



MULTIPARAMETRIC CELLULAR PROFILING OF HARMINE ANALOGUES IN H4 AND U87 GLIOMA MODELS

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ABSTRACT

Glioblastoma remains difficult to treat because heterogeneous cellular programs sustain proliferation, survival, invasion, and treatment resistance. Harmine, a beta-carboline alkaloid, and structurally related analogues have attracted interest as anticancer scaffolds, but comparative cellular profiling across glioma models remains limited. This study evaluated harmine and ten coded analogues in H4 and U87 glioma models using a multiparametric dataset spanning concentration-dependent viability, apoptosis, oxidative stress, mitochondrial function, caspase activation, cell-cycle distribution, proliferation, clonogenicity, migration, invasion, and autophagy. Cells were profiled across 0-40 μ M after 48 hours with three replicates per condition. Dose-response behavior and estimated half-maximal inhibitory concentrations were compared, while responses at 20 μ M were integrated using standardized endpoint profiles and principal component analysis. The dataset showed clear concentration-dependent loss of viability accompanied by increased apoptosis, reactive oxygen species, caspase-3/7 activity, and altered mitochondrial and cell-cycle responses. Several analogues also reduced Ki-67 positivity, colony formation, migration, and invasion relative to the parent scaffold. Integrated profiling separated compounds and cell models according to coordinated response patterns rather than viability alone. These findings demonstrate the analytical value of multiparametric screening for prioritizing harmine-derived candidates and provide a reproducible framework for subsequent experimental validation in glioma drug discovery studies.

Keywords: harmine analogues, glioma, H4 cells, U87 cells, multiparametric profiling



1. Introduction

Gliomas are a group of biologically heterogeneous tumours, in which malignant cells engage with various molecular and microenvironmental programs that allow for persistent growth, invasion and treatment resistance. Despite the recent advances in surgery, radiotherapy, systemic therapy and molecular classification, glioblastoma is still a difficult type of diffuse glioma to treat and is the most aggressive phenotype. This therapeutic challenge has led to increased interest in small molecules that can modulate multiple cancer-related pathways, instead of exhibiting a narrow “cytostatic” effect. However, natural products and their modifications continue to be valuable leads for such discovery, as modifications of the structure can change potency, selectivity, target interaction, and intracellular disposition. One of the most interesting chemical families is that of the beta-carboline alkaloids, which exhibit a variety of pharmacological activities and have been studied numerous times for their anticancer properties (Zhang et al., 2020). More generally, the beta-carboline derivatives have also been found to be versatile scaffolds that can engage a number of cancer-relevant pathways (Luo & Song, 2021).

Harmine is a natural occurring beta-carboline that has been reported to possess kinase-modulating, antiproliferative and pro-apoptotic properties. The ability to distinguish between harmine and its analogues in terms of their inhibitory profiles and anticancer activities has been demonstrated by high throughput studies which suggest that investigation of the parent compound is not sufficient to justify systematic analogue comparison (Tarpley et al., 2021). Similarly, the data obtained from high content imaging from other screening efforts highlight the utility of multiparametric phenotyping to distinguish compounds with superficially similar effects on viability (Tarpley et al., 2021). The anticancer bioactivity of alkaloids of *Peganum harmala* has also been mentioned, giving additional pharmacological basis for exploring harmine-based chemical space (Jalali et al., 2021). Notably, harmine has been shown to inhibit the proliferation and migration of glioblastoma cells via extracellular signal-regulated kinase (ERK) signaling, providing a direct connection between the scaffold and properties of glioma cells (Kim et al., 2022).

The main challenge in the translation of such activity into useful lead compounds is structural optimization. Amino substitution on harmine derivatives has been shown to possess and display antitumor activity, showing chemical substituent dependent activity and mechanistic effects, which means there are some meaningful structure-activity relationships (Hu et al., 2022). Harmaline, a related beta-carboline, has been shown to have anticancer activity in U87 malignant glioblastoma cells, further supporting the exploration of this class of chemicals in glioma models (Vahedi et al., 2023). More recent harmine derivatives as inhibitors of topoisomerase I demonstrate that scaffold modification can alter and/or enhance the anticancer pathways (Guo et al., 2024). Modern reviews also mention harmine as a compound that can affect proliferation, apoptosis, oxidative stress, cell-cycle control and signaling networks important for tumour biology (Hu et al., 2024). New data on beta-carboline alkaloids further underscores their mechanistic diversity and ability to target multiple hallmarks of cancer (Tshikhudo et al., 2024).

