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Pharmacologies! use of 5-aminophthaloylhydrazide ; combination and application thereof

Pharmakologische Verwendung von 5-Amlnophthaloylhydrazide; Ihre Zusammensetzung und Anwendung

Usage pharmacologique du 5-aminophthaloylhydrazide; leurs combinaisons et applications

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(56) References cited:
EP-A-0 612 733
WO-A-82/00641
FR-A- 1 182 224
FR-A- 2 490 074
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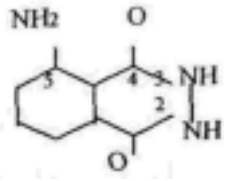
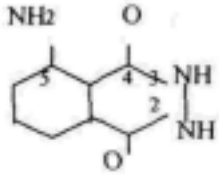
Description

[0001] The present invention refers to the use of 5-aminophtaloylhydrazide of the formula



and its pharmaceutically acceptable salts for the manufacture of a medicament.

[0002] The present invention pertains to indications of the pharmacological effectiveness of a significant group of compounds consisting of phtaloylhydrazide derivatives with the following general formula:



[0003] Certain derivatives of 5-aminophtaloylhydrazide have been used as chemical reagents in biochemical analysis. Practical applications for certain other derivatives, namely 2,3-dihydro-phtalazine, 1,4 dione, the sodium salt of 4-amino-2,3 dihydrophtalazine-l,2-dione, 4,3-diamono-2,3-dihydrophtalazine-l,2-dione have not been identified, nor have salts of the previsously indicated compounds been used.

[0004] In the FR-1 182224 phtaloylhydrazide derivatives are disclosed. In the FR-2 490 074 the use of phtaloylhydrazide derivatives as plant growing promoters is disclosed. In the WO-82 00641, finally, acyl derivatives of luminol or isoluminol are disclosed and its use in relation with a method in laboratory diagnostics of proteases.

[0005] Attempts to use 2,3-dihydrophtalazine-1,4-dione and certain derivatives for reducing serum cholesterol levels (J.H. Hall et al., "Effect of 2,3-diydrophtalazine-l,4-dion on Sprague-Dawley Rats' Lipid Metabolism and Serum Lipoproteins," Biomed. Biochem. Acta V,47 (4-5), pp.423-433, 1988) by modifying levels of lipids with extremely low densities have occurred.

[0006] It was determined, however, that this particular compound was relatively toxic when it was administered in doses of 20 mg/kg, although it did display an extremely high level of activity. Nevertheless, the anti-inflammatory and anticancer effects of derivatives belonging to this group of compounds have not been recognized and have not been described within medical literature.

[0007] For the first time, it has been possible to demonstrate phtaloylhydrazides'original and unique mode of action which, instead of emerging from analysis of their chemical properties, only became evident from in vivo administration of these compounds.

[0008] In the GB-1100911 certain phtalazine derivatives are disclosed which possess anti-inflammatory properties. Pharmacological testing of compounds belonging to the phtaloylhydrazide group and salts of these compounds allowed identification of 5-aminophtaloylhydrazide as the compound offering the most significant therapeutic effectiveness, and it is wholly non-toxic in situations where acceptable dosages are used.

[0009] Pharmacological testing of compounds belonging to the phtaloylhydrazide group and salts of these compounds allowed identification of 5-aminophtaloylhydrazide as the compound offering the most significant therapeutic effectiveness, and it is wholly non-toxic in situations where acceptable dosages are used.

[0010] Therefore, the present invention refers to the use of 5-aminophtaloylhydrazide and its pharmaceutically acceptable salts according to the wording of claim 1

[0011] The results of pharmacological and toxicological tests are provided subsequently.

Chemical Data:

[0012]

a. Physical Properties
5-aminophtaloylhydrazide is a pyridazine compound with an low molecular weight (less than 200). Its melting point is less than 250°C.
pH-solubility profile: pH *of 6.5,c=2mM*
pH of 7.4,c=12mM
The octanol/water distribution coefficient is pH dependent.
pH of 7.4,c=0.2

b. Chemical Properties
PH=6.3

[0013] Stability: this compound is stable under anhydrous conditions (storage period > 1 year). In some instances, however, it is unstable in aqueous solutions (probably on account of cooxidation with certain mixtures of substances which are present in trace quantities. Expiration period for aqueous solution > ten to twenty hours. Active rotation: absent /

Toxicological Data

[0014]

a: Acute Toxicity
Acute toxicity tests were performed upon two species (mice, rats). More than 80 mice and more than 100 rats were used. The drug was administered orally and parenterally in doses of 500 mg/kg to 2,500 mg/kg (individual doses). The observation period was fourteen days. Morphological alteration of hepatic, renal, cardiac, and cerebral tissue was not observed. Percentages of lethal outcomes within the test groups did not exceed the percentage for the control group.

