HIGH MELT POLYMORPH OF THE COMPOUND N-(3,4-DIMETHYL-5-ISOXAZOLYL)-4'-(2-OXAZOLYL)[1,1'-BIPHENYL]-2-SULFONAMIDE

Field of the Invention

The present invention relates to a high melt polymorph of the compound N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide. The high melt polymorph of the present invention is an endothelin antagonist useful, *inter alia*, for the treatment of hypertension.

Brief Description of the Invention

The present invention provides for novel high melt polymorphs of the compound N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide, having a melting point of approximately 143.07 to 145.1 °C.

Detailed Description of the Invention

The compound of the present invention may form salts which are also within the scope of this invention. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful,

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for example, in isolating or purifying the compounds of this invention.

The compound of the present invention may form salts with alkali metals such as sodium, potassium and lithium, with alkaline earth metals such as calcium and magnesium, with organic bases such as dicyclohexylamine, t-butyl amine, benzathine, N-methyl-D-glucamide and hydrabamine, and with amino acids such as arginine, lysine and the like. Such salts may be obtained by reacting these compounds with the desired ion in a medium in which the salt precipitates or in an aqueous medium followed by lyophilization.

The compound of the present invention may form salts with a variety of organic and inorganic acids. Such salts include those formed with hydrochloric acid, hydrogen bromide, methanesulfonic acid, sulfuric acid, acetic acid, maleic acid, benzenesulfonate, toluenesulfonate and various other sulfonates, nitrates, phosphates, borates, acetates, tartrates, maleates, citrates, succinates, benzoates, ascorbates, salicylates and the like. Such salts may be formed by reacting these compounds in an equivalent amount of the acid in a medium in which the salt precipitates or in an aqueous medium followed by lyophilization.

In addition, zwitterions ("inner salts") may be formed.

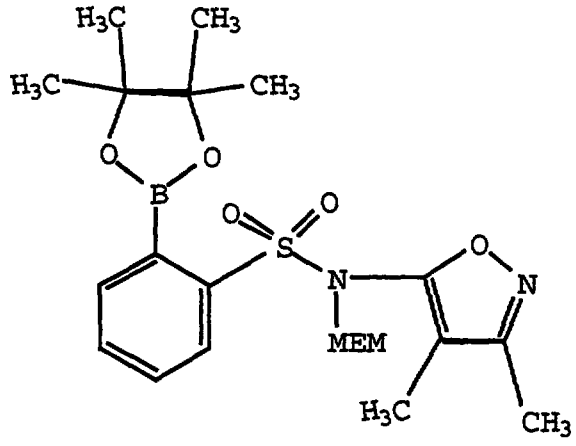
All enantiomeric and diastereomeric forms of the compound of the present invention or salts thereof are within the scope of this invention.

U.S. Patent Application Serial No. 08/493,331, filed July 24, 1995 (Attorney Docket

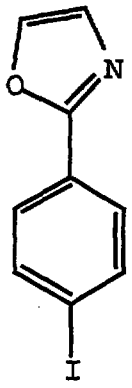
No. HA662c) by Murugesan et al. and continuation-in-part thereof U.S. Patent Application Serial No. 08/603,975, filed February 20, 1996 (Attorney Docket No. HA662d) by Murugesan et al., entitled "Substituted Biphenyl Isoxazole Sulfonamides", describing endothelin antagonists, starting materials and methods, are each incorporated herein by reference in its entirety.

Preparation of the Compound of the Present Invention

The compound of the present invention or salt thereof may be prepared by coupling a pinacol ester of the formula



(where MEM is methoxyethoxymethyl) or salt thereof with a halophenyl compound of the formula



or salt thereof, and by deprotecting the nitrogen-protected compound or salt thereof formed by the aforementioned coupling.

Coupling of the above compounds or salts thereof is conducted in the presence of a palladium(0) catalyst, preferably palladium acetate/triphenylphosphine or other palladium (II) salt/triphenylphosphine, tetrakisphenylphosphine palladium or tris(dibenzylideneacetone)dipalladium, and, preferably, a base, preferably aqueous potassium carbonate or sodium carbonate, to form a nitrogen-protected compound or salt thereof. The preferred molar ratio of palladium (II) salt to triphenylphosphine is between 1:1 and 1:3. See the conditions for catalysis described by A. Suzuki et al., *Pure & Applied Chemistry*, *63*, 419-422 (1991); A. Martin et al., *Acta. Chem. Scand.*, *47*, 221 (1993); H. Jendralla et al., *Liebig Ann.*, 1253 (1995), all incorporated herein by reference.

The coupling method is preferably conducted at a temperature of from about 25°C to about 100°C (most preferably from about 45°C to about 75°C), at a pressure of about 1 atm, and under an atmosphere of argon or nitrogen. Molar ratios of the pinacol ester II or salt thereof to the

halophenyl compound III or salt thereof are preferably from about 1:1 to about 1:1.2. Amounts of palladium(0) catalyst and base are selected to catalyze the coupling reaction and are preferably from about 2.5 mol% to about 10 mol%, and from about 2.5 equivalents to about 7 equivalents, respectively. Solvents are preferably employed which are selected from aqueous or organic liquids such as acetone, ethanol, toluene, tetrahydrofuran, dimethoxyethane and water, or mixtures thereof, preferably a mixture of toluene and ethanol. Amounts of solvent are preferably those wherein the pinacol ester or salt thereof is from about 4 to about 9% by weight, based on the combined weight of solvent and pinacol ester or salt thereof. For example, the following are exemplary ranges for solvent/pinacol ester/base: tetrahydrofuran (30 to 70 mL), toluene (100 to 200 mL), ethanol (80 to 160 mL)/pinacol ester (15 to 20 g)/aqueous 2M sodium carbonate (100 to 150 mL).

Residual palladium catalyst is preferably removed, either before or after deprotection of the compound or salt thereof, by contact with a chelating agent such as trithiocyanuric acid ("TMT"). Crystallization providing a suitable crystalline form of the compound of the present invention or salt thereof, subsequent to deprotection of the compound, is also contemplated by the present invention. Preferably, crystallization is achieved from a supersaturated ethanolic solution, with or without the presence of co-solvents such as heptane or water, especially where seeded with the desired crystalline form. Most preferably,

crystallization is conducted by the methods of the Examples herein.

Utility of Compounds of Formula I and Salts Thereof as Endothelin Antagonists

The compound of the present invention and salts thereof are antagonists of ET-1, ET-2 and/or ET-3 and are useful in treatment of conditions associated with increased ET levels (e.g., dialysis, trauma and surgery) and of all endothelin-dependent disorders. The compound of the present invention is thus useful as an antihypertensive agent. By the administration of a composition containing the compound of this invention, the blood pressure of a hypertensive mammalian (e.g., human) host is reduced. The compound of the present invention is also useful in pregnancy-induced hypertension and coma (preeclampsia and eclampsia), acute portal hypertension and hypertension secondary to treatment with erythropoietin.

The compound of the present invention is also useful in the treatment of disorders related to renal, glomerular and mesangial cell function, including acute and chronic renal failure, glomerular injury, renal damage secondary to old age or related to dialysis, nephrosclerosis (especially hypertensive nephrosclerosis), nephrotoxicity (including nephrotoxicity related to imaging and contrast agents and to cyclosporine), renal ischemia, primary vesicoureteral reflux, glomerulosclerosis and the like. The compound of this invention may also be useful in the treatment of disorders related to paracrine and endocrine function.

