

605
606

CAVELIER

ABOGADOS

WEB SITE: www.caveller.com
E-MAIL: caveller@caveller.com

EDIFICIO SISKI
CARRERA 4 No. 72 -
BOGOTÁ 8, COLOMBIA

SUPERINDUSTRIA Y COMERCIO
Radicación : 01109589 00000002
Fecha (MIB): 2002-02-07 16:47:52

Folios: 224 -3611
-4995

Trámite : 002 PATENTES y 1 REGISTRO/ 329 COMPLETEN
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S. D.

Referencia : Expediente No. 01.109.589
Solicitantes : NEUROGEN CORPORATION Y PFIZER, INC.
Asunto : Solicitud de patente para: "DERIVADOS
BENZIMIDAZOL Y PIRIDILIMIDAZOL COMO
LIGANDOS PARA GABA_A"
Fecha de solicitud : 21 de diciembre de 2001.

TRAMITE: 002 - EVENTO: 001 - ACTUACIÓN: 329

1. Yo, Emilio FERRERO, obrando como apoderado de las solicitantes en referencia, atentamente presento con este escrito la copia certificada de la solicitud de patente estadounidense No. 60/257,492 del 21 de diciembre de 2000, junto con su respectiva traducción de sus reivindicaciones y certificaciones, de la cual se reclama prioridad en esta solicitud de patente.

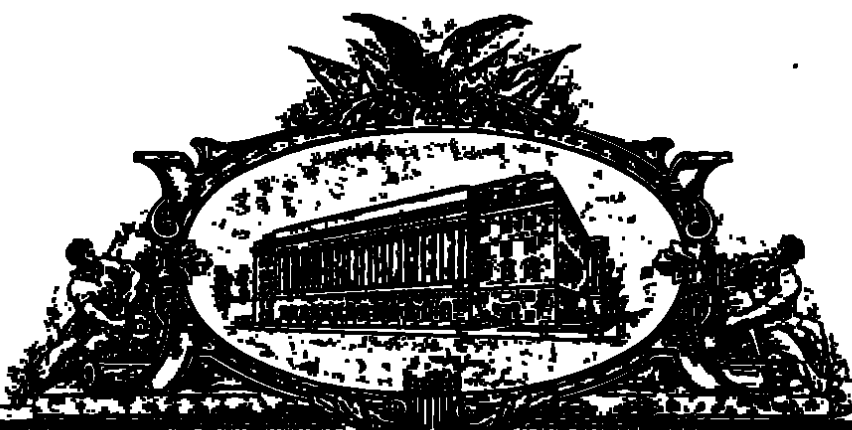
2. Ruego a la Señora Jefe se sirva aceptar este escrito con sus anexos, y se continúe con el trámite de la solicitud.

Bogotá, - 7 FEB. 2002
Señora Jefe,


EMILIO FERRERO
T.P.A. No. 31.929

COLO 12889-801-002-9
MRE-15

for
607



DA 508345

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

January 09, 2002

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/257,492

FILING DATE: December 21, 2000

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS



E. BORNETT

Certifying Officer

12-26-00

607
A/PROV 608

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. N2000.016

In re the application of: Guiying Li, et al.

For:

Assistant Commissioner For Patents
Box Provisional patent Application
Washington, DC 20231

10714 U.S. PRO
60/257492
12/21/00

COVER SHEET FOR FILING PROVISIONAL PATENT APPLICATION

Dear Sir:

The accompanying application, entitled Benzimidazole Derivatives as Ligands for GABA_A Receptors, is a provisional patent application under 37 C.F.R. § 1.51 (a)(2) and § 1.53 (b)(2).

1. ☒ The names and addresses of the inventors of this application are as follows:

	Last Name	First Name	Middle	Residence
1.	Li	Guiying		#8 Valley Court Branford, CT 06504
2.	Peterson	John	M.	28 Highland Terrace Madison, CT 06443
3.	Albaugh	Pamela		81 Long Hill Road Clinton, CT 06413
4.	Currie	Kevin	S.	33 Clear Lake Manor Road North Branford, Ct 06471
5.	Cai	Guolin		38 Grey Ledge Court Guilford, CT 06437
6.	Gustavson	Linda	M.	3 Chestnut Court Guilford, CT 06437
7.	Lee	Kyungae		6 Finch Lane Guilford, CT 06437
8.	Hutchison	Alan		29 Kimberly Lane Madison, CT 06443
9.	Singh	Vinod		4056, IIT Campus Kanpu - 208016 India

US Express Mailing No. E1074500352US

60257492-122100

10714 U.S. PRO
60/257492
12/21/00

602
609

Attorney Docket No. N200000006

2. ☐ This invention was made by an agency of the United States Government or under contract with an agency of the United States Government. The name of the U.S. Government agency and the Government contract number are:

Agency: _____
Contract No.: _____

3. ☒ The following documents are enclosed:

☒ 243 pages of Specification and Claims

☒ 1 page of abstract

4. ☐ A verified statement to establish small entity status under 37 CFR 1.9 and 1.27 is enclosed.

5. ☐ An Assignment of the invention to _____ is enclosed. A check in the amount of \$40.00 for recording this assignment and a recordation form cover sheet (Form PTO 1595) are also enclosed.

6. ☒ The fee for filing this provisional application, as set forth in 37 CFR 1.16(k), is \$150.00.

a. ☐ A check for this filing is enclosed.

b. ☒ Charge the filing fee to Deposit Account No. 501116.

c. ☐ The filing fee is not being paid at this time.

7. ☒ Please charge any fee deficiencies associated with this filing to Deposit Account No. 501116. A duplicate copy of this sheet is enclosed.

Please address all future communications to:

Patent Department
Neurogen Corporation
35 Northeast Industrial Road
Branford, CT 06405

and direct telephone calls to: Leslie-Anne Horvath or Seth A. Fidel

Respectfully submitted,

Leslie Anne Horvath

Leslie-Anne Horvath
Registration No. 44,778

12/16/00

Date

Neurogen Corporation
35 Northeast Industrial Road
Branford, CT 06405
203-488-8201

001221-26475206

US Express Mailing No. EL074500362US

609
610

**APPLICATION FOR UNITED STATES LETTERS PATENT
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**TITLE: BENZIMIDAZOLE DERIVATIVES AS LIGANDS FOR GABA_A
RECEPTORS**

Inventors:

Guiying Li
#8 Valley Court
Branford, CT 06405

John M. Peterson
28 Highland Terrace
Madison, CT 06443

Pamela Albaugh
81 Long Hill Road
Clinton, CT 06413

Kevin S. Currie
33 Clear Lake Manor
Road
North Branford, CT
06471

Guolin Cai
38 Grey Ledge Drive
Guilford, CT 06437

Linda M. Gustavson
3 Chestnut Court
Guilford, CT 06437

Kyungae Lee
6 Finch Lane
Guilford, CT 06437

Alan Hutchison
29 Kimberly Lane
Madison, CT 06443

Vinod Singh
4056, IIT Campus
Kanpur - 208016
India

Assignee: Neurogen Corporation
Branford, Connecticut
A Corporation of the State of Delaware

60257492-122100

618
611

BENZIMIDAZOLE DERIVATIVES AS LIGANDS FOR GABA_A RECEPTORS

Field of the Invention

This invention relates to novel benzimidazole and heteroarylimidazole derivatives that bind with high selectivity and high affinity to the benzodiazepine site of GABA_A receptors. This invention also relates to pharmaceutical compositions comprising such compounds and to the use of such compounds in treatment of certain central nervous system (CNS) diseases. This invention also relates to the use of these benzimidazole and heteroarylimidazole derivatives in combination with one or more other CNS agents to potentiate the effects of the other CNS agents. Additionally this invention relates to the use such compounds as probes for the localization of GABA_A receptors in tissue sections.

Background

The GABA_A receptor superfamily represents one of the classes of receptors through which the major inhibitory neurotransmitter, γ -aminobutyric acid, or GABA, acts. Widely, although unequally, distributed through the mammalian brain, GABA mediates many of its actions through a complex of proteins called the GABA_A receptor, which causes alteration in chloride conductance and membrane polarization.

A number of cDNAs for GABA_A receptor subunits have been characterized. To date at least 6 α , 3 β , 3 γ , 1 ϵ , 1 δ and 2 ρ subunits have been identified. It is generally accepted that native GABA_A receptors are typically composed of 2 α , 2 β , and 1 γ subunits. Evidence such as message distribution, genome localization and biochemical study results suggest that the major naturally occurring receptor combinations are $\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_3\gamma_2$, $\alpha_3\beta_3\gamma_2$, and $\alpha_5\beta_3\gamma_2$.

Benzodiazepines exert their pharmacological actions by interacting with the benzodiazepine binding sites associated with the GABA_A receptor. In addition to the benzodiazepine site, the GABA_A receptor contains sites of interaction for several other classes of drugs. These include a steroid binding site, a picrotoxin site, and the barbiturate site. The benzodiazepine site of the GABA_A receptor is a distinct site on the receptor complex that does not overlap with the site of interaction for GABA or for other classes of drugs that bind to the receptor. Early electrophysiological studies indicated that a major action of the benzodiazepines was enhancement of GABAergic inhibition. Compounds that selectively bind to the benzodiazepine site and enhance the ability of GABA to open GABA_A receptor channels are agonists of GABA receptors. Other compounds that interact with the same site but negatively modulate the action of GABA are called inverse agonists. Compounds belonging to a third class bind selectively to the benzodiazepine site and yet have little or no effect on GABA activity, but can block the action of GABA_A receptor agonists or inverse agonists that act at this site. These compounds are referred to as antagonists.

The important allosteric modulatory effects of drugs acting at the benzodiazepine site were recognized early and the distribution of activities at different receptor subtypes has been an area of intense pharmacological discovery. Agonists that act at the benzodiazepine site are known to exhibit anxiolytic, sedative, and hypnotic effects, while compounds that act as inverse agonists at this site elicit anxiogenic, cognition enhancing, and proconvulsant effects. While benzodiazepines have a long history of pharmaceutical use as anxiolytics, these compounds often exhibit a number of unwanted side effects. These may include cognitive impairment, sedation, ataxia, potentiation of ethanol effects, and a tendency for tolerance and drug dependence.

GABA_A selective ligands may also act to potentiate the effects of certain other CNS active compounds. For example, there is evidence that selective serotonin reuptake inhibitors (SSRIs) may show greater antidepressant activity when used in combination with GABA_A selective ligands than when used alone.

Summary of the Invention

This invention relates to certain novel benzimidazole and heteroarylimidazole derivatives, that preferably bind with both high affinity and high selectivity to the benzodiazepine site of the GABA_A receptor, including human GABA_A receptors.

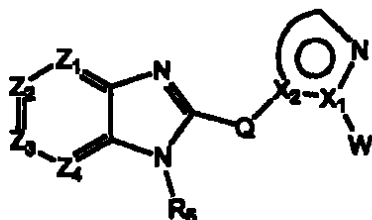
The invention provides novel compounds of Formula I (shown below), and pharmaceutical compositions comprising compounds of Formula I.

The invention further comprises methods of treating patients suffering from certain CNS disorders with an effective amount of a compound of the invention. The patient may be a human or other mammal. Treatment of humans, domesticated companion animals (pet) or livestock animals suffering from certain CNS disorders with an effective amount of a compound of the invention is encompassed by the invention.

In a separate aspect, the invention provides a method of potentiating the actions of other CNS active compounds. This method comprises administering an effective amount of a compound of the invention with another CNS active compound.

Additionally this invention relates to the use of the compounds of the invention as probes for the localization of GABA_A receptors in tissue sections.

Accordingly, a broad aspect of the invention is directed to compounds of Formula I:



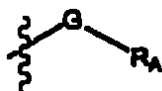
Formula I

or the pharmaceutically acceptable salts, prodrugs or solvates thereof, wherein:

Z₁, Z₂, Z₃, and Z₄ independently represent nitrogen or CR₁, CR₂, CR₃, and CR₄, respectively, provided that no more than two of Z₁, Z₂, Z₃, and Z₄ are nitrogen;

R₁, R₂, R₃, and R₄ are independently selected from

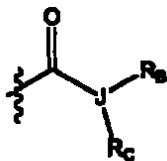
- i) hydrogen, halogen, hydroxy, nitro, cyano, amino, haloalkyl, oxo, trifluoromethoxy, trifluoromethyl, trifluorosulfonyl, and carboxylic acid,
- ii) mono or dialkylamino, aminoalkyl, mono- or dialkylaminoalkyl, alkoxy, alkyl, cycloalkyl, alkenyl, alkynyl, (cycloalkyl)alkyl, alkanoyl, alkoxycarbonyl, alkylsulfonyl, alkylthio, mono- or dialkylaminocarbonyl, heterocycloalkyl, aryl, and heteroaryl, each of which may be optionally substituted,
- iii) a group of the formula:



where G is alkyl, -O-, -C(=O)-, or -CC(=O)-, and

R_A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which may be optionally substituted,

- iv) a group of the formula



where J is N or CH and R_b and R_c are independently hydrogen, C_1 - C_8 alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which may be optionally substituted; or

R_b and R_c and the atom to which they are attached form a 4- to 10-membered monocyclic or bicyclic ring, which may contain one or more double bonds or one or more of oxo, O, S, SO, SO_2 , or N- R_d wherein R_d is hydrogen, Ar_1 , C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_3 - C_8 heterocycloalkyl, or C_1 - C_6 alkyl- Ar_1 ; wherein Ar_1 is aryl or heteroaryl, each of which may be optionally substituted; and wherein the monocyclic or bicyclic ring is optionally substituted;

v) $-OC(=O)R_E$, $-C(=O)NH_2$, $-C(=O)NHR_E$, $-C(=O)NR_ER_F$, $-S(O)_nR_E$, $-S(O)_nNH_2$, $-S(O)_nNHR_E$, $-S(O)_nNR_ER_F$, $-NHC(=O)R_E$, $-C(=NR_E)R_F$, $-C=N-OH$, $-C=N(alkoxy)$, $-C=N(alkyl)$, $-NR_EC(=O)R_F$, $-NHS(O)_nR_E$, and $-NR_ES(O)_nR_F$, where n is 0, 1 or 2, and R_E and R_F are independently selected at each occurrence from alkyl, cycloalkyl, heterocycloalkyl, alkoxy, mono- or diaminoalkyl, aryl, or heteroaryl, each of which may be optionally substituted;

R_5 represents optionally substituted alkyl, cycloalkyl, or (cycloalkyl)alkyl, each of which may contain one or more double or triple bonds, or R_5 represent optionally substituted aryl, arylalkyl, heteroaryl, or heteroarylalkyl;

Q represents CR_6R_7 , NR_6 , or oxygen when X_2 is not nitrogen;

R_6 and R_7 represent hydrogen, halogen, hydroxy, or alkyl;

R_6 represents hydrogen or alkyl;

the group:



represents 5 to 7 membered heteroaromatic ring containing up to 4 heteroatoms selected from nitrogen, sulfur, and oxygen, said 5 to 7 membered heteroaromatic ring is optionally substituted at each carbon atom by R, and optionally substituted at each nitrogen atom available for substitution by R',

R is independently chosen at each occurrence from halogen, hydroxy, nitro, cyano, amino, alkyl, alkoxy, alkoxy substituted with amino or mono- or dialkylamino, cycloalkyl, (cycloalkyl)alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, carboxamide, mono or dialkylamino, aminoalkyl, and mono- or dialkylaminoalkyl,

R' is C₁-C₆ alkyl;

X₁ and X₂ independently represent nitrogen or carbon; and

W represents aryl or heteroaryl, either of which is optionally substituted with up to three groups selected independently from halogen, hydroxy, nitro, cyano, amino, alkyl, alkoxy, alkoxy substituted with amino or mono- or di-alkylamino, cycloalkyl, (cycloalkyl)alkyl, cycloalkylalkoxy, heterocycloalkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, mono or dialkylamino, aminoalkyl, and mono- or dialkylaminoalkyl, -C(O)R_E, and -S(O)_mR_E, where R_E is as defined above and m is 0, 1 or 2.

Detailed Description of the Invention

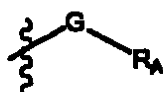
The invention further includes compounds of Formula I, wherein the variables Z₁, Z₂, Z₃, Z₄, R₃, X₁, X₂, Q, and W are defined as follows:

Z_1 , Z_2 , Z_3 , and Z_4 independently represent nitrogen or CR_1 , CR_2 , CR_3 , and CR_4 , respectively, provided that no more than two of Z_1 , Z_2 , Z_3 , and Z_4 are nitrogen;

R_1 , R_2 , R_3 , and R_4 are independently selected from

- i) hydrogen, halogen, hydroxy, nitro, cyano, amino, haloalkyl, oxo, trifluoromethoxy, trifluoromethyl, trifluorosulfonyl, and carboxylic acid,
- ii) mono or di(C_1 - C_6)alkylamino, amino(C_1 - C_6)alkyl, mono- or di(C_1 - C_6)alkylamino(C_1 - C_6)alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, (C_3 - C_8 cycloalkyl) C_1 - C_6 alkyl, C_1 - C_6 alkanoyl, C_1 - C_6 alkoxycarbonyl, C_1 - C_6 alkylsulfonyl, C_1 - C_6 alkylthio, mono- or di(C_1 - C_6)alkylaminocarbonyl, heterocycloalkyl, aryl, and heteroaryl, each of which may be optionally substituted with up to three groups R_x ,

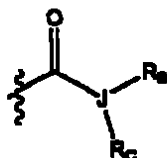
iii) a group of the formula:



where G is C_1 - C_6 alkyl, $-O-$, $-C(=O)-$, or $-CC(=O)-$, and

R_A is C_3 - C_8 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which may be optionally substituted with up to three groups R_x ,

iv) a group of the formula



where J is N or CH and R_B and R_C are independently hydrogen, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which may be optionally substituted with up to three groups R_x ; or

R_B and R_C and the atom to which they are attached form a 4- to 10-membered monocyclic or bicyclic ring, which may

contain one or more double bonds or one or more of oxo, O, S, SO, SO₂, or N-R_D wherein R_D is hydrogen, Ar₁, C₁-C₆ alkyl, C₃-C₈cycloalkyl, heterocycloalkyl, or C₁-C₆ alkyl-Ar₁; wherein Ar₁ is aryl or heteroaryl, each of which may be optionally substituted with up to three groups R_X; and wherein the monocyclic or bicyclic ring is optionally substituted with up to three groups R_X;

- v) -OC(=O)R_E, -C(=O)NH₂, -C(=O)NHR_E, -C(=O)NR_ER_F, -S(O)_nR_E, -S(O)_nNH₂, -S(O)_nNHR_E, -S(O)_nNR_ER_F, -NHC(=O)R_E, -C(=NR_E)R_F, -C=N-OH, -C=N(alkoxy), -C=N(alkyl), -NR_EC(=O)R_F, -NHS(O)_nR_E, and -NR_ES(O)_nR_F, where n is 0, 1 or 2, and R_E and R_F are independently selected at each occurrence from C₁-C₆alkyl, C₃-C₈cycloalkyl, heterocycloalkyl, C₁-C₆alkoxy, mono- or diamino(C₁-C₆)alkyl, aryl, or heteroaryl each of which may be optionally substituted with up to three groups R_X;

R₅ represents C₁-C₆ alkyl, C₃-C₈cycloalkyl, or (C₃-C₈cycloalkyl)C₁-C₆alkyl, each of which may contain one or more double or triple bonds and each of which may be optionally substituted with up to three groups R_X, or R₅ represents aryl, aryl (C₁-C₄alkyl), heteroaryl, or heteroaryl(C₁-C₄alkyl);

Q represents CR₆R₇, NR₆, or

oxygen when X₂ is not nitrogen;

R₆ and R₇ represent hydrogen, halogen, hydroxy, or C₁-C₆ alkyl;

R₆ represents hydrogen or C₁-C₆ alkyl;

the group:



represents a 5 to 7 membered heteroaromatic ring, containing up to 4 heteroatoms selected from nitrogen, sulfur, and oxygen, said 5 to 7 membered heteroaromatic ring is optionally substituted at each carbon atom with R, and optionally substituted at each nitrogen atom available for substitution with R',

R is independently chosen at each occurrence from halogen, hydroxy, nitro, cyano, amino, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy substituted with amino or mono- or di(C₁-C₆)alkylamino, C₃-C₈cycloalkyl, (C₃-C₈cycloalkyl)C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, haloalkyl, haloalkoxy, carboxamide, mono or di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, and mono- or di(C₁-C₆)alkylamino(C₁-C₆)alkyl,

R' is C₁-C₆ alkyl;

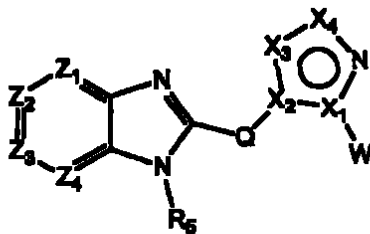
X₁ and X₂ independently represent nitrogen or carbon;

R₆ is independently selected at each occurrence from halogen, hydroxy, nitro, cyano, amino, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkoxy substituted with amino or mono- or di(C₁-C₆)alkylamino, C₃-C₈cycloalkyl, (C₃-C₈cycloalkyl)C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₁-C₆alkoxy, heterocycloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, haloalkyl, haloalkoxy, mono or di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, and mono- or di(C₁-C₆)alkylamino(C₁-C₆)alkyl; and

W represents aryl or heteroaryl, either of which is optionally substituted with up to three groups selected independently from halogen, hydroxy, nitro, cyano, amino, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkoxy substituted with amino or mono- or di(C₁-C₆)alkylamino, C₃-C₈cycloalkyl, (C₃-C₈cycloalkyl) C₁-C₆alkyl, (C₃-C₈cycloalkyl) C₁-C₆alkoxy, heterocycloalkyl, C₂-C₆alkenyl, C₂-

C₆alkynyl, haloalkyl, haloalkoxy, mono or di(C₂-C₆)alkylamino, amino(C₂-C₆)alkyl, and mono- or di(C₂-C₆)alkylamino(C₂-C₆)alkyl, -COOH, -(C=O)OR_x, -(C=O)NR_x, -C(O)R_x, and -S(O)_mR_x where R_x is as defined above and m is 0, 1 or 2. Such compounds will be referred to as compounds of Formula Ia.

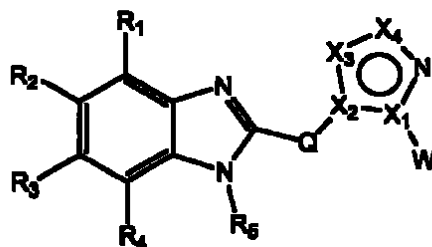
A particular embodiment of the invention includes compounds of Formula II,



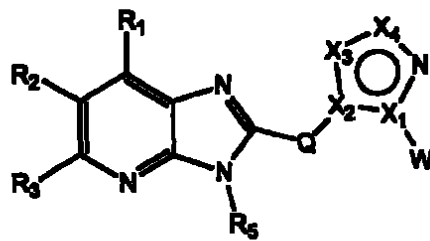
Formula II

and the pharmaceutically acceptable salts, prodrugs, or solvate thereof, wherein X₁, X₂, X₃, and X₄ independently represent CR, N, O, S, or NR' provided that at least one of X₁, X₂, X₃, and X₄ is CR; and the remaining variables, including Z₁, Z₂, Z₃, Z₄, R, R', R₂, R₃, R₄, R₅, Q, and W, are defined as for Formula Ia.

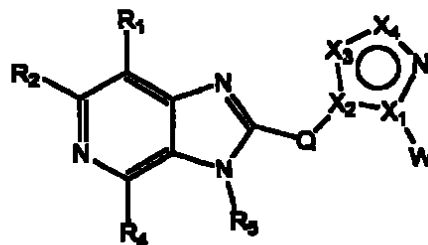
Preferred compounds of the invention include compounds of Formula III, Formula IV, Formula V, Formula VI, and Formula VII (shown below).



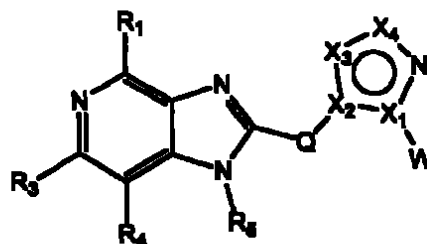
Formula III



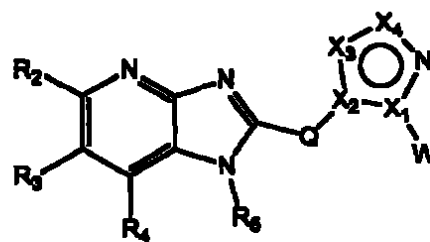
Formula IV



Formula V



Formula VI

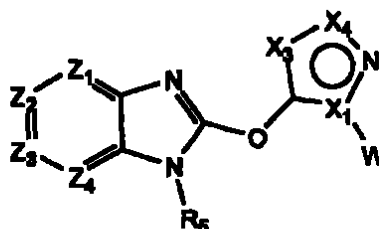


Formula VII

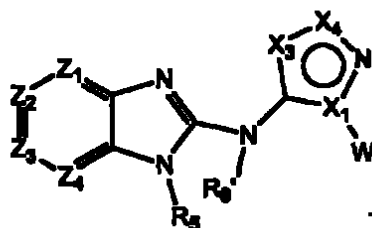
In Formulae III-VII, shown above, R_1 , R_2 , R_3 , R_4 , R_5 , Q , and W are defined as for compounds of Formula I. The variables R_1 , R_2 , R_3 , R_4 , R_5 , Q , and W may alternatively be defined as for

compounds of Formula Ia. X_1 , X_2 , X_3 , and X_4 independently represent CR, N, O, S, or NR' provided that at least one of X_1 , X_2 , X_3 , and X_4 is CR, wherein, R and R' are as defined for Formula I or may alternatively be defined as for Formula Ia.

The invention further includes compounds of Formula VIII, and Formula IX (shown below)



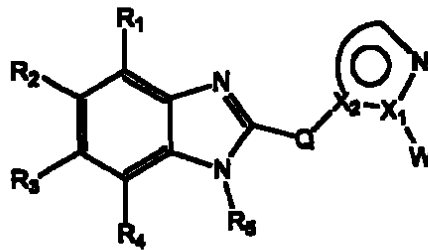
Formula VIII



Formula IX

In Formulae VIII and IX, shown above, the variables Z_1 , Z_2 , Z_3 , Z_4 , R_5 , R_6 , Q , and W are defined as for compounds of Formula I. The variables Z_1 , Z_2 , Z_3 , Z_4 , R_5 , R_6 , Q , and W may alternatively be defined as for compounds of Formula Ia. X_1 , X_3 , and X_4 independently represent CR, N, O, S, or NR' wherein, R and R' are as defined for Formula I or may alternatively be defined as for Formula Ia.

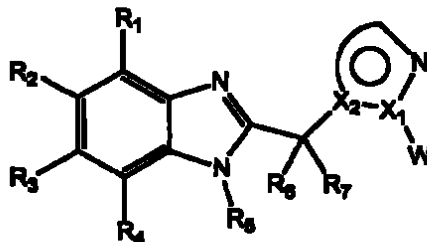
Preferably, the invention includes compounds of Formula X



Formula X

wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , X_1 , X_2 , Q , and W are as defined for Formula I. Alternatively, for compounds of Formula X, R_1 , R_2 , R_3 , R_4 , R_5 , X_1 , X_2 , Q , and W may be defined as for compounds of Formula Ia.

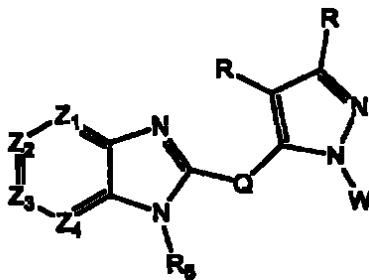
The invention further provide compounds of Formula XI, wherein



Formula XI

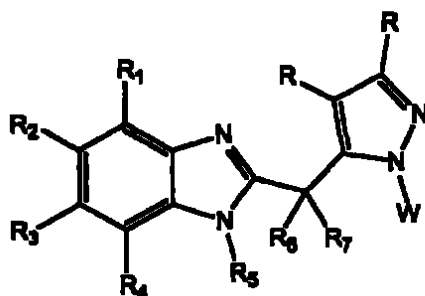
wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and W are as defined as for Formula I. Alternatively, for compounds of Formula XI, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , X_1 , X_2 , Q , and W may be defined as for Formula Ia.

Another embodiment of the invention includes compounds of Formula XII,



Formula XII

wherein R, Z₁, Z₂, Z₃, Z₄, R₅, Q, and W are as defined in for Formula I. Alternatively R, Z₁, Z₂, Z₃, Z₄, R₅, Q, and W may carry the definitions set forth for Formula Ia. Preferred compounds of Formula XII may be described by Formula XIII:



Formula XIII

wherein R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, and W are as defined as for Formula I, or may alternatively be carry the definitions of R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, and W set forth for Formula Ia. For more preferred compounds of Formula XIII:

R, R₁, and R₄ are independently selected from hydrogen, halogen, hydroxy, nitro, cyano, amino, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₈cycloalkyl, (C₃-C₈cycloalkyl) C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, haloalkyl, haloalkoxy, mono or di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, and mono- or di(C₁-C₆)alkylamino(C₁-C₆)alkyl;

R₃ represents C₁-C₆ alkyl, C₃-C₈cycloalkyl, or (C₃-C₈cycloalkyl)C₁-C₆alkyl, phenyl, benzyl, thiophenyl, pyridyl, imidazolyl, pyrazolyl, or pyrimidinyl;

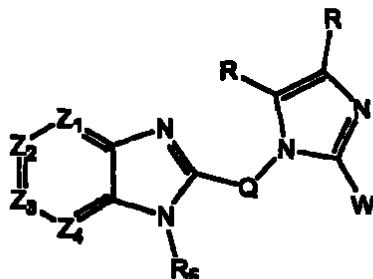
R₆ and R₇ represent C₁-C₆ alkyl; and

W represents phenyl, thiophenyl, pyridyl, imidazolyl, pyrazolyl, or pyrimidinyl, optionally substituted with up to 4 groups independently chosen from halogen, hydroxy, nitro, cyano, amino, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkoxy substituted with amino or mono- or di(C₁-C₆)alkylamino, C₃-C₈cycloalkyl, (C₃-C₈cycloalkyl)C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₁-C₆alkoxy,

heterocycloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, haloalkyl, haloalkoxy, mono or di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, and mono- or di(C₁-C₆)alkylamino(C₁-C₆)alkyl.

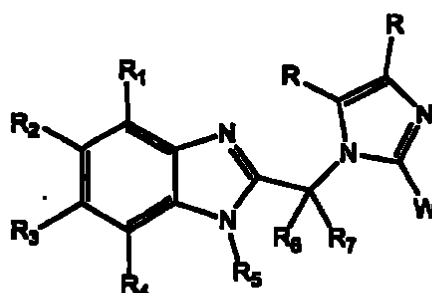
The variables R₂ and R₃ carry the definitions set forth for compounds of Formula I, or alternatively for compounds of Formula Ia.

The invention further includes compounds of Formula XIV,



Formula XIV

wherein R, Z₁, Z₂, Z₃, Z₄, R₅, Q, and W are as defined for Formula I. Alternatively R, Z₁, Z₂, Z₃, Z₄, R₅, Q, and W may carry the definitions set forth for Formula Ia. Preferred compounds of Formula XIV may be described by Formula XV:



Formula XV

wherein R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, and W are as defined as for Formula I, or may alternatively be carry the definitions of R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, and W set forth for Formula Ia. For more preferred compounds of Formula XV:

R, R₁, and R₄ are independently selected from hydrogen, halogen, hydroxy, nitro, cyano, amino, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-

C₆cycloalkyl, (C₃-C₈cycloalkyl) C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, haloalkyl, haloalkoxy, mono or di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, and mono- or di(C₁-C₆)alkylamino(C₁-C₆)alkyl;

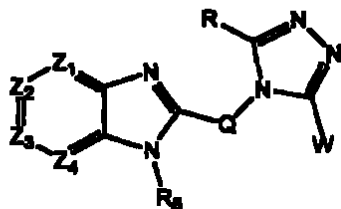
R₅ represents C₁-C₆ alkyl, C₃-C₈cycloalkyl, or (C₃-C₈cycloalkyl)C₁-C₆alkyl, phenyl, benzyl, thiophenyl, pyridyl, imidazolyl, pyrazolyl, or pyrimidinyl;

R₆ and R₇ represent C₁-C₆ alkyl; and

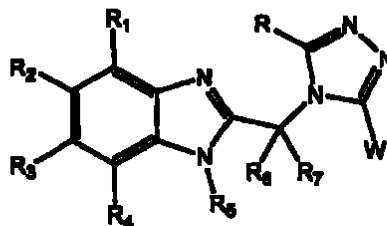
W represents phenyl, thiophenyl, pyridyl, imidazolyl, pyrazolyl, or pyrimidinyl, optionally substituted with up to 4 groups independently chosen from halogen, hydroxy, nitro, cyano, amino, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkoxy substituted with amino or mono- or di(C₁-C₆)alkylamino, C₃-C₈cycloalkyl, (C₃-C₈cycloalkyl)C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₁-C₆alkoxy, heterocycloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, haloalkyl, haloalkoxy, mono or di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, and mono- or di(C₁-C₆)alkylamino(C₁-C₆)alkyl.

The variables R₂ and R₃ carry the definitions set forth for compounds of Formula I, or alternatively for compounds of Formula Ia.

In still further embodiments the invention includes compounds of Formula XVI and preferred compounds of Formula XVII



Formula XVI

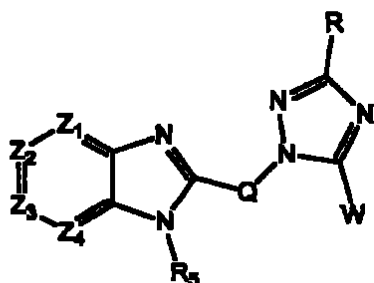


Formula XVII

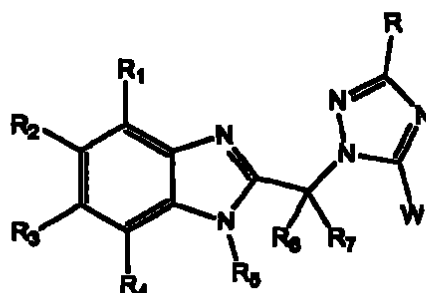
wherein R, Z₁, Z₂, Z₃, Z₄, R₁, R₂, R₃, R₄, R₅, R₆, R₇, Q, and W are as defined for Formula I. Alternatively R, Z₁, Z₂, Z₃, Z₄, R₁, R₂,

R₃, R₄, R₅, R₆, R₇, Q, and W may carry the definitions set forth for Formula Ia.

The invention also includes compounds of Formula XVIII and XIX



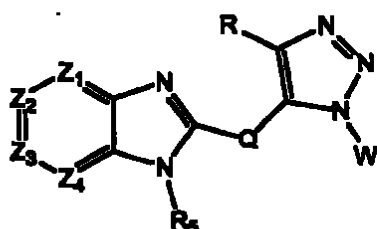
Formula XVIII



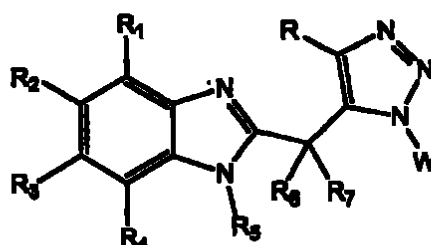
Formula XIX

wherein R, Z₁, Z₂, Z₃, Z₄, R₁, R₂, R₃, R₄, R₅, R₆, R₇, Q, and W are as defined for Formula I. Alternatively R, Z₁, Z₂, Z₃, Z₄, R₁, R₂, R₃, R₄, R₅, R₆, R₇, Q, and W may carry the definitions set forth for Formula Ia.

Another embodiment of the invention is represented by compounds of Formula XX and by preferred compounds of Formula XXI:



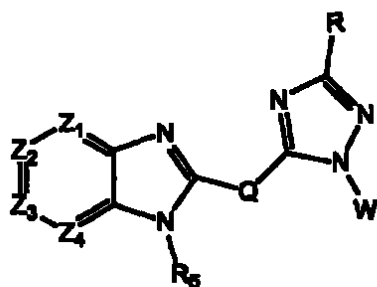
Formula XX



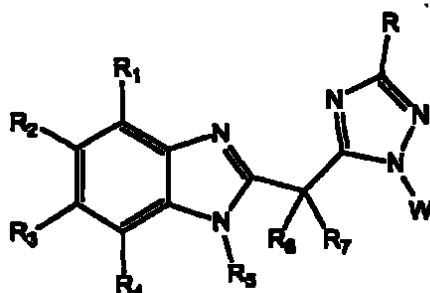
Formula XXI

wherein R, Z₁, Z₂, Z₃, Z₄, R₁, R₂, R₃, R₄, R₅, R₆, R₇, Q, and W are as defined for Formula I. Alternatively R, Z₁, Z₂, Z₃, Z₄, R₁, R₂, R₃, R₄, R₅, R₆, R₇, Q, and W may carry the definitions set forth for Formula Ia.

In still another embodiment, the invention includes compounds of Formula XXII and preferred compounds of Formula XXIII (shown below):



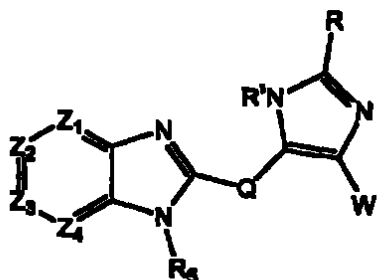
Formula XXII



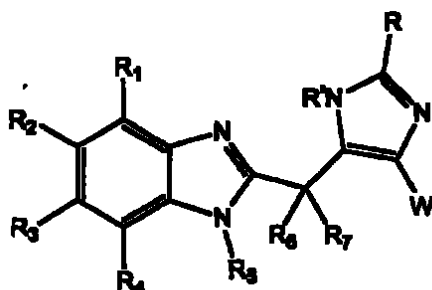
Formula XXIII

wherein R, Z₁, Z₂, Z₃, Z₄, R₁, R₂, R₃, R₄, R₅, R₆, R₇, Q, and W are as defined for Formula I. Alternatively R, Z₁, Z₂, Z₃, Z₄, R₁, R₂, R₃, R₄, R₅, R₆, R₇, Q, and W may carry the definitions set forth for Formula Ia.

The invention includes compounds of Formula XIV and preferred compounds of Formula XXV:



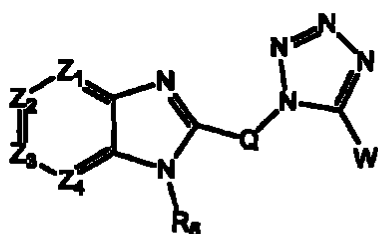
Formula XIV



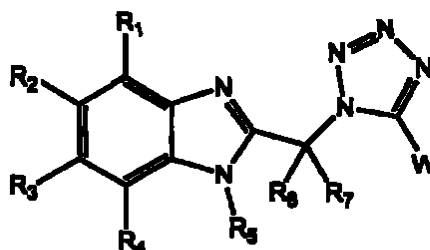
Formula XXV

wherein R, R', Z₁, Z₂, Z₃, Z₄, R₁, R₂, R₃, R₄, R₅, R₆, R₇, Q, and W are as defined for Formula I. Alternatively R, Z₁, Z₂, Z₃, Z₄, R₁, R₂, R₃, R₄, R₅, R₆, R₇, Q, and W may carry the definitions set forth for Formula Ia.

Other representative compounds of the invention include compounds of Formula XXVI and preferred compounds of Formula XXVII:



Formula XXVI



Formula XXVII

This invention relates to novel benzimidazole and heteroarylimidazole derivatives, preferred examples of which bind with high affinity to the benzodiazepine site of GABA_A receptors, including human GABA_A receptors. Preferred benzimidazole and heteroarylimidazole derivatives, that bind with high selectivity to the benzodiazepine site of GABA_A receptors, including human GABA_A receptors, are also included in this invention. Without wishing to be bound to any particular theory, it is believed that the interaction of the compounds of Formula I with the benzodiazepine site results in the pharmaceutical utility of these compounds.

The invention further comprises methods of treating patients in need of such treatment with an amount of a compound of the invention sufficient to alter the symptoms of a CNS disorder. Compounds of the inventions that act as agonists at $\alpha_2\beta_3\gamma_2$ and $\alpha_3\beta_3\gamma_2$ receptor subtypes are useful in treating anxiety disorders such as panic disorder, obsessive compulsive disorder and generalized anxiety disorder; stress disorders including post-traumatic stress, and acute stress disorders. Compounds of the inventions that act as agonists at $\alpha_2\beta_3\gamma_2$ and $\alpha_3\beta_3\beta_2$ receptor subtypes are also useful in treating depressive or bipolar disorders and in treating sleep disorders. Compounds of the

invention that act as inverse agonists at the $\alpha_3\beta_3\gamma_2$ receptor subtype or $\alpha_1\beta_2\gamma_2$ and $\alpha_3\beta_3\gamma_2$ receptor subtypes are useful in treating cognitive disorders including those resulting from Down Syndrome, neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, and stroke related dementia. Compounds of the invention that act as agonists at the $\alpha_1\beta_2\gamma_2$ receptor subtype are useful in treating convulsive disorders such as epilepsy. Compounds that act as antagonists at the benzodiazepine site are useful in reversing the effect of benzodiazepine overdose and in treating drug and alcohol addiction.

The diseases and/ or disorders that can also be treated using compounds and compositions according to the invention include:

Depression, e.g. depression, atypical depression, bipolar disorder, depressed phase of bipolar disorder.

Anxiety, e.g. general anxiety disorder (GAD), agoraphobia, panic disorder +/- agoraphobia, social phobia, specific phobia, Post traumatic stress disorder, obsessive compulsive disorder (OCD), dysthymia, adjustment disorders with disturbance of mood and anxiety, separation anxiety disorder, anticipatory anxiety acute stress disorder, adjustment disorders, cyclothymia.

Sleep disorders, e.g. sleep disorders including primary insomnia, circadian rhythm sleep disorder, dyssomnia NOS, parasomnias, including nightmare disorder, sleep terror disorder, sleep disorders secondary to depression and/or anxiety or other mental disorders, substance induced sleep disorder.

Cognition Impairment, e.g. cognition impairment, Alzheimer's disease, Parkinson's disease, mild cognitive impairment (MCI), age-related cognitive decline (ARCD), stroke, traumatic brain injury, AIDS associated dementia, and dementia associated with depression, anxiety or psychosis.

Attention Deficit Disorder, e.g. attention deficit disorder (ADD), and attention deficit and hyperactivity disorder (ADHD).

The invention also provides pharmaceutical compositions comprising compounds of the invention, including packaged pharmaceutical compositions for treating disorders responsive to GABA_A receptor modulation, e.g., treatment of anxiety, depression, sleep disorders or cognitive impairment by GABA_A receptor modulation. The packaged pharmaceutical compositions include a container holding a therapeutically effective amount of at least one GABA_A receptor modulator as described supra and instructions (e.g., labeling) indicating the contained GABA_A receptor ligand is to be used for treating a disorder responsive to GABA_A receptor modulation in the patient.

In a separate aspect, the invention provides a method of potentiating the actions of other CNS active compounds, which comprises administering an effective amount of a compound of the invention in combination with another CNS active compound. Such CNS active compounds include, but are not limited to the following: for anxiety, serotonin receptor (e.g. 5-HT_{1A}) agonists and antagonists; for anxiety and depression, neurokinin receptor antagonists or corticotropin releasing factor receptor (CRF₁) antagonists; for sleep disorders, melatonin receptor agonists; and for neurodegenerative disorders, such as Alzheimer's dementia, nicotinic agonists, muscarinic agents, acetylcholinesterase inhibitors and dopamine receptor agonists. Particularly the invention provides a method of potentiating the antidepressant activity of selective serotonin reuptake inhibitors (SSRIs) by administering an effective amount of a GABA agonist compound of the invention in combination with an SSRI.

Combination administration can be carried out in a fashion analogous to that disclosed in Da-Rocha, et al., *J. Psychopharmacology* (1997) 11(3) 211-218; Smith, et al., *Am. J.*

Psychiatry (1998) 155(10) 1339-45; or Le, et al., Alcohol and Alcoholism (1996) 31 Suppl. 127-132. Also see, the discussion of the use of the GABA_A receptor ligand 3-(5-methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl) methyloxy-1,2,4-triazolo [3,4-a]phthalzine in combination with nicotinic agonists, muscarinic agonists, and acetylcholinesterase inhibitors, in PCT International publications Nos. WO 99/47142, WO 99/47171, and WO 99/47131, respectively. Also see in this regard PCT International publication No. WO 99/37303 for its discussion of the use of a class of GABA_A receptor ligands, 1,2,4-triazolo[4,3-b]pyridazines, in combination with SSRIs.

The present invention also pertains to methods of inhibiting the binding of benzodiazepine compounds, such as Ro15-1788, to the GABA_A receptors which methods involve contacting a compound of the invention with cells expressing GABA_A receptors, wherein the compound is present at a concentration sufficient to inhibit benzodiazepine binding to GABA_A receptors *in vitro*. This method includes inhibiting the binding of benzodiazepine compounds to GABA_A receptors *in vivo*, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to inhibit the binding of benzodiazepine compounds to GABA_A receptors *in vitro*. In one embodiment, such methods are useful in treating benzodiazepine drug overdose. The amount of a compound that would be sufficient to inhibit the binding of a benzodiazepine compound to the GABA_A receptor may be readily determined via an GABA_A receptor binding assay, such as the assay described in Example 23. The GABA_A receptors used to determine *in vitro* binding may be obtained from a variety of sources, for example from preparations of rat cortex or from cells expressing cloned human GABA_A receptors.

The present invention also pertains to methods for altering the signal-transducing activity, particularly the chloride ion conductance of GABA_A receptors, said method comprising exposing

cells expressing such receptors to an effective amount of a compound of the invention. This method includes altering the signal-transducing activity of GABA_A receptors *in vivo*, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to alter the signal-transducing activity of GABA_A receptors *in vitro*. The amount of a compound that would be sufficient to alter the signal-transducing activity of GABA_A receptors may be determined via a GABA_A receptor signal transduction assay, such as the assay described in Example 24.

The GABA_A receptor ligands provided by this invention and labeled derivatives thereof are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the GABA_A receptor.

Labeled derivatives the GABA_A receptor ligands provided by this invention are also useful as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT).

Definitions

If the compounds of the present invention have asymmetric centers, then this invention includes all of the optical isomers and mixtures thereof.

In addition, compounds with carbon-carbon double bonds may occur in Z- and E- forms, with all isomeric forms of the compounds being included in the present invention.

When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^{*}, then said group may optionally be substituted with up to two R^{*} groups and R^{*} at each occurrence is selected independently from the definition of R^{*}. Also,

combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

By "alkyl", in the present invention is meant straight or branched chain alkyl groups having from 1 to about 8 carbon atoms, i.e. C₁-C₈ alkyl, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. Preferred alkyl groups are C₁-C₆ alkyl groups.

"Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl.

"Alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl.

"Alkoxy" represents an alkyl group as defined above having from 1 to about 8 carbon atoms, i.e. C₁-C₈ alkoxy, attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, 2-butoxy, t-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy. Preferred alkoxy groups include C₁-C₆ alkoxy.

The term "aryl" in the present invention means a monocyclic or bicyclic aromatic group having preferably 6 to 10 carbon atoms, such as, for example, phenyl or naphthyl or carbocyclic multiple condensed rings in which at least one is aromatic (e.g. naphthyl, 1,2,3,4-tetrahydronaphthyl).

By "arylalkyl" or "heteroarylalkyl" in the present invention is meant a branched or straight-chain alkyl group having from 1 to about 6 carbon atoms and substituted on one of the carbon atoms by an optionally substituted aryl or heteroaryl ring, such

as, for example, benzyl, phenethyl, methylpyridyl, ethylpyridyl, and the like.

By "cycloalkyl", or in the present invention is meant alkyl groups having from 3 to about 10 carbon atoms, i.e. C₃-C₁₀ cycloalkyl, forming a mono-, bi-, or polycyclic ring system, such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like. The term cycloalkyl includes bridged cycloalkyl groups. Preferred cycloalkyl groups are C₃-C₇ cycloalkyl groups.

By "(cycloalkyl)alkyl" in the present invention is meant a straight or branched alkyl substituent formed of 1 to about 6 carbon atoms attached to a mono-, bi, or polycyclic ring system having 3 to about 10 carbon atoms, such as, for example, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, and the like. Unless otherwise specified the point of attachment is in the alkyl group. Preferred (cycloalkyl)alkyl groups include (C₃-C₇cycloalkyl)C₁-C₄alkyl.

By the terms "halo" or "halogen" in the present invention is meant fluoro, chloro, bromo, and iodo.

"Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example -C_vF_w where v = 1 to 3 and w = 1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl.

By "heteroatom" in the present invention is meant oxygen or sulfur, or a nitrogen atom optionally substituted by C₁-C₆ alkyl, C₁-C₆ arylalkyl, C₁-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₈ alkanoyl, C₁-C₆ sulfonyl.

As used herein, the term "heterocycle" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered

bicyclic heterocyclic ring which is saturated ("heterocycloalkyl"), or partially unsaturated or unsaturated ("heteroaryl"), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized.

The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benzoxtetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl,

isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl, morpholiny, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl;- 1,2,5oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidiny, oxazolyl, oxazolidiny, pyrimidiny, phenanthridiny, phenanthroliny, phenaziny, phenothiaziny, phenoxathiiny, phenoxaziny, phthalaziny, piperaziny, piperidiny, pteridiny, puriny, pyranly, pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl, pyridaziny, pyridooxazole, pyridoimidazole, pyridothiazole, pyridiny, pyridyl, pyrimidiny, pyrrolidiny, pyrroliny, 2H-pyrroly, pyrroly, quinazoliny, quinoliny, 4H-quinoliziny, quinoxaliny, quinuclidiny, tetrahydrofurany, tetrahydroisoquinoliny, tetrahydroquinoliny, 6H-1,2,5-thiadiaziny, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triaziny, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

Preferred heterocycles include, but are not limited to thienyl, furany, (iso)thiazolyl, pyrroly, pyrazolyl, imidazolyl, (is)oxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidiny, pyridaziny, pyrimidyl, (iso)quinoliny, naphthyridiny, benzimidazolyl, benzoxazolyl, tetrazolyl, piperidiny, piperaziny, pyrrolidiny, morpholiny, tetrahydropyranly, and tetrahydrofurany.

The term "oxo" (i.e. =O) indicates that two geminal hydrogen atoms are replaced by a double-bond oxygen group.

The term "substituted", as used herein, means that any one or more hydrogen atoms on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound. A stable compound is defined herein

as one that can be isolated, characterized, and tested for biological activity.

When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers, By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include ^{11}C , ^{13}C , and ^{14}C .

As indicated above, various substituents of the various formulae are "optionally substituted", e.g. R_1 , R_2 , R_3 , and R_4 of Formula I, and such substituents as recited in the sub-formulae such as Formula II and the like. When substituted, those substituents (e.g. e.g. R_1 , R_2 , R_3 , and R_4) may be substituted by other than hydrogen at one or more available positions, typically 1 to 3 or 4 positions, by one or more suitable groups such as those disclosed herein. Suitable groups that may be present on a "substituted" e.g. e.g. R_1 , R_2 , R_3 , and R_4 group or other substituent include e.g. halogen such as fluoro, chloro, bromo and iodo; cyano; hydroxyl; nitro; azido; COOH , alkanoyl such as a C_{1-6} alkanoyl group such as acyl and the like; carboxamido; alkyl groups including those groups having 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon, or 2, 3, 4, 5 or 6 carbon atoms; alkoxy groups having those having one or more oxygen linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms; alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms, or 1, 2,

3, 4, 5, or 6 carbon atoms; alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms; carbocyclic aryl having 6 or more carbons, particularly phenyl (e.g. an Ar group being a substituted or unsubstituted biphenyl moiety); aralkyl having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with benzyl being a preferred group; aralkoxy having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with O-benzyl being a preferred group; or a heteroaromatic or heteroalicyclic group having 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O or S atoms, e.g. coumarinyl, quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an effective therapeutic agent.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings or animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by

making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and the like. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, p. 1418 (1985).

In the present invention, the terms "high affinity" in the context of compounds that bind to GABA_A receptors qualifies a binding affinity with a K_i of less than 10 micromolar, preferably less than 1 micromolar, and more preferably less than 100 nanomolar in a human *in vitro* GABA_A binding assay, such as the assay given in Example 23.

640
641

"Prodrugs" are intended to include any covalently bonded carriers which release the active parent drug according to Formula I, *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs are prepared by modifying functional groups present in a compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of formula Ia, formula Ib, and formula Ic wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of formula Ia, formula Ib, or formula Ic is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula Ia, formula Ib, or formula Ic, and the like.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of NPY or treat the symptoms of feeding disorders, including obesity and bulimia nervosa, some psychiatric disorders, and cardiovascular disorders.

Pharmaceutical Preparations

Those skilled in the art will recognize various synthetic methodologies that may be employed to prepare non-toxic pharmaceutically acceptable prodrugs of the compounds encompassed by Formula I. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable solvents that may be used to prepare solvates of the compounds of the invention, such as water, ethanol, mineral oil, vegetable oil, and dimethylsulfoxide.

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is particularly preferred. The term parenteral as used herein includes subcutaneous injections, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intrathecal injection or like injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or

acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

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

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

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

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

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

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical

compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

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

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

For administration to non-human animals, the composition may also be added to the animal feed or drinking water. It will be convenient to formulate these animal feed and drinking water compositions so that the animal takes in an appropriate quantity of the composition along with its diet. It will also be

convenient to present the composition as a premix for addition to the feed or drinking water.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most disorders, a dosage regimen of 4 times daily or less is preferred. For the treatment of anxiety, depression, or cognitive impairment a dosage regimen of 1 or 2 times daily is particularly preferred. For the treatment of sleep disorders a single dose that rapidly reaches effective concentrations is desirable.

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

Preferred compounds of the invention will have certain pharmacological properties. Such properties include, but are not limited to high solubility (preferably 500 ng/ ml or more) in aqueous solutions, oral bioavailability, low toxicity, low serum protein binding, lack of clinically relevant EKG effects, and desirable in vitro and in vivo half-lives. Penetration of the blood brain barrier for compounds used to treat CNS disorders is

necessary, while low brain levels of compounds used to treat peripheral disorders are often preferred.

Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocytes may be used to predict compound toxicity. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously.

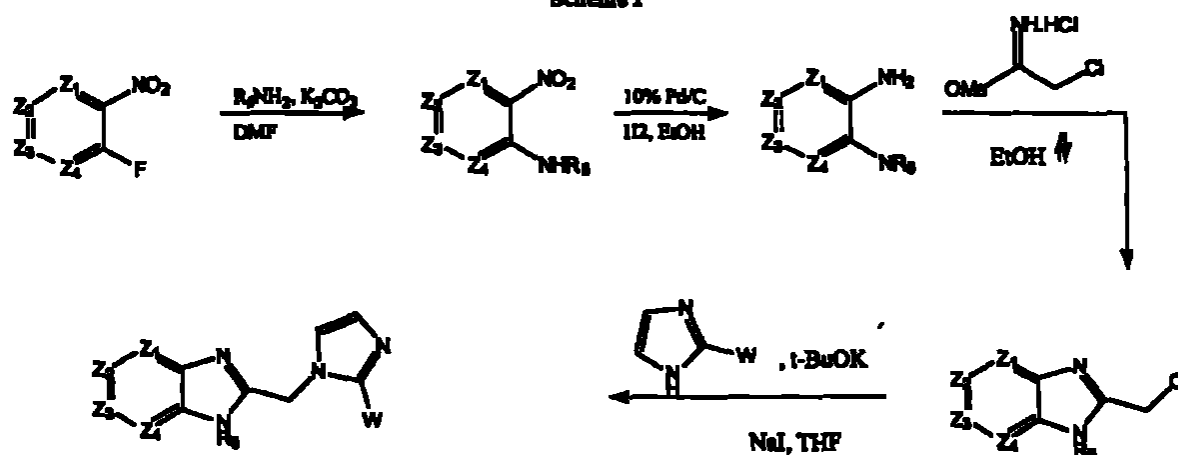
Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcová, et al. (Journal of Chromatography B (1996) volume 677, pages 1-27).

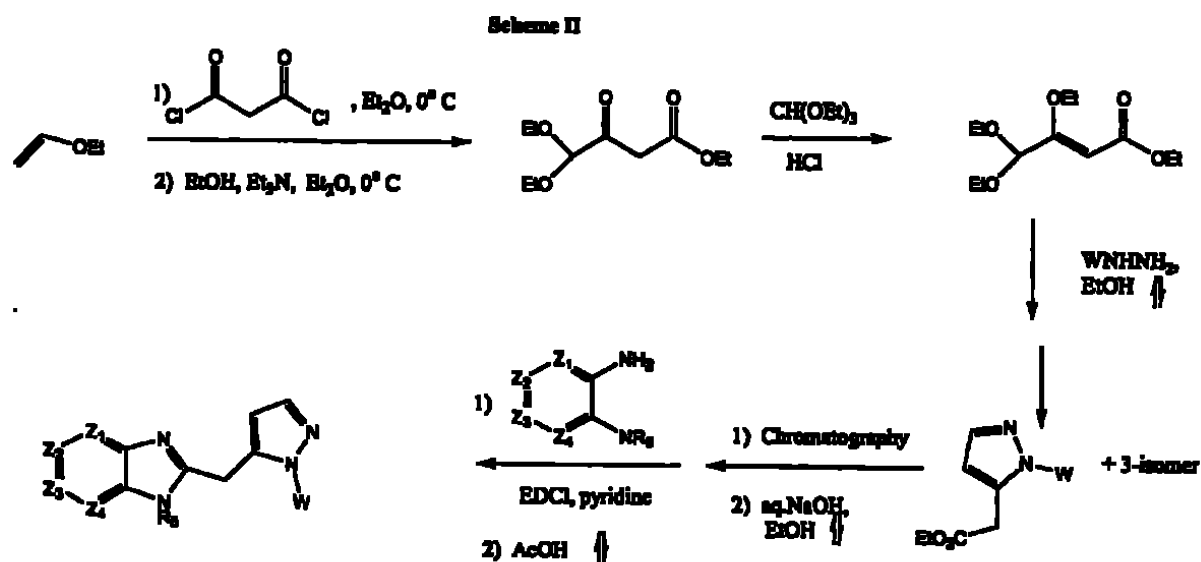
Compound half-life is inversely proportional to the frequency of dosage of a compound. In vitro half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127).

Preparation of Compounds

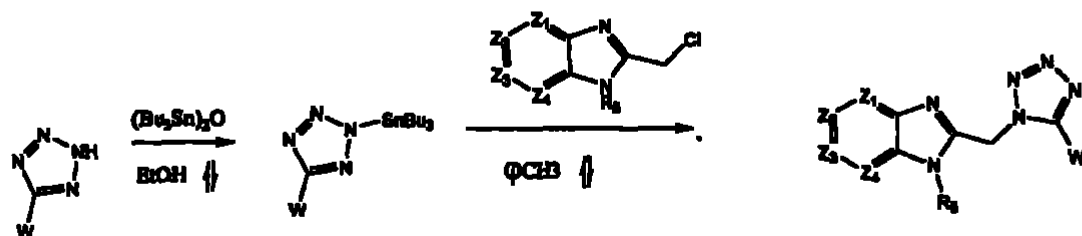
An illustration of the preparation of compounds of the present invention is given in Schemes I-V.

Scheme I

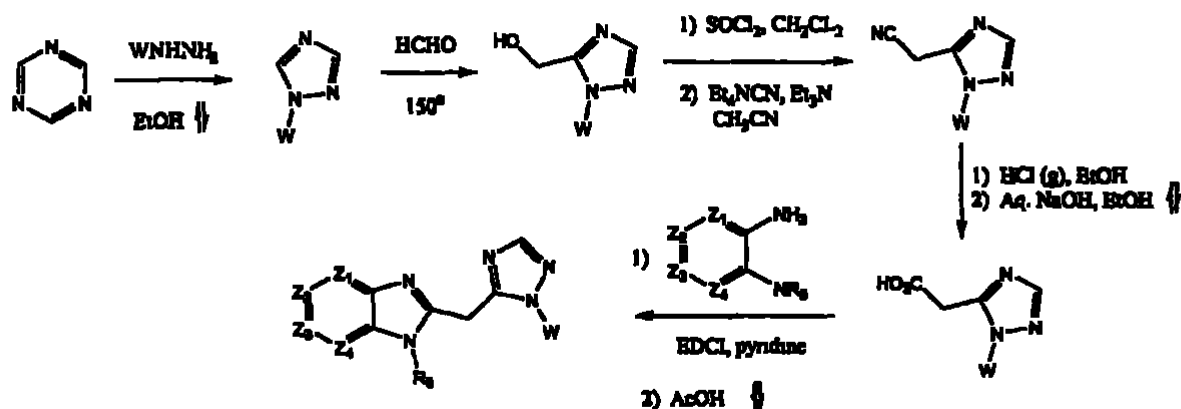




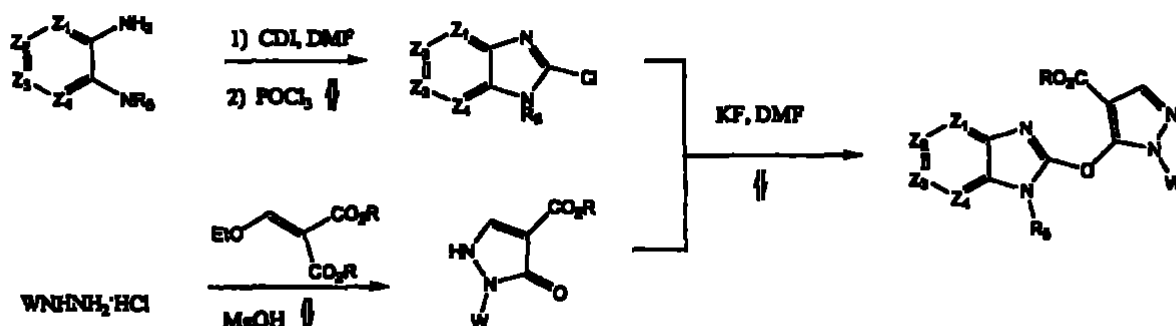
Scheme III



Scheme IV



Scheme V



The invention is illustrated further by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. Additional compounds encompassed by this invention beyond the

accompanying Examples may be prepared using standard methods well known to those skilled in the art of chemical synthesis. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present inventions, as demonstrated by the following examples. In some cases, protection of certain reactive functionalities may be necessary to achieve some of the above transformations. In general, such need for protecting groups, as well as the conditions necessary to attach and remove such groups, will be apparent to those skilled in the art of organic synthesis.

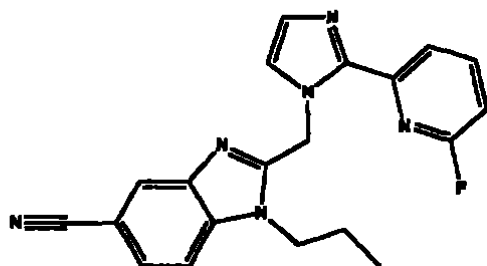
Examples

Preparation of starting materials and intermediates

The starting materials and various intermediates may be obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well-known synthetic methods. Representative examples of methods for preparing intermediates of the invention are set forth below.

Example 1

Synthesis of 1-Propyl-2-([2-(2-fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl)-5-cyano-1H-benzimidazole



1. Preparation of 4-n-Propylamino-3-nitrobenzonitrile

To a stirring suspension of 4-chloro-3-nitrobenzonitrile (7.30g, 40 mmol) in isopropanol (30 mL) is added n-propylamine (9.87 mL, 120 mmol). The mixture is stirred at room

temperature for 5 h, and the solid is then collected by filtration to give 7.63 g of 4-n-propylamino-3-nitrobenzonitrile as a yellow solid. ¹H NMR (CDCl₃) 8.51 (1H, q), 8.42 (1H, br s), 7.60 (1H, m), 6.91 (1H, d), 3.33 (2H, q), 1.84-1.74 (2H, m), 1.07 (3H, t). LRMS 206.3 (MH⁺).

2. Preparation of 3-Amino-4-n-propylaminobenzonitrile

To a Parr bottle containing 4-n-propylamino-3-nitrobenzonitrile (7.63 g, 37.2 mmol) in ethyl acetate (38 mL) is added 5% Pd/C (50% wet, 633 mg). The Parr bottle is sealed in a mechanical shaker, evacuated, and then purged with nitrogen followed by hydrogen. The system is pressurized to 50 PSI of hydrogen at room temperature and mechanical shaking engaged. After 2 hours, shaking is stopped, and the system purged with nitrogen prior to opening the vessel. The reaction mixture is filtered through celite, concentrated in vacuo, and the obtained solid recrystallized by dissolving in ethyl acetate (15 mL), heating, and adding hexanes (15 mL), to give 5.72 g of 3-Amino-4-n-propylaminobenzonitrile as gray crystals. ¹H NMR (CDCl₃) 7.14 (1H, dd), 6.92 (1H, d), 6.56 (1H, d), 3.98 (1H, br s), 3.30 (2H, br s), 3.12 (2H, t), 1.75-1.65 (2H, m), 1.03 (3H, t). LRMS calcd 175.23, found 176.2 (MH⁺).

3. Preparation of 1-Propyl-2-([2-(2-fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl)-5-cyano-1H-benzimidazole

Method A

(A) Preparation of 1-n-Propyl-2-chloromethyl-5-cyanobenzimidazole hydrochloride

i) A solution of 3-amino-4-n-propylaminobenzonitrile (7.38g, 42.1 mmol) and ethyl chloroacetimidate hydrochloride (9.92 g, 63.2 mmol) in ethanol (100 mL) is heated at reflux for 17 h, then cooled and concentrated to give 1-n-Propyl-2-chloromethyl-5-cyanobenzimidazole hydrochloride. Prior to use in the next step,

60257492-122100

this material is converted to free base by adding aqueous bicarbonate and extracting with dichloromethane, drying (Na_2SO_4), and concentrating.

ii) Alternatively, chloroacetylchloride rather than ethyl chloroacetimidate can be used: To a solution of 3-amino-4-n-propylaminobenzonitrile (5.15 g, 29.4 mmol) and triethylamine (4.51 mL) in ethyl acetate (52 mL) at room temperature, chloroacetyl chloride (2.57 mL) is added slowly. After stirring the reaction mixture for 30 minutes at room temperature, acetic acid (5 mL) is added and the reaction mixture heated to reflux. After heating for 20 h, the reaction mixture is cooled to room temperature and diluted with water (50 mL). The organic solution is washed twice with 1.0 M sodium hydroxide (2 x 50 mL), then washed with an aqueous solution of 0.25 M KH_2PO_4 (50 mL), followed by brine (50 mL). The organic layer is dried (sodium sulfate), concentrated in vacuo, and the solid recrystallized by heating in ethyl acetate (20 mL), adding hexane (40 mL) and cooling to room temperature with stirring to afford 5.32 g 1-n-Propyl-2-chloromethyl-5-cyanobenzimidazole as brown crystals. ^1H NMR (CDCl_3): 8.08 (d, $J = 0.8$ Hz, 1H), 7.57 (dd, $J = 1.65$, 8.52 Hz, 1H), 7.45 (d, $J = 8.24$ Hz, 1H), 7.26 (s, 1H), 4.84 (s, 2H), 4.24 (t, $J = 7.6$ Hz, 2H), 1.94 (pentet, $J = 7.4$, 7.6 Hz, 2H), 1.03 (t, $J = 7.4$ Hz, 3H).

(B) Preparation of 1-Propyl-2-[[2-(2-fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-5-cyano-1H-benzimidazole

To a stirring suspension of sodium hydride (2.25g of 60% in oil) in DMF (10 mL) at 0° a solution of 2-Fluoro-6-(1H-imidazol-2-yl)-pyridine (7.7 g, 47.2 mmol) in DMF (20 mL) is added. After stirring for 5 minutes, a solution of 1-n-Propyl-2-chloromethyl-5-cyanobenzimidazole (11 g, 47.2 mmol) and sodium iodide (20 mg) in DMF (80 mL) is added. The reaction mixture is stirred for 6 h, gradually warmed to room temperature. The reaction mixture is cooled, water added, the solid collected, rinsed with water and

653

dried to afford 20 g of the title compound, 1-Propyl-2-[[2-(2-fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-5-cyano-1H-benzimidazole.

Method B

Trimethylaluminum (0.54mL of 2.0M in toluene, 1.09mmol) is added dropwise to a solution of 3-Amino-4-propylaminobenzonitrile (152mg; 0.87mmol) in dichloromethane (10mL), and the mixture was stirred at room temperature for 1hr. A solution of [2-(2-Fluoropyridin-6-yl)-imidazol-1-yl] acetic acid methyl ester (102mg; 0.43mmol) in dichloromethane (5mL) is added all at once, and the mixture heated at reflux for 16 hr. The brown solution is cooled to room temperature and treated dropwise with methanol (1mL) then water (2mL) and stirred at room temperature for 15 min. Anhydrous sodium sulfate is added until the gel becomes solid, the mixture is diluted with dichloromethane (100mL) and filtered through celite. The filtrate is concentrated to give a brown oil which is dissolved in acetic acid (7 mL) and heated at 100° for 72 hr. The mixture is cooled to room temperature and concentrated. The residue is dissolved in ethyl acetate (15mL), washed with saturated aqueous NaHCO₃ (1 x 50mL), then brine (1 x 50mL), dried (MgSO₄), and concentrated, and the residue purified by preparative thin layer chromatography to give 1-n-Propyl-2-[[2-(2-fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-5-cyano-1H-benzimidazole as a light brown semi-solid (57mg).

Method C

A solution of [2-(6-Fluoropyridin-2-yl)-imidazol-1-yl]acetic acid hydrochloride (274mg; 1.06mmol) and triethylamine (0.15mL; 1.06mmol) in dichloromethane (10mL) is treated dropwise with oxalyl chloride (0.64mL of a 2M solution in dichloromethane; 1.27mmol), and the resulting suspension stirred at room temperature for 2 hr.

The mixture is concentrated and the residue suspended in dichloromethane (10mL). A solution of 3-Amino-4-

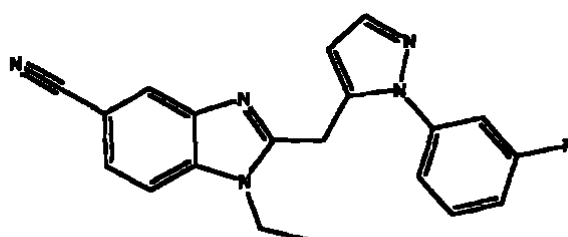
propylaminobenzonitrile (185mg; 1.06mmol) in dichloromethane (5mL) is added and the mixture stirred at room temperature for 16hr, then concentrated. The residue is dissolved in acetic acid (10mL) and heated at 100° for 1hr. The mixture is cooled to room temperature, concentrated, taken up in ethyl acetate (150mL), washed with saturated aqueous NaHCO₃ (50mL) and then washed with brine (50mL), dried (MgSO₄), and concentrated to give the crude product as a waxy brown solid (338mg). This crude product is slurried with diethyl ether (ca. 4mL) and a few drops of methanol, then filtered to give 1-n-Propyl-2-[[2-(2-fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-5-cyano-1H-benzimidazole as a pale brown solid (230mg).

¹H NMR (399.96MHz, CDCl₃): δ 8.17(dd, J = 2.0, 7.6Hz, 1H, H-18), 8.05(s, 1H, H-4), 7.88(q, J = 8.0Hz, 1H, H-19), 7.52(d, J = 8.4Hz, 1H, H-6), 7.41(d, J = 8.4Hz, 1H, H-7), 7.21(s, 1H, H-14), 7.18(s, 1H, H-15), 6.28(s, 2H, H-13), 4.28(t, J = 7.6Hz, 2H, H-10), 1.68(dt, J = 7.6Hz, 2H, H-11), 0.84(t, J = 7.6Hz, 3H, H-12).

¹³C NMR (100.57MHz, CDCl₃, ¹H decoupled at 399.957MHz): δ, 162.36(d, J_{C-F} = 239.6Hz), 152.53, 148.69(d, J_{C-F} = 13.0Hz), 142.36(d, J_{C-F} = 7.6Hz), 142.31, 142.28, 138.42, 129.96, 126.55, 125.31, 124.23, 120.27(d, J_{C-F} = 3.8Hz), 119.96, 111.23, 108.52(d, J_{C-F} = 35.9Hz), 105.70, 46.10, 44.57, 23.43, 11.27.

Example 2

Synthesis of 1-Ethyl-2-[[2-(3-fluorophenyl)-pyrazol-3-yl]methyl]-5-cyano-1H-benzimidazole



1. Preparation of 1-(3-Fluorophenyl)-5-carboxymethylpyrazole

655

To a stirring solution of ethyl vinyl ether (340 mL, 3.55 mol) in diethyl ether (200 mL), cooled in an ice bath, is added dropwise a solution of malonyl dichloride (69 mL, 0.71 mol) in ether (20 mL). Stirring is continued at 0°C for 2h, then a solution of triethylamine (196 mL) and ethanol (350 mL) in ether (210 mL) is added with cooling. More ether is added to further precipitate triethylamine hydrochloride, the mixture is then filtered, and the filtrate concentrated. The residue is taken up in ethanol (710 mL), then triethyl orthoformate (177 mL, 1.07 mol) and concentrated HCl (5 mL) is added. The mixture is stirred overnight then concentrated. To the residue is added ethanol (500 mL) and 3-Fluorophenylhydrazine hydrochloride (27.6 g, 0.17 mol). The mixture is heated at reflux for 2 h, then cooled and concentrated. Ethyl acetate is added, the mixture is washed with aqueous bicarbonate, then with water, dried (Na₂SO₄), concentrated, and the residue purified by silica gel chromatography. Ethanol (20mL) and 1 N NaOH (100 mL) are added, and heated at reflux for 1 h. The mixture is cooled and washed with ethyl acetate. The aqueous layer is cooled and acidified, the solid collected by filtration, rinsed well with water and dried to give 10.9 g of 1-(3-Fluorophenyl)-5-carboxymethylpyrazole as a gold solid. ¹H NMR (CDCl₃): 7.68 (d, J = 1.8 Hz, 1H), 7.41-7.48 (m, 1H), 7.10-7.26 (m, 3H), 6.44 (d, J = 2.1 Hz, 1H), 3.77 (s, 2H). LCMS: 221.2 (MH⁺), 219.2 (MH⁻).

2. Preparation of 1-Ethyl-2-[[2-(3-fluorophenyl)-pyrazol-3-yl]methyl]-5-cyano-1H-benzimidazole

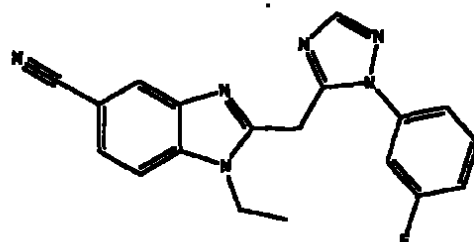
To a stirring solution of 3-amino-4-ethylaminobenzonitrile (887 mg, 5.5 mmol) and 1-(3-Fluorophenyl)-5-carboxymethylpyrazole (1.10 g, 5 mmol) in pyridine (5 mL) is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.15 g, 6 mmol). The mixture is stirred at room temperature for 17.5 h, then concentrated. The residue is cooled in an ice bath, aqueous HCl is added with stirring, the precipitate is collected by

60257492-122100

filtration, rinsed well with water and dried. The solid is added to acetic acid (75 mL) and heated at reflux for 5.5 h. The mixture is cooled, concentrated, and purified by silica gel chromatography to give 1-Ethyl-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-5-cyano-1H-benzimidazole. The product is converted to the mesylate salt in acetone. ^1H NMR (CDCl_3): 8.17 (s, 1H), 7.89 (d, $J = 8.52$ Hz, 1H), 7.68-7.75 (m 1H), 7.44-7.54 (m, 2H), 7.37-7.40 (m, 1H), 7.21-7.28 (m, 1H), 6.35 (d, $J = 1.65$ Hz, 1H), 4.65 (s, 2H), 4.29 (q, $J = 7.14$ Hz, 2H), 2.34 (s, 3H), 1.19 (t, $J = 7.14$ Hz, 3H). LCMS 346.0 (MH^+), 344.4 (MH^-).

Example 3

Synthesis of 1-Ethyl-2-([1-(3-fluorophenyl)-1,2,4-triazol-5-yl]methyl)-5-cyano-1H-benzimidazole



1. Preparation of 1-(3-Fluorophenyl)-1,2,4-triazole

A mixture of 1,3,5-triazine (1 g, 12.3 mmol) and 3-Fluorophenylhydrazine hydrochloride (2 g, 12.3 mmol) in ethanol (20 mL) is heated at reflux overnight. After concentrating, ethyl acetate is added, the mixture is washed with aqueous bicarbonate followed by saturated aqueous sodium chloride, dried (MgSO_4), and concentrated to give 1.8 g of crude 1-(3-Fluorophenyl)-1,2,4-triazole. ^1H NMR (CDCl_3): 8.57 (s, 1H), 8.12 (s, 1H), 7.46-7.51 (m, 3H), 7.08-7.15 (m, 1H). LCMS 164.1 (MH^+).

2. Preparation of 1-(3-Fluorophenyl)-5-hydroxymethyl-1,2,4-triazole

A mixture of the crude 1-(3-Fluorophenyl)-1,2,4-triazole and formaldehyde (10 mL of 37 wt % in water) is heated at 150°C in a

657
657

sealed tube for 48 h. After cooling the reaction vessel, the reaction mixture is extracted with dichloromethane, dried (MgSO_4), concentrated, and the residue purified using silica gel chromatography to afford 1.7 g of 1-(3-Fluorophenyl)-5-hydroxymethyl-1,2,4-triazole. ^1H NMR (CDCl_3): 8.02 (s, 1H), 7.42-7.53 (m, 3H), 7.22-7.29 (m, 1H), 4.81 (s, 2H). LCMS 194.2 (MH^-).

3. Preparation of 1-(3-Fluorophenyl)-5-cyanomethyl-1,2,4-triazole
1-(3-Fluorophenyl)-5-hydroxymethyl-1,2,4-triazole (1.7 g) is treated with thionyl chloride (10 mL) in dichloromethane (20 mL) at room temperature overnight. The solvent is then removed. To the residue is added acetonitrile (20 mL), tetraethylammonium cyanide (2.75 g, 17.6 mmol), and triethylamine (2.5 mL, 17.6 mmol). The mixture is stirred at room temperature for 2 h. The mixture is diluted with ethyl acetate, washed with aqueous bicarbonate, and then with saturated aqueous sodium chloride, dried (Na_2SO_4), concentrated and the residue purified by silica gel chromatography to give 0.9 g of crude of 1-(3-Fluorophenyl)-5-cyanomethyl-1,2,4-triazole. ^1H NMR (CDCl_3): 8.06 (s, 1H), 7.52-7.62 (m, 1H), 7.20-7.30 (m, 3H), 3.98 (s, 2H). LCMS 203.0 (MH^+), 201.2 (MH^-).

4. Preparation of 1-(3-Fluorophenyl)-5-carboxymethyl-1,2,4-triazole

Crude 1-(3-Fluorophenyl)-5-cyanomethyl-1,2,4-triazole (0.9 g) is taken up in ethanol (50 mL) and cooled in an ice bath. HCl gas is bubbled through for 0.5 h. Water (10 mL) is added and the mixture heated at 65°C for 2 h. After cooling, most of the ethanol is removed on a roto-evaporator, 3 N NaOH (25 mL) and ethanol (25 mL) are then added. The solution is heated at reflux for 2 h, cooled, and then extracted with diethyl ether (3X). The aqueous layer is acidified to pH 2, extracted with ethyl acetate. The organic layer is washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and concentrated to give 0.8 g

60257492.122100

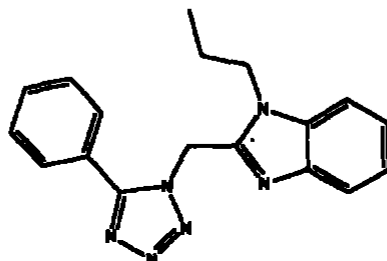
of 1-(3-Fluorophenyl)-5-carboxymethyl-1,2,4-triazole. ^1H NMR (CDCl_3): 8.08 (s, 1H), 7.50-7.57 (m, 1H), 7.22-7.32 (m, 3H), 4.01 (s, 2H).

5. Preparation of 1-Ethyl-2-([1-(3-fluorophenyl)-1,2,4-triazol-5-yl]methyl)-5-cyano-1H-benzimidazole

Using the procedure described in Example 2, Step 2, 1-(3-fluorophenyl)-5-carboxymethyl-1,2,4-triazole is converted to 1-Ethyl-2-([1-(3-fluorophenyl)-1,2,4-triazol-5-yl]methyl)-5-cyano-1H-benzimidazole. ^1H NMR (CDCl_3): 8.03 (s, 1H); 8.01 (s, 1H); 7.42-7.56 (m, 5H); 7.22 (m, 1H); 4.51 (s, 2H); 4.43 (q, 2H); 1.45 (t, 3H). LCMS 347.3 (MH^+).

Example 4

Synthesis of 1-Propyl-2-[(5-phenyl-1H-tetrazol-1-yl)methyl]-1H-benzimidazole



1. Preparation of 2-(Tri-n-butyltin)-5-phenyl -1H-tetrazole

A mixture of 5-phenyl-1H-tetrazole (200 mg, 1.22 mmol) and bis(tri-n-butyltin)oxide (0.31 mL, 0.61 mmol) in ethanol (2 mL) is heated at reflux for 10 minutes. The mixture is cooled, concentrated, and the crude 2-(Tri-n-butyltin)-5-phenyl -1H-tetrazole used directly.

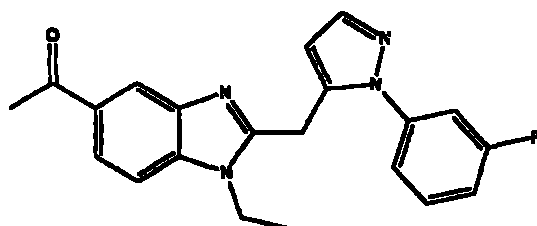
2. Preparation of 1-Propyl-2-[5-phenyl-1H-tetrazol-1-yl)methyl]-1H-benzimidazole

Crude 2-(tri-n-butyltin)-5-phenyl-1H-tetrazole (2.09 g, 4.8 mmol) and 1-propyl-2-chloromethylbenzimidazole (1.0 g, 4.8 mmol) are heated in toluene (5 mL) at reflux overnight. The solvent is removed in vacuo, the residue washed with hexane, and then

purified by preparative chromatography to give 1-Propyl-2-[(5-phenyl-1H-tetrazol-1-yl)methyl]-1H-benzimidazole as the minor isomer. ^1H NMR (CDCl_3): 8.05-8.12 (m, 2H); 7.77 (m, 1H); 7.58-7.62 (m, 2H); 7.29-7.43 (m, 3H); 5.86 (s, 2H); 4.40 (t, 2H); 1.85 (m, 2H); 1.01 (t, 3H).

Example 5

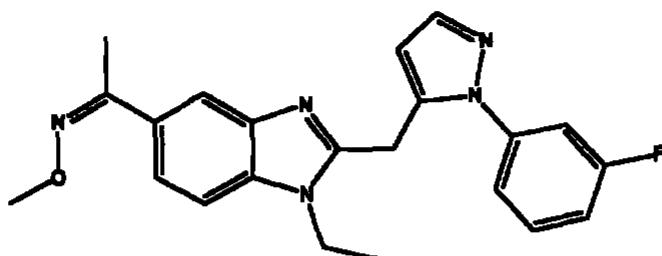
Synthesis of 1-Ethyl-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-5-acetyl-1H-benzimidazole



A mixture of 1-Ethyl-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-5-bromo-1H-benzimidazole (200mg, 0.5 mmol), tributyl(1-ethoxyvinyl)tin (0.34 ml, 1.0 mmol), and tetrakis(triphenylphosphine)palladium(0) (29 mg) in toluene (10 mL) is heated at reflux for 1 h under argon. The solvent is removed in vacuo, the residue is then dissolved in 10% HCl (5 mL) and THF (5 mL). The mixture is stirred at room temperature for 0.5 h, then extracted with ethyl acetate. The aqueous layer is adjusted to pH 9, extracted with dichloromethane, and the organic layer dried (Na_2SO_4), concentrated, and the residue purified by preparative silica gel chromatography to give 1-Ethyl-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-5-acetyl-1H-benzimidazole. ^1H NMR (CDCl_3): 8.36 (d, 1H); 7.99 (dd, 1H); 7.645 (d, 1H); 7.25-7.49 (m, 4H); 7.14 (m, 1H); 6.21 (d, 1H); 4.36 (s, 2H); 4.02 (q, 2H); 2.68 (s, 3H); 1.24 (t, 3H).

Example 6

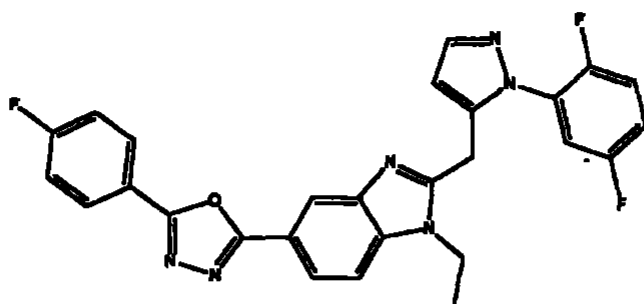
Synthesis of 1-Ethyl-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-5-[1-(methoxyimino)ethyl]-1H-benzimidazole



A mixture of 1-Ethyl-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-5-acetyl-1H-benzimidazole (23 mg), methoxylamine hydrochloride (15 mg, 3 eq.), and sodium acetate (15 mg, 3 eq.) in methanol (1 mL) is stirred at room temperature overnight. The solvent is removed in vacuo and aqueous sodium bicarbonate added to pH 9, then extracted with ethyl acetate. The organic layer is dried (Na_2SO_4) and concentrated to give 1-Ethyl-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-5-[1-(methoxyimino)ethyl]-1H-benzimidazole. ^1H NMR (CDCl_3): 7.94 (d, 1H); 7.73 (dd, 1H); 7.73 (dd, 1H); 7.63 (d, 1H); 7.52 (m, 1H); 7.38-7.40 (m, 3H); 7.27 (m, 1H); 6.19 (d, 1H); 4.32 (s, 2H); 3.87-4.10 (m, 5H); 2.30 (s, 3H); 1.22 (t, 3H).

Example 7

Synthesis of 1-Ethyl-2-([2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl)-5-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]-1H-benzimidazole



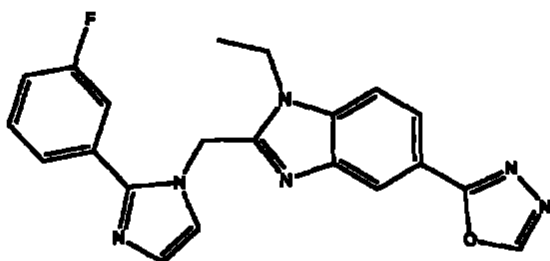
A mixture of 1-Ethyl-2-([2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl)-1H-benzimidazol-5-carboxylate (152 mg) and 4-fluorobenzhydrazide (1.05 eq.) in phosphorous oxychloride (6 mL) is heated at reflux for 1.5 h. The mixture is cooled and

666
661

concentrated, and then water (5 mL) is added to the residue. After adjusting to pH >7 with saturated aqueous bicarbonate, the solution is extracted with ethyl acetate (3X), and the combined organic layers are washed with water (2X) then with saturated aqueous sodium chloride, dried (MgSO₄), concentrated, and the residue purified by preparative silica gel chromatography to give 1-Ethyl-2-([2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl)-5-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]-1H-benzimidazole. LCMS MH⁺ 501.068.

Example 8

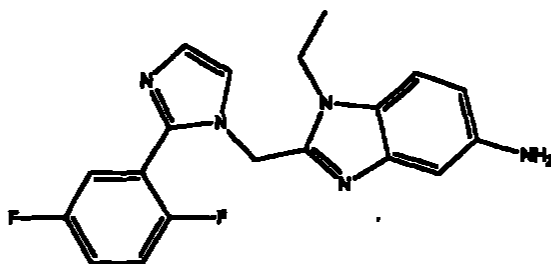
Synthesis of 1-Ethyl-2-([2-(3-fluorophenyl)-1H-imidazol-1-yl]methyl)-5-(1,3,4-oxadiazol-2-yl)-1H-benzimidazole



A mixture of 1-ethyl-2-([2-(3-fluorophenyl)-1H-imidazol-1-yl]methyl)-1H-benzimidazol-5-hydrazide (177 mg), triethylorthoformate (8 mL) and acetic acid (2 mL) is heated at reflux for 5 h. The reaction is cooled, concentrated, and the residue purified by preparative silica gel chromatography to give 1-Ethyl-2-([2-(3-fluorophenyl)-1H-imidazol-1-yl]methyl)-5-(1,3,4-oxadiazol-2-yl)-1H-benzimidazole, which was converted to the hydrochloride salt in ethyl acetate. ¹H NMR (d6 DMSO): 9.32 (s, 1H), 8.19 (s, 1H), 8.03 (d, 1H), 7.97-7.95 (m, 2H), 7.87 (d, 1H), 7.72 (m, 1H), 7.66-7.60 (m, 2H), 7.54-7.50 (m, 1H), 5.99 (s, 2H), 4.34 (q, 2H), 1.31 (t, 3H), LCMS MH⁺ 389.4

Example 9

Synthesis of 1-Ethyl-2-([2-(2,5-difluorophenyl)-1H-imidazol-1-yl]methyl)-5-amino-1H-benzimidazole



1. Preparation of 4-Fluoro-3-nitroacetanilide

4-Fluoro-3-nitroaniline (5.2 g) is treated with acetic anhydride (1.1 eq.) in dichloromethane at room temperature for 1 h. The reaction is concentrated, the residue taken up in dichloromethane and washed with aqueous sodium bicarbonate (2X) then with saturated aqueous sodium chloride, dried (MgSO_4), and concentrated to give 4.7 g of crude 4-Fluoro-3-nitroacetanilide.

2. Preparation of 3-Nitro-4-(ethylamino)acetanilide

A mixture of crude 4-Fluoro-3-nitroacetanilide (4.6 g), ethylamine (23 mL of 2M in THF), and potassium carbonate (3.5 g) in DMF (100 mL) is stirred at room temperature for 4h, then heated at 60°C for 5 h. The reaction is allowed to cool, water (150 mL) is added, and extracted with ethyl acetate (3X). The combined organic extracts are washed with water (3X), then washed with saturated aqueous sodium chloride, dried (MgSO_4), and concentrated to give 4.88 g of crude 3-Nitro-4-(ethylamino)acetanilide.

3. Preparation of N-[3-Amino-4-(ethylamino)phenyl] acetamide

Crude 3-Nitro-4-(ethylamino)acetanilide (4.8 g), 10% Pd/C (0.5 g), methanol (50 mL) and ethyl acetate (200 mL) are placed in a Paar apparatus under hydrogen at 50 psi for 5 h. The mixture is filtered through Celite and concentrated to give 4 g of crude N-[3-Amino-4-(ethylamino)phenyl] acetamide

4. Preparation of N-(2-[[2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl]-1-ethyl -1H-benzimidazol-5-yl) acetamide

Using the procedure described in Example 1 Method A, crude N-[3-amino-4-(ethylamino)phenyl] acetamide is converted to N-(2-

50257492-1E2100

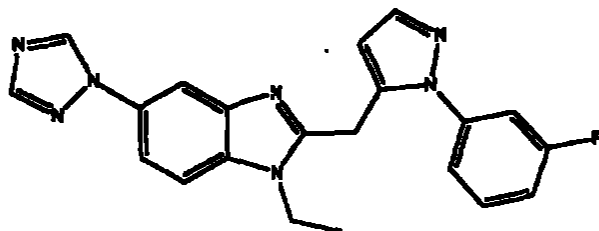
{[2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl}-1-ethyl -1H-benzimidazol-5-yl) acetamide.

5. Preparation of 1-Ethyl-2-([2-(2,5-difluorophenyl)-1H-imidazol-1-yl]methyl) -5-amino-1H-benzimidazole

Crude N-{1-Ethyl-2-([2-(2,5-difluorophenyl)-1H-imidazol-1-yl]methyl)-1H-benzimidazol-5-yl) acetamide is treated with 10% aqueous HCl (20 mL) in methanol (10 mL) at reflux for 1.5 h. After cooling, the methanol is removed in vacuo, and the aqueous layer washed with ethyl acetate. The aqueous layer is adjusted to pH 10 with 3 N NaOH, then extracted with ethyl acetate (3X), and the combined organic extracts washed with water (2X) then saturated aqueous sodium chloride, dried (MgSO₄), and concentrated to give 986 mg of 1-Ethyl-2-([2-(2,5-difluorophenyl)-1H-imidazol-1-yl]methyl) -5-amino-1H-benzimidazole. LCMS MH⁺ 354.4.

Example 10

Synthesis of 1-Ethyl-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-5-(1,2,4-triazol-1-yl)-1H-benzimidazole

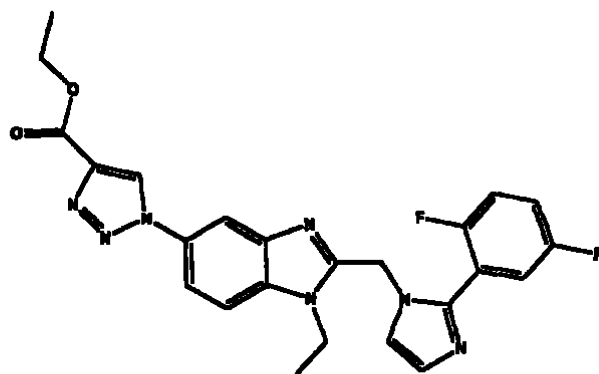


1-Ethyl-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-5-amino-1H-benzimidazole (274 mg) is treated with N,N-dimethylformamide azine hydrochloride (1 eq) in toluene (10 mL) and methoxyethanol (10 mL) and refluxed for 6 h. After cooling and concentrating, the residue is treated with water and extracted with dichloromethane (2X). The aqueous layer is adjusted to pH 8 with aqueous sodium bicarbonate and extracted with dichloromethane (2X). The combined organic extracts are washed with saturated aqueous sodium chloride, dried (MgSO₄),

concentrated, purified by preparative silica gel chromatography, and triturated with ether to afford 1-Ethyl-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-5-(1,2,4-triazol-1-yl)-1H-benzimidazole, which is converted to the hydrochloride salt in ethyl acetate. LCMS MH^+ 406.2.

Example 11

Synthesis of 1-ethyl-2-([2-(2,5-difluorophenyl)-1H-imidazol-1-yl]methyl)-5-(1,2,3-triazol-1-yl-4-carboxylate)-1H-benzimidazole



1. Preparation of 1-Ethyl-2-([2-(2,5-difluorophenyl)-1H-imidazol-1-yl]methyl)-5-azido-1H-benzimidazole

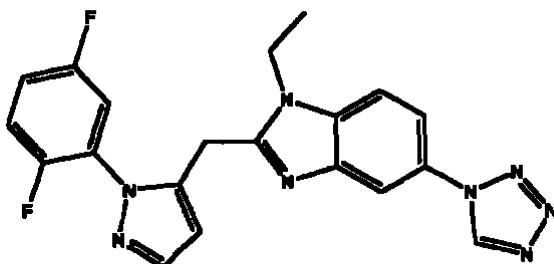
To an ice-cold solution of 1-ethyl-2-([2-(2,5-difluorophenyl)-1H-imidazol-1-yl]methyl)-5-amino-1H-benzimidazole (466 mg) in acetic acid (8 mL) a solution of sodium nitrite (1.1 eq) in water (4 mL) is added dropwise. After stirring at 0°C for 1 h, a solution of sodium azide (1.3 eq) in water (5 mL) is added dropwise. Stirring is continued for 0.5 h at 0°C, and then at room temperature for 0.5 h. The reaction mixture is concentrated to 1/3 volume, water (10 mL) is added and then mixture is then extracted with ethyl acetate (3X). The combined organic layers are washed with aqueous sodium bicarbonate (2X), then washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated to give 641 mg of crude 1-Ethyl-2-([2-(2,5-difluorophenyl)-1H-imidazol-1-yl]methyl)-5-azido-1H-benzimidazole.

2. Preparation of 1-[2-[2-(2,5-Difluoro-phenyl)-imidazol-1-ylmethyl]-1-ethyl-1H-benzimidazol-5-yl]-1H-[1,2,3]triazole-4-carboxylic acid ethyl ester

A mixture of crude 1-ethyl-2-([2-(2,5-difluorophenyl)-1H-imidazol-1-yl]methyl)-5-azido-1H-benzimidazole (143 mg) and ethyl propiolate (1 eq.) in ethanol (10 mL) is heated at reflux for 6 h. The mixture is cooled, concentrated, and the residue purified by preparative silica gel chromatography to give 1-[2-[2-(2,5-Difluoro-phenyl)-imidazol-1-ylmethyl]-1-ethyl-1H-benzimidazol-5-yl]-1H-[1,2,3]triazole-4-carboxylic acid ethyl ester. ¹H NMR (CDCl₃): 8.51s, (1H), 8.05(s, 1H), 7.74(m, 1H), 7.50-7.39(m, 4H), 7.21-7.17(m, 2H), 7.06(s, 1H), 5.54(s, 2H), 4.47(q, 2H), 3.86(q, 2H), 1.43(t, 3H), 1.04(t, 3H), LCMS MH⁺ 460.6.

Example 12

Synthesis of 1-ethyl-2-([2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl)-5-(1,2,3,4-tetrazol-1-yl)-1H-benzimidazole

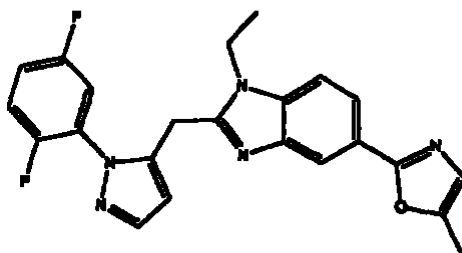


1-Ethyl-2-([2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl)-5-amino-1H-benzimidazole (104 mg) is treated with triethylorthoformate (4 eq) in acetic acid (10 mL) at reflux for 4 h. After concentrating the solution, acetic acid is re-added, sodium azide (4 eq) added, and the mixture heated at 70°C for 3 h. After cooling, water (15 mL) is added and the mixture concentrated. The residue is taken up in ethyl acetate, washed with aqueous sodium bicarbonate (2X) then saturated aqueous sodium chloride, dried (MgSO₄), concentrated, and purified by

preparative silica gel chromatography to give 1-ethyl-2-([2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl)-5-(1,2,3,4-tetrazol-1-yl)-1H-benzimidazole, which is converted to the hydrochloride salt in ethyl acetate. LCMS MH^+ 395.018 .

Example 13

Synthesis of 1-Ethyl-2-([2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl)-5-(5-methyl-oxazol-2-yl)-1H-benzimidazole



1. Preparation of N-propargyl 1-ethyl-2-([2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl)-1H-benzimidazole-5-carboxamide

Oxalyl chloride (2.5 eq of 2M in dichloromethane) is added dropwise to a solution of 1-ethyl-2-([2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl)-1H-benzimidazole-5-carboxylate (368 mg) in DMF (5 drops) and dichloromethane (30 mL) at 0°C. The mixture is stirred at 0°C for 0.5 h, then at room temperature for 1 h. The solution is concentrated, the residue taken up in DMF (30 mL), excess propargylamine added, and the mixture stirred for 6 h. Dilute aqueous sodium bicarbonate is added then extracted with dichloromethane (3X), the combined organic layers washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated to give 462 mg of crude N-propargyl 1-ethyl-2-([2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl)-1H-benzimidazole-5-carboxamide.

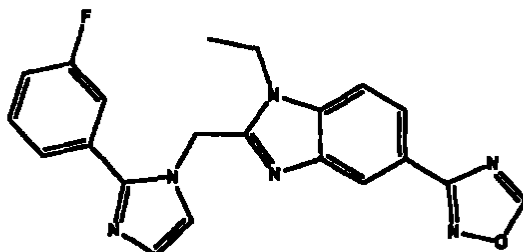
2. Preparation of 1-Ethyl-2-([2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl)-5-(5-methyl-oxazol-2-yl)-1H-benzimidazole

A mixture of crude N-propargyl 1-ethyl-2-([2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl)-1H-benzimidazole-5-

carboxamide (450 mg) and mercury(II) acetate (1 eq) is heated at reflux in acetic acid (15 mL) for 6 h. The mixture is concentrated, saturated aqueous potassium carbonate added and extracted with ethyl acetate (3X). The combined organic layers were washed with water then with saturated aqueous sodium chloride, dried (MgSO₄), concentrated, and triturated with ether to give 1-ethyl-2-([2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl)-5-(5-methyl-oxazol-2-yl)-1H-benzimidazole, which is converted to the hydrochloride salt in ethyl acetate. ¹H NMR (d₆ DMSO): 8.16(s,1H), 8.09-9.01m.(2H), 7.78(m,1H), 7.62(m,1H), 7.49-7.45(m,3H), 7.04(m,1H), 6.56(s,1H), 4.70(s,2H), 4.36(q,2H), 2.41(s,3H), 1.21(t,3H). LCMS MH⁺ 420.5.

Example 14

Synthesis of 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(1,2,4-oxadiazol-3-yl)-1H-benzimidazole

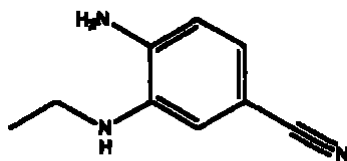


1. Preparation of 1-Ethyl-2-([2-(2,5-difluorophenyl)-1H-imidazol-1-yl]methy-1H-benzimidazol)-5-carboxamide oxime
1-Ethyl-2-([2-(3-fluorophenyl)-1H-imidazol-1-yl]methyl)-5-cyano-1H-benzimidazole (340 mg) is added to a solution of hydroxylamine hydrochloride (137 mg, 2eq) and triethylamine (0.3 mL, 2.2 eq) in methanol (3 mL), then heated at reflux for 2.5 h. The reaction is cooled, concentrated, water added, the solid collected and rinsed well with water and dried to give 305 mg of 1-Ethyl-2-([2-(2,5-difluorophenyl)-1H-imidazol-1-yl]methy-1H-benzimidazol)-5-carboxamide oxime.

2. Preparation of 1-Ethyl-2-([2-(2,5-difluorophenyl)-1H-imidazol-1-yl]methy-1H-benzimidazol)-5-carboxamide oxime
1-Ethyl-2-([2-(3-fluorophenyl)-1H-imidazol-1-yl]methy-1H-benzimidazol)-5-carboxamide oxime (161 mg) is treated with triethylorthoformate (3 mL) and boron trifluoride-THF complex (0.1 mL) at 100°C for 2.5 h. 1N HCl (0.5 mL) is added to the hot mixture; the reaction is then cooled and concentrated. After cooling in an ice bath, aqueous sodium hydroxide is added. The solid is collected, rinsed with water, then ether and dried to give 146 mg of 1-Ethyl-2-([2-(2,5-difluorophenyl)-1H-imidazol-1-yl]methy-1H-benzimidazol)-5-carboxamide oxime, which is converted to the methanesulfonate salt in acetone. Mp 183-186°C.

Example 15

Synthesis of 4-amino-3-ethylaminobenzonitrile



1. 4-nitro-3-chlorobenzonitrile

To an ice cold solution of 4-amino-3-chlorobenzonitrile (1 g, 6.6 mmol) in concentrated HCl (2.5 mL) plus water (2.5 mL) a chilled solution of sodium nitrite (0.74 g, 1.62 eq) in water (3.6 mL) is added dropwise to maintain the reaction temperature <0°C. After stirring at 0°C for 10 min, the mixture is added portion-wise to an ice cold solution of sodium nitrite (3.29 g, 7.22 eq) and copper(I) oxide (349 mg, 0.37 eq) in water 14.5 mL). Stirring is continued at 0°C for 40 min, and then at room temperature for 0.5 h. The reaction mixture is extracted with dichloromethane (2X), the combined organic layers washed with saturated aqueous sodium chloride, dried (MgSO₄), concentrated, and purified by silica gel chromatography to give 0.80 g of 4-nitro-3-chlorobenzonitrile.

^1H NMR (CDCl_3): 7.96 (d, $J = 8.24$ Hz, 1H), 7.88 (d, $J = 1.65$ Hz, 1H), 7.63 (dd, $J = 1.65, 8.24$ Hz, 1H).

2. Preparation of 4-Ethylamino-3-chloro benzonitrile

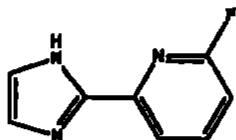
A mixture of 4-nitro-3-chlorobenzonitrile (0.74 g, 4.1 mmol), potassium carbonate (1.68 g, 12.2 mmol), and ethylamine (4 mL, 2M in THF) in DMF (2 mL) is stirred at ambient temperature for 3 h. Additional ethylamine (2.1 mL, 2M in THF) is added, the flask stoppered, and stirring continued an additional 15.5 h. Water (50 mL) is added and extracted 2X with ethyl acetate (50 mL), and the combined organic layers are washed with water, then brine, dried (MgSO_4), and concentrated to give a mixture of 3-Ethylamine-4-nitrobenzonitrile and 4-Ethylamino-3-chloro benzonitrile which was carried forward without purification.

3. Preparation of 4-Amino-3-ethylaminobenzonitrile

To a suspension of crude 4-ethylamino-3-chloro benzonitrile (above) in conc. HCl (4 mL) tin(II) chloride dihydrate (3.16 g) is added. After stirring at ambient temperature for 1.5 h, the mixture is poured onto ice and the solution made alkaline with 10 N aq. NaOH. The aqueous solution is extracted 2X with dichloromethane, and the combined organic layers washed with brine, dried (MgSO_4), and concentrated. Trituration with ether affords 4-Amino-3-ethylaminobenzonitrile as a white solid. ^1H NMR (CDCl_3): 7.00 (dd, $J = 1.65, 7.97$ Hz, 1H), 6.83 (d, $J = 1.65$ Hz, 1H), 6.67 (d, $J = 7.97$ Hz, 1H), 3.13 (q, $J = 7.14$ Hz, 1.31 (t, $J = 7.14$ Hz, 3H).

Example 16

Synthesis of 2-Fluoro-6-(1H-imidazol-2-yl)-pyridine



1. Preparation of 2-Fluoropyridine-6-carboxaldehyde

Method A

2-Fluoro-6-methylpyridine (14.4 g, 0.13 mol) and tert-butoxybis(dimethylamino)methane (Bredereck's reagent; 34.9 g, 0.20 mol) are heated at 140 °C for 24 h. The reaction is cooled and diluted with THF (100 mL). Sodium periodate (75 g) in water (400 mL) is added at 0-5 °C, and the reaction mixture is then stirred for 24 h at room temperature. The precipitate is filtered through celite, and the filtrate extracted 5X with diethyl ether. The combined ether layers are washed with water, brine, and dried (MgSO₄). Most of the solvent is removed by concentration at 0 °C (by keeping ice in the bath) to provide 2-Fluoropyridine-6-carboxaldehyde.

Method B

2-Fluoropyridine-6-carboxaldehyde can also be prepared as follows: To a solution of diisopropylamine (6.54 mL, 1.2 equiv) in 30 mL of THF at 0 °C a solution of n-butyllithium (17.1 mL, 2.5M in hexanes) is added dropwise. Stirring is continued for 15 minutes at 0 °C, the reaction is then cooled to -78 °C. 2-Fluoro-6-methylpyridine (4.00 mL, 38.9 mmol) is added dropwise to the cold solution. The reaction mixture is stirred at -78 °C for 1 h and then quenched with DMF (4.52 mL, 1.5 equiv). The reaction is maintained at -78 °C for 30 minutes and then warmed to 0 °C. The cold solution is added to a mixture of sodium periodate (24.9 g) in 120 mL of water at 0 °C. The reaction mixture is allowed to gradually warm to room temperature over 1 h and then stirred at room temperature for 24 h. The reaction mixture is filtered through a plug of celite to remove the precipitate and the plug is washed with ether. The organic layer is separated, washed with aqueous sodium bicarbonate (1 x 40 mL), then with 0.25M KH₂PO₄ (1 x 40 mL) and then brine (1 x 40 mL). The organic solution is dried (NaSO₄) and concentrated in vacuo.

