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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Antimicrobial screening of novel synthesized benzimidazole nucleus containing 4-oxo-thiazolidine derivatives

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Abstract As a part of systematic investigation of synthesis, characterization and antimicrobial screening of some novel 3-(2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(aryl)thiazolidin-4-ones (**3a–l**), have been synthesized from Schiff bases of *N*-arylidene-2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)anilines, (**2a–l**). The Schiff bases (**2a–l**) were prepared by condensation of different aldehydes with 2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)aniline (**1**). The compound (**1**) was obtained from 2-amino benzoic acid and 4-methylbenzene-1,2-diamine. All the synthesized compounds were screened for in vitro antibacterial and antifungal activities on *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Staphylococcus pyogenes*, *Candida albicans*, *Aspergillus niger*, and *Aspergillus clavatus*. The structures of the compounds synthesized were elucidated by IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra.

Keywords Benzimidazole derivatives · 4-Thiazolidinone · Antimicrobial activity

Introduction

One of the most significant achievements of the 20th century has been the discovery and commercial development of numerous therapeutic agents that now provide reliably effective treatment for many infectious diseases that had previously caused extensive mortality and morbidity. The search of novel, effective, and suitable drugs against human diseases is a continuous process. The chemistry and pharmacology of benzimidazoles have been of great interest to medicinal chemistry (Evstigneeva *et al*., 1991), because its derivatives possess various biological activities such as antioxidant (Kus *et al*., 2004), antimicrobial (Goker *et al*., 2002; Pawar *et al*., 2004), anthelmintic, fungicide (Mavrova *et al*., 2007), antihypertensive (Starcevic *et al*., 2007), antifungal (Jat *et al*., 2006), anti-inflammatory (Lazer *et al*., 1987), and antiprotozoal activities (Navarette-Vazquez *et al*., 2001). Due to this reason benzimidazole has been an important pharmacophore and privileged structure in medicinal chemistry. The benzimidazole scaffold is an useful structural motif for displaying chemical functionality in biologically active molecules (Desai *et al*., 2011a). Optimization of benzimidazole-based structures has resulted in marketed medicines such as omeprazole (Lindberg *et al*., 1986) and lead compounds in a wide range of therapeutic areas e.g., casein kinase (Pagano *et al*., 2004), factor Xa (Ueno *et al*., 2004), hepatitis C virus (Beaulieu *et al*., 2004) etc. From a combinatorial chemistry perspective, the benzimidazole scaffold allows stepwise incorporation of diverse functionality with control of regiochemistry, making it a suitable target for library synthesis. Library synthesis has been reported using solid and solution (Bendale and Sun, 2002) phase approaches as well as parallel polymer-assisted synthesis (Andrews *et al*., 2004).

For a long time, small heterocycle scaffold containing nitrogen, sulfur, and oxygen have been under investigation due to their important medicinal properties. The chemistry of thiazolidinone ring system is of considerable interest as it is a core structure in various synthetic pharmaceuticals

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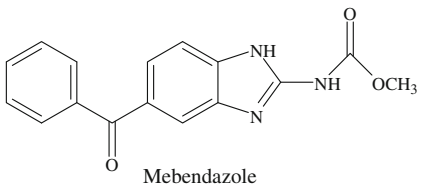
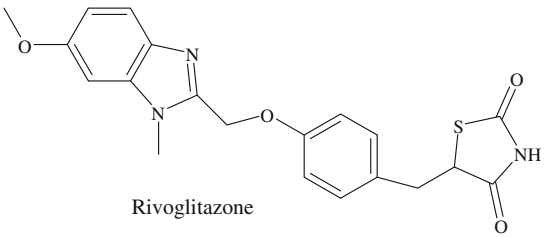
displaying a broad spectrum of biological activities (Liu *et al*., 2011). The 4-thiazolidinone nucleus also appears frequently in the structure of various natural products, notably thiamine, compounds possessing cardiac and glycemic benefits such as troglitazone (Ghazzi *et al*., 1997) and many metabolic products of fungi and primitive marine animals, including 2-(aminoalkyl)-thiazole-4-carboxylic acids (Schmidt *et al*., 1987). Numerous thiazolidinone derivatives have shown significant bioactivities such as anticonvulsant (Ergene and Capan, 1994), antimicrobial (Gouveia and de Oliveira, 2009), antidiabetic (Noboyoshi and Heroaki, 2006), antihistaminic (Previtera *et al*., 1994), anticancer (Wu *et al*., 2006), anti HIV (Rawal *et al*., 2005) etc.

Currently, 4-thiazolidinones are considered as a new class of antidiabetic (insulin-sensitizing) drugs and potent aldose reductase inhibitors. In addition, they are potent for the treatment of diabetes complications like cataract, nephropathy, and neuropathy (Gerstein *et al*., 2006) .

