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Synthesis, Characterization and Molecular Docking Studies of Substituted Benzofuran and Pyrazole Derivatives

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ABSTRACT

A series of 5-(5-bromobenzofuran-2-yl)-substituted 1,3,4-oxadiazole-2-thiol derivatives (**4a-d**) and substituted benzylidene-3-methyl-1-(5-bromobenzofuran-2-carbonyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**6a-d**) have been synthesized in good yields and characterized by IR and NMR analyses. Auto Dock 4.0/ADT program was used to investigate binding interaction of oxadiazole and pyrazole derivatives to DNA GyrB. DNA gyrase of *Mycobacterium tuberculosis* (MTB) is a type II topoisomerase and 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 **4b**, **6b** and **6c** derivatives of oxadiazole and pyrazole showed highest binding energy with the lowest inhibition constant. From the observed results, it is concluded that compounds **4b**, **6b** and **6c** showed more affinity to DNA GyrB protein.

KEYWORDS

Benofuran-oxadiazole hybrids, Benzofuran-pyrazole hybrids, DNA GyraseB, Tuberculosis, Antitubercular activity.

INTRODUCTION

The growing resistance of microbes to antibiotics is a major global problem confronted by the medicinal and bioorganic chemists. Hence, there is an instant need to develop new chemotherapeutic agents. Tuberculosis is a contagious disease and one of the leading cause of death globally due to its infective nature [1]. Tuberculosis is caused by etiological agent *Mycobacterium tuberculosis*. There has been an increased interest for research on tuberculosis, which resulted in an unveiling of several new initiatives by several organizations globally including pharmaceutical companies. The inventive focus on tuberculosis has partly been predominantly due to the persistent larger number of tuberculosis case studies in developing countries and partly by the increased occurrence of multidrug resistant (MDRTB) and extensively drug-resistant tuberculosis (XDR-TB) [2]. According to WHO report of 2017, tuberculosis happens to be the ninth foremost cause of death globally and ranking above HIV/AIDS. In 2016, there were about 1.3 million tuberculosis deaths cases among HIV-negative people and an additional

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374,000 deaths among HIV-positive people. Hence, drug-resistant tuberculosis is a cause for continuing menace. In 2016, there were 600,000 new cases with resistance to most effective first-line drug rifampicin, of which 490,000 had multidrug-resistant tuberculosis (MDR-TB) [3]. Hence, the need for exploration of new and efficient anti-tuberculosis agents with a new mechanism of action remains a vital job [4-6].

Benzofuran and its derivatives are found to be suitable structures that exist widely in natural and synthetic compounds with a diverse range of biological potential. Thus, a lot of attention has been paid by the chemists and biologists for discovery of new drugs in the field of drug discovery and development. Some of the derivatives of benzofuran such as angelicin, psoralen and 8-methoxypsoralen have been used for the treatment of skin diseases such as cancer or psoriasis [7-10] as they can cross link with DNA upon light irradiation. The unique structural features of benzofuran and its wide range of biological activities made it a privileged structure in drug invention, particularly as antimicrobial agents. In view of above a good number of benzofuran-based compounds have been developed and tested for antimicrobial activities that help the medicinal chemists to make a systematic study on the structure activity relationships (SAR) of these derivatives. Benzofuran derivatives exhibit significant activity against several viruses including antifungal [11-14], antiprotozoal [11], antitubercular [15-17], anti-inflammatory [18], anticonvulsant [19], anticancer [20], anti-HIV [21], analgesic [22], antiparasitic [23], antihyperlipidemic [24], antioxidant [25], antidiabetic [26], antihypertensive [27], antiplasmodial [28], Alzheimer's [29], vasodilating and hypotensive [30], arrhythmic activities [31] and inhibitors of mycobacterium protein tyrosine phosphatase [32]. Some compounds containing benzofuran [33-37] moiety exhibited potent anti-tuberculosis properties.

The 1,3,4-oxadiazole is a five membered heterocyclic compound and good bioisostere of amide and ester functional groups and is reported to contribute significant physical properties [38] and substantially to biological activity due to participating in hydrogen bonding interactions with various receptors [39]. The 1,3,4-oxadiazole derivatives display a wide-ranging spectrum of biological activities including cytotoxic and antimicrobial [40], anticonvulsant [41], antiepileptic [42], antiallergic [43], anticancer [44], antitubercular [45] activities. The 1,3,4-oxadiazole-2(3*H*)-thiones reported as *in vitro* antitubercular agent against Mycobacterium tuberculosis H37Rv [46-51].

In view of above and in continuation of our attention on designing oxygen based heterocycles of biologically active heterocycles [47-49], we designed benzofuran-oxadiazole and bezofuran-pyrazole hybrids with a hope of better therapeutic agents for the treatment of tuberculosis and to establish structure activity relationship as DNA gyrase B inhibitors of *Mycobacterium tuberculosis*.

EXPERIMENTAL

The melting points were determined on a Mel-Temp device by an open capillary method and are uncorrected. On a Perkin-Elmer FT-IR spectrophotometer, the IR spectra (KBr disc) were recorded and the absorptions were expressed in wavenumber (cm^{-1}). ^1H 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. Chemical shifts were expressed in δ ppm and constant (*J*) coupling values in Hertz. The mass spectra were measured using the VG 7070G mass spectrometer. The Perkin-Elmer 240C analyzer was used to execute the microanalysis. TLC monitored the progress of the reaction using aluminium sheets pre-coated with Merck F254 UV fluorescent silica gel and visualised the UV lamp. Unless otherwise specified, all of the chemicals purchased were of analytical grade and used without further purification.

