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217

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 03-049142

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **533**

DE FECHA **31 DE OCTUBRE DE 2003** EL TERMINO HABIL SEÑALADO POR

LA LEY EXPIRA EL **30 DE ENERO DEL 2004**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO ___ **X** ___

Bogotá D.C, SEPTIEMBRE DE 2007

United States Patent Office

3,776,917

Patented Dec. 4, 1973

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3,776,917

2-AMINO-6-PHENALKYL-AMINOPYRIDINES AND DERIVATIVES THEREOF

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No Drawing. Continuation-in-part of abandoned applica-
tion Ser. No. 49,577, June 24, 1970. This application
June 5, 1972, Ser. No. 259,927

Int. Cl. C07d 31/42

U.S. Cl. 260-296 R

8 Claims

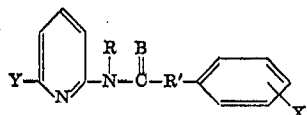
ABSTRACT OF THE DISCLOSURE

This invention relates to substituted phenylalkylaminopyridines and substituted phenacylaminopyridines, to their use as hypoglycemic agents and to the processes useful in the preparation thereof.

This application is a continuation-in-part of our co-
pending application Ser. No. 49,577 filed June 24, 1970
now abandoned.

This invention relates to compositions of matter identi-
fied in the art of chemistry as substituted phenalkyl-
aminopyridines and substituted phenacylaminopyridines,
to the preparation thereof, and to their use as hypo-
glycemic agents.

More specifically, the invention sought to be patented in
its composition of matter aspect is described as residing
in the concept of having a substituted phenalkylamino-
pyridine or a substituted phenacylaminopyridine having
the following structural formula:



and the non-toxic pharmaceutically acceptable salts there-
of, wherein Y is a member selected from the group con-
sisting of nitro and amino; R is a member selected from
the group consisting of hydrogen and lower alkyl; R' is
lower alkylene; X is a member selected from the group
consisting of hydrogen, halogen, lower alkyl, lower
alkenyl, lower alkoxy, amino, nitro and trifluoromethyl,
and B is a member selected from the group consisting of
the group (H,H) and oxygen.

As used herein, the term "lower" of "lower alkyl," and
"lower alkoxy" includes those radicals having up to six
carbon atoms represented by such radicals as methyl, ethyl,
isopropyl, cyclohexyl, methoxy, cyclopropenyl, cyclo-
pentenyl, t-butyl, and such other straight, branched-chain
and cyclized manifestations thereof.

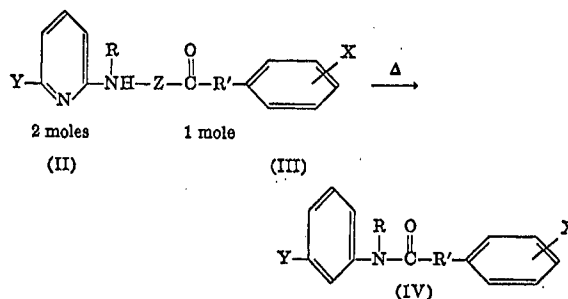
The term lower alkylene as used herein includes those
straight and branched-chain lower alkyl radicals having up
to 6 carbon atoms from which one hydrogen atom has
been removed. Exemplifying these radicals are 2-ethyl-
propylene, 1-methyl-ethylene, ethylene, propylene, 2,2-di-
methyl-butylene and the like.

The invention sought to be patented in its method-of-
use aspect is described as residing in the concept of
administering a therapeutically effective quantity of the
tangible embodiment of a composition of matter herein-
above described to a mammal suffering from a hyper-
glycemic condition thereby reducing the blood glucose
levels.

In general, the preferred method for the preparation
of the phenacylaminopyridines of this invention is ef-
fected by a condensation reaction wherein two moles of
an appropriately Y-substituted 2-aminopyridine is reacted
with one mole of an appropriately X-substituted aryl

2

halide under standard condensation reaction conditions.
Preferably, the condensation is effected by heating an ad-
mixture of equimolar quantities of the reactants in the
presence of an anhydrous non-reactive solvent (e.g., di-
oxane, chloroform, benzene, toluene and the like) in the
temperature range of about 80° C. to 120° C., although
it is preferred to have the heating done at reflux tempera-
tures. The foregoing condensation may be depicted as follows:



wherein X, Y, R and R' are as previously defined and Z
is halogeno (preferably chloro or bromo) or a reactive
equivalent thereof (e.g. hydroxy, cyanomethoxy and the
like).

The phenalkylaminopyridines are prepared by chemical-
ly reducing the phenacylaminopyridines (IV) according
to standard techniques. Preferably, the phenacylami-
nopyridines are chemically reduced with lithium alumi-
num hydride in the presence of a nonreactive solvent (e.g.
tetrahydrofuran, dioxane and the like) at reflux tem-
peratures.