Mebendazole drug is a shining example of the importance of benzimidazole nucleus. This drug is a broad spectrum anthelmintic agent producing high cure rates in infections caused by threadworms, hookworms, and whipworms (Roth *et al*., 1997). Rivoglitazone is the most appropriate example of hybrid drug in which two important moieties, benzimidazole and 4-thiazolidinone are present together. In this article, we have adopted hybrid approach for the search of novel antimicrobial agents which is very popular in medicinal chemistry (Desai *et al*., 2010; Desai and Dodiya, 2011; Goker *et al*., 1995). In view of pharmacological significance of benzimidazole derivatives and 4-thiazolidinone derivatives especially antimicrobial activity, it is planned to synthesize and screen for antimicrobial activity of some new benzimidazole derivatives containing 4-thiazolidinone moiety. The newly synthesized compounds were characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. See Scheme 1.

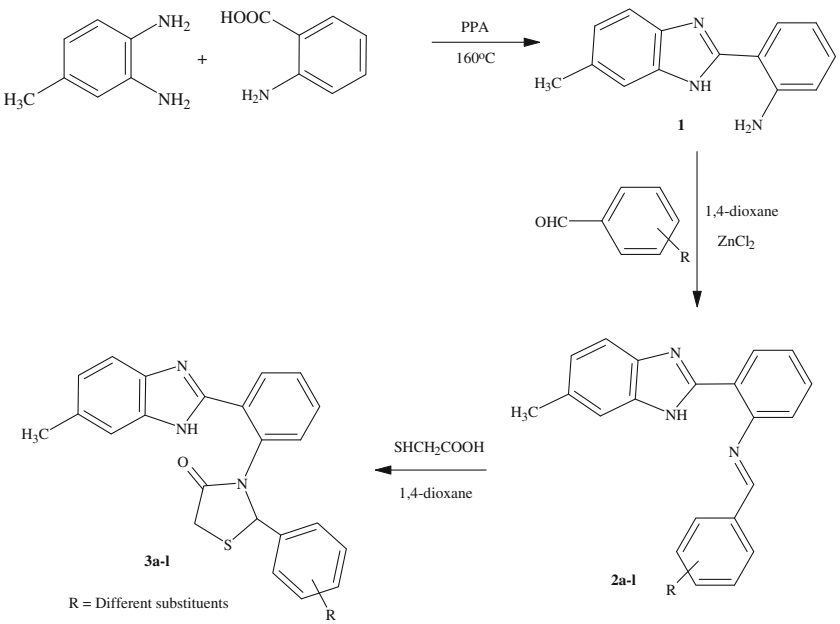


Mebendazole



Rivoglitazone

Scheme 1 Synthesis route for the final compounds



Results and discussion

IR-data

IR spectra of the title compound **3j** (molecular formula $C_{23}H_{18}N_4O_3S$, m.w. 430.48 g/mol) has given vibration at 3005 cm^{-1} over the range which shows multiple weak absorption peak corresponding to benzimidazole-H and Ar–H stretching vibration absorption peaks. The high frequency region of the IR spectra of this compound contains –NH stretching vibration at 3482 cm^{-1}. The methylene group present in thiazolidinone nucleus appeared in the range of 3025 cm^{-1}, while the bending vibration of the methylene group appeared at 1465 cm^{-1}. The stretching vibrations of the methyl group appeared at 2950 cm^{-1}, while bending vibration of the methyl group appeared in the range of 1452 cm^{-1}. The strong absorption at 1685 cm^{-1} is due to the C=O stretching vibration and the moderate absorption at 1615 cm^{-1} corresponds to C=N stretching vibration while C=C linkage absorption appeared at 1580 and 1460 cm^{-1} due to stretching vibrations. The absorption at 1310 cm^{-1} is due to the symmetric stretching of $–NO_2$ group while the absorption at 1520 cm^{-1} is due to the asymmetric stretching of $–NO_2$ group. The absorption peak at 755 cm^{-1} indicates that mono-substituted benzene ring is present.

H-NMR-data

It has been observed from the chemical structure of compound **3j** that protons of the methyl group attached to C-6 position appeared as a singlet at $\delta = 2.43$ ppm. The protons attached with C-3 and C-4 appeared as doublet at $\delta = 7.12$ and 7.54 ppm, respectively, while the proton of C-7 appeared as a singlet at $\delta = 7.43$ ppm. A proton of the secondary amine appeared as a singlet at $\delta = 10.25$ ppm. The phenyl ring contains four protons which makes nucleus between benzimidazole and 4-oxo-thiazolidine rings. The proton attached with C-11 appeared as multiplet due to mutual coupling with C-10 and C-12 at $\delta = 7.49$, while the proton attached with C-12 appeared as a multiplet at $\delta = 7.46$ due to mutual coupling with C-11 and C-13. Other protons of the phenyl ring which are attached with C-10 and C-13 appeared as a doublet at $\delta = 7.84$ and 7.33 ppm, respectively. The protons which are attached with C-16 in 4-thiazolidinone ring appeared as bis-singlet at $\delta = 4.00$; 3.90 ppm, while the other proton of 4-oxo-thiazolidine which is attached with C-17 appeared as a singlet at $\delta = 6.44$ ppm. The proton of the nitrobenzene ring which is attached with C-22 appeared as a multiplet at $\delta = 7.59$ due to mutual coupling with C-23 and C-21 ppm. The proton of C-19 appeared as a singlet at $\delta = 8.12$ ppm because C-19 has no hydrogen atom on either side at C-18 or at C-20. The proton of C-21 appeared as a doublet at $\delta = 8.07$ ppm due to the presence of C–H at C-22 on one side and nitro group containing carbon at C-20 position on the other side. The hydrogen bonded to C-23 appeared as a doublet at $\delta = 7.75$ ppm due to the presence of C-18 on one side and C–H on the other side at C-22.

