



Scholars Research Library

Der Pharmacia Lettre, 2017, 9 [7]:64-72
[<http://scholarsresearchlibrary.com/archive.html>]



Synthesis, Characterization and Docking studies of Some Novel Dihydropyridine Derivatives

Aditya Bhatt H¹, Viral Shah R^{1*}, Rakesh Rawal M²

¹Department of Chemistry, Kamani Science & Prataprai Arts College, Amreli Gujarat, India.

²Department of Life Sciences, Gujarat University, Ahmedabad, Gujarat, India.

***Corresponding author:** Viral Shah R, Department of Chemistry, Kamani Science & Prataprai Arts College, Amreli Gujarat, India. E-mail: drshahvr@gmail.com

ABSTRACT

The synthesis of a novel dihydropyridine derivatives bearing dimedone as an excellent precursor has been achieved by applying three component Hantzsch condensation. The newly synthesized compounds were characterized by IR, NMR, Mass spectra and also by C, H, N analyses. All synthesized compounds undergo docking studies and biological screening for antimicrobial activity against Gram-positive bacteria, Gram-negative bacteria and fungal species. Among all the tested compounds, it was found that compound **3d**, **3e**, **3g** and **3i** revealed better activities against the Gram-positive rather than the Gram-negative bacteria whereas compounds **3c**, **3d**, **3e**, **3g** and **3i** showed best docking score in docking studies.

Key words: 1,4-Dihydropyridine, Hantzsch synthesis, Antimicrobial activity, Docking studies

INTRODUCTION

Dihydropyridine derivatives (DHPs) form a class of heterocyclic compounds with interesting pharmacological and biological properties [1]. It is well known that the DHP nucleus serves as the scaffold of important anticancer and cardiovascular drugs and it has been well established that the calcium modulator activity of this family of compounds is determined by structural requirements [2]. The systematic structural modification of the 1,4-DHP ring yields different compounds having immense potency as anti-cancer and anti-microbial activity. Among the many different chemical scaffolds screened, 1,4-dihydropyridine compounds have attracted attention both as antimicrobial agents and MDR-reversing entities because of their ability to exert synergistic antibacterial effects in combination with known antibiotics [3-7]. Their pharmacological properties include neuro and radio protective effects, antidiabetic agents [8], anti-inflammatory [9], HIV protease inhibition and in the treatment of Alzheimer's disease [10], anti-microbial, antioxidants [11], bronchodilator, antitumor, anti-inflammatory activities [12], antitubercular agents [13]. Dihydropyridine derivatives have gained therapeutic success due to their efficient binding to the active

site of the receptors. 1,4-DHP derivatives are found to be excellent tyrosine kinase inhibitors [14]. Janus Associated Kinase-2 (JAK-2) is an important intracellular tyrosine kinase involved in the signal transduction pathways mediated by the cytokines. JAK2 in particular is a critical mediator for hormone like cytokines such as growth hormone, prolactin, erythropoietin and thrombopoietin [15]. Association of individual JAK proteins to activated cytokine receptors leads to autophosphorylation and subsequent phosphorylation of specific STAT (Signal Transducer and Activation of Transcription) proteins. Phosphorylated STAT proteins dimerize and translocate to the cell nucleus where they regulate expression of specific genes involved in proliferation, apoptosis and differentiation [16]. The function of the pseudo-kinase domain is to negatively regulate the activity of the kinase domain. An activating point mutation of JAK2- V617F (valine to phenylalanine substitution) in the pseudo-kinase domain has been identified in patients with myeloproliferative disorders (MPD), polycythemia vera (PV, overproduction of red blood cells), essential thrombocythemia (ET, overproduction of platelets), and myelofibrosis (MF, fibrosis of the bone marrow) [17],[18]. It has been demonstrated that the type of C-3, C-4 and C-5 substituent and the lipophilicity of the molecule have important effects on the antimicrobial activity of 1,4-dihydropyridine compound[19]. 1,4-DHP derivatives containing diethyl carbamoyl and ester substituents at C-3 and C-5, and substituted aromatic or heteroaromatic ring at C-4 position have also been reported as potential antimicrobial agents [20],[21]. N-1 (substituted) phenyl substitution exists in the structure of some of the antimicrobial 1,4-DHPs [22-25]. In addition, Ladani et al [26] and Gunduz et al. [27] prepared dihydropyridines with a fused cyclic ketone and a carboxylate or carboxamide moiety at the C-3 and C-5 positions of the DHP ring, finding the compounds to be antimicrobial agents. Pyrazolyl 1,4-DHP derivatives have showed potential biological activities like anti-inflammatory, calcium channel activity and anti- microbial[28]. Therefore, the synthesis of pyrazolyl 1,4-DHPs has become of interest to synthetic chemists and biologists.

