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Reaxys: Making Sense of Chemistry Information

Sandy Lawson
Director R&D
Elsevier Properties SA



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Making Sense for the User is a huge task for any System

Communication: Hearing the request as clearly as possible.

Relevance: Getting to the point as focused as possible.

Simplicity: Keeping your engine where it belongs (under the hood).

Navigation: Knowing where you are and where you should go next.

Selectivity : Balancing the benefits of brevity and comprehensiveness.

Who does it well in general terms?

Google[™]
Switzerland



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Getting Started: Querying

Please enter a chemical identifier and then click "Submit"

2-subst-benzaldehyde to salbutamol

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Query Results Synthesis Plans My Alerts Help

Reactions Substances and Properties Text, Authors and References

Generate structure from name

Double click this frame and draw reaction

Search as / by

- Product
- Starting material
- Any role
- Reagent/ Catalyst
- As drawn
- Substructure:
 - on heteroatoms
 - on all atoms

Ignore stereo
 No isotopes
 No charges
 No radicals
 No additional rings
 Keep Fragments separate
 Ignore Atom Mappings

COPY TO SUBSTANCES TAB CLEAR

Conditions (Form-based) Conditions (Advanced)

Search

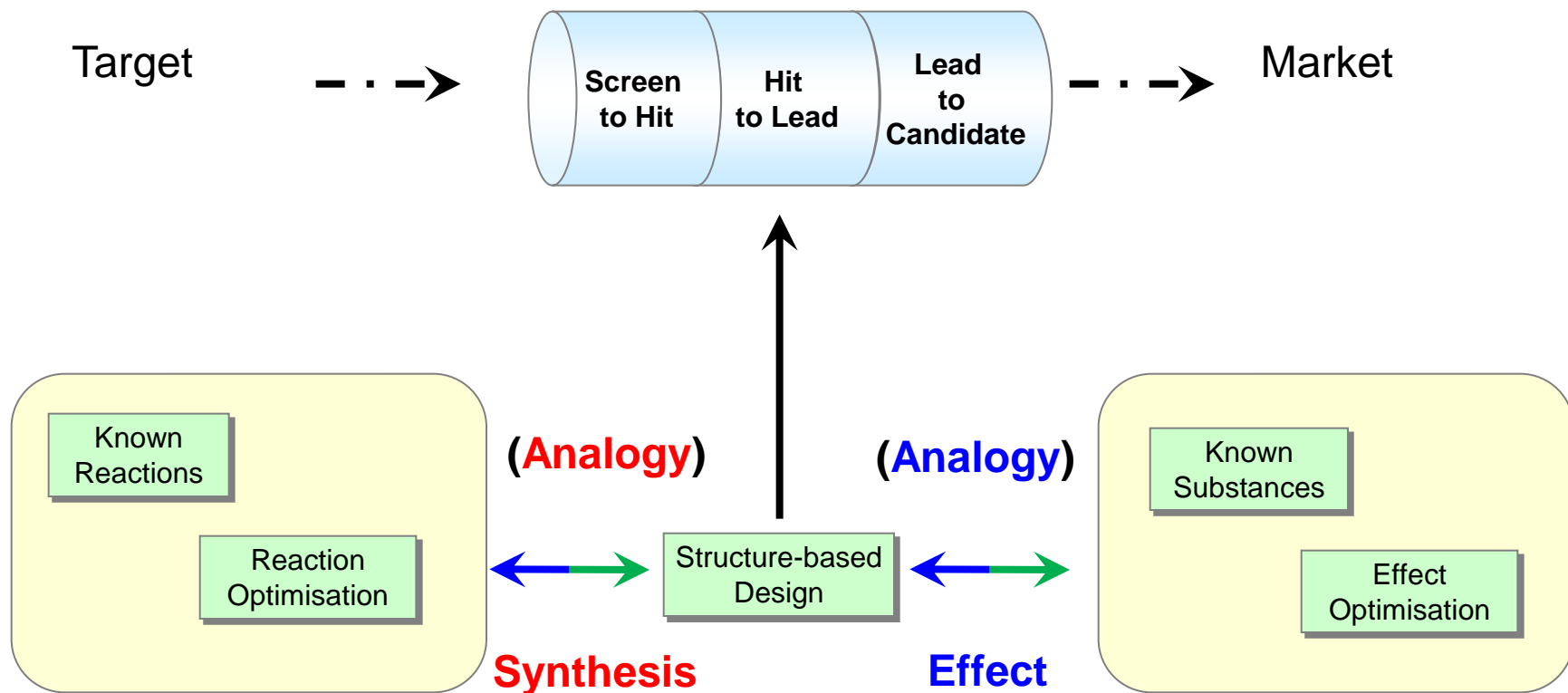
Reaction Data
Bibliographic Data

Clear Query Load Query/Batch Save Query



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***“Whatever you do, it must be new
And never been done before.. “***



What is Closest to **This** (Compound/Property/Reaction)..

