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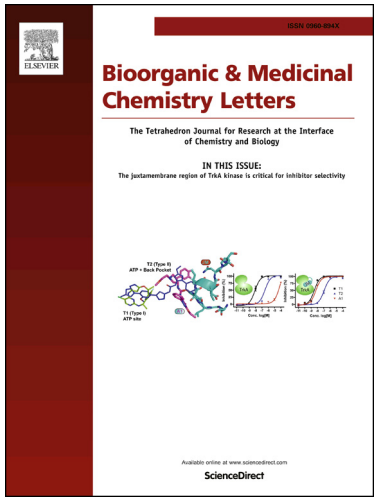

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PII: S0960-894X(17)30298-6
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.03.049
Reference: BMCL 24801

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 10 December 2016
Revised Date: 17 March 2017
Accepted Date: 20 March 2017

Please cite this article as: Masood, M.M., Hasan, P., Tabrez, S., Ahmad, d.B., Yadava, U., Daniliuc, C.G., Sonawane, Y.A., Azam, A., Rub, A., Abid, M., Anti-leishmanial and cytotoxic activities of amino acid-triazole hybrids: Synthesis, biological evaluation, molecular docking and *in silico* physico-chemical properties, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.03.049

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Anti-leishmanial and cytotoxic activities of amino acid-triazole hybrids: Synthesis, biological evaluation, molecular docking and *in silico* physico-chemical properties

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ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Click chemistry
1,2,3-Triazole
Amino acid tail
Anti-leishmanial
Docking studies
Trypanothione reductase

ABSTRACT

According to WHO, leishmaniasis is a major tropical disease, ranking second after malaria. Significant efforts have been therefore invested into finding potent inhibitors for the treatment. In this work, eighteen novel 1,2,3-triazoles appended with *L*-amino acid (Phe/Pro/Trp) tail were synthesized via azide-alkyne click chemistry with moderate to good yield, and evaluated for their anti-leishmanial activity against promastigote form of *Leishmania donovani* (Dd8 strain). Among all, compounds **40**, **43,** and **53** were identified with promising anti-leishmanial activity with IC_{50} = 88.83 ± 2.93, 96.88 ± 12.88 and 94.45 ± 6.51 μM respectively and displayed no cytotoxicity towards macrophage cells. Moreover, compound 43 showed highest selectivity index (SI = 8.05) among all the tested compounds. Supported by docking studies, the lead inhibitors (**40**, **43** and **53**) showed interactions with key residues in the catalytic site of trypanothione reductase. The results of pharmacokinetic parameters suggest that these selected inhibitors can be carried forward for further structural optimization and pharmacological investigation.

Leishmaniasis is poverty related most neglected zoonotic disease worldwide caused by protozoan parasites of the genus *Leishmania* and spread by the bite of infected female phlebotomine sandflies. Leishmaniasis is endemic in 98 countries placing 350 million people at risk. An estimated 0.9 –1.3 million new cases and 20 – 30 thousand deaths occur annually with many cases going undiagnosed. Three main forms of leishmaniasis – visceral (also known as kala-azar), cutaneous, and mucocutaneous are observed. Of these, visceral leishmaniasis (VL) is fatal if left untreated, is endemic in the Indian subcontinent and in East Africa. An estimated 0.2 to 0.4 million new cases of VL occur worldwide each year.[1-2]

Leishmaniasis control mainly depends on chemotherapy (Figure 1). The first-line therapy for leishmaniasis include pentavalent antimonial drugs like sodium stibogluconate (pentostam) and meglumine antimoniate (glucantime) being used for the last five decades. Unfortunately, about 60% of VL cases in India alone become un-responsive to pentavalent antimonial due to developed resistance.[3] Polyene antifungal drug amphotericin B, in spite of its adverse effects is the drug of choice where resistance to pentavalent antimonial is developed. Usefulness of second-line drugs such as paromomycin and pentamidine has been restricted.[4] Miltefosine (hexadecylphosphocholine [HePC]), an alkyl phosphocholine originally developed as anticancer agent, is widely used as an anti-leishmanial drug as it has a good oral profile,[5,6] causes apoptotic death[7] and exhibits activity against various *Leishmania* species.[8] However, toxicity, appearance of drug resistance and the relapse of the disease in some cases, even after 10 months of a full course of treatment with miltefosine[9] prompted health researchers to search for novel, safe and effective anti-leishmanial agents. In this regard, several studies with heterocyclic compounds as anti-leishmanial agents have been reported in the literature.[10-14] 1,2,3-triazoles flanked on each side by two randomized amino acids (peptidotriazoles) against *L. mexicana* cysteine protease has also been reported (Fig.1).[15] Peptidic compounds are susceptible to hydrolysis. However, the combination of peptides with rigid and hydrophobic molecular moieties can alter this process. Peptide based small molecules

