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725 728 73Y 774 776 777
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NF NJ NR QL QN QZ SF SJ
SU WC ZB ZF
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68 **95754g (1968)**
71 **124309t (1969)**
72 **100606g (1970)**
77 **114304x (1972)**
77 **164598s (1972)**
J. Indian Chemical Soc
51 **(12) 1031 (1974)**
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C2C
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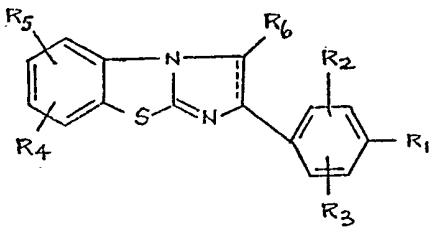
(54) 2-Phenylimidazo (2,1-b) Benzothiazole Derivatives

(57) 2-Phenylimidazo (2,1-b) benzothiazole derivatives of the formula:—



and salts thereof,
wherein R_1, R_2, R_3, R_4, R_5 and R_6 are each independently a hydrogen atom or one of various defined substituent groups, and the dotted line means the existence or absence of a double bond; with the provisos that when R_2, R_3 and R_4 all are hydrogen atoms, R_5 is a hydrogen atom, a halogen atom, a nitro group, a lower alkyl group or a lower alkoxy group, and there is a double bond in the 2—3 position of the imidazole ring,

R_1 does not represent a atom, a fluorine atom, a chlorine atom, a bromine atom, a nitro group, a lower alkyl group or a lower alkoxy group when R_6 is a hydrogen atom,

R_1 does not represent a hydrogen atom or a halogen atom when R_6 is a bromine atom or a thiocyanate group,

and R_1 does not represent a hydrogen atom or a nitro group when R_6 is a nitroso group of a nitro group,

have *immunoregulatory action* and may be used as *antiallergic agents, antiasthmatics, antirheumatics, anticancerous agents, therapeutic agents for autoimmune disease or suppressants of rejection in tissue transplantation and skin graft.*

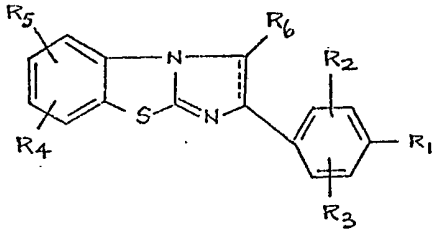
Certain of the chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

GB 2 056 982 A

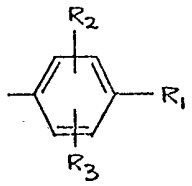
SPECIFICATION

2-Phenylimidazo (2,1-b) Benzothiazole Derivatives

This invention relates to novel 2-phenylimidazo (2,1-b) benzothiazole derivatives. More particularly, the invention provides 2-phenylimidazo (2,1-b) benzothiazole derivatives shown by formula I



wherein R_1, R_2, and R_3 are selected independently from the group comprising a hydrogen atom, halogen atoms, a hydroxy group, a nitro group, a nitroso group, an amino group, a carboxy group, a nitrile group, a carbamoyl group, a sulfamoyl group, lower alkyl groups, hydroxy lower alkyl groups, lower alkoxy groups, phenyl lower alkoxy groups, carboxy lower alkoxy groups, lower alkoxycarbonyl lower alkoxy groups, lower alkoxycarbonyl groups, acyloxy groups, lower alkylthio groups, lower alkylsulfinyl groups, lower alkylsulfonyl groups, lower alkoxysulfinyl groups, lower alkoxysulfonyl groups, mono or di lower alkylamino groups, or acylamino groups; any two adjacent R_1, R_2 and R_3 may combine with each other to form a benzene ring or a lower alkylenedioxy group; R_4, R_5, and R_6, are selected independently from the group comprising a hydrogen atom, halogen atoms, a hydroxy group, a nitro group, a nitroso group, an amino group, a thiocyanate group, lower alkyl groups, hydroxy lower alkyl groups, lower alkoxy groups, carboxy lower alkoxy groups, lower alkoxycarbonyl lower alkoxy groups, acyloxy groups, lower alkylthio groups, lower alkylsulfinyl groups, lower alkylsulfonyl groups, mono or di lower alkylamino groups, acylamino groups and a group shown by formula



and the dotted line means the existence or absence of a double bond; with the provisos that when R_2, R_3 and R_4 all are hydrogen atoms, R_5 is a hydrogen atom, a halogen atom, a nitro group, a lower alkyl group or a lower alkoxy group, and there is a double bond in the 2—3 position of the imidazole ring,

R_1 does not represent a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a nitro group, a lower alkyl group or a lower alkoxy group when R_6 is a hydrogen atom,

R_1 does not represent a hydrogen atom or a halogen atom when R_6 is a bromine atom or a thiocyanate group,

and R_1 does not represent a hydrogen atom or a nitro group when R_6 is a nitroso group or a nitro group.

By the term "lower" in general formula I described above is meant a straight or branched carbon chain having 1—5 carbon atoms. Therefore, the lower alkyl moiety of the lower alkyl group, hydroxy lower alkyl group, mono or di lower alkylamino group, lower alkylthio group, lower alkylsulfinyl group, lower alkylsulfonyl group shown by R_1, R_2, R_3, R_4, R_5 and R_6 is practically a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, a sec-butyl group, a tert-butyl group etc. Also the lower alkoxy moiety of the lower alkoxy group, phenyl lower alkoxy group, carboxy lower alkoxy group, lower alkoxycarbonyl lower alkoxy group, and lower alkoxycarbonyl group is practically a methoxy group, an ethoxy group, a propoxy group, a butoxy group, etc.

Also, as the acyl moiety of the acylamino group and acyloxy group, there are a lower alkanoyl group such as formyl group, acetyl group, propionyl group, butyryl group, etc., an aromatic acyl group such as benzoyl group, 4-methylbenzoyl group, etc., as well as an ethoxycarbonyl group, a methoxalyl group (—$COCOOCH_3$), an ethoxalyl group (—$COCOOC_2H_5$), an oxalo group (—COCOOH), a carbamoyl group, a tetrazol-5-ylcarbonyl group, a methanesulfonyl group, an ethanesulfonyl group, etc.

As halogen atoms, there are illustrated fluorine atom, chlorine atom, iodine atom, bromine atom.

Furthermore, as the alkylenedioxy group formed by combining any two adjacent ones of R_1, R_2 and R_3, there are a methylenedioxy group, an ethylenedioxy group, etc.

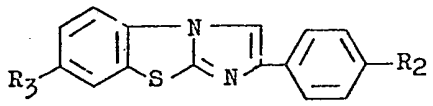
The compounds of above-shown general formula I provided by this invention form acid addition salts or form, according to the kind of substituents, salts with bases. This invention includes the pharmaceutically acceptable salts of the compounds of general formula I and examples of these salts

are acid addition salts with a mineral acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, etc., or an organic acid such as methanesulfonic acid, p-toluenesulfonic acid, etc. The salts with bases formed according to the kind of the substituent in general formula I, include salts with alkali metals such as sodium, potassium, etc., or alkaline earth metals such as calcium, etc.; salts with ammonia; and salts with organic bases such as methylamine, ethylamine, diethylamine, trimethylamine, triethylamine, pyridine, picolin, arginine, lysine, etc.

Hitherto, the following examples of as 2-phenylimidazo[2,1-b]benzothiazole derivatives are known:

2-phenylimidazo[2,1-b]benzothiazole (Chem. Abstr., *34*, 5082³(1940)), 2-(4-bromophenyl, 4-chlorophenyl or 4-fluorophenyl)imidazo[2,1-b]benzothiazole, 2-(4-chlorophenyl or phenyl)-7-(ethoxy, methoxy or methyl)imidazo[2,1-b]benzothiazole (Chem. Abstr., *65*, 7164a(1966)), 2-(4-nitrophenyl)imidazo[2,1-b]benzothiazole, 2-(4-nitrophenyl)-3-nitroimidazo[2,1-b]benzothiazole, 2-phenyl-3-nitrosoimidazo[2,1-b]benzothiazole (Chem. Abstr., *68*, 95754g(1968)), 2-(4-nitrophenyl or phenyl)-3(nitro or nitroso)-5,6,7 or 8-(methoxy or methyl)imidazo[2,1-b]benzothiazole, 2-(4-nitrophenyl or phenyl)-5,6,7 or 8-(methoxy or methyl)imidazo[2,1-b]-benzothiazole (Chem. Abstr., *71*, 124309t(1969)), 2-(4-methoxy-phenyl)imidazo[2,1-b]benzothiazole (Chem. Abstr., *72*, 100606g(1970)), 2-(4-bromophenyl, 4-chlorophenyl or phenyl)-3-(bromo or thiocyanato)imidazo[2,1-b]benzothiazole (Chem. Abstr., *77*, 114304x(1972)), 2-(4-biphenyl or 4-methylphenyl)imidazo-[2,1-b]benzothiazole, 2-(4-biphenyl, 4-methoxyphenyl, 4-methylphenyl, 4-nitrophenyl or phenyl)-7-(bromo, ethoxy, methoxy, methyl or nitro)imidazo[2,1-b]benzothiazole (Chem. Abstr., *77*, 164598s(1972)). However, there are no disclosures in the literature of the use of these compounds as medicaments.

J, Indian Chemical Soc., *51* (12), 1031(1974) (Chem. Abstr., *83*, 164112c(1975)) discloses that the 2-phenylimidazo[2,1-b]-benzothiazole derivatives shown by the formula



wherein R_2 is Cl, Ph, OMe, OEt, or Br and R_3 is H, Me or Cl have been confirmed to possess a fungicidal activity but not to possess an antihistamic activity. That is, various 2-phenylimidazo[2,1-b]benzothiazole derivatives are known as described above but it had not been known that the compounds of this kind were effective to an immunity system and possessed a strong immunoregulatory action.

On the other hand, compounds of this invention exhibit an immunoregulatory action and may be useful as antiallergic agents, antiasthmatics, antirheumatics, anticancerous agents, therapeutic agents for autoimmune disease, or suppressants of rejection in tissue transplantation and skin graft.

Compounds of this invention which have immunoregulatory action may have an immunosuppresive action or an immunostimulating action.

Compounds of this invention having an immunosuppresive action which suppress cell-mediated immunity, for example delayed type hypersensitivity reaction typified by the cell-mediated immunity to protein antigens, can be used as antiallergic agents, antirheumatics, therapeutic agents for autoimmune disease, or suppressants of rejection in tissue transplantation and skin graft. In particular, these compounds may be useful as a delayed type hypersensitive agents or antirheumatics. Hitherto, only steroids are known as an antiallergic agents, particularly delayed type hypersensitive agents. The same is true for antirheumatics. However, when steroids are used for long periods of time, they cause serious side effects and cause so-called steriod reliance and hence it has been desired to develope a non-steroid antiallergic and antirheumatic agent giving fewer side effects. The compounds of this invention having a strong delayed type hypersensitive action can be used in place of these steroids. Further, they can be used together with the steroids, thus reducing the amount of steroids used.

Compounds of this invention having an immunosuppressive action which also suppress humoral antibody formation, e.g. the production of IgE antibody, are useful as antiallergic agents since they suppress the production of IgE antibody which is the main object of immediate hypersensitivity.

Compounds of this invention having an immunostimulating action and which increase cell-mediated immunity such as the action of increasing delayed type hypersensitivity reaction, as well as having an action of lymphocyte blastogenesis, and an action of increasing humoral antibody formation, such as the action of increasing antibodies in blood, are useful as anticancerous agents and antitumor agents as well as antirheumatics or therapeutic agents for chronic hepatitis.

Compounds of this invention exhibit a suppressive action in a passive cutaneous anaphylaxises (PCA) test, which means compounds of this invention have an antiallergic action and are useful as antiallergic agents and antiasthmatics.

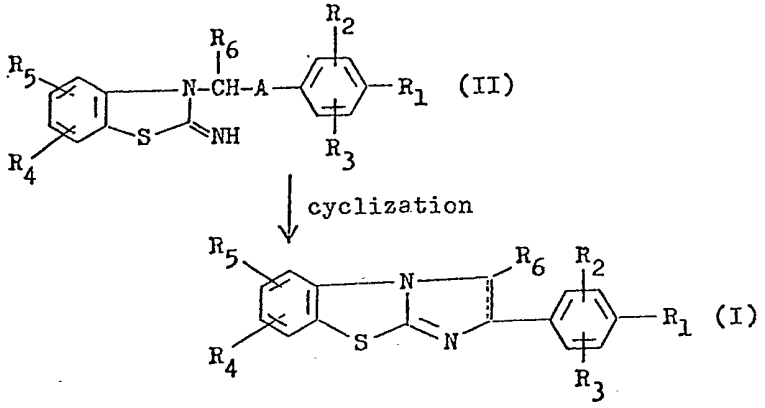
Furthermore, since compounds of this invention show very weak toxicity, the compounds can be used as medicaments for various uses above described.

The medical compositions containing the compounds of this invention as the main component can be formulated in conventional manner using conventional carriers for formulation and excipients.

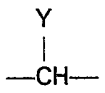
The medicaments may be administered orally as tablets, pills, capsules, granules, etc., or may be administered parenterally as injections such as intraveous injections, intramuscular injections, etc., or as aerosols, suppositories, etc. The doses of the medicaments are properly determined according to each case on considering the symptom, the age of patient, sex, etc., but are usually 50—500 mg per day for adult in case of oral administration and 20—300 mg per day for adult in case of parenteral administration, which is administered 2—3 times a day.

The compounds of this invention are prepared by any one of the following methods.

