



(86) Date de dépôt PCT/PCT Filing Date: 1999/12/18

(87) Date publication PCT/PCT Publication Date: 2000/06/29

(45) Date de délivrance/Issue Date: 2009/02/24

(85) Entrée phase nationale/National Entry: 2001/06/19

(86) N° demande PCT/PCT Application No.: US 1999/030293

(87) N° publication PCT/PCT Publication No.: 2000/037064

(30) Priorité/Priority: 1998/12/22 (US09/218,713)

(51) Cl.Int./Int.Cl. *A61K 31/53* (2006.01),
A61P 15/06 (2006.01), *A61P 25/00* (2006.01),
A61P 33/02 (2006.01)

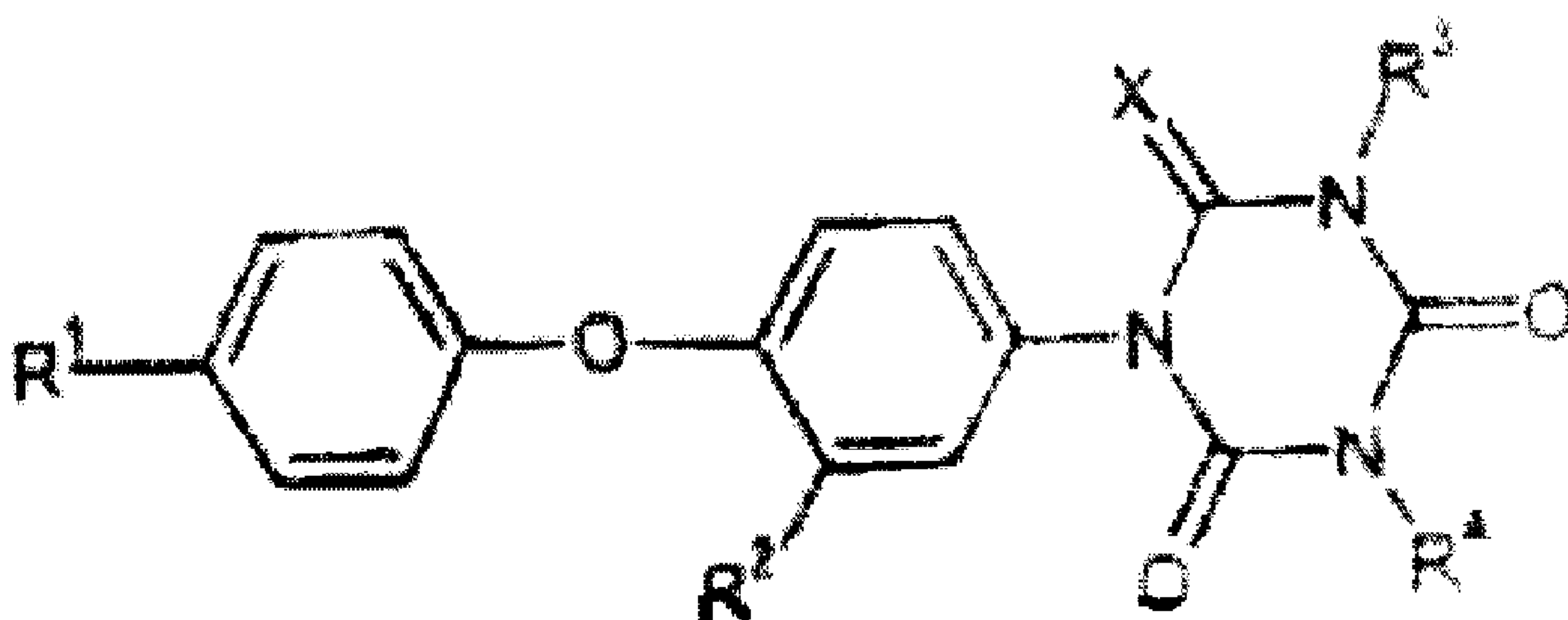
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(54) Titre : COMPOSES DE TRIAZINEONE UTILISES POUR TRAITER LES MALADIES DUES AUX SARCOSYSTIS, NEOSPORA ET TOXOPLASME

(54) Title: TRIAZINEONE COMPOUNDS FOR TREATING DISEASES DUE TO SARCOSYSTIS, NEOSPORA AND TOXOPLASMA



(I)

(57) Abrégé/Abstract:

Disclosed herein are methods of treating therapeutically, or metaphylactically infected animals susceptible to, or infected animal suffering from parasitic neurologic or abortigenic diseases due to Sarcocystis, Neospora or Toxoplasma that are treatable with triazineone compounds by administering thereto a pharmaceutically effective amount of the compound, including a single high dose therapeutic treatment.

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/53, A61P 33/02	A3	(11) International Publication Number: WO 00/37064 (43) International Publication Date: 29 June 2000 (29.06.00)
(21) International Application Number: PCT/US99/30293 (22) International Filing Date: 18 December 1999 (18.12.99) (30) Priority Data: 09/218,713 22 December 1998 (22.12.98) US (71) Applicant: BAYER CORPORATION [US/US]; 100 Bayer Road, Pittsburgh, PA 15205-9741 (US). (72) Inventor: KENNEDY, Thomas, J.; 6885 West 51st Terrace, Mission, KS 66202 (US). (74) Agents: AKORLI, Godfried, R. et al.; Bayer Corporation, 100 Bayer Road, Pittsburgh, PA 15205-9741 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 26 October 2000 (26.10.00)
(54) Title: TRIAZINEONE COMPOUNDS FOR TREATING DISEASES DUE TO SARCOSYSTIS, NEOSPORA AND TOXOPLASMA (57) Abstract Disclosed herein are methods of treating therapeutically, or metaphylactically infected animals susceptible to, or infected animal suffering from parasitic neurologic or abortigenic diseases due to <i>Sarcocystis</i> , <i>Neospora</i> or <i>Toxoplasma</i> that are treatable with triazineone compounds by administering thereto a pharmaceutically effective amount of the compound, including a single high dose therapeutic treatment.		

TRIAZINEONE COMPOUNDS FOR TREATING DISEASES DUE TO
SARCOSYSTIS, NEOSPORA AND TOXOPLASMA

BACKGROUND OF THE INVENTION

Field of the Invention:

The present invention relates to triazineone compounds for treating animals infected with parasites that cause abortigenic or neurologic diseases. More specifically, the present invention relates the triazineone compounds that are useful in treating parasitic protozoa such as coccidia
5 that cause abortigenic or neurologic diseases.

Brief Description of the Prior Art:

Triazineone compounds such as triazinediones, e.g., diclazuril compounds, and triazinetriones, e.g., toltrazuril compounds have been
10 used in treating and protecting various mammals, insects and fish from diseases caused by a broad range of protozoa. See U.S. Patents; 4,933,341; 4,935,423; 5,114,938; 5,141,938; 5,188,832, 5,196,562, 5,256,631 and 5,464,837. Protozoa sensitive to these compounds infect birds, mammals and insects and manifest as diarrhea, wasting, nausea
15 and vomiting. Generally, the mode of action of the triazineones is to attack the intermediate parasite stages found in the gut and intestinal wall cells, causing the endoplasmic reticulum, the perinuclear space and the mitochondria of the parasite to swell. This purportedly disturbs the ability for nuclear divisions causing the shizonts and microgamonts to remain
20 small forming only a few merozoites and microgametes respectively. The end result is reported to be the loss of the ability of these latter stages of the parasites to penetrate new mammalian cells, effectively halting the replication of the parasite in the host.

Of particular concern here are certain protozoa suspected of
25 causing neurologic and/or abortigenic diseases of animals since the 1970's. Successful isolation *and in vitro* cultivation of some of these protozoa proved to be difficult. For example successful isolation from the

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brain or cerebral spinal fluid were not accomplished until the late 1980s. Once it was determined that neurologic diseases could be produced by certain parasites infecting the brain and abortigenic diseases could be produced by certain parasites infecting the fetus, the need for effective
5 anti-parasite drugs which could cross the blood-brain and the placental barrier without producing deleterious side effects became imperative. Many of the art-known drugs that can to cross the blood-brain barrier and/or the placental barrier to effectively treat parasitic infections of the brain have detrimental side effects such that they cannot be used without
10 great risk. As such, there have been no effective drugs approved to date which provide an effective treatment for such neurologic or abortigenic diseases. The following is a brief description of the parasitic diseases.

Equine Protozal Myoencephalitis (EPM) is a neurologic disease of horses, with a predilection for young horses undergoing stress (e.g.,
15 thoroughbred race horses and purebred performance horses), and is thus a disease with significant monetary impact for the horse industry. EPM, first recognized as a disease in the 1970's, was cultured from a horse with EPM and given the name *Sarcocystis neurona* until 1991. In 1997, a *Neospora* spp., now named *Neospora hughesi*, was isolated from the brain
20 of a horse with EPM. Accordingly, it is now proposed that EPM may be caused by this newly recognized organism alone, by *Sarcocystis neurona* alone or the combination of the two. EPM most often results in asymmetric incoordination (ataxia), weakness, and spasticity. The disease can mimic almost any neurologic condition. It can occur as a peracute or
25 chronic condition. The chronic form is often insidious at onset, difficult to diagnose until late in the course of the disease, and can result in death. In the mildest cases, the only clinical sign may be ill-defined pelvic limb lameness or a minor respiratory noise. In the most severe cases, horses are unable to swallow or stand. It is now known that in the most severe
30 cases, the parasite, e.g., *S. neurona* infects the brain and produces significant damage therein. The clinical signs of EPM are caused by direct neuronal (brain and spinal cord) damage by the parasites as well as brain

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damage resulting from infiltration of inflammatory cells, edema, and neuronal death associated with merozoites and meronts in the central nervous system (CNS). Currently, there is no approved effective treatment or prophylaxis for the control of EPM. The human drug
5 trimethoprim-sulfonamide combination has been used. However, treatment is expensive and requires an extensive number of repeated doses.

Another coccidian parasite, *Toxoplasma gondii*, has been known for some time and was first isolated from the intestines and muscle tissue
10 of cats. The definitive host for this parasite is the cat that can harbor the organism for long periods of time spreading oocysts to other animals including bovines, ovines swine and humans. Infection of sheep, cattle and humans has been associated with abortion and congenitally acquired disorders, which primarily affect the central nervous system. It has also
15 recently been associated with abortion and malformation in kittens born to infected queens that had been seronegative prior to infection during pregnancy. Non-feline hosts such as bovines, ovines swine and humans do not produce oocysts but develop and may suffer from invasion of muscle and brain by tachyzoites and bradyzoites which produce the
20 clinical signs of disease – neurological symptoms and abortion with fetal defects. It has been reported that 60% of cats are serologically positive to *T. gondii*. Once again, there is no approved treatment or prophylactic for toxoplasmosis.

Yet another coccidia parasite, *Neospora caninum*, produces both a
25 neurologic and abortigenic disease in animals. It was first isolated from dogs in 1988, and was previously confused with *Toxoplasma gondii*. The disease caused by this parasite occurs most severely in transplacentally infected puppies and is characterized by progressive ascending paralysis in the puppies, particularly of the hind limbs; polymyositis and hepatitis
30 may also occur. This disease has more recently been recognized as a major cause of abortion and neurologically-associated limb defects in newborn calves. Microscopic lesions of non-suppurative encephalitis and

myocarditis in aborted fetuses may be seen in the brain, spinal cord and heart. A definitive host for *Neospora caninum* has recently been identified to be the dog. At this time there is no approved treatment or prophylaxis for either *Neospora caninum* of dogs or bovines or *Neospora hughesi* of horses.

Art-known references, including the above-cited references do not suggest or teach the use of triazineone compounds such as Toltrazuril or Toltrazuril Sulfone (recently renamed "Ponazuril") in treating animals infected with coccidia or, more specifically, of the family Sarcocystidae causing abortigenic or neurologic diseases without causing intolerable side effects. There is, therefore, a need for an improved and safe treatment for animals afflicted with parasitic diseases manifesting as neurologic or abortigenic diseases.