The compound of the present invention is also useful in the treatment of endotoxemia or endotoxin shock as well as hemorrhagic shock.

The compound of the present invention is also useful in hypoxic and ischemic disease and as anti-ischemic agents for the treatment of, for example, cardiac, renal and cerebral ischemia and reperfusion (such as that occurring following cardiopulmonary bypass surgery), coronary and cerebral vasospasm, and the like.

In addition, the compound of this invention may also be useful as an anti-arrhythmic agent; anti-anginal agent; anti-fibrillatory agent; anti-asthmatic agent; anti-atherosclerotic and anti-arteriosclerotic agent; additive to cardioplegic solutions for cardiopulmonary bypasses; adjunct to thrombolytic therapy; and anti-diarrheal agent. The compound of this invention may be useful in therapy for myocardial infarction; therapy for peripheral vascular disease (e.g., Raynaud's disease and Takayashu's disease); treatment of cardiac hypertrophy (e.g., hypertrophic cardiomyopathy); treatment of primary pulmonary hypertension (e.g., plexogenic, embolic) in adults and in the newborn and pulmonary hypertension secondary to heart failure, radiation and chemotherapeutic injury, or other trauma; treatment of central nervous system vascular disorders, such as stroke, migraine and subarachnoid hemorrhage; treatment of central nervous system behavioral disorders; treatment of gastrointestinal diseases such as ulcerative colitis, Crohn's disease, gastric mucosal damage, ulcer and ischemic bowel disease; treatment of

gall bladder or bile duct-based diseases such as cholangitis; treatment of pancreatitis; regulation of cell growth; treatment of benign prostatic hypertrophy; restenosis following angioplasty or following any procedures including transplantation; therapy for congestive heart failure including inhibition of fibrosis; inhibition of left ventricular dilatation, remodeling and dysfunction; and treatment of hepatotoxicity and sudden death. The compound of this invention may be useful in the treatment of sickle cell disease including the initiation and/or evolution of the pain crises of this disease; treatment of the deleterious consequences of ET-producing tumors such as hypertension resulting from hemangiopericytoma; treatment of early and advanced liver disease and injury including attendant complications (e.g., hepatotoxicity, fibrosis and cirrhosis); treatment of spastic diseases of the urinary tract and/or bladder; treatment of hepatorenal syndrome; treatment of immunological diseases involving vasculitis such as lupus, systemic sclerosis, mixed cryoglobulinemia; and treatment of fibrosis associated with renal dysfunction and hepatotoxicity. The compound of this invention may be useful in therapy for metabolic and neurological disorders; cancer; insulin-dependent and non insulin-dependent diabetes mellitus; neuropathy; retinopathy; maternal respiratory distress syndrome; dysmenorrhea; epilepsy; hemorrhagic and ischemic stroke; bone remodeling; psoriasis; and chronic inflammatory diseases such as rheumatoid arthritis, osteoarthritis,

sarcoidosis and eczematous dermatitis (all types of dermatitis).

The compound of the present invention and salts thereof can also be formulated in combination with endothelin converting enzyme (ECE) inhibitors, such as phosphoramidon; thromboxane receptor antagonists; potassium channel openers; thrombin inhibitors (e.g., hirudin and the like); growth factor inhibitors such as modulators of PDGF activity; platelet activating factor (PAF) antagonists; angiotensin II (AII) receptor antagonists; renin inhibitors; angiotensin converting enzyme (ACE) inhibitors such as captopril, zofenopril, fosinopril, ceranapril, alacepril, enalapril, delapril, pentopril, quinapril, ramipril, lisinopril and salts of such compounds; neutral endopeptidase (NEP) inhibitors; dual NEP-ACE inhibitors; HMG CoA reductase inhibitors such as pravastatin and mevacor; squalene synthetase inhibitors; bile acid sequestrants such as questran; calcium channel blockers; potassium channel activators; beta-adrenergic agents; antiarrhythmic agents; diuretics, such as chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide or benzothiazide as well as ethacrynic acid, tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamterene, amiloride and spironolactone and salts of such compounds; and thrombolytic agents such as tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase and

anisoylated plasminogen streptokinase activator complex (APSAC). If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within its approved dosage range. The compounds of this invention may also be formulated with, or useful in conjunction with, antifungal and immunosuppressive agents such as amphotericin B, cyclosporins and the like to counteract the glomerular contraction and nephrotoxicity secondary to such compounds. The compounds of this invention may also be used in conjunction with hemodialysis.

The compounds of the invention can be administered orally or parenterally to various mammalian species known to be subject to such maladies, e.g., humans, in an effective amount within the dosage range of about 0.1 to about 100 mg/kg, preferably about 0.2 to about 50 mg/kg and more preferably about 0.5 to about 25 mg/kg (or from about 1 to about 2500 mg, preferably from about 5 to about 2000 mg) in single or 2 to 4 divided daily doses.

The active substance can be utilized in a composition such as tablet, capsule, solution or suspension containing about 5 to about 500 mg per unit dosage of a compound or mixture of compounds of formula I or in topical form for wound healing (0.01 to 5% by weight compound of formula I, 1 to 5 treatments per day). They may be compounded in a conventional manner with a physiologically acceptable vehicle or carrier, excipient, binder, preservative, stabilizer, flavor, etc., or with a

topical carrier such as Plastibase (mineral oil gelled with polyethylene) as called for by accepted pharmaceutical practice.

The compound of the present invention may also be administered topically to treat peripheral vascular diseases and as such may be formulated as a cream or ointment.

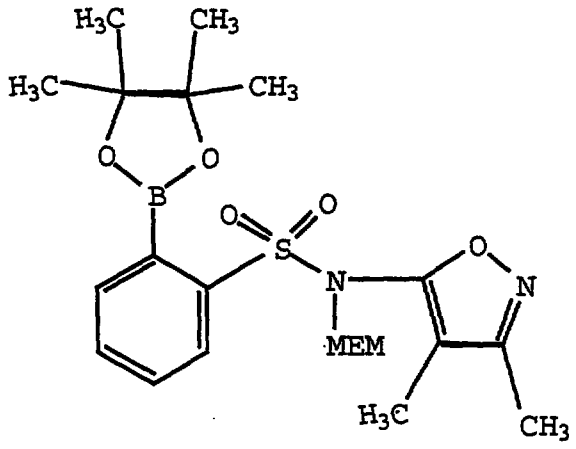
The compound of the present invention can also be formulated in compositions such as sterile solutions or suspensions for parenteral administration. About 0.1 to 500 milligrams of a compound of formula I is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

The present invention will now be further described by the following working examples, which illustrate preferred embodiments of the invention.

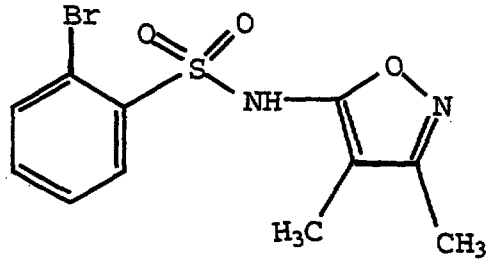
EXAMPLE 1

PREPARATION OF PINACOL ESTER II

N-[(2-Methoxyethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfanamide



A. 2-Bromo-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide



A 2 L three necked flask, equipped with an overhead mechanical stirrer, a 250 mL addition funnel and an argon line, was charged with 2-bromobenzenesulfonyl chloride (150 g, 587 mmol, commercially available) and anhydrous pyridine (150 mL). The resulting light yellow solution was cooled to -18°C (internal temperature) by an ice/salt bath. With stirring, a solution of 5-amino-3,4-dimethylisoxazole (69.1 g, 616 mmol,

commercially available) in anydrous pyridine (195 mL) was added dropwise through the addition funnel in 1 hour. The internal reaction temperature did not exceed -6°C during the course of the addition. After the addition, the ice/salt bath was removed and the reaction mixture was then warmed up to room temperature, stirred for 1 hour, and then stirred at 40°C for 21 hours.