The starting compound ethyl 5-bromobenzofuran-2-carboxylate (**1**) was procured from DENISCO CHEMICALS Pvt. Ltd., Hyderabad. The purity of the compound was checked by TLC. m.p.: 68-69 ºC. IR (KBr, ν_{max}, cm^{-1}): 3062 (CH *str*. in aromatics), 2975 (CH *str.* in aliphatics), 1729 (C=O *str.* in esters), 1430, 1052 (C-O *str.* in esters). ^1H NMR (400 MHz, DMSO-d_6): δ 1.214 (t, 3H, *J* = 7.2 Hz, CH_3); 4.177 (q, 2H, *J* = 7.2 Hz, CH_2); 7.1315 (d, 1H, *J* = 9.2 Hz, H7); 7.663 (dd, 1H, *J* = 2.4, 6.4, 2.4 Hz, H6); 8.077 (d, 1H, *J* = 2.4 Hz, H4); 8.942 (s, 1H, H3). MS *m/z*: 268.97 [M+H] (267.97); Anal. calcd. (found) % for $C_{11}H_9O_3Br$: C, 49.10 (48.83); H, 3.37 (3.28).

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 h. The excess of the solvent was distilled under reduced pressure and the reaction mixture was cooled. The separated solid was filtered, washed with petroleum ether (40-60 ºC) and recrystallized from water (**Scheme-I**). Yield 81%; m.p.: 155-157 ºC. IR (KBr, ν_{max}, cm^{-1}): 3459 (N-H *str.*), 3066 (arom. C-H *str.*), 1752 (C=O *str.* in hydrazide). ^1H 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); Anal. calcd. (found) % for $C_9H_7N_2O_2Br$: C, 42.38 (41.59); H, 2.77 (2.63); N, 10.98 (10.16).

Synthesis of 5-(5-bromobenzofuran-2-yl)-1,3,4-oxadiazole-2-thiol (3): 5-Bromobenzofuran-2-carbohydrazide (**2**) (0.01 mol), KOH 0.01 mol (0.56 g) and 10 mL of carbon disulphide were together refluxed in 50 mL of 95% ethanol for 10 h. The resultant solution was concentrated and cooled to room temperature. The product obtained was acidified with dilute HCl. The solid mass separated out was filtered, dried and purified by recrystallization from ethanol (**Scheme-I**). Yield 81%; m.p.: 214-216 ºC. IR (KBr, ν_{max}, cm^{-1}): 3049 (arom. C-H *str*.), 2786 (S-H *str*. in thiols), 1643 (C=N *str.*), 1178 (sp^2 C-O *str.*). ^1H NMR (400 MHz, DMSO-d_6): δ 3.60 (hump, 1H, SH), 7.136 (d, 1H, *J* = 8.8 Hz, H7), 7.668 (dd, 1H, *J* = 2.4, 6.4, 2.4 Hz, H6), 8.082 (d, 1H, *J* = 2.4 Hz, H4), 8.947 (s, 1H, H3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.5, 164.5, 151.6, 147.2, 146.5, 141.3, 132.4, 115.4, 103.6, 102.2. MS *m/z*: 296.93 [M+H], (295.93); Anal. calcd. (found) % for $C_{10}H_5N_2O_2SBr$: C, 40.42 (40.34); H, 1.70 (1.62); N, 9.43 (9.36).

Synthesis of 4-(5-(5-bromobenzofuran-2-yl)-1,3,4-oxadiazol-2-ylthio)pyridine (4a): Equimolar quantities of 5-(5-

bromobenzofuran-2-yl)-1,3,4-oxadiazole-2-thiol (**3**) and 4-chloropyridine were refluxed in 95% ethanol until the disappearance of starting materials as monitored by TLC. The resultant solution was concentrated under reduced pressure. The product was dissolved in ethyl acetate and the organic phase was washed successively with 5% HCl, 5% Na_2CO_3 solution, water (2 × 40 mL) and the organic layer was collected, washed with brain solution, dried over anhydrous Na_2SO_4 and ethyl acetate decanted off. The ethyl acetate was then concentrated under reduced pressure and the solid mass separated out was collected, dried and recrystallized from ethanol to obtain compound **4a**. Compounds **4b-d** were similarly synthesized using substituting 4-chloropyridine with different chloro compounds.

4-(5-(5-Bromobenzofuran-2-yl)-1,3,4-oxadiazol-2-ylthio)pyridine (4a): Yield 76%; m.p: 258-260 ºC. IR (KBr, cm^{-1}): 3056 (arom. C-H *str.*), 1624 (C=N *str.*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.129 (d, 1H, *J* = 9.2 Hz, H7), 7.661 (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), 7.118, 7.103 (d, 2H, *J* = 6.0 Hz, pyridine ring), 8.480, 8.465 (d, 2H, *J* = 6.0 Hz pyridine ring). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.8, 165.6, 151.4, 151.3, 147.4, 146.3, 141.8, 141.5, 132.7, 125.1, 115.8, 103.5, 102.6. MS *m/z*: 373.96 [M+H], (372.95); Anal. calcd. (found) % for $C_{15}H_8N_3O_2SBr$: C, 48.14 (47.61); H, 2.15 (1.95); N, 11.23 (10.85).

2-(5-(5-Bromobenzofuran-2-yl)-1,3,4-oxadiazol-2-ylthio)pyridine (4b): Yield 75%; m.p: 252-254 ºC. IR (KBr, ν_{max}, cm^{-1}): 3060 (arom. C-H *str.*), 1613 (C=N *str.*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.1315 (d, 1H, *J* = 8.8 Hz, H7); 7.663 (dd, 1H, *J* = 2.4, 6.4, 2.4, Hz, H6); 8.077 (d, 1H, *J* = 2.4 Hz, H4); 8.942 (s, 1H, H3); 6.928 (m, 2H, pyridine ring); 7.428 (d, 1H *J* = 6.8 Hz, pyridine ring); 8.311 (d, 1H, *J* = 7.2 Hz, pyridine ring). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.4, 164.6, 153.4, 151.2, 149.6, 147.5, 146.2, 141.2, 136.5, 132.4, 122.4, 121.1, 115.4, 103.3, 102.3. LCMS *m/z*: 373.96 [M+H], (372.95); Anal. calcd. (found) % for $C_{15}H_8N_3O_2SBr$: C, 48.14 (47.72); H, 2.15 (1.89); N, 11.23 (10.85).

