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(71) Applicant: E.I. DU PONT DE NEMOURS AND COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US).

(72) Inventor: WANG, Chia-Lin, Jeffrey ; 115 Wynnwood Drive, Wilmington, DE 19810 (US).

(74) Agents: HORN, Margaret, A. et al.; E.I. du Pont de Nemours and Company, Legal/Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).

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(54) Title: ANILINE DERIVATIVES OF α-STYRYL CARBINOLS AS ANTIFUNGAL AGENTS

(57) Abstract

There are provided novel aniline derivatives of α-styryl carbinols, pharmaceutical compositions comprising them and methods of using such compounds as antifungal agents.

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Title

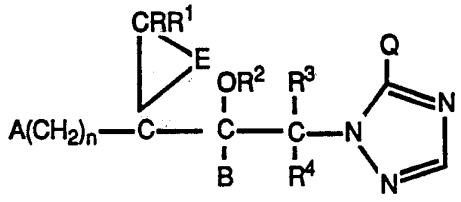
ANILINE DERIVATIVES OF α-STYRYL CARBINOLS AS ANTIFUNGAL AGENTS

Field of the Invention

This invention relates to aniline derivatives of α-styryl carbinols, pharmaceutical compositions containing them and methods of using such compounds for treating fungal infections in a mammal.

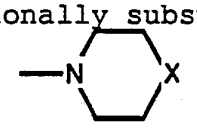
Prior Art

Commonly assigned EP 251086, describes α-styryl carbinol antifungal agents useful in medicine and/or agriculture. Also described are certain compounds useful as herbicides and plant growth regulants. The compounds described therein have the formula:



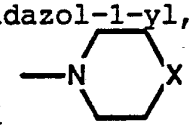
wherein:

E is a bond or -O-, provided that when E is -O-, R and R^1 are not halogen;

A is C1-C8 perfluoroalkyl, NMe_2, OH, naphthyl (optionally substituted by 1-3 of halogen and CF_3),  optionally substituted by 1 or 2 methyl groups,

phenyl optionally substituted by 1-3 substituents independently selected from: halogen, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy and maximally one of the following substituents: C1-C4 haloalkoxy,

$-S(O)_mR^5$, R^6, 2-, 3- or 4-pyridyl, imidazol-1-yl, 1, 2, 4-triazol-1-yl



and optionally substituted by 1 or 2 methyl groups,

or a heterocycle selected from imidazol-1-yl, 1, 2, 4-triazol-1-yl, 2-or 3-thienyl, and 2-, 3- or 4-pyridyl optionally substituted by 1 or 2 of halogen, C1-C4 alkyl, CF_3 and $S(O)_mR^5$;

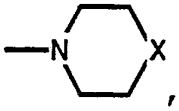
X is C, NR^{10} or O;

B is C1-C8 alkyl, naphthyl, biphenylyl, $-C(=CH_2)-R^6$, C1-C8 perfluoroalkyl, phenyl optionally substituted by 1-3 substituents independently selected from:

halogen, C1-C4 alkyl, C1-C4 haloalkyl or C1-C4 alkoxy, and maximally one of C1-C4 haloalkoxy and $-S(O)_mR^5$,

benzyl optionally substituted on the phenyl ring with halogen or C1-C4 alkyl or α-substituted by 1 or 2 methyl groups, or a heterocycle selected from 2- or 3-thienyl, and 2-, 3- or 4-pyridyl optionally substituted by 1 or 2 of halogen, C1-C4 alkyl, CF_3 and $-S(O)_mR^5$;

Q is H, halogen, $-S(O)R^{11}$, $-S-CO-NHR^{12}$, CHO, -CO-Me, $COOR^{13}$, SCN, SSR^{12}, or SH or its corresponding disulphide, provided that when Q is not H, then n=0, R, R^1 and R^4 are independently H or Me, R^3=H, and A and B are phenyl optionally substituted by 1-3 of halogen, methyl, CF_3, methoxy or $-S(O)_mR^5$;

n is 0-4, provided that when A is  , NMe_2 or OH, then n is not 0;

m is 0, 1 or 2;

R and R^1 independently are H, C1-C4 alkyl, halogen or phenyl, or together form C3-C7 cycloalkyl;

R^2 is H, allyl, propargyl, C1-C4 alkyl, $-CO-R^7$ $-CONR^8R^9$, $-COOR^7$ or C1-C4 haloalkyl;

R^3 and R^4 are H, F or C1-C4 alkyl;

R^5 is C1-C4 alkyl;

R^6 is phenyl optionally substituted by 1-3 of halogen and CF_3;

R^7 is C1-C4 alkyl, phenyl or benzyl;

R^8 and R^9 is H, C1-C4 alkyl, phenyl or benzyl;

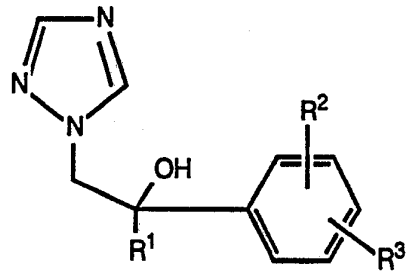
R^{10} is H, C1-C4 alkyl or acetyl;

R^{11} is C1-C4 alkyl, C1-C4 haloalkyl, $-CH_2CN$, $-CH_2SCN$, $-CH(Me)CN$, $-CH_2COOMe$ or $-CH_2COOEt$;

R^{12} is C1-C4 alkyl, allyl, or phenyl or benzyl both optionally substituted by 1 or 2 of the following halogen, methyl or methoxy; and

R^{13} is H or C1-C4 alkyl.

Fungicides useful in both the medical and veterinary field are described in BE 900063. These compounds have the formula:



Specifically claimed are those compounds of the above formula wherein:

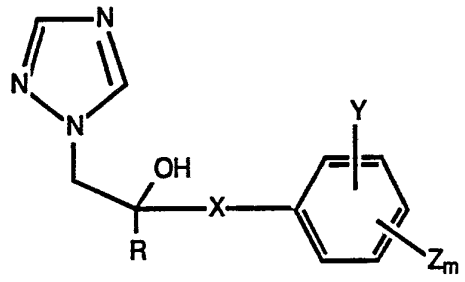
1). R^1 is $BrCH=CH-C(CH_3)_2$ or $Cl-CH=CH-C(CH_3)_2$;

R^2 is 4-Cl; and

R3 is H.

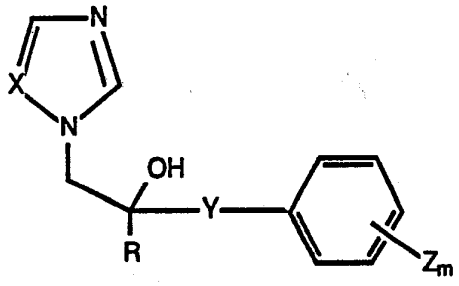
2). R^1 is $BrCH=CH-C(CH_3)_2$; and
R^2 and R^3 are 2,4-di-Cl.

DE 3314548 describes compounds which are useful as antimycotics for treating dermatomycoses and systemic mycoses caused by Candida or Aspergillus. These compounds have the formula:



wherein:
R is alkyl, cycloalkyl or Ph, each group optionally substituted;
X is $-OCH_2-$, $-SCH_2-$, $-(CH_2)_p-$ or $-CH=CH-$;
Y is $-COY_1$, its acetal or ketal derivatives, or $-C(Y_1) = NOY_2$;
Y_1 is H, alkyl, alkenyl, alkynyl, cycloalkyl, Ph or benzyl, these last 3 groups, being optionally substituted;
Y_2 is H, alkyl, alkenyl, alkynyl, cycloalkyl or benzyl, these last 2 groups being optionally substituted;
Z is halogen, alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy or haloalkylthio; and
m and p are 0, 1 or 2.

