1-(3-ACETYL PHENYL)-4-(4-ARYLIDENE)-2-PHENYL-1H-IMIDAZOL-5(4H)-ONES: SYNTHESIS, SPECTROSCOPIC CHARACTERIZATION, ANTIMICROBIAL AND MOLECULAR DOCKING STUDIES

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ABSTRACT

Imidazole rings are privileged moieties in heterocyclic chemistry since they permit functional group and structural modifications to synthesize abundant substituted heterocycles. Thus, the pursuit of exploring many more alterations on imidazole moiety needs to be continued. In the present work an array of the new imidazolone derivatives was prepared as per the expedient method. The moieties were characterized by FTIR, ¹HNMR, ¹³CNMR and Mass spectra. Docking was studied to exemplify the binding connections of intended scaffolds with the crystal structure of protein reductase of *Staphylococcus aureus* pdbid:4NZ9. The synthesized compounds were tested for antibacterial activity by the agar diffusion method. All the compounds showed potent activity against diverse bacterial species.

Keywords: Oxazolone, Glacial Acetic Acid, Imidazolone, Molecular Docking, Acetyl phenyl.

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INTRODUCTION

Amid aromatic heterocycles, predominant moieties are five-membered rings. The role and efficacy of heterocycles in organic synthesis surfaced the way to develop precursors for amino acids, medicinal drugs and other chemical components. For any organic moiety, the effectiveness is measured based on its nontoxic nature, lower dosage and inhibition of microbial growth. The research activity in heterocyclic compounds is intensified on the expansion of biologically active scaffolds, likewise on formulating novel molecules for assessing their potency as drugs, pharmaceuticals, special chemicals and agrochemicals.

In this view, the synthesis of new drugs with a different mode of action is desirable to be explored. Imidazolone-5-ones form a significant class of heterocyclic moieties and are acknowledged to display pharmacological and biological actions such as CNS depressant, antifungal, antihelminthic, anticancer, anticonvulsant, anti-parkinsonian, anti-inflammatory and monoamine oxidase inhibitory agents¹⁻¹⁰. Few new disubstituted imidazolones were proved as an anticonvulsant, monoamine oxidase suppressive and succinate dehydrogenase suppressive agents.^{11,12} Imidazoloquinazolinone derivatives which are synthesized from arylidene-2-phenyl-oxazolone derivatives, showed promising Antibacterial activity.¹³ 2,4,5-triphenyl-imidazoles are first-rate crucial ligands in Organometallic chemistry as their complexes of Cu⁺² displayed anti-E.coli non-pathogenic strain activity.¹⁴ Thus, the pursuit to explore modifications on imidazole ring desires to be sustained. The present work comprises of synthesis of novel imidazolinones (**6a-j**) and is evaluated for their antimicrobial activity. In the direction of elucidating the antibacterial assay, molecular docking studies on staphylococcus aureus were performed.

EXPERIMENTAL

Material and Methods

The experimental ingredients that were used are of analytical grade. The compounds there were prepared and checked in open-glass capillaries on Stuart-SMP10 melting point apparatus and were uncorrected.

The purity of the sample was checked by (TLC)plates DC 0.25mm,60F₂₅₄ coated sheets procured from merck, and spots were envisaged by iodine vapor(or)U.Vlight.Ten novel imidazolones were synthesized from azlactones by reported procedures.¹⁵ Molecular docking studies were done on Linux operating system using Schrodinger suite 2009. Crystal structure of reductase protein of *Staphylococcus aureus* was downloaded from the protein data bank pdbid:4NZ9. The protein fragments were set by protein groundwork wizard applying OPLS2005 forcefield, and a grid was prepared around the binding site by choosing the co-crystallized ligand. Imidazole derivatives were built in Maestro-build-panel and outfitted by Ligprep-module. These were docked in requisite-site using Glide-5.6. Ligand interaction diagrams were obtained using Maestro academic-version and figures were obtained using DS4.0 viewer.

