PCT WORLD INTELLECTUAL PROP International E

INTERNATIONAL APPLICATION PUBLISHED UNDEI WO 9518616A3

(51) International Patent Classification 6 : A61K 31/495, C07D 471/04, 487/04 — A3

(11) International Publication Number: WO 95/18616

(43) International Publication Date: 13 July 1995 (13.07.95)

(21) International Application Number: PCT/US95/00214

(22) International Filing Date: 3 January 1995 (03.01.95)

(30) Priority Data:

08/176,278	3 January 1994 (03.01.94)	US
08/289,366	11 August 1994 (11.08.94)	US

(71) Applicants: ACEA PHARMACEUTICALS, INC. [US/US]; 213 Technology Drive, Irvine, CA 92718 (US). THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US/US]; 22nd floor, 300 Lakeside Drive, Oakland, CA 94612-3550 (US). STATE OF OREGON, acting by and through THE OREGON STATE BOARD OF HIGHER EDUCATION, acting for and on behalf of THE OREGON HEALTH SCIENCES UNIVERSITY AND THE UNIVERSITY OF OREGON [US/US]; University of Oregon, Riverfront Research Park, Eugene, OR 97403-1238 (US).

(72) Inventors: CAI, Sui, Xiong; 3900 Parkview Lane #6B, Irvine, CA 92715 (US). WEBER, Eckard; 1290 Morningside Drive, Laguna Beach, CA 92651 (US). KEANA, John, F., W.; 3854 Onyx Street, Eugene, OR 97405 (US).

(74) Agents: ESMOND, Robert, W. et al.; Sterne, Kessler, Goldstein & Fox, Suite 600, 1100 New York Avenue, N.W., Washington, DC 20005-3934 (US).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

Published

With international search report.

With amended claims.

(88) Date of publication of the international search report: 21 December 1995 (21.12.95)

Date of publication of the amended claims: 29 February 1996 (29.02.96)

(54) Title: 8-AZA, 6-AZA AND 6,8-DIAZA-1,4-DIHYDROQUINOXALINE-2,3-DIONES AND THE USE THEREOF AS ANTAGONISTS FOR THE GLYCINE/NMDA RECEPTOR

(57) Abstract

Methods of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia and surgery, as well as treating neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Down's syndrome, treating or preventing the adverse consequences of the hyperactivity of the excitatory amino acids, as well as treating anxiety, chronic pain, convulsions, inducing anesthesia, and treating or preventing opiate tolerance are disclosed by administering to an animal in need of such treatment or prevention a substituted or unsubstituted 8-aza, 6-aza, or 6,8-diaza-1,4-dihydroquinoxaline-2,3-dione, N-oxides thereof and pharmaceutically acceptable salts thereof, which have high binding to the glycine receptor.

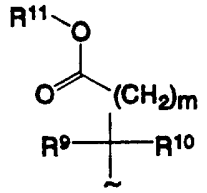
FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

AMENDED CLAIMS

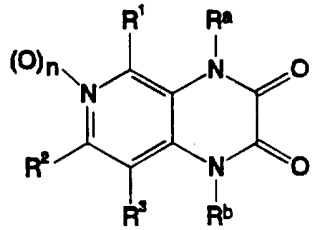
[received by the International Bureau on 15 January 1996 (15.01.96);
original claims 1, 3, 12, 14, 19, 21, 26, 28, 33, 35, 40, 42, 47, 49, 54, 56, 61, 63, 69, 71-73, 75, 77, 78 and 81 amended;
remaining claims unchanged (26 pages)]



wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that when R^a is other than hydrogen, then R^b is hydrogen and R^3 is hydrogen or fluoro, and when R^b is other than hydrogen, then R^a is hydrogen and R^1 is hydrogen or fluoro, with the further proviso that when at least one of R^1, R^2 and R^3 is nitro, amino, alkoxy, alkylsulfonyl or alkyl, then n is 1 or one of R^a and R^b is other than hydrogen.

