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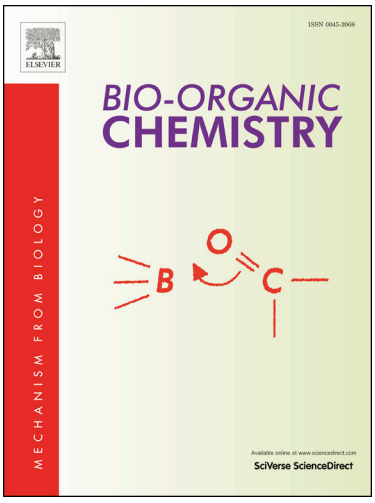

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PII: S0045-2068(20)30190-5
DOI: https://doi.org/10.1016/j.bioorg.2020.103732
Reference: YBIOO 103732

To appear in: *Bioorganic Chemistry*

Received Date: 24 January 2020
Revised Date: 20 February 2020
Accepted Date: 6 March 2020

Please cite this article as: B. Akkachairin, W. Rodphon, O. Reamtong, M. Mungthin, J. Tummatorn, C. Thongsornkleeb, S. Ruchirawat, Synthesis of Neocryptolepines and Carbocycle-Fused Quinolines and Evaluation of Their Anticancer and Antiplasmodial Activities, *Bioorganic Chemistry* (2020), doi: https://doi.org/10.1016/j.bioorg.2020.103732

Synthesis of Neocryptolepines and Carbocycle-Fused Quinolines and Evaluation of Their Anticancer and Antiplasmodial Activities

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Keywords:

Neocryptolepine
Antiplasmodial
Anticancer
Indoloquinoline
Azide
Carbocycle-fused quinolines

Abstract

This study reported the discovery of novel compounds containing five-membered ring fused quinoline core structures as anticancer and antimalarial agents. Two libraries containing these core structures, neocryptolepines and carbocycle-fused quinolines, were prepared and evaluated. Compound **3h** was found to be much more potent than other analogs against cancer cell lines with high selectivity. Meanwhile, carbocycle-fused quinolines **5h** and **5s** showed moderate anticancer properties but much less cytotoxicity to normal cell than doxorubicin. In addition, compound **3h** also showed much lower cytotoxic against human normal kidney cell line compared to doxorubicin standard. However, only compounds **3s** and **3p** provided acceptable results for antimalarial activities.

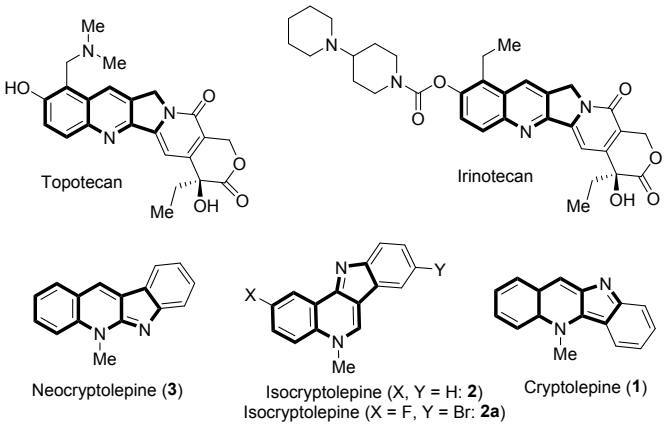
1. Introduction

According to World Health Organization (WHO), the emergence and spread of cancer and malaria are major threats to the world public health concern. Cancer is non-communicable disease which is one of major disease concerns related to human mortality. The International Agency for Research on Cancer (IARC) reported that the estimated cancer cases around the world have been rising up to 18.1 million new cases causing 9.6 million deaths in 2018. In addition, nearly one-half of the estimated cases and over one-half of cancer deaths worldwide are found in Asia for both sexes due to the high contribution to global population.[1] Another concern is malaria disease which is one of global infectious diseases caused by *Plasmodium* parasites and transmitted by female *Anopheles* mosquitos. There are four common species of *Plasmodium* that

cause human infection including *P. falciparum, P. malariae, P. ovale and P. vivax.* The *P. falciparum* is the most threatening contributing strain to the highest prevalence of malaria.[2-3] The 2018 World Malaria Report described that the number of malaria cases in 2017 was significantly lower than in 2010 by approximately 20 million cases. However, there was no significant decrease from 2015 to 2017. The estimated number of infections was up to 219 million cases in 90 countries and closely a million deaths were reported in 2017.[3] The resistance of *P. falciparum* strain against currently available anti-malarial drugs such as chloroquine and artemisinin is growing. The incidence of malarial infection is rising in both developing and industrialized countries, leading to an urgent need in the exploration of new therapeutic agents.[4-6] Therefore, the development of therapeutic treatment for both diseases is still in need and catches the interest in the pharmaceutical field.

