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Synthesis and biological activity of new 3-chloro-4-(3-substituted phenyl)-1-(5-((2-methyl-1H-benzo[d]imidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-yl) azetidin-2-one

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Abstract: A series of novel N-(substituted benzylidene)-5-((2-methyl-1H-benzo[d]imidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-amine (**VI**a-e), and 3-chloro-4-(4-substituted phenyl)-1-(5-((2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one (**VII**a-e) were synthesized and studied for their potential antimicrobial activity. All the synthesized compounds were in good agreement with elemental, IR, ^{1}H-NMR and MS spectra.
Keywords: Benzimidazoles, 1, 3, 4-thiadiazoles, Antimicrobial activity.

1. Introduction

Drug resistance is a steadily increasing process that is reaching alarming level in the treatment of infectious diseases caused by pathogenic bacteria, fungi, parasites and viruses. Over the past few decades, steadily increasing drug resistance in the treatment of infectious disease pose a serious problem in antimicrobial therapy and necessitates continuing research into novel classes of antimicrobials.[1] The 1, 3, 4-thiadiazole and its derivatives possesses wide variety of activities[2-7] and a number of researchers have reported antimicrobial activities in 2, 5-disubstituted-1, 3, 4-thiadiazoles.[8-10] Benzimidazoles posses a number of interacting biological activities such as antitubercular,[11] anticancer, [12,13] anthelmintic,[14] antiallergic, [15-16] antioxidant,[17-19] antihistaminic, [20]and antimicrobial activity.[21-27]

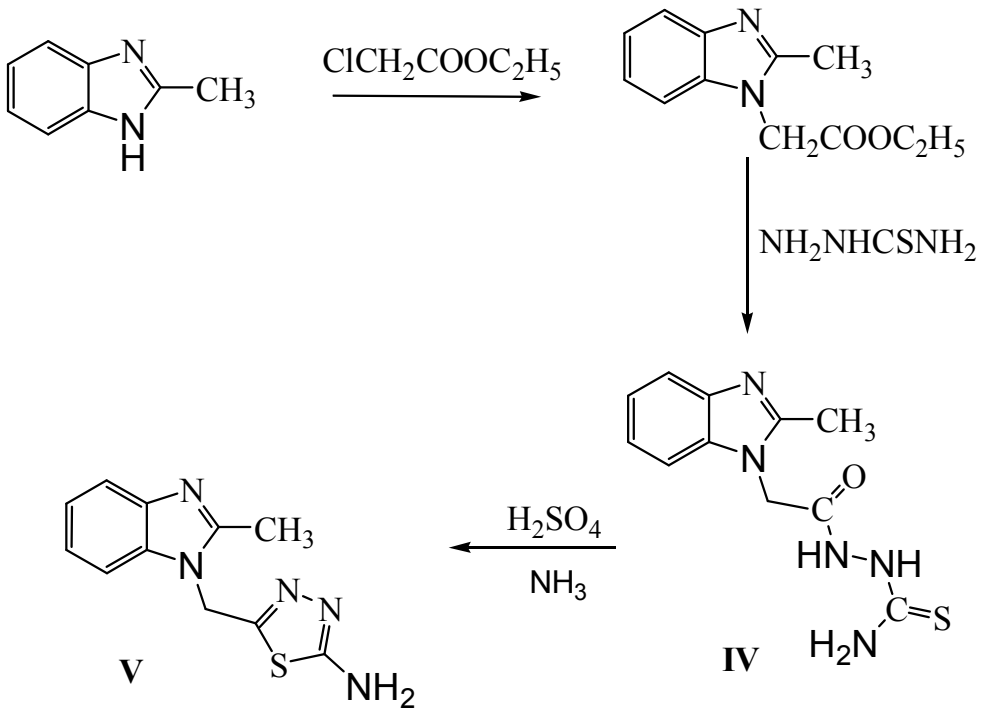
Keeping the Pharmacological activity of 1,3,4-thidiazoles and benzimidazoles it was thought worth-while to synthesized, 5-[(2-methyl-1*H*-benzimidazole-1-yl)methyl]-1,3,4-thiadiazol-2-amine (**VI**a-e), and 3-

chloro-4-(3-Substituted phenyl)-1-(5-((2-methyl-1H-benzo[d]imidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-yl) azetidin-2-one **(VII**a-e),similarly compounds are tested for their biological activity.

