Identification of Suitable Agents against Adenine Phosphoribosyl Transferase for the Management of Leishmaniasis: Synthesis, Characterization and Computational Studies

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Abstract: A leishmaniasis is a group of diseases attributable to protozoan parasites of the genus Leishmania. It is a potential disease mostly occurring in developing nations. Various quinoline substituted derivatives (11a-f, 12a-f, and 13a-f) were synthesized by refluxing amino quinolines with an equivalent number of different alkylaminoethyl chlorides and evaluated for their in vitro antileishmanial activity against promastigotes forms of Leishmania donovani by using MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] reduction assay. Compounds 11f (IC50 = 13.61μg/mL), 12f (IC50 = 11.92 μg/mL) and 13f (IC50 =10.41 μg/mL) have shown significant antileishmanial activity when compared with standard sitamaquine (IC50 = 10.09 μg/mL). Furthermore, the molecular docking analysis targeting adenine phosphoribosyltransferase of Leishmania donovani exhibits significant binding interactions. In silico, ADMET predictions revealed that these compounds, i.e., 11f, 12f, and 13f, demonstrated good absorption as well as solubility characteristics with good drug-likeness and drug score values compared to the standard drug.

Keywords: antileishmanial activity; Leishmania donovani; molecular docking study; ADMET properties; drug-likeness.

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1. Introduction

Leishmaniasis is among the most prevalent parasitic disease caused by unicellular flagellate intracellular protozoa. The biological classification of microbe indicates that it belongs to the genus Leishmania [1,2]. The disease mostly develops in deprived and developing nations. The Indian subcontinent and the African continent are most prone to the disease [3,4]. Leishmaniasis can be caused by more than 20 species of Leishmania. It may produce different clinical symptoms, which may vary from self-healing cutaneous ulcers to severe visceral diseases. The transmission mode may be from humans to humans, i.e., anthropicotic, or via a vector from an animal reservoir, i.e., zoonotic [5]. Depending upon the syndromes of leishmaniasis, it can be categorized as visceral leishmaniasis, cutaneous leishmaniasis, mucosal leishmaniasis, and post-kala-azar leishmaniasis [6]. Today approximately one billion people live in the endemic areas, and about 30,000 new cases of visceral leishmaniasis and more than a million cases of cutaneous leishmaniasis are reported annually [7,8]. All patients diagnosed with leishmaniasis must be treated properly, or the results may be fatal [9]. Figure 1 depicts the important drugs which are currently being used for curing leishmaniasis [10]. But due to the complexity of the causative organism, the treatment options for leishmaniasis need to be diversified [11].
Figure 1. Clinically employed drugs for the treatment of leishmaniasis. (1) Sodium stibogluconate, (2) Meglumine antimoniate, (3) Amphotericin B, (4) Miltefosine, (5) Paromomycin, (6) Pentamidine, (7) Sitamaquine.

Paromomycin is an antibiotic of the aminoglycoside category and is mostly a second-line drug for the treatment of leishmaniasis. It is commonly used for intestinal infections. It acts by inhibiting the synthesis of proteins by binding to 16S rRNA, causing the incorrect incorporation of amino acids in the nascent peptide chain [10, 12].

Pentavalent antimonials are the first-line remedies for treating leishmaniasis. The class includes drugs like sodium stibogluconate and meglumine antimoniate [13]. They primarily act by inhibiting the relaxation of the supercoiled plasmid pBR322 catalyzed by DNA topoisomerase of the microbe and also induce changes in the parasite cell membrane [14].

Amphotericin B isolated from Streptomyces nodosus has replaced pentavalent antimonials as the first-line drugs for treating leishmaniasis as they have about ~97% cure rate [15]. The polyene antibiotic of this class, i.e., Liposomal Amb is the most effective that attacks the cell wall of the parasite, causing the leakage of metabolites from the parasite cell, thus causing the death of the parasite [16,17].

Miltefosine is the only drug that is taken orally to treat leishmaniasis. It hinders the synthesis of phosphatidylcholine and also affects the mitochondria of the parasite. It is also observed that it disrupts intracellular Ca²⁺ homeostasis [18]. The current treatment options for leishmaniasis have great success rates (like Amphotericin B ~97%), but still, there are some problems with their usage. Amphotericin B presents many side effects like hypokalemia, immediate shocks upon infusion, which necessitates the close monitoring of the patient [19]. Pentavalent antimonials are still useful but are potentially toxic, and moreover, it requires...
painful injections for 20 days, which is also the case for Paromomycin whereas Miltefosine, shows the problem of being teratogenic [20]. Therefore, the buildout of unprecedented, innocuous, and inexpensive compounds having effective leishmanicidal activity is urgently desired.

Quinoline ring scaffold, which is considered to have efficacy against the *Leishmania* species, is one of the widely used literature frameworks for synthesizing novel derivatives with promising antiparasitic activity [21-28]. So, in the current line of work, we hereby proclaim the synthesis and characterization of 3, 6, and 8-aminoquinoline derivatives as anti-leishmanial agents. Docking analysis of the various synthetic derivatives has been conducted to assess the best in silico confirmation, and amid them, the compounds having comparable binding affinity are further ascertained for antileishmanial activity against *Leishmania donovani*.

2. Materials and Methods

2.1. General procedure for the synthesis of target molecules.

2.1.1. Synthesis of substituted N-quinoline amine derivatives.

Substituted 3, 6, or 8-amino quinolines derivatives were prepared by refluxing 3, 6, or 8-amino quinolines, i.e., (8), (9), or (10) with an equivalent amount of hydrochlorides of various alkylaminoethyl chlorides such as 4-(2-chloroethyl)-morpholine, 1-(2-chloroethyl)-piperidine, 2-chloro-N,N-dimethyl ethanamine, 1-(2-chloroethyl)-pyrrolidine, 2-chloro-N,N-dimethyl ethanamine, and 2-(2-chloroethyl)-isoindoline-1,3-dione in the presence of potassium carbonate at 80°C for 4-6 h using ethyl methyl ketone as a solvent. The formation of various compounds was confirmed by various physicochemical properties and spectral analysis (Scheme 1).

![Scheme 1. Synthesis of various substituted quinoline derivatives, i.e., 11a-f, 12a-f, and 13a-f.](https://biointerfaceresearch.com/)

| 8 | R₁ = NH₂; R₂ = R₃ = H |
|---|----------------------|
| 9 | R₁ = R₃ = H; R₂ = NH₂ |
| 10| R₁ = R₂ = H; R₃ = NH₂ |
2.2. Biological evaluation.

