SUPERINTENDENCIA DE INDUSTRIA V COMERCIO

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SUPERJNTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Ref.: Expediente No. 06-128.221
-. Solicitud de Patente a nombre de JANSSEN PHARMACEUTICA N.Y.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi
firma, domiciliada en Bogota, en la Carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad JANSSEN PHARMACEUTICA N.Y., con doniicilio en Beerse, BØlgica, solicitante de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referenda, es patentable.

Adjunto al presente memorial los recibos Nrs. 08-49,927 y 08-49,929 de 20 de junio de 2008, por la suma de $420.000.00, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

SeæorSuperintendente,

JIOA AAqc- C.C.39.779.452 de UsaquØri

T.P.No. 68228
Côd.5376

(NH20H extinguishable). MS: 379 (M - K + glycerol matrix). Potassium (SR,6S)-2-(4’-hydrozyphenyl).6.((IR)- 1 hydroxhy1]-n.2m.rboyi (32) was obtained from the allyl ester 31 in 30% yield. IR: 1735 (fl-lactam C=O).

NMR (D20): 1.16 (CH3, d, J = 8 Hz), 2.9 and 3.26 (H2),3.34 (H6, dd,J = 2, 4 Hz), 4.04-4.22 (H5 and H8, m), 8.74 and 7.17 (phenyl
H, dd, J = 4,43 Hz). UV: X (H20) 300 rim (NH20H extin-guishable).
Potassium (lR,5R,68)-2-[4’-(azidomethyl)phonyl]-6-[(IR)-l-hYdroxyethyll-i-mothylearbapen-2-em-3-carboxylate
(49) was prepared from allyl ester 45 in 39% yield. NMR (1)20):

0.9 (CHs, d, J = 8 Hz), 1.14 (CH3, d, J = 6 Hz), 3.30 (H6, dd, J = 1.5, 3 Hz), 3.22-3.40 (Hi, as), 4.14 (H6, dd, J 1.5, 5 Hz), 4.04-4.20 (H8, m), 4.27 (CH2N3, a, 2 H), 7.29 (aromatic H, 2 d,

J = 4 Hz). UV: X (H20) 286 rim (NH20H extinguishable). Potassium (1R,5R,OS)-2’[2’-(azldomethyl)-5’.pyridyl]- 6-[(1R)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (50) was obtained from allyl ester 46 in 32% yield.

NMB. (1)20): 0.94 (CH3, d, J 8 Hz), 1.16 (CH3, d, J 8 Hz), 3.39 (H6, dd, J = 1.5, 3 Hz, 1 H), 3.30-3.46 (Hi, m), 4.21 (Ho, dd, J = 1.5,5 Hz), 4.16 (H8, as), 4.42 (CH2N3, a), 7.3-8.5 (pyridyl

H, as). UV: X,, (H20) 290 rim (NH20H extinguishable). Potassium (1R,5R,RS)-2-[4’-(hydroxymethyl)phenyl]-G-((1R).1.hydroxyethyI]-1-methy1carbapen.2em3carboxylate
(53) was prepared from allyl ester 48 in 68% yield. NMR (1)20):

1.38 (CH3, d, J = 8 Hz), 1.60 (CH3, d, J = 6 Hz, 3 H), 3.78 (H6 and Hi, as, 2 H), 4.59 (HO and H8, as, 2 H), 4.92 (CH20,s, 2 H),

7.70 (phenyl H, 2 d, J = 4 Hz, 4 H). UV: Xm (H20) 288 nm (NH20H extinguishable).
(IR,5R,6S)-2-[4’-(Aminoethyl)phenyl]-6-[(IR)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxyljc Acid (51). The earbapenem azide 49 (37 mg, 0.0974 mmol) was dis-solved in 3 mL of water. Ten milligrams of 10% Pd/C and 0.39 mL (0.195 minol) of 0.5 M pH 7 4-morpholinepropanesulfonic acid

buffer were added. The mixture was hydrogenated at 45 psi on a Parr shaker apparatus for 15 ruin at room temperature. The

