

Meeting the Challenges of the Pharmaceutical Market, a Publisher Perspective

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Current challenges for the Pharma industry are numerous

- **Pipelines are drying up despite massive R&D investments**
- **Current blockbusters are losing patent protection and prospects for new ones are dim**
- **New technologies like high throughput screening and combinatorial chemistry have not fulfilled their initial promise**
- **Major advances from the human genome project, completed in 2001, have not yet materialized**
- **Clinical trials have become more lengthy and expensive**
- **While governments claim to want to speed up the “time to market,” they continue to intervene in promising areas like cloning, gene therapy, and stem cell research**
- **Although there is more published information available than ever before, information users often feel overwhelmed by the volume**

CAS also has challenges in serving the Pharma industry

- Pharma industry consolidation, reduction in research facilities, and shift to Asia are continuing at a rapid pace
- Growth in Asia is encouraging, but customers there are not accustomed to paying “developed country” prices for information
- Google is often a first place to search and is sometimes viewed as “good enough” for basic searches
- The number of “information professionals” is decreasing, so educating end-users about the value of fee-based services is increasingly difficult



But there are some encouraging developments for both pharma and information providers

- Patenting novel compounds continues to be strong
- Potential leads are coming from natural products and rational design
- Large molecules are becoming more interesting as therapeutic candidates, i.e., biologics
- Traditional medicine therapies are making a comeback
- Demands for lifestyle drugs are increasing
- Orphan diseases are being revisited



CAS is committed to doing what no one else does: Providing the most comprehensive coverage of the world's disclosed chemistry

- **CAS covers chemistry not only from journals and patents but also chemical supplier catalogs, chemical libraries, Web, and other reputable sources**
 - more than 10,000 journals
 - patents from 62 authorities
 - small molecules, proteins, peptides, enzymes and genes
 - nearly 52 million reactions and synthetic preparations
 - more than 72,000 traditional medicine patents
 - natural products
- **Combining this content with advanced search and analysis technologies (e.g., STN[®] and SciFinder[®]), CAS delivers the most current, complete, cross-linked and secure digital information environment for scientific discovery and research**

Our customers are diverse and so are their needs



U.S. Patent
& Trademark
Office



Syngene



eduserv



Chinese Patent
Office

CAS' databases are assembled, curated, and quality-controlled by a global organization of CAS scientists and technologists

- Subject experts with advanced degrees
- Monitor the entire range of scientific literature that contains chemical information
- Provide information more rapidly than other chemical information providers



For complex chemistry, CAS chemists classify substance information and verify graphical processes and structures

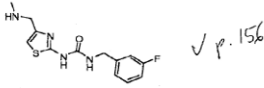
1. Review reaction and structure

WO 2000/015208 PCT/US2008/070893

Alternative process for Intermediate 4 Using Carbonyl Diimidazole:

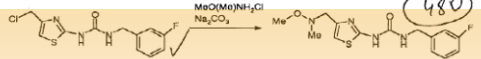
A stirred mixture of Intermediate 1: 2-amino-4-chloromethyl-thiazole hydrochloride (27.8 g, 0.15 mol), carbonyl diimidazole (25.5 g, 0.157 mol), and anhydrous THF (0.2 L) was treated dropwise with a solution of DIPEA (26.2 mL, 0.15 mol) in THF (20 mL) at 20-30 C. After 2-3 hours stirring, a solution of 3-fluorobenzylamine (18.5 mL, 0.164 mol) in THF (40 mL) was added. The reaction was diluted with water (200 mL) and THF was evaporated under reduced pressure. The residue was extracted with DCM (2 x 200 mL). The combined extracts were dried over sodium sulfate and concentrated to leave an orange resin that was purified by silica gel chromatography (acetone/hexane) to afford Intermediate 4 as a pale yellow solid (26 g, 58% yield). (1039)

Intermediate 5: 1-(3-Fluorobenzyl)-3-(4-((methylamino)methyl)thiazol-2-yl)urea (1040)



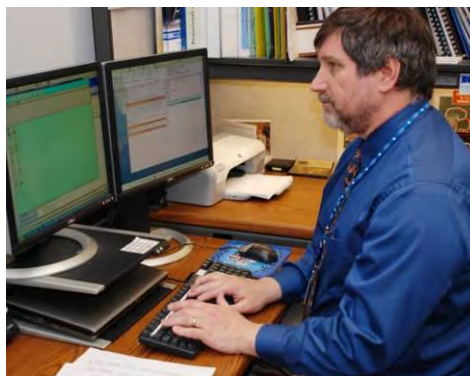
Prepared by reaction of Intermediate 4 with methylamine, following the procedure described for Intermediate 3.