SUMMARY OF THE INVENTION

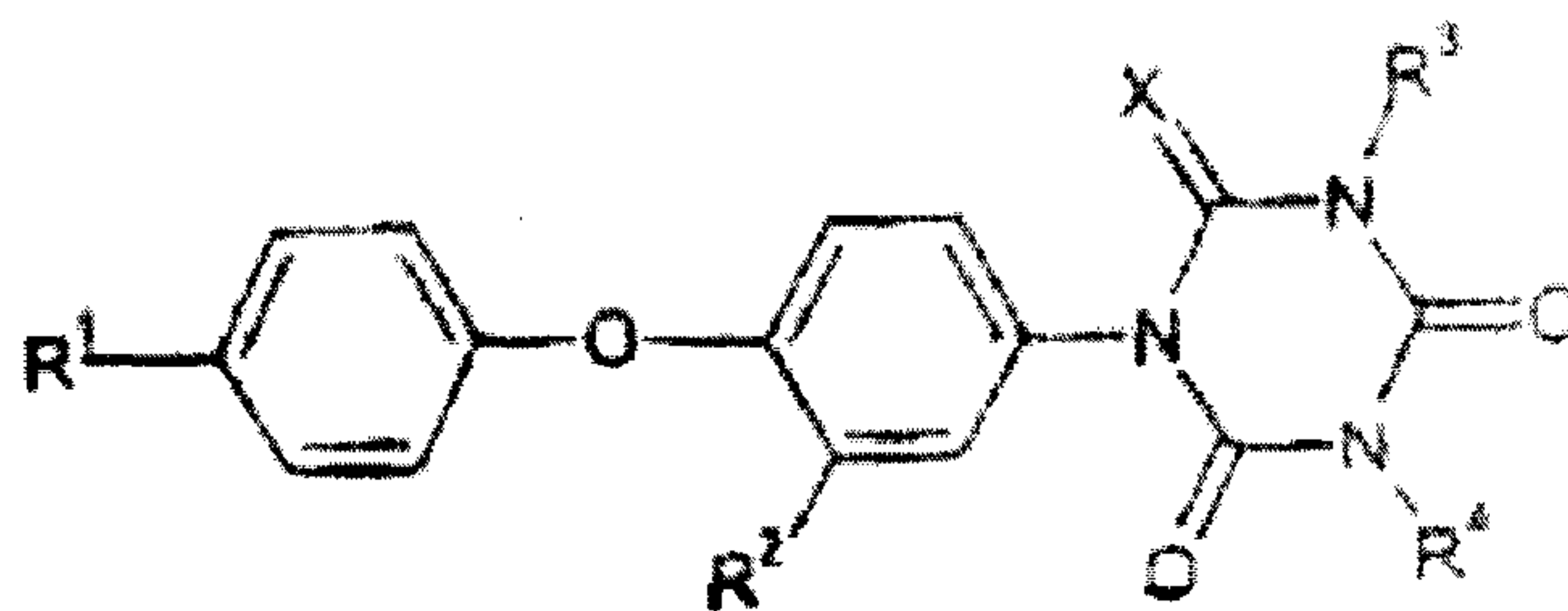
In accordance with the foregoing, the present invention encompasses a method of therapeutically treating a diseased animal suffering from a parasitic neurologic or abortigenic disease that is susceptible to being treated with a triazineone compound **with the proviso that when the disease is *Sarcocystis neurona* the compound is not diclazuril or toltrazuril.** The method comprises administering to the animal, a pharmaceutically effective amount of the compound. The term "pharmaceutically-effective amount" as used herein means that the amount of triazineone being administered is high enough to inhibit the *in vivo* or *in vitro* growth of the parasitic protozoa, typically coccidia that produce neurological disease and/or abortions. The pharmaceutically-effective amount controls the parasites in the infected tissues and consequently lead to an improvement in the animal's health.

Further, the present invention encompasses a method of metaphylactically treating an animal infected with a parasite that can cause a neurologic or abortigenic disease, that is susceptible to being treated with a triazineone compound. The metaphylactic treatment comprises administering to the animal, the triazineone compound using a

metaphylactically-effective regimen. By the term "metaphylactically-effective regimen" is meant administering scheduled intermittent doses of triazineone compounds for a prolonged period until said animal overcomes the invading parasites by, say, developing a protective immune response or otherwise clearing the parasite. Typically, the regimen is such as would effectively control the parasites and prevent clinical signs of disease. The metaphylactically-effective dose can also be administered for a prolonged period up to five years or the lifetime of the animal, especially in an instance when the parasite is difficult to control. For the metaphylactic treatment, the preferred triazineone compounds are triazinetriones, which include but are not limited to Toltrazuril, and Ponazruil.

Also, the present invention encompasses a single high dose treatment of the animals. This method comprises administering to the animals a single high dose of a pharmaceutically effective amount of the triazineone compound to a diseased animal suffering from a parasitic neurologic or abortigenic disease that is susceptible to being treated with a triazineone. By the term "single high dose" is meant an amount that is administered only once. This amount is significantly higher than the dose amount employed in the therapeutic or metapylactic treatment; is effective in controlling the disease-causing parasites, and as such would not result in detrimental effects such as toxicity. The single high dose of triazineone is accordingly greater than 10 mg/Kg. This and other aspects of the invention are described more fully hereunder.

Furthermore, in accordance with one aspect of the invention, there is provided use of a triazineone compound of the formula (I):



(I)

in which: R¹ represents halogenoalkylthio, halogenoalkyl-sulphinyl or

5a

halogenoalkylsulphonyl; R^2 represents hydrogen, alkyl, alkoxy, alkoxyalkyl, alkylmercapto, halogen, halogenoalkyl or an optionally substituted sulphamoyl, R^3 and R^4 can be identical or different and represent hydrogen, alkyl, alkenyl or alkynyl; and X is O or S, or a physiologically acceptable salt thereof, provided that
5 said compound of formula (I) is other than ponazuril; for preparing a pharmaceutical composition for the treatment of a neurologic disease or an abortigenic disease caused by Coccidia selected from the group consisting of Neospora spp and Toxoplasma spp.

In another aspect of the invention, there is provided a pharmaceutical
10 composition for the treatment of a neurologic disease or an abortigenic disease caused by Coccidia selected from the group consisting of Neospora spp and Toxoplasma spp comprising a triazineone compound of the formula (I), defined above, or a physiologically acceptable salt thereof, provided that said compound of formula (I) is other than ponazuril; in association with a pharmaceutically
15 acceptable carrier.

In still another aspect of the invention, there is provided a triazineone compound of the formula (I), defined above, or a physiologically acceptable salt thereof, provided that said compound of formula (I) is other than ponazuril; for use
20 in the treatment of a neurologic disease or an abortigenic disease caused by Coccidia selected from the group consisting of Neospora spp and Toxoplasma spp.

DETAILED DESCRIPTION OF THE INVENTION

As set forth above, the present invention relates to a method of treating an infected or diseased animal suffering from a parasitic disease that manifests as neurologic or abortigenic disease that is susceptible to being treated with a
25 triazineone compound, comprising, administering thereto a pharmaceutically effective amount of said compound. Illustrative but non-limiting examples of the animals can be equines, bovines, felines, canines, swine, ovines, birds, insects and humans. The parasites

infecting or causing disease are coccidia of the Family Sarcocystidae that can manifest as neurologic or abortigenic diseases. Illustrative but non-limiting examples thereof can be selected from the group consisting of *Sarcocystis* spp., *Neospora* spp. and *Toxoplasma* spp. The

5 Sarcocystidae are typically selected from the group consisting of *S. neurona*, *N. hughesi*, *N. caninum* and *T. gondii*. The protozoan infections or diseases include but are not limited to EPM, Neosporosis, and Toxoplasmosis.

In the practice of the invention, treatment of the parasitic

10 infections or diseases caused by the protozoa described herein results in the alleviation of the symptoms of the neurologic and abortigenic diseases. Generally, the symptoms include lameness, ataxia, paralysis, abortion, weak newborns and other related disorders. For therapeutic treatment, the regimen can be once a

15 day, two or more times a day, once every other day or even once per week, depending on factors such as the severity of the disease and the type of disease-producing parasite. In some cases, however, the treatment regimen can last indefinitely, sometimes for the remaining life of the animal. For example, in the

20 case of infection of an animal with a more resistant strain of parasite, the treatment can be extended for longer periods of time until the signs of disease are eliminated. Typically the duration of treatment is from about 28 days to 90 days and preferably from about 28 to 60 days. The most preferred treatment is once, daily

25 for about 28 days.

For the metaphylactic treatment, infected animals are treated to protect them against clinical manifestation of diseases. This treatment eventually results in the animals' acquisition of the ability to control the parasite, say, by the establishing an effective immune response to impart

30 protection against future infections, without a need for further administration of triazineone compounds. The metaphylactic activity, in accordance with the invention, refers to the use of the triazineone

compounds on a scheduled intermittent treatment regimen (metaphyl-
actically-effective regimen) to control the protozoa, which may have
infected the animal, since the previous treatment. Accordingly, the
metaphylactically-effective regimen is administered to reduce the ability of
5 the parasites to cause disease by, say, killing them or reducing them in
number. In essence, the metaphylactically effective regimen can be
administered two or more times, typically from about once per month, up
to over the lifetime of the animal or until an inherent clearance
mechanism, e.g., an effective immune response develops within the
10 animal to protect it from future infections. The latter can occur within 5
years or less. As would be realized, the metaphylactic treatment is based
on the recognition that when animals are infected with the protozoa
described herein, they do not demonstrate clinical signs such as
neurological signs or abortion until a significant time has passed (e.g., 2-6
15 months post infection). In contrast, the enteric protozoan infections
manifest themselves shortly after infection. In accordance with this
invention, the metaphylactic treatment prevents the parasite from
establishing itself and causing a clinical disease. The treatment regimen is
on an intermittent schedule of about once per month, once per two months
20 or once per two weeks.

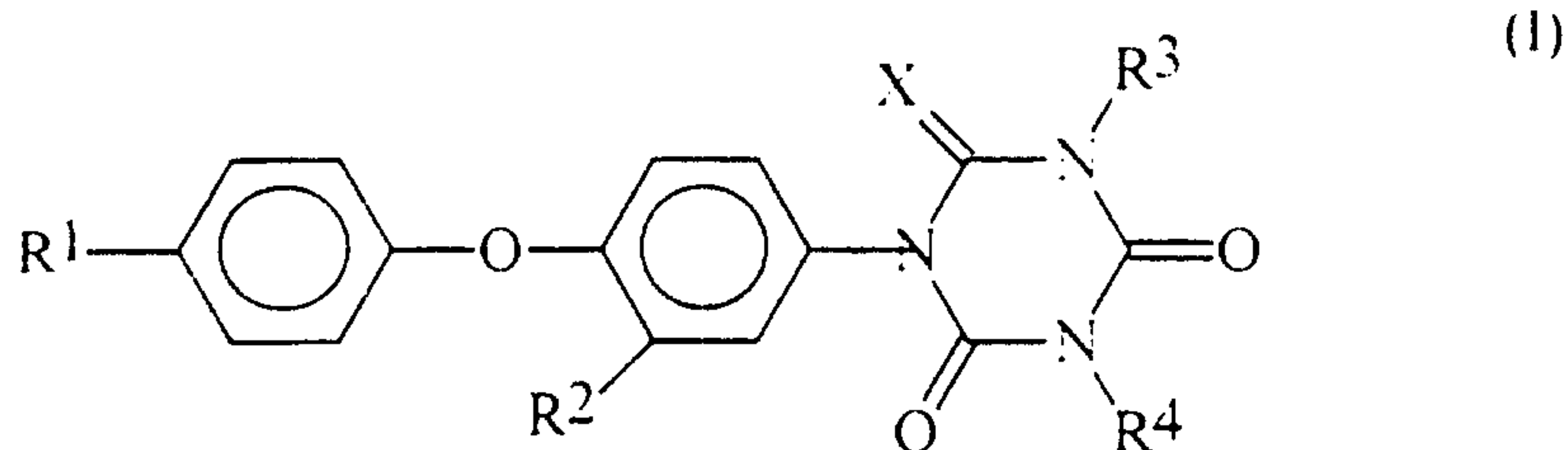
For the therapeutic and metaphylactic treatments one can employ a
dose equivalent of about between 1.0 and 100 mg/Kg, preferably about
1.0 to 25mg/Kg and more preferably about 2.5 to 10mg/Kg. The high
range would be required in particularly resistant cases (e.g. when an
25 animal is infected with a resistant strain). The required dose level and
duration of treatment are within the purview of one of ordinary skill in the
art. A preferred treatment regimen for horses with EPM or bovines with
Neosporosis is about 1.0 to 25 mg/Kg, and a more preferred range is
about 2.5 to 10 mg/Kg of triazinetrione every 28 days.