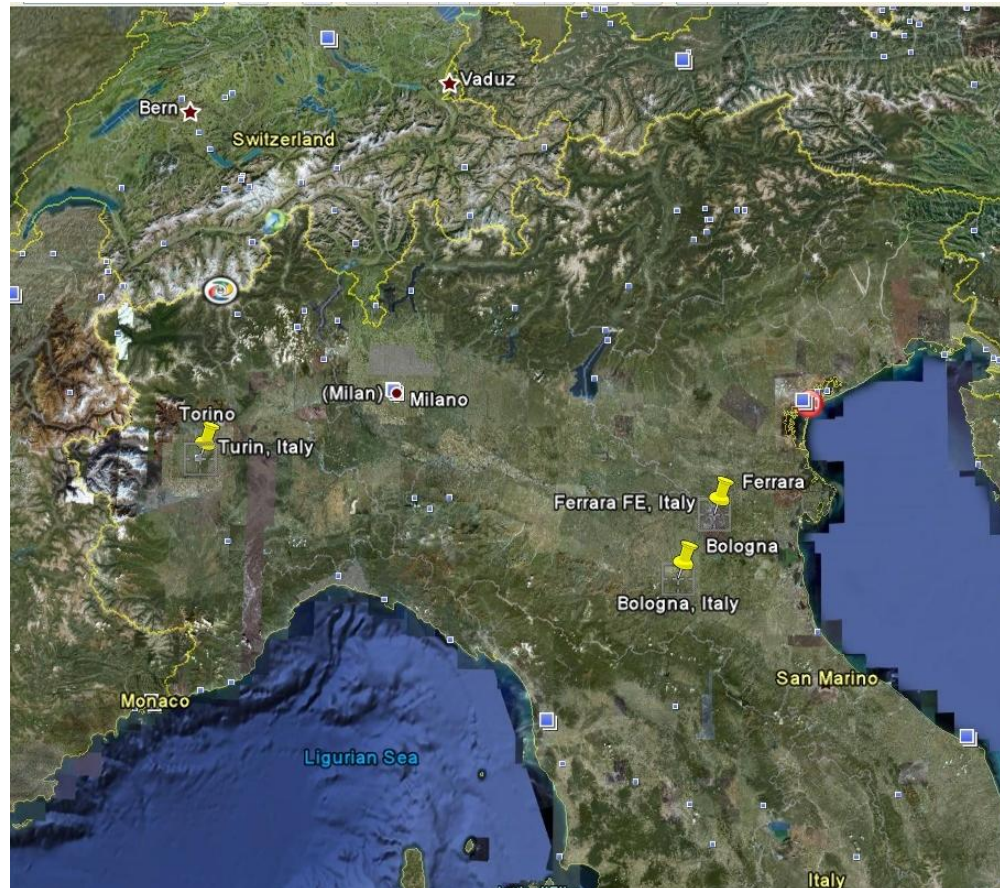
- > .. When my query gives no hits?
- > .. When my query gives too many hits?
- > .. When my browsing turns up something that interests me?
- > .. When I want to know how general **This** is?



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Navigation: sometimes you need this view..



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.. And sometimes you need this view..