Alternative Process for Intermediate 5 Using N,O-Dimethylhydroxylamine:



Step 1: 2-(3-(3-Fluorobenzyl)ureido)-4-(N-methoxy-N-methyl-amino)methyl-thiazole.

A mixture of Intermediate 4: 2-(3-(3-fluorobenzyl)ureido)-4-chloromethyl-thiazole (40 g, 0.133 mol), N,O-dimethylhydroxylamine (80 g, 0.820 mol), sodium carbonate (40 g, 0.754 mol), and abs. EtOH (0.2 L) was stirred and heated at 60-70 C for 8-12 hours. The mixture was diluted with water (0.8 L) and cooled to 20 C with continued stirring. The

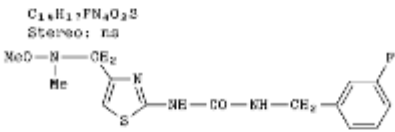


2. Create registration record

File 18772844T MW 0480 Pw 3681
 Ref 98-509999 Ww 03-227158-1880 2009-02-20 1108731-06-9
 mp 012198564M Cwe jkc56 01:49:47 Sosa-010 / 000050
 HPMC sodium salt of acetic acid and sulfonamide substituted heterocycle 110

Publ: 18772844T

Chemical structure:



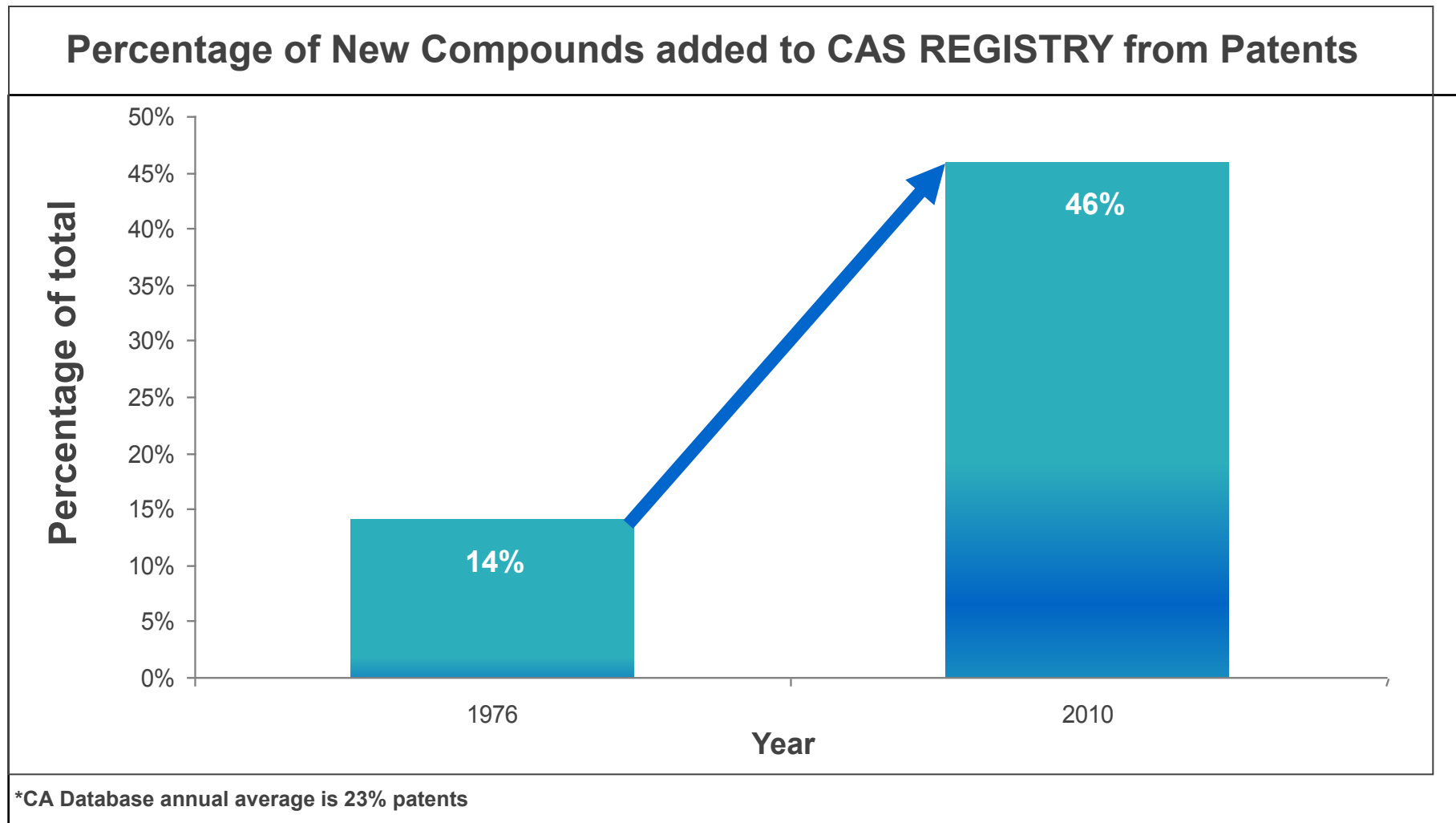
C₁₄H₁₇FN₄O₂S
 Stereo: ns
 MeO-N-Me
 K
 S
 NE-CO-NH-CH₂-C₆H₄-F

