Synthesis of 1-[3-Methyl-2(3*H*)-benzazolon-5- or 6-yl]-4-{4-[*cis*-2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyleneoxyphenyl}piperazines

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Dedicated to Professor Gilbert Stork on the occasion of his 70th birthday

Reactions of 3-methyl-6-[4-(4-hydroxyphenyl)-1-piperazinyl]-2(3*H*)-benzoxazolone, 3-methyl-6-[4-(4-hydroxyphenyl)-1-piperazinyl]-2(3*H*)-benzothiazolone and 1,3-dimethyl-5-[4-(4-hydroxyphenyl)-1-piperazinyl]-2(3*H*)-benzimidazolone with *cis*-{[2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)]-1,3-dioxolan-4-yl}methyl methanesulfonate in the presence of sodium hydride furnish the title compounds.

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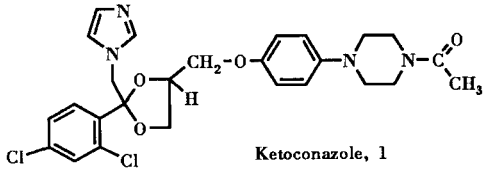
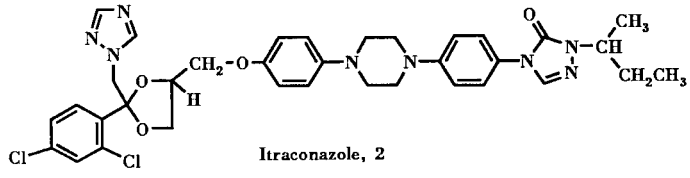
Syntheses of some analogs of the highly potent antifungal agents, ketoconazole (**1**) [1,2], itraconazole (**2**) [2,3] and saperconazole (**3**) [4] are described. Structural modifications of **1**, leading to **2** and **3** involve replacement of imidazole by 1,2,4-triazole, 2,4-dichlorophenyl by 2,4-difluorophenyl, and the *N*-acetyl by an *N*-4-{[2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-on-4-yl]phenyl} group. We present the synthesis of these different analogs **13** in which the piperazine nitrogen atoms bears the more condensed *C*-benzazol-2(3*H*)-ones instead of an azolone moiety separated by a *p*-phenylene spacer.

A number of different routes exist for the synthesis of 2(3*H*)-benzazolones. However, two major routes are used predominantly for the synthesis of 2(3*H*)-benzoxazolones and 2(3*H*)-benzimidazolones. *o*-Aminophenols and 1,2-phenylenediamines are cyclized readily by a variety of carbonic acid derivatives [5]. Alternatively, salicylic or anthranilic acids undergo Hofmann, Curtius or Lossen rearrangements to isocyanates which cyclize to the corresponding 2(3*H*)-benzazolones [5-8].

Our approach to the synthesis of 5- or 6-substituted 2(3*H*)-benzazolonyl derivatives **13** is delineated in Chart 1. Facile cyclizations of 2-substituted 4-nitroanilines **4** with many different carbonic acid derivatives **5** lead to appropriately substituted 2(3*H*)-benzazolones **6**. Methylation of **6** yields **7**, the nitro group is reduced catalytically to the amine **8**, which is usually isolated as the hydrochloride. The piperazine ring of **10** is constructed by reacting **8** with *N,N*-bis-(2-chloroethyl)-*p*-anisidine (**9**). Cleavage of the methyl ether of **10** with 48% hydrobromic acid proceeds smoothly to furnish the vital phenolic intermediates **11**, conveniently isolated as hydrobromides. In basic solutions these phenolic free bases **11**, being *p*-hydroxyanilines, tend to be relatively unstable, being susceptible to fast oxi-



Ketoconazole, 1



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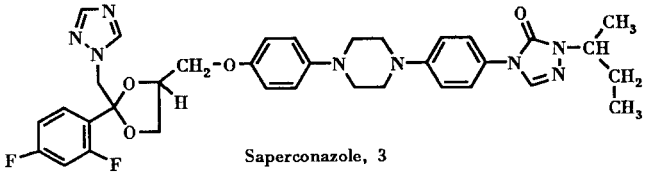
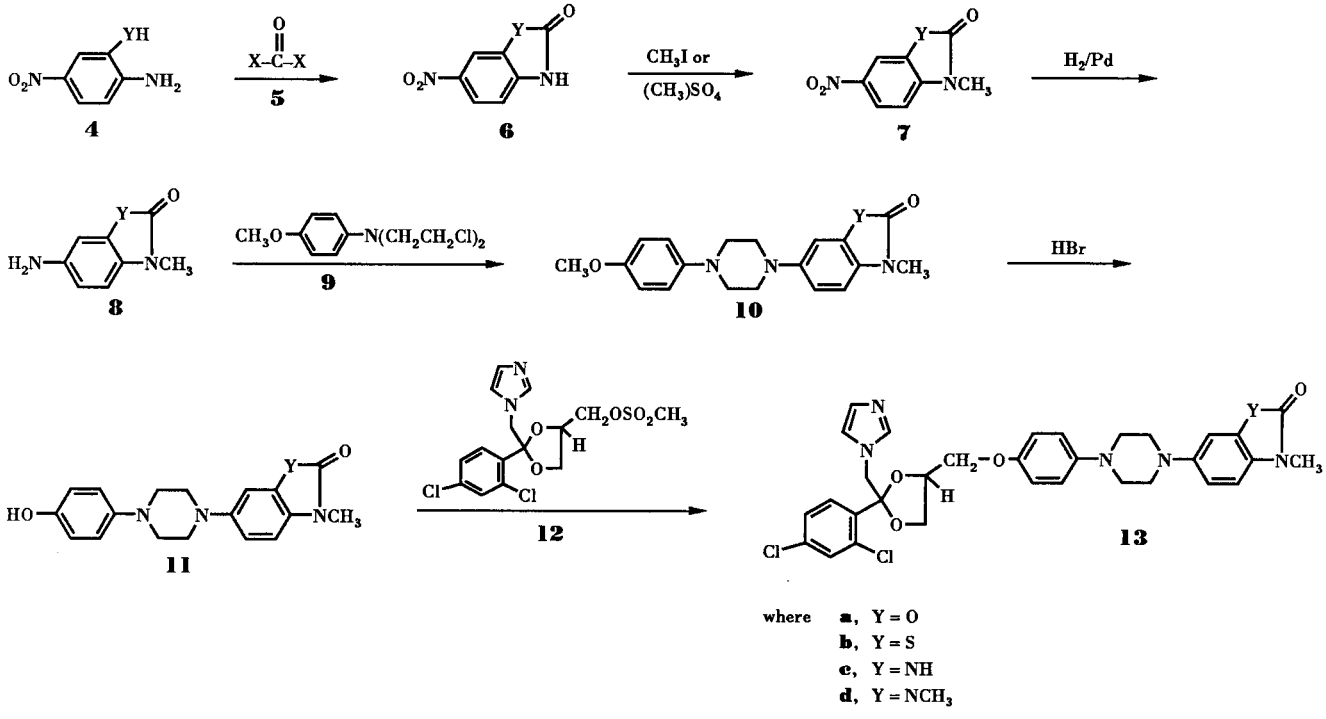


