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**Research Article**

# MICROWAVE ASSISTED SYNTHESIS OF NOVEL BENZIMIDAZOLE DERIVATIVES AS POTENT ANTILEISHMANIAL AND ANTIMALARIAL AGENTS

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**A B S T R A C T**

Novel series of novel benzimidazole derivatives were synthesized by microwave assisted synthesis as green chemistry. Six novel benzimidazole derivatives were synthesized successfully in appreciable yields and characterized physicochemically. Furthermore, the synthesized compounds were screened for antileishmanial and antimalarial activity. Some of the synthesized compounds showed significant activity.Benzimidazole derivatives were synthesised and tested in vitro for activity against promastigotes of Leishmaniatropica and L. infantum. Most of the tested compounds resulted active against both Leishmania species, with $IC_{50}$ values in the low micromolar/sub-micromolar range. 3-benzoylbenzimidazole derivative was 12-/7-fold more potent than miltefosine, but exhibited a further improved SI. Therefore, compounds 2c and 2e represent interesting hit compounds, susceptible of structural modification to improve their safety profiles. All the synthesized compound were evaluated for their antimalarial activity against a chloroquine and quinine sensitive strain of P. falciparum. All experiments were performed in duplicate and mean values of $IC_{50}$. 2d and 2f compounds displayed excellent activity against the P. falciparum strain compared to quinine compared tochloroquine.All the remaining compounds were found to be less active against chloroquine sensitive strains of P. falciparum.



## INTRODUCTION

Benzimidazole focused mainly on hybrids is of great concern because of their complex biological activity[1]. Benzimidazoles are ascertained as a capable category of bioactive heterocyclic compounds that exhibit a range of biological activities like anti-microbic, antioxidants, anti-cancer, anti-diabetic, anti-parasitic, anti-viral, antihelminthic, anti-proliferative, anti-HIV, anti-convulsant, medication, anti-hypertensive, proton pump matter, anti-neoplastic and antitrichinellosis[2]. Benzimidazoles exhibit important applications such as possible Swish muscle fiber propagation inhibitors, antincancer agents, as a treatment for urinary viscus infection and in various areas of chemistry[3]. Many benzimidazole derivatives are well associated with thyroid receptor agonist gonadotropin-releasing secretion antagonists, non-nucleoside HIV-1 reverse transcriptase inhibitors and apparently group benzimidazoles as modulators of metabotropic salt receptors[4-5]. In addition, benzimidazole moiety is a present in many natural products and pharmacologically active agents[6-7].

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Therefore, the synthesis of novel benzimidazole derivatives remains a medical investigation[8].Leishmaniasis is the second most prevalent infection of parasites for mortality in humans worldwide after malaria[9]. The application of green chemistry principles and practices renders regulation, control, clean-up, and remediation of the environment[10]. The application of green chemistry principles and practices renders regulation, control, clean-up, and remediation of the environment. Thus its benefits can be expressed in terms of economic impact[11]. The bite of a sandfly infected with a flagellate protozoan of the genus Leishmania transmits it. It identifies three different types of the disease: acute, cutaneous, and muco-cutaneous leishmaniasis. In many tropical and subtropical countries, the disease is endemic, leading to an estimated 700,000–1 million new cases annually and 20,000–30,000 deaths, mostly due to the visceral form of Leishmaniadonovani. The parasite exists in the ovoid non-flagellate form (amastigote) and in the promastigote flagellate, found in the sand fly. Leishmaniasis treatment is still focused on pentavalentantimonials (sodium stibogluconate and meglumineantimoniate) as the medication of first choice[12-13], whereas amphotericin B, miltefosine,paromomycin and pentamidine are considered second-line drug[14]. Some other drugs, such as edelfosine,

