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On the Possible Chemical Similarity of Some Common Antiepileptic Drugs

Demetrios Xenides^{1,2,a)} and Panagiotis Karamanis^{3,b)}

¹⁾High School of Oinousses, Chios, 82101, Greece

²⁾Laboratory of Predictive Analytics and Complex Systems, Department of Economics, School of Management and Economics, University of Peloponnese, Tripolis Campus, Tripolis, 22100, Greece

³⁾CNRS/ UNIV Pau & Pays Adour, Institut Des Sciences Analytiques et de Physico-Chimie pour l'environnement et les Matériaux, UMR5254, Pau, 64000, France.

^{a)}Corresponding author: xenides@uop.gr

^{b)}panagiotis.karamanis@univ-pau.fr

Abstract. Epilepsy is a disease that affects approximately 50 million people in developing countries. Though the exact mechanism has not been yet discovered, it should be said that some light has been shed on its cellular and network mechanisms. As a cause of this there are several drugs that manage to stop seizures happening, however they do not cure epilepsy. Furthermore, most of these drugs are known to cause serious side effects (i.e. birth defects when the therapy occurs during pregnancy). In the present study we are aiming on a classification of 31 of the available drugs by studying their chemical similarity. For this reason we apply a rigorous approach based on tools from mathematical analysis: in particular the metric space approach.

INTRODUCTION

Epilepsy affects the life of a vast number of people, thus lot of effort has been put on the elucidation of its mechanism. However, only some light has been shed on its cellular [1] and network mechanisms [2]. There are some drugs that have been developed as to either prolong the interval between crisis or to calm the intense of the seizures. As it is obvious to find patients in order to test the performance of different drugs, could not be seen as a trivial task. Thus, another approach should be applied and this is the path paved by computational and theoretical chemistry. Therefore, we made a group of 31 of these drugs taken from a recent study by Balasubramanian et al [3] who approached their structure activity relations via omega polynomials and topological indices.

In a recent study from our group (see Ref. [4]) we investigated the structural and chemical similarity of some analgesic and euphoric compounds. This expertise will support our aims at finding the possible patterns between the available antiepileptic drugs. For this reason we will rely on some physicochemical properties of these compounds. By doing this we will be able to approach their chemical similarity. This effort we will be supported by the metric space approach.

COMPUTATIONAL PROTOCOL

Chemical Compounds

The test set contains the following compounds: Acetazolamide (1), Brivaracetam (2), Cannabidiol (3), Carbamazepine (4), Clobazam (5), Clonazepam (6), Eslicarbazepine acetate (7), Ethosuximide (8), Everolimus (9), Gabapentin (10), Lacosamide (11), Lamotrigine (12), Levetiracetam (13), Oxcarbazepine (14), Perampanel (15), Phenobarbital (16), Phenytoin (17), Piracetam (18), Pregabalin (19), Primidone (20), Rufinamide (21) Stiripentol (22), Tiagabine (23), Topiramate (24), Valproic acid (25), Vigabarin (26), Zonisamide (27), Lorazepam (28), Diazepam (29), Retigabine (30), Felbamate (31).

For each one of them we have used their following properties (all properties have been taken from chemspider.com [5]):

- density in g/cm^3
- logP: ACD/LogP predicts the partition coefficient, a measure of hydrophobicity, from structure.

