

Electronic Acknowledgement Receipt

EFS ID:	24528763
Application Number:	14940018
International Application Number:	
Confirmation Number:	6992
Title of Invention:	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME
First Named Inventor/Applicant Name:	Neil M. Cowen
Customer Number:	20350
Filer:	Stephen E. Reiter/Ashley E. Faller
Filer Authorized By:	Stephen E. Reiter
Attorney Docket Number:	096593-001000US-0955615
Receipt Date:	05-JAN-2016
Filing Date:	12-NOV-2015
Time Stamp:	14:21:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment		no			
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		IDS.pdf	183985	yes	8
			ffe959aa3e98caf1d872620dc232e54cf956eefe		

	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	2	
	Information Disclosure Statement (IDS) Form (SB08)		3	8	
Warnings:					
Information:					
2	Non Patent Literature	Marugo_NPL.pdf	3213887 3dc5ed9485df9a6bd03b141915f3be6cb570af14	no	7
Warnings:					
Information:					
3	Non Patent Literature	Ortqvist_DiabetesCare.pdf	156900 529f74b2c2d70afd07bb14d7722c4f5e90e4fd02	no	7
Warnings:					
Information:					
4	Non Patent Literature	Ouedraogo_NPL.pdf	124462 c585f9802d65d9c9e5c43c8a51d30a211e195ffe	no	2
Warnings:					
Information:					
5	Non Patent Literature	Qvigstad_NPL.pdf	252839 a4c124b1f1a8f8f53ebcd162aba1883e60872ea9	no	3
Warnings:					
Information:					
6	Non Patent Literature	Ratzmann_NPL.pdf	120622 8e192757f7344f3567cec987c2dbf02bb9682389	no	2
Warnings:					
Information:					
7	Non Patent Literature	NPL_Reddy_2003.pdf	7258378 2ea2a53d45d426be78195c64977085e02d746148	no	9
Warnings:					
Information:					
8	Non Patent Literature	Schou_NPL.pdf	148733 09b4811b4599640e37d5caa8794c4c1ccf80e346	no	3
Warnings:					
Information:					

9	Non Patent Literature	Schwanstecher_NPL.pdf	715772	no	7
			95a6c7f1f82913b1f8937d2d6f2ed7c2440c4f31		
Warnings:					
Information:					
10	Non Patent Literature	Stanridge_NPL.pdf	135411	no	6
			93de16eae7b38352357f730ba4f3100bd59cc89d		
Warnings:					
Information:					
11	Non Patent Literature	Surwit_NPL.pdf	251002	no	8
			959c6e2664d884abd9abb74f40e3412d52b30b3		
Warnings:					
Information:					
12	Non Patent Literature	Trube_NPL.pdf	111080	no	2
			5e1b792c6ec38e4574028882eb5fbc469f61e6bc		
Warnings:					
Information:					
13	Non Patent Literature	Int_J_Obes_Relat_Metab_Disorder_2000_24_429_434.pdf	101251	no	6
			170bcab19e4ac2194694eac7fb60f600e573e5da		
Warnings:					
Information:					
14	Non Patent Literature	Wigand_NPL.pdf	60172	no	2
			510c186f72bb93af3cbb5f8bdc8c10f727280d53		
Warnings:					
Information:					
Total Files Size (in bytes):			12834494		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
on January 5, 2016.

PATENT
Attorney Docket No.: 096593-001000US-0955615

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Ashley E. Faller/
Ashley E. Faller

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Neil M. Cowen

Application No.: 14/940,018

Filed: November 12, 2015

For: METHODS FOR TREATING
SUBJECTS WITH PRADER-WILLI
SYNDROME OR SMITH-MAGENIS
SYNDROME

Customer No.: 20350

Confirmation No.: 6992

Examiner: Not Yet Assigned

Technology Center/Art Unit: 1646

INFORMATION DISCLOSURE
STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

The references cited on attached form PTO/SB/08A are being called to the attention of the Examiner. Copies of the references in compliance with the requirements of 37 CFR § 1.98(a)(2) are enclosed.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

As provided for by 37 CFR § 1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no

KILPATRICK TOWNSEND 68052512 1

representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

Applicant believes that no fee is required for submission of this statement. However, if any fees are due for the submission of this Information Disclosure Statement, please deduct those fees from Deposit Account No. 20-1430.

Respectfully submitted,

/Stephen E. Reiter/

Stephen E. Reiter
Registration No. 31,192

KILPATRICK TOWNSEND & STOCKTON LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 858-350-6100
Fax: 858-350-6111
Attachments
SER/aef



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁸ : A61K 38/31, 31/54, 31/155</p>	<p>A2</p>	<p>(11) International Publication Number: WO 98/10786 (43) International Publication Date: 19 March 1998 (19.03.98)</p>
<p>(21) International Application Number: PCT/IL97/00301 (22) International Filing Date: 10 September 1997 (10.09.97) (30) Priority Data: 119250 12 September 1996 (12.09.96) IL 119403 10 October 1996 (10.10.96) IL (71)(72) Applicant and Inventor: COHEN, Yoram (IL/IL); Hapragim Street 6, 52960 Ramat Efat (IL). (74) Agent: DR. YITZHAK HESS & PARTNERS; P.O. Box 8451, 61063 Tel Aviv (IL).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, ME, MN, MW, MX, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i></p>
<p>(54) Title: PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SYNDROME X OF REAVEN (57) Abstract The present invention relates to a pharmaceutical composition comprising as active ingredient a compound selected among somatostatin or one of its analogs, diazoxide or one of its analogs, cyclothiazide or one of its analogs and metformin, for the treatment of syndrome X of Reaven (also called "Hyper Insulinemia syndrome" or "The Deadly Quartet").</p>		

FOR THE PURPOSES OF INFORMATION ONLY

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

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	ME	The former Yugoslavia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	MK	Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PHARMACEUTICAL COMPOSITION FOR
THE TREATMENT OF SYNDROM X OF REAVEN

The present invention relates to a pharmaceutical composition comprising as active ingredient a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin, for the treatment of syndrome X of Reaven (also called "Hyper Insulinemia syndrome" or "The Deadly Quartet").

Somatostatin and its analogs, e.g. octreotide, are known for the treatment of the reduction of the secretion of Insulin caused by insulimomas. Moreover, they are known for the treatment of certain tumors, gastrointestinal diseases, etc. However, their effectivity for the reduction of the resistance to insulin has so far not been known.

It is also known that Diazoxide, Cyclothiazide and Metformin achieve the reduction of the resistance to Insulin. Moreover, it is known that Metformin is used in the treatment of Diabetes and reduces risk factors in cardiovascular diseases in NIDDM.

Diazoxide, Cyclothiazide and Metformin have the following formulae:

- a. Diazoxide: 7-chloro-3-methyl-2,4,1,2,4-benzothiadiazine 1,1-dioxide.
- b. Cyclothiazide: 3-bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
- c. Metformin: N,N-Dimethylimidodicarbonimide diamide.

However, those compounds have so far not been known for the treatment of the risk factors of syndrome X of Reaven.

Syndrome X includes, inter alia, the following risk factors:

- a. excessive blood pressure; b. dislipidemia, i.e. increase of the amount of Triglycerides in the blood, reduction of the amount of HDL and increase of the amount of LDL, c. excessive blood

coagulation due to Plasminogen Activator Inhibitor-1 (PAI-1) increased in the blood; d. central obesity; e. Glucose intolerances - from occult Diabetes to overt Diabetes f. increase of Insulin in the blood, i.e. the pancreas secretes more Insulin in order to overcome high Insulin resistance.

All the risk factors of syndrome X of Reaven are, inter alia, caused by a high resistance to Insulin. Thus, apparently said symptoms could be treated simultaneously if there would be a reduction to the resistance to Insulin.

Said risk factors either separately but mostly in combination are decisive factors in the appearance of Ischemic Heart disease, e.g. Angina Pectoris, Myocard Infarct; Cerebral Vascular Diseases and the like.

Until now, all said risk factors had to be treated separately as there was no pharmaceutical composition which could treat simultaneously all of them. However, said separate treatments are not always effective as very often the treatment of one risk factor severs the condition of another risk factor. It has therefore been desirable to find a pharmaceutical composition which can treat simultaneously all the various risk factors which are included in syndrome X of Reaven.

We have now found that due to the fact that the reduction of the resistance to Insulin can be achieved by administering a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin, said treatment may enable the treatment of all risk factors of syndrome X of Reaven simultaneously.

The present invention thus consists in pharmaceutical preparations for the treatment of the risk factors of syndrome X of Reaven comprising as active ingredient a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin.

The present invention also comprises the use of a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined),

cyclothiazide or one of its analogs (as herein defined) and metformin in the preparation of a pharmaceutical preparation for the treatment of the risk factors of syndrome X of Reaven.

Analogues of somatostatin in connection with the present invention mean any analog compound of somatostatin which biologically activate one or more somatostatin receptors. Said receptors cause the reduction of the resistance to Insulin and thus enable the combined treatment of all risk factors of syndrome X of Reaven and are thus effective in primarily & secondary preventing and/or treating Ischemic Heart disease, such as, Angina Pectoris, Myocard Infarcts ; Cerebral Vascular Diseases, etc.

As receptors there should be mentioned, inter alia, the following human somatostatin receptors, which are described in Steven W.J. Lamberts, et al. 1996. Octreotide.. The New England Journal Med. Jan. 25. pp. 246-54. These receptors are:

1. hSSTR1

Present in the brain, lung, stomach, jejunum, kidneys, liver and pancreas. It is located on chromosom 14q13.

It has 391 amino acids and its formula is given in Yamada et. al., Biochemical and Biophysical Research Communications, 1993, Vol. 195, No. 2., pages 844-852.

2. hSSTR2

Present in the brain and in the kidneys, It is located on chromosom 17q24. It has 369 amino acids and its formula is given in Yamada.

3. hSSTR3

Present in the brain and in the pancreas. It is located on chromosome 22q13.1. It has 418 amino acids and its formula is given in Yamada.

4. hSSTR4

Present in the brain and in the lung. It is located on chromosome 20. It has 388 amino acids and its molecular weight is 41,867. Its formula is given in Yamada.

5. hSSTR4

Present in the brain, heart, adrenal glands, placenta, pituitary, small intestines and skeletal muscles. It is located on chromosome 20p11.2. It has 364 amino acids,

its molecular weight is 39,176 and its formula is given in Yamada.

All receptors have common features:

1. They have a similarity in the configuration in the seven areas which do extend out of the membrane (TM1....TM7)
2. Asp-Arg-Tyr at the end of the NH₂-terminal of the second loop which is in the cell.
3. Aspartic acid (Asp) is located in the third loop outside the cell.

The receptors which are especially important in reducing the Insulin resistance are receptors 2 and 5, also but less receptor 3. Receptors 1 and 4 are less important in this respect.

The use of somatostatin is not always satisfactory as it is effective only for a short time. Therefore the use of Octreotide, the most known analog of somatostatin or of another long acting Somatostatin, is preferred.

The analogs of somatostatin should comprise the chain D-Trp-Lys. Said chain constitute the critical core of the active analogs and is essential for the activation of the receptors.

Most analogs comprise the chain Phe-D-Trp-Lys.

Many analogs comprise the chain Phe-D-Trp-Lys-Thr being present in positions 7 - 10 of Somatostatin 14.

Suitable analogs of somatostatin being part of the pharmaceutical composition according to the present invention are, for example,:

1. Octreotide.
2. Vapreotide.
3. Lanreotide.
4. Cyclopeptide somatostatin analogues selected among :
 Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]
 Cyclo[N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe]
 Cyclo[Pro-Ala-D-Trp-Lys-Thr-Phe]
 Cyclo[Pro-Tyr-D-Trp-Lys-Thr-Phe]
 Cyclo[Pro-Phe-D-Trp-Lys- β -aminobutyric-Phe]
 Cyclo[N-Me-Ala-Phe-D-Trp-Lys-Thr-Phe]
 Cyclo[Pro-Phe-D-Trp-Lys-Val-Phe]
 Cyclo[D-Ala-D-Phe-D-Trp-L-Lys-D-Thr-N-Me-D-Phe]

- Cyclo[Pro-Phe-D-Trp-Lys-Thr(Bzl)] (Bzl = (a))
 Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]
 Cyclo[Pro-D-Phe-D-Trp-Lys-Thr(Bzl)]
 Cyclo[Ahep-Lys-Asn-Phe-Phe-Trp-Lys-Thr-
 Tyr-Thr-Ser] (Ahep = (b))
 Cyclo[Ahep-Phe-D-Trp-Lys-Thr(Bzl)]
 Cyclo[Ahep-Phe-D-Trp-Lys-Thr]
 Cyclo[Ahep-Phe-D-Trp-Lys-Ser(Bzl)]
 Cyclo[Ahex-Phe-D-Trp-Lys-Thr(Bzl)] (Ahex = (c))
 Cyclo[Aoct-Phe-D-Trp-Lys-Thr(Bzl)] (Aoct = (d))
 Cyclo[Ala-Cys-Phe-D-Trp-Lys-Thr-Cys]
- (a) Bzl = benzyl
 (b) Ahep = 7-aminoheptanoyl
 (c) Ahex = 6-aminohexanoyl
 (d) Aoct = 8-amino-octanoyl;
5. D-Phe-[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thr-ol
 6. D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH₂ (Nal = (1))
 7. D-Phe-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH₂
 8. D-Phe-[Cys-Tyr-D-Trp-Lys-Thr-Cys]-Nal-NH₂
 9. D-Phe-[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Nal-NH₂ (Abu = (2))
 10. D-Phe-[Cys-Tyr-D-Trp-Lys-Ser-Cys]-Nal-NH₂
 11. D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH₂
 12. c(Ahep-Trp-D-Trp-Lys-Thr-Phe) (Ahep = (3))
 13. D-Phe-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH₂ (Cpa = (4))
 14. D-Phe-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH₂
 15. D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH₂
 16. D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH₂
 17. D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH₂
 18. D-Phe-Ala-Phe-D-Trp-Lys-Ala-Nal-NH₂
 19. D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH₂
 20. D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH₂
 21. D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH₂

- (1) Nal L-3(2-naphthyl)alanine
 (2) Abu L-α-amino-n-butyric acid
 (3) Ahep 7,aminoheptanoic acid
 (4) Cpa L-p-chlorophenylalanine

22. Polypeptides of the formula:

X-Lys-Asn-Phe-Phe-A-Lys-Thr-Phe-Thr-Ser-Y

wherein A is L- or D-Trp,

X is H-(Aeg)_m-Cys- or H-(Aeg)_m-Ala-Gly-Cys-,

Y is -Cys-(Aeg)_n-OH or

X and Y taken together are a 2-aminoethyl-glycyl
group in the ring position and

m and n are 0, 1, 2, provided that

m and n are at least 1,

and their cyclic disulfide derivatives.

23. A peptide of the formula:

Bmp-Lys-X-Phe-Phe-trp-Lys-Thr-Phe-Thr-Y-Cys-OH

3 4 5 6 7 8 9 10 11 12 13 14

in which

Bmp represents the desaminocysteine radical,

X represents Asn,

trp represents D-Trp that may be substituted
in the benzene ring by a halogen atom, and

Y represents the radical of an alpha-(lower alkyl)amino-
(lower alkyl)-carboxylic acid having a minimum of 4 and
a maximum of 8 carbon atoms, in which the two lower
alkyl radicals can be connected to one another with a
single C-C bond, an oxygen atom or a sulphur (II) atom.

24. Cyclic octapeptides of the formula

Asn-Phe-Phe-Trp-Lys-Thr-Phe-Gaba(Ar)

5 6 7 8 9 10 11 12

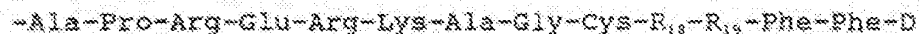
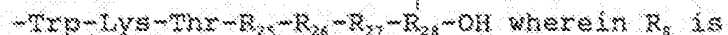
in which

Trp represents L-Trp or D-Trp, in which the
benzene ring may be substituted by a
fluorine atom, and

Gaba(Ar) represents the residue of a -aminobutyric
acid substituted by a cyclic hydrocarbyl
radical Ar selected from the group consisting
of cyclohexyl; phenyl optionally substituted
by halogen, nitro or phenoxy; and naphthyl

optionally substituted by halogen.

25. A compound of formula

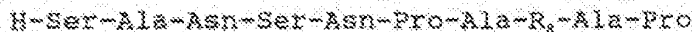


Met or Leu, R_{18} is Lys or des R_{18} , R_{19} is Asn or

des R_{19} , R_{25} is Phe or Tyr, R_{26} is Thr or des

R_{26} , R_{27} is Ser or D-Ser and R_{28} is D-Cys or Cys.

26. A compound of formula

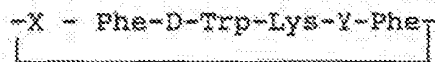


Leu, R_{18} is Lys or des R_{18} , R_{19} is Asn or des

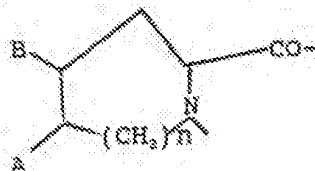
R_{19} , R_{25} is Phe or Tyr, R_{26} is Thr or des R_{26} ,

R_{27} is Ser or D-Ser and R_{28} is D-Cys or Cys, or the linear version thereof where the disulfide bridge is replaced by hydrogen.

27. A cyclic hexapeptide of the formula



in which X represents the radical of an L-aminoacid of the formula



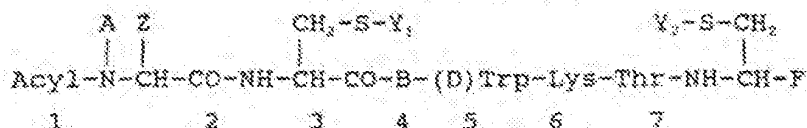
in which A and B are identical or different and denote alkyl

having 1 to 3 carbon atoms, or A and B together represent a saturated, unsaturated or aromatic monocyclic or bicyclic structure having 3 to 6 carbon atoms,

n denotes 0 or 1, and

Y represents an aliphatic or aromatic L-amino acid the side-chain of which can be hydroxylated, said amino acid being selected from the group consisting of L-alanine, L-serine, L-valine, L-leucine, L-isoleucine, L-phenylalanine and L-tyrosine.

28. An N-acyl-polypeptide of formula,



wherein

"Acyl" is a group of formula $\text{R}^{\text{I}}\text{CO-}$ wherein R^{I} is C_{1-20} alkyl or phenyl; a group of formula $\text{R}^{\text{II}}\text{SO}_2\text{-}$ wherein R^{II} is C_{1-20} alkyl, phenyl or tolyl; a group

R^{III}

N-CO- wherein

R^{IV}

R^{III} and R^{IV} are each independently hydrogen or C_{1-10} alkyl; or biotinyl,

A is hydrogen or C_{1-3} alkyl,

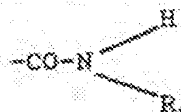
$>\text{N-CH(Z)-CO-}$ is an (L)- or (D)-phenylalanine residue optionally ring-substituted by NO_2 , or an (L) or (D)-norleucine residue,

whereby

Z in $>\text{N-CH(Z)-CO-}$ represents the remainder of said residue,

B is -Phe- optionally ring-substituted by NO_2 ,

F is a group of formula



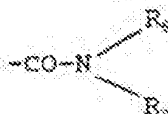
wherein R_4 is hydrogen or a group of formula

$\text{-CH(R}_5\text{)-X,}$

R_5 is $\text{CH}_2\text{CH(OH)-, i-butyl or benzyl}$

X is a group of formula -COOR_1 ,

$\text{-CH}_2\text{OR}_2$ or



wherein R_1 , R_2 and R_3 are each hydrogen or C_{1-12} alkyl, and

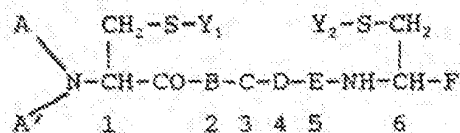
R_3 is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,

the group $-\text{CH}(\text{R}_3)-\text{X}$ having the (D)- or (L)-configuration, and

Y_1 and Y_2 are each hydrogen or together represent a direct bond, whereby the residue resides in the 2- and 7-position each independently have the (L)- or (D)-configuration, and with the proviso that:

- i) (L)- and/or (D)-cysteine residues are present at the 2- and 7-positions only.

