2019

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Recommended Citation

Dandia, A., Potlia, P., Khan, I., Kumar, V., Verma, V. P., Karnatak, M., & Dhasmana, A. (2019). Diversity-Oriented Synthesis of Novel Benzimidazoles as Antimalarial agents via post Ugi MCR. Chemistry & Biology Interface, 9(4), 9.

Chemistry & Biology Interface, 2019, 9, 4, 216-224

RESEARCH PAPER ISSN: 2249 –4820

CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Diversity-Oriented Synthesis of Novel Benzimidazoles as Antimalarial agents *via post Ugi* MCR

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Received 2019; Accepted 2019

Abstract: An efficient strategy for the syntheses of highly diverse benzimidazoles in exceptional yields via post Ugi reactions has been described. In our methodology we have utilized isocyanide based Ugi-reaction followed by acid catalyzed condensation cyclization reaction under microwave irradiations. All benzimidazole derivatives showed moderate to good antimalarial activity when compared with chloroquine as reference compound. Among these compounds, three of them **(8b), (8c), (8d)** were found to be most potent towards antimalarial activity. The synthesized hybrids were examined for their purity with the help of thin layer chromatography. Different analytical techniques were employed for further characterization like Mass studies, NMRs (^{1}H and ^{13}C) and FT-IR.

Keywords: *Antimalarial*, benzimidazole, chloroquine, synthesized hybrids and post Ugi reactions.

Malaria, a vector born infectious disease, impinges on approximately more than 500 million per annum with deaths of more than a million, mostly in Africa [1]. The bitter truth to find out is that there occurs a death of a child in each 30 seconds due to malaria [2]. Apart

from the morbidity and mortality, malaria imparts a great economic burden on the affected regions [3-4]. The scenario is getting worse with the speedy and wide-spread of multidrug-resistant parasites all over the world. Malaria is distributed chiefly in the warm tropical regions mainly Africa, South-east Asia, Pacific Islands, India, Central and Southern America [5]. The main agent or causative agent of this dreadful malaria is a protozoan parasite of genus *Plasmodium*. Out of 100s so far known species, only four species namely *P. falciparum*, *P. ovale*, *P. vivax,* and *P. malariae* are found to be infective to human beings [6].

Quinine and artemisinin both have worked as an efficient scaffold for the formation of newer valuable antimalarials. In addition researchers have reported novel synthetic compounds with unique scaffolds as antimalarials [7]. This literature review will briefly discuss about history of antimalarial chemotherapy[8]. It also covers structurally simple synthetic analogues of these natural products and novel synthetic compounds with distinctive scaffolds which have influenced or have potential to influence the course of malarial chemotherapy.

Due to development of enormous number of problems associated with the earlier natural alkaloids; like spread of resistance against former drugs, side-effects, haemolysis, toxicity and many more, it was perceived to research more on the synthetic moieties to develop newer, safer, and more effective drugs. After going through the literature of the development of the various antimalarial drugs prevalent so far; one can perceive that different structures possess different biological activities and also with change either in the core moiety, derivative or side chain, there emerges significantly varied characteristics from the parent moiety. Thus various derivations in any synthetic moiety may lead to enhancement in its biological activities.

Also, recent advancements in drug discovery have shown that by combining two or more pharmacophoric active moieties into one hybrid through molecular hybridization approach leads to more potent and progressive hybrid than the parent drug [9]. Amid heterocyclic structures for their exploration in bioactive drugs, the benzimidazole scheme is moderately widespread and is often called as '*privileged*', exhibiting wide range of diverse biological activities depending upon the changing groups or pharmacophoric moieties on the core structure, including anti-cancer, bactericidal, fungicidal, analgesic, anti-viral properties, mainly as antimalarial, cardiovascular potent and as inhibitors of HIV-1 infectivity [10-16]. **(Fig. 2)**

