New Potential Antihistaminic Compounds. Virtual Combinatorial Chemistry, Computational Screening, Real Synthesis, and Pharmacological Evaluation

María J. Duart,[†] Gerardo M. Antón-Fos,*[,‡] Pedro A. Alemán,[‡] Joan B. Gay-Roig,[‡] María E. González-Rosende,[‡] Jorge Gálvez,[§] and Ramón García-Domenech[§]

Departamento de Química, Bioquímica y Biología Molecular, Universidad Cardenal Herrera−CEU, Valencia, Spain, Departamento de Ingenieria, División Farmacia y Tecnología Farmacéutica, Universidad Miguel Hernández, Alicante, Spain, and Unidad de Diseño de Fármacos y Conectividad Molecular, Departamento de Química Física, Facultad de Farmacia, Universitat de Valencia, Valencia, Spain

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To study the utility of the virtual combinatorial chemistry coupled with computational screening, a library of amine and urea derivatives was designed by virtual combinatorial synthesis and eventually computationally screened by a mathematical topological model as antihistaminic compounds. The results reveal that virtual combinatorial synthesis and virtual screening together with molecular topology are a powerful tool in the design of new drugs.

Introduction

Histamine is a well-known neurotransmitter released in a variety of allergic conditions such as seasonal rhinitis (hay fever), urticaria (rash), pruritis, and insect stings as well as a reaction to certain drugs such as penicillin or aspirin. Histamine mediates its activity by interaction at H_1 receptors, which are closely related to, but clearly distinct from, the H_2 receptors at which antiulcer drugs bind. Agents that selectively block these receptors are therefore of benefit in histamine-related allergic responses. First-generation H_1 blockers, which appeared in clinical practice during the 1940s, suffered from two major drawbacks. First, they were highly lipid soluble ($\log P > 2$) and were able to readily penetrate the blood−brain barrier and their interaction with central H_1 receptors invariably led to side effects such as sedation and psycomothor impairment. In addition, the agents tended to be nonselective for H_1 receptors at the doses given and exhibited anticholinergic (muscarinic) and antiadrenergic activities adding to the side effect profile.[1] Therefore, the search for more potent and H_1-selective compounds still remains the topic of active current research.

Molecular topology has widely demonstrated its ability for an easy and efficient characterization of molecular structure through the so-called topological indices. In this mathematical formalism a molecule is assimilated to a graph, where each vertex represents one atom and each axis one bond. Starting from the interconnections among the different vertexes, an adjacency topological matrix can be built whose elements *ij* take the values 1 or 0, depending whether the vertex *i* is connected to the vertex *j* or not, respectively. The manipulation of this matrix gives origin to a set of topological indices or topological descriptors. When these indices are selected adequately, it is possible to have a very specific characterization of each chemical compound. Moreover, these descriptors allow us to obtain SAR and QSAR relations to select or design new drugs with a high level of accuracy.[2]

In a previous work, we have developed the concept of virtual combinatorial synthesis and computational screening aimed at the search of new pharmacologically active compounds.[3] This tandem allows us to study the possible biological activity of millions of compounds without the need to synthesize and study its activity of all them in the laboratory. Now we report our results on the development of new antihistaminic H_1 compounds according this formalism.

Results and Discussion

Discriminant Model. Recently, we demonstrated that it is possible to obtain a high degree of molecular characterization of antihistaminic activity by an adequate choice of topological indices.[4] Table 1 shows the indices used in this work, definition and the references describing their calculation in detail. All descriptors were computed from the adjacency topological matrix obtained from the hydrogen-depleted graph.

