

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

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Abogada
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Patente de Invención ☒ Patente de Modelo de Utilidad
Vía Nacional
Vía PCT (Fase Nacional) ☒ Capítulo I ☒ Capítulo II
No. Solicitud Internacional PCT/US2008/071872
Fecha de Presentación Internacional 01/Agosto/2008

Como resultado del examen de fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 97 a 186	02/Marzo/2010
Reivindicaciones:	Folios 187 a 192	02/Marzo/2010
Dibujos:	Folios 194 a 212	02/Marzo/2010
Prioridad:	US 60 953 610	02/Agosto/2007
	US 60 953 613	02/Agosto/2007
	US 60 953 614	02/Agosto/2007
	US 60 971 654	12/Septiembre/2007

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "(2S, 3R)-N-(3-piridinil)metil)-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida, formas de sal novedosas, y métodos de uso de los mismos".

El problema planteado en esta solicitud consiste en la necesidad de suministrar compuestos que afectan la función del sistema nervioso central sin afectar subtipos del receptor nicotínico que inducen efectos colaterales indeseables.

Para resolver este problema técnico la solicitud en estudio proporciona (2S, 3R)-N-(3-piridinil)metil)-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida o una sal farmacéuticamente aceptable del mismo.

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07D453/02//471/08//487/08, A61K31/444, A61P25/00//25/02//25/14//25/16//25/18//25/22//25/24//25/28//29/00//35/00//43/00.

4. Excepción a la Patentabilidad (Art 20 D 486 literal (d))

El objeto de las reivindicaciones 11 - 14 no es patentable de acuerdo con el Art citado.

5. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 15 - 22 no es patentable, de acuerdo con el Art 14.

6. De la Solicitud de Patente

Título

El título contiene el término "métodos de uso" que hace alusión a temas que están excluidos y exceptuados de patentabilidad. Se sugiere eliminar el término y ajustar el título a las categorías de producto.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las reivindicaciones 2 – 5 no son claras cuando emplean los términos "sustancialmente pura", "sustancialmente libre de isómeros", "estequiométricamente enriquecido", "donde el exceso enantiomérico o diastereoisomérico se selecciona de..." porque son resultados a alcanzar, no definen al producto porque la invención no queda definida por el resultado a alcanzar, puesto que la reivindicación incluiría no sólo la solución propuesta por el solicitante, sino todas las alternativas presentes o futuras que lleguen a ese resultado. Se sugiere reemplazarlo por las características esenciales, estructurales o funcionales, que contribuyen a la obtención de ese efecto, o eliminar las reivindicaciones del pliego reivindicatorio.

Las reivindicaciones 4, 5 y 23 contienen errores de transcripción que corresponde a los términos "enriqu° Cido", "s° Cuencial", "estereosel° Ctiva". Se solicita hacer la corrección correspondiente.

La reivindicación 19 no es clara porque indica el uso que puede darse al producto reivindicado, el cual no es una característica técnica esencial que defina a la invención. Se eliminar la reivindicación del pliego reivindicatorio.

Las reivindicaciones 25 y 26 no son claras cuando emplean los términos "hidrato" o "solvato", de los cuales, en ninguna parte de la descripción se indica como pueden ser obtenidos por la persona del oficio normalmente versada en la materia, ni tampoco se encuentra que hayan sido obtenidos. Se solicita eliminar estos términos del pliego reivindicatorio.

7. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad 02 de agosto de 2007 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación
D1	US2004002513	3-Substituted-2(arylalkyl)-1-azabicycloalkanes and methods of use thereof	01/Enero/2004
D2	Libro ¹	Handbook of pharmaceutical salts	2002

D1
http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=2004002513A1&KC=A1&FT=D&ND=&date=20040101&DB=&locale=en_EP, divulga (pg. 4, pár. 0031; pg. 13, pár. 0259; pg. 26, pár. 0279 – pg. 17, pár. 0294) los compuestos (R,R; S,R; R,S y S,S)-N-(3-piridinil)metil-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida, método de preparación y composiciones farmacéuticas que los contienen.

D2 (fls 268 - 271) divulga ácidos y bases empleados en la formación de sales farmacéuticamente aceptables, así como el mejoramiento de las propiedades fisicoquímicas y mecánicas de los fármacos mediante la formación de sales.

8. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 1 consiste en (2S, 3R)-N-(3-piridinil)metil-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida o una sal farmacéuticamente aceptable del mismo.

Comparación de las características técnicas esenciales, con las del Estado de la Técnica:

Características esenciales	D1
(2S, 3R)-N-(3-piridinil)metil-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida o una sal farmacéuticamente aceptable del mismo.	(R,R; S,R; R,S y S,S)-N-(3-piridinil)metil-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida (reivindicación 11, pg. 34, col. izquierda) o una sal farmacéuticamente aceptable del mismo (pg. 4, pár. 0031).

