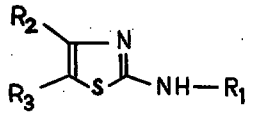
SPECIFICATION

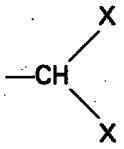
Novel Aminothiazoles

This invention relates to novel substituted aminothiazoles useful for relieving inflammatory conditions and as immune regulants.

A number of compounds have been known in the art to be useful as anti-inflammatory agents, for example the cortico steroids, phenylbutazone, indomethacin and various 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-4-carboxamide-1,1-dioxides, such as those disclosed in United States Patent No. 3,591,584. Accordingly, these compounds have been of therapeutic value in the treatment of arthritic and other inflammatory conditions such as rheumatoid arthritis. Such conditions have also been treated by administration of immunoregulatory agents, such as levamisole, as described for example in Arthritis Rheumatism *20*, 1445 (1977) and Lancet *1*, 393 (1976). In efforts to find new and improved therapeutic agents for the treatment of these conditions, it has now been found that the novel aminothiazoles of the present invention have a particularly desirable combination of pharmacological properties, namely that they are active both as anti-inflammatory agents and as regulants of the immune response in the body. Accordingly, they are of particular value in the treatment of rheumatoid arthritis and other conditions where relief of the inflammation and regulation of the body immune response is desired. Thus according to the invention there are provided novel compounds of the formula:



and the pharmaceutically acceptable acid addition salts thereof, wherein R_1 is:



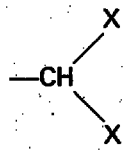
$-(CH_2)_n-X$, $-CH_2-CH_2-NH-X$ or $-(CH_2)_mY$, wherein X is phenyl optionally monosubstituted with alkyl of 1 to 3 carbon atoms, hydroxy, alkoxy of 1 to 3 carbon atoms, chloro, bromo, or fluoro; Y is thienyl or furyl each being optionally monosubstituted with alkyl of 1 to 3 carbon atoms, chloro, bromo or fluoro; n is 2; m is 1 or 2; R_2 is phenyl, thienyl or monosubstituted phenyl, said substituent being alkyl of 1 to 3 carbon atoms, hydroxy, alkoxy of 1 to 3 carbon atoms, chloro, bromo or fluoro; and R_3 is hydrogen, alkyl of 1 to 3 carbon atoms, phenyl or monosubstituted phenyl, said substituent being alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, or fluoro.

Preferred substituents for R_2 are phenyl and p-fluorophenyl and for R_3 are hydrogen and phenyl.

A preferred group of compounds is that wherein R_1 is $-(CH_2)_n-X$, where n is 2. Most preferred are those compounds where X is phenyl or p-methoxy phenyl, R_2 is phenyl or p-fluorophenyl, R_3 is phenyl, methyl or hydrogen, including 2-phenethyl-amino-4-phenyl-thiazole, 2-phenylethylamino-4,5-diphenyl-thiazole and 2-phenethylamino-5-methyl-4-phenyl-thiazole.

A further group of interest is that wherein R_1 is $-(CH_2)_m-Y$, especially where m is 1. Preferred groups for Y are thienyl and furyl especially those compounds where R_2 is phenyl or p-fluoro-phenyl and R_3 is hydrogen, methyl and phenyl.

Yet a further group of compounds are those wherein R_1 is

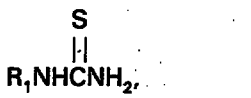


preferred compounds being those where X is phenyl, R_2 is phenyl and R_3 is hydrogen or phenyl.

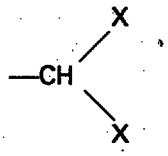
Another group of compounds of interest are those wherein R_1 is $-CH_2-CH_2-NH-X$, especially those compounds where X is phenyl, R_2 is phenyl and R_3 is hydrogen.

Also embraced by the present invention are pharmaceutical compositions comprising a novel substituted aminothiazole of this invention, as described above herein, or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier or diluent. Preferred pharmaceutical compositions are those containing the preferred compounds described above and most preferably containing 2-phenethylamino-4-phenyl-thiazole, 2-thenylamino-4-(p-fluorophenyl)-thiazole or 2-(p-methoxy)phenethylamino)-4-(p-fluorophenyl)-thiazole or pharmaceutically acceptable acid addition salts of these compounds.

The novel aminothiazoles of this invention are prepared from an appropriately substituted N-aryl thiourea of the formula



where R_1 is as previously defined. The latter compounds are readily prepared from known and readily available amines of the formula R_1NH_2. For example, when the group R_1 is $-(CH_2)_n-X$, unsubstituted or appropriately substituted phenethylamines are employed. Corresponding thenyl or furyl alkylamines will be used to prepare compounds where R_1 is $-(CH_2)_m-Y$. Where R_1 is