By means of multilinear regression and linear discriminant analysis techniques, a topological mathematical model comprising three functions was achieved for the antihistaminic activity. The first equation was relating the time to significantly suppress the histamine-induced weal and flare, t_{iw}.

$$t_{iw} = 67.19 - 32.94\ \mathrm{IShannon} - 0.72\ \mathrm{SumI} + 1.73\ \mathrm{Sum}\Delta\mathrm{I}$$

$$N = 12;\quad r = 0.975;\quad \mathrm{SEE} = 0.77;\quad \mathrm{SEE(CV)} = 0.99;\quad F = 52\quad p < 0.00001$$

where r = correlation coefficient, F = F-Snedecor function values, and SEE = standard error of estimate

With the purpose of finding a complementary discriminant function able to identify the active or inactive antihistaminic activity, two large sets of compounds were selected: one with proven pharmacological activity (in our case antihistaminic drugs) and the other one

* To whom correspondence should be addressed. Phone: 96 136 90 00. Fax: 96 139 52 72. E-mail: ganton@uch.ceu.es.
[†] Universidad Miguel Hernández.
[‡] Universidad Cardenal Herrera−CEU.
[§] Universitat de Valencia.

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Table 1. Symbols and Definitions of Topological Indices[a]

Symbol	Name	Definition	Refs.
${}^k\chi_t$	Randi -like indices of order *k* and type path (p), cluster (c) and path-cluster (pc)	${}^k\chi_t = \sum_{j=1}^{{}^kn_t}\left(\prod_{i\in S_j}\delta_i\right)^{-1/2}$	(7)
k=0-4		δ_i, number of bonds, σ or π, of the atom *i* to non-hydrogen atoms.	
t=p,c,pc		S_j *j*th sub-structure of order *k* and type *t*.	
${}^k\chi_t^{\,v}$	Kier-Hall indices of order *k* and type path (p), cluster (c) and path-cluster (pc)	${}^k\chi_t^{\,v} = \sum_{j=1}^{{}^kn_t}\left(\prod_{i\in S_j}\delta_i^{\,v}\right)^{-1/2}$	(7)
k=0-4		$\delta_i^{\,v}$, Kier-Hall valence of the atom *i*.	
t=p,c,pc		S_j *j*th sub-structure of order *k* and type *t*.	
${}^kD_t$ k=0-4 t=p,c,pc	Connectivity differences of order k and type path (p), cluster (c) and path-cluster (pc)	${}^kD_t = {}^k\chi_t - {}^k\chi_t^{\,v}$	(7)
G_k *k*=1-5	Topological charge indices of order *k*	$G_k = \sum_{i=1}^{N-1}\sum_{j=i+1}^{N}\lvert\mathbf{M}_{ij} - \mathbf{M}_{ji}\rvert\,\delta(k,\mathbf{D}_{ij})$ **M=AQ**, product of the adjacency and inverse squared distance matrices for the hydrogen-depleted molecular graph.	(8)
		D, distance matrix; , Kronecker delta	
$G_k^{\,v}$ *k*=1-5	Valence topological charge indices of order *k*	$G_k^{\,v} = \sum_{i=1}^{N-1}\sum_{j=i+1}^{N}\lvert\mathbf{M}_{ij}^{\,v} - \mathbf{M}_{ji}^{\,v}\rvert\,\delta(k,\mathbf{D}_{ij})$ $\mathbf{M}^v=\mathbf{A}^v\mathbf{Q}$, product of the electronegativity-modified adjacency and inverse squared distance matrices for the hydrogen-depleted molecular graph.	(8)
		D, distance matrix; , Kronecker delta	
J_k, $J_k^{\,v}$ *k*=1-5	Pondered topological charge indices of order *k*	$J_k = \frac{G_k}{N-1}$ $J_k^{\,v} = \frac{G_k^{\,v}}{N-1}$	(8)
Sum-I	Sum-intrinsic state values	$I_i = \frac{\delta_i^v + 1}{\delta_i}$ and $\text{Sum}-I = \sum I_i$	(9)
		δ_i, number of bonds, σ or π, of the atom *i* to non-hydrogen atoms.	
		$\delta_i^{\,v}$, Kier-Hall valence of the atom *i*.	
Sum-ΔI	Sum-Delta intrinsic state values	$\Delta I = \frac{I_i - I_j}{r_{ij}^2}$ $\text{Sum}-\Delta I = \sum\frac{I_i - I_j}{r_{ij}^2}$	(9)
		r_{ij}, number of vertex between i and j atoms.	
S_i	Sum- electrotopological indexes type.	$S_i = I_i + \Delta I_i$	(9)
L	Length	Maximal distance between atoms in terms of bonds.	(10)
$I_{Shannon}$	Shannon index	Index based in the information theory	(11)

