Cyproheptadine Analogues: Synthesis, Antiserotoninergic Activity, and Structure–Activity Relationships

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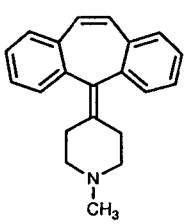
Abstract □ A series of cyproheptadine related compounds was synthesized and tested pharmacologically. In comparison with cyproheptadine, these compounds do not have a central ring and some contain groups other than *N*-methyl. Synthesis was carried out with low-valent titanium to generate the exocyclic double bond. The serotoninergic activity of the compounds was determined by standard determination of pA_2 (-log of the motor concentration of antagonist required to maintain a constant response when concentration of agonist is doubled) for the inhibition of serotonin-induced contractions in rat stomach fundus. Two of the nitrogen-containing compounds were active, but their activities were lower than that of cyproheptadine. Structure–activity relationships were studied by Mulliken net charges, molecular electrostatic potentials, and conformational analysis; activities are better correlated with electrostatic potentials than with net charges. The decrease in potency of the open cyproheptadine analogues may be due to "dilution" of the active conformer as the result of their conformational flexibility.

Cyproheptadine (Figure 1) has been widely reported to act as a mixed serotonin (5-hydroxytryptamine, 5-HT) antagonist.[1] Several series of cyproheptadine-related compounds have been synthesized and tested pharmacologically.[2] These series include variations in substitution on the piperazine nitrogen,[2,3] replacement of the piperidine ring by a linear chain,[4,5] saturation of the exocyclic double bond,[2,5] and modification of the tricyclic system by the introduction of substituents on the aromatic rings,[2,4,6] by replacement of benzene by a heterocyclic system,[4–6] by modification of the nature of the central ring,[2,6] and by elimination of one or more rings.[7]



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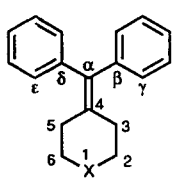

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a) X= CH_2
b) X= O
c) X= S
d) X= NCOOEt
e) X=S^+Me
f) X= NMe
g) X= NH
h) X=N^+Me_2

Figure 1—Chemical structures of all compounds studied. Carbons • and γ are placed in the opposite semi-space than the atom X. Semi-spaces are defined by the plane of double bond 4—α.

Rat stomach fundus is commonly used to study serotoninergic activity, although the nature of its 5-HT receptors is controversial;[8–18] recent research suggests the existence of a variety of $5\text{-}HT_{1C}$ receptor, although previously this idea has been questioned. Whatever the nature of its serotonin receptor, the rat stomach provides a convenient experimental model for our work because cyproheptadine, the basic compound of our series, exhibits good antagonistic activity in fundus preparations.

Recent theoretical studies have investigated the molecular features of serotoninergic receptors and of compounds acting on them.[19–25] All the postulated models require the molecules recognized by the receptor to have an aromatic system and a nitrogen, separated by a certain distance. Some authors[20–22] describe this recognition in terms of the electrostatic features of the ligands, as characterized by the molecular electrostatic potential (MEP), to analyze these characteristics. In the particular case of cyproheptadine, conformational analysis has shown that the tricyclic system is not planar,[26] and such analysis has been used to study structure–antiserotoninergic activity relationships in a series of cyproheptadine analogues.[4]

The present paper has three parts. The first describes the synthesis of a new series of cyproheptadine-related compounds that lack a central ring and have substituents other than the *N*-methyl group. The second part reports the results of pharmacological testing of the synthesized compounds for effects on contraction induced by 5-HT in isolated rat stomach fundus. The third part correlates the results of theoretical computations with the pharmacological results. Despite the previously described requirement of an aminic nitrogen for serotoninergic activity,[19,21,27] we have considered several groups different from an amine group.

