Supporting Information for

Target Guided Synthesis and Antiplasmodial Evaluation of a New Fluorinated 3-Alkylpyridine Marine Alkaloid Analog

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Figure S1. Cartesian coordinates for the optimized structure of compound **7** complex**.**

C	-13.62000000	-0.49600000	3.12660000
C	-13.49540000	-0.18440000	1.76780000
N	-12.30380000	-0.07580000	1.13060000
C	-11.19730000	-0.28340000	1.88540000
C	-11.21370000	-0.59790000	3.25490000
C	-12.46710000	-0.70350000	3.87380000
C	-9.96510000	-0.81830000	4.07550000
C	-8.64380000	-0.68450000	3.31980000
C	-7.44140000	-0.92150000	4.22990000
O	-6.27110000	-0.77410000	3.43230000
C	-5.05410000	-0.97450000	4.14710000
C	-3.90190000	-0.78150000	3.16530000
C	-2.53310000	-0.97400000	3.82710000
C	-1.36880000	-0.77940000	2.84820000
C	0.00320000	-0.97090000	3.50540000
C	1.16940000	-0.77380000	2.52940000
C	2.54080000	-0.96520000	3.18830000
C	3.70830000	-0.76490000	2.21440000
C	5.07820000	-0.95530000	2.87600000
C	6.24560000	-0.75040000	1.90290000
H	-14.60360000	-0.56950000	3.58300000
H	-14.39800000	-0.01540000	1.18120000
H	-10.24290000	-0.18990000	1.36010000
H	-12.53330000	-0.94450000	4.93320000
H	-9.97620000	-0.10990000	4.92060000
H	-10.02020000	-1.81990000	4.53400000
H	-8.60330000	-1.41880000	2.47910000
H	-8.55340000	0.31670000	2.87490000
H	-7.43180000	-0.19930000	5.06760000
H	-7.48360000	-1.93210000	4.67770000
H	-4.97850000	-0.25770000	4.98560000
H	-5.02910000	-1.98870000	4.58740000
H	-4.02410000	-1.48990000	2.33160000
H	-3.97510000	0.22620000	2.72900000
H	-2.42480000	-0.26860000	4.66660000
H	-2.47420000	-1.98150000	4.26940000
H	-1.47470000	-1.48340000	2.00730000
H	-1.42730000	0.22830000	2.40670000
H	0.10820000	-0.26730000	4.34690000
H	0.06060000	-1.97880000	3.94700000
H	1.06640000	-1.47640000	1.68680000
H	1.11170000	0.23460000	2.08920000
H	2.64360000	-0.26290000	4.03100000
H	2.59850000	-1.97370000	3.62810000
H	3.60810000	-1.46590000	1.37050000
H	3.65080000	0.24450000	1.77600000
H	5.17930000	-0.25390000	3.71940000
H	5.13810000	-1.96440000	3.31400000
H	6.14690000	-1.45050000	1.05800000
H	6.18370000	0.25980000	1.46700000
Fe	-12.22950000	0.25220000	-0.97270000
F	7.44780000	-0.91800000	2.49380000
C	-8.76350000	-0.39770000	-1.07140000
C	-12.80490000	-3.02880000	-1.59570000
C	-15.49680000	0.92280000	-0.76880000
C	-11.45630000	3.58890000	-0.45740000
C	-9.64730000	-1.45790000	-1.25410000
C	-9.21150000	-2.83640000	-1.52850000
C	-10.34990000	-3.57190000	-1.68810000
C	-11.47940000	-2.64780000	-1.50960000
C	-10.49020000	-5.02540000	-1.98270000