b.Mutagenicity

Mutagenicity was measured by means of Ames' bacterial testing method. Tests were performed with TA 100, TA 102, and TA 97 S. typhistrains. The microsome activator method using rats' livers where induction had occurred with methylcolanthrene was adopted. The respective data indicated that 5-aminophtaloylhydrazide did not possess inhibitory or mutagenic activity at levels between 0.001 mg/ml and 2 mg/ml.

c. Toxicity in terms of Reproduction

Tests pertaining to teratogenicity and embryotoxicity were performed upon fifty-eight pregnant female rats. A single dose (60mg/kg) was injected intraperitoneally on the first, third , seventh, tenth, fourteenth, or seventeenth days of gestation. These rats were decapitated on the twenty-first day of gestation, and uteri and fetuses were examined. No fetal abnormalities were found. Uterine attachment locations, numbers, weights, and. fetal mortality levels did not differ from data obtained for the control group.

d. Cytotoxicity

The cells which were targeted were lymphocytes, macrophages, and fibroblasts. Survival after twenty-four hours of in vitro exposure to 5-amino-phtaloylhydrazide in concentrations of 0.001 mmol/liter to 0.8 mmol/liter was determined by means of protein incorporation and/or synthesis. No toxicity was observed for all of the dosage levels being tested.

The allergenic activity of this drug was examined with guinea pigs, and no indications of allergies were observed for subcutaneous or oral administration. Erythema was not encountered at the site of administration, even in the instance of large doses. Properties causing local irritation were not observed in situations where 20 mg to 100 mg doses had been administered.

Research concerning influence upon the Central Nervous System

[0015] Doses of 30 mg/kg an 60 mg/kg according to body weight were used for studying phannacological properties in relation to the central nervous system. Selection of this dosage level was based upon criteria in terms of safety in using drugs.

[0016] Neuropharmacological effects were studied in sexually mature male mice from unspecified strains. A solution of the drug was administered intraabdominally to these mice, with weights of 18.0 g to 20.0 g, and neuropharma-cological effects were studied in terms of changes in the natural orientation reflex, in induced aggressiveness, and in muscle tone. Changes in natural orientation were recorded according to current methods. For determining the drug's influence upon induced aggressiveness, the electrical stimulation method (an electrical current which caused pain was transmitted) was adopted.

[0017] Changes in muscle tone were measured according to the "pivot pin" method.

[0018] In doses of 30 mg/kg and 60 mg/kg according to body weight, this drug did not suppress the natural orientation reflex, did not alter the threshold for sensitivity to pain.

[0019] The influence of this particular drug upon the duration of general anesthesia induced by Hexenalum was also studied. In this instance, it was administered in 30 mg/kg an 60 mg/kg doses, fifteen minutes prior to administration of a Hexenalum solution in 80 mg/kg doses. With the doses which were being used, 5-aminophtaloyl-hydrazide did not produce a noteworthy prolongation of unconsciousness induced by Hexenalum.

[0020] When the anticonvulsive activity of the compound was investigated, it was determined that prior administration to mice in doses of 30 mg/kg an 60 mg/kg according to weight did not prevent convulsions caused by Corazolum and strychnine, which had been induced with intravenous titration of convulsive drugs. The convulsions which occurred were not reduced by the previously cited doses of 5-aminophtaloylhydrazide.

Research concerning the Effects of the Sodium Salt of5-aminophtaloylhydrazide upon the Cardiovascular System

[0021] The influence of the sodium salt of5-aminophtaloylhydrazide upon blood pressure was studied in male rats weighting from 230.0 g to 270.0 g, in a controled experiment where the rats were anesthetized with urethane. Blood pressure levels were tape-recorded, by means of an electrical kymograph.

[0022] At the same time, electrocardiograms for the second standard position were recorded, along with frequency and depth of breathing by means of a Morey capsule, 5-aminophtaloylhydrazide was administered through the femoral vein, in the form of an aqueous solution which prepared within a 2 percent sodium bicarbonate solution (pH=8.2), in doses of 30 mg/kg, 60 mg/kg and 50 mg/kg according to weight. Research concerning 5-aminophtaloylhydrazide was performed upon sixteen rats.

[0023] Results: Intravenous administration of a 1 percent 5-aminophtaloylhydrazide solution at a rate enhance use of the drug in question belongs to this particular category of products. [0056] The method of administering the drug in increasing doses, with an increased frequency of administration, where an interval of forty-eight to seventy-two hours is adopted initially, with subsequent daily administration, ensures inhibition of the expansion of malignant tumors. If the drug is combined with radiation therapy (total dose of 60 to 90 g), the effect upon its action is intensified. [0057] Among three patients to whom the drug was administered, favourable results represented by reduction of the dimensions of tumors and by an improvement in their general condition were observed.

