New Hybrids of Quipazine and Trazodone as Selective Inhibitors of Uptake of 5-Hydroxytryptamine

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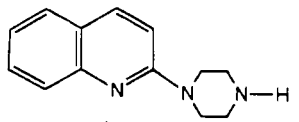
Abstract □ Two new congeners, 4-(chloropropyl)-1-(2-quinolyl)piperazine- and 2-[3-[4-[2-(quinolyl)]-1-piperazinyl]propyl]-1,2,4-triazolo]4,3-a]pyridin-3(2*H*)-one, of trazodone were synthesized and found to be potent and selective inhibitors of synpatosomal uptake of 5-hydroxytryptamine [5-HT, serotonin; IC_{50} = norepinephrine > 5 μM, 5-HT = 210–890 nM], with minimal effects in antagonizing (−)-apomorphine-induced climbing behavior and suppression of spontaneous locomotor activity in mice (ED_{50} > 50 mg/kg). The two compounds behaved like atypical antidepressants, since they weakly antagonized reserpine-induced hypothermia. The acute toxicity studies have shown that these compounds were less lethal when compared with imipramine or quipazine. Furthermore, chronic treatments (20 mg/kg, daily for 10 and 21 days) significantly decreased the isoprenaline-induced increase in cyclic AMP in the rat brain cortex, suggesting desensitization of β-adrenoceptors. These findings point to the effects of these compounds as potential antidepressants dealing with specific serotonergic mechanisms.

For more than 30 years, the tricyclic antidepressant drugs, represented by imipramine as the prototype, have been the most commonly prescribed drugs for the treatment of endogenous depression. Most of these antidepressants, however, have a broad spectrum of pharmacological activities with various unwanted anticholinergic, cardiovascular, and antihistamine side effects at therapeutic doses.[1,2] Newer antidepressants, such as the selective serotonin (5-hydroxytryptamine; 5-HT) uptake blockers zimelidine,[3] citalopram,[4] and trazodone,[5] are clinically effective and have fewer, or less severe, side effects than the tricyclic antidepressants. The clinical efficacy of these new drugs, as well as that of 5-hydroxytrytophan,[6] and the presence of low cerebrospinal fluid concentration of 5-HT metabolites in endogenously depressed patients,[7,8] support the hypothesis that derangement of 5-HT pathways is involved in the etiology of endogenous depression. Furthermore, raphe 5-HT neurons may exert an inhibitory influence on norepinephrine (NE) in the locus ceruleus.[9] Consequently, reduced firing of these 5-HT neurons by blocking of the presynaptic uptake of 5-HT could lead to activation of NE neurons at the locus ceruleus and to an ultimate antidepressant action.[10] Thus, there is compelling evidence that 5-HT uptake blockers have antidepressant activities with minimal cardiovascular effects.[11,12]

In animal models, quipazine (1), a 5-HT receptor agonist[13] with moderate 5-HT uptake-blocking properties,[14] has also demonstrated some antidepressant-like activities in common with tricyclic antidepressants.[15,16] However, it has a potential for many side effects, such as tremor and head twitching.[17]

We have recently reported that the introduction of a phenyl group on the 4-position of the quinoline ring of quipazine to produce compound 2 resulted in an increase in the potency of this compound for blocking NE uptake.[18] Further molecular modification of trazodone-type analogue compound 4 was as potent as trazodone 3 in blocking the 5-HT uptake, but was less selective.[18] It appears, therefore, that the presence of the triazolo-pyridine-3-one moiety increases the selectivity of the compound for blocking 5-HT uptake, while the phenyl group at the 4-position of the quinoline decreases the potency in inhibiting 5-HT uptake.



