

Reaxysデモンストレーション



エルゼビア・ジャパン株式会社

類似化合物の探索例

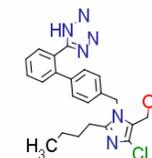


血圧降下剤

アンジオテンシンII受容体拮抗剤

アンジオテンシンIIのアンジオテンシンII受容体への結合を阻害する薬剤
このタイプの降圧剤として日本では、6種類の薬が使用されている

- ・ロサルタン(ニューロタン) 万有製薬
- ・カンデサルタン(プロプレス) 武田薬品
- ・バルサルタン(ディオバン) ノバルティス ファーマ
- ・テルミサルタン(ミカルディス) アステラス
- ・オルメサルタン(オルメテック) 第一三共
- ・イルベサルタン(イルベタン) 塩野義製薬



例: ロサルタン 1994年にメルク社が上市した化合物
血圧降下作用
2006年より、高血圧及び蛋白尿を伴う糖尿病性腎症にも
適応されている



アンジオテンシンII受容体



アンジオテシノーゲン

← レニン

↓
アンジオテンシンI

← アンジオテンシン変換酵素(ACE)

↓
アンジオテンシンII

血管

↓
アンジオテンシンII受容体 — 拮抗薬は受容体に結合し、活性を阻害

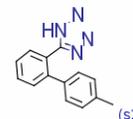
↓
血圧上昇

(血管収縮、副腎からのアルドステロンの生成・分泌促進作用)



3

シナリオ



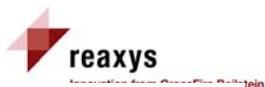
テトラゾールを有する化合物

薬理活性を持ち、効果にantiがつく化合物を検索
(antihypertensiveの検索を想定のため)



4

物質・物性値検索画面



一般名から化学構造式を作成

ダブルクリックし、構造式エディタを開く

5

骨格のみになるように編集し、ウィンドウを閉じる

6

構造が入力される

“生物活性”の“効果”の欄にantiと入力

検索開始

7

検索結果画面 (グリッド表示)

40 substances

40件ヒット

40 substances out of 829 citations go to Page 1 of 5

生物活性のある化合物に限定されている

8

検索結果画面 (表形式表示)



Hide Details

olmesartan medoxomil
CS-866
(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxylate
2,3-dihydroxy-2-butanyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)phenyl]benzyl]imidazole-5-carboxylate, cyclic-2,3-carbonate
(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)phenyl]benzyl]imidazole-5-carboxylate
olmesartan
(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)phenyl]benzyl]imidazole-5-carboxylate

Identification (18)
Physical Data (17)
Spectra (9)
Bioactivity/ECotox (122)
Use/Application (348)

69
13 prep out of 14 reactions.

stein

必要な情報をプルダウン表示

Reaxys Registry Number: 7506931
CAS Registry Number:
Chemical Name: olmesartan medoxomil, CS-866, (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxylate, 2,3-dihydroxy-2-butanyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)phenyl]benzyl]imidazole-5-carboxylate, cyclic-2,3-carbonate, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)phenyl]benzyl]imidazole-5-carboxylate, olmesartan, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)phenyl]benzyl]imidazole-5-carboxylate
Type of Substance: heterocyclic

Molecular Weight: 558.594

InChI Key: UQKIUQLKSCSZGY-VYJLDLGLSCQ

Identification

Physical Data

Spectra

Bioactivity/ECotox

Use/Application

生物活性の表示

効果	種	投与経路	濃度	ドーズ	方法	結果	文献	
抗動脈硬化	Watanabe hypertensive rabbit	peroral	0.5 mg/kg	title comp. suspended in solution containing 0.5 percent carbomethyl cellulose sodium salt and administered by gavage once a day for 32 weeks	title comp. given; animals killed; aortic tissues removed; luminal surface lesion area measured; thoracic aorta stained by HE/PAS; intimal thickness estimated; cellular components of lesion examined; MCP-1, CML protein expression measured by immunosassay	cellular components: macrophage and smooth muscle cells; MCP-1 monocyte chemoattractant; CML; MCP-1 (carbomethyl) lysine; HE; hematoxylin/eosin; EVG; elastic van Gieson (EUG); extracellular lipid deposit; vehicle control	title comp. reduced aortic surface lesion areas; slightly reduced intimal thickness; reduced smooth muscle cell and macrophage areas in lesion by 47 and 51 percent, resp.; reduced MCP-1 and CML expressions (table)	Yanagisawa, Hiroaki; Amemiya, Yoshiya; Kanazaki, Takuro; Shimoi, Yasuo; Fujimoto, Koichi; et al. J. Med. Chem., 1996, #1 p. 323 - 338 Abstract Full Text Scopus Kato, Mikio; Suda, Toshio; Mizuno, Makoto; Kitayama, Ken Inaba, Toshimori; Koike, Hiroyuki J. Cardiovasc. Pharmacol., 2005, vol. 46, # 4 p. 556 - 562 Abstract Full Text Scopus Kato, Mikio; Suda, Toshio; Mizuno, Makoto; Kitayama, Ken Inaba, Toshimori; Koike, Hiroyuki

