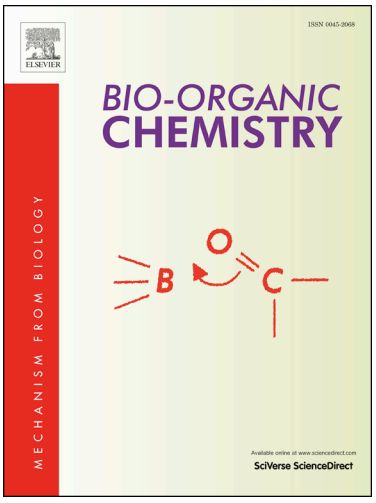


Synthesis of novel quinoline-based thiadiazole, evaluation of their antileishmanial potential and molecular docking studies

Noor Barak Almandil, Muhammad Taha, Fazal Rahim, Abdul Wadood, Syahrul Imran, Mohammed A. Alqahtani, Yasser A. Bamarouf, Mohamed Ibrahim, Ashik Mosaddik, Mohammed Gollapalli

PII: S0045-2068(18)30104-4
DOI: https://doi.org/10.1016/j.bioorg.2018.12.025
Reference: YBIOO 2689

To appear in: *Bioorganic Chemistry*

Received Date: 4 February 2018
Revised Date: 13 December 2018
Accepted Date: 19 December 2018

Please cite this article as: N. Barak Almandil, M. Taha, F. Rahim, A. Wadood, S. Imran, M.A. Alqahtani, Y.A. Bamarouf, M. Ibrahim, A. Mosaddik, M. Gollapalli, Synthesis of novel quinoline-based thiadiazole, evaluation of their antileishmanial potential and molecular docking studies, *Bioorganic Chemistry* (2018), doi: https://doi.org/10.1016/j.bioorg.2018.12.025

Synthesis of novel quinoline-based thiadiazole, evaluation of their antileishmanial potential and molecular docking studies

Noor Barak Almandil[a], Muhammad Taha*[a], Fazal Rahim[b], Abdul Wadood[c], Syahrul Imran[d], Mohammed A. Alqahtani[e], Yasser A. Bamarouf[e], Mohamed Ibrahim[a], Ashik Mosaddik[a], Mohammed Gollapalli[e],

[a]*Department of clinical pharmacy, Institute for Research and Medical Consultations (IRMC), Imam Abdulrahman Bin Faisal University, P.O. Box 1982, Dammam 31441, Saudi Arabia.*
[b]*Department of Chemistry, Hazara University, Mansehra-21300, Pakistan*
[c]*Department of Biochemistry, Abdul Wali Khan University Mardan, Mardan-23200, Pakistan.*
[d]*Atta-ur-Rahman Institute for Natural Product Discovery, Universiti Teknologi MARA (UiTM), Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor D. E. Malaysia.*
[e]*College of Computer Science & Information Technology (CCSIT) Imam Abdulrahman Bin Faisal University P.O. Box 1982, Dammam 31441, Saudi Arabia.*

Abstract:

New series of quinoline-based thiadiazole analogs **(1-20)** were synthesized, characterized by EI-MS, ^{1}HNMR and ^{13}CNMR. All synthesized compounds were subjected to their antileishmanial potential. Sixteen analogs **1-10, 12, 13, 16, 17, 18** and **19** with IC_{50} values in the range of 0.04 ± 0.01 to 5.60 ± 0.21μM showed tremendously potent inhibition as compared to the standard pentamidine with IC_{50} value 7.02 ± 0. 09μM. Analogs **11, 14, 15** and **20** with IC_{50} 8.20 ± 0.35, 9.20 ± 0.40, 7.20 ± 0.20 and 9.60 ± 0.40 μM respectively showed good inhibition when compared with the standard. Structure-activity relationships have been also established for all compounds. Molecular docking studies were performed to determine the binding interaction of the compounds with the active site target.

Keywords: Synthesis, quinoline, thiadiazole, antileishmanial, SAR, molecular docking studies

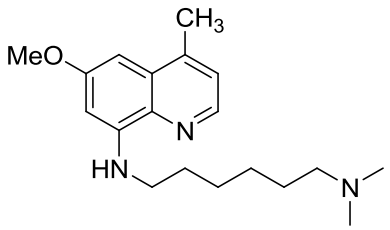
* Correspondence and reprints
E-mail: E-mail: taha_hej@yahoo.com and mtaha@uod.edu.saTel: 00966502057370

1. Introduction

The quinoline is an important heterocyclic moiety found in the basic skeleton of many natural products [1]. Substituted quinolines are potentially important compounds as they have potent anti-inflammatory, antiasthmatic, antibacterial, antimalarial activity and also have industrial applications [2-4].

Thiadiazole and their derivatives have been used from ancient time while their synthetic strategy, physical and chemical properties have studied extensively. They have not only application in medicine [5,6] and agriculture[7-10] but also widely used as proficient electron acceptor. Functional materials play important role in the field of organic electronics, in which thiadiazole have been reported [11]. They have been used as ligands for the coordination of paramagnetic cations [12]. Some derivatives of thiadiazole exhibit antiferromagnetic interactions while other also possesses photoconductivity [13-15]. Thiadiazole derivative possesses strong biological activities and thus are extensively used in the field of pesticides and medicine [16-18].

Leishmaniasis is a severing disease which is initiated by leishmania genus and belongs to family *Trypanosomatidea*. This disease is categorized into three types: visceral commonly called Kala-azar, mucocutaneous and Cutaneous [19-21]. The most dangerous form is visceral in which vital organs are targeted by the parasite. Long time fever, hyper gammaglobulinemia, pancytopenia, and splenomegaly are the properties of such severe visceral leishmaniasis. The patient is affected in very short span of time and can cause death if untreated [22]. Leishmaniasis is transferred through female sandflies and its bites can affect liver, spleen and bone marrow [23]. The parasites of leishmaniasis have two morphological forms which are amastigotes and promastigotes [24]. Each year 1.5 million people affected from cutaneous while 500,000 new cases appear from visceral leishmaniasis. Seventy (**70**) countries of the world affected by cutaneous leishmaniasis and major cases occur in Afghanistan, Pakistan, Saudi Arabia, Brazil and Syria [25, 26]. Sitamaquine **(1)** [27] **Figure 1** (WR6026), an 8-aminoquinoline derivative, has been shown to have antileishmanial activity in Phase II studies, but confirmation of such activity during Phase III studies is still lacking.



Sitamaquine

Figure 1

Allopurinol [28] and rifampicin [29] showed activity in experimental systems, but proved disappointing in clinical trials. Treatment of visceral leishmania is limited because of drug resistance

and keeping that in mind, quinoline based derivatives have been synthesized and evaluated for their antileishmanial and found to be most active **Figure 2** [30].

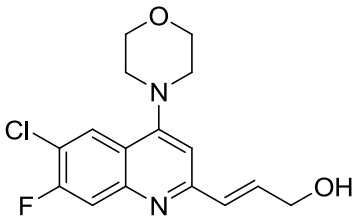


Figure 2

Quinoline-based gold complexes were synthesized, by Catherine Hemmert and subjected for antileishmanial activity, which showed good *in vivo* activity **Figure 3** [31].

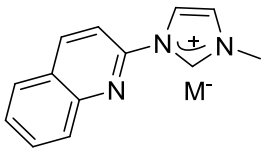


Figure 3

A series of nitro-substituted thiadiazole derivatives **Figure 4** were synthesized and evaluated for their antileishmanial activity. Compound given has high potency when compared with other analogs [32].

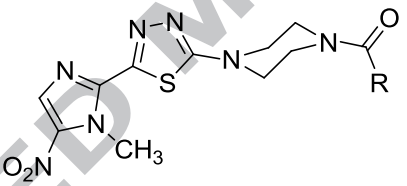


Figure 4

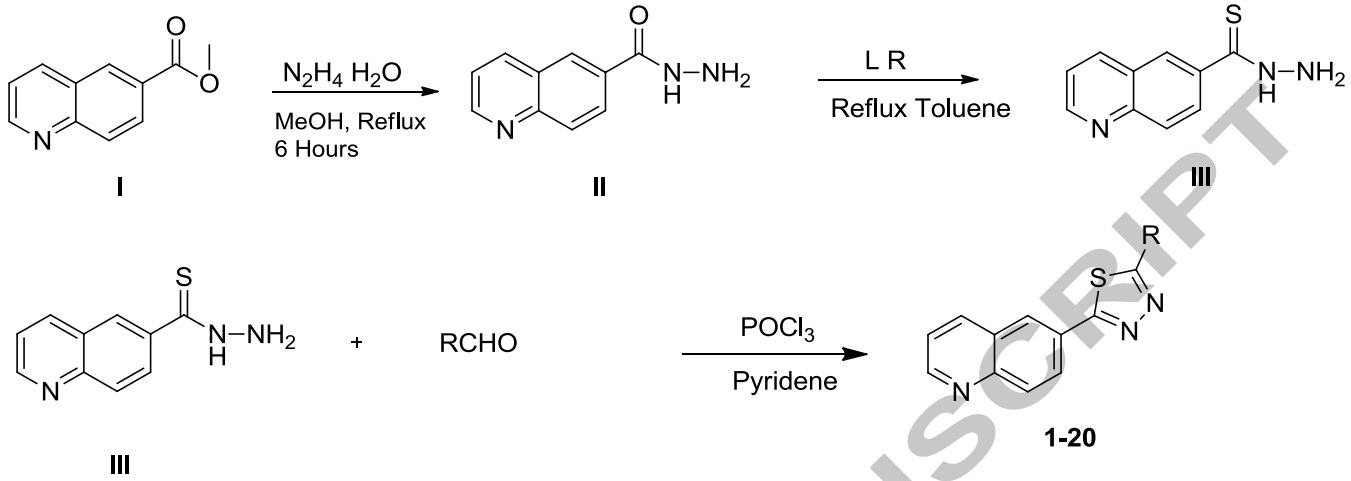
Leishmaniasis can be treat by using tolerated drugs. Currently, glucantime, pentostam, pentamidine and amphotericin are the drugs which are used for treatment of leishmaniasis [33,34]. However, treatment with these current drugs suffers from numerous limitations like toxicity, cost, parenteral administration, and banquet of drug resistance, and reverts in HIV–Leishmania co-infected patients. Therefore, there is still a horrible need for novel effective and anodyne drugs in the absence of a forthcoming vaccine.