General Procedure for Synthesis 4-benzylidene-2-phenyl-2-oxazoline-5-one (4a-j)

4-benzylidene-2-phenyl-2-oxazoline-5-ones (**4a-j**) are prepared by condensation of aromatic aldehydes with benzoyl derivative of glycine in the presence of (CH₃CO)₂O and fused anhydrous sodium acetate. 0.008mol of benzoylglycine (**3**) prepared by stirring glycine (0.33mol) with benzoyl chloride (0.385mol), 1 gram of freshly fused sodium acetate and 2-3 ml of acetic anhydride was added with slow stirring and stirring continued for 30 seconds. Then immediately, 0.008mol aromatic aldehyde was added and refluxed on a hot waterbath for about 1 hour. Continuation of the reaction was observed by using TLC. 7ml ethanol was added to it and kept overnight, which resulted in the yellow crystalline precipitate, which was purified by washing with cold ethanol followed by boiling water.

Ar = phenyl, 2-chloro phenyl, 4-chloro phenyl, 2,4 dichloro phenyl
2,6 dichlorophenyl, 2-hydroxy phenyl, 4-hydroxy phenyl, 4-nitro phenyl,
3,4,5-trimethoxy phenyl, 2,5-dimethoxy phenyl

Scheme-1: Synthetic Reactions of Oxazolones 4a-j

Synthesis of Novel-1H-imidazole-5(4H)-ones

1 mol of 4-arylidene-2-phenyl-2-oxazoline-5-ones (**4a-j**), 1mol of 3-amino acetophenone (**5**), 15 ml glacial acetic acid and CH₃COONa were refluxed for 3 hrs at 100°C in a RB flask. After checking the continuity of reaction monitored by TLC, the reaction mass was transferred into crumpled ice. The precipitate was dried and run by column chromatography (Scheme-2).

1-(3-acetylphenyl)-4-imidazole derivative (6a)

FT-IR (KBr cm⁻¹) 3421, 2922, 1800, 1633, 1448, 1295, 1170, 877, 759, 698 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 8.28 (s, 1H, aromatic), 8.11 (s, 1H, CH), 7.68 (t, *J* = 7.81 Hz, 2H, aromatic), 7.51 (t, *J* = 7.44 Hz, 2H, aromatic), 7.42 (d, *J* = 7.23 Hz, 2H, aromatic), 7.12 (d, *J* = 7.55 Hz, 2H, aromatic), 6.83 (d, *J* = 7.14 Hz, 1H, aromatic), 2.36 (s, 3H, CH₃) ppm. MS-ESI m/z 368 [M + 2H]⁺.

1-(3-acetylphenyl)-4-(2-chlorobenzylidene)-imidazole-one (6b)

FT-IR (KBr cm⁻¹) 3447, 2923, 1789, 1622, 1555, 1488, 1285, 926, 880, 755 cm⁻¹. ¹H NMR (δ): 8.15 (s, 1H, aromatic), 8.10 (s, 1H, CH), 7.62 (t, *J* = 7.5 Hz, 2H, aromatic), 7.53 (m, 6H, aromatic), 7.42 (d, 1H, aromatic), 7.14 (d, *J* = 7.6 Hz, 3H, aromatic), 2.38 (s, 3H, CH₃) ppm. MS-ESI m/z 401 [M + H]⁺.

1-(3-acetylphenyl)-4-(4-chlorobenzylidene)-1H-imidazolone (6c)

FT-IR (KBr cm⁻¹) 3449, 2920, 2849, 1784, 1634, 1550, 1289, 878, 694 cm⁻¹. ¹H NMR : 8.15 (s, 1H, aromatic), 8.10 (s, 1H, CH), 7.62 (t, *J* = 7.5 Hz, 2H, aromatic), 7.53 (m, 6H, aromatic), 7.42 (d, 2H, aromatic), 7.22 (d, *J* = 7.6 Hz, 2H, aromatic), 2.38 (s, 3H, CH₃) ppm. MS-ESI m/z 401 [M + H]⁺.

