Supplementary Information: Efficient clustering of large molecular libraries

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S1: BitBIRCH Algorithm and Complementary Similarity

Here we present the pseudo-code for the key parts of the BitBIRCH algorithm. Underlined sections indicate some of the key differences with respect to the traditional BIRCH method.

```
1: BitBIRCH(library)
2:    initialize root
3:       for molecule  in library:
4:          subcluster  = create_subcluster(1, molecule, molecule, molecule_index)
5:          split  = root.insert_bf_subcluster(root, subcluster)

6:          if split
7:              split_node(root)
8:              update root
```

Figure S1.1: Main BitBIRCH algorithm.

```
1: create_subcluster(nmols, linear_sum, centroid, indices)
2:    subcluster.number_of_molecules = nmols
3:    subcluster.linear_sum = linear_sum
4:    subcluster.centroid = centroid
5:    subcluster.indices = indices
```

Figure S1.2: Create subcluster method.

```
1: split_node(node)
2:    initialize subcluster1  and subcluster2
3:    initialize new_node1  and new_node2

4:    subcluster1.child = new_node1
5:    subcluster2.child = new_node2

6:    extreme1, extreme2  = find_separated_molecules(node.centroids)

7:    for subcluster  in node.subclusters
8:       if similarity(subcluster.centroid, extreme1) < similarity(subcluster.centroid,
extreme2)
9:          append subcluster  to new_node1
10:      else
11:         append subcluster  to new_node2
```

Figure S1.3: Split node algorithm.

In the calculations discussed here and in the main text, the **similarity** function used was the pairwise Tanimoto index (Eq. (1) in the manuscript).

```
1: insert_bf_subcluster(node, subcluster)
2:   ind  = argmax(similarity(node.centroids, subcluster.centroid))
3:   closest_sub = node.subclusters[ind]

4:    if closest_sub.child not NULL
5:       split = closest_sub.child.insert_bf_subcluster(node, subcluster)
6:       if not split
7:          merge(closest_sub, subcluster)
8:          return False
9:       else
10:         split_node(closest_sub.child)
11:         if number_of_subclusters > branching_factor
12:            return True
13:         return False

14:   else
15:      if jt_radius(closest_sub, subcluster) < threshold
16:         merge(closest_sub, subcluster)
17:         return False
18:      else if  length(node.subclusters) < branching factor
19:         return False
20:      else
21:         return True
```

Figure S1.4: Insert subcluster algorithm.

In all the calculations, we used a default value of 50 for the branching_factor.

```
1: merge(cluster1, cluster2)
2    subcluster.number_of_molecules = cluster1.number_of_molecules +
         cluster2.number_of_molecules
3:   subcluster.linear_sum = cluster1.linear_sum + cluster2.linear_sum
4:   subcluster.indices = cluster1.indices + cluster2.indices
```

Figure S1.5: Merge clusters algorithm.

An important feature of the iSIM formalism, is the ability to easily rank the molecules in a set depending on how central-like or outlier-like they are. This is done through the concept of complementary similarity which, for a given molecule, is just the iSIM value of the set after that molecule has been removed. It is clear that when we remove outliers, the iSIM of the remaining molecules will increase. Likewise, when we remove a molecule that is central to the set, the final iSIM will decrease. We use this insight to identify the medoid of the set, as the molecule with the lowest complementary similarity value, which can clearly be done in O(N).

As mentioned in the manuscript, the medoid can serve as a representative of the cluster (with the key difference between medoid and centroid being that the former is required to be an element of the set, while the former does not have to be a real molecule). However, in BitBIRCH we also used the medoid in a new way to speed up the **max_separation** function. In BIRCH, if one tries to insert a subcluster in a node that already has branching_factor subclusters, the node must be split. This is done by taking the branching_factor centroids, finding the two most separated ones, and then assigning the remaining centroids to whichever of these two maximally separated points they are closest to. This demands calculating all the pairwise distances between the centroids, which scales as O(branching_factor^2). In BitBIRCH, we take a different route, in that we do not aim to find the absolutely most separated centroids, but we only need to find two centroids that are guaranteed to be very separated, compared to the other centroids in the node. The recipe for this is very simple: 1- Find the medoid among the branching_factor centroids, 2- Find the centroid that is furthest away from the medoid (label this as molecule_1), 3- Find the molecule that is the furthest away from molecule_1 (label this as molecule_2). Then, molecule_1 and molecule_2 will serve as the two pivot points around which the node will be partitioned. This procedure scales as O(branching_factor).

Finally, for a detailed derivation of Eq. (10) in the main text:

By definition:

$$R_j = \frac{1}{N_j}\sum_{v=1}^{N_j}\left\{1 - \mathrm{T}\left(\mathbf{c}_j, \mathbf{x}^{(j,v)}\right)\right\} = 1 - \frac{1}{N_j}\sum_{v=1}^{N_j}\mathrm{T}\left(\mathbf{c}_j, \mathbf{x}^{(j,v)}\right) \quad \text{* MERGEFORMAT (1)}$$

$$iT\left(\mathbf{X}^{(j)}\right)=\frac{\sum_{v=1}\sum_{u,u>v} T\left(\mathbf{x}^{(j,u)},\mathbf{x}^{(j,v)}\right)}{\binom{N_j}{2}}$$

$$iT\left(\mathbf{X}^{(j)}\cup\{\mathbf{c}_j\}\right)=\frac{\sum_{v=1}\sum_{u,u>v} T\left(\mathbf{x}^{(j,u)},\mathbf{x}^{(j,v)}\right)+\sum_{v=1}^{N_j} T\left(\mathbf{c}_j,\mathbf{x}^{(j,v)}\right)}{\binom{N_j+1}{2}} \quad \text{* MERGEFORMAT (2)}$$

$$R_j=1-\frac{\binom{N_j+1}{2}iT\left(\mathbf{X}^{(j)}\cup\{\mathbf{c}_j\}\right)-\binom{N_j}{2}iT\left(\mathbf{X}^{(j)}\right)}{N_j}$$

$$=1-\left\{\frac{(N_j+1)iT\left(\mathbf{X}^{(j)}\cup\{\mathbf{c}_j\}\right)-(N_j-1)iT\left(\mathbf{X}^{(j)}\right)}{2}\right\} \quad \text{* MERGEFORMAT (3)}$$

S2: Details of the ChEMBL Subsets

The 30 ChEMBL subsets can be found here: https://github.com/molML/MoleculeACE/tree/main/MoleculeACE/Data/benchmark_data/old.

Library name	Number of molecules	Code
CHEMBL218_EC50	1031	[1]
CHEMBL264_Ki	2862	[2]
CHEMBL2971_Ki	976	[3]
CHEMBL238_Ki	1052	[4]
CHEMBL228_Ki	1704	[5]
CHEMBL219_Ki	1859	[6]
CHEMBL214_Ki	3317	[7]
CHEMBL2047_EC50	631	[8]
CHEMBL233_Ki	3142	[9]
CHEMBL4005_Ki	960	[10]
CHEMBL2835_Ki	615	[11]
CHEMBL287_Ki	1328	[12]
CHEMBL231_Ki	973	[13]
CHEMBL2034_Ki	750	[14]
CHEMBL237_EC50	955	[15]
CHEMBL4616_EC50	682	[16]
CHEMBL239_EC50	1721	[17]
CHEMBL4203_Ki	731	[18]
CHEMBL262_Ki	856	[19]
CHEMBL236_Ki	2598	[20]

CHEMBL244_Ki	3097	[21]
CHEMBL2147_Ki	1456	[22]
CHEMBL237_Ki	2602	[23]
CHEMBL235_EC50	2349	[24]
CHEMBL3979_EC50	1125	[25]
CHEMBL4792_Ki	1471	[26]
CHEMBL1862_Ki	794	[27]
CHEMBL1871_Ki	659	[28]
CHEMBL234_Ki	3657	[29]
CHEMBL204_Ki	2754	[30]

Table S2.1: Library name, number of molecules, and numerical code for the 30 ChEMBL subsets.

S3: Local Clustering Analysis of BitBIRCH and Taylor-Butina

In the main text we presented a type of analysis aimed to understand the relation between the local structure of the clusters obtained with BitBIRCH and with Taylor-Butina: comparing the medoids of the most populated clusters. Here we present the results of a similar analysis, but that takes into account all the elements of the top clusters and not just a single representative. To perform this comparison, we use the Jaccard-Tanimoto, JT, set similarity index. That is, for two sets A and B, we have:

$$\mathrm{JT}(A,B)=\frac{|A \cap B|}{|A \cup B|} \qquad \backslash^* \text{ MERGEFORMAT (4)}$$

In this section we show the Medoid comparison and the Set comparison for all the 30 ChEMBL subsets. In general, we see that even in the cases where the BitBIRCH and Taylor-Butina final clusters do not have a perfect agreement, they still manage to largely identify the same regions in the denser regions of chemical space.

We also complement these analyses with another metric, in order to make it more quantitative. Notice that, in an ideal case, both the Medoid and the Set results would give an identity matrix (e.g., every BitBIRCH cluster perfectly matching every Taylor-Butina counterpart). To measure this, we introduce a Score, *s*, that measures how similar are the Medoid and Set results to the identity matrix of the same rank. In short, for a matrix *M*, *s* is given by:

$$s(M)=\frac{1}{2}\left\{n(M)+n\left(M^{T}\right)\right\}$$

$$n(M)=\frac{\sum_{\substack{r=0\\ r\to rows}}^{\dim(M)-1}\left(1-r\frac{0.9}{\dim(M)-1}\right)\begin{cases}\max\left(M[r]\right)+1, \text{ if } r=\arg\max M[r]\\ \max\left(M[r]\right)+1-\left|\arg\max M[r]-r\right|*\frac{0.9}{\dim(M)-1-r}, \text{if } r\le\frac{\dim(M)-1}{2}\\ \max\left(M[r]\right)+1-\left|\arg\max M[r]-r\right|*\frac{0.9}{r}, \text{if } r>\frac{\dim(M)-1}{2}\end{cases}}{1.1*\dim(M)}$$

* MERGEFORMAT (5)

s is bounded in the [0, 1] interval, with a value of 1 indicating perfect agreement with the identity matrix, so higher scores indicate a better agreement between Taylor-Butina and BitBIRCH. As shown below, both the Medoid and Set scores are very robust with respect to changes in the similarity threshold, which showcases the stability of the BitBIRCH results.

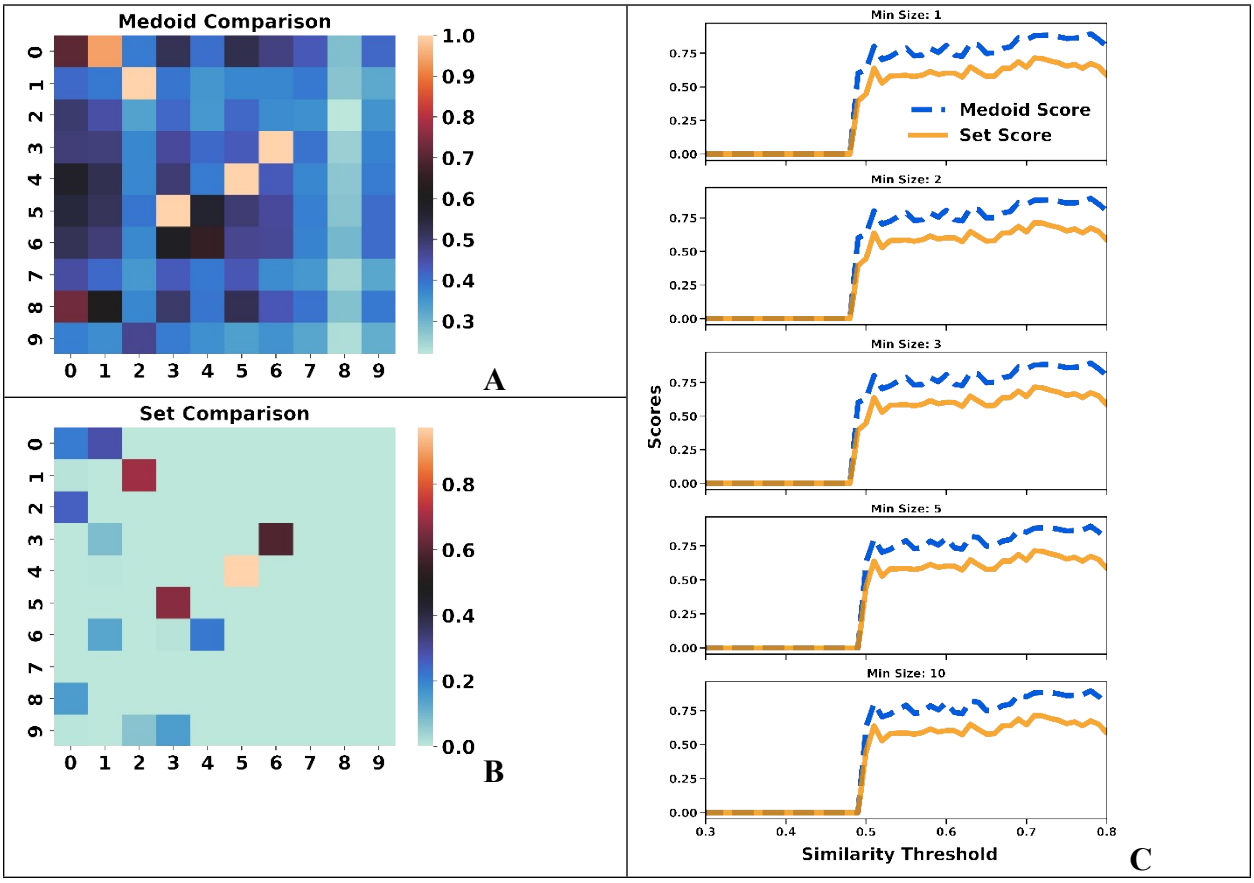


Figure S3.1: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [1] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

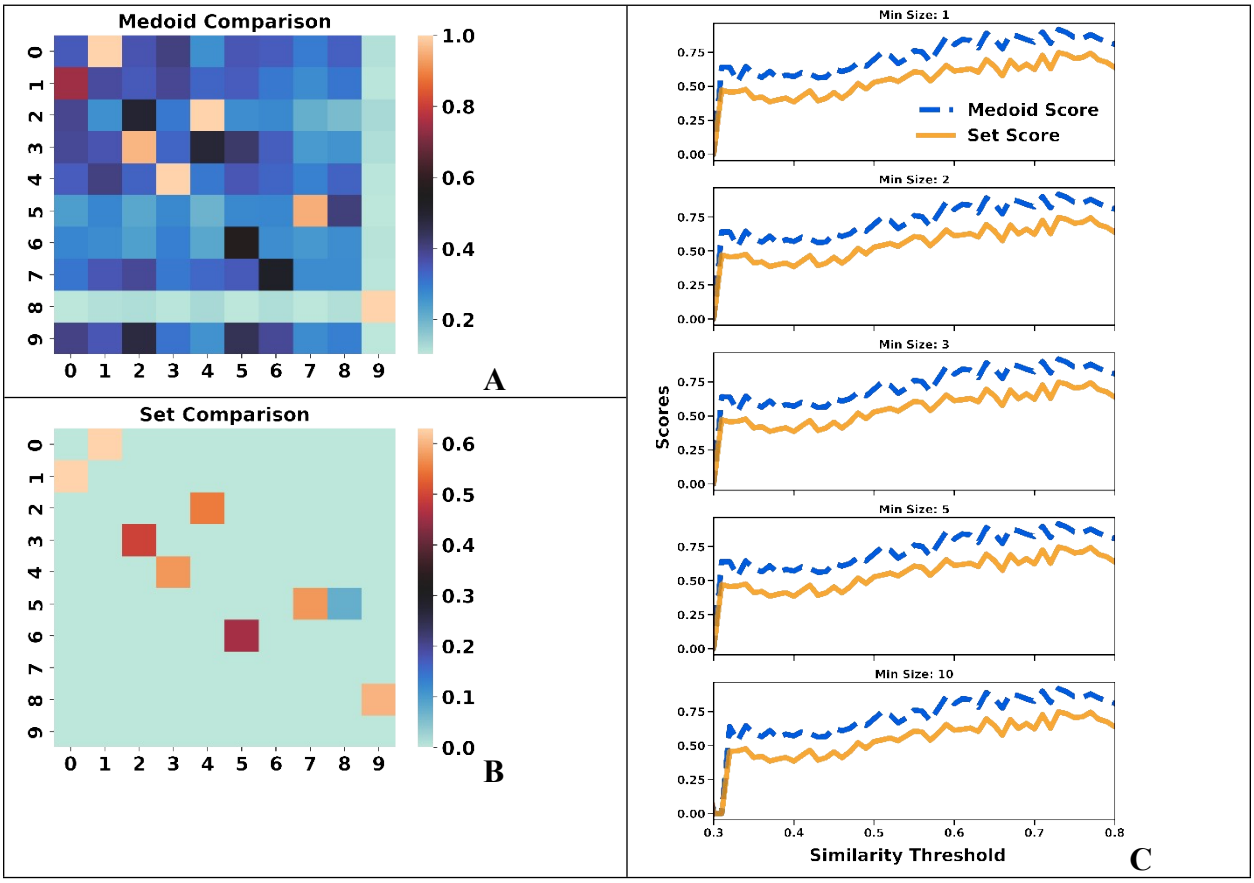
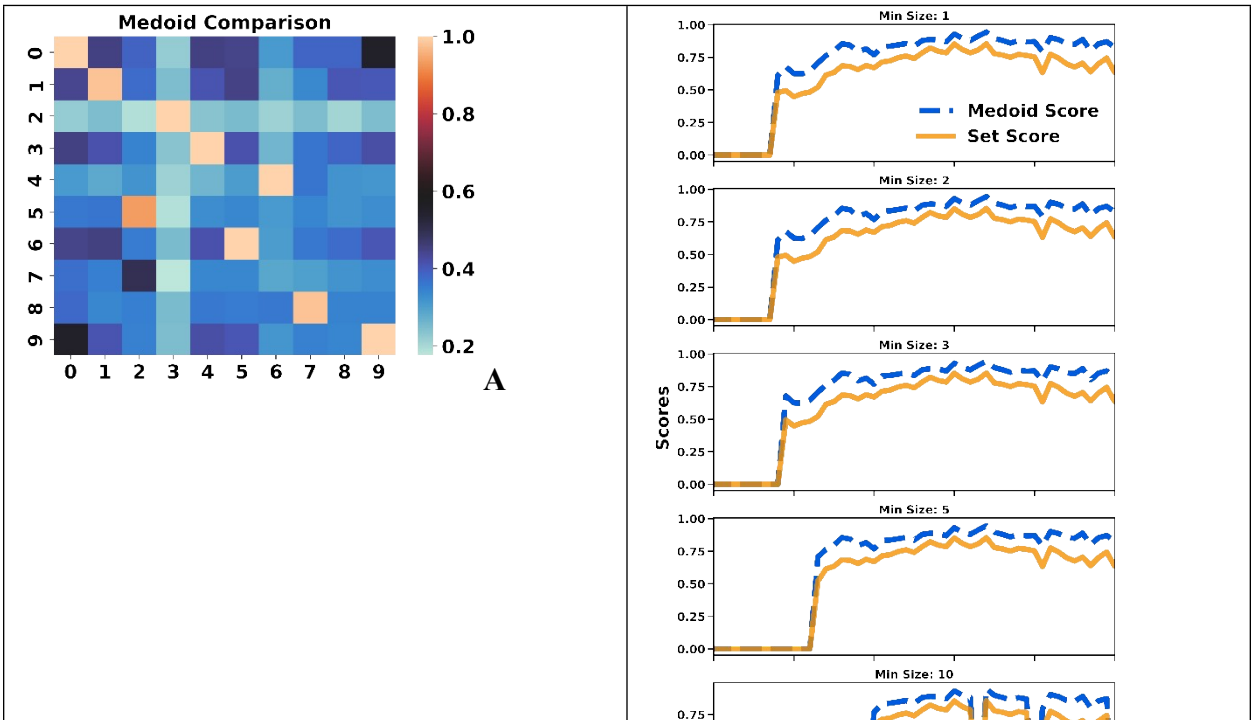


Figure S3.2: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [2] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.



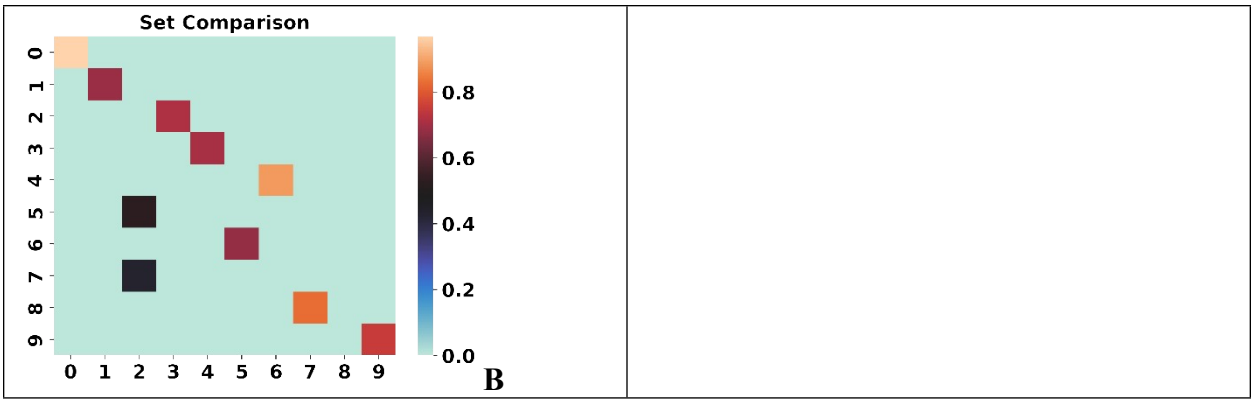


Figure S3.3: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [3] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

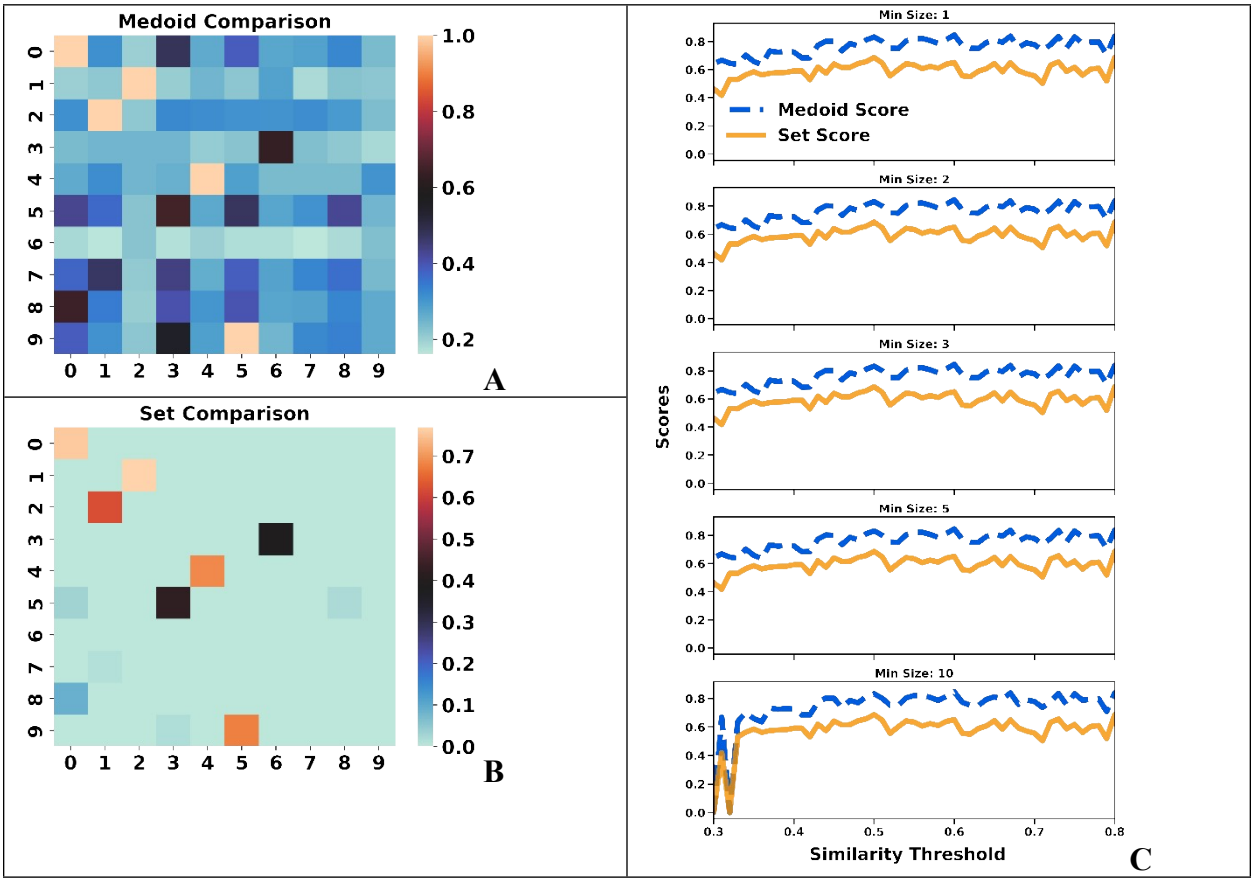


Figure S3.4: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [4] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

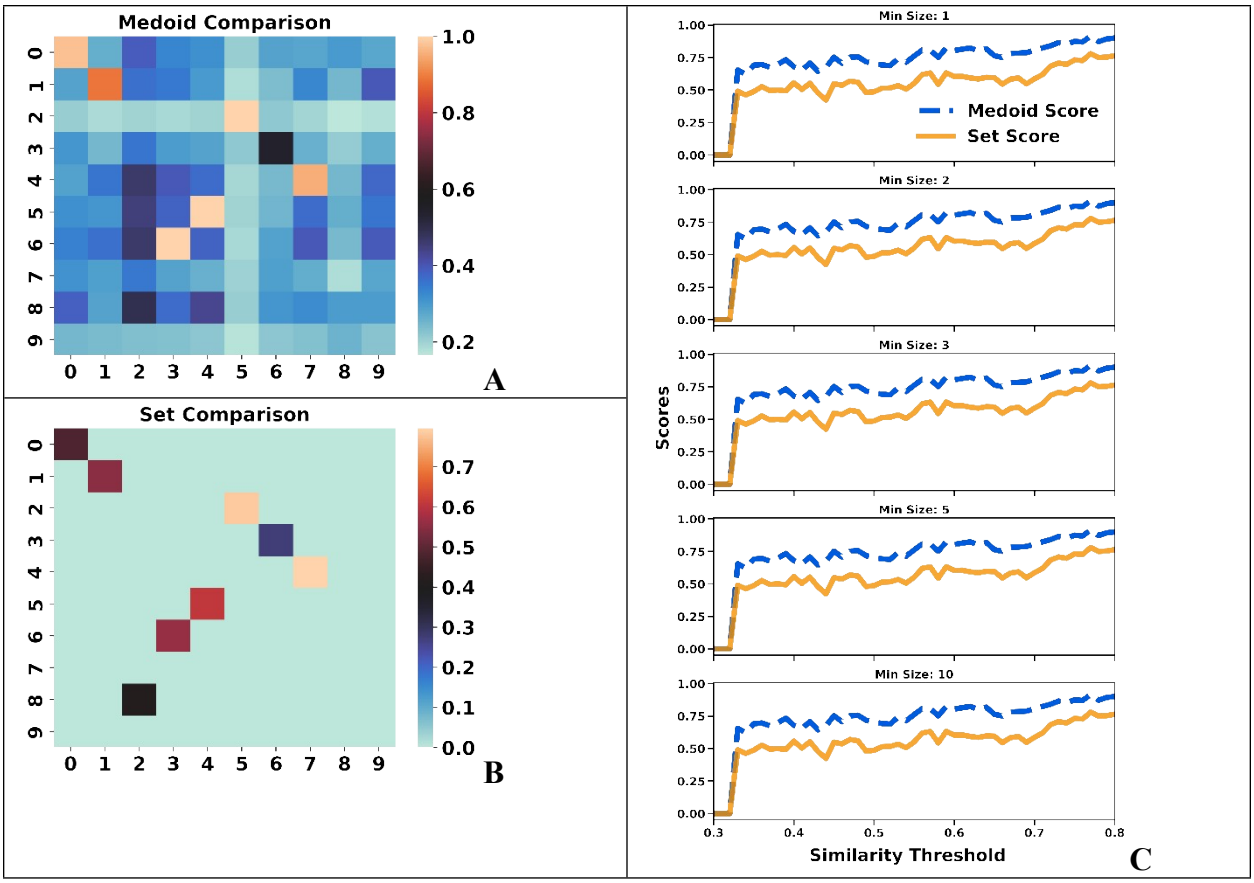
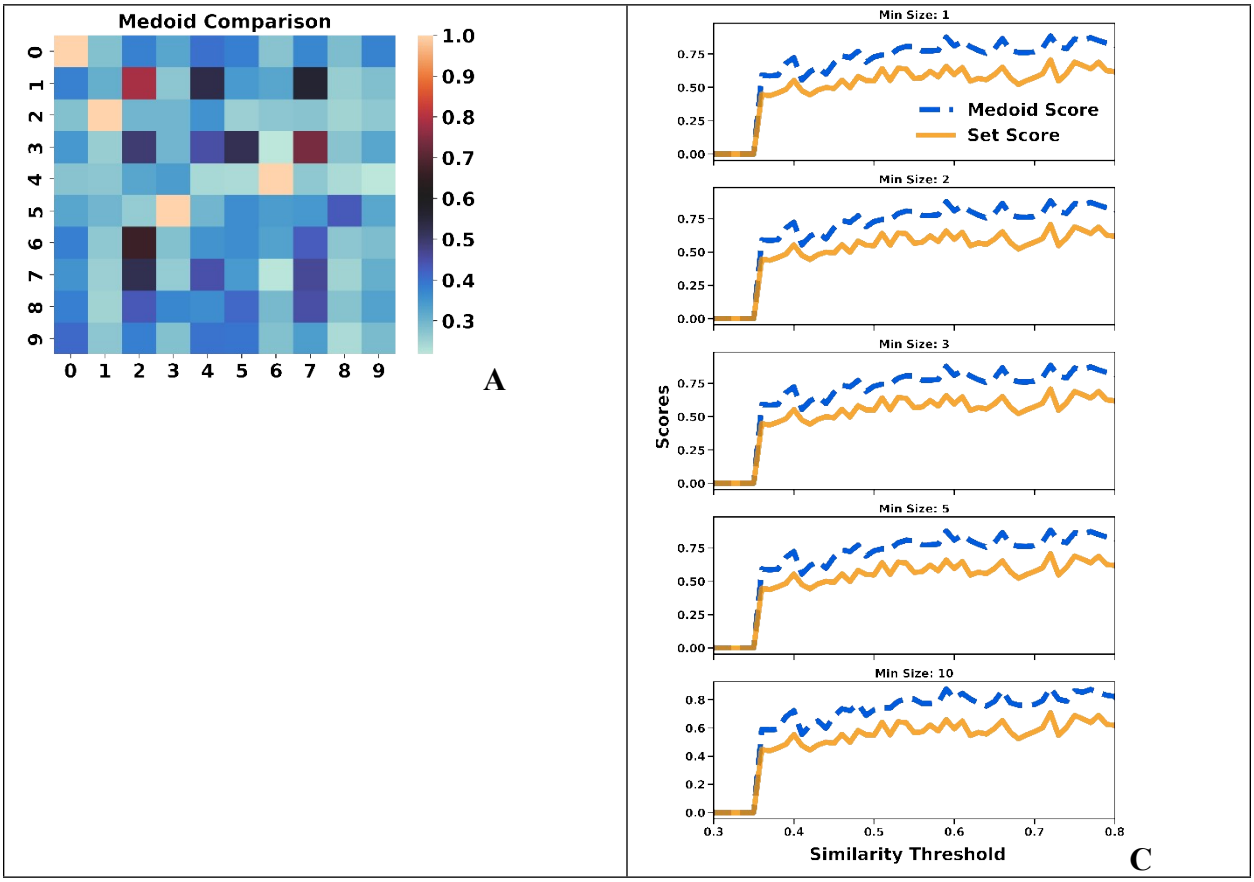


Figure S3.5: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [5] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.



