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PREPARATIONS AND METHOD FOR TREATING INFLAMMATORY CONDITIONS

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This invention relates generally to pharmaceutical preparations which inhibit or control various aspects of inflammation, and more particularly, to preparations which are especially effective in causing a remission in the symptoms and signs of inflammatory diseases such, for example, as rheumatoid arthritis, lupus erythematosus disseminatus, ankylosing spondylitis, psoriatic arthritis, gouty arthritis, fibromyosistis, osteoarthritis, bursitis, scleroderma and other inflammatory conditions such as bronchial asthma, pulmonary emphysema, pulmonary fibrosis, inflammation resulting from infection, inflammation resulting from tissue injury, inflammation resulting from allergy, skin disorders, including atopic dermatitis, contact dermatitis, dermatitis herpetiformis, angioedema, urticaria, and exfoliative dermatitis, pemphigus, inflammatory eye diseases including keratitis, allergic conjunctivitis, nongranulomatous iritis, iridocyclitis, choroiditis, uveitis, chorioretinitis, neophrotic syndrome, and the like.

Considering rheumatoid arthritis as illustrative of the inflammatory diseases, including those attended by both chronic and acute inflammatory conditions, rheumatoid arthritis is generally defined as a chronic, though non-fatal disease, of uncertain origin, which affects one or more of the patient's joints by redness, pain, heat and/or swelling. Frequently, inflammation in a joint causes deformity and loss of function.

For purposes of this disclosure, the foregoing shall be referred to as inflammatory diseases and the like and inflammation shall refer to the occurrence of one or more of the symptoms: redness, pain, heat and swelling.

The traditional approach to therapeutic treatment of the inflammatory diseases such as rheumatoid arthritis, heretofore comprised administering to the afflicted patient a variety of analgesics and antipyretics and even narcotics.

In more modern times, greater attention has been given to the use of hormones and steroids having a systemic effect, for example, ACTH, cortisone, cortisone acetate, hydrocortisone, prednisolone, and the prednisolone derivatives. In addition, the hormones and steroids have been combined with analgesics and antipyretics to provide further therapeutic approaches.

From the many approaches available, it is generally accepted that the most desirable result, when the patient can assimilate and tolerate the drug, is achieved by the administration of the glucocoricoid steroids.

However, extreme care must be exercised with the administration of these steroids because they are known to cause undesirable changes in bone structure, in electrolyte and carbohydrate metabolism as well as induce moon face, hirsutism, hypokalemia, peptic ulcers, hypertension, acne, amenorrhea, severe mental disturbances and suppression of the adrenocortical pituitary function.

Furthermore, the glucocorticoid steroids cannot be used except with extreme caution in the presence of active turberculosis, diabetes mellitus, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure or renal insufficiency. In addition, the corticosteroids are not generally acceptable to patients in early stages of pregnancy. Further, corticosteroids should not usually be administered in the presence of infection because they inhibit fibroplasia and therefore, can mask the dissemination of the causative

organism. Still further, in many cases of inflammatory disease, such as rheumatoid arthritis, the corticosteroids are ineffective, that is, the patients are resistant to steroid therapy.

Thus, in spite of the promise the glucocortico steroids bring to the field of treating the inflammatory diseases, they are fraught with sufficient disadvantages to demand that research continue for therapeutic agents having equal or better properties and substantially less, if not none, of the undesirable side effects.

The present invention is based upon our discovery of such a therapeutic agent in 5-amino-1-phenyl tetrazole which, when prepared in suitable dosage form and appropriately administered to patients afflicted with chronic or acute inflammatory conditions, such as a rheumatoid disease, has the completely unexpected and highly beneficial property of regressing and controlling the inflammatory aspects of the rheumatoid disease and thereby reduces and substantially alleviates the greatest cause of pain and discomfort to the patient so affected. Further, our preparations achieve this result without creating the myriad of side effects heretofore characterising the pharmaceutically acceptable medicaments available for treating such diseases. Still further, our preparation is found effective in treating cases which do not respond to steroid therapy.

Accordingly, a principal object of the present invention is to provide new and useful pharmaceutical preparations having anti-inflammatory properties and which are especially suited for providing relief and comfort for patients afflicted with chronic and acute inflammatory conditions.

Another object of the present invention is to provide new and useful pharmaceutical preparations which are effective in the treatment of inflammatory conditions while being relatively free from adverse side effects particularly those which have heretofore characterized the use of glucocortico steroids.

