMPLE 3

- Preparation of 5-(1,1-dioxido-1,2-thiazinan-2-yl)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide from methyl 5-bromo-8-hydroxy-1,6-naphthyridine-7-carboxylate
- 25 carboxylate

Step 1: 5-Bromo-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester





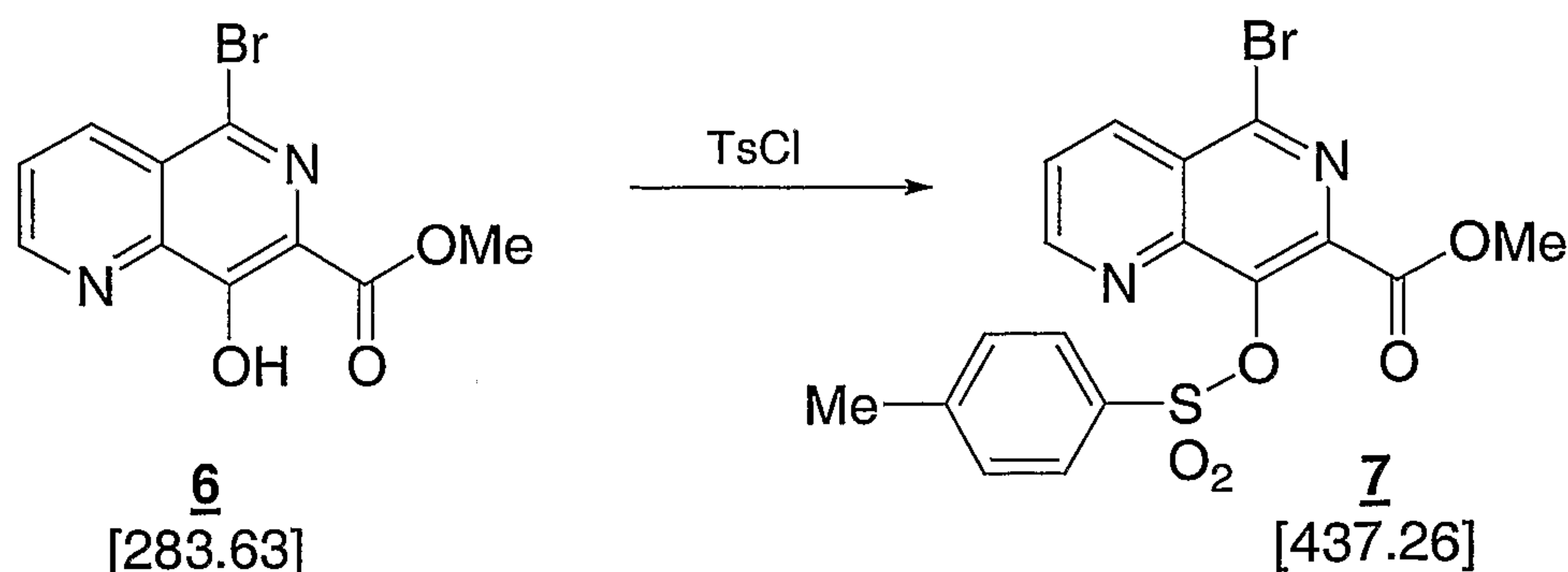
N-bromosuccinimide (7.83 g, 44.0 mmol) was added to a solution of 8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (**5**, 8.17 g, 40.0 mmol) in chloroform (32 mL) over 20 min maintaining the temperature at 20-50 °C and the mixture was aged for 30 min at 50 °C. The mixture became a thick, stirrable slurry and HPLC analysis indicated <2% starting material remaining. The mixture was cooled to 30 °C over 15 min. MeOH (64 mL) was added over 30 min then a 1:1 mixture of MeOH-water (64 mL) was added over 30 min. The mixture was cooled to -40 °C over 30 min and aged at -40 °C for 30 min. The cold mixture was filtered and the solid was washed with 1:1 MeOH:water (100 mL) at 10-20 °C. The off white crystalline solid was dried under a stream of nitrogen to provide 10.48 g (93% yield) of 5-bromo-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (**6**).

HPLC retention times: **5** = 2.2 min, **6** = 6.0 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 30% MeCN in 0.025% aq H<sub>3</sub>PO<sub>4</sub> at 1 mL/min, 25 °C with detection at 254 nm;

HPLC retention times: **5** = 1.8 min, **6** = 3.1 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 46% MeCN in 0.025% aq H<sub>3</sub>PO<sub>4</sub> at 1 mL/min, 25 °C with detection at 254 nm.

<sup>13</sup>C NMR of **6** (CDCl<sub>3</sub>, 100 MHz): 169.7, 156.3, 154.5, 143.9, 137.1, 132.4, 128.0, 126.1, 124.2, 53.4.