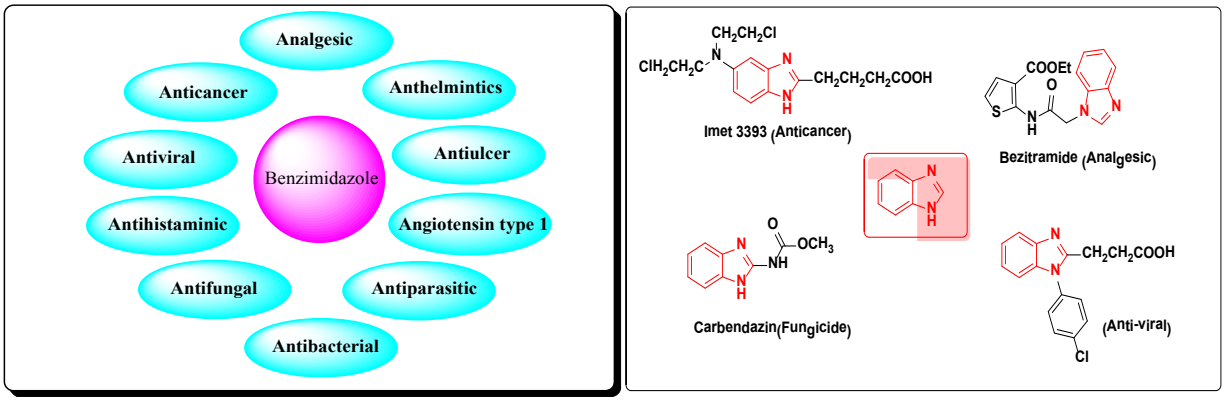


Fig. 2: Potent therapeutic activities of benzimidazole ring in varied fields.

Thus, benzimidazole moiety has been extensively studied as an important nitrogen containing heterocycle [17]; also as a promising drug in the treatment of several diseases including diabetes, infertility, epilepsy, as analgesic, anti-inflammatory, antibacterial, antihistaminic, anti ulcer, AT1 receptor antagonists, antifungal, antiparasitic, anthelmintics, antiviral agent etc. [18-20] **(Fig. 3).**

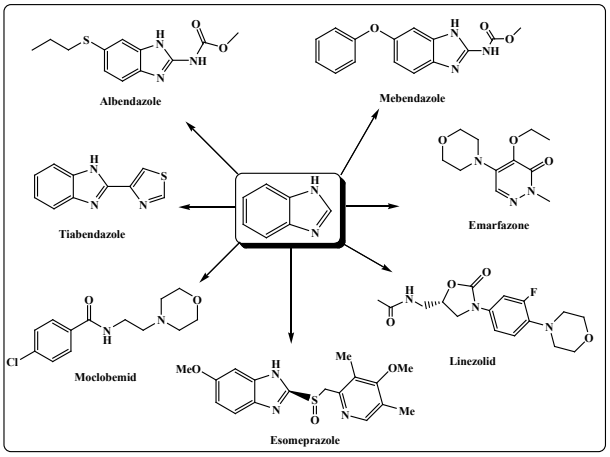


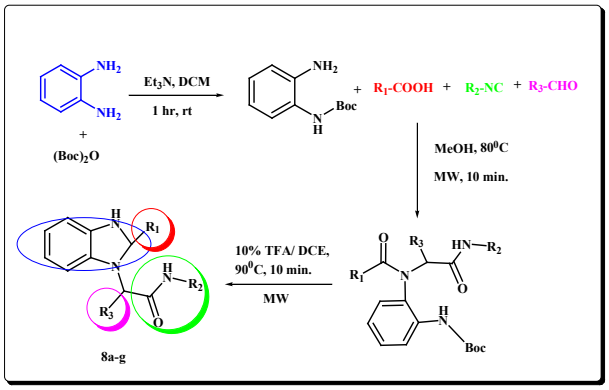
Fig. 3: Some potent clinically important drugs containing benzimidazole as the core moiety.

In persistence of our studies directed towards searching simpler, competent and dexterous synthetic procedures for assimilation of biologically imperative heterocyclic compounds, we have chosen benzimidazoles as the target molecule, subjected to addition of other biologically active pharmacophoric sites to form efficient antimalarial hybrids. They possess unique properties as the moiety shows both acidic and basic characteristics due to NH group which make it a perfect base for salt formation.

Since the chemotherapy against neglected tropical (NTDs) diseases has not developed as yet at a sufficient level, the search for more efficient and protected drugs is still desirable. Attention was focussed on the development of synthesis of substituted benzimidazoles derivatives as they have been extensively employed in the area of pharmaceuticals. These potentialities have led them to be explored more through different synthetic methodologies. A vigilant analysis revealed that most of these methodologies endured serious drawbacks which limit their efficacy and applicability at large scale production.