For preparing the stock solutions, i.e., (10 mg/mL) of the synthetic quinoline derivatives, about 10mg of the sample compounds is dissolved in 1ml of DMSO. To get required dilutions varying from 2.5 μg/mL to 100 μg/mL each stock solution was further diluted with Roswell Park Memorial Institute (RPMI) complete media. The influence of tested molecules upon the survivability of promastigote form of Leishmania donovani has been estimated by measuring the metabolism of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide] following an incubation period of 96 h. Cells were inoculated at 1 × 106 /100 μL RPMI-1640 in each cavity of 96-well flat-bottom microtiter plates. Further to accomplish preferred concentrations, 100 μL of media per well with different concentrations of synthesized compounds (2.5 μg/ml to 100 μg/ml) or standard drug (2.5 μg/ml to 50 μg/ml), dissolved in DMSO [29,30] were added in triplicate. The plates were incubated at 37 °C for a period of 72 h before the addition of MTT (10 μL per well of a 5 mg mL–1 PBS stock), and then plates were incubated additionally for 4–5 hours in CO2 incubator. MTT processing was stopped and formazan crystals solubilized by adding 50 μL of DMSO per well and incubated overnight at 37 °C. The relative amount of formazan per well produced by viable cells was measured photometrically at 590 nm. The experiments were performed in triplicate for the determination of the sensitivity of each compound.

2.3. Computational studies.

2.3.1. Molecular docking.

The molecular docking procedure was used to predict the binding interactions between the quinoline derivatives and the binding pocket of the enzyme adenine phosphoribosyltransferase from Leishmania donovani for further pharmacological evaluation. Binding energy(kcal mol–1) is the significant key parameter generated as an outcome of molecular docking, indicating the affinity and intensity of the interaction among the ligand and the receptor. The binding energy and intensity of interaction are reciprocal to each other, i.e., and the more is the binding energy, the less will be the intensity of the interaction and vice versa. Therefore, during docking studies, the ligand which displays the minimal binding energy is considered ideally suited for further evaluation.

2.3.2. Preparation of target for docking analysis.

The 3D crystal structure of the adenine phosphoribosyltransferase from Leishmania donovani [31] (PDB ID: 1QCD with a resolution of 2.48Å) was retrieved from the protein databank. After retrieving the structure, all the water and ions molecules were relinquished, and the hydrogen atoms were added to the protein by the protonation using the DS visualizer (version v20.1.0.19295) software [32]. The active site was determined using the site sphere method of Discovery visualizer. Energy minimization of protein was performed with DS using CHARMm(Chemistry at Harvard Macromolecular Mechanics) and MMFF94 (Merck molecular) force field.

2.3.3. 3D Structure validation.

To check the structural integrity, i.e., the stereochemical quality of the 3D model of protein 1QCD, PROCHECK [33,34], a program that relies on Ramachandran plots for structure verification, was used (Figure 2). Ramachandran Plot of the prepared protein represents 89.1%
(172 amino acids) of the total residues in the most favored region and 10.7% (21 amino acids) in the additionally allowed region, indicating a good quality model for study.

**Ramachandran Plot**

**Figure 2.** Stereochemical analysis of 1QCD. The red region declares the most favorable area of residues; the yellow region is additionally allowed.

### 2.3.4. Preparation of ligand for docking analysis.

Each ligand structure was built by Chem3D pro version 12.0.2.1076 and optimized using MMFF94 force field and employing conjugate gradients optimization algorithm with around 200 number of steps in PYRX software. After energy minimizations, ligands are converted into PDBQT format using Open Bable GUI software embedded in PYRX [35].

### 2.3.5. Docking methodology and analysis

Computational docking is performed to get various probable conformations and orientations of the ligands with the binding site. The grid center for docking was set X= 28.9567, Y= 28.6635, and Z= 7.588 for 1QCD. After this, virtual screening was carried by rigid molecular docking into the active site of the protein. Throughout the virtual screening, the ligand molecules were flexible, and the macromolecule was kept rigid. Finally, the result of binding energy was extracted from the software.

### 2.4. Drug-likeness and ADMET evaluation

Inadequate pharmacokinetic and toxicity studies lead to failure of the drug development process in the final stages.

Therefore, in order to escalate the drug discovery process, primary assessment of pharmacokinetics and toxicity studies is the mandate step [36-38].

#### 2.4.1. Drug-likeness

Drug-likeness is an important aspect in drug development for the screening of drug molecules promptly. This parameter is being used as a process to correlate the physicochemical aspect of a drug molecule with its biopharmaceutical aspect in the human body, particularly its impact on bioavailability in the oral route [39]. Therefore, all the synthetic derivatives were assessed for their drug-like nature under Lipinski’s rules of five by employing DruLiTo software [40]. As per Lipinski’s rule, the Log P of "drug-like" molecules should be less than 5,
molecular weight (M.W.) below 500, Total polar surface area under 140 and number of hydrogen bond acceptors (HBA), as well as the number of hydrogen bond donors (HBD) below 10 and 5 respectively [41].

2.4.2. ADMET analysis.

To assess different pharmacokinetic properties like absorption, distribution, metabolism, excretion, and toxicity of synthetic compounds within the human body ADMETlab web platform was used [42]. The ADMETlab envisaged the Human Intestinal Absorption (HIA+ or HIA-), Blood-Brain Barrier Penetration (BBB+ or BBB-), Caco-2 Permeability (permeable or non-permeable), Human Hepatotoxicity (H-HT), Solubility, i.e., LogS value, and Acute toxicity (LD50).

3. Results

3.1. Spectral data.

\[ \text{N-}(2-(\text{Piperidine-1-yl)-ethyl-quinoline-3-amine (11a)}) \]

Yield: 31%, m.p: 118-121 °C, FT-IR (KBr, cm\(^{-1}\)) 1105 (C-N), 1450 (C=C), 1671 (C=N), 3609 (-NH), \(^1\)H-NMR (DMSO-d6): \(\delta\) 1.82 (m, 6H, (-CH\(_2\)_2), piperidine), 2.70 (t, 4H, (-NCH\(_2\)_2)), 2.65 (t, 2H, -CH\(_2\)_2), 3.30 (m, 2H, -CH\(_2\)_2), 4.80 (t, 1H, -NH), 7.15 (s, 1H, CH, Ar), 7.63 (m, 2H, -CH, Ar) 7.83 (d, 2H, CH, Ar) and 8.23 (s, 1H, CH, Ar) ppm. Elemental analysis (C\(_{16}\)H\(_{21}\)N\(_3\)); Calcd. C, 75.26; H, 8.29; N, 16.46; found: C, 74.95; H, 7.70; N, 15.47.

\[ \text{N-}(2-(\text{Dimethylamino)-ethyl-quinoline-3-amine (11b)}) \]

Yield: 42%, m.p: 129-132 °C, FT-IR (KBr, cm\(^{-1}\)) 1133 (C-N), 1341 (C-H), 1516 (C=C), 1633 (C=N), 1783 (C-H, ring), 3340 (NH). \(^1\)H-NMR (DMSO-d6): \(\delta\) 2.32 (s, 6H, (-N(CH\(_3\)_2)), 2.73 (t, 2H, -CH\(_2\)_2), 3.30 (m, 1H, -CH\(_2\)-N), 4.28 (t, 1H, -NH), 7.44 (s, 1H, CH, Ar), 7.62 (m, 2H, -CH, Ar), 7.83 (d, 1H, CH, Ar) ppm. Elemental analysis (C\(_{13}\)H\(_{17}\)N\(_3\)); Calcd. C, 72.52; H, 7.96; N, 19.52; found: C, 72.23; H, 7.40; N, 18.34.