can provide inhibitors that bind to proteases as a natural peptide substrate. These compounds are more resistant to hydrolysis because of a structural mimetic within the peptide backbone and rigidity of triazole pharmacophore and hydrophobic substituent. Incorporation of triazoles into amino acids provides rationale for the small, rigid, and aromatic structure capable of resistance to enzymatic hydrolysis. We introduced phenyl ring in to our core structure with triazole, in order to achieve rigidity. Considering the present situation and in continuation to our search of potent antimicrobial agents,[16-19] it is worthwhile to synthesize 1,2,3-triazoles appended with *L*-amino acid tail (Phe/Pro/Trp) for their anti-leishmanial activity and any possible cytotoxicity. In this study, we aimed at exploiting the 1,2,3-triazole ring for the development of novel anti-leishmanial pharmacophore.

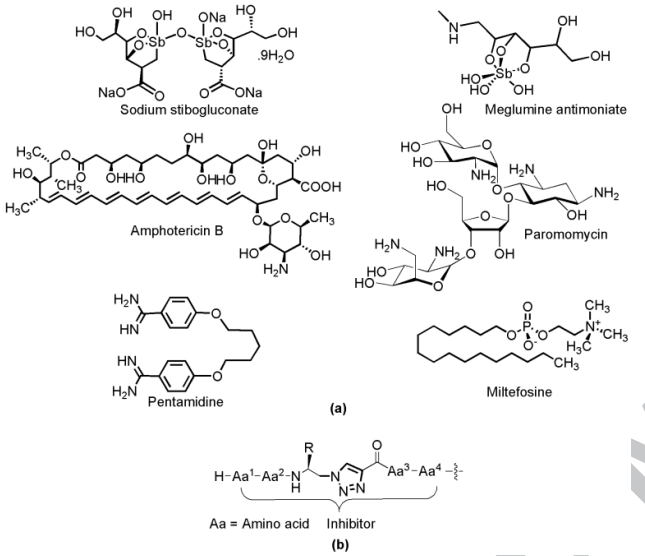
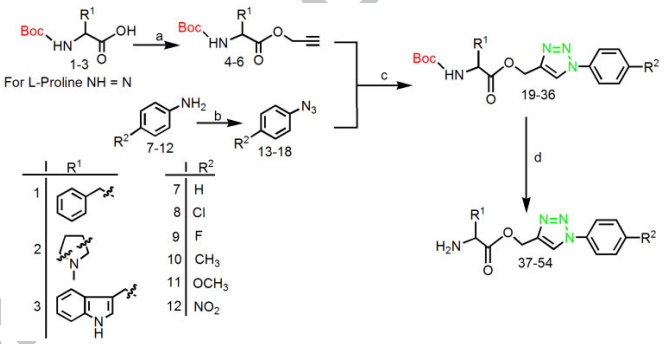


Figure 1. (a) Commonly used anti-leishmanial drugs. (b) Model for this study.[15]

The synthetic pathway to achieve title compounds **37–54** is outlined in scheme 1. Boc protected *L*-amino acid (Phe/Pro/Trp) **1–3** were separately coupled with propargyl bromide using K_2CO_3 in DMF to obtain their propargyl esters **4–6** in excellent yield.[19] On the other hand, phenyl azides **(13–18)** were prepared by the diazotization of corresponding aniline **7–12** with $NaNO_2$ and HCl followed by the reaction with NaN_3 in a single reaction vessel. Aniline and substituted anilines with electron donating as well as electron withdrawing substituents were employed to study their effect on biological activity. Finally, both alkyne and azide components were reacted to obtain the intermediate compounds **19–36** via Huisgen 1,3-dipolar cycloaddition reaction in the presence of $CuSO_4$ and sodium ascorbate in THF:H_2O (1:2) mixture. The key intermediates, **19–36** were deprotected using *p*-toluene sulfonic acid in CH_2Cl_2 to yield the title compounds **37–54** in moderate to good yields (53–98%). All the compounds and intermediates were confirmed by elemental analysis, FT-IR, ^1H, ^{13}C NMR and Mass spectral data. The characterization data of all the intermediate and title compounds along with some representative spectra are given in supplementary information.

