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(54) 2-AMINO-4-(2-IMIDAZOLYL-VINYL)-PYRIMIDINES, THEIR PREPARATION AND USE, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(71) We, INSTITUTO CHEMIOTERAPICO ITALIANO S.P.A., an Italian Joint Stock Company, of 12, Via Crocefisso, Milan, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

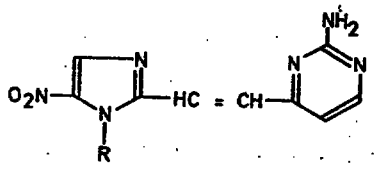
This invention relates to 2 - amino - 4 - (2 - imidazolyl - vinyl) - pyrimidines, processes for their preparation, pharmaceutical compositions containing them, and methods for their use in the therapeutic treatment of non-human hosts afflicted with protozoal diseases and bacterial infections. The methods involve their anti-protozoal (e.g., anti-amebic) activity against pathogenic protozoa, and their anti-bacterial activity against pathogenic bacteria in living warm blooded non-human animal bodies. More particularly, but not exclusively, this invention is directed to 2 - amino - 4 - [2 - (1 - alkyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidines as novel compounds.

The novel compounds, which are active anti-protozoal and antibacterial agents, are particularly effective in therapeutically treating trichomoniasis, for instance vulvovaginitis caused by *Trichomonas vaginalis*, by inhibiting the growth of or destroying the microorganism (pathogenic protozoa, causing the disease. The compounds are also provided for the therapeutic treatment of bacterial infections caused by, for instance, microorganisms (pathogenic bacteria) such as *Brucella brochiseptica, Salmonella pullorum, Streptococcus pyogenes, Diplococcus pneumoniae*, and *Klebsiella pneumoniae*, which microorganisms are inhibited in growth or destroyed by these compounds.

The compounds of the invention may be used in the treatment of vulvovaginitis, which is often caused by the protozoa *Trichomonas vaginalis*, an organism which occurs in the female population with a high frequency and also in males. Therefore, efforts have been put forth in searching for antitrichomonal agents which are very efficacious and non-toxic and, when administered to pregnant women, do not influence the regular development of the fetus. Desirably the antitrichomonal agent should not adversely affect normal varginal microflora, including *Bacillus doderlein (Lactobacillus acidophilus)*.

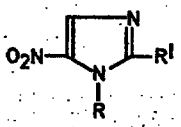
Metronidazole, 1 - (2 - hydroxyethyl) - 2 - methyl - 5 - nitroimidazole, has been proposed for use as an antitrichomonal agent by Jacob et al in United States Patent Specification No. 2,944,061, and is presently a frequently prescribed, commercially available drug for the treatment of vulvovaginitis. Although metronidazole is commonly employed for treatment of trichomoniasis, it has not been found to be completely satisfactory since certain strains of *Trichomonas vaginalis* have developed a resistance to the drug. Other proposals include the use of certain 1-lower alkyl - 2 - (2 - substituted vinyl) - 5 - nitroimidazoles as an intermediate to sulfur-containing antiprotozoal agents by Miller et al in United States Patent Specification No. 3,549,626, and the use of certain 2 - (5 - nitro - 2 - furyl) - vinyl pyrimidine derivatives as antitrichomonal agents by Minami et al in United States Patent Specification No. 3,464,982.

An object of this invention is the provision of 2 - amino - 4 - [2 - imidazolyl - vinyl] - pyrimidines (hereafter the "P-compounds"). More particularly, one aspect of the invention provides a compound of the formula:



wherein R is an alkyl group containing 1 to 6 carbon atoms. The group R preferably contains 1 to 3 carbon atoms. The invention also provides pharmaceutically-acceptable salts of these compounds, pharmaceutical compositions containing such compounds or salts, methods of preparing the compounds and methods for treating protozoan or bacterial infection in non-human animals. Exemplary of the P-Compounds are 2 - amino - 4 - [2 - (1 - methyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine, 2 - amino - 4 - [2 - (1 - ethyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine, 2 - amino - 4 - [2 - (1 - propyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine, and 2 - amino - 4 - [2 - (1 - pentyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine.

According to another aspect of the present invention, there is provided a 2 - amino - 4 - (2 - imidazolyl - vinyl) - pyrimidine when obtained by reacting together an imidazole derivative of the formula:



and a pyrimidine derivative of the formula:

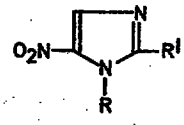
wherein R is an alkyl group containing 1 to 6 carbon atoms, one of R′ and R″ is a formyl group and the other is a methyl group, in the presence of a dehydrating agent.

