Supporting Information

Sulfoximines as Rising Stars in Modern Drug Discovery? Current Status and Perspective on an Emerging Functional Group in Medicinal Chemistry

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3.1. Studies of Drug-Like Properties of Sulfoximine Tool Compounds and Matched Molecular Pair Analysis

Table 1. Categories applied for the rating of experimental data by Gnamm and coworkers.[1]

Molecular Property	**Unit**	**Definition "Desirable"**	**Definition "Acceptable"**	**Definition "Undesirable"**
Stability in human liver microsomes ($T_{1/2}$)	[min]	>120 (<25% Q_H)	25-120 (25-75% Q_H)	<25 (>75% Q_H)
Aqueous solubility (S_w)	[µg mL^{-1}]	>100	10-100	<10
Caco-2 permeability ($P_{app\ A\rightarrow B}$)	10^{-6} cm/s	>5	5-0.5	<0.5

3.2. Sulfoximine Analogs of Marketed Drugs and Clinical Candidates

Table 2. Measured in vitro properties of compounds **27**-**38**.[2]

Cpd.	K_d [nM]			S_w pH 6.5 [mg L^{-1}]	logD pH 7.5	Cl_b [L h^{-1} kg^{-1}]		PAMPA $P_{app\ A\rightarrow B}$ [10^{-6} cm/s]	Efflux Ratio ($P_{app\ B\rightarrow A}$/ $P_{app\ A\rightarrow B}$)	MW [Da]	TPSA [Å^2]	HBD	HBA
	ABL1	KIT	PDGFRβ			rHep	hLMs						
27	1.1	13	14	112	1.9	2.3	0.48	39	2.7	493.6	86.28	2	7
28	79	11	19	54	2.0	1.9	0.34	< 2	> 134	527.6	123.96	3	8
Cpd.	**IC_{50} [nM]**			**S_w pH 6.5 [mg L^{-1}]**	**logD pH 7.5**	**Cl_b [L h^{-1} kg^{-1}]**		**PAMPA $P_{app\ A\rightarrow B}$ [10^{-6} cm/s]**	**Efflux Ratio ($P_{app\ B\rightarrow A}$/ $P_{app\ A\rightarrow B}$)**	**MW [Da]**	**TPSA [Å^2]**	**HBD**	**HBA**
	CDK2	**CDK9**	**A2780**			**rHep**	**hLMs**						
29	96	6	131	1524	1.3	1.7	0.24	1.0	92	382.2	98.91	4	4
30	522	124	351	52	1.6	0.06	0.06	1.4	37	430.3	127.89	4	5
Cpd.	**IC_{50} [nM]**			**S_w pH 6.5**	**logD pH 7.5**	**Cl_b [L h^{-1} kg^{-1}]**		**PAMPA $P_{app\ A\rightarrow B}$**	**Efflux Ratio**	**MW [Da]**	**TPSA [Å^2]**	**HBD**	**HBA**

	CDK4	CDK6	MOLM-13	[mg L^{-1}]		rHep	hLMs	[10^{-6} cm/s]	($P_{app\ B\rightarrow A}$/ $P_{app\ A\rightarrow B}$)				
31	7	57	41	34	1.9	1.3	0.45	70	2.6	447.5	103.35	2	8
32	101	240	128	30	2.0	1.1	0.24	25	9.1	495.6	132.24	2	9
33	67	803	89	334	1.7	2.3	0.52	135	1.3	434.5	91.21	2	7
34	216	> 1000	1150	22	1.8	1.1	0.21	22	11	482.6	120.10	2	8

Cpd.	**IC_{50} [nM]**	**S_w pH 6.5 [mg L^{-1}]**	**logD pH 7.5**	**Cl_b [L h^{-1} kg^{-1}]**		**PAMPA $P_{app\ A\rightarrow B}$ [10^{-6} cm/s]**	**Efflux Ratio ($P_{app\ B\rightarrow A}$/ $P_{app\ A\rightarrow B}$)**	**MW [Da]**	**TPSA [$Å^2$]**	**HBD**	**HBA**
	PDE5			**rHep**	**hLMs**						
35	0.029	220	2.6	3.0	1.1	206	0.87	488.6	109.12	1	7
36	0.025	52	2.0	2.1	0.43	0.71	288	508.6	146.80	2	8