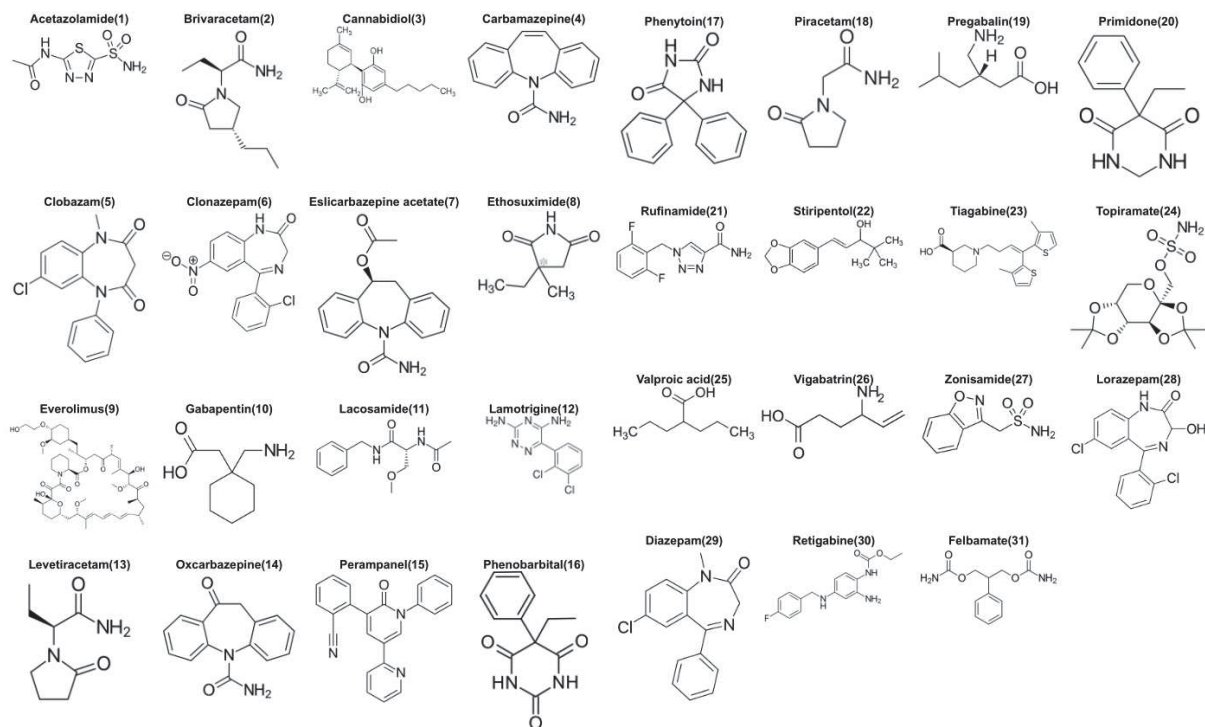


FIGURE 1. 2D Structures of Compounds

- index of refraction
- polarizability in 10^{-24}cm^3

The whole set of properties has been tabulated in Table I

Metric Space Approach

In order to quantify the similarity of compounds we relied upon a well established method [4, 6, 7, 8, 9, 10, 11, 12, 13] based on the metric space approach. In brief each compound has been transformed into a vector. This vector refers to a 4D space that is formed by the independent coordinates-values of the physicochemical properties: density, logP, Index of Refraction (IoR) and Polarizability (Pol). The distance between objects of an n-dimensional ($n=4$) is $d_{i,j}: \mathbb{R}^n \times \mathbb{R}^n \rightarrow \mathbb{R}^+$ and has been calculated via the Euclidean metric in the following form:

$$d_{i,j} = \left(\sum_p \frac{(x_{i,p} - x_{j,p})^2}{\max_{i,j} \{x_{i,p} - x_{j,p}\}^2} \right)^{1/2}, \quad i, j \in (\text{compounds}), \quad p \in (\text{properties}), \quad i \neq j \quad (1)$$

The denominator of Eq. 1 turns the $d_{i,j}$ into a plain number. To convert the distance between two methods to proximity or similarity we can use the following relation:

$$S_{i,j} = 1 - \frac{d_{i,j}}{\max_{i,j} d_{i,j}}, \quad i \neq j \quad (2)$$

Thus, we have plain real numbers in the region of $[0, 1]$ as a measure of the similarity of two methods.

TABLE I. Properties of 31 compounds used in the present study.

