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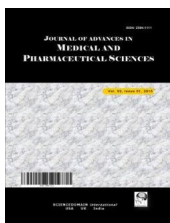
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Comparative Analysis of Antihistamines and Nonsteroidal Anti-inflammatory Drugs (NSAIDs): Properties, Structure and Prediction of New Potential Drugs

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Aims: To determine the molecular properties of common antihistamines and non-steroidal anti-inflammatory agents (NSAIDs). To identify interrelationships among these two groups of drugs utilizing pattern recognition methods and statistical analysis.

Study Design: After determination of molecular properties, values thereof are examined using pattern recognition methods and other numerical analysis for underlying relationships and similarities.

Place and Duration of Study: Durham Science Center, University of Nebraska, Omaha, Nebraska from September 2016 to January 2017.

Methodology: Thirty compounds were identified as antihistamines and 27 compounds identified as NSAIDs. Properties such as Log P, molecular weight, polar surface area, etc. are determined. Molecular properties are compared applying methods such as K-means cluster analysis, nearest neighbor joining, box plots, and statistical analysis in order to determine trends and underlying

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relationships. Pattern recognition techniques allow elucidation of underlying similarities.

Results: The molecular properties of all 57 drugs are tabulated for comparison and numerical analysis. Evaluation by Kruskal-Wallis test and one-way ANOVA indicated that antihistamines and NSAIDs' values of Log P have equal medians and equal means. However, values of polar surface area (PSA) and number of rotatable bonds for these two groups do not have equal means and medians. Box plots indicated that Log P, PSA, and molecular weight values have significant overlap in range. Neighbor-joining method showed which drugs are most similar to each other. K-means cluster analysis also divided these 57 drugs into six groups of highest similarity. Principal coordinates analysis (PCoA) with 95% ellipses indicated all but four of the drugs fall within a 95% confidence region. Multiple regression analysis generated mathematical relationship for prediction of new drugs.

Conclusion: These two groups of drugs show compelling similarities. PCoA showed all but four of 57 drugs come within a 95% confidence ellipsis. Neighbor joining and K-means cluster analysis showed drugs having similarities between the two groups.

Keywords: Antihistamines; non-steroidal anti-inflammatory drugs; pattern recognition.

ABBREVIATIONS

PSA: polar surface area; nOHNH: number of hydroxyl groups and amine groups; nON: number of oxygen and nitrogen atoms; nRotB: number of rotatable bonds; MV: molecular volume; nAtoms: number of atoms; MW: molecular weight; RO5: rule of five.

1. INTRODUCTION

The group of drugs referred to as non-steroidal anti-inflammatory agents (NSAIDs) are applied in the treatment of fever, pain, acute and chronic inflammatory conditions [1]. They are considered to be chemically heterogeneous and inhibit the intracellular cyclo-oxygenase enzymes COX-1 and COX-2 to reduce the synthesis of prostaglandins [1]. Generally, NSAIDs are highly bound to plasma proteins such as albumin, which decreases their body distribution to levels, considered low (i.e. as low as or lower than 0.2 Liter/kg) [2]. The renal excretion of the unchanged NSAID is generally less than 5% of the given dose, therefore, elimination depends greatly on hepatic biotransformation [2]. The majority of NSAIDs are nonselective inhibitors of COX-1 and COX-2 as a competitively reversible mechanism (except for aspirin which is irreversible inhibition), but still act as antipyretic agents to reduce fever [3].

Most of the NSAIDs are metabolized by oxidation and conjugation to inactive metabolites in the liver [1,2,3]. Most NSAIDs are weak acids that have a pKa ranging from 3 to 5 [3]. The range of medical conditions that NSAIDs are applied for clinical treatment is quite broad, and includes [2,3,4]: Osteoarthritis, rheumatoid arthritis, low back pain, headache, acute gout, metastatic

bone pain, renal colic, pyrexia, and macular edema. NSAIDs and antihistamines are used as therapy for ocular allergy [5], NSAIDs for beneficial effects for patients with colorectal cancer [6], and gastric pain relief with protective agents [7]. However, NSAIDs use has safety concerns [8], increased sepsis following colorectal surgery [9], association with hypertension [10], and increased risk of stroke [11]. Interestingly, stress has been shown to be an independent factor for ulcers, compared to H pylori or NSAIDs exposure [12,13]. Antihistamine use concurrent prevents to the appearance of NSAIDs induced urticarial and/or angioedema [14].

Hypersensitivity reactions, or allergic reactions, are highly frequent and represent a public health issue of importance and significant expense [15]. Various allergic reactions, like those to peanuts, shellfish, or eggs, are a serious form of reaction affecting the respiratory organs that can cause loss of consciousness and sometimes death [16]. The World Health Organization estimates that as many as 300 million people suffer from asthma [17]. The symptoms and effects of allergic reactions can vary widely from person to person, which falls into the study of epigenetics [18]. Individuals having both parents with allergies are 70% likely to suffer allergies, while that figure reduces to 48% for only one parent having allergies [19].

There are four major groups of histamine receptors (H1, H2, H3, and H4), with the H1 receptors most important in chronic urticarial and allergic rhinitis [20]. Second-generation antihistamines (such as fexofenadine) have decrease lipophilic structures and do not cross the blood-brain barrier (BBB), as do the first-generation antihistamines [20]. Interestingly, antihistamines that cross the BBB can have both stimulant and depressant effects [4]. Second-generation antihistamines developed as H1 blockers, have fewer side effects [20]. The H1 targeting antihistamines are the major means for treatment of urticaria (hives) [21].

Histamine released into the blood following the action of an allergen binds to receptors of various tissue resulting in constriction of the bronchi, dilation of blood vessels (inducing fall in blood pressure), increases permeability of blood vessels, and increases the production of hydrochloric acid in the stomach [22]. Antihistamines counteract the effects mediated by histamine, but in themselves can bring about unwanted side effects such as weight gain, urine retention, dizziness, and increased risk for ventricular arrhythmias [22,23]. The sedative effect of the first-generation antihistamines that gained for themselves attention and notoriety [24]. Research aimed towards H3 and H4 receptors in disease is a strong area of research [25,26]. Research in the area of H3 receptors may contribute to treatments for obesity, mental health problems, and inflammatory disease [27,28]. This study introduces analysis of the relative structures of NSAIDs and antihistamines. Underlying relationships found within their molecular properties leads to further understanding of pharmacokinetics and prediction of new structures.

2. METHODOLOGY

2.1 Properties and Molecular Modeling

For all drugs included in this study, the numerical values of molecular properties were determined by utilizing heuristic techniques of Molinspiration (Molinspiration Cheminformatics, Nova ulica 61, SK-900 26 Slovensky Grob, Slovak Republic). Elucidation of molecular structure components was accomplished by use of ACD/ChemSketch Modeling v. 12.01 (Advanced Chemistry Development, 110 Yonge Street, Toronto Ontario, M5C 1T4 Canada) and Molinspiration (<http://www.molinspiration.com/services/search.html>).

2.2 Pattern Recognition and Multivariate Statistical Analysis

Identification of underlying associations and patterns within the numerical values of molecular properties was accomplished by use of pattern recognition techniques. This included analysis by non-hierarchical K-means cluster analysis, neighbor joining method, principal coordinates analysis with 95% ellipses, these performed by PAST v. 2.06 (copyright Oyvind Hammer, D.A.T. Harper 1999-2008).

2.3 Various Statistical Analysis Data

Various methods of statistical analysis applied included Pearson r correlation, descriptive statistics by Microsoft EXCEL v. 14.0.6112.5000 (EXCEL Professional plus 2010).