\[ \text{N-}(2-\text{Morpholinoethyl)-quinoline-3-amine (11c)}) \]

Yield: 33%, m.p: 124-127 °C, FT-IR (KBr, cm\(^{-1}\)) 1089 (C-O), 1271 (C-N), 1595 (C=C), 1670 (C=N), 3661 (-NH). \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 2.16 (t, 4H, (-NCH\(_2\)_2), morpholine), 2.05 (t, 2H, -CH\(_2\)_2), 2.62 (m, 2H, -CH\(_2\)_2), 3.63 (t, 4H, (-OCH\(_2\)_2), morpholine), 4.18 (t, 1H, -NH), 7.05 (s, 1H, CH, Ar), 7.53 (m, 2H, -CH, Ar) ppm. Elemental analysis (C\(_{15}\)H\(_{19}\)N\(_3\)); Calcd. C, 70.01; H, 7.44; N, 16.33; found: C, 69.73; H, 6.91; N, 15.35.

\[ \text{N-}(2-(\text{Pyrrolidine-1-yl)-ethyl-quinoline-3-amine (11d)}) \]

Yield: 39%, m.p: 116-119 °C, FT-IR (KBr, cm\(^{-1}\)) 1191 (C-N), 1474 (C-H), 1520 (C=C), 1684 (C=N), 1789 (C-H), 3298 (N-H). \(^1\)H-NMR (DMSO-d6): \(\delta\) 1.72 (m, 4H, (-CH\(_2\)_2), pyrrolidine), 2.75 (t, 2H, -CH\(_2\)_2), 2.97 (t, 4H, (-NCH\(_2\)_2), pyrrolidine), 3.31 (m, 2H, -CH\(_2\)_2), 4.23 (t, 1H, -NH), 7.21 (s, 1H, CH, Ar), 7.57 (m, 2H, -CH, Ar), 8.27 (s, 1H, CH, Ar) ppm. Elemental analysis (C\(_{15}\)H\(_{19}\)N\(_3\)); Calcd. C, 74.65; H, 7.94; N, 17.41; found: C, 74.35; H, 7.38; N, 16.36.

\[ \text{N-}(2-(\text{Diethylamino)-ethyl-quinoline-3-amine (11e)}) \]

Yield: 44%, m.p: 138-139 °C, FT-IR (KBr, cm\(^{-1}\)) 1130 (C-N), 1450 (C-H), 1570 (C=C), 1620 (C=N), 1789 (C-H), 3293 (NH). \(^1\)H-NMR (DMSO-d6): \(\delta\) 1.45 (t, 6H, (-CH\(_3\)_2)), 2.67 (m, 4H, (-CH\(_2\)_2), 2.83 (t, 2H, -CH\(_2\)_2), 3.37 (m, 2H, -CH\(_2\)_2), 4.70 (t, 1H, -NH), 7.50 (s, 1H, CH, Ar), 7.63 (m, 2H, -CH, Ar), 7.85 (d, 1H, CH, Ar) ppm. Elemental analysis (C\(_{15}\)H\(_{19}\)N\(_3\)); Calcd. C, 74.65; H, 7.94; N, 17.41; found: C, 74.35; H, 7.38; N, 16.36.
ppm. Elemental analysis (C_{15}H_{21}N_{3}); Calcd. C, 74.03; H, 8.70; N, 17.27; found: C, 73.73; H, 8.09; N, 16.23.

2-(2-(Quinolin-3-ylamino)-ethyl)-isoindoline-1,3-dione (11f)

Yield: 38%, m.p: 129-132 °C, FT-IR (KBr, cm\(^{-1}\)): 1142 (C-N), 1478 (C-H), 1514 (C=C), 1684 (C=O), 1927(C-H), 3328 (N-H). \(^1\)H-NMR (CDCl\(_3\)): \(\delta\) 2.86 (t, 2H, -CH\(_2\)-), 3.60 (m, 1H, -CH\(_2\)-), 5.1 (t, 1H, -NH), 7.57 (s, 1H, CH, Ar). 7.69 (m, 2H, -CH, Ar), 7.89 (d, 1H, CH, Ar), 7.94 (m, 4H, CH, phthalimide), 8.15 (d, 1H, CH, Ar), 8.25 (s, 1H, CH, Ar) and 7.86 (m, 4H, CH, phthalimide) ppm. Elemental analysis (C\(_{19}\)H\(_{15}\)N\(_3\)); Calcd. C, 71.91; H, 4.76; N, 13.24; found: C, 71.62; H, 4.42; N, 12.44.

\(N\)-(2-(Piperidine-1-yl)-ethyl)-quinoline-6-amine (12a)

Yield: 37%, m.p: 158-161 °C, FT-IR (KBr, cm\(^{-1}\)): 1109 (C-N), 1436 (CH), 1619 (C=C), 1745 (C=N), 3656 (N-H). \(^1\)H-NMR (DMSO-\(d_6\)): \(\delta\) 1.71 (m, 6H, -(CH\(_2\))\(_2\)), 4.24 (t, 4H, -(NCH\(_2\))\(_2\)), 2.66 (t, 2H, -CH\(_2\)-), 3.32 (m, 2H, -CH\(_2\)-), 4.14 (t, 1H, -NH), 7.23 (d, 1H, CH, Ar), 7.45 (t, 1H, CH, Ar), 7.50 (s, 1H, CH, Ar), 8.10 (d, 2H, CH, Ar) and 8.73 (d, 1H, CH, Ar) ppm. Elemental analysis (C\(_{16}\)H\(_{21}\)N\(_3\)); Calcd. C, 75.26; H, 8.29; N, 16.46; found: C, 75.00; H, 7.79; N, 15.63.

\(N\)-(2-(Dimethylamino)-ethyl)-quinoline-6-amine (12b)

Yield: 40%, m.p: 154-157 °C, FT-IR (KBr, cm\(^{-1}\)): 1214 (C-N), 1462 (CH), 1575 (C=C), 1642 (C=N), 3309 (N-H). \(^1\)H-NMR (DMSO-\(d_6\)): \(\delta\) 2.28 (s, 6H, -(CH\(_2\))\(_2\)), 2.71 (t, 2H, -CH\(_2\)-), 3.29 (m, 2H, -CH\(_2\)-), 4.51 (t, 1H, -NH), 7.23 (d, 1H, CH, Ar), 7.39 (t, 1H, CH, Ar), 7.57 (s, 1H, -CH, Ar), 8.14 (d, 2H, CH, Ar) and 8.69 (d, 1H, CH, Ar) ppm. Elemental analysis (C\(_{13}\)H\(_{17}\)N\(_3\)); Calcd. C, 72.52; H, 7.96; N, 19.52; found: C, 72.30; H, 7.48; N, 18.54.