Recently, multicomponent reactions (MCRs) have been emerged as a powerful tool for the synthesis of biologically important heterocycles [21]. Among these MCRs, the isocyanide based multicomponent reactions have made their way as the most imperative ones [22]. Their significance for library synthesis can be attributed to their fast, efficient time competent one pot synthetic procedure. Among MCRs, most accepted strategy is the Ugi reaction where an isocyanide, amine, acid and aldehyde combine in a one-pot approach to form a hybrid of N-substituted acyl aminoamide [22].

With this strategy in mind, and in continuance of our research attention towards the advancement of new greener approaches for biologically active heterocyclic moiety; we have developed an efficient microwave irradiated, time-competent efficient amalgamation of novel hybrids of biologically vital benzimidazoles, amidic and various aromatic moieties. All the hybrids were screened for their antimalarial activity against the 3D7 *P. falciparum* strain **(Scheme 1).**



Scheme 1: Microwave assisted synthesis of derivatives of benzimidazole including pharmacophoric moieties of boc-protected *o*-phenylenediamine, benzoic acid, benzaldehyde and tert-butyl isocyanide.

Experimental

All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with 200, 300, 400 MHz spectrometers for ^{1}H NMR and 50, 75, 100 MHz for ^{13}C NMR on Bruker Supercon Magnet Avance DRX-300 spectrometers in deuterated solvents with TMS as internal reference (chemical shifts δ in ppm, coupling constant *J* in Hz.). Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broad singlet (br s). Mass spectra and HRMS were taken in the ESI positive ion mode. Microwave reactions were conducted using a Biotage Initiator in 10-mL glass tubes, sealed with Teflon septum and placed in the microwave cavity. The reaction progress was monitored by thin layer chromatography (TLC) on pre-coated silica gel plates. Column chromatography was performed over Merck silica gel (230-400 flash). All compounds were characterized by TLC, ^{1}H NMR and ^{13}C NMR, MS and HRMS.

SPECTRAL STUDIES

The structures of all the compounds **8(a-g)** have been explicated using various analytic studies like mass analysis, both the NMRs of ^{1}H and ^{13}C together with the assistance of IR. Lets take an example of compound **8d** as a reference.

A pale yellow solid was isolated after crystallization whose melting point was calculated as 140-142°C. When it was subjected to IR radiations, it showed important absorptions peaks which denoted particular bond stretching for example absorptions were noted at 3291 (Aliphatic N-H stretching), 2369 (Aromatic C=N stretching), 1653 (C=O stretching), 1457 (Aromatic C=C stretching), 1129 (Aromatic C-C stretching) and 755 cm-1 (Aromatic C-N Stretching).

In ^{1}HNMR spectrum different peaks at particular value signified specific proton couplings. A broad singlet at δ 1.17 ppm denotes nine protons of *tert*-butyl. Further, singlets appeared at δ 3.61 ppm and δ 3.79 ppm representing 9H of OCH_3 group; again a singlet at δ 5.92 ppm may be assigned for NH group present in the moiety. A doublet was also observed at δ 4.38-4.36 ppm for 2H of CH_2; singlet for aliphatic proton was appeared at δ 5.21 ppm. For all the 11 aromatic protons we may assign a multiplet between δ 7.8-6.20 ppm. **(Fig. 2.1)**

In ^{13}C NMR study, different peaks were studied and attributed to different carbon atoms according to the surroundings. An important peak at δ 165.2 verified carbonyl group of amidic unit in the moiety. Peaks at δ 28.4 and 29.6 denote the methyl carbons of CH_3 and OCH_3 while 52.3, 65.2 and 111.9 can be attributed to the CH_2, CH and C respectively. Peaks at δ 120.3, 122.8, 123.3, 124.5, 127.8, 128.8, 129.4, 129.9, 130.1, 130.4, 133.7, 134.5, 134.6, 143.3 and 155.1 confirmed the presence of aromatic carbons. **(Fig. 2.2)** Further, a distinctive peak was also detected at m/z: 488.1 in the mass spectral studies **(Fig. 2.3)**, which additionally confirmed the formation of compound **8d.**

Based on the above spectral studies, the compound **8d** was identified as ***2-(2-benzyl-1H-benzo [d] imidazol-1-yl)-N-tert-butyl-2-(3,4,5-trimethoxyphenyl)acetamide (8d).***

General procedure for the synthesis of imines (8a-8g):

