

Supplementary Information

Quantitative Structure-Activity Relationship and Molecular Docking Study of Some Pyrrolones Antimalarial Agents against *Plasmodium Falciparum*

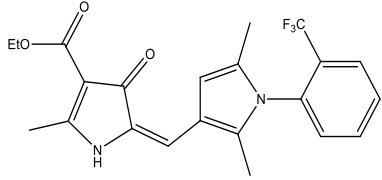
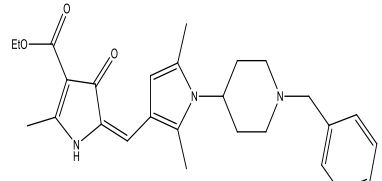
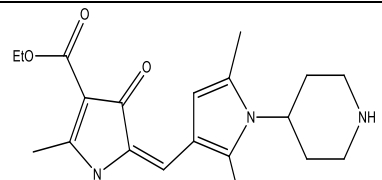
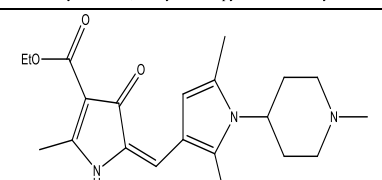
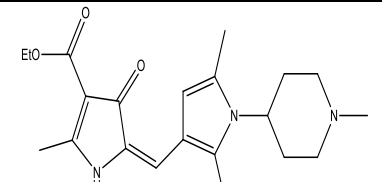
Zaharaddeen Shehu^{1*}, Adamu Uzairu², Balarabe Sagagi³

