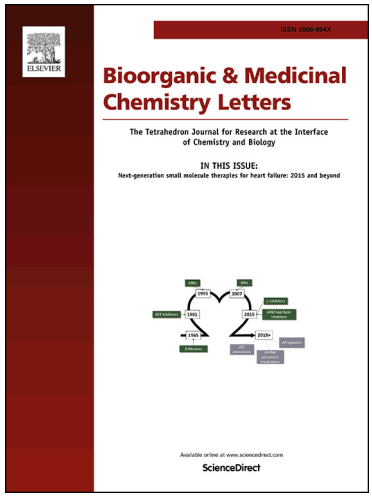
# Accepted Manuscript




Synthesis and Biological Evaluation of 2-Chloro-3-[(thiazol-2-yl)amino]-1,4-naphthoquinones

Emmanuel O. Olawode, Roman Tandlich, Earl Prinsloo, Michelle Isaacs, Heinrich Hoppe, Ronnett Seldon, Digby F. Warner, Vanessa Steenkamp, Perry T. Kaye

PII: S0960-894X(19)30287-2
DOI: https://doi.org/10.1016/j.bmcl.2019.05.001
Reference: BMCL 26421

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 1 March 2019
Revised Date: 30 April 2019
Accepted Date: 2 May 2019

Please cite this article as: Olawode, E.O., Tandlich, R., Prinsloo, E., Isaacs, M., Hoppe, H., Seldon, R., Warner, D.F., Steenkamp, V., Kaye, P.T., Synthesis and Biological Evaluation of 2-Chloro-3-[(thiazol-2-yl)amino]-1,4-naphthoquinones, *Bioorganic & Medicinal Chemistry Letters* (2019), doi: https://doi.org/10.1016/j.bmcl.2019.05.001

# Synthesis and Biological Evaluation of 2-Chloro-3-[(thiazol-2-yl)amino]-1,4-naphthoquinones

Emmanuel O. Olawode,[a*†] Roman Tandlich,[a] Earl Prinsloo,[b] Michelle Isaacs,[c] Heinrich Hoppe,[c,d] Ronnett Seldon,[e] Digby F. Warner,[f] Vanessa Steenkamp,[g] Perry T. Kaye[d,h*]

[a]*Division of Pharmaceutical Chemistry, Faculty of Pharmacy Rhodes University, Grahamstown 6140, South Africa.*
[b]*Department of Biotechnology, Rhodes University, Grahamstown 6140, South Africa.*
[c]*Department of Biochemistry and Microbiology, Rhodes University, Grahamstown 6140, South Africa*
[d]*Centre for Chemico- and Biomedicinal Research, Rhodes University, Grahamstown 6140, South Africa.*
[e]*Drug Discovery and Development Centre (H3-D), Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa*
[f]*Molecular Mycobacteriology Research Unit, Department of Pathology and Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa.*
[g]*Department of Pharmacology, University of Pretoria, Pretoria, South Africa*
[h]*Department of Chemistry, Rhodes University, Grahamstown 6140, South Africa.*

**Abstract.** A series of novel, substituted 2-chloro-3-[(thiazol-2-yl)amino]-1,4-naphthoquinones have been prepared and shown to exhibit promising concentration-dependent activity against human SH-SY5Y cells, *Plasmodium falciparum*, *Mycobacterium tuberculosis* and *P. aeruginosa*. Substituent effects on observed bioactivity have been explored; the *para*-fluorophenyl derivative **3d** exhibited activity across the range of the bioassays employed, indicating the potential of the 2-chloro-3-[(4-arylthiazol-2-yl)amino]-1,4-naphthoquinone scaffold in the development of novel, broad spectrum therapeutics.