2. A method of treating or preventing (A) neuronal loss associated with stroke, ischemia, CNS trauma, or hypoglycemia or (B) the adverse neurological consequences of surgery, comprising administering to an animal in need of such treatment or prevention an effective amount of a compound of the formula:



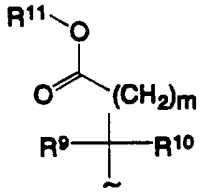
or a pharmaceutically acceptable salt thereof;

wherein n is 0 or 1; and

R^1, R^2, and R^3 are independently hydrogen, nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^4, R^5, and R^6 are independently hydrogen, nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^c and R^d are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:



wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that when R^c is other than hydrogen, then R^d is hydrogen and n is 0; and

when R^d is other than hydrogen, then R^c is hydrogen and R^4 is hydrogen or fluoro;

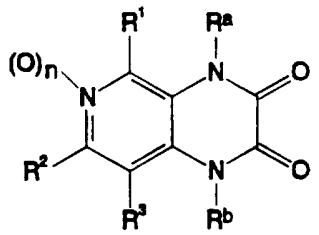
with the further proviso that when n is 0, then R^4, R^5, and R^6 are not hydrogen; or when n is 0, then R^4 and R^6 are not hydrogen, nitro, amino, alkoxy, alkylsulfonyl or alkyl; or when n is 0, then one of R^c and R^d are not hydrogen; or when n is 1, then R^4 is hydrogen or fluoro and R^c is hydrogen.

4. The method of claim 3, wherein n is 1, R^5 and R^6 are not hydrogen, and R^c, R^d, and R^4 are hydrogen.

5. A method of treating or preventing (A) neuronal loss associated with stroke, ischemia, CNS trauma, or hypoglycemia or (B) the adverse

with the proviso that when R^a is other than hydrogen, then R^b is hydrogen and R^3 is hydrogen or fluoro; and when R^b is other than hydrogen, then R^a is hydrogen and R^1 is hydrogen or fluoro, with the further proviso that when at least one of R^1, R^2 and R^3 is nitro, amino, alkoxy, alkylsulfonyl or alkyl, then n is 1 or one of R^a and R^b is other than hydrogen.

13. A method of treating a neurodegenerative disease selected from Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Down's syndrome, comprising administering to an animal in need of such treatment an effective amount of a compound of the formula:

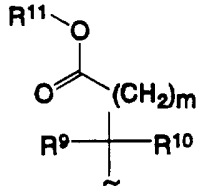


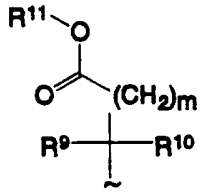
or a pharmaceutically acceptable salt thereof;

wherein n is 0 or 1; and

R^1, R^2, and R^3 are independently hydrogen, nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^a and R^b are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:





wherein R^9 is hydrogen, lower alkyl or 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

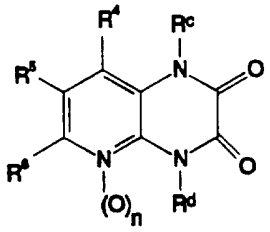
with the proviso that when R^c is other than hydrogen, then R^d is hydrogen and n is 0; and

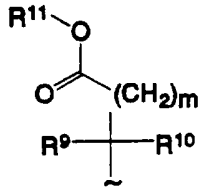
when R^d is other than hydrogen, then R^c is hydrogen and R^4 is hydrogen or fluoro;

with the further proviso that when n is 0, then R^4, R^5 and R^6 are not hydrogen; or when n is 0, then R^4 and R^6 are not hydrogen, nitro, amino, alkoxy, alkylsulfonyl or alkyl; or when n is 0, then one of R^c and R^d are not hydrogen; or when n is 1, then R^4 is hydrogen or fluoro and R^c is hydrogen.

