



## Synthesis of ethoxyphthalimido derivatized thiadizole assembled imidazolidinone and chloroazetidione systems from common intermediate Schiff's bases and evaluation of their antibacterial activity

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### ABSTRACT

In present investigation synthesis of 2-(2-(3-(5-((2-methyl-1H-enzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-4-oxo-2-phenylimidazolidin-1-yl)ethoxy)isoindoline-1,3-dione **9a-d** and 3-chloro-4-(4-phenyl)-1-(5-((2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidion-2-one **6a-d** are described. 2-Methyl benzimidazole **1** is converted to carbothioamide **3** by the reaction with ethylchloroacetate followed by thiosemicarbazide. It is cyclised to thiadizole **4** by treatment with conc. H<sub>2</sub>SO<sub>4</sub> and NH<sub>3</sub>. Condensation of **4** with different araldehyde yielded corresponding Schiff's bases **5a-d**. Compounds **5a-d** has acted as key intermediate for both series of the final compounds. In one pathway, **5a-d** are converted to azetidione plugged compounds **6a-d** by treatment with chloroacetylchloride in presence of triethylamine. In an another route, reaction of **5a-d** with glycine has afforded the formation of 3-(5-((2-methyl-1H-benzoimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-2-phenylimidazolidin-4-one **7a-d**. Finally the targeted molecules **9a-d** were obtained by the base induced condensation of **7a-d** with bromoethoxyphthalimide. Structure confirmation was accomplished by spectral studies (IR, <sup>1</sup>HNMR, Mass) and elemental analysis of all the synthesized compounds.

**Keywords:** Bromoethoxyphthalimide; Azitidinone; Benzimidazole; Thiadizole; Chloroacetylchloride.

### INTRODUCTION

Azoles have played a crucial part in the history of heterocyclic chemistry and also been used extensively as important synthons in organic synthesis. Owing to the versatile chemotherapeutical activities of azoles especially imidazole and benzimidazole, a significant amount of research activity and efforts has been directed towards this class of compounds. Benzimidazoles, its aryl and alkylsubstituted derivatives have evoked considerable attention in last three decades as these are endowed with a wide range of pharmaceutical activities like antifungal[1], antihypertensive[2], antioxidant[3], cardiotoxic[4], antithrombotic[5], HIV-IPR inhibitor[6], IL-1 inhibitor[7], anticonvulsant[8], antihepatitis B and C virus activity[9], antitubercular [10], antiulcer [11] activities etc. The cytotoxicity of 2-methyl benzimidazole derivatives was investigated against a variety of cell lines where, introduction of various heterocyclic rings

at the position 5 of 2-methyl benzimidazole led to the discovery of potent antitumor drug derivatives [12-13].

The 1, 3, 4-thiadiazole, another class ofazole group is a versatile pharmacophore, which exhibits a wide variety of biological activities. A few of them, which are worthy of mention, are diuretic [14], CNS depressant [15], antiviral, antihypertensive [16], insecticidal [17], antimicrobial[18], acaricidal, [19] fungicidal and nematocidal, [20-22] and many more. Compounds possessing the  $\beta$ -lactam skeleton are of great importance as they constitute one of the most successful classes of therapeutic agents to date [23]. It is well established as the key pharmacophore of  $\beta$ -lactam antibiotics, the most widely employed class of antibacterial agents[24]including penicillin and cephalosporin as popular antibiotic drugs. In addition, there are many important nonantibiotic uses of 2-azetidiones in fields ranging from enzyme inhibition[25] to gene activation[26]. Apart from their clinical interest, the use of  $\beta$ -lactams as versatile synthons for the preparation of compounds of biological relevance, such as  $\alpha$ - and  $\beta$ -amino acids, alkaloids, heterocycles, and taxoids [27], has triggered a renewed interest in the building of new  $\beta$ -lactam systems.

Diverse biological activities like anticonvulsant[28], anticancer[29], diuretic[30], fungicidal[31] and trypanocidal[32] have been observed for alkoxyphthalimide and related functionalities. The ability to inhibit growth of malarial parasite *Plasmodium falciparum*[33] have also been observed for several aminoxy derivatives. Heterocyclic rings attached to alkoxyphthalimide group have been synthesized [34] and tested for antimicrobial and antimalarial[35] activity.

Led by the above facts coupled with the desire for synthesizing various alkoxyphthalimide derivatives herein is reported the synthesis of some new heterocycles incorporating above moieties together in order to prepare the molecules having enhanced biological properties.

## MATERIALS AND METHODS

Melting points were determined by electro thermal method in open capillary tubes and are therefore uncorrected. Purity of the synthesized compounds was checked on silica gel G TLC plates of 2 mm thickness using n-hexane and ethylacetate as solvent system. The visualization of spot was carried out in an iodine chamber. The IR spectra of the compounds were recorded on a 4000-450  $\text{cm}^{-1}$  ranges using KBr discs on FTIR IR RX1 Perkin Elmer spectrophotometers and  $^1\text{H}$  NMR were recorded on a Bruker DRX-300 MHz spectrometer ( $\text{CDCl}_3$ ) using TMS as an internal standard. The mass spectra were recorded on a Jeol SX-102 (FAB) mass spectrometer. Phthalimidoxyethyl bromide **8** was prepared by reported method [36]. Structure of all the synthesized compounds was assigned on basis of their analytical and spectral data.

**General procedure for synthesis of Ethyl-2-(2-methyl-1H-benzimidazol-1-yl)-acetate(2):** To a solution of 2-methyl benzimidazole **1** (1.32 gm, 0.01 mole) in absolute alcohol, ethylchloroacetate (1.22 gm, 0.01 mole) was added drop wise by a dropping funnel.  $\text{K}_2\text{CO}_3$  (2.76 gm, 0.02 mole) was used as a base. The reaction mixture was refluxed for 8-10 hr. on a water bath and filtered hot. Excess of Solvent was evaporated from the filtrate at reduced pressure. On cooling, white shining crystals were obtained, recrystallization was carried out from ethanol.

