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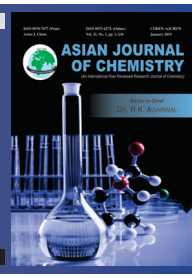

Synthesis, Molecular Docking and Antimicrobial Studies of Some Novel 1,4-Dihydropyridine Derivatives

D. ASHOKKUMAR, G. RAMALINGAM* and M. GOPALAKRISHNAN

Department of Chemistry, Annamalai University, Annamalai Nagar-608 002, India

*Corresponding author: E-mail: drgr_dde@rediffmail.com

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Three components one pot synthesis of some novel triazole substituted 1,4-dihydropyridine compounds from the simple condensation reaction of ethyl acetoacetate, 4-amino triazole and aromatic aldehyde has been demonstrated using on low cost and efficient acetic acid catalyst in solvent free condition followed by microwave irradiation method. The newly synthesized 1,4-dihydropyridine compounds exhibit in excellent yield. The synthesized dihydropyridine derivatives are screened for antimicrobial properties and molecular docking study.

Keywords: Triazole, 1,4-Dihydropyridine, Microwave irradiation, Antimicrobial activities, Molecular docking.

INTRODUCTION

German chemist, Arthur Hantzch was first organic chemist to synthesize 1,4-dihydropyridine in 1881 [1], which considered as a very important class of nitrogen containing heterocyclic compounds and these compounds exhibit a variety of biological and medicinal applications such as antitumor [2], analgesic activity [3], calcium channel blockers [4], antioxidant [5], antimicrobial [6] and anti-inflammatory activities [7]. Most of the 1,4-dihydropyridines act as a calcium channel blockers and these kinds of 1,4-dihydropyridines are important classes of medicine for the treatment of hypertension as well as cardiovascular diseases [8,9]. Some dihydropyridines used in treatment of vascular hypertrophy [10], angina pectoris diseases [11] and renal protection [12]. The dihydropyridine heterocyclic ring moieties is a common property of biologically active compounds such as geroprotective, antidiabetic, antitumor, vasodilator, hepatoprotective, antiatherosclerotic and bronchodilator agents [13-15]. Recently, 1,4-dihydropyridine derivatives used for treatment of Alzheimer's disease and tumor therapy treatment [16]. These examples distinctly demonstrate the amazing potential of novel 1,4-dihydropyridine compounds as a source of valuable medicine candidates. Several medicinally important 1,4-dihydropyridine derivative drugs *viz*., amlodipine, diludine, nimodipin, felodipine, *etc*. are now manufactured worldwide [17].

The acid catalyst used in most of the 1,4-dihydropyridine synthesis such as phenyl boronic acid [18], silica sulfuric acid [19], alumina sulfuric acid [20], Zn[(L)proline]$_2$) [21], metal triflates [22], sulfated polyborate [23], molecular iodine [24] and TMSCl-NaI [25]. In the synthesis of 1,3-dicarbonyl compounds, aryl aldehydes or substituted aryl aldehydes undergo one-pot condensation reaction in presence of acetic acid as catalyst or heating with alcohol as solvent requires longer time and also the yield percentage of 1,4-dihydropyridine is very low by using Hantzsch method. Similarly, several other methods also lead to a major drawbacks such as usage of major quantity of organic solvents, longer reaction time and lower yields. So, in order to overcome these kinds of problems, in this present work, we used low cost and efficient acetic acid as catalyst for synthesis of some novel triazole substituted 1,4-dihydropyridine.

In synthetic organic chemistry different kinds of methods are used to prepare 1,4-dihydropyridine derivatives like as solar thermal energy [26], solid support [27], ultrasound irradiation [28], green solvents [29], microwave assisted reaction [30] and visible light method [31]. Among these methods, the microwave assisted reaction method is considered as one of the best

because of solvent free condition, short reaction time, low cost and simple working procedure.