Another object of the present invention is to provide new and useful pharmaceutical preparations which are effective in providing rheumatoid patients with relief and are characterized by low-toxicity.

Still a further object of the present invention is to provide a new and useful method of treating the signs and symptoms of chronic and acute inflammatory conditions.

Still another object of the present invention is to provide a new and useful method of treating rheumatoid diseases, such as rheumatoid arthritis, which provides results superior to the results heretofore obtained with glucocortico steroids while substantially eliminating the undesirable side effects inherent in glucocortico steroid therapy.

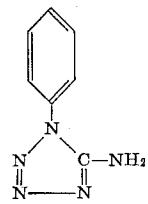
Still another object of the present invention is to provide new and useful pharmaceutical preparations which are useful in the treatment of inflammatory conditions which do not respond to steroid therapy, both when administered as the sole therapeutic agent and when employed in combination with the previously ineffective steroid.

These and still further objects, as shall hereinafter appear, are fulfilled by the present invention to a remarkably unexpected extent as shall become apparent from a consideration of the following description of embodiments exemplifying the invention.

The invention is predicated upon our discovery of novel medicinal preparations which are unique in that they are potent anti-inflammatory agents which, when compared with known preparations for treating chronic and acute inflammatory conditions, have a totally unexpected reduced incidence of side effects.

Specifically, the preparations of this invention are most advantageously in a dosage unit form and comprise a

non-toxic pharmaceutical carrier and 5-amino-1-phenyl tetrazole which has the following structural formula:



5-amino-1-phenyl tetrazole can be prepared by treating phenylthiourea with methyl iodide in anhydrous ethanol at reflux. This yields, after the solvent is removed by distillation and the residue crystallized and washed with anhydrous ether, 1-phenyl-S-methyl-isothiourea hydriodide.

The 1-phenyl-S-methyl-isothiourea hydriodide is, in turn, treated with anhydrous hydrazine in ethanol to give, on heating, a vigorous evolution of methyl mercaptan and, after removing the solvent by distillation under vacuum, a heavy syrup, viz, 1-phenyl-3-amino-guanidine hydriodide.

The syrup is then dissolved in water and treated with an aqueous solution containing silver nitrate and concentrated nitric acid. After mixing, concentrated hydrochloric acid is added and the precipitated silver halides are removed by filtration. Additional hydrochloric acid then is added and the solution is cooled to 10° C. A cold solution of sodium nitrite is then added and the pH is adjusted to a range of 8–9 by the addition of solid sodium carbonate. This mixture is stirred for a period of time at 10° C., heated to 50° C., and recooled to 10° C. The resulting precipitate is collected by filtration and washed with cold water. Recrystallization of the precipitate from anhydrous ethanol yields 5-amino-1-phenyl tetrazole.

A non-toxic pharmaceutically acceptable organic or inorganic acid addition salt of 5-amino-1-phenyl tetrazole may be used in lieu of the 5-amino-1-phenyl tetrazole, in the preparation of this invention. For example, the salt derived from acids such as hydrochloric, sulfuric, nitric, phosphoric, citric, acetic, malonic, lactic, tartaric, sulfamic, succinic, fumaric, maleic, ethanedisulfonic, hydrobromic, benzoic and similar non-toxic acids are suitable in the practice of the invention. These salts are best prepared by reacting the 5-amino-1-phenyl tetrazole with a stoichiometric amount of the desired organic or inorganic acid in a suitable solvent such as ether, ethanol, acetone, water or various combinations of solvents.

The 5-amino-1-phenyl tetrazole ingredient will be present in an amount to produce an anti-inflammatory effect. In preparations to be administered orally, pancavally and otherwise than at the actual situs of the inflammation (herein called "systemic administration," the preparation preferably will contain the active medicament in amounts calculated to provide daily dosages of from about 50 mg. to about 8000 mg., and, advantageously, from about 400 mg. to about 2400 mg. When the preparations are administered directly at the situs of the inflammation, e.g., topically, interarticularly and the like, amounts of medicament of as low as 1 mg. may be more than adequate to achieve the desired result.

