# Development of a Novel Series of (2-Quinolinylmethoxy)phenyl-Containing Compounds as High-Affinity Leukotriene $D_4$ Receptor Antagonists. 4. Addition of Chromone Moiety Enhances Leukotriene $D_4$ Receptor Binding Affinity

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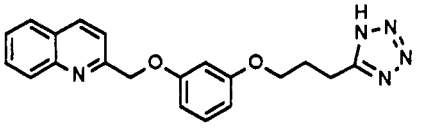
The combination of the benzopyran-4-one ring, a moiety found in the prototype leukotriene antagonist, FPL 55,712, with the (2-quinolinylmethoxy)phenyl group led to a significant increase in leukotriene receptor binding affinity. This modification resulted in a 10 000-fold improvement in binding affinity compared to FPL 55,712. Compound 7 (RG 12553), with a $K_i$ value of 0.1 nM, has higher affinity than the natural agonist $LTD_4$ and is one of the most potent $LTD_4$ antagonists reported. The structure–activity relationships of this series of potent leukotriene antagonists are discussed.

Previous publications[1-3] from our laboratories described a series of (2-quinolinylmethoxy)phenoxy-containing compounds as potent leukotriene $D_4$ antagonists. These studies led to the discovery of 1 (RG 7152) and 2 (RG 12525); both compounds are being evaluated in clinical studies as antiasthmatic agents. The results of our studies indicate that the basic structural requirements for this series of compounds as leukotriene $D_4$ antagonists can be generalized as shown in generic formula 3. Both of the two key elements, a (2-quinolinylmethoxy)phenyl group and an acidic function, are required. Apparently, they can be linked by diversified connecting group(s) to give compounds with high affinity to the leukotriene receptor. We report herein the extension of the structure–activity relationship (SAR) in this series to include compounds (4) in which the acidic function is attached to a benzopyranone ring, a commonly used moiety found in the prototype leukotriene antagonist FPL 55,712.[4] This modification resulted in a more than 10-fold improvement of binding affinity to leukotriene receptors as compared to 2, and a 10 000-fold improvement in affinity as compared to FPL 55,712. Compound 7, with a $K_i$ value of 0.1 nM, has higher affinity than the natural agonist $LTD_4$ and is one of the most potent $LTD_4$ antagonists reported.



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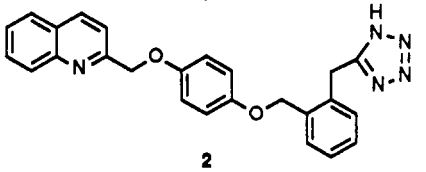

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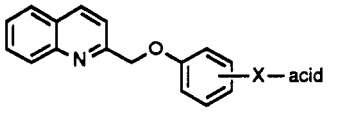


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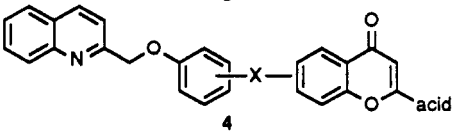


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## Chemistry

The key intermediates, 4-oxo-4*H*-1-benzopyran-2-carboxylates (5, chromones)[4-7] and (2-quinolinylmethoxy)phenyl derivatives (6),[1,2] used for the synthesis of compounds 7-19 listed in Table I were prepared according to literature methods. The chromanone moiety in 14 was synthesized from 2,4-dihydroxyacetophenone and ethyl levulinate.[8] Compounds with an ether linkage were synthesized by simple coupling reactions between appropriately substituted 5 and 6. A Wittig reaction was employed for the synthesis of olefinic compound 12. The assignment of *E* stereochemistry of the olefin is based on the chemical shift ($\delta$) of the olefinic proton at 7.2 ppm, since the chemical shift for a typical (*Z*)-stilbene is ~6.8 ppm. Catalytic hydrogenation of 12 gave saturated compound 13. The amide linkage in 18 was synthesized by a standard method starting from the corresponding acid chloride and amino compound (see also ref 7).