IR(KBr,  $\text{cm}^{-1}$ ): 2985(C-H str.,  $\text{CH}_3$ ), 2930(C-H str.,  $\text{CH}_2$ ), 1735 (C=O str.), 1030(C-O str.);  $^1\text{H}$ NMR( $\text{CDCl}_3$ ,  $\delta$ ): 7.4(m, 4H, Ar-h), 4.20 (q, 2H,  $\text{COOCH}_2\text{CH}_3$ ), 3.66(s, 2H,  $\text{NCH}_2$ ), 1.24(t, 3H,  $\text{COOCH}_2\text{CH}_3$ ).

**General procedure for synthesis of 2-(2-(2-methyl-1H-benzimidazol-1-yl)acetyl) hydrazine carbothioamide (3):** An equimolar mixture of **2** (2.18 gm, 0.01 mole) and thiosemicarbazide (0.91 gm, 0.01 mole) in acetone was refluxed for 10-12 hr. The reaction mixture was allowed to cool and the solid obtained was recrystallized from ethanol.

IR(KBr,  $\text{cm}^{-1}$ ): 3378, 3237(N-H str.), 3050(C-H str., Ar-H), 2988(C-H str.,  $\text{CH}_2$ ), 1682(C=O str., CONH), 1100 (C=S str.);  $^1\text{H}$  NMR( $\text{CDCl}_3$ ,  $\delta$ ): 8.1(m, 4H, NH.NH.C=S.NH<sub>2</sub>), 7.4-7.5(m, 4H, Ar-H), 3.68(s, 2H,  $\text{NCH}_2$ ).

**General procedure for synthesis of 5-((2-methyl-1H-benzimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine (4):** Carbothioamide **3** (2.63 gm, 0.01 mole) was dissolved in 4 mL Conc.  $\text{H}_2\text{SO}_4$ . The solution was

stirred at room temp. for 1 hr. and left overnight. It was then poured on crushed ice. The resulting suspension was kept in ammoniacal water for 2 hr., solid obtained was filtered and recrystallised from ethanol.

IR(KBr,cm<sup>-1</sup>):3355(N-H str.),3048 (C-H str., Ar-H), 2986(C-H str.,CH<sub>2</sub>),1600(C=N str.),710(C-S-C str.);<sup>1</sup>H NMR(CDCl<sub>3</sub>, δ): 7.9(m,4H, Ar-H),4.5 (s,2H,NH<sub>2</sub>); 3.68(s, 2H, NCH<sub>2</sub>), MS m/z 245 [M]<sup>+</sup>.

**General procedure for synthesis of N-substituted benzylidene-5-((2-methyl-1H-benzimidazol-1-yl)methyl)-1, 3, 4-thiadiazol-2-amine (5a-d):** The compound 4 (2.45g, 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 hr. The excess of solvent was distilled-off under reduced pressure. The residue so obtained was washed with dry diethyl ether and recrystallized from methanol. Similarly, all the compounds (5b-d) were prepared by adopting same procedure.

**N-benzylidene-5-((2-methyl-1H-benzimidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-amine (5a):** IR (KBr,cm<sup>-1</sup>): 3051 (Ar C-H str.), 2906 (aliphatic C-H str.),1605 (C=N str.), 1603 (Ar C-C str.), 821 (C-H def disubstituted benzene ring), 715 (C-S-C str.) ; <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ): 2.3 (s, 3H,CH<sub>3</sub>), 4.7 (s, 2H, CH<sub>2</sub>), 8.2 (s, 1H,CH=N), 7.1-7.8 (m,9H, Ar-H); MS m/z 333 [M]<sup>+</sup>.

**N-(4-chlorobenzylidene)-5-((2-methyl-1H-benzimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine (5b):**IR (KBr, cm<sup>-1</sup>): 3047 (Ar C-H str.),2892 (aliphatic C-H str.), 2792(N-CH<sub>3</sub> str.), 1609 (C=N str.), 1590(Ar C-C str.), 717 (C-S-C str.),742(C-Cl str.);<sup>1</sup>H NMR(CDCl<sub>3</sub>, δ): 2.5 (s, 3H, CH<sub>3</sub>), 4.9(s, 2H, CH<sub>2</sub>), 7.0-8.11 (m, 8H, Ar-H), 8.4 (s, 1H,CH=N);MS m/z 367 [M]<sup>+</sup>., 369 [M+2]<sup>+</sup>.

**N-(4-methoxybenzylidene)-5-((2-methyl-1H-benzimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine (5c):** IR (KBr, cm<sup>-1</sup>): 3038 (Ar C-H str.),3010 (aliphatic C-H str.), 2830 (O-C str. of OCH<sub>3</sub>),1615 (C=N str.), 1598(Ar C-C str.),1545 (C=N str. of Schiff base), 725 (C-S-C str.); <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ): 2.3 (s, 3H,CH<sub>3</sub>), 3.7 (s, 3H, OCH<sub>3</sub>), 5.0 (s, 2H, CH<sub>2</sub>), 8.1 (s, 1H,CH of benzylidene imine) MS m/z 363 [M]<sup>+</sup>.

**N-(4-(dimethylamino)benzylidene)-5-((2-methyl-1H-benzimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine (5d):** IR (KBr, cm<sup>-1</sup>): 3045 (Ar C-H str.),2896 (aliphatic C-H str.), 2990 (aliphatic C-H str.),2799 (N-CH<sub>3</sub> str.), 1661 (C=N), 1520 (Ar C-C str.), 1350 (tertiary C-N str.), 732(C-S-C str.);<sup>1</sup>H NMR(CDCl<sub>3</sub>, δ): 2.5 (s, 3H, CH<sub>3</sub>), 2.9 (s, 6H, CH<sub>3</sub>,P-dimethylamino), 4.9(s, 2H, CH<sub>2</sub>), 7.0-8.10 (m, 8H, Ar-H), 8.6 (s, 1H,CH=N); MS m/z 376 [M]<sup>+</sup>.

