

Supporting Information

Solution Stability and SwissADME-Guided Prioritisation of S-Glycosyl NRF2-Modulating Isothiocyanates [†]

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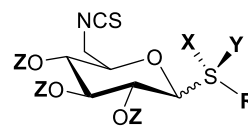
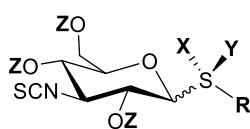
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Table S1: Compound numbering and structural features of the C3-ITC and C6-ITC S-glycosyl series.



C3-ITC				
Compound	R	Z	X	Y
1 β	Et	Ac	lp	lp
1 α	Et	Ac	lp	lp
2 β	Ph	Ac	lp	lp
2 α	Ph	Ac	lp	lp
3 β	Me	Ac	lp	lp
4 β	Ph	Me	lp	lp
(S)-5 β	Et	Ac	lp	O
(R)-5 β	Et	Ac	O	lp
(R)-5 α	Et	Ac	O	lp
(S)-6 β	Ph	Ac	lp	O
(R)-6 β	Ph	Ac	O	lp
(R)-6 α	Ph	Ac	O	lp
(S)-7 β	Ph	Me	lp	O
(R)-7 β	Ph	Me	O	lp
8 β	Et	Ac	O	O
8 α	Et	Ac	O	O
9 β	Ph	Ac	O	O
9 α	Ph	Ac	O	O
10 β	Me	Ac	O	O
11 β	Ph	Me	O	O

C6-ITC				
Compound	R	Z	X	Y
12 β	Ph	Ac	lp	lp
12 α	Ph	Ac	lp	lp
13 β	Me	Ac	lp	lp
14 β	Et	Ac	lp	lp
(S)-15 β	Ph	Ac	lp	O
(R)-15 β	Ph	Ac	O	lp
(S)-16 β	Et	Ac	lp	O
(R)-16 β	Et	Ac	O	lp
17 β	Ph	Ac	O	O
18 β	Et	Ac	O	O

