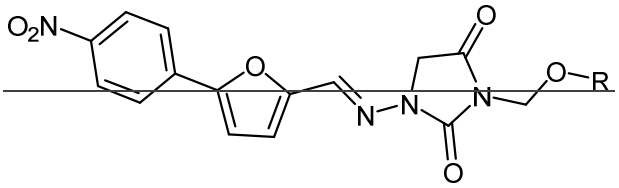
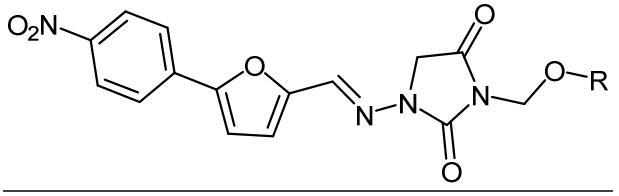
What is claimed is:

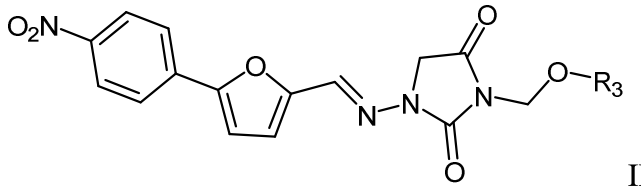
~~A method of treating a subject that has been or will be exposed to radiation comprising administering to the subject a~~

~~1.~~ 1. A pharmaceutical composition comprising a therapeutically effective amount of dantrolene, a compound of formula I, a compound of formula II, or a pharmaceutically acceptable salt thereof, or a combination thereof





I



II

wherein R is $-P(O)(OH)_2$ or $-P(O)(OR_1)(OR_2)$;

R_1 is H, $-C_{1-26}$alkyl, aryl, C_{1-6}alkC(O)O-C_{1-26}alkyl, $-C_1$alkOC(O)C_{1-26}alkyl, or C_1alkOC(O)OC_{1-26}alkyl; and

R_2 is $-C_{1-26}$alkyl, aryl, C_{1-6}alkC(O)O-C_{1-26}alkyl, $-C_1$alkOC(O)C_{1-26}alkyl, or C_1alkOC(O)OC_{1-26}alkyl;

_____R_3 is H, -C(O)-Z-N(R_4)(R_5), –C(O)Z-C(O)-OH, or –C(O)-NH-Y-CH_2-OC(O)-Z-C(O)-OH; Z is C_{1-6}alk; Y is arylene; R_4 is H or C_{1-6}alkyl; R_5 is H or C_{1-6}alkyl; or R_4 and R_5, together with the nitrogen to which they are attached, form a heterocycloalkyl; or a pharmaceutically acceptable salt thereof;

for use in treating a human subject that has been or will be exposed to radiation.

~~or a pharmaceutically acceptable salt thereof.~~

~~2.~~ 2. The ~~method~~pharmaceutical composition of claim 1, wherein R is -P(O)$(OH)_2$.

~~3.~~ 3. The ~~method~~pharmaceutical composition of claim 1, wherein R is P(O)$(OR_1)(OR_2)$.

~~4.~~ 4. The ~~method~~pharmaceutical composition of claim 3, wherein R_1 is H.

~~5.~~ 5. The ~~method~~pharmaceutical composition of claim 3, wherein R_1 is -C_{1-26}alkyl.

~~6.~~ 6. The ~~method~~pharmaceutical composition of claim 3, wherein R_1 is aryl.

~~7.~~ 7. The ~~method~~pharmaceutical composition of claim 3, wherein R_1 is C_{1-6}alkC(O)O-C_{1-26}alkyl.

~~8.~~ 8. The ~~method~~pharmaceutical composition of claim 3, wherein R_1 is -C_1alkOC(O)C_{1-26}alkyl.

~~9.~~ 9. The ~~method~~pharmaceutical composition of claim 3, wherein R_1 is C_1alkOC(O)OC_{1-26}alkyl.

~~10.~~ 10. The ~~method~~pharmaceutical composition of any one of claims 4 to 9, wherein R_2 is -C_{1-26}alkyl, aryl.

~~11.~~ 11. The ~~method~~pharmaceutical composition of any one of claims 4 to 9, wherein R_2 is C_{1-6}alkC(O)O-C_{1-26}alkyl.

~~12.~~ 12. The ~~method~~pharmaceutical composition of any one of claims 4 to 9, wherein R_2 is -C_1alkOC(O)C_{1-26}alkyl.

~~13.~~ 13. The ~~method~~pharmaceutical composition of any one of claims 4 to 9, wherein R_2 is C_1alkOC(O)OC_{1-26}alkyl.