4-(5-(5-Bromobenzofuran-2-yl)-1,3,4-oxadiazol-2-ylthio)benzenamine (4c): Yield 76%; m.p: 258-260 ºC. IR (KBr, ν_{max}, cm^{-1}): 3036 (arom. C-H *str.*), 1615 (C=N *str.*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.50 (s, 2H, $ArNH_2$); 6.579 (d, 2H, *J* = 4.4 Hz, ArH); 6.950 (d, 2H, *J* = 4.8 Hz, ArH); 7.1315 (d, 1H, *J* = 9.2 Hz, H7); 7.663 (dd, 1H, *J* = 2.4, 6.4, 2.4, H6); 8.077 (d, 1H, *J* = 2.4 Hz, H4); 8.942 (s, 1H, H3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.2, 164.3, 151.0, 146.4, 146.1, 144.2, 141.5, 132.1, 128.6, 127.3, 116.2, 115.7, 103.5, 102.5. MS *m/z*: 387.97 [M+H], (386.97); Anal. calcd. (found) % for $C_{16}H_{10}N_3O_2SBr$: C, 49.50 (49.35); H, 2.60 (2.52); N, 10.82 (10.69).

2-(5-(5-Bromobenzofuran-2-yl)-1,3,4-oxadiazol-2-ylthio)benzenamine (4d): Yield 81%; m.p: 262-264 ºC. IR (KBr, ν_{max}, cm^{-1}): 3058 (arom. C-H *str.*), 1621 (C=N *str.*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.46 (s, 2H, $ArNH_2$); 6.591-7.014 (m, 4H, ArH); 7.131 (d, 1H, *J* = 8.8 Hz, H7); 7.663 (dd, 1H, *J* = 2.4, 6.4, 2.4, H6); 8.077 (d, 1H, *J* = 2.4 Hz, H4); 8.942 (s, 1H, H3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.4, 164.5, 151.2, 146.5, 146.2, 145.0, 141.2, 131.4, 128.9, 128.7, 124.6, 118.3, 115.5, 115.0, 103.3, 102.4. MS *m/z*: 387.97 [M+H], (386.97); Anal. calcd. (found) % for $C_{16}H_{10}N_3O_2SBr$: C, 49.50 (49.42); H, 2.60 (2.52); N, 10.82 (10.64).

Synthesis of 1-(5-bromobenzofuran-2-carbonyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (5): A mixture of ethyl acetoacetate (0.01 mol) and 5-bromobenzofuran-2-carbohydrazide (**2**) (0.02 mol) in ethanol (20 mL) was heated under reflux for 10 h on a water bath. After completion of the reaction, ethanol was evaporated. The residue was treated with water, neutralized with $NaHCO_3$ and extracted with ether. Then ethereal solution was evaporated under reduced pressure to get pure compound **3**. It was recrystallized from ethanol. Yield 73%; m.p: 72-74 ºC. IR (KBr, ν_{max}, cm^{-1}): 3045 (arom. C-H *str.*), 2918, 2863 (C-H *str.* in CH_3/CH_2), 1660 (C=O *str.* in heterocyclics), 1567 (C=N *str.*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H, pyrazoline-5-one CH_3); 3.23 (s, 2H, CH_2 heterocyclic ring); 7.131 (d, 1H, *J* = 9.2 Hz, H8); 7.663 (dd, 1H, *J* = 2.4, 6.4, 2.4 Hz, H6); 8.077 (d, 1H, *J* = 2.4 Hz, H4); 8.942 (s, 1H, H3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.5, 162.5, 159.5, 151.5, 146.3, 146.0, 141.4, 131.6, 115.7, 103.4, 102.6, 42.1, 27.5. MS *m/z*: 320.98 [M+H], (319.98); Anal. calcd. (found) % for $C_{13}H_9N_2O_3Br$: C, 48.62 (48.41); H, 2.82 (2.68); N, 8.72 (8.64).

Synthesis of 4-benzylidene-3-methyl-1-(5-bromobenzofuran-2-carbonyl)-1*H*-pyrazol-5(4*H*)-one (6a): 1-(5-Bromobenzofuran-2-carbonyl)-3-methyl-1*H*-pyrazol-5[4*H*]-one (**5**) (0.01 mol) and benzaldehyde (0.01 mol) suspended in dry toluene were taken in a flask equipped with a Dean-Stark apparatus fitted with a calcium chloride guard tube. A catalytic amount of piperidine (0.5 mL) was added and the reaction mixture was refluxed with stirring for about 8 h. The progress of the reaction was monitored by TLC until the disappearance of starting materials. The product **6a** precipitated on cooling was washed with methanol and purified by recrystallization from a mixture of ethanol and chloroform (1:1). Compounds **6b-d** were synthesized similarly using other substituted aldehydes.

4-Benzylidene-3-methyl-1-(5-bromobenzofuran-2-carbonyl)-1*H*-pyrazol-5(4*H*)-one (6a): Yield 69%; m.p: 185-187 ºC. IR (KBr, ν_{max}, cm^{-1}): 3052 (arom. C-H *str.*), 2930 (C-H *str.* in CH_3/CH_2), 1665 (C=O *str.* pyrazolin-5-one ring), 1630 (C=N *str.*), 1240 (sp^2 C-O *str.*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H, pyrazolin-5-one CH_3), 6.82 (s, 1H, =CH), 7.131 (d, 1H, *J* = 8.8 Hz, H8); 7.663 (dd, 1H, *J* = 2.4, 6.4, 2.4 Hz, H6); 8.077 (d, 1H, *J* = 2.4 Hz, H4); 8.942 (s, 1H, H3), 7.40 - 7.60 (m, 3H, ArH), 7.75 (m, 2H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.7, 162.6, 159.0, 154.6, 151.3, 146.5, 146.1, 141.6, 137.4, 134.0, 131.8, 129.6, 129.2, 129.0, 115.8, 103.6, 102.5, 27.5. LCMS *m/z*: 409.02 [M+H], (408.01); Anal. calcd. (found) % for $C_{20}H_{13}N_2O_3Br$: C, 58.70 (58.40); H, 3.20 (3.11); N, 6.85 (6.71).

