Title: USEFUL FORMULATIONS OF ACID ADDITION SALT DRUGS

Abstract

Methods of and formulations for administering acid addition salts of compounds of Formula (A) or Formula (B), wherein R₁ comprises an aryl or alkyl group with a hydrogen bond acceptor site accessible to interaction with said tertiary nitrogen of Formula (A) or said quaternary ammonium ion of Formula (B), R₂, R₃ and R₄ are alkyl or aryl groups, and X⁻ is an anion. In the methods, a sterile injectable formulation of a liquid vehicle containing the acid addition salt in solution is adjusted in pH for reducing the development of undesirable side effects of the material or provided at a pH within a range of about 5.5 to 7.0, and administering these acid addition salts by intramuscular injection contain the salt at a concentration of at least about 50 mg/ml and are at a pH within a range of about 5.5 to 7.0.
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USEFUL FORMULATIONS OF ACID ADDITION SALT DRUGS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of copending U.S. patent application Serial No. 08/479,113 filed June 7, 1995, which is a division of copending U.S. patent application Serial No. 08/218,072 filed March 25, 1994. The disclosures of both of these patent applications are incorporated herein by this reference.

BACKGROUND OF THE INVENTION

This invention relates to acid addition salt drugs having utility in the treatment of human patients. More particularly it relates to new and improved formulations and methods of administration of such acid addition salt drugs.

Regardless of the precise mechanism(s) the ultimate result is accumulation of DNA damage and an increase in tumor cytotoxicity either by necrosis or apoptosis (Kerr and Winterford, Cancer 73:2013-2026, 1993). As a result, these agents are all potential cancer therapy drugs even though they may have other well defined clinical uses. For example, metoclopramide, an N-substituted benzamide, has been used as an antiemetic for over 30 years (Harrington et al, Drugs 25: 451-494, 1983) but recently it has been shown to be an effective radio- and chemo-sensitizer (Pero et al, Biochimie 77:385-391, 1995, Kjellén et al, Eur. J. Cancer 31A(13/ 14):2196-2202, 1995). Furthermore, most drugs having well established clinical uses are known to mediate their effects by antagonizing high affinity receptors capable of initiating physiological responses relating to many disease processes. Conformation and charge of these chemical structures, in turn, determine their abilities to antagonize receptors and mediate drug related efficacious responses.
SUMMARY OF THE INVENTION


One of the most popular chemical functionalities (i.e. structures, substitutions) used in drug design is a tertiary or a quarternary nitrogen usually introduced via an alkylaminodialkyl side chain, so that drugs such as the nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics and anaesthetics
could be converted to more water soluble formulations for clinical administration. However, drug formulation research with the N-substituted benzamides (incident to the development of the present invention) has so far shown that this structure can dramatically alter the pharmacological properties of, for example, metoclopramide simply by changing the pH of the formulation. Molecular modeling experiments support that Neu-Sensamide™ ("neutral" metoclopramide) has been formulated without the presence of a hydrogen mediated-bond between the tertiary ammonium ion and the carboxamide oxygen atom, whereas this hydrogen mediated-bond is present in Sensamide™ ("acidic" metoclopramide) (Schwartz et al unpublished 1996). Neu-Sensamide™ has a reduced extrapyramidal side effect profile in rats and humans but the radiosensitizing properties remain unaltered compared to Sensamide™ at equimolar doses (Amiri et al unpublished 1996; Hua et al, Anti-Cancer Drugs 6:451-453, 1995, Pero et al, Biochimie 77:385-393, 1995; Pero et al unpublished 1996; Rotmensch et al unpublished 1996). Therefore, it is logical to extrapolate these data to other drugs containing acid addition salt structures in the following way:

Compounds that can form acid salts of types A or B:

![Diagram](image)

\[ R_{1,4} = \text{alkyl or aryl groups}; \ X^- = \text{any anion, normally Cl}^- \text{ or Br}^- \text{ or I}^- \]
Wherein:

(1) A tertiary nitrogen is present that can form an acid addition salt (Type A) or a quarternary ammonium ion is present (Type B) and/or

(2) \( R_1 \) comprises an aryl or alkyl group with a hydrogen bond acceptor site accessible to interaction with the tertiary/quarternary nitrogen, e.g. a carbonyl or carboxylic oxygen atom.

Have the potential to become pharmacologically altered because:

(1) Most drugs express their biological activity by binding receptors.

(2) Receptor affinities are determined by conformation and charge-distribution of the ligand drugs.

(3) Altering the pH of acid addition salt drugs can alter their receptor affinity by either conformation or charge-distribution or both.

(4) Altering receptor affinity as has been accomplished with Sensamide™/Neu-Sensamide™ does not alter radiosensitizing potency (Hua et al, Anti Cancer Drugs 6:451-453, 1995; Pero et al unpublished 1996).

There are at least 143 clinically available drugs (listed in Table 2 below) having potential properties of radiosensitization, and altering their receptor affinities by pH adjusting their formulations that in turn contain acid addition salt.
substitutions, could affect side effect profiles permitting higher doses to be used for radiosensitization or other pharmacological indications. This point is a novel discovery not obvious as previously known in the literature. Although the 143 clinically available drugs have been the subject of many patents and patent applications, including recent patents and applications concerned with the radio-chemo-sensitizing and antiemetic properties of N-substituted aryl compounds such as the benzamides and nicotinamides (U.S. provisional Patent Application No. 60/013,072, U.S. Patent No. 4,576,386, U.S. Patent No. 5,340,565, U.S. Patent No. 5,215,738, U.S. Patent No. 5,032,617 and U.S. Patent No. 5,041,653), the latter citations do not disclose that the pH of acid addition salt drugs could alter chemical structure, and in turn change the pharmacological properties of the formulations. Examples of compounds that are not as yet clinically available but that are capable of forming acid addition salts with a potential for alteration of pharmacological properties by pH adjustment are 3-chloro procainamide, N-(2-diethylamino-ethyl) nicotinamide, nimorazole and 2,3-dimethyl(dimethylaminoethyl)-5H-indolo-(2,3-b) quinoxline (procedures for synthesizing 3-chloro procainamide and N-(2-diethylamino-ethyl) nicotinamide are described in copending U.S. provisional patent application No. 60/013,072, filed March 8, 1996, the disclosure of which is incorporated herein by this reference). Hence in a broad sense this invention is not confined to the 143 clinically available drugs listed in Table 2, but embraces the use of all compounds formulated to possess water solubility by formation of a substituted amide acid addition salt structure. The aforementioned U.S. Patent Application Serial No. 08/218,072 discloses that metoclopramide, a N-substituted benzamide, can undergo pH-sensitive conformational changes. However, the claims of this application and its division, Serial No. 08/479,113, are respectively directed to
the N-substituted benzamides and phenothiazines and do not include claims covering other acid addition salt drugs.

The present invention, in a first aspect, contemplates the provision of a method of administering to a human patient material selected from the group consisting of acid addition salts of chemical or pharmacological structures such as nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics, and anaesthetics as identified and listed in Table 2 below, comprising the steps of providing a sterile injectable formulation comprising a liquid vehicle containing the material in solution and injecting the formulation into the patient in an amount for delivering to the patient a dose of about one to about 100 mg/kg of the material. In important embodiments of this method, the injection is intramuscular, also, conveniently or preferably, the material to be administered is in the acid addition salt form, pH adjusted to 5.5 - 7.0.

Intramuscular injection, to achieve a dose of 1 - 100 mg/kg, requires a much more concentrated formulation than i.v. injection of a like dose, owing to the limited tolerance of muscle tissue for injected fluid. Whereas a solution at a 5 mg/ml concentration of metoclopramide hydrochloride is suitable for i.v. injection of a dose of 5 mg/kg, a concentration of at least about 50 mg/ml or even more (preferably, in many cases, as much as 100 mg/ml) is needed to administer a like dose by intramuscular injection. At these high concentrations, present-day commercial acid addition salt formulations tend to produce local tissue toxic reactions at the injectable site if not pH adjusted to 5.5 - 7.0 (U.S. Patent application No. 08/218,072, Pero et al unpublished 1996).
Further in accordance with the invention, a concentrated acid addition salt formulation (e.g. 100 - 7000 mg/ml) is advantageously provided at a pH of about 5.5 to 7.0, for intramuscular injection. At pH values within this range (which is substantially higher, i.e. less acidic, than the pH of currently available formulations of equivalent concentration), local tissue toxic reactions are satisfactorily minimized or avoided, yet without adversely affecting the solubility of acid addition salt drugs or their therapeutic activity. A pH above 7.0 would derogate from solubility, while values below about 5.5 are insufficient to achieve the desired reduction in local tissue side effects. It has been shown that this is the case because an acid addition salt formulation of metoclopramide at pH 2.5 - 3.5 caused local tissue irritation but when neutralized to pH 6.5 - 7.0 a substantially reduced local tissue reaction was observed (U.S. Patent application No. 08/218,072, Pero et al unpublished 1996).

