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MECHANISTIC TRENDS IN ANTICANCER ACTIVITY OF SOME KNOWN DIHYDROPHENANTHRIDINETRIONES (DPT); A CLUSTERED QSAR ANALYSIS

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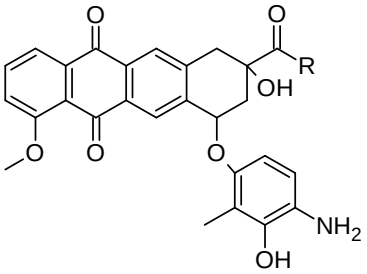
ABSTRACT

The anticancer activity trends of 24 known 3,4-dihydrophenanthridine-1,7,10(2H)-triones were analyzed through QSAR methodology. Their anticancer activity against human gastric adenocarcinoma (AGS) cell line as IC_{50} was regressed with the logarithm of their octanol/water partition coefficient (log P) and molar refractivity (MR). Statistical metrics show poor correlation (R^2=0.14 for Log P and R^2=0.37 for MR and R^2 =0.38 for both Log P and MR combined). As these compounds show good activity against AGS cell line, clustering was utilized to expose possible mechanistically distinct subgroups nesting inside the main data set. This was done through a kind of a previously reported regression clustering procedure based on log P which was chosen owing to its wide-spread use in QSAR. This procedure was found to yielded four clusters with high R^2 values (~ 0.8) which exhibit distinct trends in their respective regression lines suggesting different operational mechanism for each. Molar refractivity was used afterwards to give depth to the clustering procedure through emphasizing the distinction of each clusters from the others.

KEYWORDS: dihydrophenanthridinetriones (DPT), anticancer activity, clustered regression analysis, QSAR.

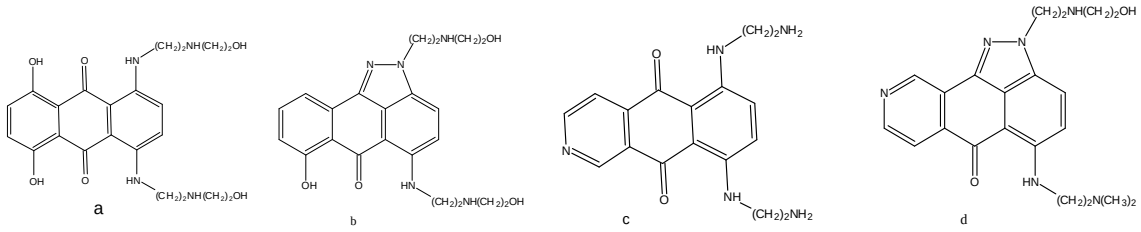
INTRODUCTION

Quinone-containing intercalating anticancer agents have received tremendous interest since the advent of anthracycline era in early 1960`s.[1] anthracyclines comprise several potent agents such as daunorubicin1a and doxorubicin 1b which are used in the treatment of several types of tumours.[2]



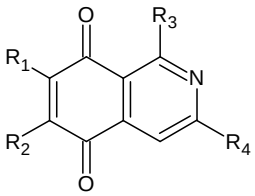
1 a R=H daunorubicin, b R=OH doxorubicin

These agent, however, exhibited several adverse effects, chief among which dose-dependent cadiotoxicity.[3] This warrants a fervent search for a "better anthracycline" with enhanced therapeutic effects and subdued adverse ones which culminated in the emergence, alongside several members of anthracycline class, of many related classes such as dialkylaminoalkyl anthracenediones, anthrapyrazoles and their aza analogues.[4] The representatives of each are mitoxantrone[5] 2a, losoxantrone[6]2b, pixantrone[7] 2c and BBR 3576[8] 2d respectively.



2 a Mitoxantrone b Losoxantrone c Pixantrone d BBR 3576

The aza analogues mentioned above contains, in addition to quinone or quasi quinone moiety, isoquinoline scaffolds which appear in some naturally occurring as well as synthetic anticancer agents. For instance, cribrostatin 3[9] 3a, caulibugulone A[10] 3b, and mansouramycin C[11] 3c are characterized with these structural features in addition of the presence of amino side chains.