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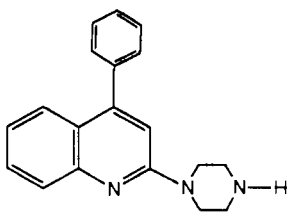

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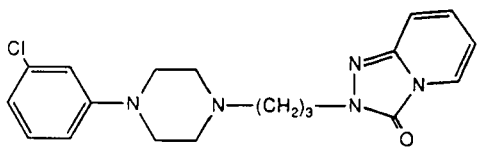

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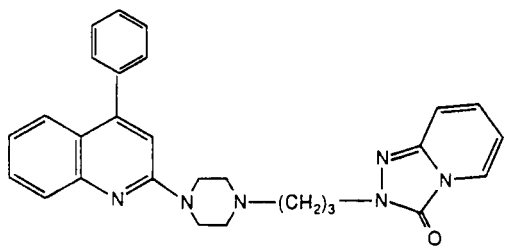

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Based on the above structure–activity relationship approach, it was thought that the incorporation of the triazolo-pyridine-3-one moiety of trazodone into the quipazine molecule would produce compounds that show greater selectivity for blocking 5-HT uptake as compared with NE uptake. The present work involves the synthesis of this targeted compound **10**. Biological studies were also undertaken to investigate the neurochemical, behavioral, and pharmacological properties of **10**, as well as those of its precursor 8 (Scheme I) as 5-HT uptake inhibitors. Since most antidepressant drugs cause desensitization of β-adrenoceptor after chronic administration,[19] the effects of 8 and **10**, as well as quipazine, trazodone, and imipramine on the noradrenergic cyclic AMP-generating system in the rat brain cortex after chronic

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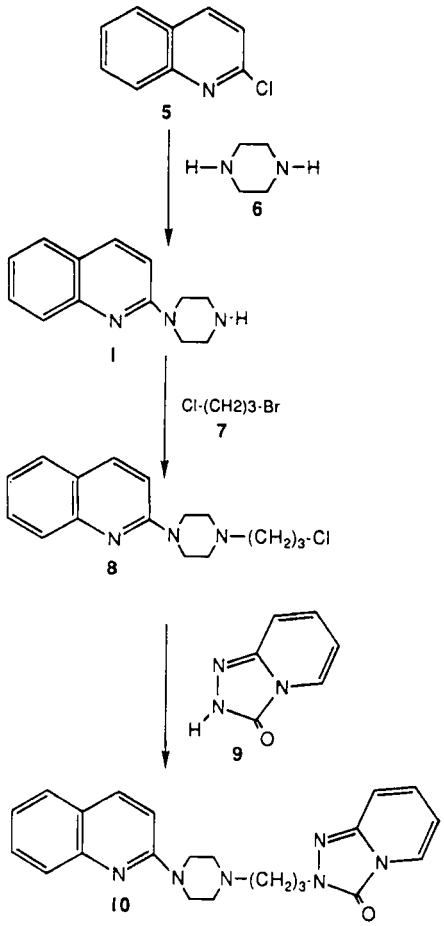

Scheme I

treatment were also determined to further assess the relative antidepressant potential of the new compounds.

Experimental Section

Chemicals—Isoprenaline · HCl, 2-chloroquinoline, 3-chloro-1-bromopropane, and piperazine were purchased from Aldrich Chemical Company (Milwaukee, WI), and 1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one was a gift from Professor Bruno Silvestrini of Angelini Research Institute (Italy). Imipramine · HCl, trazodone · HCl, and haloperidol · HCl were kindly donated by Ciba-Geigy, Mead Johnson Pharmaceutical Division, and Arab Pharmaceutical Manufacturing, respectively. Apomorphine · HCl was obtained from Research Biochemicals Incorporated (Natick, MA), and c-AMP kits were purchased from Amersham Corporation (Arlington, IL). Tritiated 5-HT ([^{3}H]5-HT; hydroxytryptamine bioxalate) and norepinephrine ([^{3}H]NE; levo-norepinephrine) were from NEN Research Products (Boston, MA).

Drug doses reported are based on the weights of the salt supplied.

Methods—Melting points were determined on a Mettler FB51 apparatus and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were obtained on a Varian XL 200 spectrometer using deuteriochloroform or DMSO-d6 as internal standards. Infrared spectra (IR) were recorded on a Perkin-Elmer 727 B spectrophotometer using KBr pellets. Elemental analyses were obtained on a Perkin-Elmer 240 B elemental analyzer. Results were within 0.4% of theoretical values.

