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AN OVERVIEW ON MICROWAVE ASSISTED SYNTHESIS OF ANTIMALARIAL COMPOUNDS

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ABSTRACT

The present review article offers a detailed account of the microwave irradiation synthesis of novel ligands for antimalarial potential. Microwave synthesis being an economical method, time saving and environmental friendly will be best suitable for future of antimalarial drugs. The synthesis by microwave irradiation and antimalarial studies of various drugs as per the future need of medical and pharmaceuticals have been discussed. Some of the derivatives synthesised by microwave irradiation method discussed here includes: benzothiazole-spirooxindole derivatives; pyrimidine derivatives; 4-benzyloxy- and 4-aryloxy-2 trichloromethylquinazolines; 2, N_6-disubstituted 1,2-dihydro-1,3,5-triazine-4,6-diamines; 4-aminoquinolines; etc.

KEYWORDS: Malaria, Microwave irradiation, Antimalarial potential.

INTRODUCTION

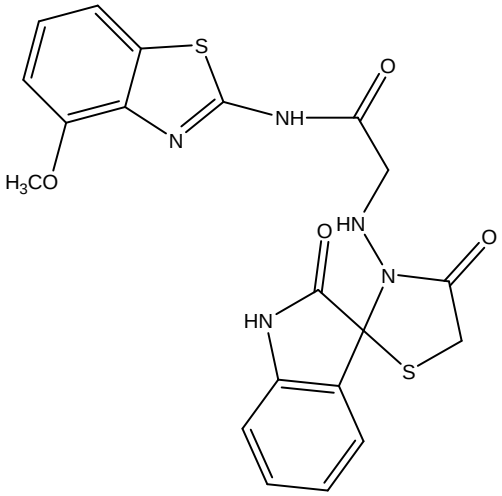
Malaria is a major health concern in many tropical and subtropical nations. Over the last fifteen years, further efforts in the development of novel antimalarials have lowered the frequency of this global illness.[1] Plasmodium falciparum, Plasmodium Vivax, Plasmodium Ovale, and Plasmodium Malariae are all Plasmodium species that pose a serious health risk to humans. *Plasmodium falciparum* considered most threat full in terms of death and *Plasmodium Vivax* considered major cause of illness and death across large parts of the world.[2] The simian parasite *Plasmodial knowlesi* has lately emerged as a major cause of malaria in Malaysia and Southeast Asia. There is no evidence of human-to-human transmission of this parasite.[3]

Green chemistry is a new and fast growing alternative to standard chemical synthesis methods. Even after maximal resource use, it refers to the generation of the smallest amount of chemical waste possible. Green chemistry prevents the creation of by-products as well as the usage of toxic and dangerous solvents. As a result, they are adaptable for use in chemistry's combinatorial synthesis.[4] In 1986, Gedye and Giguere proposed using microwaves to speed up organic chemistry reactions. Microwave irradiation was thus introduced into organic chemical synthesis.[5] Because of the quick reaction time and rapid optimization of chemical reactions, it became a popular technology.[6-8] This method is gaining popularity as a means of speeding up the drug research and development process.

REVIEW

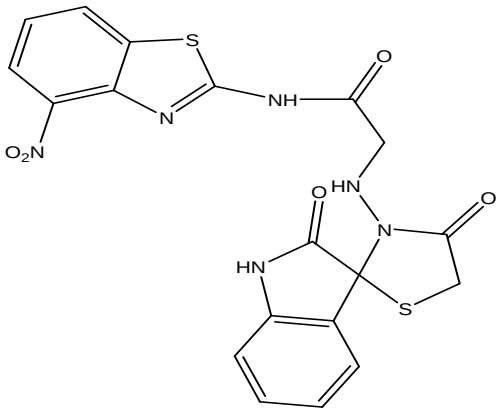
a. Benzothiazole Spiro-Oxindole Derivatives

