Taylor & Francis
Taylor & Francis Group

Natural Product Research
Formerly Natural Product Letters

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gnpl20

Synthesis of novel artesunate-benzothiophene and artemisinin-benzothiophene derivatives

Omruye Ozok, Emrah Kavak & Arif Kivrak

To cite this article: Omruye Ozok, Emrah Kavak & Arif Kivrak (2021): Synthesis of novel artesunate-benzothiophene and artemisinin-benzothiophene derivatives, Natural Product Research, DOI: 10.1080/14786419.2021.1928116

To link to this article: https://doi.org/10.1080/14786419.2021.1928116

View supplementary material

Published online: 23 May 2021.

Submit your article to this journal

Article views: 90

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=gnpl20

NATURAL PRODUCT RESEARCH
https://doi.org/10.1080/14786419.2021.1928116

Taylor & Francis
Taylor & Francis Group

Check for updates

Synthesis of novel artesunate-benzothiophene and artemisinin-benzothiophene derivatives

Omruye Ozok[a,b], Emrah Kavak[a] and Arif Kivrak[a,c]

[a]Department of Chemistry, Faculty of Sciences, Van Yüzüncü Yil University, Van, Turkey; [b]Department of Molecular Biology and Genetics, Faculty of Sciences, Van Yüzüncü Yil University, Van, Turkey; [c]Faculty of Sciences and Arts, Department of Chemistry, Eskisehir Osmangazi University, Eskişehir, Turkey

ABSTRACT

Natural products are used for the treatment of a variety of diseases for many years. Last decades, design and synthesis of novel biologically active hybrid molecules including natural product is gained big importance due to their unique and new biological properties. In the present study, novel artemisinin-benzothiophene derivatives (**12 A-F**) are synthesised. Initially, benzothiophene derivatives (**4 A-4F**) are prepared via the Pd-catalyzed coupling reactions and iodocyclisation reactions. Then, Suzuki-Miyaura coupling reactions were used for the formation of intermediates **6 A-6F** (between 64% and 91% yields). Finally, the Steglich esterification reaction between intermediate **6** and artesunate formed the artemisinin-benzothiophene hybrids (**9 A-9F**) in moderate to excellent yields under very mild reaction conditions. When intermediate **6** was reacted with dihydroartemisinin, product **12 A-12F** was also obtained with high yields.

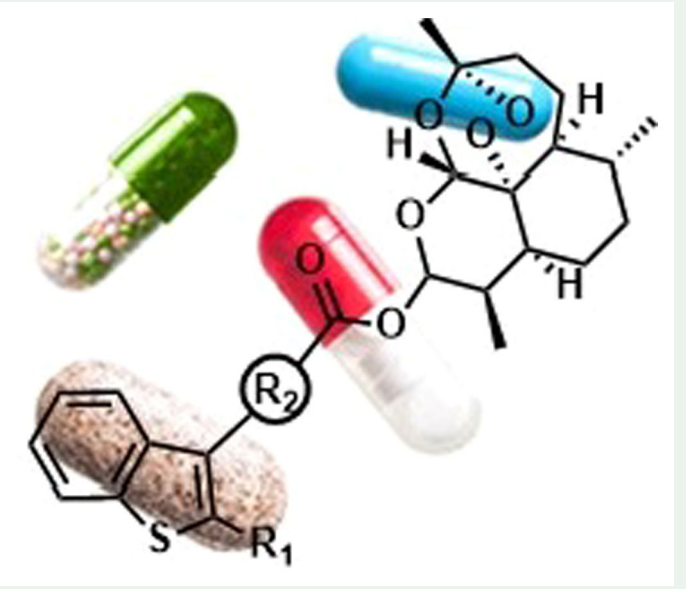
ARTICLE HISTORY
Received 8 February 2021
Accepted 4 May 2021

KEYWORDS
Artemisinin; artesunate; benzothiophene; natural products; drug design; wormwood plant

CONTACT Arif Kivrak arifkivrak@yahoo.com

Supplemental data for this article can be accessed online at https://doi.org/10.1080/14786419.2021.1928116.