Cpd.	**IC_{50} [nM]**	**S_w pH 6.5**	**logD pH 7.5**	**Cl_b [L h^{-1} kg^{-1}]**	**PAMPA $P_{app\ A\rightarrow B}$**	**Efflux Ratio**	**MW [Da]**	**TPSA [$Å^2$]**	**HBD**	**HBA**

	ESR1 WT	MCF7 E2 stim.	[mg L^{-1}]		rHep	hLMs	[10^{-6} cm/s]	($P_{app\ B\rightarrow A}$/ $P_{app\ A\rightarrow B}$)				
37	2.0	9.2	< 0.1	4.2	3.5	1.2	0	0	606.7	57.53	2	3
38	1.8	7.1	< 0.1	3.8	3.5	1.1	0	0	621.7	81.38	3	4

For assay details, refer to.[2] rHep = rat hepatocytes; hLMs = pooled human liver microsomes.

Table 3. Biological activities of compounds **39-42**.[3]

Compound[a]	**IC_{50} [nM]**		**SI**[b]	**LogD**[c]
	Aβ1-42	**Notch**		
39	5	132	26	3.6
***rac*-40**	40	1050	26	2.5
41b	98	3150	32	2.7
42	3	111	40	3.8
42a	63	1600	25	2.6
42b	78	2300	29	2.6

[a] Sulfonimidamides **40** and **42** have two diastereoisomers (a and b) depending on the chirality of the stereogenic sulfur center.

[b] Selectivity index (SI) is given by the ratio of IC_{50} (Notch)/IC_{50} (Aβ1–42).

[c] Experimental lipophilicity distribution coefficient.

Table 4. (ADME)-related properties of the matched sulfonamide (**39**/**41**) and sulfonimidamide (**40**/**42**) pairs.[3]

Entry	Parameter	Compound pairs			
		39	**40**[a]	**41**	**42**[a]
1	Anhydrous DMSO solubility [µM]	360	330	160	> 330
2	Human plasma protein binding [% free]	11	27	8	25
3	Fraction unbound in rat brain [% free]	7	8	4	10
4	Unbound brain/plasma ratio in mouse	-	-	1.0	0.7
5	Caco-2 AB/BA (x 10^{-6}) [cm s^{-1}]	51/26	41/28	37/19	52/34
6	Caco-2 efflux ratio	0.5	0.7	0.5	0.7
7	CL_{int} (microsomes/hepatocytes)[b]	< 26/< 5	10/-	56/61	77/51
8	GSH adducts in human microsomes (ratio)[c]	< LOQ	0.05	< LOQ	< LOQ

[a] Diastereoisomers of **40** and **42** showed similar data for these properties, which explains why the data for only one stereoisomer are shown.

[b] Intrinsic clearance (CL_{int}) by human microsomes (mL min^{-1} mg^{-1}) and human hepatocytes (mL/min/10E6 cells).

[c] Limit of quantification (LOQ).

4.1 Antineoplastic Agents

4.1.1 CDK Inhibitors

Table 5. Properties of BAY-1000394 (**47**) and its sulfone analog (**48**).[4,5]

Entry	Parameter	Compound	
		47	**48**
1	Aqueous thermodynamic solubility at pH = 7.4 [mg L^{-1}]	182	25
2	Human liver microsome stability [% recovery rate][a]	94	93
	Mouse liver microsome stability [% recovery rate][a]	100	91
	Rat liver microsome stability [% recovery rate][a]	100	96
3	Caco-2 Permeability ($P_{app\ A\rightarrow B}$) [nm/s^{-1}]	79	ND
4	CL_{int} (mouse) [mL/min mg^{-1}]	0.51	ND
	CL_{int} (rat) [mL/min mg^{-1}]	0.78	
	CL_{int} (dog) [mL/min mg^{-1}]	0.50	
5	$T_{1/2}$ (rat) [h]	2.1	ND
6	In vivo efficacy (daily dosing scheme) [T/C][b]	3% at 2 mg kg^{-1}	2% at 5 mg kg^{-1}
7	In vivo efficacy (intermittent dosing scheme) [T/C][b, c]	2% at 2.5 mg kg^{-1}	25% at 5 mg kg^{-1}
8	Average F (rat, mouse, dog) [%]	50	ND

ND = not determined

[a] 60 min incubation time.