2. Preparation of 2-Fluoro-6-(1H-imidazol-2-yl)-pyridine

670
671

To a solution of the crude aldehyde from step 1, Method B (above) in methanol (12 mL) aqueous glyoxal (6.21 mL, 40 wt.% in water) is added dropwise. The solution is cooled to 0 °C and aqueous ammonium hydroxide (6.0 mL, 28 wt.% in water) is added. The reaction is allowed to warm to room temperature gradually over about an hour and then stirred another 3 h at room temperature. Most of the methanol is removed in vacuo, the reaction mixture diluted with water (10 mL) and extracted with ethyl acetate (30 mL). The organic layer is washed with brine (20 mL), diluted with hexanes (15 mL), passed through a plug of silica gel (1/4 inch deep x 1 1/4 inch diameter), and the plug washed with more 2:1 ethyl acetate/hexanes (20 mL). The combined eluents are concentrated in vacuo to crude 1.98 g of 2-Fluoro-6-(1H-imidazol-2-yl)-pyridine.

Example 17

Synthesis of 2-Fluoro-6-(1H-imidazol-2-yl)-pyridine acetic acid

1. Preparation of [2-(6-fluoropyridin-2-yl)-imidazol-1-yl]acetic acid tert-butyl ester

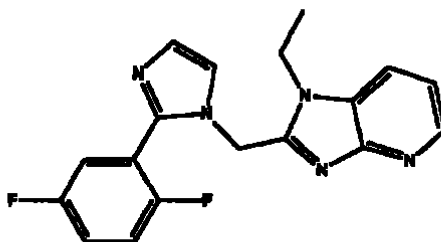
A mixture of 2-Fluoro-6-(1H-imidazol-2-yl)pyridine (410mg; 2.51mmol), tert-butyl bromoacetate (539mg; 2.76mmol), potassium carbonate (520mg; 3.77mmol), and N,N-dimethylformamide (20mL) is stirred at room temperature for 16h. Water (60mL) is added and the mixture extracted with ethyl acetate (3 x 70mL). The organic extracts are washed with water (3 x 40mL) and brine (1 x 40mL), dried (MgSO₄), and concentrated to give [2-(6-Fluoropyridin-2-yl)-imidazol-1-yl]acetic acid tert-butyl ester as an orange oil (630mg). ¹H NMR (CDCl₃) 8.12 (dd,1H), 7.82(q,1H), 7.16(s,1H), 6.98(s,1H), 6.81(dd,1H), 5.14(s,2H), 1.44s,(9H), LCMS: 276.1(M⁺).

2. Preparation of 2-Fluoro-6-(1H-imidazol-2-yl)-pyridine acetic acid

A solution of [2-(6-fluoropyridin-2-yl)-imidazol-1-yl]acetic acid tert-butyl ester (630mg; 2.27mmol) and trifluoroacetic acid (4mL) in dichloromethane (4mL) is stirred at room temperature for 5hr. The reaction mixture is concentrated. The residue is treated with 3M HCl in ethyl acetate (10mL) and the suspension stirred at room temperature for 1hr. The precipitate is collected, washed with ethyl acetate, and dried to give 2-Fluoro-6-(1H-imidazol-2-yl)-pyridine acetic acid as a tan solid (581mg), ^1H NMR (d_6 DMSO) 8.35-8.26(m, 2H), 7.83(s, 1H), 7.76(s, 1H), 7.44-7.41(m, 1H), 5.40(s, 2H). LCMS: 222.1(MH^+).

Example 18

Synthesis of 2-([2-(2,5-di-fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-1H-imidazo[4,5-b]pyridine



1. Preparation of 3-ethylamino-2-nitro-pyridine

Ice cold ethylamine (0.55 mL) was added to a solution of 3-fluoro-2-nitropyridine (400 mg, 2.8 mmol; prepared according to N. Plé and G. Quéguiner, *J. Heterocyclic Chem*, 1989, 26, 475-476) in 2:1 DMF:THF (6mL) at ambient temperature, and the mixture stirred for 0.75 h. Water was added, then extracted 2X with ethyl acetate. The combined organic layers were washed with water then with saturated aqueous sodium chloride, dried (MgSO_4), and concentrated to give 404 mg of 3-ethylamino-2-nitro-pyridine as a gold solid. ^1H NMR (CDCl_3): 7.87 (d, 1H), 7.43 (dd, 1H), 7.35 (d, 1H), 3.38 (pentet, 2H), 1.4 (t, 3H). LCMS: 121.1($\text{MH}^+ - \text{NO}_2$).

2. Preparation of 2-Amino-3-ethylaminopyridine

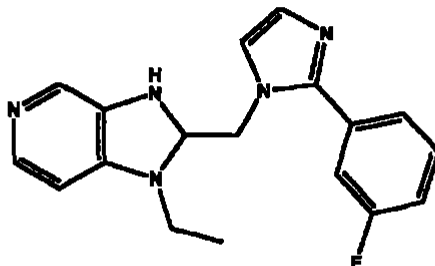
A mixture of 3-ethylamino-2-nitro-pyridine (400 mg), 10% palladium on carbon (40 mg) and 1:1 ethyl acetate:methanol (30 mL) were placed in a Parr apparatus under hydrogen (50 psi) for 50 min. The mixture was filtered through Celite, concentrated, and the product triturated with hexane to give 0.2 g of 2-Amino-3-ethylaminopyridine as a brown solid. More material was recovered from the filtrate. ^1H NMR (CDCl_3): 7.59 (d, $J = 4.94$ Hz, 1H), 6.81 (d, $J = 6.32$ Hz, 1H), 6.71 (dd, $J = 4.94, 7.69$ Hz, 1H), 3.12 (q, $J = 7.14$ Hz, 2H), 1.31 (t, $J = 7.14$ Hz, 3H).

3. Preparation of 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-1H-imidazo[4,5-b]pyridine

2-Amino-3-ethylaminopyridine (60 mg, 0.43 mmol) and methyl 1-carboxymethyl-2-(2,5-difluorophenyl)-imidazole (193 mg, 0.76 mmol) were used according to Example 1 Method B to prepare 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-1H-imidazo[4,5-b]pyridine, which is converted to the hydrochloride salt in ethyl acetate. m.p. 214-216 °C. LCMS MH^+ 322.2, MH^- 320.3.

Example 19

Synthesis of 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-3H-imidazo[4,5-c]pyridine



1. Preparation of 3-Chloro-4-nitropyridine N-oxide

Aqueous hydrogen peroxide (30 mL of 30%) is added dropwise to an ice cold mixture of 3-chloropyridine (6.0 g, 53 mmol) in acetic anhydride (30 mL). The mixture is allowed to stir at ambient temperature for 24 h, water is then added and the mixture

concentrated. The residue is taken up in concentrated sulfuric acid (10 mL) and fuming sulfuric acid (5 mL), and then cooled to 0°C. Concentrated nitric acid (24 mL) is added slowly, and the ice bath removed. The reaction is then heated at reflux for 2 h, cooled, and poured into ice water. Ammonium bicarbonate is added carefully until pH 8 is achieved, the solution is then extracted with dichloromethane. The organic layer is washed with water, dried (NaSO₄), and concentrated to give 2.93 g of 3-Chloro-4-nitropyridine N-oxide as a yellow solid. ¹H NMR (CDCl₃): 8.47 (d, J = 4 Hz, H), 8.35 (dd, J = 5, 12 Hz, 1H), 7.73 (ddd, J = 4, 9, 12 Hz, 1H).

2. Preparation of 3-Ethylamino-4-nitro-3-pyridine N-oxide

To an ice cold solution of 3-chloro-4-nitropyridine N-oxide (2.93 g, 16.8 mmol) in ethanol (30 mL) ethylamine (25 mL of 2M in THF) is added. The mixture is allowed to stir overnight at ambient temperature, then concentrated in vacuo to afford crude 3-Ethylamino-4-nitro-3-pyridine N-oxide as a yellow oil. ¹H NMR (CDCl₃): 8.01 (d, J = 7 Hz, H), 7.91 (s, 1H), 7.45 (d, J = 7 Hz, 1H), 3.31 (q, J = 7 Hz, 2H), 1.40 (t, J = 7 Hz, 3H).

3. Preparation of 3-Ethylamino-4-aminopyridine

Crude 3-ethylamino-4-nitro-3-pyridine N-oxide and 10% palladium on carbon (1 g) in methanol (30 mL) are placed in a Parr apparatus under hydrogen (60 psi) for 2 days. Additional 10% palladium on carbon (880 mg) is added and returned under hydrogen (60 psi) for 2 days. The mixture was filtered through Celite, concentrated, and the product triturated with hexane-ether to afford 1.3 g of 3-Ethylamino-4-aminopyridine. ¹H NMR (d6-DMSO): 7.63 (d, J = 6 Hz, 1H), 7.47 (s, 1H), 6.57 (d, J = 6 Hz, 1H), 3.05 (q, J = 7 Hz, 2H), 1.21 (t, J = 7 Hz, 3H).

4. Preparation of 2-{[2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl}-1-ethyl-3H-imidazo[4,5-c]pyridine

3-Ethylamino-4-aminopyridine (548 mg, 3.99 mmol) and methyl 1-carboxymethyl-2-(3-fluorophenyl)-imidazole (467 mg, 1.99 mmol)

were used according to Example 1 Method B to prepare 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-3H-imidazo[4,5-c]pyridine (193 mg). ¹H NMR (CDCl₃): 1.08(t, J = 7 Hz, 3H), 3.89(q, J = 7 Hz, 2H), 5.52(s, 2H), 7.04(s, 1H), 7.16-7.20(m, 2H), 7.37-7.50(m, 3H), 7.68(d, J = 6 Hz, 1H), 8.47(d, J = 6 Hz, 1H), 8.78(s, 1H).

Example 20

The following compounds are prepared essentially according to the procedures described in Examples 1-19:

(a) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-1H-benzimidazole. 7.78 (m, 1H), 7.38 (m, 1H), 7.17-7.31 (m, 6H), 7.03 (d, 1H), 5.36 (s, 2H), 3.73 (t, 2H), 1.44 (m, 2H), 0.76 (t, 3H).

(b) 2-([2-(2-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-1H-benzimidazole. 7.78 (m, 1H), 7.66 (m, 1H), 7.51 (m, 1H), 7.23-7.37 (m, 5H), 7.17 (d, 1H), 7.03 (d, 1H), 5.35 (s, 2H), 3.68 (t, 2H), 1.40 (m, 2H), 0.72 (t, 3H).

(c) 2-([2-(3-Trifluoromethylphenyl)-1H-imidazol-1-yl]methyl)-1-propyl-1H-benzimidazole. ¹H NMR (CDCl₃): 7.61-8.00 (m, 5H), 7.09-7.31 (m, 5H), 5.47 (s, 2H), 3.69 (t, 2H), 1.43 (m, 2H), 0.73 (t, 3H).

(d) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-1H-benzimidazole. ¹H NMR (CDCl₃): 7.79 (m, 1H), 7.69 (m, 1H), 7.44-7.58 (m, 3H), 7.27-7.30 (m, 3H), 7.14 (d, 1H), 7.07 (d, 1H), 5.49 (s, 2H), 3.69 (t, 2H), 1.42 (m, 2H), 0.75 (t, 3H).

(e) 2-([2-(3-Chloro-4-fluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-1H-benzimidazole. ¹H NMR (CDCl₃): 7.76-7.81 (m, 2H),

7.56 (m, 1H), 7.25-7.32 (m, 4H), 7.14 (d, 1H), 7.05 (d, 1H), 5.46 (s, 2H), 3.74 (t, 2H), 1.47 (m, 2H), 0.78 (t, 3H).

(f) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-1H-benzimidazole. ^1H NMR (CDCl_3): 7.80 (m, 1H), 7.41-7.53 (m, 3H), 7.29-7.31 (m, 3H), 7.14-7.22 (m, 2H), 7.06 (d, 1H), 5.51 (s, 2H), 3.69 (t, 2H), 1.43 (m, 2H), 0.74 (t, 3H).

(g) 2-([2-(4-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-1H-benzimidazole. ^1H NMR (CDCl_3): 7.80 (m, 1H), 7.65-7.69 (m, 2H), 7.18-7.32 (m, 5H), 7.13 (d, 1H), 7.04 (d, 1H), 5.47 (s, 2H), 3.68 (t, 2H), 1.42 (m, 2H), 0.74 (t, 3H).

(h) 2-(4-Methyl-2-phenyl-imidazol-1-ylmethyl)-1-propyl-1H-benzimidazole. ^1H NMR (CDCl_3): 7.80 (m, 1H), 7.25-7.67 (m, 8H), 6.74 (q, 1H), 5.43 (s, 2H), 3.62 (t, 2H), 2.20 (d, 3H), 1.38 (m, 2H), 0.69 (t, 3H).

(i) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.40 (dd, 1H), 8.05 (dd, 1H), 7.38 (m, 1H), 7.17-7.28 (m, 4H), 7.08 (d, 1H), 5.39 (s, 2H), 3.89 (t, 2H), 1.50 (m, 2H), 0.79 (t, 3H).

(j) 2-([2-(3-Trifluoromethylphenyl)-1H-imidazol-1-yl]methyl)-1-propyl-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.40 (dd, 1H), 7.60-8.07 (m, 5H), 7.21-7.26 (m, 2H), 7.11 (d, 1H), 5.49 (s, 2H), 3.89 (t, 2H), 1.51 (m, 2H), 0.76 (t, 3H).

(k) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.40 (dd, 1H), 8.06 (dd, 1H), 7.68 (m, 1H), 7.43-7.56 (m, 3H), 7.26 (m, 1H), 7.18 (d, 1H), 7.09 (d, 1H), 5.50 (s, 2H), 3.89 (t, 2H), 1.52 (m, 2H), 0.79 (t, 3H).

(l) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.40 (dd, 1H), 8.06 (dd, 1H), 7.39-7.50 (m, 3H), 7.15-7.29 (m, 3H), 7.08 (d, 1H), 5.52 (s, 2H), 3.88 (t, 2H), 1.51 (m, 2H), 0.77 (t, 3H).

(m) 2-([2-(2-Phenyl-4-methyl-1H-imidazol-1-yl]methyl)-1-propyl-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.39 (dd, 1H), 8.06 (dd, 1H), 7.63-7.65 (m, 2H), 7.45-7.55 (m, 3H), 7.26 (m, 1H), 6.77 (q, 1H), 5.46 (s, 2H), 3.82 (t, 2H), 2.23 (d, 3H), 1.46 (m, 2H), 0.73 (t, 3H).

(n) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-methyl-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.40 (dd, 1H), 8.03 (dd, 1H), 7.36 (m, 1H), 7.15-7.27 (m, 4H), 7.03 (d, 1H), 5.41 (s, 2H), 3.51 (s, 3H).

(o) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-methyl-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.40 (dd, 1H), 8.05 (dd, 1H), 7.40-7.51 (m, 3H), 7.13-7.29 (m, 3H), 7.02 (d, 1H), 5.53 (s, 2H), 3.51 (s, 3H).

(p) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-isobutyl-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.38 (dd, 1H), 8.04 (dd, 1H), 7.38 (m, 1H), 7.16-7.27 (m, 4H), 7.09 (d, 1H), 5.38 (s, 2H), 3.73 (d, 2H), 1.98 (m, 1H), 0.72 (d, 6H).

(q) 2-([2-(3-Trifluoromethylphenyl)-1H-imidazol-1-yl]methyl)-1-isobutyl-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.39 (dd, 1H), 7.60-8.07 (m, 5H), 7.21-7.26 (m, 2H), 7.12 (d, 1H), 5.49 (s, 2H), 3.71 (d, 2H), 1.98 (m, 1H), 0.69 (d, 6H).

(r) 2-([2-(3-Trifluoromethylphenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.40 (dd, 1H), 7.60-8.06 (m 5H), 7.21-7.28 (m, 2H), 7.09 (d, 1H), 5.49 (s, 2H), 4.01 (q, 2H), 1.09 (t, 3H).

(s) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.40 (dd, 1H), 8.06 (dd, 1H), 7.67 (m, 1H), 7.43-7.57 (m, 3H), 7.26 (m, 1H), 7.19 (d, 1H), 7.08 (d, 1H), 5.51 (s, 2H), 4.00 (q, 2H), 1.09 (t, 3H).

(t) 2-([2-(3-Fluorophenyl)-4-methyl-1H-imidazol-1-yl]methyl)-1-ethyl-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.39 (dd, 1H), 8.06 (dd, 1H), 7.38-7.50 (m, 3H), 7.12-7.29 (m, 2H), 6.77 (q, 1H), 5.46 (s, 2H), 3.98 (q, 2H), 2.22 (d, 3H), 1.08 (t, 3H).

(u) 2-([2-(3-Trifluoromethylphenyl)-1H-imidazol-1-yl]methyl)-1-cyclopropylmethyl-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.39 (dd, 1H), 7.60-8.03 (m, 5H), 7.21-7.26 (m, 2H), 7.11 (d, 1H), 5.51 (s, 2H), 3.84 (d, 2H), 0.70 (m, 1H), 0.44 (m, 2H), 0.24 (m, 2H).

(v) 1-Cyclopropylmethyl-2-([2-(2,5-difluorophenyl)-imidazol-1-yl]methyl)-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.37 (dd, 1H), 8.04 (dd, 1H), 7.38 (m, 1H), 7.09-7.28 (m, 4H), 7.09 (d, 1H), 5.42 (s, 2H), 3.83 (d, 2H), 0.68 (m, 1H), 0.38-0.43 (m, 2H), 0.24-0.29 (m, 2H).

(w) 1-Cyclopropylmethyl-2-[2-(2,5-difluorophenyl)-4-methyl-imidazol-1-yl]methyl)-1H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.38 (dd, 1H), 8.04 (dd, 1H), 7.40 (m, 1H), 7.15-7.27 (m, 3H), 6.79 (d, 1H), 5.35 (s, 2H), 3.82 (d, 2H), 2.22 d, 3H), 0.75 (m, 1H), 0.39-0.44 (m, 2H), 0.23-0.28 (m, 2H).

(x) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-cyclopropylmethyl-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.39 (dd, 1H), 8.06 (dd, 1H), 7.68 (m, 1H), 7.40-7.68 (m, 3H), 7.27 (m, 1H), 7.18 (d, 1H), 7.10 (d, 1H), 5.53 (s, 2H), 3.83 (d, 2H), 0.73 (m, 1H), 0.40-0.46 (m, 2H), 0.24-0.28 (m, 2H).

(y) 2-([2-(2,5-Difluorophenyl)-4-methyl-1H-imidazol-1-yl]methyl)-1-(2,2,2-trifluoroethyl)-3H-imidazo[4,5-b]pyridine. LCMS MH^+ 394.2.

(z) 2-([2-(3-Trifluoromethylphenyl)-4-methyl-1H-imidazol-1-yl]methyl)-1-(2,2,2-trifluoroethyl)-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 8.44 (dd, 1H), 8.07 (dd, 1H), 7.54-7.89 (m, 4H), 7.24-7.34 (m, 2H), 7.12 (d, 1H), 5.51 (s, 2H), 4.51 (q, 2H).

(aa) 2-([2-(3-Chlorophenyl)-4-methyl-1H-imidazol-1-yl]methyl)-1-(2,2,2-trifluoroethyl)-3H-imidazo[4,5-b]pyridine. LCMS MH^+ 392.2.

(bb) 2-([2-(3-Fluorophenyl)-4-methyl-1H-imidazol-1-yl]methyl)-1-(2,2,2-trifluoroethyl)-3H-imidazo[4,5-b]pyridine. LCMS MH^+ 376.2.

(cc) 2-([2-(3-Trifluoromethylphenyl)-1H-imidazol-1-yl]methyl)-1-propyl-6-chloro-3H-imidazo[4,5-b]pyridine. ^1H NMR (CDCl_3): 7.60-7.97 (m, 5H), 7.22-7.27 (m, 2H), 7.09 (d, 1H), 5.45 (s, 2H), 3.85 (t, 2H), 1.51 (m, 2H), 0.76 (t, 3H).

(dd) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-cyclopropylmethyl-5-chloro-1H-benzimidazole. ^1H NMR (CDCl_3): 7.68 (d, 1H), 7.38 (m, 1H), 7.32 (d, 1H), 7.19-7.28 (m, 4H), 7.04 (d, 1H), 5.36 (d, 2H), 3.62 (d, 2H), 0.65 (m, 1H), 0.46-0.51 (m, 2H), 0.07-0.11 (m, 2H).

(ee) 2-([2-(3-Trifluoromethylphenyl)-1H-imidazol-1-yl]methyl)-1-cyclopropylmethyl-5-chloro-1H-benzimidazole. ^1H NMR (CDCl_3): 7.60-7.96 (m, 5H), 7.05-7.31 (m, 4H), 5.45 (s, 2H), 3.58 (d, 2H), 0.65 (m, 1H), 0.47 (m, 2H), 0.05 (m, 2H).

(ff) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-cyclopropylmethyl-5-chloro-1H-benzimidazole. ^1H NMR (CDCl_3): 7.67-7.71 (m, 2H), 7.42-7.56 (m, 3H), 7.24-7.33 (m, 2H), 7.15 (d, 1H), 7.06 (d, 1H), 5.47 (s, 2H), 3.58 (d, 2H), 0.69 (m, 1H), 0.47-0.53 (m, 2H), 0.03-0.09 (m, 2H).

(gg) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-5-chloro-1H-benzimidazole. ^1H NMR (CDCl_3): 7.67 (d, 1H), 7.37 (m, 1H), 7.17-7.29 (m, 5H), 7.02 (d, 1H), 5.34 (s, 2H), 3.69 (t, 2H), 1.43 (m, 2H), 0.77 (t, 3H).

(hh) 2-([2-(2-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-5-chloro-1H-benzimidazole. ^1H NMR (CDCl_3): 7.62-7.69 (m, 2H), 7.51 (m, 1H), 7.22-7.34 (m, 4H), 7.18 (d, 1H), 7.02 (d, 1H), 5.34 (s, 2H), 3.64 (t, 2H), 1.40 (m, 2H), 0.73 (t, 3H).

(ii) 2-([2-(3-Chloro-4-fluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-6-chloro-1H-benzimidazole. ^1H NMR (CDCl_3): 7.75 (dd, 1H), 7.69 (dd, 1H), 7.55 (m, 1H), 7.24-7.30 (m, 3H), 7.15 (d, 1H), 7.03 (d, 1H), 5.43 (s, 2H), 3.71 (t, 2H), 1.47 (m, 2H), 0.79 (t, 3H).

(jj) 2-([2-(3-Fluorophenyl)-4-chloro-1H-imidazol-1-yl]methyl)-1-propyl-6-chloro-1H-benzimidazole. ^1H NMR (CDCl_3): 7.70 (d, 1H), 7.37-7.50 (m, 3H), 7.17-7.32 (m, 3H), 6.96 (s, 1H), 5.43 (s, 2H), 3.70 (t, 2H), 1.49 (m, 2H), 0.77 (t, 3H).

(kk) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-6-chloro-1H-benzimidazole. ¹H NMR (CDCl₃): 7.69 (d, 1H), 7.38-7.52 (m, 3H), 7.15-7.29 (m, 4H), 7.04 (d, 1H), 5.48 (s, 2H), 3.65 (t, 2H), 1.42 (m, 2H), 0.75 (t, 3H).

(ll) 2-([2-(4-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-6-chloro-1H-benzimidazole. ¹H NMR (CDCl₃): 7.62-7.70 (m, 3H), 7.13-7.28 (m, 5H), 7.02 (d, 1H), 3.64 (t, 2H), 1.41 (m, 2H), 0.75 (t, 3H).

(mm) 2-([2-(2-Phenyl-4-methyl-1H-imidazol-1-yl]methyl)-1-propyl-6-chloro-1H-benzimidazole. ¹H NMR (CDCl₃): 7.62-7.71 (m, 3H), 7.45-7.53 (m, 3H), 7.23-7.27 (m, 2H), 6.74 (q, 1H), 5.42 (s, 2H), 3.59 (t, 2H), 2.21 (d, 3H), 1.37 (m, 2H), 0.70 (t, 3H).

(nn) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-6-chloro-1H-benzimidazole. ¹H NMR (CDCl₃): 7.69 (d, 1H), 7.39-7.51 (m, 3H), 7.16-7.30 (m, 4H), 7.03 (d, 1H), 5.49 (s, 2H), 3.75 (q, 2H), 0.98 (t, 3H).

(oo) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-6-chloro-1H-benzimidazole. ¹H NMR (CDCl₃): 7.67 (d, 1H), 7.37 (m, 1H), 7.17-7.30 (m, 5H), 7.01 (d, 1H), 5.35 (s, 2H), 3.79 (q, 2H), 0.99 (t, 3H).

(pp) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-6-chloro-1H-benzimidazole. ¹H NMR (CDCl₃): 7.67-7.71 (m, 2H), 7.45-7.56 (m, 3H), 7.24-7.30 (m, 2H), 7.16 (d, 2H), 7.04 (d, 1H), 5.47 (s, 2H), 3.76 (q, 2H), 0.99 (t, 3H).

(qq) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-6-cyano-1H-benzimidazole. LCMS MH⁺ 346.2, MH⁻ 344.3.

(rr) 2-([2-(3-Cyanophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-methylsulfonyl-1H-benzimidazole. LCMS 406.3 (MH⁺), 404.3 (MH⁻).

(ss) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-trifluoromethylsulfonyl-1H-benzimidazole. LCMS: MH⁺ 453.8, MH⁻ 451.2.

(tt) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-trifluoromethoxy-1H-benzimidazole. ¹H NMR (CDCl₃): 7.65 (s, 1H), 7.18-7.41 (m, 6H), 7.06 (s, 1H), 5.35 (s, 2H), 3.82 (q, 2H), 1.0 (t, 3H).

(uu) 2-([2-(3-Cyanophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-trifluoromethoxy-1H-benzimidazole LCMS: MH⁺ 412.2, MH⁻ 410.2.

(vv) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-nitro-1H-benzimidazole. Hydrochloride ¹H NMR (d6 DMSO): 8.42 (1H, d), 8.17 (1H, dd), 8.00 (1H, s), 7.90 (1H, s), 7.85 (1H, d), 7.70 (1H, m), 7.56-7.51 (2H, m), 5.90 (2H, s), 4.31 (2H, q), 1.24 (3H, t), LCMS MH⁺ 384.1.

(ww) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-nitro-1H-benzimidazole. LCMS MH⁺ 381.95.

(xx) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-nitro-1H-benzimidazole. Hydrochloride ¹H NMR (d6 DMSO): 8.47 (1H, d), 8.19 (1H, dd), 8.00 (1H, m), 7.96 (1H, m), 7.88 (1H, d), 7.71-7.50 (4H, m), 5.98 (2H, s), 4.35 (2H, q), 1.30 (3H, t), LCMS MH⁺ 366.2.

(yy) 2-([2-(2-Pyrid-2-yl-1H-imidazol-1-yl]methyl)-1-ethyl-5-nitro-1H-benzimidazole. LCMS: MH⁺ 349.1.

(zz) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(1,2,4-triazol-4-yl)-1H-benzimidazole. Hydrochloride ¹H NMR (d6 DMSO): 9.57(2H, s), 8.11(1H, m), 8.01-7.99(1H, m), 7.86(1H, d), 7.78-7.74(1H, m), 7.66-7.52(3H, m), 5.95(2H, s), 4.31(2H, q), 1.26(3H, t), LCMS MH⁺ 406.5.

(aaa) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(1,2,4-triazol-4-yl)-1H-benzimidazole. LCMS 388.2 (MH⁺).

(bbb) 2-([2-(2-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole. (L)-Tartrate salt ¹H NMR (CD₃OD): 7.07-7.58 (m, 9H), 5.53 (s, 2H), 4.51 (s, 2H), 4.03 (q, 2H), 1.07 (t, 3H).

(ccc) 2-([2-(3-Pyrid-2-ylphenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole. LCMS MH⁺ 398.18.

(ddd) 2-([2-(3-Bromophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole. Hydrochloride ¹H NMR (d6-DMSO): 7.41-8.00 (m, 8H), 7.18 (m, 1H), 5.92 (s, 2H), 4.28 (q, 2H), 1.27 (t, 3H).

(eee) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole. (L)-Tartrate salt ¹H NMR (CD₃OD): 7.08-7.60 (m, 9H), 5.66 (s, 2H), 4.51 (s, 2H), 4.12 (s, 2H), 1.18 (t, 3H).

(fff) 2-([2-(3-Cyanophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole. LCMS MH⁺ 346.11.

(ggg) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-5-fluoro-1H-benzimidazole. ¹H NMR (CDCl₃): 7.43 (m, 1H),

7.37 (m, 1H), 7.19-7.25 (m, 4H), 7.03-7.10 (m, 2H), 5.35 (s, 2H), 3.82 (q, 2H), 1.00 (t, 3H).

(hhh) 2-([2-(3-Carboxyphenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole. LCMS MH⁺ 364.10.

(iii) 2-([2-(3-Methylphenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole.

(jjj) 2-([2-(3-Methoxyphenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole. LCMS MH⁺ 351.15.

(kkk) 2-([2-(3-Fluoro-4-hydroxyphenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole. LCMS MH⁺ 355.12.

(lll) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-6-chloro-1H-benzimidazole. LCMS MH⁺ 380.4, MH⁻ 378.2.

(mmm) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5,6-dicyano-1H-benzimidazole. LCMS MH⁺ 371.0.

(nnn) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-5-cyano-1H-benzimidazole. LCMS 378.2 (MH⁺).

(ooo) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-5-cyano-1H-benzimidazole. LCMS 376.2 (MH⁺), 374.2 (MH⁻).

(ppp) 2-([2-(3-Chloro-4-fluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-5-cyano-1H-benzimidazole. LCMS 394.4 (MH⁺), 392.1 (MH⁻).

(qqq) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-5-cyano-1H-benzimidazole. LCMS 360.2 (MH⁺), 358.2 (MH⁻).

(rrr) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. ^1H NMR (CDCl_3): 8.09 (d, 1H), 7.56 (m, 1H), 7.33-7.40 (m, 2H), 7.16-7.24 (m, 3H), 7.04 (d, 1H), 5.41 (s, 2H), 3.89 (q, 2H), 1.03 (t, 3H).

(sss) 2-([2-(2-Fluoro-5-bromophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. LCMS MH^+ 425.98.

(ttt) 2-([2-(3,4-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. LCMS MH^+ 379.11.

(uuu) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. 8.00 (s, 1H), 7.38-7.72 (m, 7H), 7.24 (s, 1H), 5.71 (s, 2H), 4.50 (s, 2H), 4.20 (q, 2H), 1.22 (t, 3H).

(vvv) 2-([2-(3-Cyanophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. LCMS MH^+ 353.15.

(www) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. LCMS 346.3 (MH^+), 344.2 (MH^-).

(xxx) 2-([2-(2-Pyrid-3-yl-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. Dihydrochloride ^1H NMR (d_6 DMSO): 8.96(1H, s), 8.82 (1H, d), 8.24(1H, d), 8.14(1H, s), 8.05(1H, d), 7.98(1H, d), 7.85(1H, d), 7.69-7.65(2H, m), 6.01(2H, s), 4.33(2H, q), 1.29(3H, t).

(yyy) 2-([2-(2-Pyrid-2-yl-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. Dihydrochloride ^1H NMR (d_6 DMSO): 8.55(1H, d), 8.41 (1H, d), 8.10-7.98(4H, m), 7.85(1H, d), 7.64(1H, d), 7.54-7.51(1H, m), 6.39 (2H, s), 4.45(2H, q), 1.41(3H, t), LCMS MH^+ 329.4.

(zzz) 2-([2-(3-Nitrophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. LCMS MH^+ 373.15.

(aaaa) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-chloro-1H-benzimidazole. ^1H NMR ($CDCl_3$): 7.75 (d, 1H), 7.37 (m, 1H), 7.20-7.27 (m, 5H), 7.02 (d, 1H), 5.36 (s, 2H), [0.99 T, 3H], 3.82 (q, 2H).

(bbbb) 2-([2-(3-Bromophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-chloro-1H-benzimidazole. Hydrochloride ^1H NMR (d_6 -DMSO): 7.32-8.00 (m, 9H), 5.95 (s, 2H), 4.29 (q, 2H), 1.27 (t, 3H).

(cccc) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-chloro-1H-benzimidazole. (L)-Tartrate salt ^1H NMR (CD_3OD): 7.24-7.59 (m, 9H), 5.66 (s, 2H), 4.51 (s, 2H), 4.12 (q, 2H), 1.28 (t, 3H).

(dddd) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-chloro-1H-benzimidazole. ^1H NMR ($CDCl_3$): 7.22-7.60 (m, 9H), 5.67 (s, 2H), 4.49 (s, 2H), 4.11 (q, 2H), 1.16 (t, 3H).

(eeee) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-trifluoromethyl-1H-benzimidazole. LCMS 407.3 (MH^+).

(ffff) 2-([2-(3-Trifluoromethylphenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-trifluoromethyl-1H-benzimidazole. ^1H NMR ($CDCl_3$): 8.09 (d, 1H), 7.37-7.95 (m, 6H), 7.19 (d, 1H), 7.05 (d, 1H), 5.49 (s, 2H), 3.85 (q, 2H), 1.02 (t, 3H).

(gggg) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-trifluoromethyl-1H-benzimidazole. LCMS MH^+ 389.2.

(hhhh) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(1,2,3,4-tetrazol-5-yl)-1H-benzimidazole. LCMS MH^+ 389.2.

(iiii) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-bromo-1H-benzimidazole. ^1H NMR ($CDCl_3$): 7.93 (d, 1H), 7.68 (m, 1H), 7.40-7.57 (m, 2H), 7.15-7.19 (m, 2H), 7.03 (d, 1H), 5.48 (s, 2H), 3.77 (q, 2H), 0.98 (t, 3H).

(jjjj) 2-([2-(3-Cyanophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-bromo-1H-benzimidazole. Hydrochloride ^1H NMR (CD_3OD): 7.71-8.25 (m, 9H), 6.18 (s, 2H), 4.50 (br s, 2H), 1.50 (br s, 3H).

(kkkk) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-bromo-1H-benzimidazole. ^1H NMR ($CDCl_3$): 7.93 (d, 1H), 7.39-7.52 (m, 4H), 7.15-7.22 (m, 3H), 7.025 (d, 1H), 5.49 (s, 2H), 3.76 (q, 2H), 0.97 (t, 3H).

(llll) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(thien-3-yl)-1H-benzimidazole. ^1H NMR ($CDCl_3$): 8.0 (m, 1H), 7.16-7.59 (m, 10H), 7.07 (d, 1H), 5.52 (s, 2H), 3.81 (q, 2H), 1.01 (t, 3H).

(mmmm) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(3-fluorophenyl)-1H-benzimidazole. ^1H NMR ($CDCl_3$): 7.98 (m, 1H), 7.27-7.54 (m, 8H), 7.16-7.22 (m, 2H), 7.01-7.07 (m, 2H), 5.53 (s, 2H), 3.82 (q, 2H), 1.02 (t, 3H).

(nnnn) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(3,5-difluorophenyl)-1H-benzimidazole. ^1H NMR ($CDCl_3$): 7.96 (d, 1H), 7.35-7.70 (m, 6H), 7.06-7.23 (m, 4H), 6.78 (m, 1H), 5.52 (s, 2H), 3.81 (q, 2H), 1.00 (t, 3H).

(oooo) 2-([2-(3-Cyanophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(3,5-difluorophenyl)-1H-benzimidazole. ^1H NMR (CDCl_3): 7.93-8.02 (m, 2H), 7.37-7.77 (m, 6H), 7.08-7.19 (m, 3H), 6.77 (m, 1H), 5.49 (s, 2H), 3.89 (q, 2H), 1.10 (t, 3H).

(pppp) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(2,5-dimethylisoxazol-4-yl)-1H-benzimidazole. ^1H NMR (CDCl_3): 7.66 (d, 1H), 7.34-7.54 (m, 4H), 7.15-7.22 (m, 3H), 7.06 (d, 1H), 5.52 (s, 2H), 3.83 (q, 2H), 2.41 (s, 3H), 2.28 (s, 3H), 1.02 (s, 3H).

(qqqq) 2-([2-(3-Cyanophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(2,5-dimethylisoxazol-4-yl)-1H-benzimidazole. ^1H NMR (CDCl_3): 7.94-8.01 (m, 2H), 7.75 (m, 1H), 7.61-7.66 (m, 2H), 7.38 (dd, 1H), 7.18-7.22 (m, 2H), 7.10 (d, 1H), 5.49 (s, 2H), 3.90 (q, 2H), 2.42 (s, 3H), 2.29 (s, 3H), 1.12 (t, 3H).

(rrrr) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(5-trifluoromethyl-1,2,3,4-tetrazol-1-yl)-1H-benzimidazole. LCMS MH^+ 475.1.

(ssss) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-acetyl-1H-benzimidazole. ^1H NMR (CDCl_3): 8.40 (s, 1H), 8.00 (dd, 1H), 7.33-7.53 (m, 4H), 7.17-7.22 (m, 2H), 7.05 (d, 1H), 5.53 (s, 2H), 3.82 (q, 2H), 2.67 (s, 3H), 1.01 (t, 3H).

(tttt) 2-([2-(3-Cyanophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-acetyl-1H-benzimidazole. ^1H NMR (CDCl_3): 8.40 (d, 1H), 7.93-8.05 (m, 3H), 7.76 (m, 1H), 7.63 (m, 1H), 7.37 (dd, 1H), 7.21 (d, 1H), 7.09 (d, 1H), 5.50 (s, 2H), 3.91 (q, 2H), 2.68 (s, 3H), 1.11 (t, 3H).

(uuuu) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-acetyl-1H-benzimidazole. ^1H NMR (CDCl_3): (8.40 (d, 1H), 8.01 (dd, 1H), 7.68 (m, 1H), 7.55 (m, 1H), 7.45-7.52 (m, 2H), 7.35 (d, 1H), 7.17 (d, 1H), 7.06 (d, 1H), 5.52 (s, 2H), 3.85 (q, 2H), 2.68 (s, 3H), 1.03 (t, 3H).

(vvvv) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-[1-(methoxyimino)ethyl]-1H-benzimidazole. Syn and anti ^1H NMR (CDCl_3): 7.98 (d, 1H), 7.94 (d, 1H¹), 7.75 (dd, 1H+H¹), 7.14-7.22 (m, 2H+H¹), 7.32-7.52 (m, 4H+H¹), [7.03 (d, 1H), 7.01 (d, 1H¹)], 5.49 (s, 2H+H¹), [4.00 (s, 2H), 3.86 (s, 2H¹)], 3.79 (q, 2H+H¹), [2.30 (s, 3H), 2.26 (s, 3H¹)], 0.98 (t, 3H+H¹).

(www) N-Methyl,N-methoxy 2-([2-(3-fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-1H-benzimidazole-5-carboxamide. ^1H NMR (CDCl_3): 8.19 (d, 1H), 7.71 (dd, 1H), 7.40-7.55 (m, 3H), 7.32 (dd, 1H), 7.16-7.23 (m, 2H), 7.05 (d, 1H), 5.53 (s, 2H), 3.80 (q, 2H), 3.59 (s, 3H), 3.41 (s, 3H), 1.00 (t, 3H).

(xxxx) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-3-yl) -1H-benzimidazole. LCMS 403.8 (MH^+), 401.4 (MH^-).

(yyyy) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-imidazol-2-yl -1H-benzimidazole. Dihydrochloride ^1H NMR (d_6 DMSO): 8.43(1H, s), 8.13-8.11(2H, m), 7.99(1H, d), 7.89(1H, d), 7.79-7.75(3H, m), 7.60-7.51(3H, m), 5.95(2H, s), 4.31(2H, q), 1.26 (3H, t). LCMS MH^+ 405.3.

(zzzz) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(1-methyl-imidazol-2-yl) -1H-benzimidazole. MH^+ 433.2.

(aaaaa) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl) -1H-benzimidazole.

Hydrochloride ¹H NMR (d6 DMSO): 8.11 (1H, s), 8.00(1H, d), 7.95(1H, d), 7.90-7.82(2H, m), 7.74-7.72(1H,m), 7.64-7.58(2H, m), 7.53-7.49(1H, m), 5.96(2H, s), 4.329(2H, q), 2.56(3H, s), 1.30(3H, t). LCMS MH⁺ 403.3.

(bbbbb) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(5-methyl-oxazol-2-yl) -1H-benzimidazole. Hydrochloride ¹H NMR (d6 DMSO): 8.05(1H, s), 7.99(1H, d), 7.97(1H, s), 7.88-7.86(1H, m), 7.76-7.72(2H, m), 7.65-7.59(2H, m), 7.54-7.51(1H, m), 6.99(1H, s), 5.9392H, s), 4.31(2H, q), 2.36(3H, s), 1.29(3H, t). LCMS MH⁺ 402.5.

(ccccc) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(5-pyrid-3-yl-1,3,4-oxadiazol-2-yl) -1H-benzimidazole. Hydrochloride ¹H NMR (d6 DMSO): 9.36(1H, d), 8.84(1H, dd); 8.57(1H, m), 8.44(1H, s), 8.10(1H, dd), 8.03(1H, d), 7.98(1H, d), 7.90(1H, d), 7.75-7.51(5H, m), 5.99(2H, s), 4.35(2H, q), 1.33(3H, t). LCMS MH⁺ 466.5.

(ddddd) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-ethoxycarbonyl-1H-benzimidazole.

(eeeeee) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-hydroxymethyl-1H-benzimidazole.

(ffffff) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-[(4-methylpiperazin-1-yl)methyl]-1H-benzimidazole.

(ggggg) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(morpholin-4-yl)methyl-1H-benzimidazole.

(hhhhh) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-1H-benzimidazol-5-carboxylate.

(iiii) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-1H-benzimidazol-5-carboxamide.

(jjjjj) N-Methyl 2-([2-(3-chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-1H-benzimidazol-5-carboxamide.

(kkkkk) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(morpholin-4-yl)methyl-1H-benzimidazole. LCMS MH⁺ 420.4, MH⁻ 418.2.

(lllll) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-1H-benzimidazol-5-carboxylate. LCMS MH⁺ 365.1.

(nnnnnn) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-1H-benzimidazol-5-carboxamide.

(nnnnn) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-1H-benzimidazol-5-carboxylate. LCMS MH⁺ 383.2.

(ooooo) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(morpholin-4-yl)methyl-1H-benzimidazole. LCMS MH⁺ 432.4.

(ppppp) N-[(N,N-Di-n-propylamino)ethyl] 2-([2-(2,5-difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-1H-benzimidazol-5-carboxamide. LCMS MH⁺ 509.5.

(qqqqq) 2-([2-(4-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole. ¹H NMR(CDCl₃): 7.65-7.71 (m, 2H), 7.47 (d, 1H), 7.03-7.23 (m, 6H). 5.47 (s, 2H), 3.65 (t, 2H), 1.41 (h, 2H), 0.71 (t, 3H).

(rrrrr) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole. ¹H NMR(CDCl₃): 7.65 (s, 1H),

7.41-7.53 (m, 3H), 7.06-7.24 (m, 5H), 5.47 (s, 2H), 3.65 (t, 2H), 1.47 (h, 2H), 0.71 (t, 3H).

(sssss) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole. ^1H NMR(CDCl_3): 7.35-7.47 (m, 4H), 7.0-7.1 (m, 5H), 5.47 (s, 2H), 3.65 (t, 2H), 1.35 (h, 2H), 0.71 (t, 3H).

(ttttt) 2-([2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-amino-1H-benzimidazole. LCMS MH^+ 354.4.

(uuuuu) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-amino-1H-benzimidazole. ^1H NMR(CDCl_3): 7.38-7.5 (m, 4h), 7.15 (t, 3H), 7.1 (s, 1H), 7.05 (t, 2H), 6.7 (d, 1H), 5.4 (s, 2H), 3.70 (q, 2H), 0.9 (t, 3H).

(vvvvv) 2-([2-(3-Bromophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. ^1H NMR (CDCl_3): 8.11 (d, 1H), 7.81 (s, 1H), 7.55-7.67 (m, 3H), 7.35 -7.41 (m, 2H), 7.19 (m, 1H), 7.04 (d, 1H), 5.51 (s, 2H), 3.84 (q, 2H), 1.04 (t, 3H).

(wwwww) 2-([2-(3-Hydroxyphenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole. LCMS MH^+ 337.01.

(xxxxx) 2-([2-(3-Trifluoromethoxyphenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. LCMS MH^+ 411.96.

(yyyyy) 2-([2-(3-Nitrophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole. LCMS MH^+ 365.99.

(zzzzz) 2-([2-(3-Methylphenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. LCMS MH^+ 343.06.

(aaaaa) 2-([2-(3-Acetylphenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole. LCMS MH^+ 363.05.

(bbbbbb) 2-([2-(3-Trifluoromethylphenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. LCMS MH⁺ 396.06.

(ccccc) 2-([2-(2-Thienyl-1H-imidazol-1-yl)methyl]-1-ethyl-5-cyano-1H-benzimidazole. LCM: MH⁺ 334.04.

(ddddd) 2-([2-(3-Formylphenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-fluoro-1H-benzimidazole. LCMS MH⁺ 349.17.

(eeeeee) Methyl 2-([2-(phenyl-3-carboxylate)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. LCMS MH⁺ 386.17.

(ffffff) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-1H-imidazo[4,5-c]pyridine. ¹H NMR (CDCl₃): 9.10 (s, 1H), 8.44 (d, 1H), 7.38-7.52 (m, 3H), 7.18-7.20 (m, 2H), 7.16 (s, 1H), 7.04 (d, 1H), 5.53 (s, 2H), 3.79 (q, 2H), 1.00 (t, 3H).

(gggggg) 2-([2-(2-Nitrothien-4-yl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. LCMS MH⁺ 379.05.

(hhhhhh) 2-([2-(2-Aminothien-4-yl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. LCM: MH⁺ 397.12.

(iiiiii) 2-([2-(3-Aminophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. LCMS MH⁺ 391.17.

(jjjjjj) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-[1-(hydroxyimino)ethyl]-1H-benzimidazole. ¹H NMR (CDCl₃): 11.03 (s, 1H), 7.81 (s, 1H), 7.52-7.67 (m, 4H), 7.40-7.45 (m, 2H), 7.31 (s, 1H), 7.07 (s, 1H), 5.67 (s, 2H), 4.17 (q, 2H), 2.18 (s, 3H), 1.16 (t, 3H).

(kkkkkk) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-[1-(methoxyimino)ethyl]-1H-benzimidazole. Syn and anti ¹H NMR (CDCl₃): 7.99 (dd, 1H), 7.95 (dd, 1H¹), 7.76 (dd, 1H+H¹), 7.65 (m, 1H+H¹), 7.44-7.57 (m, 3H+H¹), 7.27 (d, 1H+H¹), 7.15 (d, 1H+H¹), 7.04 (d, 1H+H¹), 5.49 (s, 2H+H¹), 4.01 (s, 3H), 3.87 (s, 3H¹), 3.80 (q, 2H+H¹), [2.30 (s, 3H), 2.27 (s, 3H¹)], 1.00 (t, 3H+H¹).

(lllllll) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-[1-(ethoxyimino)ethyl]-1H-benzimidazole. Syn and anti ¹H NMR (CDCl₃): 8.00 (dd, 1H+H¹), 7.76 (dd, 1H+H¹), 7.69 (m, 1H+H¹), 7.44-7.57 (m, 3H+H¹), 7.27 (dd, 1H+H¹), 7.15 (d, 1H+H¹), 7.04 (d, 1H), 7.03 (d, 1H¹), 5.49 (s, 2H+H¹), 4.26 (q, 2H), 4.13 (q, 2H¹), 3.80 (q, 2H+H¹), 2.27 (s, 3H¹), 1.34 (t, 3H), 1.25 (t, 3H¹), 1.00 (t, 3H+H¹).

(mmmmmm) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-1H-imidazo[4,5-b]pyridine. LCMS MH⁺ 336.2, MH⁻ 334.2.

(nnnnnn) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-1H-imidazo[4,5-b]pyridine. LCMS MH⁺ 322.2, MH⁻ 320.3.

(ooooooo) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-1H-imidazo[4,5-c]pyridine. ¹H NMR (CDCl₃): 9.11 (s, 1H), 8.45 (d, 1H), 7.38-7.52 (m, 3H), 7.16-7.26 (m, 3H), 7.06 (s, 1H), 5.53 (s, 2H), 3.71 (t, 2H), 1.43 (q, 2H), 0.75 (t, 3H).

(pppppp) 2-([2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. LCMS MH⁺ 347.07.

(qqqqqq) 2-([2-(3-Methoxypyrid-2-yl)-1H-imidazol-1-yl]methyl)-1-ethyl-1H-benzimidazole. LCMS MH⁺ 359.08.

(rrrrrr) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-[1-(hydroxyimino)ethyl]-1H-benzimidazole. Hydrochloride ¹H NMR (d6-DMSO): 11.10 (s, 1H), 7.52-7.99 (m, 9H+H¹), 5.923 (s, 2H+H¹): 4.30 (q, 2H+H¹), 2.18 (s, 3H), 2.14 (s, 3H¹), 1.29 (t, 3H+H¹).

(ssssss) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-[1-(ethoxyimino)ethyl]-1H-benzimidazole. Hydrochloride ¹H NMR (d6-DMSO): 7.52-7.99 (m, 9H), 5.93 (s, 2H), 4.28 (q, 2H), 4.14 (q, 2H), 2.20 (s, 3H), 1.23-1.29 (m, 6H).

(tttttt) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(1-oxopropyl)-1H-benzimidazole. ¹H NMR (CDCl₃): 8.42 (d, 1H), 8.02 (dd, 1H), 7.32-7.54 (m, 4H), 7.17-7.24 (m, 2H), 7.06 (d, 1H), 5.53 (s, 2H), 3.83 (q, 2H), 3.09 (q, 2H), 1.27 (t, 3H), 1.02 (t, 3H).

(uuuuuu) 2-([2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-acyl-1H-benzimidazole. LCMS MH⁺ 364.2, MH⁻ 362.6.

(vvvvvv) 2-([2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-trifluoromethyl-1H-benzimidazole. LCMS MH⁺ 390.2, MH⁻ 388.2.

(wwwww) 2-([2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl)-1-propyl-5-cyano-1H-benzimidazole. LCMS MH⁺ 361.2, MH⁻ 359.2.

(xxxxxx) 2-([2-(3-Chlorophenyl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-(isoxazol-5-yl)-1H-benzimidazole. ¹H NMR (CDCl₃): 8.30 (d, 1H), 8.21 (dd, 1H), 7.78 (dd, 1H), 7.69 (m, 1H), 7.56 (m, 1H), 7.45-7.48 (m, 2H), 7.39 (dd, 1H), 7.17 (d, 1H), 7.07 (d, 1H), 6.53 (d, 1H), 5.52 (s, 2H), 3.83 (q, 2H), 1.03 (t, 3H).

(yyyyyy) 2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-(2-fluoroethyl)-5-[1-(hydroxyimino)ethyl]-1H-benzimidazole. LCMS MH⁺ 339.2.

(zzzzzz) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[(4-methylpiperazin-1-yl)methyl]-1H-benzimidazole. ¹H NMR (CDCl₃): 7.65 (d, 1H), 7.61 (d, 1H), 7.45 (m, 1H), 7.22-7.31 (m, 4H), 7.11 (m, 1H), 6.16 (d, 1H), 4.31 (s, 2H), 3.96 (q, 2H), 3.62 (s, 2H), 2.40-2.60 (m, 8H), 2.25 (s, 3H), 1.22 (t, 3H).

(aaaaaaa) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[(4-ethylpiperazin-1-yl)methyl]-1H-benzimidazole. ¹H NMR (CDCl₃): 7.65 (d, 1H), 7.62 (d, 1H), 7.45 (m, 1H), 7.23-7.30 (m, 4H), 7.13 (m, 1H), 6.16 (d, 1H), 4.31 (s, 2H), 3.96 (q, 2H), 3.62 (s, 2H), 2.40-2.60 (m, 10H), 1.21 (t, 3H), 1.078 (t, 3H).

(bbbbbbb) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[(4-cyclopentylpiperazin-1-yl)methyl]-1H-benzimidazole. ¹H NMR (CDCl₃): 7.65 (d, 1H), 7.61 (d, 1H), 7.45 (m, 1H), 7.22-7.31 (m, 4H), 7.13 (m, 1H), 6.15 (d, 1H), 4.31 (s, 2H), 3.96 (q, 2H), 3.63 (s, 2H), 2.40-2.60 (m, 9H), 1.31-1.90 (m, 8H), 1.21 (t, 3H.)

(ccccccc) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[(4-cycloheptylpiperazin-1-yl)methyl]-1H-benzimidazole. LCMS MH⁺ 515.5.

(ddddddd) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[(4-cyclopentylpiperidin-1-yl)methyl]-1H-benzimidazole. ¹H NMR (CDCl₃): 7.62 (m, 2H), 7.45 (m, 1H), 7.23-7.31 (m, 4H), 7.13 (m, 1H), 6.16 (d, 1H), 4.31 (s, 2H), 3.96 (q, 2H), 3.61 (s, 2H), 2.90 (m, 2H), 2.60 (m, 4H), 1.55-2.25 (m, 11H), 1.22 (t, 3H).

(eeeeeee) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-
 ([4-(piperidin-1-yl)piperidin-1-yl)methyl]-1H-benzimidazole. ¹H
 NMR (CDCl₃): 7.63 (d, 1H), 7.61 (d, 1H), 7.44 (m, 1H), 7.2307.31
 (m, 4H), 7.13 (m, 1H), 6.16 (d, 1H), 4.31 (s, 2H), 3.96 (q, 2H),
 3.61 (s, 2H), 2.96 (m, 2H), 2.50 (m, 4H), 1.40-2.31 (m, 13H),
 1.23 (t, 3H).

(ffffff) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-
 [(4-phenylpiperazin-1-yl)methyl]-1H-benzimidazole. ¹H NMR
 (CDCl₃): 7.69 (d, 1H), 7.62 (s, 1H), 7.45 (m, 1H), 7.21-7.33 (m,
 6H), 7.13 (m, 1H), 6.82-6.94 (m, 3H), 6.16 (d, 1H), 4.33 (s, 2H),
 3.97 (q, 2H), 3.69 (s, 2H), 3.15-3.23 (m, 4H), 2.59-2.67 (m, 4H),
 1.21 (t, 3H).