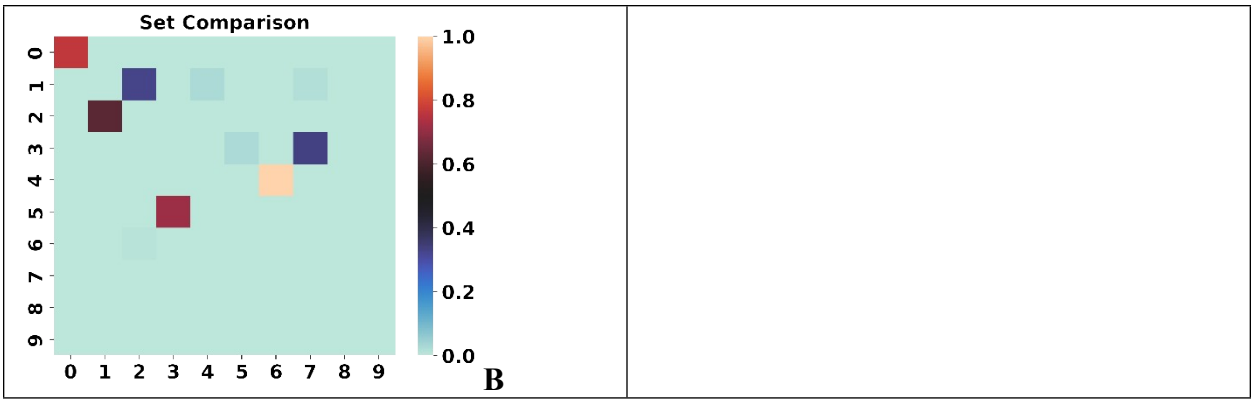


Figure S3.6: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [6] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

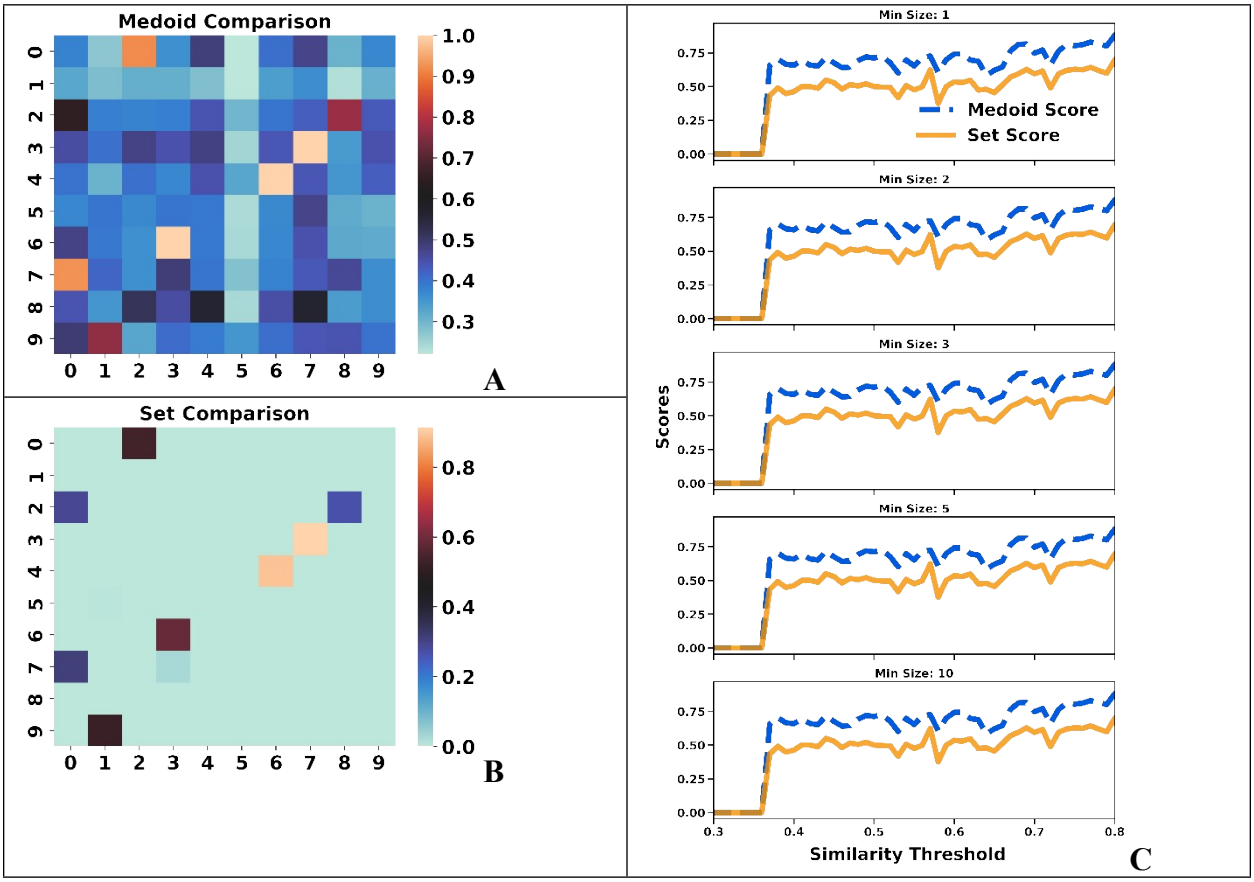


Figure S3.7: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [7] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

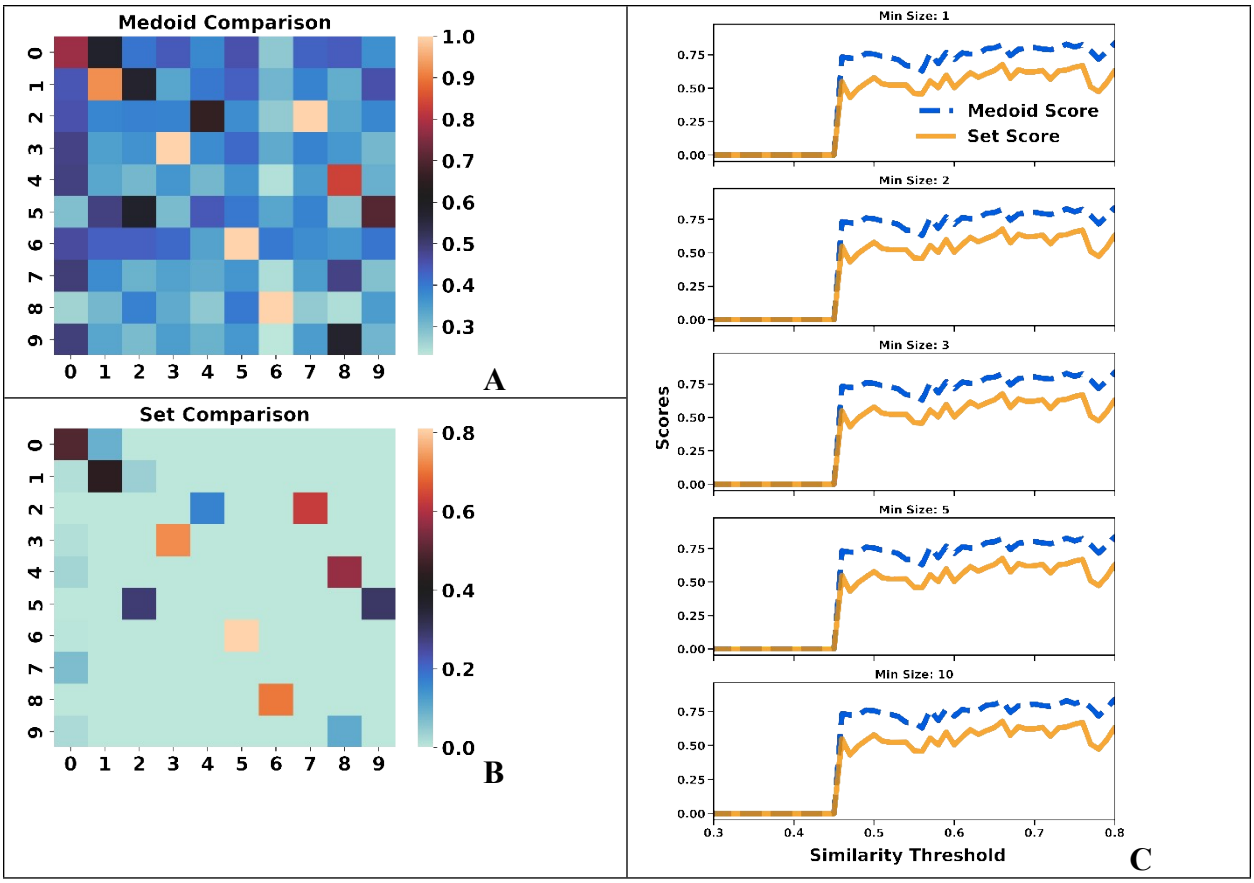
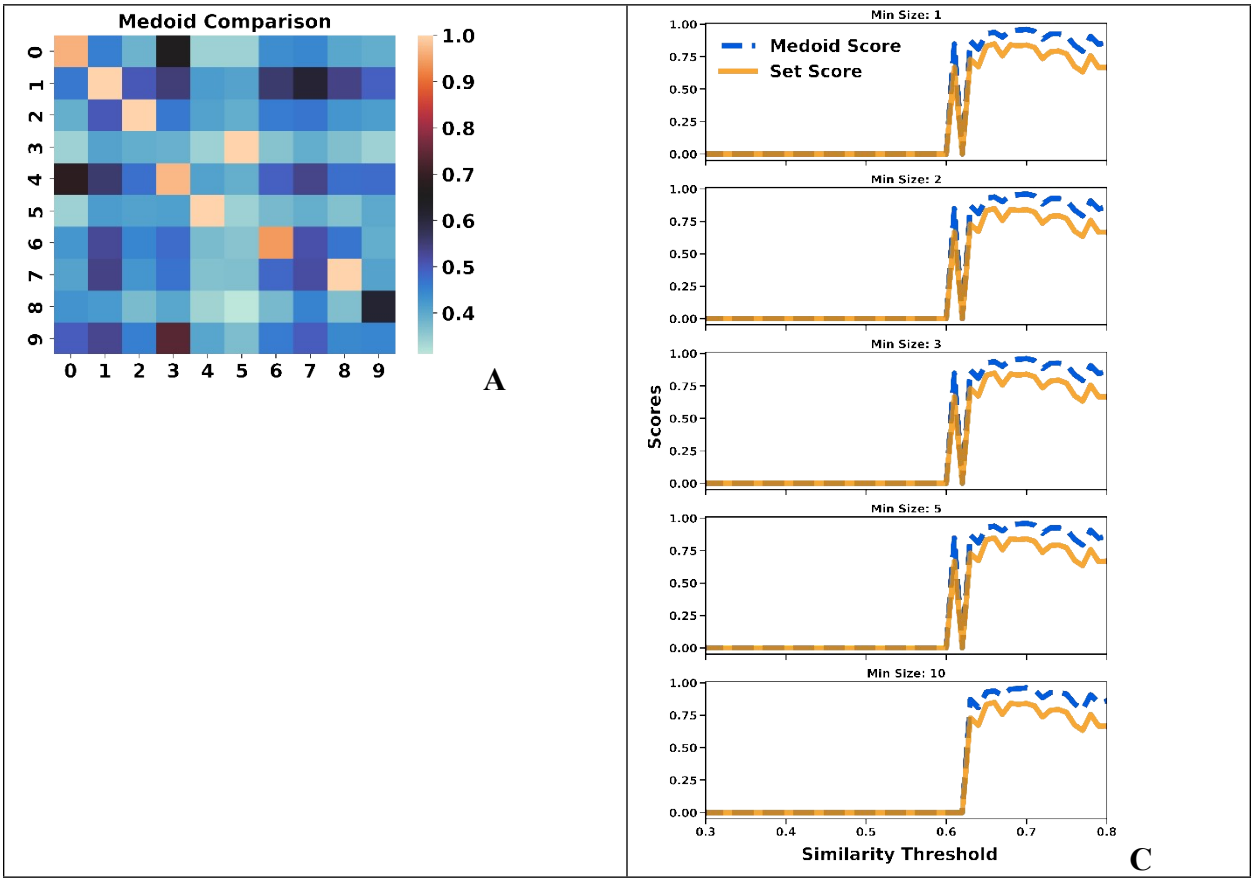


Figure S3.8: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [9] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.



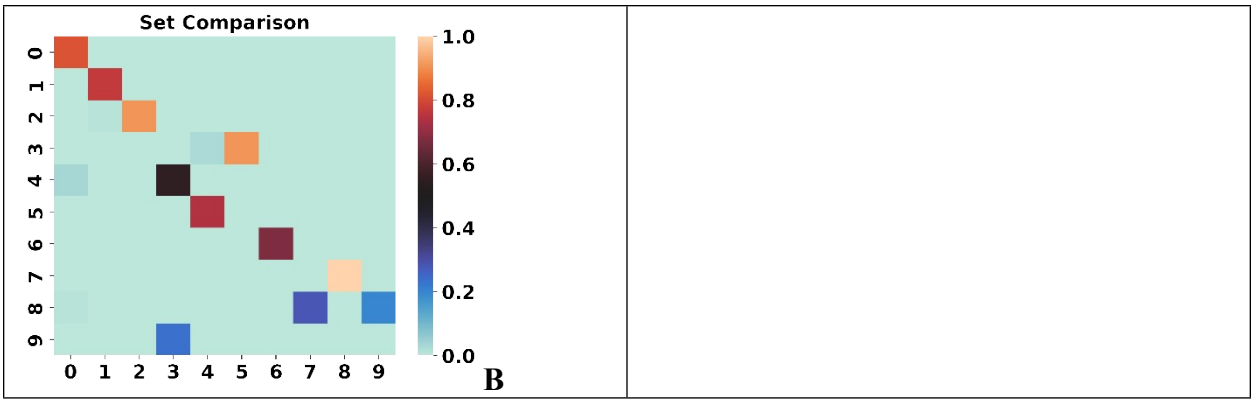


Figure S3.9: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [10] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

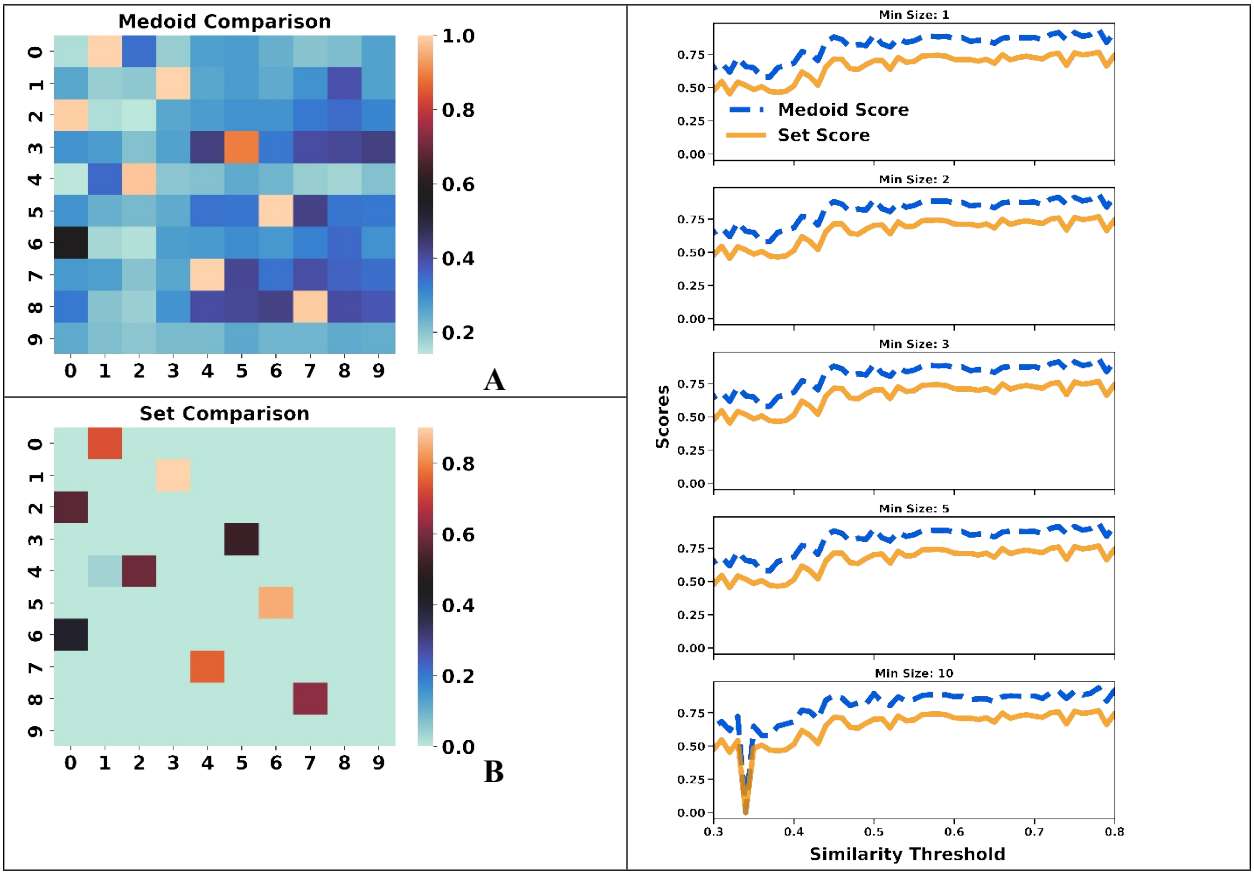


Figure S3.10: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [12] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

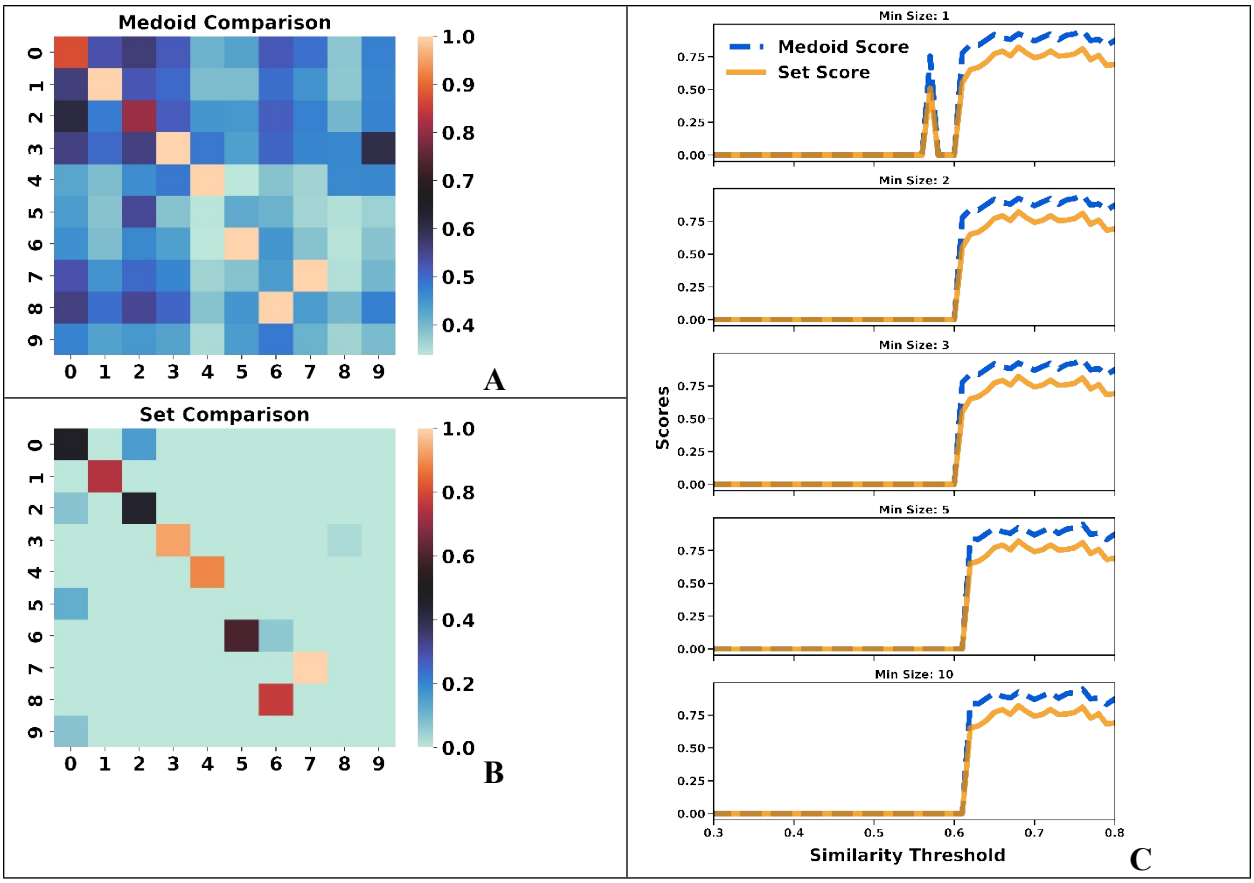
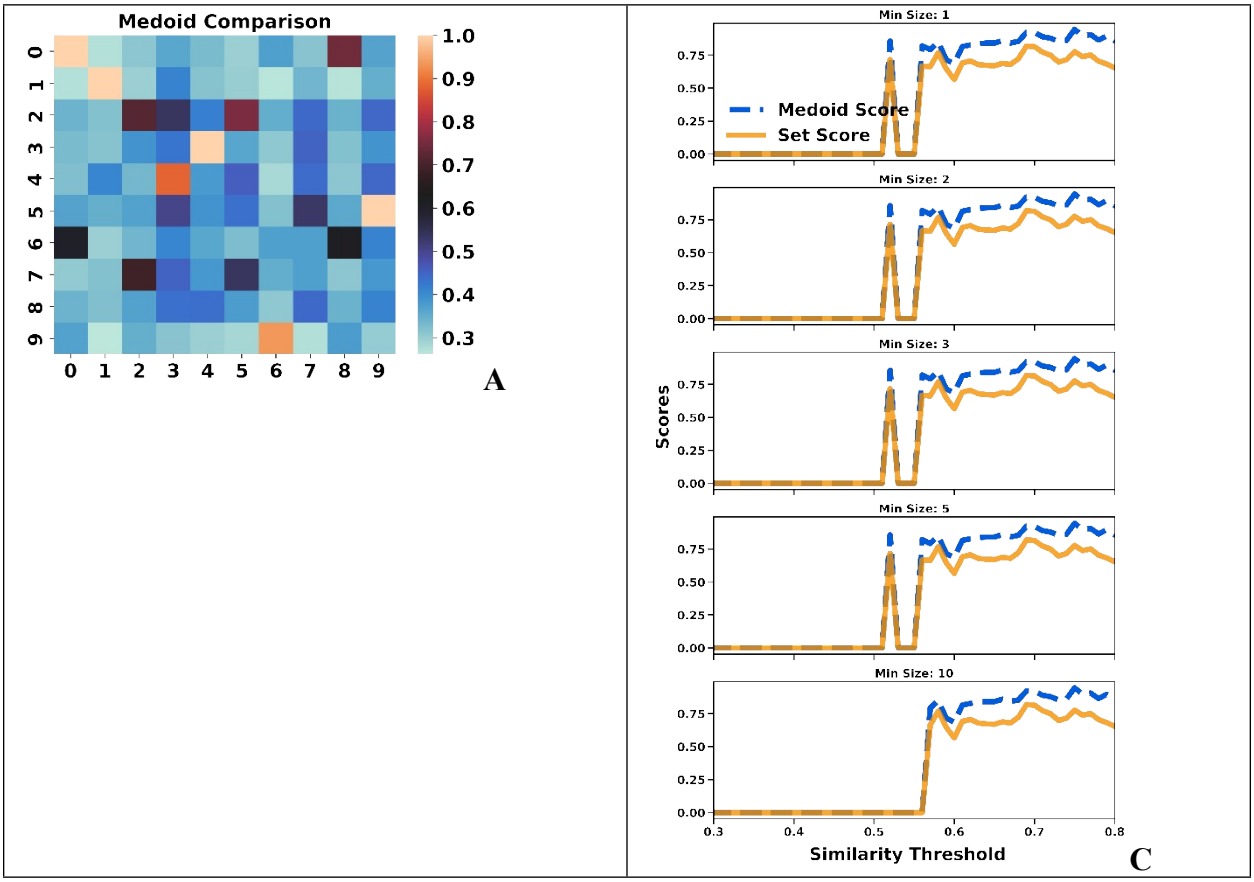


Figure S3.11: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [14] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.



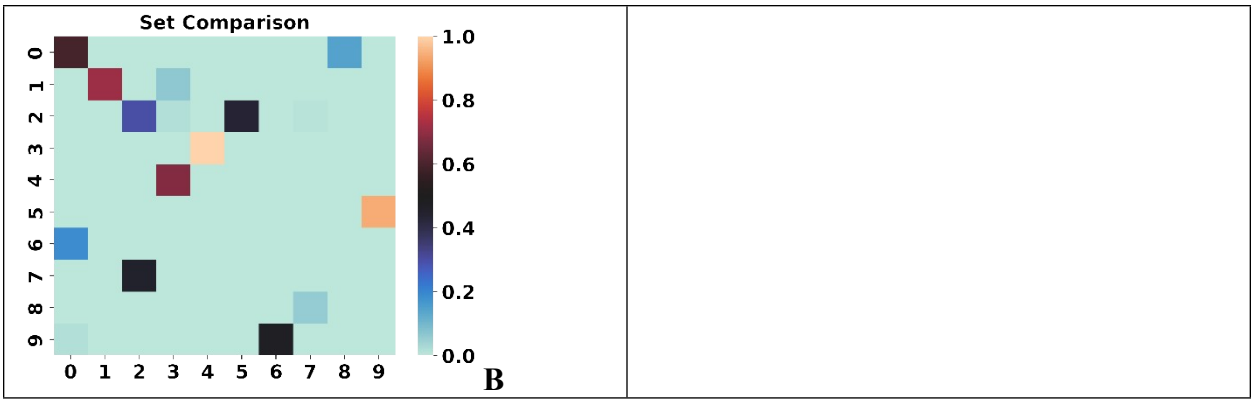


Figure S3.12: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [16] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

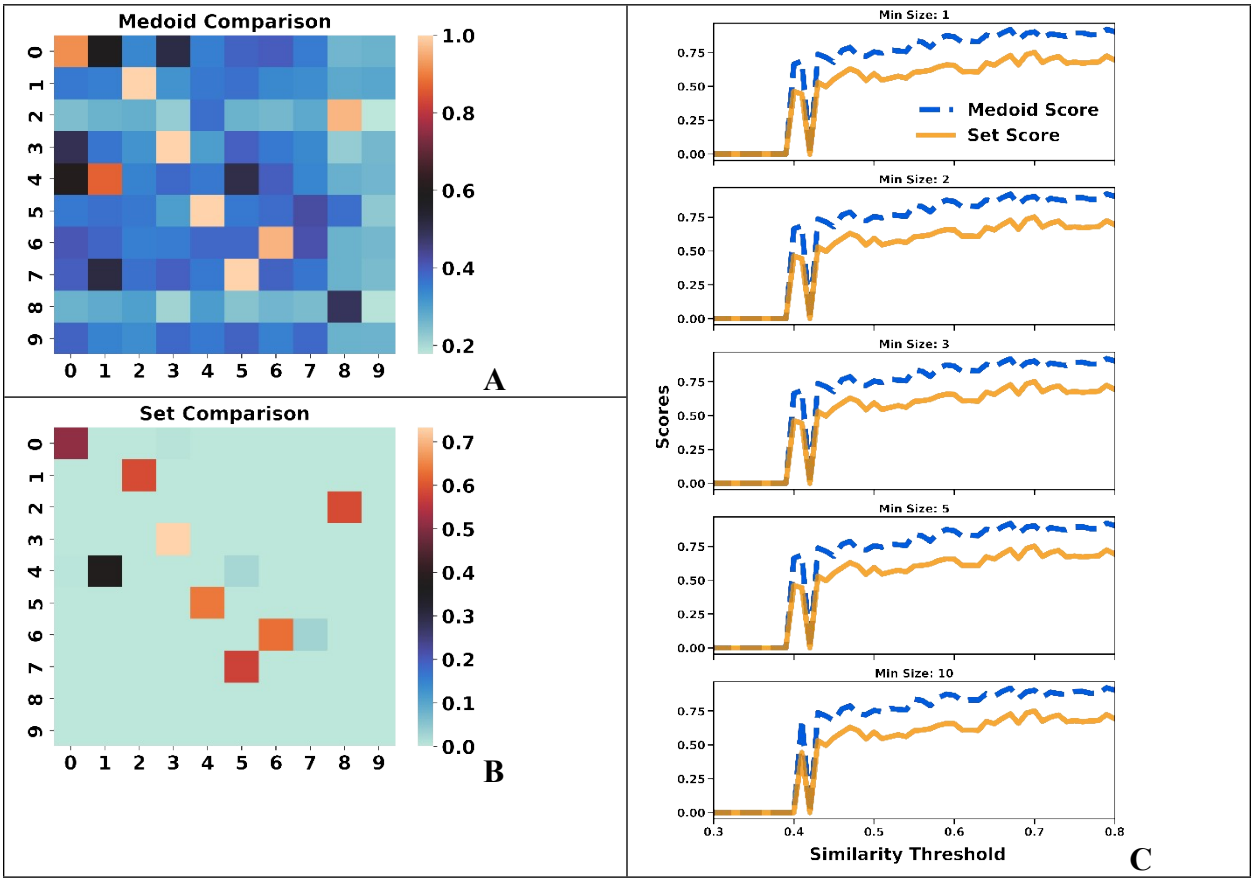


Figure S3.13: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [17] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

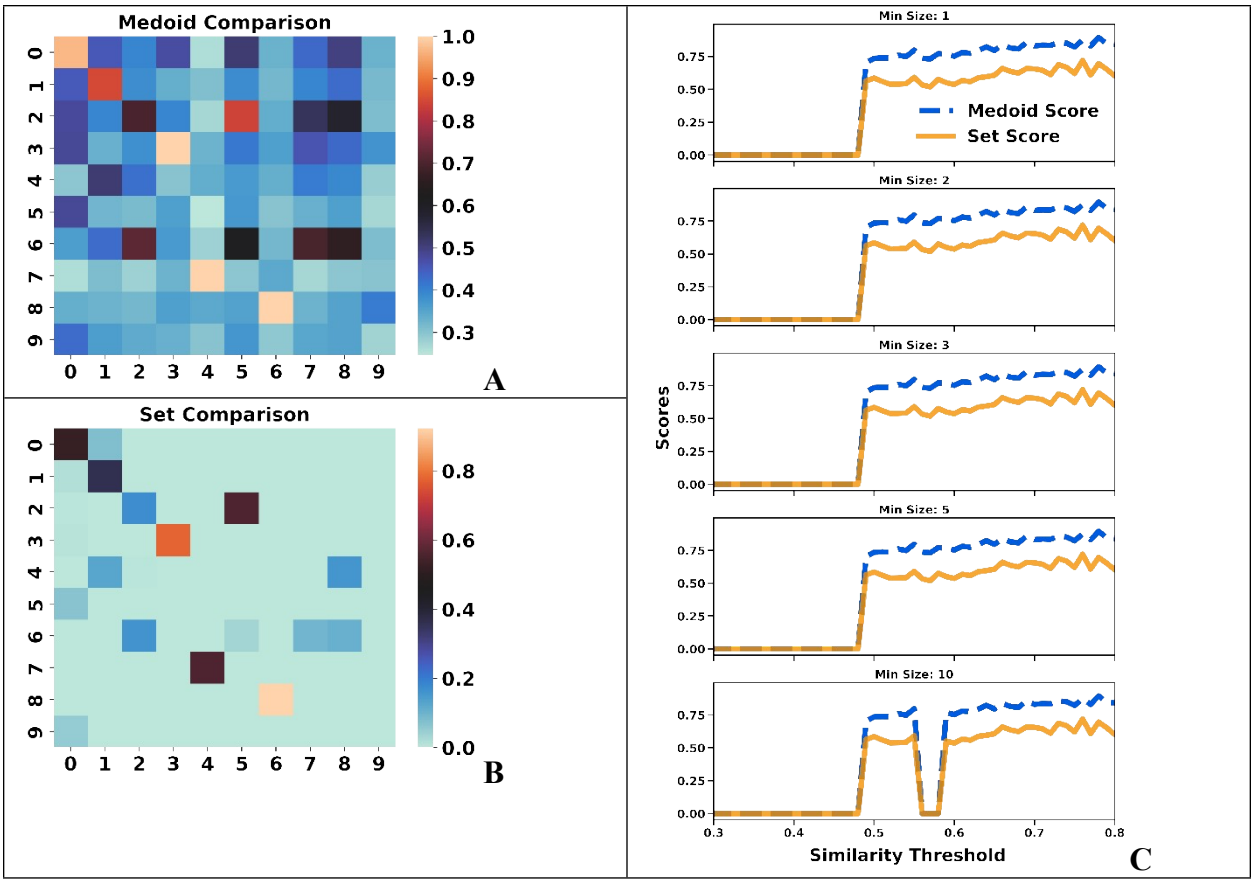
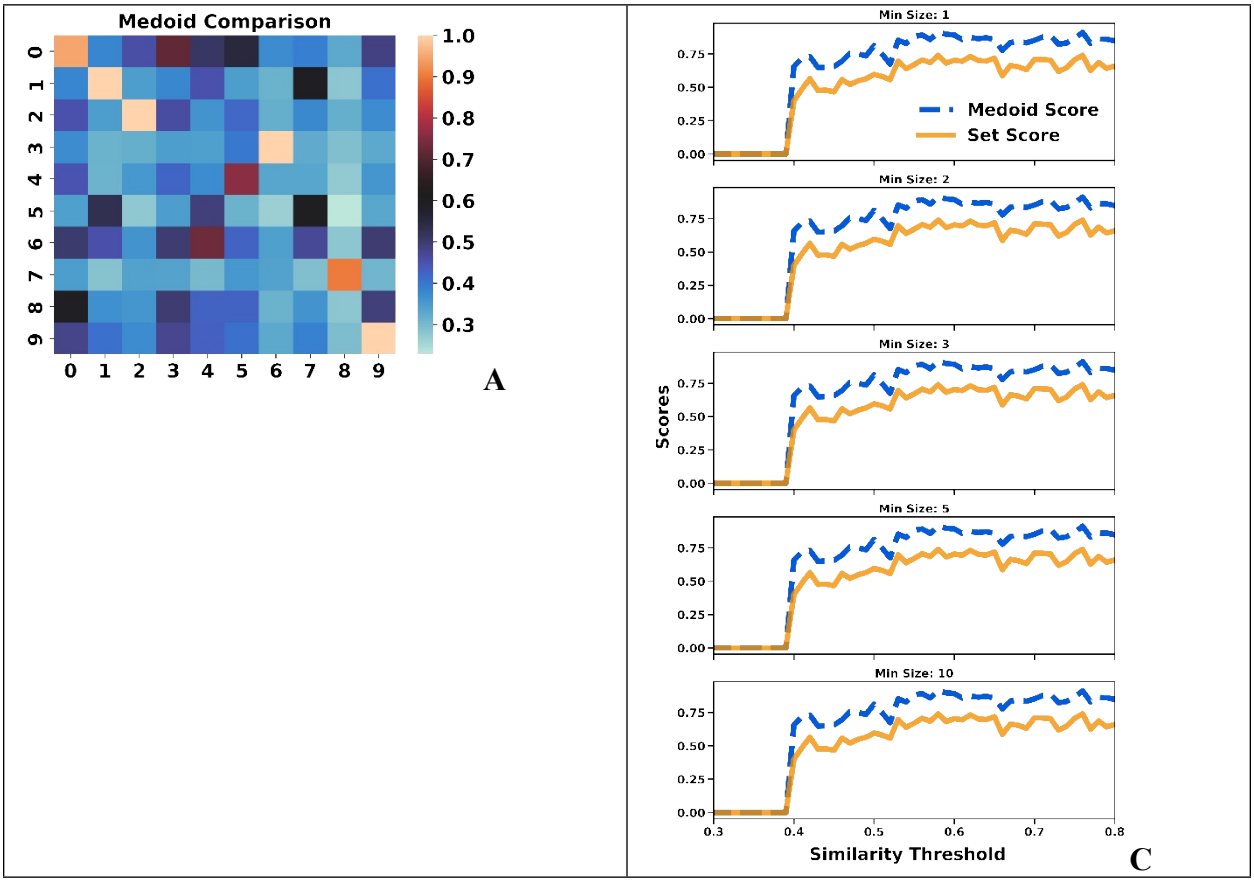


Figure S3.14: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [20] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.