15. The method of claim 14, wherein n is 1, R^5 and R^6 are not hydrogen, and R^c, R^d, and R^4 are hydrogen.

16. A method of treating a neurodegenerative disease selected from Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Down's syndrome, comprising administering to an animal in need of such treatment an effective amount of a compound of the formula:

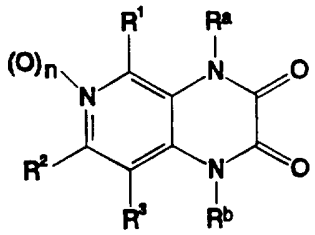




wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that when R^a is other than hydrogen, then R^b is hydrogen and R^3 is hydrogen or fluoro; and when R^b is other than hydrogen, then R^a is hydrogen and R^1 is hydrogen or fluoro, with the further proviso that when at least one of R^1, R^2 and R^3 is nitro, amino, alkoxy, alkylsulfonyl or alkyl, then n is 1 or one of R^a and R^b is other than hydrogen.

20. A method of antagonizing excitatory amino acids at the NMDA receptor complex, comprising administering to an animal in need of such treatment an effective amount of a compound of the formula:



or a pharmaceutically acceptable salt thereof;

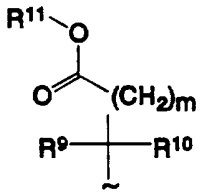
wherein n is 0 or 1; and

R^1, R^2, and R^3 are independently hydrogen, nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^a and R^b are independently hydrogen, hydroxy, amino,

alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^c and R^d are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:



wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

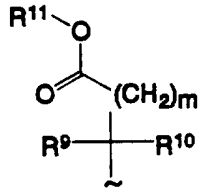
with the proviso that when R^c is other than hydrogen, then R^d is hydrogen and n is 0; and

when R^d is other than hydrogen, then R^c is hydrogen and R^4 is hydrogen or fluoro;

with the further proviso that when n is 0, then R^4, R^5 and R^6 are not hydrogen; or when n is 0, then R^4 and R^6 are not hydrogen, nitro, amino, alkoxy, alkylsulfonyl or alkyl; or when n is 0, then one of R^c and R^d are not hydrogen; or when n is 1, then R^4 is hydrogen or fluoro and R^c is hydrogen.

22. The method of claim 21, wherein n is 1, R^5 and R^6 are not hydrogen, and R^c, R^d, and R^4 are hydrogen.

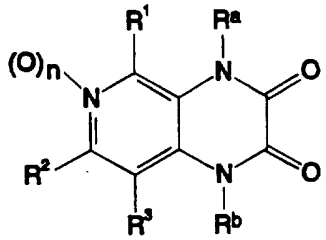
23. A method of antagonizing excitatory amino acids at the NMDA receptor complex, comprising administering to an animal in need of such treatment an effective amount of a compound of the formula:



wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that when R^a is other than hydrogen, then R^b is hydrogen and R^3 is hydrogen or fluoro; and when R^b is other than hydrogen, then R^a is hydrogen and R^1 is hydrogen or fluoro, with the further proviso that when at least one of R^1, R^2 and R^3 is nitro, amino, alkoxy, alkylsulfonyl or alkyl, then n is 1 or one of R^a and R^b is other than hydrogen.

27. A method of treating chronic pain, comprising administering to an animal in need of such treatment an effective amount of a compound of the formula:



or a pharmaceutically acceptable salt thereof;

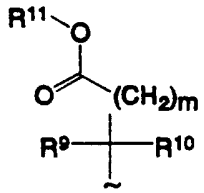
wherein n is 0 or 1; and

R^1, R^2, and R^3 are independently hydrogen, nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^a and R^b are independently hydrogen, hydroxy, amino,

alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy or haloalkoxy;

R^c and R^d are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:



wherein R^9 is hydrogen, lower alkyl or 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

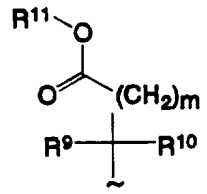
with the proviso that when R^c is other than hydrogen, then R^d is hydrogen and n is 0; and

when R^d is other than hydrogen, then R^c is hydrogen and R^4 is hydrogen or fluoro;

with the further proviso that when n is 0, then R^4, R^5, and R^6 are not hydrogen; or when n is 0, then R^4 and R^6 are not hydrogen, nitro, amino, alkoxy, alkylsulfonyl or alkyl; or when n is 0, then one of R^c and R^d are not hydrogen; or when n is 1, then R^4 is hydrogen or fluoro and R^c is hydrogen.

