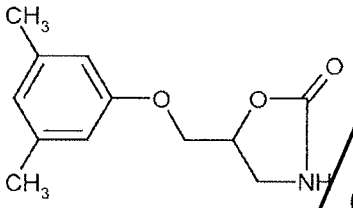
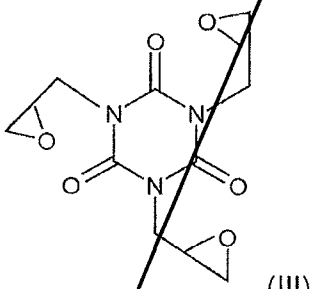
## CLAIMS

1. A method of preparation of metaxalone having the following structural formula (I):



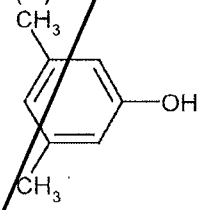
(I)

comprising reaction of triglycidyl isocyanurate (TGIC) of formula (III)



(III)

with m-xylenol of formula (V)



(V)

characterized in that said reaction is carried out in a solvent mixture comprising a first solvent selected from the group comprising aprotic polar solvents with dielectric constant greater than or equal to 30 and a second solvent selected from the group comprising apolar solvents and aprotic polar solvents with dielectric constant below 30 said solvent mixture comprising from 5 to 40 wt. % of said first solvent and from 95 to 60 wt. % of said second solvent,

adding the TGIC at a temperature between 30°C and 50°C and

after adding the TGIC raising the temperature of the reaction solution to a value between 80°C and 180°C in a time between 120 and 180 minutes at a rate of increase not greater that 1.25°C per minute.

2. Method of preparation of metaxalone according to Claim 1, characterized in that said aprotic polar solvent is selected from the group consisting of N-methylpyrrolidone, dimethylformamide, dimethylsulphoxide, hexamethylphosphoramide, dimethylacetamide and acetonitrile, preferably N-methylpyrrolidone and dimethylformamide.

3. Method of preparation of metaxalone according to Claim 1, characterized in that said apolar solvent is selected from the group consisting of cyclohexane, heptane, benzene, toluene, xylene, mesitylene, naphthalene, chlorobenzene, chloroxylene, chloroform, propyl ether, isopropyl ether, butyl ether, pentyl ether, benzylethyl ether, tetrahydrofuran (THF) and 2-methyl tetrahydrofuran, preferably toluene and xylene.

4. Method of preparation of metaxalone according to Claim 1, characterized in that said aprotic polar solvent with dielectric constant below 30 is selected from the group consisting of acetone, methyl ethyl ketone, methyl butyl ketone, methyl isobutyl ketone, 2-pentanone, cyclopentanone and 2-heptanone, preferably methyl isobutyl ketone.

5. Method of preparation of metaxalone according to Claim 1, characterized in that said solvent mixture comprises from 10 to 30 wt.%, of said first solvent and from 90 to 70 wt.%, of said second solvent.

6. Method of preparation of metaxalone according to Claim 1, characterized in that the reaction solution further comprises an organic or inorganic base, preferably an inorganic base selected from the group comprising oxides or hydroxides of alkali metals and carbonates of alkali metals or alkaline earth metals, and a phase transfer catalyst, preferably a halide of quaternary ammonium or phosphonium.

7. Method of preparation of metaxalone according to Claim 6, characterized in that the reaction solution comprises an amount of said organic or inorganic base between 3 and 10 mol.%, preferably between 3 and 6 mol.%, relative to the molar amount of TGIC present in said reaction solution.

8. Method of preparation of metaxalone according to Claim 6, characterized in that the reaction solution comprises an amount of said phase transfer catalyst between 0.5 and 5 mol.%, preferably between 1 and 3 mol.%, relative to the amount of TGIC present in said reaction solution.

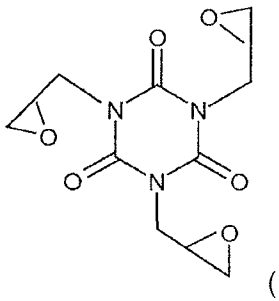
9. Method of preparation of metaxalone according to Claim 6, characterized in that the solution comprising m-xylenol, the base and the phase transfer catalyst dissolved in the solvent mixture is heated to a temperature between 35°C and 45°C, before adding the TGIC.

