Mapana - Journal of Sciences
2023, Vol. 22, No.2, *141-168*
ISSN 0975-3303 | https://doi.org/10.12723/mjs.65.10

A Comprehensive Review on the Therapeutic Applications and Synthetic Approaches of Buparvaquone

Sanjay Sukumar Saralaya*, Shashiprabha† & Shridhara Kanakamajalu‡

Abstract

Buparvaquone **1a** is a predominant anti-protozoal drug, it belongs to the pharmacologically active class of hydroxy-naphthoquinones. There are numerous publications on the wide therapeutic applications of **1a**, but only a few approaches were reported towards its synthesis. Most of the prior arts report the synthesis from expensive raw materials with low yield, whereas only a few involves the use of readily available and less expensive raw materials with moderate to better yield. The present review work covers the developments on therapeutic applications of **1a** along with the synthetic approaches disclosed till date.

Keywords: Buparvaquone, Therapeutic application, Synthesis, Isomer, Epimerization, Recrystallization

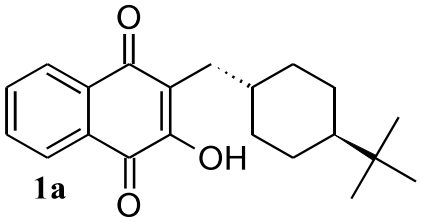
* Department of Chemistry, Sri Dharmasthala Manjunatheshwara Institute of Technology, SDM IT (affiliated to Visvesvaraya Technological University,VTU, Belagavi), Ujire-574 240, Karnataka, India. E-mail: *sanjayss@sdmit.in*

† PG Department of Chemistry, Sri Dharmasthala Manjunatheshwara College (Autonomous), Ujire-574 240, Karnataka, India. E-mail: shashi-sudha@sdmcujire.in

‡ Technical Coordinator, ArkGen Pharma Private Limited, Peenya Industrial Area, Bangalore-560 058, Karnataka, India. E-mail: shridharabhat@yahoo.co.in

Introduction

Buparvaquone, 2-(*trans*-4-*tert*-butylcyclohexyl)-3-chloro-1,4-naphthoquinone **1a**, it is a popular second-generation drug having the hydroxy-naphthoquinone framework with a molecular formula: $C_{21}H_{26}O_3$, molecular weight: 326.43 g/mol and the CAS registry number: 88426-33-9. It is used for the therapy and prophylaxis of numerous theileriosis forms with the trade name, Butalex or Coopers. Disclosed therapeutic applications and synthetic approaches of **1a**, as per prior arts were tabulated chronologically as below.



Buparvaquone, 2-(*trans*-4-*tert*-butylcycolohexyl)-3-chloro-1,4-napththoquinone **1a**

Therapeutic Applications of 1a

A thorough literature search was carried out on the therapeutic applications of **1a**, the collected research papers were sorted out as per the yearly chronology and carefully examined. Key notes of such an examination were tabulated in **Table 1**, which gives an insight on to the therapeutic wideness of **1a**.

Table 1: Prior art highlights regarding the widespread therapeutic utility of **1a**.

Work disclosed by	**Highlights of the disclosed research work**	**Reference/s**
Hudson, A. T., *et al*, 1983	Reports the anti-malarial, anti-coccidial and anti-inflammatory of **1a** along with a few other hydroxy naphthoquinones.	[1]
Victoria, L. S., *et al*, 1984	Discloses the combination of **1a** with Clopidol, it was proved to be very effective as an anti-malarial against *Plasmodium falciparum.*	[2]

Work disclosed by	**Highlights of the disclosed research work**	**Reference/s**
McHardy, N., *et al*, 1985	Reveales a comparison of drug efficacy studies towards anti-theilerial activity of **1a** and Parvaquone (a popular anti-protozoan drug) againt *Theileria parva* and *Theileria annulata* in cattle. From the results, it was evident that **1a** was twenty-fold more active than Parvaquone.	[3]
Dhar, S., *et al*, 1986 and 1987	Reports the studies related to chemotherapy of *Theileria annulata* infection by the use of **1a** and also the effective chemoimmunoprophylaxis by **1a** over theileriosis in calves.	[4, 5]
Mutugi, J. J., *et al*, 1988	Discloses a dilution based induced infection study of *Theileria parva* to impart immunization in cattle and its treatment by **1a**.	[6]
Dhar, S., *et al*, 1988	Reports the intramuscular intrusion of **1a** to treat *Theileria annulata* in cross-bred calves. No toxicity indicatives were observed post treatment with **1a** in calves.	[7]
Zaugg, J. L., *et al*, 1989	Discloses the application of **1a** to treat equine babesiosis existed in European origin horses.	[8]
Michael, S. A., *et al*, 1989	Reports the use of **1a** to cure chronic, undulating *Theileria annulata* infection in cows. In about seven weeks, all the cows had recovered completely from the infection. The milk yield was significantly low in cows prior to the infection, it was	[9]

Work disclosed by	**Highlights of the disclosed research work**	**Reference/s**
	improved drastically post treatment for the induced infection.	
Bansal, G. C., *et al*, 1989	Discloses a study related to anti-theilerial ability of **1a** in male calves, which are infected for experimentation with *Theileria annulata*.	[10]
Sharma, N. N., *et al*, 1990	Reveals the intramuscular treatment of male calves infected by *Theileria annulata* using **1a**, curing the entire treated bunch of male calves.	[11]
Dhar, S., *et al*, 1990	Reports a comparative study of **1a** and Oxytetracycline. Study was conducted towards the chemoimmunoprophylaxis over bovine tropical theileriosis in young calves, splitting them into two groups for the medication. Post thirty days, the immunity status of all calves in both groups was found to be similar.	[12]
Rintelen, M., *et al*, 1990	Discloses a work on the impact of **1a** in preventing *Theileria annulata* infection. The infected cells were cured by **1a**, but certainly not by Cyclosporin A. It was by retarding the generation of mixed lymphocyte reaction.	[13]
Motzel, S. L., *et al*, 1990	Reports a work on the efficacy tests of **1a** and Parvaquone, domestic cats are experimentally infected by *Cytauxzoon felis*. It was observed that,	[14]

Work disclosed by	**Highlights of the disclosed research work**	**Reference/s**
	both the drugs found ineffective to treat the infection satisfactorily.	
Stewart, N. P., *et al*, 1990	Reveals an attempt to treat the *Theileria buffeli* infections in calves by **1a**, as alone or in combination with Primaquine phosphate. Alone **1a** was not effective, but the drug combination had suppressed the parasites effectively and antibodies were not observed after eight weeks of treatment.	[15]
Hashemi-Fesharki, R., 1991	Reports a work which was done in Iran to treat the infections caused by *Theileria annulata* in cattle. It reports the use of Parvaquone and **1a** for the treatment, its therapeutic efficacy was estimated from the studies. From the results, **1a** was found more effective to eliminate infections than Parvaquone.	[16]
McHardy, N., 1991	Reports a unified pathway to treat the fatal East Coast Fever in calves using **1a**.	[17]
Mutugi, J. J., *et al*, 1991	Discloses a comparative work, where both **1a** and Oxytetracycline were used separately in two sets to eliminate the *Theileria parva* infection in calves. It was evident from the results that, both the drugs were found equally effective in imparting immunization in calves.	[18]
Mitema, E. S., *et al*, 1991	Reports a therapeutic work executed over a bunch of white tailed deer.	[19]