Compounds of the following formula, described in DE 3018865, are useful in human and veterinary medicine for the treatment of dermatomycoses and systemic mycoses due to Trichophyton mentagrophytes:



wherein:

R is alkyl, optionally substituted cycloalkyl, or optionally substituted phenyl;

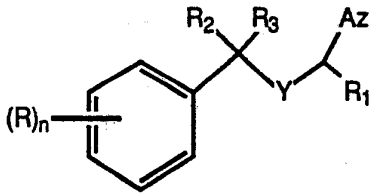
X is N or CH;

Y is OCH_2, $-CH_2CH_2-$ or CH=CH;

Z is halogen, alkyl, cycloalkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, haloalkylthio, optionally substituted phenyl, optionally substituted phenoxy, optionally substituted phenylalkyl or optionally substituted phenylalkoxy; and

m is 0-3.

EP 129798 describes fungicides active against phytopathogenic fungi. These fungicides have the formula:



wherein:

n is 0-5;

R is H, halogen, alkyl, alkoxy, alkylthio, alkylsulphonyl, haloalkyl, NO_2, CN, optionally substituted phenyl or optionally substituted phenoxy;

R_1 is alkyl, cycloalkyl, cycloalkylalkyl or an optionally substituted aryl, aralkyl, aryloxy, benzyloxyalkyl, alkenyl or alkynyl group;

R_2 and R_3 are alkyl are taken together are $(CH_2)_m$;

m is 2-7;

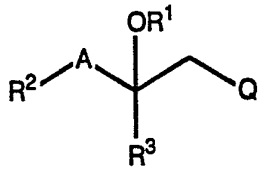
Az is 1, 2, 4-triazol-1-yl, 1, 2, 4-triazol-4-yl, 1-imidazolyl, 1-pyrazolyl or 1-benzimidazolyl;

Y is CO or $C(R_4)OR_5$;

R_4 is H, C1-C4 alkyl, vinyl or allyl;

R_5 is H, C1-C3 alkyl or optionally substituted alkenyl, alkynyl or benzyl.

EP 117578 describes orally active antimycotic agents as well as fungicides for agricultural use. These compounds having the formula:



or an acid addition salt thereof wherein:

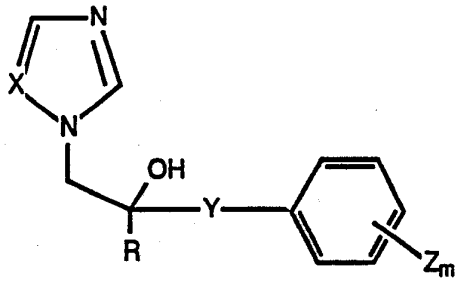
A is CO, CHOH or C(C1-C5 alkyl)(OH);

Q is imidazolyl or 1-H or 4H-1,2,4-triazol-1-yl;

R^1 = H, C1-C5 alkyl, or C1-C8 acyl;

R^2 and R^3 are C1-C5 alkyl, C3-C6 cycloalkyl, C2-C6 alkenyl, benzyl optionally substituted with 1-3 halogens, pyridyl, furyl, thienyl, or phenyl optionally substituted by 1-3 halogens, C1-C3 alkyl or C1-C3 alkoxy.

Azole derivatives and their acid addition salts are described in EP 40345. These compounds are described as being useful as fungicides and as plant growth regulators, and have the formula:



wherein:

R is alkyl or optionally substituted cycloalkyl or phenyl;

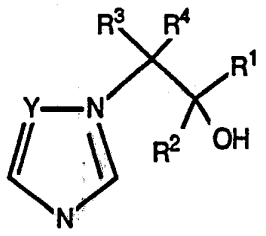
X is N or CH;

Y is OCH_2, CH_2CH_2 or CH=CH;

Z is halo, alkyl (optionally substituted by halo), cycloalkyl, alkoxy or alkylthio (both optionally substituted by halo), or optionally substandard phenyl, phenoxy, phenylalkyl or phenylalkoxy; and

m is 0-3.

GB 2175301 describes triazole and imidazole compounds useful as plant regulating agents. These triazole and imidazole compounds have the formula:



wherein:

R^1 is alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl or optionally substituted aryl, aralkyl or heterocyclyl;

R^2 is alkyl, alkenyl, alkynyl, alkynylalkenyl, alkenyl alkynyl, cycloalkyl, cycloalkenyl or cycloalkylalkyl, all optionally substituted;

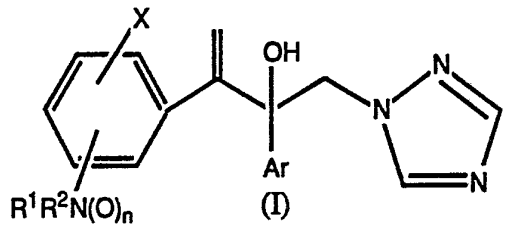
R^3 and R^4 are H (but not both H), C1-C4 alkyl, C1-C4 alkoxy, OCF_3, CF_3 or halo; or R_3 and R_4 taken together are a C3-C6-membered ring; and

Y is CH or N; provided that all hydrocarbyl moieties (including cycloalkyl, cycloalkenyl and cycloalkylalkyl) contain up to 8C unless otherwise stated.

None of the prior art references teaches or suggests the antifungal activity of the aniline derivatives of the α-styryl carbinols that are the subject matter of the present application.

Summary of the Invention

There are provided antifungal compounds having the formula:

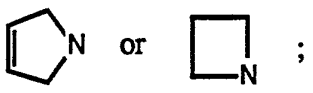


(I)

or pharmaceutically acceptable salts thereof wherein:

R^1 is H or C1-C4 alkyl;

R^2 is H, C1-C4 alkyl, R^3 C=O, or R^1R^2N is



;

R^3 is H, C1-C4 alkyl or CH_2X;

X is Cl or Br;

Ar is 2,4-$F_2C_6H_3$, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$; and

n is 0 or 1.

Preferred compounds of this invention are those compounds of formula (I) or their pharmaceutically acceptable salts, wherein:

R^1 and R^2 independently are H or C1-C3 alkyl; and/or

n is 0; and/or

Ar is 2,4-$F_2C_6H_3$ or 4-ClC_6H_4; and/or

R^1R^2N is substituted at the 4-or 5-position; and/or

X is 2-Cl or 2-Br.

More preferred compounds of the present invention are those compounds of formula (I) or their pharmaceutically acceptable salts, wherein:

R^1 and R^2 independently are H or C1-C3 alkyl; and/or

n is 0; and/or

Ar is 2,4-$F_2C_6H_3$; and/or

R^1R^2N is substituted at the 4-or 5-position; and/or

X is 2-Cl.

Specifically preferred compounds of the present invention are those more preferred compounds wherein:

a) R^1R^2N is 5$(CH_3)_2N$.

b) R^1R^2N is 4-H_2N.