Results and Discussion

Chemistry—Our interest in the use of low-valent titanium (LVT) for organic synthesis[28] led us to apply McMurry's method to generate the exocyclic double bond present in cyproheptadine and related compounds.[29] This method reduces the synthetic problem to the performance of a mixed reductive dicarbonylic coupling between two suitable ketones. One of the advantages of mixed dicarbonylic coupling is that when one of the two ketones is aliphatic and the other biarylic, the difference between their secondary reduction potentials gives the mixed coupled product almost exclusively instead of the symmetric ones.[30]

Following this general synthetic route, the cyproheptadine analogues **2a–d** were synthesized in good yield by coupling between benzophenone and the corresponding ketone. Compounds **2e–h** were obtained by further transformation of **2c** or

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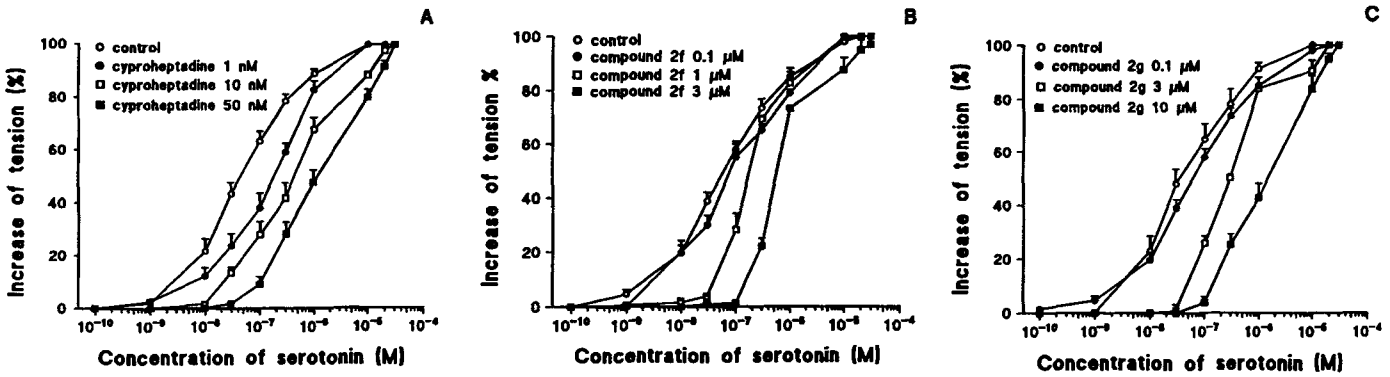

Figure 2—Antagonism of 5-HT concentration–effect curves in rat stomach fundus by cyproheptadine (**A**), **2f** (**B**), and **2g** (**C**). Vertical bars show the SEM of six individual experiments.

2d. The transformation of **2c** into its methiodide **2e** was achieved by treatment with excess iodomethane for several days at room temperature.[31] Reduction of **2d** with lithium aluminium hydride afforded the *N*-methyl derivative **2f**, which was easily transformed by treatment with iodomethane into its quaternary salt **2h**. Alternatively, potassium hydroxide hydrolysis of **2d** gave **2g**[29] (Figure 1).

LVT is usually prepared by reduction of $TiCl_3$ with a suitable reducing agent. We chose lithium in boiling dimethoxy ethane (DME), the most widely used reagent for mixed coupling. All coupling reactions were carried out by adding an equimolar mixture of benzophenone and the respective ketone in DME to a slurry of LVT at room temperature, stirring for 4 h, and then refluxing for 13 h. Yields were always >76%. These results illustrate the wide applicability of LVT, proving that the reductive conditions created are resisted by cyclic ethers and sulfides as well as by the *N*-carbethoxy group. Of additional synthetic interest is the fact that the latter is easily transformed to either *N*-methyl or N-H.

Pharmacology—The antiserotoninergic activity of the compounds was determined as pA_2 (-log of the motor concentration of antagonist required to maintain a constant response when concentration of agonist is doubled) for the inhibition of 5-HT-induced contractions in rat stomach fundus. The three active compounds (cyproheptadine, **2f**, and **2g**) were used at three increasing doses for calculation of pA_2 by Schild plot analysis[32] (Figure 2). The 5-HT dose–effect curves were displaced dose dependently to the right without depression of their maximum effect. The pA_2 values and Schild slopes, implied competitive antagonism. The pA_2 values for **2f** and **2g** (6.07 and 6.18, respectively) were smaller than that for cyproheptadine (9.14).

