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Synthesis and Biological Evaluation of Novel N' (4-aryloxybenzylidene)-*1H*-Benzimidazole-2 Carbohydrazide Derivatives as Anti-Tubercular Agents

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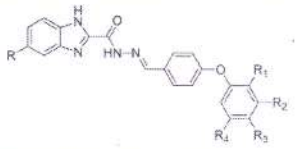
Abstract: A series of structurally novel, (E)-N'-(4-aryloxybenzylidene)-*1H*-benzimidazole-2-carbohydrazide derivatives were synthesized by molecular hybridization technique. All these compounds were evaluated against *Mycobacterium tuberculosis* H37Rv strains using Resazurin Microtiter assay (REMA) method. These compounds showed good antituberculosis activity with minimum inhibitory concentration (MIC) value of the range of 1.5-25 μg/mL.



Keywords: Anti-tubercular, benzimidazole, carbohydrazide esters, triclosan, molecular hybridization.

INTRODUCTION

The complex chronic infectious disease, tuberculosis (T.B), caused by *Mycobacterium tuberculosis* (M.tb) is responsible for suffering of one-third of the world's population and has been declared a global health emergency due to increase in fatality rate all around the world in combination with diseases like HIV/AIDS (1.8 million people died from TB including 5,00,000 HIV infected people) and diabetes [1-2]. Bacteria of TB reside in the macrophages and their unusual cell wall barrier along with multi-drug-resistant tuberculosis (MDR TB) and extensive drug-resistant tuberculosis (XDR TB) makes TB treatment difficult. Also, in low-income and middle -income countries, especially those of sub-Saharan Africa, where tuberculosis is still a leading cause of death because of increased susceptibility conferred by HIV infection, treatment is difficult due to low income group society, the unaffordability of costly drugs, poor adherence and prescribing practices [3-5].

Today, in addition to increasing the knowledge of tuberculosis, more attention needs to be given to basic clinical and operational approaches, thus providing new line diagnostics, treatment and preventive measures, which remains a challenge to employ in the infected population.

Many vaccines, such as BCG (Bacilli Calmette-Guerin) which have been most widely used for the last eight decades as well as other T.B drugs have limitations for their prevention of primary infection, namely toxicity, decreased bioavailability, cost, etc. This has put pressure on scientists to develop a new class of drugs and vaccines [6-9]. TB treatment follows two main approaches; the first one is multi-drug treatment and the other strategy involves attempting to create new and better drugs or vaccines with lesser side effects. As current studies in tuberculosis research are focused on drug development, several new antitubercular agents are believed to be in the pipeline and the standard of care for tuberculosis might soon change in the near future.

CHEMISTRY

The Benzimidazole unit is a well-known heterocyclic pharmacophore and a privileged structure of medicinal chemistry which plays a wide role in biological systems such as an antibacterial [10-13], antitumor [14], antimalarial [15], antitubercular [16-17], anticonvulsant [18], anthelmintic [19-20], analgesic [21], antiulcer [22-23], anti-inflammatory [24-25] and antidiabetic [26], etc. The majority of benzimidazoles e.g. Albendazole (structure shown in Fig. **1**) and their derivatives are mainly used as antifungal and anthelmintic agents. However, in recent years, benzimidazole derivatives have attracted much attention due to their antimicrobial properties. The positive outcome of these molecules opens a new door for the search of novel biologically active molecules in the field of tuberculosis.

On the other hand, the biphenyl ether moiety which has been known since the last three decades, has been found in a number of molecules such as Vancomycin, Dityromycin, Merchantins (structure shown in Fig. **1**), cepharanthine, triclosan, etc., which show antibacterial [27-29], antitubercular [30-32], and antifungal activity [33]. Triclosan shows direct inhibition of ENR involved in mycolic acid biosynthesis, which leads to the lysis of *Mycobacterium tuberculosis* and it is confirmed through pervasive biochemical and structural studies [34-38].

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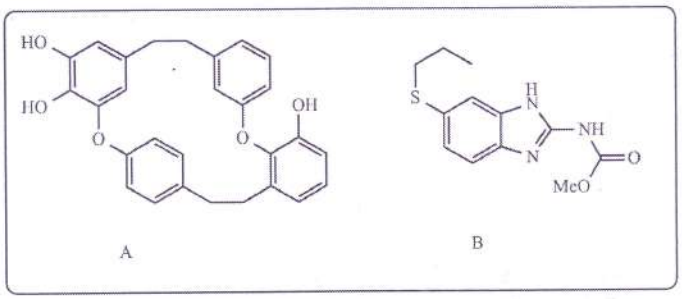


Fig. (1). A- Merchantins; B- Albendazole.

Drug discovery using conventional methods includes step-wise synthesis and screening of a large number of compounds to optimize activity profiles. Over the past two decades, research has involved the use of computer tools for developing models of new chemical entities to help define activity profiles, geometries and reactivities. Being a repetitive process, drug design begins with the identification of a compound having an interesting biological profile by a chemist and ends when both the activity profile and the chemical synthesis of the new chemical entity have been optimized. Molecular hybridization is a recent concept where two pharmacophoric moieties of bioactive substance combine to give hybrid molecules a better efficacy than the parent compound.

A series of novel molecules containing benzimidazol-2-carbohydrazide and 4-(aryloxy) benzaldehydes moiety were designed with the help of suitable tools (i.e. molecular hybridization) and then synthesized by simple condensation method.