C	-7.79050000	-3.30450000	-1.60320000
C	-7.22050000	-3.84060000	-0.26570000
C	-7.26680000	-2.80660000	0.83420000
O	-8.21600000	-2.56920000	1.55480000
O	-6.10070000	-2.11150000	0.92750000
C	-13.88920000	-2.17230000	-1.42180000
C	-15.28580000	-2.60210000	-1.51310000
C	-16.05250000	-1.48970000	-1.27260000
C	-15.10750000	-0.37830000	-1.04920000
C	-15.73050000	-3.98240000	-1.85320000
C	-17.49940000	-1.33840000	-1.26510000
C	-18.37870000	-2.26920000	-0.86980000
C	-14.61890000	1.98810000	-0.58530000
C	-15.05570000	3.36340000	-0.33240000
C	-13.91640000	4.12350000	-0.25970000
C	-12.78300000	3.19660000	-0.45120000
C	-16.47300000	3.78570000	-0.15360000
C	-13.76320000	5.54860000	-0.00790000
C	-14.61660000	6.50520000	-0.39790000
C	-10.37800000	2.72170000	-0.61600000
C	-8.97390000	3.15720000	-0.57730000
C	-8.21100000	2.03450000	-0.73250000
C	-9.14930000	0.91320000	-0.87790000
C	-8.53770000	4.56870000	-0.38200000
C	-6.71510000	1.93810000	-0.72200000
C	-6.04780000	2.16560000	-2.09170000
C	-5.97850000	0.90840000	-2.95090000
O	-6.12760000	-0.21800000	-2.53990000
O	-5.67870000	1.09850000	-4.26310000
N	-11.02710000	-1.35490000	-1.24400000
N	-13.79170000	-0.81680000	-1.13900000
N	-13.23260000	1.89670000	-0.64090000
N	-10.47160000	1.35560000	-0.79940000
H	-7.70010000	-0.60650000	-1.13720000
H	-13.01750000	-4.07180000	-1.80880000
H	-16.55950000	1.13130000	-0.70120000
H	-11.23710000	4.64420000	-0.33180000
H	-11.12170000	-5.19670000	-2.86230000
H	-10.94820000	-5.55830000	-1.14030000
H	-9.51890000	-5.48780000	-2.17700000
H	-7.13630000	-2.50750000	-1.98360000
H	-7.72810000	-4.12270000	-2.33400000
H	-7.81240000	-4.70340000	0.06530000
H	-6.18370000	-4.16070000	-0.42430000
H	-6.16950000	-1.46890000	1.66920000
H	-16.74740000	-3.97140000	-2.25750000
H	-15.73320000	-4.63470000	-0.97080000
H	-15.07620000	-4.44330000	-2.60030000
H	-17.87880000	-0.37660000	-1.61200000
H	-19.44520000	-2.08450000	-0.91110000
H	-18.07380000	-3.22830000	-0.47010000
H	-16.52780000	4.72300000	0.40890000
H	-17.05140000	3.03290000	0.39210000
H	-16.97200000	3.94980000	-1.11700000
H	-12.86850000	5.84050000	0.54300000
H	-14.43850000	7.54610000	-0.15680000
H	-15.50040000	6.29440000	-0.98720000
H	-8.94740000	4.98760000	0.54490000
H	-7.44900000	4.64940000	-0.32830000
H	-8.87760000	5.20890000	-1.20550000
H	-6.32550000	2.69080000	-0.02300000
H	-6.39170000	0.96140000	-0.33700000
H	-5.00820000	2.49690000	-1.93740000
H	-6.55310000	2.97350000	-2.63980000
H	-5.56610000	2.03710000	-4.49190000
C	10.85520000	-1.39310000	0.50170000
C	8.64350000	-4.10640000	3.84540000
C	7.40230000	-0.08340000	6.28490000