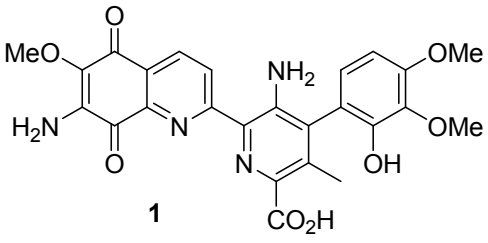
***Keywords.*** 2-Chloro-3-[(thiazol-2-yl)amino]-1,4-naphthoquinones, anti-malarial, anti-bacterial, anti-tuberculosis, cytotoxicity, HeLa cells

*Corresponding authors: Dr E.O. Olawode. E-mail: eolawode@binghamton.edu and Prof P.T. Kaye. Tel.: +27 46 6038268; fax: +27 46 6225109. E-mail: P.Kaye@ru.ac.za.
†Current address: School of Pharmacy and Pharmaceutical Sciences, Binghamton University, 96 Corliss Avenue, Johnson City 13790, New York, U.S.A.

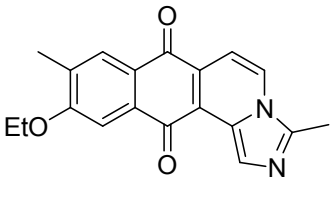
Compounds containing the 1,4-naphthoquinone moiety are commonly found in antibiotics isolated from marine microorganisms, particularly bacteria and sponges.[1-7] These compounds have been reported to exhibit wide-ranging pharmacological properties including antimicrobial,[1,2,8-12] anti-cancer,[2,3,13-15] antiviral,[16] trypanocidal,[17] antifungal,[18] antiparasitic,[19] antimalarial[20] and antimycobacterial[21] activity. The main mechanism for the pharmacological action of 1,4-naphthoquinone derivatives depends on their capacity to form radicals *in vivo*, especially *via* the metabolic effects of the cytochrome P450 enzyme complex in the liver.[22] This may explain the anti-oxidant, anti-cancer and anti-diabetic activities exhibited by various 1,4-naphthoquinone derivatives. Nicotinamide adenosine diphosphate (NADP), or its reductive analogue, NADPH-dependent quinone oxidoreductase (NQO1),[15,23,24] are key targets in the design and development of quinone-based anti-cancer agentsThe 5,8-quinolinedione analogues, streptonigrin **1** [25] and lavendamycin,[26] have been shown to inhibit the latter enzyme.

Pettit *et al.*[2] reported the anti-cancer activity of cribrostatin **2** against various cancer cell lines, including pancreas-adenocarcinoma BXPC-3, breast-adenocarcinoma MCF-7, CNS glioblastoma SF-268, lung-NSC NCI-H460, colon-adenocarcinoma KM20L2, prostate DU-145 and mouse leukemia P388; the $GI_{50}$ values were mostly in the 0.21-1 μg/mL range. Atamanyuk *et al.*[27] evaluated the anti-neoplastic and anti-mycobacterial potential of 1,4-naphthoquinone-derived 3,11-dihydro-2*H*-benzo[6,7]thiochromeno[2,3-d][1,3]-thiazole-2,5,10-triones, while Cai *et al.*[8] reported the total synthesis of hygrocin A and B, which contain the 1,4-naphthoquinone motif and exhibit moderate antibacterial activity against *Neisseria gonorrheae* (a Gram-negative bacterium) and *Aspergillus fumigates* (a fungus). Stasevych *et al.*[28] have used disc-diffusion susceptibility antimicrobial assays to demonstrate the capacity of certain 2-substituted-3-mercapto-1,4-naphthoquinones to selectively inhibit either *Escherichia coli* (Gram-negative) or *Staphylococcus aureus* (Gram-positive) bacteria.

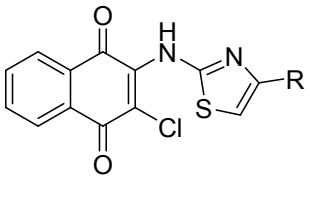
In this communication, we report the preparation and biological evaluation of a series of 1,4-naphthoquinone-derived 3-(thiazolylamino)naphthoquinones **3a-g** as potential multifunctional anti-cancer, anti-mycobacterial and anti-malarial agents.




