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Experimental Supporting Information

PhI(OAc)₂ and Iodine-Mediated Synthesis of N-Alkyl Sulfonamides Derived from Polycyclic Aromatic Hydrocarbon Scaffolds and Determination of Their Antibacterial and Cytotoxic Activities

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Materials and Instrumentation: All solvents and reagents were purchased from commercial sources and used without further purification. I_2 (99.99+%, metal basis) was purchased from Alfa Aesar. ¹H and ¹³C NMR spectra were recorded on a Varian 400 MHz spectrometer in deuterated chloroform (CDCI₃) or deuterated acetone ((CD₃)₂CO). Solvent residual peak used as internal reference (CDCI₃: ¹H = 7.26 ppm, ¹³C = 77.02 ppm; (CD₃)₂CO: ¹H = 2.05 ppm, ¹³C = 29.84 ppm). Data are reported in the following order: chemical shifts (δ) are reported in ppm, and spin-spin coupling constants (*J*) are reported in Hz, while multiplicities are abbreviated by s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), dd (doublet of doublets), t (triplet), bt (broad triplet), dt (doublet of triplets), td (triplet of doublets), and m (multiplet). A Nicolet iS50 FT-IR spectrometer with peaks reported in reciprocal centimeters (cm⁻¹) was used for recording infrared spectra. Melting points (uncorrected) were recorded using a Mel-Temp II (Laboratory Devices, USA). HRMS were obtained using a Thermo Scientific Exactive spectrometer in positive ion electrospray mode (ESI-electrospray ionization).

Procedure for the preparation of 2,9-dibromo-9H-fluorene¹

To a stirred solution of fluorenone substrate (5 mmol; 1.30 g) in THF/H2O (2.25 mL, v:v = 9:1) was added NaBH₄ (3.5 mmol; 0.132 g) in one portion. The mixture was stirred at rt for 20 h. The reaction was then quenched with H₂O (3 mL), extracted with Et₂O (2 X 10 mL), dried over Na₂SO₄, and concentrated to give 2-bromo-9H-fluoren-9-ol.

2-bromo-9H-fluoren-9-ol: White solid. M.p. 146-148 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.70 (s, 1H), 7.56 (dd, J_1 = 7.4 Hz , J_2 = 1.6 Hz, 2H), 7.46 (m, 2H), 7.35 (td, J_1 = 7.4 X (2) Hz, J_2 = 1.2 Hz, 1H), 7.31 (td, J_1 = 7.4 X (2) Hz, J_2 = 1.2 Hz, 1H), 5.46 (br s, 1H), 2.73 (br s, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 147.6, 145.2, 139.0, 138.9, 132.1, 129.3, 128.6, 128.2, 125.2, 121.5, 121.3, 120.1, 74.9 ppm. IR (neat): v = 3279, 1464, 1028, 759 cm⁻¹. HRMS (ESI): calculated for C₁₃H₈Br₁ [M-H₂O]⁺ requires *m/z* 242.98094, found *m/z* 242.98358.

To a stirred solution of 2-bromo-9H-fluoren-9-ol (2.5 mmol; 0.653 g) in DCM (5 mL) at rt was added PBr₃ (1.33 mmol; 0.126 mL). The mixture was stirred at rt for 1h. The reaction was then quenched with sat. aqueous NaHCO₃ (10 mL), extracted with DCM (2 X 10 mL), dried over Na₂SO₄, and concentrated to give final brominated product.

2,9-dibromo-9H-fluorene: White solid. M.p. 122-124 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.71 (t, J_1 = 1.2 X (2) Hz, 1H), 7.57 (m, 1H), 7.53 (dd, J_1 = 5.9 Hz, J_2 = 1.6 Hz, 1H), 7.41 (m, 2H), 7.31 (dtd, J_1 = 12.9 Hz, J_2 = 7.4 X (2) Hz, 2H), 5.83 (s, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 146.1, 143.8, 138.7, 132.3, 129.6, 129.4, 128.5, 126.4, 121.7, 121.6, 120.4, 44.9 ppm. IR (neat): v = 2967, 1447, 1409, 1181, 1058, 819, 732, 647, 462 cm⁻¹. HRMS (ESI): calculated for C₁₃H₇Br₂ [M-H]⁻ requires *m/z* 320.891446, found *m/z* 320.88831.