One of the most important core structures in drug discovery and development for treatment of cancer and malaria is quinoline as this core structure plays an important role in increasing potency of biologically active compounds. Nowadays, several anticancer and antimalarial drugs in global markets contain quinoline moiety in the molecules.[7-9] The examples of quinoline antimalarial drugs include chloroquine, quinine, mefloquine, amodiaquine, and hydroxychloroquine.[9-11] In addition, quinoline core structure also has high impact on the development of anticancer therapeutic agents.[12] For examples, bosulif is a synthetic chronic myeloid leukemia drug which was reported as one of the best-selling anticancer drugs.[13] Therefore, several libraries of quinoline analogs were designed, synthesized and evaluated for their anticancer properties leading to the discovery of new lead anticancer compounds. In addition, polycyclic quinoline is a privileged core structure used as a structure-based drug design to improve biological activities of compounds. This core structure also is also present in the structure of well-known anticancer drugs, topotecan and irinotecan.[9,14] These two synthetic analogs of polycyclic quinoline were originally developed from camptothecin natural product and used for treatment of ovarian cancer, and metastatic colon and rectal cancer, respectively.[15-18]

Moreover, plants are rich sources of five-membered ring fused quinoline core structure. Cryptolepine (**1**), neocryptolepine (**2**) and isocryptolepine (**3**) are examples of polycyclic quinoline natural products which were isolated from the West and Central African plant, *Cryptolepis sanguinolenta*.[19-21]This plant has been used in traditional medicine to treat various health disorders including malaria, inflammation, urinary tract infections, and other diseases.[22-25] These natural quinoline alkaloids have revealed potent antiplasmodial and anticancer properties which show the potential to be developed as antimalarial and anticancer agents.[26-28] They also display biological functions including intercalation of DNA, inhibition of topoisomerease II enzyme, cytotoxicity, antibacterial activity, and antifungal activity.[26,29-30] However, due to their ability to intercalate DNA and inhibit topoisomerease II, these indoloquinoline alkaloids can cause toxicity to human. Cryptolepine shows stronger DNA-intercalation and inhibition of human topoisomerase II compared to neocryptolepine and isocryptolepine.[31-33]



Scheme 1. Natural indoloquinoline and five-membered *N*-heterocyclic-fused quinoline alkaloids.

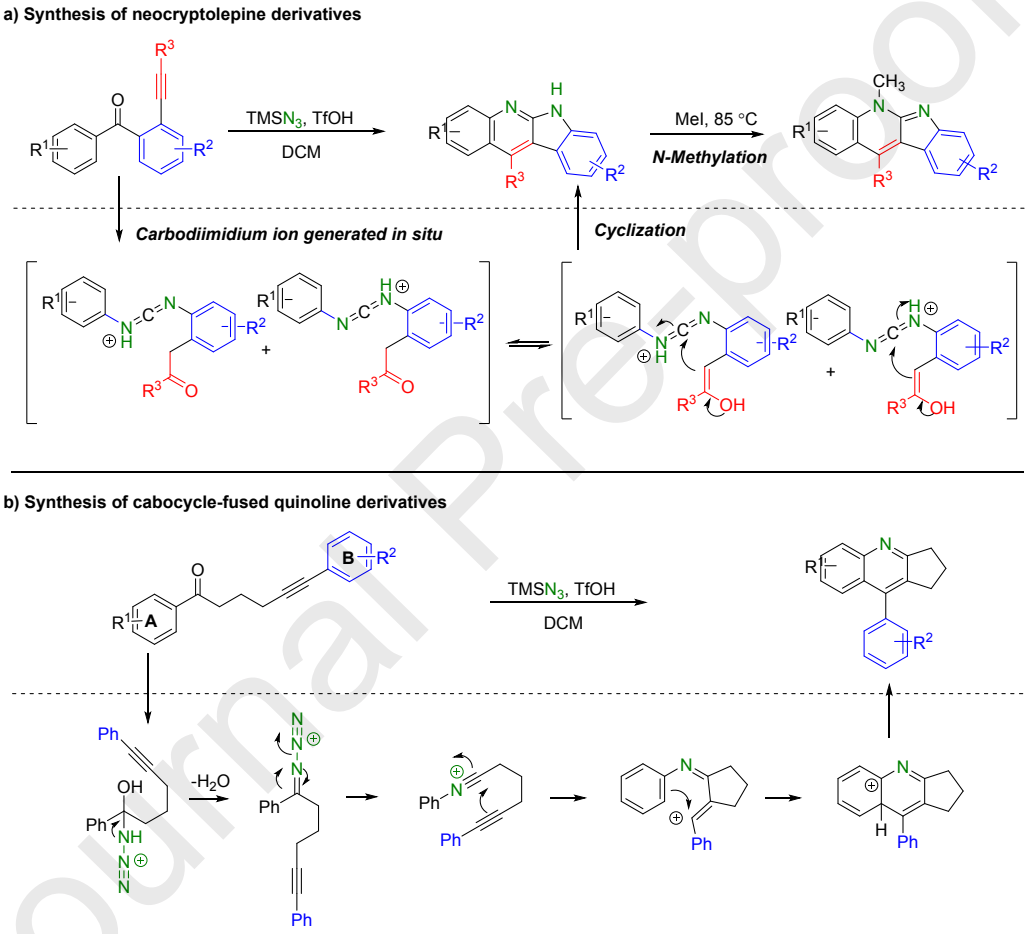
Previously, our group reported the synthesis and structure–activity relationship (SAR) studies of isocryptolepine derivatives as anticancer and antimalarial agents.[34] The novel isocryptolepines were conveniently synthesized in four steps from simple substrates, arylmethyl azides and *N*-phenylsulfonyl indoles, via azide rearrangement chemistry.[35] The results demonstrated that halogen-substituted isocryptolepines (**2a**) showed high activities against and selectivities for four *Plasmodium falciparum* strains and four primary cancer cell lines.[34] As numerous compounds containing five-membered nitrogen ring fused with quinoline core structure showed a broad spectrum of biological activities including anticancer and antimalarial properties; this inspired us to study the structure-activity relationship of neocryptolepine and carbocycle-fused quinolines, as anticancer and antimalarial agents.