In a second aspect, the invention contemplates the provision of a sterile injectable formulation for intramuscular administration to a human patient, comprising a material selected from the group consisting of acid addition salts of chemical or pharmacological structures such as nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics, and anaesthetics as identified and listed in Table 2 below, a liquid vehicle in which the material is in solution being present in the formulation in a concentration of at least about 50 mg/ml; and the formulation being at a pH within a range of about 5.5 to 7.0. In these formulations, the solution pH, once established, may be stabilized to a less variable range (e.g. <0.5 pH unit) by the inclusion of a phosphate or other buffer, or alternatively, by the inclusion of a preservative such as sodium metabisulfite to prevent auto-oxidation.
Also surprisingly, it has been found that the administration of an acid addition salt, metoclopramide hydrochloride, in otherwise conventional formulations (which contain Na⁺ ions, present in the saline solution and/or introduced as sodium metabisulfite) but at a pH of about 5.5 to 7.0 substantially prevents the extrapyramidal side effects of known metoclopramide treatments (Pero et al, Biochimie 77:385-393, 1995, Pero et al unpublished 1996). In a third aspect, which is not limited to intramuscular injection, the invention contemplates the provision of a method of administering to a human patient material selected from the group consisting of acid addition salts of chemical or pharmacological structures such as nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics, and anaesthetics as identified and listed in Table 2 below, comprising a liquid vehicle containing the material in solution (and, in some instances, also containing Na⁺ ions), adjusting the pH of the formulation for reducing the development of undesirable side effects or improving pharmacological indications of the material, and administering the formulation having the adjusted pH to the patient. A preferred or effective range of formulation pH for reduction or avoidance of extrapyramidal side effects is between about 5.5 and 7.0.

Stated in some respects more broadly, the invention in each of the above described aspects may be embodied in a method or formulation wherein the aforementioned material is selected from the group consisting of acid addition salts of compounds that can form acid salts of Formula (A) having a tertiary nitrogen present, acid addition salts of compounds that can form acid salts of
Formula (B) having a quaternary ammonium ion present, and mixtures thereof, Formula (A) and Formula (B) being as follows:

\[
\begin{align*}
R_1 - (CH_2)_n &- N^+ - R_3 \\
&- R_2 \quad X^- \\
&- R_4
\end{align*}
\]

wherein \( R_1 \) comprises an aryl or alkyl group with a hydrogen bond acceptor site accessible to interaction with the tertiary nitrogen of Formula (A) or the quaternary ammonium ion of Formula (B), \( R_2 \) and \( R_3 \) and \( R_4 \) are alkyl or aryl groups, and \( X^- \) is an anion. In specific embodiments, the hydrogen bond acceptor site is a carbonyl or carboxylic oxygen atom, and \( X^- \) is Cl\(^-\), F\(^-\), Br\(^-\) or I\(^-\). Advantageously or preferably, the material is selected from the group consisting of nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics and anaesthetics which are acid addition salts of compounds that can form acid salts of Formula (A) or Formula (B), and mixtures thereof.

Further features and advantages of the invention will be apparent from the detailed description herein below set forth, together with the accompanying drawings.
Fig. 1 is a graph on which the UV absorption intensity is plotted against wavelength of UV absorption between 195 nm and 215 nm for 100 μM solutions of metoclopramide pH adjusted between 4.8 and 6.0 with 1 N HCl or 1 N NaOH.

Fig. 2A is a graph on which the UV absorption intensity of 100 μM solutions of aqueous (pH 5-6) and acidic (pH 2-3) 3-chloroprocainamide are plotted against the wavelength of UV absorption between 195 nm and 380 nm.

Fig. 2B is a graph on which the UV absorption intensity of 100 μM solutions of aqueous (pH 5-6) and acidic (pH 2-3) lidocaine are plotted against the wavelength of UV absorption between 195 nm and 380 nm.

Fig. 2C is a graph on which the UV absorption intensity of 100 μM solutions of aqueous (pH 5-6) and acidic (pH 2-3) metoclopramide are plotted against the wavelength of UV absorption between 195 nm and 380 nm.

Fig. 2D is a graph on which the UV absorption intensity of 100 μM solutions of aqueous (pH 5-6) and acidic (pH 2-3) remoxipride are plotted against the wavelength of UV absorption between 195 nm and 380 nm.

Fig. 2E is a graph on which the UV absorption intensity of 100 μM solutions of aqueous (pH 5-6) and acidic (pH 2-3) procainamide are plotted against the wavelength of UV absorption between 195 nm and 380 nm.
Fig. 2F is a graph on which the UV absorption intensity of 100 μM solutions of aqueous (pH 5-6) chlorpromazine are plotted against the wavelength UV absorption between 195 nm and 380 nm.

Fig. 2G is a graph on which the UV absorption intensity of 100 μM solutions of acidic (pH 2-3) chlorpromazine are plotted against the wavelength of UV absorption between 195 nm and 380 nm.

**DETAILED DESCRIPTION**

The invention is embodied in methods involving the use of pH adjustment of acid addition salts of chemical or pharmacological structures such as nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics, and anaesthetics as identified and listed in Table 2 below, to reduce the development of undesirable side effects of the drug without affecting or enhancing the pharmacological properties such as antiemetics, antiarrhythmics, antidepressants, antipsychotics, antihypertensives, adrenergics, anaesthetics, or the enhancement of radio- and chemotherapies of cancer.

In addition, the invention is embodied in methods involving the use of preparing aqueous sterile injectable formulations of acid addition salts of chemical or pharmacological structures such as nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics, and anaesthetics as identified and listed in Table 2 below, with pH adjustment, in order to avoid undesirable side effects of the drug without affecting or improving the indicated clinically useful
pharmacological properties (e.g. enhancement of radio- and chemo-therapies of cancer).

In another aspect, the practice of this invention involves consideration of the pH of acid addition salts of chemical or pharmacological structures such as nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics, and anaesthetics as identified and listed in Table 2 below. The 1993 Physicians’ Desk Reference lists over 145 hydrochloride salt formulations as available for clinical use. Most of these hydrochloride salt formulations are acidic solutions ranging in pH from 2 to 6.5 depending on the initial drug concentration and formulation ingredients (American Society of Hospital Pharmacists, 1993, Sveriges Läkaremedels Information AB, FASS, 1993). In order to deliver doses of 1-100 mg/kg by intramuscular injection to patients, the injectable formulations would require initial drug concentrations of around 100 to 7000 mg/ml, which in most cases is a concentration having a pH range of 1 to 4.5 depending on its formulation (American Society of Hospital Pharmacists, 1993, FASS, 1993). Because commercial preparations of solutions of acid addition salt drugs drastically vary in pH, and because they can be pH adjusted from 2 to 6.5 without regulatory restrictions, the prior art teaches that there is no difference in biological activity associated with changes in pH between 2 and 6.5. However, applicant herein has found that when acidic formulations of metoclopramide hydrochloride solutions within a pH range of 2 to 3.7 are compared to a neutralized formulation at around pH 7.0, the local tissue toxic reaction at the site of intra-muscular injection and the extrapyramidal side effect of sedation, are substantially reduced when the neutralized formulation is administered (Pero et al, Biochimie 77:385-393, 1995; Pero et al unpublished 1996). Hence, this
invention embraces the feature that high concentrations of metoclopramide hydrochloride (e.g. 100 mg/ml), and by analogy other acid addition salt drugs because the drug itself is acidic, which would be required for intramuscular administration of metoclopramide or other acid addition salt drugs as pharmacological agents, have fewer toxic side effects in the near neutral pH range than in the acidic form, which in turn are currently the clinically available forms of these drugs.

Metoclopramide and the other acid addition salt drugs listed in Table 2 below are known to bind to high affinity receptors such as both the dopamine$_2$ (D2) receptor and the 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor (Pharmacokinetic principles in the use drugs, in Medical Pharmacology, A. Goth ed., C.V. Mosby Company, tenth edition, St. Louis, MO, pages 15-30, 1981; Harrington et al, Drugs 25:451-494, 1983, Blower, Eur. J. Cancer 26 (Suppl. 1): S8-S11, 1990). The side effects of acid addition salt drugs are believed to be delivered from receptor binding; for example, extrapyramidal side effects generated from D2 binding (King and Sanger, Drugs of the Future 14(9):875-889, 1989). These data from the scientific literature support and are consistent with the altered systemic biological effects of acidic metoclopramide hydrochloride salt formulations described herein (Pero et al unpublished 1996). As already mentioned above, acidic metoclopramide has a conformation altering pH sensitive hydrogen mediated-bond which is lacking in neutralized metoclopramide (Pero et al, Biochimie 77:385-393, 1995; Schwartz et al unpublished 1996). This finding is supported by the data revealed in Examples 1-3 which establish that a wide variety of drugs containing tertiary nitrogen substitutions that can convert drugs to acid addition salts, have very similar UV spectra changes indicative of the pH
sensitive conformational changes observed for metoclopramide especially at 
A<sub>200</sub> (wavelength of 200 nm). In addition, it would have been an unexpected 
observation for one skilled in the art to have been able to predict that 
metoclopramide or other acid addition salt drugs could form a chemical 
interaction (e.g. a hydrogen bond) stable enough to be transported from the site 
of intramuscular injection to receptors in the brain in order to mediate an 
enhanced efficacy or side effect (e.g. sedation).

The UV spectra of the Examples below were run using a Beckman scanning UV-
visible spectrophotometer with a quartz cell having a 1 cm path length. The 
spectra were produced by scanning the UV absorption produced between 195 

nm and 380 nm (379 nm in Fig. 1) at a bandwidth of 5 nm. 100 µM samples of 
the drugs or model compounds were acidified to pH 2-3 and their UV spectra 
were recorded. These UV spectra were compared with the UV spectra 
determined at ambient (aqueous) pH which was normally between pH 5 and 6. 
In some cases the ambient drug solutions were titrated with 1N HCl and 1N 
NaOH to produce pH gradient solutions which were then subjected to scanning 
of the UV spectrum between A<sub>195</sub> and A<sub>380</sub>. The UV spectra were corrected 
for absorption from appropriate solvent blanks.
Example I

UV spectral evidence for the pH sensitive conformation change in metoclopramide.

