

Thiazolodiazepines: New Ultra-short Acting Hypnotics

Named Inventors and Addresses

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Field of Invention

The present invention relates to new derivatives of thiazolodiazepine analogs which are useful ultra-short acting hypnotic agents.

Abstract

The synthesis and hypnotic evaluation of a new generation of thiazolo[3,2-*a*]-[1,3]diazepine analogs are described. Those compounds exhibit potent *in vivo* activities as ultra-short acting hypnotics.

Background of the Invention

Surgical procedures require the administration of several intravenous drugs to ensure hypnosis, analgesia, relaxation and control of visceral reflex responses. The use of intravenous drugs adds flexibility and permits the administration of lower doses of inhalational anesthetic agents. Intravenous anesthetic, appropriate to the requirements of surgery, becomes available with the introduction of thiopental, an ultrashort -acting barbiturate. General anesthesia most often is initiated by an injection

of thiopental to induce sleep prior to administration of the agents that are necessary for maintaining anesthesia during the surgical procedure. Thiopental sodium, other ultrashort- acting barbiturates and benzodiazepines have an important place in the practice of anesthesiology. Thiopental sodium remains the standard for comparison with new agents.

Barbiturates act throughout the CNS and can produce all degrees of depression of CNS ranging from mild sedation to general anesthesia. Barbiturates are able to enhance the action of the inhibitory neurotransmitter GABA acting at GABA_A receptors. GABA_A receptors, the major type of GABA receptors in the brain, is an integral membrane chloride channel that mediates most of the rapid, inhibitory neurotransmission in the CNS. Single intravenous anesthetic dose of thiopental sodium produces unconsciousness within 10-20 seconds. The depth of anesthesia may increase for up to 40 seconds then decreases progressively until consciousness returns in 20-30 minutes. However, recovery may require many hours if large dose of thiopental is administered (Hughes et al in *Anesthesiology*, 1992, 76, 334-341). Thiopental is metabolized slowly in the liver, which together with other factors such as binding of thiopental by plasma proteins, changes in blood pH or changes in the distribution of blood flow may influence the depth of anesthesia, time of recovery and duration of action of thiopental (Breimer in *Clin. Pharmacokinet.* 1997, 2, 93-109).

Thiopental sodium is administered intravenously. It may be injected either as a single bolus, intermittently or as a continuous infusion. The use of continuous infusion however, increases the likelihood of overdose, with a subsequent prolonged recovery time. For single or intermittent injections of thiopental sodium, the concentration employed should not exceed 2.5 % in aqueous solution. When concentration greater than 2.5% is injected extravascularly, the pain may be severe

and tissue necrosis may occur. Meanwhile, following intraarterial injection of concentrated solution of thiopental, arterial endothelium and deeper layer are immediately damaged and endarteries follows, often with thrombosis exacerbated by subsequent arteriolar spasm. Vascular ischemia and even gangrene may result (Marshall and Longnecker in *Goodman and Gilman, the pharmacological basis of therapeutics*, 1996, pp. 321-323).

The anesthetic effect of thiopental sodium is closely parallel to its concentration in the blood reaching the brain, because the high lipid solubility of thiopental sodium allows it to cross the blood brain barrier without noticeable delay. Recovery from the anesthetic effect occurs rapidly "about 5 minutes", governed entirely by redistribution of the drug to well-perfused tissues. After the initial rapid decline, the blood concentration drops more slowly over several hours, as the drug is taken up by the body fat and metabolized. Consequently, thiopental sodium produces a long lasting hangover (Rang et al in *Pharmacology*, Rang, H.P., Dale, M.M. and Ritter, J.M., eds. Churchill Livingstone, 1999, pp. 515-527). A total dose of 1 g of thiopental generally should not be exceeded if prolonged recovery is to be avoided. The larger the initial dose of thiopental sodium is required, the larger the supplementary doses must be, even in patient of the same size. Patients who use large initial dose of thiopental sodium will awaken despite plasma concentration that normally would cause sleep. The nature of this acute tolerance is not known (Marshall et al in *Goodman and Gilman, the pharmacological basis of therapeutics* 1996, pp. 321-323). For this reason, thiopental sodium can not be used to maintain surgical anesthesia, but only as an induction agent.

Recovery following the administration of thiopental should be characterized by smooth and rapid awakening to consciousness. However, if there is postoperative

pain, restlessness may become evident and analgesia should be given. Thiopental and other barbiturates are poor analgesics and may even increase sensitivity to pain when administered in proper amounts. Additionally, recovery following thiopental is often accompanied by shivering as heat is generated to restore body temperature that has decreased during anesthesia and surgery. Postural hypotension may be encountered and patient should not be moved too hurriedly.

Thiopental sodium produces a dose-related depression of the respiration that can be profound. Following a dose of thiopental sodium sufficient to cause sleep, tidal volume is decreased and despite a small increase of respiratory rate, the minute volume is reduced. The functional residual capacity may be reduced, especially if coughing occurs (Marshall et al in *A Practice of Anesthesia*, Henly, D. and Cohen, P., eds. 1995, 119-145). Larger doses of thiopental sodium cause more profound changes and respiration is maintained only by movements of the diaphragm.