One, or a combination, of the P-Compounds may be therapeutically administered, in microorganism-growth inhibiting amounts, to a living warm blooded animal suffering from a protozoal disease or a bacterial infection caused by a microorganism. They may be administered to the subject in any convenient form, for instance, in a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and one or more of the P-Compounds, and exhibit activity in urine and in serum.

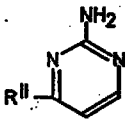
The P-Compounds are very efficacious against *Trichomonas vaginalis* even at low concentrations, say, at a concentration of 1 or 2 micrograms per milliliter in *in vitro* tests. The amount of a P-Compound administered to a human patient suffering from trichomoniasis may frequently be from 50 to 2000 milligrams per day, especially for an individual weighing 50 to 70 kilograms.

The protozoal diseases and bacterial infections which may be treated by the method of this invention include, as protozoal diseases, trichomoniasis, enterohepatitis, amoebiasis, trypanosomiasis and enteric protozoal diseases, and, as bacterial infections, important Gram positive and Gram negative strains of pathogenic bacteria, particularly members of the coccus form of bacteria, including species of *Diplococcus* and *Streptococcus;* and, for instance, species of *Salmonella, Brucella, Klebsiella;* and pleuropneumonia-like organisms (PPLO), the growth of which are inhibited by the P-Compounds. These compounds do not damage normal vaginal microflora, including *Bacillus doderlein (Lactobacillus acidophilus)*.

The P-Compounds may be produced by a number of syntheses, for instance, by a dehydration reaction between



and



wherein R is as previously designated, and one of R′ and R″ is



and the other is —CH_3. The reaction is conducted in the presence of dehydrating amounts of a dehydrating agent under dehydrating conditions including temperatures which promote the dehydration reaction to react the formyl group and methyl group to yield water and provide the desired P-Compound. The dehydration conditions generally include ambient pressures, and temperatures ranging from 25° to 150°C., preferably from 30 to 90°C.

The dehydrating agent is preferably a strong mineral acid and is advantageously employed in excess of that stoichiometrically required for completion of the reaction. Exemplary of strong mineral acids suitable for use as dehydrating agents are sulfuric acid, hydrochloric acid, and phosphoric acid. Other acids, e.g., aromatic sulfonic acids containing from 6 to 11 carbon atoms, such as para-toluene sulfonic acid, can be used. Lower fatty acid anhydrides, e.g. acetic anhydride, can also be used. The dehydrating agent can also be used as a solvent as well in solvent-providing amounts. Generally, the amount of dehydrating agent employed is at least 1.1 times the stoichiometric amount required for completion of the reaction and may be 20 or 30 or more times that required for completion of the reaction when the dehydrating

agent serves also as the solvent medium for the reaction. Greater amounts may be employed, but such amounts would appear to be impractical.

Suitable solvents are usually employed, preferably an organic carboxylic acid, e.g. an acrylic saturated monoacid containing from 1 to 6 carbon atoms such as acetic or propionic acids, and among these, glacial acetic acid is preferred. The solvent is frequently provided in a weight ratio to the reactants including the dehydrating agent of at least 2:1, preferably from 3:1 to 10:1, although greater amounts may be employed.

A particularly advantageous process for making the P-Compounds comprises reacting 5 - nitro - 1 - alkyl - 2 - formyl imidazole, where the alkyl group contains from 1 to 6 carbon atoms and corresponds to the alkyl group (R) at the 1 position on the imidazolyi nucleus. For instance, one process for the preparation of 2 - amino - 4 - [2 - (1 - methyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine (the "P'-Compound") comprises reacting 5 - nitro - 1 - methyl - 2 - formyl imidazole with 2 - amino - 4 - methyl pyrimidine to provide the P'-Compound. The 2 - amino - 4 - methyl pyrimidine may be used in a slight stoichiometric excess, e.g. 1 to 50 weight percent in excess of that required to react with the imidazole reactant, and the reaction is advantageously conducted in the presence of a dehydrating agent, preferably at a temperature from 30° to 90°C., advantageously from 35° to 75°C. The resultant reaction mixture may be diluted with water and neutralized with a suitable base, for instance a saturated solution of sodium bicarbonate, to form the novel compound as a precipitate.