**General procedure for synthesis of 3-chloro-4-(4-substituted phenyl)-1-(5-((2-methyl-1H-benzimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetid-2-one (6a-d):** Compound 5 (0.01 mol) and triethylamine (1.1g,0.01mol) was dissolved in absolute alcohol (50mL).To this mixture, chloroacetylchloride (2.2 mL,0.02 mol) was added dropwise with constant stirring over period of 1h on magnetic stirrer. Further the reaction mixture was stirred for 3-4 h, followed by cooling and was poured on ice cold water. The separated solid was filtered off, dried and recrystallized from petroleum ether (60-80°). Similarly, all the compounds (6a-d) were synthesized by adopting the above method with minor change in reaction condition.

**3-chloro-4-(4-phenyl)-1-(5-((2-methyl-1H-benzimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetid-2-one (6a):**IR (KBr, cm<sup>-1</sup>): 3046 (Ar CH str.), 2910 (aliphatic C-H str.), 1640(C=N of thiadiazole), 1607 (Ar C-C str.), 1718 (C=O str.), 741 (C-S-C str.), 728 (C-Cl str.); <sup>1</sup>H NMR(CDCl<sub>3</sub>, δ): 2.4 (s, 3H, CH<sub>3</sub>), 4.8 (s, 2H, CH<sub>2</sub>), 5.4 (d,1H, CH of C-Cl bond), 4.8 (d,1H, CH of C-N bond), 7.1-7.8 (m, 9H, Ar-H).

**3-chloro-4-(4-chlorophenyl)-1-(5-((2-methyl-1H-benzimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetid-2-one (6b):** IR (KBr, cm<sup>-1</sup>): 3041(Ar C-H str.), 2977 (aliphatic C-H str.),2789 (CH<sub>3</sub>-N Str.),

1691(C=O str.), 1643 (C=N of thiadiazole), 1600 (Ar C-C str.), 734 (C-Cl str.), 739 (C-S-C str.) ; <sup>1</sup>H NMR(CDCl<sub>3</sub>, δ): 2.3 (s, 3H, CH<sub>3</sub>), 2.9 (s, 6H, N-(CH<sub>3</sub>)<sub>2</sub>), 4.8 (s, 2H, CH<sub>2</sub>), 5.6 (d,1H, CH of C-Cl bond) ,4.9 (d,1H, CH of C-N bond) , 7.1-7.8 (m, 8H, Ar-H).

**3-chloro-4-(4-methoxyphenyl)-1-(5-((2-methyl-1H-benzoimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetid-2-one (6c):** IR (KBr, cm<sup>-1</sup>): 3020 (aliphatic C-H str.),3041 (Ar C-H str.), 1720 (C=O str), 1652 (C=N of thiadiazole), 1601 and 1504 (Ar C-C str.), 1034 (C-O str. of OCH<sub>3</sub>), 820 (C-H def disubstituted benzene ring), 780 (C-Cl str.), 751 (C-S-C str.); <sup>1</sup>H NMR(CDCl<sub>3</sub>, δ): 2.4 (s, 3H, CH<sub>3</sub>),3.8 (s, 3H, O-CH<sub>3</sub>), 4.9 (s, 2H, CH<sub>2</sub>), 5.2 (d,1H, CH of C-Cl bond) ,4.7 (d,1H, CH of C-N bond), 6.6-7.8 (m, 8H, Ar-H).

**3-chloro-4-(4-(dimethylamino)phenyl)-1-(5-((2-methyl-1H-benzoimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetid-2-one (6d):** IR (KBr, cm<sup>-1</sup>): 3040 (Ar C-H str), 2977 (aliphatic C-H str), 2790 (CH<sub>3</sub>-N Str), 1691 (C=O str), 1645 (C=N of thiadiazole),1335(N-O str.), 1020(C-O str.) ; <sup>1</sup>H NMR(CDCl<sub>3</sub>, δ): 2.1 (s, 3H, CH<sub>3</sub>), 2.8 (s, 6H, N-(CH<sub>3</sub>)<sub>2</sub>), 4.8 (s, 2H, CH<sub>2</sub>), 5.4 (d,1H, CH of C-Cl bond) ,5.0 (d,1H, CH of C-N bond) 6.6-7.8 (m, 8H, Ar-H).

**General procedure for synthesis of 3-(5-((2-methyl-1H-benzoimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-2-phenylimidazolidin-4-one (7a-d):** Schiff's base **5**(3.33g, 0.01 mole) was dissolved in a mixture of dry benzene and methanol (1:1,30ml),glycine (0.75 g,0 .01 mole) was added with constant stirring. This mixture was refluxed for 8-10h. Water formed during the reaction was removed by a Dean-Stark Apparatus using azeotropic distillation. Solid separated was filtered from remaining concentrated solution and pressed dry. Some of this was recrystallized from ethanol and rest was used for next step. Compounds (7b-d)were also prepared in similar method with required change in reflux time.

**3-(5-((2-methyl-1H-benzimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-2-phenylimidazolidin-4-one (7a):** IR (KBr,cm<sup>-1</sup>): 3062 (Ar C-H str.), 2900 (aliphatic C-H str.), 1610 (Ar C-C str.),1710 (C=O str.) , 725 (C-S-C str.) ; <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ): 2.1 (s, 3H,CH<sub>3</sub>), 4.9 (s, 2H, CH<sub>2</sub>), 7.0-7.8 (m,9H, Ar-H), 3.32 (s, 2H, NCH<sub>2</sub>C of imidazolidinone ring); MS m/z 390 [M]<sup>+</sup>.