Scheme-2: Synthetic Reactions of Imidazolones 6a-j

1-(3-acetylphenyl)-4-(2,4-benzylidenedichloro)-2-phenyl-imidazol-5(4H)-one(6d)

FT-IR (KBr cm^{-1}) 3557, 3313, 2923, 1644, 1563, 1267, 828, 780, 536 cm^{-1} ; ^1H NMR :8.15 (s, 1H, aromatic), 8.10 (s, 1H, CH), 7.62 (t, $J = 7.36$ Hz, 2H, aromatic), 7.53 (m, 5H, aromatic), 7.42 (d, 3H, aromatic), 7.12 (d, $J = 7.52$ Hz, 1H, aromatic), 2.38 (s, 3H, CH_3) ppm. MS-ESI m/z 437 $[\text{M} + \text{H}]^+$.

4-(2,6-dichlorobenzylidene)-1-(3-acetylphenyl)-2-phenyl-1H-imidazol-5(4H)-one(6e)

FT-IR (KBr cm^{-1}) 3300, 2927, 1707, 1619, 1457, 1151, 955, 777, 637 cm^{-1} ; ^1H NMR δ 8.15 (s, 1H, aromatic), 8.10 (s, 1H, CH), 7.62 (t, $J = 7.42$ Hz, 2H, aromatic), 7.51 (m, 5H, aromatic), 7.42 (d, $J = 7.61$ Hz, 2H, aromatic), 7.11 (d, $J = 7.52$ Hz, 2H, aromatic), 2.38 (s, 3H, CH_3) ppm. MS-ESI m/z 437 $[\text{M} + \text{H}]^+$.

4-(2-hydroxybenzylidene)-1-(3-acetylphenyl)-2-phenyl-1H-imidazol-5(4H)-one(6f)

FT- IR (KBr cm^{-1}) 3499, 2923, 2853, 1643, 1539, 1429, 1397, 1099, 712, 668 cm^{-1} . ^1H NMR δ 8.28 (s, 1H, CH), 8.10 (s, 1H, aromatic), 7.64 (t, $J = 7.42$ Hz, 2H, aromatic), 7.61 (t, $J = 7.53$ Hz, 2H, aromatic), 7.51 (m, 3H, aromatic), 7.42 (d, $J = 7.72$ Hz, 2H, aromatic), 7.11 (d, $J = 7.43$ Hz, 1H, aromatic), 6.82 (d, $J = 7.10$ Hz, 1H, aromatic), 6.63 (d, $J = 7.33$ Hz, 1H, aromatic), 4.82 (s, 1H, OH), 2.41 (s, 3H, CH_3) ppm. MS-ESI m/z 383 $[\text{M} + \text{H}]^+$.

4-(4-hydroxybenzylidene)-1-(3-acetylphenyl)-2-phenyl-1H-imidazol-5(4H)-one(6g)

FT-IR (KBr cm^{-1}) 3419, 2924, 1629, 1550, 1321, 891, 750, 676 cm^{-1} . ^1H NMR: 8.11 (s, 1H, aromatic), 7.86 (s, 1H, CH), 7.61 (t, $J = 7.44$ Hz, 2H, aromatic), 7.51 (m, 3H, aromatic), 7.48 (m, 5H, aromatic), 6.82 (d, $J = 7.10$ Hz, 2H, aromatic), 4.87 (s, 1H, OH), 2.36 (s, 3H, CH_3) ppm. MS-ESI m/z 383 $[\text{M} + \text{H}]^+$.

1-(3-acetylphenyl)-4-(4-nitrobenzylidene)-2-phenyl-1H-imidazol-one(6h)

FT-IR (KBr cm^{-1}) 3010, 2925, 1665, 1622, 1548, 1444, 1307, 1053, 703, 678 cm^{-1} . ^1H NMR δ : 8.25 (t, $J = 7.46$ Hz, 3H, aromatic), 8.09 (d, $J = 7.22$ Hz, 2H, aromatic), 7.93 (s, 1H, CH), 7.59 (t, $J = 7.44$ Hz, 2H, aromatic), 7.51 (m, 3H, aromatic), 7.41 (d, $J = 7.64$ Hz, 2H, aromatic), 7.29 (t, $J = 7.10$ Hz, 1H, aromatic), 2.39 (s, 3H, CH_3) ppm. MS-ESI m/z 412 $[\text{M} + \text{H}]^+$.