MATERIALS AND METHODS

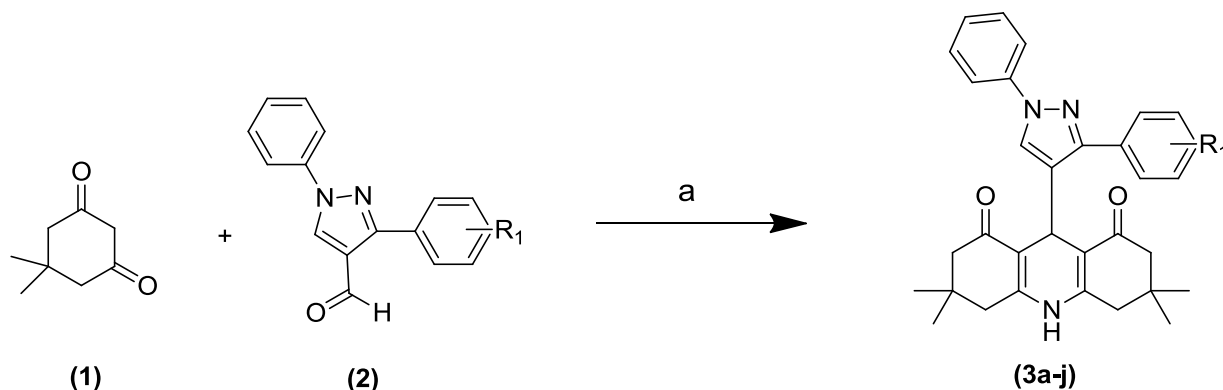
All research chemicals for the reactions were purchased from Sigma–Aldrich Ltd., Merck, and Spectrochem. Melting points were taken in open capillary method and are uncorrected. IR spectra were recorded on Shimadzu FTIR-8400 spectrophotometer, using DRS probe. KBr pellet method. ^1H -NMR and C^{13} -NMR spectra of the synthesized compounds were recorded on a Bruker-Avance-II (400 MHz) DMSO- d_6 solvent. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a Shimadzu GCMS-QP 2010 mass spectrometer. The purity of the compounds was checked by thin layer chromatography (TLC) GF254 silica gel plates from E-Merck Co. using Hexane: Ethyl acetate as eluent and spots were detected in UV.

Experimental

General procedure for synthesis of 3-(aryl)-1-phenyl-1H-pyrazole-4-carbaldehydes (2a-2j) Synthesis of 3-(aryl)-1-phenyl-1H-pyrazole-4-carbaldehydes was achieved by reported method. [29].

General procedure for synthesis of 9-(3-(aryl)-1-phenyl-1H-pyrazol-4-yl)-3,3,6,6-tetramethylacridine-3,4,6,7,9,10-hexahydro-1,8(2H,5H)-dione derivatives (3a-3j): A mixture of the 5,5-dimethylcyclohexane-1,3-dione (dimedone) (0.02

mol), 3-(aryl)-1-phenyl-1H-pyrazole-4-carbaldehyde (0.01 mol), ammonium acetate (0.016 mol) and piperidine (2-3 drops) was refluxed in ethanol as a solvent at 60-80°C for 4-6 hrs. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the reaction mass was poured into ice-cold water, the product was filtered, washed with water, dried and crystallized from ethanol-DMF (9:1) mixture.



Reagents & conditions: (a) NH_4OAc , piperidine (2-3) drops, 60-80°C, reflux 4-6 hrs, ethanol (solvent)

Figure 1: Synthetic route for 3-a to 3-j

Table 1: Substitutions of compound-3 (3a-3j)

Code	Substitutions (R_1)
3a	3-Cl
3b	2-Cl
3c	3- OCH_3
3d	4- CH_3
3e	3- CH_3
3f	3-F
3g	3-Br
3h	2,4-dichloro
3i	2,5-dimethoxy
3j	4-phenoxy