物性値表示

Physical Data

Spectra

NMR Spectroscopy (3)

Description	Nucleus	Solvents	Frequency	Original Text	Comment	Reference
Chemical shifts	1H	dimethylsulfoxide-d6				Yanagisawa, Hiroaki; Amemiya, Yoshiya; Kanazaki, Takuro; Shimoi, Yasuo; Fujimoto, Koichi; et al. J. Med. Chem., 1996, vol. 39, #1 p. 323 - 338 Abstract Full Text Scopus
Spin-spin coupling constants		dimethylsulfoxide-d6			1H-1H	Yanagisawa, Hiroaki; Amemiya, Yoshiya; Kanazaki, Takuro; Shimoi, Yasuo; Fujimoto, Koichi; et al. J. Med. Chem., 1996, vol. 39, #1 p. 323 - 338 Abstract Full Text Scopus
	1H	chloroform-d3	250MHz	1H NMR (250 MHz, CDCl3) δ: 0.82 (3H, t, J = 7.5 Hz); 1.50 (6H, s); 1.54-1.63 (2H, m); 2.07 (3H, s); 2.48 (2H, t, J = 7.5 Hz); 4.86 (2H, s); 5.32 (2H, s); 6.70 (2H, d, J = 8 Hz); 6.99 (2H, d, J = 8 Hz); 7.3-7.5 (3H, m); 7.72 (1H, dd, J = 1.7 Hz).		ZENTIVA, A.S. Patent WO2007/48361, 2007 Abstract Full Text

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13 prep out of 14 reactions.

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特許由来のデータはケミカルシフトも掲載

IR Spectroscopy (2)

合成計画機能



Hide Data

olmesartan medoxomil
CS-866
(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxylate
2,3-dihydroxy-2-butanyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)phenyl]benzyl]imidazole-5-carboxylate, cyclic-2,3-carbonate
(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)phenyl]benzyl]imidazole-5-carboxylate
olmesartan
(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)phenyl]benzyl]imidazole-5-carboxylate

Reaxys RN: 7506931
MF: C29H30N6O6
MW: 558.594
CAS-RN:
Show Details
Plan a Synthesis
Copy Structure to Clipboard

Identification (18)
Physical Data (17)
Spectra (9)
Bioactivity/ECotox (122)
Use/Application (348)

69
13 prep out of 14 reactions.

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reaxys

Naoko Si

Query Results Synthesis Plans History My Settings Help

Synthesis 1

Undo Open Save Copy plan to new page Synthesis representation Vertical tree

Synthesize

Hints

- Click on "Synthesize" to find all preparations of the comp
- In the browser below review the preparations and Add it synthesis tree
- Click on "Modify" if you want to select different starting m
- Click on the button "Copy plan to new page" if you want routes.

Hide selected details Hide all details Show all details

合成反応の選択

Query Results Synthesis Plans History My Settings Help Logout stein

Synthesis 1

Undo Open Save Copy plan to new page Synthesis representation Vertical tree Hide Hints

Hints

- Click on "Synthesize" to find all preparations of the compound.
- In the browser below review the preparations and "Add" the best one to the synthesis tree.
- Click on "Modify" if you want to select different starting materials.
- Click on the button "Copy plan to new page" if you want to investigate alternative routes.