30 For the single high dose treatment the triazineone is administered
in pharmaceutically effective amounts that are greater than 10 mg/Kg and
up to about 100 mg/Kg. It is a distinct feature of the invention the

compounds of this invention can be non-toxic, thus they can be administered at high dose levels. The advantage of the high dose administration resides in the fact repeated doses are not required. For the single high dose treatment, Ponazuril has been found to be both safe and effective at doses as high as 100 mg/Kg body weight. Unlike art-related compounds, the triazineone compounds which are equivalent to Ponazuril are preferred in that they do not cause detrimental side effects if administered at very high dose levels.

Without being bound to any particular theory of the invention, it is believed that the unexpected success of the treatments described herein results from the ability of the triazineone compounds to cross the blood-brain barrier or placental barrier. It is believed that the compounds of this invention easily cross the blood-brain barrier and, also, are able to penetrate the placenta and kill the protozoa *in situ* in the brain and cerebral spinal fluid/spinal cord. It has been further found that the compounds of this class are non-toxic and non-mutagenic even at the high doses necessary for the single high dose treatment regimen described herein.

Heretofore, no cost-effective, easily administered drugs have been available for effectively treating and protecting against these diseases without producing unacceptable side effects such as toxicity or mutagenicity in animals. The following is a description of the triazineone compounds with particularity but without limitation to Toltrazuril compounds. This disclosure and the claimed invention also encompass other triazineone compounds that are useful in the manner of the Toltrazuril compounds. The Toltrazuril compounds useful herein are of formula (1):



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in which

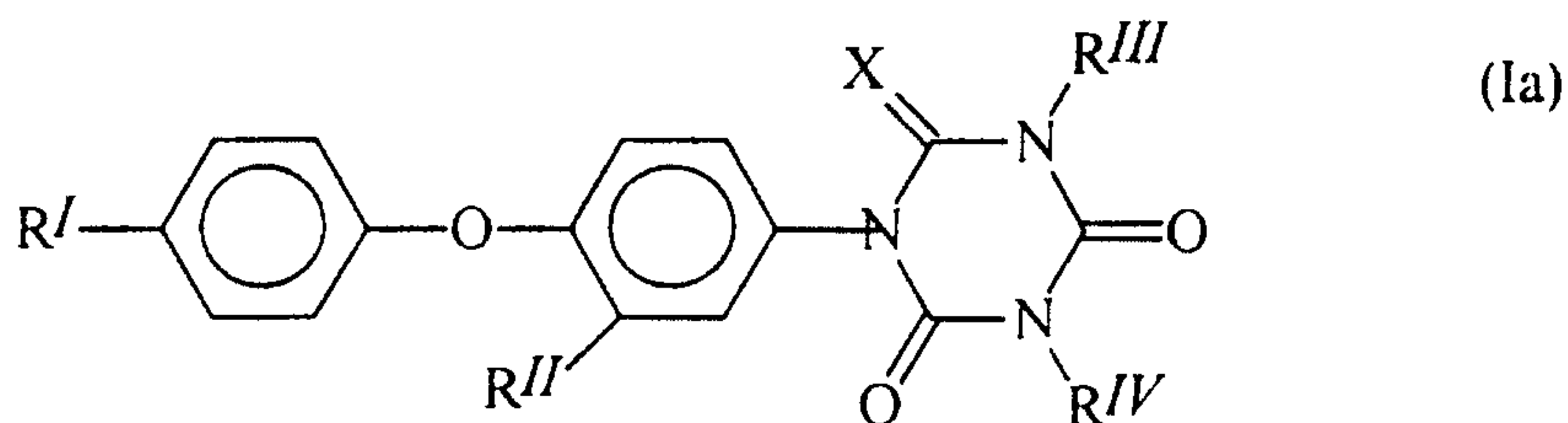
R^1 represents halogenoalkylthio, halogenoalkyl-sulphinyl or halogenoalkylsulphonyl,

R^2 represents hydrogen, alkyl, alkoxy, alkoxyalkyl, alkylmercapto, halogen, halogenoalkyl or an optionally substituted sulphamoyl, such as dialkyl sulphamoyl, radical,

R^3 and R^4 can be identical or different and represent hydrogen, alkyl, alkenyl or alkynyl and X is O or S, and their physiologically acceptable salts.

Furthermore, it has been found that, in particular, the following compounds of the formula Ia and their physiologically acceptable salts have, can be useful herein:

15



20

in which

R^I represents halogenoalkyl(C_1 - C_4)-thio, halogenoalkyl(C_1 - C_4)-sulphinyl or halogenoalkyl(C_1 - C_4)-sulphonyl,

R^{II} represents hydrogen, alkyl (C_1 - C_4), alkoxy (C_1 - C_4), halogen, alkoxy(C_1 - C_4)alkyl(C_1 - C_4), alkyl (C_1 - C_4)-mercapto, dialkyl (C_1 - C_4)aminosulphonyl or halogenoalkyl (C_1 - C_4) and

R^{III} and R^{IV} can be identical or different and represent hydrogen, alkyl (C_1 - C_4) or alkenyl (C_2 - C_4) and X is O or S. and X is O or S. Finally, it has been found that

30

(a) 1-(4-phenoxy-phenyl)-1,3,5-triazines of the formula I are obtained when compounds of the formula II

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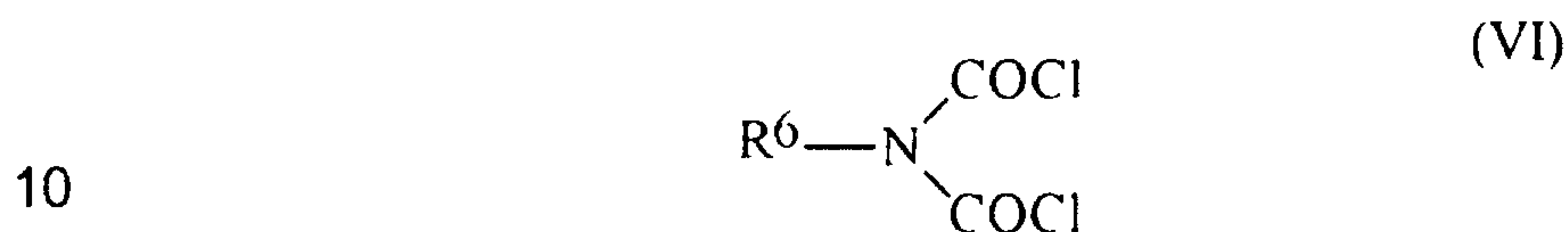
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A represents alkyl, alkenyl or alkynyl and

Z represents halogen;

or that

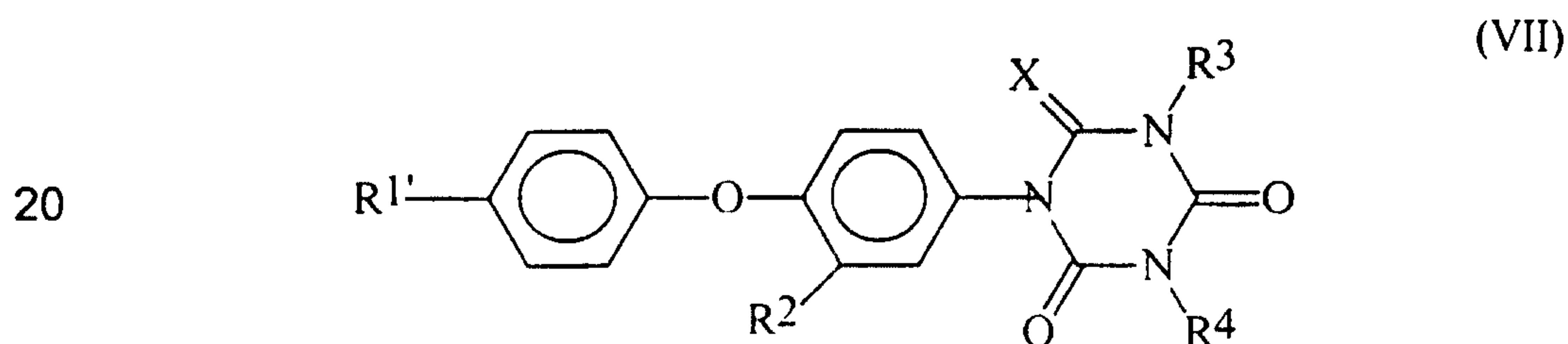
(b) 1-(4-phenoxy-phenyl)-1,3,5-triazine derivatives of the general
 5 formula I are obtained when compounds of the formula II, in which R^1 , R^2 ,
 R^3 and X have the meaning indicated above, are reacted with bis-
 (chlorocarbonyl)-amines of the formula VI



in which

R^6 represents alkyl, optionally in the presence of acid acceptors or that

(c) in order to obtain compounds of the formula I in which the
 15 substituents R^2 , R^3 and R^4 as well as X have the meaning indicated above
 and R^1 represents halogenoalkylsulphinyl or halogenoalkylsulphonyl, com-
 pounds of the formula



in which

R^2 , R^3 and R^4 have, the meaning indicated above and

25 R^1 represents halogenalkylthio,

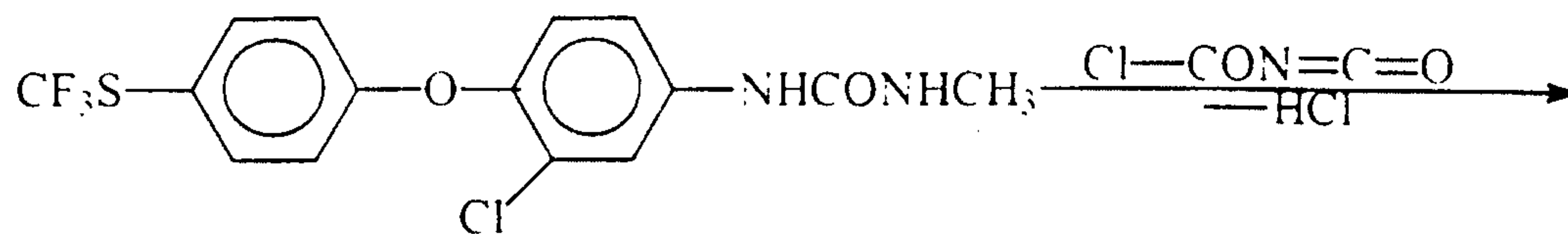
are reacted with the appropriate amount of a suitable oxidizing agent..

