Supplementary Materials: Design, Synthesis and Antifungal Activity Evaluation of New Thiazolin-4-ones as Potential Lanosterol 14α-Demethylase Inhibitors

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Table S1. The results of VS carried out for detection of non-peptidic inhibitors of PPI and UMSs (with prediction of toxicity risks).

ID	PPI Friendly	UMSs		
		Detected Functional Group	Main Mechanism	Alternative Mechanisms
2	No	LR: Michael acceptors (double bonds)	Warhead	-
		LR: terminal vinyl	Problematic	-
3a	No	HR: Michael acceptors (double bonds)	Warhead	-
		LR: terminal vinyl	Problematic	-
3b	No	HR: Michael acceptors (double bonds)	Warhead	-
		LR: terminal vinyl	Problematic	-
3c	No	HR: Michael acceptors (double bonds)	Warhead	-
		LR: nitro	Reactive	Binder
		LR: nitrobenzene	Reactive	CovB, DNAB
		LR: terminal vinyl	Problematic	-
3d	No	HR: Michael acceptors (double bonds)	Warhead	-
		LR: terminal vinyl	Problematic	-
		LR: thiazole	Oxidative	-
3e	No	HR: Michael acceptors (double bonds)	Warhead	-
		LR: terminal vinyl	Problematic	-
3f	No	HR: Michael acceptors (double bonds)	Warhead	-
		LR: terminal vinyl	Problematic	-
3g	No	HR: Michael acceptors (double bonds)	Warhead	-
		LR: phenol		
		LR: terminal vinyl	Problematic	-
3h	No	HR: Michael acceptors (double bonds)	Warhead	-
		LR: phenol		
		LR: terminal vinyl	Problematic	-
5	No	not detected	-	-
6a	No	LR: Michael acceptors (double bonds)	Warhead	-
6b	No	LR: Michael acceptors (double bonds)	Warhead	-
6c	Yes	LR: Michael acceptors (double bonds)	Warhead	-
		LR: nitro	Reactive	Binder
		LR: nitrobenzene	Reactive	Cov_B, DNA_B
6d	Yes	LR: Michael acceptors (double bonds)	Warhead	-
		LR: thiazole	Oxidative	-
6e	Yes	LR: Michael acceptors (double bonds)	Warhead	-
8	No	not detected	-	-
9a	Yes	LR: Michael acceptors (double bonds)	Warhead	-
9b	Yes	LR: Michael acceptors (double bonds)	Warhead	-
9c	Yes	LR: Michael acceptors (double bonds)	Warhead	-
		LR: nitro	Reactive	Binder
		LR: nitrobenzene	Reactive	Cov_B, DNA_B
9d	Yes	LR: Michael acceptors (double bonds)	Warhead	-
		LR: thiazole	Oxidative	-
9e	Yes	LR: Michael acceptors (double bonds)	Warhead	-

Table S1. *Cont.*

ID	PPI Friendly	UMSs		
		Detected Functional Group	Main Mechanism	Alternative Mechanisms
10	No	-	-	-
11	No	-	-	-
Flu	No	HR: triazole	CYP450I	CYP450B
Ket	Yes	LR: cyclic acetal LR: imidazole	Problematic CYP-OXs	- CYP450B

LR: low risk UMSs detected; HR: high risk UMSs detected; - Indicates not detected UMSs/mechanisms; Warhead: functional group responsible for electrophilic protein-reactive false positives; Problematic: functional group with inherent or indirect toxicity; Reactive (metabolite): structural alert requiring metabolism to generate a reactive metabolite (can form adducts with endogenous biomolecules); Binder: indicate the existence of all following binding mechanisms: covalent binding (CovB: problematic group involved in covalent binding with biological macromolecules), CYP450 binding (CYP45B: structural alerts exhibiting tight binding to CYP450s enzymes), DNA binding (DNAB: structural alert with a propensity for DNA binding); Oxidative: oxidative ring scission catalyzed by P450 enzymes resulting in the formation of the corresponding α; CYP450I: structural alert requiring metabolism to generate a reactive metabolite which inhibits P450 enzymes; CYP-OXs: structural alert referring at a reactive metabolite used as substrate for CYP oxidation

Table S2. The results of VS carried out for detection of covalent inhibitors and PAINS (with resolution from the build-in decisional three).

