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A REVIEW ON ATOVAQUONE AND BUPARVAQUONE PRODRUGS

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ABSTRACT

Naphthoquinone ring forms a prominent structural feature in many pharmaceutical compounds having therapeutic efficacy for various pathogens. Both Atovaquone and Buparvaquone drugs belong to this class, these drugs were predominantly used for treating malaria and protozoal infections. Both the parent drug molecules have very low bioavailability due to poor solubility, contributing to the need of inducing high dose during the treatment. Various studies have been carried out to overcome these issues, with a considerable focus on reducing the particle size or to introduce the novel prodrugs of these molecules. Noticeable work has been done to reduce the particle size, whereas very less volume of published literature is available on the prodrugs of these two under-focus drug molecules. In this review, efforts were put in to compile the available literature towards the progressive disclosures on the synthesis and the therapeutic advantages of Atovaquone and Buparvaquone prodrugs.

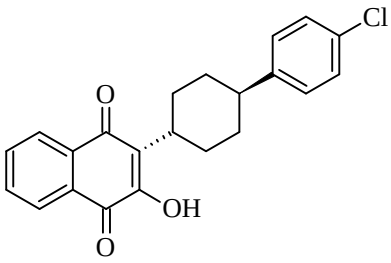
KEYWORDS: Atovaquone, Buparvaquone, Prodrugs, Solubility, Bioavailability, Drug efficacy.

INTRODUCTION

A prodrug is a compound, which after administration will get metabolized and release the therapeutically active parent drug. This innovative concept of drug administration is used to

improve the ADME of the orally administered low solubility drugs. Prodrugs will act as the carriers of parent drug molecule, hence satisfactorily contribute to the drug bioavailability at a relatively lower administered dose. Lowering the drug dose always helps in reducing the associated drug side effects and also the costlier drugs can be brought into the regular clinical practice. The present review is focused about the available prior arts towards the disclosures on the synthesis and the therapeutic advantages of prodrugs pertaining to the key drug molecules, like Atovaquone and Buparvaquone.

Atovaquone (**1**) [{2-[*trans*-4-(4-chlorophenyl) cyclohexyl]-3-hydroxy-1,4-naphthoquinone}] has the alternate names as 566C80, Mepron or Wellvone. It is a substituted hydroxy naphthoquinone, a chiral molecule. It has displayed significant clinical activity towards the treatment of the disease malaria.[1,2] Buparvaquone (**2**) [2-((4-*tert*-butyl cyclohexyl) methyl)-3-hydroxy-1,4-naphthoquinone] has the alternate name as Butalex. It is an antiprtozoal drug, comprising the hydroxy naphthoquinone moiety in its molecular structure. It is a potential drug for the therapy and prophylaxis of all forms of theileriosis.[3,4] It is reported to exhibit a significant anti-leishmanial activity *in vitro*.[5]



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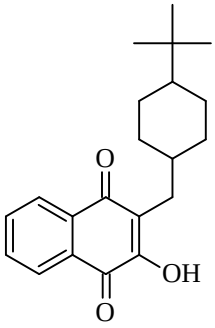
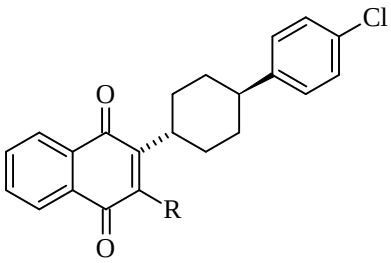


(2) CAS No.: 88426-33-9

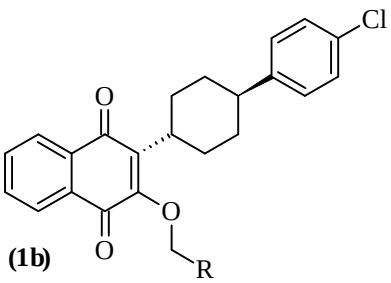
Disclosures on Atovaquone prodrugs

A novel carbamate prodrug of Atovaquone (**1a**) was synthesized, characterized and the pharmacokinetic aspects were evaluated.[6,7] Prophylactic efficacy study of (**1a**) was conducted in a severe combined immunodeficient mouse model of Pneumocystis carinii pneumonia. The prophylactic activity obtained was comparable to that of oral micro-particulate formulation of (**1**) [micronized form]. By converting (**1**) to its prodrug, the bioavailability had increased along with substantial increase in its clinical efficacy.[8] This enhanced drug efficacy can be attributed to the increased solubility of the resultant novel prodrug (**1a**).