C	9.40400000	2.61920000	2.80860000
C	10.37560000	-2.47950000	1.23500000
C	10.59200000	-3.88070000	0.83660000
C	9.95100000	-4.64660000	1.76500000
C	9.35620000	-3.71250000	2.73660000
C	9.84850000	-6.13000000	1.84770000
C	11.38460000	-4.31990000	-0.35370000
C	12.87580000	-4.60430000	-0.03840000
C	13.57820000	-3.40540000	0.55810000
O	13.58830000	-3.09770000	1.72940000
O	14.20380000	-2.64960000	-0.38890000
C	8.10370000	-3.23350000	4.79810000
C	7.38350000	-3.68220000	5.98210000
C	7.03810000	-2.54780000	6.68150000
C	7.54530000	-1.41320000	5.89920000
C	7.07090000	-5.10310000	6.30070000
C	6.29100000	-2.40850000	7.92270000
C	6.31720000	-3.26990000	8.94860000
C	7.85690000	0.99700000	5.55190000
C	7.67180000	2.39250000	5.96660000
C	8.22320000	3.16040000	4.97630000
C	8.76120000	2.22050000	3.96820000
C	7.04600000	2.82470000	7.24720000
C	8.34180000	4.60760000	4.87860000
C	7.45460000	5.49540000	5.34780000
C	9.95140000	1.74490000	1.87960000
C	10.68610000	2.19210000	0.68850000
C	11.11420000	1.06630000	0.04230000
C	10.62840000	-0.07590000	0.83040000
C	10.90750000	3.62050000	0.32810000
C	11.95250000	0.99870000	-1.19890000
C	11.16270000	1.04510000	-2.52010000
C	10.65230000	-0.31550000	-2.97560000
O	11.04900000	-1.37770000	-2.55780000
O	9.71460000	-0.30110000	-3.95920000
N	9.62590000	-2.38610000	2.38430000
N	8.19160000	-1.84780000	4.75250000
N	8.52790000	0.90790000	4.33200000
N	9.91590000	0.36180000	1.95590000
H	11.40970000	-1.59950000	-0.40870000
H	8.50950000	-5.17210000	4.00750000
H	6.89610000	0.12230000	7.22310000
H	9.49960000	3.68310000	2.61750000
H	8.80460000	-6.45670000	1.92350000
H	10.37830000	-6.51570000	2.72760000
H	10.28200000	-6.60900000	0.96570000
H	11.31270000	-3.57880000	-1.16210000
H	10.95340000	-5.24780000	-0.75410000
H	12.94810000	-5.41810000	0.69420000
H	13.38020000	-4.91230000	-0.96220000
H	14.65370000	-1.90270000	0.05740000
H	6.21070000	-5.16720000	6.97460000
H	7.91470000	-5.60120000	6.79520000
H	6.83430000	-5.67620000	5.39850000
H	5.66550000	-1.51900000	8.00460000
H	5.71670000	-3.10290000	9.83460000
H	6.95000000	-4.14900000	8.95720000
H	7.37890000	3.83170000	7.51800000
H	7.30880000	2.15240000	8.07070000
H	5.95110000	2.84750000	7.17690000
H	9.23420000	4.97840000	4.37340000
H	7.62390000	6.56090000	5.24900000
H	6.52540000	5.19960000	5.81870000
H	11.40380000	4.16420000	1.14120000
H	11.53160000	3.71860000	-0.56410000
H	9.95850000	4.13320000	0.12690000
H	12.64630000	1.85070000	-1.19090000
H	12.57410000	0.09290000	-1.19730000

H	11.82270000	1.41480000	-3.32160000
H	10.32960000	1.75920000	-2.44990000
H	9.47010000	0.59910000	-4.23570000
Fe	9.15220000	-0.72800000	3.40080000

Figure S2. Cartesian coordinates for the optimized structure of compound **5a** complex.

