(57) Compounds useful in the treatment of cyclooxygenase-2 mediated diseases are provided of formula (I): (see formula I) wherein $R^1$ is selected from the group consisting of (a) $\text{SO}_2\text{CH}_3$, and (b) $\text{SO}_2\text{NH}_2$, and $R^2$ is unsubstituted, mono or di- substituted phenyl wherein the substituents are selected from the group consisting of halo, methoxy, methyl, said halo being selected from the group consisting of fluoro, chloro and bromo; the compounds (I) are produced in a process of treating in a non-aqueous polar solvent a compound of formula (A) (see formula A) wherein $R^1$ and $R^2$ are as defined above, in the presence of a strong base; to yield said compound of formula (I).
ABSTRACT

Compounds useful in the treatment of cyclooxygenase-2 mediated diseases are provided of formula (I):

wherein

R¹ is selected from the group consisting of
(a)  S(O)²CH₃, and
(b)  S(O)²NH₂, and

R² is unsubstituted, mono or di-substituted phenyl wherein the substituents are selected from the group consisting of halo, methoxy, methyl, said halo being selected from the group consisting of fluoro, chloro and bromo; the compounds (I) are produced in a process of treating in a non-aqueous polar solvent a compound of formula (A)
wherein $R^1$ and $R^2$ are as defined above, in the presence of a strong base; to yield said compound of formula (I).
TITLE OF THE INVENTION
PHENYL HETERO CYCLES AS COX-2 INHIBITORS

BACKGROUND OF THE INVENTION

This invention relates to compounds and pharmaceutical compositions for the treatment of cyclooxygenase mediated diseases and methods of treatment thereof.

This Application is a Divisional of Canadian Patent Application, Serial No. 2,176,974 which is a division of Serial No. 2,163,888, filed June 9, 1994.

Non-steroidal, antiinflammatory drugs exert most of their antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Up until recently, only one form of cyclooxygenase had been characterized, this corresponding to cyclooxygenase-1 or the constitutive enzyme, as originally identified in bovine seminal vesicles. Recently the gene for a second inducible form of cyclooxygenase (cyclooxygenase-2) has been cloned, sequenced and characterized from chicken, murine and human sources. This enzyme is distinct from the cyclooxygenase-1 which has now also been cloned, sequenced and characterized from sheep, murine and human sources. The second form of cyclooxygenase, cyclooxygenase-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. As prostaglandins have both physiological and pathological roles, we have concluded that the constitutive enzyme, cyclooxygenase-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, we have concluded that the inducible form, cyclooxygenase-2, is mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Thus, a selective inhibitor of cyclooxygenase-2 will have
similar antiinflammatory, antipyretic and analgesic properties to a conventional non-steroidal antiinflammatory drug, and in addition would inhibit hormone-induced uterine contractions and have potential anti-cancer effects, but will have a diminished ability to induce some of the mechanism-based side effects. In particular, such a compound should have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

SUMMARY OF THE INVENTION

The invention encompasses novel compounds of Formula I useful in the treatment of cyclooxygenase-2 mediated diseases.

The invention also encompasses certain pharmaceutical compositions, uses and methods for treatment of cyclooxygenase-2 mediated diseases comprising the use of compounds of Formula I.

The invention also encompasses use of a compound of formula (I), in the manufacture of a medicament for the treatment of a inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

The invention also encompasses non-steroidal anti-inflammatory compositions and cyclooxygenase-2 selective inhibitor pharmaceutical compositions containing a compound of formula (I).

More especially the invention is concerned with compounds of formula (I):
wherein:

$R^1$ is selected from the group consisting of

(a) $\text{S(O)}_2 \text{CH}_3$, and
(b) $\text{S(O)}_2 \text{NH}_2$, and

unsubstituted, mono- or di- substituted phenyl

wherein the substituents are selected from the group consisting of halo, methoxy and methyl,
said halo being selected from the group consisting of fluoro, choro and bromo.

In particular there is provided, in accordance with the invention a process of making a compound of formula (I), as defined above, comprising treating in a non-aqueous polar solvent a compound of formula (A)
wherein $R^1$ and $R^2$ are as defined above, in the presence of a strong base; to yield said compound of formula (I).

In another aspect there is provided a process of making a compound of formula (I), as defined above, comprising reacting an acetylene compound of the formula (XLVIII)

\[
\begin{array}{c}
\text{R}^1 \quad \text{C} \equiv \text{C} \quad \text{R}^2 \\
\end{array}
\]

XLVIII

in which $R^1$ and $R^2$ are as defined above with carbon monoxide and water in the presence of a suitable catalyst to yield a compound of formula (I) and a compound of formula XXXV

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\end{array}
\]

I

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\end{array}
\]

XXXV
in which \( R^1 \) and \( R^2 \) are as defined above and recovering said compound of formula (I).

In still another aspect of the invention there is provided a process for preparing a compound of formula (I), as defined above comprising (cl) reacting a compound of formula (LIII)

\[
\text{LIII}
\]

with a reagent of the formula \( \text{HO}_2\text{BR}^2 \), in which \( R^2 \) is as defined above, in an aqueous solvent and in the presence of a suitable catalyst to yield a compound of formula (LV), and

\[
\text{LV}
\]
(c2) oxidizing the compound of formula (LV) to yield the compound of formula (I).

In still another aspect of the invention there is provided a compound of formula (A)

![Chemical structure](image)

wherein

R$^1$ is selected from the group consisting of (a) S(O)$_2$CH$_3$ and (b) S(O)$_2$NH$_2$ and
R$^2$ is an unsubstituted, mono- or di-substituted phenyl, wherein the substituents are selected from the group consisting of halo, methoxy and methyl, halo being selected from the group consisting of fluoro, chloro and bromo.

**DETAILED DESCRIPTION OF THE INVENTION**

Novel compounds (I) produced by the process of the invention include the following:

(a) 3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
(b) 3-(4-Fluorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(5H)-furanone,
(c) 3-(3-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
(d) 3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
(e) 3-(3,4-Dichlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,
(f) 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone.

