SYNTHESIS, CHARACTERIZATION, QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP, DOCKING, ANTIBACTERIAL ACTIVITY, AND BRINE SHRIMP LETHAL STUDIES ON L-PHENYLALANINE SCHIFF BASES

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INTRODUCTION

Development of new antibiotic drug with high resistivity and control over the disease-causing in medicine and agriculture field is a well-documented problem [1]. It was found that the Schiff bases are the key intermediates for the synthesis of numerous bioactive medicinal compounds from the primary amine, medicinal activities so far. They possess antimalarial possess antimalarial [2], anticancer [3], antimicrobial [4,5], antioxidant [6], and analgesic [7] characters. The Schiff bases are used as a reactant for the preparation of a number of bioactive heterocyclic compounds such as benzoxazines, formazones, 2-azetidinones, and 4-thiazolidinones [8]. Apart from the various Schiff base molecules, recently amino acid Schiff bases and their metal complexes have received great attention owing to their biological importance [9]. The metal complexes of amino acid Schiff bases and their antimicrobial activities [10-19] were reported earlier. But the quantitative (QSR) properties [20], docking, and toxicity assay of the different hydroxyl group substituted Schiff bases of the Schiff bases of L-phenylalanine were not reported in detail so far. Therefore, this research studied the QSR parameters of the Schiff bases using offline and online tools such as Data-Warrior, tomcat, mosksoft [21,22], and molinspiration [21,22] to reduce the wastage of chemical and time. Similarly, this research used cell division protein ZipA (PDB id-1s1j) of Escherichia coli for the molecular docking instead of cell wall protein. ZipA is bitopic cytoplasmic membrane protein with a short periplasmic N-terminal region of an E. coli [23]. Based on the literature survey, we derived five Schiff bases from L-phenylalanine using 2-hydroxy (1a), 3-methoxy, 2-hydroxy (1b), 4-hydroxy (1c), 3-hydroxy (1d), and 2,4-dihydroxy (1e) benzaldehydes in 2:1 ratio methanol, water solvent, and the compounds were characterized by Fourier transform infrared (FTIR), 1H-nuclear magnetic resonance (NMR), and 13C-NMR spectral studies. We also performed molecular docking to realize how various positions of substituted hydroxyl group in Schiff bases binding with cell division ZipA protein of E. coli and compared with standard antibiotics such as amoxicillin and gentamicin. Docking study of cell division ZipA protein was carried out using online mucle server and CLC Drug Discovery Workbench 3 tool. The Schiff bases were carried for experimental antibacterial activity against E. coli [25] pathogen and Brine Shrimp [26,27] toxicity study for the serially diluted solutions. Finally, the computational outcomes were compared with experimental results.

METHODS

L-phenylalanine, 2-hydroxy benzaldehyde, 3-methoxyalicylaldehyde, 4-hydroxy benzaldehyde, and 2, 4-dihydroxy benzaldehyde were purchased from Sigma-Aldrich, USA. 3-hydroxy benzaldehyde was purchased from HiMedia, Mumbai. The solvents and all other chemicals were purchased from SRL chemicals, India. Melting points were measured by an open capillary method using Sunsim electric melting point apparatus. The FTIR spectra of Schiff bases were obtained by Jasco-6300 FTIR spectrometer.1H-NMR and 13C-NMR
spectra were recorded using a Bruker NMR400 spectrometer in dimethyl sulfoxide (DMSO) solvent. The tools used for the virtual screening are Java based tools such as Data molinspiration are the Java-based virtual screening tools. Structures were drawn using ChemDraw software. Docking tools such as mcscale 1-lick docking and CLC drug discovery workbench 3 were used. Similarly, cell division protein ZipA, PDB id-1s1j, UnProt name-ZIPA_ECOLI, and resolution-2.180 were used for the docking study.

E. coli ATCC 8739 was obtained from Biomaterial Contributor Network, USA. The Artemia cyst eggs were purchased from Aquamarine (Guindy, Chennai, India) and sea water was collected at Besant Nagar beach, Chennai, India.