Las características esenciales de la composición de la reivindicación 1 habían sido divulgadas previamente en D1, el cual da a conocer los compuestos (R,R; S,R; R,S y S,S)-N-(3-piridinil)metil-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida (reivindicación 11, pg. 34, col. izquierda).

En consecuencia, la reivindicación 1 no es nueva, según lo divulgado en el documento D1.

Además, D1 enseña las sales de adición de ácido de (R,R; S,R; R,S y S,S)-N-(3-piridinil)metil-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida, donde el ácido se selecciona de ácido clorhídrico, sulfúrico, fosfórico, maléico, toluenosulfónico, tartárico, metanosulfónico, entre otros (pg. 4, pár. 0031).

Las reivindicaciones dependientes 2 – 8, 10, 19 y 25 no mencionan alguna característica que haga nueva al compuesto de la reivindicación 1, por lo cual se considera que no son nuevas.

La reivindicación 23 consiste en un método para fabricar (2S, 3R)-N-(3-piridinil)metil-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida que comprende resolución dinámica secuencial y aminación reductiva estereoselectiva de (2-((3-piridinil)metil-1-azabiciclo[2.2.2]oct-3-ona.

¹ Handbook of pharmaceutical salts. Properties, selection and use; 2002; pgs. 19, 28, 162-163, 271, 272, 282, 283, 287-290, 292, 306; (fls 268-271).

Comparación de las características técnicas esenciales, con las del Estado de la Técnica:

Características esenciales	D1
Método para fabricar (2S, 3R)-N-(3-piridinil)metil)-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida que comprende resolución dinámica secuencial y aminación reductiva estereoselectiva de (2-((3-piridinil)metil-1-azabiciclo[2.2.2]oct-3-ona	Método para fabricar (R,R; S,R; R,S y S,S)-N-(3-piridinil)metil)-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida que comprende resolución dinámica secuencial y aminación reductiva estereoselectiva de (2-((3-piridinil)metil-1-azabiciclo[2.2.2]oct-3-ona (pg. 13, pár. 0259)

Las características esenciales de la composición de la reivindicación 23 habían sido divulgadas previamente en D1, el cual enseña un método para fabricar (R,R; S,R; R,S y S,S)-N-(3-piridinil)metil)-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida que comprende resolución dinámica secuencial y aminación reductiva estereoselectiva de (2-((3-piridinil)metil-1-azabiciclo[2.2.2]oct-3-ona (pg. 13, pár. 0259).

En consecuencia, la reivindicación 23 carece de novedad, según lo divulgado en el documento D1.

Además, D1 enseña que el método para preparar (R,R; S,R; R,S y S,S)-N-(3-piridinil)metil)-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida comprende (R,R; S,R; R,S y S,S)-(2-((3-piridinil)metil)-1-azabiciclo[2.2.2]octano (pg. 13, pár. 0259).

Por lo tanto, las reivindicaciones dependientes 9 y 24 no mencionan alguna característica que haga nueva al proceso de la reivindicación 23, por lo cual se considera que no es nueva.

Nivel Inventivo (Art18 D486)

La reivindicación 26 consiste en monoclórhidrato (2S, 3R)-N-(3-piridinil)metil)-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida o un hidrato o solvato del mismo.

Comparación de las características técnicas esenciales, con las del Estado de la Técnica:

Características esenciales	D1	D2
Monoclórhidrato (2S, 3R)-N-(3-piridinil)metil)-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida	Sal farmacéuticamente aceptable de (R,R; S,R; R,S y S,S)-N-(3-piridinil)metil)-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida (pg. 4, pár. 0031)	Sal de clórhidrato de principios activos farmacéuticos (fls 268-271)

El documento D1 se considera el estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulga sales farmacéuticamente aceptables de (R,R; S,R; R,S y S,S)-N-(3-piridinil)metil)-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida.

La diferencia entre la invención, definida en la reivindicación 26 y las sales de D1 consiste en divulga que la sal corresponde específicamente a una sal monoclórhidrato.

El efecto que logra el incluir esta característica es que proporciona sales farmacéuticamente aceptables específicas estables del compuesto (2S, 3R)-N-(3-piridinil)metil)-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida con mejores propiedades fisicoquímicas.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular como la necesidad de suministrar sales de (2S, 3R)-N-(3-piridinil)metil)-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida que tengan mejores propiedades fisicoquímicas.