\(N\)-(2-(Morpholinoethyl)-quinoline-6-amine (12c)

Yield: 39%, m.p: 163-166 °C, FT-IR (KBr, cm\(^{-1}\)): 1022 (C-O), 1100 (C-N), 1471 (C=C), 1594 (C=N), 3697 (N-H). \(^1\)H-NMR (CDCl\(_3\)): \(\delta\) 2.47 (t, 4H, -(NCH\(_2\))\(_2\), morpholine), 2.66 (t, 2H, -CH\(_2\)-), 3.37 (m, 2H, -CH\(_2\)-), 3.59 (t, 4H, -(OCH\(_2\))\(_2\), morpholine), 4.80 (t, 1H, -NH), 7.24 (d, 1H, CH, Ar), 7.43 (t, 1H, CH, Ar), 7.48 (s, 1H, -CH, Ar), 8.11 (d, 2H, CH, Ar) and 8.68 (d, 1H, CH, Ar) ppm. Elemental analysis (C\(_{15}\)H\(_{19}\)N\(_3\)); Calcd. C, 70.01; H, 7.44; N, 16.33; found: C, 69.79; H, 6.99; N, 15.51.

\(N\)-(2-(Pyrrolidin-1-yl)-ethyl)-quinoline-6-amine (12d)

Yield: 44%, m.p: 144-147 °C, FT-IR (KBr, cm\(^{-1}\)): 1058 (C-N), 1257 (C-N), 1530 (C-H), 1637 (C=C), 1664 (C=N), 1775 (C-H). \(^1\)H-NMR (DMSO-\(d_6\)): \(\delta\) 1.14 (m, 4H, -(CH\(_2\))\(_2\), pyrrolidine), 1.23 (t, 2H, -CH\(_2\)-), 1.89 (t, 4H, -(NCH\(_2\))\(_2\), pyrrolidine), 2.39 (m, 2H, -CH\(_2\)-), 3.50 (t, 1H, -NH), 7.22 (d, 1H, CH, Ar), 7.42 (t, 1H, CH, Ar), 7.59 (s, 1H, -CH, Ar), 8.12 (d, 2H, CH, Ar) and 8.71 (d, 1H, CH, Ar) ppm. Elemental analysis (C\(_{15}\)H\(_{19}\)N\(_3\)); Calcd. C, 74.65; H, 7.94; N, 17.41; found: C, 74.42; H, 7.46; N, 16.53.

\(N\)-(2-(Diethylamino)-ethyl)-quinoline-6-amine (12e)

Yield: 47%, m.p: 168-171 °C, FT-IR (KBr, cm\(^{-1}\)): 1050 (C-N), 1150 (C-N), 1380 (C-N), 1480 (C-H), 1575 (C=N), 1660 (C=C), 3280 (N-H). \(^1\)H-NMR (DMSO-\(d_6\)): \(\delta\) 1.18 (t, 6H, -(CH\(_3\))\(_2\)), 2.36 (m, 4H, (NCH\(_2\))\(_2\)), 2.72 (t, 2H, -CH\(_2\)-), 3.31 (m, 2H, -CH\(_2\)-), 3.0 (t, 1H, -NH), 7.25 (d, 1H, CH, Ar), 7.37 (t, 1H, CH, Ar), 7.52 (s, 1H, -CH, Ar), 8.13 (d, 2H, CH, Ar) and 8.73 (d, 1H, CH, Ar) ppm. Elemental analysis (C\(_{15}\)H\(_{21}\)N\(_3\)); Calcd. C, 74.03; H, 8.70; N, 17.27; found: C, 73.80; H, 8.17; N, 16.40.

2-(2-(Quinolin-6-ylamino)-ethyl)-isoindoline-1,3-dione (12f)

Yield: 43%, m.p: 162-165 °C, FT-IR (KBr, cm\(^{-1}\)): 1157 (C-N), 1468 (C-H), 1606 (C=C), 1673 (C=N), 1738 (C=O). \(^1\)H-NMR (CDCl\(_3\)): \(\delta\) 3.88 (m, 2H, -CH\(_2\)-), 3.88 (t, 2H, -CH\(_2\)-), 4.90 (t, 1H, -NH), 7.25 (d, 1H, CH, Ar), 7.44 (t, 1H, CH, Ar), 7.56 (s, 1H, -CH, Ar), 8.14 (d, 2H, -CH, Ar), ppm. Elemental analysis (C\(_{19}\)H\(_{13}\)N\(_3\)); Calcd. C, 74.03; H, 8.70; N, 17.27; found: C, 73.80; H, 8.17; N, 16.40.
CH, Ar), 8.76 (d, 1H, CH, Ar) and 7.86 (m, 4H, CH, phthalimide) ppm. Elemental analysis (C₁₉H₁₅N₃); Calcd. C, 71.91; H, 4.76; N, 13.24; found: C, 71.69; H, 4.47; N, 12.57.

\textbf{N-(2-(Piperidine-1-yl)-ethyl)-quinoline-8-amine (15a)}

Yield: 39\%, m.p: 108-111 °C, FT-IR (KBr, cm⁻¹): 1140 (C-N), 1487 (-CH), 1520 (C=C), 1634 (C=N), 3601 (-NH-). \textsuperscript{1}H-NMR (DMSO-d₆): δ 1.69 (m, 6H, (-CH₂)₂), 2.46 (t, 4H, (-NCH₂)₂), 2.67 (t, 2H, -CH₂), 3.39 (m, 2H, -CH₂), 4.33 (t, 1H, -NH), 7.29 (d, 1H, CH, Ar), 7.50 (m, 2H, CH, Ar) and 8.27 (m, 3H, CH, Ar) ppm. Elemental analysis (C₁₆H₂₁N₃); Calcd. C, 75.26; H, 8.29; N, 16.46; found: C, 75.10; H, 7.87; N, 15.80.

\textbf{N-(2-(Dimethylamino)-ethyl)-quinoline-8-amine (13b)}

Yield: 37\%, m.p: 119-122 °C, FT-IR (KBr, cm⁻¹): 1214 (C-N), 1462 (CH), 1522 (C=C), 1730 (C=N), 3369 (-NH-). \textsuperscript{1}H-NMR (DMSO-d₆): δ 2.27 (s, 6H, (-CH₃)₂), 2.72 (t, 2H, -CH₂), 3.35 (t, 2H, -CH₂), 4.37 (t, 1H, -NH), 7.52 (m, 4H, CH, Ar) and 8.23 (d, 2H, CH, Ar) ppm. Elemental analysis (C₁₃H₁₇N₃); Calcd. C, 72.52; H, 7.96; N, 19.52; found: C, 72.37; H, 7.56; N, 18.73.

\textbf{N-(2-Morpholinoethyl)-quinoline-8-amine (13c)}

Yield: 41\%, m.p: 113-116 °C, FT-IR (KBr, cm⁻¹): 1083 (C-O), 1122 (C-N), 1451 (CH₂), 1570 (C=C), 1676 (C-N). \textsuperscript{1}H-NMR (CDCl₃): δ 2.48 (t, 4H, (-NCH₂)₂, morpholine), 2.69 (t, 2H, -CH₂), 3.38 (m, 2H, -CH₂), 3.62 (t, 4H, (-OCH₂)₂, morpholine), 4.80 (t, 1H, -NH), 7.28 (d, 1H, CH, Ar), 7.44 (t, 1H, CH, Ar), 7.47 (t, 1H, CH, Ar), 7.85 (d, 2H, CH, Ar) and 8.74 (d, 1H, CH, Ar) ppm. Elemental analysis (C₁₃H₁₉N₃); Calcd. C, 70.01; H, 7.44; N, 16.33; found: C, 69.87; H, 7.06; N, 15.67.