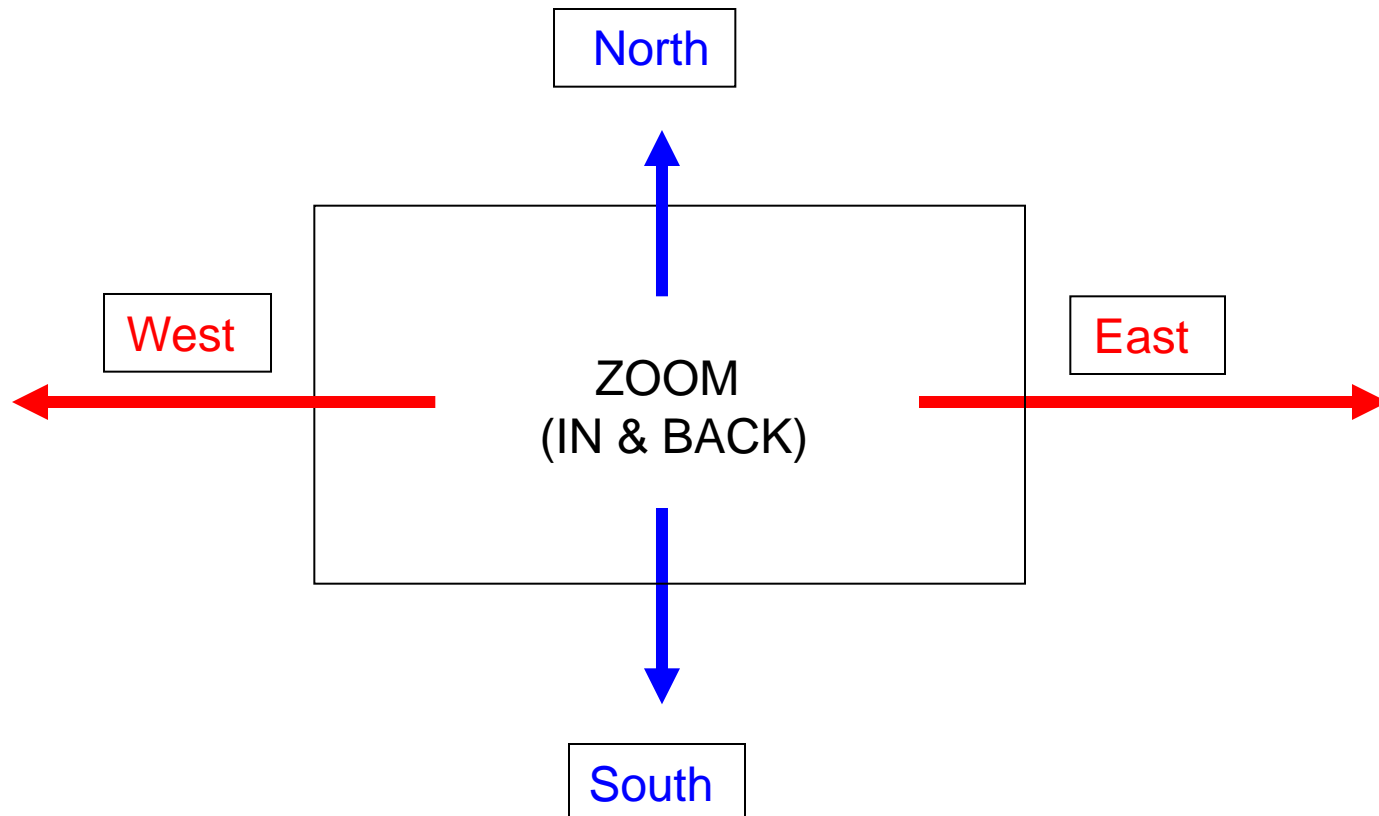
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Navigation: Google uses 2 Axes and a Zoom for Real Space



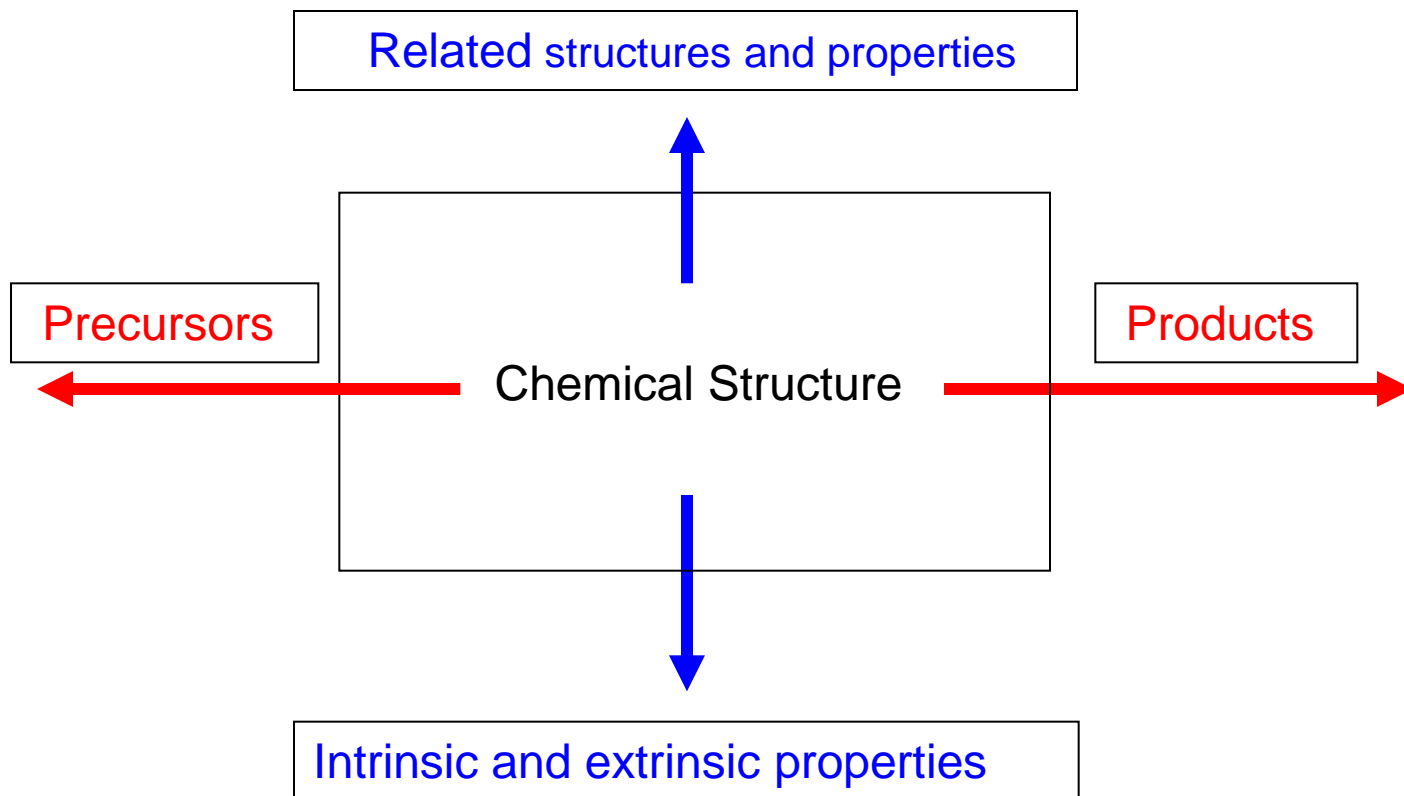
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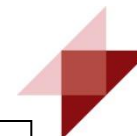
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Navigation: Also in Structure/Property/Reaction Space