With increasing globalization, CAS' coverage of Asian literature is growing

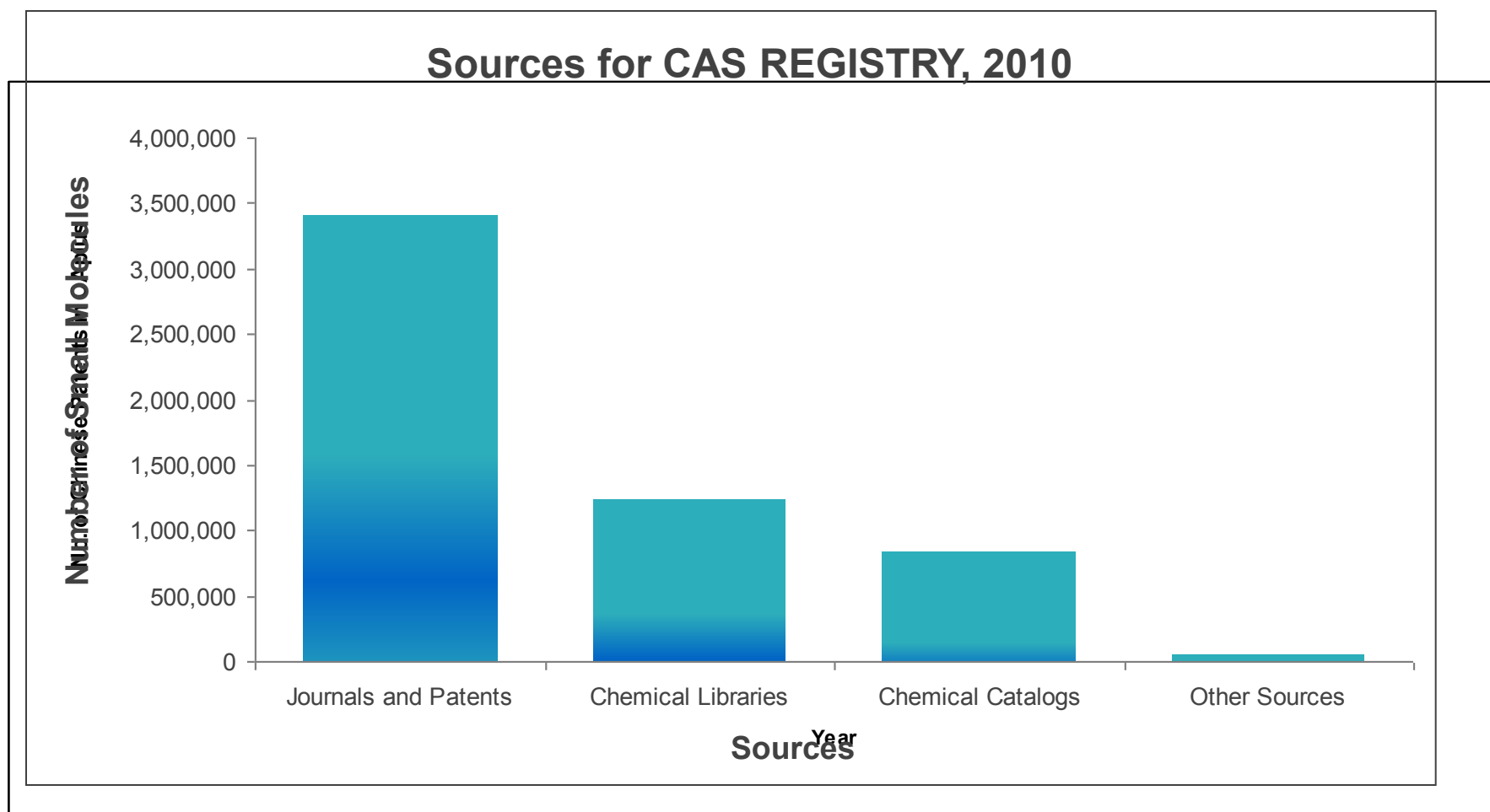
- **2,100 Asian serial journal titles**
- **All major Asian patent authorities, including:**
 - Hong Kong (HK)
 - India (IN)
 - Japan (JP)
 - Malaysia (MY)
 - Philippines (PH)
 - People's Republic of China (CN)
 - Singapore (SG)
 - South Korea (KR)
 - Taiwan (TW)
- **Country-specific STN databases for Asian nations**
 - KOREAPAT
 - JAPIO
 - RUSSIAPAT



