

## Enzyme-Inhibitors

**Web URL:** www.locatorplus.gov

### 1. **Effects of total coumarins from the fruits of *Cnidium monnieri* on production of NO, IL-1 and IL-6 from osteoblast in neonatal rat calvaria cultures**

Qiaoyan, Z., Luping, Q., Yeping, T., Hanchen, Z., Baokang, H., Zude, L. and Mao, H.

Department of Pharmacognosy, College of Pharmacy, Second Military Medical University, Shanghai, Peop. Rep. China 200433

*Zhongguo Yaoxue Zazhi* (Beijing, China) 2003, **38**(5), 345-348; C.A. **141**(1): 1139u

**Abstract:** Studies were conducted to analyze the effects of total coumarins from the fruits of *Cnidium monnieri* (TC-FC), on the production of NO, IL-1 and IL-6 from the osteoblasts in neonatal calvaria cultures.

**Activity and bioassay:** Thymic cells proliferation and bioassay of B9 cells as target cells by Griess agents were performed to monitor the levels of NO, IL-1 and IL-6. <sup>3</sup>H-TdR assay was used for the proliferation assessment of the osteoblasts. TC-FC displayed remarkable inhibition on the production of NO, IL-1 and IL-6, either spontaneous or induced by TNF, IL-1 and LPS from osteoblasts. As a result of this inhibition, TC-FC exhibited anti-osteoparotic activity.

**Origin:** Osteoblastic cells from the new born rat calvaria through trypsin and collagenase digestion.

### 2. **Use of an RAR receptor antagonist for potentiating the action of TGF $\beta$ , and therapeutic use**

Serge, M., Andre, J., Michel, D., Alain and Valerie, P.

Galderma Research & Development, S.N.C., France

**PCT Int. Appl. WO 2004, 45,595** (Cl. A61K31/192), 3 Jun 2004, US Appl. PV430, 671, 4 Dec. 2002; 25 pp; C.A. **141**(1): 1297u

**Abstract:** The RAR receptor antagonist, for instance 4-(5,5-dimethyl-8-*p*-tolyl-5,6-dihydronaphthalene-2-ylethynyl)benzoic acid, exhibited potency for TGF $\beta$  action, used to treat deficient conditions of TGF $\beta$  signals and enhancement of these signals as well.

**Activity:** Potential for TGF $\beta$  signal

**Origin:** Molecular biology

### 3. **Drug for inhibiting production of matrix metalloprotease-9**

Takashi, K.

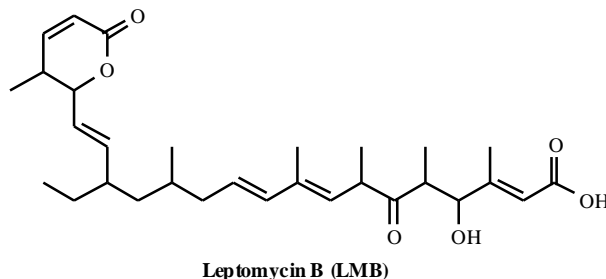
Japan Science and Technology Agency, Japan

**PCT Int. Appl. WO 2004, 45, 602** (Cl. A61K31/351), 3 Jun 2004, JP Appl. 2003/286, 386, 5 Aug. 2003; 38 pp; C.A. **141**(1): 1299w

**Abstract:** Leptomycin B and its analogs inhibited the production of matrix metalloprotease-9 (MMP-9), as compared to MMP-2. MMP-9 inhibition in other conditions is also discussed in the present patent.

**Activity:** MMP-9 and MMP-2 inhibitors

**Origin:** Natural product



**Web URL:** [www.bentham.org/lddd](http://www.bentham.org/lddd)

#### 4. Somatostatin receptor subtype 4 (sst<sub>4</sub>) ligands: Synthesis and evaluation of indol-3-yl- and 2-pyridyl-thioureas

Crider, A. M., Liu, S., Li, T., Mahajan, S., Ankersen, M. and Stidsen, C. E.

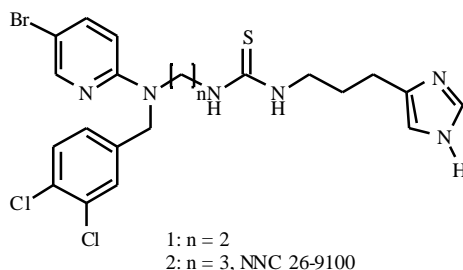
Department of Basic Pharmaceutical Sciences, School of Pharmacy, University of Louisiana at Mooroe, LA 71209 USA

*Letters in Drug Design & Discovery* 2004, **1**(1), 84-87; *C.A.* **141**(1): 416v

**Abstract:** The thiourea group acts as a scaffold to attach the pharmacophoric group of somatostatin. Thiourea analogs of NNC 26-9100 (**2**) were prepared as somatostatin receptor subtype 4 (sst<sub>4</sub>) ligands. The replacement and substitution of various groups on **1** and its intermediates play a major role in the affinity and selectivity of these thioureas as sst<sub>4</sub>. Detailed studies on preparation and SAR of these derivatives are also provided.

**Activity and bioassay:** Somatostatin receptor inhibition assay. The indole exhibited high affinity (K<sub>i</sub> = 23 nM) and about a 100-fold selectivity at sst<sub>4</sub> compared to sst<sub>2</sub> receptors.

**Origin:** Synthetic



**Web URL:** <http://www.tandf.co.uk>

#### 5. Some aryl substituted 2-(4-Nitrophenyl)-4-oxo-4-phenylbutanoates and 3-(4-nitrophenyl)-1-phenyl-1, 4-butanediols and related compounds as inhibitors of rat liver microsomal retinoic acid metabolising enzymes

Peter, M., Valerie, G. P., Andrew, J. K., Claire, S., Paul, J. N. and John, S. H.

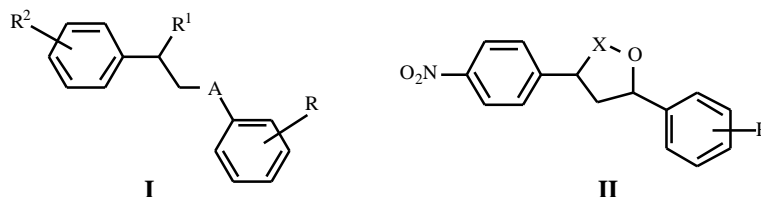
*Journal of Enzyme Inhibition and Medicinal Chemistry* 2003, **18**(6), 511-528; *C.A.* **141**(1): 6874q

**Abstract:** The present investigations described the studies of compounds displaying inhibition against rat liver microsomal retinoic acid metabolising enzymes compared with ketoconazole, which itself exhibited 80% inhibition. Me 2-(4-nitrophenyl)-4-oxo-4-phenylbutanoates **I** [R<sup>2</sup>=4-NO<sub>2</sub>, A=C(:O), R<sup>1</sup>=CO<sub>2</sub>Me, R=4-Br,2,5-Cl<sub>2</sub>, 3-Cl, etc.] showed 4-73% inhibition, whereas transformation of **I** to the corresponding 3-(4-nitrophenyl)-1-aryl-1,4-butanediols **I** [R<sup>2</sup>=4-NO<sub>2</sub>, A=CH(OH), R<sup>1</sup>=CH<sub>2</sub>OH, R = H, 4-Br, 2,5-Cl<sub>2</sub> etc.] enhanced the activity to 29-78%. The most significant activity was shown by compounds **I** [R<sup>2</sup>=4-NO<sub>2</sub>,A=C(:O), R<sup>1</sup>=CO<sub>2</sub>Me, R=iodo; X=4-NO<sub>2</sub>, A=CH(OH), R<sup>1</sup>=CH<sub>2</sub>OH, R =iodo, MeO] in both the series.

**Activity:** The corresponding 5-membered lactones **II** [X= C(:O), CH<sub>2</sub>; R=H, 4-Br, 2,4-Cl<sub>2</sub>], showed 52%, 67% and 69% inhibition. The enzyme activator oxime Me 4-(2,4-dichlorophenyl)-4-hydroxyimino-2-(4-nitrophenyl)-butanoate on Beckmann rearrangement gave potent inhibitors, Me 3-(2,4-dichlorophenylamino)-4-oxo-2-(4-nitrophenyl)butanoate and Me 3-(2,4-dichlorophenylamino)-2-(4-nitrophenyl)propanoate with 75% and 74% inhibition, respectively.

**Bioassay:** Inhibition studies on rat liver microsomal retinoic acid metabolising enzymes

**Origin:** Synthetic



## 6. Preparation of aryltriazolecarboxylates as cytokine inhibitors

Derek, C. A., Ming-Hong, H., Chungeng, Q. K. and David, S. A.

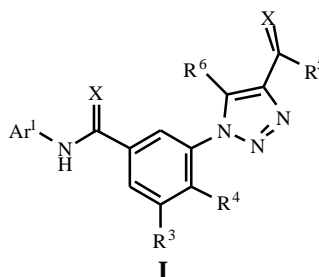
Boehringer Ingelheim Pharmaceuticals, Inc., USA

**U.S. Pat. Appl. Publ. U.S 2004, 102,492** (Cl. 514-359; C07D249/04), 27. May 2004, US appl. PV430,519, 27 Nov 2002; 68 pp; C.A. **141**(1): 7121d

**Abstract:** This patent describes the synthesis of aryltriazolecarboxylates derivatives [**I**; Ar<sup>1</sup> = substituted carbocyclyl; R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup> = H, halo, alkyl, alkoxy, OH, hydroxyalkyl, amino; R<sup>5</sup> = bond, O, S, NH, CO, (substituted) aryl, heteroaryl; X = O, S]. These are useful as cytokine inhibitors. Other pharmacological uses are also given.

**Activity:** Cytokine inhibitor

**Origin:** Synthetic



## 7. Preparation of 4-hydroxy-5,6,9,10-tetrahydro-10-[(2-methyl-1h-imidazol-1-yl)methyl]-4H-pyrido-[3,2,1-jk]-carbazol-11(8H)-one and diastereomers thereof as 5-HT<sub>3</sub> antagonists

Reinhard, B., Christian, E., Email, F., Holger, F., Eric, R., Marco, R., Holger, S., Jochen, S. and Paul, V.