Further illustrating the invention are
(a) 3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone, and
(b) 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone.

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

In a particular embodiment of the invention the process of producing said compound (I) comprises i) reacting in a non-aqueous polar solvent a compound of formula (XXXII)
wherein $R^1$ is as defined above, with a compound of formula

$$R^2\text{CO}_2\text{H}$$

wherein $R^2$ is as defined above, in the presence of a base to produce said compound of formula (A), and ii) treating in a non-aqueous polar solvent said compound of formula (A) with a strong base to yield said compound of formula (I).

In a further particular embodiment of the invention the process comprises

(al) reacting in an organic solvent a compound of formula (XXXIII)
wherein \( R^1 \) is as defined above with a bromine reagent to yield a compound of formula (XXXII)

wherein \( R^1 \) is as defined above, (a2) reacting in a non-aqueous polar solvent said compound of formula (XXXII) with a compound of formula
wherein $R^2$ is as defined above, in the presence of a base to produce said compound of formula (A), and
(a3) treating in a non-aqueous polar solvent said compound of formula (A) with strong base to yield said compound of formula (I).

The invention contemplates pharmaceutical compositions for inhibiting cyclooxygenase and for treating cyclooxygenase mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

Within this embodiment the invention contemplates pharmaceutical compositions for inhibiting cyclooxygenase-2 and for treating cyclooxygenase-2 mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

The invention also contemplates a method of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases, advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 as disclosed herein comprising: administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

For purposes of this specification a compound is said to selectively inhibit COX-2 in preference to COX-1 if the ratio of the IC50 concentration for COX-1 inhibition to COX-2 inhibition is 100 or greater.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient, and may also contain
a pharmaceutically acceptable carrier and optionally other therapeutic ingredients.

The Compound of Formula I is useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries, following surgical and dental procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastatic tumor growth and hence can be used in the treatment of cancer. Compounds of formula I may also be useful for the treatment of dementia including pre-senile and senile dementia, and in particular, dementia associated with Alzheimer Disease (ie Alzheimer’s dementia).

Compounds of formula I will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor and asthma.

By virtue of its high cyclooxygenase-2 (COX-2) activity and/or its selectivity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1) as defined above, compounds of formula I will prove useful as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID’S) particularly where such non-steroidal antiinflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; Gi bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems (including those relating to reduced or impaired platelet function); kidney disease (eg impaired renal function); those prior to surgery or taking anticoagulants; and those susceptible to NSAID induced asthma.

Similarly, compounds of formula I, will be useful as a partial or complete substitute for conventional NSAID’S in preparations wherein they are presently co-administered with other agents or ingredients. Thus in further
aspects, the invention encompasses pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of the compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetaminophen or phenacetin; a potentiator including caffeine; an H2-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antiitusive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; a sedating or non-sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated diseases comprising: administration to a patient in need of such treatment a non-toxic therapeutically effect amount of the compound of Formula I, optionally co-administered with one or more of such ingredients as listed immediately above.

Compounds of the present invention are inhibitors of cyclooxygenase-2 and are thereby useful in the treatment of cyclooxygenase-2 mediated diseases as enumerated above. This activity is illustrated by their ability to selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Accordingly, in one assay, the ability of the compounds of this invention to treat cyclooxygenase mediated diseases can be demonstrated by measuring the amount of prostaglandin E₂ (PGE₂) synthesized in the presence of arachidonic acid, cyclooxygenase-1 or cyclooxygenase-2 and a compound of formula I. The IC₅₀ values represent the concentration of inhibitor required to return PGE₂ synthesis to 50 % of that obtained as compared to the uninhibited control. Illustrating this aspect, we have found that the Compounds of the Examples are more than 100 times more effective in inhibiting COX-2 than they are at inhibiting COX-1. In addition they all have a COX-2 IC₅₀ of 1 nM to 1 µM. By way of comparison, Ibuprofen has an IC₅₀ for COX-2 of 1 µM, and Indomethacin has an IC₅₀ for COX-2 of approximately 100 nM.
For the treatment of any of these cyclooxygenase mediated diseases, compounds of formula I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

As indicated above, pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S.
Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethyl-cellulose, methylcellulose, hydroxy-propylmethcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in
admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of formula I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore
melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day, preferably 2.5 mg to 1 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Methods of Synthesis

The compounds of the present invention can be prepared according to the following methods.
Method A:

An appropriately substituted aryl bromomethyl ketone is reacted with an appropriately substituted aryl acetic acid in a solvent such as acetonitrile in the presence of a base such as triethylamine and then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford either the lactone XXXIII or XXXV.

METHOD A

R¹
Br

CO₂H  R²
Base

R¹

XXXII

R¹

XXXIII

HO₂C

R¹

R²
Base

XXXIV

XXXV

R² is a mono- or disubstituted phenyl or a mono- or disubstituted heteroaryl
Method B

\[
\begin{array}{c}
\text{XLVIII} \\
\text{XXXIII} \\
\text{XXXV}
\end{array}
\]

By reacting acetylene XLVIII with carbon monoxide and water in the presence of suitable catalysts, a mixture of compound XXXIII and its isomer XXXV is obtained. The isomers are separable by standard procedures in the art such as chromatography or crystallization. Examples of useful catalysts and conditions are PdCl₂ in aqueous HCl and EtOH, heated at 50-150°C and 50-150 atmospheres of pressure, or Rh₄(CO)₁₂ (or Rh₆(CO)₁₆) in aqueous THF (or acetone, acetonitrile, benzene, toluene, EtOH, MeOH) containing a trialkylamine, at 50-150°C and 20-300 atmospheres pressure. See Takahashi et al., Organometallics 1991, 10, 2493-2498; and Tsuji et. al., J. Am. Chem. Soc. 1966, 88, 1289-1292.
Method C

$$\text{O}$$  
$$\text{M}$$ 
$$\begin{align*} 
\text{XLIX} & \quad + \quad \text{M} = \text{Li, Mg} \\
\text{L} & \quad \rightarrow \\
\text{SM} & \quad \text{TMSO} \\
\text{LI} & \quad 
\end{align*}$$