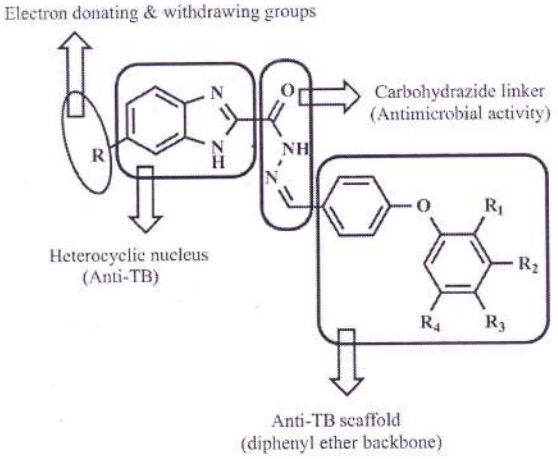


Fig. (2). N'-(4-aryloxybenzylidene)-*1H*-benzimidazole-2-carbohydrazide derivatives.

Earlier, the synthesis and evaluation of a novel series of 2-(2-(4-aryloxybenzylidene)hydrazinyl)benzothiazole derivatives designed by molecular hybridization of common pharmacophores of 2-hydrazinyl benzothiazole derivatives with 4-(aryloxy) benzaldehyde have been reported by our group [32]. As we are continuously working on the synthesis of novel antitubercular molecules, we have further explored our previous method where benzothiazole ring was isosterically replaced by benzimidazole ring. Fig. (2) represents a motive behind the selection and design of N'-(4-aryloxybenzylidene) -*1H*-benzimidazole-2-carbohydrazide derivatives.

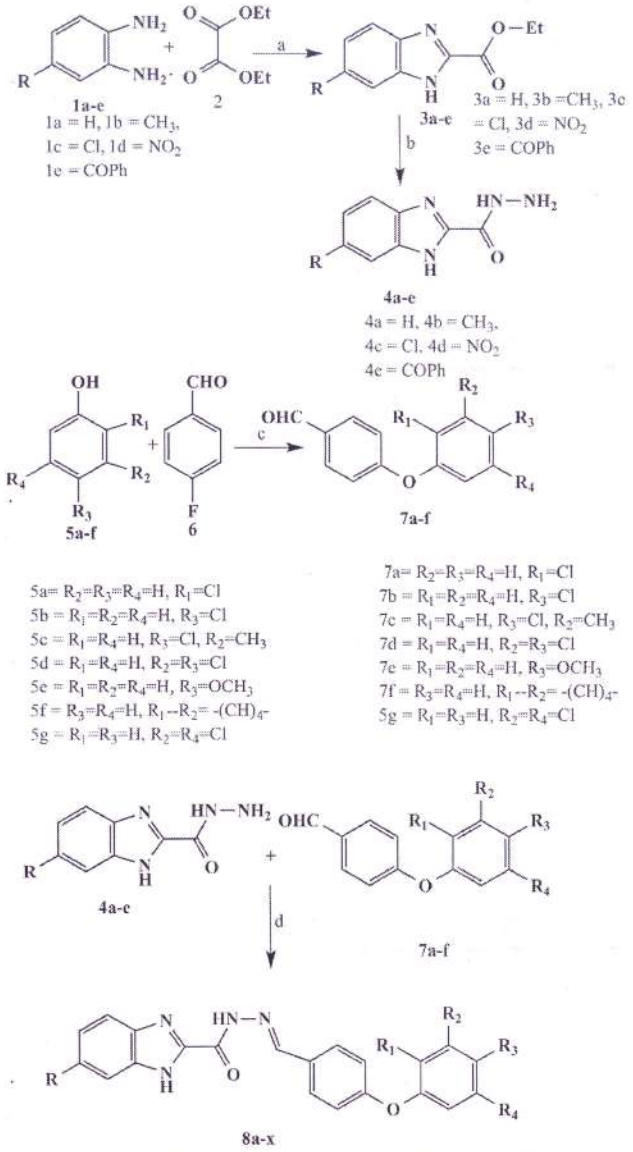
EXPERIMENTAL

Scheme **1** depicts the synthesis of N'-(4-aryloxy-benzylidene)-*1H*-benzimidazole-2-carbohydrazide derivatives **(8a-x)** which were synthesized by a simple condensation reaction of *1H*-benzimidazole-2-carbohydrazide derivatives **(4a-e)** and 4-phenoxybenzaldehyde derivatives **(7a-f)**. Ethyl *1H*-benzimidazole-2-carboxylate derivatives **(3a-e)** were required as starting substrate and *1H*-benzimidazole-2-carbohydrazide derivatives **(4a-e)** and 4-phenoxy-benzaldehyde derivatives **(7a-f)** were synthesized by the respective methods mentioned below. All the synthesized compounds were screened for *Mycobacterium tuberculosis* H37Rv and MIC values were obtained ranging from 1.5 to 25 μg/mL (Table **1**).

General procedure for synthesis of benzimidazole-2-carboxylate derivatives (3a-e) [39]: Substituted 1,2-diamino-benzene (10 mmol) and diethyl oxalate (12 mmol) were stirred in 100 mL of EtOH. The reaction mixture was refluxed for 4h. The reaction was monitored by Thin Layer Chromatography (TLC). After completion of the reaction, the mixture was cooled and diluted with 200mL of ice cold water. A solid organic precipitate was obtained (55-85% yield) which was filtered, dried and used for further synthesis.