The reaction mixture was cooled to room temperature and poured into a mixture of ice water (3 L) and celite (37.5 g). After stirring for 20 minutes, it was filtered and rinsed with water (250 mL x 3). Charcoal (45 g) was added to the filtrate. The mixture was stirred at room temperature for 40 minutes and was filtered through a pad of celite. The celite pad was rinsed with water (500 mL x 3). The filtrate was acidified by dropwise addition of cold HCl (6N, 750 mL) with vigorous stirring over 2 hours. Precipitation of the product occurred and the mixture was stirred for another 1 hour after the addition of HCl.

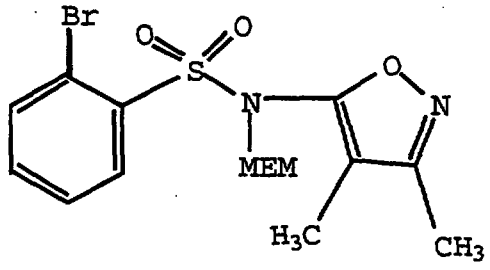
The mixture was filtered, the solid was rinsed with cold water (750 mL x 4), and suction dried for 3 days. The title compound of this step was obtained as a yellowish white solid (171 g) in 88% yield (HPLC area percent = 97.4%).

Thin layer chromatography (TLC): Rf = 0.47 (Silica gel from Whatman; Ethyl acetate (EtOAc):hexanes/1:1; Visualization CAM or UV)

Alternative preparation for title compound of this step:

A 1 L three necked flask was charged with 2-bromobenzenesulfonyl chloride (50 g, 196 mmol) and anhydrous 1,2-dichloroethane (125 mL) under an argon atmosphere. The resulting colorless solution was cooled to 0°C and anhydrous pyridine (40 mL, 396 mmol) was added, followed by the addition of 5-amino-3,4-dimethylisoxazole (24.1 g, 196 mmol) as a solid. After the addition, the ice bath was removed and the reaction mixture was heated to 55°C for 21 hours, yielding a crude reaction mixture containing the title compound of this step.

B. <u>2-Bromo-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-methoxyethoxy)methyl]benzene-sulfonamide</u>



A 1 L three necked flask, equipped with a mechanical stirrer, was charged with potassium carbonate (130.5 g, 944 mmol) and anhydrous dimethylformamide (DMF, 286 mL) under an argon atmosphere. The heterogeneous mixture was stirred for 15 minutes at room temperature. The title

compound of step A (125 g, 378 mmol) was added as a solid. The mixture was stirred again for 15 minutes at room temperature. Methoxyethoxymethylchloride (MEMCl, 47.5 mL, 415.8 mmol) was added dropwise through an addition funnel in 40 minutes. After the addition, the reaction mixture was stirred for 40 minutes. The reaction was monitored by HPLC.

The reaction mixture was diluted with the addition of ethyl acetate (400 mL), stirred for 5 minutes and filtered. The solid was washed with ethyl acetate (200 mL x 2) and hexanes (250 mL x 2). The filtrate was treated with charcoal (25 g), stirred at room temperature for 1 hour and filtered through a celite pad. The celite pad was rinsed with ethyl acetate (50 mL x 3). The ethyl acetate layers were combined and washed with Na_2CO_3 (1M, 500 mL). Precipitation occurred in the aqueous layer. It was suppressed by addition of water (750 mL). The aqueous layer was separated and discarded. The organic layer was washed with water (750 mL), brine (500 mL x 2), dried over Na_2SO_4, filtered and concentrated to a yellowish semi-solid (157.3 g, 99% mass balance).

The residue was dissolved in ethanol (125 mL) and set aside in a freezer (0°C) for 20 hours. Crystallization occurred. The solid was filtered and suction dried. The title compound of this step was obtained as a yellowish white solid (75.65% yield, HPLC area percent = 98.2%).
TLC: Rf = 0.55 (Silica gel from Whatman; EtOAc:hexanes/1:1; visualization: CAM or UV)

Alternative preparation for the title compound of this step:

The reaction mixture obtained by the alternative method for the preparation of the title compound of Step A was cooled to room temperature and concentrated at reduced pressure on a rotary evaporator to a dark thick oil (102 g) at 40°C. The dark oil (98 g, 188 mmol) was dissolved in anhydrous dichloromethane (240 mL). Diisopropylethylamine (97 mL, 4 equivalents) was added followed by dropwise addition of methoxyethoxymethyl chloride (25.7 mL, 225.6 mmol). The reaction mixture was stirred at room temperature for 4 hours.

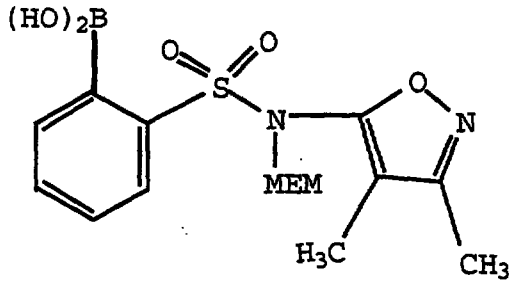
The reaction mixture was concentrated at reduced pressure on a rotary evaporator to a thick oil, dissolved in EtOAc (400 mL) and charcoal (10 g) was added. The charcoal mixture was stirred at room temperature for 30 minutes and was filtered through a celite pad. The celite pad was rinsed with EtOAc (100 mL x 3) and hexanes (200 mL x 2). The filtrate was transferred to a separatory funnel and washed with water (100 mL x 2), HCl (0.5N, 100 mL x 2), water (100 mL x 2) and brine (100 mL x 2), dried over Na_2SO_4, filtered and concentrated to a thick oil (64.9 g, 83% mass balance).

The thick oil was dissolved in ethanol (EtOH, 65 mL), cooled to 0°C with an ice bath, seeded with the title product of this step and stirred at 0°C for 6 hours. Crystallization occured. The solid was filtered and suction dried. The title compound of this step was obtained as a yellowish

solid (62% overall yield, HPLC area percent = 98.2%).

TLC: Rf = 0.55 (silica gel from Whatman; EtOAc:hexanes/1:1; visualization: CAM or UV)

C. 2-Borono-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-methoxyethoxy)methyl]benzene-sulfonamide



A dry 3-necked 1-liter round-bottomed flask equipped with an overhead mechanical stirrer, gas adapter, thermocouple, and septum was charged with the title compound of Step B (40.0 g; 95.4 mmol), and then thoroughly degassed and placed under an argon atmosphere. Tetrahydrofuran (THF, 185 mL) was added via syringe and the mixture was cooled to about -100°C (internal temperature). n-Butyl lithium (n-BuLi, 42.5 mL, 101 mmol, 2.38 M in hexanes) was dropwise added over a period of 16 minutes, while maintaining the internal temperature between -97°C and -101°C. The pale yellow-orange solution was stirred at about -98°C to -101°C for an additional 16 minutes.