unsubstituted or substituted diphenylmethylamines are appropriate starting materials, while when R_1 is $-CH_2-CH_2-NH-X$, unsubstituted or substituted n-phenethylenediamines are employed. In the above, X, Y, n and m are as previously defined. The amine starting material is first converted to the hydrochloride or other hydrohalide salt by reaction with hydrogen chloride or other hydrogen halide, generally by bubbling the gas into a solution of the amine in an inert organic solvent, typically an ether such as diethyl ether, at a temperature of about −10°C to about 10°C. The amine hydrohalide salt is then reacted with ammonium thiocyanate or an alkali metal thiocyanate, such as potassium thiocyanate, in an inert organic solvent, generally an aromatic solvent such as bromobenzene, chlorobenzene, xylene and the like, to form the desired N-aralkyl thiourea. The reaction is preferably conducted in an inert atmosphere, for example under nitrogen, at a temperature of about 110°C to about 250°C, preferably 150°C to 200°C, for example at the reflux temperature in bromobenzene. The reaction will generally be complete in about 30 minutes to about 6 hours depending on the temperature employed, generally in about 1 to 3 hours at 150 to 200°C. In preparing the N-aralkyl thioureas as described above, it is usually found that some bis-aralkyl substituted thiourea is formed, but this can be readily separated from the desired monosubstituted product, for example by recrystallization. It has, however, been found that the reaction of substituted or unsubstituted diphenylmethylamine hydrohalides and ammonium thiocyanate yields predominantly the bis-substituted thiourea, although smaller amounts of the monosubstituted compounds can be obtained in this reaction, and after separation can be used as starting material for the novel aminothiazoles. It has, however, also been found that the bis-substituted thioureas can be used as starting material for the formation of the desired diphenylmethylaminothiazoles of this invention, the bis-substituted thiourea decomposing in situ to generate the monosubstituted compound.

The appropriate N-aralkyl thiourea is converted to the desired aminothiazole by reaction with an appropriately substituted α-halo-ketone or aldehyde of the formula $R_2COCH(Z)R_3$, wherein R_2 and R_3 are as previously defined and Z is halo, preferably chloro or bromo. For example, when R_2 is phenyl and R_3 is hydrogen, α-bromoacetophenone may be employed, while when R_2 and R_3 are both phenyl an appropriate reagent is a desyl halide, for example 2-chloro-2-phenyl-acetophenone. Other appropriate α-halo ketones or aldehydes will be readily selected in order to give the desired R_2 and R_3 substituents in the thiazole ring. The reaction is conducted in an inert organic solvent, typically an n-alkanol of 1 to 6 carbon atoms, preferably in absolute ethanol. Reaction temperatures between about 50° and 175°C are employed, preferably the reflux temperature of the solvent. The reaction is preferably conducted in an inert atmosphere, for example, under nitrogen or another inert gas. The reaction is generally essentially complete in about 1 to 15 hours depending on the temperature employed, for example in about 1 to 4 hours when using ethanol at reflux temperature. The desired compound will be obtained as the hydrohalide salt and the free base can then be prepared from the salt by conventional means, for example by contacting with an excess of a base such as an alkali metal hydroxide or carbonate, followed by extraction of the desired free base aminothiazole with a suitable organic solvent, for example an ether like diethyl ether.

The pharmaceutically acceptable acid addition salts of the novel aminothiazoles are also embraced by the present invention and are readily prepared by contacting the free base with the appropriate mineral or organic acid in either aqueous solution or in a suitable organic solvent. The solid salt may then be obtained by precipitation or by evaporation of the solvent. The pharmaceutically acceptable acid addition salts of this invention include, but are not limited to, the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, nitrate, phosphate, acetate, lactate, maleate, fumarate, oxalate, citrate, tartrate, succinate, gluconate, methansulfonate, and the like.

The novel aminothiazoles of this invention and their pharmaceutically acceptable acid addition salts are useful as anti-inflammatory agents and as regulants of the immune response in warm-blooded

animals. The combination of anti-inflammatory activity and immune regulant activity is particularly valuable in the treatment of conditions such as rheumatoid arthritis and other diseases associated with immune deficiency and accompanied by inflammation. Thus, the compounds of the present invention act to relieve the pain and swelling associated with such conditions while also regulating the immune response of the subject and thereby alleviating the underlying immune disorder by maintaining immune competence. The compounds of the present invention may be administered to the subject in need of treatment by conventional routes, such as orally or parentally, dosages in the range of about 0.10 to about 50 mg/kg body weight of the subject per day, preferably about 0.15 to about 15 mg/kg body weight per day being suitable. However, the optimum dosage for the individual subject being treated will be determined by the person responsible for treatment, generally smaller doses being administered initially and thereafter gradual increments made to determine the most suitable dosage. This will vary according to the particular compound employed and with the subject being treated.

The compounds may be used in pharmaceutical preparations containing the compound or a phamaceutically acceptable acid addition salt thereof in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The active compound will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described above. Thus, for oral administration the compounds may be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions may, if desired, contain additional components such as flavorants, sweeteners, excipients and the like. For parental administration the compounds may be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions of the aminothiazoles in sesame or peanut oil, aqueous propylene glycol and the like may be used, as well as aqueous solutions of water-soluble pharmaceutically acceptable acid addition salts of the compounds. The injectable solutions prepared in this manner may then by administered intraveneously, interperitoneally, subcutaneously or intramuscularly, with intravenous and interperitoneal administration being preferred. For local treatment of inflammation the compounds may also be administered topically in the form of ointments, creams, pastes and the like in accord with conventional pharmaceutical practice.