29. A polypeptide of the formula



wherein

A is C_{1-12} alkyl, C_{7-10} phenylalkyl or a group of formula $\text{RCO}-$, whereby

- i) R is hydrogen, C_{1-11} alkyl, phenyl or C_{7-10} phenylalkyl, or
- ii) $\text{RCO}-$ is a) an L- or D-phenylalanine residue optionally ring-substituted by halogen and/or C_{1-12} alkyl,
 - b) H-Asn-, or
 - c) H-Nle-Asn-,

the α -amino group of amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di- C_{1-12} alkylated,

A' is hydrogen or, when A is C_{1-12} alkyl or

C_{7-10} phenylalkyl, also C_{1-12} alkyl or C_{7-10} phenylalkyl,

- B is -Phe- optionally ring-substituted by halogen and/or C_{1-4} alkyl,
- C is -(L)- or -(D)-Trp- optionally α -N-methylated and optionally benzene-ring-substituted by halogen and/or C_{1-4} alkyl,
- D is -Lys- optionally α -N-methylated and optionally ϵ -N- C_{1-4} -alkylated,
- E is -Thr- or -Ala- each in (D)- or (L)-form and each being optionally α -N-methylated,

F is a group of formula $-\text{COOR}_1$, $-\text{CH}_2\text{OR}_2$, $-\text{CO}-\text{N} \begin{array}{l} \text{R}_3 \\ \text{R}_4 \end{array}$ or



wherein R_1 is hydrogen or C_{1-4} alkyl,

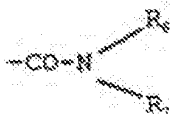
R_2 is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,

R_3 is hydrogen, C_{1-4} alkyl, phenyl or C_{7-10} -phenylalkyl,

R_4 is hydrogen, C_{1-4} alkyl or, when R_3 is hydrogen or methyl, also a group of formula $-\text{CH}(\text{R}_5)-\text{X}$,

R_5 is hydrogen, $-(\text{CH}_2)_2-\text{OH}$, $-(\text{CH}_2)_3-\text{OH}$, $-\text{CH}_2-\text{OH}$, $-\text{CH}(\text{CH}_3)-\text{OH}$, isobutyl or benzyl

X is a group of formula $-\text{COOR}_1$, $-\text{CH}_2\text{OR}_2$ or



wherein

R_1 and R_2 have the meanings given above,

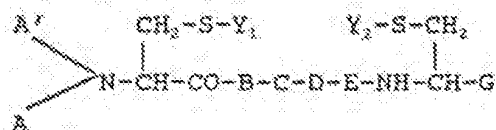
R_4 is hydrogen or C_{1-4} alkyl and

R_3 is hydrogen, C_{1-4} alkyl, phenyl or C_{7-10} phenylalkyl,

the group $-\text{CH}(\text{R}_5)-\text{X}$ having the D- or L- configuration, and Y_1 and Y_2 are each hydrogen or together represent a direct

bond, whereby the residues in the 1- and 6-position each independently have the L- or D-configuration.

30. A compound of formula



wherein

A is C₁₋₁₂alkyl, C₇₋₁₀phenylalkyl or a group of formula RCO-, whereby

i) R is hydrogen, C₁₋₁₂alkyl, phenyl or C₇₋₁₀phenylalkyl or

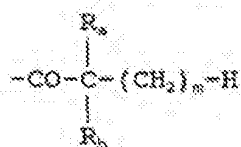
ii) RCO- is

- a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br, NO₂, NH₂, OH, C₁₋₄alkyl and/or C₁₋₄alkoxy;
- b) the residue of a natural or synthetic α-amino acid other than defined under a) above or of a corresponding D-amino acid, or
- c) a dipeptide residue in which the individual amino acid residues are the same or different and are selected from those defined under a) and/or b) above,

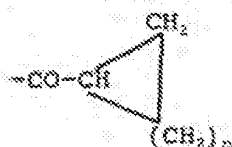
C₁₋₈alkanoyl,

A' is hydrogen,

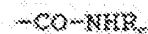
Y₁ and Y₂ represent together a direct bond or each of Y₁ and Y₂ is independently hydrogen or a radical of formulae (1) to (5).



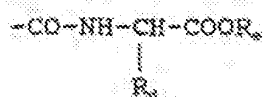
(1)



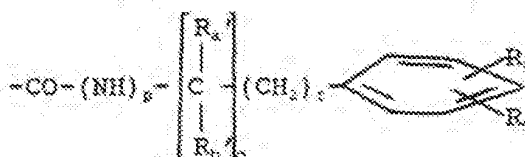
(2)



(3)



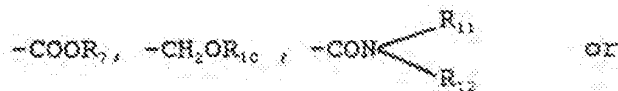
(4)



(5)

wherein

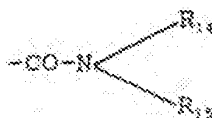
- R_1 is methyl or ethyl
 R_2 is hydrogen, methyl or ethyl
 m is a whole number from 1 to 4
 n is a whole number from 1 to 5
 R_3 is (C_{1-5}) alkyl
 R_4 represents the substituent attached to the α -carbon atom of a natural or synthetic α -amino acid (including hydrogen)
 R_5 is (C_{1-5}) alkyl
 R_6 and R_7 are independently hydrogen, methyl or ethyl,
 R_8 and R_9 are independently hydrogen, halogen, (C_{1-5}) alkyl or (C_{1-5}) alkoxy,
 P is 0 or 1,
 Q is 0 or 1, and
 r is 0, 1 or 2,
 B is -Phe- optionally ring-substituted by halogen, NO_2 , NH_2 , OH, C_{1-5} alkyl and/or C_{1-5} alkoxy (including pentafluorocalanine), or β -naphthyl-Ala
 C is (L)-Trp- or (D)-Trp- optionally α -N-methylated and optionally benzene-ring-substituted by halogen, NO_2 , NH_2 , OH, C_{1-5} alkyl and/or C_{1-5} alkoxy,
 D is Lys, Lys in which the side chain contains O or S in β -position, β F-Lys or δ F-Lys, optionally α -N-methylated, or a 4-aminocyclohexylAla or 4-aminocyclohexylGly. residue
 E is The, Ser, Val, Phe, Ile or an aminoisobutyric or aminobutyric acid residue
 G is a group of formula



wherein

- R_7 is hydrogen or C_{1-5} alkyl,

- R_{10} is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,
 R_{11} is hydrogen, C_{1-10} alkyl, phenyl or C_{7-10} phenyl-alkyl,
 R_{12} is hydrogen, C_{1-10} alkyl or a group of formula $-CH(R_{13})-X_1$,
 R_{13} is CH_2OH , $-(CH_2)_2-OH$, $-(CH_2)_3-OH$, or $-CH(CH_3)OH$ or represents the substituent attached to the α -carbon atom of a natural or synthetic α -amino acid (including hydrogen) and
 X_1 is a group of formula $-COOR_7$, $-CH_2OR_8$, or



wherein

R_7 and R_{10} have the meanings given above,

R_{14} is hydrogen or C_{1-10} alkyl and

R_{15} is hydrogen, C_{1-10} alkyl, phenyl or C_{7-10} phenylalkyl, and

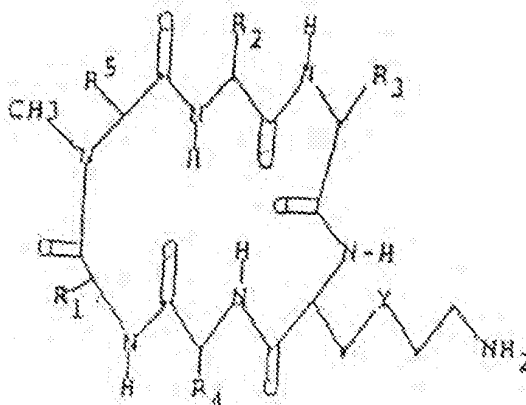
R_{16} is hydrogen or hydroxy,

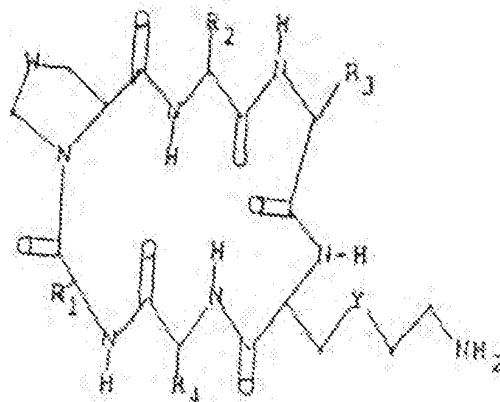
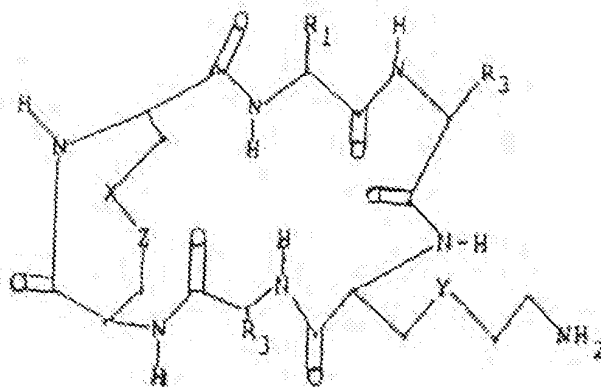
with the proviso that

when R_{12} is $-CH(R_{13})-X_1$ then R_{11} is hydrogen or methyl,

wherein the residues B, D and E have the L-configuration, and the residues in the 2- and 7-position and any residues Y_1 , 4) and Y_2 , 4) each independently have the (L)- or (D)- configuration.

31. A somatostatin analog selected from the compounds of the following formulae





wherein

W is

one of X and Z

Y is

each of R₁ and R₂

S or (CH₂)_s, where s is 0, 1 or 2;

is S and the other is S or CH₂;

S or (CH₂)_t, where t is 0, 1 or 2;

independently of the other, is C₁₋₈

alkyl, benzyl, benzyl having one or two

C₁₋₈ alkyl, halogen, hydroxy, amino,

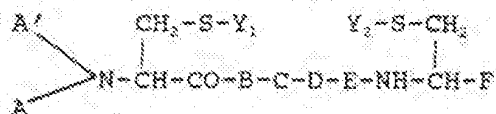
nitro, and/or C₁₋₈ alkoxy substituents,

or C₁₋₈ alkyl substituted with 5- or 6-

membered heterocyclic ring;

- R_1 is 3-indolymethyl, either unsubstituted or having C_{1-3} alkyl, C_{1-3} alkoxy or halogen substitution;
- R_2 C_{1-3} alkyl, C_{1-3} hydroxyalkyl, benzyl, carboxy-(C_{1-3} alkyl), amino (C_{1-3} alkyl) or benzyl having a C_{1-3} alkyl, halogen, hydroxy, amino, nitro and/or C_{1-3} alkoxy substituent;
- R_3 is C_{1-3} alkyl, benzyl, or benzyl having a C_{1-3} alkyl, halogen, hydroxy, amino, nitro, and/or C_{1-3} alkoxy substituent,

compounds of Formula



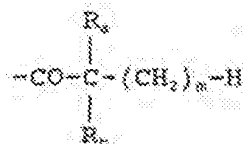
wherein

A is C_{1-12} alkyl, C_{7-10} phenylalkyl or a group of formula RCO-, whereby

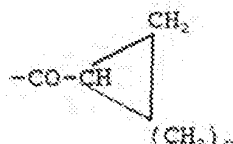
- i) R is hydrogen, C_{1-11} alkyl, phenyl or C_{7-10} phenylalkyl,
- or
- ii) RCO-is
- a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br, NO_2 , NH_2 , OH, C_{1-3} alkyl and/or C_{1-3} alkoxy
- b) the residue of a natural α -amino acid other than defined under a) above or of a corresponding D-amino acid, or
- c) a dipeptide residue in which the individual amino acid residues are the same or different and are selected from those defined under a) and/or b) above, the α -amino group or amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di- C_{1-12} alkylated,

A' is hydrogen or, when A is C_{1-12} alkyl or C_{7-10} phenylalk- also C_{1-12} alkyl or C_{7-10} phenylalkyl,

Y_1 and Y_2 represent together a direct bond or each of Y_1 and Y_2 is independently hydrogen or a radical of the formulae



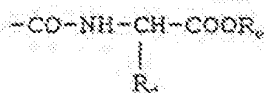
(1)



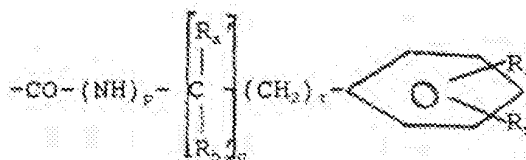
(2)



(3)



(4)



(5)

wherein R_x is methyl or ethyl

R_y is hydrogen, methyl or ethyl

m is a whole number from 1 to 4

n is a whole number from 1 to 5

R_x is (C_{1-4}) alkyl

R_z represents the substituent attached to the α -carbon atom of a natural α -amino acid (including hydrogen)

R_6 is (C_{1-3}) alkyl

R_4' and R_5' are independently hydrogen, methyl or ethyl,

R_6 and R_5 are independently hydrogen, halogen, (C_{1-3}) alkyl or (C_{1-3}) alkoxy,

p is 0 or 1,

q is 0 or 1, and

r is 0, 1 or 2,

B is -Phe- optionally ring-substituted by halogen, NO_2 , NH_2 , OH, C_{1-3} alkyl and/or C_{1-3} alkoxy, or naphthylalanine.

C is (L)-Trp- or (D)-Trp- optionally α -N-methylated and optionally benzene-ring-substituted by halogen, NO_2 , NH_2 , OH, C_{1-3} alkyl and/or C_{1-3} alkoxy,

D is -Lys-, Thialys, F-Lys, δ F-Lys or Orn, optionally α -N-methylated, or a 4-aminocyclohexyl Ala or 4-aminocyclohexyl Gly residue,

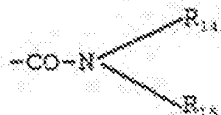
E is Thr, Ser, Val, Phe, Ile or an aminoisobutyric acid residue

F is a group of formula $-\text{COOR}_9$, $-\text{CH}_2\text{OR}_{10}$, $-\text{CON} \begin{array}{l} \nearrow \text{R}_{11} \\ \searrow \text{R}_{12} \end{array}$ or



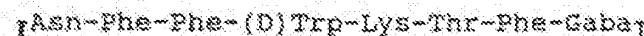
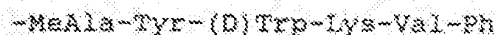
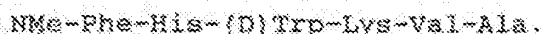
wherein R_9 is hydrogen or C_{1-3} alkyl,
 R_{10} is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,
 R_{11} is hydrogen, C_{1-3} alkyl, phenyl or C_{7-10} -phenylalkyl,
 R_{12} is hydrogen, C_{1-3} alkyl or a group of formula $-\text{CH}(\text{R}_{13})-\text{X}_1$,
 R_{13} is CH_2OH , $-(\text{CH}_2)_2-\text{OH}$, $-(\text{CH}_2)_3-\text{OH}$, or $-\text{CH}(\text{CH}_3)\text{OH}$
 or

represents the substituent attached to the α -carbon atom of a natural α -amino acid (including hydrogen) and X_1 is a group of formula $-\text{COOR}_7$, $-\text{CH}_2\text{OR}_{10}$ or

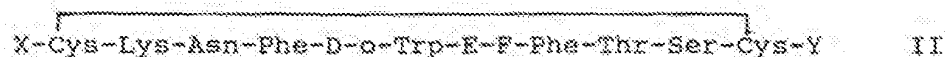


wherein
 R_7 and R_{10} have the meanings given above,
 R_{14} is hydrogen or C_{1-3} alkyl and
 R_{15} is hydrogen, C_{1-3} alkyl, phenyl or C_{7-10} phenylalkyl, and
 R_{16} is hydrogen or hydroxy,
 with the proviso that
 when R_{12} is $-\text{CH}(\text{R}_{13})-\text{X}_1$ then R_{11} is hydrogen or methyl,
 wherein the residues B, D and E have the L-configuration,
 and the residues in the 2- and 7-position and any residues Y₁ 4) and Y₂ 4) each independently have the (L)- or (D)-configuration

and compounds of the following formulae

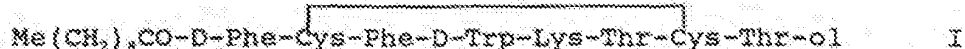


32. Somatostatin analogs



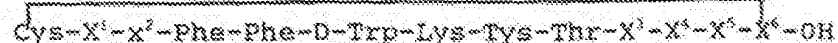
I, II, X = N-terminus anchor; Y = C-terminus anchor, G-I or its alc; wherein at least I of X, Y = cationic anchor; D = Phe Tyr, 3-(p-fluorophenyl)alanine or 3 (p-chlorophenyl)alanine residue; E = Lys, Lys(R¹); R¹ = C₁₋₆(fluoro)alkyl; F = Thr, Val, Ser; G = D- or L-Thr, Phe, or 3-(2-naphthyl)alanine residue; I = OH, NH₂, NHR¹.

33. Peptides RR¹NCHR²CONHCH(CH₂SR⁴)CO-Phe-Trp-Lys-X-NHCHR³CH₂SR⁵
[R = inorg. or org. acyl group, R¹ = H, alkyl, NCHR²CO moiety = I.



or D-Phe (optionally ring substituted by halo, NO₂, OH, alkyl, alkoxy); Phe, Trp, (D or L), may be ring substituted by NO₂, NH₂, OH, alkyl, alkoxy; Lys may be α-N-methylated and ε-N-alkylated; X = D- or L-α-amino acid residue optionally α-N-methylated; R² = CO₂H, CH₂OH, carbamoyl, R⁴ = R⁵ = H, R⁴R⁵ = bond]

34. H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-X-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-



35. H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Leu-Ala-Pro-Arg-Glu-Arg-Lys
-Ala-Gly-

Cys-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr-Thr-Ser-Cys-OH

Said compounds (34 and 35) appear in Chemical Abstracts 98,
1983 1 43839 g

36. c(Spacer-Phe-D-Trp-Lys-Thr)

Spacer may stand for:

- a) R,S- δ -Bn-o-AMPA
- b) R- α -Bn-NMe-o-AMPA
- c) Phe-Pro

Said compounds and similar ones appear in Brex et al., Lett.
Pept. Sci. 1995, 2 (3/4): 165-8, "Somatostatin analogs
containing O-amino methyl phenyl acetic acid as a bridge
unit"; and Tourwe, Lett. Pept. Sci. 1995, 2 (3/4): 182-6,
"Conformation directed design of cyclic Somatostatin
containing a BVI-turn mimetic".

37. H₂N-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-
OH
38. H₂N-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys-
Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH
39. D- β -Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂
40. Ac-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂
41. D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Trp-NH₂
42. D-Trp-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂
43. D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂
44. D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH₂
45. 3-(2-naphthyl)-D-Ala-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂
46. c(Aha-Phe-p-Cl-Phe-D-Trp-Lys-Thr-Phe)

Aha = 7 -amino heptanoic acid.

Analogues of Diazoxide and Cyclothiazide are compounds which
affect the receptor being adenosine 5'- triphosphate sensitive K'
channels.

Suitable analogues of Diazoxide and of Cyclothiazide are
indicated, for example, in a paper of Bertolino et al., appearing
in Receptor-Channels 1993 1(4):267-78 "Modulation of AMPA/Kainate
Receptors by Analogs of diazoxide and cyclothiazide in thin

slices of rat hippocampus". However, the analogs which may be used in the pharmaceutical composition according to the present invention are not restricted to the analogs given in said paper and any other analog having the proper properties may be used.

The pharmaceutical preparation according to the present invention may also comprise additional compounds such as compounds having an additional pharmaceutical effect, carriers, solvents, emulgators, etc.

In view of the fact that diazoxide sometimes has undesired salt and water retention, which may be relieved by certain thiazide diuretics, e.g. 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Chlorothiazide); 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Hydrochlorothiazide); 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Trichlormethiazide); or 6-chloro-3,4-dihydro-2-methyl-3[(2,2,2-trifluoroethyl)thiomethyl]-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Polythiazide), the pharmaceutical compositions according to the present invention may comprise, in addition to Diazoxide and/or one of its analogs, as an additional compound having a pharmaceutical effect, one or more of the above thiazides or a thiazide having similar properties. Said thiazide diuretics may prevent the salt and water retention.

The present invention also comprises a method for the treatment of the risk factors of syndrome X of Reaven by applying to a patient a pharmaceutically effective dosage of a pharmaceutical preparation according to the present invention comprising a pharmaceutically effective dosage of a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin.

Said dosage should preferably not exceed 50 µg/kg/day of the active ingredient (calculated on Octreotide), preferably not exceeding 40 µg/kg/day. Said dosage is given in any suitable manner. It may be given as one portion once a day or even in two days or more when given in slow release form, or being divided into 3-4 dosages which are applied in equal periods of time for Octreotide, or 1 - 2 times a day for analogs with a higher $t_{1/2}$.

Said dosage should preferably not exceed 8 mg/kg/day in the treatment of the active ingredient (calculated on diazoxide) in adults, and preferably not exceed 15/mg/day in the treatment of children. The amount of Metformin applied should preferably not exceed 2.5 g/day divided into 2 - 3 portions.

Should any of the above thiazide diuretics be added the added amounts are, for example, the following:

Chlorothiazide: 500 - 3000 mg a day;
Hydrochlorothiazide: 50 - 200 mg a day;
Trichloromethiazide: 12.5 - 50 mg a day;
Polythiazide: 1- 4 mg a day.

Said dosage has to be re-calculated on the basis of the analog being the active ingredient. Moreover, the exact dosages have to be adapted to the condition of the patients and to its specific properties e.g. weight, age, etc.

The composition may be administered in various manners. This depends in particular on the analog being the active ingredient. Thus octreotide is advantageously injected sub-cutaneously as a saline solution. Cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe) is advantageously administered per os.

