N-Acetyl-3,5-dimethyl-2,4-dinitroaniline. To a cold (ice) solution of N-acetyl-3,5-dimethylaniline (25 g, 153 mmol) in concentrated sulfuric acid (500 mL) is added potassium nitrate (48 g, 474 mmol). The mixture is stirred for 45 minutes at 0 °C then 15 hours at room temperature. The mixture is poured into ice/water and extracted with chloroform. The extract is dried (magnesium sulfate) and rotary evaporated. The residue is purified by flash chromatography on silica gel (30% ethyl acetate/hexane) to afford N-acetyl-3,5-dimethyl-2,4-dinitroaniline (14.6 g).

3,5-Dimethyl-2,4-dinitroaniline. A mixture of N-acetyl-3,5-dimethyl-2,4-dinitroaniline (14.6 g, 57 mmol) and sodium methoxide (25 wt% solution in methanol) (26 mL) and methanol (200 mL) is heated to reflux for 90 minutes. The mixture is rotary evaporated and the residue is partitioned between water and chloroform. The organic layer is dried (magnesium sulfate) and rotary evaporated. The residue is purified by flash chromatography on silica gel (25% ethyl acetate/hexane) to afford 3,5-dimethyl-2,4-dinitroaniline (8.0 g) as an orange solid.

1,2-Diamino-3,5-dimethyl-4-nitrobenzene. A solution of 3,5-dimethyl-2,4-dinitroaniline (1.5 g, 7 mmol) in ethyl acetate (100 mL) is treated with hydrogen at atmospheric pressure for 2 hours. The mixture is filtered on Celite and the filtrate is rotary evaporated to afford 1,2-diamino-3,5-dimethyl-4-nitrobenzene (1.25 g) as a red solid.

2-Amino-4,6-dimethyl-5-nitrobenzimidazole. A mixture of 1,2-diamino-3,5-dimethyl-4-nitrobenzene (0.87 g, 4.83 mmol) and cyanogen bromide (0.87 g, 7.73 mmol) in methanol (50 mL) is stirred at room temperature for 16 hours. The mixture is rotary evaporated to afford 2-amino-4,6-dimethyl-5-nitrobenzimidazole. The product is used in the next step without further purification.

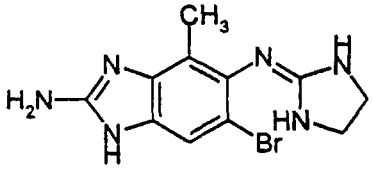
2-(t-Butoxycarbonyl)amino-4,6-dimethyl-5-nitrobenzimidazole. A mixture of 2-amino-4,6-dimethyl-5-nitrobenzimidazole (1.3 g, 6.31 mmol), di-t-butyl dicarbonate (2.5 mL of 1M solution in tetrahydrofuran, 7.56 mmol), triethylamine (2.6 mL, 18.9 mmol) and dimethylaminopyridine (0.1 g) in 20% methanol/ethyl acetate (60 mL) is stirred at room temperature for 16 hours. The mixture is rotary evaporated. The residue is partitioned between chloroform and 3% aqueous sodium carbonate. The organic layer is dried (magnesium sulfate) and rotary evaporated. The residue is purified by flash chromatography on silica gel (30% ethyl acetate/hexane) to afford 2-(t-butoxycarbonyl)amino-4,6-dimethyl-5-nitrobenzimidazole.

5-Amino-2-(t-butoxycarbonyl)amino-4,6-dimethylbenzimidazole. A suspension of 2-(t-butoxycarbonyl)amino-4,6-dimethyl-5-nitrobenzimidazole (0.625 g, 2.04 mmol) in ethanol (70 mL) is treated with hydrogen at 45 psi for 15 hours.

The mixture is filtered on Celite and the filtrate is rotary evaporated to afford 5-amino-2-(t-butoxycarbonyl)amino-4,6-dimethylbenzimidazole (0.5 g).

2-Amino-4,6-dimethyl-5-(2-imidazolinylamino)benzimidazole. A mixture of 5-amino-2-(t-butoxycarbonyl)amino-4,6-dimethylbenzimidazole (0.4 g, 1.44 mmol), di-2-pyridyl thionocarbonate (1.0 g, 4.32 mmol) and dimethylaminopyridine (0.1 g) in methylene chloride (40 mL) and methanol (2 mL) is stirred at room temperature for 15 hours. This mixture is then slowly added to a solution of 1,2-ethylene diamine (0.6 mL, 8.97 mmol) in methylene chloride (10 mL). The resulting mixture is stirred at room temperature for 1 hour. The mixture is rotary evaporated and the residue is triturated with ethyl acetate and filtered. The solid is suspended in methanol (300 mL), mercuric acetate is added (0.56 g, 1.75 mmol) and the resulting mixture is stirred at room temperature for 15 hours. The mixture is filtered through Celite and the filtrate is rotary evaporated. The residue is purified by preparative HPLC (C4 column, solvent gradient: 0.1% trifluoroacetic acid (in water)/acetonitrile starting at 95/5 and going to 0/100) to afford 2-amino-4,6-dimethyl-5-(2-imidazolinylamino)benzimidazole as a trifluoroacetic acid salt.