Synthesis of benzimidazole-2-carbohydrazide derivatives ((4a-e) from benzimidazole-2-carboxylate derivatives [40]: The starting material **3a** (10 mmol) was taken in 50 mL ethanol and allowed to stir for 10 minutes. A 6 mL mixture of $H_2NNH_2.H_2O$ and HCl (1:1) was prepared at 5 to 10 °C. This mixture was transferred to the RBF containing **3a** at room temperature. The reaction mixture was refluxed for 4h. Progress of the reaction was monitored by TLC and after completion, the reaction mixture was poured on ice water to obtain the crude solid compound. After filtration and drying of the crude material (60-70% yields), it was taken to the next step.

Synthesis of 4-phenoxybenzaldehyde derivatives (7a-f) [41]: A mixture of phenolic compound **5a** (19.35 mmol) and dried K_2CO_3 (58 mmol) was added to 30 mL DMSO solvent. This mixture was stirred for one hour at room temperature. 4-



Reagent and reaction conditions: a) EtOH, reflux, 6h b) $H_2NNH_2.H_2O$: HCl (1:1), Ethylene glycol, reflux, 4h c) K_2CO_3, DMSO, 90 °C, 16h d) EtOH, Acetic acid, reflux, 3h

Scheme 1. Synthesis of N'-(4-aryloxybenzylidene)-*1H*-benzimidazole-2-carbohydrazide derivatives (scaffold 1).

Fluorobenzaldehyde **6** (16.13 mmol) was added to the above stirred solution and the reaction mixture was heated at 90 °C for 16h. After completion of the reaction, the mixture was poured on crushed ice and extracted with ethyl acetate (50 mL × 3 times). The organic layer was dried over sodium sulphate and then evaporated to get crude product. The pure product was obtained as a pale yellow solid (65-75% yields) by silica gel column chromatography using hexane as solvent.

General procedure for the synthesis of N'-(4-phenoxybenzylidene)-*1H*-benzimidazole-2-carbohydrazide derivatives (8a-x) [42]: Benzimidazole-2-carbohydrazide derivative (0.57 mmol) was added to 10 mL 2 necked round bottom flask containing 4-phenoxybenzaldehyde derivatives (0.51 mmol) and 0.5 mL acetic acid. The reaction mixture was stirred for 1-3 h at 80 °C. Progress of the reaction was monitored by TLC. After completion of the reaction, a precipitate was formed which was cooled and filtered to give the desired product in 80-90% yields.

BIOLOGICAL RESULTS AND DISCUSSION

The synthesized compounds (**8a-x**) were screened against *M. tuberculosis* H37Rv in order to determine the MIC values with the REMA method by using isoniazid as the reference

drug. In this method, homogenous mycobacterial (H37Rv) culture suspension was seeded in microtitre plates at a density of 10^5 cells per well containing 100 µL of the Middlebrook 7H9 broth (Difco laboratories, Detroit, MI, USA) and the test compounds were serially diluted directly on the plate. The control received an equivalent amount of DMSO. The plates were covered, sealed in a plastic bag and incubated at 37 °C for 7 days. To avoid evaporation during the incubation, sterile water was added to the perimeter wells. Freshly prepared Resazurin dye (0.02%) was added and plates were again incubated for 48 h. A change in colour from blue to pink indicated the growth of bacteria, and the MIC was defined as the lowest concentration of drug that prevented this change in colour (Table **1**) [32, 43-44].

Previously, the active benzothiazole derivatives **10i** with 2,4-dichlorobiphenyl ether moiety having antitubercular activity of 1.5 µg/mL have been reported by us [32]. We reported benzothiazole derivatives **10v** with pyridin-4-yl moiety with antitubercular activity of 1.35 µg/mL [45]. Based on these findings, we predict that the hybrid of 2,4-dichlorobiphenyl ether moiety with benzimidazole may give good antitubercular activity. However, benzimidazole derivative **8j** with 2,4-dichlorobiphenyl ether moiety showed activity at a concentration of 3.125 µg/mL. Among the currently synthesized benzimidazole derivatives, the compound with 3-methyl-4-chlorobiphenyl ether moiety **8k** & **8p** showed activity at a concentration of 1.5 µg/mL.

The results of antitubercular activity are summarized in Table **1**, which showed that compounds (**8b-c**, **8h-k**, **8n** and **8p**) possessed excellent activity (1.5-3.125 µg/mL) against *Mycobacterium tuberculosis* H37Rv strains except compounds **8e** and **8s**. Compounds **8f**, **8o**, **8r** and **8t-x** displayed moderate to weak activity (6.25-12.5 µg/mL). Compounds **8k** and **8p** having electron releasing (methyl) and electron withdrawing (chloro) substituent on diphenyl ether moiety exhibited better activity (1.5 µg/mL), whereas other compounds showed good activity (3.125-12.5 µg/mL) except compounds **8e** and **8s**. It has been observed that *para* chloro substitution on the diphenyl ring

Table 1. Antitubercular activities of synthesized N'-(4-aryloxybenzylidene)-*1H*-benzimidazole-2-carbohydrazide derivatives.