In the presence of hemorrhage or other form of hypovolemia, circulatory instability, sepsis, toxemia or shock, the administration of a normal dose of thiopental sodium may result in hypotension, circulatory collapse and cardiac arrest. Cerebral blood flow and cerebral metabolic rate are reduced with thiopental sodium and other barbiturate. Intracerebral pressure is reduced markedly and this effect is utilized clinically in circumstances when elevated intracrineal pressures are expected (Shapiro, in *Anesthesiology*, 1975, 43, 445-471). Thiopental sodium has little effect on uterine contraction, but it does cross the placenta and depress the fetus.

Benzodiazepines were first introduced for the treatment of anxiety and large number of these compounds with sedative, antianxiety, anticonvulsant and muscle relaxant properties have been synthesized. Hypnosis and unconsciousness may be produced with large doses of benzodiazepine. Benzodiazepines are not analgesics, nor

can they produce a state of surgical anesthesia when used alone. It is necessary to combine several drugs to achieve surgical levels of anesthesia with a balance of sedation, analgesia, amnesia, relaxation and freedom from reflex stimulation. Benzodiazepines are useful as the sole agent for procedures that do not require analgesia, such as endoscopy, cardiodepression, cardiac catheterization and a spectrum of radiodiagnostic procedures (Marshall et al in *Goodman and Gilman, the pharmacological basis of therapeutics* 1996, pp. 233-235).

For induction of anesthesia, the benzodiazepines are given intravenously. To minimize the burning sensation and avoid venous thrombosis that might accompany the administration of diazepam, benzodiazepines should be injected very slowly into the side port of a running intravenous infusion. Following intravenous injection of diazepam, the drug is rapidly distributed to the brain, but unlike thiopental, several minutes pass before the onset of drowsiness. Therefore, diazepam should be administered for preanesthetic medication one hour before the patient is transported to the operating area. In the doses used to supplement or induce anesthesia, benzodiazepines cause sedation, reduction of anxiety and amnesia in 50 % or more of patients. The amnesia may last up to 6 hours (Marshall et al in *Goodman and Gilman, the pharmacological basis of therapeutics* 1996, pp. 233-335).

Benzodiazepines cause only moderate depression of the circulation and respiration. Large doses may cause 20% decrease in systemic blood pressure and vascular resistance. Transient apnea may follow the rapid injection of diazepam and facilities for the support of respiration always should be available. Diazepam neither causes emesis nor prevents it and has little effect on renal, hepatic or reproductive functions. Although diazepam induces relaxation of spastic muscle, which is centrally mediated, it has no effect on the neuromuscular junction and does not enhance or

antagonize the actions of specific muscle relaxants. Benzodiazepines cross placenta rapidly and can depress the fetus (Marshall et al in *Goodman and Gilman, the pharmacological basis of therapeutics* 1996, pp. 233-235).

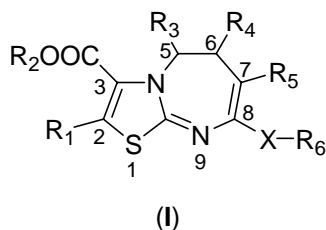
The major molecular targets of the benzodiazepines are inhibitory neurotransmitter receptors directly activated by the amino acid GABA. The major type of GABA receptors in the brain, termed GABA_A receptors, is an integral membrane chloride channel that mediates most of the rapid, inhibitory neurotransmission in the CNS. GABA_B receptors are not altered by benzodiazepines. Benzodiazepines directly bind to the receptor/ion channel complex and allosterically modulate its activity. Unlike barbiturates, benzodiazepines do not directly gate GABA_A receptors but require GABA to express their effects (Marshall et al in *Goodman and Gilman, the pharmacological basis of therapeutics* 1996, pp. 233-235).

The present invention overcomes many of the disadvantages and problems that usually accompanied the administration of thiopental sodium or benzodiazepines as intravenous anesthetic agents and create an intravenous anesthetic agent that not only induce anesthesia but also maintain the anesthetic state during the surgical procedure, the synthesized series of the new compounds when compared with thiopental sodium showed very rapid onset of action and shorter duration of action with no acute tolerance or noticeable side effects related to the administration of thiopental sodium.

Brief Description of the Invention

The invention is directed to the synthesis of a new generation of thiazolo-[3,2-*a*][1,3]diazepine analogs. These derivatives possess potential to exhibit

promising ultra-short acting hypnotic activity. These compounds have the general formula (I):