The pharmaceutically acceptable carrier may be, for example, either a solid or a liquid. Exemplary of suitable solid carriers are lactose, magnesium stearate, sucrose, talc, stearic acid, gelatin, agar pectin, acacia and the like. Exemplary of suitable liquid carriers are glycols, polyglycols, peanut oil, olive oil, sesame oil, and the like. If desired, the carrier or diluent may include a time delay material such as glycerol monostearate or glycerol distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, used as a pharmaceutical powder, placed in a hard gelatin capsule, or in the form of a troche or lozenge.

The amount of solid carrier per dosage unit will vary widely but preferably will be from about 25 mg. to about 1 gram.

If a non-solid carrier is used, the preparation may be in the form of a soft gelatin capsule, a liquid suspension, an emulsion, an ointment, a suppository, a gel or a solution. The amount of non-solid carrier per dose is not critical and may be adjusted to suit convenience. This form of the preparation may be administered orally, topically, intravenously or pancavally, the carrier being preselected according to the administration route desired.

All of the various dosage forms of these preparations can be made by following such of the conventional and well known manufacturing techniques of mixing, granulating, compressing, suspending and dissolving as may be appropriate to the desired end product.

The method of using these materials in accordance with this invention comprises administering to a patient afflicted with the inflammatory condition, 5-amino-1-phenyl tetrazole or a non-toxic organic or inorganic acid addition salt thereof, preferably combined with a non-toxic pharmaceutical carrier of the type disclosed in an amount to produce an anti-inflammatory effect. As with prior therapeutic agents, the amount required in each case must of necessity be subjective and take into account the diagnosis of the cause of the inflammation, the medical history of the patient and the like. The active medicament in dosage units in most cases will be sufficient to provide a convenience oral or pancaval daily regimen by administering from 50 mg. to about 8000 mg. per day, advantageously from about 400 mgs. to about 2400 mgs. per day. As indicated previously, administration to the direct situs of inflammation requires substantially less medicament to achieve the desired result.

Thus, the administration of the preparation to the patient may be intramuscularly, parenterally, topically, pancavally, or orally, the latter being the preferable route of administration. "Pancavally" as used herein defines administration via all of the body's openings whether natural as the vagina, the anus, the nares, or artificial, e.g. colostomy.

In a practice of the invention, when systemic administration as indicated, the preparation is preferably administered orally one to four times daily to provide a daily regimen of from about 50 mg. to about 8000 mg. of active medicament, advantageously from about 400 mg. to about 2400 mg.

When local administration is indicated, the preparation is preferably administered topically or interarticularly and can contain as little as 1 mg. of active medicament per dose, depending on the specific condition being treated.

When the administration described above is carried out, the anti-inflammatory action is produced rapidly and effectively. This method of producing anti-inflammatory action by this invention is particularly effective when applied to human beings having rheumatoid diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, gouty arthritis, fibromyositis, osteoarthritis and bursitis. The method is also useful in the treatment of collagen diseases such as scleroderma, lupus erythematosus disseminatus and in treating other inflammatory conditions as are associated with allergic bronchial asthma, pulmonary emphysema, pulmonary fibrosis, infection, tissue injury and the like.

The preparations are also effective in the treatment of inflammatory conditions accompanying intractable hay fever (pollinosis); skin disorders including atopic dermatitis (eczema), contact dermatitis, poison ivy dermatitis, neuro-dermatitis, dermatitis herpetiformis, angioedema, urticaria, and exfoliative dermatitis, pemphigus, inflammatory eye diseases including keratitis, allergic conjunctivitis, non-granulomatous iritis, iridocyclitis, choroiditis, uveitis, chorioretinitis, marginal corneal ulcers and secondary glaucoma complicating inflammatory eye diseases; nephrotic syndrome and adrenogenital syndrome.

The following examples are presented to aid in pro-

viding a clear understanding of the present invention and of the pharmaceutical compositions therein involved and are not intended in any way to be limiting.

Example I

A mixture of 152 g. (1.0 mole) of phenylthiourea, 142 g. (1.0 mole) of methyl iodide and 1 liter of anhydrous ethanol was refluxed with stirring for 1 hour. The solvent was removed by distillation under vacuum, an the residue which crystallized upon standing, was washed with anhydrous ether and dried to yield 274 g. (93% of theory) of 1-phenyl-S-methylisothiourea hydriodide, (M.P. 145–6° C.).