ID	Detected Covalent Inhibitors	PAINS		
		Filter A	Filter B	Filter C
2	Michael acceptors (double bonds)	Accepted	Accepted	Accepted
3a	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate (90)	Accepted
3b	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate (90)	Accepted
3c	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate(90)	Accepted
3d	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate (90)	Accepted
3e	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate (90)	Accepted
3f	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate (90)	Accepted
3g	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate (90)	Accepted
3h	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate (90)	Accepted
5	-	Accepted	Accepted	Accepted
6a	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate (90)	Accepted
6b	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate (90)	Accepted
6c	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate (90)	Accepted
6d	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate (90)	Accepted
6e	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate (90)	Accepted
8	-	Accepted	Accepted	Accepted

Table S2. *Cont.*

ID	Detected Covalent Inhibitors	PAINS		
		Filter A	**Filter B**	**Filter C**
9a	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate [90]	Accepted
9b	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate [90]	Accepted
9c	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate [90]	Accepted
9d	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate [90]	Accepted
9e	Michael acceptors (double bonds) α, β-unsaturated carbonyl	Accepted	Intermediate [90]	Accepted
10	-	Accepted	Accepted	Accepted
11	-	Accepted	Accepted	Accepted
Flu	-	Accepted	Accepted	Accepted
Ket	-	Intermediate [246]	Accepted	Accepted

- Indicates not detected covalent inhibitors; Accepted: compounds with no structural alerts for PAINS and, concomitantly, satisfying the physicochemical filter (those results are displayed in Table 6); Intermediate: compounds which embeds low-risk structural PAINS alerts with a number of occurrences below the threshold (to not be confused with the intermediate thiazolin-4-one derivatives, which are reaction intermediates); [90] PAIN substructure filter name: ene_five_het_B; [246] PAIN substructure filter name: anil_di_alk_C.

Table S3. The results of VS carried out for drug safety profiling.

ID	4/400 Rule	3/75 Rule	Phospholipidosis	MedChem Rules (Rule Name)
2	good	warning	non inducer	isothiourea_sulfonamide
3a	good	bad	non inducer	isothiourea_sulfonamide
3b	good	bad	non inducer	isothiourea_sulfonamide
3c	good	good	non inducer	isothiourea_sulfonamide
3d	good	warning	non inducer	isothiourea_sulfonamide
3e	good	warning	non inducer	isothiourea_sulfonamide
3f	good	bad	non inducer	isothiourea_sulfonamide
3g	good	good	non inducer	isothiourea_sulfonamide
3h	good	good	non inducer	isothiourea_sulfonamide
5	good	warning	non inducer	isothiourea_sulfonamide
6a	good	bad	non inducer	isothiourea_sulfonamide
6b	good	bad	non inducer	isothiourea_sulfonamide
6c	good	warning	non inducer	isothiourea_sulfonamide
6d	good	warning	non inducer	isothiourea_sulfonamide
6e	good	warning	non inducer	isothiourea_sulfonamide
8	good	warning	non inducer	amino_naphthalene
9a	good	bad	non inducer	amino_naphthalene
9b	good	bad	non inducer	amino_naphthalene
9c	good	warning	non inducer	amino_naphthalene
9d	bad	warning	non inducer	amino_naphthalene
9e	bad	warning	non inducer	amino_naphthalene
10	good	warning	non inducer	isothiourea_sulfonamide
11	good	warning	non inducer	-
Flu	good	good	non inducer	-
Ket	good	bad	inducer	too_many_atoms aniline_no_h_newd acetal_both_in_ring

- Indicates not detected substructures according MedChem rules; isothiourea_sulfonamide: this rule is an acylating-class rule and is referring to the presence of isothiourea sulfonylated on imine nitrogen; amino_naphthalene: this rule is a nuisance-class rule and is referring at a type of interference that is not amenable to the substructure search, developed to flag interfering compounds that passed the substructure rules; too_many_atoms: this rule is a miscellaneous-class rule and is referring to the presence of over 25 non-hydrogen atoms; positive: this rule is an miscellaneous-class rule and is referring to the 50 demerits for each positive charge >1; aniline_no_h_newd: this rule is a nitrogen-class rule and is referring to the presence of aniline (cannot have *ortho* or *para* electron withdrawing group); acetal_both_in_ring: this rule is an aldehyde-class rule and is referring to the presence of acetal with both oxygen or sulphur in ring.