1. CuX (X = Cl, Br, I)  
2. TMSCl solvent

$$\begin{align*} 
P(\text{OAc})_2/\text{Cu(OAc)}_2, \text{O}_2 \\
\text{or PhilO/TMSN}_3, \text{n-Bu}_4\text{NF} \\
\rightarrow \\
\text{LII} & \quad \rightarrow \\
\text{LIII} & \quad \text{I}_2, \text{pyridine} \\
\end{align*}$$

$$\begin{align*} 
\text{LV} & \quad \rightarrow \\
\text{LVI} & \quad [\text{O}] \\
R & = \text{alkyl, aryl} \\
\end{align*}$$

1, 4-Addition to XLIX of 4-methylthiophenyl organometallic reagents L in the presence of copper salts and the trapping of the resultant enolate with trialkyl silyl chloride such as TMSCl or TIPSCI provide the ketene acetal LI. The ketene acetal can then be oxidized to the substituted butenolide LII by the method of Ito using catalytic amounts of Pd(II)(OAc)$_2$ and Cu(OAc)$_2$ and O$_2$ in MeOH or by the method of Magnus using PhilO/TMSN$_3$ and Bu$_4$NF.

Introduction of the iodine can be accomplished by treating LII with I$_2$ in the presence of pyridine to afford LIII. Palladium catalyzed Susuki or Stille coupling of LIII with the appropriate aryl or alkyl partner such as the boronic acid LIV provides the butenolide LV. The sulfide can be oxidized to a sulfone by various oxidizing agents such as peracetic acid, MPPM, MMPP or H$_2$O$_2$ to give the

Accordingly, in a further aspect the invention is directed to a process of making a compound of formula XXXIII

```
  R^1
 /\  \
R^2
   \  
    \O
 XXXIII
```

comprising:
(a1) reacting in an organic solvent a compound of formula XXXII'

![Chemical structure](image1.png)

XXXII'

with a bromine reagent to yield a compound of formula XXXII

![Chemical structure](image2.png)

XXXII

For purposes of this specification the organic solvent shall be defined to include, but not be limited to methylene chloride, chloroform, carbon tetrachloride and acetic acid. Similarly, the bromine reagent shall be defined to include, but not be limited to bromine, pyridinium perbromide hydrobromide, CuBr₂, and N-bromosuccinimide.

(a2) reacting in a non-aqueous polar solvent a compound of formula XXXII

with a compound of formula

![Chemical structure](image3.png)
in the presence of a base to produce a compound of formula A

\[
\begin{align*}
\text{R}^1 & \\
\text{O} & \\
\text{R}^2 & \\
\text{A}
\end{align*}
\]

(a3) treating in a non-aqueous polar solvent a compound of formula A with strong base to yield a compound of formula XXXIII.

For purposes of this specification the non-aqueous polar solvent shall be defined to include, but not be limited to, acetonitrile propionitrile, acetone, 2-butanone and tetrahydrofuran. Similarly, the base is defined to include, but not be limited to a tri-C\(_1\)-3alkylamine such as tri-ethylamine. Moreover, the strong base is defined to include, but not be limited to, an amidine, a guanidine, lithium diisopropylamide and potassium bis-(trimethylsilyl) amide.
In an alternative, the invention is directed to a process of making a compound of formula XXXIII

\[
\begin{array}{c}
\text{XXXIII} \\
R^1 \\
R^2 \text{-} \\
\text{CO}
\end{array}
\]

comprising:

(b1) reacting an acetylene compound of the formula XLVIII

\[
\begin{array}{c}
\text{XLVIII} \\
^1R \text{-} \\
\text{C} \equiv \text{C} \text{-} \\
R^2
\end{array}
\]

with carbon monoxide and water in the presence of a suitable catalyst to yield a compound of formula XXXIII and XXXV

\[
\begin{array}{c}
\text{XXXV} \\
R_1 \\
\text{CO}
\end{array}
\]
For purposes of this specification suitable catalysts include, but are not limited to Ru₄(CO)₁₂, Co₂(CO)₈ or PdCl₂ in aqueous THF or acetone, acetonitrile, benzene, toluene, methyl alcohol or ethyl alcohol.

In a second alternative, the invention is directed to a process of making a compound of formula XXXIII

\[
\begin{array}{c}
\text{XXXIII} \\
\end{array}
\]

comprising:

(c1) reacting a compound of formula LIII

\[
\begin{array}{c}
\text{LIII} \\
\end{array}
\]
with a reagent of the formula $(\text{HO})_2\text{BR}^2$ in an aqueous solvent such as benzene, toluene, THF, MeOH, DME or EtOH and in the presence of a suitable palladium catalyst to yield a compound of formula LV, and

\begin{tikzpicture}[scale=0.8]
  \draw[thick] (0,0) -- (0,1) -- (1,1) -- (1,0) -- cycle;
  \draw[thick] (0,0) -- (0,-2) -- (1,-2) -- (1,0);
  \node at (0.5,-1) {R_2};
  \node at (0.5,-0.5) {\text{O}};
  \node at (0,0) {\text{SCH}_3};
  \node at (1,0) {\text{LV}};
\end{tikzpicture}

(c2) oxidizing the compound of formula LV to yield a compound of formula XXXIII.

For purposes of this specification, the catalyst is defined to include, but not be limited to palladium catalysts. Similarly, the solvent is intended to include, but not be limited to benzene, toluene, THF, MeOH, DME or EtOH.

In all of the process alternatives, R_1 and R_2 are as defined above for the portion of Detailed Description and Claims directed to the compounds of formula I.