Increasingly, new chemical discoveries are being disclosed through patent activities



Growth in small molecules is coming from diverse content sources covered by CAS



The CAS REGISTRY handles all of the different salt forms of an active ingredient

1.

CAS Registry Number: 54910-89-3

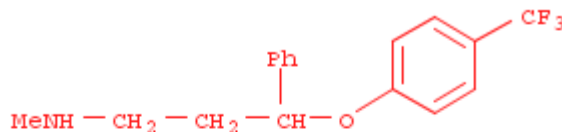
C₁₇ H₁₈ F₃ N O

Benzenepropanamine, N-methyl-γ-[4-(trifluoromethyl)phenoxy]-
Benzenepropanamine, N-methyl-γ-[4-(trifluoromethyl)phenoxy]-,
(±)-; (±)-Fluoxetine; (±)-N-Methyl-3-phenyl-3-[4-
(trifluoromethyl)phenoxy]propylamine; 3-(p-
Trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine; Deprex;
Fluoxetin Ratiopharm; Fluoxetine; Fluoxin; Fluval; N-Methyl-3-(p-
trifluoromethylphenoxy)-3-phenylpropylamine; N-Methyl-3-[4-
(trifluoromethyl)phenoxy]-3-phenylpropanamine; NSC 283480;
Nikomede; Seronil; Symbiax; dl-3-(p-Trifluoromethylphenoxy)-N-
methyl-3-phenylpropylamine

Deleted CAS Registry Numbers: 52341-67-0;57226-07-0

~6,451 References

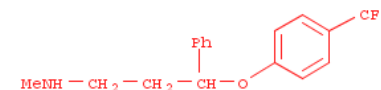
Document Types: Book, Conference, Dissertation, Journal, Patent, Report



CAS Registry Number: 56296-78-7
(Component: 54910-89-3)

C₁₇ H₁₈ F₃ N O · Cl H

Benzenepropanamine, N-methyl-γ-[4-(trifluoromethyl)phenoxy]-,
hydrochloride (1:1)
Benzenepropanamine, N-methyl-γ-[4-(trifluoromethyl)phenoxy]-,
hydrochloride (9CI); (±)-N-Methyl-3-phenyl-3-[4-(trifluoromethyl)
phenoxy]propylamine hydrochloride; Adofen; Affectine; Alzac 20;
Ansilan; Deproxin; Digassim; Erocap; Fluctin; Fluctine; Fludac;
Flufuran; Flunil; Flunirin; Fluox-Puren; Fluoxac; Fluoxeren;
Fluoxetine hydrochloride; Fluoxil; Flutin; Flutine; Fluxen; Fluxetyl;
Fluxil; Fontex; Foxetin; LY 110140; Lilly 110140; Lorien; Lovan;
Margrilan; Modipran; N-Methyl-3-(4-trifluoromethylphenoxy)-3-
phenylpropylamine hydrochloride; N-methyl-3-[4-
(trifluoromethyl)phenoxy]-3-phenylpropanamine hydrochloride;
Neupax; Nodepe; Nopres; Nuzak; Octozac; Oxedep; Pluzac;
Pragmaten; Prizma; Proctin; Prodep; Profluzac; Prozac; Prozac
20; Reconcile; Reneuron; Rowexetina; Salipax; Sanzur;
Sarafem; Sinzac; Zactin; Zedprex; Zepax