2. Results and Discussion

2.1. Chemistry

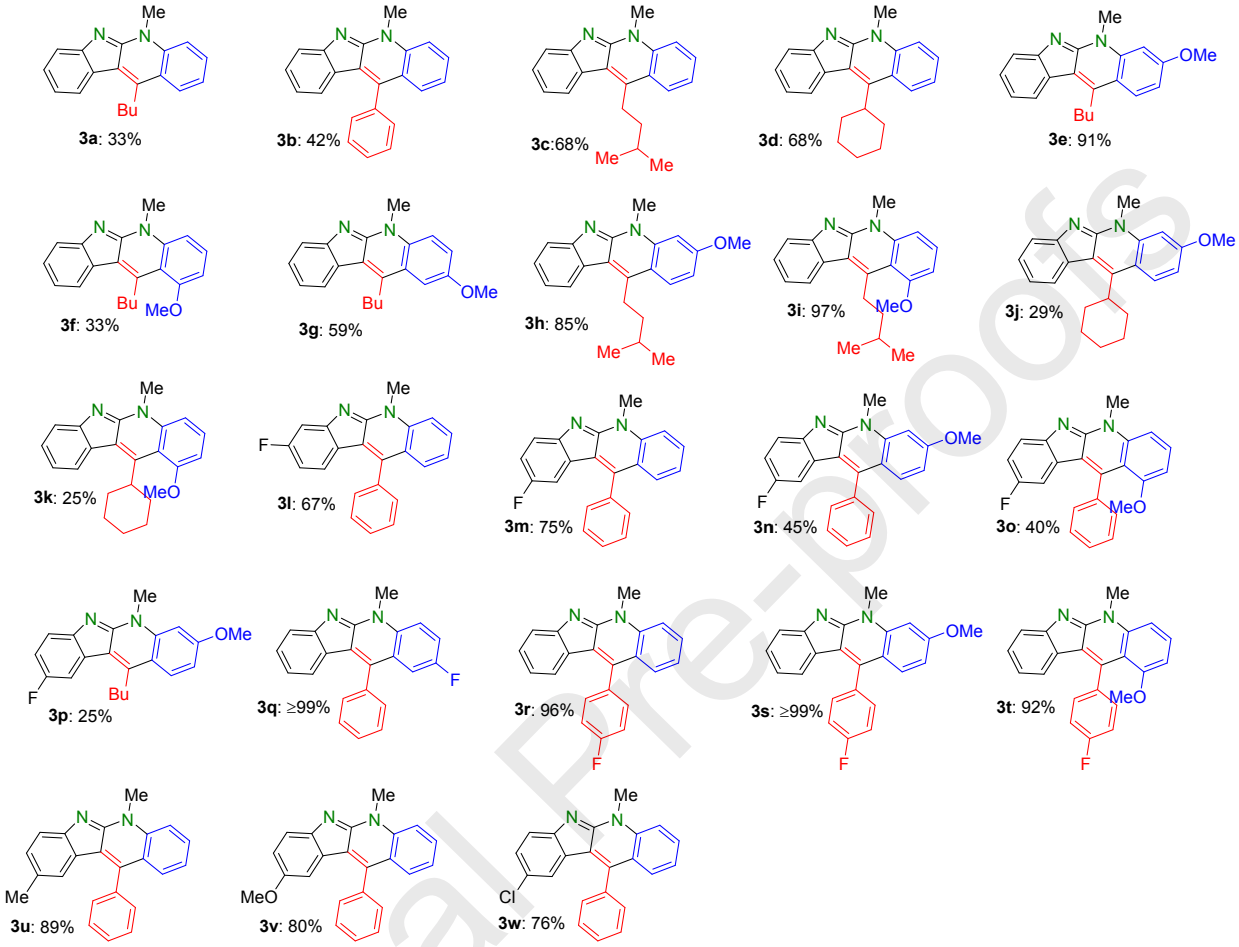
Recently, our research group developed synthetic methodology for the construction of 6*H*-indolo[2,3-*b*]quinoline and carbocycle fused-quinoline derivatives using the N_2-extrusion of azido complexes of alkynylarylketone derivatives as shown in Scheme 2.[36] Neocryptolepine derivatives could be synthesized from regioselective methylation of indoloquinoline precursors which were prepared using our developed method. A wide variety of indoloquinoline skeletons with broad range of substituents were prepared from domino N_2-extrusion–cyclization of alkynylarylketone starting material which could be obtained by simple and convenient procedure via Sonogashira coupling of 2-iodobenzophenone derivatives with terminal alkynes. The reactions proceeded through double N_2-extrusion and double aryl migration of *ortho*-alkynylarylketones to generate carbodiimidium ion intermediate (Scheme 2a) to provide indoloquinoline products. In this work, this useful synthetic method of indoloquinolines was used to create a library of neocryptolepine analogs via regioselective methylation of these indoloquinolines. The results showed that neocryptolepine derivatives could be prepared from a broad range of substrates to give the desired products in low to excellent yields. All neocryptolepines were further used for evaluation of biological activities. In