Comp.	R	R_1	R_2	R_3	R_4	[a]MIC (µg/mL)
8a	H	Cl	H	H	H	6.25
8b	H	H	H	Cl	H	3.125
8c	H	H	Me	Cl	H	3.125
8d	H	Cl	H	Cl	H	12.5
8e	H	H	Cl	H	Cl	25
8f	H	H	H	MeO	H	6.25
8g	H	Naphthyl group				12.5
8h	Me	Cl	H	H	H	3.125
8i	Me	H	H	Cl	H	3.125
8j	Me	Cl	H	Cl	H	3.125
8k	Me	H	Me	Cl	H	1.5
8l	Me	H	Cl	H	Cl	12.5
8m	Me	Naphthyl group				12.5
8n	NO_2	H	H	Cl	H	1.75
8o	NO_2	Cl	H	Cl	H	6.25
8p	NO_2	H	Me	Cl	H	1.5
8q	NO_2	H	Cl	H	Cl	12.5
8r	NO_2	H	H	MeO	H	6.25
8s	NO_2	Naphthyl group				25
8t	Cl	H	Cl	H	Cl	12.5
8u	Cl	H	H	MeO	H	12.5
8v	Cl	Naphthyl group				12.5
8w	COPh	H	H	Cl	H	12.5
8x	COPh	Cl	H	Cl	H	12.5
[b]Isoniazid						0.40
[b]Triclosan						5.00

[a]MIC= minimum inhibitory concentration.
[b]Isoniazid & Triclosan used as a standard.

has a strong influence on the spectrum and extent of antitubercular activity than *ortho* substitution. Introduction of electron donating (methyl) and electron withdrawing (nitro) groups at C-6 position of the benzimidazole nucleus (**8k** and **8p**) had a detrimental effect on the inhibitory activity compared to **8a-e**. Further, bicyclic aromatic ring (naphthalene) system was incorporated as in **8g**, **8m**, **8s** and **8v** in the diphenyl ring. All the compounds (**8g**, **8m**, **8s** and **8v**) containing bicyclic aromatic ring in the diphenyl ether moiety showed lower activity as compared to the monocyclic aromatic ring.

The encouraging results from the antitubercular studies impelled us to go for preliminary screening of synthesized molecules against *Mycobacterium tuberculosis*. Due to better activity against tested microorganism, compounds **8k** and **8p** were selected for further development and studies to acquire more reliable information about structure-activity relationship have currently been undertaken. Thus, these compounds act as a good potential lead for further development of new antitubercular drugs.

Replacement of sulphur atom in the benzothiazole ring by -NH (isostere of sulphur atom) and insertion of carbonyl group in the final designed molecule may be responsible for enhanced activity as compared to our previously designed molecule [32]. On the other hand, the antitubercular activity was previously explored in our laboratory for 4-(aryloxy) benzaldehydes derivatives and their MIC values for the compound **7a** was 123.44 µg/mL and for compound **7b** it was 117.19 µg/mL [32] which were compared with the final designed molecule. The molecular hybrids **8k** & **8p** had significantly enhanced activity as compared to 4-(aryloxy)benzaldehyde (MIC: 117.19 µg/mL) and triclosan (MIC: 5.00 µg/mL).

Analytical study involved Melting point (M.P.) determination, Spectral analysis by IR, ^{1}H NMR, M.S and elemental analysis of all synthesized compounds (**8a-x**). IR (KBr) spectrum of all the synthesized compounds had sharp N=C, C=O and C-O absorption at 1570-1620 cm^{-1}, 1665-1685 cm^{-1} and 1240-1265 cm^{-1}, which were assigned to -

Table 2. QikProp analysis data of synthesized N'-(4-aryloxybenzylidene)-*1H*-benzimidazole-2-carbohydrazide derivatives.

Title	#Stars[a]	QPlogPo/w[b]	QPPCaco[c]	%Human Oral Absorption[d]	No of Variation from Rule of Five[e]
8a	2	4.693	781.498	100	0
8b	3	4.827	781.556	100	0
8c	2	5.075	781.541	95.482	1
8d	3	5.185	781.505	96.126	1
8e	3	5.317	781.582	96.896	1
8f	1	4.439	781.548	100	0
8g	3	5.164	781.454	96.002	1
8h	2	5	779.383	95.021	1
8i	1	5.136	781.867	95.841	1
8j	1	5.495	781.819	100	1
8k	1	5.385	781.862	100	1
8l	1	5.626	781.9	100	1
8m	2	5.474	781.761	100	1
8n	2	4.13	95.347	86.554	0
8o	2	4.487	95.345	88.641	0
8p	2	4.389	93.677	87.932	0
8q	2	4.618	95.351	89.41	0
8r	1	3.738	95.344	84.258	0
8s	2	4.478	93.668	88.451	0
8t	3	5.81	781.623	100	1
8u	1	4.929	781.578	100	0
8v	3	5.657	781.48	100	1
8w	5	5.696	307.65	91.868	1
8x	5	6.054	307.609	81.005	2

[a]#Stars: #stars are MW, dipole, IP, EA, SASA, FOSA, FISA, PISA, WPSA, PSA, volume, donorHB, acceptHB, QPlogPoct, QPlogPw, QPlogPo/w, logS, QPLogKhsa, QPlogBB. The range predicted for this parameter using QikProp is 0-5; where 0-1 indicates no violation or best candidate.