**Scheme I**

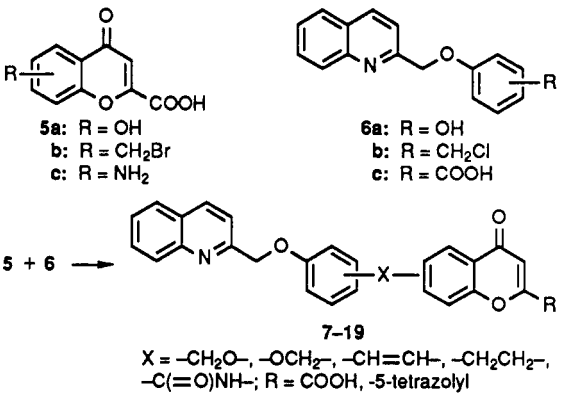


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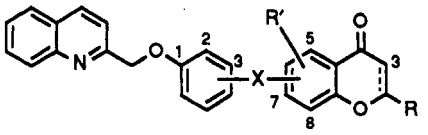
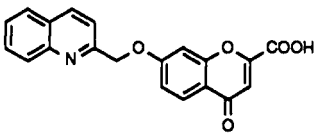
**Table I.** Radioligand Binding Assay on Guinea Pig Lung Membranes



| compd | position of X at phenyl | X | position of X at chromone | R′ | R | $K_i$[a] (nm) or % I (nM) |
|---|---|---|---|---|---|---|
| 7 | 3 | $CH_2O$ | 7 | H | 5-Tet[b] | 0.10 ± 0.03 (4) |
| 8 | 3 | $CH_2O$ | 7 | H | COOH | 2.1 ± 0.3 (3) |
| 24 | 3 | $OCH_2$ | 7 | H | COOEt | 30 ● 8 (2) |
| 9 | 3 | $CH_2O$ | 7 | 8-propyl | COOH | 22% (30 nM) |
| 10 | 3 | $CH_2O$ | 6 | H | COOH | 1.3 |
| 11 | 3 | $OCH_2$ | 7 | H | 5-Tet | 0.12 ● 0.02 (2) |
| 12 | 3 | (*E*)-CH=CH | 7 | H | 5-Tet | 2.5 |
| 13 | 3 | $CH_2CH_2$ | 7 | H | 5-Tet | 0.3 |
| 14 | 3 | $CH_2O$ | 7 | H | 2-$CH_3$ 2-$(CH_2)_2$COOH | 1.2 |
| 15 | 4 | $OCH_2$ | 7 | H | COOH | 6.3 |
| 16 | 4 | $OCH_2$ | 8 | H | COOH | 13 |
| 17 | 4 | $OCH_2$ | 8 | H | 5-Tet | 15 |
| 18 | 4 | C(=O)NH | 8 | H | 5-Tet | 1.1 |
| 19 | 4 | $CH_2O$ | 5 | 6-Cl | COOH | 18 ± 3 (2) |
| 2 | | | | | | 3.0 ± 0.3 (7) |
| ICI, 198,615 | | | | | | 0.3 ± 0.05 (3)[c] |
| FPL 55,712 | | | | | | 510 ± 130 (9) |
| 25 |  | | | | | 7000 |

[a] Radioligand binding assay on guinea pig lung membranes. Compounds were tested at multiple concentrations for competition with 0.2 nM [$^3$H]$LTD_4$ to calculate $K_i$ values from the graphic determinations of $IC_{50}$ values. Values are means ± SEM of (*N*) separate experiments or % inhibition at the concentration indicated in parentheses. [b] 5-Tetrazolyl. [c] Data generated in-house.

## Results and Discussion

The results from testing compounds for $LTD_4$ receptor affinity in a radioligand binding assay ($K_i$) are summarized in Table I. The $K_i$ for ICI 198,615,[9] one of the most potent $LTD_4$ antagonists known, and FPL 55,712, the original chromone-containing $LTD_4$ antagonist, are also included for direct comparison.

Compounds with a chromone moiety displaying leukotriene antagonist activity were first reported in a chemical series related to FPL 55,712,[4] and have since been reported in several other related series of compounds.[7,10,11] Most of these compounds do not have high affinity to the leukotriene receptor. However, the addition of a chromone moiety in this (2-quinolinylmethoxy)phenyl chemical series resulted in a series of highly potent leukotriene $D_4$ antagonists. The data in Table I show that most of these compounds have extremely high affinity for the $LTD_4$ receptor with $K_i$ values equal to or better than our clinical candidate **2** ($K_i$ = 3 nM), and some compounds have $K_i$ values rivaling the $K_d$ (ca. 0.3 nM) of the natural ligand, $LTD_4$ itself. More significantly, **7** was about 3-fold more potent than ICI 198,615 when tested side by side in a direct comparison. ICI 198,615 has a reported $K_i$ of 0.27 nM,[9] which is in good agreement with our $K_i$ value of 0.3 nM. L-660,711 (MK 571), also a quinoline derivative, has a reported $K_i$ of 0.22 nM;[12] however, a direct comparison with this compound is not available. These data indicate that several of the compounds reported here are among the most potent antagonists of $LTD_4$ reported.