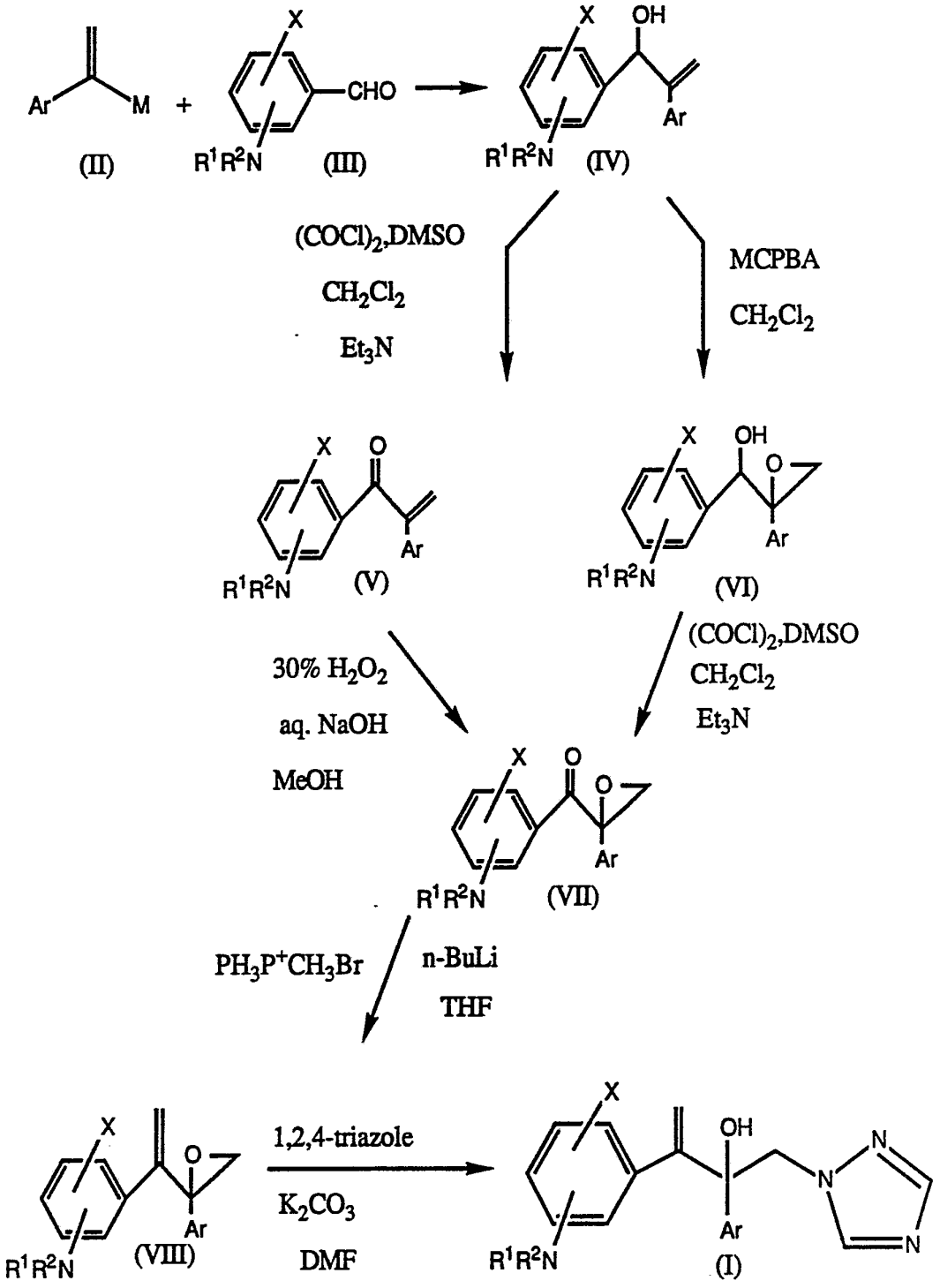
Also provided are pharmaceutical compositions comprising an antifungal effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Further provided is a method of treating a fungal infection in a mammal comprising administering to the mammal an anti-fungal effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Synthesis

Compounds of Formula (I) where n=0 can be prepared according to the procedures described in Scheme 1.

SCHEME 1


Ar
M
+
X
CHO
R1R2N
(II)
(III)
OH
Ar
(IV)
(COCl)2,DMSO
CH2Cl2
Et3N
MCPBA
CH2Cl2
O
(V)
(VI)
30% H2O2
aq. NaOH
MeOH
(VII)
PH3P+CH3Br
n-BuLi
THF
(VIII)
1,2,4-triazole
K2CO3
DMF
N
(I)

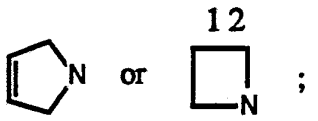
The allylic alcohols of Formula (IV) can be prepared by reaction of vinyl organometallic reagents of Formula (II), e.g. vinyl Grignard reagents, with aldehydes of Formula (III) in ethereal solvents, such as tetrahydrofuran (THF) or diethyl ether, at a temperature ranging from about -78° to 60°C, preferably 0° to 40°C, for 0.5 to 24 hours. The vinyl organometallics of Formula (II) are prepared using standard procedures from the corresponding chlorides, bromides or iodides. The aldehydes of Formula (III) are known, or can be prepared using methods known to one skilled in the art.

The compounds of Formula (IV) are converted to the keto-oxiranes of Formula (VII) by either (1) Swern oxidation, (2) basic hydrogen peroxide epoxidation of the resulting enones of Formula (V) in an aqueous alcoholic solvent such as methanol or ethanol at 0°C to room temperature for 1 to 24 hours; or (1) m-chloroperbenzoic acid epoxidation in methylene chloride or benzene at 0°C to room temperature for 10 to 30 hours, (2) Swern oxidation of the resulting epoxy-alcohols of Formula (VI).

Then, keto-oxiranes of Formula (VII) are olefinated with, for example, Wittig reagents, which provide epoxy-olefins of Formula (VIII). Benzene, toluene, THF or diethyl ether can be used as a solvent. n-Butyllithium or potassium t-butoxide can be used as a base and the temperature of this reaction can be ranging from about -20° to 80°C. The reaction time is 0.5-10 hours.

Finally, reaction of epoxy-olefins of Formula (VIII) with 1,2,4-triazole in dimethylfuran (DMF) or dimethyl sulfoxide (DMSO) in the presence of potassium carbonate or sodium carbonate at about 50° to 100°C for 1 to 24 hours affords compounds of Formula (I).

When R^1=C1-C4 alkyl, R^2=C1-C4 alkyl, or R^1R^2N=



and n is 1, compounds of Formula (I) can be prepared from compounds of Formula (I) where n=0 by oxidation methods known to one skilled in the art.

Pharmaceutically suitable salts of compounds of Formula (I) can be prepared in a number of ways known in the art. The salts include those resulting from treatment with hydrochloric, hydrobromic, sulfuric, phosphoric, methanesulfonic, succinic, fumaric, ascorbic, and glutaric acids.

Example 1

Preparation of 2-(2,4-Difluorophenyl)-3-(2-chloro-5-dimethylaminophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-buten-2-ol

(Formula I wherein X=2-Cl, R^1R^2N=5-Me_2N, Ar=2,4-$F_2C_6H_3$, and n=0)

Part A:

Preparation of Methyl 2-chloro-5-aminobenzoate

A solution of 2-chloro-5-aminobenzoic acid (85%, 50 g, 0.247 mol) in methanol (250 mL) containing concentrated H_2SO_4 (25 mL) was refluxed for 45 minutes. Methanol was removed, the residue was neutralized with saturated aqueous potassium carbonate solution and extracted with 10% MeOH/CH_2Cl_2. The organic layer was washed with brine and dried (Na_2SO_4). Removal of the solvent gave the product (27.8 g, 61%). ^{1}HNMR ($CDCl_3$) δ: 7.20 (d, 1H), 7.13 (d, 1H), 6.72 (dd, 1H), 3.90 (s, 3H), 3.73 (bs, 2H, $-NH_2$).

Part B:

Preparation of Methyl 2-chloro-5-dimethyl-aminobenzoate

A mixture of methyl 2-chloro-5-aminobenzoate from Step A (25.2 g, 0.136 mol) and methyl iodide (18.6 mL, 0.298 mol) in DMF (50 mL) containing potassium carbonate (41.4 g, 0.298 mol) was heated at 50° for 2 hours. It was then diluted with ether, washed with water. The ether layer was dried (Na_2SO_4). Removal of the solvent afforded the product (18.54 g, 64%). ^{1}HNMR ($CDCl_3$) δ: 7.28 (d, 1H), 7.13 (d, 1H), 6.77 (dd, 1H), 3.97 (s, 3H), 3.00 (s, 6H).

Part C:

Preparation of 2-Chloro-5-dimethylaminobenzyl alcohol

To a solution of methyl 2-chloro-5-dimethylaminobenzoate from Step B (18.5 g, 86.8 mmol) in THF (75 mL) at 0°, was added lithium aluminum hydride (3.95 g, 104.2 mmol) in small portions. The reaction was then stirred at room temperature for 30 minutes and quenched with 4 mL of water, 4 mL of 15% NaOH, and 12 mL of water at 0°. The mixture was stirred at room temperature for 30 minutes and dried over sodium sulfate. It was filtered and the solvent was removed to give the product (16.28 g, 100%). ^{1}HNMR ($CDCl_3$): δ 7.17 (d, 1H), 6.80 (d, 1H), 6.55 (dd, 1H), 4.70 (d, 2H), 2.93 (s, 6H).