Work disclosed by	**Highlights of the disclosed research work**	**Reference/s**
	Imidocarb, Chloroquine and **1a** were used separately for the suppression of *Theileria cervi* infection in deer. It was found that **1a** was effective with better efficacy than the other two drugs.	
Croft, S. L., *et al*, 1992	Discloses the use a few hydroxy naphthoquinones against *Leishmania donovani*. From the results, **1a** was a front runner along with other four quinone derivatives with better efficacy.	[20]
Zaugg, J. L., *et al*, 1992	Reports a study related to efficacy estimation of **1a** by using it for the horses infected from *Babesia equi*. From the outcome, it was observed that **1a** alone could not eliminate the carrier infection issue.	[21]
Dolan, T. T., *et al*, 1992	Reports a field clinical trial of **1a** executed in Kenya against the fatal East Coast Fever in the cattle bunch.	[22]
Ngumi, P. N., *et al*, 1992	Reveals a work on the immunization study in cattle against *Theileria parva* infection. Different doses of **1a** were used for the treatment, dosage optimization was done for the clinical execution.	[23]
Ahmed, J. S., *et al*, 1992	Reports a work on the impact and efficiency of **1a** on the expression of interleukin 2 receptors in *Theileria annulata* infected cells.	[24]

Work disclosed by	**Highlights of the disclosed research work**	**Reference/s**
Singh, D. K., *et al*, 1993	Discloses the efficacy comparison study of four different drugs like Parvaquone, **1a**, Oxytetracycline and Halofuginone lactate. These drugs were tested over the infection of *Theileria annulata* in cross-bred calves. Among them, **1a** was proved to be very efficient in treating infected calves.	[25]
Singh, J., *et al*, 1993	Reports a comparative study executed in Punjab to treat *Theileria annulata* infection in calves. Both Oxytetracycline and **1a** were used to treat the selected infected animals, proving **1a** to be more clinically efficient.	[26]
Mishra, A. K., *et al*, 1993	Reports a study on some selected animal groups suffering from natural bovine tropical theileriosis. All the animals had shown fast recovery from the infection post treatment with **1a**, with no mortality. Furthermore, past depressed milk yield of cows was raised noticeably.	[27]
Mbogo, S. K., *et al*, 1996	Reveals a case study imposed on a few Friesian cattle which are infected from a mild *Theileria parva* parasite. Their immunization features were tabulated by the use of **1a** to treat the parasite proliferation.	[28]
Vexenat, J. A., *et al*, 1998	Discloses a study executed over dogs to treat canine visceral leishmaniosis by **1a**. Satisfactory results were not	[29]

Work disclosed by	**Highlights of the disclosed research work**	**Reference/s**
	obtained, since the disease progression was not halted in dogs.	
Wilkie, G. M., *et al*, 1998	Reveals the clinical trials and the efficacy of **1a** towards the infection caused in calves by *Theileria annulata* and *Theileria parva*. From the results obtained between 7–14-day duration, it was found beneficial to use **1a** to treat the infected ones.	[30]
Wilkie, G. M., *et al*, 1998	Reports the in-vitro method for testing the therapeutic activity of **1a** in serum on the infection, development and proliferation of Theileria in its bovine host mononuclear cells. Drug effect was found at its peak during the first 24 h and it remained till 14 days, thus **1a** contributes to eliminate the severe infection.	[31]
Muraguri, G. R., *et al*, 1999	Reports a comparative study regarding the therapeutic efficacy of Parvaquone and **1a**, both have given a similar impact to cure the East Coast fever in cattle.	[32]
el-Metenawy, T. M., 1999	Reports a work on pigeons, which are infected by *Haemoproteus columbae*. It was treated with **1a**, and other drugs like Berenil and Triquine separately. From the outcome, **1a** and Berenil drugs were found effective to treat the infection.	[33]

Work disclosed by	**Highlights of the disclosed research work**	**Reference/s**
Naziroğlu, M., *et al*, 1999	Discloses a post treatment study of **1a** in cattle with theileriosis. The level of lipid peroxidation in plasma and erythrocytes were observed to be higher post treatment. Meanwhile, plasma levels of vitamin E and β-carotene were lower.	[34]
Müller, J., *et al*, 2000	Reveals the therapeutic efficiency of **1a** against congenital toxoplasmosis in mouse model.	[35]
Penzhorn, B. L., *et al*, 2000	Reports a work conducted over cats, which are infected by *Babesia felis*. Around five drugs were used for the treatment, in that **1a** was found to have no significant anti-babesial effect.	[36]
Kumar, S., *et al*, 2003	Reveals that the combination of drugs (Arteether & **1a**) was found more effective than Imidocarb for treating *Babesia equi* infection in donkeys.	[37]
Gwamaka, M., *et al*, 2004	Reports the effect of drugs like, Dexamethasone and Promethazine in combination with **1a** to treat East Coast fever.	[38]
Mbwambo, H. A., *et al*, 2006	Discloses a field work done in Tanzania to treat East Coast Fever by **1a**. It was found efficacious and a valuable alternative to treat the infection caused by *Theileria parva,* than Parvaquone, Fruvexon etc.	[39]

Work disclosed by	**Highlights of the disclosed research work**	**Reference/s**
Osman, S. A., *et al*, 2007	Reports a case study done in Egypt over infected water buffaloes. Early-stage treatment by **1a** had improved the health condition of the animal.	[40]
Mhadhbi, M., *et al*, 2010	Reveals a case study from Tunisia about the resistance shown by *Theileria annulata* to **1a** in cows.	[41]
Mchardy, N., *et al*, 2012	Reports a work to control mites through honeybees induced with **1a** alongside sugar solution. Honey bee larvae was unaffected by **1a**, but *Varroa* mites got paralyzed, detach and die upon contact with drug ridden bees.	[42]
Müller, J., *et al*, 2015	Discloses the therapeutic efficiency of **1a** against *Neospora caninum* in infected mice. In a four-day treatment period, **1a** had successfully inhibited the tachyzoite replication to reduce the infection.	[43]
Müller, J., *et al*, 2016	Reveals a work on repurposing of anti-parasitic drugs. The vertical transmission in the pregnant neosporosis mouse was effectively inhibited by the induced **1a**.	[44]
Checa, R., *et al*, 2017	Discloses a comparative study done on sick dogs infected with *Babesia microti*. Drug efficacy studies were done by the use of Imidocarb dipropionate, Atovaquone (a popular anti-malarial drug) or (**1a** & azithromycin) to treat the infection.	[45]