Under microwave irradiation, novel benzothiazole-spirooxindole compounds were synthesised from 2-aminobenzothiazoles and spirooxindoles, which were studied using several spectroscopic techniques. The Plasmodium falciparum strain was tested in vitro for antimalarial activity.[9] Almost all of the compounds had good antimalarial action, therefore Chloroquine and Quinine remained the standard medications. Compounds 1 and 2 had MIC values (0.082 and 0.049 g/mL) that were nearly identical to the standard drug. Chloroquine, compound 3 and 4, and compound 3 and 4 had lower MIC values (0.32 and 0.38 g/mL) than Quinine. The synthesised benzothiazole-spirooxindole compounds will aid in the development of innovative antimalarial drugs in the future.[10]



1

MIC value = 0.082 µg/mL



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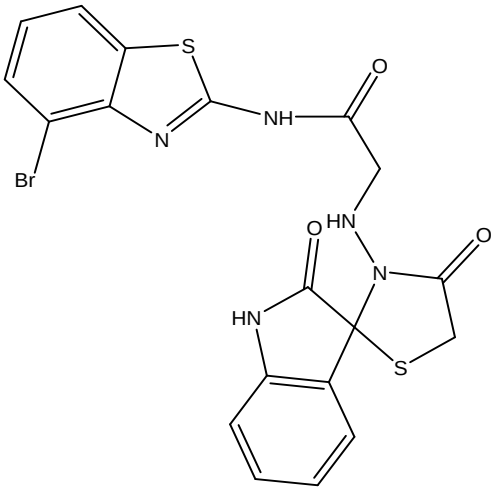
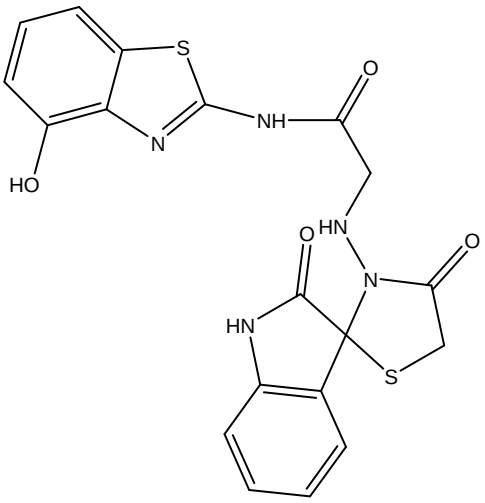
MIC value = 0.049 µg/mL



3

MIC value = 0.32 µg/mL

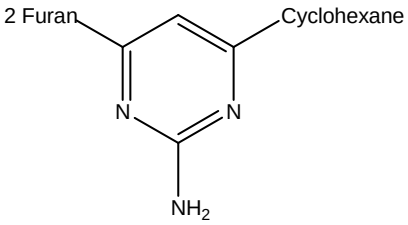


4

MIC value = 0.38 µg/mL

b. Novel Pyrimidine Derivatives

The new pyrimidine derivatives were made from chalcones and tested in vitro for antimalarial activity against Plasmodium falciparum strain cells. The reference medications were quinine and chloroquine. All of the chalcone compounds were shown to be ineffective against Plasmodium falciparum, however synthesised pyrimidine derivatives were highly effective. Compounds 5 and 6, with MIC values of 0.028 and 0.078 g/mL, respectively, showed good antimalarial activity among all produced derivatives. The bioassay revealed that pyrimidines have higher bioactivity than their chalcone counterparts, indicating that the pyrimidine ring is responsible for the increase in activity. As a result, amino-pyrimidines appeared to be more potential for future development.[11]



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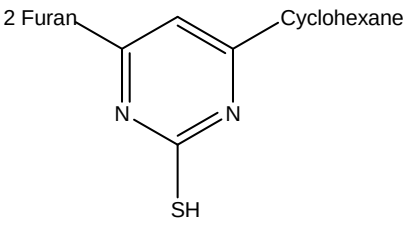
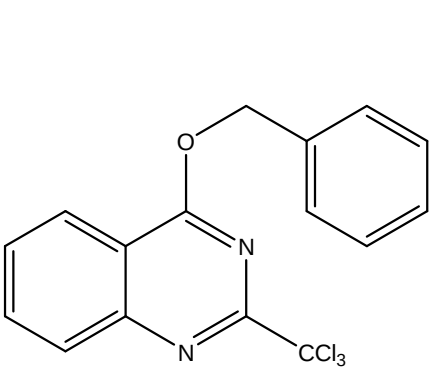