There is considerable analytical evidence supporting that a hydrogen bond is formed in acidic aqueous solutions of metoclopramide between the tertiary nitrogen of the N-ethylaminodiethyl substitution and the carbonyl of the carboxamide group of substituted benzamide (Reviewed by Schwanz et al unpublished 1996). The data in Fig. 1 report the result of a detailed UV spectral analysis of metoclopramide solutions carefully adjusted in pH between 4.8 and 6.0. The UV absorption spectra recorded between 195 nm and 215 nm show a very sharp change in maximal absorption in metoclopramide solutions around pH 5.0. These UV spectra changes around 5.0 were taken as strong supportive evidence for the shifting of equilibrium between the two conformational forms of metoclopramide, namely, one with the pH sensitive hydrogen bond present and one without it. Because acidic metoclopramide induces extrapyramidal side effects whereas neutral metoclopramide does not (Pero et al, Biochimie 77:385-393, 1995, Pero et al unpublished 1996, Rotmensch et al unpublished 1996), Fig. 1 also clarifies that unpredictable but detectable pH sensitive UV absorption spectral changes reflect conformational structural changes in metoclopramide altering the receptor mediated side effects of this drug.
Example 2

UV spectral evidence for pH sensitive changes of drugs having alkylaminodialkyl substitutions that are capable of forming acid addition salts.

First, the data in Figs. 2A-2G show that drugs that contain alkylaminodialkyl substitutions can have very different UV absorption maxima in aqueous solution, and several areas of each of these UV absorption maxima can be shifted and varied in intensity due to acidic pH adjustment into the range pH 2. Second, the most striking change in UV absorption was associated with pH adjustment at A_{200} for all the drugs containing alkylaminodialkyl substitutions.
Example 3

UV spectral evidence indicating alterations in A_{200} resulting from proposed pH sensitive conformational changes in the structure of N-alkylaminodialkyl substituted drugs.

- The data in Table 1 show that aryl N-alkylaminodialkyl substitutions contribute mainly to the pH adjusted UV spectra in the 200 nm range. This UV region has been identified as being of interest by comparison to the UV spectral changes associated with pH adjustment of metoclopramide aqueous solutions (presented in Example 1). Molecular modeling, analytical chemical analyses, extrapyramidal biologic responses and the previous scientific literature have confirmed the existence of a hydrogen mediated-bond between the carbonyl of the carboxamide and the tertiary nitrogen present in the N-ethylaminodiethyl substituted benzamide ring of metoclopramide (Schwartz et al unpublished 1996; Pero et al, Biochimie 77: 385-393 1995). Hence, acidic metoclopramide has the conformational change imposed by the presence of this pH sensitive hydrogen mediated-bond whereas neutral metoclopramide has an extended conformation due to the lack of this hydrogen bond. The pH dependence of intramolecular hydrogen bonding in metoclopramide is represented in Schwartz et al unpublished 1996 as follows:
**Metoclopramide·HCl**

- "highly structured, coplanar form"
- 2 hydrogen bonds define structure
- d-2 receptor antagonist

**"extended hydrochloride conformation"**

- Proton away from carbonyl
- 2nd hydrogen bond cannot form

**Neu-Sensamide™**

- "extended side chain conformation"
- 1 hydrogen bond defines structure
- Poorer binding at d-2 receptor
The formula in the upper left is metoclopramide-HCl in the highly structured, "coplanar" form in which two hydrogen bonds define the structure, this form, dominant at lower (more acid) pH, is a D₂ receptor antagonist. The formula at the upper right represents the "extended hydrochloride conformation" with the proton away from the carbonyl such that the second hydrogen bond (between the carbonyl oxygen and the proton of the side chain ammonium hydrogen) cannot form. The formula at the lower right, representing "Neu-Sensamide™", at higher (less acid, approaching neutral) pH, has an extended side chain conformation, again with only one hydrogen bond (that between the oxygen of the methoxy group and the amide hydrogen), and exhibits poorer binding at the D₂ receptor. In a broader sense, Table 1 also shows that changes in UV absorption at A₂₀₀ detects the conformational difference between acidic and neutral metoclopramide formulations, and as a result, other aryl compounds having N-alkylaminoalkyl substitutions capable of forming a quaternized nitrogen and hydrogen mediating-bonding site, will display a pH sensitive change in their UV spectra at A₂₀₀. For example, 3-amino benzarnide and procaine do not contain either alkylaminodialkyl- or N- substitutions nor do they exhibit pH sensitive UV absorption changes at A₂₀₀ (Table 1). On the other hand, 3-chloro procainamide, procainamide, remoxipride, lidocaine and chlorpromazine all contain N-alkylaminodialkyl substitutions, and they also display UV absorption changes at A₂₀₀.
Table 1. pH sensitive alterations in the UV spectra attributed to proposed conformational changes of the alkylaminodialkyl substructures of agents capable of forming acid addition salts. 100 μM samples of these agents were acidified to pH 2 and their UV spectra were recorded. These spectra in turn were compared with the UV spectra at ambient pH (i.e. pH 5-6).

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</table>
Example 4

List of drugs capable of forming acid addition salts via the formation of a quaternized nitrogen (e.g. alkylaminodialkyl substitutions), and thereby undergoing pH sensitive alterations, that may consequentially alter drug efficacy or side effects.

The data for this example (obtained from literature, not actual experiment) are presented in Table 2. It lists 143 drugs that are available for clinical use in Sweden (FASS 1992-1996). The data show that the chemical structures and clinical uses of the drugs listed in Table 2 are extremely diverse, but they share a common chemical substitution; namely all have been formulated as acid addition salts (i.e. usually hydrochloride acid salts) because they contain a tertiary nitrogen group (i.e. usually as alkylaminodialkyl substitutions). Because Examples 1-3 establish that compounds containing alkylaminodialkyl substitutions can undergo conformational changes due to pH adjustment, together with the fact that conformation and charge can determine the degree of drug mediated receptor binding antagonism, then Table 2 also show that all the drugs listed are capable of pH modification leading to an altered receptor mediated efficacy or side effect profile.
Table 2. List of clinically available acid addition salt drugs including their structures, chemical abstract numbers, trade marks, commercial suppliers and clinical uses. This data has been compiled from the 1992-1996 Sveriges Läkersmedels Information AB, (FASS) and the 1995 Merck Index.
1. MELPHALAN [148-82-3]

2. AMILORIDE [2609-46-3]

3. CLOMIPRAMINE [363-49-1]

4. CHLORCYCLIZINE [82-93-9]
5. HYDRALAZINE [86-54-4]

\[
\text{NHNNH}_2
\]

TRADE NAME: APRESOLIN (CIBA)
CLINICAL USE: ANTIHYPERTENSIVE

6. ALPREGOLOL [13655-52-2]

\[
\text{CH}_2\text{CH} = \text{CH}_2
\]

TRADE NAME: APTIN (HÄSSLÉ)
CLINICAL USE: ANTIHYPERTENSIVE
ANTIARRHYTHMIC

7. DOPAMINE [51-61-6]

\[
\text{OH}
\]

TRADE NAME: ABBODOP (ABBOTT)
GILUDOP (MEDA)
INTROPIN (HÄSSLÉ)
CLINICAL USE: ADRENERGIC

8. QUINAPRIL [85441-61-8]

TRADE NAME: ACCUPRO (PARKE DAVIS)
CLINICAL USE: ANTIHYPERTENSIVE
9. TETRACYCLINE [60-54-8]

TRADE NAME:
ACHROMYCIN (LEDERLE)
ACTISITE (MEDA)
TETRACYKLIN
(NM PHARMA)

CLINICAL USE: ANTIBACTERIAL

10. CIMETIDINE [51481-61-9]

TRADE NAME:
ACILOC (ORION)
ACINIL (SELENA)
CIMETIDIN (SELENA)
TAGAMET (SMITH KLINE BEECHA)

CLINICAL USE: HISTAMINE 2 RECEPTOR
ANTIAGONIST, ESPECIALLY IN
THE TREATMENT OF DUODENAL
AND GASTRIC ULCERS

11. DOXORUBICIN [23214-92-8]

TRADE NAME:
ADRIAMYCIN (PHARMACIA & UPJOHN)
DOXORUBICIN (NYCOMED)

CLINICAL USE: ANTINEOPLASTIC

12. BIPERIDEN [514-65-8]

TRADE NAME: AKINETON (MEDA)