^{13}C-NMR-data

The final compound **3j** contains two moieties like benzimidazole and 4-thiazolidinone. The chemical shift of carbons of the final compound **3j** varies from $\delta = 171.2$ to 21.3 ppm. The carbon nuclei under the influence of a strong electronegative environment appeared downfield, e.g., the C-15 carbonyl, which is directly linked to the ring nitrogen has a chemical shift at $\delta = 171.2$ ppm, whereas C-1 linked to nitrogen atoms on both sides, appeared at $\delta = 154.9$ ppm. The carbon of the methyl group i.e., C-6 appeared at $\delta = 21.3$ ppm and the carbon where it is attached, i.e., (C-5, aromatic, sp^2) appeared at $\delta = 132.7$ ppm, while the other carbons (C-2, C-3, C-4, C-7, and C-8) of the benzimidazole nucleus appeared between $\delta = 115.3$ and 135.6 ppm. The carbons of the phenyl ring (C-9 to C-14), which makes nucleus between benzimidazole and thiazolidinone rings appeared between $\delta = 114.4$ and 136.9 ppm. The carbon of $–CH_2–$, methylene group present in thiazolidinone ring, i.e., C-16 appeared at $\delta = 33.5$ ppm. The carbon which is attached on one side with nitrogen atom and on the other side with sulfur atom, i.e., (C-17) appeared at $\delta = 71.9$ ppm. The aromatic carbon C-20 which is directly attached with nitro group appeared at $\delta = 147.8$ ppm due to strong electron-withdrawing effect of nitro group, while the other carbons (C-18, C-19, C-21, C-22, and C-23) of the nitro benzene ring appeared between $\delta = 122.3$ and 140.1 ppm, respectively. The numbering of carbons is described in Fig. 1.

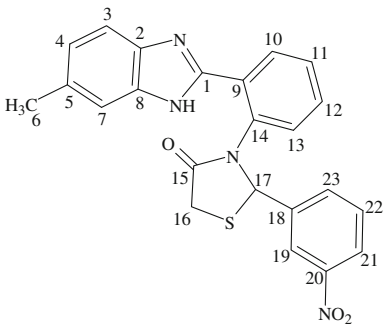


Fig. 1 Carbon numbering of the final compound **3j**

Antimicrobial activity

For antibacterial activity, compounds **3b** and **3f** are considered to be moderately active against *E. coli*. Compounds **3g** and **3l** are considered as very good active against *E. coli*, while compound **3j** is considered as excellent active against *E. coli*. Compound **3c** is considered as good active against *P. aeruginosa.* Compounds **3d**, **3e**, and **3k** are considered as good active against *S. aureus*, while compounds **3b**, **3g**, and **3j** are considered as very good active against *S. aureus*, while compound **3l** is considered as very good active against *S. aureus*. Compound **3e** is considered as moderately active against *S. pyogenes*, while compounds **3b** and **3j** are considered as very good active against *S. pyogenes*. For the antifungal activity, compounds, **3b**, **3d**, **3e**, **3g**, **3h**, and **3k** are considered as good active against *C. albican*s, while compound **3c** is considered as very good active against *C. albicans*, while compound **3j** considered as excellent active against *C. albicans*. Compounds **3b**, **3c**, and **3d** are considered as good active while compound **3j** is considered as very good active against *A. niger*. Compound **3e** is considered as good active against *A. clavatus.* The data revealed that electron-withdrawing group like $-NO_2$, present on phenyl ring was found to increase the antimicrobial properties. The most of the synthesized compounds exhibited significant antibacterial activity and moderate antifungal activity. The discussion and comparison of antibacterial and antifungal activities have been compared with ampicillin and griseofulvin, respectively.

Structure–activity relationship (SAR) study

SAR studies revealed that different substitutions on the benzimidazole and 4-thiazolidinone moieties exerted varied biological activity. The electronic nature of the substituent groups at 2nd position in benzimidazole nucleus and 2nd position in 4-thiazolidinone led to a significant variation in antimicrobial activity. A series of compounds when substituted by electron-withdrawing group like NO_2 enhances the antimicrobial activity when present on aromatic ring.

Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against gram positive bacteria *S. aureus* (MTCC-96) and *S. pyogenes* (MTCC-442) and gram negative bacteria *E. coli* (MTCC-443) and *P. aeruginosa* (MTCC-1688). Antibacterial activity was carried out by serial broth dilution method (Ghalem and Mohamed, 2009; Desai *et al*., 2011b). The standard strains used for the antimicrobial activity were procured from Institute of Microbial Technology, Chandigarh. The compounds (**3a**–**l**) were screened for their antibacterial activity in triplicate sets against these bacteria at different concentrations of 1000, 500, 200, 100, 50, and 25 μg/ml as shown in Table 1. The drugs which were found to be active in primary screening were similarly diluted to obtain 100, 50, and 25 μg/ml concentrations. 10 μg/ml suspensions were