29. The method of claim 28, wherein n is 1, R^5 and R^6 are not hydrogen, and R^c, R^d, and R^4 are hydrogen.

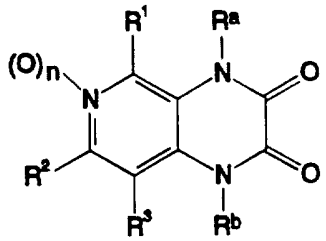
30. A method of treating chronic pain, comprising administering to an animal in need of such treatment an effective amount of a compound of the formula:



wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that when R^a is other than hydrogen, then R^b is hydrogen and R^3 is hydrogen or fluoro; and when R^b is other than hydrogen, then R^a is hydrogen and R^1 is hydrogen or fluoro, with the further proviso that when at least one of R^1, R^2 and R^3 is nitro, amino, alkoxy, alkylsulfonyl or alkyl, then n is 1 or one of R^a and R^b is other than hydrogen.

34. A method of treating or preventing anxiety, comprising administering to an animal in need of such treatment or prevention an effective amount of a compound of the formula:



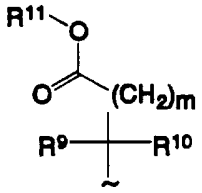
or a pharmaceutically acceptable salt thereof;

wherein n is 0 or 1; and

R^1, R^2, and R^3 are independently hydrogen, nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^c and R^d are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:



wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

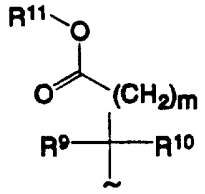
with the proviso that when R^c is other than hydrogen, then R^d is hydrogen and n is 0; and

when R^d is other than hydrogen, then R^c is hydrogen and R^4 is hydrogen or fluoro;

with the further proviso that when n is 0, then R^4, R^5 and R^6 are not hydrogen; or when n is 0, then R^4 and R^6 are not hydrogen, nitro, amino, alkoxy, alkylsulfonyl or alkyl; or when n is 0, then one of R^c and R^d are not hydrogen; or when n is 1, then R^4 is hydrogen or fluoro and R^c is hydrogen.

36. The method of claim 35, wherein n is 1, R^5 and R^6 are not hydrogen, and R^c, R^d, and R^4 are hydrogen.

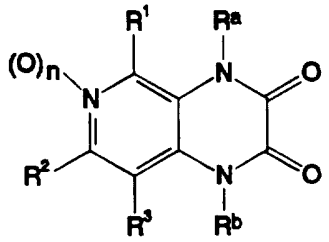
37. A method of treating or preventing anxiety, comprising administering to an animal in need of such treatment or prevention an effective amount of a compound of the formula:



wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that when R^a is other than hydrogen, then R^b is hydrogen and R^3 is hydrogen or fluoro; and when R^b is other than hydrogen, then R^a is hydrogen and R^1 is hydrogen or fluoro, with the further proviso that when at least one of R^1, R^2 and R^3 is nitro, amino, alkoxy, alkylsulfonyl or alkyl, then n is 1 or one of R^a and R^b is other than hydrogen.