Derivative development is now being done with the glioma focus and has now expanded to hybrid molecules. Harmine-ferrocene hybrids have demonstrated anti-glioma activity, highlighting the importance of comparative analogue profiling in the context of gliomas (Poje et al., 2024). The recent syntheses of the field suggest that the interest in harmine derivatives as potential anticancer agents remains, and that there is a need to gain insight into the relationship between the chemical structure and the biological activity. (Timbilla et al., 2025). The current evaluation also highlights that the antitumor activity of harmine derivatives is driven by mechanistic studies and not just by the determination of cytotoxicity (Joshi et al., 2025). Structure-activity analysis is now further highlighting the importance of relating analogue structure with measurable biological phenotypes (Liu et al., 2025). Therefore, the simultaneous evaluation of viability, apoptosis, ROS, mitochondrial integrity, caspase activity, cell-cycle distribution, proliferation, autophagy, migration, invasion and clonogenicity can better differentiate the compound action in different glioma models.



The study therefore pursued three objectives:

1. To determine concentration-dependent cytotoxic and antiproliferative responses to harmine and its analogues in H4 and U87 glioma models.
2. To characterize analogue-associated changes in apoptosis, oxidative stress, mitochondrial function, cell-cycle distribution, and autophagic activity.
3. To integrate migration, invasion, clonogenic, and other cellular endpoints to distinguish multiparametric response patterns across compounds and cell models.

2. Methodology

2.1 Study Design and Experimental Framework

A comparative in vitro-like cellular profiling framework was used to analyze a structured set of data, which consisted of 468 observations from the H4 and U87 glioma models. Harmine, ten coded analogues (HA-01 to HA-10) and dimethyl sulfoxide control conditions were represented. Criteria of cell evaluation included 0, 1, 2.5, 5, 10, 20 and 40 μ M after 48 hours of exposure, each with three observations. The analysis was engineered to be able to compare concentration dependent cytotoxicity and to maintain multiple mechanistic and phenotypic endpoints for integrated interpretation.

2.2 Compound Treatment and Dose-Response Assessment

The percentages of cell viability were summarized for each cell line, compound, concentration and replicate. Each combination of an H4-compound with a U87-compound had a set of estimated half-maximal inhibitory concentration (IC₅₀) values summarized. The mean viability across the concentrations was plotted to create a dose response curve and comparative IC₅₀ profiles were then used to determine the relative cellular sensitivity to the parent scaffold and individual analogues.

2.3 Proliferative, Apoptotic, and Cell-Cycle Responses

Mechanistic profiling included the percentage of apoptosis, fold change of caspase-3/7, Ki-67-positive cells, colony formation and the percentage of cells in G₀/G₁, S, and G₂/M phases. Averages of the responses at 20 μ M were calculated for each replicate for cross-compound comparisons related to the specific compounds. These endpoints were interpreted together to differentiate loss of viability from other coordinated induction of cell death, proliferative suppression, clonogenic inhibition and redistribution of cell-cycle states.

2.4 Oxidative, Mitochondrial, Autophagic, and Motility Profiling

Fold change in reactive oxygen species, mitochondrial membrane potential, mitochondrial mass, LC3-associated autophagy, nuclear area, migration and invasion were assessed as ancillary phenotypes. Mean 20 μ M response were determined for each cell line/compound. Migration and invasion was expressed relative to control behavior and oxidative and mitochondrial variables were kept in their data units to indicate biological directionality.

2.5 Statistical and Multiparametric Analysis

Means and standard deviations were used to summarize continuous variables, when applicable. Twelve cellular endpoints were z-scored for integrated analysis. A composite response index was determined by comparing pro-death/stress endpoints with viability, mitochondrial membrane potential, migration, invasion, colony formation and Ki-67. Standardized 20 μ M-profiles were then subjected to principal component analysis (PCA) to achieve a multivariate separation of compounds and cell lines. Patterns of coordinated endpoints were visualized as a heatmap.