EXPERIMENTAL

General procedure for the synthesis of L-phenylalanine Schiff bases (compounds 1a-1e)

Schiff bases of L-phenylalanine were prepared using 2:1 methanol and water instead of ethanol [13] in 100 ml R.B flask. 10 ml of 0.001 mol hydroxyl group substituted aromatic aldehyde dissolved methanolic solution was added dropwise to 5 ml of 0.001 mol L-phenylalanine hot water solutions. Then, the reaction mixture was refluxed for 3 h and the R.B flask was covered with silver foil. The reaction was monitored by thin layer chromatography using 8.5:1:0.5 t-butanol, water, and acetic acid elution system. Then, the reaction mixture was cooled to room temperature. After 12 hrs, the solid formed was filtered off, washed with hot methanol-water mixture. The solid Schiff base was recrystallized from 20 ml of 1:1 methanol, water mixture and stored in a vacuum desiccator over anhydrous calcium chloride.

(S, E)-2-(2-hydroxybenzylideneamino)-3-phenylpropanoic acid (1a)

Light yellow solid; yield-72%; mp-163°C (Bushra et al. 160-162°C); M.F. C_{13}H_{14}NO; molecular weight (MW): 269.3; FTIR (υ, cm^-1): OH-3525, CO (COOH)-3430, Ar-CH-3071, CH=N-1632, C-O-1276; 1H NMR (500 MHz, DMSO) δ 11.56 (s, 1H), 9.83 (s, 1H), 7.92 (s, 1H), 3.86-2.60 (m, 2H), 7.32-7.10 (m, 2H), 7.04 (d, J = 7.0 Hz, 2H), 6.85 (d, J = 7.5 Hz, 2H), 4.90-4.74 (m, 3H), 3.86 (s, 3H), 3.57 (t, J = 11.3 Hz, 1H), 3.09 (d, J = 12.3 Hz, 1H).°C NMR (125 MHz, DMSO) δ 172.61, 164.16, 162.50, 154.87, 137.07, 131.09, 124.35, 119.48, 110.78, 103.26, 76.16, 40.03.

(S, E)-2-(4-dihydroxybenzylideneamino)-3-phenylpropanoic acid (1c)

Dull yellow solid; yield-75%; mp-220°C; M.F. C_{15}H_{18}NO; M.Wt: 285.29; FTIR (υ, cm^-1): OH-3600, CO (COOH)-3570, Ar-CH-3071, CH=N-1632, C-O-1276; 1H NMR (500 MHz, DMSO-d_6) δ 14.72 (s, 1H), 9.83 (s, 1H), 7.5 (s, 1H), 7.1 (t, J = 7.4 Hz, 2H), 7.4 (t, J = 7.4 Hz, 2H), 6.41 (d, J = 7.0 Hz, 2H), 6.32 (d, J = 1.8 Hz, 1H), 4.89 (d, J = 6.7 Hz, 1H), 3.10-2.81 (m, 2H).°C NMR (125 MHz, DMSO) δ 172.61, 164.16, 162.50, 154.87, 137.07, 131.09, 124.35, 119.48, 110.78, 103.26, 76.16, 40.03.

QSAR properties of Schiff bases

Computer-aided drug innovation methods have played a major role in the development of therapeutically essential small molecules for the past decades. QSAR properties were determined for a particular synthesized new molecule for biological studies, and these properties can identify the molecule, whether it can act as a drug or not for further research. Many of the potential drugs were failed to reach the clinic because of absorption, distribution, metabolism, excretion-Tox liability problems. Hence, the structure-based design is now fairly repetitive because the important properties like molecular formula, the number of hydrogen bond acceptors and donors, mol logP, mol kgs, molecular weight, polar surface area, molecular volume, and comparative drug likeness scores were calculated to avoid the wastage of biological materials. These QSAR properties were calculated using Molinspiration and Molsoft predicting tools. The activity of all molecules and standard drugs was thoroughly examined under four criteria of effective drug activity in the areas of nuclear receptor ligand activity, ion kinase inhibition activity, channel modulation, and G protein coupled receptors ligand activity. Similarly, the preliminary computational drug-likenesses of the molecules are calculated by the methodology established by offline Data-Warrior software and tomatocloud online software. The partition coefficient (logP) value of Schiff bases was predicted using ChemSketch and compared with molinspiration tool values. All the synthesized molecules were found to fulfill the solubility requirements (logP) and showed drug character in tomtac tool. On analyzing with Lipinski’s rules of Five, compounds showed mol logP ≤5; n rot b ≥5 (except 1b), MW ≤500, nOHNH ≤5, n ON ≤10 and all the synthesized Schiff bases satisfied the rules.