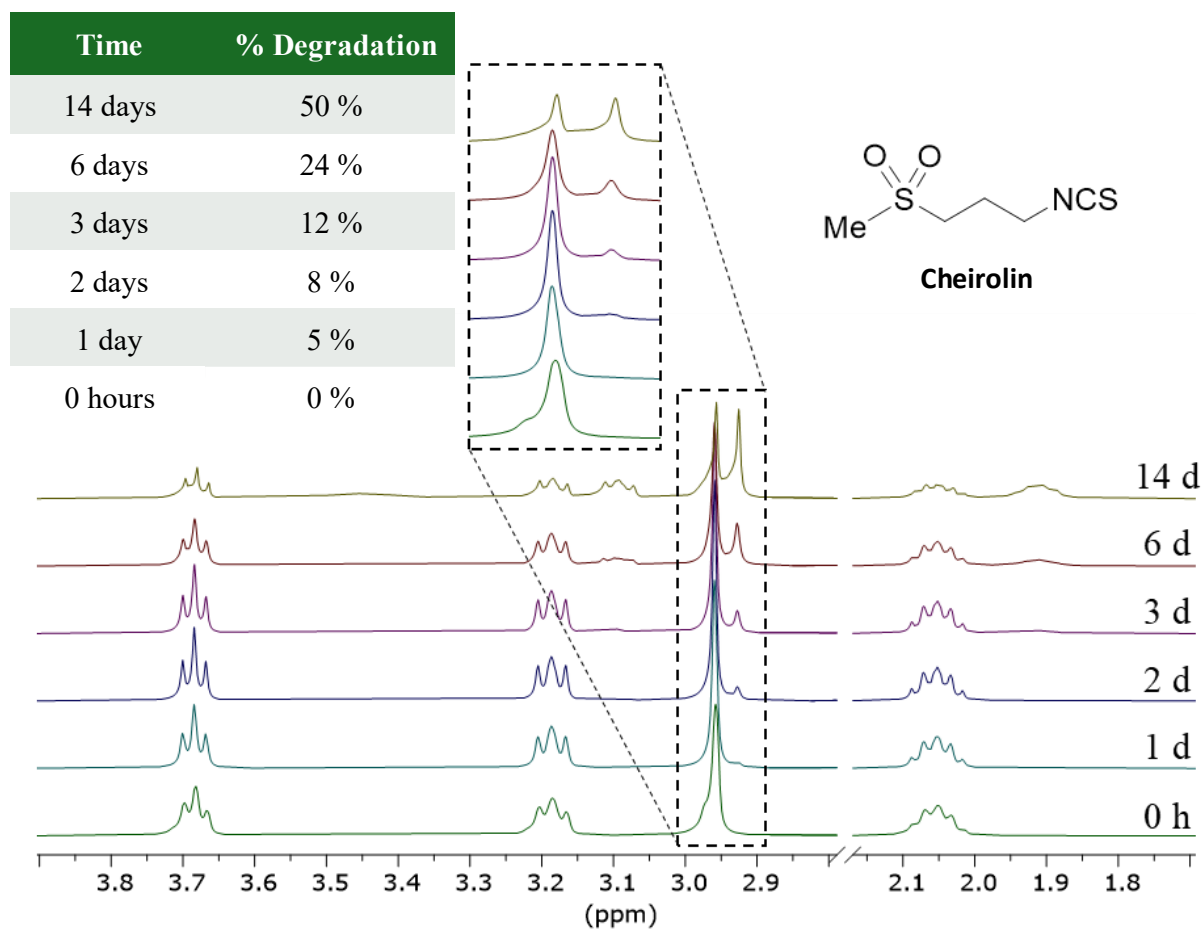


Figure S1: Time-dependent ^1H NMR spectra (400 MHz, $(\text{CD}_3)_2\text{SO}:\text{D}_2\text{O}$ (4:1)) of cheirolin at 0, 1, 2, 3, 6 and 14 days.

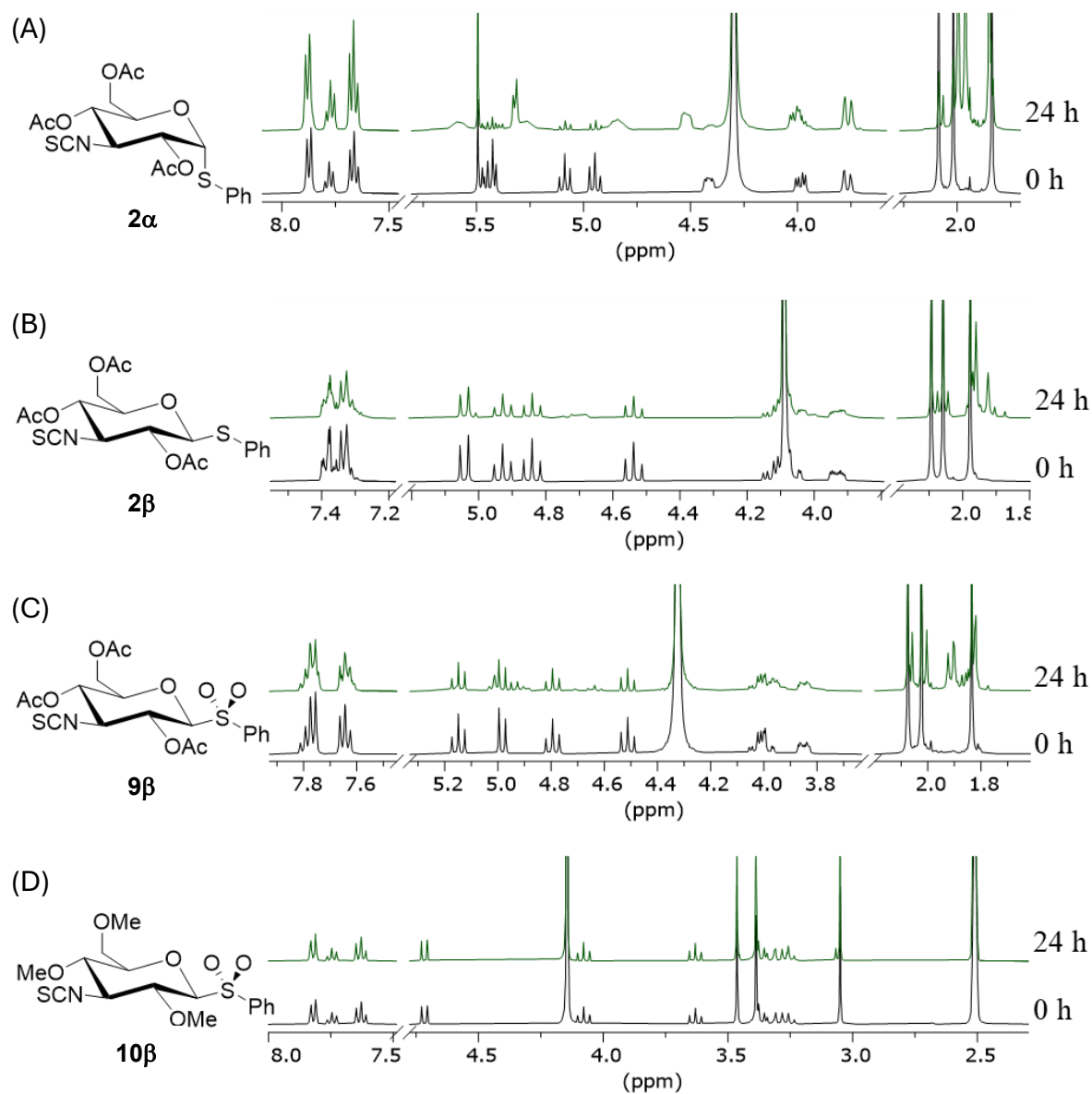


Figure S2: Selected regions of the ^1H NMR spectra [400 MHz, $(\text{CD}_3)_2\text{SO}-d_6$ (4:1)] of compounds (A) **2α**, (B) **2β**, (C) **9β**, and (D) **10β** at 0 and 24 h.