Table 1 Results of antibacterial and antifungal screening of the compounds **3a–l**

Sr.no.	Compd.	-R	Minimum inhibitory concentration for bacteria(MIC) μg/ml ± SD				Minimum inhibitory concentration for fungi (MIC) μg/ml ± SD		
			Gram negative		Gram positive				
			E. coli MTCC-443	*P. aeruginosa* MTCC-1688	*S. aureus* MTCC-96	*S. pyogenes* MTCC-442	*C. albicans* MTCC-227	*A. niger* MTCC-282	*A. clavatus* MTCC-1323
1	**3a**	-2-Cl	1000 ± 2*	1000 ± 2.54*	500 ± 3.64*	1000 ± 3.54*	1000 ± 4.36*	1000 ± 2.21*	1000 ± 4*
2	**3b**	-4-Cl	125 ± 3.05*	250 ± 1.95*	100 ± 4*	62.5 ± 3*	500 ± 3*	500 ± 2.02*	1000 ± 3.26*
3	**3c**	-2,4-$(Cl)_2$	62.5 ± 3.45*	100 ± 2*	1000 ± 2.23*	5000 ± 2.23*	250 ± 3.54*	500 ± 3*	500 ± 3.23*
4	**3d**	-4-F	250 ± 3.20*	250 ± 4.50*	250 ± 3*	250 ± 2*	500 ± 2*	500 ± 3.54*	1000 ± 3*
5	**3e**	-3-OH	500 ± 4*	250 ± 2*	250 ± 2.22*	125 ± 3.12*	500 ± 4*	1000 ± 3*	100 ± 3.46*
6	**3f**	-4-OH	125 ± 2.35*	250 ± 3.24*	500 ± 1.34*	500 ± 2.4*	1000 ± 2.27*	1000 ± 3*	1000 ± 3.21*
7	**3g**	-3,4-$(OCH_3)_2$	100 ± 3*	250 ± 2*	100 ± 4.25*	1000 ± 3.0*	500 ± 3*	1000 ± 2.25*	1000 ± 2.36*
8	**3h**	-3,4,5-$(OCH_3)_3$	500 ± 3.05*	250 ± 3.12*	500 ± 3*	250 ± 2.3*	500 ± 3.12*	1000 ± 3.43*	1000 ± 3.35*
9	**3i**	-2-$N0_2$	500 ± 3.12*	250 ± 2.34*	1000 ± 3*	250 ± 4.1*	1000 ± 3.5*	1000 ± 3.55*	1000 ± 3.3*
10	**3j**	-3-NO2	25 ± 4*	250 ± 2*	100 ± 2.24*	62.5 ± 3.2*	100 ± 2.25*	100 ± 3.54*	1000 ± 3.47*
11	**3k**	-4-NO2	500 ± 2.22*	250 ± 1.85*	250 ± 3.53*	250 ± 4*	500 ± 2.25*	1000 ± 3.26*	1000 ± 2*
12	**3l**	-2,4,-$(N0_2)_2$	62.5 ± 4*	250 ± 2*	62.5 ± 3*	1000 ± 3.5*	1000 ± 2.26*	1000 ± 3.53*	1000 ± 4.12*
	Ampicillin		100 ± 4.57*	100 ± 4.12*	250 ± 4.15*	100 ± 3.55*		–	–
	Griseofulvin		–	–	–	–	500 ± 2.64*	100 ± 3*	100 ± 3.46*

±*SD* standard deviation, * $P \leq 0.0001$

further inoculated on appropriate media and growth was noted after 24 and 48 h. The lowest concentration, which showed no growth after spot subculture was considered as MIC for each drug. The highest dilution showing at least 99% inhibition is taken as minimum inhibitory concentrations (MIC). The test mixture should contain 10^8 cells/ml. The standard drug used in this study was ampicillin for evaluating antibacterial activity which showed (100, 100, 250, and 100 μg/mL) MIC against *E. coli*, *P. aeruginosa*, *S. aureus*, and *S. pyogenes*, respectively.

Antifungal activity

Similarly, the compounds (**3a–l**) were tested for antifungal activity in triplicate sets against *C. albicans*, *A. niger*, and *A. clavatus* at various concentrations of 1000, 500, 200, and 100 μg/ml as shown in Table 1. The results were recorded in the form of primary and secondary screening. The synthesized compounds were diluted to 1000 μg/ml concentration, as a stock solution. The compounds which were found to be active in this primary screening were further tested in a second set of dilution against all microorganisms. The lowest concentration, which showed no growth after spot subculture was considered as MIC for each drug. The highest dilution showing at least 99% inhibition was taken as MIC. The test mixture should contain 10^8 spores/ml MIC. Griseofulvin was used as a standard drug for antifungal activity, which showed (500, 100, and 100 μg/ml) MIC against *C. albicans*, *A. niger*, and *A. clavatus*, respectively. The results of antimicrobial evaluation of derivatives (**3a–l**) are shown in Table 1.

Statistical analysis

The standard deviation value is expressed in terms of ±SD. On the basis of the calculated value by using ANOVA method, it has been observed that differences below 0.0001 level ($P \leq 0.001$) were considered as statistically significant.

