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A natural product inspired hybrid approach towards the synthesis of novel pentamidine based scaffolds as potential anti-parasitic agents

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ABSTRACT

A natural product inspired molecular hybridization approach led us to a series of novel pentamidine based pyrimidine and chalcone scaffolds. All the hybrids were evaluated for their anti-leishmanial potential. Most of the screened compounds have showed significant in vitro anti-leishmanial activity with less cytotoxicity in comparison to the standard drugs (pentamidine, sodium stibogluconate, and miltefosine). Additionally, anti-malarial screening of these compounds was also done and four compounds have shown superior activity against chloroquine resistance strain (K1) of *Plasmodium falciparum.*

Nowadays, neglected tropical disease (NTDs) affect more than one billion people worldwide, causes over 550,000 deaths annually.[1] Research projects aiming to discover new drugs for NTDs have discouraged drug companies from investing due to the low returns of investment.[2] Owing to this, drug discovery pipeline is still almost dry for NTDs. Among NTDs, Chagas disease, sleeping sickness, malaria, and leishmaniasis are the major NTDs with the highest rates of death.[3] In particular, *leishmania* is responsible for cutaneous and visceral infections, endemic in 88 countries in the Horn of Africa, South Asia, and Latin America.[4] Leishmaniasis is a vector born disease caused by different species belonging to the genus *Leishmania*, a protozoa transmitted by the bite of a tiny long (2–3 mm) insect vector, the phlebotomine sandfly.[5] *Leishmania* is manifested in four major clinical forms i.e. cutaneous leishmaniasis, mucocutaneous leishmaniasis, visceral leishmaniasis, and post kala-azar dermal leishmaniasis or PKDL. Among all the four forms, visceral leishmaniasis (VL), caused by the parasite *Leishmania donovani,* is nearly always fatal if not treated.[6]

The first line drugs for the treatment of *leishmania* are pentavalent antimonial compounds, which were discovered almost 70 years ago, and generally require high dose of parental administration. Moreover, this class of drugs need long-term treatment associated with severe side effects including cardiac arrhythmia and pancreatitis.[7] Pentamidine, miltefosine, and amphotericin-B, are the second line drugs for the treatment of VL, which also suffer from moderate to severe side effects.[8] Pentamidine, an aromatic diamidine, is orally inactive and may demonstrate renal, hepatic and pancreatic toxicity beside with hypotension and dysglycemia.[9] Amphotericin-B and its lipid complex is a most useful alternative, however, major draw backs associated with amphotericin-B, such as its high cost leave out of the reach of poor people.[10]

Furthermore, recently introduced first orally active drug Miltefosine, a phosphocholine analogue, has a long half-life (100–200 h) in humans and a low therapeutic ratio, presenting severe gastrointestinal problems and also shows teratogenic effects and cannot be used in the pregnant women.[11] Since the chemotherapy against leishmaniasis is still inefficient, as a result the finding of more effective and safer drug for treating leishmaniasis remains desirable.

The natural product inspired molecular hybridization approach has been emerged as a powerful tool for tackling the problems associated with the standard drugs.[12] Recently, some hybrid molecules of pentamidine with other heterocycles have been synthesized, which showed potent anti-leishmanial activity with low cytotoxicity.[13] Furthermore, following the same approach some pyrimidines and chalcone based hybrids were synthesized and evaluated for their anti-parasitic potential.[14]

Annomontin, a pyrimidine-β-carboline alkaloid, has showed antileishmanial activity 34.8 ± 1.5 against the *Leishmania braziliensis*. On the other hand, licochalcone A, is a well known anti-parasitic

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natural phenol.[15] In the continuation of our ongoing programme to develop new hybrid molecules as potent anti-parasitic agents,[16] and inspired by the antileishmanial and antimalarial activity of pyrimidine and chalcone based natural product annamontine and licochalcone A, we herein report our work on the design, synthesis and anti-protozoal evaluation of novel pentamidine based pyrimidine and chalcone hybrids (Fig. 1).

The detailed synthetic route to synthesize compounds (**7a–i**) is outlined in scheme 1. The synthesis was achieved by the coupling of substituted pyrimidine with the pentamidine fragment. In this context, pyrimidine derivatives (**2a–i**) were obtained by the condensation of 2,4-dichloro-6-methylpyrimidine with various primary or secondary amines under basic conditions. The pentamidine fragment has been synthesized via a condensation of 1,5-dibromopentane with *N*-(4-hydroxyphenyl)acetamide to furnish the intermediate **5** under basic condition, followed by the deprotection of amine in presence of 20% aq NaOH furnished the pentamidine fragment **6** in 74% yield. Finally, pentamidine fragment **6** was condensed with pyrimidine derivatives (**2a–i**) to afford the targeted pentamidine-pyrimidine hybrids (**7a–i**) in good yields (scheme 1).

