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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No. 5,633,272  
Issued: May 27, 1997  
Patentees: John Talley, et al.  
Assignee: G.D. Searle and Company  
Examiner: L. Stockon  
Group Art Unit: 1201  
TITLE: SUBSTITUTED ISOXAZOLES FOR THE TREATMENT OF INFLAMMATION

May 26, 2004

Commissioner for Patents  
Mail Stop Patent Term Extension  
P.O. Box 1450  
Alexandria, VA 22313  
Attn: Karin Ferriter

TO THE COMMISSIONER OF PATENTS AND TRADEMARKS  
SIR:

Pursuant to your telephone conversation with Sharon Rudebeck, please find a courtesy replacement copy of the Application for Extension of Patent Term, Fee Transmittal, Declaration & Exhibit I-IV, Certificate of Mailing and a copy of the stamped Return Postcard.

The fee for \$1120.00 was processed on January 25, 2002. Therefore, Applicants do not believe any additional fees are required at this time.

The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account No. 19-1025.

Respectfully submitted,

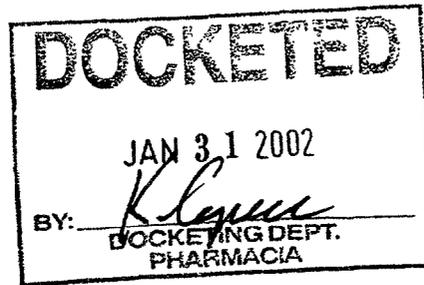
James M. Warner  
Attorney for Applicants  
Registration No. 45,199  
Tel: 314-274-3642

Pharmacia Corporation of Pfizer Inc  
Corporate Patent Department  
P.O. Box 1027  
St. Louis, Missouri 63006

CERTIFICATE OF MAILING

I certify that the foregoing correspondence in the Patent of John Talley, et al., Patent No. 5,633,272 issued May 27, 1997, is being deposited with the United States Postal Service as Express Mail No. EL586330393US in an envelope addressed to: Commissioner for Patents, Mail Stop Patent Term Extension, P.O. Box 1450, Alexandria, VA 22313, Attn: Karin Ferriter on this 26th day of May 2004.

  
Sharon Rudebeck



JMW

### United States Patent and Trademark Office

Case No. 25065/L

Inventor	John Talley, et al.
Serial No.	Patent No. 5,633,272
Reg. Date/Filing Date	Issued May 27, 1997
Received as of date stamped	FEE Transmittal (Dup); Application for
	Ext. of Patent Term including Certification,
	Declaration & Exhibit I-IV



Cert. Express mail No. EV001321386US

RECEIVED

JAN 31 2002

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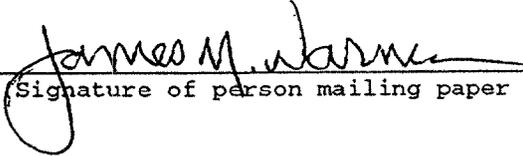
"Express Mail" mailing label number EV001321386US

Date of Deposit: January 15, 2002

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 & 1.8 on the date indicated above and is addressed to BOX Patent Extension, Asst. Commissioner of Patents and Trademarks, Washington, D.C. 20231

James M. Warner

(Typed or printed name of person mailing paper or fee)



(Signature of person mailing paper or fee)



JMW

**United States Patent and  
Trademark Office**

Case No.	2865/1
Inventor	John Talley, et al.
Serial No.	Patent No. 5,633,272
Reg. Date/Filing Date	Issued May 27, 1997
Received as of date stamped	FEE Transmittal (Dup); Application for Ext. of Patent Term including Certification, Declaration & Exhibit I-IV

Cert. Express mail No. EV001321386US



Approved for use through 10/31/2002. OMB 0651-0032  
 Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE  
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# FEE TRANSMITTAL for FY 2001

*Patent fees are subject to annual revision.*

Complete if Known	
Application Number	U.S. Patent 5,633,272
Filing Date	Issued May 27, 1997
First Named Inventor	John Talley, et al.
Examiner Name	L. Stockton
Group Art Unit	1201
Attorney Docket No.	2865/1

**TOTAL AMOUNT OF PAYMENT** **\$1,120.00**

**METHOD OF PAYMENT**

1.  The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:

Deposit Account Number: **19-1025**

Deposit Account Name: **Pharmacia Corporation**

Charge Any Additional Fee Required Under 37 CFR §§ 1.16 and 1.17

Applicant claims small entity status. See 37 CFR § 1.27

2.  Payment Enclosed:

Check  Credit card  Money Order  Other

**FEE CALCULATION (continued)**

**3. ADDITIONAL FEES**

Large Entity Fee Code	Small Entity Fee Code	Fee (\$)	Fee (\$)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non - English specification	
147	2,520	147	2,520	For filing a request for ex parte reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	390	216	195	Extension for reply within second month	
117	890	217	445	Extension for reply within third month	
118	1,390	218	695	Extension for reply within fourth month	
128	1,890	228	945	Extension for reply within fifth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,240	241	620	Petition to revive - unintentional	
142	1,240	242	620	Utility issue fee (or reissue)	
143	440	243	220	Design issue fee	
144	600	244	300	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Processing fee under 37 CFR § 1.17(q)	
126	180	126	180	Submission of Information Disclosure Statement	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	710	246	355	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	710	249	355	For each additional invention to be examined (37 CFR § 1.129(b))	
179	710	279	355	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	
Other fee (specify) <u>Extension of Patent Term -37C.F.R. 1.20(j)l</u>					1,120.00
<b>*Reduced by Basic Filing Fee Paid</b>					
<b>SUBTOTAL (3) \$1,120.00</b>					

**FEE CALCULATION**

**1. BASIC FILING FEE**

Large Entity Fee Code	Small Entity Fee Code	Fee (\$)	Fee (\$)	Fee Description	Fee Paid
101	710	201	355	Utility filing fee	
106	320	206	160	Design filing fee	
107	490	207	245	Plant filing fee	
108	710	208	355	Reissue filing fee	
114	150	214	75	Provisional filing fee	
<b>SUBTOTAL (1)</b>					

**2. EXTRA CLAIM FEES**

Total Claims	Extra Claims	Fee from below	Fee Paid
0	-20** = 0	X	0.00
0	-3** = 0	X	0.00
0			

Large Entity Small Entity  
 Fee Code (\$) Fee Code (\$) Fee Description Fee Paid

103	18	203	9	Claims in excess of 20	
102	80	202	40	Independent claims in excess of 3	
104	270	204	135	Multiple dependent claim, if not paid	
109	80	209	40	** Reissue independent claims over original patent	
110	18	210	9	** Reissue claims in excess of 20 and over original patent	
<b>SUBTOTAL (2)</b>					<b>\$0.00</b>

\*\*or number previously paid, if greater; For Reissues, see above

SUBMITTED BY		Complete (if applicable)	
Name (Print/Type)	James M. Warner	Registration No. (Attorney/Agent)	45,199
Signature	<i>James M. Warner</i>	Telephone	314-694-3642
		Date	1/15/02

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.



Attorney Docket No.: 2865/1

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re: U.S. Patent No. 5,633,272

Issued: May 27, 1997

Patentees: John J. Talley et al.

Assignee: G.D. Searle and Company

Title: SUBSTITUTED ISOXAZOLES FOR THE TREATMENT OF  
INFLAMMATION

Assistant Commissioner For Patents  
Box Patent Extension  
Washington, D.C. 20231

Sir:

The Applicant, G.D. Searle LLC (formerly G.D. Searle and Company), a company organized and existing under the laws of the state of Delaware, represents that it is the assignee of the entire interest in and to Letters Patent of the United States No. 5,633,272 granted to John J. Talley et al. on May 27, 1997 for Substituted Isoxazoles for the Treatment of Inflammation by virtue of an assignment in favor of G.D. Searle and Company, recorded August 28, 1995, Reel 7604 and Frame 0908. Your Applicant acting through its duly authorized attorney hereby requests an extension of the patent term of U. S. Patent No. 5,633,272. The following information is submitted in accordance with 35 U.S.C. 156(d) and 37 C.F.R. 1.710 et seq. and follows the numerical format set forth in 37 C.F.R. 1.740(a):

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is BEXTRA™ which is further identified as follows:

Chemical Name:

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide

Generic Name:

Valdecoxib

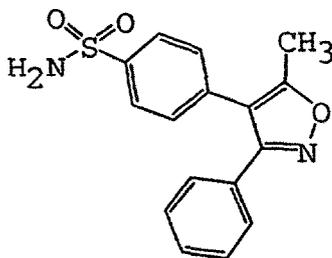
Molecular Formula:

C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>S

Molecular Weight:

314.36

Structural Formula:



Valdecoxib is the active ingredient in the product Bextra™ as may be seen from attached Exhibit I, which is the label for this product.

(2) BEXTRA™ was subject to regulatory review under section 512 of the Federal Food, Drug and Cosmetic Act (FFDCA), 21 U.S.C. 360(b).

(3) BEXTRA™ (active ingredient is valdecoxib) was approved by the Food and Drug Administration (FDA) for

commercial marketing pursuant to Section 512 of the FFDCA on November 16, 2001.

(4) As stated in Sections 1 and 3 above, the active ingredient in the product BEXTRA™ is valdecoxib. Valdecoxib has not been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act prior to approval of NDA 21-341 on November 16, 2001.

(5) The product was approved on November 16, 2001 and the last day within the sixty day period permitted for submission of an application for extension of a patent is January 15, 2002. As evident from the Certificate of Mailing by "Express Mail" pursuant to 37 C.F.R. 1.10, this application is timely filed.

(6) The complete identification of the patent for which an extension is being sought is as follows:

U.S. Patent No.:	5,633,272
Inventors:	John J. Talley David L. Brown Srinivasan Nagarajan Jeffery S. Carter Richard M. Weir Michael A. Stealey Paul W. Collins Roland S. Rogers Karen Seibert
Issued:	May 27, 1997
Expires:	February 13, 2015

(7) A copy of U.S. Patent No. 5,633,272, the patent for which extension is being sought, is attached as Exhibit II.

(8) No disclaimer, reexamination certificate or certificate of correction has issued for U.S. Patent No. 5,633,272.

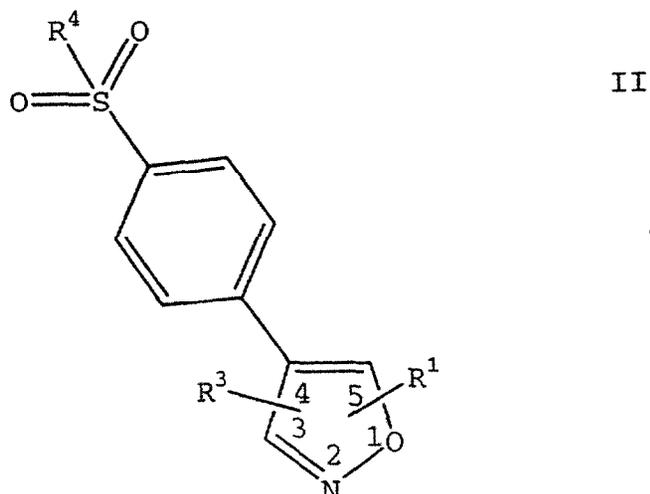
A copy of the maintenance fee statement showing timely payment of fee is attached as Exhibit III.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

U.S. Patent 5,633,272 claims the approved product, a pharmaceutical composition comprising the approved product, and a method of treating inflammation or an inflammation-associated disorder. Claims 1, 2, 3, 4, 5, 6, 7, 8, and 24 claim the approved product. Claims 9, 10, 11, 12, 13, and 26 claim a pharmaceutical composition comprising the approved product. Claims 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 28 claim a method of treating inflammation or an inflammation-associated disorder using the approved product. Accordingly, claims 1-24, 26, and 28 each read on the approved product or uses for the approved product.

Claim 1 reads as follows:

1. A compound of Formula II



wherein R<sup>1</sup> is selected from alkyl, carboxyalkyl, alkoxy carbonyl, aminocarbonyl, aminocarbonylalkyl, alkoxy carbonylalkyl, carboxyl, alkoxy, haloalkoxy, aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, aryloxyalkyl, arylthioalkyl, hydroxyl, amino, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxy carbonyloxyalkyl, alkylaminocarbonyloxyalkyl, alkoxy carbonylthioalkyl, and alkylaminocarbonylthioalkyl;

wherein R<sub>3</sub> is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R<sub>3</sub> is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxy carbonyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, halo, alkoxy and alkylthio; and

wherein R4 is selected from lower alkyl, hydroxyl, and amino;

or a pharmaceutically-acceptable salt thereof.

Claim 2 reads as follows:

2. A compound of claim 1 wherein R1 is selected from hydroxyl, amino, lower alkyl, lower carboxyalkyl, lower alkoxy-carbonyl, aminocarbonyl, carboxyl, lower aminocarbonylalkyl, lower alkoxy-carbonylalkyl, lower alkoxy, lower haloalkoxy, lower aralkoxy, lower cycloalkylalkoxy, lower alkylthio, lower aralkylthio, lower cycloalkylalkylthio, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower aryloxyalkyl, lower arylthioalkyl, lower hydroxyalkyl, lower haloalkyl, lower cycloalkyl, lower cycloalkylalkyl, lower aralkyl, halo, lower alkylamino, lower aralkylamino, lower N-alkyl-N-aralkylamino, lower N-alkyl-N-cycloalkylalkylamino, lower arylcarbonyloxyalkyl, lower alkoxy-carbonyloxyalkyl, lower alkylaminocarbonyloxyalkyl, lower alkoxy-carbonylthioalkyl, and lower alkylaminocarbonylthioalkyl; wherein R3 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R3 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, lower alkyl, cyano, carboxyl, lower alkoxy-carbonyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino,

lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy, lower alkylsulfonyl, aminosulfonyl, and lower alkylthio; and wherein R4 is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

Claim 3 reads as follows:

3. A compound of claim 2 wherein R1 is selected from hydroxyl, lower alkyl, carboxyl, lower carboxyalkyl, lower aminocarbonylalkyl, lower alkoxyalkyl, lower aralkyl, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower aryloxyalkyl, lower arylthioalkyl, lower haloalkyl, lower hydroxylalkyl, cycloalkyl, cycloalkylalkyl, and aralkyl; wherein R3 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R3 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, lower alkyl, cyano, carboxyl, lower alkoxyalkyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy, aminosulfonyl, and lower alkylthio; and wherein R4 is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

Claim 4 reads as follows:

4. A compound of claim 3 wherein R1 is selected from hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, benzyl,

phenethyl, aminocarbonylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, methoxymethyl, benzyloxymethyl, phenylethoxymethyl, methylthiomethyl, benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, phenyloxymethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxymethyl, hydroxylpropyl, hydroxyethyl, cyclohexyl, cyclobutyl, cyclopentyl, cycloheptyl, cyclohexylmethyl, cyclohexylethyl, cyclobutylethyl, cyclopentylmethyl, cycloheptylpropyl, and lower aralkyl selected from benzyl and phenylethyl, wherein the phenyl ring is optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methyl, and methoxy; wherein R3 is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, and 1-cyclopentenyl; wherein R3 is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, aminosulfonyl,

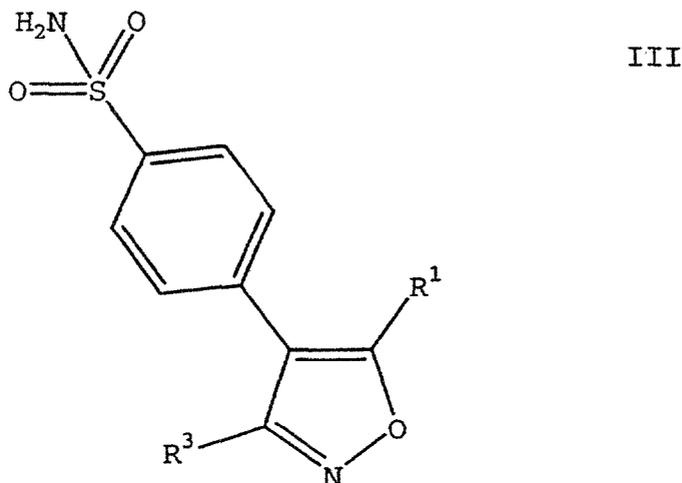
methylthio, ethylthio, butylthio, and hexylthio; and wherein R<sub>4</sub> is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

Claim 5 reads as follows:

5. The compound of claim 4 which is 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

Claim 6 reads as follows:

6. A compound of Formula III



wherein R<sub>1</sub> is selected from hydroxyl, alkyl, carboxyalkyl, aminocarbonylalkyl, alkoxy carbonylalkyl, carboxyl, alkoxy, haloalkoxy, aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, aryloxyalkyl, arylthioalkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl,

arylcarbonylthio, alkoxy-carbonyloxyalkyl, alkylaminocarbonyloxyalkyl, alkoxy-carbonylthioalkyl, and alkylaminocarbonylthioalkyl; and

wherein R3 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R3 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxy-carbonyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, aminosulfonyl, halo, alkoxy and alkylthio; or a pharmaceutically-acceptable salt thereof.

Claim 7 reads as follows:

7. A compound of claim 6 wherein R1 is selected from hydroxyl, lower alkyl, carboxyl, lower carboxyalkyl, lower aminocarbonylalkyl, lower alkoxy-carbonylalkyl, lower aralkyl, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower aryloxyalkyl, lower arylthioalkyl, lower haloalkyl, lower hydroxylalkyl, lower cycloalkyl, lower cycloalkylalkyl, and aralkyl; wherein R3 is selected from cycloalkyl, cycloalkenyl, and aryl; and wherein R3 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, aminosulfonyl, lower alkyl, cyano, carboxyl, lower alkoxy-carbonyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower

alkoxy and lower alkylthio; or a pharmaceutically-acceptable salt thereof.

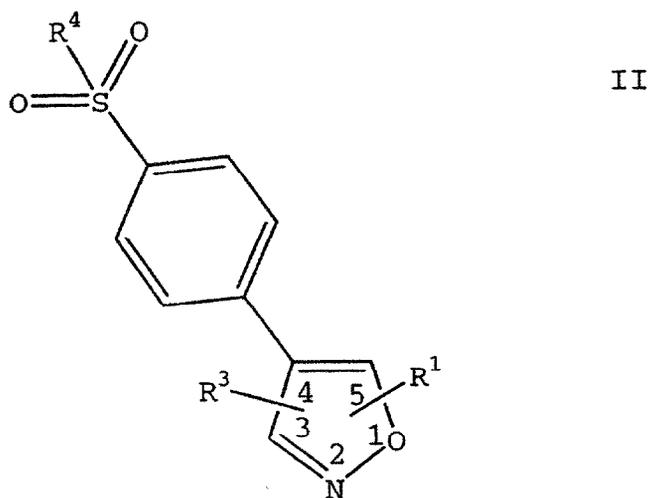
Claim 8 reads as follows:

8. A compound of claim 7 wherein R1 is selected from hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, benzyl, phenethyl, aminocarbonylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, methoxymethyl, benzyloxymethyl, phenylethoxymethyl, methylthiomethyl, benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, phenyloxymethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxylmethyl, hydroxylpropyl, hydroxyethyl, cyclohexyl, cyclobutyl, cyclopentyl, cycloheptyl, cyclohexylmethyl, cyclohexylethyl, cyclobutylethyl, cyclopentylmethyl, cycloheptylpropyl, and lower aralkyl selected from phenylethyl and benzyl optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methyl, and methoxy; and wherein R3 is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, and 1-cyclopentenyl; wherein R3 is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-

ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, aminomethyl, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, methylthio, aminosulfonyl, ethylthio, butylthio, and hexylthio; or a pharmaceutically-acceptable salt thereof.

Claim 9 reads as follows:

9. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Formula II



wherein R<sup>1</sup> is selected from alkyl, carboxyalkyl, alkoxy carbonyl, aminocarbonyl, aminocarbonylalkyl, alkoxy carbonylalkyl, carboxyl, alkoxy, haloalkoxy,

aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, aryloxyalkyl, arylthioalkyl, hydroxyl, amino, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxy carbonyloxyalkyl, alkylaminocarbonyloxyalkyl, alkoxy carbonylthioalkyl, and alkylaminocarbonylthioalkyl;

wherein R3 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R3 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxy carbonyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, halo, alkoxy and alkylthio; and

wherein R4 is selected from lower alkyl, hydroxyl, and amino;

or a pharmaceutically-acceptable salt thereof.

Claim 10 reads as follows:

10. A pharmaceutical composition of claim 9 wherein R1 is selected from hydroxyl, amino, lower alkyl, lower carboxyalkyl, lower alkoxy carbonyl, aminocarbonyl, carboxyl, lower aminocarbonylalkyl, lower alkoxy carbonylalkyl, lower alkoxy, lower haloalkoxy, lower

aralkoxy, lower cycloalkylalkoxy, lower alkylthio, lower aralkylthio, lower cycloalkylalkylthio, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower aryloxyalkyl, lower arylthioalkyl, lower hydroxyalkyl, lower haloalkyl, lower cycloalkyl, lower cycloalkylalkyl, lower aralkyl, halo, lower alkylamino, lower aralkylamino, lower N-alkyl-N-aralkylamino, lower N-alkyl-N-cycloalkylalkylamino, lower arylcarbonyloxyalkyl, lower alkoxy carbonyloxyalkyl, lower alkylaminocarbonyloxyalkyl, lower alkoxy carbonylthioalkyl, and lower alkylaminocarbonylthioalkyl; wherein R3 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R3 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, lower alkyl, cyano, carboxyl, lower alkoxy carbonyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy, lower alkylsulfonyl, aminosulfonyl, and lower alkylthio; and wherein R4 is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

Claim 11 reads as follows:

11. A pharmaceutical composition of claim 10 wherein R1 is selected from hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, benzyl, phenethyl, aminocarbonylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, methoxymethyl, benzyloxymethyl, phenylethoxymethyl, methylthiomethyl,

benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, phenyloxymethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxymethyl, hydroxylpropyl, hydroxyethyl, cyclohexyl, cyclobutyl, cyclopentyl, cycloheptyl, cyclohexylmethyl, cyclohexylethyl, cyclobutylethyl, cyclopentylmethyl, cycloheptylpropyl, and lower aralkyl selected from benzyl and phenylethyl, wherein the phenyl ring is optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methyl, and methoxy; wherein R3 is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, and 1-cyclopentenyl; wherein R3 is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, aminosulfonyl, methylthio, ethylthio, butylthio, and hexylthio; and

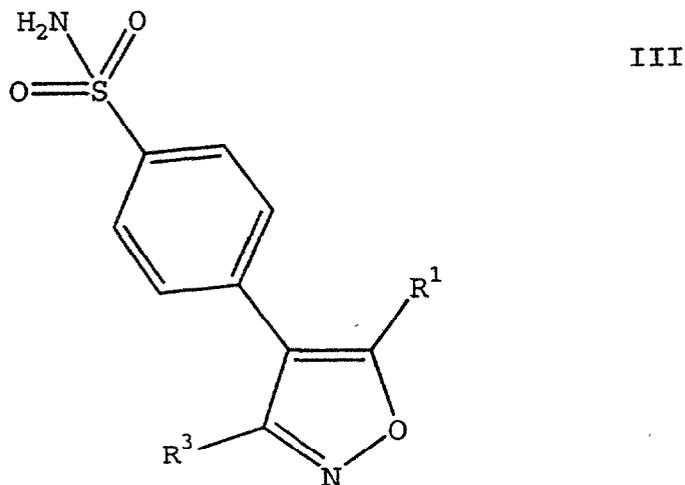
wherein R4 is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

Claim 12 reads as follows:

12. A pharmaceutical composition of claim 11 wherein said compound is 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

Claim 13 reads as follows:

13. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Formula III



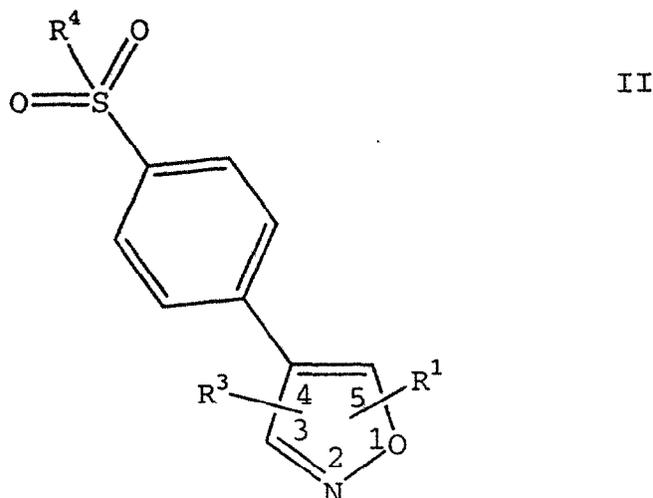
wherein R1 is selected from hydroxyl, alkyl, carboxyalkyl, aminocarbonylalkyl, alkoxy carbonylalkyl, carboxyl, alkoxy, haloalkoxy, aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl,

alkylaminoalkyl, aryloxyalkyl, arylthioalkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxycarbonyloxyalkyl, alkylaminocarbonyloxyalkyl, alkoxycarbonylthioalkyl, and alkylaminocarbonylthioalkyl; and

wherein R3 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R3 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxycarbonyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, aminosulfonyl, halo, alkoxy and alkylthio; or a pharmaceutically-acceptable salt thereof.

Claim 14 reads as follows:

14. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said inflammation or inflammation-associated disorder, a therapeutically-effective amount of a compound of Formula II



wherein R1 is selected from alkyl, carboxyalkyl, alkoxy carbonyl, aminocarbonyl, aminocarbonylalkyl, alkoxy carbonylalkyl, carboxyl, alkoxy, haloalkoxy, aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, aryloxyalkyl, arylthioalkyl, hydroxyl, amino, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxy carbonyloxyalkyl, alkylaminocarbonyloxyalkyl, alkoxy carbonylthioalkyl, and alkylaminocarbonylthioalkyl;

wherein R3 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R3 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxy carbonyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, halo, alkoxy and alkylthio; and

wherein R4 is selected from lower alkyl, hydroxyl, and amino;

or a pharmaceutically-acceptable salt thereof.