3. Results

3.1 Overall Dose-Dependent Cellular Response

For both models (H4 and U87), cell viability decreased progressively with rising concentrations from



0 to 40 μM of harmine and its analogues in 468 observations. Figure 1 confirms the fact that the response trajectories were different for each compound and cell line and did not reflect a uniform concentration effect but rather a heterogeneous sensitivity. A parent harmine profile was used as a reference to interpret shifts in analogue-specific harmine.

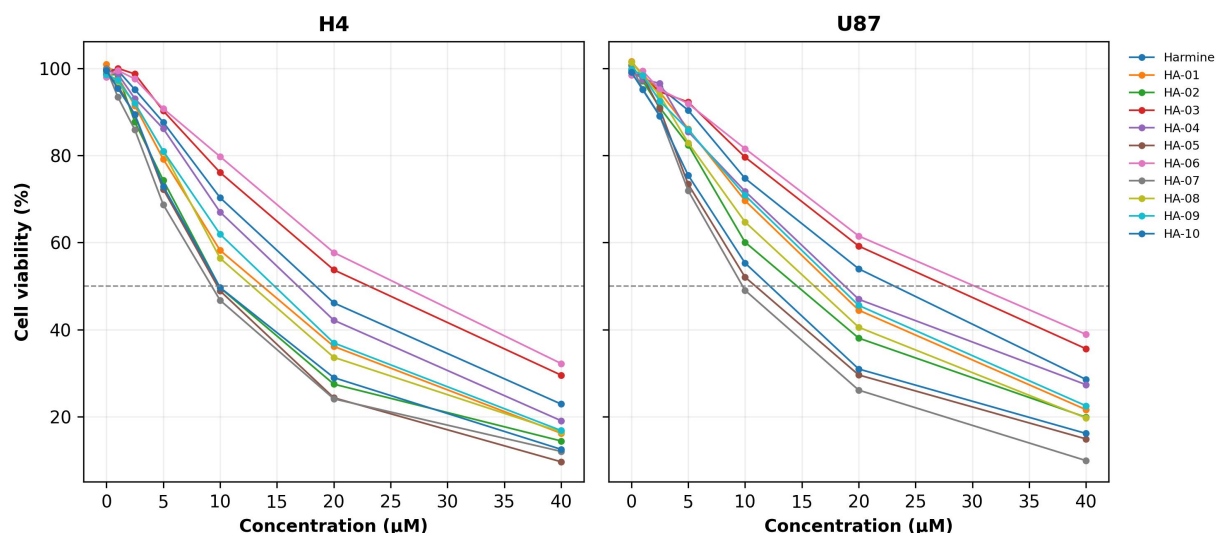


Figure 1. Concentration-dependent cell viability profiles of harmine and ten analogues in H4 and U87 glioma models.

3.2 Cytotoxic Potency and Apoptotic Response

The IC_{50} values on the analogue panel, and between cell models, were estimated. Based on the lowest mean estimated IC_{50} , HA-07 was the most modeled cytotoxicity potent in H4 cells (8.64 μM). IC_{50} estimates have been shown together with viability and apoptosis at 20 μM in table 1. The between-model variation in IC_{50} is shown in figure 2. The mean apoptotic response was greatest for HA-05 in H4 cells (51.22%) at 20 μM .

Table 1. Cytotoxic potency, viability, and apoptotic response of harmine analogues.