To a suspension of 274 g. (0.93 mole) of 1-phenyl-S-methylisothiourea hydriodide in 750 ml. of anhydrous ethanol was added 34.9 g. (1.0 mole) of 95% anhydrous hydrazine. The mixture was heated gently with stirring until the initial vigorous evolution of methyl mercaptan had subsided. The solution was refluxed with stirring for an additional hour and the solvent was removed by distillation under vacuum. The 1-phenyl-3-aminoguanidine hydriodide, which was obtained as a heavy syrup, weighed 253 g. (98% of theory).

To a solution of 253 g. (0.91 mole) of 1-phenyl-3-aminoguanidine hydriodide in 2 liters of water was added a mixture of 155 g. (0.91 mole) of silver nitrate, 500 ml. of water and 15 ml. of concentrated nitric acid.

After mixing for 5 minutes, 40 ml. of concentrated hydrochloric acid was added. The precipitated silver halides were removed by filtration and washed with 400 ml. of water. The filtration and wash were combined and diluted to approximately 4 liters. An additional 40 ml. of concentrated hydrochloric acid was added, and the solution was cooled to stirring to 10° C. in an ice-bath. A cold solution of 69.0 g. (1.0 mole) of sodium nitrite in 160 ml. of water was added dropwise at a rate to maintain the temperature at 10 to 15° C. When the addition was completed, stirring and cooling were continued for 30 minutes and the pH was adjusted to 8–9 by the addition of solid sodium carbonate. After stirring for an additional hour at 10° C., the mixture was heated to 50° C. and cooled once more to 10° C. The precipitate was collected by filtration, washed with cold water and dried. Recrystallization from anhydrous ethanol yielded 86.5 g. (59% of theory) of 5-amino-1-phenyl-tetrazole, M.P. 161–2° C., dec.

Example II

200 mg. of 5-amino-1-phenyltetrazole, 15 mg. of sorbitol and 85 g. of mannitol were milled to uniform powder and granulated into 6 mg. of gelatin as a 10% solution. The mixture was then screened onto trays and dried at 60° C. The dried granules were sized and mixed with 30 mg. of cornstarch and 4 mg. of magnesium stearate and then compressed into tablets.

Example III

Ingredients:	Weight, mg.
5-amino-1-phenyltetrazole	200
Avicel (microcrystalline cellulose)	150
Polyvinyl pyrrolidone	5
Magnesium stearate	4

The first three ingredients were mixed to uniformity and lubricated with a portion of the magnesium stearate. The mixture was compressed into slugs, and the slugs were reduced to uniformity and granulated. The powder was then lubricated with the remainder of the magnesium stearate and compressed into tablets.

Example IV

Ingredients:	Weight, mg.
5-amino-1-phenyltetrazole	200
Lactose	175
Magnesium stearate	5

The above ingredients were screened through a #40 U.S. mesh screen or mill to a uniform powder, transferred to a mixer, mixed well and filled into #1 hard gelatin capsule.

Example V

Ingredients:	Weight, mg.
5-amino-1-phenyltetrazole	50
Sesame oil	50

The ingredients are mixed into a thick slurry and filled into a soft gelatin capsule.

Example VI

Ingredients:	Weight, mg.
5-amino-1-phenyltetrazole	300
Polyethylene glycol 400	240

The ingredients are mixed into a thick slurry and filled into a soft gelatin capsule.

Example VII

Ingredients:	Amount
5-amino-1-phenyltetrazole	grams 200
Polyethylene glycol 200, q.s. up to 1 liter.	

The ingredients are added together and warmed to about 50° C.–60° C. to effect solution and stirred. The solution was then sterile filtered, cooled to room temperature, packaged in sterile vials and stored until needed.

Example VIII

A suitable suppository having a melting point of about 60° F. was prepared having the following ingredients in the amounts indicated.

Ingredients:	Amount, mg.
5-amino-1-phenyltetrazole	200
Polyethylene glycol 600	200
Polyethylene glycol 4000	800

The ingredients were mixed together and heated to about 60° C. to effect solution. The solution was then poured into cooled molds and permitted to cool and solidify.

Example IX

An ointment embodying the present invention was prepared from the following ingredients in the amounts indicated.

Ingredients:	Amount, mg.
5-amino-1-phenyltetrazole	200
Polyethylene glycol 1540	500
Polyethylene glycol 4000	80
Propylene glycol	200
Cetyl alcohol	20

The polyethylene glycols and cetyl alcohol are mixed together and warmed to about 60° C. Next, the 5-amino-1-phenyltetrazole is stirred into the mixture to effect solution. The solution is then removed from the warmer and the propylene glycol is added thereto with stirring until cool. The cool ointment is then placed in an ointment jar and is removed therefrom for topical application as needed.