addition, our research group has reported the development of a synthetic method to construct five-membered ring-fused quinoline using azide rearrangement chemistry.[36] This method could be used to create a novel library of carbocycle–fused quinolines with a broad range of substituents. Alkynylarylketones were employed as the starting material which were treated with $TMSN_3$ and TfOH to generate the nitrilium ion, followed by double cyclization to give the desired products (Scheme 2b). In this study, twenty-three neocryptolepines and twenty-five carbocycle-fused quinolines were prepared for biological evaluation. In this study, R^1, R^2 and R^3 were varied as shown in Table 1.



Scheme 2. Synthetic methods for the synthesis of neocryptolepines and carbocycle-fused quinolines

Table 1. Neocryptolepine derivatives for biological studies.

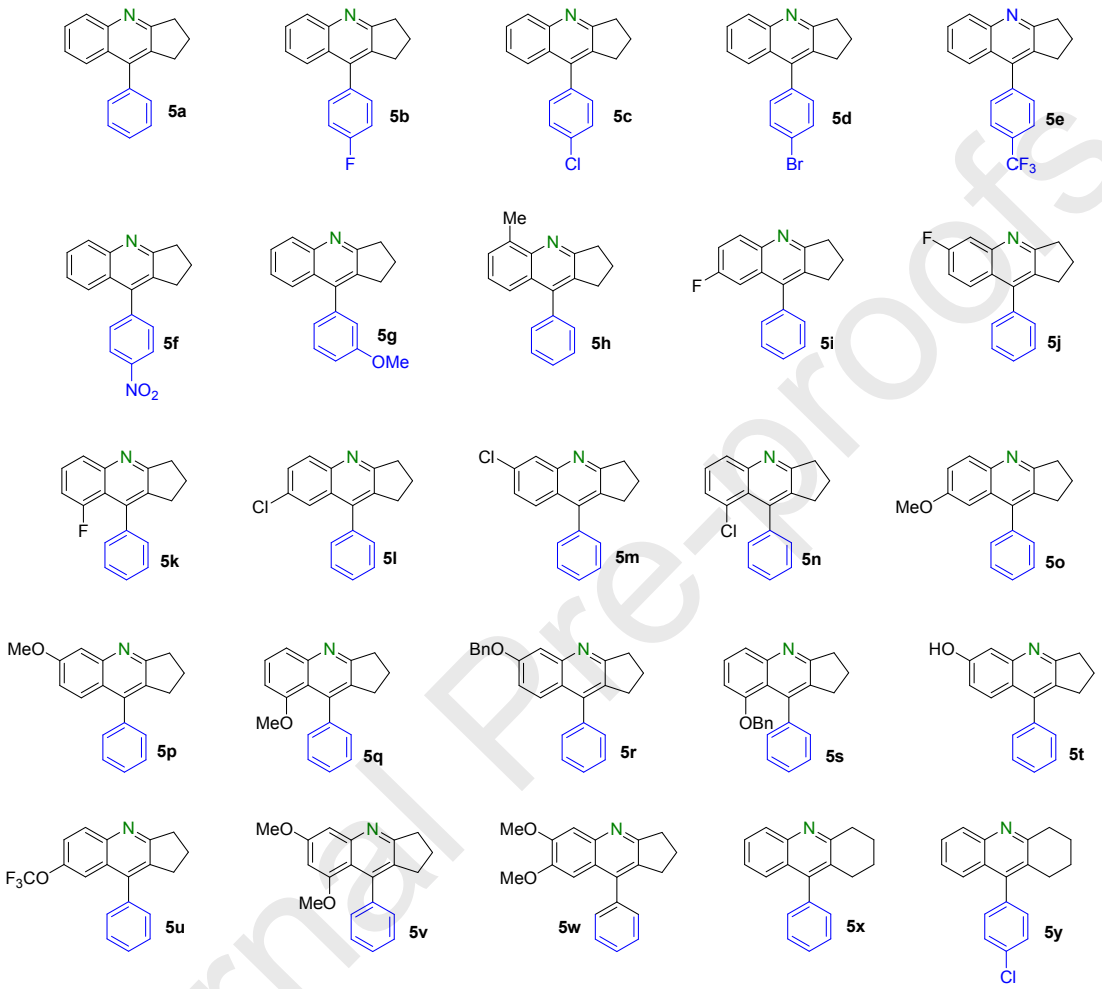


2.2. *Biological evaluation*

2.2.1. *In vitro anticancer assays*

Neocryptolepine (**3a-3w**) and carbocycle-fused quinoline (**5a-5y**) libraries were employed to evaluate the biological activities including, *in vitro* antiplasmodial activity against chloroquine-sensitive 3D7 (CQ-S) and chloroquine-resistant K1 (CQ-R) *Plasmodium falciparum* strains and antiproliferative activity against four primary cancer cell lines; HepG2 (human liver carcinoma), HuCCA-1 (human cholangiocarcinoma), MOLT-3 (human acute lymphoblastic leukemia), and A549 (human lung adenocarcinoma). The cytotoxicity against normal human embryonic kidney cell line-293 (HEK-293) was also investigated to determine the selectivity indices (SIs). The MTT assay was employed to measure cytotoxicity of HepG2, HuCCA-1, A549, and HEK-293 cell lines while XTT method was applied to MOLT-3 cell line. In this study, doxorubicin or etoposide or both were used as the positive controls for these assays. In this studies, cytotoxic activities of neocryptolepine analogs **3a-3w** were investigated with the results shown in Table 3.

Table 2. Carbocycle-fused quinoline analogs[a]



[a]All compounds were prepared using our reported method.[36]