Properties	Compounds										
	1	2	3	4	5	6	7	8	9	10	
Density	2.0	1.1	1.0	1.3	1.3	1.5	1.3	1.1	1.2	1.1	
LogP	-0.69	0.88	7.03	2.67	1.69	2.34	0.93	0.38	3.35	1.19	
IoR ^a	1.811	1.494	1.545	1.670	1.627	1.701	1.655	1.451	1.548	1.489	
Pol ^b	18.9	23.1	38.5	27.6	31.7	32.2	32.5	14.3	102.2	18.5	
Properties	11	12	13	14	15	16	17	18	19	20	
Density	1.1	1.6	1.2	1.3	1.3	1.2	1.3	1.2	1.0	1.2	
LogP	0.90	-0.29	-0.67	1.44	3.70	1.67	2.29	-1.55	1.12	0.03	
IoR	1.520	1.706	1.519	1.662	1.706	1.542	1.652	1.523	1.465	1.603	
Pol	26.9	25.1	17.5	27.8	40.8	23.5	28.7	13.9	17.5	24.1	
Properties	21	22	23	24	25	26	27	28	29	30	
Density	1.5	1.1	1.2	1.3	0.9	1.1	1.5	1.5	1.3	1.3	
LogP	0.05	3.39	5.68	2.97	2.72	-0.10	-0.10	1.93	2.91	0.81	
IoR	1.635	1.579	1.605	1.497	1.435	1.483	1.656	1.694	1.635	1.656	
Pol	22.2	27.1	42.4	29.5	16.1	13.7	20.5	32.1	32.1	33.8	
Properties	31										
Density	1.3										
LogP	1.20										
IoR	1.55										
Pol	23.9										

^a Index of Refraction^b Polarizability**TABLE II.** Similarity ($S_{i,j}$) values between 31 compounds.

