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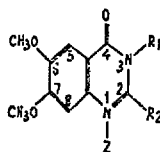
(54) NOVEL 6,7-DIMETHOXYQUINAZOLINONES USEFUL AS ANALGESIC AND TRANQUILIZER AGENTS

(71) We, PFIZER INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York 17, State of New York, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel 6,7-dimethoxyquinazolinones, which have useful therapeutic properties in the field of medicinal chemistry.

More particularly, the compounds of the invention are useful as analgesic and tranquilizer agents.

The compounds of the invention are those having the general formula:

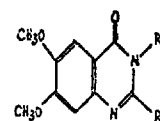


where,
 Z is CN, —COR, —COCF₃, —CONRR', or —COOR; except that Z is never COOH; R, R₁, R₂, and R' are hydrogen or lower alkyl, said lower alkyl having from 1 to 4 carbon atoms.

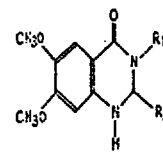
The novel compounds of the invention are useful as analgesic and tranquilizer agents in mammals. A preferred class of compounds of the invention are those in which Z represents —COOR. Specifically effective compounds exhibiting both tranquilizer and analgesic activity are 3,4 - dihydro - 6,7 - dimethoxy - 2,3 - dimethyl - 4 - oxo - 1(2H) - quinoazolinecarboxylic acid, ethyl ester; and 3,4 - dihydro - 6,7-

dimethoxy - 3 - ethyl - 2 - methyl - 4 - oxo - 1(2H) - quinazoline - carboxylic acid, ethyl ester. A particularly effective compound exhibiting tranquilizer activity is 3,4 - dihydro - 6,7 - dimethoxy - 3 - methyl - 4 - oxo - 1(2H)quinazoline - carboxylic acid, ethyl ester.

The compounds of the invention are preferably prepared by first selectively reducing with a metal hydride a substituted quinazoline-4-one compound of the formula:



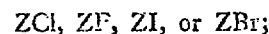
at a temperature of about 0°C. to yield a compound of the formula:



Alternatively, the quinazolin-4-one compound can be reduced in the form of the acid addition salt, preferably the hydrochloric acid addition salt. Preferable metal hydrides are LiBH₄, LiAlH₄, and NaBH₄.

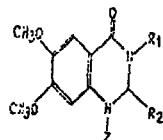
tion salt. Preferable metal hydrides are LiBH₄, LiAlH₄, and NaBH₄.

Then the reduced quinazolin-4-one compound or its acid addition salt is reacted at a temperature of about 10—25°C. with a compound of the formula



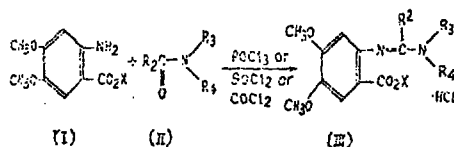
or is reacted at a temperature of about 10—

50°C. with a compound of the formula ZOR and a base to form the desired novel compounds of the invention having the formula:

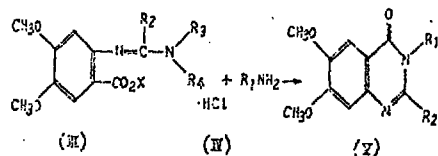


- 5 R in ZOR can be typically H, lower alkyl, and aryl (e.g. phenyl). The base to be used with ZOR can be typically an alkali metal hydride, hydroxide, and oxide.

- 10 The substituted quinazolin-4-one starting compound can be conveniently prepared by first reacting a 4,5-dimethoxy anthranilic ester (I) with an N,N-disubstituted amide (II), in the presence of either POCl₃, SOCl₂, or COCl₂ at a temperature between -10 and 15 30°C.



- 20 The resulting product (III) is then reacted with a substituted amine (IV) in a reaction inert solvent, such as ethanol or water, at a temperature of about 0 to 100°C. to yield the desired reactant substituted quinazolin-4-one starting compound (V).