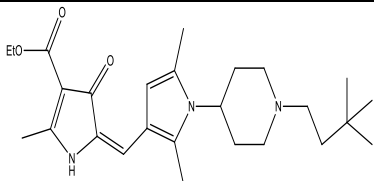
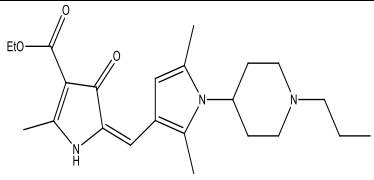
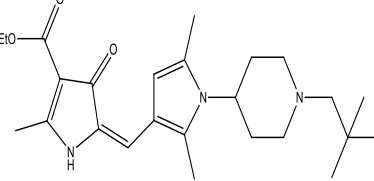
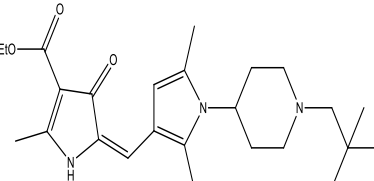
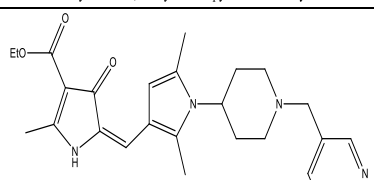
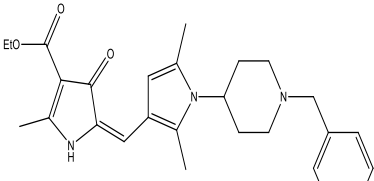
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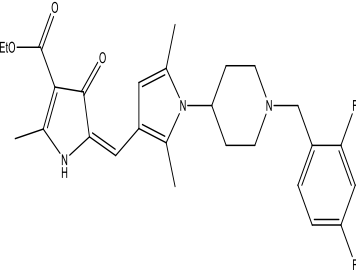
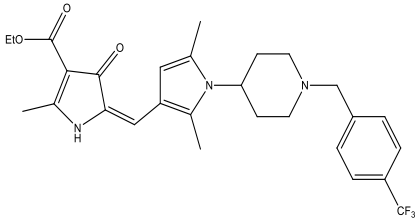
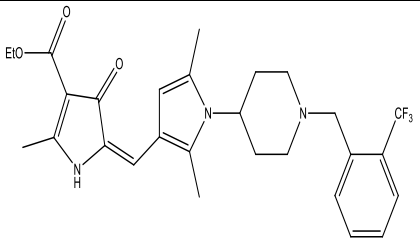
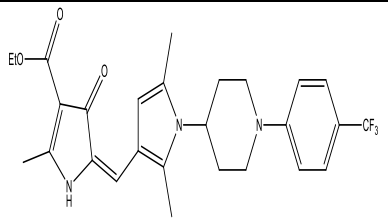
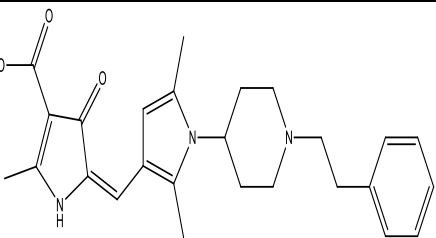
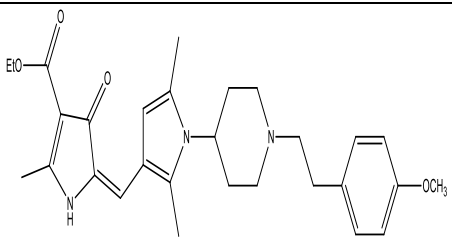
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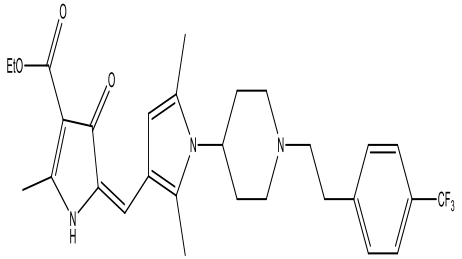
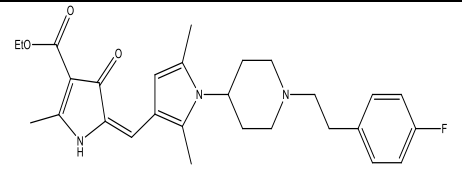
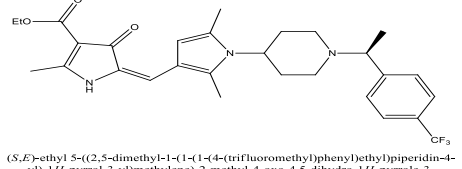
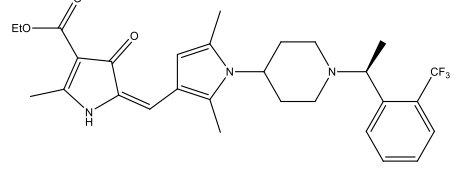
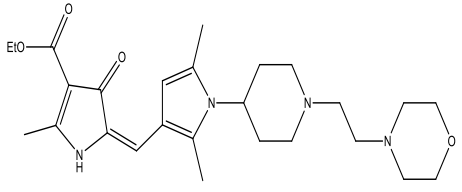
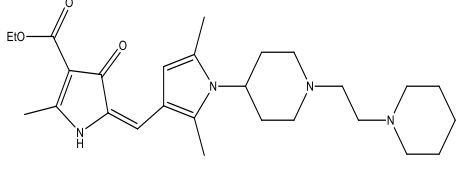
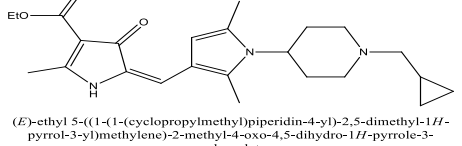
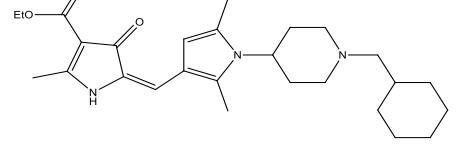
³ Department of Chemistry, Kano University of Science and Technology Wudil, Kano State, Nigeria