CLINICAL USE: ANTICHOLINERGIC
ANTIPARKINSON
13. CARTELOL [51781-06-7]

```
N
O

OCH₂CHOHCH₂NHC(CH₃)₃
```

TRADE NAME: ARTEOPTIC (CIBA VISION)
CLINICAL USE: β-RECEPTOR BLOCKER

14. RANITIDINE [66357-35-5]

```
CHNO₂

H₃C
NCH₂

CH₂SCH₂CH₂NHCNHCH₃
```

TRADE NAME: ARTONIL (SELENA)
ZANTAC (GLAXO WELLCOME)
CLINICAL USE: ANTIULCERATIVE

15. HYDROXYZINE [68-88-2]

```
Cl

CH-N
N-CH₂CH₂OCH₂CH₂OH
```

TRADE NAME: ATARAX (UCB)
HISTILOS (UCB)
VISTARIL (ROERIG)
CLINICAL USE: TRANQUILIZER

16. CHLORTETRACYCLINE [57-62-5]

TRADE NAME: AUREOMYCIN (LEDERLE)
CLINICAL USE: ANTIBIOTIC
17. **BAMBU T E R O L**

TRADE NAME: BAMBEC (DRACO)
CLINICAL USE: BRONCHODIALATOR

18. **D I P H EN H Y D R A M I N E [482-05-3]**

TRADE NAME: BENYLAN (PARK-DAVIS)
DESENTOL (PHARMACIA & UPJOHN)
CLINICAL USE: ANTIHISTAMINE
ANTI-MOTIONSICKNESS

19. **B E T A X O L O L [63659-18-7]**

TRADE NAME: BETOPTIC (ALCON)
KERLON (SEARLE)
CLINICAL USE: ANTI-GLAUCOMA
ANTIHYPERTENSIVE

20. **B R O M H E X I N E [3572-43-8]**

TRADE NAME: BISOLVON (BOEHRINGER)
BROMHEXIN (ACO)
MOLLIECT (TIKA)
CLINICAL USE: MUCOLYTIC
EXpectorant
21. PHENYLEPHRINE HYDROCHLORIDE [61-76-7]

```
HO
O
CH2NH-CH3
H
```

TRADE NAME: BLEFCON (ALLERGAN)
METAOXEDRIN (MEDA)
NEOSYNEPHRINE
(SANOFI WINTHROP)
ZINCFRIN (ALCON)

CLINICAL USE: ADRENERGIC

22. BUPIVACAINE [2180-92-9]

```
CH3
CH3

CH2CH2CH2CH3

N

N

CH3
```

TRADE NAME: BUPIVAKAIN (NORCOX)
MARCAIN (ASTRA)

CLINICAL USE: LOCAL ANAESTHETIC

23. MELPERONE [3575-80-2]

```
F

COCH2CH2CH2-N

-CH3
```

TRADE NAME: BURONIL (LUNDBECK)

CLINICAL USE: NEUROLEPTIC

24. BUSPIRONE [36505-84-7]

```
N

N

N

-CH2CH2CH2CH2-N
```

TRADE NAME: BUSPAR
(BRISTOL-MEYERS SQUIBB)

CLINICAL USE: ANXIOLYTIC
25. MEPIVACAINE [96-88-8]

![Chemical structure of MEPIVACAINE]

- TRADE NAME: CARBOCAIN (ASTRA)
- CLINICAL USE: LOCAL ANAESTHETIC

26. DILTIAZEM [42399-41-7]

![Chemical structure of DILTIAZEM]

- TRADE NAME: CARDIZEM (PHARMACIA & UPJOHN), ENTRYDIL (ORION), TILDIEM (TIKA)
- CLINICAL USE: CALCIUM ANTAGONIST, VASODILATOR

27. CLONIDINE [4205-90-7]

![Chemical structure of CLONIDINE]

- TRADE NAME: CATAPRESAN (BOEHRINGER INGELHEIM)
- CLINICAL USE: ANTIHYPERTENSIVE

28. SUCCINYLCHOLINE CHLORIDE [71-27-2]

![Chemical structure of SUCCINYLCHOLINE CHLORIDE]

- TRADE NAME: CELOCURIN (PHARMACIA & UPJOHN)
- CLINICAL USE: SKELETAL MUSCLE RELAXANT (SHORT DURATION)
29. **DAUNORUBICIN** [20830-81-3]

![Chemical structure of Daunorubicin](image)

**Trade Name:** CERUBIDIN (RHONE-POULENC RORER)
DAUNOXOME (SWEDISH ORPHAN)

**Clinical Use:** CYTOSTATIC

30. **CIPROFLOXACINE** [85721-33-1, 86393-32-0(HCl)]

![Chemical structure of Ciprofloxacin](image)

**Trade Name:** CILOXAN (ALCON)
CIPROXIN (BAYER)

**Clinical Use:** ANTIBACTERIAL

31. **CLOPENTHIXOL** [982-24-1]

![Chemical structure of Clopenthixol](image)

**Trade Name:** CISORDINOL (LUNDBECK)

**Clinical Use:** ANTIPSYCHOTIC

32. **PRILOCAINE** [721-50-6]

![Chemical structure of Prilocaine](image)

**Trade Name:** CITANEST (ASTRA)
EMLA (ASTRA)

**Clinical Use:** LOCAL ANAESTHETIC
33. **ETHYLMORPHINE** [76-58-4]

\[
\text{CH}_3\text{CH}_2\text{O} \\
\text{O} \\
\text{H} \\
\text{H} \\
\text{HO} \\
\text{H} \\
\text{N-CH}_3
\]

**TRADE NAME:** COCILLANA - ETYFIN (PHARMACIA & UPJOHN), COSYLA (PARKE-DAVIS), LEPHETON (PHARMACIA & UPJOHN)

**CLINICAL USE:** ANTITUSSIVE

34. **TACRINE** [321-64-2]

\[
\text{NH}_2 \\
\text{N}
\]

**TRADE NAME:** COGNEX (PARKE-DAVIS)

**CLINICAL USE:** CHOLINERGIC

35. **PROTRIPTYLINE** [438-60-8]

\[
\text{CH}_2\text{CH}_2\text{CH}_2\text{NHCH}_3
\]

**TRADE NAME:** CONCORDIN (MSD)

**CLINICAL USE:** ANTIDEPRESSANT

36. **AMIODARONE** [1951-25-3]

\[
\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\
\text{CH}_2\text{CH}_3 \\
\text{CH}_2\text{CH}_2\text{NCH}_2\text{CH}_3 \\
\text{CO} \\
\text{OCH}_2\text{CH}_2\text{NCH}_2\text{CH}_3
\]

**TRADE NAME:** CORDARONE (SANOFI WINTHROP)

**CLINICAL USE:** ANTIARRHYTHMIC
37. CYCLOPENTOLATE [512-15-2]

38. CLINDAMYCIN [18323-44-9]

39. PROPOXYPHENE [469-62-5]

40. HYDROMORPHONE [466-99-9]
41. **ORPHENADRINE** [83-98-7]

![Chemical structure of Orphenadrine](image1)

- **Trade Name**: DISIPAL (YAMANOUCHI)
- **Trade Name**: NORFLEX (3M)
- **Trade Name**: NORGESIC (3M)
- **Clinical Use**: MUSCLE RELAXANT
- **Clinical Use**: SCELETETAL
- **Clinical Use**: ANTIPARKINSON

42. **DOBUTAMINE** [30468-04-2]

![Chemical structure of Dobutamine](image2)

- **Trade Name**: DOBUJECT (LEIRAS)
- **Trade Name**: DOBUTREX (LILLY)
- **Trade Use**: CARDIOTONIC

43. **DOPEXAMINE** [86494-91-5(HYDROCHLORIDE)]

![Chemical structure of Dopexamine](image3)

- **Trade Name**: DOPACARD (FISON)
- **Trade Use**: CARDIOTONIC

44. **DOXYCYCLINE** [564-25-0]

![Chemical structure of Doxycycline](image4)

- **Trade Name**: DORYX (SCAND PHARM)
- **Trade Name**: DOXYCYKLIN (ENAPHARM)
- **Trade Name**: DOXYFERM (NORDIC)
- **Trade Name**: IDOCYKLIN (ROERIG)
- **Trade Name**: VIBRAMYCIN (PFIZER)
- **Clinical Use**: ANTIBACTERIAL
45. NEOMYCIN [1404-04-2, FOR THE MIXTURE]

TRADE NAME:
- ECOMYTRIN (LUNDBECK)
- CELESTON (SCHERING-PLough)
- DECARDRON (MSD)
- ISOPTO-BIOTIC (ALCON)
- NEBACETIN (LUNDBECK)

CLINICAL USE: ANTIBACTERIAL

NEOMYCIN B R = H, R¹ = CH₃NH₂
NEOMYCIN C R = CH₂NH₂, R¹ = H

46. Ephedrine [50-98-6]

TRADE NAME:
- EFEDRIN (NM PHARMA)
- LEPHETON (PHARMACIA & UPJOHN)
- LERGIOQAN (RECIP)
- MOLLIEPECT (TIKA)

CLINICAL USE: ADRENERGIC

47. Venlafaxine []

TRADE NAME:
- EFEXOR (WYETH)

CLINICAL USE: ANTIDEPRESSANT

48. Etilerfin [709-55-7]

TRADE NAME:
- EFFORTIL (BOEHRINGER INGELHEIM)

CLINICAL USE:
- ADRENERGIC
- DOPAMINERGIC
- ANTIHYPERTENSIVE
49. DEPRENYL [2323-36-6]

TRADE NAME: ELDEPRYL (ORION)
SELEGILIN (NM PHARMA)

CLINICAL USE: ANTIPARKINSON

50. EPIRUBICIN [56390-09-1(HCl), 56420-45-2(BAS)]

TRADE NAME: FARMORUBICIN
(PHARMACIA & UPJOHN)

CLINICAL USE: ANTINEOPLASTIC
ANTIBIOTIC

51. FLUPENTIXOL [2709-56-0]

TRADE NAME: FLUANXOL
(LUNDBECK)

CLINICAL USE: ANTIPOWERGESIC

52. BENOXINATE [99-43-4]

TRADE NAME: FLURESS (ABIGO)
OXIBUROKAIN (MEDA)

CLINICAL USE: ANAESTHETIC (TOPICAL)
53. **FLUOXETIN [54910-89-3]**

![Fluoxetine chemical structure]

**Trade Name:** Fontex (Lilly)
**Clinical Use:** Antidepressant

54. **GEMCITABINE []**

![Gemcitabine chemical structure]