Saperconazole, 3

Chart 1

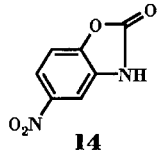


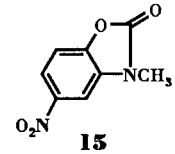
dation as witnessed by quick darkening of their solutions and these should be used as quickly as possible. Nucleophilic displacement of the sulfonate of *cis*-**12** [1] by the phenoxide ion of **11** completes the synthesis of the target compounds **13**. The structure of **13** is established by microanalysis and characteristic ^1H and ^{13}C nuclear magnetic resonance (nmr) spectra. Deviations from the general scheme, as well as some of the difficulties encountered, are discussed briefly below.

2(3*H*)-Benzoxazolones.

2(3*H*)-Benzoxazolones are readily manufactured by cyclizing *o*-aminophenols by one of many carbonic acid derivatives [5,9-15], such as phosgene (**5**, X = Cl), urea (**5**, X = NH_2), chloroformates (**5**, X = Cl, OR), and more recently, by 1,1′-carbonyldiimidazole [**5**, X = 1-(1*H*-imidazolyl)] [13]. 6-Nitro-2(3*H*)-benzoxazolone (**6a**) has been synthesized in a number of different ways: from the Lossen rearrangement of 2-hydroxy-4-nitro-(*O*-acetyl)benzohydroxamic acid, mp 241° [8], from the nitration of 2(3*H*)-benzoxazolone, mp 146° [16], or mp 249-250° [17], and by the cyclization of 2-amino-5-nitrophenol (**4a**) with 1,1′-carbonyldiimidazole, mp 145-146° [13]. Such discrepancies of melting points are difficult to reconcile. It became imperative to establish the structure of **6a**. It should be noted that the higher melting points (around 240°) are relatively close to that of the isomeric 5-nitro-2(3*H*)-benzoxazolone (**14**), 231-232° [16], and more recently, 229-230° [15].

Repetition of Nachman's condensation [13] of commercially available 2-amino-5-nitrophenol (**4a**) with 1,1′-carbonyldiimidazole produces **6a**, mp 238-241°. The ^{13}C nmr spectrum of our product is virtually identical to that reported by Llinares *et al.* [12], and almost matches that of Nachman's [13], except for the chemical shifts of C-3a, which differs by some 6 ppm (Table 1). Because of the closeness of the melting points of **6a** and **14**, we also synthesized authentic isomeric **14** from 2-amino-4-nitrophenol and 1,1-carbonyldiimidazole. The melting point of our **14** matched that of an earlier preparation [16] and that of a sample reported by Maleski *et al.* [15]. The (unassigned) ^{13}C chemical shifts of **14** made by Maleski agree with those of our sample. However, the chemical shifts of the two isomers, **6a** and **14**, are somewhat different. We conclude that **6a** melts around 240°, which is about 100° higher than reported in two previous papers [13,16].





To substantiate the structure of **6a** further, we compared its *N*-methyl derivative **7a** with that of isomer **15**. Their melting points and ^{13}C nmr spectra are quite different, but our melting point of **7a** agrees with the literature

Table 1

^{13}C NMR Chemical Shifts of Selected 2 (3*H*)-Benzoxazolones and 2(3*H*)-Benzthiazolones in Deuteriodimethyl Sulfoxide

Compound	C-2	C-3a	C-4	C-5	C-6	C-7	C-7a	CH_3
6a	154.2	136.8	109.3	120.7	142.0	105.4	142.8	--
6a [a]	154.5	137.0	109.7	121.1	142.3	105.5	143.0	--
6b [b]	154.2	130.8	109.3	120.7	142.1	105.3	142.8	--
14	153.8	130.9	118.5	143.6	104.8	109.7	147.7	--
14 [c]	154.6	131.7	119.0	144.2	105.3	110.2	148.4	--
7a	153.9	137.7	108.7	120.9	141.4	105.4	142.4	29.5
15	153.9	132.5	118.9	144.0	104.7	109.8	146.4	28.5
8a•HCl	154.2	126.3	118.1	104.6	141.6	109.4	130.7	28.1
6b	170.5	124.3	118.6	122.2	142.0	111.4	142.5	--
7b	169.3	122.4	111.2	118.9	142.7	122.6	142.8	29.5
8b•HCl	168.6	122.5	111.9	117.5	127.3	121.5	136.9	29.2
16	171.7	158.6	117.6	121.9	140.7	116.8	131.6	--
16 [d]	171.3	158.1	117.3	121.7	140.4	116.6	131.3	--

[a] Data obtained from ref [12]. [b] Reported by Nachman, ref [13]. [c] Values reported in ref [15]. [d] Data from ref [11].

