Synthesis, Biological Evaluation of novel 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-onederived Chalcones as potent Antitubercular agents

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ABSTRACT

Objectives: To synthesize a series of novel 3,4-dihydropyrimidine chalcones which has anti-mycobacterial activity and to perform docking studies for active compounds.

Methodology:A series of 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one derivatives were synthesized and evaluated their anti-mycobacterial activity against M.tuberculosis H_{37}Rv strain using Micro plate Alamar Blue dye Assay (MABA).

Results: The complete spectral and elemental analytical data of the products, confirmed the formation of novel 6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1*H*)-onederivatives. The biological evaluation of all the synthesized compounds against M. tuberculosis $H_{37}Rv$ strain using MABA exhibits one potent compound **6t** with MIC value of 3.12 µg/ml and four moderate activity compounds **6a, 6d, 6i** and **6q** with MIC values of 6.24 µg/ml, 6.24 µg/ml, 12.48 µg/ml and 12.48 µg/ml respectively.

Conclusion: A series of novel dihydropyrimidine chalcones were synthesized, characterized, and evaluated for *invitro* antimycobacterial $H_{37}Rv$ strain. Compound **6t** exhibited potent MIC value compared with reference standard.

Keywords: Antimycobacterial activity,Chalcone, Dihydropyrimidine and MABA.

INTRODUCTION

Infectious diseases are influencing the world with their morbidity and mortality. Globally, more than one-third of the world population is infected with the bacteria that cause Tuberculosis (TB) and each year approximately 9 million people effected with the disease and each year 2 million of those die[1-4]. The wide spread of TB is due to the following major

factors: the susceptibility of people infected with the acquired immune deficiency syndrome (AIDS), which enhances the risk of developing TB in 100 times, and increasing resistance to the existing drugs[5-7].Treatment of TB is a complex process because of various factors which include patient's inability to persist with combined treatment regimen, the spreading ability of non-tubercular mycobacteria (NTM) like *M. avium* complex (MAC),the ineffectiveness of the drugs on immunosuppressed patients, and multidrug resistance (MDR) [8-10]. Antibiotics are being used to treat this infection, but this pathogenic strain is becoming resistant to antibiotics. Since the resistance increases day by day, there is a need of designing newer antibiotics.

Chalcones are a diverse group of compounds which could be synthesized as well as obtained from natural sources. Chalcones are known to possess different types of biological activity: anti-leishmanial, anti-inflammatory, antimitotic, anti-invasive, anti-fungal, CyLT1 (LTD4) receptor antagonism, anti-malarial, anti-plasmodial, immunosupressive, cytotoxic, anti-tumor, and anti-oxidant properties, and modulation of P-glycoprotein-mediated multi-drug resistance[11-13]. To the best of our knowledge, there has been no previous report of analogous dihydropyrimidine chalcones as anti-tuberculosis agents. However, there are numerous examples of nitrogen containing heterocycles being used to treat TB, for example Clofazimine, Isoniazid and Pyrazinamide. These compounds provide structural precedence that our dihydropyrimidinones chalcone analogues may lead to the generation of novel anti-TB therapeutics. Herein the synthesis and *in vitro* anti-mycobacterial activity of novel dihydropyrimidine chalcone derivatives are described. Further, we propose the molecular interactions and the binding of the synthesized compounds using the X-ray crystal structure of thymidylate kinase (PDB ID: 1G3U) through docking studies[14]. We hope it will help to further development of new cheap and effective anti-mycobacterial medicines so much needed by the contemporary medicine.

MATERIALS AND METHODS

Experimental

Melting points were recorded in open capillaries on LABINDIA melting point apparatus (MEPA MP08050204) and were uncorrected. IR spectra were recorded on Perkin Elmer FT-IR Spectrometer (Spectrum RX I) using KBr pellet technique. ^{1}H NMR spectra were recorded on Bruker Advance II 400 MHz spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra (ESI) were recorded on Waters Micromass Q-TOF Micro and elemental analyses were performed using Thermo EA 2110 series elemental analyser. All chemicals used were ofanalytical grade and commercially available from E.Merck, Mumbai.

Solvents were used without further purification. Silica gel (100–200 mesh; E. Merck, Mumbai) was used for column chromatography. All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (mesh) (E. Merck, Mumbai) and spots were visualized under UV light (254 nm).

General experimental procedure for the Synthesis of 5-acetyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2-(1H)-ones (4)

A mixture of benzaldehyde, acetylacetone and urea (0.1 mol. each) was taken into a 250ml dry beaker and add soy lecithin (0.1mol.) as a catalyst. An inverted glass funnel was placed over the beaker and subjected to microwave irradiation in a *BPL-SANYO* microwave oven at 220 W for 1-2min, reaction progress was monitored by TLC, after completion of reaction triturated with 150ml of cold water and dried. Purified by recrystallization from ethanol to afford 3,4-dihydropyrimidine-2-(1H)-ones [15].

Yield: 96%; mp 210°C; IR (KBr) cm^{-1}: 3241(N-H), 3095(C-H,Ar), 1713(C=O).^{1}H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.1(s, 3H,-CH_3), 2.29(s, 3H,-CH_3), 5.26(s, 1H,H of pyrimidine ring),7.24(m, 5H,Ar-H), 7.82(s, 1H,-NH), 9.17(s, 1H,-NH). Mass (ESI-MS): m/z 231 (M+1).Elemental analysis: For $C_{13}H_{14}N_2O_2$ calculated C, 67.81%; H, 6.12%; N, 12.16%; found C, 67.82%; H, 6.08%; N, 12.17%.

6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one derivatives (6a-t)

A mixture of substituted aromatic aldehyde and compound **4**(0.1 mol. each) in 20 ml of absolute ethanol was taken into a 250ml dry beaker to the clean reaction mixture 10% NaOH was added. An inverted glass funnel was placed over the beaker and subjected to microwave irradiation at 180 W in a *BPL-SANYO*microwave oven for 2-5minreaction was monitored by TLC. After completion of reaction neutralized with dil.HCl the precipitated product is filtered, washed with water, dried and recrystallized from absolute ethanol.