6

MIC value 0.028 and 0.078 µg/Ml, respectively

c. 4-benzyloxy- and 4-aryloxy-2- trichloromethylquinazolines

An aniline[12], aryl[13], thiophenol[14], alkynyl[15], or sulphonamide moiety[16] was substituted at position 4 of the quinazoline ring to produce a range of compounds. A 4-phenoxy-2-trichloromethyl quinazoline derivative with an IC50 of 1.1 M, a CC50 of 50 M, and a selectivity index of 45 was also discovered[17], using Chloroquine and Doxycycline as standards. The multi-resistant Plasmodium falciparum strain K1 was used to investigate in vitro activity. The synthesis was carried out utilising the SnAr reaction, which was carried out with benzylic alcohols, phenols, or hydroxyheterocycles under microwave irradiation. This approach for substituting an alkoxy, phenoxy, or heteroaryloxy moiety at position 4 of 4-chloroquinazolines was efficient, simple, rapid, and inexpensive.[18]



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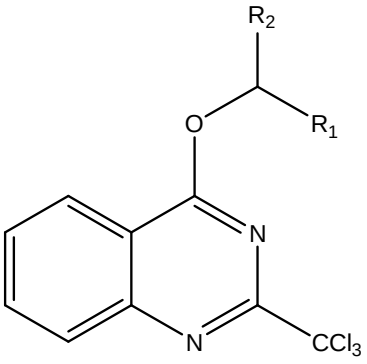

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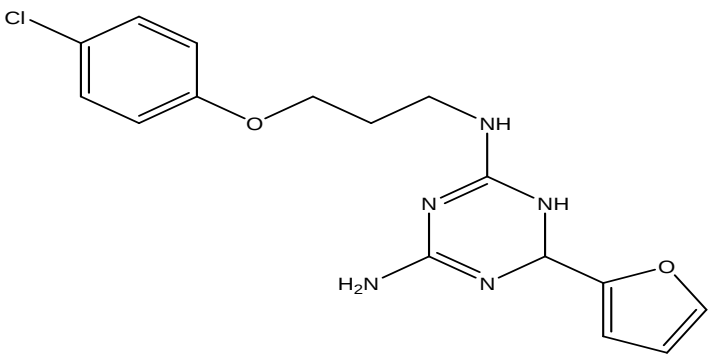
d. 2,N6-disubstituted-1,2-dihydro-1,3,5-triazine-4,6-diamines

In a variety of cycloguanil-like compounds, the flexible tether length was interpolated between the 1,2-dihydro-1,3,5-triazine-4,6-diamine heterocycle and the substituted phenyl ring.[19] Microwave synthesis, as a one-pot approach, allowing the conversion to be completed in 1-2 hours.[20-22] Because of the Asn51Ie and Ile164Leu mutations, which create a chain shift around the Plasmodium falciprum DHFR active site, minor inhibitors like cycloguanil and pyrimethamine have a decreased binding affinity. Larger substituents at C-2 on the 1,2-dihydro-1,3,5- triazine-4,6- diamine ring were introduced to accommodate the increased binding site available. Examples include cycloalkyl, phenyl, and substituted phenyl. The FCR-3 Plasmodium falciparum strain was used to test a total of 28 drugs. The majority of the compounds had antimalarial activity comparable to cycloguanil (IC50 = 4.995 M), with the exception of a molecule containing a 2-furanyl derivative, which was about 5-fold more active (IC50 = 0.99 M) than cycloguanil. The absence of haemolysis and red blood cell toxicity showed that the compounds had direct efficacy against the intra-erythrocytic parasite.[23]