Materials and methods

All the required chemicals were purchased from E. Merck. IR spectra were recorded on Perkin-Elmer FT-IR Spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker DPX-40C instrument at 400 MHz. Chemical shifts were reported in ppm in reference to the TMS signal. Mass spectra were recorded on JEOL SX-102 spectrophotometer. Elemental analysis was performed by Perkin-Elmer 2400-CHN analyzer. Melting points were recorded on Gallenkamp apparatus and were left uncorrected. Aluminum-coated TLC plates 60 F_{245} (E. Merck) were used for monitoring of reaction and purity of compounds. In the conventional method, compounds were synthesized by using Random synthesizer. Bookie Rotavapour was used for distillation.

Procedure for the synthesis of 2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)aniline (**1**)

In a round bottom flask, a mixture of 4-methylbenzene-1,2-diamine (0.01 mol), 2-amino benzoic acid (0.01 mol), and polyphosphoric acid (15 ml) was heated at 160°C in an oil bath for 4 h. The reaction mixture was cooled at room temperature and poured into cold water (100 ml) and neutralized with aqueous ammonia. The separated solid was filtered, washed with water, and dried to obtain product. The crude product was purified by dissolving in 10% HCl and re-precipitated by the addition of aqueous ammonia solution. The intermediate product (**1**) was recrystallized from ethyl acetate.

General preparation for the synthesis of *N*-arylidene-2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)anilines (**2a–l**)

In a round bottom flask, compound (**1**) (0.01 mol) was taken in 1,4-dioxane (20 ml) and different aromatic aldehydes (0.01 mol) were added. To this mixture, a pinch of anhydrous zinc chloride was added and refluxed for 6–8 h and the product was poured onto crushed ice. The intermediate products (**2a–l**) were filtered, washed with cold water, dried, and recrystallized from methanol.

General method for the synthesis of 3-(2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(aryl)thiazolidin-4-ones (**3a–l**)

In a round bottom flask, compounds (**2a–l**) (0.01 mol) in 1,4-dioxane (20 ml) and thioglycolic acid (0.01 mol) were taken. The mixture was refluxed in an oil bath for about 8 h. The reaction mixture was cooled and neutralized with saturated aqueous solution of $NaHCO_3$. The product obtained was recrystallized from rectified spirit.

Physical constants and characterization of 3-(2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(2-chlorophenyl)thiazolidin-4-one (**3a**)

Yield: 68%, m.p. 216–218°C; IR (KBr): ν = 3487 (N–H stretching), 3009 (aromatic–H), 3019 (C–H stretching, $–CH_2$ group), 2955 (C–H stretching, $–CH_3$ group), 1682 (C=O stretching), 1618 (C=N stretching), 1582, 1464 (C=C aromatic ring), 1461 ($–CH_2$, bending), 1456 (CH_3,

bending), 758 (mono-substituted benzene), 742 (C–Cl stretching) cm^{-1}; ^{1}H-NMR (DMSO-d_6) ppm: δ 2.43 (s, 3H, $–CH_3$ group), 4.00:3.90 (d, 2H, $–CH_2$ group), 6.44 (s, 1H, S–CH–N group), 7.17–7.84 (m, 11H, benzimidazole-H, and Ar–H), 10.25 (s, 1H, –NH group); ^{13}C-NMR (ppm) : δ 21.3, 33.5, 67.8, 102.5, 114.1, 115.1, 115.3, 115.5, 124.8, 124.9, 125.8, 126.7, 128.5, 128.7, 128.9, 130.7, 131.9, 132.7, 134.0, 135.6, 136.9, 154.9, 171.2; MS : *m/z* 419.04 (M^+). Anal. calc. For $C_{23}H_{18}ClN_3OS$: C, 65.78; H, 4.32; N, 10.01. Found: C, 65.84; H, 4.38; N, 10.09%.

Physical constants and characterization of 3-(2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(4-chlorophenyl)thiazolidin-4-one (**3b**)

Yield: 76%, m.p. 191–192°C; IR (KBr): *v* = 3485 (N–H stretching), 3021 (C–H stretching, $–CH_2$ group), 3006 (aromatic–H), 2951 (C–H stretching, $–CH_3$ group), 1683 (C=O stretching), 1619 (C=N stretching), 1584, 1460 (C=C aromatic ring), 1467 ($–CH_2$, bending), 1454 (CH_3, bending), 755 (mono-substituted benzene), 740 (C–Cl stretching) cm^{-1}; ^{1}H-NMR (DMSO-d_6) ppm: δ 2.43 (s, 3H, $–CH_3$ group), 4.00:3.90 (d, 2H, $–CH_2$ group), 6.44 (s, 1H, S–CH–N group), 7.17–7.84 (m, 11H, benzimidazole-H, and Ar–H), 10.25 (s, 1H, –NH group); ^{13}C-NMR (ppm): δ 21.3, 33.5, 72.9, 114.1, 115.1, 115.3, 115.5, 124.8, 124.9, 125.8, 128.9, 130.2, 130.7, 131.9, 132.7, 135.6, 136.9, 137.3, 154.9, 171.2; MS : *m/z* 419.04 (M^+). Anal. calc. For $C_{23}H_{18}ClN_3OS$: C, 65.78; H, 4.32; N, 10.01. Found: C, 65.86; H, 4.39; N, 10.07%.

