pharmaceutics

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Supplementary Materials

First description of marinoquinoline derivatives' activity against *Toxoplasma gondii*

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Supplementary Material Table S1. Spectroscopic and spectrometric characterization of MQ-2 to MQ-6.

MQ-2
7-methoxy-4-(4-(piperazin-1-yl)phenyl)-3H-pyrrolo[2,3-c]quinoline
Yellow solid. M.P.: 206-207 °C.
^{1}H NMR (500 MHz, DMSO) δ 11.68 (s, 1H), 8.16 (d, J = 8.9 Hz, 1H), 8.00 – 7.91 (m, 2H), 7.55 (d, J = 3.0 Hz, 1H), 7.46 (d, J = 2.6 Hz, 1H), 7.17 (dd, J = 8.8, 2.6 Hz, 1H), 7.14 – 7.06 (m, 3H), 3.90 (s, 3H), 3.25 – 3.16 (m, 4H), 2.95 – 2.89 (m, 4H).
^{13}C NMR (126 MHz, DMSO) δ 157.6, 151.9, 146.1, 143.6, 129.5, 129.3, 128.4, 128.1, 125.9, 124.0, 117.0, 116.4, 114.8, 108.7, 100.6, 55.2, 48.4, 45.2.
HRMS (ESI+) m/z calculated for [$C_{22}H_{23}N_4O^+$]: 359.1866. Found: 359.1867.
MQ-3
tert-butyl (4-(8-chloro-3H-pyrrolo[2,3-c]quinolin-4-yl)phenyl)carbamate
Amorphous orange solid.
^{1}H NMR (400 MHz, DMSO) δ 11.92 (s, 1H), 9.62 (s, 1H), 8.39 (d, J = 2.4 Hz, 1H), 8.04 (d, J = 8.9 Hz, 1H), 7.98 – 7.90 (m, 2H), 7.72 – 7.67 (m, 2H), 7.66 – 7.61 (m, 1H), 7.55 (dd, J = 8.9, 2.5 Hz, 1H), 7.29 (d, J = 2.9 Hz, 1H), 1.51 (s, 9H).
^{13}C NMR (101 MHz, DMSO) δ 152.8, 146.4, 140.8, 140.6, 131.4, 131.0, 129.7, 129.2, 128.5, 128.3, 126.8, 126.1, 123.9, 122.2, 118.1, 101.7, 79.4, 28.2.
HRMS (ESI+) m/z calculated for [$C_{22}H_{21}ClN_3O_2^+$]: 394.1317. Found: 394.1322.
MQ-4
tert-butyl (4-(8-(trifluoromethoxy)-3H-pyrrolo[2,3-c]quinolin-4-yl)phenyl)carbamate
Amorphous white solid.
^{1}H NMR (400 MHz, Acetone) δ 11.46 (s, 1H), 8.77 (s, 1H), 8.26 – 8.17 (m, 2H), 8.03 – 7.98 (m, 2H), 7.77 – 7.70 (m, 2H), 7.67 – 7.61 (m, 1H), 7.50 (dd, J = 9.8, 2.4 Hz, 1H), 7.26 (d, J = 3.0 Hz, 1H), 1.50 (s, 9H).
^{13}C NMR (63 MHz, DMSO) δ 153.2, 147.2, 145.9 (q, J = 1.9 Hz), 141.3, 141.2, 131.9, 131.8, 129.7, 129.2, 129.0, 127.2, 123.8, 120.8 (q, J = 256.0 Hz), 119.6, 118.5, 115.1, 102.2, 79.8, 28.6.
HRMS (ESI+) m/z calculated for [$C_{23}H_{21}F_3N_3O_3^+$]: 444.1530. Found: 444.1540.

(cont.)

MQ-5
4-(4-(4-fluoropiperidin-1-yl)phenyl)-7-methoxy-3H-pyrrolo[2,3-c]quinoline Amorphous yellow solid. ^{1}H NMR (500 MHz, Acetone) δ 11.02 (s, 1H), 8.17 (d, J = 8.8 Hz, 1H), 8.04 – 7.97 (m, 2H), 7.60 (d, J = 2.9 Hz, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.18 (dd, J = 8.8, 2.6 Hz, 1H), 7.17 – 7.11 (m, 2H), 7.11 (d, J = 2.9 Hz, 1H), 4.86 (dtt, J = 49.1, 7.1, 3.5 Hz, 1H), 3.94 (s, 3H), 3.59 – 3.49 (m, 2H), 3.30 (ddd, J = 12.9, 7.4, 3.7 Hz, 2H), 2.13 – 2.05 (m, 2H), 1.95 – 1.82 (m, 2H). ^{13}C NMR (126 MHz, Acetone) δ 159.1, 152.4, 147.2, 145.0, 130.6, 130.5, 129.6, 128.4, 127.4, 124.7, 118.3, 117.5, 116.3, 109.5, 101.5, 89.4 (d, J = 170.3 Hz), 55.6, 45.8 (d, J = 6.9 Hz), 31.8 (d, J = 19.3 Hz). HRMS (ESI+) m/z calculated for [$C_{23}H_{23}FN_3O^+$]: 376.1820. Found: 376.1806.
MQ-6
4-(5-bromopyridin-2-yl)-7-methoxy-3H-pyrrolo[2,3-c]quinoline [MQ-6] Yellow solid. M.P. 187-188 °C. ^{1}H NMR (500 MHz, DMSO) δ 12.01 (s, 1H), 8.90 (d, J = 2.2 Hz, 1H), 8.70 (d, J = 8.6 Hz, 1H), 8.32 (dd, J = 8.6, 2.4 Hz, 1H), 8.25 (d, J = 8.9 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.28 (dd, J = 8.9, 2.6 Hz, 1H), 7.17 – 7.13 (m, 1H), 3.94 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 157.8, 155.3, 149.3, 142.8, 140.7, 140.0, 130.3, 128.9, 126.0, 124.2, 123.4, 120.7, 118.3, 118.2, 108.7, 100.0, 55.2. HRMS (ESI+) m/z calculated for [$C_{17}H_{13}BrN_3O^+$]: 354.0237. Found: 354.0235.

