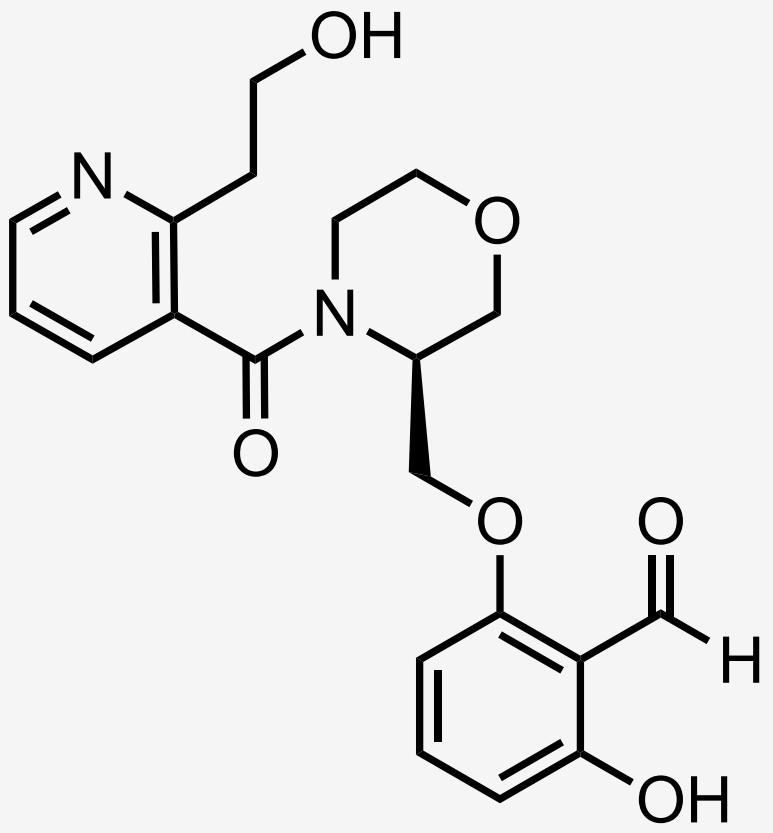
GBT-601
(HbS polymerization inhibitor)

Pfizer/Global Blood Therapeutics



GBT-601

In October 2022, Pfizer acquired Global Blood Therapeutics (GBT)

Boosting its portfolio in the rare hematology space & acquiring compounds to treat sickle cell disease (SCD)

Pfizer Completes Acquisition of Global Blood Therapeutics

Wednesday, October 05, 2022 - 09:02am

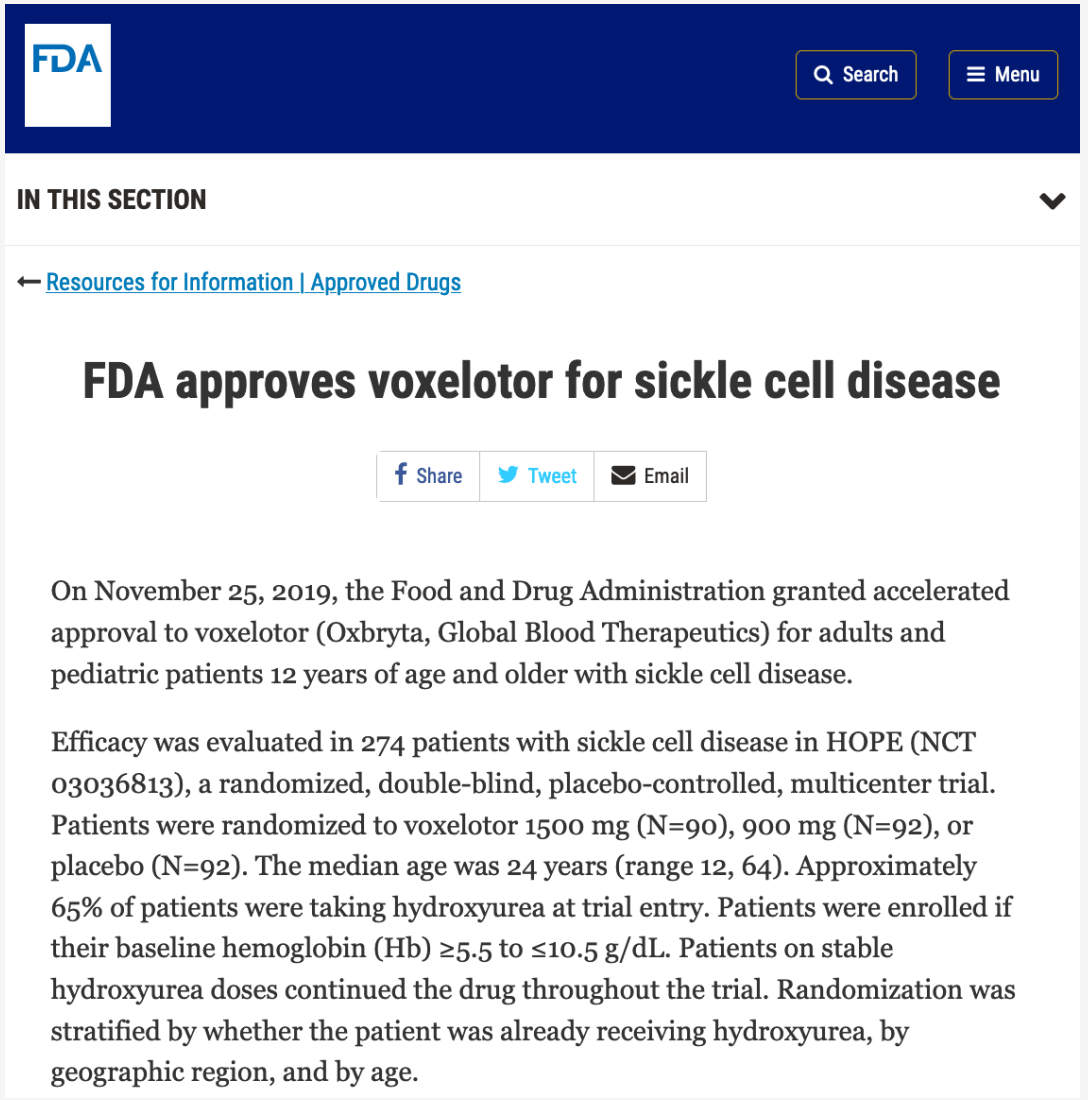
Acquisition brings leading sickle cell disease portfolio and pipeline to Pfizer with potential to address critical needs in an underserved patient community

NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) announced today the completion of its acquisition of Global Blood Therapeutics, Inc. (GBT), a biopharmaceutical company dedicated to the discovery, development and delivery of life-changing treatments that provide hope to underserved patient communities starting with sickle cell disease (SCD). The acquisition reinforces Pfizer's commitment to SCD, building on a 30-year legacy in the rare hematology space.