Molecular docking

Docking is the formation of non-covalent protein-ligand complexes in drug design. The specified structure of a protein and a ligand, the task is predicting the structure of the binder complex. A docking technique evaluates the forces involved in the protein-ligand recognition such as van der walls bonding through hydrogen, electrostatic and place of the legend appropriately in the active site [28]. After conducting an adequate literature review, E. coli cell division, ZipA protein was selected as the target for this study, which is not reported so far. The crystal structure of the above target was obtained from mce1 1-click docking server. Ligand structures were done by drawing the structures using ChemSketch and converted to word based smiles notation. Docking simulations were performed with simple and fast mce1 1-click docking server. By evaluating the affinity of the compounds, four different docking scores were shown by the software for 1a, 1b, 1c, 1d, and 1e. Docking study gave comparatively good affinity with the particular E. coli cell division target at the binding site of X韦15.61 and Y韦14.16153 and Z韦3.9038. All mce1 docking images were viewed by CLC drug designing workbench-3 software.

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Antibacterial assay
The Schiff bases were tested for their inhibitory character on the growth of *E. coli*, thus bacteria can achieve resistance to antibiotics through morphological and biochemical alterations [29]. The antimicrobial activity was tested by broth dilution method using serially diluted solutions of 25, 12.5, 6.25 µg/ml, respectively. The presence of hydroxyl groups in the Schiff base ligand plays an important role for its antimicrobial activity [30], and likewise the presence of imine group which imports in exposing the mechanism of transformation reaction in biological systems [31]. The Schiff bases showed inhibition against the growth of *E. coli* under the identical experimental conditions. The increase in biological activity of the Schiff bases may be due to the effect of the chelation on the normal cell process. Furthermore, the method of action of the Schiff bases may involve the formation of a hydrogen bond through the imine nitrogen (>C=N) with the energetic interiors of cell constituents, resulting in interference with the normal cell process [32]. After incubation at 37°C for 24 hrs, the antibacterial activity of the Schiff bases was determined by measuring the inhibition of the zone diameter in mm scale and minimum inhibitory concentrations (MICs) in µg/ml unit from the triplicated trials.

Toxicity study by brine shrimp lethal assay (BSLA) test
Brine shrimp larvae were hatched and toxicity study [33] was carried out for the 1a-e Schiff bases. 1 g of the Artemia cyst egg was added in 1 l of sea water and kept under aeration. A 60 Watts tungsten lamp was focused on the beaker for 30 hrs. After the hatching process matured, nauplii were taken for toxicity study. Toxicity test was carried out for the serially diluted Schiff base solutions of 10, 50, 100, 200, and 250 µg/ml. Test samples were diluted in 0.5 ml DMSO, and stirred well up to the clear solution. The solutions were made up to 100 µl of sea water in a 100 ml standard flask. Each trial was carried using 10 µl of test solution with 10 numbers of freshly hatched nauplii. Test solutions were kept for 24 hrs and it was focused by a 25 Watts tungsten lamp at room temperature. After 24 hrs, numbers of live nauplii were counted and percentage of mortality was tabulated. The same test triplicated for each concentration. From the data, regression graph is plotted between logistic values of concentrations and percentages of mortality. The synthesized Schiff bases exposed considerable cytotoxic activity against Brine Shrimp nauplii, and lethal concentration for 50% mortality (LC$_{50}$) value of Schiff bases was calculated from the regression equations. DMSO was used as a negative control to validate the test method. Statistical evaluations were performed using Microsoft Excel, 2010.

