Anti-malarial Compound: A mini review on 1, 3, 5-triazine derivative

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Abstract

Anti-malarial drug are the natural, chemical, synthetic and semi-synthetic agent, which works against the malaria parasite in the human. Here we summarised some selective researcher anti-malarial molecule which is derivative of 1, 3, 5-triazine along with their in vivo study.

Keywords: Triazine and Anti-malarial

Introduction

Malaria is a life-threatening disease caused by parasites that are transmitted to people through the bites of infected mosquitoes. According to the latest estimates, released in December 2013, there were about 207 million cases of malaria in 2012 (with an uncertainty range of 135 million to 287 million) and an estimated 627 000 deaths (with an uncertainty range of 473 000 to 789 000). Malaria mortality rates have fallen by 45% globally since 2000; and by 49% in the WHO African Region. Most deaths occur among children living in Africa where a child dies every minute from malaria. Malaria mortality rates among children in Africa have been reduced by an estimated 54% since 2000 (WHO, 2013).

Anti-malarial drug are the natural, chemical, synthetic and semi-synthetic agent, which works against the malaria parasite in the human. Most widely and commonly used anti-malarial drug belongs to the folate antagonist class; generally, folate antagonists are classified in to two classes like Type- I anti-folate and Type- II anti-folate (Alexis Nzila, 2005). The enzymes involved in folate pathway inhibited thus resulted in reduced DNA, serine and methionine formation; in this review, consideration about Type- II anti-folate is done (John E. Hyde 2005). Type-II anti-folate covered

Pyrimethamine, biguanides, Triazine metabolites and Quinazolines. These type of anti-folate inhibit dihydrofolate reductase (DHFR a bifunctional enzyme in plasmodia coupled with thymidylate synthase) as prevent the NADPH-dependent reduction of H2 folate (DHF); to H4 folate (THF) by DHFR (David C. Warhurst 1998, Olliaro P, 2001 & Giancarlo et al 2005).

Agarwal et al synthesized a series of 15 compounds of 2, 4, 6-trisubstituted pyrimidines derivatives; all the synthesized compounds were screened against P. Falciparum NF 54 strain. Out of the 15 compounds, about 11 compounds showed MIC in the range of 0.5-2 µg/ml. For synthesis of these derivatives, 4-acetylpyridine was reacted with different aldehydes in 10% aqueous NaOH and methanol to yield the corresponding chalcones. These chalcones were further reacted with Morpholine-4-carboxamide hydrochloride in presence of sodium hydroxide to obtain final product (2, 4, 6-trisubstituted pyrimidines) (Fig. 1).

The compound having phenyl substituent showed MIC of 2µg/ml while the second compound having substitution phenyl with methoxy group at 4th position showed MIC of 2µg/ml while the 3rd compound having phenyl substitution with methoxy group at 3rd position showed MIC of 2µg/ml.

The derivatives having 2, 3- dimethoxy phenyl substitution and 2, 5- dimethoxy substitution showed MIC of 1µg/ml. The compound having 2, 4, 5-trimethoxy substitution showed MIC value of 0.5 µg/ml which the best one among all pyrimidine derivatives.

The derivatives having 3, 4- dimethoxy substitution and 4-methoxynaphthalene showed MIC value of 1µg/ml. The compounds possed phenyl substitution with nitro group at 3rd position showed MIC of 1 µg/ml while the derivative having benzene ring substituted with thiophene at 2nd position showed MIC of 1 µg/ml (Agarwal, 2005).

Lee et al synthesized successfully combinatorial mixtures synthesis of dihydrophenyl triazines by traditional one pot three component syntheses, which is nonclassical, dihydrofolate reductase (DHFR) inhibitors. In each library eight-reaction mixture pot were designed in each pot there were three dihydroxyphenyl triazines. The compound synthesized were in number were 64.

In the three components combinatorial mixture synthesis, a mixture of 3 substituted anilines, cyanoguanidine, a ketone and concentrated hydrochloric acid were taken and reflux for half an hour to 30h. In case of second and third library gentle heating were done instead of reflux; the molecules were detected by HPLC. All the 64 compounds were screened against rat liver enzyme.

From the first library, in pot I-6, di hydro phenyl Triazine molecule inhibited 50% of rat liver enzymes at 0.022µM concentration. When these three dihydrophenyl Triazine molecules evaluated...
individually against rat liver enzyme, the first molecule show IC₅₀ at 0.084µM, II\textsuperscript{nd} molecule at 0.088µM and the III\textsuperscript{rd} molecule at 0.006µM concentration respectively (Fig. 2).