solids were filtered and washed with 2 X 2 mL of water. The filtrate was concentrated to 0.5 mL, applied on reverse-phase silica gel plates, and worked up as described for 25d to give 72% of the carbapenem amino acid 51. UV: X, (H20) 287 am (NH20H extinguishable). MS: FAB positive ion, 319 (M + H); FAB negative ion, 317 (M - H).
(IR,5R,GS)-2-[2’-(AmInomethyI)-5’-pyrldyl]-6-((1)-I-

hydroxyethyl]-1-methylcarbapen-2-em-3-carboxyjlc acid (52) was similarly obtained from the azide 50 as described above for
51 in 80% yield. NMR: 0.95 (CH3, d, J = 6 Hz), 1.16 (CH3, d, J = 6 Hz), 3.25-3.45 (H6 and Hl), 4.0-4.30 (H5 and H8), 7.20-8.50 (pyridyl H). UV: X. (He) 290 rim (NH20H extinguishable).

Acknowledgment. We thank Dr. C. Shunk for the preparation of starting material, J. Smith, H. Flynn, and Dr. B. Arison for mass spectral and 200-MHz NMR
measurements, and J. Kahan, H. Kropp, and J. Sundelof
for the antimicrobial and DHP susceptibility assays.

Anticonvulsant 0-Alkyl Sulfamates.

2,3:4,5-Bis-0-(1-methylethylidene)-$-D-fructopyranose Sulfamate and Related Compoundst

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Novel sugar sulfamate 1 (McN-4853, topiramate) has been found to exhibit potent anticonvulsant activity analogous
to that of phenytoin. In the maximal electroshock seizure test, orally at 2 h in mice, 1 had an ED20 of 39 mg/kg.
Orally, 1 had a duration of action in excess of 8 h. Other aspects of the pharmacology of 1, as well as neurochemistry
and carbonic anhydrase inhibition, are discussed. The conformational behavior of I in solution and in the solid
state is discussed. A series of analogues of 1 were synthesized and examined for anticonvulsant properties.

Anticonvulsants are the primary drugs used for the
treatment of epileptic disorders.’ However, despite the availability of several drugs, only about 75% of the epi-leptic population significantly benefits from current pharmacotherapy, and many of these patients experience adverse side effects, such as drowsiness, ataxia, or gingival hyperplasia.’ Thus, the search for less toxic, more effi-cacious agents for the treatment of seizure disorders has been a continuing endeavor.
A wide diversity of chemical structure types exhibit anticonvulsant antivity. These compounds, many ofwhich are cyclic amides (e.g., imides, carboxamides, sulfonamides, carbamates, hydantoins, and ureas),’ can be classified into two groups. There are agents (e.g., phenytoin and carbamazepine) effective for tonic-clonic seizures and

tpresented as part of the Symposium on Recent Advances in the Treatment of Seizure Disorders, 192nd National Meeting of the American Chemical Society, Anaheim, CA, September 8,1986; MEDI-6.
McNeil Pharmaceutical.
University of Pennsylvania.

Chart I

MeJ___Me

SCH2X COCH2OS02NI42

’ 0
Me

I XOSO2NH2 9 RR’ Me
2 XOSO2NHMe 10 R/R’(CH2)5
3 X=OSO2NMe2 ii R=Me; R’(CH),CH3
4 XOH

5 X=OC(0)Nk2
6 X=0S02N3
7 X=OSO2NHPh

8 X=OC(0)NHPh

R

I::xcOso2I2 OCH20$02NH2

14 X=CH2 12 X=0;R=H
IS X = 0 13 X = CH2; R = CH3

agents (e.g., ethosuximide and nitrazepam) effective for
petit mal seizures, which can be characterized pharmaco-

’c6

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jriJ lJ4.(,e

Chart II

ROCH30 (73(Me

Me Me Me 0 Me
Me Me Me
16a R=H lie R=H
17b RS02NH2 16b RSO2NH2

OrQMe

Me Q°’\Me

OR Me

o"