sitamaquine, fexinidazole, tamoxifene, imiquimod and pentoxyphylline, are reported to offer variable cure rates when used alone or better in combination with antimonials to overcome resistance[15]. All of these drugs can cause several side effects, and most of them are also costly and therefore out of reach for the poor people living in tropical and subtropical countries where the disease is endemic[16]. The mentioned drugs exhibit very different chemical structures and reach a number of biological targets but the mechanism of action is either unknown or only partly understood in some instances. In order to satisfy the need for modern, more effective, safe and affordable drugs for the treatment of leishmaniasis, a range of studies are underway to explore a broad chemical space from several groups of natural products and their semi-synthetic derivatives (sterols, mono-, sequi-, di- and tri-terpens, alkaloids, flavonoids, etc.) to the most diverse synthetic compounds, from simple chloroacetoanilides[17], to organometallics, aryldiselenides, adamantylidene alkyl phosphocoline and a variety of heterocycles, particularly indole, indazole, benzotriazole and benzimidazole derivatives[18-19].Malaria remains an important health problem worldwide, with serious social and economic consequences in the countries affected. The problem has been worsened by the emergence and spread of parasites resistant to well-established antimalarial medicines[20].Malaria swelling in the human body is through five different types of Plasmodium genus protozoa, but for most critical cases Plasmodium falciparum is responsible. The appearance of P. falciparum resistance to these drugs, however, is a grave cause of concern. The WHO has suggested combining the formulation of artemisinins with traditional antimalarial drugs such as lumefantrine, amodiaquine and mefloquine to reduce the variety of resistant parasites, and ACT (Artemisinin Combination Therapy) is currently approved in multiple countries.In medicinal chemistry, therefore, the production of new, safe, non-toxic, and inexpensive antimalarial drugs is a top priority[21].

## MATERIAL AND METHODS

Melting points of the synthesized compounds were determined in open capillary tubes and were uncorrected. Reaction Progress was observed by TLC plates, Bruker 300 MHz instrument was used to record 1H NMR spectra in DMSO/$CDCl_3$ using TMS as internal standard. Chemical shifts (d) are expressed in ppm and with ATR JASCO FTIR-4600, IR spectra were recorded and Mass spectra were recorded on Pesciex (model no. API 2000).

***General Procedure***

***Synthesis of Series 1 Compounds***

***Synthesis of 2-methylbenzimidazole***

Mixture of o-phenylenediaminediamine (0.03 mole) and 20 ml of water, acetic acid (0.09 mole) was irradiated for15min at 340watt under microwave. By gradually adding the concentrated ammonia solution, the cooled reaction mixture was made distinctly basic and the precipitated product was collected and recrystallized from 10% ethanol[22]. (scheme is shown in Fi

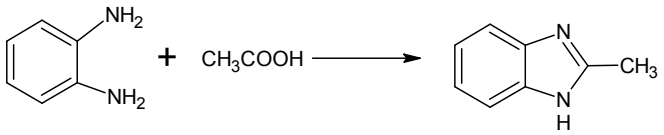



**Fig 1** Synthesis of 2-methylbenzimidazole

***Synthesis of Series 2 Compounds***

***Synthesis of 3-benzoylbenzimidazole derivative***

Dissolved 0.5g of the above product in 10mL of 10% sodium hydrogen carbonate solution and added 1g of benzoyl chloride. In a stoppered test tube, the reaction mixture was shaken vigorously. Since carbon dioxide evolved the stopper has been removed from time to time. After the benzoyl chloride odour had disappeared, it acidified to Congo red and washed with dilute hydrochloric acid. Extracted the solid with a bit of cold ether to remove any benzoic acid that may be present. Dilute ethanol recrystallized the benzoyl derivative[22]. (scheme is shown in Fig. 2).