Algorithmic software by GraphPad accomplished multiple regression analysis of molecular property values (InStat version 3.00, GraphPad Software, Inc., San Diego, California USA; www.graphpad.com). Determination of any numerical outliers accomplished by Grubb's test (also known as extreme studentized deviate). Box plots, Kruskal-Wallis test, one-way ANOVA, and F and T tests were accomplished by PAST v. 2.06.

3. RESULTS AND DISCUSSION

3.1 Structure Features and Properties

Important groups of drugs that provide substantial public health impact would certainly include NSAIDs (ATC code MO1) and antihistamines (ATC code RO6). Great interest in drugs that would be able to antagonize the action of histamine arose in clinicians concerned about the treatment of diseases in which histamine played an important role [4]. The antipyretic activity of willow bark discerned in the 19th century and scarcity prompted the need for synthetic alternates [4]. The appearance of second-generation antihistamines that avoided undesirable side effects of first-generation drugs provided a successful alternative for clinicians. The search and design of novel NSAIDs and antihistamines continues, although significant harmful side effects discerned in promising candidates gives pause to the progress made.

Drug discovery is complex and exacting pursuit of beneficial agents to enhance medicine. A broadly accepted result of the study is the importance of optimizing the absorption,

distribution, metabolism, excretion, and toxicity (ADME/Tox) properties of candidates in addition to their pharmacology (e.g., efficacy, selectivity) to obtain success [29]. Drug-like properties are an integral part of novel drug discovery [4]. The rule of five (RO5), is a set of guidelines to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans [29]. This rule of five will be determined for the representative sets of NSAIDs and antihistamines examined for this study. The structures of 18 H₁ antagonist agents are presented in Fig. 1 for comparison, showing structure features in common and descriptive of antihistamines.

Seasonal allergies are often treated with pharmaceutical agents that block H₁ receptors, thereby competing with histamine for binding to sites (H₁ antagonists) [22]. Shown in Fig. 1, each compound has at least two simple aromatic rings or aromatic ring plus heterocyclic aromatic ring, with an amine group (in or out of ring). H₁-antihistamines will readily cross the BBB and result in sedation [20,21]. Various molecular properties associated with each drug **1** to **18**, as well as drugs **19** to **30** (see Fig. 2) for all antihistamines (ATC code RO6), and **31** to **57** for all NSAIDs (ATC code MO1A), shown in Table 1.

Structure features common to H₁ antagonists include at least two aromatic rings, but the ring may be a heteroatomic ring. An amine functional group is found, but can be primary or tertiary. The orientation of the rings varies widely and the rings may have substituents covalently bonded to the ring (see Fig. 1).

Interestingly, halogen atoms (chlorine, bromine) found on drugs **2**, **4**, **6**, **8**, and **18**, are not consistent with H₁ antagonists throughout. Other functional groups present include ether groups (-O-) for drugs **3**, **6**, **7**, **8**, **9**, **10**, and **11**; and carboxyl groups (-C(O)OH) for drug **1**. Non-aromatic heteroatomic rings are also present. To visual eye inspection there appears a broad range in structure features, however, numerical analysis reveals limitations and consistency in properties important for pharmacological consideration.

The rule of five states that, in general, an orally active drug has no more than one violation of the following criteria [29]: 1) No more than 5 hydrogen bond donors (the total number of

nitrogen–hydrogen and oxygen–hydrogen bonds); 2) No more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms); 3) A molecular mass less than 500 Daltons, and; 4) An octanol-water partition coefficient log *P* not greater than 5. Interestingly, only drug **9** and **30** of the antihistamines have only one violation of the rule of five, however, all the NSAIDs drugs have zero violations of the RO5. Therefore, all 57 drugs indicated in Table 1 would be considered as orally active drugs. This finding indicates favorable drug-likeness for all 57 drugs and good bioavailability. This aspect contributing to the efficacy of patient use and popularity of clinical prescription.

An outlier is an observation that appears to deviate markedly from other observations in the sample [30,31]. Here, the Grubbs' test, also called the ESD method (extreme studentized deviate), is utilized to determine whether one of the values in the list of molecular properties (see Table 1) is a significant outlier from the rest. Among the antihistamine compounds (**1** to **30**) only, there is no outlier in Log *P* values and no outlier in the number of rotatable bonds properties. However, for each of the following properties there is one outlier detected (value indicated): Polar surface area (175.85 Angstroms²), number of atoms (35), molecular weight (500.55), number of oxygen & nitrogen atoms (9), number of –OH and –NH_n (8), rule of five (1), and molecular volume (474.23 Angstroms³). This outcome indicates that the molecular properties of common clinical antihistamines are highly consistent, with similar drug-likeness and bioavailability.

Interestingly, there are no outliers for all 27 NSAIDs compounds for Log *P*, polar surface area, number of atoms, molecular weight, number of oxygen & nitrogen atoms (nON), number of –OH & –NH_n, rule of five, number of rotatable bonds, and molecular volume. This clearly shows a strong consistency of the NSAIDs in molecular properties, including important pharmaceutical properties such as drug-likeness and bioavailability.

The mean values for molecular properties, inclusive of antihistamine drugs **1** to **30** only, are the following, by property: Log *P* (3.10), polar surface area (42.55 Angstroms²), number of atoms (22), molecular weight (315.01), number of oxygen & nitrogen atoms (~4), number of –OH & –NH_n (1), rule of five (~0), number of rotatable bonds (~6), and molecular volume (294.03 Angstroms³).

The mean values for molecular properties, inclusive of NSAIDs drugs **31** to **57** only, are the following, by property: Log P (3.27), polar surface area (62.94 Angstroms²), number of atoms (19),

molecular weight (274.27), number of oxygen & nitrogen atoms (~4), number of -OH & -NH_n (~2), rule of five (~0), number of rotatable bonds (~3), and molecular volume (234.52 Angstroms³).