**2-(4-chlorophenyl)-3-(5-((2-methyl-1H-benzoimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)imidazolidin-4-one (7b):** IR (KBr, cm<sup>-1</sup>): 3058 (Ar C-H str.),2898 (aliphatic C-H str.), 1596(Ar C-C str.), 1715 (C=O str.) ,727 (C-S-C str.),748(C-Cl str.);<sup>1</sup>HNMR(CDCl<sub>3</sub>, δ): 2.6 (s, 3H, CH<sub>3</sub>), 5.1(s, 2H, CH<sub>2</sub>), 7.4-8.11 (m, 8H, Ar-H), 3.38 (s,2H, NCH<sub>2</sub>C of imidazolidinone ring);MS m/z 424 [M]<sup>+</sup>, 426 [M+2]<sup>+</sup>.

**2-(4-methoxyphenyl)-3-(5-((2-methyl-1H-benzoimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)imidazolidin-4-one (7c):** IR (KBr, cm<sup>-1</sup>): 3055 (Ar C-H str.),3005 (aliphatic C-H str.), 2850 (O-C str. of OCH<sub>3</sub>), 725 (C-S-C str.); <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ): 2.8 (s, 3H,CH<sub>3</sub>), 3.9 (s, 3H, OCH<sub>3</sub>), 5.0 (s, 2H, CH<sub>2</sub>), 3.18 (s, 2H, NCH<sub>2</sub>C of imidazolidinone ring) MS m/z 420[M]<sup>+</sup>.

**2-(4-(dimethylamino)phenyl)-3-(5-((2-methyl-1H-benzoimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)imidazolidin-4-one (7d):**IR (KBr, cm<sup>-1</sup>): 3045 (Ar C-H str.),2916 (aliphatic C-H str.), 2789 (N-CH<sub>3</sub> str.), 1370 (tertiary C-N str.), 722(C-S-C str.);<sup>1</sup>HNMR: 2.7 (s, 3H, CH<sub>3</sub>), 2.9 (s, 6H, CH<sub>3</sub>,P-dimethylamino), 4.6(s, 2H, CH<sub>2</sub>), 7.2-8.10 (m, 8H, Ar-H), 3.23 (s, 2H, NCH<sub>2</sub>C of imidazolidinone ring), MS m/z433 [M]<sup>+</sup>.

**General procedure for synthesis of 2-(2-(3-(5-((2-methyl-1H-benzoimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-4-oxo-2-phenylimidazolidin-1-yl)ethoxy)isoindoline-1,3-dione (9a-d):** A mixture of compound **7a** (3.90g, 0.01 mole) and bromoethoxyphthalimide **8** (2.70g,0.01 mole)in acetone and K<sub>2</sub>CO<sub>3</sub> (2.76g,0.02 mole)was reflux for 24 hrs. in a round bottom flask. It was cooled at room temp. and the K<sub>2</sub>CO<sub>3</sub> was filtered. The filtrate was slowly poured on crushed ice while constant stirring. Solid obtained was filtered and washed twice with ice cooled water. It was recrystallized from rectified spirit.

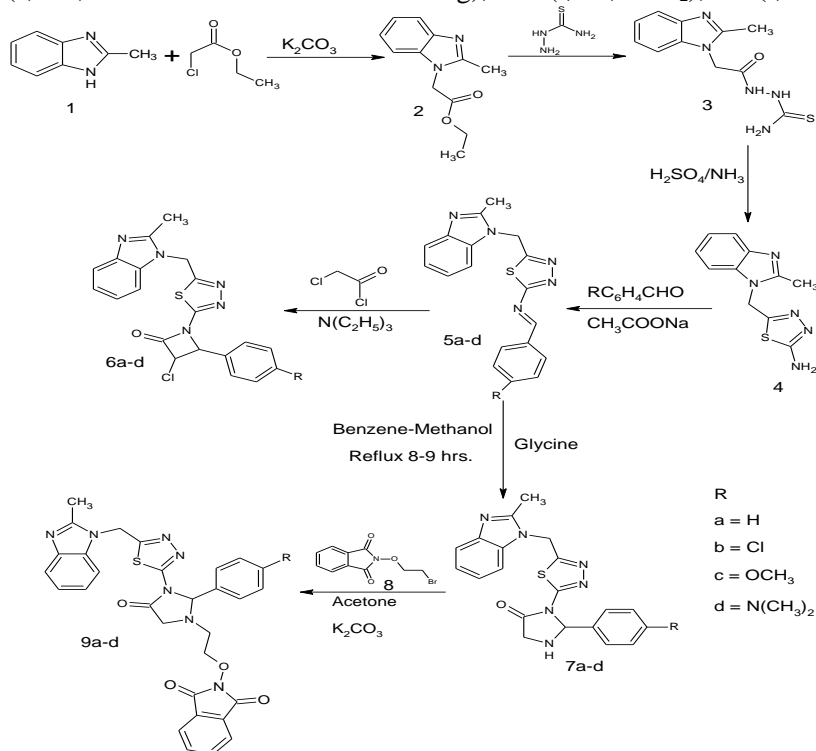
Compounds (**9b-d**) were also synthesized by similar method with minor change in reaction conditions.

**2-(2-(3-(5-((2-methyl-1H-benzoimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-4-oxo-2-henylimidazolidin-1-yl)ethoxy)isoindoline-1,3-dione (9a):** IR (KBr,  $\text{cm}^{-1}$ ): 3068 (Ar C-H str.), 2926 (aliphatic C-H str.), 1613 (Ar C-C str.), 1718 (C=O str.), 826 (C-H def disubstituted benzene ring), 705 (C-S-C str.), 1462 (N-O str.), 1026 (C-O str.);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ,  $\delta$ ): 2.8 (s, 3H,  $\text{CH}_3$ ), 4.9 (s, 2H,  $\text{CH}_2$ ), 7.1-7.8 (m, 12H, Ar-H), 3.48 (s, 2H,  $\text{NCH}_2\text{C}$  of imidazolidinone ring), 3.21 (t, 2H,  $\text{NCH}_2$ ), 4.82 (t, 2H,  $\text{OCH}_2$ ); MS  $m/z$  579  $[\text{M}]^+$ .