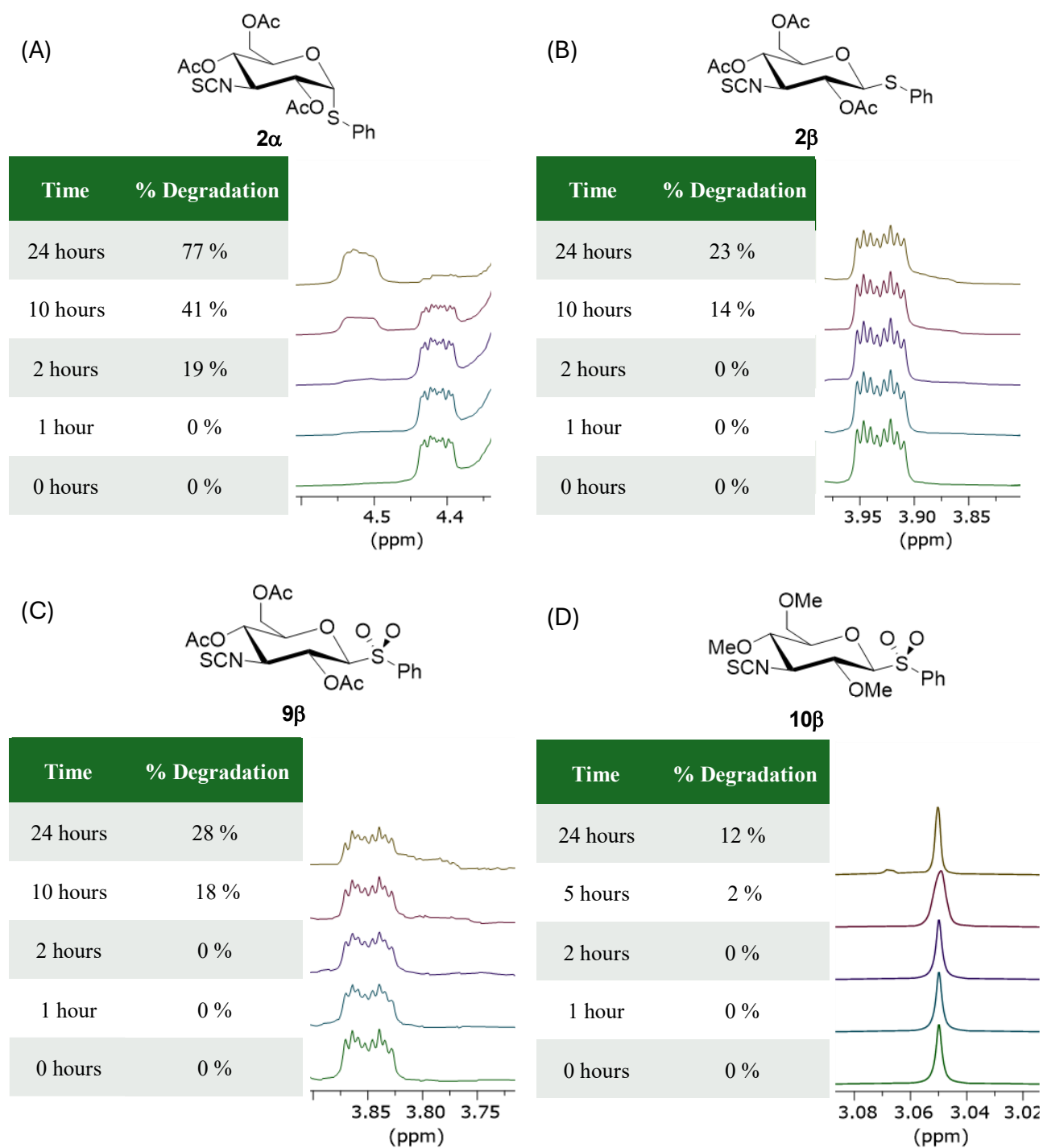


Figure S3: Selected regions of the ^1H NMR spectra [400 MHz, $(\text{CD}_3)_2\text{SO}:\text{D}_2\text{O}$ (4:1)] of compounds (A) **2α**, (B) **2β**, and (C) **9β** at 0, 1, 2, 10 and 24 h, and (D) **10β** at 0, 1, 2, 5 and 24 h.