[a] Topological descriptors were calculated for each compound by using Molconn-Z[5] and DESMOL11[6] programs.

with inactive compounds to which discriminant analysis was applied. The chosen functions were

$$DF_1 = 7.20\,{}^1\chi_c^v + 0.25G_1^v - 47.96J_1 - 22.98J_3^v - 4.89D\,{}^4\chi_{pc} - 0.36L + 12.65$$

$$N = 146; \quad F = 34.5 \quad \lambda = 0.347$$

$$DF_2 = 2.13\ \text{SdssC} + 1.37\ \text{SaaCH} - 0.68\ \text{SdsN} + 0.90\ \text{SsssN} - 0.10\ \text{SsOH} - 0.18\ \text{SdO} - 2.77$$

$$N = 146; \quad F = 44.1; \quad \lambda = 0.298$$

The quality of the discriminant functions is evaluated by the Wilk's λ parameter (also known as U-statistic), which is obtained by a multivariate analysis of variance statistics that tests the equality of group means for the variables in the discriminant functions (the files containing the values of all the descriptors used in this work are availabe from the author).

Once selected, the three equations constituting the antihistaminic activity topological model,[4] the corresponding pharmacological distribution diagrams (PDD) were built up. These plots are useful for determining the intervals of the discriminant function in which the expectancy *E* for finding antihistaminic compounds is a maximum. PDDs are histogram-like plots of connectivity functions in which the expectancies appear on the ordinate axis. For an arbitrary interval of values of a given function, we can define the expectancy of activity as $E_a = a/(i + 1)$, where "*a*" is the number of active compounds in the interval divided by the total number of active compounds and "*i*" is the number of inactive compounds. The expectancy of inactivity is defined in a symmetrical way, as $E_i = i/(a + 1)$. The PDDs obtained with each function are shown in Figure 1.