The results from cytotoxicity evaluation against HEK-293 showed that compound **3h**, **3k** and **3m** were much less toxic compared to other derivatives of neocryptolepines and at least 35 times less toxic than doxorubicin over 35 times. For the cytotoxicity against HuCCA-1, compound **3g**, **3h**, **3i**, **3p**, and **3s** were all found to have good activity among other analogs, especially compound **3s** containing both methoxy group and fluorine atom showed highest activity, although, the selectivity index of compound **3h** was highest in this cell lines. In case of A549 cancer cell line, compounds **3e**, **3f**, **3g**, **3h**, **3i** and **3s** displayed good anticancer activity. Among these compounds, compound **3i** provided highest activity while compound **3h** showed highest selectivity. The structures of both **3h** and **3i** contain methoxy and isopentyl groups in the molecules with the methoxy group located at different positions. The results from cytotoxicity evaluation against HepG2 cell line showed similar

range of IC_{50} to A549 cancer cell line (13-16 μM). Compounds **3e**, **3f**, **3g**, **3h**, **3i** and **3s** also provided good activity and compound **3h** also showed highest selectivity. Interestingly, compound **3h** has greater selectivity than doxorubicin standard and also provided better IC_{50} value than etoposide standard in this cell line. In case of MOLT-3, compounds **3a**, **3c**, **3e**, **3f**, **3g**, **3h**, and **3i** gave good biological activity against this cancer cell line with good IC_{50} values. Compound **3f** containing methoxy and butyl groups has the best activity (IC_{50} 2.54 μM) a of all analogs in the series among this library while compound **3h** again provided highest selectivity with IC_{50} of 4.90 μM and SI of 68.13. In this series of neocryptolepine anologs, compound **3h** illustrated promising medicinal property both for its cytotoxicity and selectivity in all cancer cell lines. Based on several studies of cryptolepine and its analogues, including isocryptolepine and neocryptolepine, topoisomerase II has been shown as target of inhibition by these compounds in several cancer cell lines via DNA intercalation mechanism.[37-39] Therefore, the mode of action of compound **3h** was suspected to involve the inhibition of topoisomerase II in these cancer cell lines as well.