**2-(2-(2-(4-chlorophenyl)-3-(5-((2-methyl-1H-benzoimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-4-oxoimidazolidin-1-yl)ethoxy)isoindoline-1,3-dione (9b):** IR (KBr,  $\text{cm}^{-1}$ ): 3057 (Ar C-H str.), 2898 (aliphatic C-H str.), 1598 (Ar C-C str.), 1720 (C=O str.), 727 (C-S-C str.), 745 (C-Cl str.), 1468 (N-O str.), 1036 (C-O str.);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ,  $\delta$ ): 2.1 (s, 3H,  $\text{CH}_3$ ), 4.2 (s, 2H,  $\text{CH}_2$ ), 7.6-8.11 (m, 11H, Ar-H), 3.43 (s, 2H,  $\text{NCH}_2\text{C}$  of imidazolidinone ring), 3.24 (t, 2H,  $\text{NCH}_2$ ), 4.86 (t, 2H,  $\text{OCH}_2$ ); MS  $m/z$  613  $[\text{M}]^+$ , 615  $[\text{M}+2]^+$ .

**2-(2-(2-(4-methoxyphenyl)-3-(5-((2-methyl-1H-benzoimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-4-oxoimidazolidin-1-yl)ethoxy)isoindoline-1,3-dione (9c):** IR (KBr,  $\text{cm}^{-1}$ ): 3048 (Ar C-H str.), 2892 (aliphatic C-H str.), 2880 (O-C str of  $\text{OCH}_3$ ), 735 (C-S-C str.), 1458 (N-O str.), 1016 (C-O str.);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ,  $\delta$ ): 2.6 (s, 3H,  $\text{CH}_3$ ), 3.4 (s, 3H,  $\text{OCH}_3$ ), 7.5-8.1 (m, 11H, Ar-H), 5.0 (s, 2H,  $\text{CH}_2$ ), 3.12 (s, 2H,  $\text{NCH}_2\text{C}$  of imidazolidinone ring), 3.11 (t, 2H,  $\text{NCH}_2$ ), 4.52 (t, 2H,  $\text{OCH}_2$ ); MS  $m/z$  609  $[\text{M}]^+$ .

**2-(2-(2-(4-(dimethylamino)phenyl)-3-(5-((2-methyl-1H-benzoimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-4-oxoimidazolidin-1-yl)ethoxy)isoindoline-1,3-dione (9d):** IR (KBr,  $\text{cm}^{-1}$ ): 3050 (Ar C-H str.), 2896 (aliphatic C-H str.), 2799 (N- $\text{CH}_3$  str.), 1350 (tertiary C-N str.), 732 (C-S-C str.), 1472 (N-O str.), 1056 (C-O str.);  $^1\text{H NMR}$ : 2.5 (s, 3H,  $\text{CH}_3$ ), 2.9 (s, 6H,  $\text{CH}_3$ , P-dimethylamino), 4.9 (s, 2H,  $\text{CH}_2$ ), 7.0-8.10 (m, 11H, Ar-H), 3.53 (s, 2H,  $\text{NCH}_2\text{C}$  of imidazolidinone ring), 3.21 (t, 2H,  $\text{NCH}_2$ ), 4.92 (t, 2H,  $\text{OCH}_2$ ); MS  $m/z$  622  $[\text{M}]^+$ .





## RESULTS AND DISCUSSION

2-Alkyl benzimidazole on refluxing with ethylchloroacetate using  $K_2CO_3$  base gave Ethyl-2-(2-methyl-1H-benzimidazol-1-yl)-acetate **2**. Which on condensation with thiosemicarbazide yielded 2-(2-(2-methyl-1H-benzimidazol-1-yl)acetyl)hydrazinecarbothioamide **3**. Formation of **3** was confirmed by the N-H stretching band at 3374 and 3332  $cm^{-1}$  in IR and a multiplet at  $\delta$  8.1 for NH.NH.C=S.NH<sub>2</sub> group in <sup>1</sup>H NMR spectra. Treatment of **3** with conc.  $H_2SO_4$  followed by ammonia gave 5-((2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine **4**. Appearance sharp absorption band at 710  $cm^{-1}$  in IR spectra showed the presence of C-S-C linkage of thiazole ring. <sup>1</sup>H NMR spectrum showed a fine singlet at  $\delta$  4.5 due to NH<sub>2</sub>

functionality. Compound **4** was converted to various Schiff bases N-substituted benzylidene-5-((2-methyl-1H-benzimidazol-1-yl)methyl)-1, 3, 4-thiadiazol-2-amine **5a-d** by the treatment of substituted benzaldehyde in presence of sodium acetate and a trace of conc.  $H_2SO_4$ . Appearance of IR peak at 1565  $cm^{-1}$  of C=N str. of Schiff base, 1600 and 1505  $cm^{-1}$  stretching peaks of Ar-C-C confirmed the formation of **5a-d** series of compounds. It was further confirmed by fine singlet at  $\delta$  8.0 due to presence of CH=N group in the Schiff bases. The Schiff bases **5a-d** acted as key intermediate for the synthesis of two series of compounds and the scheme is bifurcated in two routes. In first route 3-chloro-4-(4-substituted phenyl)-1-(5-((2-methyl-1H-benzimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one (**6a-d**) synthesized by treating the Schiff bases with chloroacetylchloride in presence of triethylamine using dry DMF or absolute alcohol as solvent on a magnetic stirrer at R.T. The chlorine present in the compound was detected by usual chemical tests and was also estimated by usual method. C-Cl stretch at 728  $cm^{-1}$  and a sharp band at 1718  $cm^{-1}$  for C=O functionality in IR spectra confirmed the formation of azetidinone plugged compound. It was further confirmed by doublet at 5.4, -CH of C-Cl bond and doublet at 4.8, -CH of N-C bond for  $\beta$ -lactam in <sup>1</sup>H NMR.

