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Research Article

SYNTHESIS, CHARACTERIZATION AND MOLECULAR DOCKING STUDIES OF NOVEL 2-(5-BROMOBENZOFURAN-2-YL)-5-SUBSTITUTEDPHENYL-1,3,4-OXADIAZOLE DERIVATIVES

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ABSTRACT

A series of 2-(5-bromobenzofuran-2-yl)-5-substitutedphenyl-1,3,4-oxadiazoles were synthesized in good yields using 5-bromobenzofuran-2-carbohydrazide and characterized by analytical and spectral data. Auto Dock 4.0/ADT program was used to investigate binding interaction of oxadiazole derivatives to Asp kinase. Asp kinase of *Mycobacterium tuberculosis* (MTB) is a type II topoisomerase and is a well-established and validated target for the development of novel therapeutics. The search was based on the Lamarckian genetic algorithm and the results were analyzed using binding energy. Analysis was based on lowest docked energy and inhibition constant values. Among the tested compounds, **3g, 3a, 3h**and **3f** derivatives of oxadiazole showed highest binding energy with the lowest inhibition constant. From the observed results it is concluded that **3g, 3a, 3h** and **3f** showed more affinity to **Asp Kinase** protein.

Keywords: Benzofuran, 1,3,4 oxadiazole, Aromatic carboxylic acids, Asp kinase protein, *Mycobacterium tuberculosis*, Antitubercular activity.

1. INTRODUCTION

Benzofurans have attracted a great deal of interest because of their presence in a large number of natural products, their biological activities, and their potential applications as pharmacological agents. 2,5-disubstituted benzofurans are active in enhancing insulin sensitivity [1], and benzofuran-fused benzocarbazoles have potential antitumor and antibiotic activities [2]. Several benzofuran ring systems bearing various substituents at the C-2 position are widely distributed in nature, for example, 2-arylbenzofuran has been isolated from a Chinese herbal plant and possesses various biological activities [3]. Ailanthoidol, a neolignan derivative, has been reported to have antiviral, antioxidant and antifungal activities [4]. Furthermore, most of compounds prepared from 2-acetylbenzofurans have antimicrobial, antitumor, anti-inflammatory, fungicidal, and weed-killing activities and may be used for treatment of cardiac arrhythmias [5-12].

It was observed from the literature that certain five membered heterocyclic compounds possess interesting biological activities. Among them the compounds bearing 1,3,4-oxadiazole and pyrazole nucleus have wide applications in medicinal chemistry. A number of oxadiazole derivatives were reported to possess varied biological activities such as anti-inflammatory [13], antibacterial [14, 15], fungicidal [16, 17], analgesic, muscle relaxant and tranquilising [18] properties. In continuation of our previous work [19, 20] in the synthesis of heterocyclic compounds that are biologically active, We report here in the synthesis and molecular docking of Novel 2-(5-bromobenzofuran-2-yl)-5-substituted aryl-1,3,4-oxadiazole derivatives.

The prevalence in tuberculosis (TB), together with the recent increase in the incidence of multidrug-resistance (MDR) cases, has led to the search for new drug targets and new drugs that are effective against Mycobacterium tuberculosis (MTB). TB is often a fatal disease, and one that poses a global threat to human health [21, 22]. Globally, infection associated with TB is second only to HIV/AIDS as the greatest killer due to a single initiating infectious agent (WHO. 2020). Out of the 9 million people infected with TB in a year, 3 million are left

untreated, acting as a reservoir for further infection. Many of these 3 million untreated cases live in poverty with minimal access to healthcare. With the increasing number of cases of inactive and drug-resistance tuberculosis, there is an urgent need to develop new potent molecules set for fighting this brutal disease. Medicinal chemistry concerns the discovery, the development, the identification, and the interpretation of the mode of action of biologically active compounds at the molecular level. Molecules bearing oxadiazoles are one such class that could be considered to satisfy this need [23]. In the present work, we have focused on the synthesis of Oxadiazole containing benzofuran derivatives. A set of a novel class of oxadiazole-based hybrids were synthesized and screened for their *in vitro* anti-TB activity against MTB H37Rv by Mallikarjuna and co-workers [24]. Recent efforts to target Mtb during persistence have focused on inhibiting previously ignored metabolic pathways. However, none of the amino acid biosynthetic pathways of Mtb have yet been shown to be essential during chronic infection and it is largely unknown if such building blocks can be scavenged from the host during persistence [25]. The apparent essentiality of the numerous metabolic products and absence of the aspartate pathway in humans and animals led us to investigate the effects of inhibition of the aspartate pathway in Mtb and its requirement during persistence in the host [26]. We hypothesized that disruption of the aspartate pathway leads to a metabolic imbalance and eventual collapse of this essential biosynthetic network. Bacteria enzymes of this pathway have a high importance as they constitute targets for the development of new pharmaceutical compounds. In this scenario we aimed at selective prediction of interaction sites of aspartokinase (Asp kinase) (EC 2.7.2.4) shown in (Fig. 1), which catalyses the first step i.e., conversion of L-aspartate to 4-phospho-L-aspartate, of branched biosynthetic pathway leading to the synthesis of amino acids lysine, threonine, methionine and isoleucine [27, 28]. An intermediate of lysine-biosynthetic branch, mesodiaminopimelate is also a component of peptidoglycan, constituent of bacterial cell wall. The cell wall plays a vital role in bacterial growth and survival in hostile environment [29]. In this aspect, we can conclude that Asp kinase also plays a role for the formation of the cell wall. Asp kinase control presents a unique situation, where in the presence of any deficiency in the production Asp kinase, results in the deficiency of amino acids lysine, threonine, methionine and isoleucine as well as peptidoglycan of the cell wall [30].