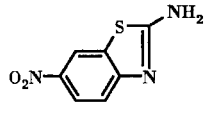
value [16]. Isomer **15** is new and is now characterized. Furthermore, hydrogenation of **7a** furnishes amine **8a** which is isolated as the hydrochloride, whose melting point agrees with that in the literature [16].

Conditions were worked out to effectively condense **8a** with the mustard **9** [19] to generate the required *p*-anisylpiperazine **10a**. Demethylation with boiling hydrobromic acid provides phenol **11a**, isolated as the hydrobromide. In the final step, sulfonate **12** reacts with the phenoxide ion of **11a** to create **13a**.

2(3*H*)-Benzothiazolones.

A logical starting material for this sequence is commercially available 2-amino-6-nitrobenzothiazole (**16**). Originally, it was thought that **16** would methylate on the ring nitrogen to form **17**. It was felt that in salt **17** the amino group, being at an activated position, would be susceptible to facile hydrolysis by base to provide **7b**, directly. However, **16** was not at all attacked by dimethyl sulfate at 95° (1 hour) and only starting material was recovered in excellent yield. When conditions were changed to dimethyl sulfate and aqueous potassium hydroxide, an *N*-methylated product was isolated (nmr, mass spectrum) and appeared to be impure **19**. It is conceivable that the inductive effect of the nitro group imparts greater than expected acidity to the amino group resulting in the easy formation of the stable anion **18**, which could then be methylated. However, this exocyclic *N*-methyl derivative was not investigated further and another approach was taken.

It seemed rather obvious to diazotize **16** to form **6b**, which could then be methylated to **7b**. However, diazotizations of **16** with nitrous acid (generated from sodium nitrite) under a variety of acidic conditions were quite unsuccessful resulting primarily in the recovery of starting material. It was not until the rather stringent conditions described for the diazotization of *p*-nitroaniline [20] are applied to that of **16**, there is formed **6b**. Methylation of **6b** proceeds smoothly to form **7b**. Other steps in the synthesis of **13b** follow those outlines in Chart 1. Reduction of **7b** yields **8b** which cyclizes with **9** to form **10b**. Methyl ether cleavage with hydrobromic acid furnishes phenol **11b** which is alkylated by **12** to provide **13b**.



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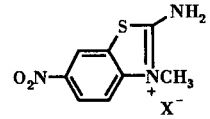

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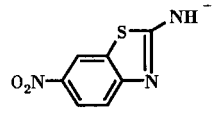

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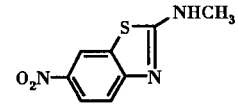

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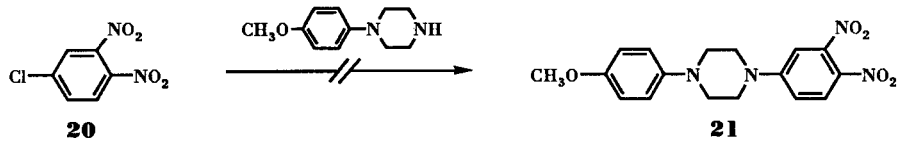
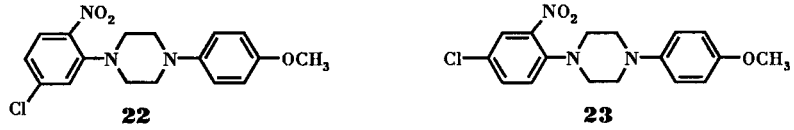
2(3*H*)-Benzimidazolones.

The synthesis of **13d** is relatively straightforward. Cyclization of 1,2-diamino-4-nitrobenzene with urea in sulfolane yields **6c**, which is methylated to furnish **7d**. Subsequent steps are those described in the general scheme in Chart I. An alternate route appeared very attractive which would have involved the displacement of the chloro group of 3,4-dinitrochlorobenzene (**20**) by 1-(4-methoxyphenyl)-piperazine to provide **21**. Reduction of the nitro groups to the corresponding diamine, followed by cyclization and methylation would lead to **10d**.



20 **21**



22 **23**

However, aromatic nucleophilic displacement of **20** by the piperazine produces a crystalline product which analyzed to be either **22** or **23**. The structure is established by means of its ^{1}H nmr spectrum (in deuteriodimethyl sulfoxide). As expected there is singlet upfield for the methyl ether protons (3.70 ppm), as well as a complex multiplet between 3.11 and 3.34 ppm for the AA'BB' spin-spin system of the piperazine protons. It is the pattern of the aromatic proton signals which distinguishes between **22** and **23**. The spectrum essentially reveals five sets of multiplets which can be interpreted as follows. Two sets of multiplets centered at 6.82 and 6.94 ppm represent aromatic protons of the *p*-methoxyphenyl ring system (AA'BB'). The other three distinct sets of proton resonances are interpreted by first order rules. The doublet furthest downfield at 7.88 ppm shows a relatively large coupling constant (J = 8.04 Hz) which is characteristic of *ortho*-coupling. The other two clear signals are a doublet at 7.38 (J = 2.01 Hz) and a doublet of doublets at 7.15 ppm (J = 8.04, 2.01 Hz). One would expect that the most deshielded proton is the one *ortho* to the nitro group. Structure **22** would accommodate such a premise, since one of the ring protons should show large *ortho*-coupling. By contrast, **23**, the proton *ortho* to the nitro group would show only (the smaller) *meta*-coupling. Incidentally, ^{1}H resonances of the protons *ortho* to the nitro group in *N*-methyl-*p*-nitroaniline are at 8.10, those *ortho* to the amine at 6.55 ppm (in deuteriochloroform) [21]. Also, in the ^{1}H nmr spectrum of *p*-chloronitrobenzene, resonances *ortho* to the nitro group are at 8.17 ppm, those *ortho* to the chlorine, at 7.52 ppm [21].