**Step 2:**            5-Bromo-8-(4-toluenesulfonyloxy)-1,6-naphthyridien-7-carboxylic acid methyl ester



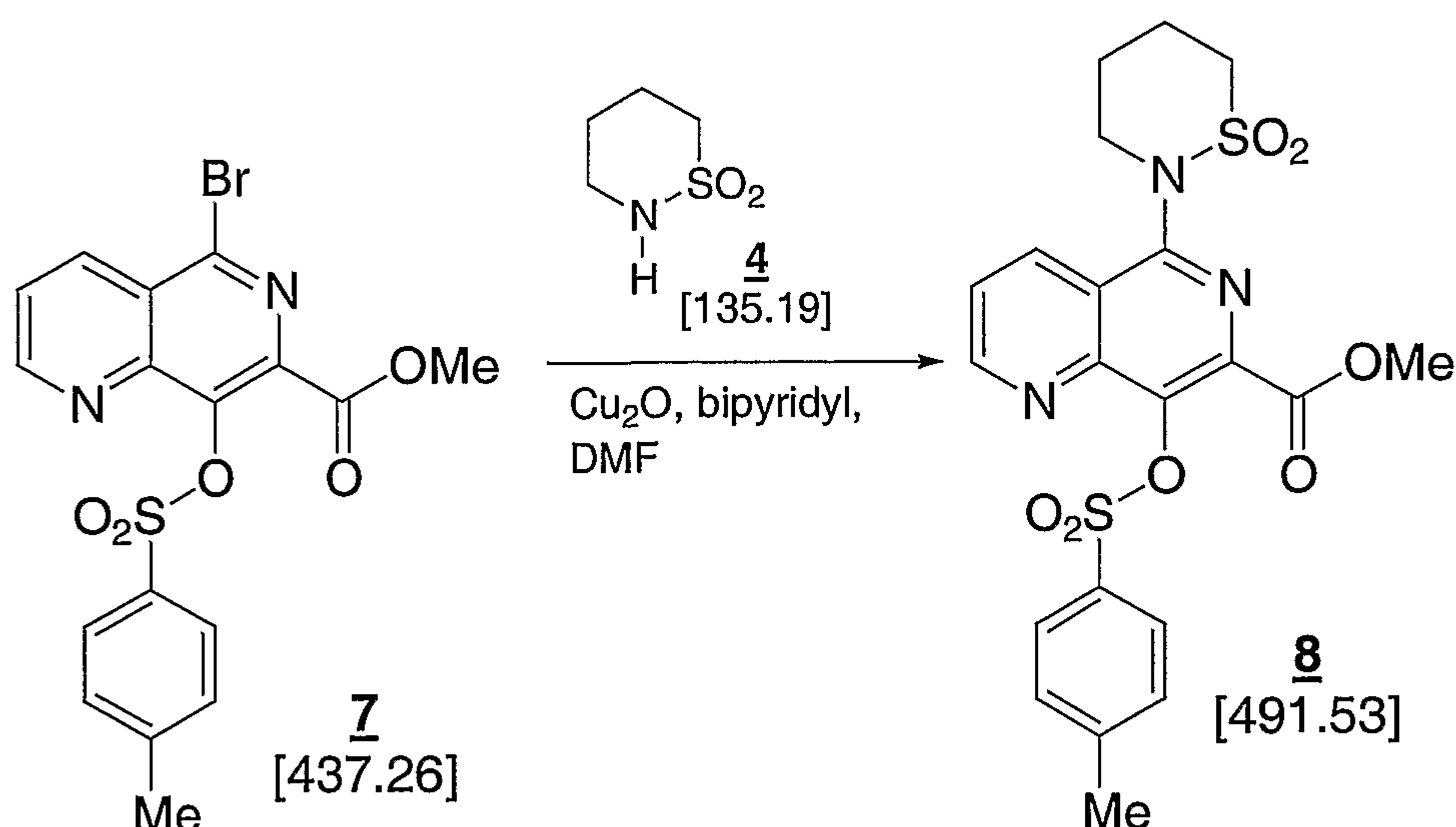
Triethylamine (0.759 g, 7.50 mmol) was added to a suspension of 5-bromo-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (6, 1.415 g, 5.000 mmol) in chloroform (5 mL) over 5 min maintaining the temperature at 20-50 °C to give a yellow suspension. *p*-Toluenesulfonyl chloride (1.15 g, 6.00 mmol) was added over 5 min maintaining the temperature at 20-40 °C to give a yellow solution. The mixture was aged at 40 °C for 2 h during which a crystalline solid precipitated out of the mixture and the color faded (HPLC analysis indicated <0.5% starting material remaining). The mixture was cooled to 20 °C over 15 min. MeOH (10 mL) was added over 30 min then a 1:1 mixture of MeOH:water (10 mL) was added over 30 min. The mixture was cooled to -40 °C over 30 min and aged at -40 °C for 30 min. The cold mixture was filtered and the solid was washed with 1:1 MeOH:water (10 mL), MeOH (5 mL), MTBE (10 mL) and hexanes (10 mL) all at 10-20 °C. The off-white crystalline solid was dried under a stream of nitrogen to provide 2.112 g (97% yield) of 5-bromo-8-(*p*-toluenesulfonyloxy)-1,6-naphthyridine-7-carboxylic acid methyl ester (7).

HPLC retention times: 6 = 3.1 min, 7 = 12.4 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 46% MeCN in 0.025% aq H<sub>3</sub>PO<sub>4</sub> at 1 mL/min, 25 °C with detection at 254 nm.

<sup>13</sup>C NMR of 7 (d<sub>6</sub>-DMSO, 100 MHz): 163.2, 157.0, 146.5, 145.8, 141.9, 141.3, 139.2, 137.2, 132.3, 130.4, 129.0, 127.6, 127.1, 53.3, 21.7.

Step 3: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-(4-toluenesulfonyloxy)-1,6-naphthyridine-7-carboxylic acid methyl ester.