Table 3 *In vitro* cytotoxic activities of neocryptolepine analogs **3a-3w** against four primary cancer cell lines and one normal lung cell line.

Comp.	HEK-293 (μM)	HuCCA-1 (μM)		A549 (μM)		HepG2 (μM)		MOLT-3 (μM)	
	IC_{50} (μM)	IC_{50} (μM)	SI	IC_{50} (μM)	SI	IC_{50} (μM)	SI	IC_{50} (μM)	SI
3a	129.87±28.44	31.68 ± 0.17	4.10	27.12 ± 0.95	4.79	19.18 ± 0.62	6.77	5.31 ± 0.38	24.46
3b	160.70±38.47	123.26 ± 0.20	1.30	103.60 ± 6.56	1.55	76.66 ± 4.86	2.10	18.55 ± 2.69	8.66
3c	152.13±37.61	30.19 ± 0.56	5.04	26.85 ± 2.48	5.67	17.62 ± 0.40	8.63	7.14 ± 2.08	21.31
3d	105.86±47.88	58.04 ± 1.12	1.82	58.90 ± 2.86	1.80	72.00 ± 3.66	1.47	19.85 ± 2.48	5.33
3e	13.04±20.43	17.21 ± 3.24	0.76	15.58 ± 0.78	0.84	15.51 ± 1.00	0.84	4.49 ± 0.44	2.90
3f	37.75±6.93	14.07 ± 0.93	2.68	13.63 ± 1.57	2.77	15.36 ± 0.79	2.46	2.54 ± 0.19	14.86
3g	142.00±4.88	13.13 ± 1.82	10.81	14.89 ± 0.46	9.54	14.57 ± 0.75	9.75	3.74 ± 0.69	37.97
3h	**333.83±27.75**	**13.39 ± 1.68**	**24.93**	**15.31 ± 0.57**	**21.80**	**15.58 ± 0.42**	**21.43**	**4.90 ± 0.45**	**68.13**
3i	95.39±26.62	13.63 ± 0.00	7.00	10.80 ± 1.57	8.83	13.72 ± 0.69	6.95	4.18 ± 0.75	22.82
3j	229.23±10.10	30.13 ± 1.46	7.61	30.89 ± 1.63	7.42	17.04 ± 0.81	13.45	13.47 ± 2.00	17.02
3k	309.79±42.30	26.13 ± 0.26	11.86	27.03 ± 0.35	11.46	15.53 ± 1.16	19.95	9.29 ± 1.34	33.35
3l	239.03±36.89	108.13 ± 5.60	2.21	103.41 ± 4.98	2.31	56.81 ± 10.63	4.21	17.62 ± 3.55	13.57
3m	469.59±64.78	Inactive	-	Inactive	-	79.36 ± 2.30	5.92	16.58 ± 1.84	28.32
3n	160.84±60.87	Inactive	-	102.55 ± 8.77	1.57	21.38 ± 2.72	7.52	8.47 ± 1.85	18.99
3o	151.66±39.14	51.43 ± 0.55	2.95	44.11 ± 0.49	3.44	26.46 ± 0.34	5.73	35.19 ± 39.56	4.31
3p	221.11±10.39	13.53 ± 0.42	16.34	24.85 ± 1.17	8.90	24.88 ± 4.19	8.89	67.92 ± 58.92	3.26
3q	142.85±44.93	Inactive	-	Inactive	-	40.60 ± 1.72	3.52	23.10 ± 1.96	6.18
3r	79.64±25.91	141.19 ± 3.99	0.56	110.92 ± 3.20	0.72	73.81 ± 6.68	1.08	20.25 ± 6.46	3.93
3s	68.44±4.33	9.65 ± 1.57	7.09	14.00 ± 1.37	4.89	15.88 ±1.32	4.31	10.19 ± 1.01	6.72
3t	50.48±8.87	29.88 ± 1.33	1.69	28.68 ± 0.30	1.76	19.39 ± 1.09	2.60	10.35 ± 1.91	4.88
3u	49.50±6.45	36.29 ± 2.32	1.36	51.33 ± 1.223	0.96	25.77 ± 3.16	1.92	11.66 ± 2.17	4.25
3v	84.35±13.59	49.17 ± 2.69	1.72	50.26 ± 7.50	1.68	21.07 ± 3.96	4.00	9.28 ± 1.42	9.09
3w	127.00±5.45	Inactive	4.10	Inactive	4.79	85.87 ± 28.35	1.48	Inactive	-

Doxorubicin	8.62±8.36	0.79 ± 0.08	10.91	0.34 ± 0.01	25.23	0.53 ± 0.09	16.26	0.01 ± 0.00	862
Etoposide	-	-	-	-	-	54.17 ± 1.67	-	0.05 ± 0.01	-

Table 4. *In vitro* cytotoxic activities of carbocycle-fused quinoline analogs **5a-5y** against four primary cancer cell lines.