EXPERIMENTAL

All laboratory standard synthetic grade chemicals are collected from Aldrich and Merck chemical companies. The melting points were determined by the open tube capillary method and are uncorrected. The thin layer chromatography (TLC) is used to monitor the reaction and checking the purity of synthesized compounds. The ^{1}H and ^{13}C NMR spectra of synthesized compounds are recorded from Bruker Avance 400 MHz spectrometer using $CDCl_3$ as a solvent TMS is internal standard. The infrared spectra of newly prepared compounds were recorded by using Agilent pro infrared spectrometer.

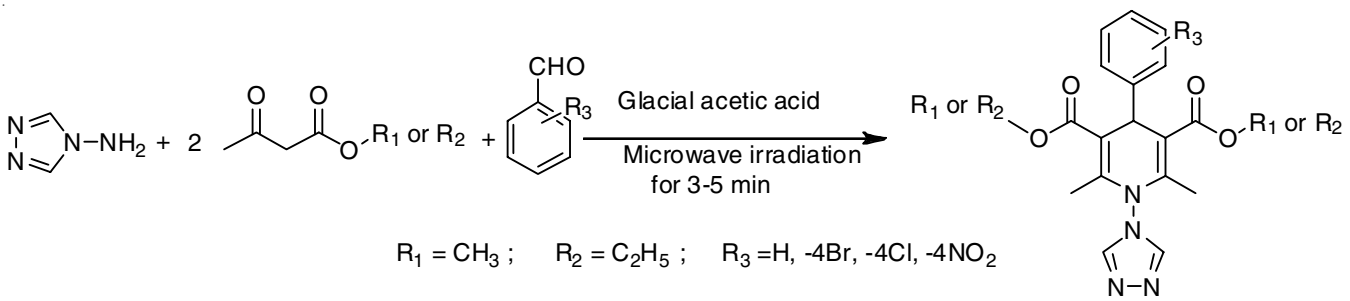
General synthetic procedure for triazole substituted 1,4-dihydropyridine derivatives (2a-f): A mixture of 1 mol 4-amino triazole, 2 mol ethyl acetoacetate or methyl acetoacetate, 1 mol aryl aldehyde or substituted aryl aldehyde and catalytic amount of glacial acetic acid is added to the reaction mixture (4-amino triazole, methyl acetoacetate or ethyl acetoacetate and simple aryl aldehyde or substituted aryl aldehyde are added 1:2:1 ratio, respectively). After adding the chemical substance in appropriate ratio the reaction mixture was converted into solid form to paste form by using on well cleaned mortar and then the reaction mixture is placed in microwave irradiation for 3-5 min. Thin layer chromatography was used to monitor the reaction process. After completion of the reaction the reaction mixture was cooled at room temperature. The reaction attained in normal room temperature and the reaction mixture was poured into ice water resulted in the formation of solid particles. The solid particles were separated by simple filtration method. The product is recrystallized in ethanol to give brown colour solid (**Scheme-I**).

Antimicrobial activity: The newly prepared triazole substituted 1,4-dihydropyridine derivatives (**2a-f**) compounds are well tested against four different set of microorganisms like as two Gram-negative bacteria, two Gram-positive bacteria are used in this present study. In this present work we used disk diffusion methodology for screening of some microorganisms. All the materials purchased from Aldrich and Merck chemical companies and Muller Hinton agar used for culture bacterial strains.

Antibacterial activity: The novel 1,4-dihydropyridine derivatives (**2a-f**) are treated *in vitro* activity screening test against four different set of bacteria like Gram-negative and Gram-positive bacteria. The main aim of this work is to identify how much amount of minimum inhibitory concentration (MIC) is required to fully inhibit the growth of culture on this disk. The synthesized compound dissolved in DMSO (dimethyl sulfoxide) the100 µg/mL concentration is used for test. The ciprofloxacin acts as a standard. After coating of the synthesized compounds the disk is placed at 37 °C after 24 h the inhibition zone is measured.

Antifungal screening: All newly prepared novel 1,4-dihydropyridine derivatives (**2a-f**) are tested against fungal species such as *Chrysosporium* sp., *Trichoderma* sp., *A. parasitica*, *Aspergillus niger* and *Trichoderma* sp. The disk diffusion methodology is used to determine the antifungal activity ability newly prepared 1,4-dihydropyridine derivatives. The Sabouraud's dextrose used as a medium. In present work we use the clotrimazole as standard drug molecule. The tested compounds concentration 100 µg/mL is prepared by using on DMSO solvent. After growth of culture the 1,4-dihydropyridine compounds (100 µg/mL) concentration is spot on this disc. The disc is placed at 37 °C for 24 h. After one day the zone of inhibition (mm) is measured.