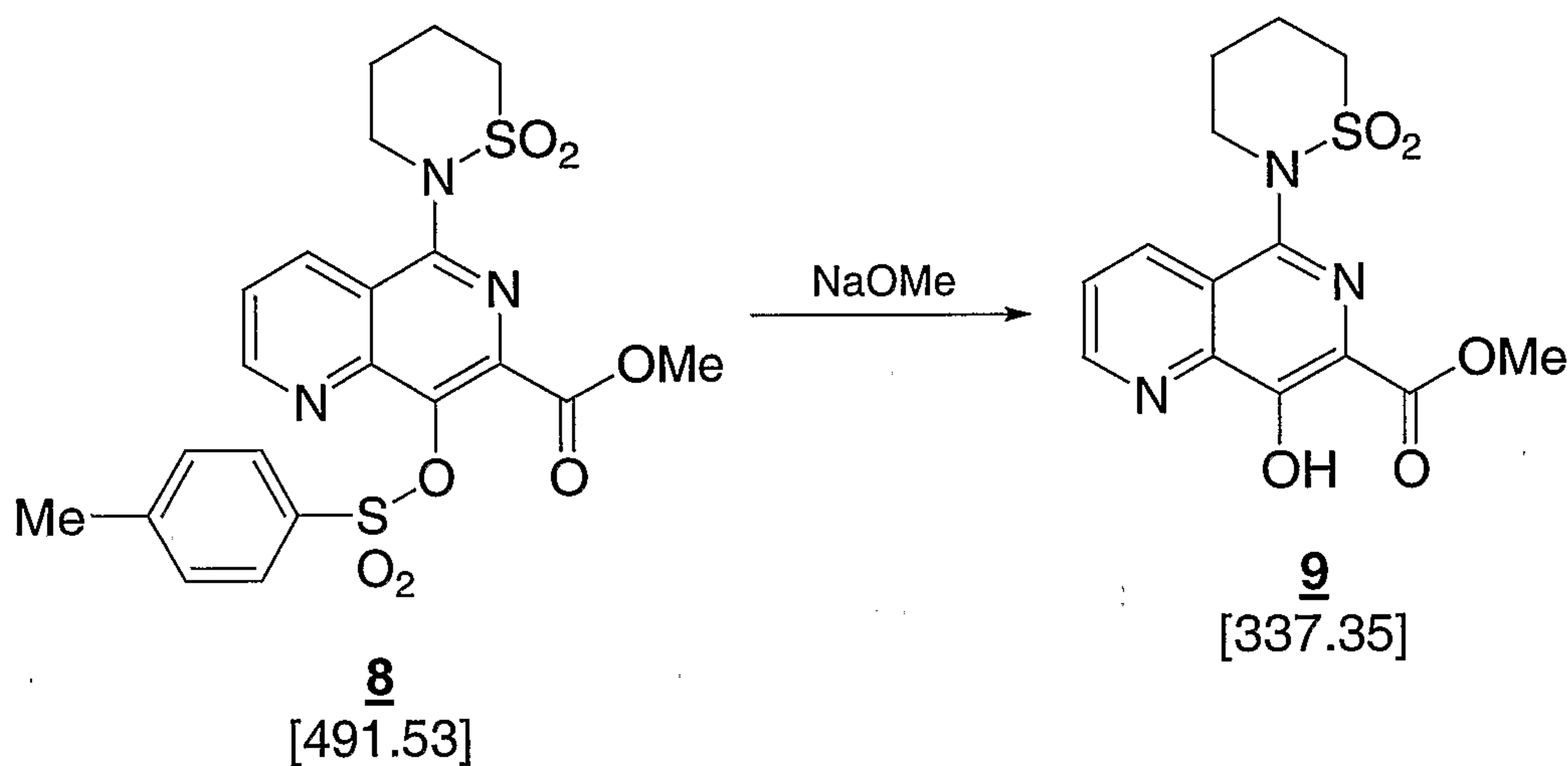
A mixture of 5-bromo-8-(*p*-toluenesulfonyloxy)-1,6-naphthyridine-7-carboxylic acid methyl ester (**7**, 2.186 g, 5.000 mmol), 1,4-butane sultam (**4**, 811 mg, 6.00 mmol), copper (I) oxide (858 mg, 6.00 mmol, <5 micron), 2,2'-bipyridyl (937 mg, 6.00 mmol) and DMF (10 mL) was degassed by stirring under a stream of nitrogen for 1 min and heated to 120 °C for 4 h. The brown suspension became a dark red solution with a small amount of undissolved copper (I) oxide remaining (HPLC analysis indicated <0.5% starting material remaining). The mixture was diluted with chloroform (10 mL), Solkaflok (200 mg) was added and the resulting mixture was filtered through a plug of Solkaflok. The plug was washed with chloroform (10 mL) and the combined filtrates were stirred vigorously with a solution of EDTA disodium salt dihydrate (3.8 g, 10.2 mmol) in water (40 mL) while air was slowly bubbled in for 40 min. The upper aqueous phase became turquoise while the lower organic phase became yellow. The organic phase was washed with a solution of EDTA disodium salt (1.9 g, 5.1 mmol) in water (30 mL) and a solution of sodium bisulfate monohydrate (0.87g, 6.3 mmol) in water (30 mL). Each of the above three aqueous phases was back extracted sequentially with one portion of chloroform (15 mL). The organic phases were dried over sodium sulfate and filtered. The dried organic extracts were concentrated and solvent switched to a final volume of 15 mL MeOH using a total of 30 mL MeOH for the switch at atmospheric pressure. Product crystallized during the solvent switch. The resulting slurry was cooled to 0 °C over 30 min and aged at 0 °C for 30 min. The slurry was filtered cold and the solid was washed with MeOH (15 mL). The off white solid was dried under a stream of

nitrogen to provide 1.910 g (78%) of 5-(*N*-1,4-butanesultam)-8-(*p*-toluenesulfonyloxy)-1,6-naphthyridine-7-carboxylic acid methyl ester (**8**).

HPLC retention times: **7** = 12.4 min, **8** = 10.3 min, DMF = 1.3 min, Bipy = 1.5 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with  
5 46% MeCN in 0.025% aq H<sub>3</sub>PO<sub>4</sub> at 1 mL/min, 25 °C with detection at 254 nm.

<sup>13</sup>C NMR of **8** (CDCl<sub>3</sub>, 100 MHz): 164.2, 155.3, 151.9, 146.7, 145.4, 141.2, 137.8, 135.3, 133.6, 129.6, 128.9, 125.4, 124.3, 53.4, 52.9, 48.7, 24.2, 22.0, 21.7.