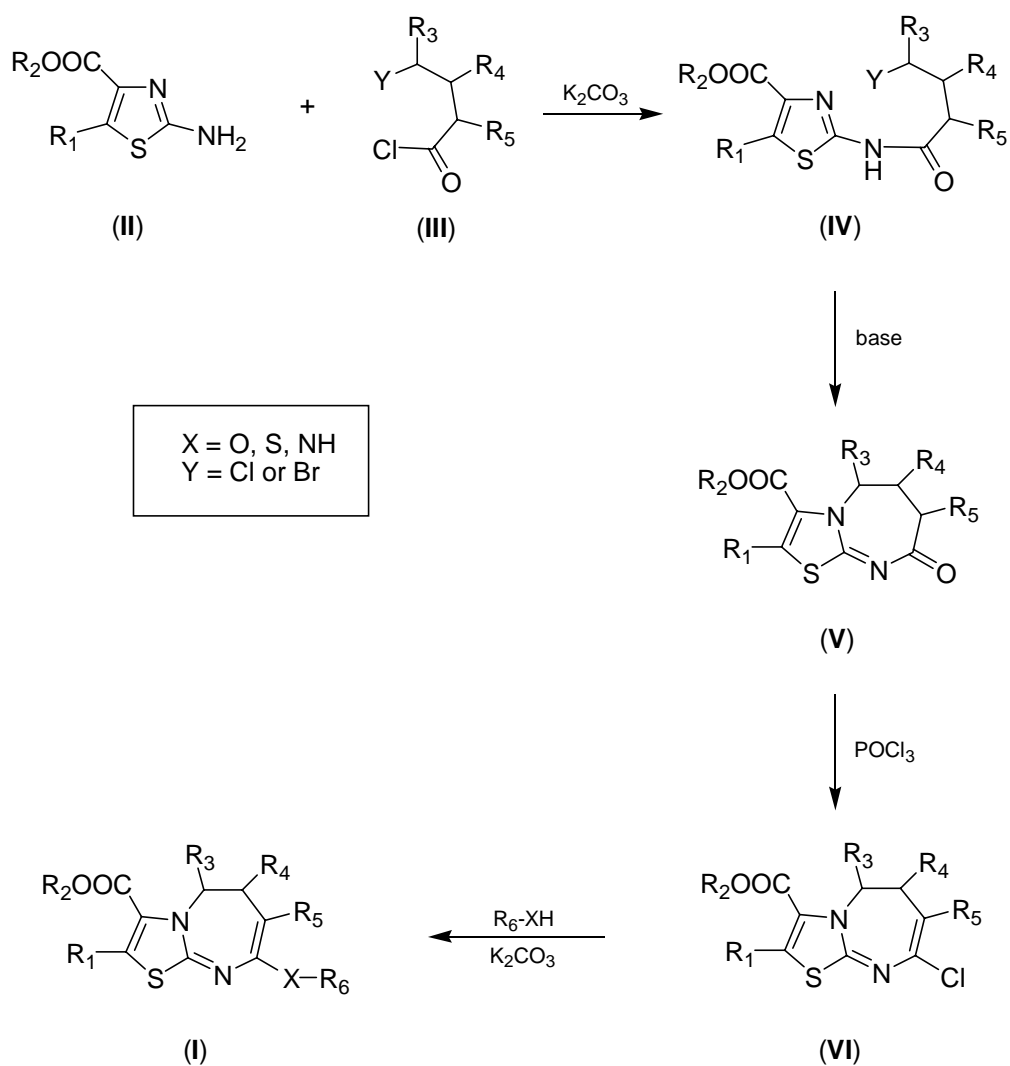
R_1 , R_3 , R_4 , R_5 and R_6 each independently represents hydrogen, optionally substituted straight-chain or branched alkyl, having 1 to 7 carbon atoms, halogen, optionally substituted haloalkyl, alkoxy or haloalkoxy in which or the alkyl is straight-chain or branched and has 1 to 4 carbon atoms and the halo derivatives are mono-, di-, tri- or poly- halosubstituted. Optional substituents include halogen, amino, substituted amino, alkyl having 1 to 4 carbon atoms, halo-(C₁-C₄) alkyl, alkoxy or haloalkoxy having 1 to 4 carbon atoms in the alkyl group. R_1 , R_3 , R_4 , R_5 and R_6 each independently represent aryl, substituted aryl heteroaryl, substituted heteroaryl. Optionally substituents include halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, alkylamino, aryl, heteroaryl, aryloxy, haloaryloxy, arylthio, arylamino. R_2 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl or substituted straight-chain or branched alkyl groups of up to 10 carbon atoms, or halogen, amino or substituted amino to form acid amides, optional substituents includes alkyl, alicyclic, aryl or heteroaryl moieties. R_3 is hydrogen or can be taken together with R_4 to form substituted alicyclic, aryl or heteroaryl ring systems. R_4 is hydrogen or can be taken together with R_5 to form substituted alicyclic, aryl or heteroaryl ring systems. X is O, S or NH or optionally reduced into hydroxyl or mercapto function. This hydroxy or mercapto function is alkylated with R_6 which is straight chain or branched alkyl groups having 1 to 7 carbons, alicyclic, aryl or heteroaryl groups.

The acids with which addition salts can be formed preferably include hydrohalic acids such as for example, hydrochloric acid and hydrobromic acid, and also phosphoric acid, nitric acid, monofunctional and bifunctional carboxylic acids hydroxy carboxylic acids, such as, acetic acid, maleic acid, succinic acid, fumaric acid, tartaric acid, salicylic acid, sorbic acid and lactic acid, as well as sulphonic acids such as, p-toluenesulphonic acid and naphthalene-1,5-disulphonic acid.