Trimethylborate (16.0 mL, 140.9 mmol) in THF (24 mL) was dropwise added over 14.5 minutes, while maintaining the internal temperature between -96°C and -99°C. The mixture was stirred for

about 44 minutes at about -93°C to -101°C, and an additional 39 minutes at about -93°C to -72°C. HCl (3.0 N, 120 mL, 360 mmol) was added to the reaction (the solution exothermed to about -7°C) and was stirred for 20 minutes (-7°C to +6°C). The two layers were separated in a separatory funnel, and the aqueous phase was washed with toluene (3 x 120 mL) and t-butyl methyl ether (MTBE, 3 x 100 mL). The combined organic layer was washed with brine (4 x 100 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator to a volume of about 100 mL containing the title compound of this step (HPLC area percent = 97.7%).

Alternative preparation of the title compound of this step:

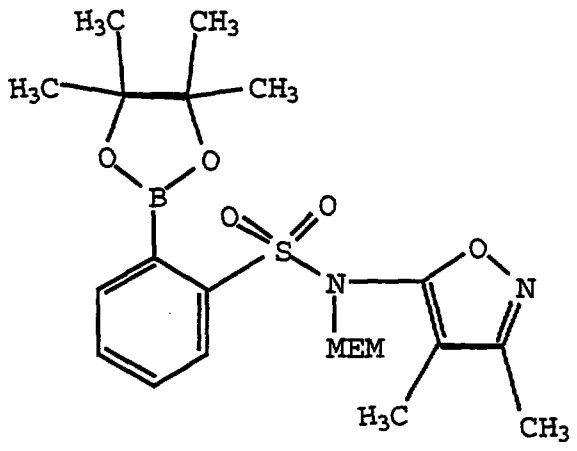
A 500 mL 3-neck flask equipped with a stir bar was charged with the title compound of Step B (20.0 g, 47.7 mmol) and purged with argon for 0.5 hr. Anhydrous THF (200 mL) was added via syringe and the flask was cooled to -78°C in an acetone/dry ice bath. Phenyl lithium (PhLi, 37.1 mL, 48.2 mmol, 1.3 M in cyclohexane-ether, titrated according to *J. Organomet. Chem.*, 186, 155 (1980), and determined to be 1.3 M) was added via an addition funnel over the course of 25 minutes. The rate of addition of PhLi was such that the internal temperature of the reaction mixture was maintained below -75°C. The resulting solution was stirred at -78°C for 15 minutes following which a solution of trimethylborate (10.8 mL, 95.4 mmol) in THF (5 mL) was cannulated dropwise into the reaction mixture over 15 minutes. The trimethylborate/THF solution was

cooled in an ice-water bath prior to addition. The rate of addition was maintained such that the internal temperature of the reaction mixture did not go above -73°C. The reaction mixture was stirred at -78°C for 0.5 hr, and then quenched by the dropwise addition of a solution of acetic acid (15 mL) in THF (10 mL). The acidified solution was stirred at -78°C for 10 minutes following which the solution was warmed to 0°C. To this was added dropwise, 1N HCl (25 mL). (1N HCl was prepared by diluting 42 ml of 12N HCl into 500 mL of water. The excess acid was added in order to ensure complete quenching. The HCl solution was pre-cooled in an ice/water bath prior to addition.) The reaction mixture was then allowed to warm to room temperature and extracted with t-butyl methyl ether (TBME, 4 X 250 mL). The organic layers were combined and extracted with 0.5N aqueous NaOH (4 X 25 mL). The aqueous layers were combined and back extracted with TBME (1 X 100 mL). The aqueous extract was cooled to 0°C and the pH adjusted to 2.0 (pH meter) by the dropwise addition of 6N HCl with rapid stirring. The acidified solution was extracted with TBME (4 X 250 mL), the organic layers pooled and dried over anhydrous $MgSO_4$. The suspension was filtered and the solution concentrated to give the boronic acid title compound of this step as a pale brown oil (17.1 g, 93%, HPLC area percent = 88%).

HPLC Conditions: Column - YMC ODS-A, 6 x 250 mm; Monitored at 233 nm; Flow rate - 1.5 mL/min; Solvent A (%): H_2O/MeOH/H_3PO_4 90:10:0.2; Solvent B (%): H_2O/MeOH/H_3PO_4 10:90:0.2; Gradient: 40% B to 100% B, linear gradient over 10 minutes, 100% B

for 5 minutes, 40% B for 4 minutes; Retention time for the title compound of this step = 8.3 minutes.

D. N-[(2-Methoxyethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfanamide



The mixture from step C was diluted with toluene (170 mL) to bring the total volume to about 270 mL, and the flask was equipped with a Dean-Stark trap and magnetic stir bar. Pinacol (11.6 g, 98.2 mmol) was added and the resulting mixture was heated to reflux for about 1.25 hr. Water was drained from the Dean-Stark trap and the solution was then used "as is" in Example 3. (98% conversion, HPLC area percent = 93.6%)
Reverse phase HPLC Column: YMC-Pack ODS-A; 150 x 6 mm; S-5 mm, 120A and monitored @233 nm; Solvent: A = 90% water, 10% methanol and 0.2% H_3PO_4; B = 10% water, 90% methanol and 0.1% $H3PO_4$;
Flow rate: 100 mL per minute; Gradient; 40% B to 100% B in 10 minutes. Hold time: 5 minutes at

100% B. Step down to 40% B and hold for 5 minutes. Retention Time for title product of this Example - 11.5 minutes.

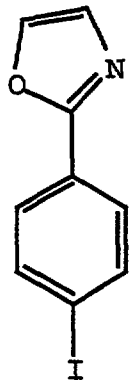
Alternative preparation of the title compound of this Example:

The boronic acid obtained in the alternative method for preparation of the title compound of Step C (17.1 g, 44.5 mmol) was dissolved in a solution of anhydrous toluene (425 mL) and pinacol (5.51 g, 46.7 mmol). The flask was placed in an oil bath and heated to 120°C for 2 hr (note: reaction was complete in first 40 minutes) and water continuously removed by the use of a Dean-Stark trap (flask and trap covered in foil; mixture boiled rapidly in approximately 0.5 hr) and condensor. Analysis of an aliquot (worked up by repeated azeotroping with $CDCl_3$) by HPLC indicated complete conversion of the boronic acid starting material to the title compound of this Example. The reaction mixture was cooled to room temperature and concentrated to afford the title compound of this Example as a toluene solution, HPLC area percent = 86%. A 100% yield was assumed for conversion of the boronic acid to pinacol ester. A portion of the crude solution of the title compound of this Example was used in Example 3. Retention time of title compound of this Example = 12.4 minutes (using HPLC conditions described for boronic acid starting material).