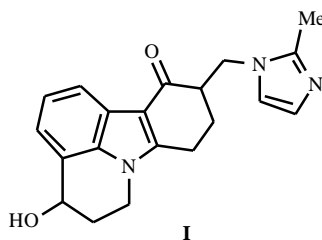
Solvay Pharmaceuticals GmbH, Germany

**Eur. Pat. Appl. EP 1, 424337** (Cl. C07D471/06), 2 Jun 2004, Appl 2002/26, 237, 26 Nov. 2002; 15 pp; C.A. **141**(1): 7122e

**Abstract:** Synthetic and biological studies of 4-hydroxy-5,6,9,10-tetrahydro-10-[(2-methyl-1h-imidazol-1-yl)methyl]-4H-pyrido-[3,2,1-jk]-carbazol-11(8H)-one and its diastereoisomers were carried out in the current patent.

**Activity and bioassay:** 5 - H<sub>3</sub> antagonist assay. This mixture of **I** and its diastereoisomers (mixture) exhibited K<sub>i</sub> = 3.0 nM for binding to human 5-HT<sub>3</sub> receptors.

**Origin:** Synthetic



## 8. Preparation of benzotriazole-5-carboxylic acids for treatment of metabolic-related disorders

Graeme, S., Philip, S.-N., Martin, C., Peter, W. and Yoshido, T. S.

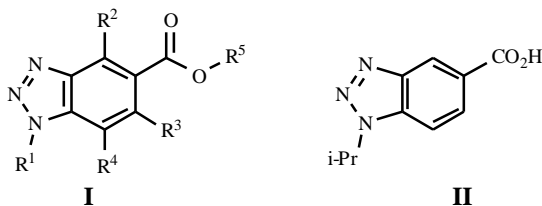
Arena Pharmaceuticals, Inc., USA

**PCT Int. Appl WO 2004, 41, 274** (Cl A61k31/4192), 21 May 2004, US Appl. PV423, 819, 5 Nov. 2002; 85 pp; C.A. **141**(1): 7118h

**Abstract:** The synthetic analogues of benzotriazolecarboxylic acid **I** [wherein  $R^1$  = (un)substituted alkyl, cycloalkyl, or haloalkyl;  $R^2$ - $R^4$  = independently H, acyl, acyloxy, alkenyl, alkoxy, alkyl, OH,  $NO_2$ , SH, etc.;  $R^5$  = H or alkyl; with provisos], or pharmaceutically acceptable salts or solvates of **I** are prepared.

**Activity and bioassay:** Metabolic related disorders. These compounds are used for curing metabolism abnormalities, for instance dyslipidemia, atherosclerosis, coronary heart diseases, insulin resistance, type **II** diabetes, syndrome-X, etc. Compound **II** exhibits inhibition of hRUP38 with  $EC_{50}$  of 388 nM.

**Origin:** Synthetic



## 9. Preparation of substituted phenyl amides as LXR and LXR agonists

Scott, T. K., James, F. S., Lara, S. K., Chun, M., Joseph, P., Michael, J. N. and Ning, W.

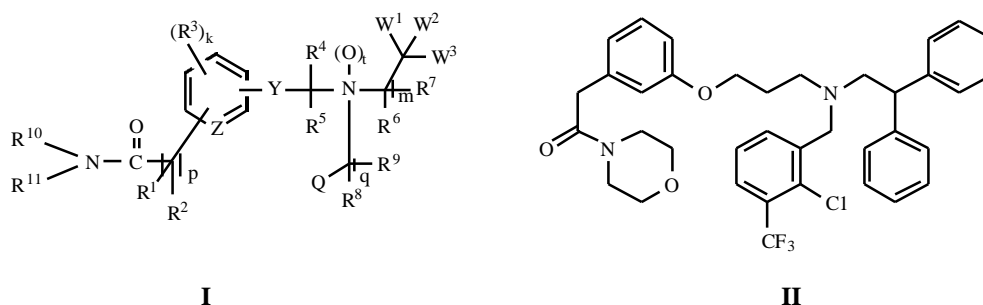
SmithKline Beecham Corporation, USA

**PCT Int Appl WO 2004, 43, 939** (Cl. C07D265/30), 27 May 2004, US Appl. PV368.427.27 Mar. 2002; 105 pp; C.A. **141**(1): 6921c

**Abstract:** The present synthesis covers the preparation of LXR agonists of LXR and LXR type eg. **I** [Z = C(H, alkyl, etc.), N; k = 0-4; t = 0-1; Y = O, S, aminoalkyl;  $W^1$  = alkyl, cycloalkyl, aryl, etc.;  $W^2$  = H, halo, alk(en/yn)yl, etc.;  $W^3$  = H, halo, alkyl, etc.; Q = cyclo, alkyl, aryl, heteroaryl; p = 0-8; n = 2 -8; m, q, t = 0-1;  $R^{1-2}$  = H halo, alk(en/yn)yl, etc.;  $R^{4-11}$  = H, halo, alkyl, etc.]. Preparation of **II** is also described in the present investigation.

**Activity:** LXR and LXR agonists

**Origin:** Synthetic



## 10. Preparation of aryl ureido benzoic and benzene-sulfonic acid derivatives, in particular benzoic acid derivatives, as selective and non-competitive antagonists of GluR5 receptor

Jon, V., Ostergaard, N. E. and Dan, P.

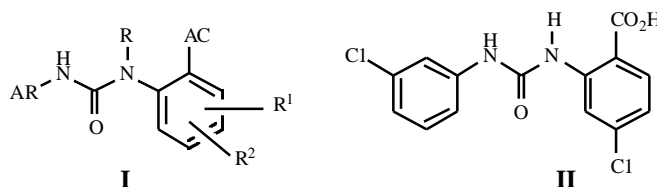
Neurose-arch A/s, Denmark

**PCT Int Appl. WO 2004, 46, 090** (Cl. C07C275/00), 3 Jun 2004, Dk Appl 2002/1,803, 21 Nov. 2002; 44 pp; C.A. 141(1): 6925g

**Abstract:** In the present research, studies have been undertaken on the preparation of synthetic analogs of aryl ureido benzoic and benzene sulfonic acid. The compounds **I** [wherein AC = acidic group selected from SO<sub>2</sub>OH, SO<sub>2</sub>NH<sub>2</sub>, (CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>H 5-oxo=4,5 -dihydro-[1,2,4] oxadiazol-3-yl, and 1H-tetrazol-5-yl, CX(OH); X= O, NR' = H, alkyl; XR' = heterocyclyl; R =H, alkyl R X = heterocyclyl; n = 0-3; R<sup>1</sup>, R<sup>2</sup> = independently H, halo, cyclo/cycloalkyl/halo/alkyl, NO<sub>2</sub>, CN, with R<sup>1</sup> = R<sup>2</sup> = H never allowed; AR = (un)substituted aromatic mono-, bi-, and polycyclic carbocyclic or heterocyclic group; any of its enantiomers or any of its mixts., or salts are biologically active.

**Activity and bioassay:** Antagonists of GluR5 receptor. These compounds were found to exhibit selective and non-competitive antagonists activity against the ionotropic GluR5 receptor. These are used in the treatment of diseases related to modulation of an aspartate or a glutamate receptor, particular CNS and PNS diseases. An IC<sub>50</sub> = 1.3 μM was exhibited against GluR5, and 37 μM against GluR6 by **II** as determined by Ca flux assay.

**Origin:** Synthetic



## 11. Preparation of imidazoquinoline derivatives as adenosine A3 receptor ligands

Peter, A., Laszlo, B., Maria, B.,

Sanofr-Synthelobo, France

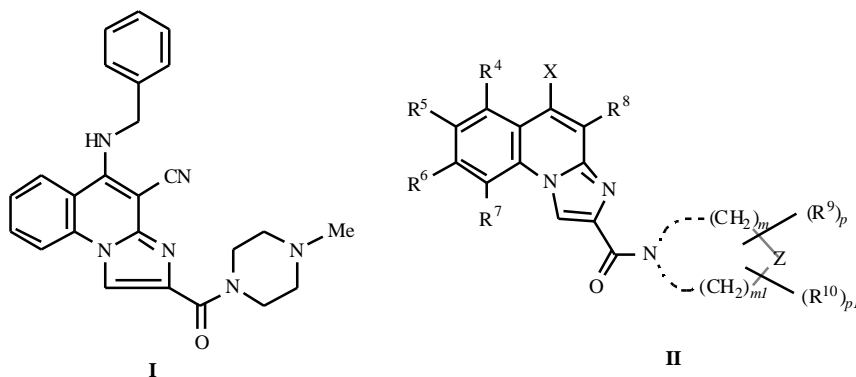
**PCT Int. Appl. WO 2004, 46, 146** (Cl. C07D471/04), 3 Jun 2004 HU Appl. 2002/200,203,976, 15 Nov. 2002; 53 pp; C.A. 141(1): 7117g

**Abstract:** The present investigations revealed the synthesis and medicinal importance of **I** [R<sup>1</sup>, R<sup>2</sup> = H, alkyl; R<sup>3</sup> = H, alkyl, cycloalkyl. (substituted) Ph, (substituted)thienyl, (substituted)furyl, a 6- or 5-membered heteroaromatic, ring containing. 1, 2, or 3 N, etc.; R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> = H, alkyl, alkoxy, OH, halo, or R<sup>4</sup>, R<sup>7</sup> = H and R<sup>5</sup>, R<sup>6</sup> = a methylenedioxy group; R<sup>8</sup> = H, CN, aminocarbonyl, alkoxy carbonyl, or carboxy; R<sup>9</sup>, R<sup>10</sup> = H, alkyl, or cycloalkyl; X = CH<sub>2</sub>-, -NH-, -NR<sup>11</sup>-, S, O, SO<sub>2</sub>, or SO wherein R<sup>11</sup> stands for alkyl or cycloalkyl; Z = O, S, -NH-, or -NR<sup>12</sup>-

where R<sup>12</sup> stands for alkyl or cycloalkyl; n = 0-2; m = 0-3; m<sub>1</sub> = 0-3; p = 0 or 1; p<sub>1</sub> = 0 or 1, with the proviso that at least one of m and m<sub>1</sub> is different from zero].

**Activity:** Adenosine A<sub>3</sub> receptor ligands. These imidazoquinoline compounds are useful ligands of adenosine A<sub>3</sub> receptor. Compound **II** displayed inhibition of adenosine receptors binding in human with K<sub>i</sub> = 0.8 nM – 700 mM.