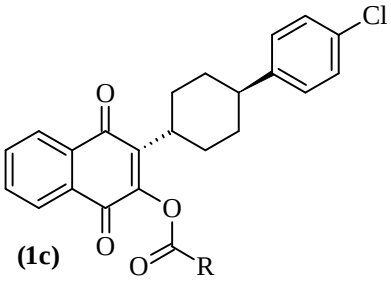


(1a) R=OC(O)N(Me)CH $_2$CH$_2$NHMe.HCl

Synthesis and antimalarial activity of around 18 novel Atovaquone derivatives/analogues [(**1b**) and **(1c**) series] were disclosed, the derivatives isolated were substituted at the 3-hydroxy group by ester and ether functional groups. The compounds were evaluated *in vitro* for their activity against the growth of *Plasmodium falciparum*, a parasite which causes the disease malaria. All the compounds have displayed potent activity, with IC_{50} values in the range of 1.25-50nM, comparable to the values obtained by administering (**1**) and are significantly higher than Chloroquine or Quinine.[9]



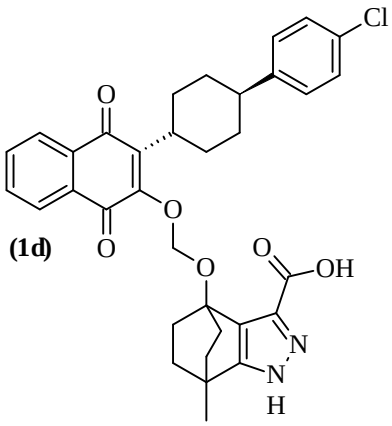
(1b)



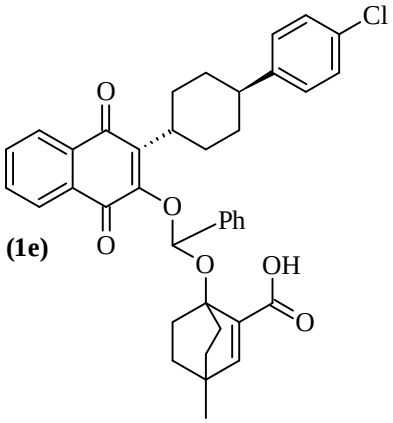
(1c)

R= [- (CH $_2$)$_n$- CH $_3$, n = 0, 4, 6, 7, 8, 18] [- C $_6$H$_5$ -] [- C $_6$H$_4$ - pF] [- C $_6$H$_4$ - pCl] [- CH = CH - C $_6$H$_5$]

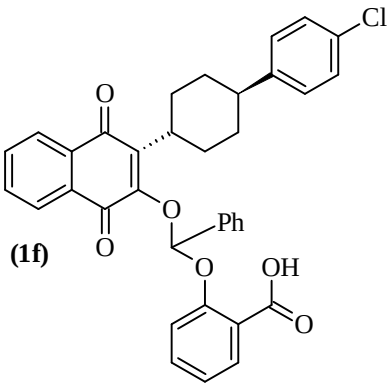
A computational study based on Density Functional Theory (DFT) and *ab initio* calculation results for the proton transfer reaction in Kirby's enzyme models, had laid the foundation for the emergence of few prodrugs [(**1d)** to (**1g**)]. The computer assisted prodrug design methodology, clearly explains the basis for designing the prodrug systems that can be used to release the parent drug in a controlled manner with a rapid release rate. The release rate of the parent drug from the prodrug can be effectively estimated according to the nature of linker through Kirby's enzyme model. According to the data gathered by the above methods, the pharmacokinetic values could be determined by *in vivo* and *in vitro* results, including the oral bioavailability, terminal elimination half life, etc. These prodrugs [(**1d**) to (**1g**)] may be used in various administrative forms like tablets, suppositories, etc, due to their enhanced solubility and the potential of carboxyl group to be converted to the carboxylate salt.[10-12]