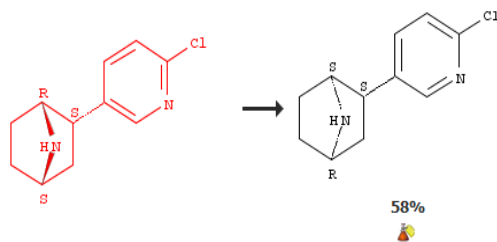
• HCl

Enhancements to CASREACT help chemists find and analyze the most suitable reaction information

- Reaction relevancy ranking
- Experimental procedures from patents and journals
- Sorting options, such as by percent yield and number of steps
- SciPlanner™ to design and communicate synthetic pathways

7. View Reaction Detail [Link](#)

Single Step *Hover over any structure for more options.*



Overview

Steps/Stages

1.1 R:t-BuOK, S:t-BuOH, 5 d, 85°C

Notes

stereoselective, scalable, Reactants: 1, Reagents: 1, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Gram-Scale Synthesis of (-)-Epibatidine
By Lee, Chi-Lik Ken and Loh, Teck-Peng
From Organic Letters, 7(14), 2965-2967; 2005
[Full Text](#)

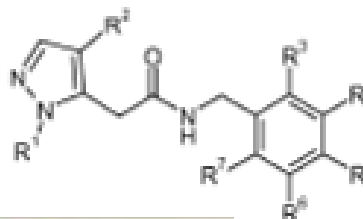
Experimental Procedure



1: exo-2-(6-Chloropyridin-3-yl)-7-azabicyclo[2.2.1]-heptane KO^tBu (3.14 g, 28.02 mmol) was added into a stirred solution of 18 (1.95 g, 9.34 mmol) in ^tBuOH (300 mL) at room temperature. The reaction mixture was then brought to reflux at 85 °C for 3 hours before the same amount of KO^tBu was added again after the reaction mixture had cooled down. The sequential addition of the base was continued for up to 5 days. The reaction mixture was then concentrated in vacuo (Another workup method involved dissolving the reaction mixture in 10% K₂CO₃ solution before extracting it with CH₂Cl₂). The crude product was then purified by flash column chromatography (100:4:1 CH₂Cl₂/MeOH/c.NH₄OH), yielding 1.13 g (5.41 mmol; 58% (isolated yield) 81%(convergent yield)] of the exo adduct 1 as a faint yellow oil. The starting material 18 was recovered (0.58 g, 2.8 mmol, 30%). 1: exo-2-(6-Chloropyridin-3-yl)-7-azabicyclo[2.2.1]-heptane, yield 1.13 g (5.41 mmol 58%) R_f = 0.51 (9:1:0.1 CH₂Cl₂/MeOH/c.NH₄OH); [α]_D 25 = - 5.10 (0.6, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 8.27 (d, J = 2.43 Hz, 1H), 7.76 (dd, J = 2.43, 8.34 Hz, 1H), 7.23 (d, J = 8.34 Hz, 1H), 3.79 (t, J = 4.20 Hz, 1H), 3.55 (s, 1H), 2.76 (dd, J = 5.22, 9.03 Hz, 1H), 1.90 (dd, J = 9.03, 12.18 Hz, 1H), 1.63 - 1.56 (m, 5H); ¹³C NMR (75.4 MHz, CDCl₃): δ 148.8, 148.6, 141.0, 137.7, 123.9, 62.8, 56.5, 44.6, 40.3, 31.4, 30.2; FTIR (neat): 3257, 2965, 2873, 1658, 1563, 1459, 1103, 1056, 1024, 820, 736 cm⁻¹; HRMS (ESI) Calcd for C₁₁H₁₃ClN₂ [M⁺]: 208.0767, found: 209.0842 (M + 1).