**Origin:** Synthetic



**Web URL:** <http://sciencedirect.com>

## 12. Small molecule biaryl FSH receptor agonists. Part 1 lead discovery via encoded combinatorial synthesis

Tao, G., Anton, A. E. P., Roland, D. E., Guizhen, D., Dan, F., Peng, G., Koc-Kan, H., Steven, K. G., Ruiyan, L., Edward, M., Brian, M. F., Kurt, S. W., Kenneth, V. J., Nicole, V. S. C. R., Dan, X. and Maria, W. L.

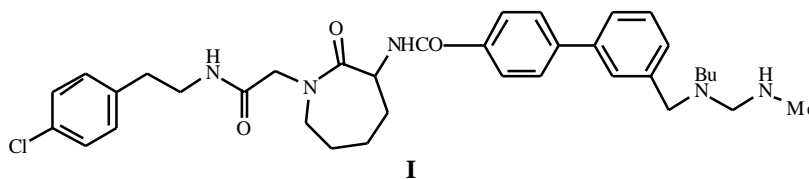
Pharmacopia, Inc., Princeton, NJ 08543-5350 USA

*Bioorganic & Medicinal Chemistry Letters* 2004, **14**(7) 1713-1716; *C.A.* **141**(1): 7009y

**Abstract:** Combinatorial library with a total of 31,372 compounds was designed, prepared and screened to identify 72 biaryl FSH receptor agonists e.g. **I** including unique combinational SAR.

**Activity:** FSH receptor agonists

**Origin:** Synthetic



**Web URL:** <http://sciencedirect.com>

## 13. Lactams as EP<sub>4</sub> prostanoid receptor subtype selective agonists. Part 1: 2-Pyrrolidinones- stereochemical and lower side-chain optimization

Todd, E. R., Denis, K. J., Woongki, K., Michael, R. G., Lina, Q.-S., David, S. B., Laurant, T. J., Audrey, C., Fujun, L., Emma, B. R., Leang, L. K., Daren, M., Diana, Y. S., San-San, C.

Department of Medicinal Chemistry, Roche Palo Alto, Palo Alto, CA94304-1397 USA

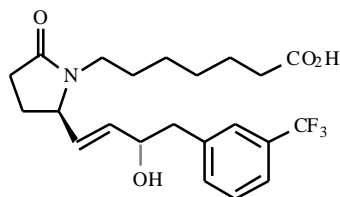
*Bioorganic & Medicinal Chemistry Letters* 2004, **14**(7), 1655-1659; *C.A.* **141**(1): 6940h

**Abstract:** The present research investigations had been undertaken for the preparation of synthetic derivatives of 7-[(5R)-substituted 2-oxo-1-pyrrolidinyl]heptanoic acids **I**, incorporating lactam moiety, followed by stereochemical and

biological studies. These compounds, possessing EP4 receptor binding affinity, were modified at lower side chain of lactam.

**Activity:** The changes resulted dramatic enhancement of EP4 receptor affinity > 1000-fold and an excellent potency for EP4, as compared to other EP prostanoid receptors.

**Origin:** Synthetic



I

#### 14. A preparation of novel thiophene derivatives useful as angiotensin II receptor agonists

Mathias, A., Anders, H., Yiqian, W., Kannan, M., Phillip, M. S.

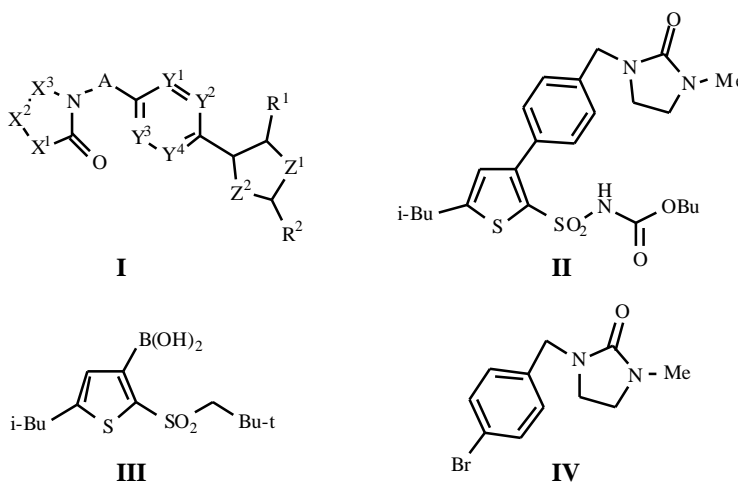
Vicore Pharma AB, Sweden

**PCT Int Appl. WO 2004, 46, 137** (Cl. C07D409/10), 3Jun 2004, US Appl. PV427, 942, 21 Nov. 2002; 64 pp; 141(1): 7115e

**Abstract:** Novel tricyclic thiophene synthetic analogues of formula I [wherein: X<sub>1</sub> is -alkyl-, -N(alkyl)-, O, etc; dotted line is an optional double bond; depending on what dotted line signifies, X<sup>2</sup> and X<sup>3</sup> independently represent -C(H/alkyl/aryl/heteroaryl)<sub>1,2</sub>-, -N(alkyl)-, O, C(O), N, etc. Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub> and Y<sub>4</sub> independently represent -CH- or -CF-; Z<sub>1</sub> is -CH-, O, S, N, -CH:CH-; Z<sub>2</sub> is -CH-, O, S, N; R<sup>1</sup> is -SO<sub>2</sub>NH-[C(O)/SO<sub>2</sub>]- (alkyl/alkoxy), etc.; R<sup>2</sup> is alkyl, alkoxy, or alkoxyalkyl, etc.; A is C(O) or CH<sub>2</sub>] were prepared. Other medicinal significant and synthetic procedures were also described for these analogs.

**Activity and bioassay:** These compounds showed selectivity for AT<sub>2</sub> receptor agonists and after screening in receptor binding assays using rat liver membrane AT<sub>1</sub> receptor and porcine myometrial membrane AT<sub>2</sub> receptor. K<sub>i</sub> = 100 nM was displayed for binding affinity of AT<sub>2</sub> receptor, whereas K<sub>i</sub> = 500 nM for AT receptor.

**Origin:** Synthetic



#### 15. Preparation of 8-substituted imidazopyridines as gastric secretion inhibitors

Wolfgang-Alexander, S., Stefan, P., Wolfgang, K., Whilm, B., Joerg, S.-B. and Jan, Z. P.

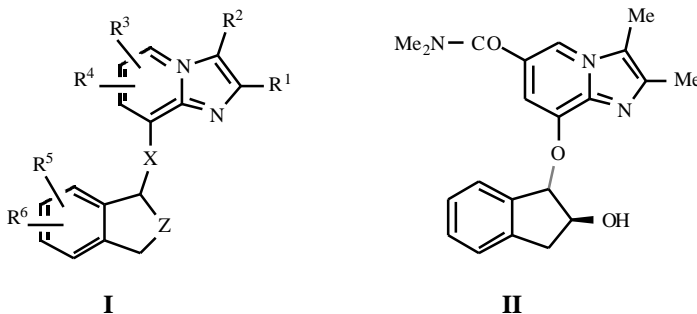
Altana Pharma Ag, Germany

PCT Int Appl, WO 2004, 46, 144 (Cl. C07D471/04), 3 Jun 2004, EP Appl. 2002/25,866, 19 Nov. 2002; 37 pp; 141(1): 7116f

**Abstract:** The present compounds of formula **I** [ $R^1 = \text{H}$ , alkyl, cycloalkyl, alkoxy, etc.;  $R^2 = \text{H}$  alkyl, aryl, cycloalkyl, halo, etc.;  $R^3, R^4 = \text{H}$ , halo, alkyl, carboxy, alkoxy, alkoxy, etc.;  $R^5 = \text{H}$ , alkyl, alkoxy, OH, nitro, (substituted) amino, etc.;  $R^6 = \text{H}$ , alkyl, alkoxy, alkoxy, etc.;  $X = \text{O}$ , NH;  $Z = (\text{substituted } \text{CH}_2)$ , (substituted  $\text{CH}_2$ )] were prepared.

**Activity and bioassay:** These compounds were tested for gastric secretion and showed remarkable inhibitory properties. These also passed gastric as well as intestinal protection actions **II** and exhibited >380% acid secretion inhibition in perfused rat stomach at 1  $\mu\text{mol/kg}$ . i.d.

**Origin:** Synthetic



**Web URL:** <http://sciencedirect.com>

## 16. Synthesis, biological activity and molecular modeling studies of novel COX-1 inhibitors

Miljen, M., Iva, T., Stribor, M., Nedjeljko, K. and Sanja, K.

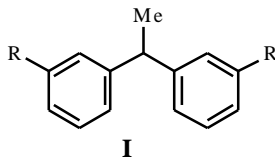
PLIVA Pharmaceutical Industry, Incorporated, Zagreb, Croatia 1000

*European Journal of Medicinal Chemistry* 2004, **39**(2), 141-151; **141**(1): 6898a

**Abstract:** Current investigation covered the biological, physiological and computational structure-based analysis of synthetic molecular targets of COX-1 and COX-2 inhibitors. These inhibitors are derived from 1,1-di-(3-carboxyphenyl)ethane e.g. **I** ( $R = \text{CO}_2\text{Me}$ ,  $\text{CO}_2\text{Et}$ ,  $\text{CO}_2\text{CHMe}_2$ ,  $\text{COPh}$ ,  $\text{CONH}_2$ , cyano).

**Activity:** COX -1 inhibitor. These compounds were also tested for monitoring potency, on combining with known drugs.

**Origin:** Synthetic



**Web URL:** <http://sciencedirect.com>

## 17. Discovery of N-propylurea 3-benzylpiperidines as selective CC chemokine receptor-3 (CCR3) antagonists

Jeffrey, V. G., Daniel, G. S., Santella, B., John, D. V., Melissa, E., Paul, W. S., Cheryl, C. M., Soo, K. S., Parricia, W., Maryanne, C., Nicole, S., Eric, W., Paul, D., Kimberley, S., Robert, N. C., George, T. L., Carlp, D., Dean, W. A.