**Trade Name:** Gemzar (Lilly)
**Clinical Use:** Antineoplastic

55. **ADRENALINE/EPINEPHRINE []**

![Adrenaline chemical structure]

**Trade Name:** Citanest Adrenalin (Astra)
Eppy (Abigo)
Glaufrin (Allergan)
Marcaid Adrenalin (Astra)
Xylocain Adrenalin (Astra)

**Clinical Use:** Adrenergic

56. **METFORMIN [657-24-9]**

![Metformin chemical structure]

**Trade Name:** Glucophage (Meda)

**Clinical Use:** Antidiabetic
57. CHLORPROMAZINE [50-53-3]

TRADE NAME: HIBERNAL
(ROHNE-POULENE RORER)
CLINICAL USE: ANTI-EMETIC,
TRANQUILIZER,
SEDATIVE

58. PRENALTEROL [57526-81-5]

TRADE NAME: HYPRENAN (HASSELE)
CLINICAL USE: ADRENERGIC

59. TERAZOSINE [63590-64-7, 70024-40-7 (HYDROCHLORIDE)]

TRADE NAME: HYTRINEX (ASTRA),
SINALFA (SINALFA ABBOTT)
CLINICAL USE: ANTIHYPERTENSIVE

60. OXYMETAZOLINE [1491-59-4]

TRADE NAME: LLIADIN (MEDA),
NASIN (TIKA),
NEZERIL (DRACO),
ZOLIN (ACO)
CLINICAL USE: ADRENERGIC
61. LOPERAMIDE [53179-11-6]

TRADE NAME: IMODIUM (JENSSEN-CILAG)
LOPERAMID (SCAND PHARM)
PRIMODIUM (JENSSEN-CILAG)
TRAVELLO (PHARMACIA & UPJOHN)

CLINICAL USE: ANTI DIARETIC

62. PROPRANOLOL [525-66-6]

TRADE NAME: INDERAL (ZENECA)
PROPRANOLOL (NM PHARMA)

CLINICAL USE: ß-ADRENERGIC BLOCKER
ANTIARRHYTHMIC

63. LIDOCAINE [137-58-6]

TRADE NAME: DEPO - MEDROL (PHARMACIA & UPJOHN); EMLA (ASTRA)
INSTILLAGEL (ELLEM)
LEDERSPAN (LEDERLE)
XYLOCAIN (ASTRA)
XYLOCARD (ASTRA)
XYLOPROCT (ASTRA)

CLINICAL USE: LOCAL ANAESTHETIC

64. APRACLONIDINE [66711-21-5]

TRADE NAME: LOPIDINE (ALCON)

CLINICAL USE: TREATMENT OF POSTSURGICAL ELEVATED INTRAOCULAR PRESSURE
65. VERAPAMIL [52-53-9]

TRADE NAME: ISOPTIN (MEDA)
VERALOC (ORION)
VERAPAMIL (NM PHARMA)

CLINICAL USE: ANTIARRHYTHMIC
VASODILATOR

66. PILOCARPINE [92-13-7]

TRADE NAME: FOTIL (LEIRAS)
ISOPTO - PILOKARPIN (ALCON)
LICARPIN (ALLERGAN)
PILOKARPIN (MEDA)
SPERSACARPINE (CIBA)
TIMPILO (MSD)

CLINICAL USE: ANTIGLAUCOMA
CHOLINERGIC

67. PROCYCLIDINE [77-37-2]

TRADE NAME: KEMADRIN
(GLAXO WELLCOME)

CLINICAL USE: ANTIPARKINSON

68. KETAMINE [6740-88-1]

TRADE NAME: KETALAR (PARKE-DAVIS)

CLINICAL USE: GENERAL ANAESTHETIC
69. KETOBEMIDON

TRADE NAME: KETOGAN (NOVUM-LUNDBECK)
CLINICAL USE: ANALGETIC, SPASMOLYTIC

70. QUINIDINE [130-95-0, 60-93-5(HYDROCHLORIDE)]

TRADE NAME: KININ (NM PHARMA)
CLINICAL USE: ANTIMALARIAL

71. GRANISETRONE [109889-09-0, 107007-99-8(HYDROCHLORIDE)]

TRADE NAME: KYTRIL (SMITH KLINE BEECHAM)
CLINICAL USE: ANTIEMETIC

72. MEFLOQUIN [51773-92-3(HYDROCHLORIDE)]

TRADE NAME: LARIAM (ROCHE)
CLINICAL USE: ANTIMALARIAL
<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Trade Name</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Promethazine</strong></td>
<td>Lergigan (Recip)</td>
<td>Antihistamine</td>
</tr>
<tr>
<td><strong>Remoxipride</strong></td>
<td>Roxiam (Astra)</td>
<td>Neuroleptic</td>
</tr>
<tr>
<td><strong>Lincomycin</strong></td>
<td>Lincocin (Upjohn)</td>
<td>Antibiotic</td>
</tr>
<tr>
<td><strong>Levocabastin</strong></td>
<td>Livostin (JenSsen-Cilag)</td>
<td>H₂-antagonist</td>
</tr>
</tbody>
</table>
77. AMOROLFINE [78613-35-1, 78613-38-4(HYDROCHLORIDE)]

TRADE NAME: LOCERYL (ROCHE)
CLINICAL USE: ANTIMYCOTIC

78. MAPROTLINE [10260-69-8]

TRADE NAME: LUDIOMIL (CIBA)
MAPROTLIN (NM PHARMA)
CLINICAL USE: ANTIDEPRESSANT

79. BENSERAZIDE [322-35-0]

TRADE NAME: MADOPARK (ROCHE)
CLINICAL USE: ANTIPARKINSON DOPAMINERGIC

80. THIORIDAZINE [50-52-2]

TRADE NAME: MALLOROL (SANDOZ)
CLINICAL USE: NEUROLEPTIC
81. CYCLIZINE [82-92-8]

TRADE NAME: MARZINE (GLAXO WELLCOME)
CLINICAL USE: ANTIHISTAMINE ANTIEMETIC

82. CEPHEPIME []

TRADE NAME: MAXIPIME (BRISTOL-MEYERS SQUIBB)
CLINICAL USE: ANTIBIOTIC

83. METHADONE [1095-90-5]

TRADE NAME: METADON (PHARMACIA & UPJOHN)
CLINICAL USE: NARCOTIC ANALGETIC

84. MEXILETINE [31828-71-4]

TRADE NAME: MEXITIL (BOEHRINGER INGELHEIM)
CLINICAL USE: ANTIARRHYTHMIC
85. MIANSERIN [24219-97-4]

TRADE NAME: MIANSERIN (NM PHARMA)
TOLVON (ORGANON)
CLINICAL USE: ANTIDEPRESSANT

86. PIVMECILLINAM []

TRADE NAME: MIRAXID (LOVENS)
CLINICAL USE: ANTIBACTERIAL

87. PHENYLPROPAHOLAMINE [154-41-61]

TRADE NAME: LUNERIN (TIKA)
MONYDRIN (TIKA)
RINEXIN (RECIPI)
RINOMAR (RECIPI)
CLINICAL USE: VASOCONSTRUCTIVE
ADRENERGIC

88. MORPHINE [52-27-2]

TRADE NAME: DOLCONTIN
(PHARMACIA & UPJOHN)
LOCEPTIN (NYCOMED)
MAXIDON (ASTRA)
MORFIN
(PHARMACIA & UPJOHN)
SPASMOFEN (ABIGO)
CLINICAL USE: NARCOTIC
ANALGESIC
89. ETHAMBUTOL [304-84-7]

\[
\text{CH}_3\text{CH}_2\text{CHNHCH}_2-\text{CH}_2\text{NHCHCH}_2\text{CH}_2\text{OH}
\]

TRADE NAME: MYAMBUTOL (LEDERLE)
CLINICAL USE: TUBERCULOSTATIC

90. AMBENONIUM CHLORIDE [115-79-7]

\[
\text{CONHCH}_2\text{CH}_2\text{N}^+\text{CH}_2\text{CH}_3
\]

TRADE NAME: MYTELASE (SANOFI WINTHROP)
CLINICAL USE: CHOLINESTERASE INHIBITOR

91. NALOXONE [465-65-6]

\[
\text{HO}
\]

TRADE NAME: NARCANTI (MEDA)
CLINICAL USE: ANTAGONIST (TO NARCOTICS)

92. XYLOMETAZOLINE [526-36-3]

\[
\text{H}_2\text{C}\text{CH}_2\text{N}(\text{H})_3
\]

TRADE NAME: NASOGERM (NORDIC) OTRIVIN (CIBA)
CLINICAL USE: ADRENERGIC VASOCONSTRICCTOR
93. PROCARBAZINE [671-16-9]

\[
\text{N} \quad \text{O} \quad \text{CONHCH(CH}_3\text{)}_2
\]

TRADE NAME: NATULANAR (ROCHE)
CLINICAL USE: ANTINEOPALSTIC

94. TROPISETRONE []

TRADE NAME: NAVOBAN (SANDOZ)
CLINICAL USE: ANTIEMETIC

95. PHENYLEPHRINE [61-76-7(HYDROCHLORIDE)]

TRADE NAME: BLEFCON (ALLERGAN)
ISOPTO-BIOTIC (ALCON)
METAOXEDRIN (MEDA)
NEOSYNEPHRINE (SANOFI WINTHROP)
ZINCFRIN (ALCON)
CLINICAL USE: ADRENERGIC

