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Preliminary Evaluation of New Benzenesulfonamides as Anticancer Agents Against DU-145 Prostate Cancer Cells

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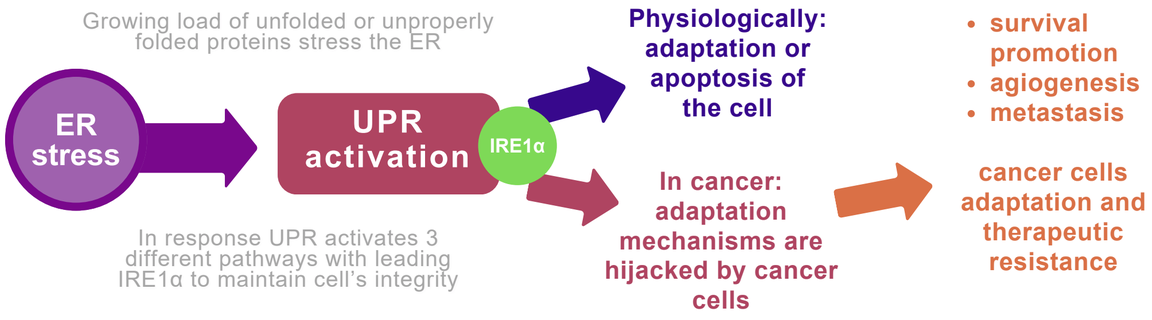
INTRODUCTION & AIM



Prostate cancer, the most common malignancy among European men, underscore the urgent need for novel therapeutic strategies. Unfolded Protein Response main sensor protein IRE1α (here marked as IRE1) has been implicated in tumor growth, survival, and resistance to therapy, making it an attractive, potential pharmacological target [1,2].

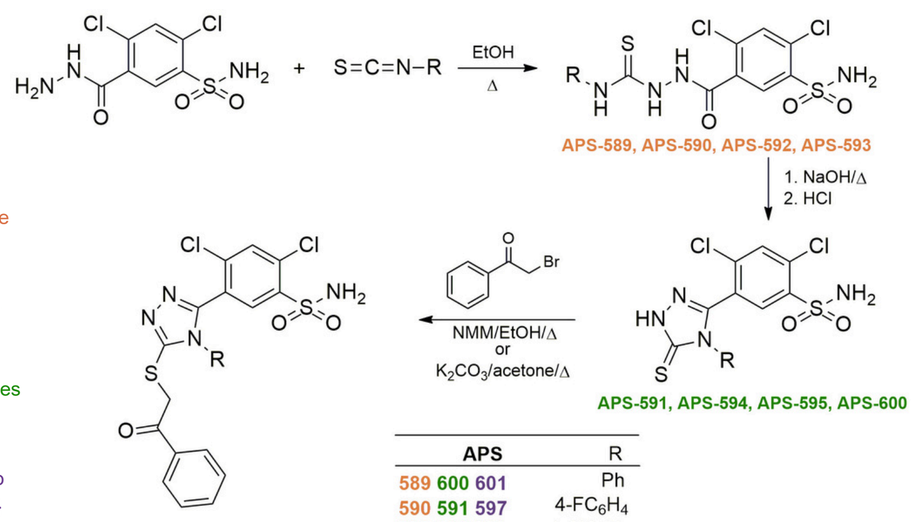
Benzenesulfonamides are a promising class of chemical compounds with reported anticancer activity [3,4]. We designed and synthesised our own series of compounds, yet their link to UPR/IRE1 signaling has not been investigated. Current IRE1 modulators remain without clinical validation, emphasizing the demand for more effective and selective agents.

Aim of the study: We performed a preliminary evaluation of 12 previously synthesized benzenesulfonamide derivatives for their cytotoxic potential in cervical prostate cancer (DU-145) cell models, as a first step toward identifying compounds that may act through IRE1-associated mechanisms.

METHOD

1. New Benzenesulfonamide Derivatives Design and Synthesis

Based on their distinct structural cores, the twelve synthesized benzenesulfonamide derivatives (APS) were classified into three main groups (synthesis scheme below). The crude products were purified by recrystallization or column chromatography. The chemical structures of all compounds were confirmed by nuclear magnetic resonance (^{1}H NMR) and infrared (IR) spectroscopy. The purity of the new derivatives was verified by melting point determination and consistency of spectral data.



Group 1: 2-(2,4-dichloro-5-sulfamoylbenzoyl)-*N*-arylhydrazinecarbothioamide derivatives

Group 2: 2,4-dichloro-5-(4-aryl-5-thioxo- 4,5-dihydro-1*H*-1,2,4-triazol-3-yl) benzenesulfonamide derivatives