5-(3-(4-chlorophenyl)acryloyl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (6a)

Yield: 95%; mp 186°C; IR (KBr) cm^{-1}: 3348 (NH), 1628 (C=O), 1571 (C=C), 1123 (C-Cl). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.29 (s, 3H, -CH_3), 5.49 (s, 1H, H of pyrimidine ring), 6.54 (d, 1H, *J*=17.6Hz, -CH=CH-), 6.70 (d, 1H, *J*=7.2Hz, -CH=CH-), 7.22 (m, 5H, Ar-H), 7.46 (d, 2H, *J*=8.8Hz), 7.70 (d, 2H, *J*=8.8 Hz), 7.89(s, 1H, -NH), 9.26 (s, 1H, -NH). Elemental analysis for $C_{20}H_{17}N_2O_2Cl$: calculated: C, 68.08%; H, 4.85%; N, 7.94%; found: C, 68.18%; H, 4.82%; N, 7.95%.

5-(3-(4-dimethylaminophenyl)acryloyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one(6b)

Yield: 88%; mp 160°C; IR (KBr) cm^{-1}: 3321 (NH), 1642 (C=O), 1629 (C=C). ^1H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.22 (s, 3H, $-CH_3$), 3.43 (s, 6H, $-N(CH_3)_2$), 5.19 (s, 1H, H of pyrimidine ring), 6.24 (d, 1H, *J*=6.8Hz, -CH=CH-), 6.44 (d, 1H, *J*= 17.6Hz, -CH=CH-), 8.15 (m, 5H, Ar-H), 8.43 (d, 2H, *J*=8.4Hz), 8.76 (d, 2H, *J*=8.4Hz), 8.33(s,1H,-NH), 9.95(s,1H,-NH). Elemental analysis for $C_{22}H_{22}N_2O_4$: calculated: C, 73.10%; H, 6.41%; N, 11.62%; found: C, 73.13%; H, 6.37%; N, 11.63%.

5-(3-(4-hydroxyphenyl) acryloyl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (6c)

Yield: 83%; mp 192°C; IR (KBr) cm^{-1}: 3526(OH), 3305(NH), 1617(C=O), 1575(C=C). ^1H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.30(s,3H, $-CH_3$), 5.19(s,1H,H of pyrimidine ring), 6.32(d,1H, *J*=8.8Hz,-CH=CH-), 6.53(d,1H, *J*=19.2Hz,-CH=CH-), 7.17(m,5H,Ar-H), 7.53(d,2H, *J*=8.4Hz), 7.67(d,2H, *J*=8.4Hz) 8.77(s,1H,-NH), 10.16(s,1H, -NH), 10.35(s, 1H, -OH). Elemental analysis for $C_{20}H_{18}N_2O_3$: calculated: C, 71.84%; H, 5.42%; N, 8.38%; found: C, 71.85%; H, 5.38%; N, 8.38%.

5-(3-(3,5-dimethoxyphenyl)acryloyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one(6d)

Yield: 87%; mp 202°C; IR (KBr) cm^{-1}:3327(NH), 1673(C=O), 1469(C=C), 1193 (C-O-C). ^1H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.35(s,3H,$-CH_3$), 3.91(s,3H,OCH_3), 3.94(s,3H,OCH_3), 5.21(s,1H,H of pyrimidine ring), 6.91 (d,1H, *J*=8.8Hz,-CH=CH-), 7.24 (d,1H,*J*=17.2Hz,-CH=CH-), 7.32(m,8H, Ar-H). Elemental analysis for $C_{22}H_{22}N_2O_4$: calculated: C, 69.83%;H, 5.85%;N, 7.40%; found: C, 69.84%; H, 5.82%; N, 7.40%.

5-(3-(3-nitrophenyl) acryloyl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (6e)

Yield: 92%; mp 201°C; IR (KBr) cm^{-1}: 3356(NH), 1652(C=O), 1584(C=C). ^1H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.53(s,3H,$-CH_3$), 4.92(s,1H,H of pyrimidine ring), 6.75(d,1H,*J*=17.6Hz,-CH=CH-), 6.85(d,1H,*J*=7.6Hz,-CH=CH-), 7.12(m,5H,Ar-H), 7.27(m,3H,Ar-H), 7.46(s,1H,-NH), 8.02(s,1H,-NH). Elemental analysis for $C_{20}H_{17}N_3O_4$: calculated: C, 66.11%; H, 4.71%; N, 11.56%; found: C, 66.11%; H, 4.68%; N, 11.57%.

5-(3-(3,4,5,-trimethoxyphenyl)acryloyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one(6f)

Yield: 91%; mp 182°C; IR (KBr) cm^{-1}: 3327(NH), 1633(C=O), 1592(C=C),1230 (C-O-C).^1H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.29(s,3H,$-CH_3$), 3.61(s,3H,$-OCH_3$), 3.91(s,6H,$-OCH_3$), 5.19(s,1H,H of pyrimidine ring), 6.24(d,1H, *J*=5.6Hz,-CH=CH-), 6.45(d,1H,*J*=16.8Hz,-CH=CH-),7.95(m,7H,Ar-H), 8.53(s,1H,-NH), 8.76(s,1H,-NH).

Elemental analysis for $C_{23}H_{24}N_2O5$: calculated: C, 67.63%; H, 5.92%; N, 6.86%; found: C, 67.64%; H, 5.88%; N, 6.86%.

5-(3-(2-hydroxyphenyl) acryloyl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (6g)

Yield: 88%; mp 187°C; IR (KBr) cm^{-1}: 3436(OH), 3320(NH), 1720(C=O), 1623(C=C).^{1}H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.35(s,3H,-CH_3), 5.42(s,1H,H of pyrimidine ring), 6.46(d,1H, *J*=8.8Hz,-CH=CH-), 6.62(d,1H, *J*=19.2Hz,-CH=CH-), 7.16(m,9H,Ar-H), 8.92(s,1H,-NH), 9.13(s,1H, -NH), 9.38(s, 1H,-OH). Elemental analysis for $C_{20}H_{18}N_2O_3$: calculated: C, 71.84%; H, 5.42%; N, 8.38%; found: C, 71.85%; H, 5.38%; N, 8.38%.