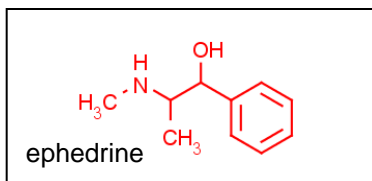
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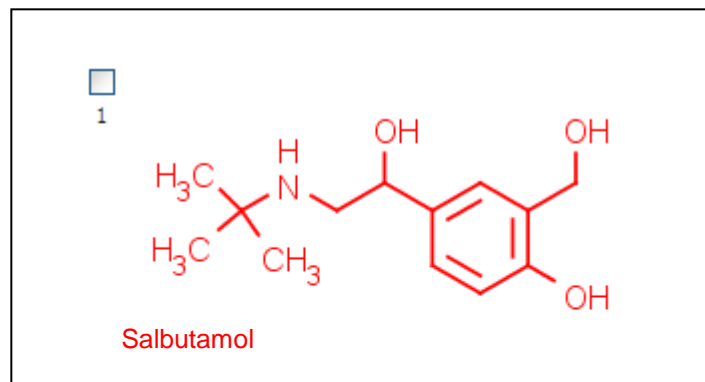
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Related structures and properties

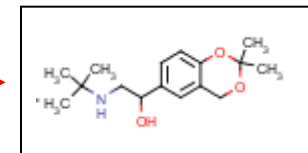


ephedrine
adrenaline
isoprenaline
etc.

Relate it



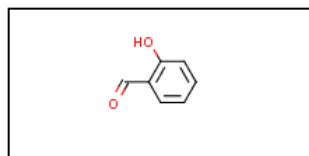
Modify it



Identification (39)
Physical Data (28)
Spectra (16)
Bioactivity/ECOTOX (312)
Use/Application (760)

Measure it

Intrinsic and extrinsic Properties



Make it

Buy it



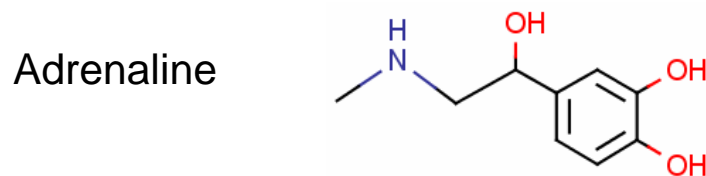
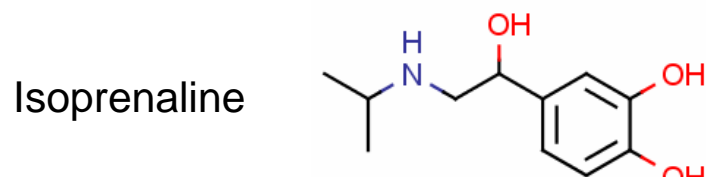
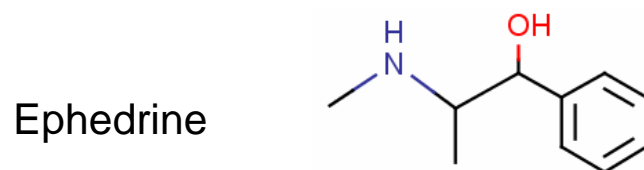
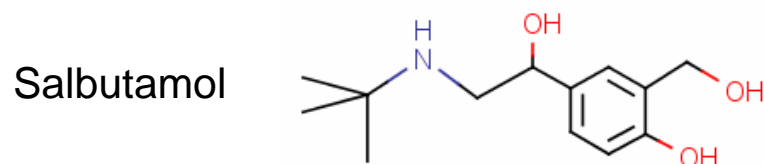
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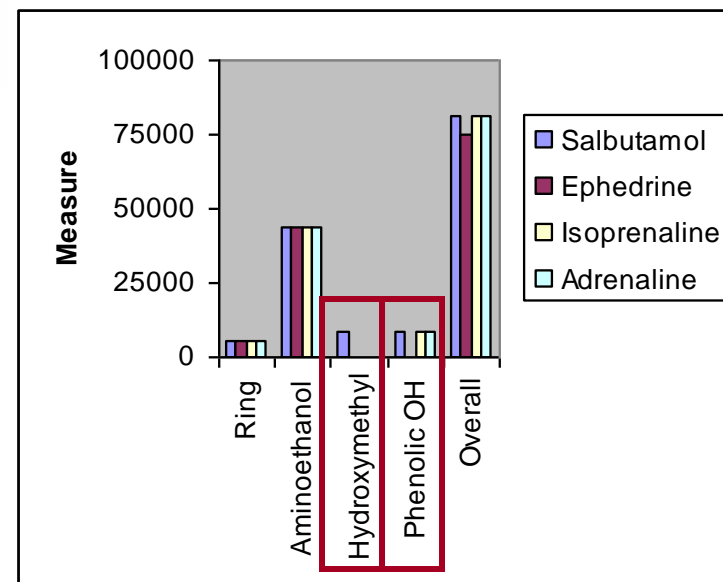
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Under the Hood: Metrics for Structure/Property Axis Example: Chemical Group Classification