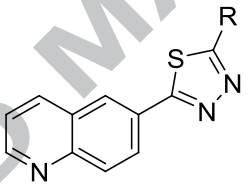
Keeping in view the biological importance of these classes of heterocycles *i.e* quinoline and thiadiazole, in this study we are going to report the synthesis of quinoline-based thiadiazole hybrid analogs, their *in vitro* leishmanicidal activity and molecular docking.

2.1. Results and Discussion

The methyl 6-quinoline carboxylate **I** was refluxed with methylated hydrazine hydrate for 6 hours to get compound **II.** The compound **II** was refluxed with Lawesson's reagent in toluene for 10 hours to

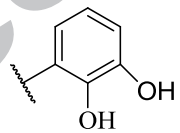
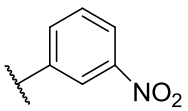
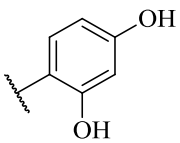
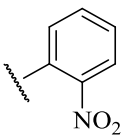
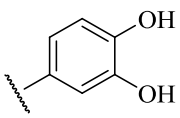
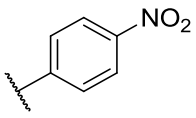
get compound **III**. The compound **III** was reacted with various aryl aldehyde in the presence of POCl3 and Pyridine to form compounds **1-20**.

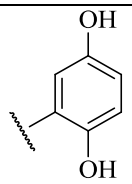
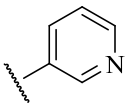
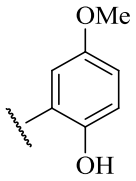
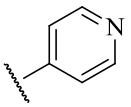
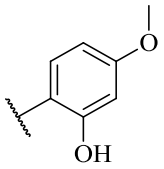
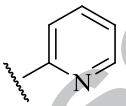
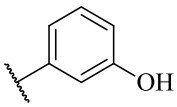
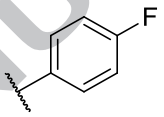
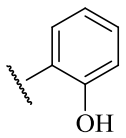
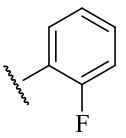
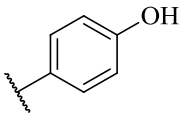
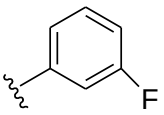
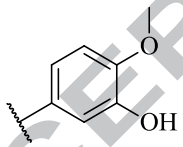
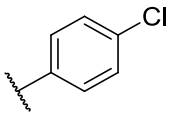




Structure of Basic skeleton

Table-1: Synthesis of quinoline based thiadiazole derivatives (**1-20**) and their antileishmanial potential

S.No.	R	IC_{50} ± SEM[a] [μM]	S.No.	R	IC_{50} ± SEM[a] [μM]
1		0.04 ± 0.01	**11**		8.20 ± 0.35
2		0.70 ± 0.1	**12**		4.68 ± 0.20
3		0.08 ± 0.01	**13**		6.30 ± 0.30

4		0.90 ± 0. 10	**14**		9.20 ± 0.40
5		2.10 ± 0. 10	**15**		7.20 ± 0.20
6		4.10 ± 0. 20	**16**		05.10 ± 0.25
7		3.40 ± 0.20	**17**		5.60 ± 0.21
8		1.18 ± 0.1	**18**		0.980 ± 0.02
9		2.10 ± 0.15	**19**		3.60 ± 0.20
10		3.20 ± 0.20	**20**		9.60 ± 0.40
				Standard Pentamidine	7.02 ± 0. 09μM

2.2. Biological activity

Our group is continuous working on bioactive molecules [35]. New series of quinoline-based thiadiazole analogs **(1-20)** were synthesized and evaluated for their antileishmanial activity. Out of twenty analogs, sixteen analogs **1-10, 12, 13, 16, 17, 18** and **19** with IC_{50} values 0.04 ± 0.01, 0.70 ± 0.1, 0.08 ± 0.01, 0.90 ± 0.10, 2.10 ± 0.10, 4.10 ± 0.20, 3.40 ± 0.20, 1.18 ± 0.1, 2.10 ± 0.15, 3.20 ± 0.20, 4.68 ± 0.20, 6.30 ± 0.30, 05.10 ± 0.25, 5.60 ± 0.21, 0.980 ± 0.02 and 3.60 ± 0.20 μM respectively showed excellent antileishmanial potential when compared with the standard drug pentamidine (IC_{50} 7.02 ± 0. 09μM). Analogs **11, 14, 15** and **20** with IC_{50} 8.20 ± 0.35, 9.20 ± 0.40, 7.20

± 0.20 and 9.60 ± 0.40 μM respectively also showed good inhibitions when compared with the standard. The structure-activity relationship was mainly based on substitution pattern on phenyl part attached to thiadiazole. Observing the potency of the compounds, it was noticed that those analogs having two hydroxyl groups present in phenyl ring *i.e* compounds **1,** a 2,3-dihydroxy analog (IC_{50} value = 0.04 ± 0.01**) 2,** a 2,4-dihydroxy analog (IC_{50} value = 0.70 ± 0.1**) 3,** a 2,3-dihydroxy analog (IC_{50} value = 0.08 ± 0.01**)** and **4,** a 2,3-dihydroxy analog (IC_{50} value = 0.90 ± 0. 10**)** showed the excellent inhibition. The greater potential shown by these compounds might be due to hydroxyl that may be involved in hydrogen bonding. The small activity difference among these analogs might be due to the position difference of the substituents. Those analogs having methoxy along with hydroxyl groups present on the same phenyl ring at various positions also showed excellent inhibition such as compounds **5,** a 2-hydroxy-5-methoxy analog (IC_{50} value = 2.10 ± 0. 10**) 6,** a 2-hydroxy-4-methoxy analog (IC_{50} value = 4.10 ± 0. 20**)** and **10,** a 3-hydroxy-4-methoxy analog (IC_{50} value = 3.20 ± 0.20**)**. The decline in the inhibitory potential of these analogs from dihydroxy analog seems to due to bulky methoxy group and less number of hydrogen bonding. All those analogs in which only one hydroxyl group is present at different position also showed potent inhibition such as compounds **7,** a 3-hydroxy analog (IC_{50} value = 3.40 ± 0.20) **8,** a 2-hydroxy analog (IC_{50} value = 1.18 ± 0.1) and **9** a 4-hydroxy analog (IC_{50} value = 2.10 ± 0.15). The compound **8** showed greater potential then analog **7** and **9** which seems due to difference in position of hydroxyl group on phenyl ring. Compounds having fluorine atom in phenyl ring at the the *ortho*, *meta* and *para* position also exhibit fantastic inhibition as shown by compounds **17,** a 3-flouro analog (IC_{50} value = 5.60 ± 0.21) **18,** a 2-flouro analog (IC_{50} value = 0.980 ± 0.02) and **19** a 4-flouro analog (IC_{50} value = 3.60 ± 0.20). The compound 18 was superior then compound 17 and 19 which that substituent at *ortho* position plays a vital role in this inhibition. Compounds having a nitro group in phenyl ring at *ortho* and *para* position also showed potent inhibition as shown by compound **12,** a 2-nitro substituted analog (IC_{50} value = 4.68 ± 0.20) and **13** a 4-nitro substituted analog (IC_{50} value = 6.30 ± 0.30) while the nitro group at 3 position also showed good inhibition such as compound **11** (IC_{50} value = 8.20 ± 0.35). Pyridine nitrogen atom at the *ortho*, *meta*, and *para* position of phenyl ring show good activity. Overall in this study, we observed that either EDG or EWG on phenyl ring play an important role in inhibition but EDG are superior to some extent. The position of substituents also played a vital role. The binding interactions of the compounds were confirmed by molecular docking studies.

2.3. Molecular docking

The molecular docking procedure was used to predict the binding interaction of the compounds in the binding pocket of the enzyme. The 3D crystal structure of the pteridine reductase 1 enzyme of L. donovani (PDB ID: 2XOX) [36] was retrieved from the protein databank. All the ions and water

molecules were discarded, and the hydrogen atoms were added to the enzyme by the 3D protonation using the MOE (Molecular Operating Environment) software. The enzyme was then energy minimized by the default parameters of the MOE for the stability and further assessment of the enzyme. The structures of the new series of quinoline-based thiadiazole compounds were built in MOE and energy minimized using the MMFF94x forcefield and gradient: 0.05. The synthesized compounds were docked into the active site of the target enzyme using MOE-Dock program with default parameters i.e., Placement: Triangle Matcher, Rescoring: London dG. For each ligand ten conformations were generated. The top-ranked conformation of each compound was used for further analysis.