Nucleophilic displacements of aromatic nitro groups are well established. There are ample examples in the literature of the displacement of an aromatic nitro group by halide ions [22,24], alkoxide ions [23], mercaptide ions [23-25], carbanions [23], cyanide ion [23] and amines [26]. Preferential displacements of a nitro to halo groups by amines are also well documented [27].

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^{1}H and ^{13}C nmr spectra (at 300 and 75.4 MHz, respectively) were recorded in deuteriodimethyl sulfoxide (unless stated otherwise) on a Varian XL-300 spectrometer. Chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane and signals are designated as singlets (s), doublets (d), triplets (t), multiplets (m), and if broad, by br. Electron impact mass spectra (EIms) were obtained on a Finnigan mass spectrometer, Model 4510, at 70 eV ionization temperature, 120-140°. Ions below m/z 100 and those less than 10% of the base peak are nor reported, unless deemed important.

Research chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, unless specified otherwise, and were used as supplied. Petroleum ether refers to that fraction boiling between 30-60°. Evaporation or removal of solvents, *in vacuo*, was carried out by means of a rotary flash evaporator at the water pump (20-30 torr) at about 40°, unless specified otherwise. Thin layer chromatograms were run on Aldrich silica gel coated polyester plates containing a 254 nm fluorescent indicator. Column chromatography was performed on silica gel (grade 60, 230-400 mesh), or basic alumina (Brockmann I, 150 mesh) unless noted otherwise. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN.

6-Nitro-2(3*H*)-benzoxazolone (**6a**).

According to Nachman's procedure [13], a stirred solution of 2-amino-5-nitrophenol (4.62 g, 30 mmoles) and 1,1'-carbonyldiimidazole (7.3 g, 45 mmoles) in anhydrous tetrahydrofuran (THF, 100 ml) was heated under reflux (4 hours). Solvents were removed, *in vacuo*, the residue was washed with 2*N* hydrochloric acid and recrystallized from methanol. There was obtained **6a** as light brown needles (5.1 g, 96%), mp 238-241°, lit [8] mp 241°, [17] 249-250°, [16] 146°, [13] 145-146°.

5-Nitro-2(3*H*)-benzoxazolone (**14**).

This compound was synthesized from 2-amino-4-nitrophenol (4.62 g, 30 mmoles) as described above for **6a**. After crystallization from methanol, the product was isolated as dark yellow prisms (4.6 g, 85%), mp 225°, lit [16] mp 231-232°, [15] 229-230°.

3-Methyl-5-nitro-2(3*H*)-benzoxazolone (**15**).

Sodium hydride (60% in petroleum jelly, 1.0 g, 0.025 mole) was washed with petroleum ether (2 x 20 ml) and then was covered by dimethylformamide (DMF, 50 ml, dried azeotropically with toluene). Neutralization of **14** (1.0 g, 0.01 mole) was effected by stirring the mixture until most of the solid had dissolved. Dimethyl sulfate (1.2 ml, 0.012 mole) was added, dropwise, at 0-5° and after 30 minutes the mixture was heated at 95° (30 minutes) and was then diluted with ice-water. The product was filtered, dried and recrystallized from methanol to provide yellow needles (1.0 g, 53%), mp 146°.

Anal. Calcd. for $C_8H_6N_2O_4$: C, 49.49; H, 3.12; N, 14.43. Found: C, 49.42; H, 3.14; N, 14.22.

3-Methyl-6-nitro-2(3*H*)-benzoxazolone (**7a**).

The literature preparation was conducted in acetone in the presence of powdered potassium hydroxide gave a relatively poor yield of **7a** (10%) [16]. Methylation of **6a** (3.45 g, 0.019 mole) as described for the preparation of **15** yielded **7a** as brown needles (2.5 g, 69%, from 1-propanol), mp 175-180°, lit [16] mp 183-184°.

3-Methyl-6-amino-2(3*H*)-benzoxazolone Hydrochloride (**8a•HCl**).

To a solution of **7a** (2.5 g, 0.013 mole) 95% ethanol (300 ml) was added 250 mg of 10% Pd/C and the mixture reduced in a Parr hydrogenator at 30 psi (2.5 hours). The catalyst was filtered and the alcoholic solution evaporated to dryness, *in vacuo*, to obtain the free (and stable) **8a**, mp 140°. It was more expeditious to remove most of the ethanol, *in vacuo*, then add concentrated hydrochloric acid and evaporate to dryness, *in vacuo*. The salt was recrystallized from ethanol to give light pink flakes (2.4 g, 93%), mp 310°, lit [16] mp 315°.

3-Methyl-6-[4-(4-methoxyphenyl)-1-piperazinyl]-2(3*H*)-benzoxazolone (**10a**).