Claim 15 reads as follows:

15. A method of claim 14 wherein R1 is selected from hydroxyl, amino, lower alkyl, lower carboxyalkyl, lower alkoxy carbonyl, aminocarbonyl, carboxyl, lower aminocarbonylalkyl, lower alkoxy carbonylalkyl, lower alkoxy, lower haloalkoxy, lower aralkoxy, lower cycloalkylalkoxy, lower alkylthio, lower aralkylthio, lower cycloalkylalkylthio, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower aryloxyalkyl, lower arylthioalkyl, lower hydroxyalkyl, lower haloalkyl, lower cycloalkyl, lower cycloalkylalkyl, lower aralkyl, halo, lower alkylamino, lower aralkylamino, lower N-alkyl-N-aralkylamino, lower N-alkyl-N-cycloalkylalkylamino, lower arylcarbonyloxyalkyl, lower alkoxy carbonyloxyalkyl, lower alkylaminocarbonyloxyalkyl, lower alkoxy carbonylthioalkyl, and lower alkylaminocarbonylthioalkyl; wherein R3 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R3 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, lower alkyl, cyano, carboxyl, lower alkoxy carbonyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy, lower alkylsulfonyl, aminosulfonyl, and lower

alkylthio; and wherein R4 is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

Claim 16 reads as follows:

16. A method of claim 15 wherein R1 is selected from hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, benzyl, phenethyl, aminocarbonylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, methoxymethyl, benzyloxymethyl, phenylethoxymethyl, methylthiomethyl, benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, phenyloxymethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxylmethyl, hydroxylpropyl, hydroxyethyl, cyclohexyl, cyclobutyl, cyclopentyl, cycloheptyl, cyclohexylmethyl, cyclohexylethyl, cyclobutylethyl, cyclopentylmethyl, cycloheptylpropyl, and lower aralkyl selected from benzyl and phenylethyl, wherein the phenyl ring is optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methyl, and methoxy; wherein R3 is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, and 1-cyclopentenyl; wherein R3 is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-

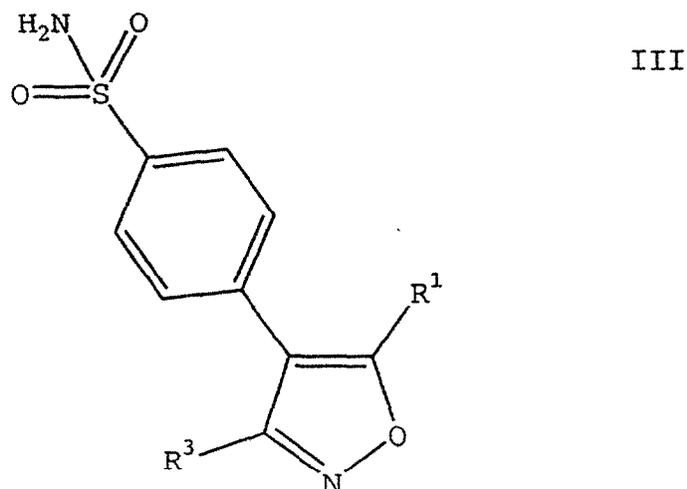
ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, aminosulfonyl, methylthio, ethylthio, butylthio, and hexylthio; and wherein R4 is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

Claim 17 reads as follows:

17. A method of claim 16 wherein said compound is 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

Claim 18 reads as follows:

18. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said inflammation or inflammation-associated disorder, a therapeutically-effective amount of a compound of Formula III



wherein R1 is selected from hydroxyl, alkyl, carboxyalkyl, aminocarbonylalkyl, alkoxycarbonylalkyl, carboxyl, alkoxy, haloalkoxy, aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, aryloxyalkyl, arylthioalkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxycarbonyloxyalkyl, alkylaminocarbonyloxyalkyl, alkoxycarbonylthioalkyl, and alkylaminocarbonylthioalkyl; and

wherein R3 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R3 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxycarbonyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, aminosulfonyl, halo, alkoxy and alkylthio; or a pharmaceutically-acceptable salt thereof.

Claim 19 reads as follows:

19. A method of claim 14 for use in treatment of inflammation.

Claim 20 reads as follows:

20. A method of claim 14 for use in treatment of an inflammation-associated disorder.

Claim 21 reads as follows:

21. A method of claim 20 wherein the inflammation-associated disorder is arthritis.

Claim 22 reads as follows:

22. A method of claim 20 wherein the inflammation-associated disorder is pain.

Claim 23 reads as follows:

23. A method of claim 20 wherein the inflammation-associated disorder is fever.

Claim 24 reads as follows:

24. The compound of claim 4 selected from compounds, or their pharmaceutically acceptable salts, of the group consisting of

4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isopropyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isobutyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-cyclohexyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-neopentyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-trifluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-chloromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-methoxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluoro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-chloro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

[4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]carboxylic acid;

4-[5-hydroxy-3-phenyl-4-isoxazolyl]benzenesulfonamide;

4-[3-methyl-5-phenyl-isoxazol-4-yl]benzenesulfonamide;

4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluoro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

[3-(3-chloro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid;

5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenyl-isoxazole;

3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole

[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]acetic acid;

[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoic acid;

ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoate;

[3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid; and

[4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid.

Claim 26 reads as follows:

26. A pharmaceutical composition of claim 11 wherein said compound is selected from compounds, or their pharmaceutically-acceptable salts, of the group consisting of

4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isopropyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isobutyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-cyclohexyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-neopentyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-trifluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-chloromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-methoxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluoro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-chloro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

[4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]carboxylic acid;

4-[5-hydroxy-3-phenyl-4-isoxazolyl]benzenesulfonamide;

4-[3-methyl-5-phenyl-isoxazol-4-yl]benzenesulfonamide;

4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluoro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

[3-(3-chloro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid;

5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenyl-isoxazole;

3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole ;

[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]acetic acid;

[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoic acid;

ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoate;

[3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid; and

[4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid.

Claim 28 reads as follows:

28. A method of claim 16 wherein said compound is selected from compounds, or their pharmaceutically-acceptable salts, of the group consisting of

4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5isopropyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isobutyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-cyclohexyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-neopentyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-trifluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-chloromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-methoxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluoro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-chloro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

[4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]carboxylic acid;

4-[5-hydroxy-3-phenyl-4-isoxazolyl]benzenesulfonamide;

4-[3-methyl-5-phenyl-isoxazol-4-yl]benzenesulfonamide;

4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluoro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

[3-(3-chloro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid;

5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenyl-isoxazole;

3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole ;

[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]acetic acid;

[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoic acid;

ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoate;

[3-(3-fluoro-4-methoxyphenyl)-4-[4-

(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid; and

[4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid.

(10) A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number: The IND application for the approved product, valdecoxib, was submitted on December 16, 1996. The IND became effective thirty days later on January 15, 1997. The IND application received IND number 52,153.

(B) The date on which a new drug application (NDA) was initially submitted and the NDA number: The NDA application for the approved product, valdecoxib, was January 16, 2001. The NDA application received NDA number 21-341.

(C) The date on which the NDA was approved: The NDA for the approved product, valdecoxib, was approved on November 16, 2001.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

As a brief description of the activities undertaken by Applicant, G.D. Searle and Company (now G.D. Searle LLC, a wholly-owned subsidiary of Pharmacia Corporation), during the applicable regulatory review period, attached hereto as Exhibit IV is a chronology of the major communication between the Applicant and the FDA from December 16, 1996 to November 16, 2001.

(12) A statement beginning on a new page that in the opinion of the Applicant the patent is eligible for extension and a statement as to the length of extension claimed, including how the length of extension was determined:

(A) The Applicant is of the opinion that U.S. Patent 5,633,272 is eligible for extension under 35 U.S.C. 156 because it satisfies all of the requirements for such extension as follows:

- (a) 35 U.S.C. 156(a)  
U.S. Patent 5,633,272 claims the product valdecoxib (4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide) as a compound, as a composition comprising the approved product, and a method of treating inflammation or an inflammation-associated disorder.
- (b) 35 U.S.C. 156(a)(1)  
The term of U.S. Patent 5,633,272 has not expired before submission of this application.
- (c) 35 U.S.C. 156(a)(2)  
The term of U.S. Patent 5,633,272 has never been extended.
- (d) 35 U.S.C. 156(a)(3)  
The application for extension is submitted by the owner of record in accordance with the requirement of 35 U.S.C. 156(d) and rules of the U.S. Patent and Trademark Office.
- (e) 35 U.S.C. 156(a)(4)  
The approved product, BEXTRA™ (active ingredient valdecoxib), has been subjected to a regulatory

review period before its commercial marketing or use.

(f) 35 U.S.C. 156(a)(5)(A)

The commercial marketing or use of the product, BEXTRA™ (active ingredient valdecoxib), after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) under which such regulatory review period occurred.

(g) 35 U.S.C. 156(c)(4)

No other patent has been extended for the same regulatory review period for the product, BEXTRA™ (active ingredient valdecoxib).

(B) The length of extension of the patent term of U.S. Patent 5,633,272 claimed by Applicant is 276 days or 0.756 years. The length of the extension was determined pursuant to 37 C.F.R. 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. 156(g)(1)(B) began on January 15, 1997 and ended on November 16, 2001 which is a total of 1766 days or 4.838 years which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. 156(g)(2)(B)(i), the "Testing Period," began on January 15, 1997 and ended on January 15, 2001 which is a total of 1461 days or 4.002 years, and

(ii) The period of review under 35 U.S.C. 156(g)(2)(B)(ii), the "Application Period," began on January 16, 2001 and

ended on November 16, 2001 which is a total of 305 days or 0.836 years;

- (b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph (12)(B)(a) above (1766 days) less:
- (i) The number of days in the regulatory review period which were on or before the date on which the patent issued (January 15, 1997 to May 27, 1997) which is 121 days, and
  - (ii) the number of days during which applicant did not act with due diligence which is zero (0) days, and
  - (iii) One-half the number of days determined in sub-paragraph (12)(B)(a)(i) after the patent issued  $[(1461-121)/2]$  or 670 days;
  - (iv) The regulatory period is calculated by subtracting the number of days determined in subparagraph (12)(B)(b)(i) through (iii) from the entire regulatory review period as determined in subparagraph (12)(B)(a) (which is 1766 days - 121 days - 0 days - 670 days) which equals 975 days;
- (c) The number of days as determined in subparagraph (12)(B)(b)(iv) (975 days) when added to the original term of the patent (February 13, 2015, as determined by 35 U.S.C. 154(c) and 37 C.F.R. 1.321) which would result in the date, October 15, 2017;

- (d) Fourteen (14) years when added to the date of NDA approval (November 16, 2001) would result in the date, November 16, 2015;
- (e) The earlier date as determined in subparagraphs (12)(B)(c) and (12)(B)(d) is November 16, 2015;
- (f) Because the original patent was not issued and a request for an exemption was not submitted before September 24, 1984 and the commercial marketing or use of the product was not approved before September 14, 1984, five (5) years when added to the original expiration date of the patent (February 13, 2015) would result in the date, February 13, 2020;
- (g) The earlier date as determined in subparagraph (12)(B)(c) and (12)(B)(f) is November 16, 2015.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee as set forth in 37 C.F.R. 1.20(j)(1) for receiving and acting upon this application:

As indicated by the letter of transmittal submitted with this application, the Assistant Commissioner for Patents has been authorized to charge the filing fee and any additional fees which may be required by this or any other related paper, or credit any overpayment to Deposit Account No. 19-1025 in the name of Pharmacia Corporation (parent company of assignee of record G.D. Searle LLC, formerly G.D. Searle and Company).

(15) Please address all inquiries and correspondence relating to the application for patent term extension to:

James M. Warner  
Pharmacia Corporation  
Patent Department  
Mail Zone O4E  
800 N. Lindbergh Blvd.  
St. Louis, Missouri 63167  
Telephone: 314-694-3642  
Facsimile: 314-694-9095

(16) The instant application for extension of patent term with regard to U.S. Patent 5,633,272 is being submitted as one original and two copies thereof.

(17) The requisite declaration pursuant to rule 37 C.F.R. 1.740(b) is attached hereto.

(18) An oath or declaration as set forth in 37 C.F.R. 1.740(b) is attached hereto.

Respectfully submitted,

Date: Jan. 15, 2002

James M. Warner  
James M. Warner  
Attorney for Applicants  
Reg. No. 45,199  
314-694-3642 (St. Louis)

Pharmacia Corporation  
Patent Department  
Mail Zone O4E  
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St. Louis, Missouri 63167  
Telephone: 314-694-3642

Attachments



**CERTIFICATION**

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. 156, including its attachments and supporting papers, is being submitted with two (2) duplicate copies thereof.

Date:

Jan. 15, 2002

James M. Warner  
James M. Warner  
Attorney for Applicants  
Reg. No. 45,199  
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Docket No.: 2865/1

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re: U.S. Patent No. 5,633,272

Issued: May 27, 1997

Patentees: John J. Talley et al.

Assignee: G.D. Searle and Company

Title: SUBSTITUTED ISOXAZOLES FOR THE TREATMENT OF  
INFLAMMATION

Assistant Commissioner For Patents  
Box Patent Extension  
Washington, D.C. 20231

DECLARATION

Sir:

The undersigned attorney for G.D. Searle LLC (formerly G.D. Searle and Company, a wholly owned subsidiary of Pharmacia Corporation), which is the Applicant for Extension of Patent Term under 35 U.S.C. 156 with regard to U.S. Patent No. 5,633,272 hereby declares as follows:

(1) That he is a patent attorney authorized to practice before the Patent and Trademark Office and has general authority from the owner to act on behalf of the owner in patent matters;

(2) That he has reviewed and understands the contents of the application being submitted pursuant to 35 U.S.C. 156 and 37 C.F.R. 1.740;

(3) That he believes the patent is subject to extension pursuant to 35 U.S.C. 156 and 37 C.F.R. 1.710;

(4) That he believes an extension of length claims is fully justified under 35 U.S.C. 156;

(5) That he believes the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. 156 and 37 C.F.R. 1.720.

The undersigned hereby declares further that all statements made herein of her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

Date:

Jan. 15, 2002

James M. Warner  
James M. Warner  
Attorney for Applicants  
Reg. No. 45,199  
314-694-3642 (St. Louis)

Pharmacia Corporation  
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## EXHIBIT I

# Approved Product Label

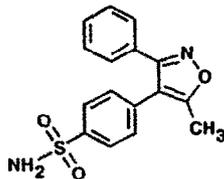
# BEXTRA™

## valdecoxib tablets

PHARMACIA 

### DESCRIPTION

Valdecoxib is chemically designated as 4-(5-methyl-3-phenyl-4-isoxazolyl) benzenesulfonamide and is a diaryl substituted isoxazole. It has the following chemical structure:



Valdecoxib

The empirical formula for valdecoxib is  $C_{16}H_{14}N_2O_3S$ , and the molecular weight is 314.36. Valdecoxib is a white crystalline powder that is relatively insoluble in water (10  $\mu\text{g/mL}$ ) at 25°C and pH 7.0, soluble in methanol and ethanol, and freely soluble in organic solvents and alkaline (pH=12) aqueous solutions.

BEXTRA Tablets for oral administration contain either 10 mg or 20 mg of valdecoxib. Inactive ingredients include lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide.

### CLINICAL PHARMACOLOGY

#### Mechanism of Action

Valdecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic properties in animal models. The mechanism of action is believed to be due to inhibition of prostaglandin synthesis primarily through inhibition of cyclooxygenase-2 (COX-2). At therapeutic plasma concentrations in humans valdecoxib does not inhibit cyclooxygenase-1 (COX-1).

#### Pharmacokinetics

##### Absorption

Valdecoxib achieves maximal plasma concentrations in approximately 3 hours. The absolute bioavailability of valdecoxib is 83% following oral administration of BEXTRA compared to intravenous infusion of valdecoxib.

Dose proportionality was demonstrated after single doses (1–400 mg) of valdecoxib. With multiple doses (up to 100 mg/day for 14 days), valdecoxib exposure as measured by the AUC, increases in a more than proportional manner at doses above 10 mg BID. Steady state plasma concentrations of valdecoxib are achieved by day 4.

The steady state pharmacokinetic parameters of valdecoxib in healthy male subjects are shown in Table 1.

Table 1  
Mean (SD) Steady State Pharmacokinetic Parameters

Steady State Pharmacokinetic Parameters after Valdecoxib 10 mg Once Daily for 14 Days	Healthy Male Subjects (n=8, 20 to 42 yr.)
AUC <sub>(0-24hr)</sub> (hr·ng/mL)	1479.0 (291.9)
C <sub>max</sub> (ng/mL)	161.1 (48.1)
T <sub>max</sub> (hr)	2.25 (0.71)
C <sub>min</sub> (ng/mL)	21.9 (7.68)
Terminal Half-life (hr)	8.11 (1.32)

No clinically significant age or gender differences were seen in pharmacokinetic parameters that would require dosage adjustments.

#### Effect of Food and Antacid

BEXTRA can be taken with or without food. Food had no significant effect on either the peak plasma concentration (C<sub>max</sub>) or extent of absorption (AUC) of valdecoxib when BEXTRA was taken with a high fat meal. The time to peak plasma concentration (T<sub>max</sub>), however, was delayed by 1-2 hours. Administration of BEXTRA with antacid (aluminum/magnesium hydroxide) had no significant effect on either the rate or extent of absorption of valdecoxib.

#### Distribution

Plasma protein binding for valdecoxib is about 98% over the concentration range (21-2384 ng/mL). Steady state apparent volume of

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## valdecoxib tablets

distribution ( $V_{ss}/F$ ) of valdecoxib is approximately 86 L after oral administration. Valdecoxib and its active metabolite preferentially partition into erythrocytes with a blood to plasma concentration ratio of about 2.5:1. This ratio remains approximately constant with time and therapeutic blood concentrations.

### **Metabolism**

In humans, valdecoxib undergoes extensive hepatic metabolism involving both P450 isoenzymes (3A4 and 2C9) and non-P450 dependent pathways (i.e., glucuronidation). Concomitant administration of BEXTRA with known CYP 3A4 and 2C9 inhibitors (e.g., fluconazole and ketoconazole) can result in increased plasma exposure of valdecoxib (see PRECAUTIONS—Drug Interactions).

One active metabolite of valdecoxib has been identified in human plasma at approximately 10% the concentration of valdecoxib. This metabolite, which is a less potent COX-2 specific inhibitor than the parent, also undergoes extensive metabolism and constitutes less than 2% of the valdecoxib dose excreted in the urine and feces. Due to its low concentration in the systemic circulation, it is not likely to contribute significantly to the efficacy profile of BEXTRA.

### **Excretion**

Valdecoxib is eliminated predominantly via hepatic metabolism with less than 5% of the dose excreted unchanged in the urine and feces. About 70% of the dose is excreted in the urine as metabolites, and about 20% as valdecoxib N-glucuronide. The apparent oral clearance (CL/F) of valdecoxib is about 6 L/hr. The elimination half-life ( $T_{1/2}$ ) is approximately 8-11 hours.

### **Special Populations**

#### **Geriatric**

In elderly subjects (>65 years), weight-adjusted steady state plasma concentrations ( $AUC_{0-12hr}$ ) are about 30% higher than in young subjects. No dose adjustment is needed based on age.

#### **Pediatric**

BEXTRA has not been investigated in pediatric patients below 18 years of age.

#### **Race**

Pharmacokinetic differences due to race have not been identified in clinical and pharmacokinetic studies conducted to date.

#### **Hepatic Insufficiency**

Valdecoxib plasma concentrations are significantly increased (130%) in patients with moderate (Child-Pugh Class B) hepatic impairment. In clinical trials, doses of BEXTRA above those recommended have been associated with fluid retention. Hence, treatment with BEXTRA should be initiated with caution in patients with mild to moderate hepatic impairment and fluid retention. The use of BEXTRA in patients with severe hepatic impairment (Child-Pugh Class C) is not recommended.

#### **Renal Insufficiency**

The pharmacokinetics of valdecoxib have been studied in patients with varying degrees of renal impairment. Because renal elimination of valdecoxib is not important to its disposition, no clinically significant changes in valdecoxib clearance were found even in patients with severe renal impairment or in patients undergoing renal dialysis. In patients undergoing hemodialysis the plasma clearance (CL/F) of valdecoxib was similar to the CL/F found in healthy elderly subjects (CL/F about 6 to 7 L/hr.) with normal renal function (based on creatinine clearance).

NSAIDs have been associated with worsening renal function and use in advanced renal disease is not recommended (see PRECAUTIONS—Renal Effects).

#### **Drug Interactions**

Also see PRECAUTIONS—Drug Interactions.

#### **General**

Valdecoxib undergoes both P450 (CYP) dependent and non-P450 dependent (glucuronidation) metabolism. In vitro studies indicate that valdecoxib is not a significant inhibitor of CYP 1A2, 3A4, or 2D6 and is only a weak inhibitor of CYP 2C9 and 2C19 at therapeutic concentrations. The P450-mediated metabolic pathway of valdecoxib predominantly involves the 3A4 and 2C9 isozymes. Using prototype inhibitors and substrates of these isozymes, the following results were obtained. Coadministration of a known inhibitor of CYP 2C9/3A4 (fluconazole) and a CYP 3A4 (ketoconazole) inhibitor enhanced the total plasma exposure (AUC) of valdecoxib. Coadministration of valdecoxib with warfarin caused a small, but statistically significant increase in plasma exposures of R-warfarin and S-warfarin, and also in the pharmacodynamic effects (International Normalized Ratio—INR) of warfarin. (See PRECAUTIONS—Drug Interactions.)

Coadministration of valdecoxib, or its injectable prodrug, with substrates of CYP 2C9 (propofol) and CYP 3A4 (midazolam, alfentanil, fentanyl) did not inhibit the metabolism of either substrate.

Coadministration of valdecoxib with a CYP 3A4 substrate (glyburide) or a CYP 2D6 substrate (dextromethorphan) did not result in clinically important inhibition in the metabolism of these agents.

### **CLINICAL STUDIES**

The efficacy and clinical utility of BEXTRA Tablets have been

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valdecoxib tablets

demonstrated in osteoarthritis (OA), rheumatoid arthritis (RA) and in the treatment of primary dysmenorrhea.

## Osteoarthritis

BEXTRA was evaluated for treatment of the signs and symptoms of osteoarthritis of the knee or hip, in five double-blind, randomized, controlled trials in which 3918 patients were treated for 3 to 6 months. BEXTRA was shown to be superior to placebo in improvement in three domains of OA symptoms: (1) the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness and functional measures in OA, (2) the overall patient assessment of pain, and (3) the overall patient global assessment. The two 3-month pivotal trials in OA generally showed changes statistically significantly different from placebo, and comparable to the naproxen control, in measures of these domains for the 10 mg/day dose. No additional benefit was seen with a valdecoxib 20-mg daily dose.

## Rheumatoid Arthritis

BEXTRA demonstrated significant reduction compared to placebo in the signs and symptoms of RA, as measured by the ACR (American College of Rheumatology) 20 improvement, a composite defined as both improvement of 20% in the number of tender and number of swollen joints, and a 20% improvement in three of the following five: patient global, physician global, patient pain, patient function assessment, and the erythrocyte sedimentation rate (ESR). BEXTRA was evaluated for treatment of the signs and symptoms of rheumatoid arthritis in four double-blind, randomized, controlled studies in which 3444 patients were treated for 3 to 6 months. The two 3-month pivotal trials compared valdecoxib to naproxen and placebo. The results for the ACR20 responses in these trials are shown below (Table 2). Trials of BEXTRA in rheumatoid arthritis allowed concomitant use of corticosteroids and/or disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, gold salts, and hydroxychloroquine. No additional benefit was seen with a valdecoxib 20-mg daily dose.

**Table 2**  
ACR20 Response Rate (%) in Rheumatoid Arthritis

	Study 1	Study 2
BEXTRA 10 mg/day	49%** (103/209)	46%** (103/226)
BEXTRA 20 mg/day	48%** (102/212)	47%* (103/219)
Naproxen 500 mg BID	44%* (100/225)	53%** (115/219)
Placebo	32% (70/222)	32% (71/220)

\* p<0.01; \*\* p<0.001 compared to placebo

## Primary Dysmenorrhea

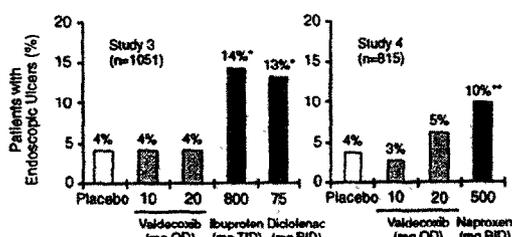
BEXTRA was compared to naproxen sodium 550 mg in two placebo-controlled studies of women with moderate to severe primary dysmenorrhea. The onset of analgesia was within 60 minutes for BEXTRA 20 mg. The onset, magnitude, and duration of analgesic effect with BEXTRA 20 mg were comparable to naproxen sodium 550 mg.

## Safety Studies

**Gastrointestinal (GI) Endoscopy Studies with Therapeutic Doses:** Scheduled upper GI endoscopic evaluations were performed with BEXTRA at doses of 10 and 20 mg daily in over 800 OA patients who were enrolled into two randomized 3-month studies using active comparators and placebo controls (Study 3 and Study 4). These studies enrolled patients free of endoscopic ulcers at baseline and compared rates of endoscopic ulcers, defined as any gastroduodenal ulcer seen endoscopically provided it was of "unequivocal depth" and at least 3 mm in diameter.

In both studies, BEXTRA 10 mg daily was associated with a statistically significant lower incidence of endoscopic gastroduodenal ulcers over the study period compared to the active comparators. Figure 1 summarizes the incidence of gastroduodenal ulcers in Studies 3 and 4 for the placebo, valdecoxib, and active control arms.