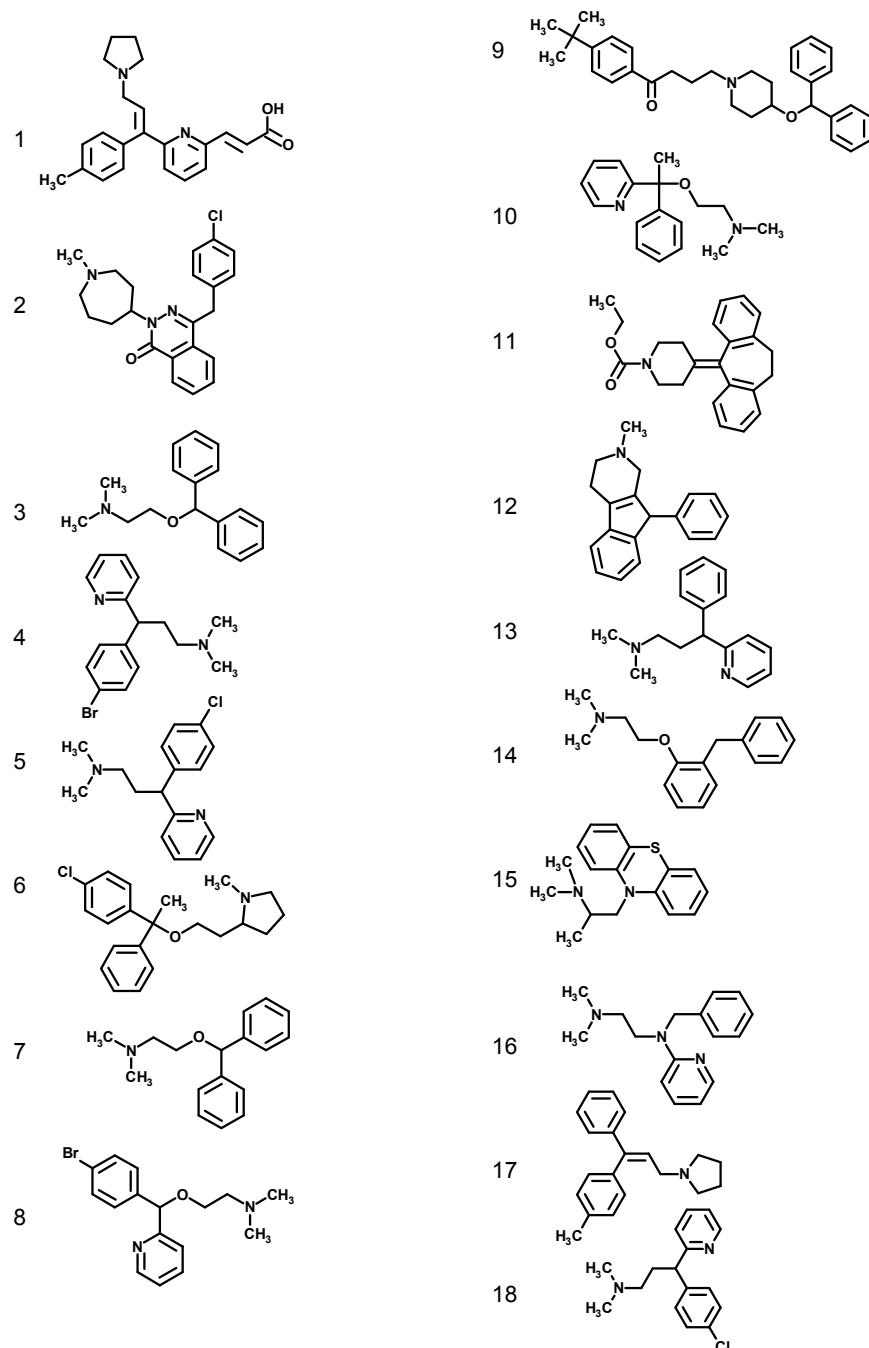


Fig. 1. H₁ Antagonists compounds **1** (acrivastine), **2** (azelastine), **3** (bromazine), **4** (brompheniramine), **5** (chlorphenamine), **6** (clemastine), **7** (diphenhydramine), **8** dexbrompheniramine), **9** (ebastine), **10** (doxylamine), **11** (loratadine), **12** (phenindamine), **13** (pheniramine), **14** (phenyltoloxamine), **15** (promethazine), **16** (tripelennamine), **17** (triprolidine), **18** (chlorpheniramine)

Analysis of medians and means of properties between drug classes can be achieved by use of the Kruskal-Wallis test, one-way ANOVA, and F and T tests [30,31]. Analysis of properties in Table 1 comparing antihistamines to NSAIDs, the Kruskal-Wallis test indicated that Log P and number of number of oxygen & nitrogen atoms

(nON) between the two groups have equal medians ($P=.35$ and $P=.26$, respectively). One-way ANOVA indicates equal means in values of Log P ($P=.64$) and nON ($P=.62$). The F and T test indicated equal means of Log P ($P=.64$), comparing antihistamines with NSAIDs (see Table 1).

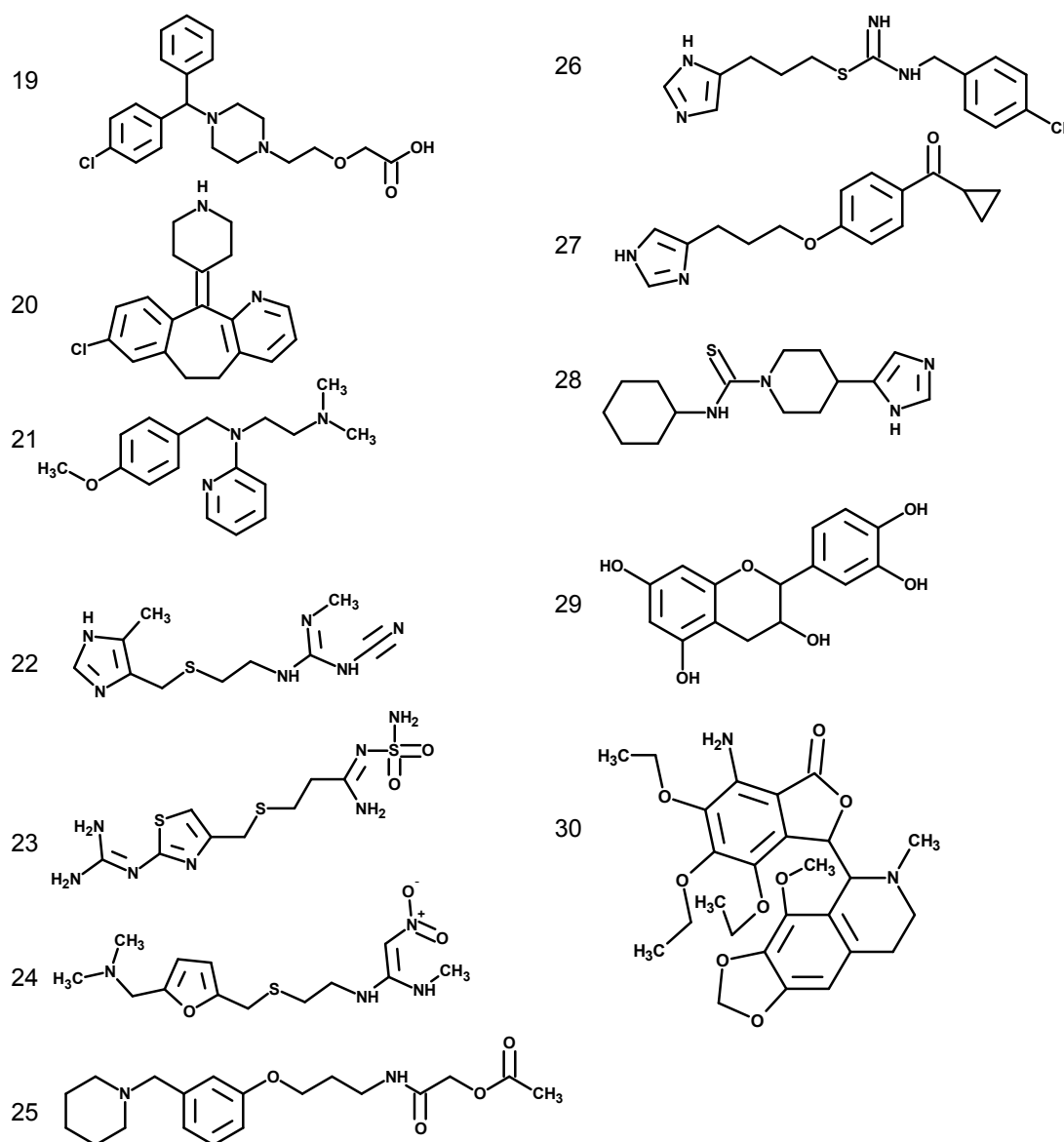


Fig. 2. Compounds H1 inverse agonists 19 (cetirizine), 20 (desloratadine), and 21 (mepyramine). Compounds H2 antihistamines 22 (cimetidine), 23 (famotidine), 24 (ranitidine), 25 (roxatidine acetate). Compounds H3 antihistamines 26 (clobenpropit) and 27 (ciproxifan). Compound 28 (thioperamide) is an HRH4 antagonist. Compounds 29 (catechin) and 30 (tritoqualine) are histidine decarboxylase inhibitor