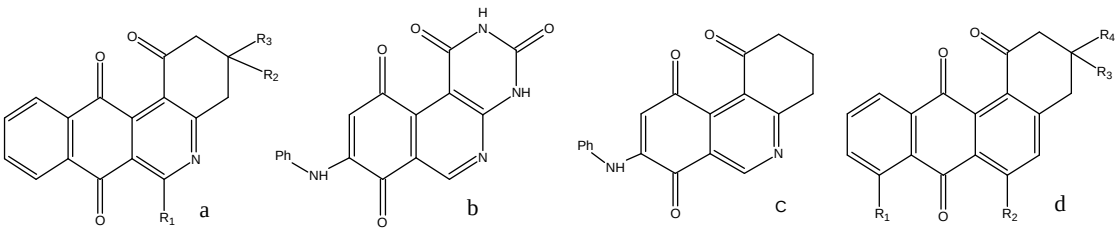


3 a R_1 = Me, R_2= NH_2, R_3=ethyl (2*Z*)-2-methylbut-2-enoate, R_4= H Cribrostatin 3

b R_1 = MeNH, R_2= H, R_3= H, R_4= H Caulibugulone A

c R_1 = MeNH, R_2= H, R_3= H, R_4= CO_2Me Mansouramycin C

Synthetic phenanthridine-7,10-quinones were reported to exert powerful cytotoxicity against breast (MCF-7), lung (NCI-H460, A549), brain (SF268), prostate (DU145), and epothilone-resistant ovarian (A8) cancer cell lines.[12] Valderrama and co-worker synthetically incorporate isoquinoline quinone scaffold into 3,4-dihydrobenzo[j]phenanthridine-1,7,12(2H)-trione,[13] pyrimido[4,5-c] isoquinoline -1,3,7,10(2H,4H)-tetrone[14] and 3,4-dihydro -phenanthridine-1,7,10(2H)-trione[15] ring systems (4a, 4b,and 4c respectively; see below). Moreover, they attached various substituent at selected position. These showed good potency against a number of cancer cell lines. The ring system 4a is the synthetic aza analogue of natural occurring carbocyclic angucyclines which show a wide range of biological activity including antitumor activity. Ring systems 4b and 4c are catered with amino phenyl moiety in line with both natural and synthetic heterocyclic amino quinones mentioned earlier. All the three ring systems were testes against three human tumor cells: AGS gastric adenocarcinoma, SK-MES-1 lung carcinoma, J82 bladder carcinoma in addition normal human lung fibroblast MRC-1 cell line.



4 **a**) 3,4-dihydrobenzo[j]phenanthridine-1,7,12(2H)-trione, **b**) pyrimido[4,5-c] isoquinoline -1,3,7,10(2H,4H)-tetrone **c**) 3,4-dihydro -phenanthridine-1,7,10(2H)-trione, **d**) angucycline

Ring system 4a is generally is more potent than ring system 4b which is more potent than ring system 4a. This indicates that the presence of phenylamino moiety in both 4c and 4b ring systems enhances their activity.

The approach of incorporating two or more pharmacophoric moieties comes to be known as molecular hybridization.[16] Hybrid molecule have several potential advantages over the combination of single-targeted molecules. These include alleviation of side effects of the parent compounds, better solubility and overcoming of multi drug resistance.[17]

Quantitative structure activity/property relationships (QSAR/QSPR) is now a fully mature scientific discipline of its own.[18] QSAR is attempt to correlate molecular descriptors and/or physicochemical parameters of molecules (or drugs) to their activity in biological systems.

QSAR is used for predictive and mechanistic studies. The basic assumption of all QSAR modeling is the existence of a mathematical correlation between chemical structure and the corresponding response. The response could be biological end point or, in case of QSPR, another property.[19] There are several algorithms to determine the mathematical equation which correlate the response to molecular descriptors or physicochemical parameters of the compounds under study.[20] Examples of such algorithm are; linear regression, partial least square regression[21] and various artificial neural networks among others.[22]

In addition to regressions, QSAR may be used for classification for which there are a number of algorithms in the use. These comprises k-nearest neighbor clustering, decision tree, random forest and discriminant analysis.[23]

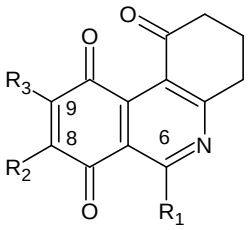
The ideal use of a QSAR model is to predict the activities of molecules not included in the building of the model or to classify them when data are treated as categoral data to obtain a yes/no answer (toxic/ not toxic, carcinogenic/not carcinogenic ……etc). if a model does not withstand statistical validation procedures, then it is must be discarded.[24] The modeler may choose to switch to other descriptors which explain the variability of biological response in a more plausible manner. The discarded model could be used to extract information regarding the existence of contradictory mechanistic subgroups or clusters whose mingling together lead to the poor validation metrics.[25][26] The present study is a continuation of our customary practice of utilizing data set unsuitable for predictive purposes to trace mechanistics trends via clustering.