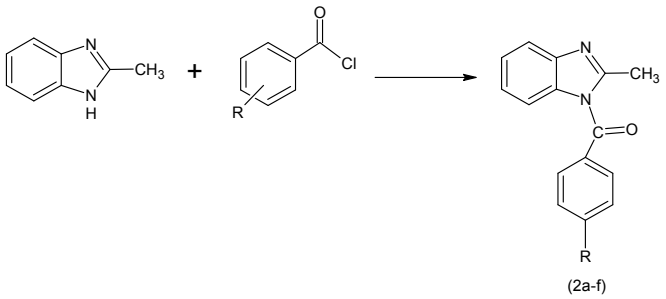
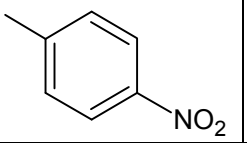
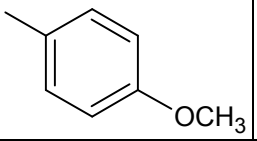
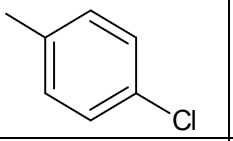
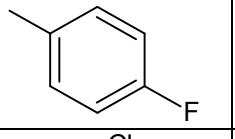
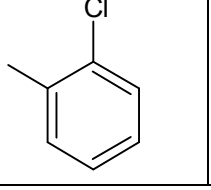
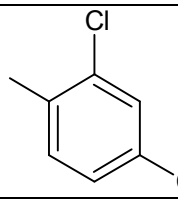



**Fig 2** Synthesis of 3-benzoylbenzimidazole

| Compound | R | Formula | MP °C | Yield (%) |
|---|---|---|---|---|
| 2a |  | $C_{15}H_{11}N_3O_3$ | 218-220°C | 72 |
| 2b |  | $C_{16}H_{14}N_2O_2$ | 234-236°C | 65 |
| 2c |  | $C_{15}H_{11}ClN_2O$ | 255-256°C | 84 |
| 2d |  | $C_{15}H_{11}FN_2O$ | 214-216°C | 72 |
| 2e |  | $C_{15}H_{11}ClN_2O$ | 240-242°C | 90 |

| | | | | |
|---|---|---|---|---|
| 2f |  | $C_{15}H_{10}Cl_2N_2O$ | 232-234°C | 88 |

***Analytical Data for Novel 3-benzoylbenzimidazole derivative***

**2a.(2-methyl-1*H*-benzimidazol-1-yl)(4-nitrophenyl)methanone**

IR (KBr, cm-$^{1}$) 1740.35 (C=0), 1332.51 (Ar-$NO_2$), 1237.40 (C-N str), 3782.82 (C-H), $^{1}$HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.41-7.78(q, 2H, Ar-H), 1.56-1.92 (t, 3H), 7.88-8.06 (q, 4H); mass m/z ($M^+$) 282.

**2b.(4-methoxyphenyl)(2-methyl-1*H*-benzimidazol-1-yl)methanone**

IR (KBr, cm-$^{1}$) 1755.12 (C=0), 2819.44 (O-$CH_3$), 1232.58 (C-N str), 3770.39 (C-H), $^{1}$HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.53-7.84 (q, 2H, Ar-H), 1.31-1.58 (t, 3H), 8.05-8.37 (q, 4H); mass m/z ($M^+$) 265.

**2c.(4-chlorophenyl)(2-methyl-1*H*-benzimidazol-1-yl)methanone**

IR (KBr, cm-$^{1}$) 1734.20 (C=0), 759.41 (C-Cl), 1239.73 (C-N str), 378.19 (C-H), $^{1}$HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.78-7.92 (q, 2H, Ar-H), 1.24-1.65 (t, 3H), 8.52-8.67 (q, 4H); mass m/z ($M^+$) 269.

**2d.(4-fluorophenyl)(2-methyl-1*H*-benzimidazol-1-yl)methanone**

IR (KBr, cm-$^{1}$) 1750.23 (C=0), 254.48(Ar-F), 1231.61 (C-N str), 3712.18 (C-H), $^{1}$HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.32-7.64 (q, 2H, Ar-H), 1.50-1.88 (t, 3H), 7.78-8.12 (q, 4H); mass m/z ($M^+$) 253.

**2e.(2-chlorophenyl)(2-methyl-1*H*-benzimidazol-1-yl)methanone**

IR (KBr, cm-$^{1}$) 1765.52 (C=0), 750.12 (C-Cl), 1240.11 (C-N str), 352.19 (C-H), $^{1}$HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.55-7.68 (q, 2H, Ar-H), 1.34-1.48 (t, 3H), 8.41-8.55 (q, 4H); mass m/z ($M^+$) 271.