Synthesis—The general reaction sequence leading to 4-(chloropropyl)-1-(2-quinolyl)piperazine (8) and 2-[3-[4-[2-(quinolyl)]-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one (10) is shown in Scheme I.

Quipazine (1) was prepared by reacting 2-chloroquinoline with excess piperazine in boiling toluene at 130 °C. The purified product was then reacted with 3-chloro-1-bromopropane in toluene to give the *N*,*N*-disubstituted piperazine derivative 8. The latter was then condensed with the sodium derivative of 1,2,4-triazolo [4,3-*a*]pyridin-3(2*H*)-one (9) to give the final product **10**.[20]

1-Quinolyl piperazine (1)—A suspension of 2-chloroquinoline (3.65 g), piperazine (6.88 g), and finely powdered KOH (1.12 g) in toluene (150 mL) was refluxed in an oil bath for 4 h. The reaction mixture was washed after cooling with water (3 × 200 mL) to remove unreacted piperazine and then evaporated under reduced pressure. The residue was dissolved in methanol and the undissolved 2-chloroquinoline was removed by filtration. The methanolic solution was evaporated under reduced pressure, and the solid residue was recrystallized from chloroform and diethyl ether to give 1 (3.93 g, 83%), mp 118–120 °C; ^{1}H NMR (DMSO-d6) δ: 10.02 (b, s, ^{1}H, NH) 8.28–7.22 (m, ^{6}H, aromatic protons), 4.18 (brs, ^{4}H, N(CH_2)$_2$), and 3.18 (brs, ^{4}H, HN (CH_2)$_2$).

Anal.—($C_{13}H_{15}N_3$): C, H, N.

4-(Chloropropyl)-1-(2-quinolyl)piperazine (8)—Finely powdered KOH (1.12 g, 0.02 mol) was added to a solution of 1-quinolyl piperazine (4.36 g, 0.02 mol) and 3-chloro-1-bromopropane (12.52 g, 0.03 mol) in dry toluene (100 mL), and the mixture was then heated under reflux in an oil bath for 4 h. The cooled mixture was added slowly to distilled water (500 mL) with stirring, and the white precipitate obtained was separated by filtration. The crude product was recrystallized twice from alcohol:water (1:1) to give 8 (4.82 g, 84%), mp 88–89 °C; ^{1}H NMR ($CDCl_3$) δ: 7.90–6.94 (m, ^{6}H, aromatic protons), 3.76–3.60 (m, ^{6}H, piperazine and -CH_2-), and 1.98 (m, ^{2}H, -CH_2-N).

Anal.—($C_{16}H_{20}N_3Cl$: C, H, N).

2-[3-[4-[2-(Quinolyl)]-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one (11)—A solution of 1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one (4 g, 0.03 mol dissolved in 80 mL of dry xylene), with the aid of heat, was added to a suspension of NaH (2 g, 0.03 mol, 50% in oil suspension that was washed three times with dry xylene under absolutely dry conditions) in xylene (10 mL), and the mixture was then heated under reflux in an oil bath for 1 h. A solution of 4-(chloropropyl)-1-(2-quinolyl)piperazine (4 g, 0.013 mol) in dry xylene (50 mL) was added in a dropwise manner to the reaction mixture, and thereafter the mixture was heated under reflux with continuous stirring at 150 °C for 20 h. After cooling, the mixture was filtered and the mother liquor was washed several times with 2% NaOH to remove any unreacted 1,2,4-triazolo[4,3-*a*]pyridine-3(2*H*)-one. The xylene was evaporated under reduced pressure, and the residue was recrystallized from 95% ethanol to give compound **10** (4.12 g, 77%), mp 148–149 °C; IR: 1715 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ: 7.98–6.44 (m, ^{10}H, aromatic protons) 4.05 (t, ^{2}H, -CH_2-N), 3.50 (m, ^{4}H, piperazine) 2.38–2.18 (m, ^{6}H, piperazine and -CH_2-), 2.05 (m, ^{2}H, -CH_2-N).