Sin embargo, D2 divulga la utilización de ácido clorhídrico, ácido sulfúrico, ácido fosfórico, ácido maléico, ácido tolueno sulfónico, ácido múlico, ácido D-mandélico,

ácido tartárico, ácido alcanfor-sulfónico y ácido hipúrico para la formación de sales farmacéuticamente aceptables (pgs. 271, 272, 282, 283, 287, 288, 289, 290, 292, 306; fls 269-271). Además, enseña que el mejoramiento de la velocidad de disolución de fármacos que son ácido o bases débiles poco solubles es uno de los principales motivos para la formación de sales (pg. 19 y 28, fl 268). Además, que la selección y la preparación de una sal adecuada dan la oportunidad de modificar características fisicoquímicas y mecánicas de los fármacos que permiten el desarrollo de formas farmacéuticas con mejor biodisponibilidad, estabilidad, entre otros (pg. 163, fl 269). Asimismo, da a conocer que la elección de una sal en particular está determinada por la acidez o basicidad del grupo ionizable, la seguridad del grupo potencial para la formación de la sal (contra-ión), indicaciones del medicamento, ruta de administración y la dosis, ya que la mayoría de las sales se desarrollan con el fin de aumentar su solubilidad.

En consecuencia, la persona del oficio normalmente versada en la materia se vería motivada para utilizar ácido clorhídrico de D2, para formar una sal farmacéuticamente aceptable con el compuesto (2S, 3R)-N-(3-piridinil)metil)-azabicilo(2,2,2)oct-3-il)banzofuran-2-carboxamida, divulgado en D1, para llegar así al objeto de la reivindicación 26 de la solicitud. Por lo cual se considera obvia.

Por lo tanto, la reivindicación 26 cumple con el requisito de novedad (Art. 16), pero no cumplen con el requisito de nivel inventivo (Art. 18).

9. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US2004002513	1 - 10, 19 y 23 - 25	Novedad
D1	US2004002513	26	Nivel inventivo
D2	Libro	26	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.


JOSÉ LUIS SALAZAR LÓPEZ
 Director de Nuevas Creaciones (C)

El anterior ^{zule}requerimiento fue notificado por fijación en lista, de fecha 02 OCT. 2012

Elaborado por: Rubiela Pacanchique Vargas
 Revisado por: Jacqueline Alfonso Roza

Expediente 10-24579 1er Art 45

okt



International Union
of Pure and Applied Chemistry (IUPAC)

Handbook of
Pharmaceutical Salts
Properties, Selection, and Use

P. Heinrich Stahl, Camille G. Wermuth (Eds.)



Verlag Helvetica Chimica Acta · Zürich



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Chapter 2

Solubility and Dissolution of Weak Acids,
Bases, and Salts

by Madhu Podipeddi*, Abu T. M. Sorajodhin, David J. W. Grant,
and P. Heinrich Stahl

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1. Introduction

Improvement of dissolution rate of weakly acidic or weakly basic drugs that are poorly soluble is one of the primary reasons for preparation of pharmaceutical salt forms [1-4]. Salt forms have also been used to control drug dissolution [8] [9]. This chapter examines the pH-dependencies of the solubility and dissolution rate of pharmaceutical acids, bases, and salts, and the relevance of these dependencies to the selection of the final form.

mation. Further confirmation of the nature of the excess solid phase may be obtained by powder X-ray diffractometry or elemental analysis. If the excess solid phase is entirely in the free form, the experiment must be repeated with a higher solid to solvent (H_2O) ratio until the excess solid contains the salt. In some cases, complete conversion of the salt to the free form may occur at all solid-to-solution ratios, often leading to formation of a 'gel'.

As a result of the above phenomenon, in some cases, an attempt to make a solution of a 1:1 salt at a concentration well below the solubility of the salt (as estimated from the K_{sp} value) will be unsuccessful due to precipitation of the free unionized form. To further develop this point *Anderson and Flora* [2] defined the term 'stoichiometric solubility'. The stoichiometric solubility of a 1:1 salt is the concentration of salt which can be dissolved in pure H_2O with no formation of a precipitate of the unionized free form. The authors pointed out that the difficulties of low 'apparent solubility' of a salt due to free form precipitation may be encountered in the preclinical stages of development when concentrated solutions in H_2O are required for toxicology testing. However, appropriate pH adjustment should overcome this problem.

3. Dissolution Behavior of Acids, Bases, and Their Salts

The term *dissolution* refers to the overall process by which a solid compound dissolves in a liquid medium, while *dissolution rate* is the kinetic descriptor giving the rate at which the dissolution takes place. The concept of solubility, on the other hand, implies that the process of dissolution has reached equilibrium, and the solution is saturated. Dissolution rate of solids is of paramount importance in the development of pharmaceutical products and quality control. Salt formation is one of the most commonly employed techniques to improve dissolution of weakly acidic or basic drugs.