© 2021 Informa UK Limited, trading as Taylor & Francis Group



1. Introduction

Natural product based medical therapy has been gained big importance for the treatment of diseases due to their amazing biological activities (Tan et al. 2011). Therefore, scientists are trying to synthesis or isolate new natural products. Artemisinin (ART), isolated from wormwood plant (*Artemisia absinthium*), was discovered by Chinese scientist Youyou Tu at the end of 1960s (Miller and Su 2011; Kong and Tan 2015) as an antimalarial. According to the World Health Organization (WHO), more than half a million people have died of the malaria (Price et al. 1996; Su and Miller 2015). ART displayed extreme activities than other antivirals, so it is known the most effective miracle drug for the treatments of malaria (Klayman 1985; Kong and Tan 2015; Guo 2016). Moreover, recent *in vivo* and *in vitro* studies showed that ART have higher activities against different cancer cells (Meshnick et al. 1996; Efferth et al. 2001; Chen et al. 2020; Li et al., 2020; Zhang 2020). Moreover, different biological properties have been reported after discovery of ART (Kong and Tan 2015). Semi-synthetic derivatives including artesunate (Efferth et al. 2008), artermer and dihydroartemisinin were also synthesised by starting from ART (Liu et al. 2013) (Figure 1). For example, artesunate was approved as a new anti-viral drug for the treatment of malaria by FDA in 2020. In addition, artesunate showed inhibitory effects against breast, melanoma, leukemia, ovarian, colon, prostate and renal cancer cells (Efferth et al. 2001; Firestone and Sundar 2009). Other semi synthetic derivative of ART is dihydroartemisinin which was also found as anti-cancer agents against osteosarcoma, pancreatic, leukemic, and lung cancer cells (Singh and Lai 2001; Chaturvedi et al. 2010).

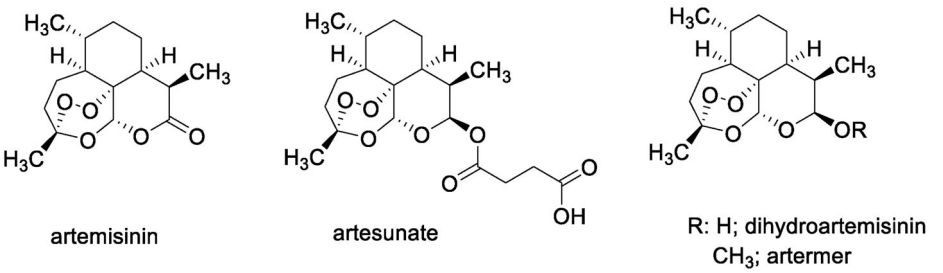


Figure 1. Artemisinin and semi-synthetic derivatives.

In recent years, new hybrid molecules consisting of artemisinin and heterocyclic compounds were designed and synthesized (Ha et al. 2016; Pepe et al. 2020). Interestingly, ART based hybrid molecules created new biological activities, or increase the known biological properties than artemisinin (Dhingra et al. 2000; Yang et al. 2020). Artemisinin-chloroquine hybrid structures displayed the higher activity for malaria as a new anti-malarial drug candidates (Pepe et al. 2020). In the lights of the previous studies, the novel hybrid molecules could be new drug candidates with unknown pharmacological activities against different kinds of cancer types and other diseases. It was known that COVID-19 has infected more than 65 million individuals worldwide, more than 1.6 million patients have died because of the infection (Gibson et al. 2020; Wu and McGoogan 2020). Anti-viral drugs like hydroxychloroquine, quinine, favipiravir etc. have been used to treatments of this viral pneumonia of SARS-CoV-2 (Nittari et al. 2020). Artemisinin hybrid molecules may be the biggest candidates for the treatment of SARS-CoV-2 as an anti-covid (Gendrot et al. 2020; Zhang 2020).