**1**

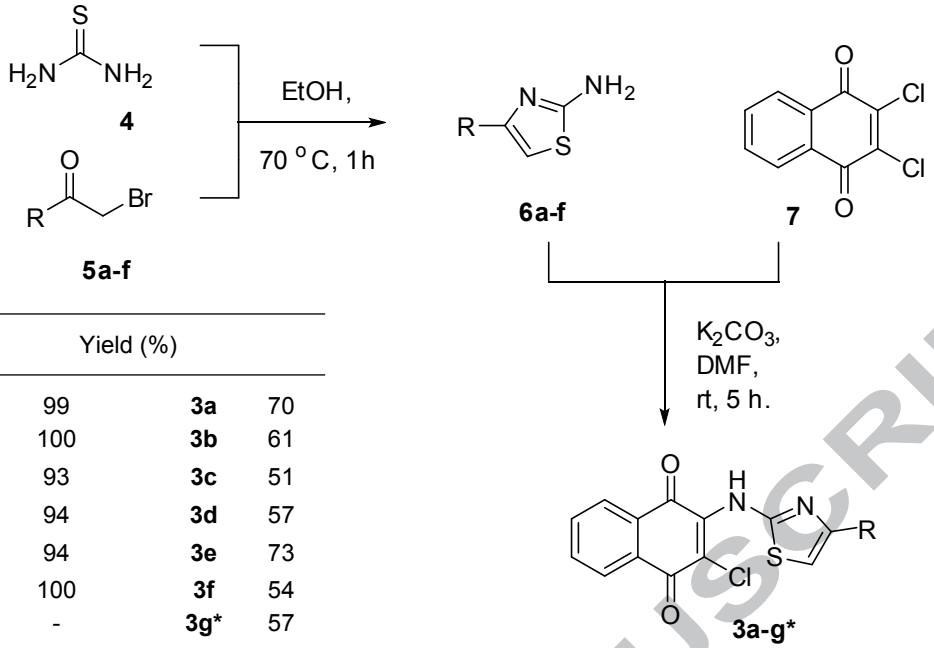



**2**




**3**

The preparation of the known 2-aminothiazoles **6a-f**,[9-11] required as precursors for the targeted 2-chloro-3-[(thiazol-2-yl)amino]-1,4-naphthoquinones **3a-f**, was accomplished by conventional Hantzsch condensation of thiourea **4** with the α-haloketones **5a-f** (Scheme 1). After completion of each reaction, the reaction mixture was poured into ice-cold water to precipitate the thiazole derivatives **6a-f** in excellent yields (93–100%). With the precursors in hand, studies were undertaken to optimise reaction conditions for the synthesis of the targeted compounds (**3**). These included the use of: i) different solvents [*viz*., polar protic solvents (EtOH and MeOH), non-polar aprotic solvents (THF, toluene and methylene chloride) and protic apolar solvents (DMSO and DMF)]; ii) different bases (triethylamine, pyridine or $K_2CO_3$); iii) different temperatures (ambient to 110 $^oC$); iv) different reaction times (1-48 hours); and v) microwave-assisted conditions with or without solvent at 150 $^oC$ for 10 minutes. Successful nucleophilic displacement of one of the chlorine atoms in 2,3-dichloro-1,4-naphthoquinone **7** by each of the 2-aminothiazoles **6a-f** was finally achieved using DMF in the presence of $K_2CO_3$ to obtain, without heating, the desired 2-chloro-3-[(thiazol-2-yl)amino]-1,4-naphthoquinones **3a-f**. All of the compounds were fully characterised using 1- and 2-D NMR, IR and HRMS methods; the 'parent' system **3a**[12,17] is known but the analogues **3b-g** are new compounds. Although overall substitution of chloride by the nucleophilic 2-aminothiazole is achieved in these reactions, the proposed mechanism involves conjugate-addition followed by elimination of HCl.[12,29] The 3-[(4-carbethoxythiazol-2-yl)amino]-2-chloro-1,4-naphthoquinone **3f** was hydrolysed in methanolic KOH to give the corresponding acid **3g** in moderate yield (53%). Experimental details and characterisation data for all of the compounds synthesised in this study are provided in the Supplementary Data file.