Detailed Description of the Invention

Thiazolo[3,2-*a*][1,3]diazepine analogs could be obtained adopting methods published by P. Molina et al in *J. Org. Chem.* 1993, 58, 5264-5270; P. Imming in *Arch. Pharm. (Wienheim)* 1995, 238, 207-215. The compounds of invention and their analogs (**I**) are synthesized according to an inventive method. The proper 2-amino-5-substituted-thiazole-4-carboxylate (**II**) prepared using methods published by R. Kuhn et al in *Ann. Chem.* 1951, 571, 44-56; B. Plouvier et al in *J. Heterocyclic Chem.* 1989, 26, 1643-51; were alkylated with the suitable acid chloride derivatives (**III**), where y is chlorine or bromine, preferably bromine, and anhydrous potassium carbonate in a suitable solvent, such as, for example, toluene, ethylbenzene, o-, m-, and p-xylene, octane, nonane and isopropylbenzene, preferably toluene and ethylbenzene at temperature ranging from about 100° to 150°C, preferably 100-120°C. The products (**IV**) can be purified by silica gel and neutral alumina chromatography. Compounds of the formula (**IV**) were cyclized using secondary amines, such as for example, diethylamine, pyrrolidine, morpholine, piperidine, N-methylpiperazine, preferably pyrrolidine and piperidine, in a suitable solvent, such as for example toluene, ethylbenzene, o-, m-, and p-xylene, isopropylbenzene, preferably toluene, o-xylene at

Scheme 1



temperature ranging 100-180°C, preferably 120-130°C. The products of the formula (V) were obtained and purified using either silica gel or alumina column chromatography. Compounds of the formula (V) were reacted with phosphorous oxychloride to produce the 8-chloro analogs (VI) which were reacted directly with R₆-XH and anhydrous potassium carbonate in a suitable solvent, such as for example, acetone, ethanol, methylethylketone, dimethylformamide, dimethylsulfoxide, diphenyl ether, preferably methylethylketone, dimethylformamide at temperature

ranging from about 60° to 200°C, preferably 120-160°C. The products (**I**) can be purified by silica gel and neutral alumina chromatography. Representative examples of such synthesis are shown in Examples 1 and 2.

R₁, R₃, R₄, R₅ and R₆, of the formula (**I**), each independently represents hydrogen, optionally substituted straight-chain or branched alkyl, having 1 to 7 carbon atoms, halogen, optionally substituted haloalkyl, alkoxy or haloalkoxy in which or the alkyl is straight-chain or branched and has 1 to 4 carbon atoms and the halo derivatives are mono-, di-, tri- or poly- halosubstituted. Optional substituents include halogen, amino, substituted amino, alkyl having 1 to 4 carbon atoms, halo-(C₁-C₄) alkyl, alkoxy haloalkoxy having 1 to 4 carbon atoms in the alkyl group.

R₁, R₃, R₄, R₅ and R₆, of the formula (**I**), each independently represents aryl substituted aryl heteroaryl, substituted heteroaryl connected directly or through NH, S or carbon bridges, such as for example, carbocyclic aromatics including phenyl and naphthyl, heterocyclic moieties can include, substituted furyl, pyrrolyl, thienyl, imidazolyl, pyridinyl, pyridazinyl, pyrimidinyl groups. Optionally substituents include halogen, such as chloro, bromo, and fluoro; C₁-C₅ linear or branched chain alkyl such as methyl, ethyl, propyl, isopropyl; alkoxy having 1 to 3 carbon atoms such as methoxy and ethoxy or halogenoalkoxy each having 1 to 3 carbon atoms; alkylthio, alkylamino, arylthio, heteroarylthio, arylamino, heteroarylamino.

R₂ is hydrogen, methyl, ethyl, propyl, isopropyl butyl or substituted straight-chain or branched alkyl groups of up to 10 carbon atoms, or halogen, amino or substituted amino to form acid amides, optional substituents include alkyl, alicyclic, aryl or heteroaryl moieties. R₃ is hydrogen or can be taken together with R₄ to form substituted alicyclic, aryl or heteroaryl ring systems. R₄ is hydrogen or can be taken together with R₅ to form substituted alicyclic, aryl or heteroaryl ring systems. X, is O,

S or NH or optionally reduced into hydroxyl or mercapto function. This hydroxy or mercapto function could be alkylated with R₆ which is straight-chain or branched alkyl groups having 1 to 7 carbons, carbocyclic aromatics such as for example, substituted phenyl and naphthyl; heterocyclic groups which include for example, substituted furyl, pyrrolyl, thienyl, imidazolyl, pyridinyl, pyridazinyl and pyrimidinyl.

Mice of both sexes (22-28 g) were used to conduct the ultra-short acting hypnotic evaluation. They were housed in cages and kept at a temperature of $20 \pm 2^{\circ}\text{C}$ with a light-dark cycle of 12 h. and fed with standard diet and water ad libitum. Compound of the formula (I) has been dissolved in 15% cremophore EL (A derivative of castor oil and ethylene oxide, Sigma Chemical Co) in distilled water. The hypnotic activity was then tested intravenously (IV) and through intraperitoneal (IP) route.

Two doses of compound of formula (I) (50 and 100 mg/kg) were injected intravenously into two groups of mice, respectively. Each group consists of 10 mice. The sleeping time were recorded for each mouse and compared with control ultrashort-acting hypnotic agent. The effect of compound of formula (I) administered intravenously on thiopental sodium (Intraval sod. May & Baker LTD, England)-induced sleeping time was also evaluated. Three groups of mice each consists of 10 mice were used. The first group (control) injected with the solvent "15% cremophore EL", the second group treated with 50 mg/kg and the third group treated with 100 mg/kg compound of formula (I) intravenously. All mice in the three groups were then injected with thiopental sodium, 50 mg/kg intravenously. The time elapsed between the loss and the recovery of righting reflex "sleeping time" was recorded for each animal and compared with control group. Representative example is shown in Example 3.