If N-[3-chloro-4-(4'-trifluoromethylthio-phenoxy)-phenyl]-N'-
 methyl-urea and chlorocarbonyl isocyanate are used in process variant
 (a), the course of the reaction can be represented by the following
 30 equation:

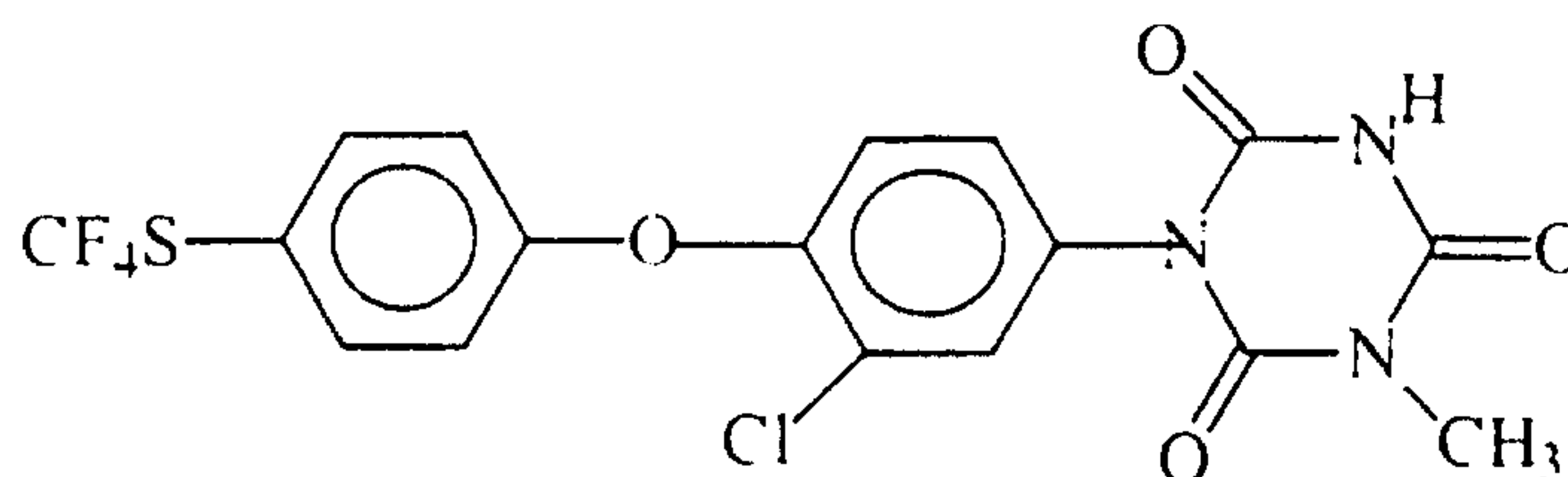
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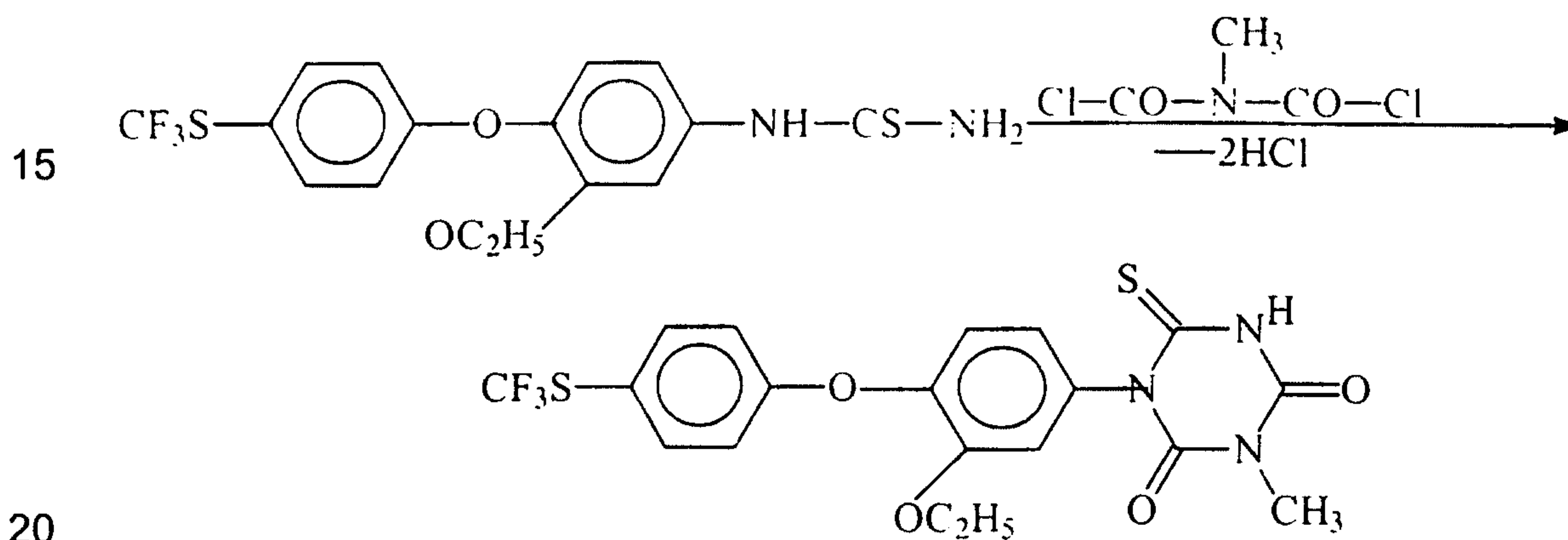
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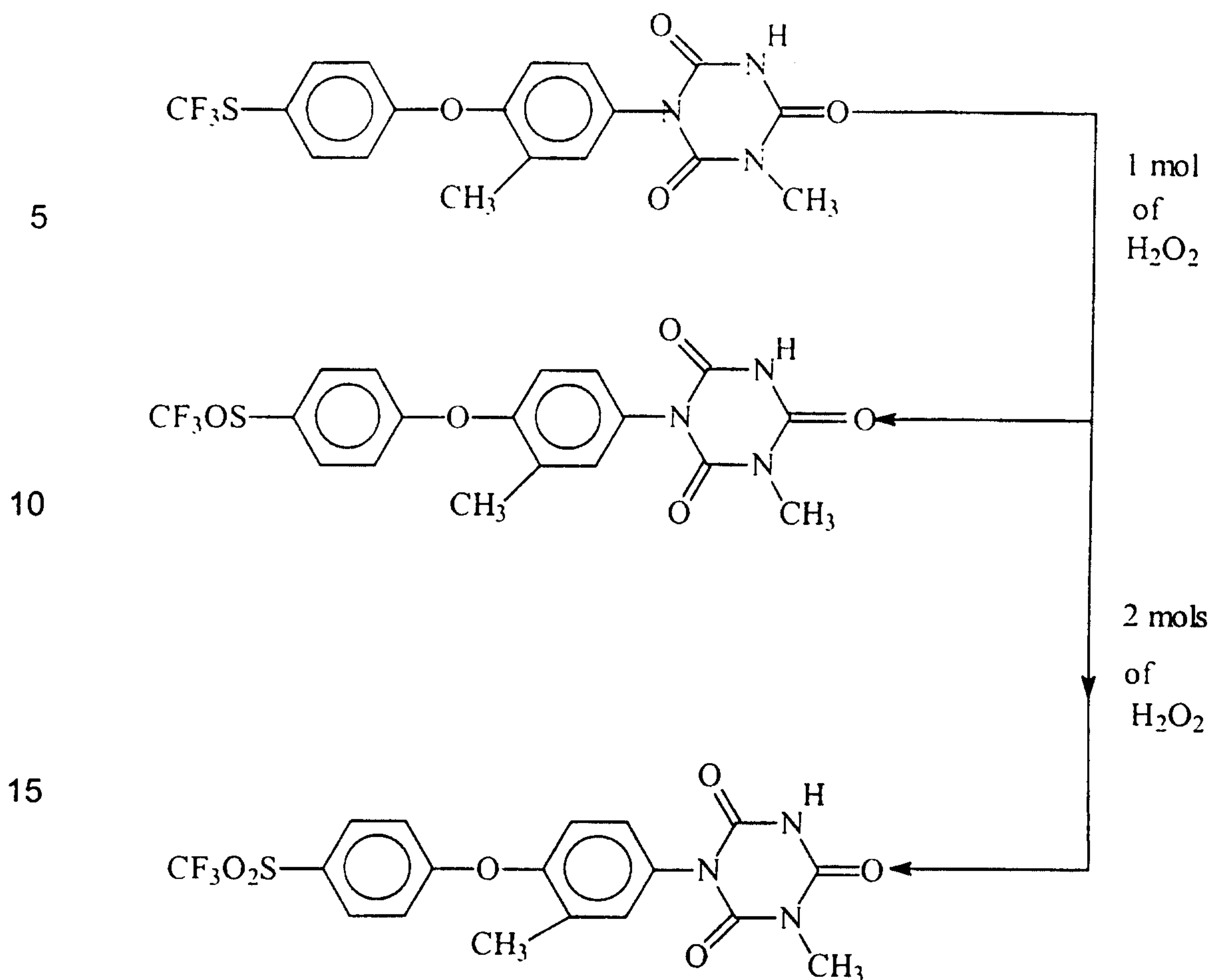
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If N-[3-ethoxy-4-(4'-trifluoromethylthio-phenoxy)-phenyl]-thiourea
 and N-methyl-bis-(chlorocarbonyl) amine are used as the starting
 materials in process variant (b), the course of the reaction can be
 represented by the following equation:



The compounds of the general formula I, obtained according to
 process variant (a) or (b), in which R₁=halogenoalkylthio and X=O can be
 oxidized according to process variant (c) to the corresponding halogeno-
 alkylsulphinyl or halogenoalkylsulphonyl derivatives. If hydrogen peroxide
 is used as the oxidizing agent, the course of the reaction can be
 represented by the following equation:



In the formulae I, II, IV, V, VI and VII, alkyl as defined in R^2 , R^3 , R^4 , R^6 or A is straight-chain or branched alkyl with preferably 1 to 6, in particular 1 to 4, carbon atoms. Examples that may be mentioned are optionally substituted methyl, ethyl, n- and i-propyl and n-, i- and t-butyl.

In the formulae I, II, IV, V and VII, alkenyl as defined in R^3 , R^4 or A is straight-chain or branched alkenyl with preferably 2 to 6, in particular 2 to 4, carbon atoms. Examples, which may be mentioned, are optionally substituted ethenyl, propen-1-yl, propen-2-yl and buten-3-yl.

In the formulae I, II, IV, V and VII, alkynyl as defined in R^3 , R^4 or A is straight-chain or branched alkynyl with preferably 2 to 6, in particular 2 to 4, carbon atoms. Examples which may be mentioned are optionally substituted ethynyl, propen-1-yl, propin-2-yl and butin-3-yl.

In the formulae I, II, III, IV and VII, alkoxy as defined in R^2 or R^5 is straight-chain or branched alkoxy with preferably 1 to 6, in particular 1 to

4, carbon atoms. Examples which may be mentioned are optionally substituted methoxy, ethoxy, n- and i-propoxy and n- and i-butoxy.

In the formulae I, II, III, IV, V and VII, halogen as defined in R^2 , R^5 or Z is preferably fluorine, chlorine, bromine and iodine, especially chlorine and bromine.

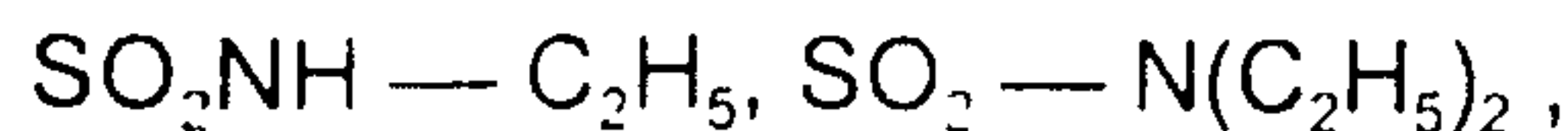
In the formulae I, II, IV and VII, halogenoalkylthio as defined in R^1 is halogenoalkylthio preferably 1 to 4, in particular 1 or 2, carbon atoms preferably 1 to 5, in particular 1 to 3, identical or different halogen atoms, halogen atoms preferably being fluorine, chlorine and bromine, especially fluorine and chlorine. Examples which may be mentioned are trifluoromethylthio, chloro-di-fluoromethylthio, bromomethylthio, 2,2,2-trifluoroethylthio and pentafluoroethylthio.