A number of theories of the dissolution of solids have been proposed [17] [29] [30]. However, the simple diffusion model may be adequate to describe the dissolution behavior of most pharmaceutical solids in aqueous and non-aqueous media. The diffusion layer model (Fig. 7) assumes that a thin film of saturated solution of concentration c_s exists at the interface of the dissolving solid and the dissolution medium. The dissolution rate is controlled by the diffusion rate of solute molecules from this thin saturated film into the bulk solution. The concentration of the solute in the bulk is denoted by c_b . As the distance x increases from $x=0$ (at the surface of the solid) to $x=h$ (at the beginning of the bulk solution), the concentration decreases from $c=c_s$ to $c=c_b$. Beyond $x=h$, the bulk concentration remains uniform at c_b . In the simplest form of the theory, following *Fick's First Law*, the rate of dissolu-

4.3.5. Basic Physicochemical Properties of the Hydrobromide RPR200765E

4.3.6. Discussion of Results

5. Optimization - Second Phase: Drug-Substance Form for Preclinical Development
6. Optimization - Third Phase: Drug-Substance Form for Clinical Development
7. Optimization - Fourth Phase: Drug-Substance Form for Marketing

REFERENCES

1. Introduction

Until ca. 15 years ago the drug discovery processes adopted by pharmaceutical companies involved the screening of large numbers of compounds that had been synthesized by the company's research laboratories over many years. Alternative sources of compounds were also available to some companies from university laboratories, or as extracts from a multitude of natural sources. In the last 15 years, there has been a rapid change towards the use of combinatorial-chemistry techniques which are now being used routinely to prepare many thousands of compounds per year. As described in *Chapt. 6*, these compounds are generally dissolved in dimethyl sulfoxide (DMSO) to enable screening for activity in an enzyme- or receptor-based assay system. Initial screening usually involves a highly automated 'high throughput screen' (HTS). If the number of 'hits' found is large, the numbers are usually refined by a more involved and specific 'low throughput screen' (LTS) and other selection processes, until a manageable number of 'leads' is available. Often, several of these 'leads' show only moderate activity, and further structural refinement and optimization is invariably necessary, using a mixture of computational techniques and intuition by the chemistry team, until a smaller number (usually 1-5) of highly active potential 'candidates' remain.

These 'candidates' are usually relatively impure free bases, free acids, or neutral molecules, and are often amorphous. Because they are dissolved and stored in DMSO prior to being used in screening procedures, there is no need to ensure that they are crystalline. Also, the preparation of any salts of these compounds is rarely necessary as the neutral/covalent molecule usually exhibits better solubility in both DMSO and the assay system to be used by the pharmacology group. As can be seen readily, these new procedures favor lipophilic molecules, whereas the majority of marketed drug substances are hydrophilic. The need for water-soluble candidates for use in drug development and the vast majority of dosage forms has been recognized [1-4] for many years before the advent of 'combinatorial chemistry'.

Because drug substances are designed to bind with a receptor, enzyme, protein *etc.*, they normally possess several functional groups capable of hydrogen bonding. Some of these functional groups may give potential for salt

formation and thus increased hydrophilicity. This salt formation also gives the pharmaceutical chemist and formulation scientist the opportunity to modify the physicochemical (*e.g.*, melting point, hygroscopicity, chemical stability, dissolution rate, solution pH, crystal form *etc.*) and mechanical (*e.g.*, hardness, elasticity *etc.*) characteristics of the potential drug substance and to develop dosage forms with good bioavailability, stability, manufacturability, and patient compliance.

For weakly basic drug substances, salts of an inorganic acid (*e.g.*, hydrochloride, sulfate or phosphate), a sulfonic acid (mesylate, esylate, or isethionate), a carboxylic acid (acetate, maleate, or fumarate), a hydroxy acid (citrate or tartrate), or possibly an amino acid (arginine or lysine) could be considered. In the past, hydrochloride salts have often been the first choice for weakly basic drugs, since, as a consequence of the low counter-ion pK_a , salts can nearly always be formed, and recrystallization from organic solvents is normally straightforward. However, the potential disadvantages of hydrochloride salts include unacceptably high acidity in formulations (*e.g.*, parenteral products), the risk of corrosion of manufacturing plant and equipment, less than optimal solubility due to the risk of salting out, and the potential for poor stability, if the drug is acid labile and hygroscopic [2].