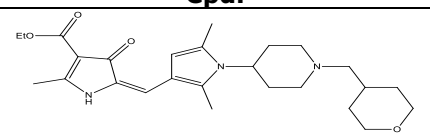
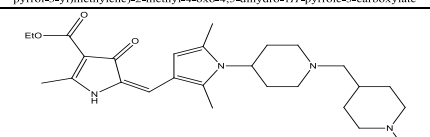
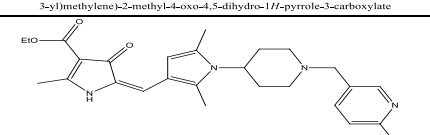
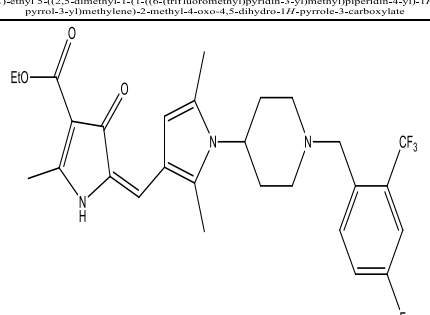
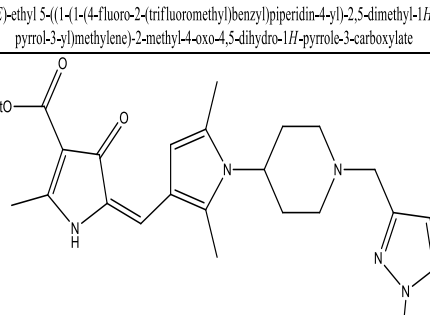
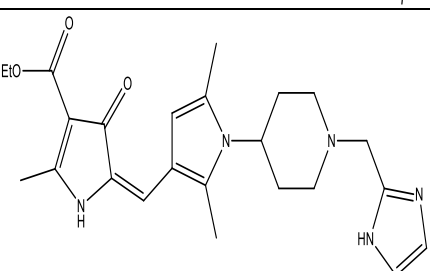
Table S1: IUPAC Name/Molecular Structures and Biological activities of Pyrrolone Antimalarial Compounds

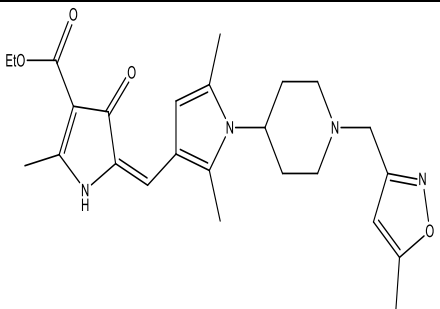
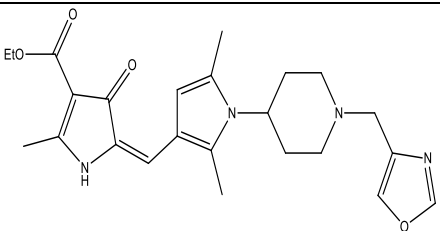
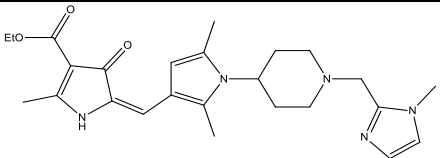
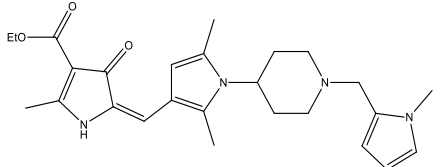
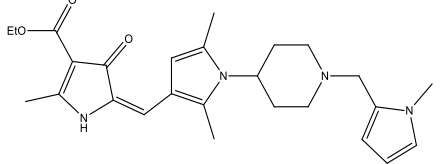
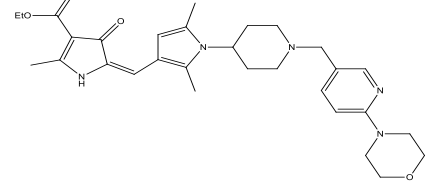
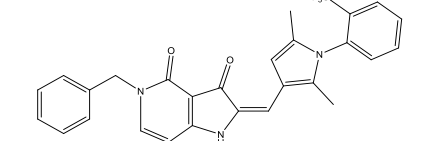
No.	Cpd.	EC ₅₀ μM	pEC ₅₀
1	 (E)-ethyl 5-((2,5-dimethyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1H-pyrrole-3-carboxylate	0.0145	7.8
2^a	 (E)-ethyl 5-((1-(1-benzylpiperidin-4-yl)-2,5-dimethyl-1H-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1H-pyrrole-3-carboxylate	0.035	7.46
3^a	 (E)-ethyl 5-((2,5-dimethyl-1-(piperidin-4-yl)-1H-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1H-pyrrole-3-carboxylate	12	4.92
4^a	 (E)-ethyl 5-((2,5-dimethyl-1-(1-methylpiperidin-4-yl)-1H-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1H-pyrrole-3-carboxylate	1.4	5.85
5a	 (E)-ethyl 5-((2,5-dimethyl-1-(1-methylpiperidin-4-yl)-1H-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1H-pyrrole-3-carboxylate	2.4	5.62

