Description

Field of the Invention

This invention is concerned with 1,2,4-Triazolo[4,3-a]quinolin-1(2H)-ones including the compounds for pharmaceutical use.

Description of the Prior Art

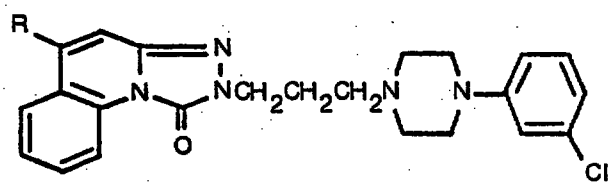
Chemical Abstracts, 9th Coll. Index 76—85 (1972—76) Page 39244 CS Col 1 describes (in the numbering used therein) certain quinoline -1(2H)-ones similar to the present quinolinones i.e. 2-(3-(4-((3-chlorophenyl)-1-piperazinyl)propyl)-5-methyl-1,2,4-triazolo (4.3-a)-quinolin-1(2H)-one and 2-(3-(4-phenyl-1-piperazinyl)propyl-5-methyl-1,2,3-triazolo (4,3-a)-quinolin-1(2H)-one.

US—A—3,381,009 refers to 1,2,4-triazolo(4,3-*a*)pyridines which are pyridine analogs of the 1,2,4-triazolo(4,3-*a*)quinolin-1(2*H*)-ones of the present invention. The preferred compound of this group of prior art substances is 2-(3-(4-(3-chlorophenyl)-1-piperazinyl)propyl)-1,2,4-triazolo(4,3-*a*)pyridin-1(2*H*)-one which is known by the name trazodone, and has also been referred to as AF 1161. Pharmacological data summarized in the foregoing patent reveals that trazodone exhibits tranquilizing action, hypotensive action, and analgesic action in various animal tests. The data resemble that of the major tranquilizers or anti-psychotic agents such as chlorpromazine more than the minor tranquilizers or anxiolytic agents such as meprobamate and diazepoxide.

The pharmacological properties of trazodone have been described in more detail by Silvestrini, et al. in International Journal of Neuropharmacology, *7*, 587—599 (1968). In clinical use the compound has proven to be an anti-depressant equivalent in effectiveness to imipramine but with fewer side effects (Fabre, et al., Current Therapeutic Research, *25* 827—834 (1979).

Summary of the Invention

The compounds with which the present invention is concerned have the following structural formula (I)



Formula I

wherein R is hydrogen or methyl. The invention includes the pharmaceutically acceptable acid additions salts of the foregoing substances and the compounds for use in the treatment of depressive disorders including endogenous depression, neurotic depression, or depression accompanying a psychosis.

The pharmaceutically acceptable acid addition salts are those in which the anion does not contribute significantly to the toxicity of pharmacological activity of the salt and, as such, they are the pharmacological equivalents of the bases of Formula (I). They are preferred for medical usage. In some instances, they have physical properties which make them more desirable for pharmaceutical formulation purposes such as solubility, lack of hygroscopicity, compressibility with respect to tablet formation and compatibility with other ingredients with which the substance may be used for pharmaceutical purposes. The salts are made by reaction of the base of Formula (I) with the selected acid preferably by contact in solution. They may also be made by metathesis or treatment with an ion exchange resin under conditions in which the anion of one salt of the substance of the formula (I) is replaced by the anion of another under conditions which allow for separation of the undesired species such as by precipitation from solution or extraction into a solvent, or elution from or retention on an ion exchange resin. Pharmaceutically acceptable acids for the purposes of said formation of the substances of Formula (I) include hydrochloric, hydrobromic, hydroidic, citric, acetic, benzoic, phosphoric, nitric, mucic, isenthionic, glucosaccharic, palmitic and hepanoic acids.

The compounds of the present invention in animal tests are comparable in antidepressant activity to thrazodone.Their physical properties are similar but they are substantially less toxic. Accordingly, they may be administered in dosage forms of similar type and size as trazodone with fewer side effects, and less toxic liability. Also, doses two or more times as great as with trazodone may be employed for enhanced effectiveness. They may be safely administered by the oral or parenteral routes in the treatment of depression in doses of from about 150 to 1200 mg daily.