Table 1. Molecular properties of compounds

Drugs	Log P	Polar surface area (Å ²)	Number of atoms	Molecular weight	Number O & N atoms	Number OH, NH _x groups	Violations of rule of 5	Number rotatable bonds	Molecular volume (Ångstroms ³)	
1	RO6	3.34	53.43	26	348.45	4	1	0	6	335.64
2		4.82	38.13	27	381.91	4	0	0	3	349.32
3		4.31	12.47	20	334.26	2	0	0	6	278.66
4		3.44	16.13	19	319.25	2	0	0	5	265.52
5		3.31	16.13	19	274.80	2	0	0	5	261.17
6		4.67	12.47	24	343.90	2	0	0	6	330.38
7		3.50	12.47	19	255.36	2	0	0	6	260.77
8		3.44	16.13	19	319.25	2	0	0	5	265.52
9		6.56	29.54	35	469.67	3	0	1	10	474.23
10		2.16	25.36	20	270.38	3	0	0	6	272.86
11		4.58	42.44	27	382.89	4	0	0	2	345.49
12		3.65	3.24	20	261.37	1	0	0	1	257.76
13		2.63	16.13	18	240.35	2	0	0	5	247.63
14		3.94	12.47	19	255.36	2	0	0	6	260.75
15		4.44	8.17	20	284.43	2	0	0	3	271.62
16		2.57	19.37	19	255.37	3	0	0	6	260.39
17		3.47	16.13	21	278.40	2	0	0	4	281.23
18		3.31	16.13	19	274.80	2	0	0	5	261.17
19		3.32	53.01	27	388.89	5	1	0	8	354.14
20		3.53	24.92	22	310.83	2	1	0	0	283.78
21		2.63	28.60	21	285.39	4	0	0	7	285.94
22		0.14	88.89	17	252.35	6	3	0	7	231.45
23		-.11	175.85	20	337.46	9	8	0	7	262.24
24		0.33	86.26	21	314.41	7	2	0	10	288.97
25		2.13	67.88	25	348.44	6	1	0	10	338.90
26		2.67	64.56	20	308.84	4	3	0	8	269.85
27		2.69	54.99	20	270.33	4	1	0	7	254.24
28		2.67	43.95	20	292.45	4	2	0	4	281.11
29		1.37	110.37	21	290.27	6	5	0	1	244.14
30		3.54	110.97	36	500.55	10	2	1	8	446.15

Drugs	Log P	Polar surface area (Å ²)	Number of atoms	Molecular weight	Number O & N atoms	Number OH, NH _x groups	Violations of rule of 5	Number rotatable bonds	Molecular volume (Ångstroms ³)
31 MO1A	1.87	57.53	10	138.12	3	2	0	1	119.06
32	3.90	57.53	18	250.20	3	2	0	2	200.33
33	1.43	63.60	13	180.16	4	1	0	3	155.57
34	3.77	83.83	19	258.23	5	2	0	4	218.44
35	3.46	37.30	15	206.28	2	1	0	4	211.19
36	3.46	37.30	15	206.28	2	1	0	4	211.19
37	3.38	46.53	17	230.26	3	1	0	3	213.97
38	3.89	46.53	18	242.27	3	1	0	4	224.83
39	3.59	54.37	19	254.28	3	1	0	4	234.83
40	2.79	54.37	18	246.31	3	1	0	4	236.61
41	3.59	54.37	19	254.28	3	1	0	4	234.83
42	4.05	37.30	18	244.26	2	1	0	3	220.77
43	3.99	68.54	25	357.79	5	1	0	4	303.24
44	2.15	54.37	25	356.42	3	1	0	4	306.98
45	4.57	49.33	19	296.15	3	2	0	4	238.73
46	2.20	59.30	19	255.27	4	1	0	3	229.39
47	0.55	99.60	23	333.37	7	2	0	2	274.29
48	0.72	99.60	23	353.43	7	2	0	2	281.56
49	1.94	99.60	22	337.38	7	2	0	2	258.76
50	2.74	99.60	23	371.83	7	2	0	2	272.30
51	4.77	49.33	18	241.29	3	2	0	3	227.98
52	5.63	49.33	19	296.15	3	2	0	3	238.49
53	5.00	49.33	18	261.71	3	2	0	3	224.95
54	4.84	49.33	20	281.23	3	2	0	4	226.15
55	3.61	77.99	26	381.38	5	2	0	4	298.65
56	2.81	101.23	21	308.31	7	1	0	5	248.17
57	3.58	62.22	18	262.70	4	2	0	3	220.80

Statistical analysis shows that Log P and nON for these two groups of drugs have equal means and medians. This indicates virtual likeness in lipophilicity and hydrogen bond acceptors for NSAIDs and antihistamines. Both descriptors (Log P and nON) are vital for drug-likeness according to the RO5 [29]. The favorable bioavailability avails these two groups much, aiding pharmacological properties and efficacy for clinical prescription as medicinal drugs. However, similarity in Log P and nON does not dictate like medicinal activity when ingested, because pharmacophore sites will dictate their biological activity.

One-way ANOVA analysis indicates that polar surface area and number of rotatable bonds between the two groups of drugs do not have equal means ($P=.01$, $P<.001$, respectively). This suggests that polar surface area is a vital indicator of drug-likeness, represented by nON and number of $-OH$ and $-NH_n$ [29].

Drugs **19**, **20**, and **21** shown in Fig. 2, are H₁ inverse agonists (an agent that binds to the same receptor as an agonist but induces a pharmacological response opposite to that agonist). Drugs **22**, **23**, **24**, and **25** shown in Fig. 2, are H₂ antihistamines act on H₂ histamine receptors found primarily in parietal cells of the gastric mucosa (reducing secretion of gastric acid) [20,21,22]. H₂-antihistamines have activity as inverse agonists and neutral antagonists [21,22]. H₃-antihistamine drugs are utilized by clinicians to inhibit the action of histamine at the H₃ receptor, which are primarily found in the brain as inhibitory auto receptors found in the histaminergic nerve terminals modulating the release of histamine [21,22]. H₃-antihistamines are dissimilar to H₁ antihistamines, having instead stimulating and cognition-modulating effects [21,22]. Drugs **26** and **27** are H₃ antihistamines. Compound **28** is an HRH4 antagonist. The preferred expression of H₄R by some immune cells and action in allergic inflammation explains the rationale for use of anti-H₄R antagonists in allergic and immune type disorders [32]. Compounds **29** and **30** are histidine decarboxylase inhibitors.

Molecular structures of NSAIDs **31** to **57** begin in Fig. 3, and are identified by their structural features. Drugs **31**, **32**, **33**, and **34** are salicylate compounds. Salicylates drugs themselves are divided into two groups: acetylated (having $-C(=O)CH_3$) and non-acetylated [1,2,3]. Aspirin or acetylsalicylic acid (**33**) is acetylated, while

others such as salsalate (**34**), salicylic acid (**31**) and diflunisal (**32**) are non-acetylated. Drugs **35**, **36**, **37**, **38**, **39**, **40**, **41**, and **42** are propionic acid derivatives in structure, having $(-CH_2CH(=O)OH)$ group.

NSAIDs compounds that are acetic acid derivatives are compounds **43** (indomethacin), **44** (sulindac), and **45** (diclofenac). Whereas drug **46** (ketorolac) is structurally defined as a pyrrolizine-1-carboxylic acid compound.

Various other forms of NSAIDs are presented in Fig. 4. Drugs **47**, **48**, **49**, and **50** are enolic acid or oxicam derivatives. Unlike most other NSAIDs, oxicams are not carboxylic acids. Oxicams are tautomeric and can exist as a number of tautomers (i.e. keto-enol tautomerism, which a chemical equilibrium between a keto form (ketone or aldehyde) and an enol (alcohol)).