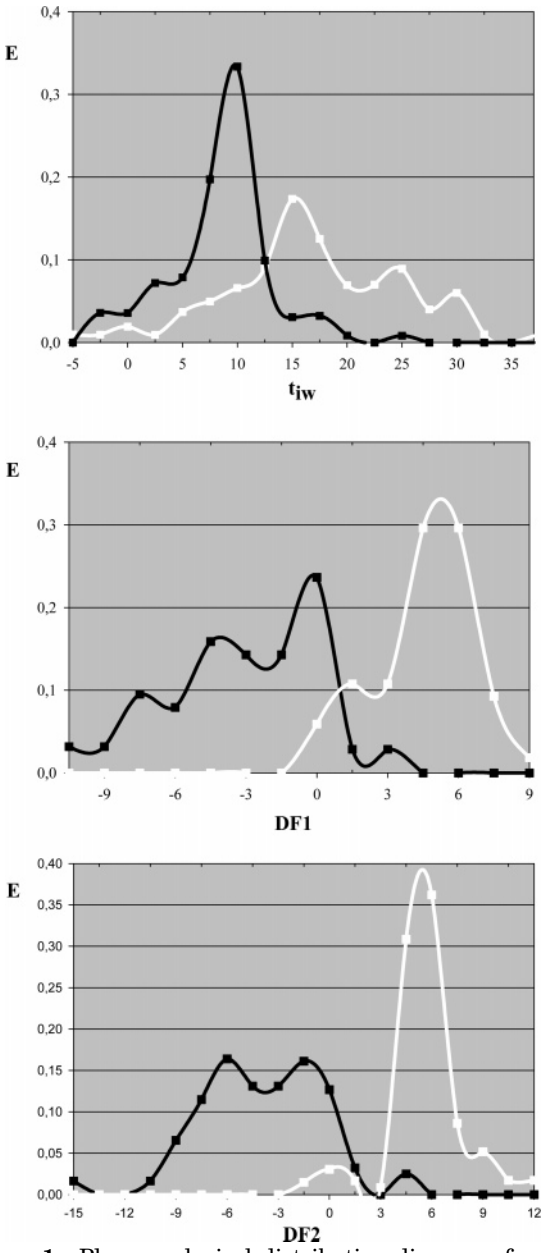


Figure 1. Pharmacological distribution diagrams for antihistaminic activity: (white line) nonantihistaminic drugs; (black line) antihistaminic drugs.

In light of the obtained results, a given compound can be selected as a potential antihistaminic if it fulfills the following requirements:

$$10 > t_{iw} > 0; \quad 9 > DF1 > 0; \quad 10.5 > DF2 > 1.5$$

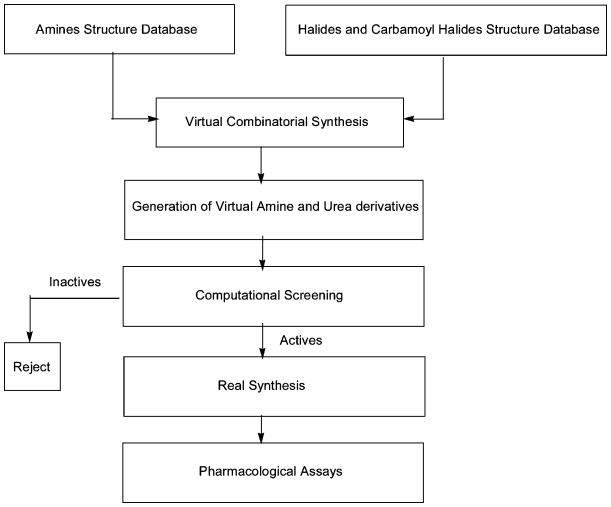


Figure 2. Stages involved in the search for new antihistaminic compounds.

With this topological pattern, in the nonantihistaminic group we get an average measure of correct prediction of 100%, and about 65% of the antihistaminic drugs are also correctly classified.[4]

Virtual Combinatorial Chemistry and Computational Screening. Virtual combinatorial synthesis,[3,12] a concept derived from combinatorial chemistry, is the computational simulation of new chemical structures generation constituting a virtual library. In the computational or virtual screening,[13,14] large collections of molecules are computationally evaluated using rules and criteria that evaluate the possibility of pharmacological activity of the compounds prior to the synthetic stage. In our research group, we have developed both concepts,[3,14] which allows us to focus the biological screening with a reduced number of compounds and high probability of success.

Therefore, with the aim of discovering new antihistaminic lead compounds, we first designed new chemical structures by virtual combinatorial chemistry and eventually we selected those active ones by a computational model. Thus, a virtual library of amines and urea derivatives was previously created from two databases of building blocks: one comprising amine fragments and the other containing halide and carbamoyl halide fragments. These compounds were chosen among the commercially available ones,[15] avoiding the presence of substitutions that could cause undesired effects in the real synthesis. The virtual combinatorial synthesis process formed the new amines and urea derivatives, and the computational screening process selected those virtual compounds that showed all the three limiting properties within their established intervals and that would likely show antihistaminic activity. Figure 2 shows the stages for finding new antihistaminic drugs.