10 Step 4: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester.



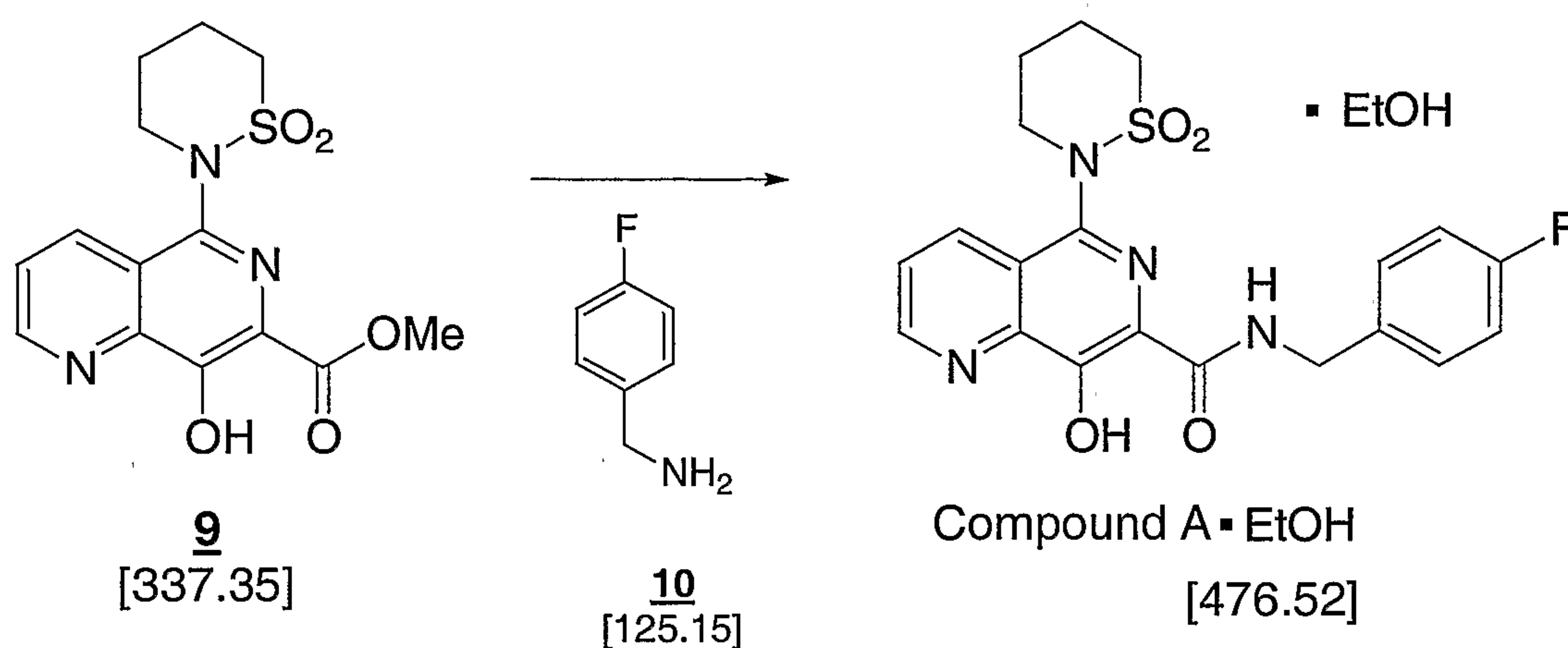
5-(*N*-1,4-butanesultam)-8-(*p*-toluenesulfonyloxy)-1,6-naphthyridine-7-carboxylic acid methyl ester (**8**, 1.597 g, 3.250 mmol) was dissolved in DMF (3.25 mL) at 40 °C and transferred to a solution of 0.5M NaOMe in MeOH (16.25 mL, 8.125 mmol) over ca 1-2 min at 20-25 °C. The resulting yellow homogenous mixture was heated to 50 °C and aged for 5 min (HPLC analysis indicated <0.5% starting material remaining). Mixture was cooled to 25 °C over 15 min and aged at 25 °C for 15 min during which a yellow crystalline precipitate was deposited. Acetic acid (390 mg, 6.50 mmol) was added over 1 min (yellow color faded) then water (32.5 mL) was  
15 added over 15 min at 25 °C. The slurry was aged for 30 min 25 °C and filtered. The filter cake was washed with 1:1 MeOH:water (32.5 mL) and then with 1:1 MTBE:hexanes (8 mL). The filter cake was dried under a stream of nitrogen to provide 1.064 g (97%) of 5-(*N*-1,4-butanesultam)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (**9**) as an off white crystalline solid.  
20



HPLC retention times: 8 = 10.3 min, 9 = 2.9 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 46% MeCN in 0.025% aq H<sub>3</sub>PO<sub>4</sub> at 1 mL/min, 25 °C with detection at 254 nm.

<sup>13</sup>C NMR of 9 (d<sub>6</sub>-DMSO, 100 MHz): 167.8, 154.4, 153.5, 143.9, 143.7, 135.2, 125.9, 125.2, 124.4, 53.2, 53.1, 49.1, 24.4, 21.9.

Step 5: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide, monoethanolate.



10 A suspension of 5-(*N*-1,4-butanesultam)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (9, 1.012 g, 3.00 mmol) and 4-fluorobenzylamine (10, 1.314 g, 10.5 mmol) in EtOH (9.0 mL) was heated to 75-77 °C for 2 h during which the mixture became a yellow homogeneous solution (HPLC analysis indicated <0.5% starting material remaining). Acetic acid (0.630 mg, 10.5 mmol) was added over 1 min (yellow color faded) then water (9.0 mL) was added over 10 min at 75 °C. An off white crystalline solid began to precipitate near the end of addition of the water. The slurry was cooled to 0 °C over 30 min then aged for 30 min at 0 °C and filtered. The filter cake was washed with 5% HOAc in 1:1 EtOH:water (5 mL) then with 1:1 EtOH:water (10 mL) and then with EtOH (5 mL). The filter cake was dried under a stream of nitrogen to provide 1.343 g (94%) of the monoethanolate of 5-(*N*-1,4-butanesultam)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide (Compound A) as an off white crystalline solid.