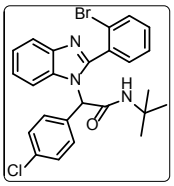
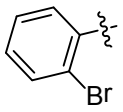
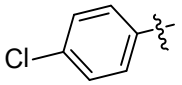
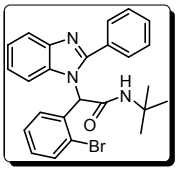
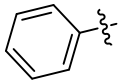
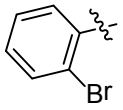
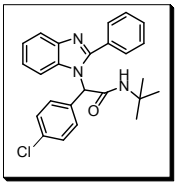
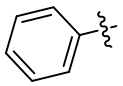
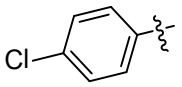
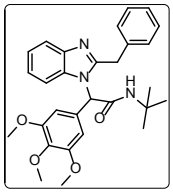
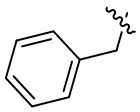
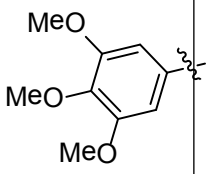
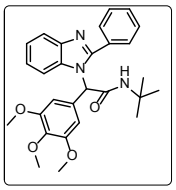
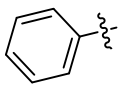
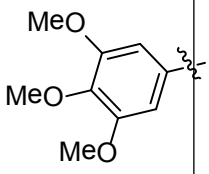
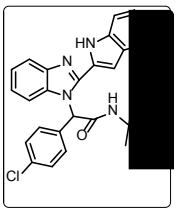
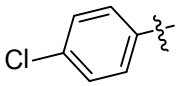
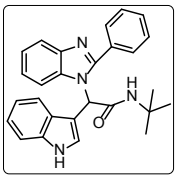
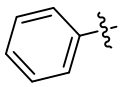
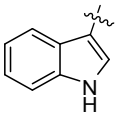
Benzoic acid (1 eq.), benzaldehyde (1 eq.), Boc-protected *o*-phenylenediamine (1 eq.) and *tert*-

butyl isocyanide (1 eq.) were taken in MeOH (2 ml) reacted under microwave conditions (80^0 C, 15 min.). The reaction was verified for completion by the TLC after consecutive period of time, then the solvent was evaporated. Without purification, the intermediate was used under microwave conditions for further deprotection and cyclization in 10% TFA and DCE as estimated by thin layer chromatography. Further progress was done by neutralizing the whole medium by using saturated solution of $NaHCO_3$. Later worked up with water and ethylacetate. Finally, from the reaction mixture, organic layer was separated, remaining mixture was dried over Na_2SO_4 later solvent was evaporated. Finally after crystallization, pure compounds **8(a-g)** were obtained in good yield.

Spectral data of compounds (8a-8g)