METHOD

Biological activity data of DPT`s was collected from literature in the form of inhibitory concentrations for 50% of the subjects for Human gastric adenocarcinoma cell line (IC_{50}) [15]

And was transformed to their logarithms ($LogIC_{50}$) their structures were drawn and their log P and MR were calculated using ACD/chemsketch 2015 freeware. Regression analysis was performed with Microsoft Excel 2016 spreadsheet program. The structures of DTP`s is shown in table (1). Their activities and physicochemical parameters are given in table (2).

Table (1) Structures of Dihydrophenanthridine-1,7,10(2H)-triones (DPT).



No	R1	R^2	R3	No	R1	R^2	R3
1	H	H	H	13	H	H	2,2,5-DiMeO-PH-NH
2	Me	H	H	14	H	H	Ph-NMe-
3	Ph	H	H	15	H	H	Ph-NEt-
4	furan-2-yl	H	H	16	Me	Ph-NH-	H
5	thiophen-3-yl	H	H	17	Me	4-MeO-PH-NH	H
6	H	Ph-NH-	H	18	Me	4-OH-PH-NH	H
7	H	4-4-MeO-PH-NH	H	19	Me	2-MeO-PH-NH	H
8	H	2,5-DiMeO-PH-NH	H	20	Me	4-F-Ph-NH-	H
9	H	Ph-NMe-	H	21	Me	2,5-DiMeO-PH-NH	H
10	H	Ph-NEt-	H	22	Ph	Ph-NH-	H
11	H	H	Ph-NH-	23	furan-2-yl	Ph-NH-	H
12	H	H	4-MeO-PH-NH	24	thiophen-3-yl	Ph-NH-	H

Table (2): Physicochemical parameters and biological activity of DPT`s.

No	Log P	MR	$LogIC_{50AGS}$	No	Log P	MR	$LogIC_{50AGS}$
1	1.15	57.91	1.287802	13	2.45	100.49	1.517196
2	1.61	62.73	1.342423	14	2.39	91.83	0.919078
3	3.14	82.5	1.143015	15	2.92	96.47	1.232996
4	2.33	74.8	1.832509	16	2.71	91.95	-0.18709
5	2.82	80.88	1.569374	17	2.66	98.63	0.079181
6	2.25	87.13	-0.63827	18	1.96	93.84	0.079181
7	2.2	93.81	-0.3279	19	2.61	98.63	-0.65758
8	2.45	100.49	-0.49485	20	3.15	91.95	-0.10237
9	2.39	91.83	0.672098	21	2.91	105.31	0.146128
10	2.92	96.47	0.643453	22	4.24	111.72	-0.48149
11	2.25	87.13	0.591065	23	3.43	104.02	-0.23657
12	2.2	93.81	0.342423	24	3.92	110.11	-0.45593

RESULTS AND DISCUSSION

Linear regression analysis of activities against Log P and MR yields the following equations:

$\log IC_{50}$= -0.44LogP+1.57…… (1).

n=24 R^2=0.14 s=0.748 F=3.570

$\log IC_{50}$= -0.036MR+3.74 ……(2).

n=24 R^2=0.37 s=0.64 F=13.17

$\log IC_{50}$= 0.17Log P -0.04MR + 3.86….(3)

n =24 R^2 =0.38 s=0.65 F=6.57

As it is apparent from the low metrics, lipophilicity, steric /polarizability effect are not the sole players in influencing the activity of DPT`s. From the R^2 values, lipophilicity accounts for only about 14%, steric/polarizability effect accounts for 37% and their combined effect account for about 38% of the variability of the biological activity. This shows that Log P and MR are not entirely separate in exerting their effect on activity. They are somewhat collinear (R^2=0.525) but not to the degree that prevents them from being included in one and the same regression equation. Moreover, negative signs of the coefficients of Log P and MR indicate the detrimental effect of both parameters on the response.

