Design, Synthesis and Biological Evaluation of Novel Tetrahydro-β-Carbolines With Potent Anti-Plasmodial Activity

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Abstract

Malaria is one of the most challenging diseases. Over three billion people are threatened by the parasite worldwide and one million are killed each year, mostly children. *Plasmodium falciparum* accounts for the most severe and fatal form of the disease. Adopting repurposing strategies for drug development, a series of novel tadalafil (an approved PDE5 inhibitor) analogs was rationally designed, synthesized, and evaluated as antimalarial agents. The novel analogs were designed to retain the tetrahydro-β-carboline nucleus of tadalafil, the pendant aryl benzodioxol was substituted by *p*-bromophenyl, *p*-chlorophenyl, 2,6 dichlorophenyl or 2,4 dimethoxyphenyl rings. Moreover, the *N*-methyl substituent of the piperazinedione ring was replaced by substituents namely: benzyl, 2,6 dichlorobenzyl, 2,6 difluorobenzyl or cyclohexylmethyl ring. Besides, we manipulated all stereochemical aspects *via* the preparation of all possible diastereomers. The newly synthesized compounds were evaluated *in vitro* for their anti-plasmodial activity against *P. falciparum* using the Plasmodium lactate dehydrogenase (pLDH) assay and for their cytotoxicity against HeLa cells. Compound 3, the most active compound, showed IC_{50} of 0.08 µM versus pLDH, CC_{50} > 20 µM and SI_{50} > 250, indicating a safe profile of most of the novel molecules. Whether the anti-plasmodial activity is facilitated *via* plasmodial PDE activity is still being investigated.

Introduction

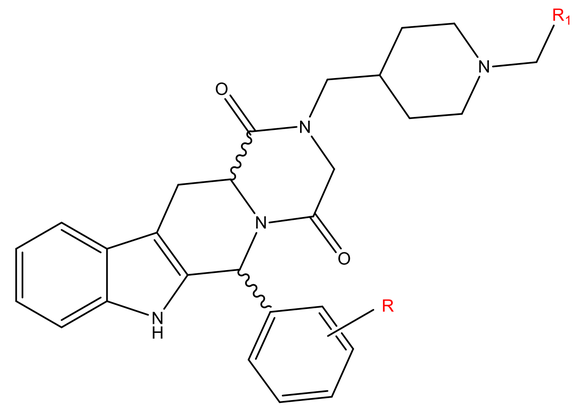
Malaria is one of the significantly fatal diseases over the decades; that has huge economic loss globally. β- carboline-containg scaffolds that are present in many pharmacologically active drugs were found to have positive results against *p. falciparum*. For example, a β-carboline alkaloid called manzamine A confirmed potent activity as an anti-plasmodial both *in vivo* and *in vitro* among the natural compounds.(1) Drug repurposing of already safe marketed drugs used for the treatment of other diseases is a useful tool for discovery of new drug candidates. Tadalafil analogues-a previously reported PDE5 inhibitor used for the treatment of Male Erectile Dysfunction (MED) was reported as potent Anti-Malarial agents. (2) Accordingly, we designed and synthesized our compounds bearing the main THBC scaffold of tadalafil , the effect of structural modifications on both the anti-plasmodial activity and cytotoxicity of the compounds were evaluated.

References

1-Gorki, V., Singh, R., Walter, N. S., Bagai, U., & Salunke, D. B. (2018). Synthesis and Evaluation of antiplasmodial efficacy of β-carboline derivatives against murine malaria. *ACS omega*, *3*(10), 13200-13210.

2-Beghyn TB, Charton J, Leroux F, Laconde G, Bourin A, Cos P, Maes L, Deprez B. (2011) Drug to genome to drug: discovery of new antiplasmodial compounds. *J Med Chem* 54(9),3222-3240.

Results and Discussion



1-7

Table 1: Antiplasmodial activity, cytotoxicity and selectivity of compounds 1-7

Cpd#	R	R_1	pLDH Assay IC_{50} ± SD (µM)	HELA cell Assay (20 µM)		Selectivity Index	Stereo -chemistry
				% viability ± SD (µM)	IC_{50} ± SD		
1	2, 4 -OCH_3	-2,6-dichloro phenyl	0.88± 0.06	97.2 ±4.3	>20	>24.39	*R,R*
2		-2,6-difluoro-phenyl	0.48± 0.10	87.3 ±1.9	>20	>52.63	*R,R*
3		-Phenyl	0.08± 0.01	91.8 ±0.2	>20	>285.71	*R,R*
4	4-Cl	-2,6-dichloro-phenyl	0.66± 0.04	95.4 ±1.9	>20	>32.26	*R,R*
5		-Cyclo hexyl	0.53± 0.05	-0.7 ±0.0	4.8± 0.03	10.06	*R,R*
6		-Phenyl	0.78± 0.005	94.6 ±2.9	>20	>25.81	*S,S*
7	4-Br	-2,6-difluoro phenyl	0.63± 0.04	83.4 ±0.7	>20	>33.90	*R,R*

Conclusion

- **Drug repurposing leads to development of novel safe drugs , it is a time saving method for screening for new treatments.**
- **The novel series of tadalafil analogues showed sub micromolar activity against *Plasmodium falciparum*.**
- **All the possible stereochamical isomers were prepared. Most of the active analogues were in a *cis* configuration (*R,R)*, this stereochemical requirement is also essential for PDE5 activity.**
- **Compounds activity was not mediated *via* plasmodial PDE5 *(data not shown).***
- ***Most of the compounds showed cytotoxicity >20 µM , compounds* with high selectivity reflect their high safety profile.**
- **Compound 3 was the most active with IC_{50} 0.08 µM and with selectivity Index more than 285.71.**