**RESEARCH PAPER**

# Investigation of H1- Antihistamine Drugs Using Topological Indices

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**ABSTRACT**

A topological index is a quantitative descriptor derived from the structure of a chemical graph and is useful for predicting the physicochemical and biological characteristics of antihistamine drugs. This study focuses on degree–based topological indices to evaluate specific drugs, including Cetirizine, Chlorpheniramine, Diphenhydramine, Pheniramine, Cyclizine, Phenyltoloxamine, Azatadine, Hydroxyzine, and Promethazine, which are used to cure a runny nose, cough, and hay fever. Various topological indices were applied to these drugs as part of a Quantitative Structure – Activity Relationship (QSPR) study.

**Keywords:** Topological index, Molecular Structure, Correlation coefficient, Zagreb index, Benzene rings.

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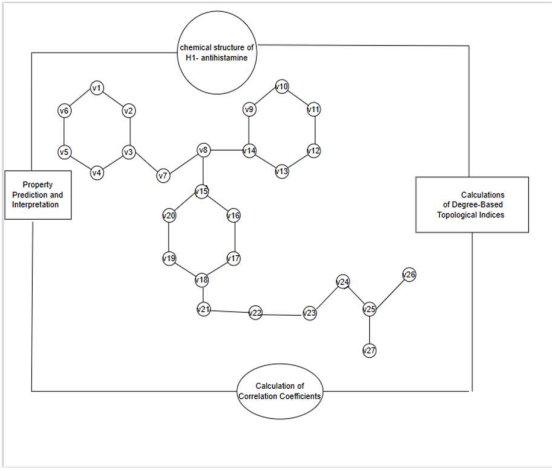
## Introduction

### Section 1

H1-type antihistamines are considered the therapeutic agents of choice for treating urticaria and angioedema The use of traditional H1 antihistamines is limited by their side effects. In recent years low-sedating H1 antihistamines with reduced sedative and anticholinergic side effects have become popular choices for the treatment of urticaria and angioedema. cetirizine and loratadine, currently under review at the Food and Drug Administration, are available in other countries. The choice of a particular low-sedating H1 antihistamine depends on pharmacokinetic considerations and frequency of administration.[7]




**The WHO** (1966) has given a more comprehensive definition: "Drug is any substances or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient [1]. Topological index is a mathematical formula which is applied to model some molecular structure. It is used to predict various physicochemical properties of drugs and they find an important place in QSPR studies. TIs can be classified into some classes such as degree- based indices, distance-based indices, neighborhood degree – based indices etc. It is very important to have a strong correlation of the TIs with the physicochemical properties of the drugs to have a good result.[2],[3],[4]

## Molecular Structures of H1 Antihistamine Drugs

### Cetirizine

Cetirizine is a highly sensitive $H_1$ antihistamine with particular antiallergic properties, which has been shown to be effective in the treatment of allergic rhinitis, urticaria, and hay-fever-associated asthma.[5]

### Chlorphenamine

Chlorpheniramine Maleate (CPM), also known as

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chlorphenamine, is a potent alkylamine first-generation H1 antihistamine that has been used since the 1950s. CPM is a widely popular drug commonly used to treat allergic conditions. Although mainly used in over-the-counter treatment for cough and colds, various studies discuss a wide range of CPM's clinical uses, such as treating asthma, plasma cell gingivitis, chronic urticaria, and depression, among others.[8]

**cyproheptadine**

cyproheptadine is a potent anti-serotonin agent and antagonist of histamine that is sometimes used as an appetite stimulant and for symptomatic relief of pruritic [9][10]

**Diphenhydramine**

Diphenhydramine was introduced into the clinical market under the brand name, Benadryl. The original chemical name, diphenymethoxyethyamine, later changed to diphenhydramine. During the 1980s, the FDA approved diphenhydramine as an over-the-counter (OTC) medication**.**

Diphenhydramine (DPHM) is a first generation H1 antagonist is the most frequently used antihistamine drugs, as a compound in over-the-counter cold medicines. The ability of (DPHM) overdose different from nonsedating, second generation, antihistamine medication.[11]

**Pheniramine**

Pheniramine is a first-generation antihistamine, which is widely available and is commonly used for allergic conditions. Initially considered to be a safe anti-allergic agent, growing evidence suggests its potential for misuse and dependence. Notably, it is reported that pheniramine is being used to mix other substances such as opioids during injection drug use. However, pheniramine misuse is not adequately studied in existing literature**.**[12]