Compound	Compound																														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
1	1.00	0.20	0.00	0.43	0.42	0.55	0.46	0.14	0.01	0.19	0.23	0.69	0.28	0.46	0.39	0.28	0.43	0.28	0.11	0.38	0.55	0.23	0.19	0.23	0.01	0.19	0.38	0.56	0.39	0.46	0.36
2	0.20	1.00	0.49	0.63	0.72	0.53	0.68	0.89	0.36	0.96	0.95	0.50	0.85	0.67	0.52	0.88	0.67	0.78	0.91	0.78	0.64	0.75	0.54	0.79	0.78	0.89	0.70	0.55	0.67	0.67	0.83
3	0.00	0.49	1.00	0.54	0.51	0.44	0.45	0.42	0.36	0.50	0.50	0.25	0.36	0.47	0.57	0.55	0.54	0.29	0.49	0.42	0.34	0.69	0.80	0.61	0.57	0.39	0.39	0.43	0.59	0.44	0.49
4	0.43	0.63	0.54	1.00	0.89	0.86	0.86	0.54	0.38	0.63	0.67	0.70	0.61	0.90	0.86	0.75	0.96	0.56	0.56	0.75	0.75	0.79	0.71	0.69	0.50	0.57	0.74	0.85	0.93	0.84	0.77
5	0.42	0.72	0.51	0.89	1.00	0.81	0.92	0.62	0.42	0.70	0.76	0.72	0.70	0.93	0.78	0.82	0.93	0.65	0.64	0.84	0.81	0.80	0.67	0.75	0.55	0.65	0.79	0.83	0.90	0.91	0.86
6	0.55	0.53	0.44	0.86	0.81	1.00	0.82	0.45	0.37	0.53	0.57	0.78	0.54	0.84	0.82	0.65	0.85	0.50	0.46	0.68	0.77	0.66	0.63	0.61	0.38	0.48	0.67	0.97	0.82	0.81	0.70
7	0.46	0.68	0.45	0.86	0.92	0.82	1.00	0.59	0.40	0.66	0.72	0.77	0.70	0.95	0.76	0.77	0.89	0.66	0.60	0.85	0.83	0.73	0.60	0.67	0.50	0.63	0.83	0.84	0.84	0.99	0.81
8	0.14	0.89	0.42	0.54	0.62	0.45	0.59	1.00	0.27	0.90	0.84	0.44	0.84	0.58	0.42	0.79	0.58	0.79	0.91	0.71	0.58	0.66	0.45	0.72	0.78	0.93	0.63	0.47	0.57	0.58	0.75
9	0.01	0.36	0.42	0.38	0.42	0.37	0.40	0.27	1.00	0.33	0.39	0.24	0.28	0.37	0.45	0.38	0.40	0.22	0.30	0.34	0.29	0.42	0.50	0.43	0.29	0.26	0.29	0.37	0.44	0.40	0.81
10	0.19	0.96	0.50	0.63	0.70	0.53	0.66	0.90	0.33	1.00	0.91	0.49	0.83	0.66	0.51	0.87	0.66	0.77	0.92	0.76	0.63	0.63	0.55	0.80	0.80	0.89	0.68	0.54	0.66	0.65	0.82
11	0.23	0.95	0.50	0.67	0.76	0.57	0.72	0.84	0.39	0.91	1.00	0.54	0.84	0.71	0.57	0.90	0.71	0.77	0.86	0.82	0.67	0.78	0.57	0.79	0.74	0.86	0.74	0.59	0.71	0.72	0.86
12	0.69	0.50	0.25	0.70	0.72	0.78	0.77	0.44	0.24	0.49	0.54	1.00	0.58	0.76	0.62	0.59	0.71	0.57	0.42	0.69	0.85	0.52	0.42	0.51	0.30	0.49	0.68	0.81	0.66	0.77	0.66
13	0.28	0.85	0.36	0.61	0.70	0.54	0.70	0.84	0.28	0.83	0.84	0.58	1.00	0.68	0.48	0.65	0.65	0.93	0.79	0.83	0.71	0.65	0.44	0.69	0.64	0.90	0.74	0.57	0.63	0.69	0.82
14	0.46	0.67	0.47	0.90	0.93	0.84	0.95	0.58	0.37	0.66	0.71	0.76	0.68	1.00	0.78	0.77	0.93	0.64	0.59	0.83	0.82	0.75	0.63	0.68	0.51	0.62	0.82	0.86	0.87	0.93	0.81
15	0.39	0.52	0.57	0.86	0.78	0.82	0.76	0.42	0.45	0.51	0.57	0.62	0.48	0.78	1.00	0.63	0.83	0.43	0.46	0.63	0.63	0.72	0.75	0.61	0.42	0.44	0.63	0.80	0.84	0.75	0.65