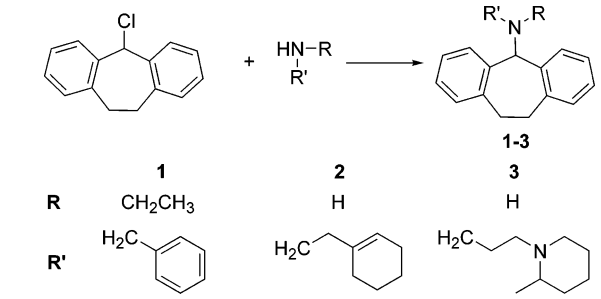
Overall, the synthetic virtual library consisted of 9000 compounds. Filtering the library using the mathematical model resulted in the selection of 236 compounds as active H1 inhibitors, and the most promising compounds from both series were synthesized and investigated for in vivo antihistaminic activity (Figure 3).

Table 2 shows the values of the topological model for the potential antihistaminic compounds **1**−**7**.

Table 2. Values of the Topological Pattern for the Compounds with Theoretical Antihistaminic Activity

compd	DF1	DF2	t_{iw}	class
1	3.04	9.64	3.02	+
2	1.72	5.40	5.45	+
3	4.16	7.83	2.74	+
4	1.30	8.63	2.90	+
5	0.34	6.71	9.15	+
6	2.67	3.28	9.70	+
7	0.71	4.22	8.32	+

Scheme 1



Synthesis and Pharmacological Results. Several synthetic strategies for the final selected compounds **1**−**7** are feasible starting from commercially available materials.[16−18] **1**−**3** were synthesized by condensation of amines with 5-chlorodibenzosuberane[17] as presented in Scheme 1.

The second strategy chosen for the target compounds **4**−**7** started with the corresponding carbamoyl chloride, and the required substituents were introduced by nucleophilic substitution methodology (Scheme 2).[18]

Compounds **1**−**7** were tested for their ability to inhibit the histamine-induced cutaneous reaction in rats following the Watanabe protocol.[19] The protocols used are described in the Supporting Information, and Table 3 summarizes the results of the pharmacological tests. An

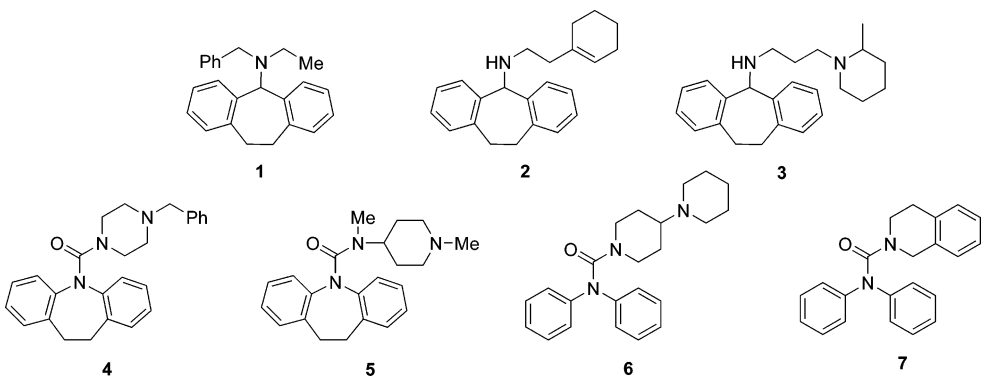


Figure 3. Compounds designed by virtual combinatorial synthesis and selected by computational screening.

Scheme 2

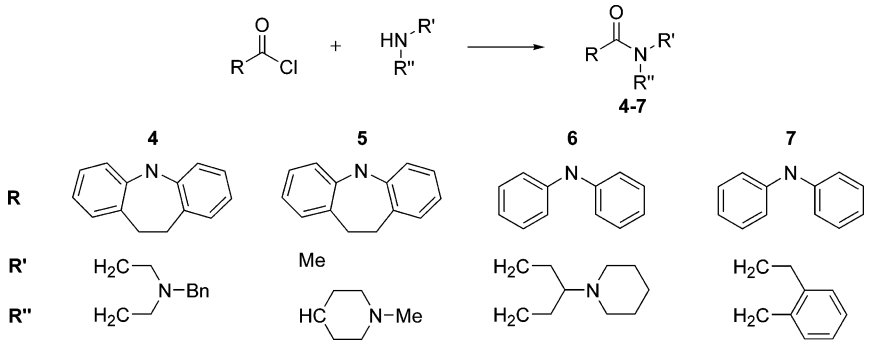


Table 3. Antihistaminic Activity by the Watanabe et al. Protocol for Compounds **1**−**7**