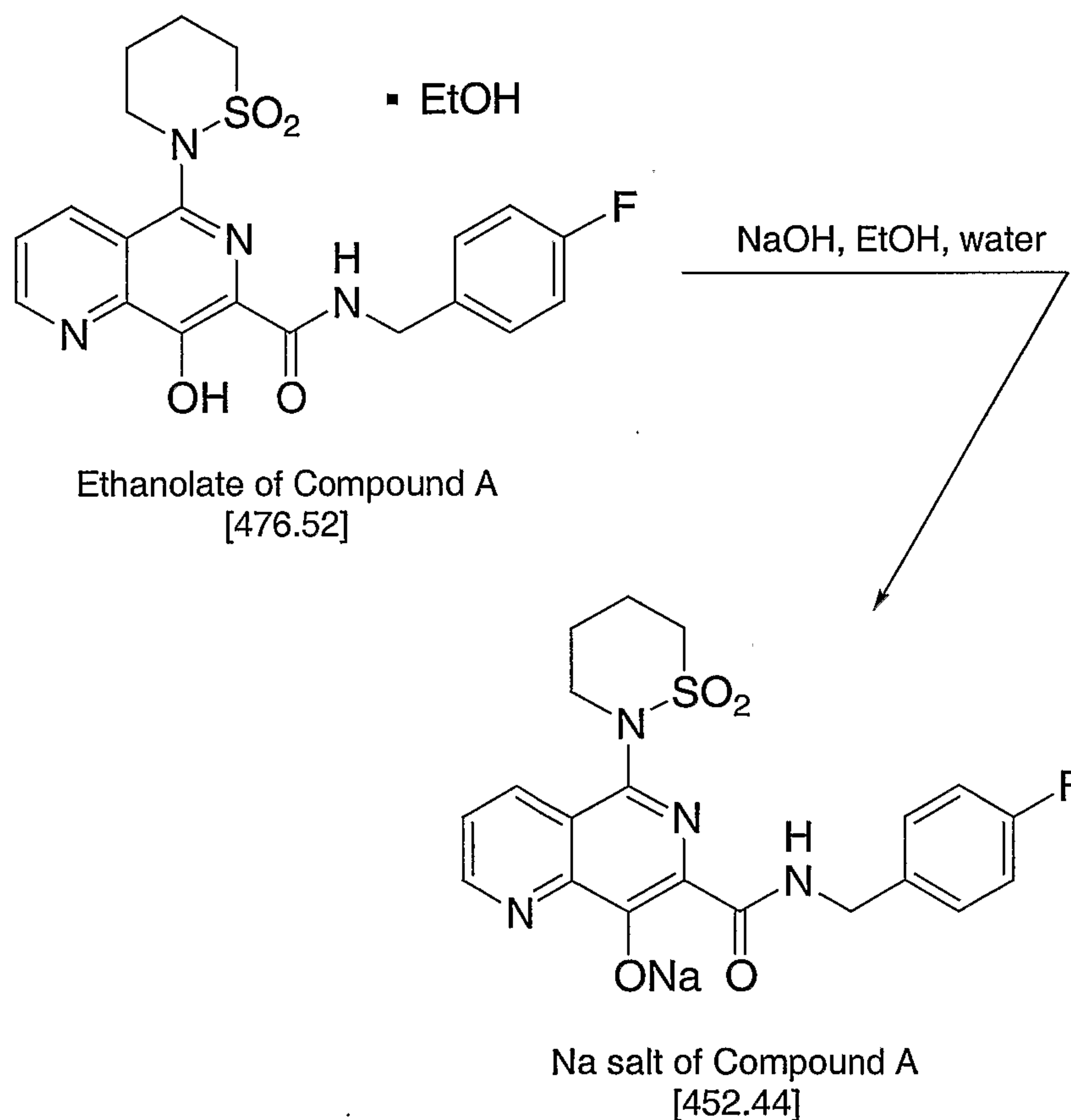
HPLC retention times: 9 = 2.9 min, Compound A = 6.7 min, 10 = 1.4 min, impurity present in 10 = 4.3 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18

column, isocratic elution with 46% MeCN in 0.025% aq H<sub>3</sub>PO<sub>4</sub> at 1 mL/min, 25 °C with detection at 254 nm;

HPLC retention time: **9** = 10.9 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 24% MeCN in 0.025% aq H<sub>3</sub>PO<sub>4</sub> at 1 mL/min, 25 °C with detection at 254 nm.

<sup>1</sup>H NMR (d6-DMSO, 400 MHz): 9.25 (t, J=6.4, 1H), 9.16 (d, J=8.4, 1H), 8.56 (d, J=8.4, 1H), 7.86 (dd, J=8.4, 4.1, 1H), 7.41 (dd, J=8.4, 5.7, 2H), 7.16, t, J=8.8, 2H), 4.60 (d, 6.3, 2H), 4.00-3.70 (m, 2H), 3.65-3.45 (m, 2H), 2.35-2.10 (m, 3H), 1.7 (m, 1H).

**Step 6:** Sodium salt of 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide



5-(*N*-1,4-Butanesultam)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide (Compound A) monoethanolate (1.207 g, 2.533 mmol) was dissolved in a mixture of EtOH (24 mL) and water (11 mL) by heating to 78 °C



for 1 h. A solution of 5M aq NaOH (0.608 mL, 3.04 mmol) was added over 15 min at 78 °C. A yellow crystalline precipitate was deposited. The mixture was aged at 78 °C for 20 min, then cooled to 20 °C over 30 min and aged for 30 min at 20 °C. The slurry was filtered and the filter cake was washed with 2:1 EtOH:water (5 mL) and EtOH (15 mL). The filter cake was dried under a stream of nitrogen to provide 1.088 g (95%) of 5-(*N*-1,4-butanediol)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide sodium salt (Compound A sodium salt) as a yellow crystalline solid.

The Na salt was analyzed by differential scanning calorimetry at a heating rate of 10°C/min in an open cup under flowing nitrogen and was found to have a DSC curve exhibiting an endotherm with a peak temperature of about 348°C and an associated heat of fusion of about 45 J/gm followed by an exotherm with a peak temperature of about 352°C and an associated heat of fusion of about 45 J/gm.

The XRPD pattern of the Na salt was generated on a Philips Analytical X-ray powder diffraction instrument with XRG 3100 generator using a continuous scan from 2 to 40 degrees 2 theta over about 126 minutes. The resulting XRPD pattern was analyzed using Philips X'Pert Graphics and Identify software. Copper K-Alpha 1 radiation was used as the source. The experiment was run under ambient conditions. The XRPD pattern was found to have characteristic diffraction peaks corresponding to d-spacings of 12.63, 5.94, 5.05, 4.94, 4.81, 4.61, 4.54, 4.34, 3.88, 3.73, 3.49, 3.45, 3.22, 3.15, 3.12, and 2.86 angstroms.