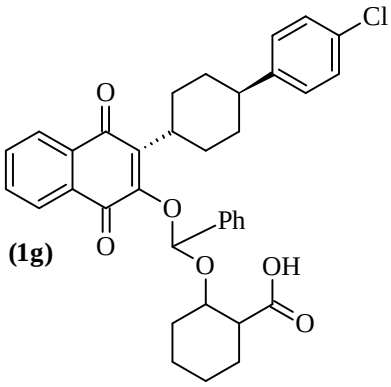
(1d)



(1e)

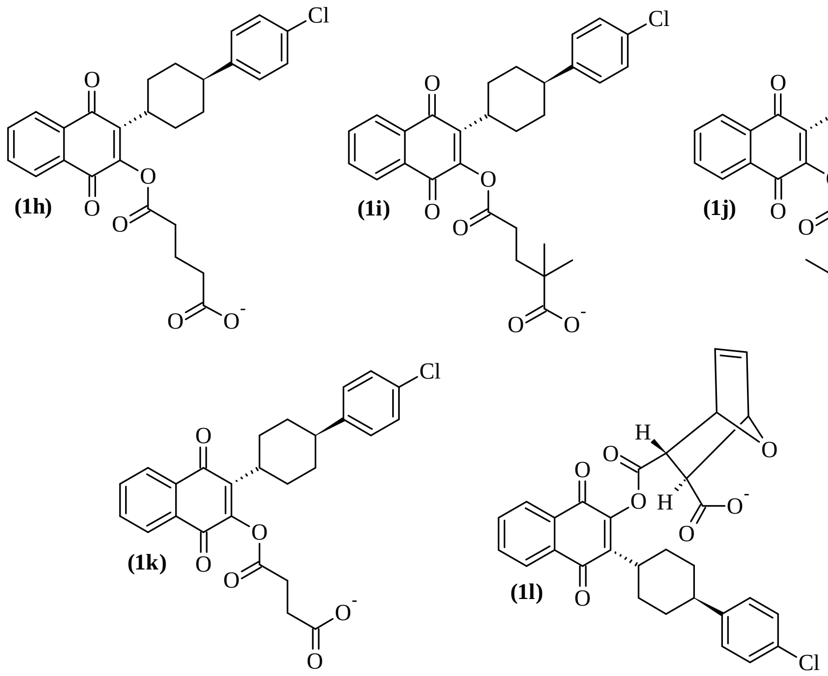


(1f)



(1g)

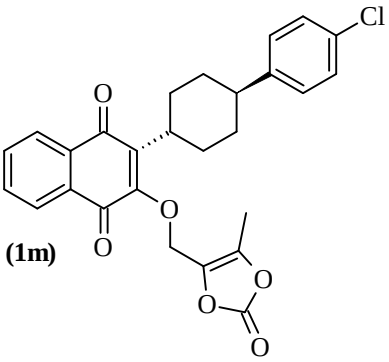
A computational study was conducted to design the prodrugs of Atovaquone by linking the parent drug molecule (**1**) to a dicarboxylic semi-ester linker (as per Bruice's enzyme model). The resultant methodology had generated a system which was more hydrophilic than its parent drug. The obtained produgs would release (**1**) in a controlled sustainable manner. This computational concept had introduced few novel prodrug analogues [(**1h**) to (**1l**)] with improved solubility, bioavailability and better clinical efficacy. The release rate of a drug from its prodrug can be predicted according to the nature of the prodrug linker. The prodrug design based on a computational methodology involves the calculations using molecular orbital (MO) and molecular mechanics (MM) concepts and correlations between the experimental and calculated values of intramolecular processes. This non enzyme mediated concept had opened up the possibilities to introduce novel prodrugs having programmable drug release capability. Parent drug (**1**) has a characteristic mechanism of action against *Plasmodium spp*, acts by inhibiting the electron transport system at the level of cytochrome bc1 complex. The prodrug design and its commercial synthesis will be the vital factor to uplift the use of variety of low solubility drugs.[13-15]