Comp.	HepG2	A549	HuCCA-1	MOLT-3
	IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)
5a	104.56±19.48	147.27±9.71	157.95±2.71	63.75±7.21
5b	91.56±12.95	133.83±18.10	140.97±15.46	45.84±6.04
5c	88.04±7.83	115.45±8.59	125.53±4.45	49.76±5.33
5d	87.56±6.51	87.29±10.03	114.52±5.00	45.09±3.27
5e	90.58±12.45	127.50±2.26	118.92±11.46	38.94±5.65
5f	inactive	inactive	inactive	105.50±14.12
5g	inactive	Inactive	inactive	42.75±8.57
5h	**62.27±8.79**	inactive	inactive	inactive
5i	90.73±8.96	137.29±5.40	156.96±1.77	53.81±0.20
5j	107.25±17.93	178.49±5.37	180.85±4.15	57.19±0.22
5k	106.49±9.34	181.68±3.79	183.43±6.80	56.78±0.22
5l	91.36±3.15	160.85±10.11	145.69±7.93	39.68±0.14
5m	124.14±14.62	166.00±7.35	178.29±0.43	50.47±0.18
5n	90.61±1.61	154.70±16.96	156.95±4.63	54.37±0.19
5o	94.68±1.60	139.46±15.66	145.23±8.73	28.87±0.10
5p	121.95±19.43	inactive	inactive	46.63±0.17
5q	90.76±3.05	122.21±6.49	143.56±6.85	27.64±0.10
5r	73.69±3.56	inactive	inactive	30.42±0.09
5s	**72.27±0.88**	**70.79±9.27**	**70.42±3.48**	**20.71±0.06**
5t	inactive	inactive	inactive	67.92±0.26
5u	77.37±5.83	111.78±17.45	113.75±12.61	25.57±0.08
5v	81.08±3.80	115.46±15.33	119.79±5.32	32.55±0.11
5w	77.54±1.18	116.32±4.88	121.65±4.88	28.00±0.09
5x	122.00±2.78	inactive	inactive	54.83±0.21
5y	87.97±9.04	inactive	inactive	inactive
Etoposide	50.21±1.78	0.34±0.00	-	0.05±0.00
Doxorubicin	0.50±0.05	0.34±0.01	0.83±0.05	0.01±0.00

The results in Table 4 displayed cytotoxic activities of carbocycle-fused quinoline analogs. Compound **5h** showed highest cytotoxicity against HepG2 cell line which was slightly less cytotoxic

than the etoposide standard. It is important to note that compound **5h** selectively inhibited only HepG2 cell line while it was inactive towards A549, HuCCA-1, and MOLT-3 cancer cell lines. Compound **5s** was found to have good cytotoxicity against all four cell lines. However, the general potency of carbocycle-fused quinoline was less than those of neocryptolepine analogs. In addition, the selectivity index of compounds **5h** and **5s** were also evaluated against human normal HEK-293 cell line. The results showed that compounds **5h** and **5s** demonstrated lower selectivities than doxorubicin standard while the cytotoxicity of compounds **5h** and **5s** are much lower than doxorubicin as shown in Table 5. Therefore, these results provided a room for improvement of their cytotoxicity against cancer cell lines while maintaining or lowering toxicity against normal cell line in the future investigation.

Table 5. Cytotoxicities and selectivity indices of carbocycle-fused quinoline analogs **5h** and **5s**.

Comp.	HEK-293 (μM)	HuCCA-1 (μM)		A549 (μM)		HepG2 (μM)		MOLT-3 (μM)	
	IC_{50} (μM)	IC_{50} (μM)	SI	IC_{50} (μM)	SI	IC_{50} (μM)	SI	IC_{50} (μM)	SI
5h	135.39±28.41	inactive	-	inactive	-	62.27±8.79		inactive	-
5s	359.70±49.21	70.42±3.48	5.11	70.79±9.27	5.08	72.27±0.88	4.98	20.71±0.06	17.39
Doxorubicin	8.62±8.36	0.79 ± 0.08	10.91	0.34 ± 0.01	25.23	0.53 ± 0.09	16.26	0.01 ± 0.00	862

2.2.2. In vitro antiplasmodial assays

In this assay, twenty-two neocryptolepine analogs (**3a-3w**) were evaluated for their antiplasmodial activity using two standard laboratory *P. falciparum* isolates, chloroquine-sensitive (CQ-S) clone 3D7 and chloroquine-resistant (CQ-R) clone K1. In these studies, chloroquine (CQ) and artesunate (ARS) were employed as positive controls for the assays. In addition, the selectivity index was also determined from the IC_{50} values of pure compounds towards normal HEK-293 cell line. However, the results showed that only compounds **3e**, **3h**, **3o**, and **3p** gave positive results in both strains as shown in Table 6. In a recent study, we found that an isocryptolepine analogue could disrupt several biological processes of *P. falciparum* 3D7, including ribosomal, proteasomal, and metabolism pathways.[40] Therefore, we suspected that neocryptolepine analogues could also inhibit *P.falciparum* in a similar manner.