Fenamates or anthranilic acid derivative compounds include **51** (mefenamic acid), **52** (meclofenamic acid), **53** (tolfenamic acid), and **54** (flufenamic acid). These NSAIDs are characterized by having the group $C_6H_4(COOH)(NH-)$. The remaining COX-2 inhibitors (COXIB) compounds include **55** (celecoxib) and **56** (nimesulide). The remaining NSAID clonixin (**57**) is a pyridine-3-carboxylic acid compound. All drugs shown in Fig. 4 have at least one aromatic ring or heteroatom arene ring.

3.2 Identification of Similarities by Pattern Recognition

Pattern recognition is the process of classifying input data into groups or classes based on principal characteristics. There are two classification methods in pattern recognition: supervised and unsupervised classification [30]. An unsupervised classification method works by finding hidden relationships in data applying segmentation or clustering techniques. A common unsupervised classification method utilized in this study is known as K-means clustering analysis [30]. K-means cluster analysis aims to partition n observations into a predetermined number of clusters, in which each observation belongs to the cluster with the most similar members [30].

Considered altogether, the 57 antihistamines and NSAIDs having properties presented in Table 1 are analyzed by K-means cluster analysis to produce six clusters containing the drugs most similar to each other (based on properties in

Table 1). The results were as follows, antihistamine drugs are in bold to distinguish from NSAIDs:

Cluster 1: **1, 2, 6, 11, 19, 25, 43, 44, 55.**

Cluster 2: **23, 24, 29, 47, 48, 49, 50, 56.**

Cluster 3: **3, 4, 8, 20, 21, 26, 28, 45, 52.**

Cluster 4: **5, 7, 10, 12, 13, 14, 15, 16, 17, 18, 27.**

Cluster 5: **22, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 46, 51, 53, 54, 57.**

Cluster 6: **9, 30.**

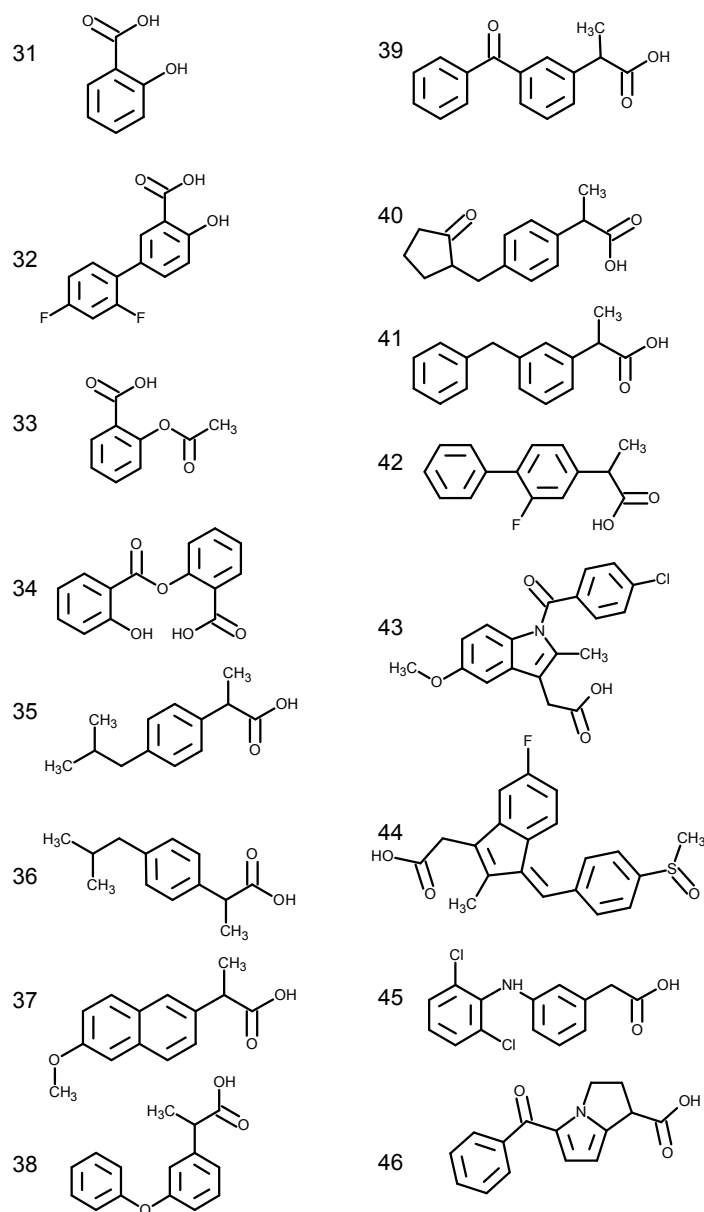


Fig. 3. Salicylate compounds 31 (salicylic acid), 32 (diflunisal), 33 (aspirin), 34 (salsalate). Propionic acid compounds 35 (ibuprofen), 36 (dexibuprofen), 37 (naproxen), 38 (fenopropfen), 39 (dexketoprofen), 40 (loxoprofen), 41 (ketoprofen), and 42 (flurbiprofen). Acetic acid derivatives are compounds 43 (indomethacin), 44 (sulindac), 45 (diclofenac); with 46 (ketorolac) as a pyrrolizine-1-carboxylic acid

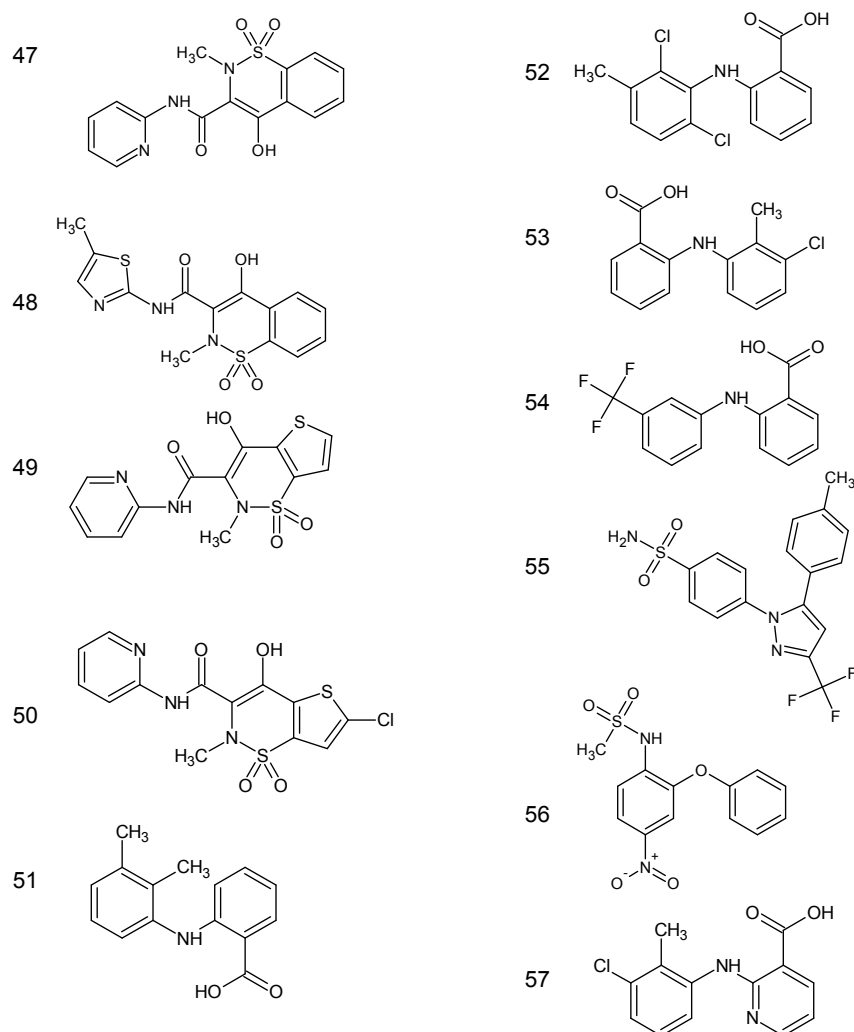


Fig. 4. Enolic acid or oxicam derivative compounds 47 (piroxicam), 48 (meloxicam), 49 (tenoxicam), and 50 (lornoxicam). Anthranilic acid derivative (fenamates) compounds 51 (mefenamic acid), 52 (meclofenamic acid), 53 (tolfenamic acid), and 54 (flufenamic acid). COX-2 inhibitors (COXIBS) compounds 55 (celecoxib) and 56 (nimesulide). Compound 57 (clonixin) is a pyridine-3-carboxylic acid