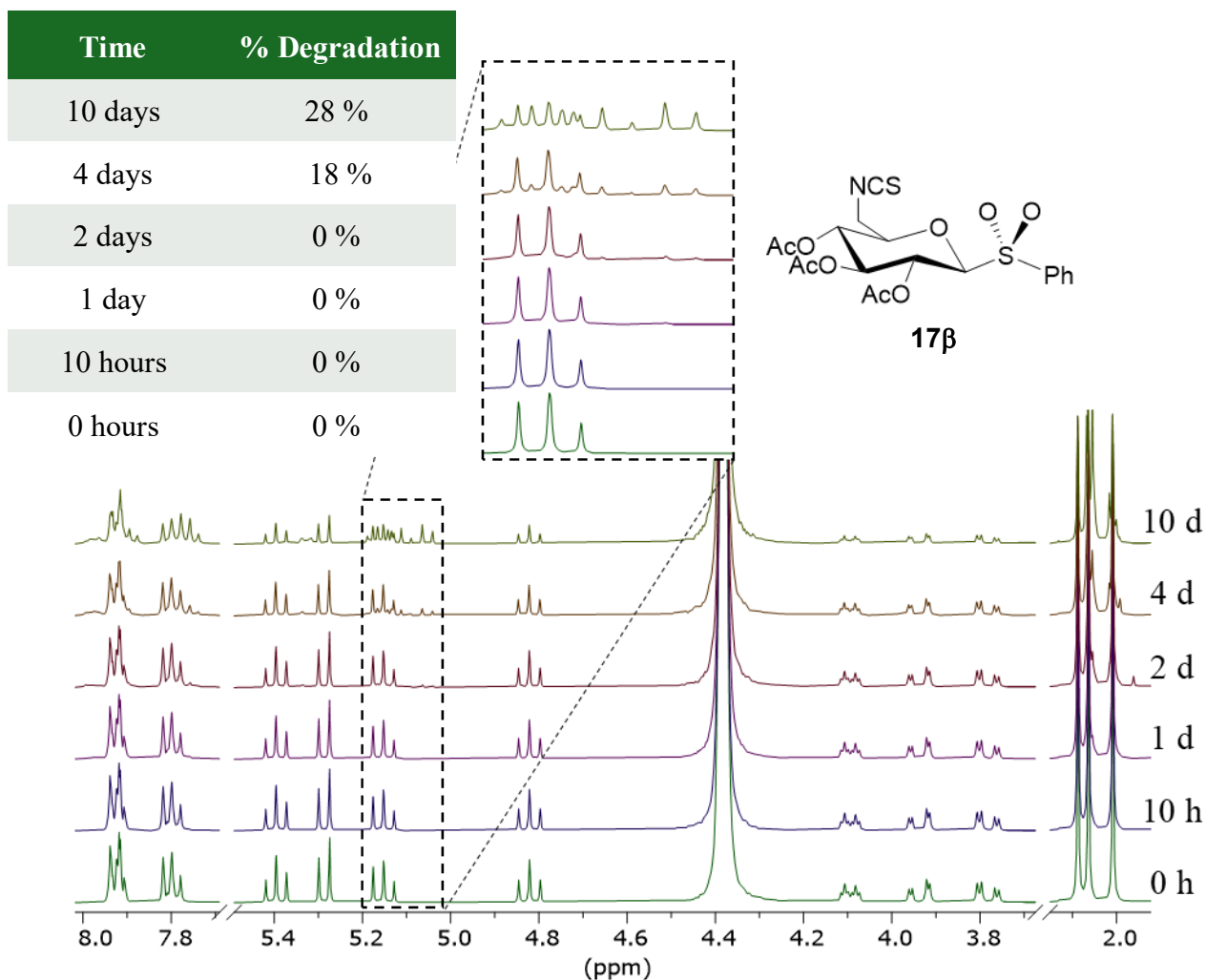
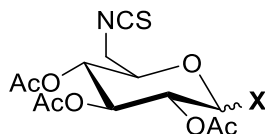


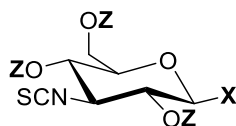
Figure S4: Time-dependent ¹H NMR spectra [400 MHz, (CD₃)₂SO:D₂O (4:1)] of C6-ITC phenylsulfone **17β** at 0, 10 h, 1, 2, 4 and 10 days.

Table S2: SwissADME-predicted solubility and Lipinski rule-of-five properties of the C6-ITC S-glycosyl series, natural isothiocyanates, and *tert*-butylhydroquinone (TBHQ).