Two doses of compound of formula (I) (100 and 200 mg/kg) were injected intraperitoneally into two groups of mice, respectively. Each group consists of 10 mice. The sleeping time were recorded for each mouse and compared with control ultrashort-acting hypnotic agent. The effect of compound of formula (I) administered intraperitoneally on thiopental sodium (Intraval sod. May & Baker LTD, England)-induced sleeping time was also evaluated. Three groups of mice each consists of 10 mice were used. The first group (control) injected with the solvent "15% cremophore EL", the second group treated with 100 mg/kg and the third group treated with 200 mg/kg compound of formula (I) intraperitoneally. All mice in the three groups were then injected with thiopental sodium, 65 mg/kg intraperitoneally (Dandiya and Cullumbine, in *J. Pharmacol. Exp. Ther.* 1959, 125, 353-359). The sleeping time was recorded for each animal and compared with control group. Representative example is shown in Example 4.

Five groups of mice, each consisting of 10 animals were used to conduct the acute toxicity test and to calculate the LD₅₀. Compound of formula (I) dissolved in 15% cremophore EL was given intraperitoneally in doses of 100, 200, 400, 800 and 1600 mg/kg, respectively. The final volume of injection in all groups did not exceed 0.2 ml ml/mouse. Twenty-four hours later, the % mortality in each group was recorded and the LD₅₀ was calculated using the method described by Litchfield and Wilcoxon in *J. Pharmacol. Exp. Ther.* 1949, 96: 99. Representative example is shown in Example 5.

Ten mice were used to conduct acute tolerance experiment. Each mouse received 200 mg/kg of compound of formula (I) dissolved in 15% cremophore intraperitoneally, 3 times/day for 3 consecutive days. After each of the 9

administrations, the sleeping time-induced by the compound of formula (I) was recorded for each mouse. Representative example is shown in Example 6.

The biological evaluation of the new compounds of the formula (I) of the invention revealed that the compounds are very short acting hypnotic. The onset of action of those compounds is very short compared to thiopental. In all animals used the onset of action was less than 60 seconds. In some animals the induction of hypnosis occurs even before the injection needle withdrawn from the animal. Its duration of action when given IV or IP is significantly shorter than the standard intravenous anesthetic agent, thiopental sodium. In addition, those compounds did not show any sign of acute tolerance reported with the second (maintenance) dose of thiopental sodium. Therefore, those compounds of the formula (I) of the invention have the potential use not only as a preanesthetic medication and induction of anesthesia but also have the potential to be used with thiopental sodium to maintain anesthesia for longer duration than using thiopental sodium alone.

The compounds of the formula (I) of the invention, and their acid addition salts, display ultra-short acting hypnotic activity. The present invention includes pharmaceutical formulations which, in addition to non-toxic, inert pharmaceutically suitable excipients, contain one or more active compounds according to the invention, or which consist of one or more active compounds according to the invention, as well as processes for the preparation of these formulations.

The present invention also includes pharmaceutical formulations in dosage units. This means that the formulations are in the form of individual parts, for example tablets, dragees, capsules, pills, and ampoules, of which the content of active compound corresponds to a fraction or a multiple of an individual dose. The dosage units can contain, for example, 1, 2, 3 or 4 individual doses or 1/2, 1/3 or 1/4 of an

individual dose. An individual dose preferably contains the amount of active compound which is given in one administration and which usually corresponds to a whole, a half, a third or a quarter of a daily dose.

By non-toxic, inert pharmaceutically suitable excipients there are to be understood solid, semi-solid or liquid diluents, fillers and formulations auxiliaries of every kind.

Tablets, dragees, capsules, pills, granules, solutions and sprays may be mentioned as preferred pharmaceutical formulations.

Tablets, dragees, capsules and pills can contain the active compound or compounds alongside the customary excipients, such as (a) fillers and extenders, for example starches, lactose, sucrose, glucose, mannitol and silica, (b) binders, for example carboxymethylcellulose, alginates, gelatin and polyvinylpyrrolidone, (c) humectants, for example agar-agar, calcium carbonate and sodium bicarbonate, (e) solution retarders, for example paraffin, and (f) resorption accelerators, for example quaternary ammonium compounds (g) wetting agents, for example cetyl alcohol and glycerol monostearate, (h) adsorbents for example kaolin and bentonite, and (i) lubricants, for example talc, calcium stearate and magnesium stearate and solid polyethylene glycols, or mixtures of the compounds listed under (a) to (i).

The tablets, dragees, capsules and pills can be provided with the customary coatings and shells, optionally containing pacifying agents, and can also be of such composition that they release the active compound or compounds only, or preferentially, in a certain part of the intestinal tract, optionally in a delayed manner, examples of embedding compositions which can be used being polymeric substances and waxes.

The active compound or compounds, optionally together with one or more of the above mentioned excipients could also be in a micro-encapsulate form.