Example X

5-amino-1-phenyltetrazole was administered orally to patients with definite rheumatoid arthritis by A.R.A. criteria. The majority of the patients had failed to previously respond to gold, corticosteroids or both. A total of thirty-two (32) patients were so treated for intervals varying from two (2) to sixty-eight (68) weeks for a mean treatment period of twelve (12) weeks.

The grade of response and duration of treatment of each patient are reported in Table I below.

Table II summarizes our results. Fifteen point six percent (15.6%) of the patients treated obtained complete suppression of disease while sixty-eight point seven percent (68.7%) obtained major improvement. Fifteen point six percent (15.6%) obtained only minor improvement.

The only side reactions noted in the group were: skin rash in six (6) patients. (Five (5) of these patients were

able to take the drug in a repurified form without further rash and the sixth quit the program.) Two (2) patients complained of slight gastric discomfort but were able to continue on the program. Two (2) patients developed leukopenia but both were females over seventy-five (75) years of age and both had relative neutropenia and lymphocytosis before treatment began.

While still further trials are desirable, it is already notable that 5-amino-1-phenyltetrazole has the ability to obtain excellent response in patients not controlled previously on corticosteroids and gold, and that the response of 5-amino-1-phenyltetrazole persisted for long periods when the administration of the drug was stopped for skin rash.

TABLE I

	Grade of Response	Duration of Treatment (Weeks)
Patient No.:		
1	II	68
2	II	36
3	I	26
4	II	26
5	I	20
6	II*	20
7	II	18
8	I	16
9	II	16
10	II	13
11	III	12
12	I	11
13	II	11
14	II	11
15	II	11
16	II	11
17	I	10
18	II	8
19	II	8
20	III	7
21	II	7
22	II	6
23	II	6
24	II	6
25	II	4
26	II	4
27	II	4
28	II	4
29	III	4
30	III	2
31	II	2
32	III	2

*Reclassified as Disseminated *Lupus erythematosus.*

TABLE II.—RESPONSE OF RHEUMATOID ARTHRITIS TO 1-PHENYL-5-AMINO TETRAZOLE

Grade of Improvement	Number of Patients	Percent
I Complete	5	15.6
II Major	*22	68.7
III Minor	5	15.6
IV	0	0

* One case reclassified as Disseminated *Lupus Erythematosus.*

Example XI

Several case histories of therapy with 5-amino-1-phenyltetrazole have been compiled from the records of the Brooklyn Hospital, Brooklyn, N.Y., and are reported below. Each patient was treated on an out-patient basis and upon admittance to the program, was given a serum glucose oxidase transaminase (SGOT), a serum glutamic pyruvate transaminase (SGPT), a complete blood count (CBC), a blood urea analysis (BUN) and urine analysis.

The incoming patients afflicted with rheumatoid arthritis were classified according to the standards promulgated by the American Rheumatism Association (ARA) and the response of the patient was measured by joint score.

"Joint score," as used herein, refers to a rating obtained by evaluating the degree of joint involvement on the basis of heat, swelling, tenderness and pain. The criteria is 0 for no involvement and actual involvement is measured in increments of from 1 to 4 pluses, 4 pluses (i.e., ++++) being maximal involvement. Each "+" comprises one unit of score. A further symbol "±," treated as 0.5 unit of score, is used to reflect a very slight involvement. Obviously, a certain amount of joint score rating is based on the skill and experience of the physician doing the rating. The physician who rated these tests is highly skilled in treating inflammatory conditions and especially the rheumatoid diseases.

In compiling the patient's joint score, ten joints are considered and each is evaluated for (a) heat; (b) swelling; (c) tenderness; and (d) pain. Thus, the final joint score is the summation of forty (40) separate evaluations.

The joints considered are: (1) the proximal interphalangeal (PIP); (2) the metacarpophalangeal (MCP); (3) the right wrist (RW); (4) the left wrist (LW); (5) the right elbow (RE); (6) the left elbow (LE); (7) the right knee (RK); (8) the left knee (LK); (9) the right angle (RA); and (10) the left angle (LA).