**Figure 1**  
Incidence of Endoscopically Observed  
Gastroduodenal Ulcers in OA Patients



\* Significantly different vs placebo and both valdecoxib treatment groups: p<0.05  
\*\* Significantly different vs placebo and valdecoxib 10 mg, p<0.05



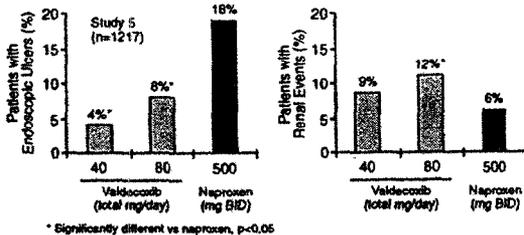
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**Safety Study with Supratherapeutic Doses:** Scheduled upper GI endoscopic evaluations were performed in a randomized 6-month study of 1217 patients with OA and RA comparing valdecoxib 20 mg BID (40 mg daily) and 40 mg BID (80 mg daily) (4 to 8 times the recommended therapeutic dose) to naproxen 500 mg BID (Study 5). This study also formally assessed renal events as a primary outcome with supratherapeutic doses of BEXTRA. The renal endpoint was defined as any of the following: new/increase in edema, new/increase in congestive heart failure, increase in blood pressure (BP; >20 mm Hg systolic, >10 mm Hg diastolic), new/increase in BP treatment, new/increase in diuretic therapy, creatinine increase over 30% (or >1.2 mg/dL if baseline <0.9 mg/dL), BUN increase over 200% or >50 mg/dL, 24-hr urinary protein increase to >500 mg (if baseline 0-150 mg or >750 if baseline 151-300 or >1000 if baseline 301-500), serum potassium increase to >6 mEq/L, or serum sodium decrease to <130 mEq/L.

Figure 2 summarizes the incidence rates of gastroduodenal ulcers and renal events that were seen in Study 5. BEXTRA 40 mg daily and 80 mg daily were associated with a statistically significant lower incidence of endoscopic gastroduodenal ulcers over the study period compared to naproxen. The incidence of renal events was significantly different between the BEXTRA 80 mg daily group and naproxen. The clinical relevance of renal events observed with supratherapeutic doses (4 to 8 times the recommended therapeutic dose) of BEXTRA is not known (see PRECAUTIONS—Renal Effects).

**Figure 2**  
Incidence of Endoscopic Gastroduodenal Ulcers and Renal Events in the High-dose Safety Study



**Renal Safety at the Therapeutic Chronic Dose:** The renal effects of valdecoxib compared with placebo and conventional NSAIDs were also assessed by prospectively designed pooled analyses of renal events data (see definition above—Supratherapeutic Doses) from five placebo- and active-controlled 12-week arthritis trials that included 995 OA or RA patients given valdecoxib 10 mg daily. The incidence of renal events observed in this analysis with valdecoxib 10 mg daily (3%), ibuprofen 800 mg TID (7%), naproxen 500 mg BID (2%) and diclofenac 75 mg BID (4%) were significantly higher than placebo-treated patients (1%). In all treatment groups, the majority of renal events were either due to the occurrence of edema or worsening BP.

**Gastrointestinal Ulcers in High-Risk Patients:** Subset analyses were performed of patients with risk factors (age, concomitant low-dose aspirin use, history of prior ulcer disease) enrolled in four upper GI endoscopic studies. Table 3 summarizes the trends seen.

The correlation between findings of endoscopic studies, and the incidence of clinically significant serious upper GI events has not been established.

**Platelets:** In four clinical studies with young and elderly (>65 years) subjects, single and multiple doses up to 7 days of BEXTRA 10 to 40 mg BID had no effect on platelet aggregation.

**INDICATIONS AND USAGE**

BEXTRA Tablets are indicated:

- For relief of the signs and symptoms of osteoarthritis and adult rheumatoid arthritis.
- For the treatment of primary dysmenorrhea.

**CONTRAINDICATIONS**

BEXTRA Tablets are contraindicated in patients with known hypersensitivity to valdecoxib. BEXTRA should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or NSAIDs. Severe, rarely fatal, anaphylactoid-like reactions to NSAIDs are possible in such patients (see WARNINGS—Anaphylactoid Reactions, and PRECAUTIONS—Preexisting Asthma).

**WARNINGS**

**Gastrointestinal (GI) Effects—Risk of GI Ulceration, Bleeding, and Perforation**

Serious gastrointestinal toxicity such as bleeding, ulceration and perforation of the stomach, small intestine or large intestine can occur at any time with or without warning symptoms in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor gastrointestinal problems such as dyspepsia are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding even in the absence of previous GI tract symptoms. Patients should be informed about the signs and symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation caused by NSAIDs appear to occur in approximately 1% of patients treated for 3 to 6 months and 2-4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status. (See CLINICAL STUDIES—Safety Studies.)

**Anaphylactoid Reactions**

Anaphylactoid reactions were not reported in patients receiving BEXTRA in clinical trials. However, as with NSAIDs in general, anaphylactoid reactions may occur in patients without known prior exposure to BEXTRA. BEXTRA should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic

**Table 3**  
Incidence of Endoscopic Gastroduodenal Ulcers in Patients With and Without Selected Risk Factors

Risk Factor	Placebo-controlled Studies		Active-controlled Studies			
	Placebo	Valdecoxib (10-20 mg daily)	Valdecoxib (10-80 mg daily)	Ibuprofen 800 mg TID	Naproxen 500 mg BID	Diclofenac 75 mg BID
<b>Age</b>						
<65 yrs	3.7% (8/219)	3.5% (17/484)	3.7% (48/1306)	8.2% (9/110)	12.8% (51/397)	13.2% (34/258)
≥65 yrs	5.8% (8/137)	4.6% (12/262)	7.6% (43/568)	21.6% (16/74)	22.0% (33/150)	18.2% (25/137)
<b>Concomitant Low Dose Aspirin Use</b>						
no	4.4% (13/298)	3.2% (21/650)	3.8% (64/1671)	9.8% (15/153)	16.0% (75/468)	12.8% (45/351)
yes	5.2% (3/58)	8.3% (8/96)	13.3% (27/203)	32.3% (10/31)	11.4% (9/79)	31.8% (14/44)
<b>History of Ulcer Disease</b>						
no	4.4% (14/317)	3.4% (22/647)	4.1% (68/1666)	13.8% (22/160)	13.3% (63/475)	14.7% (52/354)
yes	5.1% (2/39)	7.1% (7/99)	11.1% (23/208)	12.5% (3/24)	29.2% (21/72)	17.1% (7/41)

No statistical conclusions can be drawn from these comparisons.

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## valdecoxib tablets

patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS—Pre-existing Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

### Advanced Renal Disease

No information is available regarding the safe use of BEXTRA Tablets in patients with advanced kidney disease. Therefore, treatment with BEXTRA is not recommended in these patients. If therapy with BEXTRA must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS—Renal Effects).

### Pregnancy

In late pregnancy, BEXTRA should be avoided because it may cause premature closure of the ductus arteriosus.

## PRECAUTIONS

### General

BEXTRA Tablets cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of valdecoxib in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

### Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may remain transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs. In controlled clinical trials of valdecoxib, the incidence of borderline (defined as 1.2- to 3.0-fold) elevations of liver tests was 8.0% for valdecoxib and 8.4% for placebo, while approximately 0.3% of patients taking valdecoxib, and 0.2% of patients taking placebo, had notable (defined as greater than 3-fold) elevations of ALT or AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with BEXTRA. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash), BEXTRA should be discontinued.

### Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and Angiotensin Converting Enzyme (ACE) inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Caution should be used when initiating treatment with BEXTRA in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with BEXTRA. Caution is also recommended in patients with preexisting kidney disease. (See WARNINGS—Advanced Renal Disease.)

### Hematological Effects

Anemia is sometimes seen in patients receiving BEXTRA. Patients on long-term treatment with BEXTRA should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

BEXTRA does not generally affect platelet counts, prothrombin time (PT), or partial prothrombin time (PTT), and does not appear to inhibit platelet aggregation at indicated dosages (see CLINICAL STUDIES—Safety Studies—Platelets).

### Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking BEXTRA (see ADVERSE REACTIONS). Therefore, BEXTRA should be used with caution in patients with fluid retention, hypertension, or heart failure.

### Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been asso-

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## valdecoxib tablets

ciated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, BEXTRA should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

### Information for Patients

BEXTRA can cause GI discomfort and, rarely, more serious GI side effects, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS—Gastrointestinal (GI) Effects—Risk of GI Ulceration, Bleeding, and Perforation).

Patients should report to their physicians, signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, weight gain, or edema.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and flu-like symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical attention.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS—Anaphylactoid Reactions).

In late pregnancy, BEXTRA should be avoided because it may cause premature closure of the ductus arteriosus.

### Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs and symptoms of GI bleeding.

### Drug Interactions

The drug interaction studies with valdecoxib were performed both with valdecoxib and a rapidly hydrolyzed intravenous prodrug form. The results from trials using the intravenous prodrug are reported in this section as they relate to the role of valdecoxib in drug interactions.

**General:** In humans, valdecoxib metabolism is predominantly mediated via CYP 3A4 and 2C9 with glucuronidation being a further (20%) route of metabolism. In vitro studies indicate that valdecoxib is a moderate inhibitor of CYP 2C19 (IC<sub>50</sub> = 6 µg/mL), and a weak inhibitor of both 3A4 (IC<sub>50</sub> = 44 µg/mL) and 2C9 (IC<sub>50</sub> = 13 µg/mL). In view of the limitations of in vitro studies and the high valdecoxib IC<sub>50</sub> values, the potential for such metabolic inhibitory effects in vivo at therapeutic doses of valdecoxib is low.

**Aspirin:** Concomitant administration of aspirin with valdecoxib may result in an increased risk of GI ulceration and complications compared to valdecoxib alone. Because of its lack of anti-platelet effect valdecoxib is not a substitute for aspirin for cardiovascular prophylaxis.

In a parallel group drug interaction study comparing the intravenous prodrug form of valdecoxib at 40 mg BID (n=10) vs placebo (n=9), valdecoxib had no effect on in vitro aspirin-mediated inhibition of arachidonate- or collagen-stimulated platelet aggregation.

**Methotrexate:** Valdecoxib 10 mg BID did not show a significant effect on the plasma exposure or renal clearance of methotrexate.

**ACE-inhibitors:** Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking BEXTRA concomitantly with ACE-inhibitors.

**Furosemide:** Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

**Anticonvulsants:** Anticonvulsant drug interaction studies with valdecoxib have not been conducted. As with other drugs, routine monitoring should be performed when therapy with BEXTRA is either initiated or discontinued in patients on anticonvulsant therapy.

**Dextromethorphan:** Dextromethorphan is primarily metabolized by CYP 2D6 and to a lesser extent by 3A4. Coadministration with valdecoxib (40 mg BID for 7 days) resulted in a significant increase in dextromethorphan plasma levels suggesting that, at these doses, valdecoxib is a weak inhibitor of 2D6. Dextromethorphan plasma concentrations in the presence of high doses of valdecoxib were almost 5-fold lower than those seen in CYP 2D6 poor metabolizers.

**Lithium:** Valdecoxib 40 mg BID for 7 days produced significant decreases in lithium serum clearance (25%) and renal clearance (30%) with a 34% higher serum exposure compared to lithium alone. Lithium serum concentrations should be monitored closely when initiating or changing therapy with BEXTRA in patients receiving lithium. Lithium carbonate (450 mg BID for 7 days) had no effect on valdecoxib pharmacokinetics.

**Warfarin:** The effect of valdecoxib on the anticoagulant effect of war-

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### **valdecoxib tablets**

farin (1 – 8 mg/day) was studied in healthy subjects by coadministration of BEXTRA 40 mg BID for 7 days. Valdecoxib caused a statistically significant increase in plasma exposures of R-warfarin and S-warfarin (12% and 15%, respectively), and in the pharmacodynamic effects (prothrombin time, measured as INR) of warfarin. While mean INR values were only slightly increased with coadministration of valdecoxib, the day-to-day variability in individual INR values was increased. Anticoagulant therapy should be monitored, particularly during the first few weeks, after initiating therapy with BEXTRA in patients receiving warfarin or similar agents.

**Fluconazole and Ketoconazole:** Ketoconazole and fluconazole are predominantly CYP 3A4 and 2C9 inhibitors, respectively. Concomitant single dose administration of valdecoxib 20 mg with multiple doses of ketoconazole and fluconazole produced a significant increase in exposure of valdecoxib. Plasma exposure (AUC) to valdecoxib was increased 62% when coadministered with fluconazole and 38% when coadministered with ketoconazole.

**Glyburide:** Glyburide is a CYP 3A4 substrate. Coadministration of valdecoxib (10 mg BID for 7 days) with glyburide (5 mg QD or 10 mg BID) did not affect the pharmacokinetics (exposure) of glyburide.

#### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Valdecoxib was not carcinogenic in rats given oral doses up to 7.5 mg/kg/day for males and 1.5 mg/kg/day for females (equivalent to approximately 2- to 6-fold human exposure at 20 mg QD as measured by the  $AUC_{(0-24hr)}$ ) or in mice given oral doses up to 25 mg/kg/day for males and 50 mg/kg/day for females (equivalent to approximately 0.6- to 2.4-fold human exposure at 20 mg QD as measured by the  $AUC_{(0-24hr)}$ ) for two years.

Valdecoxib was not mutagenic in an Ames test or a mutation assay in Chinese hamster ovary (CHO) cells, nor was it clastogenic in a chromosome aberration assay in CHO cells or in an *in vivo* micronucleus test in rat bone marrow.

Valdecoxib did not impair male rat fertility at oral doses up to 9.0 mg/kg/day (equivalent to approximately 3- to 6-fold human exposure at 20 mg QD as measured by the  $AUC_{(0-24hr)}$ ). In female rats, a decrease in ovulation with increased pre- and post-implantation loss resulted in decreased live embryos/fetuses at doses  $\geq 2$  mg/kg/day (equivalent to approximately 2-fold human exposure at 20 mg QD as measured by the  $AUC_{(0-24hr)}$  for valdecoxib). The effects on female fertility were reversible. This effect is expected with inhibition of prostaglandin synthesis and is not the result of irreversible alteration of female reproductive function.

#### **Pregnancy**

##### **Teratogenic Effects: Pregnancy Category C.**

The incidence of fetuses with skeletal anomalies such as semipartite thoracic vertebra centra and fused sternbrae was slightly higher in rabbits at an oral dose of 40 mg/kg/day (equivalent to approximately 72-fold human exposures at 20 mg QD as measured by the  $AUC_{(0-24hr)}$ ) throughout organogenesis. Valdecoxib was not teratogenic in rabbits up to an oral dose of 10 mg/kg/day (equivalent to approximately 8-fold human exposures at 20 mg QD as measured by the  $AUC_{(0-24hr)}$ ).

Valdecoxib was not teratogenic in rats up to an oral dose of 10 mg/kg/day (equivalent to approximately 19-fold human exposure at 20 mg QD as measured by the  $AUC_{(0-24hr)}$ ). There are no studies in pregnant women. However, valdecoxib crosses the placenta in rats and rabbits. BEXTRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Non-teratogenic Effects:** Valdecoxib caused increased pre- and post-implantation loss with reduced live fetuses at oral doses  $\geq 10$  mg/kg/day (equivalent to approximately 19-fold human exposure at 20 mg QD as measured by the  $AUC_{(0-24hr)}$ ) in rats and an oral dose of 40 mg/kg/day (equivalent to approximately 72-fold human exposure at 20 mg QD as measured by the  $AUC_{(0-24hr)}$ ) in rabbits throughout organogenesis. In addition, reduced neonatal survival and decreased neonatal body weight when rats were treated with valdecoxib at oral doses  $\geq 6$  mg/kg/day (equivalent to approximately 7-fold human exposure at 20 mg QD as measured by the  $AUC_{(0-24hr)}$ ) throughout organogenesis and lactation period. No studies have been conducted to evaluate the effect of valdecoxib on the closure of the ductus arteriosus in humans. Therefore, as with other drugs known to inhibit prostaglandin synthesis, use of BEXTRA during the third trimester of pregnancy should be avoided.

#### **Labor and Delivery**

Valdecoxib produced no evidence of delayed labor or parturition at oral doses up to 10 mg/kg/day in rats (equivalent to approximately 19-fold human exposure at 20 mg QD as measured by the  $AUC_{(0-24hr)}$ ). The effects of BEXTRA on labor and delivery in pregnant women are unknown.

#### **Nursing Mothers**

Valdecoxib and its active metabolite are excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for adverse reactions in nursing infants from BEXTRA, a decision should be made whether to discontinue nurs-

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ing or to discontinue the drug, taking into account the importance of the drug to the mother and the importance of nursing to the infant.

**Pediatric Use**

Safety and effectiveness of BEXTRA in pediatric patients below the age of 18 years have not been evaluated.

**Geriatric Use**

Of the patients who received BEXTRA in arthritis clinical trials of three months duration, or greater, approximately 2100 were 65 years of age or older, including 570 patients who were 75 years or older. No overall differences in effectiveness were observed between these patients and younger patients.

**ADVERSE REACTIONS**

Of the patients treated with BEXTRA Tablets in controlled arthritis trials, 2665 were patients with OA, and 2684 were patients with RA. More than 4000 patients have received a chronic total daily dose of BEXTRA 10 mg or more. More than 2800 patients have received BEXTRA 10 mg/day, or more, for at least 6 months and 988 of these have received BEXTRA for at least 1 year.

**Osteoarthritis and Rheumatoid Arthritis**

Table 4 lists all adverse events, regardless of causality, that occurred in  $\geq 2.0\%$  of patients receiving BEXTRA 10 and 20 mg/day in studies of three months or longer from 7 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group.

In these placebo- and active-controlled clinical trials, the discontinuation rate due to adverse events was 7.5% for arthritis patients receiving valdecoxib 10 mg daily, 7.9% for arthritis patients receiving valdecoxib 20 mg daily and 6.0% for patients receiving placebo.

In the seven controlled OA and RA studies, the following adverse events occurred in 0.1–1.9% of patients treated with BEXTRA 10–20 mg daily, regardless of causality.

**Application site disorders:** Cellulitis, dermatitis contact

**Cardiovascular:** Aggravated hypertension, aneurysm, angina pectoris, arrhythmia, cardiomyopathy, congestive heart failure, coronary artery disorder, heart murmur, hypotension

**Central, peripheral nervous system:** Cerebrovascular disorder, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, tremor, twitching, vertigo

**Endocrine:** Gokter

**Female reproductive:** Amenorrhea, dysmenorrhea, leukorrhea,

mastitis, menstrual disorder, menorrhagia, menstrual bloating, vaginal hemorrhage

**Gastrointestinal:** Abnormal stools, constipation, diverticulosis, dry mouth, duodenal ulcer, duodenitis, eructation, esophagitis, fecal incontinence, gastric ulcer, gastritis, gastroenteritis, gastroesophageal reflux, hematemesis, hematochezia, hemorrhoids, hemorrhoids bleeding, hiatal hernia, melena, stomatitis, stool frequency increased, tenesmus, tooth disorder, vomiting

**General:** Allergy aggravated, allergic reaction, asthenia, chest pain, chills, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, halitosis, malaise, pain, periorbital swelling, peripheral pain

**Hearing and vestibular:** Ear abnormality, earache, tinnitus

**Heart rate and rhythm:** Bradycardia, palpitation, tachycardia

**Hemic:** Anemia

**Liver and biliary system:** Hepatic function abnormal, hepatitis, ALT increased, AST increased

**Male reproductive:** Impotence, prostatic disorder

**Metabolic and nutritional:** Alkaline phosphatase increased, BUN increased, CPK increased, creatinine increased, diabetes mellitus, glycosuria, gout, hypercholesterolemia, hyperglycemia, hyperkalemia, hyperlipemia, hyperuricemia, hypocalcemia, hypokalemia, LDH increased, thirst increased, weight decrease, weight increase, xerophthalmia

**Musculoskeletal:** Arthralgia, fracture accidental, neck stiffness, osteoporosis, synovitis, tendonitis

**Neoplasm:** Breast neoplasm, lipoma, malignant ovarian cyst

**Platelets (bleeding or clotting):** Ecchymosis, epistaxis, hematoma NOS, thrombocytopenia

**Psychiatric:** Anorexia, anxiety, appetite increased, confusion, depression, depression aggravated, insomnia, nervousness, morbid dreaming, somnolence

**Resistance mechanism disorders:** Herpes simplex, herpes zoster, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media

**Respiratory:** Abnormal breath sounds, bronchitis, bronchospasm, coughing, dyspnea, emphysema, laryngitis, pneumonia, pharyngitis, pleurisy, rhinitis

**Skin and appendages:** Acne, alopecia, dermatitis, dermatitis fungal, eczema, photosensitivity allergic reaction, pruritus, rash erythematous, rash maculopapular, rash psoriaform, skin dry, skin hypertrophy, skin ulceration, sweating increased, urticaria

**Special senses:** Taste perversion

**Table 4**  
Adverse Events with Incidence  $\geq 2.0\%$  in Valdecoxib Treatment Groups:  
Controlled Arthritis Trials of Three Months or Longer

Adverse Event	Placebo	(Total Daily Dose)				
		Valdecoxib		Diclofenac	Ibuprofen	Naproxen
Number Treated	973	1214	1358	711	207	766
<b>Autonomic Nervous System Disorders</b>						
Hypertension	0.6	1.6	2.1	2.5	2.4	1.7
<b>Body as a Whole</b>						
Back pain	1.6	1.6	2.7	2.8	1.4	1.0
Edema peripheral	0.7	2.4	3.0	3.2	2.9	2.1
Influenza-like symptoms	2.2	2.0	2.2	3.1	2.9	2.0
Injury accidental	2.8	4.0	3.7	3.9	3.9	3.0
<b>Central and Peripheral Nervous System Disorders</b>						
Dizziness	2.1	2.6	2.7	4.2	3.4	2.7
Headache	7.1	4.8	8.5	6.6	4.3	5.5
<b>Gastrointestinal System Disorders</b>						
Abdominal fullness	2.0	2.1	1.9	3.0	2.9	2.5
Abdominal pain	6.3	7.0	8.2	17.0	8.2	10.1
Diarrhea	4.2	5.4	6.0	10.8	3.9	4.7
Dyspepsia	6.3	7.9	8.7	13.4	15.0	12.9
Flatulence	4.1	2.9	3.5	3.1	7.7	5.4
Nausea	5.9	7.0	6.3	8.4	7.7	8.7
<b>Musculoskeletal System Disorders</b>						
Myalgia	1.6	2.0	1.9	2.4	2.4	1.4
<b>Respiratory System Disorders</b>						
Sinusitis	2.2	2.6	1.8	1.1	3.4	3.4
Upper respiratory tract infection	6.0	6.7	5.7	6.3	4.3	6.4
<b>Skin and Appendages Disorders</b>						
Rash	1.0	1.4	2.1	1.5	0.5	1.4

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**Urinary system:** Albuminuria, cystitis, dysuria, hematuria, micturition frequency increased, pyuria, urinary incontinence, urinary tract infection

**Vascular:** Claudication intermittent, hemangioma acquired, varicose vein

**Vision:** Blurred vision, cataract, conjunctival hemorrhage, conjunctivitis, eye pain, keratitis, vision abnormal

**White cell and RES disorders:** Eosinophilia, leukopenia, leukocytosis, lymphadenopathy, lymphangitis, lymphopenia

Other serious adverse events that were reported rarely (estimated <0.1%) in clinical trials, regardless of causality, in patients taking BEXTRA:

**Autonomic nervous system disorders:** Hypertensive encephalopathy, vasospasm

**Cardiovascular:** Abnormal ECG, aortic stenosis, atrial fibrillation, carotid stenosis, coronary thrombosis, heart block, heart valve disorders, mitral insufficiency, myocardial infarction, myocardial ischemia, pericarditis, syncope, thrombophlebitis, unstable angina, ventricular fibrillation

**Central, peripheral nervous system:** Convulsions

**Endocrine:** Hyperparathyroidism

**Female reproductive:** Cervical dysplasia

**Gastrointestinal:** Appendicitis, colitis with bleeding, dysphagia, esophageal perforation, gastrointestinal bleeding, ileus, intestinal obstruction, peritonitis

**Hemic:** Lymphoma-like disorder, pancytopenia

**Liver and biliary system:** Cholelithiasis

**Metabolic:** Dehydration

**Musculoskeletal:** Pathological fracture, osteomyelitis

**Neoplasm:** Benign brain neoplasm, bladder carcinoma, carcinoma, gastric carcinoma, prostate carcinoma, pulmonary carcinoma

**Platelets (bleeding or clotting):** Embolism, pulmonary embolism, thrombosis

**Psychiatric:** Manic reaction, psychosis

**Renal:** Acute renal failure

**Resistance mechanism disorders:** Sepsis

**Respiratory:** Apnea, pleural effusion, pulmonary edema, pulmonary fibrosis, pulmonary infarction, pulmonary hemorrhage, respiratory insufficiency

**Skin:** Basal cell carcinoma, malignant melanoma

**Urinary system:** Pyelonephritis, renal calculus

**Vision:** Retinal detachment

## OVERDOSAGE

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare.

Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Hemodialysis removed only about 2% of administered valdecoxib from the systemic circulation of 8 patients with end-stage renal disease and, based on its degree of plasma protein binding (>98%), dialysis is unlikely to be useful in overdose. Forced diuresis, alkalization of urine, or hemoperfusion also may not be useful due to high protein binding.

## DOSAGE AND ADMINISTRATION

### Osteoarthritis and Adult Rheumatoid Arthritis

The recommended dose of BEXTRA Tablets for the relief of the signs and symptoms of arthritis is 10 mg once daily.

### Primary Dysmenorrhea

The recommended dose of BEXTRA Tablets for treatment of primary dysmenorrhea is 20 mg twice daily, as needed.