Compounds **2d**, **2c**, and **2b** exhibited vestiges of pharmacological activity only at the highest concentration (10 μM) used. Their pA_2 values were computed following the method of Van Rossum[33] for this dose (pK_B calculations; -log of the antagonist dissociation constant); the results were 4.70, 4.41, and 4.6, respectively.

Compounds **2a**, **2e**, and **2h** had no effect on 5-HT-induced rat fundus contractions. Inactivity of the quaternary salts **2e** and **2h** on the fundus 5-HT "unclassifiable" receptor is interesting; quaternary salts have previously been described as active in binding to $5\text{-}HT_3$ receptors.[34]

None of the new active compounds antagonized stable $BaCl_2$ (n = 4)-induced contractions in any statistically significant way, which appears to rule out their possessing any direct relaxant activity.

Structure–Activity Relationships—A common procedure for studying structure–activity relationships is to compare molecular features of active and inactive compounds that present only controlled structural differences. Such is the case with the set of compounds studied here, which consists of molecules having only small substitutions in their position X, but very different degrees of activity. We studied the relationships between pA_2 and the electronic properties of substituents X. A classical and widely used procedure for representing these electronic properties is the net atomic charges derived from quantum mechanical wavefunctions by Mulliken population analysis.[35] The popularity of this method is due mainly to its conceptual and computational simplicity. However, the theoretical and practical shortcomings of this procedure are well known.[36–39] MEP is an alternative quantitative procedure for studying the electrostatic features of biomolecules.[40,41]

In the present study, these electronic parameters were computed on simplified structures obtained by considering only the ring which contains substituent X, replacing the two aromatic rings by hydrogens. To validate this simplification, it was not applied in the case of the molecule of cyproheptadine, and the results (Table I) show that the values of net charge on X and MEP minimum near X are almost equal to those of the simplified structure (the simplified structure of cyproheptadine is the same as **2f**). All the molecular geometries were fully optimized by the AM1 method[42] implemented on the AMPAC program.[43] Mulliken charges and MEPs were obtained from STO-3G ab initio wavefunctions computed with the GAUSSIAN 86 program.[44] It must be pointed out that Mulliken charges are highly dependent on the kind of basis set used and that only their order is meaningful. MEP minima were determined with the MEPMIN program.[45]

The Mulliken charge of the atom of X that belongs to the ring and the nearest MEP minimum are shown in Table I.

Table I—Electronic Parameters of Cyproheptadine Analogues

Compound	Activity[a]	Net Charge on X (Neutral Compounds)	Net Charge on X (Cations)	MEP Minimum Near X
Cyproheptadine	+	−0.290	—[b]	−83.905
2a	0	−0.089	—[b]	−2.508
2b	±	−0.262	—[b]	−63.664
2c	±	0.165	0.524	−27.547
2d	±	−0.311	−0.250	−51.499
2e	0	—[b]	0.548	—[c]
2f	+	−0.288	−0.231	−84.817
2g	+	−0.345	−0.296	−94.237
2h	0	—[b]	−0.172	—[c]

[a] (0) No detectable activity, (±) no significant activity, (+) active compounds. [b] Not applicable. [c] There is no MEP minimum because only the cationic species exists.

Calculations were performed for **2c**, **2d**, **2f**, and **2g** in both neutral and protonated states. MEP minima exist only in the case of neutral species. For both neutral and cationic states, the Mulliken charges for **2c**, **2d**, **2f**, and **2g** are in the same order (**2g** < **2d** < **2f** < < **2c**), thus eliminating the need to know whether the molecules are protonated or not when they interact with the receptor.

When the relationship between activity and electronic parameters is analyzed, complete agreement between the magnitude of the MEP minima and the degree of activity of the compounds is noted: cyproheptadine and the active compounds **2f** and **2g** show the lowest MEP. Of note is the fact that compounds without detectable activity (**2a**, **2e**, and **2h**) are the ones with no or almost no MEP minima, whereas compounds that present vestiges of activity (**2b**, **2c**, and **2d**) have a notably negative MEP near X. In the case of Mulliken charges, there is an important inconsistency in that the oxygen atom of **2b** and the amidic nitrogen of **2d** present large negative charges that do not agree with their lack of activity. These results represent new evidence of the limitations of the Mulliken population analysis as a source for quantitative structure–activity relationships parameters, and support the alternative use of MEP.