Anal.—($C_{22}H_{24}N_6O$): C, H, N.

Biological Evaluation Procedures—*Synaptosomal Uptake of 5-Hydroxytryptamine and Norepinephrine*—The original procedure of Snyder and Coyle,[21] with some modifications, was utilized to determine biogenic amine uptake.[22] Adult male Sprague-Dawley rats weighing 180–200 g were decapitated, and the brains were immediately removed and placed in 0.32 mM sucrose maintained at 4 °C. The cortices were dissected and homogenized in 10 volumes of isotonic sucrose (0.32 mM). The homogenate was centrifuged at 1000 × *g* for 10 min to remove nuclei and cell debris. The supernatant synaptosomal suspension was recentrifuged at 1500 × *g* for 20 min. The pellet was then resuspended in five volumes of 0.32 mM sucrose and recentrifuged for another 20 min. The pellet was gently resuspended in 2 mL of Krebs-Ringer phosphate buffer solution (pH 7.4) containing 9.4 mM glucose, 10 μM ascorbic acid, and 12 μM nialamide. For 5-HT uptake, each incubation vessel contained 50 μL of the synaptosomal suspension; for NE uptake, 100 μL was added in a final volume of 0.75 mL. A preincubation was carried out in a shaking water bath at 37 °C for 1 and 2 min for 5-HT and NE, respectively. Uptake was initiated by the addition of 5 nM (final concentration) of [^{3}H]5-HT or 2 μM of NE. Incubation times were chosen from the linear portion of uptake versus incubation time curves that were determined for each substrate and found to be 2 and 3 min for 5-HT and NE, respectively. After the incubation periods, uptake was terminated by adding 5 mL of ice-cold saline (0.9% NaCl). Samples were rapidly filtered through Millipore type AA filters (0.45 μM pore size) using a vacuum filtration manifold; the filters were washed with 5 mL of cold saline. The filters were placed in plastic scintillation vials containing 10 mL of scintillation cocktail (Liquiscint, National Diagnostics), and the radioactivity was measured by liquid scintil-

lation spectrometry (Beckman LS-335).

Nonspecific uptake was determined using samples incubated on ice. Net uptake was taken as the difference between that which occurred at 37 and 0 °C. For determining IC_{50} values, seven to nine different concentrations of each drug were used, with triplicate determinations carried out at each concentration.

Isoproterenol-Sensitive Adenylate Cyclase of Rat Brain Cortex—Male albino Wistar rats (initial weight, 170–200 g), housed in groups of five each and kept under standard laboratory conditions, were used. All drugs were injected ip (20 mg/kg). Control rats received a corresponding volume of vehicle. After certain intervals of treatment, rats were decapitated, and cerebral cortical slices were dissected as rapidly as possible and suspended in oxygenated Krebs-bicarbonate buffer (pH 7.4). Slices were preincubated for 60 min in a shaking water bath at 37 °C with two changes of medium. Cortical slices weighing 50–100 mg were placed in tubes containing 200 μL of fresh Krebs-bicarbonate buffer and 50 μL of 2 mM aminophylline and chopped with scissors.

The incubation was started by the addition of 50 μL of 120 mM isoprenaline · HCl, and the reaction mixture was oxygenated with 5% CO_2 in oxygen. The test tubes were then incubated for 15 min at 37 °C, and the reaction was terminated by boiling for 10 min. Duplicate 50-μL samples of the extract were assayed by kit method (Amersham) for c-AMP; results were expressed in pmol per mg of wet tissues. The two-tailed *t* test was utilized for statistical comparison of results.