Procedure for the preparation of 9-bromo-9H-thioxanthene

To an oven-dried round bottom flask was added thioxanthone (2 mmol; 0.425 g) and THF (20 mL). The reaction flask was purged with argon and equipped with an argon balloon. The mixture was placed in an ice bath with stirring. A 1M LAH/THF solution (4 mL) was added dropwise. Once added, the reaction was removed from the ice bath and stirred at rt for 2 hours. Once the reaction was completed, it was quenched with water and extracted with 3 X 15 mL of EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed.

9H-thioxanthen-9-ol:² White solid. M.p. 102-104 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.62 (dd, J_1 = 7.0 Hz, J_2 = 1.6 Hz, 2H), 7.49 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 2H), 7.30 (m, 4H), 5.56 (d, J_1 = 5.9 Hz, 1H), 2.39 (d, J_1 = 6.7 Hz, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 136.5, 132.0, 127.7, 127.2, 126.9, 126.7, 72.1 ppm. IR (neat): v = 3224, 3054, 1454, 1197, 1043, 734 cm⁻¹. HRMS (ESI): calculated for C₁₃H₉S₁ [M-H₂O]⁺ requires *m/z* 197.04250, found *m/z* 197.04439.

9H-Thioxanthen-9-ol (1 mmol; 0.214 g) was dissolved in glacial acetic acid (3 mL) and 48% HBr (0.136 mL) was added. The reaction was heated at 50 °C for 5 hours. After reaction time, the mixture was quenched with 1-3 mL H₂O and extracted with 3 X 5 mL EtOAc. The combined organic layers were dried (Na₂SO₄) and concentrated to yield brominated product.

9-bromo-9H-thioxanthene:³ Tan solid. M.p. 153-156 °C. ¹H NMR (400 MHz, CDCl₃) δ = 8.61 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 7.57 (m, 2H), 7.45 (m, 2H), 7.30 (dd, J_1 = 6.7 Hz, J_2 = 1.6 Hz, 1H), 7.18 (m, 2H), 3.84 (s, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 137.3, 136.2, 133.8, 132.3, 129.9, 129.2, 127.9, 126.9, 126.6, 126.5, 126.3, 126.0, 39.2 ppm. IR (neat): v = 3050, 2917, 2849, 1641, 1588, 1440, 729 cm⁻¹.

Procedure for the preparation of 9-bromo-2-iodo-9H-fluorene

2-lodofluorene (0.5 mmol; 0.146 g) and NBS (0.55 mmol; 0.0979 g) were added in CCl_4 (6.5 mL) and the mixture was refluxed overnight with benzoyl peroxide (0.004g) as initiator. After cooling, the succinimide formed was filtered. The mixture was washed with NaHCO₃ (1M; 20 mL) and brine (20 mL). The organic phase was dried over MgSO₄. The crude was purified via recrystallization from hexanes.

9-bromo-2-iodo-9H-fluorene:⁴ Pale yellow solid. M.p. 122-125 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.98 (s, 1H), 7.72 (dd, J_1 = 8.0 Hz, J_2 = 1.4 Hz, 1H), 7.64 (m, 2H), 7.41 (d, J_1 = 8.2 Hz, 2H), 7.37 (m, 1H), 5.93 (s, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 146.2, 143.6, 139.4, 138.8, 138.2, 135.4, 129.4, 128.7, 126.3, 121.8, 120.4, 92.9, 44.8 ppm. IR (neat): v = 2965, 1715, 1446, 1403, 1179, 820, 732, 663 cm⁻¹. HRMS (ESI): calculated for C₁₃H₇Br₁I₁ [M-H]⁻ requires *m/z* 368.87759, found *m/z* 368.87436.



Figure S1. Cell viability screening of compounds 2-23 (50 µM), 24 h, CellTiter-Blue assay (Promega).



Figure S2. Cell viability screening of compounds 2-23 (50 µM), 24 h, CellTiter-Glo assay (Promega).

