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Synthesis and Analgesic Activity of 1-(1-Piperidinyl)methyl-2-(4-substituted styryl)-5-chlorobenzimidazole Derivatives

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Abstract

Seven 1-(1-piperidinyl)methyl-2-(4-substituted styryl)-5-chlorobenzimidazole derivatives were synthesized by the reaction of 2-(*p*-substituted styryl)-5-chlorobenzimidazoles with formaldehyde and piperidine in methanol. Analgesic activity of the 1-(1-piperidinyl)-methyl-2-(4-substituted styryl)-5-chlorobenzimidazole derivatives was investigated by the modified Koster test in mice. No obvious relationships between analgesic activity and the nature of the substituent on the styryl group was found.

Benzimidazoles bearing an *o*- or *p*-substituted phenyl moiety at position 2 have a wide spectrum of biological activity including antihelmintic, antifungal, antituberculous and anti-inflammatory activity (Dandegaonker & Daulatabad 1967; Fuveau 1972; Garuti et al 1987; Vishnevskii 1987).

It is well known that alkylaminoalkyl groups at position 1 of 2-benzylbenzimidazoles confer analgesic activity to these derivatives (Hunger et al 1960). It was reported that some 1-substituted-2-styrylbenzimidazole derivatives also had significant analgesic, anti-inflammatory and antispasmodic activity (Hoffmann & Hunger 1962; Kamissarov et al 1982). These findings have prompted us to synthesize 1-(1-piperidinyl)methyl-2-(4-substituted styryl)-5-chlorobenzimidazole derivatives, and investigate their analgesic activity.

The classic Phillips method was used to prepare 5-chloro-2-methylbenzimidazole (**1**). As 4 M hydrochloric acid was used, the yield increased significantly. This finding is also in accordance with the literature (Weidenhagen 1936; Isikdag et al 1989).

The synthesis of 5-chloro-2-styrylbenzimidazoles, **2a**–**g** was achieved by refluxing **1** and *p*-substituted benzaldehydes in acetic anhydride for 30 h. The reaction mixture was then poured into ice-water and neutralized with concentrated ammonia (Sullivan 1970; Tosun et al 1996). Mannich derivatives were prepared by stirring **2a**–**g** with formaldehyde (formalin 35%) and piperidine in methanol at 30–35°C (Bahadur et al 1976). The synthetic route is shown in Figure 1.

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Materials and Methods

Chemistry

4-Chloro-*o*-phenylenediamine, *p*-substituted benzaldehydes, acetic anhydride, glacial acetic acid, ammonia, hydrochloric acid, piperidine and formaldehyde were all from Merck.

Melting points were determined on an Electrothermal-9200 Digital Melting Point Apparatus and are uncorrected.

IR spectra were recorded on Perkin Elmer 1330 IR Spectrophotometer using the KBr disc method and ^{1}H NMR spectra were recorded on Bruker 400 MHz Spectrometer in d_6-DMSO:$CDCl_3$ (1:2) using tetramethylsilane as an internal standard. Elemental analyses were made with Leco Model-932 Elemental Analyzer (Microanalytical Unit, Tubitak Research Center, Ankara, Turkey). Where analyses are indicated by symbols, the analytical results were within the range of ±0·4% of the theoretical values.

Synthesis

*2-Methyl-5-chlorobenzimidazole (**1**) (Isikdag et al 1989).* A mixture of 4-chloro-*o*-phenylenediamine (5·7 g; 0·04 mol) and glacial acetic acid (3·6 g; 0·06 mol) in 50 mL 4 M hydrochloric acid solution was refluxed for 6 h, cooled and neutralized with

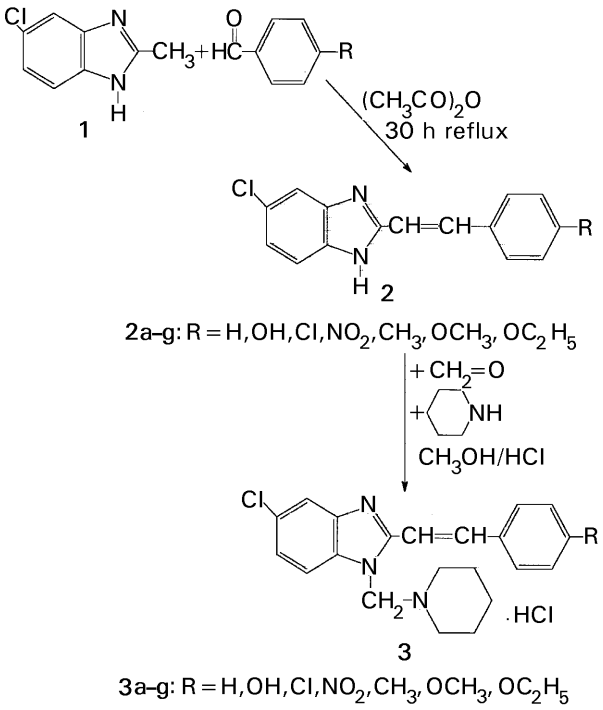


Figure 1. Synthesis of 1-(1-piperidinyl)methyl-2-(4-substituted styryl)-5-chlorobenzimidazole derivatives.

ammonia. The brown precipitate was filtered and crystallized from ethanol.