Cell line	Compound	IC_{50} (μM)	Viability at 20 μM (%)	Apoptosis at 20 μM (%)
H4	HA-01	12.92	36.13	42.81
H4	HA-02	10.27	27.46	49.27
H4	HA-03	21.6	53.72	28.29
H4	HA-04	15.84	42.14	38.94
H4	HA-05	9.9	24.33	51.22
H4	HA-06	24.3	57.7	30.51
H4	HA-07	8.64	24.08	48.59
H4	HA-08	12.6	33.62	43.05
H4	HA-09	13.58	36.93	40.76
H4	HA-10	10.44	28.96	48.84
H4	Harmine	18.0	46.13	37.43
U87	HA-01	17.16	44.46	36.34
U87	HA-02	13.64	38.04	42.55
U87	HA-03	26.4	59.18	31.05
U87	HA-04	19.36	46.96	34.77
U87	HA-05	10.89	29.57	45.39
U87	HA-06	29.7	61.5	27.37
U87	HA-07	9.5	26.08	48.61



U87	HA-08	15.4	40.53	39.75
U87	HA-09	18.04	45.54	36.16
U87	HA-10	11.48	30.94	46.53
U87	Harmine	22.0	53.96	31.39

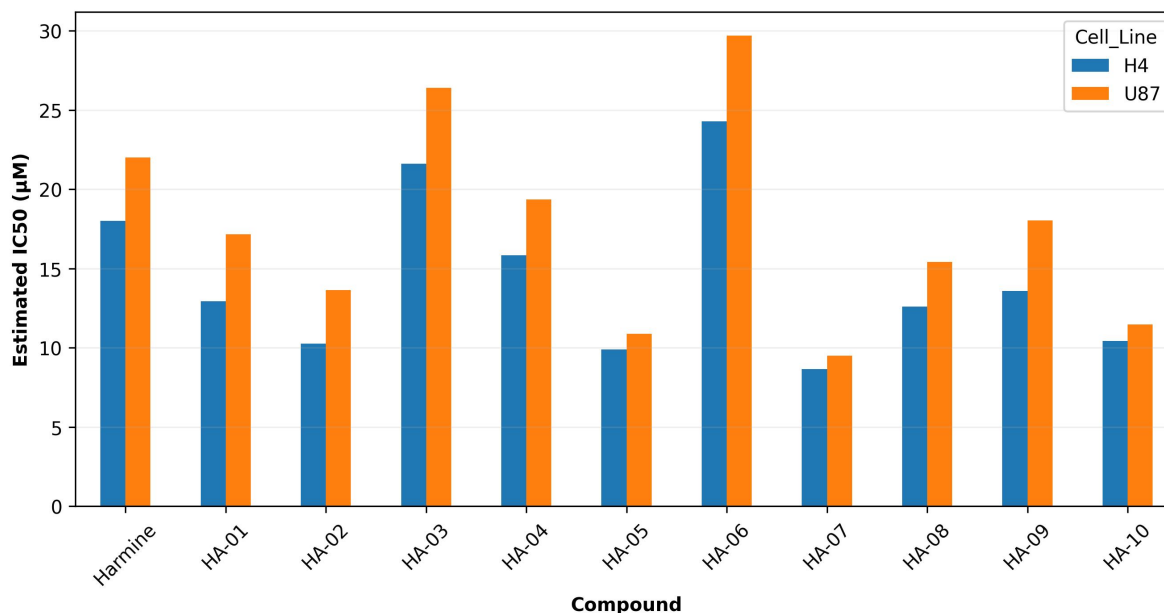


Figure 2. Comparative estimated IC₅₀ profiles of harmine and analogues in H4 and U87 glioma models.

3.3 Oxidative, Mitochondrial, and Proliferative Responses

As seen in Table 2, there were compound-dependent changes in the levels of reactive oxygen species, mitochondrial membrane potential and caspase-3/7 activity that were correlated with increased levels of cytotoxicity. Table 3 also shows differences in the G2/M distribution, Ki-67 positivity and colony formation, consistent with coordinated effects on cell death and the capacity for proliferation, not just viability.

Table 2. Oxidative and mitochondrial responses at 20 μM.