From the second library, in pot II-2 di hydro phenyl Triazine molecule inhibited 50% of rat liver enzymes at 0.078µM concentration. Again when these three molecule screened individually against rat liver enzyme, I\textsuperscript{st} molecule show IC₅₀ at 82µM, II\textsuperscript{nd} molecule at 0.096µm and III\textsuperscript{rd} molecule at 4.7µM concentration respectively (Fig. 2).

The molecules obtained from third library show least activity against the rat liver enzyme. Only one molecule obtained from pot-6 showed IC₅₀ at 3.2µM concentration (Lee; 1999).

Kumar et al (2011) synthesized a series of novel hybrid class 4-anilinoquinoline triazines derivatives; the entire molecule derived screened for their anti-malarial activity in vitro against CQ sensitive 3D7 strain of P. Falciparum. The molecules also screened for their cytotoxicity against VERO cell line.

The synthesis of 2,4,6-trisubstituted-[1,3,5] triazines obtained by consecutive nucleophilic substitution of cyanuric chloride; First chlorine of cyanuric chloride was displaced with the moderately nucleophilic aromatic amines at 0°C for 1 h to give the mono-substituted triazines followed by the reaction with more nucleophilic amine to provide the di-substituted triazines. Final chlorine of di-substituted triazines was replaced with excess of piperazine (3 times) at 0°C to afford the corresponding 2, 4, 6-trisubstituted triazines. Coupling of 4, 7 dichloroquinoline with excess of 2-amino ethanol gave the 2-(7-chloro-quinolin-4-ylamino)-ethanol in a good yield.

Chemoselective o-mesylation was achieved in pyridine at 0°C for 5 h to yield the methanesulfonic acid 2-(7-chloro-quinolin-4-ylamino)-ethyl ester. Methanesulfonic acid 2-(7-chloro-quinolin-4-ylamino)-ethyl ester was subjected to nucleophilic substitution with trisubstituted triazines to yield the corresponding targeted compounds under microwave condition. All the synthesized compounds were well characterized by IR, mass, NMR, and elemental analysis.

The target molecules were 19 in numbers, which were screened against Falciparum; in all these molecules only 5 molecules showed good suppression activity against P. falciparum. First molecules having substitution at R₁ = p-Fluoroaniline having substitution at   R₂ = Piperidine showed IC₅₀ value at 7.15 ng/ml concentration and second molecule having substitution at R₂ = Cyclohexylamine showed IC₅₀ value at 7.83ng/ml concentration.

Third molecule represent substitution at R₁ = Piperidine and R₂ = Cyclohexylamine showed IC₅₀ value at 4.43 ng/ml concentration. Fourth molecule having same substitution at R₁ aniline but having substitution at R₂ Piperidine showed IC₅₀ value at 17.82ng/ml and fifth having substitution at R₂ Cyclohexylamine showed IC₅₀ value at 7.15 ng/ml concentration.
value at 16.23ng/ml concentration. In all these molecules, molecule 3rd showed suppression about 99.9% on 4th day and 99.11% on 6th day against chloroquine resistant strain N-67 of P. yoelii in swiss mice at dose 50 mg/kg/day by intraperitoneal route (Fig. 3) (Kumar, 2011).

Katiyar et al (2005) synthesized a series of 2-[3, 5-substituted pyrazol-1-yl]-4,6-trisubstituted Triazine derivatives. The compounds synthesized were 22 in number; Substituted acetophenone react with CS₂ in the presence of NaH followed by methylation with methyl iodide give 3,3-bis-methylsulfanyl-1(substituted-phenyl)-propenone which further react with hydrazine hydrate in methanol to give 5-methylsulfanyl-3-(substituted-phenyl)-1H-pyrazole, further react with cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) in the presence of K₂CO₃ to obtain 2,4-dichloro-6-[5-methylsulfanyl-3-(substitutedphenyl)-pyrazol-1-yl]-[1,3,5]-triazine which on nucleophilic substitution with different amines to obtain the final targeted compounds.

All these final derivatives were studied by spectroscopic methods eg.IR, mass NMR and elemental analysis. All these final derivatives were screened against Plasmodium falciparum NF-54 strain.

In all these 22 final derivatives, 6 derivatives showed MIC in the range of 1 and 2 µg/ml while 6 another derivatives showed MIC 10 µg/ml (Fig. 4).