4-(2-Methoxybenzylidene)-3-methyl-1-(5-bromobenzofuran-2-carbonyl)-1*H*-pyrazol-5(4*H*)-one (6b): Yield 66%; m.p: 196-198 ºC. IR (KBr, ν_{max}, cm^{-1}): 3050 (arom. C-H *str.*), 2960 (C-H *str.* in CH_3/CH_2), 1660 (C=O *str.* pyrazolin-5-one ring), 1620 (C=N *str.*), 1210 (sp^2 C-O *str.*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H, pyrazolin-5-one CH_3), 3.84 (s, 3H, Ar-OCH_3), 6.80 (s, 1H, =CH), 7.130 (d, 1H, *J* = 8.8 Hz, H8); 7.664 (dd, 1H, *J* = 2.4, 6.4, 2.4 Hz, H6); 8.076 (d, 1H, *J* = 2.4 Hz, H4); 8.941 (s, 1H, H3), 7.042 (m, 2H, ArH), 7.442 (m, 2H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1, 162.9, 159.4, 158.0, 154.1, 151.6, 146.2, 146.0, 141.8, 137.6, 135.2,

131.6, 129.5, 122.4, 115.5, 114.6, 112.5, 104.1, 102.2, 59.6, 28.1. MS *m/z*: 439.02 [M+H], (438.02); Anal. calcd. (found) % for $C_{21}H_{15}N_2O_4Br$: C, 57.42 (56.70); H, 3.44 (3.31); N, 6.38 (6.25).

4-(2-Hydroxybenzylidene)-3-methyl-1-(5-bromobenzofuran-2-carbonyl)-1*H*-pyrazol-5(4*H*)-one (6c): Yield 65%; m.p: 182-184 ºC. IR (KBr, ν_{max}, cm^{-1}): 3435 (O-H *str.*), 3046 (arom. C-H *str.*), 2970 (C-H *str*. in CH_3/CH_2), 1632 (C=O *str.* pyrazolin-5-one ring), 1610 (C=N *str.*), 1210 (sp^2 C-O *str.*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.360 (s, 3H, pyrazolin-5-one CH_3), 5.711 (s, 1H, OH), 6.802 (s, 1H, =CH), 7.132 (d, 1H, *J* = 8.8 Hz, H8); 7.665 (dd, 1H, *J* = 2.4, 6.4, 2.4 Hz, H6); 8.076 (d, 1H, *J* = 2.4 Hz, H4); 8.940 (s, 1H, H3), 6.965 (m, 2H, ArH), 7.521 (m, 2H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.4, 163.4, 160.5, 158.2, 153.2, 151.3, 141.7, 146.5, 146.2, 136.8, 136.5, 133.4, 131.5, 121.5, 120.6, 117.5, 115.8, 104.5, 102.4, 27.9. MS *m/z*: 426.23 [M+H], (424.01); Anal. calcd. (found) % for $C_{20}H_{13}N_2O_4Br$: C, 56.49 (54.92); H, 3.08 (2.98); N, 6.59 (6.16).

4-(4-Methoxybenzylidene)-3-methyl-1-(5-bromobenzofuran-2-carbonyl)-1*H*-pyrazol-5(4*H*)-one (6d): Yield 70%; m.p: 184-186 ºC. IR (KBr, ν_{max}, cm^{-1}): 3032 (arom. C-H *str.*), 2954 (C-H *str.* in CH_3/CH_2), 1662 (C=O *str*. pyrazolin-5-one ring), 1625 (C=N *str.*), 1215 (sp^2 C-O *str.*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H, pyrazolin-5-one CH_3), 3.81 (s, 3H, Ar OCH_3), 6.82 (s, 1H, =CH), 7.131 (d, 1H, *J* = 8.8 Hz, H8); 7.665 (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), 6.902 (d, 2H, *J* = 7.6 Hz, ArH), 7.412 (d, 2H, *J* = 7.6 Hz, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.3, 163.4, 159.0, 158.2, 154.5, 151.2, 146.3, 146.0, 141.5, 137.9, 134.1, 131.8, 115.1, 114.9, 112.2, 104.0, 102.4, 57.2, 28.4. MS *m/z*: 439.02 [M+H], (438.02); Anal. calcd. (found) % for $C_{21}H_{15}N_2O_4Br$: C, 57.42 (57.02); H, 3.44 (3.35); N, 6.38 (6.31).

Docking studies of oxadiazole and pyrazole derivatives on DNA GyraseB protein

DNA Gyrase: DNA topoisomerase maintain the DNA topology during replication, transcription and recombination. Among many topoisomerase, DNA gyrase is the sole topoisomerase II enzyme present in *Mycobacterium tuberculosis* [50]. It mainly consists of GyrA and GyrB domains, in the holoenzyme complex as A2B2. While the GyrA subunit mainly interacts with the DNA and possesses the active-site tyrosine responsible for DNA cleavage and relegation, the GyrB subunit helps in the ATP hydrolysis, thus acting as a catalytic site for the enzyme. GyrB is one such antibacterial target. GyrB is a key component of the bacterial DNA replication process and the GyrB gene is essential across all bacterial genera. This enzyme is absent in the eukaryotic organisms, though a less homologous enzyme does exist; thus, it seems to be an attractive target for developing novel drugs against tuberculosis. Research efforts both from industry and academia on the development of DNA GyrB inhibitors have identified many potent inhibitors belonging to the chemical classes of thiazole-aminopiperidine [51] and oxadiazole [52] as potential hits. pyrazole and its derivatives represents one of the most desirable class of compounds with a wide variety of pharmacological activities *viz.*, antitubercular, antifungal, antidepressant, antimicrobial, anti-angiogenic, analgesic, anticancer and anticonvulsant [53].