In the second phase of our endeavour, we synthesized chalcones-pentamidine hybrid (**10a–f**, scheme 2). In this continuation intermediate **9** has been synthesized by replacing both bromo groups of 1,5-dibromopentane via 4-hydroxy benzaldehyde. Intermediate **9** was condensed with various acetophenones under the reported protocols. The use of 1 equiv of acetophenones leads to chalcone (**10d–f**), while the use of 2 equiv of acetophenones furnished the bis-chalcones **(10a–c)**. All compounds were characterized using ^{1}H NMR, ^{13}C NMR, mass spectrometry and IR spectroscopy (see Supplementary data).[17] The purity of these compounds was ascertained by TLC and spectral analysis.

All the synthesized compounds were evaluated in vitro against transgenic *Leishmania donovani* amastigotes.[18] All the pyrimidine–pentamidine hybrids (**7a–i**) (Table 1) showed very good inhibitory activity with the IC_{50} values in the range of 0.30–1.72 μM and SI

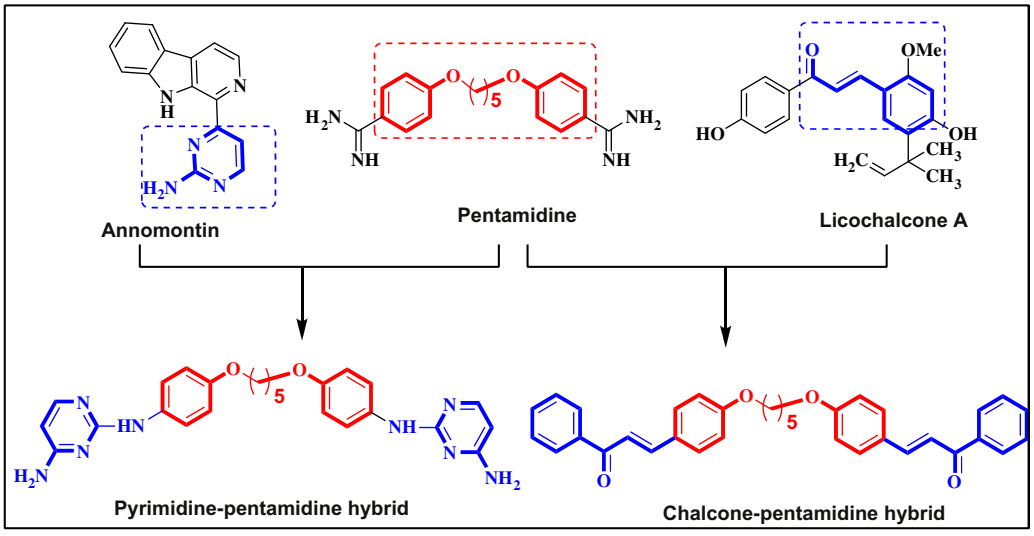
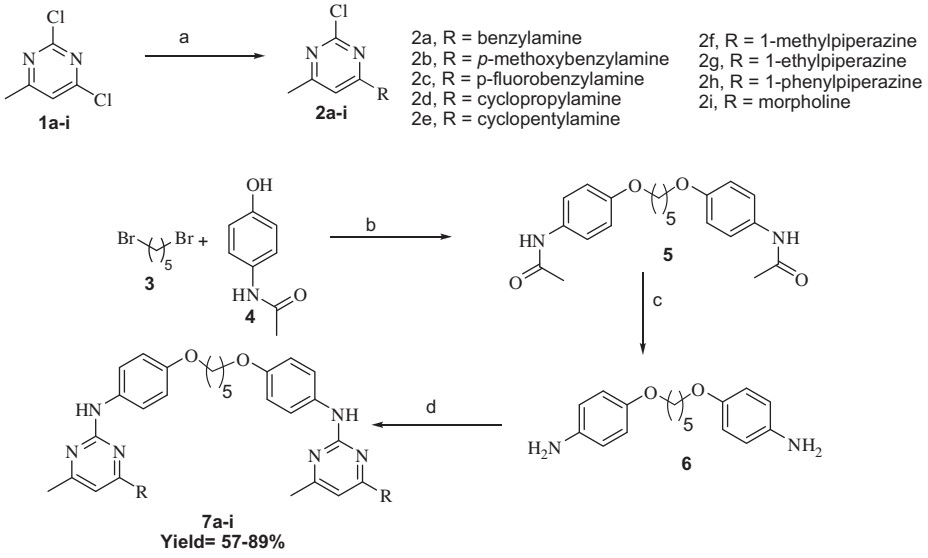


Figure 1. A natural product inspired hybrid approach to the synthesis of anti-parasitic agent.



Scheme 1. Synthesis of pyrimidine–pentamidine hybrids (**7a–i**). Reagents and conditions: (a) amines, DIPEA, EtOH, rt, 2 h (b) K_2CO_3, acetone, reflux, 10 h (c) 20% aq NaOH, H_2O:EtOH (1:1), 90 °C, 5 h (d) **2a–i**, DIPEA, DMF, MW, 200 °C, 30 min.