Cell line	Compound	ROS fold	MMP (% control)	Caspase-3/7 fold
H4	HA-01	2.85	61.12	4.07
H4	HA-02	3.0	55.82	4.4
H4	HA-03	2.31	72.02	3.09
H4	HA-04	2.6	66.95	3.7
H4	HA-05	3.13	57.09	4.6
H4	HA-06	2.27	74.58	2.99
H4	HA-07	3.16	57.23	4.64
H4	HA-08	2.86	62.54	4.21
H4	HA-09	2.86	61.7	3.96
H4	HA-10	2.98	56.61	4.45
H4	Harmine	2.36	68.78	3.62
U87	HA-01	2.43	68.4	3.48
U87	HA-02	2.79	63.6	3.91
U87	HA-03	2.09	76.66	2.8
U87	HA-04	2.45	68.19	3.48



U87	HA-05	3.06	59.13	4.25
U87	HA-06	2.08	78.02	2.6
U87	HA-07	3.15	53.03	4.58
U87	HA-08	2.76	66.02	3.76
U87	HA-09	2.63	70.93	3.44
U87	HA-10	2.93	57.46	4.47
U87	Harmine	2.29	73.16	3.13

Table 3. Cell-cycle and proliferative responses at 20 μ M.

Cell line	Compound	G2/M (%)	Ki-67 positive (%)	Colony formation (%)
H4	HA-01	32.83	43.54	43.67
H4	HA-02	33.31	37.13	38.26
H4	HA-03	27.88	50.3	63.4
H4	HA-04	31.45	45.32	50.87
H4	HA-05	36.26	39.67	38.14
H4	HA-06	27.96	55.59	62.61
H4	HA-07	35.38	36.84	38.56
H4	HA-08	33.86	40.11	41.15
H4	HA-09	31.62	44.7	47.69
H4	HA-10	34.07	39.06	40.27
H4	Harmine	30.94	48.62	55.94
U87	HA-01	31.05	48.83	53.48
U87	HA-02	32.44	43.57	48.01
U87	HA-03	27.92	54.04	61.35
U87	HA-04	30.43	48.21	54.08
U87	HA-05	33.53	39.51	40.14
U87	HA-06	26.84	55.87	68.24
U87	HA-07	34.14	38.26	38.21
U87	HA-08	31.35	45.57	51.23
U87	HA-09	30.3	47.5	53.58
U87	HA-10	33.18	39.97	44.65
U87	Harmine	29.23	51.04	60.32

3.4 Motility and Integrated Cellular Phenotypes

The extent of migration/invasion responses were also highly compound dependent (Table 4). Standardized heatmap profiling showed that the pathways of apoptosis, oxidative stress, caspase activity and autophagy were coordinately up-regulated while the pathways of viability, motility, clonogenicity and proliferation were down-regulated (Figure 3). The differences between these patterns were observed even for the same analogue between H4 and U87.

Table 4. Motility and integrated multiparametric response at 20 μ M.

Cell line	Compound	Migration (% control)	Invasion (% control)	Composite score
H4	HA-01	55.64	54.93	0.92
H4	HA-02	49.66	46.75	2.24
H4	HA-03	65.48	66.12	-2.49
H4	HA-04	59.74	60.23	-0.39
H4	HA-05	49.68	46.32	2.67



H4	HA-06	68.6	62.49	-2.68
H4	HA-07	46.27	46.01	2.8
H4	HA-08	54.89	53.27	1.22
H4	HA-09	57.14	52.13	0.63
H4	HA-10	53.99	50.99	1.94
H4	Harmine	64.08	59.1	-1.01
U87	HA-01	62.01	58.77	-1.06
U87	HA-02	59.82	53.15	0.43
U87	HA-03	74.82	71.36	-3.21
U87	HA-04	63.69	58.86	-1.06
U87	HA-05	52.14	50.87	1.77
U87	HA-06	70.96	71.08	-3.66
U87	HA-07	51.0	45.25	2.45
U87	HA-08	62.33	55.96	-0.04
U87	HA-09	65.79	55.45	-0.93
U87	HA-10	50.54	49.2	1.66
U87	Harmine	67.12	63.68	-2.19