5-(3-(4-methylphenyl) acryloyl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (6h)

Yield: 87%; mp 179°C; IR (KBr) cm^{-1}: 3328(NH), 1618(C=O), 1522 (C=C).^{1}H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.33(s,3H,-CH_3), 2.77(s,3H,-CH_3), 5.18(s,1H,H of pyrimidine ring), 6.33(d,1H, *J*=7.6Hz,-CH=CH-), 6.52(d,1H, *J*=16.4Hz,-CH=CH-), 7.18(m,5H,Ar-H), 7.56(d,2H,*J*=6Hz), 7.67(d,2H,*J*=6Hz) 8.77(s,1H,-NH), 10.16(s,1H,-NH). Elemental analysis for $C_{21}H_{20}N_2O_2$: calculated: C, 75.88%; H, 6.06%; N, 8.43%; found: C, 75.90%; H, 6.02%; N, 8.43%.

5-(3-(4-bromophenyl) acryloyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (6i)

Yield: 89%; mp 169°C; IR (KBr) cm^{-1}: 3328(NH), 1684(C=O), 1575(C=C). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.28(s,3H,-CH_3), 5.41(s,1H,H of pyrimidine ring), 6.83(d,1H, *J*=7.2Hz,-CH=CH-), 7.32(d,1H, *J*=16.5Hz,-CH=CH-), 8.12(m,9H,Ar-H), 7.83(s,1H,-NH), 8.92(s,1H,-NH). Elemental analysis for $C_{20}H_{17}N_2O_2Br$: calculated: C, 60.55%; H, 4.31%; N, 7.06%; found: C, 60.60%; H, 4.29%; N, 7.07%.

5-(3-(4-flurophenyl) acryloyl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (6j)

Yield: 84%; mp159°C; IR (KBr) cm^{-1}. 3329(NH), 1635(C=O), 1529(C=C), 1192(C-F). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.39(s,3H,-CH_3), 5.25(s,1H,H of pyrimidine ring), 6.68(d,1H,*J*=8.8Hz,-CH=CH), 7.12(m,5H,Ar-H), 7.25(d,1H, *J*=16Hz,-CH=CH-),7.53(d,2H, *J*=8.8Hz), 7.72(d,2H,*J*=8.8 Hz), 8.01(s,1H,-NH), 9.74(s,1H,-NH). Elemental analysis for $C_{20}H_{17}N_2O_2F$: calculated: C, 71.42%; H, 5.09%; N, 8.33%; found: C, 71.64%; H, 5.07%; N, 8.35%.

5-(3-(3-chlorophenyl) acryloyl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (6k)

Yield: 88%; mp 161°C; IR (KBr) cm^{-1}: 3356(NH), 1674(C=O), 1469(C=C). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.42(s,3H,-CH_3),5.31(s,1H,H of pyrimidine ring), 6.54(d,1H,*J*=16.4Hz,-CH=CH-), 6.91(d,1H, *J*=8.4Hz,-CH=CH-), 7.32(m,6H,Ar-H),

7.53(m,3H,Ar-H), 7.63(s,1H,-NH), 8.12(s,1H,-NH). Elemental analysis for $C_{20}H_{17}N_2O_2Cl$: calculated: C, 68.08%; H, 4.85%; N, 7.94%; found: C, 68.18%; H, 4.82%; N, 7.95%.

5-(3-(4-nitrophenyl) acryloyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (6l)

Yield: 84%; mp 211°C; IR (KBr) cm^{-1}: 3332 (NH), 1790(C=O), 1671(C=C). ^1H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.35(s,3H,-CH_3), 5.48(s,1H,H of pyrimidine ring), 6.97(d,1H, *J*=7.2Hz,-CH=CH-), 7.19(d,1H, *J*=16.5Hz,-CH=CH-), 7.68(m,9H,Ar-H), 8.17(s,1H,-NH), 8.91(s,1H,-NH). Elemental analysis for $C_{20}H_{17}N_3O_4$: calculated: C, 66.11%; H, 4.71%; N, 11.56%; found: C, 66.11%; H, 4.68%; N, 11.57%.

5-(3-(phenyl) acryloyl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (6m)

Yield: 94%; mp 162°C; IR (KBr) cm^{-1}: 3320(NH), 1652(C=O), 1460(C=C). ^1H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.34(s,3H,-CH_3), 5.56(s,1H,H of pyrimidine ring), 6.16(d,1H, *J*=9.2Hz,-CH=CH-), 6.51(d,1H, *J*=17.2Hz,-CH=CH-), 7.00(m,10H,Ar-H),7.80(s,1H,-NH), 8.90(s,1H,-NH). Elemental analysis for $C_{20}H_{18}N_2O_2$: calculated: C, 75.45%; H, 5.69%; N, 8.80%; found: C, 75.47%; H, 5.66%; N, 8.80%.

5-(3-(2-bromophenyl) acryloyl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (6n)

Yield: 86%; mp 167°C; IR (KBr) cm^{-1}: 3342(NH), 1644(C=O), 1627(C=C),1170 (C-Br).^1H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.52 (s,3H,-CH_3), 5.29(s,1H,H of pyrimidine ring), 6.13(d,1H, *J*=9.2Hz,-CH=CH-), 6.47(d,1H, *J*=15.6Hz,-CH=CH-),7.21(m,9H,Ar-H), 7.62 (s,1H,-NH), 8.32(s,1H,-NH). Elemental analysis for $C_{20}H_{17}N_2O_2Br$: calculated: C, 60.46%; H, 4.31%; N, 7.05%; found: C, 60.60%; H, 4.29%; N, 7.07%.

5-(3-(4-diethylaminophenyl) acryloyl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one(6o)

Yield: 92%; mp 195°C; IR (KBr) cm^{-1}: 3324(NH), 1678(C=O), 1531(C=C). ^1H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 1.04(t,6H,N-$CH_2\underline{C}H_3)_2$), 2.28(s,3H,-CH_3), 3.95(m,4H,-N($\underline{C}H_2CH_3)_2$, 5.21(s,1H,H of pyrimidine ring), 6.27(d,1H, *J*=7.2Hz,-CH=CH-), 6.45(d,1H, *J*=14.4Hz,-CH=CH), 8.12(m,5H,Ar-H), 8.32(s,1H,-NH), 8.43(d,2H,*J*=8.4Hz), 8.77(d,2H,*J*=8.4Hz), 9.89(s,1H,-NH). Elemental analysis for $C_{24}H_{27}N_3O_2$: calculated: C, 74.01%; H, 6.98%; N, 10.79%; found: C, 74.03%; H, 6.94%; N, 10.79%.