## HOW SUPPLIED

BEXTRA Tablets 10 mg are white, film-coated, and capsule-shaped, debossed "10" on one side with a four pointed star shape on the other, supplied as:

NDC Number	Size
0025-1975-31	Bottle of 100
0025-1975-51	Bottle of 500
0025-1975-34	Carton of 100 unit dose

BEXTRA Tablets 20 mg are white, film-coated, and capsule-shaped, debossed "20" on one side with a four pointed star shape on the other, supplied as:

NDC Number	Size
0025-1980-31	Bottle of 100
0025-1980-51	Bottle of 500
0025-1980-34	Carton of 100 unit dose

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

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**R<sub>x</sub>** only

November 2001

Manufactured for:  
G.D. Searle LLC  
A subsidiary of Pharmacia Corporation  
Chicago, IL 60680, USA  
Pfizer Inc.  
New York, NY 10017, USA

by: Searle Ltd.  
Caguas, PR 00725

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**EXHIBIT II**

**Copy of U.S. Patent 5,633,272**

**United States Patent** [19]

Talley et al.

[11] Patent Number: **5,633,272**

[45] Date of Patent: **May 27, 1997**

[54] **SUBSTITUTED ISOXAZOLES FOR THE TREATMENT OF INFLAMMATION**

[76] Inventors: John J. Talley, 8772 Pine Ave., Brentwood, Mo. 63144; David L. Brown, 15504 Twingate, Chesterfield, Mo. 63017; Srinivasan Nagarajan, 16209 Forest Meadows Dr., Chesterfield, Mo. 63017; Jeffery S. Carter, 15321 Grantley Dr., Chesterfield, Mo. 63017; Richard M. Weier, 240 Hickory Ct., Lake Bluff, Ill. 60044; Michael A. Stealey, 502 Juniper Pkwy., Libertyville, Ill. 60048; Paul W. Collins, 1557 Hawthorne Pl., Deerfield, Ill. 60015; Roland S. Rogers, deceased, late of Richmond Heights, Mo. 63117, by Kathy L. Rogers, legal representative; Karen Seibert, 11930 Greenwalk Dr., St. Louis, Mo. 63146

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Primary Examiner—Johann Richter  
Assistant Examiner—Laura L. Stockton  
Attorney, Agent, or Firm—Joseph W. Bullock

[21] Appl. No.: 473,884

[22] Filed: Jun. 7, 1995

**Related U.S. Application Data**

[63] Continuation-in-part of Ser. No. 387,680, Feb. 13, 1995, abandoned.

[51] Int. Cl.<sup>6</sup> ..... C07D 261/06; C07D 261/10; C07D 261/12; C07D 261/14; A61K 31/42

[52] U.S. Cl. .... 514/378; 548/182; 548/186; 548/190; 548/193; 548/202; 548/203; 548/225; 548/228; 548/229; 548/232; 548/234; 548/235; 548/243; 548/245; 548/247; 548/248; 546/272.1; 544/405; 514/255; 514/340; 514/365; 514/369; 514/370; 514/374; 514/376; 514/377; 514/380

[58] Field of Search ..... 548/247, 243, 548/245, 248; 514/380, 378

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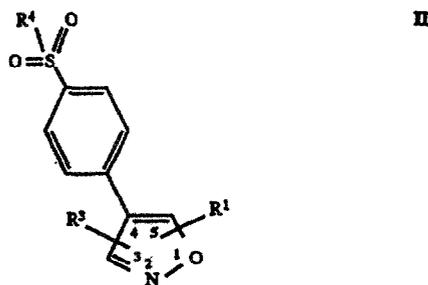
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[57] **ABSTRACT**

A class of substituted isoxazolyl compounds is described for use in treating inflammation and inflammation-related disorders. Compounds of particular interest are defined by Formula II



wherein R<sup>1</sup> is selected from hydroxyl, lower alkyl, carboxyl, lower carboxyalkyl, lower aminocarbonylalkyl, lower alkoxyalkyl, lower haloalkyl, lower hydroxyalkyl, lower alkoxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower aryloxyalkyl, lower arylthioalkyl, lower haloalkyl, lower hydroxyalkyl, cycloalkyl, cycloalkylalkyl, and aralkyl; wherein R<sup>2</sup> is selected from cycloalkyl, cycloalkenyl, aryl, and heteroaryl; wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfanyl, lower alkyl, cyano, carboxyl, lower alkoxyalkyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy, aminosulfonyl, and lower alkylthio; and wherein R<sup>4</sup> is selected from lower alkyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

29 Claims, No Drawings

1  
**SUBSTITUTED ISOXAZOLES FOR THE  
 TREATMENT OF INFLAMMATION**

RELATED CASE

This application is a continuation-in part of U.S. patent application Ser. No. 08/387,680, filed Feb. 13, 1995 now abandoned.

FIELD OF THE INVENTION

This invention is in the field of antiinflammatory pharmaceutical agents and specifically relates to compounds, compositions and methods for treating inflammation and inflammation-associated disorders, such as arthritis.

BACKGROUND OF THE INVENTION

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG<sub>2</sub>, PGH<sub>2</sub> and PGE<sub>2</sub>, has been a common target of antiinflammatory drug discovery. However, common non-steroidal antiinflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 (COX-2)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.

The references below that disclose antiinflammatory activity, show continuing efforts to find a safe and effective antiinflammatory agent. The novel isoxazoles disclosed herein are such safe and also effective antiinflammatory agents furthering such efforts. The invention's compounds are found to show usefulness in vivo as antiinflammatory agents with minimal side effects. The substituted isoxazolyl compounds disclosed herein preferably selectively inhibit cyclooxygenase-2 over cyclooxygenase-1.

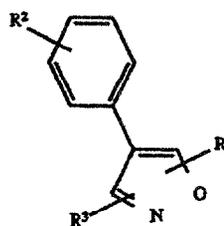
Isoxazoles have been described for various uses, including the treatment of inflammation. U.S. Pat. No. DE 4,314,966, published Nov. 10, 1994, describes 3-(2-hydroxyphenyl)isoxazoles for the treatment of inflammatory disorders. WO 92/05162, published Apr. 4, 1992, describes 5-piperazinyl-3,4-diaryl-isoxazoles as having medicinal use.

WO 92/19604, published Nov. 12, 1992, describes 5-alkene-3,4-diaryl-isoxazoles as having cyclooxygenase inhibition activity. EP 26928, published Apr. 15, 1981, describes 3,4-diaryl-isoxazole-5-acetic acids as having anti-inflammatory activity. WO 95/00501, published Jan. 5, 1995, generically describes 3,4-diaryl-isoxazoles as cyclooxygenase inhibitors.

The invention's isoxazolyl compounds are found to show usefulness in vivo as antiinflammatory agents with minimal side effects.

2  
**DESCRIPTION OF THE INVENTION**

A class of substituted isoxazolyl compounds useful in treating inflammation-related disorders is defined by Formula I:



wherein R<sup>1</sup> is selected from hydroxyl, amino, alkyl, carboxyalkyl, alkoxy carbonyl, aminocarbonyl, aminocarbonylalkyl, alkoxy carbonylalkyl, carboxyl, alkoxy, haloalkoxy, aralkoxy, heteroaralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, heteroaralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, arylalkyl, arylthioalkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocyclo, heterocycloalkyl, aryl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, heteroaralkylamino, N-alkyl-N-heteroaralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonylthio, alkylaminocarbonylthioalkyl, arylcarbonyloxyalkyl, alkoxy carbonyloxyalkyl, alkylaminocarbonyloxyalkyl, alkoxy carbonylthioalkyl, and alkylaminocarbonylthioalkyl;

wherein R<sup>2</sup> is one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxy carbonyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, aminoalkyl, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, hydroxysulfonyl, alkylsulfonyl, aminosulfonyl, haloalkylsulfonyl, alkoxy and alkylthio;

wherein R<sup>3</sup> is selected from cycloalkyl, cycloalkenyl, aryl and heterocyclo; wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxy carbonyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, aminoalkyl, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, aminosulfonyl, halo, alkoxy and alkylthio;

or a pharmaceutically-acceptable salt thereof.

Compounds of Formula I would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of Formula I would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such compounds of Formula I would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns and dermatitis. Compounds of Formula I also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention of colorectal cancer. Compounds of Formula I would be useful in treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome,

polymyositis, gingivitis, hypersensitivity, conjunctivitis, swelling occurring after injury, myocardial ischemia, and the like. The compounds are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. Besides being useful for human treatment, these compounds are also useful for treatment of mammals, including horses, dogs, cats, rats, mice, sheep, pigs, etc.

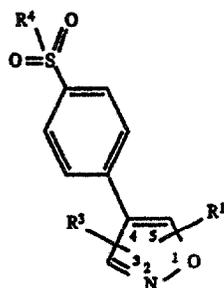
The present compounds may also be used in co-therapies, partially or completely, in place of other conventional antiinflammatories, such as together with steroids, NSAIDs, 5-lipoxygenase inhibitors, LTB<sub>4</sub> antagonists and LTA<sub>4</sub> hydrolase inhibitors.

Suitable LTB<sub>4</sub> inhibitors include, among others, ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, Terumo compound TMK-688, Lilly compounds LY-213024, 264086 and 292728, ONO compound ONO-LB457, Searle compound SC-53228, calcitrol, Lilly compounds LY-210073, LY223982, LY233469, and LY255283, ONO compound ONO-LB-448, Searle compounds SC-41930, SC-50605 and SC-51146, and SK&F compound SKF-104493. Preferably, the LTB<sub>4</sub> inhibitors are selected from ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, and Terumo compound TMK-688.

Suitable 5-LO inhibitors include, among others, masoprocil, tenidap, zileuton, pranlukast, tepoxalin, rilopirox, flizelastine hydrochloride, enazadrem phosphate, and bunaprolast.

The present invention preferably includes compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC<sub>50</sub> of less than about 0.5 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC<sub>50</sub> of greater than about 1 μM, and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

Within Formula I there is a subclass of compounds of high interest represented by Formula II:



wherein R<sup>1</sup> is selected from alkyl, carboxyalkyl, alkoxy carbonyl, aminocarbonyl, aminocarbonylalkyl, alkoxy carbonylalkyl, carboxyl, alkoxy, haloalkoxy, aralkoxy, heteroaralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, heteroaralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, aryloxyalkyl, arylthioalkyl, hydroxyl, amino, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocyclo, heterocycloalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, heteroaralkylamino,

N-alkyl-N-heteroaralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxy carbonyloxyalkyl, alkylaminocarbonyloxyalkyl, alkoxy carbonylthioalkyl, and alkylaminocarbonylthioalkyl;

wherein R<sup>3</sup> is selected from cycloalkyl, cycloalkenyl, aryl and heterocyclo; wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxy carbonyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfanyl, alkylsulfonyl, aminosulfonyl, halo, alkoxy and alkylthio; and

wherein R<sup>4</sup> is selected from alkyl, hydroxyl, and amino; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds consists of those compounds of Formula II wherein R<sup>1</sup> is selected from hydroxyl, amino, lower alkyl, lower carboxyalkyl, lower alkoxy carbonyl, aminocarbonyl, carboxyl, lower aminocarbonylalkyl, lower alkoxy carbonylalkyl, lower alkoxy, lower haloalkoxy, lower aralkoxy, lower heteroaralkoxy, lower cycloalkylalkoxy, lower alkylthio, lower aralkylthio, lower heteroaralkylthio, lower cycloalkylalkylthio, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower arylthioalkyl, lower hydroxyalkyl, lower haloalkyl, lower cycloalkyl, lower cycloalkylalkyl, 5- or 6-membered heterocyclo, lower heterocycloalkyl, lower aralkyl, halo, lower alkylamino, lower aralkylamino, lower N-alkyl-N-aralkylamino, lower heteroaralkylamino, lower N-alkyl-N-heteroaralkylamino, lower N-alkyl-N-cycloalkylalkylamino, lower arylcarbonyloxyalkyl, lower alkoxy carbonyloxyalkyl, lower

alkylaminocarbonyloxyalkyl, lower alkoxy carbonylthioalkyl, and lower alkylaminocarbonylthioalkyl; wherein R<sup>2</sup> is selected from cycloalkyl, cycloalkenyl, aryl, and heteroaryl; wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfanyl, lower alkyl, cyano, carboxyl, lower alkoxy carbonyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy, lower alkylsulfonyl, aminosulfonyl, and lower alkylthio; and wherein R<sup>4</sup> is selected from lower alkyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

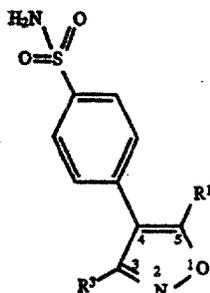
A more preferred class of compounds consists of those compounds of Formula II wherein R<sup>1</sup> is selected from hydroxyl, lower alkyl, carboxyl, lower carboxyalkyl, lower aminocarbonylalkyl, lower alkoxy carbonylalkyl, lower aralkyl, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower aryloxyalkyl, lower arylthioalkyl, lower haloalkyl, lower hydroxyalkyl, cycloalkyl, cycloalkylalkyl, and aralkyl; wherein R<sup>2</sup> is selected from cycloalkyl, cycloalkenyl, aryl, and heteroaryl; wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfanyl, lower alkyl, cyano, carboxyl, lower alkoxy carbonyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy, aminosulfonyl, and lower alkylthio; and wherein R<sup>4</sup> is selected from lower alkyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula II wherein R<sup>1</sup> is selected from

5

hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, benzyl, phenethyl, aminocarbonylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, methoxymethyl, benzoxymethyl, phenylethoxymethyl, methylthiomethyl, benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, phenyloxymethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxylmethyl, hydroxylpropyl, hydroxylethyl, cyclohexyl, cyclobutyl, cyclopentyl, cycloheptyl, cyclohexylmethyl, cyclohexylethyl, cyclobutylethyl, cyclopentylmethyl, cycloheptylpropyl, and lower aralkyl selected from benzyl and phenylethyl, wherein the phenyl ring is optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methyl, and methoxy; wherein R<sup>3</sup> is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, 1-cyclopentenyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl and pyrazinyl; wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, aminosulfonyl, methylthio, ethylthio, butylthio, and hexylthio; and wherein R<sup>4</sup> is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

Within Formula I there is a subclass of compounds of high interest represented by Formula III:



wherein R<sup>1</sup> is selected from hydroxyl, alkyl, carboxyalkyl, aminocarbonylalkyl, alkoxyalkyl, carboxyl, alkoxy, haloalkoxy, aralkoxy, heteroaralkoxy, cycloalkylalkoxy, alkylthio, heteroaralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, aryloxyalkyl, arylthioalkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocyclo, heterocycloalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, heteroaralkylamino, N-alkyl-N-heteroaralkylamino, alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxyalkoxyalkyl, alkylaminocarbonyloxyalkyl, alkoxyalkylthioalkyl, and alkylaminocarbonylthioalkyl; and

6

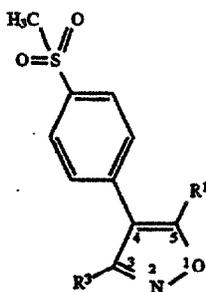
wherein R<sup>2</sup> is selected from cycloalkyl, cycloalkenyl, aryl and heterocyclo; wherein R<sup>2</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, aminosulfonyl, halo, alkoxy and alkylthio; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds consists of those compounds of Formula III wherein R<sup>1</sup> is selected from hydroxyl, lower alkyl, carboxyl, lower carboxyalkyl, lower aminocarbonylalkyl, lower alkoxyalkyl, lower aralkyl, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower aryloxyalkyl, lower arylthioalkyl, lower haloalkyl, lower hydroxyalkyl, lower cycloalkyl, lower cycloalkylalkyl, and aralkyl; wherein R<sup>2</sup> is selected from cycloalkyl, cycloalkenyl, aryl, and heteroaryl; and wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, aminosulfonyl, lower alkyl, cyano, carboxyl, lower alkoxyalkyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy and lower alkylthio; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula III wherein R<sup>1</sup> is selected from hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, benzyl, phenethyl, aminocarbonylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, methoxymethyl, benzoxymethyl, phenylethoxymethyl, methylthiomethyl, benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, phenyloxymethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxylmethyl, hydroxylpropyl, hydroxylethyl, cyclohexyl, cyclobutyl, cyclopentyl, cycloheptyl, cyclohexylmethyl, cyclohexylethyl, cyclobutylethyl, cyclopentylmethyl, cycloheptylpropyl, and lower aralkyl selected from benzyl and phenylethyl and benzyl optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methyl, and methoxy; and wherein R<sup>2</sup> is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, 1-cyclopentenyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl and pyrazinyl; wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, aminomethyl, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, methylthio, aminosulfonyl, ethylthio, butylthio, and hexylthio; or a pharmaceutically-acceptable salt thereof.

A class of compounds of more particular interest consists of those compounds of Formula III wherein  $R^1$  is selected from methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, hydroxymethyl, hydroxypropyl, methoxymethyl, difluoromethyl, trifluoromethyl, chloromethyl, cyclohexyl, cyclohexylmethyl, 4-chlorobenzyl, 3-chlorobenzyl, 4-methylbenzyl, 4-methoxybenzyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, methoxycarbonylmethyl, and ethoxycarbonyl ethyl; wherein  $R^2$  is phenyl; wherein  $R^3$  is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, aminosulfonyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, aminomethyl, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, methylthio, ethylthio, butylthio, and hexylthio; or a pharmaceutically-acceptable salt thereof.

Within Formula I there is a subclass of compounds of high interest represented by Formula IV:



wherein  $R^1$  is selected from alkyl and carboxyalkyl; and wherein  $R^2$  is selected from cycloalkyl, cycloalkenyl, aryl and heterocyclo; wherein  $R^3$  is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxy, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, aminosulfonyl, halo, alkoxy and alkylthio; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as follows:

- [3-(3-fluoro-4-methoxyphenyl)-4-phenyl-isoxazol-5-yl] propanoic acid;
- [3,4-diphenylisoxazol-5-yl]propanoic acid;
- 3-(3-fluoro-4-methoxyphenyl)-5-methyl-4-phenylisoxazole;
- 5-methyl-4-[4-(methylthio)phenyl]-3-phenylisoxazole;
- 3-(3-fluoro-4-methoxyphenyl)-5-methyl-4-[4-(methylthio)phenyl]isoxazole;
- 3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylthio)phenyl]isoxazole;
- [4-[4-(methylthio)phenyl]-3-phenylisoxazol-5-yl]acetic acid;
- (3,4-diphenylisoxazol-5-yl)acetic acid;
- [3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid;

- [3-(3-chloro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid;
- 5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenyl-isoxazole;
- 3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
- 3-(3-chloro-4-methoxyphenyl)-5-ethyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
- 3-(3-fluoro-4-methoxyphenyl)-5-ethyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
- 3-(3,4-dichlorophenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
- 3-(3,4-difluorophenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
- 3-(3,5-difluoro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
- 3-(4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
- 3-(4-chlorophenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
- 3-(4-fluorophenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
- 3-(4-methylphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
- 4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-isopropyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-isobutyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-cyclohexyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-neopentyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-trifluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-chloromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;
- 4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;
- 4-[5-methoxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
- 4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
- 4-[3-(3-fluoro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
- 4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
- 4-[3-(3-chloro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
- 4-[5-methyl-3-(3-pyridyl)isoxazol-4-yl]benzenesulfonamide;
- 4-[5-methyl-3-(4-pyridyl)-isoxazol-4-yl]benzenesulfonamide;
- 4-[3-(3-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
- 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]carboxylic acid;
- 4-[5-hydroxy-3-phenyl-4-isoxazolyl]benzenesulfonamide;

4-[3-methyl-5-phenyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-fluoro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3,5-difluoro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-chloro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3,5-dichloro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[5-methyl-3-(4-trifluoromethoxyphenyl)-isoxazol-4-yl]benzenesulfonamide;  
 4-[5-methyl-3-(4-trifluoromethylphenyl)-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(4-cyanophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(4-methylsulfinylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(4-methylthiophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(4-hydroxymethylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[5-ethyl-3-(3-fluoro-4-methoxyphenyl)isoxazol-4-yl]benzenesulfonamide;  
 4-[5-benzyl-3-(3-fluoro-4-methoxyphenyl)isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-fluoro-4-methoxyphenyl)-5-methoxy-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-fluoro-4-methoxyphenyl)-5-phenoxy-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[5-benzyloxymethyl-3-(3-fluoro-4-methoxyphenyl)-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-fluoro-4-methoxyphenyl)-5-methoxymethyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-fluoro-4-methoxyphenyl)-5-methylthiomethyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-fluoro-4-methoxyphenyl)-5-(3-thienyl) methylthio-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-fluoro-4-methoxyphenyl)-5-methoxycarbonylmethyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[5-(aminocarbonylmethyl)-3-(3-fluoro-4-methoxyphenyl)-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-fluoro-4-methoxyphenyl)-5-methylthio-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-fluoro-4-methoxyphenyl)-5-(trifluoromethoxy)isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-fluoro-4-methoxyphenyl)-5-(N-methylamino)isoxazol-4-yl]benzenesulfonamide;  
 [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]acetic acid;  
 [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]carboxamide;  
 methyl [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]acetate;  
 [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoic acid;  
 ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoate; and  
 [4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid.

A second family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as follows:

4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
 4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
 4-[5-isopropyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
 4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
 4-[5-isobutyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
 4-[5-cyclohexyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
 4-[5-neopentyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
 4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
 4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
 4-[5-trifluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
 4-[5-chloromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;  
 4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;  
 4-[5-methoxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
 4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;  
 4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-fluoro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-chloro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[5-methyl-3-(3-pyridyl)isoxazol-4-yl]benzenesulfonamide;  
 4-[5-methyl-3-(4-pyridyl)-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
 [4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]carboxylic acid;  
 4-[5-hydroxy-3-phenyl-4-isoxazolyl]benzenesulfonamide;  
 4-[3-methyl-5-phenyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;  
 4-[3-(3-fluoro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 [3-(3-chloro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid;  
 5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenyl-isoxazole;  
 3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;  
 [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]acetic acid;  
 [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoic acid;  
 ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoate;  
 [4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid; and  
 [3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido

radicals may be attached to a carbon atom to form a methylene ( $-\text{CH}_2-$ ) radical. Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. The term "cycloalkyl" embraces saturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The terms "hydroxyalkyl" and "hydroxylalkyl" embrace linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "cycloalkoxy" embraces radicals having cycloalkyl radicals, as defined above, attached to an alkoxy radical. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. The terms "heterocyclic" and "heterocyclo" embrace saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen.

Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3-to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclic group" may have 1 to 3 substituents such as lower alkyl, hydroxy, oxo, amino and lower alkylamino. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylthioalkyl" embraces radicals containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl. The term "cycloalkylalkylthio" embraces radicals having cycloalkyl radicals, as defined above, attached to an alkylthio radical. More preferred cycloalkylthio radicals are "lower cycloalkylalkylthio" radicals having cycloalkyl radicals of three to six carbon atoms. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent  $-\text{S}(=\text{O})-$  radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl

radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals  $-\text{SO}_2-$ . "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denote  $\text{NH}_2\text{O}_2\text{S}-$ . The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes  $-\text{CO}_2\text{H}$ . The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes  $-(\text{C}=\text{O})-$ . The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Examples of such "alkoxycarbonyl" ester radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The term "alkoxycarbonylalkyl" means a radical containing an alkoxycarbonyl radical, as defined above, attached to an alkyl radical. Examples of such "alkoxycarbonylalkyl" ester radicals include substituted or unsubstituted methoxycarbonylmethyl, butoxycarbonylmethyl and hexyloxycarbonylethyl. The terms "alkylcarbonyl", "arylcabonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached via an oxygen atom to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, phenylcarbonyl and benzylcarbonyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable. The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals, such as pyrrolidinylmethyl, piperazinylmethyl, piperidinylmethyl, furanylethyl, tetrahydrofurylethyl and heteroaralkyl radicals. The term "heteroaralkyl" embraces heteroaryl-substituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The term "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals such as cyclohexylmethyl, cyclopentylethyl, cyclopentylmethyl, cyclohexylethyl, and cyclobutylpropyl. The term "aralkoxy" embraces aralkyl radicals attached through an oxygen atom to other radicals. The term "aralkoxyalkyl" embraces aralkoxy radicals attached through an oxygen atom to an alkyl radical. The term "aralkylthio" embraces aralkyl radicals attached to a sulfur atom. The term "aralkylthioalkyl" embraces aralkylthio radicals attached through a sulfur atom to an alkyl radical. The term "heteroaralkoxy" embraces heteroaralkyl radicals attached through an oxygen atom to other radicals. The term "heteroaralkylthio" embraces heteroaralkyl radicals attached through a sulfur atom to other radicals. The term "aminoalkyl" embraces alkyl radicals

substituted with amino radicals. The term "alkylamino" denotes amino groups which have been substituted with one or two alkyl radicals. Suitable "alkylamino" may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "cycloalkylamino" denotes amino groups which have been substituted with one or two cycloalkyl radicals, as defined above. The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aralkylamino" embraces aralkyl radicals attached through an nitrogen atom to other radicals. The term "heteroaralkylamino" embraces heteroaralkyl radicals, as defined above, attached through an nitrogen atom to other radicals. The term "aminocarbonyl" denotes an amide group of the formula  $-\text{C}(=\text{O})\text{NH}_2$ . The term "alkylcarbonylaminoalkyl" embraces radicals having one or more alkyl radicals attached to a carbonyl radical further attached to an aminoalkyl radical. The term "alkylaminoalkyl" embraces radicals having one or more alkyl radicals attached to an aminoalkyl radical. The term "aryloxyalkyl" embraces radicals having an aryl radicals attached to an alkyl radical through a divalent oxygen atom. The term "arylthioalkyl" embraces radicals having an aryl radicals attached to an alkyl radical through a divalent sulfur atom.