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Detailed Description of the Invention

When reserpine is injected intraveneously into a mouse at a dose of 2.0 mg/kg, ptosis occurs. However, if the mouse is treated orally with one of the clinically effective antidepressant drugs such as imipramine or trazodone before the reserpine is injected, ptosis is prevented (Niemegeers, Industrial Pharmacology, Vol. 2 — Antidepressants, Ed. by S. Fielding and H. Lal, pp. 73—98, Futura, New York, N.Y. 1975). For example, an oral dose of imipramine of 6.5 mg/kg or of trazodone of 36 mg/kg will prevent resperpine from having this effect when administered subsequently in 50% of the animals (ED_{50}). The present compounds are comparable to trazodone in activity, example 1 exhibiting an ED_{50} of 29 mg/kg (per os) and example 2 exhibiting an ED_{50} of 27 mg/kg (per os) in preventing reserpine ptosis in mice.

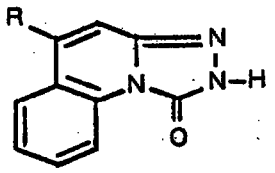
In groups of 10 mice treated variously with geometrically increasing doses of test compound of from 125 mg/kg to 2,000 mg/kg, the lethal toxicity (ALD_{50}) and the dose at which signs of pharmacologic activity are first evidenced (ATD_{50}) can be estimated. For highly active compounds lower doses of the test compound must be employed in order to estimate the ATD_{50}. The ALD_{50}/ATD_{50} ratio (mg per kg body wt/mg per kg body wt) for the compound of example 1 is 2,000/125—250 and for that of example 2 is >2,000/8—15.7. The ratio for trazodone is 940/2—4. Thus, the present substances have less than one-half the lethal toxicity of trazodone and from less then one-half to one-fiftieth the propensity for producing overt signs of physiolocial effect (ATD_{50}) on oral administration to mice. More particularly, the present substances exert less of a depressant effect on the central nervous system as reflected by less deficit in motor coordination, less interference with normal motor activity, less analgetic effect than trazodone. Laboratory test data with respect to these properties are arranged below.

ORAL DOSES
(mg/kg)

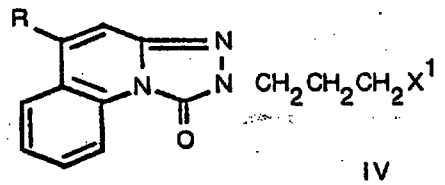
Test	Formula I R = H	Formula I R = 5—CH_3	Trazodone
Mouse, tail clip (analgetic)[1]	ED_{50} = 200	inactive at 200	ED_{50} = 55.5
Reduction of phenylquinone writhing in mice (analgetic)[2]	ED_{50} = 40.5	ED_{50} = 51.8	ED_{50} = 21.8
Reduction of spontaneous motor activity in mice[3]	$AED_{-0.3=80}$	inactive at 20, 40, & 80	$AED_{-0.3=15.3}$
Rotorod method for motor incordination in mice[4]	inactive at 800	not tested	ED_{50} = 44.4
CNS depression in mice	ED_{50} = 54	ED_{50} = 36.5	ED_{50} = 22.2
Antagonism of foot shock induced aggression[5]			
Inhibition of pernicious Preening in mice (anti psychotic or analgetic)[6]	ED_{50} = 24	ED_{50} = 62	ED_{50} = 43
Suppression of conditioned avoidance response[7]	inactive at 100 mg/kg	inactive at 100 mg/kg	ED_{50} = 131.1

[1]Bianchi, et al., Brit. J. of Pharmacology *9*, 280 (1954).
[2]Hendershot, et al., J. Pharmcol. & Exptl. Ther. *125*, 237 (1959).
[3]Kissel, U.S. Patent No. 3,100,473 (Aug. 13, 1963).
[4]Kinnaird, et al., J. Pharmacol. & Exptl. Ther. *121*, 354 (157). Cutting, et al., Archives Int. Pharmacodyn. *121*, 14 (1959).
[5]Tedeschi, et al., J. Pharmacol. & Exptl. Ther. *125*, 28 (1959).
[6]Wilfon, et al., Federation Proceedings *19*, 21 (1960).
[7]Albert, et al., Pharmacologist *4*, 152 (1962).