In the second route the key intermediate was refluxed with glycine in a mixed solvent maximally dry benzene and methanol to add an imidazolidinone nucleus to existing compound. Appearance of strong band at 1710  $cm^{-1}$  for C=O and 3290  $cm^{-1}$  for N-H of imidazolidinone ring. Disappearance of <sup>1</sup>H NMR signal for

N=CH group of 5a-d in the resultant compounds 3-(5-((2-methyl-1H-benzimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-2-phenylimidazolidin-4-one **7a-d**. there are two additional signal at  $\delta$  10.18 (singlet) for NH and  $\delta$  3.42 for CH<sub>2</sub> group of imidazolidinone ring which finally confirmed the structure of **7a-d**. Bromoethoxyphthalimide (**8**) was prepared from N-hydroxyphthalimide by the reported method [36]. Condensation of **7** with Bromoethoxyphthalimide (**8**) in acetone/ $K_2CO_3$  gave 2-(2-(3-(5-((2-methyl-1H-benzimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-4-oxo-2-phenylimidazolidin-1-yl)ethoxy)isoindoline-1,3-dione **9**. IR, <sup>1</sup>H NMR and Mass spectra confirmed this condensation. Free stretching vibration band for -NH group at 3398  $cm^{-1}$ , which was present in its precursors (**7**) disappeared and a strong band at 1300-1100  $cm^{-1}$  appeared for the C-N stretching confirmed the formation of new C-N bond. The mass spectrum also supported the proposed structure by viewing molecular ion peak  $m/z = 579$ . Analytical and spectral data for synthesized compounds are given in experimental section.

**Table 1.** Physical and analytical data of synthesized compounds

	Mol. Formula	Mol. Weight	X	M.p. (oC)	Yield (%)	Found % N (Calcd.)
2	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	218	-	210	90	11.26(12.84)
3	C <sub>11</sub> H <sub>13</sub> N <sub>5</sub> OS	263	-	119	84	24.54(26.60)
4	C <sub>11</sub> H <sub>11</sub> N <sub>5</sub> S	245	-	275	72	26.88(28.55)

5a	C <sub>18</sub> H <sub>15</sub> N <sub>5</sub> S	333	H	178	66	19.76(21.01)
5b	C <sub>18</sub> H <sub>14</sub> ClN <sub>5</sub> S	367	Cl	162	52	18.86(19.04)
5c	C <sub>19</sub> H <sub>17</sub> N <sub>5</sub> OS	363	OCH <sub>3</sub>	181	68	18.56(19.27)
5d	C <sub>20</sub> H <sub>20</sub> N <sub>6</sub> S	376	N(CH <sub>3</sub> ) <sub>2</sub>	163	54	21.86(22.32)
6a	C <sub>20</sub> H <sub>16</sub> ClN <sub>5</sub> OS	409	H	195	68	16.04(17.09)
6b	C <sub>20</sub> H <sub>15</sub> Cl <sub>2</sub> N <sub>5</sub> OS	444	Cl	188	64	14.88(15.76)
6c	C <sub>21</sub> H <sub>18</sub> ClN <sub>5</sub> O <sub>2</sub> S	439	OCH <sub>3</sub>	204	71	14.62(15.92)
6d	C <sub>22</sub> H <sub>21</sub> ClN <sub>6</sub> OS	452	N(CH <sub>3</sub> ) <sub>2</sub>	187	64	17.94(18.55)
7a	C <sub>20</sub> H <sub>18</sub> N <sub>6</sub> OS	390	H	205	56	20.94(21.52)
7b	C <sub>20</sub> H <sub>17</sub> ClN <sub>6</sub> OS	424	Cl	201	64	18.84(19.78)
7c	C <sub>21</sub> H <sub>20</sub> N <sub>6</sub> O <sub>2</sub> S	420	OCH <sub>3</sub>	198	70	18.63(19.99)
7d	C <sub>22</sub> H <sub>23</sub> N <sub>7</sub> OS	433	N(CH <sub>3</sub> ) <sub>2</sub>	212	58	21.98(22.62)
9a	C <sub>30</sub> H <sub>25</sub> N <sub>7</sub> O <sub>4</sub> S	579	H	150	65	15.86(16.92)
9b	C <sub>30</sub> H <sub>24</sub> ClN <sub>7</sub> O <sub>4</sub> S	614	Cl	158	72	14.94(15.97)
9c	C <sub>31</sub> H <sub>27</sub> N <sub>7</sub> O <sub>5</sub> S	609	OCH <sub>3</sub>	154	59	15.74(16.08)
9d	C <sub>32</sub> H <sub>30</sub> N <sub>8</sub> O <sub>4</sub> S	622	N(CH <sub>3</sub> ) <sub>2</sub>	149	74	16.14(17.99)

**Biological Properties of Synthesized Compounds:** Synthesized compounds have been evaluated for their biological properties in two ways.

(1) Theoretical prediction of various activity profiles, using computer software (**Pass**).

(2) Experimental determination of biological property which are normally available in these laboratories.

**PASS (Prediction of Activity Spectra for Substances)** is a software product designed as a tool for evaluating the general biological potential of an organic drug-like molecule. **PASS** provides simultaneous predictions of many types of biological activity based on the structure of organic compounds. Thus, **PASS** can be used to estimate the biological activity profiles for virtual and real molecules, which have been synthesized. Some of the predicted properties are displayed in the tabular form.

**Pa (probability "to be active")** estimates the chance that the studied compound is belonging to the sub-class of active compounds (resembles the structures of molecules, which are the most typical in a sub-set of "actives" in PASS training set).

**Pi (probability "to be inactive")** estimates the chance that the studied compound is belonging to the sub-class of inactive compounds (resembles the structures of molecules, which are the most typical in a sub-set of "inactives" in PASS training set).

