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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Rad: 00-065549- -00008-0000

Fec: 2006-05-19 17:17:49 Dep. 2020 NUECREACIONES

Tra. 2 PATENTES

Eve: 1 REGDEPOSITO

Act 444 RESPUESTAREQUE Folios: 26

Trámite: 002

Evento: 001

Actuación: 444

Referencia : Expediente No. 00065549

Asunto : Solicitud de patente para: **AGENTE PROMOTOR DE PRODUCCION/SECRECION DE NEUROTROFINA**

Solicitante : **TAKEDA CHEMICAL INDUSTRIES, LTD.**

Fecha de Solicitud : 12 de octubre de 2000

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al oficio número 2086 notificado por fijación en lista el 23 de febrero de 2006.

2. Mediante el oficio número 2086 se puso en conocimiento del solicitante el informe que contiene las siguientes observaciones hechas por su Despacho sobre el examen de fondo de la presente solicitud de patente:

2.1. "El solicitante presentó una solicitud europea de patente que corresponde a la misma solicitud colombiana y donde se reivindica prioridad del mismo documento citado para Colombia. Dicha solicitud Europea corresponde a la publicación EP1206472 publicada el 1 de marzo 2001, equivalente a la publicación WO0114372 del 1 de marzo de 2001. Dicha solicitud fue tramitada y se procedió a su examen al respecto de lo cual existen documentos relativos al informe de búsqueda y el resultado del examen".

3. Atiendo a las observaciones realizadas mediante el oficio número 2086 de la manera siguiente:

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Presento junto con este memorial la copia de los artículos requeridos por su Despacho para efectos de llevar a cabo el estudio de patentabilidad de la presente invención.

4. DOCUMENTOS ADJUNTOS: Junto con este memorial presento los siguientes artículos:

- SHARMA P K ET AL: Potent antiinflammatory 3-thiazole-4(5) -acetic acids of 1,2-benzisothiazole" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB , OXFORD vol. 7, no. 18, 23 September 1997 (1997-09-23), pages 2427-2430, XP004136457 ISSN: 096 0894 X.
- DATABASE CHEMABS Online CHEMICAL ABSTRACTS SERVICE. COLUMBUS. OHIO, US KAWAKITA, TAKESHI ET AL: "Preparation of benzoxazine derivatives as phospholipase A2 and interleukin 1 inhibitors" retrieved from STN Database accession no. 124:117333 XP002165594 CAS RN: 113060-20-3.
- DATABASE CHEMABS .Online CHEMICAL ABSTRACTS SERVICE COLUMBUS OHIO. US; GIELDANOWSKI. JERZY ET AL: "Pharmacological activity in the group of New substituted thiazoloacetic and thiazinocarboxyl acid derivatives" retrieved from STN Database accession no. 91:68Z96 XP002165595 CAS RN: 71013-46-2; 71013-48-4; 71013-50-8; Abstract & ARCH. IMMUNOL. THER. EXP. (1978) 26(1-6), 921-9.
- DATABASE CHEMABS Online CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HIRAI, KENTARO ET AL: "2-Dialkylamino-4-aryl-5-thiazoleacetic acids" retrieved from STN Database accession no. 86:89798 XP002165596 CAS RN: 61874-16-8; 61814-72-4; 61874-73-5; 61874-75-7; 61874-79-1 61874-80-4; 61874-81-5; 61874-82-6.
- DATABASE CHEMABS Online CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO US BROWN, KEVAN E1 AL: "Nonsteroidal antiinflammatory agents. 1. 2, 4-Diphenylthiazole-5- acetic acid and related compounds". retrieved from STN Database accession no. 82:38473 XP002165597 CAS RN: 53515-14-3; 53515-15-4; 53616-16-5 abstract & J. MED. CHEM (1974), 17(11), 1177-81.
- DATABASE CHEMABS Online CHEMICAL ABSTRACTS SERVICE, COLUMBUS OHIO, US; SHARMA, PAWAN K ET AL: "Synthesis and antiinflammatory activity of some 1,4-dihydro-3-methyl 1-(2-thiazolyl)pyrazolo 4, 3-c 1,2 benzothiazine 5,5-dioxides" retrieved from STN Database accession no. 121: 9292 XP002165598 CAS RN: 155186-51-9; 155186-52-0; 155186-53-1; 155186-48-4; 155186-49-5; 155185-50-8 abstract & BULL. CHEM. SOC. JPN. (1993), 66(12) 3843-6.
- DATABASE CHEMABS Online CHEMICAL ABSTRACTS SERVICE" COLUMBUS, OHIO. US; SAWHNEY, S. N. ET AL: Synthesis and antiinflammatory activity of some 5-thiazoleacetic acids" retrieved from STN Database accession no. 100:139014

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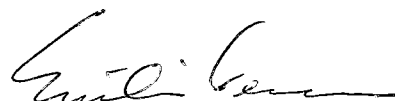
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XP002165599 CAS RN: 89402-94-8; 89402-95-9; 89402-96-0; 89402-90-4; 89402-91-5; 89402-92-6 abstract & INDIAN J. CHEM., SECT. B (1983), 22B (10), 1044-9.

- DATABASE CHEMABS Online CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STANKIEWICZ, JULIAN ET AL. "Studies on derivatives of 2-amino-4-(p-chlorophenyl) thiazole-5-acetic acid. IV. Addition reactions of thioglycolic acid to 2-n-alkylidene derivatives of 2-amino-4-(p-chlorophenyl) thiazole-5-acetic acid" retrieved from STN Database accession no. 98:53756 XP002165600 CAS RN: 84296-74-2; 84296-15-3; 84296-76-4; 84296-77-5; 84296-78-6 abstract & ARCH. IMMUNOL. THER. EXP. (1981), 29(6), 827-33.
- DATABASE CHEMABS Online CHEMICAL ABSTRACTS SERVICE COLUMBUS, OHIO US; JAKOBIEC TADEUSZ ET AL: "Studies on the derivatives of 2-amino-4-p-chlorophenylthiazole-5-acetic acid. I. Syntheses and pharmacological analysis of acyl derivatives of 2-amino-4-chlorophenylthiazole-5-acetic acid" retrieved from STN Database accession no. 93:36820 X002165601 CAS RN: 71013-46-2; 71013-48-4; 71013-50-8; 74241-16-0 abstract & ARCH. IMMUNOL. THER. EXP. (1979), 27(6), 717-94.
- DATABASE CHEMABS Online CHEMICAL ABSTRACTS SERVICE; COLUMBUS, OHIO, US; HIRAI, KENTARO ET AL: "Studies on heterocyclic cation systems. XI. Syntheses of 2-disubstituted-amino-4-arylthiazol-5-ylalkanoic acids retrieved from STN Database accession no. 88: 50706 XP002165602 CAS RN: 61874-75-7; 61814-16-8; 61874-79-1; 65358-74-9; 65358-15-0; 61874-73-5; 65358-66-9; 65358-67-0; 65358-68-1; 65358-13-8; 61874-81-5; 61874-82-6 abstract & CHEM. PHARM BULL. (1977) 25(9), 2292-9.

Bogotá, 19 MAYO 2006

Señora Jefe,



EMILIO FERRERO

T.P.A. No. 31.929

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XP 0041 36457

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PII: S0960-894X(97)00449-6

POTENT ANTIINFLAMMATORY 3-THIAZOLE-4(5)-ACETIC ACIDS OF 1,2-BENZISOTHIAZOLE

Pawan K. Sharma* and S.N. Sawhney

Department of Chemistry, Kurukshetra University, Kurukshetra-136 119, INDIA

Abstract : A number of 1,2-benzisothiazole derivatives, having 2-thiazolyl-4(5)-acetic acid moiety attached to position-3 of 1,2-benzisothiazole nucleus, were prepared and evaluated as antiinflammatory agents. Some of these were found to possess excellent level of antiinflammatory activity in carrageenin-induced rat paw edema assay.

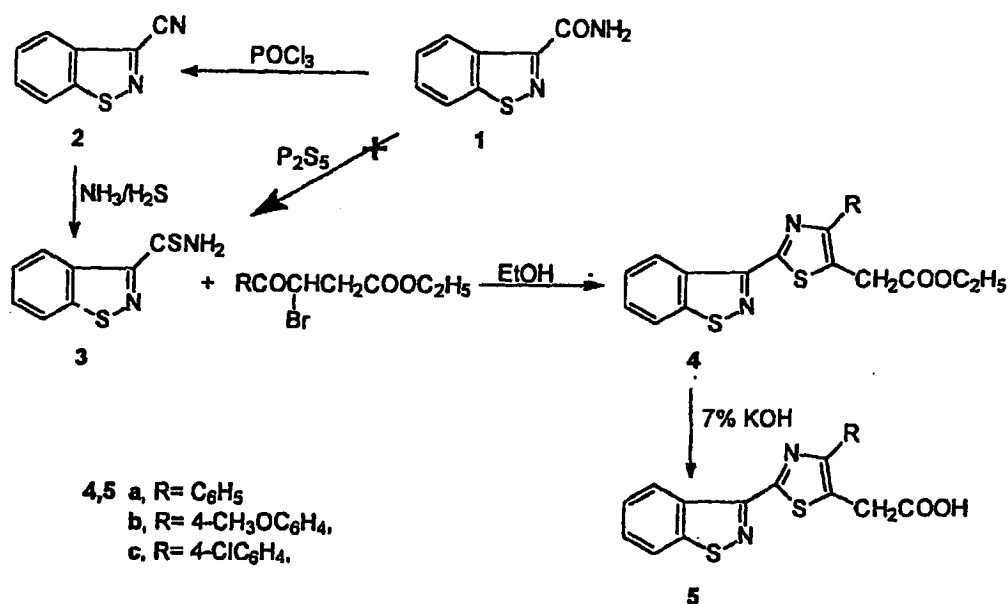
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The search for more effective antiinflammatory agents has led medicinal chemists to explore a wide variety of chemical structures^{1,2}. A majority of these compounds, especially those with proven clinical efficacy, are acidic in nature such as aspirin, indomethacin, flufenamic acid, ibuprofen, etc., or β -diketones such as phenylbutazone, etc. Since the discovery of aspirin, much efforts have been devoted to the development of acidic Non-Steroidal Antiinflammatory Drugs (NSAIDs) and some of these, having an acetic acid grouping^{3,4} are found to possess significant antiinflammatory activity. Although these drugs reduce symptoms of chronic inflammatory disease but they are by no means free from irritant side effects⁵. Therefore, investigations of new antiinflammatory agents are still continuing with a hope to find an ideal NSAID. The carrageenin-induced rat paw edema model has been used as a popular model for preliminary screening for such antiinflammatory agents⁶.