GBT brings a portfolio and pipeline that has the potential to address the full spectrum of critical needs for this underserved community. GBT discovered and developed Oxbryta® (voxelotor), a first-in-class medicine that directly targets the root cause of SCD. In addition, GBT's promising pipeline of preclinical and clinical investigational assets focused in SCD includes GBT021601 (GBT601) and inclaclumab, both of which have received Orphan Drug and Rare Pediatric Disease designations from the U.S. Food and Drug Administration (FDA).

Some background:

In 2019, the FDA approved GBT's Oxbryta (voxelotor), a first-in-class HbS polymerization inhibitor to treat SCD



FDA

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← Resources for Information | Approved Drugs

FDA approves voxelotor for sickle cell disease

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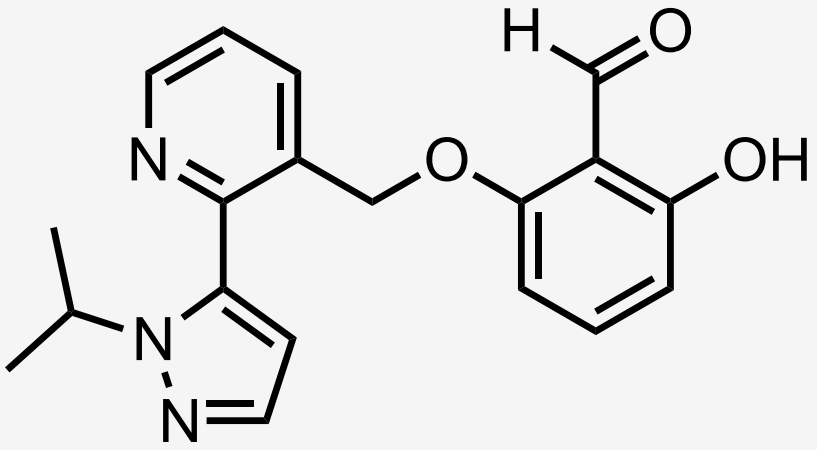
On November 25, 2019, the Food and Drug Administration granted accelerated approval to voxelotor (Oxbryta, Global Blood Therapeutics) for adults and pediatric patients 12 years of age and older with sickle cell disease.

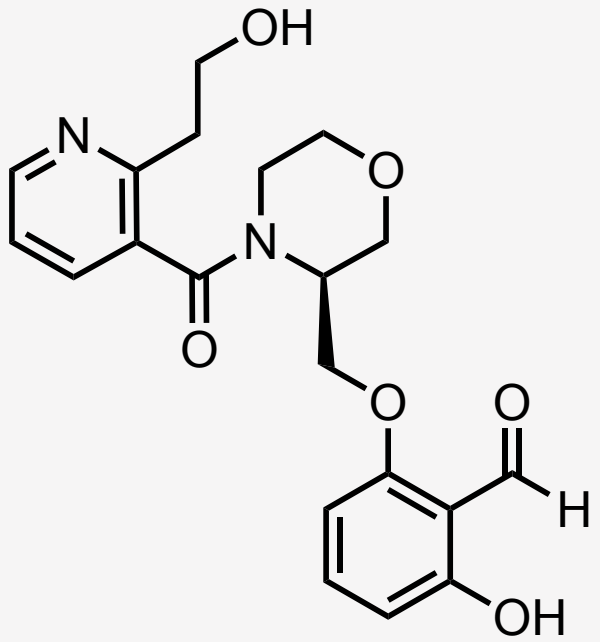
Efficacy was evaluated in 274 patients with sickle cell disease in HOPE (NCT 03036813), a randomized, double-blind, placebo-controlled, multicenter trial. Patients were randomized to voxelotor 1500 mg (N=90), 900 mg (N=92), or placebo (N=92). The median age was 24 years (range 12, 64). Approximately 65% of patients were taking hydroxyurea at trial entry. Patients were enrolled if their baseline hemoglobin (Hb) ≥5.5 to ≤10.5 g/dL. Patients on stable hydroxyurea doses continued the drug throughout the trial. Randomization was stratified by whether the patient was already receiving hydroxyurea, by geographic region, and by age.

GBT-601 is a 2nd gen HbS polymerization inhibitor that aims to be best-in-class

Voxelotor was the first-in-class drug



Voxelotor



GBT-601

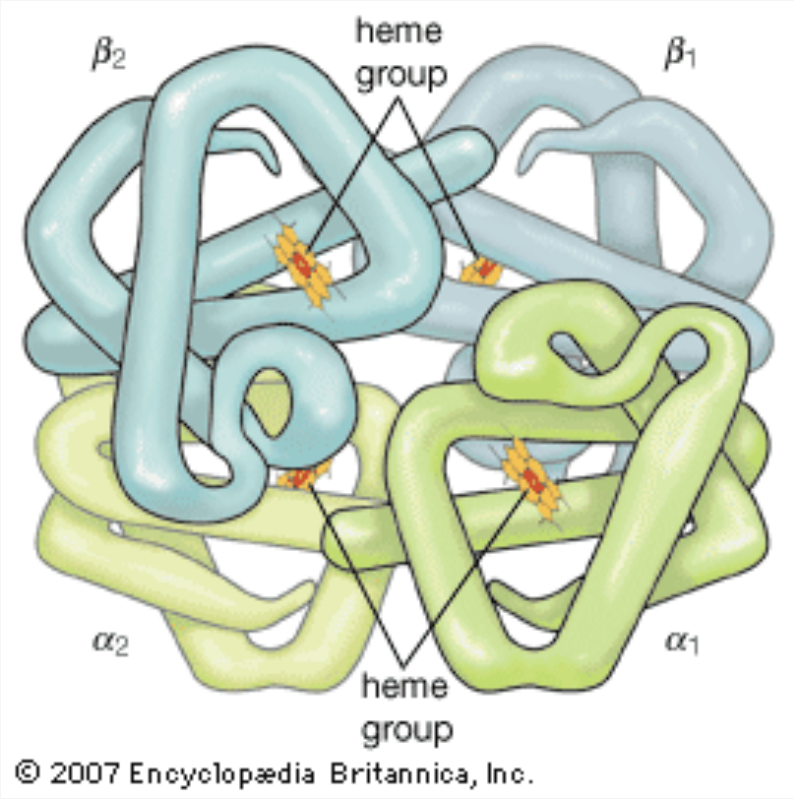
Brief biology refresh: role of HbS polymerization in SCD