The newly synthesized prodrug of Atovaquone had shown improved efficacy, pharmacokinetics profile and lower toxicity. The prodrug (**1a**) had exhibited a threefold increase in the bioavailability over the improved formulation (micronized suspension) and conventional tablets of the parent drug molecule (**1**). Using DFT molecular orbital at B3LYP 6-31G (d,p) and B3LYP/311+G (d,p) levels and molecular mechanics (MM2) calculations of the hydrolysis of Bruice's dicarboxylic semi-esters, few novel prodrug analouges [(**1h**) to (**1l**)] were designed. The interconversion rate of the designed Atovaquone prodrugs were largely determined on the strain energies of tetrahedral intermediates and the reactants. By using the information gathered from the Bruice's model, (**1k**) was synthesized by the reaction of (**1**) with Succinic anhydride in the presence of a strong base (NaH), purified and characterized. Kinetic study of the molecule was conducted at varied buffer conditions. The novel prodrug (**1k**) had displayed promising results in terms of drug efficacy, physicochemical properties and drug releasing rate, than the parent drug molecule (**1**). The oral administration of (**1k**) was feasible by administering it as the coated tablets. The coating concept was specifically intriduced to avoid the premature release of drug from its prodrug in the stomach, thus safeguarding the prodrug and allowing its release as the actual drug only in the small intestine vicinity.[16] Non enzyme mediated intra-molecular processes were found to be effective approach for the prodrug design and synthesis. Computational prodrug design pathway based of enzyme models, will give the predictive behavior of prodrug cleavage (by hydrolysis, oxidation etc) to release the drug moiety. A deeper progression on enzyme

models and the computational methods will assist in understanding enzyme catalysis concepts and will eventually contribute to the development of efficient prodrugs.[17,18]

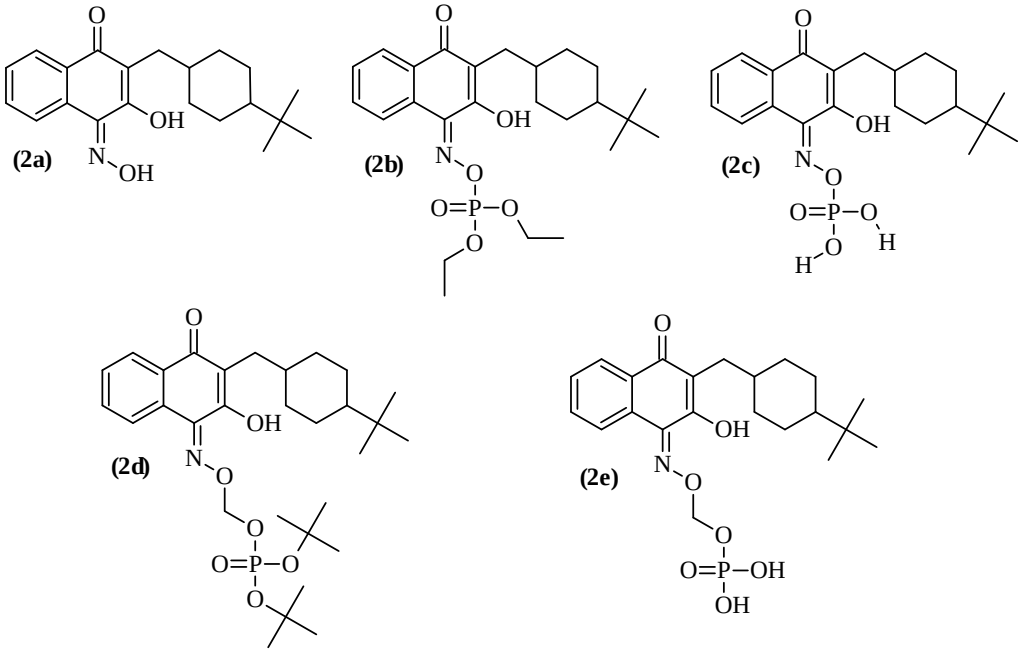
A novel prodrug [(**1m**), {3-(5-methyl-2-oxo-1, 3-dioxol-4-yl) methyloxy-2 *trans*-[(4-chloro phenyl) cyclohexyl]-1, 4-naphthoquinone}] was prepared to treat Pneumocystis carinni, Plasmodia, tachyzoite and cyst forms of Toxoplasma gondii. It was synthesized by treating (**1**) with 5-methyl, 4-chloromethyldioxalone in the presence of Potassium carbonate, purified and characterized. The compound (**1m**) isolated had better aqueous solubility than (**1**) and non-variable plasma levels of (**1**) as compared to the levels obtained after administration of the parent drug moiety. The work also emphasized to provide a compact process for the preparation of (**1m**) with high yields and purity, suitable for large scale manufacturing.[19]