RESULTS AND DISCUSSION
Synthesis and characterization
The designated compounds (1a-e) were synthesized by the addition of equimolar quantities of the hydroxyl group substituted five different aromatic aldehydes to L-phenylalanine in 2:1 methanol, water at reflux condition for 3 hrs according to Scheme 1. The reaction system was covered with silver foil to avoid the amino acid oxidation, the impurity formation and to get Schiff bases with high purity. Water is used as a solvent to dissolve the unreacted amino acid. The Schiff bases 1a-1e were obtained in good yields (70-75%) with purity after crystallization.

The FTIR spectra of compounds 1a-e have shown strong and broad absorption bands in the range of 3400-2945 cm$^{-1}$ due to stretching vibration of the −OH group of the carboxylic acid and the phenolic groups. The characteristic peak of the −NH$_2$ primary amine stretching and the vibration disappeared in the IR spectrum, and these compounds displayed at 1620-1632 cm$^{-1}$ was due to the imine group (−CH=N−) stretching vibration. Proton NMR spectrum of 1a to 1e showed singlet chemical shift at 13.3 (Bushra et al., 2011.68 (Laila et al., 11.24 (Laila et al., 11.60 (Laila et al., 14.72 (Bushra et al.) ppm for carboxylic group and am the chemical shifts are in coincidence with the reported journal values. Imine group proton identified between 8.41 ppm and 7.97 ppm (Bushra et al., 14.72 (Bushra et al.). Similarly, carbon NMR showed the chemical shift at 172 ppm for carboxyl group and Imine, carbon showed carbon peak between 159 and 154 for 1a to 1e Schiff bases.

![Scheme 1: Preparation procedure of L-phenylalanine Schiff bases 1a-1e](image)

### Table 1: Molinspiration predicted QSAR properties of Schiff bases 1a-e

| Properties | 1a   | 1b   | 1c   | 1d   | 1e   |
|------------|------|------|------|------|------|
| TPSA$^a$   | 69.89| 79.12| 69.89| 69.89| 90.12|
| No atoms   | 20   | 22   | 20   | 20   | 21   |
| Molecular weight | 269.30 | 299.33 | 269.30 | 269.30 | 285.30 |
| Number of O, N atoms | 4     | 5     | 4     | 4     | 5     |
| nOHNH      | 2    | 2    | 2    | 2    | 3    |
| Number of violations | 0    | 0    | 0    | 0    | 0    |
| Number rotatable bonds | 5    | 6    | 5    | 5    | 5    |
| Volume     | 247.36| 272.91| 247.36| 247.36| 255.33|
| GPCR$^b$ ligand | −0.12 | −0.10 | −0.09 | −0.10 | −0.05 |
| Ion channel modulator | −0.09 | −0.12 | 0.04 | 0.03 | −0.08 |
| Kinase inhibitor | −0.44 | −0.37 | −0.40 | −0.42 | −0.35 |
| Nuclear receptor ligand | −0.13 | −0.18 | −0.08 | −0.07 | −0.01 |
| Protease inhibitor | −0.21 | −0.23 | −0.25 | −0.26 | −0.16 |
| Enzyme inhibitor | 0.13 | 0.06 | 0.16 | 0.16 | 0.15 |

$^a$Total polar surface area, $^b$Guanine nucleotide-binding protein-coupled receptor. QSAR: Quantitative structure-activity relationship.
Structures of the Schiff bases were characterized thoroughly and were carried for the preliminary QSAR properties prediction for drug-likeness. We reviewed widely about the molecule based tools such as molecular descriptors and QSAR tools. Initially, the molecules were virtually screened through Molinspiration online tool and the predicted values are shown in Table 1.