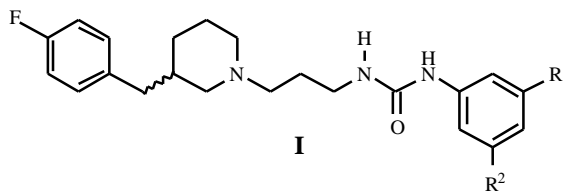
Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08542-5400, USA

*Bioorganic & Medicinal Chemistry Letters* 2004, **14**(7), 1645-1659; C.A. **141**(1): 393p

**Abstract:** The replacement of 4- to 3-benzylpiperidine derivatives dramatically enhanced their CC chemokine receptor-3 (CCR3) selectivity.

**Activity and bioassay:** CCR3 antagonists.  $IC_{50}$  below 5 nM was observed for compounds with mono- and di-substitution of the *N*-propylurea which resulted in the synthesis of several 3-benzylpiperidine *N*-propylureas. Different assays and separation techniques, described in the manuscript, were used to purify and collect statistical data, ranging from high picomolar to low nanomolar  $EC_{50}$ .

**Origin:** Synthetic



## 18. Discovery of diarylacrylonitriles as a novel series of small molecule sortase A inhibitors

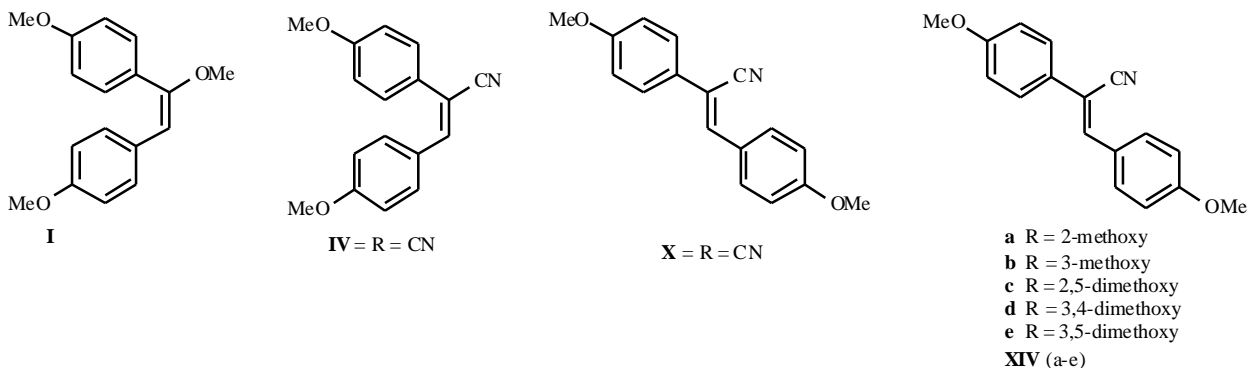
KI-Bong, O., Soo-Hwan, K., Jackwang, L., Won-Jea, C., Taeho, L. and Sanghe, K.

Natural Products Research Institute, College of Pharmacy, Seoul National University, Seoul, 110-460 S. Korea

*Journal of Medicinal Chemistry* 2004, **47**(10), 2421; *C.A.* **141**(1): 399s

**Abstract:** Both SrtA and SrtB are critical virulent factors, taking part in the formation and persistence of infections, therefore sortase inhibitors in combination with an antibacterial agent are proved to cure infections. Through the random screening and structural modifications based on the screening hit, diarylacrylonitriles were identified as SrtA inhibitors out of 1,000 small molecules screened using a recombinant SrtA. Kinetic studies and SAR were also established and described.

**Activity and bioassay:** Compound **1** displayed high micromolar inhibition of  $IC_{50} = 231 \mu\text{M}$ . **X** showed  $IC_{50} = 28 \mu\text{M}$ . **IV** displayed inhibitory activity =  $187 \mu\text{M}$ , while the range of all **XIV**(a-e) was  $< 40 \mu\text{M}$ . **XIVc** showed an excellent value of  $IC_{50}$  of 9.2 mM.



**Web URL:** <http://pubs.acs.org/journals/>

## 19. 2,3-Disubstituted 6-azabicyclo[3.2.1]octanes as novel dopamine transporter inhibitors

Jose, F. Q., Xavier, V., Josep, B., Alan, K. P. and Kenneth, J. M.

Faculty of Pharmacy, Laboratory of Organic Chemistry, University of Barcelona, Barcelona, Spain 08028

*Bioorganic & Medicinal Chemistry* 2004, **12**(6), 1383-1391; *C.A.* **141**(1): 393k

**Abstract:** Studies of dopamine (DA) uptake inhibition were conducted and correlated for compounds incorporating tropane and normophan skeleton. These compounds were compared with cocaine to observe the effects after replacing

these two skeletons with each other. In this context, a series of *cis* and *trans* 3-aryl-2-carbomethoxy-6-azabicyclo[3.2.2.1]octanes, with various substitutions at the *para*-position of the aryl group, were prepared, discussing SAR briefly.

**Activity and bioassay:** Dopamine transporter inhibitor. The compounds of *trans*-amine series **VIII** exhibited strong reuptake inhibition at DA transporter (DAT), whereas the normophan analogs **VIIIc** (bearing a *p*-chloro substituent at the -aryl group) showed  $IC_{50} = 452$  nM comparable to that of cocaine with  $IC_{50} = 459$  nM.

**Origin:** Synthetic

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**Web URL:** [www.sciencedirect.com/science/journal/09680896](http://www.sciencedirect.com/science/journal/09680896)

**20. Design, synthesis, and  $\alpha_1$ -adrenoceptor binding properties of new arylpiperazine derivatives bearing a flavone nucleus as the terminal heterocyclic molecular portion**

Laura, B., Monia, F., Gino, G., Fabrizio, M., Chiara, P., Giovannella, S. and Maurizio, B.

Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, Universita di Pisa, 56126 Pisa, Italy

*Bioorganic & Medicinal Chemistry* 2004, **12**(6), 1527-1535; *C.A.* **141**(1): 394m

**Abstract:** New series of piperazine analogs have been synthesized and tested for their  $\alpha_1$ -adrenoceptors (AR) activity. SAR of these compounds focusing on its substitution pattern and other structure-related systems were also described. The characterization of thirteen new compounds bearing flavone system linked through an ethoxy or propoxy spacer, to a phenyl- or pyridazinone-piperazine moiety is also given. These derivatives displayed potent nanomolar  $\alpha_1$ -AR binding ability, while less significant activity for  $\alpha_2$ -AR and the 5-HT<sub>1A</sub> serotonergic receptor.

**Activity and bioassay:** Biological data showed an interesting profile for the phenylpiperazine subclass found to have a nanomolar affinity toward  $\alpha_1$ -AR, and less pronounced affinity for  $\alpha_2$ -AR and the 5-HT<sub>1A</sub> serotonergic receptor.

**Origin:** Synthetic

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**21. Inhibition of lymphangiogenesis-related properties of murine lymphatic endothelial cells and lymph node metastasis of lung cancer by the matrix metalloproteinase inhibitor MMI270**

Eliane Shizuka, N., Keiichi, K., Mitsuo, K. and Ikuo, S.

Division of Pathogenic Biochemistry, Institute of Natural Medicine, Toyama Medical and Pharmaceutical University, Toyama, Japan 930-0194

*Cancer Science* 2004, **95**(1), 25-31; *C.A.* **141**(1): 619p

**Abstract:** The anti-tumor angiogenic compound MM1270 (**I**) markedly inhibited the activity of MMP-2 and -9 produced by Lewis lung cancer (LLC) cells and the invasion of these cells by Matrigel. As it downregulated both the lymphangiogenesis-related properties of LECs (lymphatic endothelial cells) and the invasive properties of LLC *in vitro*, it could be used as an anti-metastatic drug.

**Activity and bioassay:** Downregulation of lymphangiogenesis-related as well as invasive properties of LECs and LLC cells *in vitro* MMP-2, MMP-9 inhibitors.

**Origin:** Synthetic

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**Web URL:** <http://edpex104.bcarj.or.jp/cancer-sci>

**22. The purification and isolation of a new type of rabbit-origin lipopolysaccharide binding protein and the study of its biological function *in vitro***

Xiaodong, G., Yousheng, L., Xiaodong, W., Feng, P. and Ping, Z.

Southwestern Hospital, The Third Military Medical University, Chongqing, Peop. Rep. China 400038.

*Zhonghua Shaoshang Zazhi* 2003, **19**(1), 42-46; *C.A.* **141**(1): 2976b

**Abstract:** A new protein has been obtained from the burnt serum of rabbits. This protein named as P48 was isolated, purified, identified and its 10 amino acid sequence at *N* was found to be GSQGTFTSEE having mol. wt. of 48 KDa, which was different to the amino acid sequence in NCBI protein bank.

**Activity and bioassay:** Protein **I** down regulated lymphangiogenesis-related as well as invasive properties of LECs and LLC cells *in vitro*. It also inhibited MMP-2 and MMP-9. It could promote LPS in a very low concentration. It displayed function like lipopolysaccharide binding protein (LBP). Cultured human monocytes U937. Murine LECS were bioassayed by tube formation assay *in vitro*, expression of mRNAs by RT-PCR assay and invasion of MMP-2 and MMP-9 cells by Matrigel.

**Origin:** Molecular biology/natural

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**Web URL:** [www.sciencedirect.com/science/journal/00456535](http://www.sciencedirect.com/science/journal/00456535)

### 23. Variation in estrogenic activity among fractions of a commercial nonylphenol by high performance liquid chromatography

Yun-Seok, K., Takao, K., Sayaka, S., Tadashi, I., Mitsuko, M., Taketo, U., Yasuo, F. and Nobuyoshi, Y.

College of Bioresource Sciences, Nihon University, Fujisawa, Kanagawa, Japan 252-8510

*Chemosphere* 2004, **54**(8), 1127-1134; *C.A.* **141**(1): 2445c

**Abstract:** Seven isomers of commercially available nonylphenol (NP) were obtained after purification through HPLC, namely, 4-(1,3-dimethyl-1-propyl-butyl)-phenol, 4-(1,1,3-trimethyl-hexyl)-phenol, 4-(1,1-dimethyl-3-ethyl-pentyl)phenol, 4-(1,1,4-trimethyl-hexyl)-phenol, 4-(1-methyl-1-propyl-pentyl)-phenol, 4-(1,12-trimethyl-hexyl)-phenol and 4-(1-ethyl-1-methyl-hexyl)-phenol. All these isomers including another tertiary NP, which was synthesized in the present study, possessed tertiary -carbon in their structures. All these compounds showed estrogenic activity.