In the formulae I, II and IV, halogenoalkylsulphinyl as defined in R^1 is halogenoalkylsulphinyl with preferably 1 to 4, in particular 1 or 2, carbon atoms and preferably 1 to 5, in particular 1 to 3, identical or different halogen atoms, halogen atoms preferably being fluorine, chlorine and bromine, especially fluorine and chlorine. Examples which may be mentioned are trifluoromethylsulphuryl, chloro-di-fluoromethylsulphuryl, bromomethylsulphinyl, 2,2,2-trifluoroethylsulphinyl and pentafluoroethylsulphinyl.

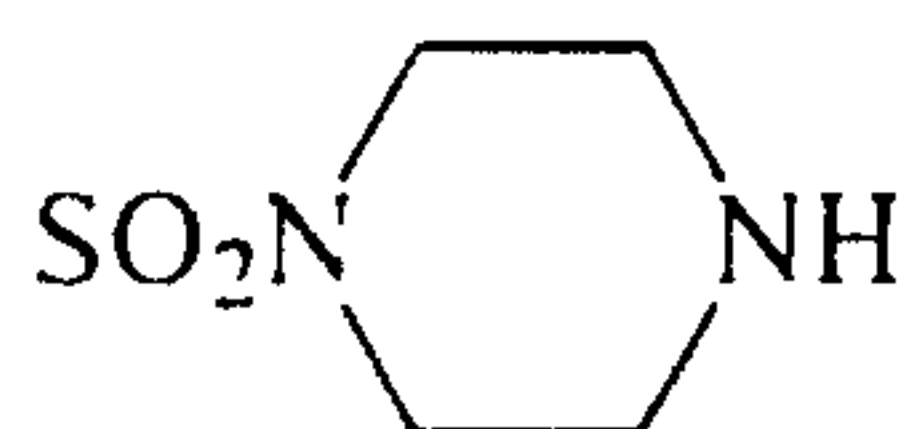
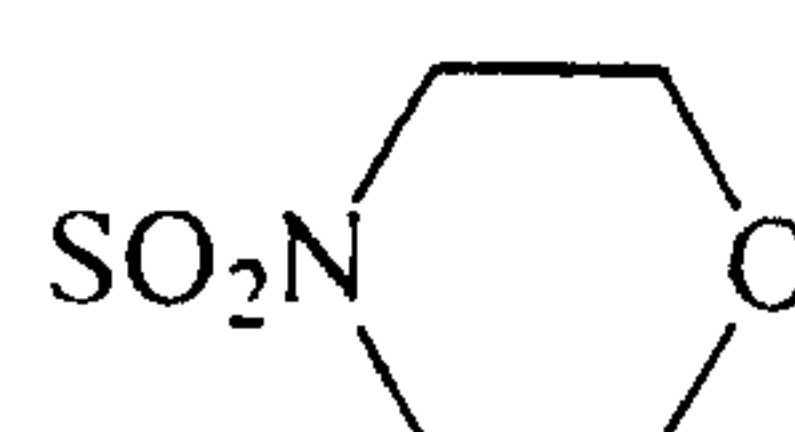
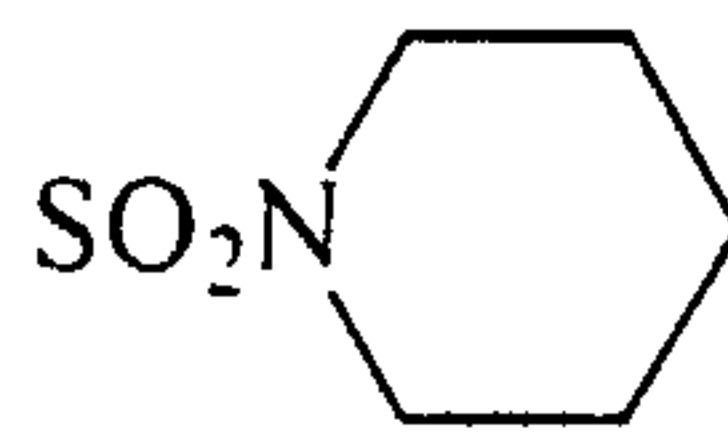
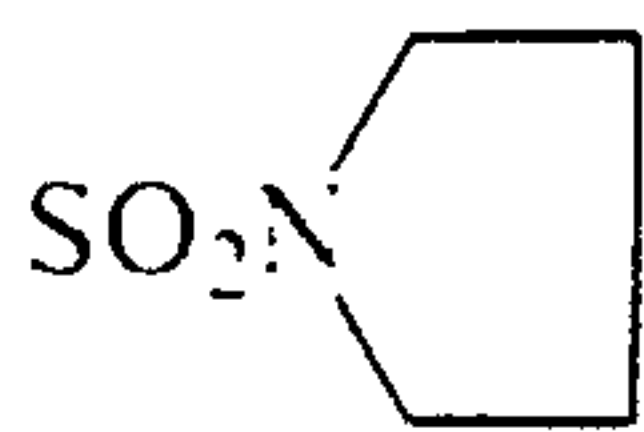
In the formulae I, II and IV, halogenoalkylsulphonyl as defined in R^1 is halogenoalkylsulphonyl with preferably 1 to 4, in particular 1 or 2, carbon atoms and preferably 1 to 5, in particular 1 to 3, identical or different halogen atoms, halogen atoms preferably being fluorine, chlorine and bromine, especially fluorine and chlorine. Examples which may be mentioned are trifluoromethylsulphonyl, chloro-di-fluoromethylsulphonyl, bromomethylsulphonyl, 2,2,2-trifluoroethylsulphonyl and pentafluoroethylsulphonyl.

In the formulae I, II, and IV, optionally substituted sulphamoyl as defined in R^2 is preferably one of the following radicals:

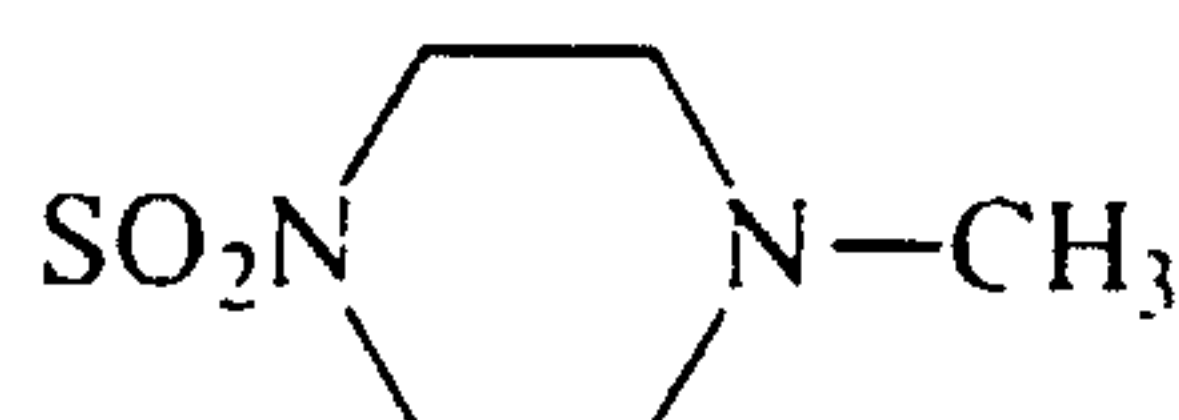




5



and



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In the formulae III, aryloxy as defined in R^5 is preferably monocyclic carbocyclic aryloxy or bicyclic carbocyclic aryloxy, particularly phenoxy.

In the formulae III, aryloxy R^5 is preferably phenoxy.

Most of the substituted ureas or thioureas of the formula II which
 15 are used as starting materials have not been known hitherto, but they can be easily prepared by methods which are in themselves known by (a) either reacting substituted 4-aminodiphenyl ethers with the corresponding substituted isocyanates or isothiocyanates in an inert solvent at temperatures between 0°C . and 100°C ., or, reversing the sequence, (b)
 20 reacting ammonia or substituted amines and the corresponding substituted isocyanato or 4-isothiocyanato-diphenyl ethers with one another under the same conditions, or by (c) subjecting substituted 4-hydroxyphenyl-ureas or -thioureas to a condensation reaction with activated halogenoaromatic compounds in aprotic solvents, such as
 25 dimethylsulphoxide, dimethylformamide or hexamethylphosphoric acid triamide, in the presence of bases, such as sodium hydride, potassium hydroxide, potassium carbonate z.a.m., at temperatures between 20°C . and 150°C .

When the amount of solvent is appropriately chosen, the reaction
 30 products generally crystallize out on cooling the solution. Literature for the alternate preparation of ureas from amines and isocyanates is: Methoden

der Org. Chemie (Methods of Organic Chemistry) (Houben-Weyl), IVth edition, Volume VIII, page 157-158.

Some of the bis-(chlorocarbonyl)-amines of the general formula VI which can be used according to the invention in process (b) are already
5 known (compare the article in Synthesis 1970, page 542-543) and, if they are not yet known, they can be prepared in an analogous manner from cyclic diacyldisulphides and chlorination in inert organic solvents, preferably in carbon tetrachloride.

Possible diluents for the reaction of the ureas or thioureas of the
10 formula II both with carbonyl isocyanates of the formula III (process variant a) and with bis(chlorocarbonyl)-amines of the formula VI (process variant b) as well as for the reaction of the 1,3,5-triazine derivatives of the formula IV with compounds of the formula A-Z are all the organic solvents which are inert in these reactions.

15 These include, in addition to the pyridine, preferably, aromatic hydrocarbons, such as benzene, toluene and xylene, halogenated aromatic hydrocarbons, such as chlorobenzene and dichlorobenzene, and ethers, such as tetrahydrofurane and dioxane.

The hydrochloric acid which may form during the reaction escapes
20 as a gas or can be bonded by organic or inorganic acid acceptors. The acid acceptors include, preferably, tertiary organic bases, such as trialkylamines, for example, triethylamine, N-hetero mono- or bi-cyclic aromatic amines, such as pyridine aza-cyclo alkyl amines which are mono- or bi-cyclic, such as diazabicyclononene, diazabicycloundecene and many
25 others, or inorganic bases, such as alkali metal carbonates, oxides or hydroxides or alkaline earth metal carbonates, oxides or hydroxides.

The reaction temperatures for the above-mentioned reaction stages can be varied within a wide range. In general, the reaction is carried out between about 0°C. and about 150°C., preferably between about 20°C.
30 and about 100°C.

In the above-mentioned reaction stages, the reaction can be carried out under normal pressure or under elevated pressure. In general, the reaction is carried out under normal pressure.

Possible oxidizing agents for the conversion, according to process variant (c) of the trifluoromethylthio compounds of the general formula 1, in which Y represents oxygen, into the corresponding sulphinyl or sulphonyl compounds are, appropriately: H_2O_2 /glacial acetic acid; H_2O_2 /acetic anhydride; H_2O_2 /methanol; peracids, such as, for example, m-chloropero-benzoic acid, and chromic acid; potassium permanganate; sodium periodate, cerise ammonium nitrate; and nitric acid.

A resulting compound can be converted into a corresponding addition salt, for example by reacting it with an inorganic or organic base.

In the practice of the invention, the triazineone compound can be formulated in any convenient manner into compositions or formulations for administration to animals. Formulations suitable for oral administration, which is preferred herein, can be suspensions, tablets, capsules, gels, pastes, boluses, or preparations in the form of powders, granules, or pellets. The preferred orally administered formulation is in the form of a paste or a feed additive. Other modes of administration that can be employed include parenteral, topical, intramuscular, and intramucosal or by other routes known to those skilled in the art. Topical administration in the form of a pour-on is also preferred.