Bronchodilator action
(anti-asthma)



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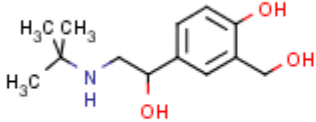
Hard Facts and Brass Tacks: Substance Properties

Query Results Synthesis Plans History My Settings Help

Reactions **Substances and Properties** 1 Authors and more

Generate structure from name

Double click this frame and draw structure query



As drawn
 Substructure:
 on heteroatoms
 on all atoms

Ignore stereo
 No salts
 No mixtures
 No isotopes
 No additional rings
 Further options

Add further search conditions

Search 2

Clear Query Load Query Save Query

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- 1: Select "Substance and Properties" to search a substance with all its data.
- 2: Click „Search“



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Zoom Back: Substance Overview

Query Results Synthesis Plans History My Settings Help Register Login

Query 5 substances

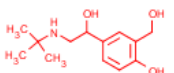
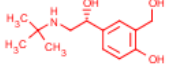
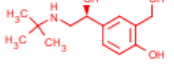
- 5 Hits: Salbutamol and its stereo-isomers
- Physical, spectral, bioactivity, application data

Substances (Grid) Substances (Table) Citations 5 substances out of 371 citations go to Page 1 of 1

Filter by:

- Molecular Weight
- Number of Fragments
- Physical Data
- Spectroscopic Data
- Bioactivity
- Document Type
- Authors
- Patent Assignee
- Journal Title
- Publication Year

Limit to Selection Output Sort by No of References

Structure	Chemical Name	Available Data	No. of ref.	N° of prep.	Boiling Point
 1	4-hydroxy-3-(hydroxymethyl)- α -[(tert-butylamino)methyl]benzenemethanol 2-(tert-butylamino)-1-(4-hydroxy-3-hydroxymethylphenyl)-ethanol (R,S)-salbutamol (R,S)-Albuterol salbutamol Ventoline albuterol	Identification Physical Data (28) Spectra (16) Bioactivity/ECotox (312) Use/Application (760) Natural Product (4)	358	12 prep out of 31 reactions.	
 2	(R)-Salbutamol (R)-salbutamol levalbuterol R-albuterol (R)-albuterol R-salbutamol (R)- α 1-[[[1,1-dimethylethyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol hydrochloride	Identification Physical Data (1) Bioactivity/ECotox (26) Use/Application (171)	29	6 prep out of 7 reactions.	
 3	(S)-salbutamol (S)-albuterol S-salbutamol	Identification Bioactivity/ECotox (27)	9	3 prep out of 3 reactions.	