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formulas I-IV in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

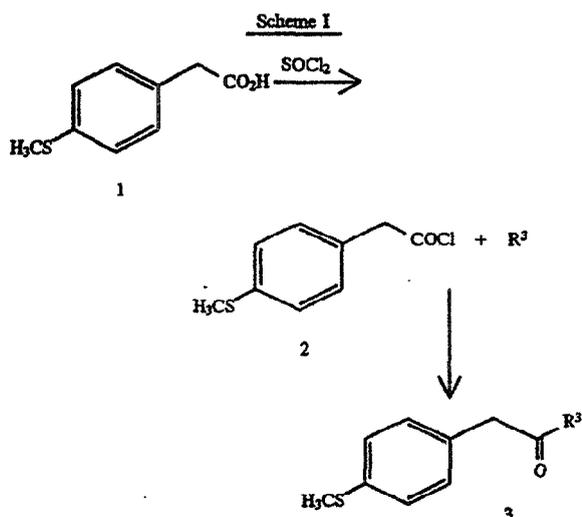
The present invention also comprises a method of treating inflammation or inflammation-associated disorders in a subject, the method comprising administering to the subject having such inflammation or disorder a therapeutically-effective amount of a compound of Formulas I-IV.

Also included in the family of compounds of Formulas I-IV are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formulas I-IV may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic,  $\beta$ -hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formulas I-IV include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formulas I-IV by reacting, for example, the appropriate acid or base with the compound of Formulas I-IV.

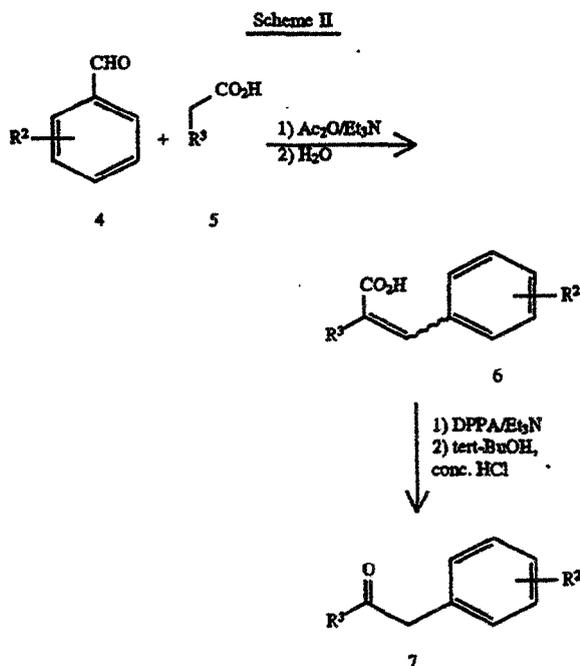
15

## GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the following procedures of Schemes I-XIII, wherein the R<sup>1</sup>-R<sup>4</sup> substituents are as defined for Formulas I-IV, above, except where further noted.



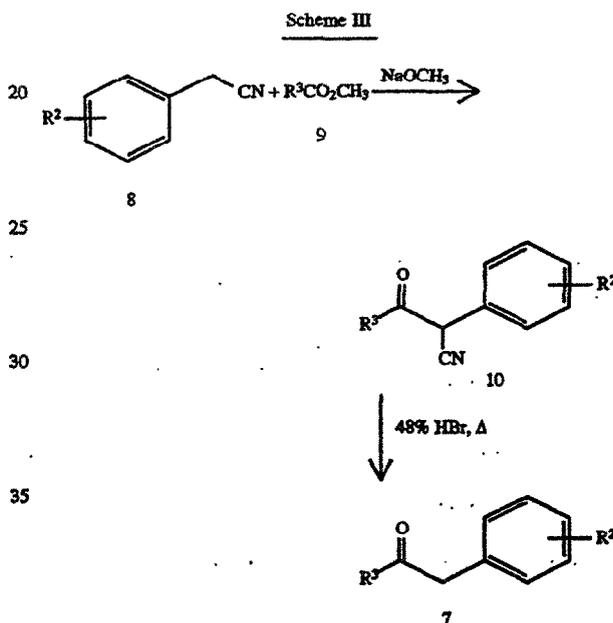
Scheme I illustrates the two step procedure used to prepare substituted desoxybenzoin derivatives 3. In step one, 4-methylthiophenylacetic acid 1 is converted to the corresponding acid chloride 2 with thionyl chloride. A variety of aromatic compounds are then acylated with 2 in the presence of a Lewis acid such as aluminum chloride to provide the desired desoxybenzoins 3 in high yield. This Friedel Crafts acylation can be performed in an inert solvent, such as dichloromethane, chloroform, nitrobenzene, 1,2-dichloroethane, 1,2-dichlorobenzene and similar solvents.



Synthetic Scheme II shows the four step procedure which can be used to prepare substituted ketone compounds 7 from

16

aldehyde 4 and acid 5. In step one, aldehyde 4 and substituted acetic acid 5 are heated together in acetic anhydride and triethylamine to form the 2,3-disubstituted acrylic acids 6 via a Perkin condensation. In step two, the addition of water produces the acids 6 free from any mixed acetic-acrylic anhydrides. In step three, the acrylic acids 6 are reacted with diphenylphosphoryl azide (DPPA) and triethylamine in toluene at about 0° C. and then at room temperature to form acylazides. In step four, the crude acylazides are heated to form a vinyl isocyanate via a Curtius rearrangement. The vinyl isocyanates are trapped with tert-butyl alcohol to produce N-tert-butoxycarbonyl enamine derivatives. Acidic hydrolysis using concentrated HCl provides the substituted ketone 7 intermediates.

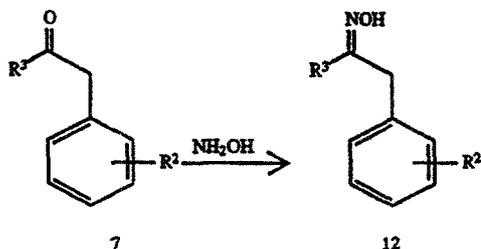


Synthetic Scheme III illustrates an alternative approach which can be used to prepare substituted ketone intermediates 7 via the Claisen reaction of a substituted phenylacetonitrile 8 and an acid ester 9. In the first step, a mixture of substituted phenylacetonitrile 8 and acid ester 9 are treated with a base such as sodium methoxide in a protic solvent like methanol to provide the cyanoketone 10. In step two, the cyanoketone 10 is hydrolyzed in aqueous acid such as concentrated HBr to effect hydrolysis of the nitrile and decarboxylation of the incipient carboxylic acid to produce the substituted ketone intermediates 7.

Other synthetic approaches are possible to form the desired ketones 7. These alternatives include reacting the appropriate Grignard or lithium reagents with Weinreb amides of substituted acids or acetic acids. The Weinreb methodology has been reported in *Tetrahedron Letters*, 4171 (1977).

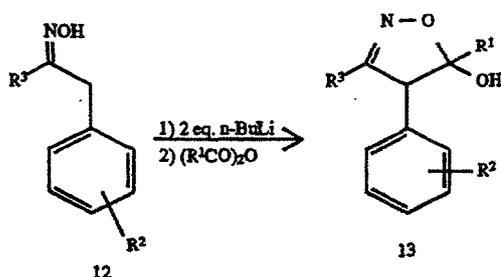
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Scheme IV



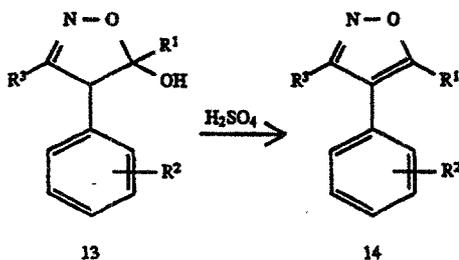
Synthetic Scheme IV shows the procedure which can be used for the preparation of oxime intermediates 12. Treatment of ketone intermediates 7 with hydroxylamine, generally prepared from hydroxylamine hydrochloride by potassium hydroxide, provides the oxime intermediates 12. A wide variety of solvents can be used for this reaction including ethanol, toluene and tetrahydrofuran.

Scheme V



Synthetic Scheme V shows the procedure which can be used for the preparation of hydrated isoxazole derivatives 13. The substituted oximes 12 are treated with two equivalents of a base such as *n*-butyllithium in hexanes to produce a dianion which is subsequently acylated. Suitable acylating agents are anhydrides, acyl imidazoles, esters and the like. Upon quenching the reaction mixture with dilute aqueous acid, hydrated isoxazole derivatives 13 can be isolated by crystallization or chromatography.

Scheme VI

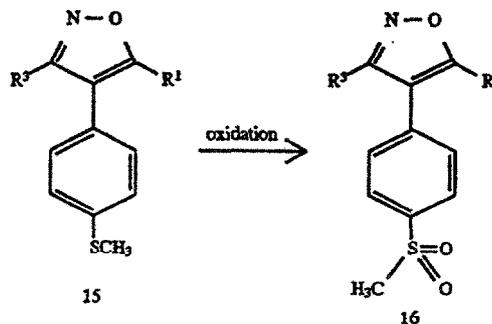


Synthetic Scheme VI shows the procedure which can be used for the preparation of isoxazole analogs 14 by dehydration of the hydrated isoxazole derivatives 13. Substituted hydrated isoxazoles 13 are dissolved in an appropriate solvent such as toluene and then treated with a catalytic to stoichiometric amount of concentrated sulfuric acid to effect

18

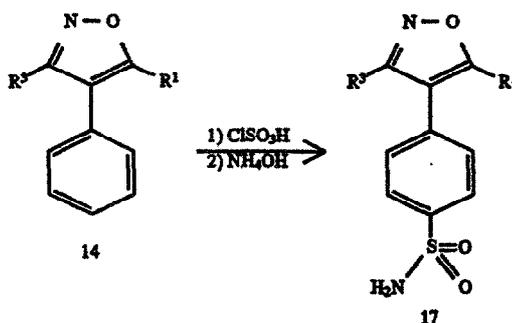
dehydration and thereby produce isoxazole derivatives 14. Other acids can also be employed to effect this transformation such as concentrated HCl, concentrated HBr and many others.

Scheme VII



Synthetic Scheme VII shows the procedure which can be used for the preparation of substituted 4-[4-(methylsulfonyl)phenyl]isoxazole analogs 16 from the corresponding 4-[4-(methylthio)phenyl]isoxazoles 15. The oxidation of an aromatic methylthio derivative 15 to the corresponding aromatic methylsulfonyl compound 16 can be accomplished in a variety of ways such as with two equivalents of meta-chloroperoxybenzoic acid (MCPBA), two equivalents of Oxone® (potassium peroxymonosulfate) and many other oxidizing agents.

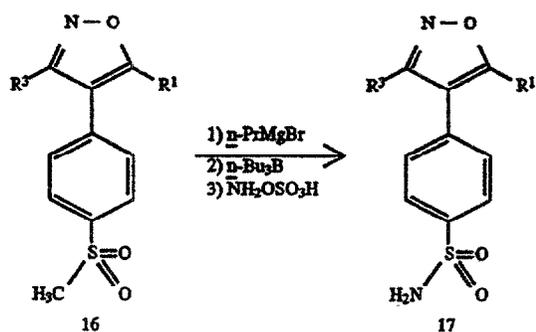
Scheme VIII



Synthetic Scheme VIII shows the procedure which can be used for the preparation of substituted 4-(4-aminosulfonyl)phenylisoxazole analogs 17 from the corresponding 4-phenylisoxazoles 14. The procedure is a two step process for the direct introduction of the sulfonamide moiety into 4-phenylisoxazoles 14 or hydrated isoxazoles 13. In step one, isoxazole 14 or hydrated isoxazole 13 is treated at about 0° C. with two or three equivalents of chlorosulfonic acid to form the corresponding sulfonyl chloride. In step two, the sulfonyl chloride thus formed is treated with concentrated ammonia to provide the sulfonamide derivative 17.

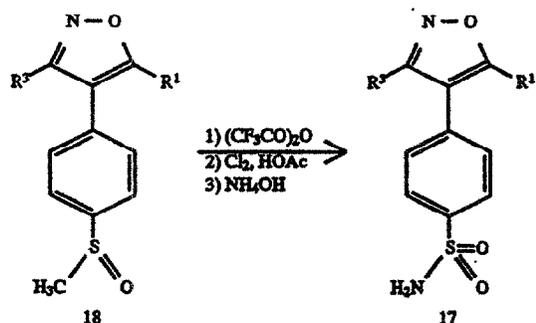
19

Scheme IX



Synthetic Scheme IX shows the three step procedure used to prepare sulfonamide antiinflammatory agents 17 from their corresponding methyl sulfones 16. In step one, a tetrahydrofuran solution (THF) of the methyl sulfones 16 are treated with an alkyl lithium or alkylmagnesium (Grignard) reagent at  $-78^{\circ}\text{C}$ , such as n-propyl magnesium bromide. In step two, the anion generated in step one is treated with an organoborane, such as tri-n-butylborane at  $-78^{\circ}\text{C}$ , then warmed to room temperature and then heated to reflux. In step three, an aqueous solution of hydroxylamine-o-sulfonic acid is added to provide the corresponding sulfonamide antiinflammatory agents 17. This procedure is essentially that of Huang et. al., *Tetrahedron Letters*, 35, 7204 (1994).

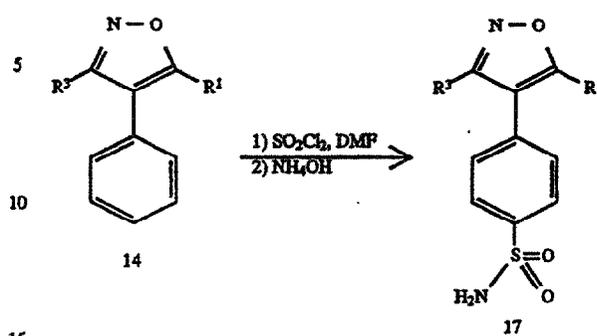
Scheme X



Synthetic Scheme X shows the three step procedure used to prepare sulfonamide antiinflammatory agents 17 from their corresponding methylsulfinyl analogs 18. Methylsulfinyl derivatives 18 are available from the corresponding methylthio compounds 15 by oxidation with one equivalent of an oxidizing agent such as MCPBA. In step one, the methylsulfinyl compounds 18 are treated with trifluoroacetic anhydride to effect Pummerer rearrangement. In step two, the crude Pummerer rearrangement product dissolved in acetic acid is treated with chlorine gas to produce a sulfonyl chloride. In step three, the sulfonyl chloride is converted to the corresponding sulfonamide antiinflammatory agents 17 by treatment with concentrated ammonia. This procedure was adapted from Kharash, *J. Am. Chem. Soc.*, 73, 3240 (1951).

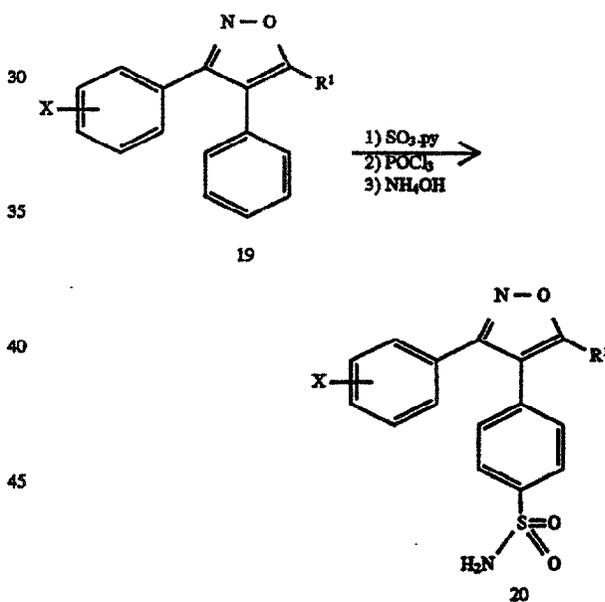
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Scheme XI

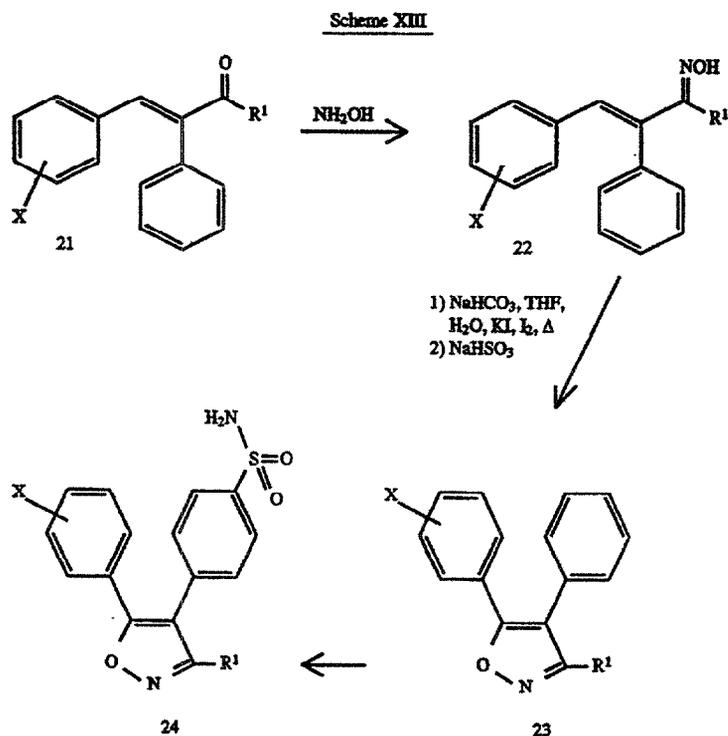


Synthetic Scheme XI shows the two step procedure used to prepare sulfonamide antiinflammatory agents 17 from their corresponding 4-phenyl isoxazole derivatives 14. In step one a mixture of sulfuryl chloride and dimethylformamide (DMF) are allowed to react at room temperature and then mixed with 4-phenylisoxazoles 14 and heated to about  $100^{\circ}\text{C}$ . The sulfonyl chloride thus formed is then treated with an excess of concentrated ammonia to provide the antiinflammatory sulfonamides 17.

Scheme XII



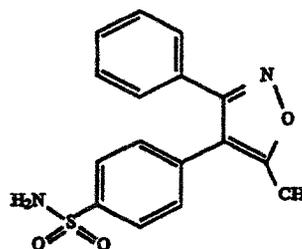
Synthetic Scheme XII shows the three step procedure used to prepare sulfonamide antiinflammatory agents 20 from 4-phenyl isoxazoles 19. In step one, the 4-phenylisoxazoles 19 are converted into the corresponding sulfonic acid by treatment with sulfur trioxide pyridine (pyridine) complex at about  $100^{\circ}\text{C}$ . In step two, the sulfonic acid is converted into the sulfonyl chloride by the action of phosphorus oxychloride and in step three the sulfonyl chloride is treated with excess concentrated ammonia to provide the antiinflammatory sulfonamides 20.



Synthetic Scheme XIII shows the three step procedure used to prepare 4,5-diphenylisoxazole antiinflammatory agents 24 from 1,2-diphenylbutenones 21. In step one, the 1,2-diphenylketones 21 are converted to the corresponding oximes 22 by treatment with hydroxylamine in a manner similar to that shown in Scheme IV. In step two, the oxime 22 is converted to the 4,5-diphenylisoxazole 23 in two steps. The oxime 22 is reacted with potassium iodide and iodine in the presence of base, such as sodium bicarbonate and heated to form the halo intermediate. Sodium bisulfite is added to form the isoxazole 23. The isoxazole 23 is converted to the sulfonamide by any of the procedures shown in Schemes VIII, XI or XII.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formulas I-IV. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated. All compounds showed NMR spectra consistent with their assigned structures.

#### EXAMPLE 1



4-[5-Methyl-3-phenylisoxazol-4-yl]  
benzenesulfonamide

##### Step 1. Preparation of desoxybenzoin keto-oxime.

Desoxybenzoin (20.0 g, 0.102 mol) was dissolved in toluene (200 mL). In a separate 500 mL round-bottom flask equipped with a magnetic stirring bar, hydroxylamine hydrochloride (9.21 g, 0.132 mol) and potassium hydroxide (7.43 g, 0.132 mol) were suspended in absolute ethanol (50 mL) and stirred vigorously at room temperature for thirty minutes. The desoxybenzoin solution was added in one portion, and the yellow suspension was held at reflux, using a Dean-Stark trap to remove generated water, under a nitrogen blanket for 16 hours. The suspension was cooled to room temperature and poured into water (200 mL). The

system was extracted with ethyl acetate (2×150 mL), then the combined organic solution was washed with brine (200 mL), dried over magnesium sulfate, and filtered. The solvents were evaporated under reduced pressure to yield a crude solid. The solid was recrystallized from hot ethanol/water, filtered and washed with water to yield, upon drying, desoxybenzoin keto-oxime as white crystals (17.7 g, 82%): mp 87°–90° C. Mass spectrum, MH<sup>+</sup>=212. High resolution mass spectrum Calc'd. for C<sub>14</sub>H<sub>13</sub>NO: 211.0997. Found: 211.0949.

Step 2. Preparation of 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide.

A solution of desoxybenzoin keto-oxime from Step 1 (6.00 g; 28.40 mmol) in anhydrous tetrahydrofuran (THF, 80 mL) was cooled to -20° C. in an oven-dried 250 mL three-neck round-bottom flask equipped with a thermometer, nitrogen gas inlet, rubber septum and provisions for magnetic stirring. To this cold solution, n-butyllithium (1.6N in hexanes, 44.4 mL) was added, via syringe, over 35 minutes, such that the reaction temperature remained at or below -10° C. The deep red solution was stirred at -10° C. for 1 hour, warmed to room temperature, then stirred at room temperature for an additional hour. Acetic anhydride (3.2 mL, 34.1 mmol) was added in one portion, and the resulting suspension was stirred without temperature control for 2 hours. Water (100 mL) was added, and the solution was poured into 1N HCl (100 mL) and extracted with ethyl acetate (2×200 mL). The combined organic solution was washed with hydrochloric acid (1N HCl, 100 mL) and brine (100 mL), dried over magnesium sulfate and filtered. The resulting solution was evaporated under reduced pressure to yield a crude oil. The oil was applied to a column of silica gel and eluted with ethyl acetate/hexane (10–50% ethyl acetate) to yield, upon concentration of the appropriate fractions, 5.0 g of 3,4-diphenyl-4-hydroxy-5-methylisoxazole. The solid was cooled to 0° C., then dissolved in cold chlorosulfonic acid (15 mL). The brown solution was stirred at 0° C. for 2 hours, then added dropwise to a stirring suspension of ice (200 mL) and dichloromethane (200 mL). The layers were separated, and the organic phase was added directly to a saturated ammonium hydroxide solution (100 mL) at 0° C. This biphasic solution was vigorously stirred at 0° C. for 2 hours, the layers were separated, and the aqueous phase was washed with dichloromethane (50 mL). The combined organic solution was dried over magnesium sulfate, filtered and evaporated under reduced pressure to approximately one-half of its original volume. Crystals formed. The stirred suspension was cooled to 0° C. and held for 30 minutes. The crystals were filtered, washed with cold dichloromethane and dried to yield 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide (2.7 g, 30%): mp 155°–157° C. <sup>1</sup>H NMR (CD<sub>3</sub>CN/500 MHz) δ 7.86 (d, J=8.39 Hz, 2H), 7.45 (m, 1H), 7.39 (s, 4H), 7.37 (d, J=8.39 Hz, 2H), 5.70 (s, 2H), 2.46 (s, 3H) Mass Spectrum, MH<sup>+</sup>=315.

Proceeding in a like manner but replacing the anhydrides with other appropriately substituted anhydrides and esters, the following compounds were prepared:

1a) 4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 140°–141° C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.93 (d, J=8.66, 2 H), 7.28–7.42 (m, 7 H), 4.81 (s, 2H), 2.83 (q, J=7.65 Hz, 2 H), 1.34 (t, J=7.45, 3 H). Mass spectrum M<sup>+</sup>H 329. Anal. Calc'd. for C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>S: C, 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 62.07; H, 4.88; N, 8.42; S, 9.61.

1a) 4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 147°–148° C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.92 (d, J=8.46, 2 H), 7.28–7.44 (m, 7 H), 4.83 (s, 2 H),

2.77 (t, J=7.25, 2 H), 1.71–1.85 (m, 2H), 0.98 (t, J=7.45, 3 H). Anal. Calc'd. for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>S<sub>1</sub>: C, 63.14; H, 5.30; N, 8.18; S, 9.36. Found: C, 63.19; H, 5.32; N, 8.23; S, 9.44. Mass spectrum M<sup>+</sup>H 343.

5 1c) 4-[5-isopropyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 166°–168° C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.93 (d, J=8.46 Hz, 2 H), 7.27–7.40 (m, 7H), 4.80 (s, 2 H), 3.08–3.20 (m, 1 H), 1.36 (d, J=6.58 Hz, 6 H). Mass spectrum M<sup>+</sup>H 343.

10 1d) 4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 129°–131° C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.93 (d, J=8.46 Hz, 2H), 7.30–7.40 (m, 7H), 4.81 (s, 2H), 2.79 (t, J=7.45, 2H), 1.67–1.79 (m, 2H), 1.30–1.42 (m, 2H), 0.91 (t, J=7.25, 3 H). Anal. Calc'd. for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S<sub>1</sub>: C, 64.02; H, 5.66; N, 7.86; S, 8.99. Found: C, 63.22; H, 5.52; N, 7.51; S, 8.67.

1e) 4-[5-isobutyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 159°–160° C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.93 (d, J=8.46, 2 H), 7.28–7.42 (m, 7H), 4.84 (s, 2H), 2.66 (d, J=7.25 Hz, 2H), 2.08–2.22 (m, 1 H), 0.94 (d, J=6.65 Hz, 6 H). High resolution mass spectrum Calc'd. for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S: 221.0841. Found: 221.0827. Anal. Calc'd. for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S<sub>1</sub>: C, 64.02; H, 5.66; N, 7.86; S, 8.99. Found: C, 63.94; H, 5.65; N, 7.86; S, 8.90.