[0058] In treating AIDS, which is currently incurable, daily administration of 5-aminophtaloyl-hydrazide in doses of 5 to 15 mg/kg according to weight is required for an extended period.

[0059] It was therefore possible to achieve significant prevention or reduction of complications associated with this serious disease, and, as a result, to extend patients'life-spans considerably. Standard doses used for treating inflammatory diseases were found to be of limited effectiveness in these situations.

Example 1 Experiments with piglets

[0060] Experiments were performed with piglets weighting from 30 to 40 kg, which were affected by dysentery.

[0061] During the first series of experiments, the sodium salt of5-aminophtaloylhydrozide was administered to nine piglets in a dose of 50 mg/kg. The animals'condition improved within sixty minutes after administration of the drug, and diarrhea ceased. Nevertheless, symptoms reappeared six to seven hours later in one group of animals. This factor rendered repeated administration of the drug necessary.

[0062] In the second series of experiments, involving sixteen animals with the same pathological condition, 5-aminophtaloylhydrazide was administered in doses of 20 and 50 mg/kg of body weight. Among this group, the therapeutic effects of 5-aminophtaloylhydrazide were only observed in six instances, and symptoms of dysentery reappeared at the end of the first day.

[0063] In the third series of experiments (twelve animals), 4-aminophtaloylhydrazide and 5-amino-phtaloylhydrazide were used in doses of 10, 25 and 50 mg/kg in order to treat diarrhea. The therapeutic effect of the drug was relatively insignificant, however.

[0064] In the fourth series of experiments, 5-aminophtaloylhydrazide an was administered to eight animals in doses of 50 mg/kg. The drug was of limited effectiveness in alleviating diarrhea, although its effects were observable at the first day after administration began. [0065] In the fifth series, a combined product consisting of the sodium salt of 5-aminophtaloyl-hydrazide mixed with 5-aminophtaloylhydrazide in 1:1 and 1:00.5 proportions was administered to eleven animals.

[0066] For 80 percent of the cases, a single administration of this compound was sufficient to relieve diarrhea and the accompanying symptoms two or three hours after administration. Changing the proportion of derivatives to 1:0.3 or 1:0.1 was not accompanied by therapeutic effects. Nevertheless, greater therapeutic effectiveness in treating animals affected by an acute intestinal infection was obtained when 5-aminophtaloylhy-drazide and its sodium salt were combined in a 1:1 proportion. On account of technical

difficulties, use of other combinations, such as a 1:2 proportion or a 2:1 proportion, was not considered.

Example 2

Treatment of proctosigmoiditis

[0067] Treatment was provided for nine patients affected by proctosigmoiditis; their ages were between forty and fifty-five years. These patients had complained of irregular defecation, protrusion of the mucosae from the anus, and minor pain in the ileum, on the left side.

[0068] During visual examination of the intestine, it was observed that the mucosae of the rectal and sigmoid portions of the colon were affected by edema. In addition, images of the capillary network were blurred, and a fibrous film was present within limited segments. The drug was administered to these patients in the form of rectal suppositories, in doses of 100 mg per day, subsequent to enemas. After initial administration of the drug, the previously cited symptoms and pain disappeared within one day, and the patients'sleep was undisturbed. By the seventh day, the patients no longer complained of symptoms. In RRS (rectosigmoidoscopy) procedures performed during checkups, renewal of normal conditions was observed within the rectal mucosae and within the sigmoid colon.

Example 3 Treatment of acute hemorrhoids

[0069] The drug was used in the form of suppositories in 0.1 g doses once daily, in order to treat acute hemorrhoids in patient whose ages were from twenty to sixty years. Seventeen to thirty minutes after insertion of the suppository into the anus, pain within the anal area ceased, and these patients were able to sleep undisturbed. Twelve hours later, significant shrinkage of the inflammatory process and reduction of edema in hemorrhoidal nodes was observed, while defecation ceased to be painful. By the fifth day, the inflammatory process and enlargement of hemorrhoidal nodes had entirely disappeared. The patients recovered fully. In contrast, treating acute hemorrhoids with previously known methods has required twenty-one days.

Example 3A

[0070] N., a male patient who was thirty-seven years of age, had been admitted to a clinic because he had complained of lethargy and continuous non-acute pain in the right hypochondrium. His medical background indicated that he was affected by hepatitis B of the viral type, which he had contracted eight months earlier. Objective analysis revealed scleral jaundice, and palpation of the abdomen was painful in the vicinity of the right hypochondrium. His liver had enlarged by 1.5 to 2 centimeters.

[0071] The reaction for bile pigments within urine was positive. Total bilirubin had increased one and one-half times, while ASt and ALt were two times the normal levels. Extensive alteration of the liver was observed during an ultrasound examination.