During the last two decades, several kinds of biological activities have been claimed for 1,2-benzisothiazoles⁷⁻⁹. It's 5- and 3-acetic acid derivatives possess some antiinflammatory activity⁹. Some thiazole-4(5)-acetic acid derivatives are also known to possess antiinflammatory activity¹⁰, e.g. fenclozic acid has significant level of activity, but has to be withdrawn due to hepatotoxicity observed in many cases¹¹. Appreciation of these findings, coupled with our ongoing interest in the synthesis and evaluation of 1,2-benzisothiazole derivatives as antiinflammatory agents¹² and as a part of our ongoing programme¹³ to develop NSAIDs, we undertook the synthesis of some acidic derivatives of thiazolyl-1,2-benzisothiazoles. The present communication reports the potent antiinflammatory activity of some 2-(1,2-benzisothiazol-3-yl)-4(5)-thiazole acetic acids and their ethyl esters.

Scheme 1 depicts the two step conversion of 1,2-benzisothiazole-3-thiocarboxamide (3) into thiazole-5-acetic acids (5). Unfortunately, the conventional method of preparing thioamides by treating the corresponding amides with phosphorus pentasulphide failed to give thioamide (3) from 1,2-benzisothiazole-3-carboxamide (1). Therefore, the required thiocarboxamide (3) was prepared from 1 through the 3-cyano compound (2). The carboxamide (1) on treatment with phosphoryl chloride afforded 1,2-benzisothiazole-3-carbonitrile (2)¹⁴ which on treatment with hydrogen sulphide and ammonia gas in ethanol gave 1,2-benzisothiazole-3-thiocarboxamide (3) in 72% yield. The condensation of 3 with various ethyl β -aroyl- β -bromopropionates¹⁵ according to well known

Scheme 1



Hantzsch thiazole synthesis gave 3-(4-aryl-5-carbomethoxymethylthiazol-2-yl)-1,2-benzisothiazoles (4) in good yields. The esters (4) on alkaline hydrolysis in methanol followed by acidification afforded the corresponding thiazole-5-acetic acids (5) in quantitative yields. We found that compound 5c possesses excellent level of antiinflammatory activity, higher than that of the standard drug ibuprofen, in carrageenin-induced rat paw edema assay (Table 1).

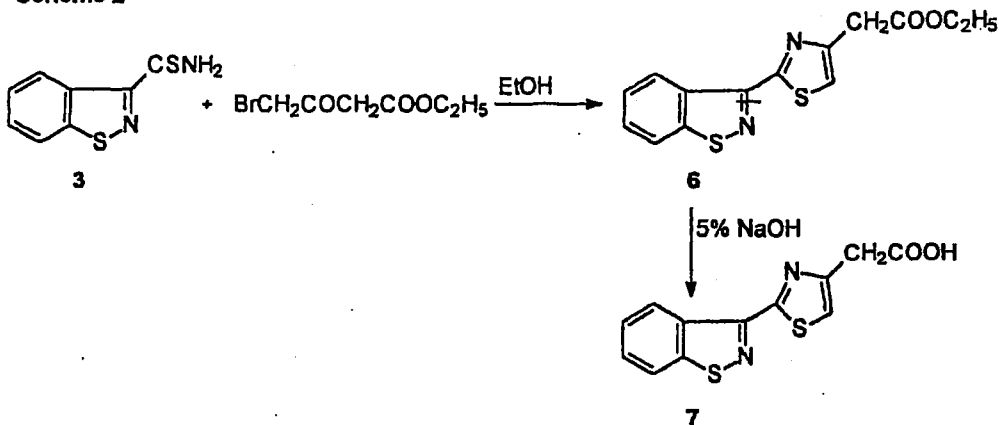
Prompted by the significant activity of thiazole-5-acetic acids (5), we undertook the synthesis of thiazole-4-acetic acid (7) (scheme 2). The condensation of thiocarboxamide (3) with ethyl γ -bromoacetoacetate¹⁶ proceeded smoothly in ethanolic solution giving 3-(4-carbomethoxymethylthiazol-2-yl)-1,2-benzisothiazole (6). 6 on hydrolysis with 5% sodium hydroxide in methanol afforded the corresponding thiazole-4-acetic acid (7). As expected, compound 7 also showed activity higher than that of ibuprofen.

The values obtained for these compounds in carrageenin-induced rat paw edema assay¹⁷ upon oral (p.o.) and intraperitoneal (i.p.) administration as suspension in gum acacia (1% w/v) in normal saline at 100 mg/kg are presented in Table 1. Each value is the mean of four animals. In every experiment one group of rats was kept as control and another group received a standard drug (ibuprofen) for comparison. Local irritant action was tested by applying different concentrations of test compounds on rabbit cornea¹⁸.

Based on the screening data some general observations are worth mentioning. In general, the compounds tested show somewhat higher activity when administered intraperitoneally (i.p.) as compared to the oral route (p.o.). This is the case with the standard drug, ibuprofen, also. The activity reduces rapidly with the passage of

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Scheme 2



time as inhibition measured after 2 hr period is generally more than that observed after 3.5 hr. This behaviour is opposite to that of ibuprofen and may be attributed to the rapid metabolism of the compounds in the system. Amongst the target compounds, the highest activity has been exhibited by compound 5c (inhibition 75% p.o.) followed by 7 with inhibition of 64% (p.o.). Moreover the compound 5c has quite high activity (69% inhibition) even at dose level of 50 mg/kg. This is somewhat expected because these compounds (5c & 7) belong to the family of heterocyclalcanoic acids. The high activity puts these two compounds in the class of potential NSAIDs and therefore they have been marked for detailed pharmacological screening and the results will be discussed in further reports. The order of activity shown by the compounds within the series 5, i.e. 5c > 5b > 5a, is in confirmation with our earlier observation that compounds with chloro or methoxy substituents show higher activity¹⁹. The esters 4, and 6 were mildly active or inactive.

Table 1 - Antiinflammatory activity of compounds 4-7 on oral (p.o.) and intraperitoneal (i.p.) administration

Compound	% inhibition ²⁰			
	oral (p.o.)		intraperitoneal (i.p.)	
	2 hr	3.5 hr	2 hr	3.5 hr
4a	N	11	N	N
4b	20	29	34	30
4c	34	22	24	13
5a	15	19	45	7
5b	36	33	40	24
5c*	75	62	78	67
	69 [†]	61	76	64
6	18	11	ND	ND
7	64	46	55	64
ibuprofen	62	65	70	74

N ≤ 10% inhibition. ND denotes not done.

*Value is the mean of eight animals.

[†]Percent inhibition at 50 mg/kg.

Acknowledgements. We are thankful to Dr R S Kapil, Director, Regional Research Laboratory, Jammu for providing biological testing facilities and to the University Grants Commission, New Delhi for financial assistance.

References and notes

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20. The procedure used to determine the inhibition has been described previously, see reference 12 (b).

(Received in Japan 7 July 1997; accepted 22 August 1997)

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P.D. 00-00-00
P. 1-4

450

W: AE, AG, AL, AM, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CN, CR,
CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG,
KR, KZ, LC, LK, LR, LT, LV, MA, MD, MG, MK, MN, MX, MZ, NO,
NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN,
YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,
BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

- As an industrially advantageous process for forming a carbon-carbon bond at the 5-position of oxazole is provided a process for prepg. compds. of general formula (I) or salts thereof (wherein R1 and R2 are each hydrogen, optionally substituted hydrocarbyl, or an optionally substituted heterocyclic group; R3 is an electron-withdrawing group; and R4, R5 and R6 are each hydrogen or optionally substituted hydrocarbyl), characterized by reacting a compd. of general formula (II) or a salt thereof (wherein R1 and R2 are as defined above) with a compd. of general formula R3R4C:CR5R6 or a salt thereof (wherein R3-R6 are defined above) in the presence of an acid or a base. The compds. I are useful as intermediates in the prepn. of preventives or remedies for diabetes and diabetes complications. Thus, 1,195 g concd. H2SO4 was added dropwise to a soln. of 794.3 g 4-(4-chlorophenyl)-2-oxo-4-oxazoline in 2,383 mL MeCN at .1toreq.10.degree. under ice-cooling, followed by adding 731 mL Me acrylate at .1toreq.10.degree., and the resulting mixt. was stirred at room temp. for 3 h and treated with 794 mL H2O at .1toreq.20.degree.. The pptd. crystals were collected by filtration and washed with 1% NaHCO3, H2O, and iso-Pr ether to give 3-[4-(4-chlorophenyl)-2-oxo-4-oxazolin-5-yl]propanoic acid Me ester (1,017.8 g and 89%).

RN - 327188-13-6 CAPLUS

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IT ***327189-29-7P*** , 2-(2-Methyl-1-imidazolyl)-5-[3-(2-methylphenoxy)propyl]-4-(4-trifluoromethylphenyl)oxazole
327189-31-1P , 4-(3,4-Dichlorophenyl)-2-(2-methyl-1-imidazolyl)-5-[3-(2-methylphenoxy)propyl]oxazole
327189-47-9P , 4-(4-Chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-[3-(2-methylphenoxy)propyl]oxazole hydrochloride
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of oxazole derivs. as intermediates for antidiabetics by addn. reaction of oxazoles with ethylenes contg. electron-withdrawing groups)

RN 327189-29-7 CAPLUS

CN Oxazole, 2-(2-methyl-1H-imidazol-1-yl)-5-[3-(2-methylphenoxy)propyl]-4-[4-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)