The 1st molecule having 3, 4, 5-trimethoxy phenyl group at position 3 of the pyrazole ring and O-tolyl amino group at positions 4 and 6 of the Triazine ring showed MIC 1µg/ml while 2nd molecule having the same substituents at positions 4 and 6 of the Triazine ring and 3, 4-dimethoxy phenyl group at position 3 of the pyrazole ring showed MIC 10µg/ml. The 3rd molecule having the 3,4,5-trimethoxy phenyl substituent having at positions 4 and 6 of the Triazine nucleus and 3,4-dimethoxy phenyl group at position 3 of the pyrazole ring showed 2µg/ml MIC. The 4th molecule having substitution 3,4,5-trimethoxy phenyl at position 3 of the pyrazole ring and benzyl amino group at positions 4 and 6 of the Triazine ring, has shown MIC of 2 µg/mL.

The 5th molecule showed MIC of 2 µg/mL, having the cyclohexyl amino group at positions 4 and 6 of the Triazine ring and 3,4,5-trimethoxy phenyl at position 3 of the pyrazole ring. The molecules 6th and 7th have shown MIC of 1 and 10 µg/mL, respectively.
Both have 3,4,5-trimethoxy phenyl substituent at position 3 of the pyrazole ring and ethyl amino morpholino and propyl amino morpholino groups, respectively, at positions 4 and 6 of the Triazine ring. Compounds 8th and 9th having 3,4-dimethoxy phenyl group at position 3 of the pyrazole ring and ethyl amino morpholino and propyl amino morpholino groups, respectively, at positions 4 and 6 of the Triazine ring have shown MIC of 2 and 10 μg/mL, respectively. In all these molecules having MIC value 1-2 μg/ml are 32 times more potent than cycloguanil, which was used as standard drug (Katiyar et al., 2005).

Sunduru et al (2009) synthesized a series of hybrid of 4-aminoquinoline with Triazine functionalities in the side chain. All the derivatives obtained (20 in numbers) were screened against CQ sensitive strain 3D7 of P. falciparum in an in vitro assay. Among the 20 molecules, 4 of them show several times more active than CQ.

The 1st derivative possessed substitution at Z= 1,2-Ethylendiamine ,R3= Piperidine and R4= N-Methylpiperazine showed IC50 value 7.88ng/ml while the 2nd molecule having same substitution at Z but having Morpholine substitution at R3 and N-Methylpiperazine substitution at R4 showed IC50 value 10.02ng/ml.

The 3rd molecule obtained having 1,3-Propanediamine substitution at Z, Piperidine substitution at R3 and 3-Aminopropylmorpholine at R4 showed the best IC50 value among all derivatives obtained. Its IC50 value was 5.23ng/ml.

Another 4th derivative obtained having 1,3-Propanediamine substitution at Z and Piperidine substitution at R3 as above molecule but having R4 substitution N,N-Diethylethylenediamine having IC50 value 8.97ng/ml. The third molecule further screened in in vivo model against CQ resistant N-67 strain of P. yoelii in swiss mice at 50mg/kg/day for four days by intraperitoneal route, it is found toxic against this strain (Fig. 5) (Sunduru, et al., 2009).

Kumar et al (2009) synthesized a new class of hybrid anti-malarial agents, which were 9-anilinoacridine Triazine. The molecules synthesized were 22 in number. The derivatives synthesized using 6,9-dichloro-2-methoxy acridine and cyanuric chloride as starting molecule.

All these hybrid molecules obtained were screened against CQ-sensitive 3D7 strain of Plasmodium falciparum for their antiplasmodial activity and their cytotoxicity were evaluated on VERO cell line. The first molecule possess substitution Aniline at R1 and 4-(2 Aminoethyl) morpholine at R2 having IC50 value 6.97nM. The second molecule having Aniline at R1 position and N,N-Dimethylethylenediamine atR2 showed IC50 value 7.95nM.

The third molecule showed IC\textsubscript{50} value 4.21nM having Aniline substitution at R\textsuperscript{1} and N,N-Dimethylpropylenediamine substitution at R\textsuperscript{2}. The fourth molecule represents aniline at R\textsuperscript{1} and 2-Amino-1-ethanol at R\textsuperscript{2} showed IC\textsubscript{50} value 9.46nM. The fifth molecule having aniline substitution at R\textsuperscript{1} and hydrazine substitution at R\textsuperscript{2} showed IC\textsubscript{50} value 4.27nM; and IC\textsubscript{50} value of CQ was 8.15 (Fig. 6) (Kumar et al., 2009).