[0072} Rectal suppositories containing the drug, which was to be administered in doses of 100 mg per day for ten days, were prescribed for this patient. On the third day, the patient's condition improved, and his lethargy, as well as pain in the right hypochondrial area, disappeared. On the tenth day, biochemical blood data attained normal levels. The bile pigments reaction was negative. No pathological conditions affecting the liver were observed during an ultrasound examination.

[0073] Observation of the patient during the six subsequent months demonstrated an absence of chronic development of the process.

Example 4

Treatment of chronic anal fissures with pain syndrome

[0074] Treatment was provided for eleven patients who had been affected by the previously cited condition for more than two years and whose ages varied from twenty-seven to sixty years. Methods which had been employed prior to this point had failed to be effective. Examination was not possible on account of acute pain in the anus and intense spasms affecting the anal sphincter.

[0075] The drug was administered to this group of patients in the form of suppositories, in doses of 100 mg every twelve hours, during a five-day period. Pain ceased twenty to thirty minutes after initial administration of the suppositories, and the patients were able to sleep undisturbed. After administration of the third suppository, defecation became painless, and spasms affecting the sphincter diminished. By the fifth day, the patients had practically recovered. Digital examination of the rectum was painless.

Example 5

Treatment of chronic inflammatory process affecting the female genitalia

[0076] Treatment was provided for eleven women between twenty-three and forty-three years of age. They had been affected by chronic inflammation for more than five years, and various treatment methods had been unsuccessful.

[0077] The drug was administered to these patients in the form of rectal suppositories (to be inserted at night), in doses of 100 mg once each day, for a five-day period. Subsequently, vaginal insertion was performed for an additional period of two days. On the second day after the commencement of treatment, the therapeutic effect was observable. There was a significant decrease in vaginal secretions, which ceased completely by the fifth day, with healing occurring by the eight day.

[0078] Clinical observations were confirmed by laboratory analysis of vaginal secretions in each instance.

Example 6

[0079] V., a female patient who was forty-seven years of age, was observed to be affected by suppuration of aparacolostomy incision in the left inguinal region, with inflammatory infiltration of adjacent soft tissues, subsequent to abdomino-perineal excision of the rectum on account of an adenocarcinoma. The patient cited pain in the region affected by infiltration, and an increase in body temperature was observed. A suppository containing 200 mg of the drug was applied to the incision. Pain ceased twenty to thirty minutes after administration again twelve hours later. Six hours later, her temperature declined. An identical dose of the drug was administered again twelve hours later. Edema within soft tissues had decreased significantly twenty-one hours after the commencement of treatment. Treatment was continued for six days, and, at the end of this period, the wound was wholly devoid of pus. It is therefore possible to conclude that it is possible to use the drug in the previously indicated doses for eliminating inflammatory processes during the post-operative period.

Example 7

Treating Malignant Tumors

[0080] Kh., a patient who was thirty years of age, had been diagnosed with an anal adenocarcinoma seven months earlier.

[0081] The diagnosis had been verified histologically. The patient cited pain in the anus, constipation, difficulty in defecating, and secretion of mucus and blood from the anus. On account of the patient's categorical refusal to undergo surgery for abdominoperineal excision of the rectum, radiation therapy had been provided in doses of 45 g. During a subsequent examination, fifty days after radiation therapy had begun, no development of the anal

tumor was observed. Forty days later, the patient underwent another cycle of radiation therapy, with doses of 45 g. During the next thirty days, the drug was administered in doses of 100 mg every four hours, in the form of rectal suppositories. During the next examination, reduction of the tumor was observed. For the next thirty days, the dosage of the drug was increased, and intramuscular administration of 100 mg per day was provided for this patient, along with a rectal suppository (100mg).

[0082] During the next examination, it was determined that the anal tumor had been reduced by two-thirds in relation to its initial dimensions. It had acquired a dense and elastic consistency, and limited mobility was observed. In addition, it was covered with a normal mucous membrane.

[0083] Subsequently, an improvement of the patient's general condition was observed.

[0084] By treating a malignant tumor with a combination of radiation therapy and administration of the drug, reduction of the tumor's dimensions was therefore obtained within a brief period and symptoms of intoxication were eliminated.

Example 8

[0085] R., a female patient who was forty-seven years of age, was affected by a perineal cutaneous melanoma accompanied by lesions within the anal wall and tumors within lymph nodes in the left inguinal region.

[0086] This diagnosis had been confirmed histologically.

[0087] Localized excision of the tumor was performed, and the group of lymph nodes in the left inguinal region was removed.

[0088] When the patient was examined during a checkup forty days thereafter, hardening was observed in the vicinity of the postoperative scar. This phenomenon was indicative of the onset of recurrence of the tumor. Intramuscular adminis-tration of the drug in 100 mg doses was provided on alternating days. On the third day after the commencement of treatment, abnormal salivation began, and vomiting occurred on the fourth day, along with an increase in diuresis. These symptoms gradually ceased on the thirteenth and fourteenth days. By increasing the dosage of the drug, it was possible to increase its therapeutic effect.