(A) Cyclization:



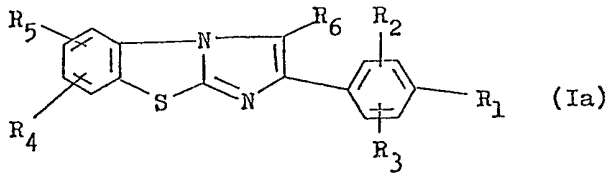
wherein A represents a carbonyl group or a group shown by



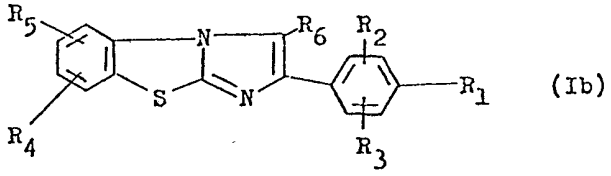
(wherein Y represents a halogen atom).

Examples of the halogen atom shown by Y are iodine, bromine, chlorine, etc.

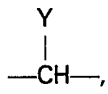
In the preparation of the 2-phenylimidazo[2,1-b]-benzothiazole derivative shown by general formula (Ia)



the compound (IIa), wherein A is a carbonyl group, is used as the raw material, whilst in the preparation of the 2-phenyl-2,3-dihydroimidazo[2,1-b]benzothiazole derivative shown by general formula (Ib)



the compound (IIb), wherein A is the group shown by



is used as the raw material.

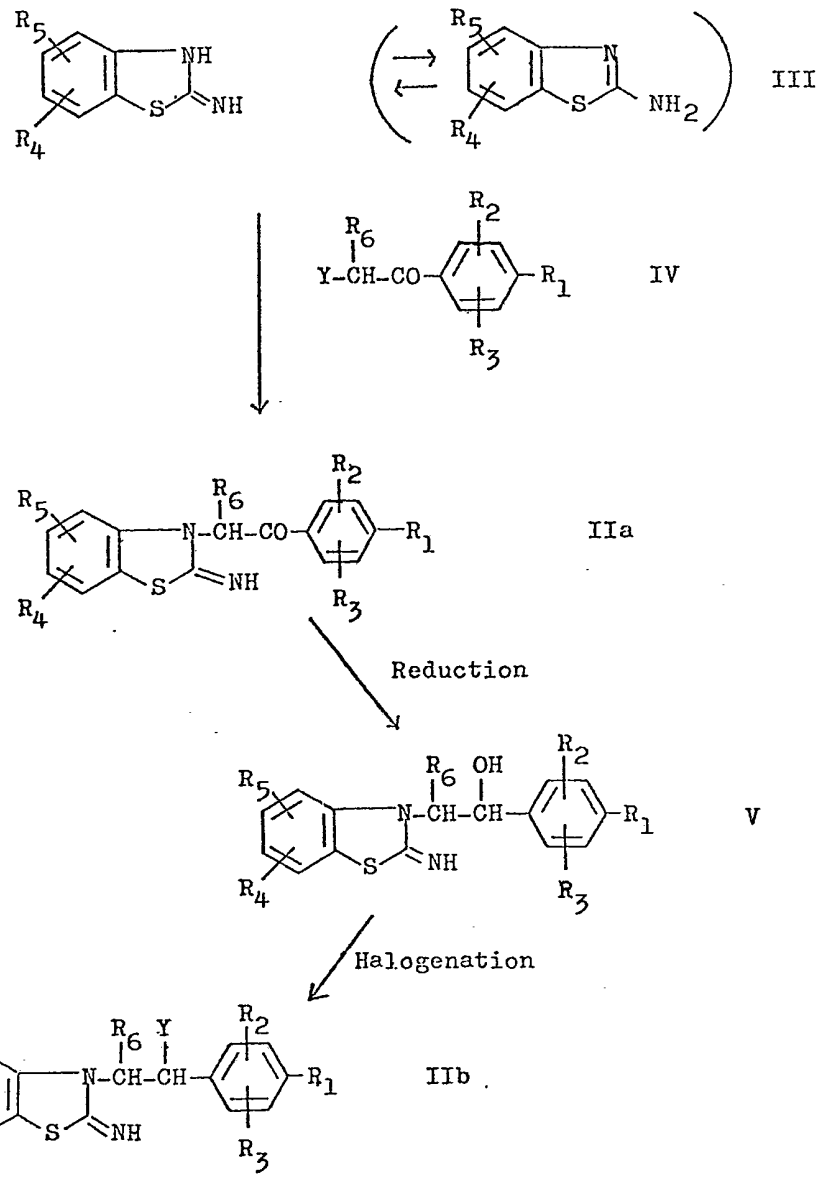
The former reaction is usually performed in a solvent for example, methanol, ethanol, isopropanol, methoxyethanol, methylcellosolve, ethylcellosolve, Diglyme, ethyl acetate, acetonitrile, chloroform, carbon tetrachloride, etc. The reaction is performed under heating, preferably under refluxing.

On the other hand, the latter reaction is performed usually in a solvent in the presence of a base under heating, preferably under refluxing. Practical examples of the solvent are organic solvents such as alcohol (methanol, ethanol, etc.) chloromethane, dichloromethane, chloroform, carbon tetrachloride,

methylcellosolve, ethylcellosolve, Diglyme, ethyl acetate, acetonitrile, etc., and water or mixtures of them. Bases used in the reaction include inorganic bases such as potassium carbonate, sodium carbonate, sodium hydrogencarbonate, potassium acetate, sodium acetate, etc., and organic bases such as trimethylamine, triethylamine, pyridine, picoline, etc. Pyridine, etc., may be also used as solvent.

In this case when the raw material (II) wherein at least one of R_1 to R_6 is an acyloxy group is used, it is hydrolyzed during the reaction to form the corresponding compound (I) of this invention wherein at least one of R_1 to R_6 is a hydroxy group.

In addition, raw materials (IIa) and (IIb) can be produced according to the following reaction formulae and they can be used in the reactions without being isolated.



(B) Hydrolysis:

The compound of this invention shown by general formula (I) having a hydroxy group, a carboxy group, or an amino group can be prepared by hydrolyzing the compound having an acyloxy group, a lower alkoxycarbonyl group, or an acylamino group in conventional manner. That is, the compound of formula (I) wherein at least one of R_1 to R_6 is a hydroxy group can be prepared by hydrolyzing the compound of formula (I) wherein at least one of R_1 to R_6 is an acyloxy group under alkaline conditions in conventional manner; the compound of formula (I) wherein at least one of R_1 to R_3 is a carboxy group or a carboxy lower alkoxy group can be prepared by hydrolyzing the compound wherein at least one of R_1 to R_3 is a lower alkoxycarbonyl group or a lower alkoxycarbonyl lower alkoxy group under alkaline conditions in conventional manner; and the compound of formula (I) wherein at least one of R_4 to R_6 is a carboxy lower alkoxy group can be prepared by hydrolyzing the compound wherein at least one of R_4

to R_6 is a lower alkoxycarbonyl lower alkoxy group under alkaline conditions in conventional manner. Also, the compound of formula (I) wherein at least one of R_1 to R_6 is an acylamino group containing carboxy group, such as an oxaloamido group (—NHCOCOOH) can be prepared by hydrolyzing the compound having a lower alkoxycarbonyl group, e.g., the compound having an ethoxyalylamido group (—NHCOCOOC$_2$H$_5$) under alkaline conditions in conventional manner. Furthermore, the compound of formula (I) wherein at least one of R_1 to R_6 is an amino group can be prepared by hydrolyzing the compound wherein at least one of R_1 to R_6 is an acylamino group under acid conditions in conventional manner.

(C) Alkylation:

The compound of this invention shown by general formula (I) having a lower alkoxy group, a phenyl lower alkoxy group, a lower alkoxycarbonyl lower alkoxy group, a lower alkylenedioxy group, a lower alkoxycarbonyl group, or a mono or di lower alkylamino group can be prepared by alkylating the compound having hydroxy groups a carboxy group, or an amino group by reacting the compound with a corresponding alkylating agent in conventional manner. That is, the compound of formula (I) wherein at least one of R_1 to R_6 is a lower alkoxy group or a lower alkoxycarbonyl lower alkoxy group can be prepared by alkylating the compound wherein at least one of R_1 to R_6 is a hydroxy group with a corresponding alkylating agent such as a lower alkyl halide or a lower alkoxycarbonylalkyl halide in conventional manner; the compound wherein at least one of R_1 to R_3 is a phenyl lower alkoxy group can be prepared by alkylating the compound wherein at least one of R_1 to R_3 is hydroxy group with a corresponding alkylating agent such as a phenyl lower alkyl halide in conventional manner; and the compound wherein optional adjacent two groups of R_1 to R_3 are combined with each other to form a lower alkylenedioxy group can be prepared by alkylating the compound wherein two groups of R_1 to R_3 are hydroxy groups with a corresponding alkylating agent such as a lower alkylene dihalide in conventional manner. Also, the compound of this invention shown by formula (I) wherein at least one of R_4 to R_6 is a lower alkoxycarbonyl group can be prepared by alkylating the compound wherein at least one of R_4 to R_6 is a carboxy group by reacting the compound with a corresponding alkylating agent such as a lower alkyl halide in conventional manner and the compound of formula (I) wherein at least one of R_1 to R_6 is a lower alkoxycarbonyl lower alkoxy group can be prepared by alkylating the compound wherein at least one of R_1 to R_6 is a carboxy lower alkoxy group with a corresponding alkylating agent in conventional manner. Furthermore, the compound of formula (I) wherein at least one of R_1 to R_6 is a mono or di lower alkylamino group can be prepared by alkylating the compound wherein at least one of R_1 to R_6 is an amino group with a corresponding alkylating agent such as a lower alkyl halide in conventional manner.

(D) Acylation:

The compound of this invention having general formula (I) wherein at least one of R_1 to R_6 is an acyloxy group or an acylamino group can be prepared by acylating the compound wherein at least one of R_1 to R_6 is a hydroxy group or an amino group with a corresponding acylating agent such as an acyl halide, acid anhydride in conventional manner.

(E) Amide Formation:

The compound of this invention of general formula (I) having carbamoyl group(s) can be prepared by amide-forming the compound having a carboxy group or a lower alkoxycarbonyl group in conventional manner. That is, the compound of formula (I) wherein at least one of R_4 to R_6 is a carbamoyl group can be prepared by reacting the compound wherein at least one of R_4 to R_6 is a carboxy group or a lower alkoxycarbonyl group with ammonia in conventional manner and the compound of formula (I) wherein at least one of R_1 to R_6 is an acylamino group having a carbamoyl group, e.g., the compound having an oxamido group (—NHCOCONH$_2$) can be prepared by reacting the compound wherein at least one of R_1 to R_6 is an acylamino group having a carboxy group or lower alkoxycarbonyl group, such as an ethoxalylamido group (—NHCOCOOC$_2$H$_5$) with ammonia in conventional manner.

(F) Halogenation:

The compound of this invention having general formula (I) wherein R_6 is a halogen atom can be prepared by halogenating the compound of formula (I) wherein R_6 is a hydrogen atom with a halogenating agent such as bromine, chlorine, iodine, sulfuryl chloride, and N-bromosuccinimide in conventional manner.

(G) Nitration:

The compound of this invention having general formula (I) wherein R_6 is a nitro group can be prepared by nitrating the compound of formula (I) wherein R_6 is a hydrogen atom by reacting the compound with a nitrating agent such as nitric acid in conventional manner.

(H) Nitroso Formation:

The compound of this invention having general formula (I) wherein R_6 is a nitroso group can be

prepared by reacting the compound of formula (I) wherein R_6 is a hydrogen atom with a nitroso-forming agent such as nitrous acid in conventional manner.

(I) Reduction:

The compound of this invention having general formula (I) having an amino group or a hydroxy lower alkyl group can be prepared by reducing the compound of formula (I) having a nitro group, a lower alkanoyl group, or a lower alkoxycarbonyl group in conventional manner. That is, the compound of formula (I) wherein at least one of R_1 to R_6 is an amino group can be prepared by reducing the compound wherein at least one of R_1 to R_6 is a nitro group in conventional manner and the compound of formula (I) wherein at least one of R_1 to R_6 is a hydroxy lower alkyl group can be prepared by reducing the compound wherein at least one of R_1 to R_6 is a lower alkanoyl group or a lower alkoxycarbonyl group in conventional manner.

(J) Lower Alkylthio Formation:

The compound of this invention having general formula (I) wherein R_6 is a lower alkylthio group can be prepared by reacting the compound of formula (I) wherein R_6 is a hydrogen atom with a lower alkylthio forming agent such as a lower alkylsulfinyl halide in conventional manner.

(K) Oxidation:

The compound of this invention having general formula (I) wherein at least one of R_1 to R_6 is a lower alkylsulfinyl group or a lower alkylsulfonyl group can be prepared by oxidizing the compound of formula (I) wherein at least one of R_1 to R_6 is a lower alkylthio group in conventional manner.

The desired compounds of formula (I) thus prepared are isolated and purified by a conventional chemical operation usually used in the field of the art, such as recrystallization, extraction, various chromatographies, etc.

Then, the experimental result indicating the excellent pharmacological effect of the compounds of this invention are shown below.

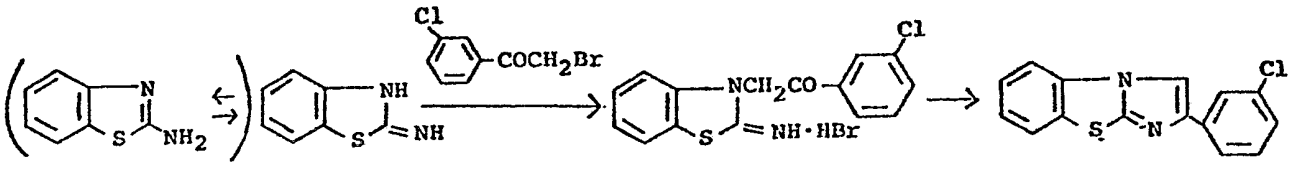
Activity to delayed type hypersensitivity of mice:

Seven week old ICR-SLC mice (Shizuoka Agric. Coop. Asoc.) were sensitized by painting 0.1 ml of 7% picryl chloride (PC) solution in absolute ethanol on the shaved abdomen. In this case, the solution was used under heating to prevent PC being precipitated. After the 7 day sensitization period, the mice were challenged by painting 0.02 ml of 1% picryl chloride solution in olive oil on inside of each ear. The ear thickness was measured with a dial thickness gauge. Increase in ear thickness was calculated as a difference between the value measured before challenge and the value 24 hours after challenge The test compounds were administered orally from day 0 to day 3 after the immunization. The results are shown in Table I.