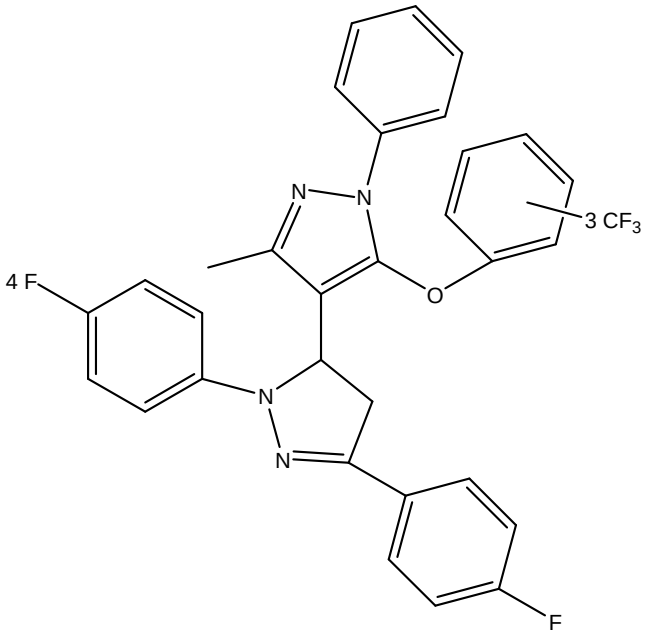
11

IC_{50} value = 0.99 µM

e. Fluorinated pyrazolylpyrazoline derivatives

In the context of the synthesis of physiologically active new heterocyclic scaffolds, a novel microwave assisted synthesis of fluorinated pyrazolylpyrazoline derivatives was reported.[24-31] Antimalarial, antibacterial, and antitubercular activities were found in the produced compounds. The substitution of fluorinated aryloxy nuceus at the C50 position in the pyrazoline scaffold had a substantial impact on the activity.The addition of electron withdrawing groups 4-F, 4-Br at R1 and –CF3 at the m-position of the aryloxy ring resulted in enhanced antimalarial and antituberculosis action. The inclusion of a fluoro group at the R1 position, as well as at the o, m, and p positions of the aryloxy ring, resulted in good antimalarial activity.

All of the compounds were evaluated for antimalarial activity against quinine and chloroquine-resistant Plasmodium falciparum isolates. The mean IC50 for the Plasmodium falciparum strain was determined to be between 0.022 and 0.088 M. Certain chemicals showed excellent action against the Pasmodium falciparum strain as compared to quinine, which has an IC50 of 0.268 M. As a result, these compounds may one day prove to be novel antimalarial agents.[32]



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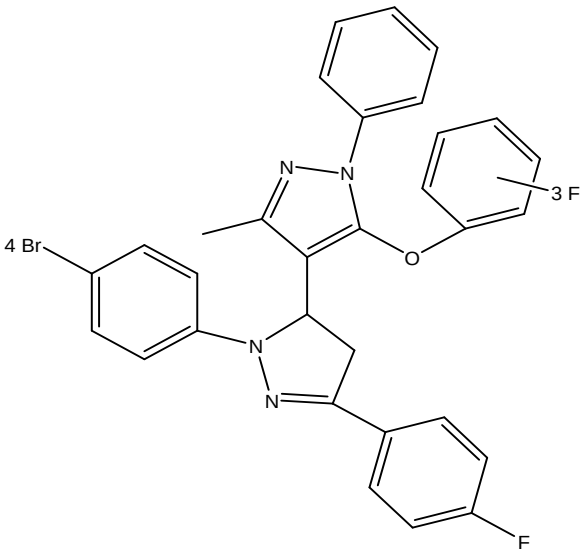
4 Br
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3 F
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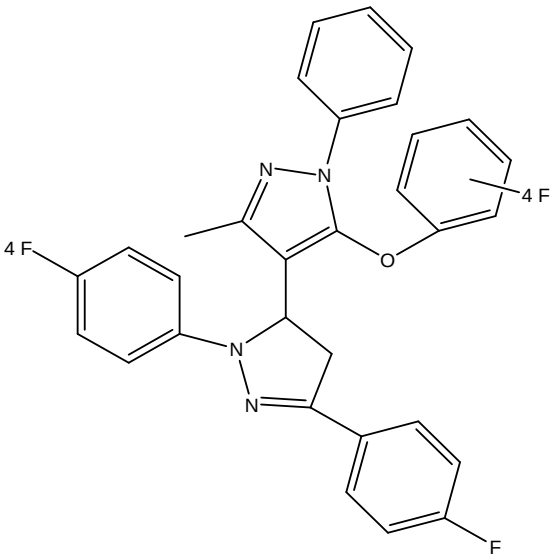
F