Analytical data

9-(3-(3-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-3,3,6,6-tetramethylacridine-1,8(2H,5H)-dione (3g): Yield: 79%; yellow solid; m.p. 192-194 °C; IR (ν_{max} cm^{-1} , KBr): 3288 (N-H str. of secondary amine), 1678 (C=O str. of carbonyl group), 3070 (C-H str. of aromatic ring), 2956 (C-H asym. Str. of CH_3), 2874 (C-H sym. Str. of CH_3), 1629 (N-H deformation of -NH group), 1602, 1570 and 1502 (C=C str. of aromatic ring), 762 (C-Br stretching); ^1H NMR (400 Hz, $\text{DMSO}-d_6$) δ ppm: 0.99 (s, 12H, CH_3), 1.99 (m, 4H, CH_2), 2.44(m, 4H, CH_2), 4.78 (s, 1H, Ar-H), 7.45 (m, 1H,

Ar-H), 7.58 (m, 1H, Ar-H), 7.62(d, 1H, Ar-H), 7.40 (m, 1H, Ar-H), 7.46(s, 1H, Ar-H), 7.73(d, 1H, Ar-H), 7.56 (d, 1H, Ar-H), 9.10 (s, 1H, NH); MS: m/z: 571; Anal. Found for $C_{32}H_{32}BrN_3O_2$; C(67.37%), H(5.65%), Br(14.01%) N (7.37%), O (5.61%).

9-(3-(3-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3,3,6,6-tetramethylacridine-3,4,6,7,9,10-hexahydro-1,8(2H,5H)-dione (3a): Yield: 77%; pale yellow solid; m.p. 180-182 °C; IR (vmax cm⁻¹, KBr): 3290 (N-H str. of secondary amine), 1675 (C=O str. of carbonyl group), 3070 (C-H str. of aromatic ring), 2955 (C-H asym. Str. of CH₃), 2875 (C-H sym. Str. of CH₃), , 1629 (N-H deformation of -NH group), 1588, 1570 and 1502 (C=C str. of aromatic ring), 755 (C-Cl stretching); ¹H NMR (400 Hz, DMSO-d₆) δ ppm: 0.99 (s, 12H, CH₃), 1.99 (m, 4H, CH₂), 2.44(m, 4H, CH₂), 4.78 (s, 1H, Ar-H), 7.45 (m, 1H, Ar-H), 7.58 (m, 1H, Ar-H), 7.62(d, 1H, Ar-H), 7.45 (d, 1H, Ar-H), 7.65(s, 1H, Ar-H), 8.01(s, 1H, Ar-H), 7.67 (d, 1H, Ar-H), 9.10 (s, 1H, NH); MS: m/z: 525; Anal. Found for $C_{32}H_{32}ClN_3O_2$; C(73.06%), H(6.13%), Br(6.74%) N (7.99%), O (6.08%).

9-(3-(3-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-3,3,6,6-tetramethylacridine-3,4,6,7,9,10-hexahydro-1,8(2H,5H)-dione (3c): Yield: 81%; white solid; m.p. 212-215 °C; IR (vmax cm⁻¹, KBr): 3265 (N-H str. of secondary amine), 1680 (C=O str. of carbonyl group), 3067 (C-H str. of aromatic ring), 2958 (C-H asym. Str. of CH₃), 2877 (C-H sym. Str. of CH₃), 1639 (N-H deformation of -NH group), 1597 and 1487 (C=C str. of aromatic ring), 1222 (C-O-C asym. Str. of OCH₃ group), 1062 (C-O-C sym. Str. of OCH₃ group), 995 (C-H in plane bending for aromatic ring); ¹H NMR (400 Hz, DMSO-d₆) δ ppm: 0.99 (s, 12H, CH₃), 1.99 (m, 4H, CH₂), 2.44(m, 4H, CH₂), 3.83 (s, 3H, CH₃), 4.78 (s, 1H, Ar-H), 7.45 (m, 1H, Ar-H), 7.58 (m, 1H, Ar-H), 7.62(d, 1H, Ar-H), 7.40 (m, 1H, Ar-H), 7.65(s, 1H, Ar-H), 7.36(s, 1H, Ar-H), 6.95 (d, 1H, Ar-H), 9.10 (s, 1H, NH); MS: m/z: 521; Anal. Found for $C_{33}H_{35}N_3O_3$; C(75.98%), H(6.763%), N (8.06%), O(9.20%).