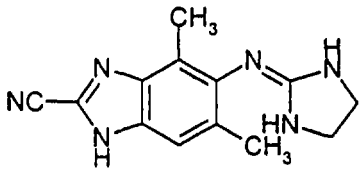
Example 12



2-Amino-6-bromo-5-(2-imidazolinylamino)-4-methylbenzimidazole

This compound is prepared by a combination of Schemes 1 and 4. Commercially available 2,6-dinitrotoluene is converted to 2,3-diamino-6-nitrotoluene according to scheme 2. Reaction with cyanogen bromide affords 2-amino-4-methyl-5-nitrobenzimidazole. After protection of the amino group with a tert-butoxycarbonyl group, the compound is reduced by hydrogenation (palladium-on-carbon) and brominated (bromine, sodium acetate, acetic acid) to afford 5-amino-6-bromo-2-tert-butoxycarbonylamino-4-methylbenzimidazole. The formation of the 5-(2-imidazolinylamino) group is completed in the usual fashion and the tert-butoxycarbonyl group is cleaved by treatment with hydrobromic acid to afford 2-amino-6-bromo-5-(2-imidazolinylamino)-4-methylbenzimidazole.

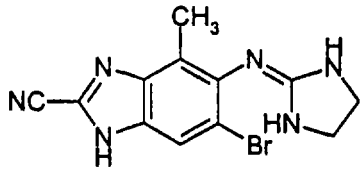
Example 13



2-Cyano-4,6-dimethyl-5-(2-imidazolinylamino)benzimidazole

2-Amino-4,6-dimethyl-5-nitrobenzimidazole (as prepared in Example 11) is converted to 2-cyano-4,6-dimethyl-5-nitrobenzimidazole by treatment with sodium nitrite and tetrafluoroboric acid followed by reaction with copper cyanide. The synthesis of 2-cyano-4,6-dimethyl-5-(2-imidazolinylamino)benzimidazole is then completed according to Scheme 5.

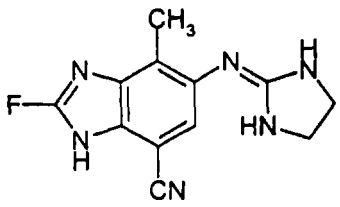
Example 14



6-Bromo-2-cyano-5-(2-imidazolinylamino)-4-methylbenzimidazole

2-Amino-4-methyl-5-nitrobenzimidazole (see Example 12) is converted to 2-cyano-4-methyl-5-nitrobenzimidazole by first treating with sodium nitrate and tetrafluoroboric acid to form the diazonium salt, followed by reaction with copper cyanide. Reduction of the 5-nitro group followed by bromination (bromine, acetic acid) affords 5-amino-6-bromo-2-cyano-4-methylbenzimidazole. The synthesis is then completed according to Scheme 5.

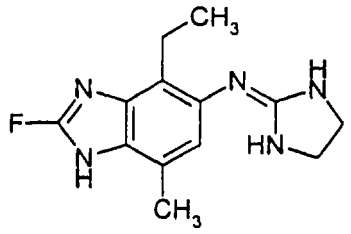
Example 15



2-Fluoro-7-cyano-5-(2-imidazolinylamino)-4-methylbenzimidazole

3-Amino-2,6-dinitro-p-toluic carboxamide is converted to 7-carboxamido-2-diazo-4-methyl-5-nitrobenzimidazole tetrafluoroborate according to Scheme 4. Conversion to 7-carboxamido-2-fluoro-4-methyl-5-nitrobenzimidazole is achieved by thermal decomposition of the diazonium salt. The synthesis is then completed in the same manner as in Example 1.

Example 16

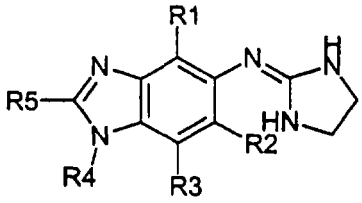


4-Ethyl-2-fluoro-5-(2-imidazolinylamino)benzimidazole

2,4-Dinitro-3-ethyl-6-methylaniline (see Example 2) is treated with sodium sulfide to afford 1,2-diamino-3-ethyl-6-methyl-4-nitrobenzene. Treatment with cyanogen bromide affords to 2-amino-4-ethyl-7-methyl-5-nitrobenzimidazole. This is converted to 2-diazo-4-ethyl-7-methyl-5-nitrobenzimidazole tetrafuoroborate with sodium nitrite and tetrafluoroboric acid. Thermal decomposition of the diazonium salt gives 4-ethyl-2-fluoro-7-methyl-5-nitrobenzimidazole. Conversion to 4-ethyl-2-fluoro-5-(2-imidazolinylamino)benzimidazole is completed according to Scheme 5.

Examples 17-39

Compounds of formula



wherein R1, R2, R3, R4, and R5 are specified in the following table. Compounds of Example 17-39 are made using the methods explained and exemplified above.

Example	R1	R2	R3	R4	R5
17	methyl	H	cyano	H	bromo
18	methyl	H	cyano	H	chloro
19	methyl	H	cyano	H	hydroxy
20	methyl	H	hydroxy	H	H

21	methyl	H	hydroxy	methyl	H
22	methyl	H	hydroxy	H	methyl
23	methyl	H	hydroxy	H	fluoro
24	methyl	H	hydroxy	H	bromo
25	methyl	H	hydroxy	h	chloro
26	methyl	bromo	H	H	fluoro
27	methyl	bromo	H	H	bromo
28	methyl	bromo	H	H	hydroxy
29	methyl	bromo	H	methyl	H
30	methyl	chloro	H	H	H
31	methyl	chloro	H	methyl	H
32	methyl	chloro	H	H	amino
33	methyl	chloro	H	H	fluoro
34	methyl	chloro	H	H	bromo
35	methyl	chloro	H	H	methyl
36	methyl	methyl	H	methyl	H
37	methyl	methyl	H	H	hydroxy
38	methyl	methyl	H	H	fluoro
39	methyl	methyl	H	H	bromo
40	methyl	methyl	methyl	H	H
41	methyl	bromo	methyl	H	H
42	ethyl	H	bromo	H	H
43	ethyl	H	chloro	H	H
44	ethyl	H	hydroxy	H	H
45	ethyl	H	chloro	methyl	H
46	cyclopropyl	H	bromo	H	H
47	cyclopropyl	H	chloro	H	H
48	cyclopropyl	H	hydroxy	H	H
49	cyclopropyl	H	methyl	methyl	H