Drug	*Dose (mg/kg)*	*N*	*Ear thickness increment (1/100 mm)*	*Inhibition (%)*
2-(m-Hydroxyphenyl)imidazo[2,1-b]benzothiazole (Ex. 8)	50	5	3.4±0.9	39.3
	400	5	0.9±0.4	83.9
Control	—	10	5.6±0.6	—
7-Hydroxy-2-(p-methoxyphenyl)imidazo[2,1-b]-benzothiazole (Ex. 23)	50	5	2.0±0.8	53.5
	400	5	2.2±0.7	48.8
Control	—	10	4.3±0.7	—
7-Hydroxy-2-(p-hydroxyphenyl)imidazo[2,1-b]benzothiazole hemihydrate (Ex. 24)	50	5	2.4±0.6	44.2
	400	5	2.5±0.8	41.9
Control	—	10	4.3±0.7	—
7-Hydroxy-2-phenylimidazo[2,1-b]benzothiazole (Ex. 25)	50	5	2.5±0.2	41.9
	400	5	2.4±0.7	44.2
Control	—	10	4.3±0.7	—
2-(3-Chloro-4-hydroxyphenyl)imidazo[2,1-b]benzothiazole (Ex. 28)	50	5	3.4±1.1	35.8
	400	5	2.7±0.5	48.6
Control	—	10	5.3±0.5	—
2-(3,5-Dichloro-4-hydroxyphenyl)imidazo[2,1-b]benzothiazole (Ex. 29)	50	5	3.4±0.7	35.8
	400	5	1.3±0.6	75.2
Control	—	10	5.3±0.5	—

Drug	Dose (mg/kg)	N	Ear thickness increment (1/100 mm)	Inhibition (%)
2-(3-Hydroxy-4-methylphenyl)imidazo[2,1-b]benzothiazole (Ex. 30)	50	5	3.3±1.3	37.7
	400	5	3.2±1.0	39.6
Control	—	10	5.3±0.5	—
2-(4-Chloro-3-hydroxyphenyl)imidazo[2,1-b]benzothiazole (Ex. 32)	50	5	2.4±0.9	44.2
Control	—	10	4.3±0.7	—
2-(m-Nitrophenyl)imidazo[2,1-b]benzothiazole (Ex. 33)	50	5	3.2±0.4	39.0
	400	5	2.1±0.5	60.0
Control	—	10	5.3±0.5	—
2-(m-Methoxycarbonylphenyl)imidazo[2,1-b]benzothiazole (Ex. 36)	50	5	1.9±0.7	63.8
	400	5	1.9±0.5	63.8
Control	—	10	5.3±0.5	—
3-Methyl-2-phenylimidazo[2,1-b]benzothiazole (Ex. 41)	50	5	3.9±0.7	31.6
	400	5	3.7±0.8	35.1
Control	—	10	5.7±0.5	—
2,3-Bis(p-chlorophenyl)imidazo[2,1-b]benzothiazole (Ex. 46)	400	5	2.0±0.6	63.6
Control	—	10	5.5±0.4	—
2-(0-Hydroxyphenyl)imidazo[2,1-b]benzothiazole (Ex. 50)	400	5	1.4±0.2	65.0
Control	—	10	4.0±0.5	—
2-(p-Hydroxyphenyl)imidazo[2,1-b]benzothiazole (Ex. 54)	50	5	3.4±0.8	44.3
	400	5	3.6±0.4	41.0
Control	—	10	6.1±0.7	—
2-(p-Carboxyphenyl)imidazo[2,1-b]benzothiazole (Ex. 60)	50	5	3.8±0.7	33.3
	400	5	2.9±0.6	49.1
Control	—	10	5.7±0.5	—
2-(m-Formamidophenyl)imidazo[2,1-b]benzothiazole (Ex. 72)	25	5	2.6±0.7	39.5
	200	5	2.2±1.1	48.8
Control	—	10	4.3±0.7	—
2-(p-Chlorophenyl)-3-nitrosoimidazo[2,1-b]benzothiazole (Ex. 90)	400	5	2.9±0.3	47.3
Control	—	10	5.5±0.4	—

Example 1



To 150 ml of anhydrous acetonitrile were added 4.5 g of 2-aminobenzothiazole and 6.8 g of m-chlorophenacyl bromide and the mixture was heated to 65—75°C for one hour with stirring. After the reaction was over, the reaction mixture was cooled, crystals formed were recovered by filtration, washed with acetonitrile, and dried to provide 8.5 g of the white crystals of 2-imino-3-(m-chlorobenzoylmethyl)-2,3-dihydrobenzothiazole hydrobromide.

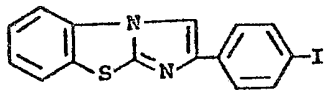
Then, 8.5 g of the crystals of the hydrobromide were refluxed under heating in 75 ml of methylcellosolve. After the reaction was over, the reaction mixture was cooled to about 50°C and then 30 ml of 5% aqueous ammonia was added to the reaction mixture, thereby white crystals formed. The reaction mixture was further ice-cooled and crystals formed were recovered by filtration and recrystallized from ethanol to provide 4.2 g of 2-(m-chlorophenyl)imidazo[2,1-b]benzothiazole.

Melting point: 173—175°C.
Elemental analysis for $C_{15}H_9N_2ClS$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	63.27	3.19	9.84	11.26
Found:	63.17	3.03	9.68	11.48

By following the same procedure as above, following compounds were prepared.

Example 2

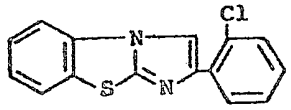


2-(p-Iodophenyl)imidazo[2,1-b]benzothiazole

melting point 177—180°C
Elemental analysis for $C_{15}H_9N_2IS$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	47.89	2.41	7.45	8.52
Found:	48.12	2.43	7.34	8.28

Example 3

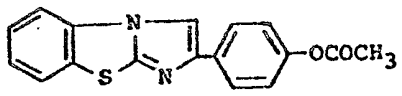


2-(o-Chlorophenyl)imidazo[2,1-b]benzothiazole

melting point 178—179°C
Elemental analysis for $C_{15}H_9N_2ClS$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	63.27	3.19	9.84	11.26
Found:	63.05	2.98	9.70	11.56

Example 4

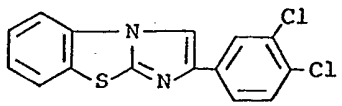


2-(p-Acetoxyphenyl)imidazo[2,1-b]-benzothiazole

melting point 177—179°C
Elemental analysis for $C_{17}H_{12}N_2O_2S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	66.22	3.92	9.08	10.40
Found:	66.19	3.74	9.01	10.52

Example 5

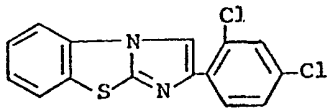


2-(3,4-Dichlorophenyl)imidazo[2,1-b]-benzothiazole

melting point 195—197°C
Elemental analysis for $C_{15}H_8N_2Cl_2S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*	*Cl(%)*
Calculated:	56.44	2.53	8.78	10.04	22.21
Found:	56.52	2.40	8.80	10.17	22.13

Example 6

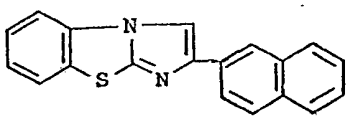


2-(2,4-Dichlorophenyl)imidazo[2,1-b]benzothiazole

melting point 198—199°C
Elemental analysis for $C_{15}H_8N_2Cl_2S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*	*Cl(%)*
Calculated:	56.44	2.53	8.78	10.04	22.21
Found:	56.48	2.55	8.80	10.21	21.91

Example 7

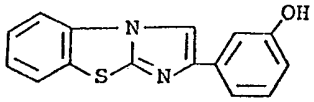


2-(2-Naphthyl)imidazo[2,1-b]benzothiazole

melting point 161—163°C
Elemental analysis for $C_{19}H_{12}N_2S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	75.97	4.03	9.33	10.67
Found:	76.12	3.89	9.28	10.77

Example 8

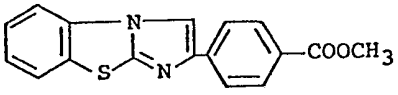


2-(m-Hydroxyphenyl)imidazo[2,1-b]benzothiazole

melting point 248°C
Elemental analysis for $C_{15}H_{10}N_2OS$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	67.65	3.78	10.52	12.04
Found:	67.47	3.76	10.32	12.17

Example 9

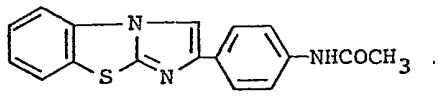


2-(p-Methoxycarbonylphenyl)imidazo[2,1-b]benzothiazole

melting point 223°C
Elemental analysis for $C_{17}H_{12}N_2O_2S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	66.22	3.92	9.08	10.40
Found:	66.03	3.85	8.89	10.36

Example 10

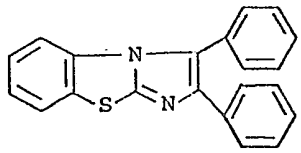


2-(p-Acetamidophenyl)imidazo[2,1-b]benzothiazole

melting point 243—245°C
Elemental analysis for $C_{17}H_{13}N_3OS$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	66.43	4.26	13.67	10.43
Found:	66.21	4.20	13.46	10.50

Example 11

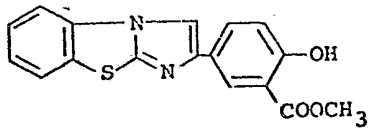


2,3-Diphenylimidazo[2,1-b]benzothiazole

melting point 161—162°C
Elemental analysis for $C_{21}H_{14}N_2S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	77.27	4.32	8.58	9.82
Found:	77.09	4.18	8.46	9.76

Example 12

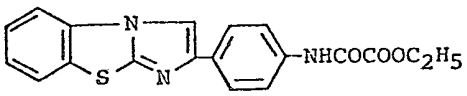


2-(4-Hydroxy-3-methoxycarbonylphenyl)-imidazo[2,1-b]benzothiazole

melting point 224—226°C
Elemental analysis for $C_{17}H_{12}N_2O_3S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	62.95	3.73	8.64	9.88
Found:	63.20	3.60	8.33	9.98

Example 13

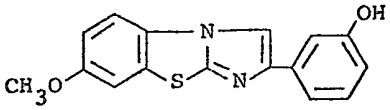


2-[p(Ethoxalylamido)phenyl]imidazo[2,1-b]benzothiazole

melting point 220°C
Elemental analysis for $C_{19}H_{15}N_3O_3S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	62.45	4.14	11.50	8.77
Found:	62.24	3.89	11.40	9.04

Example 14

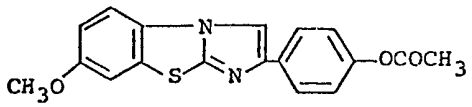


2-(m-Hydroxyphenyl)-7-methoxyimidazo[2,1-b]benzothiazole

melting point 293—295°C
Elemental analysis for $C_{16}H_{12}N_2O_2S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	64.85	4.08	9.45	10.82
Found:	64.76	4.02	9.53	11.65

Example 15

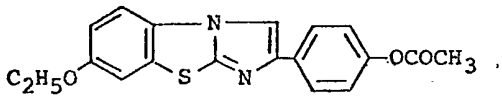


2-(p-Acetoxyphenyl)-7-methoxyimidazo[2,1-b]benzothiazole

melting point 193—195°C
Elemental analysis for $C_{18}H_{14}N_2O_3S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	63.89	4.17	8.28	9.47
Found:	63.68	4.21	8.17	9.43

Example 16

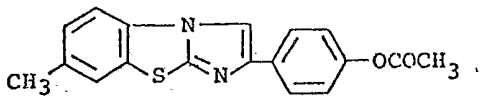


2-(p-Acetoxyphenyl)-7-ethoxyimidazo[2,1-b]benzothiazole

melting point 186—188°C
Elemental analysis for $C_{19}H_{16}N_2O_3S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	64.76	4.58	7.95	9.10
Found:	65.01	4.49	7.80	9.11

Example 17

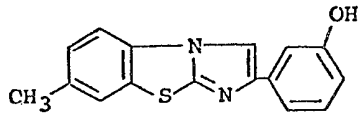


2-(p-Acetoxyphenyl)-7-methylimidazo[2,1-b]benzothiazole

melting point 209°C
Elemental analysis for $C_{18}H_{14}N_2O_2S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	66.24	4.32	8.58	11.05
Found:	66.23	4.18	8.64	11.09

Example 18

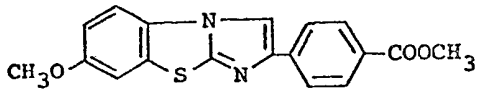


2-(m-Hydroxyphenyl)-7-methylimidazo[2,1-b]benzothiazole

melting point above 300°C
Elemental analysis for $C_{16}H_{12}N_2OS$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	68.55	4.31	9.99	11.44
Found:	68.25	4.17	10.05	11.32

Example 19

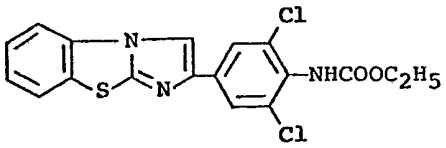


7-Methoxy-2-(p-methoxycarbonylphenyl)imidazo[2,1-b]benzothiazole

melting point 215—217°C
Elemental analysis for $C_{18}H_{14}N_2O_3S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	63.89	4.17	8.28	9.47
Found:	63.76	4.04	8.44	9.50