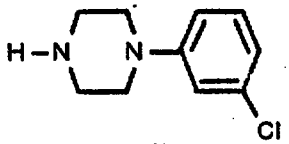
The compounds of the present invention are prepared from starting materials of Formulas (II) and (III) and a trimethylene dihalide of the formula $XCH_2CH_2CH_2X^1$ where X and X^1 are independently selected from chlorine, bromine, and iodine. Preferably at least one of X and X^1 is bromine or iodine. R has the same meaning as in Formula I.



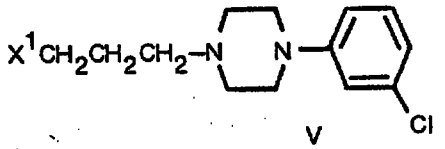
(II)



IV



III



V

A sequential process is involved in which the starting material of either Formula (II) or Formula (III) is caused to react with the dihalide and the resulting intermediate is then caused to react with the other starting material. For instance, the dihalide may be first condensed with the starting material of formula (III) and the resulting intermediate then caused to react with the starting material of Formula (II). One or the other of the intermediates shown in Formula (IV) and (V) is involved, Formula (IV) being obtained from Formula (II) by condensation of the latter with the dihalide and Formula (V) being obtained from Formula (III) by condensation of the latter with the dihalide.

In the sequence starting with Formula (II) the latter is first converted to the sodium or potassium salt by dissolving in warm aqueous sodium or potassium hydroxide and allowing the salt to crystallize from the solution on cooling. The hydrogen atom in the 2-position of Formula (II) is the acidic functional group which forms the salt. The condensation of the sodium or potassium salt of the starting material of Formula (II) with the dihalide of the Formula $XCH_2CH_2CH_2X^1$ or with the intermediate of Formula (V) is carried out by heating the two reactants at a temperature in the range of 80—150°C in equimolecular quantities in a liquid reaction medium which is inert under the reaction conditions. Preferably, a reaction medium is chosen which has a boiling point within the foregoing temperature range and refluxing of the reaction mixture is employed for temperature control during a reaction period of 2 to 24 hours. Suitable reaction inert liquid media include the liquid hydrocarbons, hydrocarbon nitriles, and hydrocarbon ethers such as xylene, acetonitrile, and dibutylether.

For preparation of the intermediate of Formula (V) by reaction of the starting material of (III) with the indicated dihalide, the two reactants are contacted in a reaction inert liquid medium at room temperature for from 2 to 18 hours in the presence of a strong base such as sodium hydroxide or potassium hydroxide when using a reaction medium containing water, or with a sodium or potassium alkoxide, hydride, oxide, or amide when using a liquid medium which is nonreactive to these bases. A mixture of equal volumes in water and acetone is a convenient and preferred reaction medium with sodium hydroxide as the base.

Starting materials of Formula (III) and the dihalides are articles of commerce or can be prepared by known methods. The triazoloquinolines of Formula (II) have been described in the literature or can be conveniently prepared by the reaction of 2-chloro-R-quinoline with semicarbazide. The preferred sequence is to treat the sodium or potassium salt of Formula (II) with the intermediate of Formula (V) which is prepared in a preliminary step from the dihalide and the starting material of Formula (III). This illustrated in Example 1 below. Improved yields are obtained according to this sequence relative the sequence involving first preparation of the intermediate of Formula (IV), and reaction thereof with Formula (III).

Description of Specific Embodiments

In the following procedures temperatures are expressed in degrees Centrigrade. Melting points are corrected values according the USP method where indicated (corr.). The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts downfield (δ) expressed as parts per million (ppm) versus tetramethylsilane as reference standard. The relative area reported for the various shifts corresponds to the number of hydrogen atoms in the individual substituent and the nature of the shift as to multiplicity is reported as broad singlet (bs), singlet (s), multiplet (m), doublet (d), triplet (t), or quadruplet (q) with coupling constant reported were appropriate. The format is NMR (solvent): δ (relative area, multiplicity, J value, and, in the some instances, indicated structural characteristics).