Part D:

Preparation of 2-Chloro-5-dimethylamino-benzaldehyde

A solution of anhydrous DMSO (18.5 mL, 0.26 mol) in methylene chloride (50 mL) was added to a solution of oxalyl chloride (11.4 mL, 0.13 mol) in methylene chloride (50 mL) at -60°C. The mixture was stirred for 10 minutes and a solution of 2-chloro-5-

dimethylaminobenzyl alcohol from Step C (16.2 g, 0.087 mol) in methylene chloride (50 mL) was added. It was stirred for 1 hour before the addition if triethylamine (60 mL, 0.436 mol). After 15 minutes, it was warmed up to room temperature and water (50 mL) was added. The separated methylene chloride layer was washed with brine and dried (Na_2SO_4). Removal of the solvent gave the product (12.6 g, 79%). ^{1}HNMR ($CDCl_3$) δ: 10.45 (s, 1H), 7.30 (d, 1H), 7.22 (d, 1H), 6.90 (dd, 1H), 3.00 (s, 6H).

Part E:

Preparation of 2-(2,4-Difluorophenyl)-3-(2-chloro-5-dimethylaminophenyl)-1-propene-3-ol

(Formula IV wherein X=2-Cl, R^1R^2N=5-Me_2N, Ar=2,4-$F_2C_6H_3$)

A solution of 1-bromo-1-(2,4-difluorophenyl) ethylene in THF (35 mL) was added to magnesium chips (1.64 g, 67.33 mmol) in THF (30 mL) at room temperature. It was stirred for 1 hour and then cooled to 0°C. A solution of 2-chloro-5-dimethylamino-benzaldehyde from Step D (10.3 g, 56.1 mmol) in THF (50 mL) was added. The mixture was stirred at 0°C for 1 hour, room temperature for 30 minutes and then quenched with ice. THF was removed, the residue was diluted with 10% MeOH/CH_2Cl_2, washed with brine and dried (Na_2SO_4). The crude product was purified by flash column chromatography to give 11.3 g (62%) of the pure product. ^{1}HNMR ($CDCl_3$) δ: 7.20 (m, 2H), 6.83 (m, 3H), 6.62 (dd, 1H), 6.00 (s, 1H), 5.63 (s, 1H), 5.43 (s, 1H), 2.93 (s, 6H).

Part F:

Preparation of 2-(2,4-Difluorophenyl)-3-(2-chloro-5-dimethylaminophenyl)-1-propene-3-one

(Formula V wherein X=2-Cl, R^1R^2N=5-Me_2N, Ar=2,4-$F_2C_6H_3$)

By following a similar procedure described in Part D, 12.5 g (100%) of the product was obtained from 11.29 g of 2-(2,4-difluorophenyl)-3-(2-chloro-5-

dimethylaminophenyl)-1-propene-3-ol. The product was directly submitted to the next reaction without purification.

Part G:

Preparation of 2-(2,4-Difluorophenyl)-2-(2-chloro-5-dimethylaminobenzoyl)oxirane

(Formula VII wherein X=2-Cl, R^1R^2N=5-Me_2N, Ar=2,4-$F_2C_6H_3$)

To a solution of 2-(2,4-difluorophenyl)-3-(2-chloro-5-dimethylaminophenyl)-1-propene-3-one from Step F (12.5 g, 34.9 mmol) in methanol-water (25 mL-12.5 mL) at 0°C was added sodium hydroxide (1.55 g, 38.9 mmol) followed by 30% hydrogen peroxide (1.2 mL, 38.9 mmol). The mixture was stirred at 0°C for 1 hour. It was extracted with methylene chloride 3 times. The methylene chloride layer was washed with brine and dried (Na2SO4). The crude product was purified by flash column chromatography to give 6.75 g (57%) of the pure product. ^{1}HNMR ($CDCl_3$) δ: 7.50 (m, 1H), 7.17 (d, 1H), 6.87 (m, 2H), 6.67 (m, 2H), 3.35 (d, 1H), 3.23 (d, 1H), 2.92 (s, 6H).

Part H:

Preparation of 2-(2,4-Difluorophenyl)-2-[1-(2-chloro-5-dimethylaminophenyl)ethenyl]oxirane

(Formula VIII wherein X=2-Cl, R^1R^2N=5-Me_2N, Ar=2,4-$F_2C_6H_3$)

Methyltriphenylphosphonium bromide (8.57 g, 24 mmol) was heated at 75°C under high vacuum for 1 hour. It was then cooled to room temperature and THF (40 mL) was added. To this mixture at 0°C was added n-butyllithium (1.6 M, 14.99 mL, 24 mmol) and the resulting dark red solution was stirred at 0°C for 20 minutes before adding to a solution of 2-(2,4-difluorophenyl)-2-(2-chloro-5-dimethylaminobenzoyl)-oxirane from Step G (6.75 g, 20 mmol) in THF (40 mL) at 0°C. The reaction was stirred at room temperature for 1

hour and quenched with ice water. THF was removed, the residue was extracted with methylene chloride and the organic layer was washed with brine and dried (Na_2SO_4). The crude product was purified by flash column chromatography to give 2.5 g (37%) of the pure product. ^{1}HNMR ($CDCl_3$) δ: 6.93 (m, 1H), 7.15 (d, 1H), 6.80 (m, 2H), 6.50 (m, 2H), 5.40 (s, 1H), 5.27 (s, 1H), 3.03 (s, 2H), 2.85 (s, 6H).

Part I:

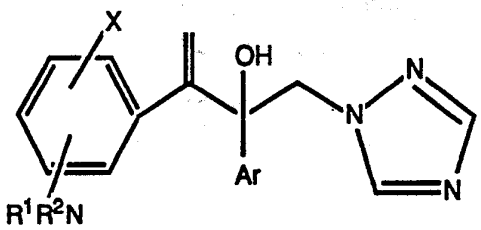
Preparation of 2-(2,4-Difluorophenyl)-3-(2-chloro-5-dimethylaminophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-buten-2-ol

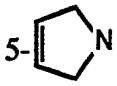
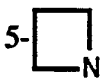
(Formula I wherein X=2-Cl, R^1R^2N=5-Me_2N, Ar=2,4-$F_2C_6H_3$, n=0)

Treatment of 2-(2,4-difluorophenyl)-2-[1-(2-chloro-5-dimethylaminophenyl)ethenyl]oxirane from Step H (2.5 g, 7.45 mmol) in DMF (20 mL) with 1,2,4-triazole (1.57 g, 22.35 mmol) and potassium carbonate (3.08 g, 22.35 mmol) at 90°C for 4 hours. It was then diluted with ether, washed with water. The ether layer was dried (Na_2SO_4). The crude product was purified by flash column chromatography to give 1.1 g (36%) of the pure product. m.p. 147-148°C; ^{1}HNMR ($CDCl_3$) δ: 7.93 (s, 1H), 7.73 (s, 1H), 7.53 (q, 1H), 7.23 (d, 1H), 6.83-6.50 (m, 3H), 6.35 (d, 1H), 5.45 (s, 1H), 5.22 (s, 1H), 5.13 (d, 1H), 4.90 (s, 1H), 4.46 (d, 1H), 2.83 (s, 6H); HRMS: m/z 404.1221 (M+), calcd. for $C_{20}H_{19}ClF_2N_4O$, 404.1215.

By using the procedures described in Example 1, the following compounds (where n is 0) in Table I were prepared or can be prepared.