NSAIDs are highly concentrated in cluster 5, however, antihistamines and NSAIDs have intermixing in clusters 1, 2, 3, and 5. This indicates that there exists similarities between various antihistamine drugs with NSAIDs. For cluster 1 the antihistamines drugs **1**, **2**, **6**, **11**, **19**, and **25** are most similar to NSAIDs **43**, **44**, and **45** (Acetic acid derivatives). In cluster 5, the H₂ antihistamine **22** (cimetidine) is determined to be most similar to the bulk of the NSAID drugs (17 total) and those including salicylates (**31**, **32**, **33**, **34**), propionic acid compounds (**34** to **42**), anthranilic acid derivatives (**51**, **53**, **54**), and **57** (clonixin) a pyridine-3-carboxylic acid. Antihistamines

9 and **30** are distinct to themselves in cluster 6.

Box plots are visual organizing data for identifying outliers and for comparing distributions [31]. Box plots provide basic information describing distribution of data. A numerical distribution with a positive skew would have a longer whisker in the positive direction than in the negative direction. A boxplot splits the data set into quartiles and are useful for indicating skewness and presence of outliers in the data set. Box and whisker plots are effective when large numbers of observations are involved and two or more data sets are analyzed [31].

The molecular weight and Log P parameters constitute one-half of the set of parameters described in the Rule of 5 [29]. These two properties, along with polar surface area, are visualized in box plots comparing these two groups of drugs (see Fig. 5).

Observing the box plots for molecular weight (MW), the medians are indicated within the box, and range by the whiskers. The median and mean of MW for antihistamine drugs is 300.65 daltons and 315.01 daltons, respectively. Similarly, for NSAIDs that MW is 258.23 daltons and 274.28 daltons, respectively. There is a generous overlap of the boxes themselves from lower quartile to upper quartile.

Observing the box plots for polar surface area (PSA), the medians are indicated within the box, and range by the whiskers. The median and mean of PSA for antihistamine drugs is 26.98 Angstroms² and 42.55 Angstroms², respectively. Similarly, for NSAIDs that PSA is 54.37 Angstroms² and 62.94 Angstroms², respectively. There is a complete overlap of the box and whisker for the NSAIDs entirely within the range of PSA for antihistamines. This may suggest a smaller range in PSA that is suitable for NSAID drugs.

Observing the box plots for Log P, the medians are indicated within the box, and range by the whiskers. The median and mean of Log P for antihistamine drugs is 3.33 and 3.10, respectively. Similarly, for NSAIDs that Log P is 3.58 and 3.27, respectively. There is a generous overlap of the boxes themselves, with the entire box range for NSAIDs contained within the box and whiskers range for antihistamines (see Fig. 5).

Principal coordinates analysis (PCoA) is a method to analyze and visualize similarities or dissimilarities within a data pool. Principal coordinates analysis is also known as metric multidimensional scaling, and represents inter-object (dis)similarity in a low-dimensional, Euclidean space [33,34]. PCoA can preserve distances generated from any (dis)similarity measurements, allowing more flexible handling of complex data [33,34]. In addition, (dis)similarity matrices calculated from quantitative, semi-quantitative, qualitative, or mixed variables, all can be analyzed by PCoA [33]. Interpretation of a PCoA plot is straightforward: objects ordinated closer to one

another are more similar than objects ordinated further away [34]. PCoA is suitable for handling a wide range of data [33].

PCoA with 95% ellipses, shown in Fig. 6, analyze the properties of Table 1. Here it is clearly shown that all drugs, save for **9**, **23**, **30**, and **31**, fall inside the 95% confidence ellipses. Drugs **9**, **23**, and **30** are antihistamines, whereas **31** is a NSAID, do not adhere to the overall 95% confidence ellipses encompassing all other drugs. This outcome suggests that drugs **9**, **23**, **30**, and **31** are unusual and would not be considered into a 95% confidence ellipses based on molecular properties (not be within the expected 95% confidence of outcomes for these types of drugs). This outcome shows a striking similarity of molecular properties and consistency within each group of drug both separately and when consider altogether.

Interestingly, K-means cluster analysis for similarity showed drugs **9** and **30** to be most similar and found in the same cluster 6 (see previous). However, drugs **23** and **31** were found to be more dissimilar and found in two separate clusters of cluster 2 and cluster 5, respectively. Pattern recognition methods are useful for identifying underlying relationships among multivariate data matrix and finely identify discrete dissimilarities among its members.

By box plot the maximum and minimum values of molecular weight, Log P, and polar surface area substantially or completely overlaps comparing NSAIDs to antihistamines. These three properties are represented in the RO5 criteria for drug-likeness (polar surface area by nON and number of -OH and -NH_n) [29]. Again, this portends to bio-activity being highly similar in nature, however, the mechanism of activity governs the realized biological activity which for NSAIDs is inhibition of COX-1 and COX-2 enzymes, and antihistamine activity for allergy treatment. For predicting novel drug structures it is important to consider the position of atoms in formation of the pharmacophore functional group. Simply applying analogous parameters of the molecular descriptors is not sufficient to ensure the desired biological activity. Each group of drugs should be consider separately in order to increase the likelihood of acquiring the desired biological activity, when applying various numerical tools for prediction of pharmacological properties.