3 main isoforms of Hb

- HbA: major isoform in adults. Consists of 2 alpha and 2 beta chains
- HbA2: minor isoform in adults. Consists of 2 alpha and 2 delta chains.
- HbF: predominant isoform in fetuses

HbS is when there is an E6V SNP in at least 1 of the beta chains of HbA.

Under low O_2 conditions, HbS polymerizes to form fibrous precipitates. This can lead to hypoxemia, ischemia, pain, necrosis, etc.



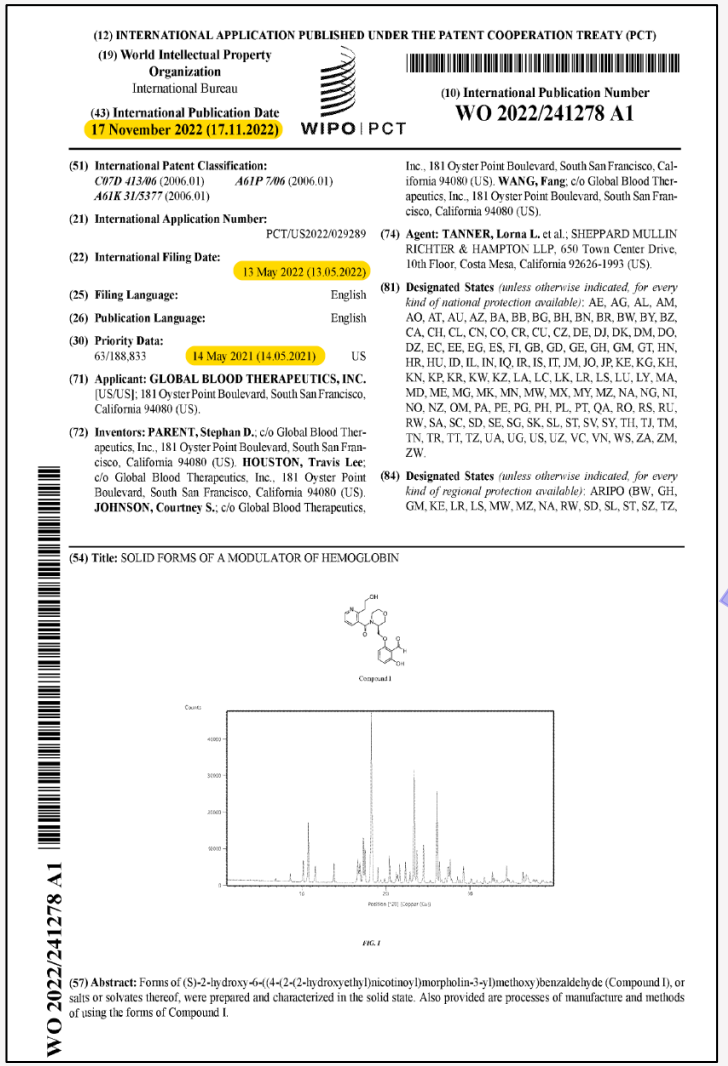
GBT's HbS patent landscape

1 solid dosage form, 4 composition of matter

No.	Title	Publication No.	Priority	Filing	Publication
1	Modulators of hemoglobin for the treatment of sickle cell disease	WO2020072377A1	Oct. 1, 2018	Sep. 30, 2019	Apr. 9, 2020
2	2-Formyl-3-hydroxyphenyloxymethyl compounds capable of modulating hemoglobin	WO2020106642A8	Nov. 18, 2019	Nov. 18, 2019	May 28, 2020
3	Modulators of hemoglobin	WO2021202284A1	Mar. 31, 2020	Mar. 26, 2021	Oct. 7, 2021
4	Methods of making a modulator of hemoglobin	WO2022241286A1	May 14, 2021	May 13, 2022	Nov. 17, 2022
5	Solid forms of a modulator of hemoglobin	WO2022241278A1	May 14, 2021	May 13, 2022	Nov. 17, 2022

Huge tip: Solid forms patent (‘278)

Includes a structure (Compound 1) but still need to verify that this is is indeed GBT-601



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A61K 31/5377 (2006.01)

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13 May 2022 (13.05.2022)

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,

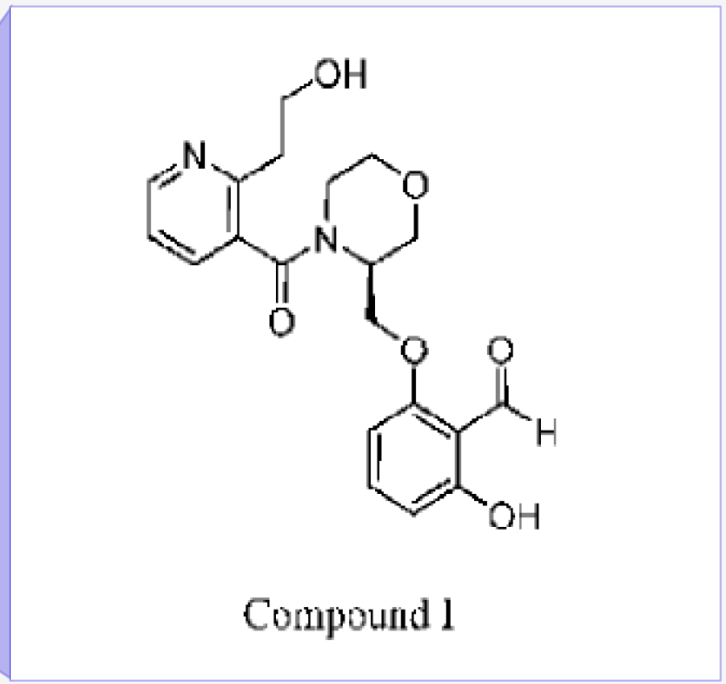
(54) Title: SOLID FORMS OF A MODULATOR OF HEMOGLOBIN