	Cell Lines (Values are shown as Percent of DMSO Control)								
Compounds	HDF	H293	HeLa	PC3	BxPC3				
DMSO	100 ± 3.4%	100.0 ± 4.7%	100.0 ± 10.8%	100.0 ± 1.0%	100.0 ± 8.2%				
2	93.2 ± 3.6%	90.4 ± 1.7%	102.7 ± 6.2%	88.2 ± 1.8%	76.1 ± 5.1%				
3	69.9 ± 1.6%	79.3 ± 3.0%	77.5 ± 0.0%	67.7 ± 2.8%	83.1 ± 1.4%				
4	85.6 ± 6.0%	83.3 ± 2.6%	93.8 ± 1.1%	90.8 ± 1.4%	95.2 ± 3.2%				
5	87.7 ± 6.1%	79.6 ± 6.0%	85.8 ± 4.5%	77.4 ± 0.0%	79.2 ± 11.3%				
6	63.4 ± 0.6%	93.4 ± 0.9%	84.8 ± 2.7%	86.5 ± 3.4%	87.4 ± 1.5%				
7	76.1 ± 1.6%	79.5 ± 3.7%	77.5 ± 7.9%	80.2 ± 1.5%	107.4 ± 8.5%				
8	83.8 ± 2.7%	82.9 ± 3.2%	86.6 ± 1.5%	79.3 ± 3.6%	88.3 ± 4.7%				
9	94.9 ± 0.1%	86.8 ± 3.6%	93.5 ± 2.3%	82.7 ± 11.6%	91.3 ± 2.0%				
10	72.8 ± 3.5%	78.7 ± 6.1%	86.7 ± 1.3%	77.4 ± 2.1%	88.3 ± 5.3%				
11	87.1 ± 1.6%	78.8 ± 5.1%	88.9 ± 2.3%	78.6 ± 5.1%	89.8 ± 3.0%				
12	101.3 ± 5.3%	78.6 ± 1.8%	90.7 ± 2.3%	85.2 ± 7.3%	127.3 ± 9.7%				
13	97.2 ± 9.6	76.6 ± 9.8%	101.0 ± 3.8%	89.2 ± 1.7%	113.5 ± 5.3%				
14	113.2 ± 2.2%	74.8 ± 3.6%	42.5 ± 0.7%	81.7 ± 4.6%	87.6 ± 12.4%				
15	144.8 ± 5.0%	85.9 ± 1.7%	91.9 ± 7.3%	75.2 ± 2.4%	140.2 ± 1.2%				
16	56.9 ± 5.2%	66.3 ± 2.0%	90.3 ± 2.7%	79.0 ± 5.2%	69.2 ± 2.8%				
17	10.5 ± 1.3%	1.9 ± 0.1%	12.1 ± 0.0%	5.9 ± 0.2%	3.2 ± 0.9%				
18	108.1 ± 3.6%	90.3 ± 1.8%	94.2 ± 5.2%	74.3 ± 3.0%	87.4 ± 3.8%				
19	97.5 ± 4.7%	86.5 ± 2.2%	109.0 ± 2.7%	95.8 ± 0.9%	110.8 ± 6.1%				
20	59.9 ± 6.4%	64.8 ± 1.2%	80.6 ± 0.3%	76.1 ± 0.1%	66.5 ± 6.9%				
21	19.0 ± 0.3%	16.0 ± 1.3%	48.7 ± 8.6%	63.0 ± 11.4%	39.4 ± 0.5%				
22	16.9 ± 0.8%	64.3 ± 8.1%	9.8 ± 1.0%	67.3 ± 0.4%	66.5 ± 1.5%				
23	117.6 ± 4.9%	88.6 ± 11.8%	91.9 ± 0.0%	82.3 ± 2.3%	81.1 ± 5.5%				

Table S1. Cell viability results from screening of compounds **2-23** (50 μ M), 24 h, CellTiter-Glo assay (Promega). Compound "hits" (<50% percent of DMSO control) are shown in red.