Example 20



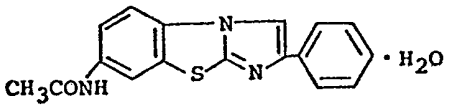
2-(3,5-Dichloro-4-ethoxycarbonylamidophenyl)imidazo[2,1-b]-benzothiazole

melting point 256—258°C

Elemental analysis for $C_{18}H_{13}N_3O_2Cl_2S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*	*Cl(%)*
Calculated:	53.21	3.22	10.34	7.89	17.45
Found:	53.05	3.12	10.34	7.79	17.28

Example 21



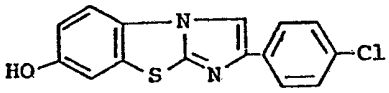
7-Acetamido-2-phenylimidazo[2,1-b]-benzothiazole monohydrate

melting point 267—269°C

Elemental analysis for $C_{17}H_{15}N_3O_2S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	62.75	4.65	12.91	9.85
Found:	62.71	4.62	12.97	10.13

Example 22



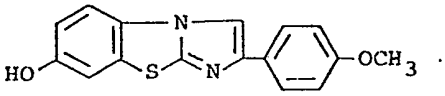
2-(p-Chlorophenyl)-7-hydroxyimidazo-[2,1-b]benzothiazole

melting point above 300°C

Elemental analysis for $C_{15}H_9N_2OSCl$:

	C(%)	*H(%)*	*N(%)*	*S(%)*	*Cl(%)*
Calculated:	59.90	3.02	9.31	10.66	11.79
Found:	59.80	2.92	9.25	10.52	12.00

Example 23



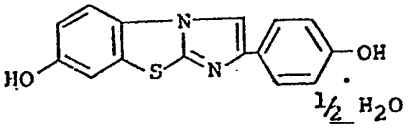
7-Hydroxy-2-(p-methoxyphenyl)imidazo[2,1-b]benzothiazole

melting point 287—289°C

Elemental analysis for $C_{16}H_{12}N_2O_2S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	64.85	4.08	9.45	10.82
Found:	64.83	4.01	9.41	10.69

Example 24



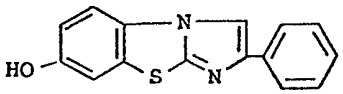
7-Hydroxy-2-(p-hydroxyphenyl)imidazo-[2,1-b]benzothiazole hemihydrate

melting point above 300°C

Elemental analysis for $C_{15}H_{10}N_2O_2S.1/2H_2O$:

	S(%)
Calculated:	11.00
Found:	11.27

Example 25

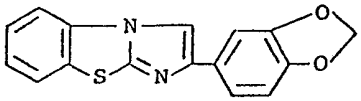


7-Hydroxy-2-phenylimidazo[2,1-b]benzothiazole

Melting point 234—236°C
Elemental analysis for $C_{15}H_{10}N_2OS$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	67.65	3.78	10.52	12.04
Found:	67.76	3.73	10.66	11.96

Example 26

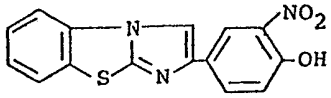


2-(3,4-Methylenedioxyphenyl)imidazo[2,1-b]benzothiazole

Melting point 210—212°C
Elemental analysis for $C_{16}H_{10}N_2O_2S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	65.29	3.42	9.52	10.89
Found:	65.34	3.35	9.55	10.74

Example 27

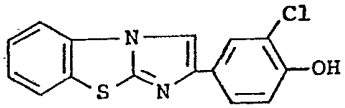


2-(4-Hydroxy-3-nitrophenyl)imidazo[2,1-b]benzothiazole

Melting point 264—266°C
Elemental analysis for $C_{15}H_9N_3O_3S$:

	C(%)	*H(%)*	*N(%)*
Calculated:	57.87	2.91	13.50
Found:	57.81	2.94	13.27

Example 28

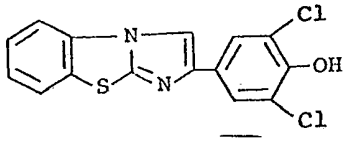


2-(3-Chloro-4-hydroxyphenyl)imidazo-[2,1-b]benzothiazole

Melting point 267—269°C
Elemental analysis for $C_{15}H_9N_2OSCl$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	59.90	3.02	9.31	10.66
Found:	59.76	3.12	9.22	10.78

Example 29

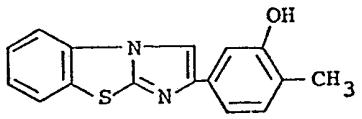


2-(3,5-Dichloro-4-hydroxyphenyl)imidazo[2,1-b]benzothiazole

Melting point above 310°C
Elemental analysis for $C_{15}H_8N_2OSCl_2$:

	C(%)	*H(%)*	*N(%)*
Calculated:	53.75	2.41	8.36
Found:	53.62	2.41	8.16

Example 30

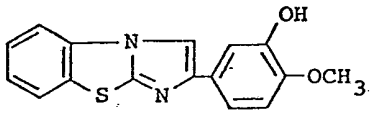


2-(3-Hydroxy-4-methylphenyl)imidazo-[2,1-b]benzothiazole

Melting point 308—310°C
Elemental analysis for $C_{16}H_{12}N_2OS$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	68.55	4.31	9.99	11.44
Found:	68.34	4.37	9.97	11.62

Example 31

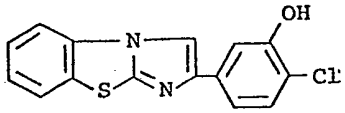


2-(3-Hydroxy-4-methoxyphenyl)imidazo[2,1-b]benzothiazole

melting point 160—162°C
Elemental analysis for $C_{16}H_{12}N_2O_2S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	64.85	4.08	9.45	10.82
Found:	64.81	4.28	9.32	10.94

Example 32

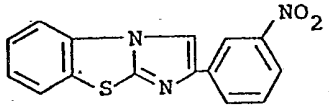


2-(4-chloro-3-hydroxyphenyl)imidazo-[2,1-b]benzothiazole

Melting point 310—312°C (decomposed)
Elemental analysis for $C_{15}H_9N_2OSCl$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	59.90	3.02	9.31	10.66
Found:	59.74	2.98	9.51	10.58

Example 33

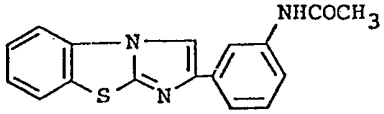


2-(m-Nitrophenyl)imidazo[2,1-b]benzothiazole

Melting point 232°C
Elemental analysis for $C_{15}H_9N_3O_2S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	61.01	3.07	14.23	10.86
Found:	60.72	2.95	14.40	10.99

Example 34

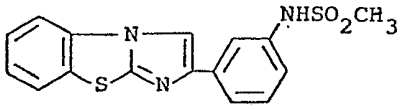


2-(m-Acetamidophenyl)imidazo[2,1-b]-benzothiazole

Melting point 232°C
Elemental analysis for $C_{17}H_{13}N_3OS$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	66.43	4.26	13.67	10.43
Found:	66.28	4.18	13.80	10.20

Example 35

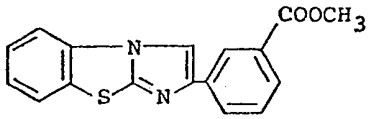


2-(m-Methylsulfonylamidophenyl)imidazo[2,1-b]benzothiazole

Melting point 194°C
Elemental analysis for $C_{16}H_{13}N_3O_2S_2$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	55.96	3.82	12.24	18.68
Found:	55.67	3.90	12.39	18.94

Example 36

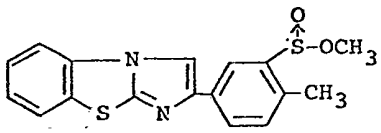


2-(m-Methoxycarbonylphenyl)imidazo-[2,1-b]benzothiazole

Melting point 146°C
Elemental analysis for $C_{17}H_{12}N_2O_2S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	66.22	3.92	9.08	10.40
Found:	66.19	3.78	9.13	10.26

Example 37

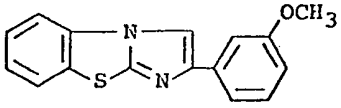


2-(3-Methoxysulfinyl-4-methylphenylimidazo[2,1-b]benzothiazole

Melting point 262—264°C
Elemental analysis for $C_{17}H_{14}N_2O_2S_2$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	59.63	4.12	8.18	18.73
Found:	59.46	3.98	8.31	18.43

Example 38

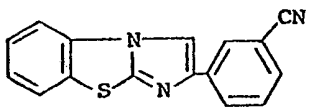


2-(m-Methoxyphenyl)imidazo[2,1-b]benzothiazole

Melting point 154—156°C
Elemental analysis for $C_{16}H_{12}N_2OS$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	68.55	4.31	9.99	11.44
Found:	68.42	4.28	10.19	11.26

Example 39

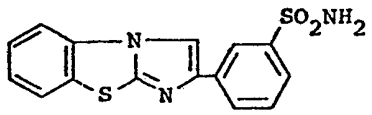


2-(m-cyanophenyl)imidazo[2,1-b]benzothiazole

Melting point 234°C
Elemental analysis for $C_{16}H_9N_3S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	69.80	3.29	15.26	11.64
Found:	69.78	3.27	15.18	11.63

Example 40



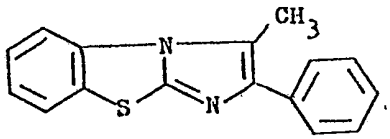
2-(m-sulfamoylphenyl)imidazo[2,1-b]benzothiazole

Melting point 306°C

Elemental analysis for $C_{15}H_{11}N_3O_2S_2$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	54.70	3.37	12.76	19.47
Found:	54.54	3.51	12.44	19.32

Example 41



To 50 ml of acetonitrile were added 10 g of 2-aminobenzothiazole and 7 g of α-bromopropiophenone and the mixture was refluxed for 3 days. After cooling the reaction mixture, precipitated hydrobromide of 2-aminobenzothiazole was filtered away and the filtrate was concentrated under reduced pressure. The residue was dissolved in 50 ml of chloroform and then 100 ml of ethyl acetate was added to the solution. The supernatent formed was recovered and concentrated under reduced pressure. The residue obtained was subjected to silica gel column chromatography and then the product was eluted using chloroform as the eluent to provide 1.5 g of 3-methyl-2-phenylimidazo[2,1-b]benzothiazole.

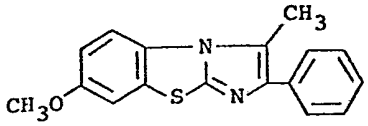
Melting point 136—137°C

Elemental analysis for $C_{16}H_{12}N_2S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	72.70	4.58	10.60	12.13
Found:	72.50	4.54	10.47	12.20

By following the above procedure, following compounds were prepared.

Example 42



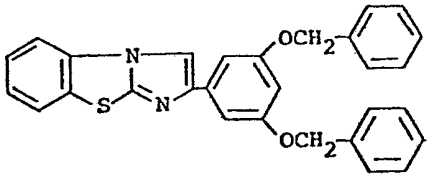
7-Methoxy-3-methyl-2-phenylimidazo[2,1-b]benzothiazole

Melting point 82—84°C

Elemental analysis for $C_{17}H_{14}N_2OS$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	69.36	4.79	9.52	10.89
Found:	69.00	4.61	9.34	10.59

Example 43



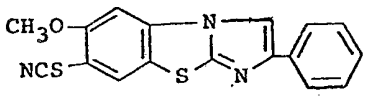
2-(3,5-Dibenzyloxyphenyl)imidazo[2,1-b]benzothiazole

Melting point 160—161°C

Elemental analysis for $C_{29}H_{22}N_2O_2S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	75.30	4.79	6.06	6.93
Found:	75.41	4.73	5.87	7.08

Example 44

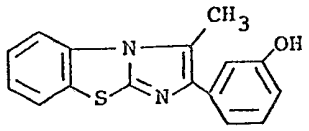


6-Methoxy-2-phenyl-7-thiocyanatoimidazo-[2,1-b]benzothiazole

Melting point 217—220°C
Elemental analysis for $C_{17}H_{11}N_3S_2O$:

	C(%)	*H(%)*	*N(%)*
Calculated:	60.52	3.29	12.45
Found:	60.38	3.22	12.26

Example 45

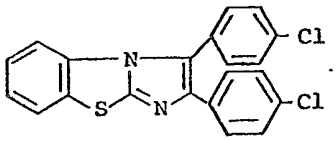


2-(m-Hydroxyphenyl)-3-methylimidazo-[2,1-b]benzothiazole

Melting point 246—248°C
Elemental analysis for $C_{16}H_{12}N_2OS$:

	N(%)
Calculated:	9.99
Found:	9.78

Example 46

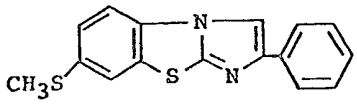


2,3-Bis(p-chlorophenyl)imidazo[2,1-b]-benzothiazole

Melting point 235°C
Elemental analysis for $C_{21}H_{12}N_2SCl_2$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	63.81	3.06	7.09	8.11
Found:	64.01	3.00	7.11	8.10

Example 47

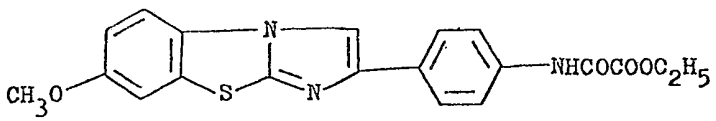


7-Methylthio-2-phenylimidazo[2,1-b]benzothiazole

Melting point 149°C
Elemental analysis for $C_{16}H_{12}N_2S_2$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	64.84	4.08	9.45	21.63
Found:	64.59	3.98	9.34	21.59

Example 48



By following the same procedure as in Example 1 using 3.6 g of 2-amino-6-methoxybenzothiazole and 6 g of p-ethoxalylamidophenacyl bromide as starting materials, 5.3 g of the white crystals of 2-imino-3-(p-ethoxalylamidobenzoylmethyl)-6-methoxy-2,3-dihydrobenzothiazole hydrobromide were obtained. The white crystals were refluxed in 150 ml of methylcellosolve for 3

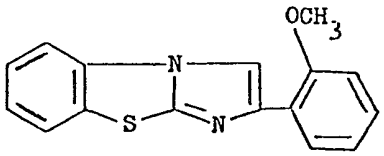
hours. After cooling the reaction mixture, crystals formed were recovered by filtration and the filtrate was concentrated under reduced pressure to form a solid. The crystals recovered above were combined with the solid and after adding thereto 30 ml of saturated sodium hydrogencarbonate solution, the product was extracted with 300 ml of chloroform. The chloroform extract was dried by anhydrous magnesium sulfate and concentrated under reduced pressure to provide 2.5 g of 2-(p-ethoxalylamidophenyl)-7-methoxy-imidazo[2,1-b]benzothiazole.