MARPAT makes the critical content captured in Markush patent representations accessible via structure searching

(54) Title: PYRAZOLE DERIVATIVES AS P2X7 MODULATORS



(I)

(57) Abstract: The present invention relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof: (I) wherein R¹ represents C₁₋₄ alkyl or C₃₋₆ cycloalkyl, either of which is optionally substituted with 1, 2 or 3 halogen atoms; and R² represents hydrogen, halogen, C₁₋₄ alkyl or C₃₋₆ cycloalkyl; and either of said C₁₋₄ alkyl or C₃₋₆ cycloalkyl is optionally substituted with 1, 2 or 3 halogen atoms. The pyrazole compounds of formula (I) or salts thereof modulate P2X7 receptor function and are capable of antagonizing the effects of ATP at the P2X7 receptor (P2X7 receptor antagonists). The invention also relates to the use of such compounds or salts, or pharmaceutical compositions thereof, in the treatment or prevention of the P2X7 receptor, for example pain, inflammation or a neurodegenerative disease.

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Explore Substances

Chemical Structure | Markush

Markush

Molecular Formula

Substance Identifier

Structure Drawing

File Edit Draw Template QueryDef Display Preferences Window Help

to change structure or view detail

Type: Allow variability on Substructure

STN (Secure Session)

L5 ANSWER 1 OF 25 MARPAT COPYRIGHT 2011 ACS on STN

MSTR 1 Assembled

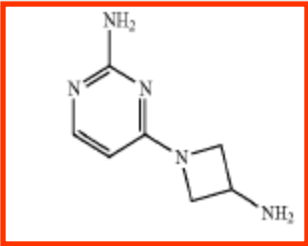
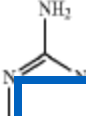
1284, 1285, 1287, 1288, 1290: opt. subst. by 1 or more G14
 G7 = F
 G16 = (1-3) CH₂
 G17 = (1-4) CH₂

Patent location: claim 1
 Note: or acid addition salts and solvates
 Note: additional ring formation also claimed

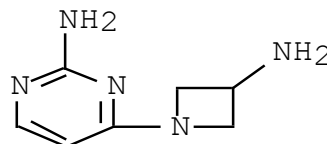
CA/CAPLUS and CAS REGISTRY provide extensive coverage on exemplified prophetic substances

TABLE 2-continued

Examples 26-51.

Starting diamines Example (HNR ¹ R ²) Number and CAS#	Product Structures	May be Prepared by the Method of (substituting the indicated starting diamine)
31 tert-butyl azetidin-3-ylcarbamate CAS # 91188-13-5		Example 7A followed by Example 7B
32 tert-butyl 2,7-diazaspiro[3.5]nonane-7-carboxylate CAS # 236406-55-6		Example 7A followed by Example 7B
33 tert-butyl 1,4-diazepane-1-carboxylate CAS # 112275-50-0		

L1 ANSWER 21 OF 75 REGISTRY COPYRIGHT 2011 ACS on STN
RN 1259941-53-1 REGISTRY
ED Entered STN: 19 Jan 2011
CN 2-Pyrimidinamine, 4-(3-amino-1-azetidiny)-
(CA INDEX NAME)
MF C7 H11 N5
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

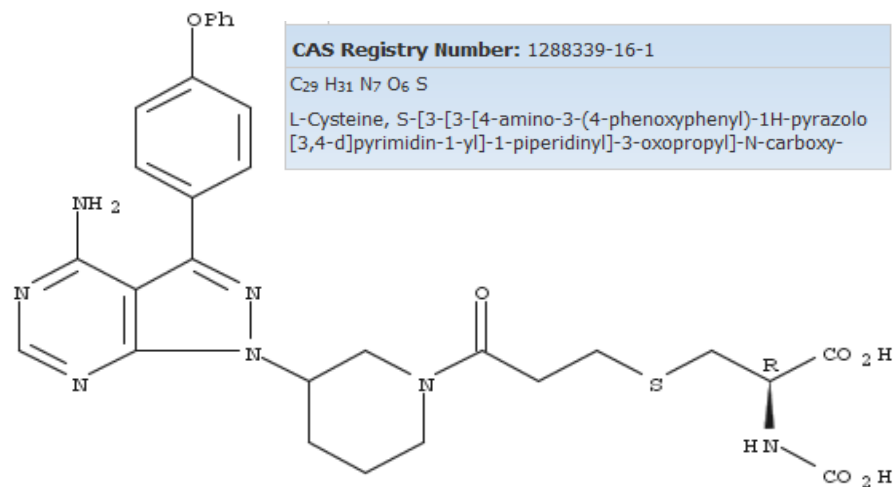
IT	1201176-36-4P	1259941-43-9P	1259941-45-1P	1259941-47-3P
	1259941-50-8P	1259941-53-1P	1259941-56-4P	1259941-58-6P
	1259941-59-7P	1259941-63-3P	1259941-64-4P	1259941-66-6P
	1259941-68-8P	1259941-71-3P	1259941-73-5P	1259941-74-6P
	1259941-77-9P	1259941-79-1P	1259941-81-5P	1259941-82-6P
	1259941-85-9P	1259941-88-2P	1259941-89-3P	1259941-92-8P
		1259941-94-0P	1259941-96-2P	