3,3,6,6-tetramethyl-9-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3d): Yield: 89%; pale yellow solid; m.p. 171-173 °C; IR (vmax cm⁻¹, KBr): 3260 (N-H str. of secondary amine), 1680 (C=O str. of carbonyl group), 3066 (C-H str. of aromatic ring), 2959 (C-H asym. Str. of CH₃), 2878 (C-H sym. Str. of CH₃), , 1638 (N-H deformation of -NH group), 1588 and 1502 (C=C str. of aromatic ring); ¹H NMR (400 Hz, DMSO-d₆) δ ppm: 0.99 (s, 12H, CH₃), 1.99 (m, 4H, CH₂), 2.44(m, 4H, CH₂), 2.34 (s, 3H, CH₃), 4.78 (s, 1H, Ar-H), 7.45 (m, 1H, Ar-H), 7.58 (m, 1H, Ar-H), 7.62(d, 1H, Ar-H), 7.65(s, 1H, Ar-H), 7.67(d, 1H, Ar-H), 7.29 (d, 1H, Ar-H), 9.10 (s, 1H, NH); MS: m/z: 505; Anal. Found for $C_{33}H_{35}N_3O_2$; C(78.38%), H(6.98%), N (8.31%), O(6.33%).

9-(3-(2,5-dimethoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-3,3,6,6-tetramethylacridine-3,4,6,7,9,10-hexahydro-1,8(2H,5H)-dione (3i): Yield: 83%; white solid; m.p. 205-208 °C; IR (vmax cm⁻¹, KBr): 3268 (N-H str. of secondary amine), 1680 (C=O str. of carbonyl group), 3068 (C-H str. of aromatic ring), 2956 (C-H asym. Str. of CH₃), 2876 (C-H sym. Str. of CH₃), 1639 (N-H deformation of -NH group), 1600 and 1502 (C=C str. of aromatic ring), 1225 (C-O-C asym. Str. of OCH₃ group), 1066 (C-O-C sym. Str. of OCH₃ group); ¹H NMR (400 Hz, DMSO-d₆) δ ppm: 0.99 (s, 12H, CH₃), 1.99 (m, 4H, CH₂), 2.44(m, 4H, CH₂), 3.83 (s, 3H, CH₃), 4.78 (s, 1H, Ar-H), 7.45 (m, 1H, Ar-H), 7.58 (m, 1H, Ar-H), 7.62(d, 1H, Ar-H), 7.40 (m, 1H, Ar-H), 7.65(s, 1H, Ar-H), 7.36(s, 1H, Ar-H), 6.95 (d, 1H, Ar-H), 9.10 (s, 1H, NH); MS: m/z: 551; Anal. Found for $C_{34}H_{37}N_3O_4$; C(74.02%), H(6.76%), N (7.62%), O(11.60%).

RESULTS AND DISCUSSION

Antimicrobial evaluation

All of the synthesized compounds (3a-3j) were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method [30,31] with two Gram-positive bacteria *Staphylococcus aureus* MTCC 96, *Streptococcus pyogenes* MTCC 443, two Gram-negative bacteria *Escherichia coli* MTCC 442, *Pseudomonas aeruginosa* MTCC 441 and three fungal strains *Candida albicans* MTCC 227, *Aspergillus Niger* MTCC 282, *Aspergillus clavatus* MTCC 1323 taking ampicillin, chloramphenicol, ciprofloxacin, nystatin and griseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC) and Gene Bank, Institute of Microbial Technology, Chandigarh, India.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds defined as the lowest concentration of the compound preventing the visible growth were determined by using microdilution broth method according to NCCLS standards. Serial dilutions of the test compounds and reference drugs were prepared in Mueller-Hinton agar. Drugs (10 mg) were dissolved in dimethylsulfoxide (DMSO, 1 mL). Further progressive dilutions with melted Mueller-Hinton agar were performed to obtain the required concentrations of 1.56, 3.12, 6.25, 10, 12.5, 25, 50, 62.5, 100, 125, 250, 500 and 1000 $\mu\text{g mL}^{-1}$. The tubes were inoculated with 10^8 cfu mL^{-1} (colony forming unit/mL) and incubated at 37 °C for 24 h. The MIC was the lowest concentration of the tested compound that yields no visible growth (turbidity) on the plate. To ensure that the solvent had no effect on the bacterial growth, a control was performed with the test medium supplemented with DMSO at the same dilutions as used in the experiments and it was observed that DMSO had no effect on the microorganisms in the concentrations studied. The results obtained from antimicrobial susceptibility testing are depicted in (Table 2).