2.4. Docking studies

The molecular docking process was carried out in order to inspect the prospective interactions between the quinoline based thiadiazole analogs and the active site of the pteridine reductase 1 (PTR1) enzyme of *L. donovani*. The docking results showed that all the compounds were well accommodated in the active site of Leishmania enzyme. From the docking conformation of the most potent compounds, compound **1** (IC_{50} = 0.04 ± 0.01) was observed that this compound formed five hydrogen bonds and one arene-cation contact with the active residues of the binding pocket. Two hydroxyl groups attached to the phenyl ring of the compound formed H-bonds with the Arg-A17 and Asp-A181 and phenyl ring showed π interaction with the Arg-A17 residue. The –NH of the Arg-A17 interacts through its H with the nitrogen of the 1, 3, 4-thiadiazole moiety of the compound as shown in the **Figure (5A)**. The strong bonding network of the compound with the residues of the active pocket might be one of the reasons to show excellent biological activity.

The docking conformation of the second most active compound, compound **3** with IC_{50} value of 0.08 ± 0.01, it was noticed that this compound has shown three polar interactions with the His-A38, Arg-A39 and Ser-A40 residues as shown in the **Figure (5B)**. The hydroxyl moieties of the phenyl ring of the compound showed polar interactions with the –NH groups of the His-A38, Arg-A39 and Ser-A40 residues. The good interactions of the compound with the residues might be due to the presence of the electron donating groups (-OH). It seemed that the presence of the *ortho*-hydroxyl substituent on the phenyl ring of compound **1** might be responsible for the additional interactions with the active site of the enzyme. If we compare the compound **1** and **3,** the only difference is in the position of the –OH groups. The docking results showed that compound **2** (IC_{50} = 0.70 ± 0.1) exhibited good interactions with the residues of the enzyme. This compound established two polar interactions, one arene-cation and one arene-arene contact with the active residues His-A38, Arg-A39 and Ser-A146 of the active site of the target protein as shown in the **Figure (5C)**. His-A38 and Arg-A39 were observed making an arene-arene linkage and arene-cation contact with the electronic cloud of the phenyl ring of the compound. Arg-A39 formed a hydrogen bond with the nitrogen atom of the 1,3,4-thiadiazole. The

hydroxyl group of the phenyl ring interacts through its H with the oxygen atom of the –OH group of the Ser-A146 residue. The good inhibitory activity of the compound might be due to the availability of the *ortho/para* –OH groups of the phenyl ring enhancing the electronic density of the compound. The compound **4** and compound **8** have shown moderate inhibitory activity as compared to compound **1**, **3** and **2**. The compound **4 (0.90 ± 0. 10)** has two *ortho* hydroxyl groups while compound **8 (1.18 ± 0.1)** has only one *ortho* hydroxyl group so the one extra –OH moiety at the phenyl ring might be the reason of the good biological activity of the compound **4**. The docked conformation of the compound **4** showed two polar interactions, two arene-cation and two arene-arene interactions with the Arg-A17, His-A38 and Arg-A39 residues as shown in the **Figure (5D)** while compound **8** exhibited three interactions. Arg-A17 formed an arene-cation linkage with the π electrons of the quinoline moiety of the compound **8** as shown in the **Figure (6A)**.

Among the halogen-based derivatives, compound **18** showed good inhibitory activity with IC50 of **0.980± 0.02** and formed one hydrogen bond with the His-A38 as shown in the **Figure (6B)**. The good biological activity of the compound may be due to the existence of the *ortho* halogen group i-e fluorine at the phenyl ring of the compound.

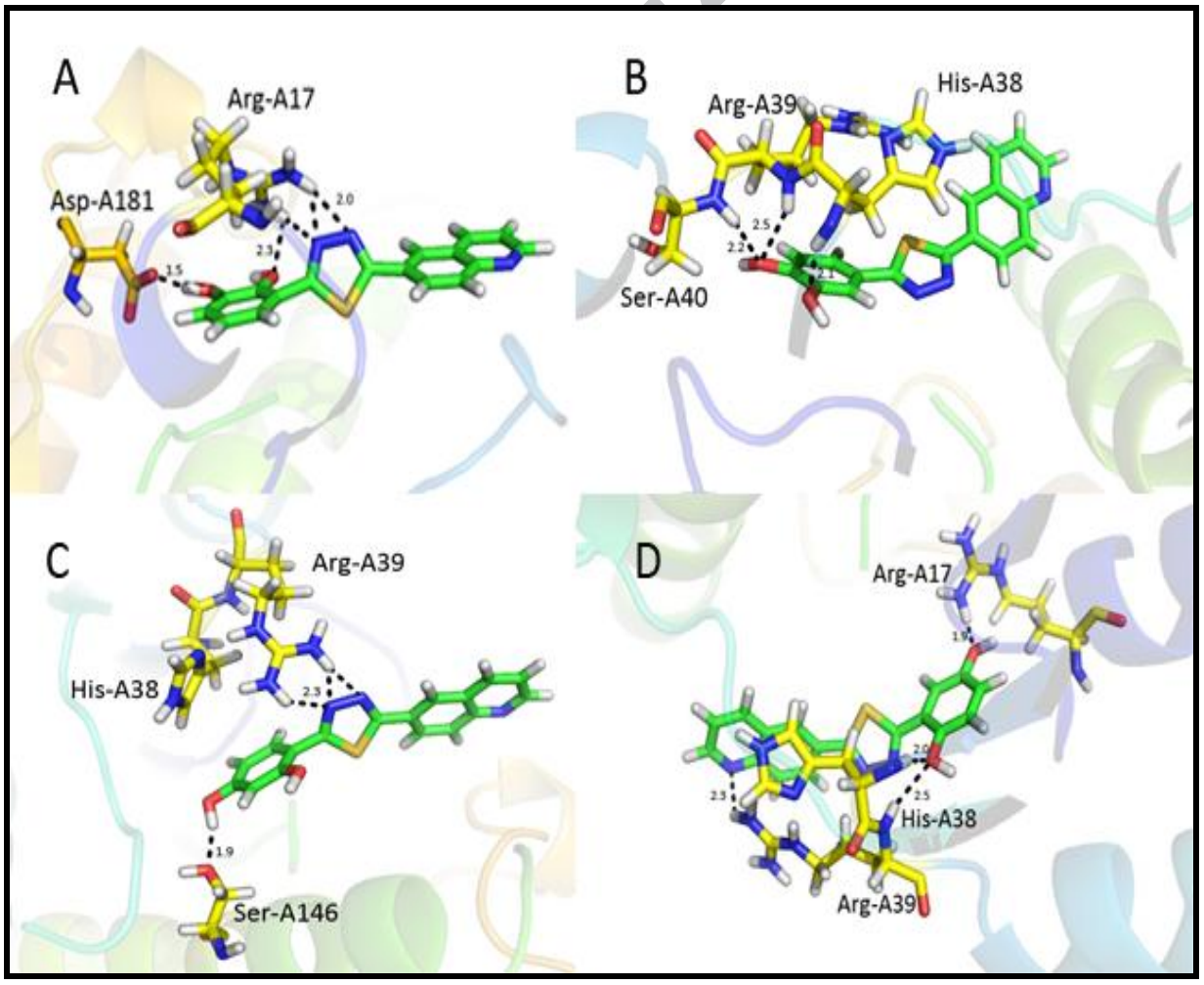


Figure 5: Docking conformation of compound **1** (**A**), **3** (**B**), **2** (**C**) and **4** (**D**) in the active site of pteridine reductase 1 enzyme.