5 - Nitro - 1 - lower alkyl - 2 - formyl imidazoles are disclosed in Henry et al., United States Patent Specification No. 3,472,864, and several methods for their preparation are disclosed therein. For instance, 5 - nitro - 1 - methyl - 2 - formyl imidazole can be prepared by contacting 5 - nitro - 1,2 - dimethyl imidazole with selenium dioxide, and heating the mixture until the reaction begins, as indicated by the evolution of heat. On conclusion of the exothermic reaction, the mixture is cooled, and the imidazoles are separated by extraction into an organic solvent. A final purification may be facilitated by the formation of an insoluble aldehyde derivative such as an oxime, hydrazone, or semicarbazone. Another method of obtaining 5 - -nitro - 1 - methyl - 2 - formyl imidazole is by the reaction of 1 - methyl - 5 - nitroimidazole with trioxymethylene in a dimethyl sulfoxide solution in a sealed tube to form 1 - methyl - 2 - hydroxymethyl - 5 - nitroimidazole which can be oxidized with an oxidant such as lead tetraacetate, manganese dioxide, nitrogen tetroxide, dimethylsulfoxide - dicyclohexyl carbodiimide, nitric acid or pyridine-chromium trioxide complex or with other reagents capable of converting the 2 - hydroxymethyl substituent to a 2 - formyl radical.

2 - Amino - 4 - methyl pyrimidine can be obtained from the reaction of guanidine hydrochloride and chlorovinylmethyl ketone as is well known in the art, and the compound is reported, for instance, as compound P—2100 in *The Handbook of Chemistry and Physics*, 46th edition, page C—523. Other preparations of pyrimidine may be found in, for instance, Gillman, *Organic Chemistry An Advanced Treatise*, Volume 4, page 866 *et seq.* (1953).

Another process for preparation of the P-Compounds comprises reacting 2 - amino - 4 - (dialkoxymethyl) - pyrimidine, a precursor to 2 - amino - 4 - formyl - pyrimidine, where the alkoxy groups may be the same or different and may each have 1 to 6 carbon atoms, and are preferably ethoxy, with a 1 - alkyl - 2 - methyl - 5 - nitroimadazole wherein the alkyl group contains 1 to 6 carbon atoms and corresponds to the alkyl substituent (R) of the P-Compound. The acetal structure, in the presence of aldehyde-forming amounts of water, will provide the corresponding aldehyde and alcohol. The conversion of the acetal to aldehyde may occur in the same reaction simultaneously with the dehydration reaction to provide the P-Compounds, or the aldehyde may be prepared prior to conducting the reaction with the imidazole component to provide the P-Compounds.

The amount of water available for reaction with the acetal should preferably be in excess of the stoichiometric amount required to provide the desired amount of pyrimidine component for the reaction to produce the P-Compounds. For instance, when the acetal is being reacted in the presence of the imidazole component, thus the 2 - amino - 4 - formyl - pyrimidine is being prepared *in situ*, the water liberated from the dehydration reaction may serve to react with the acetal on the pyrimidine group. It may be desirable to employ only catalytically-effective amounts of water to initiate the reactions, for instance 0.01 or 1 to 50 percent of the amount of water required to provide the desired amount of aldehyde. Excessive amounts of water may reduce the effectiveness of the dehydrating agent. Since the acetal and aldehyde are in an equilibrium relationship, it is often preferable to provide the acetal in an amount in excess of that stoichiometrically required for reaction with the imidazole component in order to favor the production of the aldehyde, for instance 1.1 to 5 times the amount required. If the acetal is converted to the aldehyde prior to conducting the reaction between the pyrimidine and imidazole components to prepare the P-Compounds of this invention, the water may be employed in excess of the amount stoichiometrically required for

the desired degree of conversion, e.g. 1.1 to 10, preferably 1.5 to 5, times the amount required. Generally, a temperature in the range of 25° to 150°C. may be employed. For example, the P'-Compound (where R is methyl) can be prepared through the reaction of 2 - amino - 4 - (diethoxymethyl) pyrimidine, which is described in *J. Am. Chem. Soc.*, Volume 69, page 3072 (1947), with 1,2 - dimethyl - 5 - nitroimidazole, which is described in *J. Chem. Soc.*, Volume 127, page 1832 (1925).

The dehydration reaction to provide the P-Compounds may be conducted in two stages. First, the aldehyde and methyl group may be reacted in the presence of a strong base in excess of the amount stoichiometrically required for reaction, e.g. 1.1 or 1.5 to 10 to 15 times, to form a secondary alcohol, and then the secondary alcohol can be dehydrated with a dehydrating agent as described above.

The P-Compounds may be administered, for therapeutical purposes, to a host in any convenient manner. For example, one of the P-Compounds may be topically applied on the affected area, orally administered, or parenterally administered, for instance, by cutaneous, subcutaneous, or intravenous injections. Oral and topical treatments are generally preferred for vulvovaginitis due to the ease of admininstration. Generally, the amount of a P-Compound administered to a human patient to achieve antitrichomonal activity is 50 to 2000 milligrams per day, especially for an individual weighing 50 to 70 kilograms. In females, the amount administered is preferably from 200 to 1000 milligrams per day, and for males, 100 to 800 milligrams per day is preferred. Normally, the dosage amount in treating living warm-blooded animal bodies having a protozoal disease or bacterial infection which is therapeutically-responsive to a P-Compound is 1 to 40, preferably 4 to 20, milligrams of the compound per kilogram of body weight per day. A P-Compound may be administered once a day, or fractionally at periodic intervals throughout the day. When orally administered, two or three or more fractional doses per day are preferred.