| R | Yield (%) | | | |
|---|---|---|---|---|
| Ph | **6a** | 99 | **3a** | 70 |
| *p*-ClPh | **6b** | 100 | **3b** | 61 |
| *p*-BrPh | **6c** | 93 | **3c** | 51 |
| *p*-FPh | **6d** | 94 | **3d** | 57 |
| *p*-$NO_2$Ph | **6e** | 94 | **3e** | 73 |
| COOEt | **6f** | 100 | **3f** | 54 |
| COOH | - | - | **3g*** | 57 |

**Scheme 1.** Synthesis of 2-chloro-3-[(thiazol-2-yl)amino]-1,4-naphthoquinones.
* Compound **3g** obtained by subsequent hydrolysis of **3f**.

The cytotoxic activity of compounds **3a-g** were examined in two cancer cell lines, *viz*., HeLa cervical adenocarcinoma and SH-SY5Y neuroblastoma cells. The SH-SY5Y cells showed a dose-dependent response to the compounds, with higher concentrations (particularly at 100 μM) inhibiting the growth of the cells, while lower concentrations showed similar effects to the untreated SH-SY5Y control. The xCELLigence RTCA-SP scans of the effects of different concentrations of compound **3d** on SH-SY5Y cells (Figure 1) are typical of the series of compounds examined. At lower concentrations (100 nM-1 μM), this compound (**3d**) resulted in similar patterns of growth to that observed with the untreated control, but at higher concentrations (10-100 μM) inhibited the growth of the cells at levels comparable to the negative control (*i.e.,* media without the test sample). The carboxylic acid **3g** and the precursor ester **3f** exhibited the lowest inhibitions with $IC_{50}$ values > 100 μM and 31.1 μM, respectively (Table 1). The phenyl-substituted analogues, however, exhibited significant cytotoxicity, with the unsubstituted phenyl (**3a**), *para*-chlorophenyl (**3b**), *para*-fluorophenyl (**3d**) and *para*-nitrophenyl (**3e**) derivatives exhibiting $IC_{50}$ values of 1.8, 2.7, 1.5 and 0.004 μM, respectively. These results suggest that the presence of the phenyl substituent and its electronegative *para*-substituents, particularly *p*-$NO_2$, may increase the binding affinity of these compounds to the binding pocket of the SH-SY5Y cells.

In contrast, compounds **3a-g** exhibited relatively low cytotoxicity against the HeLa cell line at a concentration of 20 µM (Table 1), indicating selective inhibition of SH-SY5Y cells by the phenyl-substituted compounds **3a-e**. Further studies are required to determine the mechanism of action of these compounds and their morphological effects on both cell lines.