Abbreviations employed are DMSO-d_6 (deuterodimethylsulfoxide), IR (infrared), KBr (potassium bromide), and d (decomposition). Others are common and have well established meanings. The infrared spectra described include only absorption wavelengths (cm^{-1}) having functional group identification value. Unless indicated otherwise, KBr was employed as diluent for IR spectra determinations.

Example 1

a) Starting materials

Procedure 1. 1,2,4-Triazolo[4,3-a]-quinolin-1(2 H)-one.

A mixture of 71.9 g (0.44 mole) of 2-chloroquinoline and 98.22 g (0.88 mole) of semicarbazide hydrochloride in 150 ml of 2-ethoxyethanol is heated to reflux and then treated with a solution of 1 ml of concentrated sulphuric acid (36 N) in 5 ml of 2-ethoxyethanol. The resulting mixture is refluxed for 18 hrs, cooled to about 60°, and treated with 150 ml of water. It is then stirred and cooled to 0° and after 0.5 hrs at 0°, the precipitated solid is collected on a filter to yield 109 g (59%) of product, m.p. 245—246°. This material is sufficiently pure to use in the next step.

Procedure 2. 1-(3-Chlorophenyl)-4-(3-chloropropyl)piperazine.

To a solution of 7.36 g (0.184 mole) of sodium hydroxide in 75 ml of water and 75 ml of acetone there is added 17.16 g (0.074 mole) of 1-(3-chlorophenyl)piperazine hydrochloride and 11.59 g (0.074 mole) of 1-bromo-3-chloropropane, and the resulting mixture is stirred at 27° for 18 hrs. The organic layer is then separated and concentrated to an oil under reduced pressure. The oil is treated with hot (85°) 6*N* HCl until solution is complete, and the resulting solution is filtered and stored at 5° for 18 hrs. The precipitate which forms is collected on a filter to afford 17.52 g (87%) of the hydrochloride salt of the product, m.p. 198—200°. Concentration of the mother liquor under reduced pressure and recrystallization of the residue from water affords an additional 1.82 g (9%) of product, m.p. 196—198°.

Procedure 3. Sodium 1,2,4-Triazolo[4,3-a]quinolin-1(2 H)-one.

The product of Procedure 1, 57.4 g (0.31 mole) is dissolved in a solution of 12.19 g (0.31 mole) of sodium hydroxide in 230 ml of water at 80°. The solution is then chilled at 5° overnight. A precipitate of the desicribed sodium salt forms during this period. It is then collected on a filter, and dried at reduced pressure to afford the desired product.

b) 2-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4.3-a]quinolin-1(2H)-one.

The hydrochloride salt of 1-(3-chloropropyl)-4-(3-chlorophenyl)piperazine, 5.79 g (0.0187 mole) is dissolved in dilute KOH solution and the free base which is formed is extracted into ether. The ether solution is washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure to afford 4.54 g (88%) of the desired free base. A suspension of 3.45 g (0.0166 mole) of the sodium salt of 1,2,4-triazolo[4,3-*a*]quinolin-1(2*H*)-one and 4.54 g (0.0166 mole) of 1-(3-chloropropyl)-4-(3-chlorophenyl)piperazine in 100 ml of acetonitrile is treated with approximately 50 mg of potassium iodide, and refluxed for 24 hrs. The mixture is then cooled and filtered, and the filtrate concentrated to an oil under reduced pressure. The residual oil solidifies when triturated with ether. This solid is recrystallized twice from ethanol to give 4.77 g (68%) of product, m.p. 99.5—100.5°.

Anal. Found: C, 65.15; H, 5.86; N, 16.56.
NMR ($CDCl_3$): 2.04 (2, m), 2.54 (6, m), 3.14 (4, m), 4.15 (2, t, 7.0 Hz), 7.10 (9, m), 9.19 (1, m).
IR: 760, 800, 940, 1230, 1460, 1565, 1600, 1715, 2820, and 2940 cm^{-1}.