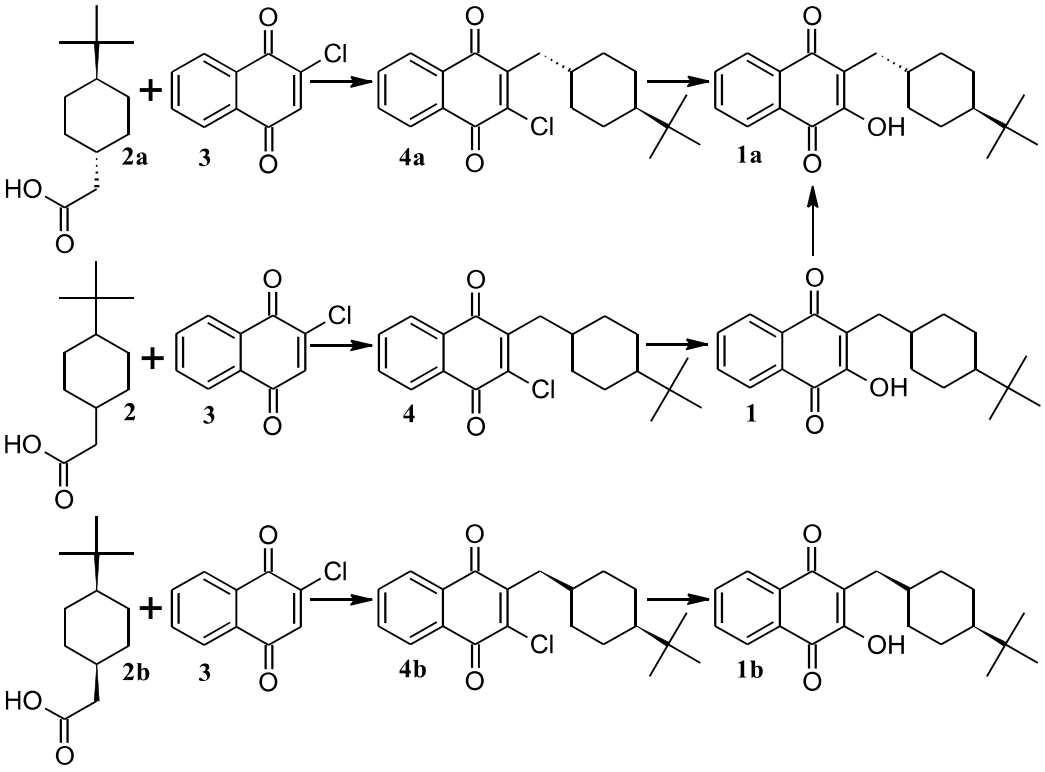
Work disclosed by	**Highlights of the disclosed research work**	**Reference/s**
Rufener, R., *et al*, 2018	Reports the use of **1a** against *Echinococcus multilocularis* under drug repurposing work. The tape-worm induced disease, alveolar echinococcosis was not effectively inhibited by **1a**.	[46]
Müller, J., *et al*, 2019	Reveals the use of **1a** for the treatment of *Besnoitia besnoiti* and a few other pharmacological aspects were also estimated with regard to inhibition of parasite growth.	[47]
Goud, K. S., *et al*, 2020	Reports the effective use of **1a** to treat *Theileria orientalis* infection in young calves. Use of **1a** along with haematinics for the treatment was found to be effective in calves.	[48]
Borba-Santos, L. P., *et al*, 2021	Discloses the antifungal activity of **1a** against *Sporothrix brasiliensis*. Experimental evidences confirmed that, the use of **1a** will be a useful alternative treatment for feline sporotrichosis.	[49]
Ferreira, V. F., *et al,* 2021	Reports a review work comprising the medicinal aspects of **1a** along with six other quinone-framework based drugs.	[50]
Nixon, G. L., *et al*, 2013	Reports a detailed study on the therapeutic action of Atovaquone. Mechanism of infection retardation by **1a** is very much similar to that of Atovaquone. It is a renowned inhibitor of ubiquinol, inhibition of bc_1 activity results in the loss of	[51]

Work disclosed by	Highlights of the disclosed research work	Reference/s
	mitochondrial functions. Meanwhile, it affects the concentrations of metabolites in the pyrimidine biosynthetic pathway.	

From the prior arts it is quite evident that, **1a** is therapeutically active as a prominent prophylactic drug.

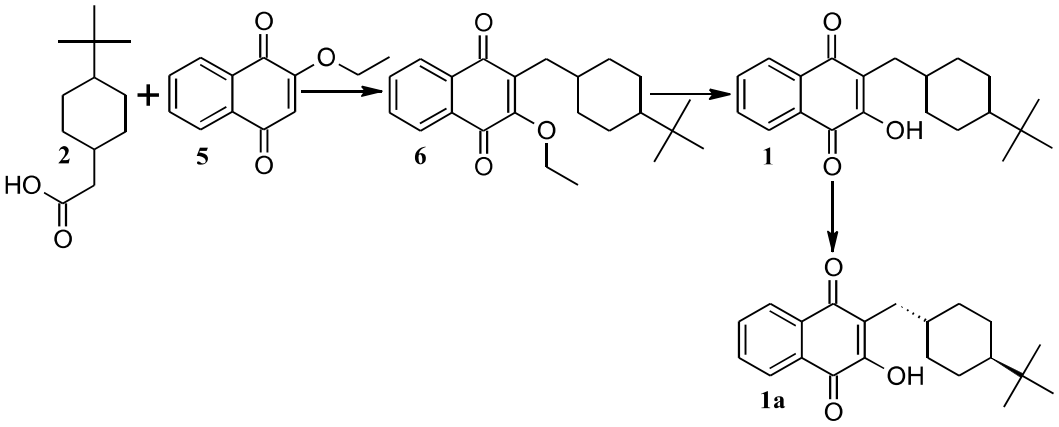
Approaches for the synthesis of 1a

Hudson, A. T., *et al,* 1983 and 1984, disclosed the synthesis of some cyclohexyl naphthoquinones (**Scheme-1**). Compound 1-(*trans*-4-*tert*-butylcyclohexyl)acetic acid **2a** was reacted with 2-chloro-1,4-naphthoquinone **3** under the mediation of silver nitrate and ammonium persulfate in acetonitrile and water at 70-75 ^{0}C for 4-5 h to isolate 2-(*trans*-4-*tert*-butylcyclohexylmethyl)-3-chloro-1,4-naphthoquinone **4a**. Its hydrolysis by potassium hydroxide in aqueous dimethoxyethane under reflux 1-2 h, followed by acidification and filtration gave **1a**. A similar pathway was followed to react **2** and **3** to get **4** (yield: 32.18%), its hydrolysis and acidification gave the crude racemic mixture **1**. It was treated with 1,4-dioxane and sodium carbonate solution at 70-75 ^{0}C and gradually added 30% hydrogen peroxide. To it, added water, acidified and then washed with water saturated by sulphur dioxide. Reaction mass was stirred at 0 ^{0}C for 2 h, followed by the addition of 25% sodium hydroxide solution and copper sulfate pentahydrate solution at ambient temperature to get the precipitate. It was filtered, acidified and recrystallized from petroleum ether to get **1a**. Furthermore, the process also reports the isolation of **1b** by the reaction of **2b** with **3**. It also provides a concentrated sulfuric acid mediated and temperature (50 to 70 ^{0}C) driven epimerization pathway for the conversion of **1** to **1a** [1, 52].



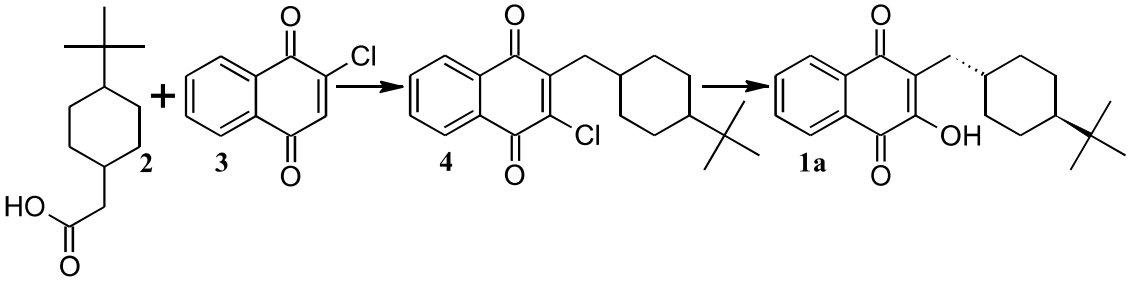
Scheme-1: Synthesis of **1a** from **2** and **3**.

Wang, Y., *et al*, 2008 and Lv, Y., 2016, revealed the reaction (**Scheme-2**) of 4-*tert*-(butylcyclohexyl)acetic acid **2** and 2-ethoxy-1,4-naphthoquinone **5** propelled by the mediation of silver nitrate and ammonium persulfate in acetonitrile and water under reflux for 5-6 h. Post reaction completion, mass was cooled, filtered, extracted to chloroform, followed by water wash and solvent evaporation gave 2-(4-*tert*-butylcyclohexylmethyl)-3-ethoxy-1,4-naphthoquinone **6**. Its hydrolysis by potassium hydroxide in methanol and water for 1-2 h under reflux, followed by acidification to pH: 3-4, toluene extraction, water wash and solvent evaporation gave the crude racemic mixture **1**. It was recrystallized from ethyl acetate to get **1a** (yield: 19.8-20.63%), [53, 54].