For oral administration, a P-Compound is usually compounded in a pharmaceutical unit dosage form such as pill, lozenge, tablet or capsule with a pharmaceutically-acceptable carrier. Such unit dosage forms, for example containing from 50 to 500 milligrams of a P-Compound, are quite satisfactory and are prepared according to techniques known to those skilled in the art. Thus, these unit dosage forms may contain the normal diluents, excepients, lubricating agents, and extenders regularly employed in compounding such forms. Exemplary carriers are solids such as lactose, magnesium stearate, calcium stearate, starch, terra alba, dicalcium phosphate, sucrose, talc, stearic acid, gelatin, agar, pectin, and acacia.

Alternatively, a P-Compound may be suspended in or dissolved in liquid vehicles suitable for oral administration. The final preparation may be in the form of a solution, emulsion, suspension, or syrup. Liquid carriers which may be employed include, for instance, peanut oil, sesame oil, olive oil, and water. The liquid preparation may also include wetting agents and other conventional additives for liquid pharmaceutical dosage forms.

For topical administration, topical jellies, creams, ointments, or suppositories are normally used. Vaginal inserts containing, as inactive ingredients, lactose, starch, hydrogenated castor oil, polyvinyl alcohol or other water soluble, non-toxic polymer, are commonly used. Vaginal inserts are normally used once a day for convenience and are often supplemented with, for instance, oral administration of a P-Compound.

A P-Compound may also be contained in a suitable, sterile solution or suspension in a pharmaceutically-acceptable carrier for parenteral injections. In addition, P-Compounds used for inhibiting the growth of or destroying microorganisms which cause protozoal diseases or bacterial infections, or compositions containing the same, may be administered in amounts sufficient to produce the desired anti-protozoal or anti-bacterial effects upon administration of a unit dosage form thereof. The compositions may include other physiologically active materials and/or medicants, e.g. buffering agents, antacids, sedatives, tranquilizers, or analgesics.

The P-Compounds also may be used in veterinary medicine in the treatment of bacterial and protozoal, particularly trichomonal infections. For instance, they may be used to treat *Trichomonas fetus* in cattle. *Trichomonas fetus* causes abortion and sterility in cattle.

It will be understood that the P-Compounds of this invention as used to treat protozoal or bacterial infections can be brought into a unit dosage form by any suitable technique known to one of ordinary skill in the art.

The following examples are provided to further illustrate this invention. All parts and percentages are by weight unless otherwise stated.

EXAMPLE 1.

Into a mixture of 1.6 grams of 2 - amino - 4 - methyl - pyrimidine with 10 milliliters of glacial acetic acid is slowly added 2.13 grams of concentrated sulfuric acid. A mixture of 2.4 grams of 2 - formyl - 1 - methyl - 5 - nitroimidazole in 20 milliliters of glacial acetic acid is slowly added to the mixture of the pyrimidine under stirring. The reaction mixture is maintained at a temperature of about 55°C. for four hours. The resultant mixture

is then diluted with 200 milliliters of distilled water and neutralized with a saturated aqueous solution of sodium bicarbonate. A brownish-yellow precipitate is formed and recovered. The product is analyzed by infrared spectroscopy and is found to conform to 2 - amino - 4 - [2 - (1 - methyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine.

EXAMPLE II.

In vitro tests to determine the activity of 2 - amino - 4 - [2 - (1 - methyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine against *Trichomonas vaginalis* are conducted using three strains of the protozoal, namely the *Serafino Belfonti* strain, hereinafter designated as S, obtained from the Institute of Serum Therapy of Milan, and strains C1 and C2 obtained from the Institute of Inspection of Foods of Animal Origin of the University of Milan. The medium for the maintenance of the strains is of the type disclosed as the Simplified Tripticase Serum by Kupferberg et al. in *Proceedings of the Society of Experimental Biological Medicine*, Volume 67, p. 304, 1948, to which 0.1 weight per cent of chloramphenicol has been added. The chloramphenicol serves to impede the development of contaminating bacteria, but is inactive against *Trichomonas vaginalis* at this low concentration. Prior to use, the medium is raised to a temperature of 100°C. for about two to three minutes to remove a significant amount of oxygen from the medium. After cooling to about 37°C., 0.5 weight percent of human serum is added under sterile conditions. To about 9 milliliters of this medium is added about 0.25 to 0.30 milliliter of the previous broth, and transfers to new broths for the maintenance of the strains are carried out every 48 to 72 hours. The incubation of the strains is at 37°C.