Example 2

a) Starting material 5-Methyl-1,2,4-triazolo(4,3-a)quinolin-1(2H)-one.

The method of Procedure 1 is repeated with substitution of 2-chloro-4-methylquinoline for the 2-chloroquinoline specified in that procedure in molecularly equivalent amount. The resulting product is recovered in 55% yield, m.p. 280—281°.

b) 2-(3-(4-(3-Chlorophenyl)-1-piperazinyl)-propyl)-5-methyl-1,2,4-triazolo(4,3-a)quinolin-1(2H)-one.

5-Methyl-1,2,4-triazolo(4,3-*a*)quinolin-1(2H)-one is treated according to the method of Procedure 3. The resulting sodium salt is then converted to the desired product according to the method b) of Example 1. in 29% yield after recrystallization from ethanol, m.p. 123—124°C.

Anal. Found: C 66.15; H 6.04; N, 16.15.
NMR ($CDCl_3$): 2.04 (2, m), 2.43 (3, s), 2.54 (6, m), 3.12 (4, m) 4.10 (2, t, 7.0 Hz), 7.26 (8, m), 9.21 (1, m).
IR: 775, 1230, 1460, 1570, 1595, 1635, 1710, 2820, 2940 cm^{-1}.

For the preparation of pharmaceutical compositions containing the compounds of Formula (I) in the form of dosage units for oral administration, the compound is mixed with a solid, pulverulent carrier such as lactose, sucrose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives, or gelatin, as well as with glidents such as magnesium sterate, calcium sterate, polyethylene glycol waxes or the like and compressed into tablets. The tablets may be used uncoated or coated by known techniques.

In the preparation of soft gelatin capsules comprised of a shell made of gelatin and glycerine or the like, the active ingredient is mixed with a vegetable oil and encapsulated in conventional manner. Hard gelatin capsules may contain granules of the active ingredient in combination with a solid, pulverulent carrier such as lactose, sucrose, sorbitol, mannitol, starch (such as e.g. potato starch, corn starch, or amylopectin), cellulose derivatives or gelatin.

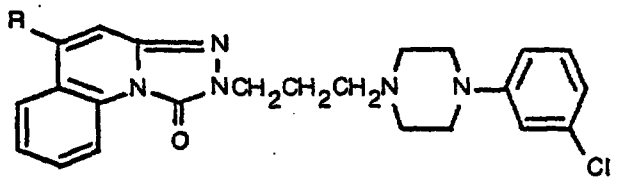
Dose units for rectal administration may be prepared in the form of suppositories containing the compound in a mixture with a neutral fat base, or in the form of a gelatin-rectal capsule with a mixture of vegetable oil or paraffin oil

Liquid preparations suitable for oral administration are suspensions, syrups and elixirs containing from about 0.2% by weight to about 20% by weight of the active ingredient.

A suitable injectible composition comprises an aqueous solution of a water soluble pharmaceutically acceptable salt adjusted to physiologically acceptable pH.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. 2-Substituted 1,2,4-triazolo[4,3-*a*]quinolin-1(2H)-ones having the formula (I)



Formula I

wherein R is hydrogen or methyl or a pharmaceutically acceptable acid addition salt thereof.

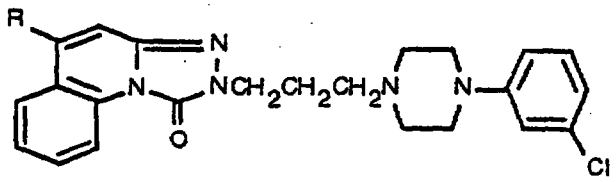
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3. 2-(3-(4-(3-chlorophenyl)-1-piperazinyl)propyl)-5-methyl-1,2,4-triazolo[4,3-*a*]-quinoline-1 (2*H*)-one.