25 1f) 4-[5-cyclohexyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 191°–193° C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.94 (d, J=8.46 Hz, 2 H), 7.27–7.41 (m, 7H), 4.85 (s, 2H), 2.62–2.85 (m, 1H), 1.67–1.95 (m, 7 H), 1.22–1.38 (m, 3 H). Mass spectrum M<sup>+</sup>H 383. High resolution mass spectrum Calc'd. for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>S: 383.1429. Found: 383.1452.

1g) 4-[5-neopentyl-3-phenylisoxazol-4-yl]benzenesulfonamide: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.94 (d, J=8.46, 2 H), 7.26–7.39 (m, 7 H), 4.82 (s, 2 H), 2.71 (s, 2 H), 0.94 (s, 9H). Mass spectrum M<sup>+</sup>H 371.

1h) 4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 151°–153° C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.93 (d, J=8.46, 2 H), 7.29–7.43 (m, 7H), 4.82 (s, 2H), 2.67 (d, J=7.05 Hz, 2 H), 1.60–1.92 (m, 5 H), 0.85–1.30 (m, 6 H). Mass spectrum M<sup>+</sup>H 397.

1i) 4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 107°–108° C. <sup>1</sup>H NMR (CDCl<sub>3</sub> and CD<sub>3</sub>OD) δ 7.91 (d, J=8.46, 2 H), 7.26–7.42 (m, 9H), 7.14 (d, J=8.46 Hz, 2 H), 4.85 (s, 2 H), 4.10 (s, 2 H). Mass spectrum M<sup>+</sup>H=425. High resolution mass spectrum Calc'd. for C<sub>22</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>3</sub>S: 425.0727. Found: 425.0736.

1j) 4-[5-trifluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide.

1k) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 172°–175° C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.97 (d, J=8.46, 2 H), 7.30–7.50 (m, 7H), 6.72 (t, J=52.57 Hz, 1 H), 4.87 (s, 2H). <sup>19</sup>F NMR (CHCl<sub>3</sub>) -116.45 (d, J=53.02 Hz). Mass spectrum M<sup>+</sup>H 351.

55 1l) 4-[5-chloromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 131°–133° C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.98 (d, J=8.46, 2 H), 7.34–7.46 (m, 7H), 4.84 (s, 2H), 4.61 (s, 2 H). Mass spectrum M<sup>+</sup>H 349. High resolution mass spectrum for C<sub>16</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>3</sub>S: 348.0335. Found: 348.0316.

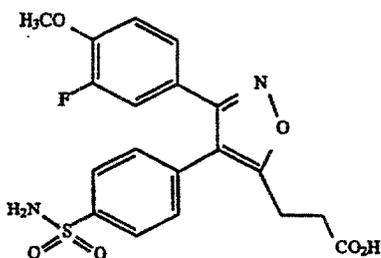
60 1m) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid: mp 260°–269° C. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 9.03 (s, >1 H exch), 8.42 (d, J=8.06 Hz, 2H), 8.12–8.28 (m, 5 H), 7.97 (d, J=8.26 Hz, 2 H). Mass spectrum M<sup>+</sup>H 316.

1n) 4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid: <sup>1</sup>H NMR (CDCl<sub>3</sub> and CD<sub>3</sub>OD) δ 7.95–7.78 (m, 2 H), 7.10–7.40 (m, 7H), 2.65–2.78 (m, 2 H), 1.65–1.80 (m, 2H), 0.88–0.99 (m, 3H). Mass spectrum M<sup>+</sup>H 344.

1o) 4-[5-methoxymethyl-3-phenylisoxazol-4-yl] benzoesulfonamide: mp 82°-118° C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.93 (d, J=8.66 Hz, 2 H), 7.31-7.45 (m, 7 H), 4.81 (s, 2 H), 4.51 (s, 2 H), 3.48 (s, 3 H). Mass spectrum M<sup>+</sup>H 345. High resolution mass spectrum Calc'd. for C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>S: 344.0831. Found: 344.0807.

1p) 4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl] benzenesulfonamide: mp 88°-142° C. <sup>1</sup>H NMR (CDCl<sub>3</sub> and CD<sub>3</sub>OD) δ 7.90 (d, J=8.66 Hz, 2 H), 7.26-7.42 (m, 7H), 3.66 (t, J=6.04 Hz, 2 H), 2.91 (t, J=7.45 Hz, 2 H), 1.93-2.02 (m, 2H). Mass spectrum M<sup>+</sup>H 349. High resolution mass spectrum Calc'd. for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>S: 358.0987. Found: 358.0958.

## EXAMPLE 2



[4-[4-(Aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic Acid

Step 1: Preparation of 1-(3-fluoro-4-methoxyphenyl)-2-phenyl-ethan-1-one.

In a 500 mL, 3-neck round-bottom flask, equipped with a pressure equalizing dropping funnel, thermometer, gas inlet tube and provisions for magnetic stirring, a suspension of aluminum chloride (9.4 g, 70.5 mmol) in a solution of 2-fluoroanisole (6.6 mL, 58.8 mmol) and anhydrous chloroform (200 mL) was cooled to 0° C. under a blanket of dry nitrogen. A solution of phenylacetyl chloride (8.6 mL, 64.7 mmol) in anhydrous chloroform (50 mL) was added to the vigorously stirred suspension over 20 minutes keeping the reaction temperature <5° C. The yellowish solution was stirred at 0° C. for 1 hour, then poured into ice (200 mL) and stirred without temperature control for 16 hours. The layers were separated, and the aqueous layer was extracted with dichloromethane (2x100 mL). The combined organic solution was dried over magnesium sulfate, filtered, and the solvent was evaporated under reduced pressure. The resulting solid was recrystallized from boiling hexane to yield, upon filtration and drying, 12.9 g (90%) of 1-(3-fluoro-4-methoxyphenyl)-2-phenyl-ethan-1-one as white crystals: <sup>1</sup>H NMR (CDCl<sub>3</sub>/300 MHz) δ 7.82-7.72 (m, 2H), 7.35-7.24 (m, 5H), 6.98 (dd, J=8.46, 8.26 Hz, 1H), 4.22 (s, 2H), 3.94 (s, 3H). <sup>19</sup>F NMR (CDCl<sub>3</sub>/282.2 MHz) -134.875 (m).

Step 2: Preparation of 1-(3-fluoro-4-methoxyphenyl)-2-phenyl-ethan-1-one oxime.

Hydroxylamine hydrochloride (3.7 g, 53.2 mmol) and potassium hydroxide (2.98 g, 53.2 mmol) were suspended in absolute ethanol (25 mL) and vigorously stirred in a 250-mL round-bottom flask equipped with a magnetic stirring bar under a dry nitrogen blanket for 30 minutes. To this, a suspension of 1-(3-fluoro-4-methoxyphenyl)-2-phenyl-ethan-1-one from Step 1 (10.0 g, 40.9 mmol) in toluene (150 mL) was added in one portion. A Dean-Stark trap and reflux condenser were added to the apparatus, and the yellow suspension was warmed to reflux. The solution was maintained at reflux 16 hours, then the suspension was cooled to

room temperature. Water (100 mL) was added, and the resulting solution was extracted with ethyl acetate (2x100 mL). The combined organic solution was washed with brine (100 mL), dried over magnesium sulfate and filtered. The resulting solution was evaporated under reduced pressure to yield a crude residue. The residue was crystallized from boiling ethanol/water to yield, upon filtration and drying, 10.0 g (94%) of 1-(3-fluoro-4-methoxyphenyl)-2-phenyl-ethan-1-one oxime as ivory-colored crystals: <sup>1</sup>H NMR (CDCl<sub>3</sub>/300 MHz) δ 7.42 (dd, J=12.69, 2.01, 1H), 7.36-7.19 (m, 6H), 6.89 (dd, J=8.66, 8.46 Hz, 1H), 4.16 (s, 2H), 3.88 (s, 3H). <sup>19</sup>F NMR (CDCl<sub>3</sub>/282.2 MHz): 135.517 (m).

Step 3: [3-(3-fluoro-4-methoxyphenyl)-4-phenylisoxazol-5-yl]propanoic acid:

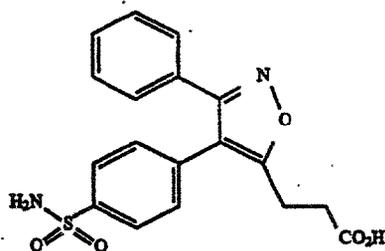
A dry, 250 mL 3-neck round-bottom flask, equipped with a thermometer, magnetic stirring bar, reflux condenser and rubber septum was charged with 1-(3-fluoro-4-methoxyphenyl)-2-phenyl-ethan-1-one oxime from Step 2 (2.00 g, 7.71 mmol) and anhydrous THF (80 mL) under a nitrogen blanket. The solution was cooled to -20° C., and n-butyllithium (1.6N, 12.0 mL) was added, via syringe, over 20 minutes, keeping the reaction temperature <-10° C. The deep red suspension was stirred at -20° C. for 1 hour, warmed to room temperature, and stirred at room temperature for 1 hour. Succinic anhydride (926 mg, 9.26 mmol) was added in one portion, and the yellow reaction was stirred for 16 hours without temperature control. Sulfuric acid (conc., 2.1 mL) was added, and the reaction was warmed to reflux. After 2 hours, the brown mixture was cooled to room temperature, diluted with water (100 mL), and extracted with ether (2x100 mL). The ethereal solution was extracted with dilute sodium hydroxide (2x100 mL), and the combined basic extracts were acidified to pH<2 with hydrochloric acid (conc.). The acidic system was extracted with ether (2x100 mL). This ethereal solution was evaporated under reduced pressure to a residue. The residue was applied to a column of silica gel (200 cc) and eluted (10% methanol in dichloromethane) to yield, upon concentration of the appropriate fractions, a crude solid. The solid was recrystallized from hot ethanol and 0.1N HCl to yield, upon filtration and drying, [3-(3-fluoro-4-methoxyphenyl)-4-phenylisoxazol-5-yl]propanoic acid as ivory colored crystals (367 mg, 14%): mp 129°-131° C. (dec). Mass Spectrum: MH<sup>+</sup>=342. <sup>1</sup>H NMR (CDCl<sub>3</sub>/300 MHz) δ 7.39 (m, 3H), 7.22-7.12 (m, 4H), 6.87 (t, J=8.46 Hz, 1H), 3.88 (s, 3H), 3.09 (t, J=8.05 Hz, 2H), 2.80 (t, J=8.05 Hz, 2H). <sup>19</sup>F NMR(CDCl<sub>3</sub>/282.2 MHz): -135.466 (m).

Step 4: Preparation of [4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid:

[3-(3-Fluoro-4-methoxyphenyl)-4-phenylisoxazol-5-yl]propanoic acid from Step 3 (250 mg, 0.73 mmol) and sulfuric acid (1 mL) were dissolved in absolute ethanol (10 mL). The colorless solution was warmed to reflux and held for 16 hours. The solution was cooled to room temperature and diluted with water (20 mL). The aqueous solution was extracted with ether (2x50 mL), and the combined ethereal solution was washed with diluted sodium hydroxide (5%, 2x30 mL) and brine (30 mL). The organic solution was dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield an oil. The oil was cooled to 0° C., and cold chlorosulfonic acid (0° C., 12 mL) was added. The reaction was kept at 0° C. under a nitrogen blanket for 2 hours, and was then carefully poured into ice. The ice was extracted with dichloromethane (2x20 mL), then the organic extract was added directly to a vigorously stirred, 0° C. saturated NH<sub>4</sub>OH solution (40 mL). The biphasic reaction was vigorously stirred at 0° C. for 3 hours. The layers were

separated, and the aqueous layer was extracted with dichloromethane (30 mL). The combined organic solution was dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a crude foam. The foam was dissolved in dioxane (30 mL), aqueous sodium hydroxide (10%, 0.9 mL) was added and the solution was heated to reflux for 1 hour. The solution was cooled to room temperature and diluted with water (20 mL). The aqueous solution was extracted with ether (2x30 mL), then the combined ethereal solution was extracted with dilute sodium hydroxide (5%, 2x30 mL). All of the aqueous phases were combined and acidified with hydrochloric acid (conc.) to pH<2. The acidic aqueous phase was extracted with ether (2x30 mL). The final ether solution was dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a crude solid. The solid was recrystallized from ethanol/0.1N HCl to yield, upon filtration and drying, [4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid as cream-colored crystals (182 mg, 59%): mp=159°-161° C. (dec). <sup>1</sup>H NMR (CDCl<sub>3</sub>/300 MHz) δ 7.91 (d, J=8.66 Hz, 2H), 7.34 (d, J=8.66 Hz, 2H), 7.14 (dd, J=11.88, 2.01 Hz), 7.02 (d, J=8.46 Hz), 6.87 (t, J=8.46 Hz, 1H), 3.86 (s, 3H), 3.05 (t, J=7.45 Hz, 2H), 2.74 (t, J=7.45 Hz, 2H). <sup>19</sup>F NMR (CDCl<sub>3</sub>/282.2 MHz): -135.020 (m).

## EXAMPLE 3



## [4-[4-(Aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]propanoic Acid

Step 1. Preparation of [3,4-diphenylisoxazol-5-yl]propanoic acid.

[3,4-Diphenylisoxazol-5-yl]propanoic acid was prepared in 45% yield from desoxybenzoin oxime (Example 1, Step 1) and succinic anhydride according to the procedure outlined in Example 2, Step 3: mp 123°-125° C. (dec). Anal. Calc'd for C<sub>18</sub>H<sub>15</sub>NO<sub>3</sub>: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.78; H, 5.18; N, 4.72.

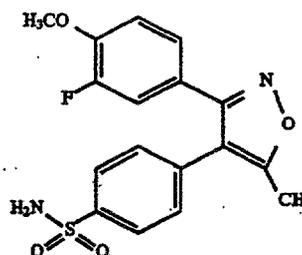
Step 2. Preparation of ethyl [4-[4-(aminosulfonyl)phenyl]-5-phenylisoxazol-5-yl]propanoate:

A solution of [3,4-diphenylisoxazol-5-yl]propanoic acid was treated with ethanol in the presence of a catalytic amount of sulfuric acid to prepare the corresponding ethyl ester which was immediately treated with chlorosulfonic acid followed by ammonia according to the procedure from Example 2, Step 4. The crude sulfonamide was purified by flash chromatography eluting with ethyl acetate/hexane (10-50% ethyl acetate) to yield, upon concentration of the appropriate fractions, ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]propanoate as a glassy solid (248 mg, 60%): Mass spectrum: MH<sup>+</sup>=401. <sup>1</sup>H NMR (CDCl<sub>3</sub>/300 MHz) δ 7.93 (d, J=8.46 Hz, 2H); 7.41-7.30 (m, 7H), 4.84 (s, 2H), 4.14 (q, J=7.04 Hz, 2H), 3.12 (t, J=7.45 Hz, 2H), 2.81 (t, J=7.45 Hz, 2H), 1.25 (t, J=7.04 Hz, 3H). This material was used directly in the next step without further purification.

Step 3. Preparation of [4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]propanoic acid.

Ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]propanoate from Step 2 (198 mg, 0.495 mmol) and aqueous sodium hydroxide (10%, 0.30 mL) were dissolved in dioxane (15 mL). The solution was heated to reflux and held for 16 hours. Upon cooling to room temperature, water (20 mL) was added, and the solution was extracted with ether (2x30 mL). The combined ethereal solution was extracted with dilute sodium hydroxide (5%, 2x30 mL). All of the aqueous phases were combined and acidified with hydrochloric acid (conc.) to pH<2. The acidic aqueous phase was extracted with ether (2x30 mL). The final ether solution was dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a crude solid. Trituration with dichloromethane yielded crystals. The suspension was cooled to 0° C., filtered, washed with hexane and dried to yield [4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]propanoic acid as a white crystalline solid (135 mg, 73%): mp 207° C. Mass spectrum: MH<sup>+</sup>=373. Anal. Calc'd for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>S: C, 58.06; H, 4.33; N, 7.52; S, 8.61. Found: C, 57.87; H, 4.35; N, 7.49; S, 8.54.

## EXAMPLE 4



## 4-[3-(3-Fluoro-4-methoxyphenyl)-5-methylisoxazol-4-yl]benzenesulfonamide

Step 1: Preparation of 3-[3-fluoro-4-methoxyphenyl]-5-methyl-4-phenylisoxazole.

A dry, 250 mL 3-neck round-bottom flask, equipped with a thermometer, magnetic stirring bar, reflux condenser and rubber septum was charged with 1-(3-fluoro-4-methoxyphenyl)-2-phenyl-ethan-1-one oxime (from Example 2, Step 2) (2.50 g, 9.64 mmol) and anhydrous THF (100 mL) under a nitrogen blanket. The solution was cooled to -20° C., and n-butyllithium (1.6N, 15.0 mL) was added, via syringe, over 20 minutes, keeping the reaction temperature <-10° C. The deep red suspension was stirred at -20° C. for 1 hour, warmed to room temperature, and stirred at room temperature for 1 hour. Acetic anhydride (1.1 mL, 11.6 mmol) was added in one portion, and the yellow reaction was stirred for 2 hours without temperature control. The reaction was poured into aqueous hydrochloric acid (1N, 100 mL) and extracted with ethyl acetate (2x100 mL). The combined organic solution was washed once each with aqueous hydrochloric acid (1N, 100 mL) and brine (100 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a crude oil. The oil was applied to a column of silica gel (250 ml) and eluted with ethyl acetate/hexane (10-40% ethyl acetate) to yield, upon concentration of the appropriate fractions, 986 mg of 3-(3-fluoro-4-methoxyphenyl)-4-hydroxy-5-hydroxy-4-phenyl-5-methylisoxazole. This intermediate was dissolved in tetrahydrofuran (40 mL). Sulfuric acid (conc., 0.9 mL) was added, and the reaction was warmed to reflux. After one hour, the

solution was cooled to room temperature, diluted with water (50 mL), and extracted with ethyl acetate (2x50 mL). The combined organic solution was washed with aqueous hydrochloric acid (1N, 50 mL), saturated aqueous sodium bicarbonate (2x50 mL) and brine (50 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a crude, dark oil. Washing the oil with 50% dichloromethane in hexane dissolved the compound but did not dissolve the dark impurities. The resulting solution was evaporated under reduced pressure to yield 797 mg (29%) of 3-(3-fluoro-4-methoxyphenyl)-5-methyl-4-phenylisoxazole as a foam. Mass Spectrum: MH<sup>+</sup>=284. Anal. Calc'd for C<sub>17</sub>H<sub>14</sub>NO<sub>2</sub>F: C, 72.07; H, 4.98; N, 4.94. Found: C, 72.13; H, 4.98; N, 4.92.

Step 2: Preparation of [3-(3-fluoro-4-methoxyphenyl)-5-methylisoxazol-4-yl]benzenesulfonamide:

Chlorosulfonic acid (8 mL) was cooled to 0° C. 3-(3-Fluoro-4-methoxyphenyl)-5-methyl-4-phenylisoxazole from Step 1 (375 mg, 1.32 mmol) was added in one portion. The brown solution was stirred at 0° C. under a nitrogen blanket for 2 hours, then added dropwise to ice (50 mL). The ice was extracted with dichloromethane (2x30 mL), and the organic extracts were added directly to a 0° C. saturated aqueous NH<sub>4</sub>OH solution. The biphasic reaction was vigorously stirred at 0° C. for 2 hours, then the layers were separated. The aqueous solution was extracted with dichloromethane, the combined organic solutions were dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a crude solid. The solid was recrystallized from ethanol and water to yield, upon filtration and drying, 4-[3-(3-fluoro-4-methoxyphenyl)-5-methylisoxazol-4-yl]benzenesulfonamide as ivory colored crystals (275 mg, 55%): mp 175° C. (dec). Mass Spectrum: MH<sup>+</sup>=363. Anal. Calc'd for C<sub>17</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub>FS: C, 56.47; H, 4.17; N, 7.73; S, 8.85. Found: C, 56.47; H, 4.19; N, 7.66; S, 8.81.

Proceeding in a like manner but replacing desoxybenzoin with other appropriately substituted ketones, the following compounds were prepared:

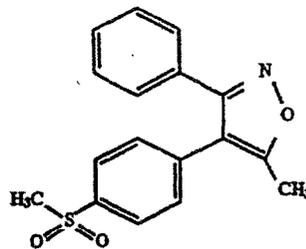
- 4a) 4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide: mp 162°-164° C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.97 (d, 2H, J=8.46 Hz), 7.33-7.26 (m, 7H), 2.48 (s, 3H). Elemental analysis Calc'd for C<sub>16</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub>SCl: C, 55.1; H, 3.76; N, 8.03. Found: C, 55.12; H, 3.78; N, 8.03.
- 4b) 4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide: mp 152°-156° C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 2.48 (s, 3H), 4.84 (bs, 2H), 7.04 (t, 1H, J=8.6 Hz), 7.33-7.40 (m, 4H), 7.94 (d, 2H, J=8.4). High resolution mass spectrum Calc'd for C<sub>16</sub>H<sub>13</sub>FN<sub>2</sub>O<sub>3</sub>S: 333.0709. Found: 333.0704.
- 4c) 4-[3-(3-fluoro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide: mp 146°-150° C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 2.24 (s, 3H), (2.48 (s, 3H), 4.97 (bs, 2H), 6.93 (t, 1H, J=9.1 Hz), 7.04 (m, 1H), 7.26-7.37 (m, 3H), 7.94 (d, 2H, J=8.3). High resolution mass spectrum Calc'd for C<sub>17</sub>H<sub>15</sub>FN<sub>2</sub>O<sub>3</sub>S: 347.0866. Found: 347.0865. Anal. Calc'd for C<sub>17</sub>H<sub>15</sub>FN<sub>2</sub>O<sub>3</sub>S: C, 58.95; H, 4.37; N, 8.03. Found: C, 58.09; H, 4.47; N, 8.03.
- 4d) 4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide.
- 4e) 4-[3-(3-chloro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide: mp 120°-122° C. <sup>1</sup>H NMR (CD<sub>3</sub>OD) 2.30 (s, 3H), 2.48 (s, 3H), 4.84 (bs, 2H), 7.11 (m, 1H), 7.33-7.40 (m, 4H), 7.92 (d, 2H, J=8.4). High resolution mass spectrum Calc'd for C<sub>17</sub>H<sub>15</sub>FN<sub>2</sub>O<sub>3</sub>S: 363.0570. Found: 363.0584. Elemental analysis. Calc'd for C<sub>17</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>3</sub>S: C, 56.28; H, 4.17; N, 7.72. Found: C, 56.02; H, 4.38; N, 7.54.

4f) 4-[5-methyl-3-(3-pyridyl)isoxazol-4-yl]benzenesulfonamide: mp 110°-115° C. (dec). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.57 (br s, 1H), 8.47 (s, 1H), 7.88, 7.24 (AB quartet, 4H), 7.51-7.41 (m, 2H), 2.43 (s, 3H). Mass spectrum M<sup>+</sup>H 316.

4g) 4-[5-methyl-3-(4-pyridyl)-isoxazol-4-yl]benzenesulfonamide: mp 108°-110° C. (dec). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.51 (d, 2H, J=6.0 Hz), 7.9 (d, 2H, J=8.46 Hz), 7.30-7.26 (m, 4H), 6.11 (s, 2H), 2.44 (s, 3H). Mass spectrum M<sup>+</sup>H 316. Anal. Calc'd for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>SO<sub>2</sub>.H<sub>2</sub>O: C, 54.05; H, 4.54; N, 12.62. Found: C, 53.65; H, 4.08; N, 12.42.

4h) 4-[3-(3-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide: mp 130°-136° C. (dec). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.95 (d, 2H, J=8.5 Hz), 7.33 (d, 2H), 7.33-7.11 (m, 4H), 2.50 (s, 3H). Mass spectrum M<sup>+</sup>H 333. Anal. Calc'd for C<sub>16</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub>SF: C, 57.82; H, 3.94; N, 8.43. Found: C, 57.42; H, 4.57; N, 7.50.

### EXAMPLE 5



5-Methyl-4-[4-(methylsulfonyl)phenyl]-3-phenylisoxazole

Step 1. Preparation of 1-phenyl-2-[4-(methylthio)phenyl]ethan-1-one.

This ketone was prepared from the Friedel Crafts acylation of benzene with 4-methylthiophenylacetyl chloride in the presence of aluminum chloride: <sup>1</sup>H NMR (CDCl<sub>3</sub>/300 MHz) δ 7.92 (d, J=8.66 Hz, 2H), 7.32-7.22 (m, 7H), 4.24 (s, 2H), 2.51 (s, 3H).

Step 2. Preparation of 1-phenyl-2-[4-(methylthio)phenyl]ethan-1-one oxime.

This oxime was prepared from 1-phenyl-2-[4-(methylthio)phenyl]ethan-1-one (Step 1) and hydroxylamine in 80% yield by the method outlined in Example 1, Step 1: <sup>1</sup>H NMR (CDCl<sub>3</sub>/300 MHz) δ 7.54 (d, J=8.66 Hz, 2H), 7.32-7.17 (m, 7H), 4.19 (s, 2H), 2.36 (s, 3H).

Step 3. Preparation of 5-methyl-4-[4-(methylthio)phenyl]-3-phenylisoxazole:

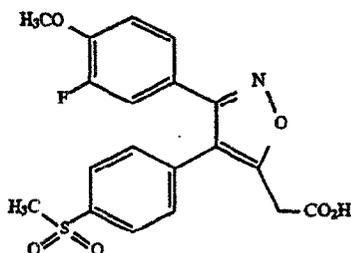
5-Methyl-4-[4-(methylthio)phenyl]-3-phenylisoxazole was prepared in 48% yield from the reaction of 1-phenyl-2-[4-(methylthio)phenyl]ethan-1-one oxime (Step 2) and acetic anhydride according to the procedure outlined in Example 4, Step 1: Mass Spectrum: MH<sup>+</sup>=282. High resolution mass spectrum Calc'd for C<sub>17</sub>H<sub>15</sub>NOS: 281.0874. Found: 281.0875. Anal. Calc'd for C<sub>17</sub>H<sub>15</sub>NOS: C, 72.57; H, 5.37; N, 4.98; S, 11.39. Found: C, 72.56; H, 5.41; N, 5.00; S, 11.34.