Representative Compounds

Tables I and II illustrate compounds of formula I.
<table>
<thead>
<tr>
<th>Example</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
</tr>
<tr>
<td>Example</td>
<td>Method</td>
</tr>
<tr>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
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<tr>
<td>4</td>
<td>A</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
</tr>
<tr>
<td>7</td>
<td>A</td>
</tr>
</tbody>
</table>
Table I (continued)

<table>
<thead>
<tr>
<th>Example</th>
<th>Method</th>
</tr>
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Table II (continued)
Assays for Determining Biological Activity

The compound of Formula I can be tested using the following assays to determine their cyclooxygenase-2 inhibiting activity.

Inhibition of Cyclooxygenase Activity

Compounds were tested as inhibitors of cyclooxygenase activity in whole cell and microsomal cyclooxygenase assays. Both of these assays measured prostaglandin E₂ (PGE₂) synthesis in response to arachidonic acid, using a radioimmunoassay. Cells used for whole cell assays, and from which microsomes were prepared for microsomal assays, were human osteosarcoma 143 cells (which specifically express cyclooxygenase-2) and human U-937 cells (which specifically express cyclooxygenase-1). In these assays, 100% activity is defined as the difference between prostaglandin E₂ synthesis in the absence and presence of arachidonate addition. IC₅₀ values represent the concentration of putative inhibitor required to return PGE₂ synthesis to 50% of that obtained as compared to the uninhibited control. Representative results are shown in Table III.

Representative Rat Paw Edema Assay – Protocol

Male Sprague-Dawley rats (150-200g) were fasted overnight and were given po either vehicle (5% tween 80 or 1% methocel) or a test compound at 9 - 10 am. One hr later, a line was drawn using a permanent marker at the level above the ankle in one hind paw to define the area of the paw to be monitored. The paw volume (V₀h) was measured using a plethysmometer (Ugo-Basile, Italy) based on the principle of water displacement. The animals were then injected subplantarly with 50 μl of a 1% carrageenan solution in saline (FMC Corp, Maine) into the paw using an insulin syringe with a 25-gauge needle (i.e. 500 μg carrageenan per paw). Three hr later, the paw volume (V₃h) was measured and the increases in paw volume (V₃h - V₀h) were calculated. The animals were euthanized by CO₂ asphyxiation and the absence or presence of
stomach lesions scored. Stomach scores were expressed as the sum of total lesions in mm. Paw edema data were compared with the vehicle-control group and percent inhibition calculated taking the values in the control group as 100%. Since a maximum of 60 - 70% inhibition (paw edema) was obtained with standard NSAIDs, ED₃₀ values were used for comparison. All treatment groups were coded to eliminate observer bias. With this protocol, the ED₃₀ for Indomethacin is 1.0 mg/kg. Representative results are shown in Table IV.
### TABLE III*

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* In the whole cell assay Ibuprofen has an IC50 for COX-1 of 1000 nM, and an IC50 for COX-2 of 3000 nM. Similarly, Indomethacin has an IC50 for COX-1 of 100 nM, and an IC50 for COX-2 of 10 nM.
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The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm. Hg) with a bath temperature of up to 60°C; the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only; melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations; the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data; yields are given for illustration only; when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal; chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w
(weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

The following abbreviations have the indicated meanings:

- **Ac** = acetyl
- **Bn** = benzyl
- **DBU** = 1,8-diazabicyclo[5.4.0]undec-7-ene
- **DIBAL** = diisobutylaluminum hydride
- **DMAP** = 4-(dimethylamino)pyridine
- **DMF** = N,N-dimethylformamide
- **Et3N** = triethylamine
- **LDA** = lithium diisopropylamide
- **m-CPBA** = metachloroperbenzoic acid
- **MMPP** = monoperoxyphthalic acid
- **MPPM** = monoperoxyphthalic acid, magnesium salt
  6H₂O
- **Ms** = methanesulfonyl = mesyl = SO₂Me
- **MsO** = methanesulfonate = mesylate
- **NSAID** = non-steroidal anti-inflammatory drug
- **OXONE®** = 2KHSO₅·KHSO₄·K₂SO₄
- **PCC** = pyridinium chlorochromate
- **PDC** = pyridinium dichromate
- **Ph** = phenyl
- **Phe** = benzenediyl
- **Py** = pyridinediyl
- **r.t.** = room temperature
- **rac.** = racemic
- **SAM** = aminosulfonyl or sulfonamide or SO₂NH₂
- **TBAF** = tetra-n-butylammonium fluoride
- **Th** = 2- or 3-thienyl
- **TFAA** = trifluoroacetic acid anhydride
- **THF** = tetrahydrofuran
Thi = thiophenediyl
TLC = thin layer chromatography
TMS-CN = trimethylsilyl cyanide
Tz = 1H (or 2H)-tetrazol-5-yl
C₃H₅ = allyl

Alkyl Group Abbreviations
Me = methyl
Et = ethyl
n-Pr = normal propyl
i-Pr = isopropyl
n-Bu = normal butyl
i-Bu = isobutyl
s-Bu = secondary butyl
t-Bu = tertiary butyl
c-Pr = cyclopropyl
c-Bu = cyclobutyl
c-Pen = cyclopentyl
c-Hex = cyclohexyl
EXAMPLE 1

3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Step 1: 2-Bromo-1-(4-(methylsulfonyl)phenyl)ethanone

A solution of 197 g of 4-(Methylthio)acetophenone (ref: JACS, 1952, 74, p. 5475) in 700 mL of MeOH and 3500 mL of CH₂Cl₂ was added 881 g of MMPP over a period of 30 min. After 3 h at room temperature the reaction mixture was filtered and the filtrate was washed with 2 L of saturated aqueous solution of NaHCO₃ and 1 L of brine. The aqueous phase was further extracted with 2 L of CH₂Cl₂. The combined extracts was dried over Na₂SO₄ concentrated to give 240 g of 4-(methylsulfonyl)acetophenone as a white solid.