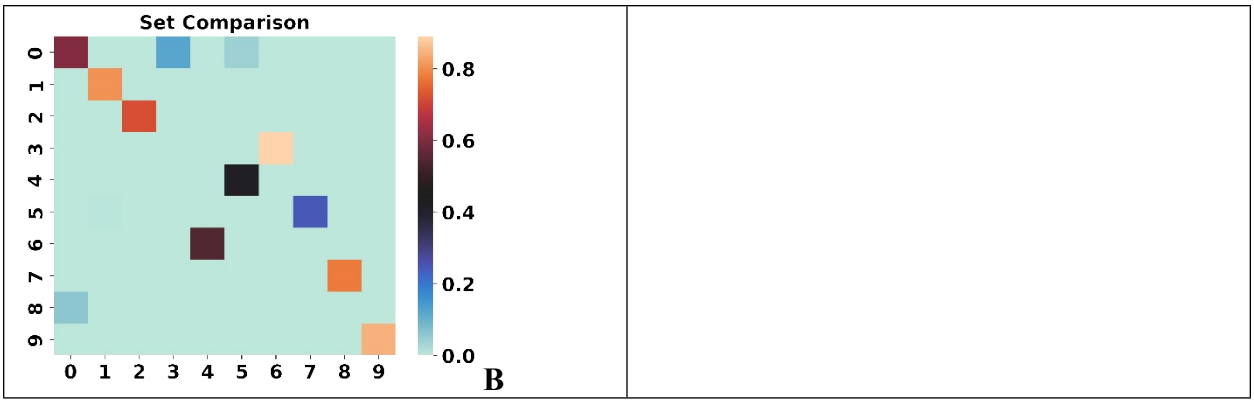


Figure S3.15: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [21] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

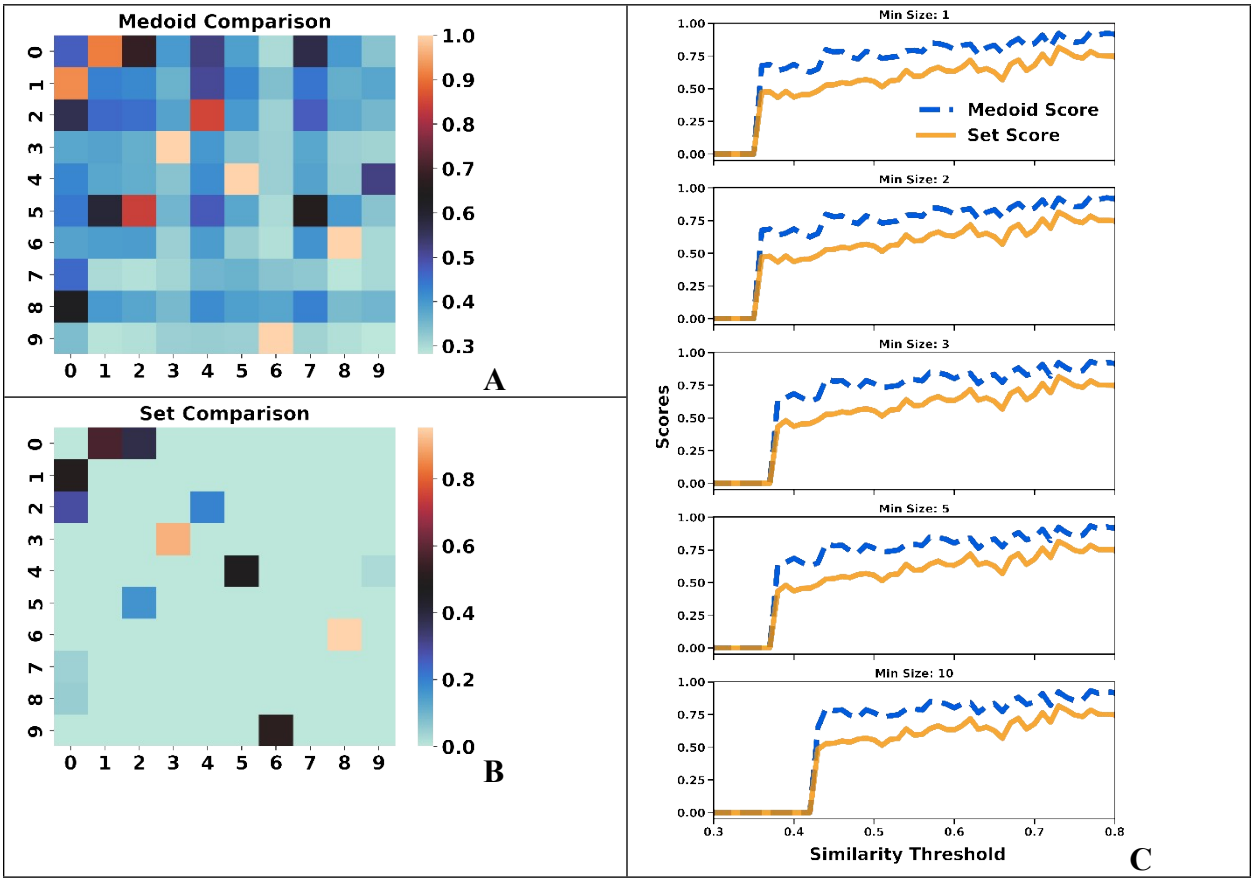


Figure S3.16: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [22] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

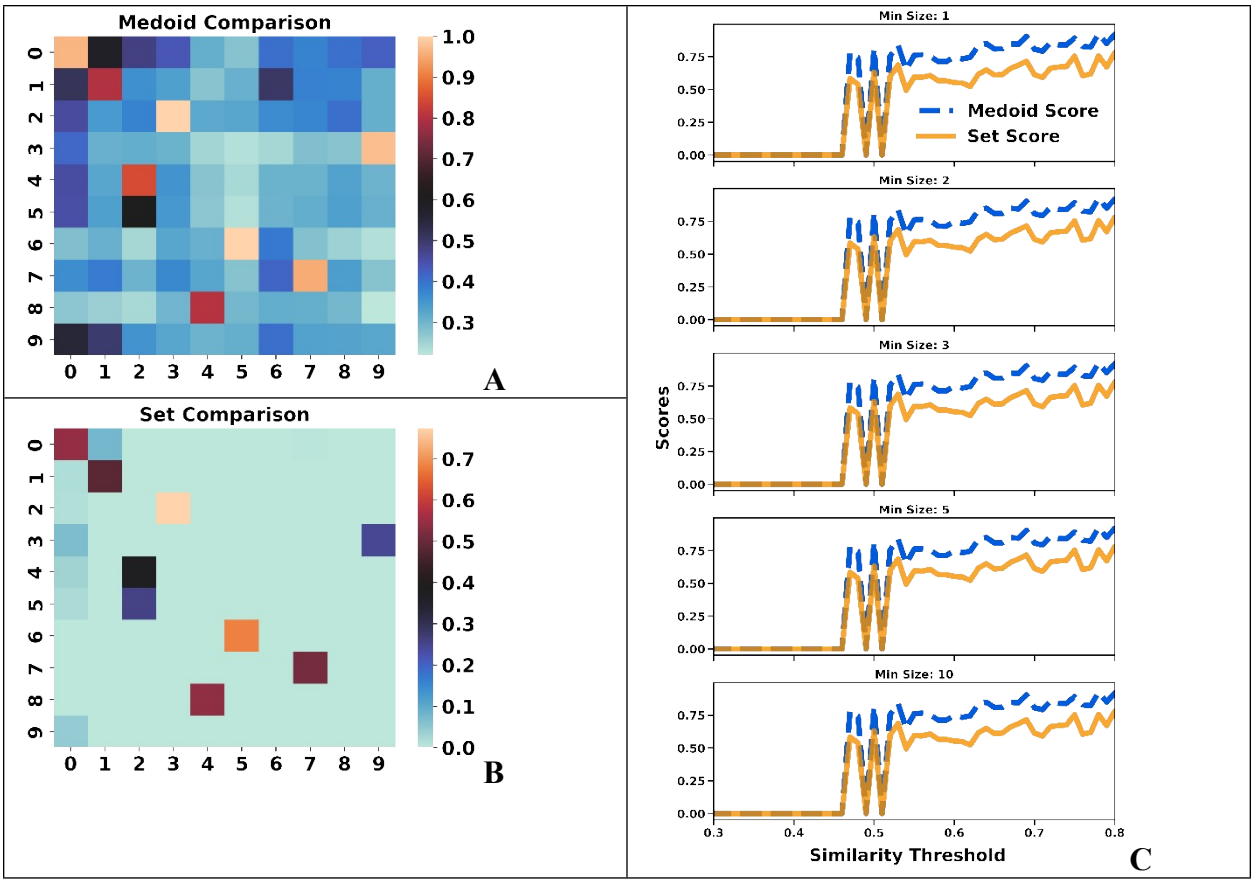
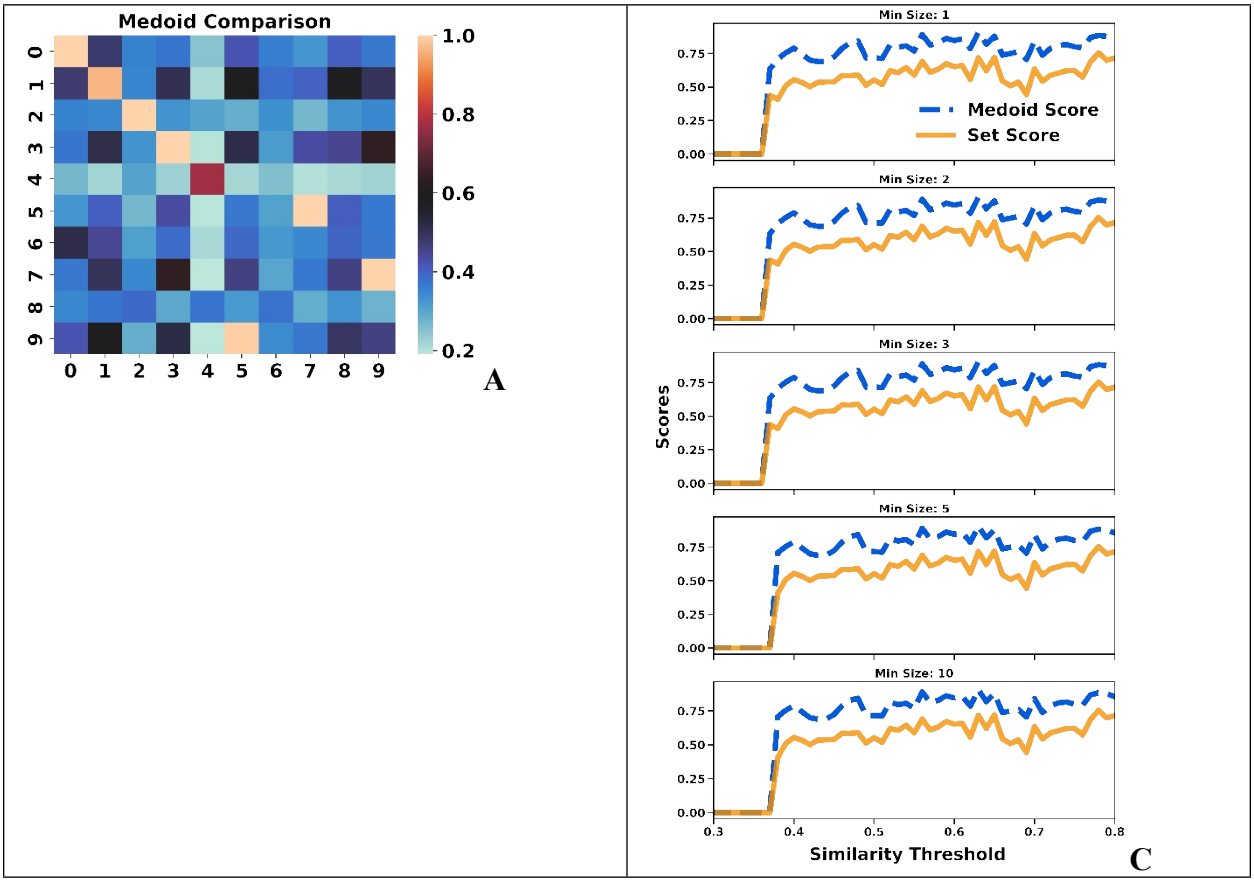


Figure S3.17: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [23] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.



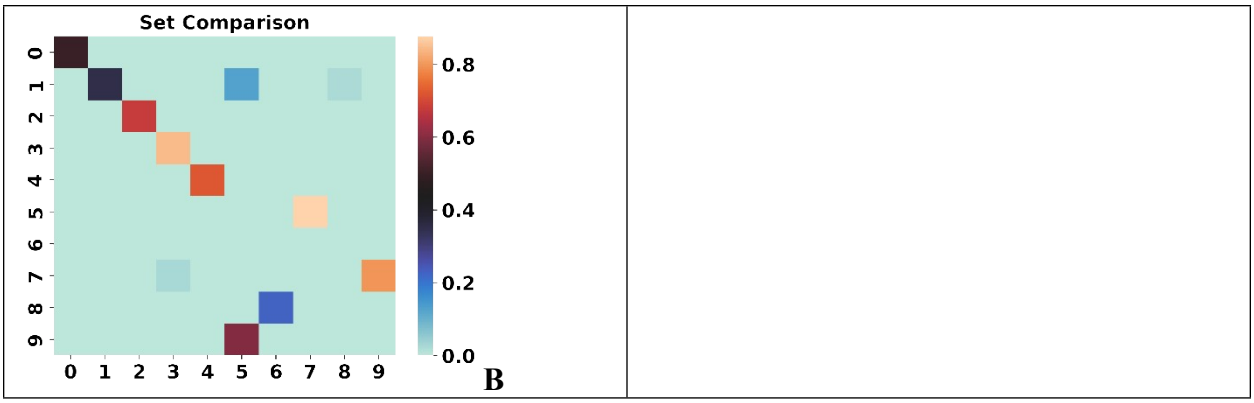


Figure S3.18: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [24] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

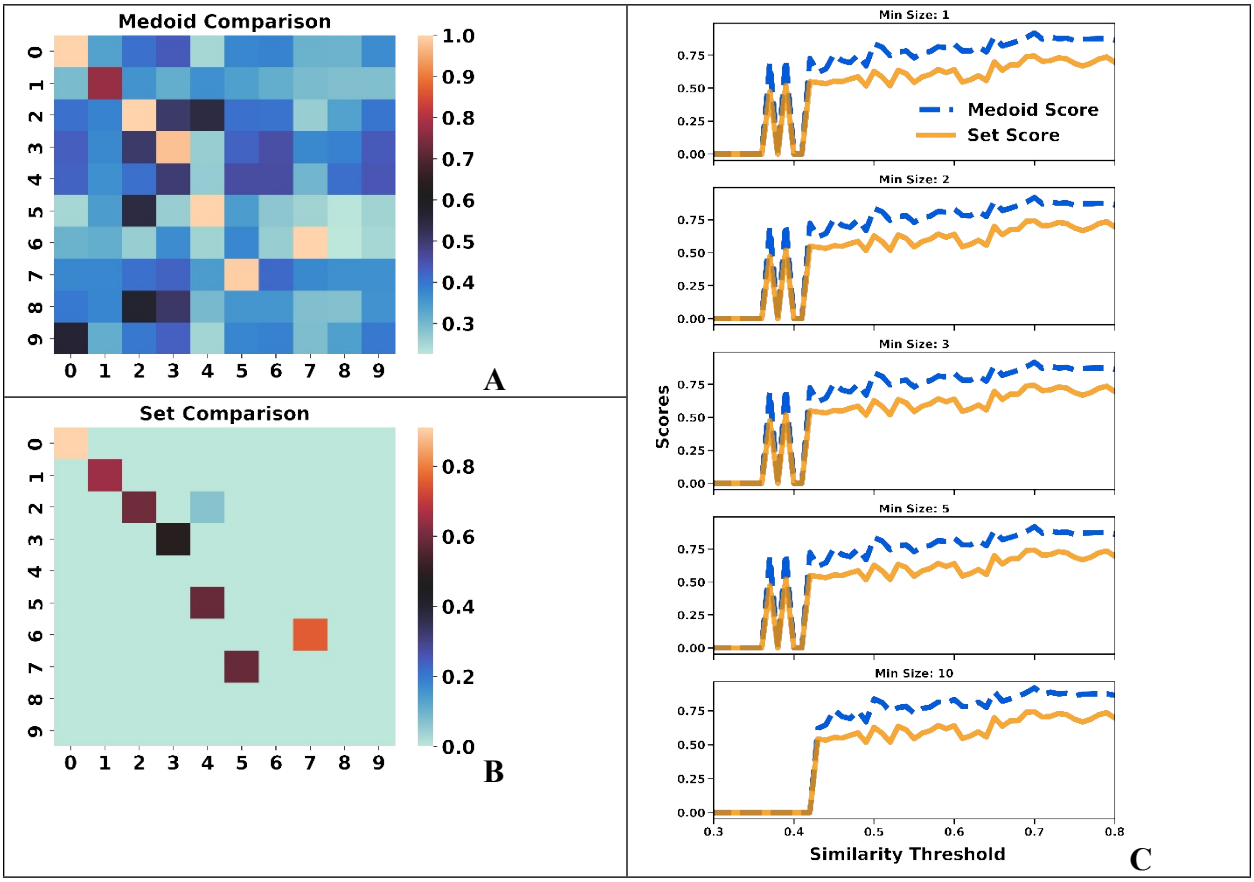


Figure S3.19: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [25] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

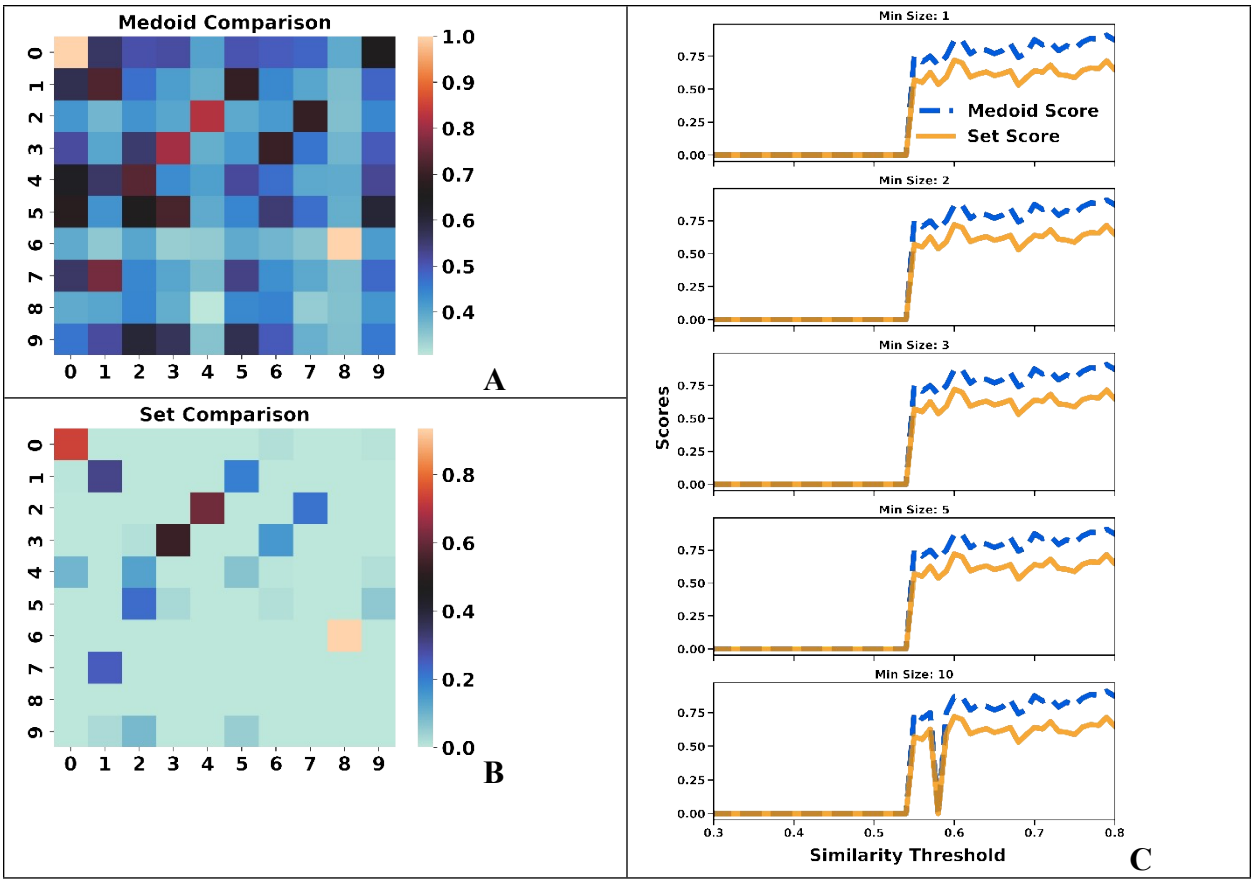
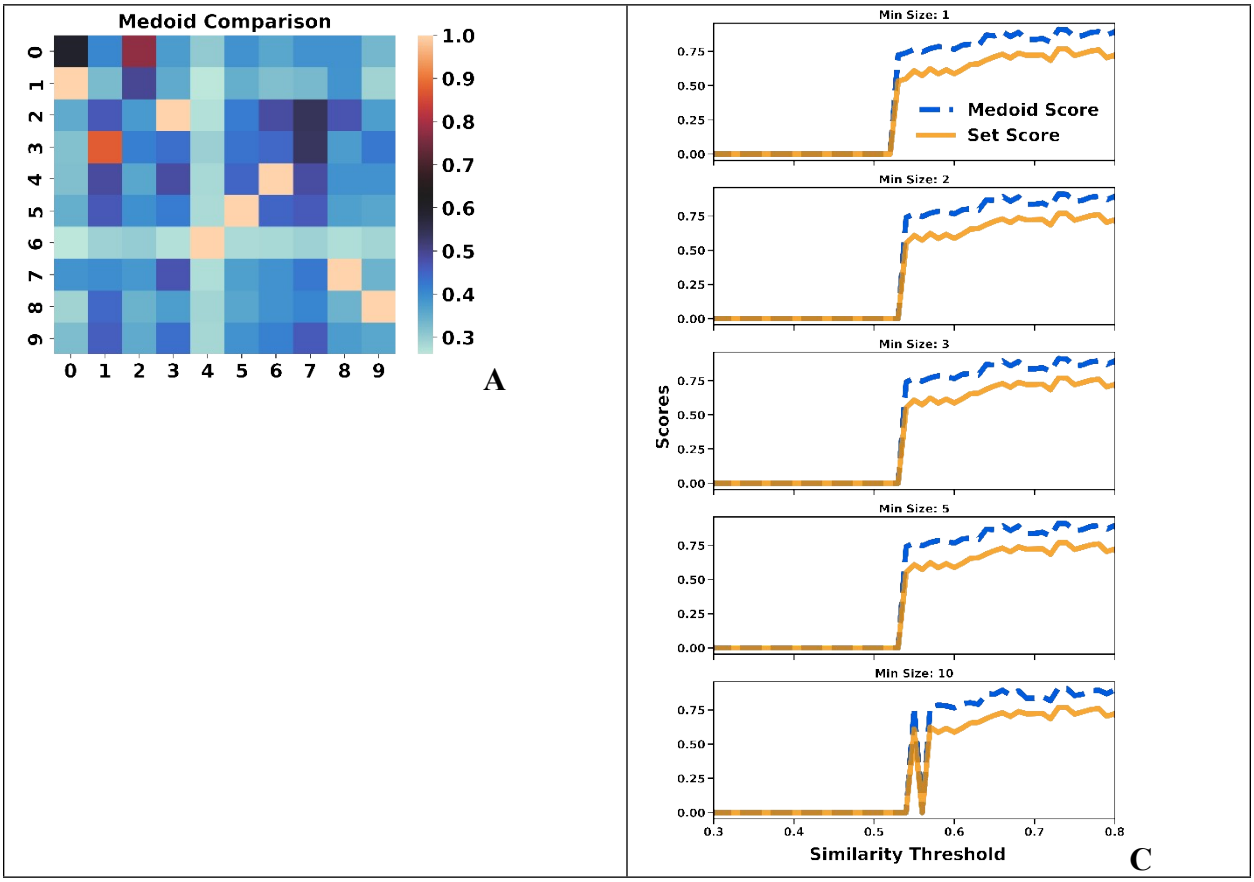


Figure S3.20: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [26] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.