**Activity and bioassay:** The highest activity was observed by the isomer 4-(1,1,4-trimethyl-hexyl)-phenol, which exhibited the highest estrogenic activity corresponding to 1/10000 that of 17 $\beta$ -estradiol (E2) determined by recombinant yeast screen assay.

**Origin:** Synthetic

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### 24. Preparation of pyridinylmethylaminobutylindolecarbonitriles as serotonin 5-HT<sub>1A</sub> and 5-HT<sub>1D</sub> receptor ligands

Guenter, H., Kai, S., Timo, H., Henning, B., Joachim, L., Christoph, V. A., Gerd, B. and Christoph, S.

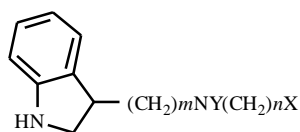
Merck Patent GmbH, Germany

**Ger, Offen. DE 10, 254, 596** (Cl. C07D403/12), 3 Jun 2004, Appl. 10, 254, 596, 22 Nov. 2002; 17 pp. *C.A.* **141**(1): 7033b

**Abstract:** The present synthesis deals with the preparation of pyridinylmethylaminobutylindolecarbonitriles **I**; X = substituted (fused) pyridyl; Y = H, A<sup>1</sup>; R<sup>1</sup>, R<sup>11</sup> = H, A, OH, OA, cyano, halo, COR<sup>4</sup>CH<sub>2</sub>R<sup>4</sup>; R<sup>4</sup> = H, OH, NH<sub>2</sub>, etc.; A<sup>1</sup> = alkyl, PhCH<sub>2</sub>; m = 2-6; n = 1-4], which were tested for 5-HT<sub>1A</sub> and 5-HT<sub>1D</sub> agonists and serotonin reuptake inhibitors (no data). Other preparations are also given.

**Activity:** 5-HT<sub>1A</sub> and 5-HT<sub>1D</sub> receptor and serotonin reuptake inhibitor.

**Origin:** Synthetic



I

## 25. Preparation of sulfonamides as antagonists of urotensin II

Linda, B. S., Christopher, L. T., Jeffrey, M. J., Micheal, N. J. and Ning, W.

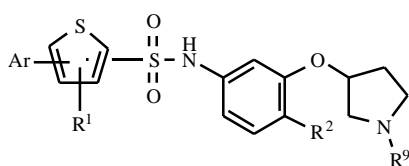
SmithKline Beecham Corporation USA

**PCT Int. Appl. WO 2004, 43, 368** (Cl.A6K), 27 May 2004, US Appl. PV424, 162, 6 Nov. 2002; 66pp; C.A. 141(1): 7014w

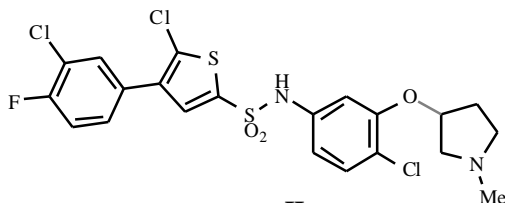
**Abstract:** Current studies are concerned with the synthesis of sulfonamides [I; R<sup>1</sup> = H, halo, alkyl; Ar = (un)substituted Ph, pyrazolyl, thiazolyl, etc.; R<sup>2</sup> = H, halo CF<sub>3</sub>; R<sup>9</sup> = H alkyl], and their formulations.

**Activity and bioassay:** Urotensin II antagonist. These compounds are U-II antagonist active with k<sub>i</sub> ranging from 1 nM to 10000 nM using U-II radioligand binding assay.

**Origin:** Synthetic



I



II

## 26. Synthesis of new aminopropanol derivatives as potential $\alpha$ -adrenoblockers

Vartanyan, R. S., Adamyan, E. A. and Sheiranyan, M. A.

Erevan. Gos. Univ., Yerevan, Armenia

*Hayastani Kimiakan Handes* 2003, **56**(3), 87-91; C.A. **141**(2): 23236a

**Abstract:** Preparation of new aminopropanol derivatives was carried out in the present studies. Development of two methods for realization of interaction of 1,2-epoxy-3-phenoxypropane was carried out where some  $\alpha$ - and  $\beta$ -aminoalcohols were employed to avoid trap products formation and solvent improvement.

**Activity:**  $\alpha$ -Adrenoblockers

**Origin:** Synthetic

## 27. Preparation of isoxazoline derivatives as inhibitors of matrix metalloproteinases and/or TNF- $\alpha$ converting enzyme

Chu-Biao, X., Thomas, M. P. and Stephen, M. E.

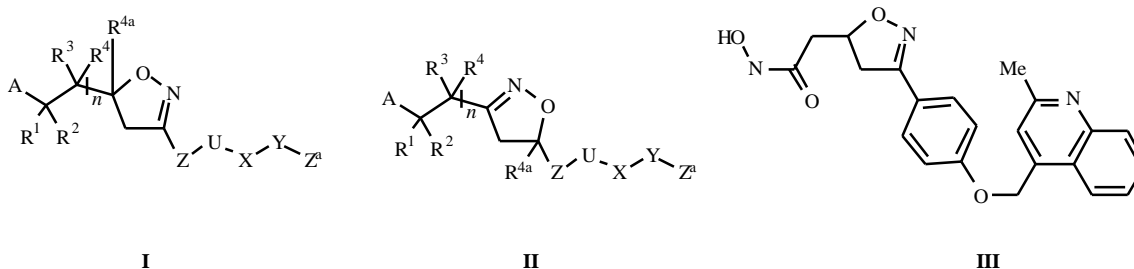
Bristol-Myers Squibb Company, USA

PTC Int. Appl WO 2004, 43, 349 (Cl. A61K), 27 May 2004, US Appl. PV 424,293, 6 Nov. 2002; 106 pp; C.A. 141(1): 7120c

**Abstract:** The present research relates to the preparation of compounds **I** and **II** [wherein A = (un)substituted N(OH)COH or CONHOH; U = absent, O, CO, CO<sub>2</sub>, OCO, (un)substituted NH, CH(OH), CONH, NHCO, etc.; X = absent, alkylene, alkenylene, or alkynylene; Y = absent, O, S, SO<sub>2</sub>, or CO; Z = substituted carbocycle or heterocycle; Z<sup>a</sup> = H, substituted carbocycle or heterocycle; R<sup>1</sup>-R<sup>4</sup> and R<sup>4a</sup> = independently Q, alkylene-Q, alkenylene-Q, alkynylene-Q etc.; Q = H, CHF<sub>2</sub>, CH<sub>2</sub>F, CF<sub>3</sub>, substituted carbocycle, or (hetero)cycle; = 0 or 1] and salts. These compounds were found to inhibit matrix metalloproteinases (MMP), TNF- converting enzyme (TACE), or a combination. These compounds are also used to treat acute infection, acute phase response, age related macular degeneration, etc.

**Activity:** Some of the compounds **I** exhibited IC<sub>50</sub> ≤ 0.01 μM for MMP inhibition. These are useful in MMP and/or TACE related diseases.

**Origin:** Synthetic



## 28. Effect of $\beta$ -sitosterol as inhibitor of 5 $\alpha$ -reductase in hamster prostate

Marisa, C., Eugene, B., Heuze, E. I. R., Mauricio, S. and Eugenio, F.

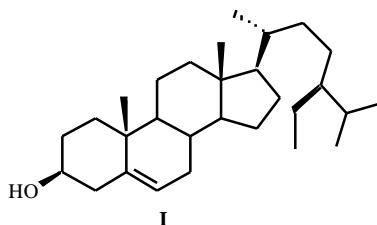
Department of Biological Systems and Animal Production, Metropolitan University-Xochimilco, Mexico, Mex

*Proceedings of the Western Pharmacology Society* 2003, **46**, 153-155, C.A. **141**(1): 541g

**Abstract:** The present study was conducted on  $\beta$ -sitosterol (**I**) as 5 $\alpha$ -reductase inhibitor. Differences in efficacy of compound **I** on humans and hamsters were also discussed.

**Activity and bioassay:** Compound **I** not only remarkably inhibited the growth of the gonadectomized hamster prostate treated with T at two different doses, but also inhibited 5 $\alpha$ -reductase with IC<sub>50</sub> = 2.7 μM.

**Origin:** Natural product



**Web URL:** <http://sciencedirect.com>

## 29. N-Acridin-9-yl-butane-1,4-diamine derivatives: high-affinity ligands of the $\alpha_2$ subunit of voltage gated calcium channels

Jongwon, L., Nicholas, S., Richard, P., Julia, B. K., Benito, M., Ashok, C., Angelina, S. M., Karia, O., Harve, S., Robert, B. E., Jayashree, A. and Shankar, V.

Department of Chemistry, Merck Research Laboratories, San Diego, CA 92121 USA

*Bioorganic & Medicinal Chemistry Letters* 2004, **14**(8), 1913-1916; *C.A.* **141**(1): 404q

**Abstract:** *N*-Acridin-9-yl-butane-1,4-diamine derivatives were identified as high-affinity ligands of the  $\alpha_2$  subunit of voltage gated calcium channels. The SAR of these derivatives was also established.

**Activity:** These compounds are binding affinity ligands of the  $\alpha_2$  subunit of voltage gated calcium channels. One of the compounds exhibited  $IC_{50} = 9$  nM, more significant than gabapentin with  $IC_{50} = 27$  nM.

**Origin:** Synthetic

### 30. Preparation of benzofuran derivatives for treatment of glucokinase-mediated disease

Darren, M. and Wall, R. J.

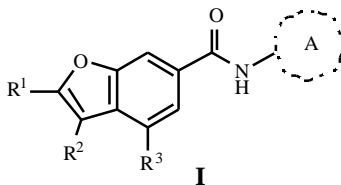
AstraZeneca Ab; AstraZeneca UK Limited, Sweden

**PCT Int. Appl. WO 2004, 46, 139** (Cl. C07D413/13), 3 Jun 2004, GB Appl. 2002/26,930, 19 Nov. 2002; 41 pp; *C.A.* **141**(2): 23428q

**Abstract:** Syntheses of **I** [wherein ring A = (un)substituted pyridin-2-yl, thiazol-2-yl;  $R^1, R^2$  = independently H alkyl;  $R^3$  = alkyl, alkoxy, carbocyclyl, carbocycloxy, heterocyclyl, heterocycloxy; their salts, prodrugs, or solvates, together with their pharmaceutically acceptable diluent or carrier], their formulation and compositions, etc. are carried out in these investigations.