Molecular docking: Synthesized 1,4-dihydropyridine derivatives were designed by Schrodinger software and docking process was carried out to all newly prepared triazole substituted 1,4-dihydropyridine compounds against 2XCT with the help of maestro 2019-2 program. The docking result of all single compounds analyzed well mannerly. Compounds exhibit excellent interaction energies. The docking scores are shown in Table-1.



Scheme-I: Synthesis of the compounds **2a-f**

TAPLE-1
DOCKING SCORE TABLE FOR NOVEL 1,4-DIHYDROPYRIDINE DERIVATIVES

Ligand	Docking score (kcal/mol)	Glide energy	Surrounding residues
2a	-3.354	-46.292	GLY1082, SER1084, LYS460, GLY456, ARG458, GLH435, GLY436, ASP437, DA13, DC14
2b	-3.475	-51.122	MN2000, SER1085, SER1084, GLY1082, ASP437, GLY436, GLY59, ARG458, DA13, DC12
2c	-0.042	-52.548	MN2000, GLU477, ASN476, GLY459, ARG458, ASP437, DA13, DC12
2d	-3.146	-46.533	MN2000, SER1085, SER1084, GLY1082, ASP437, GLY436, GLY459, ARG458
2e	-2.927	-46.219	MN2000, SER1085, GLY459, ARG458, ASP437, DA13, DC12
2f	-4.624	-53.799	MN2000, LYS460, GLY459, ARG458, ASP437, GLU477, ASN476ASN478, DA13, DC12

Spectral data for synthesized 1,4-dihydropyridines

Diethyl-1,4-dihydro-2,6-dimethyl-4-phenyl-1-(4*H*-1,2,4-triazol-4-yl)pyridine-3,5-dicarboxylate (2a): Brown solid, Yield 83 %, m.p.: 158-160 °C, IR (KBr, ν_{max}, cm^{-1}): 3097-3053 (aromatic C-H *str.*), 2952 (aliphatic C-H *str.*), 1684 (C=O *str.* for ester group), 11605 (C=N *str.*), 1574 (C=C *str.*); ^{1}H NMR (DMSO) δ = 7.24-7.87 (m, 5H, Ar-H), 5.14 (s, 1H, CH), 3.96 (m, 4H, CH_2 of ethyl), 2.24 (s, 6H, CH_3 at C-10 and C-10^1), 1.08 (t, 3H, CH_3 of ethyl), 8.41 (s, 2H, at C-17 and C-17^1) ;^{13}C NMR (DMSO) δ = 165.72 (C=O of the ester), 158.73 (C=N), 144.59 (C-11), 147.78 (C-2),122.00-152.48 (other aromatic carbon), 99.27 (C-3), 59.93 (methylene carbon), 54.01 (C-4), 18.21 (C-10), 14.43 (C-9). Anal. calcd. for $C_{21}H_{24}N_4O_4$: C, 63.62; H, 6.10; N, 14.13; O, 16.14 %.

Diethyl-4-(4-chlorophenyl)-1,4-dihydro-2,6-dimethyl-1-(4*H*-1,2,4-triazol-4-yl)pyridine-3,5-dicarboxylate (2b): Brown solid, Yield 87 %, m.p.: 163-165 °C, IR (KBr, ν_{max}, cm^{-1}): 3090 (aromatic C-H *str.*), 2793-2925 (aliphatic C-H *str.*), 1700(C=O *str.* for ester group), 1647 (C=N *str.*), 1591 (C=C *str.*); ^{1}H NMR (DMSO) δ = 7.23-7.87 (m, 4H, Ar-H), 5.15 (s, 1H, CH), 4.00 (m, 4H, CH_2 of ethyl), 2.25 (s, 6H, CH_3 at C-10 and C-10^1), 1.01 (t, 3H, CH_3 of ethyl), 8.37 (s, 2H, at C-17 and C-17^1) ;^{13}C NMR (DMSO) δ = 165.64 (C=O of the ester), 157.44 (C=N), 144.57 (C-11), 147.91 (C-2),121.99-152.39 (other aromatic carbon), 102.29 (C-3), 59.81 (methylene carbon), 54.05 (C-4), 18.27 (C-10), 14.49 (C-9). Anal. calcd. for $C_{21}H_{23}N_4O_4Cl$: C, 58.542; H, 5.38; Cl, 8.23; N, 13; O, 14.84 %.