1-(3-acetylphenyl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-imidazol-5(4H)-one(6i)

FT-IR (KBr cm^{-1}) 3449, 2920, 1784, 1638, 1550, 1289, 1164, 817, 694 cm^{-1} . ^1H NMR: 8.20 (s, 1H, aromatic), 8.09 (s, 1H, CH), 7.61 (t, $J = 7.48$ Hz, 2H, aromatic), 7.51 (m, 6H, aromatic), 6.45 (s, 2H, aromatic), 3.82 (s, 9H, OCH_3), 2.46 (s, 3H, CH_3) ppm. MS-ESI m/z 457 $[\text{M} + \text{H}]^+$.

1-(3-acetylphenyl)-4-(2,5-dimethoxybenzylidene)-2-phenyl-imidazolone(6j)

FT-IR (KBr cm^{-1}) 3436, 2925, 1787, 1638, 1599, 1555, 1451, 1332, 1188, 882, 696 cm^{-1} . ^1H NMR δ 8.21 (s, 1H, aromatic), 8.10 (s, 1H, CH), 7.60 (t, $J = 7.52$ Hz, 2H, aromatic), 7.50 (m, 6H, aromatic), 6.52 (d, $J = 7.77$ Hz, 2H, aromatic), 6.49 (s, 1H, aromatic), 3.80 (s, 6H, OCH_3), 2.48 (s, 3H, CH_3) ppm. MS-ESI m/z 427 $[\text{M} + \text{H}]^+$.

Detection Method

The prepared derivatives were checked in open glass capillaries on Stuart SMP10 melting point instrument and were uncorrected. TLC was used to identify the purity of the sample, and the single spot was visualized under U.V light. The IR spectra were obtained with IR AFFINITY-1 FTIR Shimadzu spectrometer. ^1H NMR spectra (ppm) were noted in CDCl_3 and $\text{DMSO}-d_6$ on a Varian Mercury 300 MHz spectrometer. ^{13}C NMR spectra have been recorded in CDCl_3 and $\text{DMSO}-d_6$ on a Bruker Avance II400 spectrometer at 400 MHz. And the mass spectra have been recorded on a Shimadzu. All derivatives were regularly checked by TLC by means of $\text{CHCl}_3:\text{CH}_3\text{OH}$ (9:1) solvent system and checked under UV light.

Analytical Discussion

As a representative case, the spectral analysis of (6a) is considered. In the IR spectrum of (6a), the stretching frequency at 3421cm^{-1} and 2922cm^{-1} indicates absorption due to the aliphatic (C-H) group. The characteristic (C=N) absorption was observed at 1448cm^{-1} and (C-N) group absorption 1295cm^{-1} . The ^1H NMR spectrum (400 MHz, CDCl_3) (6a) showed multiplet between δ 7.12-8.11 due to aromatic protons and δ 8.28 due to arylidene proton. ESI-MS mass spectra of derivative (6a) m/z 368 $(\text{M}+2\text{H})^+$ appeared as base peak.

RESULTS AND DISCUSSION**Proposed Mechanism**

The mechanism involves Erlenmeyer-Plochl reaction which involves Perkin condensation where acetic anhydride reacts with substituted aromatic aldehydes to undergo cyclization and

condensation reaction in presence of weak base. Inter-molecular acetylation reaction occurs via alkoxide anhydride intermediate in this mechanism.