We have also performed comparative conformational analyses of the phenyl rings of **2f** and **2g** versus those of cyproheptadine in an effort to explain the reduction in activity that is generated by opening the central ring of cyproheptadine. The similar reduction in activity for both **2f** and **2g** suggests that this phenomenon is independent of the methylation of the amino group on X, which is the sole difference between **2f** and **2g**.

Conformational analyses were performed by the AM1 method implemented in the AMPAC program. The relative positions of the phenyl rings were monitored by the angles ($4-\alpha-\beta-\gamma$ and $4-\alpha-\delta-\epsilon$) as numbered in Figure 1. These angles are 0° when atoms $4-\alpha-\beta-\gamma$ and $4-\alpha-\delta-\epsilon$ are placed in *cis* position, and their rotation direction is defined clockwise. In the case of cyproheptadine, we obtained a symmetrical butterfly conformation with angle $4-\alpha-\delta-\epsilon$ being equal to 62.8° and angle $4-\alpha-\beta-\gamma$ equal to −62.8°. In the cases of **2f** and **2g**, the preferred conformation is clearly asymmetrical, with angle $4-\alpha-\beta-\gamma$ equal to 56° and angle $4-\alpha-\delta-\epsilon$ equal to −105°. However, the rotation of the phenyl groups of these two compounds is almost free. Thus, the energetic cost of placing the phenyl rings in the same symmetrical conformation as that of cyproheptadine is only 0.9 kcal/mol. If we assume that **2f** and **2g** must mimic the geometry of cyproheptadine to interact with their common receptor, the decrease in potency of **2f** and **2g** relative to that of cyproheptadine could be related to an effective dilution of the active conformer caused by the conformational flexibility of the phenyl rings of **2f** and **2g**. Whether other factors might contribute to the decrease in potency remains to be determined.

Experimental Section

Chemistry—All melting points are uncorrected and were recorded on a Kofler-Thermogeräte apparatus. The IR spectra were recorded with a Perkin-Elmer 1420 spectrometer. Proton NMR spectra were obtained on a Bruker WM-250 (250 MHz) with $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard; all signals are expressed as δ values in ppm downfield from TMS. Mass spectra were recorded with a Kratos MS-50 spectrophotometer and with a Hewlett-Packard HP 59970 MS Chem Station at 70 eV ionizing energy. Elemental analyses were carried out in a Carlo-Erba EA1108-elemental analyzer. Dried solvents were distilled under argon from sodium benzophenone ketyl radical immediately prior to use.

General Procedure for Mixed Carbonyl Coupling using $TiCl_3$/Li—Lithium pieces (28 mmol) were added to a stirred slurry of $TiCl_3$ (8 mmol) in 30 mL of dry DME under an argon atmosphere and the mixture refluxed for 2 h. The black slurry was then cooled to room temperature, and the two carbonyl compounds (1 mmol of each) dissolved in 10 mL of DME were added. The mixture was stirred for 4 h at room temperature and then refluxed for 13 h. After cooling at room temperature, the reaction mixture was filtered, a saturated aqueous solution of K_2CO_3 was added, the organic layer was separated, and the aqueous layer was extracted with chloroform (3 × 50 mL). The pooled organic phases were dried (Na_2SO_4), and the solvent was evaporated to afford the crude product. This procedure (mmol; Li:$TiCl_3$:benzophenone:other ketone, 28:8:1:1) was used for the syntheses of **2a–d**.

Diphenylmethylenecyclohexane (2a)—Benzophenone (564 mg, 3.1 mmol) with 300 mg (3.1 mmol) of cyclohexanone gave **2a** in 86% yield as white crystals (mp, 82–83°C, hexane; lit[46] 83–83.5 °C, petrol ether); NMR: 7.28–7.10 (m, 10H, ArH); 2.22 (bs, 4H, CH_2); 1.59, (bs, 6H, CH_2); MS *m/e* (%): 248(M^+,100), 205(68), 180(28), 179(28), 167(28), 165(40), 91(26).