**Table 2.** Activity predicted by pass software

COMPOUND NO.	6a		6b		6c		6d		7a	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	-	-
Analgesic	0.695	0.010	0.689	0.010	0.617	0.018	0.667	0.012	-	-
Analgesic, non-opioid	0.770	0.005	0.762	0.005	0.689	0.007	0.736	0.005	-	-
Antiarthritic	0.657	0.021	0.638	0.024	0.618	0.026	0.590	0.030	-	-
Antiinflammatory	0.797	0.007	0.777	0.008	0.759	0.009	0.746	0.011	-	-
Antineoplastic enhancer	-	-	-	-	-	-	-	-	0.701	0.004
Gestagen antagonist	0.482	0.020	0.439	0.025	0.452	0.024	0.428	0.027	-	-
HCV NS3-helicase inhibitor	0.323	0.009	0.307	0.010	0.310	0.010	-	-	-	-
Insulin promoter	0.437	0.047	0.482	0.034	0.309	0.129	0.416	0.055	-	-
Neuropeptide Y2 antagonist	0.423	0.025	0.486	0.016	0.431	0.024	0.308	0.068	0,390	0,033
Phosphatase inhibitor	0.315	0.285	0.376	0.215	-	-	-	-	-	-
Prostaglandin E1 antagonist	0.420	0.007	0.417	0.007	0.340	0.013	0.357	0.011	-	-

COMPOUND NO.	9a		9b		9c		9d	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
Antiarthritic	0.448	0.062	0.439	0.065	0.433	0.067	0.392	0.082
Anticonvulsant	0.481	0.040	0.569	0.023	0.339	0.096	0.393	0.067
Phosphatase inhibitor	0.483	0.039	0.506	0.032	0.444	0.052	0.429	0.057

## APPLICATIONS

Synthesis of newer compounds have been carried out by different methods and these new methodology have been developed to synthesize similar type of molecules.

The synthesized molecules have been treated in two ways. Various biological activities have been predicted on statistical ground by using "Pass Software".

Nine compounds have been screened for anti microbial activities, which is available in these and related laboratories and same is compared with predictive activity. Results are found to be matching tentative conclusion of QSAR can also be drawn using these prediction & observation.

Experimental determinations of synthesized molecules have been carried out for antimicrobial (antibacterial and antifungal) properties.

**Antimicrobial Activity:** Nine compounds have been evaluated for their antibacterial and antifungal activities. Pure cultures of pathogenic strains used were *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (bacteria), *Candida albicans* and *Aspergillus fumigatus* (fungi). These were sub cultured and characterized by standard methods of identification. Both the activities have been carried out by Cup or well method. For antibacterial activity nutrient agar medium was autoclaved



(15 Psi, 121° C, 15 min). These were inoculated with suspension of organisms by spread plate method [37]. With the help of sterile borer required number of wells was made in the medium and subsequently these wells were filled with 500 ppm DMF solution of synthesized compounds. These Petri-dishes were sealed with paraffin and incubated at 37° C in an incubator. These were examined for zone of inhibition after 24 hrs. Ciprofloxacin was used as standard (control). Eight compounds have been screened. Antifungal activity was observed on sabouraud dextrose agar media using similar method (*vide supra*). Fluconazole was used as standard. Results for antibacterial and antifungal activity are represented in table 3. On the basis of zone size inhibition studies activity index is also prepared and conclusions are drawn.

**Antibacterial Activity:** Minimum Inhibitory Concentration was found above 500 ppm. All the compounds have shown good activity against *E. coli* and *K. pneumoniae* (activity index 0.43-0.93). Weaker or insignificant activity is shown by most of the compounds against *P. aeruginosa*. This series of compounds are moderately active against *B. subtilis*. Compounds (6a-d) which possess chloroazitidinone and compounds (9a-d) possess ethoxyphthalimide moiety in its molecular framework show strong activity. This indicates the enhancement of activity due to presence of this moiety in the molecule. In (6a-d) and (9a-d) series, (6a,6d and 9c) have shown highest activity which may be attributed to presence of extra chloroazitidinone moiety in the molecule (6a,6d) and extra ethoxyphthalimido moiety in the molecule (9c).

**Antifungal Activity:** Remarkable activity was noticed only above 500 ppm concentration of synthesized compounds. It is clear from the table that maximum number of compounds show strong antifungal activity. Compounds (6a), (6d), and (9c) show higher activity index than control. Activity of (6b), (9b) and (9d) are comparable to the standard. Other compounds show moderate activity. It is also observed that activities of all the compounds are similar on both the fungal strains. It is obvious from the zone size interpretative chart that compounds are strong antifungal than of their antibacterial activity. Moreover alkoxyphthalimide moiety when present in the molecule enhanced the activity appreciably.

## CONCLUSIONS

According to **Pass Software** strongest activity given by compound 7a, antineoplastic .Antimicrobial property has not been displayed in the predictive table 2. So one can assume that it should be very poor. Experiment determination shows that antibacterial activity of these compounds is shown to be moderate which may be placed in predictive table.

**Table 3.** Antibacterial and antifungal activities of compound 6a-d and 9a-d

Compound	Antibacterial Activity				Antifungal Activity	
	<i>B. subtilis</i>	<i>K. pneumoniae</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>A. fumigatus</i>	<i>C. albicans</i>
6a	+++	+++	++	++	+++	+
6b	-	-	++	+	++	+
6c	+	-	+	+	-	-
6d	+++	+	+++	++	+++	+++
7a	++	-	-	++	++	++
9a	-	-	+	-	+	-
9b	-	-	++	++	+	+
9c	+++	+	+++	+	++	++
9d	++	+	-	-	-	-
Standard	+++	+++	++	+++	++	++

Standard used: Antibacterial Activity- Ciprofloxacin: Antifungal Activity-Fluconazole, Zone of inhibition in mm, 3>=(no activity);3-5=+(mild activity);5-10=++(moderate activity); 10-15=+++ (strong activity)