Typically, pharmaceutically acceptable carriers and auxiliaries are employed in the formulations. Examples thereof can be a thickening agents selected from the group consisting of: Carbopol, inorganic thickeners such as silicates, bentonites or colloidal silica and organic thickeners such as fatty alcohols or fatty acid esters and the wetting agent is selected from the group consisting of polyethylene glycol and sodium lauryl sulfate with Carbopols, more specifically, Carbopol 974P being the most preferred thickening agent for the paste formulation preferred herein. Also employed herein can be preservatives selected from the group consisting of parabens, alcohols and aldehydes. These may be liquid,

solid, or gaseous materials, which are otherwise inert or medically acceptable and are compatible with the active ingredients.

Surprisingly, the pastes of the present invention are effective in delivering the triazineones, particularly Toltrazuril, and Ponazuril to cross the blood-brain or placenta barrier and attack the parasites which have already invaded the brain or infected the fetus of a pregnant animals. As a matter convenience, there is provided herein a description of a specific embodiment of the preferred pastes and how it is prepared. A preferred paste, according to the present invention contains a micronized suspension of the triazinetrione (e.g., Ponazuril), propylene glycol, a thickening agent such as Carbopol, preservatives such as Methylparaben and Propylparaben, and water. It can be made by combining water, typically, purified water and Propylene Glycol, heating the combination to about 70°C., and adding the preservatives, at this temperature. The resulting mixture is cooled to room temperature after which Carbopol, preferably in the form of Carbopol 974P, is added. Finally the triazinetrione is added. After complete mixing, the pH is adjusted to approximately 6.0 with sodium hydroxide. The most preferable paste includes 15% w/w Ponazuril, 20% w/w Propylene Glycol, 0.5% w/w Carbopol 974P, 0.14% w/w Methylparaben, 0.02%w/w Propylparaben, 0.1%w/w sodium hydroxide with the remainder being purified water. Sweeteners including dextrose, sucrose, lactose, fructose, sorbitol, xylitol, artificial sweeteners and molasses may be added to improve palatability. Additionally, yeast or liver flavoring may be added for the same purpose.

The invention is further described by following illustrative but non-limiting examples.

EXAMPLES

EXAMPLE 1

A pharmacokinetic study was conducted in horses comparing blood levels of Toltrazuril, Ponazuril and Toltrazuril Sulfoxide at various times post a single dose of Toltrazuril. All horses received a single dose of 10 mg/kg, which was administered orally as a suspension. Blood samples

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were drawn at the time of treatment (0) and at 0.25, 0.5, 1, 2, 4, 6, 12, 24, 48 and 72 hours post treatment. Results of the sampling are listed in Table 1. It was surprising to note that horses receiving Toltrazuril demonstrated relatively high levels of Ponazuril in their serum.

- 5 Additionally, significant levels of Toltrazuril sulfoxide were found in the bloodstream. This was an indication that Ponazuril, alone, would produce acceptable blood levels that are envisioned to pass the blood-brain barrier, a characteristic required to treat neurological diseases such as those caused by *Sarcocystis neurona*, *Toxoplasma gondii*, *Neospora*
10 *caninum* and *Neospora heugesi*.

TABLE 1 Pharmacokinetics of a Single Dose of Toltrazuril in Horses

D	Compound Measured	Concentration in mg/l of Blood				
		0	0.25	0.5	1	2
A	Toltrazuril		0.027	0.773	2.863	4.511
	Toltrazuril-Sulfoxide		<0.01	0.077	0.070	0.159
	Ponazuril		0.010	0.089	0.088	0.171
B	Toltrazuril		0.061	0.393	2.617	4.296
	Toltrazuril Sulfoxide		<0.01	0.025	0.047	0.083
	Ponazuril		<0.01	0.029	0.036	0.040
C	Toltrazuril		0.061	0.560	3.286	5.788
	Toltrazuril Sulfoxide		<0.01	0.024	0.041	0.097
	Ponazuril		<0.01	0.013	0.019	0.026
D	Toltrazuril		0.017	0.295	3.286	2.165
	Toltrazuril Sulfoxide		<0.01	0.027	0.039	0.058
	Ponazuril		<0.01	0.011	0.021	0.024
E	Toltrazuril		<0.01	0.039	1.146	3.175
	Toltrazuril Sulfoxide		<0.01	<0.01	0.021	0.064
	Ponazuril		<0.01	<0.01	0.017	0.015
F	Toltrazuril		0.110	0.428	1.741	--
	Toltrazuril Sulfoxide		<0.01	0.026	0.044	--
	Ponazuril		<0.01	0.012	<0.01	--

D	Compound Measured	Concentration in mg/l of Blood				
		6	12	24	48	72
A	Toltrazuril	5.149	5.066	6.434	7.607	6.653
	Toltrazuril-Sulfoxide	0.167	0.230	0.407	0.732	0.592
	Ponazuril	0.108	0.170	0.324	1.622	1.933
B	Toltrazuril	11.474	11.670	11.690	6.677	5.058
	Toltrazuril Sulfoxide	0.320	0.451	0.566	0.454	0.346
	Ponazuril	0.131	0.254	0.255	0.831	0.880
C	Toltrazuril	14.202	13.751	--	9.758	7.633
	Toltrazuril Sulfoxide	0.280	0.436	--	0.477	0.377
	Ponazuril	0.061	0.135	--	0.540	0.642
D	Toltrazuril	3.816	10.544	7.236	8.234	--
	Toltrazuril Sulfoxide	0.133	0.668	0.461	0.749	--
	Ponazuril	0.030	1.651	0.315	0.986	--
E	Toltrazuril	11.335	12.032	8.694	6.869	--
	Toltrazuril Sulfoxide	0.259	0.430	0.481	0.741	--
	Ponazuril	0.074	0.268	0.231	0.501	--
F	Toltrazuril	10.966	6.660	10.224	7.096	--
	Toltrazuril Sulfoxide	0.245	0.453	0.633	0.642	--
	Ponazuril	0.061	0.725	0.192	0.532	--

EXAMPLE 2:

Ponazuril, 1-methyl-3-[4-p-[trifluoromethyl)sulfonylphenoxy]-m-tolyl]-s-triazine-2,4,6 (1H,3H,5H)-trione, a representative Triazinetrione, was formulated into a paste for administration to horses. The components listed in Table 2 were used in preparing formulations as follows.

Table 2 Components of Ponazuril Horse Paste

Ingredient	Theoretical Amount	Actual Amount % w/w
Ponazuril – Micronized	22.5 Kg	15.0
Propylene Glycol	30.0 Kg	20.0
Carbopol 974P	0.750 Kg	0.5
Methylparaben, NF	0.210 Kg	0.14
Propylparaben, NF	0.030 Kg	0.02
Sodium Hydroxide, NF	0.150 Kg	0.10
Purified Water	96.365 Kg	64.24

The formulations were prepared using process (A) and (B) as follows. The first process (A) comprised: 1) Mixing a portion of the water with the Propylene Glycol; 2) adding the preservatives (Methylparaben and Propylparaben; 3) slowly adding the Carbopol 974P until an even suspension was prepared; 4) adding the Ponazuril in a micronized form; 5) adding the Sodium Hydroxide to bring the suspension to a pH of approximately 6.0; and 6) adding the remainder of the water to QS to volume. The final suspension was in the form of a paste, which can be delivered orally to a horse.

The second process (B) comprised: 1) Mixing a portion of the water with the Propylene Glycol; 2) heating to 70°C; 3) adding the preservatives (Methylparaben and Propylparaben while holding the solution at 70°C; 4) cooling the solution to room temperature; 5) slowly adding the Carbopol 974P until an even suspension was prepared; 6) adding the Ponazuril in a micronized form; 7) adding the Sodium Hydroxide to bring the suspension

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to a pH of approximately 6.0; and 8) adding the remainder of the water to QS to volume. The final suspension was also in the form of a paste, which can be delivered orally to a horse.

5 The resulting pastes were administered to horses and found to be palatable and well accepted.

EXAMPLE 3:

Ponazuril, 1-methyl-3-[4-p-[trifluoromethyl)sulfonylphenoxy]-m-tolyl]-s-triazine-2,4,6 (1H,3H,5H)-trione, a representative Triazinetrione, was tested for its ability to treat horses already demonstrating signs of Equine
10 Protozoal Myoencephalitis (EPM). The compound was formulated into a paste using Ponazuril as a 15% active ingredient (a.i.) as described in EXAMPLE 1. It was administered to horses already diagnosed with EPM once a day for 28 days at a dose rate between 2.5 mg/Kg and 10mg/Kg.

Naturally occurring clinical cases of EPM were well characterized
15 by signalment and laboratory diagnosis. The diagnosis used for incorporation of EPM-positive horses into this trial was as follows: Confirmed asymmetrical neurological deficit as determined by a standardized neurological examination, to include radiography, indicative of EPM; Positive Western Blot for *Sarcocystis neurona* IgG; Red Blood
20 Cell count below 500 cells/mL; CSF indices - Total Protein <90, IgG index >0.3. AQ quotient <2.2.

Additional requirements were that the horses were not suffering from diseases other than EPM. Therefore, they had to meet the following criteria: Negative CSF (<1:4) for EHV-1; Normal serum values for Vitamin
25 E (.2.0 µg/mL); Lack of seizure disorders; Lack of behavior disorders.

Diagnosed horses were randomly assigned to groups. Group 1 horses received the paste formulation daily at a dose rate of 5mg/Kg whereas Group 2 horses received the paste formulation daily at a dose rate of 10mg/Kg. The treatment dose was based on body weight. The
30 horses were evaluated for a period of 90 days (approximately 60 days after discontinuation of treatment) in order to determine that treatment was

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indeed effective. The response to treatment was scored using the following system:

- 1) 0 = complete success-clinically normal with a negative CSF; 2) 1 = Deficit just detected at a normal gait; 3) 2 = Deficit easily detected and exaggerated by backing, turning, swaying, jaw loin pressure and neck extension; 4) 3 = Deficit very prominent on walking, Facial turning, loin pressure or neck extension; 5) 4 = Stumbling, tripping and falling down spontaneously; 6) 5 = Recumbent, unable to rise. An improvement of one (1) unit in the score was considered a significant improvement.

- 10 Results of this study are shown in Table 3. All (100%) of the horses in the 10 mg/Kg group which were treated for 28 days showed a significant improvement in clinical score by day 90 post start of treatment with Ponazuril (day 0). Eight of nine (88.9%) horses treated with the 5mg/Kg dose demonstrated acceptable improvement. When adding all of
- 15 the scores for each group for each treatment day, a total score is obtained. The improvement in total scores demonstrated by both Group 1 and Group 2 horses is approximately equivalent. It is thus concluded that Ponazuril at either a 5mg/Kg or 10mg/Kg is effective for the active treatment of EPM in horses.

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TABLE 3: Response of EPM-Infected Horses to Treatment with Toltrazuril Sulfone

Horse ID	5 mg/Kg Dose			10 mg/Kg Dose		
	Day 0	Day 28	Day 90	Day 0	Day 28	Day 90
A	2	1	2			
B	2	1	1			
C				4	2	1
D				3	2	0
E				2	2	1
F	3	2	0			
G				2	1	1
H				2	2	1
I	2	1	0			
J	2	0	0			
K				3	0	0
L	2	3	3			
M	2	2	0			
N	2	2	0			
O	3	3	2			
TOTAL	17	13	6	19	15	4

5 EXAMPLE 4:

In order to determine the scope of protection provided by Ponazuril, *in vitro* testing was conducted. The following strains of parasites were evaluated for their sensitivity to this compound: Strain SN3 of *Sarcocystis neurona*; strain SF1 of *Sarcocystis falcatula*; strain RH of *Toxoplasma gondii*; and the NC-1 strain of *Neospora caninum*. Ponazuril was tested at 2 concentrations (1 µg/mL and 10 µg/mL).