Diethyl-4-(4-fluorophenyl)-1,4-dihydro-2,6-dimethyl-1-(4*H*-1,2,4-triazol-4-yl)pyridine-3,5-dicarboxylate (2c): Brown solid, Yield 81 %, m.p.: 167-169 °C, IR (KBr, ν_{max}, cm^{-1}): 3116 (aromatic C-H *str.*), 2946-2092 (aliphatic C-H *str.*), 1698 (C=O *str.* for ester group), 1614 (C=N *str.*), 1584 (C=C *str.*); ^{1}H NMR (DMSO) δ = 7.75-7.79 (m, 5H, Ar-H), 5.30 (s, 1H, CH), 3.99 (m, 4H, CH_2 of ethyl), 2.26 (s, 6H, CH_3 at C-10 and C-10^1), 1.07 (t, 3H, CH_3 of ethyl), 9.04 (s, 2H, at C-17 and C-17^1) ;^{13}C NMR (DMSO) δ = 165.58 (C=O of ester), 157.55 (C=N), 139.68 (C-11), 148.16 (C-2), 121.45-152.78 (other aromatic carbon), 98.90 (C-3), 59.95 (methylene carbon), 54.00 (C-4), 18.30 (C-10), 14.43 (C-9). Anal. calcd. for $C_{21}H_{23}N_4O_4F$: C, 60.86; H, 5.59; F, 5.48; N, 13.52; O, 15.44 %.

Dimethyl-4-(4-chlorophenyl)-1,4-dihydro-2,6-dimethyl-1-(4*H*-1,2,4-triazol-4-yl)pyridine-3,5-dicarboxylate (2d): Brown solid, Yield 83 %, m.p.: 162-164 °C, IR (KBr, ν_{max}, cm^{-1}): 3088 (aromatic C-H *str.*), 2967 (aliphatic C-H *str.*), 1695 (C=O *str.* for ester group), 1590 (C=N *str.*), 1530 (C=C *str.*); ^{1}H NMR (DMSO) δ = 7.21-7.87 (m, 5H, Ar-H), 5.14 (s, 1H, CH), 3.97 (m, 4H, CH_2 of ethyl), 2.24 (s, 6H, CH_3 at C-10 and C-10^1), 8.40 (s, 2H, at C-17 and C-17^1) ;^{13}C NMR (DMSO) δ = 165.71 (C=O of the ester), 157.51 (C=N), 144.32 (C-11), 149.32 (C-2), 122.00-152.87 (other aromatic carbon), 102.28 (C-3), 59.91 (methylene carbon), 54.02 (C-4), 18.12 (C-10). Anal. calcd. for $C_{19}H_{19}N_4O_4Cl$: C, 56.65; H, 4.75; Cl, 8.80; N, 13.91; O, 15.89 %

Dimethyl-4-(4-bromophenyl)-1,4-dihydro-2,6-dimethyl-1-(4*H*-1,2,4-triazol-4-yl)pyridine-3,5-dicarboxylate (2e): Brown solid, Yield 78 %, m.p.: 170-172 °C, IR (KBr, ν_{max}, cm^{-1}): 3112 (aromatic C-H *str.*), 2959-2904 (aliphatic C-H *str.*), 1681 (C=O *str.* for ester group), 1493 (C=N *str.*), 1483 (C=C *str.*); ^{1}H NMR (DMSO) δ = 6.99-8.00 (m, 5H, Ar-H), 5.15 (s, 1H, CH), 3.95 (m, 4H, CH_2 of ethyl), 2.24 (s, 6H, CH_3 at C-10 and C-10^1), 8.40 (s, 2H, at C-17 and C-17^1) ;^{13}C NMR (DMSO) δ = 166.11 (C=O of the ester), 157.59 (C=N), 144.58 (C-11), 148.91 (C-2), 115.48-152.51 (other aromatic carbon), 99.71 (C-3), 59.81 (methylene carbon), 53.79 (C-4), 18.19 (C-10). Anal. calcd. for $C_{19}H_{19}N_4O_4Br$: C, 51.02; H, 4.28; Br, 17.86; N, 12.53; O, 14.31 %