The activity of the compounds of the present invention as anti-inflammatory agents may be determined by pharmacological tests, for example the standard carrageenin-induced rat foot edema test using the general procedure described by C. A. Winter *et. al.*, see Proceedings of the Society of Experimental Biology in Medicine, volume 111, page 544 (1962). In this test, anti-inflammatory activity is determined as the percent inhibition of edema formation in the hind paw of male albino rats (generally weighing about 150 to 190 grams) in response to a sub-plantar injection of carrageenin. The carrageenin is injected as a 1% aqueous suspension 1 hour after oral administration of the drug, which is normally given in the form of an aqueous solution or suspension. Edema formation is then assessed 3 hours after the carrageenin injection by comparing the initial volume of the injected paw and the volume after a 3 hour period. The increase in volume 3 hours after carrageenin injection constitutes the individual response. Compounds are considered active if the response between the drug-treated animals (6 rats per group) and the control group i.e. the animals receiving the vehicle alone, is found to be significant on comparison with the results afforded by standard compounds like acetylsalicyclic acid at 100 mg/kg or phenylbutazone at 33 mg/kg, both by the oral route of administration.

The immune reagent activity of the compounds of the present invention may be determined by such pharmacological tests as the stimulation *in vitro* of lymphocyte proliferation of murine thymus cells cultured in the presence of Concanavalin A (Con A), employing the general evaluation procedure of V. J. Merluzzi *et. al.*, see Journal of Clinical and Experimental Immunology, Volume 22, page 486 (1975). In this study, four different levels of lymphocyte stimulation assay (LSA) activity were established for the compounds undergoing evaluation, viz., those equal to Con A alone; those superior to Con A activity but less than levamisole, the standard compound of choice in this area; those having an activity equal to levamisole; and those having an activity greater than levamisole. Compounds are considered to be active for the present purposes if they are superior to Concanavalin A.

The present invention is illustrated by the following examples. However, it should be understood that the invention is not limited to the specific details of these examples.

Example 1

A. Phenethylamine (479 grams, 3.96 moles, Eastman Scintillation Grade) was dissolved in 3500 ml of diethyl ether and the solution was cooled to 0°C. Dry halogen chloride gas was bubbled through the stirred solution for 10 minutes and the resulting solids were filtered. The filtrate was then cooled and hydrogen chloride was bubbled through the solution for 10 minutes and the solids collected. This procedure was repeated until acidification of the filtrate with dry hydrogen chloride failed to yield any precipitate. The combined solids were dried in air and then over phosphorous pentoxide under vacuum to provide 514 grams (82%) of phenethylamine hydrochloride, m.p. 216—218°C.

Phenethylamine hydrochloride (257 grams, 1.63 moles) and ammonium thiocyanate (123.6

grams, 1.63 moles) were heated to 160°C in 340 ml bromobenzene under nitrogen. After heating for 90 minutes, the mixture was cooled to room temperature and then to 5°C. This procedure was repeated with a further batch of 257 grams of phenethylamine hydrochloride. The combined solids obtained in the above reaction were stirred in 1.5 l water and filtered. Recrystallization from isopropyl alcohol yielded 261.5 grams (45%) N-phenethyl thiourea, m.p. 132—134°.

B. N-phenyethyl thiourea (225 grams, 1.25 moles) and α-bromoacetophenone (250 grams, 1.25 moles, Aldrich Chem. Co.) in 1500 ml absolute ethanol were heated to reflux temperature for 2 1/2 hours under nitrogen. After reducing the solvent volume by 10%, the reaction mixture was cooled to room temperature and then to 0°C in an ice bath. The solids were filtered off, redissolved in 2,500 ml of absolute ethanol and heated to reflux. The solvent volume was reduced to 2000 ml and the reaction mixture cooled to 0°C. This procedure was repeated and after the second recrystallization the solids were collected and dried under vacuum over phosphorus pentoxide, yielding 365 grams (81%) of 2-phenethylamino-4-phenylthiazole hydrobromide, m.p. 169—172°C.

Analysis:
Calcd for $C_{17}H_{16}N_2S{\cdot}HBr$:
C, 56.50; H, 4.74; N, 7.68
Found:
C, 57.36; H, 5.04; N, 7.83.

Example 2

N-phenethyl thiourea (140 grams, 0.779 moles) and desyl bromide (225 grams, 0.82 moles, Eastman Chem. Co) in 833 ml absolute ethanol were heated at reflux temperature for 2 hours under nitrogen a further 300 ml of absolute ethanol being added during the reaction. The reaction mixture was cooled to 10°C, the solids filtered, recrystallized from absolute ethanol and dried over phosphorous pentoxide to yield 281.0 grams (83%) of 2-phenethylamino-4,5-diphenyl-thiazole hydrobromide, m.p. 171—174°C.