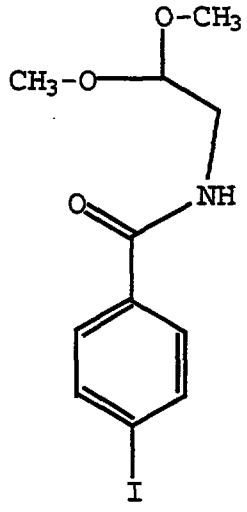
EXAMPLE 2

PREPARATION OF HALOPHENYL COMPOUND III

2-(4-Iodophenyl)oxazole



A. <u>N-(2,2-Dimethoxyethyl)-4-iodobenzamide</u>



$KHCO_3$ (80.0 g, 0.80 mol) was added to a solution of aminoacetaldehyde dimethyl acetal (82.9 g, 86.0 mL, 0.79 mol, commercially available) in water (900 mL) and acetone (400 mL) and the resulting solution was cooled in an ice bath to 0°C. A solution of 4-iodobenzoyl chloride (200.0 g, 0.75 mol) in acetone (600 mL) was added dropwise via an addition funnel, to the aminoacetaldehyde dimethyl acetal solution over the course of 1.5 hr, with mechanical stirring. The addition funnel and the walls of the flask

were washed with acetone (50 mL) and the ice bath was removed. The reaction mixture was allowed to stir at room temperature for 3 hr (reaction was completed in 1.5 hr).

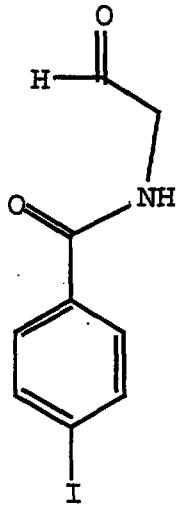
The reaction mixture was concentrated by removing 1.0 L of solvent on a rotary evaporator and then extracted with EtOAc (4 X 350 mL). The organic layers were pooled, washed with saturated $NaHCO_3$ (1 X 250 mL) followed by H_2O (1 X 250 mL), dried over anhydrous $MgSO_4$ (50.0 g), filtered and concentrated at reduced pressure to give a white solid (during solvent evaporation, the solid was occasionally scraped off the sides of the flask). The solid was dried under house vacuum for 12 hr (246.5 g, 98%, HPLC area percent = 99.7%).
melting point (mp) = 89-90°C
Elemental Analysis (%) $C_{11}H_{14}NO_3I$
Calc'd: C, 39.42; H, 4.21; N, 4.18
Found: C, 39.42; H, 4.22; N, 4.07

B. 2-(4-Iodophenyl)oxazole

Eaton's reagent was prepared by adding P_2O_5 (200 g) in approximately 50 g portions to methanesulfonic acid (2000 mL) at 95°C under argon with vigorous mechanical stirring. The addition of P_2O_5 in portions prevented it from forming a hard mass at the bottom of the flask. A clear, very pale brown solution was obtained. Eaton et al. *J. Org. Chem.*, 38, 4071-4073 (1973).

A 3 L 3-neck round-bottom flask containing the Eaton's reagent (2000 mL) was equipped with a condenser and charged with the title compound of step A (200.0 g, 0.60 mol). The reaction mixture

was placed in an oil bath and heated with stirring, under a positive pressure of argon. (It was found to be beneficial to warm the reaction mixture to the required temperature rather than set it in a pre-heated bath.) Monitoring the reaction by TLC indicated that the first step of the reaction was hydrolysis of the dimethylacetal group to the corresponding aldehyde (Rf = 0.11):



followed by cyclization. The oil bath temperature was adjusted so as to maintain the internal temperature of the reaction mixture between 130-134°C. (The temperature of the oil bath was maintained between 138-141°C). After 7.5 hr, analysis of an aliquot (worked up by addition to H_2O and extraction with EtOAc) by TLC indicated the complete disappearance of the starting material and the production of a single new spot.

The reaction mixture was cooled to 30°C under argon, divided into three approximately equal portions, and each portion was poured onto a slurry of ice/water (approximately 6.0 L) with vigorous stirring using a mechanical stirrer, with

external cooling. This resulted in the formation of a brownish-gray precipitate. The resulting suspension was stirred for 2 hr and the solid was collected by suction filtration through a medium porosity sintered glass funnel, washed with ice cold water (1 L) and the filter cake broken. The solid was air dried for 5 days to give a gray powder (151.7 g, 93%). The crude material (151.7 g) was dissolved in acetonitrile (2 L) (by warming gently with a heat gun; a small amount of black flocculent solid remained undissolved in the flask) and activated charcoal (15.2 g) was added and the mixture stirred at room temperature for 1 hr. The mixture was filtered through a pad of celite (100.0 g). The celite pad was washed with acetonitrile (2 X 100 mL). The filtrate was concentrated under reduced pressure to approximately 1180 mL in a 5 L round bottom flask. The flask was warmed with a heat gun until the solid completely dissolved. To the resulting hot solution, boiling water (295 mL) was added in two portions, the flask was heated to near boiling and gently swirled after each addition. The solution was once again heated to near boiling, the flask was covered and allowed to stand at room temperature for 48 hr (some crystals were observed within 1.5 hr), following which it was stored at 4°C for 4 days. The crystals which formed were collected by suction filtration and washed with an ice cold solution of acetonitrile:water (4:1, 150 mL), and air dried for 20 hr. The title compound of this Example was obtained as very pale yellow crystals which were further dried under house vacuum (107.2 g, 66%, HPLC area percent = 99.7%).

A second crop of the title compound was collected upon recrystallization of the yellow solid obtained upon concentration of the mother liquor (27.4 g, 17%, HPLC area percent = 98.4%).

m.p. = 107-109°C

Elemental Analysis C_9H_6NOI

Calcd: C, 39.88; H, 2.23; N, 5.17

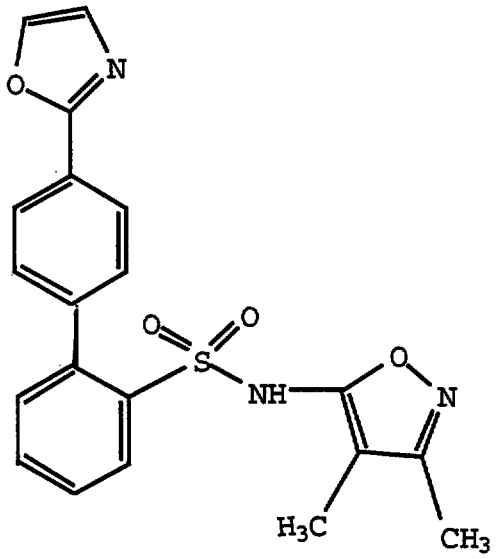
Found: C, 40.00; H, 2.09; N, 5.14

EXAMPLE 3

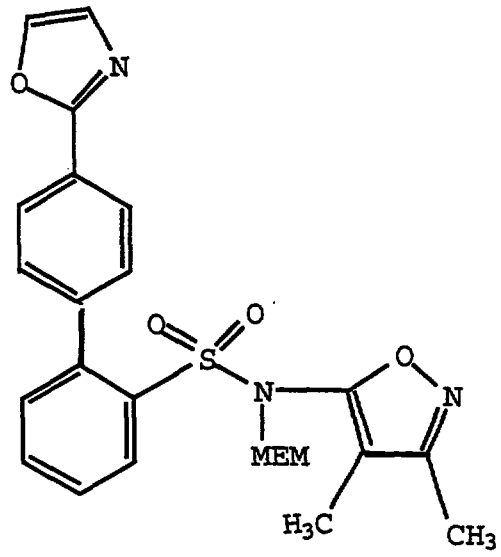
PREPARATION OF FORMULA I COMPOUND

N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide

COUPLING OF PINACOL ESTER II AND HALOPHENYL COMPOUND III



A. N-[(2-Methoxyethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-oxazol-2-yl-[1,1'-biphenyl]-2-sulfonamide



A dry 3-necked, 2-liter round-bottomed flask equipped with an overhead mechanical stirrer, gas adapter, thermocouple, reflux condenser, and septum was charged with palladium acetate ($Pd(OAc)_2$, 0.54 g, 2.38 mmol) and triphenylphosphine (Ph_3P, 1.7 g, 6.44 mmol), degassed and placed under an argon atmosphere. THF (85 mL) was added and the mixture was heated at 65°C for 70 minutes. The solution gradually changed from rust orange to bright yellow in color. A degassed, toluene (270 mL) solution of the title compound of Example 2 (25.9 g, 95.6 mmol) and the crude title compound of Example 1 as prepared above (see step D of Example 1, 44.45 g, 95.4 mmol) was added via syringe followed by degassed 95% ethanol (EtOH, 285 mL), and a degassed 2.0 M Na_2CO_3 solution (306 mL, 612 mmol). The resultant red colored solution was heated at about 75°C (internal temperature) for about 1.75 hr. The heating bath was removed, and the mixture was allowed to cool to ambient temperature. The layers were separated in a separatory funnel,