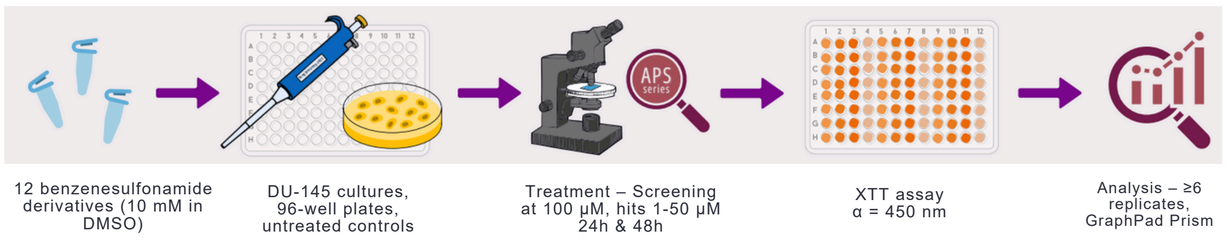
Group 3: 2,4-dichloro-5-{5-[(2-oxo-2-phenylethyl)thio -4-aryl-4*H*-1,2,4-triazol-3-yl} benzenesulfonamide derivatives

APS-597, APS-598, APS-599, APS-601

APS	R
589 600 601	Ph
590 591 597	4-FC_6H_4
592 594 598	4-ClC_6H_4
593 595 599	3,4-diClC_6H_3

2. Cytotoxicity Assessment

Stock solutions of tested compounds were prepared and solubility in culture media was verified. Human prostate (DU-145) cancer cells were grown in 96-well plates, with untreated cells serving as controls. Cytotoxicity was evaluated spectrophotometrically using the XTT assay (Roche), after 24h and 48h treatment. The initial screening included 12 derivatives at 100 μM. The most active compounds were further tested across a concentration range (1, 2.5, 5, 10, 25, and 50 μM). As for the results, inhibition of cell growth was expressed as a percentage of untreated controls. For the most potent derivatives the IC_{50} values were determined.



RESULTS & DISCUSSION

Screening (100 μM, 24h i 48h)

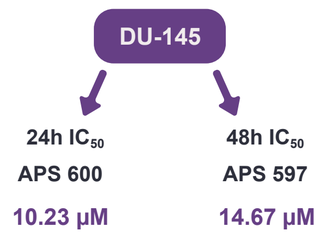
4 compounds with the best cytotoxic properties were chosen for further testing in a concentration range 1-50 μM: **APS 597, APS 598, APS 599, and APS 600.**

Hit selection and dose-response

Cytotoxic evaluation revealed an increasing potency trend from Group 1< Group 2< Group 3 of derivatives.

The incorporation of a 1,2,4-triazole moiety, particularly bearing thioether–substituted aryl ketone functionality, was associated with enhanced cytotoxicity. APS 600 (Group 2) demonstrated the strongest activity across all tested derivatives despite sharing the same phenyl substituent as the Group 3 derivative APS 601.

Among the benzenesulfonamide derivatives tested, APS 597 and APS 600 showed the strongest cytotoxic effects against DU-145 prostate cancer cells.

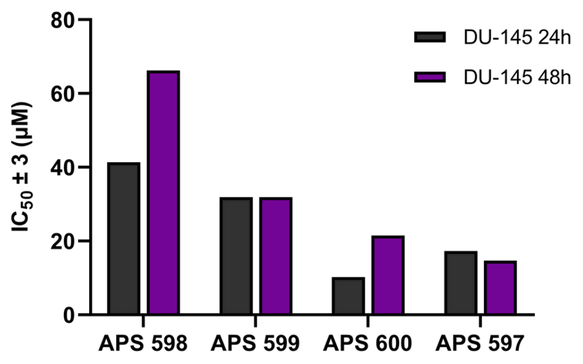


The consistent potency of Group 3 derivatives across both time periods highlights its substitution pattern as a promising framework for further structural optimization and mechanistic studies.

% of inhibition (vs. control)

	DU-145 24h	DU-145 48h
APS 589	6	6
APS 590	4	8
APS 591	44	66
APS 592	3	8
APS 593	12	27
APS 594	5	4
APS 595	41	33
APS 597	83	92
APS 598	70	90
APS 599	78	91
APS 600	88	91
APS 601	53	84

Several of 12 benzenesulfonamide derivatives showed marked cytotoxicity in DU-145 cells at 100 μM, with stronger effects generally observed after 48h treatment.



IC_{50} values of APS compounds in DU-145 cells after 24h and 48h reveal time-dependent cytotoxicity and compound-specific potency.

The 1,2,4-triazole moiety is presumed to improve binding to intracellular targets through polar interactions, while the thioether linkage likely increases lipophilicity to aid cell entry.

The higher potency of APS 600 compared with another analogue APS 601, despite an identical benzyl substituent, may originate from steric crowding or intramolecular π–π stacking between the two nearby benzyl groups. That may force the molecule into a conformation that is less favorable for binding.

CONCLUSION

- New benzenesulfonamides exhibit cytotoxic properties against prostate cancer DU-145 cell line
- Lead compounds exhibit distinct time-dependent activity: APS 600 shows the most rapid effect (24h), while APS 597 demonstrates the highest sustained potency (48h)
- Structural analysis suggests that 1,2,4-triazole moiety, particularly bearing thioether–substituted aryl ketone functionality is a key structural feature for enhancing anticancer activity

FUTURE WORK / REFERENCES

Next steps of our research will revolve around broadened cytotoxicity screening of the most potent compounds and mechanistic studies via qPCR analysis of UPR-related genes to assess the connection between benzenesulfonamide cytotoxic effect and IRE1α.

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