- 25 R₁ and R₂ are as previously defined. X, R₃ and R₄ can be typically lower alkyl, except X and R₄ are each never H, and R₃ can be H.

- 30 The starting materials necessary for the above reaction methods leading to the desired compounds are either all known compounds or else they can easily be prepared by those skilled in the art in accordance with standard organic procedures.

- 35 The novel compounds of the invention exhibit activity as tranquilizer and analgesic agents in mammals. Among these compounds, a preferred class of compounds has been found to be those in which Z represents -C(O)OR. Specifically effective tranquilizer and analgesic agents being 3,4 - dihydro - 6,7 - dimethoxy - 2,3 - dimethyl - 4 - oxo - 1(2H) - quinazolin-40 carboxylic acid, ethyl ester; and 3,4 - dihydro - 6,7 - dimethoxy - 3 - ethyl - 2 - methyl - 4 -

oxo - 1(2H) - quinazolin-4-one carboxylic acid, ethyl ester. A specifically effective tranquilizer agent is 3,4 - dihydro - 6,7 - dimethoxy - 3-methyl - 4 - oxo - 1(2H) - quinazolin-4-one carboxylic acid, ethyl ester.

The compounds of the present invention are conveniently administered in composition form. Such compositions include a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch, milk sugar, or certain types of clay. They may be administered in capsules, in admixtures with the same or equivalent excipients. They may also be administered orally in the form of oral suspensions which may contain flavoring and coloring agents. They may be injected parenterally, i.e. for example, intramuscularly or subcutaneously. For oral administration of the therapeutic agents of this invention, tablets or capsules containing from about 25 to about 500 mg. are suitable for most applications.

The physician will determine the dosage which will be most suitable for an individual patient and it will vary with the form of administration, the age, weight and response of the particular patient. Generally, however, the initial dosage in adults may range from 25 to 1000 mg. per day divided into 2 or 4 equal doses. In many instances, it is not necessary to exceed 500 mg. daily.

The following examples are given by way of illustration. Temperatures are in °C. unless otherwise specified.

EXAMPLE I

Preparation of 6,7-Dimethoxy-3-methyl-4(3H)-quinazolinone

To 150 ml. of cold (0°C.) dimethylformamide is added 21.8 g. (0.142 mole) of phosphorus oxychloride drop-wise over 5 minutes, followed by dropwise addition of a solution of 30.0 g. (0.142 mole) of methyl 4,5-dimethoxyanthranilate in 150 ml. of dimethylformamide over a 30 minute period. The temperature is maintained below 10°C. The resulting white slurry is allowed to warm to room temperature while stirring, and then chilled to 5°C. and filtered. The solid product is washed with 100 ml. of cold ethanol and finally with 200 ml. of ether and oven dried to give 41.8 g. (98%) of white microcrystalline solid, m.p. 204—204.5°. The analytical sample of 6,7 - dimethoxy - 3 - methyl - 4(3H)-quinazolinone is prepared by recrystallization of a 2 g. sample from ethanol to give 1.58 g. of material with m.p. 206°.

Anal. Calc'd for C₁₃H₁₁ClN₂O₄:

Found:

C, 51.02; H, 6.32; N, 9.22;
Cl, 11.70
C, 51.19; H, 6.43; N, 9.11;
Cl, 11.69.

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To a slurry of 3.0 g. (10 mmoles) of the solid product prepared above in 50 ml. of ethanol is passed a stream of gaseous methylamine for 10 min. There is partial solution after 5 min. followed by a heavy precipitation. The mixture is chilled to 5° and filtered to give 1.24 g. (56%) of white microcrystalline solid, m.p. 211—212°. An additional 0.76 g. (35%) of material m.p. 210—212° is obtained by concentration of the mother liquor. The combined solid (2.0 g., 91%) are recrystallized from ethyl acetate to provide 1.1 g. of 6,7-dimethoxy - 3 - methyl - 4(3H) - quinazolinone as white needles, m.p. 211—212°.

Anal. Calc'd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72.
Found: C, 59.77; H, 5.61; N, 12.75.

