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Design, synthesis and in vitro antiprotozoal activity of benzimidazole-pentamidine hybrids

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ABSTRACT

A series of ten novel hybrids from benzimidazole and pentamidine were prepared using a short synthetic route. Each compound was tested in vitro against the protozoa *Trichomonas vaginalis, Giardia lamblia, Entamoeba histolytica, Leishmania mexicana*, and *Plasmodium berghei*, in comparison with pentamidine and metronidazole. Some analogues showed high bioactivity in the low micromolar range ($IC_{50} < 1$ μM) against the first four protozoa, which make them significantly more potent than either standard. 1,5-bis[4-(5-methoxy-*1H*-benzimidazole-2-yl)phenoxy]pentane (**2**) was 3- and 9-fold more potent against*G. lamblia* than metronidazole and pentamidine, respectively. This compound was 23-, 108-, and 13-fold more active than pentamidine against *T. vaginalis*, *E. histolytica* and *L. mexicana*, respectively. Studying further structure–activity relationships through the use of bioisosteric substitution in these hybrids should provide new leads against protozoal diseases.

Parasitic infections, such as helminthiasis and protozoosis, are still major problem in developing countries, affecting mainly the infant population.[1–3]

For the treatment of some kinds of protozoosis such as giardiasis, trichomoniasis, and amoebiasis, metronidazole is the drug of choice.[4] Recent studies have shown that this drug has several toxic effects such as genotoxicity, gastric mucus irritation, and spermatozoid damage.[5–7] Although current drug therapy for the treatment of these infections is effective, most available drugs have significant side effects that restrict their use.[8]

Benzimidazole derivatives, such as mebendazole and albendazole, are clinically anthelminthic useful drugs. More recently, antiprotozoal activity of 2- and 5-substituted benzimidazoles has been reported.[9–14] Benzimidazole core is of a wide interest because of its diverse biological activities, and it is a well-known privileged structure in medicinal chemistry.[15]

Pentamidine, an aromatic diamidine, is used at primary stage in African trypanosomiasis, antimony-resistant leishmaniasis, and AIDS associated *Pneumocystis jirovecii* pneumonia.[16–18] Pentamidine is not effective when given orally and several toxic effects including hypotension, dysglycemia, renal, pancreatic, and hepatic toxicity have been reported.[18–22] The recent increase in life-threatening *P. jirovecii* pneumonia in patients with AIDS has resulted in a revived interest in pentamidine and related derivatives.[23]

As a part of our search for basic information about structural requirements for antiprotozoal activity, we have synthesized a series of hybrids between benzimidazole and pentamidine (Fig. 1).

The in vitro antiparasitic activity of these compounds on intestinal protozoa (*Giardia lamblia, Entamoeba histolytica*), a urogenital tract parasite (*Trichomonas vaginalis*), a red blood cell parasite (*Plasmodium berghei*) and an intracellular kinetoplastid parasite (*Leishmania mexicana)*, is also reported in this letter.

Compounds **1**–**10** were prepared by alkylation of appropriate 4-hydroxybenzaldehyde, followed by conversion of the resulting bis-aldehyde to the respective benzimidazole by treatment with 1,2-phenylenediamine adequately substituted, as shown in Scheme 1. The required substituted bis-aldehydes **11** and **12** were prepared in good yields, starting from 4-hydroxybenzaldehyde (**14**) or 4-hydroxy-3-methoxybenzaldehyde (**15**) with 1,5-dibromopentane (**13**) in presence of potassium carbonate under acetonitrile reflux.[24] The cyclocondensation reaction of **11** and **12** with the