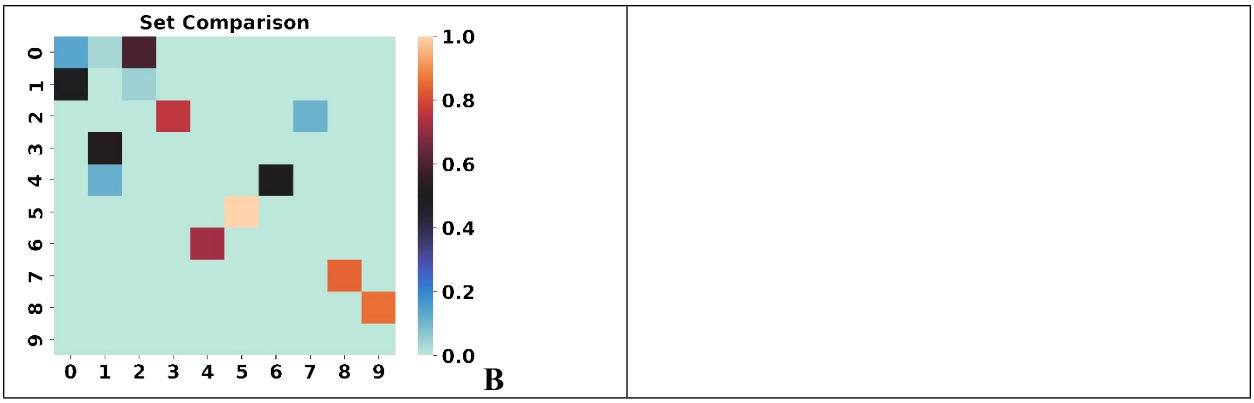


Figure S3.21: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [28] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

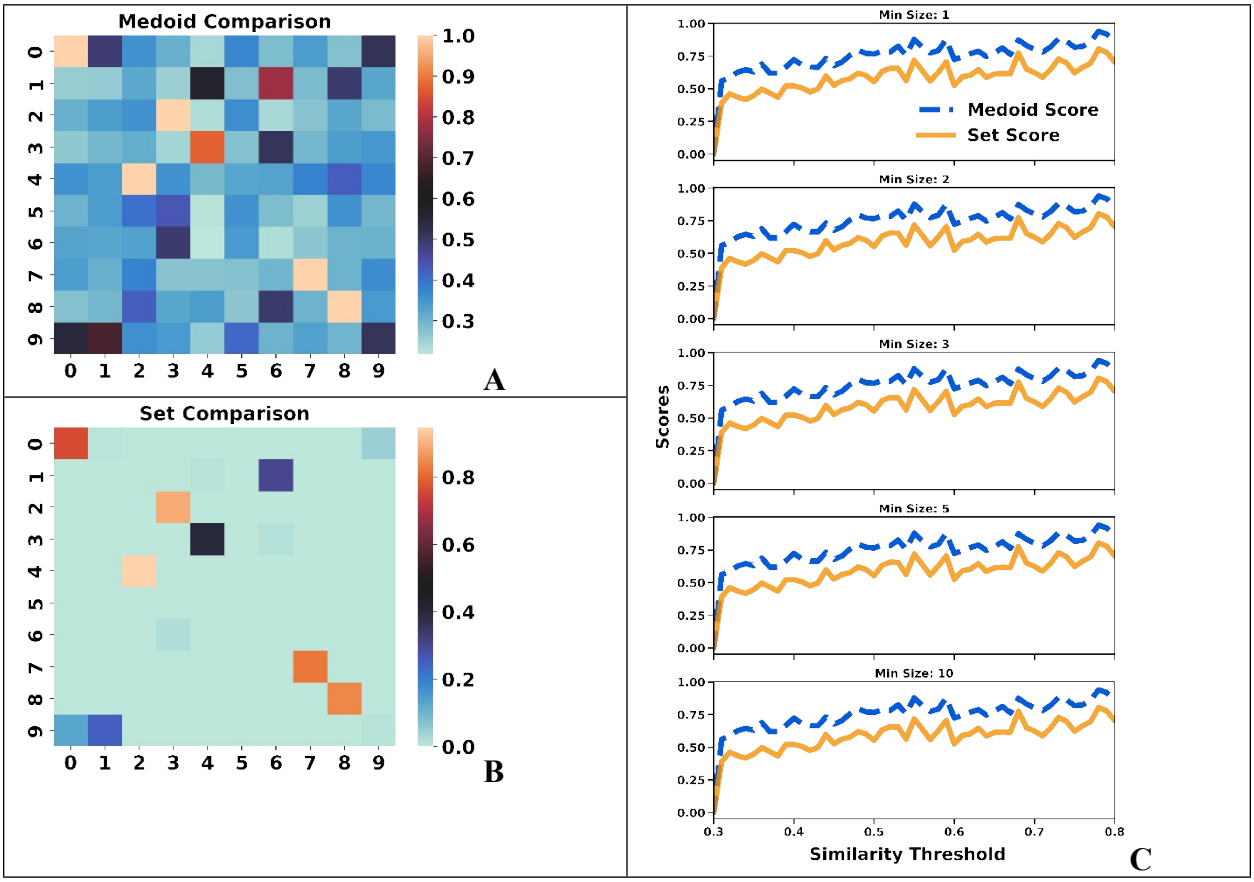


Figure S3.22: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [29] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

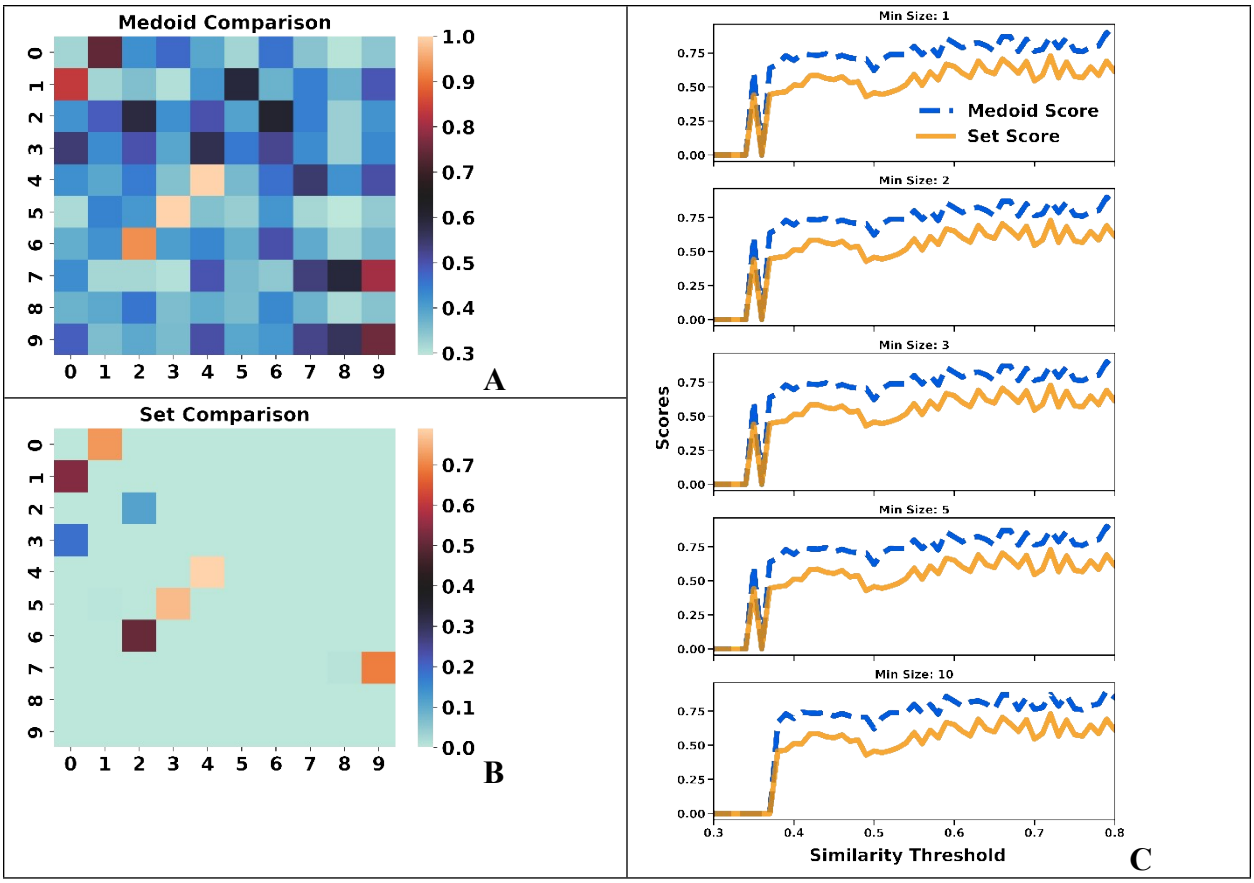


Figure S3.23: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [30] ChEMBL subset (similarity threshold = 0.65, min_size = 10). **C**: Medoid and Set scores.

S4: Clustering Performance Analysis BitBIRCH vs Taylor-Butina

The formula for the DBI used in the text is:

$$\mathrm{DBI} = \frac{1}{N_C}\sum_{j=1}^{N_C} \max_{j\neq i}\left\{\frac{\frac{1}{N_i}\sum_{v=1}^{N_i} \mathrm{T}\left(\mathbf{x}^{(i,v)},\mathbf{c}_i\right) + \frac{1}{N_j}\sum_{v=1}^{N_j} \mathrm{T}\left(\mathbf{x}^{(j,v)},\mathbf{c}_j\right)}{1-\mathrm{T}\left(\mathbf{c}_j,\mathbf{c}_i\right)}\right\} \quad \text{* MERGEFORMAT (6)}$$

The formula for the DI used in the text is:

$$\mathrm{DI} = \frac{\min\left\{1-i\mathrm{T}\left(\mathbf{X}^{(j)}\cup\mathbf{X}^{(i)}\right)\right\}}{\max\left\{i\mathrm{T}\left(\mathbf{X}^{(i)}\right)\right\}} \quad \text{* MERGEFORMAT (7)}$$

The full analysis of the quality of clustering for the 30 ChEMBL subsets is presented below.

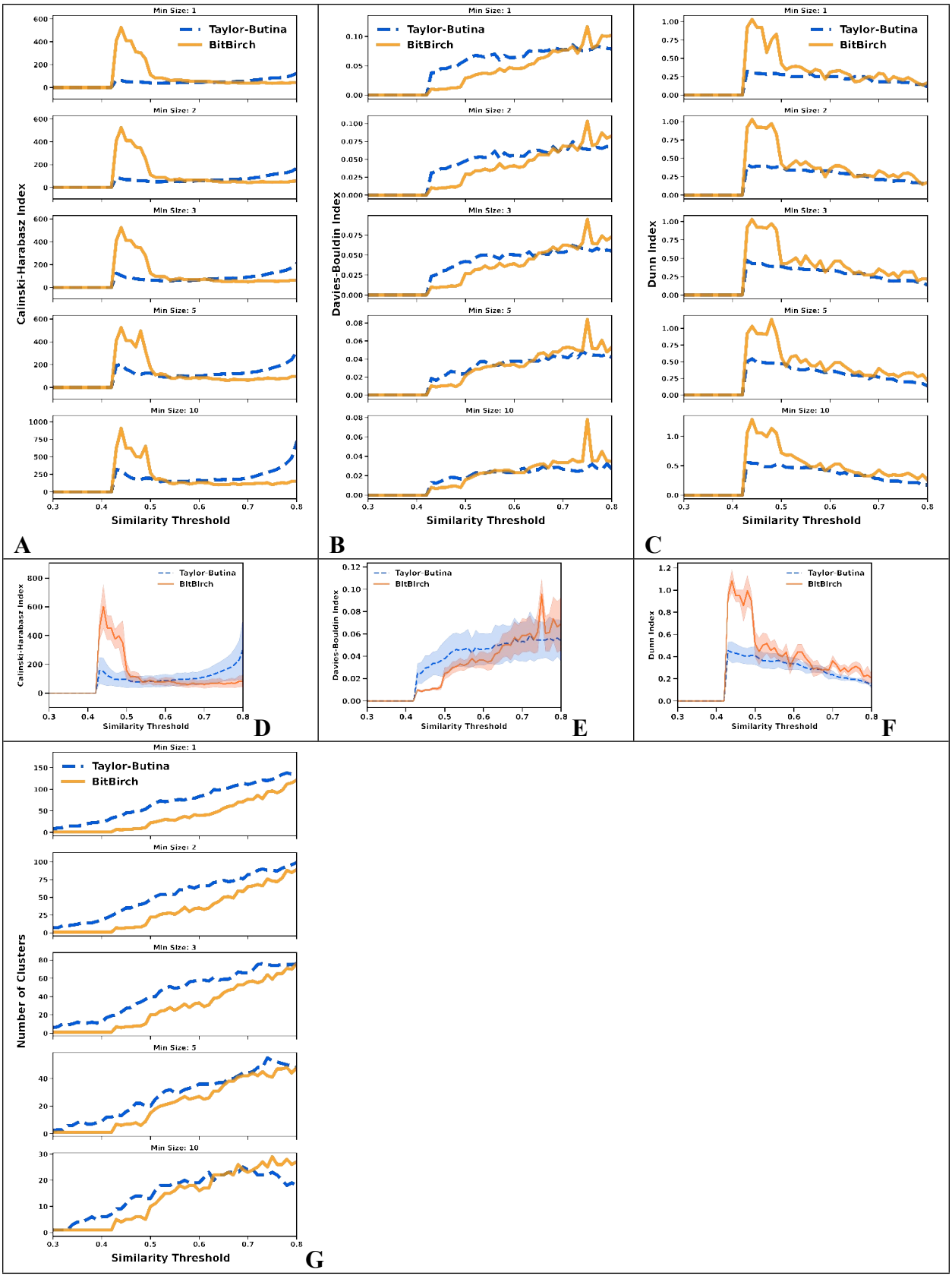
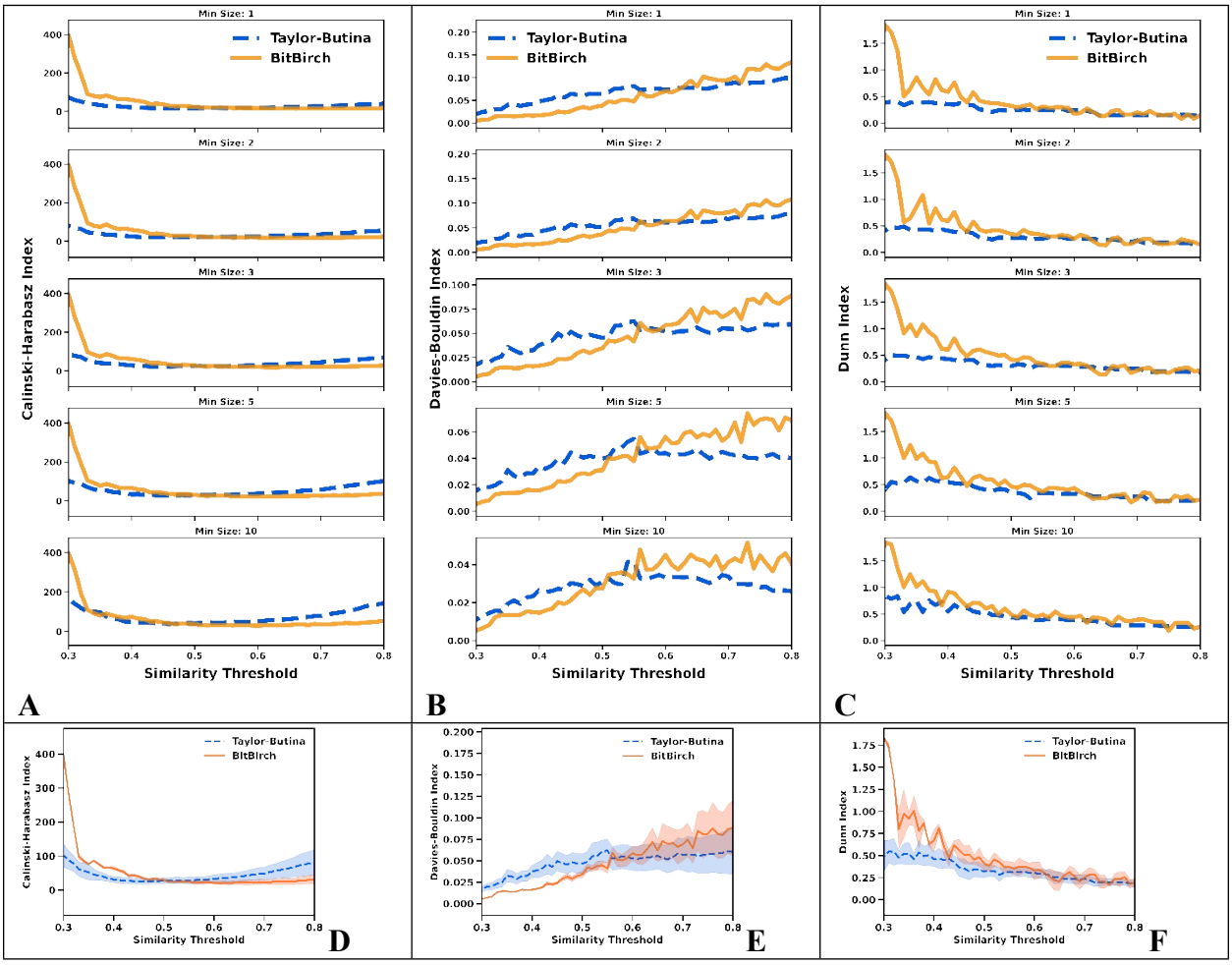

Min Size: 1
Min Size: 2
Min Size: 3
Min Size: 5
Min Size: 10
Taylor-Butina
BitBirch
Calinski-Harabasz Index
Davies-Bouldin Index
Dunn Index
Number of Clusters
Similarity Threshold
A
B
C
D
E
F
G

Figure S4.1: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [1] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



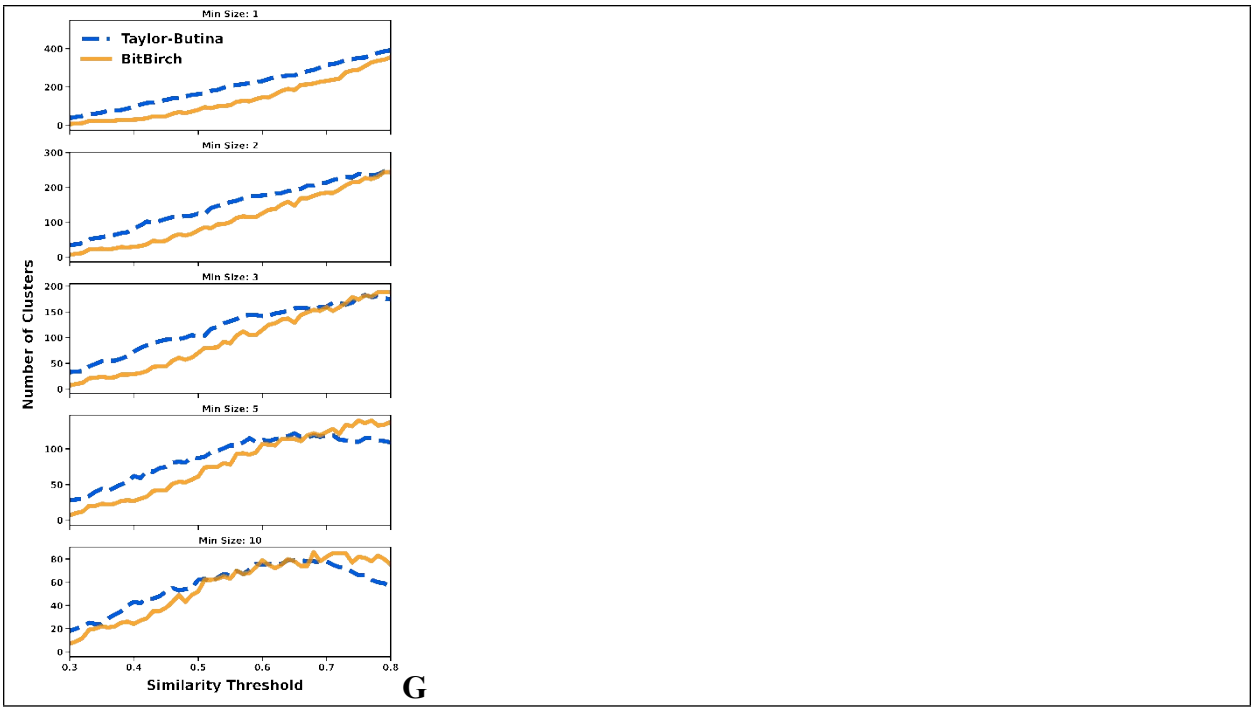
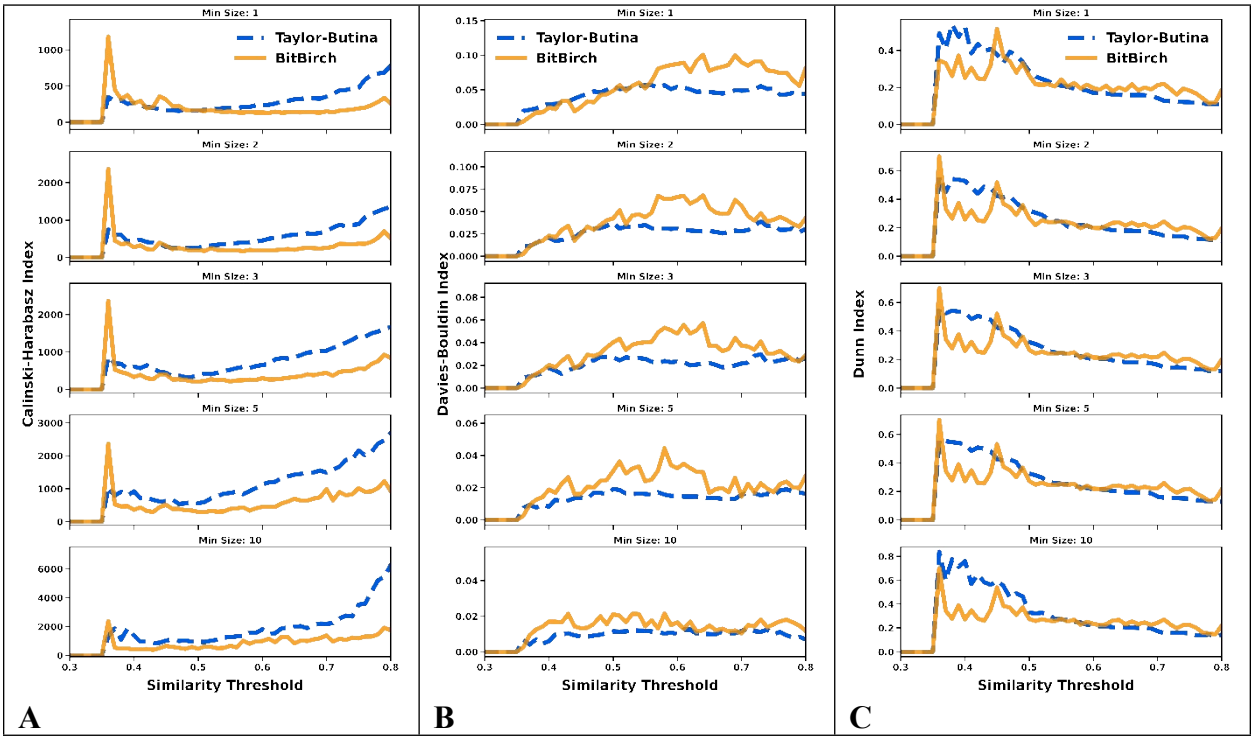


Figure S4.2: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [2] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



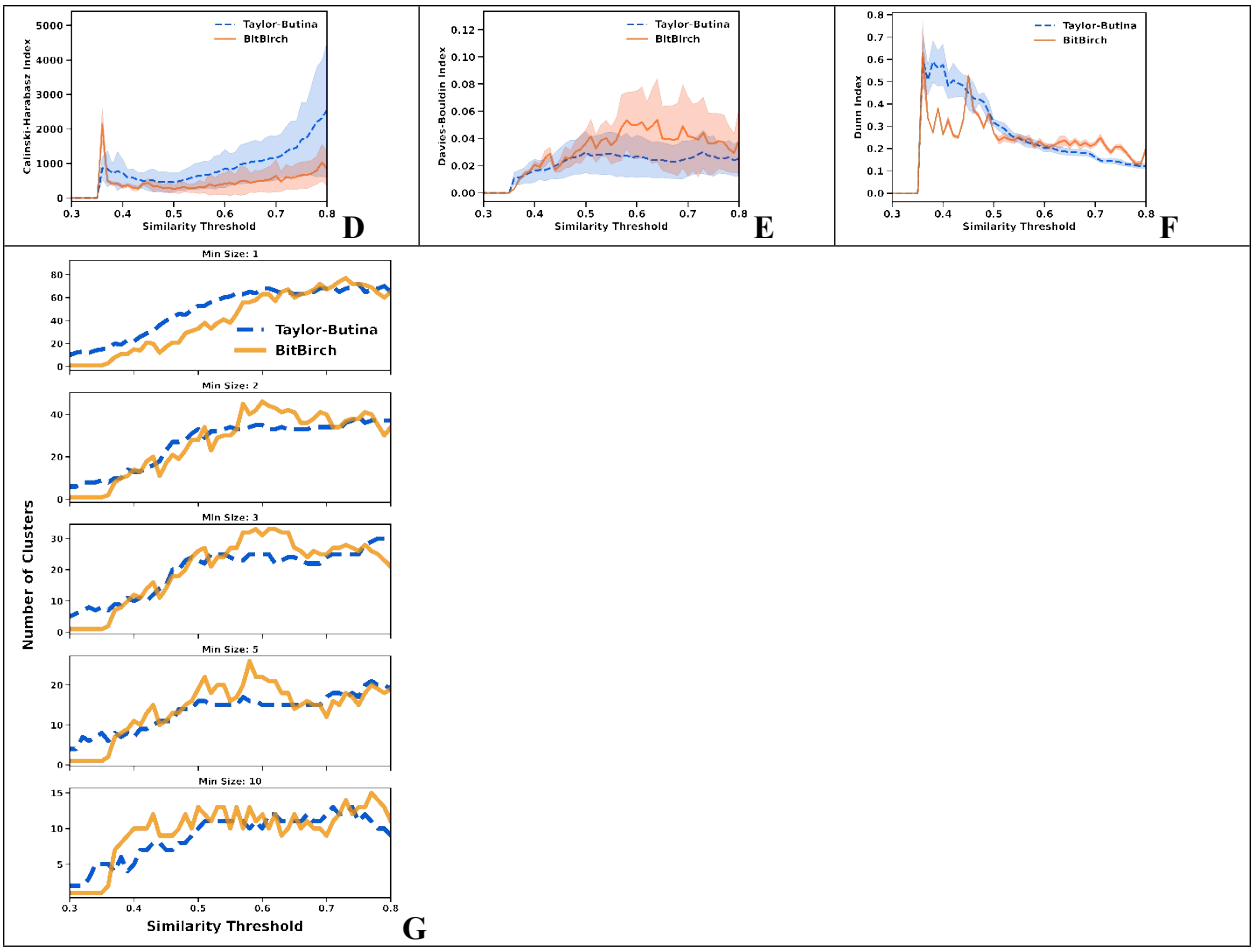
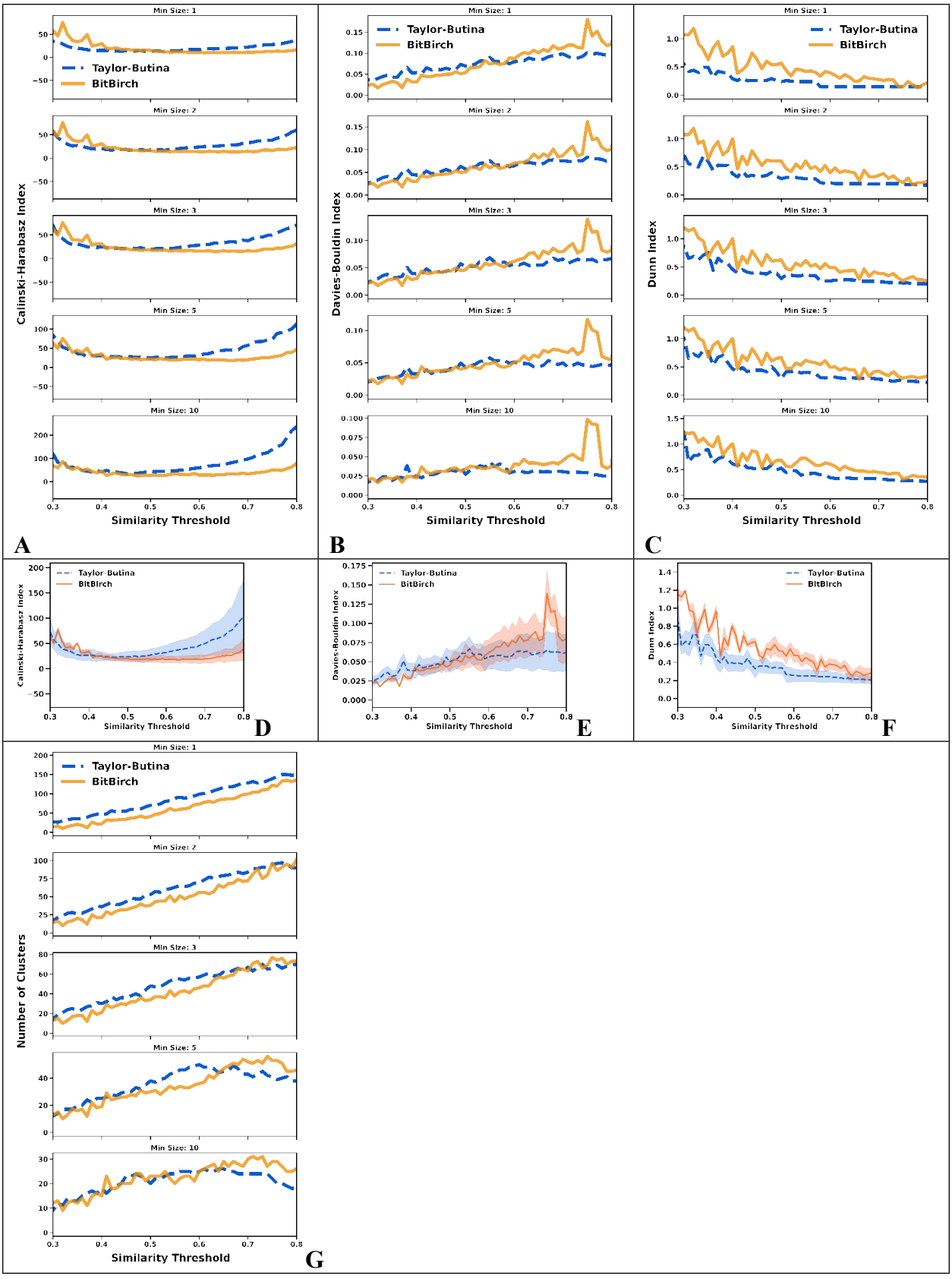


Figure S4.3: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [3] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).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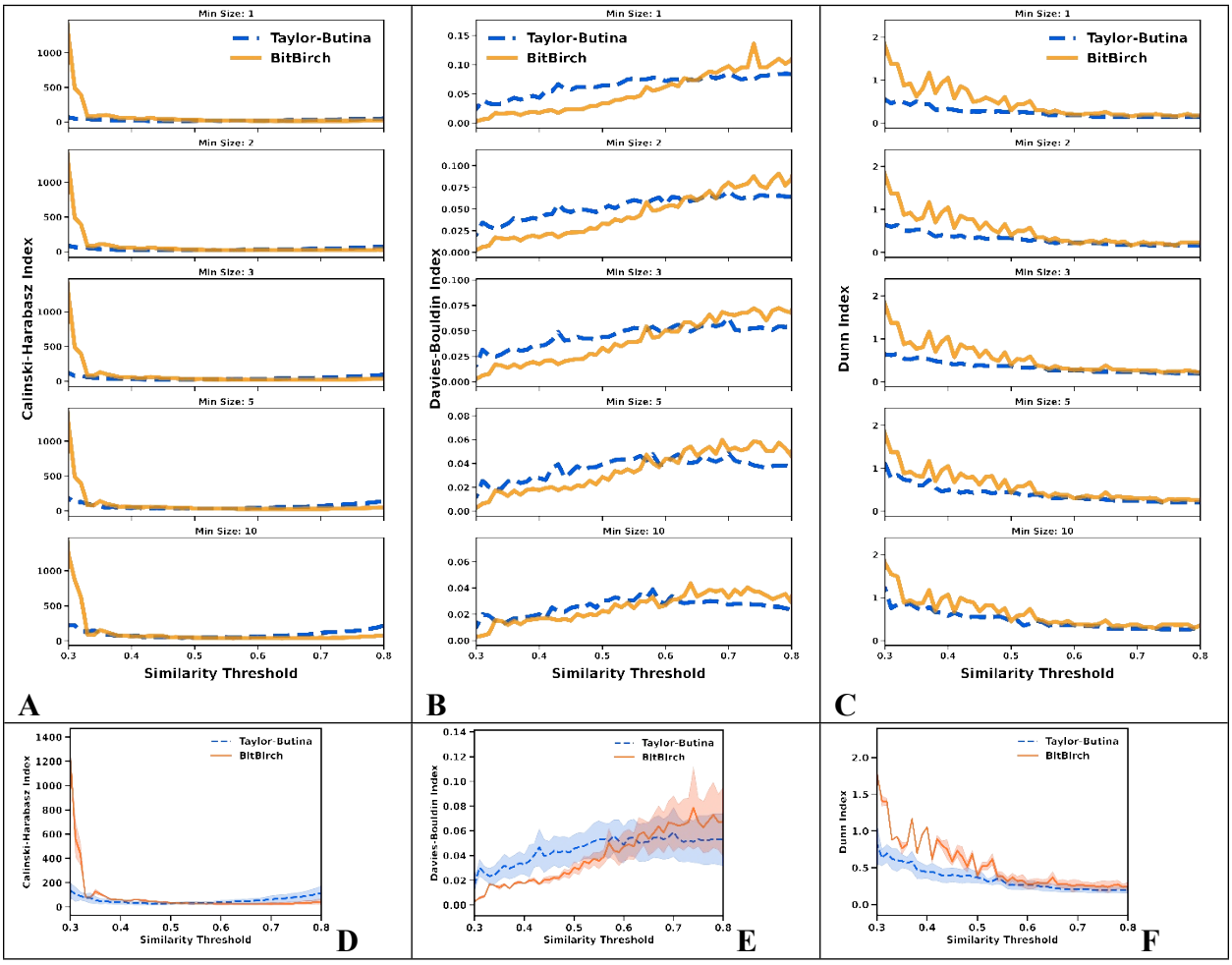
Min Size: 3
Min Size: 5
Min Size: 10
Taylor-Butina
BitBirch
Calinski-Harabasz Index
Davies-Bouldin Index
Dunn Index
Number of Clusters
Similarity Threshold
A
B
C
D
E
F
G

Figure S4.4: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [4] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