#### EXAMPLE 4

##### Crystallization of Compound A Na Salt from NMP-EtOH Solvent System

A 9 L tank equipped with an agitator was charged with NMP (6.69 kg, 6.67 L) and Compound A (1.00 kg, 2.32 mol) to form a clear yellow solution at room temperature at a concentration of 150 mg/mL. In a separate vessel, 1.1 equivalents of 5M NaOH (0.56 kg, 0.51 L) was diluted to 0.71 M in ethanol (2.45 kg, 3.10 L) at room temperature to form a clear solution. 15% of the phenol in NMP solution (1.17 kg, 1.13 L) was charged to a 16 L jacketed crystallizer equipped with a low blade agitator and heated to 68-70°C. 15% of this NaOH/EtOH solution (0.45 kg, 0.54 L) was combined with the batch in the crystallizer, and the batch aged for 30 to 45 minutes at 68-70°C. Initially, the batch remained a clear yellow solution, but became cloudy after about 5 to 15 minutes, forming a thick yellow slurry, or seed bed consisting of small, evenly distributed needles after about 30 minutes. (Note: As an alternative, the batch may also be seeded with solid seed.)

The remaining Compound A and NaOH solutions were then charged to the batch slurry simultaneously over two hours, maintaining the batch temperature at 65-70°C. The resulting slurry was aged for 1 hour at 68-70°C. Additional EtOH (3.29 kg, 4.13 L) was added as an antisolvent over two hours while still maintaining the batch at 68-70°C, and the thinner yellow slurry aged another hour at 68-70°C temperature, then cooled to 0-2°C in about 60 to 90 minutes. The yellow crystalline solid was filtered off on a filter pot at 0-5°C. The filter cake was washed twice with EtOH (8.40 kg, 5.00 L for each wash) at 0-2 °C, and the solid vacuum dried for 24-48 hours at 50°C to provide 1 kg of crystalline Na salt of Compound A.

The sodium salt crystals of Compound A were of a different shape (plates) than those obtained in Example 3 (needles or grains), but they were of the same form as confirmed by XRPD and DSC. The process described in this example exhibits improved filterability and higher productivity than the EtOH-water process exemplified in Example 3.

## EXAMPLE 5

### Formulation for Oral Administration

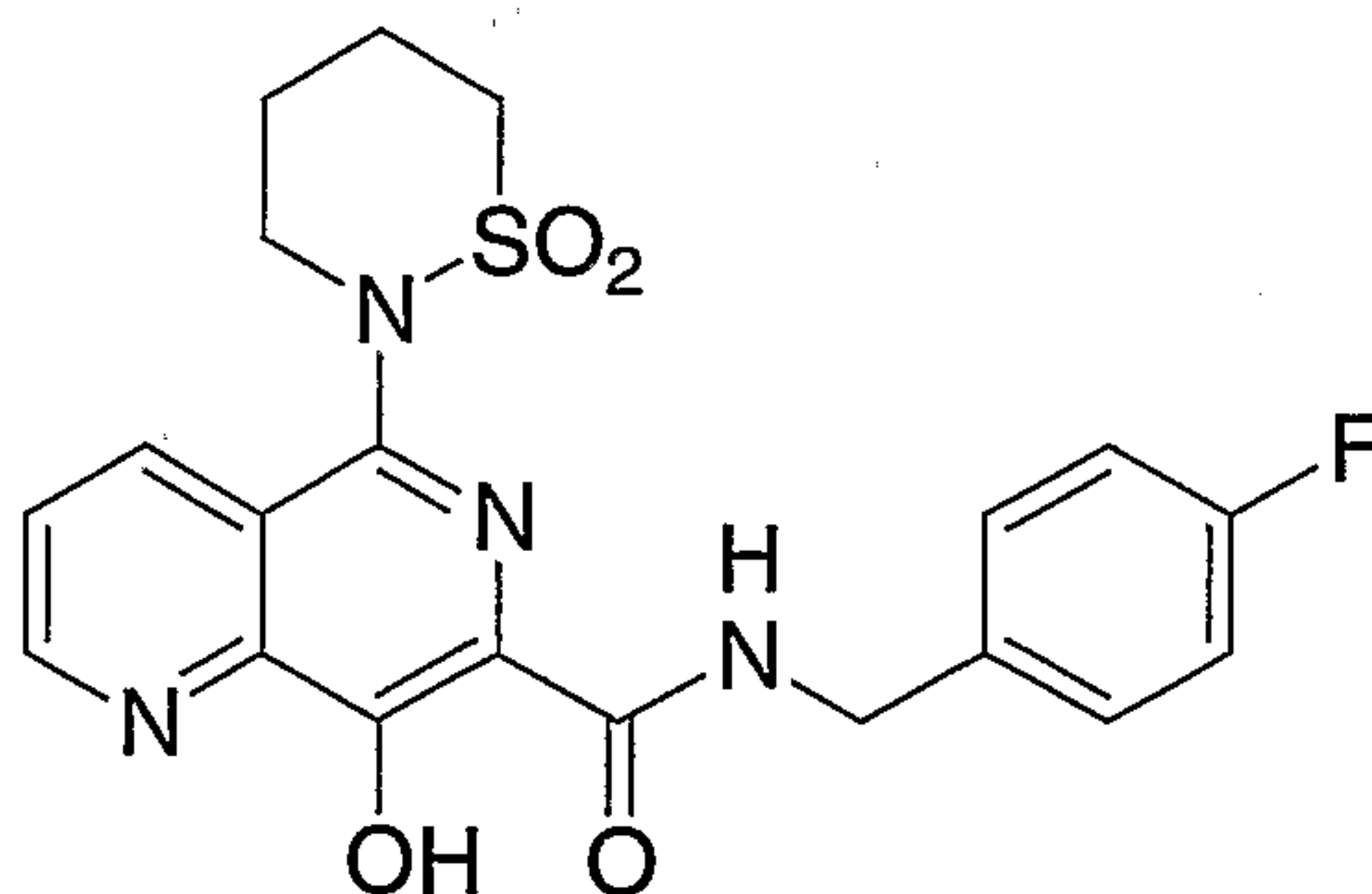
As a specific embodiment of an oral composition, 100 mg of the Na salt of Example 3, Step 6 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, the practice of the invention encompasses all of the usual variations, adaptations and/or modifications that come within the scope of the following claims.