Compound I

FIG. 1

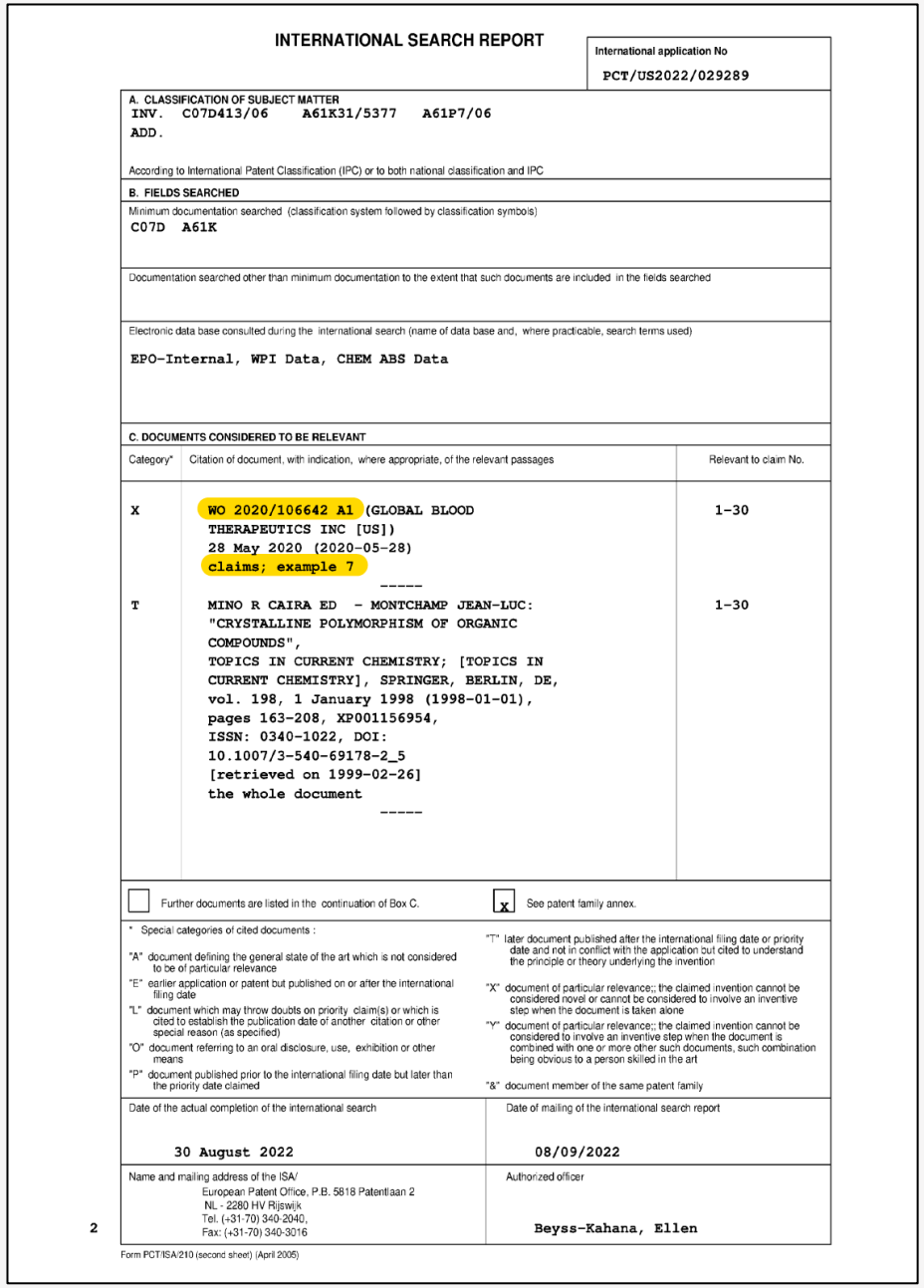
(57) Abstract: Forms of (S)-2-hydroxy-6-((4-(2-(2-hydroxyethyl)nicotinoyl)morpholin-3-yl)methoxy)benzaldehyde (Compound I), or salts or solvates thereof, were prepared and characterized in the solid state. Also provided are processes of manufacture and methods of using the forms of Compound I.

WO 2022/241278 A1



Compound I

Solid forms ISR cites example 7 in the composition of matter patent (‘643) for more info on “Compound 1”



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/029289

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/06 A61K31/5377 A61P7/06
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2020/106642 A1 (GLOBAL BLOOD THERAPEUTICS INC [US]) 28 May 2020 (2020-05-28) claims; example 7	1-30
T	MINO R CAIRA ED - MONTCHAMP JEAN-LUC: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS", TOPICS IN CURRENT CHEMISTRY; [TOPICS IN CURRENT CHEMISTRY], SPRINGER, BERLIN, DE, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP001156954, ISSN: 0340-1022, DOI: 10.1007/3-540-69178-2_5 [retrieved on 1999-02-26] the whole document	1-30