[illegible] $(\text{CH}_2)_3$

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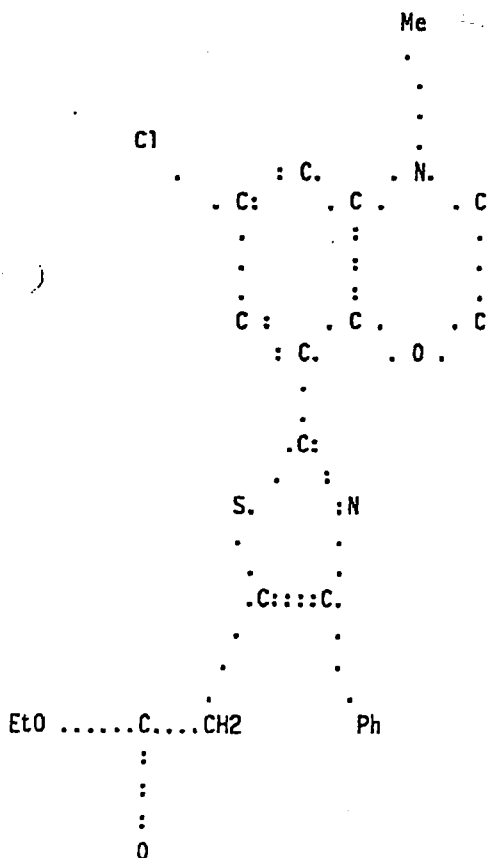
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AN - 1996:79019 CAPLUS XP-002165594
 DN - 124:117333
 TI - Preparation of benzoxazine derivatives as phospholipase A2 and interleukin 1 inhibitors
 IN - Kawakita, Takeshi; Kuroita, Takanobu; Murozono, Takahiro; Terasawa, Michio; Okamoto, Hitoshi
 PA - Yoshitomi Pharmaceutical, Japan
 SO - Jpn. Kokai Tokkyo Koho, 32 pp.
 CODEN: JKXXAF
 DT - Patent
 LA - Japanese
 FAN.CNT I

PATENT NO. KIND DATE APPLICATION NO. DATE

PN - JP7242663 A 19950919 JP 1994-31641 19940301
 OS - MARPAT 124:117333
 AB - The title compds. I [R1 = H, alkyl, etc.; R2 = H, OH, etc.; R3, R4 = H, alkyl; Het = 5,6-dihydroimidazo[2,1-b]thiazol-3-yl, etc.] are prepd. In an in vitro test for phospholipase A2 inhibiting activity, the title compd. II.HCl (prepn. given) at 10.mu.M gave 37% inhibition. Twenty-four synthetic examples dealing with the prepn. of the title compds. I are given in this document.
 IT - ---173060-20-3P---
 RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); ---THU (Therapeutic use)--- ; BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of benzoxazine derivs. as phospholipase A2 and interleukin 1 inhibitors)
 RN - 173060-20-3 CAPLUS.
 CN - 5-Thiazoleacetic acid, 2-(6-chloro-3,4-dihydro-4-methyl-2H-1,4-benzoxazin-8-yl)-4-phenyl-, ethyl ester (9CI) (CA INDEX NAME)



AN 1979:468296 CAPLUS

XP-002165595

P.D. 00-00-00

P. 1-2

DN 91:68296

TI - Pharmacological activity in the group of new substituted thiazoloacetic and thiazinocarboxyl acid derivatives

IN - Gieldanowski, Jerzy; Kowalczyk-Bronisz, Stefania H.

CS - Inst. Immunol. Exp. Ther., Polish Acad. Sci., Wroclaw, 53-114, Pol.

SO - Arch. Immunol. Ther. Exp. (1978), 26(1-6), 921-9

CODEN: AITEAT; ISSN: 0004-069X

DT - Journal

LA - English

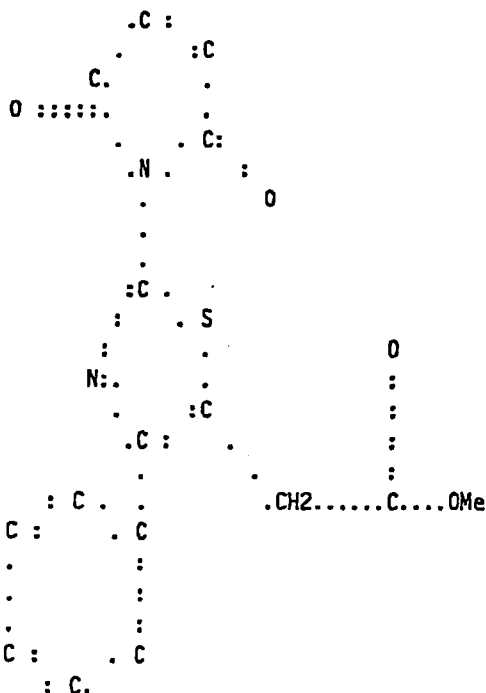
AB - Thirty-seven thioazoloacetic I (R = H or Me; R1 = NH2, NHAc, NHCHPhSO3H, etc.) and thiazinocarboxylic acid II (X = :NH, :NPH, etc.; R1 = H, alkyl, Ph, etc.) derivs. were studied for immunotropic, antiinflammatory, and addnl. pharmacol. activities in various animals. Among I, compds. substituted at C-2 and C-5 had the greatest immunotropic and antiinflammatory activity. The .alpha.-sulfonic acid derivs. of these compds. had the highest activities. II; X = :NCH2CH:CH2, R = H [70596-37-1] had a strong immunostimulatory effect and had the greatest inflammation-inhibitory activity of II. Structure-activity relations are discussed.

IT - ---71013-46-2--- ---71013-48-4--- ---71013-50-8---

RL: BAC (Biological activity or effector, except adverse); ---THU (Therapeutic use)--- ; BIOL (Biological study); USES (Uses) (pharmacol. activity of)

RN - 71013-46-2 CAPLUS

CN - 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-, methyl ester (9CI) (CA INDEX NAME)

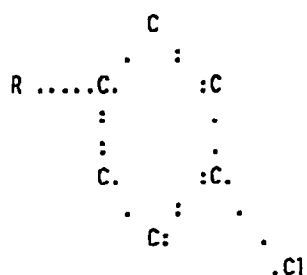


CI

RN 71013-48-4 CAPLUS

CN 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-, methyl ester (9CI) (CA INDEX NAME)

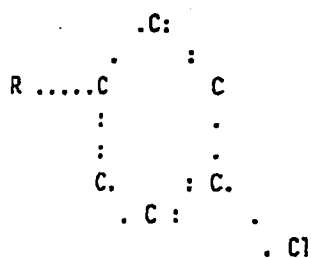
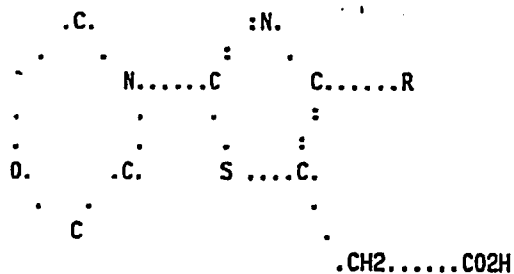


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 & & & & O & & CH_2 \dots\dots CO_2H
 \end{array}$$


AN - 1977:89798 CAPLUS XP-002165596
 DN - 86:89798
 TI - 2-Dialkylamino-4-aryl-5-thiazoleacetic acids
 IN - Hirai, Kentaro; Sugimoto, Hirohiko
 PA - Shionogi and Co., Ltd., Japan
 SO - Japan. Kokai, 5 pp.
 CODEN: JKXXAF
 DT - Patent
 LA - Japanese
 FAN.CNT 1

PATENT NO. KIND DATE APPLICATION NO. DATE

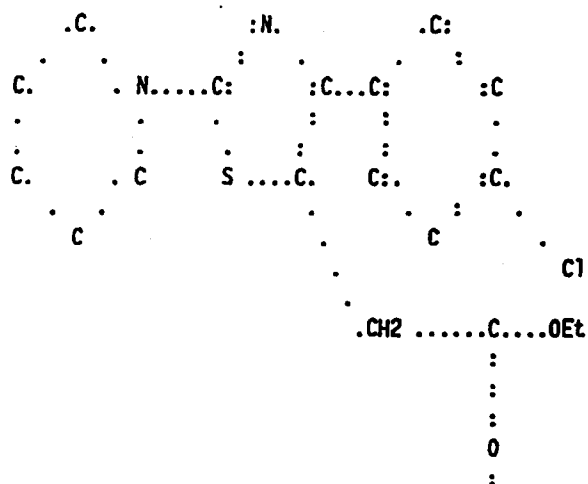
PN - JPS1088964 A 19760804 JP 1975-13159 19750130
 AB - Thiazoleacetic acids I (R = optionally substituted phenyl, arom. heterocycle; R1, R2 = alkyl or R1R2N = cyclic amino; R3 = H, alkyl; R4 = H, ester-forming group) were prepd. by acid cyclization of R1R2NC(O)SCH(COR)CHR3CO2R5 III (R5 = ester-forming group) to II (X = acid group) followed by treatment with NH3 and optional hydrolysis. I had antiinflammatory and analgesic activities in rats. Thus, III (R = p-ClC6H4, R1R2N = piperidino, R3 = H, R5 = Et), prepd. from Na piperidine-1-carbothioate and Et 3-p-chlorobenzoyl-3-bromopropionate, was stirred with 70% HClO4 in Ac2O with ice cooling for 1 h to give 82% corresponding II (X = ClO4). The perchlorate was stirred with 28% NH4OH in CHCl3 at room temp. for 1 h to give 67% corresponding I (R4 = Et), which was hydrolyzed to I.HCl (R4 = H) in 39.9% yield by heating with concd. HCl. Among 9 more I prepd. were (R, R1R2N, R3, and R4 given): p-ClC6H4, morpholino, H, H (HCl salt); Ph, piperidino, Me, H; p-ClC6H4, morpholino, Me, H; p-ClC6H4, Et2N, H, Et.
 IT - ---61874-76-8P---
 RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); ---THU (Therapeutic use)--- ; BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. and analgesic and antiinflammatory activities of)
 RN - 61874-76-8 CAPLUS
 CN - 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(4-morpholinyl)-, monohydrochloride (9CI) (CA INDEX NAME)



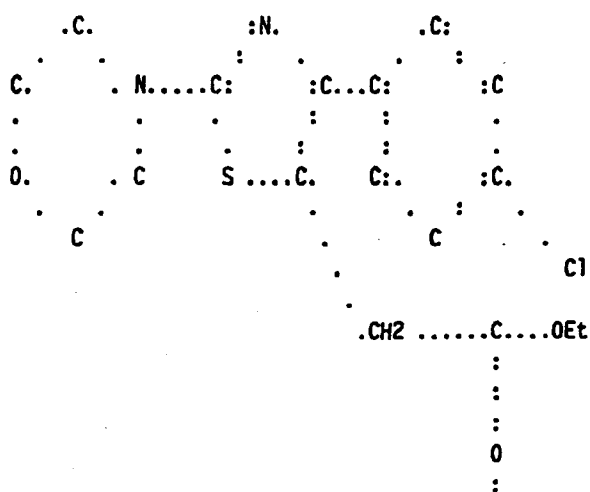
P.D. 00-00-00
 P. 5

480
 462

IT ***61874-72-4P*** ***61874-73-5P***
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
 (prepn. and hydrolysis of)
 RN 61874-72-4 CAPLUS
 CN 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(1-piperidinyl)-, ethyl
 ester (9CI) (CA INDEX NAME)