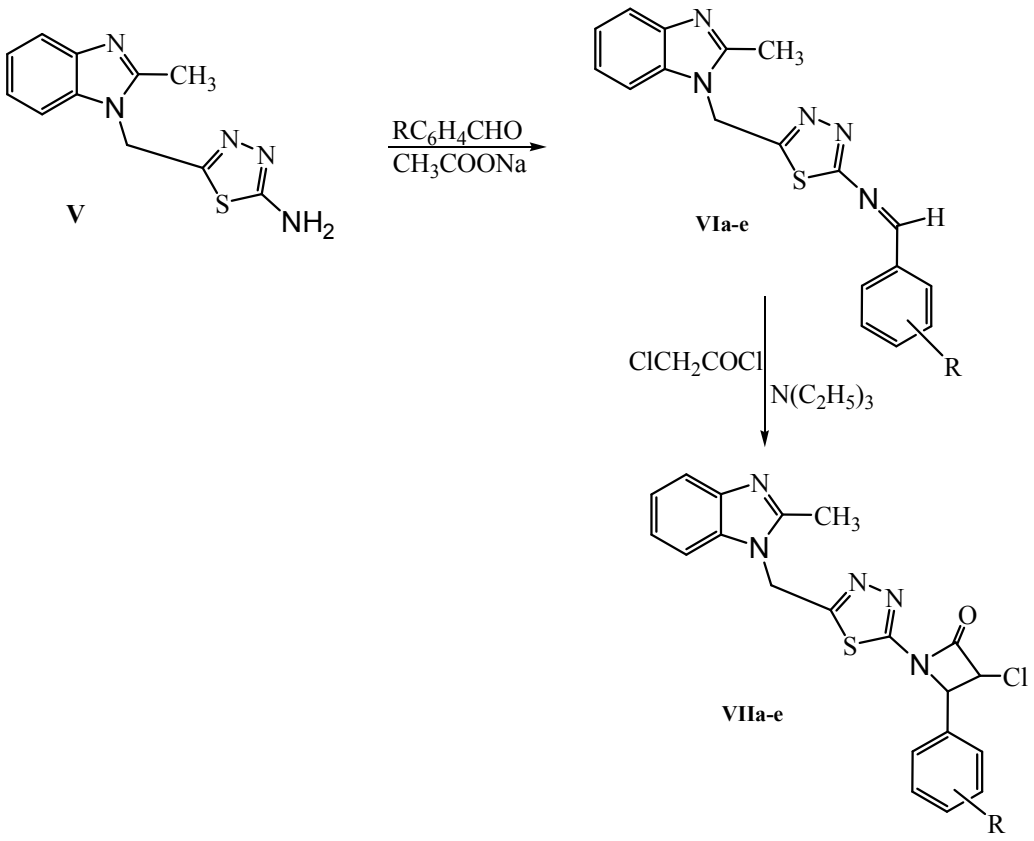
2. Results and Discussions

We are starting our research envisaged by synthesizing 5-[(2-methyl-1H-benzimidazol-1-yl) methyl]-1, 3, 4-thiadiazol-2-amine from the 2-Methyl-1*H*-benzimidazole **II** which was prepared according to the reported method.[28] further on N-ethoxylation with ethylchloroacetate in the presence of anhydrous K_2CO_3 in dry acetone gave ethyl (2-methyl-1*H*-benzimidazol-1-yl) acetate **III** which on treatment with thiosemicarbazide resulted in the formation of 2-[(2-methyl-1*H*-benzimidazol-1-yl)acetyl]-hydrazinecarbo - thioamide **IV**. Dehydrated annulation of compound **IV** with conc. H_2SO_4 followed by NH_3 treatment yielded 5-[(2-methyl-1*H*-benzimidazol-1-yl) methyl]-1, 3, 4-thiadiazol-2-amine **V** which were synthesis by adopting known method.[29]