Compositions

Another aspect of this invention is compositions which comprise a safe and effective amount of a compound of the invention, or a pharmaceutically-acceptable salt thereof, and a pharmaceutically-acceptable carrier. As used herein, "safe and effective amount" means an amount of the compound of the invention sufficient to significantly induce a positive modification in the condition to be treated, but low

enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. A safe and effective amount of the compound of the invention will vary with the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician.

Compositions of this invention preferably comprise from about 0.0001% to about 99% by weight of the compound of the invention, more preferably from about 0.01% to about 90%; also preferably from about 10% to about 50%, also preferably from about 5% to about 10%, also preferably from about 1% to about 5%, and also preferably from about 0.1% to about 1%.

In addition to the compound of the invention, the compositions of this invention contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a human or lower animal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the compound of the invention, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human or lower animal being treated.

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the Tweens®; wetting agents, such as sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the compound of the invention is basically determined by the way the compound is to be administered.

If the compound of the invention is to be injected, the preferred pharmaceutically-acceptable carrier is sterile, physiological saline, with blood-compatible suspending agent, the pH of which has been adjusted to about 7.4.

The preferred mode of administering the compound of the invention is perorally. The preferred unit dosage form is therefore tablets, capsules, lozenges, chewable tablets, and the like. Such unit dosage forms comprise a safe and effective amount of the compound of the invention, which is preferably from about 0.01 mg to about 200 mg, more preferably from about 0.1 mg to about 50 mg, more preferably still from about 0.5 mg to about 25 mg, also preferably from about 1 mg to about 10 mg. The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for peroral administration are well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of this invention, and can be readily made by a person skilled in the art.

Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Such liquid oral compositions preferably comprise from about 0.001% to about 5% of the compound of the invention, more preferably from about 0.01% to about 0.5%. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, Avicel® RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

Other modes of administration useful for attaining systemic delivery of the compounds of the invention include subcutaneous, intravenous, sublingual and buccal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

A preferred mode of administering the compound of the invention is topically to the site where activity is desired: intranasal doses for nasal decongestion, inhalants for asthma, eye drops, gels and creams for ocular disorders.

Preferred intranasal compositions of this invention include aqueous solutions comprising a safe and effective amount of a compound of the invention. Such compositions preferably comprise from about 0.001% to about 5% of a compound of the invention, more preferably from about 0.01% to about 0.5%. Such compositions also typically include safe and effective amounts of preservatives, such as benzalkonium chloride and thimerosal; buffers such as phosphate and acetate; tonicity agents such as sodium chloride; antioxidants such as ascorbic acid; aromatic agents; and acids and bases to adjust the pH of these aqueous compositions as needed.

Preferred inhalation/atomization compositions of this invention include aqueous solutions, suspensions, and dry powders comprising a safe and effective amount of a compound of the invention. Such compositions preferably comprise from about 0.1% to about 50% of a compound of the invention, more preferably from about 1% to about 20%. Such compositions are typically contained in a container with attached atomizing means. Such compositions also typically include propellants such as chlorofluorocarbons 12/11 and 12/114; solvents such as water, glycerol and ethanol; stabilizers such as ascorbic acid, sodium metabisulfite; preservatives such as cetylpyridinium chloride and benzalkonium chloride; tonicity adjustors such as sodium chloride; and flavoring agents such as sodium saccharin.

Preferred intraocular compositions of this invention include aqueous solutions comprising a safe and effective amount of a compound of the invention. Such compositions preferably comprise from about 0.0001% to about 5% of a compound of the invention, more preferably from about 0.01% to about 0.5%. Such compositions also typically include one or more of preservatives, such as benzalkonium chloride, thimerosal, phenylmercuric acetate; vehicles, such as poloxamers, modified celluloses, povidone and purified water; tonicity adjustors, such as sodium chloride, mannitol and glycerin; buffers such as acetate, citrate,

phosphate and borate; antioxidants such as sodium metabisulfite, butylated hydroxy toluene and acetyl cysteine; acids and bases may be used to adjust the pH of these formulations as needed.

Additional Drug Actives

Compositions of this invention may optionally include other drug actives. Non-limiting examples of drug actives which may be incorporated in these compositions include:

Antihistamines: Hydroxyzine preferably at a dosage range of from about 25 to about 400mg; Doxylamine, preferably at a dosage range of from about 3 to about 75mg; Pyrilamine, preferably at a dosage range of from about 6.25 to about 200mg; Chlorpheniramine, preferably at a dosage range of from about 1 to about 24mg; Phenindamine, preferably at a dosage range of from about 6.25 to about 150mg; Dexchlorpheniramine, preferably at a dosage range of from about 0.5 to about 12mg; Dexbrompheniramine, preferably at a dosage range of from about 0.5 to about 12mg; Clemastine, preferably at a dosage range of from about 1 to about 9mg; Diphenhydramine, preferably at a dosage range of from about 6.25 to about 300mg; Azelastine, preferably at a dosage range of from about 140 to about 1,680ug (when dosed intranasally); 1 to about 8 mg (when dosed orally); Acrivastine, preferably at a dosage range of from about 1 to about 24mg; Levocarbastine (which can be dosed as an intranasal or ocular medicament), preferably at a dosage range of from about 100 to about 800ug; Mequitazine, preferably at a dosage range of from about 5 to about 20mg; Astemizole, preferably at a dosage range of from about 5 to about 20mg; Ebastine;Loratadine, preferably at a dosage range of from about 5 to about 40mg; Cetirizine, preferably at a dosage range of from about 5 to about 20mg; Terfenadine, preferably at a dosage range of from about 30 to about 480mg; Terfenadine metabolites; Promethazine, preferably at a dosage range of from about 6.25 to about 50mg; Dimenhydrinate, preferably at a dosage range of from about 12.5 to about 400mg; Meclizine, preferably at a dosage range of from about 6.25 to about 50mg; Tripelennamine, preferably at a dosage range of from about 6.25 to about 300mg; Carbinoxamine, preferably at a dosage range of from about 0.5 to about 16mg; Cyproheptadine, preferably at a dosage range of from about 2 to about 20mg; Azatadine, preferably at a dosage range of from about 0.25 to about 2mg; Brompheniramine, preferably at a dosage range of from about 1 to about 24mg; Triprolidine, preferably at a dosage range of from about 0.25 to about 10mg; Cyclizine, preferably at a dosage range of from about 12.5 to about 200mg; Thonzylamine, preferably at a dosage range of from

about 12.5 to about 600mg; Pheniramine, preferably at a dosage range of from about 3 to about 75mg; Cyclizine, preferably at a dosage range of from about 12.5 to about 200mg and others.

Antitussives: Codeine, preferably at a dosage range of from about 2.5 to about 120mg; Hydrocodone, preferably at a dosage range of from about 2.5 to about 40mg; Dextromethorphan, preferably at a dosage range of from about 2.5 to about 120mg; Noscapine, preferably at a dosage range of from about 3 to about 180mg; Benzonatate, preferably at a dosage range of from about 100 to about 600mg; Diphenhydramine, preferably at a dosage range of from about 12.5 to about 150mg; Chlophedianol, preferably at a dosage range of from about 12.5 to about 100mg; Clobutinol, preferably at a dosage range of from about 20 to about 240mg; Fominoben, preferably at a dosage range of from about 80 to about 480mg; Glaucine; Pholcodine, preferably at a dosage range of from about 1 to about 40mg; Zipeprol, preferably at a dosage range of from about 75 to about 300mg; Hydromorphone, preferably at a dosage range of from about 0.5 to about 8mg; Carbetapentane, preferably at a dosage range of from about 15 to about 240mg; Caramiphen, Levopropoxyphene, preferably at a dosage range of from about 25 to about 200mg and others.

Antiinflammatories, preferably Non-Steroidal Anti-inflammatories (NSAIDS): Ibuprofen, preferably at a dosage range of from about 50 to about 3,200mg; Naproxen, preferably at a dosage range of from about 62.5 to about 1,500mg; Sodium naproxen, preferably at a dosage range of from about 110 to about 1,650mg; Ketoprofen, preferably at a dosage range of from about 25 to about 300mg; Indoprofen, Indomethacin, preferably at a dosage range of from about 25 to about 200mg; Sulindac, preferably at a dosage range of from about 75 to about 400mg; Diflunisal, preferably at a dosage range of from about 125 to about 1,500mg; Ketorolac, preferably at a dosage range of from about 10 to about 120mg; Piroxicam, preferably at a dosage range of from about 10 to about 40mg; Aspirin, preferably at a dosage range of from about 80 to about 4,000mg; Meclofenamate, preferably at a dosage range of from about 25 to about 400mg; Benzydamine, preferably at a dosage range of from about 25 to about 200mg; Carprofen, preferably at a dosage range of from about 75 to about 300mg; Diclofenac, preferably at a dosage range of from about 25 to about 200mg; Etodolac, preferably at a dosage range of from about 200 to about 1,200mg; Fenbufen, preferably at a dosage range of from about 300 to about 900mg; Fenoprofen, preferably at a dosage range of from about 200 to about 3,200mg; Flurbiprofen, preferably at a dosage range of from about 50 to about 300mg; Mefenamic acid, preferably at a

dosage range of from about 250 to about 1,500mg; Nabumetone, preferably at a dosage range of from about 250 to about 2,000mg; Phenylbutazone, preferably at a dosage range of from about 100 to about 400mg; Pirprofen, preferably at a dosage range of from about 100 to about 800mg; Tolmetin, preferably at a dosage range of from about 200 to about 1,800mg and others.

Analgesics: Acetaminophen, preferably at a dosage range of from about 80 to about 4,000mg; and others including narcotic and non-narcotic analgesics.

Expectorants/Mucolytics: Guaifenesin, preferably at a dosage range of from about 50 to about 2,400mg; N-Acetylcysteine, preferably at a dosage range of from about 100 to about 600mg; Ambroxol, preferably at a dosage range of from about 15 to about 120mg; Bromhexine, preferably at a dosage range of from about 4 to about 64mg; Terpin hydrate, preferably at a dosage range of from about 100 to about 1,200mg; Potassium iodide, preferably at a dosage range of from about 50 to about 250mg and others.