EXAMPLE II

Part A: Preparation of 2,3 - Dihydro - 6,7-dimethoxy - 3 - methyl - 4(1H) - quinazolinone (1).

6,7 - Dimethoxy - 3 - methyl - 4(3H) - quinazolinone (11.0 g., 50 mmoles), prepared in a similar manner to that described in Example I, is suspended in 100 ml. of tetrahydrofuran (THF), cooled to 0°, and treated with 1.20 g. (55 mmoles) of $LiBH_4$. The suspension is heated at reflux under H_2 for 20 hours, cooled, and poured carefully into ice water. After thorough extraction of the mixture with CH_2Cl_2 , the extract is dried using $MgSO_4$ and evaporated *in vacuo* to yield a white, crystalline residue, 13.4 g., m.p. 112—115°. One crystallization from ethyl acetate provides 9.23 g. of pure (1): m.p. 115—116.5°; ir (KBr) 3.01 (NH), 6.10 μ (C=O); uv_{max} (C_2H_5OH) 233, 267, 307 m μ (log ϵ 4.4, 3.8, 3.6); nmr ($CDCl_3$) δ 3.0 (s, 3H, CH_3N), 3.8 (s, 6H, CH_3O), 4.6 (s, 2H, CH_2), 4.9 (broad s, 1H, exchanges with D_2O , NH), 6.3 (s, 1H, H—8), 7.4 (s, 1H, H—5).

Anal. Calc'd for $C_{11}H_{11}N_2O_3$: C, 59.45; H, 6.35; N, 12.60.
Found: C, 59.34; H, 6.35; N, 12.51.

Similar results are obtained using $LiAlH_4$ or $NaBH_4$ in place of $LiBH_4$.

Part B: Preparation of 3,4-Dihydro-6,7-dimethoxy-3-methyl-4-oxo-1(2H)-quinazoline-carboxylic acid, ethyl ester (2).

A well-stirred suspension of (1) (6.66 g., 30 mmoles) and anhydrous K_2CO_3 (20.8 g., 150 mmoles) in 50 ml. is treated with a solution of ethyl chloroformate (3.80 g., 35 mmoles) in 25 ml. of CH_2Cl_2 at such a rate so as to maintain a reaction temperature of 25°. The pale yellow mixture is stirred for 20 hours at room temperature, then worked up by adding water and isolating the product by CH_2Cl_2 extraction. Chromatography of the crude residue on silica gel (elution with THF) yields a colorless oil (7.3 g.), which crystallizes from isopropyl alcohol. One recrystallization affords 4.4 g. of pure (2): m.p. 117.5—119°; ir (KBr) 5.80 (carbamate carbonyl), 6.03 μ (amide carbonyl) uv_{max} (C_2H_5OH) 232, 265, 307 m μ (log ϵ 4.6, 3.9, 3.7); nmr ($CDCl_3$) δ 1.3 (t, J=7 cps, 3H, $C-CH_3$), 3.1 (s, 3H, NCH_3), 3.9 (s, 3H, OCH_3), 4.3 (q, J=7 cps, 2H, OCH_2), 5.1 (s, NCH_2), 7.2 (s, 1H, H—8), 7.5 (s, 1H—5).

Anal. Calc'd for $C_{14}H_{15}N_2O_5$: C, 57.13; H, 6.16; N, 9.52.
Found: C, 56.90; H, 6.29; N, 9.47.

For Examples III and IV, 6,7-dimethoxy-2,3 - dimethyl - 4(3H) - quinazolinone starting material is prepared in a similar manner to the procedure described in Example I using the appropriate stoichiometric amounts of reactants, except that dimethylacetamide is substituted for dimethylformamide.

For Example V, 6,7 - dimethoxy - 3 - ethyl - 2 - methyl - 4(3H) - quinazolinone starting material is prepared similarly according to the procedure described in Example I and using the appropriate stoichiometric amounts of reactants, except that dimethylacetamide and ethylamine are substituted for dimethylformamide and methylamine, respectively.