All the 24 DPT`s included in the present study show high degree of cytotoxicity against AGS cell line. Then what is the reason for the poor metrics of the correlations of Log P and MR to IC_{50}? The answer to this question may be put as follows; either that their activity as whole is dependent on other factor/s not included in this study and we stop here or there are nesting subgroups of these compounds each exert a different mechanism in their activity against gastric carcinoma with net result manifested in lowering of the correlations. The first answer is borne out by the results of regression just described above; around 73% of the variation of biological activity is accountable for by other factors.

The justification of the second assumption need a kind of clustering to probe for the supposed mechanistically distinct nesting subgroups inside our set of DPT`s.

A plausible classification was simply performed using clustered regression analysis described previously.[25] This led to breaking the main data set down into smaller highly correlated Clusters. This segregation is indicative of a mechanistic distinction among resulted clusters or subsets. In this paper, we discuss the resulted subgroup just to enumerate their possible mechanistic trend. Cause and effect of mechanistic segregation will be the topic of a

subsequent part 2 of this analysis. We chose Log P as a base of clustering because Log P is used more frequently in QSAR analyses compared with MR.[24] The aforementioned process of clustering based on Log P yielded cluster 1-4, which will be elaborated on below.

Before we discuss every cluster individually we make general remarks about the clustering as a whole. Interestingly, the first five compounds, which carry no phenylamino side chain, partitioned into each of the four cluster in the following details; compounds 1(parent compound) and 2 (6-methyl analogue) partitioned with cluster 1 which is also consist of compounds 18,20,21,22,23 and 24. Compound 3 (6-phenyl analogue) partitioned into cluster 2 which comprises compounds 6,7,8 and 10. Compound 4 (6-furan2-yl analogue) partitioned into cluster 4 which also contains compounds 9,16,17and 19. Finally compound 5(6-Thiophen-3-yl analogue) partitioned into cluster 3 which contain compounds 11, 12, 13,14 and15. The cause behind such a partitioning may be clarified when we discuss this segregation of the main DPT data set based on quantum mechanical considerations in the subsequent part 2 of this study. The clustered regression analysis outcome appears to be very fitting considering the members of each cluster. Each cluster is generally comprised of similar members as far as the pattern of substitution is concerned. Equations 4-11 summaries the results of simple regression analyses of the four clusters. The IC_{50}`s of the clusters generated by clustered regression analysis based on Log P, were regressed a second time with the corresponding MR values to assess the impact of steric effects on the obtained clusters.

Cluster 1: Compounds 1,2, 18,20,21,22,23 and 24

With exception of the two parent compounds, 1 and 2, the other compounds of this cluster are substituted at both positions 6 and 8. Compounds 18, 20 and 21 are substituted with 4-hydroxyphenylamino, 4-flourophenylamino and 2,5-dimethoxyphenylamino groups at position 8 respectively. Moreover, there is a methyl group in position 6 in each of them which is also the case for compound 2. On the other hand, compounds 22, 23 and 24 have all unsubstituted phenylamino groups at position 8 and aromatic rings at position 6. These are phenyl, furan-2-yl and thiophen-3-yl respectively. Equations (4) and (5) are the two linear equations resulting from regressing IC_{50} against Log P and MR respectively.

Log P:

log IC50 = -0.59 log P + 1.85 ……..(4)

n= 8 R^2 =0.8 3 s= 0.32 F =29.16 (significant F=0.00166)

MR:

log IC50 = -0.03 MR + 3.11 ……..(5)

n= 8 R^2 =0.87 s= 0.28 F =40.57 (significant F=0.0007)

From R^2 values, the variability of biological activity is more explained by MR (R^2 =0.8 7) than by Log P (R^2 =0.8 3). It appears that these two molecular descriptors are not independent in exerting their effect on IC_{50} owing to their appreciable collinearity (R^2 =0.77). the activity among the compounds of cluster1follows the following order:

22 > 24 > 23> 20> 21> 18 >1>2

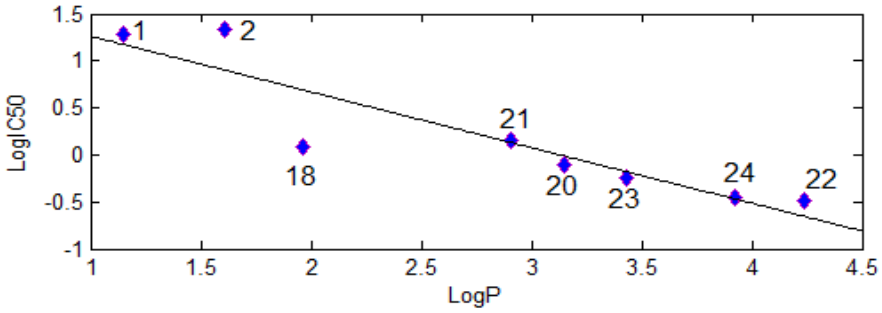


Figure 1: Plot of activity (logIC_{50}) versus lipophilicity (Log P) for subset 1.

The correlation between activity and lipophilicity is shown in "Fig. 1". The appearance of regression line shows that the smaller the logarithmic value of activity, which mean higher activity, the larger is the lipophilicity. Thus activity is directly proportional to lipophilicity.

Cluster 2: Compounds 3,6,7,8 and 10

Excluding compound 3, other compounds 6,7,8 and 10 are substituted at position 8. Compounds 6 and 10 substituted with phenylamino group but the amino groups of these compounds are each substituted with an ethyl group. Compounds 7 and 8 are substituted with 4-methoxyphenylamino and 2,5-dimethoxyphenylamino at position 8 respectively. Only compound 3 is substituted at position 6 with a phenyl group.

Equation (6) and (7) shows the two linear equations resulting from regressing IC_{50} against Log P and MR respectively.

Log P:

log IC_{50} = -1.79logP -4.58……(6)

n=5 R^2 =0.92 s=0.26 F = 32.72 (significant F=0.01060)

MR:

log IC_{50} = -0.046MR + 4.33……(7)

n=5 R^2 =0.18 s=18.7 F = 6.92 (significant F= 0.47)

Log P explain 92% of the variability of IC_{50} while MR is poorly correlated with it. It appears that these two molecular descriptors are independent in exerting their effect on IC_{50} for this cluster owing to the absence of collinearity between them (R^2 =0.1088). The activity among the compounds of cluster 2 follows the following order:

6 > 8 > 7> 10> 3

In contrast to cluster 1, Log P for cluster 2 is directly proportional to log IC_{50} – inversely proportional to activity (see "Fig. 2" below) This is indicative of a distinct mechanistic profile compared to cluster 1.

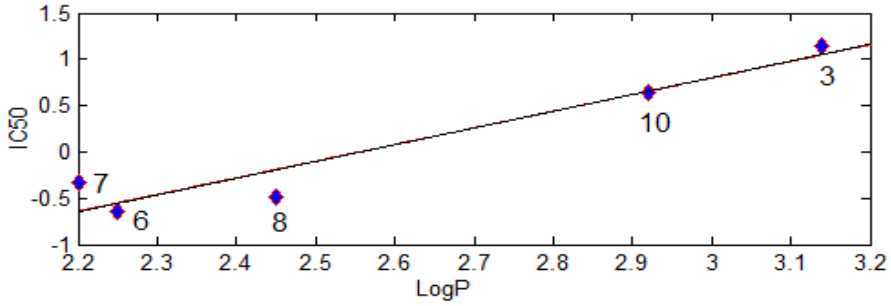


Figure 2: Plot of activity (logIC_{50}) versus lipophilicity (Log P) for subset 2.

The mechanistic profile of cluster 2 is almost independent from steric/ polarizability effects which is another point of distinction from cluster 1.

Cluster 3: containing compounds 5, 11, 12, 13,14 and15

All compounds of this cluster are substituted at position 9 except compound 5 which is only substituted at position 6 with thiophen-3-yl group. In compounds11,14 and15 the position 9 amino group is N-unsubstituted while the same group is N-substituted with methyl and ethyl group respectively for Compounds14 and15. Another observation is that in compounds 11and 12, the 9-phenylamino moiety are substituted with 4-methoxy and 2,5-dimethoxy groups respectively.

The linear dependence of log IC_{50} on Log P for this cluster is modest (R^2=0.6). The correlation between activity and lipophilicity is direct proportionality. MR, However, shows complete absence of any correlation with logIC_{50} (R^2 = $6.41x10^{-6}$). Equations (8) and (7) show the correlations of LogIC50 with Log P and MR respectively.