Atropinics, preferably intranasally or orally administered atropinics: Ipratroprium (preferably intranasally), preferably at a dosage range of from about 42 to about 252ug; Atropine sulfate (preferably oral), preferably at a dosage range of from about 10 to about 1,000ug; Belladonna (preferably as an extract), preferably at a dosage range of from about 15 to about 45mg equivalents; Scopolamine, preferably at a dosage range of from about 400 to about 3,200ug; Scopolamine methobromide, preferably at a dosage range of from about 2.5 to about 20mg; Homatropine methobromide, preferably at a dosage range of from about 2.5 to about 40mg; Hyoscyamine (preferably oral), preferably at a dosage range of from about 125 to about 1,000ug; Isopropramide (preferably oral), preferably at a dosage range of from about 5 to about 20mg; Orphenadrine (preferably oral), preferably at a dosage range of from about 50 to about 400mg; Benzalkonium chloride (preferably intranasally) preferably a 0.005 to about 0.1% solution and others.

Mast Cell Stabilizers, preferably intranasally, or orally administered mast cell stabilizers: Cromalyn, preferably at a dosage range of from about 10 to about 60mg; Nedocromil, preferably at a dosage range of from about 10 to about 60mg; Oxatamide, preferably at a dosage range of from about 15 to about 120mg; Ketotifen, preferably at a dosage range of from about 1 to about 4mg; Lodoxamide, preferably at a dosage range of from about 100 to about 3,000ug and others.

LT Antagonists: Zileuton and others.

Methylxanthines: Caffeine, preferably at a dosage range of from about about 65 to about 600mg; Theophyllene, preferably at a dosage range of from about 25 to about 1,200mg; Enprofylline; Pentoxifylline, preferably at a dosage

range of from about 400 to about 3,600mg; Aminophylline, preferably at a dosage range of from about 50 to about 800mg; Dyphylline, preferably at a dosage range of from about 200 to about 1,600mg and others.

Antioxidants or radical inhibitors: Ascorbic acid, preferably at a dosage range of from about 50 to about 10,000mg; Tocopherol, preferably at a dosage range of from about 50 to about 2,000mg; Ethanol, preferably at a dosage range of from about 500 to about 10,000mg and others.

Steroids, preferably intranasally administered steroids: Beclomethasone, preferably at a dosage range of from about 84 to about 336ug; Fluticasone, preferably at a dosage range of from about 50 to about 400ug; Budesonide, preferably at a dosage range of from about 64 to about 256ug; Mometasone; Triamcinolone, preferably at a dosage range of from about 110 to about 440ug; Dexamethasone, preferably at a dosage range of from about 168 to about 1,008ug; Flunisolide, preferably at a dosage range of from about 50 to about 300ug; Prednisone (preferably oral), preferably at a dosage range of from about 5 to about 60mg; Hydrocortisone (preferably oral), preferably at a dosage range of from about 20 to about 300mg and others.

Bronchodilators, preferably for inhalation: Albuterol, preferably at a dosage range of from about 90 to about 1,080ug; 2 to about 16mg (if dosed orally); Epinephrine, preferably at a dosage range of from about 220 to about 1,320ug; Ephedrine, preferably at a dosage range of from about 15 to about 240mg (if dosed orally); 250 to about 1,000ug (if dosed intranasally); Metaproterenol, preferably at a dosage range of from about 65 to about 780ug or 10 to about 80mg if dosed orally; Terbutaline, preferably at a dosage range of from about 200 to about 2,400ug; 2.5 to about 20mg if dosed orally; Isoetharine, preferably at a dosage range of from about 340 to about 1,360ug; Pirbuterol, preferably at a dosage range of from about 200 to about 2,400ug; Bitolterol, preferably at a dosage range of from about 370 to about 2,220ug; Fenoterol, preferably at a dosage range of from about 100 to about 1,200ug; 2.5 to about 20mg (if dosed orally); Rimeterol, preferably at a dosage range of from about 200 to about 1,600ug; Ipratroprium, preferably at a dosage range of from about 18 to about 216ug (inhalation) and others.

Antivirals: Amantadine, preferably at a dosage range of from about 50 to about 200mg; Rimantadine, preferably at a dosage range of from about 50 to about 200mg; Enviroxime; Nonoxinols, preferably at a dosage range of from about 2 to about 20mg (preferably an intranasal form); Acyclovir, preferably at a dosage range of from about 200 to about 2,000mg (oral); 1 to about 10mg (preferably an intranasal form); Alpha-Interferon, preferably at a dosage range of from about 3 to

about 36 MIU; Beta-Interferon, preferably at a dosage range of from about 3 to about 36 MIU and others.

Ocular Drug actives: acetylcholinesterase inhibitors, e.g., echothiophate from about 0.03% to about 0.25% in topical solution and others; and

Gastrointestinal actives: antidiarrheals, e.g., loperamide from about 0.1 mg to about 1.0 mg per dose, and bismuth subsalicylate from about 25 mg to about 300 mg per dose and others.

An active may be useful for more than one of the above uses, and these uses are clearly contemplated as well. This overlap is recognized in the art and adjusting dosages and the like to fit the indication is well within the ability of the skilled medical practitioner.

Methods of use

The compounds of the present invention are useful in treating many medical disorders, including for example, respiratory disorders, ocular disorders, gastrointestinal disorders, disorders associated with sympathetic nervous system activity, migraine, peripheral pain, and disorders where vasoconstriction would provide a benefit.

The preferred routes of administration are peroral; intranasal; parenteral; subcutaneous; and topical.