To a cooled (-5 °C) solution of 174 g of 4-(methylsulfonyl)acetophenone in 2.5 L of CHCl₃ was added 20 mg of AlCl₃, followed by a solution of 40 mL of Br₂ in 300 mL CHCl₃. The reaction mixture was then treated with 1.5 L of water and the CHCl₃ was separated. The aqueous layer was extracted with 1 L of EtOAc. The combined extracts was dried over Na₂SO₄ and concentrated. The crude product was recrystallized from 50/50 EtOAc/hexane to give 210 g of 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone as a white solid.

Step 2:

To the product of Step 1 (216 mg) dissolved in acetonitrile (4 mL) was added Et₃N (0.26 mL), followed by 4-fluorophenylacetic acid (102 mg). After 1.5 h at room temperature 0.23 mL of DBU was added. The reaction mixture was stirred for another 45 min and then treated with 5 mL of 1N HCl. The product was extracted with EtOAc, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (40% EtOAc in hexane) to yield 150 mg of the title compound as a solid.

¹H NMR (CD₃COCD₃) δ 3.15 (3H, s), 5.36 (3H, s), 7.18 (2H, J=8.9 Hz, t), 7.46 (2H, m), 7.7 (2H, J=8.65 Hz, d), 7.97 (2H, J=8.68, d).
EXAMPLE 2

3-(4-Fluorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2H)-furanone

$^1$H NMR (CD$_3$COCD$_3$) $\delta$ 5.34 (2H, s), 6.67 (2H, bd), 7.18 (2H, m), 7.46 (2H, m), 7.61 (2H, m), 7.90 (2H, m).
M.P. 187-188 C (d).

EXAMPLE 3

3-(2,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C$_{17}$H$_{12}$F$_2$O$_4$S
C, 58.28; H, 3.45; S, 9.15
Found: C, 58.27; H, 3.50; S, 9.27

EXAMPLE 4

3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone
To a solution of 3,4-difluorophenylacetic acid (ALDRICH CHIMICAL) (10 g) and 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone (Example 9, Step 1) (17.3 g) in acetonitrile (200 mL) at room temperature was added slowly triethylamine (20.2 mL). After 1 h at room temperature, the mixture was cooled in an ice bath and treated with 17.4 mL of DBU. After 2 h at 0°C, the mixture was treated with 200 mL of 1N HCl and the product was extracted with EtOAc, dried over Na$_2$SO$_4$ and concentrated. The residue was applied on top of a silica gel plug (sintered glass funnel) eluted with 75% EtOAc/hexane, giving after evaporation of the solvent and swish in ethyl acetate, 10 g of the title compound.
Analysis calculated for $\text{C}_{17}\text{H}_{12}\text{F}_{2}\text{O}_{4}\text{S}$

C, 58.28; H, 3.45; S, 9.15

Found: C, 58.02; H, 3.51; S, 9.35

EXAMPLE 5

3-(2,6-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for $\text{C}_{17}\text{H}_{12}\text{F}_{2}\text{O}_{4}\text{S}$

C, 58.28; H, 3.45; S, 9.15

Found: C, 58.18; H, 3.50; S, 9.44

EXAMPLE 6

3-(2,5-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for $\text{C}_{17}\text{H}_{12}\text{F}_{2}\text{O}_{4}\text{S}$

C, 58.28; H, 3.45; S, 9.15

Found: C, 58.89; H, 3.51; S, 9.11

EXAMPLE 7

3-(3,5-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for $\text{C}_{17}\text{H}_{12}\text{F}_{2}\text{O}_{4}\text{S}$

C, 58.28; H, 3.45; S, 9.15

Found: C, 58.27; H, 3.62; S, 9.32
EXAMPLE 8

3-(4-Bromophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C_{17}H_{13}BrO_{4}S
C, 51.94; H, 3.33; S, 8.16
Found: C, 51.76; H, 3.42; S, 8.21

EXAMPLE 9

3-(4-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

{\textsuperscript{1}H} NMR (300 MHz, CDCl_{3}) \delta 7.93 (2H, d), 7.49 (2H, d), 7.35 (4H, m), 5.16 (2H, s), 3.06 (3H, s)

EXAMPLE 10

3-(4-Methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C_{18}H_{16}O_{5}S
C, 62.78 H, 4.68; S, 9.31
Found: C, 62.75; H, 4.72; S, 9.39

EXAMPLE 11

3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

To a solution of phenylacetic acid (27.4 g, 201 mmol) and 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone (Example 1, Step 1) (60 g, 216 mmol, 1.075 eq.) in acetonitrile (630 mL) at 25 °C was added slowly triethylamine (30.8 mL, 1.1 eq.). The mixture was stirred for 20 min. at room temperature and then cooled in an ice bath. DBU (60.1 mL, 3 eq.) was slowly added. After stirring for 20 min. in the ice bath, the reaction was complete and the mixture was acidified
with 1N HCl (color changes from dark brown to yellow). Then 2.4 L of ice and water were added, stirred for a few minutes, then the precipitate was filtered and rinsed with water (giving 64 g of crude wet product). The solid was dissolved in 750 mL of dichloromethane (dried over MgSO₄, filtered) and 300 g of silica gel was added. The solvent was evaporated to near dryness (silica gel a bit sticky) and the residue was applied on top of a silica gel plug (sintered glass funnel) eluted with 10% EtOAc/CH₂Cl₂, giving after evaporation of the solvent and swish in ethyl acetate, 36.6 g (58%) of the title compound.