5-(3-(2, 4-dichlorophenyl) acryloyl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one(6p)

Yield: 91%; mp 192°C; IR (KBr)cm^{-1}: 3364(NH), 1656(C=O), 1612(C=C),1185(C-Cl). ^1H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.48(s,3H,-CH_3), 5.46(s,1H,H of pyrimidine ring), 6.90(d,1H,*J*=8.8 Hz,-CH=CH-), 7.15(d,1H,*J*=17.2Hz,-CH=CH-), 7.34(m,8H,Ar-H),

8.77(s,1H,-NH), 9.62(s,1H,-NH). Elemental analysis for $C_{20}H_{16}N_2O_2Cl_2$: calculated: C, 62.03%; H, 4.16%; N, 7.23%; found: C, 62.17%; H, 4.14%; N, 7.25%.

5-(3-(4-methoxyphenyl) acryloyl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (6q)

Yield: 82%; mp 170°C; IR (KBr)cm^{-1}: 3332(NH), 1668(C=O), 1520(C=C). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.32 (s,3H,-CH_3), 3.79(s,3H, -OCH_3), 5.26(s,1H,H of pyrimidine ring), 6.97(d,1H, *J*=9.04Hz,-CH=CH-), 6.97(d,1H, *J*=16.8Hz,-CH=CH-), 7.26(m,9H,Ar-H),7.89(s,1H,-NH), 9.26(s,1H,-NH). Elemental analysis for $C_{21}H_{20}N_2O_3$: calculated: C, 72.39%; H, 5.78%; N, 8.04%; found: C, 72.41%; H, 5.74%; N, 8.04%.

5-(3-(3, 4-dimethoxyphenyl) acryloyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one(6r)

Yield: 87%; mp 202 °C; IR (KBr) cm^{-1}: 3332(NH), 1647(C=O), 1607(C=C). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.34 (s,3H,-CH_3), 4.863 (s,6H,-OCH3), 5.15(s,1H,H of pyrimidine ring), 6.51(d,1H,*J*=8.8Hz,-CH=CH-), 6.89(d,1H,*J*=16.8Hz,-CH=CH-), 8.27(m,8H,Ar-H), 8.65(s,1H,-NH), 9.44(s,1H,-NH).Elemental analysis for $C_{22}H_{22}N_2O_4$: calculated: C, 69.83%; H, 5.85%; N, 7.40%; found: C, 69.84%; H, 5.82%; N, 7.40%.

5-(3-(2-furfuryl) acryloyl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (6s)

Yield: 94%; mp 192°C; IR (KBr) cm^{-1}: 3329 (NH), 1629(C=O), 1469(C=C). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.98(s,3H,-CH_3),4.92(s,1H,H of pyrimidine ring),7.13(d,1H,*J*=16Hz,-CH=CH-),7.18(m,9H,Ar-H),7.60(s,1H,-NH), 8.02(s,1H,-NH). Elemental analysis for $C_{18}H_{16}N_2O_3$: calculated: C, 70.12%; H, 6.12%; N, 9.08%; found: C, 70.12%; H, 5.19%; N, 9.09%.

5-(3-(2-thienyl) acryloyl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (6t)

Yield: 91%; mp 201°C; IR (KBr) cm^{-1}: 3364 (NH), 1720(C=O), 1472(C=C). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, ppm)δ: 2.54(s,3H,-CH_3), 5.21(s,1H,H of pyrimidine ring), 6.35(d,1H,*J*=15.6Hz,-CH=CH-), 7.08(d,1H,*J*=3.7Hz,-CH=CH-), 7.28(m,5H,Ar-H), 7.59(m,3H), 7.19(s,1H,-NH), 8.32(s,1H,-NH). Elemental analysis for $C_{18}H_{16}N_2O_2S$: calculated: C, 66.64%; H, 4.96%; N, 8.63%; found: C, 66.66%; H, 4.93%; N, 8.64%.

Anti-Tubercular Activity

The anti-mycobacterial activity of compounds was assessed against *M.tuberculosis* H_{37}Rv strain usingMABA [16]. Briefly, 200µl of sterile deionized water was added to all outer perimeter wells of sterile 96 plate to minimize evaporation of medium in the test wells during incubation. The 96 wells plate received 100 µl of the middle brook 7H9 broth and serial

dilution of compounds was made directly on plate. The final drug concentrations tested were 100 to 0.8 µg/ml and compound with standards pyrazinamide 3.125µg/ml and streptomycin 6.25µg/ml plates were covered and sealed with parafilm and incubated at 37°c for five days. After this time 25 µl freshly prepared 1:1 mixture of Almar blue reagent and 10% tween 80 was added to the plate and incubated for 24h. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. The MIC was defined as lowest drug concentration which prevented the color change from blue to pink.

RESULTS AND DISCUSSION

Chemistry

To formation of products **(6a-6t)**, the reaction took place between acetylacetone**(1)**,benzaldehyde**(2)** and urea**(3)** by one pot condensation method (Biginelli reaction) leads to formation of 5-acetyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2-(1H)-ones**(4)** and **4** was subjected to Claisen–Schmidt condensation using different substituted aromatic aldehydes **(5a–5t)** in the presence of sodium hydroxide and absolute ethanol keeping the Micro Wave Irradiation (MWI) results in the formation of different chalcones **(6a–6t)**, Scheme 1.The synthesized compounds were purified by column chromatography. All of the derivatives were characterized by FT-IR, ^{1}H NMR, and mass spectral data. The chemical structures were confirmed through physical and spectral data.

Antimycobacterial activity

Synthesized compounds were evaluated for their inhibition potential against *M.tuberculosis* $H_{37}Rv$ strain which shows better docking scores. The current research program is the design and development of DHPMs and the objective is to identify some lead molecules with $H_{37}Rv$ strain inhibitory activity. The minimum inhibitory concentrations (MIC) of the compounds were compared with Streptomycin and Pyrazinamide as standards. The results obtained from in vitro screening of test compounds are summarized in Figure 2.

The complete spectral and elemental analytical data of the products, confirmed the formation of novel 6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1*H*)-onederivatives**(6a-6t)**. Initially, compound **4** was confirmed by the FT-IR spectra of the compound revealed absorption bands in the region around 3241, 2985, and 1713 cm^{-1} regions, resulting from the -NH, Ar-H and C=O functions respectively. Further, in the ^{1}H NMR spectra the signal derived from acetyl group (-$COCH_3$) was observed at 2.29 ppm (singlet), the aromatic protons are shown in multiplets around 7.24 ppm and broad singlets in the range 7.82 ppm and 9.17 ppm due to –NH protons. The LC-MS showed its molecular ion peak at 231 (M+H).