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 August 2022	08/09/2022

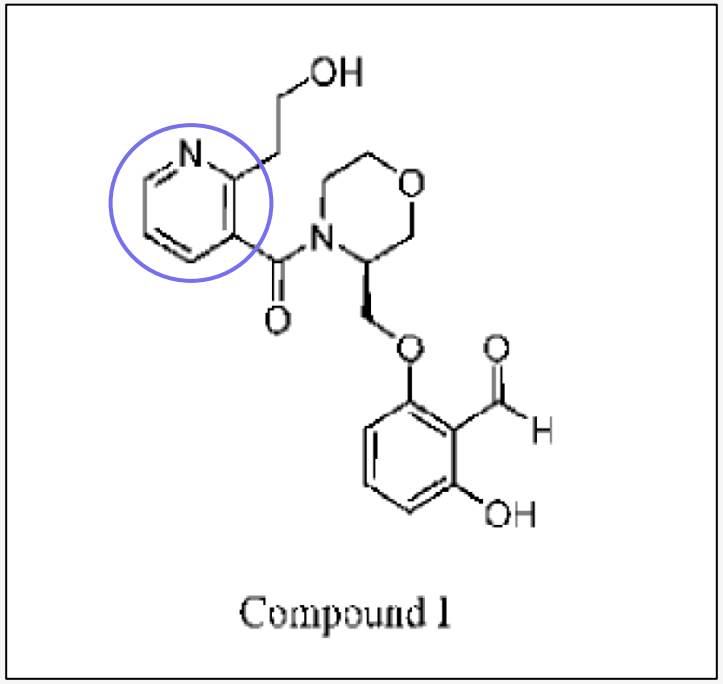
Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Beyss-Kahana, Ellen

2

Form PCT/ISA/210 (second sheet) (April 2005)

However, ISR is wrong and example 8 in ‘642 is actually the same structure as “Compound 1”

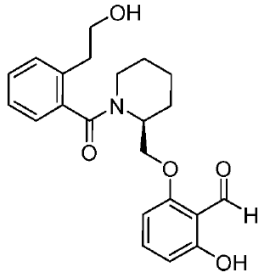
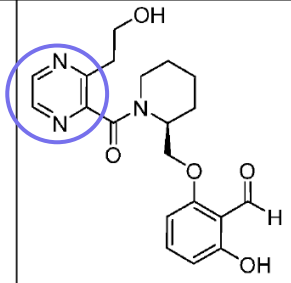
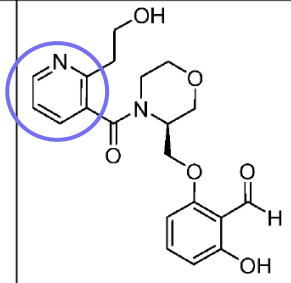
Pyradinyl vs. pyrazinyl



Compound 1

Solid forms patent
WO2022241278A1

WO 2020/106642 PCT/US2019/062054

Compound Number	Structure	IUPAC name
6		(S)-2-hydroxy-6-((1-(2-(2-hydroxyethyl)benzoyl)piperidin-2-yl)methoxy)benzaldehyde
7		(S)-2-hydroxy-6-((1-(3-(2-hydroxyethyl)pyrazine-2-carbonyl)piperidin-2-yl)methoxy)benzaldehyde
8		(S)-2-hydroxy-6-((4-(2-(2-hydroxyethyl)nicotinoyl)morpholin-3-yl)methoxy)benzaldehyde

Summary of biology data for example 8 in the composition of matter ('642) patent.

These are potential clues for verifying whether this is indeed GBT-601

[0453] Whole blood assay: Oxygen equilibrium curves (OECs) were collected using a TCS Hemox Analyzer (TCS Scientific Company, New Hope, PA, USA) to measure changes in the binding affinity of O_2 to Hb. Whole blood was incubated for 1 h at 37°C with the indicated compounds in an equimolar ratio of hemoglobin to compound and diluted into TES (2-[[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]amino]ethanesulfonic acid)/saline buffer prior to measurements. For example, for whole blood at 20% hematocrit [Hct], which corresponds to 1 mM Hb, a compound concentration of 1 mM was used (for example, for compounds 1-5), and the incubated sample diluted 50- to 100-fold. The concentration for compounds 6-44 (Diastereomers 1 and 2) varied but remained in equimolar ratio to hemoglobin. The diluted samples were then oxygenated with compressed air within the Hemox Analyzer and the OECs were collected during deoxygenation as previously described (Guarnone *et al.*, *Haematologica*, 1995, 80, 426–430). p50 (partial pressure of O_2 at which Hb is 50% saturated with O_2) values were obtained using a non-linear regression analysis. Percentage change in p50 [Δp50 (%)] was calculated as follows: Δp50 (%) = [(p50 of control)–p50 with compound)/p50 control] x 100. Resulting data is shown in **Table 4**. Enantiomer 1 and Enantiomer 2 of Compound 13 also exhibit a Δp50 of about 61.0% to about 80.6%.

Table 4

Compound Number	Delta-p50 (%)
1	77.3
2	84.4
3	85.8
4	75.5
5	81.0
6	74.5
7	62.7
8	79.8
9	62.2

Table 6

Compound	CYP (PXR) Flag
Reference Compound A	Y
Reference Compound B	Y
Reference Compound C	Y[1]
1	N[1]
8	N
12	N
Compound 13 (Enantiomer 1)	N

CYP (PXR) Flag based on fold PXR activation (human, at 30 μM):
Y, PXR activation ≥ 2.5-fold;
N, PXR activation < 2.5-fold.
[1] at 25 μM.

Table 7 PK in S-D rats

Compound	$T_{1/2}$ (h)	Blood/Plasma ratio
Reference Compound A	29	75
Reference Compound B	29.8	98
1	58	162
8	69	105
10 (Enantiomer 2)	112	212
11	55	126
12	58	131
20	65	45
23	62	59
36	56	115
39	52	52
40 (Enantiomer 2)	117	424
13 (Enantiomer 1)	88	230
35 (Diastereomer 1)	102	493
35 (Diastereomer 2)	89	636