Physical constants and characterization of 3-(2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(2,4-dichlorophenyl)thiazolidin-4-one (**3c**)

Yield: 66%, m.p. 188–190°C; IR (KBr): *v* = 3480 (N–H stretching), 3022 (C–H stretching, $–CH_2$ group), 3007 (aromatic–H), 2952 (C–H stretching, $–CH_3$ group), 1681 (C=O stretching), 1614 (C=N stretching), 1580, 1461 (C=C aromatic ring), 1463 ($–CH_2$, bending), 1459 (CH_3, bending), 748 (ortho disubstituted benzene), 742, 746 (C–Cl stretching) cm^{-1}; ^{1}H-NMR (DMSO-d_6) ppm: δ 2.43 (s, 3H, $–CH_3$ group), 4.00:3.90 (d, 2H, $–CH_2$ group), 6.44 (s, 1H, S–CH–N group), 7.11–7.84 (m, 10H, benzimidazole-H, and Ar–H), 10.25 (s, 1H, –NH group); ^{13}C-NMR (ppm): δ 21.3, 33.5, 67.8, 100.6, 114.1, 115.1, 115.3, 115.5, 124.8, 124.9, 125.8, 126.8, 128.9, 130.3, 131.5, 131.9, 132.7, 134.1, 135.4, 135.6, 136.9, 154.9, 171.2; MS: *m/z* 453.05 (M^+). Anal. calc. For $C_{23}H_{17}Cl_2N_3OS$: C, 60.80; H, 3.77; N, 9.25. Found: C, 60.87; H, 3.83; N, 9.32%.

Physical constants and characterization of 3-(2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(4-fluorophenyl)thiazolidin-4-one (**3d**)

Yield: 76%, m.p. 199–201°C; IR (KBr): *v* = 3488 (N–H stretching), 3000 (aromatic–H), 3024 (C–H stretching, $–CH_2$ group), 2951 (C–H stretching, $–CH_3$ group), 1683 (C=O stretching), 1619 (C=N stretching), 1582, 1458 (C=C aromatic ring), 1467 ($–CH_2$, bending), 1454 (CH_3, bending), 1002 (C–F stretching), 755 (mono-substituted benzene), cm^{-1}; ^{1}H-NMR (DMSO-d_6) ppm: δ 2.43 (s, 3H, $–CH_3$ group), 4.00:3.90 (d, 2H, $–CH_2$ group), 5.35 (s, 1H, –OH group), 6.44 (s, 1H, S–CH–N group), 7.12–7.84 (m, 11H, benzimidazole-H, and Ar–H), 10.25 (s, 1H, –NH group); ^{13}C-NMR (ppm): δ 21.3, 33.5, 72.9, 114.1, 115.1, 115.3, 115.5, 115.8, 124.8, 124.9, 125.8, 128.9, 130.3, 131.9, 132.7, 134.8, 135.6, 136.9, 154.9, 161.3, 171.2; MS: *m/z* 403.12 (M^+). Anal. calc. For $C_{23}H_{18}FN_3OS$: C, 68.47; H, 4.50; N, 10.41. Found: C, 68.54; H, 4.58; N, 10.49%.

Physical constants and characterization of 3-(2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(3-hydroxyphenyl)thiazolidin-4-one (**3e**)

Yield: 67%, m.p. 188–190°C; IR (KBr): *v* = 3478 (N–H stretching), 3423 (–OH stretching), 3018 (C–H stretching, $–CH_2$ group), 3010 (aromatic–H), 2957 (C–H stretching, $–CH_3$ group), 1690 (C=O stretching), 1611 (C=N stretching), 1577, 1460 (C=C and aromatic ring), 1461 ($–CH_2$, bending), 1450 (CH_3, bending), 751 (mono-substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6) ppm: δ 2.43 (s, 3H, $–CH_3$ group), 4.00:3.90 (d, 2H, $–CH_2$ group), 5.35 (s, 1H, –OH group), 6.44 (s, 1H, S–CH–N group), 6.76–7.84 (m, 11H, benzimidazole-H, and Ar–H), 10.25 (s, 1H, –NH group); ^{13}C-NMR (ppm): δ 21.3, 33.5, 73.2, 114.1, 114.3, 114.7, 115.1, 115.3, 115.5, 119.5, 124.8, 124.9, 125.8, 128.9, 130.0, 131.9, 132.7, 135.6, 136.9, 140.6, 154.9, 156.9, 171.2; MS: *m/z* 401.12 (M^+). Anal. calc. For $C_{23}H_{19}N_3O_2S$: C, 68.21; H, 4.77; N, 10.47. Found: C, 68.29; H, 4.82; N, 10.54%.