X	Compounds	ESOL Log S	ESOL Solubility (mg/mL)	ESOL Class	MW	H-bond acceptors	H-bond donors	MLog P	Lipinski violations
MeS	13b	-2.83	0.562	Soluble	377.43	8	0	1.16	0
EtS	14b	-3.08	0.325	Soluble	391.46	8	0	1.42	0
PhS	12b	-4.28	0.023	Moderately soluble	439.50	8	0	2.41	0
PhS	12a	-4.28	0.023	Moderately soluble	439.50	8	0	2.41	0
(R)-EtSO	(R)-16b	-2.14	2.95	Soluble	407.46	9	0	0.56	0
(S)-EtSO	(S)-16b	-2.14	2.95	Soluble	407.46	9	0	0.56	0
(S)-PhSO	(S)-15b	-3.44	0.166	Soluble	455.50	9	0	1.55	0
(R)-PhSO	(R)-15b	-3.44	0.166	Soluble	455.50	9	0	1.55	0
EtSO ₂	18b	-2.47	1.42	Soluble	423.46	10	0	0.52	0
PhSO ₂	17b	-3.67	0.101	Soluble	471.50	10	0	1.52	0
-	Iberverin	-2.81	0.587	Soluble	377.4	8	0	1.97	0
-	Iberin	-3.06	0.339	Soluble	391.5	8	0	2.23	0
-	Cheirolin	-4.26	0.024	Moderately soluble	439.5	8	0	3.22	0
-	TBHQ	-2.96	0.183	Soluble	166.2	2	2	2.10	0

Predicted aqueous solubility (ESOL Log S), molecular weight (MW), hydrogen-bond acceptors (HBA), hydrogen-bond donors (HBD), MLogP and Lipinski violations were obtained from SwissADME.

Table S3: SwissADME-predicted solubility and Lipinski rule-of-five properties of the C3-ITC S-glycosyl series.

X	Z	Compound	ESOL Log S	ESOL solubility (mg/mL)	ESOL class	MW	HBA	HBD	MLogP	Lipinski violations
EtS	Ac	1β	-3.06	0.339	Soluble	391.46	8	0	1.42	0
EtS	Ac	1α	-3.06	0.339	Soluble	391.46	8	0	1.42	0
PhS	Ac	2β	-4.26	0.024	Moderately soluble	439.50	8	0	2.41	0
PhS	Ac	2α	-4.26	0.024	Moderately soluble	439.50	8	0	2.41	0
MeS	Ac	3β	-2.81	0.587	Soluble	377.43	8	0	1.16	0
PhS	Me	4β	-3.91	0.043	Soluble	355.47	5	0	1.90	0
(S)-EtSO	Ac	(S)-5β	-2.12	3.12	Soluble	407.46	9	0	0.56	0
(R)-EtSO	Ac	(R)-5β	-2.12	3.12	Soluble	407.46	9	0	0.56	0
(R)-EtSO	Ac	(R)-5α	-2.12	3.12	Soluble	407.46	9	0	0.56	0
(S)-PhSO	Ac	(S)-6β	-3.42	0.174	Soluble	455.50	9	0	1.55	0
(R)-PhSO	Ac	(R)-6β	-3.42	0.174	Soluble	455.50	9	0	1.55	0
(R)-PhSO	Ac	(R)-6α	-3.42	0.174	Soluble	455.50	9	0	1.55	0
(S)-PhSO	Me	(S)-7β	-3.06	0.321	Soluble	371.47	6	0	1.00	0
(R)-PhSO	Me	(R)-7β	-3.06	0.321	Soluble	371.47	6	0	1.00	0
EtSO ₂	Ac	8β	-2.45	1.49	Soluble	423.46	10	0	0.52	0
EtSO ₂	Ac	8α	-2.45	1.49	Soluble	423.46	10	0	0.52	0
PhSO ₂	Ac	9β	-3.65	0.107	Soluble	471.50	10	0	1.52	0
PhSO ₂	Ac	9α	-3.65	0.107	Soluble	471.50	10	0	1.52	0
MeSO ₂	Ac	10β	-2.21	2.54	Soluble	409.43	10	0	0.26	0
PhSO ₂	Me	11β	-3.29	0.200	Soluble	387.47	7	0	0.94	0