Another aspect of the invention involves methods for preventing or treating nasal congestion by administering a safe and effective amount of a subject compound to a human or lower animal experiencing or at risk of experiencing nasal congestion. Such nasal congestion may be associated with human diseases or disorders which include, but are not limited to, seasonal allergic rhinitis, acute upper respiratory viral infections, sinusitis, perennial rhinitis, and vasomotor rhinitis. Each administration of a dose of the subject compound preferably administers a dose within the range of from about 0.001 mg/kg to about 10 mg/kg of a compound, more preferably from about 0.01 mg/kg to about 5 mg/kg, more preferably still from about 0.1 mg/kg to about 1 mg/kg. Peroral or intranasal administration of such doses is preferred. The frequency of administration of a subject compound according to this invention is preferably from about once to about six times daily, more preferably from about 2 times to about 4 times daily. Such doses and frequencies are also preferred for treating other respiratory conditions, such as otitis media, cough, COPD and asthma.

Another aspect of this invention involves methods for preventing or treating glaucoma by administering a safe and effective amount of a subject compound to a

mammal experiencing or at risk of experiencing glaucoma. If administered systemically, each administration of a dose of the subject compound preferably administers a dose within the range of from about 0.0001 mg/kg to about 5 mg/kg of a compound, more preferably from about 0.001 mg/kg to about 0.5 mg/kg. If intraocular dosing is used then preferably one administers a typical volume (for example, 1 or 2 drops) of a liquid composition, comprising from about 0.0001% to about 5% of a subject compound, more preferably from about 0.01% to about 0.5% of the compound. Determination of the exact dosage and regimen is within the purview of the skilled artisan. Intraocular administration of such doses is preferred. The frequency of administration of a subject compound according to this invention is preferably from about once to about six times daily, more preferably from about once to about 4 times daily.

Another aspect of this invention involves methods for preventing or treating migraine, by administering a safe and effective amount of a subject compound to a human or lower animal experiencing or at risk of experiencing migraine. Each administration of a dose of the subject compound preferably administers a dose within the range of from about 0.001 mg/kg to about 10 mg/kg of a compound, more preferably from about 0.01 mg/kg to about 5 mg/kg, more preferably still from about 0.1 mg/kg to about 1 mg/kg. Peroral or intranasal administration of such doses is preferred. The frequency of administration of a subject compound according to this invention is preferably from about once to about six times daily, more preferably from about 2 times to about 4 times daily.

Another aspect of this invention involves methods for preventing or treating functional bowel disorders, such as diarrhea, by administering a safe and effective amount of a subject compound to a human or lower animal experiencing or at risk of experiencing diarrhea. Each administration of a dose of the subject compound preferably administers a dose within the range of from about 0.001 mg/kg to about 10 mg/kg of a compound, more preferably from about 0.01 mg/kg to about 5 mg/kg, more preferably still from about 0.1 mg/kg to about 1 mg/kg. Peroral administration of such doses is preferred. The frequency of administration of a subject compound according to this invention is preferably from about once to about six times daily, more preferably from about 2 times to about 4 times daily.

Dosages may be varied based on the patient being treated, the condition being treated, the severity of the condition being treated, the route of administration, etc. to achieve the desired effect.

Composition and Method Examples

The following non-limiting examples illustrate the subject invention. The following composition and method examples do not limit the invention, but provide guidance to the skilled artisan to prepare and use the compounds, compositions and methods of the invention. In each case other compounds within the invention may be substituted for the example compound shown below with similar results. The skilled practitioner will appreciate that the examples provide guidance and may be varied based on the condition being treated and the patient.

Example A

Oral Tablet Composition

Ingredient	Amount per tablet (mg)
Compound of Example 1	20.0
Microcrystalline cellulose (Avicel PH 102®)	80.0
Dicalcium phosphate	96.0
Pyrogenic silica (Cab-O-Sil®)	1.0
Magnesium stearate	3.0
Total =	200.0

One tablet is swallowed by a patient with nasal congestion. The congestion is substantially diminished.

Example B

Chewable Tablet Composition

Ingredient	Amount per tablet (mg)
Compound of Example 2	15.0
Mannitol	255.6
Microcrystalline cellulose (Avicel PH 101®)	100.8
Dextrinized sucrose (Di-Pac®)	199.5
Imitation orange flavor	4.2
Sodium saccharin	1.2
Stearic acid	15.0
Magnesium stearate	3.0
FD&C Yellow #6 dye	3.0
Pyrogenic silica (Cab-O-Sil®)	2.7
Total =	600.0

One tablet is chewed and swallowed by a patient with nasal congestion. The congestion is substantially reduced.

Example C

Sublingual Tablet Composition

Ingredient	Amount per tablet (mg)
Compound of Example 3	2.00
Mannitol	2.00
Microcrystalline cellulose (Avicel PH 101®)	29.00
Mint flavorants	0.25
Sodium saccharin	0.08
Total =	33.33

One tablet is placed under the tongue of a patient with nasal congestion and allowed to dissolve. The congestion is rapidly and substantially diminished.

Example D

Intranasal Solution Composition

Ingredient	Composition (% w/v)
Compound of Example 4	0.20
Benzalkonium chloride	0.02
Thimerosal	0.002
d-Sorbitol	5.00
Glycine	0.35
Aromatics	0.075
Purified water	q.s.
Total =	100.00

One-tenth of a mL of the composition is sprayed from a pump actuator into each nostril of a patient with nasal congestion. The congestion is substantially diminished.