Step 4. Preparation of 5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenylisoxazole:

5-Methyl-4-[4-(methylthio)phenyl]-3-phenylisoxazole from Step 3 (100 mg, 0.355 mmol) was dissolved in methanol (20 mL). Oxone® (0.765 g, 1.24 mmol) and water (2 mL) were added, and the suspension was stirred at room

temperature for 2 hours. Water was added (30 mL) and the resulting suspension was cooled to 0° C. and held for 30 minutes whereupon the product crystallized. The product was isolated by filtration, washed with water and dried to yield 5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenylisoxazole (32 mg, 29%); mp 54°-56° C. Mass Spectrum:  $MH^+$ =320. High resolution mass spectrum Calc'd for  $C_{17}H_{15}NO_3S$ : 313.077. Found: 313.078.

## EXAMPLE 6



[3-(3-Fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic Acid

Step 1. Preparation of 1-(3-fluoro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]ethan-1-one.

1-(3-Fluoro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]ethan-1-one was prepared by Friedel Crafts acylation of 2-fluoroanisole with 4-(methylthio)phenylacetyl chloride in the presence of aluminum chloride:  $^1H$  NMR ( $CDCl_3/300$  MHz)  $\delta$  7.80-7.70 (m, 2H), 7.24-7.15 (m, 4H), 6.98 (t,  $J=8.26$  Hz), 4.17 (s, 2H), 3.95 (s, 3H), 2.46 (s, 3H).  $^{19}F$  NMR ( $CDCl_3/282.2$  MHz): -134.804 (m).

Step 2. Preparation of 1-(3-fluoro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]ethan-1-one oxime.

1-(3-Fluoro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]ethan-1-one oxime was prepared in yield by treatment of 1-(3-fluoro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]ethan-1-one from Step 1 with hydroxylamine:  $^1H$  NMR ( $CDCl_3/300$  MHz)  $\delta$  7.40 (dd,  $J=12.69, 2.22$  Hz, 1H), 7.30 (d,  $J=8.66$  Hz, 1H), 7.18-7.12 (m, 4H), 6.88 (dd,  $J=8.66, 8.46$  Hz, 1H), 4.10 (s, 2H), 3.87 (s, 3H), 2.43 (s, 3H).

Step 3. Preparation of 3-(3-fluoro-4-methoxyphenyl)-5-methyl-4-[4-(methylthio)phenyl]isoxazole:

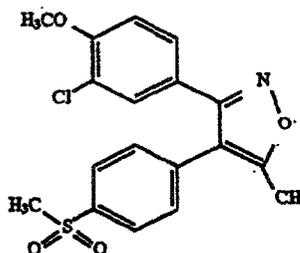
3-(3-Fluoro-4-methoxyphenyl)-5-methyl-4-[4-(methylthio)phenyl]isoxazole was prepared in 30% yield from 1-(3-fluoro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]ethan-1-one oxime from Step 2 and acetic anhydride by the procedure described in Example 4, Step 1 and used directly in the next step.

Step 4. Preparation of [3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid.

3-(3-Fluoro-4-methoxyphenyl)-5-methyl-4-[4-(methylthio)phenyl]isoxazole (326 mg, 0.99 mmol) was charged to an oven-dried 100 mL 3-neck round-bottom flask equipped with a thermometer, nitrogen inlet, rubber septum and a magnetic stirring bar. Anhydrous THF (35 mL) was added, and the solution was cooled to -78° C. under a dry nitrogen blanket. To this solution, *n*-butyllithium (1.6N in hexane; 0.74 mL) was added, via syringe over approximately 3 minutes, keeping the reaction temperature <-75° C. The deep red suspension was stirred at -78° C. for 1 hour. Simultaneously, anhydrous tetrahydrofuran (80 mL) was cooled to -78° C. in an oven-dried 250 mL round-bottom flask. This solvent was saturated with carbon dioxide gas.

The red reaction solution was quenched into the carbon dioxide-saturated THF. The yellow reaction was warmed to room temperature over 2 hours, then diluted with water (50 mL) and ether (80 mL). The solution was extracted with aqueous sodium hydroxide (5%, 2x50 mL), and the combined aqueous solution was acidified to pH<2 with aqueous hydrochloric acid (conc.). The acidic solution was extracted with dichloromethane (2x50 mL). The combined organic solution was dried over magnesium sulfate, filtered and evaporated under reduced pressure to a crude solid. The solid was dissolved in methanol (20 mL) in a 100 mL round-bottom flask equipped with a magnetic stirring bar and a nitrogen gas inlet. Oxone® (2.13 g, 3.47 mmol) and water (3 mL) were added, the suspension was stirred at room temperature for 2 hours, warmed to reflux and held for an additional 2 hours. Upon cooling to room temperature, water (35 mL) and aqueous hydrochloric acid (6N, 1 mL) were added. The resulting suspension was cooled to 0° C., held for 30 minutes, filtered and washed with cold water to yield, upon drying, [3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid as white crystals (173 mg, 43%); mp 89° C. Mass spectrum:  $MH^+$ =406. Anal. Calc'd for  $C_{19}H_{16}NO_6FS$ : C, 56.29; H, 3.98; N, 3.46; S, 7.91. Found: C, 56.22; H, 4.00; N, 3.44; S, 7.85.

## EXAMPLE 7



3-(3-Chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole

Step 1. Preparation of 3-Chloro-4-methoxyacetophenone.

A 5 L round bottomed flask equipped with mechanical stirrer, reflux condenser, constant pressure addition funnel and nitrogen inlet was charged with anhydrous aluminum chloride (281 g, 2.104 mol) and 1 L of ethanol-free chloroform. The solution was maintained at 0° C. with an ice bath while a solution of acetyl chloride (162 g, 2.28 mol) in 300 mL of chloroform was added from the addition funnel over 25 minutes. To this solution was added 2-chloroanisole (250 g, 1.75 mol) in 250 mL of chloroform over 1 hour. The solution was stirred at room temperature for 16 hours and the contents of the flask were poured into a mixture of ice and water. The phases were separated and the aqueous phase extracted with dichloromethane and combined with the original organic phase, dried over anhydrous  $MgSO_4$ , filtered and concentrated in vacuo to afford a solid that was crystallized from dichloromethane/hexane to give 3-chloro-4-methoxyacetophenone (246 g, 76%) that was used directly in the next step without further purification.

Step 2. Preparation of 3-chloro-4-methoxyphenylacetic acid.

A mixture of 3-chloro-4-methoxyacetophenone from Step 1 (10.0 g, 54.2 mmol) and boron trifluoride etherate complex (26.6 mL, 0.216 mol) in 20 mL of methanol was added to a suspension of lead tetraacetate (24 g, 54.2 mmol) in 50 mL of toluene. The mixture was stirred at room temperature for

16 hours, treated with 50 mL of water and poured into a separatory funnel. The phases were separated and the aqueous phase washed with toluene. The toluene solution was dried over anhydrous  $MgSO_4$ , filtered and concentrated in vacuo to provide an oil that was dissolved in 40 mL of dioxane and treated with excess 2.5N sodium hydroxide solution. The solution was stirred at room temperature for 2 hours and concentrated in vacuo. The residue was extracted with dichloromethane and the aqueous phase acidified with concentrated HCl. The acidic solution was extracted with dichloromethane. The dichloromethane extract was dried over anhydrous  $MgSO_4$ , filtered and concentrated in vacuo to afford pure 3-chloro-4-methoxyphenylacetic acid (9.11 g, 84%) that was used directly in the next step.

Step 3. Preparation of 2-(3-chloro-4-methoxyphenyl)-3-[4-(methylthio)phenyl]-2-propenoic acid.

A mixture of 3-chloro-4-methoxyphenylacetic acid from Step 2 (4.50 g, 22.4 mmol), 4-methylthiobenzaldehyde (2.70 g, 20.4 mmol) and triethylamine (2.8 mL, 20.4 mmol) were dissolved in 40 mL of acetic anhydride and heated to reflux for 3 hours. The solution was cooled to 110° C. and treated cautiously with 70 mL of water and cooled to room temperature, whereupon crystals of 2-(3-chloro-4-methoxyphenyl)-3-[4-(methylthio)phenyl]-2-propenoic acid formed that were isolated by filtration and air dried to afford 5.68 g (75%) of pure compound which was used directly in the next step.

Step 4. Preparation of 1-(3-chloro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]-ethan-1-one.

A solution of 1-(3-chloro-4-methoxyphenyl)-3-[4-(methylthio)phenyl]propenoic acid from Step 3 (5.00 g, 14.9 mmol) and triethylamine (2.20 g, 15.7 mmol) in 50 mL of toluene was cooled to 0° C. and treated with diphenylphosphoryl azide (3.20 g, 14.9 mmol) via syringe. The solution was maintained at 0° C. for 30 minutes and then diluted with water. The phases were separated and the aqueous phase washed with ether. The original toluene solution was combined with the ethereal extract, dried over anhydrous  $MgSO_4$ , filtered and concentrated to remove the ether. The remaining toluene solution was heated to 115° C. for 90 minutes, treated with *tert*-butyl alcohol (1.50 g, 16.4 mmol) and maintained at this temperature for an additional 30 minutes. The solution was cooled to 90° C., treated with 1.4 mL of concentrated HCl and cooled to room temperature. The solution was washed with saturated aqueous  $NaHCO_3$ , and with brine and dried over anhydrous  $MgSO_4$ , filtered and concentrated to give 1-(3-chloro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]-ethan-1-one as a solid that was used directly in the next step:  $^1H$  NMR ( $CDCl_3$ /300 MHz)  $\delta$  7.90 (d,  $J=8.66$  Hz, 2H), 7.29–7.24 (m, 3H), 7.11 (dd,  $J=8.46$ , 2.21 Hz, 1H), 6.88 (d,  $J=8.46$  Hz, 1H), 4.19 (s, 2H), 3.86 (s, 3H), 2.55 (s, 3H).

Step 5. Preparation of 1-(3-chloro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]-ethan-1-one oxime.

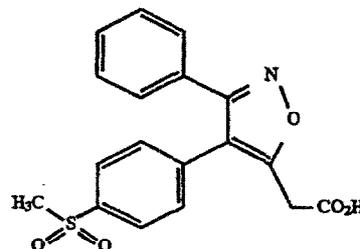
1-(3-Chloro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]-ethan-1-one oxime was prepared in 41% yield from the reaction of 1-(3-chloro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]-ethan-1-one from Step 4 with hydroxylamine by the method outlined in Example 1, Step 1:  $^1H$  NMR ( $CDCl_3$ /300 MHz)  $\delta$  7.69 (d,  $J=2.22$  Hz, 1H), 7.47 (dd,  $J=8.66$ , 2.22 Hz, 1H), 7.21–7.16 (m, 4H), 6.86 (d,  $J=8.66$  Hz, 1H), 4.11 (s, 2H), 3.89 (s, 3H), 2.44 (s, 3H).

Step 6. Preparation of 3-(3-chloro-4-methoxyphenyl)-4-[4-methylsulfonylphenyl]-5-methylisoxazole

3-(3-Chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylthio)phenyl]isoxazole was prepared in 26% yield

from 1-(3-chloro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]-ethan-1-one oxime from Step 5 and acetic anhydride by the method described in Example 4, Step 1 and then oxidized to 3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-methylsulfonylphenyl]isoxazole with Oxone® by the method described in Example 5, Step 4: Mass spectrum:  $MH^+=384$ . High resolution mass spectrum Calc'd. For  $C_{18}H_{16}ClNO_4S$ : 378.0567. Found: 378.0573.

## EXAMPLE 8



[4-[4-(Methylsulfonyl)phenyl]-3-phenyl]isoxazol-5-yl]acetic Acid

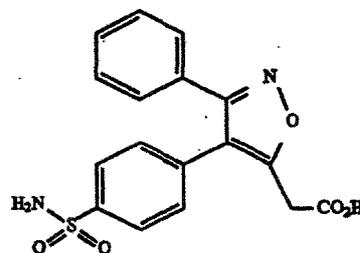
Step 1. Preparation of [4-[4-(methylthio)phenyl]-3-phenylisoxazol-5-yl]acetic acid.

[4-[4-(Methylthio)phenyl]-3-phenylisoxazol-5-yl]acetic acid was prepared in 35% yield by carboxylation of 4-[4-(methylthio)phenyl]-5-methyl-3-phenylisoxazole [Example 5, Step 3] according to the procedure detailed in Example 6, Step 4: Mass spectrum:  $MH^+=326$ . High resolution mass spectrum Calc'd. for  $C_{18}H_{15}NO_3S$ : 325.0773. Found: 325.0776.

Step 2. Preparation Of [4-[4-(methylsulfonyl)phenyl]-3-phenylisoxazol-5-yl]acetic acid.

[4-[4-(Methylsulfonyl)phenyl]-3-phenyl]isoxazol-5-yl]acetic acid was prepared in 80% yield from [4-[4-(methylthio)phenyl]-3-phenylisoxazol-5-yl]acetic acid (Step 1) by oxidation with Oxone® according to the procedure detailed in Example 5, Step 4: Mass spectrum:  $MH^+=326$ . High resolution mass spectrum Calc'd. For  $C_{18}H_{15}NO_3S$ : 358.0749. Found: 358.0769.

## EXAMPLE 9



[4-[4-(Aminosulfonyl)phenyl]-3-phenyl]isoxazol-5-yl]acetic Acid

Step 1. Preparation of 3,4-diphenyl-5-methylisoxazole.

A solution of desoxybenzoin keto-oxime (Example 1, Step 1) (6.00 g, 28.40 mmol) in anhydrous tetrahydrofuran (80 mL) was cooled to -20° C. in an oven-dried 250 mL three-neck round-bottom flask equipped with a thermometer, nitrogen gas inlet, rubber septum and provisions for magnetic stirring. To this cold solution,

n-butyllithium (1.6N in hexanes, 44.4 mL) was added, via syringe, over 35 minutes, such that the reaction temperature remained at or below  $-10^{\circ}\text{C}$ . The deep red solution was stirred at  $-10^{\circ}\text{C}$  for 1 hour, warmed to room temperature, then stirred at room temperature for an additional hour. Acetic anhydride (3.2 mL, 34.1 mmol) was added in one portion, and the resulting suspension was stirred without temperature control for 2 hours. Water (100 mL) was added, and the solution was poured into 1N HCl (100 mL) and extracted with ethyl acetate ( $2 \times 200$  mL). The combined organic solution was washed with HCl (1N HCl, 100 mL) and brine (100 mL), dried over anhydrous  $\text{MgSO}_4$  and filtered. The resulting solution was concentrated in vacuo to yield a crude oil. The oil was applied to a column of silica gel and eluted with ethyl acetate/hexane (10–50% ethyl acetate) to yield, upon concentration of the appropriate fractions, 5.0 g of 3,4-diphenyl-4-hydroxy-5-hydroxy-5-methylisoxazole. A 100 mL round bottomed flask equipped with reflux condenser was charged with 3,4-diphenyl-4-hydroxy-5-hydroxy-5-methylisoxazole (5.00 g, 19.74 mmol), 300 mg of concentrated  $\text{H}_2\text{SO}_4$  and 30 mL of toluene. The solution was heated to reflux for 1 hour, poured into a separatory funnel and washed with water. The toluene solution was dried over anhydrous  $\text{MgSO}_4$ , filtered, and concentrated in vacuo and the residue used directly in the next step without further purification.

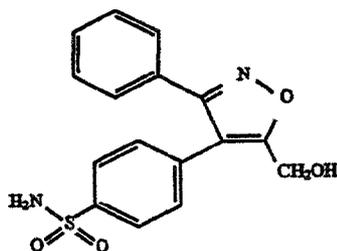
Step 2. Preparation of (3,4-diphenylisoxazol-5-yl)acetic acid:

(3,4-Diphenylisoxazol-5-yl)acetic acid was prepared in 53% yield by carboxylation of 3,4-diphenyl-5-methylisoxazole (Step 1) according to the procedure outlined in Example 6, Step 4: Mass spectrum:  $\text{MH}^+ = 280$ . High resolution mass spectrum Calc'd. for  $\text{C}_{17}\text{H}_{13}\text{NO}_3$ : 280.0894. Found: 280.0897. Anal. Calc'd. for  $\text{C}_{17}\text{H}_{13}\text{NO}_3$ : C, 73.11; H, 4.69; N, 5.01. Found: C, 72.91; H, 4.73; N, 4.97.

Step 3. Preparation of [4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]acetic acid:

[4-[4-(Aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]acetic acid was prepared in 60% yield by chlorosulfonation followed by ammonolysis of 1-(3,4-diphenylisoxazol-5-yl)acetic acid according to the procedure outlined in Example 2, Step 4: mp  $61^{\circ}\text{C}$ . Mass spectrum:  $\text{MH}^+ = 359$ .

#### EXAMPLE 10

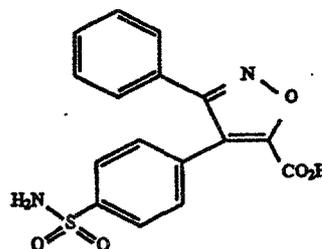


4-[5-Hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide

4-[5-Methyl-3-phenyl-4-yl]benzenesulfonamide (Example 1) (20.965 g, 66.69 mmol) and THF (1.4 L) were cooled to  $-78^{\circ}\text{C}$  (dry-ice/acetone bath) and a premeasured volume of n-BuLi (167 mL, 266.76 mmol) in a 250 mL round bottomed flask was added via cannula causing the reaction solution to become bright red. After 15 minutes the dry ice/acetone bath was replaced with a NaCl/ice/water bath and the reaction warmed to  $-5^{\circ}\text{C}$  over 15 minutes and

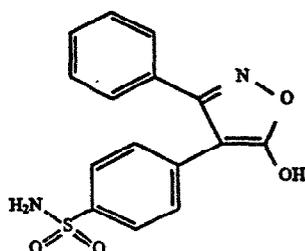
was maintained at  $-5^{\circ}\text{C}$  for 30 more minutes. The NaCl/ice/ $\text{H}_2\text{O}$  bath was replaced with a dry ice/acetone bath and the reaction chilled to  $-71^{\circ}\text{C}$ . Oxygen was added via two 14 gauge needles (ca. 4 psi) and a similar outlet provided. Within 10 minutes the reaction, formerly a red suspension, became an ocre-yellow suspension. Oxygen addition was continued for 30 more minutes. The oxygen line and vents were removed and trimethyl phosphite (67 mL, 566.97 mmol) was added via syringe. After 15 minutes, the septum was removed and a solution of HOAc (125 mL) and  $\text{H}_2\text{O}$  (125 mL) was added in one portion causing the solution to become a hazy bright yellow and the reaction temperature to rise to  $-50^{\circ}\text{C}$ . The dry ice bath was removed and the reaction was warmed to room temperature. Brine (700 mL) and 1N HCl (134 mL) were added and stirred for 15 minutes. Ethyl acetate (700 mL) was added and the layers were separated in a separatory funnel. The aqueous phase was washed with ethyl acetate (150 mL) and the organic layers combined. The organic layer was washed with water,  $\text{NaHCO}_3$  ( $5 \times 100$  mL) and brine, dried over anhydrous  $\text{MgSO}_4$ , and filtered. The resulting organic phase was diluted with toluene (125 mL) and concentrated in vacuo three times yielding a brown viscous oil. The crude product was purified by flash chromatography (silica gel,  $10 \times 18$  cm column, hexane/ethyl acetate (1/2) with a step gradient to hexane/ethyl acetate (1/2)) yielding a yellow solid (11.25 g). The product was dissolved in ethyl acetate (500 mL) and acetone (60 mL). Partial concentration of this solution and addition of hexane yielded a yellow solid which was collected by vacuum filtration. This solid was dissolved in a minimum of acetone and added to hot  $\text{H}_2\text{O}$  (800 mL at  $70^{\circ}\text{C}$ ) yielding the desired product as a very fine crystalline yellow product (7.89 g, 36%): mp  $188^{\circ}\text{--}189^{\circ}\text{C}$ .  $^1\text{H}$  NMR (DMSO  $d_6$ )  $\delta$  7.81 (d,  $J=8.26$  Hz, 2H), 7.26–7.55 (m, 9H), 5.77 (t,  $J=4.84$ , 1H), 4.54 (d,  $J=4.84$ , 2H). Anal. Calc'd. for  $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_4\text{S}_2$ : C, 58.17; H, 4.27; N, 8.48. Found: C, 58.22; H, 4.31; N, 8.50. Mass spectrum:  $\text{M}^+ + \text{H}$ : 331.

#### EXAMPLE 11



[4-[4-(Aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]carboxylic Acid

To a solution of 4-[5-hydroxymethyl-3-phenyl-4-yl]benzenesulfonamide (Example 10) (0.64 g, 1.94 mmol) in acetone at  $-78^{\circ}\text{C}$  (dry ice/acetone bath) was added carefully Jones reagent (0.7 mL of 2.44M  $\text{CrO}_3$  in aqueous  $\text{H}_2\text{SO}_4$  solution). The reaction was warmed to  $0^{\circ}\text{C}$  and an additional 0.7 mL (2.44M  $\text{CrO}_3$  in aqueous  $\text{H}_2\text{SO}_4$  solution) was added. The reaction was warmed to room temperature and stirred overnight. Isopropanol (2 mL) was added and was stirred for 2 hour. The reaction was diluted with ethyl acetate, washed with  $\text{H}_2\text{O}$ , dried over anhydrous  $\text{MgSO}_4$ , filtered through Celite® and concentrated in vacuo yielding a solid. Recrystallization of this solid from toluene yielding the desired product (0.075 g, 11%) as a tan solid: mp  $300^{\circ}\text{C}$ .  $^1\text{H}$  NMR (DMSO  $d_6$ )  $\delta$  7.70 (d,  $J=8.46$  Hz, 2H), 7.08–7.50 (m, 9H).

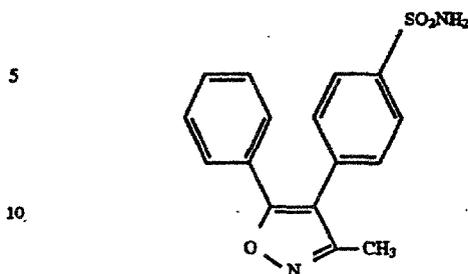
37  
EXAMPLE 124-[5-Hydroxy-3-phenyl-4-isoxazolyl]  
benzenesulfonamide

## Step 1. Preparation of 3,4-diphenylisoxazolin-5-one.

To a stirred solution of the deoxybenzoin oxime (50.59 g, 239 mmol) in anhydrous THF (1 L) in a 2000 mL 2-neck round bottomed flask fitted with septum, under nitrogen atmosphere, and chilled to  $-78^{\circ}\text{C}$ . (dry ice/acetone bath) was added *n*-BuLi (375 mL of 1.6M in hexanes, 599 mmol) via cannula over 15 minutes. After twenty minutes at  $-78^{\circ}\text{C}$ . the dry ice/acetone bath was replaced with a NaCl/ice/ $\text{H}_2\text{O}$  and the reaction was warmed to  $0^{\circ}\text{C}$ . over 1 hour. The NaCl/ice/ $\text{H}_2\text{O}$  bath was replaced with a dry ice/acetone bath. When  $-78^{\circ}\text{C}$ . was reached, the reaction solution was transferred via cannula to a 4 L Erlenmeyer flask filled with 1500 cc of powdered dry ice and the resulting yellow mixture was let stand overnight at room temperature. The clear, straw colored solution was transferred to a 3 L round bottomed flask, and 700 mL of 3N HCl was added. The reaction was heated to reflux for 1 hour and cooled to room temperature. The reaction was diluted with brine (500 mL) and the layers were separated in a separatory funnel. The aqueous layer was extracted with dichloromethane/ethyl acetate (2/1) (400 mL). The organic layers were combined and washed with brine (200 mL), dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated yielding a brown solid. The solid was re-dissolved in warm THF and hexanes were added yielding a fluffy off-white crystalline solid (30.4 g, 54%). A second crop was obtained (12.66 g, 22 %): mp  $162^{\circ}\text{--}163^{\circ}\text{C}$ . (dec.). This material was suitable for use without further purification.

## Step 2. Preparation of 4-[5-hydroxy-3-phenyl-4-yl]benzenesulfonamide.

3,4-Diphenylisoxazolin-5-one from step 1 (15.6 g, 65.75 mmol) was added carefully to  $\text{ClSO}_3\text{H}$  (160 mL) in a 250 mL round bottomed flask chilled in a NaCl/ice bath. After 2 hours, the crude reaction mixture was carefully poured over ice, yielding the crude sulfonyl chloride as a precipitate which was collected by vacuum filtration. The solid was dissolved in dichloromethane yielding two phases which were separated, and the organic phase dried over anhydrous  $\text{MgSO}_4$ . This clear pale yellow solution was slowly added to a chilled ( $0^{\circ}\text{C}$ .) saturated solution of  $\text{NH}_3$ , in dichloromethane. The resulting suspension was diluted with  $\text{CH}_3\text{OH}$  and was washed with  $\text{KHSO}_4$  (0.25M aq soln.). The organic layer was dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated in vacuo yielding a tan solid which was collected by vacuum filtration. This solid was dissolved in a minimum of 1N NaOH solution, filtered, and washed with dichloromethane. The aqueous layer was acidified with concentrated HCl yielding and off-white solid (3.70 g, 18%): mp  $207^{\circ}\text{C}$ . (dec.).  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$  with NaOD)  $\delta$  7.48 (d,  $J=8.46$  Hz, 2 H), 7.38–7.20 (m, 5 H), 7.14, (d,  $J=8.26$ , 2 H). The methanolic/aqueous  $\text{KHSO}_4$  wash phase, upon partial evaporation yielded additional desired product as a tan solid (8.94 g, 43%).