EXAMPLE III

Part A: Preparation of 2,3-Dihydro-6,7-dimethoxy-2,3-dimethyl-4(1H)-quinazolinone (3).

6,7 - Dimethoxy - 2,3 - dimethyl - 4(3H)-quinazolinone (11.7 g., 50 mmoles) is converted to the hydrochloride salt in ether with dry HCl. The salt is filtered and suspended in 150 ml. of diglyme under N_2 . After cooling the suspension to 0°, $NaBH_4$ (2.8 g., 75 mmoles) is added in portions and the mixture stirred at room temperature for one hour. Water is added to hydrolyze the excess $NaBH_4$ and the mixture is evaporated to dryness under reduced pressure. The residue is partitioned

- between CH_2Cl_2 and H_2O , the CH_2Cl_2 layer is dried using MgSO_4 , and the solvent evaporated. Trituration of the residual yellow oil yields a colorless, crystalline product, 10.9 g., m.p. 92—95°. Recrystallization from benzene provides (3), which contains a fraction of a mole of benzene: m.p. 95—97°; ir (KBr) 2.95, 3.10 (NH), 6.14 μ (C=O); nmr (CHCl_3) δ 1.4 (d, J=6, 3H, C—CH₃), 3.0 (s, 3H, NCH₃), 3.8 (two s, 6H, OCH₃), 4.8 (q, J=6, 1H, CH), 5.0 (broad s, 1H, exchanges with D_2O , NH), 6.2 (s, 1H, H—8), 7.35 (s, 2H, solvent), 7.4 (s, 1H, H—5).

Analysis: Calc'd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_5 \cdot 1/3 \text{C}_6\text{H}_6$: C, 64.10; H, 6.92; N, 10.68.
Found: C, 63.52; H, 6.89; N, 10.95.

Part B: Preparation of 3,4-Dihydro-6,7-Dimethoxy-2,3-dimethyl-4-oxo-1(2H)-quinazolinecarboxylic acid, ethyl ester (4)

- A solution of (3) (5.75 g., 25 mmoles) in 50 ml. of CH_2Cl_2 was cooled to 0°. Anhydrous K_2CO_3 (17.4 g., 125 mmoles) is added, followed by careful addition of ethyl chloroformate (2.98 g., 28 mmoles) in 25 ml. of CH_2Cl_2 . Reaction temperature is maintained below 10° during the addition, then the mixture is stirred at room temperature for 20 hours. Water is added and the organic phase is washed with H_2O , 1N aqueous HCl, and

H_2O . Evaporation of the solvent yielded a yellow oil which is chromatographed on silica gel (elution with ethyl acetate). The final two fractions afford a colorless oil, which is crystallized from a mixture of Et.O-pet. ether to provide (4): m.p. 70—74°; ir (KBr) 5.79 (carbamate C=O), 6.04 μ (amide C=O); nmr (CDCl_3) δ 1.3 (t, J=7, 3H, ester CH₃), 1.3 (d, J=7, 3H, 2—CH₃), 3.1 (s, 3H, N—CH₃), 3.9 (s, 6H, OCH₃), 4.3 (q, J=7, 2H, ester CH₂), 5.9 (q, J=7, 1H, H—2), 7.2 (s, 1H, H—8), 7.5 (s, 1H, H—5).

Analysis: Calc'd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_5$: C, 58.44; H, 6.54; N, 9.09.
Found: C, 58.10; H, 6.76; N, 9.10.

EXAMPLE IV

- Part A: The Preparation of 2,3-Dihydro-6,7-dimethoxy-2,3-dimethyl-4(1H)-quinazolinone (3)

A 22 l. round-bottomed flask is charged with 4.4 l. of dry tetrahydrofuran, 252.0 g. (6.67 mmoles) of sodium borohydride and 627.0 g. (2.68 mmoles) of 6,7-dimethoxy-2,3-dimethyl-4(3H)-quinazolinone. The slurry is vigorously stirred at 0°C. as a solution of 226.0 g. (3.74 mmoles) of glacial acetic acid in 2.5 l. of tetrahydrofuran is slowly added over a 2 hour period. The cooling bath is removed and the reaction mixture is allowed to warm to room temperature over a 16 hour period.