**Activity and bioassay:** These compounds were found to be useful for the treatment of glucokinase-mediated disease.

**Origin:** Synthetic



### 31. Preparation of 4- and/or 7-hydroxyindoles as phosphodiesterase 4 inhibitors

Norbert, H., Hildegard, K., Ute, E., Chris, R., Helge, H. and Antje, G.

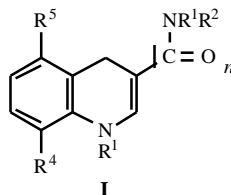
Elbion Ag, Germany

**Ger. Offen. DE 10, 253, 426** (Cl. C07D401/04), 3 Jun. 2004, Appl. 10,253,426, 15 Nov. 2002; 17 pp. *C.A.* **141**(2): 23423j

**Abstract:** Compounds of **I** [ $n = 1, 2$ ;  $R^1$  = (substituted) (branched) alkyl, (substituted) (branched) unsaturated alkenyl;  $R^2, R^3 = H$ , (substituted) alkyl, pyridyl, etc.;  $R^4, R^5 = H, OH$ ] were synthesized.

**Activity and bioassay:** *N*-(3,5-Dichloropyridin-4-yl)-[1-(4-chlorobenzyl)-7-hydroxyindol-3-yl]glyoxyamide exhibited  $IC_{50} = 0.002$   $\mu$ mol/L for phosphodiesterase 4 (PDE 4) inhibition.

**Origin:** Synthetic



### 32. Preparation of indole-3-carboxamides as cannabinoid receptor CB2 ligands, in particular CB2 agonists and their therapeutical application

Francis, B., Murielle, R. C. and Claude, V.

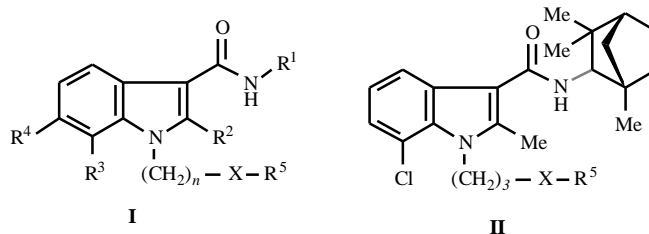
Sanofi-Synthelabo, France

**Demande FR 2, 847, 899** (Cl. C07D2209/36), 4 Jun 2004, Appl. 2002/15,086, 29 Nov. 2002; 16 pp; C.A. 141(2): 2348m

**Abstract:** Syntheses of indole-3-carboxamides with formula **I** [wherein  $R^1$  = (un)substituted carbocyclyl;  $R^2$  = H, alkyl;  $R^3$  = halo, alkyl;  $R^4$  = H, halo, alkyl;  $R^5$  = alkyl; X = S, NHSO<sub>2</sub>, SO<sub>2</sub>; n = 2-3; and their hydrates and solvates] and **II** were reported in this patent.

**Activity and bioassay:** These compounds exhibited selectivity for CB2 receptors (200-fold over CB1) in an *in vivo* binding study against human cannabinoid receptors.

**Origin:** Synthetic



### 33. Preparation of N-arylsulfonyl-3-aminoalkoxy indoles as 5-HT and/or melatonin receptor modulators

Nirogi, R. V. S., Shreekrishna, S. V., Sastri, K. R., Vadlamudi, R. V. S. V. and Venkateswarlu, J.

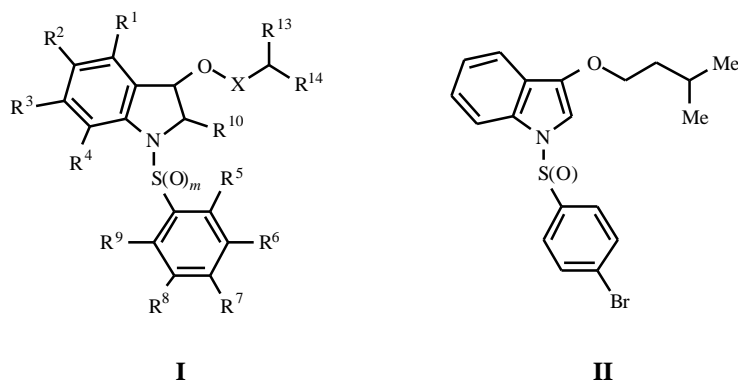
Suven Life Sciences Limited, India

**PCT Int. Appl. WO 2004, 48, 328** (Cl. C07D209/00), 10 Jun 2004, IN Appl. 2002/MA883, 28 Nov. 2002; 106 pp; C.A. 141(2): 23419n

**Abstract:** These compounds with general formula **I** [wherein X = (CR<sup>11</sup>R<sup>12</sup>)<sub>n</sub>; n = 1-8; R<sup>1</sup>-R<sup>12</sup> = independently H, thio/halo, perhaloalkyl, OH, SH, CN, CHO, amidino guanidino, (un)substituted cyclo/ bicyclo/ar/heterocyclyl/amino/alkoxy/alkyl, cyclo/bicycloalkenyl, alkynyl, aryloxy, hetero/aryl, acyl/monoalkyl/ dialkyl/aryl/diaryl/aralkyl/alkoxy carbonyl/amino, alkoxy carbonyl, alkylamidino, alkylguanidino, hydrazine, hydroxylamino, CO<sub>2</sub>H and derivatives, alkylamidino, alkylamidino, alkylguanidino, hydrazine hydroxylamino, CO<sub>2</sub> H and derivatives, SO<sub>3</sub>H and derivatives; R<sup>1</sup> CCR<sup>2</sup>, R<sup>2</sup>CCR<sup>3</sup>, R<sup>3</sup>CCR<sup>4</sup>, R<sup>5</sup>CCR<sup>8</sup>, R<sup>7</sup>CCR<sup>8</sup>, R<sup>8</sup>CCR<sup>9</sup> = 5-or 6-membered ring; R<sup>11</sup>CCR<sup>12</sup> = 3-6 membered ring R<sup>13</sup>, R<sup>14</sup> = H ar/alkyl, aryl or R<sup>13</sup> NR<sup>14</sup> = 3-7 membered ring; their stereoisomers, radioisotopes, geometric forms, N-oxides, polymorphs, pharmaceutically acceptable salts and solvates, their useful bio-active metabolites and any suitable combination of the above], and **II** were synthesized and claimed to be useful as 5-HT and/or melatonin receptor modulators (no data).

**Activity and bioassay:** These compounds are pharmaceutically significant as 5-HT ligands e.g. agonists or antagonists, as well as melaton 5-HT and/or melatonin receptors. Data about the biological activity had not been provided.

**Origin:** Synthetic



**Web URL:** <http://pubs.acs.org>

**34. Approaches to a scaleable synthesis of CH757: A potent inhibitor of matrix metalloproteinases**

Graham, F. A., Duncan, H. R., Neil, H., Ruth, B., Ian, S. H., Neil, T., Robert, W. J. and Indrani, W.

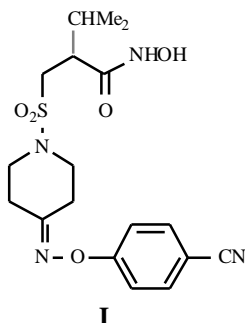
Celltech R & D, Cambridge UK CB1 6GS

*Organic Process Research & Development* 2004, **8**(3), 415-417; *C.A.* **141**(2): 23401a

**Abstract:** Preparation of compound CH8757 (**I**) is described.

**Activity and bioassay:** Compound **I** exhibited matrix metalloproteinase (MMP) inhibitory activity.

**Origin:** Synthetic



**Web URL:** <http://sciencedirect.com>

**35 Structure-activity relationships of untenone A and its derivatives for inhibition of DNA polymerases**

Fumiyo, S., Ryo, T., Yomyuki, K., Kouji, K., Fumio, S., Kengo, S. and Susumu, K.

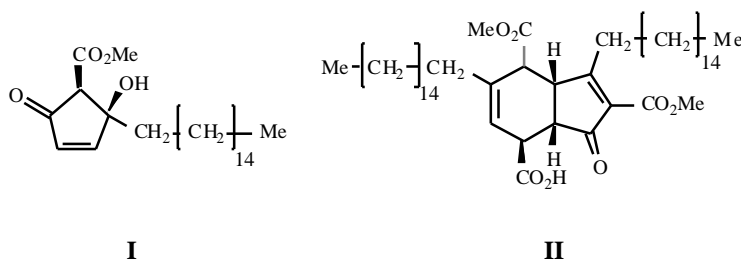
Frontier Research Center for Genome and Drug Discovery, Yokyo University of Science, Nodia, Chiba, Japan 278-8510

*Bioorganic & Medicinal Chemistry Letters* 2004, **14**(8), 1975-1977; *C.A.* **141**(2): 23337j

**Abstract:** Preparations of untenone A (**I**), and its synthetic analogs and manzamenone A (**II**) were undertaken along with their SARs.

**Activity and bioassay:** The compounds **I** and **II** were found to inhibit mammalian DNA polymerases and human terminal deoxynucleotidyl transferase (TdT) enzymes.

**Origin:** Synthetic



**Web URL:** <http://sciencedirect.com>

### 36. Inhibitors of Sir2: Evaluation of splitomicin analogs

Jeff, P., Maki, H., Sam, S., Julian, S. A. and Antonio, B.

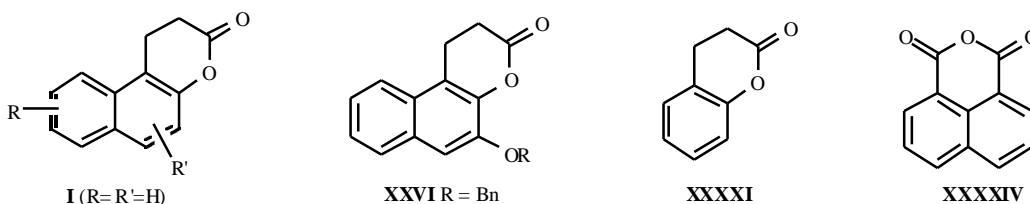
Clinical Research and Human Biology Divisions, Fred Hutchinson Cancer Research Center, Seattle, WA 98109 USA

*Journal of Medicinal Chemistry* 2004, **47**(10), 2635-3644; *C.A.* **141**(2): 23321z

**Abstract:** Splitomicin (**I**), identified as micromolar inhibitor of Sir2, was derivatized to furnish forty one analogs which were biologically evaluated for their Sir2 growth stimulating activity in both *in vivo* and *in vitro* assays. SARs of these compounds are also discussed alongwith their detailed biological and synthetic studies.