The chemical structures of chalcones **(6a–6t)**were confirmed through physical and spectral data. The ^{1}H NMR spectrum **6a** showed signal 6.719 ppm (*J*=7.2 Hz) and 6.592 ppm (*J*=17.6Hz), the aromatic protons are shown in multiplets around 7.22-7.78 ppm. The LC-MS showed its molecular ion peak at 353 (M+H), the higher magnitude of coupling constants (*J* value) for both protons indicate *trans* configuration.

In the biological evaluation of all the synthesized compounds against M. tuberculosis *$H_{37}Rv$* strain using MABA exhibits one potent compound **6t** with MIC value of 3.12 µg/ml and four moderate activity compounds **6a, 6d, 6i** and **6q** with MIC values of 6.24 µg/ml, 6.24 µg/ml, 12.48 µg/ml and 12.48 µg/ml respectively.

CONCLUSION

A series of novel dihydropyrimidine chalcones were synthesized, characterized, and evaluated for *invitro* antimycobacterial *$H_{37}Rv$* strain. Compound **6t** exhibited potent MIC value compared with reference standard.

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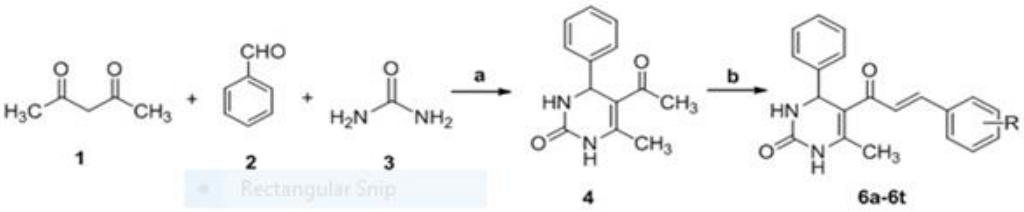
REFERENCES

1) Dye C. Doomsday postponed? Preventing and reversing epidemics of drug-resistant tuberculosis. Nat rev Micro. 2009; 17:81-87.
2) Ginsbeng AM. Emerging drugs for acute tuberculosis.Am J Respir Crit Care Med. 2009; 29:552-559.
3) Showalter HDH, Denny WA. A road map for drug discovery and its translation to small molecule agents in clinical developments for tuberculosis. Tuber.2008; 88:S3-S17.
4) Tomica H, Totano Y,Yasumoto K and Shimizu T.Recent advances in anti-tuberculous drug development and novel targets. Exp RevResp Med.2008; 2(4):455-471.
5) Bloom BR ,Murray CJ. Tuberculosis: commentary on a reemergent killer.Sci.1992;257:1055.
6) Snider DEJ and Roper WL. The New Tuberculosis. New Engl J Med 1992; 326:703-705.
7) Bass JB, Farer LS,Hopewell PC, BrienOR, Jacobs RF, Ruben F,Snider DE, Thornton G. Treatment of tuberculosis and tuberculosis infection in adults and children.

American Thoracic Society and the Centers for Disease Control and Prevention. Am J Res CriCar Med.1994; 149(5):1359-74.

8) Inderlied CB, Kemper CA ,Bermudez LE. The Mycobacterium avium complex. Clin Micro Rev.1993; 6:266-310.
9) MandellGL,Petri WAJ.Goodman and Gilman's The Pharmacological Basis of Therapeutics, McGraw Hill, New York 1996.
10) Sensi P, Grassi G. Burger's Medicinal Chemistry and Drug Discovery. John Wiley &Sons. Inc, New York 1996.
11) Sahu NK, Balbhadra SS, Choudhary J and Kohli DV. Exploring pharmacological significance of chalcone scaffold: a review.Curr Med Chem. 2012; 19:209-225.
12) Bukhari SN, Jasamai M, Jantan I. Synthesis and biological evaluation of chalcone derivatives (mini review).Mini Rev. Med Chem. 2012; 12:1394-1403.
13) Sahu U, Panda NC, Ravikumar BVV, Kumar A.Activity of chalcone and its derivatives - a review.PharmaTutor. 2014; 2:62-75.
14) Krishna BM, Rajesh KP and Hitendra SJ.In silico study of noveldihydropyrimidines against Anticancer, Antituberculosis, Anti HIV and Antimalarial activity.Int J Sci Eng Res.2013; 4.
15) Rasapelly Ramesh Kumar, Kannappan N, Devilal J. A novel, efficient, cost-effective, and green methodology for biginelli-reaction: soy lecithin-catalyzed synthesis of 4 aryl-1, 2, 3, 4 -tetrahydropyrimidine-2(1h)ones / thiones in water. Int J Pharm BiolSci. 2019; 9 (2): 811-818.
16) Maria CSL and De'SonzaMVN, Alessandra C. Evaluation of antitubercular activity of Nicotine and Isonicotine analogues.Arkivoc.2007; 15:181-190.
17) Jones G, Willett P ,Glen RC. Molecular recognition of receptor sites using a genetic algorithm with a description of desolvation. J Mol Biol.1995; 6:43-53.
18) Gareth J, Peter W, Robert CG, Andrew RL, Robin T.Development and validation of a genetic algorithm for flexible docking.J Mol Biol. 1997; 267:727–748.
19) Lakshmi NB, Amandeep K, Ramandish A, Sangeeta, Raghuram RA, Narashima MJ. Synthesis, evaluation of 6,8-dibromo-2-aryl-2,3-dihydroquinolin-4(1H)-ones in MCF-7 (breast cancer) cell lines and their docking studies. Med Chem Res.2012; 21:1741–1750.



Scheme 1: (a) Soy Lecithin, MWI, 220wts, 1-3 min; (b) 5a-5t, absolute ethanol, 10% NaOH, MWI, 180wts, 3-5 min.