The three strains are employed to determine the efficacy of 2 - amino - 4 - [2 - (1 - methyl - 5 - nitro - 2 -imidazolyl) - vinyl] - pyrimidine by transferring a standard 0.25 to 0.30 milliliter inoculum to a new 9 milliliter broth containing 0.5, 1.0, 1.5 or 2.0 micrograms of the compound per milliliter. After 48 to 72 hours, the broth is examined visually for the degree of turbidity in the culture tubes, and thus the development of the protozoa. The turbidity due to the coagulation of the protein of the serum is distinguished from the development of the protozoa due to the decolorization of the medium since the development of the protozoa is accompanied by a reduction of the methylene blue in the medium. The broth is also examined using a phase contrast microscope to evaluate the degree of mobility or lack of mobility of the *Trichomonas vaginalis*. The microscopic examinations also show the morphology of the cells in that young cells have a pear-shaped structure whereas older cells are more rounded. As a comparison, identical tests are conducted using metronidazole as the active ingredient. Controls are run using no active ingredient. The results are provided in Tables 1 to 6 wherein the following symbols are employed: 2 - amino - 4 - [2 - (1 - methyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine (P'-Compound) is represented as F; metronidazole, MET; cells very mobile, VM; cells mobile, M; cells slightly mobile, SM; cells immobile or absent, I; culture very turbid, VT; culture turbid, T; culture slightly turbid, ST; culture clear, C. Tables 1 to 4 illustrate the range of variability to be expected with tests of this sort, in which the minimum inhibiting concentration (MIC) of the active ingredient can be seen to vary; nevertheless in each case the MIC of the P'-Compound is less than that of MET.

TABLE 1

Trichomonas vaginalis – Strain S –

Microscopic Examination

	Run	Control	Microgram active compound per milliliter of broth			
			0.5	1.0	1.5	2.0
F	I	VM	VM	SM	I	I
	II	VM	VM	SM	I	I
	III	VM	VM	SM	I	I
MET	I	VM	VM	M	SM	I
	II	VM	VM	M	SM	I
	III	VM	VM	M	SM	I
Culture Appearance						
F	I	VT	T	ST	C	C
	II	VT	T	ST	C	C
	III	VT	T	ST	C	C
MET	I	VT	VT	T	ST	C
	II	VT	VT	T	ST	C
	III	VT	VT	T	ST	C

TABLE 2

Trichomonas vaginalis – Strain S –

Microscopic Examination

	Run	Control	Microgram active compound per milliliter of broth			
			0.5	1.0	1.5	2.0
F	I	VM	SM	I	I	I
	II	VM	SM	I	I	I
	III	VM	SM	I	I	I
MET	I	VM	M	M	SM	I
	II	VM	M	M	SM	I
	III	VM	M	M	SM	I
Culture Appearance						
F	I	VT	ST	ST	C	C
	II	VT	ST	C	C	C
	III	VT	ST	C	C	C
MET	I	VT	T	T	T	ST
	II	VT	T	T	T	ST
	III	VT	T	T	T	ST

TABLE 3

Trichomonas vaginalis – Strain S –

Microscopic Examination

	Run	Control	Microgram active compound per milliliter of broth			
			0.5	1.0	1.5	2.0
F	I	VM	SM	I	I	I
	II	VM	SM	I	I	I
	III	VM	SM	I	I	I
MET	I	VM	M	M	M	I
	II	VM	M	M	M	I
	III	VM	M	M	M	M
Culture Appearance						
F	I	VT	ST	C	C	C
	II	VT	T	C	C	C
	III	VT	T	C	C	C
MET	I	VT	T	T	ST	C
	II	VT	T	T	ST	C
	III	VT	T	T	ST	ST

TABLE 4

Trichomonas vaginalis – Strain S –

Microscopic Examination

	Run	Control	Microgram active compound per milliliter of broth			
			0.5	1.0	1.5	2.0
F	I	VM	I	I	I	I
	II	VM	I	I	I	I
	III	VM	I	I	I	I
MET	I	VM	VM	I	I	I
	II	VM	M	SM	I	I
	III	VM	M	SM	I	I
			Culture Appearance			
F	I	VT	C	C	C	C
	II	VT	C	C	C	C
	III	VT	ST	C	C	C
MET	I	VT	T	C	C	C
	II	VT	T	ST	C	C
	III	VT	T	ST	C	C