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Identification

Physical Data

Melting Point (7)

Crystal Phase (1)

Dissociation Exponent (4)

Dissociation Exponent (pK)	Dissociation Group	Temperature	Solvent	Method	Type	Comment	Reference
9.01	N-H	22°C	H2O	spectrophotometric	a1/apparent		Ochsner, Martin; Jaekel, Klaus; Mutz, Michael; Anderson, Gary P.; John, Edgar European Journal of Medicinal Chemistry, 1999 , vol. 34, # 6 p. 451 - 462 Title/Abstract Full Text Scopus
10.1		22°C	H2O	spectrophotometric	a2/apparent		Ochsner, Martin; Jaekel, Klaus; Mutz, Michael; Anderson, Gary P.; John, Edgar European Journal of Medicinal Chemistry, 1999 , vol. 34, # 6 p. 451 - 462 Title/Abstract Full Text Scopus
-0.96		25°C	H2O various solvent(s)	potentiometric	b1/apparent	Ratio of solvents: 0.1 M	Ijzerman, A. P.; Bultsma, T.; Timmerman, H.; Zaagsma, J. Journal of Pharmacy and Pharmacology, 1984 , vol. 36, p. 11 - 15 Title/Abstract Full Text Scopus
-1.02		25°C	H2O various solvent(s)	potentiometric	b2/apparent	Ratio of solvents: 0.1 M	Ijzerman, A. P.; Bultsma, T.; Timmerman, H.; Zaagsma, J. Journal of Pharmacy and Pharmacology, 1984 , vol. 36, p. 11 - 15 Title/Abstract Full Text Scopus

Further Information (1)

Solubility (MCS) (4)

Partition octan-1-ol/water (MCS) (2)

Liquid/Liquid Systems (MCS) (4)

Liquid/Solid Systems (MCS) (1)

Association (MCS) (4)

Spectra

Bioactivity/ECOTOX



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Zoom IN: Biological and Pharmaceutical Data in Depth

⚡ Pharmacological Data (305)

1 of 305	Effect	[3H]CGP 12177 binding; inhibition of
	Species or Test-System	Sf-9 cell membranes; genetically modified/infected with: human β_2 receptor
	Further Details	inhibitory concentration (IC); IC50 related to: β_2 -adrenergic receptor
	Type	IC50
	Value of Type	0.98 $\mu\text{mol/l}$
	Reference	Kern, Christopher; Meyer, Thorsten; Miculka, Christian; Droux, Serge; Schollmeyer, Dieter Journal of Medicinal Chemistry, 2009 , vol. 52, # 6 p. 1773 - 1777 Title/Abstract Full Text View citing articles Show Details
2 of 305	Effect	carbachol-induced contraction; relaxation of
	Species or Test-System	trachea rings of guinea pig
	Kind of Dosing	comparative comp. dissolved in DMSO
	Further Details	EC50 related to: β_2 -adrenergic receptor; effective concentration (EC)
	Type	EC50
	Value of Type	19 nmol/l
Reference	Kern, Christopher; Meyer, Thorsten; Miculka, Christian; Droux, Serge; Schollmeyer, Dieter Journal of Medicinal Chemistry, 2009 , vol. 52, # 6 p. 1773 - 1777 Title/Abstract Full Text View citing articles Show Details	



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Zoom IN: Prep of R-Isomer → Source Document (e.g. Journal)

2 reactions out of 2 citations go to Page Page 1 of 1

Filter by:

- Yield
- Record Type
- Reagent/Catalyst
- Solvent
- Reaction Type
- No. of Steps
- Document Type
- Authors
- Patent Assignee
- Journal Title

Reactions Citations

Limit to Selection Output Sort by Reaxys-Ranking

1

Yield Conditions

Rx-ID: 3708604

2

With $\text{BH}_3^*\text{Me}_2\text{S}$; chiral oxazaborolidine derivative in toluene
1.) 3 h, 0 deg C, 2.) 5 h, reflux; other catalysts, solvents, temperatures and amount of catalyst; Product distribution;

Hong, Yaping; Gao, Yun; Nie, Xiaoyi; Zepp, Charles M.
Tetrahedron Letters, 1994, vol. 35, # 31 p. 5551-5554
Hide Title/Abstract Full Text Scopus

1

Asymmetric Reduction of α -Ketoimines with Oxazaborolidine Catalysts: A Novel, Practical Approach to Chiral Arylethanolamines
Asymmetric borane reduction of α -ketoimines with oxazaborolidine catalysts has been studied. The ee's of the resulting arylethanolamines are up to 93 percent using 20 mol percent of the catalyst.

2

3

Rx-ID: 23242366

90%

With hydrogen gas; triethylamine; (2R,4R)-4-(dicyclohexylphosphino)-2-(diphenylphosphino-methyl)-N-methylaminocarbonyl-pyrrolidine in methanol; toluene
T=50°C; P=15001.5 Torr; 23 h; 3587189 605283; 7418452; 1098229 635760; Product distribution / selectivity;

Boehringer Ingelheim Pharma GmbH and Co. KG
Patent: US2005/9926, 2005
Title/Abstract Full Text



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Zoom IN to Scopus: Other Relevant Papers

Scopus: 21

21 Documents that cite:

[Hong Y.](#), [Gao Y.](#), [Nie X.](#), [Zepp C.M.](#)

Asymmetric reduction of α -ketoimines with oxazaborolidine catalysts: A novel, practical approach to chiral arylethanolamines (1994) *Tetrahedron Letters*, 35 (31), pp. 5551-5554.