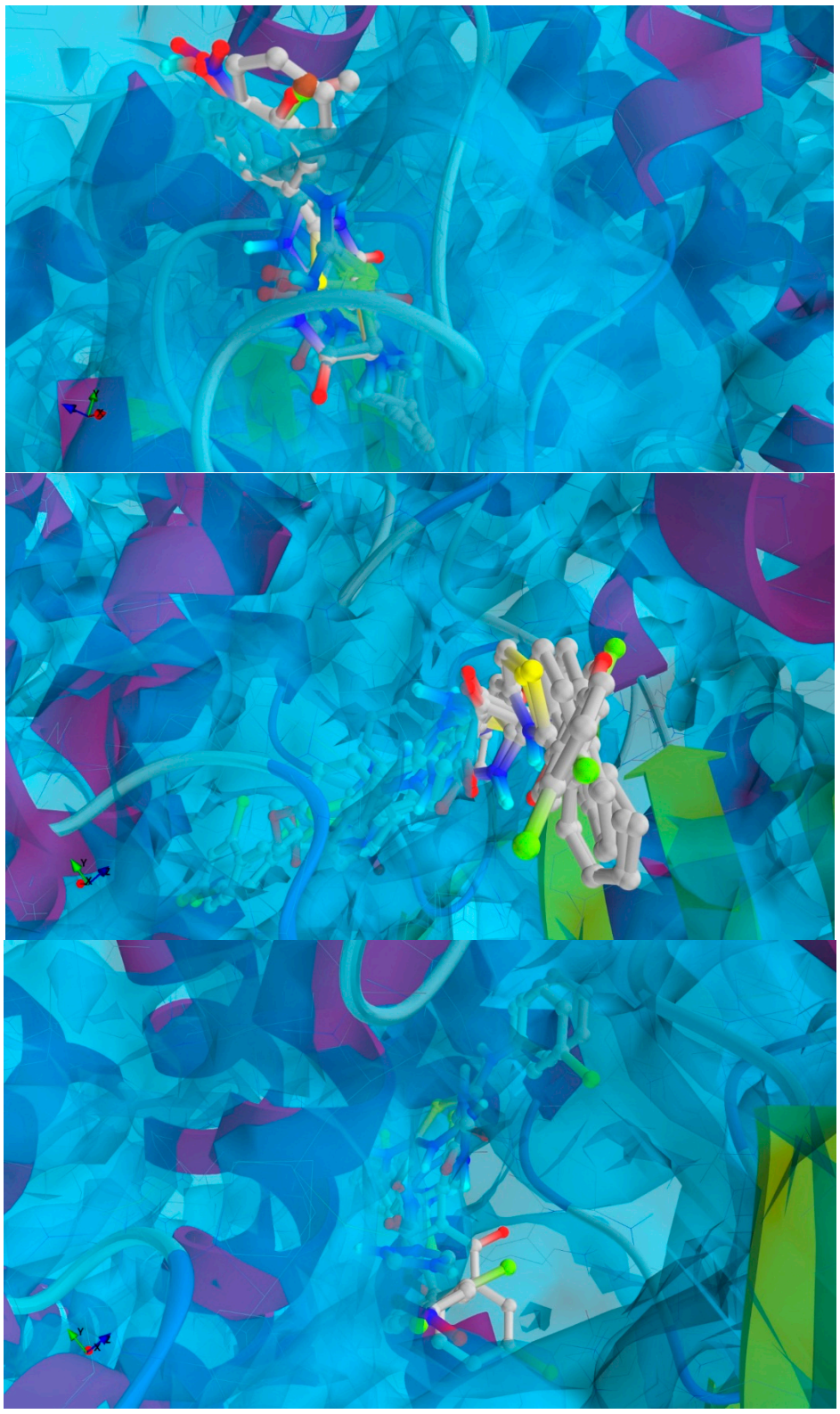

Figure S1. Detailed views of the docking poses of the screened compounds in the active site of lanosterol-14α-demethylase (target is depicted as thin sticks with secondary structure drawn as cartoon backbone with simulation of the molecular surface (semitransparent light blue) for a better understanding of tridimensional positioning in the active site of enzyme, meanwhile ligands are figured as sticks): group A (top image: at the entry of the active site): **2**, **3a**, **3c**, **3f–h**, **5**, **8**, **10** and **11**; group B (middle image: at opposite entry of the active site): **3b**, **3d–e**, **6d**, **9a–9c** and **Ket** (**9b–c** and **Ket** are binding in the distal region of this entry); group C (down image: deeply inside of the active site): **6a–c**, **6e** and **Flu**.