TABLE I



Ex.	X	R^1R^2N	Ar	m.p. (°C)
1	2-Cl	5-Me*$_2$N	2,4-$F_2C_6H_3$	147-148
2	2-Cl	5-Me_2N	4-ClC_6H_4	122-124
3	2-Cl	5-Et*$_2$N	2,4-$F_2C_6H_3$	128-129
4	2-Cl	5-n-Pr*$_2$N	2,4-$F_2C_6H_3$	114-115
5	2-Cl		2,4-$F_2C_6H_3$	118-125
6	2-Cl	5-$(H_2C{=}CCH_2)_2N$	2,4-$F_2C_6H_3$	122-124
7	2-Br	3-MeNBu*-i	2,4-$F_2C_6H_3$	
8	2-Br	6-Me_2N	2,4-$Cl_2C_6H_3$	
9	3-Cl	2-n-Bu_2N	4-ClC_6H_4	
10	3-Cl		2,4-$F_2C_6H_3$	
11	3-Cl	6-Et_2N	2,4-$Cl_2C_6H_3$	
12	4-Cl	2-Me_2N	2,4-$F_2C_6H_3$	
13	4-Cl	3-MeNH	4-ClC_6H_4	
14	4-Br	3-EtNPr-i	2,4-$F_2C_6H_3$	

* Me is methyl
* Et is ethyl
* Pr is propyl
* Bu is butyl

Example 15

Preparation of 2-(2,4-Difluorophenyl)-3-(2-chloro-4-acetamidophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-buten-2-ol

(Formula I wherein X=2-Cl, R^1R^2N=4-MeC(=O)NH, Ar=2,4-$F_2C_6H_3$, n=0)

Part A:

Preparation of Methyl 2-chloro-4-aminobenzoate

By following a similar procedure described in Example 1, Part A, 20.8 g (96%) of the product was obtained from 20 g (0.116 mole) of 2-chloro-4-aminobenzoic acid. ^{1}HNMR ($CDCl_3$) δ: 7.77 (d, 1H), 6.67 (d, 1H), 6.50 (dd, 1H), 4.20 (bs, 2H), 3.83 (s, 3H).

Part B:

Preparation of Methyl 2-chloro-4-acetamidobenzoate

Treatment of methyl 2-chloro-4-aminobenzoate from Step A (20 g, 0.108 mol) with acetic anhydride (11.2 mL, 0.119 mole) and triethylamine (16.5 mL, 0.119 mol) in refluxing methylene chloride (75 mL) for 3 hours. It was then washed with 10% aqueous hydrochloric acid, brine, and dried (Na2SO4). Removal of the solvent gave the product (25 g, 100%). ^{1}HNMR ($CDCl_3$) δ: 8.42 (bm, 1H), 7.88 (d, 1H), 7.79 (s, 1H), 7.57 (d, 1H), 3.93 (s, 3H), 2.23 (s, 3H).

Part C:

Preparation of 2-Chloro-4-acetamidobenzyl alcohol

To a refluxing solution of methyl 2-chloro-4-acetamidobenzoate from Step B (24.3 g, 0.107 mol) and sodium borohydride (12.18 g, 0.32 mol) in t-butyl alcohol (200 mL) was added methanol (80 mL) slowly over 1 hour. The mixture was continually refluxed for 16 hours and then quenched with water. The solvent was removed, the residue was diluted with water and extracted with chloroform. The chloroform layer was dried (Na_2SO_4). Removal of the solvent afforded 18.4 g

(86%) of the product. ^{1}HNMR (d_6-DMSO) δ: 10.07 (s, 1H), 7.80 (s, 1H), 7.43 (s, 2H), 5.30 (t, 1H), 4.50 (d, 2H), 2.03 (s, 3H).

Part D:

Preparation of 2-Chloro-4-acetamidobenzaldehyde

Treatment of 2-chloro-4-acetamidobenzyl alcohol from Step C (9.6 g, 48 mmol) with manganeous (IV) oxide (20.9 g, 240 mmol) in refluxing chloroform (100 mL) for 16 hours. It was then filtered through Celite®. The crude product was purified by flash column chromatography to give 7.5 g (79%) of the product. ^{1}HNMR ($CDCl_3$) δ: 10.37 (s, 1H), 7.92 (s, 1H), 7.90 (d, 1H), 7.77 (bs, 1H), 7.40 (d, 1H), 2.23 (s, 1H).

Part E:

Preparation of 2-(2,4-Difluorophenyl)-3-(2-chloro-4-acetamidophenyl)-1-propene-3-ol

(Formula IV wherein X=2-Cl, R^1R^2N=4-MeC(=O)NH, Ar=2,4-$F_2C_6H_3$)

By following a similar procedure described in Example 1, Part E, 8.8 g (69%) of the product was obtained from 18.3 g (83.5 mmol) of 1-bromo-1-(2,4-difluorophenyl)ethylene and 7.5 g (38 mmol) of 2-chloro-4-acetamidobenzaldehyde from Step D. ^{1}HNMR ($CDCl_3$) δ: 8.00-6.73 (m, 7H), 6.02 (d, 1H), 5.60 (s, 1H), 5.38 (s, 1H), 2.17 (s, 3H).

Part F:

Preparation of 2-(2,4-Difluorophenyl)-2-[1-(2-chloro-4-acetamidophenyl)methyl-1-ol]oxirane

(Formula VI wherein X=2-Cl, R^1R^2N=4-MeC(=O)NH, Ar=2,4-$F_2C_6H_3$)

A mixture of 2-(2,4-difluorophenyl)-3-(2-chloro-4-acetamidophenyl)-1-propene-3-ol from Step E (4.6 g, 13.63 mmol) and MCPBA (3.7 g, 17.72 mmol) in methylene chloride (75 mL) was stirred at room temperature for 16 hours. It was then washed with saturated aqueous sodium

bicarbonate solution, brine, and dried (Na_2SO_4). The crude product was purified by flash column chromatography to give 3.11 g (65%) of the product. ^{1}HNMR ($CDCl_3$) δ: 7.93-6.67 (m, 7H), 5.67 (d, 1H), 3.24 (d, 1H), 2.90 (d, 1H), 2.17 (s, 3H).

Part G:

Preparation of 2-(2,4-Difluorophenyl)-2-(2-chloro-4-acetamidobenzoyl)oxirane

(Formula VII wherein X=2-Cl, R^1R^2N=4-MeC(=O)NH, Ar=2,4-$F_2C_6H_3$)

2-(2,4-Difluorophenyl)-2-[1-(2-chloro-4-acetamidophenyl)methyl-1-ol]oxirane from Step F (15.9 g, 44.98 mmol) was converted to the product (8.5 g, 54%) by a similar procedure described in Example 1, Part D. ^{1}HNMR ($CDCl_3$) δ: 7.70-6.75 (m, 7H), 3.25 (q, 2H), 2.18 (s, 3H).

Part H:

Preparation of 2-(2,4-Difluorophenyl)-2-[1-(2-chloro-4-acetamidophenyl)ethenyl]oxirane

(Formula VIII wherein X=2-Cl, R^1R^2N=4-MeC(=O)NH, Ar=2,4-$F_2C_6H_3$)

By following a similar procedure described in Example 1, Part H, 4.4 g (52%) of the product was obtained from 8.5 g (24.18 mmol) of 2-(2,4-difluorophenyl)-2-(2-chloro-4-acetamidobenzoyl)oxirane from Step G and 19 g (53.2 mmol) of methyltriphenylphosphonium bromide. ^{1}HNMR ($CDCl_3$) δ: 7.65-6.70 (m, 7H), 5.46 (s, 1H), 5.28 (s, 1H), 3.04 (ABq, 2H), 2.19 (s, 3H).

Part I:

Preparation of 2-(2,4-Difluorophenyl)-3-(2- chloro-4-acetamidophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-buten-2-ol

(Formula I, X=2-Cl, R^1R^2N=4-MeC(=O)NH, Ar=2,4-$F_2C_6H_3$, n=0)

2-(2,4-Difluorophenyl)-2-[1-(2-chloro-4-acetamidophenyl)ethenyl]oxirane from Step H (2.7 g, 7.72 mmol) was converted to 0.66 g (20%) of the product by a similar procedure described in Example 1, Part I. ^{1}HNMR ($CDCl_3$) δ: 7.93 (s, 1H), 7.75 (s, 1H), 7.72 (s, 1H), 7.50 (m, 1H), 7.25 (m, 1H), 7.07 (d, 1H), 6.73 (m, 2H), 5.48 (s, 1H), 5.20 (s, 1H), 5.13 (d, 1H), 5.05 (s, 1H), 4.45 (d, 1H), 2.17 (s, 3H); HRMS: m/z 418.1001 (M+), calcd. for $C_{20}H_{17}F_2ClN_4O_2$, 418.1008.