(ggggggg) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-
 fluoro-1H-benzimidazole. (L)-Tartrate salt ¹H NMR (CD₃OD): 7.67
 (s, 1H), 7.05-7.46 (m, 7H), 6.31 (s, 1H), 4.53 (s, 2H), 4.47 (s,
 2H), 4.14 (q, 2H), 1.21 (t, 3H).

(hhhhhhh) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-
 bromo-1H-benzimidazole. (L)-Tartrate salt ¹H NMR (d6-DMSO):
 7.72 (d, 1H), 7.65 (d, 1H), 7.21-7.53 (m, 6H), 6.26 (s, 1H), 4.48
 (s, 2H), 4.30 (s, 2H), 4.16 (q, 2H), 1.14 (t, 3H).

(iiiiiii) 2-([2-(3-Chlorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-
 bromo-1H-benzimidazole. ¹H NMR (CDCl₃): 7.87 (d, 1H), 7.63 (d,
 1H), 7.50 (m, 1H), 7.35-7.42 (m, 4H), 7.18 (d, 1H), 6.18 (d, 1H),
 4.31 (s, 2H), 3.96 (q, 2H), 1.21 (t, 3H).

(jjjjjjj) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-
 chloro-1H-benzimidazole. (L)-Tartrate salt ¹H NMR (d6-DMSO):
 7.65 (s, 1H), 7.21-7.58 (m, 7H), 6.26 (s, 1H), 4.48 (s, 2H), 4.30
 (s, 2H), 4.16 (q, 2H), 1.15 (t, 3H).

(kkkkkkk) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-phenyl-1H-benzimidazole. ^1H NMR (CDCl_3): 7.96 (d, 1H), 7.27-7.66 (m, 11H), 7.14 (m, 1H), 6.21 (d, 1H), 4.38 (s, 2H), 4.01 (q, 2H), 1.25 (t, 3H).

(llllllll) 2-([2-(2,5-Difluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. LCMS MH^+ 364.2.

(nnnnnnnn) 2-([2-(3-Chlorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. ^1H NMR (CDCl_3): 8.05 (d, 1H), 7.36-7.65 (m, 7H), 6.21 (d, 1H), 4.36 (s, 2H), 4.02 (q, 2H), 1.24 (t, 3H).
(nnnnnnnn) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(thiazol-2-yl)-1H-benzimidazole. Hydrochloride ^1H NMR (CD_3OD): 9.725 (s, 1H), 8.67 (s, 1H), 8.13 (s, 1H), 8.01-8.08 (m, 2H), 7.79 (s, 1H), 7.21-7.57 (m, 4H), 6.59 (d, 1H), 4.97 (s, 2H), 4.50 (q, 2H), 1.39 (t, 3H).

(oooooooo) N-Methoxy, N-methyl 1-ethyl-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-1H-benzimidazole-5-carboxamide. ^1H NMR (CDCl_3): 8.13 (d, 1H), 7.63-7.70 (m, 2H), 7.24-7.49 (m, 4H), 7.13 (m, 1H), 6.19 (d, 1H), 4.36 (s, 2H), 4.00 (q, 2H), 3.60 (s, 3H), 3.40 (s, 3H), 1.23 (t, 3H).

(pppppppp) N-Methoxy, N-methyl 1-ethyl-2-([2-(3-chlorophenyl)-pyrazol-3-yl]methyl)-1H-benzimidazole-5-carboxamide. ^1H NMR (CDCl_3): 8.13 (d, 1H), 7.63-7.70 (m, 2H), 7.51 (m, 1H), 7.31-7.41 (m, 4H), 6.20 (d, 1H), 4.35 (s, 2H), 4.00 (q, 2H), 3.60 (s, 3H), 3.40 (s, 3H), 1.23 (t, 3H).

(qqqqqqqq) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(3-cyanophenyl)-1H-benzimidazole. ^1H NMR (CDCl_3): 7.84-7.92 (m,

0257492.122100

3H), 7.40-7.64 (m, 6H), 7.26-7.33 (m, 2H), 7.14 (m, 1H), 6.21 (d, 1H), 4.37 (s, 2H), 4.03 (q, 2H), 1.26 (t, 3H).

(rrrrrrrr) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(3-acetamidophenyl)-1H-benzimidazole. ^1H NMR (CDCl_3): 7.93 (d, 1H), 7.26-7.72 (m, 10H), 7.14 (m, 1H), 6.20 (d, 1H), 4.36 (s, 2H), 4.01 (q, 2H), 2.21 (s, 3H), 1.24 (t, 3H).

(ssssssss) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(4-trifluoromethoxyphenyl)-1H-benzimidazole. ^1H NMR (CDCl_3): 7.92 (d, 1H), 7.27-7.65 (m, 10H), 7.14 (m, 1H), 6.20 (d, 1H), 4.37 (s, 2H), 4.08 (q, 2H), 1.25 (t, 3H).

(tttttttt) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(3-chloro-4-fluorophenyl)-1H-benzimidazole. ^1H NMR (CDCl_3): 7.897 (d, 1H), 7.63-7.66 (m, 2H), 7.11-7.50 (m, 8H), 6.21 (d, 1H), 4.36 (s, 2H), 4.02 (q, 2H), 1.25 (t, 3H).

(uuuuuuuu) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(3-fluorophenyl)-1H-benzimidazole. ^1H NMR (CDCl_3): 7.95 (d, 1H), 7.64 (d, 1H), 7.27-7.53 (m, 8H)/ 7.14 (m, 2H), 7.03 (m, 1H), 6.20 (d, 1H), 4.36 (s, 2H), 4.02 (q, 2H), 1.25 (t, 3H).

(vvvvvvvv) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(3,5-difluorophenyl)-1H-benzimidazole. ^1H NMR (CDCl_3): 7.91 (d, 1H), 7.64 (d, 1H), 7.27-7.50 (m, 5H), 7.10-7.18 (m, 3H), 6.77 (m, 1H), 6.20 (d, 1H), 4.36 (s, 2H), 4.02 (q, 2H), 1.25 (t, 3H).

(wwwwwww) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(pyrid-3-yl)-1H-benzimidazole. ^1H NMR (CDCl_3): 8.90 (d, 1H), 8.59 (m, 1H), 7.90-7.95 (m, 2H), 7.64 (d, 1H), 7.25-7.53 (m, 6H), 7.14 (m, 1H), 6.21 (d, 1H), 4.37 (s, 2H), 4.03 (q, 2H), 1.26 (t, 3H).

(xxxxxxx) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(pyrid-4-yl)-1H-benzimidazole. ¹H NMR (CDCl₃): 8.67 (d, 1H), 8.65 (d, 1H), 8.03 (d, 1H), 7.26-7.65 (m, 8H), 7.15 (m, 1H), 6.21 (d, 1H), 4.37 (s, 2H), 4.03 (q, 2H), 1.26 (t, 3H).

(yyyyyyy) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(5-methoxyphen-2-yl-2-carboxaldehyde)-1H-benzimidazole. ¹H NMR (CDCl₃): 9.86 (s, 1H), 8.03 (d, 1H), 7.26-7.78 (m, 7H), 6.94-7.18 (m, 3H), 6.22 (dd, 1H), 4.38 (s, 2H), 4.04 (q, 2H), 3.91 (s, 3H), 1.27 (t, 3H).

(zzzzzzz) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(3,5-dimethylisoxazol-4-yl)-1H-benzimidazole. ¹H NMR (CDCl₃): 7.62-7.64 (m, 2H), 7.25-7.50 (m, 4H), 7.11-7.18 (m, 2H), 6.21 (d, 1H), 4.36 (s, 2H), 4.02 (q, 2H), 2.42 (s, 3H), 2.29 (s, 3H), 1.26 (t, 3H).

(aaaaaaaa) 2-([2-(3-Chlorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-acetyl-1H-benzimidazole. ¹H NMR (CDCl₃): 8.37 (d, 1H), 8.03 (dd, 1H), 7.65 (d, 1H), 7.38-7.50 (m, 5H), 6.24 (d, 1H), 4.49 (s, 2H), 4.03 (q, 2H), 2.68 (s, 3H), 1.24 (t, 3H).

(bbbbbbbbb) 2-([2-(3-Chlorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(1-hydroxyethyl)-1H-benzimidazole. ¹H NMR (CDCl₃): 7.10-7.73 (m, 8H), 6.16 (d, 2H), 5.04 (q, 1H), 4.43 (s, 2H), 3.97 (q, 3H), 1.54 (d, 3H), 1.20 (t, 3H).

(cccccccc) 2-([2-(2,5-Difluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-nitro-1H-benzimidazole. Mesylate ¹H NMR (d6 DMSO) 8.38 (1H, d), 8.15-8.12 (1H, m), 7.77 (1H, d), 7.71 (1H, s), 7.51-7.34 (3H, m), 6.40 (1H, s), 4.21 (2H, q), 2.32 (3H, s), 1.11 (3H, t). LCMS MH⁺ 384.2.

(dddddddd) 2-([2-(2,5-Difluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-isocyano-1H-benzimidazole. ¹H NMR (CDCl₃): 7.70-7.67(2H, m), 7.31-7.14(5H, m), 6.16(1H, s), 4.28(2H, s), 4.02(2H, q), 1.22(3H, t), LCMS MH⁺ 64.1.

(eeeeeeee) 2-([2-(2,5-Difluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(1,2,4-triazol-4-yl)-1H-benzimidazole. LCMS MH⁺ 405.95.

(fffffff) 2-([2-(2,5-Difluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(trifluoromethylacetamide)-1H-benzimidazole. LCMS MH⁺ 449.96.

(gggggggg) 2-([2-(2,5-Difluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(1,2,3,4-tetrazol-1-yl)-1H-benzimidazole. ¹H NMR (DMSO): 10.07 (s, 1H), 8.07 (s, 1H), 7.86 (d, 1H), 7.79 (d, 1H), 7.71 (s, 1H), 7.36-7.57 (m, 3H), 6.4 (s, 2H), 4.46 (s, 2H), 4.21 (q, 2H), 1.14 (t, 3H).

(hhhhhhhh) 2-([2-(2,5-Difluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[5-trifluoromethyl-(1,2,3,4-tetrazol-1-yl)]-1H-benzimidazole. LCMS MH⁺ 474.99.

(iiiiiii) 2-([2-(2,5-Difluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-benzimidazole. LCMS MH⁺ 437.02.

(jjjjjjjj) 2-([2-(2,5-Difluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(1,3,4-oxadiazol-2-yl)-1H-benzimidazole. LCMS MH⁺ 425.10.

(kkkkkkkk) 2-([2-(3-Chlorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[1-(methoxyimino)ethyl]-1H-benzimidazole. ¹H NMR (CDCl₃): 7.94 (d, 1H), 7.73 (dd, 1H), 7.73 (dd, 1H), 7.63 (d, 1H), 7.52 (m, 1H), 7.38-7.40 (m, 3H), 7.27 (m, 1H), 6.19 (d, 1H), 4.32 (s, 2H), 3.87-4.10 (m, 5H), 2.30 (s, 3H), 1.22 (t, 3H).

(lllllllll) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[1-(ethoxyimino)ethyl]-1H-benzimidazole. Syn and anti ¹H NMR (CDCl₃): 7.95 (d, 1H+H¹), 7.73 (dd, 1H+H¹), 7.63 (d, 1H+H¹), 7.44 (m, 1H+H¹), 7.24-7.33 (m, 3H+H¹), [6.18 (d, 1H+H¹), 7.13 (d, 1H+H¹)], 4.33 (s, 2H), [4.26 (q, 2H), 4.13 (q, 2H¹)], 3.98 (q, 2H+2H¹), [2.31 (s, 3H), 2.27 (s, 3H¹)], [1.35 (t, 3H), 1.28 (t, 3H¹)], 1.22 (t, 3H+H¹).

(mmmmmmmm) 2-([2-(3-Chlorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[1-(ethoxyimino)ethyl]-1H-benzimidazole. Syn and anti ¹H NMR (CDCl₃): 7.94 (d, 1H), 7.95 (d, 1H¹), 7.73 (dd, 1H+H¹), 7.63 (d, 1H+H¹), 7.52 (m, 1H+H¹), 7.38-7.40 (m, 3H+H¹), 7.29 (s, 1H+H¹), 6.19 (d, 1H), 6.18 (d, 1H¹), 4.32 (s, 2H+H¹), 4.26 (q, 2H), 4.13 (q, 2H¹), 3.99 (q, 2H+H¹), 2.31 (s, 3H), 2.27 (s, 3H¹), 1.35 (t, 3H), 1.28 (t, 3H¹), 1.22 (t, 3H+H¹).

(nnnnnnnn) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[1-(hydroxyimino)ethyl]-1H-benzimidazole. ¹H NMR (CD₃OD): 7.81 (d, 1H), 7.64-7.68 (m, 2H), 7.42-7.53 (m, 2H), 7.16-7.32 (m, 3H), 6.28 (d, 1H), 4.44 (s, 2H), 4.12 (q, 2H), 2.30 (s, 3H), 1.23 (t, 3H).

(oooooooo) 2-([2-(3-Chlorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[1-(hydroxyimino)ethyl]-1H-benzimidazole. ¹H NMR (CDCl₃): 10.92 (br s, 1H), 8.58 (s, 1H), 7.52-7.64 (m, 3H), 7.29 (d, 1H), 6.20 (d, 1H), 4.36 (s, 2H), 3.97 (q, 2H), 2.38 (s, 3H), 1.21 (t, 3H).

(ppppppppp) 2-([2-(3-Chlorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[1-(t-butoxyimino)ethyl-1H-benzimidazole. Syn and anti ¹H NMR (CDCl₃): 8.00 (d, 1H+H¹), 7.75 (dd, 1H+H¹), 7.63 (d, 1H+H¹), 7.27 (d, 1H+H¹), 7.38-7.40 (m, 3H+H¹), 6.20 (d, 1H) [6.18 (d, 1H¹)], 4.32 (s, 2H+H¹), 3.99 (q, 2H+H¹), 2.28 (s, 3H), [2.27 (s, 3H¹)], 1.37 (s, 9H), [1.32 (s, 9H¹)], 1.22 (t, 3H, t3H).

(qqqqqqqqq) 2-([2-(3-Chlorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[1-(tetrahydropyranyloxyimino)ethyl-1H-benzimidazole. ¹H NMR (CDCl₃): 7.95 (d, 1H), 7.79 (dd, 1H), 7.63 (d, 1H), 7.52 (m, 1H), 7.37-7.40 (m, 3H), 7.26 (dd, 1H), 6.19 (d, 1H), 5.43 (m, 1H), 4.32 (s, 2H), 3.85-4.02 (m, 4H), 3.66 (m, 2H), 1.62-1.92 (m, 4H), 1.22 (t, 3H).

(rrrrrrrrr) N,N-Dimethyl 2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-1H-benzimidol-1-ethyl-5-carboxamide. ¹H NMR (CDCl₃): 7.78 (s, 1H), 7.63 (s, 1H), 7.10-7.48 (m, 6H), 6.18 (s, 1H), 4.35 (s, 2H), 4.00 (q, 2H), 3.13 (s, 3H), 3.05 (s, 3H), 1.22 (t, 3H).

(sssssssss) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-cyanomethyl-1H-benzimidazole. 7.66 (m, 1H), 7.63 (d, 1H), 7.24-7.49 (m, 5H), 7.13 (m, 1H), 6.17 (d, 1H), 4.34 (s, 2H), 3.99 (q, 2H), 3.87 (s, 2H), 1.22 (t, 3H).

(ttttttttt) 2-([2-(2,5-Difluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[5-(pyrid-3-yl)-1,3,4-oxadiazol-2-yl]-1H-benzimidazole. Dihydrochloride ¹H NMR (d6 DMSO): 9.40 (1H, s), 8.87 (1H, s), 8.63 (1H, d), 8.41 (1H, s), 8.20 (1H, d), 8.01 (1H, d), 7.76 (2H, m), 7.59 (1H, m), 7.48-7.41 (2H, m), 6.50 (1H, s), 4.61 (2H, s), 4.31 (2H, q), 1.19 (3H, t), LCMS MH⁺ 484.5.

50257492.122100

(uuuuuuuu) 2-([2-(2,5-Difluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[5-(pyrid-4-yl)-1,3,4-oxadiazol-2-yl]-1H-benzimidazole. Dihydrochloride ¹H NMR (d6 DMSO): 8.98(2H, m), 8.43(1H, s), 8.35(2H, m), 8.19(1H, d), 7.99(1H, d), 7.75(1H, d), 7.59-7.569(1H, m), 7.50-7.41(2H, m), 6.49(1H, s), 4.58(2H, s), 4.30(2H, q), 1.19(3H, t), LCMS MH⁺ 484.5.

(vvvvvvvvv) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-benzimidazole. Hydrochloride ¹H NMR (d6 DMSO): 9.35(1H, s), 8.22(1H, s), 8.04-7.94(2H, m), 7.71(1H, d), 7.55-7.41(3H, m), 7.28-7.24(1H, m), 6.38(1H, s), 4.71(2H, s), 4.33(2H, q), 1.23(3H, t), LCMS MH⁺ 389.4.

(wwwwwww) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(1,3,4-oxadiazol-2-yl)-1H-benzimidazole. Hydrochloride ¹H NMR (d6 DMSO): 8.17(1H, s), 8.04-7.98(2H, m), 7.71(1H, d), 7.55-7.50(2H, m), 7.45-7.43(1H, m), 7.29-7.249(1H, m), 6.40(1H, d), 4.77(2H, s), 4.36(2H, q), 2.58(3H, s), 1.24(3H, t), LCMS MH⁺ 403.6.

(xxxxxxxxx) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[morpholin-4-yl]methyl]-1H-benzimidazole. LCMS MH⁺ 420.3.

(yyyyyyyyy) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-ethoxycarbonyl-1H-benzimidazole. LCMS MH⁺ 393.3.

(zzzzzzzzz) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-1H-benzimidazol-5-carboxylate. LCMS MH⁺ 365.2.

(aaaaaaaaa) N-(N,N-Dipropylaminoethyl) 2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-1H-benzimidazol-5-carboxamide. LCMS MH⁺ 491.4.

(bbbbbbbbb) N-Ethyl 2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-1H-benzimidazol-5-carboxamide. LCMS MH⁺ 392.3.

(ccccccccc) N-Phenyl 2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-1H-benzimidazol-5-carboxamide. LCMS MH⁺ 440.3.

(ddddddddd) 2-([2-(3-Chlorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[morpholin-4-yl]methyl-1H-benzimidazole. LCMS MH⁺ 436.3, MH⁻ 434.3.

(eeeeeeeee) N-(4-Cycloheptylpiperazin-1-yl) 2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-1H-benzimidazol-5-carboxamide. LCMS MH⁺ 545.4, MH⁻ 543.4.

(fffffffff) N-(N,N-Dipropylaminoethyl) 2-([2-(3-chlorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-1H-benzimidazol-5-carboxamide. LCMS MH⁺ 487.4.

(ggggggggg) 2-([2-(3-Chlorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-1H-benzimidazol-5-carboxamide. LCMS MH⁺ 364.6.

(hhhhhhhhh) 2-([2-(2,5-Difluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-amino-1H-benzimidazole. LCMS MH⁺ 354.2

(iiiiiiiiiii) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[(1,2,4-triazol-1-yl)methyl]-1H-benzimidazole. LCMS MH⁺ 402.4.

(jjjjjjjjj) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[(1,2,3,4-tetrazol-1-yl)methyl]-1H-benzimidazole. LCMS MH⁺ 403.2, MH⁻ 401.4.

(kkkkkkkkk) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[(1,2,3,4-tetrazol-2-yl)methyl]-1H-benzimidazole. LCMS MH^+ 403.4, MH^- 401.4.

(llllllllll) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-methylthiomethyl-1H-benzimidazole. LCMS MH^+ 381.3, MH^- 379.3.

(nnnnnnnnnn) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-1H-imidazo[4,5-c]pyridine. ^1H NMR (CD_3OD): 8.79 (s, 1H), 8.31 (d, 1H), 7.69 (s, 1H), 7.60 (d, 1H), 7.46 (dd, 1H), 7.30 (d, 2H), 7.16-7.20 (m, 1H), 6.37 (s, 1H), 4.55 (s, 2H), 4.20 (q, 2H), 1.24 (t, 3H).

(nnnnnnnnnn) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-1H-imidazo[4,5-b]pyridine. LCMS MH^+ 322.3, MH^- 320.3.

(ooooooooo) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-6-cyano-1H-benzimidazole. LCMS MH^+ 346.3, MH^- 344.3.

(pppppppppp) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(1-oxopropyl)-1H-benzimidazole. Dihydrochloride ^1H NMR (d_6DMSO): 9.41(1H, s), 8.88(1H, d), 8.67(1H, d), 8.46(1H, s), 8.25(1H, d), 8.10(1H, d), 7.81-7.72(2H, m), 7.55-7.46(3H, m), 7.30-7.26(1H, m), 6.43(1H, s), 4.84(2H, s), 4.40(2H, q), 1.27(3H, t).

(qqqqqqqqqq) 1-(2-Methoxyethyl)-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-6-cyano-1H-benzimidazole. LCMS MH^+ 376.3, MH^- 374.3.

(rrrrrrrrrr) 1-(3-Methoxypropyl)-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-6-cyano-1H-benzimidazole. LCMS MH^+ 390.1, MH^- 388.3.

(ssssssssss) 1-(2-Cyanoethyl)-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-6-cyano-1H-benzimidazole. LCMS MH^+ 371.3.

(tttttttttt) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(5-ethyl-1,3,4-oxadiazol-2-yl)-1H-benzimidazole. ^1H NMR (d6DMSO): 8.17(1H, s), 8.01-7.94(2H, m), 7.71(1H, s), 7.53-7.51(2H, m), 7.44-7.42(1H, m), 7.28-7.24(1H, m), 6.39(1H, s), 4.73(2H, s), 4.33(2H, q), 2.94(2H, q), 1.32(3H, t), 1.23(3H, t), LCMS MH^+ 417.5.

(uuuuuuuuuu) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(5-amino-1,3,4-oxadiazol-2-yl)-1H-benzimidazole. LCMS MH^+ 404.13.

(vvvvvvvvvv) 2-Hydroxy-2-([2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. ^1H NMR ($CDCl_3$): 7.93 (d, 1H), 7.67 (d, 1H), 7.55 (dd, 1H), 7.40 (dd, 1H): 7.24 (m, 1H), 7.10-7.15 (m, 2H), 6.20 (d, 1H), 6.01 (s, 1H), 4.98 (br, s, 1H): 4.04 (q, 2H), 1.21 (t, 3H).

(wwwwwwww) 2-Fluoro-2-([2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. ^1H NMR ($CDCl_3$): 8.07 (d, 1H), 7.77 (d, 1H), 7.60 (dd, 1H), 7.47 (dd, 1H), 7.11-7.23 (m, 3H), 6.85 [d, 1H, $J(H,F) = 47.4$], 6.50 (t, 1H), 4.27 (m, 2H), 1.36 (t, 3H).

(xxxxxxxxxx) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-[5-(pyrid-3-yl)-1,3,4-oxadiazol-2-yl]-1H-benzimidazole. ^1H NMR (d6DMSO): 9.41(1H, s), 8.88(1H, d), 8.67(1H, d), 8.46(1H, s), 8.25(1H, d), 8.10(1H, d), 7.81-7.72(2H, m), 7.55-7.46(3H, m),

7.30-7.26(1H, m), 6.43(1H, s), 4.84(2H, s), 4.40(2H, q), 1.27(3H, t).

(yyyyyyyyyy) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-(isoxazol-5-yl)-1H-benzimidazole. ^1H NMR (CDCl_3): 8.30 (d, 1H), 8.16 (dd, 1H), 7.76 (dd, 1H), 7.64 (d, 1H), 7.38-7.50 (m, 2H), 7.25-7.32 (m, 2H), 7.14 (m, 1H), 6.52 (d, 1H), 6.21 (d, 1H), 4.37 (s, 2H), 4.01 (q, 2H), 1.25 (t, 3H).

(zzzzzzzzzz) 2-Hydroxy-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. ^1H NMR (CDCl_3): 8.02 (dd, 1H), 7.47-7.62 (m 5H), 7.39 (d, 1H), 7.18 (m, 1H), 6.12 (d, 1H), 6.00 (s, 1H), 5.05 (brs, 1H), 3.83 (q, 2H), 1.08 (t, 3H).

(aaaaaaaaaa) 2-Fluoro-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. ^1H NMR (CDCl_3): 8.12 (dd, 1H), 7.73 (d, 1H), 7.62 (dd, 1H), 7.44-7.53 (m, 2H), 7.31-7.39 (m, 2H), 7.17 (m, 1H), 6.83 (d, 1H, $J_{\text{H,F}}=46.8$ MZ), 4.39 (m, 2H), 1.43 (t, 3H).

(bbbbbbbbbb) 2-[2-(3-Fluorophenyl)-4-methoxycarbonyl-pyrazol-3-yl]oxy-1-ethyl-6-cyano-1H-benzimidazole. LCMS MH^+ 406.3.

(cccccccccc) 2-([2-(2,5-Difluorophenyl)-pyrazol-3-yl]difluoromethyl)-1-ethyl-5-cyano-1H-benzimidazole. ^1H NMR (CDCl_3): 8.09 (m, 1H), 7.84 (m, 1H), 7.64 (dd, 1H), 7.48 (dd, 1H), 6.96-7.18 (m, 3H), 6.85 (d, 1H), 4.33 (q, 2H), 1.38 (t, 3H).

(dddddddddd) 2-[2-(3-Fluorophenyl)-pyrazol-3-yl]oxy-1-ethyl-6-cyano-1H-benzimidazole. LCMS MH^+ 348.2, MH^- 364.2.

(eeeeeeeeee) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-6-(1,3,4-oxadiazol-2-yl)-1H-benzimidazole. LCMS MH^+ 389.2.

(fffffffffff) 2-([2-(3-Fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-benzimidazole. LCMS MH^+ 403.3.

(ggggggggggg) 1-(2-Oxopropyl)-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-1H-benzimidazole. LCMS MH^+ 349.3, MH^- 347.2.

(hhhhhhhhhhh) 2-([2,2-Difluoro-2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole. ^1H NMR ($CDCl_3$): 8.078 (m, 1H), 7.80 (m, 1H), 7.63 (dd, 1H), 7.48 (dd, 1H), 7.13-7.28 (m, 3H), 6.99 (m, 1H), 6.81 (d, 1H), 4.35 (q, 2H), 1.39 (t, 3H).

(iiiiiiiiiii) 1-(3-Fluoropropyl)-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-1H-benzimidazole. LCMS MH^+ 353.2, MH^- 351.2.

(jjjjjjjjjjj) 1-(2-Fluoroethyl)-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-1H-benzimidazole. LCMS MH^+ 339.2,

(kkkkkkkkkkk) 1-(3-Cyanopropyl)-2-([2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-1H-benzimidazole. LCMS MH^+ 360.2, MH^- 358.3.

(lllllllllll) 2-([2,2-Difluoro-2-(3-fluorophenyl)-pyrazol-3-yl]methyl)-5-(trifluoromethylacetyl)-1H-benzimidazole. LCMS MH^+ 417.2.

(mmmmmmmmmm) 2-([2,2-Difluoro-2-(3-chlorophenyl)-pyrazol-3-yl]methyl)-5-(trifluoromethylacetyl)-1H-benzimidazole. LCMS MH^+ 433.3.

710

(nnnnnnnnnn) 2-[2-(6-Fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-1-propyl-1H-benzoimidazole-5-carbonitrile

¹H NMR (399.96MHz, CDCl₃): δ 8.17(dd, J = 2.0, 7.6Hz, 1H, H-18), 8.05(s, 1H, H-4), 7.88(q, J = 8.0Hz, 1H, H-19), 7.52(d, J = 8.4Hz, 1H, H-6), 7.41(d, J = 8.4Hz, 1H, H-7), 7.21(s, 1H, H-14), 7.18(s, 1H, H-15), 6.28(s, 2H, H-13), 4.28(t, J = 7.6Hz, 2H, H-10), 1.68(dt, J = 7.6Hz, 2H, H-11), 0.84(t, J = 7.6Hz, 3H, H-12).

¹³C NMR (100.57MHz, CDCl₃, ¹H decoupled at 399.957MHz): 2-[2-(6-Fluoro-pyridin-2-yl)-imidazol-1-ylmethyl]-1-propyl-1H-benzoimidazole-5-carbonitrile. δ 162.36(d, J_{C-F} = 239.6Hz), 152.53, 148.69(d, J_{C-F} = 13.0Hz), 142.36(d, J_{C-F} = 7.6Hz), 142.31, 142.28, 138.42, 129.96, 126.55, 125.31, 124.23, 120.27(d, J_{C-F} = 3.8Hz), 119.96, 111.23, 108.52(d, J_{C-F} = 35.9Hz), 105.70, 46.10, 44.57, 23.43, 11.27.

Example 21

Additional Compounds

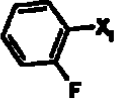
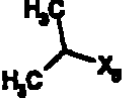
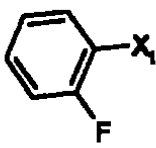
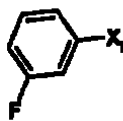
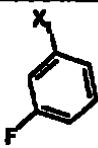
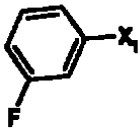
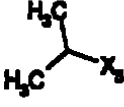
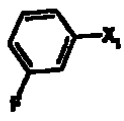
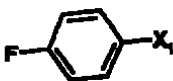
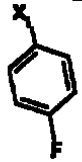
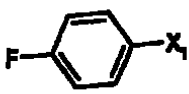
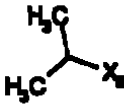
Using the methods described above in examples 1-20 the following compounds are synthesized. In each of Tables I - V "X_n" indicates the point of attachment of the group in which it occurs to the core structure shown in that table, i.e. X₁ indicates the point of attachment of the group R₁ to the shown core structure. The variables shown in the tables, e.g., R₁, R₂, and R₃ do not necessarily correlate to these values of these variable in Formula I.

50257492.122100

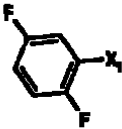
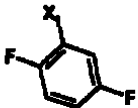
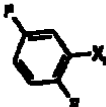
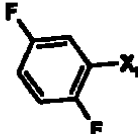
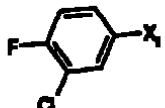
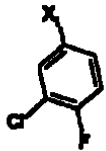
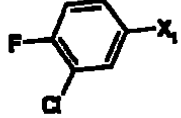
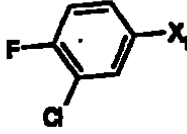
760
741

60257492.122100

Table I					
Ex	R1	R5	RT	Mass	GC/FID or LC/MS
a		H_3C-X_2	1.33	288.2	LC/MS
b			1.80	303.1	LC/MS
c			1.80	317.1	LC/MS
d			1.80	317.1	LC/MS
e		H_3C-X_2	5.08		GC/FID
f			5.08		GC/FID

g			5.07		GC/FID
h			5.17		GC/FID
i			5.12		GC/FID
j			5.11		GC/FID
k			5.10		GC/FID
l			5.20		GC/FID
m			5.12		GC/FID
n			5.12		GC/FID
o			5.11		GC/FID

60257492-122106

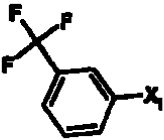
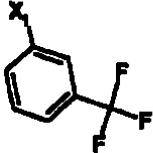
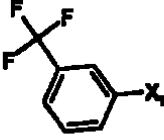
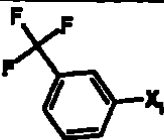
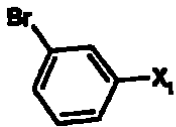
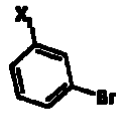
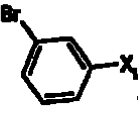
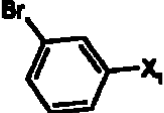
p		$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{X}_2$	5.21		GC/FID
q		$\text{H}_3\text{C}-\text{X}_2$	4.95		GC/FID
r		$\text{X}_2-\text{CH}_2-\text{CH}_3$	4.95		GC/FID
s		$\text{H}_3\text{C}-\text{CH}(\text{X}_2)-\text{CH}_3$	4.95		GC/FID
t		$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{X}_2$	5.05		GC/FID
u		$\text{H}_3\text{C}-\text{X}_2$	5.45		GC/FID
v		$\text{X}_2-\text{CH}_2-\text{CH}_3$	5.43		GC/FID
w		$\text{H}_3\text{C}-\text{CH}(\text{X}_2)-\text{CH}_3$	5.42		GC/FID
x		$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{X}_2$	5.51		GC/FID

60257492 . 122100

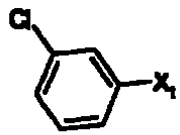
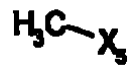
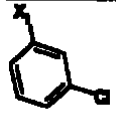
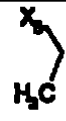
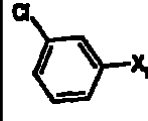
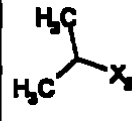
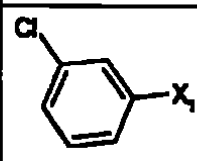
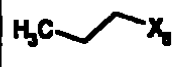
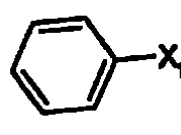
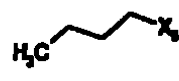
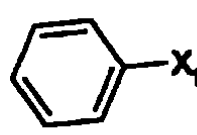
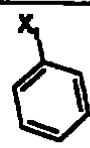
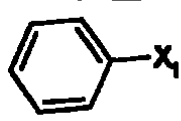
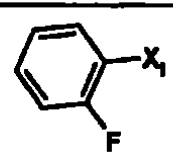
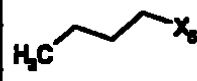
y		$\text{H}_3\text{C}-\text{X}_5$	5.75		GC/FID
z		$\text{X}_5-\text{CH}_2-\text{CH}_3$	5.75		GC/FID
aa		$\text{H}_3\text{C}-\text{CH}(\text{X}_5)-\text{CH}_3$	5.75		GC/FID
bb		$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{X}_5$	5.82		GC/FID
c		$\text{H}_3\text{C}-\text{X}_5$	5.27		GC/FID
cd		$\text{X}_5-\text{CH}_2-\text{CH}_3$	5.27		GC/FID
ee		$\text{H}_3\text{C}-\text{CH}(\text{X}_5)-\text{CH}_3$	5.28		GC/FID
ff		$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{X}_5$	5.37		GC/FID

60257492.122100

60257452.122100

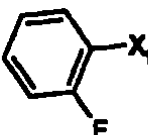
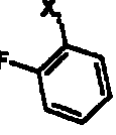
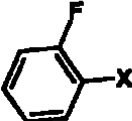
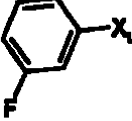
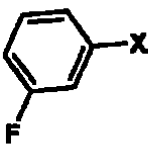
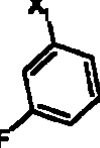
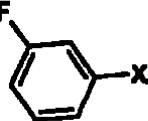
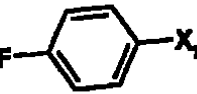
gg		$\text{H}_3\text{C}-\text{X}_9$	4.88		GC/FID
hh		$\text{X}_9-\text{CH}_2-\text{CH}_3$	4.98		GC/FID
ii		$\text{H}_3\text{C}-\text{CH}(\text{X}_9)-\text{CH}_3$	4.98		GC/FID
jj		$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{X}_9$	5.07		GC/FID
kk		$\text{H}_3\text{C}-\text{X}_9$	5.88		GC/FID
ll		$\text{X}_9-\text{CH}_2-\text{CH}_3$	5.87		GC/FID
mm		$\text{H}_3\text{C}-\text{CH}(\text{X}_9)-\text{CH}_3$	5.86		GC/FID
nn		$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{X}_9$	5.74		GC/FID

716..

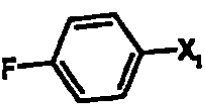
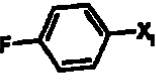
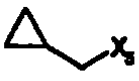
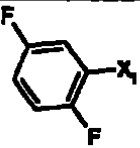
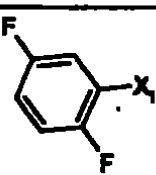
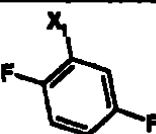
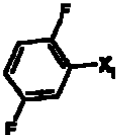
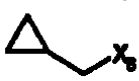
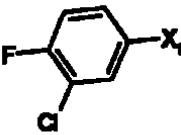
oo			1.87	323.1	LC/MS
pp			1.87	337.3	LC/MS
qq			2.00	351.1	LC/MS
rr			2.07	351.3	LC/MS
ss			2.00	331.3	LC/MS
tt			2.20	387.2	LC/MS
uu			1.80	303.3	LC/MS
vv			1.87	329.2	LC/MS
ww			5.15		GC/FID

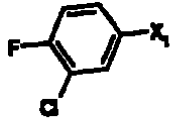
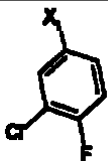
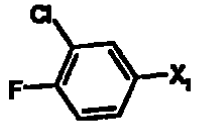
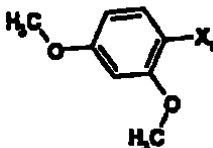
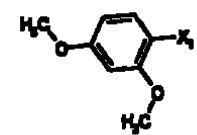
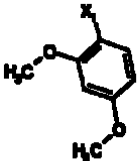
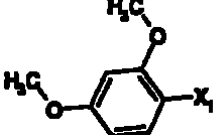
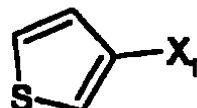
50257492.122100

60257492.1E2100

xx			5.28		GC/FID
yy			4.92		GC/FID
zz			5.28		GC/FID
aaa			5.18		GC/FID
bbb			5.32		GC/FID
ccc			4.97		GC/FID
ddd			5.31		GC/FID
eee			5.18		GC/FID

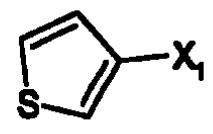
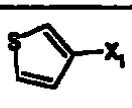
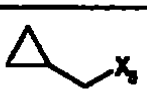
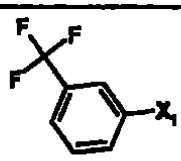
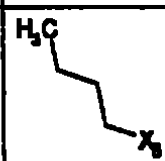
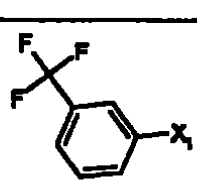
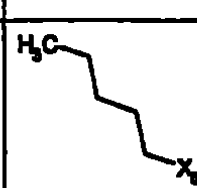
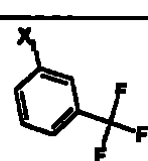
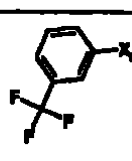
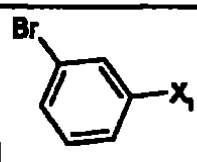
60257492-122100

ff			5.32		GC/FID
ggg			4.87		GC/FID
hhh			5.31		GC/FID
ii			5.04		GC/FID
jj			5.18		GC/FID
kkk			4.82		GC/FID
ll			5.16		GC/FID
mmm			5.47		GC/FID

mm			5.68		GC/FID
ooo			5.28		GC/FID
ppp			5.68		GC/FID
qqq			5.77		GC/FID
rrr			5.68		GC/FID
sss			5.80		GC/FID
ttt			5.68		GC/FID
uuu			5.33		GC/FID

60257492-122100

60257492-122100

vvv			5.46		GC/FID
www			5.12		GC/FID
xxx			5.48		GC/FID
yyy			5.04		GC/FID
zzz			5.17		GC/FID
ssss			4.83		GC/FID
bbbb			5.17		GC/FID
cccc			5.88		GC/FID

725
721

60257492.122100

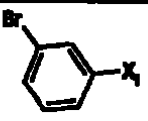
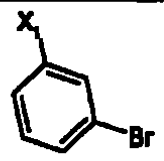
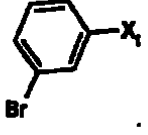
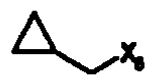
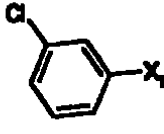
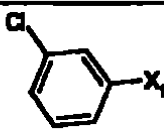
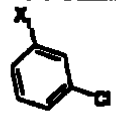
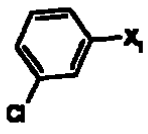
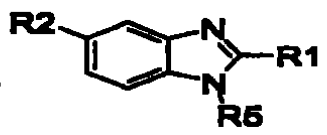
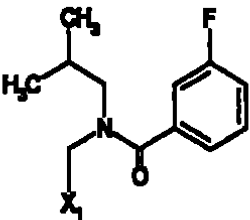
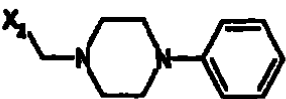
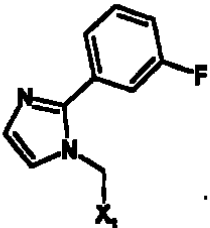
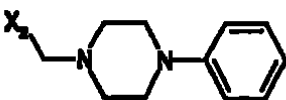
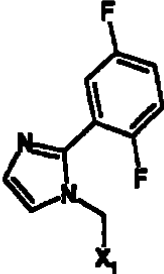
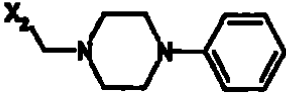
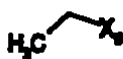
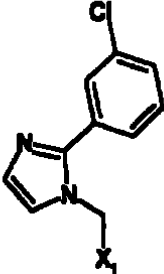
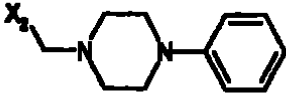
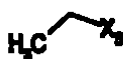
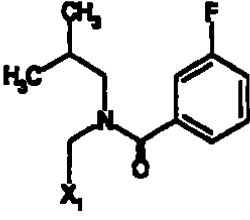
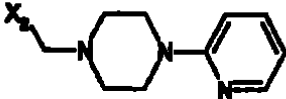
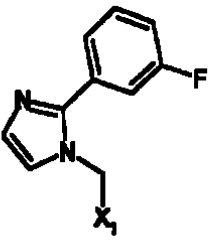
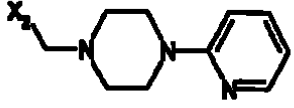
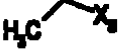
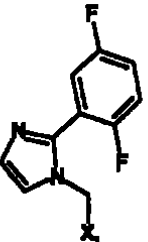
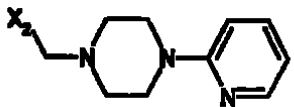
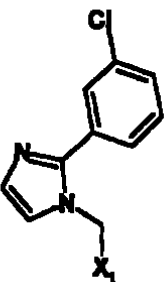
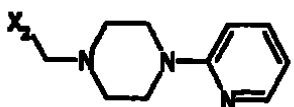
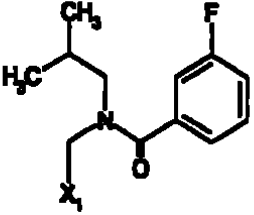
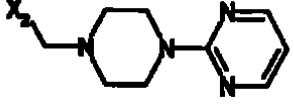
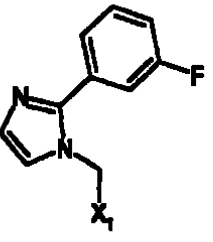
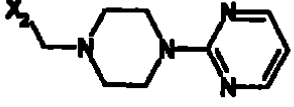
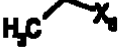
dddd			5.80		GC/FID
eeee			5.50		GC/FID
ffff			5.81		GC/FID
9999			2.20	385.2	LC/MS
hhhh			2.40	379.3	LC/MS
iiii			1.57	337.3	LC/MS
jjjj			2.07	363.3	LC/MS

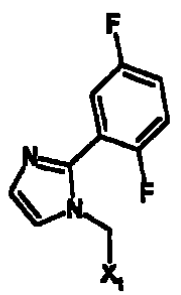
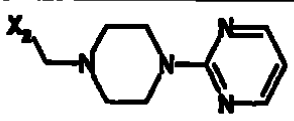
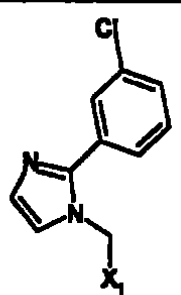
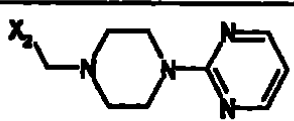
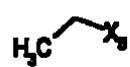
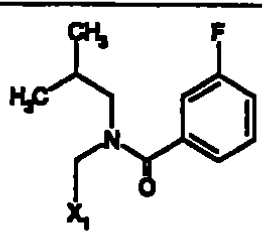
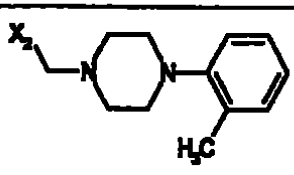
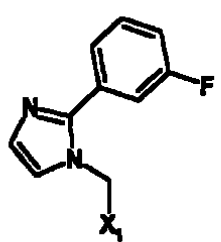
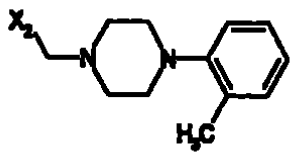
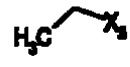
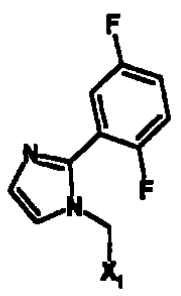
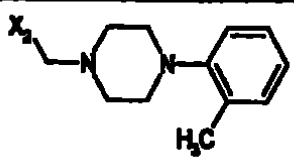
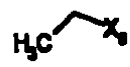
Table II 						
Ex.	R1		R5	RT	Min	GC/FID or LC/MS

Ex.	R1	R2	R5	RT	Mass	GC/FID or LC/MS
a				8.28		GC/FID
b				9.18		GC/FID
c				8.87		GC/FID
d				10.58		GC/FID
e				8.48		GC/FID

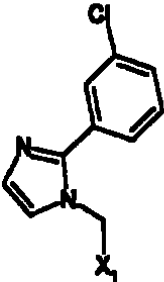
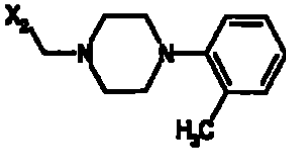
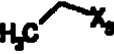
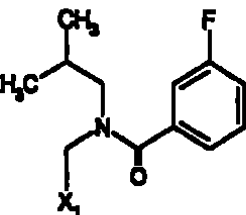
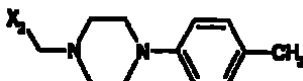
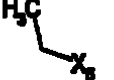
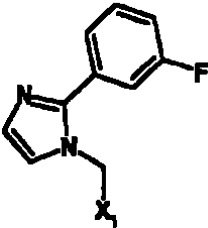
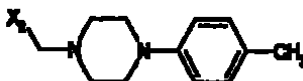
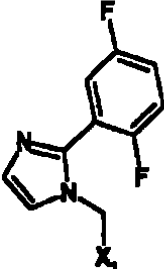
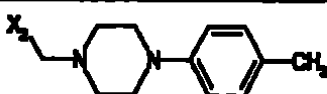
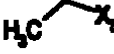
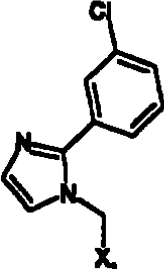
60257493.122100

f				9.39		GC/FID
g				8.87		GC/FID
h				10.91		GC/FID
i				8.25		GC/FID
j				9.12		GC/FID

60257492.1221 0

k				8.61		GC/FID
l				10.46		GC/FID
m				8.14		GC/FID
n				8.98		GC/FID
o				8.49		GC/FID

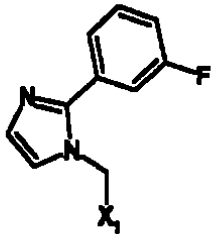
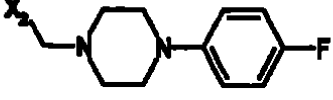
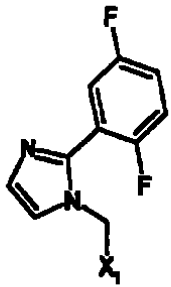
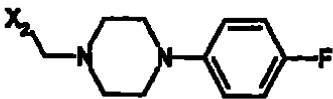
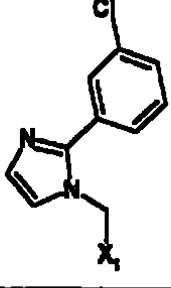
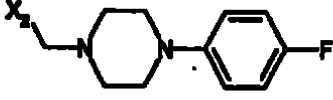
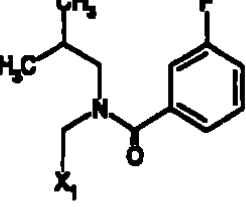
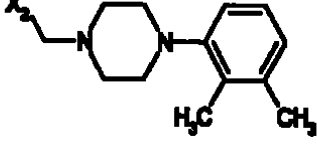
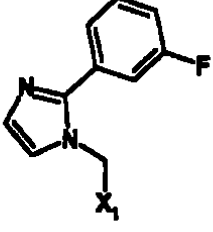
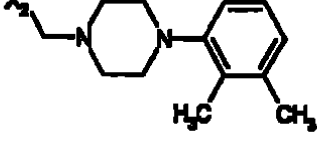
60257492.122100

p				10.28		GC/FID
q				8.72		GC/FID
r				9.77		GC/FID
s				9.17		GC/FID
t				11.41		GC/FID

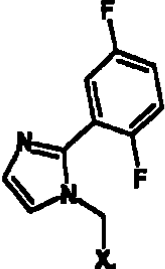
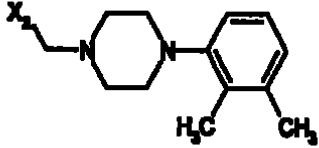
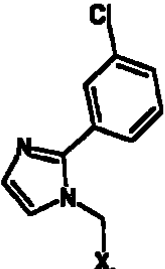
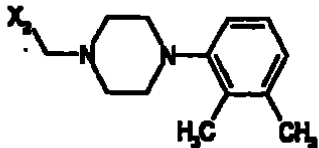
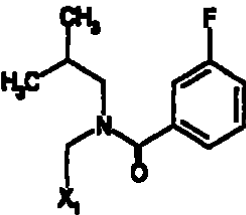
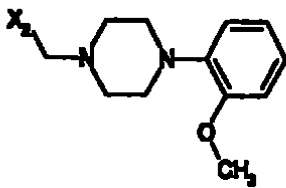
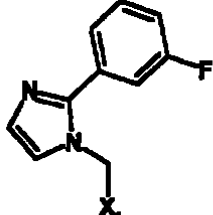
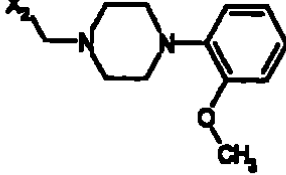
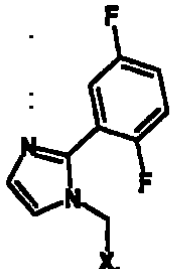
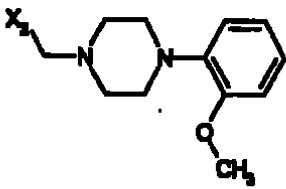
60557492.122100

60257492-162100

u				7.98		GC/FID
v				8.75		GC/FID
w				8.31		GC/FID
x				9.97		GC/FID
y				8.18		GC/FID

z				9.04		GC/FID
aa				8.55		GC/FID
bb				10.38		GC/FID
cc				8.78		GC/FID
dd				9.81		GC/FID

60257492.122100.

ee				9.21		GC/FID
ff				11.49		GC/FID
gg				8.62		GC/FID
hh				9.64		GC/FID
ii				9.05		GC/FID

60257492-122100

j				11.22		GC/FID
kk				9.52		GC/FID
l				10.86		GC/FID
mm				10.08		GC/FID
m				12.97		GC/FID

60257492-122100

60257492.122100

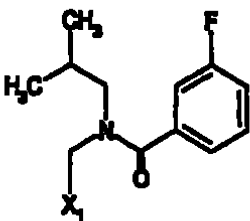
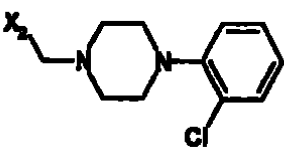
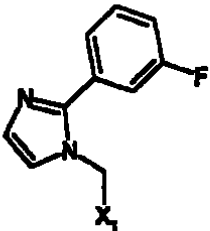
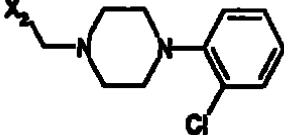
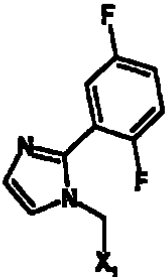
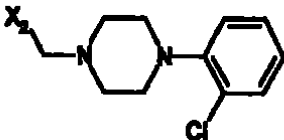
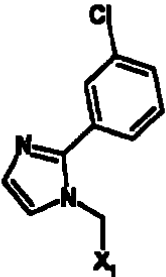
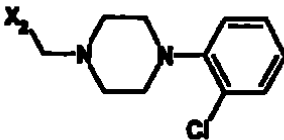
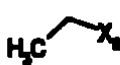
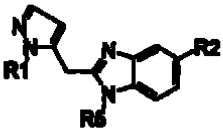
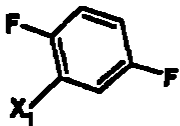
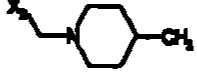
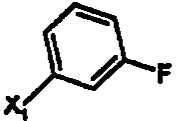
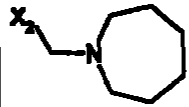
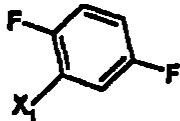
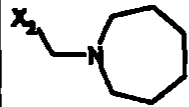
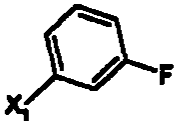
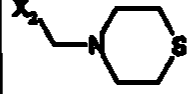
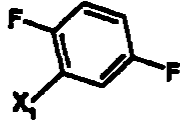
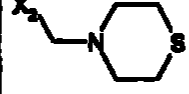
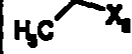
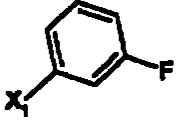
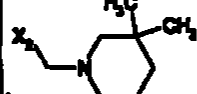
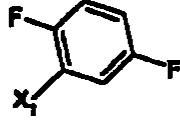
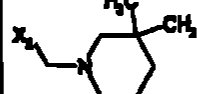
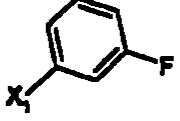
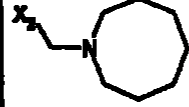
oo				8.78		GC/FID
pp				9.85		GC/FID
qq				9.23		GC/FID
rr				11.52		GC/FID