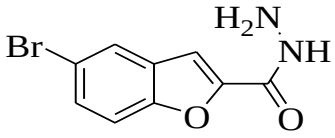
2. EXPERIMENTAL

2.1. Material and methods

The melting points were determined by open capillary method on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker NMR spectrometer using dimethylsulphoxide (DMSO-d_6)/chloroform ($CDCl_3$) as solvent and tetramethylsilane (TMS) as an internal standard. The chemical shifts were expressed in δ ppm and values of coupling constant (*J*) in Hertz. The mass spectra were recorded using mass spectrometer VG 7070G. The microanalysis was carried out using Perkin-Elmer 240C analyzer. Progress of the reaction was monitored by TLC using aluminium sheets precoated with UV fluorescent silica gel Merck F254 and were visualized by UV lamp. All the chemicals purchased were of analytical grade and used without further purification unless otherwise specified.

2.2. General procedure for Synthesis of 5-bromobenzofuran-2-carbohydrazide (2)

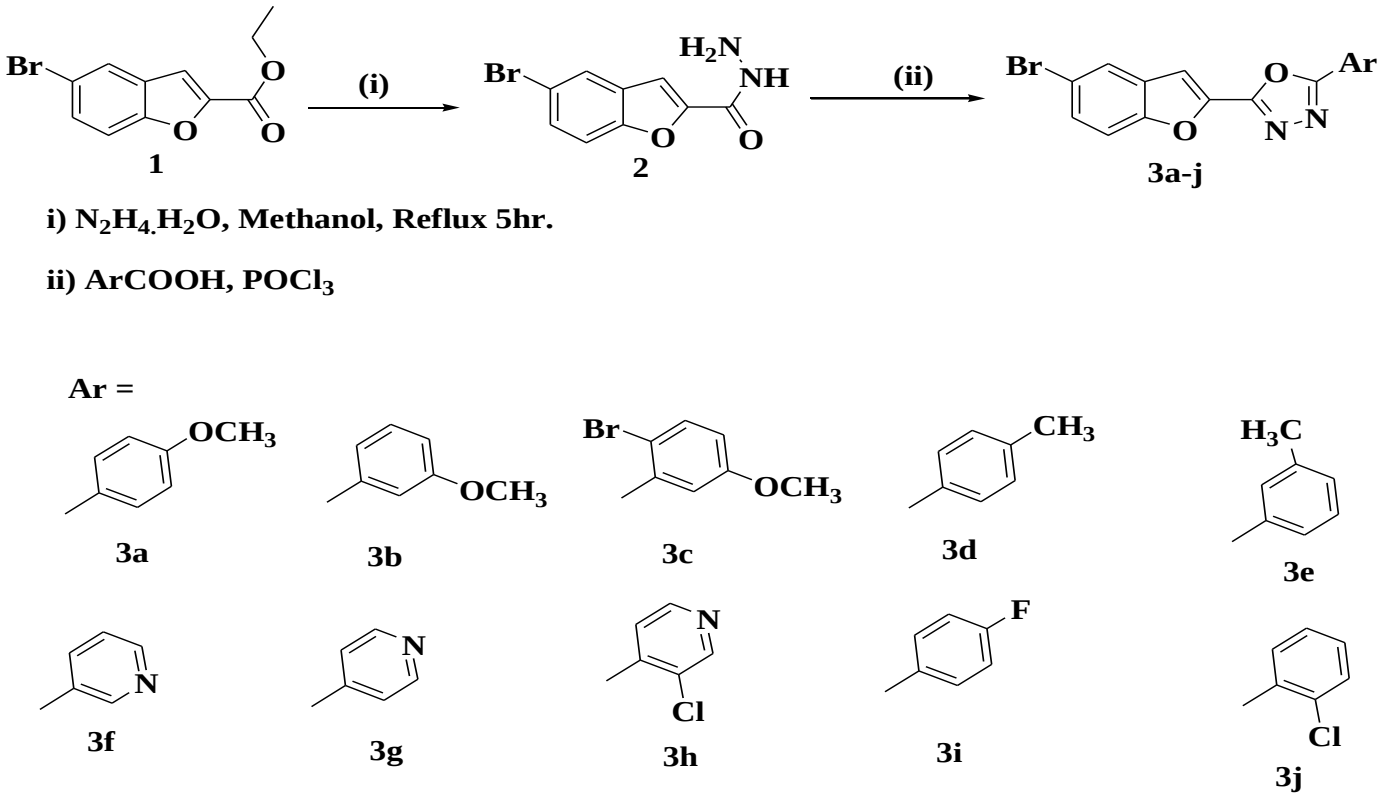
A solution of Ethyl 5-bromobenzofuran-2-carboxylate **(1)** (0.01 mol) in methanol, was treated with hydrazine hydrate (0.02 mol) and the reaction mixture was refluxed for 8 hr. The excess of the solvent was distilled under reduced pressure and the reaction mixture was cooled. The separated solid was filtered, washed with pet. Ether (40°-60°C) and recrystallized from water.