Benzothiophene derivatives are very important heteroaromatic compounds, and are used as; analgesic, antipyretic, antibacterial, antiparasitic, antitumor and anticancer agents (Keri et al. 2017; Algso et al. 2018; Algso and Kivrak 2019). Commercially available Raloxifene, Zileton, and Sertaconazole are the best examples of benzothiophene motifs. Herein, novel hybrid molecules consisting of artemisinin and biologically important benzothiophene were designed and synthesised by using Sonogashira coupling reaction, iodocyclisation reaction, Suzuki-Miyaura coupling reaction and Steglich esterification reaction.

2. Result and discussion

Initially, 3-iodobenzothiophene derivatives were prepared by starting from the 2-iodothioanisole. Sonogashira coupling reactions and iodocyclisation reaction was used to preparation of desired 3-iodobenzothiophene structures (Table S2). In literature, Pd-catalyzed coupling reaction like Sonogashira (Chinchilla and Najera 2007), Suzuki-Miyaura (Karabiyikoglu and Zora 2016) and Heck (Peris and Crabtree 2004) reactions are the most popular reactions for the formation of new carbon-carbon bonds. These reactions need mild reaction conditions, catalytic amounts of Pd-catalyst, and give the higher yields in a short time. Therefore, Sonogashira coupling reaction and Suzuki-Miyura coupling reaction were chosen in the present study. If the reaction between 2-iodothianisole and terminal alkyne was carried out in the presence of $PdCl_2(PPh_3)_2$ in

triethylamine under inert atmosphere, corresponding methyl(2-(aryl/alkyl-ethynyl)phenyl)sulfane derivatives (**3 A-F**) were obtained. The yields changed between 72% and 94% yields (Table S2). Then, iodocyclisation reactions were performed to synthesis of 3-iodobenzothiophene derivatives. Iodocyclisation reactions have played critical roles for the formation of heteroaromatic such as; indoles, pyrazoles, benzothiophenes, benzofurans etc. (Yue and Larock 2004; Cho et al. 2009; Zora and Kivrak 2011; Zora et al. 2011). 3-Iodo-benzothiophene derivatives **4** were regioselectively synthesised by using iodocyclisation cyclisation reaction. When compounds **3** was allowed to react with molecular iodide in dichloromethane, 3-iodo-benzothiophenes were isolated between 75% and 95% yields (Table S2). After iodocyclisation reaction, we focused on the synthesis of corresponding aldehydes **6**. Recently, we reported a new modified Suzuki-Miyaura coupling reaction for the affording benzothiophene derivatives including aldehyde functional groups. When **4 A** was reacted with 4-formylphenylboronic acid in the presence of Pd-catalyst and Li_2CO_3 in methyl alcohol, aldehyde **6 A** was obtained in 76% yields (Table S1). By using this reaction condition, aliphatic, aromatic and polyaromatic substituted benzothiophene derivatives **6B**, **6 C**, **6 D**, **4E** and **4 F** were synthesised in moderate to high yields (Table S2).

Next, we examined the esterification reaction between artesunate and alcohols **7**. Actually, there are a variety of esterification reactions such as; Steglich Esterification, Yamaguchi Esterification, Fischer Esterification etc. in literature. The Steglich esterification reaction is the more efficient methods, and it needs mild reaction conditions with shorter reaction time. This reaction also most convenient methods for the synthesis of some natural products. Therefore, Steglich esterification reaction was chosen for the synthesis of our final products. Firstly, we needed to prepare the corresponding alcohols from the aldehydes via reduction reaction. When aldehydes **6** was reacted with $NaBH_4$ in Chloroform/MeOH (4:1), the desired alcohols were formed. These alcohols were not stable, so we used alcohols without any purification. The reaction between artesunate and **7 A** in dichloromethane with DCC/DMAP catalyst systems, 98% yield of desired product **9 A** was obtained. By using same methodology, corresponding **9B**, **9 C**, **9 D**, **9E** and **9 F** were isolated in good yields (Table S3).