The treatment is performed, as indicated above, against the risk factors of syndrome X of Reaven, in particular against the following diseases in order to primarily and secondarily prevent and to treat:

- A.
 1. Ischemic Heart diseases, e.g. Angina Pectoris and Myocard Infarcts;
 2. Cerebral vascular diseases in order to prevent Transient Ischemic attack (TIA) and Cerebrovascular accident (CVA);
 3. Intermittent Claudication;
 4. Ischemic Bowel disease; and
 5. Impotence due to a Periferal vascular disease.
- B. Prevent excessive blood coagulation (high PAI-1 in the blood) in order to primarily prevent MI, CVA, Renal vein trombosis, etc.
- C. Lower body weight (which is also a risk factor for high blood pressure, Glucose Intolerance, etc.)

Said diseases are mainly caused, as indicated above, by a

high resistance to Insulin.

The present invention will now be illustrated with reference to the following experiment (all injections are given into the hollow space of the Peritoneum):

60 fat male rats of the Zucker species, aged 7 weeks having an average weight of 225 g. 54 rats of same are divided into 3 groups:

Group A receives injections of Octreotide in a 0.9% NaCl saline solution in a high dosage (40 μ g/kg/day);

Group B receives injections of Octreotide in a 0.9% NaCl saline solution in a low dosage (20 μ g/kg/day); and

Group C the control group, receives an injection of a 0.9% saline solution. The volume of the 0.9% NaCl is identical with the volume being injected into Group A and B (At the beginning of the tests the rats have approximately the identical weight and they therefore receive the identical volume of injections).

All rats receive the same amount of Food (Pair Fed). Said amount is chosen according to the group eating the lowest amount. Thus, the influence of the drug is isolated.

The rats are located in a room changing light and darkness in order to simulate natural surroundings, as in general they eat in darkness. The rats drink water freely.

The rats are weighed twice a week. At the end of the experiment the rate change of the weight is being calculated. The amount of food eaten per week is measured and the amount eaten each day is calculated. (The influence of the Octreotide on the amount of food eaten by the rats is not checked. They eat the identical amount of food.)

Six rats are tested before the beginning of the experiment. Six rats from each group are separated after 2 weeks, 4 weeks and 8 weeks and an Intra-Peritoneal Glucose Tolerance Test (GTT 1.0g Glucose/kg BW) is performed after a fast of 12 hours during which the rats do not receive any medicament or food.

Blood is taken from the Supra-orbital sinus with slow anaesthesia with CO₂.

At zero time, i.e. before the Glucose load 2 cc of blood are taken from each rat.

$\frac{1}{2}$ cc of blood is put into a test tube which contains Heparin

and the concentrations of Glucose and Insulin are determined; and

1½ cc of blood is put into a test tube which contains Na₂EDTA 0.1% and the concentrations of Cholesterol, Triglycerides, HDL and LDL are determined.

At 15, 30 and 60 minutes after the Glucose load, ½ cc of blood is taken from each rat and put into a test tube which contains Heparin and the concentrations of Glucose and Insulin are determined.

After the Glucose tolerance test each tested rat "leaves" the experiment.

The materials used in the experiments:

Octreotide manufactured by Sandoz Basel.

0.9% NaCl

30% Glucose

Not sterilized food for mice and rats manufactured by Kopolk, Petach Tikva. Catalogue No. 19510. Gross energy 3,950 kCal/kg. Digestibility energy of the food in rats 3,150 kCal/kg.

The laboratory tests are performed as follows:

1. Glucose is tested by the Glucose Oxidase method in a kit of Boehringer Mannheim called Glucose GOD-Perid Method 2 x 300ml catalogue No. 124028. The test is performed on the day or the following day on which the blood is taken.

2. The Insulin is tested by the Radio Immuno Assay (RIA) by a SB INSIK-5 kit of Scrin Biomedica.

The method is performed by the general method known for the test of Insulin by said kit.

3. The total Cholesterol is tested by the CHOD-PAP method. The total cholesterol comprises VLDL + LDL + HDL. The kit with which the test is performed is manufactured by Boehringer Mannheim and the cholesterol reagent is MPA3 catalogue No. 236691 4 x 500ml.

The HDL is tested by precipitating LDL and VLDL with Heparin MnCl₂ and then the total cholesterol is tested. VLDL is calculated by T.G./5. LDL is calculated by the formula

$$\text{LDL} = \text{total cholesterol} - (\text{VLDL} + \text{HDL})$$

4. The Triglycerides are being tested by the peridochrom T.G. GPO-PAP method. The kit is manufactured by Boehringer

Mannheim and the reagent has catalogue No. 701904 15 x 32ml.

The data received are worked up by standard methods for this purpose. The results show that the Insulin resistance is significantly lowered, there is an increase in the level of HDL and a decrease in the level of LDL and of the Triglycerides. A decrease in the rate of weight gain of young obese rats is observed, which implies a decrease in the weight of adult obese rats.

The Insulin resistance (Insulin Sensitivity Index) is determined using the dynamic test - the Glucose Tolerance Test (GTT). An integration of the area under the curve (AUC) of Glucose and Insulin in the period of $1\frac{1}{2}$ hours is measured and the determination of the ratio between them gives a good estimate of the Insulin resistance.

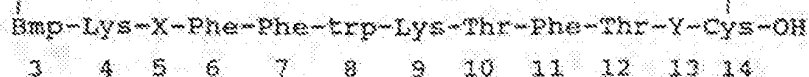
Claims:

1. A pharmaceutical composition for the treatment of the risk factors of syndrome X of Reaven comprising as active ingredient a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin.
2. A pharmaceutical composition comprising an additional compound.
3. A pharmaceutical composition comprising an additional compound having an additional pharmaceutical effect.
4. A pharmaceutical composition according to Claim 2 or 3 wherein the additional compound is selected among carriers, solvents and emulgators.
5. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog of somatostatin is Octreotide.
6. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog of somatostatin is Vapreotide.
7. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog of somatostatin is Lanreotide.
8. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analogs of somatostatin are Cyclopeptide somatostatin analogues selected among :
 - Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]
 - Cyclo[N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe]
 - Cyclo[Pro-Ala-D-Trp-Lys-Thr-Phe]
 - Cyclo[Pro-Tyr-D-Trp-Lys-Thr-Phe]
 - Cyclo[Pro-Phe-D-Trp-Lys- β -aminobutyric-Phe]
 - Cyclo[N-Me-Ala-Phe-D-Trp-Lys-Thr-Phe]
 - Cyclo[Pro-Phe-D-Trp-Lys-Val-Phe]
 - Cyclo[D-Ala-D-Phe-D-Trp-L-Lys-D-Thr-N-Me-D-Phe]
 - Cyclo[Pro-Phe-D-Trp-Lys-Thr(Bzl)] (Bzl = (a))
 - Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]
 - Cyclo[Pro-D-Phe-D-Trp-Lys-Thr(Bzl)]
 - Cyclo[Ahep-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Tyr-Thr-Ser] (Ahep = (b))
 - Cyclo[Ahep-Phe-D-Trp-Lys-Thr(Bzl)]
 - Cyclo[Ahep-Phe-D-Trp-Lys-Thr]

Cyclo[Ahep-Phe-D-Trp-Lys-Ser(Bzl)]
 Cyclo[Ahex-Phe-D-Trp-Lys-Thr(Bzl)] (Ahex = (c))
 Cyclo[Aoct-Phe-D-Trp-Lys-Thr(Bzl)] (Aoct = (d))
 Cyclo[Ala-Cys-Phe-D-Trp-Lys-Thr-Cys]
 (a) Bzl = benzyl
 (b) Ahep = 7-aminoheptanoyl
 (c) Ahex = 6-aminohexanoyl
 (d) Aoct = 8-amino-octanoyl;

9. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thr-ol
10. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH₂ (Nal = (1))
11. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH₂
12. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Thr-Cys]-Nal-NH₂
13. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Nal-NH₂ (Abu = (2))
14. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Ser-Cys]-Nal-NH₂
15. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH₂
16. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
c(Ahep-Trp-D-Trp-Lys-Thr-Phe) (Ahep = (3))
17. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH₂ (Cpa = (4))
18. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH₂

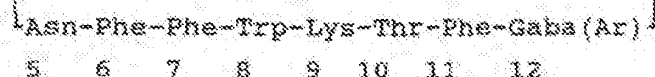
19. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH₂
20. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH₂
21. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH₂
22. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Ala-Phe-D-Trp-Lys-Ala-Nal-NH₂
23. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH₂
24. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH₂
25. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH₂
26. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are polypeptides of the formula:
X-Lys-Asn-Phe-Phe-A-Lys-Thr-Phe-Thr-Ser-Y
wherein A is L- or D-Trp,
X is H-(Aeg)_m-Cys- or H-(Aeg)_m-Ala-Gly-Cys-,
Y is -Cys-(Aeg)_n-OH or
X and Y taken together are a 2-aminoethyl-glycyl
group in the ring position and
m and n are 0, 1, 2, provided that
m and n are at least 1,
and their cyclic disulfide derivatives.
27. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are peptides of the formula:



in which

- Bmp represents the desaminocysteine radical,
 X represents Asn,
 trp represents D-Trp that may be substituted in the benzene ring by a halogen atom, and
 Y represents the radical of an alpha-(lower alkyl)amino-(lower alkyl)-carboxylic acid having a minimum of 4 and a maximum of 8 carbon atoms, in which the two lower alkyl radicals can be connected to one another with a single C-C bond, an oxygen atom or a sulphur (II) atom.

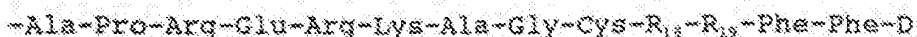
28. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are cyclic octapeptides of the formula



in which

- Trp represents L-Trp or D-Trp, in which the benzene ring may be substituted by a fluorine atom, and
 Gaba(Ar) represents the residue of α -aminobutyric acid substituted by a cyclic hydrocarbyl radical Ar selected from the group consisting of cyclohexyl; phenyl optionally substituted by halogen, nitro or phenoxy; and naphthyl optionally substituted by halogen.

29. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are compounds of formula



Met or Leu, R_{11} is Lys or des R_{11} , R_{12} is Asn or

des R_{12} , R_{23} is Phe or Tyr, R_{24} is Thr or des

R_{26} , R_{27} is Ser or D-Ser and R_{28} is D-Cys or Cys.

30. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are compounds of formula

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala- R_8 -Ala-Pro

-Arg-Glu-Arg-Lys-Ala-Gly-Cys- R_{13} - R_{14} -Phe-Phe-D-Trp-Lys

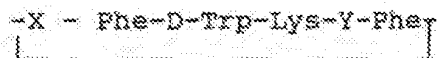
-Thr- R_{25} - R_{26} - R_{27} - R_{28} -OH wherein R_8 is Met or

Leu, R_{13} is Lys or des R_{13} , R_{14} is Asn or des

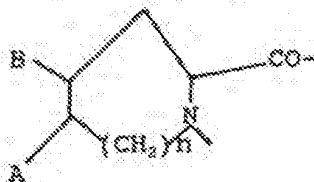
R_{16} , R_{23} is Phe or Tyr, R_{24} is Thr or des R_{26} ,

R_{27} is Ser or D-Ser and R_{28} is D-Cys or Cys, or the linear version thereof where the disulfide bridge is replaced by hydrogen.

31. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are cyclic hexapeptides of the formula



in which X represents the radical of an L-aminoacid of the formula



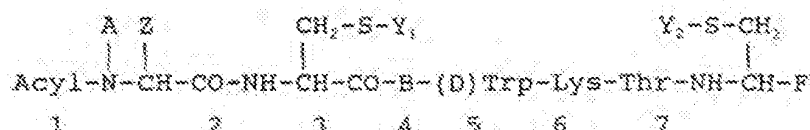
in which A and B are identical or different and denote alkyl having 1 to 3 carbon atoms, or A and B together represent a saturated, unsaturated or aromatic monocyclic or bicyclic structure having 3 to 6 carbon atoms,

n denotes 0 or 1, and

Y represents an aliphatic or aromatic L-aminoacid the side-

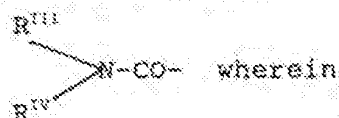
chair of which can be hydroxylated, said amino acid being selected from the group consisting of L-alanine, L-serine, L-valine, L-leucine, L-isoleucine, L-phenylalanine and L-tyrosine.

32. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are N-acyl-polypeptides of formula,



wherein

"Acyl" is a group of formula $\text{R}^{\text{I}}\text{CO-}$ wherein R^{I} is C_{1-20} alkyl or phenyl; a group of formula $\text{R}^{\text{II}}\text{SO}_2\text{-}$ wherein R^{II} is C_{1-20} alkyl, phenyl or tolyl; a group



R^{III} and R^{IV} are each independently hydrogen

or C_{1-12} alkyl; or biotinyl,

A is hydrogen or C_{1-3} alkyl,

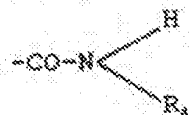
$>\text{N-CH(Z)-CO-}$ is an (L)- or (D)-phenylalanine residue optionally ring-substituted by NO_2 , or an (L) or (D)-norleucine residue,

whereby

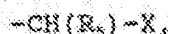
Z in $>\text{N-CH(Z)-CO-}$ represents the remainder of said residue,

B is -Phe- optionally ring-substituted by NO_2 ,

F is a group of formula



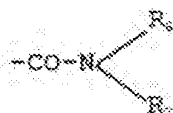
wherein R_4 is hydrogen or a group of formula



R_5 is $\text{CH}_2\text{CH(OH)-}$, i-butyl or benzyl

X is a group of formula $-\text{COOR}_1$,





wherein R_1 , R_2 and R_3 are each hydrogen or C_{1-12} alkyl, and

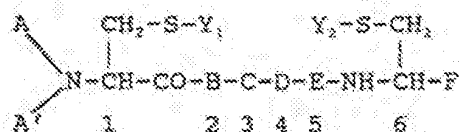
R_4 is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,

the group $-\text{CH}(\text{R}_5)-\text{X}$ having the (D)- or (L)-configuration, and

Y_1 and Y_2 are each hydrogen or together represent a direct bond, whereby the residue resides in the 2- and 7-position each independently have the (L)- or (D)-configuration, and with the proviso that:

- i) (L)- and/or (D)-cysteine residues are present at the 2- and 7-positions only.

33. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are polypeptides of the formula



wherein

A is C_{1-12} alkyl, C_{7-12} phenylalkyl or a group of formula $\text{RCO}-$, whereby

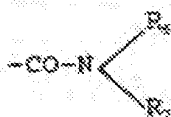
- i) R is hydrogen, C_{1-11} alkyl, phenyl or C_{7-11} phenylalkyl, or
- ii) $\text{RCO}-$ is a) an L- or D-phenylalanine residue optionally ring-substituted by halogen and/or C_{1-7} alkyl,
 - b) H-Asn-, or
 - c) H-Nle-Asn-,
 - the α -amino group of amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di- C_{1-12} alkylated,

- A' is hydrogen or, when A is C₁₋₁₂alkyl or C₇₋₁₂phenylalkyl, also C₁₋₁₂alkyl or C₇₋₁₂phenylalkyl,
 B is -Phe- optionally ring-substituted by halogen and/or C₁₋₃alkyl,
 C is -(L)- or -(D)-Trp- optionally α-N-methylated and optionally benzene-ring-substituted by halogen and/or C₁₋₃alkyl,
 D is -Lys- optionally α-N-methylated and optionally ε-N-C₁₋₃-alkylated,
 E is -Thr- or -Ala- each in (D)- or (L)-form and each being optionally α-N-methylated,

F is a group of formula -COOR₁, -CH₂OR₂, -CO-N  or



- wherein R₁ is hydrogen or C₁₋₃alkyl,
 R₂ is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,
 R₃ is hydrogen, C₁₋₃alkyl, phenyl or C₇₋₁₀-phenylalkyl,
 R₄ is hydrogen, C₁₋₃alkyl or, when R₃ is hydrogen or methyl, also a group of formula -CH(R₅)-X,
 R₅ is hydrogen, -(CH₂)₂-OH, -(CH₂)₃-OH, -CH₂-OH, -CH(CH₃)-OH, isobutyl or benzyl
 X is a group of formula -COOR₁, -CH₂OR₂ or

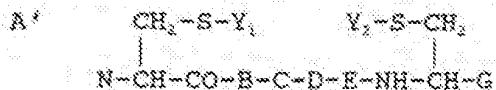


wherein

- R₆ and R₇ have the meanings given above,
 R₆ is hydrogen or C₁₋₃alkyl and
 R₇ is hydrogen, C₁₋₃alkyl, phenyl or C₇₋₁₂phenylalkyl,

the group $-\text{CH}(\text{R}_a)-\text{X}$ having the D- or L- configuration, and Y_1 and Y_2 are each hydrogen or together represent a direct bond, whereby the residues in the 1- and 6-position each independently have the L- or D-configuration.

34. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is a compound of formula



A

wherein

A is C_{1-12} alkyl, C_{7-10} phenylalkyl or a group of formula $\text{RCO}-$, whereby

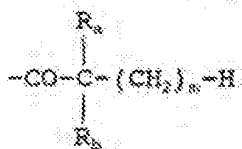
- i) R is hydrogen, C_{1-11} alkyl, phenyl or C_{7-10} phenylalkyl or
ii) $\text{RCO}-$ is

- a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br, NO_2 , NH_2 , OH, C_{1-3} alkyl and/or C_{1-3} alkoxy;
b) the residue of a natural or synthetic α -amino acid other than defined under a) above or of a corresponding D-amino acid, or
c) a dipeptide residue in which the individual amino acid residues are the same or different and are selected from those defined under a) and/or b) above,

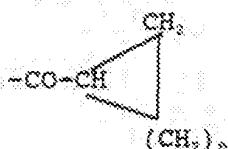
C_{1-10} alkanoyl,

A' is hydrogen,

Y_1 and Y_2 represent together a direct bond or each of Y_1 and Y_2 is independently hydrogen or a radical of formulae (1) to (5).



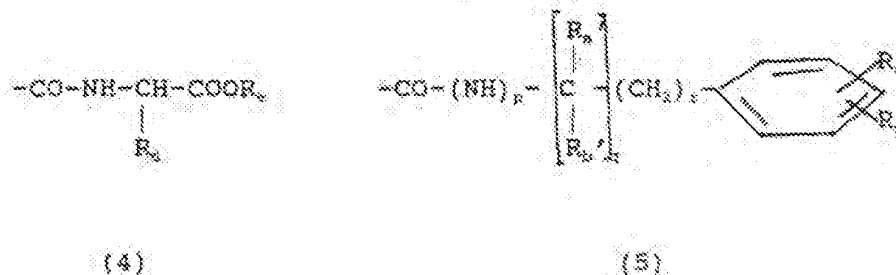
(1)



(2)

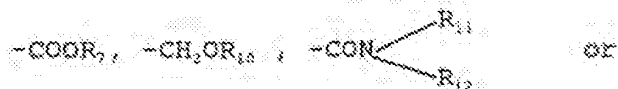


(3)



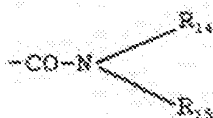
wherein

- R_x is methyl or ethyl
- R_b is hydrogen, methyl or ethyl
- m is a whole number from 1 to 4
- n is a whole number from 1 to 5
- R_c is (C_{1-5}) alkyl
- R_d represents the substituent attached to the α -carbon atom of a natural or synthetic α -amino acid (including hydrogen)
- R_e is (C_{1-5}) alkyl
- R_a' and R_b' are independently hydrogen, methyl or ethyl,
- R_c and R_d are independently hydrogen, halogen, (C_{1-5}) alkyl or (C_{1-5}) alkoxy,
- P is 0 or 1,
- q is 0 or 1, and
- r is 0, 1 or 2,
- B is -Phe- optionally ring-substituted by halogen, NO_2 , NH_2 , OH , C_{1-5} alkyl and/or C_{1-5} alkoxy (including pentafluoroalanine), or β -naphthyl-Ala
- C is (L)-Trp- or (d)-Trp- optionally α -N-methylated and optionally benzene-ring-substituted by halogen, NO_2 , NH_2 , OH , C_{1-5} alkyl and/or C_{1-5} alkoxy,
- D is Lys, Lys in which the side chain contains O or S in β -position, F-Lys or δ F-Lys, optionally α -N-methylated, or a 4-aminocyclohexylAla or 4-aminocyclohexylGly residue
- E is The, Ser, Val, Phe, Ile or an aminoisobutyric or aminobutyric acid residue
- G is a group of formula



wherein

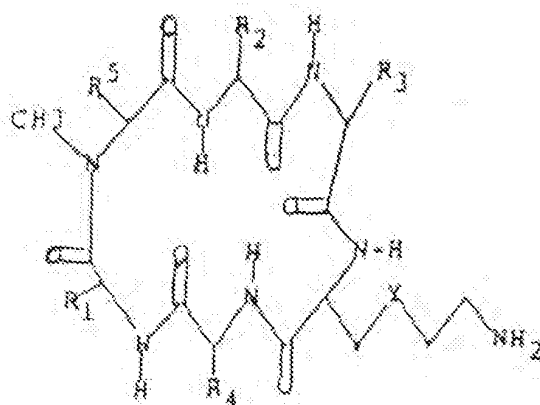
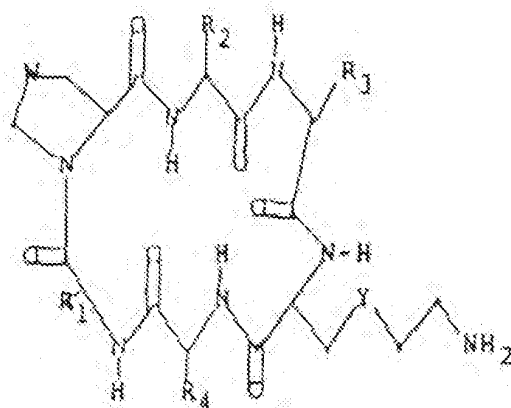
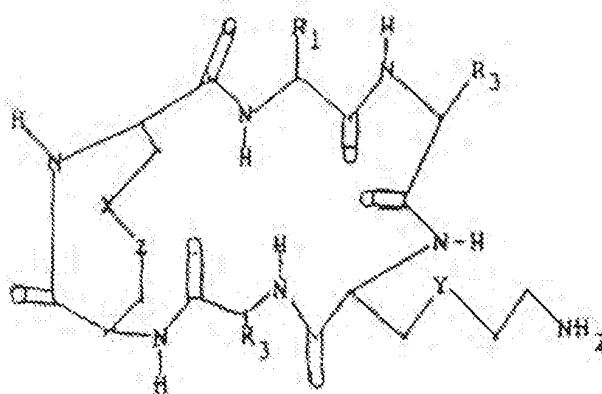
- R_7 is hydrogen or C_{1-3} alkyl,
 R_{10} is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,
 R_{11} is hydrogen, C_{1-3} alkyl, phenyl or C_{7-10} phenyl-alkyl,
 R_{12} is hydrogen, C_{1-3} alkyl or a group of formula $-\text{CH}(\text{R}_{13})-\text{X}_1$,
 R_{13} is CH_2OH , $-(\text{CH}_2)_2-\text{OH}$, $-(\text{CH}_2)_3-\text{OH}$, or $-\text{CH}(\text{CH}_3)\text{OH}$ or represents the substituent attached to the α -carbon atom of a natural or synthetic α -amino acid (including hydrogen) and
 X_1 is a group of formula $-\text{COOR}_7$, $-\text{CH}_2\text{OR}_{10}$ or



wherein

- R_7 and R_{10} have the meanings given above,
 R_{14} is hydrogen or C_{1-3} alkyl and
 R_{15} is hydrogen, C_{1-3} alkyl, phenyl or C_{7-10} phenylalkyl, and
 R_{16} is hydrogen or hydroxy,
 with the proviso that
 when R_{12} is $-\text{CH}(\text{R}_{13})-\text{X}_1$ then R_{11} is hydrogen or methyl,
 wherein the residues B, D and E have the L-configuration, and the residues in the 2- and 7-position and any residues Y_1 4) and Y_2 4) each independently have the (L)- or (D)- configuration.