C4CHOSO2NH2

Me

C0_

Me
ISa R=H

ISb RS02M3 f,
lie R=S02NH2

.CH2OS02Nl2 OMe

HO \4"’CH2OSO2NH2 Me
HO’ HO ON Me

Chart HI

20 22

HOI1III( ).ç

1-OS,CHOSO2NH,

I CH20SO,NH, ON
HC(ON

21 23

Me Me

X1_CH2OSO2NH2 PhHCH2OSO2NH2
CH2SO2NH2 25 9H
24 26 RPh 27

logically by the ability to prevent maximal electroshock seizures (MES) or pentylenetetrazole-induced seizures,
respectively.’ We discovered that 2,3:4,5-bis-041-
methylethylidene)-$-D-fructopyranose sulfamate (1, McN-4853, topiramate) exerts a potent anticonvulsant effect in the MES assay. Since this compound is structurally dis-tinct from known agents, in the sense that it is a mono-saccharide derivative and contains a sulfamate function-ality, we synthesized and studied some analogues to as-certain those features associated with biological activity. This paper describes some structure-activity work and the biological evaluation of I.

Results and Discussion

Chemistry. Most of the sulfamate derivatives (1-3, 7, 9-18, 23-26; Charts I-Ill) were synthesized from the corresponding alcohols, many of which were obtained commercially or in one step from reduction of a com-mercially available ester, or from ketalization of glycerol. Three different procedures were employed to make these sulfamate compounds: (1) the alcohol was reacted with the appropriate sulfamoyl chiorideZS in the presence of

(1) (a) AntiepUeptic Drugs; Woodbury, D. M., Penry, J. K., Schmidt, R. P., Eds.; Raven: New York, 1972. (b) Anticon-vulsants; Vida, J. A., Ed.; Academic: New York, 1977. (c) Isaacson, E. I.; Delgado, J. N. In Burger’s Medicinal Chemis-try, 4th ed.; Wolff, M. B., Ed.; Wiley: New York, 1981; Part
III, Chapter 55. (d) Woodbury, D. M.; Fingl, B. In The Pharmacological Basis of Therapeutics; Goodman, L. S., Gilman, A., Eds.; MacMillan: New York, 1977; pp 201-226.

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NaH (for 1-3, 7, 9-17b, 23-26), (2) the alcohol was re-
acted with sulfuryl chloride in the presence of pyridine to
give a chiorosulfate intermediate," which was then treated \X01\ with an appropriate amine (for 1 and or (3) the al-cohol-derived chiorosulfate was converted with sodium

azide to an azidosulfate (6 and 18b), which was reduced
by copper in methanol or by catalytic hydrogenation with palladium on carbon (for 1 and 18c).35
Sulfamate 22 (mixture of isomers enriched in furano-sides) was prepared by acid-catalyzed methanolysis of 1, and 19 was obtained by reaction of 1 with 1-(trimethyl-sioxy)cyclohexene and HCl.’ NMR spectroscopic data for 19 allowed us to assign the 4,5-cyclohexylidene sub-stitution. The hydrolysis products of 1, i.e., 20 and 21, were prepared under acid catalysis. The nature of 21 is a mixture of furanose (ca. 30%) and pyranose (ca. 70%) forms with the S02NH2 group linked to the anomeric center (anhydro compounds).
Carbamate 5 was obtained by reacting alcohol 4 with chlorosulfonyl isocyanate followed by hydrolysis,7 or with trichioromethyl chioroformate (phosgene equivalent8) followed by ammonolysis; 8 was produced from 4 and phenyl isocyanate.
Anticonvulsant Testing. Anticonvulsant activity was generally determined by using a standard MES test.9 In this test, activity is indicated by a block of the hind-limb tonic-extensor seizure caused by application of an electric shock to mice via corneal electrodes. Data for the com-

pounds of interest are presented in Tables I and II. A number of the compounds were evaluated for anticon-vulsant activity, in a preliminary fashion, by using a maximal electroshock seizure threshold (MEST) test,’° a modification of the CS50 method of Chen et al." The MEST method is related to the maximal electroshock seizure (IVIES) test, but it employs a much smaller current (8 vs. 50 mA). It follows that compounds inactive in the MEST assay could not exhibit activity in the MES assay, because the latter has a much higher seizure-inducing current. Compounds inactive in the MEST test, which were not subsequently tested in the MES test, are so noted in Table I. A listing of 95% confidence limits for the MES ED0 data is furnished in Table 111.12

Considering the data in Table I (30-60 min after dos-ing), sulfamates 1, 2, 9, 14, 15, 17b, 25, and 26 showed significant activity (ED 150 mg/kg) in the MES test, with 14, 25, and prototype 1 having the greatest potency.