C	11.89494981	-1.28276224	3.54876165
C	12.03704981	-0.91106224	2.20356165
N	10.99774981	-0.40256224	1.48586165
C	9.79414981	-0.22546224	2.09336165
C	9.55804981	-0.56786224	3.44596165
C	10.64134981	-1.11626224	4.17406165
C	8.18574981	-0.29616224	4.09346165
C	6.99504981	-0.96626224	3.33006165
C	5.63884981	-0.51286224	3.94406165
O	4.60064981	-0.63686224	2.88486165
C	3.21874981	-0.54246224	3.44746165
C	2.20974981	-0.71546224	2.28086165
C	0.74154981	-0.63106224	2.80866165
C	-0.30695019	-0.78826224	1.66346165
C	-1.76985019	-0.68896224	2.19936165
C	-2.83225019	-0.84056224	1.06576165
H	12.75504981	-1.69336224	4.09486165
H	12.99084981	-1.01686224	1.66476165
H	8.99914981	0.22493776	1.47736165
H	10.50804981	-1.39966224	5.22956165
H	8.21294981	-0.63906224	5.14206165
H	8.01904981	0.79773776	4.09356165
H	7.00904981	-0.63806224	2.27856165
H	7.07344981	-2.06596224	3.36216165
H	5.33304981	-1.14896224	4.79676165
H	5.67314981	0.54733776	4.26306165
H	3.11674981	-1.34716224	4.20086165
H	3.11354981	0.44443776	3.94006165
H	2.38774981	0.07543776	1.53176165
H	2.38864981	-1.69196224	1.79996165
H	0.58004981	-1.41956224	3.56466165
H	0.59234981	0.34183776	3.30906165
H	-0.13895019	-0.00376224	0.90496165
H	-0.16255019	-1.76356224	1.16666165
H	-1.93295019	-1.47356224	2.95896165
H	-1.90815019	0.28533776	2.70006165
H	-2.67655019	-0.05176224	0.30906165
H	-2.69285019	-1.81246224	0.56086165
Fe	11.17000000	-0.00960000	-0.44350000
C	7.87670000	0.50090000	-1.37160000
C	11.48040000	3.26660000	0.42810000
C	14.61000000	-0.27410000	-0.80120000
C	10.83400000	-3.36610000	-0.94110000
C	8.61210000	1.60180000	-0.91980000
C	8.04330000	2.92920000	-0.68120000
C	9.04090000	3.68990000	-0.10130000
C	10.22530000	2.83410000	-0.01700000
C	8.98210000	5.14270000	0.35930000
C	6.59450000	3.32510000	-0.97400000
C	5.69330000	3.37940000	0.31690000
C	5.79350000	2.09660000	1.16340000
O	6.82090000	1.71540000	1.73050000
O	4.61490000	1.41710000	1.23580000
C	12.66510000	2.53600000	0.25620000
C	14.00770000	3.08690000	0.43410000
C	14.89750000	2.11890000	-0.01780000
C	14.08310000	0.96320000	-0.41940000
C	14.31770000	4.49130000	0.94110000
C	16.37930000	2.16250000	-0.12200000
C	17.19970000	2.92100000	0.62940000
C	13.84910000	-1.44070000	-0.96150000
C	14.41440000	-2.77560000	-1.13140000
C	13.35080000	-3.66960000	-1.06260000
C	12.13720000	-2.85610000	-0.89990000