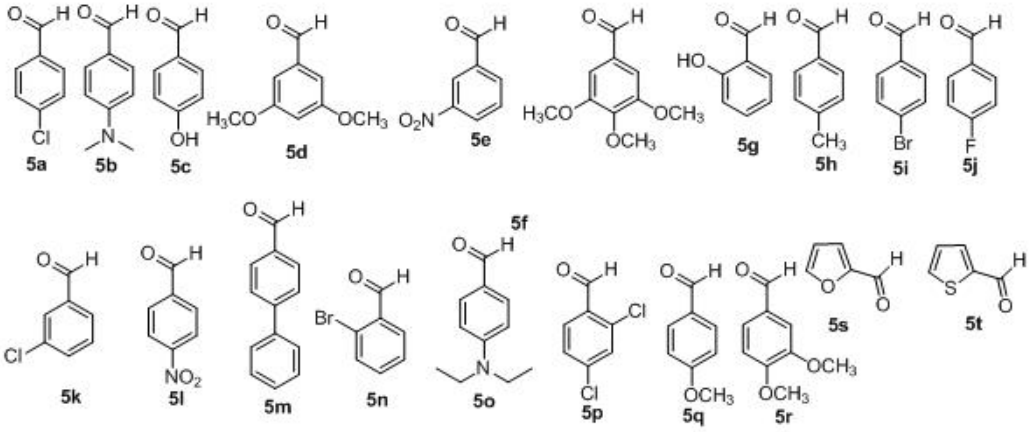


Figure 1:Various aldehyde used in the present study 5a-5t

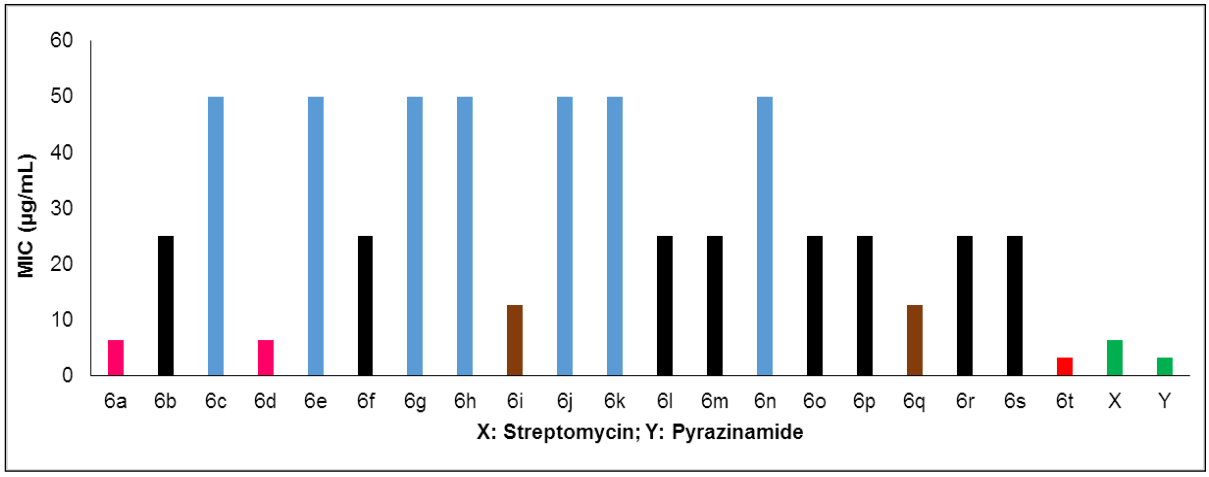
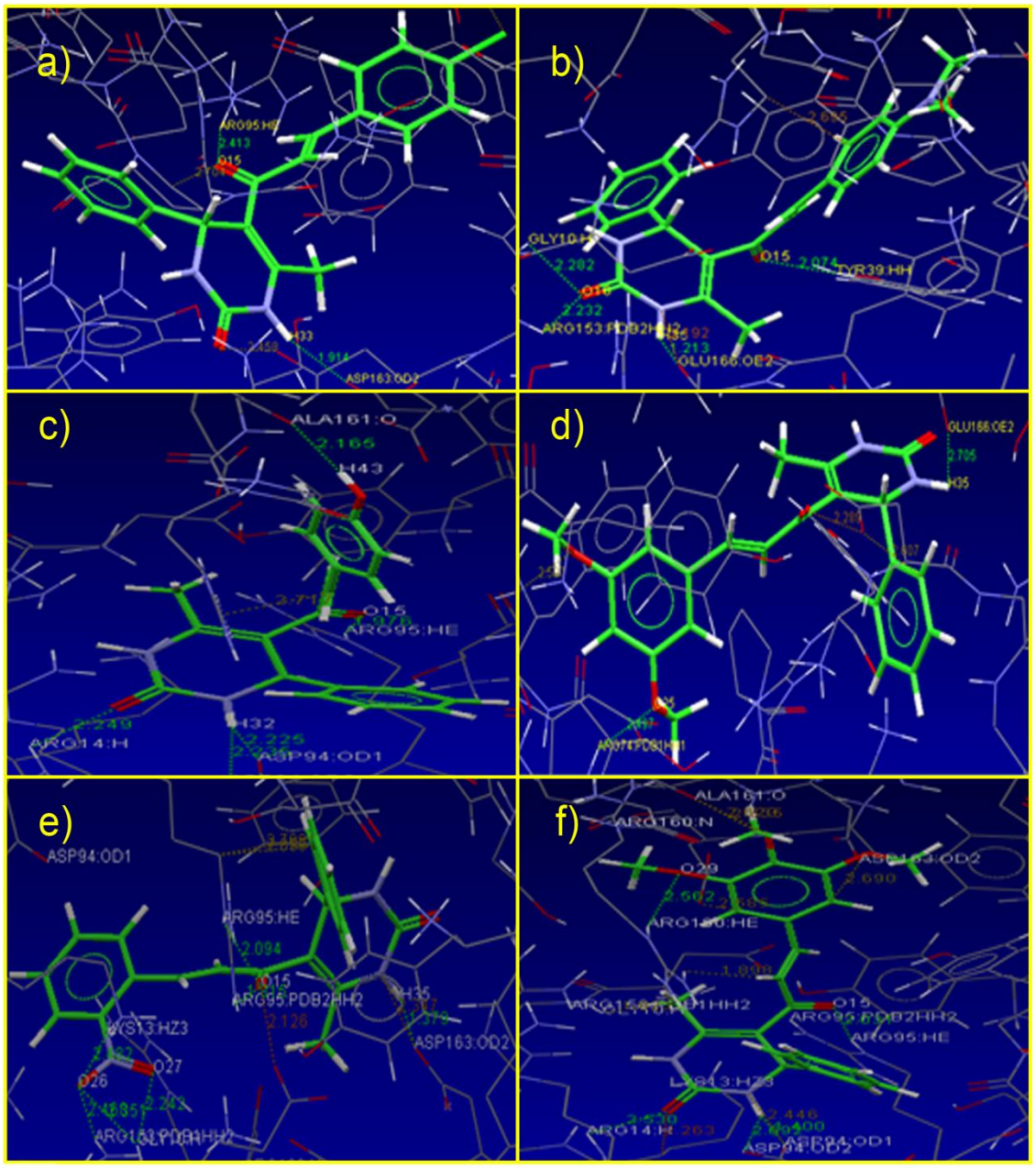
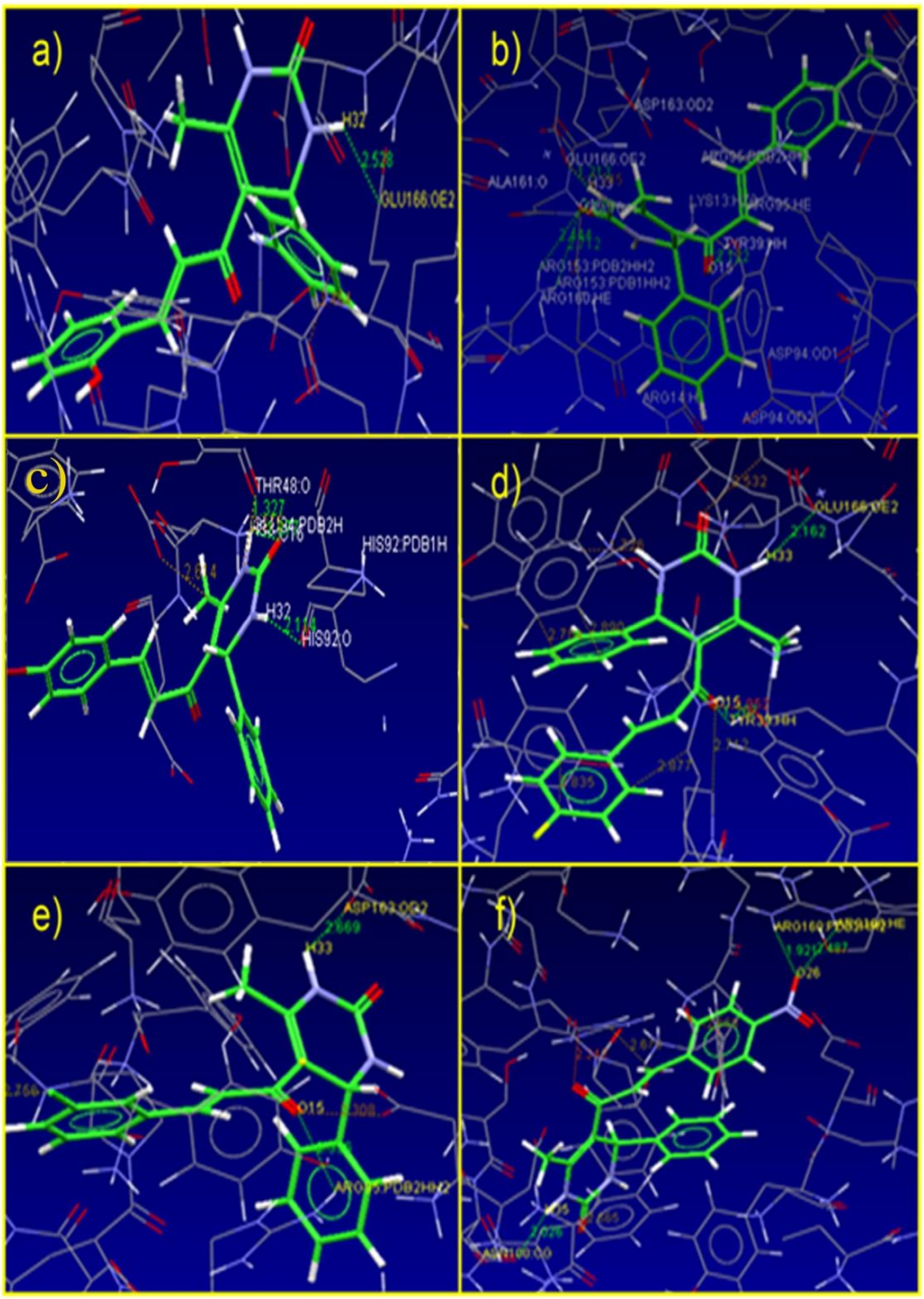