The intermediate mustard **9** was synthesized by some literature modifications. Ross' method [19] of hydroxyethylation of *p*-anisidine was conducted in toluene which yielded a cleaner product. To a chilled mixture of *p*-anisidine (40.0 g, 0.325 mole) in toluene (100 ml) was added cold ethylene oxide (40 ml, 0.8 mole). The stainless steel pressure vessel was sealed quickly and heated in an oil bath at 140° (18 hours). The ice-cold vessel was opened carefully and the dark brown solution transferred to a glass flask. Upon cooling to 4°, *N,N*-bis(2-hydroxyethyl)-*p*-anisidine (50.0 g, 73%) precipitated as a colorless solid, which was filtered, washed with toluene and dried (vacuum desiccator), mp 68-70°, lit [19] mp 70-71°; ^{1}H nmr (deuteriochloroform): δ 3.42 (t, NCH_2), 3.74 (t, OCH_2, J = 6.0 Hz), 3.76 (s, OCH_3), 3.89 (br s, exchangeable, O*H*), 6.70, 6.83, (AA'BB', Ar*H*); ^{13}C nmr (deuteriochloroform): δ 55.7, 55.9 (CH_2's), 60.6 (OCH_3), 114.8, 115.3, 142.5, 152.1 (aromatic carbons).

Although this diol can be converted to *N,N*-bis(2-chloroethyl)-*p*-anisidine (**9**) by means of thionyl chloride, we found the ensuing method produced a cleaner product, consistently. *N,N*-Bis(2-hydroxyethyl)-*p*-anisidine (52.75 g, 0.25 mole) was added, in portions, to stirred phosphorus oxychloride (47.0 ml, 0.5 mole) at room temperature. An exothermic reaction ensued and the mixture was heated at 90° (30 minutes). The clear solution was poured into a mixture of benzene and crushed ice and the product extracted by benzene. The benzene solution was washed with water, dried over anhydrous magnesium sulfate and passed through a short column of activated alumina. Elution with benzene produced **9** (47.0 g, 77%), which was recrystallized from petroleum ether, mp 49°, lit [19] mp 52°; ^{1}H nmr (deuteriochloroform): δ 3.58-3.65 (m, CH_2's, AA'BB'), 3.78 (s, OCH_3), 6.70-6.88 (m, AA'BB', Ar*H*); ^{13}C nmr (deuteriochloroform): δ 40.8 (CH_2Cl), 54.4 (CH_2)N, 55.7 (OCH_3), 114.9, 115.2, 140.6, 152.7 (aromatic carbons).

A stirred mixture of **8a•HCl** (0.5 g, 0.03 mole) and **9** (0.35 g, 0.0014 mole) in 50% aqueous acetone (25 ml) was refluxed for 2 hours. Anhydrous potassium carbonate (0.4 g) was added and reflux was continued for another 30 minutes during which time a white solid began to separate. The solid (0.30 g, 53%) was filtered, washed with 50% aqueous acetone and dried, mp 215-219°; ^{1}H nmr (deuteriochloroform): δ 3.23-3.27 (m, 8H, CH_2N, AA'BB'), 3.37 (s, CH_3N), 3.78 (s, CH_3O), 6.82-6.98 (m, 7 aromatic *H*); ms: (EI) m/z (relative intensity) 339 (M^+, 100), 198 (18), 176 (24), 164 (14), 162 (37), 136 (14), 135 (50).

Anal. Calcd. for $C_{19}H_{21}N_3O_3 \cdot 0.25H_2O$: C, 66.41; H, 6.23; N, 12.23. Found: C, 66.55; H, 6.08; N, 12.46.

3-Methyl-6-[4-(4-Hydroxyphenyl)-1-piperazinyl]-2(3*H*)-benzoxazolone (**11a**).

Ether **10a** (1.3 g, 0.0038 mole) was refluxed with 48% hydrobromic acid (20 ml) for 4 hours. Excess hydrobromic acid was removed, *in vacuo* and the salt crystallized from ethanol to provide **11a** as light brown crystals (0.7 g, 57%), mp 280-283°; ^{1}H nmr: δ 3.34 (s, CH_3N), 3.59 and 3.70 (m's, NCH_2, AA'BB'), 6.90-7.57 (m, aromatic *H*); ms: (EI) m/z (relative intensity) 325 (M^+, 100), 176 (34), 148 (19), 121 (32), 120 (11), 103 (11).

Anal. Calcd. for $C_{18}H_{19}N_3O_3 \cdot HBr \cdot H_2O$: C, 50.96; H, 5.22; N, 9.90. Found: C, 51.16; H, 4.85; N, 9.96.

1-[3-Methylbenzoxazol-2(3*H*)-on-6-yl]-4-{4-[[*cis*-2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyleneoxy]phenyl}piperazine (**13a**).

A solution of **11a** (0.5 g, 1.2 mmoles) in DMF (15 ml) was dried azetropically with benzene (15 ml, Dean-Stark). The solution was cooled (25°) and sodium hydride (60% in petroleum jelly, 0.11 g, 2.7 mmoles) was added and the mixture was stirred at room temperature (20 minutes). Then **12** (0.7 g, 1.6 mmoles) was added and the mixture was heated at 100-110° (12 hours). Solvents were evaporated, *in vacuo* (5 torr). The residue was triturated with ice-water and the dark purple solid filtered. When exposed to air, it turned into a dark gummy mass. This resin was dissolved in chloroform (50 ml), filtered, dried (magnesium sulfate) and was chromatographed on a basic alumina column. Elution with dichloromethane gave a red oil which crystallized from ethyl acetate to give faint pink crystals of **13a** (72 mg, 11%), mp 186-189°; tlc, R_f = 0.5, dichloromethane; ^{13}C nmr (deuteriochloroform): δ 28.0 (NCH_3); 1,3-dioxolane: 107.9 (C-2), 74.7 (C-4), 51.2 (2-CH_2), 67.5, 67.7 (C-5 or 4-CH_2); imidazole: 138.7 (C-2), 128.4 (C-4), 121.1 (C-5); piperazine: 50.6, 50.7; aromatic carbons: 100.1, 108.0, 112.3, 115.2, 118.3, 125.2, 127.1, 129.4, 131.3, 132.9, 134.5, 135.7, 143.4, 145.8, 148.1, 152.5; 154.9 (C=O); ms: (EI) m/z (relative intensity) 635 (M^+, 100), 339 (32), 311 (17), 75 (16), 57 (16).