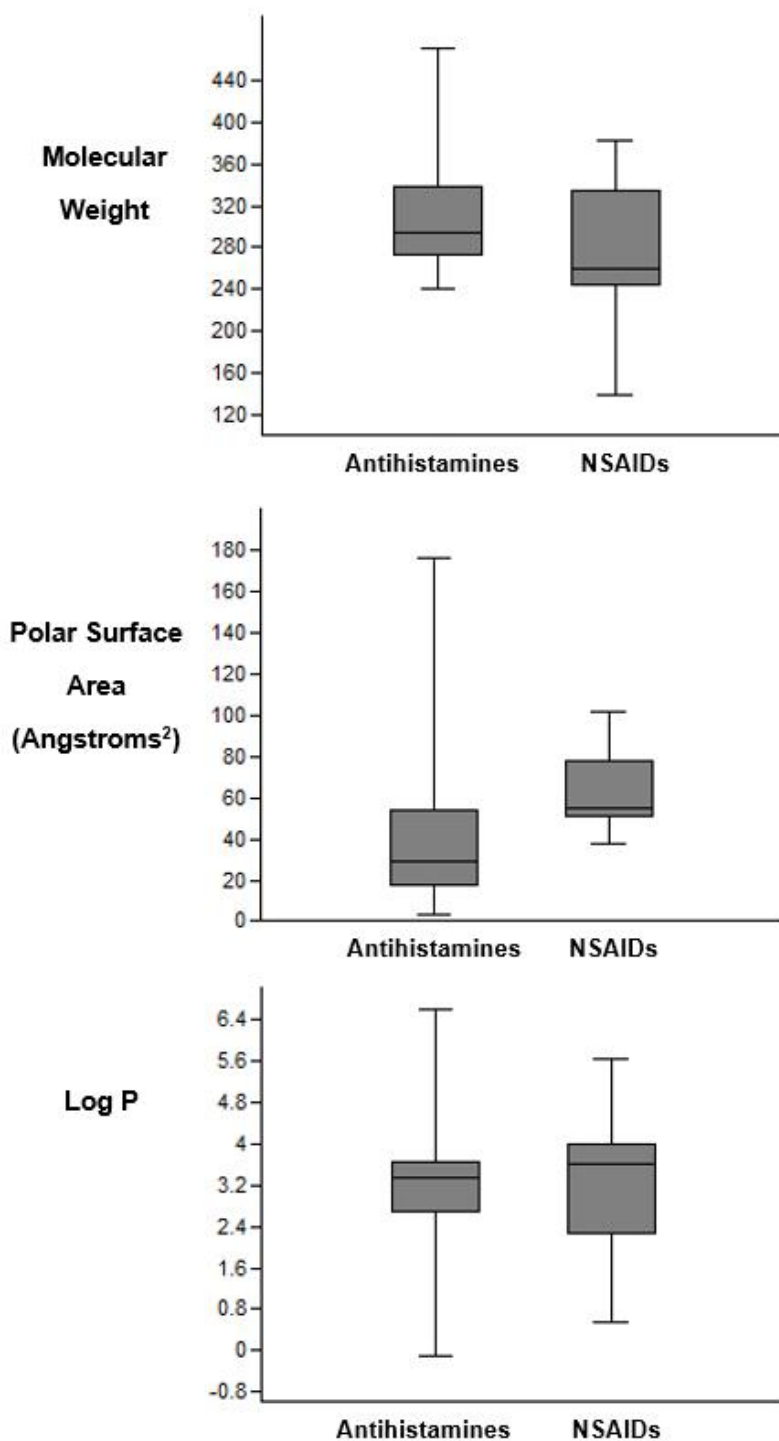


Fig. 5. Boxplots (box and whisker plot) of molecular weight, polar surface area, and Log P; for comparison of antihistamines to NSAIDs. The minimum and maximum values indicated by the whiskers ends. The first quartile found from the minimum value to the lower box end, the third quartile is from upper box end to maximum value. The median indicated by solid line within the box itself

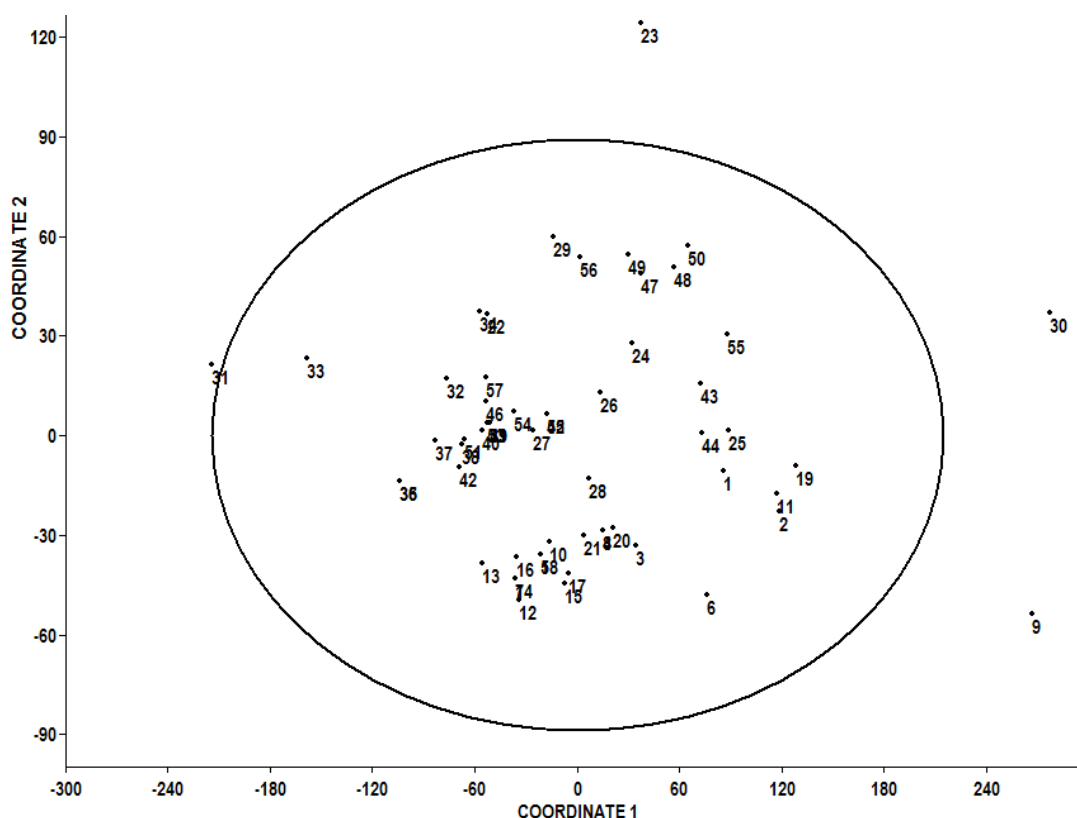


Fig. 6. Principal coordinates analysis with 95% ellipses for all compounds of Table 1. Closest proximity indicates most similar agents. The 95% confidence ellipses is the smallest ellipses that will cover 95% of the points. Only drugs 9, 23, 30, and 31 fall outside the 95% ellipses

The neighbor-joining cluster analysis (NJ) is a distance based method requiring and based on a current distance matrix [35]. NJ finds the least distant pair or the closest neighbors and creates a new node on the tree joining the two closest nodes with the two nodes linked through their common ancestral node [35]. Advantages of NJ are [35]: fast (suited for large datasets), does not require ultra-metric data, suited for datasets comprising lineages with largely numerical varying rates, and permits correction for multiple substitutions.

In this approach to cluster analysis, the objects (drugs) are arranged in branches having those of highest similarity [35]. The range (length) or distance of the individual branches are an indicative of the closeness (similarity) of individual members. The outcome of NJ analysis produced four branches, having drugs as follows in order beginning from most distant object (antihistamines in bold): **1) drugs 30, 9, 19, 2, 11, 24, 1, 6, 43, 44, 3, 14, 8, 20, 29, 21, 14, 17, 10, 5, 18, 7, 14, 12, 16, and 13;** **2) 23, 55, 50, 48, 47,**

49, 24, 29, 56, 26, 45, 52, 27, 54, 53; **3) 31, 33, 35, 36, 37, 32, 42, 38, 51;** **4) 22, 34, 57, 46, 39, 41, and 40.**

By utilizing NJ, the differences (i.e. dissimilarity) between NSAIDs and antihistamines becomes apparent. Noticeably, the NSAIDs dominate branches 2, 3, and 4. Antihistamines dominate branch 1, with a minimal number found in branches 2 and 4 (no antihistamine found in branch 3). NJ is able to distinguish these groups into separate groups, which follow intuitive reasoning based upon their separate and different biological activity. Therefore, even though the molecular properties are highly similar, analysis by NJ successfully shows an expected departure of similarity that corresponds to their quite different biological activity. It is important to understand for future purposes of drug design to realize that likeness in molecular properties does not assure similar biological activity and each group of drugs should be consider separately.