The structure of the compound **29** was unequivocally established by X-ray crystallographic analysis. Single crystal of **29** was obtained through the slow evaporation of its hexane-ethylacetate solution. A crystal of suitable size was mounted and single-crystal data was collected at 223K.The crystal structure was solved by direct methods using SHELXS-97[20] and refined with SHELXL-97.[21] The molecular graphics were prepared using XP (Bruker AXS, 2000).The molecule crystallizes in the monoclinic crystal system with $P2_1$ space group. The hydrogen atoms were calculated and refined as riding atoms.The crystal structure (unit cell diagram) and crystal data of the compound are given in Figure 2 and Table 1 respectively. The crystal packing structure of **29** and method of analysis is given in supplementary information.

Scheme 1: Synthesis of 1,2,3-triazole-amino acid hybrids. Reagents and conditions: (a) propargyl bromide, DMF, K_2CO_3, 0 °C–rt, 18–24 h, 94–98%;



(b) $NaNO_2$ in HCl, NaN_3, 0 °C–rt, 2.5 h; (c) $CuSO_4.5H_2O$, sodium ascorbate, THF/H_2O (1:2), rt, 22–24 h, 71–97%; (d) *p*-TSA, DCM, rt, 3–4 h, 53–98%.

Table 1. Crystal data and structure refinement details for **29.**

Identification code	**29**
CCDC number	**1469760**
Empirical formula	$C_{20}H_{26}N_4O_5$
Formula weight	402.45
Temperature	223(2) K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic, $P2_1$ (No. 4)
Unit cell dimensions	a = 5.7080(2), b = 17.1084(5), c = 10.6589(5) Å, β = 92.741(1)°
Volume	1039.7(1) Å^3
Z, calculated density	2, 1.286 gcm^{-3}
Absorption coefficient	0.094 mm^{-1}
Crystal size	0.14 x 0.12 x 0.03 mm
Limiting indices	$\pm h$, $\pm k$, $\pm l$
Reflections collected/unique	6343/3154 [R_{int} = 0.040]
Absorption correction	0.987 ≤ T ≤ 0.997
Final R indices [I > 2s(I)]	R = 0.062, wR^2 = 0.146
Largest diff. peak and hole	0.13 and -0.16 e.Å^{-3}

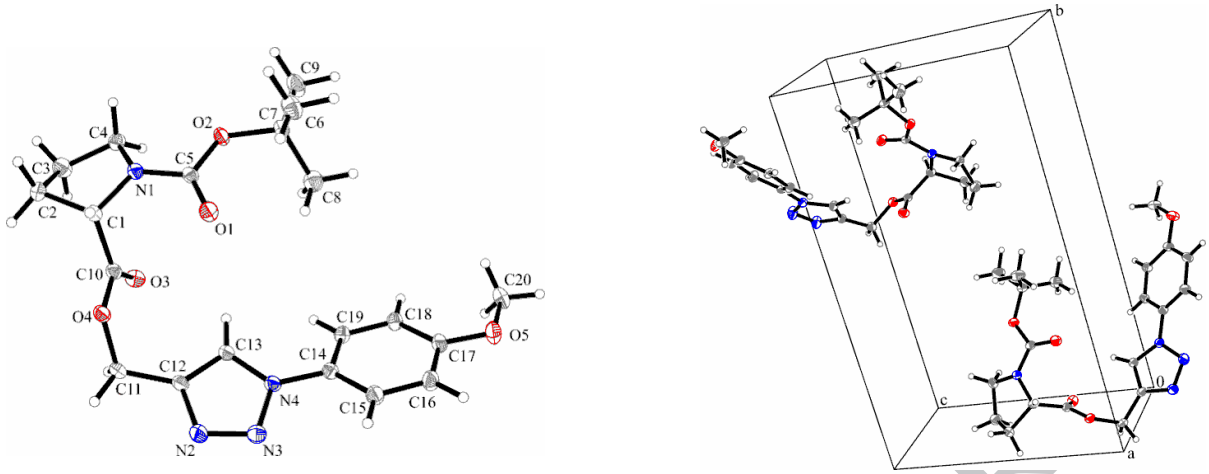
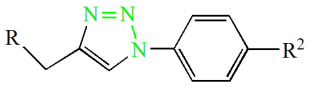
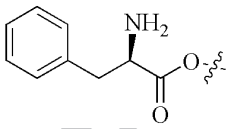
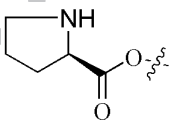
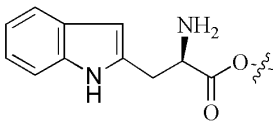


Figure 2. Crystal structure and unit cell diagrams of compound **29** (thermals ellipsoids are shown with 15% probability).