**2f.(2,4-dichlorophenyl)(2-methyl-1*H*-benzimidazol-1-yl)methanone**

IR (KBr, cm-$^{1}$) 1742.89 (C=0), 757.09 (C-Cl), 1238.12 (C-N str), 345.10 (C-H), $^{1}$HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.88-7.94 (q, 2H, Ar-H), 1.41-1.55 (d, 2H), 8.04-8.23 (q, 4H); mass m/z ($M^+$) 304.

***Evaluation of Antileishmanial activity***

(a) Promastigote stage of L. infantum strain MHOM/TN/80/IPT1 (kindly provided by Dr M. Gramiccia, ISS, Roma) and L. tropica (MHOM/IT/2012/ISS3130) were cultured in RPMI 1640 medium (EuroClone) supplemented with 10% heat-inactivated fetal calf serum (EuroClone), 20mM Hepes, and 2mM L-glutamine at 24°C. To estimate the 50% inhibitory concentration (IC50), Compounds were dissolved in DMSO and thendiluted with medium to achieve the required concentrations. Drugs were placed in 96 wells round-bottom microplates and seven serial dilutions made. Amphotericin B or miltefosine were used as reference anti-Leishmania drugs. Parasites were diluted in complete medium to 5X10$^{6}$ parasites/mL and 100µL of the suspension was seeded into the plates, incubated at 24C for 72h and then 20mL of MTT solution (5mg/mL) was added into each well for 3h. The plates were then centrifuged at 1000 X g for 8min at r.t., the supernatants discarded and the resulting pellets dissolved in 100mL of lysing buffer consisting of 20% (w/v) of a solution of SDS (Sigma), 40% of DMF (Merck) in $H_2O$. The absorbance was measured spectrophotometrically at a test wavelength of 550nm and a reference wavelength of 650nm. The results are expressed as IC50 which is the dose of compound necessary to inhibit parasite growth by 50%; each IC50 value is the mean of separate experiments performed in duplicate.

(b) In vitro intracellular amastigote susceptibility assays. THP-1 cells (human acute monocytic leukaemia cell line) were maintained in RPMI supplemented with 10% FBS, 50µM 2-mercaptoethanol, 20mM Hepes, 2mM glutamine, at 37C in 5% $CO_2$. For Leishmania infections, THP-1 cells were plated at 5X10$^{5}$ cells/mL in 16-chamber Lab-Tek culture slides (Nunc) and treated with 0.1lM phorbolmyristate acetate (PMA, Sigma) for 48h to achieve differentiation into macrophages. Cells were washed and infected with metacyclic L. infantumpromastigotes at a macrophage/promastigote ratio of 1/10 for 24h. Cell monolayers were then washed and incubated with compounds for 72h. Slides were fixed with methanol and stained with Giemsa. The percentage of infected macrophages in treated and non-treated cells was determined by light microscopy[23].

***Antimalarial screening***

The in vitro antimalarial assay was carried out in 96well microliter plates (Lee *et al*., 2002). The cultures of Plasmodium falciparum RKL-2 strain were maintained in medium RPMI 1640 supplemented with 25 mM HEPES, 1% D-glucose, 0.2% sodium bicarbonate and 10% heat inactivated human serum. 180 mL of 1% D-sorbitol synchronized ring stage parasitemia in 3% hematocrit in a total volume of 200 µL of medium RPMI-1640 was assessed after converting to final dose. A stock solution of 5 mg/mL of each of the test samples was prepared in DMSO, and subsequent dilutions were prepared with culture medium to obtain 5 and 50 mg/mL. The test plates, as well as the positive and negative control (chloroquine and without sample respectively), were incubated at 37°C for 40 hours after treating with 5% $CO_2$[24].