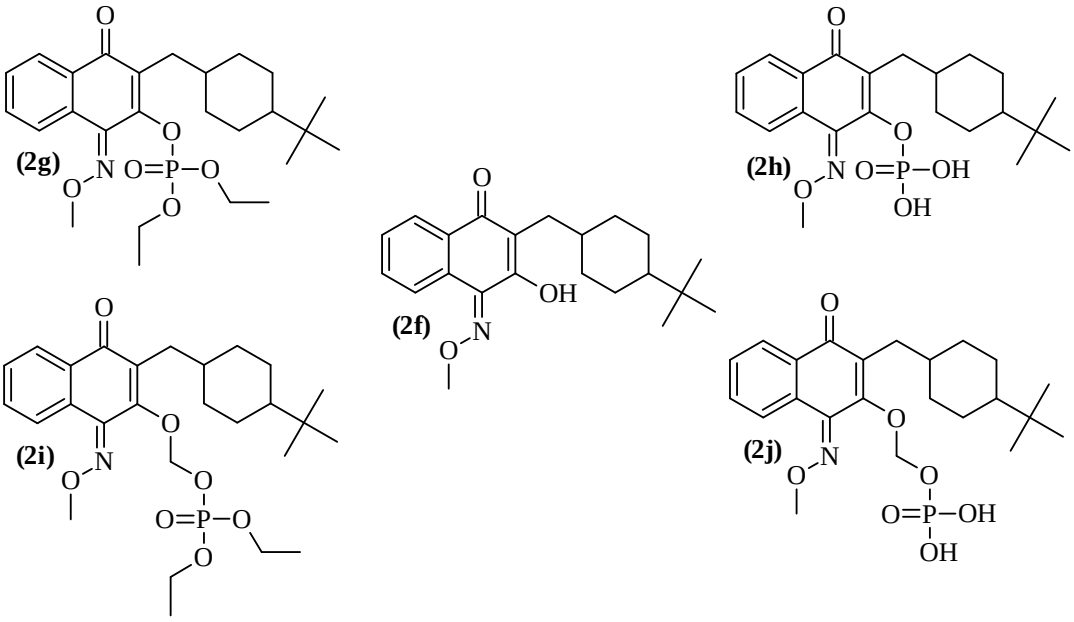
(1m)

Disclosures on Buparvaquone prodrugs

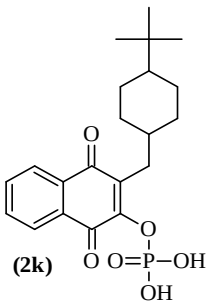
Few novel water soluble phosphate prodrugs [(**2b**) to (**2e**) and (**2g**) to (**2j**)] of Buparvaquone-oxime (**2a**) and Buparvaquone-O-methyloxime (**2f**) were synthesized and evaluated *in vitro* for their biological activity against leishmaniasis. The novel prodrugs practically exhibited greater water solubility (4mg/ml) than the parent drug (0.03 mg/ml) at a pH of around 3.0 to 7.4. The prodrugs [(**2c**), (**2e**) and (**2j**)] were released relatively faster ($t^{1/2}$ = 7min), but the Buparvaquone-oximes [(**2a**) and (**2f**)] and the prodrug (**2h**) were released at a moderate rate ($t^{1/2}$ = 22.5min) in the alkaline phosphatase solution *in vitro*. The prodrug (**2e**) displayed the better solubility features and it was the most stable in the aqueous solutions over a wide range of pH of around 3.0-7.4 ($t^{1/2}$ > 8 days). As a part of bioreversibility, (**2e**) gets hydrolyzed to (**2a**) which in turn gets oxidized to release (**2**). Similar to (**2**), the compound (**2a**) has the applicability issues as an oral drug due to its lower aqueous solubility. The innovative phosphorylation process of Buparvaquone oxime had enormously increased its water solubility and opens up its applicability as the potential prodrug. Among the variants prepared, (**2e**) was the most promising prodrug for the oral drug delivery.[20]