The title compounds (**37–54**) were subjected to their *in vitro* anti-leishmanial activity against *L. donovani* promastigotes (Dd8 strain) and cytotoxicity towards THP-1 macrophages. The IC_{50} values in µM were estimated and the results are presented in Table 2. The standard antileishmanial agent miltefosine was also screened under identical conditions for comparison. None of the compounds showed better anti-leishmanial activity as compare to miltefosine (IC_{50} = 27.07±1.84µM). Moreover, compounds **40, 43** and **53** were found better growth inhibitor with IC_{50} = 88.83 ± 2.93, 96.88 ± 12.88 and 94.45 ± 6.51 µM respectively with no cytotoxicity towards macrophages. The percent cell viability of *L. donovani* and macrophages cells with increasing concentration of the selected inhibitors (**40, 43** and **53**) was also evaluated as shown in Figure 3 and 4, respectively. The results showed dose dependent killing of the promastigotes of *L. donovani*. Even at 100 µM concentration of the inhibitor, no significant decrease in mammalian cell viability was observed, indicating their non-cytotoxic nature.

Table 2. Anti-leishmanial activity of compounds (37–54) against *L. donovani* promastigotes.



Compound	R	R^2	IC_{50} (mean ± SD)[a] µM		Selectivity Index (SI)[b]
			L. donovani promastigotes	THP-1 differentiated macrophages	
37		H	163.33 ± 12.05	504.16 ± 90.10	3.09
38		Cl	132.46 ± 2.48	388.76 ± 79.91	2.94
39		F	132.96 ± 2.48	196.36 ± 12.20	1.48
40		CH_3	88.83 ± 2.93	291.56 ± 26.08	3.28
41		OCH_3	144.33 ± 8.1	260.26 ± 25.57	1.80
42		NO_2	171.23 ± 16.26	179.86 ± 15.36	1.05
43		H	96.88 ± 12.88	780.01 ± 92.61	8.05
44		Cl	157.03 ± 3.69	346.16 ± 29.42	2.20
45		F	121.7 ± 9.84	308.76 ± 15.18	2.54
46		CH_3	175.43 ± 7.48	420.63 ± 54.49	2.40
47		OCH_3	103.50 ± 7.36	217.96 ± 18.81	2.11
48		NO_2	189.36 ± 8.84	343.73 ± 9.75	1.82
49		H	137.80 ± 7.1	190.96 ± 17.51	1.39
50		Cl	129.1 ± 9.87	317.40 ± 15.26	2.46
51		F	151.4 ± 4.34	352.10 ± 37.61	2.32
52		CH_3	99.38 ± 6.09	293.46 ± 30.50	2.95
53		OCH_3	94.45 ± 6.51	194.66 ± 18.49	2.06
54		NO_2	118.60 ± 3.08	174.36 ± 21.39	1.47
Miltefosine			27.07 ± 1.84	54.08 ± 5.07	1.99

[a]SD: Standard Deviation; [b]SI: The ratio of IC_{50} value on macrophage cell line to the IC_{50} value on *L. donovani* promastigotes.

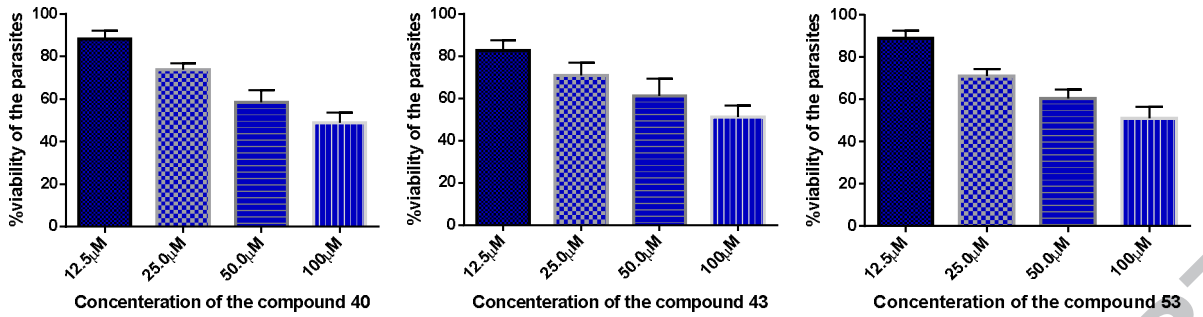


Figure 3. Leishmanicidal effect of **40**, **43** and **53** on promastigotes of *L. donovani*. *L. donovani* promastigotes were treated for 48 h with increasing concentrations of three different compounds.