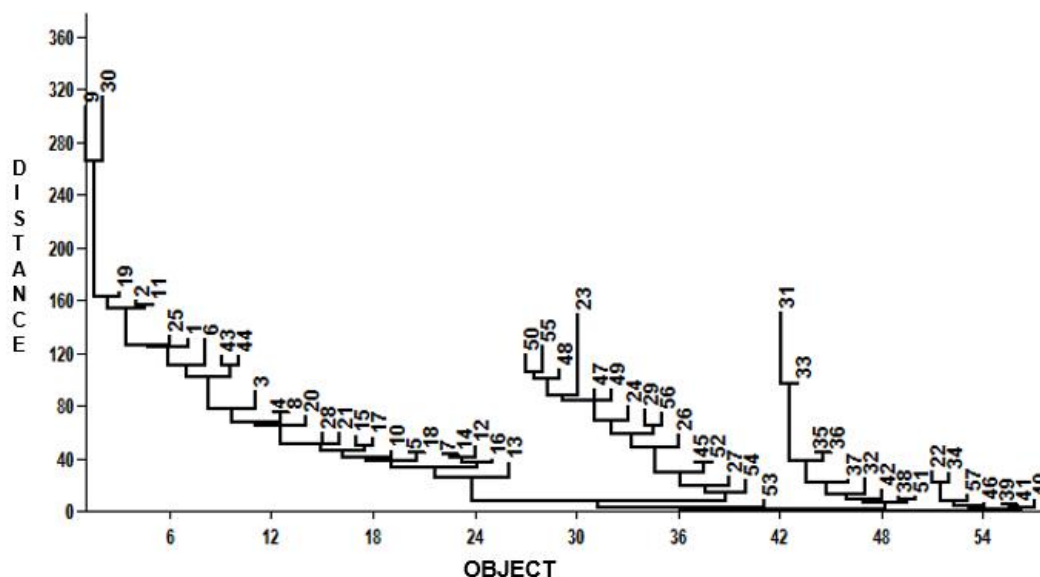


Fig. 7. Neighbor joining cluster analysis of all 57 compounds shown in Table 1. Identity of drugs most similar to another drug (based on molecular properties) are closest to each other and contained within the same branch

To distinguish what drugs are most similar by molecular properties is a useful endeavor for relating bioavailability. However, the pattern recognition methods will not identify pharmacological active functional groups within the whole of the molecular structure. For both NSAIDs and antihistamines, the arrangement of atoms, even similar atoms, within the molecular framework (i.e. formation of the pharmacophore) will dictate the anti-inflammatory or antihistamine activity of the drug.

The actual prediction of new molecular structures would then be greatly aided by application of techniques such as multiple regression, to be discussed next. An advantage of multiple regression here is the continued use of determined molecular properties (see Table 1), but with the concurrent calculation of accompanying descriptors to match the overall framework of the desired pharmacological activity (i.e. NSAID or antihistamine).

3.3 Molecular Regression Analysis and Prediction

3.3.1 Antihistamines

Multiple regression analysis is a powerful technique for predicting the value of a dependent variable (or outcome variable) from the known value of two or more independent variables, also

referred to as predictor variables [36,37]. In this analysis, the predictors such as Log P and polar surface area, have significance as pharmaceutical properties. For compounds **1** to **30**, and utilizing the properties given in Table 1, we can form analysis with independent variables Log P, polar surface area (PSA), number of atoms (nAtoms), number of oxygen & nitrogen atoms (nON), number of -OH and -NH_n, molecular weight (MW), molecular volume (MV), and number of rotatable bonds (nRotB):

$$MW = 16.100 + 19.358(\text{LogP}) + 1.145(\text{PSA}) - 10.663(\text{nAtoms}) + 4.418(\text{nON}) - 8.066(\text{nOHNH}) - 3.265(\text{nRotB}) + 1.479(\text{MV}) \quad (1)$$

The relationship (1) shows an R² of 0.9377, indicating the model accounts for 93.77% of the variance in dependent variable MW based on the model. The independent variables of greatest significance are the Log P (*P*=.02) and molecular volume (*P*=.01). The prediction of novel drug structures can be accomplished, with calculation of these important properties as each independent variable is modified, to get the final dependent variable molecular weight (MW).

3.3.2 Non-steroidal anti-inflammatory drugs

For compounds **1** to **30**, and utilizing the properties given in Table 1, we can form analysis with independent variables Log P, polar surface

area (PSA), number of atoms (nAtoms), number of oxygen & nitrogen atoms (nON), number of –OH and –NH_n, molecular volume (MV), and number of rotatable bonds (nRotB):

$$\begin{aligned} MW = & -55.633 + 2.750(\text{LogP}) - 0.2267(\text{PSA}) \\ & + 9.206(\text{nAtoms}) + 8.629(\text{nON}) + \\ & 11.892(\text{nOHNH}) - 3.055(\text{nRotB}) + \\ & 0.4958(\text{MV}) \end{aligned} \quad (2)$$

The relationship (2) shows an R² of 0.9740, indicating the model accounts for 97.40% of the variance in MW based on the model. The independent variables of greatest significance are the constant (P=.02) and the number of atoms (P=.01). Regression coefficients represent the mean change in the response variable for one unit of change in the predictor variable while holding other predictors in the model constant [36]. Again, it is now possible to predict parameters for novel drugs by inserting the appropriate independent variable values, followed by solving for the dependent variable (MW).

Prediction by multiple regression has been shown to be effective in establishing numerical values for variables selected by investigators [36]. Causality is a different matter, however, and it has been demonstrated by NJ that these two groups of drugs can be differentiated despite their great similarity in various molecular properties. The use of multiple regression algorithms is effective for generating legitimate numerical values based on the model. However, that does not ensure by itself the creation of a new drug structure having the same biological activity. The position of the atoms is important when pursuing a pharmacophore effective for the desired biological activity. Nevertheless, the consideration of known proven drug designs can guide the assimilation of atoms into novel structures suitable for clinical usage. Formation of an effective pharmacophore as well as the appropriate molecular properties go hand in hand in the design of novel drugs.

Pattern recognition methods have much to contribute to design of new pharmaceuticals. This is particularly true for studies involving calculation and collation of data that becomes easier with the widespread use of computer databases, molecular modeling systems, and property prediction packages, this for both biological and physicochemical fields [38]. The wider use and understanding of these methods should enhance their utility in drug design [38].

4. CONCLUSION

Antihistamines and NSAIDs are two groups of drugs highly important for public health. A comparison of 30 antihistamines to 27 NSAIDs showed important similarities useful for design of novel drug structures. One-way ANOVA and Kurskal-Wallis test showed that means and medians of Log P and number of oxygen & nitrogen atoms of these two groups are equal. Properties NSAIDs showed high level of consistent values, with no outliers for Log P, polar surface area, molecular weight, molecular volume, and numbers of –OH, –NH_n, rotatable bonds, and atoms. However, antihistamines showed outliers in all properties except Log P and number of rotatable bonds. Multiple regression produced algorithms for both groups accounting for over 93% of variance in molecular weight. Box plots showed substantial overlap of values for the two groups of drugs for molecular weight, polar surface area, and Log P. K-means cluster analysis showed that members of antihistamines are most similar to members of NSAIDs. Similarity among members of the two groups is visualized in neighbor joining tree cluster analysis. Principal coordinates analysis with 98% ellipses showed clearly that all members of the 57 drugs studied (save for **9, 23, 30, 31**) would fall within a 95% confidence area based upon molecular properties. This study reveals relationships between antihistamines and NSAIDs useful for understanding their pharmacological activity and the design of novel molecular structures.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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