Solutions and emulsions for parenteral administration can contain, in addition to the active compound or compounds, the customary excipients, such as solvents, solubilizing agents and emulsifiers, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, especially cotton seed oil, groundnut oil, maize germ oil, olive oil, castor oil and sesame oil, glycerol, glycerol-formal, tetrahydrofurfuryl alcohol, polyethylene glycol and fatty acid esters of sorbitol, or mixtures of these substances, in a sterile form which is isotonic with blood.

The therapeutically active compounds should preferably be present in the above-mentioned pharmaceutical formulations in a concentration of about 0.1 to 99.5, preferably of about 0.5 to 95% by weight of the total mixture.

The above-mentioned pharmaceutical formulations can also contain other pharmaceutical formulations, can also contain other pharmaceutical active compounds in addition to the active compounds according to the invention.

The above-mentioned pharmaceutical formulations are prepared in the customary manner according to known methods, for example by mixing the active compound or compounds with the excipient or excipients.

The present invention also includes the use of the active compounds according to the invention, and of pharmaceutical formulations which contain one or more active compounds according to the invention in human and veterinary medicine.

The actual dosage unit will be determined by such generally recognized factors as body weight of the patient and/or severity and type of pathological

condition the patient might be suffering. With these considerations in mind, the dosage unit for a particular patient can be readily determined by the medical practitioner in accordance with the techniques known in the medical arts.

The precise instructions for pharmaceutical administration of the compounds and agents according to the invention necessarily depends on the requirements of the individual case, the nature of treatment, and of course the opinion of the treating doctor.

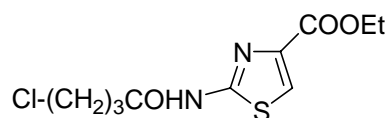
It will be understood by those skilled in the art that various modifications and substitutions may be made to the invention as described above without departing from the spirit and scope of the invention. Accordingly, it is understood that the present invention has been described by way of illustration and not limitation.

Example 1

Ethyl 2-[4-chloro-butanamido]thiazole-4-carboxylate.

A mixture of ethyl 2-aminothiazole-4-carboxylate (7.0 g, 0.04 mol) and 4-chloro-butyryl chloride (11.3 g, 9.0 ml, 0.08 mol) in toluene (100 ml) was heated under reflux for 4 h. The toluene was then evaporated under reduced pressure. The residue was then quenched with water, stirred, and filtered. The solid obtained was washed, dried and recrystallized from water to give the required product (10.2 g, 92% yield), mp 171°C, m/e 276.6 (consistent with molecular formula $C_{10}H_{13}ClN_2O_3S$, calcd. 276.73). 1H NMR and ^{13}C NMR (Table 1).

Table 1. ^1H NMR and ^{13}C NMR assignments of ethyl 2-[4-chloro-butanamido]-thiazole-4-carboxylate (Example 1).



δH	δC	Assignments
1.27 (t, 3H, $J=7.0$)	14.1	CH_3CH_2-
2.02-2.08 (m, 2H, $J=6.5, 7.3$)	27.7	$\text{ClCH}_2\text{CH}_2\text{CH}_2\text{N}-$
2.59 (t, 2H, $J=7.3$)	32.4	$\text{Cl}(\text{CH}_2)_2\text{CH}_2\text{N}-$
3.66 (t, 2H, $J=6.5$)	44.9	$\text{ClCH}_2(\text{CH}_2)_2\text{N}-$
4.27 (q, 2H, $J=7.0$)	60.8	CH_3CH_2-
7.96 (s, 1H)	122.7	Thiazole-H
12.5 (brs, 1H)	----	NH
----	141.3, 158.3	Quaternaries
----	161.3, 171.3	C=O

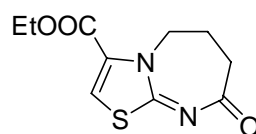
Spectra recorded in CDCl_3 . Chemical shifts are reported in ppm and J values in Hz.

Example 2

Ethyl 8-oxo-5,6,7,8-tetrahydro-thiazolo[3,2-*a*][1,3]diazepin-3-carboxylate.

A mixture of ethyl 2-[4-chloro-butanamido]thiazole-4-carboxylate (1.0 g, 0.004 mol) and piperidine (0.7 g, 0.8 ml, 0.008 mol) in toluene (50 ml) was heated under reflux for 3 h. The reaction mixture was cooled, poured into water and stirred. Toluene was separated, dried and evaporated to give a crude product which was purified by repeated silica gel and neutral alumina column chromatography eluting with EtOAc/hexane (50:50 v/v) and CHCl_3 /hexane (80:20 v/v); mp 210°C , m/e 240.2 (consistent with molecular formula $\text{C}_{10}\text{H}_{12}\text{SN}_2\text{O}_3$, calcd. 240.28) ^1H NMR and ^{13}C NMR (Table 2).

Table 2. ¹H NMR and ¹³C NMR assignments of ethyl 8-oxo-5,6,7,8-tetrahydro-thiazolo[3,2-*a*][1,3]diazepin-3-carboxylate (Example 2).