Example E

Intranasal Gel Composition

Ingredient	Composition (% w/v)
Compound of Example 5	0.10
Benzalkonium chloride	0.02

Thimerosal	0.002
Hydroxypropyl methylcellulose (Metolose 65SH4000®)	1.00
Aromatics	0.06
Sodium chloride (0.65%)	q.s.
Total =	100.00

One-fifth of a mL of the composition is applied as drops from a dropper into each nostril of a patient with nasal congestion. The congestion is substantially reduced.

Example F

Inhalation Aerosol Composition

Ingredient	Composition (% w/v)
Compound of Example 1	5.0
Alcohol	33.0
Ascorbic acid	0.1
Menthol	0.1
Sodium Saccharin	0.2
Propellant (F12, F114)	q.s.
Total =	100.0

Two-puffs of the aerosol composition is inhaled from a metered-dose inhaler by a patient with asthma. The asthmatic condition is effectively relieved.

Example G

Topical Ophthalmic Composition

Ingredient	Composition (% w/v)
Compound of Example 7	0.10
Benzalkonium chloride	0.01
EDTA	0.05
Hydroxyethylcellulose (Natrosol M®)	0.50
Sodium metabisulfite	0.10
Sodium chloride (0.9%)	q.s.
Total =	100.0

One-tenth of a mL of the composition is administered directly into each eye of a patient with glaucoma. The intraocular pressure is substantially reduced.

Example H

Oral Liquid Composition

Ingredient	Amount/15 mL Dose
Compound of Example 1	15 mg
Chlorpheniramine maleate	4 mg
Propylene glycol	1.8 g
Ethanol (95%)	1.5 mL
Methanol	12.5 mg
Eucalyptus oil	7.55 mg
Flavorants	0.05 mL
Sucrose	7.65 g
Carboxymethylcellulose (CMC)	7.5 mg
Microcrystalline cellulose and Sodium CMC (Avicel RC 591®)	187.5 mg
Polysorbate 80	3.0 mg
Glycerin	300 mg
Sorbitol	300 mg
FD&C Red #40 dye	3 mg
Sodium saccharin	22.5 mg
Sodium phosphate monobasic	44 mg
Sodium citrate monohydrate	28 mg
Purified Water	q.s.
Total =	15 mL

One 15 mL dose of the liquid composition is swallowed by a patient with nasal congestion, runny nose and sneezing due to allergic rhinitis. The congestion, runny nose and sneezing are effectively reduced.

Example J

Oral Liquid Composition

Ingredient	Amount/15 mL Dose
Compound of Example 7	30 mg
Sucrose	8.16 g
Glycerin	300 mg

Sorbitol	300 mg
Methylparaben	19.5 mg
Propylparaben	4.5 mg
Menthol	22.5 mg
Eucalyptus oil	7.5 mg
Flavorants	0.07 mL
FD&C Red #40 dye	3.0 mg
Sodium saccharin	30 mg
Purified water	q.s.
Total =	15 mL

One 15 mL dose of the alcohol-free liquid medication is swallowed by a patient with nasal congestion. The congestion is substantially diminished.

Example K

Oral Tablet composition

Ingredient	Amount per tablet (mg)
Chlorpheniramine maleate, USP	4.0
Compound of Example 8	4.0
Microcrystalline cellulose, NF	130.0
Starch 1500, NF	100.0
Magnesium stearate, USP	2.0
Total =	240.0

For the relief of nasal congestion due to the common cold, hay fever, or other upper respiratory allergies, or associated with sinusitis; relieves runny nose, sneezing, and itchy watery eyes as may occur in allergic rhinitis. Restores freer breathing through the nose. Adults 12 and over take one tablet every four hours.

Example L

Oral Tablet Composition

Ingredient	Amount per tablet (mg)
Loratadine	5.0
Compound of Example 9	12.0
Hydroxypropyl methylcellulose, USP	12.0
Magnesium stearate, USP	2.0
Lactose anhydrous, USP	200.0

Total =	231.0

For the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, and nasal congestion. Adults 12 and over take one tablet every twelve hours.

Example M

Oral Caplet Composition

Ingredient	Amount per caplet (mg)
Naproxen sodium anhydrous, USP	220.0
Compound of Example 10	6.0
Hydroxypropyl methylcellulose, USP	6.0
Magnesium stearate, USP	2.0
Povidone K-30, USP	10.0
Talc, USP	12.0
Microcrystalline cellulose, NF	44.0
Total =	300.0

For relief of symptoms associated with the common cold, sinusitis, or flu including nasal congestion, headache, fever, body aches, and pains. Adults 12 and over take two caplets every twelve hours.

Example N

Oral Tablet Composition

Ingredient	mg/tablet
Acetaminophen, USP	500.0
Compound of Example 1	6.0
Hydroxypropyl methylcellulose, USP	6.0
Silicon dioxide, colloidal, NF	30.0
Pregelatinized starch, NF	50.0
Magnesium stearate, USP	4.0
Total =	596.0

For relief of nasal/sinus congestion and pressure, sinus headache pain associated with sinusitis, hay fever, upper respiratory allergies, or the common cold. Adults 12 and over take one tablet every six hours.

Example O

Oral Caplet Composition

Ingredient	Amount per caplet (mg)
Naproxen sodium anhydrous, USP	220.0
Loratadine	2.5
Compound of Example 3	6.0
Hydroxypropyl methylcellulose, USP	6.0
Magnesium stearate, USP	2.0
Povidone K-30, USP	10.5
Yalc, USP	12.0
Microcrystalline cellulose, NF	44.0
Total =	303.0

For the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, nasal congestion, sinus pain, and headache. Adults 12 and over take two caplets every twelve hours.