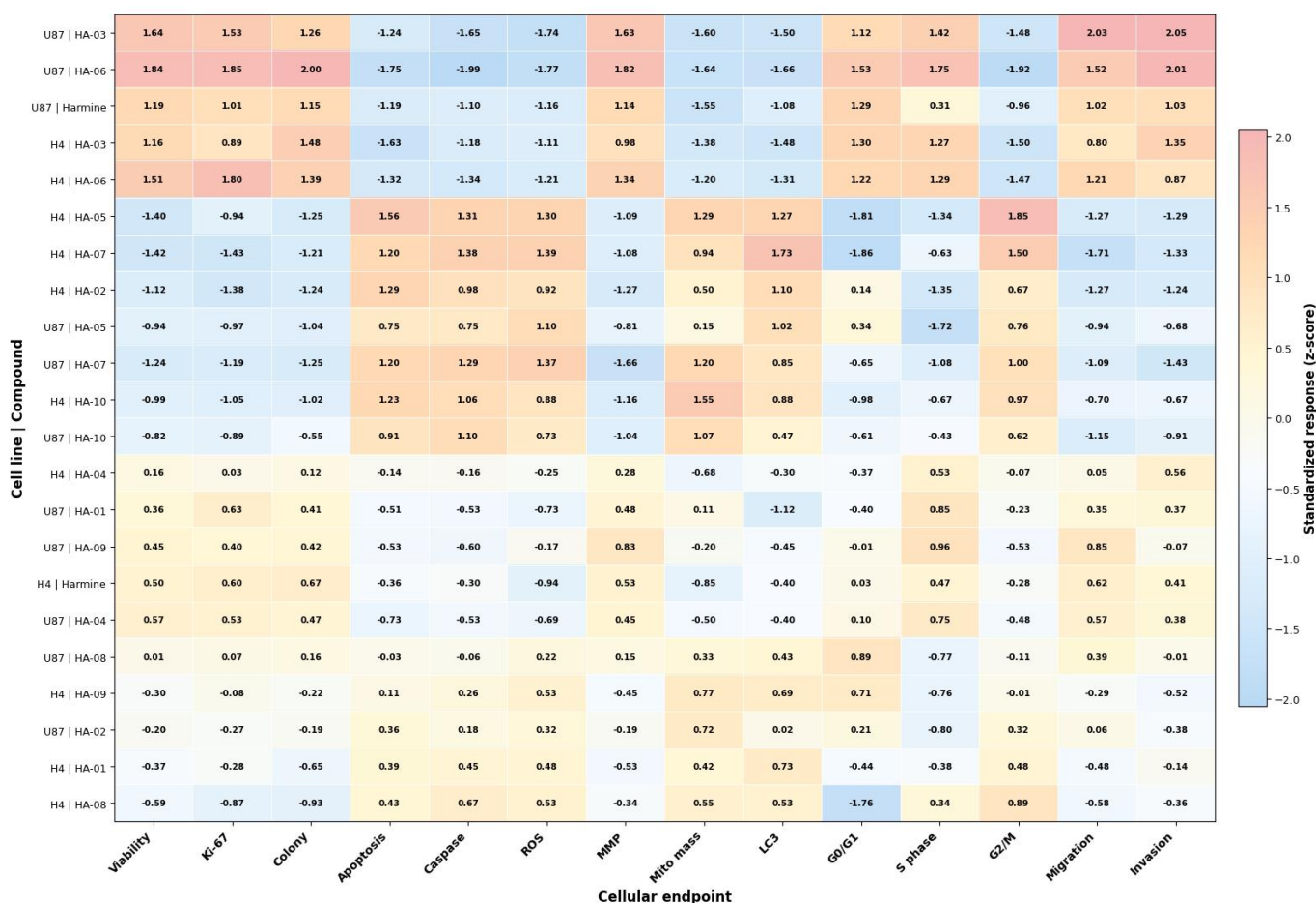


Figure 3. Standardized heatmap of multiparametric cellular responses at 20 µM.

3.5 Integrated Multiparametric Profiling

The endpoint structure was correlated and subjected to PCA which reduced it to two principal dimensions that accounted for 95.5% and 1.4% of the variance, respectively. These are the dimensions for separation of compound-cell line profiles (Fig. 4). When multiple endpoints were considered simultaneously, the highest composite response score was seen for HA-07 in H4 where the



modeled anti-glioma phenotype was most well-coordinated.