Docking studies

Screening of DNA GyrB with oxadiazole and pyrazole derivatives: Auto Dock 4.0/ADT [52] program was used to investigate oxadiazole derivatives binding to DNA GyrB 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 [55] and the results were analyzed using binding energy. 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 synthesized oxadiazole and pyrazole derivatives was performed onto DNA GyrB with the same parameters and PMV 1.4.5 viewer was then used to observe the interactions of the docked compound to the DNA GyrB protein, further docking analysis was carried out on pymole software.

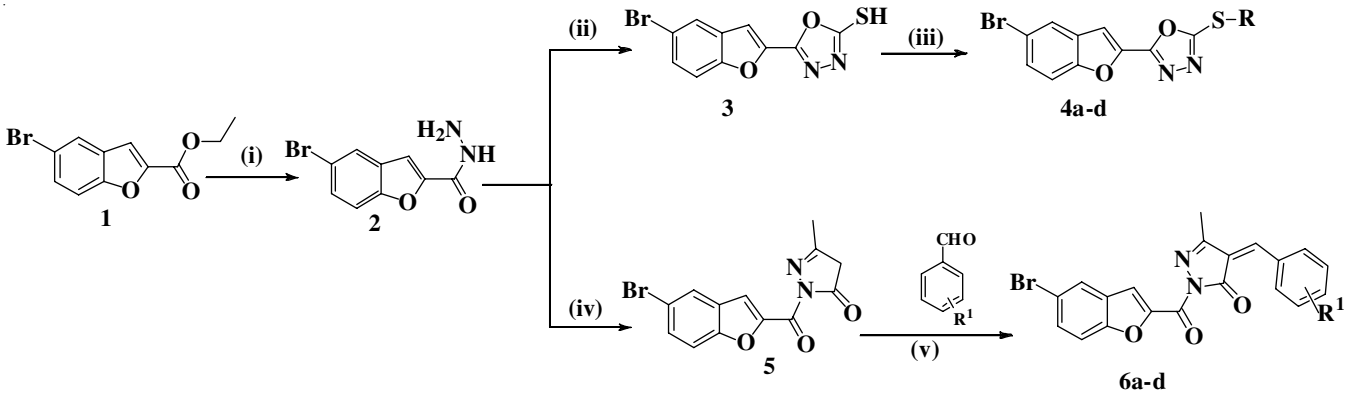
RESULTS AND DISCUSSION

The IR spectrum of compound **1** displayed absorption bands at 3062, 2975, 1729, 1430 and 1052 cm^{-1} corresponding to aromatic C-H stretching, C-H stretching in CH_3/CH_2, C=O stretching in esters, sp^2 C-O stretching and sp^3 C-O stretching respectively. The ^{1}H NMR spectrum of compound **2** exhibited a three proton triplet at δ 1.21 and a two proton quartet at 4.17 ppm due to ethyl group of the ester besides the signals of aromatic ring protons.

The reactive intermediate 5-bromobenzofuran-2-carbohydrazide (**2**) was synthesized by the reaction of ethyl 5-bromobenzofuran-2-carboxylate (**1**) with hydrazine hydrate in distilled methanol. The IR spectrum of compound **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 compound **2** exhibited a singlet at δ 4.97 due to NH_2 and another singlet at 10.34 due to NH. The mass spectrum of compound **2** exhibited [M+H] peak at *m/z* 254.97 that confirms the chemical structure of the compond.

Reaction of compound **2** with CS_2 in presence of KOH led to the 5-(5-bromobenzofuran-2-yl)-1,3,4-oxadiazole-2-thiol (**3**). The IR spectrum of **3** displayed absorption bands at 3049, 2786, 1643 for C-H stretching in aromatics, S-H stretching in thiols and C=N stretching in oxadiazole ring, respectively. The ^{1}H NMR spectrum of compound **3** displayed a hump at δ 3.60 ppm due to SH proton. The ^{13}C NMR spectrum of **3** exhibited two signals at δ 166.5 and 164.5 ppm due the two carbon atoms in the oxadiazole ring.

Reaction of equimolar quantities of 5-(5-bromobenzofuran-2-yl)-1,3,4-oxadiazole-2-thiol **3** and 4-chloropyridine furnished 4-(5-(5-bromobenzofuran-2-yl)-1,3,4-oxadiazol-2-ylthio)pyridine (**4a**) (**Scheme-I**). IR spectrum of **4a** displayed absorption bands at 3056 and 1624 cm^{-1} corresponding to C-H stretching in aromatics and C=N stretching in oxadiazole ring, respectively. The characteristic absorption bands observed in the IR spectrum of compound **3** at 2786 cm^{-1} corresponding to SH stretching in thiols and a hump at δ 3.60 characteristic of



Scheme-I

SH proton in proton NMR that are absent in the spectra of compounds **4a-d** confirm the successful reaction of compound **3** with aromatic halogen compounds to furnish the desired target molecules.