While it is not clear how the chromone moiety contributes to binding affinity, it is clear from the binding data of FPL 55,712 and **20** that the presence of the chromone moiety itself is not sufficient to account for high binding affinity. In this chemical series, there are several strucural features that appear to affect the receptor binding. As in the earlier series,[1-3] compounds with a tetrazolyl group as the acidic function are generally much more potent than the corresponding carboxylic acid derivatives as $LTD_4$ antagonists. For example, **7** is 20 times more potent than **8**. It is not obvious why the tetrazole group should make such a profound difference.

The type of linkage between the middle phenyl ring and the chromone ring affects receptor binding affinity only when it is connected by a rigid olefinic bond. Thus, **12** is 10 times less potent than the corresponding saturated **13**. There are no significant differences in receptor binding affinity among the three more flexible connecting groups, i.e., $-CH_2O-$ (**7**), $-OCH_2-$ (**11**), and $-CH_2CH_2-$ (**13**). These results seem to suggest that the connecting group functions as a spacer and itself does not play an important binding role; however, the flexibility of the connecting group allows the molecule to adopt a suitable conformation for optimal

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interaction with the receptor. In addition, it is evident from the structure of **25** that the proper distance between the quinoline and acidic function is critical.

The combined substitution patterns of the middle phenyl ring and chromone ring also influence binding affinity. This is demonstrated by **16–18**, compounds with substitution at the 8-position of the chromone ring. For example, compound **16** is less potent than **8**, **10**, and **15**, while **17** has lower affinity than **7** and **11**. It is probable that the substitution patterns control the spatial orientation of the acidic functional group and the quinoline ring and thereby exert considerable influence upon activity.

We also examined the effect of propyl substitution at the 8-position of the chromone. FPL 55,712 has a propyl group at the 8-position and such a substitution has been commonly used in several different chemical series[10,11] related to the original prototype structure. It is interesting to note that **9** with 22% inhibition at 30 nM is much less potent than the corresponding unsubstituted **8** ($K_i$ = 2 nM).

These compounds were determined to be competitive antagonists of $LTD_4$ from the following pieces of information: (a) these are closely related structurally to several compounds which have been shown to be competitive antagonists;[2] (b) the plotting of the % inhibition of [$^3$H]$LTD_4$ binding vs concentration for all of these compounds were parallel to each other, to others reported earlier, to known standard such as ICI 198,615, and to $LTD_4$; (c) the data from all the experiments with **7** were analyzed by the LIGAND computer program (Biosoft) and Scathard analysis, which indicated that this compound is a competitive inhibitor with a $K_i$ of 0.095 and 0.08 nM, respectively; (d) **7** has been shown to compete with the high-affinity binding site of $^3$H-ICI 198,615 in membranes from guinea pig lung with a $K_i$ of 0.05 nM (data not shown).

Since radioligand binding assays do not differentiate between agonists and antagonists, **7** was tested for leukotriene antagonism in a spasmogenic assay.[1] With use of guinea pig lung parenchmal strips, **7** has an $IC_{50}$ of 0.5 ± 0.1 nM ($N$ = 4) vs 0.2 nM $LTD_4$. This functional antagonist activity agrees well with the binding data. Furthermore, this assay was used to show that these compounds are highly selective for $LTD_4$ receptors. For example, **7** at 10 μM had no significant effects on contractions induced by histamine, methacholine, and $PGF_{2\alpha}$ (data not shown). Taken together, these data show that **7** is an extremely potent and specific $LTD_4$ antagonist.

In an in vivo assay, 1 mg/kg of **7** (iv) inhibited 82% of mortality caused by antigen induced anaphylaxis[1] (data not shown). When administered orally at 10 mg/kg, **7** inhibited only 45% of mortality. Compound **2** has an $ED_{50}$ of 2 mg/kg in the same assay, thus indicating that **7** was poorly absorbed. Further clinical development of **7** by aerosol route is being pursued.