15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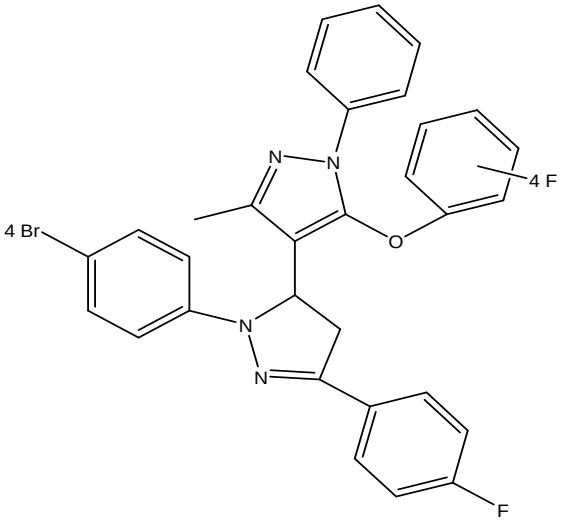
16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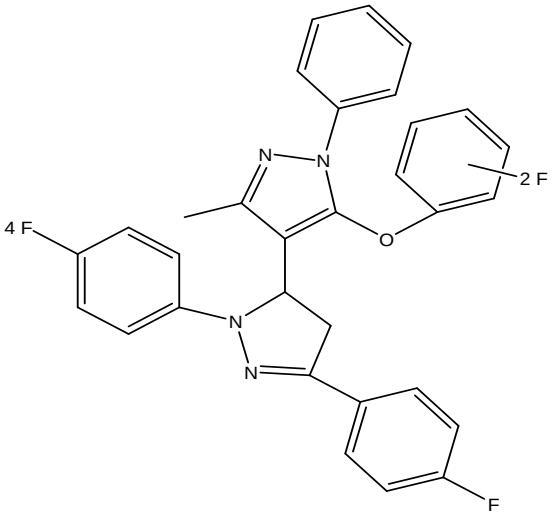
17


4 F
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2 F
O
N
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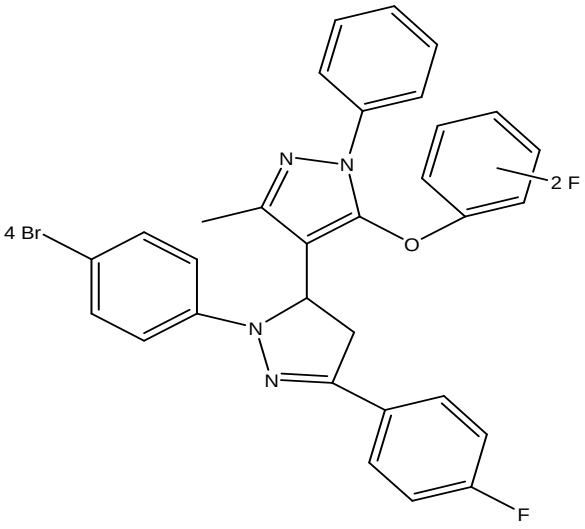
F

18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19

CONCLUSION

As per the future need of the environment the microwave irradiation is the most required method for any synthesis. The method is very time saving, environment friendly and economical as well. Many antimalarials were developed against the *Plasmodium* species, but due to development of resistance for the compound synthesized, there is dire need for the new novel antimalarial compounds. Also, environment is the basic topic of concern and use of benign chemicals for synthesis of antimalarials is required. Here, this review covers some compounds that can be synthesized in microwave by use of environmentally benign chemicals.