C	15.89960000	-3.08300000	-1.29260000
C	13.34560000	-5.15320000	-1.13910000
C	14.27310000	-5.91590000	-1.74880000
C	9.69070000	-2.57000000	-1.09380000
C	8.37070000	-3.09130000	-1.44680000
C	7.55820000	-1.99560000	-1.67310000
C	8.36990000	-0.80860000	-1.40500000
C	8.03440000	-4.57460000	-1.56970000
C	6.08480000	-2.00490000	-2.09170000
C	5.86590000	-1.87060000	-3.64080000
C	5.65570000	-0.40420000	-4.08720000
O	5.41070000	0.54170000	-3.36000000
O	5.71870000	-0.17610000	-5.46110000
N	9.96010000	1.55750000	-0.53070000
N	12.71670000	1.23170000	-0.25960000
N	12.44920000	-1.49250000	-0.84710000
N	9.68470000	-1.16980000	-1.07240000
H	6.83010000	0.65770000	-1.65850000
H	11.55600000	4.28540000	0.82560000
H	15.69850000	-0.35770000	-0.89570000
H	10.70720000	-4.45370000	-0.98880000
H	9.80540000	5.72950000	-0.08090000
H	9.06450000	5.20990000	1.45800000
H	8.03020000	5.60160000	0.05480000
H	6.14700000	2.62380000	-1.69910000
H	6.57160000	4.33130000	-1.43050000
H	6.02510000	4.21210000	0.96290000
H	4.64040000	3.53950000	0.03150000
H	15.22410000	4.87900000	0.45010000
H	14.49410000	4.48910000	2.03160000
H	13.48630000	5.18130000	0.73270000
H	16.81980000	1.50220000	-0.88360000
H	18.28640000	2.89530000	0.47770000
H	16.83720000	3.57500000	1.43030000
H	16.13910000	-4.05370000	-0.83090000
H	16.52040000	-2.30870000	-0.81750000
H	16.17800000	-3.13420000	-2.36040000
H	12.49060000	-5.64850000	-0.65590000
H	14.18940000	-7.01030000	-1.75040000
H	15.13080000	-5.49450000	-2.28470000
H	8.36060000	-5.12780000	-0.67370000
H	6.95030000	-4.71700000	-1.68860000
H	8.53750000	-5.02080000	-2.44530000
H	5.63490000	-2.95830000	-1.76730000
H	5.53400000	-1.18700000	-1.59490000
H	4.94840000	-2.41530000	-3.93790000
H	6.70950000	-2.30210000	-4.20930000
H	5.92110000	-1.02020000	-5.94140000
H	4.71380000	0.58920000	1.85550000
C	-5.45870000	2.24990000	0.65340000
C	-5.71880000	0.83240000	5.32050000
C	-6.42360000	-3.76490000	3.82540000
C	-7.16830000	-2.11800000	-0.71270000
C	-5.47680000	2.25430000	2.07910000
C	-5.22660000	3.46410000	2.89340000
C	-5.35900000	3.07840000	4.20630000
C	-5.65210000	1.62590000	4.18910000
C	-5.21300000	3.91330000	5.47350000
C	-4.87320000	4.85600000	2.35950000
C	-6.10270000	5.82050000	2.23460000
C	-6.93700000	5.57620000	0.96630000
O	-6.57340000	5.05340000	-0.07900000
O	-8.22030000	6.07430000	1.12630000
C	-5.85090000	-0.58850000	5.30350000
C	-5.75290000	-1.42120000	6.50910000
C	-5.89200000	-2.73470000	6.08540000
C	-6.10310000	-2.67100000	4.61120000
C	-5.49590000	-0.89610000	7.91750000
C	-5.85530000	-4.00070000	6.85250000
C	-6.11460000	-4.13170000	8.17080000
C	-6.77990000	-3.69170000	2.44690000
C	-7.29260000	-4.83780000	1.68500000
C	-7.55900000	-4.36670000	0.40760000
C	-7.17410000	-2.92700000	0.41140000
C	-7.52400000	-6.23410000	2.25260000
C	-8.11510000	-5.06030000	-0.77610000