The compound **V** is converted to Schiff base by treatment with substituted benzaldehyde in presence of sodium acetate and few drops of sulphuric acid resulted in the formation of N-(substituted benzylidene)-5-((2-methyl-1H-benzo[d]imidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-amine **(VIa-e)**, which on treatment with chloroacetylchloride in presence of triethylamine in alcoholic solution yielded 3-chloro-4-(4-substituted phenyl)-1-(5-((2-methyl-1H-benzo[d] imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one **(VIIa-e)**, the analytical data confirming the formation of molecules**.** IR (KBr, cm^{-1}): 3195.6 (N-H str of Schiff base), 3052.9 (Ar C-H str), 2909.2 (aliphatic C-H str), 1647.5 (C=N of thiadiazole), 1614.9 (C=N of benzimidazole ring), 1569.9 (C=N str. of Sciff base), 1603 and 1505.8 (Ar C-C str), 821.9 (C-H def disubstituted benzene ring), 738.3 (C-S of thiadiazole nucleus) ; ^{1}H NMR (300 MHz, DMSO-d6, TMS, δ ppm): 2.3 (s, 3H, CH_3), 4.7 (s, 2H, CH_2), 8.2 (s, 1H, CH of benzylidine imine) 7.1-7.8 (m, 9H, benzimidazole and benzylidine); Mass spectra and elemental analysis also support the structure elucidation of molecules.



Scheme-1



Antimicrobial activity

The antimicrobial properties of the synthesized compounds were investigated against bacterial strains *i.e.*, Gram negative; *Proteus mirabilis* (MTCC-425), *Pseudomonas aeruginosa* (MTCC-424), Gram positive; *Bacillus subtilis* (MTCC-619), and *Staphylococcus aureus* (MTCC-96) and fungal strains *i.e.*, *Aspergillus niger* (MTCC-1344) and *Candida albicans* (MTCC-227) using disk diffusion method[30-31] (Table-I). The standard drugs used for comparison were norfloxacin and clotrimazole for antibacterial and antifungal studies respectively. Nutrient agar, Czapek yeast extract agar and malt yeast agar with pH 7.0 was employed as culture media for antibacterial, antimycotic evaluation against *Aspergillus niger* and *Candida albicans* respectively.[32] For antibacterial studies, incubation was carried out at 37±1ºC for 48 h except for *Bacillus subtilis* where incubation was carried out at 26±1º C for similar time period. Incubation conditions for *Aspergillus niger* and *Candida albicans* was 25±1ºC for 72 h.

The cell density of each inoculum was adjusted with hemocytometer in order to procure a final concentration of approximately 105 CFU/mL and 0.5 of the culture of test organism was inoculated and uniformly spread over the agar surface using a sterile L-shaped glass rod. Solutions of the test compound (100 µg/mL) were prepared by dissolving in dimethyl formamide (DMF). The sterile filter paper disc (8 mm diameter) were moistened with the test compounds solution in DMF of specific concentration (100 µg/disc) placed on the agar culture plates that had been previously inoculated with specific microorganisms. All the tests were performed in triplicate, and inhibition zones were measured. The activity index of synthesized compounds has been calculated using formula.[33]

$$\text{Activity index} = \frac{\text{Inhibition zone of sample}}{\text{Inhibition zone of standard}}$$

By careful study of the antimicrobial activity data and activity index it can be observed that most of the synthesized compounds possess significant antibacterial and antifungal activity. The results of antimicrobial activity have been reported in Table-I.