4. Compounds of claim 1 for use in the treatment of neurotic or endogenous depression.

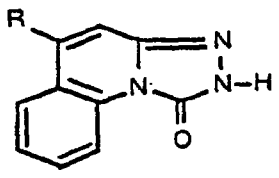
Claims for the Contracting State: AT

1. A process for the preparation of a 2-substituted 1,2,4-triazolo-[4,3-*a*]quinolin-1(2*H*)-one having the formula I



Formula I

said process being characterized by recting the sodium or potassium salt of a compound of the formula (II)



(II)

with a compound of the formula (V)

In the preparation of soft gelatin capsules comprised of a shell made of gelatin and glycerine or the like, the active ingredient is mixed with a vegetable oil and encapsulated in conventional manner. Hard gelatin capsules may contain granules of the active ingredient in combination with a solid, pulverulent carrier such as lactose, sucrose, sorbitol, mannitol, starch (such as e.g. potato starch, corn starch, or amylopectin), cellulose derivatives or gelatin.

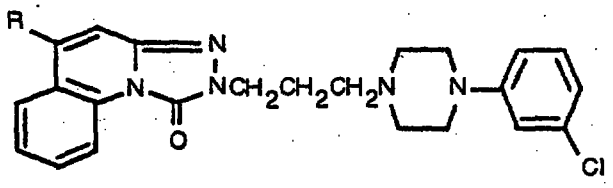
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Formula I

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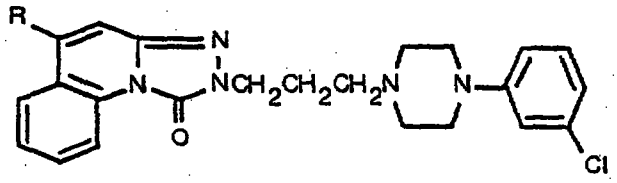
2. 2-(3-(4-(3-chlorophenyl)-1-piperazinyl)propyl)-1,2,4-triazolo[4,3-*a*]-quinoline-1(2*H*)-one.

3. 2-(3-(4-(3-chlorophenyl)-1-piperazinyl)propyl)-5-methyl-1,2,4-triazolo[4,3-*a*]-quinoline-1 (2*H*)-one.

4. Compounds of claim 1 for use in the treatment of neurotic or endogenous depression.

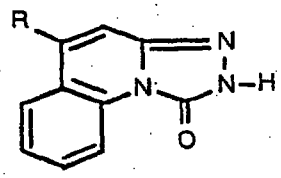
Claims for the Contracting State: AT

1. A process for the preparation of a 2-substituted 1,2,4-triazolo-[4,3-*a*]quinolin-1(2*H*)-one having the formula I



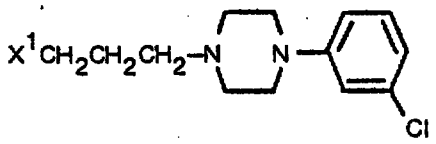
Formula I

said process being characterized by recting the sodium or potassium salt of a compound of the formula (II)



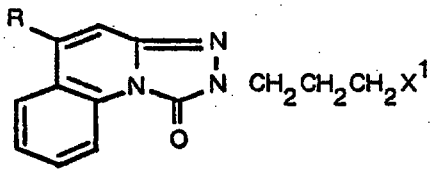
(II)

with a compound of the formula (V)



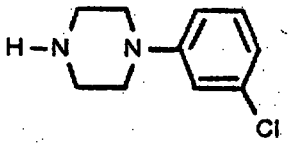
V

or by reacting a compound of the formula (IV)



IV

with a compound of the formula (III)



III

wherein R is hydrogen or methyl and X^1 is chlorine, bromine or iodine, the process being effected at a temperature in the range of 80 –150°C.

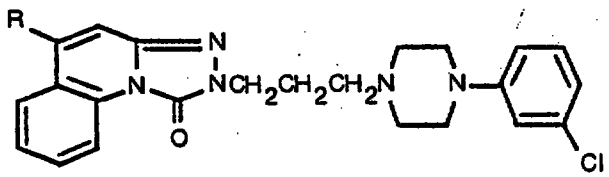
2. A process according to claim 1 characterized in that the compound of formula III is first reacted with a dihalide having the formula X—CH_2—CH_2—CH_2X^1 to produce the compound of formula V, which is then reacted with sodium or potassium salt of a compound of formula II, X and X^1 being, independently, chlorine, bromine or iodine.