The reaction mixture is added portionwise to 16 l. of ice and water with stirring. Chloroform (16 l.) then is added to the stirred mixture and the layers separated. The aqueous phase is extracted a second time with a 10 l. portion of chloroform and the extracts are combined. The chloroform solution is dried over anhydrous sodium sulfate and then concentrated *in vacuo* to a volume of ca. 1.5 l. Benzene (6 l.) is added and the mixture re-concentrated to a volume of ca. 2 l. With stirring and at room temperature, 6.0 l. of diethyl ether is slowly added as the product crystallizes. The resulting slurry is filtered, washed with ether and dried in the atmosphere to give 630.0 g. (100% of theory) of product (3); m.p. 93.0—100.0°C.

Part B: Preparation of 3,4-Dihydro-6,7-dimethoxy-2,3-dimethyl-4-oxo-1(2H)-quinazolinecarboxylic acid, Ethyl Ester (4)

A 12 l. round-bottomed flask is charged with 3.0 l. of dry diethyl carbonate, 155.0 g. of a 60.2% sodium hydride in oil suspension (93.3 g. or 3.88 mmoles of NaH) and 600.0 g. (2.54 mmoles) of 2,3-dihydro-6,7-dimethoxy-2,3-dimethyl-4(1H)-quinazolinone (3). The slurry is stirred at room temperature under an atmosphere of dry nitrogen as 6.0 ml. of ethanol is added. After stirring about one hour a vigorous reaction commences. Hydrogen gas is evolved and the temperature rises to a maximum of 45°C. over a 5 minute period. The reaction mixture is stirred an additional hour at the ambient temperature and then carefully poured into 6 l. of ice and water mixture under an atmosphere of nitrogen. The aqueous mixture is extracted twice with 4 l. portions of chloroform. The chloroform extracts are combined, back-washed with 2.0 l. of 1N HCl solution and then with 1.0 l. of saturated aqueous sodium chloride solution. The chloroform layer is concentrated *in vacuo* to an oil and the concentrate stirred with 4 l. of n-hexane giving a crystalline slurry. The slurry is cooled to 0°C. and filtered. Air drying gives 698.0 g. of crude product.

The crude product is taken up in 14 l. of diisopropyl ether at about 50°C., treated with "Darco" G—60 (Registered Trade Mark),

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5 filtered and the solution then concentrated *in vacuo* to a volume of about 4 liters. The resulting slurry is cooled to 20°C. and filtered. The cake is washed with cold di-isopropyl ether and dried in the atmosphere to give 597.0 g. (76.5% of theory) of pure material (4); m.p., 100.0—101.0°C.

EXAMPLE V

10 Part A: Preparation of 2,3-Dihydro-6,7-dimethoxy-3-ethyl-2-methyl-4(3H)-quinazolinone (5)

15 A suspension of 6,7 - dimethoxy - 3 - ethyl - 2 - methyl - 4(1H) - quinazolinone (9 g., 36 mmoles) and 2.82 g. (72 mmoles) of sodium borohydride in 90 ml. of dry tetrahydrofuran (THF) was stirred and cooled at approximately 0° while 3.22 g. (54 mmoles) of acetic acid in

25 ml. of THF was added over 30 min. The yellow suspension was stirred 0.5 hours at 0°, and allowed to warm to room temperature, then poured onto 300 ml. of water and extracted with CH₂Cl₂ (3×300 ml.). The combined CH₂Cl₂ extracts were dried over Na₂SO₄ and evaporated *in vacuo* to give a cloudy oil which crystallized upon standing. Recrystallization 25
 from benzene/hexane gave 7.55 g. (83%) of a white solid product (5), m.p. 118—121°; ir (KBr) 3.0 (NH), 6.1μ (C=O); nmr (CDCl₃); δ 1.22 (t, J=7 cps, 3H, CH₂CH₃), 1.42 (d, J=6 cps, 3H, CHCH₃), 3.15 (p, J=7 cps, 1H, NCH₂CH₃), 3.79 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 3.90 (p, J=7 cps, 1H, NCH₂CH₃), 4.32 (broad s, 1H, NH), 4.83 (q, J=6 cps, 1H, C—2 H), 6.20 (s, 1H, C—8H), and 7.40 (s, 1H, C—5 H). 30
 35