water (250 mL) was added and the aqueous layer was washed with CH_2Cl_2 (6 x 400 mL). The combined organic layers were dried over $MgSO_4$, treated with neutral charcoal (Norit, 5.0 g), filtered through celite, concentrated, and kept under dynamic, high vacuum overnight to afford the title compound of this step (62.4 g, 140%) as a red colored oil. (HPLC area percent >85%.)

Alternative preparation of the title compound of this step:

Catalyst Preparation:

A 2L three necked flask equipped with overhead mechanical stirrer, reflux condenser, and argon inlet was charged with $Pd(OAc)_2$ and triphenylphosphine. The flask was purged with a slow bleed of argon for 18 hr. Anhydrous, degassed THF (67 mL) was added via syringe, the flask immersed in an oil bath preheated to 75°C, and stirred. After 20 minutes, the internal temperature reached 60°C. The mixture was stirred for 1 hr at which time it was burgundy in color, then cooled to room temperature under a slight head pressure of argon. See *J. Org. Chem.*, **1994**, *59*, 8151; *Organometallics*, **1992**, *11*, 3009.

Coupling

The title compound of Example 2 (10.0 g) was added to a portion of the toluene solution of pinacol boronate prepared in the alternative preparation of the title compound of step D of Example 1 (110 mL, 38.74 mmol of the pinacol boronate, 87% of total volume of crude boronate

solution). The mixture was swirled, anhydrous ethanol (55 mL) was added, the flask sealed with a septum and swirled until a solution was obtained. The solution was degassed by bubbling argon into the solution at a moderate rate for 1 hr. The solution was then charged into the reaction vessel containing the cooled solution of catalyst via cannula under a positive pressure of argon. The flask was rinsed with anhydrous, degassed ethanol (55 mL) and transferred via cannula to the reaction vessel under a positive pressure of argon. A degassed 2M Na_2CO_3 solution (118 mL) was added via cannula, stirring was initiated, the flask immersed in a preheated oil bath at 78°C, and the internal temperature brought to 69-70°C. HPLC and TLC analysis after 1.75 hr indicated that the reaction was complete. After 2 hr of reaction time, the mixture was cooled to 27°C, and water (100 mL) and EtOAc (100 mL) were added with stirring. The mixture was transferred to a separatory funnel, the layers separated, and the aqueous extracted with EtOAc (3 X 100 mL, 1 X 50 mL). The combined organics were washed with half-brine (1 X 60 mL) and dried over anhydrous $MgSO_4$ (40 g) with stirring. The solution was filtered, and the initial flask and filter funnel washed with EtOAc (2 X 100 mL). This process afforded a crude coupling solution with a total volume of 785 mL. HPLC analysis afforded a crude HPLC area percent of 88.9%. The solution was divided into portions for purification evaluation. For example, 5% by volume of the crude coupling solution (39 mL) was taken and concentrated on a rotary evaporator. The residue was dissolved in

toluene (12 mL), C (0.9 g, 100 wt %) was added and the mixture stirred in an 88°C oil bath for 30 min. Trithiocyanuric acid (TMT, 407 mg, 2.3 mmol, 50 mol equiv relative to assumed Pd content) was added and the mixture stirred for 30 minutes in the oil bath, cooled to 0°C in an ice bath, filtered through celite, the celite pad rinsed with toluene (2 X 10 mL), and the filtrate washed with 1N NaOH (2 X 10 mL). The phase separation required ~ 3 minutes. The toluene layer was dried over $MgSO_4$, filtered and concentrated to afford the crude title compound of this step, 0.76 g, 87% mass balance. The palladium content was determined to be <1 ppm. Further experimentation indicated that 25 equivalents of TMT were adequate to reduce Pd to < 10 ppm.

10% by volume of the crude coupling solution (78 mL) described above was stirred with 50 weight % C (0.9 g) to ~60°C and allowed to cool for 30 minutes, filtered through celite, rinsed with EtOAc, and this process repeated with a fresh portion of charcoal. The solution was concentrated to afford 2.29 g (131% mass balance). The residue was azeotroped twice with anhydrous ethyl ether. The residue was dissolved in ether (11 mL), the solution cooled to 0°C, seeded with the title compound and stirred. A solid precipitated from solution. After 1 hr, hexanes (5 mL) were added dropwise, the mixture stirred at 0°C for 2 hr, collected and washed with ice-cold 2:1 ether:hexane, affording the title compound of this step (1.07 g, 58% from the title compound of step B of Example 1) as a faint yellow powder, HPLC area percent = 95.8% (in process).

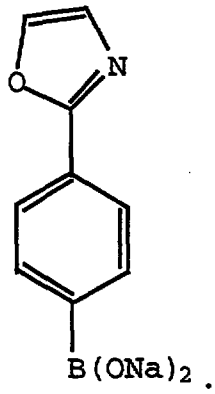
HPLC Conditions:
Column - YMC ODS-A, 6 X 250 mm
Monitored at 233 nm,
Flow Rate - 1.5 mL/min.
Solvent A (%): H_2O/MeOH/H_3PO_4 90:10:0.2
Solvent B (%): H_2O/MeOH/H_3PO_4 10:90:0.2
Gradient: 40% B to 100% B; linear gradient over 10 min, 100% B for 5 min,
40% B for 4 min.
Retention time for the title compound of this step: 12.8 min.

Second Alternative preparation of the title compound of this step, Reverse Coupling Method:

A 500 L oven dried round bottom flask was charged with the title compound of Example 2 (10 g, 37.3 mmol), anhydrous THF (250 mL), toluene (50 mL) and triisopropylborate ($B(OiPr)_3$, 50 mL) under an argon atmosphere. The resulting colorless solution was cooled to -75°C and n-butyl lithium (36 mL, 1.43 M in hexanes, 51.5 mmol) was added dropwise in 1 hour. The internal temperature was kept below -73°C during the addition. The reaction was quenched with addition of acetic acid (4 mL) in THF (25 mL) and concentrated on a rotary evaporator. Toluene (100 mL) and methanol (100 mL) were added and the solvent was removed on the rotary evaporator at 40°C. This was repeated one more time.