All the synthesized molecules were used for the partition coefficient prediction (clogP) using computational software such as Molinspiration, Molsoft, Chemsketch, Data-warrior, and pasilla Tomcat tools. The predicted clogP and drug likeness values are shown in Table 2, and the result demonstrated the substituent effect on the Schiff bases. Data-warrior result showed the same drug score (−0.9911) due to the standard 3000 molecules were referred for the prediction. However, molsoft showed different position effect because it used the maximum of 15,000 compounds for prediction. Similarly, clogP values are in decreasing order from 1a to 1e. When compare the drug score of the starting materials such as 2-hydroxy benzaldehyde (−1.81), 2-hydroxy 3-methoxy benzaldehyde (−1.68), 3-hydroxy benzaldehyde (−1.41), 4-hydroxy benzaldehyde (−1.44), 2, 4-dihydroxy benzaldehyde (−0.98), Schiff bases showed the enhanced drug score. Out of five compounds, 1e (−0.01) has shown higher and more resemblances to commercial drug. Our synthesized compounds were passed in pasilla tomcat drug-likeness test, and all the virtual screening tools were supported our Schiff bases.

Finally, computer aided, molecular docking was done for the Schiff bases and compared with standard antibiotics Amoxicillin and Gentamicin against cell division protein ZipA. It is observed that the Schiff bases showed more binding affinity than amoxicillin and shown in Table 3. New mechanism arrived from the docking study result that is molecules may also control the division of E. coli pathogen. The binding affinity of the chiral Schiff bases with the cell division protein are shown in Figs. 1 and 2.

All the synthesized Schiff bases are active against human disease causing pathogen E. coli at low concentrations and shown in Fig. 3. The serially diluted solutions and their inhibitions in mm are shown in Table 4. The result clearly showed that the antimicrobial character of the hydroxyl group substituted Schiff bases. Apart from the five Schiff bases, three Schiff bases 1c-e have shown the higher zone of inhibition than standard and the synthesized Schiff bases may have lower side effects than gentamicin due to the protected amine group. Schiff bases 1c-e showed the higher zone of inhibition for the various concentrations. 12.5 µg/ml concentrations of 1-e Schiff bases showed the zone of inhibition in the order of 8 mm, 5 mm, 13 mm, 13 mm and 15 mm, respectively, which is shown in Fig. 3. The MIC of Schiff bases are exist from 3.25 µg/ml to 5.25 µg/ml. 1e showed the higher zone of inhibition (25 mm) at low concentration (3.25 µg/ml).

After the preliminary trials against the pathogens, toxicity study has done on the Schiff bases by brine shrimp lethal assay method for the future study. Serially diluted solutions and their mortality percentages were calculated and shown in Table 5. It was correlated with the logarithmic values of concentrations by regression method. From the regression equation, LC50 was calculated for the Schiff bases and observed that the toxicity of the compounds decreased with increasing clogP values. 1c, 1d-e Schiff bases showed higher LC50 (Table 5) value due to lower clogP value. LC50 values of the Schiff bases 1a-e were displayed 58.73, 83.93,

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### Table 2: Chemsketch, molinspire, data warrior, molsoft, tomcat tools predicted clogP and drug score of 1a-e

| Serial number | Compound ID | c logP  |
|---------------|-------------|---------|
|               |             | Chemsketch | molinspiration |
| 1             | 1a          | 3.46±0.43  | 1.29          |
| 2             | 1b          | 3.24±0.41  | 0.90          |
| 3             | 1c          | 3.32±0.45  | 0.88          |
| 4             | 1d          | 3.28±0.44  | 0.85          |
| 5             | 1e          | 3.22±0.44  | 0.79          |

| Drug score/drug-Likeness |
|--------------------------|
| Data warrior | Molsoft | tomcat |
| -0.9911       | -0.57   | Drug   |
| -0.8817       | -0.39   | Drug   |
| -0.9911       | -0.43   | Drug   |
| -0.9911       | -0.48   | Drug   |
| -0.9911       | -0.01   | Drug   |

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Fig. 1: Three-dimensional (3D) molecule docking images of Schiff bases and standard against protein 1s1j. (a). 3D docking image of 1e, (b). 3D docking image of amoxicillin