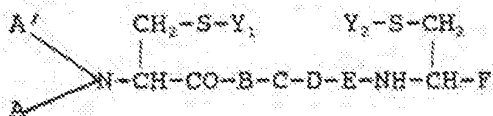
35. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog is a somatostatin analog selected from the compounds of the following formulae



wherein

W is S or $(CH_2)_s$, where s is 0, 1 or 2;
 one of X and Z is S and the other is S or CH_2 ;
 Y is S or $(CH_2)_t$, where t is 0, 1 or 2;
 each of R_1 and R_2 independently of the other, is C_{1-6} alkyl, benzyl, benzyl having one or two C_{1-6} alkyl, halogen, hydroxy, amino, nitro, and/or C_{1-6} alkoxy substituents, or C_{1-6} alkyl substituted with 5- or 6-membered heterocyclic ring;
 R_3 is 3-indolylmethyl, either unsubstituted or having C_{1-6} alkyl, C_{1-6} alkoxy or halogen substitution;
 R_4 is C_{1-6} alkyl, C_{1-6} hydroxyalkyl, benzyl, carboxy- $(C_{1-6}$ alkyl), amino $(C_{1-6}$ alkyl) or benzyl having a C_{1-6} alkyl, halogen, hydroxy, amino, nitro and/or C_{1-6} alkoxy substituent;
 R_5 is C_{1-6} alkyl, benzyl, or benzyl having a C_{1-6} alkyl, halogen, hydroxy, amino, nitro, and/or C_{1-6} alkoxy substituent,

compounds of formula



wherein

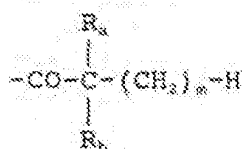
A is C_{1-12} alkyl, C_{7-10} phenylalkyl or a group of formula $RCO-$, whereby

- i) R is hydrogen, C_{1-11} alkyl, phenyl or C_{7-10} phenylalkyl, or
- ii) $RCO-$ is
 - a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br, NO_2 , NH_2 , OH, C_{1-3} alkyl and/or C_{1-3} alkoxy
 - b) the residue of a natural α -amino acid other than defined under a) above or of a corresponding D-amino acid, or
 - c) a dipeptide residue in which the individual amino acid

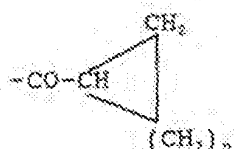
residues are the same or different and are selected from those defined under a) and/or b) above, the α -amino group or amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di- C_{1-12} alkylated,

A' is hydrogen or, when A is C_{1-12} alkyl or C_{7-10} phenylalk- also C_{1-12} alkyl or C_{7-10} phenylalkyl,

Y_1 and Y_2 represent together a direct bond or each of Y_1 and Y_2 is independently hydrogen or a radical of the formulae



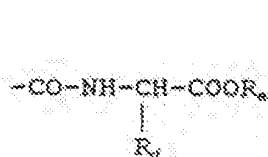
(1)



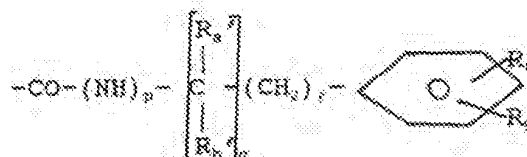
(2)



(3)



(4)



(5)

wherein R_a is methyl or ethyl

R_b is hydrogen, methyl or ethyl

m is a whole number from 1 to 4

n is a whole number from 1 to 5

R_c is (C_{1-6}) alkyl

R_d represents the substituent attached to the α -carbon atom of a natural α -amino acid (including hydrogen)

R_e is (C_{1-3}) alkyl

R_a' and R_b' are independently hydrogen, methyl or ethyl,

R_s and R_t are independently hydrogen, halogen, (C_{1-3}) alkyl or (C_{1-3}) alkoxy,

p is 0 or 1,

q is 0 or 1, and

r is 0, 1 or 2,

B is -Phe- optionally ring-substituted by halogen, NO_2 , NH_2 ,

OH, C_{1-3} alkyl and/or C_{1-3} alkoxy, or naphthylalanine,

C is (L)-Trp- or (D)-Trp- optionally α -N-methylated and optionally benzene-ring-substituted by halogen, NO_2 , NH_2 , OH, C_{1-3} alkyl and/or C_{1-3} alkoxy,

D is -Lys-, ThiaLys, F-Lys, δ F-Lys or Orn, optionally α -N-methylated, or a 4-aminocyclohexyl Ala or 4-aminocyclohexyl Gly residue,

E is Thr, Ser, Val, Phe, Ile or an aminoisobutyric acid residue

F is a group of formula $-COOR_9$, $-CH_2OR_{10}$, $-CON$  or



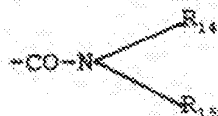
wherein R_9 is hydrogen or C_{1-3} alkyl,

R_{10} is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,

R_{11} is hydrogen, C_{1-3} alkyl, phenyl or C_{7-16} -phenylalkyl,

R_{12} is hydrogen, C_{1-3} alkyl or a group of formula $-CH(R_{13})-X_1$,

R_{13} is CH_2OH , $-(CH_2)_2-OH$, $-(CH_2)_3-OH$, or $-CH(CH_3)OH$ or represents the substituent attached to the α -carbon atom of a natural α -amino acid (including hydrogen) and X_1 is a group of formula $-COOR_9$, $-CH_2OR_{10}$ or



wherein

R_9 and R_{10} have the meanings given above,

R_{14} is hydrogen or C_{1-3} alkyl and

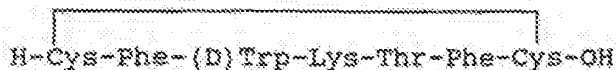
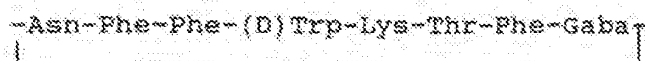
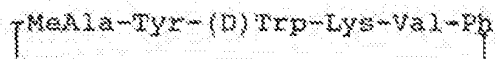
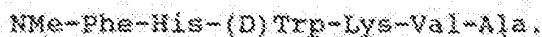
R_{15} is hydrogen, C_{1-3} alkyl, phenyl or C_{7-16} phenylalkyl, and

R_{16} is hydrogen or hydroxy,

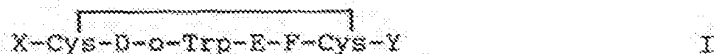
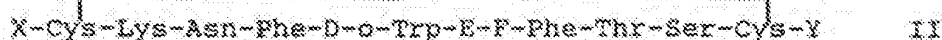
with the proviso that

when R_{12} is $-CH(R_{13})-X_1$ then R_{11} is hydrogen or methyl,

wherein the residues B, D and E have the L-configuration, and the residues in the 2- and 7-position and any residues Y, 4) and Y, 4) each independently have the (L)- or (D)-configuration and compounds of the following formulae



36. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analogs are Somatostatin analogs

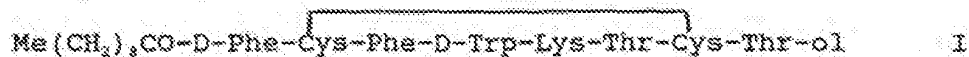


I, II, X = N-terminus anchor; Y = C-terminus anchor, G-I or its alc; wherein at least I of X, Y = cationic anchor; D = Phe Tyr, 3-(p-fluorophenyl)alanine or 3 (p-chlorophenyl)alanine residue; E = Lys, Lys(R¹); R¹ = C₁₋₆(fluoro)alkyl; F = Thr, Val, Ser; G = D- or L-Thr, Phe, or 3-(2-naphthyl)alanine residue; I = OH, NH₂, NHR¹.

37. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are peptides:



[R = inorg. or org. acyl group, R¹ = H, alkyl, NCHR²CO moiety = I.



or D-Phe (optionally ring substituted by halo, NO₂, OH, alkyl, alkoxy); Phe, Trp, (D or L), may be ring substituted by NO₂, NH₂, OH, alkyl, alkoxy; Lys may be α-N-methylated and ε-N-alkylated; X = D- or L-α-amino acid residue optionally α-N-methylated; R² = CO₂H, CH₂OH, carbamoyl, R⁴ = R⁵ = H, R⁴R⁵

= bond]

38. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-X-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly

Cys-X¹-X²-Phe-Phe-D-Trp-Lys-Tys-Thr-X³-X⁴-X⁵-X⁶-OH

39. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Leu-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-

Cys-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr-Thr-Ser-Cys-OH

40. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is

c(Spacer-Phe-D-Trp-Lys-Thr)

Spacer may stand for:

- a) R,S- δ -Bn-o-AMPA
- b) R- α -Bn-NMe-o-AMPA
- c) Phe-Pro

41. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

H₂N-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH

42. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

H₂N-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH

43. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

D-B-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂

44. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

Ac-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂

45. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Trp-NH₂

46. A pharmaceutical composition according to any of Claims 1 to

- 4, wherein the somatostatin analog is:
D-Trp-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂
47. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂
48. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH₂
49. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
3-(2-naphthyl)-D-Ala-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂
50. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
c(Aha-Phe-p-Cl-Phe-D-Trp-Lys-Thr-Phe)
Aha = 7 -amino heptanoic acid.
51. A pharmaceutical composition according to any of Claims 1 to 4, wherein the active ingredient is diazoxide and comprises in addition a thiazide selected among chlorothiazide, hydrochlorothiazide, trichloromethiazide and polythiazide.
52. A method for the treatment of symptoms of syndrome X by applying to a patient a pharmaceutical composition according to any of Claims 1 to 51 comprising a pharmaceutically effective dosage of a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin.
53. A method according to Claim 52, wherein the pharmaceutically effective dosage (calculated on octreotide) does not exceed 50 µ/kg/day.
54. A method according to Claim 53, wherein said dosage does not exceed 40 µ/kg/day.
55. A method according to any of Claims 52 to 54 wherein the analog is Octreotide which is applied in the form of an injection in a 0.9% saline solution.
56. A method according to Claim 52, wherein said dosage does not exceed 8 mg/kg/day in the treatment of the active ingredient (calculated on diazoxide) in adults, and does not exceed 15/mg/day in the treatment of children.

57. A method according to Claim 52, wherein the amount of metformin applied does not exceed 2.5 g/day divided into 2 - 3 portions.
58. Use of a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin in a preparation for the treatment of the risk factors of syndrome X of Reaven substantially as described in the specification.

Electronic Acknowledgement Receipt

EFS ID:	24528478
Application Number:	14940018
International Application Number:	
Confirmation Number:	6992
Title of Invention:	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME
First Named Inventor/Applicant Name:	Neil M. Cowen
Customer Number:	20350
Filer:	Stephen E. Reiter
Filer Authorized By:	
Attorney Docket Number:	096593-001000US-0955615
Receipt Date:	05-JAN-2016
Filing Date:	12-NOV-2015
Time Stamp:	14:27:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment		no			
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Foreign Reference	WO1998010786A2_1.pdf	2540132	no	45
			b87bf0c9b2ef2473d2f044d6870afe97f200edd3		
Warnings:					
Information:					

2	Non Patent Literature	Aguilar-Bryan.pdf	4124596	no	19
			c0c4170862b8c020e3ecfaed90a16b2c1f535dbb		
Warnings:					
Information:					
3	Non Patent Literature	AIZAWA_NPL.pdf	61557	no	2
			0e8d989e651b20944a1adff1b07f659623a6cb9a1		
Warnings:					
Information:					
4	Non Patent Literature	Alemzadeh_Metabolism_NPL.pdf	111697	no	2
			762a8b8031835ecdca861ef2423b10734fbc8e5		
Warnings:					
Information:					
5	Non Patent Literature	Alemzadeh_Beneficial_NPL.pdf	370353	no	5
			82bbd536bf326d9a11c0d2bfcdb4cae8282ca40c		
Warnings:					
Information:					
6	Non Patent Literature	Alemzadeh_Endocrinology.pdf	152278	no	6
			4790ea0b2df702be5dd29f12a2641c019219566b		
Warnings:					
Information:					
7	Non Patent Literature	Alemzadeh_Tushaus_Endocrinology_NPL.pdf	566457	no	9
			d7cb3c95949505885c3afd01c060483dd3a8a20e		
Warnings:					
Information:					
8	Non Patent Literature	Alemzadeh_133_NPL.pdf	108366	no	2
			eb5aa21c974a8521ec43ab8409c557b4dc4e7a8b		
Warnings:					
Information:					
9	Non Patent Literature	Babenko_NPL.pdf	470753	no	5
			5e9d465b1ec56456c8b3b7bb68b0d9900ea6da04		
Warnings:					
Information:					
10	Non Patent Literature	Bertolino_NPL.pdf	113461	no	2
			533b0614d5001cba816825fbcadda90249f268e1		
Warnings:					
Information:					

11	Non Patent Literature	Bjork_NPL.pdf	88073	no	2
			6c8e61d9caa82d439a96aaee205f0853e79918b		
Warnings:					
Information:					
12	Non Patent Literature	Bjorklund_NPL.pdf	128011	no	9
			68ec6781ebdf04b6e1e2a1965db44a068a232628		
Warnings:					
Information:					
13	Non Patent Literature	Butler_NPL.pdf	114152	no	2
			5c93fc0fa3d7168bf85e746a01cb70c4c4fce12a		
Warnings:					
Information:					
14	Non Patent Literature	Cosgrove.pdf	387101	no	9
			e4c30de564a407945c33960740b48fe1ee694d04		
Warnings:					
Information:					
15	Non Patent Literature	Dabrowski_NPL.pdf	258796	no	11
			d85a1720f713409820036e79fb4321f3f41c3498		
Warnings:					
Information:					
16	Non Patent Literature	DeTullio_NPL.pdf	827578	no	2
			c580859955f4fc172a8935bce7a664fa24a4e0ce		
Warnings:					
Information:					
17	Non Patent Literature	calesnick_NPL.pdf	256447	no	2
			20d938ed3ea40942f71d6df77945d9a70386e00c		
Warnings:					
Information:					
18	Non Patent Literature	Guldstrand_NPL.pdf	349493	no	2
			319c2c23e836e488bf643e74740e04377e541cad		
Warnings:					
Information:					
19	Non Patent Literature	J_Clin_Endocrinol_Metab_NPL.pdf	140058	no	9
			b04cb87708ab3d37c5d8b573cb3ea20705a8a35b		
Warnings:					
Information:					

20	Non Patent Literature	Alemzadeh_Med_Sci_Monit_N PL_Scan.pdf	7168218	no	9
8be79641df4417dc53b4012d7c8b2db578 11294e					
Warnings:					
Information:					
Total Files Size (in bytes):				18337577	
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/940,018	11/12/2015	Neil M. Cowen	096593-001000US-0955615

CONFIRMATION NO. 6992

20350
KILPATRICK TOWNSEND & STOCKTON LLP
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

PUBLICATION NOTICE



OC000000083030921

Title:METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

Publication No.US-2016-0136178-A1

Publication Date:05/19/2016

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently <http://www.uspto.gov/patft/>.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently <http://pair.uspto.gov/>. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/940,018	11/12/2015	Neil M. Cowen	096593-001000US-0955615	6992
20350 7590 10/12/2016 KILPATRICK TOWNSEND & STOCKTON LLP Mailstop: IP Docketing - 22 1100 Peachtree Street Suite 2800 Atlanta, GA 30309			EXAMINER OH, TAYLOR V	
			ART UNIT 1625	PAPER NUMBER
			NOTIFICATION DATE 10/12/2016	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipefiling@kilpatricktownsend.com
jlhice@kilpatrick.foundationip.com

Office Action Summary	Application No. 14/940,018	Applicant(s) COWEN, NEIL M.	
	Examiner TAYLOR V OH	Art Unit 1625	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 11/12/15.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 1-28 is/are pending in the application.
5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☐ Claim(s) _____ is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☒ Claim(s) 1-28 are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☐ The specification is objected to by the Examiner.

11) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Restriction and Election

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claim(s) 1-19, drawn to a method of treating a subject having Prader – Willi Syndrome(PWS) or Smith-Magenis Syndrome(SMS) comprising administering to the subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of a K_{ATP} channel opener, classified in class 514 and subclass 223.2.
- II. Claim(s) 20-22, drawn to a method of increasing the lean body mass of a subject having Prader –Willi Syndrome(PWS) or Smith-Magenis Syndrome(SMS) by co-administering growth hormone and an effective amount of a K_{ATP} channel opener, classified in class 514 and subclasses 5.1 and 11.4.
- III. Claim 23, drawn to a kit comprising a unit dose of a K_{ATP} channel opener and a unit dose of growth hormone, classified in class 424 and subclass 198.1.
- IV. Claim(s) 24-25, drawn to a method of reducing one or more aggressive behaviors in a subject having Prader –Willi Syndrome(PWS) or Smith-Magenis Syndrome(SMS) comprising administering to the subject for at

least 10 weeks a pharmaceutical formulation comprising an effective amount of a K_{ATP} channel opener, classified in class 514 and subclass 223.5.

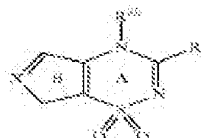
- V. Claim(s) 26-28, drawn to a method of reducing hyperghrelinemia in a subject having Prader –Willi Syndrome(PWS) or Smith-Magenis Syndrome(SMS) comprising administering to the subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of a K_{ATP} channel opener, classified in class 514 and subclass 13.5.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06).

In the instant case, Invention II is directed to the method of increasing the lean body mass of a subject having Prader –Willi Syndrome(PWS) or Smith-Magenis Syndrome(SMS) by co-administering growth hormone and an effective amount of a K_{ATP} channel opener the compound comprising, whereas Invention I is the method of treating a subject having Prader –Willi Syndrome(PWS) or Smith-Magenis Syndrome(SMS) comprising administering to the subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of a K_{ATP} channel opener.

However, Cowen et al (US 2014/0364425) shows the method of treating various diseases such as diabetes, hypertension, dyslipidemia, nonalcoholic steatohepatitis, myocardical infarction and poly-cystic ovarian syndrome by using a K_{ATP} channel opener such as Formula VI as shown below:

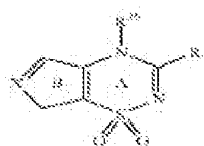


Although both inventions have shared the same compound for the K_{ATP} channel opener, Invention I applies the Formula VI for the treatment different from the treatments shown from Cowen et al. So, there is no direct relationship between Inventions I and II. Therefore, each of them has a different mode of operation, different functions and effects. From this, they are unrelated to each other. Therefore, Group I is not directly related to the Group II.

Inventions I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, Invention I is directed to the method of treating a subject having Prader –Willi Syndrome(PWS) or Smith-Magenis Syndrome(SMS) comprising administering to the subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of a K_{ATP} channel

opener, whereas Invention III is directed to the kit comprising a unit dose of a K_{ATP} channel opener and a unit dose of growth hormone.