16	0.28	0.88	0.55	0.75	0.82	0.65	0.77	0.79	0.38	0.87	0.90	0.59	0.81	0.77	0.60	1.00	0.78	0.73	0.80	0.83	0.72	0.84	0.63	0.85	0.72	0.80	0.74	0.66	0.79	0.76	0.92
17	0.43	0.67	0.54	0.96	0.93	0.85	0.89	0.58	0.40	0.66	0.71	0.71	0.65	0.93	0.83	0.78	1.00	0.60	0.60	0.79	0.78	0.80	0.70	0.72	0.53	0.61	0.77	0.85	0.94	0.88	0.81
18	0.28	0.78	0.29	0.56	0.65	0.50	0.66	0.79	0.22	0.77	0.77	0.57	0.93	0.64	0.43	0.73	0.60	1.00	0.73	0.79	0.69	0.58	0.37	0.62	0.58	0.85	0.72	0.53	0.57	0.66	0.75
19	0.11	0.91	0.49	0.56	0.64	0.46	0.60	0.91	0.30	0.92	0.86	0.42	0.79	0.59	0.46	0.80	0.60	0.73	1.00	0.71	0.56	0.71	0.51	0.74	0.85	0.88	0.64	0.47	0.60	0.59	0.75
20	0.38	0.78	0.42	0.75	0.84	0.68	0.85	0.71	0.34	0.76	0.82	0.69	0.83	0.83	0.63	0.83	0.79	0.79	1.00	0.81	0.72	0.53	0.69	0.58	0.76	0.88	0.71	0.75	0.85	0.86	
21	0.55	0.64	0.34	0.75	0.81	0.77	0.83	0.58	0.29	0.63	0.67	0.85	0.71	0.82	0.63	0.72	0.78	0.69	0.56	0.81	1.00	0.62	0.49	0.64	0.44	0.63	0.75	0.80	0.73	0.83	0.80
22	0.23	0.75	0.69	0.79	0.80	0.66	0.73	0.66	0.42	0.75	0.78	0.52	0.65	0.75	0.72	0.84	0.80	0.58	0.71	0.72	0.62	1.00	0.77	0.80	0.70	0.66	0.69	0.66	0.83	0.72	0.78
23	0.19	0.54	0.80	0.71	0.67	0.63	0.60	0.45	0.50	0.55	0.57	0.42	0.44	0.63	0.75	0.63	0.70	0.37	0.51	0.53	0.49	0.77	1.00	0.69	0.53	0.45	0.50	0.61	0.75	0.60	0.61
24	0.23	0.79	0.61	0.69	0.75	0.61	0.67	0.72	0.43	0.80	0.79	0.51	0.69	0.68	0.61	0.85	0.72	0.62	0.74	0.69	0.64	0.80	0.69	1.00	0.71	0.70	0.60	0.62	0.75	0.67	0.82
25	0.01	0.78	0.57	0.50	0.55	0.38	0.50	0.78	0.29	0.80	0.74	0.30	0.64	0.51	0.42	0.72	0.53	0.58	0.85	0.58	0.44	0.70	0.53	0.71	1.00	0.73	0.53	0.39	0.55	0.49	0.64
26	0.19	0.89	0.39	0.57	0.65	0.48	0.63	0.93	0.26	0.89	0.86	0.49	0.90	0.62	0.44	0.80	0.61	0.85	0.88	0.76	0.63	0.66	0.45	0.70	0.73	1.00	0.68	0.50	0.59	0.63	0.78
27	0.38	0.70	0.39	0.74	0.79	0.67	0.83	0.63	0.29	0.68	0.74	0.68	0.74	0.82	0.63	0.74	0.77	0.72	0.64	0.88	0.75	0.69	0.50	0.60	0.53	0.68	1.00	0.69	0.72	0.83	0.76
28	0.56	0.55	0.43	0.85	0.83	0.97	0.84	0.47	0.37	0.54	0.59	0.81	0.57	0.86	0.80	0.66	0.85	0.53	0.47	0.71	0.80	0.66	0.61	0.62	0.39	0.50	0.69	1.00	0.82	0.83	0.72
29	0.39	0.67	0.59	0.93	0.90	0.82	0.84	0.57	0.44	0.66	0.71	0.66	0.63	0.87	0.84	0.79	0.94	0.57	0.60	0.75	0.73	0.83	0.75	0.75	0.55	0.59	0.72	0.82	1.00	0.83	0.80
30	0.46	0.67	0.44	0.84	0.91	0.81	0.99	0.58	0.40	0.65	0.72	0.77	0.69	0.93	0.75	0.76	0.88	0.66	0.59	0.85	0.83	0.72	0.60	0.67	0.49	0.63	0.83	0.83	1.00	0.81	0.81
31	0.36	0.83	0.49	0.77	0.86	0.70	0.81	0.75	0.38	0.82	0.86	0.66	0.82	0.81	0.65	0.92	0.81	0.75	0.75	0.86	0.80	0.78	0.61	0.82	0.64	0.78	0.76	0.72	0.80	0.81	1.00