4-Diphenylmethylenetetrahydropyran (2b)—Benzophenone (583 mg, 3.2 mmol) with 325 mg (3.2 mmol) of tetrahydropyran-4-one gave **2b** in 93% yield as white crystals (mp, 127 °C, ethyl acetate/hexane); NMR: 7.29–7.11 (m, 10H, ArH); 3.73 (t, J = 5.3 Hz, 4H, OCH_2); 2.40 (t, J = 5.3 Hz, 4H, CCH_2); MS *m/e* (%): 250(M^+,100), 205(76), 192(27), 191(45), 165(26), 91(25).

Anal—Calcd for $C_{18}H_{18}O$: C, 86.35; H, 7.26. Found: C, 86.63; H, 7.47.

4-Diphenylmethylenetetrahydrothiopyran (2c)—Benzophenone (470 mg, 2.6 mmol) with 300 mg (2.6 mmol) of tetrahydrothiopyran-4-one gave **2c** in 76% yield as white crystals (mp, 134 °C, methanol/dichloromethane); NMR: 7.31–7.09 (m, 10H, ArH); 2.73–2.69 (m, 4H, SCH_2); 2.59–2.56 (m, 4H, CCH_2); MS *m/e* (%): 266(M^+,32), 220(21), 206(20), 205(100), 97(23), 95(22), 91(25).

Anal—Calcd for $C_{18}H_{18}S$: C, 81.16; H, 6.82. Found: C, 81.23; H, 6.64.

4-Diphenylmethylene-1-piperidinecarboxylic acid ethyl ester (2d)—Benzophenone (319 mg, 1.75 mmol) with 300 mg (1.75 mmol) of *N*-carbethoxy-4-piperidone gave **2d** in 93% yield as white crystals (mp, 125 °C, methanol/hexane[29]); IR (KBr): 1700 cm^{-1}; NMR: 7.32–7.09 (m, 10H, ArH); 4.13 (q, J = 7.1 Hz, 2H, OCH_2CH_3); 3.49 (t, J = 5.8 Hz, 4H, NCH_2); 2.34 (t, J = 5.8 Hz, 4H, CCH_2); 1.25 (t, J = 7.1 Hz, 2H, OCH_2CH_3); MS *m/e* (%): 323(15), 322(M^+,63), 206(32), 191(32).

Formation of 1-Methyl-4-diphenylmethylenetetrahydrothiopyranium Iodide (2e)—A mixture of 400 mg (1.5 mmol) of **2c**, 3 mL of benzene, 5.3 mL of nitromethane, and 2.129 g (15 mmol) of methyl iodide was allowed to stand for 3 days at room temperature, and then the solvent was evaporated to afford the crude product that was recrystallized in methanol as yellow crystals in 82% yield (mp, 138–143 °C, methanol/ether); NMR: 7.32–7.08 (m, 10H, ArH); 4.09–4.02 (m, 1H, CH_2); 3.78–3.70 (m, 1H, CH_2); 3.41 (s, 3H, SMe); 2.93–2.85 (m, 1H, CH_2); 2.74–2.68 (m, 1H, CH_2); MS *m/e* (%): 266(M^+ −Me,87), 205(85), 142(100), 127(44), 91(51).

Anal.—Calcd for $C_{19}H_{21}IS$: C, 55.89; H, 5.19. Found: C, 55.49; H, 5.02.

Synthesis of 4-Diphenylmethylene-1-methyl-piperidine (2f)—To a stirred solution of **2d** (141 mg, 0.44 mmol) in 25 mL of dry tetrahydrofuran (THF), 36 mg (0.95 mmol) of lithium aluminium hydride were added under argon. The solution was refluxed for 2 h. After cooling at room temperature, a saturated aqueous solution of NH_4Cl was added, the solvent was evaporated, and the mixture was extracted with dichloromethane. The organic layer was dried (Na_2SO_4) and the solvent was eliminated under reduced pressure to give 245 mg (93% yield) of **2f** as an oil; NMR: 7.32–7.09 (m, 10H, ArH); 2.68 (t, J = 5.9 Hz, 4H, NCH_2); 2.57 (t, J = 5.9 Hz, 4H, CCH_2); 2.45 (s, 3H, NMe).