compound	*N*	F_{act}	SEM	statistical analysis[a]	activity
methyl cellulose	7	5.43	0.843	a	−
terfenadine[b]	7	2.83	1.081	b, c	Yes
1	7	3.72	0.720	b	Yes
2	5	2.43	0.808	b, c	Yes
3	5	2.89	0.710	b, c	Yes
4	6	3.09	1.420	b, c	Yes
5	6	2.47	1.120	c	Yes
6	7	2.96	0.606	b, c	Yes
7	7	4.75	0.92	a	Non

[a] Groups with different letters are statistically different for the parameter at the 5% significance level; *N* = number of animals; F_{act} = medium of the factor of activity; SEM = standard error of means. [b] Reference drug.

amount of 87% of the compounds exhibited antihistaminic activity. Therefore, the pharmacological assays confirmed the accurate discriminant ability of the proposed topological model.

Compounds **2** and **5** show more antihistaminic activity than terfenadine (reference drug); therefore, these molecules would be selected as lead structures in a later work of molecular modeling and activity optimization.

Compound **3** was administered as a racemic form. Actually we are studying the influence of **3** stereochemistry on biological activity. Enantiomers of **3** will be synthesized separately, and the corresponding pharmacological assays will be realized.

Conclusion

In summary, a new class of potential antihistaminic compounds has been designed by virtual combinatorial chemistry coupled with computational screening. In this study, 6 out of 7 selected compounds showed in vivo antihistaminic activity in the rat histamine induced cutaneous assay. The new compounds might serve as novel important leads for further pharmacological investigations. In this way we have demonstrated the utility of the virtual combinatorial methodology in conjunction with virtual screening in drug development.

Experimental Section

Chemistry. General. All reagents were purchased from Aldrich and used without purification unless stated otherwise. All reactions were made under nitrogen atmosphere. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Thin-layer chromatography (TLC) was run on Merck silica gel 60 F-254 plates. Flash column chromatography was performed using silica gel (Merck 60, 70−230 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument in $CDCl_3$, unless otherwise indicated. Chemical shifts (δ values) are given in ppm relative to internal tetramethylsilane, and coupling constants (*J* values) are expressed in Hz. ^{1}H and ^{13}C NMR assignments have been confirmed by DEPT experiments. MS and HRMS were obtained using a VG Autospec TRIO 1000 instrument. The ionization mode used in mass spectra was electron impact (EI) or fast atom bombardment (FAB).

General Procedure for Alkylation Reaction. A solution of 5-chlorobenzosuberane (1 g, 4.4 mmol) in CH_2Cl_2 (20 mL) was treated with anhydrous sodium carbonate (0.9 g, 8.8 mmol), sodium iodide (0.07 g, 4.7 mmol), and the corresponding amine (5.3 mmol) under stirring. After the addition was complete, the reaction mixture was refluxed for 1 h and then cooled to room temperature and washed with saturated aqueous $NaHCO_3$ solution (3 × 25 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash chromatography.