However, Cowen et al (US 2014/0364425) shows the method of treating various diseases such as diabetes, hypertension, dyslipidemia, nonalcoholic steatohepatitis, myocardial infarction and poly-cystic ovarian syndrome by using a K_{ATP} channel opener such as Formula VI as shown below:



and it also teaches a kit containing the K_{ATP} channel opener such as Formula VI in combination with a formulation of niacin.

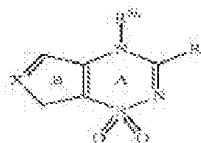
Although both inventions have shared the same compound for the K_{ATP} channel opener, Invention I applies the formula VI for a different treatment, whereas the kit does not need to contain growth hormone as seen from Cowen et al. So, there is no direct relationship between Inventions I and III. Therefore, each of them has a different mode of operation, different functions and effects. From this, they are unrelated to each other. Therefore, Group I is not directly related to the Group III.

Inventions I and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06).

In the instant case, Invention IV is directed to the method of reducing one or more aggressive behaviors in a subject having Prader –Willi Syndrome(PWS) or Smith-

Magenis Syndrome(SMS) comprising administering to the subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of a K_{ATP} channel opener, whereas Invention I is the method of treating a subject having Prader –Willi Syndrome(PWS) or Smith-Magenis Syndrome(SMS) comprising administering to the subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of a K_{ATP} channel opener.

However, Cowen et al (US 2014/0364425) shows the method of treating various diseases such as diabetes, hypertension, dyslipidemia, nonalcoholic steatohepatitis,myocardical infarction and poly-cystic ovarian syndrome by using a K_{ATP} channel opener such as Formula VI as shown below:

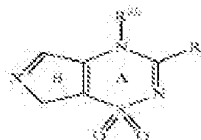


Although both inventions have shared the same compound for the K_{ATP} channel opener, Invention I applies the Formula VI for the treatment different from the treatments shown from Cowen et al. So, there is no direct relationship between Inventions I and IV. Therefore, each of them has a different mode of operation, different functions and effects. From this, they are unrelated to each other. Therefore, Group I is not directly related to the Group IV.

Inventions I and V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06).

In the instant case, Invention V is directed to the method of reducing hyperghrelinemia in a subject having Prader –Willi Syndrome(PWS) or Smith-Magenis Syndrome(SMS) comprising administering to the subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of a K_{ATP} channel opener, whereas Invention I is the method of treating a subject having Prader –Willi Syndrome(PWS) or Smith-Magenis Syndrome(SMS) comprising administering to the subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of a K_{ATP} channel opener.

However, Cowen et al (US 2014/0364425) shows the method of treating various diseases such as diabetes, hypertension, dyslipidemia, nonalcoholic steatohepatitis, myocardical infarction and poly-cystic ovarian syndrome by using a K_{ATP} channel opener such as Formula VI as shown below:



Although both inventions have shared the same compound for the K_{ATP} channel opener, Invention I applies the Formula VI for the treatment different from the treatments shown from Cowen et al. So, there is no direct relationship between Inventions I and V. Therefore, each of them has a different mode of operation, different functions and effects. From this, they are unrelated to each other. Therefore, Group I is not directly related to the Group V.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, Group III, Group IV or Group V, restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

- (a) the inventions have acquired a separate status in the art in view of their different classification;
- (b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;
- (c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);
- (d) the prior art applicable to one invention would not likely be applicable to another invention;
- (e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after

the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAYLOR V OH whose telephone number is (571)272-0689. The examiner can normally be reached on 10:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Kosar can be reached on 571-272-0913. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1625

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TAYLOR V OH/

Primary Examiner, Art Unit 1625

10/06/16

<i>Index of Claims</i> 	Application/Control No. 14940018	Applicant(s)/Patent Under Reexamination COWEN, NEIL M.
	Examiner VICTOR OH	Art Unit 1625

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47										
CLAIM		DATE								
Final	Original	10/06/2016								
	1	+								
	2	+								
	3	+								
	4	+								
	5	+								
	6	+								
	7	+								
	8	+								
	9	+								
	10	+								
	11	+								
	12	+								
	13	+								
	14	+								
	15	+								
	16	+								
	17	+								
	18	+								
	19	+								
	20	+								
	21	+								
	22	+								
	23	+								
	24	+								
	25	+								
	26	+								
	27	+								
	28	+								



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 6992

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.		
14/940,018	11/12/2015	514	1625 096593-001000US-0955615			
RULE						
APPLICANTS Essentialis, Inc., Carlsbad, CA; INVENTORS Neil M. Cowen, Carlsbad, CA; ** CONTINUING DATA ***** This appln claims benefit of 62/080,150 11/14/2014 and claims benefit of 62/138,245 03/25/2015 and claims benefit of 62/170,035 06/02/2015 and claims benefit of 62/221,359 09/21/2015 ** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED *** SMALL ENTITY ** 11/24/2015						
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and /VICTOR V.OH/ Acknowledged Examiner's Signature		☐ Met after Allowance Initials	STATE OR COUNTRY CA	SHEETS DRAWINGS 4	TOTAL CLAIMS 28	INDEPENDENT CLAIMS 7
ADDRESS KILPATRICK TOWNSEND & STOCKTON LLP Mailstop: IP Docketing - 22 1100 Peachtree Street Suite 2800 Atlanta, GA 30309 UNITED STATES						
TITLE METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME						
FILING FEE RECEIVED 1960	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:			☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit		

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
on October 20, 2016.

PATENT
Attorney Docket No.: 096593-001000US-0955615

KILPATRICK TOWNSEND & STOCKTON LLP

By: /William H. Gorman/
William H. Gorman

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Neil M. Cowen

Application No.: 14/940,018

Filed: November 12, 2015

For: METHODS FOR TREATING

SUBJECTS WITH PRADER-WILLI

SYNDROME OR SMITH-MAGENIS

SYNDROME

Customer No.: 20350

Confirmation No.: 6992

Examiner: Taylor V. Oh

Technology Center/Art Unit: 1625

AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Responsive to the Restriction Requirement mailed October 12, 2016, please consider the following amendments and remarks:

Amendments to the Claims are reflected in the **Listing of Claims**, which begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

Amendments to the Claims/Listing of Claims

Please amend claims 2, 7, 8, 15, 19, 27 and 28 as follows. In addition, please cancel non-elected claims 10-14 and 16-18 without prejudice. This listing of claims will replace all prior versions, and listings of claims in the application:

1. (Withdrawn) A method of treating a subject having Prader-Willi Syndrome (PWS) or Smith–Magenis syndrome (SMS), said method comprising administering to said subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of a K_{ATP} channel opener.
2. (Withdrawn; Currently amended) The method of claim ~~[[1]]~~ **24** wherein said K_{ATP} channel opener is diazoxide or a pharmaceutically acceptable salt thereof.
3. (Withdrawn) The method of claim 2 wherein the pharmaceutically acceptable salt is diazoxide choline.
4. (Withdrawn) The method of claim 2 wherein said diazoxide or a pharmaceutically acceptable salt thereof is administered orally.
5. (Withdrawn) The method of claim 2 wherein the pharmaceutical formulation includes at least one excipient which affects the rate of release of diazoxide or a pharmaceutically acceptable salt thereof.
6. (Withdrawn) The method of claim 5 wherein the pharmaceutical formulation includes at least one excipient that delays release of diazoxide or a pharmaceutically acceptable salt thereof.
7. (Withdrawn; Currently amended) The method of claim ~~[[1]]~~ **24** wherein the formulation further comprises at least one other active ingredient.
8. (Withdrawn; Currently amended) The method of claim ~~[[1]]~~ **24** further comprising administering human growth hormone to the subject.

9. (Withdrawn) The method of claim 8 wherein said human growth hormone is administered by injection.

10. – 14. (Cancelled)

15. (Withdrawn; Currently amended) The method of claim ~~[[1]]~~ 24 wherein said administering is carried out for 1 one or more years.

16. – 18. (Cancelled)

19. (Withdrawn; Currently amended) The method of claim ~~[[1]]~~ 24, wherein the circulating concentration of IGF-1 is not increased.

20. (Withdrawn) A method of increasing the lean body mass of a subject having Prader-Willi Syndrome, wherein said subject is already being treated by administration thereto of growth hormone, said method comprising co-administering to said subject an effective amount of a K_{ATP} channel opener in addition to said growth hormone.

21. (Withdrawn) A method of increasing the lean body mass of a subject having Prader-Willi Syndrome, wherein said subject is already being treated by administration thereto of an effective amount of a K_{ATP} channel opener, said method comprising co-administering to said subject an effective amount of growth hormone in addition to said K_{ATP} channel opener.

22. (Withdrawn) A method of increasing lower limb muscle mass of a subject having Smith–Magenis syndrome (SMS), said method comprising administering to said subject an effective amount of a K_{ATP} channel opener.

23. (Withdrawn) A kit comprising:
a unit dose of a K_{ATP} channel opener, and
a unit dose of growth hormone.

24. (Original) A method of reducing one or more aggressive behaviors in a subject having Prader-Willi syndrome (PWS) or Smith–Magenis syndrome (SMS), the method comprising administering to said subject for at least 10 weeks an effective amount of a K_{ATP} channel opener, wherein administration reduces one or more aggressive behaviors in the subject.

25. (Original) The method of claim 24 in which a second therapeutic product is administered, wherein the second product is intended to further reduce the one or more aggressive behaviors.

26. (Withdrawn) A method of reducing hyperghrelinemia in a subject having Prader-Willi syndrome (PWS) or Smith–Magenis syndrome (SMS), the method comprising administering to said subject for at least 10 weeks an effective amount of a K_{ATP} channel opener, wherein administration reduces one or more aggressive behaviors in the subject.

27. (Withdrawn; Currently amended) The method of claim ~~[[1]]~~ 24 wherein the pharmaceutical formulation is administered twice per day.

28. (Withdrawn; Currently amended) The method of claim ~~[[1]]~~ 24 wherein the pharmaceutical formulation is administered once per day.

REMARKS

By the present communication, claims 2, 7, 8, 15, 19, 27 and 28 have been amended. No new matter is introduced by the subject amendments as the amended claim language is fully supported by the specification and original claims.

In addition, by the present communication, non-elected claims 10-14 and 16-18 have been cancelled without prejudice, subject to Applicant's right to pursue the subject matter thereof in a subsequent application claiming priority to the present application.

Upon entry of the present amendment, claims 1-9, 15 and 19-28 will be pending in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

The restriction of claims 1-28 under 35 USC § 121 into five (5) separate groups, is respectfully traversed. It is respectfully submitted that a search of one group would, of necessity, entail a search of one or more of the other groups; in addition, each of the method groups (i.e., Groups I, II, IV and V) contemplates administering to a subject a therapeutically effective amount of a compound selected from a defined group—which defined group is the same for each of the restriction groups). Accordingly, no savings of USPTO resources will be realized by maintaining the requirement for restriction as presently asserted.

Accordingly, reconsideration and withdrawal of the requirement for restriction of claims 1-28 are respectfully requested.

In order to be fully responsive, but without conceding the propriety thereof, Applicants hereby elect Group IV, claims 24 and 25 (plus claims 2-9, 15, 19, 27 and 28 now dependent therefrom), with traverse. All of claims 2-9, 15, 19, 24, 25, 27 and 28 encompass the elected invention.

Non-elected claims 20-23 and 26 are retained in the application pending final disposition of the elected claims, and subject to a request for rejoinder thereof.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Except for the issue fees payable under 37 C.F.R. § 1.18, the Director is authorized to charge any additional fees during pendency of this application, including any required extension of time fees, or credit any overpayment to Deposit Account Number 20-1430. This paragraph is intended to be a constructive petition for extension of time in accordance with 37 C.F.R. § 1.136(a)(3).

In the event any issues remain to be resolved in view of this communication, the Examiner is invited to contact the undersigned at 858 350 3862 or sreiter@kilpatricktownsend.com so that a prompt disposition of this application can be achieved.

Respectfully submitted,

/Stephen E. Reiter/

Stephen E. Reiter
Registration No. 31,192

KILPATRICK TOWNSEND & STOCKTON LLP
1100 Peachtree Street, Suite 2800
Atlanta, GA 30309
Tel: 858-350-6100
Fax: 858-350-6111

Electronic Acknowledgement Receipt

EFS ID:	27279447
Application Number:	14940018
International Application Number:	
Confirmation Number:	6992
Title of Invention:	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME
First Named Inventor/Applicant Name:	Neil M. Cowen
Customer Number:	20350
Filer:	Stephen E. Reiter/William Gorman
Filer Authorized By:	Stephen E. Reiter
Attorney Docket Number:	096593-001000US-0955615
Receipt Date:	20-OCT-2016
Filing Date:	12-NOV-2015
Time Stamp:	18:37:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
------------------------	----

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2016-10-20_Response_Restriction_Requirement_096593-001000US-0955615.pdf	86277	yes	6
			59569f5a9fd24f64eb909853d5bf55e6b5460209		

	Multipart Description/PDF files in .zip description		
	Document Description	Start	End
	Response to Election / Restriction Filed	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	6
Warnings:			
Information:			
Total Files Size (in bytes):		86277	
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>			

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875					Application or Docket Number 14/940,018		Filing Date 11/12/2015		☐ To be Mailed
ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO									
APPLICATION AS FILED – PART I									
(Column 1)		(Column 2)							
FOR		NUMBER FILED		NUMBER EXTRA		RATE (\$)		FEE (\$)	
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A		N/A		N/A			
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))		N/A		N/A		N/A			
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A		N/A		N/A			
TOTAL CLAIMS (37 CFR 1.16(i))		minus 20 =		*		X \$ =			
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =		*		X \$ =			
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).							
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))									
						TOTAL			
* If the difference in column 1 is less than zero, enter "0" in column 2.									
APPLICATION AS AMENDED – PART II									
(Column 1)		(Column 2)		(Column 3)					
AMENDMENT	10/20/2016	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 20	Minus	** 28	= 0	X \$40 =		0	
	Independent (37 CFR 1.16(h))	* 7	Minus	***7	= 0	X \$210 =		0	
	☐ Application Size Fee (37 CFR 1.16(s))								
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE		0	
(Column 1)		(Column 2)		(Column 3)					
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =			
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =			
	☐ Application Size Fee (37 CFR 1.16(s))								
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE			
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.									

LIE
RENEE HAWKINS

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/940,018	11/12/2015	Neil M. Cowen	096593-001000US-0955615	6992
20350 7590 11/16/2016 KILPATRICK TOWNSEND & STOCKTON LLP Mailstop: IP Docketing - 22 1100 Peachtree Street Suite 2800 Atlanta, GA 30309			EXAMINER OH, TAYLOR V	
			ART UNIT 1625	PAPER NUMBER
			NOTIFICATION DATE 11/16/2016	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipefiling@kilpatricktownsend.com
jlhice@kilpatrick.foundationip.com

Office Action Summary	Application No. 14/940,018	Applicant(s) COWEN, NEIL M.	
	Examiner TAYLOR V OH	Art Unit 1625	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 10/20/16.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 1-9, 15 and 19-28 is/are pending in the application.
5a) Of the above claim(s) 1, 20-23 and 26 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☒ Claim(s) 2-9, 15, 19, 24, 25, 27 and 28 is/are rejected.

8) ☒ Claim(s) 15 is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☐ The specification is objected to by the Examiner.

11) ☒ The drawing(s) filed on 11/12/15 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date 1/05/2016.

3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

The Status of Claims:

Claims 1-9,15,19-28 are pending.

Claims 2-9,15,19,24-25,27-28 are rejected.

Claims 1,20-23,26 are withdrawn from consideration.

DETAILED ACTION

1. Claims 2-9,15,19,24-25,27-28 are under consideration in this Office Action.

Priority

2. It is noted that this application claims benefit of 62/080,154(11/14/2014) and claims benefit of 62/138,245(03/25/2015) and claims benefit of 62/170,035(06/02/2015) and claims benefit of 62/221,359(09/21/2015).

Drawings

3. The drawings filed on 11/12/15 are accepted by the examiner.

IDS

4. The IDS filed on 1/05/2016 is reviewed by the examiner.

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Election/Restriction

Applicant's election with traverse of Group IV (claims 2-9,15,19,24-25,27-28) on 10/20/16 is acknowledged.

Claims 1,20-23,26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group I, II,III,V, there being no allowable generic or linking claim.

Applicants argue in the following:

The restriction of claims 1-28 under 35 USC § 121 into five (5) separate groups, is respectfully traversed. It is respectfully submitted that a search of one group would, of necessity, entail a search of one or more of the other groups; in addition, each of the method groups (i.e., Groups I, II, IV and V) contemplates administering to a subject a therapeutically effective amount of a compound selected from a defined group—which defined group is the same for each of the restriction groups). Accordingly, no savings of USPTO resources will be realized by maintaining the requirement for restriction as presently asserted.

Accordingly, reconsideration and withdrawal of the requirement for restriction of claims 1-28 are respectfully requested.

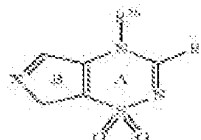
The examiner has noted applicants' argument, but applicants' arguments are not persuasive. However, regardless of how each of the Groups is so closely related to one

and another, there are at least more than two distinct, unrelated, different classes and different subclasses involved in the search of the unrestricted claims. The search is a burden whether or not they are so closely related to their searches. Furthermore, M.P.E.P. Section 808.02 gives legitimate reasons for the Examiner to insist on restriction such as the case of separate classification, which indicates that “each distinct subject has attained recognition in the art as a separate subject for the inventive effort, and also a separate field of search .”

In the instant case, Inventions I and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06).

In the instant case, Invention IV is directed to the method of reducing one or more aggressive behaviors in a subject having Prader –Willi Syndrome(PWS) or Smith-Magenis Syndrome(SMS) comprising administering to the subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of a K_{ATP} channel opener, whereas Invention I is the method of treating a subject having Prader –Willi Syndrome(PWS) or Smith-Magenis Syndrome(SMS) comprising administering to the subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of a K_{ATP} channel opener.

However, Cowen et al (US 2014/0364425) shows the method of treating various diseases such as diabetes, hypertension, dyslipidemia, nonalcoholic steatohepatitis, myocardial infarction and poly-cystic ovarian syndrome by using a K_{ATP} channel opener such as Formula VI as shown below:



Although both inventions have shared the same compound for the K_{ATP} channel opener, Invention I applies the Formula VI for the treatment different from the treatments shown from Cowen et al. So, there is no direct relationship between Inventions I and IV. Therefore, each of them has a different mode of operation, different functions and effects. From this, they are unrelated to each other. Therefore, Group I is not directly related to the Group IV.

The requirement is still deemed proper and is therefore made **FINAL**.

Claim Objections

Claim 15 is objected to because of the following informalities:

In claim 15, the phrase "for 1 one or more years" is recited. This is improper because there are "1" and "one" written twice. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person

Art Unit: 1625

having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating

obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

5. Claims 2-9,15,19,24-25,27-28 are rejected under 35 U.S.C. 103 as being unpatentable over Cotter (US2014/0364367) which has a provisional application No. 61/832,779 filed on Jun. 8, 2013.

Cotter discloses a method of treating Prader Willi Syndrome and a psychotic behavior associated with Prader Willi Syndrome in the followings:

[0003] Given the complexity of PWS, its symptoms are treated with a number of different medications, including human growth hormone (GH), psychiatric/mood stabilizing medications.

(see page 2, a paragraph#0003)

[0010] The inventor has made the surprising discovery that administering a K_{ATP} channel opener (e.g., diazoxide) in combination with other therapies used to treat Prader-Willi Syndrome (PWS) allows the dosages of these other therapies to be reduced relative to the dosages [REDACTED]

(see page 3, a paragraph#0010)

a. Combined treatment with reduced dosage of growth hormone

[0058] The K_{ATP} channel opener may be coadministered with a human growth hormone (GH) to treat PWS. The combination therapy may be used to improve body composition abnormalities and improve linear growth of an infant or child with PWS, or to improve body composition abnormalities in an adult with PWS. The combination therapy may also be used to improve lean body mass, decrease body fat, modulate bone mineral density, or normalize adult height. The therapy may also be used to improve cognition, tone, endurance, stamina, strength, agility, or motor development, or to positively affect nitrogen balance or increase energy expenditure.