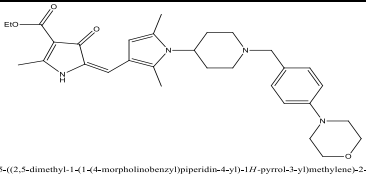
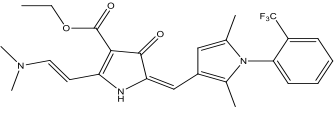
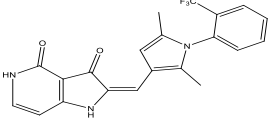
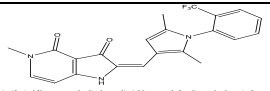
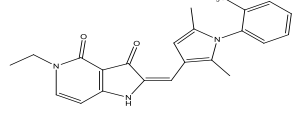
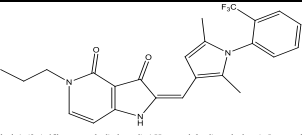
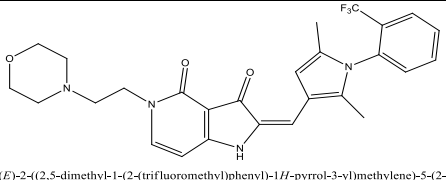
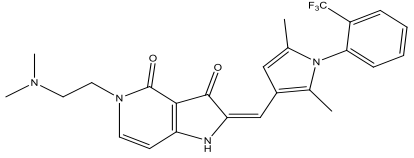
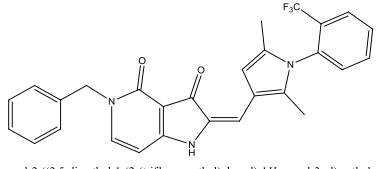
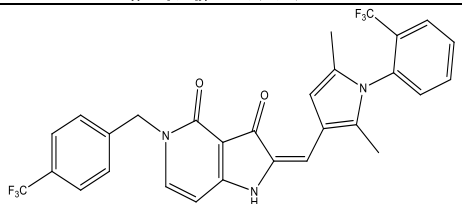
No.	Cpd.	EC ₅₀ μM	pEC ₅₀
6 ^a	 (<i>E</i>)-ethyl 5-((1-(1-(3,3-dimethylbutyl)piperidin-4-yl)-2,5-dimethyl-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.19	6.72
7 ^a	 (<i>E</i>)-ethyl 5-((2,5-dimethyl-1-(1-propylpiperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	1.1	5.96
8 ^a	 (<i>E</i>)-ethyl 5-((2,5-dimethyl-1-(1-neopentylpiperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.058	7.23
9 ^a	 (<i>E</i>)-ethyl 5-((2,5-dimethyl-1-(1-neopentylpiperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.058	6.42
10 ^a	 (<i>E</i>)-ethyl 5-((2,5-dimethyl-1-(1-(pyridin-3-ylmethyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.46	6.33
11 ^b	 (<i>E</i>)-ethyl 5-((1-(1-(4-fluorobenzyl)piperidin-4-yl)-2,5-dimethyl-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.024	7.62