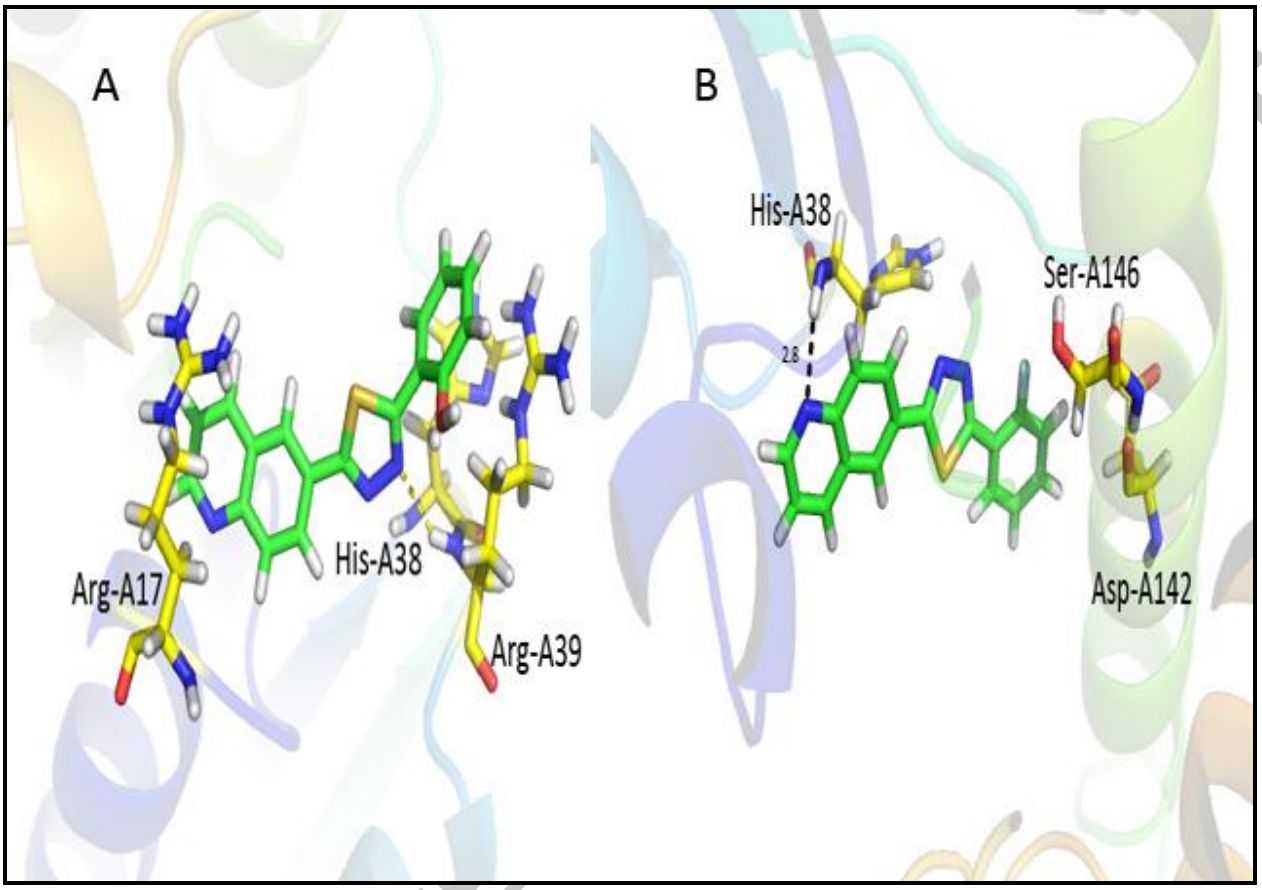


Figure 6: Docking conformation of compound **8** (**A**) and **18** (**B**) in the active site of pteridine reductase 1 enzyme.

3. Conclusion

It is concluded that a new series of quinoline based thiadiazole showed excellent antileishmanial activity. Fourteen analogs **1-10, 12, 13, 16, 17, 18** and **19** with IC_{50} values 0.04 ± 0.01, 0.70 ± 0.1, 0.08 ± 0.01, 0.90 ± 0.10, 2.10 ± 0.10, 4.10 ± 0.20, 3.40 ± 0.20, 1.18 ± 0.1, 2.10 ± 0.15, 3.20 ± 0.20, 4.68 ± 0.20, 6.30 ± 0.30, 05.10 ± 0.25, 5.60 ± 0.21, 0.980 ± 0.02 and 3.60 ± 0.20 μM respectively, showed extremely potent inhibition as compared to the standard pentamidine with IC_{50} is 7.02 ± 0. 09μM. Analogs **11, 14, 15** and **20** with IC_{50} 8.20 ± 0.35, 9.20 ± 0.40, 7.20 ± 0.20 and 9.60 ± 0.40 μM respectively also showed good inhibition.

4.

Acknowledgment:

The authors would like to acknowledge University of Dammam for the financial support. Syahrul Imran would like to thank Universiti Teknologi MARA for the support under Bestari Perdana grant file No. 600-IRMI/PERDANA 5/3 BESTARI (041/2018).

Experimental

General procedure

Synthesis of quinoline-6-carbothiohydrazide.

The 20 mmole (3.74g) quinoline-6-carbohydrazide was refluxed with 20 mmole (8.09g) Lawesson's reagent in toluene for 10 hours to get quinoline-6-carbothiohydrazide. The crude product was washed with diethyl ether and recrystallized in methanol to get pure quinoline-6-carbothiohydrazide with 90 % (3.65 g).

General Procedure for the synthesis of quinoline based thiadiazole derivatives (1-20)

A mixture of quinoline-6-carbothiohydrazide (0.5 mmol) and various aromatic acid (0.5 mmol) in POCl3 (5 ml) was refluxed for 4-6 hours. The mixture was cooled and poured onto crushed ice. It was neutralized with NaHCO3 solution and the resulting solid mass precipitated out was filtered, dried, and crystallized in methanol.

***In vitro* bioassay**

The assay was carried out according to Seifert. Briefly, THP-1 cells (ATCC) were cultured in RPMI-1640 (R5886 Sigma) supplemented with 1% L-glutamine and 10% HI-FBS (complete medium) before harvested at 1.0 x 106 cells/mL. Cells were diluted to 2.0 x 105 cells/mL with the complete medium, seeded in 16-well Lab Tek tissue culture chamber slide (Fisher Scientific) at a seeding density of 5.0x104 macrophage/well (100µL) and allowed to adhere by the addition of PMA (Phorbol -12 myristate Acetate P8139 Sigma) for 3 days at 37°C in a 5% CO_2 – 95% air mixture. Macrophages were then infected with long-slender (stationary stage) of Leishmania major promastigote (JISH118) obtained from The London School of Hygiene and Tropical Medicine (LSHTM) United Kingdom, which were cultured at 26°C in Schneiders Drosophila Medium (S0146 Sigma), at a macrophage-

promastigote ratio of 1:5. Infected macrophages were maintained at 34°C in a 5% CO_2 – 95% air mixture. After 48 hours, extracellular parasites were removed by substituting the overlay with new fresh RPMI-1640 medium supplemented with 1% L-glutamine. Fresh drug and test compounds with various concentrations were added and drug or compound activity was determined from the percentage of infected cells in drug-treated cultures in relation to non-treated cultures using GraphPad Prism after methanol fixation and Giemsa staining.

3-(5-(Quinolin-6-yl)-1,3,4-thiadiazol-2-yl)benzene-1,2-diol (1)

IR (KBr): 3306 (OH), 3070 (Ar CH), 1573 (C=N), 1230 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.11 (s, 1H, OH), 9.25 (s, 1H, OH), 9.04 (dd, 1H, *J* = 1.5, *J* = 4.0 Hz), 8.64 (d, 1H, *J* = 1.0 Hz), 8.56 (d, 1H, *J* = 8.0 Hz), 8.27 (dd, 1H, *J* = 1.5, *J* = 8.5 Hz), 8.18 (d, 1H, *J* = 8.5 Hz), 7.67 (dd, 1H, *J* = 4.0, *J* = 8.0 Hz), 7.03 (d, 1H, *J* = 7.0 Hz), 6.90(d, 1H, *J* = 7.5 Hz), 6.79 (t, 1H, *J* = 8.0, *J* = 15.5 Hz); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.0, 174.0, 149.8, 148.4, 145.4, 143.8, 136.2, 134.2, 133.6, 129.2, 128.3, 127.1, 125.0, 123.1, 121.3, 121.3, 117.1; Anal. Calcd for, $C_{17}H_{11}N_3O_2S$: C, 63.54; H, 3.45; N, 13.08; Found C, 63.53; H, 3.43; N, 13.06; HR-ESI-MS: m/z calcd for $C_{22}H_{17}N_5O_3$, $[M + H]^+$ 322.0650; Found 322.0334.

4-(5-(Quinolin-6-yl)-1,3,4-thiadiazol-2-yl)benzene-1,3-diol (2)

IR (KBr): 3423 (OH), 3074 (Ar CH), 1588 (C=N), 1228 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.44 (s, 1H, OH), 9.99 (s, 1H, OH), 9.03 (dd, 1H, *J* = 1.5, *J* = 4.0 Hz), 8.61 (d, 1H, *J* = 1.0 Hz), 8.54 (d, 1H, *J* = 8.0 Hz), 8.25 (dd, 1H, *J* = 2.0, *J* = 9.0 Hz), 8.16 (d, 1H, *J* = 9.0 Hz), 7.67 (dd, 1H, *J* = 4.5, *J* = 8.5 Hz), 7.37 (d, 1H, *J* = 8.5 Hz), 6.40 (dd, 1H, *J* = 2.0, *J* = 8.5 Hz), 6.35 (d, 1H, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.2, 174.2, 159.8, 156.4, 149.6, 148.4, 136.2, 134.2, 133.6, 130.2, 129.3, 128.3, 127.1, 121.4, 116.3, 109.1, 105.3; Anal. Calcd for, $C_{17}H_{11}N_3O_2S$: C, 63.54; H, 3.45; N, 13.08; Found C, 63.52; H, 3.46; N, 13.09; HR-ESI-MS: m/z calcd for $C_{22}H_{17}N_5O_3$, $[M + H]^+$ 322.0650; Found 322.0564.