***N*-Benzyl-*N*-ethyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]-annulen-5-amine ($C_{24}H_{25}N$) (1).** Eluent: hexane/EtOAc (99:1). White solid, mp 59−61 °C. Yield 88%. ^{1}H NMR ($CDCl_3$) δ 0.87 (t, *J* = 7 Hz, 3H), 2.57 (c, *J* = 7 Hz, 2H, NCH_2CH_3), 2.92 (m, 2H), 3.62 (s, 2H, CH_2Ph), 4.20 (m, 2H), 4.59 (s, 1H), 7.15 (m, 7H), 7.28 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 7.6 (CH_3), 31.6 (CH_2), 42.7 (CH_2), 54.5 (CH_2), 75.0 (CH), 125.5 (CH=), 126.3 (CH=), 127.6 (CH=), 128.0 (CH=), 128.6 (CH=), 130.4 (CH=), 130.9 (CH=), 139.6 (C), 140.1 (C), 140.6 (C).

***N*-(2-Cyclohex-1-en-1-ylethyl)-10,11-dihydro-5*H*-dibenzo-[*a*,*d*][7]annulen-5-amine ($C_{23}H_{27}N$) (2).** Eluent: hexane/EtOAc (97:3). Colorless oil. Yield 90%. ^{1}H NMR ($CDCl_3$) δ 1.7 (m, 4H), 2 (m, 4H), 2.2 (m, 2H), 2.4 (m, 2H), 2.8 (m, 2H), 3.2 (m, 2H), 3.9 (m, 2H), 5 (m, 1H), 5.6 (m, 1H), 7.3 (m, 6H), 7.5 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 22.4 (CH_2), 22.8 (CH_2), 25.1 (CH_2), 27.9 (CH_2), 32.3 (CH_2), 38.2 (CH_2), 45.8 (CH_2), 69.0 (CH), 122.5 (CH=), 125.7 (CH=), 127.2 (CH=), 128.9 (CH=), 130.2 (CH=), 135.4 (C), 139.7 (C), 140.4 (C). HRMS (EI) calcd for ($C_{23}H_{27}N$) 317.2143; found 317.2130.

***N*-[3-(2-Methylpiperidin-1-yl)propyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-amine ($C_{24}H_{32}N_2$) (3).** Eluent: hexane/ethyl ether (1:2). Yellow oil. Yield 87%. ^{1}H NMR ($CDCl_3$) δ 1.0 (d, *J* = 6.2 Hz, 3H), 1.25 (m, 3H), 1.55 (m, 6H), 2.05 (m, 1H), 2.15 (m, 1H), 2.32 (m, 1H), 2.48 (m, 2H), 2.65 (m, 1H), 2.71 (m, 1H), 2.98 (m, 2H), 3.69 (m, 2H), 4.8 (s, 1H), 7.12 (m, 6H), 7.24 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 19.1 (CH_3), 24.0 (CH_2), 25.9 (CH_2), 26.2 (CH_2), 32.3 (CH_2), 34.7 (CH_2), 47.4 (CH_2), 52.1 (CH_2), 52.3 (CH_2), 55.9 (CH), 69.3 (CH), 125.8 (CH=), 127.3 (CH=), 128.8 (CH=), 130.3 (CH=), 139.8 (C), 140.6 (C).

Acylation Reaction. Procedure A. To a solution of 10,-11-dihydro-5*H*-dibenzo[*b*,*f*]azepine-5-carbamoyl chloride (0.334 g, 1.26 mmol) in CH_2Cl_2 (20 mL) at 0 °C under stirring was added dropwise triethylamine (0.351 mL, 2.52 mmol) and the corresponding amine (1.26 mmol). The reaction mixture was refluxed for 2 h. The solvent was evaporated under reduced pressure, and the resulting crude was purified by flash chromatography.

5-[(4-Benzylpiperazin-1-yl)carbonyl]-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine ($C_{26}H_{27}N_3O$) (4). Eluent: hexane/EtOAc (1:1). White solid, mp 185.5−187 °C. Yield 75%. ^{1}H NMR ($CDCl_3$) δ 2.85 (m, 4H), 3.08 (s, 4H), 3.31(m, 4H), 3.4 (s, 2H), 7.0 (m, 7H), 7.27 (m, 4H), 7.42 (d, *J* = 8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 29.5 (CH_2), 45.9 (CH_2), 52.5 (CH_2), 62.8 (CH_2),

126.4 (CH=), 126.7 (CH=), 127.3 (CH=), 128.1 (CH=), 128.9 (CH=), 129.7 (CH=), 130.8 (CH=), 135.2 (C), 137.7 (C), 142.9 (C), 158.5 (C=O). MS 398 (M + 1, 100%).