Yield 81%; m.p.: 155-157°C (Literature m. p. 165°C), **^{1}H NMR (400 MHz, DMSO-d_6):** δ 4.975 (s, 2H, NH_2), 7.133 (d, 1H, *J*=8.8 Hz, H7), 7.665 (dd, 1H, *J*= 2.4, 6.4, 2.4 Hz, H6), 8.079 (d, 1H, *J*=2.4 Hz, H4), 8.944 (s, 1H, H3), 10.341 (s, 1H, NH). MS m/*z*: 254.97 [M+H], (253.97).

2.3. General procedure for Synthesis of 2-(5-bromobenzofuran-2-yl)-5-substitutedphenyl-1, 3, 4-oxadiazoles (3a-j)

A mixture of 5-bromobenzofuran-2-carbohydrazide (0.5 mmol) and various aromatic acid (0.5 mmol) in $POCl_3$ (5 ml) was refluxed for 6-10 h. The mixture was cooled and poured onto crushed ice. It was neutralized with $NaHCO_3$ solution and the resulting solid mass precipitated out was filtered, dried, and crystallized.



Scheme 1: Synthesis of 2-(5-bromobenzofuran-2-yl)-5-substitutedphenyl-1,3,4-oxadiazoles (3a-j)

2.4. Molecular Docking studies of oxadiazole derivatives

2.4.1. Screening of DNA Asp kinase with Oxadizole derivatives

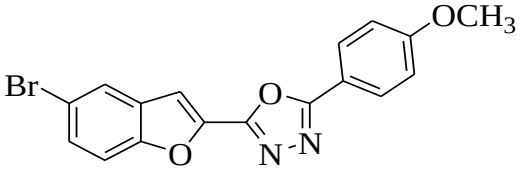
Auto Dock 4.0/ADT program was used to investigate oxadiazole derivatives binding to Asp kinase [31, 32]. A grid spacing of 0.375 Å and the grid points in *X*, *Y,* and *Z* axis were set to 60 × 60 × 60. The search was based on the Lamarckian genetic algorithm and the results were analysed using binding energy [33-35]. For each ligand, a docking experiment consisting of 100 stimulations was performed and the analysis was based on binding-free energies and root-mean-square deviation (RMSD) values. Docking with synthesised oxadiazole derivatives was performed onto Asp kinase with the same parameters and PMV 1.4.5 viewer was then used to observe the interactions of the docked compound to the Asp kinase protein, further docking analysis was carried out on pymole software.

3. RESULTS AND DISCUSSION

Ethyl 5-bromo benzofuran-2-carboxylate on reaction with hydrazine hydrate yielded corresponding 5-bromobenzofuran-2-carbohydrazide. The 5-bromobenzofuran-2- carbohydrazide when refluxed with substituted aromatic acids in the presence of phosphorous oxychloride yielded 2-(5-bromobenzofuran-2-yl)-5-substitutedphenyl-1,3,4-oxadiazoles **3a-j** in 80-85% yields. The newly synthesized compounds were characterized by elemental, IR, ^{1}H NMR, ^{13}C NMR and mass spectral studies.