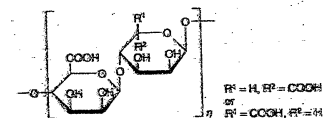
Historically, prior to the severe regulatory constraints that abound today, it had been possible to develop the neutral species (free acid or free base) together with one or more different salts. These different chemical forms were often used for specific purposes. An excellent example of this concerns the phenothiazine drug substance, prochlorperazine. The free base was used in suppositories, as it was the most lipophilic form, the mesylate salt was used in injections and in sachets for the preparation of an oral solution, whilst the less soluble maleate was used for the manufacture of tablets.

Occasionally, salts were also prepared in former times to decrease drug substance solubility for use in suspension formulations where very low solubility is necessary to prevent 'Ostwald ripening', for taste masking (*e.g.*, dextropropoxyphene napsylate suspension), or to prepare an extended release product. Emmonate salts have been used in suspension formulations to increase the duration of action (*e.g.*, chlorpromazine emmonate). On some occasions, the selection of a salt with only modest aqueous solubility may be more suitable for use in tablet products prepared by wet granulation, since the use of highly soluble salts can be detrimental to the granulation process. Depending on the dose required, aqueous solubilities in the range of 0.1–1.0 mg/ml will normally be sufficient to satisfy the dissolution requirements for standard, solid, oral dosage forms of drugs with good-to-moderate potency. However, for parenteral solution products, higher solubilities, perhaps 10 mg/ml or greater, depending on the required dose and dose volume, may be required. For parenteral formulations, the pH of solution (normally

Alginic Acid

Polymannuronuronic acid; 1-gulo-D-mannoglycuronate

A hydrophilic, colloidal linear polysaccharide obtained from seaweeds that, in the form of mixed salts of calcium, magnesium, and other bases, occurs as a structural element of the cell wall.



$(C_6H_8O_6)_{200}$ M_n typically 20000–250000

pK_a

D-Mannuronic acid: 3.38 (A),
L-guluronic acid: 3.65 (A).

Properties

Colorless and tasteless solid.
Insoluble but swelling and gel-forming in H_2O , slightly soluble in boiling H_2O , soluble in alkaline solutions. Capable of absorbing 200–300 times its weight of H_2O and salts to the extent of 60%.
pH of aq. dispersion (3% w/v): 1.5–3.5.

Safety, Toxicology

Generally regarded as a neutral and nonirritant material.

LD_{50} rat i.p., 1.6 g/kg.

Salt

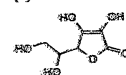
Alginate

Use and Examples

May be used as ion exchanger for the retarded release of basic drugs.
Calcium alginate, magnesium alginate.

Ascorbic Acid

(+)-L-Ascorbic acid, vitamin C



$C_6H_8O_6$ M_n 176.13

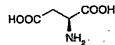
pK_a

(1) 4.17 (A) (2) 11.57 (A)

Properties	M.p. 190–192 °C (some dec.). Sensitive to light and oxygen, rapidly oxidized in alkaline solution. <i>Solubility</i> (20 °C): H ₂ O: 1 in 3.5, EtOH (95%): 1 in 25, EtOH: 1 in 50, pract. insoluble in CHCl ₃ , Et ₂ O, fatty oils.
Safety, Toxicology	<i>Acid</i> : LD ₅₀ : mouse oral, 3367 mg/kg; i.v., 518 mg/kg; i.p., 643 mg/kg. <i>Monosodium salt</i> : LD ₅₀ : rat oral, >10 g/kg; s.c., >793 mg/kg.
Salt	Ascorbate
Use and Examples	Rarely used as a salt former for basic substances that are liable to oxidative degradation (reserpine, epinephrine). Diphenhydramine, dihydrostreptomycin.

L-Aspartic Acid

(S)-2-Aminobutanedioic acid



C₄H₇NO₄, M_r 133.10

pK _a	(1) 1.88 (A) (2) 3.65 (A) (3) 9.60 (B)
Properties	M.p. 270–271 °C (sealed capillary, preheated bath). <i>Solubility</i> (g/kg H ₂ O (temp. [°C])): 1.72 (0), 4.18 (20), 5.94 (30), 8.38 (40), 68.93 (100). Forms easily supersaturated solutions. More soluble in salt solutions. Insoluble in EtOH.
Safety, Toxicology	<i>Monosodium DL-aspartate</i> : LD ₅₀ : mouse i.p., >1 g/kg. <i>Potassium L-aspartate</i> : LD ₅₀ : rat oral, 7937 mg/kg; s.c., 4061 mg/kg; i.v., 667 mg/kg.
Salt	Aspartate
Examples	Salts with other amino acids; ajmaline; Mg.
Remarks	L-Aspartic acid is a nonessential amino acid.

Salt	Formate, formiate.
Examples	Furterene, quinine (†).