DISCUSSION

In Table II we have collected similarity values between the compounds used in the present study. The larger the value the higher the similarity between two compounds. Only values equal to or larger than 0.90 would be discussed.

The Acetazolamide (AZM) (1) is quite dissimilar to all other compounds, however what is worth noticing is the very low similarity between Acetazolamide and Zonisamide (ZNS) (27). This is interesting since both compounds have the same exotic group $-SO_2(NH_2)$: the respective similarity value is $S_{1,27} = 0.378$. This is in perfect accordance to the observation that ZNS is 100–1,000 times less potent than AZM [14]. Another compound that is chemical

dissimilar to all other is Everolimus (9). This is in accordance to its structure that is unique.

Next compound is Brivaracetam (2) which quite similar to Gabapentin (10) ($S_{2,10} = 0.956$), Lacosamide (11) ($S_{2,11} = 0.995$) and Pregabalin (19) ($S_{2,19} = 0.907$). The high similarity to Lacosamide further supported by their common structural features, this is also manifested in a study towards [15] their common effects on lactation during pregnancy.

The Carbamazepine (4) shows some similarity to Oxcarbazepine (14) ($S_{4,14} = 0.902$), Phenytoin (17) ($S_{4,17} = 0.995$) and Diazepam (29) ($S_{4,29} = 0.926$). The most similar from the structural point of view are 4 to 14, however they do not show the highest chemical similarity. The Carbamazepine and Phenytoin they are virtually identical in anticonvulsant and neurotoxic activity as it was shown in an old study by Morris et al [16].

Then we found Clobazam (5) that is quite similar to Eslicarbazepine acetate (7) ($S_{5,7} = 0.921$), Oxcarbazepine (14) ($S_{5,14} = 0.928$), Phenytoin (17) ($S_{5,17} = 0.931$), Diazepam (29) ($S_{5,29} = 0.903$) and Retigabine (30) ($S_{5,30} = 0.912$). We note that Clobazam and Diazepam are quite similar when we are considering the structure, however this is not the case when we are taking into account the chemical similarity. On the other hand Clobazam and Phenytoin exhibit the same efficacy in the treatment of childhood epilepsy [17].

Another compound of interest is Clonazepam (6) that only matches to Lorazepam (28) ($S_{6,28} = 0.965$). It is pro-found that chemical and structural similarity are going hand by hand in this case. Furthermore, in a recent study by Alvarez et al [18] they found that these two compounds have the same efficacy as first-line treatment for status epilepticus.

An exotic structure that comes next is Ethosuximide (8). Its properties show some similarity to these from Gabapentin (10) ($S_{8,10} = 0.901$), Pregabalin (19) ($S_{8,19} = 0.908$) and Vigabatrin (26) ($S_{8,26} = 0.931$). In a study by Swiader et al [19] they found that acute treatment of Vigabatrin along with Ethosuximide may enhance the anti-convulsant activity of the latter.

Gabapentin (10) while structural dissimilar to Lacosamide (11) they are showing a $S_{10,11} = 0.912$ value. This is also the case when compared to Pregabalin with a ($S_{10,19} = 0.924$) value. This high similarity is further advocated by a study by Ifucu et al [20] on the analgesic action of Gabapentin and Pregabalin, where the latter used instead of the former and found six times more potent.

On the other hand Lacosamide (11) shows a $S_{11,19} = 0.912$ value towards Pregabalin, that supports the fact that both exhibit anticonvulsant activity.

Of some interest is the accordance between structural and chemical similarity of Levetiracetam (13) and Piracetam (18): $S_{13,18} = 0.925$. However in a recent study they have been found to exhibit different pharmacological and clinical profiles [21].

Potentially different in structure are Oxcarbazepim (14) and Phenytoin (17) while their $S_{14,17} = 0.930$. This chemical similarity has been also observed in a study by Nevitt et al [22], who found that there is not clear difference between them in aspect of side effect, seizure recurrence and seizure remission.

Finally, Phenytoin (17) and Diazepam (29) are quite similar when we are talking about chemical similarity: $S_{17,29} = 0.937$. In addition, the former enhances the activity of the latter as it has been know since 1982 [23].

CONCLUSION

We have made a group of 31 drugs that are quite common in the fight against epilepsy and its symptoms. We approached their similarity via selected physicochemical properties. Quite distinct similarities have been found and some subgroups have been formed. The largest subgroup is one that contains Oxcarbazepine, Carbamazepine, Clobazam, Eslicarbazepine acetate, Phenytoin and Diazepam. Another one is made by Brivaracetam, Gabapentin, Lacosamide and Pregabalin. This Pregabalin could also be grouped with Diazepam, Oxcarbazepine, Carbamazepine and Clobazam. On the other hand we note two compounds, Acetazolamide and Everolimus, that are similar only to themselves. These subgroups could assist experts as to provide the proper medication to patients, thus improving their quality of life,

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