

Synthesis and Formulation of a p53 Inhibitor to Control Side Effects of Cancer Radiotherapy

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ABSTRACT

An anti-apoptosis agent, 1Y-41, was synthesized and formulated into ointment form. Prevention of irradiation induced skin damage and promotion of healing were observed in drug treated hairless mice.

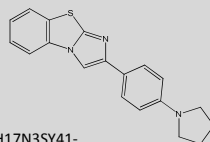


Figure 1- 1Y-41
Chemical Formula: C19H17N3SY41-
Exact Mass: 408.04
Molecular Weight: 408.35
m/z: 408.02 (100.0%), 409.02 (22.5%), 410.02 (4.9%), 410.03 (2.0%)
Elemental Analysis: C, 55.88; H, 4.20; N, 10.29; S, 7.85; Y, 21.77

INTRODUCTION

Previous studies have shown that 1Q-229, the HBr salt of 1Y-41, prevents and rescues thymocytes from irradiation-induced and dexamethasone induced apoptosis in vitro. In vivo, systemic treatment of mice with 1Q229, 30 min before lethal dose of γ -irradiation, prevents the irradiation-induced death.

The main goal of this project was to investigate if this category of anti-apoptosis agents can prevent irradiation induced skin damage when applied topically.

This project was divided and completed in three separate phases: synthesis, formulation, and animal experiments.

METHODS

SYNTHESIS

1Q229 was synthesized by alkylation of 2-aminobenzothiazole by 2-bromo-1-(4-(pyrrolidin-1-yl)phenyl)ethanone followed by ring closure in a polar protic solvent.

1Y-41 was synthesized from 1Q229 by two-phase basification-extraction in NaOH/Ethyl acetate system.

See Figure 2 for details.

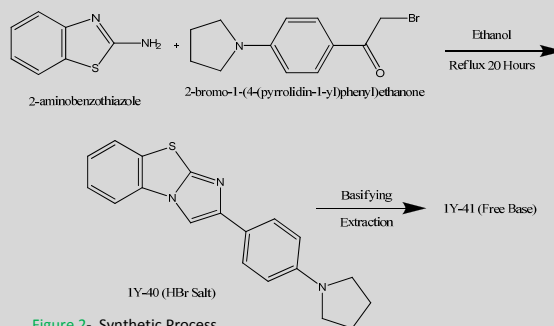


Figure 2- Synthetic Process

FORMULATION

Both 1Q229 and 1Y-41 were formulated into ointment form by classic dispersion method using light mineral oil as levigating agent and a commercially available base, Aquaphor. (Figure 3)

Formulations were kept under extreme conditions of heat, oxygen, and light for stability assays.

Figure 3- Vehicle alone and 2% 1Y-41



ANIMAL EXPERIMENTS

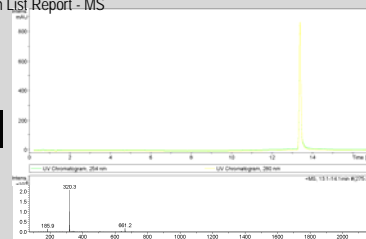
- Partial irradiation 10Gy on Day 0, 1, and 2 (Figure 4)
- 2 hours before irradiation, 1Y41 or vehicle was applied
- Observation up to day 21



Figure 4- Radiation shield

RESULTS

Figure 5- Compound Mass Spectrum List Report - MS



SYNTHESIS

ANIMAL EXPERIMENTS

Protection (Day 12)



Figure 6- Vehicle vs. 1Y-41 (stained)

Figure 7- Vehicle vs. 1Y-41 (unstained)

Healing (Day 19)

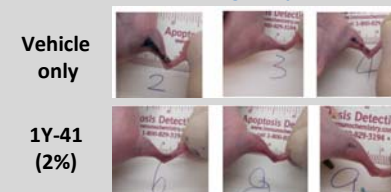


Figure 8- Vehicle vs. 1Y-41 (stained)

Control mice still have ulcer, while ulcer in 1Y-41 treated mice almost disappears.

DISCUSSION

Preliminary studies suggest pre-treatment of animals with 1Y-41, compared to vehicle treated control animals, attenuates the severity of the skin damage and promotes healing following localized gamma radiation exposure. The mechanism of activity of 1Y-41 is the subject of further investigation.

ACKNOWLEDGMENTS

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REFERENCES

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- 2 - Barchéath SD et al.Bioorg Med Chem Lett. 2005 Apr 1;15(7):1785-8.