Table III 						
Ex.	R1	R2	R5	RT	MASS	GC/FID or LC/MS

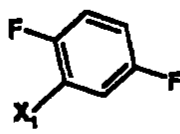
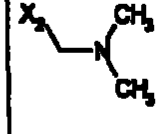
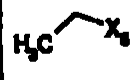
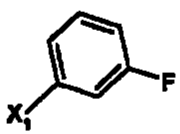
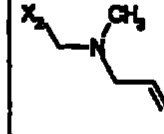
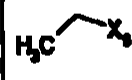
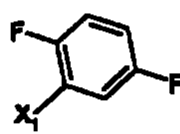
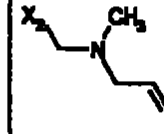
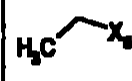
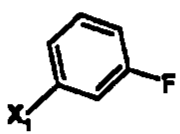
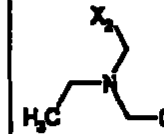
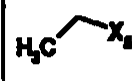
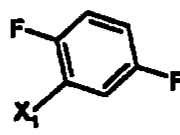
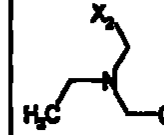
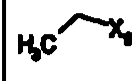
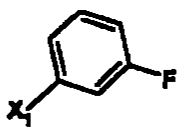
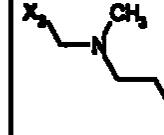
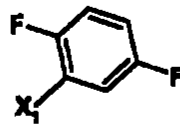
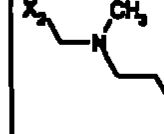
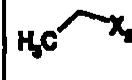
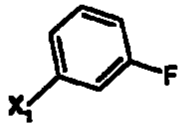
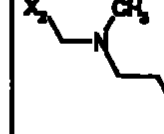
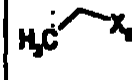
730
731

Ex.	R1	R2	R5	RT	MASS	GC/FID or LC/MS
a				8.17		GC/FID
b				8.02		GC/FID
c				8.32		GC/FID
d				8.15		GC/FID
e				8.37		GC/FID
f				8.20		GC/FID
g				8.40		GC/FID

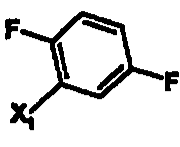
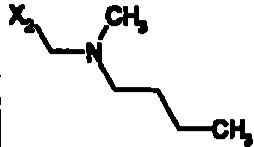
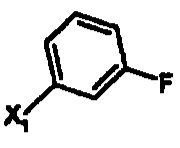
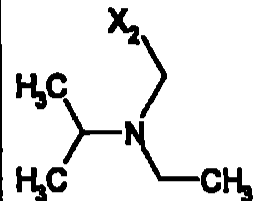
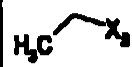
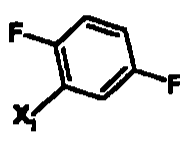
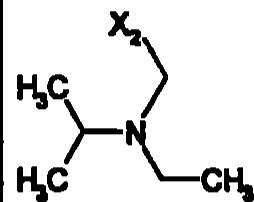
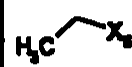
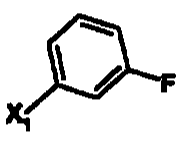
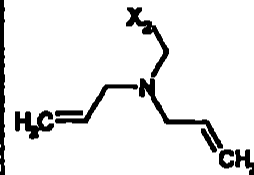
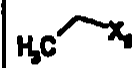
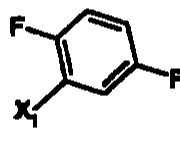
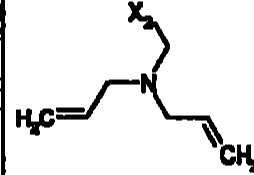
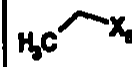
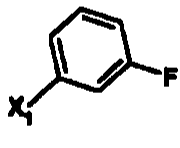
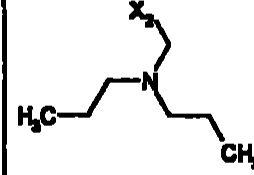
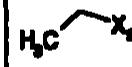
50257492-122100

h				1.32	450.5	LC/MS
i				6.52		GC/FID
j				6.38		GC/FID
k				6.77		GC/FID
l				6.80		GC/FID
m				6.37		GC/FID
n				6.22		GC/FID
o				1.40	448.8	LC/MS

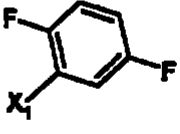
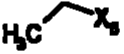
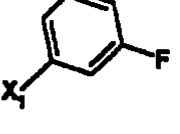
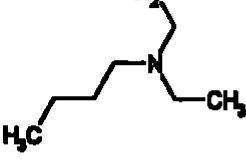
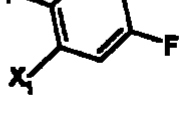
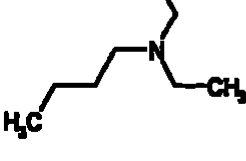
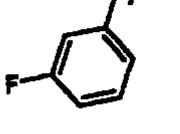
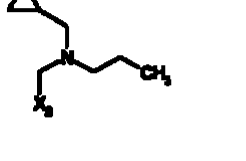
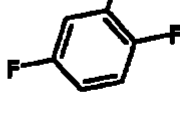
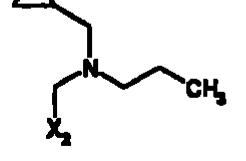
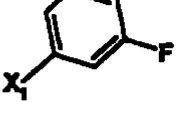
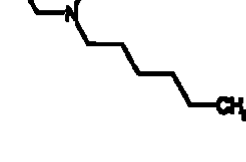
p				8.50		GC/FID
q				8.58		GC/FID
r				8.51		GC/FID
s				7.15		GC/FID
t				8.91		GC/FID
u				7.13		GC/FID
v				8.91		GC/FID
w				5.84		GC/FID

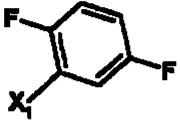
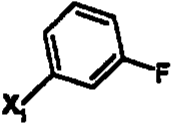
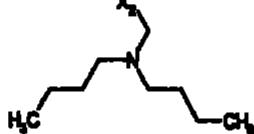
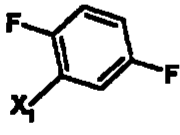
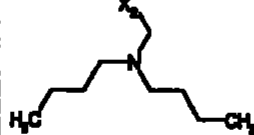
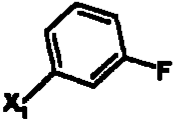
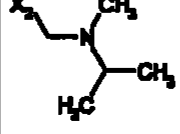
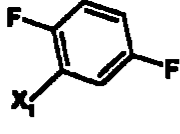
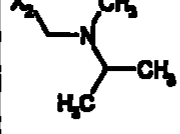
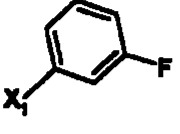
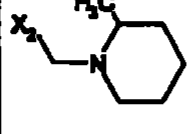
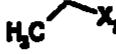
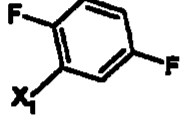
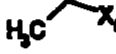
x				5.47		GC/FID
y				5.92		GC/FID
z				5.75		GC/FID
aa				1.13	408.4	LC/MS
bb				5.71		GC/FID
cc				5.91		GC/FID
dd				5.74		GC/FID
ee				6.05		GC/FID

50257492.122100

π				5.89		GC/FID
gg				5.89		GC/FID
hh				5.82		GC/FID
ii				8.11		GC/FID
jj				5.98		GC/FID
kk				5.08		GC/FID

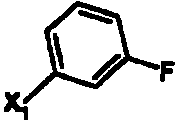
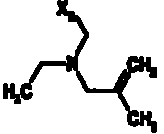
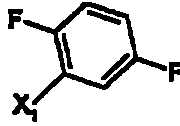
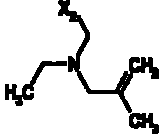
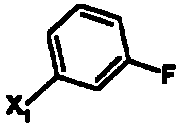
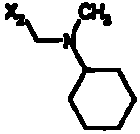
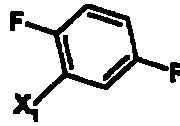
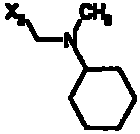
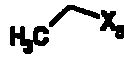
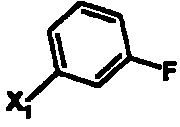
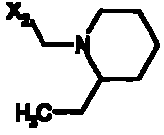
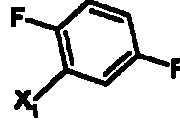
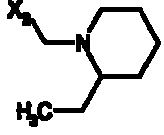
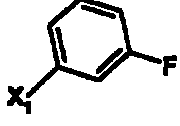
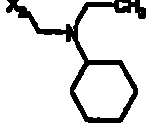
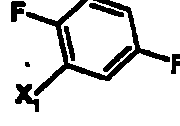
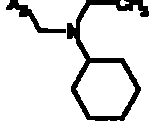
60257492.122100

ii						
				5.94		GC/FID
mm						
				6.11		GC/FID
nn						
				5.88		GC/FID
oo						
				6.33		GC/FID
pp						
				6.18		GC/FID
qq						
				6.35		GC/FID

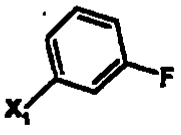
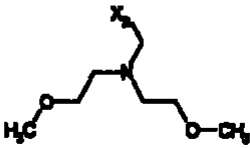
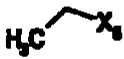
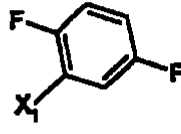
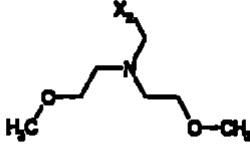
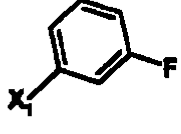
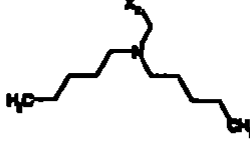
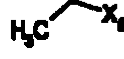
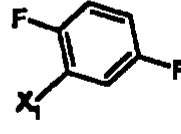
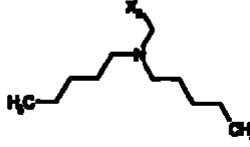
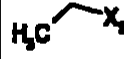
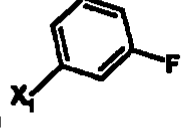
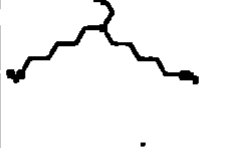
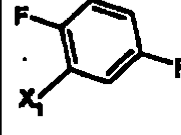
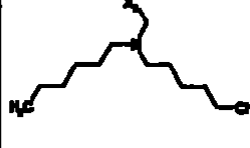
tt				8.18		GC/FID
ss				8.21		GC/FID
tt				8.07		GC/FID
uu				5.81		GC/FID
vv				5.84		GC/FID
ww				8.28		GC/FID
xx				8.13		GC/FID

60257492-122100

60257492.122100

yy				6.87		GC/FID
zz				6.82		GC/FID
aaa				6.61		GC/FID
bbb				6.38		GC/FID
ccc				6.42		GC/FID
ddd				6.28		GC/FID
eee				6.52		GC/FID
fff				6.38		GC/FID

60257492.122100

ggg						
				8.34		GC/FID
hhh						
				8.18		GC/FID
ii						
				8.46		GC/FID
jj						
				8.32		GC/FID
kdk						
				8.71		GC/FID
ll						
				2.18	558.8	LC/MS

740

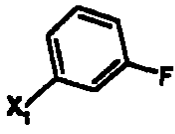
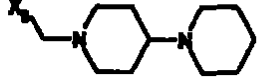
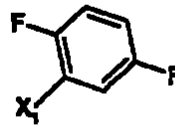
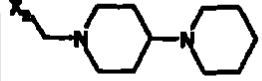
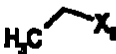
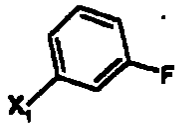
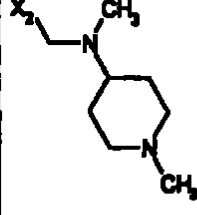
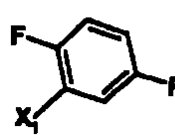
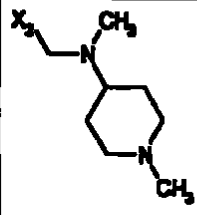
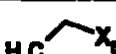
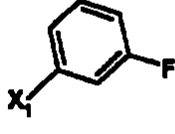
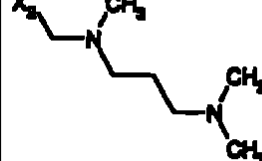
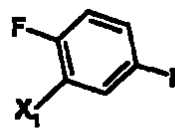
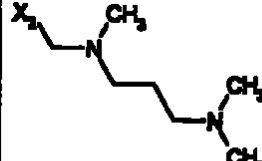
60257492.122100

mmm				8.28		GC/FID
nnn				8.12		GC/FID
ooo				7.38		GC/FID
ppp				7.11		GC/FID
qqq				1.48	515.8	LC/MS
rrr				7.86		GC/FID
sss				8.34		GC/FID
ttt				8.18		GC/FID

745
741

uuu				8.47		GC/FID
vvv				8.32		GC/FID
www				8.10		GC/FID
xxx				8.95		GC/FID
yyy				8.15		GC/FID
zzz				8.00		GC/FID
aaaa				7.43		GC/FID
bbbb				7.15		GC/FID

60257492.12210

cccc				7.74		GC/FID
dddd				7.41		GC/FID
eeee				8.85		GC/FID
fff				8.50		GC/FID
gggg				8.23		GC/FID
hhhh				8.08		GC/FID

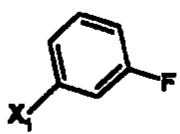
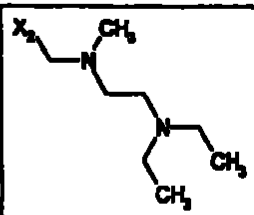
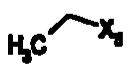
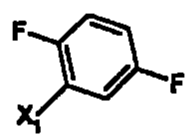
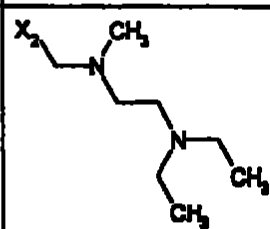
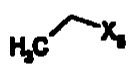
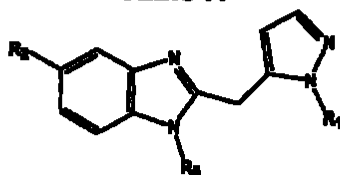
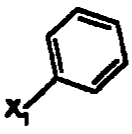
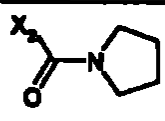
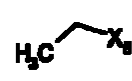
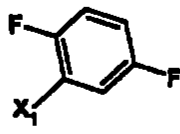
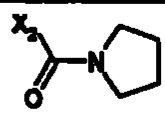
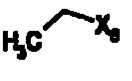
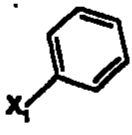
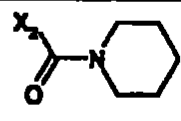
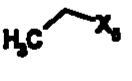
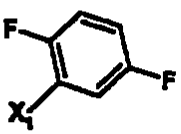
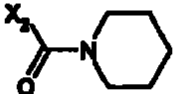
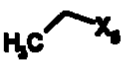
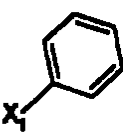
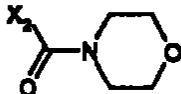
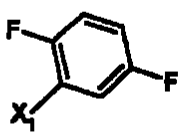
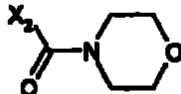
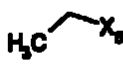
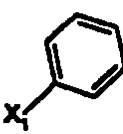
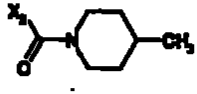
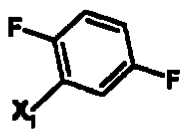
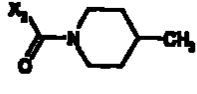
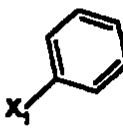
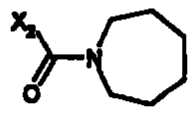
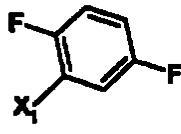
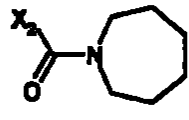
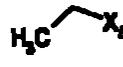
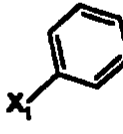
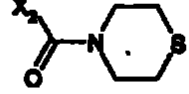
III				6.30	GC/FID
III				6.15	GC/FID

Table IV



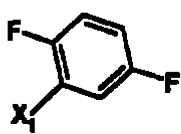
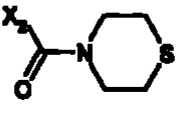
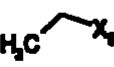
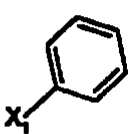
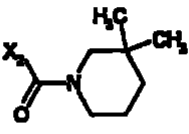
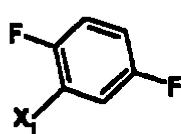
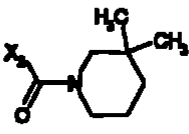
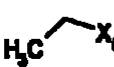
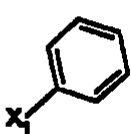
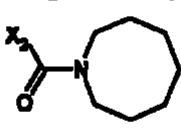
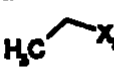
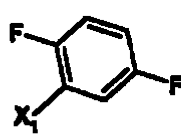
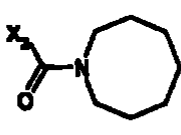
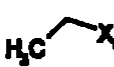
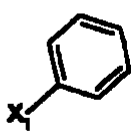
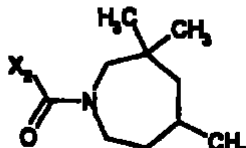
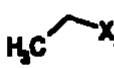
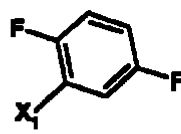
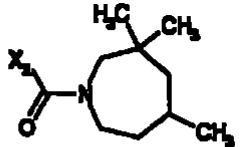
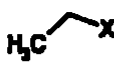
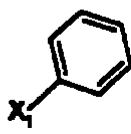
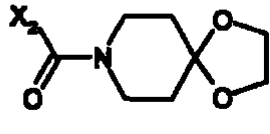
Ex	R1	R2	R3	RT	Mass	GC/FID or LC/MS
a				7.12		GC/FID
b				6.77		GC/FID
c				7.17		GC/FID

60257492.122100

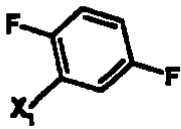
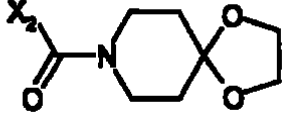
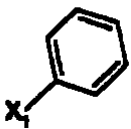
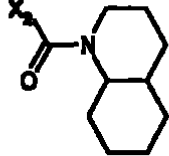
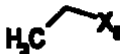
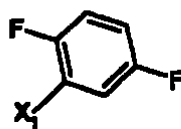
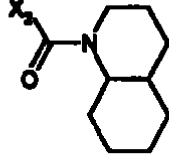
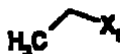
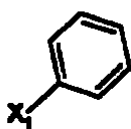
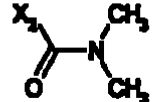
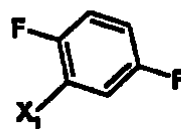
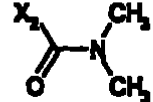
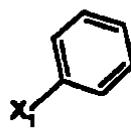
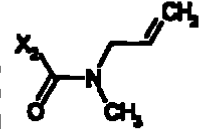
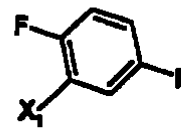
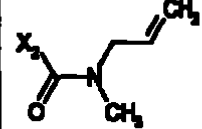
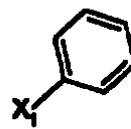
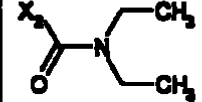
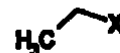
d				8.82		GC/FID
e				7.10		GC/FID
f				8.77		GC/FID
g				7.30		GC/FID
h				8.82		GC/FID
i				7.53		GC/FID
j				7.07		GC/FID
k				7.78		GC/FID

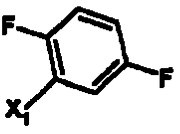
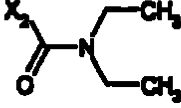
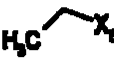
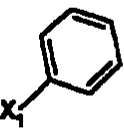
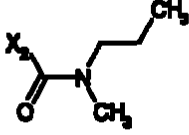
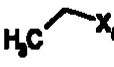
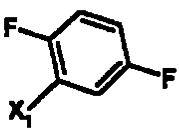
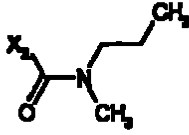
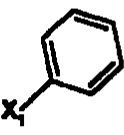
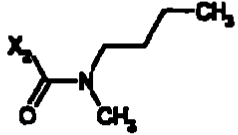
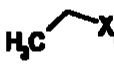
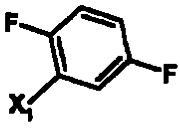
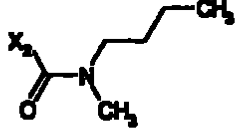
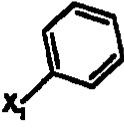
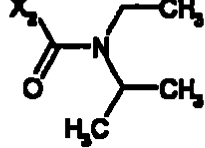
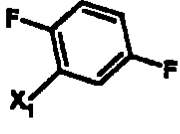
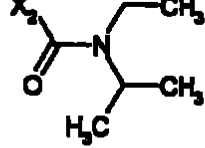
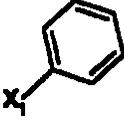
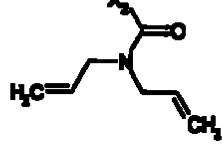
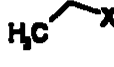
745.

60257492-122100

l				7.28		GC/FID
m				7.28		GC/FID
n				8.82		GC/FID
o				7.88		GC/FID
p				7.34		GC/FID
q				7.77		GC/FID
r				7.28		GC/FID
s				1.44	472A	LC/MS

60257492-122100

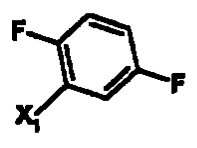
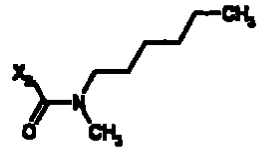
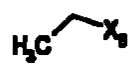
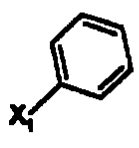
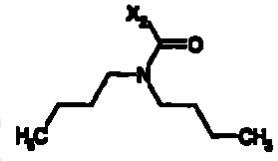
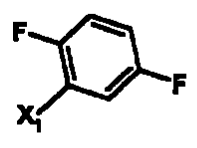
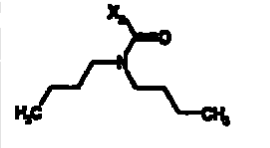
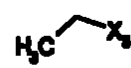
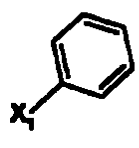
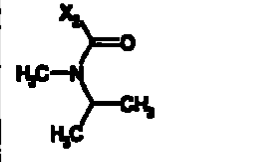
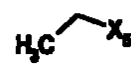
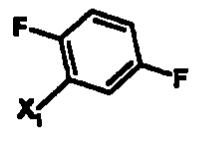
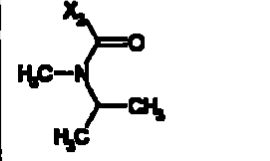
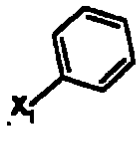
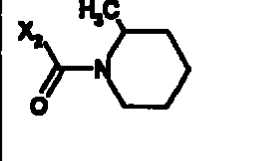
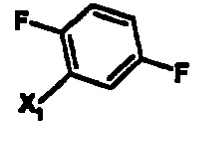
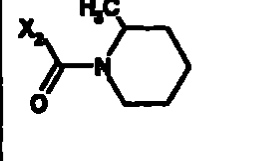
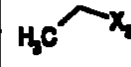
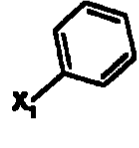
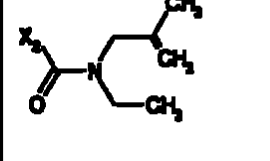
t				1.58	608.4	LC/MS
u				2.02	488.5	LC/MS
v				7.84		GC/FID
w				8.41		GC/FID
x				1.32	410.3	LC/MS
y				8.58		GC/FID
z				8.35		GC/FID
aa				8.54		GC/FID

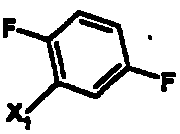
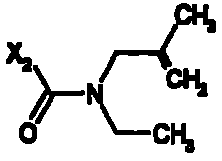
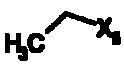
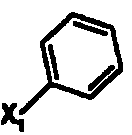
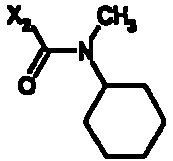
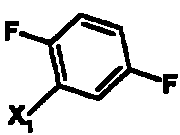
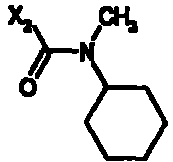
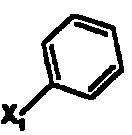
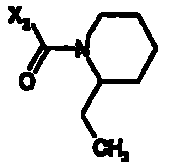
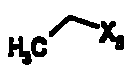
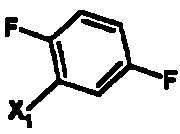
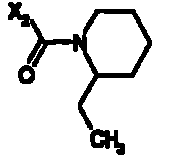
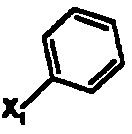
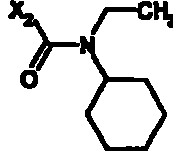
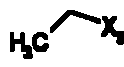
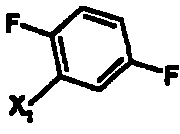
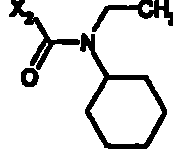
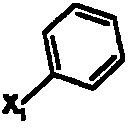
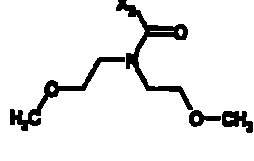
bb				8.28		GC/FID
gc				8.81		GC/FID
dd				8.37		GC/FID
ee				8.78		GC/FID
ff				8.50		GC/FID
gg				8.68		GC/FID
hh				8.34		GC/FID
ii				8.72		GC/FID

60257492, 122100

j				8.47		GC/FID
kk				8.74		GC/FID
l				8.80		GC/FID
mm				8.78		GC/FID
nn				8.52		GC/FID
oo				7.06		GC/FID
pp				8.74		GC/FID
qq				7.13		GC/FID

60257492.122100

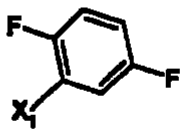
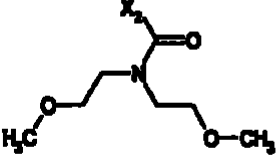
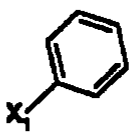
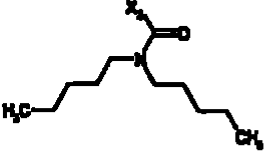
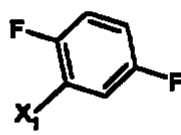
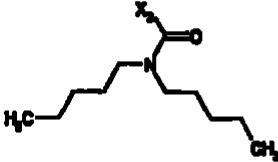
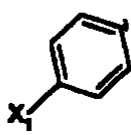
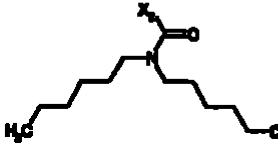
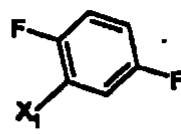
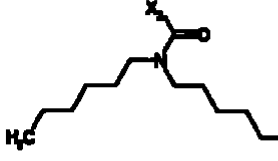
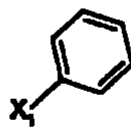
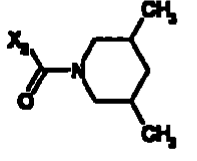
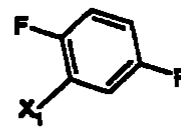
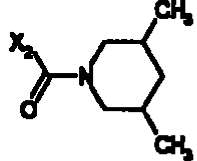
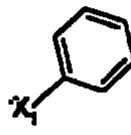
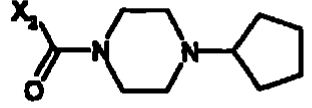
tt				2.14	480.5	LC/MS
ss				6.98		GC/FID
tt				8.87		GC/FID
uu				8.48		GC/FID
vv				8.28		GC/FID
ww				7.13		GC/FID
xx				8.77		GC/FID
yy				8.85		GC/FID

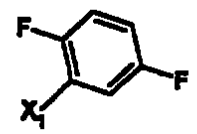
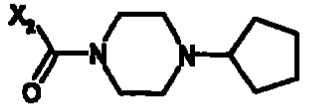
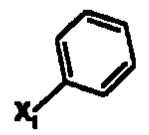
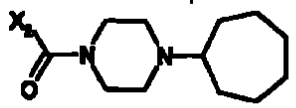
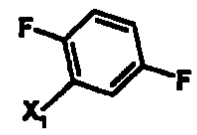
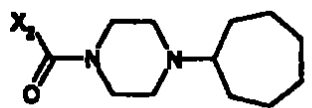
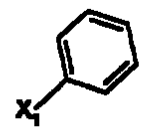
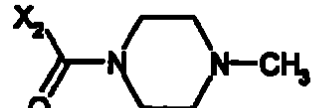
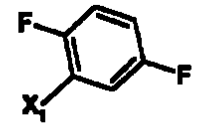
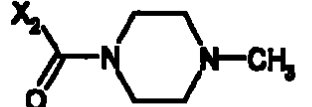
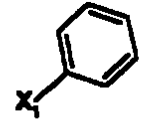
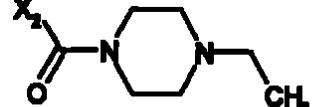
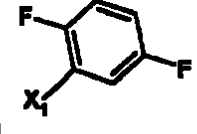
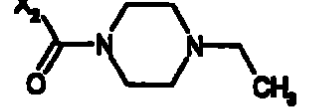
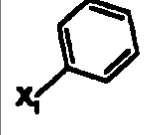
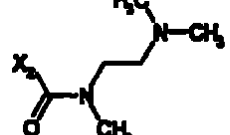
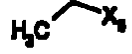
zz				8.42		GC/FID
888				7.39		GC/FID
bbb				7.00		GC/FID
ccc				7.28		GC/FID
ddd				8.80		GC/FID
eee				1.89	458.5	LC/MS
fff				2.08	482.5	LC/MS
ggg				7.00		GC/FID

60257492.122100

756
751

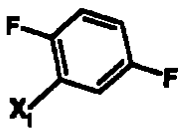
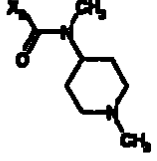
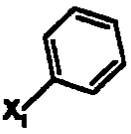
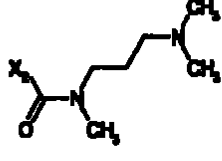
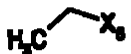
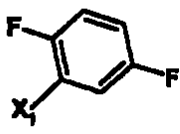
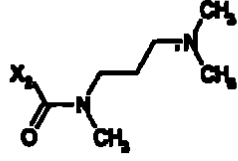
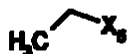
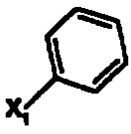
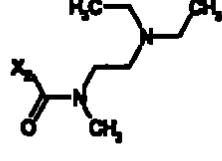
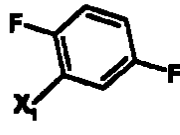
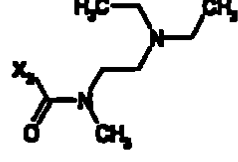
60257492-122100

hhh				8.71		GC/FID
iii				7.31		GC/FID
jjj				2.45	545.8	LC/MS
kkk				7.98		GC/FID
lll				2.85	550.7	LC/MS
mnn				7.14		GC/FID
nnn				8.81		GC/FID
ooo				8.51		GC/FID

PPP				8.84		GC/FID
QQQ				11.84		GC/FID
TTT				1.48	547.7	LC/MS
SSS				7.22		GC/FID
RR				8.83		GC/FID
UUU				7.44		GC/FID
VVV				7.04		GC/FID
WWW				8.83		GC/FID

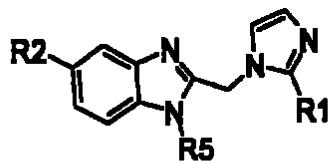
60257492-1EE100

xxx				8.58		GC/FID
yyy				8.84		GC/FID
zzz				8.58		GC/FID
aaaa				8.83		GC/FID
bbbb				8.84		GC/FID
cccc				1.05	487.8	LC/MS
dddd				8.18		GC/FID
eeee				7.81		GC/FID

fff				7.17		GC/FID
gggg				7.02		GC/FID
hhhh				8.72		GC/FID
iii				1.05	488.5	LC/MS
iiii				8.79		GC/FID

755:

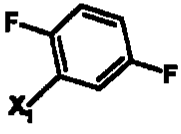
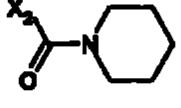
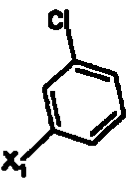
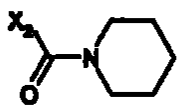
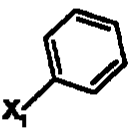
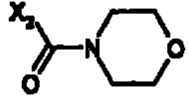
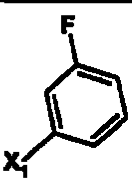
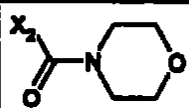
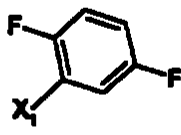
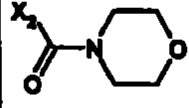
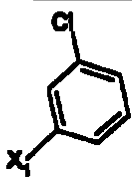
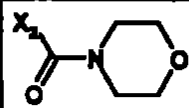
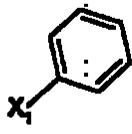
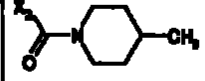
Table V



Ex.	R1	R2	R5	RT	Mass	GC/FID or LC/MS
a				NA		
b				1.73	432.1	LC/MS
c				1.87	460.4	LC/MS
d				1.87	448.3	LC/MS
e				1.87	428.4	LC/MS
f				1.94	448.4	LC/MS

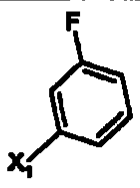
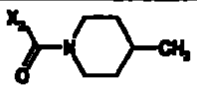
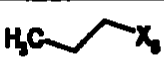
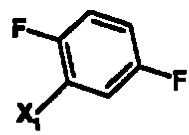
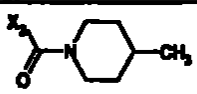
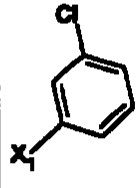
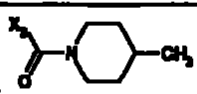
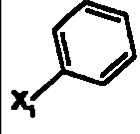
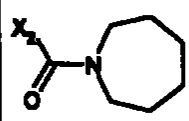
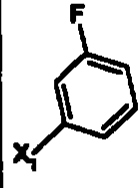
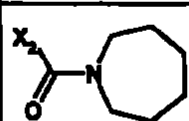
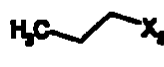
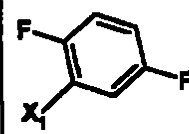
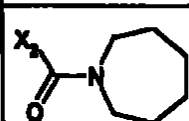
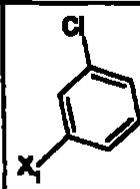
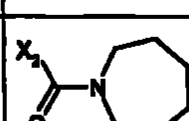
60257492, 122100

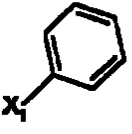
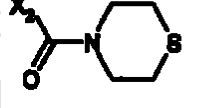
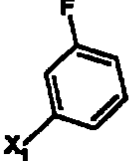
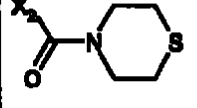
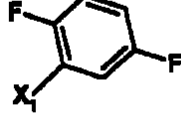
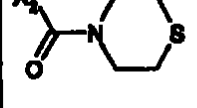
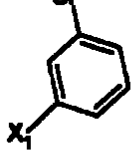
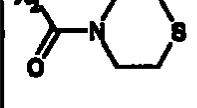
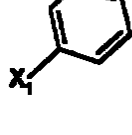
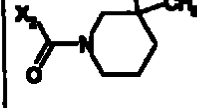
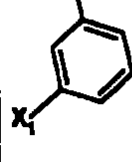
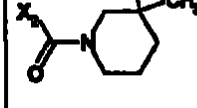
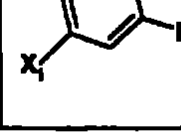
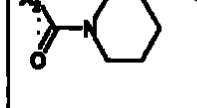
7561

g				1.87	484.4	LC/MS
h				2.07	482.4	LC/MS
i				2.87	430	LC/MS
j				1.53	448.3	LC/MS
k				1.47	488.5	LC/MS
l				1.87	484.4	LC/MS
m				2.07	442.8	LC/MS

757

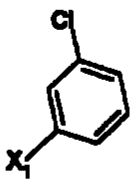
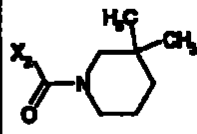
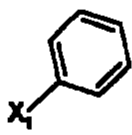
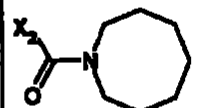
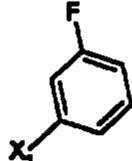
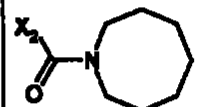
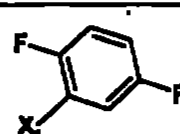
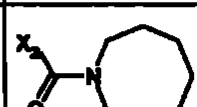
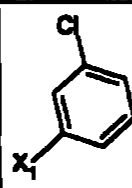
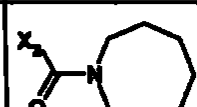
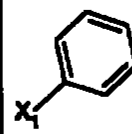
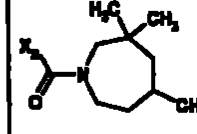
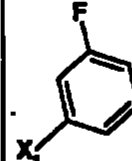
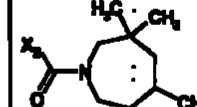
60257492-122100

n				213	480.3	LC/MS
o				NA		
p				220	488.3	LC/MS
q				200	442.6	LC/MS
r				207	480.3	LC/MS
s				200	500.4	LC/MS
t				213	488.3	LC/MS

u				1.73	468.4	LC/MS
v				1.80	464.4	LC/MS
w				1.73	482.2	LC/MS
x				NA		
y				2.13	468.4	LC/MS
z				NA		
aa				2.13	482.4	LC/MS

60257492-122100

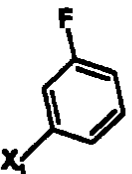
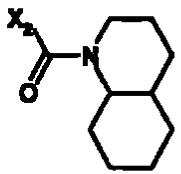
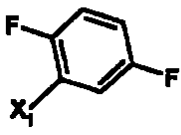
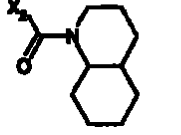
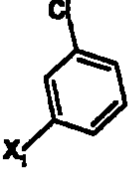
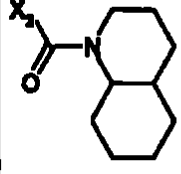
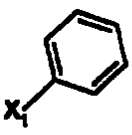
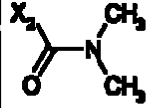
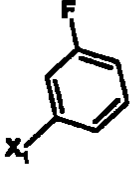
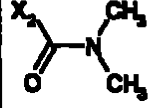
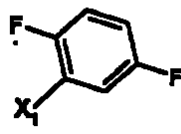
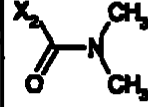
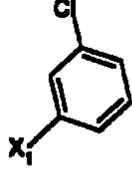
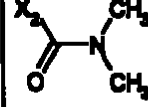
759

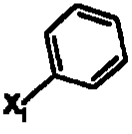
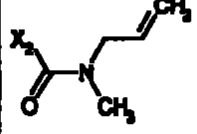
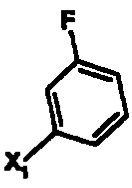
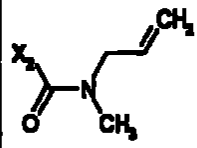
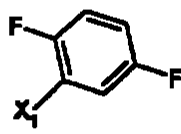
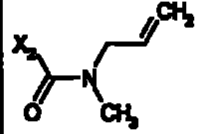
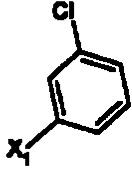
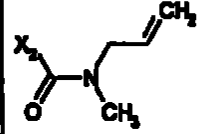
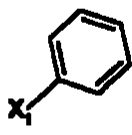
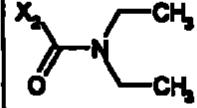
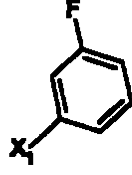
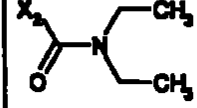
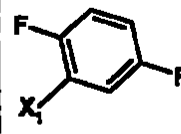
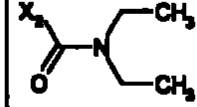
bb				2.27	480.3	LC/MS
cc				2.13	458.4	LC/MS
dd				NA		
ee				2.13	482.4	LC/MS
ff				2.27	480.5	LC/MS
gg				2.40	484.5	LC/MS
hh				2.47	502.3	LC/MS

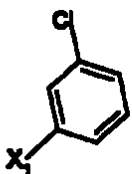
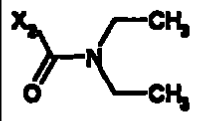
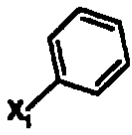
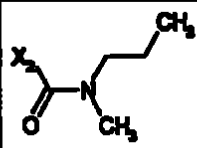
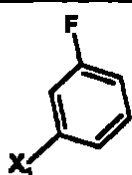
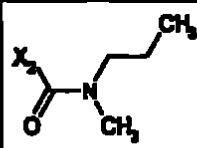
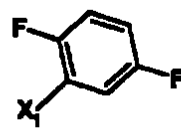
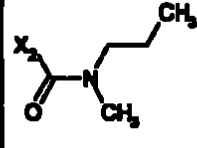
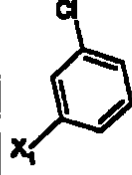
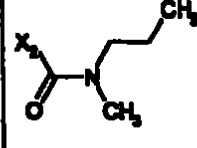
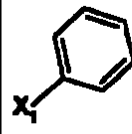
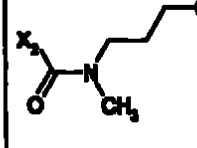
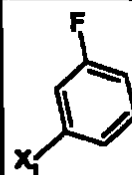
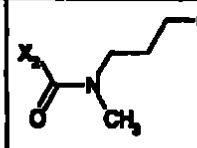
760

I				NA		
J				NA		
kk				1.73	488.3	LC/MS
ll				1.73	504.3	LC/MS
mm				NA		
nn				1.87	520.2	LC/MS
oo				2.34	482.5	LC/MS

766
761

pp				240	500.4	LC/MS
qq				234	518.4	LC/MS
rr				247	516.4	LC/MS
ss				1.47	388.5	LC/MS
tt				1.53	408.3	LC/MS
uu				1.47	424.2	LC/MS
vv				1.73	522.2	LC/MS

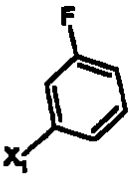
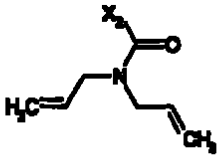
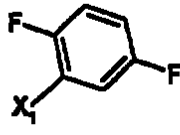
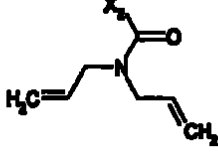
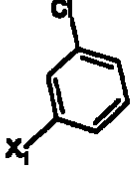
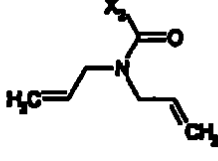
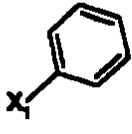
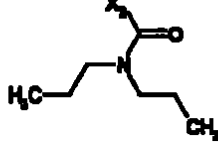
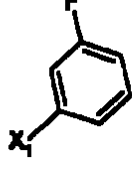
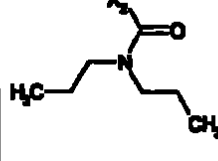
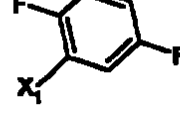
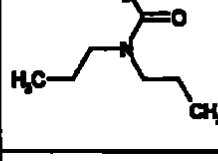
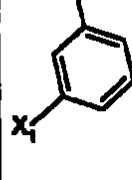
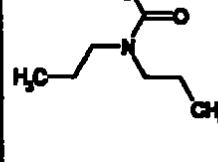
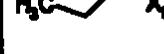
ww				1.80	414.4	LC/MS
xx				1.87	432.1	LC/MS
yy				1.73	450.3	LC/MS
zz				1.83	448.5	LC/MS
aaa				1.80	418.4	LC/MS
bbb				1.87	434.5	LC/MS
ccc				1.80	462.4	LC/MS

ddd				2.00	480.3	LC/MS
eee				1.80	418.4	LC/MS
fff				1.87	434.5	LC/MS
ggg				1.80	452.4	LC/MS
hhh				2.00	450.3	LC/MS
ii				2.00	430.2	LC/MS
jj				2.07	448.8	LC/MS

60257492-122100

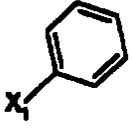
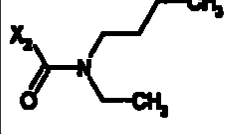
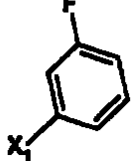
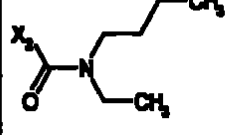
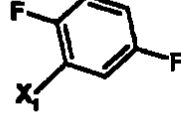
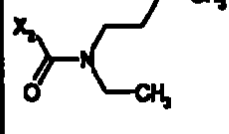
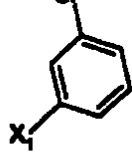
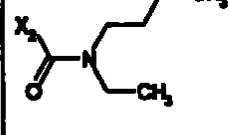
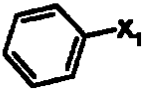
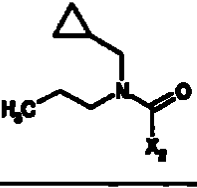
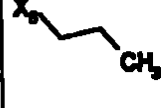
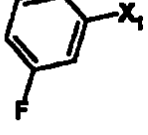
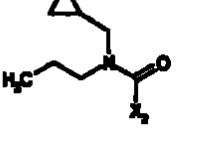
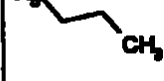
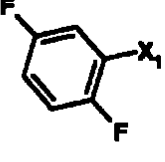
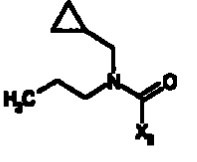
kkk				2.00	488.3	LC/MS
lll				2.20	484.4	LC/MS
mmm				1.93	430.2	LC/MS
nnn				2.00	448.8	LC/MS
ooo				1.93	488.3	LC/MS
ppp				2.13	484.4	LC/MS
qqq				2.00	440.7	LC/MS

765:

III				2.07	458.4	LC/MS
III				NA		
III				NA		
UUU				2.13	444.8	LC/MS
VVV				2.20	482.4	LC/MS
WWW				NA		
XXX				NA		

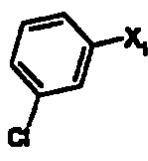
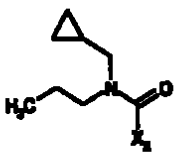
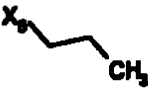
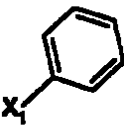
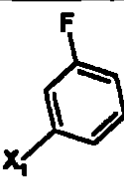
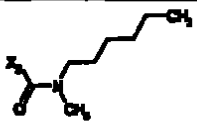
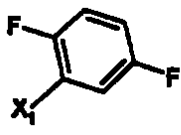
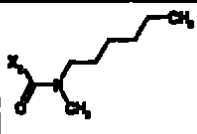
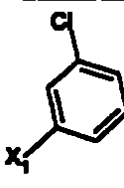
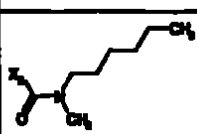
60257492.122100

266

yyy				213	444.8	LC/MS
zzz				220	482.4	LC/MS
ssss				NA		
bbbb				NA		
cccc				220	458.4	LC/MS
dddd				NA		
eeee				NA		

60257492-122100

767

III				234	480.3	LC/MS
9999				234	488.4	LC/MS
hhhh				NA		
III				234	484.5	LC/MS
III				247	482.4	LC/MS

60257492-122100

TABLE VI

Ex.	Name	Analytical Data
a	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-1H-imidazo[4,5-b]pyridine	(HCl salt) H-1 NMR (dmsO): 1.05 (t, 3H), 2.03 (h, 2H), 4.62 (t, 2H), 6.58 (s, 2H), 7.24(d, 1H), 7.82 (t, 1H), 7.95 (s, 1H), 8.05 (m, 2H), 8.25(q, 1H), 8.62(d, 1H), 8.93 (d, 1H) LC-MS: M + 1, 337
b	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-ethyl-1H-imidazo[4,5-b]pyridine	(HCl salt) H-1 NMR (dmsO): 1.63(t, 3H), 4.72(q, 2H), 6.58(s, 2H), 7.30 (d, 1H), 7.82(m, 1H), 7.96(s, 1H), 8.03(m, 2H), 8.24(q, 1H), 8.60(d, 1H), 8.90(d, 1H) LC-MS: M + 1, 323
c	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-isobutyl-1H-imidazo[4,5-b]pyridine	(HCl salt) H-1 NMR (dmsO): 1.05 (d, 6H), 2.40 (h, 1H), 4.50 (d, 2H), 6.57 (s, 2H), 7.30 (d, 1H), 7.82 (m, 1H), 7.93(s, 1H), 8.03(m, 2H), 8.23(q, 1H), 8.62(d, 1H), 8.95(d, 1H) LC-MS: M + 1, 351
d	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-cyclopropylmethyl-1H-imidazo[4,5-b]pyridine	(free base) H-1 NMR (CDCl ₃): 0.30 (m, 2H), 0.57(m, 2H), 1.05 (m, 1H), 4.23(d, 2H), 6.38(s, 2H), 6.80(d, 1H), 7.08(s, 1H), 7.22 (m, 1H), 7.39(s, 1H), 7.73(d, 1H), 7.90(q, 1H), 8.20(d, 1H), 8.58(d, 1H) LC-MS: M + 1, 349
e	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-allyl-1H-imidazo[4,5-b]pyridine	(HCl) salt Melting point: 225-231 (decompose) H-1 NMR (dmsO): 5.22-5.53 (m, 4H), 6.21(m, 1H), 6.53 (s, 2H), 7.24(d, 1H), 7.82 (m, 1H), 7.95(s, 1H), 8.05(m, 2H), 8.25(q, 1H), 8.62(d, 1H), 8.82(d, 1H) LC-MS: M + 1, 335
f	2-[[2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-ethyl-4-fluoro-1H-imidazo[4,5-c]pyridine	1H nmr (CDCl ₃): 7.97(1H, dd), 7.53-7.48(1H, m), 7.44-7.38(2H, m), 7.22-7.12(3H, m), 7.04(1H, s), 5.55(2H, s), 3.75(2H, q), 0.96(3H, t), LRMS calcd. 339.34, found 340.1(MH ⁺).
g	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-5-(1,2,4-oxadiazol-3-yl)-1H-benzimidazole	Formate d6-DMSO: 9.62 (s, 1H), 7.99-8.09 (m, 3H), 7.90 (d, J = 8.24 Hz, 1H), 7.79 (d, J = 8.79 Hz, 1H), 7.52 (s, 1H), 7.17 (s, 1H), 7.02 (d, J = 7.41 Hz, 1H), 6.16 (s, 2H), 4.34-4.39 (m, 2H), 1.7-1.84 (m, 2H), 0.92 (t, J = 7.14 Hz, 3H).
h	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-5-(1,3,4-oxadiazol-3-yl)-1H-benzimidazole	CDCl ₃ : 8.45 9s, 1H), 8.43 (s, 1H), 8.19 (d, J = 7.14 Hz, 1H), 8.10 (d, J = 8.38 Hz, 1H), 7.90(q, J = 7.96 Hz, 1H), 7.48 (d, J = 8.52 Hz, 1H), 7.19 (s, 1H), 6.89-6.92 (m, 1H), 6.33 (s, 2H), 4.3 (t, J = 7.42 Hz, 2H), 1.67-1.74 9m, 2H), 0.86 (t, J = 7.42 Hz, 3H). LCMS MH ⁺ 404.6, MH ⁺ 402.3.
i	2-[[2-(2-Chloropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-5-(1,3,4-oxadiazol-3-yl)-3H-imidazo[4,5-b]pyridine	1H nmr (CDCl ₃): 9.14(1H, d), 8.63(1H, d), 8.51(1H, s), 8.26(1H, d), 7.76(1H, t), 7.28-7.24(3H, m), 6.36(2H, s), 4.42(2H, t), 1.81-1.74(2H, m), 0.88(3H, t), LRMS calcd. 420.9, found 421.3(MH ⁺).