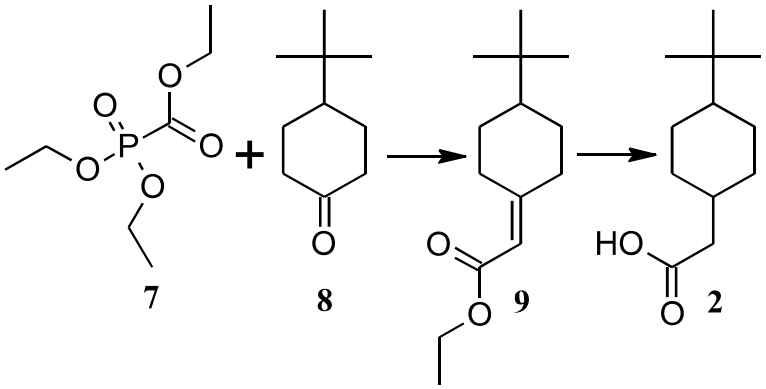


Scheme-2: Synthesis **1a** from **2** and **5**.

Arulmoli, T., *et al*, 2012, disclosed a few reactions (**Scheme-3a**) of **2** and **3**, mediated by silver nitrate and ammonium persulfate in acetonitrile and water at 75-80 ^{0}C for 2-3 h to get **4**. Its hydrolysis by potassium hydroxide solution in methanol at 60-65 ^{0}C for 4-5 hrs, followed by acidification to pH: 1-2, to get the crude racemic mixture **1**. It was taken in methylisobutylketone and heated to 80-85 ^{0}C, followed by water addition, layer separation, gradual cooling and filtration gave the crude solid. It was again taken in methylisobutylketone and heated to 95-100 ^{0}C, cooled gradually and filtered to get **1a** (yield: 33.4%). Furthermore, the reaction (**Scheme-3b**) between triethyl phosphono acetate **7** and 4-*tert*-(butylcyclohexane) **8** under the mediation of sodium methoxide in toluene at 40-45 ^{0}C for 2-3 h, followed by water quenching, extraction, water wash and solvent evaporation gave the syrupy liquid of ethyl 2-(4-*tert*-butylcyclohexylidene) acetate **9** (yield: 87.5%). It was taken in methanol and potassium hydroxide solution was added gradually. Then the reaction mixture was heated to 60-65 ^{0}C for 5-6 h, followed by distillation, water addition, acidification to pH: 1-2 and filtration gave **2** (yield: 88.92%) [55].

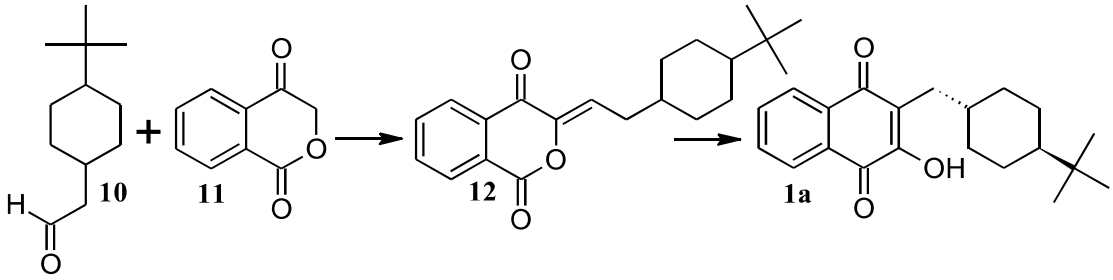


Scheme-3a: Synthesis of **1a** from **2** and **3**.

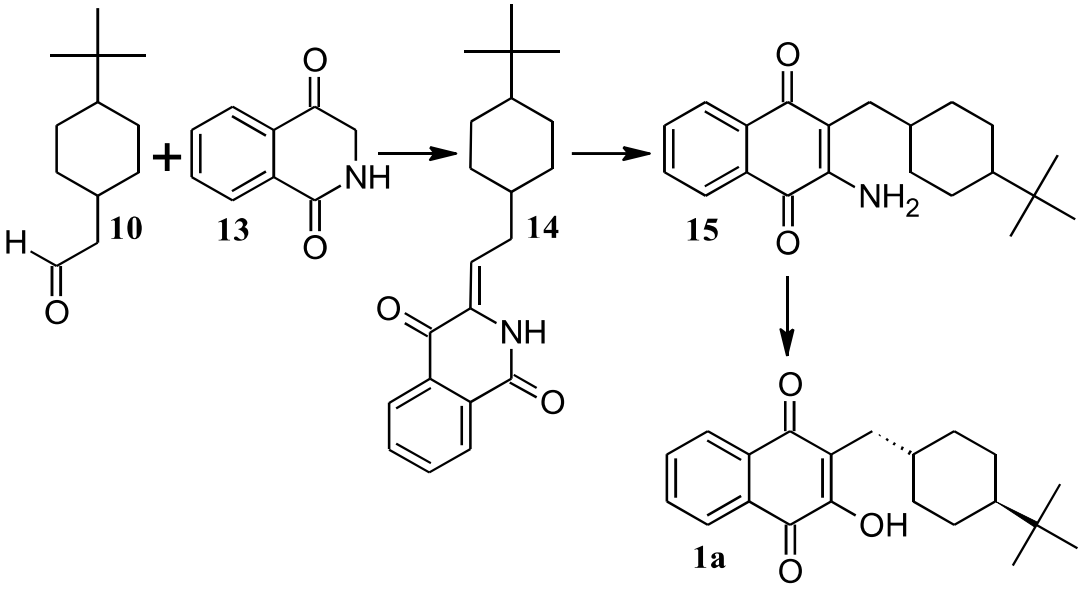


Scheme-3b: Synthesis of **2** from **7** and **8**.

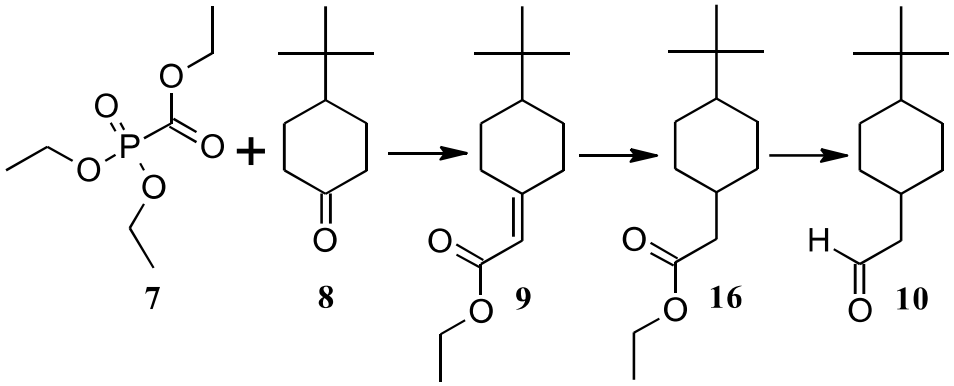
Balaya, L., *et al*, 2014, disclosed the condensation (**Scheme-4a**) of 4-*tert*-butyl-1-cyclohexaneacetaldehyde **10** and 1,4-isochromandione **11** using ammonium acetate and acetic acid at 55-60 ^{0}C for 10-12 h. Post reaction completion, water was added and filtered to get 3-[(4-*tert*-butylcyclohexyl)methylene]-lH-isochromene-l,4(3H)-dione **12**. It was treated with sodium methoxide in methanol at 30-35 ^{0}C for 22-24 h, followed by water addition and filtration gave the crude racemic mixture **1**. It was recrystallized from methylisobutylketone to isolate **1a** (yield: 24.85%). Similarly, the reaction (**Scheme-4b**) of **10** and 2,3-dihydroisoquinoline-1,4-dione **13** in the presence of ammonium acetate and acetic acid at 45-55 ^{0}C for 10-12 h, followed by water addition and filtration gave 3-[(4-*tert*-butylcyclohexyl) methylene]-lH-isoquinoline-l,4-dione **14**. Impact of sodium methoxide in methanol on **14** for 20-24 h at 30-35 ^{0}C, followed by water addition and filtration gave 2-(4-*tert*-butylcyclohexylmethyl)-3-amino-1,4-naphthoquinone **15**. It was treated with sodium nitrite in hydrochloric acid at 0-5 ^{0}C, followed by water addition to get the precipitation and filtration gave the crude racemic mixture **1**. It was recrystallized from methylisobutylketone to get **1a** (yield: 10%). Furthermore, the process also provides a three step process (**Scheme-4c**) for the synthesis of **10** from **7** and **8** [56].