Compounds 3d, 3e, 3g and 3i displayed broad spectrum antibacterial activity against both gram-positive and gram-negative bacteria as compared with ciprofloxacin. Compounds 3d, 3e and 3i were found to be 4-fold (MIC = 12.5 $\mu\text{g/mL}$) more active against *S. aureus* and 2-fold active (MIC = 25 $\mu\text{g/mL}$) against *S. pyogenes* whereas compound 3g was found to be 4-fold more potent against *S. pyogenes* and 2-fold active against *S. aureus* compared to the standard drug. While compounds 3d, 3i showed equivalent activity against *E. coli* and 3g, 3i showed equivalent potency against *P. aeruginosa*. High antibacterial potency of 3d, 3e and 3i against gram-positive bacteria may be attributed to the presence of electron donating substituents such as methyl and methoxy, present on phenyl ring of pyrazolyl substitution. In comparison to the standard drug griseofulvin, antifungal activity results indicated that compound 3g substituted with bromo group at 3rd position of phenyl ring was found to be the most potent against *A. clavatus* and *C. albicans*. The plates were incubated at 37°C for 24h and the control was also maintained with 0.05 ml of DMF in similar manner. The zone of inhibition of the bacterial growth was measured in mm. *Aspergillus niger* was employed for testing antifungal activity using cup-plate method. The culture was maintained in Sabouraud's agar slants. Sterilised Sabouraud's agar medium was inoculated with 72h old 0.5 ml suspension of fungal spores in a separate flask. About 25 ml of the inoculated medium was evenly spreaded on a sterilised petridish and allowed to set for 2h. The cups (10 mm in diameter) were punched in petridish and loaded with 0.5 ml of (0.5 mg/mL) solution of sample in DMF. The plates were inoculated at 30°C for 48h. After the completion of inoculation period the zone of inhibition of growth in form of diameter was measured in mm. along the test solution in each petridish one cup was filled with solvent which acts as control. The zone of inhibition was recorded in (Table 2).

Table 2: Anti-microbial activity of 9-(3-(aryl)-1-phenyl-1H-pyrazol-4-yl)-3,3,6,6-tetramethylacridine-3,4,6,7,9,10-hexahydro-1,8(2H,5H)-dione derivatives (3a-3j)

Code	Minimum inhibition concentration ($\mu\text{g mL}^{-1}$)						
	(MIC)						
	Gram-positive		Gram-negative		Fungal species		
	<i>S.a.</i>	<i>S. p.</i>	<i>E.c.</i>	<i>P.a.</i>	<i>C. a.</i>	<i>A. n.</i>	<i>A.c.</i>
3a	500	1000	500	100	1000	>1000	1000
3b	100	100	500	1000	>1000	500	1000
3c	100	100	250	125	500	500	1000
3d	12.5	25	25	50	500	500	250
3e	12.5	25	50	50	500	500	250

3f	500	1000	250	1000	500	500	>1000
3g	25	12.5	50	25	25	250	25
3h	250	100	100	250	1000	500	250
3i	12.5	25	25	25	500	250	250
3j	100	500	250	100	500	1000	>1000
Ampicillin	250	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Ciprofloxacin	50	50	25	25	-	-	-
Nystatin	-	-	-	-	100	100	100
Griseofulvin	-	-	-	-	500	100	100
Note: Sa= Staphylococcus aureus, Sp= Streptococcus pyogenes, Ec= Escherichia coli, Pa=Pseudomonas aeruginosa, Ca= Candida albicans, An= Aspergillus niger, Ac= Aspergillus clavatus							

Docking study

Molecular docking is an important tool which predicts the extended orientation by showing the interactions between ligand and the protein and the aim is to achieve an optimized conformation for both the protein and the ligand and the relative orientation obtained should be such that the free energy of the overall system should be decreased. Molecular docking studies have been carried out with series of dihydropyridine derivatives which are potent and highly selective JAK-2 inhibitors. We have carried out ligand based molecular docking using Molegro Virtual Docker 5.0 (MVD) software to identify the binding modes of synthesized derivatives required for the potential anticancer activity. The crystal structure of protein was downloaded from RCSB protein data bank (PDB ID: 5AEP). The database of molecular docking study consisted of 5AEP with 10 ligand molecules. Docking studies of the title compounds was done on MVD using grid-based docking method. The crystal structure of 5AEP obtained from protein data bank was further used for docking purpose by removing water molecule. The 2D structures of the compounds were built and then converted into 3D structures. The 3D structures were energetically minimized up to the rms gradient of 0.01 using Molecular Force Field (MFF). The cavities in the receptor were mapped to assign an appropriate active site. All the cavities present in receptor were identified and ranked based on their size and hydrophobic surface area. Finally, ligand molecules were docked into the active site of receptor to check their interactions. Results of molecular docking study are tabulated in (Table 3).