δ H	δ C	Assignments
1.22 (t, 3H, <i>J</i> =7.1)	14.6	CH ₃ CH ₂ -
2.08-2.14 (m, 2H, <i>J</i> =8.0, 4.5)	18.3	-COCH ₂ CH ₂ CH ₂ N-
2.54 (t, 2H, <i>J</i> =8.0)	31.9	-COCH ₂ CH ₂ CH ₂ N-
4.07 (t, 2H, <i>J</i> =4.5)	48.3	-COCH ₂ CH ₂ CH ₂ N-
4.19-4.23 (q, 2H, <i>J</i> =7.1)	61.4	CH ₃ CH ₂ -
7.7 (s, 1H)	122.7	Thiazole-H
----	142.1, 157.7	Quaternaries
----	161.7, 174.3	C=O

Spectra recorded in CDCl₃. Chemical shifts are reported in ppm and *J* values in Hz.

The NMR spectral data of compounds of Example 1 and Example 2 are listed in Tables 1 and 2. These assignments are based on analysis of the ¹H, Attached Proton Test (APT), the Distortionless Enhancement Polarization Transfer (DEPT), correlated spectroscopy (COSY), Heteronuclear Multiple Quantum Coherence Spectroscopy (HMQC), NMR spectra for each compound.

Example 3

Intravenous administration of ethyl 8-oxo-5,6,7,8-tetrahydro-thiazolo[3,2-*a*]-[1,3]diazepin-3-carboxylate (Example 2), 50 and 100 mg/kg, respectively, induced hypnosis in all mice within few seconds (table 3). Tachypnea was observed in 3 mice out of ten received 100 mg/kg and dyspnea was also observed in 1 mouse out of 10 mice received 100 mg/kg. Both doses of the compound, 50 and 100 mg/kg, potently potentiated the hypnotic effect produced by 50 mg/kg IV thiopental sodium (table 3).

Table 3. Hypnotic effect of ethyl 8-oxo-5,6,7,8-tetrahydro-thiazolo[3,2-*a*]-[1,3]diazepin-3-carboxylate (Example 2), 50 and 100 mg/kg IV, and its effect on the thiopental sodium ,50 mg/kg IV,-induced hypnosis in mice.

Treatment	Dose mg/kg IV	Sleeping time "min"
Thiopental Sodium	50	4.9 ± 1.13
Compound	50	0.75 ± 0.01 *
Compound	100	1.48 ± 0.21 *
Compound + Thiopental	50 + 50	19.9 ± 5.21 *
Compound + Thiopental	100 + 50	25.7 ± 5.11 *

Data are expressed as means ± S.E. n = 10.

*Significantly different as compared to thiopental, using student's t-test, P< 0.05.

Table 4. Hypnotic effect of ethyl 8-oxo-5,6,7,8-tetrahydro-thiazolo[3,2-*a*][1,3]-diazepin-3-carboxylate (Example 2) 100 and 200 mg/kg IP, and its effect on the thiopental sodium , 65 mg/kg IP,-induced hypnosis in mice.

Treatment	Dose mg/kg IP	Sleeping time "min"
Thiopental Sodium	65	15.2 ± 1.40
Compound	100	2.4 ± 0.83 *
Compound	200	9.1 ± 1.23 *
Compound + Thiopental	100 + 65	49.2 ± 3.71 *
Compound + Thiopental	200 + 65	155.7 ± 16.35 *

Data are expressed as means ± S.E. n = 10.

* Significantly different as compared to thiopental , using student's t-test, P< 0.05.

Example 4

Intraperitoneal administration of ethyl 8-oxo-5,6,7,8-tetrahydro-thiazolo- [3,2-*a*][1,3]diazepin-3-carboxylate (Example 2), 100 and 200 mg/kg, respectively, induced hypnosis in all mice with onset of action less than 1 minute (table 4). Tachypnea was observed in 2 mice out of ten received 100 mg/kg and ataxia and tachypnea were also observed in 3 mice out of 10 mice received 200 mg/kg. Both

doses of the compound, 100 and 200 mg/kg, potently potentiated the hypnotic effect produced by 65 mg/kg IP thiopental sodium (table 4).

Example 5

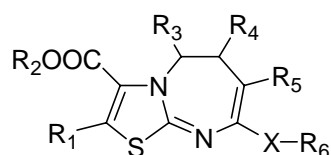
Acute toxicity test was adopted according to the method described by Litchfield and Wilcoxon, *J. Pharmacol. Exp. Ther.* 1949, 96: 99. the calculated LD₅₀ ethyl 8-oxo-5,6,7,8-tetrahydro-thiazolo[3,2-*a*][1,3]diazepin-3-carboxylate (Example 2) was found to be 681.4 mg/kg with 95% confidence limits of 482.8-876.4.

Example 6

Acute tolerance test was conducted following the IP administration of 200 mg/kg of ethyl 8-oxo-5,6,7,8-tetrahydro-thiazolo[3,2-*a*][1,3]diazepin-3-carboxylate (Example 2), 3 times/day for 3 consecutive days. There was no significant differences among the sleeping times after the first and the ninth (the last) administration of the compound. The sleeping time after the first administration of the compound was 10.3 ± 1.4 min., while after the ninth administration, the sleeping time was 8.7 ± 2.1 minutes.