96. THIAMINE [67-03-8]

TRADE NAME: ASTRATONIL FORTE (ASTRA)
BETABION (MEDA)
CLINICAL USE: ENZYME
CO-FACTOR-VITAMIN B1
97. TRAMADOL [27203-92-5, 22204-88-2(HYDROCHLORIDE)]

TRADE NAME: NOBLIGAN (SEARLE)
CLINICAL USE: ANALGESIC

98. HYDROCHLOROTHIAZIDE [58-93-5]

TRADE NAME: SPARKAL (SELENA)
TRIATEC COMP (HOECHST)
AMILOFERM (NORDIC)
CLINICAL USE: DIURETIC

99. QUINAGOLIDE []

TRADE NAME: NORPROLAC (SANDOZ)
CLINICAL USE: PROLACTIN ANTAGONIST

100. NOSCAPINE [128-62-1, 912-60-7(HYDROCHLORIDE)]

TRADE NAME: NIPAXON (PHARMACIA & UPJOHN)
NOSKAPIN (ACO)
SPAMOFEN (ABIGO)
CLINICAL USE: ANTITUSCIVE
101. MITOXANTRONE [65271-80-90, 76476-82-3(HYDROCHLORIDE)]

OH  O  NHCH₂CH₂NHCH₂CH₂OH
    O  NHCH₂CH₂NHCH₂CH₂OH

TRADE NAME: NOVANTRONE (LEDERLE)
CLINICAL USE: ANTINEOPALSTIC

102. DIPIVEFRIN [52365-63-6, 64019-93-8(HYDROCHLORIDE)]

(CH₃)₂CCOO  (CH₃)₂CCOO
     CHCH₂NHCH₃  OH

TRADE NAME: OFTAPINEX (LEIRAS)
PROPINE (ALLERGAN)
CLINICAL USE: ANTI-GLAUCOMA
ADRENERGIC

103. OXYTETRACYCLINE [79-57-2, 2058-46-0(HYDROCHLORIDE)]

OH  O  OH  O  CONH₂
    OH  H  H  NCH₃
    HO  CH₃  H  CH₃

TRADE NAME: OXYTETRAL (DUMEX)
TERRACORTIL (PFIZER)
TERRAMYCIN (PFIZER)
CLINICAL USE: ANTIBIOTIC

104. FLUPHENAZINE [69-23-8, 146-56-5(HYDROCHLORIDE)]

S
CH₂CH₂CH₂-N  N-CH₂CH₂OH

TRADE NAME: PACINOL (SCHERING-PLOUGH)
SQUALONE (BRISTOL MEYERS-SQUIBB)
CLINICAL USE: ANTIPSYCHOTIC
105. CHLORGUANIDE [500-92-5]

TRADE NAME: PALUDRINE (ZENECAL)
CLINICAL USE: ANTIMALARIAL

106. TRIHEXYPHENIDYL [52-49-3]

TRADE NAME: PARGITAN (ABIGO)
CLINICAL USE: ANTIPARKINSON

107. BACAMPICILLIN [50972-17-3, 37661-08-8(HYDROCHLORIDE)]

TRADE NAME: PENGLOBE (ASTRA)
CLINICAL USE: ANTIBACTERIAL

108. CYPROHEPTADINE [129-03-3, 41354-29-4(HYDROCHLORIDE)]

TRADE NAME: PERIACTIN (MSD)
CLINICAL USE: H1 ANTAGONIST ANTIHISTAMINE
109. **PRAZOSIN** [19216-56-9, 19237-84-4(HYDROCHLORIDE)]

![Prazosin Chemical Structure]

**Trade Name:** PERIPRESS (PFIZER)

**Clinical Use:** α1-ADRENERGIC BLOCKER
ANTIHYPERTENSIVE

110. **MEPERIDINE** [57-42-1, 50-13-5(HYDROCHLORIDE)]

![Mepерidine Chemical Structure]

**Trade Name:** PETIDIN (PHARMACIA & UPJOHN)

**Clinical Use:** NARCOTIC
ANALGETIC

111. **MECLIZINE** [569-65-3, 31884-77-2(HYDROCHLORIDE)]

![Meclizine Chemical Structure]

**Trade Name:** HISTILOS (UCB)
POSTAFEN (UCB)

**Clinical Use:** ANTIEMETIC

112. **METOCLOPRAMIDE** [364-62-5, 54143-57-6(HYDROCHLORIDE)]

![Metoclopramide Chemical Structure]

**Trade Name:** PRIMPERAN (LUNDBECK)

**Clinical Use:** ANTIEMETIC
113. **PROCAINAMIDE** [614-39-1]

H₂N—CONHCH₂CH₂N(CH₂CH₃)₂

**TRADE NAME:** PROKAINAMID (HASSLE)

**CLINICAL USE:** ANTIARRHYTHMIC

114. **PYRIDOXINE** [58-56-0]

CH₃

HOCH₂

OH

CH₂OH

**TRADE NAME:** ASTRANOIL FORTE (ASTRA)

**CLINICAL USE:** VITAMIN B6

115. **ALFENTANIL** [71195-28-6, 70879-28-6(HYDROCHLORIDE)]

CH₃CH₂

O

N N

CH₂CH₂—N

CH₂OCH₃

N—COCH₂CH₃

**TRADE NAME:** RAPIFEN (JENSSSEN-CILAG)

**CLINICAL USE:** NARCOTIC ANALGESIC

116. **NAPHAZOLINE** [835-31-4, 550-29-2(HYDROCHLORIDE)]

**TRADE NAME:** ANTASTEN-PRIVIN (CIBA VISION)

RIMIDOL (UCB)

**CLINICAL USE:** ADRENERGIC (VASOCONSTRICTOR)

DECONGESTANT
117. METHACYCLINE [914-00-1, 3963-85-9(HYDROCHLORIDE)]

TRADE NAME: RONDOMYCIN (ROERIG)
CLINICAL USE: ANTIBACTERIAL

118. ROXATIDINE []

TRADE NAME: ROXIT (HOECHST)
CLINICAL USE: ANTI-ULCERATIVE

119. PROPafenone [54063-53-5, 34183-22-7(HYDROCHLORIDE)]

TRADE NAME: RYTMONORM (MEDA)
CLINICAL USE: ANTIARRHYTHMIC

120. AMITRIPTYLINE [50-48-6, 549-18-8(HYDROCHLORIDE)]

TRADE NAME: SAROTEN (LUNDBECK)
TRYPTIZOL (MSD)
CLINICAL USE: ANTIDEPRESSANT
121. Nortriptyline [72-69-5, 894-71-3 (Hydrochloride)]

| TRADE NAME: | SENSAVAL (LUNDBECK) |
| CLINICAL USE: | ANTIDEPRESSANT |

122. Paroxetine [61869-08-7]

| TRADE NAME: | SEROXAT (NOVO NORDISK) |
| CLINICAL USE: | ANTIDEPRESSANT |

123. Clobutinol [14860-49-2]

| TRADE NAME: | SIOMAT (BOEHRINGER INGELHEIM) |
| CLINICAL USE: | ANTIITUSSIVE |

124. Sotalol [3930-20-9, 959-24-0 (Hydrochloride)]

| TRADE NAME: | SOTACOR (BRISTOL-MEYERS SQUIBB) SOTALOL (NM PHARMA) |
| CLINICAL USE: | ANTIANGINAL ANTIARRHYTHMIC ANTIHYPERTENSIVE |
125. **BUPRENORPHINE** [52485-79-7, 53152-21-9(HYDROCHLORIDE)]

![Chemical Structure of Buprenorphine]

**TRADE NAME:** TEMGESIC (MEDA)
**CLINICAL USE:** ANALGESIC

126. **TETRACAINE** [136-47-0]

![Chemical Structure of Tetracaine]

**TRADE NAME:** TETRACAIN (ALCON)
**CLINICAL USE:** ANAESTHETIC (TOPICAL)

127. **TICLOPIDINE** [55142-85-3, 53885-31-1(HYDROCHLORIDE)]

![Chemical Structure of Ticlopidine]

**TRADE NAME:** TICLID (SANOFI WINTHROP)
**CLINICAL USE:** PLATELET AGGREGATION INHIBITOR

128. **TOCAINIDE** [41708-72-9]

![Chemical Structure of Tocainide]

**TRADE NAME:** TONOCARD (HÄSSLE)
**CLINICAL USE:** ANTIARRHYTHMIC
129. **OBIDOXIME CHLORIDE** [114-90-9]

\[
\text{HON=CH-} \begin{array}{c}
\text{N}^+ \text{-CH}_2 \\
\text{O} \\
\text{HON=CH-} \\
\text{N}^+ \text{-CH}_2
\end{array}
\]

**TRADE NAME:** TOXOGONIN (MEDA)

**CLINICAL USE:** CHOLINESTERASE REACTIVATOR

130. **IMIPRAMINE** [50-49-7, 113-52-0(HYDROCHLORIDE)]

\[
\text{CH}_2\text{CH}_2\text{CH}_2\text{N(CH}_3\text{)}_2
\]

**TRADE NAME:** TOFRANAL (CIBA)

**CLINICAL USE:** ANTIDEPRESSANT

131. **LABETALOL** [36894-69-6, 32780-64-6(HYDROCHLORIDE)]

\[
\text{H}_2\text{NCO} \ 	ext{OH} \ 	ext{CH}_3 \\
\text{HO-CHCH}_2\text{NHCHCH}_2\text{CH}_2
\]