RN 61874-73-5 CAPLUS
CN 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(4-morpholinyl)-, ethyl ester (9CI) (CA INDEX NAME)



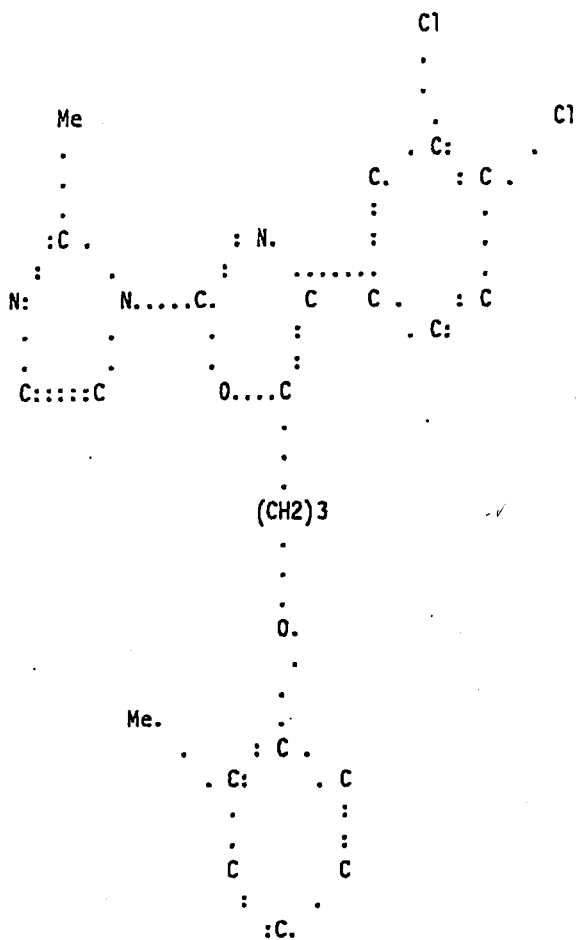
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IT  ***61874-75-7P***      ***61874-79-1P***      ***61874-80-4P***
    ***61874-81-5P***      ***61874-82-6P***
    RL: SPN (Synthetic preparation); PREP (Preparation)
        (prepn. of)
RN  61874-75-7  CAPLUS
CN  5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(1-piperidiny)-,
    monohydrochloride (9CI) (CA INDEX NAME)

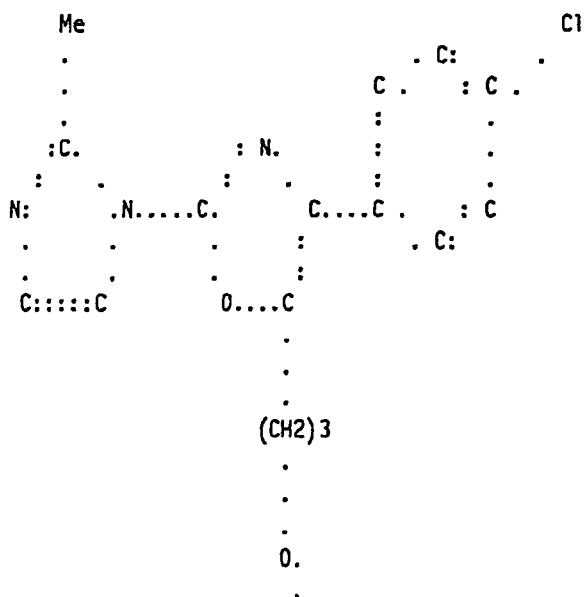
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RN 327189-31-1 CAPLUS
CN Oxazole, 4-(3,4-dichlorophenyl)-2-(2-methyl-1H-imidazol-1-yl)-5-[3-(2-methylphenoxy)propyl]- (9CI) (CA INDEX NAME)



RN 327189-47-9 CAPLUS
CN Oxazole, 4-(4-chlorophenyl)-2-(2-methyl-1H-imidazol-1-yl)-5-[3-(2-methylphenoxy)propyl]-, monohydrochloride (9CI) (CA INDEX NAME)



483

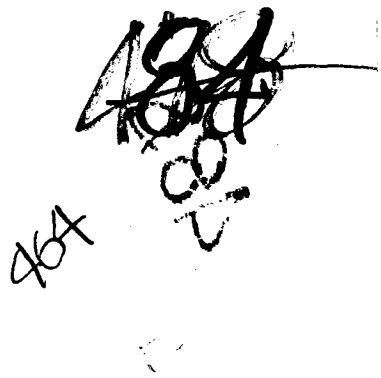
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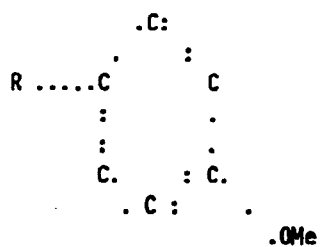
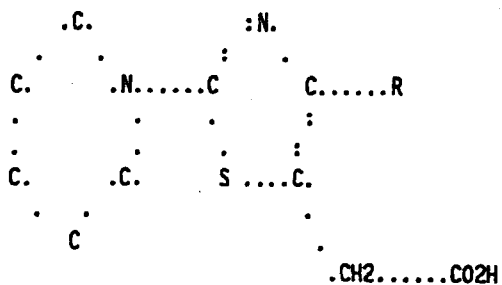
- (1) Anon; J Heterocycl Chem 1988, V25(3), P815
- (2) Takeda Chemical Industries Ltd; JP 09323983 A CAPLUS
- (3) Takeda Chemical Industries Ltd; EP 891340 A CAPLUS
- (4) Takeda Chemical Industries Ltd; WO 9736882 A1 1997 CAPLUS


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 & \cdot C \cdot \cdot \cdot \cdot S & & & & &
 \end{array}$$

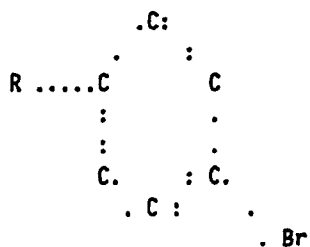
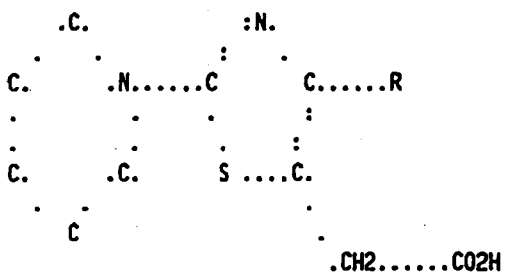

@ HCL

RN 61874-80-4 CAPLUS
CN 5-Thiazoleacetic acid, 4-(4-methoxyphenyl)-2-(1-piperidiny)- (9CI)

4850



RN 61874-81-5 CAPLUS
 CN 5-Thiazoleacetic acid, 4-(4-bromophenyl)-2-(1-piperidiny)- (9CI)
 (CA INDEX NAME)



RN 61874-82-6 CAPLUS
 CN 5-Thiazoleacetic acid, 2-(4-morpholiny)-4-(2-thienyl)- (9CI) (CA
 INDEX NAME)

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465

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AN - 1975:38473 CAPLUS

DN - 82:38473

TI - Nonsteroidal antiinflammatory agents. 1. 2,4-Diphenylthiazole-5-acetic acid and related compounds

IN - Brown, Kevan; Cater, David P.; Cavalla, John F.; Green, David; Newberry, Robert A.; Wilson, Alan B.

CS - Wyeth Inst. Med. Res., Taplow/Maidenhead/Berkshire, Engl.

SO - J. Med. Chem. (1974), 17(11), 1177-81
CODEN: JMCMAR

DT - Journal

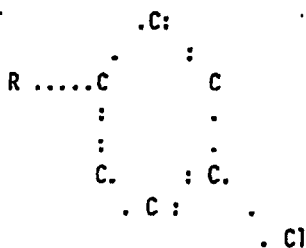
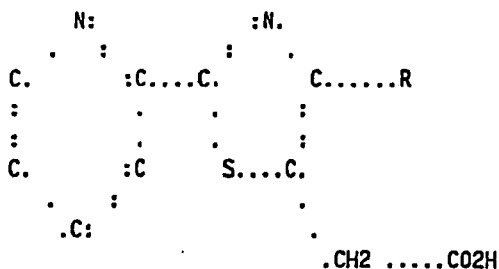
LA - English

AB - Two title compds., 4-(4-chlorophenyl)-2-phenylthiazole-5-acetic acid (I) [18046-21-4] and 4-(4-chlorophenyl)-2-(3-methylphenyl)thiazole-5-acetic acid (II) [53514-97-9], had antiinflammatory activity comparable to that of indomethacin [53-86-1] on carrageenin induced rat paw edema. I was 5 times as effective as phenylbutazone [50-33-9] against adjuvant-induced polyarthritis in rats. The acidic side chain derivs. were less active than the parent compds. The compds. were prepd. by the Hantzsch thiazole synthesis.