Claims

1. A compound of the formula I:

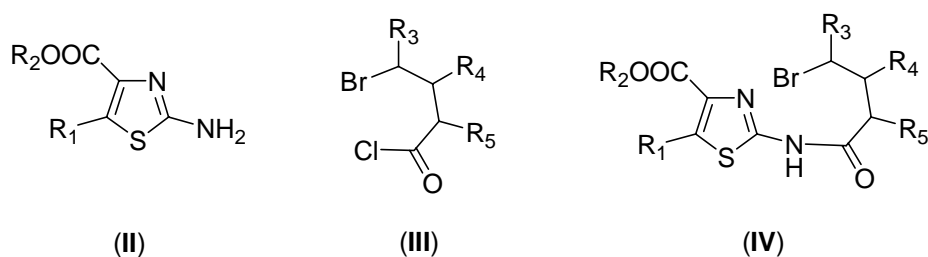


in which R₁, R₃, R₄, R₅ and R₆, each independently represents hydrogen, optionally substituted straight-chain or branched alkyl, halogen, optionally substituted haloalkyl, alkoxy or haloalkoxy, optionally substituted aryl, heteroaryl, connected directly or through NH, S or carbon bridges. R₃ can be taken together with R₄ or R₅ to form substituted alicyclic, aryl or heteroaryl ring systems. R₂ is hydrogen, optionally substituted straight-chain or branched alkyl groups, halogen, substituted amino to form acid amides, alicyclic, aryl and heteroaryl moieties. X is O, S or NH optionally reduced into hydroxyl or mercapto function and optionally substituted.

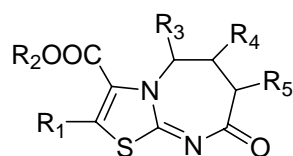
2. The compound of claim 1, wherein R₁, R₃, R₄, R₅ and R₆ each independently represents hydrogen, optionally substituted straight-chain or branched alkyl having 1 to 7 carbon atoms, halogen, optionally substituted haloalkyl alkoxy or haloalkoxy in which the alkyl is a straight-chain or branched alkyl having 1 to 4 carbon atoms and the halo- substituents are mono-, di-, or poly-substituted.

3. The compound of claim 2, wherein the optional substituents comprise halogen, C₁-C₄ alkyl, halo-(C₁-C₄)alkyl, or alkoxy or haloalkoxy having 1 to 4 carbon atoms in the alkyl group.
4. The compound of claim 1, wherein R₁, R₃, R₄, R₅ and R₆ are carbocyclic aromatics comprise phenyl, naphthyl or heterocyclic groups comprise optionally substituted furyl, pyrrolyl, thienyl, imidazolyl, pyridinyl, pyridazinyl, pyrimidinyl.
5. The compound of claim 4, wherein the optional substituents comprise chloro, bromo, and fluoro; C₁-C₅ linear or branched chain alkyl, methyl, ethyl, propyl isopropyl; methoxy, ethoxy or halogenalkoxy; alkylthio, alkylamino, arylthio, arylamino, heteroarylthio, heteroarylamino.
6. The compound of claim 1, wherein R₂ is hydrogen, methyl, ethyl, propyl isopropyl, butyl or substituted straight-chain or branched alkyl groups of up to 10 carbon atoms; halogen, amino or substituted amino to form acid amides; optional substituents include alkyl, alicyclic, aryl or heteroaryl moieties.
7. The compound of claim 1, wherein X is O, S or NH or optionally reduced into hydroxyl or mercapto function which could be alkylated with R₆ which is straight-chain or branched alkyl having 1 to 7 carbons, carbocyclic aromatics, heterocyclic ring systems.

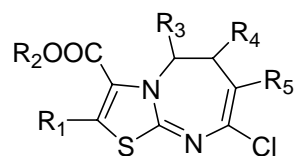
8. The compound of claim 1 and claim 7, wherein R₆ is substituted phenyl, naphthyl; substituted furyl, pyrrolyl, thienyl, imidazolyl, pyridinyl, pyridazinyl and pyrimidinyl.
9. The compound of claim 1, wherein an addition salts could be formed including hydrochloride, hydrobromide, phosphate, nitrate, acetate, malate, succinate, fumarate, tartarate, salicylate, sorbate, lactate, p-toluenesulphate, naphthaline-1,5-disulphonate salts.
10. A process for the preparation of a compound according to claim 1, comprising reacting a compound of the formula **II** with acid chlorides of the formula **III** to give compounds of formula **IV**.



11. The compound of claim 10, in which compound of the formula **IV** was cyclized into compound of the formula **V** using diethylamine, pyrrolidine, morpholine, piperidine, N-methylpiperazine. Compound of the formula **V** was chlorinated to afford compound of the formula **VI** which then condensed with R₆-XH to produce compound of the formula **I**.



(V)



(VI)

12. A pharmaceutical composition comprising at least one compound of claim 1, 2, 4, 6, 7, and 8 and a pharmaceutically acceptable carrier or excipient.
13. A method of hypnotizing an individual comprising and administering to the individual an effective amount of at least one compound of claim 1, 2, 4, 6, 7 and 8, which induce and maintain safe hypnosis with rapid onset and short duration of action with no acute tolerance.
14. A method of anesthetizing an individual comprising and administering to the individual an effective amount of at least one compound of claim 1, 2, 4, 6, 7 and 8, which potentiate the effect of currently clinically used IV anesthetic agents.