The ^{1}H-NMR spectra of the artesunate-benzothiophene **9** gave aromatic peaks between 7–8 ppm belonging to benzothiophene. The characteristic peaks of artesunate can be seen around 5.4 ppm as a doublet and 5.7 ppm as a singlet due to electronegative effect of the oxygen atoms on the ring. There is a singlet at 2.30 ppm came from the CH_3 where neighbors peroxide bridge. As seen in H-NMR spectra, Artesunate's remain CH_3 peaks are detected around 0.96 ppm and 0.84 ppm. In addition, there is a singlet at 5 ppm belonging to alcohol's CH_2. The ^{13}C-NMR spectra are important to determination of carbonyl (C = O) peaks of hybrid molecule. There are two ester functional groups on the hybrid molecule, so carbonyl's peaks are shifted around 170 ppm in ^{13}C-NMR spectra. Moreover, there are four artesunate's peaks between 110 and 80 ppm (Figure S1).

The plausible reaction pathway is shown in Figure 2. Firstly, carboxyl group was activated with a carbodiimide reagent to form the O-acylisourea. This intermediate takes a proton from the alcohol to give the carbocation intermediate. Then, DMAP reagent attacked this carbocation for the formation of second carbocation

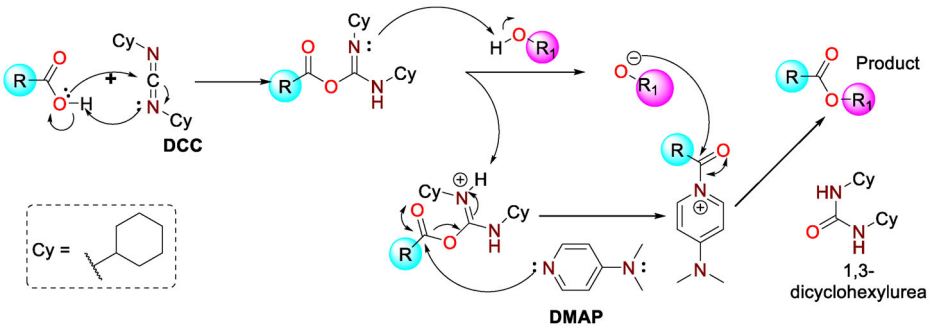


Figure 2. Proposed reaction mechanism for the formation of artesunate-benzothiophenes.

intermediates. Finally, the alcohol reacts with the activated carboxylic acid to form the desired product and dicyclohexylurea as a side product.

A series of artemisinin-benzothiophene hybrid derivatives **12** were also synthesized by using esterification reactions (Table S4). The aldehyde functional group of **6** was selectively oxidised, converting the aldehyde group to carboxylic acid **10**. Then, carboxylic acid derivatives **10** were underwent to esterification reaction without additional purification. When dihydroartemisinin was allowed to react with carboxylic acid **10 A** in the presence of EDCI/DMAP as catalyst system in dichloromethane, we isolated in 62% yield of **12 A**. When pentyl substituted carboxylic acid **10B** was used for esterification, the corresponding product **12B** was obtained in 50% yield. As seen in Table S4, a variety of artemisinin-benzothiophene hybrids including naphthyl, p-MePh, p-MeOPh groups were synthesized in moderate to high yields.

3. Conclusion

In the present study, novel artesunate-benzothiophene and artemisinin-benzothiophene hybrids were synthesized. Initially, 3-iodobenzothiophene derivatives were prepared by using Sonogashira Coupling reaction and electrophilic cyclization reactions. Then, Pd-catalyzed Suzuki-Miyaura coupling reactions were applied for the formation of aldehyde functionalised benzothiophenes (**6 A-6F**). Then, we focused on the synthesis of artesunate-benzothiophenes by using the Steglich esterification reaction. The corresponding alcohols **7** was prepared via reduction reaction, then underwent to esterification reaction for the synthesis of artesunate-benzothiophene hybrids **9**. We obtained **9 A-9F** in good yields. In the last part, novel artemisinin-benzothiophene **12 A-F** hybrids were synthesized from the reaction between carboxylic acid **10** and dihydroartemisinin in moderate to high yields. As a result, novel artemisinin based hybrid molecules were synthesized and characterized, and plausible reaction mechanism was proposed. Our new hybrid molecules may be new generation anti-viral candidates for the treatments of viral diseases.