(2) (a) McDermott, S. D.; Spillane, W. J. Org. Prep. Proced. mt. 1984, 16, 49. (b) Hainprecht, G.; Konig, K.-H.; Stubenrauch,
G. Angew. Chem., mt. Ed. Engl. 1981, 20, 151. (c) Klock, J.
A.; Leschinsky, K. L. J. Org, Chem. 1976, 41, 4028.
(3) Benson, G. A.; Spillane, W. J. Chem. Rev. 1980, 80,151.
(4) Tsuchiya, T.; Watanabe, I.; Yoshida, M.; Nakamura, F.; Usui, T.; Kitamura, M.; Unezawa, S. Tetrahedron Lett. 1978, 3365.
(5) (a) 1-Iedayatullah, M.; Guy, A. Synthesis 1978, 375. Hedaya-tuilah, M.; Guy, A. Tetrahedron Lett. 1975, 2455. (b) Bundle, D. R. J. Chem. Soc., Perkin Trans. 11979, 2751. (C) Naidoo, N. T.; Parolis, H. Carbohydr. Res. 1978, 62, CS. (d) Kochetkov, N. K.; Ueov, A. I.; Deryabin, V. V. J. Gen. Chem. USSR 1971, 41, 1874.
(6) Larson, G. L.; Hernandez, A. J. Org. Chem, 1973, 38, 3935.
(7) Szabo, W. A. Aidrichimica Acta 1977, 10, 23.
(8) Kurita, K.; Matsumura, T.; Iwakura, V. J. Org. Chem. 1976, 41, 2070.
(9) Swinyard, E. A.; Brown, W. C.; Goodman, L. S. J. Pharmacol. Exp. Ther. 1952, 106, 319.
(10) Maryanoff, B. B.; Nortey, S. 0.; Gardocki, J. F. J. Med. Chem. 1984, 27, 1067.
(11) Chen, G.; Ensor, C. R.; Bohuer, B. Life Sci. 1968, 7, 1063.
(12) Ninety-five percent confidence limits were calculated accord-ing to a published method: Litchfield, J. T.; Wilcoxon, F. J. Pharrnacol. Exp. Ther. 1949, 96, 99.

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Table I. Chemical and Biological Data

compound formula° mp, °C (solv)b [a]0 (C, solv)’ MRS (ip/po) ED0, mg/kgd

1 C12}121N088’ 125-126 (EA/H) -34.0 (0.40, M) 64/61
2 C13HNO8S It yel syrup (LC) -30.0 (0.29, M) 50-100/ "200
3 C,4HnN0.S’ 57-58 (E/W) -31.3 (0.31, M) >100/>200
41 CuHnOo 97_97.5 (EE/P) -35.0 (0.50, W)" 1200/1400’
5 C13H21N07 122-126 (E/PE) -34.2 (0.40, M)
6 C12H,9N308S 105-107 (I) -27.0 (0.20, NO >100/ 200
7 C15H25NO5S 115-116 (C/H) -36.3 (0.30, M) 1100200
8 C29H20N07 165.5-167.5 (EA/H) 44.7 (0.30, M) 60/1400’
9 C5H13NO5S it yel syrup (LC) -100/-75
10 C5H17N05S’ soft wax (HPLC) 169/-150
ii,,’ C14H20N058 49-51 (HPLC) 319/>200
12 C5H13N04S colorless syrup (LC) 195/154
13 C8H17NO3S 40-42 (C/H) 270/-400
14 C11H15NO3S 108-109 (C/H) 66/82
15 C5H11N05S 94-96 (C) -400/118
16b° C12H21N08SP 48-50 (LC) -53.6 (0.32, C)h ’-175/>200
17b C12H31N08S 133-135 (HPLC) -5.5 (0.93,M) -.1001-450
ISo C12H21NO3S white foam (LC)
19 C1H20NO8S 179-180 (EA/H) -29.9 M) 1100/>400
C5H17N08S 130-132 (EA/H) +25.7 (0.82, M)’
21" CeH,INO,Sq yel syrup’ -28.4 M)
22"’ C7H15N05S’ it yel syrup’ -14.8 (0.50,
23 C11H,5N038 140-141 (E/W) >100/-200
C10H1NO3S 51-53 -14.7 (0.12, M)
25 C8H11N038 It yel syrup’" -50/-100
26 116-118