Bovine turbinate (BT) cells were used for all *in vitro* studies. Cells were grown to confluency in 25 cm² flasks in RPMI 1640 media supplemented with 10% v/v fetal bovine serum (FBS), 100 Units penicillin (G/mL), 100 mg streptomycin/mL and 5 X 10⁻² mM 2-mercaptoethanol.

- 5 After cell confluence was obtained, cells were maintained in the same media with reduced FBS (2% v/v). Cell cultures were incubated at 37°C in a humidified atmosphere containing 5% carbon dioxide and 95% air.

For growth of parasites, BT cell monolayers were infected with parasites and examined with an inverted microscope for the development
10 of lesions (cytopathic effect, "CPE") or the presence of many extracellular merozoites. Once lesions were observed, or many extracellular parasites were present, the monolayer was scraped with the tip of a 5 mL pipette and 1 to 3 drops of the merozoite-containing fluid was transferred to two flasks of fresh BT cells. Merozoites of *S. neurona* and *S. falcatula* were
15 passaged in this manner every 5 to 10 days while the tachyzoites of *T. gondii* and *N. caninum* were passaged every 3 to 4 days.

The assay used to determine the effectiveness of Ponazuril was the Microtiter Monolayer Disruption Assay (MMDA). This assay was used to determine if the parasites or compound were toxic for BT cells. Flat
20 bottomed 96-well microtiter plates were inoculated with BT cells and the resulting monolayers were used to determine the effects of Toltrazuril and Ponazuril on merozoite production as measured by CPE (plaque formation). Monolayers were inoculated with parasites (*S. neurona* or *S. falcatula* at a count of 50,000/well, *T. gondii* at a level of 10,000/well, and
25 *N. caninum* at 20,000/well. All wells were inoculated with the test compound 2 hours after infection. Untreated and uninfected monolayer wells served as parasite controls and uninfected agent treated BT cells served as toxicity controls. Each treatment was examined in replicates of 6. Each well was visually monitored daily and the assay was stopped
30 when 90-100% of the untreated merozoite infected cells had lysed (90-100% CPE). All wells of the plates were rinsed in Phosphate Buffered Saline (PBS) and fixed in 100% methanol for 5 minutes after which they

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were stained in crystal violet solution. Areas of merozoite induced destruction or BT cell death due to toxicity do not take up the crystal violet. An ELISA plate reader was used to quantitate the crystal violet incorporation and these data were used to determine the concentration of Ponazuril that inhibits destruction by 50% (Inhibitory Concentration₅₀ or IC₅₀). The data demonstrating inhibition are presented in Table 4. It is noted that as little as 1µg/mL of Ponazuril provided 100% inhibition of cell destruction produced by *N. caninum*, *T. gondii* and *S. falcatula* whereas 10µg/mL of Ponazuril was required to produce 100% inhibition of cell destruction by *S. neurona*. This indicates that triazineones such as Toltrazuril and Ponazuril would be efficacious for treatment of diseases caused by the Coccidia known to associated with neurological and abortigenic disease syndromes including diseases caused by *S. neurona*, *N. caninum*, *N. hughesi* and *T. gondii*. Additionally, Ponazuril was not toxic to the BT cells.

TABLE 4: In vitro Data on Ponazuril

Organism	Percent Inhibition of Cell Destruction			
	0.1µg/mL	1µg/mL	5.0µg/mL	10µg/mL
<i>Sarcocystis neurona</i>	0	40	90	100
<i>Sarcocystis falcatula</i>	61	100	100	100
Organism	Percent Inhibition of Cell Destruction			
	0.001µg/mL	0.01µg/mL	0.1µg/mL	1.0µg/mL
<i>Neospora caninum</i> NC-1	3	13	100	100
<i>Toxoplasma gondii</i>	11	16	100	100

EXAMPLE 5:

This experiment was conducted in order to determine whether triazineones such as Toltrazuril can pass the blood-brain barrier. Normal horses were divided into three groups of three horses per group. Group 1 horses received Toltrazuril administered orally as a 5% suspension at a dose level of 2.5 mg/Kg. Group 2 horses received Toltrazuril administered orally as a 5% suspension at a dose level of 5.0 mg/Kg. Group 3 horses received Toltrazuril administered orally as a 5% suspension at a dose level of 7.5 mg/Kg. The dosing was repeated daily for 10 days. Blood samples were drawn at 48, 96 and 240 hours and the concentration of Toltrazuril, Toltrazuril sulfoxide and Ponazuril in the serum was measured. Ten days after the start of the treatment (Day 10), a sample of cerebral spinal fluid was removed from each horse and the concentrations of Toltrazuril, Toltrazuril Sulfoxide and Ponazuril were again measured in these samples. The concentrations of Toltrazuril, Toltrazuril Sulfoxide and Ponazuril in the serum and cerebral spinal fluid are reported in TABLES 5a and 5b. Concentration of Ponazuril in the blood and cerebral spinal fluid after treatment of horses with Toltrazuril was significant, in that the concentration of Ponazuril in the cerebral spinal fluid after treatment of horses with Toltrazuril was essentially equivalent to the concentration of Toltrazuril itself. This is evidence that both Toltrazuril and Ponazuril effectively cross the blood-brain barrier and that Ponazuril crosses this barrier more effectively than does Toltrazuril. The data would suggest to one skilled in the art that the triazineones can also effectively cross the placental barrier.

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TABLE 5a Drug Levels after Repeated Doses of Toltrazuril in Horses

Horse ID	10 Day Dose (mg/Kg)	Toltrazuril Level			Cerebral Spinal Fluid – Day 10
		48 Hrs	96 Hrs	240 Hrs	
1	2.5	4.49	9.85	15.29	0.23
2	2.5	4.0	9.09	9.60	0.06
3	2.5	11.6	13.1	15.21	0.15
4	5.0	7.28	14.17	24.92	0.19
5	5.0	9.18	14.03	16.54	0.12
6	5.0	9.26	18.19	17.59	0.26
7	7.5	N/A	27.74	30.08	0.50
8	7.5	9.90	19.55	24.15	0.21
9	7.5	10.46	18.47	23.53	0.45
AVG	2.5mg/Kg Dose	6.70	10.68	13.37	0.15
AVG	5.0 mg/Kg Dose	8.57	15.46	19.68	0.19
AVG	7.5 mg/Kg Dose	10.18	21.92	25.95	0.39

TABLE 5b Drug Levels after Repeated Doses of Ponazuril in Horses

Horse ID	10 Day Dose (mg/Kg)	Ponazuril Level			Cerebral Spinal Fluid – Day 10
		48 Hrs	96 Hrs	240 Hrs	
1	2.5	0.29	0.99	2.61	0.09
2	2.5	0.24	1.15	2.36	0.07
3	2.5	3.70	3.13	4.04	0.11
4	5.0	0.48	2.09	5.44	0.12
5	5.0	0.63	2.03	2.03	0.14
6	5.0	0.48	2.66	5.61	0.21
7	7.5	6.35	2.69	6.31	0.23
8	7.5	0.78	2.89	6.37	0.17
9	7.5	0.52	3.09	7.06	0.27
AVG	2.5mg/Kg Dose	1.41	1.76	3.00	0.09
AVG	5.0 mg/Kg Dose	0.53	2.26	5.02	0.16
AVG	7.5 mg/Kg Dose	2.55	2.89	6.58	0.22

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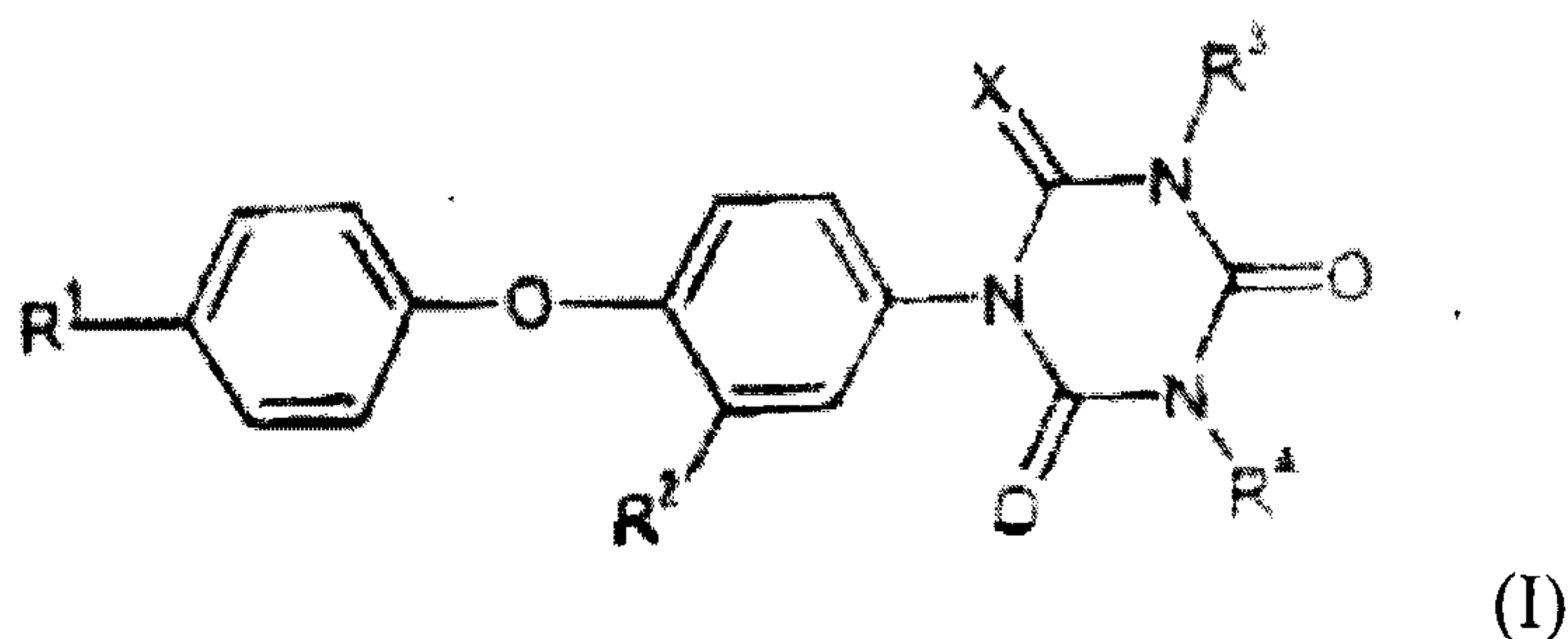
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Although the invention has been described in detail in the foregoing
for the purpose of illustration, it is to be understood that such detail is
solely for that purpose and that variations can be made therein by those
skilled in the art without departing from the spirit and scope of the
5 invention except as it may be limited by the claims.