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## REFERENCES

- [1] C.Enguehard, J.L. Renou, H.Allouchi, J.M.Leger, A.Guiffier, *Chem Pharm Bull*, **2000**, 48, 935.
- [2] F.Hadzizadeh, M.Bamashad, H.Poorsoghat, M.Fatehi-Hassanabad, *Indian J Chem*, **2005**, 44B, 2343.
- [3] H.Goker, C.Kus, D.Botkin, N.Altanlar, *Bioorg Med Chem*, **10**, **2002**, 2589.
- [4] B.Insuasty, F.Fernandez, J.Qulroga, R.Martinez, R.Gavino, E.Angeles, *Heterocycl Commun*, **8**, **2002**, 151.
- [5] J.F.Zhou, Y.Z.Song, *Synth Commun*, **2005**, 35, 1364.
- [6] S.Avrar, I.Svad, C.Bologa, M.L.Flont, *J Cell Moll Med*, **7**(3), **2003**, 287.
- [7] L.L.Chang, K.L.Sidler, M.A.Cascieri, *Bioorg Med Chem Lett*, **2001**, 11(18), 2549.
- [8] A.Shafiee, N.Rastkari, Sharifzadeh, *DARU*, **2004**, 12, 81.
- [9] P.Zhang, N.Zhang, B.Korba & S.R.Hasmane, *Bioorg Med Chem Res*, **2005**, 15, 397.
- [10] R.S.Lamani, N.S.Shetty, R.R.Kamble, I.A.Khazi, *Eur J Med Chem*, **2009**, 44, 2828.
- [11] S.M.Sondhi, A.Nagar, R.Sahu, V.K.Mahesh, R.Shukla, G.K.Patnaik, *Int.J.Chem.Tech*, **1994**, 1175- 1180.
- [12] M.M.Ramla, A.M.Omar, M.M.El-Khamry, El- Diwani H.I., *Bioorg. Med. Chem.* **2006**, 14, 7324.
- [13] S.I.El- Naem, A.O.El-Nzhawy, H.I.El-Diwani, A.O.Abdel Hamid, *Mans. Sci. Bull.* **2002**, 28, 325.
- [14] S.K.Jain, A.Mishra, *Indian J Chem*, 43B, **2004**, 184.
- [15] P.Mishra, A.K.Shakya, R.K.Agarwal, G.K.Patnaik, *J Indian Chem Soc*, **1990**, 67, 520.
- [16] V.K.Pandey, T.Sarah, T.Zarah, *Indian J Chem*, 43B, **2004**, 180.
- [17] K.S.Rao, K.Shridhar & V.G.Bhat, *Indian J Chem*, 43B, **2004**, 2170.
- [18] A.A.Aly, R.El-Sayed, *Chem Pap*, 60(1), **2006**, 56.
- [19] I.A.Belen'kaya, E.A.Prokhorchuk, L.A.Uskova, T.A.Shulla, S.A.Sirik, E.F.Goritskaya, O.K.Grib. *Fiziolog. Aktiv. Veshch.* **1989**, 21, 52, *Chem. Abstr.* **1990**, 113, 186545.
- [20] Zh.S.Dyachina, I.A.Belen'kaya, E.A.Prokhorchuk, G.P.Krokhina, O.K.Grib, S.A.Andronati, *Fiziolog. Aktiv. Veshch.* **1986**, 18, 79; *Chem. Abstr.* **1987**, 106, 133633.
- [21] I.A.Belen'kaya, A.A.Umarov, M.Kh.Khamidov, I.M.Kozyr, E.A.Berezovskaya, T.A.Shulla, S.A.Sirik, *Fiziolog. Aktiv. Veshch.* **1990**, 22, 47; *Chem. Abstr.* **1991**, 115, 108434.
- [22] I.A.Belen'kaya; Zh.S.Dyachina, Mukhomorov, V. K.; Sirik, S. A. *Khim-Farmats. Zhur.* **1991**, 25, 49; *Chem. Abstr.* **1992**, 116, 128802.
- [23] C.M.Cimarusti, R.B.Sykes, *Med. Res. Rev.* **1984**, 4, 1.
- [24] E.L.Setti, R.G.Micetich, *Curr. Med. Chem.* **1998**, 5, 101.
- [25] G.Veinberg, M.Vorona, I.Shestakova, I.Kanepe, E.Lukevics, *Curr. Med. Chem.* **2003**, 10, 1741.
- [26] J.D.Rothstein, S.Patel, M.R.Regan, C.Haenggeli, Y.H.Huang, D.E.Bergles, L.Jin, M.D.Hoberg, S.Vidensky, D.S.Chung, S.V.Toan, L.I.Bruijn, Z.Z.Su, P.Gupta, P.B.Fisher. *Nature* **2005**, 433, 73.
- [27] B.Alcaide, P.Almendros, *Curr. Med. Chem.* **2004**, 11, 1921.
- [28] W.G.Loscher, *Eur J Pharmacol*, **1946**, 51, 342.

- [29] I.O.Edafiogho, C.N.Hinko, V.A.Farrar, J.A.Moore, J.M.Nicholson, K.R.Scot, *Drugs of the Future*, **1992**, 17, 395.
- [30] E.J.Cornish, G.E.Lee, W.R.Wargg, *J Pharma Pharmacol*, **1966**, 18, 65.
- [31] H.Kaunowasky, R.Cherawat, B.Delage, A.Jondet, *Chim Therap*, **1966**, 209.
- [32] W.H.Finley, W.C.Carlson, *J Med Sci*, 1946, 1, 1657.
- [33] P.Mamalis, *Xenobiotica*, **1971**, 1, 569.
- [34] T.Banu, S.Rajora, D.Khatri, G.L.Talesara, *J Indian Chem Soc*, **2000**, 77, 300.
- [35] B.Singh, D.Mehta, L.K.Baregama , G.L,Talesara, *Indian J Chem*, **2004**,43B, 1306.
- [36] L.Bauer, K.S.Suresh, *J Org.Chem*, **1963**, 28, 1604.
- [37] J.G.Black, *Microbiology Principles and Explorations*, 4th Edition; Prentice Hall: New Jersey, **1999**, 363.