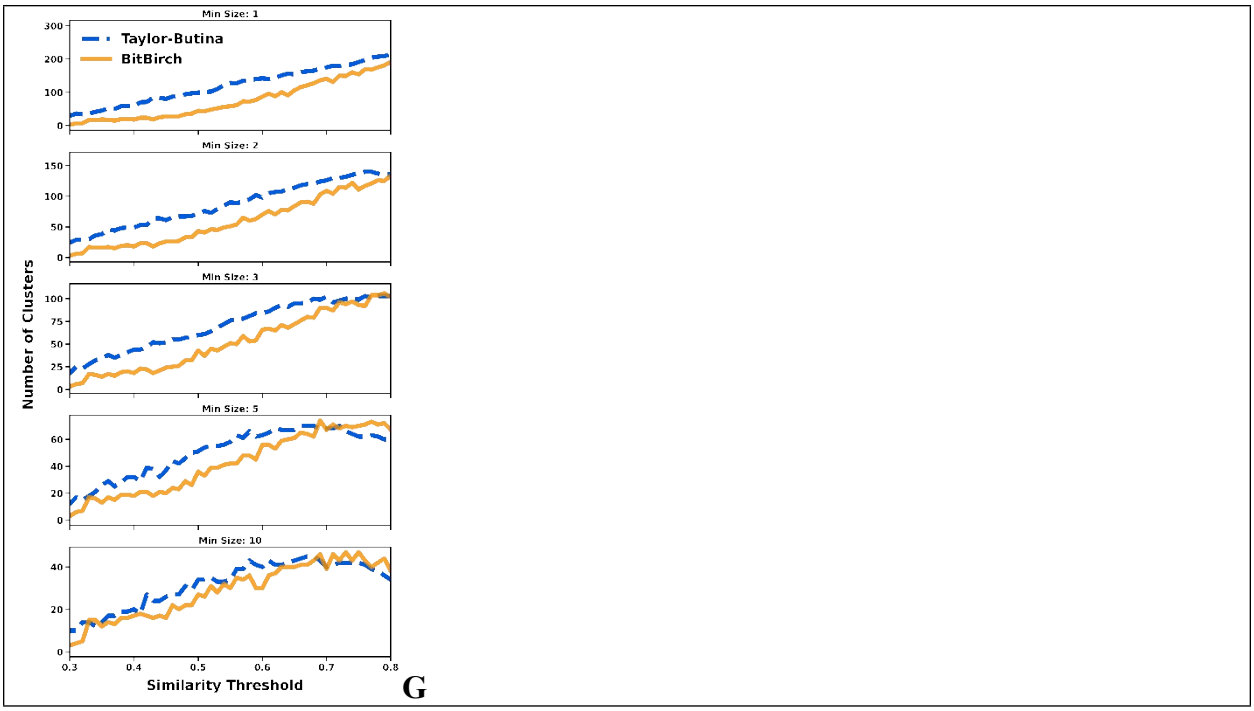
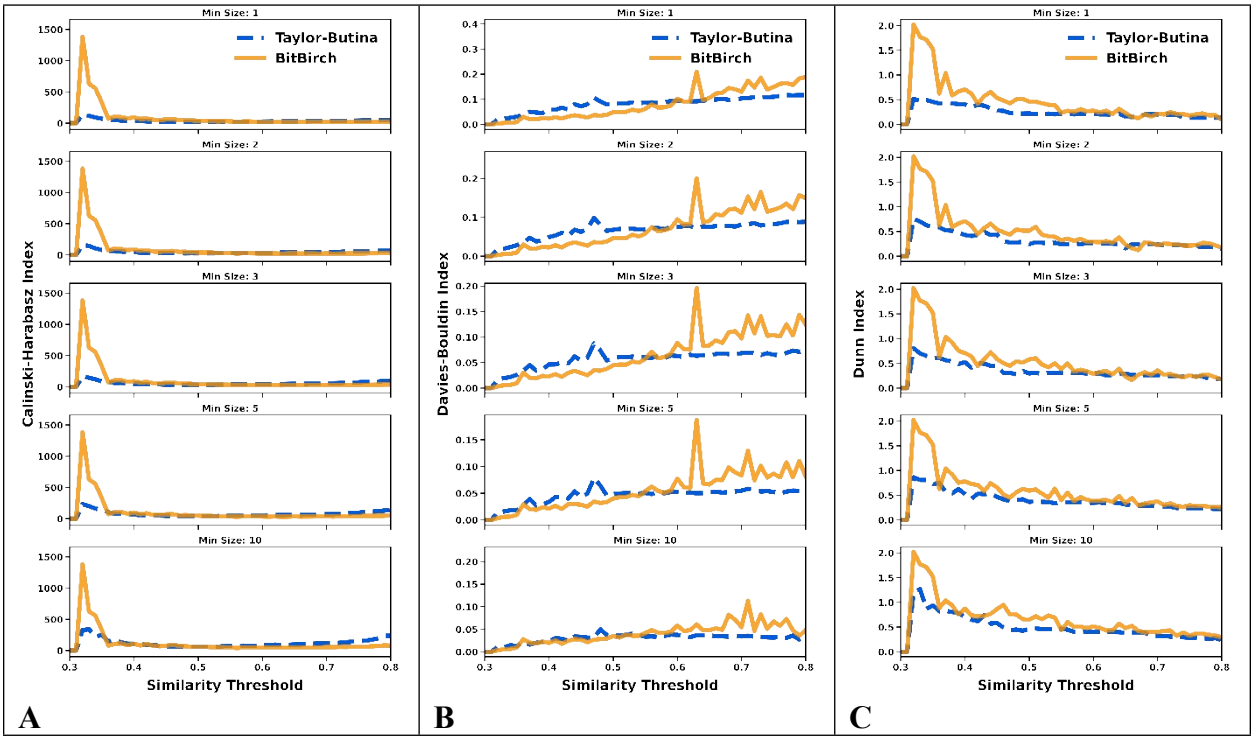


Figure S4.5: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [5] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



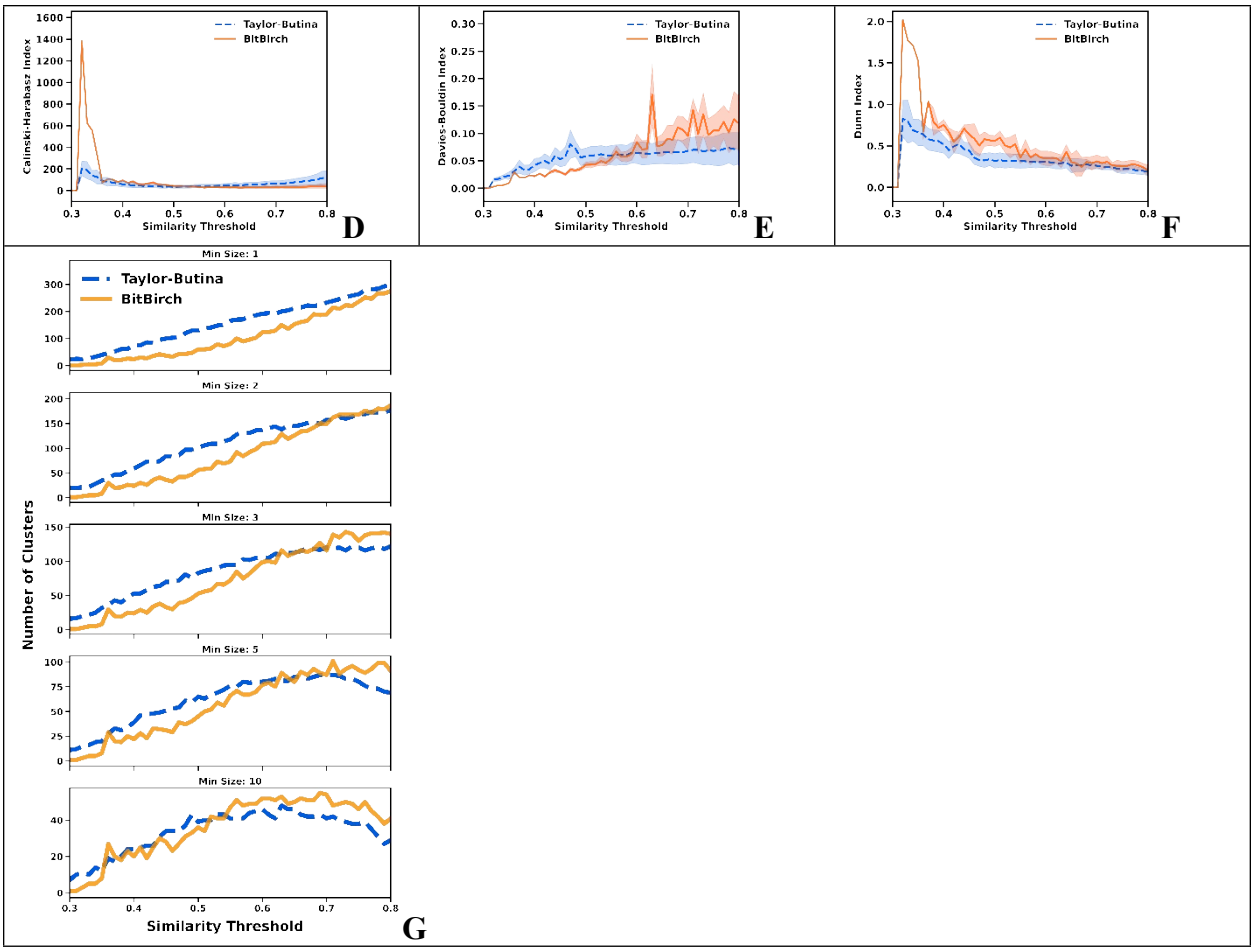
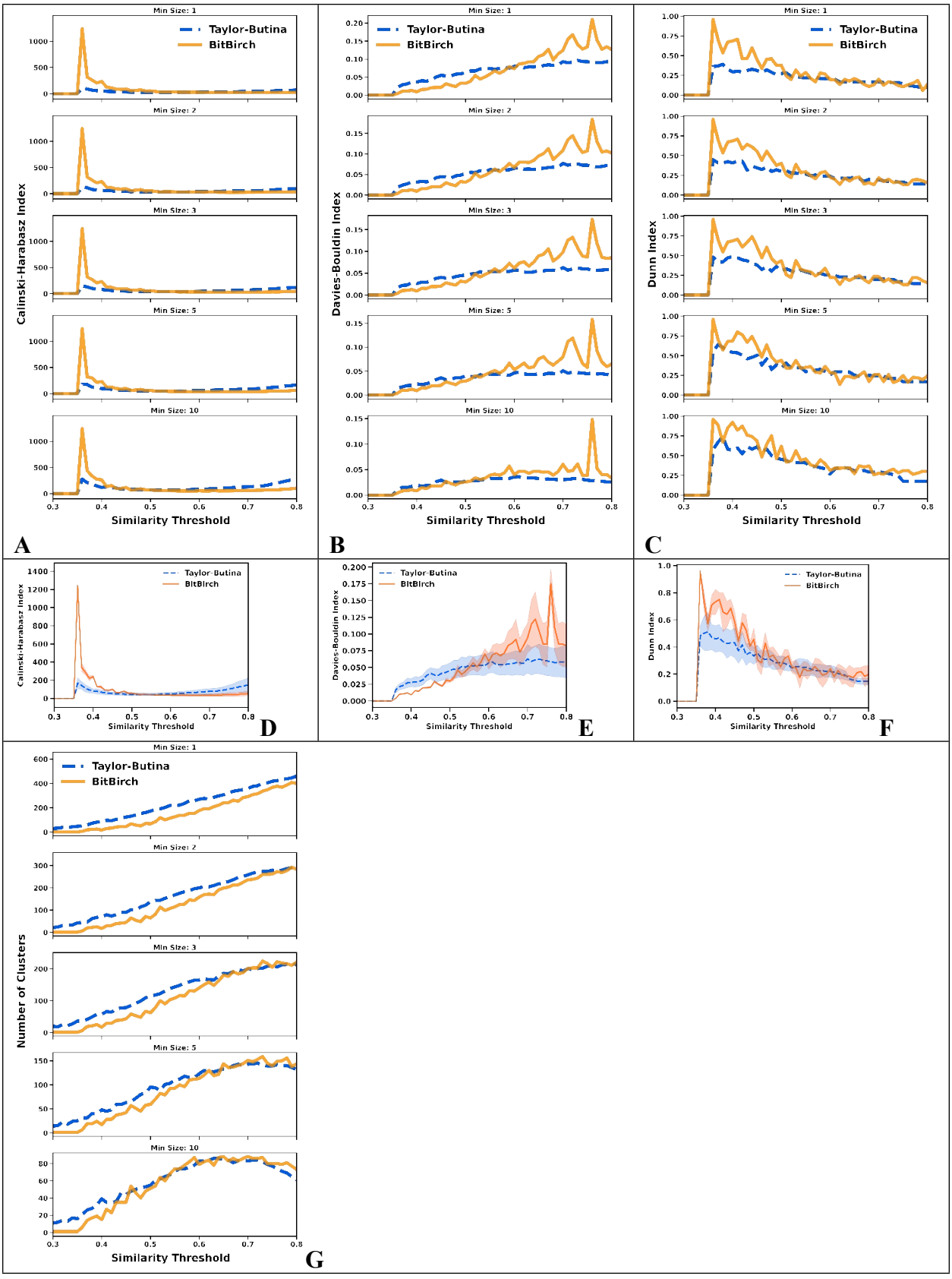


Figure S4.6: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [6] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).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Min Size: 3
Min Size: 5
Min Size: 10
Taylor-Butina
BitBirch
Calinski-Harabasz Index
Davies-Bouldin Index
Dunn Index
Number of Clusters
Similarity Threshold
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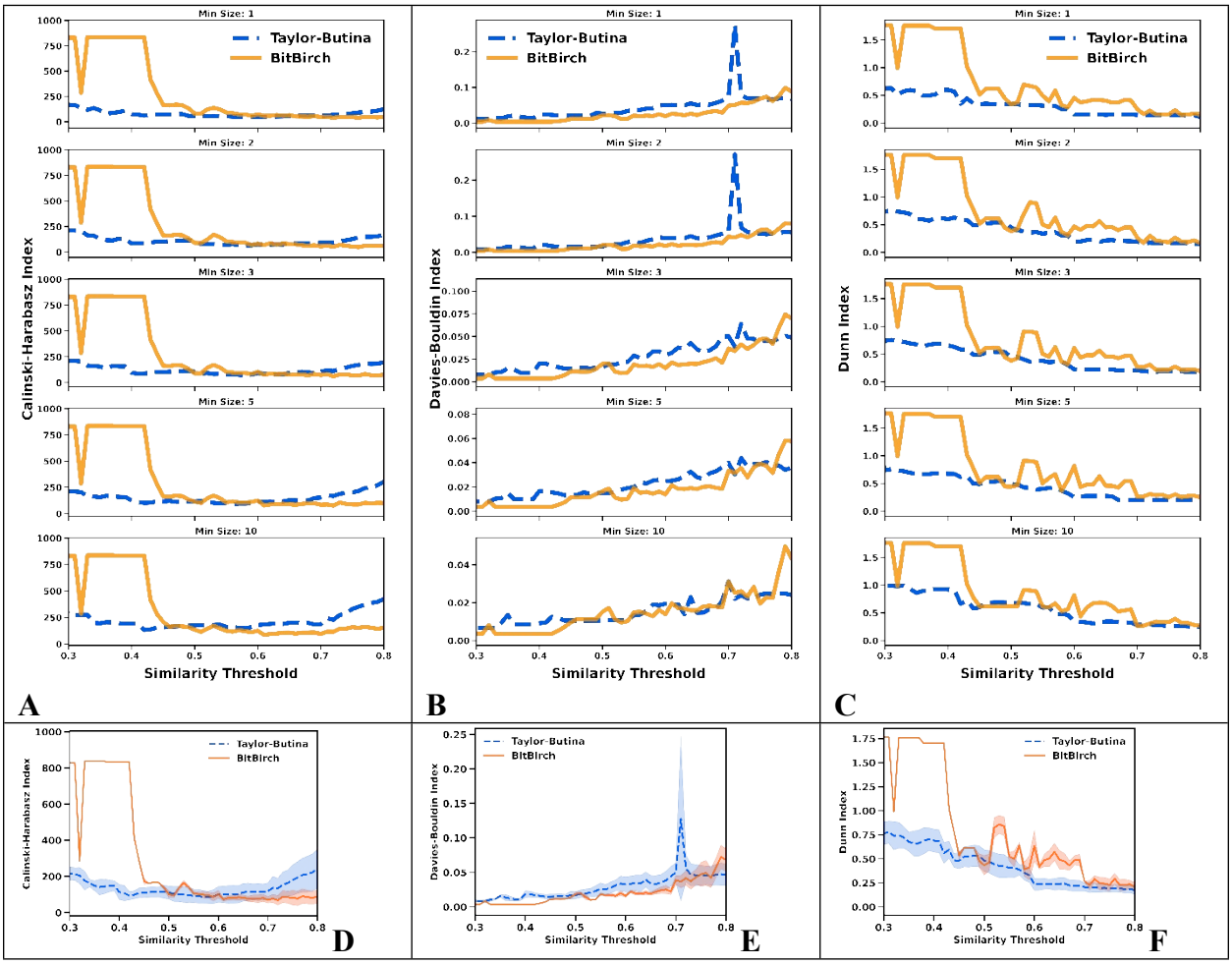
Figure S4.7: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [7] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



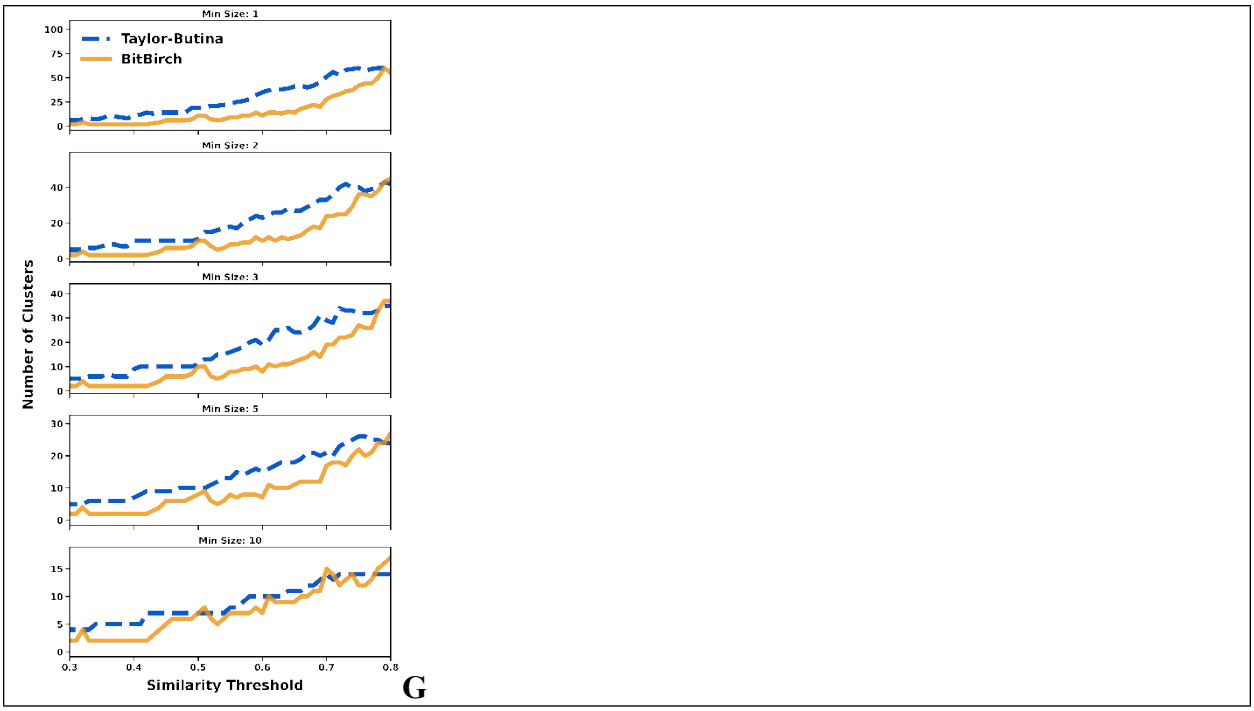
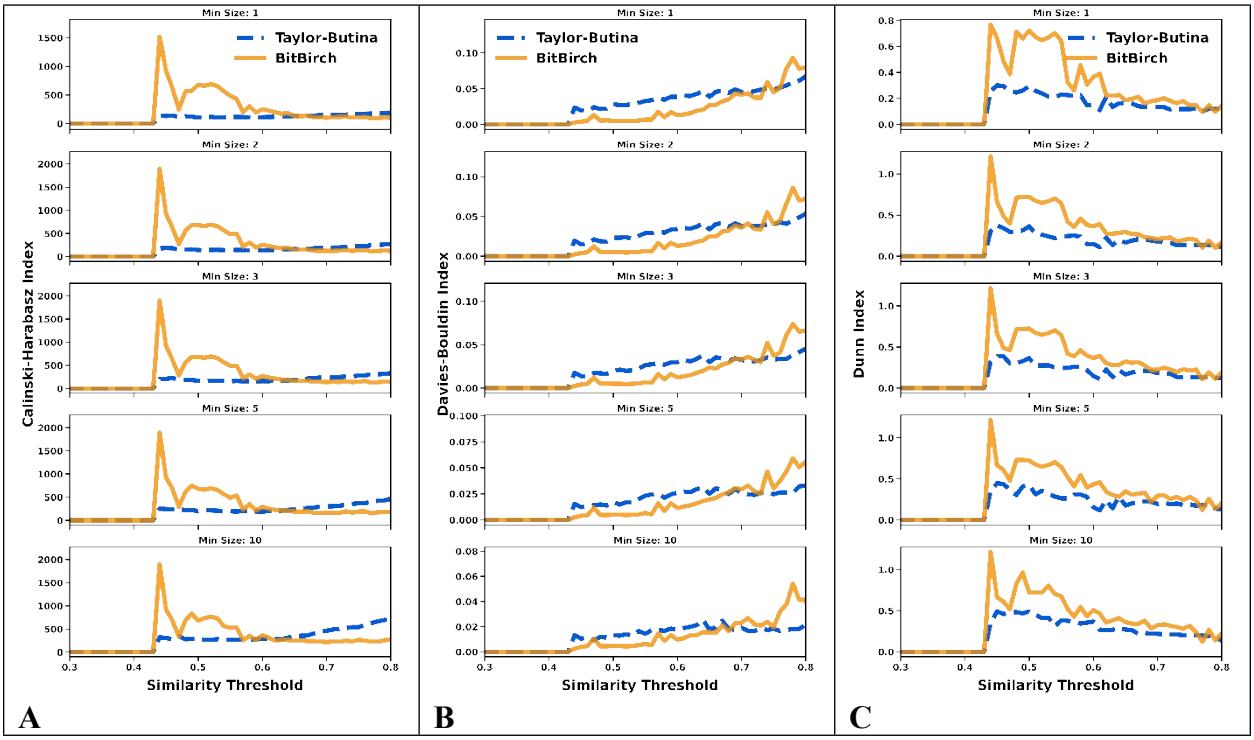


Figure S4.8: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [8] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



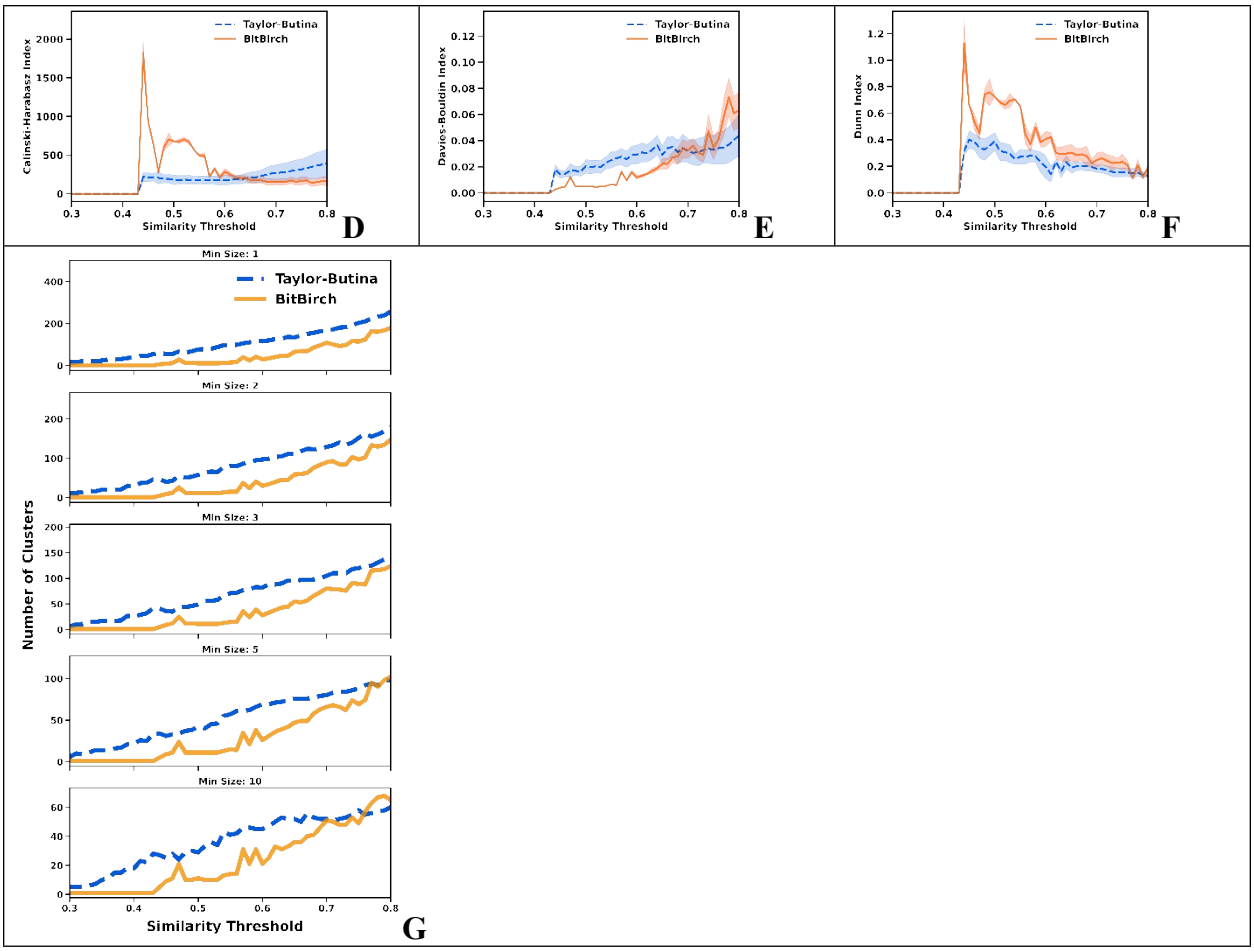


Figure S4.9: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [9] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).

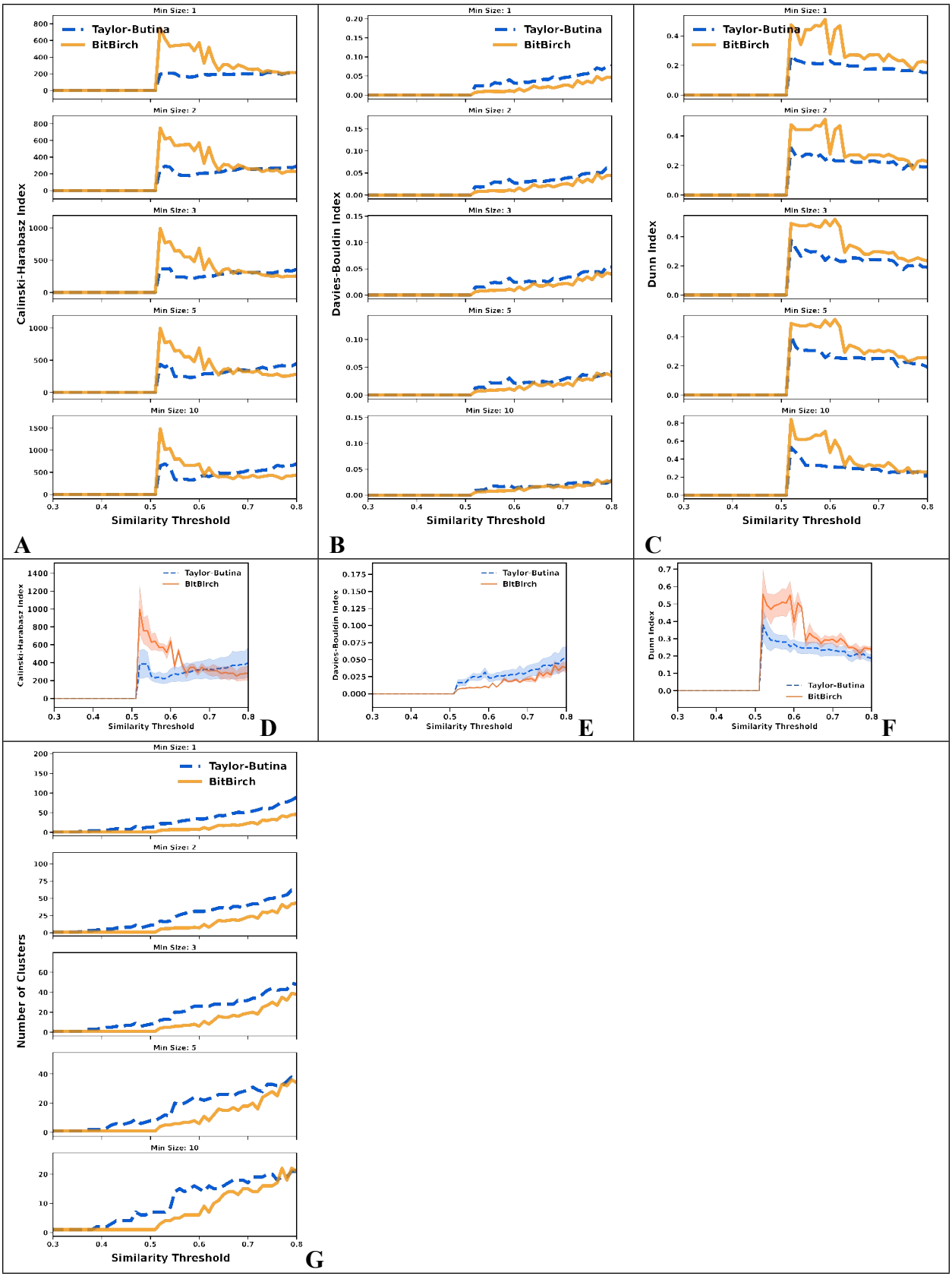

Min Size: 1
Min Size: 2
Min Size: 3
Min Size: 5
Min Size: 10
Taylor-Butina
BitBirch
Calinski-Harabasz Index
Davies-Bouldin Index
Dunn Index
Number of Clusters
Similarity Threshold
A
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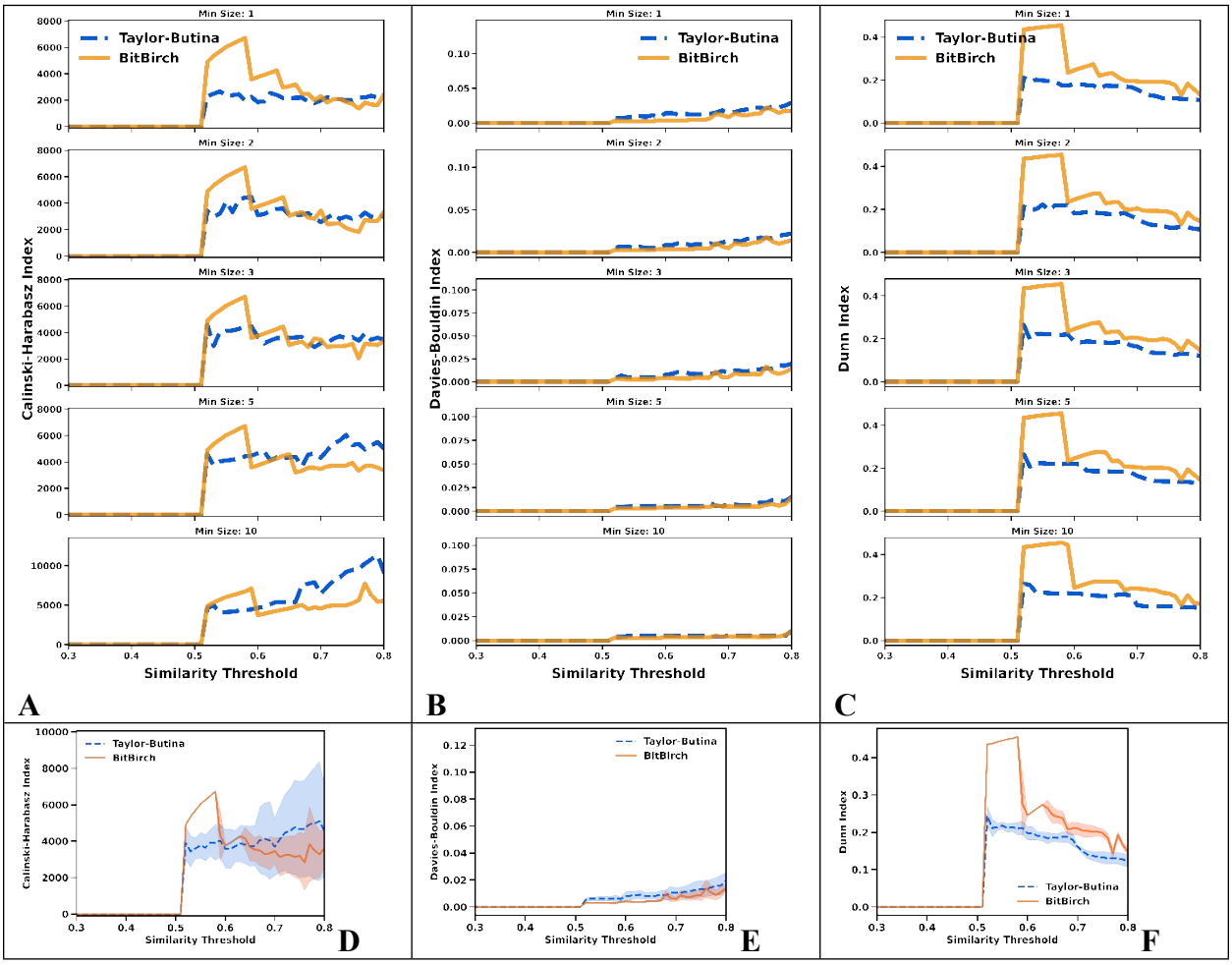
Figure S4.10: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [10] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