Synthesis of 4-Diphenylmethylenepiperidine (2g)—Potassium hydroxide (6.3 g, 112.5 mmol) was dissolved in absolute ethanol (30 mL) by heating under argon. Compound **2d** (430 mg, 1.34 mmol) was then added to the mixture and the solution was refluxed for 5.5 h under argon. The solvent was evaporated, water (20 mL) was added, and the aqueous mixture was extracted with dichloromethane (3 × 15 mL). The dried (Na_2SO_4) organic extracts were concentrated under reduced pressure, and the residue was purified by preparative TLC to yield 287 mg (86%) of **2g** (mp, 84 °C, methanol/ether[47]): NMR: 7.09 (m, 10H, ArH); 2.86 (t, J = 5.3 Hz, 4H, NCH_2); 2.53 (m, 1H, NH); 2.30 (t, J = 5.3 Hz, 4H, CCH_2).

Formation of 1,1-Dimethyl-4-diphenylmethylenepiperidinium

Iodide (2h)—Methyl iodide (6.84 g, 48 mmol) was added to a solution of **2f** (2.630 g, 10 mmol) in acetone (15 mL) and the mixture was stirred overnight at room temperature. The methiodide precipitated quantitatively as a yellow solid (mp, 249 °C, acetone; lit[48] 258–260 °C); NMR: 7.35–7.13 (m, 10H, ArH); 3.72 (t, J = 6.0 Hz, 4H, CH_2); 3.56 (s, 6H, 2 × Me); 2.72 (t, J = 6.0 Hz, 4H, CH_2); MS *m/e* (%): 279(M^++1,18), 205(25), 191(32), 157(48), 149(100), 123(46), 111(64), 97(86), 91(54).

Pharmacology—Male 250–300 g Sprague-Dawley rats were killed by cervical dislocation. Stomachs were dissected free from the abdomen and immersed in modified Krebs solution of the following composition (mM): NaCl (118), KCl (4.7), $MgSO_4 \cdot 7H_2O$ (1.2), $CaCl_2 \cdot 2H_2O$ (2.5), KH_2PO_4 (1.18), $NaHCO_3$ (25), glucose (11). Strips of stomach fundus were prepared by Vane's[49] method, mounted in organ baths containing 10 mL of the same Krebs solution, and maintained at 37 °C with aeration by carbogen (95% O_2, 5% CO_2). Before addition of drugs, the tissue strips were equilibrated for 1 h under a 1-g load. Isometric contractions were recorded during cumulative addition of 5-HT or $BaCl_2$ (to test for nonspecific relaxant activity) with a Letica transducer and a Letica-Graph 1000-100 polygraph.

Concentration–response curves for 5-HT were constructed as per Van Rossum.[33] Stable contractions were achieved in the initial control runs in the range 0.01 nM–10 μM. Following the initial control run, each tissue strip was run alternately with and without antagonist, the concentration of antagonist increasing in successive antagonist runs. Between runs, the tissues were washed, allowed to rest for 30 min, and treated for 45 min with potential antagonist (present in the Krebs medium) when used. No tachyphylaxis was observed. Antagonist potency was measured according to the method of Arunlaksana and Shild,[50] in terms of pA_2 (−log concentration of competitive antagonist that would yield the same agonist effect as would half the agonist concentration without antagonist). In the $BaCl_2$ assays, 0.3 mM $BaCl_2$[51] was used in control runs and in the presence of 10 μM of the compounds.

The 5-HT hydrochloride and cyproheptadine hydrochloride were supplied by Sigma. Aqueous solutions of all drugs were prepared daily with distilled water; the biphenylmethylenepiperidine compounds were initially dissolved in a small quantity of absolute alcohol, which did not influence tissue response at its final concentration in the organ bath (<0.01%, v/v). All concentrations mentioned are expressed as final molar concentrations in the tissue bath.

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