Anal. Calcd. for $C_{32}H_{31}Cl_2N_5O_5 \cdot 0.5H_2O$: C, 59.54; H, 4.99; N, 10.85. Found: C, 59.49; H, 4.79; N, 10.66.

6-Nitro-2(3*H*)-benzothiazolone (**6b**).

2-Amino-6-nitrobenzothiazole (10.0 g, 0.05 mole) was dissolved in concentrated sulfuric acid (200 ml), with stirring. The dark yellow solution was cooled to 0-5°. A solution of sodium nitrite (6.9 g, 0.1 mole) in cold water (10 ml) was delivered quickly to the bottom of the acidic solution by means of a separatory funnel, at 0-10°. The mixture was stirred at 0-10° for 15 minutes, then was permitted to warm to room temperature. This mixture was added carefully to a boiling mixture of water (300 ml) and concentrated sulfuric acid (150 ml), as vigorous boiling and foaming occurred upon each addition. Boiling was continued for about 15 minutes when a thick creamy solid commenced to separate. The product was filtered, washed with water, dried and recrystallized from ethanol to afford **6b** (7.0 g, 71%), mp 248-250° lit [27a, 27b] mp 245-248°, 255-257°; ^{1}H nmr: δ 7.23 (d, H-4, $J_{4,5}$ = 8.8 Hz), 8.11 (d, H-5), 8.55 (s, H-7), 12.53 (s, NH); ms: (EI) m/z (relative intensity)

196 (M^+, 100), 166 (12), 150 (15), 138 (24), 122 (48).

3-Methyl-6-nitro-2(3*H*)-benzothiazolone (**7b**).

To a suspension of **6b** (5.0 g, 0.026 mole) and anhydrous potassium carbonate (10.35 g, 0.075 mole) in dry ethanol (125 ml), was added quickly iodomethane (6.25 ml, 0.1 mole) and the mixture was refluxed for 4 hours. Solvent were evaporated, *in vacuo*, and the residue was extracted with chloroform. Evaporation of chloroform furnished **7b** as pale yellow crystals (from methanol, 3.5 g, 67%), mp 159-161° lit [27] mp 163-165°; ^{1}H nmr: δ 3.39 (s, NCH_3), 7.49 (d, H-4), 8.25, (dd, H-5, $J_{4,5}$ = 8.8, $J_{5,7}$ = 2.3 Hz), 8.67 (d, H-7).

6-Amino-3-methyl-2(3*H*)-benzothiazolone Hydrochloride (**8b•HCl**).

The reduction of **7b** (3.0 g, 0.014 mole) in dry ethanol (200 ml) was carried out in the presence of 300 mg of 10% Pd/C under 35 psi of hydrogen at room temperature (3 hours). The catalyst was filtered off, the solution concentrated, *in vacuo*, to about 50 ml. Concentrated hydrochloric acid (2 ml) was added and evaporation was continued until a colorless solid began to form. Upon cooling, the salt was isolated and was recrystallized (ethanol) to produce colorless crystals (1.6 g, 53%), mp 309-310°; ^{1}H nmr: δ 3.39 (s, NCH_3), 7.39 (H-4, H-5), 7.72 (H-7, complex m, aromatic *H*), 10.39 (br s, N*H*).

Neutralization of the hydrochloride furnished the free base **8b** which was analyzed.

Anal. Calcd. for $C_9H_8N_2SO \cdot 0.125H_2O$: C, 52.65; H, 4.42; N, 15.36. Found: C, 52.70; H, 4.43; N, 15.28.

3-Methyl-6-[4-(4-methoxyphenyl)-1-piperazinyl]-2(3*H*)-benzothiazolone (**10b**).

When the hydrochloride was used initially, a cleaner product resulted. A solution of **8b•HCl** (1.5 g, 0.007 mole) and **9** (1.4 g, 0.0058 mole) 50% aqueous acetone (50 ml) was refluxed for 2 hours. Anhydrous potassium carbonate (1.3 g) was added slowly and reflux was continued for another 3 hours during which time a white solid began to separate. This solid was filtered hot, washed with hot 50% aqueous acetone and dried. It weighed 1.15 g (56%), mp 202-203°; ^{1}H nmr (deuteriochloroform): δ 3.22-3.28 (m, 8H, CH_2N, AA'BB'), 3.40 (s, CH_3N), 3.77 (s, CH_3O), 6.85-7.06 (m, 7H, aromatic *H*); ^{13}C nmr (deuteriochloroform): δ 28.9 (CH_3N), 50.5, 55.5 (CH_2N), 110.7, 110.9, 114.6, 115.8, 118.5, 123.5, 131.5, 145.4, 148.2, 154.1 (aromatic carbons), 169.6 (C=O).

Anal. Calcd. for $C_{19}H_{21}N_3SO_2$: C, 64.19; H, 5.95; N, 11.82. Found: C, 63.82; H, 5.82; N, 11.66.

3-Methyl-6-[4(4-hydroxyphenyl)-1-piperazinyl]-2(3*H*)-benzothiazolone (**11b**).