Melting point 218—219°C

Elemental analysis for $C_{20}H_{17}N_3O_4S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	60.75	4.33	10.63	8.11
Found:	60.61	4.27	10.45	8.03

Example 49



To 70 ml of methyl ethyl ketone were added 7 g of 2-aminobenzothiazole and 10 g of o-methoxyphenacyl bromide and the mixture was refluxed for 10 hours. The reaction mixture was filtered while it was hot to recover crystals precipitated. The crystals were washed with methyl ethyl ketone, and dried to provide 3.0 g of 2-(o-methoxyphenyl)imidazo[2,1-b]-benzothiazole hydrobromide having melting point of 263—265°C.

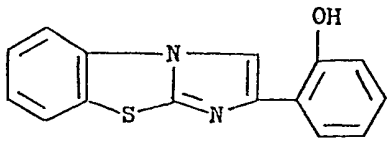
Then, 3 g of the hydrobromide was added to a mixture of 50 ml of chloroform and 20 ml of 10% aqueous ammonia and after stirring the mixture for 20 minutes at room temperature, the chloroform layer formed was recovered. The chloroform layer obtained was washed with water, dried by anhydrous magnesium sulfate, and concentrated under reduced pressure to form a white solid, which was recrystallized from toluene-n-hexane to provide 1.9 g of 2-(o-methoxyphenyl)imidazo[2,1-b]-benzothiazole.

Melting point 183—185°C

Elemental analysis for $C_{16}H_{12}N_2OS$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	68.55	4.31	9.99	11.44
Found:	68.65	4.26	9.95	11.32

Example 50



To 50 ml of methyl ethyl ketone were added 7.5 g of 2-aminobenzothiazole and 12 g of o-acetoxyphenacyl bromide and the mixture was refluxed for 3 hours. After the reaction was over, the reaction mixture was cooled, the hydrobromide of 2-aminobenzothiazole precipitated was filtered off and the filtrate was concentrated under reduced pressure and then toluene was added to the residue, thereby crystals precipitated. The crystals were recovered by filtration and dried to provide 3.5 g of the white crystals of 2-imino-3-(o-hydroxybenzoylmethyl)-2,3-dihydrobenzothiazole.

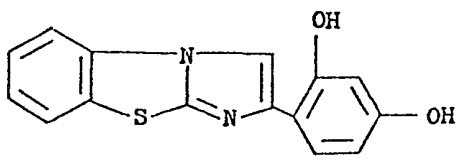
Then, 2.2 g of the crystals were treated with alcoholic hydrochloric acid to form the hydrochloride, which was heated together with 50 ml of methylcellosolve and treated as in Example 1 to provide 1.6 g of the white crystals of 2-(o-hydroxyphenyl)imidazo[2,1-b]benzothiazole.

Melting point 191—192°C

Elemental analysis for $C_{15}H_{10}N_2OS$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	67.65	3.78	10.52	12.04
Found:	67.51	3.79	10.40	11.73

Example 51



A solution of 6.8 g of 2-aminobenzothiazole and 7.2 g of 2,4-diacetoxy-α-bromoacetophenone in

100 ml of methyl ethyl ketone was refluxed for 3 hours. After cooling the reaction mixture, 50 ml of ether was added, precipitates formed were filtered off, and the mother liquor was concentrated under reduced pressure. The residue formed was dissolved in 10 ml of tetrahydrofuran and 10 ml of ether and then the solution was acidified by the addition of a hydrogen chloride-ethanol solution. Crystals formed were recovered by filtration, dried and then refluxed together with 50 ml of methylcellosolve for 5 hours. The reaction mixture was alkalified by the addition of concentrated aqueous ammonia and then cooled to form crystals, which were recovered by filtration and recrystallized from tetrahydrofuran-n-hexane to provide 1 g of 2-(2,4-dihydroxyphenyl)imidazo[2,1-b]benzothiazole.

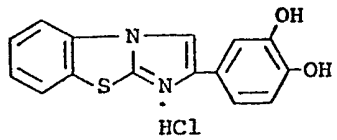
Melting point 254—257°C

Elemental analysis for $C_{15}H_{10}N_2O_2S$:

	C(%)	*H(%)*	*N(%)*
Calculated:	63.82	3.57	9.92
Found:	63.62	3.53	9.77

By following the above procedure, following compound was prepared.

Example 52



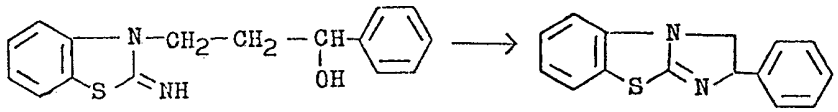
2-(3,4-Dihydroxyphenyl)imidazo[2,1-b]-benzothiazole hydrochloride

Melting point 235°C

Elemental analysis for $C_{15}H_{11}N_2O_2SCl$:

	S(%)	*Cl(%)*
Calculated:	10.06	11.12
Found:	9.76	11.18

Example 53



After refluxing 4 g of 2-imino-3-(β-hydroxyphenetyl)2,3-dihydrobenzothiazole hydrochloride together with 40 ml of chloroform and 9 ml of thionyl chloride for 2 hours, the reaction mixture was concentrated under reduced pressure to provide 4.2 g of the crude crystals of 2-imino-3-(β-chlorophenetyl)-2,3-dihydrobenzothiazole hydrochloride. To the product were added 50 ml of chloroform, 50 ml of water, and 5 g of sodium hydrogencarbonate and the mixture was refluxed for 3 hours. After the reaction was over, the chloroform layer was washed with water, dried by anhydrous magnesium sulfate, and concentrated under reduced pressure to provide a tacky material. The tacky product was treated with hydrochloric acid-ethanol and the white solid thus obtained was recrystallized from ethanol to provide 1.4 g of 2-phenyl-2,3-dihydroimidazo[2,1-b]benzothiazole hydrochloride.

Nuclear magnetic resonance spectra (D_6—DMSO)

δ(ppm): 4.39 5.03 (2H, —CH_2—)

6.01 (1H, —CH—)

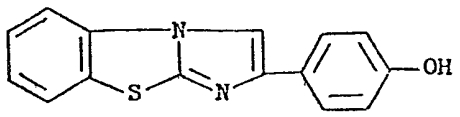
7.2—8.2 (9H, H of aromatic ring)

In addition, 2-imino-3-(β-hydroxyphenetyl)-2,3-dihydro-benzothiazole hydrochloride used above as the raw material was prepared as follows:

In 100 ml of ethanol was suspended 7.5 g of 2-imino-3-phenacyl-2,3-dihydrobenzothiazole hydrobromide and after cooling the suspension to 0°C to 5°C, 1.2 g of sodium borohydride was gradually added to the suspension, and the mixture was stirred for one hour. The reaction mixture was mixed with 5 ml of water and concentrated under reduced pressure. The residue was extracted with toluene and the extract was washed with water, dried by anhydrous magnesium sulfate, and then the solvent was distilled off to provide a tacky residue. The tacky product was dissolved in ethanol and hydrochloric acid-ethanol was added to the solution to provide 6 g of 2-imino-3-(β-hydroxyphenetyl)-2,3-dihydrobenzothiazole hydrochloride.

Melting point 253—255°C

Example 54



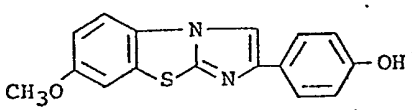
In a solution of 2.5 g of potassium hydroxide in 90% methanol was suspended 2 g of 2-(p-acetoxyphenyl)imidazo-[2,1-b]benzothiazole and the suspension was stirred for one hour at 40—50°C, thereby the additive was completely dissolved. Then, 3 ml of acetic acid was gradually added dropwise to the reaction mixture with stirring, thereby crystals precipitated. The crystals were recovered by filtration, washed with water and then methanol, and dried to provide 1.5 g of 2-(p-hydroxy-phenyl)imidazo[2,1-b]benzothiazole.

Melting point 296—298°C
Elemental analysis for $C_{15}H_{10}N_2OS$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	67.65	3.78	10.52	12.04
Found:	67.48	3.77	10.39	12.07

By following the above procedure, following compounds were prepared.

Example 55

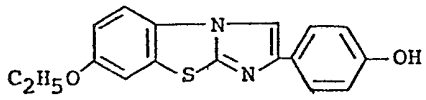


2-(p-Hydroxyphenyl)-7-methoxyimidazo-[2,1-b]benzothiazole

Melting point 285—286°C
Elemental analysis for $C_{16}H_{12}N_2O_2S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	64.85	4.08	9.45	10.82
Found:	64.64	3.98	9.49	10.99

Example 56

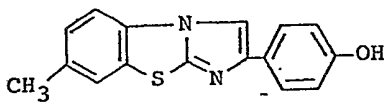


7-Ethoxy-2-(p-hydroxyphenyl)imidazo-[2,1-b]benzothiazole

Melting point 261—263°C
Elemental analysis for $C_{17}H_{14}N_2O_2S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	65.79	4.55	9.03	10.33
Found:	65.51	4.73	8.78	10.20

Example 57

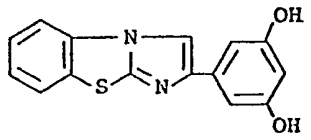


2-(p-Hydroxyphenyl)-7-methylimidazo[2,1-b]benzothiazole

Melting point 279—282°C
Elemental analysis for $C_{16}H_{12}N_2OS$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	68.55	4.31	9.99	11.44
Found:	68.25	4.20	9.82	11.57

Example 58

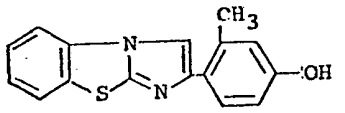


2-(3,5-Dihydroxyphenyl)imidazo[2,1-b]-benzothiazole

Melting point 287—290°C (decomposed)
Elemental analysis for $C_{15}H_{10}N_2O_2S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	63.82	3.57	9.92	11.36
Found:	63.54	3.72	9.71	11.20

Example 59

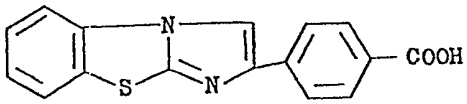


2-(4-Hydroxy-2-methylphenyl)imidazo-[2,1-b]benzothiazole

Melting point 253—255°C
Elemental analysis for $C_{16}H_{12}N_2OS$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	68.55	4.31	9.99	11.44
Found:	68.50	4.21	10.16	11.31

Example 60



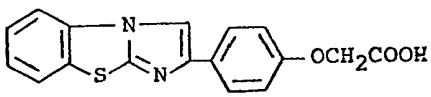
To a mixture of 15 ml of an aqueous solution of 20% potassium hydroxide and 50 ml of methanol was added 2.2 g of 2-(p-methoxycarbonylphenyl)imidazo[2,1-b]benzothiazole and the mixture was refluxed for 30 minutes. After the reaction was over, 4 ml of acetic acid was added to the reaction mixture and crystals precipitated were recovered by filtration, washed successively with water, methanol and then ethanol, and dried to provide 1.7 g of 2-(p-carboxyphenyl)imidazo[2,1-b]benzothiazole.

Melting point above 300°C
Elemental analysis for $C_{16}H_{10}N_2O_2S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	65.29	3.42	9.52	10.89
Found:	65.24	3.34	9.33	11.07

By following the above procedure, the following compounds were prepared.

Example 61

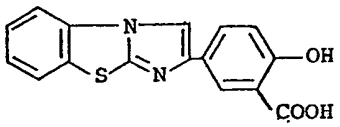


2-[p-(Carboxymethoxy)phenyl]imidazo[2,1-b]benzothiazole

Melting point 255°C
Elemental analysis for $C_{17}H_{12}N_2O_3S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	62.95	3.73	8.64	9.88
Found:	62.65	3.84	8.59	9.66

Example 62

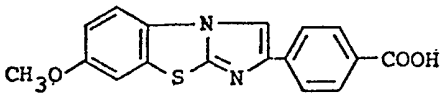


2-(3-Carboxy-4-hydroxyphenyl)imidazo-[2,1-b]benzothiazole

Melting point above 300°C
Elemental analysis for $C_{16}H_{10}N_2O_3S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	61.93	3.25	9.03	10.33
Found:	61.81	3.19	9.11	10.61

Example 63

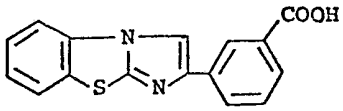


2-(p-Carboxyphenyl)-7-methoxyimidazo[2,1-b]benzothiazole

Melting point above 300°C
Elemental analysis for $C_{17}H_{12}N_2O_3S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	62.95	3.73	8.64	9.88
Found:	62.71	3.57	8.80	10.25

Example 64

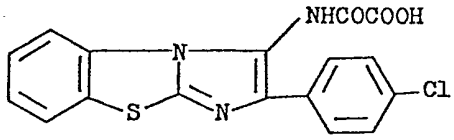


2-(m-Carboxyphenyl)imidazo[2,1-b]-benzothiazole

Melting point above 300°C
Elemental analysis for $C_{16}H_{10}N_2O_2S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	65.29	3.42	9.52	10.89
Found:	65.32	3.39	9.51	10.94

Example 65

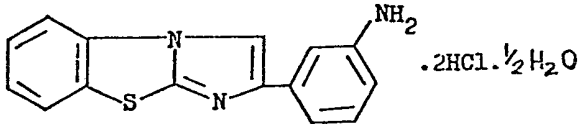


In 600 ml of water was suspended 2.08 g of 2-(p-chlorophenyl)-3-ethoxalylamidoimidazo[2,1-b]benzothiazole and then after adding 10 ml of a 1 normal sodium hydroxide solution to the suspension, the mixture was stirred for 3 hours at room temperature. Insoluble matters were filtered off and acetic acid was added to the filtrate to form crystals, which were recovered by filtration, washed with water, and dried to provide 1.1 g of 2-(p-chlorophenyl)-3-oxalamidoimidazo[2,1-b]-benzothiazole.