[b]QPlogPo/w: This gives the predicted octanol/water partition coefficient. The range predicted for this parameter using QikProp is - 2.0-6.5.

[c]QPPCaco: QikProp predictions are for nonactive transport, where <25 is considered poor and >500 is considered excellent.

[d]% Human-Oral Absorption: This gives the predicted human oral absorption on 0-100% scale where >80% is considered high and <25% is considered.

[e]No of variation from rule of five: This property denotes the number of violations of Lipinski's rule of five.

C(O)-NHN=C-, -C(O)-NHN= and Ar(C)-O-(C)Ar stretching respectively. The ^{1}H NMR spectrum exhibited singlets at 8-9 ppm, which were assigned to azomethine -N=CH-. The Mass spectrum showed M+1. All the above spectral data are in agreement with the synthesized compounds.

From the QikProp analysis of designed molecules, it was observed that the designed molecules exhibited good drug likeness (Table **2**). Most of the molecules exhibited physicochemical properties which fall in the range of known drugs as evident from # stars for compounds being 1 or 2 [46]. Also, the molecules did not contain any known toxicophores or reactive functional groups. The partition coefficient calculated by QPlogPo/w were within the range of 3.5-6.1. It was observed that most of the designed molecules exhibited QPPCaco within acceptable limits (**8a-m** and **8t-v** exhibited excellent value of QPPCaco). Human oral absorption of majority of compounds was >80, which is considered to be good. Most of the designed molecules also satisfied the Lipinski's rule of five.

CONCLUSION

In continuation of our previous work on the synthesis of a series of novel, 2-(2-(4-aryloxybenzylidene) hydrazinyl)benzothiazole derivatives, a novel series of N'-(4-aryloxybenzylidene)-*1H*-benzimidazole-2-carbohydrazide derivatives were successfully synthesized by molecular hybridization technique and evaluated against *Mycobacterium tuberculosis* H37Rv strains. Experimental studies demonstrated that the newly synthesized compounds can act as promising leads for the development of novel antimycobacterial agents.

APPENDIX

Supplementary Data for Compound (8a-x)

1. **(E)-N'-(4-(2-chlorophenoxy)benzylidene)-1H-benzo[d] imidazole-2-carbohydrazide (8a):** Buff white solid; 238-240 °C; yield 78%; IR (KBr): 3451, 3191, 3076, 2951, 1619, 1578, 1503, 1442, 1260, 1123, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.73 (s, 1H, -N=CH-Ar), 7.92-7.09 (m, 12H, Ar-H); LC-MS : 392 $[M+1]^+$; Elemental Analysis for $C_{21}H_{15}ClN_4O_2$ (390.82): C, 64.54; H, 3.87; N, 14.34 found: C, 64.04; H, 3.62; N, 13.87.

2. **(E)-N'-(4-(4-chlorophenoxy)benzylidene)-1H-benzo[d] imidazole-2-carbohydrazide (8b):** Buff white solid; 224-226 °C; yield 76% ; IR (KBr): 3422, 3182, 3066, 2951, 1615, 1575, 1503, 1482, 1236, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.71 (s, 1H, -N=CH-Ar), 7.95-7.06 (m, 12H, Ar-H); LC-MS: 391.89 $[M+1]^+$; Elemental Analysis for $C_{21}H_{15}ClN_4O_2$ (390.82) : C, 64.54; H, 3.87; N, 14.34 found: C, 64.14; H, 3.57; N, 14.01.

3. **(E)-N'-(4-(4-chloro-3-methylphenoxy)benzylidene)-1H-benzo[d]imidazole-2-carbohydrazide (8c):** Buff white solid; 232-234 °C; yield 68 %; IR (KBr): 3413, 3172, 3076, 2883, 1629, 1595, 1490, 1445, 1267, 1128, 623cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ (ppm) 8.54 (s,1H,-N=CH-Ar), 7.88-6.92 (m, 11H, Ar-H), 2.41(s, 3H, - CH_3); LC-MS : 405.84 $[M+1]^+$; Elemental Analysis for $C_{22}H_{17}ClN_4O_2$ (404.85): C, 65.27; H, 4.23; N, 13.84 found: C, 65.04; H, 3.95; N, 13.42.

4. **(E)-N'-(4-(2,4-dichlorophenoxy)benzylidene)-1H-benzo[d]imidazole-2-carbohydrazide (8d):** Buff white solid; 235-237 °C; yield 72% ; IR (KBr): 3422, 3182, 3066, 2951, 1625, 1575, 1503, 1482, 1236, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.68 (s,1H, -N=CH-Ar), 7.95-7.06 (m, 11H, Ar-H); LC-MS: 426.2 $[M+1]^+$; Elemental Analysis for $C_{21}H_{14}Cl_2N_4O_2$ (425.27): C, 59.31; H, 3.32; N, 13.17 found: C, 58.91; H, 3.02; N, 12.94.