4-(5-(Quinolin-6-yl)-1,3,4-thiadiazol-2-yl)benzene-1,2-diol (3)

IR (KBr): 3260 (OH), 3075 (Ar CH), 1576 (C=N), 1224 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.34 (s, 2H, 2 x OH), 9.02 (dd, 1H, *J* = 1.5, *J* = 4.0 Hz), 8.58 (d, 1H, *J* = 1.5 Hz), 8.54 (dd, 1H, *J* = 1.5, *J* = 8.5 Hz), 8.23 (dd, 1H, *J* = 1.5, *J* = 8.5 Hz), 8.15 (d, 1H, *J* = 8.5 Hz), 7.66 (dd, 1H, *J* = 4.0, *J* = 3.0 Hz), 7.29 (d, 1H, *J* = 2.0 Hz), 6.99 (dd, 1H, *J* = 2.0, *J* = 8.0 Hz), 6.82 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.0, 174.0, 148.4, 145.7, 149.7, 147.1, 136.2, 134.2, 133.6, 129.3, 128.3, 127.1, 127.3, 116.0, 121.4, 114.2, 121.3; Anal. Calcd for, $C_{17}H_{11}N_3O_2S$; C, 63.54; H, 3.45; N, 13.08; Found C, 63.51; H, 3.42; N, 13.06; HR-ESI-MS: m/z calcd for $C_{22}H_{17}N_5O_3$, $[M^+ + H]^+$ 322.0650; Found 322.0370.

2-(5-(Quinolin-6-yl)-1,3,4-thiadiazol-2-yl)benzene-1,4-diol (4)

IR (KBr): 3520 (OH), 3070 (Ar CH), 1569 (C=N), 1232 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.35 (s, 1H, OH), 9.03 (dd, 1H, *J* = 1.5, *J* = 4.0 Hz), 8.99 (s, 1H, OH), 8.63 (d, 1H, *J* = 2.0 Hz), 8.54 (d, 1H, *J* = 8.0 Hz), 8.27 (dd, 1H, *J* = 2.0, *J* = 9.0 Hz), 8.17 (d, 1H, *J* = 8.5 Hz), 7.67 (dd, 1H, *J* = 4.0, *J* = 8.0 Hz), 7.04 (d, 1H, *J* = 2.5 Hz), 6.80 - 6.76 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.0, 174.0, 150.2, 149.8, 148.4, 147.6, 136.3, 134.2, 133.6, 129.3, 128.3, 121.4, 127.1, 125.0, 117.4, 117.2, 114.2; Anal. Calcd for, $C_{17}H_{11}N_3O_2S$, C, 63.54; H, 3.45; N, 13.08; Found C, 63.52; H, 3.44; N, 13.05; HR-ESI-MS: m/z calcd for $C_{22}H_{17}N_5O_3$, $[M + H]^+$ 322.0650; Found 322.1098.

4-Methoxy-2-(5-(quinolin-6-yl)-1,3,4-thiadiazol-2-yl)phenol (5)

IR (KBr): 3366 (OH), 3074 (Ar CH), 1590 (C=N), 1231 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.66 (s, 1H, OH), 9.04 (dd, 1H, *J* = 1.5, *J* = 4.0 Hz), 8.63 (d, 1H, *J* = 1.0 Hz), 8.55 (d, 1H, *J* = 8.0 Hz), 8.27 (dd, 1H, *J* = 1.5, *J* = 8.5 Hz), 8.17 (d, 1H, *J* = 9.0 Hz), 7.67 (dd, 1H, *J* = 4.0, *J* = 8.0 Hz), 7.18 (d, 1H, *J* = 3.0 Hz), 6.95 (dd, 1H, *J* = 2.5, *J* = 8.5 Hz), 6.90 (d, 1H, *J* = 9.0 Hz), 3.76 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.0, 174.0, 153.6, 149.8, 148.4, 147.4, 136.2, 134.2, 133.6, 129.3, 128.3, 127.1, 124.5, 121.4, 117.2, 115.6, 112.4, 55.7; Anal. Calcd for, $C_{18}H_{13}N_3O_2S$, C, 64.46; H, 3.91; N, 12.53; Found C, 64.43; H, 3.90; N, 12.52; HR-ESI-MS: m/z calcd for $C_{18}H_{13}N_3O_2S$, $[M+H]^+$ 336.0801; Found 336.1090.

5-Methoxy-2-(5-(quinolin-6-yl)-1,3,4-thiadiazol-2-yl)phenol (6)

IR (KBr): 3430 (OH), 3071 (Ar CH), 1585 (C=N), 1234 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.59 (s, 1H, OH), 9.04 (dd, 1H, *J* = 1.5, *J* = 4.5 Hz), 8.62 (s, 1H), 8.55 (d, 1H, *J* = 8.0 Hz), 8.26 (dd, 1H, *J* = 2.0, *J* = 9.0 Hz), 8.17 (d, 1H, *J* = 8.5 Hz), 7.67 (dd, 1H, *J* = 4.0, *J* = 8.5 Hz), 7.49 (d, 1H, *J* = 8.5 Hz), 6.57 (dd, 1H, *J* = 2.0, *J* = 8.5 Hz), 6.53 (d, 1H, *J* = 2.0 Hz), 3.80 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.0, 174.0, 162.1, 156.1, 149.8, 148.5, 136.2, 134.2, 133.6, 129.8, 129.3, 128.3, 127.1, 121.4, 116.0, 107.3, 104.1, 55.6; Anal. Calcd for, $C_{18}H_{13}N_3O_2S$, C, 64.46; H, 3.91; N, 12.53; Found C, 64.45; H, 3.90; N, 12.52; HR-ESI-MS: m/z calcd for $C_{18}H_{13}N_3O_2S$, $[M+H]^+$ 336.0801; Found 336.0695.

3-(5-(Quinolin-6-yl)-1,3,4-thiadiazol-2-yl)phenol (7)

IR (KBr): 3417 (OH), 3067 (Ar CH), 1586 (C=N), 1237 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.66 (s, 1H, OH), 9.03 (dd, 1H, *J* = 1.5, *J* = 4.0 Hz), 8.54 (d, 1H, *J* = 8.0 Hz), 8.43 (s, 1H), 8.25 (d, 1H, *J* = 9.0 Hz), 8.16 (d, 1H, *J* = 9.0 Hz), 7.66 (dd, 1H, *J* = 4.0, *J* = 8.0 Hz), 7.30 (d, 1H, *J* = 7.5 Hz), 7.27 (d, 1H, *J* = 5.0 Hz), 7.15 (d, 1H, *J* = 7.5 Hz), 6.87(d, 1H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.0, 174.0, 162.1, 156.1, 149.8, 148.5, 136.2, 134.2, 133.6, 129.8, 129.3, 128.3, 127.1, 121.4, 116.0, 107.3, 104.1, 55.6. Anal. Calcd for, $C_{17}H_{11}N_3OS$, C, 66.87; H, 3.63; N, 13.76; Found C, 66.85; H, 3.62; N, 13.73; HR-ESI-MS: m/z calcd for $C_{18}H_{13}N_3O_2S$, $[M+H]^+$ 306.0696; Found 306.1070.

2-(5-(Quinolin-6-yl)-1,3,4-thiadiazol-2-yl)phenol (8)

IR (KBr): 3423 (OH), 3072 (Ar CH), 1584 (C=N), 1227 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.04 (dd, 1H, *J* = 1.5, *J* = 4.0 Hz), 8.64 (s, 1H, OH), 8.55 (d, 1H, *J* = 8.0 Hz), 8.41 (s, 1H), 8.27 (dd, 1H, *J* = 1.5, *J* = 8.5 Hz), 8.18 (d, 1H, *J* = 9.0 Hz), 7.67 (dd, 1H, *J* = 4.0, *J* = 8.0 Hz), 7.61 (d, 1H, *J* = 7.5 Hz), 7.35 (dd, 1H, *J* = 1.0, *J* = 8.0 Hz), 6.98 (dd, 2H, *J* = 8.0, *J* = 13.5 Hz); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.0, 174.0, 162.1, 156.1, 149.8, 148.5, 136.2, 134.2, 133.6, 129.8, 129.3, 128.3, 127.1, 121.4, 116.0, 107.3, 104.1, 55.6. Anal. Calcd for, $C_{17}H_{11}N_3OS$, C, 66.87; H, 3.63; N, 13.76; Found C,

66.85; H, 3.62; N, 13.74; HR-ESI-MS: m/z calcd for $C_{18}H_{13}N_3O_2S$, $[M+H]^+$ 306.0696; Found 306.0432.

4-(5-(Quinolin-6-yl)-1,3,4-thiadiazol-2-yl)phenol *(9)*

IR (KBr): 3395 (OH), 3073 (Ar CH), 1583 (C=N), 1233 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.97 (s, 1H, OH), 9.02 (t, 1H, *J* = 2.5, *J* = 4.0 Hz), 8.53 (d, 1H, *J* = 8.0 Hz), 8.42 (s, 1H), 8.24 (t, 1H, *J* = 8.0, *J* = 9.0 Hz), 8.15 (d, 1H, *J* = 8.5 Hz), 7.65 (dd, 1H, *J* = 4.0, *J* = 8.0 Hz), 7.62 (d, 2H, *J* = 8.5 Hz), 6.88(d, 2H, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.0, 174.0, 162.1, 156.1, 149.8, 148.5, 136.2, 134.2, 133.6, 129.8, 129.3, 128.3, 127.1, 121.4, 116.0, 107.3, 104.1, 55.6. Anal. Calcd for, $C_{17}H_{11}N_3OS$, C, 66.87; H, 3.63; N, 13.76; Found C, 66.85; H, 3.62; N, 13.75; HR-ESI-MS: m/z calcd for $C_{18}H_{13}N_3O_2S$, $[M+H]^+$ 306.0696; Found 306.0634**.**

2-Methoxy-5-(5-(quinolin-6-yl)-1,3,4-thiadiazol-2-yl)phenol (10)

IR (KBr): 3376 (OH), 3071 (Ar CH), 1590 (C=N), 1233 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.03 (dd, 1H, *J* = 1.5, *J* = 4.0 Hz), 8.59 (s, 1H, OH), 8.54 (t, 1H, *J* = 7.5, *J* = 8.0 Hz), 8.36 (s, 1H), 8.24 (dd, 1H, *J* = 1.0, *J* = 8.5 Hz), 8.15 (d, 1H, *J* = 9.0 Hz), 7.66 (dd, 1H, *J* = 4.0, *J* = 8.5 Hz), 7.32 (s, 1H), 7.11 (t, 1H, *J* = 6.5, *J* = 8.0 Hz), 7.01 (d, 1H, *J* = 8.5 Hz), 3.83 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.0, 174.0, 162.1, 156.1, 149.8, 148.5, 136.2, 134.2, 133.6, 129.8, 129.3, 128.3, 127.1, 121.4, 116.0, 107.3, 104.1, 55.6; Anal. Calcd for, $C_{18}H_{13}N_3O_2S$, C, 64.46; H, 3.91; N, 12.53; Found C, 64.45; H, 3.90; N, 12.51; HR-ESI-MS: m/z calcd for $C_{18}H_{13}N_3O_2S$, $[M+H]^+$ 336.0801; Found 336.0695.