The resulting residue was dissolved in NaOH (100 mL, 100 mmol, 1N) and extracted with

hexanes (25 mL) and TBME (25 mL) twice. The following compound was obtained:



The aqueous layer was added to a mixture of $NaHCO_3$ (8.4 g, 100 mmol) in EtOH (100 mL), and a solution of the title compound of step B of Example 1 (14.4 g, 34.4 mmol) in toluene (100 mL) was added. The resulting mixture was bubbled with argon for 15 minutes.

While the above reaction was worked up, a 50 mL round bottom flask was charged with triphenylphosphine (676.8 mg, 2.58 mmol) and THF (30 mL), bubbled with argon for 15 minutes. $Pd(OAc)_2$ (193.4 mg, 0.86 mmol) was added and the mixture was heated to 65°C for 1 hour under argon. The mixture was cooled to room temperature and was added to the above ethanol/toluene/water mixture. The resulting heterogeneous mixture was heated to 75°C for 6 hours. HPLC indicated all starting material was consumed.

The reaction mixture was cooled to room temperature and concentrated on a rotary evaporator. Ethyl acetate (250 mL) and charcoal (10 g) were added. The mixture was stirred at

room temperature for 30 minutes and filtered through a celite pad. The celite pad was rinsed with ethyl acetate (25 mL x 4). The filtrate was transferred to a 500 mL separatory funnel and washed with water (100 mL x 2) and brine (100 mL x 2). The ethyl acetate layers were combined, mixed with trithiocyanuric acid (TMT, 4 g) and heated at 45°C for 45 minutes. It was filtered through a celite pad. The celite pad was rinsed with ethyl acetate (25 mL x 4). The organic layers were combined and washed with NaOH (200 mL x 2, TMBE (300 mL) was added to minimize emulsion), water (200 mL) and brine (200 mL), dried over Na_2SO_4, filtered and concentrated to 17.5 g (98% mass balance).

The crude product was dissolved in ethanol (17.5 mL). Half of the solution (~8.8 mL) was put aside in a 0°C freezer for 2 days. Crystallization occurred. The solid was filtered and suction dried. The product was obtained as a yellowish solid (6 g, 67% overall yield from the title compound of Example 2, HPLC area percent = 99.1%.)

HPLC conditions:

Column - YMC ODS-A, 6 X 250 mm

Monitored at 233 nm,

Flow Rate - 1.5 mL/min.

Solvent A (%): H_2O/MeOH/H_3PO_4 90:10:0.2

Solvent B (%): H_2O/MeOH/H_3PO_4 10:90:0.2

Gradient: 40% B to 100% B; linear gradient over 10 min, 100% B for 5 min,

40% B for 4 min.

Retention time of the title compound of this step: 12.8 min.

B. N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide

A three-necked, 3-L round-bottomed flask equipped with an overhead mechanical stirrer, a thermocouple, and a reflux condenser was charged with a bright yellow solution of the crude title compound from step A (62.45 g) in 95% ethanol (620 mL). While stirring, 6 N HCl (620 mL) was added rapidly and the mixture was heated to reflux at 87°C for 100 minutes, resulting in a pale orange solution. The reaction mixture was cooled to room temperature followed by cooling to ~0-4°C using an ice bath and was then basified to pH ~13 using 5 N NaOH (~850 mL). The sodium hydroxide solution was added slowly over 10 minutes without allowing the temperature to rise over 30°C. The mixture was recooled to 0°C and 250 mL of water was added and the resulting precipitate was filtered and washed with water (200 mL). The filtrate was concentrated under vacuum on a rotary evaporator at ~40°C to remove most of the ethanol. Precipitation of the sodium salt of the title compound of this Example occurred during the concentration. The suspension was cooled to ~10°C and filtered and washed with brine (2 x 150 mL). The solid was air dried for 15 minutes and transferred to a 2-L flask and dissolved in 1-L of hot water. The solution was polish filtered and washed with water (150 mL) and transferred to a 2-L separatory funnel. The aqueous layer was washed with 1:1 ethyl acetate:hexane (2 x 1-L) and hexane

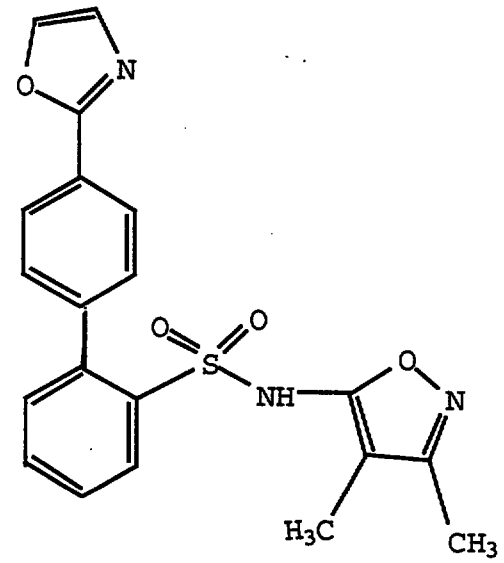
(500 mL). The yellow aqueous layer was then cooled to ~7°C and while stirring vigorously, very slowly acidified from pH ~9.0 to 2.6 to precipitate the the title compound of this Example. After stirring for ~10 minutes the slurry was filtered and washed with excess water to remove any residual acid and air dried to afford 31.5 g (84%) of product as an off-white solid.

A 5.0 g portion of the above solid was dissolved in ethyl acetate (25 mL) and treated with trithiocyanuric acid (TMT, 0.23 g). The TMT is a chelating agent added to facilitate removal of residual palladium from the product. The mixture was gently boiled and then heated in an oil bath for 15 minutes at ~65°C. Norit charcoal (5.1 g) was added to the mixture and heating was continued for an additional 30 minutes. The mixture was then cooled in an ice bath and filtered through a bed of celite and washed with ethyl acetate (25 mL). The filtrate was transferred to a separatory funnel and washed with 1.0 N HCl (1 x 75 mL) and water (1 x 75 mL). The HCl wash removed residual TMT. The organic layer was then treated with Norit charcoal (0.5 g), heated to a gentle boil and filtered through a bed of celite. The filtrate was concentrated and the residue was dissolved in absolute ethanol (20 mL), boiled and then water (10 mL) was added. The solution was seeded and allowed to cool with stirring and crystallize over 16 hours. The resultant crystals were filtered, washed with ethanol:water (1:1; 10 mL) and vacuum dried to afford 4.0 g of pure title compound of this

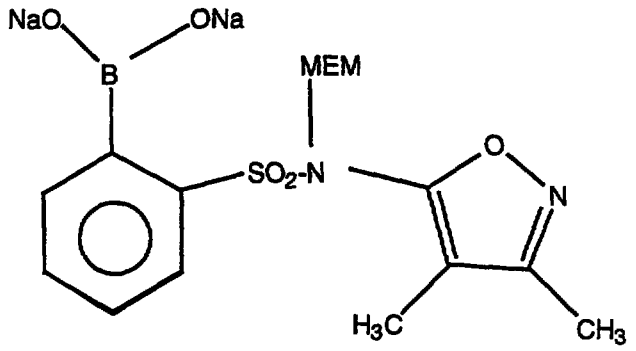
Example (overall yield of 66% from the title compound of step A, HPLC area percent = 99.02%). m.p. = 145.1°C (high melt polymorph)

Example 4

PREPARATION OF FORMULA I COMPOUND N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide COUPLING OF BORONIC ACID SALT IX WITH IODOPHENYL COMPOUND III