**Activity and bioassay:** Sir2 inhibitory activity of splitomicin analogs was evaluated *in vivo* using a functional assay for telomeric silencing in yeast. **XXXXI** showed low toxicity with  $IC_{50} = 122 \mu M$  and induced the most growth in yeast proliferation assays. **XXXXIV** exhibited the highest toxicity among all the analogs and could suppress any growth induction. Many of these synthetic analogs were highly active *in vivo* (e.g., **I**, **XXVI**, and **XXXXI**), and inhibited Sir2 *in vitro*, affording 15-66% of the activity, relative to dimethyl sulfoxide (DMSO) control at 75  $\mu M$ .

**Origin:** Synthetic



### 37. A preparation of unsaturated hydroxamic acid derivatives useful as histone deacetylase inhibitors

Norbert, W. L. and Hsuan-yin, L.-H.

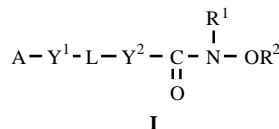
Circagen Pharmaceutical, USA

**PCT Int. Appl. WO 2004, 46,104** (Cl. C07D) 3 Jun 2004, US Appl. PC427, 567, 20 Nov. 2002; 27 pp; *C.A.* **141**(2): 23197p

**Abstract:** Syntheses of unsaturated hydroxamic acid derivatives with formula **I** [wherein; A is (hetero)cycloalk(en)yl, (hetero)aryl, etc.;  $Y^1$  and  $Y^2$  were independently selected from  $CH_2$ , O, S,  $OC(O)O$ , NH, or  $-NHC(O)O-$ , etc.; L is (un)substituted  $C_{2-12}$  hydrocarbon chain optionally containing one double bond, at least one triple bond, or at least one double bond and one triple bond;  $R^1$  is H, alk(en/yn)yl, alkoxy, OH, etc.;  $R^2$  is H, alkyl, hydroxyalkyl, or haloalkyl, etc.] were carried out.

**Activity and bioassay:** These compounds are histone deacetylase inhibitors, and are used to treat cystic fibrosis, chronic obstructive pulmonary disease asthma, etc. All compounds were subject to cystic fibrosis assay and to bronchial epithelial electrolyte transport. One of the prepared compounds 7-phenyl-2,4,6-heptatrienoylhydroxamic acid displayed 69.2% mean inhibition of sodium transport. The same compound was concentration dependent with a half-maximal inhibitory concentration of 11.9  $\mu\text{M}$  for the inhibition of sodium transport.

**Origin:** Synthetic



**38. *In vitro* acetylcholinesterase inhibition by novel OP compounds in various tissues of the fish *Channa punctatus***

Rahman, M. F., Mahboob, M. and Grover, P.

Biochemical Toxicology, Biology Division, Indian Institute of Chemical Technology, Hyderabad, 500 007 India

*Bulletin of Environmental Contamination and Toxicology* 2004, **72**(1), 38-44; C.A. **141**(1): 2652t

**Abstract:** Three organophosphorous (OP) compounds were evaluated for their effects on acetylcholinesterase (AChE) enzyme. SAR with these biological studies are discussed.

**Activity and bioassay:** The comparative neurotoxic potential was monitored by the relative toxicity of these OP compounds in different fish tissues. 2-Butenoic acid-3-(diethoxyphosphinothioyl)-Me ester (RPR-II), RPR-V and MCP showed AchE enzyme inhibition in RBC, brain and fish liver of *Channa punctatus*. MCP exhibited strong inhibition than RPR-II and RPR-V in enzyme AChE in RBC. RPR-V displayed high inhibition potency for brain AChE.

**Origin:** Synthetic

**Web URL:** <http://www3.interscience.wiley.com>

**39. Development of novel 1,2,3,4-tetrahydroisoquinoline derivatives and closely related compounds as potent and selective dopamine D<sub>3</sub> receptor ligands**

Ulrich, M. R., Anneke, H. E., Sylvie, P., Sandrine, F., Camille, W. G., Jean-Charles, S., Pierre, S. and Kolger, S.

Institut fuer Pharmazetische Chemie, Johann Wolfgang Goethe-Universities, 60439 Frankfurt am Main, Germany

*ChemBioChem* 2004, **5**(4), 508-518; C.A. **141**(1): 414t

**Abstract:** Fifty-five selective dopamine D<sub>3</sub> receptor antagonists are prepared. These were *N*-alkylated 1,2,3,4-tetrahydroisoquinoline derivatives. Modifications at tetrahydroisoquinoline and especially at arylamide moiety significantly enhanced the biological potential.

**Activity and bioassay:** (*E*)-3-(4-Iodophenyl)-*N*-(4-(1,2,3,4-tetrahydroisoquinolin-2-yl)butyl) arylamide exhibited dopamine D<sub>3</sub> receptor affinity with ( $k_i(\text{hD}_3) = 12 \text{ nM}$ ), showing a 123-fold preference for the D<sub>3</sub> receptor relative to the D<sub>2</sub> receptor subtype.

**Origin:** Synthetic

**40. N-Acyl-N-arylmethylaniline acrylates as non-steroidal farnesoid X receptor modulators**

Michael, D. R. and Ronald, E. M.

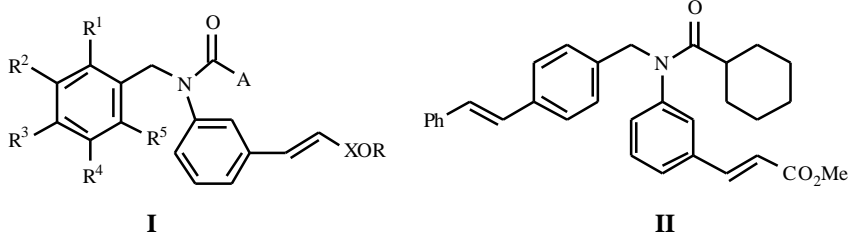
The Salk Institute for Biological Studies, The Scripps Research Institute, USA

**PCT Int. Appl. WO 2004, 46, 068** (Cl. C07C), 3 Jun 2004, US Appl. 658,115,8 Sep. 2003; 98 pp; C.A. **141(2)**: 17647u

**Abstract:** The compounds incorporating *N*-acyl-*N*-arylmethylaniline acrylates with formula **I** [A = (substituted) alkyl, cycloalkyl, aryl, heteroaryl; X = CO, CH<sub>2</sub>; R = Me, Et; R<sup>1</sup> = H, OH, alkoxy, PhCO<sub>2</sub>, mesityloxy, OCH<sub>2</sub>CO<sub>2</sub>Et; R<sup>2</sup> = H; R<sup>3</sup> = alkenyl, (substituted) aryl, heteroaryl, aralkenyl, heteroaralkenyl; R<sup>2</sup> R<sup>3</sup> = atoms to form a (substituted) (unsaturated) pyran ring; R<sup>4</sup> = H, OH; R<sup>5</sup> = H, OH, alkoxy, aryloxy] and **II** were biologically evaluated in the present studies.

**Activity and bioassay:** These compounds were found to be farnesoid X receptor modulators. **II** activated FXR with EC<sub>50</sub> = 36 nM.

**Origin:** Synthetic

**41. N-acyl-N-benzylaniline acrylates as non-steroidal farnesoid X receptor (FXR) modulators**

Michael, D. R., Mark, E. R., Robert, H., Kyriacos, N. C. and Anthony, R. J.

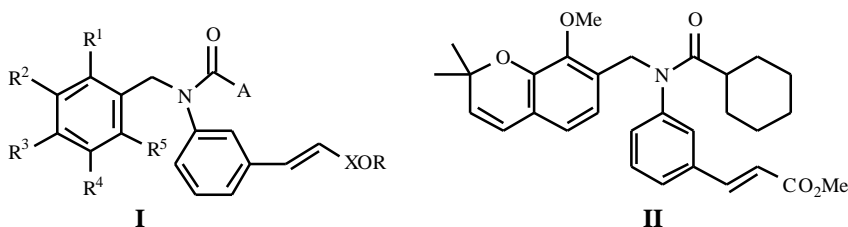
The Salk Institute for Biological Studies, The Scripps Research Institute, USA

**PCT Int. Appl. WO 2004, 45, 511** (Cl. A61K), 3 Jun 2004, US Appl. 658,115 8 Sep. 2003; 62 pp; C.A. **141(2)**: 17646t

**Abstract:** Preparation of *N*-acyl-*N*-benzylaniline acrylates with general formula **I** [A = (substituted) alkyl, cycloalkyl, aryl, heteroaryl; X = CO, CH<sub>2</sub>; R = Me Et; R<sup>1</sup> = H, OH, alkoxy, PhCO<sub>2</sub>, mesityloxy, OCH<sub>2</sub>CO<sub>2</sub>Et; R<sup>2</sup> = H; R<sup>3</sup> = alkenyl, (substituted) aryl, heteroaryl, aralkenyl, heteroaralkenyl; R<sup>2</sup>R<sup>3</sup> = atoms to form a substituted (unsaturated) pyran ring; R<sup>4</sup> = H, OH; R<sup>5</sup> = H, OH, alkoxy, aryloxy], was undertaken.

**Activity and bioassay:** Compounds **II** (benzopyran derivatives) exhibited EC<sub>50</sub> of 358 nM for activated FXR receptors

**Origin:** Synthetic



Web URL: <http://sciencedirect.com>

**42. Equol, a natural estrogenic metabolite from soy isoflavones, convenient preparation and resolution of R- and S- equols and their differing binding and biological activity through estrogen receptors alpha and beta**

Rajeev, M. S., Young, J. H., Shubin, S., Lee, W. D., Daniel, D. R., Benita, K. S., William, H. G. and John, K. A.