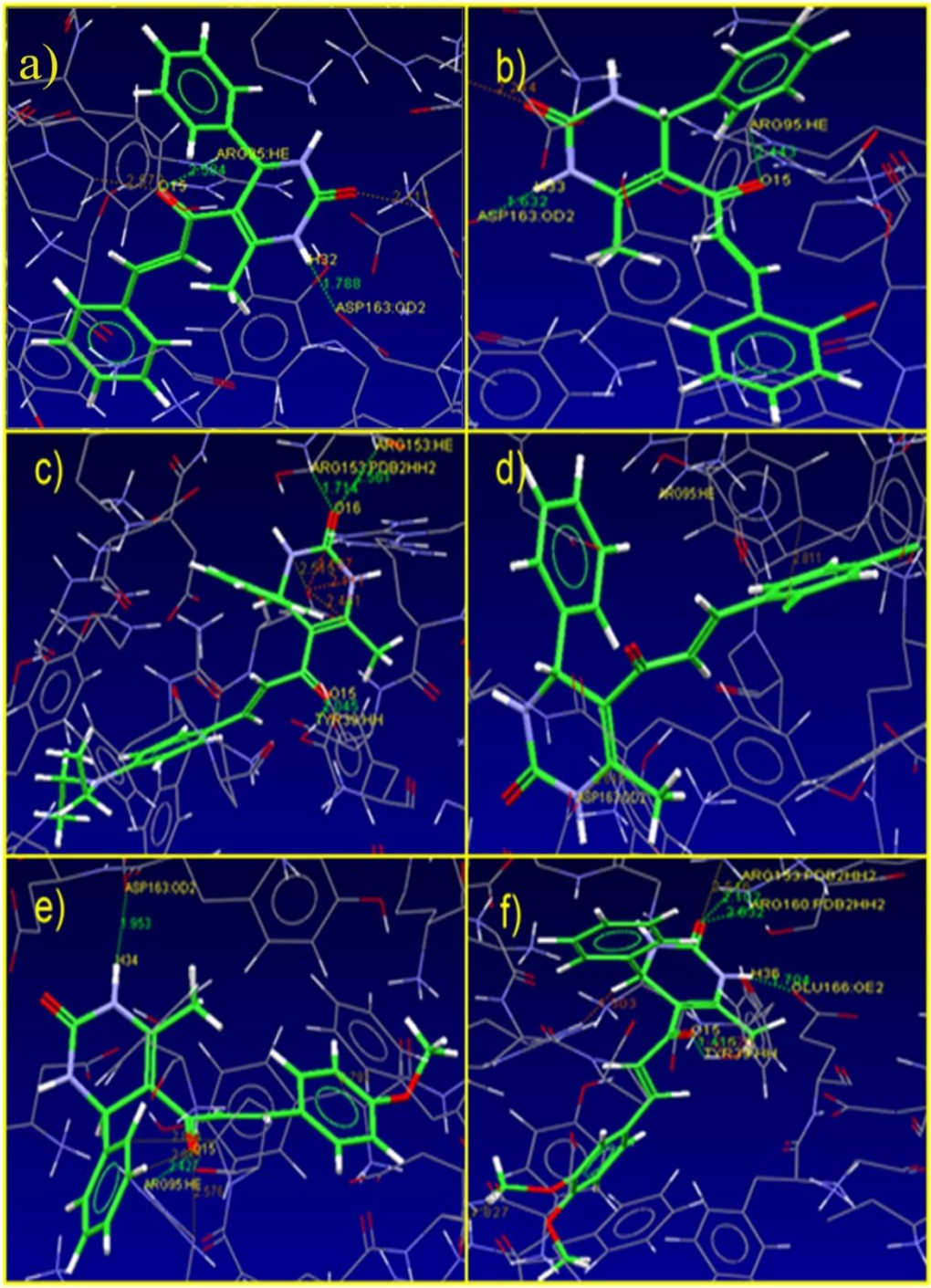
Figure 2: Inhibitory activity of synthesized DHPM chalcone derivatives 6a-6t against M.tuberculosis H_{37} Rvstrain