5. **(E)-N'-(4-(3,5-dichlorophenoxy)benzylidene)-1H-benzo[d]imidazole-2-carbohydrazide (8e):** Buff white solid; 234-236 °C; yield 69 %; IR (KBr): 3441, 3134, 3047, 2941, 2854, 1611, 1560, 1502, 1448, 1251, 1127, 743cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (s, 1H, -N=CH-Ar), (ppm) 8.02-6.89 (m, 11H, Ar-H); LC-MS: 425.8 $[M+1]^+$; Elemental Analysis for $C_{21}H_{14}Cl_2N_4O_2$ (425.27): C, 59.31; H, 3.32; N, 13.17 found: C, 58.91; H, 3.02; N, 13.10.

6. **(E)-N'-(4-(4-methoxyphenoxy)benzylidene)-1H-benzo[d]imidazole-2-carbohydrazide (8f):** Buff white solid; 222-224 °C; yield 80 %; IR (KBr): 3432, 3193, 3085, 2989, 1627, 1587, 1465, 1364, 1250, 1127cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.64 (s, 1H, -N=CH-Ar), 7.98-7.08 (m,12H, Ar-H), 3.84 (s,3H, -OCH_3); LC-MS: 386.4 $[M+1]^+$; Elemental Analysis for $C_{22}H_{18}N_4O_3$ (386.40): C, 68.38; H, 4.70; N, 14.50 found: C, 68.13; H, 4.35; N, 14.10.

7. **(E)-N'-(4-(naphthalen-1-yloxy)benzylidene)-1H-benzo[d]imidazole-2-carbohydrazide (8g):** Buff white solid; 221-223 °C; yield 66% ; IR (KBr): 3442, 3182, 3067, 2955, 1620, 1565, 1490, 1434, 1280, 1128, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.46 (s,1H, -N=CH-Ar), 8.25-7.26 (m, 15H, Ar-H); LC-MS: 407.2 $[M+1]^+$; Elemental Analysis for $C_{25}H_{18}N_4O_2$ (406.66): C, 73.88; H, 4.46; N, 13.78 found: C, 73.35; H, 4.22; N, 13.47.

8. **(E)-N'-(4-(2-chlorophenoxy)benzylidene)-6-methyl-1H-benzo[d]imidazole-2-carbohydrazide (8h):** Buff white solid; 227-229 °C; yield 78%; IR (KBr): 3451, 3191, 3076, 2951, 1618, 1578, 1503, 1442, 1260, 1123, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.73 (s, 1H, -N=CH-Ar), 7.92-7.09 (m, 11H, Ar-H), 2.43 (s, 3H, - CH_3); LC-MS: 406 $[M+1]^+$; Elemental Analysis for $C_{22}H_{17}ClN_4O_2$ (404.85): C, 65.27; H, 4.23; N, 13.84 found: C, 65.07; H, 4.12; N, 13.77.

9. **(E)-N'-(4-(4-chlorophenoxy)benzylidene)-6-methyl-1H-benzo[d]imidazole-2-carbohydrazide (8i):** Buff white solid; 234-236 °C; yield 70% ; IR (KBr): 3422, 3182, 3066, 2951, 1621, 1575, 1503, 1482, 1236, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.72 (s,1H, -N=CH-Ar), 7.95-7.06 (m, 11H, Ar-H), 2.43 (s, 3H, - CH_3); LC-MS: 406 $[M+1]^+$; Elemental Analysis for $C_{22}H_{17}ClN_4O_2$ (404.85): C, 65.27; H, 4.23; N, 13.84 found: C, 65.12; H, 4.03; N, 13.63.

10. **(E)-N'-(4-(2,4-dichlorophenoxy)benzylidene)-6-methyl-1H-benzo[d]imidazole-2-carbohydrazide (8j):** Buff

white solid; 229-231 °C; yield 70 %; IR (KBr): 3441, 3210, 3085, 2970, 1625, 1585, 1506, 1460, 1261, 1133, 711cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ (ppm) 8.70 (s, 1H, -N=CH-Ar), 7.94-7.04 (m, 10H, Ar-H), 2.43 (s, 3H, - CH_3); LC-MS: 439 $[M+1]^+$; Elemental Analysis for $C_{22}H_{16}Cl_2N_4O_2$ (439.29): C, 60.15; H, 3.67; N, 12.75 found: C, 59.85; H, 3.51; N, 12.67.

11. **(E)-N'-(4-(4-chloro-3-methylphenoxy)benzylidene)-6-methyl-1H-benzo[d]imidazole-2-carbohydrazide (8k):** Buff white solid; 236-238 °C; yield 68 %; IR (KBr): 3413, 3172, 3076, 2883, 1616, 1595, 1490, 1445, 1267, 1128, 623cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ (ppm) 8.54 (s,1H,-N=CH-Ar), 7.88-6.92 (m,10H, Ar-H), 2.41(s, 6H, - CH_3 at benzimidazole ring & -CH_3 at phenoxy ring); LC-MS: 419 $[M+1]^+$; Elemental Analysis for $C_{23}H_{19}ClN_4O_2$ (418.88): C, 65.95; H, 4.57; N, 13.38 found: C, 65.89; H, 4.38; N, 13.22.

12. **(E)-N'-(4-(3,5-dichlorophenoxy)benzylidene)-6-methyl-1H-benzo[d]imidazole-2-carbohydrazide (8l):** Buff white solid; 218-220 °C; yield 67 %; IR (KBr): 3441, 3210, 3085, 2970, 1625, 1585, 1506, 1460, 1261, 1133, 711cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ (ppm) 8.62 (s,1H, -N=CH-Ar), 7.98-7.02 (m, 10H, Ar-H), 2.43 (s, 3H, - CH_3); LC-MS: 439.8 $[M+2]^+$; Elemental Analysis for $C_{22}H_{16}Cl_2N_4O_2$ (439.29): C, 60.15; H, 3.67; N, 12.75 found: C, 60.10; H, 3.57; N, 12.63.