Table 6. *In vitro* antiplasmodial activities of neocryptolepine analogs

Comp.	HEK-293	3D7		K1	
	IC_{50} (nM)	IC_{50} (nM)	SI	IC_{50} (nM)	SI
3e	13037.6±20427	1479.1 ± 596.4	8.81	1326.3 ± 24.9	9.83
3h	**333831.7±27749**	2028.6 ± 252.1	164.6	**1575.1± 9.1**	**211.9**
3o	151661.1±39142	1225.7 ± 11.9	123.7	1041.7 ± 157.2	145.6

3p	221109.6±10386	**1233.1 ± 176.5**	**179.3**	1361.3 ± 6.4	162.4
CQ	-	19.1 ± 1.5	-	82.2 ± 8.9	-
ARS	-	4.6 ± 0.1	-	2.8 ± 0.1	-

3. Conclusion

In summary, we investigated new neocryptolepine (**3a-3w**) and cyclopentyl-fused quinoline (**5a-5y**) analogs for their anticancer and antiplasmodial activities. Through these studies, we found that compound **3h** exhibited good anticancer activities in four primary cancer cell lines; HepG2, HuCCA-1, MOLT-3, and A549 and also showed higher selectivity in HepG2 and HuCCA-1 cell line than doxorubicin while its selectivity in A549 cell line was comparable to this standard and was lower than the standard MOLT-3 cancer cell line. Moreover, the results also showed that neocryptplepine derivatives had higher potency than carbocycle-fused quinoline analogs. In case of antiplasmodial activities, compound **3h** also showed the best activity among these analogs against K1 strain with good selectivity while compound **3p** showed good activity and selectivity against 3D7 strain. Based on these results and on our previous results,[34] isocryptolepine analogs had superior activities in inhibiting cancer cell lines and plasmodium activities than both neocryptolepines and carbocycle-fused quinolines and warrant further investigation.

Acknowledgments

This research work was supported by Chulabhorn Research Institute, Mahidol University, and the Center of Excellence on Environmental Health and Toxicology, Science & Technology Postgraduate Education and Research Development Office (PERDO), Ministry of Education Education, and Thailand Research Fund through the Royal Golden Jubilee (RGJ) Ph.D. Program (Grant number PHD/0181/2559) and Thailand Research Fund (RSA6080085).

Appendix A. Supplementary data

Supplementary data related to this article can be found at *http:// to be inserted.*

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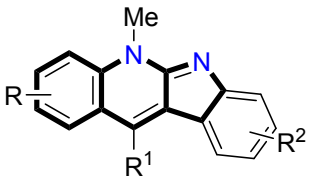
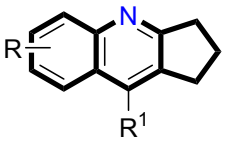
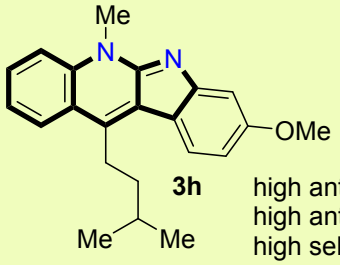
Graphical abstract



- 23 examples of neocryptolepine analogs
- anticancer activities
- antiplasmodial activities

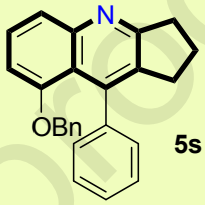


- 25 examples of carbocycle-fused quinoline analogs
- anticancer activities



3h

high anticancer activity
high antiplasmodial activity
high selectivity



5s

high anticancer activity

Highlights

- Twenty-three neocryptolepine and twenty-five carbocycle-fused quinoline analogues were conveniently and rapidly synthesized.
- The synthetic procedures allowed for structure-activity relationship studies of these compounds against cancer cell lines and *P. falciparum* strains.
- Some of these analogues were identified to possess high activities against four primary cancer cell lines and two *P. falciparum* strains.
- These novel analogues also showed high selectivities when tested in normal human kidney cell.
- These compounds demonstrated potential for future development as medicinal agents against cancer and malaria.