10. Method of preparation of metaxalone according to any one of the preceding claims, characterized in that, after adding TGIC, the reaction solution is gradually heated to a temperature between 80°C and 180°C in a time between 120 and 180 minutes.

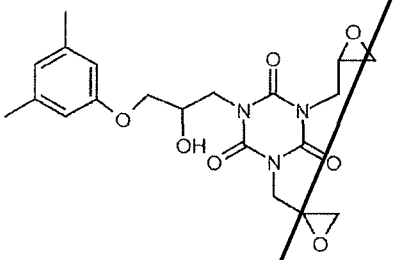
11. Method of preparation of metaxalone according to any one of the preceding claims, characterized in that the reaction solution is gradually heated at a rate of increase not greater than 1.00°C per minute, preferably not greater than 0.75°C per minute.

12. Method of preparation of metaxalone according to Claim 11, where at the end of the phase of gradual temperature rise, an amount of base between 3 and 10 mol.%, preferably between 5 and 8 mol.%, relative to the molar amount of TGIC present in the starting reaction solution, is again added to the starting reaction solution.

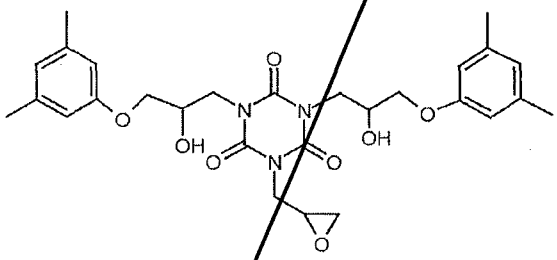
13. Metaxalone comprising less than 1 ppm of genotoxic impurities containing epoxides represented by the following compounds of formula (III), (VII) and (VIII)



(III)



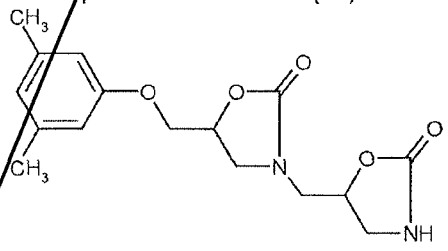
(VII)



(VIII)

14. Metaxalone according to Claim 13 comprising less than 0.5 ppm, preferably less than 0.1 ppm of said genotoxic impurities containing epoxides.

15. Metaxalone comprising less than 500 ppm of impurities represented by the compound of formula (IX)



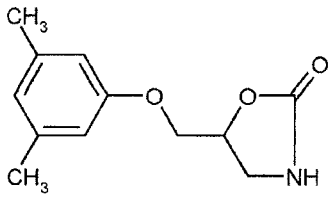
(IX)

16. Metaxalone according to Claim 15 comprising less than 300 ppm, preferably less than 100 ppm of said impurities.

17. Pharmaceutical composition comprising metaxalone according to any one of Claims 13 to 16 and at least one pharmaceutically acceptable excipient.

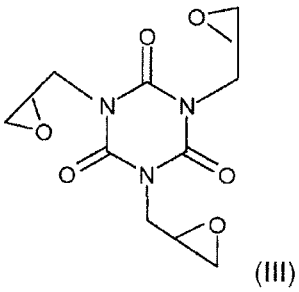
**CLAIMS**

1. A method of preparation of metaxalone having the following structural formula (I):



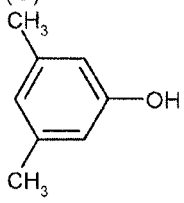
(I)

comprising reaction of triglycidyl isocyanurate (TGIC) of formula (III)



(III)

with m-xylenol of formula (V)



(V)

characterized in that said reaction is carried out in a solvent mixture comprising a first solvent selected from the group comprising aprotic polar solvents with dielectric constant greater than or equal to 30 and a second solvent selected from the group comprising apolar solvents and aprotic polar solvents with dielectric constant below 30 said solvent mixture comprising from 5 to 40 wt. % of said first solvent and from 95 to 60 wt. % of said second solvent,

adding the TGIC at a temperature between 30°C and 50°C and

after adding the TGIC raising the temperature of the reaction solution to a value between 80°C and 180°C in a time between 120 and 180 minutes at a rate of increase not greater that 1.25°C per minute.

2. Method of preparation of metaxalone according to Claim 1, characterized in that said aprotic polar solvent is selected from the group consisting of N-methylpyrrolidone, dimethylformamide, dimethylsulphoxide, hexamethylphosphoramide, dimethylacetamide and acetonitrile.

