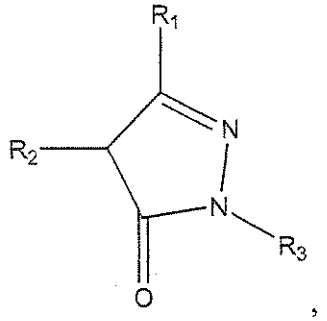
SUMMARY

Pyrazolone derivative formulations are provided. The formulations include a pyrazolone derivative active agent, e.g., edaravone, and an amphiphilic solubilizing agent. Also provided are methods of making and using the subject formulations.

In a first aspect, there is provided a non-emulsion formulation comprising:

a pyrazolone derivative active agent having the formula:



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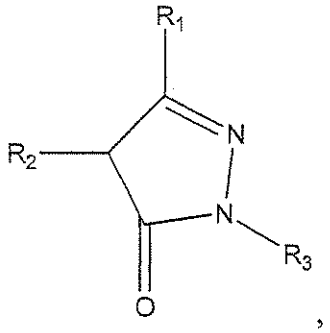
wherein:

R_1 represents hydrogen atom, an aryl, an alkyl having 1 to 5 carbon atoms or an alkoxycarbonylalkyl having 3 to 6 carbon atoms in total; R_2 represents hydrogen atom, an aryloxy, an arylmercapto, an alkyl having 1 to 5 carbon atoms or a hydroxyalkyl having 1 to 3 carbon atoms; or R_1 and R_2 are coupled together to form an alkylene having 3 to 5 carbon atoms; and

R_3 is hydrogen atom, an alkyl having 1 to 5 carbon atoms, a cycloalkyl having 5 to 7 carbon atoms, a hydroxyalkyl having 1 to 3 carbon atoms, benzyl, a naphthyl or phenyl, or a phenyl substituted by 1 to 3 substituents, which may be the same or different and selected from the group consisting of an alkoxy having 1 to 5 carbon atoms, a hydroxyalkyl having 1 to 3 carbon atoms, an alkoxycarbonyl having 2 to 5 carbon atoms in total, an alkylmercapto having 1 to 3 carbon atoms, an alkylamino having 1 to 4 carbon atoms, a dialkylamino having 2 to 8 carbon atoms in total, a halogen atom, trifluoromethyl, carboxyl, cyano, hydroxyl group, nitro, amino and acetamido or physiologically acceptable salt thereof, or a hydrate or solvate thereof; and an amphiphilic solubilizing agent.

In a second aspect, there is provided a method comprising parenterally administering to a subject a non-emulsion formulation comprising:

a pyrazolone derivative active agent having the formula:



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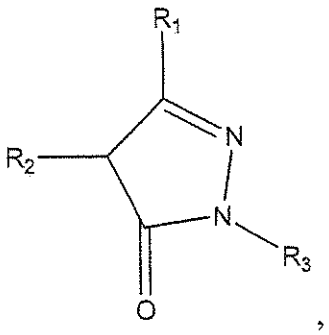
wherein:

R_1 represents hydrogen atom, an aryl, an alkyl having 1 to 5 carbon atoms or an alkoxycarbonylalkyl having 3 to 6 carbon atoms in total; R_2 represents hydrogen atom, an aryloxy, an arylmercapto, an alkyl having 1 to 5 carbon atoms or a hydroxyalkyl having 1 to 3 carbon atoms; or R_1 and R_2 are coupled together to form an alkylene having 3 to 5 carbon atoms; and

R_3 is hydrogen atom, an alkyl having 1 to 5 carbon atoms, a cycloalkyl having 5 to 7 carbon atoms, a hydroxyalkyl having 1 to 3 carbon atoms, benzyl, a naphthyl or phenyl, or a phenyl substituted by 1 to 3 substituents, which may be the same or different and selected from the group consisting of an alkoxy having 1 to 5 carbon atoms, a hydroxyalkyl having 1 to 3 carbon atoms, an alkoxycarbonyl having 2 to 5 carbon atoms in total, an alkylmercapto having 1 to 3 carbon atoms, an alkylamino having 1 to 4 carbon atoms, a dialkylamino having 2 to 8 carbon atoms in total, a halogen atom, trifluoromethyl, carboxyl, cyano, hydroxyl group, nitro, amino and acetamido or physiologically acceptable salt thereof, or a hydrate or solvate thereof; and an amphiphilic solubilizing agent.

In a third aspect, there is provided a kit comprising a non-emulsion formulation comprising:

a pyrazolone derivative active agent having the formula:



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wherein:

R_1 represents hydrogen atom, an aryl, an alkyl having 1 to 5 carbon atoms or an alkoxycarbonylalkyl having 3 to 6 carbon atoms in total; R_2 represents hydrogen atom, an aryloxy, an arylmercapto, an alkyl having 1 to 5 carbon atoms or a hydroxyalkyl having 1 to 3 carbon atoms; or R_1 and R_2 are coupled together to form an alkylene having 3 to 5 carbon atoms; and

R_3 is hydrogen atom, an alkyl having 1 to 5 carbon atoms, a cycloalkyl having 5 to 7 carbon atoms, a hydroxyalkyl having 1 to 3 carbon atoms, benzyl, a naphthyl or phenyl, or a phenyl substituted by 1 to 3 substituents, which may be the same or different and selected from the group consisting of an alkoxy having 1 to 5 carbon atoms, a hydroxyalkyl having 1 to 3 carbon atoms, an alkoxycarbonyl having 2 to 5 carbon atoms in total, an alkylmercapto having 1 to 3 carbon atoms, an alkylamino having 1 to 4 carbon atoms, a dialkylamino having 2 to 8 carbon atoms in total, a halogen atom, trifluoromethyl, carboxyl, cyano, hydroxyl group, nitro, amino and acetamido or physiologically acceptable salt thereof, or a hydrate or solvate thereof; and an amphiphilic solubilizing agent.

DEFINITIONS

When describing the compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms have the following meanings unless otherwise indicated. It should also be understood that any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope.

"Alkyl" refers to monovalent saturated aliphatic hydrocarbyl groups having up to 10 carbon atoms, or up to 9 carbon atoms, up to 8 carbon atoms, or up to 3 carbon atoms. The hydrocarbon chain may be either straight-chained or branched. This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, n-hexyl, n-octyl, tert-octyl and the like. The term "alkyl" also includes "cycloalkyls" as defined herein.

"Cycloalkyl" refers to cyclic hydrocarbyl groups having from 3 to 10 carbon atoms and having a single cyclic ring or multiple condensed rings, including fused and bridged ring systems, which optionally can be substituted with from 1 to 3 alkyl groups. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, 1-methylcyclopropyl, 2-methylcyclopentyl, 2-methylcyclooctyl, and the like.

"Heterocycloalkyl" refers to a stable heterocyclic non-aromatic ring and fused rings containing one or more heteroatoms independently selected from N, O and S. A fused heterocyclic ring system may include carbocyclic rings and need only include one heterocyclic ring. Examples of such heterocyclic non-aromatic rings include, but are not limited to, aziridinyl, azetidinyl, piperazinyl, and piperidinyl.