Hide selected details Hide all details Show all details

候補が12反応あった

12 reactions out of 10 citations go to Page Page 1 of 2

Sort by Reaxys-Ranking

Add

Rx-ID: 17750700

Multi-step reaction with 6 steps

- 86 percent / HCl / Ambient temperature
- 95 percent / diethyl ether; CH2Cl2 / 1 h / 10 - 15 °C
1. t-BuOK / 1. DMA, 0 deg C, 10 min, 2. DMA, RT, 1 h
- LiOH*H2O / dioxane; H2O / 20 h / Ambient temperature

Yanagisawa, Hiroaki; Anemiyama, Yoshiyuki; Kanazaki, Takuro; Shimoi, Yasuo; Fujimoto, Koichi; et al. Journal of Medicinal Chemistry, 1996, vol. 39, # 1 p. 323 - 338 Abstract Full Text Scopus

ELSEVIER

13

合成ルートの結果表示

Query Results Synthesis Plans History My Settings Help Logout stein

Synthesis 1

Undo Open Save Copy plan to new page Synthesis representation Vertical tree Hide Hints

Hide selected details Hide all details Show all details

選択した合成ルートが入力される

12 reactions out of 10 citations go to Page Page 1 of 2

Step	Yield	Conditions	References
1	81%	With 25percent aq. AcOH T=60°C; 2-5 h;	Yanagisawa, Hiroaki; Anemiyama, Yoshiyuki; Kanazaki, Takuro; Shimoi, Yasuo; Fujimoto, Koichi; et al. Journal of Medicinal Chemistry, 1996, vol. 39, # 1 p. 323 - 338 Abstract Full Text
		With acetic acid in water T=55 - 60°C; 2 - 3 h; 506007; 3587155; Product distribution / selectivity;	DR. REDDY'S LABORATORIES LTD. Patent: WO2007/17135

反応条件は下に表示

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反応画面へのリンク

Query Results Synthesis Plans History My Settings Help Logout stein

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Show Details

olmesartan medoxil

CS-866
(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-((1-hydroxy-1-methyl-2-propyl-1-(2-(1H-tetrazol-5-yl)-1,1-biphenyl-4-yl)methyl)-1H-imidazole-5-carboxylate

Identification (18)
Physical Data (17)
Spectra (9)
Bioactivity/Toxic (122)
Use/Application (348)

69

13 prep out of 14 reactions

反応をクリックすると反応画面へリンク

Yield	Conditions	Ref.
81%	With 25percent aq. AcOH T=60°C; 2-5 h;	Yanagisawa, Hiroaki; Anemiyama, Yoshiyuki; Kanazaki, Takuro; Shimoi, Yasuo; Fujimoto, Koichi; et al. Journal of Medicinal Chemistry, 1996, vol. 39, # 1 p. 323 - 338 Abstract Full Text
	With acetic acid in water T=55 - 60°C; 2 - 3 h; 506007; 3587155; Product distribution / selectivity;	DR. REDDY'S LABORATORIES LTD.; DR. REDDY'S LABORATORIES, INC. Patent: WO2007/17135, 2007 Abstract Full Text
	With hydrogen chloride in methanol; dichloromethane T=0 °C; 1 - 2 h; 1046214; 1046214; 1730800;	DR. REDDY'S LABORATORIES LTD.; DR. REDDY'S LABORATORIES, INC. Patent: WO2007/17135, 2007 Abstract Full Text

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収率でフィルタリング

Query Results Synthesis Plans History My Settings Help Logout stein

40 substances 13 reactions

13 reactions out of 11 citations go to Page Page 1 of 2

Filter by:

Yield

- >=85 - 90 4
- >=80 - 85 2
- >=70 - 75 1
- >=55 - 60 1

More

Limit to Exclude

Filter by:

Record Type

Reagent/Catalyst

Solvent

Reaction Type

No. of Steps

Document Type

Authors

Patent Assignee

Journal Title

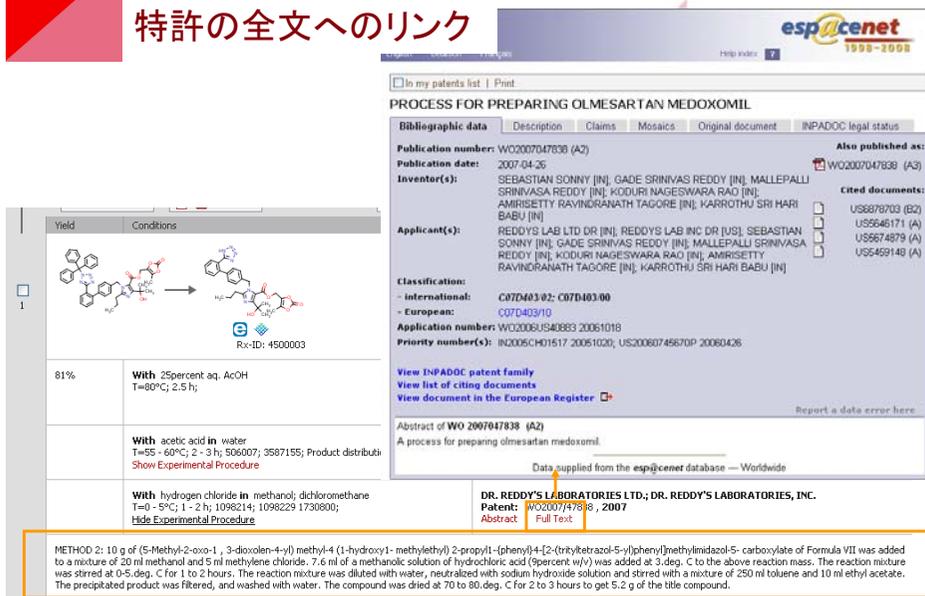
9 reactions out of 11 citations go to Page Page 1 of 2

作業履歴はグラフィックで表示

Yield	Conditions	Ref.
90%	In water; acetone 1 h; 3587155; 635680; Heating / reflux; Show Experimental Procedure	Hochuli, Ilkay; Pflücker, Gidon Patent: US2006/149078, 2006 Abstract Full Text
	In butan-2-one T=60°C; 20 - 22 h; 741880; Heating / reflux; Purification / work up; Show Experimental Procedure	KRKA Patent: WO2007/17135, 2007 Abstract Full Text

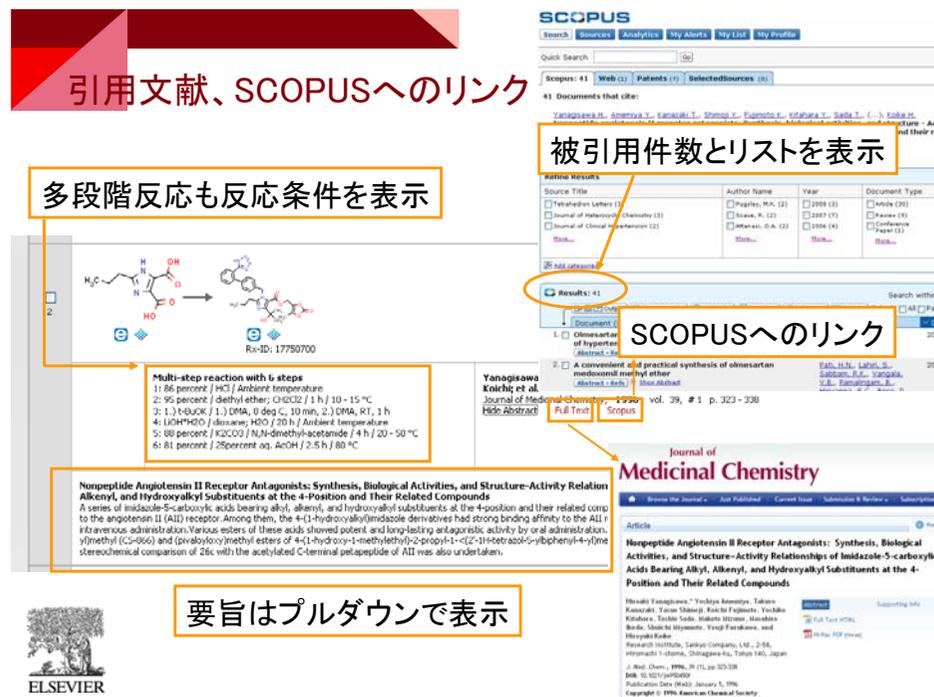
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特許の全文へのリンク