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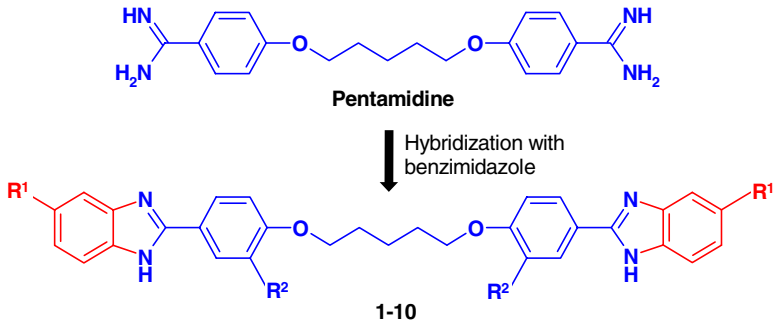
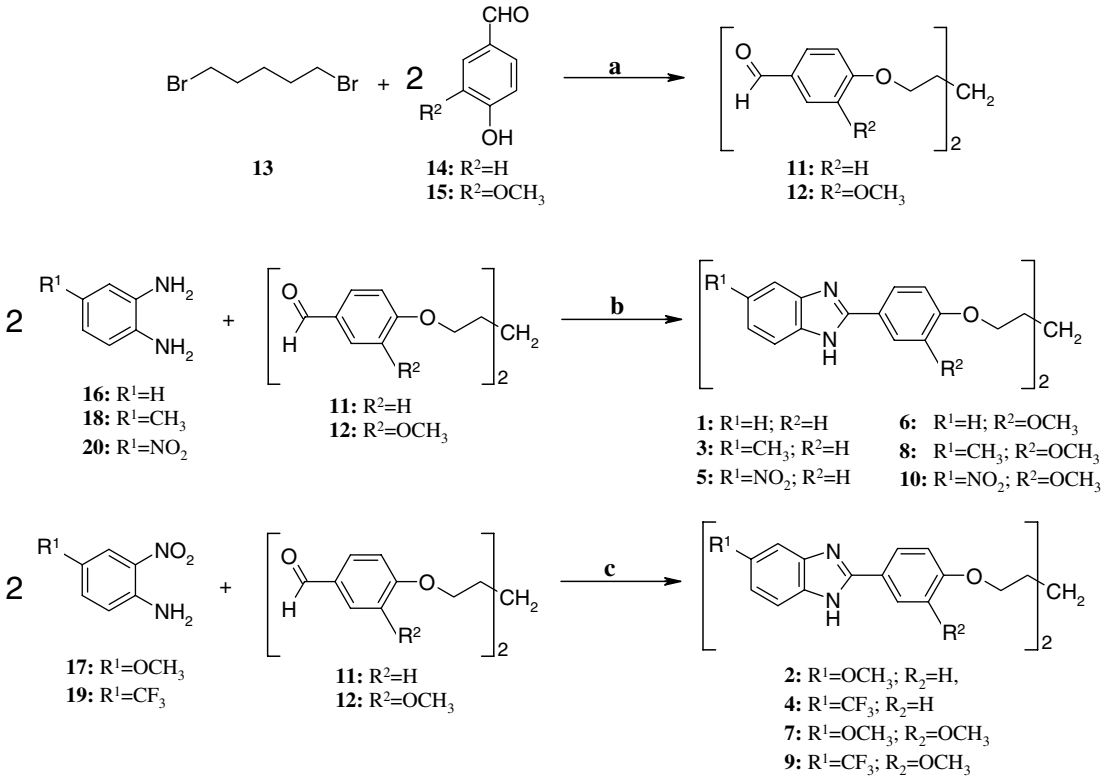


Figure 1. Drug design of hybrids **1**–**10**.



Scheme 1. Reagents and conditions: (a) MeCN, K_2CO_3, 78 °C, 17–19 h; (b) 2.1 equiv $Na_2S_2O_5$, DMF, 90 °C, 20 h; (c) 10 equiv $Na_2S_2O_4$, H_2O:EtOH, 80 °C, 10–14 h.

corresponding 4-substituted-1,2-phenylendiamines **16**, **18** and **20**, and sodium metabisulfite in DMF afforded the corresponding hybrids **1**, **3**, **5**, **6**, **8**, and **10** (Scheme 1).[25]

Compounds **2**, **4**, **7** and **9** were prepared using a one-pot reduction–cyclization reaction according to the previous described method,[26,27] where bis-aldehydes **11** and **12** reacted with the corresponding 5-substituted-2-nitroaniline (**17**, **19**) in the presence of sodium dithionite (reducing reagent) and a mixture of tap water and ethanol as solvent (Scheme 1).

The chemical structures of the synthesized compounds were confirmed on the basis of their spectral data (NMR and mass spectra), and their purity ascertained by microanalysis. The elemental analysis was within ±0.4% of the theoretical values. Physical constants of the title compounds are shown in Table 1.

In the nuclear magnetic resonance spectra (^{1}H NMR; δ ppm), the signals of the respective protons of the compounds were verified on the basis of their chemical shifts, multiplicities and coupling constants. To elucidate the structures of the compounds, one and two-dimensional (homo- and heteronuclear correlation spectra HH and CH COSY) have been carried, in order to assign the signals of the ^{1}H and ^{13}C NMR spectra correctly.[28]

The aromatic region of the ^{1}H NMR spectrum contained an ABX pattern signals ranging from δ 7.01 to 8.34 (dd, J_{meta} = 1.2–2.2; J_{para} = 0.0–1.0 Hz), 6.84 to 8.06 (dd, J_{ortho} = 8.4–8.9; J_{meta} = 1.2–2.2 Hz), and 7.11 to 7.69 (dd, J_{meta} = 1.2–2.2; J_{para} = 0.0–1.0 Hz) attributable to H-4, H-6, and H-7, of the benzimidazole 5-substituted core, respectively. For compounds **1**–**5** the aromatic region of the ^{1}H NMR spectrum also contained an A_2B_2 pattern signals ranging from *δ 7.15 to 8.12 (d, J_{ortho}* = 8.1–8.8 Hz) and 7.09 to 8.11 (d, J_{ortho} = 8.1–8.9 Hz) attributable to the equivalents H-2′, H-6′ and H-3′, H-5′, respectively, of the benzene ring. For the compounds **6**–**10**, another ABX pattern signals ranging from *δ 7.11 to 7.83 (d, J_{meta}* = 0.0–1.6 Hz), 7.11 to 7.18 (d, J_{ortho}= 8.4–8.8 Hz) and 7.69 to 7.77 (dd, J_{ortho} = 8.4–8.8; J_{meta} = 0.0–1.6 Hz) attributable to H-2′, H-5′ and H-6′, respectively, of the benzene ring.

The new hybrids from benzimidazole and pentamidine (**1**–**10**) were tested in vitro as antiprotozoal agents. Biological assays results against the five protozoa tested are summarized in Table 1.