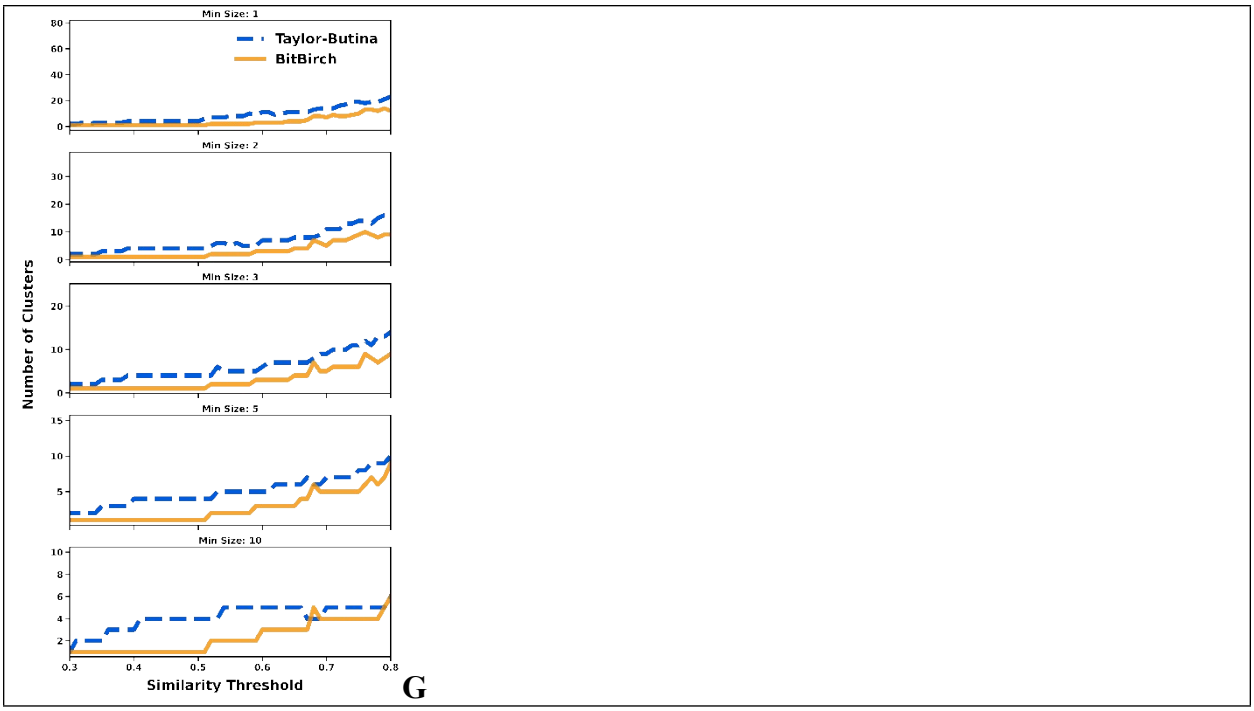
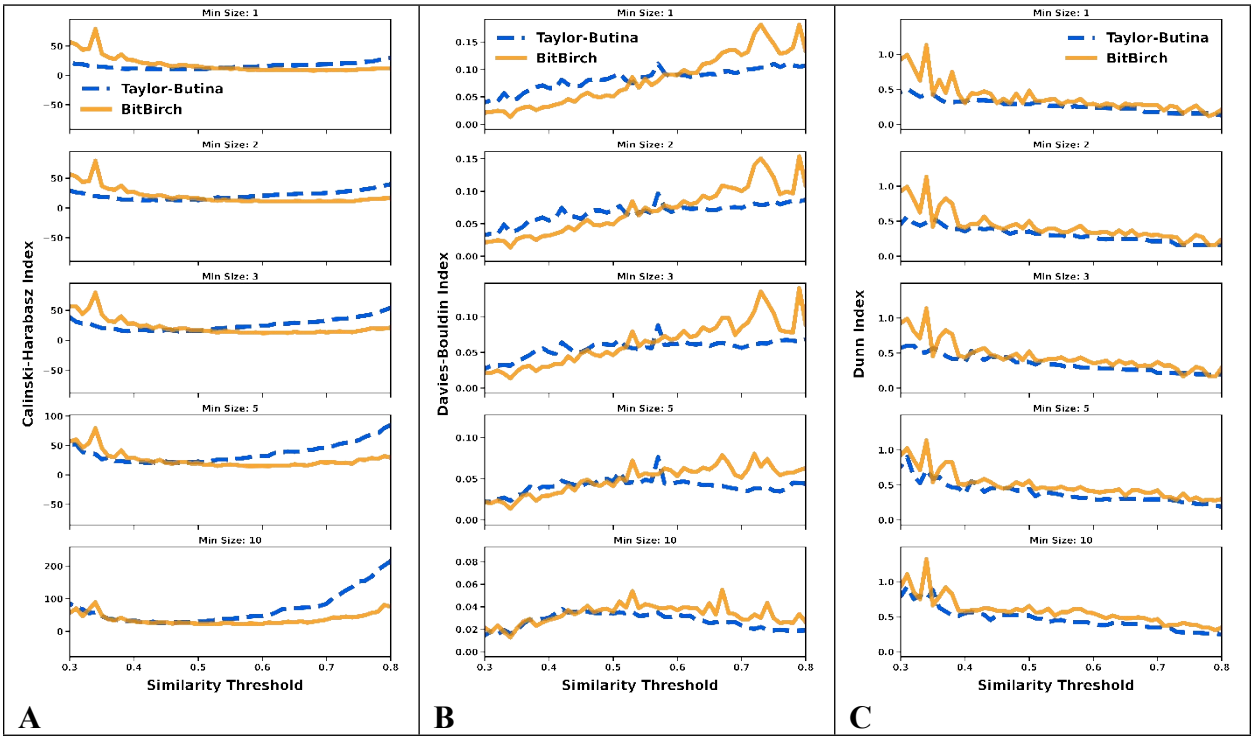


Figure S4.11: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [11] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



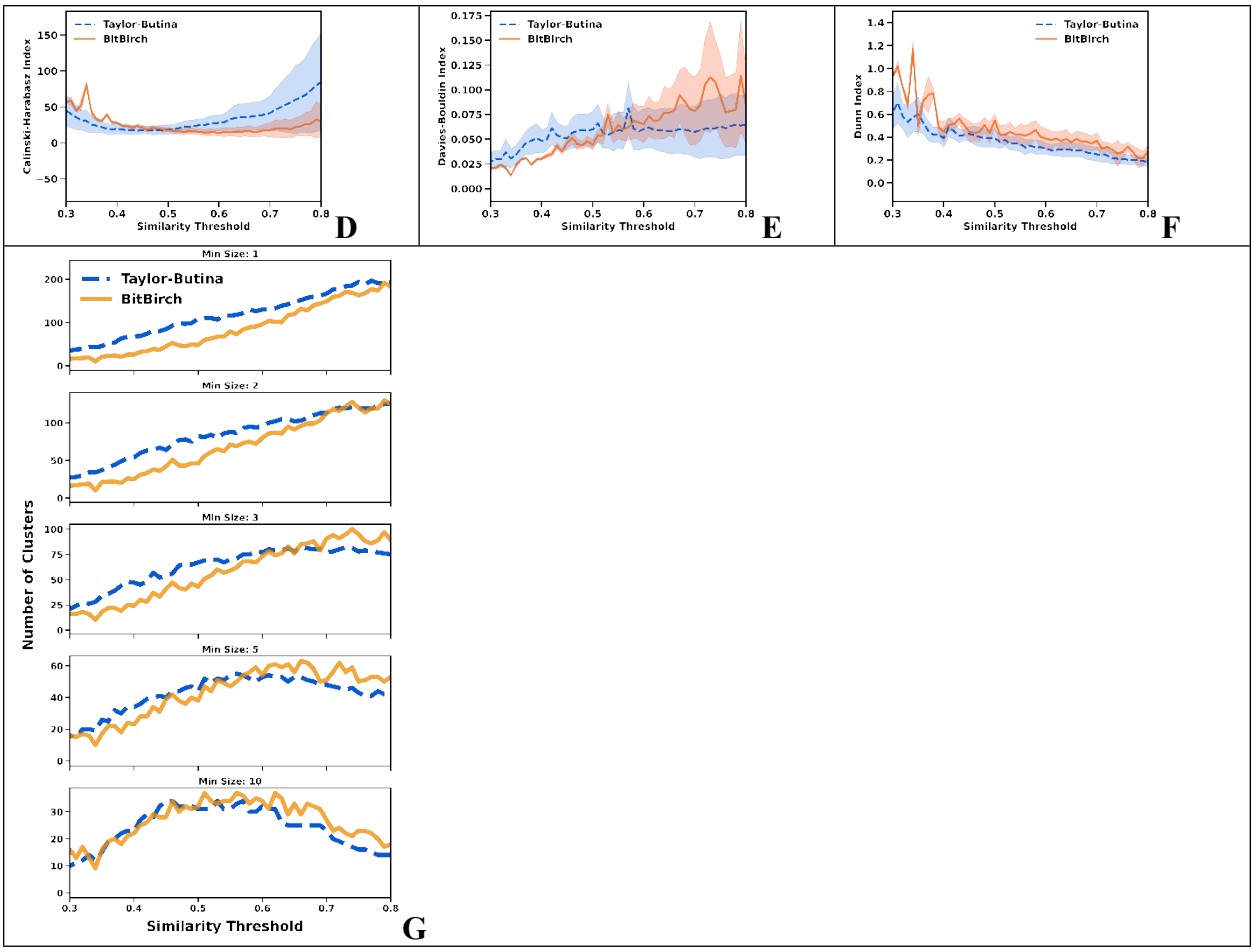


Figure S4.12: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [12] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).

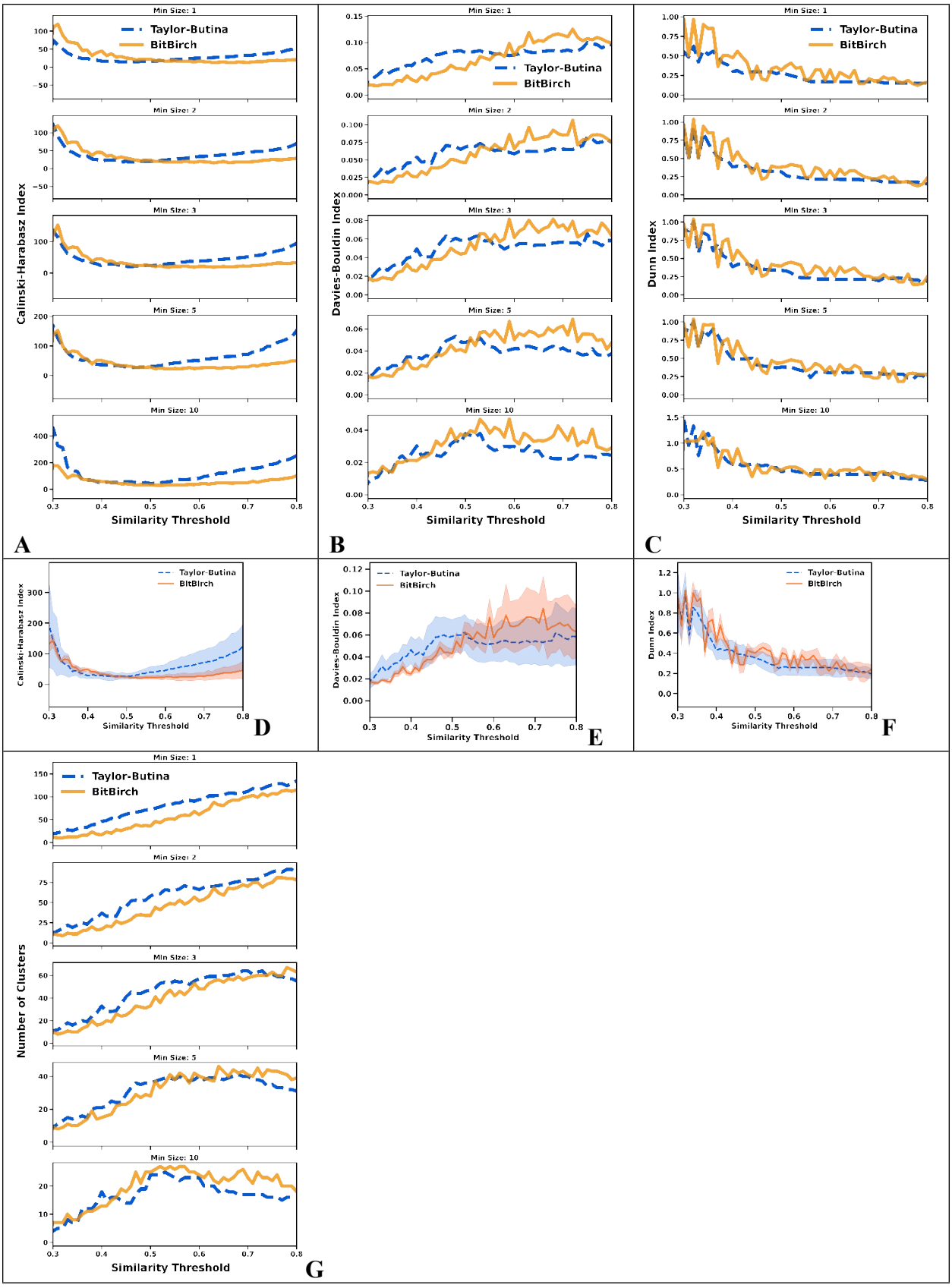

Min Size: 1
Min Size: 2
Min Size: 3
Min Size: 5
Min Size: 10
Taylor-Butina
BitBirch
Calinski-Harabasz Index
Davies-Bouldin Index
Dunn Index
Number of Clusters
Similarity Threshold
A
B
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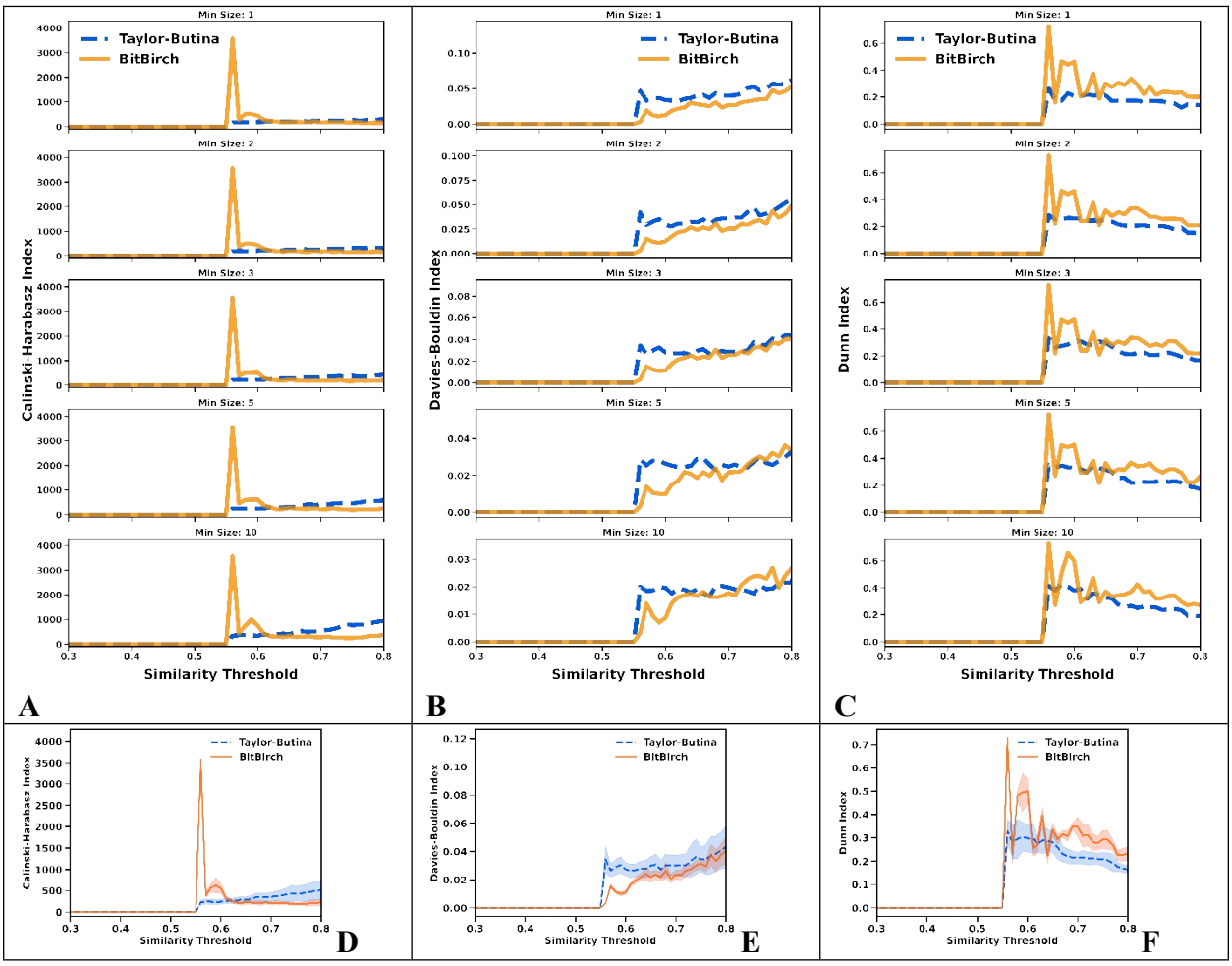
Figure S4.13: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [13] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



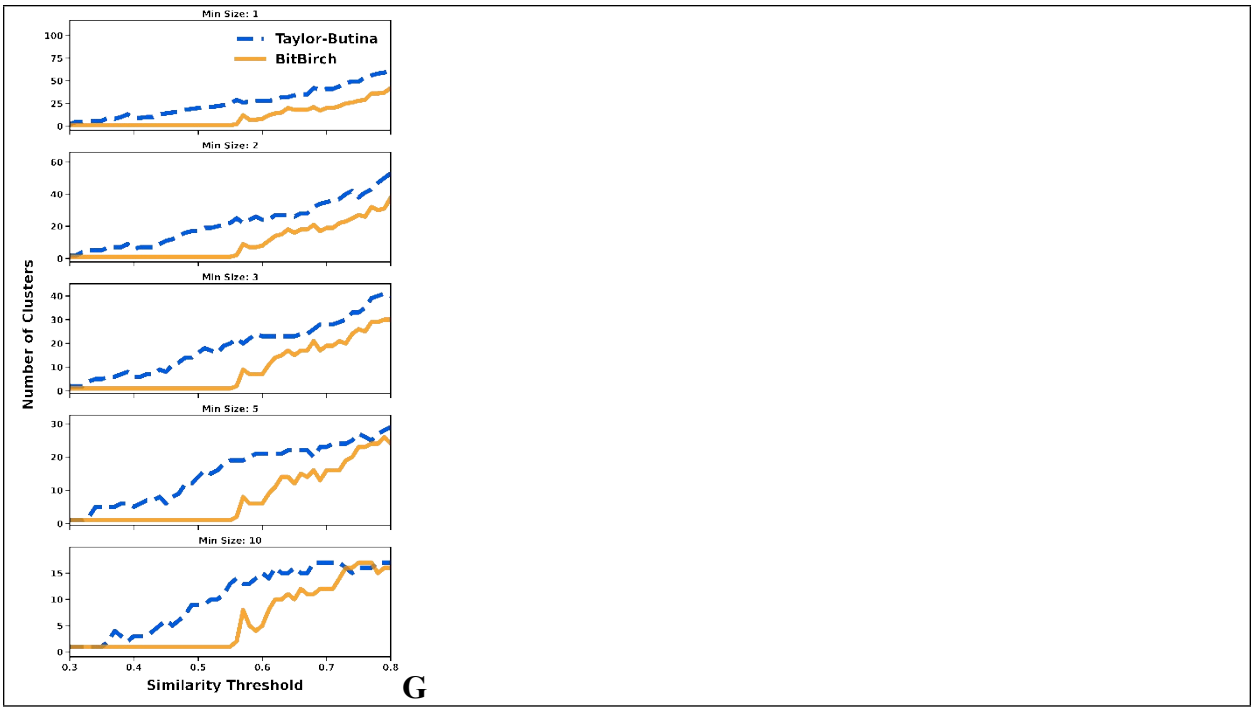
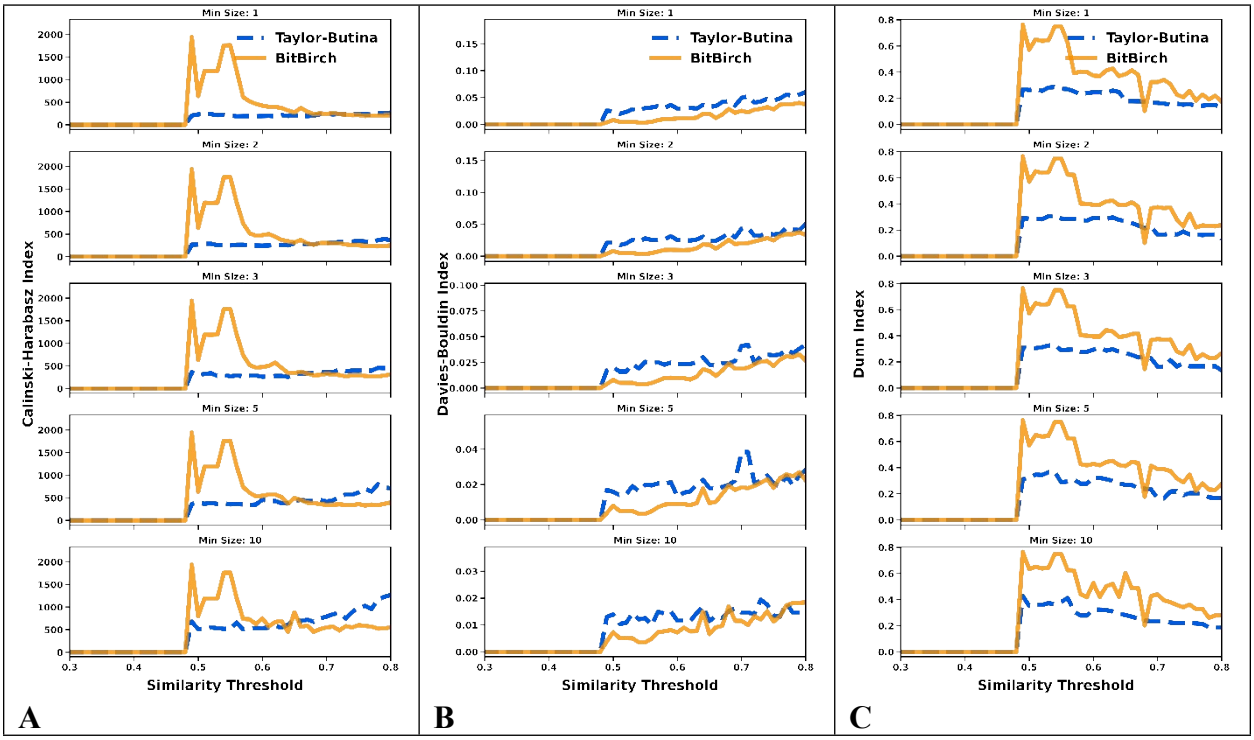


Figure S4.14: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [14] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



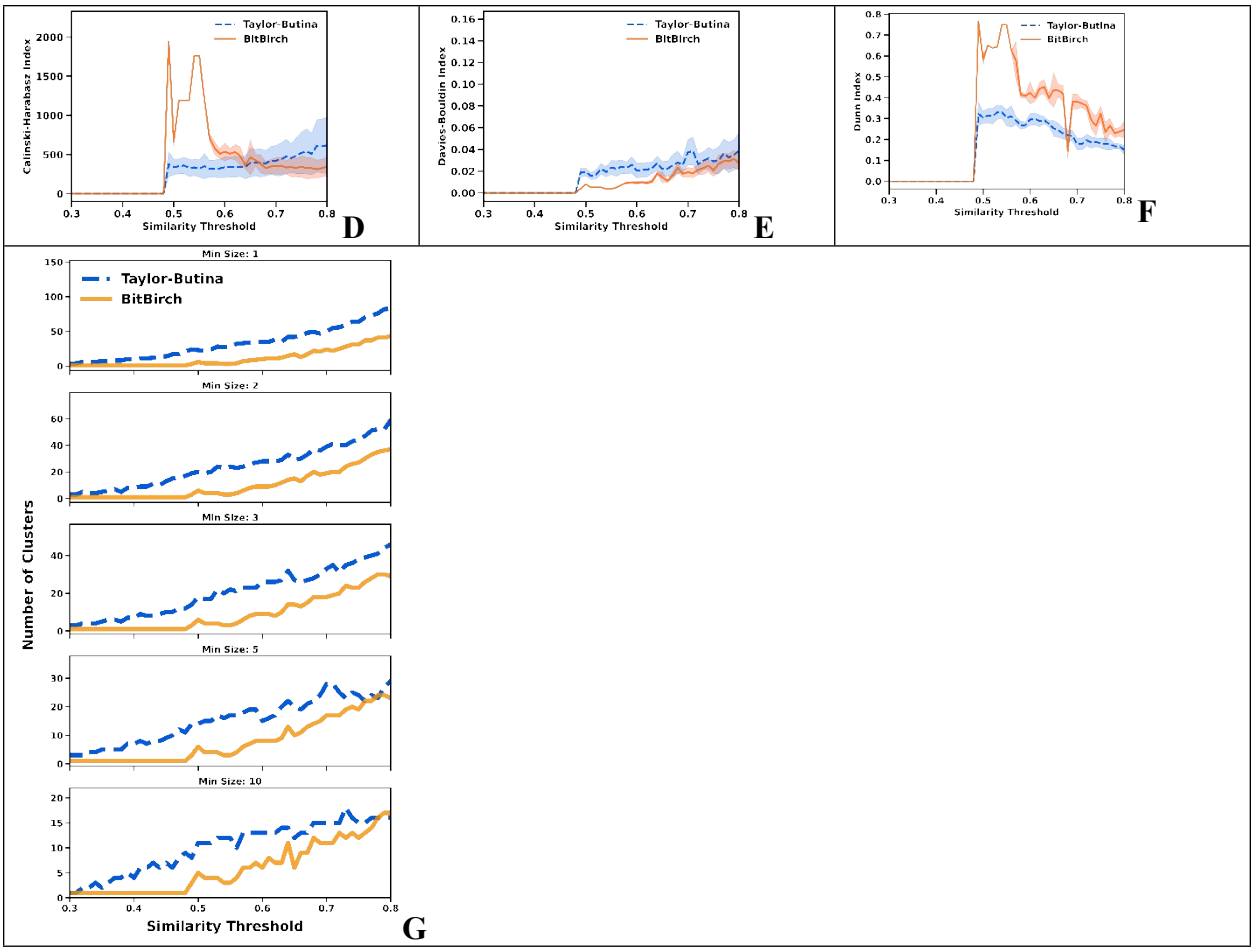
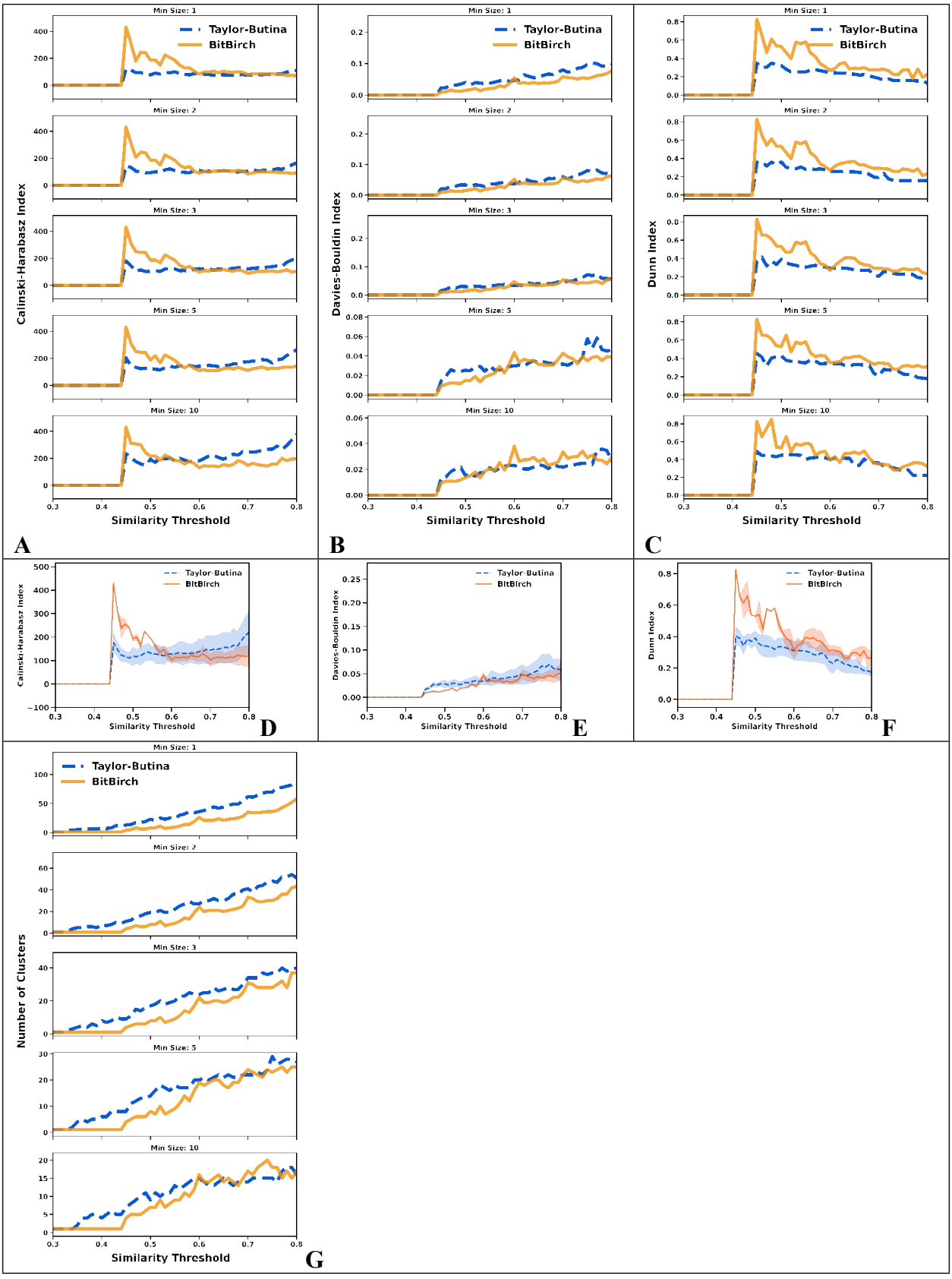