Mass spectrum m/e: 271(M^+)
Elemental analysis for $C_{17}H_{10}N_3O_3SCl$)

	S(%)
Calculated:	8.62
Found:	8.68

Example 66



To a mixture of 30 ml of a 2 normal hydrochloric acid solution and 20 ml of methanol was added

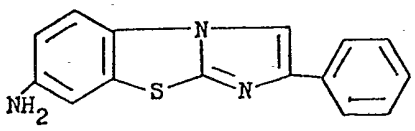
4 g of 2-(m-acetamidophenyl)imidazo[2,1-b]benzothiazole and the mixture was refluxed for 2 hours. The reaction mixture was concentrated under reduced pressure to form a solid, which was recrystallized from ethanol to provide 4.2 g of 2-(m-aminophenyl)-imidazo[2,1-b]benzothiazole dihydrochloride hemihydrate.

Melting point 241°C

Elemental analysis for $C_{15}H_{13}N_3SCl_2.1/2H_2O$)

	C(%)	H(%)	N(%)	S(%)	Cl(%)
Calculated:	51.88	4.06	12.10	9.23	20.42
Found:	52.13	3.94	12.04	9.19	20.15

Example 67



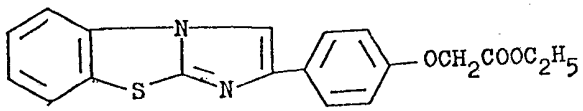
To a mixture of 100 ml of concentrated hydrochloric acid solution and 300 ml of methylcellosolve was added 8.5 g of 7-acetamido-2-phenylimidazo[2,1-b]benzothiazole mono-hydrate and the mixture was stirred for 4 hours at 100—110°C. The reaction mixture was cooled to form crystals, which were recovered by filtration. The crystals were suspended in 200 ml of methylcellosolve and after alkalifying the suspension by adding concentrated aqueous ammonia, 80 ml of water was added to the mixture followed by cooling, thereby crystals precipitated. The crystals precipitated were recovered by filtration and dried to provide 5.76 g of 7-amino-2-phenyl-imidazo[2,1-b]benzothiazole.

Melting point 161—163°C

Elemental analysis for $C_{15}H_{11}N_3S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	67.90	4.18	15.84	12.08
Found:	67.99	4.11	15.80	12.12

Example 68



To 40 ml of methyl ethyl ketone were added 2.6 g of 2-(p-hydroxyphenyl)imidazo[2,1-b]benzothiazole, 1.7 g of monobromo-acetic acid ethyl ester, and 1.5 g of potassium carbonate and the mixture was refluxed overnight. After the reaction was over, the reaction mixture was cooled, insoluble matters were filtered away, and the filtrate was concentrated under reduced pressure to provide a solid, which was recrystallized from toluene-n-hexane to provide 1.8 g of 2-(p-ethoxycarbonylmethoxyphenyl)imidazo[2,1-b]benzothiazole.

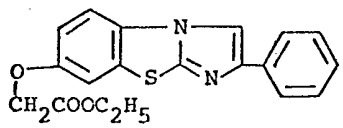
Melting point 129—130°C

Elemental analysis for $C_{19}H_{16}N_2O_3S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	64.76	4.58	7.95	9.10
Found:	64.58	4.51	7.73	8.80

By following the above procedure, the following compound was prepared.

Example 69



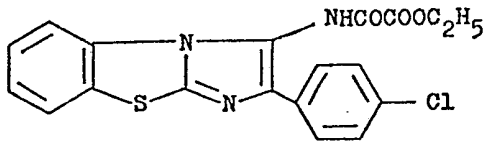
7-Ethoxycarbonylmethoxy-2-phenylimidazo-[2,1-b]benzothiazole

Melting point 114—116°C

Elemental analysis for $C_{19}H_{16}N_2O_3S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	64.76	4.58	7.95	9.10
Found:	64.61	4.56	7.89	9.15

Example 70



In a mixture of 15 ml of pyridine and 15 ml of methylene chloride was dissolved 1.8 g of 3-amino-2-(p-chlorophenyl)-imidazo[2,1-b]benzothiazole and then a solution of 1.5 g of ethyloxalyl chloride in 10 ml of methylene chloride was added dropwise to the solution at temperatures below 5°C. The temperature of the mixture was allowed to raise to room temperature and after stirring the mixture for 3 hours, the reaction mixture was concentrated under reduced pressure. The residue was extracted with 400 ml of ethyl acetate and the extract was washed with water, dried by anhydrous magnesium sulfate, and concentrated under reduced pressure to form crystals, which were recovered and recrystallized from ethanol to provide 1.72 g of 2-(p-chlorophenyl)-3-ethoxalylamidoimidazo[2,1-b]benzothiazole.

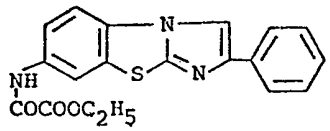
Melting point 243—245°C

Elemental analysis for $C_{19}H_{14}O_3N_3SCl$:

	C(%)	*H(%)*	*N(%)*
Calculated:	57.07	3.53	10.51
Found:	57.05	3.47	10.35

By following the above procedure, the compound shown in the following example was prepared.

Example 71



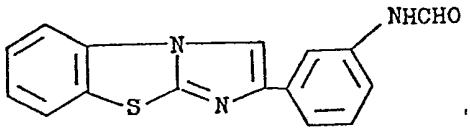
7-Ethoxalylamido-2-phenylimidazo[2,1-b]benzothiazole

Melting point 238—241°C

Elemental analysis for $C_{19}H_{15}N_3O_3S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	62.45	4.14	11.50	8.77
Found:	62.20	4.07	11.43	9.07

Example 72



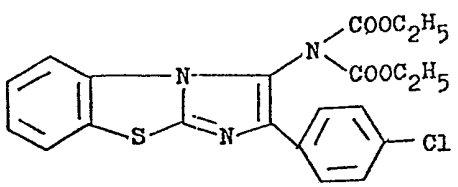
To 15 ml of a mixture of acetic anhydride and formic acid in 5:3 by volume ratio was added 1.2 g of 2-(m-aminophenyl)-imidazo[2,1-b]benzothiazole under cooling to 3—10°C and then the mixture was stirred for one hour at room temperature. To the reaction mixture was added 100 ml of water and then the product was extracted with a mixture of 25 ml of toluene and 25 ml of ethyl acetate. The extract was washed with water and then an aqueous sodium hydrogencarbonate solution, dried by anhydrous magnesium sulfate, and concentrated under reduced pressure to provide 1.2 g of the white crystals of 2-(m-formamidophenyl)imidazo[2,1-b]benzothiazole.

Melting point 163°C

Elemental analysis for $C_{16}H_{11}N_3OS$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	65.51	3.78	14.32	10.93
Found:	65.54	3.82	14.40	11.00

Example 73



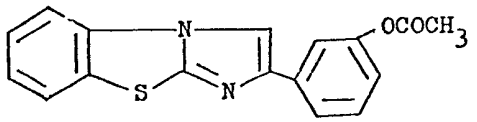
To a solution of 1.5 g of 3-amino-2-(p-chlorophenyl)-imidazo[2,1-b]benzothiazole in 10 ml of

pyridine was added dropwise a solution of 1.2 g of ethyl chlorocarbonate in 5 ml of methylene chloride at temperatures below 10°C. Thereafter, the mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was extracted with ethyl acetate. The extract was washed with water, dried by anhydrous magnesium sulfate, and concentrated under reduced pressure to form crystals, which were recovered and recrystallized from ethanol to provide 1.56 g of 2-(p-chlorophenyl)-3-bis(ethoxycarbonyl)amidoimidazo[2,1-b]benzothiazole.

Melting point 140—142°C
Elemental analysis for $C_{21}H_{18}N_3O_4SCl$:

	C(%)	H(%)	N(%)	S(%)	Cl(%)
Calculated:	56.82	4.09	9.47	7.22	7.99
Found:	56.67	4.08	9.39	7.35	8.13

Example 74

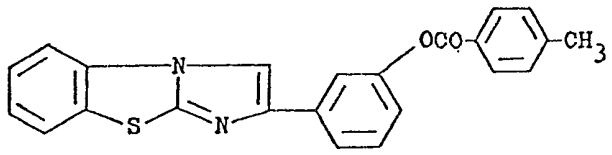


A solution of 2.3 g of 2-(m-hydroxyphenyl)imidazo[2,1-b]-benzothiazole in 3 ml of acetic anhydride and 10 ml of pyridine was stirred overnight at 80°C. The reaction mixture was concentrated under reduced pressure and the residue formed was extracted with ethyl acetate. The extract was washed with water, dried by anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography using a 10:3 mixture of toluene and ethyl acetate as an eluent and the crystals obtained were recrystallized from a mixture of toluene and n-hexane to provide 1.35 g of 2-(m-acetoxyphenyl)imidazo[2,1-b]benzothiazole.

Melting point 101—102°C
Elemental analysis for $C_{17}H_{12}N_2O_2S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	66.22	3.92	9.08	10.40
Found:	66.01	3.92	8.87	10.53

Example 75

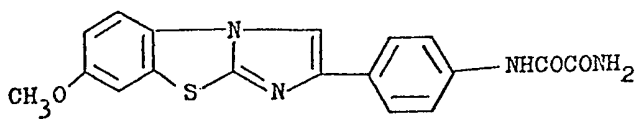


To a solution of 1.5 g of 2-(m-hydroxyphenyl)imidazo-[2,1-b]benzothiazole in 100 ml of tetrahydrofuran and 2 ml of triethylamine was added a solution of 0.96 g of p-toluoyl chloride in 10 ml of tetrahydrofuran at temperatures below 10°C and the mixture was stirred overnight at room temperature. The reaction mixture was mixed with 100 ml of toluene, washed with water, dried by anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from a mixture of toluene and n-hexane to provide 2 g of 2[3-(p-toluoyloxy)phenyl]imidazo[2,1-b]benzothiazole.

Melting point 173—175°C
Elemental analysis for $C_{23}H_{16}N_2O_2S$:

	S(%)
Calculated:	8.34
Found:	8.36

Example 76



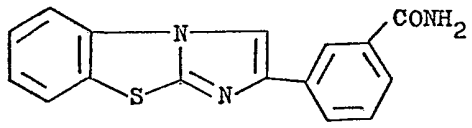
To 2.5 g of 2-(p-ethoxalylamidophenyl)-7-methoxyimidazo-[2,1-b]benzothiazole were added 50 ml of methyl cellosolve and 10 ml of 30% aqueous ammonia and after stirring the mixture for one hour at room temperature, crystals formed were recovered by filtration, washed successively with

chloroform and then methanol and dried to provide 1.9 g of 7-methoxy-2-(p-oxamidophenyl)imidazo[2,1-b]benzothiazole.

Melting point above 300°C
Elemental analysis for $C_{18}H_{14}N_4O_3S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	59.01	3.85	15.29	8.75
Found:	58.74	3.82	15.02	8.63

Example 77

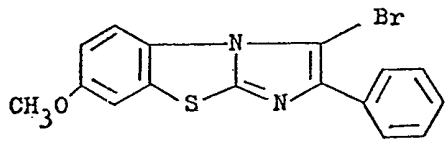


To 50 ml of a methanol solution containing 9 g of ammonia was added 3.2 g of 2-(m-methoxycarbonylphenyl)imidazo[2,1-b]-benzothiazole and the mixture was stirred overnight in a closed tube at 100—110°C. After cooling the mixture, crystals precipitated were recovered by filtration, washed with chloroform, and dried to provide 2 g of the white crystals of 2-(m-carbamoylphenyl)imidazo[2,1-b]benzothiazole.

Melting point 261°C
Elemental analysis for $C_{16}H_{11}N_3OS$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	65.51	3.78	14.32	10.93
Found:	65.26	3.65	14.18	10.97

Example 78



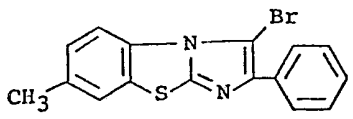
While stirring vigorously a mixture of a solution of 2.0 g of 7-methoxy-2-phenylimidazo[2,1-b]benzothiazole in 50 ml of chloroform and 30 ml of a saturated aqueous sodium hydrogen-carbonate solution, a solution of 1.2 g of bromine in 5 ml of chloroform was gradually added dropwise to the mixture at room temperature. Thereafter, the chloroform layer was recovered, dried by anhydrous magnesium sulfate, and concentrated under reduced pressure to form a solid. The solid product was recrystallized from a mixture of toluene and n-hexane to provide 2.0 g of 3-bromo-7-methoxy-2-phenylimidazo-[2,1-b]benzothiazole.