41. A method of treating or preventing convulsions, comprising administering to an animal in need of such treatment or prevention an effective amount of a compound of the formula:



or a pharmaceutically acceptable salt thereof;

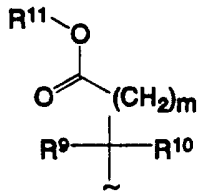
wherein n is 0 or 1; and

R^1, R^2, and R^3 are independently hydrogen, nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^a and R^b are independently hydrogen, hydroxy, amino,

alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy or haloalkoxy;

R^c and R^d are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:



wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that when R^c is other than hydrogen, then R^d is hydrogen and n is 0; and

when R^d is other than hydrogen, then R^c is hydrogen and R^4 is hydrogen or fluoro;

with the further proviso that when n is 0, then R^4, R^5 and R^6 are not hydrogen; or when n is 0, then R^4 and R^6 are not hydrogen, nitro, amino, alkoxy, alkylsulfonyl or alkyl; or when n is 0, then one of R^c and R^d are not hydrogen; or when n is 1, then R^4 is hydrogen or fluoro and R^c is hydrogen.

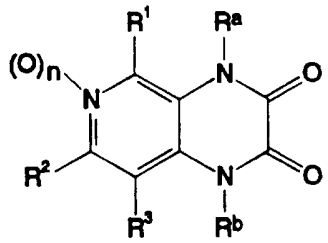
43. The method of claim 42, wherein n is 1, R^5 and R^6 are not hydrogen, and R^c, R^d, and R^4 are hydrogen.

44. A method of treating or preventing convulsions, comprising administering to an animal in need of such treatment or prevention an effective amount of a compound of the formula:

wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that when R^e is other than hydrogen, then R^f is hydrogen and n is 0; when R^f is other than hydrogen, then R^e is hydrogen and R^7 is hydrogen or fluoro.

47. A method of inducing anesthesia, comprising administering to an animal in need of such anesthesia an effective amount of a compound of the formula:



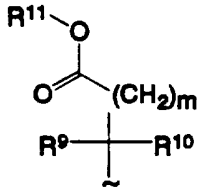
or a pharmaceutically acceptable salt thereof;

wherein n is 0 or 1; and

R^1 and R^2 are independently nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy; and R^3 is hydrogen or fluoro; or

R^1 is hydrogen or fluoro; and R^2 and R^3 are independently nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^a and R^b are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:



wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that when R^a is other than hydrogen, then R^b is hydrogen and R^3 is hydrogen or fluoro; and when R^b is other than hydrogen, then R^a is hydrogen and R^1 is hydrogen or fluoro, with the further proviso that when at least one of R^1, R^2 and R^3 is nitro, amino, alkoxy, alkylsulfonyl or alkyl, then n is 1 or one of R^a and R^b is other than hydrogen.

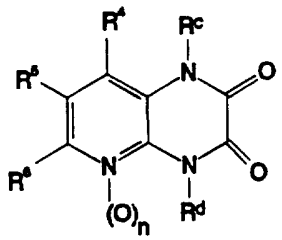
with the proviso that when R^c is other than hydrogen, then R^d is hydrogen and n is 0; and

when R^d is other than hydrogen, then R^c is hydrogen and R^4 is hydrogen or fluoro;

with the further proviso that when n is 0, then R^4, R^5, and R^6 are not hydrogen; or when n is 0, then R^4 and R^6 are not hydrogen, nitro, amino, alkoxy, alkylsulfonyl or alkyl; or when n is 0, then one of R^c and R^d are not hydrogen; or when n is 1, then R^4 is hydrogen or fluoro and R^c is hydrogen.

50. The method of claim 49, wherein n is 1, R^5 and R^6 are not hydrogen, and R^c, R^d, and R^4 are hydrogen.

51. A method of inducing anesthesia, comprising administering to an animal in need of such anesthesia an effective amount of a compound of the formula:



or a pharmaceutically acceptable salt thereof;

wherein n is 0 or 1;

R^4, R^5, and R^6 are independently nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^c and R^d are independently hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:

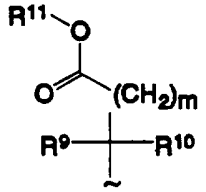
or a pharmaceutically acceptable salt thereof;

wherein n is 0 or 1; and

R^1 and R^2 are independently nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy; and R^3 is hydrogen or fluoro; or