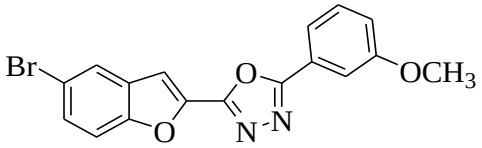
3.1. Characterization data of synthesized compounds

3.1.1. 2-(5-bromobenzofuran-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (3a)



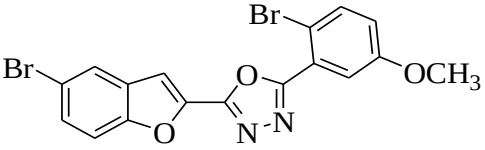
Yield 80%; m. p: 242-244°C, **^{1}H NMR (400 MHz, DMSO-d_6):** δ 3.815 (s, 3H, OCH_3), 6.985 (d, 2H, *J*= 6.8 Hz, ArH), 7.132 (d, 1H, *J*= 9.2 Hz, H7), 7.663 (dd, 1H, *J*= 2.4, 6.4, 2.4 Hz,H6), 7.744 (d, 2H, *J*= 6.8 Hz, ArH), 8.079 (d, 1H, *J*=2.4 Hz, H4); 8.942 (s, 1H, H3). **^{13}C NMR (100 MHz, DMSO-d_6):** δ 55.46, 105.64, 114.42, 114.78, 115.84, 117.41, 126.22, 128.72, 128.92, 129.31, 155.04, 155.66, 157.38, 160.41, 163.69. **MS m/z**: 371.18 [M+H], (370.18).

3.1.2. 2-(5-bromobenzofuran-2-yl)-5-(3-methoxyphenyl)-1,3,4-oxadiazole (3b)



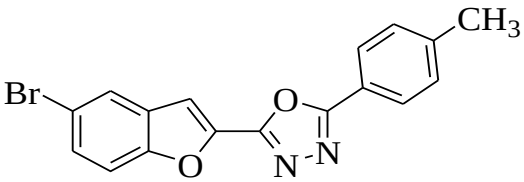
Yield 85%; m. p:182-184°C, **^{1}H NMR (400 MHz, DMSO-d_6):**δ 3.812 (s, 3H, OCH_3), 6.802 (d, 1H, *J*= 6.8 Hz, ArH), 7.05- 7.18 (m, 4H, H7 & ArH), 7.665 (dd, 1H, *J*= 2.4, 6.4, 2.4 Hz, H6), 8.074 (d, 1H, *J*=2.4 Hz, H4); 8.938(s, 1H, H3). **^{13}C NMR (100 MHz, DMSO-d_6):**δ 55.44, 105.54,113.25, 114.42, 114.93, 117.43, 125.51, 126.21, 127.11, 128.93, 129.32, 130.03, 155.05, 155.56, 157.37, 159.89, 163.68. **MS m/*z***: 371.18 [M+H], (370.18).

3.1.3. 2-(2-bromo-5-methoxyphenyl)-5-(5-bromobenzofuran-2-yl)-1,3,4-oxadiazole (3c)



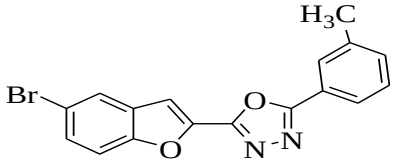
Yield 83%; m. p: 199-201°C, **^{1}H NMR (400 MHz, DMSO-d_6):**δ 3.812 (s, 3H, OCH_3), 6.881-6.972 (m, 2H,ArH),), 7.133 (d, 1H, *J*= 9.2 Hz, H7), 7.412 (d, 1H, *J*= 6.8 Hz, ArH), 7.664 (dd, 1H, *J*= 2.4, 6.4, 2.4 Hz, H6), 8.075 (d, 1H, *J*=2.4 Hz, H4); 8.940 (s, 1H, H3).**^{13}C NMR (100 MHz, DMSO-d_6):** δ 55.46, 105.74, 111.02, 114.45, 117.03, 117.42, 121.85, 126.21, 128.92, 129.33, 129.60, 133.59, 155.04, 155.66, 157.38, 157.67, 164.56. **MS m/*z***:450.08 [M+H], (449.08).

3.1.4. 2-(5-bromobenzofuran-2-yl)-5-p-tolyl-1,3,4-oxadiazole (3d)



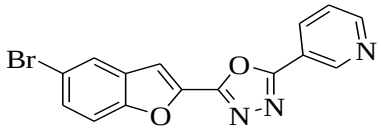
Yield 84%; m. p: 178-180°C, **^{1}H NMR (100 MHz, DMSO-d_6):**δ 2.313 (s, 3H, CH_3), 7.132 (d, 1H, *J*= 9.2 Hz, H7), 7.243 (dd, 2H, *J*= 7.4 Hz, ArH), 7.661 (dd, 1H, *J*= 2.4, 6.4, 2.4 Hz, H6), 7.862 (dd, 2H, *J*= 7.2 Hz ArH), 8.078 (d, 1H, *J*=2.4 Hz, H4), 8.941 (s, 1H, H3).**^{13}C NMR (100 MHz, DMSO-d_6):**δ 21.26, 105.69, 114.41, 117.42, 123.90, 126.21, 126.84, 128.92, 129.32, 129.64, 139.75, 155.04, 155.66, 157.38, 163.69. **MS m/*z***: 355.19 [M+H], (354.21).