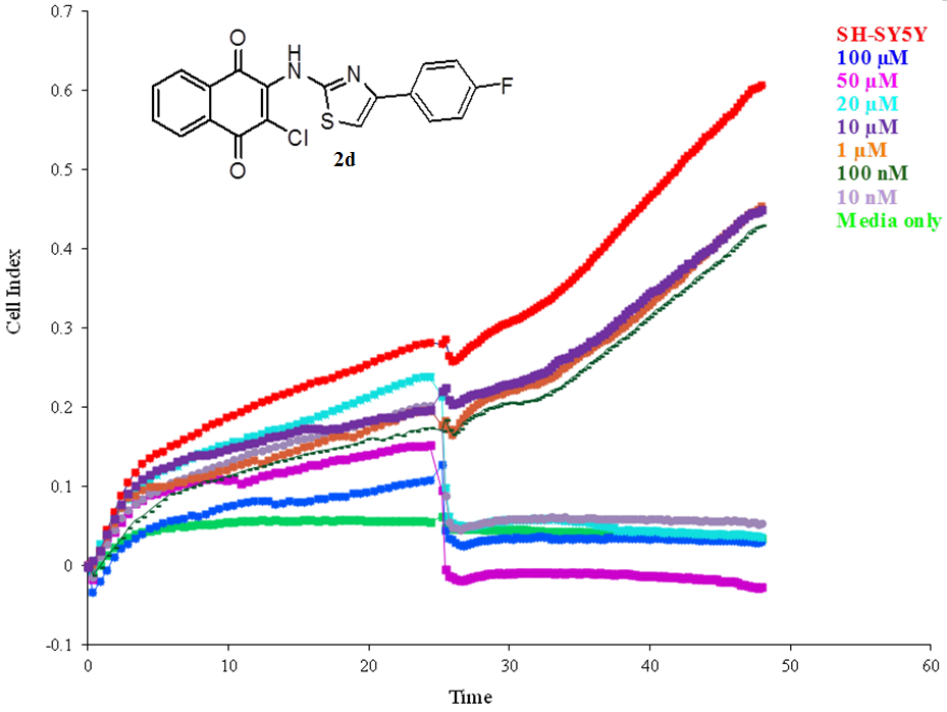



**Figure 1.** Scans of Cell Index (CI) of SH-SY5Y *vs* time (h) for different concentrations of 2-chloro-3-[4-(4-fluorophenyl)thiazol-2-ylamino]-1,4-naphthoquinone **3d** over 48 h using an xCELLigence RTCA-SP instrument.

The results of the anti-TB bioassay of the 2-chloro-3-[(thiazol-2-yl)amino]-1,4-naphthoquinones **3a-g** against the virulent *M. tuberculosis* $H_{37}$Rv strain are presented in Table 1 (dose-response curve are provided in the Supporting Information file). While the carboxylic acid **(3g)** and ester **(3f)** derivatives exhibited low levels of anti-TB activity, with $MIC_{90}$ and $MIC_{99}$ values > 20 µM, certain phenyl derivatives showed promising anti-TB activities with $MIC_{90}$ and $MIC_{99}$ values < 10 µM (**3a**: $MIC_{90}$ = 9.19 µM and $MIC_{99}$ = 10.2 µM); **3d**: $MIC_{90}$ = 9.39 µM and $MIC_{99}$ = 10.4 µM). All of the naphthoquinone derivatives (**3**) were found to have favourable (<5) Log P values, but the predicted aqueous solubilities (0.15 mg/mL and 0.08 mg/mL) of compounds **3a** and **3d**, respectively, were significantly higher than those of their aryl-substituted analogues **3b, 3c** and **3f** which may enhancetheir absorption across the mycolic-rich lipophilic cell wall of *M. tuberculosis*.

Whole-cell *Pf*LDH bioassays were conducted to determine the antimalarial activities of the 2-chloro-3-[(thiazol-2-yl)amino]-1,4-naphthoquinones **3a-g**, using 20 μM as the baseline concentration before determining $IC_{50}$ values for compounds with significant levels of inhibition. Chloroquine was used as the positive control. The results showed that the 'parent' compound **3a**, and the *p*-chlorophenyl (**3b**) and ethyl ester (**3f**) analogues exhibited low levels of inhibition against *P. falciparum* at the tested concentration, with values of 10%, 30% and 40% respectively, while analogues **3c-e** exhibited 80-90% inhibition of parasite viability at the tested concentration; $IC_{50}$ values of 50.6, 44.7 and 20.3 μM were determined for the latter compounds, **3c**, **3d** and **3e** respectively (Table 1). The acid derivative **3g**, on the other hand, enhanced the growth *P. falciparum,* recording 115% viability of the cells. Graphs showing the $IC_{50}$ plots and the % parasite viabilities with related standard deviations are provided in the Supplementary Data file. The results clearly reveal the importance of the thiazole substituent.

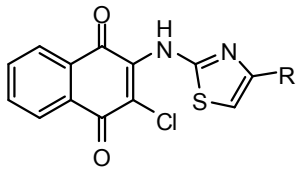
i) The acyl derivatives are clearly the least promising, with the ethyl ester **3f** exhibiting the lowest inhibition (10%) and its carboxylic acid derivative **3g** actually stimulating proliferation of *P. falciparum* by 15%
ii) Compared to the 'parent' system **3a** (R = Ph), the introduction of the electronegative *para*-substituents Br, F and $NO_2$ in the phenyl group in compounds **3c**, **3d** and **3e**, respectively, appears to decrease the viability of the parasite significantly.