4-Benzylidene-3-methyl-1-(5-bromobenzofuran-2-carbonyl)-1*H*-pyrazol-5(4*H*)-one (**6a**) was obtained by the Knovenegel condensation of 1-(5-bromobenzofuran-2-carbonyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (**5**) with benzaldehyde suspended in dry toluene with a catalytic amount of piperidine (**Scheme-I**). IR spectrum of compound **6a** displayed absorbtions at 3052, 2930, 1665 and 1630 cm^{-1} due to C-H stretching in aromatics, C-H stretching in CH_3/CH_2, C=O stretching in pyrazolin-5-one ring and C=N stretching, respectively. The proton NMR spectrum of compound **5** showed a signal δ 3.23 ppm corresponding to the methylene proton of heterocyclic ring. The disappearance of this characteristic signal of methylene protons of compound **5** and the appearance of new signal at around δ 6.82 ppm corresponding to the methine proton of Knovenegel adducts along with other characteristic signals confirms the successful formation of the adducts **6a-d**. Further the ^{13}C NMR spectrum of compound **5** showed a signal at δ 42.1 ppm for the methylene carbon atom of the pyrazolin-

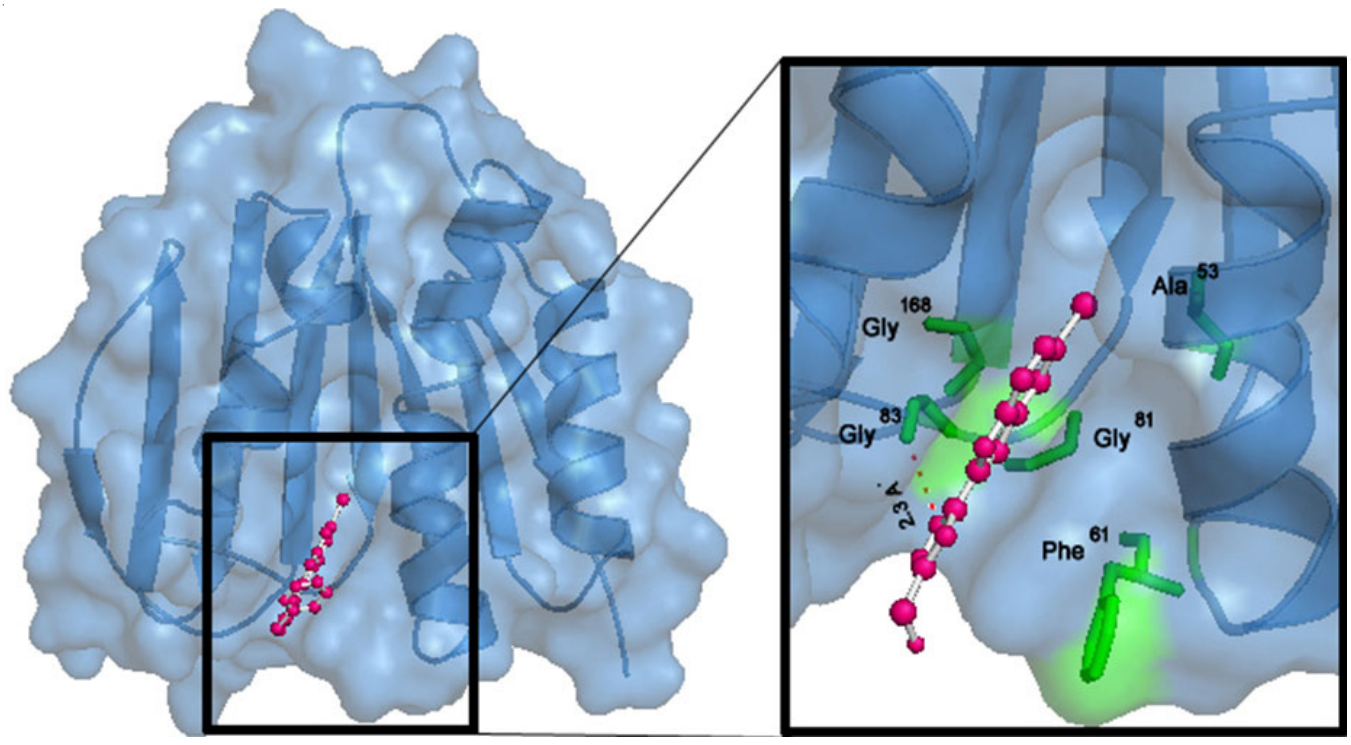


Fig. 1. Docking conformation of derivative (**3**) on DNA GyrB protein and ligand represented by ball and stick with hot pink and the residues interacting with are represented by sticks with green

TABLE-1
BINDING ENERGIES AND INHIBITION CONSTANTS OF DOCKED OXADIAZOLE COMPOUNDS CALCULATED BY AUTODOCK

Protein name	Protein pdb id	Ligand name	Cluster	Cluster run	Binding energy (kcal/mol)	Inhibition constant (μM)
DNA Gyrase B	4B6C	**3**	1	33	-7.76	2.04
		4a	1	22	-6.73	11.59
		4b	1	17	-7.88	1.67
		4c	1	17	-5.92	45.44
		4d	1	21	-7.27	50.06