j	2-[(2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl)methyl]-1-propyl-5-(1,3,4-oxadiazol-3-yl)-3H-imidazo[4,5-b]pyridine	LRMS calcd. 404.4, found 405.3(MH ⁺).
k	N-(2-Aza-5-oxabicyclo[2.2.1]heptane)-2-[(2-(2-fluoropyrid-6-yl)-1H-imidazol-1-yl)methyl]-1-propyl-1H-benzimidazole-5-carboxamide	CDCl ₃ : 8.18 (d, 7.97 Hz, 1H), 7.85-7.94 (m, 2H), 7.52-7.54 (m, 1H), 7.38-7.42 (m, 1H), 7.17-7.26 (m, 2H), 6.90 (d, J = 7.96 Hz, 1H), 6.30 (s, 2H), 4.73-5.06 (m, 1H), 4.56 (d, 1H), 4.24-4.35 (m, 2H), 4.04-4.10 (m, 1H), 3.81-3.89 (m, 1H), 3.51-3.7 (m, 2H), 1.96 (s, 1H), 1.86 (s, 1H), 1.64-1.71 (m, 2H), 0.83 (t, J = 7.28 Hz, 3H).
l	2-[(2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl)methyl]-1-propyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)-1H-benzimidazole	d ₆ -DMSO: 7.94-8.09 (m, 3H), 7.82 (d, 1H), 7.76 (d, 1H), 7.47 (s, 1H), 7.18 (s, 1H), 7.03 (d, 1H), 6.15 (s, 2H), 4.35 (t, 2H), 2.65 (s, 3H), 1.74-1.82 (m, 2H), 0.94 (t, 3H). LCMS MH ⁺ 418.3, MH ⁺ 416.2.
m	2-[(2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl)methyl]-1-propyl-5-(5-methyl-1,3,4-oxadiazol-3-yl)-1H-benzimidazole	CDCl ₃ : 8.36 (s, 1H), 8.18 (dd, 1H), 8.03 (dd, 1H), 7.89 (q, 1H), 7.44 (d, 1H), 7.25 (s, 1H), 7.17 (s, 1H), 6.90 (dd, 1H), 6.33 (s, 2H), 4.29 (t, 2H), 2.59 (s, 3H), 1.59-1.74 (m, 2H), 0.82 (t, 3H). LCMS MH ⁺ 418.3, MH ⁺ 416.2.
n	2-[(2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl)methyl]-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-3-yl)-3H-imidazo[4,5-b]pyridine	¹ H nmr (CDCl ₃): 9.08(1H, d), 8.58(1H, d), 8.45-8.43(1H, m), 7.65-7.59(1H, m), 7.39-7.30(2H, m), 7.18(1H, s), 6.14(2H, s), 4.43(2H, q), 2.66(3H, s), 1.23(3H, t), LRMS calcd. 404.4, found 405.3(MH ⁺).
o	2-[(2-(3-Fluorophenyl)-1H-imidazol-1-yl)methyl]-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-3-yl)-3H-imidazo[4,5-b]pyridine	dihydrochloride (KC 1084-118-4) ¹ H nmr (d ₆ DMSO): 9.96(1H, d), 8.50(1H, d), 7.98-7.91(2H, m), 7.72-7.50(4H, m), 6.01(2H, s), 4.35(2H, q), 2.58(3H, s), 1.35(3H, t), LRMS calcd. 403.4, found 404.3(MH ⁺).
p	2-[(2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl)methyl]-1-propyl-5-(5-methyl-1,3,4-oxadiazol-3-yl)-3H-imidazo[4,5-b]pyridine	(KC 1084-85-2) ¹ H nmr (CDCl ₃): 9.07(1H, d), 8.56(1H, d), 8.20(1H, dd), 7.88(1H, q), 7.26-7.22(2H, m), 6.88(1H, dd), 6.32(2H, s), 4.40(2H, t), 2.65(3H, s), 1.81-1.74(2H, m), 0.88(3H, t), LRMS calcd. 418.4, found 419.3(MH ⁺).
q	N-[(S)-1-(2-Hydroxymethylpyrrolidine)]-2-[(2-(2-fluoropyrid-6-yl)-1H-imidazol-1-yl)methyl]-1-propyl-1H-benzimidazole-5-carboxamide	CDCl ₃ : 8.18 (d, J = 7.69 Hz, 1H), 7.86-7.94 (m, 2H), 7.51 (d, J = 8.52 Hz, 1H), 7.38 (d, J = 8.52 Hz, 1H), 7.22 (s, 1H), 7.17 (s, 1H), 6.9 (dd, J = 2.75, 8.24 Hz, 1H), 6.30 (s, 2H), 4.43-4.46 (m, 1H), 4.23-4.28 (m, 2H), 3.76-3.79 (m, 2H), 3.52-3.62 (m, 2H), 2.16-2.19 (m, 1H), 1.25-1.85 (m, 5H), 0.82 (t, J = 7.23 Hz, 2H).
r	N-[(S)-1-(2-Methoxymethylpyrrolidine)]-2-[(2-(2-fluoropyrid-6-yl)-1H-imidazol-1-yl)methyl]-1-propyl-1H-benzimidazole-5-carboxamide	CDCl ₃ : 8.17 (d, J = 7.42 Hz, 1H), 7.85-7.93 (m, 2H), 7.51-7.53 (m, 1H), 7.35 (d, J = 8.51 Hz, 1H), 7.21 (s, 1H), 7.16 (s, 1H), 6.89 (dd, J = 2.47, 7.97 Hz, 1H), 6.28-6.3 (m, 2H), 4.46 (bs, 1H), 4.21-4.26 (m, 2H), 3.51-3.68 (m, 4H), 3.40 (s, 3H), 1.95-2.05 (m, 4H), 1.62-1.72 (m, 2H), 0.81 (t, J = 7.42 Hz, 3H). LCMS MH ⁺ 475.2, MH ⁺ 477.2.

e	N-[2-(Pyrid-3-yl)piperidine] 2-[[2-(2-fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-1H-benzimidazole-5-carboxamide	CDCl ₃ : 8.61 (s, 1H), 8.52 (d, J = 4.67 Hz, 1H), 8.15-8.18 (m, 1H), 7.87-7.93 (m, 1H), 7.85 (s, 1H), 7.66 (d, J = 7.69 Hz, 1H), 7.30-7.45 (m, 3H), 7.21 (s, 1H), 7.16 (s, 1H), 6.88-6.91 (m, 1H), 6.29 (s, 2H), 4.25 (t, J = 7.42 Hz, 2H), 2.82-2.91 (m, 1H), 2.42-2.46 (m, 1H), 1.60-1.79 (m, 9H), 0.82 (t, J = 7.42 Hz, 3H). LCMS MH ⁺ 524.0, MH ⁺ 522.4.
t	N-[4-(Pyrid-3-yl)piperidine] 2-[[2-(2-fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-1H-benzimidazole-5-carboxamide	CDCl ₃ : 8.15-8.2 (m, 2H), 7.82-7.94 (m, 2H), 7.44-7.53 (m, 1H), 7.35-7.44 (m, 2H), 7.18 (q, 2H), 6.88 (d, 1H), 6.71 (s, 1H), 6.65 (s, 1H), 6.29 (s, 2H), 4.21-4.29 (m, 2H), 3.53-4.0 (m, 8H), 1.53-1.71 (m, 2H), 0.82 (t, 3H).
u	2-[[2-(2,6-Difluorophenyl)-1H-imidazol-1-yl]methyl]-1ethyl-5-acetyl-1H-imidazole	(GL1005-149) ¹ H NMR, δppm (CDCl ₃): 8.39(dd, 1H), 8.01(dd, 1H), 7.34-7.41(m, 2H), 7.18-7.24(m, 3H), 7.04(d, 1H), 5.40(s, 2H), 3.88(q, 2H), 2.69(s, 3H), 1.03(t, 3H) LC-MS: calcd: 380.40, found 381.4 (M+1)
v	2-[[2-(2-Methylthiazol-4-yl)-1H-imidazol-1-yl]methyl]-1ethyl-5-acetyl-1H-imidazole	(GL1101-125) ¹ H NMR, δppm (CDCl ₃): 8.41(d, 1H), 8.01(dd, 1H), 7.89(s, 1H), 7.38 (d, 1H), 7.10(d, 1H), 7.05(d, 1H), 6.30(s, 2H), 4.27(q, 2H), 2.79(s, 3H), 2.69(s, 3H), 1.12(t, 3H) LC-MS: calcd: 365.46, found 366.2(M+1)
w	2-[[2-(2-Pyrimid-2-yl-1H-imidazol-1-yl)methyl]-1ethyl-5-acetyl-1H-imidazole	¹ H NMR, δppm (CDCl ₃): 8.87(d, 2H), .8.41(dd, 1H), 8.02(dd, 1H), 7.40(dd, 1H), 7.26-7.31(m, 2H), 7.16(d, 1H), 6.40(s, 2H), 4.27(q, 2H), 2.69(s, 3H), 1.17(t, 3H)
x	2-[[2-(2-Trifluoromethylpyrid-6-yl)-1H-imidazol-1-yl]methyl]-1ethyl-5-acetyl-1H-imidazole	¹ H NMR, δppm (CDCl ₃): 8.52(d, 1H), 8.40(d, 1H), 7.99-8.03(m, 2H), 7.64(d, 1H), 7.40(d, 1H), 7.20-7.22(m, 2H), 6.41(s, 2H), 4.34(q, 2H), 2.68(s, 3H), 1.15(t, 3H) LC-MS: calcd: 413.41, found 414.2(M+1)
y	2-[[2-(2-Chloropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1ethyl-5-acetyl-1H-imidazole	¹ H NMR, δppm (CDCl ₃): 8.40(d, 1H), 8.23(d, 1H), 8.01(dd, 1H), 7.77(t, 1H), 7.41(d, 1H), 7.30(d, 1H), 7.24(d, 1H), 7.18(d, 1H), 6.36(s, 2H), 4.41(q, 2H), 2.68(s, 3H), 1.25(t, 3H) LC-MS: calcd: 379.85, found 380.3(M+1)
z	2-[[2-(4-Chloropyrid-2-yl)-1H-imidazol-1-yl]methyl]-1ethyl-5-acetyl-1H-imidazole	¹ H NMR, δppm (CDCl ₃): 8.36-8.47(m, 3H), 8.01(dd, 1H), 7.38(d, 1H), 7.29(dd, 1H), 7.16-7.18(m, 2H), 6.43(s, 2H), 4.30(q, 2H), 2.68(s, 3H), 1.14(t, 3H) LC-MS: calcd: 379.85, found 380.3(M+1)
aa	2-[[2-(Thiazol-2-yl)-1H-imidazol-1-yl]methyl]-1ethyl-5-acetyl-1H-imidazole	¹ H NMR, δppm (CDCl ₃): 8.39(d, 1H), .8.00(dd, 1H) 7.84 (d, 1H), 7.39(d, 1H), 7.37(d, 1H), 7.18(d, 1H), 7.13(d, 1H), 6.35(s, 2H), 4.27(q, 2H), 2.67(s, 3H), 1.12(t, 3H) LC-MS: calcd: 351.43 found 352.2

770
771

bb	2-[(2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl)methyl]-1-propyl-5-acetyl-3H-imidazo[4,5-b]pyridine	¹ H nmr (CDCl ₃): 9.01(1H, d), 8.53(1H, d), 8.20-8.17(1H, m), 7.87(1H, q), 7.24-7.21(2H, m), 6.88-6.84(1H, m), 6.30(2H, s), 4.40(2H, t), 2.66(3H, s), 1.80-1.73(2H, m), 0.88(3H, t), LRMS calcd. 378.4, found 379.3(MH ⁺).
cc	2-[(2-(2,3-Difluorophenyl)-1H-imidazol-1-yl)methyl]-1-ethyl-1H-imidazo[4,5-c]pyridine	dihydrochloride ¹ H nmr (d ₆ DMSO): 9.44(1H, s), 8.70(1H, d), 8.37(1H, d), 8.04(1H, s), 7.89(1H, s), 7.73(1H, q), 7.49(1H, d), 7.37(1H, t), 6.05(2H, s), 4.44(2H, q), 1.30(3H, t), LRMS calcd. 339.3, found 340.2.
cd	2-[(2-(2,6-Difluorophenyl)-1H-imidazol-1-yl)methyl]-1-propyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.05 (s, 1H), 8.43 (d, 1H), 7.5 – 7.4 (m, 1H), 7.27-7.23 (m, 2H), 7.07 – 7.01 (m, 3H), 5.34 (s, 2H), 3.75 (t, 2H), 1.47 (q, 2H), 0.77 (t, 3H); LRMS m/e 354.
ce	2-[(2-(2,6-Difluorophenyl)-1H-imidazol-1-yl)methyl]-1-ethyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.05 (s, 1H), 8.43 (d, 1H), 7.52 – 7.42 (m, 1H), 7.27 – 7.23 (m, 2H), 7.08 – 7.01 (m, 3H), 5.35 (s, 2H), 3.85 (q, 2H), 1.02 (t, 3H); LRMS m/e 340.
cf	2-[(2-(2-Methyl-5-fluorophenyl)-1H-imidazol-1-yl)methyl]-1-propyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.07 (s, 1H), 8.43 (d, 1H), 7.31 – 7.23 (m, 3H), 7.12 – 7.04 (m, 3H), 5.24 (s, 2H), 3.73 (t, 2H), 2.21 (s, 3H), 1.49 (q, 2H), 0.75 (t, 3H); LRMS m/e 350.
cg	2-[(2-(2-Methyl-5-fluorophenyl)-1H-imidazol-1-yl)methyl]-1-ethyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.08 (s, 1H), 8.44 (d, 1H), 7.31 – 7.24 (m, 3H), 7.12 – 7.04 (m, 3H), 5.25 (s, 1H), 3.83 (q, 2H), 2.22 (s, 3H), 1.06 (t, 3H); LRMS m/e 336.
ch	2-[(1-Pyrazin-2-yl-1H-imidazol-1-yl)methyl]-1-propyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.58 (s, 1H), 9.09 (d, 1H), 8.61 – 8.42 (m, 3H), 7.32 – 7.24 (m, 3H), 6.33 (s, 2H), 4.16 (t, 2H), 1.63 (q, 2H), 0.81 (t, 3H); LRMS m/e 320.
ci	2-[(2-(3,4-Difluorophenyl)-1H-imidazol-1-yl)methyl]-1-ethyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.10 (s, 1H), 8.46 (d, 1H), 7.56 – 7.51 (m, 1H), 7.42 – 7.30 (m, 1H), 7.31 – 7.26 (m, 2H), 7.16 (d, 1H), 7.03 (d, 1H), 5.48 (s, 2H), 3.83 (q, 2H), 1.05 (t, 3H); LRMS m/e 340.
cj	2-[(2-(3-Trifluoromethylphenyl)-1H-imidazol-1-yl)methyl]-1-ethyl-1H-imidazo[4,5-c]pyridine	dihydrochloride ¹ H nmr (d ₆ DMSO): 10.02(1H, s), 8.70(1H, d), 8.37(1H, d), 8.08(1H, s), 7.97-7.94(3H, m), 7.82(1H, s), 7.75(1H, t), 6.09(2H, s), 4.45(2H, q), 1.32(3H, t).
ck	2-[(2-(2-Trifluoromethylpyrid-6-yl)-1H-imidazol-1-yl)methyl]-1-propyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.08 (s, 1H), 8.52 (d, 1H), 8.44 (d, 1H), 7.99 (dd, 1H), 7.65 (d, 1H), 7.29 (d, 1H), 7.26 (d, 1H), 7.21 (d, 1H), 6.40 (s, 2H), 4.19 (t, 2H), 1.54 (q, 2H), 0.71 (t, 3H); LRMS m/e 387.
cl	2-[(2-(2-Chloropyrid-6-yl)-1H-imidazol-1-yl)methyl]-1-propyl-1H-imidazo[4,5-c]pyridine	dihydrochloride (KL 1028-96) ¹ H nmr (DMSO-d ₆) δ 9.32 (s, 1H), 8.68 (d, 1H), 8.47 (d, 1H), 8.45 (d, 1H), 8.09 – 8.03 (m, 2H), 7.80 (d, 1H), 7.54 (d, 1H), 6.45 (s, 2H), 4.61 (t, 2H), 1.88 (q, 2H), 0.95 (t, 3H); LRMS m/e 352.

60257492.122100

mm	2-[[2-(2-Cyanopyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.03 (s, 1 H), 8.56 (d, 1 H), 8.44 (d, 1 H), 7.91 (dd, 1 H), 7.60 (d, 1 H), 7.32 (d, 1 H), 7.30 (d, 1 H), 7.25 (d, 1 H), 6.25 (s, 2 H), 4.31 (t, 2 H), 1.78 (q, 2 H), 0.90 (t, 3 H); LRMS m/e 344.
nn	2-[[2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-(2-Fluoroethyl)-1H-imidazo[4,5-c]pyridine	H-1 NMR (CDCl ₃): 4.02 (t, 1H), 4.05 (t, 1H), 4.32 (t, 1H), 4.47 (t, 1H), 5.58 (s, 2H), 7.05-7.33 (m, 5H), 7.44 (m, 2H), 8.47 (d, 1H), 9.10 (s, 1H) LC-MS: M + 1, 340
oo	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.06 (s, 1 H), 8.42 (d, 1 H), 8.18 (d, 1 H), 7.88 (dd, 1 H), 7.28 (d, 1 H), 7.22 (d, 1 H), 7.18 (d, 1 H), 6.88 (d, 1 H), 6.29 (s, 2 H), 4.26 (t, 2 H), 1.69 (q, 2 H), 0.84 (t, 3 H); LRMS m/e 337.
pp	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-isopropyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.03 (s, 1 H), 8.35 (d, 1 H), 8.14 (d, 1 H), 7.87 (dd, 1 H), 7.42 (d, 1 H), 7.15 (d, 1 H), 7.09 (d, 1 H), 6.87 (d, 1 H), 6.28 (s, 2 H), 5.08 (septet, 1 H), 1.49 (d, 6 H); LRMS m/e 337.
qq	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-isobutyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.03 (s, 1 H), 8.39 (d, 1 H), 8.15 (d, 1 H), 7.85 (dd, 1 H), 7.27 (d, 1 H), 7.24 (s, 1 H), 7.17 (s, 1 H), 6.85 (d, 1 H), 6.25 (s, 2 H), 4.08 (d, 2 H), 2.09 (septet, 1 H), 0.85 (d, 6 H); LRMS m/e 323.
rr	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-ethyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 8.82 (s, 1 H), 8.45 (d, 1 H), 8.18 (d, 1 H), 7.88 (dd, 1 H), 7.65 (d, 1 H), 7.23 (d, 1 H), 7.20 (d, 1 H), 6.88 (d, 1 H), 6.30 (s, 2 H), 4.47 (q, 2 H), 1.33 (t, 3 H); LRMS m/e 323.
ss	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-(2-methoxyethyl)-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.02 (s, 1 H), 8.41 (d, 1 H), 8.16 (d, 1 H), 7.84 (dd, 1 H), 7.36 (d, 1 H), 7.25 (d, 1 H), 7.21 (d, 1 H), 6.83 (d, 1 H), 6.18 (s, 2 H), 4.57 (t, 2 H), 3.56 (t, 2 H), 3.20 (s, 3 H); LRMS m/e 353.
tt	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-allyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.05 (s, 1 H), 8.40 (d, 1 H), 8.14 (d, 1 H), 7.85 (dd, 1 H), 7.26 (d, 1 H), 7.22 (d, 1 H); 7.17 (6.85 (d, 1 H), 6.19 (s, 2 H), 5.82 – 5.70 (m, 1 H), 5.12 (d, 1 H), 4.99 – 4.96 (m, 2 H), 4.82 (d, 1 H); LRMS m/e 335.
uu	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propargyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.04 (s, 1 H), 8.46 (d, 1 H), 8.15 (d, 1 H), 7.86 (dd, 1 H), 7.41 (d, 1 H), 7.26 (d, 1 H), 7.21 (d, 1 H), 6.85 (d, 1 H), 6.23 (s, 2 H), 5.21 (d, 2 H), 2.33 – 2.32 (m, 1 H); LRMS m/e 333.
vv	2-[[2-(4-Chloropyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-propyl-1H-imidazo[4,5-c]pyridine	dihydrochloride ¹ H nmr (DMSO-d ₆) δ 9.31 (s, 1 H), 8.66 (d, 1 H), 8.45 (s, 1 H), 8.41 (d, 1 H), 8.32 (d, 1 H), 7.86 (d, 1 H), 7.63 (d, 1 H), 7.52 (d, 1H), 6.42 (s, 2 H), 4.55 (t, 2 H), 1.91 (q, 2 H), 0.97 (t, 3 H); LRMS m/e 353.

ww	2-[[2-(4-Cyanopyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-propyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.07 (s, 1 H), 8.68 (d, 1 H), 8.60 (s, 1 H), 8.44 (d, 1 H), 7.45 (d, 1 H), 7.29 (d, 1 H), 7.26 (d, 1 H), 7.22 (d, 1 H), 6.37 (s, 2 H), 4.16 (t, 2 H), 1.63 (q, 2 H), 0.81 (t, 3 H); LRMS m/e 344.
xx	2-[[2-(2-Thiazol-2-yl-1H-imidazol-1-yl)methyl]-1-propyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.07 (s, 1 H), 8.41 (d, 1 H), 7.82 (d, 1 H), 7.38 (d, 1 H), 7.25 (d, 1 H), 7.19 (s, 1 H), 7.12 (s, 1 H), 6.35 (s, 2 H), 4.14 (t, 2 H), 1.53 (q, 2 H), 0.74 (t, 3 H); LRMS m/e 325.
yy	2-[[2-(2-Thiazol-2-yl-1H-imidazol-1-yl)methyl]-1-ethyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 9.08 (s, 1 H), 8.43 (d, 1 H), 7.85 (d, 1 H), 7.38 (d, 1 H), 7.38-7.26 (m, 1 H), 7.17 (s, 1 H), 7.14 (s, 1 H), 6.35 (s, 2 H), 4.25 (q, 2 H), 1.11 (t, 3 H); LRMS m/e 311.
zz	2-[[2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]difluoromethyl]-1-ethyl-5-chloro-1H-benzimidazole	
aaa	2-[[2-(2,3-Difluorophenyl)-1H-imidazol-1-yl]methyl]-1-ethyl-5-cyano-1H-benzimidazole	¹ H NMR, δppm (CDCl ₃): 8.09(dd, 1H) 7.55 (dd, 1H), 7.19-7.40(m, 5H), 7.04(d, 1H), 5.40(s, 2H), 3.86(q, 2H), 1.02(t, 3H)
bbb	2-[[2-(3-Fluoropyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-propyl-5-cyano-1H-benzimidazole	<u>hydrochloride</u> ¹ H nmr (d ₆ DMSO): 8.45(1H, m), 8.08-8.02(3H, m), 7.93(1H, s), 7.83(1H, d), 7.69-7.62(2H, m), 6.16(2H, s), 4.29(2H, t), 1.72-1.20(2H, m), 0.86(3H, t), LRMS calcd. 360.4, found 361.2(MH ⁺).
ccc	2-[[2-(2-Methyl-5-fluorophenyl)-1H-imidazol-1-yl]methyl]-1-ethyl-5-cyano-1H-benzimidazole	<u>hydrochloride</u> ¹ H nmr (d ₆ DMSO): 8.10(1H, s), 8.07(1H, d), 7.95(1H, d), 7.78(1H, d), 7.64(1H, dd), 7.52(1H, dd), 7.38-7.35(2H, m), 5.82(2H, s), 4.23(2H, q), 2.17(3H, s), 1.18(3H, t).
ddd	2-[[2-(2-Pyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-propyl-5-cyano-1H-benzimidazole	
eee	2-[[2-(2-Pyrimid-2-yl)-1H-imidazol-1-yl]methyl]-1-propyl-5-cyano-1H-benzimidazole	<u>dihydrochloride</u> ¹ H nmr (d ₆ DMSO): 8.92(2H, d), 8.18(1H, d), 8.00-7.99(2H, m), 7.88(1H, dd), 7.65-7.62(2H, m), 6.46(2H, s), 4.42(2H, t), 1.93-1.84(2H, m), 0.97(3H, t), LRMS calcd. 343.4, found 344.2(MH ⁺).
fff	2-[[2-(2-Quinolin-2-yl)-1H-imidazol-1-yl]methyl]-1-propyl-5-cyano-1H-benzimidazole	<u>dihydrochloride</u> ¹ H nmr (d ₆ DMSO): 8.60(1H, d), 8.35(1H, d), 8.02-7.99(2H, m), 7.88-7.85(2H, m), 7.79-7.60(5H, m), 6.54(2H, s), 4.47(2H, t), 1.85-1.77(2H, m), 0.89(3H, t), LRMS calcd. 392.5, found 393.4(MH ⁺).
ggg	2-[[2-(2-Chloropyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-propyl-5-cyano-1H-benzimidazole	¹ H nmr(d ₆ DMSO): 8.02 (1H, d, J = 7.7 Hz), 8.08(1H, s), 7.76(1H, t, J = 8 Hz), 7.55(1H, dd, J = 8, 1.4 Hz), 7.428 (1H, d, J = 8.5 Hz), 7.18-7.32(3H, m), 6.34(1H, s), 4.29(2H, t, J = 8.7 Hz), 1.66(2H, m), 0.81(3H, t, J = 8.7 Hz), LRMS calcd. 376.5, found 377.3(MH ⁺).

hhh	2-([2-(2-Chloropyrid-2-yl)-1H-imidazol-1-yl]methyl)-1-ethyl-5-cyano-1H-benzimidazole	Mesylate d6- DMSO: 8.02-8.14 (m, 3H), 7.97 (s, 1H), 7.86 (d, J = 8.52 Hz, 1H), 7.77 (s, 1H), 7.6 (d, J = 8.51 Hz, 1H), 7.57 (d, J = 7.97 Hz, 1H), 6.26 (s, 2H), 4.44-4.51 (m, 2H), 2.30 (s, 3H), 1.39 (t, J = 7.14 Hz, 3H). LCMS: MH ⁺ 363.2.
■	2-([2-(2-Fluoropyrid-4-yl)-1H-imidazol-1-yl]methyl)-1-propyl-5-cyano-1H-benzimidazole	¹ H nmr (CDCl ₃): 8.28(1H, d), 8.04(1H, s), 7.54-7.49(2H, m), 7.40(1H, d), 7.25-7.22(2H, m), 7.11(1H, s), 5.55(2H, s), 3.89(2H, t), 1.60-1.53(2H, m), 0.83(3H, t), LRMS calcd. 360.4, found 361.2(MH ⁺).
■	2-([2-(4-Chloropyrid-2-yl)-1H-imidazol-1-yl]methyl)-1-propyl-5-cyano-1H-benzimidazole	¹ H nmr(d6 DMSO): 8.42 (1H, d, J = 5 Hz), 8.35(1H, s), 8.08(1H, s), 7.1-7.65(1H, m), 6.41(1H, s), 4.19(2H, t, J = 7.4 Hz), 1.57(2H, m), 0.78(3H, t, J = 7.4 Hz), LRMS calcd. 376.5, found 377.3(MH ⁺).
■	2-([2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl)-1-propyl-3H-imidazo[4,5-b]pyridine-5-carboxylate methyl ester	¹ H nmr (CDCl ₃): 9.05(1H, d), 8.62(1H, d), 8.19(1H, dd), 7.88(1H, q), 7.26-7.21(2H, m), 6.89-6.85(1H, m), 6.31(2H, s), 4.39(2H, t), 3.96(3H, s), 1.79-1.72(2H, m), 0.87(3H, t), LRMS calcd. 394.4, found 395.3(MH ⁺).
■	N-Dimethyl 2-([2-(Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl)-1-propyl-1H-benzimidazole-5-carboxamide	CDCl ₃ : 8.17 (d, J = 7.42 Hz, 1H), 7.85-7.92 (m, 1H), 7.80 (s, 1H), 7.34-7.42 (m, 2H), 7.21 (s, 1H), 7.15 (s, 1H), 6.89 (d, J = 7.97 Hz, 1H), 6.29 (s, 2H), 4.21-4.26 (m, 2H), 3.04-3.11 (br d, 6H), 1.61-1.69 (m, 2H), 0.80(t, J = 7.42 Hz, 3H).
■	N-Dimethyl 2-([2-(2-Ethoxypyrid-6-yl)-1H-imidazol-1-yl]methyl)-1-propyl-3H-imidazo[4,5-b]pyridine-5-carboxamide	¹ H nmr (CDCl ₃): 8.49(1H, d), 8.10(1H, d), 7.88(1H, d), 7.71(1H, t), 7.13(1H, d), 7.00(1H, d), 6.74(1H, d), 6.45(2H, s), 4.27(2H, q), 4.08(2H, t), 3.15-3.06(6H, br d), 1.48-1.35(5H, m), 0.67(3H, t), LRMS calcd. 433.5, found 434.6(MH ⁺).
■	2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-6-(1,2,4-oxadiazol-3-yl)-1H-benzimidazole	¹ H nmr (CDCl ₃) δ 8.89 (s, 1 H), 8.15 (s, 1 H), 8.12 – 8.03 (m, 1 H), 7.81 – 7.73 (m, 1 H), 7.40 – 7.02 (m, 6 H), 5.47 (s, 2 H), 3.82 (t, 2 H), 1.55 (q, 2 H), 0.79 (t, 3 H); LRMS m/e 403.
■	2-([2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl)-1-propyl-6-(1,3,4-oxadiazol-2-yl)-1H-benzimidazole	¹ H nmr (CDCl ₃) δ 8.50 (s, 1 H), 8.15 (d, 1 H), 7.98 – 7.89 (m, 2 H), 7.56 – 7.39 (m, 3 H), 7.24 – 7.05 (m, 3 H), 5.57 (s, 2 H), 3.78 (t, 2 H), 1.47 (q, 2 H), 0.80 (t, 3 H); LRMS m/e 403.
■	2-([2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl)-1-propyl-6-(1,3,4-oxadiazol-2-yl)-1H-benzimidazole	¹ H nmr (CDCl ₃) δ 8.46 (s, 1 H), 8.18 – 8.14 (m, 2 H), 7.95 – 7.83 (m, 3 H), 7.24 (d, 1 H), 7.17 (d, 1 H), 6.87 (d, 1 H), 6.31 (s, 2 H), 4.30 (t, 2 H), 1.71 (q, 2 H), 0.85 (t, 3 H); LRMS m/e 404.
■	N-(4-Pyridyl-2-yl)piperazine 2-([2-(Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl)-1-propyl-1H-benzimidazole-6-carboxamide	¹ H nmr (CDCl ₃) δ 8.19 – 8.16 (m, 2 H), 7.88 (dd, 1 H), 7.77 (d, 1 H), 7.53 (s, 1 H), 7.48 (d, 1 H), 7.32 (d, 1 H), 7.26 (d, 1 H), 7.17 (d, 1 H), 6.89 (d, 1 H), 6.69 – 6.65 (m, 2 H), 6.30 (s, 2 H), 4.25 (t, 2 H), 3.59 (br s, 8 H), 1.67 (q, 2 H), 0.82 (t, 3 H); LRMS m/e 525.

775

60257492-122100

rr	2-[[2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-propyl-6-(5-ethyl-1,2,4-oxadiazol-3-yl)-1H-benzimidazole	¹ H nmr (CDCl ₃) δ 8.05 (d, 1 H), 8.03 (s, 1 H), 7.85 (d, 1 H), 7.52 – 7.41 (m, 3 H), 7.21 – 7.17 (m, 2 H), 7.08 (d, 1 H), 5.52 (s, 2 H), 3.76 (t, 2 H), 3.00 (q, 2 H), 1.51 – 1.45 (m, 5 H), 0.77 (t, 3 H); LRMS m/e 431.
sss	2-[[2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-propyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-1H-benzimidazole	¹ H nmr (CDCl ₃) δ 8.03 (d, 1 H), 8.02 (s, 1 H), 7.85 (d, 1 H), 7.51 – 7.40 (m, 3 H), 7.21 – 7.16 (m, 2 H), 7.07 (d, 1 H), 5.52 (s, 2 H), 3.75 (t, 2 H), 2.67 (s, 3 H), 1.47 (q, 2 H), 0.76 (t, 3 H); LRMS m/e 417.
tt	2-[[2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-propyl-6-(5-ethyl-1,3,4-oxadiazol-2-yl)-1H-benzimidazole	¹ H nmr (CDCl ₃) δ 8.04 (s, 1 H), 7.94 – 7.84 (m, 2 H), 7.50 (7.39 (m, 3 H), 7.22 – 7.16 (m, 2 H), 7.08 (d, 1 H), 5.52 (s, 2 H), 3.76 (t, 2 H), 2.63 (s, 3 H), 1.47 (q, 2 H), 0.77 (t, 3 H); LRMS m/e 417.
uuu	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-6-(5-ethyl-1,2,4-oxadiazol-3-yl)-1H-benzimidazole	¹ H nmr (CDCl ₃) δ 8.17 (d, 1 H), 8.07 (s, 1 H), 7.91 – 7.80 (m, 3 H), 7.23 (d, 1 H), 7.16 (d, 1 H), 6.87 (d, 1 H), 6.29 (s, 2 H), 4.28 (t, 2 H), 2.61 (s, 3 H), 1.69 (q, 2 H), 0.84 (t, 3 H); LRMS m/e 418.
vvv	N-(2-aza-5-oxabicyclo[2.2.1]heptane)-2-[[2-(2-fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-1H-benzimidazole-6-carboxamide	¹ H nmr (CDCl ₃) δ 8.18 (d, 1 H), 7.89 (dd, 1 H), 7.78-7.72 (m, 1 H), 7.62 (s, 1 H), 7.42-7.33 (m, 1 H), 7.22 (s, 1 H), 7.17 (s, 1 H), 6.89 (d, 1 H), 6.30 (s, 2 H), 5.06-4.51 (m, 2 H), 4.25 (t, 2 H), 4.11-3.48 (m, 4 H), 1.96-1.87 (m, 2 H), 1.68 (q, 2 H), 0.83 (t, 3 H); LRMS m/e 461.
www	2-[[2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl]-1-ethyl-6-chloro-3H-imidazo[4,5-b]pyridine	¹ H nmr (CDCl ₃): 7.96(1H, d), 7.38-7.34(1H, m), 7.26-7.17(4H, m), 7.04(1H, d), 5.37(1H, s), 3.96(2H, q), 1.06(3H, t), LRMS calcd. 373.8, found 374.2(MH ⁺).
xxx	2-[[2-(2-Chloropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-ethyl-6-chloro-3H-imidazo[4,5-b]pyridine	¹ H nmr (CDCl ₃): 8.22(1H, d), 7.94(1H, d), 7.75(1H, t), 7.29-7.20(4H, m), 6.31(2H, s), 4.45(2H, q), 1.30(3H, t), LRMS calcd. 373.2, found 373.3(M).
yyy	2-[[2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-ethyl-6-chloro-3H-imidazo[4,5-b]pyridine	LRMS calcd. 355.8, found 356.2(MH ⁺)
zzz	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-ethyl-6-chloro-3H-imidazo[4,5-b]pyridine	(KC 1084-36-2) ¹ H nmr (CDCl ₃): 8.17(1H, dd), 7.94-7.84(2H, m), 7.23-7.20(3H, m), 6.89-6.85(1H, m), 6.27(2H, s), 4.45(2H, q), 1.31(3H, t), LRMS calcd. 356.8, found 357.2(MH ⁺).
aaaa	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-6-chloro-3H-imidazo[4,5-b]pyridine	<u>hydrochloride</u> ¹ H nmr (d6 DMSO): 8.35(1H, dd), 8.24(1H, q), 8.02(1H, s), 7.95(1H, dd), 7.90(1H, s), 7.33(1H, dd), 7.28(1H, d), 7.26(1H, d), 6.32(2H, s), 4.33(2H, t), 1.90-1.85(2H, m), 0.94(3H, t), LRMS calcd. 370.8, found 371.3(MH ⁺).
bbbb	2-[[2-(4-Chloropyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-ethyl-6-chloro-3H-imidazo[4,5-b]pyridine	¹ H nmr (CDCl ₃): 8.41(1H, d), 8.35(1H, dd), 7.94(1H, d), 7.26-7.17(4H, m), 6.36(2H, s), 4.36(2H, q), 1.22(3H, t), LRMS calcd. 373.2, found 373.2(M)

cccc	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-1H-benzimidazole-6-carboxylate methyl ester	¹ H nmr (CDCl ₃) δ 8.18 (d, 1 H), 8.09 (s, 1 H), 7.98 – 7.87 (m, 2 H), 7.76 (d, 1 H), 7.24 (s, 1 H), 7.17 (s, 1 H), 6.88 (d, 1 H), 6.31 (s, 2 H), 4.29 (t, 2 H), 3.94 (s, 3 H), 1.69 (q, 2 H), 0.85 (t, 3 H); LRMS m/e 394.
dddd	N-Dimethyl 2-[[2-(2-fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-1H-benzimidazole-6-carboxamide	¹ H nmr (CDCl ₃) δ 8.17 (d, 1 H), 7.89 (dd, 1 H), 7.74 (d, 1 H), 7.49 (s, 1 H), 7.30 (d, 1 H), 7.21 (d, 1 H), 7.15 (d, 1 H), 6.89 (d, 1 H), 6.29 (s, 2 H), 4.23 (t, 2 H), 3.07 (br d, 6 H), 1.66 (q, 2 H), 0.81 (t, 3 H); LRMS m/e 407.
cccc	2-[[2-(2,5-Difluorophenyl)-1H-imidazol-1-yl]methyl]-1-ethyl-6-fluoro-3H-imidazo[4,5-b]pyridine	<u>hydrochloride</u> ¹ H nmr (d6 DMSO): 8.15(1H, t), 8.08(1H, d), 7.99(1H, d), 7.76-7.72(1H, m), 7.62-7.50(2H, m), 7.02(1H, d), 5.92(2H, s), 4.20(2H, q), 1.26(3H, t), LRMS calcd. 357.3, found 358.2(MH ⁺)
nn	2-[[2-(3-Cyanophenyl)-1H-imidazol-1-yl]methyl]-1-ethyl-6-fluoro-3H-imidazo[4,5-b]pyridine	<u>hydrochloride</u> ¹ H nmr (d6 DMSO): 8.30(1H, s), 8.16(1H, dd), 8.11(1H, d), 8.04(1H, d), 8.00(1H, d), 7.96(1H, d), 7.74(1H, t), 7.03(1H, d), 5.97(2H, s), 4.22(2H, q), 1.30(3H, t), LRMS calcd. 346.4, found 347.3(MH ⁺)
cccc	2-[[2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-ethyl-6-fluoro-3H-imidazo[4,5-b]pyridine	<u>dihydrochloride</u> ¹ H nmr(d6 DMSO): 8.18(1H, t), 7.99(1H, d), 7.94(1H, d), 7.72-7.69(1H, m), 7.66-7.61(1H, m), 7.58-7.50(2H, m), 7.03(1H, d), 5.96(2H, s), 4.23(2H, q), 1.31(3H, s), LRMS calcd. 339.3, found 340.2(MH ⁺).
nnnn	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-6-fluoro-3H-imidazo[4,5-b]pyridine	<u>hydrochloride</u> ¹ H nmr (d6 DMSO): 8.42(1H, d), 8.26(1H, q), 8.10-8.05(2H, m), 7.96(1H, d), 7.36(1H, dd), 6.97(1H, d), 6.33(2H, s), 4.30(2H, t), 1.90-1.83(2H, m), 0.93(3H, t).
nn	2-[[2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-propyl-6-methyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 8.95 (s, 1 H), 7.49 – 7.36 (m, 3 H), 7.19 – 7.15 (m, 2 H), 7.04 (m, 2 H), 5.48 (s, 2 H), 3.64 (t, 2 H), 2.64 (s, 3 H), 1.40 (q, 2 H), 0.73 (t, 3 H); LRMS m/e ???.
nn	2-[[2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-ethyl-6-methyl-1H-imidazo[4,5-c]pyridine	<u>dihydrochloride</u> ¹ H nmr (DMSO-d6) δ 9.28 (s, 1 H), 8.24 (s, 1 H), 8.23 (d, 1 H), 7.94 (d, 1 H), 7.69 – 7.48 (m, 4 H), 6.12 (s, 2 H), 4.39 (q, 2 H), 2.77 (s, 3 H), 1.35 (t, 3 H); LRMS m/e 336.
lddd	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-6-methyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 8.93 (s, 1 H), 8.16 (d, 1 H), 7.87 (dd, 1 H), 7.20 (d, 1 H), 7.16 (d, 1 H), 7.10 (d, 1 H), 6.87 (d, 1 H), 6.26 (s, 2 H), 4.19 (t, 2 H), 2.65 (s, 3 H), 1.65 (q, 2 H), 0.83 (t, 3 H); LRMS m/e 351.
nn	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-6-ethyl-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃) δ 8.93 (s, 1 H), 8.16 (d, 1 H), 7.87 (dd, 1 H), 7.18 (d, 1 H), 7.12 (s, 1 H), 6.87 (d, 1 H), 6.26 (s, 2 H), 4.30 (q, 2 H), 2.65 (s, 3 H), 1.22 (t, 3 H); LRMS m/e 337.

277#
777

mmnm	N-Morpholino 2-[[2-(2-fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-1H-benzimidazole-6-carboxamide	¹ H nmr (CDCl ₃) δ 8.17 (d, 1 H), 7.88 (dd, 1 H), 7.75 (d, 1 H), 7.51 (s, 1 H), 7.28 – 7.25 (m, 1 H), 7.21 (s, 1 H), 7.16 (s, 1 H), 6.89 (d, 1 H), 6.29 (s, 2 H), 4.24 (t, 2 H), 3.69 (br s, 8 H), 1.67 (q, 2 H), 0.82 (t, 3 H); LRMS m/e 449.
nnnn	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-ethyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.39(dd, 1H), 8.19(m, 1H), 8.02(dd, 1H), 7.89(m, 1H), 7.20-7.26(m, 3H), 6.89(m, 1H), 6.32(s, 2H), 4.47(q, 2H), 1.30(t, 3H) LC-MS: calcd: 322.35, found 323.3(M+1)
oooo	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-isobutyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.38(dd, 1H), 8.18(dd, 1H), 8.01(dd, 1H), 7.88(m, 1H), 7.20-7.27(m, 3H), 6.87(dd, 1H), 6.29(s, 2H), 4.21(d, 2H), 2.27(m, 1H), 0.87(d, 6H) LC-MS: calcd: 350.40, found 351.3(M+1)
pppp	2-[[2-(1,5-Dimethylpyrazol-3-yl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H nmr (CDCl ₃): 8.37(1H, dd), 8.04(1H, dd), 7.22(1H, dd), 7.06(1H, d), 7.02(1H, d), 6.66(1H, s), 6.20(1H, s), 4.19(2H, t), 3.83(3H, s), 2.33(3H, s), 1.60-1.53(2H, m), 0.76(3H, t), LRMS calcd. 335.4, found 336.2(MH ⁺).
qqqq	2-[[2-(1-Methylpyrazol-3-yl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H nmr (CDCl ₃): 8.38(1H, dd), 8.05(1H, dd), 7.42(1H, d), 7.23(1H, dd), 7.09(1H, d), 7.04(1H, d), 6.91(1H, d), 6.21(2H, s), 4.19(2H, t), 3.97(3H, s), 1.61-1.50(2H, m), 0.76(3H, t), LRMS calcd. 321.4, found 322.3(MH ⁺).
rrr	2-[[2-(2,3,6-Trifluorophenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.40(dd, 1H), 8.02(dd, 1H), 7.24-7.32(m, 3H), 7.11(d, 1H), 7.00(m, 1H), 5.36(s, 2H), 4.02(q, 2H), 1.09(t, 3H) LC-MS: calcd: 357.34 found 358.2
ssss	2-[[2-(2,3-Dichlorophenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.38(dd, 1H), 8.02(dd, 1H), 7.59(dd, 1H), 7.39(dd, 1H), 7.21-7.29(m, 3H), 7.10(d, 1H), 5.29(s, 2H), 3.90 (t, 2H), 1.53 (m, 2H), 0.79(t, 3H). LC-MS: calcd: 386.29, found 386.3
ttt	2-[[2-(2,3-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-ethyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.40(dd, 1H), 8.04(dd, 1H), 7.22-7.43(m, 5H), 7.08(d, 1H), 5.40(s, 2H), 3.99 (q, 2H), 1.05(t, 3H). LC-MS: calcd: 339.35 found 340.1
uuuu	2-[[2-(2,3-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.39(dd, 1H), 8.03(dd, 1H), 7.22-7.42(m, 5H), 7.09(d, 1H), 5.39(s, 2H), 3.86(t, 2H), 1.50(m, 2H), 0.78(t, 3H) LC-MS: calcd: 353.38 found 354.2
vvv	2-[[2-(2,4,5-Trifluorophenyl)-1H-imidazol-1-yl]methyl]-1-(2-fluoroethyl)-3H-imidazo[4,5-b]pyridine	¹ H-1 NMR (CDCl ₃): line list provided 4.23 (t, 1H), 4.31 (t, 1H), 4.50 (t, 1H), 4.66 (t, 1H), 5.40 (s, 2H), 7.01-7.09 (m, 2H), 7.20-7.26 (m, 2H), 7.43 (m, 1H), 7.99 (d, 1H), 8.32 (d, 1H) LC-MS: M + 1, 376
wwww	2-[[2-(2,4,6-Trifluorophenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.41(dd, 1H), 8.03(dd, 1H), 7.50(m, 1H), 7.22-7.29(m, 2H), 7.07-7.15(m, 2H), 5.37(s, 2H), 3.93(t, 2H), 1.53(m, 2H), 0.82(t, 3H). LC-MS: calcd: 371.37, found 372.2(M+1)

60257492.122100

60257442.122100

xxxx	2-[[2-(2,4-Difluorophenyl)-1H-imidazol-1-yl]methyl]-1-ethyl-3H-imidazo[4,5-b]pyridine	<u>dihydrochloride</u> ¹ H nmr (d6 DMSO): 8.35-8.33(1H, m), 8.07-8.06(1H, m), 7.99-7.96(2H, m), 7.86-7.80(1H, m), 7.63-7.57(1H, m), 7.35-7.32(1H, m), 7.28-7.25(1H, m), 5.89(2H, s), 4.27(2H, q), 1.28(3H, t), LRMS calcd. 339.3, found 340.2(MH ⁺).
yyyy	2-[[2-(2,6-Difluorophenyl)-1H-imidazol-1-yl]methyl]-1-(2-fluoroethyl)-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): line list provided 4.14 (t, 1H), 4.24 (t, 1H), 4.46 (t, 1H), 4.64 (t, 1H), 5.40 (s, 2H), 6.98 (m, 2H), 7.11 (s, 1H), 7.26-7.40 (m, 3H), 8.01 (d, 1H), 8.34 (d, 1H) LC-MS: M + 1, 358
zzzz	2-[[2-(2-Trifluoromethylphenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.39(dd, 1H), 8.02(dd, 1H), 7.84 (dd, 1H), 7.53-7.65(m, 2H), 7.45(m, 1H), 7.21-7.27(m, 2H), 7.09(d, 1H), 5.17 (s, 2H), 3.93(t, 2H), 1.59(m, 2H), 0.80(t, 3H) LC-MS: calcd: 385.40, found 386.2 (M+1)
aaaa	2-[[2-(2-Chlorophenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.38(dd, 1H), 8.02(dd, 1H), 7.33-7.56(m, 4H), 7.19-7.27(m, 2H), 7.09(d, 1H), 5.30 (s, 2H), 3.85(t, 2H), 1.50(m, 2H), 0.76(t, 3H) LC-MS: calcd: 351.84, found 352.2(M+1)
bbbb	2-[[2-(2-Cyanophenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	<u>dihydrochloride</u> ¹ H nmr (d6 DMSO): 8.31(1H, d), 8.15(1H, s), 8.05-8.03(2H, m), 7.94-7.92(2H, m), 7.85-7.77(2H, m), 7.27-7.24(1H, m), 5.97(1H, s), 4.14(2H, t), 1.72-1.64(2H, m), 0.75(3H, t), LRMS calcd. 342.4, found 343.3(MH ⁺).
cccc	2-[[2-(2-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.39(dd, 1H), 8.03(dd, 1H), 7.65(m, 1H), 7.50(m, 1H), 7.20-7.35(m, 3H), 7.07(d, 1H), 5.38 (s, 2H), 3.84(t, 2H), 1.46(m, 2H), 0.74(t, 3H) LC-MS: calcd: 335.39, found 336.2(M+1)
ddddd	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.39(dd, 1H), 8.35(m, 1H), 8.12(m, 1H), 8.02(dd, 1H), 7.35(m, 1H), 7.22-7.29(m, 2H), 7.10(d, 1H), 5.43(s, 2H), 3.95 (t, 2H), 1.54 (m, 2H), 0.80(t, 3H). LC-MS: calcd: 336.37, found 337.2
eeee	2-[[2-(2-Fluoro-5-trifluoromethylphenyl)-1H-imidazol-1-yl]methyl]-1-ethyl-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): line list provided 1.08 (t, 3H), 3.99 (q, 2H), 5.38 (s, 2H), 7.10 (s, 1H), 7.22-7.39 (m, 2H), 7.75 (m, 1H), 7.93 (m, 1H), 8.02 (d, 1H), 8.38 (d, 1H) LC-MS: M + 1, 390
fff	2-[[2-(2-Fluoro-5-methylphenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.38(dd, 1H), 8.04(dd, 1H), 7.44(dd, 1H), 7.22-7.30(m, 2H), 7.19(d, 1H), 7.12(dd, 1H), 7.05(d, 1H), 5.37(s, 2H), 3.84(t, 2H), 2.36 (s, 3H), 1.46(m, 2H), 0.76(t, 3H) LC-MS: calcd: 349.41 found 350.3
ggggg	2-[[2-(3-Fluoropyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	<u>dihydrochloride</u> ¹ H nmr (d6 DMSO): 8.48-8.46(1H, m), 8.30(1H, dd), 8.12-8.03(2H, m), 7.96(1H, d), 7.90(1H, dd), 7.72-7.65(1H, m), 7.22(1H, dd), 6.18(2H, s), 4.27(2H, t), 1.83-1.75(2H, m), 0.87(3H, t), LRMS calcd. 336.4, found 337.2.

779

60257492.122100

hhhhh	2-[[2-(2-Methylphenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): line list provided 0.73 (t, 3H), 1.49 (m, 2H), 2.24 (s, 3H), 3.81 (m, 2H), 5.22 (s, 2H), 7.10 (s, 1H), 7.18-7.36 (m, 6H), 8.02 (d, 1H), 8.37 (d, 1H) LC-MS: M + 1, 332
hh	2-[[2-(2-Methyl-3-fluorophenyl)-1H-imidazol-1-yl]methyl]-1-(2-fluoroethyl)-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): 2.13 (s, 3H), 4.14 (m, 1H), 4.24 (m, 1H), 4.48 (m, 1H), 4.64 (m, 1H), 5.29 (s, 2H), 7.09-7.26 (m, 6H), 8.02 (d, 1H), 8.35 (d, 1H) LC-MS: M + 1, 354
hh	2-[[2-(2-Methyl-5-fluorophenyl)-1H-imidazol-1-yl]methyl]-1-(2-fluoroethyl)-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): line list provided 2.16 (s, 3H), 4.19 (t, 1H), 4.26 (t, 1H), 4.49 (t, 1H), 4.57 (t, 1H), 5.28 (s, 2H), 7.02-7.07 (2H), 7.14 (s, 1H), 7.21-7.26 (m, 3H), 8.02 (d, 1H), 8.35 (d, 1H) LC-MS: 354
hhhhh	2-[[2-(2-Methyl-5-fluorophenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.39(dd, 1H), 8.03(dd, 1H), 7.20-7.31(m, 3H), 7.07-7.13(m, 3H), 5.24(s, 2H), 3.88(t, 2H), 2.22(s, 3H), 1.54(m, 2H), 0.78(t, 3H) LC-MS: calcd: 349.41 found 350.3
hh	2-[[2-(2-Methylthiazol-4-yl)-1H-imidazol-1-yl]methyl]-1-ethyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.40(dd, 1H), 8.05(dd, 1H), 7.88(s, 1H), 7.25(m, 1H), 7.11(d, 1H), 7.07(d, 1H), 6.29(s, 2H), 4.35(q, 2H), 2.78(s, 3H), 1.18(t, 3H) LC-MS: calcd: 324.41, found 325.2(M+1)
hhhhhh	2-[[2-(2-Methylthiazol-4-yl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.40(dd, 1H), 8.05(dd, 1H), 7.91(s, 1H), 7.24(m, 1H), 7.11(d, 1H), 7.07(d, 1H), 6.30(s, 2H), 4.22(t, 2H), 2.78(s, 3H), 1.62(m, 2H), 0.79(t, 3H) LC-MS: calcd: 338.44, found 339.2(M+1)
hhhhh	2-[[2-(2-Methoxyphenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	<u>dihydrochloride</u> ¹ H nmr (d ₆ DMSO): 8.33(1H, dd), 8.02-7.99(2H, m), 7.93(1H, d), 7.65-7.59(1H, m), 7.51-7.48(1H, m), 7.29-7.21(2H, m), 7.11-7.06(1H, m), 5.75(2H, s), 4.12(2H, t), 3.64(3H, s), 1.69-1.61(2H, m), 0.74(3H, t), LRMS calcd. 347.4, found 348.3(MH ⁺).
ooooo	2-[[2-(2-Methoxypyrid-3-yl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.38(dd, 1H), 8.30(dd, 1H), 8.03(dd, 1H), 7.87(dd, 1H), 7.19-7.27(m, 2H), 7.01-7.05(m, 2H), 5.33(s, 2H), 3.97(s, 3H), 3.86(t, 2H), 1.47(m, 2H), 0.77(t, 3H). LC-MS: calcd: 348.41, found 349.3(M+1)
ppppp	2-[[2-(2-Methoxy-5-fluorophenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.39(dd, 1H), 8.03(dd, 1H), 7.15-7.32(m 4H), 7.03(d, 1H), 6.96(dd, 1H), 5.30(s, 2H), 3.84(t, 2H), 3.79(s, 3H), 1.46(m, 2H), 0.76(t, 3H) LC-MS: calcd: 365.41 found 366.2
ooooo	2-[[2-(3,4-Difluorophenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H nmr (CDCl ₃): 8.38(1H, dd), 8.04(1H, dd), 7.56-7.50(1H, m), 7.41-7.36(1H, m), 7.30-7.21(2H, m), 7.15(1H, d), 7.04(1H, d), 5.45(2H, s), 3.92(2H, t), 1.60-1.50(2H, m), 0.80(3H, t), LRMS calcd. 353.4, found 354.3(MH ⁺).