3.1.5. 2-(5-bromobenzofuran-2-yl)-5-m-tolyl-1,3,4-oxadiazole (3e)



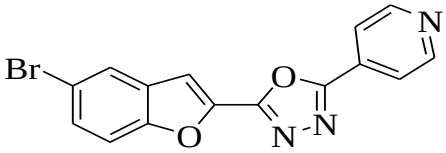
Yield 82%; m. p: 220-225°C, **^{1}H NMR (400 MHz, DMSO-d_6):** δ 2.316 (3H, s), 7.05 (d, 1H, *J*= 7.2 Hz ArH), 7.133 (d, 1H, *J*= 9.2 Hz, H7), 7.203 (dd, 1H, *J*= 7.4 Hz ArH), 7.282-7.291 (m, 2H, ArH), 7.659 (dd, 1H, *J*= 2.4, 6.4, 2.4 Hz, H6), 8.076 (d, 1H, *J*=2.4 Hz, H4), 8.944 (s, 1H, H3).**^{13}C NMR (100 MHz, DMSO-d_6):**δ 20.91, 104.54, 114.4, 117.4, 125.51, 126.2, 126.46, 127.11, 127.69, 128.92, 129.31, 130.45, 134.89, 155.04, 155.66, 157.38, 163.69. **MS m/*z***: 355.19 [M+H], (354.19).

3.1.6. 3-(5-(5-bromobenzofuran-2-yl)-1,3,4-oxadiazol-2-yl)pyridine (3f)



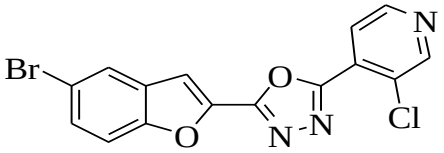
Yield 80%; m. p: 249-251°C, **^{1}H NMR (400 MHz, DMSO-d_6) :** δ 7.134 (d, 1H, *J*=8.8 Hz, H7), 7.665 (dd, 1H, *J*= 2.4, 6.4, 2.4, Hz, H6), 8.078 (d, 1H, *J*=2.4 Hz, H4), 8.944 (s, 1H, H3),6.935 (m, 2H, pyridine ring), 7.429 (d, 1H *J*=6.8 Hz, pyridine ring),8.321 (d, 1H, *J*=7.2 Hz, pyridine ring). **^{13}C NMR (100 MHz, DMSO-d_6):**δ 105.58, 114.45, 117.49, 123.48, 123.93, 126.25, 128.92, 129.35, 134.35, 148.25, 149.75, 155.04, 155.66, 157.38, 164.56. **MS m/*z***: 342.15 [M+H], (341.15).

3.1.7. 4-(5-(5-bromobenzofuran-2-yl)-1,3,4-oxadiazol-2-yl)pyridine (3g)



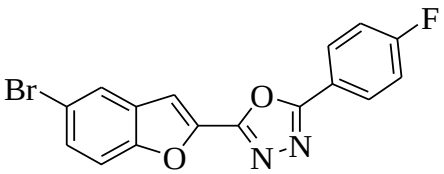
Yield 81%; m. p: 247-249°C, **^{1}H NMR (400 MHz, DMSO-d_6) :** δ 7.133 (d, 1H, *J*=9.2 Hz, H7), 7.662 (dd, 1H, *J*= 2.4, 6.4, 2.4 Hz, H6), 8.074 (d, 1H, *J*=2.4 Hz, H4), 8.942 (s, 1H, H3), 7.108 (d, 2H, *J*=6.0 Hz, pyridine ring), 8.480 (d, 2H, *J*=6.0 Hz pyridine ring). **^{13}C NMR (100 MHz, DMSO-d_6):**δ 105.70, 114.43, 117.45, 119.61, 125.51, 126.22, 128.92, 129.33, 150.55, 155.06, 155.68, 157.38, 163.69. **MS m/*z***: 342.15 [M+H], (341.15).