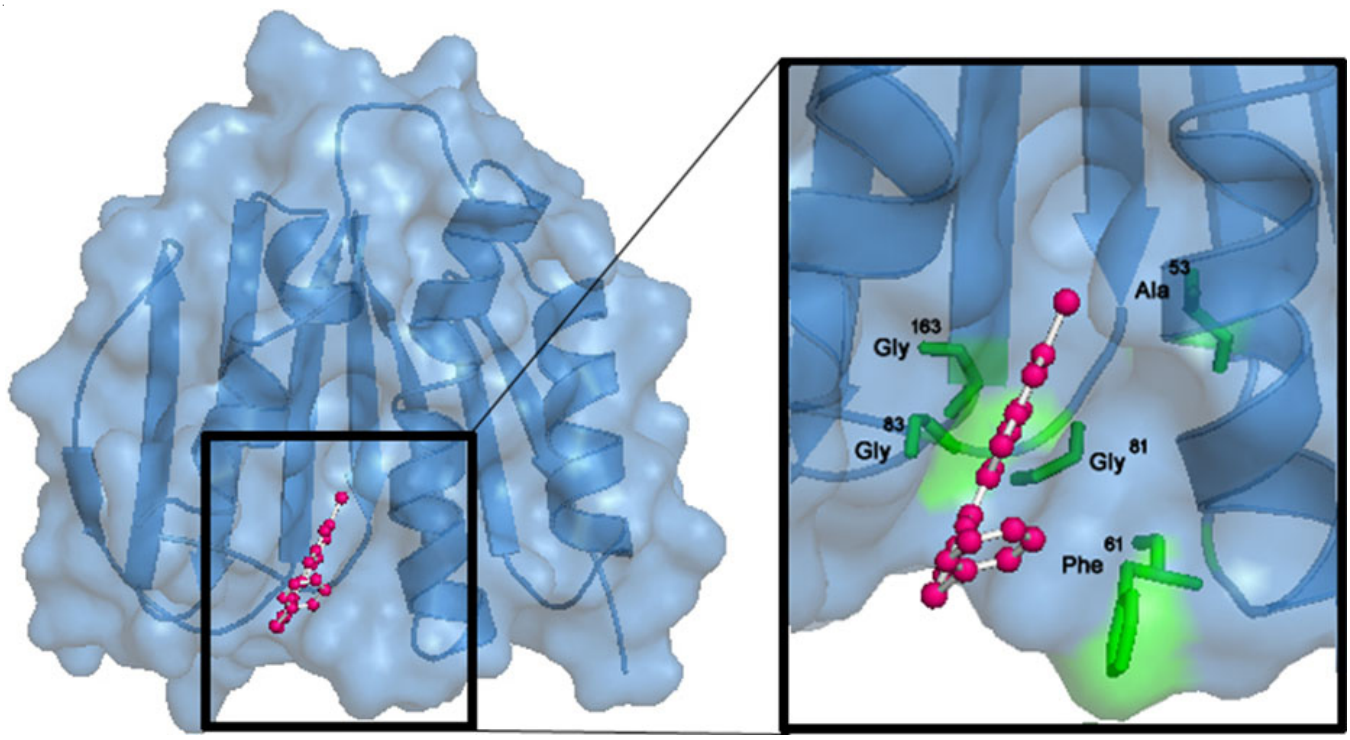


Fig. 2. Docking conformation of derivative (**4b**) on DNA GyrB protein and ligand represented by ball and stick with hot pink and the residues interacting with are represented by sticks with green

5-one ring which was absent in the ^{13}C NMR spectra of compounds **6a-d**.

Molecular docking of oxadizole and pyrazole derivatives onto DNA GyrB protein: All 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). Among the five derivatives (**3**, **4a**, **4b**, **4c** and **4d**) of oxadizoles, compounds **3** and **4b** showed highest binding energy (-7.78 and -7.76) with DNA GyrB protein. All docked derivatives interacted by the same mode of DNA GyrB protein binding site. Derivative **3** showed a hydrogen one bond interaction with amino acid Gly 83, while Ala 53, Gly 81, Phe 61 and Gly 168 formed the hydrophobic interactions (Fig. 1). Derivative **4b** shows hydrophobic interactions with amino acids Gly 81, Gly 83, Gly 163, Ala 53 and Phe 61 (Fig. 2), for this reason it is concluded that the greater negative value of the binding energy for compound **4b** demonstrates a better interaction of this molecule towards target receptor than that of compounds **3**, **4a**, **4c** and **4d**.

The higher binding affinities/lower docking scores and low inhibition constant values of the synthesized compounds are given in Table-2. Among the tested compounds (**5**, **6a**, **6b**, **6c** and **6d**) pyrazole derivatives **6b** and **6c** showed highest binding energy (-8.52 and -8.97) with DNA GyrB protein. All five docked derivatives interacted by the same mode of DNA GyrB protein binding site. Compound **6b** showed one hydrogen bond interaction with amino acid Asn 52, while Ila 84, Val 103,

TABLE-2
BINDING ENERGIES AND INHIBITION CONSTANTS OF DOCKED PYRAZOLE COMPOUNDS CALCULATED BY AUTODOCK

Protein name	Protein pdb id	Ligand name	Cluster	Cluster run	Binding energy (kcal/mol)	Inhibition constant (μM)
DNA Gyrase B	4B6C	**5**	1	49	-7.81	1.89
		6a	1	1	-8.51	567.03
		6b	1	3	-8.52	569.72
		6c	1	1	-8.97	572.1
		6d	1	15	-7.05	861.05