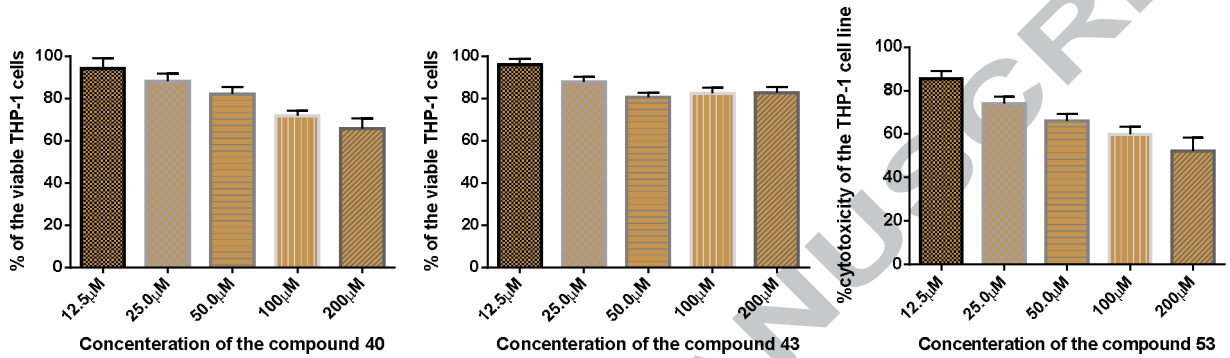


Figure 4. Toxic effect of the inhibitors on THP-1 macrophage. THP-1 macrophages were treated for 24 h with increasing concentrations of the inhibitors and cell viability was assessed.

Compound **43** showed lowest cytotoxicity (IC_{50} = 780.01 ± 92.61 μM) against macrophages and found 14-fold less cytotoxic than miltefosine. Selectivity indices (SIs) (IC_{50} towards normal cells/IC_{50} towards *L. donovani*) were calculated to guide the selection of lead compound for further SAR and *in vivo* testing. Compounds (**40**, **43** & **53**) showed a better toxicity–activity relation than miltefosine and compound **43** showed the highest selectivity index (SI = 8.05) proving it as a good candidate among all the tested compounds.

Structural-activity relationship (SAR) revealed that 1,2,3-triazole pharmacophore flanked with three different amino acid tail show varied antileishmanial activity (Table2). At one end, modification with different amino acid tail (Phe/Pro/Trp) and various substituents on phenyl ring such as halogen, methyl, methoxy and nitro at para position at the other end were performed to explore the SAR of the synthesized compounds **37-54**. Amino acids selected for this study bear heterocyclic ring necessary for hydrophobic interactions as one of the driving force for drug discovery. Among all the triazoles containing phenylalanine tail (**37-42**), compound **40** with *p*-CH_3 substituted phenyl group showed best antileishmanial activity (IC_{50}= 88.83 ± 2.93 μM), while compounds with unsubstituted phenyl ring (**37**) and *p*-NO_2 substituted phenyl (**42**) showed least activity among them. Replacement of phenylalanine with proline tail in compound **43**with unsubstituted phenyl ring (**43**) showed good antileishmanial activity (IC_{50}= 96.88 ± 12.88 μM) followed by *p*-OCH_3 **47** (IC_{50}= 103.50 ± 7.36 μM) while compound **48** with *p*-NO_2 shows least activity (IC_{50}= 189.36 ± 8.84 μM) among them. Among the compounds bearing tryptophan tail, **53** having *p*-OCH_3 on phenyl ring showed potent antileishmanial activity (IC_{50}= 94.45 ± 6.51 μM) followed by *p*-CH_3 **52** (IC_{50}= 99.38 ± 6.09 μM). As observed from the activity data, introduction of halogen substituent (*p*-Cl or *p*-F) on phenyl ring did not showed significant antileishmanial activity among all the compounds. Similarly, compounds **42**, **48** and **54** with *p*-NO_2 group were found less effective than compounds **40**, **47**, **52** and **53** with electron donating substituent at phenyl ring. Though activity was also related with the amino acid tail. The effect of phenyl substituents was predicted by docking investigations. The substituents on phenyl ring in compounds **40, 43** and **53** are making hydrophobic interactions with hydrocarbon side chain of non-polar Ile458.