Table I- Antimicrobial activity[#] of the synthesized compounds using disc-diffusion method

Compd	Zone of inhibition in millimeter[a] (Activity index)					
	Antibacterial activity				Antifungal activity	
	S.aureus	*B. subtilis*	*P. mirabilis*	*P. aeruginosa*	*A. niger*	*C. albicans*
VIa	13 (0.54)	11 (0.65)	12 (0.55)	11 (0.55)	13 (0.62)	14 (0.61)
VIb	15 (0.63)	12 (0.72)	13 (0.59)	13 (0.65)	13 (0.63)	12 (0.48)
VIc	15 (0.63)	14 (0.82)	13 (0.59)	15 (0.75)	13 (0.62)	13 (0.62)
VId	14 (0.58)	12 (0.72)	14 (0.64)	15 (0.75)	13 (0.62)	14 (0.61)
VIe	14 (0.58)	15 (0.88)	14 (0.64)	13 (0.65)	11 (0.52)	12 (0.48)
VIIa	14 (0.58)	15 (0.88)	13 (0.59)	12 (0.6)	13 (0.62)	13 (0.62)
VIIb	14 (0.58)	13 (0.76)	15 (0.68)	16 (0.8)	14 (0.67)	14 (0.61)
VIIc	17 (0.71)	14 (0.82)	16 (0.73)	17 (0.85)	15 (0.71)	17 (0.74)
VIId	14 (0.58)	13 (0.76)	15 (0.68)	14 (0.7)	14 (0.67)	15 (0.65)
VIIe	16 (0.67)	14 (0.82)	16 (0.73)	16 (0.8)	15 (0.71)	14 (0.61)
Nfc	24	17	22	20	NT	NT
Ctz	NT	NT	NT	NT	21	23

[a]concentration of test compounds and standard 100 µg/8 mm disc
(Activity index) = Inhibition zone of the sample / Inhibition zone of the standard,
Nfc: Norfloxacin, Ctz: Clotrimazole.
NT: Not Tested
#Microbial strains were procured from Institute of Microbial Technology (IMTECH) Chandigarh, INDIA.

3. Experimental

The melting points of the compounds were determined in open capillaries using Thermonik Precision Melting point cum Boiling point apparatus (C-PMB-2, Mumbai, India) in the Celsius scale and are uncorrected. IR spectra of compounds were recorded using Shimadzu FTIR-8400s spectrophotometer on KBr discs. ^{1}H-NMR spectra were recorded in $CDCl_3$/DMSO-δ6 on Varian EM 390 Spectrophotometer using TMS as internal standard and electro spray mass spectra were recorded on Micromass Quattro II triple-quadrupole mass spectrometer (Methanol) (Micromass, Manchester, UK). The homogeneity of the compounds was established by TLC on silica gel plate. The spots were visualized in iodine vapor.

General procedure for synthesis of N-substituted benzylidene-5-((2-methyl-1H-benzo[d]imidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-amine (VIa-e): The compound **V** (0.01 mol) was dissolved in ethanol (100 mL), sodium acetate (0.8 g, 0.02 mol), benzaldehyde (2.1mL) and two drops of concentrated sulphuric acid was added and the reaction mixture was heated under reflux for 16 h. The excess of solvent was distilled-off under reduce pressure. The residue so obtained was washed with diethyl ether and recrystallized from methanol. Similarly, all the compounds (**VIa-e**) were prepared by adopting this procedure.

N-benzylidene-5-((2-methyl-1H-benzo[d]imidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-amine **(VIa)**:Yield 66%, m.p.178-179 ^{0}C, R_f=0.53, λ_{max} 235 nm; IR (KBr, cm^{-1}): 3052.9 (Ar C-H str), 2909.2 (aliphatic C-H str), 1647.5 (C=N of thiadiazole), 1614.9 (C=N), 1603-1505.8 (Ar C-C str), 821.9 (C-H def disubstituted benzene ring), 738.3 (C-S of thiadiazole nucleus) ; ^{1}H NMR (300 MHz, DMSO-d6, TMS, δ ppm): 2.3 (s, 3H, CH_3), 4.7 (s, 2H, CH_2), 8.2 (s, 1H,CH=N), 7.1-7.8 (m, 9H, Ar-H); ESMS (Methanol) *m/z* 334.3 (M+); Anal. Calcd. for $C_{18}H_{15}N_5S$ (333.41): C, 64.84; H, 4. 53; N, 21.01; S, 9.62; Found: C, 64.83; H, 4.55; N, 21.02; S, 9.61.