The results of the disc diffusion susceptibility studies of the 2-chloro-3-[(thiazol-2-yl)amino]-1,4-naphthoquinones **3a-g** against an environmental strain of *P. aeruginosa* are summarised in Table 1. As was the case with the antimalarial bioassays, neither the carboxylic acid **3g** nor the ester precursor **3f** showed any inhibition potential, even at the highest concentration (2000 μM). The phenyl derivatives **3a**,**b**,**d**,**e**, on the other hand, exhibited dose-dependent antibacterial activity, with the *para*-fluorophenyl derivative **3d** exhibiting the highest inhibition across the different concentrations tested by clearing zones of 5 mm, 8 mm, 11 mm, 15 mm and 19.5 mm at 1 μM, 10 μM, 100 μM, 1000 μM and 2000 μM, respectively.

A series of 2-chloro-3-[(thiazol-2-yl)amino]-1,4-naphthoquinones derivatives **3a-g** have thus been successfully synthesised in moderate to good yield (51–73%). Various compounds exhibited concentration-dependent activities in each of the biological studies. The presence of the phenyl ring,

particularly when bearing electronegative *para*-substitutuents, clearly increases the levels of antimalarial and antibacterial activity, with the *para*-fluorophenyl derivative **3d** proving to be consistently active across all of the bioassays. These results indicate the potential of the title compounds **3a-e** to serve as lead compounds in the development of novel, multifunctional therapeutics.

**Table 1.** Biological evaluation of the 2-chloro-3-[(thiazol-2-yl)amino]-1,4-naphthoquinones **3a-g**.




| | R | *Cytotoxicity* | | *Anti-TB* | | *Antimalarial* | *Antimicrobial* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | SH-SY5Y $IC_{50}$ (µM) | HeLa % Viability[a] | $MIC_{90}$ (µM) | $MIC_{99}$ (µM) | *Pf*LDH $IC_{50}$ (µM) | Zone of inhibition (mm) 2000 µM | 1000 µM | 100 µM | 10 µM | 1 µM |
| **3a** | Ph | 1.8 | 80±5.9 | 9.19[b] | 10.2[b] | - | 13.2±0.6 | 11.4±0.9 | 9.1±0.4 | 5.3±0.5 | - |
| **3b** | *p*-ClPh | 2.7 | 80±2.1 | > 20.0 | > 20.0 | - | 12±0.7 | 9.7±0.5 | 7.6±1 | - | - |
| **3c** | *p*-BrPh | - | 55±1.8 | > 20.0 | > 20.0 | 50.6 | - | - | - | - | - |
| **3d** | *p*-PhF | 1.5 | 75±2.6 | 9.37[b] | 10.4[b] | 44.7 | 19.5±0.5 | 15±0.4 | 11±0.6 | 8±0.7 | 5±0.3 |
| **3e** | *p*-$NO_2$Ph | 0.004 | 80±3.6 | > 20.0 | > 20.0 | 20.3 | 14.10±0.8 | 11±013 | 7.2±0.7 | - | - |
| **3f** | COOEt | 31.1 | 82±2.8 | 19.5 | > 20.0 | - | - | - | - | - | - |
| **3g** | COOH | > 100 | 75±1.8 | > 20.0 | > 20.0 | - | - | - | - | - | - |
| ***Controls*** | | | | | | | | | | | |
| Chloroquine | | - | 3.6±0.1 | - | - | 0.0143 | - | - | - | - | - |
| Rifampicin | | - | - | 0.0015 | 0.00167 | - | | | | | |
| Ampicillin (25 µg/disc) | | - | - | - | - | - | | | 24.7±1.2 | | |
| Streptomycin (10 µg/disc) | | - | - | - | - | - | | | 20.0±0.8 | | |

[a] At 20 µM. [b] MIC values approximately 10 µM or lower.

**Acknowledgments**

The authors wish to thank Rhodes University for bursary support (to E.O.O.) and the South African Medical Research Council (SAMRC) and Rhodes University for research funding.