Physical constants and characterization of 3-(2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(4-hydroxyphenyl)thiazolidin-4-one (**3f**)

Yield: 70%, m.p. 196–198°C; IR (KBr): *v* = 3476 (N–H stretching), 3423 (–OH stretching), 3020 (C–H stretching, $–CH_2$ group), 3012 (aromatic–H), 2948 (C–H stretching, $–CH_3$ group), 1692 (C=O stretching), 1607 (C=N stretching), 1580, 1462 (C=C, aromatic ring), 1458 ($–CH_2$, bending), 1448 (CH_3, bending), 751 (mono-substituted

benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6) ppm: δ 2.43 (s, 3H, $–CH_3$ group), 4.00:3.90 (d, 2H, $–CH_2$ group), 5.35 (s, 1H, –OH group), 6.44 (s, 1H, S–CH–N group), 6.63–7.54 (m, 11H, benzimidazole-H, and Ar–H), 10.25 (s, 1H, –NH group); ^{13}C-NMR (ppm): δ 21.3, 33.5, 72.9, 114.1, 115.1, 115.3, 115.5, 115.8, 124.8, 124.9, 125.8, 128.9, 130.1, 131.9, 132.7, 135.6, 136.9, 154.9, 156.9, 171.2; MS: *m/z* 401.12 (M^+). Anal. calc. For $C_{23}H_{19}N_3O_2S$: C, 68.21; H, 4.77; N, 10.47. Found: C, 68.28; H, 4.84; N, 10.56%.

Physical constants and characterization of 3-(2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(3,4-dimethoxyphenyl)thiazolidin-4-one (**3g**)

Yield: 76%, m.p. 206–208°C; IR (KBr): ν = 3482 (N–H stretching), 3025 (C–H stretching, $–CH_2$ group), 3005 (aromatic–H), 2950 (C–H stretching, $–CH_3$ group), 2828 (C–H stretching, $–OCH_3$ group), 1685 (C=O stretching), 1615 (C=N stretching), 1580, 1460 (C=C, aromatic ring), 1470 ($–CH_2$, bending), 1452 (CH_3, bending), 1424 ($–OCH_3$ bending), 745 (di-substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6) ppm: δ 2.43 (s, 3H, $–CH_3$ group), 4.00:3.90 (d, 2H, $–CH_2$ group), 6.44 (s, 1H, S–CH–N group), 6.76–7.54 (m, 10H, benzimidazole-H, and Ar–H), 10.25 (s, 1H, –NH group); ^{13}C-NMR (ppm): δ 21.3, 33.5, 56.1, 73.2, 112.3, 113.8, 114.1, 115.1, 115.3, 115.5, 122.0, 124.8, 124.9, 125.8, 128.9, 131.9, 132.4, 132.7, 135.6, 136.9, 148.2, 149.7, 154.9, 171.2; MS: *m/z* 445.53 (M^+). Anal. calc. For $C_{25}H_{23}N_3O_3S$: C, 67.40; H, 5.20; N, 9.43. Found: C, 67.48; H, 5.28; N, 9.50%.

Physical constants and characterization of 3-(2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(3,4,5-trimethoxyphenyl)thiazolidin-4-one (**3h**)

Yield: 66%, m.p. 202–204°C; IR (KBr): ν = 3005 (aromatic–H), 3482 (N–H stretching), 3020 (C–H stretching, $–CH_2$ group), 2950 (C–H stretching, $–CH_3$ group), 2835 (C–H stretching, $–OCH_3$ group), 1685 (C=O stretching), 1615 (C=N stretching), 1580, 1460 (C=C, aromatic ring), 1473 ($–CH_2$, bending), 1452 (CH_3, bending), 1425 ($–OCH_3$ bending), 740 (substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6) ppm: δ 2.43 (s, 3H, $–CH_3$ group), 3.83 (s, 9H, $–OCH_3$ group), 4.00:3.90 (d, 2H, $–CH_2$ group), 6.44 (s, 1H, S–CH–N group), 7.07–7.54 (m, 9H, benzimidazole-H, and Ar–H), 10.25 (s, 1H, –NH group); ^{13}C-NMR (ppm): δ 21.3, 33.5, 56.1, 60.3, 60.8, 67.3, 104.6, 109.8, 114.1, 115.1, 115.3, 115.5, 123.0, 124.8, 124.9, 125.8, 128.9, 131.9, 132.7, 135.6, 136.9, 142.0, 151.1, 152.3, 154.9, 171.2; MS: *m/z* 475.56 (M^+). Anal. calc. For $C_{26}H_{25}N_3O_4S$: C, 65.67; H, 5.30; N, 8.84. Found: C, 65.73; H, 5.37; N, 8.90%.

Physical constants and characterization of 3-(2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(2-nitrophenyl)thiazolidin-4-one (**3i**)

Yield: 73%, m.p. 200–202°C; IR (KBr): ν = 3476 (N–H stretching), 3022 (C–H stretching, $–CH_2$ group), 3014 (aromatic–H), 2943 (C–H stretching, $–CH_3$ group), 1688 (C=O stretching), 1606 (C=N stretching), 1577, 1462 (C=C, aromatic ring), 1524 ($–NO_2$ asymmetric stretching), 1454 ($–CH_2$, bending), 1447 (CH_3, bending), 1313 ($–NO_2$ symmetric stretching), 751 (mono-substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6) ppm: δ 2.43 (s, 3H, $–CH_3$ group), 4.00:3.90 (d, 2H, $–CH_2$ group), 6.44 (s, 1H, S–CH–N group), 7.12–8.12 (m, 11H, benzimidazole-H, and Ar–H), 10.25 (s, 1H, –NH group); ^{13}C-NMR (ppm): δ 21.3, 33.5, 68.3, 114.1, 115.1, 115.3, 115.5, 124.5, 124.8, 124.9, 125.8, 128.0, 128.9, 129.6, 131.9, 132.7, 133.4, 134.7, 135.6, 136.9, 149.0, 154.9, 171.2; MS: *m/z* 430.48 (M^+). Anal. calc. For $C_{23}H_{18}N_4O_3S$: C, 64.17; H, 4.21; N, 13.01. Found: C, 64.23; H, 4.28; N, 13.09%.