Dimethyl-1,4-dihydro-4-(4-nitrophenyl)-1-(4*H*-1,2,4-triazole-4-yl)pyridine-3,5-dicarboxylate (2f): Brown solid, Yield 86 %, m.p.: 166-168 °C, IR (KBr, ν_{max}, cm^{-1}): 3115 (aromatic C-H *str.*), 2775 (aliphatic C-H *str.*), 1699 (C=O *str.* for ester group), 1614 (C=N *str.*), 1583 (C=C *str.*); ^{1}H NMR (DMSO) δ = 7.23-7.78 (m, 5H, Ar-H), 5.14 (s, 1H, CH), 3.98 (m, 4H, CH_2 of ethyl), 2.24 (s, 6H, CH_3 at C-10 and C-10^1), 8.40 (s, 2H, at C-17 and C-17^1) ;^{13}C NMR (DMSO) δ = 165.68 (C=O of the ester), 157.53 (C=N), 144.57 (C-11), 149.32 (C-2), 122.00-152.45 (other aromatic carbon), 99.23 (C-3), 59.88 (methylene carbon), 54.05 (C-4), 18.25 (C-10). Anal. calcd. for $C_{19}H_{19}N_5O_6$: C, 55.20; H, 4.63; N, 16.94; O, 23.22 %.

RESULTS AND DISCUSSION

In present work we are describe herein the alternative versatile, solvent free, ego-friendly, multicomponent one-pot synthesis of 1,4-dihydropyridine by the reaction of aryl aldehyde, 4-amino triazole and ethylacetoacetate under microwave irradiation in presence of acetic acid catalyst. The Hantzsch 1,4-dihydropyridine reaction is carried out well mannerly controlled microwave owen with optimized reaction conditions. The advance features of this method are to avoid more environmentally polluted solvents, to reduce reaction time for 3-5 min and maximizing product yield. The formation of product is confirmed by using various spectral techniques. From IR spectral data the region 3097-3053 cm^{-1} indicates presence of aromatic C-H vibrations. The well defined characteristic sharp absorption peaks observed at 2952 cm^{-1} it's corresponding to aliphatic region. The ester carbonyl moiety is appears at 1684 cm^{-1}. The triazole ring C=N vibration appears at 1605 cm^{-1}. The ^{1}H NMR spectral signals show some important characteristic signals at δ - 1.08 ppm (t, 6H, CH_3 of ethyl) this signal inform presence of two methyl group in newly prepared 1,4-dihydropyridine derivatives. The aromatic hydrogen signal appears at δ - 7.24 to 7.87 ppm (m, 5H). The δ - 5.14 ppm signal indicates presence of -CH- proton in synthesized compounds. The ethyl group –CH_2- protons appears at δ - 3.96 ppm. The methyl group appears at δ - 2.24 ppm and the triazole –N=CH proton singlet signal appears at δ - 8.41 ppm. The ^{13}C NMR spectrum shows aromatic signals at δ - 122-152 ppm. The ester carbonyl (-C=O) group appears at δ - 165 ppm. The strong instance signal appears at δ - 54 ppm is due to (C-4) carbon. The methylene carbon signal appears at δ - 59 ppm. The C-11 carbon appears at δ - 144 ppm. The δ - 99 ppm is corresponding to C-3 carbon. The triazole -C=N (C-17, carbon) appears at δ - 158 ppm. The methyl carbon C-9 appears at δ - 99 ppm.