Agarwal et al synthesized a series in 2005 of 2,4,6-trisubstitued-1,3,5-triazines. All the 19 molecules were screened against P. falciparum NF54 strain. Out of the 19 derivatives, 8 derivatives show MIC in the range of 1-2 \(\mu\)g/ml while 7 derivatives show 10 \(\mu\)g/ml MIC. All these compounds were synthesized from 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) by reacting with different nucleophiles in presence of THF. The 1\textsuperscript{st} molecule having R as N-methyl piperazine showed MIC value of 1 \(\mu\)g/ml while the 2\textsuperscript{nd} molecule possessed N-benzyl piperazine as R showed 2 \(\mu\)g/ml MIC value. In the 3\textsuperscript{rd} molecule when R value represents imidazole, MIC value observed 1 \(\mu\)g/ml. The 4\textsuperscript{th} molecule having R as 4-(3-aminopropyl) morpholine and in 5\textsuperscript{th} molecule when R value represent 4-(2-aminoethyl) morpholine MIC value obtained 2 \(\mu\)g/ml in both cases; When the R group was cyclohexylamine in 6\textsuperscript{th} molecule, MIC value 1 \(\mu\)g/ml. In 7\textsuperscript{th} molecule Substitution at R cycloheptylamine MIC value observed 2\(\mu\)g/ml; When the R group was n-butylamine in 8\textsuperscript{th} it showed a MIC of 2\(\mu\)g/ml. All these derivatives showed MIC in the range of 1-2\(\mu\)g/ml, which were 32-64 times more potent than cycloguanil (Fig. 7) (Agarwal et al., 2005).

Manohar et al (2009) synthesized 22, 4-aminooquinoline–triazine conjugates with different substitution. All the conjugates were evaluated against CQ sensitive and resistant strain of Plasmodium Falciparum (D6 clone) and Plasmodium Falciparum (w2 clone). The target compounds were synthesized by the consecutive nucleophilic substitution of cyanuric chloride with different nucleophiles and characterized spectroscopically. In all 22 conjugates 4 of them show good activity in the range of 0.21-0.48\(\mu\)M; The first molecule has R as Morpholine, R\textsuperscript{1} as 3,5-Dimethoxy aniline and X as 1,3-Propanediamine showed IC\textsubscript{50} value 0.25\(\mu\)M against CQ sensitive strain (P. falciparum -D6 clone) and 0.22 \(\mu\)M against CQ resistant strain (P. falciparum -W2 clone). When the R, R\textsuperscript{1} and X groups were Morpholine, 3,5-Dimethoxy aniline and 1,8-Octanediamine respectively in second compound, IC\textsubscript{50} value observed 0.48 \(\mu\)M against CQ sensitive strain and 0.35 \(\mu\)M against CQ resistant strain. In the third molecule at both R and R\textsuperscript{1} aniline group present and X group as 1,2-Ethylenediamine having 0.21\(\mu\)M IC\textsubscript{50} against CQ sensitive strain and 0.25 \(\mu\)M IC\textsubscript{50} against CQ resistant strain.
In fourth molecule o-Toluidine group present at both R and R' and 1,6-Hexanediamine group present at X having IC\textsubscript{50} value 0.31 µM against CQ sensitive strain and 0.38 µM against CQ resistant strain (Fig. 8) (Manohar et al., 2009).

Bhat et al (2011) synthesized a novel series of 4-aminoquinolines-1,3,5-triazine hybrid; The synthesis carried out by displacement of chlorine atoms of 2,4,6-trichloro-1,3,5-triazine by different aromatic nucleophiles. Total 7 novel molecules have been synthesized in which three molecule have showed comparative good antimalarial activity (in comparison with chloroquine under same condition) when further screened against chloroquine sensitive RKL 2 strain of Plasmodium falciparum (Fig. 9).

The first molecule anti-malarial activity (% dead rings+schizonts) obtained 47.5. The second molecule anti-malarial activity (% dead rings+schizonts) obtained 56.0 and; The anti-malarial activity of third molecule is (% dead rings+schizonts) obtained 51.5, while the dose of all derivatives 50 µg/ml whereas for chloroquine 0.4 µg/mL. (The anti-malarial activity (% dead rings+schizonts) for CQ was 50.5) (Fig. 9) (Bhat, et al., 2011; 2013).

David Gravestock et al (2011) synthesized a small novel set of 2,N\textsuperscript{6} -disubstituted 1,2-dihydro-1,3,5-triazine-4,6-diamines possessing a flexible tether between the exocyclic nitrogen bonded to C-6 of the 1,2-dihydro-1,3,5-triazine-4,6diamine heterocycle and the distal aryl ring. All the compound collected screened against the FCR-3 P. falciparum strain, which was originally isolated from the Gambia, West Africa, resistant against cycloguanil. Several compounds were tested displayed antimalarial activity against cycloguanil (IC\textsubscript{50} = 4.995µM). The compounds (4 in numbers) having furanyl derivative were approx. 5 fold more active than cycloguanil (Fig. 10).
Conflict of interest

No

Reference


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