Analysis:
Calcd for $C_{23}H_{20}N_2S{\cdot}HBr$:
C, 63.14; H, 4.84; N, 6.40
Found:
C, 62.62; H, 4.82; N, 6.48.

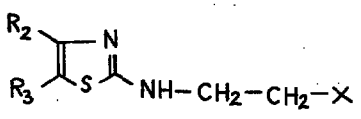
Example 3

N-phenethyl thiourea (2.0 grams, 0.011 moles) and α-bromopropiophenone (2.34 grams, 0.011 moles, Aldrich Chem. Co.) in 10 ml absolute ethanol were heated to reflux temperature for 90 minutes under nitrogen. The ethanol was then removed under vacuum, excess ethyl acetate added and the solids filtered and dried over phosphorous pentoxide. Recrystallization from absolute ethanol yielded 2.86 grams (70%) of 5-methyl-2-phenethylamino-4-phenylthiazole hydrobromide, m.p. 172—175°C.

Analysis:
Calcd for $C_{18}H_{18}N_2S{\cdot}HBr$:
C, 57.59; H, 5.10; N, 7.46
Found:
C, 57.67; H, 5.11; N, 7.39

Example 4

Following the procedures of Examples 1 and 2, hydrohalide salts of the following compounds were prepared:



Salt	*X*	R_2	R_3	*m.p.°C*
HBr	phenyl	p-methoxyphenyl	hydrogen	135—139
HCl	phenyl	p-fluorophenyl	hydrogen	163—165
HBr	p-bromophenyl	phenyl	hydrogen	171—174
HBr	p-bromophenyl	phenyl	methyl	150—151.5
HBr	p-methoxyphenyl	phenyl	hydrogen	169—171
HBr	p-methoxyphenyl	phenyl	methyl	149—150.5
HBr	p-methoxyphenyl	phenyl	phenyl	201—205
HCl	p-methoxyphenyl	p-fluorophenyl	hydrogen	156—158

Example 5

A. 2-thenylamine (30 grams, 0.265 moles, Fairfield Chemical Co.) was dissolved in 400 ml of diethyl ether and cooled to 0°C in an ice bath. Dry hydrogen chloride gas was bubbled through the solution for 5 minutes. The resulting solids were filtered and dried over phosphorous pentoxide to yield 26.7 grams (61%) of 2-thenylamine hydrochloride, m.p. 186—190°C.

2-thenylamine hydrochloride (13.35 grams, 0.089 moles) and ammonium thiocyanate (7.4 grams, 0.089 moles) in 20 ml bromobenzene were heated to reflux temperature for 90 minutes. The reaction mixture was cooled and the filtered solids washed three times with water. Recrystallization from chloroform and drying over phosphorous pentoxide yielded 5.0 grams (33%) of N-thenyl thiourea, m.p. 99—101°.

Analysis:
Calcd for $C_6H_8N_2S_2$:
C, 41.83; H, 4.68; N, 16.26
Found:
C, 41.56; H, 4.58; N, 16.07.

B. N-thenyl thiourea (2.0 grams, 0.0116 moles) and α-bromoacetophenone (2.3 grams, 0.0116 moles, Aldrich Chem. Co.) in 15 ml absolute ethanol were heated to reflux temperature for 90 minutes under nitrogen. The reaction mixture was cooled and the ethanol removed under vacuum. On dissolving the residue in hot isopropyl alcohol and diluting with diethyl ether, an oil was formed. The diethyl ether was decanted, the oil dissolved in a small amount of ethanol and cooled. The resulting solids were filtered and dried over phosphorous pentoxide, yielding 3.20 grams (78%) of 2-thenylamino-4-phenyl-thiazole hydrobromide, m.p. 115—118°C.

Analysis:
Calcd for $C_{14}H_{12}N_2S_2 \cdot HBr$:
C, 47.58; H, 3.71; N, 7.93
Found:
C, 47.75; H, 3.74; N, 7.90

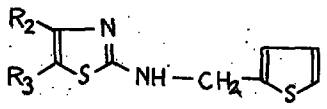
Example 6

N-thenyl thiourea (0.80 grams, 0.0046 moles) and α-chloro-p-fluoroacetophenone (0.80 grams, 0.0046 moles, Aldrich Chem. Co.) in 11 ml absolute ethanol were heated at reflux temperature under nitrogen for 90 minutes. After cooling, the ethanol was removed under vacuum and the solids triturated with ethanol, filtered and vacuum dried over phosphorous pentoxide, yielding 0.848 grams (56%) of 2-thenylamino-4(p-fluorophenyl)-thiazole hydrochloride, m.p. 184—187°C.

Analysis:
Calcd for $C_{14}H_{11}N_2S_2F \cdot HCl$:
C, 51.45; H, 3.70; N, 8.57
Found:
C, 51.41; H, 3.63; N, 8.39

Example 7

Following the procedures of Examples 5 and 6, hydrohalide salts of the following compounds were prepared:



Salt	R_2	R_3	*m.p.°C*
HBr	p-methoxyphenyl	hydrogen	154—158
HBr	phenyl	methyl	179.5—181.5
HCl	thienyl	hydrogen	137—142

Example 8

A. Furfurylamine (25.0 grams, 0.257 moles, Pfaltz & Bauer Co.) was dissolved in 1300 ml diethyl ether and cooled to 0°C in an ice bath. Dry hydrogen chloride gas was bubbled through the solution until no further precipitation occurred. The solids were filtered and dried in vacuum over phosphorous pentoxide to yield 33.46 (97%) of furfurylamine hydrochloride, m.p. 147—149°C.