C	-8.10380000	-6.39340000	-0.98940000
C	-6.67750000	-0.78110000	-0.73360000
C	-6.52350000	0.00490000	-1.97480000
C	-5.97790000	1.21120000	-1.60380000
C	-5.84510000	1.17430000	-0.12830000
C	-6.91200000	-0.48690000	-3.36520000
C	-5.60120000	2.39520000	-2.49900000
C	-4.30600000	2.15070000	-3.34310000
C	-3.05110000	1.91890000	-2.47230000
O	-3.00150000	1.90240000	-1.25660000
O	-1.86600000	1.69620000	-3.18080000
N	-5.74310000	1.15770000	2.86340000
N	-6.05300000	-1.34130000	4.16260000
N	-6.71640000	-2.54160000	1.68260000
N	-6.26540000	-0.07670000	0.37110000
H	-5.18990000	3.18680000	0.15230000
H	-5.60830000	1.31780000	6.29740000
H	-6.46860000	-4.75000000	4.30300000
H	-7.50940000	-2.54150000	-1.66430000
H	-4.45530000	3.47640000	6.14560000
H	-6.16950000	3.95780000	6.02300000
H	-4.90750000	4.94040000	5.22610000
H	-4.38400000	4.77690000	1.37360000
H	-4.15340000	5.32440000	3.05360000
H	-6.77400000	5.75700000	3.10870000
H	-5.74420000	6.86650000	2.16450000
H	-8.69640000	5.93620000	0.25920000
H	-4.90690000	-1.62760000	8.49280000
H	-6.44500000	-0.72090000	8.45500000
H	-4.93860000	0.05230000	7.89070000
H	-5.60660000	-4.90120000	6.27200000
H	-6.06260000	-5.11420000	8.65850000
H	-6.41160000	-3.28890000	8.80570000
H	-8.40910000	-6.69120000	1.78260000
H	-7.69120000	-6.19700000	3.33940000
H	-6.65600000	-6.89010000	2.06080000
H	-8.56200000	-4.40880000	-1.54130000
H	-8.54590000	-6.81980000	-1.89980000
H	-7.64290000	-7.10430000	-0.29390000
H	-7.94130000	-0.88230000	-3.36680000
H	-6.85950000	0.33700000	-4.09210000
H	-6.23800000	-1.29320000	-3.70360000
H	-6.42430000	2.58860000	-3.21150000
H	-5.46980000	3.30490000	-1.88950000
H	-4.11260000	3.02840000	-3.98920000
H	-4.42410000	1.26930000	-4.00130000
H	-2.03390000	1.75210000	-4.15700000
Fe	-6.17744981	-0.70993776	2.27423835
O	-4.16787185	-0.75688065	1.56975783
H	-4.79036721	-0.85260867	0.84523339

Table S1. UB3LYP absolute electronic energies (E) calculated for compounds **5a** and **7** complexes in 2:1 molar ratio. The energies are given in hartree.

	Absolute electronic energies
Compound	**E**
5a	-7090.6138690
7	-7090.6197357

Uv-Vis experiments

Heme binding experiments

Heme titrations experiments were carried out in a Shimadzu UV-2600 UV-Visible spectrophotometer equipped with a Peltier S-1700 thermoregulator, at 25 ºC using 1 cm path cuvettes.

Heme stock solution preparation

A 2.5 mmol/L heme stock solution was prepared by dissolving 13 mg of hematin chloride (Sigma-Aldrich) in 1 mL of DMSO.

Ligands stock solution preparation

Concentrated solutions of ligands were prepared by dissolving 10.3 mg of compound **7** in 1 mL of DMSO, furnishing solutions of 34.1 mmol/L.

Buffer

A 0.25 mol/L HEPES 40% DMSO buffer with apparent pH 7.4 was prepared by adding 100 mL of DMSO, 5 mL of 1 mol/L HEPES solution and made up to a final volume of 250 mL with distilled water. The buffer was stored at 4º C.

Stoichiometry studies

The continuous variation method was applied according to MacCarthy, P. (1978).[20] Equimolar solutions of heme, and compound **7** was prepared in HEPES buffer to a final concentration of 40 μmol/L. Heme solution was titrated with increasing volumes of the ligand solutions in order to obtain solutions with mole fractions of heme ranging from 1 to 0.1. The absorbances of each addition were measured from 300 to 500 nm. Each addition was plotted in a mole fraction versus corrected absorbance ($Abs_{theoretical\ for\ Heme}$ - Abs_{obs}) graph.

Figure S3. Job's plot for the binding of heme to compound **7**.