***in silico* Molecular docking study:** The novel 1,4-dihydropyridine derivative synthesis is achieved followed by Hantzsch method. The structure of the compounds conformed by using

various spectral techniques. After conformation the novel 1,4-dihydropyrdine are subjected into *in silico* molecular docking study. 2XCT considered as a target protein. The selected 2XCT protein was downloaded from protein data bank (PDB). This molecular docking study is used to identify the convincing silico conformation and comparative docking data of the synthesized 1,4-dihydropyridine derivatives. All the prepared 1,4-dihydropyridine ligands are docked with 2XCT target protein, the docking images are shown in Figs. 1 and 2. The docking score and glide energy of the some novel 1,4-dihydropyridine derivatives are illustrated in Table-1. The finding results from *in silico* molecular docking study is used to identify affinity of the newly synthesized compounds and activity of the compound against the target protein. This information is supporting evidence for *in vitro* antimicrobial screenings study whether these compounds are active or less active against the selected micro organisms.

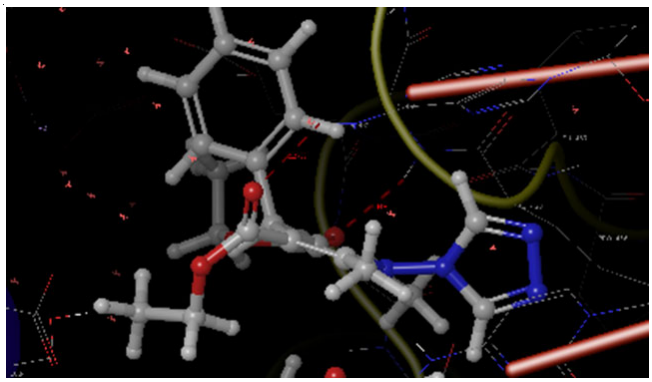


Fig. 1. 3D Docked structure of **2a** with target protien 2XCT

From this docking result the compound **2f** shows the best docking score (-4.624 kcal/mol) and glide energy (-53.799) comparing to the other compounds in this 1,4-dihydropyridine series. According this experimental it is suggested that the compound **2f** has greater tendency to inhibit growth of micro organisms compared to the other 1,4-dihydropyridine derivatives.

Antibacterial activity: The newly prepared triazole substituted 1,4-dihydropyridine compounds were subjected in to antibacterial activity against Gram-positive bacteria and Gram-negative bacteria, respectively. The antibacterial activity is expressed in MIC (minimum inhibitory concentration). In this present work we have prepared four different kinds of compounds concentrations like as 25, 50, 75, 100 µg/mL among these concentrations the 100 µg/mL show the best activity

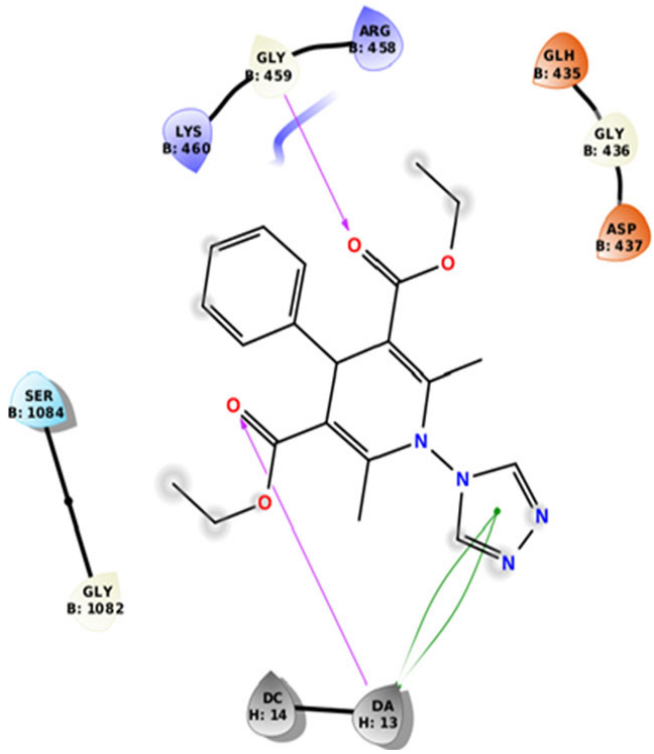


Fig. 2. 2D Docked structure of **2a** with target protien 2XCT

against both Gram-positive and Gram-negative bacteria. In this present study we are use ciprofloxacin as a control molecule. The inhibition zone is measured in mm. Table-2 shows the antibacterial activities of 1,4-dihydropyridine against both Gram-negative and Gram-positive bacteria.