R^1 is hydrogen or fluoro; and R^2 and R^3 are independently nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^a and R^b are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:



wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that when R^a is other than hydrogen, then R^b is hydrogen and R^3 is hydrogen or fluoro; and when R^b is other than hydrogen, then R^a is hydrogen and R^1 is hydrogen or fluoro, with the further proviso that when at least one of R^1, R^2 and R^3 is nitro, amino, alkoxy, alkylsulfonyl or alkyl, then n is 1 or one of R^a and R^b is other than hydrogen.

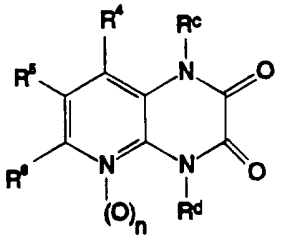
55. A method of treating or preventing NMDA receptor-ion channel related psychosis, comprising administering to an animal in need of such treatment or prevention an effective amount of a compound of the formula:

when R^d is other than hydrogen, then R^c is hydrogen and R^4 is hydrogen or fluoro;

with the further proviso that when n is 0, then R^4, R^5, and R^6 are not hydrogen; or when n is 0, then R^4 and R^6 are not hydrogen, nitro, amino, alkoxy, alkylsulfonyl or alkyl; or when n is 0, then one of R^c and R^d are not hydrogen; or when n is 1, then R^4 is hydrogen or fluoro and R^c is hydrogen.

57. The method of claim 56, wherein n is 1, R^5 and R^6 are not hydrogen, and R^c, R^d, and R^4 are hydrogen.

58. A method of treating or preventing NMDA receptor-ion channel related psychosis, comprising administering to an animal in need of such treatment or prevention an effective amount of a compound of the formula:



or a pharmaceutically acceptable salt thereof;

wherein n is 0 or 1;

R^4, R^5, and R^6 are independently nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^c and R^d are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:

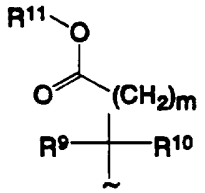
or a pharmaceutically acceptable salt thereof;

wherein n is 0 or 1; and

R^1 and R^2 are independently nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy; and R^3 is hydrogen or fluoro; or

R^1 is hydrogen or fluoro; and R^2 and R^3 are independently nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^a and R^b are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:



wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that when R^a is other than hydrogen, then R^b is hydrogen and R^3 is hydrogen or fluoro; and when R^b is other than hydrogen, then R^a is hydrogen and R^1 is hydrogen or fluoro, with the further proviso that when at least one of R^1, R^2 and R^3 is nitro, amino, alkoxy, alkylsulfonyl or alkyl, then n is 1 or one of R^a and R^b is other than hydrogen.

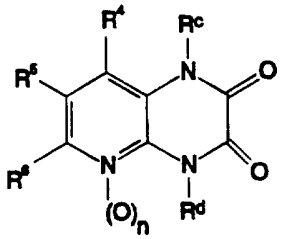
62. A method of treating or preventing opiate tolerance, comprising administering to an animal in need of such prevention an effective amount of a compound of the Formula

when R^d is other than hydrogen, then R^c is hydrogen and R^4 is hydrogen or fluoro;

with the further proviso that when n is 0, then R^4, R^5, and R^6 are not hydrogen; or when n is 0, then R^4 and R^6 are not hydrogen, nitro, amino, alkoxy, alkylsulfonyl or alkyl; or when n is 0, then one of R^c and R^d are not hydrogen; or when n is 1, then R^4 is hydrogen or fluoro and R^c is hydrogen.