1. **2-(2-(2-bromophenyl)-1*H*-benzo[d]imidazol-1-*yl*)-N-*tert*-butyl-2-(4-chlorophenyl) acetamide (8a):** IR (KBr) ν: 3344, 1678, 1452, 1371, 1220, 1092, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.28 (s, 9H, CH_3), 5.66 (s, 1H, CH), 5.92 (s, 1H, NH), 7.88-6.94 (m, 12H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.7, 48.1, 51.6, 108.8, 112.8, 114.6, 117.4, 119.2, 119.4, 134.7, 134.8, 135.0, 143.0, 145.8, 146.3, 148.7, 149.6, 151.8, 151.9, 164.6; MS (ESI) m/z: 498.1 $[M+H]^+$.
2. **2-(2-bromophenyl)-N-*tert*-butyl-2-(2-phenyl-1*H*-benzo[d]imidazol-1yl) acetamide (8b):** IR (KBr) ν: 3278, 1660, 1638, 1565, 1219, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 9H, CH_3), 5.50 (s, 1H, CH), 6.24 (s, 1H, NH), 8.10-7.14 (m, 13H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 60.8, 62.9, 104.8, 112.1, 119.8, 122.4, 122.9, 127.3, 128.4, 129.1, 129.7, 134.1, 136.2, 137.8, 136.2, 137.8, 142.7, 153.2, 153.4, 165.8; MS (ESI) m/z: 462.2 $[M+H]^+$.
3. **N-*tert*-butyl-2-(4-chlorophenyl)-2-(2-phenyl-1*H*-benzo[d]imidazol-1-yl) acetamide (8c):** IR (KBr)ν: 2922, 1679, 1455, 1369, 1220, 1018, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 9H, CH_3), 5.50 (s, 1H, CH), 6.14 (s, 1H, NH), 8.10-7.14 (m, 13H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.3, 62.6, 64.5, 107.9, 113.3, 119.7, 123.5, 124.1, 128.4, 130.2, 130.6, 133.9, 134.3, 136.7, 137.2, 138.8, 141.7, 154.7, 154.9, 166.4; MS (ESI) m/z: 418.2 (100) $[M+1]^+$.
4. **2-(2-benzyl-1*H*-benzo[d]imidazol-1-yl)-N-tert-butyl-2-(3,4,5-trimethoxyphenyl) acetamide (8d):** IR (KBr)ν: 3291, 2369, 1653, 1457, 1129, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (s, 9H, CH_3), 3.61 (s, 6H, OCH_3), 3.79 (s, 3H, OCH_3), 4.38-4.36 (d, 2H, CH_2), 5.21 (s, 1H, CH), 5.92 (s, 1H, NH), 7.8-6.20 (m, 11H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4, 29.6, 52.3, 65.2, 111.9, 120.3, 122.8, 123.3, 124.5, 127.8, 128.8, 129.4, 129.9, 130.1, 130.4, 133.7, 134.5, 134.6, 143.3, 155.1, 165.2; MS (ESI) m/z: 488.1 $[M+H]^+$.
5. **N-tert-butyl-2-(2-phenyl-1H-benzo[d]imidazol-1-yl)-2-(3,4,5-trimethoxyphenyl) acetamide (8e):** IR (KBr)ν: 3408, 1652, 1524, 1380, 1225, 1159, 1058, 786 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 9H, CH_3), 1.46 (s, 9H, OCH_3), 6.09 (s, 1H, CH), 6.38 (s, 1H, NH), 8.55-6.86 (m, 11H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.6, 29.3, 30.5, 72.7, 79.8, 111.4, 117.6, 121.8, 123.6, 123.8, 126.7, 130.4, 130.9, 137.1, 138.5, 140.2, 144.3, 144.7, 148.9, 150.3, 156.6, 157.1, 164.3; MS (ESI) m/z: 558.1 $[M+H]^+$.
6. **2-(2-(1H-indol-2-yl)-1H-benzo[d]imidazol-1-yl)-N-tert-butyl-2-(4-chlorophenyl) acetamide (8f):** IR (KBr) ν: 3426, 2366, 1638, 1220, 772, 673 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (s, 9H, CH_3), 5.58 (s, 1H, CH), 6.74 (s, 1H, NH), 10.84-6.80 (m, 14H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.3, 38.6, 39.2, 62.6, 66.7, 106.2, 119.1, 123.3, 123.6, 129.7, 132.4, 135.7, 136.1, 136.3, 138.5, 139.2,

Table 1: Details of syntheses of derivatives under microwave irradiation.[#]

S.No	Comp.	Hybrid	R_1	R_2	R_3	Time (min.)	Yield*
1	8a					15	75
2	8b					15	87
3	8c					15	82
4	8d					15	88
5	8e					15	82
6	8f					15	78
7	8g					15	85

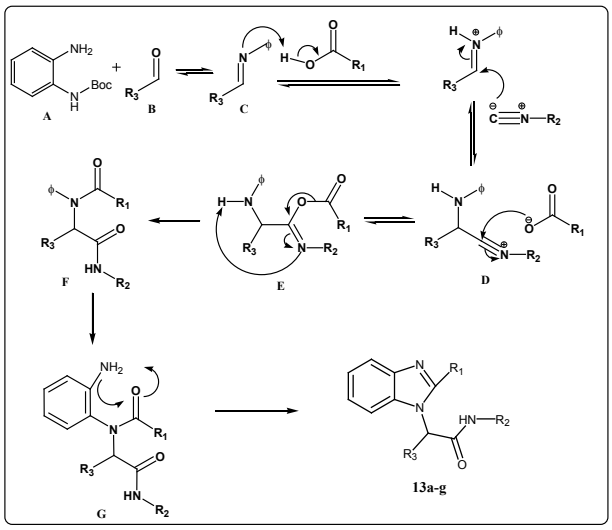
#boc-protected *o*-phenylenediamine, substituted benzoic acid, substituted benzaldehyde and tert-butyl isocyanide under micro wave irradiations.
*Isolated yield.