Scheme-4a: Synthesis of **1a** from **10** and **11**.



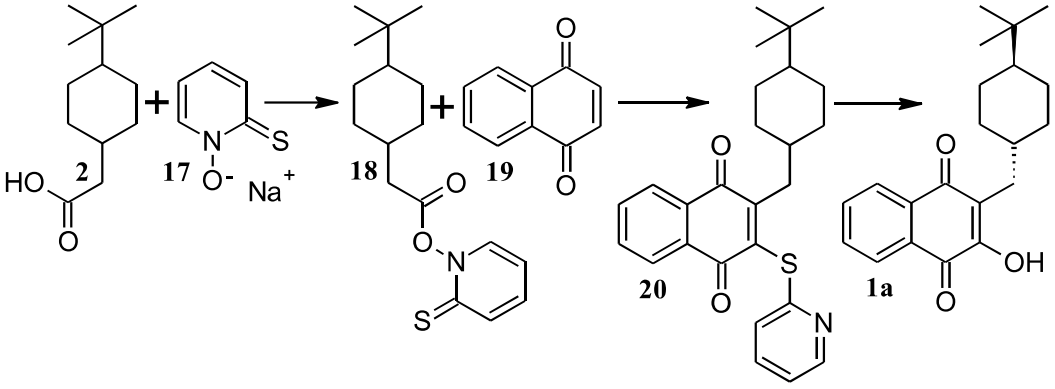
Scheme-4b: Synthesis of **1a** from **10** and **13**.



Scheme-4c: Synthesis of **10** from **7** and **8**.

Ma, H., *et al*, 2013 and 2014, disclosed the reaction of **10** and **11** for the synthesis of **12**. Various experiments were conducted (**Scheme-4a**) by the use of reagents like, isobutylamine (yield: 64.8%) and morpholine (yield: 63.5%) to isolate **12**. Crystallization of **12** was carried out using a few solvents like, ether, isopropylether and methyl-*tert*-butylether. Conversion of **12** to **1** was done by the reagents like, sodium methoxide (yield: 95.8%), sodium ethoxide (yield: 96%) and potassium-*tert*-butoxide (yield: 93.5%). Crude racemic mixture **1** was recrystallized from alcohol and water in a few different ratios to get **1a** [57, 58].

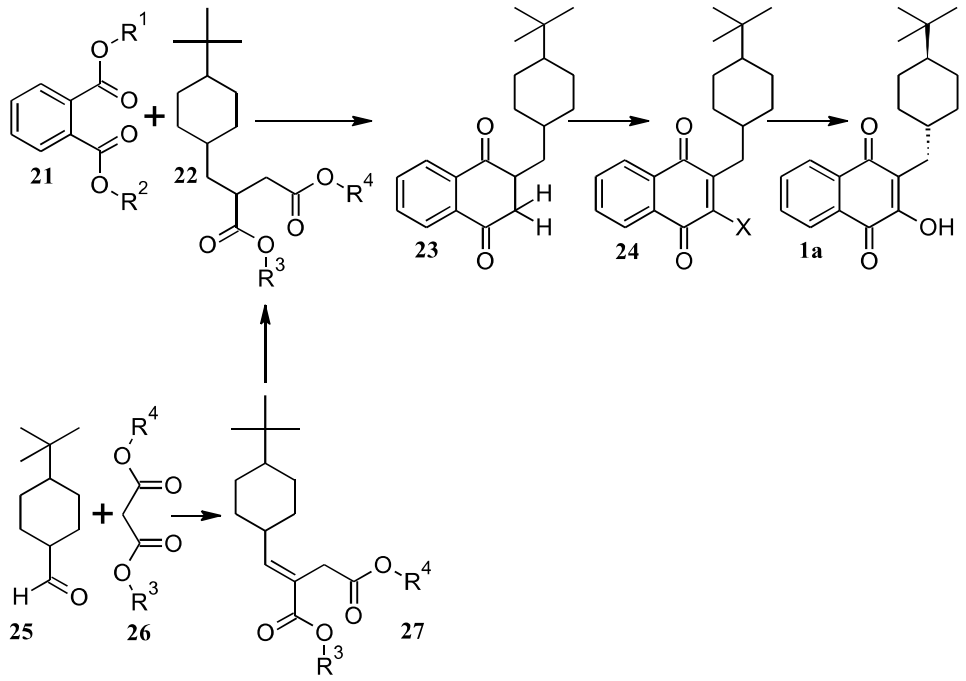
Shen, N., *et al*, 2015, revealed the reaction (**Scheme-5**) of **2** with thionyl chloride in dichloromethane at low temperature, followed by the introduction of 2-mercaptopyridine oxide sodium salt **17** along with triethylamine in dichloromethane to get *tert*-butylcyclohexyl acetic acid 2-thioxo-pyridin-1-yl ester **18** (yield: 90-94%). It was treated with 1,4-naphthoquinone **19** in toluene to get 2-[(4-*tert*-butylcyclohexyl)methyl]-3-(2-pyridinylsulfanyl)-1,4-naphthaquinone **20** (yield: 30-50%). It was hydrolyzed in the presence of tri-potassiumphosphatetrihydrate in aqueous methanol, followed by acidification to pH: 4-5 and filtration gave the crude racemic mixture **1** with 87.5-93.4% of purity by HPLC (yield: 65-85%). It was decolorized, clarity filtered and recrystallized from isopropyl alcohol to isolate **1a**, with 99.86% of purity by HPLC (yield: 75-80%) [59].



Scheme-5: Synthesis of **1a** from **2**, **17** and **19**.

Cui, Q., *et al*, 2020, disclosed a few reactions (**Scheme-6**) of phthalic acid diesters **21** and 2-(4-*tert*-butyl cyclohexylmethyl)succinate diesters **22** in tetrahydrofuran under the influence of sodium methoxide at 40-45 ^{0}C for 4-6 h, followed by water addition, heating, acidification to pH: 1-2, extraction to dichloromethane, bicarbonate wash, water wash and solvent evaporation gave 2-{(4-*tert*-butylcyclohexyl)methyl}-2,3- dihydro-1,4-naphthoquinone **23** (yield: 88.5%). Similar reaction was carried out in the presence of potassium *tert*-butoxide in toluene, to get **23** (yield: 90.7%). Halogenation of **23** by (Bromine/HBr/HCl) in dichloroethane at 30-35 ^{0}C for 3 h and the alkali influenced elimination at 50-55 ^{0}C for 2 h gave 2-{(4-*tert*-butylcyclohexyl)methyl}-3-halo-1,4-naphthoquinone **24**, which was not isolated. An in-situe hydrolysis of it at 75-80 ^{0}C for 2 h, followed

by acidification, extraction to dichloroethane and solvent evaporation gave the crude racemic mixture **1**. It was decolourized, clarity filtered and recrystallized from isopropyl alcohol to isolate **1a** (yield: 80-93%), with 97.2-99.7% of liquid phase purity. Furthermore, the process also provides a pathway to prepare **22**. The reaction of 4-*tert*-butylcyclohexyl formaldehyde **25** and succinic acid diesters **26** in piperidine and acetic acid at 90-120 ^{0}C for 5-9 h, followed by quenching to water, extraction to toluene, solvent evaporation and high vacuum distillation gave 4-(4-*tert*-butylcyclohexyl)-3-methoxycarbonyl-3-butenoate **27**. Its reduction in autoclave using Pd/C in methanol at 40-60 ^{0}C for 3-4 h with a hydrogen pressure of 5-7 Kg, followed by filtration, solvent evaporation and high vacuum distillation gave **22** with a reasonably good yield [60].