RL: PAC (Pharmacological activity); PRPH (Prophetic); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of diaminopyrimidine derivs. as histamine H3 receptor ligands useful in treatment of diseases)



CAS coverage of multiple patent basics results in comprehensive substance coverage in REGISTRY

- Since mid-2008, both the PCT application and the core country national equivalent(s) with oldest priority are covered as basic patents in CA/CPlus
- When basics for the same invention have exactly the same substance RN content, a tag of Chemical Indexing Equivalent is included in the SO field
- It is possible to manage the multiple basic content of your answer set using STN Express[®] wizard – you can retain the PCT, the national, the oldest priority, etc.



CAS Registry Number: 1288339-16-1

C₂₉ H₃₁ N₇ O₆ S

L-Cysteine, S-[3-[3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo
[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-3-oxopropyl]-N-carboxy-

Absolute stereochemistry.

Several emerging trends and customer needs continue to drive future enhancements

- **More and more new substances are disclosed in the patent literature**
- **Unique substances will continue to be found in chemical catalogs and chemical libraries**
- **Internet sources provide some otherwise undisclosed substance information**
- **The Pacific Rim, especially Asia, is increasingly productive**
- **More new chemical entities, not fewer, are being disclosed every year thanks to the inventiveness of today's chemists**

A completely new STN will be phased into the market beginning in 2012

It will bring improved efficiency and usability at the expert level. Powerful new elements include:

- **Project-oriented workflow**
- **Combined text and structure queries**
- **Simultaneous query and results interaction**
- **Real-time analysis of results**
- **Virtually no system limits**

The new system will retain the unique value of STN

Our goal is to remain the choice of patent experts:

- STN command line
- Search precision
- High-quality content
- Secure and confidential environment
- Training and support by scientists

The current STN system will continue to be available and supported throughout the development of the new platform

CAS' world class content and powerful functionality will improve efficiency for expert patent search professionals

Content

Asset Library

How do we allow users to better manage saved projects, queries, and alerts?

**Graphical
User
Interaction**

Query Building & Analysis

How can we retain precision and comprehensiveness yet provide better efficiency?

**Command-
Driven
Interaction**

Post-processing

What do users do with their results? How can we help?

**Graphical
User
Interaction**

In summary, CAS is the world's authority for chemical information

- **CAS provides the most complete, curated, quality-controlled, and current coverage of the world's disclosed chemistry**
 - Expanded coverage of Asian literature
 - Cover multiple content sources (e.g., journals, patents, web, chemical catalogs and libraries, etc.)
 - Continually enhanced content and functionality
 - Convenient delivery of information for increased productivity, faster breakthroughs and better decision-making
- **Continuing trends and customer collaboration drive CAS' product enhancements**



A division of the American Chemical Society

CAS is the preferred source for chemical information when customers need to understand complex chemistry and gain advantages to make breakthroughs

"We selected SciFinder because it is the most comprehensive source for peer-reviewed chemical literature."

Carol Hoover, digital information resources manager, Los Alamos National Laboratory.



"We are pleased to select SciFinder to advance our R&D competitiveness."

Dr. Ge Li, chairman and CEO, WuXi AppTec.



"CAS is an invaluable partner for our ongoing success in a dynamic global marketplace."

Dr. Manoj Nerurkar, Head of Small Molecule Discovery & Development, Syngene