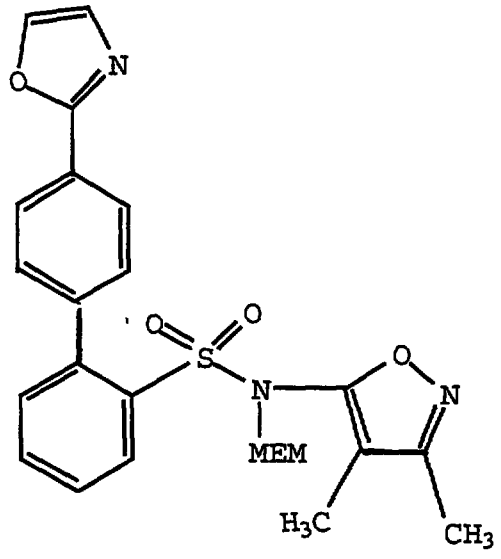
A. 2-Borono-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-methoxyethoxy)methyl]benzene-sulfonamide, disodium salt



A dry 3-necked 100 mL round-bottomed flask which was equipped with: magnetic stir bar, gas adapter, thermocouple, and septum was charged with the title compound of step B of Example 1 (5.0 g; 11.9 mmol), and then thoroughly degassed and placed under an argon atmosphere. THF (23 mL) was added via a syringe and the mixture was cooled to -100°C (internal temperature) and vigorously stirred. While vigorously stirring the mixture, *n*-BuLi (5.30 mL, 12.6 mmol) was dropwise added over a period of 19 minutes, while maintaining the internal temperature between -95°C and -100°C. The pale yellow-orange solution was stirred for an additional 12 minutes at about -100°C. Trimethylborate (2.0 mL, 17.6 mmol) dissolved in THF (3.0 mL) was dropwise added over 12.0 minutes, while maintaining the temperature between -95°C and -100°C. The mixture was stirred for about 50 minutes at about -95°C to -100°C, and then stirred for an additional 40 minutes at about -78°C to -72°C. The borate ester was hydrolyzed by the addition of 1.0 N HCl (2.0 mL, 2.0 mmol) at about -72°C, the solution was warmed to ambient temperature and stirred for about 60 minutes. A solution of Na_2CO_3 (55 mL, 2.0 M, 110 mmol) was added, and the mixture was thoroughly degassed and placed under an atmosphere of argon. This

material was then used "as is" in the following steps (purity = 95.9%, HPLC). YMC ODS-A column, 150 mm x 6.0 mm, S-3 µm, 120 A; flow rate 1.0 mL/min. At 0.0 min. the solvent system was composed of A (40%) (A = 90% MeOH/10% H_2O/0.1% H_3PO_4) and B (60%) (B = 90% H_2O/10% MeOH/0.2% H_3PO_4). At 15.0 min the solvent composition was 100% A. From 15.1 min to 20.0 min the solvent composition was A (40%) and B (60%). Retention time Rt for the title compound of this step was 7.5 min. The detector was operating at 233 nm.

B. <u>N-[(2-Methoxyethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-oxazol-2-yl-[1,1'-biphenyl]-2-sulfonamide</u>



A dry 3-necked, 300 mL round-bottomed flask which was equipped with: a mechanical stirrer, gas adapter, thermocouple, reflux condenser, and septum was charged with $Pd(OAc)_2$ (0.16 g, 0.71 mmol) and Ph_3P (0.5 g, 1.93 mmol), degassed and placed under an argon atmosphere. THF (30 mL) was

added and the mixture was heated at ~ 65°C for about 70 minutes. The color gradually changed from rust-orange to yellow. A degassed solution of toluene (85 mL) and EtOH (64 mL) solution of the title compound of Example 2 (3.23 g, 11.9 mmol) was added via a syringe followed by the degassed solution of the title compound of Step A. The red colored solution was heated at ~ 75°C (internal temperature) for 1.5 hr. The heating bath was removed, and the mixture was allowed to cool to ambient temperature. The layers were separated in a separatory funnel, water (50 mL) was added to the aqueous layer and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (1 x 75 mL), dried with $MgSO_4$, treated with 5.0 g of Norit neutral charcoal, filtered through celite, concentrated, and kept under vacuum (about 0.1 mm Hg) overnight to afford the title compound of this step (6.17 g, 111%) as a red colored oil. (purity > 80%, HPLC)

C. N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide

A dry 250 mL round-bottomed flask equipped with a reflux condenser and magnetic stir bar was charged with the crude product of step B (6.17 g, theoretical 5.56 g, 11.9 mmol), 95% EtOH (60 mL), 6.0 N HCl (60 mL) and heated at reflux for 2 hr. The mixture was cooled to approximately 5°C, aqueous NaOH added to pH approximately 13 with a moderate temperature rise to less than approximately 25°C, polish filtered, and water (50

mL) was added. The solution was concentrated at 40°C to remove most of the EtOH (~ 55-60 mL), whereupon a white solid formed. The mixture was cooled to 0°C for 20 minutes, filtered and the resultant white solid was washed with brine (2 x 50 mL), and then dryed under vacuum (~ 0.1 mm Hg) for 12 hr. The white solid was dissolved in hot water (80 mL) and polish filtered. The aqueous solution was placed in a separatory funnel and washed with 1/1 EtOAc/hexanes (2 x 50 mL) and hexanes (75 mL). The solution was cooled to 0°C, stirred vigorously, 1.0 N HCl was slowly added until pH = 1.0, and then the mixture was kept at 0°C for 15 minutes. It was filtered and washed with water (3 x 50 mL) to afford an off-white solid, which was suction dried for 3 hr. The white solid was then dissolved in EtOAc (65 mL), trithiocyanuric acid (0.20 g, 1.13 mmol) was added and the mixture was stirred at 65°C for 30 minutes. Charcoal (Norit neutral, 5.0 g) was added and the mixture was stirred for an additional 30 minutes at 65°C. The mixture was cooled to 0°C, filtered through a pad of celite, washed with EtOAc (3 x 50 mL), and concentrated to a volume of ~ 60 mL. The mixture was washed with 1.0 N NaOH (3 x 50 mL), and to the aqueous layer was added NaCl (3.0 g, 637 mmol) as well as brine (50 mL). The aqueous mixture was cooled to 0°C, filtered, and washed with brine (2 x 50 mL). The resultant white solid was dissolved in hot water (200 mL), cooled to 0°C, stirred vigorously, and 1.0 N HCl was slowly added until pH = 1.0, and the mixture was kept at 0°C for 15 minutes. It was filtered and washed with water (3 x 50 mL)

affording an off-white solid, which was dryed at ~ 45°C under vacuum (0.1 mm Hg) for ~ 16 hr to afford 2.4 g (50 % yield) of an off-white solid. The solid (2.25 g) was dissolved in 95% EtOH/water (9.0 mL/5.0 mL) at 70°C. Slow cooling to ambient temperature (1.5 hr) followed by cooling to 5°C overnight afforded a white crystalline material, which was filtered and washed with cold 95% EtOH/water (3.0 mL/ 5.0 mL) and dryed under vacuum (~ 0.1 mm Hg) for 48 hr to afford 2.1 g of the title compound of this Example as a white solid (46.9% overall yield from the title compound of step B). TLC indicated (2/1 hexane/EtOAc, stain $KMnO_4$) that the reaction was completed after 2 hours. m.p. = 143.07°C

* C L M S *

What is claimed is:

1. A high melt polymorph of the compound N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide, which has a melting point of approximately 143.07 to 145.1°C.