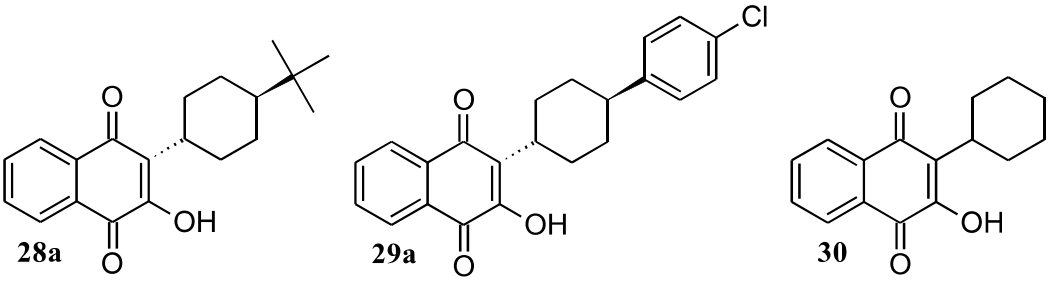


R^1, R^2, R^3 & R^4 = Methyl/Ethyl/Propyl/t-Butyl

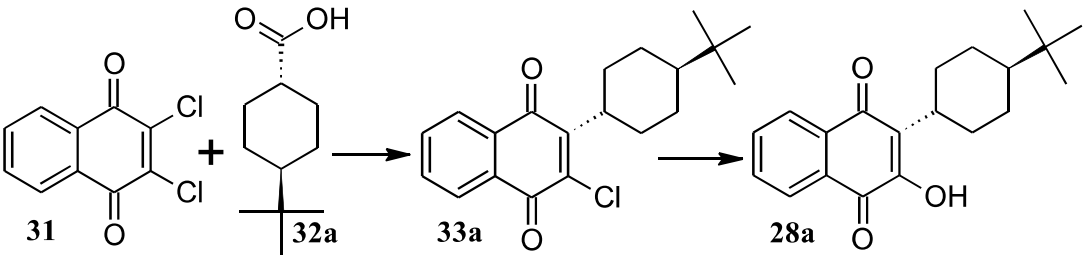
Scheme-6: Synthesis of **1a** from **21** and **22**.

Saralaya, S, S., *et al,* 2012 & 2022, revealed the synthesis of three derivatives of hydroxy naphthoquinone, such as 2-*trans*-(4-*tert*-butylcyclohexyl)-3-hydroxy-1,4- naphthoquinone **28a** (has a close structural resemblance to **1a**), 2-*trans*-4-(4-chlorophenyl)cyclohexyl)-3-hydroxy-1,4-naphthoquinone **29a** and 2-cyclohexyl-3-hydroxy-1,4-naphthoguinone **30** respectively, with the use of readily available

and commercially viable raw material 2,3-dichloro-1,4-naphthoquinone **31**. The reaction optimization studies were performed to isolate **29a** in good yield and purity with a reproducible solvent combination for recrystallization. Furthermore, the recovery of silver salt and some major solvents like acetonitrile and dichloromethane were achieved. Meanwhile, the reuse studies of recovered reagents and solvents were also performed. These initiatives had collectively contributed to lower process costs and had favoured the commercialization of **29a**.



Condensation (**Scheme-7**) of **31** with 1-*trans*-(4-*tert*-butyl-cyclohexyl)-carboxylic acid **32a** was done under the catalytic influence of silver nitrate in association with the oxidizer ammonium persulfate in acetonitrile and water. Reaction mixture was refluxed for 3-5 h, followed by filtration, extraction to dichloromethane, water wash and solvent evaporation gave 2-(*trans*-4-*tert*-butylcyclohexyl)-3-chloro-1,4-naphthoquinone **33a** (yield: 21.35%). Alkali driven hydrolysis of **33a** in methanol and water, followed by acidification, filtration and recrystallization from acetonitrile gave **28a** (yield: 63.5%). Similar strategy could be drafted for the synthesis of **1a** and the cost reduction can be achieved by lowering the solvent volume, recovery and reuse of silver salt, acetonitrile, dichloromethane, etc to commercialize **1a** [61, 62, 63].



Scheme-7: Synthesis of **28a** from **31** and **32a**.

Conclusions

Present review work covers the till date prior arts for the therapeutic applications and the approaches adopted for the synthesis of **1a**. It had a wide range of therapeutic utility, it was clearly evident from the numerous field trial outcomes and also from the drug repurposing initiatives. Synthesis of **1a** was achieved by using different raw materials with low to moderate yields. Many synthetic methods were explored to harmonize the molar efficiencies and also to improve the yield and purity. Widespread applications of **1a**, necessitate the development of a commercially viable approach for its synthesis. This has attracted many synthetic chemists to venture the possibility to develop new routes of synthesis for the large scale manufacturing of **1a**. The drug under focus surprisingly had received less synthetic interest compared to Atovaquone and Parvaquone. Hence, this review work can effectively contribute to the therapeutic widening of **1a** under drug combinational and repurposing initiatives.

Acknowledgements

We the authors, would like to thank the management of SDM Educational Society, Ujire, for their motivation and constant support for this review work. Furthermore, we all gratefully acknowledge the guidance got from Dr. Kuppuswamy Nagarajan (retired Consultant) for the work on Naphthoquinones.

References

[1]. Hudson, A. T., & Randall, A. W. (1983). 1.4-Naphthoquinones, methods for their preparation, pharmaceutical and veterinary formulations thereof. *European Patent Application*, EP 0077551 A2.

[2]. Latter, V. S., Hudson, A. T., Richards, W. H. G., & Randall, A. W. (1984). Antiprotozoal agents containing naphthoquinones and 4-pyridinol derivatives. *European Patent Application*, EP 123239 A2.

[3]. McHardy, N., Wekesa, L. S., Hudson, A. T., & Randall, A. W. (1985). Antitheilerial activity of BW720C (buparvaquone): a comparison with parvaquone. *Research in Veterinary Science*, *39*(1), 29–33.

[4]. Dhar, S., Malhotra, D. V., Bhushan, C., & Gautam, O. P. (1986). Chemotherapy of Theileria annulata infection with buparvaquone. *The Veterinary Record*, *119*(25–26), 635–636.

[5]. Dhar, S., Malhotra, D. V., Bhushan, C., & Gautam, O. P. (1987). Chemoimmunoprophylaxis with buparvaquone against theileriosis in calves. *The Veterinary Record*, *120*(15), 375.

[6]. Mutugi, J. J., Young, A. S., Maritim, A. C., Linyonyi, A., Mbogo, S. K., & Leitch, B. L. (1988). Immunization of cattle using varying infective doses of Theileria parva lawrencei sporozoites derived from an African buffalo (Syncerus caffer) and treatment with buparvaquone. *Parasitology*, *96*(2), 391–402.

[7]. Dhar, S., Malhotra, D. V., Bhushan, C., & Gautam, O. P. (1988). Treatment of experimentally induced Theileria annulata infection in cross-bred calves with buparvaquone. *Veterinary Parasitology*, *27*(3–4), 267–275.

[8]. Zaugg, J. L., & Lane, V. M. (1989). Evaluations of buparvaquone as a treatment for equine babesiosis (Babesia equi). *American Journal of Veterinary Research*, *50*(5), 782–785.