Alternatively, the phenalkylaminopyridines may be pre-
pared directly by the use of analogously known alkylation
procedures such as by the condensation of an appropri-
ately Y-substituted 2-aminopyridine with an appropri-
ately X-substituted aralkyl halide; said condensation taking
place in the presence of an alkali metal hydride and di-
oxane.

Still another alternate procedure for preparing the
phenalkylaminopyridines is the condensation of the ap-
propriately Y-substituted 2-aminopyridine with an ap-
propriately X-substituted aldehyde according to standard
procedures to produce an unsaturated intermediate which
is chemically reduced by standard procedures such as cata-
lytic hydrogenation. Alternatively, this same reaction can
be effected in a one-step process by reacting the aldehyde
and aminopyridine in the presence of sodium borohydride.
Still another alternate procedure for the preparation of the
phenalkylaminopyridines of this invention is the condensa-
tion of an appropriately Y-substituted 2-aminopyridine
with an activated unsaturated aralkyl reactant using
standard Michael Addition techniques.

The foregoing generally described methods for the prep-
aration of the compounds of this invention will be par-
ticularly illustrated by the following specific examples.

EXAMPLE 1

6-amino-2-(phenylacetyl-amino)-pyridine

To a solution of 33 g. of 2,6-diaminopyridine in 150 ml.
of dry dioxane maintained at a temperature of 25-30° C.,
add, in a dropwise manner, a solution of 23 g. of phenyl-
acetyl chloride in 25 ml. of dry dioxane. Stir for 2-3
hours, maintaining the temperature, and filter. Concen-
trate to dryness in vacuo on a steam bath, leaving a thick
brown oil which can be used directly in Example 2. For
identification, recrystallize a small sample of the oil from
a saturated solution of HCl (gas) in ethanol to give the
hydrochloride salt of this compound. M.P. 206-208° C.

3,776,917

7

TABLET FORMULATION

The following formulation provides for the manufacture of 1000 tablets:

	Grams	
(1) 6-amino-2-N-phenethylaminopyridine	25.0	5
(2) Lactose, U.S.P.	181.0	
(3) Corn starch, U.S.P.	92.5	
(4) Magnesium stearate	1.5	

Thoroughly granulate a mixture of 72.5 g. of corn starch and the lactose with a paste prepared by dissolving 20 g. of corn starch in 100 ml. of hot distilled water. Dry the resulting granulation, add a blended mixture of the active ingredient (1) and the magnesium stearate. Thoroughly blend and then press into tablets of 300 mg. each.

CAPSULE FORMULATION

The following formulation provides for the manufacture of 1000 capsules:

	Grams	
(1) 6-amino-2-N-phenethylaminopyridine	25.0	20
(2) Lactose	273.5	
(3) Magnesium stearate	1.5	

Mix active ingredient (1) with the lactose and blend in the magnesium stearate. Fill hard gelatin capsules with 300 mg. of each of the blended mixture to produce capsules containing 25 mg. of 6-amino-2-N-phenethylaminopyridine.

PARENTERAL FORMULATION

The following formulation provides for the manufacture of 1000 vials each containing 10 mg. of active ingredient, as the hydrochloride salt.

	Grams	
(1) 6 - amino-2-N-phenethylaminopyridine(hydrochloride salt)	10.00	35
(2) Monobasic potassium phosphate	6.00	
(3) Water for injection, U.S.P., q.s., ad. 1.00 l.		

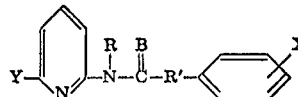
Dissolve ingredients (1), (2) and (3) in approximately 80% of the volume of water and filter the resulting solution. Add to the filtrate sufficient water to bring up to

8

volume. Sterile-filter the solution and aseptically fill one milliliter portions of the solution into two milliliter vials, then lyophilize. After the lyophilized cake is dry, aseptically stopper the vials with rubber plugs and seal.

We claim:

1. A compound of the structural formula



and the non-toxic pharmaceutically acceptable salts thereof, wherein Y is a member selected from the group consisting of nitro and amino; R is a member selected from the group consisting of hydrogen and lower alkyl; B is a member selected from the group consisting of (H,H) and oxygen; R' is lower alkylene and X is a member selected from the group consisting of halogen, lower alkyl, lower alkoxy, amino, nitro and trifluoromethyl.

2. A compound of claim 1 wherein Y is amino; R is lower alkyl; B is (H,H); and X is hydrogen.

3. A compound of claim 1 wherein Y is amino; R is hydrogen; B is (H,H); and X is hydrogen.

4. A compound of claim 3, said compound being 6-amino-N-phenethylaminopyridine.

5. A compound of claim 1 wherein Y is amino; R is hydrogen and X is lower alkoxy.

6. A compound of claim 5, said compound being 6-amino-2(β -p-methoxyphenethylamino)-pyridine.

7. A compound of claim 1 wherein Y is amino; R is hydrogen; B is (H,H); and X is halogen.

8. A compound of claim 7, said compound being 6-amino-2(β -p-chlorophenethylamino)-pyridine.

References Cited

Vohra et al., Chem. Abstracts, vol. 62, No. 13, 16, 231h, June 21, 1965.