TABLE 5

Trichomonas vaginalis – Strain Cl –
Microscopic Examination

	Run	Control	Microgram active compound per milliliter of broth			
			0.5	1.0	1.5	2.0
F	I	VM	SM	I	I	I
	II	VM	I	I	I	I
	III	VM	SM	I	I	I
MET	I	VM	M	M	SM	I
	II	VM	M	M	SM	I
	III	VM	M	M	SM	I
			Culture Appearance			
F	I	VT	ST	C	C	C
	II	VT	ST	C	C	C
	III	VT	ST	C	C	C
MET	I	VT	T	T	ST	C
	II	VT	T	T	ST	C
	III	VT	T	T	ST	C

TABLE 6

Trichomonas vaginalis – Strain C2 –

Microscopic Examination

Run		Control	Microgram active compound per milliliter of broth 0.5	1.0	1.5	2.0
F	I	VM	SM	I	I	I
	II	VM	I	I	I	I
	III	VM	SM	I	I	I
MET	I	VM	VM	M	SM	I
	II	VM	VM	M	SM	I
	III	VM	M	M	SM	I

Culture Appearance

F	I	VT	ST	C	C	C
	II	VT	C	C	C	C
	III	VT	T	C	C	C
MET	I	VT	VT	T	T	C
	II	VT	VT	T	T	C
	III	VT	VT	T	T	C

The results summarized in Example II illustrate that the P' - Compound inhibits *Trichomonas vaginalis*, including resistant strains of the microorganism, at a substantially lower concentration in the *in vitro* test, than metronidazole.

EXAMPLE III.

2 - Amino - 4[2 - (1 - methyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine is tested to determine its effect *in vitro* on mature cultures of *Trichomonas vaginalis*. Nine milliliter samples of strains S, C1 and C2 of *Trichomonas vaginalis* are prepared in accordance with Example II and incubated for 48 hours. The cultures are then transferred to sterile tubes containing the same concentrate of active compound as in Example II. Microscopic evaluations for mobility are conducted after 24 and 48 hours of incubation after the addition of the active compound. The results are given in Tables 7 and 8, using the same symbols as were employed in Tables 1 to 6. Visual evaluation of the broth is not taken into consideration due to the nature of the test.

TABLE 7

Microscopic evaluation at 24 hours after addition of active compound

	Strains	Control	Microgram active compound per milliliter of broth 0.5	1.0	1.5	2.0
F	S	VM	M	SM	SM	SM
	C1	VM	SM	SM	SM	SM
	C2	VM	M	SM	SM	SM
MET	S	VM	VM	M	M	SM
	C1	VM	M	M	M	SM
	C2	VM	M	M	M	SM

TABLE 8

Microscopic evaluation at 48 hours after addition of active compound

	Strains	Control	Microgram active compound per milliliter of broth 0.5	1.0	1.5	2.0
F	S	M	SM	SM	SM	I
	C1	M	SM	SM	I	I
	C2	M	SM	SM	SM	I
MET	S	M	M	M	M	I
	C1	M	M	M	SM	I
	C2	M	M	M	M	I

The results summarized in Example III illustrate that the P-Compounds inhibit *Trichomonas vaginalis*, including resistant strains of the microorganism, at substantially lower concentrations in *in vitro* tests than metronidazole.

EXAMPLE IV.

The activity of 2 - amino - 4 - [2 - (1 - methyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine against certain other microorganisms is determined by the use of the well-known streak plate method. The microorganisms are obtained from a 24-hour slant of Difco (Registered Trade Mark) Brain Heart Infusion Agar which is incubated at 37°C. The streaks are made with a suspension of the microorganism in 5 to 6 milliliters of sterile physiological solution. In the case of the strains belonging to the group of mycetes, Difco Malt Agar broth is used and incubation is at 30°C. The streaks so prepared, are incubated for 24 hours. The results are given in Table 9.

TABLE 9

Microorganism	Minimal inhibitory concentration (microgram of active compound per milliliter of broth) F	MET
Aerobacter aerogenes 20 (1)	>100	>100
Bacillus cereus var. *mycoides* ATCC 9634	<12.5–25	>100
Bacillus subtilis ATCC 6633	<12.5	>100
Brucella bronchiseptica	<12.5	>100
Escherichia coli 46 (1)	>100	>100
Micrococcus flavus ATCC 10240	>100	>100
Proteus mirabilis 61 (1)	>100	>100
Proteus vulgaris ATCC 6897	>100	>100
Pseudomonas aeruginosa 77 (1)	>100	>100
Salmonella pullorum ATCC 9120	<12.5	>100
Salmonella typhimurium	>100	>100
Shigella dissenteriae Madsen (1)	>100	>100
Staphylococcus aureus 168 (1) (2)	>100	>100
Streptococcus faecalis	>100	>100
Streptococcus pyogenes	<12.5	>100
Diplococcus pneumoniae	<12.5	>100
Klebsiella pneumoniae	<12.5	>100
Candida albicans	>100	>100
Schizosaccharomyces pombe	>100	>100
Aspergillus niger	>100	>100
Aspergillus flavus	>100	>100

(1) Virulent strain isolated in hospital

(2) Penicillin-resistant strain

It is demonstrated through Example IV that the P-Compounds can be classified as limited spectrum antibacterial agents in that microorganisms which are Gram positive as well as a few Gram negative types are inhibited at 12.5 μg/ml or less.