A solution of **10b** (1.2 g) in 48% hydrobromic acid (40 ml) was stirred and refluxed for 5 hours. Excess hydrobromic acid was evaporated to dryness, *in vacuo*, (5 torr) and the residue crystallized from ethanol to provide beige crystals (1.0 g, 83%), mp 270-273°.

Anal. Calcd. for $C_{18}H_{19}N_3SO_2 \cdot 2HBr \cdot H_2O$: C, 41.47; H, 4.44; N, 8.06. Found: C, 41.10; H, 4.02; N, 7.72.

1-[3-Methyl-benzthiazol-2(3*H*)-on-6-yl]-4-{4-[[*cis*-2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyleneoxy]phenyl}piperazine (**13b**).

A solution of **11b** (0.55 g, 1 mmole) in DMF (15 ml) was dried azeotropically with benzene (10 ml) using an attached Dean-Stark trap. The mixture was cooled to room temperature, sodium hydride (0.135 g of 60% dispersion in petroleum jelly, 3.3 mmoles) was added and the mixture was stirred at room temperature for 1 hour. After the addition of **12** [1] (0.41 g, 1 mmole) the mixture was stirred and heated at 75-85° for 6 hours. The solvent was evaporated *in vacuo* (5 torr) and the dark brown residue was diluted with ice-water where it solidified to beige solid. This solid (0.8 g) was extracted with hot ethyl acetate (20 ml), filtered when **13b** crystallized as a faint beige solid (0.1 g, 15%), mp 165°; ^{13}C nmr (deuteriochloroform): δ 28.8 (NCH_3); 1,3-dioxolane: 107.8 (C-2), 74.7 (C-4), 51.1 (2-CH_2), 67.4, 67.6 (C-5 or 4-CH_2); imidazole: 138.6 (C-2), 128.3 (C-4), 121.1 (C-5); piperazine: 50.4, 50.5; aromatic carbons: 110.7, 110.8, 115.1, 115.7, 118.2, 123.4, 127.1, 128.2, 129.4, 131.2, 132.8, 134.5, 135.7, 136.6, 145.8, 148.1, (aromatic carbons); 152.5 (C=O); ms: positive FAB (using xenon, glycerol as matrix at 8000 volts) m/z (relative intensity) 652 (M+1, 100), 618 (54), 407 (23), 342 (14), 313 (24), 311 (24), 219 (11).

Anal. Calcd. for $C_{32}H_{31}Cl_2N_5SO_4$: C, 58.89; H, 4.79; N, 10.73. Found: C, 58.58; H, 4.79; N, 10.53.

5-Nitro-2(3*H*)-benzimidazolone (**6c**).

A mixture of 1,2-diamino-4-nitrobenzene (5.0 g, 0.326 mole), urea (5.87 g, 0.978 mole) in sulfolane (30 ml) was stirred and heated between 170-180° (3 hours). After cooling to room temperature, the mixture was diluted with water and recrystallized from 60% aqueous ethanol to give **6c** (4.1 g, 71%), mp 309°, lit [28,29] mp 308°; ^{13}C nmr: δ 155.6 (C-2), 129.7 (C-3a), 108.0 (C-4), 141.2 (C-5), 117.7 (C-6), 103.7 (C-7), 137.7 (C-7a).

5-Amino-1,3-dimethyl-2(3*H*)-benzimidazolone (**8d**).

To a mixture of **6c** (1.32 g, 0.0075 mole), potassium hydroxide (2.5 g) in acetone (20 ml) was added methyl iodide (3.2 g) in acetone (20 ml) over 10 minutes. After a 4 hour reflux period, solvents were removed, *in vacuo*, to produce **7d** (1.15 g, 75%), mp 206-208°, lit [18] mp 208-209°; ^{13}C nmr: δ 154.1 (C-2), 129.5 (C-3a), 107.1 (C-4), 141.5 (C-5), 117.7 (C-6), 103.1 (C-7), 135.0 (C-7a).

Hydrogenation of 1.0 g of this product, using the method described for the synthesis of **8b**, yielded **8d•HCl** (0.81 g, 95%), mp 310°, identical to lit mp [18]; ^{13}C nmr (on the amine, in deuteriochloroform): δ 26.85, 26.9 (NCH_3), 154.6 (C-2), 122.5, 130.7 (C-3a, C-7a), 95.4 (C-4), 141.6 (C-5), 116.0 (C-6), 107.7 (C-7).

1,3-Dimethyl-5-[4-(4-methoxyphenyl)-1-piperazinyl]-2(3*H*)-benzimidazolone (**10d**).

A mixture of **8d** (2.57 g, 0.014 mole), **9** (3.0 g, 0.012 mole) and *N,N*-dimethylcyclohexylamine (8.4 ml, 0.056 mole) in 1-butanol (50 ml) was heated under reflux (5 hours). Solvents were evaporated under reduced pressure, and 30 ml of water was added to the residue. The solid was dissolved in chloroform and was passed through a short 5 cm silica column with chloroform. After evaporation of the solvent, the residue was recrystallized from chloroform:petroleum ether (1:5) to provide yellow needles, 2.8 g (57%), mp 195-200°; ^{1}H nmr (deuteriochloroform): δ 3.26-3.45 (m, piperazine CH_2), 3.38, 3.39 (s, NCH_3), 3.77 (s, OCH_3), 6.66-7.25 (m, aromatic *H*); ^{13}C nmr (deuteriochloroform): δ 27.1, 27.2, (NCH_3), 51.2, 51.5 (piperazine N-CH_2), 55.6 (OCH_3), 98.1, 107.6, 110.7, 114.5, 118.5, 124.6, 145.6, 147.4, 154.1 (aromatic carbons), 156.0 (C=O).