Table 3: Docking score of compounds (3a-3j)

Ligand	MolDockScore	Rerank Score	HBond
3g	-183.811	-25.959	-5.139
3i	-174.011	-89.353	-4.498
3d	-173.119	-60.036	-0.672
3e	-172.819	-90.605	-2.941
3c	-166.522	-72.038	-0.702

PTR 1007	-165.762	-122.942	-9.663
3f	-164.889	-69.576	-0.709
3a	-164.671	-68.180	-0.693
3b	-162.848	-74.941	-0.714
3h	-161.255	-79.475	-0.741
3j	-140.663	-75.175	-2.761

Note: PTR1007 is o-phosphotyrosine ligand [(2S)-2-amino-3-(4-phosphonooxyphenyl)propanoic acid].
Compounds are arranged based on their highest docking score.

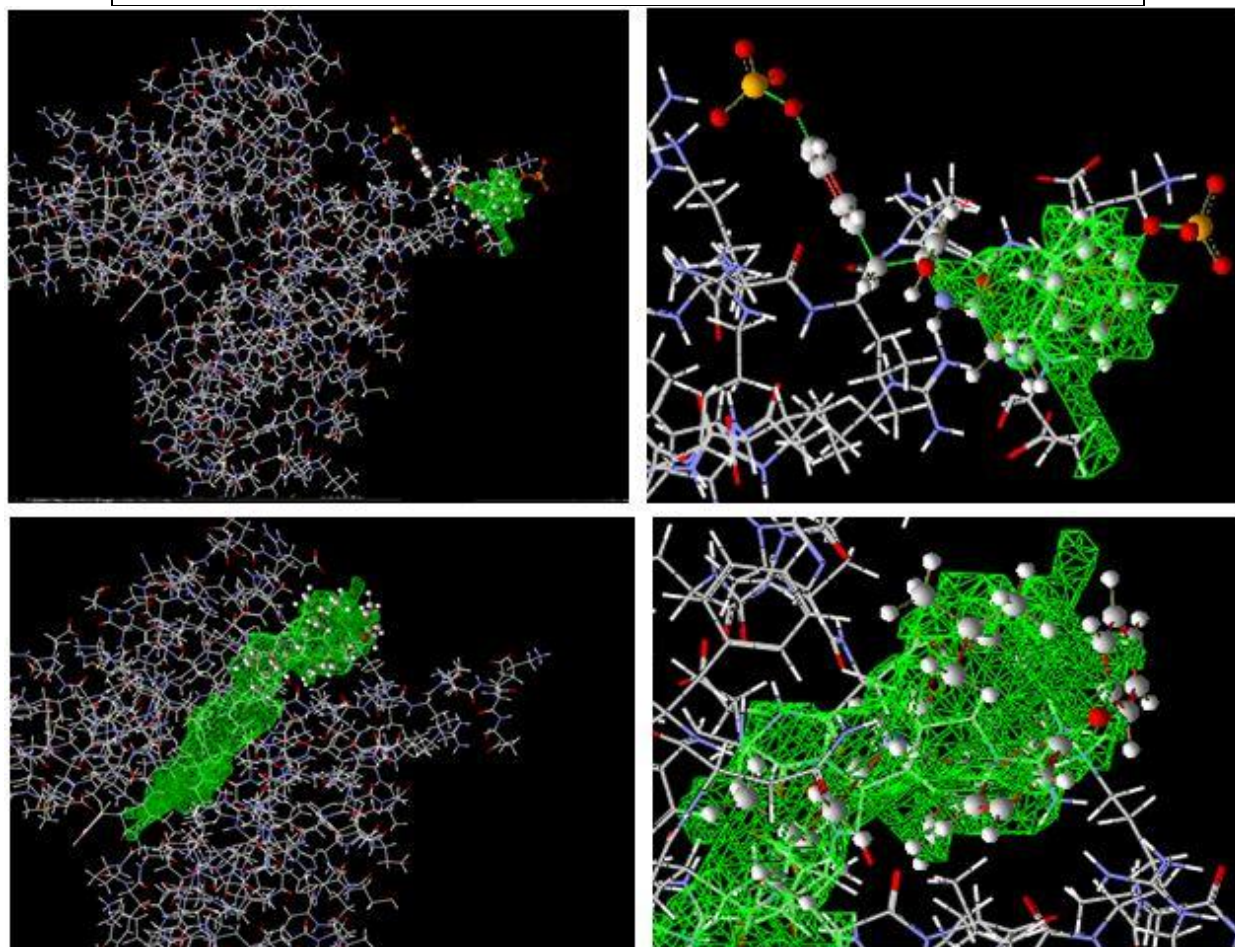


Figure 1: Showing best binding affinity of synthesized molecular scaffolds in to the active site of receptor of JAK-2 protein.