2-(4-Substituted styryl)-5-chlorobenzimidazoles ***2a–g*** *(Uzunoglu et al 1997).* Compound **1** (1 g; 0·006 mol) and an appropriate benzaldehyde (0·006 mol) were dissolved in 20 mL acetic anhydride and the final solution was refluxed for 30 h. The reaction mixture was poured into ice-water and neutralized with ammonia. The crude precipitate was filtered and crystallized from ethanol.

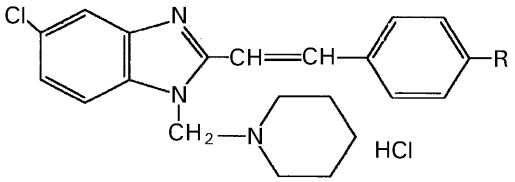
1-(1-Piperidinyl)methyl-2-(4-substituted styryl)-5-chlorobenzimidazole hydrochlorides ***3a–g***. Compound **2** (0·002 mol), formaldehyde (0·006 mol) and piperidine (0·004 mol) were dissolved in 30 mL methanol and the mixture was stirred for 2 h at 30–35°C. The solvent was removed in a rotatory evaporator. The residue was treated with methanolic hydrochloride. The precipitate was filtered and crystallized from methanol. The yields, melting points and elemental analyses of title compounds are given in Table 1.

Biology

Analgesic activity. Albino mice (local strain), 20–25 g, were used. Eight animals were used in each group. The animals were allowed to acclimatize to the room conditions for two days, and were maintained on standard pellet diet and water. Food was withdrawn on the day before the experiment but free access to water was maintained.

The modified Koster test (Boisser & Simon 1966; Gyires & Torma 1984) was used. Aspirin was used as the reference drug. Each compound was suspended in 0·5% aqueous carboxymethyl cellulose and given orally to mice at 100 mg kg^{-1} dose. One hour after administration, pain was induced by intraperitoneal injection of a 3% solution of acetic

Table 1. Yield, melting points and elemental analysis of 1-(1-piperidinyl)methyl-2-(4-substituted styryl)-5-chlorobenzimidazole hydrochloride derivatives.



Compound	R	Yield (%)	Mp (°C)	Elemental analysis					
				Calculated			Found		
				C	H	N	C	H	N
3a ($C_{21}H_{23}N_3Cl_2$)	H	57	245–246	64·95	5·97	10·82	65·04	5·88	10·76
3b ($C_{21}H_{23}N_3Cl_2O$)	OH	63	256–258	62·38	5·73	10·39	62·24	5·67	10·46
3c ($C_{21}H_{22}N_3Cl_3$)	Cl	70	222–224	59·65	5·24	9·94	59·53	5·37	10·02
3d ($C_{21}H_{22}N_4Cl_2O_2$)	NO_2	85	212–213	58·20	5·11	12·92	58·36	5·19	12·89
3e ($C_{22}H_{25}N_3Cl_2$)	CH_3	68	234–236	65·67	6·28	10·44	65·81	6·31	10·33
3f ($C_{22}H_{25}N_3Cl_2O$)	OCH_3	75	192–194	63·15	6·02	10·04	63·27	5·93	9·92
3g ($C_{23}H_{27}N_3Cl_2O$)	OC_2H_5	78	142–144	63·88	6·29	9·71	64·03	6·18	9·65

acid at a dose of 300 mg kg^{-1}. The control group received carboxymethyl cellulose 1 h before injection of acetic acid. Each animal was placed in a separate cage 5 min after acetic acid injection and the number of abdominal constrictions per animal was recorded during the following 10-min period. Percent analgesic activity was calculated using the formula:

$$\text{analgesic activity } (\%) = ((n - n^1)/n) \times 100$$

where n = average number of constrictions of control group n^1 = average number of constrictions of test group.

Acetylsalicylic acid was used as the reference compound and administered according to the test protocol.

Results and Discussion

Spectral data of the compounds synthesized are given.

*1-(1-Piperidinyl)methyl-2-styryl-5-chlorobenzimidazole hydrochloride (**3a**)*
IR ν (cm^{-1}): 3300 (N^+ -H); ^{1}H NMR δ (ppm): 9·38 (s, 1H, N^+ -H), 7·92–7·05 (m, 10H, Ar-H), 3·12 (s, 2H, N-CH_2 -N), 2·66 (t, 4H, piperidine $C_{2,6}$ -H), 1·84 (m, 4H, piperidine $C_{3,5}$ -H), 1·63 (m, 2H, piperidine C_4 -H).