**Supplementary data**

Supplementary data associated with this article can be found in the online version.

**References and Notes**

1. Pettit RK, Fakoury BR, Knight JC, et al. Antibacterial activity of the marine sponge constituent cribrostatin 6. *J Med Microbiol*. 2004;53(1):61. doi:10.1099/jmm.0.05250-0.
2. Pettit GR, Collins JC, Knight JC, et al. Antineoplastic agents. 485. Isolation and structure of cribrostatin 6, a dark blue cancer cell growth inhibitor from the marine sponge *Cribrochalina* sp. *J Nat Prod*. 2003;66(4):544. doi:10.1021/np020012t.
3. Pettit GR, Knight JC, Collins JC, et al. Antineoplastic agents 430. Isolation and structure of cribrostatins 3, 4, and 5 from the Republic of Maldives *Cribrochalina* species. *J Nat Prod*. 2000;63(6):793. doi:10.1021/np990618q.
4. Nakahara S, Kubo A. Synthesis of cribrostatin 6. *Heterocycles*. 2004;63(10):2355. doi:10.3987/COM-04-10196.
5. Nakahara S, Kubo A, Mikami Y, Ito J. Synthesis of cribrostatin 6 and its related compounds. *Heterocycles*. 2006;68(3):515. doi:10.3987/COM-06-10674.
6. Yokoya M, Ito H, Saito N. Chemistry of renieramycins. Part 11: Total synthesis of (±)-cribrostatin 4. *Tetrahedron*. 2011;67(47):9185. doi:10.1016/j.tet.2011.09.076.
7. Knueppel D, Martin SF. Total synthesis of cribrostatin 6. *Angew Chemie - Int Ed*. 2009;48(14):2569. doi:10.1002/anie.200806269.
8. Cai P, Kong F, Ruppen ME, Glasier G, Carter GT. Hygrocins A and B, naphthoquinone macrolides from *Streptomyces hygroscopicus*. *J Nat Prod*. 2005;68(12):1736. doi:10.1021/np050272l.

9. Kesteleyn B, De Kimpe N. Synthesis of mimosamycin. *J Org Chem*. 2000;65(3):635. doi:10.1021/jo990767d.
10. Papageorgiou VP, Assimopoulou AN, Couladouros EA, Hepworth D, Nicolaou KC. The chemistry and biology of alkannin, shikonin, and related naphthazarin natural products. *Angew Chemie - Int Ed*. 1999:270. doi:10.1002/(SICI)1521-3773(19990201)38:3<270::AID-ANIE270>3.0.CO;2-0.
11. Tandon VK, Yadav DB, Maurya HK, Chaturvedi AK, Shukla PK. Design, synthesis, and biological evaluation of 1,2,3-trisubstituted-1,4-dihydrobenzo[g]quinoxaline-5,10-diones and related compounds as antifungal and antibacterial agents. *Bioorganic Med Chem*. 2006;14(17):6120. doi:10.1016/j.bmc.2006.04.029.
12. Osman SAA, Abdalla AA, Alaib MO. Synthesis of sulfanilamido-naphthoquinones as potential antituberculous agents. *J Pharm Sci*. 1983;72(1):68. doi:10.1002/jps.2600720116.
13. Milanowski DJ, Gustafson KR, Kelley JA, McMahon JB. Caulibugulones A-F, Novel cytotoxic isoquinoline quinones and iminoquinones from the marine bryozoan *Caulibugula intermis*. *J Nat Prod*. 2004;67(1):70. doi:10.1021/np030378l.
14. Hassani M, Cai W, Koelsch KH, et al. Lavendamycin antitumor agents: Structure-based design, synthesis, and NAD(P)H:quinone oxidoreductase 1 (NQO1) model validation with molecular docking and biological studies. *J Med Chem*. 2008;51(11):3104. doi:10.1021/jm701066a.
15. Hawas UW, Shaaban M, Shaaban KA, et al. Mansouramycins A-D, cytotoxic isoquinolinequinones from a marine streptomycete. *J Nat Prod*. 2009; 72(12):2120. doi:10.1021/np900160g.
16. Brinkworth RI, Fairlie DP. Hydroxyquinones are competitive non-peptide inhibitors of HIV-1 proteinase. *Biochim Biophys Acta (BBA)/Protein Struct Mol*. 1995;1253(1):5. doi:10.1016/0167-4838(95)00183-U.
17. Salmon-Chemin L, Buisine E, Yardley V, et al. 2- and 3-substituted 1,4-naphthoquinone derivatives as subversive substrates of trypanothione reductase and lipoamide dehydrogenase from Trypanosoma cruzi: Synthesis and correlation between redox cycling activities and in vitro cytotoxicity. *J Med Chem*. 2001;44(4):548. doi:10.1021/jm001079l.