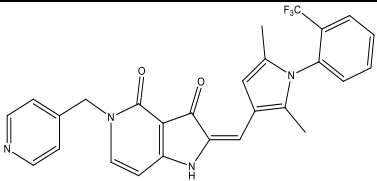
No.	Cpd.	EC ₅₀ μM	pEC ₅₀
12^a	 <i>(E)</i>-ethyl 5-((1-(1-(2,4-difluorobenzyl)piperidin-4-yl)-2,5-dimethyl-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.023	7.64
13^a	 <i>(E)</i>-ethyl 5-((2,5-dimethyl-1-(1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.002	8.69
14a	 <i>(E)</i>-ethyl 5-((2,5-dimethyl-1-(1-(2-(trifluoromethyl)benzyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.0005	9.30
15^b	 <i>(E)</i>-ethyl 5-((2,5-dimethyl-1-(1-(4-(trifluoromethyl)phenyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.024	7.62
16^a	 <i>(E)</i>-ethyl 5-((2,5-dimethyl-1-(1-phenethyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.32	6.49
17^a	 <i>(E)</i>-ethyl 5-((1-(1-(4-methoxyphenethyl)piperidin-4-yl)-2,5-dimethyl-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.083	7.08

No.	Cpd.	EC ₅₀ μM	pEC ₅₀
18a	 (<i>E</i>)-ethyl 5-((2,5-dimethyl-1-(1-(4-(trifluoromethyl)phenyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.13	6.89
19 ^b	 (<i>E</i>)-ethyl 5-((1-(1-(4-fluorophenyl)piperidin-4-yl)-2,5-dimethyl-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.096	7.02
20 ^a	 (<i>S,E</i>)-ethyl 5-((2,5-dimethyl-1-(1-(1-(4-(trifluoromethyl)phenyl)ethyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.07	8.15
21 ^a	 (<i>S,E</i>)-ethyl 5-((2,5-dimethyl-1-(1-(1-(2-(trifluoromethyl)phenyl)ethyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.001	9.00
22 ^b	 (<i>E</i>)-ethyl 5-((2,5-dimethyl-1-(1-(2-(morpholinoethyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	5.3	5.28
23a	 (<i>E</i>)-ethyl 5-((2,5-dimethyl-1-(1-(2-(piperidin-1-yl)ethyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	2.4	5.62
24 ^a	 (<i>E</i>)-ethyl 5-((1-(1-(cyclopropylmethyl)piperidin-4-yl)-2,5-dimethyl-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	3.5	5.46
25 ^a	 (<i>E</i>)-ethyl 5-((1-(1-(cyclohexylmethyl)piperidin-4-yl)-2,5-dimethyl-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.016	7.79

No.	Cpd.	EC50 μ M	pEC ₅₀
26 ^a	 (E)-ethyl 5-((2,5-dimethyl-1-(1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)-1H-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1H-pyrrole-3-carboxylate	0.11	6.96
27 ^a	 (E)-ethyl 5-((2,5-dimethyl-1-(1-(1-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1H-pyrrole-3-carboxylate	1.4	5.85
28 ^a	 (E)-ethyl 5-((2,5-dimethyl-1-(1-(6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)-1H-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1H-pyrrole-3-carboxylate	0.004	8.39
29 ^b	 (E)-ethyl 5-((1-(1-(4-fluoro-2-(trifluoromethyl)benzyl)piperidin-4-yl)-2,5-dimethyl-1H-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1H-pyrrole-3-carboxylate	0.0004	9.39
30 ^a		0.15	6.82
31 ^a	 (E)-ethyl 5-((1-(1-(1H-imidazol-2-yl)methyl)piperidin-4-yl)-2,5-dimethyl-1H-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1H-pyrrole-3-carboxylate	1.2	5.92