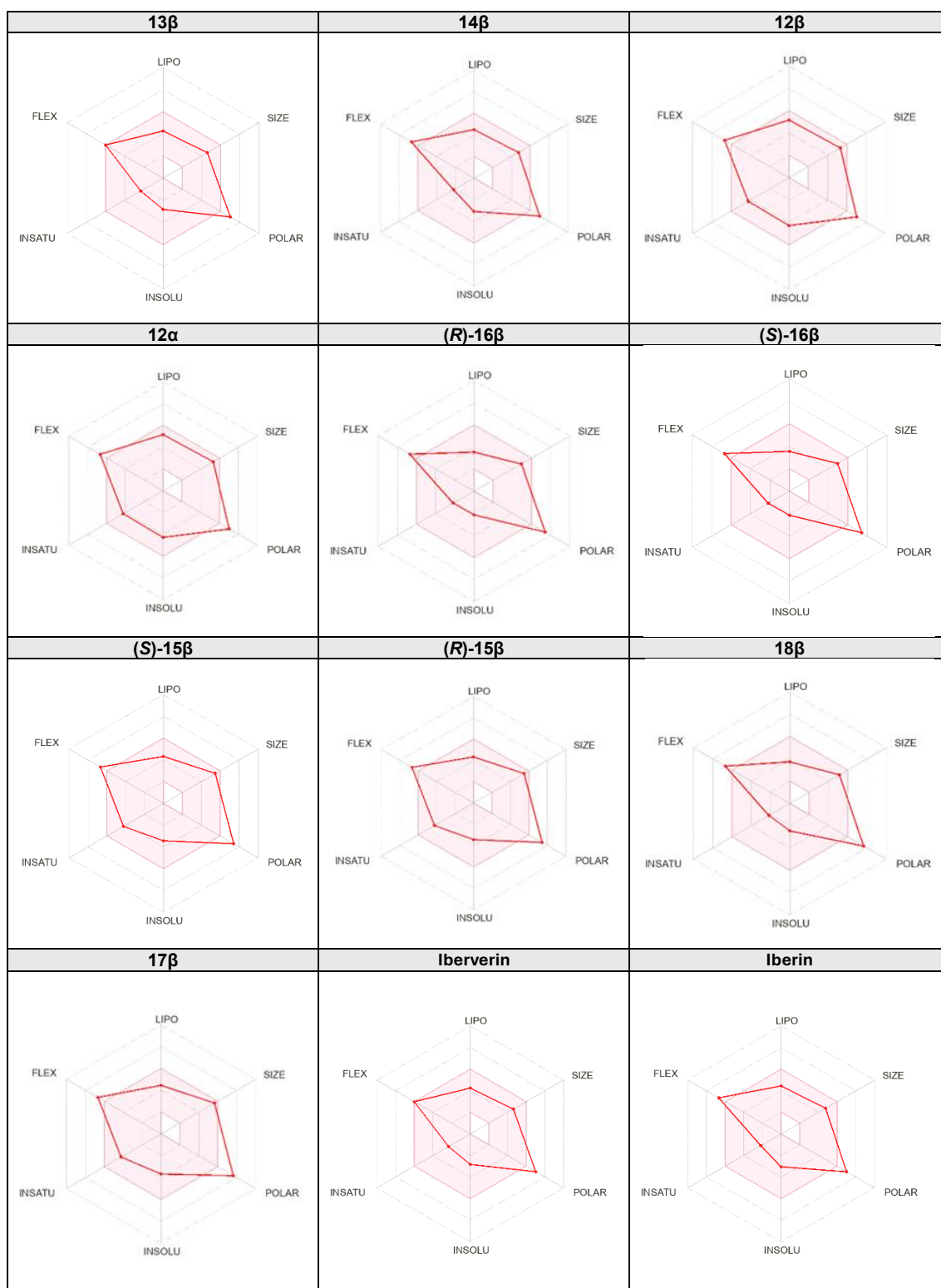
Predicted aqueous solubility (ESOL Log S), molecular weight (MW), hydrogen-bond acceptors (HBA), hydrogen-bond donors (HBD), MLogP and Lipinski violations were obtained from SwissADME.

PARAMETER	
Solubility scale (Log S)	Insoluble < -10 < Poorly < -6 < Moderately < -4 < Soluble < -2 < Very < 0 < Highly
Lipinski violations	Based on Lipinski rules: MW $\leq$ 500 MLogP $\leq$ 4.15 N or O $\leq$ 10 NH or OH $\leq$ 5

Table S4: SwissADME comparison of strictly matched C3-ITC and C6-ITC regioisomeric pairs.

C3	C6	Sulfur substituent	MW (both)	HBA/HBD (both)	MLogP (both)	TPSA (both)	RotB (both)	ESOL Log S C3	ESOL Log S C6	ESOL mg/mL C3	ESOL mg/mL C6
1 β	14 β	EtS	391.46	8/0	1.42	157.88	10	-3.06	-3.08	0.339	0.325
2 β	12 β	PhS	439.50	8/0	2.41	157.88	10	-4.26	-4.28	0.024	0.023
3 β	13 β	MeS	377.43	8/0	1.16	157.88	9	-2.81	-2.83	0.587	0.562
(S)-5 β	(S)-16 β	EtSO	407.46	9/0	0.56	168.86	10	-2.12	-2.14	3.12	2.95
(S)-6 β	(S)-15 β	PhSO	455.50	9/0	1.55	168.86	10	-3.42	-3.44	0.174	0.166
8 β	18 β	EtSO ₂	423.46	10/0	0.52	175.10	10	-2.45	-2.47	1.49	1.42
9 β	17 β	PhSO ₂	471.50	10/0	1.52	175.10	10	-3.65	-3.67	0.107	0.101