Further to gain insights into the possible reasons for activity and binding of the potent compounds **40**, **43** and **53**, we docked them against three-dimensional trypanothione reductase (TryR) of *L. infantum*. Since trypanothione is absent in humans and is essential for survival of the parasitic protozoa like *Leishmania* and *Trypanosoma*, the uniqueness of the parasite thiol metabolism renders trypanothione reductase (TryR) as an attractive target for the development of new antiparasitic drugs.[22] The molecular docking was carried out using X-ray crystal structures of trypanothione reductase from *L. infantum* (PDB code: 2jk6, resolution:2.95 Å).[23,24] as there is 98% similarity between the trypanothione reductase of *L. donovani* and *L. infantum*.[23] Compound **40**, **43** and **53** occupied a pocket near to catalytic site (Cys52-His461-Cys57) and displayed strong hydrogen bond of N-H in **40** and **53** and tertiary nitrogen of triazole in **43** with Thr463. Compound **40** and **53** adopted similar conformation, and shows π-π stacking of trizole with His461 and hydrophobic interaction with Pro462, this stabilizes the structural orientation of ligands in to the protein. Terminal aromatic ring is showing hydrophobic interactions with Asn340, Arg472, and Ile458. The three representative examples **40**, **43**, and **53** revealing the mode of interactions are provided in Figure 5. Overall, these hypothetical docking observations indicate that the compounds are showing sufficiently strong inhibition, which may play important role against promastigotes of *L. donovani*.

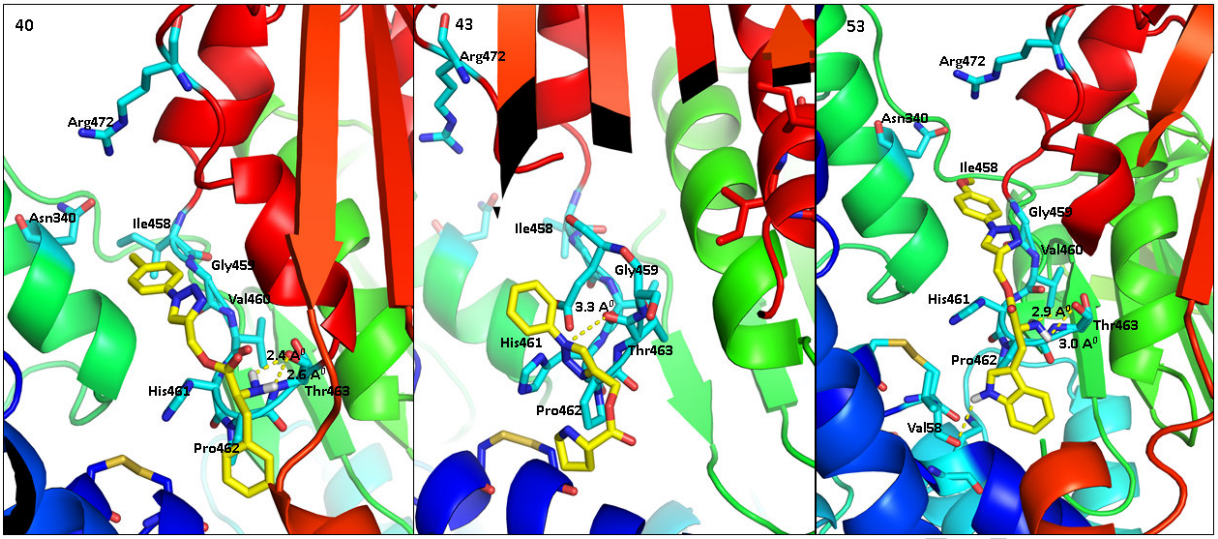


Figure 5. Predicted binding mode and docking in to the TryR homodimer. Ligands **40**, **43**, and **53** are shown in stick models (yellow color). Hydrogen bonding interactions are shown as yellow dashes. Residues involved in hydrophobic interactions and hydrogen bonding are represented in stick models.