Furfurylamine hydrochloride (33.46 grams, 0.250 moles) and ammonium thiocyanate (38.14 grams, 0.501 moles) in 71 ml bromobenzene were heated under nitrogen at reflux temperature for 20 minutes and then cooled to room temperature. The reaction mixture was mixed with a solution of 125 ml water and 100 ml ethyl acetate and left at room temperature overnight. The mixture was then diluted to give 500 ml ethyl acetate and 350 ml water and the aqueous layer separated. The organic layer was washed with water and dried over sodium sulfate. After filtration, the organic layer was

evaporated to dryness and bromobenzene removed under vacuum. The resulting solids were ground in a mortar and pestle and the fine particles stirred in diethyl ether to remove residual bromobenzene. The solids were then filtered, washed with diethyl ether and vacuum dried over phosphorous pentoxide, yielding 12.06 grams (30%) of N-furfuryl thiourea, m.p. 80—91°C.

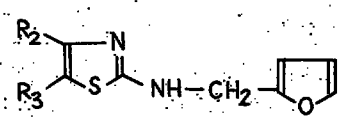
Analysis:
Calcd for $C_6H_8N_2OS$:
C, 46.14; H, 5.16; N, 17.93
Found:
C, 46.91; H, 4.90; N, 17.57

B. N-furfuryl thiourea (0.82 grams, 0.005 moles) and α-bromopropiophenone (1.07 grams, 0.005 moles, Aldrich Chem. Co.) in 11 ml absolute ethanol were heated to reflux temperature under nitrogen for 3 hours. After cooling to room temperature, the solvent was removed under vacuum to give a thick brown oil, which was triturated with five 35 ml portions of refluxing ethyl acetate. The ethyl acetate was reduced in volume to about 25 ml and cooled to room temperature. The precipitated solids were filtered, washed with ethyl acetate and vacuum dried over phosphorous pentoxide, yielding 0.585 grams (33%) of 2-furfurylamino-5-methyl-4-phenyl-thiazole hydrobromide, m.p. 150—153°C.

Analysis:
Calcd for $C_{15}H_{14}N_2OS \cdot HBr$:
C, 51.29; H, 4.30; N, 7.97
Found:
C, 51.97; H, 4.47; N, 8.42

Example 9

Following the procedure of Example 8 hydrohalide salts of the following compounds were prepared:



Salt	R_2	R_3	*m.p.°C*
HBr	phenyl	hydrogen	123—126
HBr	phenyl	phenyl	192—194

Example 10

A. Diphenylmethylamine (25.0 grams, 0.136 moles, Matheson, Coleman & Bell Co.) was dissolved in 660 ml of diethyl ether and cooled to 0°C. Dry hydrogen chloride gas was bubbled through the solution for 10 minutes, during which time an additional 300 ml of diethyl ether was added to the mixture. The precipitate was filtered, washed with diethyl ether and vacuum dried over phosphorous pentoxide, to yield 28.3 grams (95%) diphenylmethylamine hydrochloride, m.p. 303—310°C (decomposes).

Diphenylmethylamine hydrochloride (28.3 grams, 0.129 moles) and ammonium thiocyanate (9.81 grams, 0.129 moles) in 37 ml bromobenzene were heated at reflux temperature under nitrogen for 3-1/2 hours and then cooled to room temperature. The solids were filtered and triturated twice with 200 ml water. The solids were then dissolved in 850 ml ethanol, filtered and evaporated to a volume of about 350 ml. After cooling, the solids were filtered, washed with ethanol and vacuum dried over phosphorous pentoxide to yield 14.72 grams (56%) of N,N'-bis-(diphenylmethyl) thiourea, m.p. 216—217.5°C.

Analysis:
Calcd for $C_{27}H_{24}N_2S$:
C, 79.37; H, 5.92;; N, 6.86
Found:
C, 79.84; H, 6.05; N, 6.93

B. N,N'-bis-(diphenylmethyl) thiourea (1.21 grams, 0.005 moles) and desyl chloride (1.21 grams, 0.005 moles, Aldrich Chem. Co.) in 11 ml absolute ethanol were heated to reflux temperature under nitrogen for 3 hours. After cooling, the reaction mixture was evaporated to dryness, the resulting oil being mixed with about 40 ml diethyl ether. The solids were filtered, cooled with diethyl ether and vacuum dried over phosphorous pentoxide, yielding 1.01 grams (75%) of 4,5-diphenyl-2-diphenylmethylamino-thiazole hydrochloride, m.p. 195—198°C.

Analysis:
Calcd for $C_{28}H_{22}N_2S \cdot HCl$:
C, 73.91; H, 5.09; N, 6.16
Found:
C, 73.12; H, 5.28; N, 6.06

Example 11

Following the procedures of Example 10, 4-phenyl-2-diphenylmethylamino-thiazole hydrobromide was prepared, m.p. 166—168°C.