Anal. Calcd. for $C_{20}H_{24}N_4O_2$: C, 68.16; H, 6.86; N, 15.90.

Found: C, 68.78; H, 6.68; N, 16.16.

1,3-Dimethyl-5-[4-(4-hydroxyphenyl)-1-piperazinyl]-2(3*H*)-benzimidazolone (**11d**).

5-[4-(4-Methoxyphenyl)-1-piperazinyl]-1,3-dimethyl-2(3*H*)-benzimidazolone (3.0 g, 0.007 mole) was refluxed with 48% hydrobromic acid (20 ml) for 4 hours after which time excess hydrobromic acid was removed under reduced pressure. The residue was neutralized with 20 ml of ammonium hydroxide, the product filtered and recrystallized from DMF/water (1:1) to provide a light gray solid (1.96 g, 83%), mp 275-280°; ms: (EI) m/z (relative intensity) 338 (M^+, 100), 189 (55), 121 (30); ^{1}H nmr: δ 3.15, 3.19 (m, NCH_2), 3.27, 3.29 (s, NCH_3), 6.08-7.00 (m, aromatic *H*), 8.84 (s, O*H*); ^{13}C nmr (deuteriochloroform): δ 26.3, (NCH_3), 50.3 (piperazine N-CH_2), 97.5, 107.6, 109.3, 115.4, 115.5, 123.5, 130.4, 144.1, 146.9, 151.1 (aromatic carbons), 153.5 (C=O).

Anal. Calcd. for $C_{19}H_{22}N_4O_2$: C, 67.43; H, 6.55; N, 16.56. Found: C, 67.38; H, 6.47; N, 16.56.

1-[1,3-Dimethyl-benzimidazol-2(3*H*)-on-5-yl]-4-{4-[[*cis*-2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyleneoxy]phenyl}piperazine (**13d**).

Sodium hydride (60% in petroleum jelly, 1.20 g, 0.03 mole) was washed with petroleum ether (to remove the hydrocarbon medium) and was suspended in dry DMF (100 ml) under a nitrogen atmosphere. After the neutralization of **11d** (5.0 g, 0.015 mole) at room temperature (20 minutes) there was added a solution of **12** [1] (6.02 g, 0.015 mole) in DMF (20 ml) was added dropwise over 10 minutes. The mixture was heated at 80-90° (5 hours), then the solvent was removed, *in vacuo* (<5 torr). The residue was dissolved in chloroform (100 ml) and washed with saturated sodium bicarbonate solution, dried (sodium sulfate) and evaporated to a dark gummy residue, which was triturated with ethyl acetate. The beige solid was collected by filtration and dried.

This solid consisted of a mixture of starting materials and product (^{13}C nmr) which were separated best by chromatography on alumina. Elution with dichloromethane-ethanol (9:1) gave a product which was chromatographed once more on neutral alumina (100 g) using dichloromethane-methanol (95:5) as eluent. The major fraction (R_f = 0.9) consisted of **13d** which was recrystallized from dichloromethane-ethyl acetate to give a cream colored crystalline solid (3.58 g, 37%), mp = 186-187°; ^{13}C nmr (deuteriochloroform): δ 27.0, 27.1 (NCH_3); 1,3-dioxolane: 107.9 (C-2), 74.8 (C-4), 51.4 (2-CH_2), 67.5, 67.6 (C-5 or 4-CH_2); imidazole: 138.8 (C-2), 128.5 (C-4), 121.1 (C-5); piperazine ring: 50.8, 51.2; aromatic carbons: 98.0, 107.5, 110.6, 115.2, 118.3, 124.5, 127.2, 129.5, 130.7, 131.3, 132.9, 134.6, 135.8, 145.9, 147.3, 152.5; 154.4 (C=O).

Anal. Calcd. for $C_{33}H_{34}Cl_2N_6O_4$: C, 61.01; H, 5.28; N, 12.95. Found: C, 60.66; H, 5.20; N, 12.72.

The Reaction of 4-(Methoxyphenyl)piperazine with 3,4-Dinitrochlorobenzene.

A mixture of 3,4-dinitrochlorobenzene (3.85 g, 0.019 mole), 1-[4-(methoxyphenyl)]piperazine hydrochloride (5.0 g, 0.019 mole), potassium carbonate (10.5 g, 0.076 mole), water (20 ml) and ethanol (100 ml) was heated under reflux (5 hours). Solvents were evaporated *in vacuo*. The residue was dissolved in chloroform, washed with brine and dried (sodium sulfate). The solution was evaporated to dryness and the residue chromatographed on silica gel. Elution with hexane/ethanol/triethylamine (7:1:2) afforded red crystals of **22** (4.13 g, 62%), mp 110°; ms: (EI) m/z (relative intensity) 349, 347 (40, 100, M^+), 302, 200 (8, 18); ^{1}H nmr (deuteriochloroform): δ 3.2 (s, 8H, piperazine CH_2), 3.76 (s, OCH_3), two signals (m), centered at 6.84, 6.91 (AA'BB' system of 4-methoxyphenyl H), 6.97 (dd, J = 8.7, J = 2.1 Hz), 7.10 (d, J = 2.1 Hz), 7.60 (d, J = 8.7 Hz); ^{13}C nmr (deuteriochloroform): δ 50.5, 51.4 (piperazine C), 55.5 (OCH_3), 114.4, 118.5, 120.6, 121.3, 127.5, 138.7, 145.2, 146.9, 154.9 (aromatic carbons).

Anal. Calcd. for $C_{17}H_{18}ClN_3O_3$: C, 58.71; H, 5.22; N, 12.08. Found: C, 59.01; H, 5.23; N, 12.06.

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