N-(4-(Dimethylamino)benzylidene)-5-((2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine(VIb): Yield 52%, m.p.162-163 ^{0}C, R_f=0.62, λ_{max} 238 nm; IR (KBr, cm^{-1}): 3048.2 (Ar C-H str), 2889.7 (aliphatic C-H str), 2980.7 (aliphatic C-H str), 2798.6 (N-CH_3 str), 1663.7 (C=N), 1502.4 (Ar C-C str), 1352.1 (tertiary C-N str), 742.3 (C-S of thiadiazole nucleus);^{1}HNMR: 2.52 (s, 3H, CH_3), 2.88 (s, 6H, CH_3,P-dimethylamino), 4.90(s, 2H, CH_2), 7.0-8.11 (m, 8H, Ar-H), 8.44 (s, 1H,CH=N);ESMS (Methanol) *m/z* 375.13 (M+); Anal. Calcd. for $C_{20}H_{20}N_6S$ (376.48): C, 63.81; H, 5.35; N, 22.32; S, 8.52; Found: C, 63.80; H, 5.37; N, 22.32; S, 8.51.

N-(4-Methoxybenzylidene)-5-((2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine (VIc): Yield 69%, m.p.181-183 ^{0}C, R_f=0.58, λ_{max} 248 nm; IR (KBr, cm^{-1}): 3036.3 (Ar C-H str), 3019.2 (aliphatic C-H str), 2832.7 (O-C str of O-CH3), 1654.1 (C=N of thiadiazole), 1619.9 (C=N of benzimidazole ring), 1612.7 and 1512.4 (Ar C-C str), 1549.8 (C=N str of Schiff base), 1282.5 (Ar-O str of Schiff base), 749.2 (C-S str of thiadiazole nucleus); ^{1}H NMR (300 MHz, DMSO-d6, TMS, δ ppm): 2.4 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 5.2 (s, 2H, CH_2), 8.3 (s, 1H, CH of benzylidine imine) 6.8-7.5 (m, 8H, benzimidazole and benzylidine); ESMS (Methanol) *m/z* 363.60 (M+); Anal. Calcd. for $C_{19}H_{17}N_5OS$ (363.44): C, 62.79; H, 4.71; N, 19.27; S, 8.82; Found: C, 62.80; H, 4.70; N, 19.28; S, 8.82.

N-(2-Hydroxybenzylidene)-5-((2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine (VId): Yield 83%, m.p.174-176 ^{0}C, R_f=0.61, λ_{max} 252 nm; IR (KBr, cm^{-1}): 3663.4 (O-H str), 3197.8 (N-H str of Schiff base), 3047.7 (Ar C-H str), 2993.5 (aliphatic C-H str), 2904.4 (aliphatic C-H str), 1664.4 (C=N of thiadiazole), 1617.9 (C=N of benzimidazole ring), 1554.2 (C=N str of Schiff base), 1510.1 and 1052.9 (Ar C-C str), 1427.2 (C-O str of phenol), 744.3 (C-S of thiadiazole nucleus); ^{1}H NMR: 2.35 (s, 3H, CH_3), 5.11 (s, 2H, CH_2), 5.58 (s,1H,OH), 8.3 (s, 1H, CH=N), 6.8-7.5 (m, 8H, Ar-H); ESMS (Methanol) *m/z* 348.7 (M+); Anal. Calcd. for $C_{18}H_{15}N_5OS$ (349.41): C, 61.87; H, 4.33; N, 20.04; S, 9.18; Found: C, 61.86; H, 4.32; N, 20.02; S, 9.20.