Department of Chemistry, University of Illinois, Urbana, IL 61801 USA

*Bioorganic & Medicinal Chemistry* 2004, **12**(6), 1559-1567; *C.A.* **141**(2): 17526d

**Abstract:** Equol (**I**) is synthesized, purified to its enantiomers and subjected to binding assays.

**Activity and bioassay:** The activities for the enantiomers on the two estrogen receptors ER $\alpha$  and ER $\beta$  are reported. ER $\alpha$  ( $K_i$ [ER $\alpha$ ]=16 nM;  $\Delta$  =13 fold), was shown by S-equol suggesting strong binding affinity genistein ( $k_i$ [ER $\alpha$ ]=6.7 nM;  $\Delta$  =16), whereas R-equol displayed ER $\beta$  ( $K_i$ [ER $\beta$ ]=50 nM;  $\Delta$  =0.29) showing weak preference for ER $\alpha$  and ER $\beta$  enantiomers of **I** were found to display strong binding affinity to the estrogen receptors ER $\alpha$  and ER $\beta$ .

**Origin:** Synthetic

Web URL: <http://sciencedirect.com>

**43. Synthesis and pharmacological characterization of bivalent ligands of epibatidine at neuronal nicotinic acetylcholine receptors**

Zhi-Laing, W., Yingxian, X., Kenneth, K. J. and Alan, K. P.

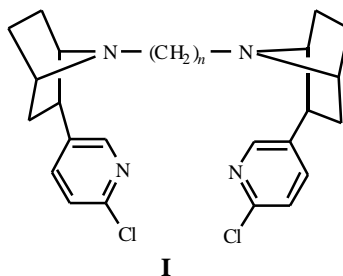
College of Pharmacy, Department of Medicinal Chemistry and Pharmacognosy, University of Illinois Chicago, IL 60610 USA

*Bioorganic & Medicinal Chemistry Letters* 2004, **14**(8), 1855-1858; *C.A.* **141**(2): 23763v

**Abstract:** Preparation of bivalent ligands of epibatidine (**I**) with n = 2, 3, 10 and their biological studies were carried out.

**Activity and bioassay:** These ligands of **I** are weak partial agonists at the  $\alpha_3\beta_4$  nAChR determined by functional assays, whereas in competition binding assays, they exhibited nanomolar binding affinities at six neuronal acetylcholine receptor (nAChR) subtypes.

**Origin:** Synthetic



**44. Preparation of new carbamic acid esters with anticholinergic effectiveness**

Matthias, G., Matthias, H., Michael, P. P., Speck, G. and Steffen, B.

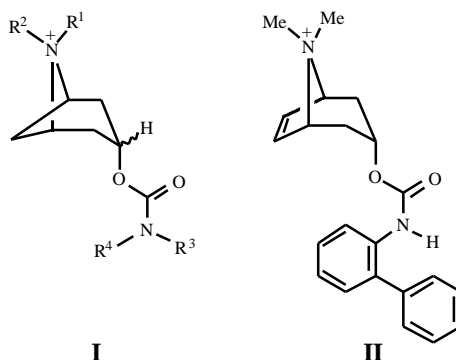
Boehringer Ingelheim Pharma GmbH & Co.Kg, Germany

**Ger. Offen. 10, 255, 040** (Cl.C07D45/02), 3 Jun 2004, Appl. 10255,040, 26 Nov. 2002; 40 pp; C.A. **141(2)**: 23766y

**Abstract:** Synthesis of new carbamic acid esters with general formula **I.X** [X = negatively charged ion (Cl, Br, I, sulfate, phosphate, MeSO<sub>3</sub>, NO<sub>3</sub> maleate, OAc, citrate, fumarate, tartrate, oxalate, succinate, PhCO<sub>2</sub>, *p*-MeC<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>); A = CH<sub>2</sub>CH<sub>2</sub>, CH:CH, oxirane-2,3-diyl, cyclopropane-1,2-diyl; R<sup>1</sup>, R<sup>2</sup> = C<sub>1-5</sub>-alkyl, hydroxyalkyl, haloalkyl, (C<sub>3-6</sub>-cycloalkyl)alkyl; R<sup>1</sup>R<sup>2</sup> = C<sub>3-6</sub>=alkylene; R<sup>3</sup>, R<sup>4</sup> = H, (un)substituted C<sub>1-5</sub>-alkyl, C<sub>6-10</sub>-aryl, (C<sub>6-10</sub>-aryl)-(C<sub>1-4</sub>-alkylene)], their enantiomers, diastereoisomers, salts, solvates and hydrates and **II.Br**<sup>-</sup> is described.

**Activity and bioassay:** These compounds are claimed to possess anticholinergic activity.

**Origin:** Synthetic



#### 45. Preparation of indino acid derivatives as somatostatin agonists or antagonists

Hidenori, A., Shinichiro, M., Shiro, T. and Masanori, W.

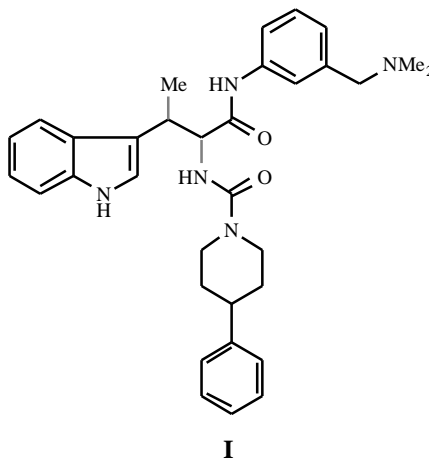
Takeda Chemical Industries, Ltd., Japan

**PCT Int. Appl. WO 2004, 46,107** (Cl.C07D209/20), 3 Jun 2004, JP Appl. 2003/76,435,19 Mar 2003; 482 pp; C.A. **141(2)**: 23903r

**Abstract:** Synthetic analogs of indole amino acid having general formula Z-Y-N(Y<sup>a</sup>-Z<sup>a</sup>) CH (CR<sup>4</sup>R<sup>5</sup>R<sup>6</sup>)-CONR<sup>3</sup>-A-B-NR<sup>1</sup>R<sup>2</sup> [A is an arom. Ring optionally having substituent; B, Y and Y<sup>a</sup> are a bond or spacer; R<sup>1</sup>, R<sup>2</sup> are H, (un)substituted hydrocarbyl or heterocyclyl or R<sup>1</sup>,R<sup>2</sup>N is a ring or forms a ring with ring A; R<sup>3</sup> is H, (un)substituted hydrocarbyl or heterocyclyl; R<sup>4</sup>,R<sup>5</sup> are H or (un)substituted hydrocarbyl or form a ring R<sup>6</sup> si (un) substituted indolyl; Z, Z<sup>a</sup> are H halo or a cyclic group], are described.

**Activity and bioassay:** These compounds exhibited binding inhibition for somatostatin receptor.

**Origin:** Synthetic



**46. Design and synthesis of galectin inhibitors**

Prenilla, S., Barbro, K.-K., Ulf, W., Bengt-Goeran, M., Hakon, L. and Ulf, N. J.

Department of Bioorganic Chemistry, Lund University, SE-22100 Lund, Sweden

*Methods in Enzymology* 2003, **363**(Recognition of Carbohydrates in Biological Systems, Part B), 157-169; *C.A.* **141**(2): 23785d

**Abstract:** Galectin inhibitors incorporating C3 amide, sulfonamide and urea *N*-acetylglucosamine skeleton were derivatized and their analogs were prepared and studied for their galectin-3 inhibition.

**Activity and bioassay:** Derivatives of *N*-acetylglucosamine C3'benzamido and 3'-*O*-benzyl were found to display significant galectin-3 inhibition. 3'-*O*-Benzylated *N*-acetylglucosamine exhibited less potency but was still a potent inhibitor.

**Origin:** Synthetic

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**Web URL:** <http://sciencedirect.com>

**47. Synthesis or novel potent dipeptidyl peptidase IV inhibitors with enhanced chemical stability: Interplay between the *N*-terminal amino acid alkyl side chain and the cyclopropyl group of  $\alpha$ -aminoacyl-*L*-*cis*-4,5-methanoprolinenitrile-based inhibitors**

David, M. R., Jeffrey, R. A., Richard, S. B., David, A. J., Yanting, H., Ligya, S. M., Prakash, T. C., David, B. A., James, R. G., Benoni, A-b-o. E., Aiyang, W., Michel, C., Li, X., Li, T., Doree, S. F., Mary, M. F., Jaack, G. Z., Ashish, K., Song-Ping, H. Q. H., Rex, P. A. and Lawrence, H. G.

Departments of Discovery Chemistry, Metabolic Research, Exploratory Pharmaceutical Computer-Assisted Drug Design, Solid State Chemistry and Pharmaceutical Candidate Optimization, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400 USA

*Journal of Medicinal Chemistry* 2004, **47**(10), 2587-2598; *C.A.* **141**(2): 23891k

**Abstract:** Preparation of dipeptide mimetics of methanoprolinenitrile was carried out and further tested for their bioactivity. SAR and stability factor are also discussed.

**Activity and bioassay:** These derivatives displayed high to moderate inhibition potency for *N*-terminal sequence-specific serine protease dipeptidyl peptidase **IV** (DPP-IV). *Cis*-4,5-methanoprolinenitriles with  $\alpha$ -branching in the *N*-terminal amino acid exhibited high inhibition for DPP-IV. These compounds reduced prandial glucose elevations after an oral glucose challenge in male Zucker rats.

**Origin:** Synthetic

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**Web URL:** <http://sciencedirect.com>

**48. Proteasome inhibitors: synthesis and activity of arecoline oxide tripeptide derivatives**

Mauro, M., John, M.-D., Anna, B., Alessandro, C., Car-mela, D. R.; Piero, P. G. and Roberto, T.

Department of Pharmaceutical Sciences and Biotechnology Centre, University of Ferrara, 1-44100 Ferrara, Italy

*Bioorganic Medicinal Chemistry Letters* 2004, **14**(8), 1965-1968; *C.A.* **141**(2): 23887p

**Abstract:** Synthetic and biological studies were conducted for the derivatives of Me-3,4-epoxypiperidine-3-carboxylate tripeptide.

**Activity and bioassay:** One of the compounds 2,3-Me(HO)C<sub>6</sub>H<sub>3</sub>CO-Val-Ser-Leu-AE (AE = Me 3,4-epoxypiperidine-3-carboxylate) was found to exhibit high potency for proteasome inhibition with IC<sub>50</sub> < 1  $\mu$ M.

**Origin:** Synthetic