[0089] Beginning on the twentieth day, the drug was administered in 100 mg intramuscular doses every day. During a checkup thirty days later, disappearance of infiltration in the region of the postoperative scar was observed. This phenomenon demonstrated dissolution of tumoral tissue, and it was likewise confirmed by a subsequent histological examination.

Example 9

Endotoxin experiments

[0090] These experiments were performed upon rabbits. Salmonella typhinurium endotoxin which had been purified by Bolvin's method was used in doses of 1 mg/kg according to body weight. In the first series of experiments, endotoxin inoculation resulted in the onset of intoxication symptoms only ten minutes after the experiment began, with more significant clinical manifestations occurring one hour thereafter.

[0091] During the second series of experiments, the drug was administered intravenously in doses of 15 mg/kg according to body weight when clinical manifestations appeared (thirty to forty minutes after the commencement of the experiment). Reduction of intoxication symptoms was observed five minutes after endotoxin inoculation. In this instance, partial alleviation of symptoms was observed.

[0092] During the ensuing series of experiments, 2 5 mg/kg of the drug, according to body weight, was administered to the animals, and complete alleviation of intoxication symptoms and diarrhea was obtained.

[0093] Conclusion: according to the duration of the respective disease, 15 to 25 mg/kg doses of 5-aminophtaloylhydrazide prevent or eliminate intoxication symptoms.

Example 10
Induced abortion

[0094] Experiments were performed upon twenty pregnant rabbits. During the first series of experiments, abortions were observed in eighty percent of the animals, at the peak of clinical manifestations of intoxicatian, forty to sixty minutes after inoculation with Salmonella typhinurium endotoxin, in a dose of 1 mg/kg according to body weight.

[0095] During the second series of experiments, the drug was administered in doses of 15 mg/kg, and abortion was prevented in seven among every ten rabbits, notwithstanding the endotoxin.

[0096] It was therefore demonstrated that the drug was capable of preventing premature abortion resulting from intoxication in the animals which were used in this experiment.

Example 11

[0097] It is known that diarrhea often occurs in newborn calves, at the point when artificial feeding is introduced. In order to prevent or alleviate its occurrence, the drug was used in a combined form, and it was particularly effective.

[0098] Experiments were performed upon twenty newborn calves.

[0099] 20 mg/kg intramuscular doses of a combined drug consisting of5-aminophtaloyl-hydrazide and its sodium salt in a 1:1 proportion were administered on the first day after birth. Two days later, the drug was administered again in doses of 10 mg/kg according to body weight.

[0100] A positive therapeutic effect was obtained, with diarrhea being eliminated in 80 percent of the cases.

[0101] It was therefore concluded that it is possible for the combined drug to be used to prevent diarrhea from occurring in newbom calves.

Example 12

[0102] Suppuration and abscesses affecting the jaw necessarily require surgical intervention. Operations are only possible, however, after elimination of the inflammatory reaction occurring in adjacent tissue. Characteristic clinical symptoms of inflammation such as pain, edema, uncomfortable sensations, fever, etc. were observed in all of the eighteen patients being studied.
[0103] The patients were subdivided into three groups according to alphabetical order. The drug was prescribed for every patient on one occasion, although different dosages were adopted (1 mg/kg;

2 mg/kg; 4 mg/kg). Another examination of the patients, one day after administration of the drug, offered the following conclusions: no therapeutic effect had occurred among four patients in the second group; and a therapeutic effect was observed in each of the six patients constituting the third group.

[0104] Histological analyses which were performed for a sample consisting of five patients from the different groups confirmed the results which had been obtained.

[0105] Conclusion: minimum therapeutic doses of the drug - from 2 to 4 mg/kg, according to the patient's body weight

Example 13

[0106] The antitoxic effect of the drug was confirmed among patients with acute intestinal infections.

[0107] Example: N., a male patient who was forty-two years of age, was admitted to a hospital clinic on account of spasmodic pain in various portions of the abdominal region, nausea, vomiting, recurrent fluid stools which did not contain extraneous substances (blood, mucus), a higher body temperature, headaches, and lethargy, 200 mg of the drug in an isotonic aqueous solution was administered to this patient. Forty to fifty minutes later, his condition improved, and a significant decrease in abdominal pain occurred, along with cessation of diarrhea.

[0108] One day after admission to the clinic, all of the symptoms of intoxication had disappeared. The patient was released in satisfactory condition on the third day.

[0109] Fecal cultures for bacillary dysentery and Salmonella were negative.

Example 14

Treatment of non-specific ulcerative colitis and Crohn's disease

[0110] Treatment was provided for three patients whose ages were between thirty-three and forty-one years and who were affected by non-specific ulcerative colitis in the intense form of its active phase, and for a patient who was forty-two years of age and was affected by Crohn's disease within the colon. These patients complained of periodic worsening of their symptoms over periods of three to five years.