Analysis calculated for C₁₇H₁₄O₄S
C, 64.95; H, 4.49; S, 10.20
Found: C, 64.63; H, 4.65; S, 10.44

EXAMPLE 12

3-(2-Chlorophenyl)-4-(4-(methyIsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C₁₇H₁₃ClO₄S
C, 58.54; H, 3.76; S, 9.19
Found: C, 58.59; H, 3.80; S, 9.37

EXAMPLE 13

3-(2-Bromo-4-fluorophenyl)-4-(4-(methyIsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C₁₇H₁₂BrFO₄S
C, 49.75; H, 2.93
Found: C, 49.75; H, 3.01
EXAMPLE 14

3-(2-Bromo-4-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

$^1$H NMR (300 MHz, acetone-d$_6$) $\delta$ 7.95 (2H, d), 7.85 (1H, d), 7.63 (2H, dd), 7.55 (1H, dd), 7.45 (1H, d), 5.50 (2H, s), 3.15 (3H, s)

EXAMPLE 15

3-(4-Chloro-2-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

$^1$H NMR (300 MHz, acetone-d$_6$) $\delta$ 8.0 (2H, d), 7.70 (2H, d), 7.50-7.30 (3H, m), 5.35 (2H, s), 3.15 (3H, s)

EXAMPLE 16

3-(3-Bromo-4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C$_{17}$H$_{12}$BrFO$_4$S

C, 49.75; H, 2.93

Found: C, 49.44; H, 2.98

EXAMPLE 17

3-(3-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C$_{17}$H$_{13}$ClO$_4$S

C, 58.54; H, 3.76

Found: C, 58.29; H, 3.76
EXAMPLE 18

3-(2-Chloro-4-fluorophenyl)-4-(4-(methyIsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C_{17}H_{12}ClFO_{4}S
C, 55.67; H, 3.30

Found: C, 55.67; H, 3.26

EXAMPLE 19

3-(2,4-Dichlorophenyl)-4-(4-(methyIsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C_{17}H_{12}Cl_{2}O_{4}S
C, 53.28; H, 3.16; S, 8.37

Found: C, 52.89; H, 3.23; S, 8.58

EXAMPLE 20

3-(3,4-Dichlorophenyl)-4-(4-(methyIsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C_{17}H_{12}Cl_{2}O_{4}S
C, 53.28; H, 3.16; S, 8.37

Found: C, 53.07; H, 3.32; S, 8.51

EXAMPLE 21

3-(2,6-Dichlorophenyl)-4-(4-(methyIsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C_{17}H_{12}Cl_{2}O_{4}S
C, 53.28; H, 3.16; S, 8.37

Found: C, 52.99; H, 3.22; S, 8.54
EXAMPLE 22

3-(3-Chloro-4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

$^1$H NMR (300 MHz, acetone-d$_6$) d 8.0 (2H, d), 7.70 (2H, d), 7.60 (1H, d), 7.25-7.40 (2H, m), 5.35 (2H, s), 3.15 (3H, s)

EXAMPLE 23

3-(3-Fluoro-4-methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C$_{18}$H$_{15}$FO$_5$S
C, 59.66; H, 4.17
Found: C, 59.92; H, 4.37

EXAMPLE 24

3-(3-Chloro-4-methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C$_{18}$H$_{15}$ClO$_5$S
C, 57.07; H, 3.99
Found: C, 57.29; H, 4.15

EXAMPLE 25

3-(3-Bromo-4-methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C$_{18}$H$_{15}$BrO$_5$S
C, 51.08; H, 3.57
Found: C, 51.38; H, 3.62
EXAMPLE 26

3-(2-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C₁₇H₁₃FO₄S
C, 61.44; H, 3.94
Found: C, 61.13; H, 3.85

EXAMPLE 27

3-(3-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

¹H NMR (300 MHz, CDCl₃) d 7.93 (2H, d), 7.49 (2H, d), 7.35 (1H, m), 7.12 (3H, m), 5.18 (2H, s), 3.06 (3H, s)

EXAMPLE 28

3-(2-Chloro-6-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

¹H NMR (300 MHz, acetone-d₆), d 8.0 (2H, d), 7.70 (2H, d), 7.55-7.65 (1H, m), 7.40 (1H, d), 7.30 (1H, m), 5.60 (2H, s), 3.15 (3H, s)

EXAMPLE 29

3-(3-Bromo-4-methylphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C₁₈H₁₅BrO₄S
C, 53.08; H, 3.71
Found: C, 53.06; H, 3.83
EXAMPLE 30

3-(4-Bromo-2-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C_{17}H_{12}BrFO_{4}S
C, 49.65; H, 2.94
Found: C, 49.76; H, 3.00

EXAMPLE 31

3-(3,4-Dibromophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

1H NMR (300 MHz, acetone-d6) δ 8.0 (2H, d), 7.80 (1H, d), 7.75 (3H, m), 7.25 (1H, d), 5.35 (2H, s), 3.15 (sH, s)

EXAMPLE 32

3-(4-Chloro-3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C_{17}H_{12}ClFO_{4}S
C, 55.67; H, 3.30
Found: C, 55.45; H, 3.30

EXAMPLE 33

3-(4-Bromo-3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C_{17}H_{12}BrFO_{4}S
C, 49.66; H, 2.94; S, 7.80
Found: C, 49.79; H, 3.01; S, 7.51
EXAMPLE 34

3-(4-Bromo-2-chlorophenyl)-4-(4-(methyIsulfonyl)phenyl)-2-(5H)-furanone

Analysis calculated for C$_{17}$H$_{12}$BrClO$_4$S
C, 47.74; H, 2.83; S, 7.50
Found: C, 47.92; H, 2.84; S, 7.42

EXAMPLE 35

3-(3,4-Dichlorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2H)-furanone

$^1$H NMR (400 MHz, CD$_3$COCD$_3$) $\delta$ 7.92 (2H, dd), 7.64 (3H, dm), 7.60 (1H, dd), 7.32 (1H, dd), 6.70 (1H, bs), 5.38 (2H, s)

EXAMPLE 36

3-(3,4-Difluorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2H)-furanone

$^1$H NMR (400 MHz, CD$_3$COCD$_3$) $\delta$ 7.92 (2H, dd), 7.64 (2H, dd), 7.30-7.45 (2H, m), 7.22 (1H, m), 6.68 (2H, bs), 5.37 (2H, s)

EXAMPLE 37

3-(3-Chloro-4-methoxyphenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2H)-furanone