In summary, we have described the synthesis of a series of chromone compounds that are extremely high affinity $LTD_4$ antagonists. Several compounds are among the most potent leukotriene antagonists known. Factors affecting the binding affinity were also discussed.

## Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with the assigned structure. Proton NMR were recorded on a Varian EM-390 spectrometer at 90 MHz. All compounds had elemental analyses for C, H, N within ± 0.4% of the theoretical value unless otherwise indicated. Physical data for new compounds are listed in Table II.

**2-Cyano-7-methyl-4-oxo-4*H*-1-benzopyran (20).** This compound was prepared from ethyl 7-methyl-4-oxo-4*H*-1-benzopyran-2-carboxylate according to the procedures described previously:[7] mp 155–156 °C; $^1$H NMR ($CDCl_3$) δ 3.5 (s, 3 H), 6.7 (s, 1 H), 7.3 (m, 2 H), 8.0 (d, 1 H).

**Table II.** Summary of Physical Data for Compounds Listed in Table I

| compd | mp, °C | formula |
|---|---|---|
| 7 | 203 dec | $C_{27}H_{19}N_5O_4 \cdot H_2O$ |
| 8 | 201 dec | $C_{27}H_{19}NO_6 \cdot H_2O$ |
| 9 | 218–222 | $C_{30}H_{25}NO_6$ |
| 10 | 253–254 | $C_{27}H_{19}NO_6 \cdot 0.25H_2O$ |
| 11 | 246–247 | $C_{27}H_{19}N_5O_4 \cdot H_2O$ |
| 12 | 147–150 | $C_{28}H_{19}N_5O_3 \cdot 6H_2O$ |
| 13 | 201–205 | $C_{28}H_{21}N_5O_3 \cdot 6H_2O$ |
| 14 | 152–154 | $C_{30}H_{27}NO_6$ |
| 15 | 216–219 | $C_{27}H_{19}NO_6$ |
| 16 | 221–224 | $C_{27}H_{19}NO_6$ |
| 17 | >250 | $C_{27}H_{19}N_5O_4 \cdot 4.75H_2O$ |
| 18 | 245–247 | $C_{27}H_{18}N_6O_4 \cdot 1.5H_2O$ |
| 19 | 175 dec | $C_{27}H_{18}N_6O_6Cl \cdot 0.5H_2O$ |
| 24 | 123–124 | $C_{29}H_{23}NO_6 \cdot 0.25H_2O$ |
| 25 | 250–253 | $C_{20}H_{13}NO_5$ |

**7-(Bromomethyl)-2-cyano-4-oxo-4*H*-1-benzopyran (21).** A solution of 4.5 g (24.3 mmol) of the nitrile **20** obtained above, 4.33 g (24.3 mmol) of NBS, and 100 mg of benzoyl peroxide in 75 mL of $CCl_4$ was refluxed under a sun lamp for 4 h. The precipitate was filtered off and the filtrate was concentrated in vacuo. Purification by flash chromatography through silica gel gave 3 g (47%) of yellow crystalline solid, mp 162–166 °C. This bromide was used without further characterization.

**2-Cyano-7-[2-[3-(2-quinolinylmethoxy)phenyl]ethenyl]-4-oxo-4*H*-1-benzopyran (22).** To a suspension of 4.37 g (8.3 mmol) of the Wittig reagent (prepared from 3.0 g of bromide **21** and 2.98 g of triphenylphospine in refluxing toluene) in 100 mL of DMF at 0 °C was added 0.27 g (9.13 mmol) of an 80% NaH in oil dispersion. After the mixture was stirred at 0 °C for 1 h, 2.18 g (8.3 mmol)of 3-(2-quinolinylmethoxy)benzaldehyde in 20 mL of DMF was added in one portion and stirred for 2 h. The mixture was poured into water and extracted with EtOAc, which was then washed well with water, dried, and concentrated. The crude product thus obtained was purified by flash chromatography through silica gel, affording 1.1 g (31%) of **22** as a yellow oil: $^1$H NMR ($CDCl_3$) δ 5.2 (s, 2 H), 6.4–8.1 (m, 15 H).