* * *

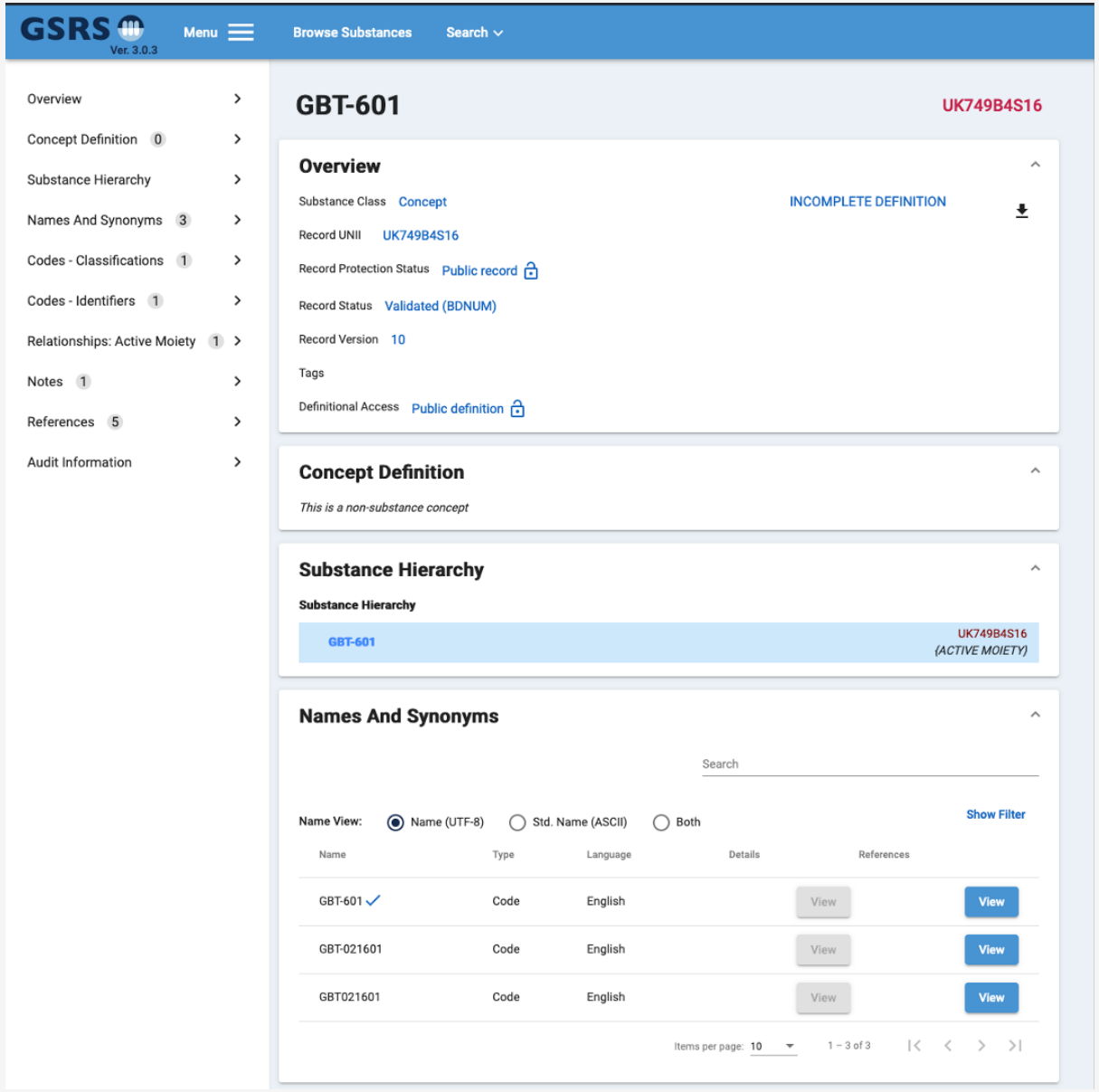
Pages 180-184

Now that we have a structure in mind, let's move beyond patents.

First stop: the Global Substance Registration System (GSRS)

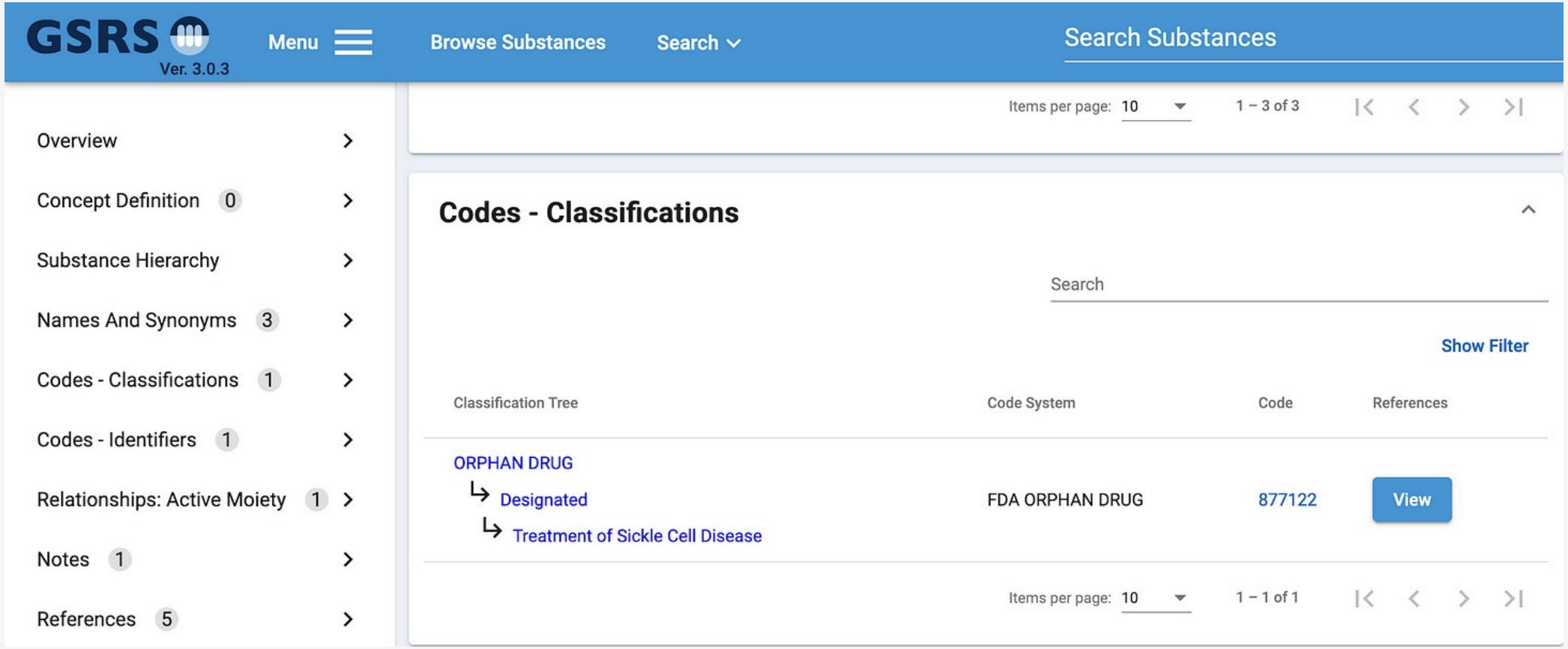
The GSRS database was created by NCATS and contains registered active pharmaceutical ingredients (APIs) under clinical investigation. But not all APIs in clinical trials are in this database!