The evaluation of important physico-chemical properties of drug like molecules is an important step in the process of drug discovery. Most of the drugs fail at clinical trial because of the poor physico-chemical properties. This prediction became very popular in drug discovery and designing process to screen out the drug like molecules at an initial stage. Here, we did *in silico* physico-chemical prediction for all the tested amino acid-triazole hybrids (**37-54**) using QikProp version 3.2, Schrödinger software. Along with Lipinski's parameters, the values for other important physico-chemical parameters such as molecular weight (MW), dipole moment (D), solvent accessible surface area (SASA), total polar surface area (PSA), number of rotatable bonds (NRB), predicted aqueous solubility (QP log S), prediction of binding to human serum albumin (QP log Khsa), predicted brain/blood partition coefficient (QP log BB) etc were also calculated and found within the range with reference of 95% drugs. Aqueous solubility, lipophilicity, polar surface area and molecular weight are important parameters, which define absorption, movement and action of drug molecule. The results of physico-chemical properties showed that all the compounds have drug like properties. All the eighteen compounds follow Lipinski's rule of 5. According to Lipinski rule of five, any orally active drugs should not violate more than one of its parameters. The important Lipinski parameters are number of hydrogen bond acceptor HBA (not more than 10), number of hydrogen bond donor HBD (not more than 5), molecular mass (< 500), octanol-water partition coefficient (QP log Po/w) ≤ 5 and molar refractivity (in the range of 40-130). No compound showed violation of Lipinski rule of 5. Moreover, compounds **40**, **43** & **53** have 78-84% predicted bioavailability along with other favorable physico-chemical properties. Therefore, these compounds have potential for ensuing development as oral agents and can be potentially active drug candidates after extended SAR and pharmacological investigations. All the results of *in silico* physico-chemical prediction are summarized in Table 4.

In conclusion, a series of eighteen new 1,2,3-triazole-amino acid hybrids (**37-54**) were synthesized using click chemistry approach. All the newly synthesized intermediates and final compounds were well characterized by ^{1}H, ^{13}C NMR, mass spectroscopic techniques and elemental analysis. In the pharmacological evaluation, compounds **40, 43** and **53** exhibited good inhibitory activity against promastigote form of *L. donovani* (Dd8 strain) with IC_{50} of 88.83 ± 2.93, 96.88 ± 12.88 and 94.45 ± 6.51 μM respectively. The lead inhibitors were also found non-toxic against THP-1 macrophages using MTT assay. Selected compounds showed a better toxicity–activity relation than miltefosine. In docking study, we predicted that our compounds might bind to the catalytic site of TryR and fit well into the functional catalytic pocket with favorable hydrophobic and hydrogen bonding interactions. *In silico* prediction of physico-chemical properties for all the compounds was found within the permitted range and no compound violate Lipinski's rule of 5. The inhibitors **40**, **43** and **53** with better IC_{50} and high selectivity indices can be taken as lead for further development for the search of better and safe anti-leishmanial agents.

Acknowledgments

M. Abid gratefully acknowledges University Grants Commission (UGC), Govt. of India for awarding RAMAN Postdoctoral Fellowship in USA (F. No. 5-123/2016(IC)). M. M. Masood acknowledges the financial support from University Grants Commission (UGC), Govt. of India in the form of Teacher Fellow (F. No. 27–109/2014 (TF/NRCB)).

Conflict of interest

No conflict of interest.

Supplementary data

CCDC 1469760 (compound **29**) contain the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version.

Table 4. Physico-chemical parameters of compounds **37 – 54.**

Comp	MW	D	SASA	PSA	NRB	HBD	HBA	QP log Po/w	QP logS	QP log Khsa	QP log BB	App. Caco-2	App. MDCK	QPog Kp (cm/hr)	VLR5	%HOA
37	322.36	5.750	646.860	90.642	6.00	2.00	5.00	2.976	-3.95	0.329	-0.814	129	60	-3.979	0	82