3.1.8. 4-(5-(5-bromobenzofuran-2-yl)-1,3,4-oxadiazol-2-yl)pyridine (3h)



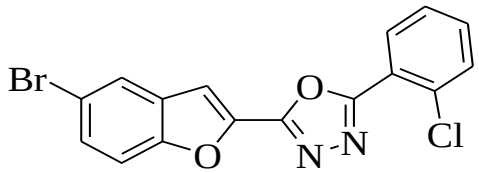
Yield 80%; m. p: 190-194°C, **^{1}H NMR (400 MHz, DMSO-d_6) :** δ 7.131 (d, 1H, *J*=9.2 Hz, H7), 7.662 (dd, 1H, *J*= 2.4, 6.4, 2.4 Hz, H6),7.79 (d, 1H, *J*=6.0 Hz, pyridine ring), 8.074 (d, 1H, *J*=2.4 Hz, H4), 8.683 (d, 1H, *J*=6.0 Hz, pyridine ring), 8.825 (d, 2H, *J*=6.0 Hz pyridine ring) 8.942 (s, 1H, H3). **^{13}C NMR (100 MHz, DMSO-d_6):**δ 104.95, 114.50, 117.47, 120.73, 126.24, 126.72, 127.99, 128.92, 129.3, 147.69, 149.07, 155.04, 155.66, 157.38, 164.58. **MS m/z**: 376.59 [M+H], (375.59).

3.1.9. 2-(5-bromobenzofuran-2-yl)-5-(4-fluorophenyl)-1,3,4-oxadiazole (3i)



Yield 84%; m. p: 234-236°C, **^{1}H NMR (400 MHz, DMSO-d_6):**7.135 (d, 1H, *J*= 9.2 Hz, H7), 7.413 (m, 2H, ArH), 7.661 (dd, 1H, *J*= 2.4, 6.4, 2.4 Hz, H6), 7.752 (m, 2H, ArH), 8.076 (d, 1H, *J*=2.4 Hz, H4), 8.944 (s, 1H, H3).**^{13}C NMR (100 MHz, DMSO-d_6):**δ 105.64, 157.38, 163.69, 128.92, 114.49, 126.27, 133.39, 163.35, 155.66, 122.82, 117.4, 129.3, 116.5, 116.5, 155.04. **MS m/z**: 359.15 [M+H], (358.15).

3.1.10. 2-(5-bromobenzofuran-2-yl)-5-(2-chlorophenyl)-1,3,4-oxadiazole (3j)



Yield 82%; m. p: 243-245°C, **^{1}H NMR (400 MHz, DMSO-d_6):**δ 7.134 (d, 1H, *J*=9.2 Hz, H7), 7.30-7.52 (m, 4H, ArH), 7.663 (dd, 1H, *J*= 2.4, 6.4, 2.4 Hz, H6), 8.077 (d, 1H, *J*=2.4 Hz, H4); 8.945 (s, 1H, H3). **^{13}C NMR (100 MHz, DMSO-d_6):**δ 105.44, 114.45, 117.46, 126.24, 126.41, 127.99, 128.92, 129.32, 130.38, 130.55, 131.17, 133.23, 155.04, 155.66, 157.38, 164.56. **MS m/z**:375.6 [M+H], (374.6).

The IR spectrum of **(2)** showed absorptions at 3459, 3066 and 1752 cm^{-1} due to N-H stretching, aromatic C-H stretching and C=O stretching in hydrazide respectively. The ^{1}H NMR spectrum of **(2)** exhibited a singlet at δ 4.975 due to NH_2 and another singlet at 10.341 due to NH. The mass spectrum of **(2)** exhibited [M+H] peak at m/z 254.97 that confirms the chemical structure of the compond.

Reaction between equimolar quantities of 5-bromobenzofuran-2-carbohydrazide **2** and 4-methoxybenzoic acid furnished 2-(5-bromobenzofuran-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole **3a (Scheme 1)**. IR spectrum of 3**a** displayed absorption bands at 3050 and 1645 cm^{-1} corresponding to C-H stretching in aromatics and C=N stretching in oxadiazole ring respectively. Compound **2** showed a characteristic absorption band at 1752 cm^{-1} corresponding to C=O stretching in hydrazide. The ^{1}H NMR spectrum of **(2)** exhibited a singlet at δ 4.975 due to NH_2 and another singlet at 10.341 due to NH. The absence of these characteristic signals of NH_2 and NH in compounds **3a-j** confirms the successful reaction of compound **2** with aromatic carboxylic acids to furnish the desired target molecules.

3.2. Molecular docking of Oxadizole derivatives onto Asp kinase

All the docking calculations were carried out using AutoDock 4.0/ADT and the dlg files generated were analyzed for their binding conformations. Analysis was based on higher binding affinities/lower docking scores and low inhibition constant values (Table 1, Fig.1 &2). Among the 10 derivatives of oxadizoles, 3g, 3a, 3h and 3f showed highest binding energy (-8.31,-7.81,-7.74 and -7.02) with Asp kinase protein. All docked derivatives interacted by the same mode of Asp kinase protein binding site. 3g derivative shows two hydrogen bond interactions with amino acids Asn 43 and Ile 44 (Fig.2), 3a derivative shows two hydrogen interactions with amino acids Asn 43 and Lys 97 (Fig.1), 3h derivative shows two hydrogen interactions with amino acids Asp 12 and Glu 15 (Fig.2), 3f derivative shows two hydrogen interactions with amino acids Asn 43 and Val 42 (Fig.2). 3j and remaining derivatives shows one hydrogen bond with Asn 43 for this reason it is concluded that greater the negative value of the binding energy for **3g ,3a, 3h** and **3f** better is the interaction towards target receptor than that of **3b, 3c,3d,3e,3i** and **3j**.