Log P:

log IC_{50} =1.26logP -2.13……(8)

n=6 R^2 = 0.60 s=0.37 F=5.25 (significant F =0.0837)

MR:

log IC_{50}= 0.0002MR + 1.05……(9)

n=6 R^2 = =-6.41x10^{-6} s=0.634 F= 2.56 x10^{-5} (significant F =0.996)

Figure 3 reflects the distinction of cluster 3 from either cluster 1 and cluster 2. Thus it represents a third mechanistic profile.

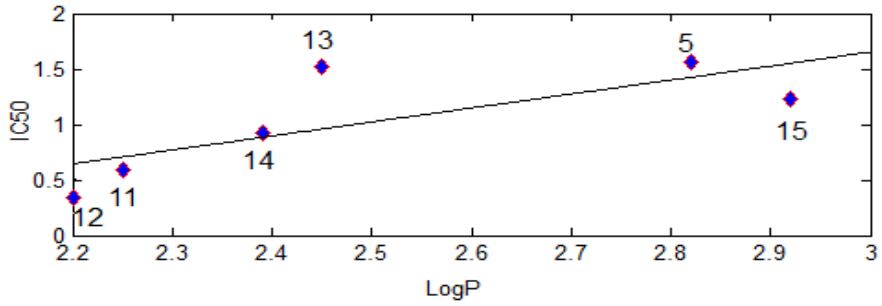


Figure 3: Plot of activity (logIC_{50}) versus lipophilicity (Log P) for subset 3.

Cluster 4: containing compounds 4,9,16,17and 19

With exception of compound 4, all compounds of this cluster are substituted at position 8 with N-methyl phenylamino, phenylamino, 4-methoxy phenylamino and 2-methoxy phenylamino groups for componds 9,16,17and 19 respectively. It can also be noted that compounds 16,17 and 19 are substituted at position 6 with methyl group while compound 4 is substituted with furan-2-yl group. In Compound 9 the methyl group is shifted from position 6 to N atom of the 8-phenylamino group.

Log P:

log IC_{50} =-4.83logP + 12.60……(10)

n=5 R^2 = 0.73 s=0.58 F=7.97 (significant F = 0.0665)

MR:

log IC_{50} = -0.1MR + 8.50……(11)

n=5 R^2 = 0.83 s=0.46 F=14.33 (significant F = 0.0323)

As it is apparent from equation (10) and (11) the variability of biological activity is more explained by MR (R^2 = 0.83) than by Log P (R^2 = 0.73). both descriptor show a direct proportionality with activity.

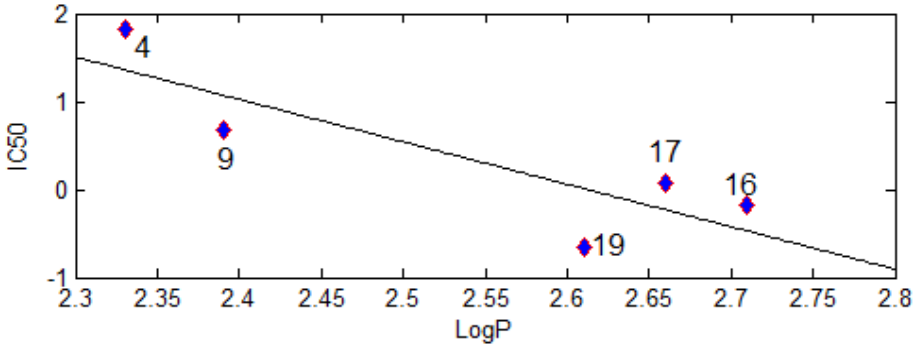


Figure 4: Plot of activity (logIC_{50}) versus lipophilicity (Log P) for subset 4.

CONCLUSION

In this study we elaborated a simple method to segregate a group of 24 DTP`s into smaller highly correlated clusters based on log P. Each cluster traverse a different lipophilicity-response space as described by their respective regression lines. This is considered to be resulting from the existence of a distinct mechanistic profile for each of these clusters. Molar refractivity was utilized to support this clustering procedure and add emphasis to presence of mechanistic nesting subgroup inside the main data set.

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