Apomorphine-Induced Climbing Behavior—Female albino Wistar mice weighing 30 ± 2.1 g were used. Animals were placed in individual climbing cages with 1-cm diameter wire mesh sides (30 cm long, 30 cm wide, 40 cm high). Following a short habituation period (10–15 min), each animal was removed and a dose of apomorphine · HCl (0.5 mg/kg dissolved in 0.1% sodium metabisulphite solution) was administered sc in a volume of 0.5 mL per 100 g of body weight. The animals were then returned to the cages and the ability to climb was measured at 5-min intervals from 5 to 30 min following apomorphine administration.[23] An Opto-Varimex activity meter (Columbus Instruments) equipped with a sensor to detect vertical activity was used to measure the climbing behavior. The climbing cages were placed in front of the sensors every time climbing was measured. Test drugs were injected ip 30 min before apomorphine administration. The number of climbing activities was recorded automatically on a timer-controlled printer at 5-min intervals for a period of 30 min. Groups of six mice per dose of test drug were used. The percent inhibition was calculated for various doses of each compound, log dose–effect curves were constructed, and ED_{50} values were determined graphically.

Spontaneous Locomotor Activity in Mice—Female albino Wistar mice weighing 30 ± 3.2 g were used. The mice were injected ip with drug solutions and placed in an Opto-Varimex activity meter (Columbus Instruments). Four groups of six mice each were used for each test, and six saline-treated mice were used as control. Experiments were run at the same time of the day and same room temperature. Noise and light were kept at the same level each day. Activity was automatically counted on a time-controlled printer at 10-min intervals for a period of 2 h. Haloperidol was used as standard for comparison. The effect of each compound was expressed as the percentage of its mean activity counts of the saline-treated group. The ED_{50} value of each compound was calculated from the log concentration–effect curves.

Catalepsy Assessment—Male albino Wistar rats weighing 220–250 g were used. The ability of the test compounds to induce a cataleptic state in the rat was assessed by application of a scoring system that allows the demonstration of a dose dependency for the cataleptic action of haloperidol (0.15–2 mg/kg, ip, gave scores ranging from 1 to 5). Catalepsy was measured by carefully placing an animal with its front limbs extended over a 10-cm high bar and noting the time the animal maintained the imposed position.[24,25] Animals were tested every 10–30 min after drug administration, and the catalepsy was scored as follows: 0 = no catalepsy, 1 = 1.0–3.1 min, 2 = 3.2–5.0 min, 3 = 5.1–10 min, 4 = 10.1–25.0 min, 5 > 25 min.

Antagonism of Reserpine-Induced Hypothermia—The method of Askew[26] was adopted with some modification.[20] Male albino Wistar mice (18–26 g body weight) were housed in groups of five in a room with an ambient temperature of 24 °C. Mice were injected sc with reserpine (3 mg/kg); this was followed immediately by ip injection of the test compound in normal saline. Control rectal temperatures were taken immediately prior to the injection of reserpine. After 4 h, the rectal temperature of each mouse was measured with a microthermometer. The ED_{50} was defined as the dose that caused 50% inhibition of the reserpine-induced decrease in the rectal temperature.

LD_{50} Determinations—Male albino Wistar mice were used. The animals were divided into six groups of 10 mice each. Increasing doses of test compound were given at increments of 25 or 50 mg/kg, and then death in each group was scored for a period of 12 h. The mean mortality was calculated and multiplied by the dose increments used. A special formula of Karber[27] was then used to calculate the LD_{50} of each compound.

Results and Discussion

The aim of this study was to synthesize selective 5-HT uptake blockers and to observe the resulting biochemical, behavioral, and pharmacological effects of these compounds. The IC_{50} values for the in vitro inhibition of uptake of [^{3}H]NE- and [^{3}H]5-HT by **1**, **8**, **10**, imipramine, and trazodone are shown in Table I. Relative to imipramine, **1**, **8**, **10**, and trazodone inhibited 5-HT uptake to a greater extent than NE uptake.