3. A process according to claim 2 characterized in that the dihalide is reacted with the compound of formula III at room temperature in an inert liquid medium for 2 to 18 hours in the presence of a strong base.

4. A process according to claim 1 characterized in that the sodium or potassium salt is reacted with a dihalide of the formula X—CH_2—CH_2—CH_2X^1 to form the compound of formula IV, which then is reacted with the compound of formula III, X and X^1 being as hereinbefore defined.

Revendications pour les Etats Contractants: BE CH DE FR GB IT LI LU NL SE

1. 1,2,4-Triazolo[4,3-*a*]quinoléine-1(2H)-ones 2-substituées de formula (I)



Formula I

où R représente un atome d'hydrogène ou radical méthyle ou un de leurs sels d'addition d'acides pharmaceutiquement acceptables.

2. La 2-[3-[4-(3-chlorophényl)-1-pipérazinyl]propyl]-1,2,4-triazolo[4,3-*a*]quinoléine-1(2H)-one.

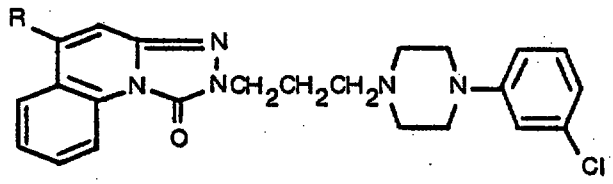
3. La 2-[3-[4-(3-chlorophényl)-1-pipérazinyl]propyl]-5-méthyl-1,2,4-triazolo[4,3-*a*]quinoléine-1(2*H*)-one.

4. Composés suivant la revendication 1 à utiliser pour le traitement d'une dépression névrotique ou endogène.

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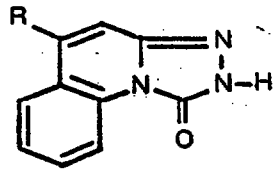
Revendications pour l'Etat Contractant: AT

1. Procédé de préparation d'une 1,2,4-triazolo[4,3-*a*]quinoléine-1(2*H*)-one 2-substituée de formule I



Formula I

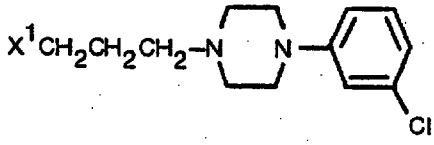
caractérisé en ce qu'on fait réagir le sel de sodium ou de potassium d'un composé de formule (II)



II

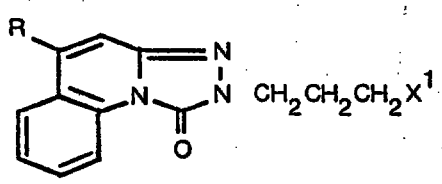
(II)

avec un composé de formule (V)



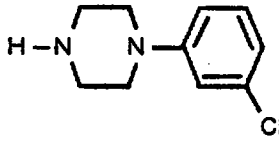
V

ou on fait réagir un composé de formule (IV)



IV

avec un composé de formule (III)



III

où R représente un atome d'hydrogène ou radical méthyle et X1 représente le chlore, le brome ou l'iode, le procédé étant exécuté à une température de l'intervalle de 80—150°C.

2. Procédé suivant la revendication 1, caractérisé en ce qu'on fait réagir le composé de formule III d'abord avec un dihalogénure de formule X—CH_2—CH_2—CH_2X^1 pour former le composé de formule V qu'on fait réagir ensuite avec le sel de sodium ou de potassium d'un composé de formule II, X et X^1 représentant indépendamment le chlore, le brome ou l'iode.

3. Procédé suivant la revendication 2, caractérisé en ce qu'on fait réagir le dihalogénure avec le composé de formule III à la température ambiante dans un milieu liquide inerte pendant 2 à 18 heures en présence d'une base forte.