Figure S4.15: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [15] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).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Min Size: 3
Min Size: 5
Min Size: 10
Taylor-Butina
BitBirch
Calinski-Harabasz Index
Davies-Bouldin Index
Dunn Index
Number of Clusters
Similarity Threshold
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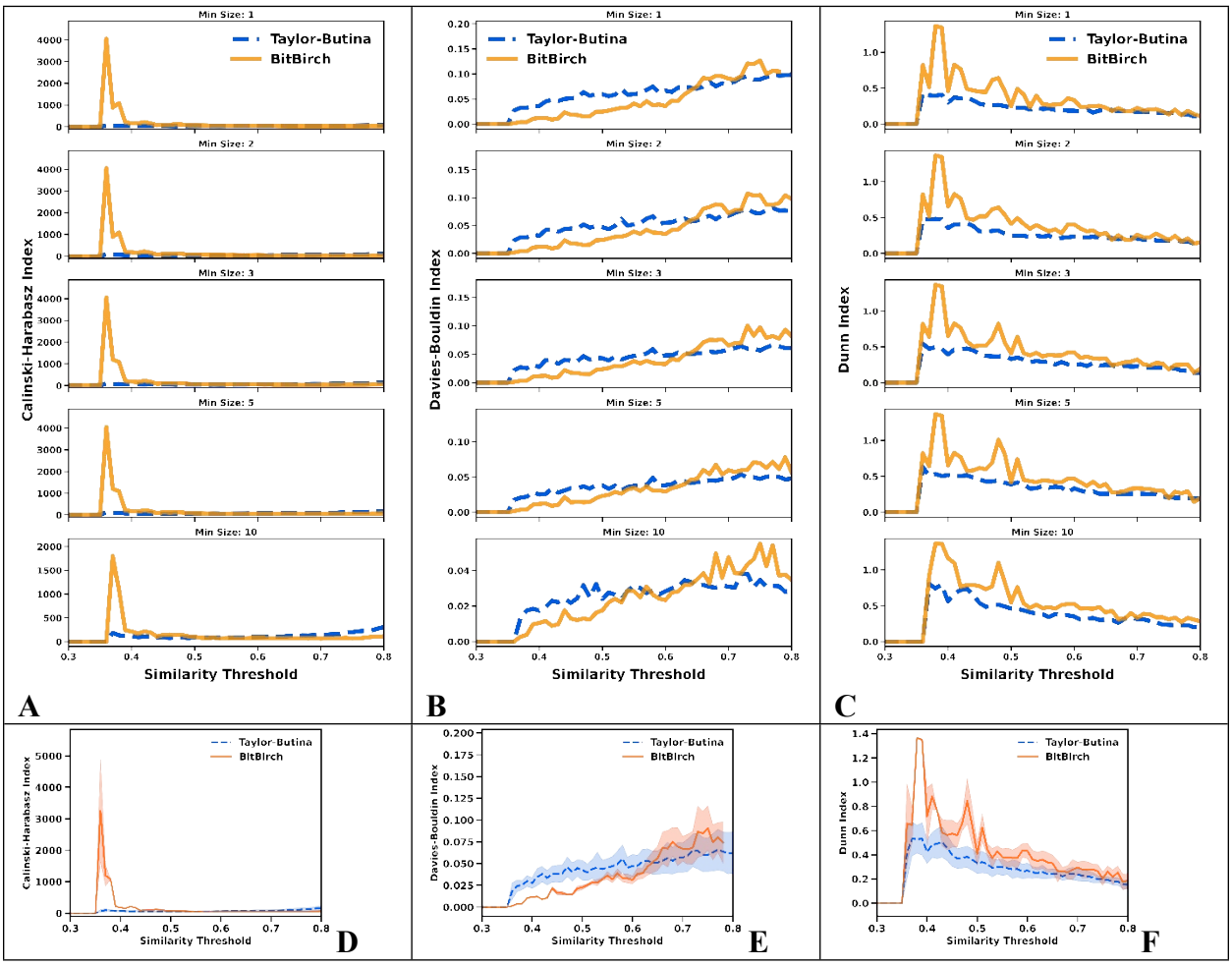
Figure S4.16: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [16] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



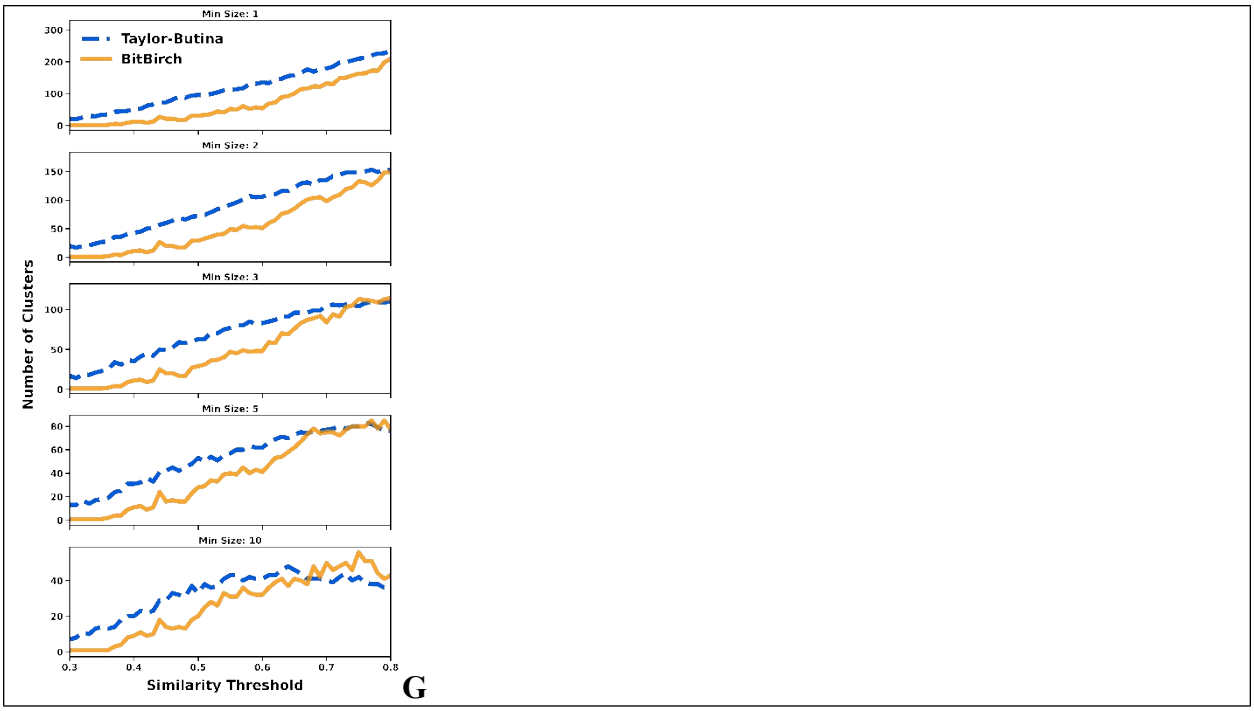
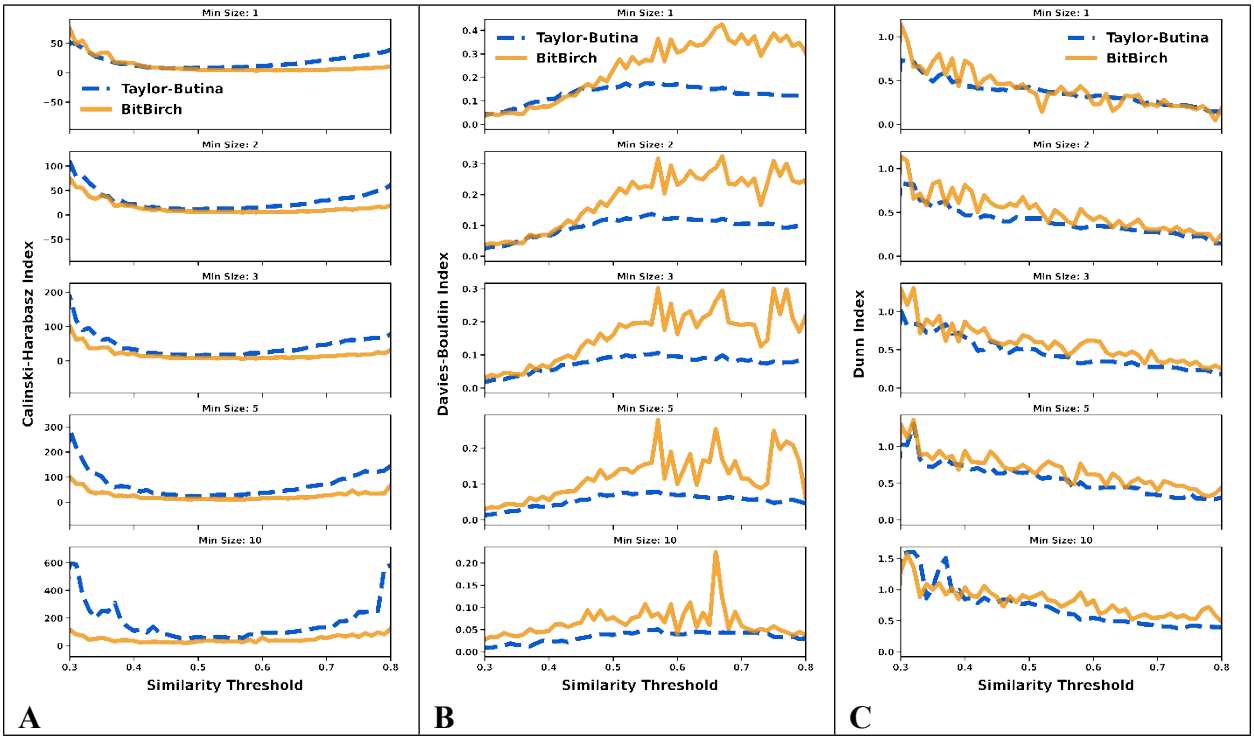


Figure S4.17: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [17] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



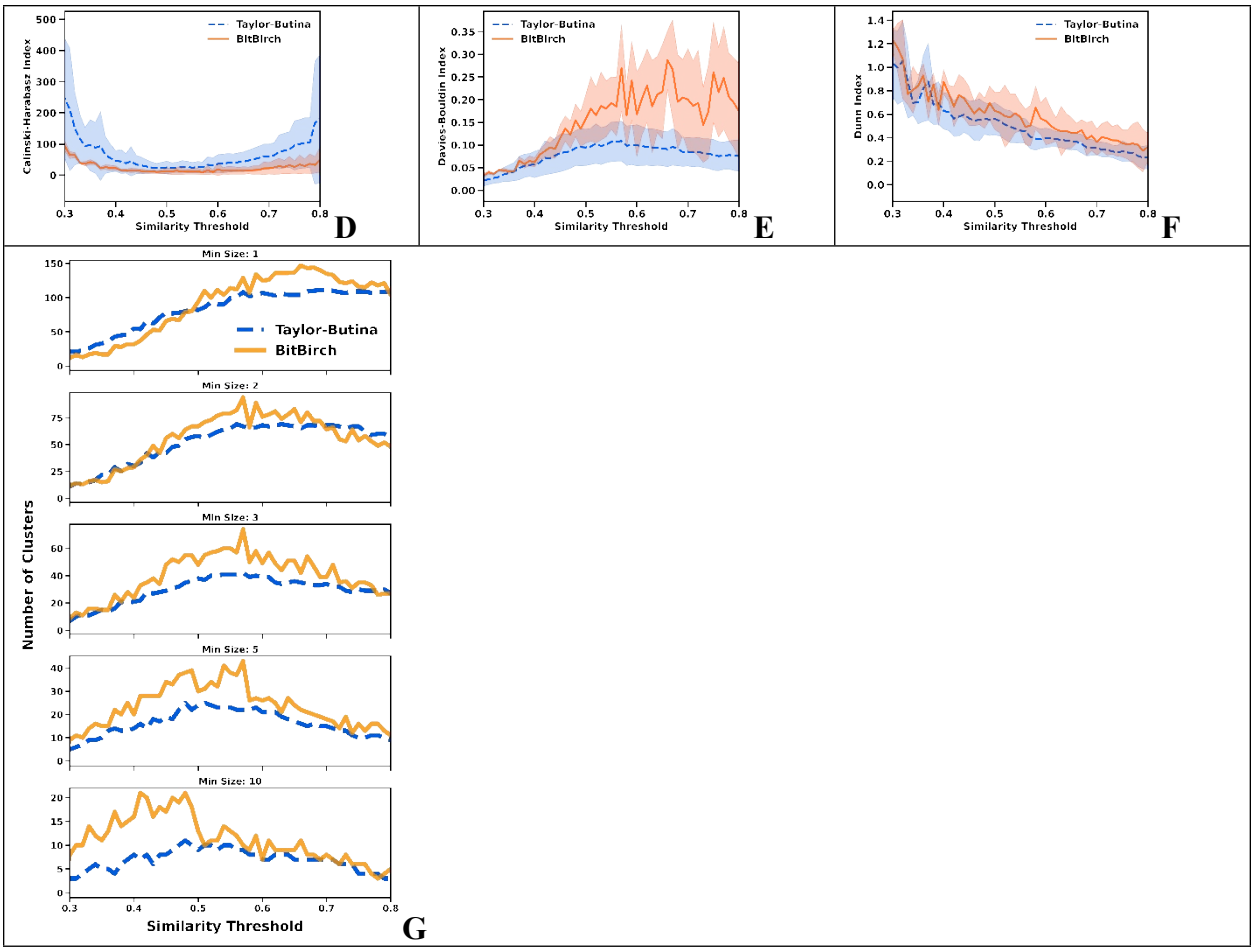
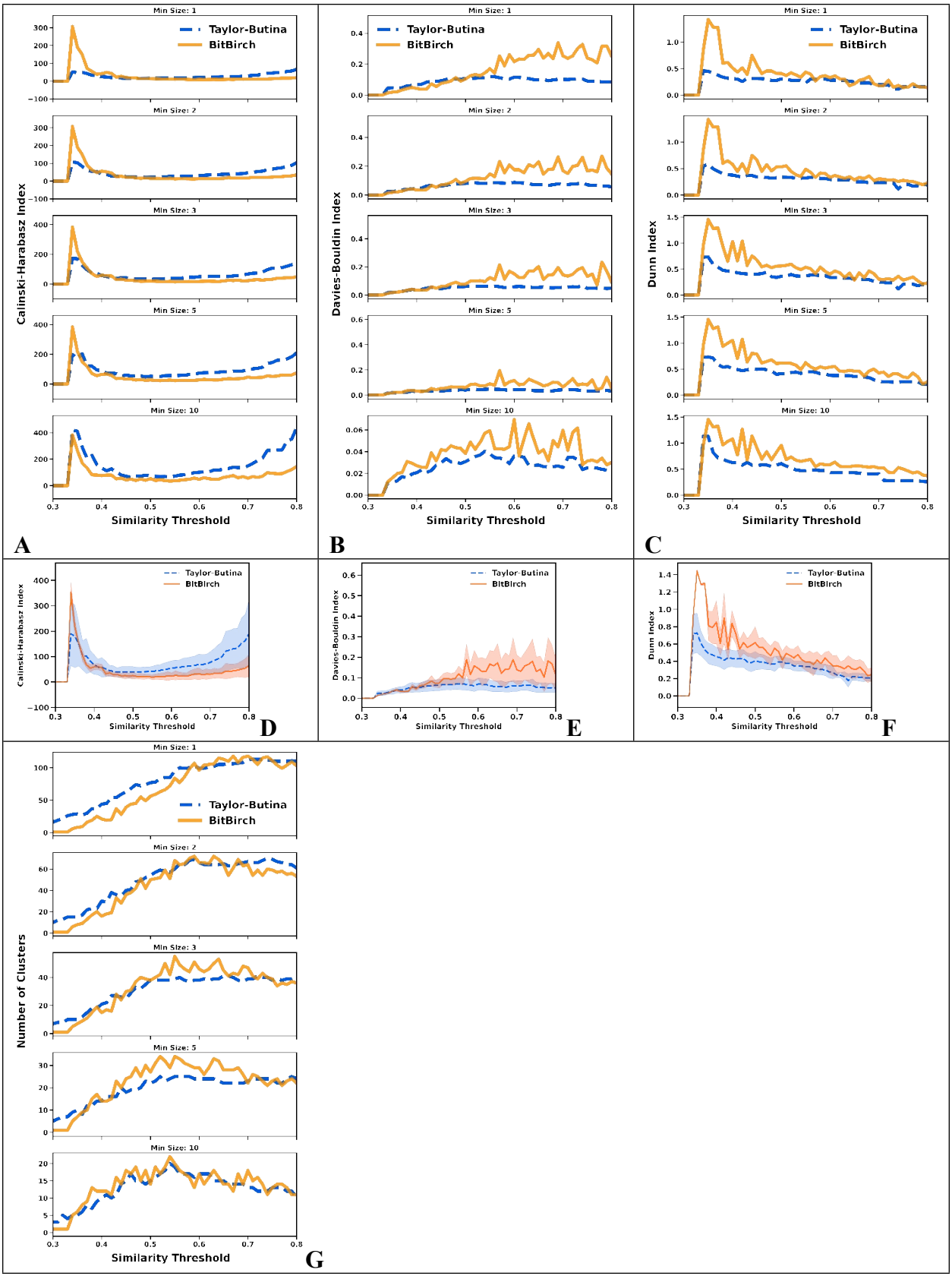


Figure S4.18: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [18] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).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Min Size: 2
Min Size: 3
Min Size: 5
Min Size: 10
Taylor-Butina
BitBirch
Calinski-Harabasz Index
Davies-Bouldin Index
Dunn Index
Number of Clusters
Similarity Threshold
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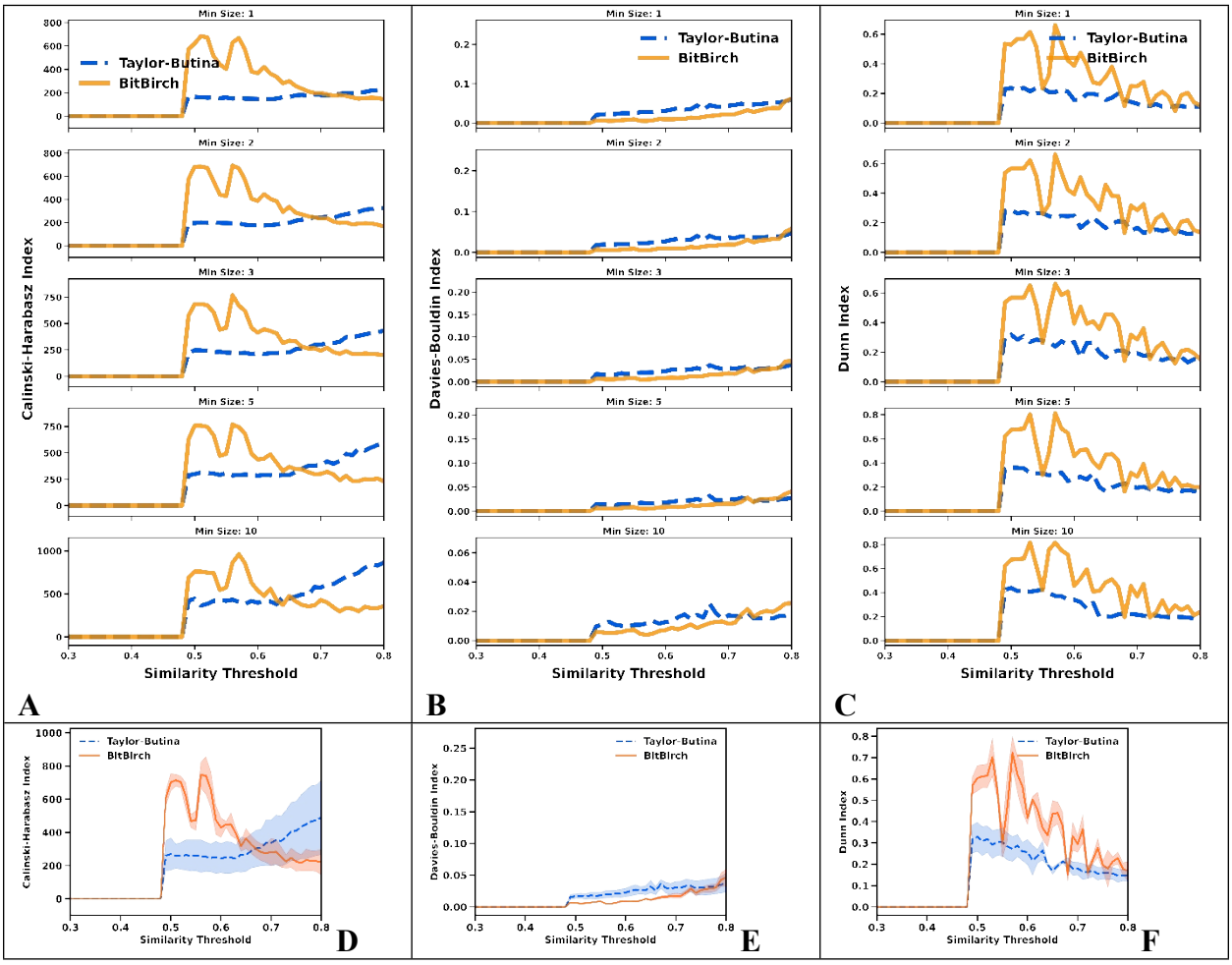
Figure S4.19: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [19] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



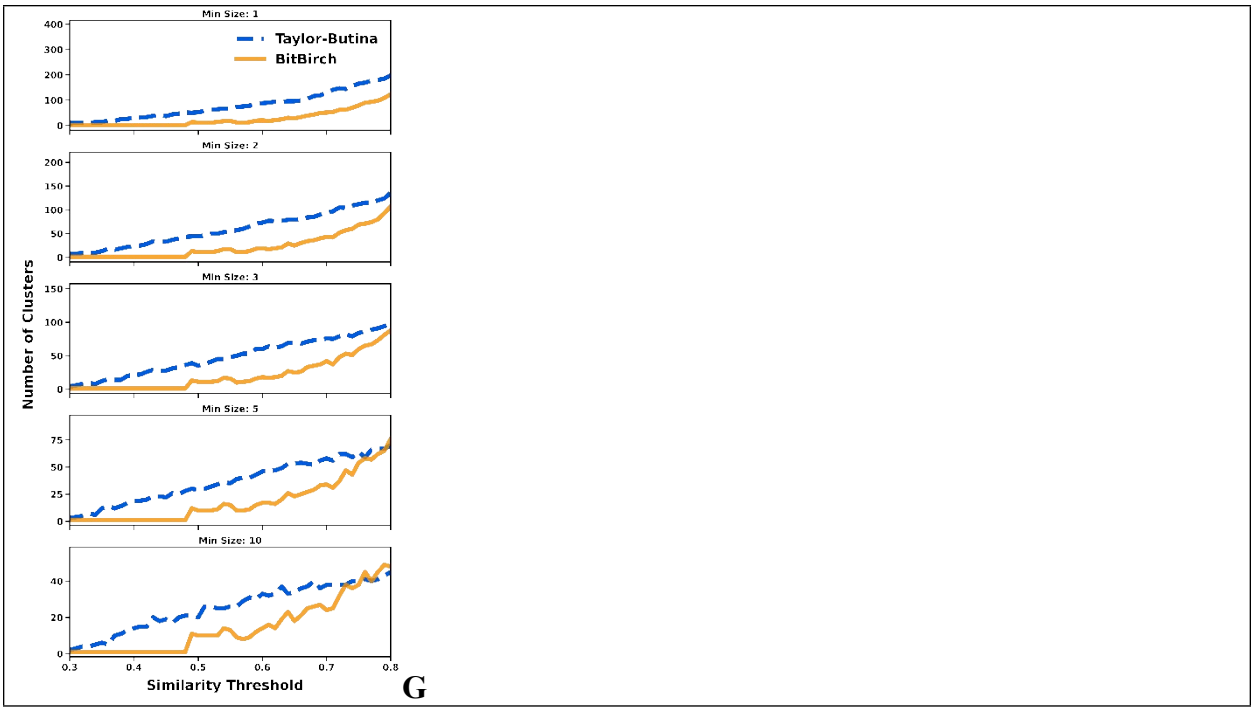
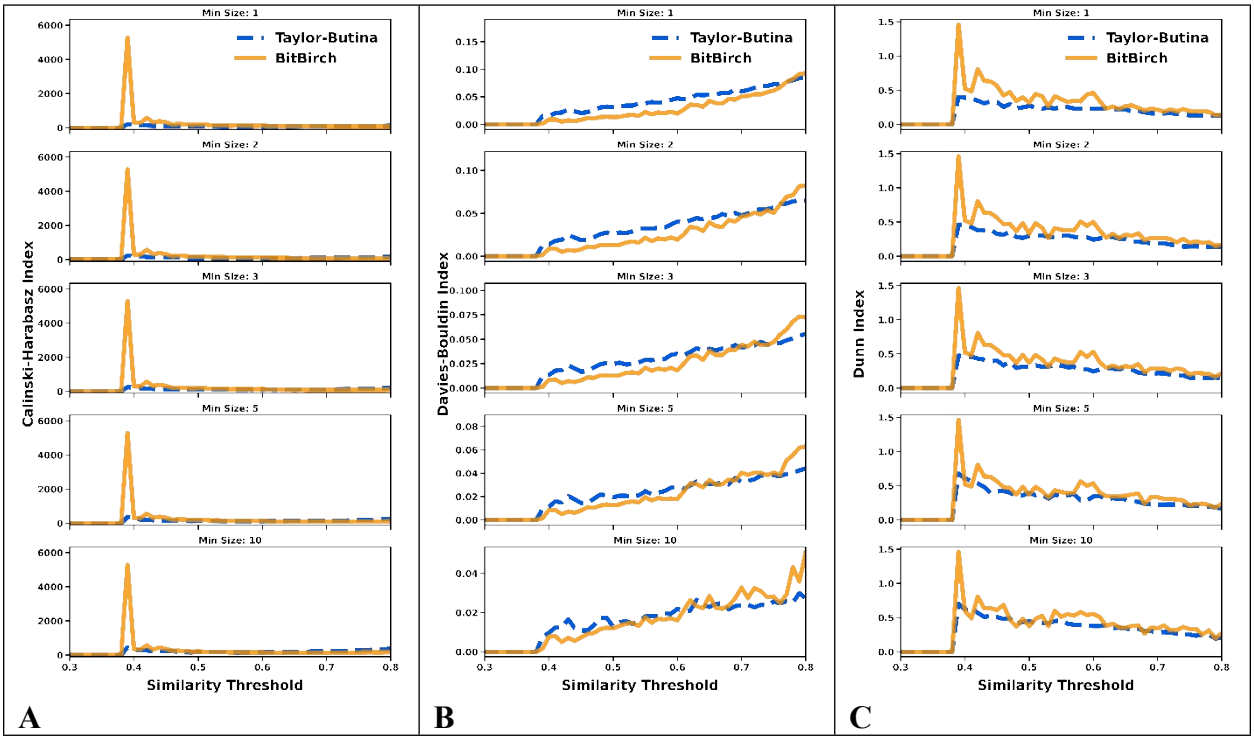


Figure S4.20: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [20] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



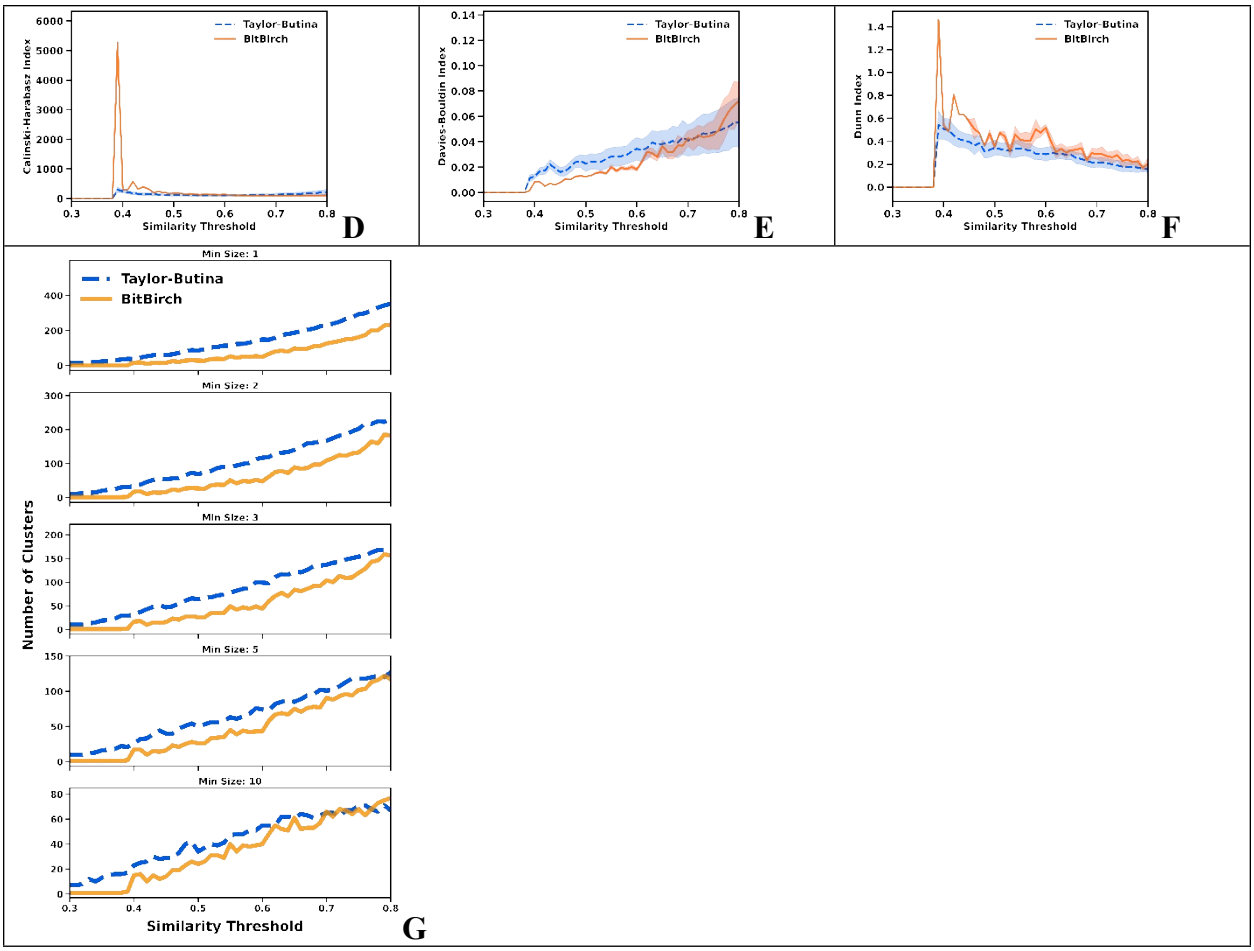


Figure S4.21: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [21] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).