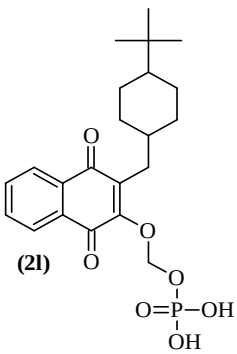
The synthesized and characterized prodrugs [(**2k**) and (**2l**)] have exhibited good biological activity against the several Leishmania species which is responsible for causing both cutaneous and visceral Leishmaniasis. The prodrugs [(**2k**) and (**2l**)] were prepared from the intermediates [(**2o**) and (**2p**)] obtained by the phosphorylation of (**2**). These prodrugs are the promising bio-reversible analogues for the enhanced topical and oral bioavailability of (**2**). The prodrug (**2l**) would easily release the parent drug molecule in the human skin homogenate, hence it will be a promising prodrug to deliver (**2**) through the skin for the treatment of cutaneous leishmaniasis.[21]



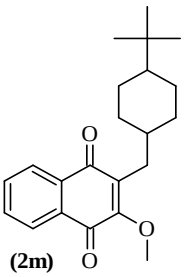
Prodrug approaches are promising and significant alternatives to resolve the issues arising from the existing drugs. The prodrug pathway had enormously improved the pharmacokinetics properties of drugs related to few neglected diseases. Improved efficacy was observed for the two series of phosphate prodrugs of Buparvaquone [(**2c**), (**2e**), (**2h**), (**2j**)] and (**2k**, **2l**)] due to higher aqueous solubility. Hence the prodrugs had shown significant enhancement in the drug bioavailability. The prodrug (**2e**) had the highest solubility and rapid hydrolysis capability to form (**2a**), which later oxidizes *in vivo* to generate the parent drug (**2**).[22] The prodrugs [(**2a**), (**2f**), (**2m**) and (**2n**)] were synthesized and their biological activity against Leishmania donovani, was estimated. The bioreversible characteristic of (**2a**) was determined upon its induction into the rat liver microsomes, *in vitro* pathway. The release of NO from the compound (**2a**) will provide an additional therapeutic effect in the treatment of leishmaniasis.[23] The *in vivo* studies were conducted towards antileishmanial activity of (**2**) and its prodrugs [(**2k**) and (**2l**)]. The use of these prodrugs had a significant impact towards the treatment of simple cutaneous lesions. The prodrug (**2l**) had released the parent drug (**2**) readily during the experimentation. In particular, the avoidance of the parenteral antimonials had genuinely increased the patient compliance and reduces the expenditure towards the treatment. Several formulations of (**2**) and (**2l**) were introduced to increase the drug penetration and efficacy [hydrous gel, anhydrous gel and emulsions], showed greater skin penetration ability.[24-28]



(2k)



(2l)



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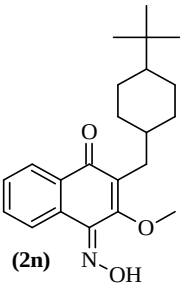
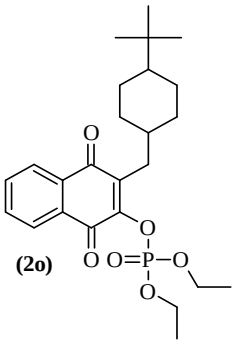
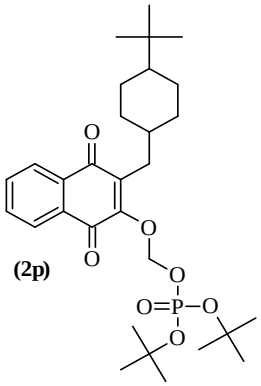


(2n)



(2o)



(2p)

CONCLUSION

The drugs under the focus in this review [(**1**) and (**2**)] have displayed poor solubility, hence high drug dose has to be administered during the treatment. The best solution for this acute issue would be to prepare the prodrugs, which are the bio-reversible derivatives of the parent drug. If the prodrug and its metabolites are clinically inactive, then the innovative produg methodology forms an effective strategy to administer the therapeutically required quantity of the parent drug. Upon considering the process steps, handling issues and the expenditure input, innovative prodrug pathway looks commercially much viable than the micro/nano formulation strategies employed to enhance the clinical efficacy of the parent drug. The present review article provides an essential overview about the available literature towards the synthesis and therapeutic advantages of Atovaquone and Buparvaquone prodrugs. Few prodrug analogues were reported regarding the above drugs [(**1**) and (**2**)], which are being prepared either by the conventional synthetic strategies or by employing the computational design methodologies. Future scope for the novel prodrugs of [(**1**) and (**2**)] is enormous because most of the reported ones have shown the considerable enhancement in the drug efficacy due to substantial increase in the bioavailability.

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