60257492-122100

rrrr	2-[[2-(3,4-Difluorophenyl)-1H-imidazol-1-yl]methyl]-1-(2-fluoroethyl)-3H-imidazo[4,5-b]pyridine	¹ H NMR (CDCl ₃): line list provided 4.33 (t, 1H), 4.42 (t, 1H), 4.56 (t, 1H), 4.73 (t, 1H), 5.51 (s, 2H), 7.07 (s, 1H), 7.18-7.26 (m, 2H), 7.39 (m, 1H), 7.55 (m, 1H), 8.07 (d, 1H), 8.37 (s, 1H) LC-MS: M + 1, 358
ssss	2-[[2-(3,5-Difluorophenyl)-1H-imidazol-1-yl]methyl]-1-ethyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.41(dd, 1H), 8.06(dd, 1H), 7.19-7.29(m, 4H), 7.08(d, 1H), 6.93(m, 1H), 5.52(s, 2H), 3.96(t, 2H), 1.57(m, 3H), 0.82(t, 3H) LC-MS: calcd: 353.38, found 354.3(M+1)
ttt	2-[[2-(3,5-Difluorophenyl)-1H-imidazol-1-yl]methyl]-1-(2-fluoroethyl)-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.41(dd, 1H), 8.06(dd, 1H), 7.19-7.31(m, 4H), 7.07(d, 1H), 6.93(m, 1H), 5.52(s, 2H), 4.05(q, 2H), 1.14(t, 3H). LC-MS: calcd: 339.36, found 340.3(M+1)
uuuuu	2-[[2-(3-Trifluoromethylphenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H nmr (CDCl ₃): 9.09(1H, s), 8.43(1H, d), 7.93(1H, s), 7.84(1H, d), 7.72(1H, d), 7.62(1H, t), 7.25(1H,), 7.19(1H, d), 7.09(1H, d), 5.50(2H, s), 3.63(2H, t), 1.49-1.39(2H, m), 0.75(3H, t).
vvvv	2-[[2-(2-Trifluoromethylpyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.53(d, 1H), 8.39(dd, 1H), 7.96-8.06(m, 2H), 7.64(dd, 1H), 7.20-7.27(m, 3H), 6.42(s, 2H), 4.26(t, 2H), 1.61(m, 2H), 0.72(t, 3H) LC-MS: calcd: 386.38, found 387.3(M+1)
wwwww	2-[[2-(2-Trifluoromethylpyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-ethyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.52(d, 1H), 8.39(dd, 1H), 7.90-8.05(m, 2H), 7.64(d, 1H), 7.21-7.27(m, 3H), 6.42(s, 2H), 4.39(q, 2H), 1.17(t, 3H) LC-MS: calcd: 372.36, found 373.3(M+1)
xxxxx	2-[[2-(2-Trifluoromethylpyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-(2-fluoroethyl)-3H-imidazo[4,5-b]pyridine	¹ H NMR (CDCl ₃): line list provided 4.60-4.81 (m, 4H), 6.30 (s, 2H), 7.18-7.30 (m, 3H), 7.54 (d, 1H), 7.88-8.00 (m, 2H), 8.33(d, 1H), 8.49(d, 1H) LC-MS: M + 1, 391, M - 1, 389
yyyyy	2-[[2-(3-Chloropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-(2-fluoroethyl)-3H-imidazo[4,5-b]pyridine	HCl salt ¹ H NMR (dmso): line list provided 4.77 (s, 2H), 4.90 (m, 2H), 6.28 (s, 2H), 7.24 (m, 1H), 7.62 (d, 1H), 7.93 (m, 2H), 8.12 (m, 2H), 8.36(m, 2H) LC-MS: M + 1, 357
zzzzz	2-[[2-(2-Chloropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-ethyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.39(dd, 1H), 8.23(dd, 1H), 8.03(dd, 1H), 7.76(t, 1H), 7.19-7.29(m, 4H), 6.36(s, 2H), 4.48(q, 2H), 1.29(t, 3H) LC-MS: calcd: 338.80, found 339.2(M+1)
nnnnn	2-[[2-(2-Chloropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.39(dd, 1H), 8.23(dd, 1H), 8.02(dd, 1H), 7.76(t, 1H), 7.19-7.29(m, 4H), 6.36(s, 2H), 4.34(t, 2H), 1.72(m, 2H), 0.83(t, 3H)
bbbbbb	2-[[2-(2-Cyanopyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.56(dd, 1H), 8.39(dd, 1H), 8.00(dd, 1H), 7.92(dd, 1H), 7.63(dd, 1H), 7.20-7.29(m, 3H), 6.32(s, 2H), 4.36(t, 2H), 1.80(m, 2H), 0.89(t, 3H) LC-MS: calcd: 343.39, found 344.1(M+1)

780
781

60257432-1EE100

ccccc	2-[[2-(2-Cyanopyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-ethyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.56(dd, 1H), 8.40(dd, 1H), 8.01(dd, 1H), 7.93(t, 1H), 7.63(dd, 1H), 7.21-7.29(m, 3H), 6.33(s, 2H), 4.44(q, 2H), 1.35(t, 3H) LC-MS: calcd: 329.37, found 330.1(M+1)
cdcdcd	2-[[2-(2-Cyanopyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-(2-fluoroethyl)-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): line list provided 4.74 (m, 1H), 4.84-4.95 (m, 3H), 6.16 (s, 2H), 7.19-7.28 (m, 2H), 7.39 (s, 1H), 7.54 (d, 1H), 7.83 (t, 1H), 7.89 (d, 1H), 8.34 (m, 1H), 8.53 (d, 1H) LC-MS: M + 1, 348
ccccc	2-[[2-(2-Cyanopyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-cyclopropyl-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): line list provided 1.28 (m, 4H), 3.37 (m, 1H), 3.48 (s, 2H), 6.36 (s, 2H), 7.15-7.28 (m, 3H), 7.56 (d, 1H), 7.86 (m, 2H), 8.38 (m, 1H), 8.54 (d, 1H) LC-MS: M + 1, 342, M - 1, 340
mm	2-[[2-(2-Pyrid-6-ylcarboxamide)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.88(s, 1H), 8.42(dd, 1H), 8.38(dd, 1H), 8.15(dd, 1H), 7.98(dd, 1H), 7.93(d, 1H), 7.22-7.27(m, 3H), 6.18 (s, 2H), 5.67(s, 1H), 4.07(t, 2H), 1.54(m, 2H), 0.83(t, 3H) LC-MS: calcd: 361.41, found 362.2(M+1)
ccccc	2-[[2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-(2-fluoroethyl)-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): 4.26(t, 1H), 4.35(t, 1H), 4.51(t, 1H), 4.67(t, 1H), 5.54(s, 2H), 7.09-7.45 (m, 4H), 8.06(d, 1H), 8.36(d, 1H) LC-MS: M + 1, 340
hhhhh	2-[[2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-ethyl-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): 4.59-4.62 (m, 3H), 5.03 (d, 1H), 5.43(s, 2H), 5.70 (m, 1H), 7.03 (s, 1H), 7.17 (m, 1H), 7.25 (m, 2H), 7.43(m, 3H), 8.04 (d, 1H), 8.40 (d, 1H) LC-MS: M + 1, 334, M - 1 332
mm	2-[[2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-propargyl-3H-imidazo[4,5-b]pyridine	H-1 NMR (dms _o): 3.47 (s, 1H), 4.78 (s, 2H), 5.65 (s, 2H), 7.07-7.45 (m, 5H), 7.45(m, 2H), 8.07(m, 1H), 8.42(m, 1H) LC-MS: M + 1, 332, M - 1, 330
mm	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-cyclopropyl-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): line list provided 1.20-1.24 (m, 4H), 3.35 (m, 1H), 6.29 (s, 2H), 6.79 (d, 1H), 7.15 (m, 3H), 7.82 (q, 1H), 7.92 (d, 1H), 8.15 (d, 1H), 8.37(d, 1H) LC-MS: M + 1, 335
hhhhh	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-allyl-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): line list provided 4.87 (d, 1H), 5.14 (m, 3H), 5.87 (m, 1H), 6.24 (s, 2H), 6.86 (dd, 1H), 7.23 (m, 3H), 7.84 (m, 1H), 8.02 (d, 1H), 8.15 (m, 1H), 8.38 (d, 1H) LC-MS: M + 1, 335, M - 1, 333
mm	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-(2,2,2-trifluoroethyl)-3H-imidazo[4,5-b]pyridine	HCl salt H-1 NMR (CD ₃ OD): 5.42 (q, 2H), 6.40 (s, 2H), 7.24 (d, 1H), 7.37 (m, 1H), 7.90 (m, 2H), 8.03 (m, 2H), 8.22 (m, 1H), 8.43 (m, 1H) LC-MS: M + 1, 377
mmmmmm	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-cyclopropylmethyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.37(dd, 1H), 8.18(dd, 1H), 8.01(dd, 1H), 7.88(m, 1H), 7.20-7.26(m, 3H), 6.87(dd, 1H), 6.31(s, 2H), 4.31(d, 2H), 1.22(m, 1H), 0.42-0.53(m, 4H) LC-MS: calcd: 348.39, found 349.3(M+1)

60257492-122100

nnnnnn	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.38(dd, 1H), 8.19(m, 1H), 8.02(dd, 1H), 7.89(m, 1H), 7.20-7.26(m, 3H), 6.88(m, 1H), 6.32(s, 2H), 4.35(t, 2H), 1.74(m, 2H), 0.85(t, 3H) LC-MS: calcd: 336.37, found 337.2(M+1)
oooooo	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-isopropyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.36(dd, 1H), 8.18(m, 1H), 8.00(dd, 1H), 7.90(m, 1H), 7.18-7.22(m, 2H), 7.13(d, 1H), 6.89(m, 1H), 6.32(s, 2H), 5.04(m, 1H), 1.63(d, 6H) LC-MS: calcd: 336.37, found 337.2(M+1)
pppppp	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-cyclobutyl-3H-imidazo[4,5-b]pyridine	<u>dihydrochloride</u> ¹ H nmr (d6 DMSO): 8.39(1H, dd), 8.33(1H, dd), 8.25(1H, q), 8.03(1H, d), 7.95(1H, d), 7.87(1H, dd), 7.33(1H, dd), 7.21(1H, dd), 6.34(2H, s), 5.18(1H, m), 3.28-1.20(2H, m), 2.58-2.42(2H, m), 2.00-1.86(2H, m), LRMS calcd. 348.4, found 349.3(MH+).
qqqqqq	2-[[2-(3-Fluoro-4-methylphenyl)-1H-imidazol-1-yl]methyl]-1-(2-fluoroethyl)-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): line list provided 2.35 (s, 3H), 4.26 (t, 1H), 4.35 (t, 1H), 4.51 (t, 1H), 4.67 (t, 1H), 5.53 (s, 2H), 7.07 (s, 1H), 7.18 (s, 1H), 7.26-7.34 (m, 4H), 8.07 (d, 1H), 8.36 (d, 1H) LC-MS: M + 1, 354
nnnn	2-[[2-(3-Fluorophenyl)-1H-imidazol-1-yl]methyl]-1-cyclopropyl-3H-imidazo[4,5-b]pyridine	HCl salt H-1 NMR (DMSO): line list provided 1.03-1.22 (m, 4H), 3.37 (m, 1H), 5.96 (s, 2H), 7.22 (m, 1H), 7.45-7.78 (m, 4H), 7.95-8.03 (m, 3H), 8.37 (d, 1H) LC-MS: M + 1 334, M - 1 332
ssssss	2-[[2-(1-Methy-4-chloropyrazol-3-yl)-1H-imidazol-1-yl]methyl]-1-(2-fluoroethyl)-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): line list provided 3.89 (s, 3H), 4.55 (s, 2H), 4.69 (m, 1H), 4.71 (m, 1H), 5.93 (s, 2H), 7.11 (s, 1H), 7.25 (m, 2H), 7.47 (s, 1H), 8.04 (d, 1H), 8.36 (d, 1H) LC-MS: M + 1, 360
ttttt	2-[[2-(3-Methoxyphenyl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	<u>dihydrochloride</u> ¹ H nmr (d6 DMSO): 8.35(1H, dd), 8.04-7.98(2H, m), 7.93(1H, d), 7.48(1H, t), 7.35-7.19(4H, m), 5.95(2H, s), 4.22(2H, t), 3.69(3H, s), 1.79-1.68(2H, m), 0.81(3H, t), LRMS calcd. 347.4, found 348.39MH+).
uuuuuu	2-[[2-Thien-3-yl-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.40(dd, 1H), 8.05(dd, 1H), 7.66(dd, 1H), 7.43-7.49(m, 2H), 7.25(dd, 1H), 7.14(d, 1H), 7.02(d, 1H), 5.55(s, 2H), 3.91(t, 2H), 1.51(m, 2H), 0.79(t, 3H) LC-MS: calcd: 323.42 found 324.3
vvvvv	2-[[2-(1-Methy-4-chloropyrazol-3-yl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H nmr (CDCl ₃): 8.38(1H, dd), 8.04(1H, dd), 7.52(1H, s), 7.26-7.21(2H, m), 7.05(1H, d), 5.98(2H, s), 4.15(2H, t), 3.94(3H, s), 1.62-1.52(2H, m), 0.80(3H, t), LRMS calcd. 355.8, found 356.2(MH+).
wwwwww	2-[[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H nmr (CDCl ₃): 8.53-8.51(1H, m), 8.40(1H, dd), 8.16-8.14(1H, m), 8.03(1H, dd), 7.28-7.23(2H, m), 7.11(1H, d), 7.05(1h, dd), 5.46(2H, s), 4.00(2H, t), 1.65-1.59(2H, m), 0.84(3H, t), LRMS calcd. 336.4, found 337.1(MH+).

60257492.122100

xxxxxx	2-[[2-(4-Chloropyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-ethyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.44(dd, 1H), 8.39(m, 1H), 8.03(dd, 1H), 7.18-7.28(m, 5H), 6.41(s, 2H), 4.39(q, 2H), 1.20(t, 3H) LC-MS: calcd: 338.80, found 339.2(M+1)
yyyyyy	2-[[2-(4-Chloropyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.36-8.45(m, 3H), 8.03(dd, 1H), 7.18-7.29(m, 4H), 6.40(s, 2H), 4.28(t, 2H), 1.66(m, 2H), 0.81(t, 3H)
zzzzzz	2-[[2-(4-Chloropyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-cyclopropyl-3H-imidazo[4,5-b]pyridine	HCl salt H-1 NMR (DMSO): line list provided 1.24 (m, 4H), 3.48 (m, 1H), 6.43 (s, 2H), 7.19 (m, 1H), 7.67 (m, 1H), 7.86 (d, 1H), 7.97 (s, 1H), 8.06(s, 1H), 8.31 (d, 1H), 8.56 (d, 1H), 8.64 (m, 1H) LC-MS: M + 1, 351, M - 1, 349
aaaaaa	2-[[2-(4-Chloropyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-(2-fluoroethyl)-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): 4.60-4.77 (m, 2H), 4.81 (s, 2H), 6.35(s, 2H), 7.20-7.25 (m, 5H), 8.03 (d, 1H), 8.38 (m, 1H) LC-MS: M + 1 357
bbbbbb	2-[[2-(4-Cyanopyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	<u>dihydrochloride</u> ¹ H nmr (d6 DMSO): 8.78(1H, s), 8.72(1H, d), 8.32(1H, dd), 7.99(1H, d), 7.93-7.86(3H, m), 7.21(1H, dd), 6.34(2H, s), 4.37(2H, t), 1.91-1.82(2H, m), 0.93(3H, t), LRMS calcd. 343.4, found 344.2(MH+).
ccccc	2-[[2-(5-Methylisoxazol-3-yl)-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.39(dd, 1H), 8.04(dd, 1H), 7.19-7.27(m, 3H), 6.65(d, 1H), 6.10(s, 2H), 4.26(t, 2H), 1.63(m, 2H), 0.83(t, 3H) LC-MS: calcd: 322.37 found 323.2
ddddd	2-[[2-(3-Fluoropyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-(2-fluoroethyl)-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): line list provided 4.58-4.66 (m, 2H), 4.75 (s, 2H), 6.03 (s, 2H), 7.21-7.35 (m, 4H), 7.57 (m, 1H), 8.04 (d, 1H), 8.41(m, 1H) LC-MS: M + 1, 341
eeeeee	2-[[2-(3-Fluoropyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-ethyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.47(m, 1H), 8.40(dd, 1H), 8.04(dd, 1H), 7.62(m, 1H), 7.36(m, 1H), 7.23-7.28(m, 2H), 7.16(d, 1H), 6.10(s, 2H), 4.37(q, 2H), 1.19(t, 3H) LC-MS: calcd: 322.35, found 323.3(M+1)
ffff	2-[[2-(3-Fluoropyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-propargyl-3H-imidazo[4,5-b]pyridine	HCl salt H-1 NMR (dmso): line list provided 3.51 (s, 1H), 5.25 (s, 2H), 6.25(s, 2H), 7.27(m, 1H), 7.72(m, 1H), 7.94-8.15 (m, 4H), 8.35(m, 1H), 8.50(1H) LC MS: M + 1, 333
gggggg	2-[[2-(3-Fluoropyrid-2-yl)-1H-imidazol-1-yl]methyl]-1-cyclopropyl-3H-imidazo[4,5-b]pyridine	HCl salt H-1 NMR (dmso): line list provided 1.19 (m, 4H), 3.36 (m, 2H), 6.24 (s, 2H), 7.21 (m, 1H), 7.70 (m, 1H), 7.88 (d, 2H), 8.00 (s, 1H), 8.07 (m, 3H), 8.31 (d, 1H), 8.52 (d, 1H) LC-MS: M + 1, 335
hhhhhh	2-[2-Thiazol-2-yl-1H-imidazol-1-yl]methyl]-1-propyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.40(dd, 1H), 8.05(dd, 1H), 7.86(d, 1H), 7.40(d, 1H), 7.25(d, 1H), 7.22(d, 1H), 7.15(d, 1H), 6.37(s, 2H), 4.27(t, 2H), 1.62(m, 2H), 0.78(t, 3H). LC-MS: calcd: 324.41, found 325.3(M+1)

mm	2-[2-Thiazol-2-yl-1H-imidazol-1-yl)methyl]-1-isopropyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.37(dd, 1H), .8.02(dd, 1H) 7.84 (d, 1H), 7.39(d, 1H), 7.11-7.23(m, 3H), 6.32(s, 2H), 4.92(m, 1H), 1.56(d, 6H) LC-MS: calcd: 324.41 found 325.4
mm	2-[2-(3,4-Difluorophenyl)-1H-imidazol-1-yl)methyl]-1-ethyl-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.39(dd, 1H), 8.04(dd, 1H), 7.54(m 1H), 7.40(m, 1H), 7.26-7.32(m, 2H), 7.16(d, 1H), 7.04(d, 1H), 5.47(s, 2H), 4.02(q, 2H), 1.09(t, 3H) LC-MS: calcd: 339.35 found 340.2
kkkkkk	2-[2-Thiazol-2-yl-1H-imidazol-1-yl)methyl]-1-3H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): line list provided 5.32 (q, 2H), 6.19 (s, 2H), 7.19 (s, 1H), 7.26 (m, 2H), 7.43 (s, 1H), 7.79 (d, 1H), 8.04 (d, 1H), 8.41 (m, 1H) LC-MS: M + 1, 365
mm	2-[2-Thiazol-2-yl-1H-imidazol-1-yl)methyl]-1-cyclopropylmethyl-3H-imidazo[4,5-b]pyridine	<u>dihydrochloride</u> ¹ H nmr (d6 DMSO): 8.35(1H, dd), 7.95(1H, dd), 7.90-7.87(2H, m), 7.81(1H, s), 7.52(1H, s), 7.27(1H, dd), 6.35(2H, s), 4.31(2H, d), 1.42-1.38(1H, m), 0.55-0.52(4H, m), LRMS calcd. 336.4, found 335.1(M-).
mmmmmm	2-[2-(3-Fluorophenyl)-1H-imidazol-1-yl)methyl]-1-ethyl-1H-benzimidazole	MH+ 321.3
mmmmmm	2-[2-(3-Fluorophenyl)-1H-imidazol-1-yl)methyl]-1-phenyl-1H-benzimidazole	H-1 NMR (CDCl ₃): 5.38(s, 2H), 6.91-7.17(m, 8H), 7.22-7.45 (m, 6H), 7.84 (d, 1H) LC-MS: 369
ooooooo	2-[2-(2-Fluoropyrid-6-yl)-1H-imidazol-1-yl)methyl]-1-phenyl-1H-benzimidazole	H-1 NMR: 6.22 (s, 2H), 6.78 (m, 1H), 7.03-7.37 (m, 9H), 7.65-7.92 (m, 3H) LC-MS: M-1, 368
pppppp	2-[2-(3-Fluorophenyl)-1H-imidazol-1-yl)methyl]-1-ethyl-6-methyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine	LRMS calcd. 339.41, found 340.2(MH+)
qqqqqq	2-[2-(6-Methyl-pyridin-2-yl)-imidazol-1-yl)methyl]-1-propyl-1H-benzimidazole-5-carboxylic acid hydrazide	CD3OD: 8.10-8.29 (m, 6H), 8.03 (s, 1H), 7.29 (d, 1H), 6.4 (s, 2H), 4.59-4.65 (m, 2H), 2.0-2.12 (m, 2H), 1.06-1.07 (m, 3H). LCMS: MH+ 394.3
mmmm	3-Ethyl-2-[2-(3-fluoro-phenyl)-2H-pyrazol-3-ylmethyl]-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.36(dd, 1H), 7.99(dd, 1H), 7.65(d, 1H), 7.44(m, 1H), 7.20-7.30(m, 3H), 7.13(m, 1H), 6.23(d, 1H), 4.36 (s, 2H), 4.15(q, 2H), 1.27(t, 3H)
ssssss	3-Ethyl-2-[2-(2,5-difluoro-phenyl)-2H-pyrazol-3-ylmethyl]-3H-imidazo[4,5-b]pyridine	¹ H NMR, δppm (CDCl ₃): 8.35(dd, 1H), 7.95(dd, 1H), 7.68(d, 1H), 7.09-7.27(m, 4H), 6.21(d, 1H), 4.29(s, 2H), 4.17(q, 2H), 1.27(t, 3H) LC-MS: calcd: 339.35, found 340.2(M+1)

785

60257492.122100

TABLE VII		
Ex.	Name	Analytical Data
a	1-Cyclopropyl-2-[[2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl]-1H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): 0.22 (m, 2H), 0.54(m, 2H), 0.95(m, 1H), 3.84(d, 2H), 4.32(s, 2H), 6.18(s, 2H), 7.13-7.25 (m, 4H), 7.65 (m, 2H), 8.52 (d, 1H) (line list enclosed) LC-MS: M + 1, 366
b	1-Cyclopropyl-2-[[2-(3-fluorophenyl)-pyrazol-3-yl]methyl]-1H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): 0.22 (m, 2H), 0.54(m, 2H), 0.95(m, 1H), 3.82 (d, 2H), 4.41(s, 2H), 6.22(s, 2H), 7.05-7.70 (m, 7H), 8.50 (m, 1H) LC-MS: M + 1 348
c	1-Propyl-2-[[2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl]-1H-imidazo[4,5-b]pyridine	H-1 NMR (CDCl ₃): 0.82(t, 3H), 1.62(h, 2H), 3.85(t, 2H), 4.33 (s, 2H), 6.20 (s, 1H), 7.05-7.25(m, 4H), 7.82(m, 2H), 8.53(d, 1H) LC-MS: M + 1, 354
d	1-Ethyl-2-[[2-(3-fluorophenyl)-pyrazol-3-yl]methyl]-4-chloro-1H-imidazo[4,5-c]pyridine	¹ H nmr (CDCl ₃): 8.19(1H, d), 7.61(1H, d), 7.48-7.44(1H, m), 7.28-7.13(4H, m), 6.14(1H, m), 4.44(2H, s), 3.93(2H, q), 1.17(3H, t), LRMS calcd. 355.8, found 356.2(MH ⁺).
e	N-Dimethyl 1-ethyl-2-[[2-(3-fluorophenyl)-pyrazol-3-yl]methyl]-1H-benzimidazole-6-carboxamide	¹ H NMR, δppm (CDCl ₃): 7.72(dd, 1H), 7.63(d, 1H), 7.40-7.49 (m, 2H), 7.24-7.34(m, 3H), 7.13(d, 1H), 6.18(d, 1H), 4.35(s, 2H), 3.99(q, 2H), 3.13(s, 2H), 3.07(s, 3H), 1.23(t, 3H)
f	1-Ethyl-2-[[2-(3-fluorophenyl)-pyrazol-3-yl]methyl]-6-methoxy-3H-imidazo[4,5-b]pyridine	LC-MS: calcd: 391.45, found 392.3 (M+1)
g	1-Ethyl-2-[[2-(3-fluorophenyl)-pyrazol-3-yl]methyl]-3H-imidazo[4,5-b]pyridine	
h	1-Ethyl-2-[[2-(2,5-difluorophenyl)-pyrazol-3-yl]methyl]-3H-imidazo[4,5-b]pyridine	
i	1-Isopropyl-2-[[2-(3-fluorophenyl)-pyrazol-3-yl]methyl]-3H-imidazo[4,5-b]pyridine	
j	1-Propyl-2-[[2-(3-fluorophenyl)-pyrazol-3-yl]methyl]-3H-imidazo[4,5-b]pyridine	
k	1-Ethyl-2-[[2-(3-fluorophenyl)-pyrazol-3-yl]methyl]-5-trifluoroacetyl-1H-benzimidazole	
l	1-Ethyl-2-[[2-(3-chlorophenyl)-pyrazol-3-yl]methyl]-5-trifluoroacetyl-1H-benzimidazole	
m	1-Ethyl-2-[[2-(3-fluorophenyl)-pyrazol-3-yl]methyl]-5-(1-	¹ H NMR, δppm (CDCl ₃): 7.95(m, 1H), 7.72(dd, 1H), 7.63(d, 1H), 7.45(m, 1H)

	(ethoxyethoxyimino)ethyl-1H-benzimidazole	7.72(dd, 1H), 7.63(d, 1H), 7.45(m, 1H), 7.11-7.31(m, 4H), 6.18(d, 1H), 4.34-4.37(m, 4H), 3.98(q, 2H), 3.77(t, 2H), 3.58(q, 2H), 2.33(s, 3H), 1.18-1.26(m, 6H)
	1-(3-Cyanopropyl)-2-[[2-(3-fluorophenyl)-pyrazol-3-yl]methyl]-1H-benzimidazole	LC-MS: calcd: 449.53, found 450.3(M+1)
	1-(2-Fluoroethyl)-2-[[2-(3-fluorophenyl)-pyrazol-3-yl]methyl]-1H-benzimidazole	
	1-Ethyl-2-[[2-(3-fluorophenyl)-pyridin-3-yl]methyl]-5-cyano-1H-benzimidazole	
	1-Ethyl-2-[[2-(3-chlorophenyl)-pyridin-3-yl]methyl]-5-cyano-1H-benzimidazole	

Example 22**Preparation of radiolabeled probe compounds of the invention**

The compounds of the invention are prepared as radiolabeled probes by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. The radioisotope is preferably selected from of at least one of carbon (preferably ^{14}C), hydrogen (preferably ^3H), sulfur (preferably ^{35}S), or iodine (preferably ^{125}I). Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds. Such suppliers include Amersham Corporation, Arlington Heights, IL; Cambridge Isotope Laboratories, Inc. Andover, MA; SRI International, Menlo Park, CA; Wizard Laboratories, West Sacramento, CA; ChemSyn Laboratories, Lexena, KS; American Radiolabeled Chemicals, Inc., St. Louis, MO; and Moravsek Biochemicals Inc., Brea, CA.

Tritium labeled probe compounds are also conveniently prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas. Such preparations are also conveniently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate.

Example 23**Receptor autoradiography**

Receptor autoradiography (receptor mapping) is carried out in vitro as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New

788

York, using radiolabeled compounds of the invention prepared as described in the preceding Example.

Example 24

Binding Assay

This assay is a standard assay for GABA_A binding affinity. The high affinity and high selectivity of compounds of this invention for the benzodiazepine site of the GABA_A receptor is confirmed using the binding assay described in Thomas and Tallman (*J. Bio. Chem.* 1981; 156:9838-9842, and *J. Neurosci.* 1983; 3:433-440).

Rat cortical tissue is dissected and homogenized in 25 volumes (w/v) of Buffer A (0.05 M Tris HCl buffer, pH 7.4 at 4 °C). The tissue homogenate is centrifuged in the cold (4 °C) at 20,000 x g for 20 minutes. The supernatant is decanted, the pellet rehomogenized in the same volume of buffer, and centrifuged again at 20,000 x g. The supernatant of this centrifugation step is decanted and the pellet stored at -20 °C overnight. The pellet is then thawed and resuspended in 25 volumes of Buffer A (original wt/vol), centrifuged at 20,000 x g and the supernatant decanted. This wash step is repeated once. The pellet is finally resuspended in 50 volumes of Buffer A.

Incubations containing 100 µl of tissue homogenate, 100 µl of radioligand, (0.5 nM ³H-Ro15-1788 [³H-Flumazenil], specific activity 80 Ci/mmol), and test compound or control (see below), and are brought to a total volume of 500 µl with Buffer A. Incubations are carried for 30 min at 4°C and then rapidly filtered through Whatman GFB filters to separate free and bound ligand. Filters are washed twice with fresh Buffer A and counted in a liquid scintillation counter. Nonspecific binding (control) is determined by displacement of ³H Ro15-1788 with 10 µM Diazepam (Research Biochemicals International, Natick, MA). Data were collected in triplicate, averaged, and percent inhibition of

60257492-122100

789

total specific binding (Total Specific Binding = Total - Nonspecific) was calculated for each compound.

A competition binding curve is obtained with up to 11 points spanning the compound concentration range from 10^{-12} M to 10^{-5} M obtained per curve by the method described above for determining percent inhibition. K_i values are calculated according the Cheng-Prussoff equation. When tested in this assay compounds of the invention exhibit K_i values of less than 1 μ M, preferred compounds of the invention have K_i values of less than 500 nM and more preferred compounds of the invention have K_i values of less than 100 nM.

Example 25

Electrophysiology

The following assay is used to determine if a compound of the invention act as an agonist, an antagonist, or an inverse agonist at the benzodiazepine site of the GABA_A receptor.

Assays are carried out as described in White and Gurley (NeuroReport 6: 1313-1316, 1995) and White, Gurley, Hartnett, Stirling, and Gregory (Receptors and Channels 3: 1-5, 1995) with modifications. Electrophysiological recordings are carried out using the two electrode voltage-clamp technique at a membrane holding potential of -70 mV. *Xenopus Laevis* oocytes are enzymatically isolated and injected with non-polyadenylated cRNA mixed in a ratio of 4:1:4 for α , β and γ subunits, respectively. Of the nine combinations of α , β and γ subunits described in the White et al. publications, preferred combinations are $\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_3\gamma_2$, $\alpha_3\beta_3\gamma_2$, and $\alpha_5\beta_3\gamma_2$. Preferably all of the subunit cRNAs in each combination are human clones or all are rat clones. The sequence of each of these cloned subunits is available from GENBANK, e.g., human α_1 , GENBANK accession no. X14766, human α_2 , GENBANK accession no. A28100; human α_3 , GENBANK accession no.

790

A28102; human α_3 , GENBANK accession no. A28104; human β_2 , GENBANK accession no. M82919; human β_3 , GENBANK accession no. Z20136; human β_2 , GENBANK accession no. X15376; rat α_1 , GENBANK accession no. L08490, rat α_2 , GENBANK accession no. L08491; rat α_3 , GENBANK accession no. L08492; rat α_5 , GENBANK accession no. L08494; rat β_1 , GENBANK accession no. X15467; rat β_3 , GENBANK accession no. X15468; and rat γ_2 , GENBANK accession no. L08497. For each subunit combination, sufficient message for each constituent subunit is injected to provide current amplitudes of >10 nA when 1 μ M GABA is applied.

Compounds are evaluated against a GABA concentration that evokes <10% of the maximal evokable GABA current (e.g. 1 μ M - 9 μ M). Each oocyte is exposed to increasing concentrations of compound in order to evaluate a concentration/effect relationship. Compound efficacy is calculated as a percent-change in current amplitude: $100 * ((I_c/I) - 1)$, where I_c is the GABA evoked current amplitude observed in the presence of test compound and I is the GABA evoked current amplitude observed in the absence of the test compound.

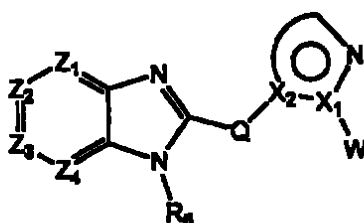
Specificity of a compound for the benzodiazepine site is determined following completion of a concentration/effect curve. After washing the oocyte sufficiently to remove previously applied compound, the oocyte is exposed to GABA + 1 μ M RO15-1788, followed by exposure to GABA + 1 μ M RO15-1788 + test compound. Percent change due to addition of compound is calculated as described above. Any percent change observed in the presence of RO15-1788 is subtracted from the percent changes in current amplitude observed in the absence of 1 μ M RO15-1788. These net values are used for the calculation of average efficacy and EC_{50} values by standard methods. To evaluate average efficacy and EC_{50} values, the concentration/effect data are averaged across cells and fit to the logistic equation.

60257492.122100

792
791

What is claimed is:

1. A compound of the formula:



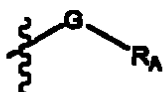
or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Z₁, Z₂, Z₃, and Z₄ independently represent nitrogen or CR₁, CR₂, CR₃, and CR₄, respectively, provided that no more than two of Z₁, Z₂, Z₃, and Z₄ are nitrogen;

R₁, R₂, R₃, and R₄ are independently selected from

- i) hydrogen, halogen, hydroxy, nitro, cyano, amino, haloalkyl, oxo, trifluoromethoxy, trifluoromethyl, trifluorosulfonyl, and carboxylic acid,
- ii) mono or dialkylamino, aminoalkyl, mono- or dialkylaminoalkyl, alkoxy, alkyl, cycloalkyl, alkenyl, alkynyl, (cycloalkyl)alkyl, alkanoyl, alkoxy carbonyl, alkylsulfonyl, alkylthio, mono- or dialkylaminocarbonyl, heterocycloalkyl, aryl, and heteroaryl, each of which may be optionally substituted,

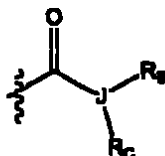
iii) a group of the formula:



where G is alkyl, -O-, -C(=O)-, or -CC(=O)-, and

RA is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which may be optionally substituted,

iv) a group of the formula



50257492.122100

793
792

where J is N or CH and R_8 and R_9 are independently hydrogen, C_1 - C_8 alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which may be optionally substituted; or

R_8 and R_9 and the atom to which they are attached form a 4- to 10-membered monocyclic or bicyclic ring, which may contain one or more double bonds or one or more of oxo, O, S, SO, SO₂, or N- R_0 wherein R_0 is hydrogen, Ar_1 , C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_3 - C_8 heterocycloalkyl, or C_1 - C_6 alkyl- Ar_1 ; wherein Ar_1 is aryl or heteroaryl, each of which may be optionally substituted; and wherein the monocyclic or bicyclic ring is optionally substituted;

v) $-OC(=O)R_E$, $-C(=O)NH_2$, $-C(=O)NHR_E$, $-C(=O)NR_ER_F$, $-S(O)_nR_E$, $-S(O)_nNH_2$, $-S(O)_nNHR_E$, $-S(O)_nNR_ER_F$, $-NHC(=O)R_E$, $-C(=NR_E)R_F$, $-C=N-OH$, $-C=N(alkoxy)$, $-C=N(alkyl)$, $-NR_EC(=O)R_F$, $-NHS(O)_nR_E$, and $-NR_ES(O)_nR_F$, where n is 0, 1 or 2, and R_E and R_F are independently selected at each occurrence from alkyl, cycloalkyl, heterocycloalkyl, alkoxy, mono- or diaminoalkyl, aryl, or heteroaryl each of which may be optionally substituted;

R_3 represents optionally substituted alkyl, cycloalkyl, or (cycloalkyl)alkyl, each of which may contain one or more double or triple bonds, or R_3 represents optionally substituted aryl, arylalkyl, heteroaryl, or heteroarylalkyl;

Q represents CR_6R_7 , NR_6 , or oxygen when X_2 is not nitrogen;

R_6 and R_7 represent hydrogen, halogen, hydroxy, or alkyl;

R_8 represents hydrogen or alkyl;

the group:



794
-293

represents 5 to 7 membered heteroaromatic ring containing up to 4 heteroatoms selected from nitrogen, sulfur, and oxygen, said 5 to 7 membered heteroaromatic ring is optionally substituted at each carbon atom by R, and optionally substituted at each nitrogen atom available for substitution by R',

R is independently chosen at each occurrence from halogen, hydroxy, nitro, cyano, amino, alkyl, alkoxy, alkoxy substituted with amino or mono- or dialkylamino, cycloalkyl, (cycloalkyl)alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, carboxamide, mono or dialkylamino, aminoalkyl, and mono- or dialkylaminoalkyl,

R' is C₁-C₆ alkyl;

X₁ and X₂ independently represent nitrogen or carbon; and

W represents aryl or heteroaryl, either of which is optionally substituted with up to three groups selected independently from halogen, hydroxy, nitro, cyano, amino, alkyl, alkoxy, alkoxy substituted with amino or mono- or di-alkylamino, cycloalkyl, (cycloalkyl)alkyl, cycloalkylalkoxy, heterocycloalkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, mono or dialkylamino, aminoalkyl, and mono- or dialkylaminoalkyl, -C(O)_mR_g, and -S(O)_mR_g, where R_g is as defined above and m is 0, 1 or 2.

2. A compound according to Claim 1, wherein:

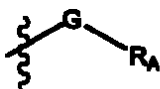
Z₁, Z₂, Z₃, and Z₄ independently represent nitrogen or CR₁, CR₂, CR₃, and CR₄, respectively, provided that no more than two of Z₁, Z₂, Z₃, and Z₄ are nitrogen;

R₁, R₂, R₃, and R₄ are independently selected from

795
794

- i) hydrogen, halogen, hydroxy, nitro, cyano, amino, haloalkyl, oxo, trifluoromethoxy, trifluoromethyl, trifluorosulfonyl, and carboxylic acid,
- ii) mono or di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, mono- or di(C₁-C₆)alkylamino(C₁-C₆)alkyl, C₁-C₆alkoxy, C₁-C₆alkyl, C₃-C₆cycloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₆cycloalkyl)C₁-C₆alkyl, C₁-C₆alkanoyl, C₁-C₆alkoxycarbonyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylthio, mono- or di(C₁-C₆)alkylaminocarbonyl, heterocycloalkyl, aryl, and heteroaryl, each of which may be optionally substituted with up to three groups R_x,

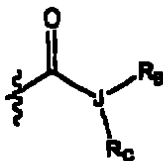
iii) a group of the formula:



where G is C₁-C₆alkyl, -O-, -C(=O)-, or -CC(=O)-, and

R_A is C₃-C₆cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which may be optionally substituted with up to three groups R_x,

iv) a group of the formula



where J is N or CH and R_B and R_C are independently hydrogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which may be optionally substituted with up to three groups R_x; or

R_B and R_C and the atom to which they are attached form a 4- to 10-membered monocyclic or bicyclic ring, which may contain one or more double bonds or one or more of oxo, O, S, SO, SO₂, or N-R_D wherein R_D is hydrogen, Ar₁, C₁-C₆alkyl, C₃-C₆cycloalkyl, heterocycloalkyl, or C₁-C₆alkyl-Ar₁; wherein Ar₁ is aryl or heteroaryl, each of

60257492.122100

795
795

which may be optionally substituted with up to three groups R_X ; and wherein the monocyclic or bicyclic ring is optionally substituted with up to three groups R_X ;

v) $-OC(=O)R_E$, $-C(=O)NH_2$, $-C(=O)NHR_E$, $-C(=O)NR_ER_F$, $-S(O)_nR_E$, $-S(O)_nNH_2$, $-S(O)_nNHR_E$, $-S(O)_nNR_ER_F$, $-NHC(=O)R_E$, $-C(=NR_E)R_F$, $-C=N-OH$, $-C=N(alkoxy)$, $-C=N(alkyl)$, $-NR_EC(=O)R_F$, $-NHS(O)_nR_E$, and $-NR_ES(O)_nR_F$, where n is 0, 1 or 2, and

R_E and R_F are independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_8 cycloalkyl, heterocycloalkyl, C_1-C_6 alkoxy, mono- or diamino(C_1-C_6)alkyl, aryl, or heteroaryl each of which may be optionally substituted with up to three groups R_X ;

R_5 represents C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or $(C_3-C_8$ cycloalkyl) C_1-C_6 alkyl, each of which may contain one or more double or triple bonds and each of which may be optionally substituted with up to three groups R_X , or R_5 represents aryl, aryl(C_1-C_6 alkyl), heteroaryl, or heteroaryl(C_1-C_6 alkyl) each of which may be optionally substituted with up to three groups R_X ;

Q represents CR_6R_7 , NR_6 , or

oxygen when X_2 is not nitrogen;

R_6 and R_7 represent hydrogen, halogen, hydroxy, or C_1-C_6 alkyl;

R_6 represents hydrogen or C_1-C_6 alkyl;

the group:



represents a 5 to 7 membered heteroaromatic ring, containing up to 4 heteroatoms selected from nitrogen, sulfur, and oxygen, said 5 to 7 membered heteroaromatic ring is optionally substituted at each carbon atom with R , and optionally

297
296

substituted at each nitrogen atom available for substitution with R',

R is independently chosen at each occurrence from halogen, hydroxy, nitro, cyano, amino, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy substituted with amino or mono- or di(C₁-C₆)alkylamino, C₃-C₆cycloalkyl, (C₃-C₆cycloalkyl)C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, haloalkyl, haloalkoxy, carboxamide, mono or di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, and mono- or di(C₂-C₆)alkylamino(C₁-C₆)alkyl,

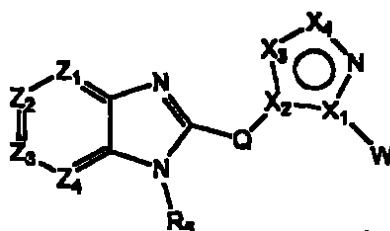
R' is C₁-C₆ alkyl;

X₁ and X₂ independently represent nitrogen or carbon;

R_x is independently selected at each occurrence from halogen, hydroxy, nitro, cyano, amino, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkoxy substituted with amino or mono- or di(C₁-C₆)alkylamino, C₃-C₆cycloalkyl, (C₃-C₆cycloalkyl)C₁-C₆alkyl, (C₃-C₆cycloalkyl)C₁-C₆alkoxy, heterocycloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, haloalkyl, haloalkoxy, mono or di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, and mono- or di(C₁-C₆)alkylamino(C₁-C₆)alkyl; and

W represents aryl or heteroaryl, either of which is optionally substituted with up to three groups selected independently from halogen, hydroxy, nitro, cyano, amino, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkoxy substituted with amino or mono- or di(C₁-C₆)alkylamino, C₃-C₆cycloalkyl, (C₃-C₆cycloalkyl) C₁-C₆alkyl, (C₃-C₆cycloalkyl) C₁-C₆alkoxy, heterocycloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, haloalkyl, haloalkoxy, mono or di(C₂-C₆)alkylamino, amino(C₂-C₆)alkyl, and mono- or di(C₂-C₆)alkylamino(C₂-C₆)alkyl, -COOH, -(C=O)OR_E, -(C=O)NR_E, -C(O)R_E, and -S(O)_mR_E where R_E is as defined above and m is 0, 1 or 2.

3. A compound of the formula:

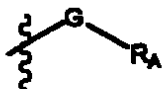


or a pharmaceutically acceptable salt, prodrug, or solvate thereof, wherein:

Z₁, Z₂, Z₃, and Z₄ independently represent nitrogen or CR₁, CR₂, CR₃, and CR₄, respectively, provided that no more than two of Z₁, Z₂, Z₃, and Z₄ are nitrogen;

R₁, R₂, R₃, and R₄ are independently selected from

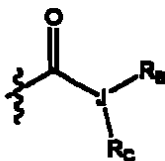
- i) hydrogen, halogen, hydroxy, nitro, cyano, amino, haloalkyl, oxo, trifluoromethoxy, trifluoromethyl, trifluorosulfonyl, and carboxylic acid,
- ii) mono or di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, mono- or di(C₁-C₆)alkylamino(C₁-C₆)alkyl, C₁-C₆alkoxy, C₁-C₆alkyl, C₃-C₆cycloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₆cycloalkyl)C₁-C₆alkyl, C₁-C₆alkanoyl, C₁-C₆alkoxycarbonyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylthio, mono- or di(C₁-C₆)alkylaminocarbonyl, heterocycloalkyl, aryl, and heteroaryl, each of which may be optionally substituted with up to three groups R_x,
- iii) a group of the formula:



where G is C₁-C₆alkyl, -O-, -C(=O)-, or -CC(=O)-, and

R_A is C₃-C₆cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which may be optionally substituted with up to three groups R_x,

- iv) a group of the formula



where J is N or CH and R_b and R_c are independently hydrogen, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which may be optionally substituted with up to three groups R_x ; or

R_b and R_c and the atom to which they are attached form a 4- to 10-membered monocyclic or bicyclic ring, which may contain one or more double bonds or one or more of oxo, O, S, SO, SO_2 , or N- R_d wherein R_d is hydrogen, Ar_1 , C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, heterocycloalkyl, or C_1 - C_6 alkyl- Ar_1 ; wherein Ar_1 is aryl or heteroaryl, each of which may be optionally substituted with up to three groups R_x ; and wherein the monocyclic or bicyclic ring is optionally substituted with up to three groups R_x ;

- v) $-OC(=O)R_E$, $-C(=O)NH_2$, $-C(=O)NHR_E$, $-C(=O)NR_ER_F$, $-S(O)_nR_E$, $-S(O)_nNH_2$, $-S(O)_nNHR_E$, $-S(O)_nNR_ER_F$, $-NHC(=O)R_E$, $-C(=NR_E)R_F$, $-C=N-OH$, $-C=N(alkoxy)$, $-C=N(alkyl)$, $-NR_EC(=O)R_F$, $-NHS(O)_nR_E$, and $-NR_ES(O)_nR_F$, where n is 0, 1 or 2, and R_E and R_F are independently selected at each occurrence from C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, heterocycloalkyl, C_1 - C_6 alkoxy, mono- or diamino(C_1 - C_6)alkyl, aryl, or heteroaryl each of which may be optionally substituted with up to three groups R_x ;

R_5 represents C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, or $(C_3$ - C_8 cycloalkyl) C_1 - C_6 alkyl, each of which may contain one or more double or triple bonds and each of which may be optionally substituted with up to three groups R_x , or R_5 represents aryl, aryl(C_1 - C_4 alkyl), heteroaryl, or heteroaryl(C_1 - C_4 alkyl) each of which may be optionally substituted with up to three groups R_x ;

800
799

Q represents CR₆R₇, NR₆, or

oxygen when X₂ is not nitrogen;

R₆ and R₇ represent hydrogen, halogen, hydroxy, or C₁-C₆ alkyl;

R₈ represents hydrogen or C₁-C₆ alkyl;

X₁, X₂, X₃, and X₄ independently represent CR, N, O, S, or NR' provided that at least one of X₁, X₂, X₃, and X₄ is CR;

R is independently chosen at each occurrence from hydrogen, halogen, hydroxy, nitro, cyano, amino, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy substituted with amino or mono- or di(C₁-C₆)alkylamino, C₃-C₈cycloalkyl, (C₃-C₈cycloalkyl)C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, haloalkyl, haloalkoxy, carboxamide, mono or di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, and mono- or di(C₁-C₆)alkylamino(C₁-C₆)alkyl,

R' is hydrogen or C₁-C₆ alkyl;

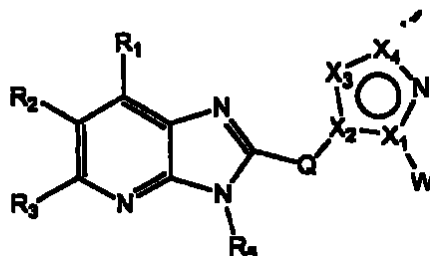
R_x is independently selected at each occurrence from halogen, hydroxy, nitro, cyano, amino, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkoxy substituted with amino or mono- or di(C₁-C₆)alkylamino, C₃-C₈cycloalkyl, (C₃-C₈cycloalkyl)C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₁-C₆alkoxy, heterocycloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, haloalkyl, haloalkoxy, mono or di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, and mono- or di(C₁-C₆)alkylamino(C₁-C₆)alkyl; and

W represents aryl or heteroaryl, either of which is optionally substituted with up to three groups selected independently from halogen, hydroxy, nitro, cyano, amino, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkoxy substituted with amino or mono- or di(C₁-C₆)alkylamino, C₃-C₈cycloalkyl, (C₃-C₈cycloalkyl) C₁-C₆alkyl, (C₃-C₈cycloalkyl) C₁-C₆alkoxy, heterocycloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, haloalkyl, haloalkoxy, mono or

204:
80

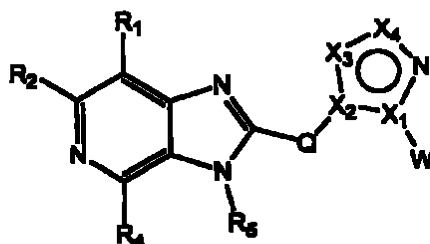
di(C₂-C₆)alkylamino, amino(C₂-C₆)alkyl, and mono- or di(C₂-C₆)alkylamino(C₂-C₆)alkyl, -COOH, -(C=O)OR_E, -(C=O)NR_E, -C(O)R_E, and -S(O)_mR_E where R_E is as defined above and m is 0, 1 or 2.

4. A compound according to Claim 3, of the formula:



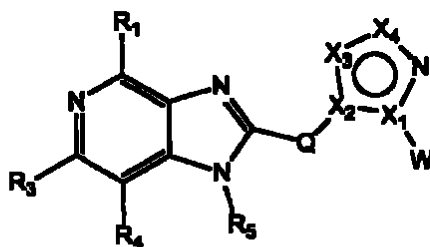
where X₁, X₂, X₃, X₄, R₁, R₂, R₃, R₅, Q, and W are as defined in Claim 3.

5. A compound according to Claim 3, of the formula



where X₁, X₂, X₃, X₄, R₁, R₂, R₄, R₅, Q, and W are as defined in Claim 3.

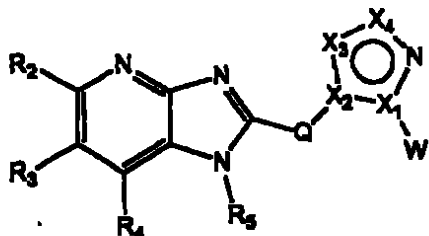
6. A compound according to Claim 3, of the formula



60257492-122100

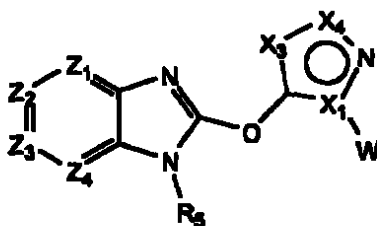
where X_1 , X_2 , X_3 , X_4 , R_1 , R_3 , R_4 , R_5 , Q , and W are as defined in Claim 3.

7. A compound according to Claim 3, of the formula



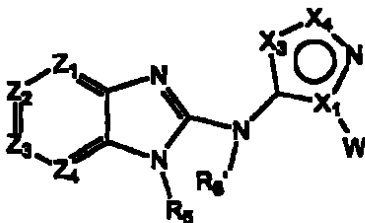
where X_1 , X_2 , X_3 , X_4 , R_2 , R_3 , R_4 , R_5 , Q , and W are as defined in Claim 3.

8. A compound according to Claim 3, of the formula



where X_1 , X_3 , X_4 , Z_1 , Z_2 , Z_3 , Z_4 , R_5 and W are as defined for Claim 3.

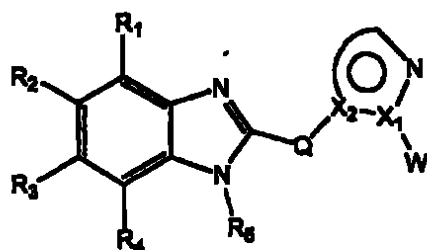
9. A compound according to Claim 3, of the formula



where X_1 , X_3 , X_4 , Z_1 , Z_2 , Z_3 , Z_4 , R_5 , R_6 , and W are as defined for Claim 3.

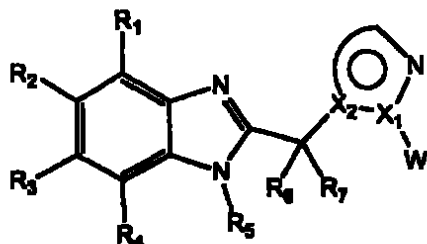
10. A compound according to Claim 1 of the formula

803
802



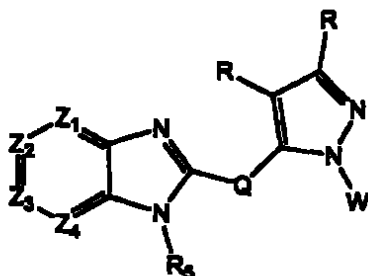
wherein R_1 , R_2 , R_3 , R_4 , R_5 , X_1 , X_2 , Q , and W are as defined in Claim 1.

11. A compound according to Claim 1 of the formula



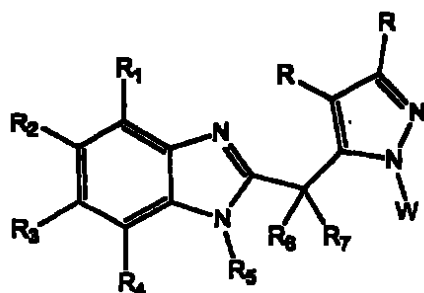
wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and W are as defined in Claim 1.

12. A compound according to Claim 1 of the formula



wherein R , Z_1 , Z_2 , Z_3 , Z_4 , R_5 , Q , and W are as defined in Claim 1.

13. A compound according to Claim 1 of the formula:



wherein R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, and W are as defined in Claim 1.