Cmp	MW	TPSA ^a	cLogP ^b	cLogP ^c	Solby ^d	Log Kp ^e	Drug	Drug-likeness (Number of violations) ^f			Drug score ^g	
d			(calc)	(expmtl)			Lipinsk	Ghose	Veber	Egan	Muegge	
							i					
2	368	100.4	2.52	3.69	-4.04	-6.06	0	0	0	0	0	0.38
3	335	54.6	3.70	3.96	-5.1	-5.40	0	0	0	0	0	0.10
4	351	63.8	3.37	3.57	-4.77	-5.78	0	0	0	0	0	0.11
5	356	54.6	3.89	4.30	-5.49	-5.34	0	0	0	0	0	0.09
6	389	54.6	4.42	4.48	-5.53	-5.36	0	1	0	1	0	0.08
7	339	54.6	3.67	3.70	-5.07	-5.62	0	0	0	0	0	0.11
8	321	54.6	3.24	3.49	-4.75	-5.58	0	0	0	0	0	0.11
9	366	100.4	2.79	3.59	-5.21	-5.97	0	0	0	0	0	0.11
10	356	54.6	3.88	4.29	-5.49	-5.34	0	0	0	0	0	0.09
11	339	54.6	3.67	3.77	-5.07	-5.62	0	0	0	0	0	0.11
12	356	54.6	3.88	3.67	-5.49	-5.34	0	0	0	0	0	0.09
13	339	54.6	3.59	3.38	-5.07	-5.62	0	0	0	0	0	0.11
14	357	54.6	3.94	3.67	-5.38	-5.65	0	1	0	0	0	0.10
15	357	54.6	3.96	3.13	-5.38	-5.65	0	1	0	0	0	0.10
16	357	54.6	3.96	4.16	-5.38	-5.65	0	1	0	0	0	0.10
17	411	54.6	4.80	4.43	-6.32	-5.77	1	1	0	1	0	0.08
18	425	54.6	4.91	5.17	-6.96	-4.87	1	1	0	1	1	0.04
19	259	54.6	2.15	1.80	-4.51	-6.31	0	0	0	0	0	0.14
20	435	54.6	4.50	4.99	-6.32	-5.33	1	1	0	1	1	0.11
21	482	54.6	4.54	5.08	-6.5	-5.65	1	2	0	0	1	0.12
22	388	79.9	4.25	2.15	-5.19	-5.22	0	1	0	0	0	0.46
23	383	89.1	3.65	0.86	-4.47	-5.66	0	0	0	0	0	0.57

a) TPSA = Topological polar surface area; calculated by SwissADME. b) Calculated by SwissADME (average of 5 calculations – iLOGP; XLOGP3; WLOGP; MLOGP; SILICOS-IT). c) Experimentally obtained. d) Solubility (Log S) calculated by OSIRIS. e) Indicates skin permeation in cm/s; calculated by SwissADME. f) Calculated by SwissADME. g) Calculated by OSIRIS.

Table S2. Drug-likeness and physicochemical properties of compounds 2-23 as predicted by OSIRIS and SwissADME.

Reference Compounds								
Compound	Tr	T0 (ethyl acetate)	k	log(k)	log(P)			
Nitrobenzene	4.528	3.809	0.1888	-0.7240	1.9			
Toluene	6.93	3.814	0.8170	-0.0878	2.7			
Naphthalene	8.466	3.827	1.2122	0.0836	3.6			
Biphenyl	11.637	3.83	2.0384	0.3093	4.0			
Bibenzyl	18.179	3.831	3.7452	0.5735	4.8			
DDT	41.243	3.827	9.7768	0.9902	6.5			



Figure S3. Calibration curve and raw data for calculation of LogP values of known calibration compounds.⁵

In Silico Predicted Properties (obtained using SwissADME):⁶

For a description of BOILED Egg, see reference 7.



SMILES: [O-][N+](=O)C1=CC=C(C=C1)S(=O)(=O)NC1C2C=CC=CC2C2=C1C=CC=C2

Figure S4. BOILED EGG and graphical physicochemical property summary of product 2.



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SMILES: CC1=CC=C(C=C1)S(=O)(=O)NC1C2=C(C=CC=C2)C2=C1C=CC=C2
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Figure S5. BOILED EGG and graphical physicochemical property summary of product 3.



SMILES: COC1=CC=C(C=C1)S(=O)(=O)NC1C2=C(C=CC=C2)C2=C1C=CC=C2

Figure S6. BOILED EGG and graphical physicochemical property summary of product 4.



SMILES: CIC1=CC=C(C=C1)S(=O)(=O)NC1C2=C(C=CC=C2)C2=C1C=CC=C2

Figure S7. BOILED EGG and graphical physicochemical property summary of product 5.



SMILES: FC(F)(F)C1=CC=C(C=C1)S(=O)(=O)NC1C2=C(C=CC=C2)C2=C1C=CC=C2

Figure S8. BOILED EGG and graphical physicochemical property summary of product 6.



SMILES: FC1=CC=C(C=C1)S(=O)(=O)NC1C2=C(C=CC=C2)C2=C1C=CC=C2

Figure S9. BOILED EGG and graphical physicochemical property summary of product 7.



SMILES: O=S(=O)(NC1C2=C(C=CC=C2)C2=C1C=CC=C2)C1=CC=CC=C1

Figure S10. BOILED EGG and graphical physicochemical property summary of product 8.



SMILES: [O-][N+](=O)C1=CC(=CC=C1)S(=O)(=O)NC1C2=C(C=CC=C2)C2=C1C=CC=C2

Figure S11. BOILED EGG and graphical physicochemical property summary of product 9.