Anal. Calc'd for C₁₅H₁₅O₃N₂: C, 62.38; H, 7.25; N, 11.19.
 Found: C, 62.47; H, 7.55; N, 11.17.

40 Part B: Preparation of 3,4-Dihydro-6,7-dimethoxy-3-ethyl-2-methyl-4-oxo-1(2H)-quinazolinecarboxylic acid, ethyl ester (6)

45 A suspension of 4.9 g. (20 mmoles) of 2,3-dihydro - 6,7 - dimethoxy - 3 - ethyl - 2 - methyl - 4(1H) - quinazolinone (5) and 1.48 g. (equivalent to 30 mmoles) of sodium hydride (40% dispersion in mineral oil) in 60 ml. of dry diethyl carbonate was stirred for 3 hours at room temperature. The tan suspension was poured onto ice-water and extracted with chloroform. The combined chloroform extracts 50
 were dried over magnesium sulfate and concen-

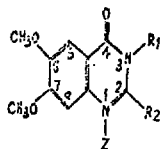
trated *in vacuo* to give an orange oil which was chromatographed on silica gel. The least polar fraction was collected and crystallized upon standing. Recrystallization from cyclohexane gave 3.9 g. (62%) of product (6), m.p. 55
 80—85°, ir (KBr) 5.80 (ester C=O) and 6.02μ (C=O); nmr (CDCl₃); δ 1.1—1.5 (m, 9H, CHCH₃, CO₂CH₂CH₃), 3.7 (p, J=7, cps, 1H, NCH₂CH₃), 3.93 (s, 3H, OCH₃), 3.8—4.2 (p, J=7 cps, 1H, NCH₂CH₃), 42.9 (q, J=7 cps, 1H, OCH₃), 4.33 (q, J=7 cps, 1H, OCH₃), 5.92 (q, J=6 cps, 1H, CHCH₃), 7.15 (s, 1H, C—8H), and 7.50 (s, 1H, C—5H). 60

65 *Anal.* Calc'd for C₁₆H₂₂N₂O₅: C, 59.61; H, 6.88; N, 8.69.
 Found: C, 59.59; H, 6.86; N, 8.61.

EXAMPLE VI

The following 6,7-dimethoxyquinazolinones described in Examples I to V from the appropriate starting compounds:

5



Compound	R ₁	R ₂	Z
1	<i>n</i> C ₄ H ₉	<i>n</i> C ₄ H ₉	—CN
2	CH ₃	H	—C(O)H
3	CH ₃	CH ₃	—C(O)CH ₃
4	CH ₃	H	—C(O) <i>n</i> C ₄ H ₉
5	CH ₃	CH ₃	—C(O) <i>i</i> C ₃ H ₇
6	<i>i</i> C ₃ H ₇	<i>i</i> C ₃ H ₇	—3(O)CF ₃
7	C ₂ H ₅	C ₂ H ₅	—C(O)NH(CH ₃)
8	<i>t</i> C ₄ H ₉	H	—C(O)NH ₂
9	<i>n</i> C ₃ H ₇	H	—C(O)N(CH ₃) ₂
10	CH ₃	CH ₃	—C(O)NH(<i>t</i> C ₄ H ₉)
11	H	H	—C(O)N(<i>i</i> C ₄ H ₉) ₂
12	<i>i</i> C ₃ H ₇	<i>i</i> C ₃ H ₇	—C(O)OCH ₃
13	CH ₃	CH ₃	—C(O)O <i>n</i> C ₄ H ₉
14	CH ₃	CH ₃	—C(O)OCH ₃
15	H	CH ₃	—C(O)OC ₂ H ₅
16	CH ₃	H	—C(O)O <i>n</i> C ₃ H ₇
17	C ₂ H ₅	C ₂ H ₅	—C(O)OC ₂ H ₅
18	<i>n</i> C ₃ H ₇	<i>n</i> C ₃ H ₇	—C(O)OC ₂ H ₅
19	<i>n</i> C ₄ H ₉	<i>n</i> C ₄ H ₉	—C(O)OC ₂ H ₅
20	C ₂ H ₅	H	—C(O)OC ₂ H ₅
21	<i>n</i> C ₃ H ₇	H	—C(O)OC ₂ H ₅
22	<i>n</i> C ₄ H ₉	H	—C(O)OC ₂ H ₅