14. A compound according to Claim 13, wherein:

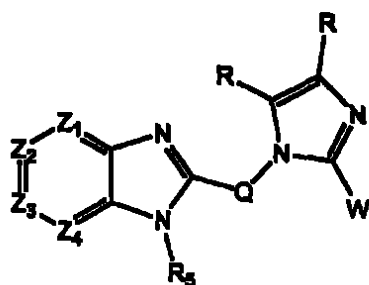
R, R₁, and R₄ are independently selected from hydrogen, halogen, hydroxy, nitro, cyano, amino, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆cycloalkyl, (C₃-C₆cycloalkyl) C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, haloalkyl, haloalkoxy, mono or di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, and mono- or di(C₁-C₆)alkylamino(C₁-C₆)alkyl;

R₃ represents C₁-C₆ alkyl, C₃-C₆cycloalkyl, or (C₃-C₆cycloalkyl)C₁-C₆alkyl, phenyl, benzyl, thiophenyl, pyridyl, imidazolyl, pyrazolyl, or pyrimidinyl;

R₆ and R₇ represent C₁-C₆ alkyl; and

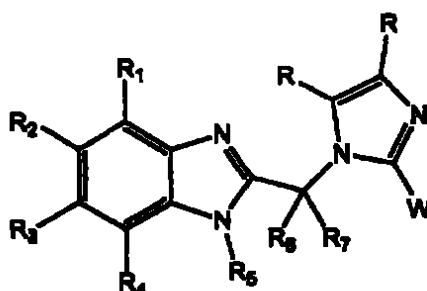
W represents phenyl, thiophenyl, pyridyl, imidazolyl, pyrazolyl, or pyrimidinyl, optionally substituted with up to 4 groups independently chosen from halogen, hydroxy, nitro, cyano, amino, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkoxy substituted with amino or mono- or di(C₁-C₆)alkylamino, C₃-C₆cycloalkyl, (C₃-C₆cycloalkyl)C₁-C₆alkyl, (C₃-C₆cycloalkyl)C₁-C₆alkoxy, heterocycloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, haloalkyl, haloalkoxy, mono or di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, and mono- or di(C₁-C₆)alkylamino(C₁-C₆)alkyl.

15. A compound according to Claim 1, of the formula



wherein R, Z₁, Z₂, Z₃, Z₄, R₅, Q, and W are as defined in Claim 1.

16. A compound according to Claim 1 of the formula:



wherein R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, and W are as defined in Claim 1.

17. A compound according to Claim 16, wherein:

R, R₁, and R₄ are independently selected from hydrogen, halogen, hydroxy, nitro, cyano, amino, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, (C₃-C₈ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, haloalkyl, haloalkoxy, mono or di(C₁-C₆) alkylamino, amino(C₁-C₆) alkyl, and mono- or di(C₁-C₆) alkylamino(C₁-C₆) alkyl;

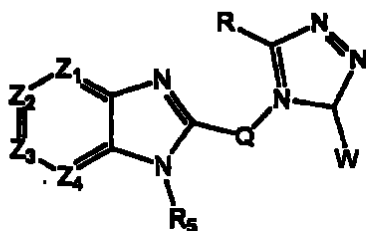
R₃ represents C₁-C₆ alkyl, C₃-C₈ cycloalkyl, or (C₃-C₈ cycloalkyl) C₁-C₆ alkyl, phenyl, benzyl, thiophenyl, pyridyl, imidazolyl, pyrazolyl, or pyrimidinyl;

R₆ and R₇ represent C₁-C₆ alkyl; and

W represents phenyl, thiophenyl, pyridyl, imidazolyl, pyrazolyl, or pyrimidinyl, optionally substituted with up to 4 groups independently chosen from halogen, hydroxy, nitro, cyano, amino, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy substituted

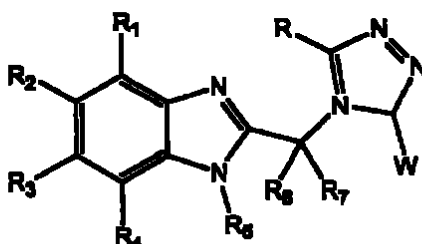
with amino or mono- or di(C₁-C₆)alkylamino, C₃-C₈cycloalkyl, (C₃-C₈cycloalkyl)C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₁-C₆alkoxy, heterocycloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, haloalkyl, haloalkoxy, mono or di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, and mono- or di(C₁-C₆)alkylamino(C₁-C₆)alkyl.

18. A compound according to Claim 1, of the formula



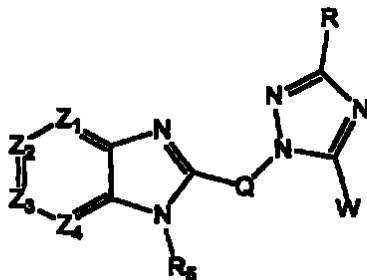
wherein R, Z₁, Z₂, Z₃, Z₄, R₅, Q, and W are as defined in Claim 1.

19. A compound according to Claim 1, of the formula



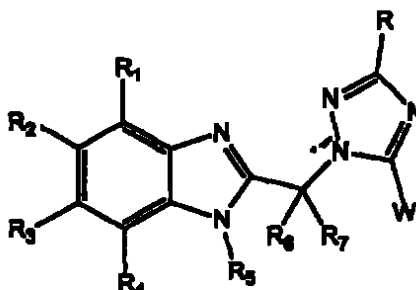
wherein R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, and W are as defined in Claim 1.

20. A compound according to Claim 1, of the formula



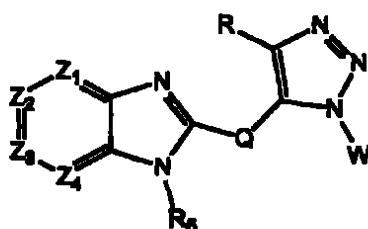
wherein R, Z₁, Z₂, Z₃, Z₄, R₅, Q, and W are as defined in Claim 1.

21. A compound according to Claim 1, of the formula



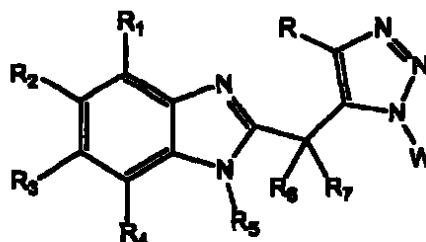
wherein R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, and W are as defined in Claim 1.

22. A compound according to Claim 1, of the formula



wherein R, Z₁, Z₂, Z₃, Z₄, R₆, Q, and W are as defined in Claim 1.

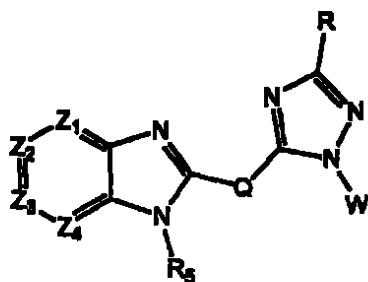
23. A compound according to Claim 1, of the formula



wherein R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, and W are as defined in Claim 1.

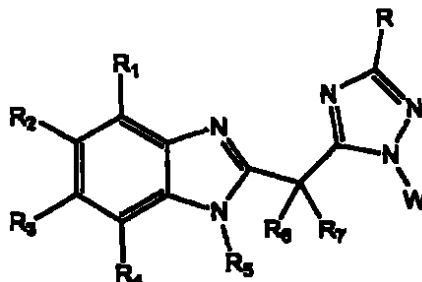
24. A compound according to Claim 1, of the formula

888
807



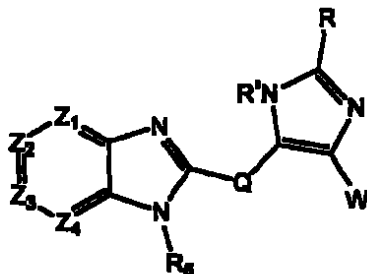
wherein R, Z₁, Z₂, Z₃, Z₄, R₅, Q, and W are as defined in Claim 1.

25. A compound according to Claim 1, of the formula



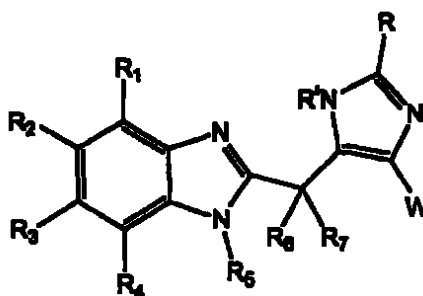
wherein R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, and W are as defined in Claim 1.

26. A compound according to Claim 1, of the formula



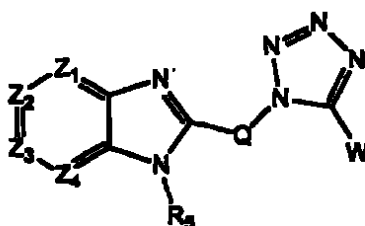
wherein R, R', Z₁, Z₂, Z₃, Z₄, R₅, Q, and W are as defined in Claim 1.

27. A compound according to Claim 1, of the formula



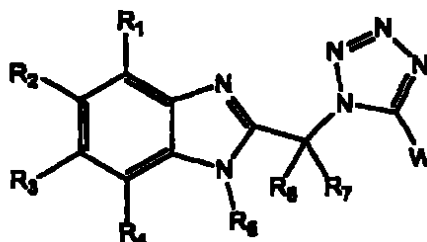
wherein R, R', R₁, R₂, R₃, R₄, R₅, R₆, R₇, Q, and W are as defined in Claim 1.

28. A compound according to Claim 1, of the formula



wherein Z₁, Z₂, Z₃, Z₄, R₅, Q, and W are as defined in Claim 1.

29. A compound according to Claim 1, of the formula



where R₁, R₂, R₃, R₄, R₅, R₆, R₇ and W are as defined above.

30. A compound according to Claim 1 for use in therapeutic treatment of a disease or disorder associated with pathogenic agonism, inverse agonism or antagonism of the GABA_A receptor.

210
809

31. A pharmaceutical composition comprising a compound according to Claim 1 combined with at least one pharmaceutically acceptable carrier or excipient.

32. A method for the treatment of a disease or disorder associated with pathogenic agonism, inverse agonism or antagonism of the GABA_A receptor, said method comprising administering to a patient in need of such treatment or prevention an effective amount of a compound of claim 1.

33. A method according to Claim 9 wherein the disease or disorder associated with pathogenic agonism, inverse agonism or antagonism of the GABA_A receptor is anxiety, depression, a sleep disorder, or cognitive impairment.

34. The use of a compound according to Claim 1 for the manufacture of a medicament for the treatment of a disease or disorder associated with pathogenic agonism, inverse agonism or antagonism of the GABA_A receptor.

35. The use of a compound according to Claim 1 for the manufacture of a medicament for the treatment of anxiety, depression, sleep disorders, or cognitive impairment.

844
B10

36. A method for localizing GABA_A receptors in a tissue sample comprising:

contacting with the sample a detectably-labeled compound of claim 1 under conditions that permit binding of the compound to GABA_A receptors, washing the sample to remove unbound compound, and detecting the bound compound.

37. A method of inhibiting the binding of a benzodiazepine compound to a GABA_A receptor, said method comprising contacting a compound of claim 1 with cells expressing such a receptor in the presence of the benzodiazepine, wherein the compound is present at a concentration sufficient to inhibit the binding a benzodiazepine compound to a GABA_A receptor *in vitro*.

38. A method for altering the signal-transducing activity of GABA_A receptors, said method comprising exposing cells expressing such receptors to a compound according to claim 1 at a concentration sufficient to inhibit R013-1798 binding to cells expressing a cloned human GABA_A receptor *in vitro*.

39. A packaged pharmaceutical composition comprising the pharmaceutical composition of Claim 31 in a container and instructions for using the composition to treat a patient suffering from a disorder responsive to agonism, inverse agonism or antagonism of the GABA_A receptor.

811 812

40. The packaged pharmaceutical composition of claim 39, wherein said patient is suffering from anxiety, depression, a sleep disorder, attention deficit disorder, Alzheimer's dementia, or cognitive impairment.

41. A compound according to claim 1 wherein in a assay of GABA_A receptor binding the compound exhibits an K_i of 1 micromolar or less.

42. A compound according to claim 1 wherein in a assay of GABA_A receptor binding the compound exhibits an K_i of 100 nanomolar or less.

43. A compound according to claim 1 wherein in a assay of GABA_A receptor binding the compound exhibits an K_i of 10 nanomolar or less.

60257492.122100

813
812

ABSTRACT

Novel benzimidazole derivatives and related compounds are disclosed. These compounds are highly selective agonists, antagonists or inverse agonists for GABA_A brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABA_A brain receptors and are therefore useful in the diagnosis and treatment of anxiety, depression, Down Syndrome, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. Pharmaceutical compositions, including packaged pharmaceutical compositions, are further provided. Compounds of the invention are also useful as probes for the localization of GABA_A receptors in tissue samples.

60257492.122100

815
813



LOS ESTADOS UNIDOS DE AMERICA

A TODO AQUEL A QUIEN CONCIERNA LO PRESENTE
DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos

9 de enero de 2002

**LA PRESENTE ES PARA CERTIFICAR QUE ADJUNTA A LA MISMA HAY
UNA COPIA FIEL DE LOS REGISTROS DE LA OFICINA DE PATENTES Y
MARCAS DE LOS ESTADOS UNIDOS DE LOS DOCUMENTOS DE LA
SOLICITUD DE PATENTE IDENTIFICADA EN LO QUE SIGUE, QUE
CUMPLEN LOS REQUISITOS PARA OTORGARLE UNA FECHA DE
PRESENTACIÓN BAJO 35 USC 111.**

NÚMERO DE SOLICITUD: 60/257,492
FECHA DE PRESENTACIÓN: 21 de diciembre de 2000



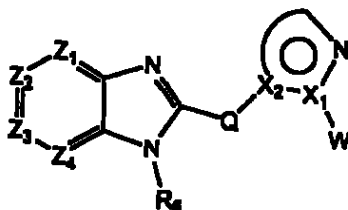
Por la Autoridad del
COMISARIO DE PATENTES Y MARCAS

E. BORNETT

Oficial certificador

REIVINDICACIONES

1. Un compuesto que tiene la fórmula:



o una sal farmacéuticamente aceptable, prodroga o solvato del mismo, en la cual:

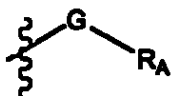
Z₁, Z₂, Z₃, y Z₄ son independientemente nitrógeno o CR₁, CR₂, CR₃ y CR₄, respectivamente, con la condición de que no más de dos de Z₁, Z₂, Z₃, y Z₄ sean nitrógeno;

R₁, R₂, R₃ y R₄ están independientemente seleccionados de

i) hidrógeno, halógeno, hidroxi, nitro, ciano, amino, haloalquilo, oxo, trifluorometoxi, trifluorometilo, trifluorosulfonilo, y ácido carboxílico,

ii) mono o dialquilamino, aminoalquil, mono o dialquilaminoalquilo, alcoxi, alquilo, cicloalquilo, alquenilo, alquinilo, (cicloalquil)alquilo, alcanofilo, alcoxicarbonilo, alquilsulfonilo, alquiltio, mono- o dialquilaminocarbonilo, heterocicloalquilo, arilo, y heteroarilo, cada uno de los cuales está opcionalmente sustituido,

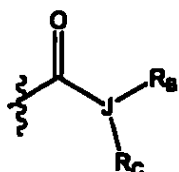
iii) un grupo de la fórmula:



en la cual G es alquilo, -O-, -C(=O), o -CC(=O)-, y

RA es cicloalquilo, heterocicloalquilo, arilo, heteroarilo, donde cada uno puede estar opcionalmente sustituido,

iv) un grupo de la fórmula



en la cual J es N o CH y RB y RC están independientemente seleccionados de hidrógeno, alquilo C₁-C₈, cicloalquilo, heterocicloalquilo, arilo, o heteroarilo, cada uno de los cuales está opcionalmente sustituido; o

RB y RC y el átomo al cual están unidos forman un anillo monocíclico o bicíclico de 4- a 10 miembros, que puede contener uno o más dobles enlaces o uno o más de oxo, O, S, SO, SO₂, o N-

817
815

R_D donde R_D es hidrógeno, Ar_1 , alquilo C_1-C_6 , cicloalquilo C_3-C_6 , heterocicloalquilo C_3-C_6 , o Ar_1 -alquilo C_1-C_6 ; donde Ar_1 es arilo o heteroarilo, cada uno de los cuales está opcionalmente sustituido; y en donde el anillo monocíclico o bicíclico está opcionalmente sustituido;

v) $-OC(=O)R_E$; $-C(=O)NH_2$, $-C(=O)NHR_E$, $-C(=O)NR_ER_F$,
 $-S(O)_nR_E$, $-S(O)_nNH_2$, $-S(O)_nNHR_E$, $-S(O)_nNR_ER_F$, $-NHC(=O)R_E$,
 $-C(=NR_E)R_F$, $-C=N-OH$, $-C=N(\text{alcoxi})$, $-C=N(\text{alquilo})$,
 $-NR_EC(=O)R_F$, $-NHS(O)_nR_E$, y $-NR_ES(O)_nR_F$, donde n es 0, 1 ó 2, y

R_E y R_F están independientemente seleccionados cada vez que ocurre entre alquilo, cicloalquilo, heterocicloalquilo, alcoxi, mono- o dialquilamino, arilo, o heteroarilo cada uno de los cuales está opcionalmente;

R_5 representa alquilo, cicloalquilo, o (cicloalquil)alquilo opcionalmente sustituidos, cada uno de los cuales puede contener uno o más dobles enlaces o triples enlaces, o R_5 representa arilo, arilalquilo, heteroarilo, o heteroarilalquilo cada uno de los cuales está opcionalmente sustituido;

Q representa $-C(R_6)(R_7)$, NR_6 , u oxígeno cuando X_2 no es nitrógeno;

R_6 y R_7 representan hidrógeno, halógeno, hidroxilo o alquilo;

R_6 representa hidrógeno o alquilo;

el grupo:



representa un anillo heteroaromático de 5 a 7 miembros que contiene hasta 4 heteroátomos seleccionados entre nitrógeno, azufre, y oxígeno, y dicho anillo heteroaromático de 5 a 7 miembros está opcionalmente sustituido en cada átomo de carbono con R , y está opcionalmente sustituido en cada átomo de nitrógeno disponible para sustitución con R' , donde

R está independientemente elegido cada vez que ocurre entre halógeno, hidroxilo, nitro, ciano, amino, alquilo, alcoxi, alcoxi sustituido con amino o mono- o dialquilamino, cicloalquilo, (cicloalquil)alquilo, alquenilo, alquinilo, haloalquilo, haloalcoxi, carboxamido, mono- o dialquilamino, aminoalquilo, y mono- o dialquilaminoalquilo;

R' es alquilo C_1-C_6 ;

X_1 y X_2 representan independientemente nitrógeno o carbono; y

W representa arilo o heteroarilo, donde el grupo arilo o heteroarilo está opcionalmente sustituido con hasta 3 grupos independientemente seleccionados entre halógeno, hidroxilo, nitro, ciano, amino, alquilo, alcoxi, alcoxi sustituido con amino o mono- o dialquilamino, cicloalquilo, (cicloalquil)alquilo, cicloalquilalcoxi, heterocicloalquilo,

815
816

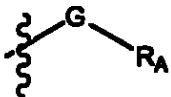
alquenilo, alquinilo, haloalquilo, haloalcoxi, mono- o dialquilamino, aminoalquilo, y mono- o dialquilaminoalquilo, $-C(O)R_E$, y $-S(O)_m R_E$, donde R_E es tal como se ha definido anteriormente y m es 0, 1 ó 2.

2. Un compuesto de acuerdo con la reivindicación 1, en el cual

Z_1 , Z_2 , Z_3 , y Z_4 son independientemente nitrógeno o CR_1 , CR_2 , CR_3 y CR_4 , respectivamente, con la condición de que no más de dos de Z_1 , Z_2 , Z_3 , y Z_4 sean nitrógeno;

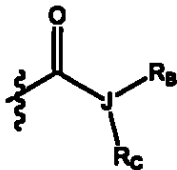
R_1 , R_2 , R_3 , y R_4 están independientemente seleccionados entre

- (i) hidrógeno, halógeno, hidroxilo, nitro, ciano, amino, haloalquilo, oxo, trifluorometoxi, trifluorometilo, trifluorosulfonilo, y ácido carboxílico,
- (ii) mono o dialquil(C_1-C_6)amino, aminoalquil(C_1-C_6), mono o dialquil(C_1-C_6)aminoalquilo(C_1-C_6), alcoxi(C_1-C_6), alquilo(C_1-C_6), cicloalquilo(C_3-C_8), alquenilo(C_2-C_6), alquinilo(C_2-C_6), (cicloalquil(C_3-C_8))alquilo(C_1-C_6), alcanóilo(C_1-C_6), alcoxi(C_1-C_6)carbonilo, alquil(C_1-C_6)sulfonilo, alquil(C_1-C_6)tio, mono- o dialquil(C_1-C_6)aminocarbonilo, heterocicloalquilo, arilo, y heteroarilo, cada uno de los cuales está opcionalmente sustituido con hasta tres grupos R_x ,
- (iii) un grupo que tiene la fórmula:



en la cual G es (C_1-C_6)alquilo, $-O-$, $-C(=O)-$, o $-CC(=O)-$, y R_A es cicloalquilo(C_3-C_8), heterocicloalquilo, arilo o heteroarilo, cada uno de los cuales puede estar sustituido con hasta tres grupos R_x ,

iv) un grupo de la fórmula:



en la cual J es N o CH y R_B y R_C están independientemente seleccionados del grupo que consiste en hidrógeno, (C_1-C_6)alquilo, (C_3-C_8)cicloalquilo, heterocicloalquilo, arilo, o heteroarilo, cada uno de los cuales puede estar sustituido con hasta tres grupos R_x ; o

R_B y R_C y el átomo al cual están unidos forman un anillo monocíclico o bicíclico de 4 a 10 miembros, que puede contener uno o más dobles enlaces o uno o más de oxo, O, S, SO, SO_2 , o N- R_D donde R_D es hidrógeno, Ar_1 , (C_1-C_6)alquilo, (C_3-C_8)cicloalquilo, heterocicloalquilo, o $Ar_1(C_1-C_6)$ alquilo; donde Ar_1 es arilo o heteroarilo, cada uno de los cuales está opcionalmente sustituido con hasta tres grupos R_x ;

819
817

v) $-\text{OC}(=\text{O})\text{R}_E$, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NHR}_E$, $-\text{C}(=\text{O})\text{NR}_E\text{R}_F$,
 $-\text{S}(\text{O})_n\text{R}_E$, $-\text{S}(\text{O})_n\text{NH}_2$, $-\text{S}(\text{O})_n\text{NHR}_E$, $-\text{S}(\text{O})_n\text{NR}_E\text{R}_F$, $-\text{NHC}(=\text{O})\text{R}_E$,
 $\text{C}(=\text{NR}_E)\text{R}_F$, $-\text{C}=\text{N}-\text{OH}$, $-\text{C}=\text{N}(\text{alcoxi})$, $-\text{C}=\text{N}(\text{alquilo})$, $-\text{NR}_E\text{C}(=\text{O})\text{R}_F$,
 $-\text{NHS}(\text{O})_n\text{R}_E$, y $-\text{NR}_E\text{S}(\text{O})_n\text{R}_F$, donde n es 0, 1 ó 2, y

R_E y R_F están independientemente seleccionados cada vez que ocurre entre (C_1-C_6) alquilo, (C_3-C_8) cicloalquilo, heterocicloalquilo, (C_1-C_6) alcoxi, mono- o di (C_1-C_6) alquilamino, arilo, o heteroarilo cada uno de los cuales está opcionalmente sustituido con hasta con tres grupos R_x ;

R_5 representa (C_1-C_6) alquilo, (C_3-C_8) cicloalquilo, o (C_3-C_8) cicloalquilo (C_1-C_6) alquilo, cada uno de los cuales puede contener uno o más dobles o triples enlaces, y cada uno de los cuales está opcionalmente sustituido con hasta tres grupos R_x ; o R_5 representa arilo, aril (C_1-C_4) alquilo, heteroarilo, o heteroaril (C_1-C_4) alquilo cada uno de los cuales está opcionalmente sustituido con hasta tres grupos R_x ;

Q representa $-\text{C}(\text{R}_6)(\text{R}_7)$, NR_6 , u oxígeno cuando X_2 no es nitrógeno;

R_6 y R_7 representan hidrógeno, halógeno, hidroxilo o alquilo (C_1-C_6) ;

R_6 representa hidrógeno o alquilo (C_1-C_6) ; el grupo:



representa un anillo heteroaromático de 5 a 7 miembros que contiene hasta 4 heteroátomos seleccionados entre nitrógeno, azufre, y oxígeno, dicho anillo heteroaromático de 5 a 7 miembros está opcionalmente sustituido en cada átomo de carbono con R, y está opcionalmente sustituido en cada átomo de nitrógeno disponible para sustitución con R' , donde

R está independientemente elegido cada vez que ocurre entre halógeno, hidroxilo, nitro, amino, ciano, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_6 alcoxi sustituido con amino o mono- o dialquil C_1-C_6 amino, (C_3-C_8) cicloalquilo, (C_3-C_8) cicloalquilo (C_1-C_6) alquilo, (C_2-C_6) alquenilo, (C_2-C_6) alquinilo, haloalquilo, haloalcoxi, carboxamido, mono- o dialquil C_1-C_6 amino, amino (C_1-C_6) alquilo, y mono- o dialquil C_1-C_6 amino (C_1-C_6) alquilo,

R' es C_1-C_6 alquilo;

X_1 y X_2 representan independientemente nitrógeno o carbono;

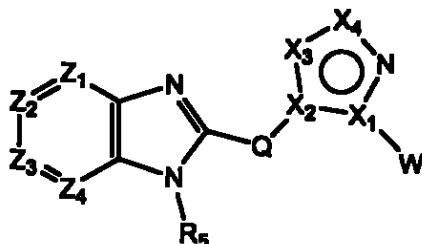
R_x se selecciona independientemente en cada ocurrencia de halógeno, hidroxilo, nitro, ciano, amino, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_6 alcoxi sustituido con amino o mono- o dialquil C_1-C_6 amino, (C_3-C_8) cicloalquilo, (C_3-C_8) cicloalquil (C_1-C_6) alquilo, $(\text{C}_3-$

818 ~~828~~

C₆cicloalquil) C₁-C₆alcoxi, heterocicloalquilo, (C₂-C₆)alquenilo, (C₂-C₆)alquinilo, haloalquilo, haloalcoxi, mono- o dialquilC₁-C₆amino, amino(C₁-C₆)alquilo, y mono- o dialquilC₁-C₆amino(C₁-C₆)alquilo; y

W representa arilo o heteroarilo, donde el grupo arilo o heteroarilo está opcionalmente sustituido con hasta 3 grupos independientemente seleccionados entre halógeno, hidroxilo, nitro, ciano, amino, alquilo(C₁-C₆), alcoxi(C₁-C₆), alcoxi(C₁-C₆) sustituido con amino o mono- o dialquil(C₁-C₆)amino, cicloalquilo(C₃-C₈), (cicloalquil(C₃-C₈))alquilo(C₁-C₆), cicloalquil(C₃-C₈) alcoxi(C₁-C₆), heterocicloalquilo, alquenilo(C₂-C₆), alquinilo(C₂-C₆), haloalquilo, haloalcoxi, mono- o dialquil(C₂-C₆)amino, aminoalquilo(C₂-C₆), y mono- o dialquil(C₂-C₆)aminoalquilo(C₂-C₆), -COOH, -(C=O)OR_E, -(C=O)NR_E, -C(O)R_E, y -S(O)_mR_E, donde R_E es tal como se ha definido anteriormente y m es 0, 1 ó 2.

3. Un compuesto que tiene la fórmula:



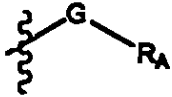
o una sal, prodroga o solvato del mismo farmacéuticamente aceptables, en donde:

Z₁, Z₂, Z₃, y Z₄ son independientemente nitrógeno o CR₁, CR₂, CR₃ y CR₄, respectivamente, con la condición de que no más de dos de Z₁, Z₂, Z₃, y Z₄ sean nitrógeno;

R₁, R₂, R₃, y R₄ están independientemente seleccionados entre

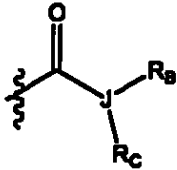
- (i) hidrógeno, halógeno, hidroxilo, nitro, ciano, amino, haloalquilo, oxo, trifluorometoxi, trifluorometilo, trifluorosulfonilo, y ácido carboxílico,
- (ii) mono o dialquil(C₁-C₆)amino, aminoalquil(C₁-C₆), mono o dialquil(C₁-C₆)aminoalquilo(C₁-C₆), alcoxi(C₁-C₆), alquilo(C₁-C₆), cicloalquilo(C₃-C₈), alquenilo(C₂-C₆), alquinilo(C₂-C₆), (cicloalquil(C₃-C₈))alquilo(C₁-C₆), alcanofilo(C₁-C₆), alcoxi(C₁-C₆)carbonilo, alquil(C₁-C₆)sulfonilo, alquil(C₁-C₆)tio, mono- o dialquil(C₁-C₆)aminocarbonilo, heterocicloalquilo, arilo, y heteroarilo, cada uno de los cuales está opcionalmente sustituido con hasta tres grupos R_x,

(iii) un grupo que tiene la fórmula:



en la cual G es (C₁-C₆)alquilo, -O-, -C(=O)-, o -CC(=O)-, y R_A es cicloalquilo(C₃-C₈), heterocicloalquilo, arilo o heteroarilo, cada uno de los cuales puede estar sustituido con hasta tres grupos R_x,

iv) un grupo de la fórmula:



en la cual J es N o CH y R_B y R_C están independientemente seleccionados del grupo que consiste en hidrógeno, (C₁-C₆)alquilo, (C₃-C₈)cicloalquilo, heterocicloalquilo, arilo, o heteroarilo, cada uno de los cuales puede estar sustituido con hasta tres grupos R_x; o

R_B y R_C y el átomo al cual están unidos forman un anillo monocíclico o bicíclico de 4 a 10 miembros, que puede contener uno o más dobles enlaces o uno o más de oxo, O, S, SO, SO₂, o N-R_D donde R_D es hidrógeno, Ar₁, (C₁-C₆)alquilo, (C₃-C₈)cicloalquilo, heterocicloalquilo, o Ar₁(C₁-C₆)alquilo; donde Ar₁ es arilo o heteroarilo, cada uno de los cuales está opcionalmente sustituido con hasta tres grupos R_x; y en donde el anillo bicíclico o monocíclico está opcionalmente sustituido con hasta tres grupos R_x;

v) -OC(=O)R_E, -C(=O)NH₂, -C(=O)NHR_E, -C(=O)NR_ER_F, -S(O)_nR_E, -S(O)_nNH₂, -S(O)_nNHR_E, -S(O)_nNR_ER_F, -NHC(=O)R_E, C(=NR_E)R_F, -C=N-OH, -C=N(alcoxi), -C=N(alquilo), -NR_EC(=O)R_F, -NHS(O)_nR_E, y -NR_ES(O)_nR_F, donde n es 0, 1 ó 2, y

R_E y R_F están independientemente seleccionados cada vez que ocurre entre (C₁-C₆)alquilo, (C₃-C₈)cicloalquilo, heterocicloalquilo, (C₁-C₆)alcoxi, mono- o di(C₁-C₆)alquilamino, arilo, o heteroarilo cada uno de los cuales está opcionalmente sustituido con hasta con tres grupos R_x;

R₅ representa (C₁-C₆)alquilo, (C₃-C₈)cicloalquilo, o (C₃-C₈cicloalquilo)(C₁-C₆)alquilo, cada uno de los cuales puede contener uno o más dobles o triples enlaces, y cada uno de los cuales está opcionalmente sustituido con hasta tres grupos R_x; o R₅ representa arilo, aril(C₁-C₄)alquilo, heteroarilo, o heteroaril(C₁-C₄)alquilo cada uno de los cuales está opcionalmente sustituido con hasta tres grupos R_x;

Q representa -C(R₆)(R₇), NR₆, u oxígeno cuando X₂ no es nitrógeno;

R₆ y R₇ representan hidrógeno, halógeno, hidroxilo o alquilo(C₁-C₆);

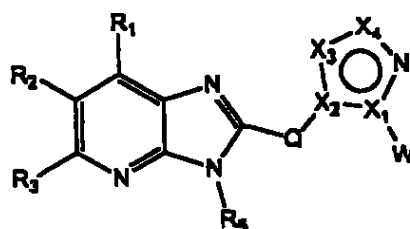
R₈ representa hidrógeno o alquilo(C₁-C₆);

X_1, X_2, X_3 , y X_4 representan independientemente CR, N, O, S o NR' con la condición que al menos uno de X_1, X_2, X_3 , y X_4 sea CR;
 R está independientemente elegido cada vez que ocurre entre hidrógeno, halógeno, hidroxilo, nitro, amino, ciano, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_6 alcoxi sustituido con amino o mono- o dialquil C_1-C_6 amino, (C_3-C_8) cicloalquilo, (C_3-C_8) cicloalquil (C_1-C_6)alquilo, (C_2-C_6) alqueno, (C_2-C_6) alquino, haloalquilo, haloalcoxi, carboxamido, mono- o dialquil C_1-C_6 amino, amino (C_1-C_6) alquilo, y mono- o dialquil C_1-C_6 amino (C_1-C_6) alquilo,
 R' es hidrógeno o C_1-C_6 alquilo;

R_x se selecciona independientemente en cada ocurrencia de halógeno, hidroxilo, nitro, ciano, amino, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_6 alcoxi sustituido con amino o mono- o dialquil C_1-C_6 amino, (C_3-C_8) cicloalquilo, (C_3-C_8) cicloalquil (C_1-C_6)alquilo, (C_3-C_8) cicloalquil C_1-C_6 alcoxi, heterocicloalquilo, (C_2-C_6) alqueno, (C_2-C_6) alquino, haloalquilo, haloalcoxi, mono- o dialquil C_1-C_6 amino, amino (C_1-C_6) alquilo, y mono- o dialquil C_1-C_6 amino (C_1-C_6) alquilo; y

W representa arilo o heteroarilo, donde el grupo arilo o heteroarilo está opcionalmente sustituido con hasta 3 grupos independientemente seleccionados entre halógeno, hidroxilo, nitro, ciano, amino, alquilo (C_1-C_6) , alcoxi (C_1-C_6) , alcoxi (C_1-C_6) sustituido con amino o mono- o dialquil (C_1-C_6) amino, cicloalquilo (C_3-C_8) , (cicloalquil (C_3-C_8))alquilo (C_1-C_6) , cicloalquil (C_3-C_8) alcoxi (C_1-C_6) , heterocicloalquilo, alqueno (C_2-C_6) , alquino (C_2-C_6) , haloalquilo, haloalcoxi, mono- o dialquil (C_2-C_6) amino, aminoalquilo (C_2-C_6) , y mono- o dialquil (C_2-C_6) aminoalquilo (C_2-C_6) , $-COOH$, $-(C=O)OR_E$, $-(C=O)NR_E$, $-C(O)R_E$, y $-S(O)_mR_E$, donde R_E es tal como se ha definido anteriormente y m es 0, 1 ó 2.

4. Un compuesto de acuerdo con la reivindicación 3, de la fórmula:

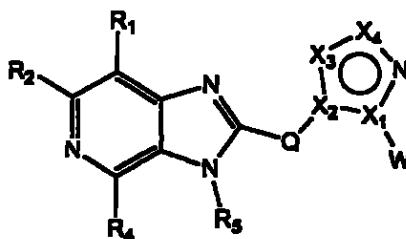


donde $X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_5, Q$, y W se definen como en la reivindicación 3.

5. Un compuesto de acuerdo con la reivindicación 3, de la fórmula:

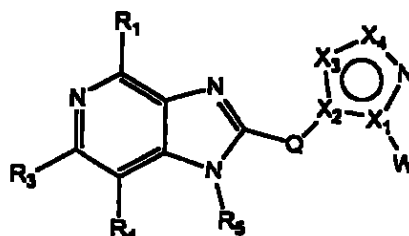
821

823



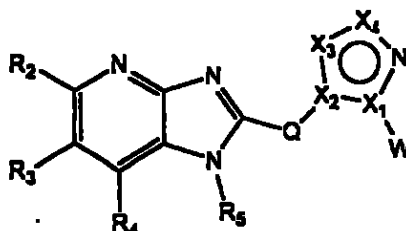
donde X_1 , X_2 , X_3 , X_4 , R_1 , R_2 , R_4 , R_5 , Q , y W se definen como en la reivindicación 3.

6. Un compuesto de acuerdo con la reivindicación 3, de la fórmula:



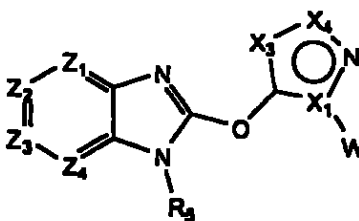
donde X_1 , X_2 , X_3 , X_4 , R_1 , R_3 , R_4 , R_5 , Q , y W se definen como en la reivindicación 3.

7. Un compuesto de acuerdo con la reivindicación 3, de la fórmula:



donde X_1 , X_2 , X_3 , X_4 , R_2 , R_3 , R_4 , R_5 , Q , y W se definen como en la reivindicación 3.

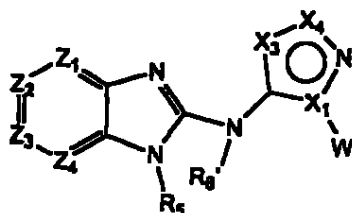
8. Un compuesto de acuerdo con la reivindicación 3, de la fórmula:



donde X_1 , X_3 , X_4 , Z_1 , Z_2 , Z_3 , Z_4 , R_5 , y W se definen como en la reivindicación 3.

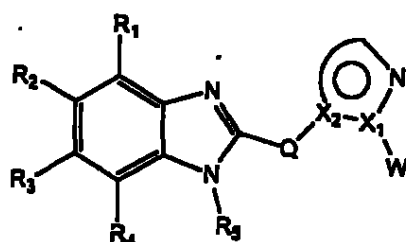
822 824

9. Un compuesto de acuerdo con la reivindicación 3, de la fórmula:



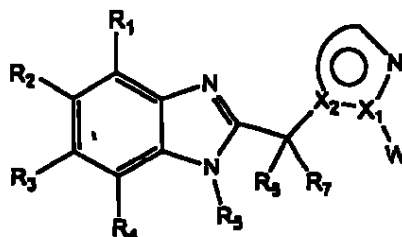
donde X_1 , X_3 , X_4 , Z_1 , Z_2 , Z_3 , Z_4 , R_5 , R_6 , y W se definen como en la reivindicación 3.

10. Un compuesto de acuerdo con la reivindicación 1, de la fórmula:



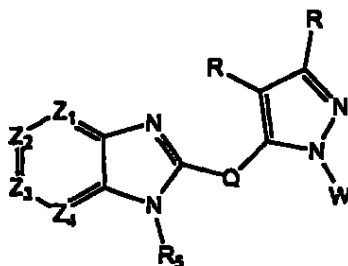
donde R_1 , R_2 , R_3 , R_4 , R_5 , X_1 , X_2 , Q , y W se definen como en la reivindicación 1.

11. Un compuesto de acuerdo con la reivindicación 1, de la fórmula:



donde R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , y W se definen como en la reivindicación 1.

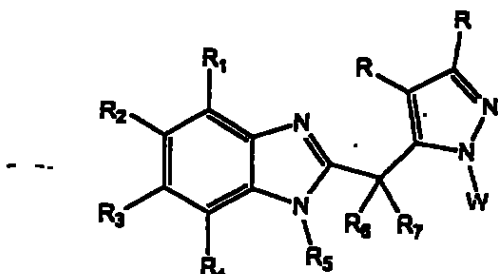
12. Un compuesto de acuerdo con la reivindicación 1, de la fórmula:



803 325

donde R, Z₁, Z₂, Z₃, Z₄, R₅, Q, y W se definen como en la reivindicación 1.

13. Un compuesto de acuerdo con la reivindicación 1 que tiene la fórmula



en la cual R, R₁, R₂, R₃, R₄, R₅, R₆, R₇ y W son tal como se han definido en la reivindicación 1.

14. Un compuesto de acuerdo con la reivindicación 13, en el cual

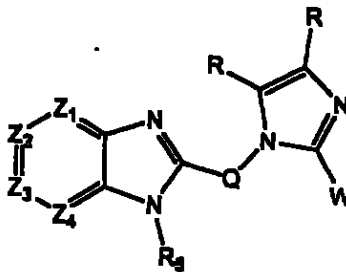
R, R₁, y R₄ están independientemente seleccionados entre hidrógeno, halógeno, hidroxilo, nitro, ciano, amino, (C₁-C₆)alquilo, (C₁-C₆)alcoxi, (C₃-C₈)cicloalquilo, (C₃-C₈)cicloalquilo(C₁-C₆)alquilo, (C₂-C₆)alqueno, (C₂-C₆)alquino, haloalquilo, haloalcoxi, mono o di(C₁-C₆)alquilamino, amino(C₁-C₆)alquilo, y mono- y di(C₁-C₆)alquilamino(C₁-C₆)alquilo;

R₅ representa (C₁-C₆)alquilo, (C₃-C₈)cicloalquilo, o (C₃-C₈)cicloalquilo(C₁-C₆)alquilo, fenilo, bencilo, tiofenilo, piridilo, imidazolilo, pirazolilo, o pirimidinilo;

R₆ y R₇ representan C₁-C₆alquilo; y

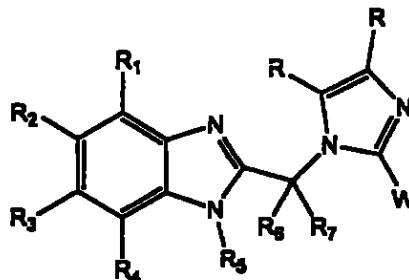
W representa fenilo, tiofenilo, piridilo, imidazolilo, pirazolilo, o pirimidinilo, cada uno de los cuales está opcionalmente sustituido con hasta 4 seleccionados independientemente de halógeno, hidroxilo, nitro, ciano, amino, (C₁-C₆)alquilo, (C₁-C₆)alcoxi, (C₁-C₆)alcoxi sustituido con amino o mono- o dialquil(C₁-C₆)amino, (C₃-C₈)cicloalquilo, (C₃-C₈)cicloalquilo(C₁-C₆)alquilo, (C₃-C₈)cicloalquilo(C₁-C₆)alcoxi, heterocicloalquilo, (C₂-C₆)alqueno, (C₂-C₆)alquino, haloalquilo, haloalcoxi, mono o di(C₁-C₆)alquilamino, amino(C₁-C₆)alquilo, y mono- o di(C₁-C₆)alquilamino(C₁-C₆)alquilo.

15. Un compuesto de acuerdo con la reivindicación 1 que tiene la fórmula



en la cual R, Z₁, Z₂, Z₃, Z₄, R₅, Q, y W son tal como se han definido en la reivindicación 1.

16. Un compuesto de acuerdo con la reivindicación 1 que tiene la fórmula



en la cual R, R₁, R₂, R₃, R₄, R₅, R₆, R₇ y W son tal como se han definido en la reivindicación 1.

17. Un compuesto de acuerdo con la reivindicación 16, donde:

R, R₁, y R₄ están independientemente seleccionados entre hidrógeno, halógeno, hidroxí, nitro, ciano, amino, (C₁-C₆)alquilo, (C₁-C₆)alcoxi, (C₃-C₈)cicloalquilo, (C₃-C₈)cicloalquilo(C₁-C₆)alquilo, (C₂-C₆)alqueno, (C₂-C₆)alquino, haloalquilo, haloalcoxi, mono o di(C₁-C₆)alquilamino, amino(C₁-C₆)alquilo, y mono- y di(C₁-C₆)alquilamino(C₁-C₆)alquilo;

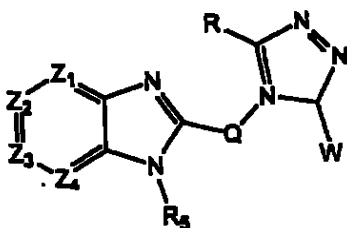
R₅ representa (C₁-C₆)alquilo, (C₃-C₈)cicloalquilo, o (C₃-C₈)cicloalquilo(C₁-C₆)alquilo, fenilo, bencilo, tiofenilo, piridilo, imidazolilo, pirazolilo, o pirimidinilo;

R₆ y R₇ representan C₁-C₆alquilo; y

W representa fenilo, tiofenilo, piridilo, imidazolilo, pirazolilo, o pirimidinilo, cada uno de los cuales está opcionalmente sustituido con hasta 4 grupos seleccionados independientemente de halógeno, hidroxí, nitro, ciano, amino, (C₁-C₆)alquilo, (C₁-C₆)alcoxi, (C₁-C₆)alcoxi sustituido con amino o mono- o dialquil(C₁-C₆)amino, (C₃-C₈)cicloalquilo, (C₃-C₈)cicloalquilo(C₁-C₆)alquilo, (C₃-C₈)cicloalquilo(C₁-C₆)alcoxi, heterocicloalquilo, (C₂-C₆)alqueno, (C₂-C₆)alquino, haloalquilo, haloalcoxi, mono o di(C₁-C₆)alquilamino, amino(C₁-C₆)alquilo, y mono- o di(C₁-C₆)alquilamino(C₁-C₆)alquilo.

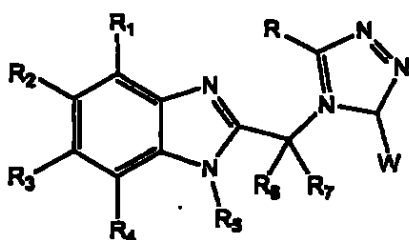
18. Un compuesto de acuerdo con la reivindicación 1, de fórmula

825
827
825



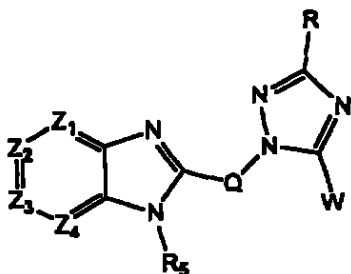
en la cual R, Z₁, Z₂, Z₃, Z₄, R₅, Q, y W son tal como se han definido en la reivindicación 1.

19. Un compuesto de acuerdo con la reivindicación 1 que tiene la fórmula



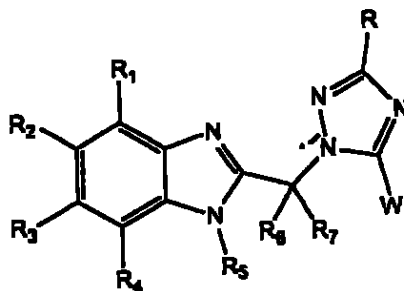
en la cual R, R₁, R₂, R₃, R₄, R₅, R₆, R₇ y W son tal como se han definido en la reivindicación 1.

20. Un compuesto de acuerdo con la reivindicación 1, de fórmula



en la cual R, Z₁, Z₂, Z₃, Z₄, R₅, Q, y W son tal como se han definido en la reivindicación 1.

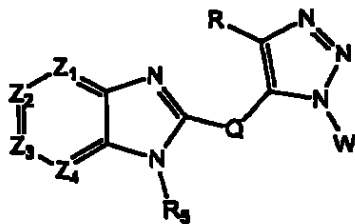
21. Un compuesto de acuerdo con la reivindicación 1 que tiene la fórmula



825
828
826

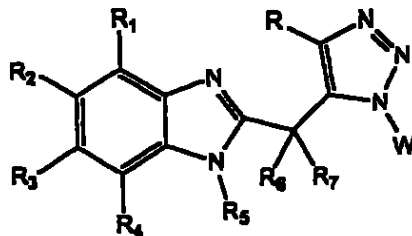
en la cual R, R₁, R₂, R₃, R₄, R₅, R₆, R₇ y W son tal como se han definido en la reivindicación 1.

22. Un compuesto de acuerdo con la reivindicación 1, de fórmula



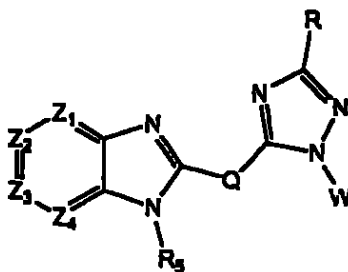
en la cual R, Z₁, Z₂, Z₃, Z₄, R₅, Q, y W son tal como se han definido en la reivindicación 1.

23. Un compuesto de acuerdo con la reivindicación 1 que tiene la fórmula



en la cual R, R₁, R₂, R₃, R₄, R₅, R₆, R₇ y W son tal como se han definido en la reivindicación 1.

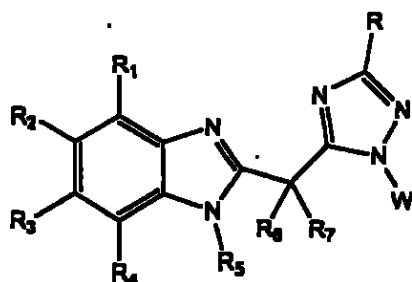
24. Un compuesto de acuerdo con la reivindicación 1, de fórmula



en la cual R, Z₁, Z₂, Z₃, Z₄, R₅, Q, y W son tal como se han definido en la reivindicación 1.

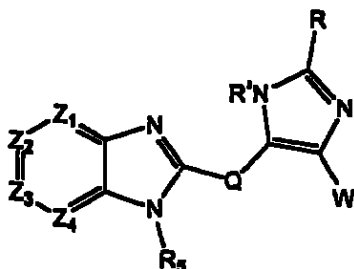
25. Un compuesto de acuerdo con la reivindicación 1 que tiene la fórmula

829
829
829



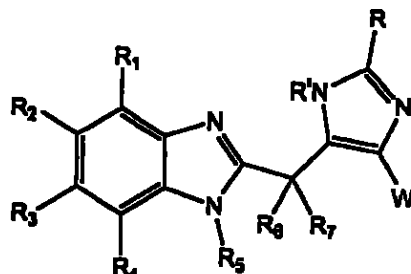
en la cual R, R₁, R₂, R₃, R₄, R₅, R₆, R₇ y W son tal como se han definido en la reivindicación 1.

26. Un compuesto de acuerdo con la reivindicación 1, de fórmula



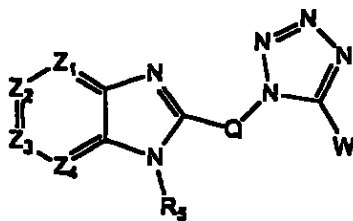
en la cual R, R', Z₁, Z₂, Z₃, Z₄, R₅, Q, y W son tal como se han definido en la reivindicación 1.

27. Un compuesto de acuerdo con la reivindicación 1 que tiene la fórmula



en la cual R, R', R₁, R₂, R₃, R₄, R₅, R₆, R₇, Q y W son tal como se han definido en la reivindicación 1.

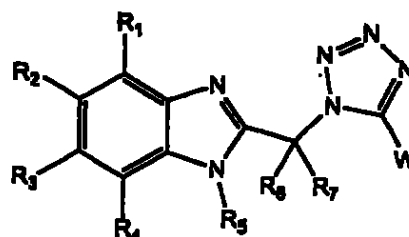
28. Un compuesto de acuerdo con la reivindicación 1, de fórmula



en la cual Z₁, Z₂, Z₃, Z₄, R₅, Q, y W son tal como se han definido en la reivindicación 1.

24
830
828

29. Un compuesto de acuerdo con la reivindicación 1 que tiene la fórmula



en la cual R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 y W son tal como se han definido anteriormente.

30. Un compuesto de acuerdo con la reivindicación 1 para uso en el tratamiento terapéutico de una enfermedad o desorden asociado con agonismo patológico, agonismo reverso o antagonismo del receptor $GABA_A$.

31. Una composición farmacéutica que comprende un compuesto de acuerdo con la reivindicación 1 en combinación con por lo menos un portador o excipiente farmacéuticamente aceptable.

32. Un método para el tratamiento de una enfermedad o desorden asociado con agonismo patológico, agonismo reverso o antagonismo del receptor $GABA_A$, dicho método comprende administrar a un paciente en necesidad de dicho tratamiento o como prevención, una cantidad efectiva de un compuesto de la reivindicación 1.

33. Un método de acuerdo con la reivindicación 9 en donde el desorden asociado con agonismo patológico, agonismo reverso o antagonismo del receptor $GABA_A$ es la ansiedad, depresión, desórdenes del sueño, o deterioro cognitivo.

34. El uso de un compuesto de acuerdo con la reivindicación 1, para la fabricación de un medicamento para el tratamiento de una enfermedad o desorden asociado con agonismo patológico, agonismo reverso o antagonismo del receptor $GABA_A$.

35. El uso de un compuesto de acuerdo con la reivindicación 1, para la fabricación de un medicamento para el tratamiento de la ansiedad, depresión, desórdenes del sueño, o deterioro cognitivo.

36. Un método para localizar receptores $GABA_A$ en unas muestras de tejido, que comprende:

poner en contacto con la muestra un compuesto rotulado de acuerdo con la reivindicación 1, bajo condiciones que permitan la unión del compuesto a los receptores $GABA_A$;

828
834
829

lavar la muestra para eliminar el compuesto rotulado no adherido; y

detectar la presencia del compuesto adherido.

37. Un método para inhibir la adhesión de un compuesto de benzodiazepina a un receptor GABA_A, donde dicho método comprende poner en contacto un compuesto de la reivindicación 1 con células que expresan dicho receptor en presencia de la benzodiazepina, en donde el compuesto está en una concentración suficiente para inhibir la adhesión de un compuesto de benzodiazepina al receptor GABA_A *in vitro*.

38. Un método para alterar la actividad transductora de señales de los receptores GABA_A, donde dicho método comprende exponer las células que expresan dichos receptores a un compuesto de acuerdo con la reivindicación 1 en una concentración suficiente para inhibir la adhesión R015-1788 a las células que expresan un receptor GABA_A humano clonado *in vitro*.

39. Un paquete de composición farmacéutica que comprende una composición farmacéutica de la reivindicación 31, en un recipiente e instrucciones para usar la composición para tratar un paciente que sufre de un desorden en respuesta a agonismo, agonismo reverso o antagonismo del receptor GABA_A.

40. Un paquete de composición farmacéutica de la reivindicación 39, en donde el paciente sufre de ansiedad, depresión, desórdenes del sueño, desorden de deficiencia de atención, demencia de Alzheimer o deterioro cognitivo.

41. Un compuesto de acuerdo con la reivindicación 1 en donde en un ensayo de adhesión del receptor GABA_A, el compuesto exhibió un K_i de 1 micromolar o menos.

42. Un compuesto de acuerdo con la reivindicación 1 en donde en un ensayo de adhesión del receptor GABA_A, el compuesto exhibió un K_i de 100 nanomolar o menos.

43. Un compuesto de acuerdo con la reivindicación 1 en donde en un ensayo de adhesión del receptor GABA_A, el compuesto exhibió un K_i de 10 nanomolar o menos.