***N*-Methyl-*N*-(1-methylpiperidin-4-yl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide ($C_{22}H_{27}N_3O$) (5).** Eluent: CH_2Cl_2/MeOH (98:2). White solid, mp 137.1−138.5 °C. Yield 90%. ^{1}H NMR (MeOH-d_4) δ 1.32 (m, 2H), 1.57 (m, 2H), 1.85 (m, 2H), 2.12 (s, 3H), 2.46 (s, 3H), 2.75 (m, 2H), 3.04 (s, 4H), 3.81 (m, 1H), 7.0 (m, 6H), 7.27 (m, 4H), 7.42 (m, 2H). ^{13}C NMR (MeOH-d_4) δ 29.7 (CH_2), 31.8 (CH_3), 32.2 (CH_2), 46.4 (CH_3), 56.6 (CH_2), 56.7 (CH), 128.2 (CH=), 128.4 (CH=), 128.8 (CH=), 131.5 (CH=), 137.2 (C), 145.0 (C), 161.9 (C=O).

Procedure B. To a solution of diphenylcarbamoyl chloride (1 g, 4.3 mmol) in CH_2Cl_2 (25 mL) at 0 °C under stirring was added dropwise a solution of 4-piperidinopiperidine (4.4 g, 8.6 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred at 0 °C for 1 h. The precipitated solid was removed by filtration, and the mother liquor was concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/MeOH with gradient polarity) to afford **6** and **7**.

***N*,*N*-Diphenyl-4-piperidino-1-piperidincarboxamide ($C_{23}H_{29}N_3O$) (6).** Yellow solid, mp 85−88 °C. Yield 1.70 g, 92%. ^{1}H NMR ($CDCl_3$) δ 1.4 (m, 4H), 1.7 (m, 6H), 2.6 (m, 2H), 2.8 (m, 4H), 3.1 (t, J = 8.7 Hz, 1H), 4.0 (d, J = 9.3 Hz, 2H), 6.9 (m, 4H), 7 (m, 2H), 7.2 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 22.9 (CH_2), 23.7 (CH_2), 25.7 (CH_2), 44.3 (CH_2), 48.7 (CH_2), 61.8 (CH), 124.3 (CH=), 124.5 (CH=), 128.7 (CH=), 144.3 (C), 159.0 (C), 175.8 (C=O). HRMS (EI) calculated for ($C_{23}H_{29}N_3O$) 363.2211; found 363.2325.

3,4-Dihydro-1*H*-isoquinoline-2-carboxylic Acid Diphenylamide ($C_{22}H_{20}N_2O$) (7). White solid, mp 111.3−113.4 °C. Yield 0.586 g (95%). ^{1}H NMR ($CDCl_3$) δ 2.60 (t, J = 7.2 Hz, 2H), 3.50 (t, J = 7.2 Hz, 2H,), 4.40 (s, 2H), 7.00−7.20 (m, 12H), 7.25−7.36 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 28.4 (CH_2), 43.6 (CH_2), 47.5 (CH_2), 124.7 (CH=), 125.2 (CH=), 126.2 (CH=), 126.3 (CH=), 126.4 (CH=), 128.6 (CH=), 128.9 (CH=), 129.2 (C), 134.4 (C), 144.8 (C), 159.9 (C=O).

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Supporting Information Available: Experimental section of histaminic H1 receptor antagonist potency in vivo in rats. This material is available free of charge via the Internet at http://pubs.acs.org. The files containing the values of all the descriptors used in the building of the topological model antihistaminic is available from the corresponding author by e-mail.

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