4.5.11. 2-(3-Nitrophenyl)-5-(quinolin-6-yl)-1,3,4-thiadiazole (11)

IR (KBr): 3076 (Ar CH), 1593 (C=N), 1538 (N-O), 1360 (N-O), 1237 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.04 (dd, 1H, *J* = 1.5 *J* = 4.0 Hz), 8.60 (s, 2H), 8.56 (t, 1H, *J* = 1.0, *J* = 8.5 Hz), 8.30 - 8.20 (m, 3H), 8.18 (d, 1H, *J* = 8.5 Hz), 7.81 (t, 1H, *J* = 8.0, *J* = 16.0 Hz), 7.67 (dd, 1H, *J* = 4.0, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.2, 174.2, 149.8, 148.3, 148.6, 137.1, 136.5, 134.5, 134.2,

133.8, 130.2, 129.5, 128.5, 127.1, 123.8, 122.9, 121.5. Anal. Calcd for, $C_{17}H_{10}N_4O_2S$, C, 61.07; H, 3.01; N, 16.76; Found C, 61.06; H, 3.01; N, 16.75. HR-ESI-MS: m/z calcd for $C_{17}H_{10}N_4O_2S$, $[M+H]^+$ 335.0592; Found 335.0998

2-(2-Nitrophenyl)-5-(quinolin-6-yl)-1,3,4-thiadiazole (12)

IR (KBr): 3074 (Ar CH), 1591 (C=N), 1536 (N-O), 1356 (N-O), 1235 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.04 (d, 1H, *J* = 3.0 Hz), 8.65 (s, 1H), 8.56 (dd, 1H, *J* = 1.5, *J* = 8.5 Hz), 8.27 (d, 1H, *J* = 9.0 Hz), 8.20 (dd, 2H, *J* = 8.0, *J* = 12.5 Hz), 8.12 (d, 1H, *J* = 7.5 Hz), 7.88 (t, 1H, *J* = 7.0, *J* = 14.5 Hz), 7.73 (t, 1H, *J* = 7.0, *J* = 15.0 Hz), 7.68 (dd, 1H, *J* = 4.0, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, DMSO-d6): δ174.2, 174.2, 149.8, 148.3, 146.6, 136.5, 135.4, 134.4, 133.8, 131.7, 129.7, 129.6, 128.5, 128.5, 127.3, 124.5, 121.6. Anal. Calcd for, $C_{17}H_{10}N_4O_2S$, C, 61.07; H, 3.01; N, 16.76; Found C, 61.05; H, 3.01; N, 16.74. HR-ESI-MS: m/z calcd for $C_{17}H_{10}N_4O_2S$, $[M+H]^+$ 335.0592; Found 335.0634

2-(4-Nitrophenyl)-5-(quinolin-6-yl)-1,3,4-thiadiazole (13)

IR (KBr): 3075 (Ar CH), 1594 (C=N), 1534 (N-O), 1359 (N-O), 1233 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.04 (dd, 1H, *J* = 1.5, *J* = 4.0 Hz), 8.62 (s, 1H), 8.56 (dd, 1H, *J* = 1.5, *J* = 8.5 Hz), 8.34 (d, 2H, *J* = 8.0 Hz), 8.26 (d, 1H, *J* = 8.0 Hz), 8.20 (d, 1H, *J* = 9.0 Hz), 8.06 (d, 2H, *J* = 8.0 Hz), 7.68 (dd, 1H, *J* = 4.5, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, DMSO-d6): δ174.2, 174.2, 149.8, 148.6, 147.8, 139.5, 136.5. 134.4, 133.8, 129.5, 128.6, 128.5, 128.5, 127.3, 124.5, 124.5, 121.6, Anal. Calcd for, $C_{17}H_{10}N_4O_2S$, C, 61.07; H, 3.01; N, 16.76; Found C, 61.05; H, 3.01; N, 16.75; HR-ESI-MS: m/z calcd for $C_{17}H_{10}N_4O_2S$, $[M+H]^+$ 335.0592; Found 335.0498.

2-(Pyridin-3-yl)-5-(quinolin-6-yl)-1,3,4-thiadiazole (14)

IR (KBr): 3084 (Ar CH), 1592 (C=N), 1236 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.26 (s, 1H, NH), 9.03 (dd, 1H, *J* = 1.5, *J* = 4.5 Hz), 8.91 (s, 1H, CH=N), 8.65 (d, 1H, *J* = 4.0 Hz), 8.62 (s, 1H), 8.57 (s, 1H), 8.55 (dd, 1H, *J* = 1.0, *J* = 8.0 Hz), 8.25 (d, 1H, *J* = 8.5 Hz), 8.20 (dd, 2H, *J* = 7.5, *J* =

16.0 Hz), 7.66 (dd, 1H, *J* = 4.0, *J* = 8.0 Hz), 7.53 (dd, 1H, *J* = 5.0, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.2, 174.2, 149.8, 148.8, 148.6, 147.7, 136.5. 134.4, 134.1, 133.8, 133.5, 129.5, 128.6, 127.3, 124.1, 121.4, Anal. Calcd for, $C_{16}H_{10}N_4S$, C, 66.19; H, 3.47; N, 19.30; Found C, 66.18; H, 3.45; N, 19.30. HR-ESI-MS: m/z calcd for $C_{17}H_{10}N_4O_2S$, $[M+H]^+$ 291.0693; Found 290.0329.

2-(Pyridin-4-yl)-5-(quinolin-6-yl)-1,3,4-thiadiazole (15)

IR (KBr): 3082 (Ar CH), 1590 (C=N), 1234 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.37 (s, 1H, NH), 9.04 (dd, 1H, *J* = 1.5, *J* = 4.0 Hz), 8.68 (s, 2H), 8.63 (s, 1H, CH=N), 8.56 (d, 1H, *J* = 8.0 Hz), 8.51 (s, 1H), 8.25 (d, 1H, *J* = 8.5 Hz), 8.17 (d, 1H, *J* = 9.0 Hz), 7.72 (s, 2H), 7.67 (dd, 1H, *J* = 4.0, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.2, 174.2, 149.8, 149.9, 148.6, 149.7, 143.8, 136.5, 134.4, 133.8, 129.5, 128.3, 127.3, 121.6, 121.5, 121.4; Anal. Calcd for, $C_{16}H_{10}N_4S$, C, 66.19; H, 3.47; N, 19.30; Found C, 66.17; H, 3.45; N, 19.30; HR-ESI-MS: m/z calcd for $C_{17}H_{10}N_4O_2S$, $[M+H]^+$ 291.0693; Found 290.1004.

2-(Pyridin-2-yl)-5-(quinolin-6-yl)-1,3,4-thiadiazole (16)

IR (KBr): 3080 (Ar CH), 1591 (C=N), 1234 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.04 (dd, 1H, *J* = 1.0, *J* = 4.0 Hz), 8.64 (s, 1H, , H-6), 8.57 (d, 2H, *J* = 10.0 Hz), 8.26 (d, 1H, *J* = 8.5 Hz), 8.18 (d, 1H, *J* = 9.0 Hz), 8.04 (d, 1H, *J* = 7.5 Hz), 7.93 (t, 1H, *J* = 7.5, *J* = 15.0 Hz), 7.67 (dd, 1H, *J* = 4.0, *J* = 8.5 Hz), 7.46 (t, 1H, *J* = 6.0, *J* = 11.5 Hz); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.2, 174.2, 157.5, 149.8, 149.3, 148.4, 136.5, 137.3. 134.4, 133.8, 129.3, 128.5, 127.3, 124.1, 123.7, 121.6; Anal. Calcd for, $C_{16}H_{10}N_4S$, C, 66.19; H, 3.47; N, 19.30; Found C, 66.18; H, 3.46; N, 19.30. HR-ESI-MS: m/z calcd for $C_{17}H_{10}N_4O_2S$, $[M+H]^+$ 291.0693; Found 291.0856.