Table-1: Physical Characterization of Compounds (6a-j)

Compound	Systemic Name	Molecular Formula	Yield %	M.P (⁰ C)	Color of Compound
6a	1-(3-acetyl phenyl)-4-benzylidene-2-phenyl-1H-imidazol -5(4H)-one	C ₂₄ H ₁₈ N ₂ O ₂	80	232°C	Orange solid
6b	1-(3-acetylphenyl)-4-(2-chlorobenzylidene)-2-phenyl-1H-imidazol-5(4H)-one	C ₂₄ H ₁₇ ClN ₂ O ₂	82	195°C	Yellowish Orange solid
6c	1-(3-acetylphenyl)-4-(4-chlorobenzylidene)-2-phenyl-1H-imidazol -5(4H)-one	C ₂₄ H ₁₇ ClN ₂ O ₂	85	256°C	Yellowish Orange solid
6d	1-(3 -acetylphenyl)-4-(2,4dichlorobenzylidene)-2-phenyl-imidazol-5(4H)-one	C ₂₄ H ₁₆ Cl ₂ N ₂ O ₂	78	278°C	light orange solid
6e	1-(-3-acetylphenyl)-4-(2,6dichlorobenzylidene)-2-phenyl-imidazolone	C ₂₄ H ₁₆ Cl ₂ N ₂ O ₂	82	280°C	Yellowish orange solid

6f	1-(3-acetylphenyl)-4-(2-hydroxybenzylidene)-2-phenyl-1H-imidazol-5-one	C ₂₄ H ₁₈ N ₂ O ₃	80	267°C	Yellowish orange solid
6g	1-(3-acetyl phenyl)-4-(4-hydroxy benzylidene)-2-phenyl-1H-imidazol-(4H)-one	C ₂₄ H ₁₈ N ₂ O ₃	83	273°C	Yellow color solid
6h	4-(4-nitrobenzylidene)-1-(3-acetyl phenyl)-2-phenyl-imidazol-5(4H)-one	C ₂₄ H ₁₇ N ₃ O ₄	84	241°C	Yellow color solid
6i	4-(3,4,5-trimethoxybenzylidene)-1-(3-acetylphenyl)-2-phenyl-1H-imidazolone	C ₂₇ H ₂₄ N ₂ O ₅	81	239°C	Yellow color solid
6j	2,5dimethoxybenzylidene)-1-(3-acetylphenyl)-4-(2-phenyl-1H-imidazol-5(4H)-one	C ₂₆ H ₂₂ N ₂ O ₄	86	272°C	Yellow color solid

Antibacterial Assay

The antibacterial assay of synthesized moieties were checked against *gram positive bacteria B. subtilis* and *S. aureus* and two *gramnegative bacteria E. coli* and *S. typhi*. A stock solution of 2mg/ml was prepared. Wells were made in the agar plate using a borer. The sample solution is pipetted into the wells.¹⁶ And the plates were incubated for around 24hrs. Then the region of restrained and recorded as shown in Table-2. All compounds exhibited moderate to potent activity against *gram(+)* and *gram(-)* bacteria.

Table-2: Antibacterial Activity of 4-(4-arylidene)-1-(3-acetyl phenyl)-2-phenyl-1H-imidazol-5(4H)-ones(6a-j)

Compound	Zone of inhibition(mm) in 2µg/ml concentration			
	gram -ve	gram -ve	gram +ve	gram +ve
	<i>E.coli</i>	<i>P. aeruginosa</i>	<i>B.subtilis</i>	<i>S. aureus</i>
6a	12	14	12	10
6b	12	11	13	14
6c	13	14	12	13
6d	13	12	14	13
6e	12	8	14	12
6f	13	14	10	14
6g	12	15	13	18
6h	10	12	11	13
6i	9	11	12	12
6j	11	13	14	14