SMILES: CIC1=CC(=CC=C1)S(=O)(=O)NC1C2=C(C=CC=C2)C2=C1C=CC=C2

Figure S12. BOILED EGG and graphical physicochemical property summary of product 10.



SMILES: FC1=CC(=CC=C1)S(=O)(=O)NC1C2=C(C=CC=C2)C2=C1C=CC=C2

Figure S13. BOILED EGG and graphical physicochemical property summary of product 11.



SMILES: CIC1=CC=CC=C1S(=O)(=O)NC1C2=C(C=CC=C2)C2=C1C=CC=C2

Figure S14. BOILED EGG and graphical physicochemical property summary of product 12.



Figure S15. BOILED EGG and graphical physicochemical property summary of product 13.



SMILES: FC1=CC=C(C(F)=C1)S(=O)(=O)NC1C2=C(C=CC=C2)C2=C1C=CC=C2

Figure S16. BOILED EGG and graphical physicochemical property summary of product 14.



SMILES: FC1=CC=CC(F)=C1S(=O)(=O)NC1C2=C(C=CC=C2)C2=C1C=CC=C2

Figure S17. BOILED EGG and graphical physicochemical property summary of product 15.



Figure S18. BOILED EGG and graphical physicochemical property summary of product 16.



SMILES: FC1=C(F)C(F)=C(C(F)=C1F)S(=O)(=O)NC1C2=C(C=CC=C2)C2=C1C=CC=C2

Figure S19. BOILED EGG and graphical physicochemical property summary of product 17.



SMILES: CIC1=CC(CI)=C(C(CI)=C1)S(=O)(=O)NC1C2=C(C=CC=C2)C2=C1C=CC=C2

Figure S20. BOILED EGG and graphical physicochemical property summary of product 18.



Figure S21. BOILED EGG and graphical physicochemical property summary of product 19.



SMILES: CIC1=CC=C(C=C1)S(=O)(=O)NC1C2=C(C=CC=C2)C2=C1C=C(Br)C=C2

Figure S22. BOILED EGG and graphical physicochemical property summary of product 20.



SMILES: CIC1=CC=C(C=C1)S(=O)(=O)NC1C2=C(C=CC=C2)C2=C1C=C(I)C=C2

Figure S23. BOILED EGG and graphical physicochemical property summary of product 21.



SMILES: CIC1=CC=C(C=C1)S(=O)(=O)NC1C2=C(SC3=C1C=CC=C3)C=CC=C2

Figure S24. BOILED EGG and graphical physicochemical property summary of product 22.



SMILES: COC1=CC=C(C=C1)S(=O)(=O)NC1C2=C(SC3=C1C=CC=C3)C=CC=C2

Figure S25. BOILED EGG and graphical physicochemical property summary of product 23.

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Product Characterization:

All products were isolated according to general procedure unless otherwise noted and display the characterizational data shown below.



Figure S26. ¹H NMR and ¹³C NMR of Product 2.



Figure S27. ¹H NMR and ¹³C NMR of Product 3.



Figure S28. ¹H NMR and ¹³C NMR of Product 4.



Figure S29. ¹H NMR and ¹³C NMR of Product 5.



Figure S30. ¹H NMR and ¹³C NMR of Product 6.



Figure S31. ¹H NMR and ¹³C NMR of Product 7.



Figure S32. ¹H NMR and ¹³C NMR of Product 8.



Figure S33. ¹H NMR and ¹³C NMR of Product 9.



Figure S34. ¹H NMR and ¹³C NMR of Product **10**.



Figure S35. ¹H NMR and ¹³C NMR of Product **11**.



Figure S36. ¹H NMR and ¹³C NMR of Product 12.



Figure S37. ¹H NMR and ¹³C NMR of Product **13**.

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Figure S38. ¹H NMR and ¹³C NMR of Product **14**.

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Figure S39. ¹H NMR and ¹³C NMR of Product 15.



Figure S40. ¹H NMR and ¹³C NMR of Product **16**.



Figure S41. ¹H NMR and ¹³C NMR of Product **17**.



Figure S42. ¹H NMR and ¹³C NMR of Product 18.



Figure S43. ¹H NMR and ¹³C NMR of Product **19**.



Figure S44. ¹H NMR and ¹³C NMR of Product 20.



Figure S45. ¹H NMR and ¹³C NMR of Product 21.



Figure S46. ¹H NMR and ¹³C NMR of Product **22**.

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Figure S47. ¹H NMR and ¹³C NMR of Product 23.