appro-

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The activity of compounds of the invention as a tranquilizing agent has been shown by their effectiveness in one or more of the following tests:

- 5 (a) conditioned avoidance behaviour and (b) symptomatological effects.

The activity of compounds of the invention as an analgesic agent has been shown by their effectiveness in one or more of the following tests:

- 10 (c) suppression of writhing (d) suppression of the "jump" component of the Evans flinch-jump test; and (e) altered escape threshold on the rat escape-titration test.

EXAMPLE VII

- 15 Tranquilizer Activity of Compound (4) in Example III or IV

- 20 (a) *Conditioned avoidance behaviour.* A modification of the method of Maffii (J. Pharm. Pharmacol., 11, 129 (1959)) was employed. Compound (4) suppresses conditioned avoidance behaviour in the jump-box test in rats at 32 mg/kg i.p. and above; the oral ED_{50} is about 100 mg/kg. Its intraperitoneal potency is thus about 6 times less than that of chlorpromazine. Its duration of action at equivalent doses is slightly shorter. Both orally and intraperitoneally, the selectivity of the avoidance suppressing effect is comparable to that of chlorpromazine; that is, compound (4) does not exhibit the pronounced selectivity of such drugs as thiothixene.

- 30 In Sidman avoidance behaviour, compound (4), at 17.8 mg/kg i.p. in rats, exerts a disruptive effect for about an hour after treatment.

- 35 (b) *Symptomatological effects.* Compound (4) is acutely lethal to mice at 1000 mg/kg i.p. Symptoms preceding include ataxia, loss of righting, and labored respiration. At non-lethal doses (316 mg/kg to 32 mg/kg) behavioral depression including reduced motor activity and rotarod deficit, are seen. At 10 mg/kg i.p. mice are asymptomatic.

- 45 The i.p. LD_{50} in rats lies between 178 and 316 mg/kg. Symptoms at and below toxic doses are similar to those seen in mice. At 32 mg/kg motor activity is decreased, but other overt signs are absent.

- 50 In dogs, 10 mg/kg orally produces ataxia and obvious central nervous system (CNS) depression; one of four dogs at this dose in fact went to sleep in a noisy animal room.

- 55 Analgesic Activity of Compound (4) in Example III or IV

- 60 (c) *Suppression of writhing.* The phenyl-p-benzoquinone (PBQ) writhing experiments were performed according to the method of Sigmund and coworkers (E. Sigmund, R. Cadmus, and G. Lu, Proc. Soc. Exp. Biol., 95, 729 (1957)). In mice, compound (4), given orally, suppresses writhing (repetitive abdominal con-

tractions) produced by intraperitoneal injections of phenylbenzoquinone (PBQ), acetylcholine and tryptamine. Its oral ED_{50} versus PBQ, is 18.5 mg/kg, which compares with ED_{50} 's of .5 and 245 mg/kg, respectively, for morphine sulfate and aspirin. Its blockade of acetylcholine writhing (ED_{50} =31.4 mg/kg p.o.) is unaccompanied by evidence of anticholinergic activity.