2-(4-Fluorophenyl)-5-(quinolin-6-yl)-1,3,4-thiadiazole (17)

IR (KBr): 3080 (Ar CH), 1588 (C=N), 1260 (F-C), 1234 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.11 (s, 1H, NH), 9.03 (dd, 1H, *J* = 1.5, *J* = 4.0 Hz), 8.61 (s, 1H, CH=N), 8.54 (d, 1H, *J* = 1.0 Hz), 8.53 (d, 1H, *J* = 3.5 Hz), 8.25 (d, 1H, *J* = 8.5 Hz), 8.16 (d, 1H, *J* = 8.5 Hz), 7.85 (t, 2H, *J* = 7.5, *J* = 13.5 Hz), 7.66 (dd, 1H, *J* = 4.0, *J* = 8.0 Hz), 7.34 (t, 2H, *J* = 9.0, *J* = 17.5 Hz); ^{13}C NMR (125 MHz,

DMSO-d6): δ 174.2, 174.2, 162.8, 149.8, 148.6, 136.5, 134.4, 133.8, 129.2, 129.5, 129.2, 129.2, 128.5, 127.3, 121.6, 116.2, 116.1; Anal. Calcd for, $C_{17}H_{10}FN_3S$, C, 66.43; H, 3.28; N, 13.67; Found C, 66.42; H, 3.26; N, 13.65; HR-ESI-MS: m/z calcd for $C_{17}H_{10}N_4O_2S$, $[M+H]^+$ 308;0647 Found 308.0800

2-(2-Fluorophenyl)-5-(quinolin-6-yl)-1,3,4-thiadiazole (18)

IR (KBr): 3078 (Ar CH), 1587 (C=N), 1258 (F-C), 1235 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.22 (s, 1H, NH), 9.04 (dd, 1H, *J* = 1.5, *J* = 4.0 Hz), 8.77 (s, 1H, CH=N), 8.63 (s, 1H), 8.55 (t, 1H, *J* = 7.5, *J* = 8.5 Hz), 8.26 (d, 1H, *J* = 8.5 Hz), 8.17 (d, 1H, *J* = 9.0 Hz), 8.02 (t, 1H, *J* = 7.0, *J* = 14.0 Hz), 7.67 (dd, 1H, *J* = 4.5, *J* = 8.5 Hz), 7.55 (dd, 1H, *J* = 6.5, *J* = 13.5 Hz), 7.35 (dd, 2H, *J* = 7.0, *J* = 11.0 Hz); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.0, 174.0, 158.4, 149.7, 148.4, 136.5, 134.4, 133.8, 130.4, 129.5, 129.2, 128.6, 127.3, 124.9, 123.6, 121.6, 114.8; Anal. Calcd for, $C_{17}H_{10}FN_3S$, C, 66.43; H, 3.28; N, 13.67; Found C, 66.42; H, 3.26; N, 13.65; HR-ESI-MS: m/z calcd for $C_{17}H_{10}N_4O_2S$, $[M+H]^+$ 308;0647; Found 308.1073.

2-(3-Fluorophenyl)-5-(quinolin-6-yl)-1,3,4-thiadiazole (19)

IR (KBr): 3083 (Ar CH), 1586 (C=N), 1261 (F-C), 1236 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.21 (s, 1H, NH), 9.04 (dd, 1H, *J* = 1.5, *J* = 4.0 Hz), 8.62 (s, 1H, CH=N), 8.56 (dd, 1H, *J* = 1.5, *J* = 8.5 Hz), 8.52 (s, 1H), 8.25 (d, 1H, *J* = 8.5 Hz), 8.17 (d, 1H, *J* = 9.0 Hz), 7.67 (dd, 1H, *J* = 4.0, *J* = 8.5 Hz), 7.63 (d, 1H, *J* = 7.5 Hz), 7.59 (d, 1H, *J* = 10.5 Hz), 7.55 (t, 1H, *J* = 6.5, *J* = 13.5 Hz), 7.32 (t, 1H, *J* = 7.5, *J* = 15.5 Hz); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.0, 174.1, 162.1, 149.8, 148.4, 136.5, 135.2, 134.4, 133.8, 129.3, 128.5, 127.6, 127.3, 126.6, 121.6, 115.8, 115.6, Anal. Calcd for, $C_{17}H_{10}FN_3S$, C, 66.43; H, 3.28; N, 13.67; Found C, 66.42; H, 3.27; N, 13.65; HR-ESI-MS: m/z calcd for $C_{17}H_{10}N_4O_2S$, $[M+H]^+$ 308;0647; Found 308.0417.

2-(4-Chlorophenyl)-5-(quinolin-6-yl)-1,3,4-thiadiazole (20)

IR (KBr): 3077 (Ar CH), 1583 (C=N), 1233 (C-S-C), 747 (Cl-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.00(t, 1H, J = 2.0, J = 4.0 Hz), 8.55 (d, 1H, J = 8.0 Hz), 8.40 (s, 1H), 8.21 (t, 1H, J = 8.0, J = 8.0 Hz), 8.12 (d, 1H, J = 8.0 Hz), 7.62 (dd, 1H, J = 4.0, J = 8.0 Hz), 7.60 (d, 2H, J = 8.0 Hz), 6.94 (d, 2H, J = 8.0 Hz); ^{13}C NMR (125 MHz, DMSO-d6): δ 174.1, 174.0, 149.8, 148.4, 136.5, 134.4, 134.4, 133.8, 131.7, 129.5, 129.4, 129.2, 128.8, 128.8, 128.3, 127.3, 121.4, Anal. Calcd for, $C_{17}H_{10}ClN_3S$, C, 63.06; H, 3.11; N, 12.98; Found C, 63.05; H, 3.10; N, 12.97; HR-ESI-MS: m/z calcd for $C_{17}H_{10}N_4O_2S$, $[M+H]^+$ 324.0351; Found 324.0319.

References

1. L. Mah Qiao, J. L. Wang, Bioresour. Technol. 101 (2010) 7683-7686.
2. J. Akbari, A. Heydari, H. R. Kalhor, S. A. Kohan, J. Comb. Chem. 12 (2010) 137-140.
3. S. Ray, P. B. Madrid, P. Catz, S .E. LeValley, M. J. Furniss, L. L. Rausch, R. K. Guy, J. L. DeRisi, L. V. Iyer, C. E. Green, J. C. Mirsalis. J. Med. Chem. 53 (2010) 3685–3695.
4. A. M. Alguinaldo, V. M. Dalangin-Mallari, A. P. G. Macabeo, L. T. Byrne, F. Abe, T. Yamauchi, S. G. Franzblau, Int. J. Antimicrob. Ag. 29 (2007) 738-739.
5. P. A. Koutentis,. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor, Eds, In Comprehensive Heterocyclic Chemistry III, Elsevier. Oxford. UK. Vol. 5 (2008) 516-564 Ch. 5.09.
6. P. A. Koutentis, R. C. Storr, T. L. Gilchrist, Eds, Georg Thieme, Stuttgart, In Science of Synthesis, Germany. Vol. 13 (2003) 297-348; Ch. 13.11.
7. Z. V. Todres, Chalcogenadiazoles, Chemistry and Applications, CRC/Taylor & Francis, Boca Raton, FL (2012).
8. B. A. D. Neto, A. A. M. Lapis, E. N. da Silva Junior, J. Dupont. Eur. J. Org. Chem. (2013) 228-255.
9. S. Azuma, M. Kusu, H. Sasamori, K. Hirasawa, S. Kutsuma, Jpn. Pat. 292719, (1999) (Chem. Abstr. 1999, 131, 296489).
10. S. Niizuma, M. Kusu, H. Sasamori, K. Hirasawa, S. Kutsuma, Jpn. Pat. 292863, (1999) (Chem. Abstr. 1999, 131, 286523).