IT - ---53515-14-3P--- ---53515-15-4P--- ---53515-16-5P---
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); ---THU (Therapeutic use)--- ; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and antiinflammatory activity of)

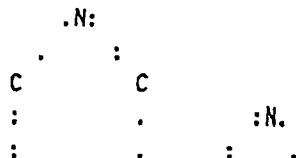
RN - 53515-14-3 CAPLUS

CN - 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(2-pyridinyl)- (9CI)
(CA INDEX NAME)



RN 53515-15-4 CAPLUS

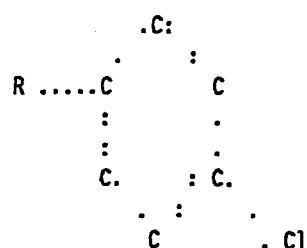
CN 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(3-pyridinyl)- (9CI)
(CA INDEX NAME)



13 188

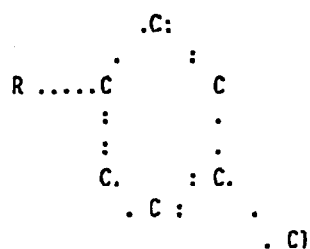
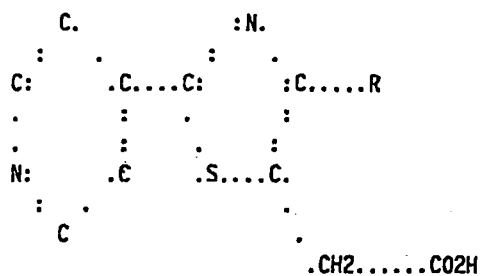
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.CH2 CO2H



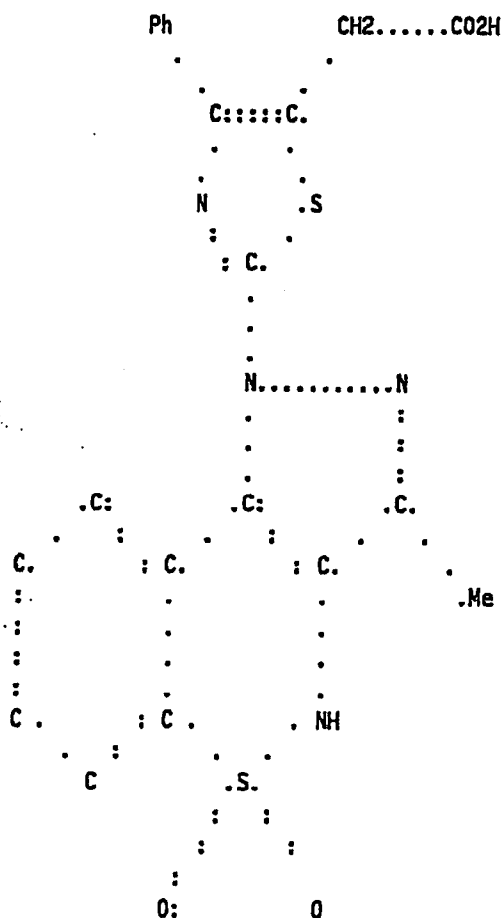
RN 53515-16-5 CAPLUS

CN 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(4-pyridinyl)- (9CI)
(CA INDEX NAME)



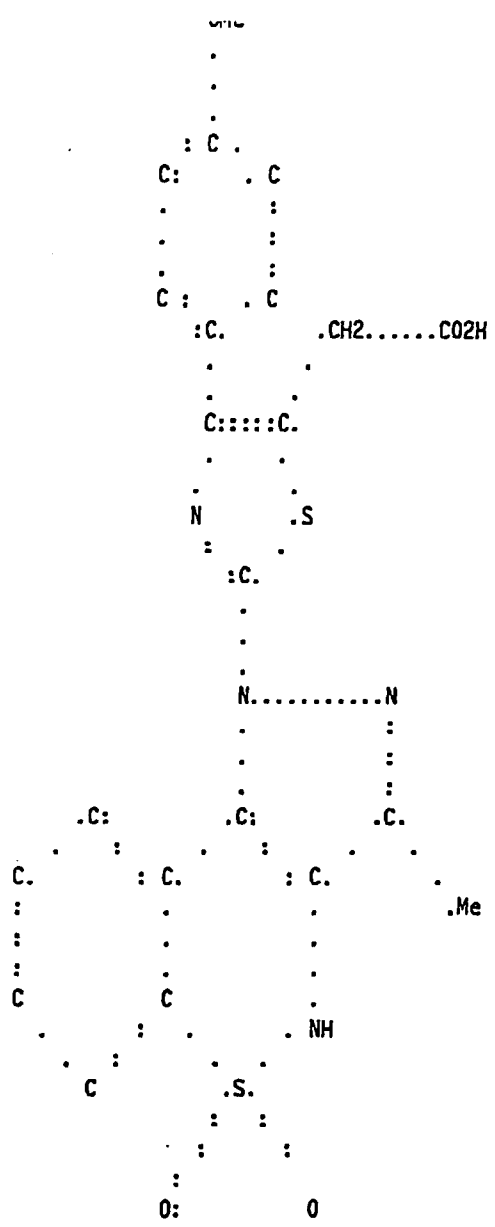
1

CN - 5-Thiazoleacetic acid, 2-(3-methyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-1(4H)-yl)-4-phenyl- (9CI) (CA INDEX NAME)

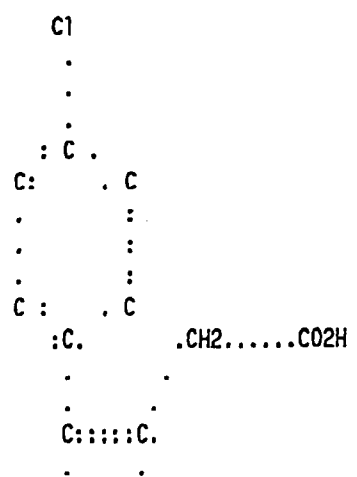


CN 5-Thiazoleacetic acid, 4-(4-methoxyphenyl)-2-(3-methyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-1(4H)-yl)- (9CI) (CA INDEX NAME)

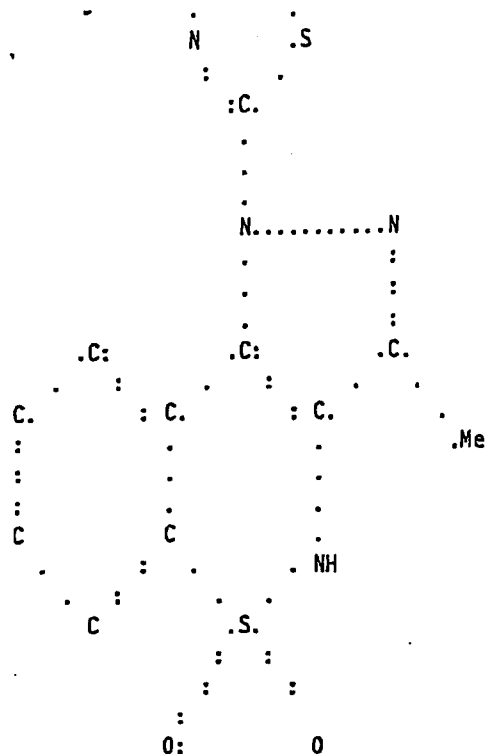
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490



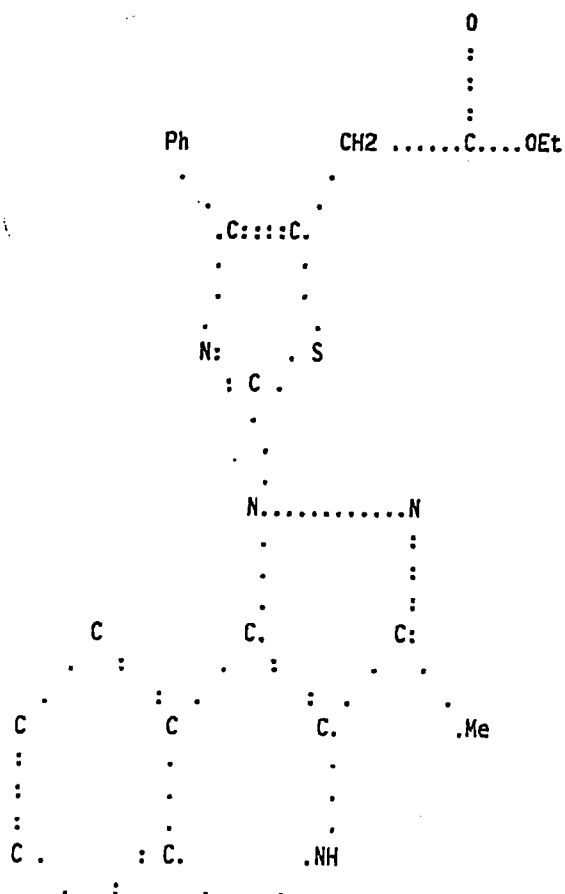
RN 155186-53-1 CAPLUS
CN 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(3-methyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-1(4H)-yl)- (9CI) (CA INDEX NAME)



497
460



IT ***155186-48-4P*** ***155186-49-5P*** ***155186-50-8P***
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
 (prepn. and sapon. of)
 RN 155186-48-4 CAPLUS
 CN 5-Thiazoleacetic acid, 2-(3-methyl-5,5-dioxidopyrazolo[4,3-
 c][1,2]benzothiazin-1(4H)-yl)-4-phenyl-, ethyl ester (9CI) (CA
 INDEX NAME)



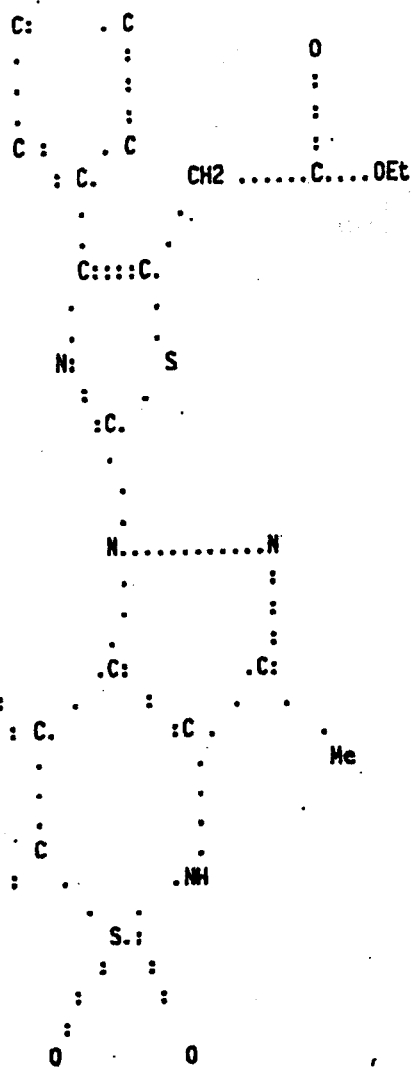
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483

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AN 1984:139014 CAPLUS

XP-002165599

DN 100:139014

TI - Synthesis and antiinflammatory activity of some 5-thiazoleacetic acids

IN - Sawhney, S. N.; Dhindsa, G. S.; Singh, S. P.