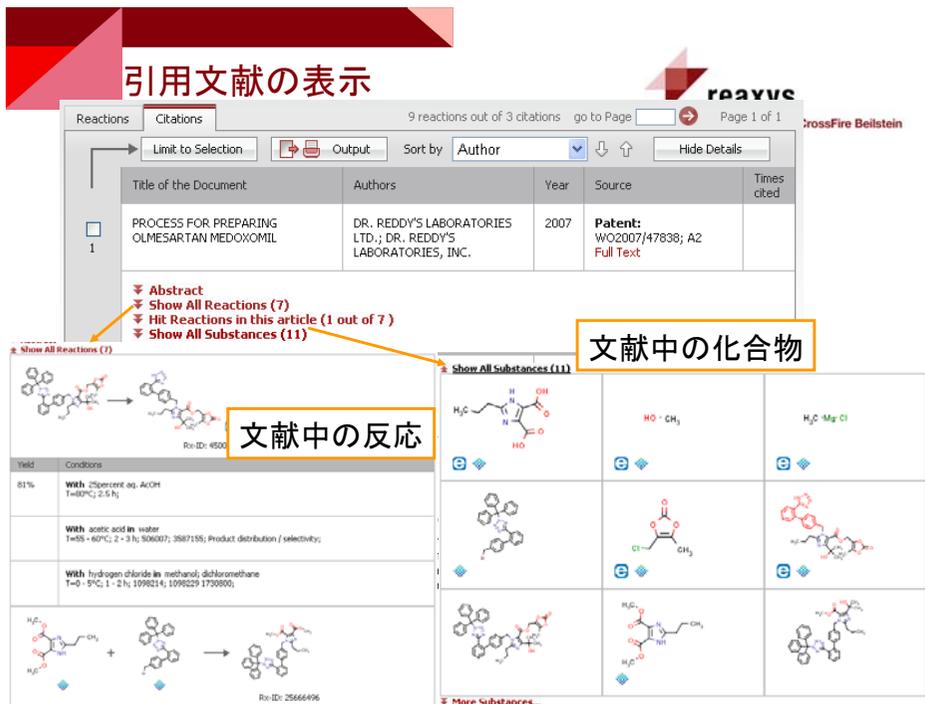
実験項の表示

引用文献、SCOPUSへのリンク



要旨はプルダウンで表示

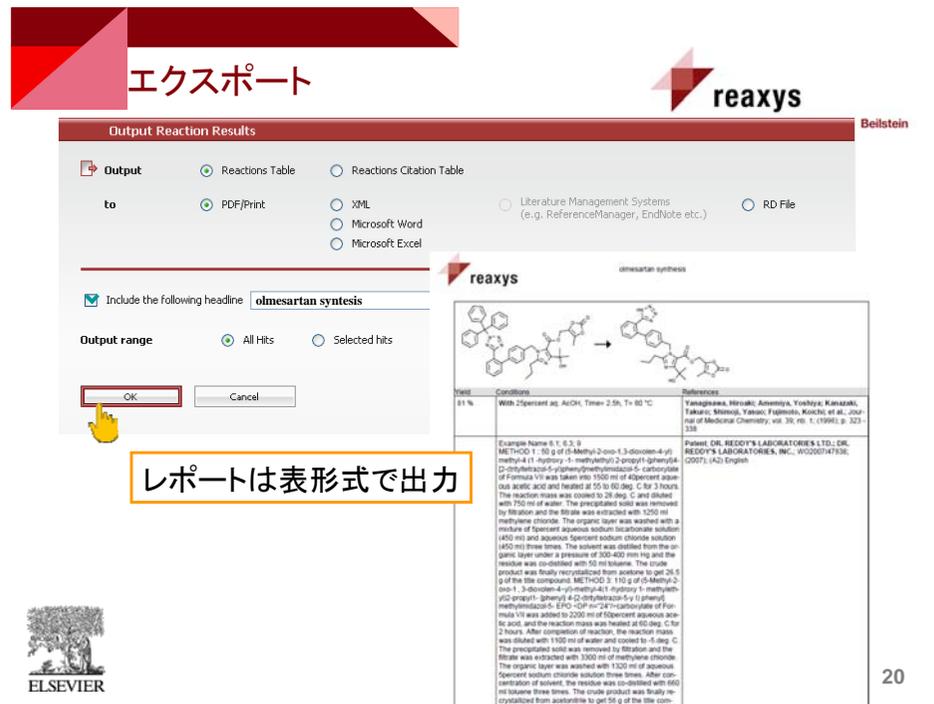
引用文献の表示



文献中の化合物

文献中の反応

エクスポート



レポートは表形式で出力