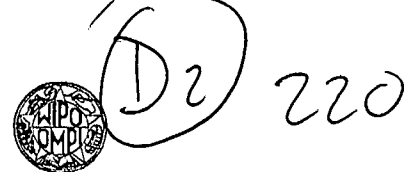
ALAN L. ROTMAN, Primary Examiner

U.S. Cl. X.R.

260—295 AM, 295 S; 424—263, 266

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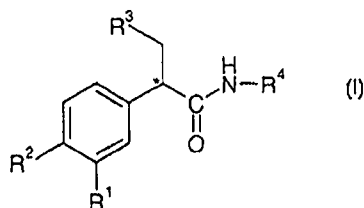
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 277/46, A61K 31/426, C07D 277/56, 213/75, 213/80, 213/82, 213/85, 233/88, 237/20, 239/42, 241/20, 253/06, 261/14, 263/48, 285/12, C07C 275/50, A61K 31/42, 31/421, 31/4164, 31/433, 31/4402, 31/4965, 31/501, 31/505, 31/53, 31/17, 31/4168, A61P 3/10	A2	(11) International Publication Number: WO 00/58293 (43) International Publication Date: 5 October 2000 (05.10.00)
(21) International Application Number: PCT/EP00/02450 (22) International Filing Date: 20 March 2000 (20.03.00) (30) Priority Data: 60/126,707 29 March 1999 (29.03.99) US 60/165,948 17 November 1999 (17.11.99) US 60/165,944 17 November 1999 (17.11.99) US (71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; Grenzacherstrasse 124, CH-4070 Basle (CH).		(72) Inventors: BIZZARRO, Fred, Thomas; 85 Sterling Drive, Colonia, NJ 07067 (US). CORBETT, Wendy, Lea; 36 Ridgewood Drive, Randolph, NJ 07869-3754 (US). FOCELLA, Antonino; 61 Warner Way, Wayne, NJ 07470 (US). GRIPPO, Joseph, Francis; 324 Somerset Street #7, Stirling, NJ 07980 (US). HAYNES, Nancy-Ellen; 508 Linden Place, Cranford, NJ 07016 (US). HOLLAND, George, William; 10 Acorn Place, North Caldwell, NJ 07006 (US). KESTER, Robert, Francis; Apartment 438, 240 Prospect Avenue, Hackensack, NJ 07601 (US). MAHANEY, Paige, E.; Apartment 1A, 828 Bloomfield Avenue, Montclair, NJ 07042 (US). SARABU, Ramakanth; 73 Forest Road, Cedar Grove, NJ 07009 (US). (74) Agent: WITTE, Hubert; Grenzacherstrasse 124, CH-4070 Basle (CH). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>

(54) Title: GLUCOKINASE ACTIVATORS



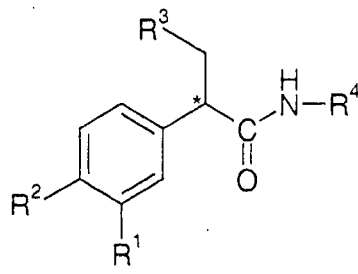
(57) Abstract

The present invention relates to compounds of formula (I) wherein R¹, R², R³ and R⁴ are as defined in claim 1 and pharmaceutically acceptable salts thereof. The compounds are glucokinase activators which increase insulin secretion in the treatment of type II diabetes.

-334-

Claims

1. A compound comprising an amide of the formula I:



5 wherein

the * indicates an asymmetric carbon atom;

R^1 and R^2 are independently hydrogen, halo, amino, hydroxyamino, nitro, cyano, sulfonamido, lower alkyl, $-OR^5$, $-C(O)OR^5$, perfluoro-lower alkyl, lower alkyl thio, perfluoro-lower alkyl thio, lower alkyl sulfonyl, perfluoro-lower alkyl sulfonyl or lower alkyl sulfinyl;

R^3 is cycloalkyl having from 3 to 7 carbon atoms or lower alkyl having from 2 to 4 carbon atoms;

R^4 is $-C(O)NHR^{40}$; or an unsubstituted or mono-substituted five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amine group shown, which five- or six-membered heteroaromatic ring contains from 1 to 3 heteroatoms selected from sulfur, oxygen or nitrogen, with one heteroatom being nitrogen which is adjacent to the connecting ring carbon atom; said mono-substituted heteroaromatic ring being monosubstituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl, halo, nitro, cyano, $-(CH_2)_n-OR^6$, $-(CH_2)_n-C(O)OR^7$, $-(CH_2)_n-C(O)NHR^6$, $-C(O)-C(O)OR^8$, $-(CH_2)_n-NHR^6$;