CS - Dep. Chem., Kurukshetra Univ., Kurukshetra, 132 119, India

SO - Indian J. Chem., Sect. B (1983), 22B(10), 1044-9

CODEN: IJSBDB; ISSN: 0376-4699

DT - Journal

LA - English

AB - Thiazoleacetic acids I (R, R1 = H, Cl, MeO), II (R2 = H, Cl, F, Me, MeO), and III, and IV (R3 = H, Br, Cl, MeO) were prepd. E.g., III were prepd. by cyclocondensation of 4-R3C6H4CHBrCH2CO2Et with H2NC(S)C(S)NH2 followed by alk. hydrolysis. III showed good antiinflammatory activity.

IT - ---89402-94-8P--- ---89402-95-9P--- ---89402-96-0P---

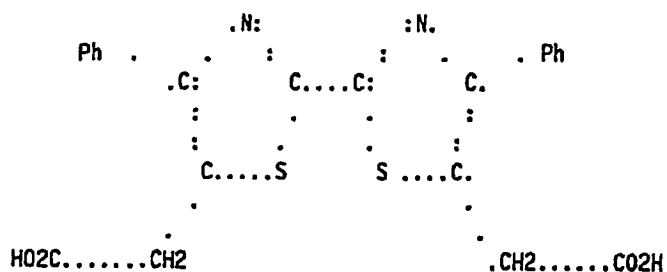
RL: BAC (Biological activity or effector, except adverse); SPN

(Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(prepn. and antiinflammatory activity of)

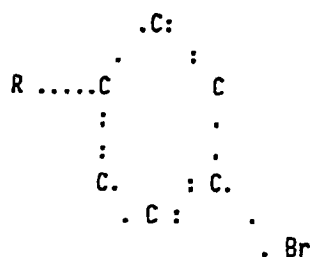
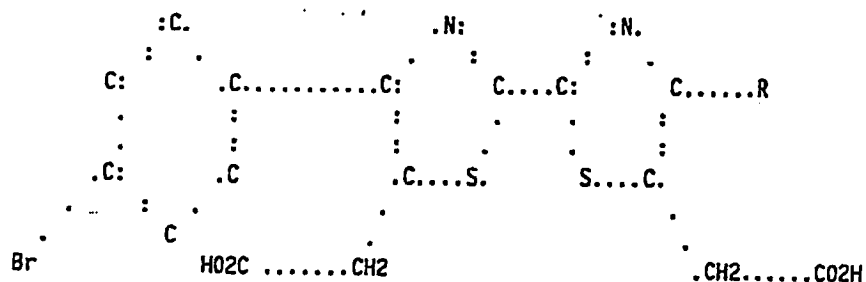
RN - 89402-94-8 CAPLUS

CN - [2,2'-Bithiazole]-5,5'-diacetic acid, 4,4'-diphenyl- (9CI) (CA INDEX NAME)

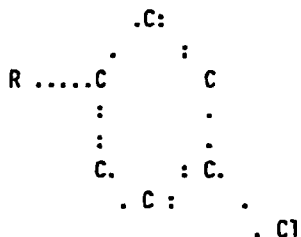
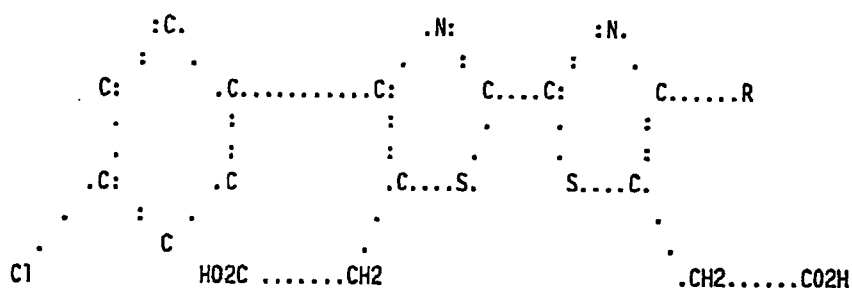


RN 89402-95-9 CAPLUS

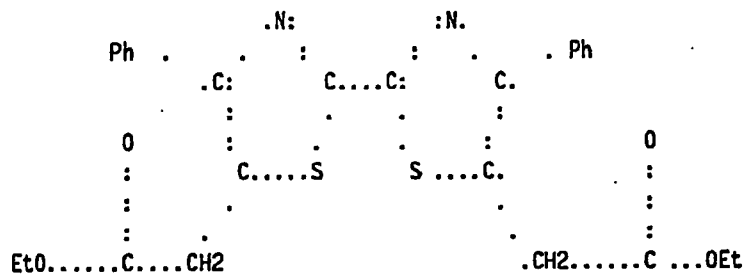
CN [2,2'-Bithiazole]-5,5'-diacetic acid, 4,4'-bis(4-bromophenyl)- (9CI) (CA INDEX NAME)



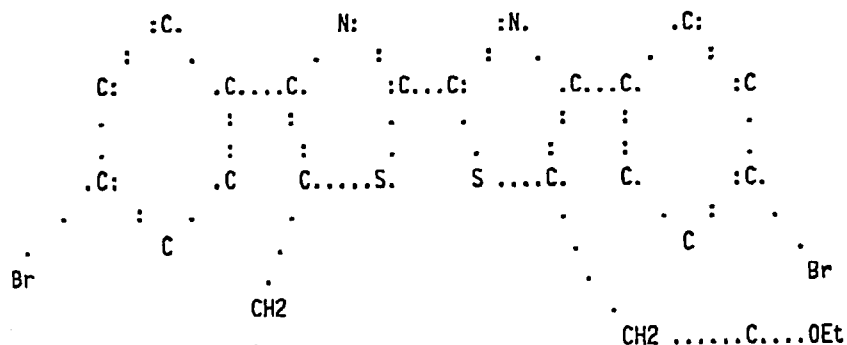
12
0495
(9CI) (CA INDEX NAME)



IT ***89402-90-4P*** ***89402-91-5P*** ***89402-92-6P***
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and hydrolysis of)
RN 89402-90-4 CAPLUS
CN [2,2'-Bithiazole]-5,5'-diacetic acid, 4,4'-diphenyl-, diethyl ester
(9CI) (CA INDEX NAME)



RN 89402-91-5 CAPLUS
CN [2,2'-Bithiazole]-5,5'-diacetic acid, 4,4'-bis(4-bromophenyl)-,
diethyl ester (9CI) (CA INDEX NAME)

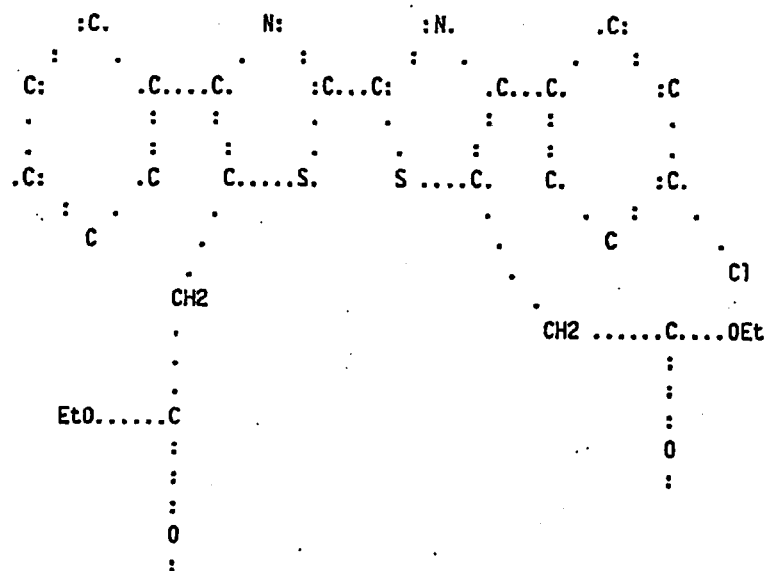


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RN 89402-92-6 CAPLUS

CN [2,2'-Bithiazole]-5,5'-diacetic acid, 4,4'-bis(4-chlorophenyl)-, diethyl ester (9CI) (CA INDEX NAME)



AN 1983:53756 CAPLUS

XP-002165600

DN 98:53756

TI - Studies on derivatives of 2-amino-4-(p-chlorophenyl)thiazole-5-acetic acid. IV. Addition reactions of thioglycolic acid to 2-n-aralkylidene derivatives of 2-amino-4-(p-chlorophenyl)thiazole-5-acetic acid

IN - Stankiewicz, Julian; Jakobiec, Tadeusz; Zawisza, Tadeusz

CS - Dep. Pharm. Chem., Med. Acad., Wroclaw, 50-137, Pol.

SO - Arch. Immunol. Ther. Exp. (1981), 29(6), 827-33

CODEN: AITEAT; ISSN: 0004-069X

DT - Journal

LA - English

AB - The thiazoleacetates I (R = H, p-HO, p-Cl, p-MeO, p-Me2N) and II were prepd. as potential inflammation inhibitors and immunosuppressants by addn. of the benzylideneaminothiazoleacetates III with HSCH2CO2H.

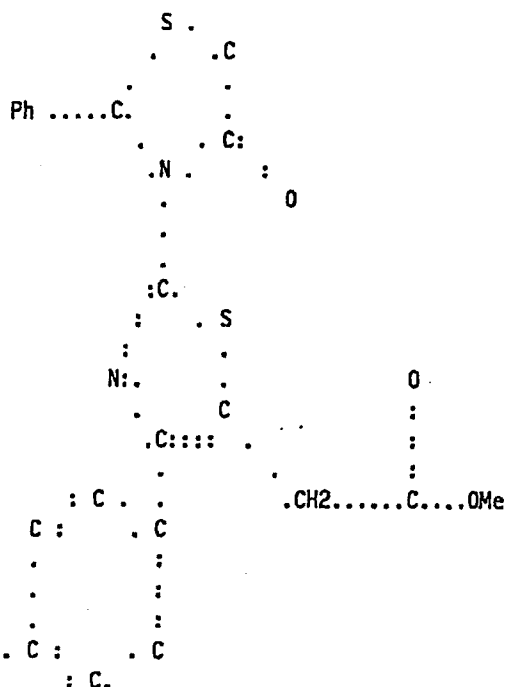
IT ---84296-74-2P--- ---84296-75-3P--- ---84296-76-4P---

---84296-77-5P--- ---84296-78-6P---

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN - 84296-74-2 CAPLUS

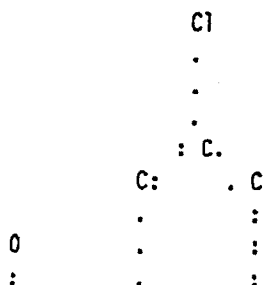
CN - 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(4-oxo-2-phenyl-3-thiazolidinyl)-, methyl ester (9CI) (CA INDEX NAME)