Molecular Docking Studies

Imidazole derivatives have accomplished much contemplation for their anti-microbial activity. Bacterial ENRs are believed to be fine explicit targets for antibacterial agents development and are one of the target proteins that are inhibited by imidazole derivatives.^{17,18} In order to explicate the mode of interaction and binding of synthesized imidazole derivatives, molecular docking studies were carried out on X-ray crystal structure of FabI of *Staphylococcus aureus*, pdbid:4NZ9 found from databank (www.rcsb.org).¹⁹⁻²² The docking results are provided in Table-3. The highest dock score of -10.318 kcal/mol and least dock score of -9.014 kcal/mol were obtained for molecules 6a and 6g, respectively. All molecules showed a good

dock score, indicating that all molecules are good inhibitors of enoylacylcarrier protein reductase (Fab I). Dock pose of molecule 6g in the active location of Fab I is shown in Fig.-1 and hydrophobic interaction of the molecules with active site amino acid residues is visible in Fig.-2. The hydrogen bonding interaction of ligand is shown in Fig.-3. The molecule showed 2 H-bond interactions with amino acid residue Asn156 and Ser197; the other major interaction with the protein was of hydrophobic nature with amino acid residues Met 99, Tyr147, Tyr157, Met160, Pro 192 and Ile207 in Fig.-3.

Fig.-1: Dock Pose of Molecule 6g in the Active Site of FABI

Fig.-2: Hydrophobic Interaction of the Molecules with Dynamic Site Amino Acid Residues

Fig.-3: Ligand Interaction Diagram representing the Hydrogen Bond Interaction.

Table-3: Dockscore of imidazole derivatives docked into the active site of FabI of *S. aureus* using extra precision (XP) docking protocol of Glide 5.6.

S.No.	Entry	Dockscore (kcal/mol)
1.	6a	-10.318
2.	6b	-9.021
3.	6c	-9.648
4.	6d	-9.781
5.	6e	-9.159
6.	6f	-9.488
7.	6g	-9.014
8.	6h	-9.603
9.	6i	-9.121
10.	6j	-9.511

CONCLUSION

The synthesized novel imidazole scaffolds exhibited wide spectrum antibacterial activity. Compounds **6a, 6c, 6d, 6g** and **6h** displayed potent activity against gram +ve and gram -ve bacteria. Molecular docking studies with bacterial host DNA inferred confirmative outcomes for the binding affinity of derivatives in accord with experimental data. All the derivatives have shown moderate to good docking scores indicating that they are inhibitors of enoyl acyl carrier protein reductase. Among all the entries, **6a** showed the least dock score of -9.014 kcal/mol and **6g** maximum dock score of -10.318 kcal/mol. The twang on docking is to computationally conjure up the molecular recognition process.

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REFERENCES

1. Prasad Pullagura, M. Krishna, S. Avdhut Kanvinde, S. Raja, *International Journal of Pharmacy and Pharmaceutical Sciences*, **8(12)**, 22(2016), <https://doi.org/10.22159/ijpps.2016v8i12.14949>
2. D. Huang, F. Qiu, Z. Zhang, L. Shi, C. Cao, S. Ke, *Journal of Heterocyclic Chemistry*, **56(9)**, 2494(2019), <https://doi.org/10.1002/jhet.3639>
3. P. Köhler, *International Journal for Parasitology*, **31(4)**, 336(2001), [https://doi.org/10.1016/S0020-7519\(01\)00131-X](https://doi.org/10.1016/S0020-7519(01)00131-X)
4. A. El Rashedy, H. Y. Aboul-Enein, *Mini Reviews in Medicinal Chemistry*, **13(3)**, 399-(2013), <https://doi.org/10.2174/138955713804999847>
5. P. M. Vasil'ev, K. Y. Kalitin, A. A. Spasov, O. Y. Grechko, V. V. Poroikov, D. A. Filimonov, V. Anisimova, *Pharmaceutical Chemistry Journal*, **50(12)**, 775(2017), <https://doi.org/10.1007/s11094-017-1530-6>
6. S. P. Singh, S. S. Parmar, B. R. Pandey, *Journal of Heterocyclic Chemistry*, **14(6)**, 1093(1977), <https://doi.org/10.1021/jm00260a027>
7. N. Anastassova, D. Aluani, A. Kostadinov, M. Rangelov, N. Todorova, N. Hristova-Avakumova, D. Yancheva, *Neural Regeneration Research*, **16(11)**, 2299(2021), <https://doi.org/10.4103/1673-5374.309843>
8. S. N. A. Bukhari, A. Lauro, G. Jantan, I. Fei, C. Chee, M. W. Amjad, G. Bifulco, N. A. Rahman, *Future Medicinal Chemistry*, **8(16)**, 1953(2016), <https://doi.org/10.4155/fmc-2016-0062>
9. G. Chen, Z. Liu, Y. Zhang, X. Shan, L. Jiang, Y. Zhao, G. Liang, *ACS Medicinal Chemistry Letters*, **4(1)**, 69(2013), <https://doi.org/10.1021/ml300282t>
10. O. D. Can, D. Osmaniye, U. D. Özkay, B. N. Sağlık, S. Levent, S. Ilgın, Z. A. Kaplancıklı, *European Journal of Medicinal Chemistry*, **131**, 92(2017), <https://doi.org/10.1016/j.ejmech.2017.03.009>