## WHAT IS CLAIMED IS:

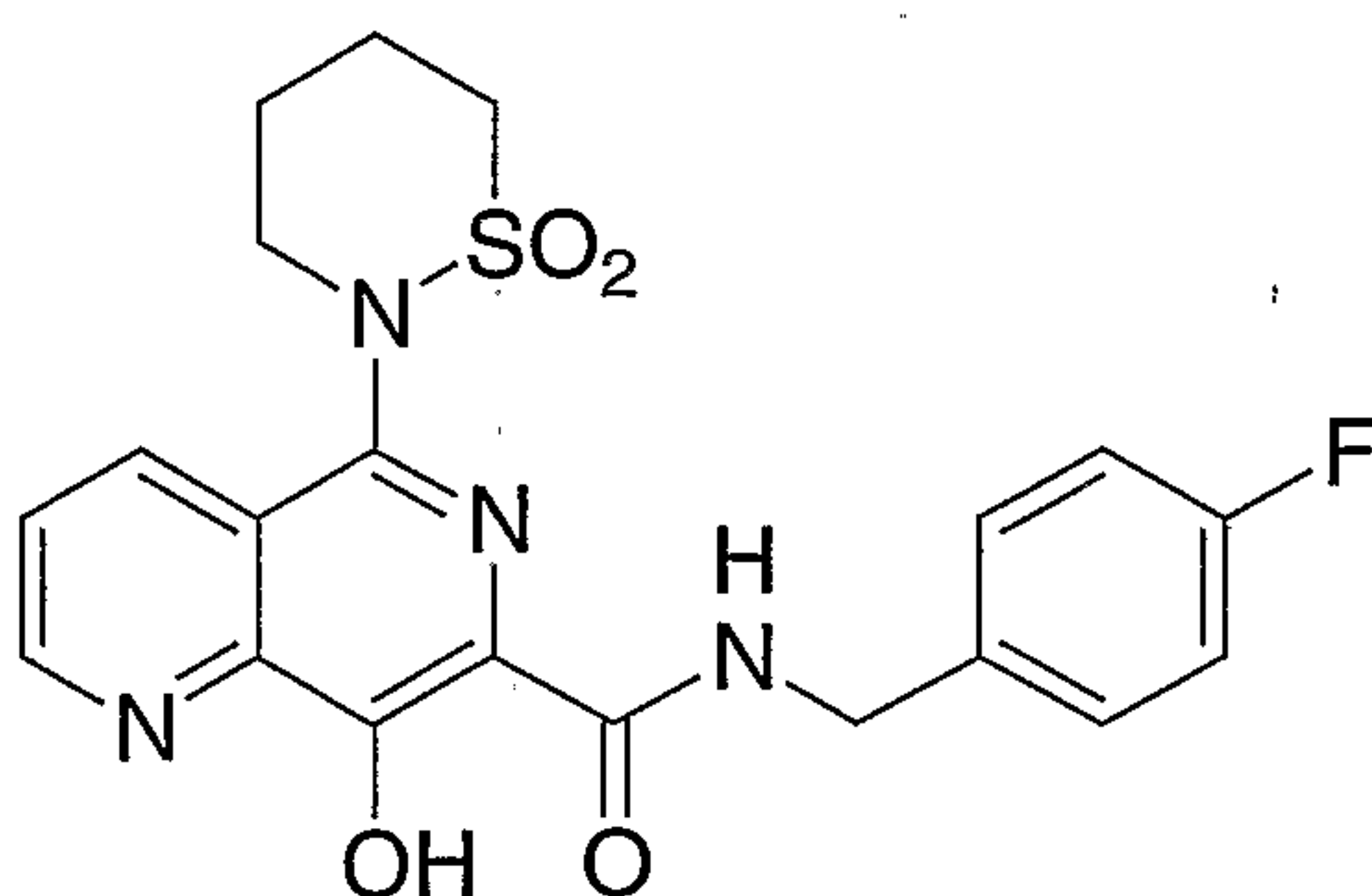
1. A sodium salt of Compound A, wherein Compound A is of formula:



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2. The sodium salt according to claim 1, which is a crystalline sodium salt of Compound A.

10 3. A crystalline monosodium salt of Compound A, characterized by crystallographic d-spacings of 12.6, 5.0, and 4.6 angstroms; wherein Compound A is of formula:



15 4. The crystalline Na salt of Compound A according to claim 3, which is further characterized by a differential scanning calorimetry curve, at a heating rate of 10°C/min in an open cup under flowing nitrogen, exhibiting an endotherm with a peak temperature of about 348°C and an associated heat of fusion of about 45 J/gm followed by an exotherm with a peak temperature of about 352°C and  
20 an associated heat of fusion of about 45 J/gm.

5. The crystalline Na salt of Compound A according to claim 3, which is characterized by crystallographic d-spacings of 12.6, 5.0, 4.8, 4.6, 3.9, and 3.5 angstroms.

5

6. The crystalline Na salt of Compound A according to claim 5, which is further characterized by a differential scanning calorimetry curve, at a heating rate of 10°C/min in an open cup under flowing nitrogen, exhibiting an endotherm with a peak temperature of about 348°C and an associated heat of fusion of about 45 J/gm followed by an exotherm with a peak temperature of about 352°C and an associated heat of fusion of about 45 J/gm.

10

7. The crystalline Na salt of Compound A according to claim 3, which is characterized by crystallographic d-spacings of 12.6, 5.9, 5.0, 4.9, 4.8, 4.6, 4.5, 4.3, 3.9, 3.7, 3.5, 3.2, 3.1, and 2.9 angstroms.

15

8. The crystalline Na salt of Compound A according to claim 7, which is further characterized by a differential scanning calorimetry curve, at a heating rate of 10°C/min in an open cup under flowing nitrogen, exhibiting an endotherm with a peak temperature of about 348°C and an associated heat of fusion of about 45 J/gm followed by an exotherm with a peak temperature of about 352°C and an associated heat of fusion of about 45 J/gm.

20

9. The crystalline Na salt of Compound A according to claim 3, which is characterized by crystallographic d-spacings of 12.63, 5.94, 5.05, 4.94, 4.81, 4.61, 4.54, 4.34, 3.88, 3.73, 3.49, 3.45, 3.22, 3.15, 3.12, and 2.86 angstroms.

25

10. The crystalline Na salt of Compound A according to claim 9, which is further characterized by a differential scanning calorimetry curve, at a heating rate of 10°C/min in an open cup under flowing nitrogen, exhibiting an endotherm with a peak temperature of about 348°C and an associated heat of fusion of about 45 J/gm followed by an exotherm with a peak temperature of about 352°C and an associated heat of fusion of about 45 J/gm.