Example 12

A. N-phenylethylenediamine (25 grams, 0.184 moles, Aldrich Chem. Co.) was dissolved in diethyl ether, cooled to 0°C and dry hydrogen chloride gas bubbled through the solution until no more precipitation occurred. The filtered solids were dried over phosphorous pentoxide, yielding 31.2 grams (98%) N-phenylethylenediamine hydrochloride.

N-phenylethylenediamine hydrochloride (31.2 grams, 0.149 moles) and ammonium thiocyanate (11.3 grams, 0.149 moles) in 31 ml bromobenzene were heated to reflux temperature under nitrogen for 2 hours. After cooling, the resulting solids were filtered off and the bromobenzene was removed from the filtrate under vacuum. The resulting solids were stirred in 250 ml of water, filtered and dissolved in hot isopropyl alcohol. After cooling, the solids were filtered and dried over phosphorous pentoxide, yielding 2.8 grams (8%) of N-(2′-anilinoethyl)-thiourea, m.p. 137—140°C.

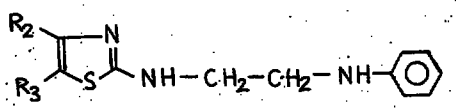
Analysis:
Calcd for $C_9H_{13}N_3S$:
C, 55.35; H, 6.71; N, 21.52
Found:
C, 55.64; H, 6.75; N, 21.03

B. N-(2′-anilinoethyl)-thiourea (0.90 grams, 0.0046 moles) and α-bromoacetophenone (0.92 grams, 0.0046 moles, Aldrich Chem. Co.) in 6 ml absolute ethanol were heated to reflux under nitrogen for 2 hours. After cooling the reaction mixture, the solvent was removed under vacuum. The resulting oil was dissolved in hot isopropyl alcohol, filtered and cooled. The solids were filtered and dried over phosphorous pentoxide, yielding 1.25 grams (73.5%) 2-(2′-anilinoethylamino)-4-phenyl-thiazole, m.p. 161—165°C.

Analysis:
Calcd for $C_{17}H_{17}N_3S \cdot HBr$:
C, 54.24; H, 4.82; N, 11.16
Found:
C, 54.51; H, 4.59; N, 11.02

Example 13

Following the procedures of Example 12, hydrohalide salts of the following compounds were prepared:

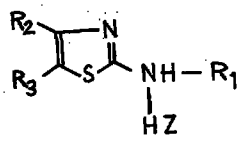


Salt	R_2	R_3	*m.p.°C*
HCl	phenyl	phenyl	139—143
HBr	phenyl	methyl	133—136

The immune regulant activity of the aminothiazoles described in Examples 1 to 13 was evaluated by determining their ability to stimulate, *in vitro*, the lymphocyte proliferation of murine thymus cells cultured in the presence of Concanavalin A (Con A) by employing the procedure of V. J. Merluzzi et. al., as essentially described in the *Journal of Clinical and Experimental Immunology*, Vol. 22, p. 486 (1975). The cells were derived from male C57B1/6 mice of from 6—8 weeks age, purchased from the Jackson Laboratories of Bar Harbour, Maine and the Con A was obtained from Sigma Chemicals of St. Louis, Missouri. Each cell culture (consisting of 0.10 ml thymus cells stock solution 0.05 ml of Con A stock solution and 0.05 ml of drug solution) was performed in quadruplicate and cellular proliferation was measured, after 48 hours of incubation at 37°C., by pulsing each culture with ^{3}H-thymidine (0.01 ml of specific activity 1.9 C/mM, obtained from Schwarz-Mann, Inc. of Orangeburg, N.Y.) and then determining the incorporation of ^{3}H-thymidine into cellular desoxyribonucleic acid (DNA) by an assessment of radioactivity using a liquid scintillation counter. The results obtained in this manner are

expressed quantitatively in terms of the average counts per minute (cpm) of ^{3}H-thymidine incorporated at the drug level with maximum activity by the quadruplicate cell cultures. These quadruplicate determinations are employed at eight different concentrations of drugs in the range 0.02 to 50 μg/ml. The highest cpm value obtained is employed in the scoring system. On this basis, four different levels of activity were established in the present lymphocyte stimulation assay (LSA) and these are defined in the manner hereinafter indicated, viz., those levels equal to Con A alone (6,000±300 cpm) were assigned a negative value or score of zero; those superior (10,000±700 cpm) to Con A activity but less than levamisole were scored as +; while those equal to levamisole (22,000±900 cpm) were scored as ++ and those having an activity (27,000±1,000 cpm) greater than levamisole were scored as +++. The LSA activity for the compounds described in the above Examples was +++ in each case.

