The Development of 1-(1H-indol-3-yl)-2-(methylamino)ethan-1-ol (IMAE) as a Prophylactic Medical Countermeasure Against Acute Radiation Syndrome (ARS)

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INTRODUCTION

Currently there are no FDA approved medical countermeasures to protect military personnel entering radioactively contaminated areas. The Nebraska Drug Discovery and Development Pipeline (ND^3P) is collaborating with the National Strategic Research Institute (NSRI) to develop new medical countermeasures to address the operational requirements of the Department of Defense (DOD). The ND^3P is a multidisciplinary, cross-campus initiative that draws on expertise, facilities and technology that already exists at the university and other partner organizations including the Armed Force Radiobiology Research Institute (AFRRI). A focus area within the ND^3P portfolio is the development of prophylactic drugs for the prevention of Acute Radiation Syndrome (ARS). One of the candidate compounds being evaluated, 1-(1H-indol-3-yl)-2-(methylamino)ethan-1-ol or IMAE has shown very encouraging results on efficacy studies in mice.

1-(1H-indol-3-yl)-2-(methylamino)ethan-1-ol (IMAE)

Indralin was developed in Russia as a radioprotective agent to mitigate the effects of ionizing radiation. There is conflicting information in publicly available databases regarding the precise chemical structure of Indralin for the registered CAS number 156799-03-0. One set of sources indicates a molecular formula of $C_{23}H_{28}O_2S$, while another suggests a structure corresponding to an indole derivative, which is more consistent with its classification as a "derived biogenic amine" and the known expertise of its developers in indole chemistry. Our group was able to track down the Russian patent to synthesize the correct compound (IMAE, Figure 1).

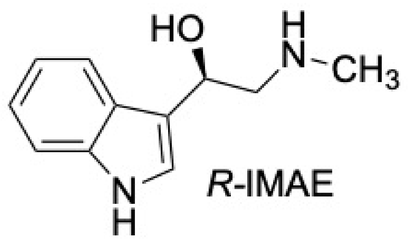
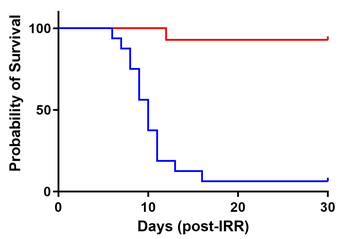


Figure 1. Synthesized structure of the R-enantiomer of IMAE

HYPOTHESIS

The newly synthesized IMAE is the correct structure and will be efficacious as a radioprotective agent against ARS.

RESULTS



- 10-12 week male CD2F1 mice
- IMAE (400 mg/kg) given orally 15 min prior to WBI

Figure 2. Racemic IMAE given 15 minutes prior to WBI radiation protects from hARS

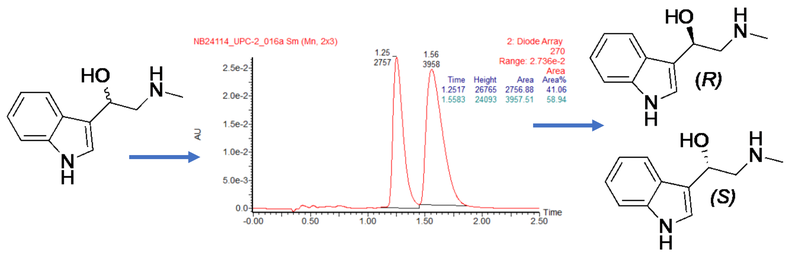
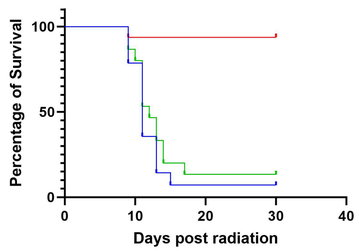
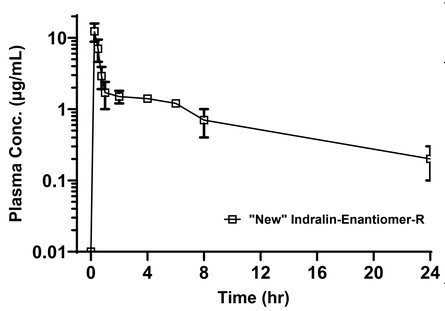


Figure 3. Separation of racemic IMAE using chiral chromatography into R and S enantiomers



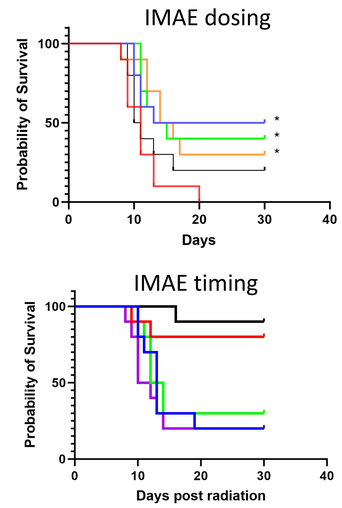
- 10-12 week male CD2F1 mice
- IMAE isolates (200 mg/kg) given orally 15 min prior to WBI

Figure 4. Only the R-enantiomer of IMAE given 15 minutes prior to WBI radiation protects from hARS



PK Parameters	"New" Indralin Enantiomer-R (Mean ± SD)
	PO (400 mg/kg)
Cmax (µg/mL)	13.1 ± 1.8
Tmax (h)	0.3 ± 0.1
$t_{1/2}$ (h) (Terminal Half life)	5.7± 1.8
AUC(0-24h) (h*µg/mL)	16.5 ± 5.5
AUC (0-∞) (h*µg/mL)	18.1 ± 5.8
AUC_%Extrap_obs	9.1 ± 4.1
Vz_F (L/Kg)	184.2 ± 30.2
CL_F (L/h/Kg)	24.0 ± 7.4
MRT (h)	4.3 ± 1.7

Figure 5. Plasma concentration time profile and PK parameters of R-enantiomer of IMAE. R-IMAE exhibits rapid initial absorption with a terminal half life of 5.7 hr in CD2F1 mice.



- 10-12 week male CD2F1 mice
- IMAE R given at different concentrations given orally 15 min prior to WBI

- 10-12 week male CD2F1 mice
- IMAE R (200 mg/kg) given orally at different times prior to WBI

Figure 6. IMAE significantly enhances survival from hARS at 25-200 mg/kg given 15 min prior to radiation. IMAE (200 mg/kg) enhances survival when given 15-30 minutes prior to WBI.

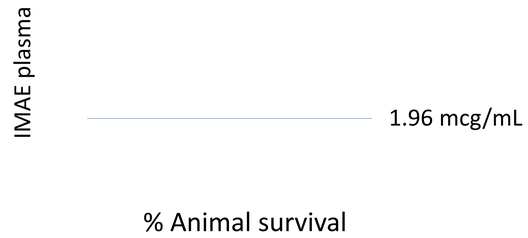


Figure 7. IMAE needs to be at a concentration at or greater than 2 µg/mL in the serum to significantly enhance survival against hARS.

CONCLUSIONS

- The R enantiomer of IMAE is the active molecule as a radioprotector
- IMAE is cleared in the serum quickly, half life of 20 minutes
- IMAE (25-200 mg/kg) is the effective dose range when given 15 minutes prior to WBI
- IMAE (200 mg/kg) is protective from hARS when given 15-30 minutes prior to WBI
- IMAE plasma concentrations need to be over 2 µg/mL to enhance survival against hARS.

NSRI is the DOD-designated University Affiliated Research Center of the University of Nebraska System and U.S. Strategic Command.