Physical constants and characterization of 3-(2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(3-nitrophenyl)thiazolidin-4-one (**3j**)

Yield: 68%, m.p. 221–222°C; IR (KBr): ν = 3482 (N–H stretching), 3021 (C–H stretching, $–CH_2$ group), 3005 (aromatic–H), 2950 (C–H stretching, $–CH_3$ group), 1685 (C=O stretching), 1615 (C=N stretching), 1580, 1460 (C=C, aromatic ring), 1465 ($–CH_2$, bending), 1452 (CH_3, bending), 1520 ($–NO_2$ asymmetric stretching), 1310 ($–NO_2$ symmetric stretching), 755 (mono-substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6) ppm: δ 2.43 (s, 3H, $–CH_3$ group), 4.00:3.90 (d, 2H, $–CH_2$ group), 6.44 (s, 1H, S–CH–N group), 7.12–8.12 (m, 11H, benzimidazole-H, and Ar–H), 10.25 (s, 1H, –NH group); ^{13}C-NMR (ppm): δ 21.3, 33.5, 71.9, 114.4, 115.1, 115.3, 115.5, 122.3, 124.8, 124.9, 125.1, 125.8, 128.9, 129.5, 131.9, 132.7, 133.0, 135.6, 136.9, 140.1, 147.8, 154.9, 171.2; MS: *m/z* 430.48 (M^+). Anal. calc. For $C_{23}H_{18}N_4O_3S$: C, 64.17; H, 4.21; N, 13.01. Found: C, 64.24; H, 4.29; N, 13.11%.

Physical constants and characterization of 3-(2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(4-nitrophenyl)thiazolidin-4-one (**3k**)

Yield: 70%, m.p. 238–240°C; IR (KBr): ν = 3476 (N–H stretching), 3025 (C–H stretching, $–CH_2$ group), 3001 (aromatic–H), 2957 (C–H stretching, $–CH_3$ group), 1677 (C=O stretching), 1604 (C=N stretching), 1583, 1463 (C=C, aromatic ring), 1458 ($–CH_2$, bending), 1458 (CH_3,

bending), 1312 (–NO_2 symmetric stretching), 1514 (–NO_2 asymmetric stretching), 751 (mono-substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6) ppm: δ 2.43 (s, 3H, –CH_3 group), 4.00:3.90 (d, 2H, –CH_2 group), 6.44 (s, 1H, S–CH–N group), 7.12–8.14 (m, 11H, benzimidazole-H, and Ar–H), 10.25 (s, 1H, –NH group); ^{13}C-NMR (ppm): δ 21.3, 33.5, 72.9, 114.1, 115.1, 115.3, 115.5, 123.8, 124.8, 124.9, 125.8, 128.9, 129.6, 131.9, 132.7, 135.6, 136.9, 145.3, 146.3, 154.9, 171.2; MS: *m/z* 430.48 (M^+). Anal. calc. For $C_{23}H_{18}N_4O_3S$: C, 64.17; H, 4.21; N, 13.01. Found: C, 64.25; H, 4.27; N, 13.10%.

Physical constants and characterization of 3-(2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(2,4-dinitrophenyl)thiazolidin-4-one (**3l**)

Yield: 76%, m.p. 246–248°C; IR (KBr): ν = 3476 (N–H stretching), 3022 (C–H stretching, –CH_2 group), 3017 (aromatic–H), 2954 (C–H stretching, –CH_3 group), 1678 (C=O stretching), 1607 (C=N stretching), 1583, 1462 (C=C, aromatic ring), 1517 (–NO_2 asymmetric stretching), 1314 (–NO_2 symmetric stretching), 1461 (–CH_2, bending), 1458 (CH_3, bending), 738 (di-substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6) ppm: δ 2.43 (s, 3H, –CH_3 group), 4.00:3.90 (d, 2H, –CH_2 group), 6.44 (s, 1H, S–CH–N group), 7.12–8.80 (m, 10H, benzimidazole-H, and Ar–H), 10.25 (s, 1H, –NH group); ^{13}C-NMR (ppm): δ 21.3, 33.5, 71.9, 114.1, 115.1, 115.3, 115.5, 124.2, 124.8, 124.9, 125.8, 126.0, 128.9, 131.9, 132.7, 135.6, 135.8, 136.9, 143.2, 146.2, 150.1, 154.9, 171.2; MS: *m/z* 430.48 (M^+). Anal. calc. For $C_{23}H_{17}N_5O_5S$: C, 68.10; H, 3.60; N, 14.73. Found: C, 68.18; H, 3.68; N, 14.80%.

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