**TRADE NAME:** TRANDATE (GLAXO WELLCOME)

**CLINICAL USE:** ANTIHYPERTENSIVE

132. **METHIZENE** [4969-02-2, 7081-4-5(HYDROCHLORIDE)]

\[
\text{S} \\
\text{H}_2\text{C-} \begin{array}{c}
\text{N} \\
\text{CH}_3
\end{array}
\]

**TRADE NAME:** TREMOQUIL (ASTRA)

**CLINICAL USE:** ANTICHOLINERGIC ANTI-PARKINSON
133. SPECTINOMYCIN [1695-77-8, 22189-32-3(HYDROCHLORIDE)]

TRADE NAME: TROVICIN (PHARMACIA & UPJOHN)
CLINICAL USE: ANTIBIOTIC

134. DORZOLAMIDE []

TRADE NAME: TRUSOPT (MSD)
CLINICAL USE: ANTIGLAUCOMA, CARBONIC ANHYDRASE ANTAGONIST

135. CHLORPROTHIXENE [113-59-7]

TRADE NAME: TRUXAL (LUNDBECK)
CLINICAL USE: ANTIPSYCHOTIC

136. LOFEPRAMINE [23047-25-8, 26786-32-3(HYDROCHLORIDE)]

TRADE NAME: TYMELYT (LUNDBECK)
CLINICAL USE: ANTIDEPRESSANT
137. VALACIKLOVIR

TRADE NAME: VALTREX (GLAXO WELLCOME)
CLINICAL USE: ANTIVIRAL AGENT

138. VANCOMYCIN [1404-90-6, 1404-93-09 (HYDROCHLORIDE)]

TRADE NAME: VANCOCIN (LILLY)
VANCOMYCIN (DUMEX)
VANCOMYCIN (NORCOX)
CLINICAL USE: ANTIBACTERIAL

139. AMANTADINE [768-94-5, 665-66-7 (HYDROCHLORIDE)]

TRADE NAME: VIROFRAIL (FERROSAN)
CLINICAL USE: ANTIVIRAL (INFLUENZA A)

140. ALFLUZOSINE []

TRADE NAME: XATRAL (ASTRA)
CLINICAL USE: α1-RECEPTOR ANTAGONIST
141. IDARUBICIN

TRADE NAME: ZAVEDOS
(PHARMACIA & UPJOHN)
CLINICAL USE: CYTOSTATIC

142. ONDANSETRON [99614-02-5, 99614-01-4 (HYDROCHLORIDE)]

TRADE NAME: ZOFTRAN
(GLAXO WELLCOME)
CLINICAL USE: ANTIEMETIC

143. CETIRIZINE [83881-51-0, 83881-52-1 (HYDROCHLORIDE)]

TRADE NAME: ZYRLEX (UCB)
CLINICAL USE: ANTIHISTAMINE
It is to be understood that the invention is not limited to the features and embodiments hereinabove specifically set forth, but may be carried out in other ways without departure from its spirit.
What is claimed is:

1. A method of administering to a human patient material selected from the group consisting of acid addition salts of compounds that can form acid salts of Formula (A) having a tertiary nitrogen present, acid addition salts of compounds that can form acid salts of Formula (B) having a quaternary ammonium ion present, and mixtures thereof, said Formula (A) and Formula (B) being as follows:

\[
\begin{align*}
R_1-(CH_2)_n-N^+R_2 & \quad (A) \\
R_2 & \quad (B)
\end{align*}
\]

wherein \( R_1 \) comprises an aryl or alkyl group with a hydrogen bond acceptor site accessible to interaction with said tertiary nitrogen of Formula (A) or said quaternary ammonium ion of Formula (B), \( R_2, R_3 \), and \( R_4 \) and alkyl or aryl groups, and \( X^- \) is an anion, said method comprising the steps of (a) providing a sterile injectable formulation comprising a liquid vehicle containing the material in solution, at a pH within a range of about 5.5 to 7.0, and
(b) injecting the formulation into the patient in an amount for delivering to the patient a dose of about one to 100 mg/kg of the material while the pH of the formulation is within said range.

2. A method according to claim 1, wherein said hydrogen bond acceptor site is a carbonyl or carboxylic oxygen atom.

3. A method according to claim 1, wherein $X^-$ is Cl⁻, F⁻, Br⁻ or I⁻.

4. A method according to claim 1, wherein said material is selected from the group consisting of nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics and anaesthetics which are acid addition salts of compounds that can form acid salts of Formula (A), acid addition salts of compounds that can form acid salts of Formula (B), and mixtures thereof.

5. A method according to claim 1, wherein said formulation is provided at a concentration of about 100 to 7000 mg/ml.

6. A method according to claim 1, wherein the injecting step comprises injecting the formulation intramuscularly into the patient.

7. A sterile injectable formulation for intramuscular administration to a human patient, comprising
(a) a material selected from the group consisting of acid addition salts of compounds that can form acid salts of Formula (A) having a tertiary nitrogen present, acid addition salts of compounds that can form acid
salts of Formula (B) having a quaternary ammonium ion present, and mixtures thereof, said Formula (A) and Formula (B) being as follows:

\[
\begin{align*}
\text{(A)} & \quad \begin{array}{c}
\text{H} \\
R_1-(\text{CH}_2)_n \quad \text{N}^+ \quad R_2 \\
\text{R}_3
\end{array} \\
\text{(B)} & \quad \begin{array}{c}
\text{R}_2 \quad \text{X}^- \\
R_1-(\text{CH}_2)_n \quad \text{N}^+ \quad \text{R}_3 \\
\text{R}_4
\end{array}
\end{align*}
\]

wherein \( R_1 \) comprises an aryl or alkyl group with a hydrogen bond acceptor site accessible to interaction with said tertiary nitrogen of Formula (A) or said quaternary ammonium ion of Formula (B), \( R_2, R_3 \) and \( R_4 \) are alkyl or aryl groups, and \( X^- \) is an anion;

(b) a liquid vehicle in which said material is in solution;

(c) said material being present in said formulation in a concentration of at least about 50 mg/ml, and

(d) the formulation being at a pH within a range of about 5.5 to 7.0.

8. A formulation as defined in claim 7, wherein said material is selected from the group consisting of nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics and anaesthetics which are acid addition salts of compounds that can form acid salts of Formula (A), acid addition salts of compounds that can form acid salts of Formula (B), and mixtures thereof.
9. A formulation as defined in claim 7, also including an amount of a buffer or preservative effective to stabilize the pH of the formulation.

10. A formulation as defined in claim 9, including an amount of a phosphate buffer effective to stabilize the pH of the formulation to a range of less than 0.5 pH unit.

11. A formulation as defined in claim 9, including an amount of sodium metabisulfite effective to stabilize the pH of the formulation to a range of less than 0.5 pH unit.

12. A method of administering to a human patient material selected from the group consisting of acid addition salts of compounds that can form acid salts of Formula (A) having a tertiary nitrogen present, acid addition salts of compounds that can form acid salts of Formula (B) having a quaternary ammonium ion present, and mixtures thereof, said Formula (A) and Formula (B) being as follows:

\[
\begin{align*}
\text{H} & \quad X^- \\
R_1-(CH_2)_n-N^+ & \quad R_2 \\
R_3 &
\end{align*}
\]

(A)

\[
\begin{align*}
R_2 & \quad X^- \\
R_1-(CH_2)_n-N^+ & \quad R_3 \\
R_4 &
\end{align*}
\]

(B)
wherein R₁ comprises an aryl or alkyl group with a hydrogen bond acceptor site accessible to interaction with said tertiary nitrogen of Formula (A) or said quaternary ammonium ion of Formula (B), R₂, R₃ and R₄ are alkyl or aryl groups, and X⁻ is an anion, said method comprising the steps of
(a) providing a sterile formulation, comprising a liquid vehicle containing the material in solution,
(b) adjusting the pH of said formulation for reducing the development of undesirable side effects of the material, and
(c) administering the formulation having the adjusted pH to the patient.

13. A method according to claim 12, wherein said material is selected from the group consisting of nicotinamides, benzamides, calcium antagonists, antiemetics, antipsychotics and anaesthetics which are acid addition salts of compounds that can form acid salts of Formula (A), acid addition salts of compounds that can form acid salts of Formula (B), and mixtures thereof.