Use of typical antidepressant drugs like imipramine is usually associated with a high incidence of cardiovascular side effects such as tachycardia and myocardial infarction.[28,29] These effects may be attributed to the inhibition of NE uptake in the heart. New antidepressants, like trazodone, zimelidine, fluoxetine, and recently sertraline, are clinically effective and have minimum cardiovascular manifestations.[2,3,11] These compounds have minimum effect on the synaptosomal uptake of NE, but potentially block the uptake of 5-HT.[5,30]

In the present work, **8** shows greater selectivity than trazodone in blocking 5-HT uptake relative to NE uptake. The actual difference in selectivity is probably much greater than that shown, because drugs producing no effect at concentrations higher than 10 μM can be considered inactive[14] (the highest concentration used was 15 μM). Selective 5-HT uptake blockers may be effective antidepressants due to the influence of 5-HT neurons in the brain. Raphe 5-HT neurons may exert inhibitory control on NE neurons of the locus ceruleus.[9] These 5-HT neurons could be effectively inhibited by applied 5-HT, 5-HT agonists, or 5-HT uptake blockers.[31,32] Therefore, inhibition of the firing of these 5-HT neurons by 5-HT uptake blockers may activate the NE neurons at the locus ceruleus and could lead to ultimate antidepressant response.[10,30]

Chronic treatments (10 and 21 days) with **8**, **10**, quipazine, or imipramine produced a significant decrease of isoprenaline-induced c-AMP generation. In contrast, trazodone attenuated this response with less magnitude only after 21 days of chronic treatment and had no significant effect at 10 days (Table II). Vetulani and Sulser[19] have demonstrated that the sensitivity of the isoprenaline-stimulated adenylate cyclase system in rat brain cortex is diminished by chronic administration of antidepressants such as desipramine and iprin-

Table I—Blocking Activities of Compounds 8 and 10 on Reuptake of Norepinephrine and 5-Hydroxytryptamine

Compound	Blocking Activity (IC_{50}), μM[a]		
	[^{3}H]Norepinephrine	[^{3}H]5-HT	NE:5-HT Ratio
Imipramine	0.818 ± 0.63	0.111 ± 0.02	7.4
Trazodone	7.91 ± 2.74	0.473 ± 0.02	16.7
Quipazine	4.12 ± 0.36	0.340 ± 0.08	12.1
8	>15.00	0.630 ± 0.04	>24
10	4.51 ± 2.20	0.210 ± 0.63	21

[a] IC_{50} refers to the concentration of inhibitors required to block 50% of the monoamine uptake; results are expressed as mean ± SEM.

Table II—Effect of Imipramine, Trazodone, Quipazine, 8, and 10 on Isoproterenol-Stimulated Formation of c-AMP in Rat Cerebral Cortex

Treatment	Dose, mg/kg	Duration of Treatment, days	c-AMP, pmol/mg of wet tissue[a]	Percent of Control Response
Vehicle		1	126.01 ± 7.48	100
		10	123.00 ± 5.02	100
		21	125.71 ± 5.02	100
Imipramine	20	1	128.21 ± 5.01	100
		10	93.01 ± 5.53[b]	76
		21	26.71 ± 2.37[c]	21
Trazodone	20	1	122.12 ± 5.19	100
		10	116.36 ± 5.60	95
		21	61.57 ± 2.89[b]	49
Quipazine	20	1	123.00 ± 3.12	100
		10	90.23 ± 4.23[b]	74
		21	36.89 ± 13.24[c]	28
8	20	1	124.12 ± 3.58	100
		10	82.01 ± 8.32[b]	70
		21	26.23 ± 3.45[c]	21
10	20	1	126.14 ± 6.35	100
		10	89.33 ± 6.54[b]	72
		21	34.78 ± 6.72[c]	27

[a] Results are expressed as mean ± SEM (n = 5). [b] Values are significantly different from the corresponding control groups injected with saline ($p < 0.05$). [c] Significantly different ($p < 0.001$).

dole. Furthermore, chronic treatment with drugs which are known to have profound 5-HT uptake blocking action with a negligible effect on NE uptake, such as zimelidine, trazodone, and fluovoxamine, results in the desensitization of the β-adrenoceptor.[32,33] The results in Table II clearly indicate that 8 and 10 share this property with the established antidepressants and further suggest the potential antidepressant activity for the compounds. The rapid desensitization of these receptors elicited by 10 days of treatment with these compounds also points to another important advantage of these compounds over trazodone.