Supplementary Material Table S2. ADMET properties predictions for six marinoquinoline derivatives and pyrimethamine according to SwissModel.

		MQ-1	MQ-2	MQ-3	MQ-4	MQ-5	MQ-6	PYR[1]
Physicochemical properties	Formula Molecular	$C_{20}H_{15}N_3O$	$C_{22}H_{22}N_4O$	$C_{22}H_{20}ClN_3O_2$	$C_{23}H_{20}F_3N_3O_3$	$C_{23}H_{22}FN_3O$	$C_{17}H_{12}BrN_3O$	$C_{13}H_8Cl_2N_2O_4$
	Molecular Weight	313.35	358.44	393.87	443.42	375.44	354.2	248.71
	#Heavy atoms	24	27	28	32	28	22	17
	#Aromatic heavy atoms	22	19	19	19	19	19	12
	Fraction Csp3	0.05	0.23	0.18	0.22	0.26	0.06	0.17
	#Rotatable bonds	2	3	5	7	3	2	2
	#H-bond acceptors	2	3	3	7	3	3	2
	#H-bond donors	2	2	2	2	1	1	2
	MR	97.38	116.89	114.29	115.96	115.03	91.02	71.06
	TPSA[2]	53.7	53.18	67.01	76.24	41.15	50.8	77.82
Lipophilicity	iLOGP	2.46	3.06	3.76	3.88	3.27	3.31	2.15
	XLOGP3	4.08	3.42	5.17	5.72	4.97	3.61	2.69
	WLOGP	4.87	3.04	6.19	7.7	5.37	4.55	2.54
	MLOGP	2.32	2.08	3.44	2.94	3.23	2.12	1.64
	Silicos-IT Log P	5.08	4.12	5.14	5.13	5.07	4.66	2.44
	Consensus Log P	3.76	3.14	4.74	5.07	4.38	3.65	2.29
Water solubility	ESOL Log S	-4.9	-4.54	-5.71	-6.17	-5.6	-4.82	-4.9
	ESOL Solubility (mg/ml)	3.95e-03	1.03e-02	7.66e-04	3.00e-04	9.37e-04	5.39e-03	0.00395
	ESOL Solubility (mol/l)	1.26e-05	2.89e-05	1.94e-06	6.76e-07	2.49e-06	1.52e-05	0.0000126
	ESOL Class	MS[3]	MS	MS	PS[4]	MS	MS	MS
	Ali Log S	-4.91	-4.22	-6.32	-7.09	-5.57	-4.36	-4.91
	Ali Solubility (mg/ml)	3.83e-03	2.18e-02	1.87e-04	3.62e-05	1.00e-03	1.53e-02	0.00383
	Ali Solubility (mol/l)	1.22e-05	6.07e-05	4.75e-07	8.17e-08	2.67e-06	4.32e-05	0.0000122
	Ali Class	MS	MS	PS	PS	MS	MS	MS
	Silicos-IT LogSw	-8.1	-7.68	-8.6	-8.56	-7.95	-7.67	-8.1
	Silicos-IT Solubility (mg/ml)	2.49e-06	7.44e-06	9.94e-07	1.21e-06	4.25e-06	7.61e-06	0.00000249
	Silicos-IT Solubility (mol/l)	7.94e-09	2.07e-08	2.52e-09	2.74e-09	1.13e-08	2.15e-08	7.94E-09
	Silicos-IT class	PS	PS	PS	PS	PS	PS	MS

(cont.)

