From our lab to a European library: bioprofiling our compounds through EU-OPENSCREEN

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Initiatives such as EU-OPENSCREEN offer academic medicinal chemistry groups a unique opportunity to deposit compound libraries into a European infrastructure and obtain systematic bioprofiling across diverse targets and organisms, a scale of characterisation rarely accessible to a single group. We report the first bioprofiling results from our contribution to the EU-OPENSCREEN Chemical Academic Library: a 120-compound 3-arylcoumarin series screened in 13 assay panels at five partner sites.

Invasive fungal infections caused by *C. auris*, *C. albicans* and *A. fumigatus* are a growing clinical threat, with rising azole resistance limiting the available treatments and highlighting the need for chemically diverse antifungal scaffolds. The dataset revealed marked, selective antifungal activity: 35, 21 and 11 compounds inhibited *C. auris*, *C. albicans* and *A. fumigatus* by ≥70% at 50 µM, respectively, and 10 were active against all three. This activity was highly selective, with no inhibition observed against *E. coli*, *K. pneumoniae* or *P. aeruginosa*. Moreover, none of the target-based assays showed significant activity, while all 120 compounds were inactive in three redox counter-screens, supporting the interpretation that the antifungal readouts primarily reflect inhibition of fungal growth rather than assay interference.

Structure-activity analysis showed that activity requires an o*rtho*-dioxygenated motif on the coumarin benzo ring. Masking the catechol as the diacetate retained this activity while eliminating the firefly-luciferase interference carried by the free catechols. The two diacetate hits, **MJM561** and **MJM560**, were pan-antifungal (82–98% inhibition across the three fungi), with high kinetic solubility and no flag in any of the six interference counter-screens. These compounds therefore provide promising starting points for subsequent MIC determination against both wild-type and fluconazole-resistant isolates.

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