Acknowledgment

The authors thank to The Scientific and Technological Research Council of Turkey (TUBITAK) project 218Z028 for chemicals and solvents. O. Ozok thanks to the council of higher education

(YOK) for 100/2000 scholarships. In addition, E. Kavak and O. Ozok thank to TUBITAK STAR scholarships.The author (A. Kivrak) would like to acknowledge networking contribution by the COST Action CA17104 'New diagnostic and therapeutic tools against multidrug resistant tumours'.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Omruye Ozok http://orcid.org/0000-0002-4164-8650

References

Algso MAS, Kivrak A. 2019. New strategy for the synthesis of 3-ethynyl-2-(thiophen-2-yl)benzo b thiophene derivatives. Chem Pap. 73(4):977–985.

Algso MAS, Kivrak A, Konus M, Yilmaz C, Kurt-Kizildoğan A. 2018. Synthesis and biological evaluation of novel benzothiophene derivatives. J Chem Sci. 130(9).

Chaturvedi D, Goswami A, Saikia PP, Barua NC, Rao PG. 2010. Artemisinin and its derivatives: a novel class of anti-malarial and anti-cancer agents. Chem Soc Rev. 39(2):435–454.

Chen GQ, Benthani FA, Wu J, Liang DG, Bian ZX, Jiang XJ. 2020. Artemisinin compounds sensitize cancer cells to ferroptosis by regulating iron homeostasis. Cell Death Differ. 27(1): 242–254.

Chinchilla R, Najera C. 2007. The sonogashira reaction: a booming methodology in synthetic organic chemistry. Chem Rev. 107(3):874–922.

Cho CH, Neuenswander B, Lushington GH, Larock RC. 2009. Solution-phase parallel synthesis of a multi-substituted benzo[b]thiophene library. J Comb Chem. 11(5):900–906.

Dhingra V, Rao KV, Narasu ML. 2000. Current status of artemisinin and its derivatives as antimalarial drugs. Life Sci. 66(4):279–300.

Efferth T, Dunstan H, Sauerbrey A, Miyachi H, Chitambar CR. 2001. The anti-malarial artesunate is also active against cancer. Int J Oncol. 18(4):767–773.

Efferth T, Romero MR, Wolf DG, Stamminger T, Marin JJG, Marschall M. 2008. The antiviral activities of artemisinin and artesunate. Clin Infect Dis. 47(6):804–811.

Firestone GL, Sundar SN. 2009. Anticancer activities of artemisinin and its bioactive derivatives. Expert Rev Mol Med. 11.

Gendrot M, Duflot I, Boxberger M, Delandre O, Jardot P, Le Bideau M, Andreani J, Fonta I, Mosnier J, Rolland C, et al. 2020. Antimalarial artemisinin-based combination therapies (ACT) and COVID-19 in Africa: In vitro inhibition of SARS-CoV-2 replication by mefloquine-artesunate. Int J Infect Dis. 99:437–440.

Gibson PG, Qin L, Puah SH. 2020. COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS . Med J Aust. 213(2):54–56.e1.

Guo Z. 2016. Artemisinin anti-malarial drugs in China. Acta Pharm Sin B. 6(2):115–124.

Ha VT, Kien VT, Binh LH, Tien VD, My NTT, Nam NH, Baltas M, Hahn H, Han BW, Thao DT, et al. 2016. Design, synthesis and biological evaluation of novel hydroxamic acids bearing artemisinin skeleton. Bioorg Chem. 66:63–71.

Karabiyikoglu S, Zora M. 2016. Facile synthesis of alkynyl-, aryl- and ferrocenyl-substituted pyrazoles via Sonogashira and Suzuki-Miyaura approaches. Appl Organometal Chem. 30(10): 876–885.