[9]. Michael, S. A., el Refaii, A. H., McHardy, N., & Rae, D. G. (1989). Effect of treatment of chronic theileriosis with buparvaquone on milk yields. *Tropical Animal Health and Production*, *21*(4), 218–222.

[10]. Bansal, G. C., & Sharma, N. N. (1989). Prophylactic efficacy of buparvaquone in experimentally induced Theileria annulata infection in calves. *Veterinary Parasitology*, *33*(3–4), 219–224.

[11]. Sharma, N. N., & Mishra, A. K. (1990). Treatment of bovine tropical theileriosis with buparvaquone. *Tropical Animal Health and Production*, *22*(1), 63–65.

[12]. Dhar, S., Malhotra, D. V., Bhushan, C., & Gautam, O. P. (1990). Chemoimmunoprophylaxis against bovine tropical theileriosis in young calves: a comparison between

buparvaquone and long-acting oxytetracycline. *Research in Veterinary Science*, *49*(1), 110–112.

[13]. Rintelen, M., Schein, E., & Ahmed, J. S. (1990). Buparvaquone but not cyclosporin A prevents Theileria annulata-infected bovine lymphoblastoid cells from stimulating uninfected lymphocytes. *Tropical Medicine and Parasitology*, *41*(2), 203–207.

[14]. Motzel, S. L., & Wagner, J. E. (1990). Treatment of experimentally induced cytauxzoonosis in cats with parvaquone and buparvaquone. *Veterinary Parasitology*, *35*(1–2), 131–138.

[15]. Stewart, N. P., de Vos, A. J., McHardy, N., & Standfast, N. F. (1990). Elimination of Theileria buffeli infections from cattle by concurrent treatment with buparvaquone and primaquine phosphate. *Tropical Animal Health and Production*, *22*(2), 116–122.

[16]. Hashemi-Fesharki, R. (1991). Chemotherapeutic value of parvaquone and buparvaquone against Theileria annulata infection of cattle. *Research in Veterinary Science*, *50*(2), 204–207.

[17]. McHardy, N. (1991). Integrated strategy to control East Coast fever. *The Veterinary Record*, *129*(21), 475.

[18]. Mutugi, J. J., Young, A. S., Kariuki, D. P., Tameno, J. M., & Morzaria, S. P. (1991). Epidemiological observations on theileriosis following field immunisation using infection and treatment. *Tropical Animal Health and Production*, *23*(2), 75–82.

[19]. Mitema, E. S., Kocan, A. A., Mukolwe, S. W., Sangiah, S., & Sherban, D. (1991). Activity of buparvaquone against Theileria cervi in white-tailed deer. *Veterinary Parasitology*, *38*(1), 49–53.

[20]. Croft, S. L., Hogg, J., Gutteridge, W. E., Hudson, A. T., & Randall, A. W. (1992). The activity of hydroxynaphthoquinones against Leishmania

donovani. *The Journal of Antimicrobial Chemotherapy*, *30*(6), 827–832.

[21]. Zaugg, J. L., & Lane, V. M. (1992). Efficacy of buparvaquone as a therapeutic and clearing agent of Babesia equi of European origin in horses. *American Journal of Veterinary Research*, *53*(8), 1396–1399.

[22]. Dolan, T. T., Injairu, R., Gisemba, F., Maina, J. N., Mbadi, G., Mbwiria, S. K., Mulela, G. H., and Othieno, D. A. (1992). A clinical trial of buparvaquone in the treatment of East Coast fever. *The Veterinary Record*, *130*(24), 536–538.

[23]. Ngumi, P. N., Young, A. S., Lampard, D., Mining, S. K., Ndungu, S. G., Lesan, A. C., Linyonyi, S. M., and Kariuki, D. P. (1992). Further evaluation of the use of buparvaquone in the infection and treatment method of immunizing cattle against Theileria parva derived from African buffalo (Syncerus caffer). *Veterinary Parasitology*, *43*(1–2), 15–24.

[24]. Ahmed, J. S., Rintelen, M., Schein, E., Williams, R. O., & Dobbelaere, D. (1992). Effect of buparvaquone on the expression of interleukin 2 receptors in Theileria annulata-infected cells. *Parasitology Research*, *78*(4), 285–290.

[25]. Singh, D. K., Thakur, M., Raghav, P. R., & Varshney, B. C. (1993). Chemotherapeutic trials with four drugs in crossbred calves experimentally infected with Theileria annulata. *Research in Veterinary Science*, *54*(1), 68–71.

[26]. Singh, J., Gill, J. S., Kwatra, M. S., & Sharma, K. K. (1993). Treatment of theileriosis in crossbred cattle in the Punjab. *Tropical Animal Health and Production*, *25*(2), 75–78.

[27]. Mishra, A. K., Sharma, N. N., & Viswanathan, C. B. (1993). Efficacy of Butalex in field cases of bovine theileriosis—short communication. *Acta Veterinaria Hungarica*, *41*(3–4), 361–363.

[28]. Mbogo, S. K., Kariuki, D. P., Ngumi, P. N., & McHardy, N. (1996). A mild Theileria parva parasite with potential for immunisation against East Coast fever. *Veterinary Parasitology*, *61*(1–2), 41–47.

[29]. Vexenat, J. A., Croft, S. L., Furtado Campos, J. H., & Miles, M. A. (1998). Failure of buparvaquone (Butalex) in the treatment of canine visceral leishmaniosis. *Veterinary Parasitology*, *77*(1), 71–73.

[30]. Wilkie, G. M., Brown, C. G., Kirvar, B. E., Thomas, M., Williamson, S. M., Bell-Sakyi, L. J., & Sparagano, O. (1998). Chemoprophylaxis of Theileria annulata and Theileria parva infections of calves with buparvaquone. *Veterinary Parasitology*, *78*(1), 1–12.

[31]. Wilkie, G. M., Kirvar, E., Thomas, E. M., Sparagano, O., & Brown, C. G. (1998). Stage-specific activity in vitro on the Theileria infection process of serum from calves treated prophylactically with buparvaquone. *Veterinary Parasitology*, *80*(2), 127–136.

[32]. Muraguri, G. R., Kiara, H. K., & McHardy, N. (1999). Treatment of East Coast fever: a comparison of parvaquone and buparvaquone. *Veterinary Parasitology*, *87*(1), 25–37.

[33]. El-Metenawy, T. M. (1999). Therapeutic effects of some antihaematozoal drugs against Haemoproteus columbae in domestic pigeons. *DTW. Deutsche Tierarztliche Wochenschrift*, *106*(2), 72.

[34]. Naziroğlu, M., Saki, C. E., & Sevgili, M. (1999). The effect of buparvaquone treatment on the levels of some antioxidant vitamins, lipid peroxidation and glutathione peroxidase in cattle with theileriosis. *Zentralblatt Für Veterinarmedizin. Reihe B. Journal of Veterinary Medicine. Series B*, *46*(4), 233–239.

[35]. Müller, J., Aguado-Martínez, A., Ortega-Mora, L.-M., Moreno-Gonzalo, J., Ferre, I., Hulverson, M. A., … Hemphill, A. (2017). Development of a murine vertical transmission model for Toxoplasma gondii oocyst infection and studies on the efficacy of bumped kinase inhibitor (BKI)-1294 and the naphthoquinone buparvaquone against congenital toxoplasmosis. *The Journal of Antimicrobial Chemotherapy*, *72*(8), 2334–2341.

[36]. Penzhorn, B. L., Lewis, B. D., López-Rebollar, L. M., & Swan, G. E. (2000). Screening of five drugs for efficacy against Babesia felis in experimentally infected cats. *Journal of the South African Veterinary Association*, *71*(1), 53–57.