Melting point 180°C
Elemental analysis for $C_{16}H_{11}BrN_2OS$:

	C(%)	H(%)	N(%)	S(%)	Br(%)
Calculated:	53.50	3.09	7.80	8.92	22.24
Found:	53.36	2.94	7.33	9.08	22.42

By following the above procedure, the following compounds were prepared.

Example 79

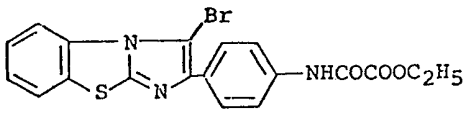


3-Bromo-7-methyl-2-phenylimidazo[2,1-b]-benzothiazole

Melting point 178—180°C
Elemental analysis for $C_{16}H_{11}BrN_2S$:

	C(%)	H(%)	N(%)	S(%)	Br(%)
Calculated:	55.99	3.23	8.16	9.34	23.28
Found:	55.94	3.08	8.01	9.44	23.47

Example 80

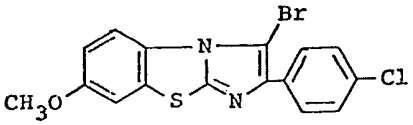


3-Bromo-2-[p(ethoxalylamido)phenyl]imidazo[2,1-b]benzothiazole

Melting point 237—238°C
Elemental analysis for $C_{19}H_{14}O_3N_3SBr$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	51.36	3.18	9.46	7.22
Found:	51.27	3.03	9.27	7.24

Example 81

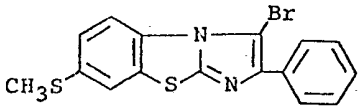


3-Bromo-2-(p-chlorophenyl)-7-methoxy-imidazo[2,1-b]benzothiazole

Melting point 239°C
Elemental analysis for $C_{16}H_{10}NOSClBR$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	48.81	2.56	7.12	8.14
Found:	48.76	2.40	7.07	8.34

Example 82

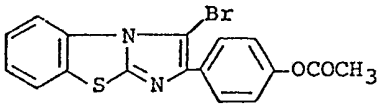


3-Bromo-7-methylthio-2-phenylimidazo[2,1-b]benzothiazole

Melting point 144°C
Elemental analysis for $C_{16}H_{11}N_2S_2Br$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	51.21	2.95	7.46	17.08
Found:	51.37	2.91	7.71	17.27

Example 83

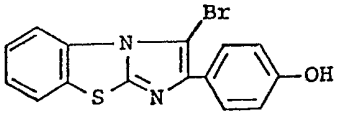


2-(p-Acetoxyphenyl)-3-bromoimidazo-[2,1-b]benzothiazole

Melting point 210°C
Elemental analysis for $C_{17}H_{11}N_2O_2SBr$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	52.73	2.86	7.23	8.28
Found:	52.81	2.71	7.18	8.30

Example 84

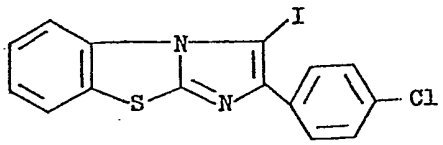


3-Bromo-2-(p-hydroxyphenyl)imidazo-[2,1-b]benzothiazole

Melting point 219°C
Elemental analysis for $C_{15}H_9N_2OSBr$:

	C(%)	*H(%)*	*N(%)*	*S(%)*	*Br(%)*
Calculated:	52.19	2.63	8.11	9.29	23.15
Found:	52.09	2.54	7.88	9.20	23.43

Example 85

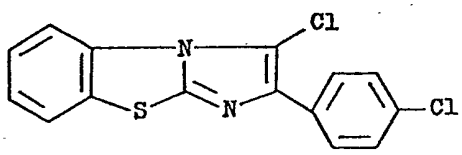


In 100 ml of methylene chloride was dissolved 2 g of 2-(p-chlorophenyl)imidazo[2,1-b]benzothiazole and after adding thereto 20 ml of an aqueous 10% potassium hydrogencarbonate solution and 1.8 g of iodine, the mixture was stirred overnight vigorously at room temperature. Crystals formed were recovered by filtration and recrystallized from a mixture of methylcellosolve and water to provide 2.4 g of 2-(p-chlorophenyl)-3-iodoimidazo[2,1-b]benzothiazole.

Melting point 253—255°C
Elemental analysis for $C_{15}H_8N_2SClI$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	43.87	1.96	6.82	7.81
Found:	43.90	1.80	6.78	8.08

Example 86



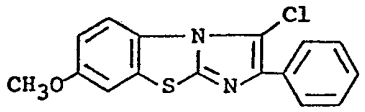
To a solution of 2 g of 2-(p-chlorophenyl)imidazo[2,1-b]-benzothiazole in 40 ml of methylene chloride was added a solution of 0.95 g of sulfuryl chloride in 5 ml of methylene chloride and after stirring for 10 minutes, 40 ml of an aqueous 10% potassium hydrogencarbonate solution was added to the mixture followed by stirring. The organic layer formed was recovered, washed with water, dried by anhydrous magnesium sulfate, and concentrated under reduced pressure to form crystals, which were recrystallized from ethanol to provide 1.4 g of 3-chloro-2-(p-chlorophenyl)imidazo[2,1-b]benzothiazole.

Melting point 152—155°C
Elemental analysis for $C_{15}H_8N_2SCl_2$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	56.44	2.53	8.79	10.04
Found:	56.70	2.56	8.76	10.06

By following the above procedure, the following compounds were prepared.

Example 87

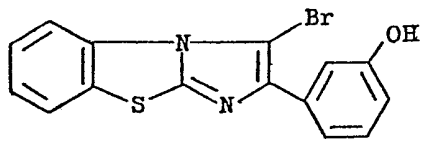


3-Chloro-7-methoxy-2-phenylimidazo[2,1-b]benzothiazole

Melting point 180°C
Elemental analysis for $C_{16}H_{11}N_2OSCl$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	60.28	3.48	8.79	11.31
Found:	60.25	3.51	8.80	11.22

Example 88



To 30 ml of chloroform were added 1.35 g of 2-(m-acetoxy-phenyl)imidazo[2,1-b]benzothiazole and 0.94 g of N-bromosuccinimide and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was washed with ether and dried to provide 2-(m-acetoxyphenyl)-3-bromoimidazo[2,1-b]-benzothiazole. The product was

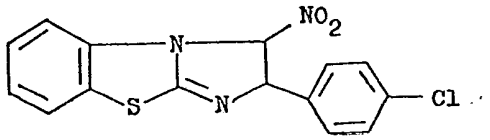
suspended in 50 ml of methanol and after adding thereto 4 ml of 0.84 normal methanol solution of potassium hydroxide, the mixture was stirred for 30 minutes at room temperature. To the reaction mixture was added acetic acid to acidify the mixture and then 50 ml of water was added to the mixture to form crystals, which were recovered by filtration and recrystallized from a mixture of methylcellosolve and water to provide 1.2 g of 3-bromo-2-(m-hydroxyphenyl)imidazo[2,1-b]benzothiazole.

Melting point 218—220°C

Elemental analysis for $C_{15}H_9N_2BrOS$:

	C(%)	H(%)	N(%)	Br(%)
Calculated:	52.19	2.63	8.11	23.15
Found:	52.25	2.62	7.99	23.18

Example 89



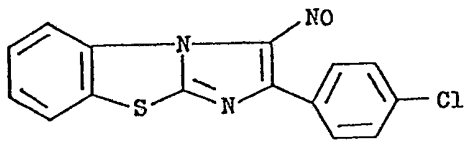
After cooling 30 ml of fuming nitric acid to —35 to —45°C, 3 g of 2-(p-chlorophenyl)imidazo[2,1-b]benzothiazole was gradually added thereto. The reaction mixture was poured into ice water and crystals formed were recovered by filtration and recrystallized from acetic acid to provide 2.2 g of 2-(p-chlorophenyl)-3-nitroimidazo[2,1-b]benzothiazole.

Melting point 180—183°C

Elemental analysis for $C_{10}H_8O_2N_3SCl$:

	S(%)	Cl(%)
Calculated:	9.72	10.75
Found:	9.53	10.75

Example 90

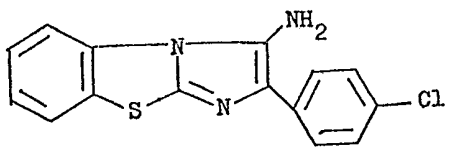


To 700 ml of acetic acid was added 14 g of 2-(p-chlorophenyl)imidazo[2,1-b]benzothiazole and after adding thereto 5 g of sodium nitrite with stirring at room temperature, the mixture was stirred for 3 hours. Thereafter, 500 ml of water was added to the mixture and crystals thus formed were recovered by filtration and washed with water and then n-hexane, and further 400 ml of chloroform to provide 10 g of 2-(p-chlorophenyl)-3-nitrosoimidazo[2,1-b]benzothiazole. The product was recrystallized from chloroform to provide crystals having melting point of 203—206°C.

Elemental analysis for $C_{15}H_8ON_3SCl$:

	C(%)	H(%)	N(%)	Cl(%)	S(%)
Calculated:	57.42	2.57	13.39	11.30	10.22
Found:	57.34	2.42	13.26	11.48	10.29

Example 91



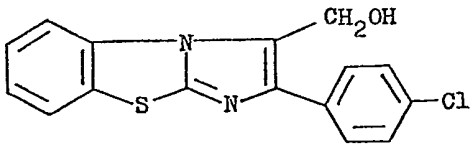
While suspending 9 g of 2-(p-chlorophenyl)-3-nitroso-imidazo[2,1-b]benzothiazole in 200 ml of acetic acid, 6 g of zinc powder was gradually added to the suspension at temperatures below 15°C. Insoluble matters were filtered off and 3 drops of concentrated sulfuric acid were added to the filtrate to form a precipitate. After filtering off the precipitate, 20 ml of concentrated sulfuric acid was added to the mother liquor and the mixture was allowed to stand overnight. Crystals formed were recovered by filtration and added to a mixture of ethyl acetate and water. After adding thereto potassium carbonate followed by stirring, the ethyl acetate layer formed was recovered, washed with water, dried by anhydrous magnesium sulfate, and concentrated under reduced pressure to form crystals, which were

recovered and recrystallized from toluene to provide 2.3 g of 3-amino-2-(p-chlorophenyl)imidazo[2,1-b]benzothiazole.

Melting point 193—196° (decomposed)
Elemental analysis for $C_{15}H_{10}N_3SCl$:

	C(%)	H(%)	N(%)	Cl(%)	S(%)
Calculated:	60.10	3.36	14.02	11.83	10.69
Found:	60.42	3.24	13.99	12.01	10.87

Example 92

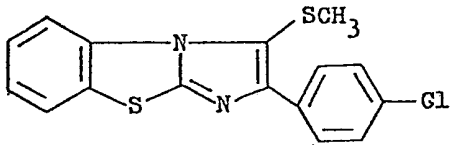


To a suspension of 2 g of 2-(p-chlorophenyl)-3-formyl-imidazo[2,1-b]benzothiazole in 100 ml of chloroform and 200 ml of ethanol was added 1 g of sodium borohydride and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and 900 ml of chloroform was added to the residue. After removing insoluble matters formed, the residue was washed with water, dried by anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue obtained was recrystallized from isopropyl alcohol to provide 1.2 g of 2-(p-chlorophenyl)-3-hydroxymethylimidazo[2,1-b]benzothiazole.

Melting point 218—220°C
Elemental analysis for $C_{16}H_{11}N_2OSCl$:

	C(%)	H(%)	N(%)	S(%)	Cl(%)
Calculated:	61.05	3.52	8.90	10.18	11.26
Found:	60.90	3.42	8.97	10.24	11.24

Example 93

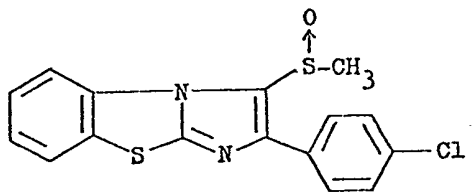


To a solution of 10 g of 2-(p-chlorophenyl)imidazo[2,1-b]-benzothiazole in 70 ml of methylene chloride was added dropwise a 1,1,2,2-tetrachloroethane solution of methylsulfinyl chloride obtained from 4 g of dimethyl disulfide and 5.2 g of sulfuryl chloride under ice cooling. Thereafter, the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and then the residue was extracted by 200 ml of chloroform. The extract was washed with an aqueous 5% sodium hydrogencarbonate solution and then water, dried by anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from methylcellosolve to provide 10.9 g of 2-(p-chlorophenyl)-3-methylthioimidazo[2,1-1]benzothiazole.

Melting point 190—192°C
Elemental analysis for $C_{16}H_{11}N_2S_2Cl$:

	C(%)	H(%)	N(%)	S(%)	Cl(%)
Calculated:	58.09	3.35	8.47	19.38	10.72
Found:	57.80	3.16	8.62	19.12	11.01

Example 94



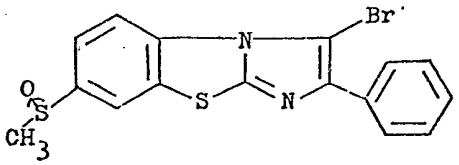
To a solution of 1.5 g of 2-(p-chlorophenyl)-3-methylthioimidazo[2,1-b]benzothiazole in 50 ml of chloroform was added 1.7 g of m-chloroperbenzoic acid and the mixture was stirred overnight at room temperature. The reaction mixture was washed with an aqueous 5% sodium hydrogencarbonate solution and then water, dried by anhydrous magnesium sulfate, and concentrated under reduced

pressure. The residue was recrystallized from methylcellosolve to provide 1.25 g of 2-(p-chlorophenyl)-3-methylthiosulfinylimidazo[2,1-b]benzothiazole.