We will now report a summary of the specific case histories in Table III, below,

TABLE III.—SUMMARY OF CASE HISTORIES

Case No.	Sex	Age	ARA		Joint Score	
			Grade	Class	S	F
1	F	62	iv	iii	37	10
2	F	50	iii	iv	18	3.5
3	F	40	ii	i	11	0
4	F	34	----------	----------	6.5	2.0
5	F	31	iii	iii	12	0
6	M	53	iii	i	26	1.0
7	F	47	ii	ii	9	1.5
8	M	----------	iii	ii	3	0
9	F	40	ii	iii	16	2.5
10	F	51	iii	iii	18	0.5
11	F	57	iii	i	9	1.5
12	F	41	ii	i	5	0
13	F	54	iv	iv	18	7
14	F	71	----------	----------	8	2.5
15	F	77	iii	iv	18	4
16	F	50	----------	----------	15.5	4
17	F	36	iii	iii	31.5	*8.5
8	F	44	i	ii	12	0.5

*Combined therapy employed throughout test period.
Explanation of abbreviations used in Table III:
ARA—American Rheumatism Association Classification.
S—At start of therapy with 5-amino-1-phenyltetrazole.
F—At withdrawal from drug or completion of program.

From the foregoing description and examples, it becomes apparent that new and useful anti-inflammatory preparations and methods of producing anti-inflammatory action therewith have been discovered which fulfill all of the aforestated objectives in a remarkably unexpected manner. It is of course understood that the several examples herein disclosed are for illustrative purposes only and that such alterations, modifications and applications as readily occur to the artisan confronted with this disclosure are intended within the spirit of this invention, especially as it is defined by the scope of the claims appended hereto.

Accordingly, what we claim is:

1. A pharmaceutical preparation having anti-inflammatory activity comprising a pharmaceutically acceptable carrier and from about 1 mg. to about 8000 mg. of a member selected from the group consisting of 5-amino-1-phenyl tetrazole and its non-toxic pharmaceutically acceptable acid addition salts.

2. A preparation according to claim 1 in unit dosage form.

3. A preparation according to claim 2 containing from about 50 to about 8000 mg. of 5-amino-1-phenyl tetrazole.

4. A preparation according to claim 2 for topical administration in which said carrier is selected from the group comprising lactose, magnesium stearate, sucrose, talc, stearic acid, gelatin, agar pectin, acacia, glycols, polyglycols, peanut oil, olive oil, and sesame oil.

5. A preparation for the treatment of a patient having rheumatoid arthritis containing a pharmaceutically acceptable carrier and as an essential therapeutic agent from about 1 mg. up to about 8000 mg. of 5-amino-1-phenyl tetrazole effective to obtain a control on the overt manifestations of rheumatoid arthritis as evidenced by the patient's joint score.

6. A method of providing anti-inflammatory action in animals, including man, comprising administering to an animal suffering from an inflammatory condition a

compound selected from the group consisting of 5-amino-1-phenyl tetrazole and its non-toxic pharmaceutically acceptable acid addition salts in an amount sufficient to provide anti-inflammatory action.

7. The method of claim 6 in which the administration is to human beings afflicted with rheumatoid diseases and the route of administration is pancavally.

8. The method of claim 6 in which the administration is to humans afflicted with rheumatoid arthritis and the route of administration is oral.

9. The method of controlling an inflammatory condition in animals, including man, comprising administering to an animal so afflicted, a daily dose of up to about 8000 mg./daily of a compound selected from the group consisting of 5-amino-1-phenyl tetrazole and its non-toxic pharmaceutically acceptable acid addition salts.

10. The method of claim 9 in which said daily dose comprises at least about 200 mg. of said compound and the administration is systemic.

11. The method of claim 9 in which said daily dose comprises at least about 1 mg. of said compound and said administration is directly to the situs of the inflammatory condition.

12. The method of controlling and suppressing the inflammatory aspects of rheumatoid arthritis in man comprising administering to a man afflicted with rheumatoid arthritis via the oral route a small but effective amount up to about 80000 mg./daily of a compound selected from the group consisting of 5-amino-1-phenyl tetrazole and its non-toxic pharmaceutically acceptable acid addition salts.

13. The method of controlling and reducing in an afflicted patient the overt manifestations of rheumatoid arthritis as measured by joint score comprising administering to said patient a drug containing as an essential active ingredient a compound selected from 5-amino-1-phenyl tetrazole and its non-toxic pharmaceutically acceptable acid addition salts on a daily regimen.

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