11. D. van den Berg, K. R. Zoellner, M. O. Ogunremi, S. F. Malan, G. Terre 'Blanche, N. Castagnoli Jr, J. P. Pitzer, *Bioorganic & Medicinal Chemistry*, **15(11)**, 3692(2007), <https://doi.org/10.1016/j.bmc.2007.03.046>
12. Y. H. Ye, L. Ma, Z. C. Dai, Y. Xiao, Y. Y. Zhang, D. D. Li, H. L. Zhu, *Journal of Agricultural and Food Chemistry*, **62(18)**, 4063(2014), <https://doi.org/10.1021/jf405437k>
13. Solankee, Anjani, Sejal Solankee, and Ghanshyam Patel, *Rasayan Journal of Chemistry*, **1**, 228(2008).
14. T. H. Sucipto, W. Setyarini, F. Martak, D. Raharjo, *Rasayan Journal of Chemistry*, **14(2)**, 672(2021), <http://dx.doi.org/10.31788/RJC.2021.1425826>
15. S. Furniss, A. J. Hannaford, Furniss, Tatchell, A. R. Vogel's Text Book of Practical Organic Chemistry, 5th edition, Longman Group, Essex, UK(1989).
16. S. Magali, S. Mata-Essaying, C. Hartung de Capriles, *International Journal of Infectious Diseases*, **8**, 39(2004).
17. L. L. Ling, J. Xian, S. Ali, B. Geng, J. Fan, D. M. Mills, D. T. Moir, *Antimicrobial Agents and Chemotherapy*, **48(5)**, 1541(2004), <https://doi.org/10.1128/AAC.48.5.1541-1547.2004>
18. A. E. Cho, V. Guallar, B. J. Berne, R. Friesner, *Journal of Computational Chemistry*, **26(9)**, 915(2005), <https://doi.org/10.1002/jcc.20222>
19. H. J. Böhm, *Journal of Computer-aided Molecular Design*, **8(3)**, 243(1994), <https://doi.org/10.1007/BF00126743>
20. G. Klebe, T. Mietzner, *Journal of Computer-Aided Molecular Design*, **8(5)**, 583(1994), <https://doi.org/10.1007/BF00123667>
21. R. A. Friesner, J. L. Banks, R. B. Murphy, T. A. Halgren, J. J. Klicic, D. T. Mainz, P. S. Shenkin, *Journal of Medicinal Chemistry*, **47(7)**, 1739(2004), <https://doi.org/10.1021/jm0306430>
22. T. A. Halgren, R. B. Murphy, R. A. Friesner, H. S. Beard, L. L. Frye, W. T. Pollard, J. L. Banks, *Journal of Medicinal Chemistry*, **47(7)**, 1750(2004), <https://doi.org/10.1021/jm030644s>
23. Y. Aparna, L. N. Sharada, N. J. P. Subhashini, S. Sreekanth, *Russian Journal of General Chemistry*, **89(6)**, 1202(2019), <https://doi.org/10.1134/S1070363219060161>

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