Fumaric Acid

(E)-Butenedioic acid



C₄H₄O₄, M_r 116.07

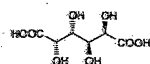
pK _a	(1) 3.03 (A) (2) 4.38 (A) (25 °C)
Properties	M.p. 287 °C (closed capillary, rapid heating); sublimes at 200 °C; partial dec. at 230 °C. <i>Solubility</i> (H ₂ O, g/100 g solution (temp. [°C])): 0.231 (0), 0.330 (10), 0.499 (20), 0.605 (25), 0.734 (30), 1.077 (40), 2.328 (60), 5.028 (80).
Safety, Toxicology	<i>Acid</i> : LD ₅₀ : rat oral, 9300 mg/kg; mouse i.p., 100 mg/kg; LDLo: rat i.p., 587 mg/kg; rabbit oral, 5000 mg/kg. <i>Disodium salt</i> : LDLo: rat i.p., 2420 mg/kg; rabbit i.v., 500 mg/kg; mouse oral, 3680 mg/kg; TDLo: human oral, 215 mg/kg (gastro-intestinal effects: diarrhea, hypermotility, nausea, vomiting). <i>Magnesium salt</i> : LD ₁₀ : mouse oral, 1394 mg/kg.
Salt	Fumarate; hydrogenfumarate, acid fumarate.
Use and Examples	<i>1:1 Salts</i> : aminorex, bencyclane, bisoprolol, brovincamine, clemastine, ebastine, Fe ³⁺ , medifoxamine, metapramine, methafurylene, nizofenone, oxetorone, pentapiperide, piberaline, propiram, racefemine, rilmenidine, semotiadil, thioproperezine, tiamulin. <i>2:1 Salts</i> : aminopromazine, cotinine, formoterol, ibutilide, ketotifen, metofenazate, nebracetam. <i>2:3 Salt</i> : methapyrilene.
Remarks	Warning: 1. As covalent addition of amines to the C(2)=C(3) has been encountered, the chemical compatibility of the acid with primary or secondary amines should be carefully examined

(recrystallization, stability under temperature stress conditions).

2. In a few patients who have been treated for psoriasis with high doses of fumaric acid *alkyl esters*, reversible renal failure had occurred [10–13]. Hence, there had been concern about the use of fumaric acid for drug salts. However, no nephrotoxicity has been reported for fumaric acid in animals or man [14] so far. Nevertheless, it is recommended to monitor renal function parameters in case of high fumarate doses, although a nephrotoxic risk can be practically excluded for the use of drug fumarate salts.

Galactaric Acid

Mucic acid



$C_6H_{10}O_8$, M_r 210.14

pK_a (1) 3.08 (A) (2) 3.63 (A)

Properties Crystalline, dec. at -255°C with rapid heating.
Solubility: 1 g dissolves in 300 g of cold, in 60 g of boiling H_2O ; practically insoluble in EtOH, Et_2O .

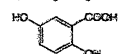
Safety, Toxicology LD_{50} : mouse oral, 8 g/kg; s.c., 960 mg/kg.

Salt Galactarate, mucate.

Examples Isometheptene

Gentisic Acid

2,5-Dihydroxybenzoic acid



$C_7H_6O_4$, M_r 154.12

pK_a 2.93 (A) (25°C)

Properties M.p. 113.5°C
Solubility: freely soluble in H_2O , EtOH; very sparingly soluble in Et_2O .

Safety, Toxicology Diammonium salt: LD_{50} : rat i.p., 901 mg/kg.

Salt Oxoglutarate

Use and Examples Diormithine salt (anabolic and anticatabolic properties [19–21]).

Glycolic Acid

2-Hydroxyacetic acid



$C_2H_4O_3$, M_r 76.05

pK_a 3.82 (A) (25°C)

Properties M.p. 80°C

Safety, Toxicology Acid: LD_{50} : rat oral, 1950 mg/kg; guinea pig oral, 1920 mg/kg.
Monosodium salt: LD_{50} : rat oral, 7110 mg/kg; mouse oral, 6700 mg/kg.

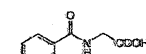
Salt, Ester Glycolate

Use and Examples No drug salts are known. Used to generate H_2O -soluble derivatives by ether bond.

Hexanoic Acid (see Caproic Acid)

Hippuric Acid

2-(Benzoylamino)acetic acid



$C_9H_9NO_3$, M_r 179.18

pK_a -3.55 (A)

Properties M.p. $187-188^\circ\text{C}$
Solubility: 1 g dissolves in ca. 250 ml of cold H_2O , 1000 ml of $CHCl_3$, 400 ml of Et_2O ; slightly

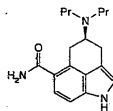
soluble in cold EtOH, freely soluble in hot EtOH or hot H₂O.