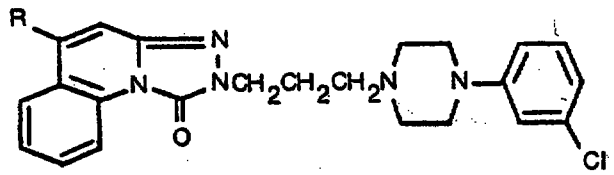
4. Procédé suivant le revendication 1, caractérisé en ce qu'on fait réagir le sel de sodium ou de

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potassium avec un dihalogénure de formule $X—CH_2CH_2—CH_2X^1$ pour former le composé de formule IV, qu'on fait réagir ensuite avec le composé de formule III, X et X^1 étant tels que définis ci-dessus.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

2-substituierte 1,2,4-Triazol [4,3-a]chinolin-1(2H)-one der Formel (I)



Formula I

in der R Wasserstoff oder Methyl ist, oder ein Für die pharmazeutische Verwendung geeignetes Säureadditionssalz einer derartigen Verbindung.

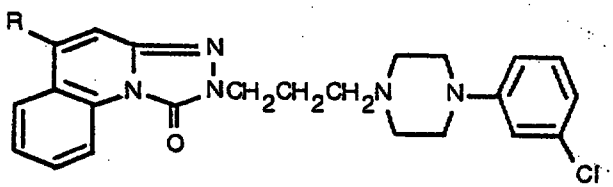
2. 2-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazol[4,3-a]-chinolin-1-(2H)-on.

3. 2-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-5-methyl-1,2,4-triazol [4,3-a]chinolin-1(2H)on. 1(2H)on.

4. Verbindungen nach Anspruch 1 für die Verwendung zur Behandlung von neurotischen oder endogenen Depressionen.

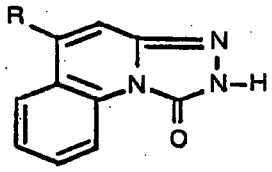
Patentansprüche für den Vertragsstaat: AT

1. Verfahren zum Erzeugen eines 2-substituierten 1,2,4-Triazol[4,3-a]chinolin-1(2H)-ons der Formel (I)



Formula I

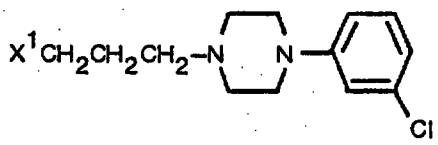
dadurch gekennzeichnet, daß das Natrium- oder Kaliumsalz einer Verbindung der Formel (II)



II

(II)

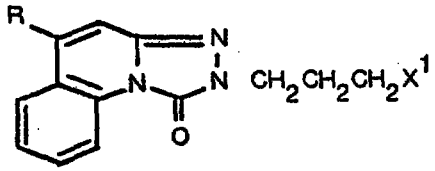
mit einer Verbindung der Formel (V)



V

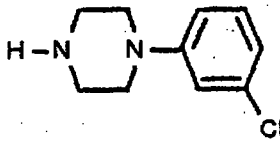
umgesetzt wird oder eine Verbindung der Formel (IV)

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IV

mit einer Verbindung der Formel (III)



III

umgesetzt wird, wobei R Wasserstoff oder Methyl ist und X^1 Chlor, Brom oder Jod ist und wobei das Verfahren bei einer Temperatur im Bereich von 80 bis 150°C durchgeführt wird.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß zunächst durch Umsetzen der Verbindung der Formel III mit einem Dihalogenid der Formel $X—CH_2—CH_2—CH_2—X^1$ die Verbindung der Formel V erzeugt und diese dann mit einem Natrium-oder Kaliumsalz einer Verbindung der Formel II umgesetzt wird, wobei X und X^1 unabhängig voneinander Chlor, Brom oder Jod sind.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß das Dihalogenid mit der Verbindung der Formel III in Gegenwart einer starken Base bei Zimmertemperatur 2 bis 18 Stunden in einem inerten flüssigen Medium umgesetzt wird.

4. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß durch Umsetzen des Natrium- oder Kaliumsalzes mit einem Dihalogenid der Formel $X—CH_2—CH_2—CH_2—X^1$ die Verbindung der Formel IV erzeugt und diese dann mit der Verbindung der Formel III umgesetzt wird, wobei X und X^1 die vorstehend angegebene Bedeutung haben.