[b] Use of HeLa–MaTu human cervical tumor xenograft model in athymic mice.

[c] b.i.d. 2 days on/5 days off.

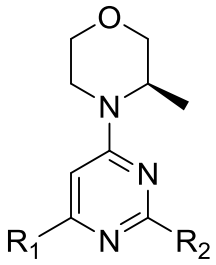
Table 6. Key properties of CDK9-selective inhibitors **49**-**53**.[6-8]

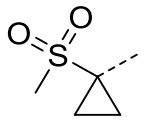
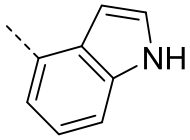
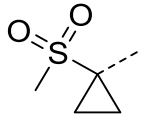
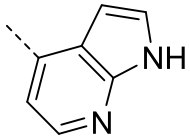
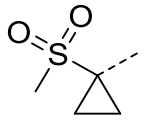
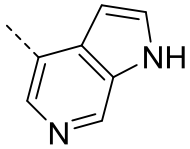
Entry	Parameter	Compound				
		49	**50**	**51**	**52**	**53**
1	IC_{50} (CDK9) [nM]	11	13	37	104	4
2	IC_{50} (CDK2) [nM]	1,078	1,300	3,959	10,504	2,920
3	Aqueous solubility (pH = 6.5) [mg L^{-1}]	11	479	24	91	699
4	Caco-2 permeability ($P_{app\ A\rightarrow B}$) [nm/s^{-1}]	22	35	ND	ND	ND
5	Efflux ration	15	6	ND	ND	ND
6	F (p.o., rat) [%]	10	54	ND	ND	ND
7	F_{max} (rHeps) [%]	ND	ND	54	51	84
8	CL_b (rat) [L/h kg^{-1}]	ND	ND	1.3	3.3	1.1
9	V_{SS} (rat) [L kg^{-1}]	ND	ND	1.6	2.2	0.74

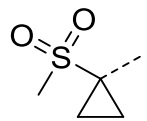
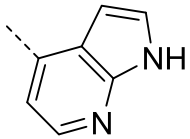
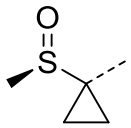
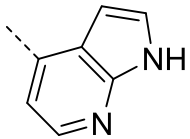
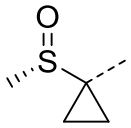
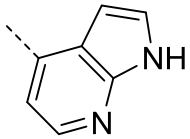
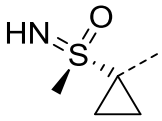
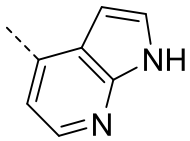
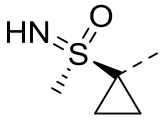
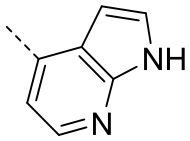
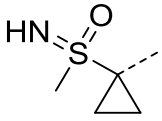
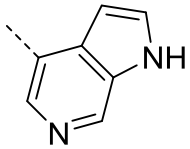
ND = not determined

4.1.2 Ataxia Telangiectasia and Rad3 Related (ATR) Kinase Inhibitors

Table 7. Results of the biochemical and cellular assays of selected ATR inhibitors.[9]



Entry	Cpd.	R_1	R_2	ATR IC_{50} [nM]	ATR cell IC_{50} [nM]	$LogD_{7.4}$	LLE[a]	S_W (pH 7.4) [µM]	CYP3A4 [%] TDI, 10 µM
1	**54**			5	61	2.5	4.7	10	50
2				5	100	2.6	4.4	8	<10
3				2	12	2.1	5.8	108	<20

4	**57**			5	100	2.6	4.4	8	<10
5	(*R*)-**56**			16	180	2.5	4.2	240	ND
6	(*S*)-**56**			11	90	2.5	4.6	198	ND
7	**55**			4	74	1.9	5.2	661	<20
8				ND	240	1.8	4.8	179	<11
9				ND	14	1.4	6.5	>2120	<20

ND = not determined

[a] Lipophilicity ligand efficiency: ATR cell $pIC_{50} - \log D_{7.4}$.