Safety, Toxicology *Acid*: LD₅₀: rat i.p., 1500 mg/kg.
 Monosodium salt: LD₅₀: mouse i.v., 4150 mg/kg.

Salt	Hippurate
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Examples Compound LY 228729 (*Lilly*); methenamine.

Remarks	Compound LY 228729 (see structure below; indication: anxiety, depression) was prepared within the frame of a 5-HT1A receptor agonist program [15]. It turned out that the hippurate was the only anion in a series of 27 that gave a crystalline salt.
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Hydrobromic Acid

 $\text{HB}_I, \bar{M}_r 80.91$

pK_2 Estimations: -9 to -6 (A) [2] [16].

Properties Colorless gas, hygroscopic and corrosive.
Aq. solutions: 66% (saturated at 25 °C);
-47.5% (constant boiling azeotrope, b.p. 126 °C).

Safety, Toxicology *Ammonium salt:* LD₅₀: 2700 mg/kg; mouse oral, 2860 mg/kg, i.p., 559 mg/kg; guinea pig i.p., 535 mg/kg.
 Potassium salt: LD₅₀: rat oral, 3070 mg/kg; mouse oral, 3120 mg/kg; i.p., 1030 mg/kg; guinea pig i.p., 980 mg/kg.
 Sodium salt: LD₅₀: rat oral, 3500 mg/kg; s.c., 2900 mg/kg; mouse oral, 7 g/kg; i.p., 5 g/kg; s.c., 5020 mg/kg; rabbit oral, 580 mg/kg.

Salt	Hydrobromide, bromide.
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Use and Examples *Bromides* are frequently obtained from quaternization of *tert*-amines by means of CH_3Br :
ambutonium, benzenonium, homatropine methylbromide, clidinium, etybezatropine, fenpiverinium, glycopyrronium, octatropine methylbromide, oxitetonium, oxypyrrolone, pinaverium, pipenzolate, pirfenium, propantheline, propyromazine, rocuronium, tropenziline, xentropium.

Hydrobromides: butopirine, citalopram, dextromethorphan, fenoterol, galantamine, rimeterol, scopolamine (= hyoscine), tigloidine; Li.

Remarks	In the past, bromides have been used as sedative.
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Hydrochloric Acid

HCl, *M*, 36.46

pK_a Estimations: ~ -6.1 to -3 (A) (25°C).

Properties Colorless gas, hygroscopic and corrosive.
Aq. solutions: ~38% (fuming); 20.22%
(constant boiling azeotrope, b.p. 108.58 °C).

Safety, Toxicology Acid: LD₅₀: mouse i.p., 40 mg/kg; rabbit oral, 900 mg/kg.

Sodium salt: LD₅₀: rat oral, 3 g/kg; mouse oral, 4 g/kg; i.p., 2602 mg/kg; s.c., 3 g/kg; i.v., 645 mg/kg; LDLo: man oral, 1 g/kg; dog i.v., 2 g/kg; rabbit oral, 8 g/kg; i.v., 1100 mg/kg; guinea pig, 2160 mg/kg; i.v., 300 mg/kg.

Salt	Hydrochloride, chloride.
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Note: 'Hyclate' is a contracted term used for the hydrochloride hemiethanolate hemihydrate of doxycycline.

Use and Examples No examples are shown here, since almost half of all salts of basic drug substances are hydrochlorides or chlorides.

Remarks	Because of the easy availability and for physiological tolerability, the hydrochlorides and chlorides have been by far the most frequent choice
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for salts of basic drugs; 650 out of 1346 salts are hydrochlorides. Hydrochloride salts of the drugs frequently exhibit less than desirable solubility in gastric and other physiological fluids because of the abundance of chloride ion in such media [17] [18] due to the law of mass action (so called 'common-ion effect').

(+)-L-Lactic Acid, (±)-DL-Lactic Acid



pK_a

Properties

Safety, Toxicology

Salt

Use and Examples

Remarks

$\text{C}_3\text{H}_5\text{O}_3$, M_r 90.08

3.86 (A) (25 °C)

(+)-L: m.p. 53 °C

(±)-DL: m.p. 16.8 °C

Supplied as aq. solution in various concentrations, up to ca. 90%.

Acid: LD_{50} : rat oral, 3543 mg/kg; mouse oral, 4875 mg/kg; rabbit skin, >2 g/kg; guinea pig oral, 1810 mg/kg; $LDLo$: rabbit oral, 5 g/kg.
Sodium salt: LD_{50} : rat i.p., 2 g/kg; i.v., >1 g/kg; mouse i.v., 2190 mg/kg.
L-Potassium salt: LD_{50} : rat i.v., 299 mg/kg; mouse i.v., 245 mg/kg.
Calcium salt (2:1): $LDLo$: mouse i.v., 140 mg/kg.
Magnesium salt (2:1): $LDLo$: mouse i.v., 45 mg/kg.