***in vitro* Antifungal screening:** The inhibition zone values (mm) for some newly prepared compounds are shown in Table-3. Compounds (**2a-f**) were treated against *Chrysosporium* sp., the compounds **2a** and compound **2f** show the best activity against *Chrysosporium* sp. compound **2d** show highest activity against *Trichoderma* sp. compared to the other 1,4-dihydropyridine derivatives. Compound **2c** shows less activity against show *Trichoderma* sp. The compounds **2a-f** were screened for *A. parasitica* all compounds show moderately activity compared to the standard drug molecule clotrimazole. Compounds **2a-f** was tested against *A. nigar*. The compound **2b** exhibit significant activity compared with control. All newly prepared 1,4-dihydropyridine compounds (**2a-f**) are tested against four different fungal species. From this activity result the compound **2f** exhibits best activity compared to the standard clotrimazole drug molecule.

TABLE-2
ANTIBACTERIAL ACTIVITY OF THE NEWLY SYNTHESIZED 1,4-DIHYDROPYRIDINE DERIVATIVES (**2a-f**)

Compd.	*E. coli*				*Shigella*				*Streptococcus*				*Staphylococcus*			
Conc. (µg/mL)	25	50	75	100	25	50	75	100	25	50	75	100	25	50	75	100
2a	–	–	8	10	–	–	–	13	–	–	–	8	–	–	–	7
2b	–	–	9	11	–	–	–	11	–	–	–	8	–	–	–	10
2c	–	–	9	11	–	–	–	9	–	–	–	8	–	–	–	9
2d	–	–	8	11	–	–	–	9	–	–	–	7	–	–	–	12
2e	–	–	8	11	–	–	–	9	–	–	–	11	–	–	–	9
2f	–	–	–	10	–	–	8	11	–	–	9	11	–	–	8	13
Control	15				18				19				19			

TABLE-3
ANTIFUNGAL ACTIVITY OF THE NEWLY SYNTHESIZED 1,4-DIHYDROPYRIDINE DERIVATIVES (**2a-f**)

Compd.	*Chrysosporium* sp.				*Trichoderma* sp.				*A. parasitica*				*A. nigar*			
Conc. (µg/mL)	25	50	75	100	25	50	75	100	25	50	75	100	25	50	75	100
2a	–	–	9	11	–	–	8	10	–	–	–	8	–	–	7	9
2b	–	–	7	10	–	–	7	11	–	–	–	8	–	–	9	10
2c	–	–	8	10	–	–	6	9	–	–	7	9	–	–	–	8
2d	–	–	9	11	–	–	8	12	–	–	–	9	–	–	7	9
2e	–	–	8	10	–	–	9	11	–	–	–	7	–	–	–	8
2f	–	–	10	12	–	–	8	11	–	–	–	9	–	–	–	9
Control	24				26				26				23			

Conclusion

This present work describes the synthesis of triazole substituted 1,4-dihydropyridine derivatives by normal Hantzch reaction followed by microwave assisted reaction method. The new 1,4-dihydropyridine derivatives were prepared by using an low cost and efficient glacial acetic acid catalyst. The 1,4-dihydropyridine derivatives (**2a-f**) were screened for antimicrobial activity out of this six compounds (**2a-f**) compound **2f** shows best activity against both bacterial and fungal species. From molecular docking study the compound **2f** show the best docking score (-4.624 kcal/mol) and glide energy (-53.79) compared to the other compounds in this series. The theoretical calculation is also matching the experimental results. From this results it is concluded that the compound **2f** is best antimicrobial agent and the 1,4-dihydropyridine derivatives are developing next level antimicrobial agent.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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