phenytoin’
acetazolamide’ --/45

All new compounds were analyzed within –0.4% for C, H, and N, unless otherwise noted; some compounds also were analyzed for S or water (within –0.4%). Water composition was confirmed by Karl-Fischer analysis, and solvent additives were confirmed by ’H NMR integration (90- or 360-MHz spectra, as required). bThe recrystallization solvent is given in parentheses: EA = ethyl acetate, H hexane, W = water, E = ethanol, EE = ethyl ether, P = pentane, PE = petroleum ether (30-60 °C), I 2-propanol, C = chloroform. Other materials were purified by column chromatography (LC) or preparative HPLC and isolated by evaporation of solvent from the appropriate fractions. Optical rotations (units of degrees) were measured at 23-24 °C, unless otherwise indicated. Concentration (c) in g/ 100 mL and solvent (M methanol, W = water, C = chloroform) are given in parentheses. aMaxfral electroshock seizure test in mice; ip and/or po data are given. Activity was measured at 30-80 rain following administration of drug. I = inactive, 0-10% block at the subscripted maximum dose (mg/kg). See Table II for time-course data. Results in the MEST assay (see text) are indicated for a few compounds. C, H analysis. ’C, H, S analysis. ’Lit.20 mp 97 °C h Rotation was measured at 25 °C. ’Inactive In the MEST assay at 100 mg/kg (ip). JRotation was measured at 260C. hED50 in the MEST assay (ip) was 402 mg/kg (262-816). 1Contains 0.05 mol of cyclohexanone and 0.2 mol of water. ’a Mixture of diastereomers. The carbamate analogue of 11(1:1 mixture of two diastereomers; mp 59-62 °C (PE))" was found to have an ED40 of 85 mg/kg (74.3-98.3), ip. "Contains 0.1 mol of 2-undecanone and 0.2 mol of water. "Reported as a syrup in the literature: Kochetkov, N. K.; Usov, A. L; Deryabin, V. V. J. Gen. Chem. USSR 1972, 42, 2755; lit. [aID _580 (c 0.58, CHC13). P Contains 0.2 mol of water. A different sample, purified by HPLC and containing 0.02 mol of water, had mp 91-93 °C. 9Contains 0.8 mol of water. rNot subjected to chroma-tography. Contains 0.5 mol of water; C, H, and water analysis. I From (-)-cis-niyrantol. "Distilled by Kugelrohr at 80 °C (pot temperature) (0.07 torr). ’Reference compound.

Anticonvulsant Testing. Time Data’

block in MES test (mice) at specific time in mm

dose, dose,
mg/kg 30 120 240 mg/kg 30 120 240
40 80 80 50 60 70 50
2 200 70 30 90 30
3 200 30 80 80 30 30 50 30
4 200
200 30 50 70 20
7 200
400 200
9 200 70 90 50 70 70
200 70 30 20
13 400 30 200 30
80 80 80 50 50
15 200 80 80 60
400 50 80 90 80 200 20 40 50
17b 200 70 80 20

20

200 20

23 40 90 200 20
24
25

200

200 70 80 90 70
26 80 70

phenytoin 15 50 80 70 60
zonisamide 40 20 40 50

"See Experimental Section. Ten mice were used for each time point.