Pharmacokinetics properties	GI[5] absorption	High	High	High	Low	High	High	High
	BBB[6] permeant	Yes	Yes	No	No	Yes	Yes	Yes
	Pgp[7] substrate	Yes	Yes	No	No	Yes	Yes	No
	CYP1A2 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	CYP2C19 inhibitor	Yes	No	Yes	Yes	Yes	Yes	Yes
	CYP2C9 inhibitor	No	No	Yes	Yes	No	Yes	No
	CYP2D6 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	No
	CYP3A4 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	log Kp (cm/s)	-5.31	-6.06	-5.03	-4.94	-5.06	-5.9	-5.91
Drug likeness	Lipinski #violations	0	0	0	0	0	0	0
	Ghose #violations	0	0	1	1	0	0	0
	Veber #violations	0	0	0	0	0	0	0
	Egan #violations	0	0	1	1	0	0	0
	Muegge #violations	0	0	1	1	0	0	0
	Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55	0.55
Medicinal Chemistry	PAINS #alerts	0	0	0	0	0	0	0
	Brenk #alerts	0	0	0	0	0	0	0
	Lead likeness #violations	1	1	2	2	2	2	1
	Synthetic Accessibility	2.58	2.85	2.95	3.11	2.81	2.63	2.43
Toxicity	Mutagenic	No	No	No	No	No	No	Yes
	Tumorigenic	No	No	No	No	No	No	Yes
	Reproductive Effective	No	No	No	No	No	No	Yes
	Irritant	No	No	No	No	No	No	Yes

[1]Pyrimethamine, used as positive control. [2]Total polar surface area. [3]MS: Moderately soluble. [4]PS: Poorly soluble. [5]Gastrointestinal. [6]Blood-brain barrier. [7]P-glycoprotein substrate.

Supplementary Material Table S3. ADMET properties predictions for six marinoquinoline derivatives and pyrimethamine according to AdmetSAR.

	MQ-1	MQ-2	MQ-3	MQ-4	MQ-5	MQ-6	PYR[1]
Ames mutagenesis	+	+	+	+	+	+	-
Acute Oral Toxicity (c)	III	III	III	III	III	III	II
Androgen receptor binding	+	+	+	+	+	+	+
Aromatase binding	+	+	+	+	+	+	+
Blood Brain Barrier	+	+	+	+	+	+	+
BRCP inhibitor	-	-	-	-	-	-	-
BSEP inhibitor	+	+	+	+	+	+	+
Caco-2	+	-	-	-	-	+	+
Carcinogenicity (binary)	-	-	-	-	-	-	-
Carcinogenicity (trinary)	Non-re-quired	Non-re-quired	Danger	Danger	Non-re-quired	Non-re-quired	Non-re-quired
CYP1A2 inhibition	+	+	+	+	+	+	+
CYP2C19 inhibition	+	-	+	+	+	+	-
CYP2C8 inhibition	+	+	+	+	+	+	+
CYP2C9 inhibition	-	-	+	+	+	-	-
CYP2C9 substrate	-	-	-	-	-	-	-
CYP2D6 inhibition	+	-	-	-	-	+	+
CYP2D6 substrate	-	+	-	-	+	-	-
CYP3A4 inhibition	+	+	-	-	+	+	-
CYP3A4 substrate	+	+	+	+	+	+	-
CYP inhibitory promiscuity	+	+	+	+	+	+	+
Eye corrosion	-	-	-	-	-	-	-
Eye irritation	+	-	-	-	-	-	-
Estrogen receptor binding	+	+	+	+	+	+	+
Glucocorticoid receptor binding	+	+	+	+	+	+	+
Hepatotoxicity	+	+	+	+	+	+	+
Human Ether-a-go-go-Related Gene inhibition	+	+	+	+	+	-	-

(cont.)

Human Intestinal Absorption	+	+	+	+	+	+	+
Human oral bioavailability	+	+	+	+	+	+	+
MATE1 inhibitor	-	-	-	-	-	-	-
Mitochondrial toxicity	-	+	-	-	+	-	+
Micronuclear	+	+	+	+	+	+	+
Nephrotoxicity	-	-	+	+	-	-	+
Acute Oral Toxicity	2.777612209	3.192592621	3.563766003	4.35090971	3.287763119	2.658835411	2.981128
OATP1B1 inhibitor	+	+	+	+	+	+	+
OATP1B3 inhibitor	+	+	+	+	+	+	+
OATP2B1 inhibitor	-	-	-	-	-	-	-
OCT1 inhibitor	-	-	-	-	+	-	+
OCT2 inhibitor	-	+	-	-	-	-	+
P-glycoprotein inhibitor	-	+	-	+	+	-	-
P-glycoprotein substrate	-	+	-	-	+	-	-
PPAR gamma	+	+	+	+	+	+	+
Plasma protein binding	1.003971338	0.955927551	1.032086134	0.9817757010000001	0.998464346	1.035541773	0.92094641
Reproductive toxicity	+	+	+	+	+	+	+
Respiratory toxicity	-	+	-	+	+	+	+
Skin corrosion	-	-	-	-	-	-	-
Skin irritation	-	-	-	-	-	-	-
skin sensitization	-	-	-	-	-	-	-
Subcellular localization	Mitochon-dria	Mitochon-dria	Mitochon-dria	Mitochon-dria	Mitochon-dria	Mitochon-dria	Lysosomes
Thyroid receptor binding	+	+	+	+	+	+	+
UGT catalyzed	-	-	-	-	-	-	-
Water solubility	-3.237773778	-2.510816114	-5.165401196	-5.326074509	-3.462040937	-3.853552013	-

[1]Pyrimethamine, used as positive control.