\textbf{N-(2-(Pyrrolidine-1-yl)-ethyl)-quinoline-8-amine (13d)}

Yield: 43\%, m.p: 106-109 °C, FT-IR (KBr, cm⁻¹): 1463 (C-H), 1570 (C=C), 1665 (C-N), 1960 (C-H). \textsuperscript{1}H-NMR (DMSO-d₆): δ 1.83 (m, 4H, (-CH₂)₂, pyrrolidine), 2.67 (t, 2H, -CH₂), 2.82 (t, 4H, (-NCH₂)₂, pyrrolidine), 3.41 (m, 2H, -CH₂), 3.25 (t, 1H, -NH), 7.43 (m, 5H, -CH, Ar) and 8.19 (d, 1H, CH, Ar) ppm. Elemental analysis (C₁₅H₁₉N₃); Calcd. C, 74.65; H, 7.94; N, 17.41; found: C, 74.5; H, 7.54; N, 16.71.

\textbf{N-(2-(Diethylamino)-ethyl)-quinoline-8-amine (13e)}

Yield: 48\%, m.p: 123-126 °C, FT-IR (KBr, cm⁻¹): 1212 (C-N), 1478 (C-H), 1605 (C=C), 1670 (C=N), 1768 (C-H). \textsuperscript{1}H-NMR (DMSO-d₆): δ 1.12 (t, 6H, (-CH₃)₂), 3.45 (t, 1H, -NH), 2.57 (m, 4H, (-NCH₂)₂), 2.69 (t, 2H, -CH₂), 3.32 (m, 2H, -CH₂), 7.40 (m, 5H, -CH, Ar) and 8.72 (d, 1H, CH, Ar) ppm. Elemental analysis (C₁₅H₂₁N₃); Calcd. C, 74.03; H, 8.70; N, 17.27; found: C, 73.88; H, 8.26; N, 16.57.

\textbf{2-(2-(Quinolin-8-ylamino)-ethyl)-isoindoline-1,3-dione (13f)}

Yield: 54\%, m.p: 116-119 °C, FT-IR (KBr, cm⁻¹): 1172 (C-N), 1442 (C-H), 1580 (C=C), 1658 (C=N). \textsuperscript{1}H-NMR (CDCl₃): δ 3.57 (m, 2H, -CH₂), 3.90 (t, 2H, -CH₂), 4.41(t, 1H, -NH), 7.25 (d, 1H, CH, Ar), 7.46 (m, 2H, -CH, Ar), 7.69 (d, 1H, CH, Ar), 7.88 (m, 4H, CH, phthalimide) and 8.57 (d, 2H, CH, Ar) ppm. Elemental analysis (C₁₉H₁₅N₃); Calcd. C, 71.91; H, 4.76; N, 13.24; found: C, 71.76; H, 4.52; N, 12.71.

\textit{3.2. Biological activity.}

Resistance of different strains of Leishmania species to conventional antileishmanial treatment has emerged as one of the world's most pressing issues. Thus, the development of new heterocyclic compounds having substantial biological and medicinal importance is a key objective of our study. Accordingly, various synthesized derivatives were screened for their in-vitro antileishmanial activity against the promastigote form of \textit{Leishmania donovani}. The
inhibitory concentration that reduces the parasitic growth by 50% (IC50), as listed in Table 1,
was calculated by projecting percentage inhibition against the concentration of drug-using
statistical analysis and the parasite inhibition curve of compounds (11a-f, 12a-f, and 13a-13f),
and sitamaquine is shown in Figure 3.

Table 1. IC50 of newly synthesized quinoline-based compounds.

| S. No. | Compound No. | IC50 (µg/mL) |
|--------|--------------|--------------|
| 1.     | 11a          | 17.73        |
| 2.     | 11b          | 30.94        |
| 3.     | 11c          | 18.83        |
| 4.     | 11d          | 21.06        |
| 5.     | 11e          | 39.71        |
| 6.     | 11f          | 13.61        |
| 7.     | 12a          | 23.08        |
| 8.     | 12b          | 35.79        |
| 9.     | 12c          | 21.70        |
| 10.    | 12d          | 23.52        |
| 11.    | 12e          | 40.76        |
| 12.    | 12f          | 11.92        |
| 13.    | 13a          | 17.47        |
| 14.    | 13b          | 26.44        |
| 15.    | 13c          | 17.87        |
| 16.    | 13d          | 23.23        |
| 17.    | 13e          | 30.55        |
| 18.    | 13f          | 10.41        |
| 19.    | Sitamaquine  | 10.09        |

The results of antileishmanial activity elucidated that most of the derivatives
demonstrated good activity against promastigote form of *Leishmania donovani* with IC50 value
ranging from 10.41 to 40.76 µg/ml as compared to standard sitamaquine with IC50 value of
10.09 µg/ml.
Figure 3. The parasite inhibition curve of compounds 11a-f, 12a-f, and 13a-f.

Amid the synthetic derivatives, the compounds 11f, 12f and 13f displayed comparable activity to standard with IC$_{50}$ values of 13.61, 11.92, 10.41, whereas compounds 11a, 11c, 13a, and 13c exhibit moderate activity with IC$_{50}$ values of 17.73, 18.83, 17.47, and 17.87. On the other hand, the rest of the compounds exhibit inferior activity as compared to the standard.
3.3. Molecular docking.

The molecular docking procedure was used to predict the binding interactions between the quinoline derivatives and the binding pocket of the enzyme adenine phosphoribosyltransferase from *Leishmania donovani* for further pharmacological evaluation. Binding energy (kcal/mol) is the significant key parameter of molecular docking that indicates the affinity and intensity of the interaction between the ligand and the receptor. The binding energy and intensity of interaction are reciprocal to each other, i.e., the more is the binding energy, the less will be the intensity of the interaction and vice versa. Therefore, during docking studies, the ligand that displays the minimal binding energy is considered ideally suited for further evaluation.