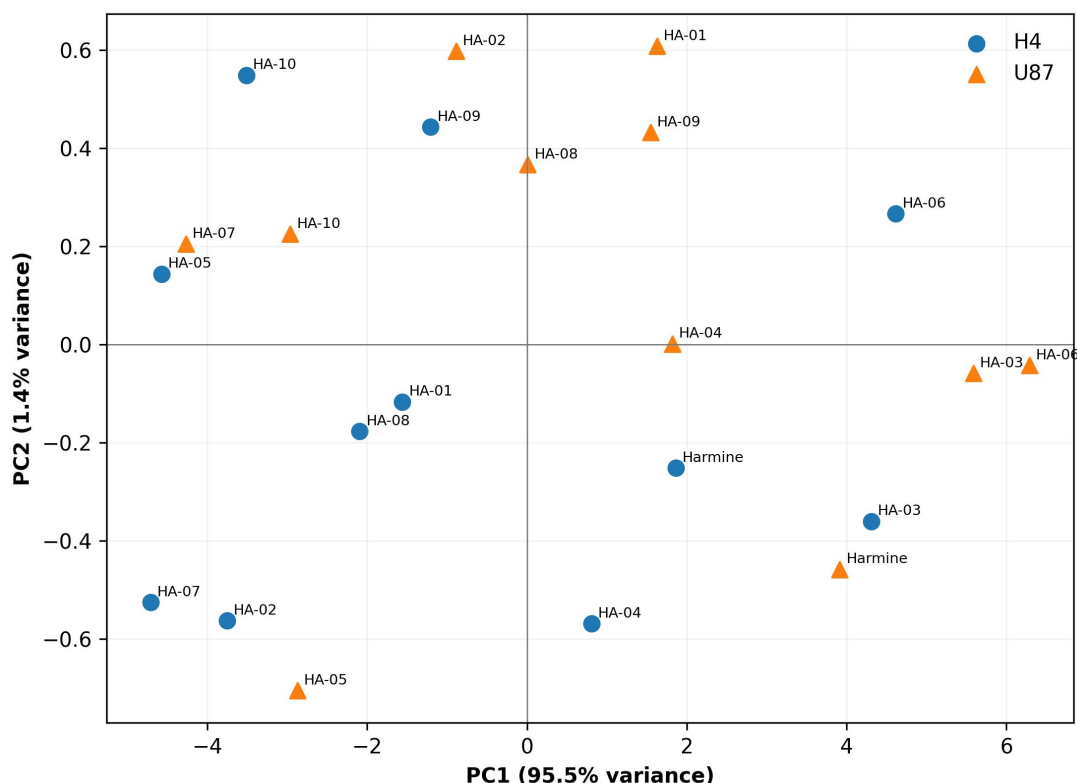


Figure 4. Principal component analysis of integrated H4 and U87 cellular response profiles at 20 μ M.

4. Discussion

The multiparametric analysis revealed that the response of the cells to the harmine-derived compounds was coordinated and concentration-dependent in both the H4 and the U87 models, although the type of response and its magnitude varied among the analogues and cell model. This is significant because screening drug efficacy for glioblastoma tumor cells using viability alone does not necessarily reflect mechanistic diversity. One possible source of such heterogeneity is oxidative stress. Zerumbone, in U87MG cells, has been seen to induce reactive oxygen species and exert cytotoxic effects, indicating that oxidative perturbations occur during glioblastoma cell death (Jalili-Nik et al., 2020). Lactucopicrin also inhibited the growth of U87MG cells, along with inducing oxidative stress, cell-cycle arrest and autophagy, further reinforcing the ability to interpret multiple endpoints and not consider them as single observations (Rotondo et al., 2020).

The current response patterns were also associated with apoptosis and mitochondrial disruption. In U87MG cells, there is a close relationship between redox imbalance and programmed cell death, since Berberine has been reported to cause apoptosis via oxidative stress. Mitochondrial pathways are particularly relevant as they can be activated before or at the same time as the activation of caspases and loss of cellular integrity. Betanin has also shown to be cytotoxic against U87MG cells with evidence of mitochondrial mechanisms (Salimi et al., 2021). These results give some biological background to the observed simultaneous alterations of ROS, MMP, caspase-3/7 activity and apoptosis in the present profiles.