Example 16

Preparation of 2-(2,4-Difluorophenyl)-3-(2-chloro-4-aminophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-buten-2-ol

(Formula I wherein X=2-Cl, R^1R^2N=4-NH2, Ar=2,4-$F_2C_6H_3$, n=0)

A solution of 2-(2,4-difluorophenyl)-3-(2-chloro-4-acetamidophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-buten-2-ol from Example 15 (450 mg, 1.07 mmol) in ethanol-water (4 mL-2 mL) containing potassium hydroxide (300 mg, 5.35 mmol) was refluxed for 16 hours. The solvent was removed in vacuo, the residue was diluted with ether, washed with brine and dried (Na_2SO_4). Purification by flash column chromatography gave 307 mg (76%) of the product. ^{1}HNMR ($CDCl_3$) δ: 7.93 (s, 1H), 7.75 (s, 1H), 7.50 (m, 1H), 6.87 (d, 1H), 6.70 (m, 3H), 6.47 (dd, 1H), 5.45 (s, 1H), 5.20 (s, 1H), 5.13 (d, 1H), 4.87 (s, 1H), 4.45 (d, 1H), 3.75 (bs, 2H); HRMS: m/z 376.0921 (M+), calcd. for $C_{18}H_{15}F_2ClN_4O$, 376.0902.

Example 17

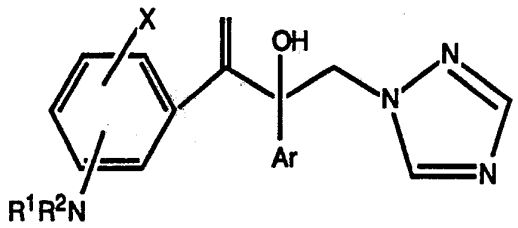
Preparation of 2-(2,4-Difluorophenyl-3-(2-chloro-4-dimethylaminophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-buten-2-ol

(Formula I wherein X=2-Cl, R^1R^2N=4-Me_2N, Ar=2,4-$F_2C_6H_3$, n=0)

A mixture of 2-(2,4-difluorophenyl)-3-(2-chloro-4-aminophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-buten-2-ol from Example 16 (1 g, 2.65 mmol), methyl iodide (0.366 mL, 5.83 mmol) and potassium carbonate (805 mg, 5.83 mmol) was heated at 50°C for 5 hours. It was then diluted with ether and washed with water. The aqueous layer was extracted with ether and the combined ether layer was dried (Na_2SO_4). Purification by flash column chromatography afforded 302 mg (28%) of the product. ^{1}HNMR ($CDCl_3$) δ: 7.94 (s, 1H), 7.75 (s, 1H), 7.54 (m, 1H), 6.96 (d, 1H), 6.70 (m, 3H), 6.53 (dd, 1H), 5.45 (s, 1H), 5.23 (s, 1H), 5.13 (d, 1H), 4.84 (s, 1H), 4.46 (d, 1H), 2.95 (s, 6H); HRMS: m/z 404.1218 (M^+), calcd. for $C_{20}H_{19}F_2ClN_4O$, 404.1215.

By using the procedures described in Examples 15-17, the following compounds in Table II were prepared or can be prepared.

TABLE II



Ex.	X	R^1R^2N	Ar	HRMS (m/z)
15	2-Cl	4-MeC(=O)NH	$2,4\text{-}F_2C_6H_3$	418.1001 (M+)
16	2-Cl	4-NH2	$2,4\text{-}F_2C_6H_3$	376.0921 (M+)
17	2-Cl	$4\text{-}Me_2N$	$2,4\text{-}F_2C_6H_3$	404.1218 (M+)
18	2-Cl	3-MeC(=O)NH	$2,4\text{-}Cl_2C_6H_3$	
19	2-Cl	$3\text{-}NH_2$	$4\text{-}ClC_6H_4$	
20	2-Cl	5-MeC(=O)NH	$2,4\text{-}F_2C_6H_3$	418.1017 (M+)
21	2-Cl	$5\text{-}NH_2$	$2,4\text{-}F_2C_6H_3$	376.0902 (M+)
22	2-Cl	4-MeNH	$2,4\text{-}F_2C_6H_3$	
23	2-Cl	4-i-Pr_2N	$2,4\text{-}F_2C_6H_3$	
24	2-Br	4-HC(=O)NMe	$4\text{-}ClC_6H_4$	
25	2-Br	$6\text{-}NH_2$	$2,4\text{-}F_2C_6H_3$	
26	3-Br	4-EtC(=O)NPr-n	$2,4\text{-}Cl_2C_6H_3$	
27	3-Cl	$4\text{-}Et_2N$	$2,4\text{-}F_2C_6H_3$	
28	3-Cl	5-i-BuC(=O)NH	$2,4\text{-}Cl_2C_6H_3$	
29	4-Cl	$2\text{-}NH_2$	$2,4\text{-}F_2C_6H_3$	
30	4-Cl	3-MeC(=O)NH	$2,4\text{-}F_2C_6H_3$	
31	4-Br	$3\text{-}NH_2$	$2,4\text{-}F_2C_6H_3$	
32	4-Br	$2\text{-}ClCH_2C(=O)NEt$	$2,4\text{-}F_2C_6H_3$	
33	4-Br	$3\text{-}BrCH_2C(=O)NH$	$2,4\text{-}Cl_2C_6H_3$	

Example 34

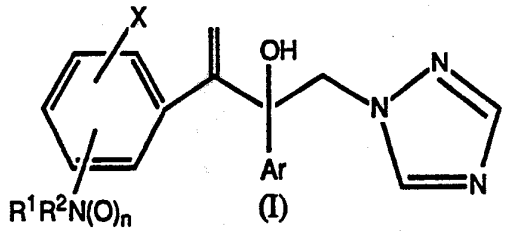
Preparation of 2-(2,4-Difluorophenyl)-3-(2-chloro-5-dimethylaminooxidephenyl)-1-(1H-1,2,4-triazol-1-yl)-3-buten-2-ol

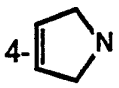
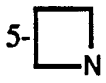
(Formula I wherein X=2-Cl, R^1R^2N=5-Me_2N, Ar=2,4-$F_2C_6H_3$, n=1)

A mixture of 2-(2,4-difluorophenyl)-3-(2-chloro-5-dimethylaminophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-buten-2-ol from Example 1 (270 mg, 0.67 mmol) and MCPBA (170 mg, 0.8 mmol) in methylene chloride (5 mL) was stirred at room temperature for 30 minutes. The solvent was removed in vacuo and the residue was chromatographed to give 284 mg (100%) of the product. ^{1}HNMR ($CDCl_3$) δ: 8.00 (m, 2H), 7.77 (s, 1H), 7.72 (s, 1H), 7.50 (m, 2H), 6.73 (m, 2H), 5.55 (s, 1H), 5.27 (s, 1H), 5.23 (d, 1H), 4.47 (d, 1H), 3.53 (s, 6H); MS: m/z 421 (M^+ +1).

By using the procedure described in Example 34, the following compounds in Table III were prepared or can be prepared.