38  
EXAMPLE 134-[3-Methyl-5-phenyl-4-isoxazolyl]  
benzenesulfonamide

## Step 1. Preparation of 1,2-diphenyl-1-butene-3-one oxime.

A solution of 1,2-diphenyl-1-butene-3-one (1.5 g, 7 mmol) in EtOH (15 ml) and was added to a solution of hydroxylamine hydrochloride (500 mg, 7 mmol) and  $\text{NaHCO}_3$  (1 g) in water (7 ml). The mixture was heated to reflux for 5 hours at which time thin layer chromatography indicated the reaction was incomplete. Additional hydroxylamine hydrochloride (500 mg, 7 mmol) was added and heating at reflux was continued overnight. The reaction was cooled, poured into water (100 ml) and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and the filtrate concentrated in vacuo. The crude material was chromatographed on silica gel using 5% ethyl acetate in toluene as the eluant to give 450 mg (30%) of the desired oxime as a crystalline solid, m.p.  $138^{\circ}\text{--}141^{\circ}$ . Anal. Calc'd for  $\text{C}_{16}\text{H}_{15}\text{NO}$ : C, 80.98; H, 6.37; N, 5.90. Found: C, 80.79; H, 6.25; N, 6.09.

## Step 2. Preparation of 3,4-diphenyl-5-methylisoxazole

To a solution of oxime from Step 1 (450 mg, 1.9 mmol) and sodium bicarbonate (650 mg, 7.7 mmol) in tetrahydrofuran (6 ml) and water (6 ml) in a vessel wrapped in aluminum foil was added a solution of potassium iodide (1.1 g, 6.6 mmol) and iodine (525 mg, 2 mol) in water (4 ml). The reaction was heated to reflux for 7 hours and stirred at room temperature overnight. Saturated aqueous sodium bisulfite solution (5 ml) was added and the reaction mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and the crude material was isolated after filtration and concentration of the filtrate. Chromatography on silica gel using toluene as the eluant gave 290 mg (57%) of the isoxazole as an oil which crystallized on standing: mp  $92^{\circ}\text{--}94^{\circ}\text{C}$ . Anal. Calc'd for  $\text{C}_{16}\text{H}_{13}\text{NO}$ : C, 81.31; H, 5.57; N, 5.95. Found: C, 81.31, H, 5.71; N, 6.18.

## Step 3. Preparation of 4-[3-methyl-5-phenyl-4-isoxazolyl]benzenesulfonamide.

A solution of the isoxazole from step 1 (250 mg, 1.1 mmol) in chlorosulfonic acid (1 ml) was stirred at  $0^{\circ}$  for 3 hours. The reaction was cautiously added to concentrated ammonium hydroxide (6 ml) in the cold ( $0^{\circ}\text{C}$ .) The resultant reaction mixture was stirred at  $0^{\circ}$  for 1 hour. The reaction was cautiously diluted with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and the filtrate concentrated in vacuo to give the crude product. This material was chromatographed on silica gel using 25% ethyl acetate in toluene as the eluant to give the desired sulfonamide as a crystalline solid (110 mg, 40%): mp  $85^{\circ}\text{--}87^{\circ}\text{C}$ . Anal. Calc'd for  $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$ : C, 61.13; H, 4.49; N, 8.91; S, 10.20. Found: C, 60.88; H, 4.61; N, 8.55; S, 10.40.

## Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test was performed with materials, reagents and procedures essentially as described by Winter, et al., (*Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962)). Male Sprague-Dawley rats were selected in each group so that the average body weight was as close as possible. Rats were fasted with free access to water for over sixteen hours prior to the test. The rats were dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline was administered and the volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a group of drug-treated animals was compared with that of a group of placebo-treated animals and the percentage inhibition of edema was determined (Otterness and Bliven, *Laboratory Models for Testing NSAIDs, in Non-steroidal Anti-Inflammatory Drugs*, (J. Lombardino, ed. 1985)). The % inhibition shows the % decrease from control paw volume determined in this procedure and the data for selected compounds in this invention are summarized in Table I.

## Rat Carrageenan-induced Analgesia Test

The rat carrageenan analgesia test was performed with materials, reagents and procedures essentially as described by Hargreaves, et al., (*Pain*, 32, 77 (1988)). Male Sprague-Dawley rats were treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats were placed in a special plexiglass container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty minute period, thermal stimulation was begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell turned off the lamp and timer when light was interrupted by paw withdrawal. The time until the rat withdraws its foot was then measured. The withdrawal latency in seconds was determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal determined. Results are shown in Table I.

TABLE I

Example	RAT PAW EDEMA		ANALGESIA	
	% Inhibition @ 10 mg/kg body weight		% Inhibition @ 10 mg/kg body weight	
1	29		33	

## Evaluation of COX-1 and COX-2 activity in vitro

The compounds of this invention exhibited inhibition in vitro of COX-2. The COX-2 inhibition activity of the compounds of this invention illustrated in the Examples was determined by the following methods.

## a. Preparation of recombinant COX baculoviruses

Recombinant COX-1 and COX-2 were prepared as described by Gierse et al., [*J. Biochem.*, 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 was cloned into a BamHI site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the

method of D. R. O'Reilly et al. (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses were isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells ( $2 \times 10^6$ ) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. Sec M. D. Summers and G. E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses were purified by three rounds of plaque purification and high titer ( $10^7$ - $10^8$  pfu/ml) stocks of virus were prepared. For large scale production, SF9 insect cells were infected in 10 liter fermentors ( $0.5 \times 10^6$ /ml) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate was centrifuged at 10,000×G for 30 minutes, and the resultant supernatant was stored at -80° C. before being assayed for COX activity.

## b. Assay for COX-1 and COX-2 activity

COX activity was assayed as PGE<sub>2</sub> formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme were incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 µM). Compounds were pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after ten minutes at 37° C./room temperature by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE<sub>2</sub> formed was measured by standard ELISA technology (Cayman Chemical). Results are shown in Table II.

TABLE II

Example	COX-2 ID <sub>50</sub> µM	COX-1 ID <sub>50</sub> µM
1	<0.1	>100
1a	<0.1	17.4
1b	<0.1	13.2
1c	<0.1	6.2
1d	<0.1	25.8
1e	<0.1	37.7
1f	0.2	54
1g	<0.1	>100
1h	<0.1	4.7
1i	<0.1	8.6
1k	<0.1	>100
1l	<0.1	50.7
1m	1.5	>100
1n	51	>100
1o	<0.1	>100
1p	0.1	>100
2	0.9	17.4
3	2.6	0.6
4	3	>100
4a	<0.1	90.5
4b	<0.1	>100
4c	<0.1	66.5
4d	<0.1	44
4e		
4f	2	>100
4g	>100	>100
5	4.0	>100
6	35.7	>100
7	86.7	>100
8	>100	>100
9	1.4	>100

TABLE II-continued

Example	COX-2 ID <sub>50</sub> μM	COX-1 ID <sub>50</sub> μM
10	0.2	>100
11	35	
12	2.5	>100
13	<0.1	6.4

Also embraced within this invention is a class of pharmaceutical compositions comprising one or more compounds of Formula I in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and composition may, for example, be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably between about 1 to 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

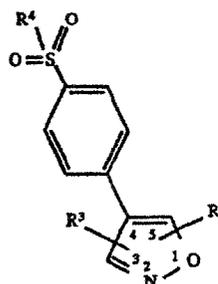
For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxy-propylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn

oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What is claimed is:

1. A compound of Formula II



wherein R<sup>1</sup> is selected from alkyl, carboxyalkyl, alkoxyalkyl, aminocarbonyl, aminocarbonylalkyl, alkoxyalkyl, haloalkoxy, aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, arylalkoxyalkyl, arylthioalkyl, hydroxyl, amino, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxyalkyl, alkoxyalkyl, alkylaminocarbonyloxyalkyl, alkoxyalkyl, and alkylaminocarbonylthioalkyl;

wherein R<sup>2</sup> is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxyalkyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, halo, alkoxy and alkylthio; and

wherein R<sup>4</sup> is selected from lower alkyl, hydroxyl, and amino;

or a pharmaceutically-acceptable salt thereof.

2. A compound of claim 1 wherein R<sup>1</sup> is selected from hydroxyl, amino, lower alkyl, lower carboxyalkyl, lower alkoxyalkyl, aminocarbonyl, carboxyl, lower aminocarbonylalkyl, lower alkoxyalkyl, lower alkoxy, lower haloalkoxy, lower aralkoxy, lower cycloalkylalkoxy, lower alkylthio, lower aralkylthio, lower cycloalkylalkylthio, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower arylalkoxyalkyl, lower arylthioalkyl, lower hydroxyalkyl, lower haloalkyl, lower cycloalkyl, lower cycloalkylalkyl, lower aralkyl, halo, lower alkylamino, lower aralkylamino, lower N-alkyl-N-aralkylamino, lower N-alkyl-N-cycloalkylalkylamino, lower arylcarbonyloxyalkyl, lower alkoxyalkyl, lower alkylaminocarbonyloxyalkyl, lower alkoxyalkyl, and lower alkylaminocarbonylthioalkyl; wherein R<sup>2</sup> is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, lower alkyl, cyano, carboxyl, lower alkoxyalkyl, lower haloalkyl,

43

hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy, lower alkylsulfonyl, aminosulfonyl, and lower alkylthio; and wherein R<sup>4</sup> is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

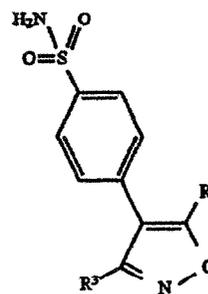
3. A compound of claim 2 wherein R<sup>1</sup> is selected from hydroxyl, lower alkyl, carboxyl, lower carboxyalkyl, lower aminocarbonylalkyl, lower alkoxyalkyl, lower aralkyl, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower aryloxyalkyl, lower arylthioalkyl, lower haloalkyl, lower hydroxyalkyl, cycloalkyl, cycloalkylalkyl, and aralkyl; wherein R<sup>2</sup> is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, lower alkyl, cyano, carboxyl, lower alkoxyalkyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy, aminosulfonyl, and lower alkylthio; and wherein R<sup>4</sup> is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

4. A compound of claim 3 wherein R<sup>1</sup> is selected from hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, benzyl, phenethyl, aminocarbonylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, methoxymethyl, benzyloxymethyl, phenylethoxymethyl, methylthiomethyl, benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, phenyloxymethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxymethyl, hydroxylpropyl, hydroxyethyl, cyclohexyl, cyclobutyl, cyclopentyl, cycloheptyl, cyclohexylmethyl, cyclohexylethyl, cyclobutylethyl, cyclopentylmethyl, cycloheptylpropyl, and lower aralkyl selected from benzyl and phenylethyl, wherein the phenyl ring is optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methyl, and methoxy; wherein R<sup>2</sup> is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, and 1-cyclohexenyl; wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, aminosulfonyl, methylthio, ethylthio, butylthio, and hexylthio; and wherein R<sup>4</sup> is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

5. The compound of claim 4 which is 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

44

6. A compound of Formula III



wherein R<sup>1</sup> is selected from hydroxyl, alkyl, carboxyalkyl, aminocarbonylalkyl, alkoxyalkyl, carboxyl, alkoxy, haloalkoxy, aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, aryloxyalkyl, arylthioalkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxyalkoxyalkyl, alkylaminocarbonyloxyalkyl, alkoxyalkoxyalkyl, and alkylaminocarbonylthioalkyl; and

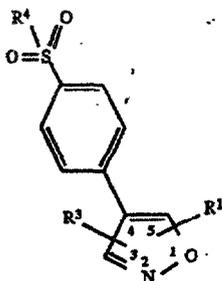
wherein R<sup>2</sup> is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxyalkyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, aminosulfonyl, halo, alkoxy and alkylthio; or a pharmaceutically-acceptable salt thereof.

7. A compound of claim 6 wherein R<sup>1</sup> is selected from hydroxyl, lower alkyl, carboxyl, lower carboxyalkyl, lower aminocarbonylalkyl, lower alkoxyalkyl, lower aralkyl, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower aryloxyalkyl, lower arylthioalkyl, lower haloalkyl, lower hydroxyalkyl, lower cycloalkyl, lower cycloalkylalkyl, and aralkyl; wherein R<sup>2</sup> is selected from cycloalkyl, cycloalkenyl, and aryl; and wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, aminosulfonyl, lower alkyl, cyano, carboxyl, lower alkoxyalkyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy and lower alkylthio; or a pharmaceutically-acceptable salt thereof.

8. A compound of claim 7 wherein R<sup>1</sup> is selected from hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, benzyl, phenethyl, aminocarbonylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, methoxymethyl, benzyloxymethyl, phenylethoxymethyl, methylthiomethyl, benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, phenyloxymethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, hydroxylpropyl, hydroxyethyl, cyclohexyl, cyclobutyl, cyclopentyl, cycloheptyl,

cyclohexylmethyl, cyclohexylethyl, cyclobutylethyl, cyclopentylmethyl, cycloheptylpropyl, and lower aralkyl selected from phenylethyl and benzyl optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methyl, and methoxy; and wherein R<sup>3</sup> is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, and 1-cyclopentenyl; wherein R<sup>2</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, aminomethyl, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, methylthio, aminosulfonyl, ethylthio, butylthio, and hexylthio; or a pharmaceutically-acceptable salt thereof.

9. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Formula II



wherein R<sup>1</sup> is selected from alkyl, carboxyalkyl, alkoxyalkyl, aminocarbonyl, aminocarbonylalkyl, alkoxyalkyl, alkoxy, haloalkoxy, aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, arylalkoxyalkyl, arylthioalkyl, hydroxyl, amino, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxyalkoxyalkyl, alkylaminocarbonyloxyalkyl, alkoxyalkoxythioalkyl, and alkylaminocarbonylthioalkyl;

wherein R<sup>2</sup> is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxyalkoxy, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, halo, alkoxy and alkylthio; and

wherein R<sup>4</sup> is selected from lower alkyl, hydroxyl, and amino;

or a pharmaceutically-acceptable salt thereof.

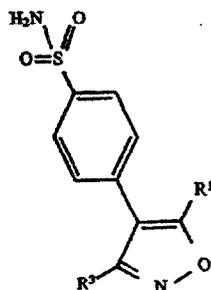
10. A pharmaceutical composition of claim 9 wherein R<sup>1</sup> is selected from hydroxyl, amino, lower alkyl, lower

carboxyalkyl, lower alkoxyalkoxy, aminocarbonyl, carboxyl, lower aminocarbonylalkyl, lower alkoxyalkoxyalkyl, lower alkoxy, lower haloalkoxy, lower aralkoxy, lower cycloalkylalkoxy, lower alkylthio, lower aralkylthio, lower cycloalkylalkylthio, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower arylalkoxyalkyl, lower arylthioalkyl, lower hydroxyalkyl, lower haloalkyl, lower cycloalkyl, lower cycloalkylalkyl, lower aralkyl, halo, lower alkylamino, lower aralkylamino, lower N-alkyl-N-aralkylamino, lower N-alkyl-N-cycloalkylalkylamino, lower arylcarbonyloxyalkyl, lower alkoxyalkoxyalkyl, lower alkylaminocarbonyloxyalkyl, lower alkoxyalkoxythioalkyl, and lower alkylaminocarbonylthioalkyl; wherein R<sup>3</sup> is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R<sup>2</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, lower alkyl, cyano, carboxyl, lower alkoxyalkoxy, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy, lower alkylsulfonyl, aminosulfonyl, and lower alkylthio; and wherein R<sup>4</sup> is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

11. A pharmaceutical composition of claim 10 wherein R<sup>1</sup> is selected from hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, benzyl, phenethyl, aminocarbonylmethyl, methoxyalkoxyalkyl, methoxyalkoxyethyl, methoxymethyl, benzyloxymethyl, phenylethoxymethyl, methylthiomethyl, benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, phenylethoxymethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxylmethyl, hydroxypropyl, hydroxyethyl, cyclohexyl, cyclobutyl, cyclopentyl, cycloheptyl, cyclohexylmethyl, cyclohexylethyl, cyclobutylethyl, cyclopentylmethyl, cycloheptylpropyl, and lower aralkyl selected from benzyl and phenylethyl, wherein the phenyl ring is optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methyl, and methoxy; wherein R<sup>2</sup> is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, and 1-cyclopentenyl; wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, aminosulfonyl, methylthio, ethylthio, butylthio, and hexylthio; and wherein R<sup>4</sup> is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

12. A pharmaceutical composition of claim 11 wherein said compound is 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

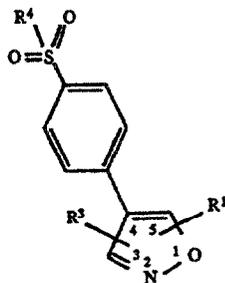
13. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Formula III



wherein  $R^1$  is selected from hydroxyl, alkyl, carboxyalkyl, aminocarbonylalkyl, alkoxy, haloalkoxy, aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, arylthioalkyl, arylthioalkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxycarbonyloxyalkyl, alkylaminocarbonyloxyalkyl, alkoxycarbonylthioalkyl, and alkylaminocarbonylthioalkyl; and

wherein  $R^3$  is selected from cycloalkyl, cycloalkenyl, and aryl; wherein  $R^3$  is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxy, haloalkoxy, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, aminosulfonyl, halo, alkoxy and alkylthio; or a pharmaceutically-acceptable salt thereof.

14. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said inflammation or inflammation-associated disorder, a therapeutically-effective amount of a compound of Formula II



wherein  $R^1$  is selected from alkyl, carboxyalkyl, alkoxy, haloalkoxy, aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, arylthioalkyl, arylthioalkyl, hydroxyl, amino, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio,

alkoxycarbonyloxyalkyl, alkylaminocarbonyloxyalkyl, alkoxycarbonylthioalkyl, and alkylaminocarbonylthioalkyl;

wherein  $R^2$  is selected from cycloalkyl, cycloalkenyl, and aryl; wherein  $R^3$  is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxy, haloalkoxy, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, halo, alkoxy and alkylthio; and wherein  $R^4$  is selected from lower alkyl, hydroxyl, and amino;

or a pharmaceutically-acceptable salt thereof.

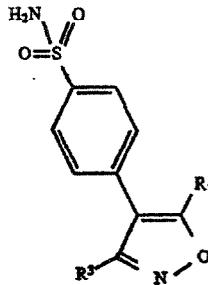
15. A method of claim 14 wherein  $R^1$  is selected from hydroxyl, amino, lower alkyl, lower carboxyalkyl, lower alkoxy, lower haloalkoxy, lower aralkoxy, lower aminocarbonylalkyl, lower alkoxy, lower haloalkoxy, lower aralkoxy, lower cycloalkylalkoxy, lower alkylthio, lower aralkylthio, lower cycloalkylalkylthio, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower arylthioalkyl, lower arylthioalkyl, lower hydroxyalkyl, lower haloalkyl, lower cycloalkyl, lower cycloalkylalkyl, lower aralkyl, halo, lower alkylamino, lower aralkylamino, lower N-alkyl-N-aralkylamino, lower N-alkyl-N-cycloalkylalkylamino, lower arylcarbonyloxyalkyl, lower alkoxycarbonyloxyalkyl, lower alkylaminocarbonyloxyalkyl, lower alkoxycarbonylthioalkyl, and lower alkylaminocarbonylthioalkyl; wherein  $R^3$  is selected from cycloalkyl, cycloalkenyl, and aryl; wherein  $R^3$  is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkyl, cyano, carboxyl, lower alkoxy, lower haloalkoxy, lower amino, lower hydroxyalkyl, lower haloalkoxy, lower alkylamino, lower aralkylamino, lower aminoalkyl, nitro, lower alkoxy, lower alkylsulfonyl, aminosulfonyl, and lower alkylthio; and wherein  $R^4$  is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

16. A method of claim 15 wherein  $R^1$  is selected from hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, benzyl, phenethyl, aminocarbonylmethyl, methoxycarbonylmethyl, methoxycarbonylpropyl, methoxymethyl, benzylmethyl, phenylethoxymethyl, methylthiomethyl, benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, phenylmethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoropropyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxymethyl, hydroxylpropyl, hydroxyethyl, cyclohexyl, cyclobutyl, cyclopentyl, cycloheptyl, cyclohexylmethyl, cyclohexylethyl, cyclobutylethyl, cyclopentylethyl, cycloheptylpropyl, and lower aralkyl selected from benzyl and phenylethyl, wherein the phenyl ring is optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methyl, and methoxy; wherein  $R^2$  is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, and 1-cyclopentenyl; wherein  $R^3$  is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino,

N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, aminosulfonyl, methylthio, ethylthio, butylthio, and hexylthio; and wherein R<sup>4</sup> is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

17. A method of claim 16 wherein said compound is 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

18. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said inflammation or inflammation-associated disorder, a therapeutically-effective amount of a compound of Formula III



wherein R<sup>1</sup> is selected from hydroxyl, alkyl, carboxyalkyl, aminocarbonylalkyl, alkoxyalkyl, aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, aryloxyalkyl, arylthioalkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxyalkoxyalkyl, alkylaminocarbonyloxyalkyl, alkoxyalkoxyalkyl, and alkylaminocarbonylthioalkyl; and

wherein R<sup>3</sup> is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R<sup>3</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxy, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, aminosulfonyl, halo, alkoxy and alkylthio; or a pharmaceutically-acceptable salt thereof.

19. A method of claim 14 for use in treatment of inflammation.

20. A method of claim 14 for use in treatment of an inflammation-associated disorder.

21. A method of claim 20 wherein the inflammation-associated disorder is arthritis.

22. A method of claim 20 wherein the inflammation-associated disorder is pain.

23. A method of claim 20 wherein the inflammation-associated disorder is fever.

24. The compound of claim 4 selected from compounds, or their pharmaceutically acceptable salts, of the group consisting of

4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isopropyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isobutyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-cyclohexyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-neopentyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-trifluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-chloromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-methoxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[3-(4-chlorophenyl)-5-methylisoxazol-4-yl]benzenesulfonamide;

4-[3-(4-fluorophenyl)-5-methylisoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluoro-4-methylphenyl)-5-methylisoxazol-4-yl]benzenesulfonamide;

4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methylisoxazol-4-yl]benzenesulfonamide;

4-[3-(3-chloro-4-methylphenyl)-5-methylisoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluorophenyl)-5-methylisoxazol-4-yl]benzenesulfonamide;

4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

[4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]carboxylic acid;

4-[5-hydroxy-3-phenyl-4-isoxazolyl]benzenesulfonamide;

4-[3-methyl-5-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluoro-4-methoxyphenyl)-5-methylisoxazol-4-yl]benzenesulfonamide;

[3-(3-chloro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid;

5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenylisoxazole;

3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;

[4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]acetic acid;

[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl] propanoic acid;

ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoate;

[3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid; and

[4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid.

25. The compound of claim 4 which is 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

26. A pharmaceutical composition of claim 11 wherein said compound is selected from compounds, or their pharmaceutically-acceptable salts, of the group consisting of

4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isopropyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isobutyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-cyclohexyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-neopentyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-trifluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-chloromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-methoxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluoro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-chloro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

[4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]carboxylic acid;

4-[5-hydroxy-3-phenyl-4-isoxazolyl]benzenesulfonamide;

4-[3-methyl-5-phenyl-isoxazol-4-yl]benzenesulfonamide;

4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluoro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

[3-(3-chloro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid;

5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenyl-isoxazole;

3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;

[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]acetic acid;

[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoic acid;

ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoate;

[3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid; and

[4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid.

27. A pharmaceutical composition of claim 11 wherein said compound is 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

28. A method of claim 16 wherein said compound is selected from compounds, or their pharmaceutically-acceptable salts, of the group consisting of

4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isopropyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isobutyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-cyclohexyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-neopentyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-trifluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-chloromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-methoxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-fluoro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

53

4-[3-(3-chloro-4-methylphenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;  
 4-[3-(3-fluorophenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;  
 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;  
 [4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl] carboxylic acid;  
 4-[5-hydroxy-3-phenyl-4-isoxazolyl] benzenesulfonamide;  
 4-[3-methyl-5-phenyl-isoxazol-4-yl] benzenesulfonamide;  
 4-[5-methyl-3-phenyl-isoxazol-4-yl] benzenesulfonamide;  
 4-[3-(3-fluoro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;  
 [3-(3-chloro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid;  
 5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenyl-isoxazole;

54

3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;  
 [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl] acetic acid;  
 [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl] propanoic acid;  
 ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoate;  
 [3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid; and  
 [4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid.

29. A method of claim 16 wherein said compound is 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl] benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

\* \* \* \* \*

**EXHIBIT III**

**Maintenance Fee Statement**



Patent and Trademark Office  
Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

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COMPUTER PACKAGES INC  
SUITE 300  
414 HUNGERFORD DRIVE  
ROCKVILLE MD 20850

## MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. **TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(h).**

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. **THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.**

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY SML YR ENT	STAT
1	5,633,272	183	850	----	08/473,884	05/27/97	06/07/95	04 NO	PAID

ITM NBR	ATTY DKT NUMBER
1	2865/1

**DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:  
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, D.C. 20231**

**EXHIBIT IV**

**Brief Description of  
Significant Activities**

**Exhibit IV**

**BEXTRA™ (Valdecoxib)**

**Brief Description of Significant Activities**

Date	Event
December 16, 1996	Investigational New Drug Application submitted to FDA (IND 52,153).
January 15, 1997	Permission granted by FDA to begin study proposed in initial IND.
January 16, 2001	New Drug Application initially submitted to FDA (NDA 21-341).
October 22, 2001	Clinical safety discussion held with FDA.
November 1, 2001	Clinical efficacy discussion held with FDA.
November 12, 2001	Labeling discussion held with FDA.
November 13, 2001	Labeling discussion held with FDA.
November 14, 2001	Labeling discussion held with FDA.
November 15, 2001	Labeling discussion held with FDA.
November 16, 2001	NDA for BEXTRA™ approved by FDA.