[0059] The GH dose may be 0.18-0.3 mg/kg/week, and may be administered as a daily subcutaneous injection. The baseline GH dose may also be at least 0.01, 0.05, 0.1, 0.15, 0.2, 0.3, 0.4, 0.5, 1.0, 1.5, or 2.0 mg/kg/week. The baseline GH dose may also be less than 0.01, 0.05, 0.1, 0.15, 0.2, 0.3, 0.4, 0.5, 1.0, 1.5, or 2.0 mg/kg/week. The GH dose may be adjusted based on the weight of the patient. The dose may also be adjusted based on the patient's lean mass or on insulin growth factor (IGF-1) levels, such that the IGF-1 levels do not exceed 3 standard deviations above the upper limit of normal. The upper limit of normal for IGF-1 levels may be 25-1000 ng/mL, and may be in a range as described in Table 1. (see page 10, paragraphs#0058-0059)

b. Combined treatment with reduced dosage of psychiatric or mood stabilizing drugs

[0063] The K_{ATP} channel opener may be coadministered with a psychiatric or mood stabilizing drug, such as a psychotropic medication, to treat PWS by treating a PWS behavioral symptom. The PWS behavioral symptom may be obsessions, compulsions, addiction, autism or autistic tendencies, anxiety, depression, mood swings, skin picking or psychotic behavior. The psychotropic medication may be a selective serotonin reuptake inhibitor (SSRI), norepinephrine reuptake inhibitor (NRI), noradrenergic and specific serotonergic antidepressant (NaSSA), serotonin-norepinephrine reuptake inhibitor (SNRI), serotonin antagonist and reuptake inhibitor (SARI), norepinephrine-dopamine reuptake inhibitor, selective serotonin reuptake enhancer, norepinephrine-dopamine disinhibitor, tricyclic antidepressant, tetracyclic antidepressant, monoamine oxidase inhibitor (MAOI), N-acetylcysteine, cysteamine, oxytocin, mood stabilizer, anticonvulsant, metabotropic glutamate receptor modulator, typical antipsychotic, or atypical antipsychotic. The SSRI may be citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline. The NRI may be atomoxetine, bupropion, reboxetine, edivoxetine, tapentadol or viloxazine. The NaSSA may be mianserin or mirtazapine. The SNRI may be desvenlafaxine, duloxetine, milnacipran, or venlafaxine. The SARI may be etoperidone, nefazodone, or trazodone. The norepinephrine-dopamine reuptake inhibitor may be bupropion.

Art Unit: 1625

aripiprazole, asenapine, blonanserin, caripramine, clocapramine, clotiapine, clozapine, iloperidone, lurasidone, mosapramine, olanzapine, paliperidone, perospirone, quetiapine, remoxipride, risperidone, serindole, sulpiride, ziprasidone, zotepine, bitopertin (RG1678), cariprazine (RGH-188), LY2140023, pimavanserin (ACP-103), vabicaserin (SCA-136), or ziconapine (Lu 31-130). The baseline psychiatric drug dose may be at least 1, 5, 10, 15, 20, 30, 40, 50, 100, 200, 300, 400, 500, 1000, or 2000 mg. The dose may also be less than 1, 5, 10, 15, 20, 30, 40, 50, 100, 200, 300, 400, 500, 1000, or 2000 mg. The psychiatric drug may be administered once, twice, three times, four times, five times, seven times, eight times, nine times, ten times, eleven times, or twelve times daily. The psychiatric drug may also be administered once every 1, 2, 3, 4, or 5 weeks.

(see pages 11-12, a paragraph#0063)

cation may not be sodium. In solutions suitable for intravenous use, if the cation is sodium, then the anion may not be an anion of diazoxide. If the salt includes an anion of diazoxide and a sodium cation, then the salt may not be in liquid form. The KATP channel opener may be a salt of a compound of one of Formulae I-VIII in which the cation is sodium, potassium, choline or hexamethyl hexamethylene diammonium.

(see page 25, a paragraph#0137)

d. Formulation

[0142] The compositions provided herein may be in the form of capsules, sprinkle formulation, tablets or lozenges formulated in a conventional manner. For example, tablets and capsules for oral administration may contain conventional excipients including, but not limited to, binding agents, fillers, lubricants, disintegrants and wetting agents. Binding agents include, but are not limited to, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch and polyvinylpyrrolidone.

(see page 26, a paragraph#0142)

The instant invention, however, differs from the prior art in that administering the an effective amount of a K_{ATP} channel opener for at least 10 weeks or a year or more and the use of an excipient delaying release of diazoxide are unspecified in the prior art.

With respect to the duration of administering the an effective amount of a K_{ATP} channel opener, the prior art does mention generally that there were no side effects for using diazoxide in the treatment of PWS for 56 weeks (see page 28, a paragraph#0151). Therefore, it is expressly relevant to the claimed invention.

Regarding the use of an excipient delaying release of diazoxide, the prior art is silent about it. Even so, the prior art does offer some guidance as to what kinds of excipients are available for delaying release of diazoxide; for example, it describes gelatin, mucilage of starch , polyvinylpyrrolidone as the binding agents. So, it would have been obvious to the skilled artisan in the art before the effective filing date of the claimed invention to be motivated to use one of the binding agents in the composition in order to develop the delay-release of a formulation containing diazoxide. This is because the skilled artisan in the art would expect such a manipulation to be successful and feasible as guidance shown in the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAYLOR V OH whose telephone number is (571)272-0689. The examiner can normally be reached on 10:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Kosar can be reached on 571-272-0913. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TAYLOR V OH/
Primary Examiner, Art Unit 1625
11/10/16

Notice of References Cited	Application/Control No. 14/940,018	Applicant(s)/Patent Under Reexamination COWEN, NEIL M.	
	Examiner TAYLOR V OH	Art Unit 1625	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2014/0364367 A1	12-2014	Cotter; Sara Paige	A61K38/11	514/11.4
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

WEST Search History for Application 14940018

Creation Date: 2016111013:45

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
(aggressive or psychotic) and behavior	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	42652	ADJ	YES		11-10-2016
((aggressive or psychotic) and behavior) and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	4353	ADJ	YES		11-10-2016
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms)) and diazoxide	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	390	ADJ	YES		11-10-2016
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide) and katp channel opener	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	10	ADJ	YES		11-10-2016
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide and katp channel opener) and human growth hormone	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	4	ADJ	YES		11-10-2016
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms) and	PGPB, USPT, USOC,	3	ADJ	YES		11-10-2016

diazoxide and katp channel opener and human growth hormone) and choline	EPAB, JPAB, DWPI, TDBD, FPRS					
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide and katp channel opener and human growth hormone and choline) and igf\$2	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	3	ADJ	YES		11-10-2016
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide) and (514/\$.ccls. or (a61k31/\$ or a61k9/\$ or a61k45/\$ or a61k38/\$).cpc.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	299	ADJ	YES		11-10-2016
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide and (514/\$.ccls. or (a61k31/\$ or a61k9/\$ or a61k45/\$ or a61k38/\$).cpc.)) and katp and channel opener	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	10	ADJ	YES		11-10-2016
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide) and (514/\$.ccls. or (a61k31/\$ or a61k9/\$ or a61k45/\$ or a61k38/\$ or a61k2300/\$).cpc.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	299	ADJ	YES		11-10-2016
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide and (514/\$.ccls. or (a61k31/\$ or a61k9/\$ or a61k45/\$ or a61k38/\$ or a61k2300/\$).cpc.)) and katp and channel opener	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	10	ADJ	YES		11-10-2016
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide and katp channel opener and human growth hormone and choline) and igf\$2 and choline	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	3	ADJ	YES		11-10-2016

Search Notes 	Application/Control No. 14940018	Applicant(s)/Patent Under Reexamination COWEN, NEIL M.
	Examiner T.VICTOR OH	Art Unit 1625

CPC- SEARCHED		
Symbol	Date	Examiner
A61K31/549,155,137,551;A61K9/5026,2054,0004,5042,5047,00;A61K45/06	11/10/16	t.o.
A61K38/27	11/10/16	t.o.

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner
A61K31/549; A61K31/155; A61K31/551;A61K61/137;A61K38/27	11/10/16	t.o.
A61K2300/00; A61K2300/00; A61K2300/00; A61K2300/00;A61K2300/00	11/10/16	t.o.

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	5.1,11.4,223.2,223.5	11/10/16	t.o.

SEARCH NOTES		
Search Notes	Date	Examiner
west search done. p. 2	11/10/16	t.o.
inventor's name search done. p. 1	11/10/16	t.o.
Scifinder search done.p. 3	11/10/16	t.o.

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

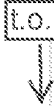
	/T.O./ Primary Examiner.Art Unit 1625
--	--

PALM Resource Center

PALM Explorer

PALM

General Information
Employee Locator
Examiner Docket
Examiner Reports
Count Calculator
Workflow Posting
PCT Transmission Report
IDS Flag Clearance
Bib Data Sheet Maint
Transfer Inquiry
TSS Activity Record
Application Information
Search
Fees
Reference
File/Box Management
Dispatch and Receive



Inventor Information for 14/940018

Inventor Name	City	Sta
COWEN, NEIL M.	CARLSBAD	CA
Appin Info	Contents	Petition Info
Atty/Agent Info	Continuity Data	Foreign Data
Inventors	Applicants	

Search Another: Application # or Patent # or International Reg
PCT / / or PG PUBS #
Attorney Docket #
Bar Code #

To Go BACK Use BACK Button on Your BROWSER Tool Bar
Back to [PALM ASSIGNMENT](#) | [OASIS](#) | Home page

t.o.
11/10/16

Doc code: IDS

PTO/SB/08a (01-10)

Doc description: Information Disclosure Statement (IDS) Field

Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		14/940,018	
	Filing Date		November 12, 2015	
	First Named Inventor		Neil M. Cowen	
	Art Unit		1629	
	Examiner Name		Not Yet Assigned	
	Attorney Docket Number		096593-001000US-0955615	

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/T.V.O/	1.	2,986,573		05-30-1961	Topliss, et al.	
/T.V.O/	2.	4,880,830		11-14-1989	Rhodes, Alan	
/T.V.O/	3.	5,284,845	A	02-08-1994	Paulsen	
/T.V.O/	4.	5,399,359		03-21-1995	Baichwal, Anand R.	
/T.V.O/	5.	5,415,871		05-16-1995	Pankhania, et al.	
/T.V.O/	6.	5,629,045		05-13-1997	Veech, et al.	
/T.V.O/	7.	6,022,562		02-08-2000	Autant, et al.	
/T.V.O/	8.	6,197,765		03-06-2001	Vardi, et al.	

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/T.V.O/	9.	2002/0035106	A1	03-21-2002	Hansen, et al.	
/T.V.O/	10.	2003/0035106	A1	02-20-2003	Yeh, et al.	
/T.V.O/	11.	2004/0204472	A1	10-14-2004	Briggs, et al.	

FOREIGN PATENT DOCUMENTS							
Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
/T.V.O/	12.	1998/10786	WO	A2	03-19-1998	Cohen, Yarom	

Doc code: IDS

PTO/SB/08a (01-10)

Doc description: Information Disclosure Statement (IDS) Field

Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		14/940,018
	Filing Date		November 12, 2015
	First Named Inventor	Neil M. Cowen	
	Art Unit	1629	
	Examiner Name	Not Yet Assigned	
	Attorney Docket Number	096593-001000US-0955615	

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
/T.V.O./	13.	AGUILAR-BRYAN, et al., Toward Understanding the Assembly and Structure of KATP Channels, Physiological Review, 78(1), 227-245 (1998).	
/T.V.O./	14.	AIZAWA, et al., Prophylaxis of genetically determined diabetes by diazoxide: a study in rat model of naturally occurring obese diabetes. J of Pharma Exp Ther 275(1):194-199 (1995). Abstract Only.	
/T.V.O./	15.	ALEMZADEH, et al., Antiobesity effect of diazoxide in obese Zucker rats. Metabolism: Clinical and Experimental, 45(3):334-341 (1996). Abstract only.	
/T.V.O./	16.	ALEMZADEH, et al., Beneficial Effect of Diazoxide in Obese Hyperinsulinemic Adults, J. Clinical Endocrinology and Metabolism, 83:1911-1915 (1998).	
/T.V.O./	17.	ALEMZADEH, et al., Diazoxide enhances adipose tissue protein kinase B activation and glucose transporter-4 expression in obese Zucker rats, Med Sci Monit, 2004; 10(3): BR53-60.	
/T.V.O./	18.	ALEMZADEH, et al., Effect of Diazoxide on Brian Capillary Insulin Receptor Binding and Food Intake in Hyperphagic Obese Zucker Rats. Endocrinology, 140:3197-3202 (1999).	
/T.V.O./	19.	ALEMZADEH, et al., Modulation of Adipoinular Axis in Prediabetic Zucker Diabetic Fatty Rats by Diazoxide. Endocrinology 145(12):5476-5484 (2004).	
/T.V.O./	20.	ALEMZADEH, R., et al., Modification of insulin resistance by diazoxide in obese Zucker rats. Endocrinology 133:705-712 (1993). Abstract Only.	
/T.V.O./	21.	BABENKO, et al., Pharmacology of Sulfonylurea Receptors, J. Biol. Chem., 275(2), 717-720 (2000).	

Doc code: IDS

PTO/SB/08a (01-10)

Doc description: Information Disclosure Statement (IDS) Field

Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		14/940,018
	Filing Date		November 12, 2015
	First Named Inventor	Neil M. Cowen	
	Art Unit	1629	
	Examiner Name	Not Yet Assigned	
	Attorney Docket Number	096593-001000US-0955615	

/T.V.O/	22.	BERTOLINO, et al., Receptors and Channels, 1, 267-278 (1993). Abstract Only.	
/T.V.O/	23.	BJÖRK, et al., Induction of β -Cell Rest in Type 1 Diabetes: Studies on the effects of octreotide and diazoxide, Diabetes Care 21(3):427-430 (1998). Abstract Only.	
/T.V.O/	24.	BJÖRKLUND, et al., Glucose-Induced Ca^{2+} Abnormalities in Human Pancreatic Islets, Important Role of Overstimulation, Diabetes, 49:1840-1848 (2000).	
/T.V.O/	25.	BUTLER, et al., Energy expenditure and physical activity in Prader-Willi syndrome: comparison with obese subjects, Am. J. Med Genet A 143A(5):449-459 (2007). Abstract Only.	
/T.V.O/	26.	COSGROVE, BPDZ 154 Activates Adenosine 5'-Triphosphate-Sensitive Potassium ChannelsL <i>In Vitro</i> Studies Using Rodent Insulin-Secreting Cells and Islets Isolated from Patients with Hyperinsulinism, J. Clin. Endocrinol. Metab., 87, 4860-4868 (2002).	
/T.V.O/	27.	DABROWSKI, The Novel Diazoxide Analog 3-Isopropylamino-7-Methoxy-H01,2,4-Benzothiadiazine 1,1-Dioxide Is a Selective Kir6.2/SUR1 Channel Opener, Diabetes, 51, 1896-1906 (2002).	
/T.V.O/	28.	De TULLIO, et al., Toward Tissue-Selective Pancreatic B-Cells K(ATP) Channel Openers Belonging to 3-Alkylamino-7-halo-4H-1,2,4-benzothiadiazine 1, 1-Dioxides, J. Med. Chem., 46:3342-3353 (2003.) Abstract only.	
/T.V.O/	29.	Calesnick et al., Importance of Dissolution Rates in Producing Effective Diazoxide Blood Levels in Man, J. Pharm. Sci. 54:1277-1280 (1965). Abstract Only.	
/T.V.O/	30.	GULDSTRAND, et al., Improved beta cell function after short-term treatment with diazoxide in obese subjects with type 2 diabetes, Diabetes and Metabolism 28:448-456 (2002). Abstract only.	
/T.V.O/	31.	RODERICK, F.A., et al., "Cardiovascular and Metabolic Risk Profile and Acylation-Stimulating Protein Levels in Children with Prader-Willi Syndrome and Effects of Growth Hormone Treatment." J Clin Endocrinol Metab 95(4):1758-1766 (2010).	
/T.V.O/	32.	Marugo, et al., <i>Boll Spec It Biol Sper</i> 53:1860-1866 (1977).	

Doc code: IDS

PTO/SB/08a (01-10)

Doc description: Information Disclosure Statement (IDS) Field

Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		14/940,018
	Filing Date		November 12, 2015
	First Named Inventor	Neil M. Cowen	
	Art Unit	1629	
	Examiner Name	Not Yet Assigned	
	Attorney Docket Number	096593-001000US-0955615	

/T.V.O/	33.	ORTQVIST, et al., Temporary Preservation of β -Cell Function by Diazoxide Treatment in Childhood Type 1 Diabetes, Diabetes Care, 27(9):2191-2197 (2004).	
/T.V.O/	34.	OUEDRAOGO, 2-Alkyl-3-Alkylamino-2H-Benzo- and Pyridothiadiazine 1,1-Dioxides: From K ⁺ ATP Channel Openers to Ca ⁺⁺ Channel Blockers, Biol. Chem., 383, 1759-1768 (2002). Abstract Only.	
/T.V.O/	35.	QVIGSTAD, et al., Nine weeks of bedtime diazoxide is well tolerated and improves β -cell function in subjects with Type 2 diabetes, Diabetic Medicine 21:73-76 (2004). Abstract Only.	
/T.V.O/	36.	RATZMANN, et al., Int J. Obesity 7(5):453-458 (1983). Abstract Only.	
/T.V.O/	37.	REDDY, et al., Once-Daily Sustained-Release Matrix Tablets of Nicorandil: Formulation and In Vitro Evaluation, AAPS PharmSciTech 2003; 4(4) 1-98, 9 (2003).	
/T.V.O/	38.	SCHOU, et al., Synthesis and pharmacological evaluation of 4H-1-benzothiazine-2-carbonitrile 1,1-dioxide and N-(2-cyanomethylsulfonylphenyl)acylamide derivatives as potential activators of ATP sensitive potassium channels, Bioorg. Med. Chem., 13, 141-155 (2005). Abstract Only.	
/T.V.O/	39.	SCHWANSTECHER, et al., Potassium Channel openers require ATP to bind to and act through sulfonylurea receptors, EMBO, 17,5529-5535 (1998).	
/T.V.O/	40.	STANRIDGE, et al., Diazoxide down-regulates leptin and lipid metabolizing enzymes in adipose tissue of Zucker rats. FASEB J 14:455-460 (2000).	
/T.V.O/	41.	SURWIT, et al., Diazoxide Restores β 3-Adrenergic Receptor Function in Diet-Induced Obesity and Diabetes, Endocrinology 141:3630-3637 (2000).	
/T.V.O/	42.	TRUBE, et al., Opposite effects of tolbutamide and diazoxide on the ATP-dependent K ⁺ channel in mouse pancreatic β -cells, Pfluegers Arch kEur J Physiol, 407, 493-99 (1986). ABSTRACT ONLY.	

Doc code: IDS

PTO/SB/08a (01-10)

Doc description: Information Disclosure Statement (IDS) Field

Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		14/940,018
	Filing Date		November 12, 2015
	First Named Inventor	Neil M. Cowen	
	Art Unit	1629	
	Examiner Name	Not Yet Assigned	
	Attorney Docket Number	096593-001000US-0955615	

/T.V.O/	43.	Van MIL, et al., Activity related energy expenditure in children and adolescents with Prader-Willi syndrome, Int. J. Obes. 24(4), 429-434 (2000).	
/T.V.O/	44.	WIGLAND, et al., Downregulation of Insulin Receptors in Obese Man, Diabetes 28(4):287-291 (1979). Abstract Only.	

EXAMINER SIGNATURE			
Examiner Signature	/TAYLOR V OH/	Date Considered	11/10/2016
<p>*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.</p>			
<p>¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.</p>			

Doc code: IDS

Doc description: Information Disclosure Statement (IDS) Field

PTO/SB/08a (01-10)

Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	14/940,018
	Filing Date	November 12, 2015
	First Named Inventor	Neil M. Cowen
	Art Unit	1629
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	096593-001000US-0955615

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Stephen E. Reiter/	Date (YYYY-MM-DD)	2016-01-05
Name/Print	Stephen E. Reiter	Registration Number	31192

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

<i>Index of Claims</i> 	Application/Control No. 14940018	Applicant(s)/Patent Under Reexamination COWEN, NEIL M.
	Examiner VICTOR OH	Art Unit 1625

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant				☐ CPA		☐ T.D.		☐ R.1.47	
CLAIM		DATE							
Final	Original	10/06/2016	11/10/2016						
	1	÷	N						
	2	÷	✓						
	3	÷	✓						
	4	÷	✓						
	5	÷	✓						
	6	÷	✓						
	7	÷	✓						
	8	÷	✓						
	9	÷	✓						
	15	÷	✓						
	19	÷	✓						
	20	÷	N						
	21	÷	N						
	22	÷	N						
	23	÷	N						
	24	÷	✓						
	25	÷	✓						
	26	÷	N						
	27	÷	✓						
	28	÷	✓						

Task History

Task Began November 09, 2016 12:05 PM

Explore references by research topic: katp channel opener

Research Topic: katp channel opener
Result Count: 2

Candidates Selected (ID 1)

865 references were found containing "katp channel opener" as entered.
Automatically removed 588 duplicate MEDLINE answer(s)
2903 references were found containing the concept "katp channel opener".
Automatically removed 588 duplicate MEDLINE answer(s)

Answer Type: References
Result Count: 2315

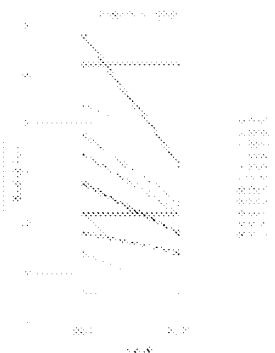
Refine by research topic (ID 3)

Research Topic: aggressive
From ID: 1
Answer Type: References
Result Count: 4

1. Methods for treating subjects with prader-willi syndrome or smith-magenis syndrome

By Cowen, Neil M.

From PCT Int. Appl. (2016), WO 2016077629 A1 20160519, Language: English, Database: CAPLUS



Provided are immediate or prolonged administration of certain potassium ATP (K_{ATP}) channel openers, optionally in combination with growth hormone, to a subject to achieve novel pharmacodynamic, pharmacokinetic, therapeutic, physiologic, metabolic and compositional outcomes in the treatment of diseases or conditions involving K_{ATP} channels. Also provided are pharmaceutical formulations, methods of administration and dosing of K_{ATP} channel openers that achieve these outcomes and reduce the incidence of adverse effects in treated individuals. Further provided are methods of co-administering K_{ATP} channel openers with other drugs (e.g., in combination with growth hormone) to treat diseases of humans and animals (e.g., Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like).