All the docked conformations were analyzed, and the best-scored pose for each compound was selected for further interaction studies. The docking scores of various compounds are given in Table 2.

| S.No. | Compound Name | Docking Score (kcal/mol) | Probable interacting Residues |
|-------|---------------|--------------------------|-------------------------------|
| 1.    | 11a           | -6.6                     | Ser157, Leu156, Met129, Glu127, Pro126, Pro116 |
| 2.    | 11b           | -6.0                     | Leu156, Glu127, Pro126        |
| 3.    | 11c           | -6.6                     | Ser157, Leu156, Pro126        |
| 4.    | 11d           | -6.5                     | Ser157, Leu156, Met129, Glu127, Pro126, Phe79 |
| 5.    | 11e           | -5.8                     | Ser157, Leu156, Ala155, Leu149, Glu127, Pro126, Pro116, Phe79 |
| 6.    | 11f           | -7.2                     | Ile187, Ala183, Ser157, Ala155, Leu156, Pro126 |
| 7.    | 12a           | -6.4                     | Lys186, Leu156, Pro126, Glu120, Glu118, Pro116 |
| 8.    | 12b           | -5.9                     | Ser157, Leu156, Glu127, Pro126 |
| 9.    | 12c           | -6.5                     | Ser157, Leu156, Glu127, Pro126, Asp80 |
| 10.   | 12d           | -6.4                     | Ser157, Leu156, Met129, Glu127, Pro126, Phe79 |
| 11.   | 12e           | -5.8                     | Ile187, Lys186, Ala183, Ser157, Leu156, Pro126 |
| 12.   | 12f           | -7.6                     | Ser157, Leu156, Ala155, Asp146, Glu127, Pro126, Asp80, Phe79 |
| 13.   | 13a           | -6.6                     | Ile187, Ala183, Leu156, Ala155, Pro126, Pro116 |
| 14.   | 13b           | -6.2                     | Ser157, Leu156, Glu127, Pro126, Pro116 |
| 15.   | 13c           | -6.6                     | Ser157, Leu156, Pro126, Pro116, Asp80 |
| 16.   | 13d           | -6.4                     | Ser157, Leu156, Met129, Glu127, Pro126, Pro116, Phe79 |
| 17.   | 13e           | -6.0                     | Ala183, Leu156, Pro126        |
| 18.   | 13f           | -7.4                     | Lys186, Ala183, Leu156, Pro126, Glu120, Tyr117 |
| 19.   | Sitamaquine   | -6.9                     | Ser157, Leu156, Pro126, Tyr117, Pro116 |

The outcome of the docking results showed that all the compounds were well acclimatized in the active site of the Leishmania enzyme. Among the various quinolone derivatives, the compound 12f was found to be the most active with a docking score of -7.6 followed by other compounds such as 13f and 11f with docking scores of -7.4 and -7.2, respectively. From the docking conformations of most potent compounds among series, the docking pose of 12f shows three hydrogen bond interactions with Asp80, Ala155, and Leu156 amino acid residues of the target. Among these, Asp80 exhibits conventional hydrogen bonding with the nitrogen of the quinoline ring, whereas the other two form hydrogen bonding with the doubly bonded oxygen atom of the phthalimide ring. The carbon atom of the alkyl chain connecting the quinoline ring with phthalimide moiety exhibit carbon-hydrogen bonding with Glu127 and Ser157. The cyclic ring of quinoline moiety shows Pi anion with Phe79 and pi-pi stacked interactions with Glu127 and Asp146, respectively. The five-membered rings of phthalimide display pi-alkyl interactions with Leu156, whereas six-membered rings of
phthalimide moiety exhibit pi-sigma and pi-alkyl interactions with Leu156 and Pro126, respectively.

The docking pose of the second-highest compound, i.e., 13f from the series, displays two hydrogen bonding with Tyr117 and Glu120. The nitrogen-containing ring of quinoline moiety exhibited alkyl linkage with Leu156 and Lys186, whereas the other ring of quinoline exhibits pi-alkyl and alkyl linkage with Leu156 and Lys186, respectively. The phthalimide moiety similarly displays alkyl linkage with Pro126 and Leu156.

The docking pose of 11f manifests three hydrogen bond interactions with Ala155, Leu156, and Ser157 amino acid residues of the target. Ser157 among these forms’ conventional hydrogen bonding with the nitrogen of quinoline moiety whereas other two form hydrogen bonding with the doubly bonded oxygen atom of phthalimide ring. The cyclic ring of quinoline moiety forms a pi-alkyl linkage with Pro126 and Leu156. The six-membered rings of phthalimide form pi-alkyl linkage with Ala183, Lys186, and Ile187, whereas five-membered heterocyclic rings reveal alkyl linkage with Alkyl Ala155 and Ile187.

The docking conformation of standard drug sitamaquine exhibits conventional hydrogen bonding as well as alkyl/pi-alkyl interactions with the various active residues of the target molecule. The nitrogen of substituted secondary amine moiety of sitamaquine exhibit hydrogen bonding with the Tyr117, where other residue Ser157 showed hydrogen bonding with the substituted oxygen moiety available at sixth carbon of quinoline ring. Other residues such as Pro116, Pro126, and Leu156 displayed alkyl interactions with the sitamaquine. Among these, Leu156 exhibits alkyl interactions with the quinoline ring and alkyl chain of the ligand, whereas Pro116 and Pro126 exhibit alkyl interactions with the methyl and alkyl chain of the ligand.

Among the remaining derivatives, the compounds 11a, 11c, 13a, 13c, and 13d, showed comparable binding affinity compared to standard drug sitamaquine. The docking pose and ligand interactions along with bonding types of various derivatives are given in Table 3.

| S.No | Compd No. | Binding Surface | Ligand Interactions | Bonding |
|------|-----------|----------------|---------------------|---------|
| 1.   | 11a       | ![image](image1) | ![image](image2)   | Conventional hydrogen bonding, Vander wall, and pi-alkyl interactions |
| 2.   | 11b       | ![image](image3) | ![image](image4)   | Vander wall, pi-sigma, and pi-alkyl interactions |
| 3.   | 11c       | ![image](image5) | ![image](image6)   | pi-sigma, pi-alkyl, and unfavorable donor-donor interactions |

https://doi.org/10.33263/BRIAC126.75037522

https://biointerfaceresearch.com/
| S.No | Compd No. | Binding Surface | Ligand Interactions | Bonding |
|------|-----------|----------------|--------------------|---------|
| 4.   | 11d       | ![Image](https://https://doi.org/10.33263/BRIAC126.75037522) | ![Image](https://https://biointerfaceresearch.com/) | Conventional hydrogen bonding, Vander wall, and pi-alkyl interactions |
| 5.   | 11e       | ![Image](https://https://doi.org/10.33263/BRIAC126.75037522) | ![Image](https://https://biointerfaceresearch.com/) | Conventional hydrogen bonding, Vander wall, and pi-alkyl interactions |
| 6.   | 11f       | ![Image](https://https://doi.org/10.33263/BRIAC126.75037522) | ![Image](https://https://biointerfaceresearch.com/) | Conventional hydrogen bonding, alkyl, and pi-alkyl interactions |
| 7.   | 12a       | ![Image](https://https://doi.org/10.33263/BRIAC126.75037522) | ![Image](https://https://biointerfaceresearch.com/) | Conventional hydrogen bonding, Vander wall |
| 8.   | 12b       | ![Image](https://https://doi.org/10.33263/BRIAC126.75037522) | ![Image](https://https://biointerfaceresearch.com/) | Carbon hydrogen bond, alkyl and pi-alkyl interactions |
| 9.   | 12c       | ![Image](https://https://doi.org/10.33263/BRIAC126.75037522) | ![Image](https://https://biointerfaceresearch.com/) | Conventional hydrogen bonding, Carbon hydrogen bond, alkyl, and pi-alkyl interactions |
| 10.  | 12d       | ![Image](https://https://doi.org/10.33263/BRIAC126.75037522) | ![Image](https://https://biointerfaceresearch.com/) | Conventional hydrogen bonding, van der wall, Carbon hydrogen bond, alkyl pi-alkyl, and pi-sigma interactions |
| S.No | Compd No. | Binding Surface | Ligand Interactions | Bonding |
|------|-----------|-----------------|---------------------|---------|
| 11.  | 12e       | ![Image](https://biointerfaceresearch.com/) | ![Image](https://biointerfaceresearch.com/) | Conventional hydrogen bonding, Van der wall, alkyl, and pi-alkyl interactions |
| 12.  | 12f       | ![Image](https://biointerfaceresearch.com/) | ![Image](https://biointerfaceresearch.com/) | Conventional hydrogen bonding, van der wall bond, Carbon hydrogen bond, alkyl, pi-alkyl Pi-anion, Pi-Pi stacked, and pi-sigma interactions |
| 13.  | 13a       | ![Image](https://biointerfaceresearch.com/) | ![Image](https://biointerfaceresearch.com/) | Alkyl and pi-alkyl interactions |
| 14.  | 13b       | ![Image](https://biointerfaceresearch.com/) | ![Image](https://biointerfaceresearch.com/) | Conventional hydrogen bonding, van der wall, Carbon hydrogen bond, alkyl, and pi-sigma interactions |
| 15.  | 13c       | ![Image](https://biointerfaceresearch.com/) | ![Image](https://biointerfaceresearch.com/) | Conventional hydrogen bonding, van der wall, Carbon hydrogen bond, alkyl, and pi-sigma interactions |
| 16.  | 13d       | ![Image](https://biointerfaceresearch.com/) | ![Image](https://biointerfaceresearch.com/) | Conventional hydrogen bonding, carbon-hydrogen bond, alkyl, and pi-alkyl interactions |
| 17.  | 13e       | ![Image](https://biointerfaceresearch.com/) | ![Image](https://biointerfaceresearch.com/) | Carbon hydrogen bond, alkyl, pi-alkyl, and pi-sigma interactions |
3.4. Drug-likeness and ADMET analysis.