Today, we are lucky! GBT-601 is in the GSRS.



GSRS is helpful because it shows the other code names associated with GBT-601.

Here, we find the FDA orphan drug code 877122.



Clicking on the “877122” hyperlink returns the FDA database for orphan drug designations & approvals.

We can see the IUPAC name for GBT-601!

FDA U.S. FOOD & DRUG ADMINISTRATION

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Search Orphan Drug Designations and Approvals

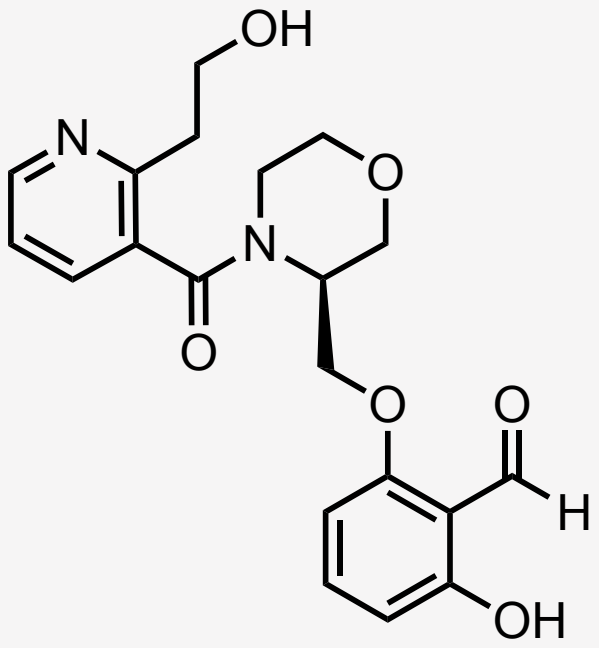
FDA Home › Developing Products for Rare Diseases & Conditions

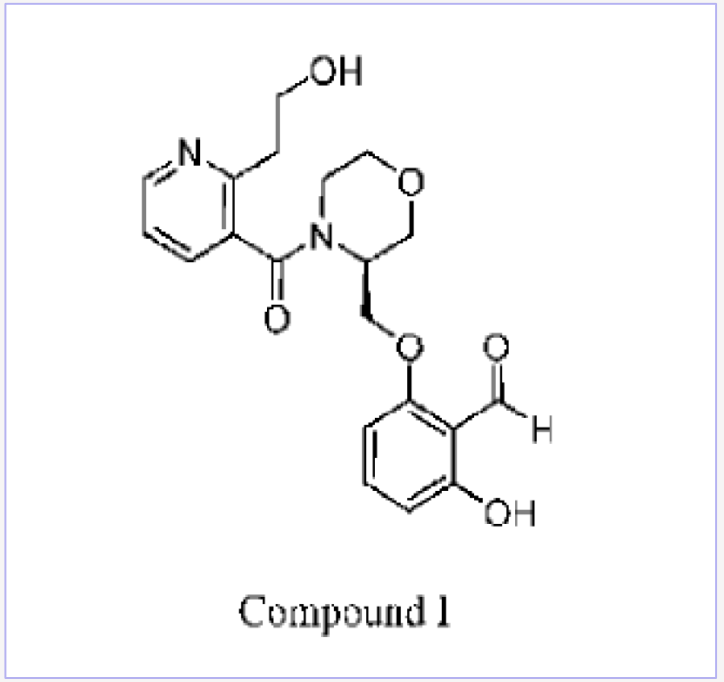
Generic Name:	(S)-2-hydroxy-6-((4-(2-(2-hydroxyethyl)nicotinoyl)morpholin- 3-yl)methoxy)benzaldehyde
Date Designated:	05/16/2022
Orphan Designation:	Treatment of Sickle Cell Disease
Orphan Designation Status:	Designated
FDA Orphan Approval Status:	Not FDA Approved for Orphan Indication
Sponsor:	Global Blood Therapeutics, Inc. 181 Oyster Point Blvd South San Francisco, California 94080 United States *The sponsor address listed is the last reported by the sponsor to OOPD.*

*Exclusivity Protected Indications are shown for approvals from Jan. 1, 2013, to the present.

Plugging the IUPAC name into ChemDraw “Name to Structure” returns the same structure as Compound 1 in the solid forms patent

(S)-2-hydroxy-6-((4-(2-(2-hydroxyethyl)nicotinoyl)morpholin-3-yl)methoxy)benzaldehyde