13. **(E)-6-methyl-N'-(4-(naphthalen-1-yloxy)benzylidene)-1H-benzo[d]imidazole-2-carbohydrazide (8m):** Buff white solid; 220-222 °C; yield 70% ; IR (KBr): 3438, 3192, 3056, 2906, 1612, 1575, 1503, 1482, 1359, 1236, 1118, 1054, 995, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.56 (s,1H, -N=CH-Ar), 8.34-7.16 (m, 14H, Ar-H), 2.38 (s, 3H, - CH_3); LC-MS: 421.3 $[M+1]^+$; Elemental Analysis for $C_{26}H_{20}N_4O_2$ (420.46): C, 74.27; H, 4.79; N, 13.33 found: C, 74.12; H, 4.63; N, 13.13.

14. **(E)-N'-(4-(4-chlorophenoxy)benzylidene)-6-nitro-1H-benzo[d]imidazole-2-carbohydrazide (8n):** Buff white solid; 251-253 °C; yield 74 %; IR (KBr): 3422, 3170, 3076, 2960, 1619, 1569, 1505, 1483, 1437, 1325, 1238, 1123, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.65 (s, 1H, -N=CH-Ar), 8.38(S, 1H, O_2N-C-CH-C-), 8.04(d, *J*=8.9 Hz, 1H, O_2N-C-CH-CH-), 7.65(d, *J*=8.9 Hz, 1H, O_2N-C-CH-CH-), 8.02-7.05 (m, 8H, Ar-H); LC-MS: 437 $[M+1]^+$; Elemental Analysis for $C_{21}H_{14}ClN_5O_4$ (435.82): C, 57.87; H, 3.24; N, 16.07 found: C, 57.68; H, 3.16; N, 15.79.

15. **(E)-N'-(4-(2,4-dichlorophenoxy)benzylidene)-6-nitro-1H-benzo[d]imidazole-2-carbohydrazide (8o):** Yellow solid; 247-249 °C; Yield 74 %; IR (KBr): 3422, 3170, 3076, 2960, 1622, 1569, 1505, 1483, 1437, 1325, 1238, 1123, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.62 (s, 1H, -N=CH-Ar), 8.38(s, 1H, O_2N-C-CH-C-), 8.04(d, *J*=8.9 Hz, 1H, O_2N-C-CH-CH-), 7.65(d, *J*=8.9 Hz, 1H, O_2N-C-CH-CH-), 8.02-7.06 (m, 7H, Ar-H); LC-MS: 471 $[M+1]^+$; Elemental Analysis for $C_{21}H_{13}Cl_2N_5O_4$ (470.27): C, 53.63; H, 2.79; N, 14.89 found: C, 53.52; H, 2.63; N, 14.75.

16. **(E)-N'-(4-(4-chloro-3-methylphenoxy)benzylidene)-6-nitro-1H-benzo[d]imidazole-2-carbohydrazide (8p):** Yellow solid; 250-252 °C; Yield 74 %; IR (KBr): 3422, 3170, 3076, 2960, 1623, 1569, 1505, 1483, 1437, 1325, 1238, 1123, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.62 (s, 1H, -N=CH-Ar), 8.38(s, 1H, O_2N-C-CH-C-), 8.04(d, *J*=8.9 Hz, 1H, O_2N-C-CH-CH-), 7.65(d, *J*=8.9 Hz, 1H, O_2N-C-CH-CH-), 8.02-7.09 (m, 7H, Ar-H), 2.41(s, 3H, - CH_3); LC-MS: 451 $[M+1]^+$; Elemental Analysis for $C_{22}H_{16}ClN_5O_4$ (449.85): C, 58.74; H, 3.59; N, 15.57 found: C, 58.63; H, 3.51; N, 15.49.

17. **(E)-N'-(4-(3,5-dichlorophenoxy)benzylidene)-6-nitro-1H-benzo[d]imidazole-2-carbohydrazide (8q):** Yellow solid; 254-256 °C; Yield 60 %; IR (KBr): 3422, 3170, 3076, 2960, 1619, 1569, 1505, 1483, 1437, 1325, 1238, 1123, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.64 (s, 1H, -N=CH-Ar), 8.42 (s, 1H, O_2N-C-CH-C-), 8.12 (d, *J*=8.9 Hz, 1H, O_2N-C-CH-CH-), 7.61 (d, *J*=8.9 Hz, 1H, O_2N-C-CH-CH-), 8.02-7.11 (m, 7H, Ar-H); LC-MS: 471 $[M+2]^+$; Elemental Analysis for $C_{21}H_{13}Cl_2N_5O_4$ (470.27): C, 53.63; H, 2.79; N, 14.89 found: C, 53.57; H, 2.68; N, 14.81.