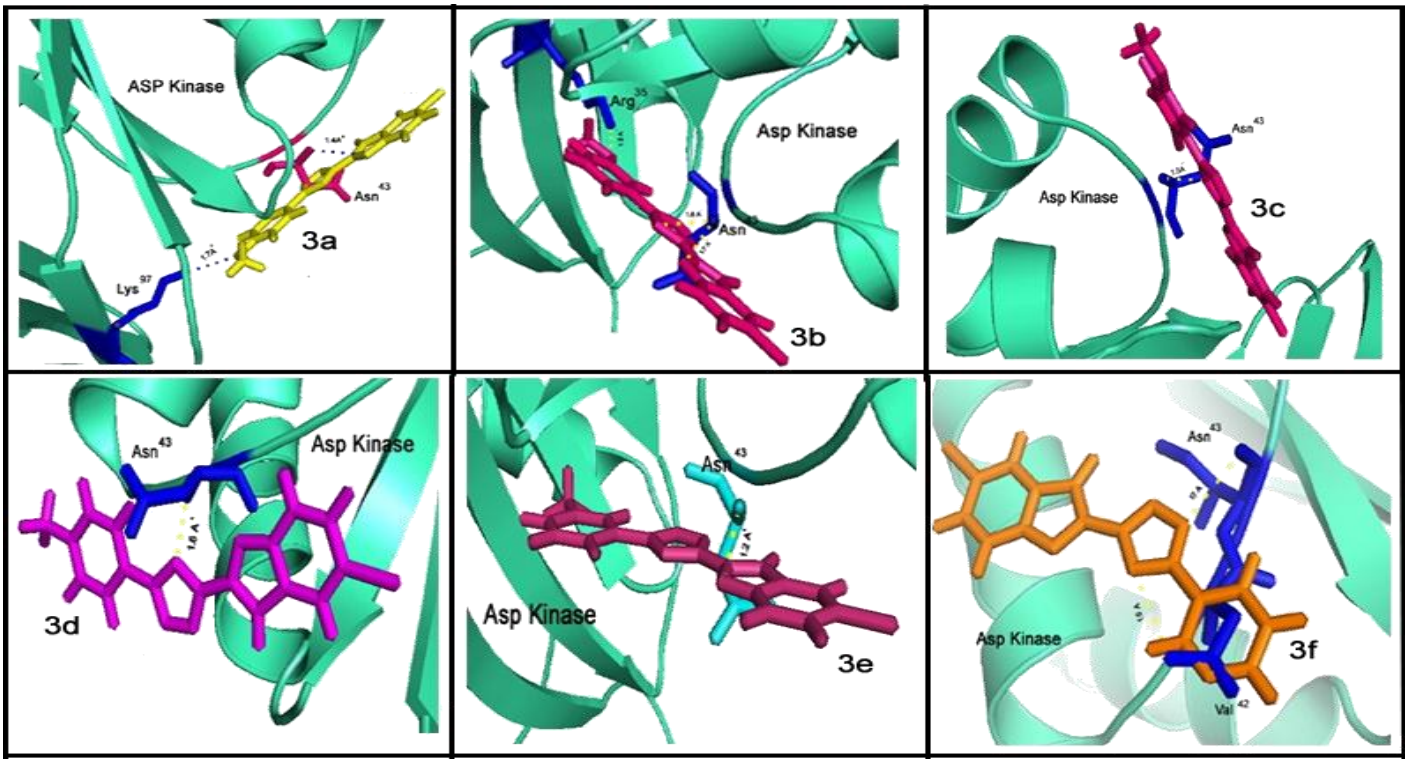


Fig. 1: Docking conformation of 3a, 3b, 3c, 3d, 3e and 3f on Asp kinase protein in cartoon with green cyan and ligand represented stick with different colours and the residues interacting with are represented by sticks different colours