Example P

Oral Tablet Composition

Ingredient	Amount per tablet (mg)
Naproxen sodium anhydrous, USP	220.0
Chlorpheniramine maleate, USP	6.0
Compound of Example 2	6.0
Hydroxypropyl methylcellulose, USP	12.0
Magnesium stearate, USP	2.0
Povidone K-30, USP	10.0
Talc, USP	12.0
Microcrystalline cellulose, NF	44.0
Total =	312.0

For the relief of symptoms due to the common cold, flu, hay fever, or other upper respiratory allergies, or associated with sinusitis; relieves runny nose, sneezing, and itchy watery eyes as may occur in allergic rhinitis. Relieves headache, fever, body aches, and pains. Restores freer breathing through the nose. Adults 12 and over take two tablets every twelve hours.

Example Q

Oral Tablet Composition

Ingredient	Amount per tablet (mg)
Acetaminophen, USP	500.0
Loratadine	1.3
Compound of Example 4	3.0
Hydroxypropyl methylcellulose, USP	3.0
Silicon dioxide, colloidal, NF	30.0
Pregelatinized starch, NF	50.0
Magnesium stearate, USP	2.7
Total =	590.0

For the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, nasal congestion, sinus pain, and headache. Adults 12 and over take two tablets every six hours.

Example R

Oral Tablet Composition

Ingredient	Amount per tablet (mg)
Compound of Example 1	20.0
Microcrystalline cellulose (Avicel PH 102®)	80.0
Dicalcium phosphate	96.0
Pyrogenic silica (Cab-O-Sil®)	1.0
Magnesium stearate	3.0
Total =	200.0

One tablet is swallowed by a patient with migraine. The pain and aura of migraine is substantially diminished.

Example S

Oral Tablet Composition

Ingredient	Amount per tablet (mg)
Compound of Example 1	20.0
Microcrystalline cellulose (Avicel PH 102®)	80.0
Dicalcium phosphate	96.0
Pyrogenic silica (Cab-O-Sil®)	1.0
Magnesium stearate	3.0

Total = 200.0

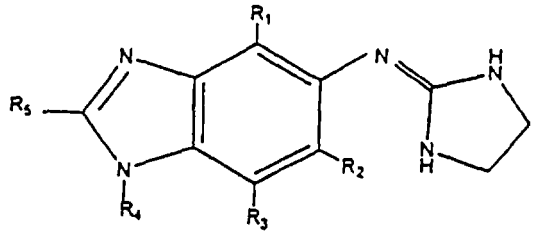
One tablet is swallowed by a patient with diarrhea. The diarrhea is substantially diminished.

Other examples of combination actives are contemplated. Examples of medicaments which can be combined with the primary active are included in U.S. Patent No. 4,552,899 to Sunshine, et al., hereby incorporated by reference. All other references referred to throughout this specification are hereby incorporated by reference.

While particular embodiments of this invention have been described, it will be obvious to those skilled in the art that various changes and modifications of this invention can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

CLAIMS:

1. A compound having the following structure:



characterized in that:

(a) R1 is alkyl;

(b) R2 is selected from the group consisting of: hydrogen, alkyl, methoxy, cyano, and halo;

(c) R3 is selected from the group consisting of: hydrogen, methyl, hydroxy, cyano and halo;

(d) R4 is hydrogen;

(e) R5 is selected from the group consisting of: hydrogen, methyl, amino, methoxy, hydroxy, cyano, and halo;

(f) provided that at least one of R2, R3 or R5 is other than hydrogen or fluorine;

(g) provided that when R1 is methyl and both R2 and R5 are hydrogen, R3 is other than methyl or halo;

(h) provided that when R3 is cyano, R1 is methyl; and

any tautomer of the above structure or a pharmaceutically acceptable salt, or biohydrolyzable ester, amide, or imide thereof.

2. The compound according to Claim 1 characterized in that R2 and R5 are independently selected from the group consisting of: hydrogen, methyl, and halo.

3. The compound according to Claim 1 or 2 characterized in that R1 is methyl and R3 is cyano or hydroxy.

4. The compound according to Claim 1 or 2 characterized in that R1 is ethyl or

cyclopropyl and R3 is selected from the group consisting of: methyl, hydroxy, and halo.

5. The compound according to Claim 1 characterized in that the compound is selected from the group consisting of: 7-cyano-5-(2-imidazolinylamino)-4-methylbenzimidazole, 7-hydroxy-5-(2-imidazolinylamino)-4-methylbenzimidazole, 4-ethyl-5-(2-imidazolinylamino)-7-methylbenzimidazole, and 4-cyclopropyl-5-(2-imidazolinylamino)-7-methylbenzimidazole.

6. A pharmeceutical composition comprising:

(a) a safe and effective amount of a compound of any of the preceding Claims, and

(b) A pharmaceutically-acceptable carrier.

7. A pharmaceutical composition according to Claim 6 further comprising one or more actives chosen from the group consisting of an antihistamine, antitussive, mast cell stabilizer, LT antagonist, expectorant/mucolytic, antioxidant or radical inhibitor, steroid, bronchodilator, antiviral, analgesic, antiinflammatory, gastrointestinal and ocular active.

8. The use of a compound according to any of the preceding claims in the manufacture of a medicament for treating alpha-2 mediated disorders in a human or other mammal.

9. The use of Claim 9 characterized in that the disorder is selected from the group consisting of: respiratory disorder, ocular disorder, gastrointestinal disorder, a disorder associated with sympathetic nervous system activity, migraine, peripheral pain, and a disorder where vasoconstriction would provide a benefit.