[0111] Notwithstanding continuous treatment, including hormonal therapy, the patients'condition became worse. They lost weight, they cited constant pain within the large intestine, frequent voiding of fluid stools containing mucus, blood, and pus, as often as fifteen times daily, pains in their joints, and skin eruptions. Considerable quantities of pus were observed within the rectum during rectosigmoidoscopy, and the mucosae were usually edematous, enlarged, porous, and filled with blood.

[0112] 100 mg per day of the drug was administered intravenously to these patients for three days. Thirty minutes after intravenous administration, abdominal pain and pain in their joints lessened, and the patients'condition already improved on the first day. During the first three days, frequency of intramuscular administration was modified (every twelve hours).

[0113] On the sixth day, the patients cited decisive improvement. They were no longer experiencing pain, their skin eruptions had -. disappeared, and defecation was occurring two or three times daily, without the continued presence of blood or pus.

[0114] On subsequent days, intramuscular administration of the drug was provided once daily, along with a 100 mg rectal suppository.

[0115] On the fourteenth day, the patients did not cite further difficulties, and defecation had nearly become normal, occurring once or twice each day.

[0116] Rectosigmoidoscopy examinations did not reveal the presence of pus or blood, although traces of an inflammatory process were observed within mucous membranes.

Example 15

[0117] V., a female patient who was thirty-seven years of age, had undergone a mastectomy on account of cancer affecting the left breast. During subsequent years, she had undergone radiation therapy and chemotherapy on multiple occasions on account of metastatic tumors.

[0118] At the point when treatment began, the patient's condition was already severe on account of cancerous intoxication.

[0119] She had lost her appetite and was experiencing persistent intense pain within the left humeral cingulum and within the upper left arm.

[0120] Advanced lymphatic stasis was observed above the previeously cited regions and in the left subaxillary region. On account of the severity of the patient's condition, intramuscular administration of the drug in 100 mg doses every two days was initiated. After the first injection of the drug, the intensity of her pain decreased significantly. On the fourth day after the commencement of treatment, abnormal salivation began.

[0121] On the sixth day, vomiting began, and the patient's stools were malodorous. On the seventh and eighth days, her urine became more dense, frequent urination began, and her perspiration acquired a rather foul odor. On the thirteenth and fourteenth days, edema within the left humeral cingulum, the left arm, and the left subaxillary region had diminished significantly.

[0122] On the twentieth day, the patient's condition improved, and her appetite was restored. After the twentieth day, intramuscular administration of the drug took place on alternate days. Subsequently, a steady improvement in the patient's general condition was observed.

Example 16

Treatment of proctitis and cystitis occurring after radiation therapy

[0123] B., a male patient who was thirty-five years of age, complained of burning sensations in the anus, along with frequent and painful urination, after having received radiation therapy for a period of forty-five days. During a rectosigmoidoscopy examination, intense edema and contact hemorrhaging within the rectal mucosae were observed above the tumor. The diagnosis was:

proctitis and cystitis arising from radiation therapy. On account of a lack of specific therapeutic measures, the drug was prescribed for the patient according to a dose of 100 mg per day. Observation of the patient for three days demonstrated the absence of any significant clinical effect, and the dosage of the drug was therefore increased.

[0124] Rectal suppositories containing 100 mg of the drug were administered to the patient for ten days, in the morning and in the evening. Anal burning and painful urination diminished in one day. The patient began to sleep adequately. By the third day, pain and burning were no longer present.

Urination became normal on the fifth day, after the dosage was increased. Ten days later, during a rectosigmoidoscopy examination, regeneration of the capillary network within the rectal mucosae was observed.

Example 17

[0125] N., a male patient who was forty-two years old, had been admitted to a clinical department with the following diagnosis: erysipelas on the left foot. During the patient's hospitalization, his condition was determined to be of moderate severity. *An* edematous portion of skin protruding from the cutaneous surface was observed in the front portion of his left foot. This area was painful and warm when it was palpated. General loss of strength and a higher body temperature, up to 38.6°C, were also observed.

[0126] The respective compound was applied to the affected area of the patient's skin in the form of a 1 percent ointment. Suppositories contain ing 100 mg of the drug were prescribed at the same time. Pain became less intense five to six hours after administration and within twenty-four hours, congestion and edema within the patient's foot had diminished.

[0127] His general condition improved thereafter.

[0128] Subsequently, the patient was treated with the drug in the form of suppositories for five days.

[0129] By the end of the sixth day, the patient no longer cited difficulties, and pigmented segment of skin remained in the affected area.

[0130] On the seventh day after the commencement of treatment, the patient was released in presumably satisfactory condition.

Example 18

Treatment of dermatitis of unknown etiology

[0131] A patient who was seven months old had experienced dermatitis of unknown etiology since the age of two weeks. Skin on the child's face, within the humeral cingulum, and on the legs had been affected.