**5-[7-[2-[3-(2-Quinolinylmethoxy)phenyl]ethenyl]-4-oxo-4*H*-1-benzopyran-2-yl]-1*H*-tetrazole (12).** A mixture of 0.9 g (2.1 mmol) of **22**, 0.56 g (10.45 mmol) of ammonium chloride, and 0.68 g (10.45 mmol) of sodium azide in 20 mL of DMF was heated at 100 °C for 18 h. The reaction was poured into water and the precipitated product was collected on a filter. Recrystallization from $CH_2Cl_2$ gave 0.7 g (70%) of **12**: mp 148–152 °C; $^1$H NMR (DMSO-$d_6$) δ 5.3 (s, 2 H), 6.7–8.1 (m, 14 H), 8.3 (d, 1 H).

**5-[7-[3-(2-Quinolinylmethoxy)phenethyl]-4-oxo-4*H*-1-benzopyran-2-yl]-1*H*-tetrazole (13).** A mixture of 0.2 g (0.42 mmol) of **12** and 0.08 g of 10% Pd/C in 30 mL of EtOH was hydrogenated at 30 psi for 4 h. After filtration through Celite, the filtrate was concentrated and the resulting oil was triturated with $CH_2Cl_2$ to give a precipitate which was recrystallized from $CH_2Cl_2$ to give 0.12 g (60%) of **13**: mp 201–205 °C; $^1$H NMR ($CD_3OD$) δ 2.9 (br s, 4 H), 5.2 (s, 2 H), 6.6–8.2 (m, 13 H).

**2-Cyano-7-[[3-(2-quinolinylmethoxy)phenyl]methoxy]-4-oxo-4*H*-1-benzopyran (7a).** To a solution of 2-cyano-7-hydroxy-4-oxo-4*H*-1-benzopyran[4] (2.22 g, 11.87 mmol) and 3-(2-quinolinylmethoxy)benzyl chloride[2] (3.37 g, 11.87 mmol) in 20 mL of DMSO was added 475 mg (11.87 mmol) of powdered NaOH. The reaction mixture was poured into water after stirring at room temperature for 5 days. The resulting precipitate was collected on a filter and purified by HPLC to give 1.3 g (25%) of **7a**: $^1$H NMR ($CDCl_3$) δ 5.1 (s, 2 H), 5.3 (s, 2 H), 6.7–8.1 (m, 14 H).

This compound was converted to the corresponding tetrazole **7** according to the procedure described for the synthesis of **12**.

Compounds **11** and **17** were synthesized according to the examples described above.

**Ethyl 7-[[3-(2-Quinolinylmethoxy)phenyl]methoxy]-4-oxo-4*H*-1-benzopyran-2-carboxylate (24).** When ethyl 7-

hydroxy-4-oxo-4*H*-1-benzopyran-2-carboxylate was used instead of 2-cyano-7-hydroxy-4-oxo-4*H*-1-benzopyran in the synthesis of **7a**, **24** was obtained in 32% after recrystallization from EtOAc, mp 123–124 °C.

**7-[[3-(2-Quinolinylmethoxy)phenyl]methoxy]-4-oxo-4*H*-1-benzopyran-2-carboxylic Acid (8).** A mixture of 850 mg (1.77 mmol) of **24** and 773 mg (9.2 mmol) of sodium bicarbonate in 4 mL of water and 40 mL of EtOH was heated at 70 °C for 1 h and then stirred at room temperature overnight. The reaction mixture was poured into 100 mL of water and acidified to pH 3. The precipitated product was collected on a filter, triturated with methylene chloride, and filtered to give 350 mg (44%) of **8**, mp 201 °C dec.

Compounds **9**, **10**, **15**, **16**, and **19** were prepared according to the procedure for the synthesis of **8**.

**Ethyl 3-(3,4-Dihydro-7-hydroxy-2-methyl-4-oxo-4*H*-1-benzopyran-2-yl)propanoate (23).** A mixture of 2,4-dihydroxyacetophenone (10.0 g, 65.7 mmol) and pyrrolidine (6.6 mL, 79.1 mmol) in 75 mL of toluene were refluxed under a Dean–Stark trap for 2 h, cooled down to room temperature, and then ethyl levulinate (15 mL, 105.5 mmol) was added. The reaction was refluxed for 2 h and diluted with ethyl acetate. The organic solution was washed with 10% HCl solution, water, and a brine solution, dried, and evaporated to give an oil. Purification by chromatography (EtOAc–hexane = 3:7) gave 2.5 g (14%) of **23**: $^1$H NMR ($CDCl_3$) $\delta$ 1.2 (t, 3 H), 1.4 (s, 3 H), 1.9–2.6 (m, 6 H), 4.1 (q, 2 H), 6.3 (d, 1 H), 6.5 (dd, 1 H), 7.7 (d, 1 H).