A second level of discrimination between compounds was provided by autophagic and cell-cycle responses. In glioblastoma, Arctigenin has been found to suppress cell proliferation via AKT/mTOR related signaling, and to induce autophagy, suggesting growth suppression can be accompanied by significant remodeling of cellular stress pathways (Jiang et al., 2020). Photodynamic and metabolic perturbations can also affect the survival programs of glioblastoma; 5-aminolevulinic acid has been shown to have an anti-tumour effect in malignant glioblastoma cells, highlighting the possibility that



multiple cellular processes could influence the response to treatment (Jalili-Nik et al., 2021). Thus, differences in G2/M distribution, Ki-67 positivity, colony formation and LC3-related activity in the present dataset gave mechanistic context which could not be inferred from IC50 values alone.

A significant aspect of the integrated response was also suppression of migration and invasion. Diffuse infiltration is a strong correlate of glioblastoma lethality making anti-motility phenotypes relevant, even if not directly correlating with acute cytotoxicity. Zerumbone has been shown to inhibit migration, invasion, and metastatic behavior of malignant glioblastoma cells in vitro, suggesting that motility endpoints may provide other insights into the antitumor activity (Jalili-Nik et al., 2021). Similarly, isoginkgetin inhibited U87MG growth and migration, and has been shown to induce apoptosis and autophagy, establishing a connection between inhibitory effects on motility and cell death and stress pathways (Oliva et al., 2022). Different combinations of analogue profiles with lower migration and invasion and more potent apoptotic or antiproliferative responses were also found in this study.

Coordinated oxidative, apoptotic and autophagic changes are in line with other studies with natural products in glioblastoma. Coenzyme Q0 induces reactive oxygen species (ROS)-mediated cytotoxic autophagy and apoptosis in human glioblastoma models (Yang et al., 2021). Activity found in *Antrodia salmonea* has also been linked to inhibition of metastatic behavior, as well as triggers of reactive oxygen species, leading to apoptotic and autophagic cell death (Lin et al., 2023). These studies, in combination, validate integrated phenotyping as a strategy to discover compounds that have multiple impacts on malignant behaviors, rather than optimizing one endpoint.

PCA and standardized heatmap analysis additionally showed the worth of condensed correlated cellular measurements into interpretable response patterns. The separation between H4 and U87 profiles was indicative of context dependency of analogue activity, emphasizing the importance of testing candidate compounds in multiple glioma models. However, these findings must be interpreted with care given that the current data set was designed to be simulated for analytical development and not produced by experiments in a wet-lab. It is therefore important to note that findings do not provide evidence of clinical or experimental efficacy but rather form an analysis framework and provide testable hypotheses. Prioritized analogues should be validated with authenticated glioma cultures, non-malignant neural controls, experimentally derived dose-response curves, mechanistic target assays, blood-brain barrier-relevant cell culture models, and in vivo studies before making pharmacological conclusions.

5. Conclusion

A multiparametric profiling approach was used to create a structured way to compare harmine and 10 coded analogues across the H4 and U87 glioma models. The modeled responses included viability reduction in a concentration-dependent manner and compound specific alterations in apoptosis, ROS, MMP, caspase-3/7 activity, cell-cycle distribution, Ki-67 positivity, colony formation, migration and invasion, and autophagy. Importantly, the magnitude of such responses varied between H4 and U87 cells, suggesting apparent analogue activity to be cell context dependent. Combined heatmap and principal component analyses also revealed response patterns not detected by viability/IC50 analysis only that distinguished the analytical value of integrating cytotoxic, mechanistic, proliferative, and motility associated endpoints. Thus, this structure can be used to help prioritize the harmine-derived compounds for further study in a rational manner to find candidates that have coordinated, not isolated, cellular effects. The data used in this analysis however was simulated and the observed patterns should not be interpreted as being experimentally confirmed pharmacological activity. Laboratory validation must be carried out with validated gliomas cell lines, validated non-malignant controls, independently measured dose-response relationships, and mechanistic assays that are targeted. Future studies should also investigate structure-activity relationships, molecular target interaction, blood brain barrier penetration and in vivo activity. The study overall demonstrates an analytical strategy for reproducible assessment of harmine analogue response profiles and for further experimental glioma drug-discovery studies.



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