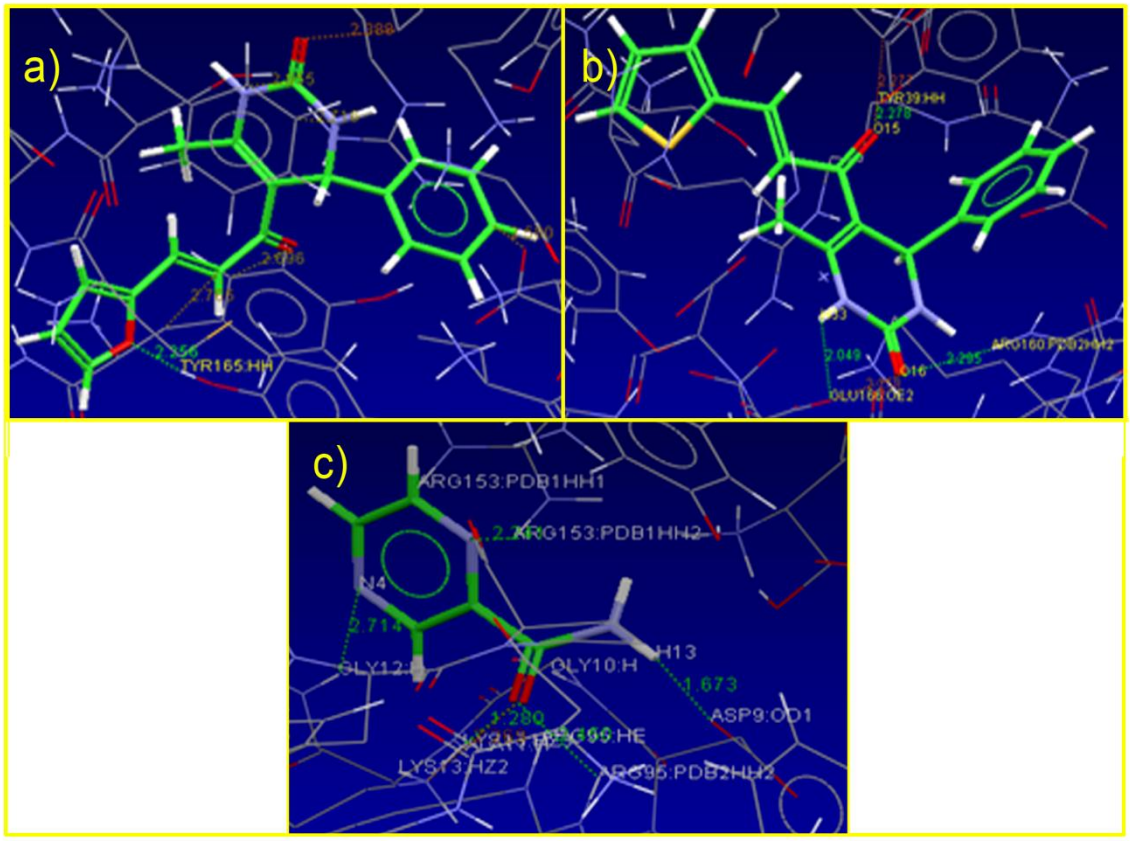
(a) Interactions of H-bond (Green) amongst 6-a& 1G3U Compound (b) 6-b& 1G3U Compound (c) 6-c& 1G3U Compound (d) compound 6-d& 1G3U (e) compound 6-e and 1G3U (f) compound 6-f and 1G3U



(a) H-bond interactions (inexperienced) amongst compound 6-g& 1G3U (b) 6-h and 1G3U Compound (c) 6-i& 1G3U Compound (d) Compound 6-j& 1G3U (e) compound 6-k and 1G3U (f) compound 6-l and 1G3U



(a) Interactions of H-bond (Green) among 6-m& 1G3U Compound (b) 6-n& 1G3U Compound (c) 6-o & 1G3U Compound (d) compound 6-p& 1G3U (e) compound 6-q and 1G3U (f) compound 6-r and 1G3U



(a) Interactions of H-bond (Green) among 6-s& 1G3U Compound (b) 6-t& 1G3U Compound (c) Pyrazinamide & 1G3U Compound