30



20951Y

11. A pharmaceutical composition comprising a therapeutically effective amount of a sodium salt of Compound A as recited in any one of claims 1 to 10 and a pharmaceutically acceptable carrier.

5

12. A pharmaceutical composition which comprises the product made by combining a therapeutically effective amount of a sodium salt of Compound A as recited in any one of claims 1 to 10 and a pharmaceutically acceptable carrier.

10

13. Use of a sodium salt of Compound A as recited in any one of claims 1 to 10 as a medicament for preventing or treating HIV infection, delaying the onset of AIDS, or treating AIDS.

15

~~14. Use of a sodium salt of Compound A as recited in any one of claims 1 to 10 as a medicament for inhibiting HIV integrase.~~

20

15. Use of a pharmaceutical composition as recited in either claim 11 or claim 12 for preventing or treating HIV infection, delaying the onset of AIDS, or treating AIDS.

16. Use of a pharmaceutical composition as recited in either claim 11 or claim 12 for inhibiting HIV integrase.

25

17. Use of a sodium salt of Compound A as recited in any one of claims 1 to 10 in the preparation of a medicament for preventing or treating HIV infection, delaying the onset of AIDS, or treating AIDS.

30

18. Use of a sodium salt of Compound A as recited in any one of claims 1 to 10 in the preparation of a medicament for inhibiting HIV integrase.

19. A process for preparing a crystalline sodium salt of Compound A, which comprises:

(A) dissolving Compound A in a solvent to form a solution; and  
(B) treating the solution formed in Step A with NaOH to form the crystalline sodium salt of Compound A.

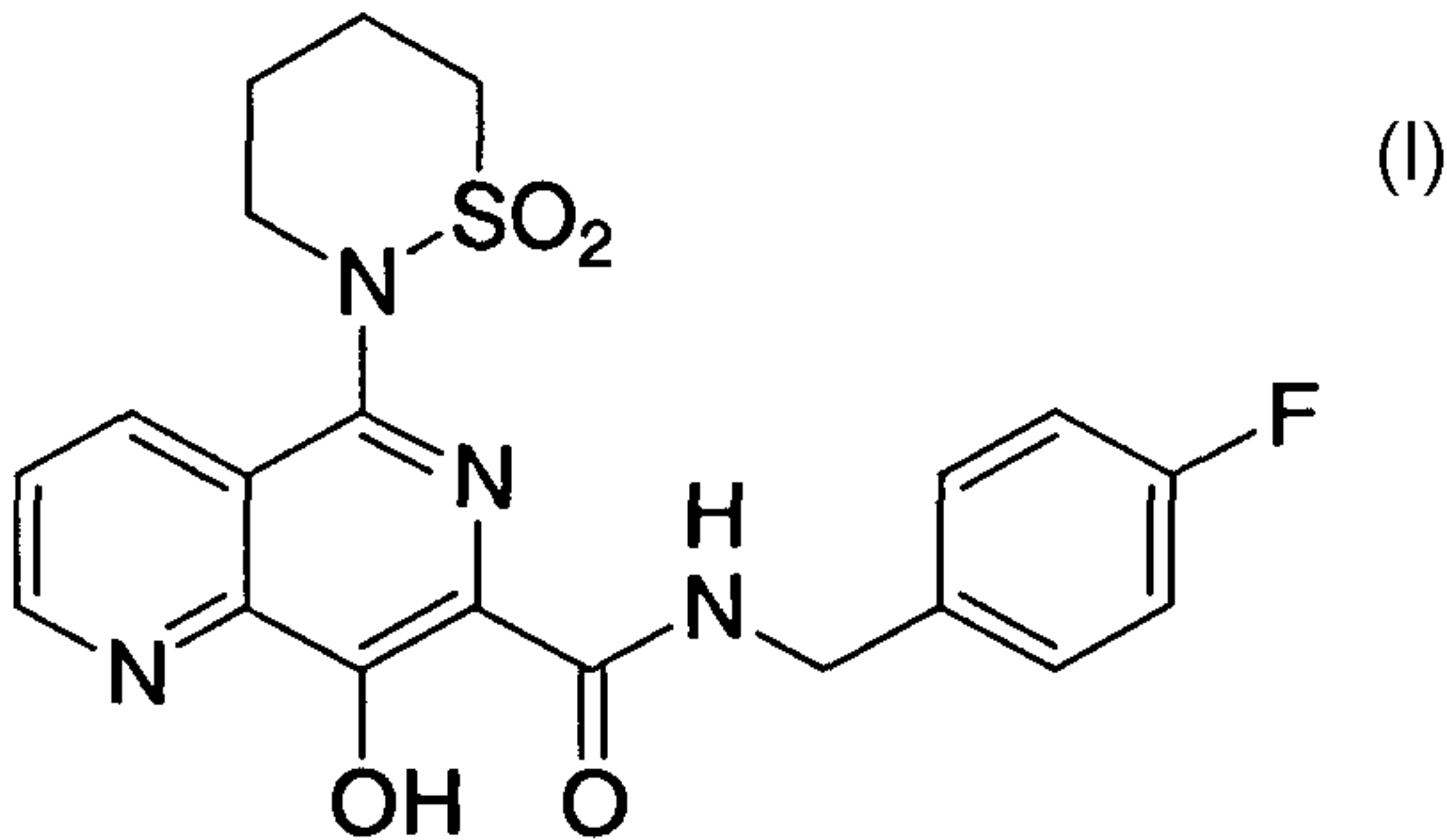
5                    20.    The process according to claim 19, wherein the solvent is acetone.

                  21.    The process according to claim 19, wherein the solvent is NMP and treatment with NaOH comprises mixing the NMP solution of Compound A with  
10    an ethanol-water solution of NaOH.

                  22.    A process for preparing a crystalline sodium salt of Compound A, which comprises:  
(A) dissolving Compound A monoethanolate in a solvent to form a  
15    solution; and  
(B) treating the solution formed in Step A with NaOH to form the crystalline sodium salt of Compound A.

                  23.    The process according to claim 22, wherein the solvent is  
20    ethanol.





Compound A