Analysis calculated for C$_{17}$H$_{14}$ClNO$_5$S
C, 53.76; H, 3.72, N, 3.69
Found: C, 53.32; H, 3.84, N, 3.59
M.S. (DCI, CH$_4$) calculated for M$^+$, 379
Found for M$^+$+1, 380
EXAMPLE 38

3-(3-Bromo-4-methoxyphenyl)-4-(4-aminosulfonyle phenyl)-2-(2H)-furanone

Analysis calculated for C_{17}H_{14}BrNO_{5}S  
C, 48.13; H, 3.33, N, 3.30  
Found: C, 48.26; H, 3.40, N, 3.28  
M.S. (DCI, CH_{4}) calculated for M^{+}, 423  
Found for M^{+}+1, 424

EXAMPLE 39

3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Into a 20 ml glass ampule are added 1 g of 2-(4- (methylsulfonyl)phenyl)phenylacetylene, 20 mg of Rh_{4}(CO)_{12}, 1.5 g of Et_{3}N, 10 ml of THF, 1 ml of water under nitrogen atmosphere, and the ampule is placed in a 100-ml stainless steel autoclave. The reaction system is flushed three times with CO then charged at room temperature to a initial CO pressure of 100 atm. The reaction is carried at 100 °C for 5 h. The solution is then diluted with 50 ml of benzene and washed with brine, 1N HCl. The benzene solution is dried over Na_{2}SO_{4}, and concentrated. The crude products are separated by column chromatography on silica gel eluted with 2:1 EtOAc/hexane to give the title compound and its regioisomer.

EXAMPLE 40

3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

Step 1: 2-trimethylsilyloxy-4-(4-(methylthio)phenyl)-3,4-dihydrofuran

To a solution of 3.86 g (19 mmol) of 4-bromothioanisole in 90 mL of Et_{2}O cooled at -78°C, is added 22 mL of 1.7 M solution of t-BuLi in pentane (38 mmol) dropwise. The reaction mixture is stirred for 15 min at -78°C and 3.8 g of Cul is added and the reaction mixture is allowed to warm to -40 °C over a period
of 30 min. A solution of 1.7 g of 2(5H)-furanone in 10 ml of THF is added. After stirring for 1 h, 2 ml of freshly distilled TMSCl is added dropwise. The reaction mixture is then treated with 2 ml of Et₃N and 50 ml of sat. NaHCO₃, and extracted with 100 ml of ether. The ether layer is dried over Na₂SO₄ and concentrated to the crude title compound which is used for the next step without further purification.

**Step 2:** 4-(4-(methylthio)phenyl)-2-(5H)-furanone

To a solution of 4 g of Pd(OAc)₂ in 100 ml of acetonitrile is added dropwise the crude product from Step 1(5 g) under nitrogen at room temperature. After 10 h at room temperature, the mixture is condensed under reduced pressure and the residue is purified by flash chromatography on silica gel eluted with 2:1 hexane/EtOAc to give the title compound.

**Step 3:** 3-iodo-4-(4-(methylthio)phenyl)-2-(5H)-furanone

To a solution of 3 g of the product of Step 2 in 30 ml of pyridine is added 8.7 g of I₂. The mixture is stirred for 24 h and then diluted with 200 ml of ether, washed with 100 ml of 5N HCl and 50 ml of 5N Na₂S₂O₃. The ether layer is dried over Na₂SO₄ and concentrated to give the title compound.

**Step 4:** 3-(Phenyl)-4-(4-(methylthio)phenyl)-2-(5H)-furanone

A mixture of 4 g of the product of Step 3, 3.7 g of PhB(OH)₂, 0.4 g of Ph₃As, 0.4 g of PdCl₂(PhCN)₂ in 100 ml of benzene and 15 ml of 2N NaOH is refluxed for 6 h. Ether(200 ml) is then added and the mixture is washed with 100 ml of saturated NaHCO₃. The organic layer is dried over MgSO₄ and concentrated. The residue is purified by flash chromatography on silica gel eluted with 4:1 hexane/EtOAc to give the title compound.
Step 5: 3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

To a solution of 3 g of the product of Step 4 in 80 mL of 10:1 CH2Cl2/MeOH is added 5.5 g of MPPM. The reaction mixture is stirred at room temperature for 2 h and then diluted with 100 mL of 1:1 hexane/EtOAc. After filtration and concentration, the residue is purified by flash chromatography eluted with 2:1 EtOAc/hexane to give the title product.
CLAIMS

1. A process of making a compound of formula (I)

\[ \text{(I)} \]

wherein:

- $R^1$ is selected from the group consisting of
  - (a) $\text{SO}_2\text{CH}_3$, and
  - (b) $\text{SO}_2\text{NH}_2$

- $R^2$ is an unsubstituted, mono- or di-substituted phenyl, wherein the substituents are selected from the group consisting of halo, methoxy and methyl, said halo being selected from the group consisting of fluoro, chloro and bromo, comprising treating in a non-aqueous polar solvent a compound of formula (A)

\[ \text{(A)} \]
wherein R¹ and R² are as defined above, in the presence of a strong base; to yield said compound of formula (I).

2. A process according to claim 1, comprising:
   i) reacting in a non-aqueous polar solvent a compound of formula (XXXII)

   \[
   \begin{array}{c}
   \text{XXXII} \\
   \text{Br} \quad \text{R}^1 \\
   \end{array}
   \]

   wherein R¹ is as defined in claim 1, with a compound of formula:

   \[
   \begin{array}{c}
   \text{R}^2 \text{CO}_2\text{H} \\
   \end{array}
   \]

   wherein R² is as defined in claim 1, in the presence of a base to produce said compound of formula (A), and

   ii) treating in a non-aqueous polar solvent said compound of formula (A) with a strong base to yield said compound of formula (I).