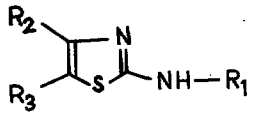
The anti-inflammatory activity of aminothiazoles of this invention was determined using the standard carrageenin-induced rat foot edema test, according to the procedure essentially as described by C. A. Winter et. al., and reported in the *Proceedings of the Society for Experimental Biology and Medicine, Vol. 111*, p. 544 (1962). The compounds were administered orally in the form of their previously reported hydrohalide salts at a dose level of 33 mg/kg. The results obtained in this manner are presented in the table below in terms of the percent inhibition of edema formation afforded by each test compound as compared to the non-drug treated control (i.e., aqueous solution with no compound):



R_1	R_2	R_3	HZ	*% Inhibition of edema (33 mg/kg, p.o.*
2-thenyl	4-fluorophenyl	hydrogen	HBr	49
2-phenethyl	phenyl	hydrogen	HBr	47
2-phenethyl	phenyl	phenyl	HBr	48
4-methoxyphenethyl	4-fluorophenyl	hydrogen	HBr	29

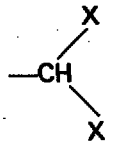
Claims

1. A compound of the formula



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and the pharmaceutically acceptable acid addition salts thereof, wherein R_1 is:

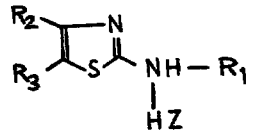


$-(CH_2)_n-X$, $-CH_2-CH_2-NH-X$ or $-(CH_2)_mY$, wherein X is phenyl optionally monosubstituted with alkyl of 1 to 3 carbon atoms, hydroxy, alkoxy of 1 to 3 carbon atoms, chloro, bromo, or fluoro; Y is thienyl or furyl each being optionally monosubstituted with alkyl of 1 to 3 carbon atoms, chloro, bromo or fluoro; n is 2; m is 1 or 2; R_2 is phenyl, thienyl or monosubstituted phenyl, said substituent being alkyl of 1 to 3 carbon atoms, hydroxy, alkoxy of 1 to 3 carbon atoms, chloro, bromo or fluoro; and R_3 is hydrogen, alkyl of 1 to 3 carbon atoms, phenyl or monosubstituted phenyl, said substituent being alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, or fluoro.

2. A compound of Claim 1 wherein R_2 is phenyl.
3. A compound of Claim 2 wherein R_3 is hydrogen.
4. A compound of Claim 2 wherein R_3 is phenyl.
5. A compound of Claim 1 wherein R_1 is $-(CH_2)_n-X$.
6. A compound of Claim 5 wherein X is p-methoxyphenyl.
7. A compound of Claim 5 wherein X is phenyl.
8. A compound of Claim 7 wherein R_2 is phenyl.
9. A compound of Claim 8 wherein R_3 is hydrogen.
10. A compound of Claim 8 wherein R_3 is phenyl.
11. A compound of Claim 8 wherein R_3 is methyl.
12. A compound of Claim 6 wherein R_2 is p-fluorophenyl and R_3 is hydrogen.

expressed quantitatively in terms of the average counts per minute (cpm) of ^{3}H-thymidine incorporated at the drug level with maximum activity by the quadruplicate cell cultures. These quadruplicate determinations are employed at eight different concentrations of drugs in the range 0.02 to 50 μg/ml. The highest cpm value obtained is employed in the scoring system. On this basis, four different levels of activity were established in the present lymphocyte stimulation assay (LSA) and these are defined in the manner hereinafter indicated, viz., those levels equal to Con A alone (6,000±300 cpm) were assigned a negative value or score of zero; those superior (10,000±700 cpm) to Con A activity but less than levamisole were scored as +; while those equal to levamisole (22,000±900 cpm) were scored as ++ and those having an activity (27,000±1,000 cpm) greater than levamisole were scored as +++. The LSA activity for the compounds described in the above Examples was +++ in each case.

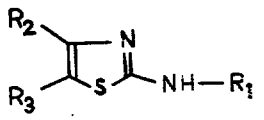
The anti-inflammatory activity of aminothiazoles of this invention was determined using the standard carrageenin-induced rat foot edema test, according to the procedure essentially as described by C. A. Winter et. al., and reported in the *Proceedings of the Society for Experimental Biology and Medicine, Vol. 111*, p. 544 (1962). The compounds were administered orally in the form of their previously reported hydrohalide salts at a dose level of 33 mg/kg. The results obtained in this manner are presented in the table below in terms of the percent inhibition of edema formation afforded by each test compound as compared to the non-drug treated control (i.e., aqueous solution with no compound):



R_1	R_2	R_3	HZ	% Inhibition of edema (33 mg/kg, p.o.)
2-thenyl	4-fluorophenyl	hydrogen	HBr	49
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2-phenethyl	phenyl	phenyl	HBr	48
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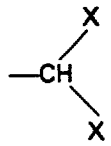
Claims

1. A compound of the formula



---(I)

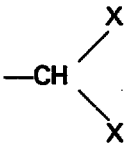
and the pharmaceutically acceptable acid addition salts thereof, wherein R_1 is:



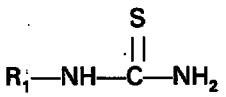
$-(CH_2)_n-X$, $-CH_2-CH_2-NH-X$ or $-(CH_2)_mY$, wherein X is phenyl optionally monosubstituted with alkyl of 1 to 3 carbon atoms, hydroxy, alkoxy of 1 to 3 carbon atoms, chloro, bromo, or fluoro; Y is thienyl or furyl each being optionally monosubstituted with alkyl of 1 to 3 carbon atoms, chloro, bromo or fluoro; n is 2; m is 1 or 2; R_2 is phenyl, thienyl or monosubstituted phenyl, said substituent being alkyl of 1 to 3 carbon atoms, hydroxy, alkoxy of 1 to 3 carbon atoms, chloro, bromo or fluoro; and R_3 is hydrogen, alkyl of 1 to 3 carbon atoms, phenyl or monosubstituted phenyl, said substituent being alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, or fluoro.