Fig. 2: Three-dimensional (3D) CLC work bench docking images with target protein 1s1j. (a). 3D docking image of 1a, (b). 3D docking image of 1b, (c). 3D docking image of 1c, (d). 3D docking image of 1d, (e). 3D docking image of 1e, (f). 3D docking image of amoxicillin
Table 3: Mcule 1-click docking scores of 1a-e and antibiotics against cell division protein ZipA

| Serial Number | Substituent position in benzaldehyde (Shift base) | Docking scores in kcal/mol | Best score kcal/mol |
|---------------|-----------------------------------------------|---------------------------|--------------------|
|               |                                               | 1             | 2       | 3       | 4       |
| 1             | 2-hydroxyl (1a)                               | -6.4          | -6.1   | -5.8    | -5.6    | -6.4    |
| 2             | 2-hydroxy, 3-methoxy (1b)                     | -6.0          | -6.0   | -5.7    | -5.3    | -6.0    |
| 3             | 4-hydroxy (1c)                                | -6.4          | -6.3   | -5.8    | -5.4    | -6.4    |
| 4             | 3-hydroxy (1d)                                | -6.6          | -5.9   | -5.2    | -5.2    | -6.6    |
| 5             | 2, 4-hydroxy (1e)                             | -6.8          | -6.3   | -5.8    | -5.6    | -6.8    |
| 6             | Amoxicillin                                   | -5.8          | -5.7   | -5.4    | -5.4    | -5.8    |
| 7             | Gentamicin                                    | -5.1          | -4.8   | -4.8    | -4.3    | -5.1    |

Table 4: Diameter of inhibition zone (in mm)

|                  | Concentration (µg/ml) | 6.25 | 12.5 | 25   | MIC in µg/ml* |
|------------------|-----------------------|------|------|------|---------------|
| E. coli          |                       |      |      |      |               |
| 1a (mL)          | 5±0.2                 | 13±0.0 | 4.25±0.00 |
| 1b (mL)          | 3±0.1                 | 10±0.1 | 5.25±0.00 |
| 1c (mL)          | 8±0.1                 | 21±0.2 | 3.5±0.00  |
| 1d (mL)          | 8±0.2                 | 21±0.2 | 4.2±0.00  |
| 1e (mL)          | 10±0.0                | 25±0.1 | 3.25±0.2  |
| Control DMSO     |                       |      |      |      |               |
| Gentamicin (mM)  | 7±0.0                 | 12±0.0 | 15±0.1 |

*MIC: Minimum inhibitory concentration, DMSO: Dimethyl sulfoxide,
E. coli: Escherichia coli

Table 5: Brine shrimp lethal assay and LC₅₀

| Compound | Concentrations in µg/ml | LC₅₀ in µg/ml |
|----------|-------------------------|--------------|
| ID(%)    |                        | 10 | 50 | 100 | 200 | 250 |         |
| a of mortality |                  | 26.6 | 56.6 | 80 | 100 | 58.73 |
| b of mortality |                  | 33.33 | 46.66 | 70 | 86.66 | 83.93 |
| c of mortality |                  | 20 | 30 | 63.33 | 80 | 121.5 |
| d of mortality |                  | 20 | 30 | 63.33 | 80 | 121.5 |
| e of mortality |                  | 10 | 26.66 | 63.33 | 80 | 135.6 |

LC₅₀ : Lethal concentration for 50% mortality

This research further revealed that the anti-bacterial MIC of Schiff bases were in increasing order from 1e < 1c < 1d < 1a < 1b and almost coincident with docking score and drug score. LC₅₀ values are 1e < 1d < 1c < 1b < 1a are coincident with solubility partition coefficient slope, and all the Schiff bases are fulfilling Lipinski rules of five. From the results and discussion, di hydroxyl group substituted 1e Schiff base showed stable result against the urinary tract infection causing E. coli and low toxicity.

CONCLUSION

The chiral Schiff bases (1a-e) were synthesized from the nutritional reputed analgesic and anti-inflammatory supplement L-phenylalanine with hydroxyl group by the simple aqueous reaction. This research successfully completed the Q SAR, docking, antibacterial, and toxicity study for the Schiff bases. Furthermore, this research confirmed that, the three (1c-e) Schiff bases showed enhanced antibacterial activity, particularly against human urinary tract infections causing bacterial strain E. coli when compared with gentamicin drug. Q SAR parameters of our molecules satisfied with experimental results. Out of five Schiff bases, 1e showed excellent inhibition against the urinary tract infection causing E. coli, and further oral study will be carried for the efficacy in future.

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