Drug-likeness assessment and ADMET investigation for various compounds along with reference drugs are given in Tables 4 and 5, respectively. Inadequate pharmacokinetic and toxicity studies lead to failure of the drug development process in the final stages. Therefore, to escalate the drug discovery process, primary assessment of pharmacokinetics and toxicity studies is the mandate step.

The outcome of DruLiTo software demonstrates that all the synthesized compounds have admissible physicochemical properties such as hydrogen-bonding capacity, i.e., the numbers of hydrogen bond acceptors are under 10, and hydrogen bond donors are under 5, an important determinant of permeability. The molecular weight of the synthesized compounds is under 500, which predicts that these compounds can be easily transported, diffused, and absorbed compared to large molecules. LogP value, i.e., the octanol-water partition coefficient that usually quantified molecular lipophilicity is in the range of 0.087-1.562, i.e., under 5, which suggests the good permeability across the cell membrane and the polar surface area (TPSA), which is a good indicator of the bioavailability of the drug molecule is in the range of 27.63-61.77 and is well below the limits. All the values are in the acceptable range; hence all the synthesized drug molecules follow the Lipinski rule of five, as shown in Table 4.

Table 4. Drug-likeness assessment of various synthesized derivatives along with the standard drug.

| Compound No. | Mass | Log P | PSA | Hydrogen acceptor | Hydrogen donor | Molar refractivity | No. of rotatable bonds |
|--------------|------|-------|-----|-------------------|----------------|-------------------|-----------------------|
| 11a          | 255.17 | 1.562 | 27.63 | 3                 | 1              | 80.04             | 4                     |
| 11b          | 215.14 | 0.698 | 27.63 | 3                 | 1              | 73.28             | 4                     |
| 11c          | 257.15 | 0.298 | 36.86 | 4                 | 1              | 82.35             | 4                     |
| 11d          | 241.16 | 1.204 | 27.63 | 3                 | 1              | 77.13             | 4                     |
| 11e          | 243.17 | 1.544 | 27.63 | 3                 | 1              | 81.86             | 6                     |
| 11f          | 317.12 | 0.821 | 61.77 | 5                 | 1              | 99.88             | 4                     |
| 12a          | 255.17 | 1.351 | 27.63 | 3                 | 1              | 79.97             | 4                     |
| 12b          | 215.14 | 0.487 | 27.63 | 3                 | 1              | 73.20             | 4                     |
| 12c          | 257.15 | 0.087 | 36.86 | 4                 | 1              | 82.28             | 4                     |
| 12d          | 241.16 | 0.993 | 27.63 | 3                 | 1              | 77.06             | 4                     |
| 12e          | 243.17 | 1.333 | 27.63 | 3                 | 1              | 81.79             | 6                     |
| 12f          | 317.12 | 0.610 | 61.77 | 5                 | 1              | 99.81             | 4                     |
| 13a          | 255.17 | 1.351 | 27.63 | 3                 | 1              | 79.97             | 4                     |
| 13b          | 215.14 | 0.487 | 27.63 | 3                 | 1              | 73.20             | 4                     |

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All the synthetic derivatives displayed optimal Caco-2 permeability in a range of -4.442 to -4.693. Since most of the drugs are administered through the oral route, so it is essential that the drug should be highly absorbed in intestinal tissue as all the compounds are HIA positive so they can be easily absorbed by the human intestine. The half-life (T1/2) values of various derivatives were in the range of 1.533 to 1.981 hours.

The median lethal dose (LD50) is the dose amount of a tested molecule to kill 50 % of the treated animals within a given period and, in the present, the LD50 of various derivatives is in the comparable range with the reference since most of the synthesized compounds showed an acceptable range of ADMET profiles so they can be used efficiently as potent drug candidates (Table 5).