[37]. Kumar, S., Gupta, A. K., Pal, Y., & Dwivedi, S. K. (2003). In-vivo therapeutic efficacy trial with artemisinin derivative, buparvaquone and imidocarb dipropionate against Babesia equi infection in donkeys. *The Journal of Veterinary Medical Science*, *65*(11), 1171–1177.

[38]. Gwamaka, M., Matovelo, J. A., Mtambo, M. M. A., Mbassa, G. K., Maselle, R. M., & Boniphace, S. (2004). The effect of dexamethasone and promethazine in combination with buparvaquone in the management of East Coast fever. *The Onderstepoort Journal of Veterinary Research*, *71*(2), 119–128.

[39]. Mbwambo, H. A., Magwisha, H. B., & Mfinanga, J. M. (2006). Evaluation of buparvaquone (BUTA-Kel KELA, Belgium) as a treatment of East Coast fever in cattle, in the peri-urban of Dar Es Salaam city, Tanzania. *Veterinary Parasitology*, *139*(1–3), 67–73.

[40]. Osman, S. A., & Al-Gaabary, M. H. (2007). Clinical, haematological and therapeutic studies on tropical theileriosis in water buffaloes (Bubalus bubalis) in Egypt. *Veterinary Parasitology*, *146*(3–4), 337–340.

[41]. Mhadhbi, M., Naouach, A., Boumiza, A., Chaabani, M. F., BenAbderazzak, S., & Darghouth, M. A. (2010). In vivo evidence for the resistance of Theileria annulata to buparvaquone. *Veterinary Parasitology*, *169*(3–4), 241–247.

[42]. Mchardy, N., Smith, R., & Brady, P. D. (2013). Use of buparvaquone for controlling mites parasitising honeybees, EP *Patent No. 2433624:B1*.

[43]. Müller, J., Aguado-Martinez, A., Manser, V., Balmer, V., Winzer, P., Ritler, D., … Hemphill, A. (2015). Buparvaquone is active against Neospora caninum in vitro and in experimentally infected mice. *International Journal for Parasitology, Drugs and Drug Resistance*, *5*(1), 16–25.

[44]. Müller, J., Aguado-Martínez, A., Manser, V., Wong, H. N., Haynes, R. K., & Hemphill, A. (2016). Repurposing of antiparasitic drugs: the hydroxy-naphthoquinone buparvaquone inhibits vertical transmission in the pregnant neosporosis mouse model. *Veterinary Research*, *47*(1), 32.

[45]. Checa, R., Montoya, A., Ortega, N., González-Fraga, J. L., Bartolomé, A., Gálvez, R., … Miró, G. (2017). Efficacy, safety and tolerance of imidocarb dipropionate versus atovaquone or buparvaquone plus azithromycin used to treat sick dogs naturally infected with the Babesia microti-like piroplasm. *Parasites & Vectors*, *10*(1), 145.

[46]. Rufener, R., Dick, L., D'Ascoli, L., Ritler, D., Hizem, A., Wells, T. N. C., … Lundström-Stadelmann, B. (2018). Repurposing of an old drug: In vitro and in vivo efficacies of buparvaquone against Echinococcus multilocularis. *International Journal for Parasitology, Drugs and Drug Resistance*, *8*(3), 440–450.

[47]. Müller, J., Manser, V., & Hemphill, A. (2019). In vitro treatment of Besnoitia besnoiti with the naphto-quinone buparvaquone results in marked inhibition of tachyzoite proliferation, mitochondrial alterations and rapid adaptation of tachyzoites to increased drug concentrations. *Parasitology*, *146*(1), 112–120.

[48]. Goud, K. S., & Vijayakumar, K. (2020). Molecular diagnosis and treatment of oriental theileriosis in calves. *The Pharma Innovation*, *9*(9), 568–571.

[49]. Borba-Santos, L. P., Barreto, T. L., Vila, T., Chi, K. D., Dos Santos Monti, F., de Farias, M. R., … Rozental, S. (2021). In vitro and in vivo antifungal activity of buparvaquone against Sporothrix brasiliensis. *Antimicrobial Agents and Chemotherapy*, *65*(9), e0069921.

[50]. Ferreira, V. F., de Carvalho, A. S., Ferreira, P. G., Lima, C. G. S., & de C da Silva, F. (2021). Quinone-based drugs: An important class of molecules in medicinal

chemistry. *Medicinal Chemistry {Shariqah (United Arab Emirates)}*, *17*(10), 1073–1085.

[51]. Nixon, G. L., Moss, D. M., Shone, A. E., Lalloo, D. G., Fisher, N., O'Neill, P. M., … Biagini, G. A. (2013). Antimalarial pharmacology and therapeutics of atovaquone. *The Journal of Antimicrobial Chemotherapy*, *68*(5), 977–985.

[52]. Hudson, A. T., & Randall, A. W. (1984). Antiprotozoal compounds. *United States Patent*, US 4485117 A.

[53]. Wang, Y., Tan, W., Ding, D., & Ma, J. (2008). Technique for synthesizing buparvaquone. *Chinese Patent Application*, CN 101265172 A.

[54]. Lv, Y. (2016). Buparvaquone synthesis process, *Chinese Patent Application*, CN 105646175 A.

[55]. Arulmoli, T., Balaya, L., Adithya, S, V, R., Pallikere, V, M., Kunder, K., & Udupa, K, V. (2012). A process for preparation of 2-((4-*tert*-butylcyclohexyl)methyl)-3-hydroxy-1,4-naphthoquinone. *Indian Patent Application*, IN 2012MU00356 A.

[56]. Balaya, L., Udupa, K, V., Arulmoli, T., Das, G, K., Adithya, S, V, R., Kunder, K., Shet, K., & Shettipal, A, B. (2014). A process for preparation of 2-((4-*tert*-butylcyclohexyl)methyl)-3- hydroxy-1,4-naphthoquinone. *Indian Patent Application*, IN 2012MU03303 A.

[57]. Ma, H., Guo, Q., Yan, B., Dong, K., Peng, X., & Sang, Y. (2013). Benzopyranone compound, as well as preparation method and application thereof. *Chinese Patent Application*, CN 103450141 A.

[58]. Ma, H., Guo, Q., Yan, B., Dong, K., Peng, X., & Sang, Y. (2014). Preparation method of buparvaquone. *Chinese Patent Application*, CN 103483176 A.

[59]. Shen, N., Han, L., Li, W., Guo, M., Liu, H., Zhou, Y., & Dong, H. (2015). Preparation method for buparvaquone. *Chinese Patent Application*, CN 105198718 A.

[60]. Cui, Q., Wang, B., Zhang, M., & Xu, X. (2020). Preparation method of buparvaquone. *Chinese Patent Application*, CN 110734368 A.

[61]. Saralaya, S. S., Shashikumar, H. S., Shashiprabha, Kanakamajalu, S., Ranganathan, K. R., Veeraswamy, A., Govindaraju, J., Kothapalli, S. R., & Nagarajan, K. (2012). Preparation of naphthoquinone compounds using 2,3-dihalonaphthoquinone. *United States Patent*, US 8283499 B2.

[62]. Saralaya, S. S., Shashiprabha, Kanakamajalu, S., Nagarajan, K., & Ranganathan, K. R. (2022). A systematic study towards the synthesis, isolation, and recrystallization of atovaquone, an antimalarial drug: A sustainable synthetic pathway. *Mapana Journal of Sciences*, *21*(1), 19–37.

[63]. Saralaya, S. S., Shashiprabha, Kanakamajalu, S., Nagarajan, K., & Ranganathan, K. R. (2022). A Novel and Sustainable Method for the Synthesis of 2-chloro-3-[trans-4-(4-chlorophenyl) cyclohexyl]-1,4-naphthoquinone, accomplished by systematic process development studies - Trans-Cl synthesis. *Mapana Journal of Sciences*, *21*(3).