This compound was used for the synthesis of **14** without further purification.

**5-[8-[4-(2-Quinolinylmethoxy)benzamido]-4-oxo-4*H*-1-benzopyran-2-yl]-1*H*-tetrazole (18).** A mixture of 4-(quinolinyl-2-methoxy)benzoic acid[1] (1.28 g, 4.59 mmol) and oxalyl chloride (4.6 mL) in 50 mL of $CH_2Cl_2$ and 5 mL of DMF was refluxed for 30 min. After concentration of the solvent in vacuo, the residue in 10 mL of $CH_2Cl_2$ was added dropwise to a solution of 5-(8-amino-4-oxo-1*H*-1-benzopyran-2-yl)-1*H*-tetrazole[7] (1.05 g, 4.59 mmol) in 40 mL of $CH_2Cl_2$ and 14 mL of pyridine in an ice bath. After stirring at room temperature overnight, the reaction mixture was poured in to 1 N HCl solution and extracted with EtOAc. The organic solution was dried and evaporated to dryness, and the residue was recrystallized from methanol to give 130 mg (6%) of **18**: mp 245–247 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 5.4 (s, 2 H), 7.0 (s, 1 H), 7.2 (d, 2 H), 7.4–8.0 (m, 10 H), 8.1 (d, 1 H), 8.4 (d, 1 H).

**Biological Assays.** All biological assays are described in the first paper of this series.[1]

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# Conformational Properties of Semirigid Antipsychotic Drugs: The Pharmacophore for Dopamine D-2 Antagonist Activity

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Conformational energy calculations using the MM2-87 program have been performed on the tetracyclic spiro amines **1** (A23887) and **2** (A31472) which have previously been shown to have considerable affinity for dopamine D-2 receptors. These compounds are important for defining the pharmacophore for D-2 antagonist activity due to their limited conformational freedom. Possible foldings of the multicyclic structure were energy minimized and the barriers for inversion and for rotation of the ammonium group were computed. The conformational properties of **1** and **2** are consistent with a pharmacophore recently proposed by Liljefors and Bøgesø. The greater affinity of (*S*)-octoclothepin for D-2 receptors as compared with its enantiomer was attributed to the latter having an incorrect orientation of the ammonium hydrogen despite the correct folding of the tricyclic structure. Other D-2 antagonists with limited conformational freedom such as butaclamol, isobutaclamol, loxapine, clozapine, and resolved cyproheptadine analogues were also found to be consistent with the pharmacophore. In addition, **1**, **2**, and their enantiomers were tested on radioligand binding assays for dopamine D-1, dopamine D-2, noradrenergic $\alpha$-1, serotonergic 5-$HT_2$, muscarinic, and $\sigma$ receptors. **1** and **2** have greater affinities than their enantiomers in the D-1, D-2, $\alpha$-1, and 5-$HT_2$ assays though there was little difference between **2** and its enantiomer in the latter two assays. In the muscarinic assays, **2** and its enantiomer, which were approximately equipotent, had greater affinity than **1** and its enantiomer. None of the compounds had substantial affinity for $\sigma$ receptors. Since the same enantiomers of **1**, **2**, butaclamol, and the resolved cyproheptadine analogues also have greater affinities for D-1 receptors, the conformational requirements of D-1 ligands appear to be quite similar to those of D-2 ligands.

## Introduction

An implicit assumption made by most medicinal chemists is that compounds that interact with the same receptor site have some common three-dimensional structure (pharmacophore) that is responsible for their activity at the site. However, the structural flexibility present in virtually all pharmacologically active compounds makes it difficult to assign the biologically active conformer. In this work, we examine the conformational properties of antipsychotic drugs with limited conformational freedom in an effort to define a common pharmacophore.

The pharmacological property of antipsychotic drugs that is believed to be responsible for their clinical activity is their ability to antagonize the binding of dopamine to D-2 receptors.[1,2] Two series of conformationally restricted compounds with this property are tetracyclic spiro amines (Figures 1 and 2) that contain two asymmetric centers resulting in two pairs of enantiomers Only one of the four isomers in each series had significant affinity for D-2 receptors and activity in in vivo assays assumed to predict antipsychotic activity.[3-5] However, the X-ray structures[6,7]

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