REFERENCES

1. WHO, World Malaria Report, World Health Organization: Geneva (2015).
2. Naing C, Whittaker MA, Nyunt Wai V, Mak JW. **(2014).** Is Plasmodium vivax malaria a severe malaria?: a systematic review and meta-analysis. PLoS Negl. Trop. Dis, 8: 3071.
3. Ahmed MA, Cox-Singh J. **(2015).** Plasmodium knowlesi - an emerging pathogen. ISBT Sci. Ser., 10: 134–140.
4. Domling A. **(2006).** Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. Chem. Rev, 106: 17–89.
5. Lafitte D, Lamour V, Tsvetkov P, Markov AA, Deprez M, Klich P, Moras D, Briand C, Gilli R. **(2002).** DNA gyrase intgeraction with coumarin-based inhibitors-the role of the hydroxyl benzoate isopentenyl moiety and the 5'-methyl group of the noviose. Biochemistry, 41: 7217–7223.
6. Surducan E, Surducan V, Nagy G, Filip SV. **(2001).** Installation for Treatment in Microwave Field. Romanian Patent, 8(2): 70-80.
7. Surducan E, Surducan V. **(2001).** The process and device for heating fluids without dielectric losses. Romanian Patent, 8(2): 70-80.
8. Surducan E, Surducan V. **(2001).** The thermographic transducer for high power microwave radiation. Romanian Patent, 8(2): 70-80.
9. Rieckmann KH, Campbell GH, Sax LJ, Ema JE. **(1978).** Drug sensitivity of Plasmodium falciparum: an in-vitro microtechnique. The Lancet, 311: 22-23.
10. Borad MA, Bhoi MN, Patel HD. **(2016).** Microwave assisted synthesis of benzothiazole-spirooxindole derivatives as an antibacterial, antifungal and antimalarial agent. Journal of Medicinal Chemistry and Drug Discovery, 2: 1-12.

11. Christian DJ, Bhoi MN, Borad MA, Rajani DP, Rajani SD, Patel HD. **(2003).** Microwave assisted synthesis and *in vitro* antimalarial screening of novel pyrimidine derivatives. World journal of pharmacy and pharmaceutical sciences, 3(8): 1955-1971.
12. Verhaeghe P, Azas N, Hutter S, Castera-Ducros C, Laget M, Dumètre A, Gasquet M, Reboul JP, Rault S, Rathelot P, Vanelle P. **(2009).** Synthesis and *in vitro* antiplasmodial evaluation of 4-anilino-2-trichloromethylquinazolines. Bioorg. Med. Chem, 17: 4313– 4322.
13. Verhaeghe P, Azas N, Gasquet M, Hutter S, Ducros C, Laget M, Rault S, Rathelot P, Vanelle P. **(2008).** Synthesis and antiplasmodial activity of new 4-aryl-2-trichloromethylquinazolines. Bioorg. Med. Chem. Lett, 18: 396–401.
14. Verhaeghe P, Dumètre A, Castera-Ducros C, Hutter S, Laget M, Fersing C, Prieri M, Yzombard J, Sifredi F, Rault S, Rathelot P, Vanelle P, Azas N. **(2011).** 4-Thiophenoxy-2-trichloromethyquinazolines display *in vitro* selective antiplasmodial activity against the human malaria parasite *Plasmodium falciparum*. Bioorg. Med. Chem. Lett, 21: 6003– 6006.
15. Kieffer C, Verhaeghe P, Primas N, Castera-Ducros C, Gellis A, Rosas R, Rault S, Rathelot P, Vanelle P. **(2013).** Sonogashira cross-coupling reaction in 4-chloro-2-trichloromethylquinazoline series is possible despite a side dimerization reaction. Tetrahedron, 69: 2987-2995.
16. Primas N, Verhaeghe P, Cohen A, Kieffer C, Dumètre A, Hutter S, Rault S, Rathelot P, Azas N, Vanelle P. **(2012).** A New Synthetic Route to Original Sulfonamide Derivatives in 2-Trichloromethylquinazoline Series: A Structure-Activity Relationship Study of Antiplasmodial Activity. Molecules, 17: 8105–8117.
17. Castera-Ducros C, Azas N, Verhaeghe P, Hutter S, Garrigue P, Dumètre A, Mbatchi L, Laget M, Remusat V, Sifredi F, Rault S, Rathelot P, Vanelle P. **(2011).** Targeting the human malaria parasite *Plasmodium falciparum*: *In vitro* identification of a new antiplasmodial hit in 4-phenoxy-2-trichloromethylquinazoline series. Eur. J. Med. Chem, 46: 4184–4191.
18. Gellis A, Primas N, Hutter S, Lanzada G, Remusat V, Verhaeghe P, Vanelle P, Azas N. **(2016).** Looking for new antiplasmodial quinazolines: DMAP-catalyzed synthesis of 4-benzyloxy- and 4-aryloxy-2-trichloromethylquinazolines and their in vitro evaluation toward Plasmodium falciparum. European Journal of Medicinal Chemistry, 119: 34-44.
19. Rousseau AL, Gravestock D, Lourens ACU. PCT Application PCT/IB2010/ 053570, **2010**.