~~14.~~ ~~The method~~14. The pharmaceutical composition of any one of the preceding claims, wherein the dantrolene, the compound of formula I, and/or formula II is in the form of a pharmaceutically acceptable salt.

~~15.~~ 15. The ~~method~~pharmaceutical composition of any one of the preceding claims, wherein the human subject is to be administered a pharmaceutical composition comprising dantrolene or a pharmaceutically acceptable salt thereof.

~~16.~~ 16. The ~~method~~pharmaceutical composition of any one of the preceding claims, wherein the human subject is to be administered a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof.

~~17.~~ 17. The ~~method~~pharmaceutical composition of any one of the preceding claims, wherein the human subject is to be administered a pharmaceutical composition comprising a compound of formula II or a pharmaceutically acceptable salt thereof.

~~18.~~ 18. The ~~method~~pharmaceutical composition of any one of the preceding claims, wherein the human subject has been or will be exposed to a radiation dose of between 0.3 Gy and 50 Gy.

~~19.~~ 19. The ~~method~~pharmaceutical composition of any one of the preceding claims, wherein the human subject has been or will be exposed to a radiation dose of at least 0.7 Gy.

~~20.~~ 20. The ~~method~~pharmaceutical composition of any one of the preceding claims, wherein the human subject has been or will be exposed to a radiation dose of at least 6 Gy, at least 10 Gy, or at least 50 Gy.

21. The method21. The pharmaceutical composition of any one of the preceding claims, wherein the radiation is X-ray radiation, gamma ray radiation, neutron radiation, or a combination thereof.

22. 22. The methodpharmaceutical composition of any one of the preceding claims, wherein the radiation exposure is chemoradiation exposure.

23. The method23. The pharmaceutical composition of any one of claims 1 to 21, wherein the radiation exposure is nuclear power plant leakage exposure.

24. 24. The method pharmaceutical composition of any one of claims 1 to 21, wherein the radiation exposure is nuclear weapon exposure.

25. 25. The methodpharmaceutical composition of any one of the preceding claims, wherein the pharmaceutical composition is to be administered to the human subject 24 hours or less after the human subject has been exposed to the radiation.

26. The method of any one of the preceding claims, wherein the subject is a mammal.

27. The method of any one of the preceding claims, wherein the subject is a human.

28. The method26. The pharmaceutical composition of any one of the preceding claims, wherein the therapeutically effective amount is 1 mg/kg to about 30 mg/kg of dantrolene.

29. 27. The method of any one of the preceding claims, wherein the pharmaceutical composition isof any one of the preceding claims, wherein the pharmaceutical composition is to be administered to the human subject prior to the subject being exposed to the radiation.

30. 28. The methodpharmaceutical composition of any one of the preceding claims, wherein the pharmaceutical composition is to be administered intravenously, subcutaneously, intramuscularly, intraosseously, or transdermally.

~~31.~~ ~~The method~~29. The pharmaceutical composition of any one of the preceding claims, wherein the pharmaceutical composition comprises dantrolene or a pharmaceutically acceptable salt thereof, mannitol, a polysorbate, a povidone, an optional pH adjustor, and water.

~~32.~~ 30. The ~~method~~pharmaceutical composition of any one of the preceding claims, wherein the treatment lowers the mortality of the human subject as a result of the radiation exposure, as compared to a control subject that did not receive the treatment.

~~33.~~ ~~The method~~31. The pharmaceutical composition of any one of the preceding claims, wherein the treatment improves at least one hematological parameter of the human subject, as compared to a control subject that did not receive the treatment.

~~34.~~ ~~The method~~32. The pharmaceutical composition of any one of the preceding claims, wherein the treatment is effective for treating hematopoietic syndrome occurring in the human subject as a result of the radiation exposure.

~~35.~~ ~~The method~~33. The pharmaceutical composition of any one of the preceding claims, wherein the treatment is effective for treating gastrointestinal syndrome occurring in the human subject as a result of the radiation exposure.

~~36.~~ ~~The method~~34. The pharmaceutical composition of any one of the preceding claims, wherein the treatment is effective for treating cardiovascular syndrome occurring in the human subject as a result of the radiation exposure.

~~37.~~ ~~The method~~35. The pharmaceutical composition of any one of the preceding claims, wherein the treatment is effective for treating central nervous system syndrome occurring in the human subject as a result of the radiation exposure.

~~38.~~ ~~The method~~36. The pharmaceutical composition of any one of the preceding claims, wherein the treatment is effective for treating anorexia, nausea, vomiting, cramps, or diarrhea occurring in the human subject as a result of the radiation exposure.

~~The method~~37. The pharmaceutical composition of any one of the preceding claims, wherein the treatment is effective for treating cognitive changes or behavior changes occurring in the human subject as a result of the radiation exposure.

~~39.~~