### Table 5. ADMET analysis of various synthesized derivatives along with the standard drug.

| S. No. | Compound No. | LogS | Mass (Da) | Log P | PSA (Å²) | Hydrogen acceptor | Hydrogen donor | Molar refractivity | No. of rotatable bonds | Human Intestinal absorption | Caco2 Permeability | Blood-Brain Barrier | Life Time (T 1/2) | LD50 mol/kg |
|--------|--------------|------|-----------|-------|----------|-------------------|---------------|-------------------|-------------------------|--------------------------|--------------------|-------------------|-----------------|-------------|
| 1.     | 11a          | -3.777 | 257.15    | 0.087 | 36.86    | 4                 | 1             | 82.28             | 4                       | ++                       | -4.538             | +++               | 1.745           | 2.674       |
| 2.     | 11b          | -2.691 | 243.17    | 0.333 | 27.63    | 3                 | 1             | 77.06             | 4                       | ++                       | -4.462             | +++               | 1.533           | 2.728       |
| 3.     | 11c          | -3.038 | 271.12    | 0.610 | 61.77    | 5                 | 1             | 99.81             | 4                       | ++                       | -4.643             | +++               | 1.646           | 2.674       |
| 4.     | 11d          | -3.294 | 317.12    | 0.610 | 61.77    | 5                 | 1             | 99.81             | 4                       | ++                       | -4.444             | +++               | 1.787           | 2.606       |
| 5.     | 11e          | -3.287 | 343.26    | 3.242 | 24.50    | 4                 | 1             | 94.38             | 11                      | ++                       | -4.691             | +++               | 1.981           | 2.601       |
| 6.     | 11f          | -4.455 | 343.26    | 3.242 | 24.50    | 4                 | 1             | 94.38             | 11                      | ++                       | -4.691             | +++               | 1.981           | 2.601       |
| 7.     | 12a          | -3.594 | 343.26    | 3.242 | 24.50    | 4                 | 1             | 94.38             | 11                      | ++                       | -4.691             | +++               | 1.981           | 2.601       |
| 8.     | 12b          | -2.702 | 343.26    | 3.242 | 24.50    | 4                 | 1             | 94.38             | 11                      | ++                       | -4.691             | +++               | 1.981           | 2.601       |
| 9.     | 12c          | -3.037 | 343.26    | 3.242 | 24.50    | 4                 | 1             | 94.38             | 11                      | ++                       | -4.691             | +++               | 1.981           | 2.601       |
| 10.    | 12d          | -3.284 | 343.26    | 3.242 | 24.50    | 4                 | 1             | 94.38             | 11                      | ++                       | -4.691             | +++               | 1.981           | 2.601       |
| 11.    | 12e          | -3.278 | 343.26    | 3.242 | 24.50    | 4                 | 1             | 94.38             | 11                      | ++                       | -4.691             | +++               | 1.981           | 2.601       |
| 12.    | 12f          | -4.466 | 343.26    | 3.242 | 24.50    | 4                 | 1             | 94.38             | 11                      | ++                       | -4.691             | +++               | 1.981           | 2.601       |
| 13.    | 13a          | -3.698 | 343.26    | 3.242 | 24.50    | 4                 | 1             | 94.38             | 11                      | ++                       | -4.691             | +++               | 1.981           | 2.601       |
| 14.    | 13b          | -2.868 | 343.26    | 3.242 | 24.50    | 4                 | 1             | 94.38             | 11                      | ++                       | -4.691             | +++               | 1.981           | 2.601       |
| 15.    | 13c          | -2.975 | 343.26    | 3.242 | 24.50    | 4                 | 1             | 94.38             | 11                      | ++                       | -4.691             | +++               | 1.981           | 2.601       |
| 16.    | 13d          | -3.368 | 343.26    | 3.242 | 24.50    | 4                 | 1             | 94.38             | 11                      | ++                       | -4.691             | +++               | 1.981           | 2.601       |
| 17.    | 13e          | -3.329 | 343.26    | 3.242 | 24.50    | 4                 | 1             | 94.38             | 11                      | ++                       | -4.691             | +++               | 1.981           | 2.601       |
| 18.    | 13f          | -4.441 | 343.26    | 3.242 | 24.50    | 4                 | 1             | 94.38             | 11                      | ++                       | -4.691             | +++               | 1.981           | 2.601       |
| 19.    | Sitamaquine  | -5.124 | 343.26    | 3.242 | 24.50    | 4                 | 1             | 94.38             | 11                      | ++                       | -4.691             | +++               | 1.981           | 2.601       |

### 4. Discussion

In tropical countries, leishmaniasis is among one of the primary public problems leading to illness and death. Owing to the advent of widespread tolerance and toxicity of leishmaniasis, the available treatment opportunities are limited [43]. Quinoline scaffold is one of the widely used frameworks to synthesize novel derivatives with promising antiparasitic activity. The molecular structures of the newly synthesized quinoline derivatives were established based on spectral data. The infrared spectra of various synthesized compounds showed an absorption band at 3293-3709 cm⁻¹ which confirms the presence of -NH functionality, the appearance of bands around 1450–1660 cm⁻¹ and 1105-1271 cm⁻¹ corresponding to C=C aromatic stretching and C–N, respectively were also observed. Spectral data of all the compounds were consistent with the chemical structures. The triplet at δ3-5 ppm...
revealed the presence of the NH group. The multiplet at around δ2.39-3.88 ppm and a triplet at around δ1.23-3.90 ppm accounted for two methylene groups of the aliphatic chain.

Resistance of different strains of *Leishmania* species to conventional antileishmanial treatment has emerged as one of the world’s most pressing issues. Thus, the development of new heterocyclic compounds having substantial biological and medicinal importance is a key objective of our study. Accordingly, various synthesized derivatives were screened for their *in-vitro* antileishmanial activity against the promastigote form of *Leishmania donovani*. The results of antileishmanial activity elucidated that most of the derivatives demonstrated good activity against promastigote form of *Leishmania donovani* with IC50 value ranging from 10.41 to 40.76 µg/ml as compared to standard sitamaquine with IC50 value of 10.09 µg/ml. Amid the synthetic derivatives, the compounds 11f, 12f and 13f displayed comparable activity to standard with IC50 values of 13.61, 11.92, 10.41, whereas compounds 11a, 11c, 13a 13c exhibit moderate activity with IC50 values of 17.73, 18.83, 17.47, and 17.87. On the other hand, the rest of the compounds exhibit inferior activity as compared to the standard.

The outcome of DruLiTo software demonstrates that all the synthesized compounds have admissible physicochemical properties such as hydrogen-bonding capacity, i.e., the numbers of hydrogen bond acceptors are under 10, and hydrogen bond donors are under 5, an important determinant of permeability. The molecular weight of the synthesized compounds is under 500, which predicts that these compounds can be easily transported, diffused, and absorbed compared to large molecules.[LogP value, i.e., the octanol-water partition coefficient that usually quantified molecular lipophilicity is in the range of 0.087-1.562, i.e., under 5, which suggests the good permeability across the cell membrane and the polar surface area (TPSA), which is a good indicator of the bioavailability of the drug molecule is in the range of 27.63-61.77 and is well below the limits. All the values are in the acceptable range; hence all the synthesized drug molecules follow the Lipinski rule of five [44-45].

All the synthesized compounds showed optimal Caco-2 permeability in a range of -4.442 to –4.693. As most of the drugs are administered through the oral route, it is required that the drug be highly absorbed in intestinal tissue since all the compounds are HIA positive so the human intestine can easily absorb them, and all of them exhibit blood-brain-barrier crossing ability. The half-life (T1/2) values of various derivatives were in the range of 1.533 to 1.981 hours. The median lethal dose (LD50) usually represents the acute toxicity of compounds. It is the dose amount of a tested molecule to kill 50 % of the treated animals within a given period. In the present work, the LD50 of various derivatives is in the comparable range with the reference. Since most synthesized compounds showed an acceptable range of ADMET profiles, they can be used efficiently as potent drug candidates.

5. Conclusions

The current investigation reports the synthesis, spectral characterization, the computational and antileishmanial activity of the newly synthesized series of quinoline derivatives, i.e., **11a to 13f**. The results of antileishmanial activity reveal that 11f, 12f, and 13f were comparable in their action to standard drugs showing good human absorption and better log P values, so it could be concluded that these compounds possessing quinoline moiety have significant antileishmanial activity and could lead to drug discovery of lead molecule for antileishmanial therapy. However, further thorough investigation such as *in-vivo* pharmacokinetics profiles is desired to appraise their potential to evolve into therapeutic agents.
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Conflicts of Interest

The authors declare no conflict of interest.

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