3. A process according to claim 1, comprising:
   (a) reacting in an organic solvent a compound of formula (XXXIII)
wherein $R^1$ is as defined in claim 1, with a bromine reagent to yield a compound of formula (XXXII)

wherein $R^1$ is as defined in claim 1,
(a2) reacting in a non-aqueous polar solvent said compound of formula (XXXII) with a compound of formula

$$R^2 \text{CO}_2\text{H}$$
wherein $R^2$ is as defined in claim 1, in the presence of a base to produce said compound of formula (A), and (a3) treating in a non-aqueous polar solvent said compound of formula (A) with strong base to yield said compound of formula (I).

4. A process according to claim 1, 2 or 3, wherein $R^1$ is $S(O)_2CH_3$.

5. A process according to claim 1, 2 or 3, wherein $R^2$ is unsubstituted phenyl.

6. A process of making a compound of formula (I)

\[
\begin{align*}
R^1 & \\
\text{R}^2 & \text{C} \text{O} \\
(\text{I}) & \\
\end{align*}
\]

wherein

$R^1$ is selected from the group consisting of
(a) $S(O)_2CH_3$ and
(b) $S(O)_2NH_2$.

$R^2$ is an unsubstituted, mono- or di-substituted phenyl in which the substituents are selected from the group consisting of halo, methoxy and methyl, halo being selected from the group consisting of fluoro, chloro and bromo,

reacting an acetylene compound of formula (XLVIII)
in which $R^1$ and $R^2$ are as defined above with carbon monoxide and water in the presence of a suitable catalyst to yield a compound of formula (I) and a compound of formula XXXV

in which $R^1$ and $R^2$ are as defined above and recovering said compound of formula (I).
7. A process of making a compound of formula (I)

\[
\begin{align*}
R^1 & \\
R^2 & \\
\text{wherein} \\
R^1 & \text{is } S(O)_{2}\text{CH}_3, \\
R^2 & \text{is an unsubstituted, mono- or di-substituted phenyl in which the substituents} \\
& \text{are selected from the group consisting of halo, methoxy and methyl, said halo} \\
& \text{being selected from fluoro, chloro and bromo,} \\
& (\text{cl}) \text{ reacting a compound of formula (LIII)}
\end{align*}
\]
with a reagent of the formula \((\text{HO})_2\text{BR}^2\), in which \(\text{R}^2\) is as defined above, in an aqueous solvent and in the presence of a suitable catalyst to yield a compound of formula (LV), and

$$\begin{align*}
\text{SCH}_3 \\
\text{R}_2-	ext{C}=	ext{O}
\end{align*}$$

LV

(c2) oxidizing the compound of formula (LV) to yield the compound of formula (I).

8. A process according to claim 1, 2, 3, 4, 5, 6 or 7, wherein the compound of formula (I) is 3-(3,4-difluorophenyl)-4-(4-methylsulfonyl)-phenyl)-2-(5H)-furanone.

9. A process according to claim 1, 2, 3, 4, 5, 6 or 7, wherein the compound of formula (I) is 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone.

10. A process according to claim 1, 2 or 3, wherein \(\text{R}^1\) is \(\text{SO}_2\text{CH}_3\) and \(\text{R}^2\) is unsubstituted phenyl.

11. A process according to claim 1, 2 or 3, wherein \(\text{R}^1\) is \(\text{SO}_2\text{CH}_3\) and \(\text{R}^2\) is 4-fluorophenyl.
12. A process according to claim 2, comprising reacting 2-bromo-1-(4-(methylsulfanyl)phenyl) ethanone as said compound of formula (XXXII) with 4-fluorophenylacetic acid to produce 3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone.

13. A process according to claim 2, comprising reacting 2-bromo-1-(4-(methylsulfanyl)phenyl) ethanone as said compound of formula (XXXII) with phenyl acetic acid to produce 3-(phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone.

14. A compound of formula (A)

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

wherein

- \( \text{R}^1 \) is selected from the group consisting of
  - (a) \( \text{SO}_2\text{CH}_3 \), and
  - (b) \( \text{SO}_2\text{NH}_2 \)

- \( \text{R}^2 \) is an unsubstituted, mono- or di-substituted phenyl, wherein the substituents are selected from the group consisting of halo, methoxy and methyl, halo being selected from the group consisting of fluoro, chloro and bromo.

15. A compound according to claim 14, wherein \( \text{R}^1 \) is \( \text{SO}_2\text{CH}_3 \) and \( \text{R}^2 \) is unsubstituted phenyl.
16. A compound according to claim 14, wherein \( R^1 \) is \( \text{SO}_2\text{CH}_3 \) and \( R^2 \) is 4-fluorophenyl.

17. A process of making a compound of formula

\[
\begin{align*}
\text{O} & \\
\text{R}^1 & \\
\text{R}^2 & \\
\text{C} = \text{O} & \\
\end{align*}
\]

wherein:
\( R^1 \) is selected from the group consisting of
(a) \( \text{SO}_2\text{CH}_3 \) and
(b) \( \text{SO}_2\text{NH}_2 \)

\( R^2 \) is an unsubstituted, mono- or di-substituted phenyl, wherein the substituents are selected from the group consisting of halo, methoxy and methyl, said halo being selected from the group consisting of fluoro, chloro and bromo, comprising:

i) treating in a non-aqueous polar solvent a compound of formula (A)
wherein $R^1$ and $R^2$ are as defined above, in the presence of a strong base, to yield said compound of formula (I), or

ii) reacting an acetylene compound of the formula (XLVIII)

![Chemical Structure](image)

in which $R^1$ and $R^2$ are as defined above with carbon monoxide and water in the presence of a suitable catalyst to yield a compound of formula (I), and a compound of formula (XXXV)
in which \( R^1 \) and \( R^2 \) are as defined above and recovering said compound of formula (I); or

iii) (c) reacting a compound of formula (LIII)
with a reagent of the formula \((\text{HO})_2\text{BR}_2\) in which \(R^2\) is as defined above, in an aqueous solvent and in the presence of a suitable catalyst to yield a compound of formula (LV), and

\[ \text{LV} \]

(c2) oxidizing the compound of formula (LV) to yield the compound of formula (I).