~0 Citings

0 Tags

0 Comments

Copyright © 2016 American Chemical Society (ACS). All Rights Reserved.

2. Dose-related shortening of ventricular tachycardia cycle length after administration of the K_{ATP} channel opener bimakalim in a 4-day-old chronic infarct anesthetized pig model

By Aidonidis, Isaac; Poyatzi, Aphrodite; Stamatiou, Georgia; Lymberi, Maria; Stamatoyannis, Nikolaos; Molyvdas, Paschalis-Adam

From Journal of Cardiovascular Pharmacology and Therapeutics (2009), 14(3), 222-230. Language: English, Database: CAPLUS, DOI:10.1177/1074248409338929

Potassium channel openers are known to act on potassium ATP-dependent channels in cardiac tissue. Such agents may exacerbate acceleration of acute ischemia-induced ventricular repolarization and aggravate arrhythmias. To test whether activation of K_{ATP} channels during the healing period of myocardial infarction (MI) can still influence the electrophysiological properties and the type of inducible arrhythmias, we investigated the effects of bimakalim (BIM) on sustained ventricular tachycardia (VT) 4 days after ligation of the left anterior descending (LAD) coronary artery in pigs. Programmed stimulation was performed to elicit VT prior to and after i.v. BIM. Combination monophasic action potential (MAP)/PACING catheters were used to enable simultaneous ventricular MAP recording and pacing. Ventricular effective refractory period (ERP) and MAP duration detd. at 50% and 90% repolarization were measured prior to and after BIM. After completion of baseline measurements, BIM was consecutively given at 0.5, 1, and 3 $\mu\text{g/kg}$ bolus followed by 0.025, 0.05, and 0.1 $\mu\text{g/kg}$ per min maintenance infusion, resp. From a total of 23 pigs subjected to LAD ligation, 4 animals succumbed to infarction and the remaining 19 animals were studied by programmed stimulation. Only animals that exhibited reproducible and hemodynamically stable monomorphic VTs during control stimulation were selected for evaluation ($n = 14$). After the first, second, and third dose of BIM, the mean VT rate was increased by 6%, 14% ($P < .01$), and 47% ($P < .001$) compared to control values, resp. Ventricular ERP and repolarization were significantly shortened only by the second and third dose of BIM. Of 14 pigs receiving the highest BIM dosage, 3 revealed polymorphic VTs degenerating into ventricular fibrillation (VF). Our data suggest that high BIM doses may lead to faster and more aggressive pacing-induced reentrant VTs after subacute MI. This is consistent with the drug-induced acceleration of ventricular repolarization with shortening of MAP duration and refractoriness.

~1 Citing

0 Tags

0 Comments

Copyright © 2016 American Chemical Society (ACS). All Rights Reserved.

3. Cardioprotection by opening of the K_{ATP} channel in unstable angina: Is this a clinical manifestation of myocardial preconditioning? Results of a randomized study with nicorandil

By Patel, D. J.; Purcell, H. J.; Fox, K. M.

From European Heart Journal (1999), 20(1), 51-57. Language: English, Database: CAPLUS, DOI:10.1053/euhj.1998.1354

Aims To assess the anti-ischemic and anti-arrhythmic effects and overall safety of nicorandil, an ATP sensitive potassium (K⁺) channel opener, with 'cardioprotective' effects, in patients with unstable angina. **Methods** In a multicenter, randomized, double-blind, parallel-group, placebo-controlled study, oral nicorandil 20 mg twice daily or a matching placebo was administered for a min. of 48 h to patients admitted with unstable angina. Treatment was standardized to include, where tolerated, oral aspirin, a beta-blocker and diltiazem. Continuous Holter ECG monitoring was performed for 48 h to assess the frequency and duration of transient myocardial ischemia and any tachyarrhythmia, as the predefined end-points of the study. A pain chart recorded the incidence and severity of chest pain throughout the study period. Patients with myocardial infarction identified retrospectively from troponin-T anal. were excluded. Results Two hundred and forty-five patients were recruited into the study. Forty-three patients were excluded with an index diagnosis of myocardial infarction, two were not randomized and 12 had unsatisfactory tape data. In the remaining 188 patients, six out of 89 patients (6.7%) on nicorandil experienced an arrhythmia, compared with 17 out of 99 patients (17.2%) on placebo (P=0.04). Three nicorandil patients experienced three runs of non-sustained ventricular tachycardia compared to 31 runs in 10 patients on placebo (P=0.087 patients; P<0.0001 runs). Three nicorandil patients had four runs of supraventricular tachycardia, compared to 15 runs in nine patients on placebo (P=0.14 patients; P=0.017 runs). Eleven (12.4%) patients on nicorandil had 37 episodes of transient myocardial ischemia (mostly silent) compared with 74 episodes in 21 (21.2%) patients on placebo (P=0.12 patients; P=0.0028 episodes). In the overall safety anal., which included all patients who received at least one dose of study medication, there were no significant differences in the rates of myocardial infarction or death between the nicorandil or placebo-treated groups. **Conclusions** Nicorandil, added to aggressive anti-anginal treatment for unstable angina, reduces transient myocardial ischemia, non-sustained ventricular, and supraventricular arrhythmia compared to placebo. The anti-arrhythmic activity with nicorandil is probably a secondary effect resulting from its anti-ischemic action and we suggest that this may be related to its effect on the ATP sensitive potassium channel causing pharmacol. preconditioning.

~81 Citings

0 Tags

0 Comments

Copyright © 2016 American Chemical Society (ACS). All Rights Reserved.

4. Effects of nicorandil on experimentally induced gastric ulcers in rats: a possible role of K_{ATP} channels

By Sakai, Kazushige; Akima, Michitaka; Katsuyama, Iwao

From Japanese Journal of Pharmacology (1999), 79(1), 51-57. Language: English, Database: CAPLUS, DOI:10.1254/jjp.79.51

The anti-ulcer effects of nicorandil [N-(2-hydroxyethyl)nicotinamide nitrate ester] were examd. on water-immersion plus restraint stress-induced and aspirin-induced gastric ulcers in rats, compared with those of cimetidine. Nicorandil (3 and 10 mg/kg) given orally to rats dose-dependently inhibited the development of acid-related damage (water-immersion- and aspirin-induced gastric lesions) in the models. Cimetidine (50 mg/kg, p.o.) also had anti-ulcer effects in the same models. However, in the presence of glibenclamide (20 mg/kg, i.v.), an antagonist of K_{ATP} channels, nicorandil did not inhibit the formation of gastric lesions. Nicorandil (10 mg/kg) given intraduodenally (i.d.), like cimetidine (50 mg/kg), significantly reduced the vol. of the gastric content, total acidity and total acid output in the pylorus ligation model. Glibenclamide reversed the changes caused by i.d. nicorandil. I.v. infusion of nicorandil (20 µg/kg per min) significantly increased gastric mucosal blood flow, without affecting blood pressure and heart rate, but the increase in the blood flow was not obsd. after i.v. treatment with glibenclamide (20 mg/kg). These results indicate that nicorandil administered orally to rats produces the anti-ulcer effect by reducing the aggressive factors and by enhancing the defensive process in the mucosa through its K_{ATP} channel-opening property.

~8 Citings

0 Tags

0 Comments

Copyright © 2016 American Chemical Society (ACS). All Rights Reserved.

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
on November 30, 2016.

PATENT
Attorney Docket No.: 096593-001000US-0955615

KILPATRICK TOWNSEND & STOCKTON LLP

By: /William H. Gorman/
William H. Gorman

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Neil M. Cowen

Application No.: 14/940,018

Filed: November 12, 2015

For: METHODS FOR TREATING

SUBJECTS WITH PRADER-WILLI

SYNDROME OR SMITH-MAGENIS

SYNDROME

Customer No.: 20350

Confirmation No.: 6992

Examiner: Taylor V. Oh

Technology Center/Art Unit: 1625

AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Responsive to the Office Action mailed November 16, 2016, please consider the following amendments and remarks:

Amendments to the Claims are reflected in the **Listing of Claims**, which begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

Amendments to the Claims/Listing of Claims

Please amend claim 15, and add new claim 29 as follows. This listing of claims will replace all prior versions, and listings of claims in the application:

1. (Withdrawn) A method of treating a subject having Prader-Willi Syndrome (PWS) or Smith–Magenis syndrome (SMS), said method comprising administering to said subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of a K_{ATP} channel opener.
2. (Previously presented) The method of claim 24 wherein said K_{ATP} channel opener is diazoxide or a pharmaceutically acceptable salt thereof.
3. (Original) The method of claim 2 wherein the pharmaceutically acceptable salt is diazoxide choline.
4. (Original) The method of claim 2 wherein said diazoxide or a pharmaceutically acceptable salt thereof is administered orally.
5. (Original) The method of claim 2 wherein the pharmaceutical formulation includes at least one excipient which affects the rate of release of diazoxide or a pharmaceutically acceptable salt thereof.
6. (Original) The method of claim 5 wherein the pharmaceutical formulation includes at least one excipient that delays release of diazoxide or a pharmaceutically acceptable salt thereof.
7. (Previously presented) The method of claim 24 wherein the formulation further comprises at least one other active ingredient.
8. (Previously presented) The method of claim 24 further comprising administering human growth hormone to the subject.
9. (Original) The method of claim 8 wherein said human growth hormone is administered by injection.

10. – 14. (Cancelled)

15. (Currently amended) The method of claim 24 wherein said administering is carried out for **[[1]]** one or more years.

16. – 18. (Cancelled)

19. (Previously presented) The method of claim 24, wherein the circulating concentration of IGF-1 is not increased.

20. (Withdrawn) A method of increasing the lean body mass of a subject having Prader-Willi Syndrome, wherein said subject is already being treated by administration thereto of growth hormone, said method comprising co-administering to said subject an effective amount of a K_{ATP} channel opener in addition to said growth hormone.

21. (Withdrawn) A method of increasing the lean body mass of a subject having Prader-Willi Syndrome, wherein said subject is already being treated by administration thereto of an effective amount of a K_{ATP} channel opener, said method comprising co-administering to said subject an effective amount of growth hormone in addition to said K_{ATP} channel opener.

22. (Withdrawn) A method of increasing lower limb muscle mass of a subject having Smith–Magenis syndrome (SMS), said method comprising administering to said subject an effective amount of a K_{ATP} channel opener.

23. (Withdrawn) A kit comprising:
a unit dose of a K_{ATP} channel opener, and
a unit dose of growth hormone.

24. (Original) A method of reducing one or more aggressive behaviors in a subject having Prader-Willi syndrome (PWS) or Smith–Magenis syndrome (SMS), the method comprising administering to said subject for at least 10 weeks an effective amount of a K_{ATP} channel opener, wherein administration reduces one or more aggressive behaviors in the subject.

25. (Original) The method of claim 24 in which a second therapeutic product is administered, wherein the second product is intended to further reduce the one or more aggressive behaviors.

26. (Withdrawn) A method of reducing hyperghrelinemia in a subject having Prader-Willi syndrome (PWS) or Smith–Magenis syndrome (SMS), the method comprising administering to said subject for at least 10 weeks an effective amount of a K_{ATP} channel opener, wherein administration reduces one or more aggressive behaviors in the subject.

27. (Previously presented) The method of claim 24 wherein the pharmaceutical formulation is administered twice per day.

28. (Previously presented) The method of claim 24 wherein the pharmaceutical formulation is administered once per day.

29. (New) A method of reducing one or more aggressive behaviors in a subject having Prader-Willi syndrome (PWS) or Smith–Magenis syndrome (SMS), the method comprising administering to said subject for at least 10 weeks an effective amount of formulation consisting essentially of a K_{ATP} channel opener, wherein administration reduces one or more aggressive behaviors in the subject.

REMARKS

By the present communication, claim 15 has been amended, and new claim 29 has been added. No new matter is introduced by the subject amendments as the new and amended claim language is fully supported by the specification and original claims.

Upon entry of the present amendment, claims 1-9, 15 and 19-29 will be pending in this application, with claims 2-9, 15, 19, 24, 25 and 27-29 under active consideration, and non-elected claims 1, 20-23 and 26 withdrawn from consideration subject to a request for rejoinder thereof.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

The objection to claim 15 for alleged informalities therein has been rendered moot by the amendments submitted herewith.

The rejection of claims 2-9, 15, 19, 24-25 and 27-28 under 35 USC § 103 as allegedly being unpatentable over Cotter (US2014/0364367), is respectfully traversed.

Applicant's invention, as defined, for example, by claim 24, distinguishes over Cotter at least by requiring a method of reducing one or more aggressive behaviors in a subject having Prader-Willi syndrome (PWS) or Smith-Magenis syndrome (SMS), the method comprising administering to said subject for at least 10 weeks an effective amount of a K_{ATP} channel opener, wherein administration reduces one or more aggressive behaviors in the subject.

Cotter does not disclose or suggest treating such a patient population. Indeed, as acknowledged by the Examiner, "[t]he instant invention, however, differs from the prior art in that administering the an effective amount of a K_{ATP} channel opener for at least 10 weeks or a year or more and the use of an excipient delaying release of diazoxide are unspecified in the prior art" (see lines 1-3 at p 10 of the Office Action). Moreover, the art does not contemplate

reducing one or more aggressive behaviors in a subject having Prader-Willi syndrome (PWS) or Smith–Magenis syndrome (SMS), as required by the present claims.

Applicant's invention, as defined, for example, by claim 29, further distinguishes over Cotter at least by requiring a method of reducing one or more aggressive behaviors in a subject having Prader-Willi syndrome (PWS) or Smith–Magenis syndrome (SMS), the method comprising administering to said subject for at least 10 weeks an effective amount of formulation consisting essentially of a K_{ATP} channel opener, wherein administration reduces one or more aggressive behaviors in the subject. Only Applicant has recognized that K_{ATP} channel openers alone (i.e., with no other actives) are effective for the treatment of the defined patient population, i.e., aggressive behaviors in subjects having PWS or SMS.

In contrast, Cotter requires the use of a cocktail of active ingredients for the treatment of PWS—“[t]he inventor has made the surprising discovery that administering a K_{ATP} channel opener (e.g., diazoxide) in combination with other therapies used to treat Prader-Willi syndrome (PWS) allows the dosages of these other therapies to be reduced relative to the dosages. . . .” (emphasis added; see lines 9-11 at page 7 of the Office Action). There is no recognition in the art, however, that administration of K_{ATP} channel openers alone (i.e., with no other actives) is effective for the treatment of the defined patient population, i.e., aggressive behaviors in subjects having PWS or SMS.

Accordingly, reconsideration and withdrawal of the rejection under 35 USC § 103 are respectfully requested.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Except for the issue fees payable under 37 C.F.R. § 1.18, the Director is authorized to charge any additional fees during pendency of this application, including any required extension of time fees, or credit any overpayment to Deposit Account Number 20-1430. This paragraph is

intended to be a constructive petition for extension of time in accordance with 37 C.F.R. § 1.136(a)(3).

In the event any issues remain to be resolved in view of this communication, the Examiner is invited to contact the undersigned at 858 350 3862 or sreiter@kilpatricktownsend.com so that a prompt disposition of this application can be achieved.

Respectfully submitted,

/Stephen E. Reiter/
Stephen E. Reiter
Registration No. 31,192

KILPATRICK TOWNSEND & STOCKTON LLP
1100 Peachtree Street, Suite 2800
Atlanta, GA 30309
Tel: 858-350-6100
Fax: 858-350-6111

Electronic Acknowledgement Receipt

EFS ID:	27658319
Application Number:	14940018
International Application Number:	
Confirmation Number:	6992
Title of Invention:	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME
First Named Inventor/Applicant Name:	Neil M. Cowen
Customer Number:	20350
Filer:	Stephen E. Reiter/William Gorman
Filer Authorized By:	Stephen E. Reiter
Attorney Docket Number:	096593-001000US-0955615
Receipt Date:	30-NOV-2016
Filing Date:	12-NOV-2015
Time Stamp:	18:59:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
------------------------	----

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2016-11-30_Amendment_096593-001000US-0955615.pdf	89054	yes	7
			a020b6ea397a918a49c4fc2f2fe093fdb6393891		

	Multipart Description/PDF files in .zip description		
	Document Description	Start	End
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	7
Warnings:			
Information:			
Total Files Size (in bytes):		89054	
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>			

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 14/940,018		Filing Date 11/12/2015		☐ To be Mailed		
ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO										
APPLICATION AS FILED – PART I										
(Column 1)		(Column 2)								
FOR	NUMBER FILED	NUMBER EXTRA			RATE (\$)	FEE (\$)				
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A			N/A	140				
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A			N/A					
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A			N/A					
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*			X \$	=				
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*			X \$	=				
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))			If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).							
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))										
* If the difference in column 1 is less than zero, enter "0" in column 2.					TOTAL	140				
APPLICATION AS AMENDED – PART II										
(Column 1)		(Column 2)		(Column 3)						
AMENDMENT	11/30/2016	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)			
	Total (37 CFR 1.16(i))	* 21	Minus	** 28	= 0	x \$40 =	0			
	Independent (37 CFR 1.16(h))	* 8	Minus	***7	= 1	x \$210 =	210			
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE	210			
(Column 1)		(Column 2)		(Column 3)						
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)			
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$	=			
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$	=			
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE				
<p>* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.</p> <p>** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".</p> <p>*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".</p> <p>The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.</p>										

LIE
GWENDOLYN MYERS

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

20350 7590 02/01/2017
KILPATRICK TOWNSEND & STOCKTON LLP
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

EXAMINER

OH, TAYLOR V

ART UNIT

PAPER NUMBER

1625

DATE MAILED: 02/01/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/940,018	11/12/2015	Neil M. Cowen	096593-001000US-0955615	6992

TITLE OF INVENTION: METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	05/01/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

20350 7590 02/01/2017
KILPATRICK TOWNSEND & STOCKTON LLP
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/940,018	11/12/2015	Neil M. Cowen	096593-001000US-0955615	6992

TITLE OF INVENTION: METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	05/01/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
OH, TAYLOR V	1625	514-223500

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

- (1) The names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____
- (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____
- 3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
- ☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/940,018	11/12/2015	Neil M. Cowen	096593-001000US-0955615	6992

20350 7590 02/01/2017
KILPATRICK TOWNSEND & STOCKTON LLP
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

EXAMINER

OH, TAYLOR V

ART UNIT	PAPER NUMBER
----------	--------------

1625

DATE MAILED: 02/01/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 14/940,018	Applicant(s) COWEN, NEIL M.	
	Examiner TAYLOR V OH	Art Unit 1625	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 11/30/16.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 3-9,15,19,24,25,28 and 29. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some *c) ☐ None of the:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|---|--|
| 1. ☐ Notice of References Cited (PTO-892) | 5. ☒ Examiner's Amendment/Comment |
| 2. ☐ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date _____ | 6. ☒ Examiner's Statement of Reasons for Allowance |
| 3. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 7. ☐ Other _____. |
| 4. ☒ Interview Summary (PTO-413),
Paper No./Mail Date <u>1/25/17</u> . | |

--	--

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Examiner's Amendment & Reasons of Allowance

The Status of Claims

Claims 3-9,15,19,24-25,28-29 are pending.

Claims 3-9,15,19,24-25,28-29 are allowed.

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with an attorney of record, Stephen E. Reiter on 1/25/17.

I. The application has been amended as follows:

Claims 1-2, 20-23 and 26 are cancelled.

In claims 3-5, line 1 on page 2 (amendment dated on 11/30/16):

The number " -- 2 --" after the term " claim " is replaced with the number " 24 ".

In claim 24, lines 3-4 on page 3 (amendment dated on 11/30/16):

The terms "--a K_{ATP} channel opener --" after the term "of " is replaced with another phrase "diazoxide or a pharmaceutically acceptable salt thereof ".

In claim 29, line 4 on page 4 (amendment dated on 11/30/16):

The terms "--a K_{ATP} channel opener --" after the term "of " is replaced with another phrase "diazoxide or a pharmaceutically acceptable salt thereof ".

I. The following is an examiner's statement of reasons for allowance:

- The rejection of Claims 2-9,15,19,24-25,27-28 are rejected under 35 U.S.C. 103 as being unpatentable over Cotter (US2014/0364367) which has a provisional application No. 61/832,779 filed on Jun. 8, 2013 is withdrawn due to the modification of the claim and applicants' convincing arguments.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning the communication after allowance such as sending all post-allowance correspondence should be directed to “ Box Issue Fee” or faxed directly to PUBS at 703-305-8755. This will expedite the process of these papers.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/TAYLOR V OH/

Primary Examiner, Art Unit 1625

1/25/17

Examiner-Initiated Interview Summary	Application No. 14/940,018	Applicant(s) COWEN, NEIL M.	
	Examiner TAYLOR V OH	Art Unit 1625	

All participants (applicant, applicant's representative, PTO personnel):

(1) TAYLOR V OH. (3)_____.

(2) Stephen E. Reiter. (4)_____.

Date of Interview: 25 January 2017.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☒ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.

If Yes, brief description: _____.

Issues Discussed ☐101 ☒112 ☐102 ☐103 ☒Others

(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 1-5,20-24,26 and 29.

Identification of prior art discussed: _____.

Substance of Interview

(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☒ Attachment

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: The examiner and applicants' representative have come to agree on the followings prior to allowance:
Claims 1-2, 20-23 and 26 are cancelled.