Table 8. Physicochemical and ADME characterization of compounds **54** and **55**.[9]

#		**54**	**55**
1	$logD_{7.4}$	2.5	1.9
2	solubility, pH 7.4 [μM]	10	661
3	PPB (mouse/human) [% free]	14/9.2	54/26
4	CYP3A4 IC_{50} [μM][a]	>10	>10
5	CYP3A4 %TDI, 10 μM	50	<20
6	hERG IC_{50} [μM]	50	166
7	Caco-2 P_{app}(A→B) (pH 6.5/7.4)[b]	23/37	6.8/12
8	CL_{int} (rat/human)[c]	25/<3	<3.5/<3
9	rat AUC [μM h]	1.0	0.8

[a] >10 μM against 1A2, 2C19, 2C9, and 2D6.

[b] 10 μM compound concentration.

[c] 1 μM compound concentration.

4.2.1 Antimalarial Agents

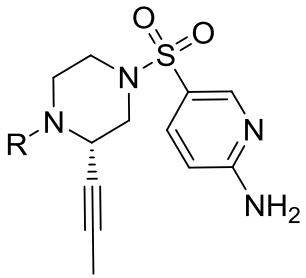
Table 9. Available classes of antimalarial drugs and their mode of action.[10-15]

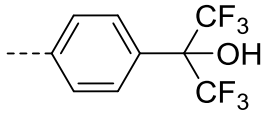
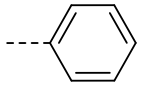
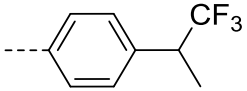
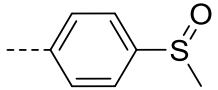
Class	Selected Drug Examples	Mode of Action
Quinoline derivatives	chloroquine amodiaquine quinine quinidine mefloquine primaquine	Binding of heme (or FP) to form the FP-drug complex Inhibition of heme polymerase activity Accumulation of cytotoxic-free heme As a result: cell lysis, and parasite cell autodigestion
Antifolates	pyrimethamine/ sulfadoxine atovaquone/ proguanil	Competitive inhibition of dihydrofolate reductase (DHFR) activity of DHFR-thymidylate synthetase (TS) protein or Competitive inhibition of dihydropteroate synthetase (DHPS) activity of hydroxymethylpterin pyrophosphokinase (HPPK)-DHPS
Artemisinin derivatives	artesunate artemether dihydroartemisinin	Interaction of endoperoxide moiety with heme iron in the parasite and generation of oxygen radicals Induction of membrane protein binding, lipid peroxidation, damage of endoplasmic reticulum, and inhibition of protein synthesis As a result: lysis of the parasite
Antimicrobials	tetracycline doxycycline clindamycin	Inhibition of 70S ribosomes in the parasite mitochondrion

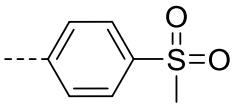
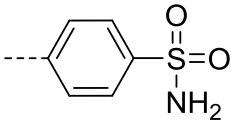
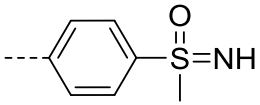
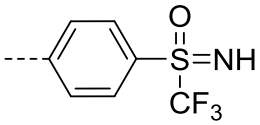
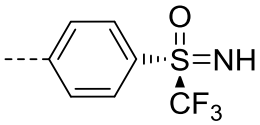
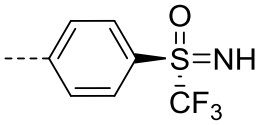
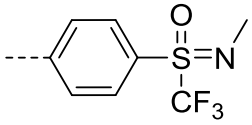
	azithromycin	

4.3 Antidiabetic Agents

Table 10. Results of the biochemical and cellular assays of selected GK-GKRP disruptors.[16]



Entry	Cpd.	R	Results of the biochemical and cellular assays		
			hGK-hGKRP IC_{50} [nM]	Mouse translocation EC_{50} [nM]	RLM CL_{int} [µL/min/mg]
1	**88**		4	202	42
2	**89**		25,000	NA	>399
3			10,500	15,600	>399
4			33,600	>12,500	17

5			401	936	34
6	**90**		61	37	30
7	**91**		310	704	<14
8	**92**		45	567	38
9	**(*R*)-92**		182	22,200	47
10	**(*S*)-92**		17	388	21
11	**93**		266	20,600	257