*1-(1-Piperidinyl)methyl-2-(4-hydroxystyryl)-5-chlorobenzimidazole hydrochloride (**3b**)*
IR ν (cm^{-1}): 3320 (N^+ -H); ^{1}H NMR δ (ppm): 12·83 (s, 1H, OH), 9·27 (s, 1H, N^+ -H), 7·78–6·93 (m, 9H, Ar-H), 3·18 (s, 2H, N-CH_2 -N), 2·54 (m, 4H, piperidine $C_{2,6}$ -H), 1·81 (m, 4H, piperidine $C_{3,5}$ -H), 1·64 (m, 2H, piperidine C_4 -H).

*1-(1-Piperidinyl)methyl-2-(4-chlorostyryl)-5-chlorobenzimidazole hydrochloride (**3c**)*
IR ν (cm^{-1}): 3380 (N^+ -H); ^{1}H NMR δ (ppm): 9·18 (s, 1H, N^+ -H), 8·21–7·23 (m, 9H, Ar-H), 3·09 (s, 2H, N-CH_2 -N), 2·57 (t, 4H, piperidine $C_{2,6}$ -H), 1·78 (m, 4H, piperidine $C_{3,5}$ -H), 1·62 (m, 2H, piperidine C_4 -H).

*1-(1-Piperidinyl)methyl-2-(4-nitrostyryl)-5-chlorobenzimidazole hydrochloride (**3d**)*
IR ν (cm^{-1}): 3310 (N^+ -H); ^{1}H NMR δ (ppm): 9·18 (s, 1H, N^+ -H), 7·92–7·21 (m, 9H, Ar-H), 3·09 (s, 2H, N-CH_2 -N), 2·61 (t, 4H, piperidine $C_{2,6}$ -H), 1·81 (m, 4H, piperidine $C_{3,5}$ -H), 1·65 (m, 2H, piperidine C_4 -H).

*1-(1-Piperidinyl)methyl-2-(4-methylstyryl)-5-chlorobenzimidazole hydrochloride (**3e**)*
IR ν (cm^{-1}): 3390 (N^+ -H); ^{1}H NMR δ (ppm): 9·45 (s, 1H, N^+ -H), 7·83–7·32 (m, 9H, Ar-H), 3·07 (s, 2H, N-CH_2 -N), 2·58 (t, 4H, piperidine $C_{2,6}$ -H), 2·14 (s, 3H, Ar -CH_3), 1·87 (m, 4H, piperidine $C_{3,5}$ -H), 1·65 (m, 2H, piperidine C_4 -H).

*1-(1-Piperidinyl)methyl-2-(4-methoxystyryl)-5-chlorobenzimidazole hydrochloride (**3f**)*
IR ν (cm^{-1}): 3370 (N^+ -H); ^{1}H NMR δ (ppm): 9·32 (s, 1H, N^+ -H), 7·88–7·38 (m, 9H, Ar-H), 3·72 (s, 3H, Ar -OCH_3), 3·09 (s, 2H, N-CH_2 -N), 2·62 (t, 4H, piperidine $C_{2,6}$ -H), 1·83 (m, 4H, piperidine $C_{3,5}$ -H), 1·68 (m, 2H, piperidine C_4 -H).

*1-(1-Piperidinyl)methyl-2-(4-ethoxystyryl)-5-chlorobenzimidazole hydrochloride (**3g**)*
IR ν (cm^{-1}): 3335 (N^+ -H); ^{1}H NMR δ (ppm): 10·08 (s, ^{1}H, N^+ -H), 8·12–7·36 (m, 9H, Ar-H), 4·32 (q, 2H, Ar -O-CH_2 -CH_3), 3·28 (s, 2H, N-CH_2 -N), 2·64 (t, 4H, piperidine $C_{2,6}$ -H), 1·86 (m, 4H, piperidine $C_{3,5}$ -H), 1·61 (m, 2H, piperidine C_4 -H), 1·37 (t, 3H, Ar -O-CH_2 -CH_3).

Results of the analgesic activity test are given as the percentage inhibition of abdominal constriction in Table 2.

Compounds **3a**, **3b** and **3e** exhibited lower analgesic activity than aspirin, compounds **3d** and **3f** were almost as potent and compounds **3c** and **3g** had higher analgesic activity. Compounds **3a**, **3c**, **3d** and **3g** also caused drowsiness in the experimental animals. This could provide evidence for their mode of antinociceptive activity which is not known at present. Further investigation of these derivatives is therefore necessary. No obvious relationships between analgesic activity and the nature of the substituent on the styryl group was found.

Table 2. Analgesic activity of 100 mg kg^{-1} 1-(1-piperidinyl)methyl-2-(4-substituted styryl)-5-chlorobenzimidazole hydrochloride derivatives.

Compound	Activity (%)
3a	25·6
3b	24·2
3c	78·1
3d	37·3
3e	11·3
3f	41·7
3g	77·5
Aspirin	40·8

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