141.6, 143.7, 143.9, 147.2, 149.8, 154.5, 155.2, 166.1; MS (ESI) m/z: 308 $[M+H]^+$.

7. **N-tert-butyl-2-(1H-indol-3-yl)-2-(2-phenyl-1H-benzo[d]imidazol-1-yl) acetamide (8g):** IR (KBr) ν: 3479, 2932, 1632, 1446, 1220, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.29 (s, 9H, CH_3), 5.58 (s, 1H, CH), 6.74 (s, 1H, NH), 10.84-6.80 (m, 15H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.7, 42.9, 43.2, 61.2, 65.9, 117.3, 118.2, 121.4, 125.6, 128.5, 130.8, 134.7, 138.2, 138.6, 140.1, 142.3, 145.3, 147.7, 147.8, 153.3, 167.3; MS (ESI) m/z: 308 $[M+H]^+$.

Plausible Mechanism:

For further understanding and investigation in the reaction we have gone through the literature survey and found out a plausible mechanism for the reaction (**Scheme 2)**. First of all, reactivity of *o*-phenylenediamine was reduced by protecting one amino group by Boc. The other lewis basic site of *o*-phenylenediamine initiated the electrophilic activation at the aldehydic site which in turn enhances condensation of **A** with **B** to give an imine **C**, which was further activated by the lewis acidic site of acid to make it more electrophilic in nature. The activated imine C was attacked by the nucleophilic isocynide to form a complex **D**, which again combine with the acid to form an intermediate **E** which underwent subsequent intramolecular nucleophilic cyclization reaction from the required hybrids containing benzimidazole moiety.



Scheme 2: Plausible mechanism.

BIOLOGICAL EVALUATION

Antimalarial assay:

For augmenting the biological importance of the hybrids so synthesized, they were examined for their antimalarial activity using MSF assay [23-24]. In this diagnostic assay, activity is tested against CQ-sensitive 3D7 strain. **(Table 2)** Derivatives to be examined were incubated for 72 hrs with insertion of 1% parasitized cell suspension which contained 0.8-1% initial parasitaemia at 37^0C in CO_2 incubator. After prescribed time period, each well plate was injected with SYBR Green-I dye for better differentiation. After an hour of incubation, using Chloroquine (CQ) as standard, plates were observed for excitation at 485±20nm and for emission at 530±20nm. For calculating IC_{50} (i.e the inhibitory concentration where 50% of the parasitemia are suppressed) and SI (Selectivity Index) the procedure prescribed in the literature was followed. For detecting multi-drug-resistance, *P. yoelii nigeriensis* was used as standard to show the deviation in activity against CQ, mefloquine and halofantrine.

Table 2: Antimalarial '*in vitro*' activity of benzimidazole derivatives.

Comp. no.	Antimalarial activity 3D7 IC_{50} (ng/mL)[a]	Selectivity Index (SI)
8a	55.45	429.15
8b	16.69	288.28
8c	32.41	1051.51
8d	11.25	89.6
8e	313.29	57.71
8f	245.0	43.97
8g	39.15	157.9
CQ	2.45+1.03	75.000

[a] (IC_{50}) inhibitory concentration for 50% suppression of the parasitemia.

All benzimidazole derivatives showed moderate to good antimalarial activity when compared with chloroquine as reference compound. Among these compounds (8b), (8c) and (8d) were found to be more potent towards antimalarial activity. By SAR (Structure Activity Relationship) analysis, we may predict that the antimalarial activity is enhanced by the electronegative groups like methoxy, chloro, and bromo. The CH_2 group of the benzyl moiety further boost the reactivity. Thus, we can say that benzimidazole nucleus possess immense potential to be optimized for the generation of novel, secure, and more effecient drugs that can assure the increasing requirement of more potent therapeutic agent.

Conclusions

In summary, a series of novel benzimidazole derivatives was designed, synthesized *via* post Ugi MCR and evaluated as antimalarial activity. The results showed that most of synthesized compounds exhibited moderate to high antimalarial activities against 3D7 cell line.

Acknowledgements

Work was supported by the DST-SERB grant no. DST-YSS/2015/001838 to V.P.V.The authors also acknowledges Department of Chemistry, Banasthali University Newai and SAIF-CDRI for providing spectral and analytical data.

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