TABLE III



Ex.	X	R^1R^2N	n	Ar	MS (m/z)
34	2-Cl	5-Me_2N	1	2,4-$F_2C_6H_3$	421 (M++1)
35	2-Cl	5-Me_2N	1	4-ClC_6H_4	419 (M++1)
36	2-Cl	4-Me_2N	1	2,4-$F_2C_6H_3$	
37	2-Cl	3-Et_2N	1	2,4-$Cl_2C_6H_3$	
38	2-Br	3-MeNEt	1	2,4-$F_2C_6H_3$	
39	2-Br	6-MeNPr-n	1	2,4-$F_2C_6H_3$	
40	3-Cl	2-MeNBu-i	1	2,4-$Cl_2C_6H_3$	
41	3-Cl		1	2,4-$F_2C_6H_3$	
42	3-Cl		1	2,4-$Cl_2C_6H_3$	
43	3-Cl	6-Me_2N	1	2,4-$F_2C_6H_3$	
44	4-Cl	2-MeNPr-i	1	2,4-$F_2C_6H_3$	
45	4-Br	3-MeNBu-n	1	2,4-$F_2C_6H_3$	

Example 46

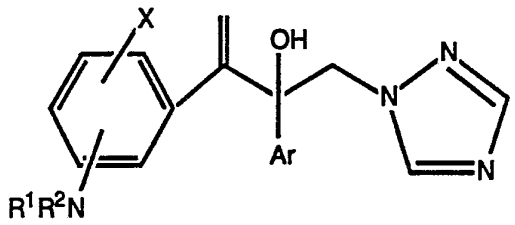
Preparation of Methanesulfonate salt of 2-(2,4-difluorophenyl)-3-(2-chloro-5-dimethylaminophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-buten-2-ol

To a solution of 2-(2,4-difluorophenyl)-3-(2-chloro-5-dimethylaminophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-buten-2-ol from Example 1 (520 mg, 1.288 mmol) in THF

(3 mL) was added methanesulfonic acid (0.17 mL, 2.576 mmol). The mixture was stirred at room temperature for 15 minutes. Removal of the solvent in vacuo gave 690 mg (90%) of the product. ^{1}HNMR (d_6-DMSO) δ: 9.08 (s, 1H), 8.23 (s, 1H), 7.50-6.89 (m, 6H & H_2O, $-SO_3H$), 5.63 (s, 1H), 5.20 (s, 1H), 5.17 (d, 1H), 4.80 (d, 1H), 2.97 (s, 6H).

By using a similar procedure described in Example 46, the following compounds in Table IV were prepared or can be prepared.

TABLE IV



Ex.	X	R^1R^2N	Ar	Salt
46[a]	2-Cl	5-Me_2N	2,4-$F_2C_6H_3$	2CH_3SO_3H
47	2-Cl	4-Me_2N	2,4-$F_2C_6H_3$	2CH_3SO_3H
48	2-Cl	5-Me_2N	4-ClC_6H_4	2HBr
49	2-Cl	4-Et_2N	2,4-$Cl_2C_6H_3$	2HCl
50	2-Cl	3-MeNEt	2,4-$F_2C_6H_3$	2H_2SO_4
51	2-Br	6-MeNPr-n	2,4-$F_2C_6H_3$	2H_3PO_4
52	3-Cl	2-Me_2N	2,4-$F_2C_6H_3$	2CH_3SO_3H
53	3-Cl	4-Me_2N	2,4-$F_2C_6H_3$	2CH_3SO_3H
54	3-Cl	5-i-Pr_2N	2,4-$F_2C_6H_3$	2HBr
55	3-Br	6-Me_2N	2,4-$Cl_2C_6H_3$	2HCl
56	4-Cl	2-Me_2N	2,4-$F_2C_6H_3$	2CH_3SO_3H
57	4-Cl	3-MeNBu-n	2,4-$F_2C_6H_3$	2CH_3SO_3H
58	4-Cl	3-i-Bu_2N	2,4-$F_2C_6H_3$	2H_3PO_4

Footnotes for Table IV

a ^{1}HNMR (d_6-DMSO) δ: 9.08 (s, 1H), 8.23 (s, 1H), 7.50-6.89 (m, 6H & H_2O, $-SO_3H$), 5.63 (s, 1H), 5.20 (s, 1H), 5.17 (d, 1H), 4.80 (d, 1H), 2.97 (s, 6H).

Pharmaceutical Utility

In vitro activity (Table V) is expressed in terms of the minimal inhibitory concentration (MIC) of the test compound which inhibits the growth of yeasts and fungi.

The target organisms, Candida albicans ATCC 11651 and Aspergillus fumigatus ATCC 28214 are standardized, [V. Bezjak, J. Clinical Micro., 21 509-512 (1984)] to a concentration of 107 organisms/mL and maintained at -70° until use. Test compounds are solubilized in dimethyl sulfoxide (DMSO) and diluted in Eagle's Minimum Essential Medium (EMEM) broth to achieve a final concentration of 200 µg/ml. Stock solutions of standard antifungal agents are stored at -70° and diluted in EMEM as required.

The in vitro assay utilizes a microtiter broth dilution technique [L. Polonelli and G. Morace, Mycopathologia, 86, 21-28 (1984)] and C. Hughes, et al. Antimicrob. Ag. and Chemo., 25, 560-562(1984)]. Test compounds are serially diluted in EMEM to give graded concentrations ranging from 100 to 0.4 µg/mL. The appropriate wells are inoculated with the required organism (C. albicans at 1 x 10^4 organisms/mL and A. fumigatus at 5 x 10^5 organisms/mL) and the assay incubated at 30° for 24 hours. The extent of fungal growth is determined at an optical density equal to 540 nm using a scanning spectrophotometer (Flow® MCC) and MIC values, representing the minimal concentration of a compound which inhibited growth, are determined, [V.

Grenta, et al. Antimicrob. Ag. and Chemo., 22, 151-153 (1982)].

The in vivo activity of test compounds is based on the percent (%) survival of infected animals receiving test or standard agent compared to that in an infected untreated group (Table VI). The in vivo assays are chronic systemic infections lethal to mice within 7 days post infection, [J. Barnes, et al. Lab Investigation, 49 460-467 (1963), and T. Rogers and E. Balish, Infection and Immunity, 14 33-38 (1976)].

Candida albicans ATCC 11651, from a frozen stock culture (10^9 organisms/mL) maintained at -70°, is diluted in saline to 1 x 10^7 organisms/mL and 0.2 mL inoculated intravenously (caudal vein) into 20.0 gm CF-1 female mice (Charles River).

Test compounds are routinely solubilized in 0.25% (w/v) methylcellulose (Methocel®) but for those compounds difficult to solubilize 10% (w/v) Emulophor® (EL620 GAF Corp.) is used. The standard antifungal agents, amphotericin B (Fungizone®) in water and ketoconazole (Nizoral®) in Methocel®, are administered at 1.0 mg/kg/day and 150 mg/kg/day, respectively.

In a primary assay, mice (10 per group) are infected with C. albicans, and receive test compounds at 50 or 150 mg/kg/day via the subcutaneous route. Animals are dosed with the test compound at 1 and 6 hour post-infection and then once daily for the next three days. Survival of mice in each group is recorded for 21 days.

Compounds which protect ≥70% of the infected animals for 14 days at a dose 150 mg/kg/day or less are viewed as active.

TABLE V

In Vitro Antifungal Results

Example	MIC values (µg/mL) C. albicans (CAND-1)	A. fumigatus (ASFU-4)
1	≤0.4	6.3
2	≤0.4	50
3	≤0.03	>100
4	0.2	>100
5	≤0.4	>100
6	0.05	>100
15	0.2	12.5
16	≤0.03	1.6
17	≤0.03	0.4
20	0.4	100
21	0.1	1.6
34	0.8	>100
35	≤0.4	>100
46	≤0.03	6.3
Amphotericin B*	0.33±0.2	1.4±0.5
Nystatin*	1.3 ±0	3.0±1.0
5-Fluorocytosine*	0.14±0.1	5.7±4.0
Ketoconazole*	≤0.1	11.0±5.0
Miconazole*	≤0.1	1.3±0

*MIC values of the standard drugs are the mean of five determinations + Standard deviation

The data indicate that compounds of this invention have in vitro activity comparable to standard antifungal agents.