NA = not active

Table 11. Pharmacokinetic properties of selected GK-GKRP disruptors.[16]

Entry	Cpd.	In vivo rat PK				In vivo mouse PK					
		i.v.[a]		p.o.[b]		i.v.[a]		p.o.[b]			
		CL [L kg^{-1} h^{-1}]	$t_{1/2}$ [h]	F [%]	AUC [µM h]	CL [L kg^{-1} h^{-1}]	$t_{1/2}$ [h]	F [%]	AUC [µM h]	C_{max} [µM]	T_{max} [h]
1	**88**	0.75	3.6	75	20.0	0.11	6.7	40	64.8	5.82	5.0
2	**90**	2.82	1.6	5	0.26	ND					
3	**(*S*)-92**	0.42	2.8	51	25.3	0.025	3.1	53	362	46.6	1.0

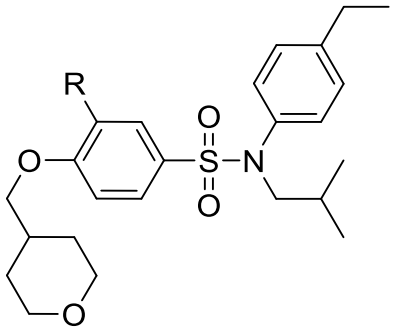
ND = not determined

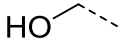
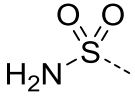
[a] Dosed at 2 mg/kg as a solution in DMSO.

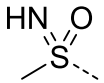
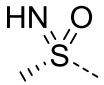
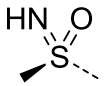
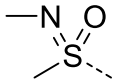
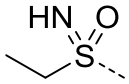
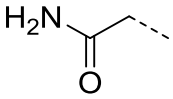
[b] Dosed orally at 10 mg/kg (in 1% Tween 80 containing 2% hydroxypropyl methylcellulose (**90**); in 1% Tween 80, 2% hydroxypropyl methylcellulose, pH 2.2 with methanesulfonic acid.

4.5 Agents for Treatment of Skin Diseases

Table 12. Results of the biochemical and cellular assays of selected inverse agonist of RORγ.[17,18]



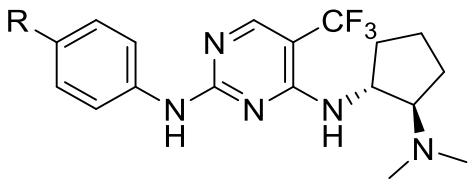
Entry	Cpd.	R	RORγ-GAL4 IC_{50} [nM]	CD4 IL17 IC_{50} [nM]	ChromLog $D_{6.5}$/LipE
1	**100**		17	3.2	5.9/1.9
2			390	ND	7.2/-0.8
3			97	ND	5.4/1.6
4			210	ND	5.8/0.9
5			89	ND	5.3/1.7

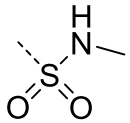
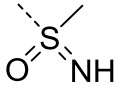
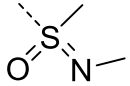
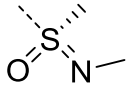
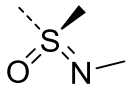
6	*rac*-**101**		47	ND	4.6/2.7
7	(*S*)-**101**		26	17	
8	(*R*)-**101**		45	20	
9			290	ND	5.2/1.4
10			81	ND	3.1/-0.4
11			39	ND	4.8/2.6

ND = not determined

4.8 Proline-Rich Tyrosine Kinase 2 (PYK2) Inhibitors

Table 13. Biological data on arylsulfoximine-substituted PYK2 inhibitors **117**-**120**.[19]



Entry	Cpd.	R	PYK2 IC_{50} [nM]	PYK2 Cell IC_{50} [nM]	FAK IC_{50} [nM]	HLM Eh	MDCK (A > B) P_{app} x 10^{-6} cm/s	Dofetilide % binding
1	**117**		95	60	1,000	< 0.29	9.5	48
2	**118**		140	88	1,300	0.66	5.3	50
3	**119**		65	320	ND	< 0.29	1	12
4	**120**		67	76	1,800	0.46	4.4	11
5	(*S*)-**120**		43	29	1,100	0.45	5.1	1.1
6	(*R*)-**120**		67	98	2,300	0.52	5.7	4

ND = not determined

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