Melting point 185—187°C (decomposed)
Elemental analysis for $C_{16}H_{11}N_2S_2OCl$:

	C(%)	H(%)	N(%)	Cl(%)	S(%)
Calculated:	55.41	3.20	8.08	10.22	18.49
Found:	55.28	3.25	7.92	10.31	18.32

Example 95

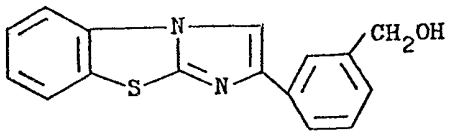


To 1.5 g of 7-methylthio-2-phenylimidazo[2,1-b]benzothiazole were added 50 ml of chloroform and 20 ml of a saturated aqueous sodium hydrogencarbonate solution and while stirring vigorously, a solution of 1.6 g of bromine in 5 ml of chloroform was gradually added dropwise to the mixture. Thereafter, the chloroform layer formed was recovered, dried by anhydrous magnesium sulfate, and concentrated under reduced pressure. The residual solid was subjected to silica gel column chromatography and the product was eluted using a mixture of chloroform and ethyl acetate to provide 0.8 g of 3-bromo-7-methylsulfinyl-2-phenylimidazo[2,1-b]benzothiazole.

Melting point 206°C
Elemental analysis for $C_{16}H_{11}N_2OS_2Br$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	49.11	2.83	7.16	16.39
Found:	48.95	2.77	7.01	16.32

Example 96



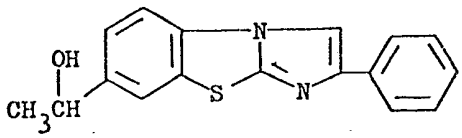
To a solution prepared by adding 0.2 g of lithium aluminum hydride to 20 ml of tetrahydrofuran cooled at 0—5°C was gradually added dropwise a solution of 1.2 g of 2-(m-methoxycarbonylphenyl)imidazo[2,1-b]benzothiazole in 10 ml of tetrahydrofuran and further the mixture was stirred for 10 minutes at 0—5°C. After gradually adding 5 ml of 10% acetic acid to the reaction mixture, 50 ml of ethyl acetate was added to the mixture and the product was extracted. The extract was dried by anhydrous magnesium sulfate and concentrated to form 10 g of solid, which was recrystallized from isopropanol to provide 0.8 g of 2-(m-hydroxymethylphenyl)-imidazo[2,1-b]benzothiazole.

Melting point 159°C
Elemental analysis for $C_{16}H_{12}N_2OS$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	68.55	4.31	9.99	11.44
Found:	68.36	4.30	10.07	11.56

By following the above procedure, the compound shown in the following example was prepared.

Example 97



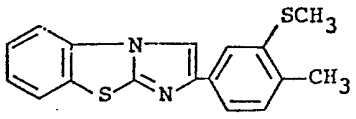
7-(1-Hydroxyethyl)-2-phenylimidazo[2,1-b]benzothiazole

Melting point 132°C
Elemental analysis for $C_{17}H_{14}N_2OS$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	69.36	4.79	9.52	10.89
Found:	69.20	5.01	9.49	10.75

By following the same procedure as example 1, following compounds were prepared.

Example 98

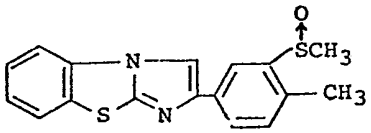


2-(4-Methyl-3methylthiophenyl)imidazo[2,1-b]benzothiazole

Melting point 130—132°C
Elemental analysis for $C_{17}H_{14}N_2S_2$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	65.85	4.55	9.03	20.84
Found:	65.78	4.55	9.02	20.66

Example 99

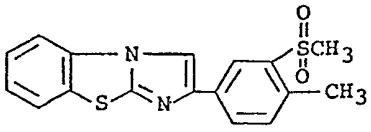


2-(4-Methyl-3-methylsulfinylphenyl)-imidazo[2,1-b]benzothiazole

Melting point 220—222°C
Elemental analysis for $C_{17}H_{14}N_2OS_2$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	62.37	4.27	8.35	19.49
Found:	62.55	4.32	8.58	19.64

Example 100

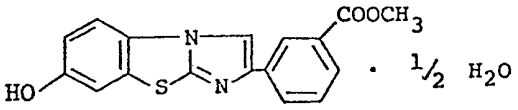


2-(4-Methyl-3-methylsulfonylphenyl)-imidazo[2,1-b]benzothiazole

Melting point 261—263°C
Elemental analysis for $C_{17}H_{14}N_2O_2S_2$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	59.56	4.05	8.02	18.55
Found:	59.63	4.12	8.18	18.73

Example 101

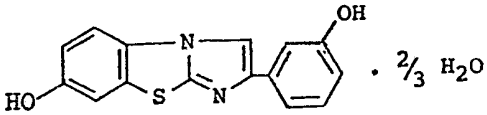


7-Hydroxy-2-(m-methoxycarbonyl)-phenyl)imidazo[2,1-b]benzothiazole hemihydrate

Melting point 210—212°C
Elemental analysis for $C_{17}H_{12}N_2O_3S.1/2H_2O$

	C(%)	H(%)	N(%)	S(%)
Calculated:	61.25	3.93	8.40	9.62
Found:	61.50	3.70	8.40	9.91

Example 102



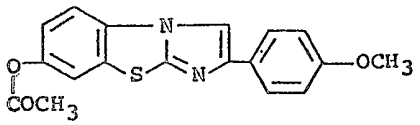
7-Hydroxy-2-(m-hydroxyphenyl)-imidazo[2,1-b]benzothiazole 2/3 hydrate

Melting point 178—180°C
Elemental analysis for $C_{15}H_{10}N_2O_2S.2/3H_2O$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	61.21	3.88	9.52	10.89
Found:	61.36	3.81	9.35	10.61

By following the same procedure as example 75, following compound was prepared.

Example 103



7-Acetoxy-2-(p-methoxyphenyl)imidazo[2,1-b]benzothiazole

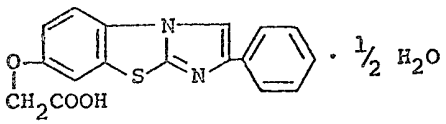
Melting point 215°C

Elemental analysis for $C_{18}H_{14}N_2O_3S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	63.89	4.17	8.28	9.47
Found:	63.95	4.03	8.23	9.52

By following the same procedure as example 60, following compound was prepared.

Example 104



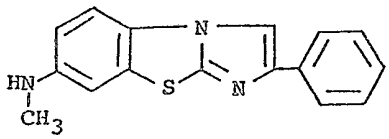
7-Carboxymethyloxy-2-phenylimidazo[2,1-b]benzothiazole hemihydrate

Melting point 240—243°C

Elemental analysis for $C_{17}H_{12}N_2O_3S.1/2H_2O$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	61.25	3.93	8.40	9.62
Found:	61.42	3.96	8.15	9.36

Example 105



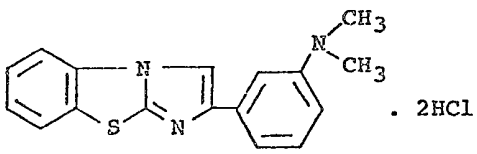
To 50 ml of ethanol were added 500 mg of 7-amino-2-phenylimidazo[2,1-b]benzothiazole, 265 mg of methyl iodide and 260 mg of potassium carbonate anhydride and while stirring vigorously, the mixture was refluxed for 2 days. The reaction mixture was cooled and then concentrated under reduced pressure. The residue was extracted with 50 ml of ethyl acetate and the extract was washed with water, dried by anhydrous magnesium sulfate, and then the extract was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (eluent: toluene: ethyl acetate=4:1) and the crystals obtained were recrystalized from toluene to provide 50 mg of 7-methylamino-2-phenylimidazo-[2,1-b]benzothiazole.

Melting point 175—176°C

Elemental analysis for $C_{16}H_{13}N_3S$:

	C(%)	*H(%)*	*N(%)*	*S(%)*
Calculated:	68.79	4.69	15.04	11.48
Found:	68.85	4.57	14.93	11.59

Example 106



To 50 ml of methylethylketone were added 2.6 g of 2-(m-aminophenyl)imidazo[2,1-b]benzothiazole, 2.8 g of methyl iodide and 2.8 g of potassium carbonate and the mixture was refluxed for 2 hours, and then insoluble matters were filtered and filtrate was concentrated under reduced pressure. The residue was mixed with 50 ml of water and extracted with 50 ml of ethyl acetate. The ethyl acetate layer formed was recovered, dried by anhydrous magnesium sulfate, and then the solvent

was distilled off to provide oily product. The oily product was dissolved in 20 ml of 1 N hydrochloric acid ethanol and 20 ml of ether was added to the solution, and then white crystals formed were recovered by filtration to provide 2.0 g of 2-[m-N,N-dimethyl)phenyl]imidazo[2,1-b]benzothiazole dihydrochloride.

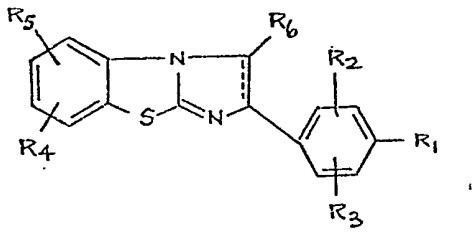
Melting point 218—220°C

Elemental analysis for $C_{17}H_{17}N_3SCl_2$:

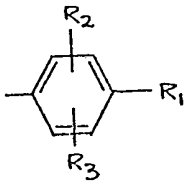
	C(%)	H(%)	N(%)	Cl(%)
Calculated:	55.74	4.68	11.48	19.36
Found:	55.89	4.91	11.17	19.06

Claims

1. A 2-phenylimidazo (2,1-b) benzothiazole derivative represented by the following formula



wherein R_1, R_2, and R_3 are selected independently from the group comprising a hydrogen atom, halogen atoms, a hydroxy group, a nitro group, a nitroso group, an amino group, a carboxy group, a nitrile group, a carbamoyl group, a sulfamoyl group, lower alkyl groups, hydroxy lower alkyl groups, lower alkoxy groups, phenyl lower alkoxy groups, carboxy lower alkoxy groups, lower alkoxycarbonyl lower alkoxy groups, lower alkoxycarbonyl groups, acyloxy groups, lower alkylthio groups, lower alkyl sulfinyl groups, lower alkylsulfonyl groups, lower alkoxysulfinyl groups, lower alkoxysulfonyl groups, mono or di lower alkylamino groups, or acylamino groups; any two adjacent R_1, R_2, and R_3 may combine with each other to form a benzene ring or a lower alkylenedioxy group; R_4, R_5, and R_6, are selected independently from the group comprising a hydrogen atom, halogen atoms, a hydroxy group, a nitro group, a nitroso group, an amino group, a thiocyanate group, lower alkyl groups, hydroxy lower alkyl groups, lower alkoxy groups, carboxy lower alkoxy groups, lower alkoxycarbonyl lower alkoxy groups, acyloxy groups, lower alkylthio groups, lower alkylsulfinyl groups, lower alkylsulfonyl groups, mono or di lower alkylamino groups, acylamino groups and a group shown by formula



and the dotted line means the existence or absence of a double bond; with the provisos that when R_2, R_3 and R_4 all are hydrogen atoms, R_5 is a hydrogen atom, a halogen atom, a nitro group, a lower alkyl group or a lower alkoxy group, and there is a double bond in the 2—3 position of the imidazole ring.

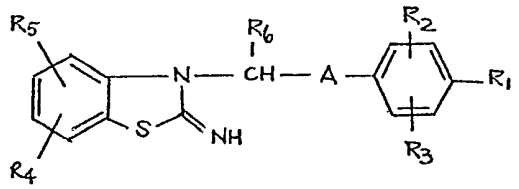
R_1 does not represent a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a nitro group, a lower alkyl group or a lower alkoxy group when R_6 is a hydrogen atom,

R_1 does not represent a hydrogen atom or a halogen atom when R_6 is a bromine atom or a thiocyanate group,

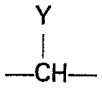
and R_1 does not represent a hydrogen atom or a nitro group when R_6 is a nitroso group or a nitro group.

2. 2-(m-Hydroxyphenyl) imidazo (2,1-b) benzothiazole.
3. 2-(o-Hydroxyphenyl) imidazo (2,1-b) benzothiazole.
4. 2-(p-Hydroxyphenyl) imidazo (2,1-b) benzothiazole.
5. 2-(m-Nitrophenyl) imidazo (2,1-b) benzothiazole.
6. 2-(m-Methoxycarbonylphenyl) imidazo (2,1-b) benzothiazole.
7. 2-(3-Chloro-4-hydroxyphenyl) imidazo (2,1-b) benzothiazole.
8. 2-(3,5-Dichloro-4-hydroxyphenyl) imidazo (2,1-b) benzothiazole.
9. 7-Hydroxy-2-(p-hydroxyphenyl) imidazo (2,1-b) benzothiazole.
10. Pharmaceutically acceptable salts of a 2-phenylimidazo (2,1-b) benzothiazole derivative according to any one of claims 1 to 9.

11. A process of producing the 2-phenylimidazo (2,1-b) benzothiazole derivative claimed in claim 1, which method comprises cyclizing the benzothiazole derivative represented by the formula



wherein A represents a carbonyl group or a group shown by



(wherein Y represents a halogen atom) and R_1 to R_6 are as defined in claim 1, and then, hydrolyzing, alkylating, acylating, amide-forming, halogenating, nitrating, nitroso-forming, reducing, lower alkylthio-forming, or oxidizing the product as necessary.

12. 2-phenylimidazo (2,1-b) benzothiazole derivatives described in the Examples herein.

13. A process for producing 2-phenylimidazo (2,1-b) benzothiazole derivatives, the process being substantially as hereinbefore described with reference to any one of the Examples.

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