In claims 3-5, line 1 on page 2 (amendment dated on 11/30/16):
The number " -- 2 --" after the term " claim " is replaced with the number " 24 ".

In claim 24, lines 3-4 on page 3 (amendment dated on 11/30/16):
The terms "--a KATP channel opener --" after the term" of " is replaced with another phrase "diazoxide or a pharmaceutically acceptable salt thereof ".
In claim 29, line 4 on page 4 (amendment dated on 11/30/16):
The terms "--a KATP channel opener --" after the term" of " is replaced with another phrase "diazoxide or a pharmaceutically acceptable salt thereof ".

WEST Search History for Application 14940018

Creation Date: 2017012522:48

Interference Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
(aggressive or psychotic) and behavior	PGPB, USPT	42143	ADJ	YES		01-25-2017
((aggressive or psychotic) and behavior) and (prader \$ 1willi syndrome or pws or smith \$ 1magenis syndrome or sms)	PGPB, USPT	4066	ADJ	YES		01-25-2017
((aggressive or psychotic) and behavior and (prader \$ 1willi syndrome or pws or smith \$ 1magenis syndrome or sms)) and diazoxide	PGPB, USPT	387	ADJ	YES		01-25-2017
((aggressive or psychotic) and behavior and (prader \$ 1willi syndrome or pws or smith \$ 1magenis syndrome or sms) and diazoxide) and katp channel opener	PGPB, USPT	8	ADJ	YES		01-25-2017
((aggressive or psychotic) and behavior and (prader \$ 1willi syndrome or pws or smith \$ 1magenis syndrome or sms) and diazoxide and katp channel opener) and human growth hormone	PGPB, USPT	2	ADJ	YES		01-25-2017
((aggressive or psychotic) and behavior and (prader \$ 1willi syndrome or pws or smith \$ 1magenis syndrome or sms) and diazoxide and katp channel opener and human growth hormone) and choline	PGPB, USPT	2	ADJ	YES		01-25-2017
((aggressive or psychotic) and behavior and (prader \$ 1willi syndrome or pws or smith \$ 1magenis syndrome or sms) and diazoxide) and (514/ \$.ccls. or (a61k31/ \$ or a61k9/ \$ or a61k45/ \$ or a61k38/ \$ or a61k2300/ \$).cpc.)	PGPB, USPT	296	ADJ	YES		01-25-2017
((aggressive or psychotic) and behavior and (prader \$ 1willi syndrome or pws or smith \$ 1magenis syndrome or sms) and diazoxide and (514/ \$.ccls. or (a61k31/ \$ or a61k9/ \$ or a61k45/ \$ or a61k38/ \$ or a61k2300/ \$).cpc.)) and katp channel opener	PGPB, USPT	8	ADJ	YES		01-25-2017

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
(aggressive or psychotic) and behavior	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	43520	ADJ	YES		01-25-2017
((aggressive or psychotic) and behavior) and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	4469	ADJ	YES		01-25-2017
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms)) and diazoxide	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	390	ADJ	YES		01-25-2017
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide) and katp channel opener	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	10	ADJ	YES		01-25-2017
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide and katp channel opener) and human growth hormone	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	4	ADJ	YES		01-25-2017
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms) and	PGPB, USPT, USOC,	3	ADJ	YES		01-25-2017

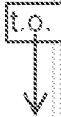
diazoxide and katp channel opener and human growth hormone) and choline	EPAB, JPAB, DWPI, TDBD, FPRS					
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide) and(514/\$.ccls. or (a61k31/\$ or a61k9/\$ or a61k45/\$ or a61k38/\$ or a61k2300/\$).cpc.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	299	ADJ	YES		01-25-2017
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide and(514/\$.ccls. or (a61k31/\$ or a61k9/\$ or a61k45/\$ or a61k38/\$ or a61k2300/\$).cpc.)) and katp channel opener	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	10	ADJ	YES		01-25-2017
((aggressive or psychotic) and behavior and (prader\$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide and(514/\$.ccls. or (a61k31/\$ or a61k9/\$ or a61k45/\$ or a61k38/\$ or a61k2300/\$).cpc.) and katp channel opener) and choline	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	9	ADJ	YES		01-25-2017

PALM Resource Center

PALM Explorer

PALM

General Information
Employee Locator
Examiner Docket
Examiner Reports
Count Calculator
Workflow Posting
PCT Transmission Report
IDS Flag Clearance
Bib Data Sheet Maint
Transfer Inquiry
TSS Activity Record
Application Information
Search
Fees
Reference
File/Box Management
Dispatch and Receive



Inventor Information for 14/940018

Inventor Name	City	Sta
COWEN, NEIL M.	CARLSBAD	CA
Appin Info	Contents	Petition Info
Atty/Agent Info	Continuity Data	Foreign Data
Inventors	Applicants	

Search Another: Application # or Patent # or International Reg
PCT / / or PG PUBS #
Attorney Docket #
Bar Code #

To Go BACK Use BACK Button on Your BROWSER Tool Bar
Back to [PALM ASSIGNMENT](#) | [OASIS](#) Home page

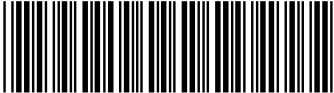
t.o.
1/25/17

Issue Classification 	Application/Control No. 14940018	Applicant(s)/Patent Under Reexamination COWEN, NEIL M.	
	Examiner T. VICTOR OH	Art Unit 1625	

CPC					
Symbol				Type	Version
A61K	31	/	549	F	2013-01-01
A61K	38	/	27	A	2013-01-01
A61K	45	/	06	I	2013-01-01
A61K	9	/	00	I	2013-01-01
A61K	31	/	137	I	2013-01-01
A61K	31	/	155	I	2013-01-01
A61K	31	/	551	I	2013-01-01
A61K	9	/	0004	I	2013-01-01
A61K	9	/	2054	I	2013-01-01
A61K	9	/	5026	I	2013-01-01
A61K	9	/	5042	I	2013-01-01
A61K	9	/	5047	I	2013-01-01
		/			
		/			
		/			

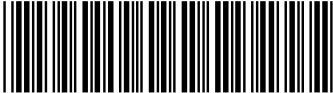
CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
A61K		31	/	549	I	1	1	2013-01-01
A61K		2300	/	00	A	1	2	2013-01-01
A61K		31	/	155	I	2	1	2013-01-01
A61K		2300	/	00	A	2	2	2013-01-01
A61K		31	/	551	I	3	1	2013-01-01
A61K		2300	/	00	A	3	2	2013-01-01
A61K		31	/	137	I	4	1	2013-01-01
A61K		2300	/	00	A	4	2	2013-01-01
A61K		38	/	27	A	5	1	2013-01-01
A61K		2300	/	00	A	5	2	2013-01-01

NONE		Total Claims Allowed:	
		13	
(Assistant Examiner)	(Date)		
/T. VICTOR OH/ Primary Examiner.Art Unit 1625	1/25/17	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	24	1

Issue Classification 	Application/Control No. 14940018	Applicant(s)/Patent Under Reexamination COWEN, NEIL M.
	Examiner T. VICTOR OH	Art Unit 1625

US ORIGINAL CLASSIFICATION						INTERNATIONAL CLASSIFICATION									
CLASS		SUBCLASS				CLAIMED						NON-CLAIMED			
514		223.5				A	6	1	K	31 / 54 (2006.01.01)					
CROSS REFERENCE(S)															
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)														
514	5.1	11.4	223.2												

NONE		Total Claims Allowed:	
		13	
(Assistant Examiner) /T. VICTOR OH/ Primary Examiner.Art Unit 1625	(Date) 1/25/17	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	24	1

Issue Classification 	Application/Control No. 14940018	Applicant(s)/Patent Under Reexamination COWEN, NEIL M.
	Examiner T. VICTOR OH	Art Unit 1625

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
2	3														
3	4														
4	5														
5	6														
6	7														
7	8														
8	9														
9	15														
10	19														
1	24														
11	25														
12	28														
13	29														

NONE		Total Claims Allowed:	
		13	
(Assistant Examiner)	(Date)		
/T. VICTOR OH/ Primary Examiner.Art Unit 1625	1/25/17	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	24	1

Search Notes 	Application/Control No. 14940018	Applicant(s)/Patent Under Reexamination COWEN, NEIL M.
	Examiner T.VICTOR OH	Art Unit 1625

CPC- SEARCHED		
Symbol	Date	Examiner
A61K31/549,155,137,551;A61K9/5026,2054,0004,5042,5047,00;A61K45/06	1/25/17	t.o.
A61K38/27	1/25/17	t.o.

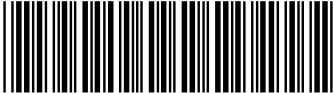
CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner
A61K31/549; A61K31/155; A61K31/551;A61K61/137;A61K38/27	1/25/17	t.o.
A61K2300/00; A61K2300/00; A61K2300/00; A61K2300/00;A61K2300/00	1/25/17	t.o.

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	5.1,11.4,223.2,223.5	1/25/17	t.o.

SEARCH NOTES		
Search Notes	Date	Examiner
west search updated .p.3	1/25/17	t.o.
inventor's name search done. p. 1	1/25/17	t.o.

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K	31/549,155,137,551;9/5026,2054,0004,5042,5047,00;4 5/06	1/25/17	t.o.
514/A61K	5.1/38/27	1/25/17	t.o.
514/A61K	223.2/31/54	1/25/17	t.o.

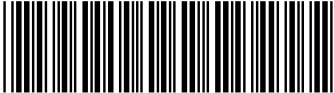
	/T.O./ Primary Examiner.Art Unit 1625
--	--

Issue Classification 	Application/Control No. 14940018	Applicant(s)/Patent Under Reexamination COWEN, NEIL M.	
	Examiner T. VICTOR OH	Art Unit 1625	

CPC					
Symbol				Type	Version
A61K	31	/	549	F	2013-01-01
A61K	38	/	27	A	2013-01-01
A61K	45	/	06	I	2013-01-01
A61K	9	/	00	I	2013-01-01
A61K	31	/	137	I	2013-01-01
A61K	31	/	155	I	2013-01-01
A61K	31	/	551	I	2013-01-01
A61K	9	/	0004	I	2013-01-01
A61K	9	/	2054	I	2013-01-01
A61K	9	/	5026	I	2013-01-01
A61K	9	/	5042	I	2013-01-01
A61K	9	/	5047	I	2013-01-01
		/			
		/			
		/			

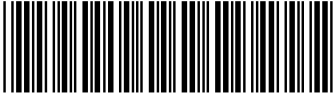
CPC Combination Sets								
Symbol				Type	Set	Ranking	Version	
A61K		31	/	549	I	1	1	2013-01-01
A61K		2300	/	00	A	1	2	2013-01-01
A61K		31	/	155	I	2	1	2013-01-01
A61K		2300	/	00	A	2	2	2013-01-01
A61K		31	/	551	I	3	1	2013-01-01
A61K		2300	/	00	A	3	2	2013-01-01
A61K		31	/	137	I	4	1	2013-01-01
A61K		2300	/	00	A	4	2	2013-01-01
A61K		38	/	27	A	5	1	2013-01-01
A61K		2300	/	00	A	5	2	2013-01-01

NONE		Total Claims Allowed:	
		14	
(Assistant Examiner)	(Date)		
/T. VICTOR OH/ Primary Examiner.Art Unit 1625	2/19/17	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	24	1

Issue Classification 	Application/Control No. 14940018	Applicant(s)/Patent Under Reexamination COWEN, NEIL M.
	Examiner T. VICTOR OH	Art Unit 1625

US ORIGINAL CLASSIFICATION						INTERNATIONAL CLASSIFICATION									
CLASS		SUBCLASS				CLAIMED						NON-CLAIMED			
514		223.5				A	6	1	K	31 / 54 (2006.01.01)					
CROSS REFERENCE(S)															
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)														
514	5.1	11.4	223.2												

NONE		Total Claims Allowed:	
		14	
(Assistant Examiner) /T. VICTOR OH/ Primary Examiner.Art Unit 1625	(Date)	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	2/19/17	24	1
	(Date)		

Issue Classification 	Application/Control No. 14940018	Applicant(s)/Patent Under Reexamination COWEN, NEIL M.
	Examiner T. VICTOR OH	Art Unit 1625

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
2	3														
3	4														
4	5														
5	6														
6	7														
7	8														
8	9														
9	15														
10	19														
1	24														
11	25														
12	27														
13	28														
14	29														

NONE		Total Claims Allowed:	
		14	
(Assistant Examiner)	(Date)		
/T. VICTOR OH/ Primary Examiner.Art Unit 1625	2/19/17	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	24	1



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/940,018	11/12/2015	Neil M. Cowen	096593-001000US-0955615	6992
20350 7590 02/23/2017 KILPATRICK TOWNSEND & STOCKTON LLP Mailstop: IP Docketing - 22 1100 Peachtree Street Suite 2800 Atlanta, GA 30309			EXAMINER OH, TAYLOR V	
			ART UNIT 1625	PAPER NUMBER
			NOTIFICATION DATE 02/23/2017	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipefiling@kilpatricktownsend.com
jlhice@kilpatrick.foundationip.com

Corrected Notice of Allowability	Application No. 14/940,018	Applicant(s) COWEN, NEIL M.	
	Examiner TAYLOR V OH	Art Unit 1625	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 2/14/17.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 3-9,15,19,24,25 and 27-29. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some *c) ☐ None of the:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|--|--|
| 1. ☐ Notice of References Cited (PTO-892) | 5. ☐ Examiner's Amendment/Comment |
| 2. ☐ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date _____ | 6. ☒ Examiner's Statement of Reasons for Allowance |
| 3. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 7. ☐ Other _____. |
| 4. ☐ Interview Summary (PTO-413),
Paper No./Mail Date _____. | |

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

The Corrected Notice of Allowability

The Status of Claims

Claims 3-9,15,19,24-25,27-29 are pending.

Claims 3-9,15,19,24-25,27-29 are allowed.

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with an attorney of record, Stephen E. Reiter on 1/25/17.

I. The application has been amended as follows:

Claims 1-2, 20-23 and 26 are cancelled.

In claims 3-5, line 1 on page 2 (amendment dated on 11/30/16):

The number " -- 2 --" after the term " claim " is replaced with the number " 24 ".

In claim 24, lines 3-4 on page 3 (amendment dated on 11/30/16):

The terms "--a K_{ATP} channel opener --" after the term "of" is replaced with another phrase "diazoxide or a pharmaceutically acceptable salt thereof".

In claim 29, line 4 on page 4 (amendment dated on 11/30/16):

The terms "--a K_{ATP} channel opener --" after the term "of" is replaced with another phrase "diazoxide or a pharmaceutically acceptable salt thereof".

I. The following is an examiner's statement of reasons for allowance:

- The rejection of Claims 2-9,15,19,24-25,27-28 under 35 U.S.C. 103 as being unpatentable over Cotter (US2014/0364367) which has a provisional application No. 61/832,779 filed on Jun. 8, 2013 is withdrawn due to the modification of the claim and applicants' convincing arguments.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning the communication after allowance such as sending all post-allowance correspondence should be directed to “ Box Issue Fee” or faxed directly to PUBS at 703-305-8755. This will expedite the process of these papers.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/TAYLOR V OH/

Primary Examiner, Art Unit 1625

2/19/17

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
on March 1, 2017.

PATENT
Attorney Docket No.: 096593-001000US-0955615

KILPATRICK TOWNSEND & STOCKTON LLP

By: /William H. Gorman/
William H. Gorman

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Neil M. Cowen

Application No.: 14/940,018

Filed: November 12, 2015

For: METHODS FOR TREATING

SUBJECTS WITH PRADER-WILLI

SYNDROME OR SMITH-MAGENIS

SYNDROME

Customer No.: 20350

Confirmation No.: 6992

Examiner: Taylor V. Oh

Technology Center/Art Unit: 1625

AMENDMENT AFTER ALLOWANCE
UNDER 37 CFR § 1.312

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Notice of Allowance mailed February 1, 2017, please amend the
above-identified application as follows:

Amendments to the Claims are reflected in the **Listing of Claims**, which begins on
page 2 of this paper.

Remarks begin on page 4 of this paper.

Electronic Acknowledgement Receipt

EFS ID:	28508401
Application Number:	14940018
International Application Number:	
Confirmation Number:	6992
Title of Invention:	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME
First Named Inventor/Applicant Name:	Neil M. Cowen
Customer Number:	20350
Filer:	Stephen E. Reiter/William Gorman
Filer Authorized By:	Stephen E. Reiter
Attorney Docket Number:	096593-001000US-0955615
Receipt Date:	01-MAR-2017
Filing Date:	12-NOV-2015
Time Stamp:	19:43:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
------------------------	----

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2017-03-01_Amendment_312_096593-001000US-0955615.pdf	86091	yes	5
			8dbde28b497cb588a5ca50b8f1122ff17734061b		

	Multipart Description/PDF files in .zip description		
	Document Description	Start	End
	Applicant Arguments/Remarks Made in an Amendment	4	5
	Claims	2	3
	Amendment after Notice of Allowance (Rule 312)	1	1
Warnings:			
Information:			
Total Files Size (in bytes):		86091	
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>			

REMARKS

By the present communication, it is proposed to amend claims 4, 7, 24 and 29 as follows. No new matter is introduced by the proposed amendments as the amended claim language is fully supported by the specification and original claims. Moreover, the proposed amendments merely address inadvertent informalities in the claims as originally allowed.

Specifically, the amendments to claims 4, 7 and 24 address an inadvertent lack of antecedent basis; and the amendment to claim 29 clarifies the language thereof by introducing the article “a” as appropriate.

Upon entry of the present amendment, claims 3-9, 15, 19, 24-25, and 27-29 will remain pending in this application.

A detailed listing of claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented herein, beginning on page 2 of the present communication, with an appropriate status identifier. The claims provided herewith reflect the amendments made by way of the Examiner’s amendment (included in the Notice of Allowance dated February 1, 2017).

CONCLUSION

Entry of this amendment is respectfully urged since no additional search is required, no more than a cursory review of the record is needed, and the amendments do not require a substantial amount of work on the part of the Office.

Except for the issue fees payable under 37 C.F.R. § 1.18, the Director is authorized to charge any additional fees during pendency of this application, including any required extension of time fees, or credit any overpayment to Deposit Account Number 20-1430. This paragraph is intended to be a constructive petition for extension of time in accordance with 37 C.F.R. § 1.136(a)(3).

In the event any issues remain to be resolved in view of this communication, the Examiner is invited to contact the undersigned at 858-350-3862 or sreiter@kilpatricktownsend.com so that a prompt disposition of this application can be achieved.

Respectfully submitted,

/Stephen E. Reiter/
Stephen E. Reiter
Registration No. 31,192

KILPATRICK TOWNSEND & STOCKTON LLP
1100 Peachtree Street, Suite 2800
Atlanta, GA 30309
Tel: 858-350-6100
Fax: 858-350-6111

Amendments to the Claims/Listing of Claims:

Please amend claims 4, 7, 24 and 29 as follows. This listing of claims will replace all prior versions, and listings of claims in the application:

1.-2. (Cancelled)

3. (Previously presented) The method of claim 24 wherein the pharmaceutically acceptable salt is diazoxide choline.

4. (Currently Amended) The method of claim 24 wherein said **pharmaceutical formulation** ~~diazoxide or a pharmaceutically acceptable salt thereof~~ is administered orally.

5. (Previously presented) The method of claim 24 wherein the pharmaceutical formulation includes at least one excipient which affects the rate of release of diazoxide or a pharmaceutically acceptable salt thereof.

6. (Original) The method of claim 5 wherein the pharmaceutical formulation includes at least one excipient that delays release of diazoxide or a pharmaceutically acceptable salt thereof.

7. (Currently Amended) The method of claim 24 wherein the **pharmaceutical** formulation further comprises at least one other active ingredient.

8. (Previously presented) The method of claim 24 further comprising administering human growth hormone to the subject.

9. (Original) The method of claim 8 wherein said human growth hormone is administered by injection.

10. – 14. (Cancelled)

15. (Previously Presented) The method of claim 24 wherein said administering is carried out for one or more years.

16. – 18. (Cancelled)

19. (Previously presented) The method of claim 24, wherein the circulating concentration of IGF-1 is not increased.

20.-23. (Cancelled)

24. (Currently Amended) A method of reducing one or more aggressive behaviors in a subject having Prader-Willi syndrome (PWS) or Smith–Magenis syndrome (SMS), the method comprising administering to said subject for at least 10 weeks **a pharmaceutical formulation comprising** an effective amount of diazoxide or a pharmaceutically acceptable salt thereof, wherein administration reduces one or more aggressive behaviors in the subject.

25. (Original) The method of claim 24 in which a second therapeutic product is administered, wherein the second product is intended to further reduce the one or more aggressive behaviors.

26. (Cancelled).

27. (Previously presented) The method of claim 24 wherein the pharmaceutical formulation is administered twice per day.

28. (Previously presented) The method of claim 24 wherein the pharmaceutical formulation is administered once per day.

29. (Currently Amended) A method of reducing one or more aggressive behaviors in a subject having Prader-Willi syndrome (PWS) or Smith–Magenis syndrome (SMS), the method comprising administering to said subject for at least 10 weeks an effective amount of **a** formulation consisting essentially of diazoxide or a pharmaceutically acceptable salt thereof, wherein administration reduces one or more aggressive behaviors in the subject.