Values indicated as “both” were identical within each matched C3/C6 pair. ESOL predictions showed a small systematic positional difference: C3 analogues displayed Log S values 0.02 units higher (less negative) than the corresponding C6 derivatives at the precision reported by SwissADME. Equivalent R/S sulfoxide epimers and α/β anomers gave the same values for the descriptors shown



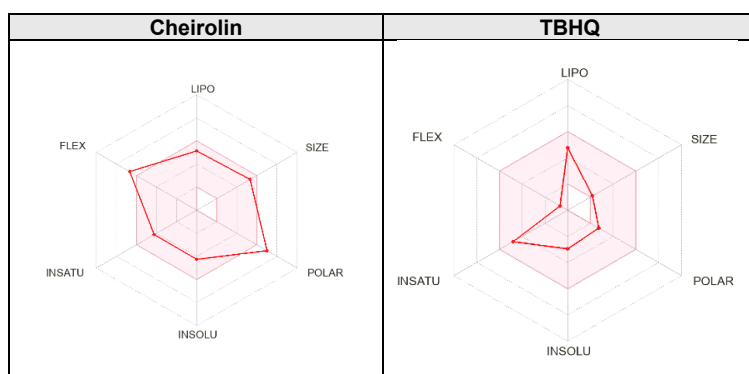
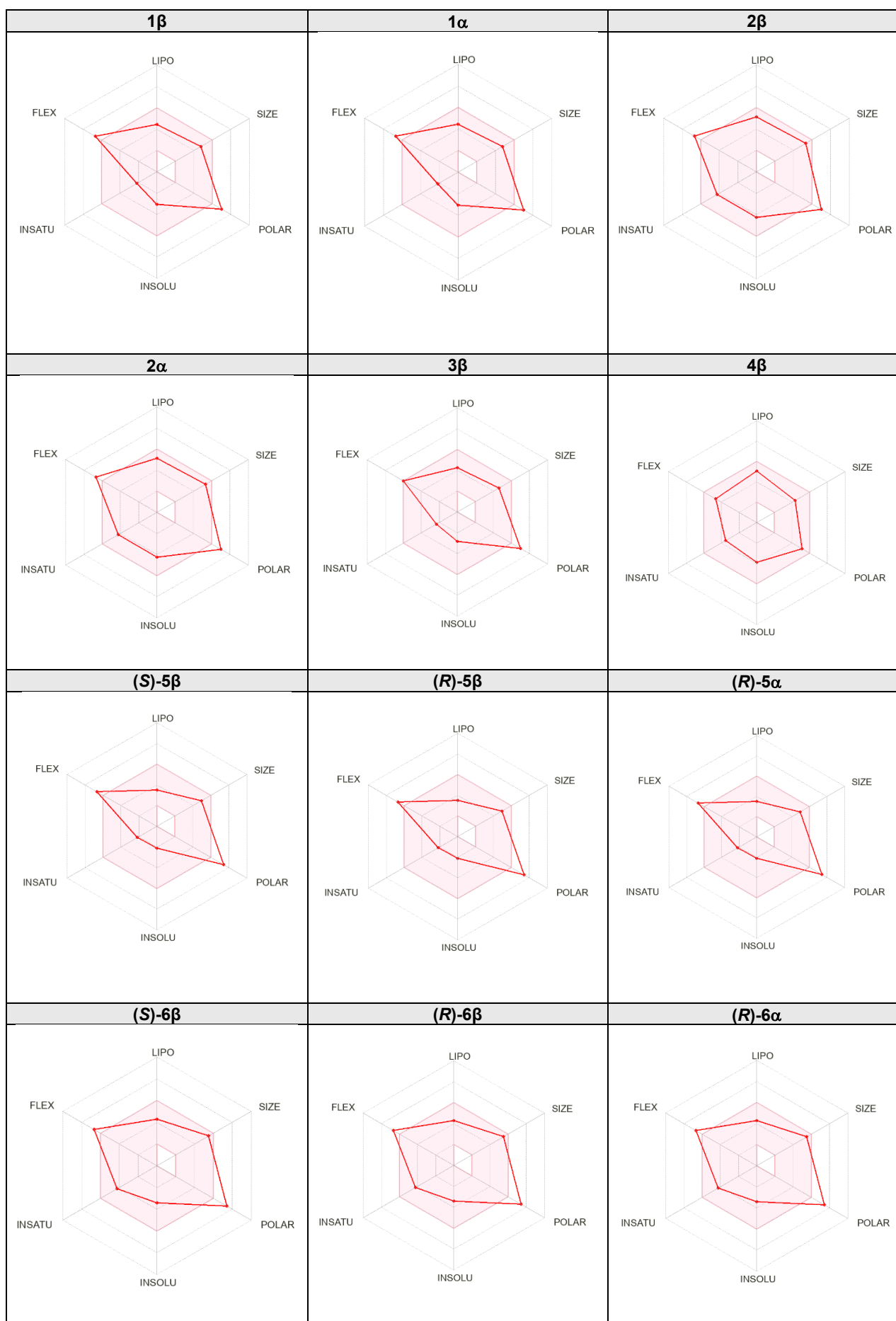


Figure S5: Bioavailability radar plots of the C6-ITC *S*-glycosyl derivatives, natural isothiocyanates (iberiverin, iberin and cheirolin), and the reference NRF2 activator *tert*-butylhydroquinone (TBHQ). Parameters include lipophilicity (LIPO), size (SIZE), polarity (POLAR), solubility (INSOLU), flexibility (FLEX), and saturation (INSATU).