64. The method of claim 63, wherein n is 1, R^5 and R^6 are not hydrogen, and R^c, R^d, and R^4 are hydrogen.

65. A method of treating or preventing opiate tolerance, comprising administering to an animal in need of such prevention an effective amount of a compound of the Formula



or a pharmaceutically acceptable salt thereof;

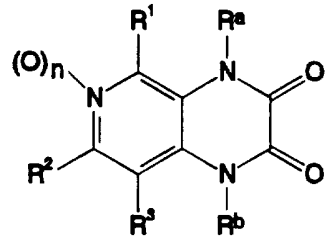
wherein n is 0 or 1;

R^4, R^5, and R^6 are independently nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^c and R^d are independently hydroxy, amino, $-CH_2CONHAr$, -NHCONHAr, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:

with the proviso that when R^a is other than hydrogen, then R^b is hydrogen and R^3 is hydrogen or fluoro; and when R^b is other than hydrogen, then R^a is hydrogen and R^1 is hydrogen or fluoro, with the further proviso that when at least one of R^1, R^2 and R^3 is nitro, amino, alkoxy, alkylsulfonyl or alkyl, then n is 1 or one of R^a and R^b is other than hydrogen.

70. A compound having the formula:

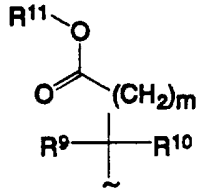


or a pharmaceutically acceptable salt thereof;

wherein n is 0 or 1; and

R^1, R^2, and R^3 are independently hydrogen, nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^a and R^b are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:



wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

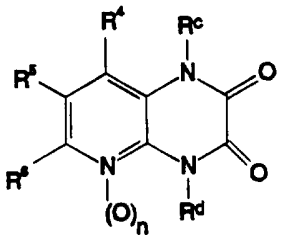
with the proviso that when R^c is other than hydrogen, then R^d is hydrogen and n is 0; and

when R^d is other than hydrogen, then R^c is hydrogen,

with the further proviso that when one of R^5 and R^6 is nitro, amino, alkoxy, alkylsulfonyl, or alkyl, then n is 1 or one of R^a and R^b is other than hydrogen.

72. The compound of claim 71, wherein n is 1, R^5 and R^6 are not hydrogen, and R^c, R^d, and R^4 are hydrogen.

73. A compound having the formula:

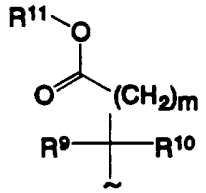


or a pharmaceutically acceptable salt thereof;

wherein n is 0 or 1;

R^4, R^5, and R^6 are independently hydrogen, nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^c and R^d are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:



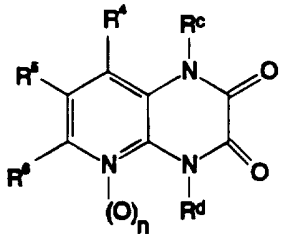
wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that when R^c is other than hydrogen, then R^d is hydrogen and n is 0; and

when R^d is other than hydrogen, then R^c is hydrogen and R^4 is hydrogen or fluoro;

with the further proviso that when n is 0, then R^4, R^5, and R^6 are not hydrogen; or when n is 0, then R^4 and R^6 are not hydrogen, nitro, amino, alkoxy, alkylsulfonyl or alkyl; or when n is 0, then one of R^c and R^d are not hydrogen; or when n is 1, then R^4 is hydrogen or fluoro and R^c is hydrogen.

74. A compound having the formula:



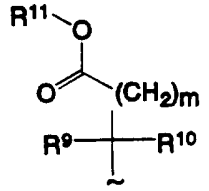
or a pharmaceutically acceptable salt thereof;

wherein n is 0 or 1;

R^4, R^5, and R^6 are independently hydrogen, nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted

R^7 and R^8 are independently hydrogen, nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^e and R^f are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:

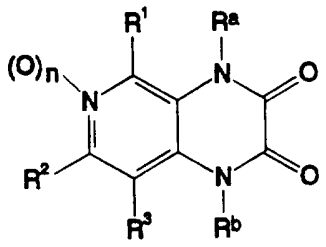


wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that when R^e is other than hydrogen, then R^f is hydrogen and n is 0; when R^f is other than hydrogen, then R^e is hydrogen and R^7 is hydrogen or fluoro or when n is 0 and R^e and R^f are hydrogen, then at least one of R^7 and R^8 is other than hydrogen, hydroxy, alkoxy, alkyl, amino, aryl or halo.