## RESULTS AND DISCUSSION

**Table 1** In vitro data on antileishmanial activity against L. tropica and L. infantumpromastigotes and cytotoxicity on the human endothelial cell line (HMEC-1) and/ or monkey kidney cell (Vero-76) of benzimidazole derivatives 1 and 6.

| Comp. | $IC_{50}$ (mM)[a] L. Tropica | $IC_{50}$amph. B X100/$IC_{50}$ Compd. | Ratio[c] $IC_{50}$miltef./$IC_{50}$ Compd. | $C_{50}$ (mM)[a] L. infantum | $IC_{50}$amph. B X100/$IC_{50}$compd.[b] | Ratio[c] $IC_{50}$miltef./$IC_{50}$ compd. | SI[c] L. tropica | SI[c] L. infantum |
|---|---|---|---|---|---|---|---|---|
| 2a | 12.61±4.54 | 0.69 | 3.4 | 12.47±3.51 | 0.95 | 2.5 | 1.90 | 1.92 |
| 2b | 34.84±13.52 | 0.25 | 1.4 | 12.78±6.01 | 0.68 | 1.8 | / | / |
| 2c | 3.78±1.19 | 4.7 | 11.4 | 4.71±1.58 | 4.2 | 6.1 | 4.54/>21 | 3.48/>28 |
| 2d | 24.52±0.24 | 0.51 | 1.9 | >52.0 | / | / | >100 | / |
| 2e | 0.19±0.02 | 41.7 | 229.5 | 0.32±0.18 | 22.1 | 94.8 | 4.16/30.9 | 2.32/18.5 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 2f | 0.68* | 11.2 | 51.3 | 0.59±0.02 | 21.8 | 55.2 | 1.31±0.15 | 1.29 |
| Amph B. | 0.112±0.04 | 100 | / | 0.138±0.032f | 100 | / | 229.2 | 189.2 |
| Miltefosine | 42.28±14.28 | 0.25 | 1.0 | 30.22±11.25 | 0.29 | 1.0 | 2.1 | 3.5 |

[a]The results are expressed as IC50±SD of at least three different experiments performed in duplicate or triplicate, with the exception of the starred* values that are the means of two experiments performed in duplicate.
[b]Ratios between the IC50 of amphotericin BX 100 and IC50 of each compound against L. tropica or L. infantum, calculated for each experiment. The IC50 values of amphotericin B ranged from 0.082 to 0.177mM for L. tropica, and from 0.094 to 0.209mM for L. infantum. [c]Ratios between the IC50 of miltefosine and that of each compound against L. tropica or L. infantum.

[e]Selectivity index: IC50 HMEC-1 or Vero76/IC50 for the two species of Leishmania.

For a better insight of the real value of the studied compounds as antileishmanial agents, compounds 3 and 5, representative of the two subsets of benzimidazole derivatives that display the highest activity against the promastigote stage, were tested against the intra macrophagic amastigote stage of L. infantum.

**Antimalarial activity**

**Table 2** In vitro data of synthesized compounds(2a-f) for antimalarial activity

| Sample code | % Dead parasites (rings + trophozites +schizonts | |
|---|---|---|
| | 5µg/ml | 50µg/ml |
| 2a | 19 | 41 |
| 2b | 25 | 34 |
| 2c | 15 | 25 |
| 2d | 30 | 49 |
| 2e | 22 | 37 |
| 2f | 28 | 45 |
| chloroquine | 32 | 52 |

The in vitro antimalarial assay results showed that the representative compounds exhibited antimalarial activity at 50µg/mL.

## CONCLUSION

Benzimidazole derivatives (2a-f) were tested in vitro for activity against promastigotes of L. tropica and L. infantum. A first set was formed by long chain alkyl/benzyl benzimidazoles, whose heterocyclic head was, in most cases, quaternised to mimic the ammonium head of miltefosine and related analogous anti-leishmanial drugs. Therefore, several compounds and particularly the benzimidazoles2c and 2e, whose activity was confirmed on intramacrophagicamastigote stage of L. infantum, represent interesting hit compounds, whose structure can be further variate in order to improve their safety profiles (toxicity/activity ratios). Based on the chemical features of the relevant compounds, their interaction with the acidic components (mainly the phospholipids) of cell membrane, with consequent disruption of its function, may explain the observed anti-leishmanial activity. The internalisation of compounds and their interaction with different targets inside the cell might also have an important role, but its investigation is beyond the aim of the present preliminary study. The in vitro antimalarial assay results showed that the representative compounds exhibited antimalarial activity at 50 mg/mL.The smears when accessed for a number of dead cells, as expected the compounds showed good activity.

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