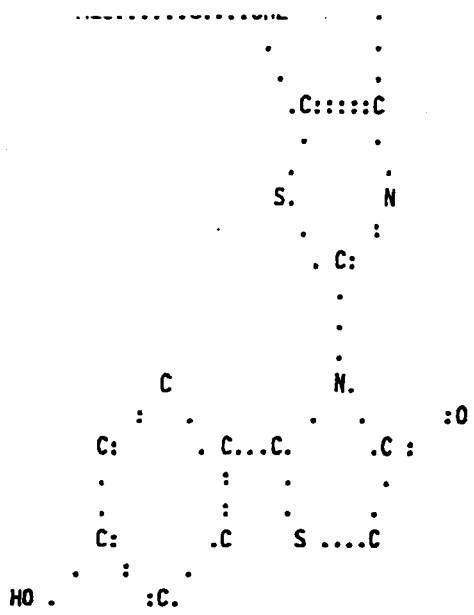
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RN 84296-75-3 CAPLUS

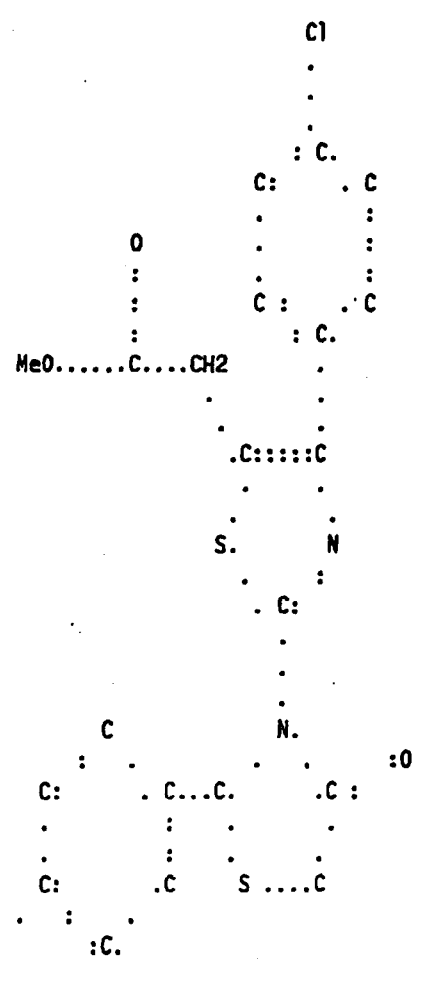
CN 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-[2-(4-hydroxyphenyl)-4-oxo-3-thiazolidinyl]-, methyl ester (9CI) (CA INDEX NAME)



19
72 130

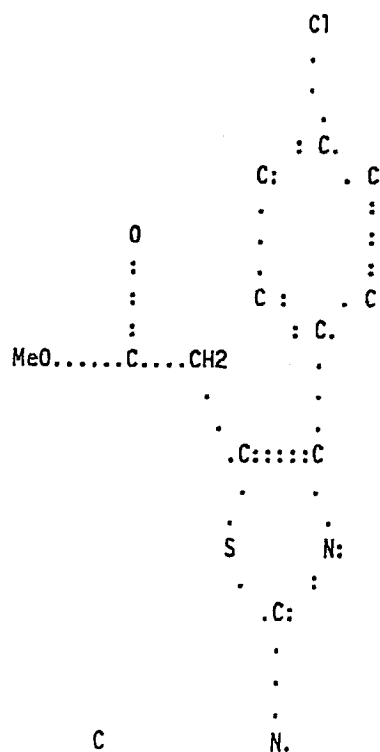
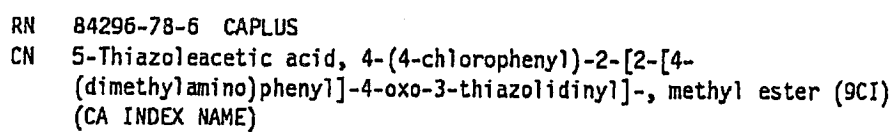


RN 84296-76-4 CAPLUS
 CN 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-[2-(4-chlorophenyl)-4-oxo-3-thiazolidinyl]-, methyl ester (9CI) (CA INDEX NAME)

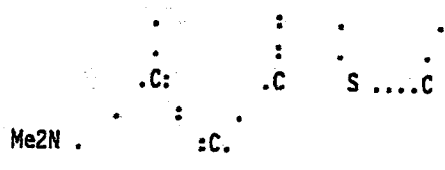


RN 84296-77-5 CAPLUS
 CN 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-[2-(4-methoxyphenyl)-4-oxo-3-thiazolidinyl]-, methyl ester (9CI) (CA INDEX NAME)

423



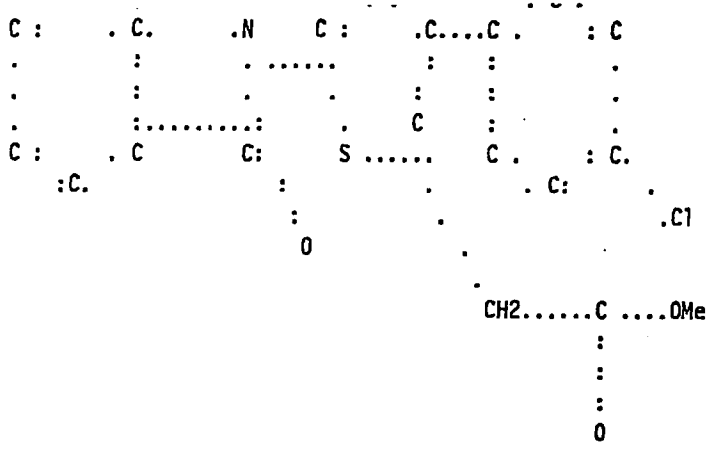
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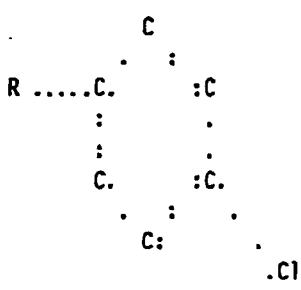
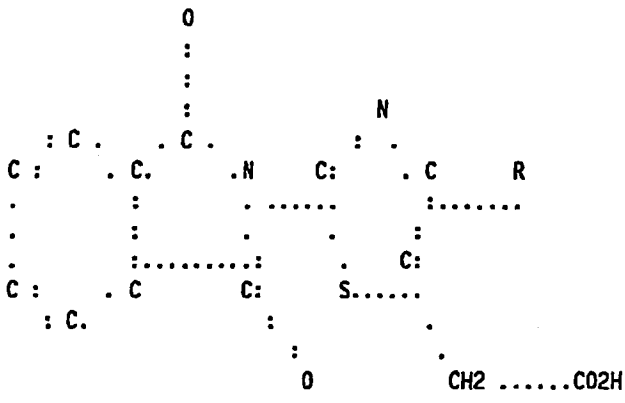
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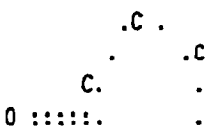
21 00250



RN 71013-50-8 CAPLUS
CN 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)- (9CI) (CA INDEX NAME)



IT ***74241-16-0P***
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and hydrolysis of)
RN 74241-16-0 CAPLUS
CN 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(2,5-dioxo-1-pyrrolidinyl)-, methyl ester (9CI) (CA INDEX NAME)



AN - 1978:50706 CAPLUS

DN - 88:50706

XP-002165602

TI - Studies on heterocyclic cation systems. XI. Syntheses of 2-disubstituted-amino-4-arylthiazol-5-ylalkanoic acids

IN - Hirai, Kentaro; Sugimoto, Hirohiko

CS - Shionogi Res. Lab., Shionogi and Co., Ltd., Osaka, Japan

SO - Chem. Pharm. Bull. (1977), 25(9), 2292-9

CODEN: CPBTAL

DT - Journal

LA - English

AB - 2-Disubstituted-amino-4-arylthiazol-5-ylalkanoic acids I (R = piperidino, morpholino, MeNH, BzNH, p-ClC6H4CONH, R1 = H, Me; R2 = Ph, 2-thienyl, p-ClC6H4, p-BrC6H4) were prepd. Thus, dehydration of S-(.alpha.-benzoyl-.beta.-ethoxycarbonyl)ethyl 1-piperidinethiocarbonate in the presence of aq. HClO4-Ac2O yielded 4-ethoxycarbonylmethyl-5-phenyl-2-piperidino-1,3-oxathiolium perchlorate, which underwent nucleophilic reaction with NH3 and the 5-ethoxycarbonylmethyl-4-phenyl-2-piperidinethiazole hydrolyzed to give I (R = piperidino, R1 = H, R2 = Ph). I were also synthesized by the classical Hantzsch method. I were evaluated as antiinflammatory agents on carrageenin induced abscess in rats.