AnticonvuLsant 0-Alkyl Sulfamates

Table Ill. 95% Confidence Limits for the MES ED60 Data

compd time, min MES ED, ip MES ED50, P0
1 30 64(50-93) 61(50-87)
9 30 105 (75-160)
10 30 169 (140-223)
11 30 319 (290-349)
12 60 195 (138-274) 154 (126-188)
13 60 270 (206-354)
14 60 56(50-62) 82(66-102)
15 45 118 (92-158)
26 45 147 (127-171)

However, 26 showed only oral activity. Compounds 10-13, lob, and 23 possessed modest activity, and compounds 4-6, iSo, 19-22, and 24 were virtually inactive. Considering the time-course data in Table II, it is clear that several com-pounds show substantial activity, including some com-pounds not recognized above. On the basis of oral dosing, sulfamates 1-3, 6, 9, 14, 15, 17b, 25, and 26 exhibit notable potency and duration of action (80% block at 200 mg/kg at >120 mm). Of these compounds, 1, 9, and 25 exhibit high potency on ip administration. In the case ofstructure 1, from an SAR point of view, activity is reduced slightly with monomethyl substitution on nitrogen and greatly with dimethyl substitution. The azidosulfate analogue of 1 (i.e.,
6) is moderately active, but phenyl sulfamate 7 is inactive. The carbainate analogue 5 also lacks anticonvulsant ac-tivity, which underscores the importance ofthe sulfamate group (also alcohol 4 is inactive). However, a comparison of 11 with its carbamate analogue contradicts this ar-rangement.13 Removal of the acetonide units from 1, as with methanolysis product 22 or hydrolysis products 20 and 21,14 resulted in loss of activity. The isomeric C-3 fructopyranose sulfamate iSo, galactopyranose sulfamate lOb, and the monocyclohexylidene analogue 19 showed relatively poor activity. The weak activity for 19 is par-ticularly striking, as it is modified only slightly from I and assumes the same conformation that 1 does in solution

(vide infra).
Because of the structural complexity of the sugar sul-famates, we sought to find anticonvulsant activity in sim-pler sulfamate derivatives. On the basis of our early SAR with some sugar derivatives, the S02NH2 unit on a primary alcohol was retained, along with suitable lipophilicity. Monocycles 12 and 13 were found to possess modest ac-tivity, being around 4-5 times less potent than 1. Ben-zo-fused derivatives 14 and 15 exhibited quite respectable anticonvulsant activity. Bicydic sulfamate 24 and ada-mantane derivative 23 were hardly active. Diphenylethyl sulfamate, 26, showed moderate oral activity, whereas monophenyl compound 25 showed reasonable activity by both routes of administration.
Glycidol derivatives 9-11 were particularly interesting as "half-structures" of prototype 1. Sulfaniate acetonide 9 showed significant activity even though it is very water soluble. The more lipophilic congeners 10 and 11 also were active, but less so than 9.
The majority of compounds were examined over a 4-h time course, both pa and ip, in the MES test. Data, re-ported as percent block ofseizures, are collected in Table II. Compounds that showed significant oral activity at

(13) The carbamate analogue of 11, dioxamate, is reported to have anticonvulsant properties: Merck Index, 10th ed.; 1983; p 440,

No. 3303.

(14) The hydrolysis product of 1, obtained by treating 1 with 90% aqueous trifluoroacetic acid at 25 °C, had lost both iso-

propylidene units. Characterization of the syrup was compli- cated by the presence of both furanoid and pyranoid struc-

tures, each a mixture of two diastereomers (’SC NMR).

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100-200 mg/kg are 1-3, 6, 9, 14, 15, 17b, 23, 25, and 26; and those that showed significant intraperitoneal activity

at 50-100 mg/kg are 1, 2, 9, 14, 17b, and 25. Moderate ’ activity was exhibited by 10, 13 and lOb, pa, and by 3, 13,
15, 16b, and 23, ip. Good duration of action on oral ad-ministration was demonstrated by 1-3, 6, 9, 15, lOb, 17b, 25, and 26; good duration ip was demonstrated by 1 and
9.