[Abstract + Refs](#) [View at Publisher](#) [RSS](#)

Refine Results

Close

Source Title	Author Name	Year	Document Type	Subject Area
<input type="checkbox"/> Tetrahedron Asymmetry (4)	<input type="checkbox"/> Wald, S.A. (3)	<input type="checkbox"/> 2008 (1)	<input type="checkbox"/> Article (16)	<input type="checkbox"/> Chemistry (19)
<input type="checkbox"/> Chinese Journal of Organic Chemistry (3)	<input type="checkbox"/> Gao, Y. (2)	<input type="checkbox"/> 2007 (2)	<input type="checkbox"/> Review (5)	<input type="checkbox"/> Pharmacology, Toxicology and Pharmaceutics (7)
<input type="checkbox"/> Tetrahedron Letters (3)	<input type="checkbox"/> Effenberger, F. (2)	<input type="checkbox"/> 2006 (2)		<input type="checkbox"/> Biochemistry, Genetics and Molecular Biology (4)
More...	More...	More...		More...

[Limit to](#) [Exclude](#)

Results: 21

Search within results [Go](#)

[Output](#) [Citation tracker](#) [Add to List](#) [Download](#) [References](#) [Cited by](#) Select: All Page

1 to 20 [Next](#)

	Document (sort by relevance)	Author(s)	Date	Source Title	Cited By
1.	<input type="checkbox"/> Solvent control of optical resolution of 2-amino-1-phenylethanol using dehydroabiatic acid Abstract + Refs View at Publisher Show Abstract	Taniguchi, K. , Aruga, M. , Yasutake, M. , Hirose, T.	2008	<i>Organic and Biomolecular Chemistry</i> 6 (3), pp. 458-463	2
2.	<input type="checkbox"/> Enantioselective synthesis of (R)-salbutamol hydrochloride Show Abstract	Cheng, Q.-F. , Wang, Q.-F. , Xu, X.-Y. , Ye, Y.-B. , Zhang, H.	2007	<i>Chinese Journal of Organic Chemistry</i> 27 (12), pp. 1558-1561	0
3.	<input type="checkbox"/> Recent development in the asymmetric synthesis of optically active 2-amino-1-phenylethanol derivatives	Zhao, S.-Y.	2007	<i>Chinese Journal of Organic Chemistry</i> 27 (11), pp. 1309-1317	0



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Zoom IN to Scopus: Review Articles

4. <input type="checkbox"/>	Synthesis of (R)-salbutamol via asymmetric transfer hydrogenation of α-iminoketone Show Abstract	Xiao, Y.-J. , Yang, S.-N. , Shi, W. , Yang, L.-P.	2006	<i>Chinese Journal of Organic Chemistry</i> 26 (8), pp. 1103-1105
5. <input type="checkbox"/>	Asymmetric synthesis of active pharmaceutical ingredients Abstract + Refs View at Publisher Show Abstract	Farina, V. , Reeves, J.T. , Senanayake, C.H. , Song, J.J.	2006	<i>Chemical Reviews</i> 106 (7), pp. 2734-2793
6. <input type="checkbox"/>	Chemoenzymatic syntheses of (R)-2-bromo-, (R)2-chloro- and (R)2-azido-1-(1,3-benzodioxol-5-yl)-1-ethanol Abstract + Refs View at Publisher Show Abstract	Antunes, H. , Fardelone, L.C. , Rodrigues, J.A.R. , Moran, P.J.S.	2004	<i>Tetrahedron Asymmetry</i> 15 (17), pp. 2615-2620
7. <input type="checkbox"/>	Industrial methods for the production of optically active intermediates Abstract + Refs View at Publisher Show Abstract	Breuer, M. , Ditrich, K. , Habicher, T. , Hauer, B. , Keßler, M. , Stürmer, R. , Zelinski, T.	2004	<i>Angewandte Chemie - International Edition</i> 43 (7), pp. 788-824
8. <input type="checkbox"/>	Boron-based reducing agents for the asymmetric reduction of functionalized ketones and ketimines Abstract + Refs View at Publisher	Cho, B.T.	2002	<i>Aldrichimica Acta</i> 35 (1), pp. 3-16
9. <input type="checkbox"/>	Application of the chiral acyl anion equivalent, trans-1,3-dithiane 1,3-dioxide, to an asymmetric synthesis of (R)-salbutamol Abstract + Refs View at Publisher Show Abstract	Aggarwal, V.K. , Esquivel-Zamora, B.N.	2002	<i>Journal of Organic Chemistry</i> 67 (24), pp. 8618-8621
10. <input type="checkbox"/>	Stereoselective synthesis of (R)-(-)-denopamine, (R)-(-)-tembamide and (R)-(-)-aegeline via asymmetric reduction of azidoketones by <i>Daucus carota</i> in aqueous medium Abstract + Refs View at Publisher Show Abstract	Yadav, J.S. , Reddy, P. , Thirupathi, Nanda, S. , Rao, A. , Bhaskar	2002	<i>Tetrahedron Asymmetry</i> 12 (24), pp. 3381-3385
11. <input type="checkbox"/>	A convenient stereoselective synthesis of (R)-(-)-denopamine and (R)-(-)-salmeterol Abstract + Refs View at Publisher Show Abstract	Goswami, J. , Bezbaruah, R.L. , Goswami, A. , Borthakur, N.	2002	<i>Tetrahedron Asymmetry</i> 12 (24), pp. 3343-3348
12. <input type="checkbox"/>	Asymmetric reduction of α-functionalized ketones with organoboron-based chiral reducing agents Show Abstract	Cho, B.T. , Chun, Y.S.	2001	<i>ACS Symposium Series</i> 783, pp. 122-135
13. <input type="checkbox"/>	Diastereoselective alkoxy-methylation of aromatic aldehydes with chiral lithiomethyl ethers. Synthesis of optically active monoprotected glycols Abstract + Refs View at Publisher Show Abstract	Ponzo, V.L. , Kaufman, T.S.	1998	<i>Canadian Journal of Chemistry</i> 76 (10), pp. 1338-1343