20. Newman H, Moon EL. U.S. Patent 3287366, **1966**.
21. Timmer RT, Alexander CW, Pillarisetti S, Saxena U, Alluri SS, Krishna RVV, Pal M, Reddy JT, Yeleswarapu KR, Reddy GO, Kumar PR. U.S. Patent 227983, **2005**.
22. Yuvaniyama J, Chitnumsub P, Kamchonwongpaisan S, Vanichtanankul J, Sirawaraporn W, Taylor P, Walkinshaw MD, Yuthavong Y. **(2003).** Nat. Struct. Biol, 10: 357-365.
23. Gravestock D, Rousseau AL, Lourens ACU, Moleele SS, van Zyl RL, Steenkamp PA. **(2011).** Expeditious synthesis and biological evaluation of novel 2,N6-disubstituted 1,2-dihydro-1,3,5-triazine-4,6-diamines as potential antimalarials. European Journal of Medicinal Chemistry, 46: 2022-2030.
24. Kalaria PN, Satasia SP, Raval DK. **(2014).** New. J. Chem, 38: 1512-1521.
25. Avalani JR, Patel DS, Raval DK. **(2013).** J. Mol. Catal. B e Enzym, 90: 70- 75.
26. Satasia SP, Kalaria PN, Raval DK. **(2013).** RSC Adv, 3: 3184-3188.
27. Kalaria PN, Satasia SP, Raval DK. **(2014).** Eur. J. Med. Chem., 78: 207-216.
28. Kalaria PN, Satasia SP, Raval DK. **(2014).** New. J. Chem, 38: 2902-2910.
29. Satasia SP, Kalaria PN, Raval DK. **(2014).** Org. Biomol. Chem, 12: 1751-1758.
30. Satasia SP, Kalaria PN, Raval DK. **(2014).** J. Mol. Catal. A e Chem, 391: 41-47.
31. Satasia SP, Kalaria PN, Avalani JR, Raval DK. Tetrahedron **(2014)**, http:// dx.doi.org/10.1016/j.tet.2014.06.050.
32. O'Neill PM, Ward SA, Berry NG, Jeyadevan JP, Biagini GA, Asadollaly E, Park BK, Bray PG. **(2006).** A medicinal chemistry perspective on 4-aminoquinoline antimalarial drugs. Current Topics in Medicinal Chemistry, 6: 479-507.