Considering this limited data set, an unsubstituted sulfamate group and a certain type of lipophilic attachment are preferred for anticonvulsant activity.
Carbonic Anhydrase Inhibition. Since the sulfamate functionality appears to be important for anticonvulsant activity (cf. I and 5), and since there are anticonvulsant sulfonamides, such as acetazolamide, which inhibit the enzyme carbonic anhydrase,15 we tested 1 for its ability to inhibit carbonic anhydrase in mouse and human erythro-cytes.16 The K, values for 1 were 2.0 AM in lysed mouse erythrocytes and Ca. 200 jiM in intact human erythrocytes. This is much weaker than the activity of acetazolamide, with a K, value of 0.017 jiM in lysed mouse erythrocytes. In lysed human erythrocytes, the K, values for acetazol-amide and 1 were 0.005 and 120 MM, respectively. Our results demonstrate that 1 is a relatively weak inhibitor of erythrocyte carbonic anhydrase.
In preliminary experiments, we evaluated six congeners of I for their inhibition of carbonic anhydrase. In lysed mouse erythrocytes, 9, 14, and 24 were moderately potent inhibitors (K, values of 0.20, 0.16, and <0.5 AM, respec-tively), lOb was weak (K, = 7.3 AM), and 5 and 6 were inactive (0% inhibition at 83 and 2 AM, respectively). From these results, there appears to be a lack of correlation between inhibition of erythrocyte carbonic anhydrase and anticonvulsant activity.
Additional Testing of 1.17a Compound 1 was partic-ularly interesting because of its potency and duration of activity. In mice, 1 was active beyond 8 h after dosing. Its ED50 values in mice at 2 h were 38 mg/kg (27.2-49.5) ip and 39 mg/kg (27.5-52.5) po. The EDsc value, po, in rats was 17.5 mg/kg (at 2 h) vs. 40 mg/kg for phenytoin and 18.5 mg/kg for acetazolamide. Oral activity of 1 at 4 h was essentially the same as that at 2 h (EDsc of 36 mg/kg in mice, 18 mg/kg in rats).
Consequently, we assessed the neurotoxicity of 1 in the rotoreel test.171 In mice, 1 had TD30 values (po in mice; TDse = neurotoxic dose EDsc) of 1095 mg/kg at 4 h (ap-proximate peak time for NMS EDse) and 407 mg/kg at 1 h (peak for TD50) vs. 48.5 mg/kg at 2 h (peak for TD50) for phenytoin. The LD (ip) for 1 was >1000 mg/kg (after 24 h). Compound 1 showed marginal activity at 100 mg/kg against PTZ-induced seizures, like phenytoin but unlike acetazolamide. It was also virtually inactive against sei-zures caused by bicuculline, picrotoxin, and strychnine, in analogy to phenytoin and carbamazepine. The loss of

(15) (a) Woodbury, D. M. In Antiepileptic Drugs: Mechanism of

Action; Glaser, G. H., Penry, J. K., Woodbury, D. M., Eds.; Raven: New York, 1980; pp 617-630. (b) Millichap, J. G.; Woodbury, D. M.; Goodman, L. S. J. Pharmacol. Exp. Ther.

1955, 116, 251. (c) Hansch, C.; McClorin, J.; Klein, T.; Lan-gridge, R. Mot. Pharmacol. 1985, 27, 493 and references cited.

(16) The method used for determining carbonic anhydrase activity has been described previously: (a) Itada, N.; Forster, R. E., II

J. Biol. Chem. 1977, 252, 3881. (b) Dodgson, S. J.; Forster, R. E., II; Storey, B. T.; Mela, L. Proc. NatI. Acad. Sci. U.S.A. 1980, 77, 5562. (c) Dodgson, S..1.; Forster, R. E., II; Storey, B.
T. J. Biol. Chem. 1982, 257, 1705.

(17) (a) Information on the methods employed in this subsection is given in the Experimental Section. (b) Dunham, N. W.; Miya, T. S. J. Am. Pharm. Assoc., Sci. Ed. 1957, 46, 208.