**Cyclizine**

Cyclizine is a first-generation H1 antihistamine widely used for the treatment of nausea and motion sickness. In addition to its antiemetic properties, it has anticholinergic and central nervous system effects that may confer psychoactive potential. Although generally regarded as a low-risk medication, increasing evidence suggests a potential for misuse, particularly among adolescents and individuals with mental health disorders or substance-use vulnerabilities. Published data on cyclizine toxicity are limited, and paediatric reports of intentional overdose remain scarce. Cyclizine is a first-generation H1 antihistamine with sedative and anticholinergic properties, commonly used in the management of nausea, vomiting, and dizziness associated with motion sickness . The recommended oral dose for adults and adolescents is 50 mg taken approximately 30 minutes before travel, which may be repeated every four to six hours to a maximum of 200 mg in 24 hours. Therapeutic plasma concentrations are reported to range between 0.1 and 0.25 mg/L [13].

**Phenyltoloxamine**

Phenyltoloxamine (fen" il tol ox' a meen) is a first-generation antihistamine that is used to treat the symptoms of the common cold, including sneezing, cough, runny note, watery eyes and itching. Because of its sedating side effects, it is also used as a mild sleeping aid and sedative. Phenyltoloxamine belongs to the ethanolamine class of antihistamines (with clemastine and dimenhydrinate) and is currently used largely in combination with other agents such as phenylephrine and acetaminophen in over-the-counter products for relief of symptoms of the common cold and nighttime relief of minor aches and pains. Representative brand names of products that include phenyltoloxamine include Dologesic and Relagesic. [14]

**Azatadine**

Azatadine is a potent antagonist of H1 histamine receptors which has been recently introduced for the treatment of hay fever, acute urticaria and other allergic disorders. [15]

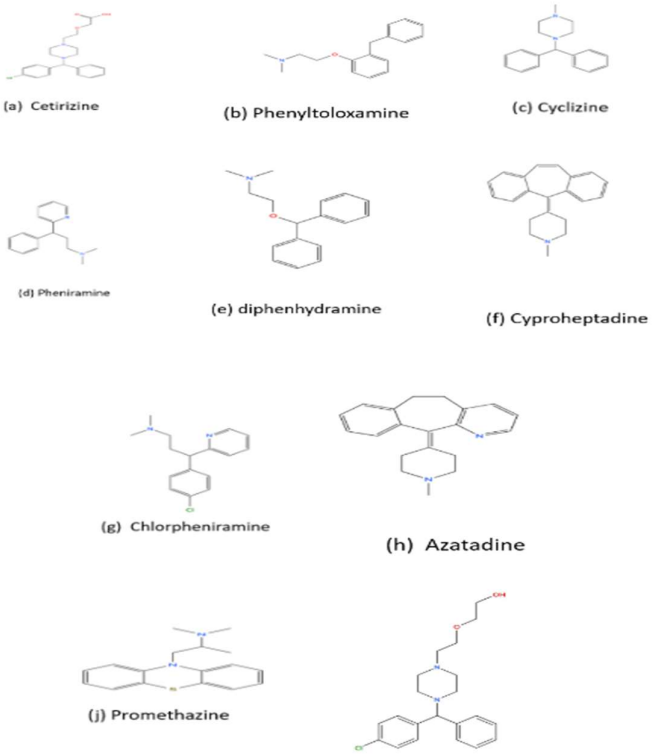
**Hydroxyzine**

Hydroxyzine is a first - generation antihistamine in the piperazine family of chemicals. It can also be used for the treatment of allergic conditions, such as chronic, urticaria, insomnia and anxiety.[16]

**Promethazine**

Promethazine is a first - generation antihistamine and can also have sedative effects. It has been used for the treatment of nausea and vomiting caused by narcotic therapy, cancer chemo therapy
and allergic symptoms such as itching, runny nose, sneezing watery eyes and skin rashes. [17]

**Section2 Diagrammatic representation of molecular structure of H1 – antihistamine drugs**




**Results and Discussions**

Several graph invariants found applications and are currently used in chemistry, pharmacology, environmental sciences, etc. One of these is the so-called "atom–bond connectivity index" (ABC). It is defined as follows