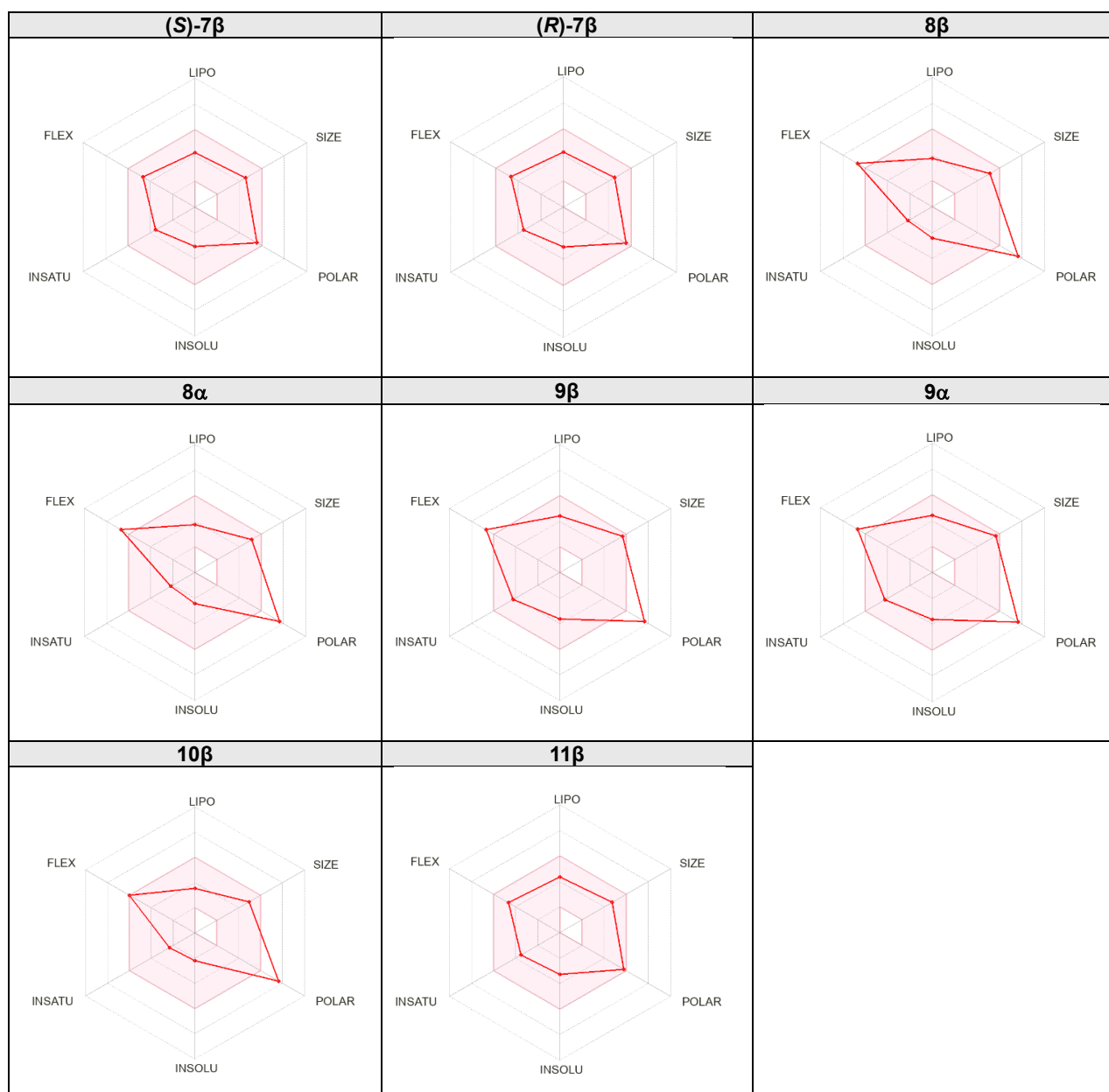


Figure S6: Bioavailability radar plots of the C3-ITC S-glycosyl derivatives. Parameters include lipophilicity (LIPO), size (SIZE), polarity (POLAR), solubility (INSOLU), flexibility (FLEX), and saturation (INSATU).