11. L. B. Dungan, E. G. Rowley, J. A. Dixson, S. F. Ali, S. D. Crawford, S. Sehgel, M. P. Whiteside, T. M. Zydowsky, W. H. Yeager, PCT Int. Appl. (WIPO Pat. Appl.) 6858 (2005), (Chem. Abstr. 2005, 142, 150261).
12. F. J. Gozzo, Agric. Food Chem. 51 (2003) 4487-4503.
13. (a) W. Chen, Q. Zhang, T. Salim, S. A. Ekahana, X. Wan, T. C. Sum, Y. M. Lam, A. C. Hon Huan, Y. Chen, Q. Zhang, Tetrahedron 2014, http://dx.doi. org/10.1016/j.tet.2014.01.026; (b) Y C. Chen, C. Y. Hsu, C. Y. Ho, Y. T. Tao, J.T. Lin, Org. Electron. 14 (2013) 2290-2298; (c) S. Uchiyama, K. Kimura, C. Gota, K. Okabe, K. Kawamoto, N. Inada, T. Yoshihara, S. Tobita,. Chem. Eur. J. 18 (2012) 9552-9563; (d) P. L. T. Boudreault, A. Najari, Leclerc, M. Chem. Mater. 23 (2011) 456-469; (e) S. Ellinger, K. R. Graham, P. Shi, R. T. Farley, T. T. Steckler, R. N. Brookins, P. Taranekar, J. Mei, L. A. Padilha, T. R. Ensley, H. Hu, S. Webster, D. J. Hagan, E. M. Van Stryland, K. S. Schanze, J. R. Reynolds, Chem. Mater. 23 (2011) 3805-3817.
14. (a) Y. Shuku, R. Suizu, K. Awaga, O. Sato, Cryst Eng Comm 11 (2009) 2065-2068; (b) N. Motokawa, H. Miyasaka, M. Yamashita, K. R. Dunbar, Angew. Chem. Int. Ed. 47 (2008) 7760-7763.
15. N. P. Gritsan, A. V. Zibarev, Izv. Akad. Nauk. Ser. Khim. 2011, 2091-2100, Russ. Chem. Bull. 60 (2011) 2131-2140).
16. N. A. Semenov, N. A. Pushkarevsky, E. A. Suturina, E. A. Chulanova, N. V. Kuratieva, A. S. Bogomyakov, I. G. Irtegova, N. V. Vasilieva, L. S. Konstantinova, N. P. Gritsan, O. A. Rakitin, V. I. Ovcharenko, S. N. Konchenko, A. V. Zibarev, Inorg. Chem. 52 (2013) 6654-6663.
17. N. A. Pushkarevsky, A. V. Lonchakov, N. A. Semenov, E. Lork, L. I. Buravov, L. S. Konstantinova, G. T. Silber, N. Robertson, N. P. Gritsan, O. A. Rakitin, J. D. Woollins, E. B. Yagubskii, J. Beckmann, A. V. Zibarev, Synth. Met. 162 (2012) 2267-2276.
18. (a) S.G. Küçükgüzel, I. Küçükgüzel, E. Tatar, S. Rollas, F. S¸ ahin, M. Güllüce, E.D. Clercq, L. Kabasakal, Eur. J. Med. Chem. 42 (2007) 893-901, (b) M. T. Javid, F. Rahim, M. Taha, H. Rehman, M. Nawaz, A. wadood, S. Imran, I. Uddin, A. Mosaddik, K. M. Khan, bioorg. Chem. 78 (2018) 201-209, (c) M. Taha, M. T. Javid, S. Imran, M. Selvaraj, S. Chigurupati, H. Ullah, F. Rahim, F. Khan, J. I. Mohammad, K. M. Khan, Bioorg. Chem. 74, (2017) 179-186, (d) M. Lv, G. Liu, M. Jia, H. Xu, Bioorg. Chem.81 (2018) 88-92 (e) S. K. Talapatra, C. L. Tham, P. Guglielmi, R. Cirilli, B. Chandrasekaran, R. Karpoormath, S. Carradori, F. Kozielski, Eur. J. Med. Chem. 156, 2018, 641-651, (f) S. P. Khathi, B. Chandrasekaran, S. Karunanidhi, C. L. Tham, F. Kozielski, N. Sayyad, R. Karpoormath, Bioorg. Chem. Lett. 28, (2018), 2930-2938, (g) K. Jakovljević, I. Z.Matić, T. Stanojković, A. Krivokuća, V. Marković, M. D. Joksović, N. Mihailović, M. Nićiforović, L. Joksović, Bioorg. Chem. Lett.27 (2017) 3709-3715
19. H. W. Murray, J. D. Berman, C. R. Davies, N. G. Saravia. Advances in leishmaniasis. Lancet. 366 (2005) 1561–77.

20. R. Reithinger, J. C. Dujardin, H. Louzir, C. Pirmez, B. Alexander, S. Brooker, Cutaneous leishmaniasis. Lancet Infect Dis. 7 (2007) 581–96.
21. M. Boelaert, B. Criel, J. Leeuwenburg, W. Van Damme, D. Le Ray, P. Van der Stuyft. Visceral leishmaniasis control, a public health perspective. Trans R Soc Trop Med Hyg 94 (2000) 465–71.
22. S. Kamhawi, Phlebotomine sand flies and Leishmania parasites: friends or foes? Trends Parasitol 22 (2006) 439–45.
23. R. J. Burchmore, M. P. Barrett, Life in vacuoles—nutrient acquisition by Leishmania amastigotes. Int J Parasitol 31 (2001)1311–20.
24. N. C. Hepburn, Cutaneous leishmaniasis. Clin Exp Dermatol. 25 (2000) 363–70.
25. World Health Organization. Visceral leishmaniasis therapy: statement on the outcome of a meeting. Geneva, WHO. 2009. Available at: http://www.who.int/ leishmaniasis/resources/Leish_VL_Therapy_statement.pdf (accessed August,16, 2010).
26. H. C. Maltezou, Drug resistance in visceral leishmaniasis. J Biomed Biotechnol. (2010) 2010 617521.
27. R. Dietze, S. F. Carvalho, L.C. Valli, J. Berman, T. Brewer, W. Milhous, J. Sanchez, B. Schuster, M. Grogl, Phase 2 trial of WR6026, an orally administered 8-aminoquinoline, in the treatment of visceral leishmaniasis caused by Leishmania chagasi, Am. J. Trop. Med. Hyg. 65 (2001) 685-689.
28. B.C. Walton, J. Harper, R.A. Neal, Effectiveness of Allopurinol against Leishmania braziliensis panamensis in Aotus trivirgatus, Am. J. Trop. Med. Hyg. 32 (1983) 46-50.
29. R.A. Bumb, R.D. Mehta, Oral rifampicin in cases of cutaneous leishmaniasis with multiple 478 lesions (A pilot study), Indian J. Dermatol. Venereol. Leprol. 68 (2002) 272-272.
30. S. Gupta *et al*, Bioorg. Med. Chem. Lett. 24(9) (2014) 2046-52)
31. Paloque L, Eur. J. Med. Chem. 94 (2015) 22-9
32. Alireza Foroumadi, Eur. J. Med. Chem 44 (2009) 1758-1762
33. World Health Organization. Leishmaniasis: magnitude of the problem. Geneva: WHO; 2009. at:http://www.who.int/leishmaniasis/burden/ magnitude/burden_magnitude/en/index.html November 30 (2010)
34. J. Shaw, The leishmaniases-survival and expansion in a changing world, Mem. Inst. Oswaldo. Cruz 102 (2007) 541-547.
35. a) K.M. Khan, F. Rahim, A. Wadood, N. Kosar, M. Taha, S. Lalani, A. Khan, M.I. Fakhri, M. Junaid, W. Rehman, M. Khan, S. Perveen, M. Sajid, M.I. Choudhary, Eur. J. Med. Chem. 81 (2014) 245-252; b) M. Taha, N. H. Ismail, S. Imran, A. Wadood, F. Rahim, M. Ali, A. U. Rehman. Med. Chem. Commun., 6 (2015) 1826; c) N.K.N.A. Zawawi, M. Taha, N. Ahmat, A. Wadood, N.H. Ismail, F. Rahim, S.S. Azam, N. Abdullah, Bioorg. Chem. 64 (2016) 29-36; d) S. Imran, M. Taha, N.H. Ismail, S. M. Kashif, F. Rahim, W. Jamil, H. Wahab,

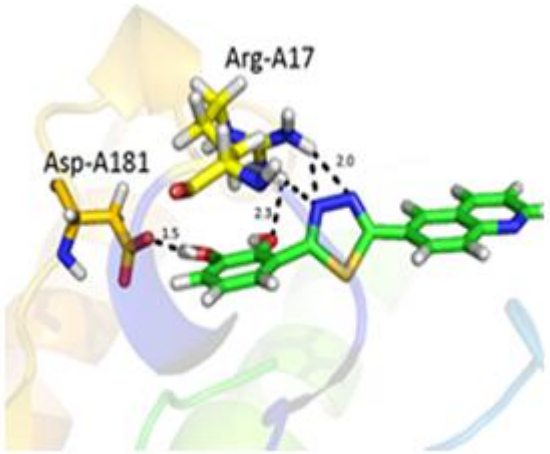
K.M. Khan. Synthesis, In-vitro, and Docking studies of New Flavone ethers as α-glucosidase inhibitors. Chem. Biol. Drug. Des. 87 (2016) 361-373; e) M. Taha, N.H. Ismail, S. Imran, M.H. Mohamad, A. Wadood, F. Rahim, S.M. Saad, A. U. Rehman, K.M. Khan. Bioorg. Chem. 65 (2016) 100-109; f) M. Taha, N.H. Ismail, S. Imran, A. Wadood, F. Rahim, S.M. Saad, K.M. Khan, A. Nasir. Synthesis, Molecular Docking and α-Glucosidase Inhibition of 5-Aryl-2-(6'-nitrobenzofuran-2'-yl)-1,3,4-oxadiazoles. 66 (2016) 117-123; g) F. Rahim, H. Ullah, M.T. Javid, A. Wadood, M. Taha, M. Ashraf, A. Shaukat, M. Junaid, S. Hussain, W. Rehman, R. Mehmood, M. Sajid, M. N. Khan, K.M. Khan. Bioorg. Chem. 62 (2015) 15-21; h) F. Rahim, F. Malik, H. Ullah, A. Wadood, F. Khan, M.T. Javid, M. Taha, W. Rehman, A.U. Rehman, K.M. Khan, Bioorg. Chem. 60 (2015) 42-48.

36. Barrack, K. L.; Tulloch, L. B.; Burke, L. A.; Fyfe, P. K.; Hunter, W. N. Acta Cryst. 2011, F67, 33.

Highlights:

- **Novel Quinoline based thiadiazole scaffold 1-20**
- **Evaluation of antileishmanial potential**
- **Identification of a new antileishmanial compounds**
- **Molecular docking**

Graphical abstract



New series of quinoline based thiadiazole analogs **(1-20)** were synthesized and evaluated for antileishmanial Potential