3. Method of preparation of metaxalone according to Claim 1, characterized in that said apolar solvent is selected from the group consisting of cyclohexane, heptane, benzene, toluene, xylene, mesitylene, naphthalene, chlorobenzene, chloroxylene, chloroform, propyl ether, isopropyl ether, butyl ether, pentyl ether, benzylethyl ether, tetrahydrofuran (THF) and 2-methyl tetrahydrofuran.

4. Method of preparation of metaxalone according to Claim 1, characterized in that said aprotic polar solvent with dielectric constant below 30 is selected from the group consisting of acetone, methyl ethyl ketone, methyl butyl ketone, methyl isobutyl ketone, 2-pentanone, cyclopentanone and 2-heptanone.

5. Method of preparation of metaxalone according to Claim 1, characterized in that said solvent mixture comprises from 10 to 30 wt.%, of said first solvent and from 90 to 70 wt.%, of said second solvent.

6. Method of preparation of metaxalone according to Claim 1, characterized in that the reaction solution further comprises an organic or inorganic base, and a phase transfer catalyst.

7. Method of preparation of metaxalone according to Claim 6, characterized in that the reaction solution comprises an amount of said organic or inorganic base between 3 and 10 mol.% relative to the molar amount of TGIC present in said reaction solution.

8. Method of preparation of metaxalone according to Claim 6, characterized in that the reaction solution comprises an amount of said phase transfer catalyst between 0.5 and 5 mol.% relative to the amount of TGIC present in said reaction solution.

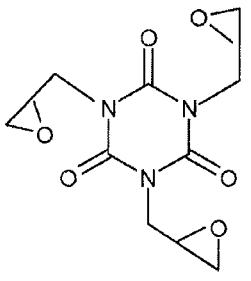
9. Method of preparation of metaxalone according to Claim 6, characterized in that the solution comprising m-xylenol, the base and the phase transfer catalyst dissolved in the solvent mixture is heated to a temperature between 35°C and 45°C, before adding the TGIC.

10. Method of preparation of metaxalone according to any one of the preceding claims, characterized in that, after adding TGIC, the reaction solution is gradually heated to a temperature between 80°C and 180°C in a time between 120 and 180 minutes.

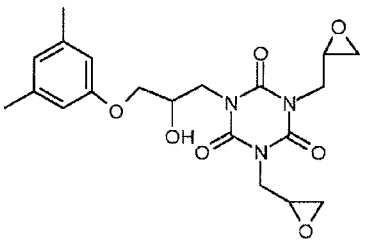
11. Method of preparation of metaxalone according to any one of the preceding claims, characterized in that the reaction solution is gradually heated at a rate of increase not greater than 1.00°C per minute.

12. Method of preparation of metaxalone according to Claim 11, where at the end of the phase of gradual temperature rise, an amount of base between 3 and 10 mol.% relative to the molar amount of TGIC present in the starting reaction solution, is again added to the starting reaction solution.

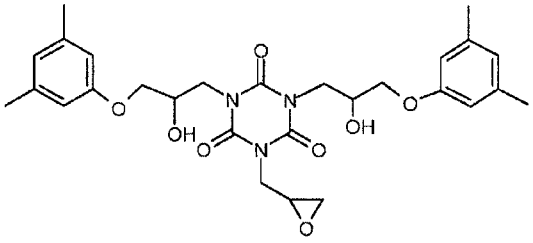
13. Metaxalone comprising less than 1 ppm of genotoxic impurities containing epoxides represented by the following compounds of formula (III), (VII) and (VIII)



(III)



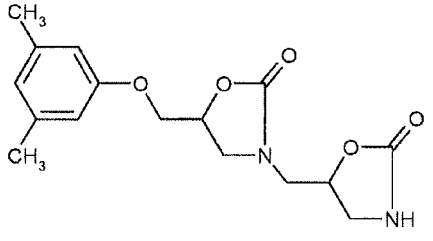
(VII)



(VIII)

14. Metaxalone according to Claim 13 comprising less than 0.5 ppm of said genotoxic impurities containing epoxides.

15. Metaxalone comprising less than 500 ppm of impurities represented by the compound of formula (IX)



(IX)

16. Metaxalone according to Claim 15 comprising less than 300 ppm of said impurities.

17. Pharmaceutical composition comprising metaxalone according to any one of Claims 13 to 16 and at least one pharmaceutically acceptable excipient.