Keri RS, Chand K, Budagumpi S, Somappa SB, Patil SA, Nagaraja BM. 2017. An overview of benzo[b]thiophene-based medicinal chemistry . Eur J Med Chem. 138:1002–1033.

Klayman DL. 1985. QINGHAOSU (artemisinin): an antimalarial drug from China. Science. 228(4703):1049–1055.
Kong LY, Tan RX. 2015. Artemisinin, a miracle of traditional Chinese medicine. Nat Prod Rep. 32(12):1617–1621.
Li Y, Shan NN, Sui XH. 2020. Research progress on artemisinin and its derivatives against hematological malignancies. Chin J Integr Med. 26:947–955.
Liu YJ, Liu ZJ, Shi JY, Chen HM, Mi B, Li P, Gong P. 2013. Synthesis and cytotoxicity of novel 10-substituted dihydroartemisinin derivatives containing N-arylphenyl-ethenesulfonamide groups. Molecules. 18(3):2864–2877.
Meshnick SR, Taylor TE, Kamchonwongpaisan S. 1996. Artemisinin and the antimalarial endoperoxides: From herbal remedy to targeted chemotherapy. Microbiol Rev. 60(2):301–315.
Miller LH, Su X. 2011. Artemisinin: discovery from the Chinese herbal garden. Cell. Sep. 146(6): 855–858.
Nittari G, Pallotta G, Amenta F, Tayebati SK. 2020. Current pharmacological treatments for SARS-COV-2: A narrative review. Eur J Pharmacol. 882:173328.
Pepe DA, Toumpa D, André-Barrès C, Menendez C, Mouray E, Baltas M, Grellier P, Papaioannou D, Athanassopoulos CM. 2020. Synthesis of novel G factor or chloroquine-artemisinin hybrids and conjugates with potent antiplasmodial activity. ACS Med Chem Lett. 11(5):921–927.
Peris E, Crabtree RH. 2004. Recent homogeneous catalytic applications of chelate and pincer N-heterocyclic carbenes. Coord Chem Rev. 248(21-24):2239–2246.
Price RN, Nosten F, Luxemburger C, ter Kuile FO, Paiphun L, Price RN, Luxemburger C, Chongsuphajaisiddhi T, White NJ, Price RN, et al. 1996. Effects of artemisinin derivatives on malaria transmissibility. Lancet. 347(9016):1654–1658.
Singh NP, Lai H. 2001. Selective toxicity of dihydroartemisinin and holotransferrin toward human breast cancer cells. Life Sci. 70(1):49–56.
Su X-Z, Miller LH. 2015. The discovery of artemisinin and the Nobel Prize in Physiology or Medicine. Sci China Life Sci. 58(11):1175–1179.
Tan W, Lu J, Huang M, Li Y, Chen M, Wu G, Gong J, Zhong Z, Xu Z, Dang Y, et al. 2011. Anti-cancer natural products isolated from chinese medicinal herbs. Chin Med. 6(1):27.
Wu Z, McGoogan JM. 2020. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA-J Am Med Assoc. 323(13): 1239–1242.
Yang P, Lu ML, Li K, Xie Y. 2020. Artemisinin-derived dimers and their antimalarial activities. J Heterocycl Chem. 57(2):526–534.
Yue DW, Larock RC. 2004. Synthesis of 3-iodoindoles by electrophilic cyclization of N,N-dialkyl-2-(1-alkynyl)anilines. Org Lett. 6(6):1037–1040.
Zhang B. 2020. Artemisinin-derived dimers as potential anticancer agents: Current developments, action mechanisms, and structure-activity relationships. Arch Pharm Chem Life Sci. 353(2):1900240.
Zora M, Kivrak A. 2011. Synthesis of pyrazoles via CuI-mediated electrophilic cyclizations of alpha, beta-alkynic hydrazones. J Org Chem. 76(22):9379–9390.
Zora M, Kivrak A, Yazici C. 2011. Synthesis of pyrazoles via electrophilic cyclization. J Org Chem. 76(16):6726–6742.