2. A compound of Claim 1 wherein R_2 is phenyl.
3. A compound of Claim 2 wherein R_3 is hydrogen.
4. A compound of Claim 2 wherein R_3 is phenyl.
5. A compound of Claim 1 wherein R_1 is $-(CH_2)_n-X$.
6. A compound of Claim 5 wherein X is p-methoxyphenyl.
7. A compound of Claim 5 wherein X is phenyl.
8. A compound of Claim 7 wherein R_2 is phenyl.
9. A compound of Claim 8 wherein R_3 is hydrogen.
10. A compound of Claim 8 wherein R_3 is phenyl.
11. A compound of Claim 8 wherein R_2 is methyl.
12. A compound of Claim 6 wherein R_2 is p-fluorophenyl and R_3 is hydrogen.

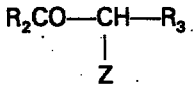
13. A compound of Claim 1, wherein R_1 is $—(CH_2)_m—Y$.
14. A compound of Claim 13 wherein Y is thienyl.
15. A compound of Claim 14 wherein m is 1.
16. A compound of Claim 15 wherein R_2 is phenyl.
17. A compound of Claim 15 wherein R_2 is p-fluorophenyl.
18. A compound of Claim 16 wherein R_3 is hydrogen.
19. A compound of Claim 17 wherein R_3 is hydrogen.
20. A compound of Claim 13 wherein Y is furyl.
21. A compound of Claim 20 wherein m is 1 and R_2 is phenyl.
22. A compound of Claim 21 wherein R_3 is hydrogen.
23. A compound of Claim 21 wherein R_3 is methyl.
24. A compound of Claim 21 wherein R_3 is phenyl.
25. A compound of Claim 1 wherein R_1 is



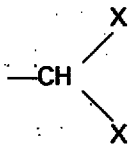
26. A compound of Claim 25 wherein X is phenyl.
27. A compound of Claim 26 wherein R_2 is phenyl.
28. A compound of Claim 27 wherein R_3 is hydrogen.
29. A compound of Claim 27 wherein R_3 is phenyl.
30. A compound of Claim 1 wherein R_1 is $—CH_2—CH_2—NH—X$.
31. A compound of Claim 30 wherein X is phenyl.
32. A compound of Claim 31 wherein R_2 is phenyl.
33. A compound of Claim 32 wherein R_3 is hydrogen.
34. A pharmaceutical composition comprising an immune-regulant effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.
35. A composition of Claim 34 wherein the compound is 2-phenylethylamino-4-phenyl-thiazole.
36. A composition of Claim 34 wherein the compound is 2-thenylamino-4-(p-fluorophenyl)-thiazole.
37. A composition of Claim 34 wherein the compound is 2-(p-methoxyphenethylamino)-4-(p-fluorophenyl)-thiazole.
38. A compound of the formula (I) as claimed in any one of Claims 1 to 33 or a pharmaceutical composition as claimed in claims 34 to 37 for use in the treatment of rheumatoid arthritis and other diseases associated with immune deficiency and accompanied by inflammation.
39. A process for preparing a compound of formula (I) as defined in claim 1 which comprises reacting a compound of the formula:



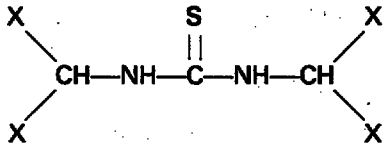
with a compound of the formula:



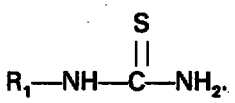
where R_1, R_2, and R_3 are as defined in claim 1 and Z is chlorine or bromine, and isolating the compound of formula (I) as the hydrochloride or hydrobromide salt and optionally neutralising or converting to another pharmaceutically acceptable acid addition salt.
40. A process as claimed in claim 39 wherein the compound of formula $R_2CO—CH(Z)—R_3$ is 2-chloro-2-phenylacetophenone.
41. A process as claimed in claim 39 wherein the compound of formula $R_2CO—CH(Z)—R_3$ is α-bromoacetophenone.
42. A process as claimed in claim 39 for preparing a compound of the formula (I) wherein R^1 is a group



and R_2, R_3 and X are as defined in claim 1, wherein a bis-substituted thiourea of the formula:



is used in situ as starting material for the compound of the formula:



43. A process as claimed in claim 39 substantially as hereinbefore described with reference to the Examples.

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