No.	Cpd.	EC50 μ M	pEC ₅₀
32 ^b	 (<i>E</i>)-ethyl 5-(2,5-dimethyl-1-(1-((5-methylisoxazol-3-yl)methyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.1	7.00
33 ^a	 (<i>E</i>)-ethyl 5-(2,5-dimethyl-1-(1-(oxazol-4-ylmethyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.018	7.74
34 ^b	 (<i>E</i>)-ethyl 5-(2,5-dimethyl-1-(1-((1-methyl-1<i>H</i>-imidazol-2-yl)methyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	1.0	6.00
35 ^a	 (<i>E</i>)-ethyl 5-(2,5-dimethyl-1-(1-((1-methyl-1<i>H</i>-pyrrol-2-yl)methyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.012	7.92
36 ^a	 (<i>E</i>)-ethyl 5-(2,5-dimethyl-1-(1-((1-methyl-1<i>H</i>-pyrrol-2-yl)methyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	0.001	9.00
37 ^a	 (<i>E</i>)-ethyl 5-(2,5-dimethyl-1-(1-(6-morpholinopyridin-3-yl)methyl)piperidin-4-yl)-1<i>H</i>-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1<i>H</i>-pyrrole-3-carboxylate	1.5	5.82
38 ^a	 (<i>E</i>)-5-benzyl-2-(2,5-dimethyl-1-(2-(trifluoromethyl)phenyl)-1<i>H</i>-pyrrol-3-yl)methylene)-1<i>H</i>-pyrrolo[3,2-<i>c</i>]pyridine-3,4(2<i>H</i>,5<i>H</i>)-dione	0.0075	8.12

No.	Cpd.	EC ₅₀ μM	pEC ₅₀
39 ^b	 (E)-ethyl 5-((2,5-dimethyl-1-(1-(4-morpholinobenzyl)piperidin-4-yl)-1H-pyrrol-3-yl)methylene)-2-methyl-4-oxo-4,5-dihydro-1H-pyrrole-3-carboxylate	2.6	5.59
40 ^a			
	 (E)-ethyl 5-(2-(2,5-dimethyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-2-((E)-2-(dimethylamino)vinyl)-4-oxo-4,5-dihydro-1H-pyrrole-3-carboxylate	0.061	7.21
41 ^a	 (E)-2-(2-(2,5-dimethyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-1H-pyrrolo[3,2-c]pyridine-3,4(2H,5H)-dione	0.047	7.33
42 ^a	 (E)-2-(2-(2,5-dimethyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-5-methyl-1H-pyrrolo[3,2-c]pyridine-3,4(2H,5H)-dione	0.014	7.85
43 ^a	 (E)-2-(2-(2,5-dimethyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-5-ethyl-1H-pyrrolo[3,2-c]pyridine-3,4(2H,5H)-dione	0.021	7.68
44 ^a	 (E)-2-(2-(2,5-dimethyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-5-propyl-1H-pyrrolo[3,2-c]pyridine-3,4(2H,5H)-dione	0.15	6.82
45 ^a	 (E)-2-(2-(2,5-dimethyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-5-(2-morpholinoethyl)-1H-pyrrolo[3,2-c]pyridine-3,4(2H,5H)-dione	0.23	6.64
46 ^a	 (E)-2-(2-(2,5-dimethyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-5-(2-(dimethylamino)ethyl)-1H-pyrrolo[3,2-c]pyridine-3,4(2H,5H)-dione	0.25	6.60
47 ^a	 (E)-5-benzyl-2-(2-(2,5-dimethyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-1H-pyrrolo[3,2-c]pyridine-3,4(2H,5H)-dione	0.23	6.64
48 ^a	 (E)-2-(2-(2,5-dimethyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-5-(4-(trifluoromethyl)benzyl)-1H-pyrrolo[3,2-c]pyridine-3,4(2H,5H)-dione	0.046	7.34

No.	Cpd.	EC50 μ M	pEC ₅₀
49a	 <chem>Cc1cc(C)c(C2=CC(=O)N(C2Cc3ccncc3)C(=O)c4ccc5c(c4)nc(=O)c6ccncc65)c1C7=CC=C(C=C7)C(F)(F)F</chem> <i>(E)</i> -2-((2,5-dimethyl-1-(2-(trifluoromethyl)phenyl)-1 <i>H</i> -pyrrol-3-yl)methylene)-5-(pyridin-4-ylmethyl)-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridine-3,4(2 <i>H</i> ,5 <i>H</i>)-dione	0.077	7.11

^aTraining Set; ^bTest Set; Cpd = Compound, reference compounds: chloroquine, EC₅₀=0.095–0.172 μ M The EC₅₀ values are the mean of two independent assays, which varied less than _50%; Calculated using StarDrop (<http://www.optibrium.com>) (16)