EXAMPLE V.

Four female patients suffering from vulvovaginitis are orally administered 2 - amino - 4 - [2 - (1 - methyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine in the amount of 500 milligrams per day. Two of the patients

continue with the treatment for one day, and the other two continue with the treatment for three days. Urine samples are taken and are evaluated to determine the concentration of the active compound therein. In all cases, the concentration of the active compound in the urine is maintained at least three times as much as the average concentration required to kill *Trichomonas vaginalis in vitro.*

EXAMPLE VI.

Six female patients who are to undergo colpohysterectomy are orally administered two capsules containing 250 milligrams of 2 - amino - 4 - [2 - (1 - methyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine each per day for a few days prior to surgery. The concentration of the active compound is determined microbiologically using plates of vaginal homogenates. The concentration is found to be about 8 micrograms per gram of homogenate.

EXAMPLE VII.

Thirty female patients suffering from vulvovaginitis and having *Trichomonas vaginalis* present in the vaginal secretion, are orally administered two capsules containing 250 milligrams of 2 - amino - 4 - [2 - (1 - methyl - 5 - nitro - imidazolyl) - vinyl] - pyrimidine each per day. After five days, the presence of *Trichomonas vaginalis* is not found, and no sign of leukorrhea is observed, evidencing successful treatment. In comparison, using metronidazole administered orally in the same amount, ten days of medication are usually required for complete treatment.

As with other imidazole-containing drugs, some secondary effects may be reported in select cases such as nausea, diarrhea, bad breath, urticaria, uretheral and vaginal burning, dizziness, headache, insomnia, and in rare cases, temporary leucopenia.

EXAMPLE VIII.

Example I is repeated except employing as reactants 1,2 - dimethyl - 5 - nitroimidazole and 2 - amino - 4 - (diethoxymethyl) - pyrimidine. The concentrated sulfuric acid (98%) provides sufficient water to initiate and sustain the conversion of the diethoxymethyl group on the pyrimidine to a formyl group and ethanol, and 2 - amino - 4 - [2 - (1 - methyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine is formed *in situ.*

EXAMPLE IX

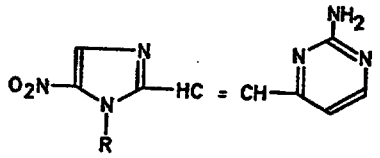
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EXAMPLE X.

Example I is repeated except employing, as reactants, 2 - amino - 4 - methyl pyrimidine and 2 - formyl - 1 - pentyl - 5 - nitroimidazole. 2 - Amino - 4 - [2 - (1 - pentyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine is formed. It is recovered and a sample is used to *in vitro* inhibit the growth of *Trichomonas vaginalis* in vitro tests in accordance with Example II. Another sample is used to form a dosage unit capsule of 250 milligrams, and two capsules per day are orally administered to therapeutically treat a patient suffering from trichomoniasis.

WHAT WE CLAIM IS:—

1. A compound of the formula:



wherein R is an alkyl group containing 1 to 6 carbon atoms.

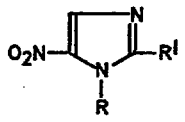
2. A compound according to claim 1, wherein R is an alkyl group containing 1 to 3 carbon atoms.

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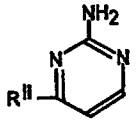
4. A compound according to claim 2, wherein R is ethyl.

5. A compound according to claim 2, wherein R is n-propyl.

6. A 2 - amino - 4 - (2 - imidazolyl - vinyl) - pyrimidine when obtained by reacting together an imidazole derivative of the formula:



and a pyrimidine derivative of the formula:



wherein R is an alkyl group containing 1 to 6 carbon atoms, one of R′ and R″ is a

continue with the treatment for one day, and the other two continue with the treatment for three days. Urine samples are taken and are evaluated to determine the concentration of the active compound therein. In all cases, the concentration of the active compound in the urine is maintained at least three times as much as the average concentration required to kill *Trichomonas vaginalis in vitro.*

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EXAMPLE IX

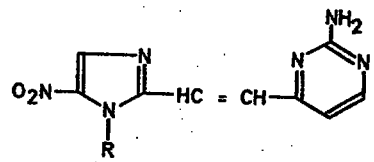
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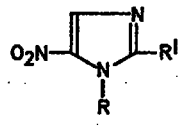
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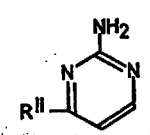
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5. A compound according to claim 2, wherein R is n-propyl.