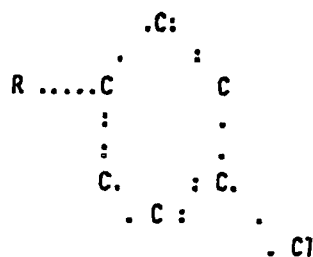
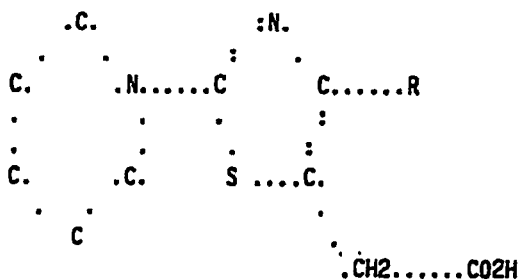
IT - ---61874-75-7P--- ---61874-76-8P--- ---61874-79-1P---

---65358-74-9P--- ---65358-75-0P---

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation) (prepn. and antiinflammatory activity of)

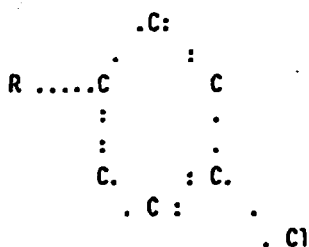
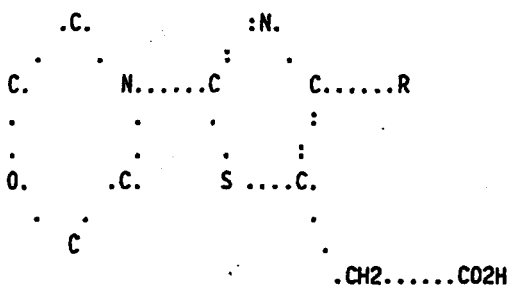
RN - 61874-75-7 CAPLUS

CN - 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(1-piperidinyl)-, monohydrochloride (9CI) (CA INDEX NAME)



23 504
202

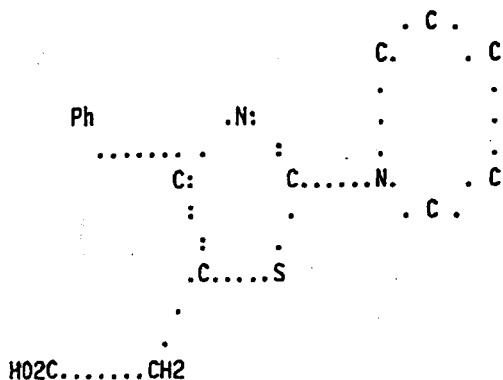
CN 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(4-morpholinyl)-,
monohydrochloride (9CI) (CA INDEX NAME)



@ HCl

RN 61874-79-1 CAPLUS

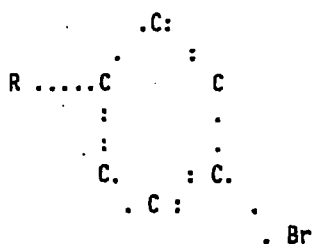
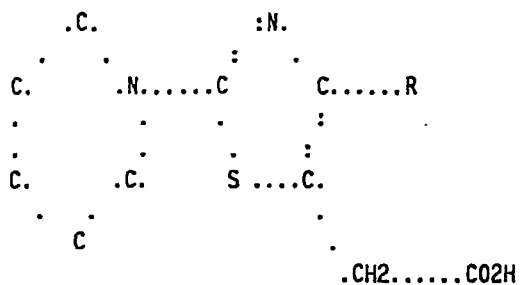
CN 5-Thiazoleacetic acid, 4-phenyl-2-(1-piperidiny)-,
monohydrochloride (9CI) (CA INDEX NAME)



@ HCl

RN 65358-74-9 CAPLUS

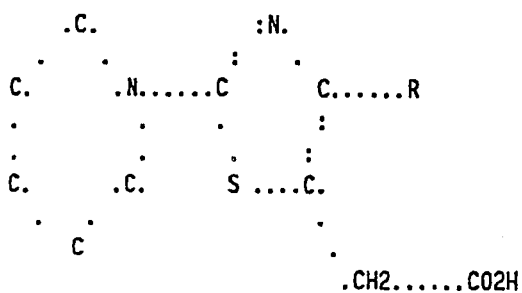
CN 5-Thiazoleacetic acid, 4-(4-bromophenyl)-2-(1-piperidiny)-,
monohydrochloride (9CI) (CA INDEX NAME)



@ HCl

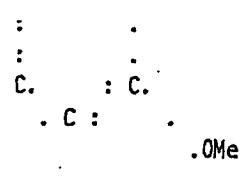
.N 65358-75-0 CAPLUS

CN 5-Thiazoleacetic acid, 4-(4-methoxyphenyl)-2-(1-piperidiny)-,
monohydrochloride (9CI) (CA INDEX NAME)



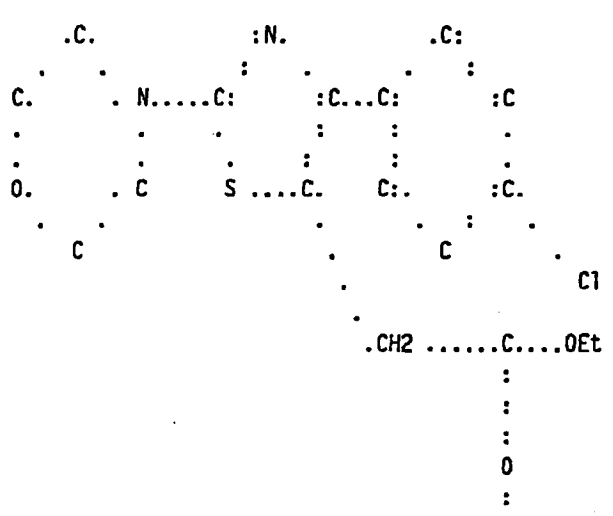
.C:

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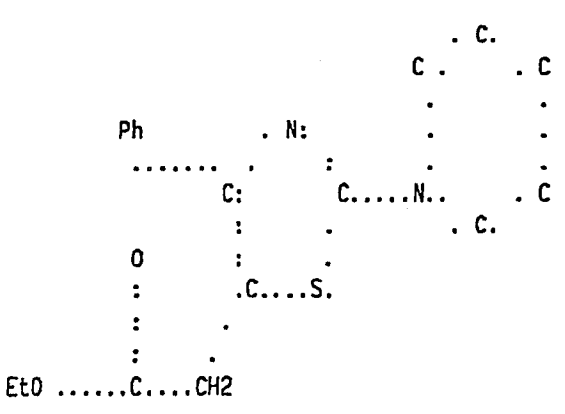


@ HCl

IT ***61874-73-5P*** ***65358-66-9P*** ***65358-67-0P***
 65358-68-1P ***65358-73-8P***
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
 (prepn. and hydrolysis of)
 RN 61874-73-5 CAPLUS
 CN 5-Thiazoleacetic acid, 4-(4-chlorophenyl)-2-(4-morpholinyl)-, ethyl
 ester (9CI) (CA INDEX NAME)

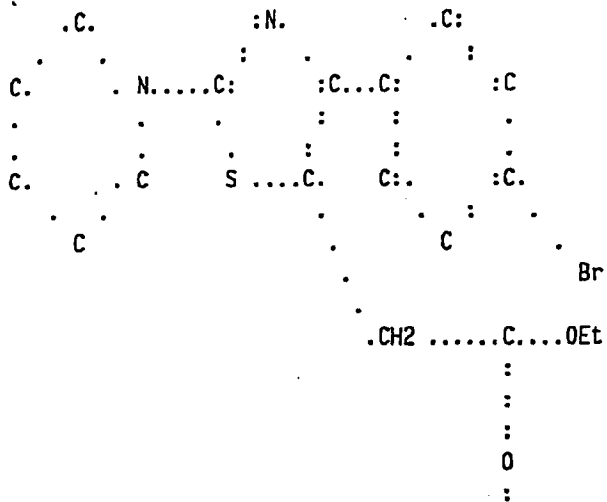


RN 65358-66-9 CAPLUS
 CN 5-Thiazoleacetic acid, 4-phenyl-2-(1-piperidinyl)-, ethyl ester
 (9CI) (CA INDEX NAME)



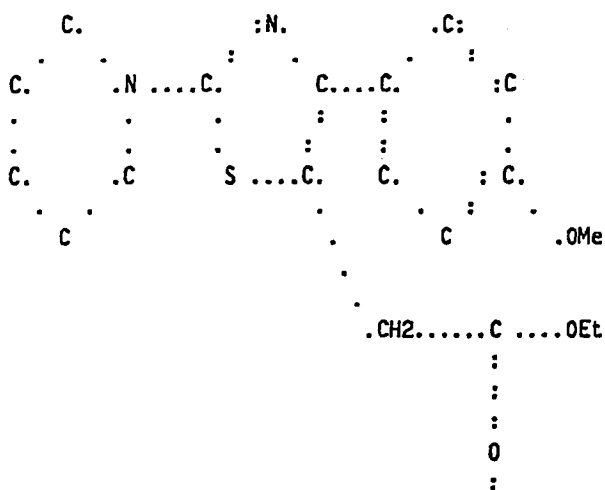
RN 65358-67-0 CAPLUS
 CN 5-Thiazoleacetic acid, 4-(4-bromophenyl)-2-(1-piperidinyl)-, ethyl
 ester (9CI) (CA INDEX NAME)

478



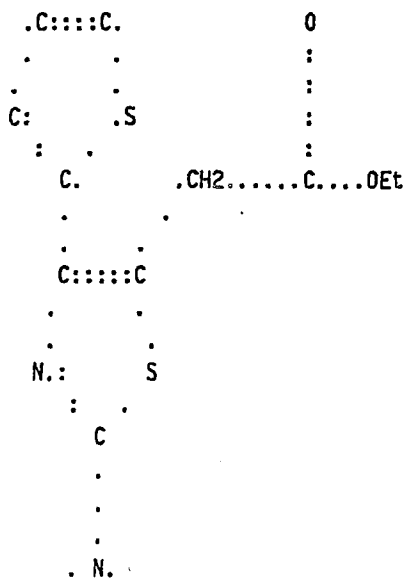
RN 65358-68-1 CAPLUS

CN 5-Thiazoleacetic acid, 4-(4-methoxyphenyl)-2-(1-piperidiny)-, ethyl ester (9CI) (CA INDEX NAME)



RN 65358-73-8 CAPLUS

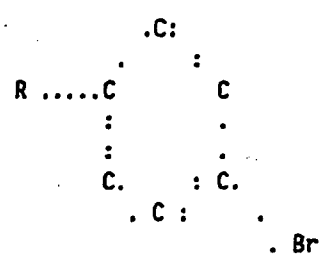
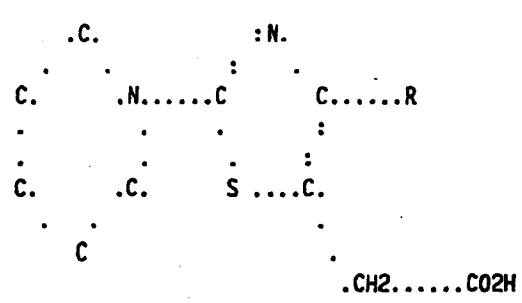
N 5-Thiazoleacetic acid, 2-(4-morpholinyl)-4-(2-thienyl)-, ethyl ester
(9CI) (CA INDEX NAME)



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IT ***61874-81-5P*** ***61874-82-6P***
RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of)
RN 61874-81-5 CAPLUS
CN 5-Thiazoleacetic acid, 4-(4-bromophenyl)-2-(1-piperidinyl)- (9CI)
 (CA INDEX NAME)



RN 61874-82-6 CAPLUS
CN 5-Thiazoleacetic acid, 2-(4-morpholinyl)-4-(2-thienyl)- (9CI) (CA
 INDEX NAME)