[0132] Troughout this period, various methods had been applied without success.

[0133] The patient was treated for fourteen days.

[0134] The affected cutaneous areas were treated three times daily with a water-soluble emulsion containing 30 mg of the drug, and, on alternating days, suppositories containing 50 mg of the drug (5mg/kg according to weight) were administered rectally.

[0135] After the second day, the affected cutaneaous areas began to become drier, and epithelization was completed by fourteenth day.

Example 19

[0136] N., a thirty-nine year old male patient, was admitted to a clinical department with the following diagnoses: erysipelas of the right leg. Objective indications included: a congested segment of skin on the front surface of the leg; this area protruded from the surface and it was experiencing generally disagreeable sensations, and intense pain in the vicinity of the inflamed area.

[0137] A 4 percent solution of the drug within a 20 percent DMSO solution was applied to the affected cutaneous area. Pain diminished forty to sixty minutes after the commencement of treatment.

[0138] Congestion diminished twenty-four hours later. The patient did not cite pain, and his general condition improved. Treatment was continued for three days, until complete elimination of pathological symptoms.

[0139] It is therefore possible to affirm that the solution containing 4 percent of the drug combined with 20 percent DMSO possesses significant therapeutic effectiveness in terms of reducing clinical manifestations of the disease.

Example 20

[0140] I., a thirty-seven year old male patient who was hospitalized, cited frequent fluid stools which contained mucus and blood, occurring as many as seven times daily. The well-known symptoms of intoxication were observed. During a rectosigmoidoscopy examination, pronounced indications of inflammation were observed within the rectum.

[0141] The preliminary diagnoses which was suggested was: non-specific ulcerative colitis.

[0142] Treatment began with intramuscular administration of 100 mg doses of the drug, once daily.

[0143] Because no therapeutic effects had been observed three days later, the daily dose was doubled. Even in that instance, the therapeutic action of the drug was still not observable.

[0144] On the fifth day, AIDS was diagnosed on the basis of laboratory analyses.

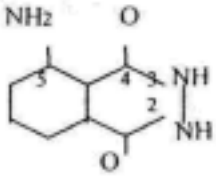
[0145] The daily dosage of the drug was then increased to 400 mg. On the third day after the patient's dosage had been increased, diarrhea disappeared, symptoms of intoxication disappeared, and his general condition improved.

[0146] When daily administration of the drug was continued, further symptoms of the disease did not appear.

[0147] It is therefore obvious that it is possible for the drug to be used with favorable results in combatting the complications which arise in patients affected by *AIDS.*

Claims

1. Use of5-aminophtaloylhydrazide of the

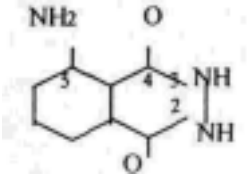


formula
and its pharmaceutically acceptable salts for the manufacture of a medicament for treating antiinflammatory and intoxication symptoms.

2. Use according to claim 1 for the manufacture of a medicament intended for treating inflammatory diseases of any etiology.
3. Use according to claim 1 as separate anti-cancer agent for the manufacture of a medicament.
4. Use of a mixture of5-aminophtaloylhydrazide and the sodium salt thereof in portions of 1:1 to 1:0.5 for the manufacture of a medicament intended for effective treatment of acute intestinal diseases in animals.
5. Use according to claim 1 of the sodium salt of 5-aminophtaloylhydrazide for the manufacture of a medicament intended for therapeutic treatment procedures in human pathology, by administration of doses of 2 to 5 mg/kg according to the body weight.
6. Use of the sodium salt cited within claim 5 for the manufacture of a medicament intended to be administered in chronic situations involving treatment of malignant autoimmune disorders.
7. Use according to claim 1 of the salt of5-aminophtaloylhydrazide for the manufacture of a medicament which is to be administered externally or parenterally or rectally, for effective treatment of cutaneous conditions and accessible tumors.
8. Use according to claim 1 for the manufacture of a medicament as an external therapeutic agent in a solution containing from 10 to 30 percent DMSO, for treating subcutaneous lesions and suppuration.
9. Use according to claim 1 for the manufacture of a medicament for eliminating the principal symptoms of AIDS in doses of 15 mg/kg, according to body weight.
10. Use according to claim 1 for the manufacture of a medicament for treating disorders selected from the group consisting of non-specific ulcerative colitis, Crohn's disease, diffuse sclerosis, diarrhea, proctitis attributable to radiation therapy, hemorrhoids, anal fissures, dyspepsia, intestinal infection and proctosigmoiditis

Patentansprüche

1. Verwendung von 5-AminophtaIoylhydrazid der Formel

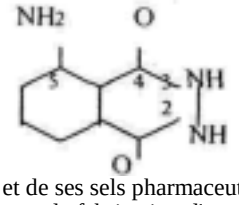


und seiner pharmazeutisch akzeptablen Salze zur Herstellung eines Medikaments zum Behandeln von antiinflammatorischen und Intoxikations-symptomen.