76. A pharmaceutical composition, comprising the compound of any one of claims 69-75 and a pharmaceutically acceptable carrier.

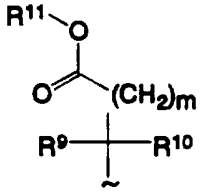
77. An isotopically labelled compound having the formula



wherein n is 0 or 1; and

R^1, R^2, and R^3 are independently hydrogen, nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

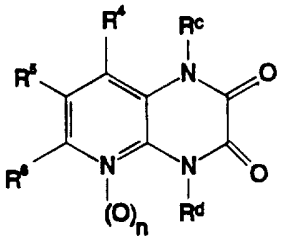
R^a and R^b are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:



wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl or 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that when R^a is other than hydrogen, then R^b is hydrogen and R^3 is hydrogen or fluoro; and when R^b is other than hydrogen, then R^a is hydrogen and R^1 is hydrogen or fluoro, with the further proviso that when at least one of R^1, R^2 and R^3 is nitro, amino, alkoxy, alkylsulfonyl or alkyl, then n is 1 or one of R^a and R^b is other than hydrogen.

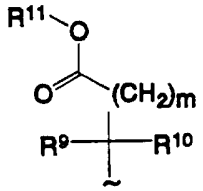
78. An isotopically labelled compound having the formula:



wherein n is 0 or 1;

R^4, R^5, and R^6 are independently hydrogen, nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^c and R^d are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:



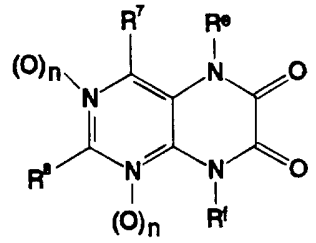
wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that at least one of R^4, R^5 and R^6 is halo or haloalkyl, that when R^c is other than hydrogen, then R^d is hydrogen and n is 0; and

when R^d is other than hydrogen, then R^c is hydrogen and R^4 is hydrogen or fluoro.

79. The compound of claim 78, wherein n is 1, R^5 and R^6 are not hydrogen, and R^c, R^d, and R^4 are hydrogen.

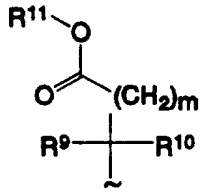
80. An isotopically labelled compound having the formula:



wherein n is 0 or 1;

R^7 and R^8 are independently hydrogen, nitro, amino, halo, haloalkyl, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, azido, acylamino, alkylsulfonyl, aryl, substituted aryl, heteroaryl, alkoxy, trialkylsilyl-substituted alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, a heterocyclic group, a heterocyclicoxy group, aralkoxy, or haloalkoxy;

R^e and R^f are independently hydrogen, hydroxy, amino, $-CH_2CONHAr$, $-NHCONHAr$, $-NHCOCH_2Ar$, or $-COCH_2Ar$, wherein Ar is an aryl group, or a radical having the Formula:



wherein R^9 is hydrogen, lower alkyl of 1-6 carbon atoms, or aryl; R^{10} is hydrogen or lower alkyl of 1-6 carbon atoms; m is an integer from 0 to 5; and R^{11} is hydrogen, C_{1-6} alkyl, or aralkyl;

with the proviso that when R^e is other than hydrogen, then R^f is hydrogen and n is 0; when R^f is other than hydrogen, then R^e is hydrogen and R^7 is hydrogen or fluoro.

81. The labelled compound of any one of claims 77-80, wherein said label is ^2H, ^3H, ^{11}C, ^{14}C, ^{15}N, or ^{18}F.