O- 0 R1 II / I R I (CH2)aOSN
ClasificaciOn Internacional de Patentes (IPC.): A61 K311353; A61 K31/357; C07D31 1/58.

3. De la solicitud de Patente

a. Reivindicaciones (artIculo 30 0 486)

La reivindicaciôn 1 carece de concisiOn debido a que la expresiôn "alquilo inferior", da lugar a un nümero indeterminados de posibilidades. Se recomienda limitar en forma concisa el alcance de la solicitud.

La reivindicaciôn 10 caracteriza una composiciOn por su mØtodo de elaboraciôn. Las composiciones pueden caractenzarse mediante las sustancias que las constituyen. Por lo que el mØtodo de preparaciOn no se considera una caracterIstica tØcnica de un producto.

4. Excepción a la patentabilidad (articulo 20 D486 literal d)

Las reivindicaciones 12 a 14 reclaman un mØtodo de tratamiento de epilepsia. Estas reivindicaciones no son patentables.

S. Reivindicaciones relativas a un uso o a un segundo uso (articulos 14y
21 D486)

La reivindicaciOn 15 reclama el uso del compuesto de la reivindicación 1. Esta reivindicaciOn no es patentable.

’Th 6. Determinación del Estado de la TØcnica

La fecha que se ha tenido en cuenta para determinar el Estado de la TØcnica es:

Fecha de presentación de la solicitud prioritaria 16-06-2004

Teniendo en cuenta la fecha indicada se realizO la büsqueda en el estado de la tØcnica de documentos relacionados con la solicitud encontrÆndose los siguientes documentos mÆs relevantes:

No Documento TItulo Fecha de prioridad
The anticonvulsant 0-Alkyl

J. Med. Chem. 1987, Sulfamates. 2,3:4,5-Bis-0-(1-

Dl 0.

880-887 methylethylidene)-3-D- 1987 fructopranose sulfamate and related
compounds.

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7. AnÆlisis dePatentabilidad (Art 14 D486)

Nivel inventivo (Art18 0486)

reivindicaciones I - 8: Un compuesto de formula (II)
reivindicaciones 9 - 10: Una composiciOn farmacØutica que comprende uno de los compuestos.
reivindicaciôn 11: Un mØtodo para preparar la composiciOn

AnÆlisis delas diferencias con respecto al estado de la tØcnica:

CaracterIsticas esenciales de la Solicitud Dl

R40 R1

NSN
II

0 (II)(ax

R=

X=CH210

R’ R2 H

El documento del Estado de la TØcnica mÆs prOximo es Dl que enseæa compuestos de sulfamato, quº son Utiles como anticonvulsivantes (pag 880).

La (mica diferencia con D2 es que esta solicitud menqiona que los compuestos son tipo sulfamida, Pero estas no parecen conceder un efecto tØcnico inesperado porque estos compuestos siguen siendo agentes anticonvulsivos. Igualmente Dl enseæaensayos de actividad anticonvulsiva de los compuestos divulgado los cuales presentan valores MES ED50 < 150 mg/kg (vertablas I y Ill), los cuales son incluso mejores que los divulgados por el solicitante en el cuadro 4 de la descripciôn para las sulfamidas ensayadas.

De aill que el objetivo de esta solicitud consiste en la necesidad de compuestos Utiles para el tratamiento de la epilepsia. Este problema ya se habla resuelto previamente mediante el mismo tipo de compuestos divulgados en Dl. Por esta razôn se considera que la sustituciôn por el grupo sulfamido no aporta ninguna ventaja o efecto sorprendente. Por lo tanto los compuestos reclamados son alternativos a los conocidos en el estado de la tØcnica.

En consecuencia, las reivindicaciones I a 8 carecen de Nivel Inventivo.

Las reivindicaciones 9y 10 reclaman una composiciOn farmacØutica que contiene un derivado de la fOrmula I y Ia reivindicaciôn 11 reclama un proceso para lograr
dichas composiciones. Las reivindicaciones mencionadas carecen de nivel
inventivo puesto que los compuestos que las caracterizan no son inventivos.

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