N-(4-Hydroxybenzylidene)-5-((2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine(VIe): Yield 74%, m.p.182-183 ^{0}C, R_f=0.64, λ_{max} 238 nm; IR (KBr, cm^{-1}): 3657.3 (O-H str), 3201.3 (N-H str of Schiff base), 3051.3 (Ar C-H str), 3015.2 (aliphatic C-H str), 2999.9 (aliphatic C-H str), 1653.5 (C=N of thiadiazole), 1618.3 (C=N of benzimidazole ring), 1564.7 (C=N str of Schiff base), 1614.7 and 1507.4 (Ar C-C str), 1353.2 (C-O str of phenol), 747.9 (C-S of thiadiazole nucleus); ^{1}H NMR: 2.30 (s, 3H, CH_3), 5.11 (s, 2H, CH_2), 5.25 (s, 1H, OH), 8.2 (s, 1H, CH=N), 6.8-7.8 (m, 8HAr-H); ESMS (Methanol) *m/z* 349.4 (M+); Anal. Calcd. for $C_{18}H_{15}N_5OS$ (349.41): C, 61.87; H, 4.33; N, 20.04; S, 9.18; Found: C, 61.85; H, 4.30; N, 20.05; S, 9.19.

General procedure for synthesis of 3-chloro-4-(4-substituted phenyl)-1-(5-((2-methyl-1H-benzo [d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one (VIIa-e): Required quantity of the compound **VIa** (0.01 mol) and triethylamine (1.1 g, 0.01mol) was dissolved in absolute alcohol (50 mL).To this mixture, chloroacetylchloride (2.2 mL, 0.02 mol) was added dropwise with constant stirring over period of 1h on mechanical stirrer. Further the reaction mixture was stirred for 3-4 h, followed by cooling and poured onto ice cold water. The separated solid was filtered off, dried and recrystallized from petroleum ether (60-80°). Similarly, all the compounds **(VIIa-e)** were synthesized by adopting the above said method.

3-Chloro-4-(phenyl)-1-(5-((2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one (VIIa):Yield 68%, m.p.195-196 ^{0}C, R_f=0.44, λ_{max} 248 nm; IR (KBr, cm^{-1}); 3048.2 (Ar C-H str), 2909.2 (aliphatic C-H str), 1643.7 (C=N of thiadiazole), 1609.4 (C=N of benzimidazole ring), 1603.6 and 1505.8 (Ar C-C str), 1718.46 (C=O str), 740.4 (C-S of thiadiazole nucleus), 727.7 (C-Cl str); ^{1}H NMR: 2.4 (s, 3H, CH3), 4.8 (s, 2H, CH_2), 5.4 (s, 2H, CH of propiolactam), 7.1-7.8 (m, 9H, Ar-H); ESMS (Methanol) *m/z* 407.1 (M+); Anal. Calcd. for $C_{20}H_{16}ClN_5OS$ (409.89): C, 58.60; H, 3.93; Cl, 8.65; N, 17.09; S, 7.82; Found: C, 58.61; H, 3.93; Cl, 8.66; N, 17.08; S, 7.82.

3-Chloro-4-(4-(dimethylamino)phenyl)-1-(5-((2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one (VIIb): Yield 64%, m.p.187-188 ^{0}C, R_f=0.47, λ_{max} 261 nm; IR (KBr, cm^{-1}): 3042.8 (Ar C-H str), 2979.2 (aliphatic C-H str), 2791.1 (CH_3-N Str), 1693.3 (C=O str), 1647.4 (C=N of thiadiazole), 1616.5 (C=N of benzimidazole ring), 1607.7 and 1508.7 (Ar C-C str), 787.7 (C-Cl str), 738.3 (C-S of thiadiazole nucleus) ; ^{1}H NMR: 2.3 (s, 3H, CH3), 2.9 (s, 6H, N-$(CH_3)_2$), 4.8 (s, 2H, CH_2), 5.2-5.6 (s, 2H, CH of propiolactam), 6.6-7.8 (m, 8H, Ar-H and benzimidazole); ESMS (Methanol) *m/z* 455.4 (M+); Anal. Calcd. for $C_{22}H_{21}ClN_6OS$ (452.96): C, 58.34; H, 4.67; Cl, 7.83; N, 18.55; S, 7.08; Found: C, 58.35; H, 4.66; Cl, 7.82; N, 18.58; S, 7.07.