14. A method of administering to a human patient material selected from the group consisting of acid addition salts of malphalan, amiloride, clomipramine, chlorcyclizine, hydralazine, alpenolol, dopamine, quinapril, tetracycline, cimetidine, doxorubicin, biperiden, carteolol, ranitidine, hydroxyzine, chlortetracycline, bambuterol, diphenhydramine, betaxolol, bromhexine, phenylephrine, bupivacaine, melperone, buspirone, mepivacaine, diltiazem, clonidine, succinylcholine, daunorubicin, ciprofloxacin, clopenthixol, prilocaine, ethylmorphine, tacrine, protriptyline, amiodarone, cyclophentolate, clindamycin, propoxyphene, hydromorphone, orphenadrine, dobutamine, dopexamine, doxycycline, neomycin, ephedrine, venlafaxine, etilefrin, deprenyl, epirubicin,
flupentixol, benoxinate, fluoxetine, gemcitabine, adrenaline, metformin,
chlorpromazine, prenalterol, terazosine, oxymetazoline, loperamide,
propanolol, lidocaine, apraclonidine, verapamil, pilocarpine, procyclidine,
ketamine, ketobemidon, quinidine, granisetron, mefloquin, promethazine,
remoxipride, lincomycin, levocabastin, amorolfine, maprotiline, benserazide,
thioridazine, cyclizine, cephepime, methadone, mexiletine, mianserin,
pivmecillinam, phenylpropanolamine, morphine, ethambutol, ambenonium,
naloxone, xylometazoline, procarbazine, tropisetron, phenytoin, thiamine,
tramadol, hydrochlorotiazid, quinagolide, noscapine, mitoxantrone, dipivefrin,
oxytetracycline, fluphenazine, chlorguanide, trihexyphenidyl, bacampicillin,
cyproheptadine, prazosin, meperidine, meclizine, metoclopramide,
procainamide, pyridoxine, alfentanil, naphazoline, methacycline, roxatidine,
propafenone, amitriptyline, nortriptyline, paroxetine, clobutinol, sotalol,
buprenorphin, tetracaine, ticlopidine, tocainide, obidoxime, imipramine, labetalol,
methixene, spectinomycin, dorzolamide, chlorprothixene, lefepramine
valaciclovir, vancomycin, amantadine, alfluzosine, idarubicin, ondansetron,
cetirizine, 3-chloro procainamide, N-(2-diethylamino-ethyl) nicotinamide,
nimorazole and 2,3-dimethyl(dimethylaminoethyl)-5H-indolo-2,3-b) guinoxline
and mixtures thereof, said method comprising the steps of

(a) providing a sterile injectable formulation comprising a liquid vehicle
containing the material in solution, at a pH within a range of about 5.5 to
7.0, and

(b) injecting the formulation into the patient in an amount for delivering to
the patient a dose of about one to 100 mg/kg of the material while the pH
of the formulation is within said range.
15. A method according to claim 14, wherein the injecting step comprises injecting the formulation intramuscularly into the patient.

16. A sterile injectable formulation for intramuscular administration to a human patient, comprising

(a) a material selected from the group consisting of acid addition salts of malphalan, amiloride, clomipramine, chlorcyclizine, hydralazine, alpenolol, dopamine, quinapril, tetracycline, cimetidine, doxorubicin, biperiden, carteolol, ranitidine, hydroxyzine, chlortetracycline, bambuterol, diphenhydramine, betaxolol, bromhexine, phenylephrine, bupivacaine, melperone, buspirone, mepivacaine, diltiazem, clonidine, succinylcholine, daunorubicin, ciprofloxacin, clopenthixol, prilocaine, ethylmorphine, tacrine, protriptyline, amiodarone, cyclopentolate, clindamycin, propoxyphene, hydromorphone, orphenadrine, dobutamine, dopexamine, doxycycline, neomycin, ephedrine, venlafaxine, etilefrin, deprenyl, epirubicin, flupentixol, benoxinate, fluoxetine, gemcitabine, adrenaline, metformin, chlorpromazine, prenalterol; terazosine, oxymetazoline, loperamide, propanolol, lidocaine, apraclonidine, verapamil, pilocarpine, procyclidine, ketamine, ketobemidon, quinidine, granisetron, mefloquin, promethazine, remoxipride, lincomycin, levocabastin, amorolfine, maprotiline, benzerazide, thioridazine, cyclizine, cephepime. methadone, mexiletine, mianserin, pivmecillinam, phenylpropanolamine, morphine, ethambutol, ambenonium, naloxone, xylometazoline, procarbazine, tropisetrone, phenyephrine; thiamine, tramadol, hydrochlorotiazid, quinagolide, noscapine, mitoxantrone, dipivefrin, oxytetracycline, fluphenazine,
chlordiazepoxide, trihexyphenidyl, bacampicillin, cyproheptadine, prazosin,
meperidine, meclizine, metoclopramide, procainamide, pyridoxine,
alfentanil, naphazoline, methacycline, roxatidine, propafenone,
amitriptyline, nortriptyline, paroxetine, ciobutinol, sotalol,
buprenorphin, tetracaine, ticlopidine, tocainide, obidoxime, imipramine,
labetalol, methixene, spectinomycin, dorzolamide, chloroprothixene,
lefepramine, valaciclovir, vancomycin, amantadine, alfluzosine,
idarubicin, ondansetron, cetirizine, 3-chloro procainamide, N-(2-
diethylamino-ethyl) nicotinamide, nimorazole and 2,3-dimethyl-
(dimethylaminoethyl)-5H-indolo-2,3-b) guinoxline and mixtures thereof.
(b) a liquid vehicle in which said material is in solution,
(c) said material being present in said formulation in a concentration of at
least about 50 mg/ml, and
(d) the formulation being at a pH within a range of about 5.5 to 7.0.

17. A method of administering to a human patient material selected from
the group consisting of acid addition salts of malphalan, amiloride, clomipramine,
chlorcyclizine, hydralazine, alprenolol, dopamine, quinapril, tetracycline,
cimetidine, doxorubicin, biperiden, carteolol, ranitidine, hydroxyzine,
chlorotetracycline, bambuterol, diphenhydramine, betaxolol, bromhexine,
phenylephrine, bupivacaine, melperone, buspirone, mepivacaine, diltiazem,
clonidine, succinylcholine, daunorubicin, ciprofloxacin, clopenthixol, prilocaine,
ethylmorphine, tacrine, protriptyline, amiodarone, cyclopentolate, clindamycin,
propoxyphene, hydromorphone, orphenadrine, dobutamine, dopexamine,
doxycycline, neomycin, ephedrine, venlafaxine, etilefrin, deprenyl, epirubicin,
flupentixol, benoxinate, fluoxetine, gemcitabine, adrenaline, metformin,
chloropromazine, prenalterol, terazosine, oxymetazoline, loperamide,
propanolol, lidocaine, apraclonidine, verapamil, pilocarpine, procyclidine,
ketamine, ketobemidon, quinidine, granisetron, mefloquin, prommethazine,
remoxipride, lincomycin, levocabastin, amorolfine, maprotiline, benserazide,
thioridazine, cyclazine, cephepime, methadone, mexiletine, mianserin,
pivmecillinam, phenylpropanolamine, morphine, ethambutol, ambenonium,
naloxone, xylometazoline, procarbazine, tropisetron, phenytoin, thiamine,
tramadol, hydrochlorothiazid, quinagolide, noscapine, mitoxantrone, dipivefrin,
oxytetracycline, fluphenazine, chlorguanide, trihexyphenidyl, bacampicillin,
cyproheptadine, prazosin, meperidine, meclizine, metoclopramide,
procainamide, pyridoxine, alfentanil, naphazoline, methacycline, roxatidine,
propafenone, amitriptyline, nortriptyline, paroxetine, clobutinol, sotalol,
buprenorphin, tetracaine, ticlopidine, tocainide, obidoxime, imipramine, labetalol,
methixene, spectinomycin, dorzolamide, chloroprothixene, lefepramine,
valaciclovir, vancomycin, amantadine, alfuzosine, idarubicin, ondansetron,
cetirizine, 3-chloro procainamide, N-(2-diethylamino-ethyl) nicotinamide,
nimorazole and 2,3-dimethyl(dimethylaminoethyl)-5H-indolo-2,3-b) guinoxline
and mixtures thereof

(a) providing a sterile formulation, comprising a liquid vehicle containing the
material in solution,

(b) adjusting the pH of said formulation for reducing the development of
undesirable side effects of the material, and

(c) administering the formulation having the adjusted pH to the patient.
A. CLASSIFICATION OF SUBJECT MATTER
   IPC(6): A61K 38/16, 31/13, 31/135, 31/14, 31/155, 31/16, 31/165, 31/18
   US Cl.: Please See Extra Sheet.

B. FIELDS SEARCHED
   Minimum documentation searched (classification system followed by classification symbols)

   Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

   Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
   CAS ON-LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US 4,536,386 A (KEENAN) 20 August 1985, see entire document.</td>
<td>1-13</td>
</tr>
<tr>
<td>Y</td>
<td>US 5,260,289 (HYODO ET AL.) 09 November 1993, see entire document.</td>
<td>14-17</td>
</tr>
</tbody>
</table>

□ Further documents are listed in the continuation of Box C. □ See patent family annex.

* Special categories of cited documents.
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier document published on or after the international filing date
  "L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed
  "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  "Z" document member of the same patent family

Date of the actual completion of the international search: 06 AUGUST 1997
Date of mailing of the international search report: 03 SEP 1997

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks
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Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER:
US CL:
514/8, 24, 25, 34, 152, 210, 211, 217, 223.2, 225.5, 225.8, 31/195, 31/215, 31/22, 31/225, 31/275, 31/325, 31/34,
31/38, 31/40, 31/415, 31/44, 31/445, 31/47, 31/395, 31/495, 31/505, 31/51, 31/52, 31/535, 31/54, 31/55, 31/65,
325, 326, 327, 330, 331, 332, 338, 345, 397, 400, 401, 428, 432, 437, 452, 469, 471, 523, 530, 535, 546, 547, 567,
605, 614, 615, 619, 620, 626, 635, 643, 646-648, 651-6, 659, 662, 669

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.
514/8, 24, 25, 34, 152, 210, 211, 217, 223.2, 225.5, 225.8, 31/195, 31/215, 31/22, 31/225, 31/275, 31/325, 31/34,
31/38, 31/40, 31/415, 31/44, 31/445, 31/47, 31/395, 31/495, 31/505, 31/51, 31/52, 31/535, 31/54, 31/55, 31/65,
325, 326, 327, 330, 331, 332, 338, 345, 397, 400, 401, 428, 432, 437, 452, 469, 471, 523, 530, 535, 546, 547, 567,
605, 614, 615, 619, 620, 626, 635, 643, 646-648, 651-6, 659, 662, 669

Form PCT/ISA/210 (extra sheet)(July 1992)*