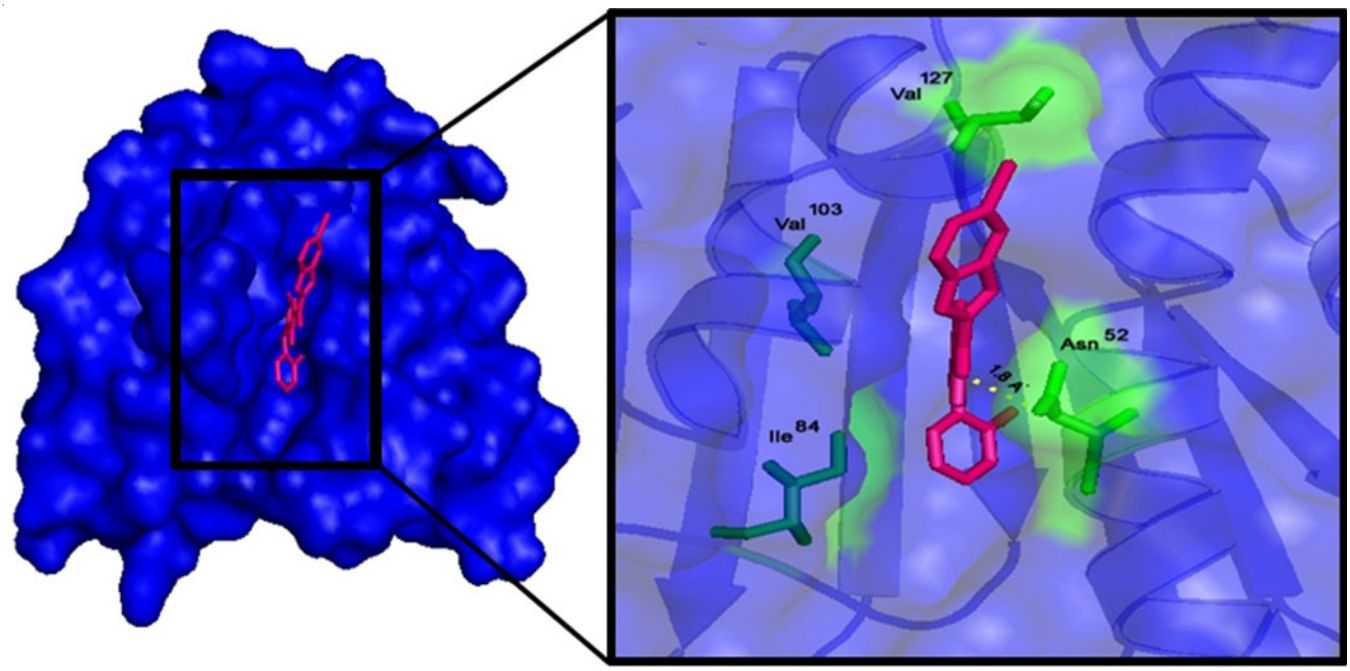


Fig. 3. Docking conformation of derivative (**6b**) on DNA GyrB protein and ligand represented by ball and stick with hot pink and the residues interacting with are represented by sticks with green

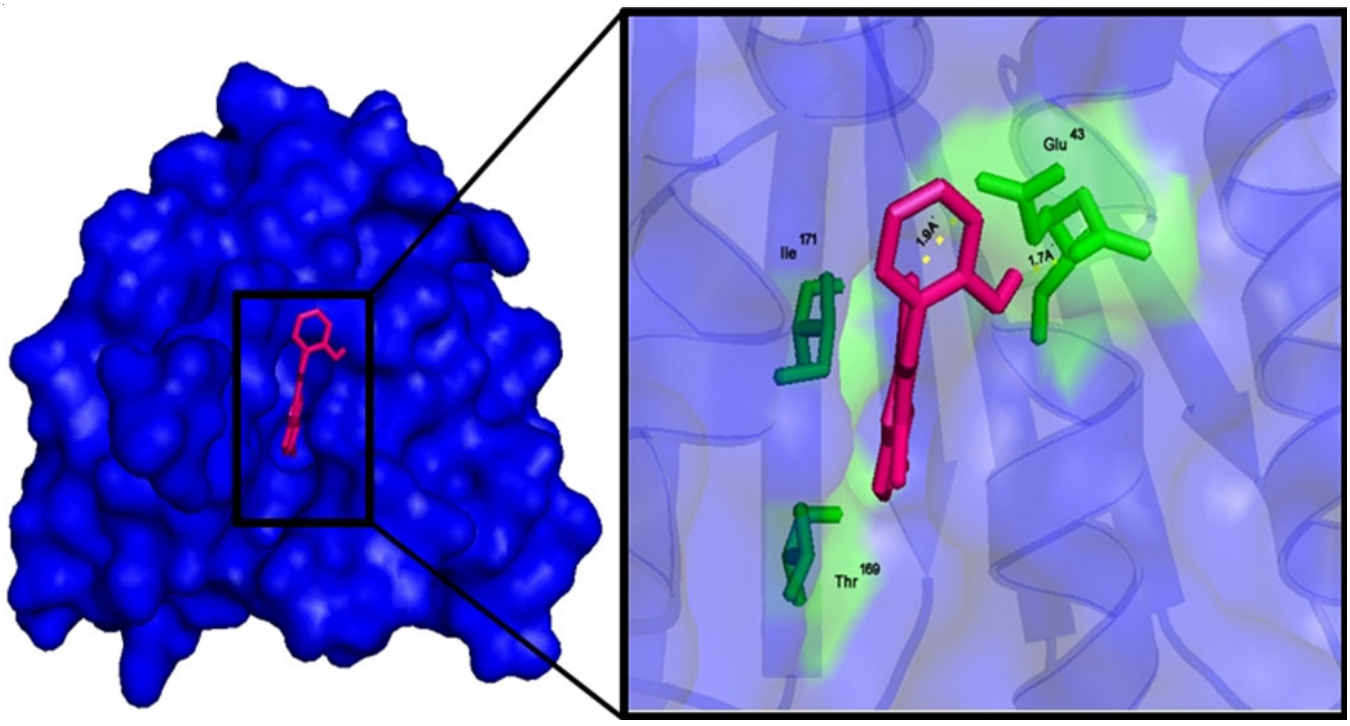


Fig. 4. Docking conformation of **6c** on DNA GyrB protein and ligand represented by ball and stick with hot pink and the residues interacting with are represented by sticks with green

Val 127 formed the hydrophobic integrations (Fig. 3). Compound **6c** derivative formed two hydrogen bonds with amino acid Glu 43 and hydrophobic interactions with amino acids Ile 171 and Thr 169 (Fig. 4). For this reason, it is concluded that docking study of pyrazole derivatives **6b** and **6c** showed more affinity to DNA GyrB protein, The greater negative value of the binding energy for compound **6c** demonstrates a better interaction of this molecule towards target receptor than rest of the compounds **5**, **6a**, **6b** and **6d**.

Conclusion

The newly designed hybrid compounds of oxadizoles and pyrazole possessed to have a good synthetic accessibility which indicates that these compounds can be easily synthesized in the laboratory. From the docking studies, the residues in binding responsible for binding to the inhibitors of oxadizoles and pyrazole substrates with DNA GyrB protein exhibited a high binding affinity. Hence, it is concluded that these hybrid oxadizoles and pyrazole derivatives could be a potential anti-

tuberculosis lead molecules for modulating the expression of DNA GyrB protein.

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