Lactate

Amoxicillin, ethacridine, haloperidol, isoxsuprine, prenylamine, trimethoprim.

1. Otherwise sparingly soluble and weak bases could be dissolved by means of lactic acid [22].
2. Aq. lactic acid solutions contain varying amounts of lactoyllactic and higher polylactic acids as intermolecular esters of lactic acid. The quantities depend on the concentration and age of the solution. Aq. solutions as weak as 6.5 wt-% will contain ca. 0.2 wt-% lactoyllactic acid; an 88 wt-% solution contains ca. 60% free lactic

Maleic Acid

(Z)-Butenedioic acid



pK_a

Properties

Safety, Toxicology

Salt

Examples

Remarks

$\text{C}_4\text{H}_4\text{O}_4$, M_r 116.07

(1) 1.92 (A) (2) 6.23 (A)

M.p. 131 °C

Solubility (H_2O , g/100 g solution (temp. [°C])): 28.2 (0), 34.6 (10), 41.1 (20), 44.3 (25), 47.5 (30), 54.1 (40), 64.0 (60), 73.9 (80).

Acid: LD_{50} : mouse oral, 2400 mg/kg; rat oral, 708 mg/kg.

Disodium salt: LD_{50} : rat oral, 3380 mg/kg.

Sodium salt: LD_{50} : i.p., 600 mg/kg; $TDLo$: rat oral, 9 g/kg in 30 days.

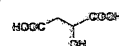
In a drug-maleate study in dogs, acute tubular necrosis could be traced back to the maleate moiety corresponding to 9 mg/kg maleic acid (see *Remarks*).

Maleate

Azetadine, brompheniramine, chlorpheniramine, dimetindene, enalapril, levomepromazine, lisuride, mepyramine, methylethometrine, methysergide, midazolam, nomifensine, perhexiline, pheniramine, pirisudanol, prochlorperazine, triethylperazine, timokol, trimebutate, trimipramine.

1. May potentially isomerize to fumaric acid.
2. In a recent report [23] maleic acid could be made responsible for acute tubular necrosis in dogs after a single peroral dose of a test substance supplied as a maleate (pravastatin maleate) corresponding to a dose of 9 mg/kg maleic acid.

(-)-L-Malic Acid



$\text{C}_4\text{H}_5\text{O}_5$, M_r 134.09

	<i>Solubility:</i> sparingly soluble in H ₂ O (g/100 g solution (temp. [°C])): 2.72 (0), 4.32 (10), 6.45 (20), 7.46 (25), 9.57 (30), 13.95 (40), 26.38 (60), 41.45 (80).
Safety, Toxicology	<i>Acid:</i> LD ₅₀ : rat oral, 2260 mg/kg; mouse i.p., 2702 mg/kg; i.v., 1400 mg/kg. <i>Disodium salt:</i> LD ₅₀ : mouse i.v., 4500 mg/kg. <i>Monosodium salt:</i> LD ₅₀ : rat oral, >8 g/kg; LDLo: cat i.v., 2 g/kg; guinea pig i.m., 3 g/kg.
Salt	Succinate; hydrogensuccinate, acid succinate.
Examples	Benfurodil, bamethan, chloramphenicol, cibenzoline, deanol, doxylamine, ergotamine, loxapine, metoprolol, oxafiumazine, sumatriptan, Fe ^{II} .

Sulfuric Acid



	H ₂ O ₄ S, <i>M_r</i> 98.08
pK _a	(1) -3 (A) (2) 1.92 (A)
Properties	Colorless, odorless, highly hygroscopic liquid, <i>d</i> = 1.83, b.p. ~290 °C. Supplied as aq. solution in various concentrations up to ~98%. Miscible with H ₂ O and EtOH with generation of heat.
Safety, Toxicology	LD ₅₀ : rat oral, 2140 mg/kg.
Salt	Sulfate; hydrogensulfate.
Examples	Amantadine, amphetamine, amikacine, ampicine, atropine, berberine, betanidine, bleomycine, butacaine, capreomycine, cefpirome, clopidogrel, cyclomethycaine, debrisoquine, dibekacin, dihydralazine, dihydrostreptomycin, ephedrine, gentamicin, guanoxan, indinavir, isoprenaline, kanamycine, lividomycine, mefentermine, morphine, neomycin, orciprenaline, paromomycine, polymyxine B, quinine, salbutamol, sparteine, streptomycin, terbutaline, tuaminoheptane, vinblastine, vincristine, viomycine.