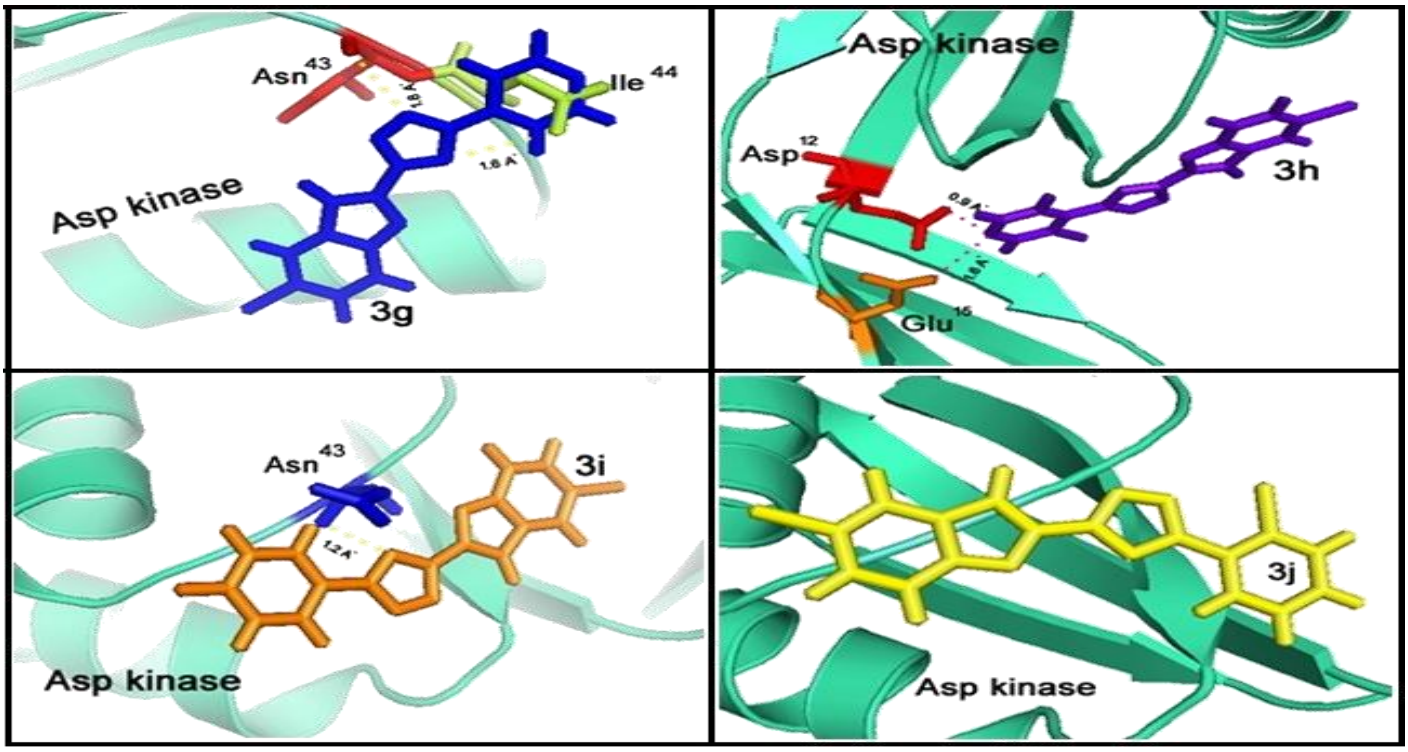


Fig. 2: Docking conformation of 3g, 3h, 3i and 3f on Asp kinase protein in cartoon with green cyan and ligand represented stick with different colours and the residues interacting with are represented by sticks different colours

Table 1: Binding energies and inhibition constants of docked Oxadizoles derivatives calculated by AutoDock

Protein Name & Pdb id	Ligand Name	Cluster	Cluster Run	Binding energy (kcal/mol)	Inhibition Constant (μM)
ASP kinase & (4GO5)	3a	1	19	-7.81	53.04
	3b	1	43	-6.12	200.9
	3c	1	27	-4.03	300.86
	3d	1	9	-5.13	320.7
	3e	2	16	-4.61	210.1
	3f	1	14	-7.02	69.08
	3g	1	35	-8.31	34.08
	3h	1	21	-7.74	81.06
	3i	1	24	-5.02	290.14
	3j	1	36	-4.88	420.71

4. CONCLUSION

The newly designed compounds of oxadizole hybrids have been found to have good synthetic accessibility which indicates that these newly designed compounds can be easily synthesized in the laboratory. To understand the molecular interaction between oxadiazole derivatives with Asp kinase we performed molecular docking analysis. Docking studies reveals all the derivatives of oxadizoles showed high binding affinity with Asp kinase and detailed interactions were done. Hence we conclude that these oxadizoles derivatives could be potential anti-tuberculosis lead molecules for inhibiting the expression of **Asp kinase** protein. **Asp kinase** control presents a unique situation, where in the presence of any deficiency in the production Asp kinase, results in the deficiency of amino acids lysine, threonine, methionine and isoleucine as well as peptidoglycan of the cell wall and supports for experimental testing.

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Conflict of interest

None declared

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