CONCLUSION

In this present work, we have described the synthesis of a series of 9-(3-(aryl)-1-phenyl-1H-pyrazol-4-yl)-3,3,6,6-tetramethylacridine-3,4,6,7,9,10-hexahydro-1,8(2H,5H)-dione derivatives. The synthesized compounds were characterized by ^1H NMR, Mass and IR spectroscopy and the obtained results are showing good agreement with the synthesized structures. Amongst the synthesized compounds screened for their antimicrobial activity, compounds 3d, 3e, 3g & 3i showed good potency and rest are moderately active as compared to standard drugs. Docking studies revealed that compounds 3c, 3d, 3e, 3g & 3i showed best binding affinity to JAK-2 receptor active site compared to standard ligand. This provides future scope for their In vitro anti-cancer study.

ACKNOWLEDGMENT

Authors are thankful to Department of Chemistry, Kamani Science & Prataprai Arts College for providing laboratory facilities. The authors are also thankful to Department of Life Sciences, Gujarat University for providing facilities for docking studies. Authors also express their gratitude towards NFDD (National Facility for Drug Discovery), Saurashtra University, Rajkot for providing instrumentation support. Authors are also thankful to Institute of Microbial Technology, Chandigarh, India for providing facility for antimicrobial activity.

REFERENCES

- [1] Mehta, P., Verma, P., Antimicrobial activity of some derivatives of 1,4-dihydropyridines., *J Chem.*, **2013**. 865128.
- [2] Sirisha, K., Achaiah, G., Reddy, VM., Facile synthesis and antibacterial, antitubercular, and anticancer activities of novel 1,4-dihydropyridines., *Arch Pharm Chem Life Sci.*, **2010**. 343: 342–352.
- [3] Sirisha, K., Bikshapathi, D., Achaiah, G., et al. Synthesis, antibacterial and antimycobacterial activities of some new 4-aryl/heteroaryl-2,6-dimethyl-3,5-bis-N-(aryl)-carbamoyl-1,4-dihydropyridines. *Eur J Med Chem.*, **2011**. 46:1564–1571.
- [4] Chillar, AK., Arya, P., Microwave-assisted synthesis of antimicrobial dihydropyridines and tetrahydropyrimidin-2-ones. Novel compounds against aspergillosis., *Bioorg Med Chem.*, **2006**. 14: 973–981.
- [5] H, Engi., Tumour-specific cytotoxicity and mdr-reversal activity of dihydropyridines, *In Vivo*, **2006**. 20(5): 637-643.
- [6] Duburs, G., Vigante, B., Plotniece, A., et al. Dihydropyridine Derivatives as Bioprotectors, chimica oggi, *Chemistry Today*, 2008. 26(2).
- [7] Brijeshkunvar, M., and Richa, M., Synthesis of some 1, 4-dihydropyridine derivatives for anti-inflammatory activity, *The Pharmacist*, **2007**. 2(1): 13-16.
- [8] Carosati, E., Ioan, P., Micucci, M., et al. *Current Medicinal Chemistry*, **2012**. 19(25): 4306-4323(18)
- [9] Vijesh, AM., Hantzsch reaction: Synthesis and characterization of some new 1,4-dihydropyridine derivatives as potent antimicrobial and antioxidant agents, *Eur J Med Chem*, **2011**. 46(11):5591-5597.
- [10] Sanchez, LM., Sathicq, AG., Thomas, HJ., et al. Synthesis of Dihydropyridines: Patented Catalysts and Biological Applications, *Recent Patents on Catalysis*, **2012**. 1(2): 119-128.
- [11] Manvar, AT., Pissurlenkar, RRS., Virsodia, VR., et al., *Mol Divers* 2010. 14: 285.
- [12] Evans, GJ., Pocock, JM., Modulation of neurotransmitter release by dihydropyridine-sensitive calcium channels involves tyrosine phosphorylation, *Eur J Neurosci*, **1999**. 11(1): 279-92.
- [13] Robert, A., Ortmann, TC., Roberta, V., et al. Janus kinases and signal transducers and activators of transcription: their roles in cytokine signaling, development and immunoregulation, *Arthritis Res*, **2000**. 2(1): 16–32.
- [14] Meyer, T., Marg, A., Lemke, P., Wiesner, B., et al. DNA binding controls inactivation and nuclear accumulation of the