TABLE VI

In Vivo Antifungal Results

Murine Candidiasis Model

% Survival

Ex. No.	Days 7	14	21
1	100	100	90
2	100	100	90
3	NT	NT	NT
4	90	80	80
5	100	50	50
6	80	60	60
15	100	70	50
16	100	90	80
17	100	100	90
20	80	40	30
21	70	50	20
34	100	70	60
34	100	70	60
35	70	30	10
46	NT	NT	NT
Amphotericin B	100	100	100
Ketoconazole	100	80	50

NT= not tested

Compounds which protect ≥70% of the infected animals for 14 days at a dose of ≤150 mg/kg/day are active. Therefore the data indicate the compounds of this invention demonstrate in vivo activity comparable to standard antifungal agents.

Dosage Forms

The antifungal agents of this invention can be administered by any means that effects contact of the

active ingredient with the agent's site of action in the body. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will, of course, vary depending on the use and known factors such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration: age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired.

Dosage forms (compositions) suitable for administration contain from about 200 milligram to about 2000 milligrams of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition. For use in the treatment of said diseases, a daily dose of active ingredient can be about 10 to 50 milligrams per kilogram of body weight.

The composition of the invention may be in a conventional pharmaceutical form suitable for oral administration, for example a tablet, a capsule, an emulsion or an aqueous or oily solution or suspension, or suitable for topical application, for example a cream, ointment or gel. It can also be administered parenterally in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid and the

like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

The pharmaceutical compositions which are ointments, creams and gels can, for example, contain the usual diluents, e.g. animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide or mixtures of these substances.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite or ascorbic acid, either alone or combined, are suitable stabilizing agents.

All the pharmaceutical compositions according to the invention can also contain coloring and flavoring to increase patient acceptance.

Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, (1985) 17th

Edition, A. Osol, a standard reference text in this field.

Useful pharmaceutical dosage forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol. The solution is made to volume with water for injection and sterilized.

Suspension

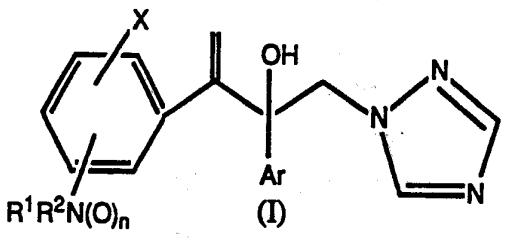
An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

Cream

A cream for topical application is prepared by incorporating 100 milligrams of the finely pulverized active ingredient in 5 grams of a cream base which comprises 40% white petrolatum, 3% microcrystalline wax, 10% lanolin, 5% Span®20, 0.3% Tween®20 and 41.7% water.

WHAT IS CLAIMED IS:

1. A compound of the formula:

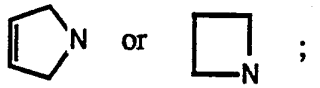


(I)

or pharmaceutically acceptable salts thereof wherein:

R^1 is H or C1-C4 alkyl;

R^2 is H, C1-C4 alkyl, R^3 C=O, or R^1R^2N is



;

R^3 is H, C1-C4 alkyl or CH_2X;

X is Cl or Br;

Ar is 2,4-$F_2C_6H_3$, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$; and

n is 0 or 1.

2. A compound of claim 1 wherein R^1 and R^2 independently are H or C1-C3 alkyl.

3. A compound of claim 1 wherein n is 0.

4. A compound of claim 1 wherein Ar is 2,4-$F_2C_6H_3$ or 4-ClC_6H_4.

5. A compound of claim 1 wherein R^1R^2N is substituted at the 4- or 5- position.

6. A compound of claim 1 wherein X is 2-Cl or 2-Br.

7. A compound of claim 1 wherein:

R^1 and R^2 independently are H or C1-C3 alkyl;

n is 0;

Ar is 2,4-$F_2C_6H_3$ or 4-ClC_6H_4;

R^1R^2N is substituted at the 4- or 5- position; and

X is 2-Cl or 2-Br.

8. A compound of claim 4 wherein Ar is 2,4-$F_2C_6H_3$.

9. A compound of claim 7 wherein Ar is 2,4-$F_2C_6H_3$.

10. A compound of claim 6 wherein X is 2-Cl.

11. A compound of claim 7 wherein X is 2-Cl.

12. A compound of claim 7 wherein:

R^1 and R^2 independently are H or C1-C3 alkyl;

n is 0;

Ar is 2,4-$F_2C_6H_3$;

R^1R^2N is substituted at the 4- or 5- position; and

X is 2-Cl.

13. The compound of claim 12 wherein R^1R^2N is 5$(CH_3)_2N$.

14. The compound of claim 12 wherein R^1R^2N is 4-H_2N.

15. The compound of claim 13 wherein the pharmaceutically acceptable salt thereof is the methanesulfonate salt.

16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-fungal effective amount of a compound of claim 1.

17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-fungal effective amount of a compound of claim 2.

18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-fungal effective amount of a compound of claim 3.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-fungal effective amount of a compound of claim 4.

20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-fungal effective amount of a compound of claim 5.

21. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-fungal effective amount of a compound of claim 6.

22. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-fungal effective amount of a compound of claim 7.

23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-fungal effective amount of a compound of claim 8.

24. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-fungal effective amount of a compound of claim 9.

25. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-fungal effective amount of a compound of claim 10.

26. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-fungal effective amount of a compound of claim 11.

27. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-fungal effective amount of a compound of claim 12.

28. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-fungal effective amount of the compound of claim 13.

29. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-fungal effective amount of the compound of claim 14.

30. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-fungal effective amount of the compound of claim 15.

31. A method of treating a fungal infection in a mammal comprising administering to the mammal an anti-fungal effective amount of a compound of claim 1.

32. A method of treating a fungal infection in a mammal comprising administering to the mammal an antifungal effective amount of a compound of claim 2.

33. A method of treating a fungal infection in a mammal comprising administering to the mammal an antifungal effective amount of a compound of claim 3.

34. A method of treating a fungal infection in a mammal comprising administering to the mammal an antifungal effective amount of a compound of claim 4.

35. A method of treating a fungal infection in a mammal comprising administering to the mammal an antifungal effective amount of a compound of claim 5.

36. A method of treating a fungal infection in a mammal comprising administering to the mammal an antifungal effective amount of a compound of claim 6.

37. A method of treating a fungal infection in a mammal comprising administering to the mammal an antifungal effective amount of a compound of claim 7.

38. A method of treating a fungal infection in a mammal comprising administering to the mammal an antifungal effective amount of a compound of claim 8.

39. A method of treating a fungal infection in a mammal comprising administering to the mammal an antifungal effective amount of a compound of claim 9.

40. A method of treating a fungal infection in a mammal comprising administering to the mammal an antifungal effective amount of a compound of claim 10.

41. A method of treating a fungal infection in a mammal comprising administering to the mammal an antifungal effective amount of a compound of claim 11.

42. A method of treating a fungal infection in a mammal comprising administering to the mammal an antifungal effective amount of a compound of claim 12.

43. A method of treating a fungal infection in a mammal comprising administering to the mammal an anti-fungal effective amount of the compound of claim 13.

44. A method of treating a fungal infection in a mammal comprising administering to the mammal an anti-fungal effective amount of the compound of claim 14.

45. A method of treating a fungal infection in a mammal comprising administering to the mammal an anti-fungal effective amount of the compound of claim 15.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/00193

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61K 31/41; C07D 249/08

U.S. CL.: 514/383; 548/267.8

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	514/383
	548/267.8

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

CAS Online Structure Search

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	US, A, 4,980,367 (CUOMO ET AL.) 25 December 1990, See the entire document.	1-45
Y	US, A, 4,655,820 (WORTHINGTON ET AL.) 07 April 1987, See the entire document.	1-45
Y	US, A, 4,243,405 (BALASUBRAMANYAN ET AL.) 06 January 1981, See the entire document.	1-45

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
04 MARCH 1991	18 APR 1991
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	PATRICIA L. MORRIS

Form PCT/ISA/210 (second sheet) (May 1986)