(d) *Suppression of the "jump" component of the Evans flinch-jump test.* The Evans flinch-jump experiments were performed according to the method of Evans (W. O. Evans, Psychopharmacologia, 2, 318 (1961)). In rats, compound (4), at 17.8 mg/kg and above increases the minimal shock intensity required to elicit a "jump" response. Intensities required to elicit a "flinch" response, or an audible "squeak" are essentially unchanged, even after 56 mg/kg. At 100 mg/kg i.p., however, even these measures are affected.

(e) *Altered escape threshold on the rat escape-titration test.* This procedure is based on a modification of the method of Weiss and Laties (B. Weiss and V. G. Laties, Science, 128, 1575 (1958)). At about 17.8 mg/kg i.p., compound (4) causes a rapid rise in shock thresholds required to cause the animal to emit a learned escape response of lever pressing. This sudden rise diminishes over a period of several hours.

EXAMPLE VIII

- Tranquilizer Activity of Compound (2) in Example II

- 95 (a) *Conditioned avoidance behaviour.* A modification of the method of Maffii (J. Pharm. Pharmacol., 11, 129 (1959)) was employed. Compound (2) suppresses conditioned avoidance behaviour in the jump-box test in rats at 56 mg/kg i.p. and above. It is inactive at 32 mg/kg i.p. Its intraperitoneal potency is thus about 10 times that of chlorpromazine.
- 100 (b) *Symptomatological effects.* Compound (2) is acutely lethal to mice at 1000 mg/kg i.p. At a non-lethal dose (100 mg/kg) reduced motor activity is seen.

EXAMPLE IX

- Tranquilizer Activity of Compound (6) in Example V.

- 110 (b) *Symptomatological effects.* Compound (6) is acutely lethal to mice at 316 and 1000 mg/kg i.p. Symptoms preceding the mortality include ataxia, convulsions and tremors. At the non-lethal dose of 100 mg/kg, behavioral depression, included reduced motor activity and rotarod deficit, are seen. At 32 mg/kg i.p. mice are asymptomatic.

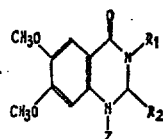
- Analgesic Activity of Compound (6) in Example V

- 120 (c) *Suppression of writhing.* The phenyl-p-benzoquinone (PBQ) writhing experiments were performed according to the method of

- Sigmund and coworkers (E. Sigmund, R. Cadmus, and G. Lu, Proc. Soc. Exp. Biol., 95, 729 (1957)). In mice, compound (6), given orally at a dose of 100 mg/kg, suppresses writhing (repetitive abdominal contractions) produced by intraperitoneal injections of phenylbenzoquinone (PBQ).
- (e) *Altered escape threshold on the rat escape-titration test.* This procedure is based on a modification of the method of Weiss and Laties (B. Weiss and V. G. Laties, Science, 128, 1575 (1958)). At about 17.8 mg/kg i/p., compound (6) causes a rapid rise in shock thresholds required to cause the animal to emit a learned escape response of lever pressing. This sudden rise diminishes over a period of several hours.

WHAT WE CLAIM IS:—

1. A compound having the formula:



wherein:

Z is CN, —COR, —COCF₃, —CONRR', or —COOR; except that Z is never COOH; R, R₁, R₂ and R' are the same or different and are hydrogen or lower alkyl, said lower alkyl having from 1 to 4 carbon atoms.

2. 3,4 - Dihydro - 6,7 - dimethoxy - 2,3-dimethyl - 4 - oxo - 1(2H) - quinazolinecarboxylic acid, ethyl ester.

3. 3,4 - Dihydro - 6,7 - dimethoxy - 3 - methyl - 4 - oxo - 1(2H) - quinazolinecarboxylic acid, ethyl ester.

4. 3,4 - Dihydro - 6,7 - dimethoxy - 3-ethyl - 2 - methyl - 4 - oxo - 1(2H) - quinazolinecarboxylic acid, ethyl ester.

5. A compound according to claim 1, wherein Z is —COOR.

6. A pharmaceutical composition comprising a compound as defined in any one of the preceding claims, in a pharmaceutical carrier.

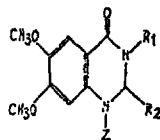
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