- transcription factor Stat1. *Genes Dev*, **2003**. 17: 1992.
- [15] Kralovics, R., Passamonti, F., Buser, AS., et al. "A gain-of-function mutation of JAK2 in myeloproliferative disorders", *The New England Journal of Medicine*, **2005**. 352(17): 1779–90.
- [16] Gu, L., Liao, Z., Hoang, DT., et al. "Pharmacologic inhibition of Jak2-Stat5 signaling By Jak2 inhibitor AZD1480 potently suppresses growth of both primary and castrate-resistant prostate cancer", *Clinical Cancer Research*, **2013**. 19(20):5658–74.
- [17] Trivedi, AR., Dodiya, DK., Dholariya, BH., et al. Synthesis and biological evaluation of some novel N-aryl-1,4-dihydropyridines as potential antitubercular agents, *Bioorg Med Chem Lett*, **2011**. 21(18): 5181-5183.
- [18] Prakash, O., Hussain, K., Kumar, R., et al. Synthesis and antimicrobial evaluation of new 1,4-dihydro-4-pyrazolylpyridines and 4-pyrazolylpyridines, *Org Med Chem Lett*, **2011**. 1: 1-6.
- [19] Maya, JD., Morello, A., Repetto, Y., et al. Effects of 3-chloro-phenyl-1,4-dihydropyridine derivatives on trypanosome cruzi epimastigotes, *Comp Biochem Phys C*, 2000. 125: 103-109.
- [20] Kohno, K., Kikuchi, J., Sato, S., et al. Vincristine-resistant human cancer KB cell line and increased expression of multidrug-resistance gene, *Jpn J Cancer Res*, **1988**. 79(11):1238-1246.
- [21] Ferry, DR., Russell, MA., Cullen, MH., P-glycoprotein possesses a 1,4-dihydropyridine-selective drug acceptor site which is allosterically coupled to a vinca-alkaloid-selective binding site, *Biochem Biophys Res Commun*, **1992**. 188(1): 440-445.
- [22] Ecker, G., Huber, M., Schmid, D., et al. The importance of a nitrogen atom in modulators of multidrug resistance, *Mol Pharm*, 1999. 56(4): 791-796.
- [23] Zamora, JM., Pearce, HL., Beck, WT., Physical-chemical properties shared by compounds that modulate multidrug resistance in human leukemic cells, *Mol Pharmacol*, **1988**. 33(4): 454-462.
- [24] Ladani, NK., Mungra, DC., Patel, MP., et al. Microwave assisted synthesis of novel Hantzsch 1,4-dihydropyridines, acridine-1,8-diones and polyhydroquinolines bearing the tetrazolo[1,5-a]quinoline moiety and their antimicrobial activity assess, *Chinese Chem Lett*, **2011**. 22(12): 1407-1410.
- [25] Gunduz, MG., Ekizoglu, M., Kart, D., et al. Antimicrobial screening of 2-methyl-3-acyl-4-aryl-2,6,6 and/or 2,7,7-trimethyl-1,4,5,6,7,8-hexahydroquinoline derivatives, *J Faculty Pharm*, **2011**. 31: 51-58.
- [26] Samaunnisa, AA., Venkataramana, CHS., Madhavan, V., Synthesis, characterization and biological activity of novel derivatives of bis pyrazolidine-3,5-dione tethered with 1,4-dihydropyridine moiety, *Contemp Investigat Observ Pharm*, **2013**. 2: 36-42.
- [27] Kira, MA., Abdel-Rahman, MO., Gadalla, KZ., *Tetrahedron Lett.*, **1969**. 10: 109-110.
- [28] Furniss, BS., *Vogel's textbook of practical organic chemistry*; Pearson Education India, 1989.
- [29] National Committee for Clinical and Laboratory Standards, Method for Dilution, Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically Approved Standard, fourth ed. NCCLS, Villanova, Italy, 1997, Document M 100-S7., S100-S157.