18. **(E)-N'-(4-(4-methoxyphenoxy)benzylidene)-6-nitro-1H-benzo[d]imidazole-2-carbohydrazide (8r):** Yellow solid; 258-260 °C; Yield 74 %; IR (KBr): 3422, 3170, 3076, 2960, 1619, 1569, 1505, 1483, 1437, 1325, 1238, 1123, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.64 (s, 1H, -N=CH-Ar), 8.41 (s, 1H, O_2N-C-CH-C-),8.13 (d, *J*=8.8 Hz, 1H, O_2N-C-CH-CH-), 7.61 (d, *J*=8.8 Hz, 1H, O_2N-C-CH-CH-), 7.98-7.08 (m, 8H, Ar-H), 3.84 (s, 3H, -OCH_3); LC-MS: 432 $[M+1]^+$; Elemental Analysis for $C_{22}H_{17}N_5O_5$ (431.40): C, 61.25; H, 3.97; N, 16.23 found: C, 61.15; H, 3.91; N, 16.03.

19. **(E)-N'-(4-(naphthalen-1-yloxy)benzylidene)-6-nitro-1H-benzo[d]imidazole-2-carbohydrazide (8s):** Yellow solid; 255-257 °C; Yield 60 %; IR (KBr): 3422, 3170, 3076, 2960, 1619, 1569, 1505, 1483, 1437, 1325, 1238, 1123, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.64 (s, 1H, -N=CH-Ar), 8.42 (s, 1H, O_2N-C-CH-C-), 8.13 (d, *J*=8.9 Hz 1H, O_2N-C-CH-CH-), 7.62 (d, *J*=8.9 Hz, 1H, O_2N-C-CH-CH-), 8.26-7.19 (m, 11H, Ar-H); LC-MS: 451.23 $[M+1]^+$; Elemental Analysis for $C_{25}H_{17}N_5O_4$ (451.53): C, 66.51; H, 3.80; N, 15.51; found: C, 66.38; H, 3.69; N, 15.47.

20. **(E)-6-chloro-N'-(4-(3,5-dichlorophenoxy)benzylidene)-1H-benzo[d]imidazole-2-carbohydrazide (8t):** Buff white solid; 231-233 °C; yield 77 %; IR (KBr): 3413, 3191, 3076, 2960, 1626, 1571, 1503, 1470, 1445, 1257, 1133, 762cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.61 (s, 1H, -N=CH-Ar), 8.45-7.08 (m, 10H, Ar-H); LC-MS: 460 $[M+1]^+$; Elemental Analysis for $C_{21}H_{13}Cl_3N_4O_2$ (459.71): C, 54.87; H, 2.85; N, 12.19 found: C, 54.80; H, 2.75; N, 12.11.

21. **(E)-6-chloro-N'-(4-(4-methoxyphenoxy)benzylidene)-1H-benzo[d]imidazole-2-carbohydrazide (8u):** Buff white solid; 235-237 °C; yield 66% ; IR (KBr): 3436, 3046, 2955, 1620, 1565, 1490, 1434, 1280, 1128, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.64 (s,1H, -N=CH-Ar), 8.36-7.20 (m, 11H, Ar-H), 3.84 (s, 3H, -OCH_3) ; LC-MS: 422 $[M+2]^+$; Elemental Analysis for $C_{22}H_{17}ClN_4O_3$ (420.85): C, 62.79; H, 4.07; N, 13.31 found: C, 62.68; H, 4.01; N, 13.28.

22. **(E)-6-chloro-N'-(4-(naphthalen-1-yloxy)benzylidene)-1H-benzo[d]imidazole-2-carbohydrazide (8v):** Buff white solid; 221-223° °C; yield 66% ;.IR (KBr): 3436, 3047, 2955, 1620, 1565, 1490, 1434, 1280, 1128, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.64 (s,1H, -N=CH-Ar), 8.36-7.20 (m, 14H, Ar-H); LC-MS: 442 $[M+2]^+$; Elemental Analysis for $C_{25}H_{17}ClN_4O_2$ (440.88): C, 68.11; H, 3.89; N, 12.71 found: C, 68.01; H, 3.84; N, 12.66.

23. **(E)-6-benzoyl-N'-(4-(4-chlorophenoxy)benzylidene)-1H-benzo[d]imidazole-2-carbohydrazide (8w):** Buff white solid; 241-243 °C; yield 62% ; IR (KBr): 3422, 3182, 3066, 2951, 1615, 1575, 1503, 1482, 1236, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.58 (s,1H, -N=CH-Ar), 7.98-7.08 (m, 16H, Ar-H); LC-MS: 496 $[M+2]^+$; Elemental Analysis for $C_{28}H_{19}ClN_4O_3$ (494.93): C, 67.95; H, 3.87; N, 11.32 found: C, 67.88; H, 3.81; N, 11.22.

24. **(E)-6-benzoyl-N'-(4-(2,4-dichlorophenoxy)benzylidene) -1H-benzo[d]imidazole-2-carbohydrazide (8x):** Buff white solid; 244-246 °C; yield 65% ; IR (KBr): 3441, 3220, 3047, 2937, 1683, 1606, 1571, 1505, 1472, 1390, 1263, 1161, 1097, 828 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.58 (s,1H, -N=CH-Ar), 7.98-7.02 (m, 15H, Ar-H); LC-MS: 530 $[M+2]^+$; Elemental Analysis for $C_{28}H_{18}Cl_2N_4O_3$ (529.37): C, 63.53; H, 3.43; N, 10.58; found: C, 63.47; H, 3.37; N, 10.41.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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