Compounds 8 and 10 demonstrated a negligible effect in reducing the spontaneous locomotor activity in mice and in inducing a cataleptic response in rats as compared with haloperidol (Table III). Furthermore, both compounds are very weak inhibitors of apomorphine-induced climbing in mice when compared with haloperidol and quipazine. These results indicate that, like the tricyclics, 8 and 10 demonstrate

Table III—Antagonism to Apomorphine-Induced Climbing Behavior, Inhibition of Spontaneous Locomotor Activity, and Catalepsy Scores of 8 and 10

Compound	Apomorphine Antagonism ED_{50} (ip), mg/kg[a]	Inhibition of Spontaneous Locomotor Activity ED_{50} (ip), mg/kg[a]	Catalepsy Scores[b]
Haloperidol	5.0 ± 1.34	3.2 ± 0.26	5[c]
Imipramine	>50	>50	0
Quipazine	25 ± 4.21	42.3 ± 3.71	0
Trazodone	>50	>50	0
8	>50	>50	0
10	>50	>50	0

[a] Results are expressed as mean ± SE (n = 6). [b] "0" means no catalepsy at doses up to 50 mg/kg. [c] Maximum response at a dose of 2 mg/kg (see text).

Table IV—Antagonism to Reserpine-Induced Hypothermia in Mice and Toxicological Activities of 8 and 10

Compound	Antihypothermia ED_{50} (ip), mg/kg[a]	LD_{50} (ip), mg/kg[b]	Therapeutic Index[c]
Imipramine	21.0 (16.1–25.9)	163.0 (15.0)	7.76
Trazodone	>50.0	255.0 (22.2)	—
Quipazine	35.4 (27.5–43.3)	135.0 (17.2)	3.01
8	>50.0	250.0 (14.3)	—
10	>50.0	395.0 (21.8)	—

[a] 95% Confidence limit is shown in parentheses. [b] Standard deviation is shown in parentheses. [c] LD_{50}/ED_{50}.

no central dopaminergic blockade, an apparent problem with quipazine.

In contrast to the typical antidepressants like imipramine, 8 and 10 have an extremely weak effect on antagonizing the reserpine-induced hypothermic response in mice (Table IV). This points to similarity of these compounds with the atypical antidepressants such as trazodone. In a previous work,[20] it has been shown that analogues of 8 and 10 having a phenyl group substituted at position 4 of the quinoline ring were effective in antagonizing reserpine-induced hypothermia. This phenyl substitution also enhances the ability of these compounds to inhibit the synaptosomal uptake of NE over that of 5-HT.[18] These findings are consistent with the assumption that reversal of reserpine-induced hypothermia correlates with inhibition of NE, but not 5-HT uptake.[34]

The acute lethality of 8 and 10 was determined to be less than that of either imipramine or quipazine. Interestingly, the tremor and head twitches that were observed in mice administered quipazine (>50 mg/kg) and the potent sedative effect of trazodone (>100 mg/kg) were absent with 8 and 10. This fact, along with the observed selectivity for 5-HT uptake inhibition, suggests important advantages for these compounds over quipazine or trazodone.

In view of the fact that most antidepressants (particularly imipramine and amitriptyline types) also interact with other neurotransmitter receptors,[1,2] more study is needed to establish the receptor selectivity of the new compounds (preliminary data using guinea-pig ileum indicate that the compounds have only a weak anticholinergic effect as compared with that of imipramine).

In conclusion, two congeners related in structure to quipazine and trazodone have demonstrated considerable selectivity for inhibiting the uptake of 5-HT. Unlike imipramine, both derivatives have been found to be least effective in antagonizing reserpine-induced hypothermia in mice and are relatively less toxic. Both compounds have some pharmacological advantages over trazodone by their ability to desensitize β-adrenoceptors at 10 days of chronic treatment. In addition, the absence of the dopaminergic blocking activity, tremor, and head twitches, as well as the relative high LD_{50} values of these compounds, add important advantages over quipazine. Further derivatives should be developed to extend these findings.

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