3-Chloro-4-(4-methoxyphenyl)-1-(5-((2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one (VIIc): Yield 71%, m.p. 202-204 ^{0}C, R_f=0.48, λ_{max} 238 nm; IR (KBr, cm^{-1}): 3019.2 (aliphatic C-H str),3040.7 (Ar C-H str), 1718.46 (C=O str), 1654.3 (C=N of thiadiazole), 1627.9 (C=N of benzimidazole ring), 1603.6 and 1505.8 (Ar C-C str), 1035.7 (C-O str of OCH_3), 823.9 (C-H def disubstituted benzene ring), 781.6 (C-Cl str), 750.5 (C-S of thiadiazole nucleus); ^{1}H NMR: 2.4 (s, 3H, CH3), 3.8 (s, 3H, O-CH_3), 4.9 (s, 2H, CH_2), 5.1-5.4 (s, 2H, CH of propiolactam), 6.6-7.8 (m, 8H, Ar-H and benzimidazole); ESMS (Methanol) *m/z* 4 41.9(M+); Anal. Calcd. for $C_{21}H_{18}ClN_5O_2S$ (439.92): C, 57.33; H, 4.12; Cl, 8.06; N, 15.92; S, 7.29; Found: C, 57.32; H, 4.12; Cl, 8.08; N, 15.91; S, 7.29.

3-Chloro-4-(2-hydroxyphenyl)-1-(5-((2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one (VIId): Yield 79%, m.p.213-214 ^{0}C, R_f=0.58, λ_{max} 242 nm; IR: 3388.2 (O-H str), 3035.8 (Ar C-H str), 2980.7 (aliphatic C-H str), 1718.46 (C=O str), 1642.7 (C=N of thiadiazole),1618.3 (C=N of benzimidazole ring), 1613.6 and 1501.7 (Ar C-C str), 1369.8 (C-O str), 783.9 (C-Cl str), 762.5 (C-S of thiadiazole nucleus); ^{1}H NMR : 2.4 (s, 3H, CH3), 5.0 (s, 1H, O-H), 4.8 (s, 2H, CH_2), 5.1-5.4 (s, 2H, CH of propiolactam), 6.6-7.7 (m, 8H, Ar-H and benzimidazole); ESMS (Methanol) *m/z* 425.10; Anal. Calcd. for $C_{20}H_{16}ClN_5O_2S$ (425.89): C, 56.40; H, 3.79; Cl, 8.32; N, 16.44; S, 7.53; Found: C, 56.41; H, 3.79; Cl, 8.33; N, 16.45; S, 7.53.

3-Chloro-4-(4-hydroxyphenyl)-1-(5-((2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one (VIIe): Yield 76%, m.p.221-223 ^{0}C, R_f=0.47, λ_{max} 273 nm; IR (KBr, cm^{-1}): 3600.2 (O-H str), 3036.3 (Ar C-H str), 2980.7 (aliphatic C-H str), 1722.46 (C=O str), 1641.4 (C=N of thiadiazole), 1619.7 (C=N of benzimidazole ring), 1613.6 and 1501.7 (Ar C-C str), 1353.7 (C-O str), 813.5 (C-Cl str), 760.1 (C-S of thiadiazole nucleus); ESMS (Methanol) *m/z* 425.98; Anal. Calcd. for $C_{20}H_{16}ClN_5O_2S$ (425.89): C, 56.40; H, 3.79; Cl, 8.32; N, 16.44; S, 7.53; Found: C, 56.42; H, 3.80; Cl, 8.31; N, 16.42; S, 7.52.

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