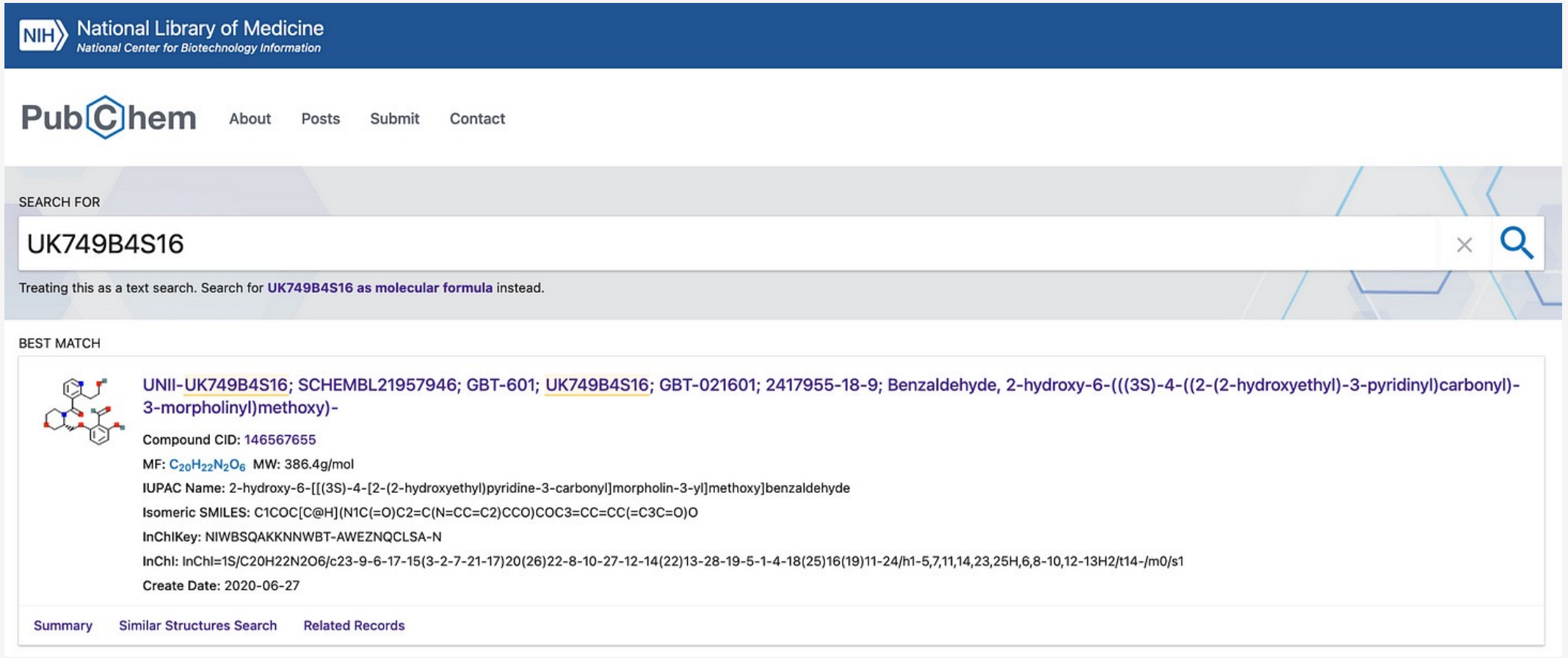




Compound 1

2x verification: plug in the UNII code into PubChem

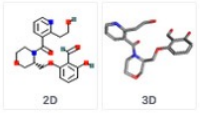
UNII code can be found at the top of the GSRS search result. Search “UK749B4S16” as text in PubChem.



PubChem corroborates ChemDraw IUPAC search

COMPOUND SUMMARY

Unii-UK749B4S16

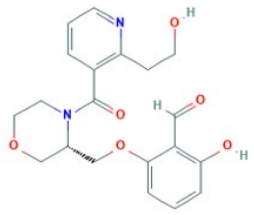
PubChem CID	146567655
Structure	 2D 3D Find Similar Structures
Molecular Formula	$C_{20}H_{22}N_2O_6$
Synonyms	UNII-UK749B4S16 SCHEMBL21957946 GBT-601 UK749B4S16 GBT-021601 More...
Molecular Weight	386.4
Dates	Modify 2023-02-18 Create 2020-06-27

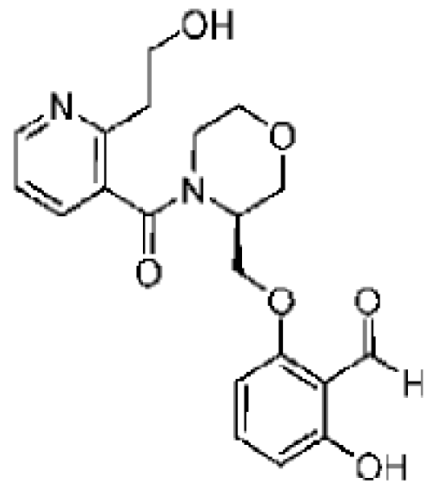
1 Structures

1.1 2D Structure

Find Similar Structures | Get Image | Download

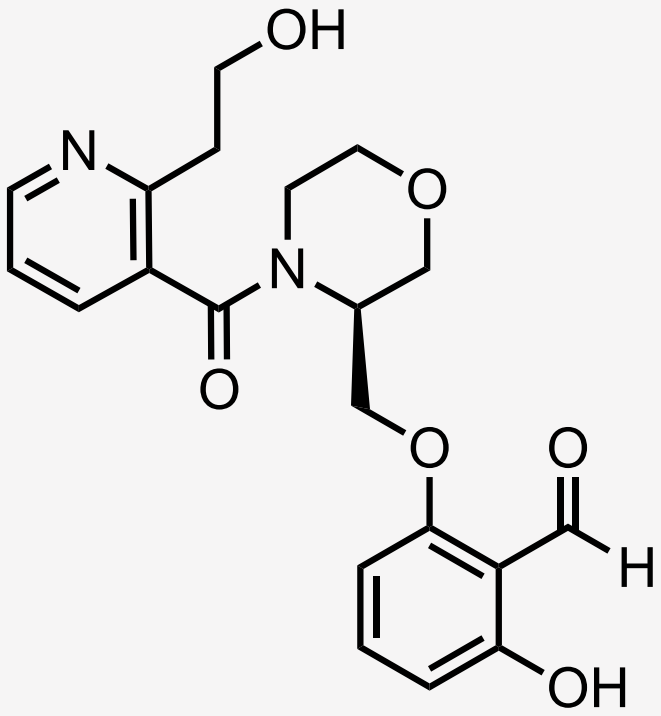
Chemical Structure Depiction





Compound 1

Therefore



Example 8 in ‘642 = Compound 1 in ‘278 = GBT-601

Turns out, the patent work was only somewhat relevant for this case!!

Questions?

Email: victoriacyanide@gmail.com

Twitter: @victoriacyanide