ABC(G)=$\sum_{uv\in E(G)}\sqrt{\frac{d_u+d_v-2}{d_u d_v}}$

The First and Second Zagreb indices are defined as

$$M_1(G) = \sum_{v\in V(G)} d(v)^2$$

$$M_2(G) = \sum_{v\in V(G)} d(u)d(v)$$

Harmonic index is defined as [6]

$$H(G) = \sum_{uv\in E(G)} \frac{2}{d_u + d_v}$$

Hyper Zagreb index is defined as $HM(G) = \sum_{uv\in E(G)}[d(u) + d(v)]^2$

Randi'c Index is defined as $R(G) = \sum_{uv\in E(G)} \frac{1}{\sqrt{d(u)d(v)}}$

Geometric Arithmetic mean index is defined as $GA(G) = \sum_{uv\in E(G)} \frac{2\sqrt{d(u)d(v)}}{d_u+d_v}$

**Section 3**

Computed Edge Partition values for the Drugs in terms of Vertex Degrees

| S. No | Drugs | $E_{1,2}$ | $E_{1,3}$ | $E_{1,4}$ | $E_{2,2}$ | $E_{2,3}$ | $E_{2,4}$ | $E_{3,3}$ | $E_{3,4}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Cetirizine | 0 | 3 | 0 | 11 | 12 | 0 | 3 | 0 |
| 2 | Chlorpheniramine | 0 | 3 | 0 | 7 | 8 | 0 | 2 | 0 |
| 3 | cyproheptadine | 0 | 1 | 0 | 9 | 10 | 0 | 5 | 0 |
| 4 | Diphenhydramine | 0 | 2 | 0 | 10 | 6 | 0 | 2 | 0 |
| 5 | Pheniramine | 0 | 2 | 0 | 9 | 6 | 0 | 2 | 0 |
| 6 | Cyclizine | 0 | 2 | 0 | 12 | 14 | 0 | 3 | 0 |
| 7 | Phenyltoloxamine | 0 | 2 | 0 | 13 | 13 | 0 | 3 | 0 |
| 8 | Azatadine | 0 | 1 | 0 | 11 | 14 | 0 | 6 | 0 |
| 9 | Hydroxyzine | 1 | 1 | 0 | 12 | 11 | 0 | 3 | 0 |
| 10 | Promethazine | 0 | 3 | 0 | 6 | 8 | 0 | 5 | 0 |

As an example, Theorem 1 presents the detailed computation of the DTIs of Cetirizine.

**Theorem 1**

For the chemical graph G of Cetirizine,

$M_1(G)= E_{1,3}(1+3) +E_{2,2}(2+2) + E_{2,3}(2+3) +E_{3,3}(3+3) = 134$

$M_2(G) = E_{1,3}(1\times3) +E_{2,2}(2\times2) + E_{2,3}(2\times3) +E_{3,3}(3\times3) =$

152

$H(G)= E_{1,3}(\frac{2}{1+3}) + E_{2,2}(\frac{2}{2+2}) + E_{2,3}(\frac{2}{2+3}) + E_{3,3}(\frac{2}{3+3}) = 12.80$

$E_{2,3}\sqrt{\frac{2+3-2}{2\times3}} + E_{3,3}\sqrt{\frac{3+3-2}{3\times3}} = 20.71$

$ABC\ (G)= E_{1,3}\sqrt{\frac{1+3-2}{1\times3}} + E_{2,}\sqrt{\frac{2+2-2}{2\times2}} +$

Table 1 Topological Indices of the H1- Antihistamines

| S. No | Drugs | $M_1(G)$ | $M_2(G)$ | $H(G)$ | $HM(G)$ | ABC(G) | R(G) | GA(G) |
|---|---|---|---|---|---|---|---|---|
| 1 | Cetirizine | 134 | 152 | 12.80 | 632 | 20.71 | 13.13 | 28.35 |
| 2 | Chlorpheniramine | 92 | 103 | 8.86 | 432 | 14.38 | 9.16 | 19.43 |
| 3 | cyproheptadine | 120 | 144 | 10.66 | 590 | 17.58 | 10.82 | 24.66 |
| 4 | Diphenhydramine | 90 | 100 | 9.06 | 414 | 14.28 | 9.27 | 19.61 |
| 5 | Pheniramine | 86 | 96 | 8.56 | 398 | 13.57 | 8.77 | 18.61 |
| 6 | Cyclizine | 98 | 102 | 9.90 | 442 | 14.69 | 10.11 | 20.65 |
| 7 | Phenyltoloxamine | 73 | 81 | 8.43 | 333 | 11.90 | 8.67 | 16.63 |
| 8 | Azatadine | 85 | 104 | 9.40 | 426 | 13.98 | 9.61 | 19.65 |
| 9 | Hydroxyzine | 128 | 146 | 12.56 | 600 | 19.78 | 12.77 | 27.58 |
| 10 | Promethazine | 56 | 64 | 6.33 | 196 | 9.12 | 5.41 | 13.2 |