38	356.81	3.705	670.892	90.644	6.00	2.00	5.00	3.464	-4.679	0.440	-0.668	129	148	-4.147	0	85
39	340.35	3.520	655.858	90.644	6.00	2.00	5.00	3.209	-4.311	0.369	-0.710	129	108	-4.114	0	84
40	336.39	6.346	678.053	90.642	6.00	2.00	5.00	3.272	-4.491	0.478	-0.849	129	60	-4.180	0	84
41	352.39	6.107	681.235	98.933	7.00	2.00	5.75	3.067	-4.147	0.343	-0.899	129	60	-4.089	0	83
42	369.38	7.300	693.731	135.071	7.00	2.00	6.00	2.325	-4.282	0.330	-1.993	15	5	-6.037	0	62
43	272.31	5.801	570.791	81.251	3.00	1.00	5.50	1.858	-3.008	0.006	-0.408	182	87	-4.657	0	78
44	306.75	3.799	594.866	81.250	3.00	1.00	5.50	2.346	-3.737	0.118	-0.258	182	214	-4.825	0	81
45	290.30	3.621	579.817	81.250	3.00	1.00	5.50	2.091	-3.369	0.047	-0.303	182	157	-4.791	0	80
46	286.33	6.383	601.723	81.251	3.00	1.00	5.50	2.152	-3.544	0.155	-0.439	182	87	-4.859	0	80
47	302.33	6.653	605.652	89.541	4.00	1.00	6.25	1.934	-3.181	0.006	-0.491	182	87	-4.765	0	79
48	319.32	6.209	597.375	124.830	4.00	1.00	6.50	1.106	-2.949	-0.046	-1.410	22	9	-6.669	0	58
49	361.40	8.422	693.954	104.097	6.00	3.00	5.00	3.196	-4.596	0.471	-1.112	79	35	-4.322	0	80
50	395.85	6.376	718.018	104.098	6.00	3.00	5.00	3.683	-5.323	0.581	-0.970	79	87	-4.491	0	82
51	379.39	6.176	702.969	104.098	6.00	3.00	5.00	3.428	-4.956	0.510	-1.010	79	63	-4.457	0	81
52	375.43	9.023	725.865	104.096	6.00	3.00	5.00	3.495	-5.146	0.620	-1.155	79	35	-4.521	0	81
53	391.43	8.845	728.720	112.387	7.00	3.00	5.75	3.297	-4.818	0.493	-1.203	79	35	-4.431	0	80
54	408.42	4.893	732.441	147.528	7.00	3.00	6.00	2.534	-4.810	0.462	-2.253	10	3	-6.296	0	60

Abbreviations: Comp = compound; MW = molecular weight; D = dipole moment (D); SASA = solvent-accessible surface area; PSA = total polar surface area; NRB = number of rotatable bonds; HBD = hydrogen bond donor; HBA = hydrogen acceptor; QP log P o/w = predicted octanol/water partition coefficient; QP log S = predicted aqueous solubility; QP log Khsa = prediction of binding to human serum albumin; QP log BB = predicted brain/blood partition coefficient; App. Caco-2 = apparent Caco-2 cell permeability (nm/sec); App. MDCK = apparent MDCK cell permeability (nm/sec); QP log Kp = predicted skin permeability; VLR5 = violence of Lipinski rule of 5; %HOA = % Human Oral Absorption.

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Graphical Abstract

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Anti-leishmanial and cytotoxic activities of amino acid-triazole hybrids: Synthesis, biological evaluation, molecular docking and *in silico* physico-chemical properties.

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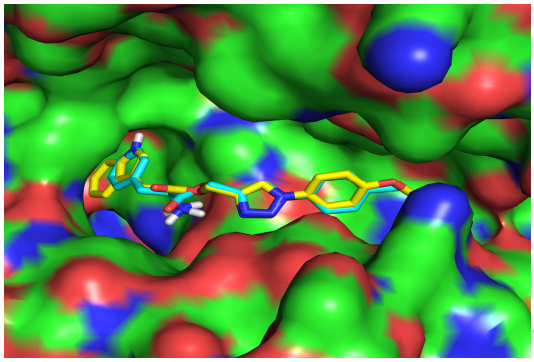

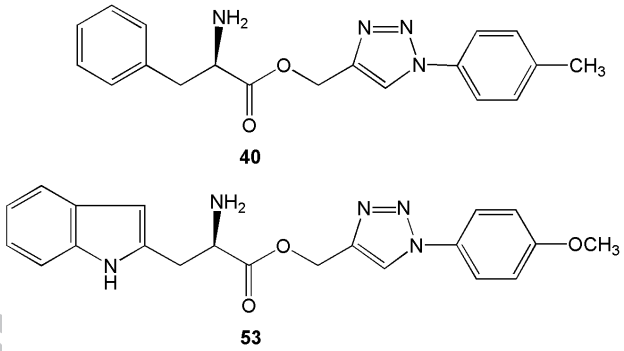

Surface overlay of compounds 40 (cyancolor) and 53 (yellow color) with Trypanothione reductase.