6. A 2 - amino - 4 - (2 - imidazolyl - vinyl) - pyrimidine when obtained by reacting together an imidazole derivative of the formula:



and a pyrimidine derivative of the formula:



wherein R is an alkyl group containing 1 to 6 carbon atoms, one of R′ and R″ is a

formyl group and the other is a methyl group, in the presence of a dehydrating agent.

7. A compound as claimed in claim 6, wherein R is an alkyl group containing 1 to 3 carbon atoms.

8. A pharmaceutically-acceptable salt of a compound as claimed in any preceding claim.

9. A pharmaceutical composition comprising a compound or salt as claimed in any preceding claim together with a pharmaceutically-acceptable carrier therefor.

10. A pharmaceutical composition as claimed in claim 9, wherein the compound is 2 - amino - 4 - [2 - (1 - methyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine.

11. A pharmaceutical composition as claimed in claim 9, in unit dosage form.

12. A pharmaceutical composition as claimed in claim 9, 10 or 11, which includes one or more inert excipients.

13. A pharmaceutical composition as claimed in claim 9, 10, 11 or 12, in a form suitable for oral administration.

14. A method for therapeutically treating a living warm-blooded non-human animal body afflicted with a protozoal disease or bacterial infection caused by members of the coccus form of bacteria, by species of *Brucella, Salmonella, Klebsiella,* or by pleuropneumonia-like organisms, which comprises therapeutically administering, to the body, a compound, a salt or a pharmaceutical composition as claimed in any preceding claim.

15. A method according to claim 14, wherein the protozoal disease is trichomoniasis, enterohepatitis, trypanosomiasis, amoebiasis, or enteric protozoal disease.

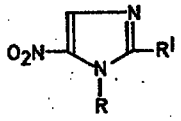
16. A method according to claim 14 or 15, wherein the amount, administered to the body, of said compound, salt or pharmaceutical composition, calculated as the compound, is 1 to 40 milligrams per kilogram of body weight per day.

17. A method according to claim 14, wherein the compound is 2 - amino - 4 - [2 - (1 - methyl - 5 - nitro - 2 - imidazolyl) - vinyl] - pyrimidine.

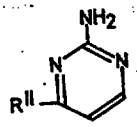
18. A method according to claim 14, 15, 16 or 17, wherein the compound, salt or pharmaceutical composition is administered orally.

19. A method according to claim 17, wherein the animal body has trichomoniasis and the compound is administered in an amount of 1 to 40 milligrams per kilogram of body weight per day.

20. A process for preparing a compound according to claim 1, which comprises reacting a) an imidazole compound of the formula:



with b) a pyrimidine compound of the formula:



where R is an alkyl group containing 1 to 6 carbon atoms, and one of R′ and R″ is



and the other is —CH_3, in the presence of a dehydrating agent to effect a condensation reaction at the



group and the —CH_3 group to form water and a compound of claim 1.

21. A process according to claim 20, wherein R′ is



and R″ is —CH_3 and the reaction is carried out at a temperature in the range from 25° to 150°C.

22. A process according to claim 21, wherein the dehydrating agent is a strong mineral acid and is employed in an amount at least 1.1 times the stoichiometric amount required for completion of the reaction.

23. A process according to claim 20, wherein R′ is —CH_3 and R″ is



and the reaction is carried out at a temperature in the range from 25° to 150°C.

24. A process according to claim 23, wherein the pyrimidine compound is prepared by reacting 2 - amino - 4 - (dialkoxymethyl) - pyrimidine, wherein the alkoxy groups are the same or different and contain 1 to 6 carbon atoms, with water.

25. A process according to claim 24, wherein the pyrimidine compound is prepared *in situ.*

26. A process according to claim 20, wherein R is methyl.

27. A pharmaceutical composition contain-

ing a compound or salt as claimed in claim 1 or 12 and substantially as hereinbefore described.

28. A method of preparing an imidazolyl - pyrimidine derivative substantially as described in one of the foregoing Examples I, VIII, IX and X.

29. A method of treating protozoan or bacterial infection with a compound as claimed in claim 1, substantially as described in one of the foregoing Examples II, III and IV.

HASELTINE, LAKE & CO.,
Chartered Patent Agents,
Hazlitt House,
28, Southampton Buildings,
Chancery Lane, London WC2A 1AT,
— also —
Temple Gate House, Temple Gate,
Bristol BS1 8PT,
— and —
9, Park Square,
Leeds LS1 2LH, Yorks.

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