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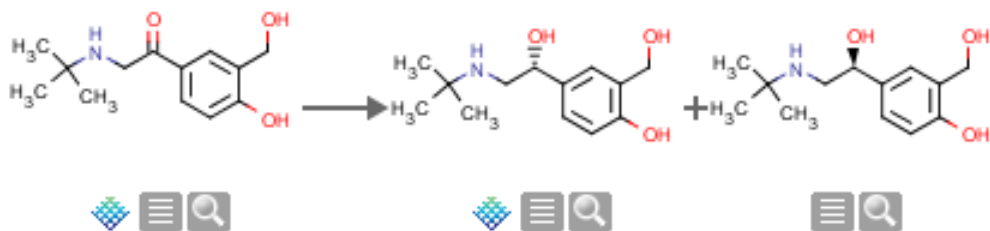
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Zoom IN: Source Document (Patent)

1. Experimental reaction procedure extracted from the patent
2. Abstract of this patent document
3. Click on "Full Text", to link to the EspaceNet-patent server

3



Rx-ID: 23242366

90%

With hydrogen gas; triethylamine; (2R,4R)-4-(dicyclohexylphosphino)-2-(diphenylphosphino-methyl)-N-methyl-aminocarbonyl-pyrrolidine **in** methanol; toluene T=50°C; P=15001.5 Torr; 23 h; 3587189 605283; 7418452; 1098229 635760; Product distribution / selectivity;
[Hide Experimental Procedure](#)

Boehringer Ingelheim Pharma GmbH and Co. KG
Patent: US2005/9926, 2005
[Hide Title/Abstract](#) [Full Text](#)

3

1

10 g of salbutamone are dissolved in 100 ml of methanol (degassed) and 0.13 ml of triethylamine. 4.7 mg of (RhCODCl)₂ and 10 mg of (2R, 4R)-4-dicyclohexylphosphino)-2-(diphenylphosphino-methyl)-N-methyl-aminocarbonyl) pyrrolidine (as a toluenic solution) are added and the mixture is stirred for 23 h at 50.deg. C. and 20 bar hydrogen pressure. The reaction solution is concentrated by rotary evaporation and the residue is recrystallised from ethanol. The salbutamol is obtained in a yield of 90percent in an optical purity of approx. 70percent e.e.

2

Process for preparing (R) salbutamol

The present invention relates to an improved process for preparing levosalbutamol or the pharmacologically acceptable salts thereof on an industrial scale, using asymmetric hydrogenation as the key step and optionally a special sequence of subsequent steps, using rhodium as catalyst and a chiral bidentate phosphine ligand such as (2R, 4R)-4-(dicyclohexylphosphino)-2-(diphenyl-phosphino-methyl)-N-methyl-aminocarbonyl-pyrrolidine as catalyst system.

In this example you have seen:

- > How can Salbutamol be synthesized?
Process details? Yields? Patents? ✓
- > How to buy or synthesize the starting materials?
Supplier data? Reactions? ✓
- > Are there spectral or physical data to identify the
compound? ✓
- > Which physical, bioactivity and application data does it
have? ✓
- > **Which key publications should I read?** ✓



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Making Sense for the User is a huge task for any System

Communication: Hearing the request as clearly as possible.

Relevance: Getting to the point as focused as possible.

Simplicity: Keeping your engine where it belongs (under the hood).

Navigation: Knowing where you are and where you should go next.

Selectivity : Balancing the benefits of brevity and comprehensiveness.



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Thanks for your attention!

😊 *I hope it made sense* 😊

Any Questions?..