2. Verwendung nach Anspruch l zur Herstellung eines Medikaments, das für die Behandlung inflammatorischer Krankheiten jeglicher Ätiologie bestimmt ist.
3. Verwendung nach Anspruch l als gesondertes Antikrebsmittel zur Herstellung eines Medikaments.
4. Verwendung eines Gemisches aus 5-Aminophtaloylhydrazid und dessen Natrium-salz in Portionen von l: l bis l :0.5 zur Herstellung eines Medikaments, das für die wirkungsvolle Behandlung akuter Darmerkrankungen bei Tieren bestimmt ist.
5. Verwendung nach Anspruch l des Natriumsalzes von 5-Aminophtaloylhydrazid zur Herstellung eines Medikaments, das bestimmt ist für therapeutische Behandlungs-verfahren in der Humanpathologie durch Verabreichung von Dosen von 2 bis 5 mg/kg entsprechend dem Körpergewicht.
6. Verwendung des in Anspruch 5 genannten Natriumsalzes zur Herstellung eines Medikaments, das zur Verabreichung in chronischen Situationen bestimmt ist, bei denen die Behandlung bösartiger Autoimmun-störungen vorkommt.
7. Verwendung nach Anspruch l des Salzes von 5-Aminophtaloylhydrazid zur Herstellung eines Medikaments, das extern oder parenteral oder rektal zu verabreichen ist für die wirkungsvolle Behandlung von kutanen Leiden und zugänglichen Tumoren.
8. Verwendung nach Anspruch l zur Herstellung eines Medikaments als externes therapeutisches Mittel in einer Lösung, die 10 bis 30 Prozent DMSO enthält, für die Behandlung subkutaner Schädigungen und Eiterungen.
9. Verwendung nach Anspruch l zur Herstellung eines Medikaments zum Beseitigen der AIDS-Hauptsysmptome in Dosen von 5 bis 15 mg/kg entsprechend dem Körpergewicht.
10. Verwendung nach Anspruch l zur Herstellung eines Medikaments zum Behandeln folgender Störungen: unspezifische colitis ulcerosa, Crohn-Krankheit, diffuse Sklerose, Durchfall, Proktitis aufgrund von Bestrahlungstherapie, Hämorrhoiden, Analfissuren, Dyspepsie, Darm Infektion und Proktosigmoiditis.

Revendications

1. Utilisation du 5-aminophtaloylhydrazide de formule:



et de ses sels pharmaceutiquement acceptables pour la fabrication d'un medicament pour le traitement des symptömes de l'inflammation et de l'intoxication.

2. Utilisation selon la revendication 1, pour la fabrication d'un medicament destine au traitement des maladies inflammatories d'une quelconque etiologie.

3. Utilisation selon la revendication 1 en tant qu'agent anti cancereux separe, pour la fabrication d'un medicament.

4. Utilisation d'un melange de 5-aminophtaloyl-hydrazide et du sel de sodium de celui-ci dans un rapport de 1:1 a 1:0,5, pour la fabrication d'un medicament destine au traitement efficace des maladies intestinales aigues chez 1'animal.

5. Utilisation selon la revendication l du sel de sodium du 5-aminophtaloylhydrazide, pour la fabrication d'un medicament destine aux procedures des traitement therapeutique en pathologie humaine, par administration de doses de 2 a 5 mg/kg selon le poids corporel

6. Utilisation du sel de sodium cité dans la revendication 5, pour la fabrication d'un médicament destiné à etre administré dans des états chroniques impliquant le traitement de troubles auto-immuns malins.

7. Utilisation selon la revendication 1 du sel du 5-aminophtaloyihydrazide, pour la fabrication d'un médicament à administrer par vole externe, parentérale ou rectale, pour le traitement efficace des troubles cutanés et des tumeurs accessibles.

8. Utilisation selon la revendication 1, pour la fabrication d'un médicament en tant qu'agent thérapeutique externe dans une solution contenant 10 à 30 % de DMSO, pour le traitement de lésions sous-cutanées et de la suppuration

9. Utilisation selon la revendication 1, pour la fabrication d'un médicament pour éliminer les symptômes principaux du SIDA à des doses de 5 à 15 mg/kg selon le poids corporel.

10. Utilisation selon la revendication 1, pour la fabrication d'un médicament pour le traitement des troubles choisis dans le groupe constitué par la rectocolite ulcéro-hémorrogique non spécifique, la maladie de Crohm, la sclérose diffuse, la diarrhée, la proctite attribuable à une thérapie par rayonnement, les hémorroïdes, les fissures anales, la dyspepsie, l'infection intestinale et la proctosigmoidite.