CLAIMS:

1. Use of a triazineone compound of the formula (I):



in which:

R¹ represents halogenoalkylthio, halogenoalkyl-sulphinyl or halogenoalkylsulphonyl,

R² represents hydrogen, alkyl, alkoxy, alkoxyalkyl, alkylmercapto, halogen, halogenoalkyl or an optionally substituted sulphamoyl,

R³ and R⁴ can be identical or different and represent hydrogen, alkyl, alkenyl or alkynyl and

X is O or S,

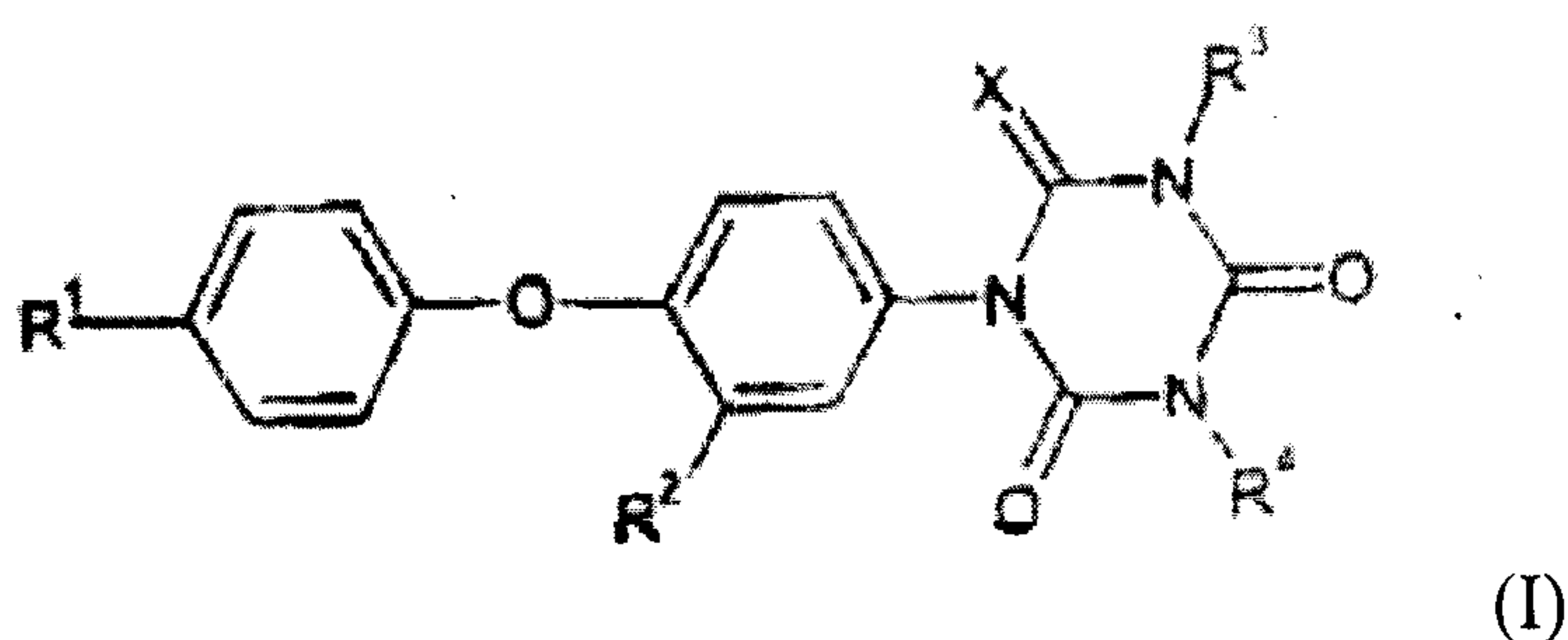
or a physiologically acceptable salt thereof, provided that said compound of formula (I) is other than ponazuril;

for preparing a pharmaceutical composition for the treatment of a neurologic disease or an abortigenic disease caused by Coccidia selected from the group consisting of Neospora spp and Toxoplasma spp.

2. Use according to claim 1, wherein the Neospora spp is Neospora caninum.
3. Use according to claim 1, wherein the Toxoplasma spp is Toxoplasma gondii.
4. Use according to any one of claims 1 to 3, wherein said composition is for the metaphylactic treatment of said disease.
5. Use according to any one of claims 1 to 4, wherein R² is dialkyl sulphamoyl.

6. Use according to any one of claims 1 to 4, wherein the triazineone compound is Toltrazuril.

7. A pharmaceutical composition for the treatment of a neurologic disease or an abortigenic disease caused by Coccidia selected from the group consisting of Neospora spp and Toxoplasma spp comprising a triazineone compound of the formula (I):



in which:

R¹ represents halogenoalkylthio, halogenoalkyl-sulphinyl or halogenoalkylsulphonyl,

R² represents hydrogen, alkyl, alkoxy, alkoxyalkyl, alkylmercapto, halogen, halogenoalkyl or an optionally substituted sulphamoyl,

R³ and R⁴ can be identical or different and represent hydrogen, alkyl, alkenyl or alkynyl and

X is O or S,

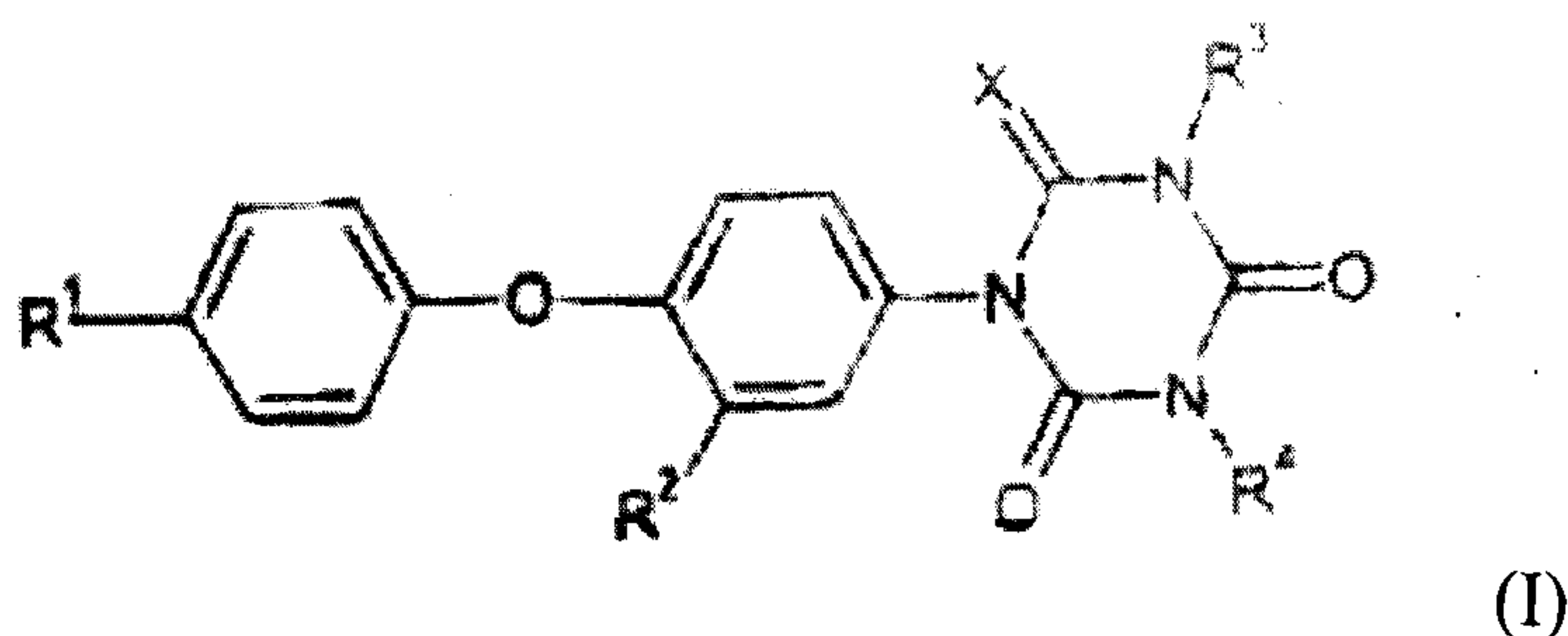
or a physiologically acceptable salt thereof, provided that said compound of formula (I) is other than ponazuril;

in association with a pharmaceutically acceptable carrier.

8. A pharmaceutical composition according to claim 7, wherein the Neospora spp is Neospora caninum.

9. A pharmaceutical composition according to claim 7, wherein the Toxoplasma spp is Toxoplasma gondii.

10. A pharmaceutical composition according to any one of claims 7 to 9, wherein said composition is for the metaphylactic treatment of said disease.
11. A pharmaceutical composition according to any one of claims 7 to 10, wherein R^2 is dialkyl sulphamoyl.
12. A pharmaceutical composition according to any one of claims 7 to 10, wherein the triazineone compound is Toltrazuril.
13. A triazineone compound of the formula (I):



in which:

R^1 represents halogenoalkylthio, halogenoalkyl-sulphinyl or halogenoalkylsulphonyl,

R^2 represents hydrogen, alkyl, alkoxy, alkoxyalkyl, alkylmercapto, halogen, halogenoalkyl or an optionally substituted sulphamoyl,

R^3 and R^4 can be identical or different and represent hydrogen, alkyl, alkenyl or alkynyl and

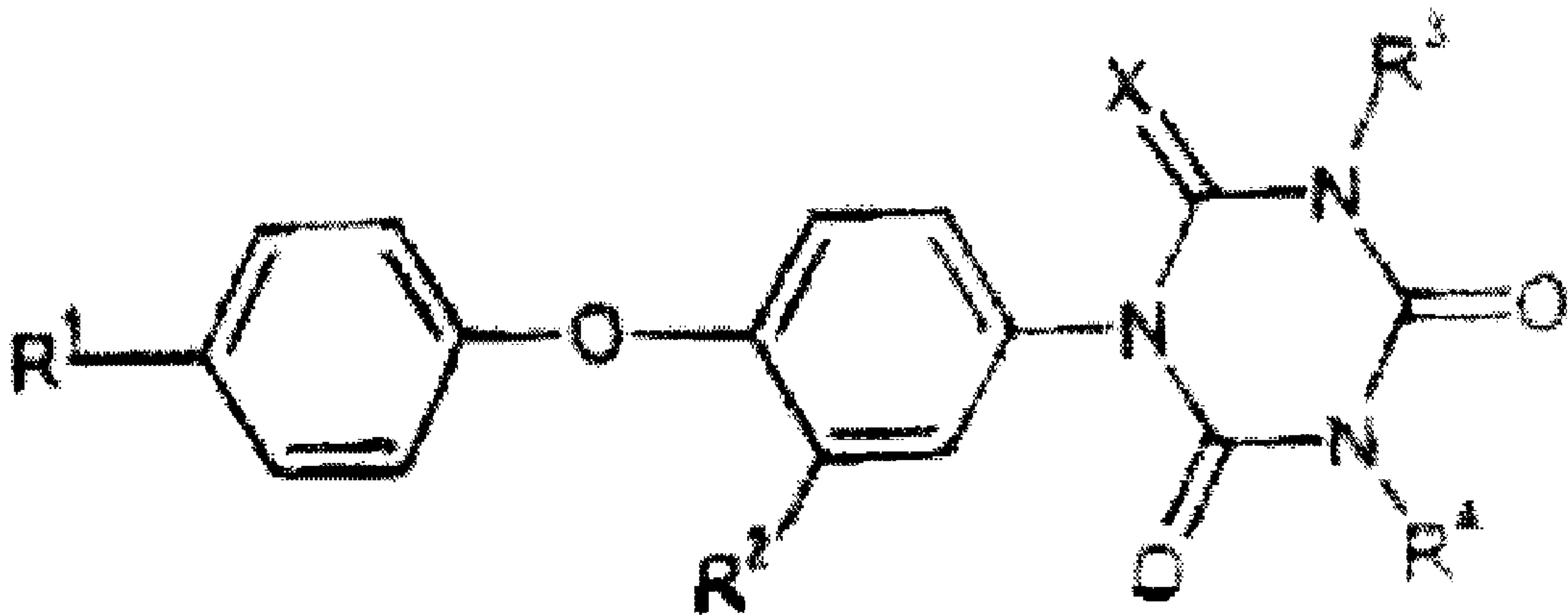
X is O or S,

or a physiologically acceptable salt thereof, provided that said compound of formula (I) is other than ponazuril;

for use in the treatment of a neurologic disease or an abortigenic disease caused by Coccidia selected from the group consisting of Neospora spp and Toxoplasma spp.

14. A triazineone compound according to claim 13, wherein the Neospora spp is Neospora caninum.

15. A triazineone compound according to claim 13, wherein the *Toxoplasma* spp is *Toxoplasma gondii*.
16. A triazineone compound according to any one of claims 13 to 15, for the metaphylactic treatment of said disease.
17. A triazineone compound according to any one of claims 13 to 16, wherein R^2 is dialkyl sulphamoyl.
18. A triazineone compound according to any one of claims 13 to 16, wherein the triazineone compound is Toltrazuril.



(I)