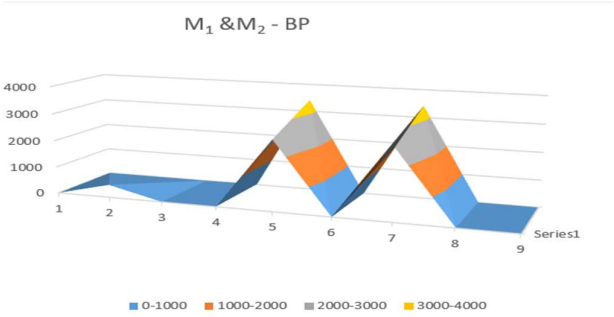
Table 2 Physicochemical properties of the H1 – Antihistamines

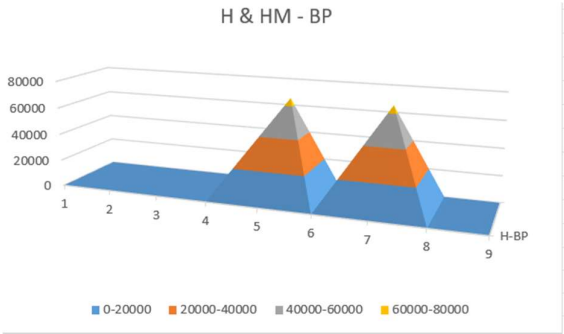
| S. No | Drugs | BP | EV | FP | MR | $\alpha$ | MV |
|---|---|---|---|---|---|---|---|
| 1 | Cetirizine | 542.1 | 86.3 | 281.6 | 105.9 | 42 | 314.2 |
| 2 | Chlorpheniramine | 379.0 | 62.7 | 183.0 | 80.8 | 32.0 | 248.0 |
| 3 | cyproheptadine | 440.1 | 69.7 | 194.5 | 91.6 | 36.3 | 257.5 |
| 4 | Diphenhydramine | 343.7 | 58.8 | 101.5 | 79.6 | 31.5 | 249.2 |
| 5 | Pheniramine | 348.3 | 59.3 | 164.5 | 75.9 | 30.1 | 236.1 |
| 6 | Cyclizine | 495.0 | 75.5 | 252.0 | 116.0 | 46.0 | 335.0 |
| 7 | Phenyltoloxamine | 420.0 | 68.0 | 210.0 | 98.0 | 38.0 | 280.0 |
| 8 | Azatadine | 460.0 | 72.0 | 220.0 | 110.0 | 41.0 | 300.0 |
| 9 | Hydroxyzine | 499.2 | 80.8 | 255.7 | 105.9 | 42 | 317.1 |
| 10 | Promethazine | 403.7 | 65.5 | 198 | 87.8 | 34.8 | 251.3 |

**Computation of Regression coefficients**

The properties considered includes boiling point (BP in ℃ ), enthalpy of vaporization (EV in kJ/mol), flash point (FP in℃), molar refraction (MR in $cm^3$/mol),
polarizability ($\alpha$in $A^3$), and molar volume (MV in $cm^3$/mol). The corresponding values were taken from ChemSpider and are given in Table 2.

| Regression Coefficient | $M_1$-BP | $M_2$-BP | H-BP | HM-BP |
|---|---|---|---|---|
| r | 0.688 | 0.670 | 0.787 | 0.642 |
| $r^2$ | 474 | 0.449 | 0.620 | 0.412 |
| Adjusted $r^2$ | 0.408 | 0.380 | 0.53 | 0.338 |
| Standard Error of the Estimate | 18.93433 | 22.89403 | 12.7452 | 107.87588 |
| Sum of Squares | 2581.528 | 3418.507 | 21.211 | 65158.968 |
| Degrees of Freedom | 1 | 1 | 1 | 1 |
| Mean Square | 2581.528 | 3418.507 | 21.211 | 65158.968 |
| F test | 7.201 | 6.522 | 13.058 | 5.599 |
| Significant values | 0.28 | 0.28 | 0.07 | 0.46 |




**Conclusion**

In this study, QSPR -based approach using topological indices was applied to model and predict the physicochemical properties of H1 antihistamines. The obtained correlation coefficients suggest a moderate yet meaningful relationship between molecular structure and the studied property. The work can be extended by exploring other types of indices, such as neighborhood-based topological indices and by modelling additional physicochemical properties. Such analyses can be conducted not only on the same class of drugs but also across other classes of drugs, thereby strengthening the applicability and scope of the QSPR framework.

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