18. Perry NB, Blunt JW, Munro MHG. A cytotoxic and antifungal 1,4-Naphthoquinone and related compounds from a New Zealand brown alga, *Landsburgia quercifolia*. *J Nat Prod*. 1991;54(4):978. doi:10.1021/np50076a009.
19. Hughes LM, Lanteri CA, Oneil MT, Johnson JD, Gribble GW, Trumpower BL. Design of anti-parasitic and anti-fungal hydroxy-naphthoquinones that are less susceptible to drug resistance. *Mol Biochem Parasitol*. 2011;177(1):12. doi:10.1016/j.molbiopara.2011.01.002.
20. Ehrhardt K, Davioud-Charvet E, Ke H, Vaidya AB, Lanzer M, Deponte M. The antimalarial activities of methylene blue and the 1,4-naphthoquinone 3-[4-(Trifluoromethyl)Benzyl]-menadione are not due to inhibition of the mitochondrial electron transport chain. *Antimicrob Agents Chemother*. 2013;57(5):2114.. doi:10.1128/AAC.02248-12.
21. Ollinger J, Bailey MA, Moraski GC, et al. A dual read-out assay to evaluate the potency of compounds active against *Mycobacterium tuberculosis*. *PLoS One*. 2013;8(4):e60531. doi:10.1371/journal.pone.0060531.
22. Wellington KW. Understanding cancer and the anticancer activities of naphthoquinones-a review. *RSC Adv*. 2015:20309. doi:10.1039/c4ra13547d.
23. Hassani M, Cai W, Holley DC, et al. Novel lavendamycin analogues as antitumor agents: Synthesis, in vitro cytotoxicity, structure-metabolism, and computational molecular modeling studies with NAD(P)H:quinone oxidoreductase 1. *J Med Chem*. 2005;48(24):7733. doi:10.1021/jm050758z.
24. Siegel D. NAD(P)H:Quinone Oxidoreductase 1: Role as a superoxide scavenger. *Mol Pharmacol*. 2004;65(5):1238. doi:10.1124/mol.65.5.1238.
25. Beall HD, Liu Y, Siegel D, Bolton EM, Gibson NW, Ross D. Role of NAD(P)H:quinone oxidoreductase (DT-diaphorase) in cytotoxicity and induction of DNA damage by streptonigrin. *Biochem Pharmacol*. 1996;51(5):645. doi:10.1016/S0006-2952(95)00223-5.
26. Hou TJ, Xu XJ. ADME Evaluation in drug discovery. 3. Modeling blood-brain barrier partitioning using simple molecular descriptors. *J Chem Inf Comput Sci*. 2003;43(6):2137. doi:10.1021/ci034134i.
27. Atamanyuk D, Zimenkovsky B, Atamanyuk V, et al. Synthesis and biological activity of new Thiopyrano[2,3-d]thiazoles containing a naphthoquinone moiety. *Sci Pharm*. 2013;81(2):423.

28. Stasevych M V, Chervetsova VG, Plotnikov MY, et al. Synthesis and antimicrobial evaluation of novel 2-substituted-3-mercapto-1,4-naphthoquinones. *Ukr Bioorganica Acta*. 2006;4(2):33.

29. Tandon VK, Maurya HK, *Tetrahedron Lett*. 2009;50(43):5896. doi:10.1016/j.tetlet.2009.07.149.