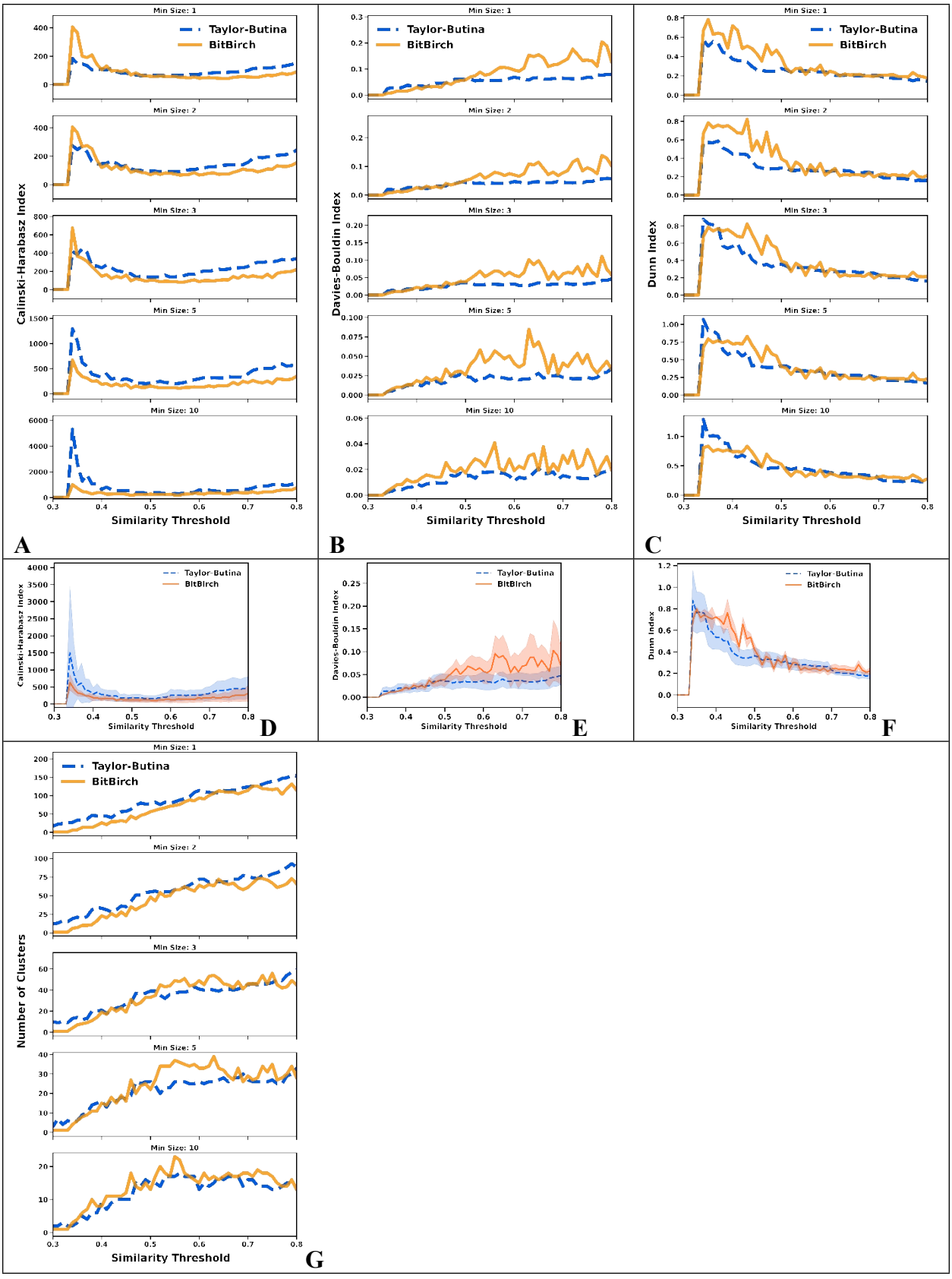
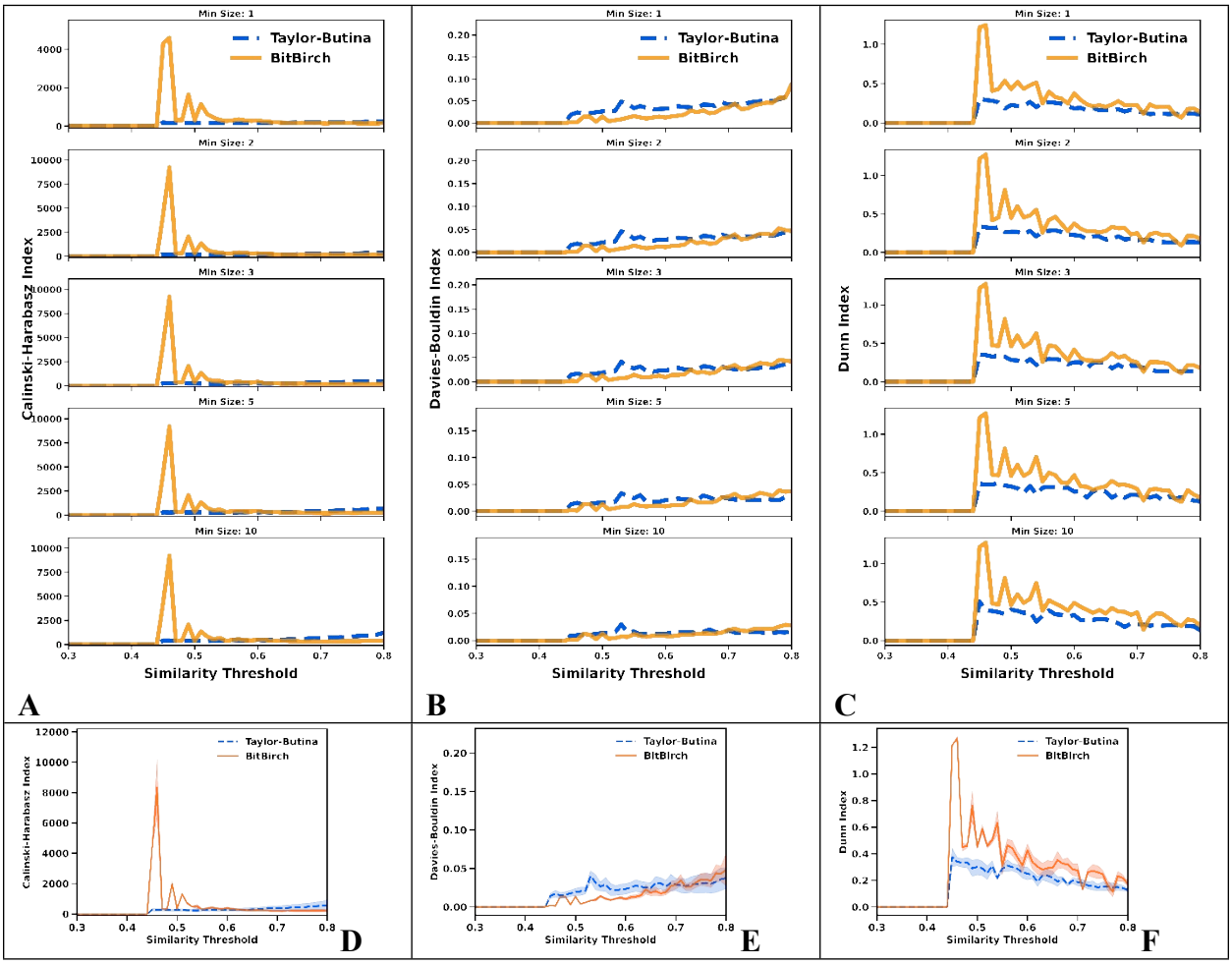

Min Size: 1
Min Size: 2
Min Size: 3
Min Size: 5
Min Size: 10
Taylor-Butina
BitBirch
Calinski-Harabasz Index
Davies-Bouldin Index
Dunn Index
Number of Clusters
Similarity Threshold
A
B
C
D
E
F
G

Figure S4.22: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [22] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



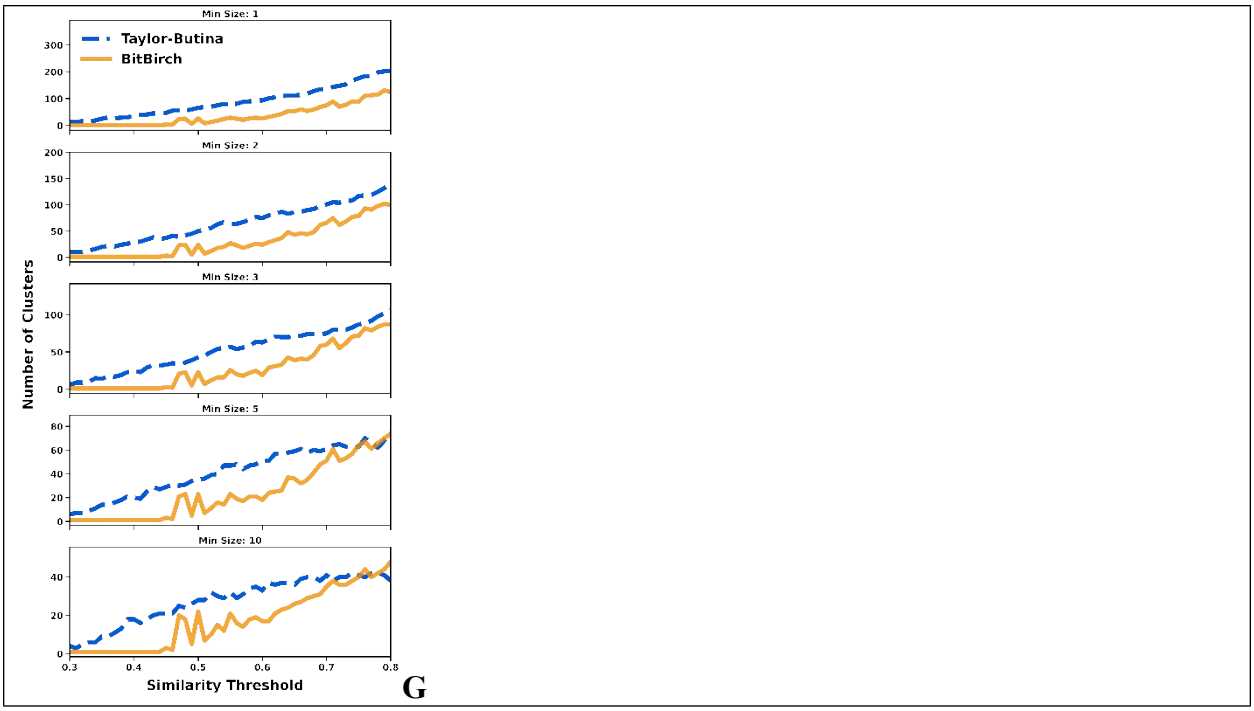
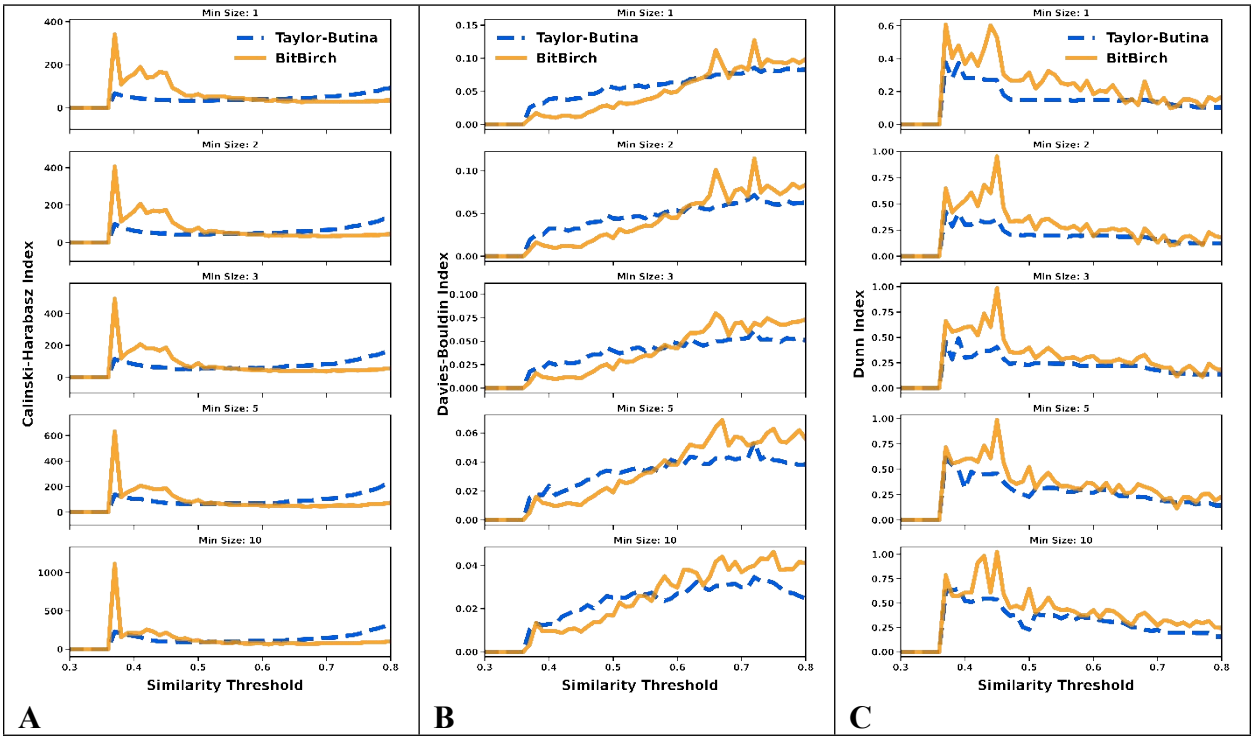


Figure S4.23: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [23] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



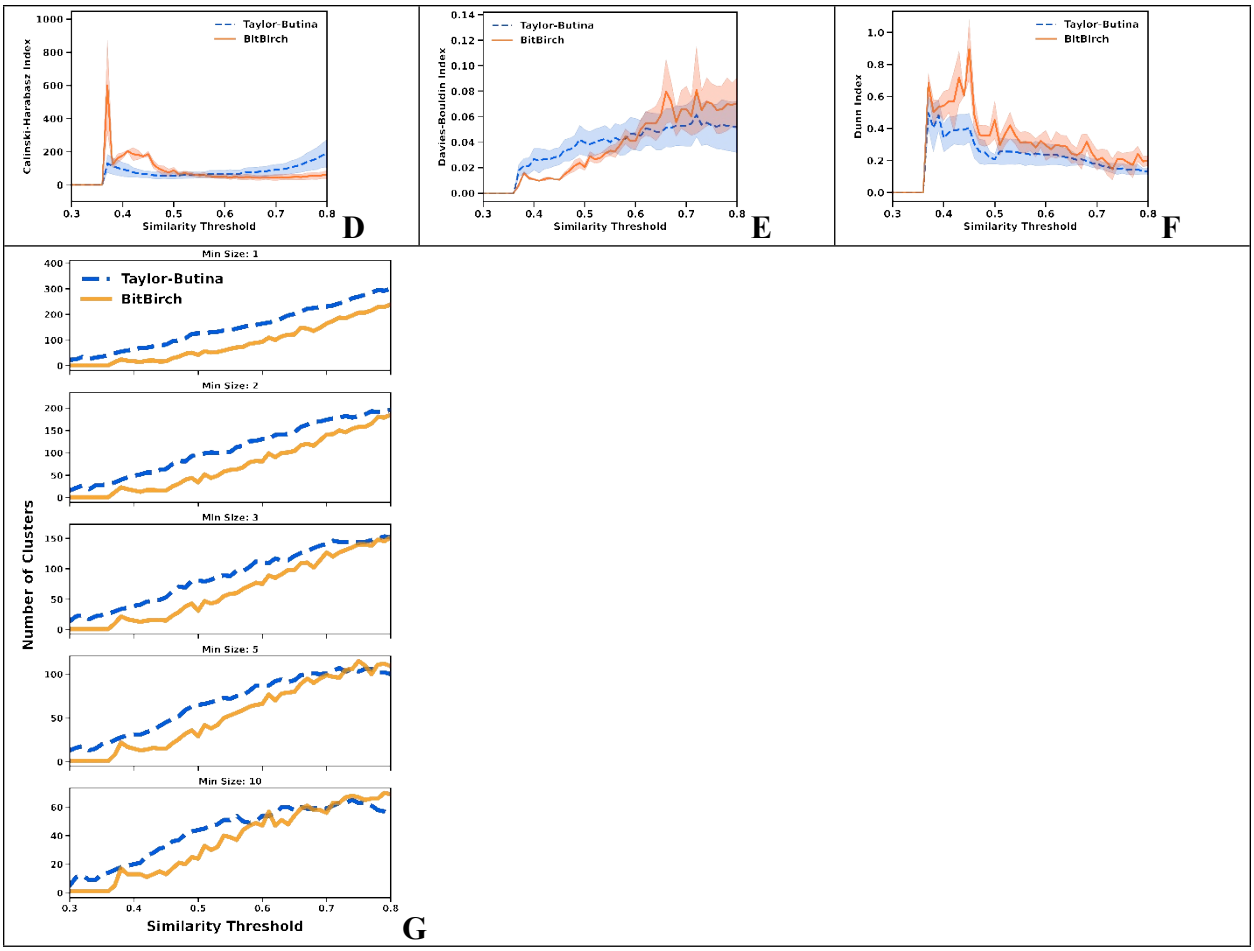


Figure S4.24: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [24] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).

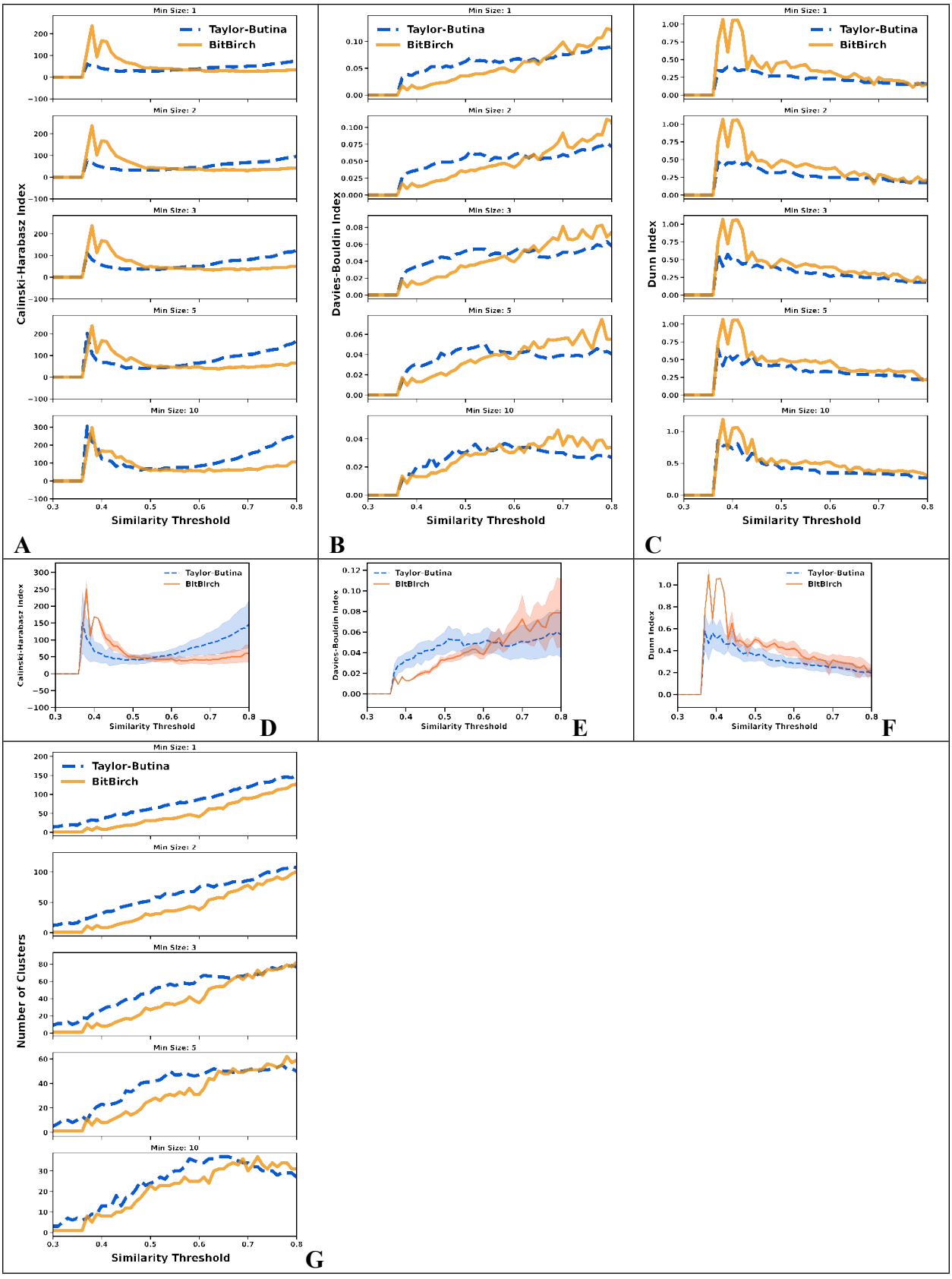
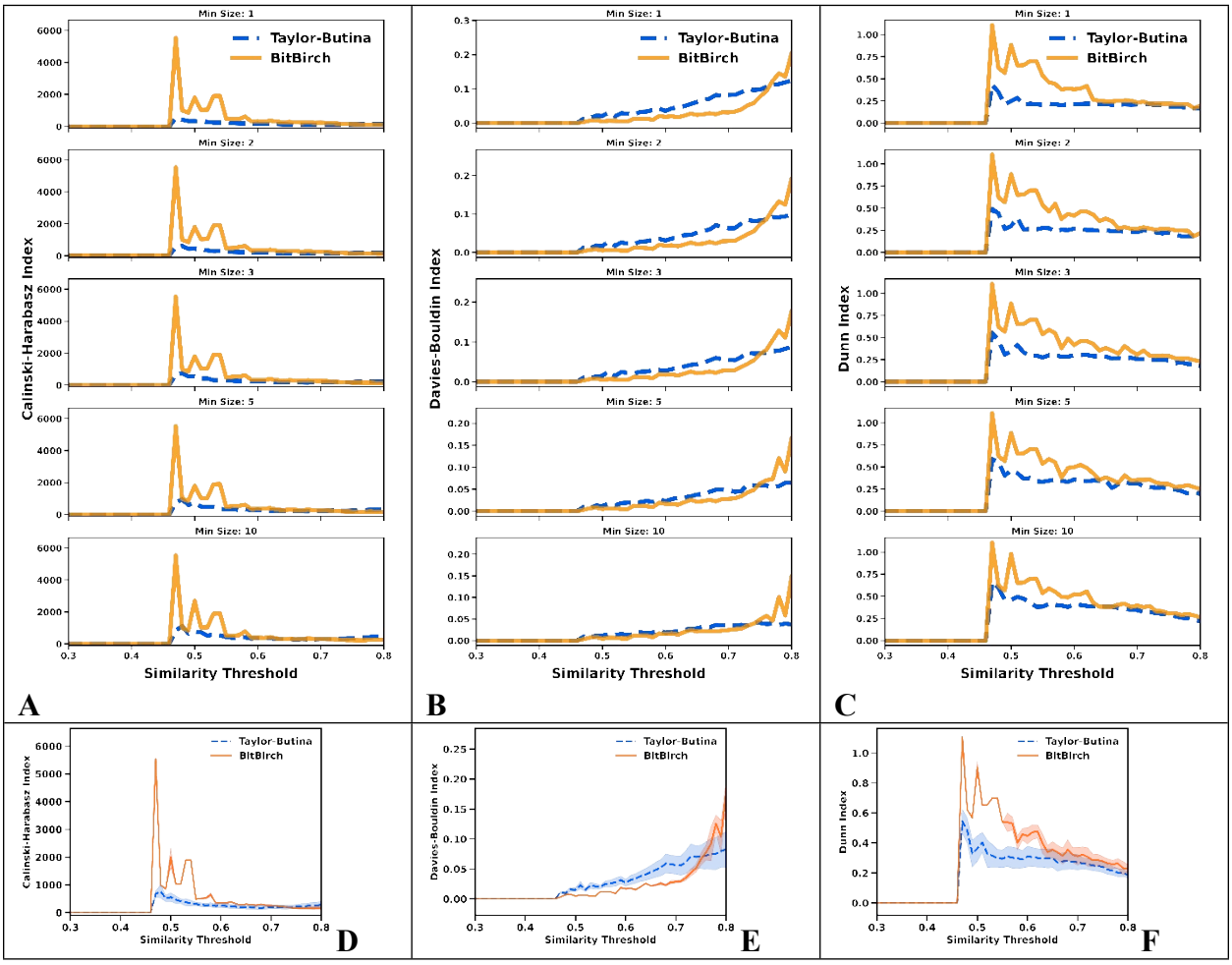

Min Size: 1
Min Size: 2
Min Size: 3
Min Size: 5
Min Size: 10
Taylor-Butina
BitBirch
Calinski-Harabasz Index
Davies-Bouldin Index
Dunn Index
Number of Clusters
Similarity Threshold
A
B
C
D
E
F
G

Figure S4.25: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [25] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



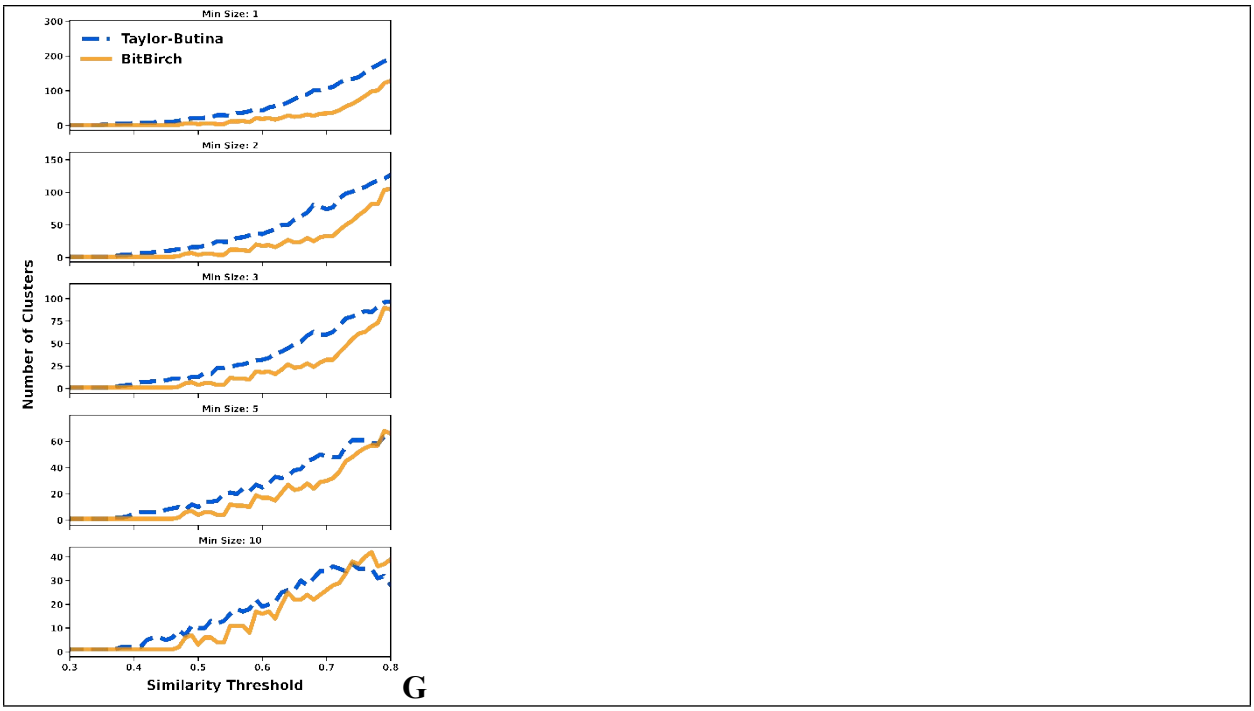
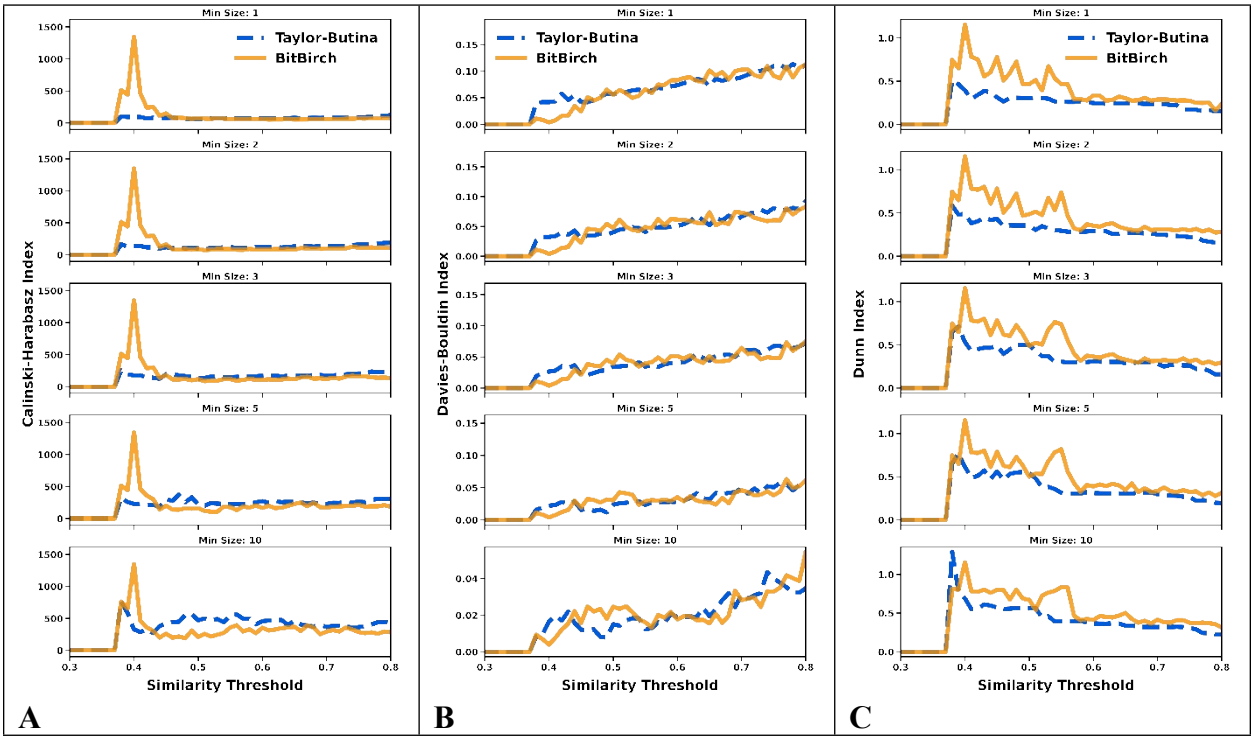


Figure S4.26: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [26] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



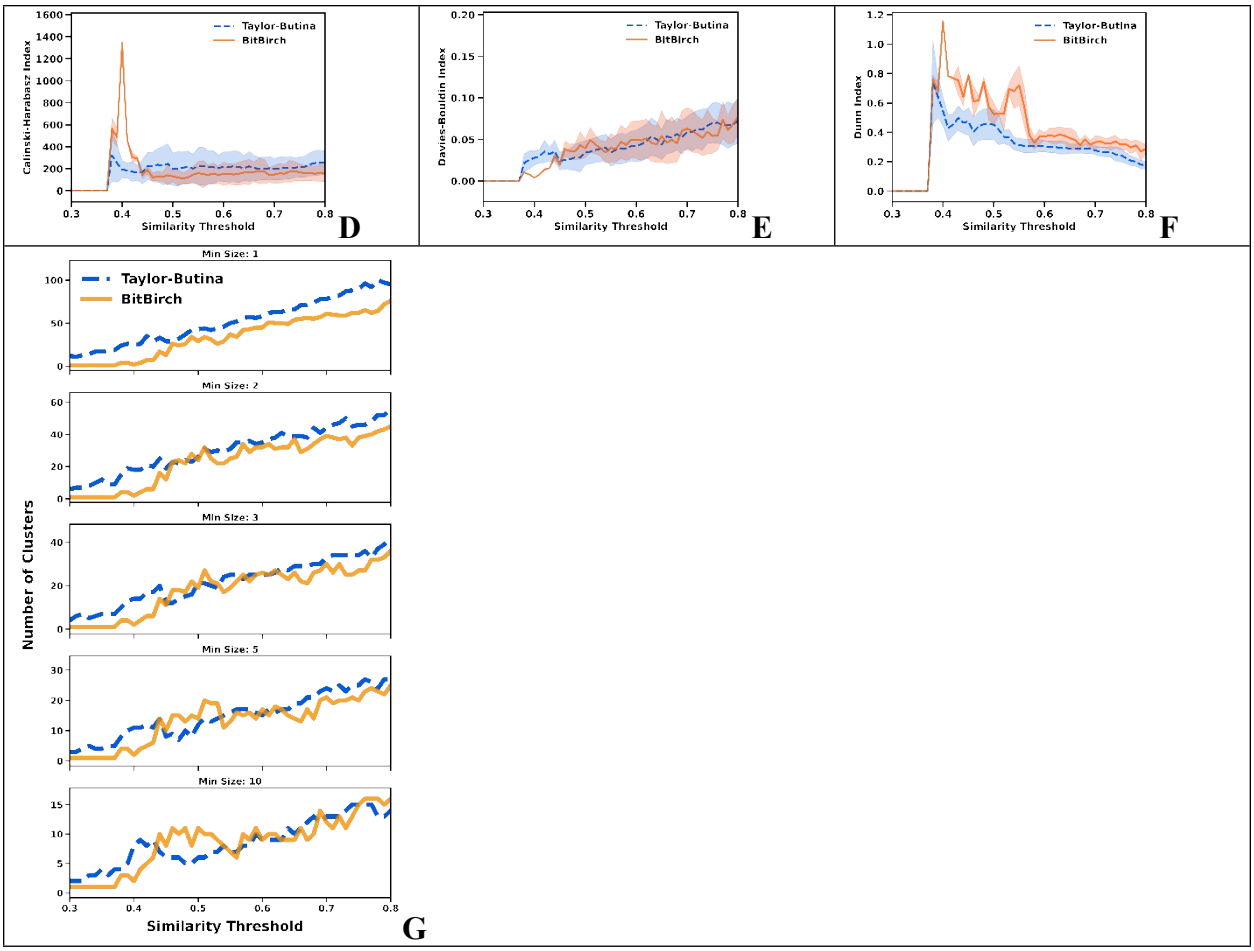


Figure S4.27: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [27] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).

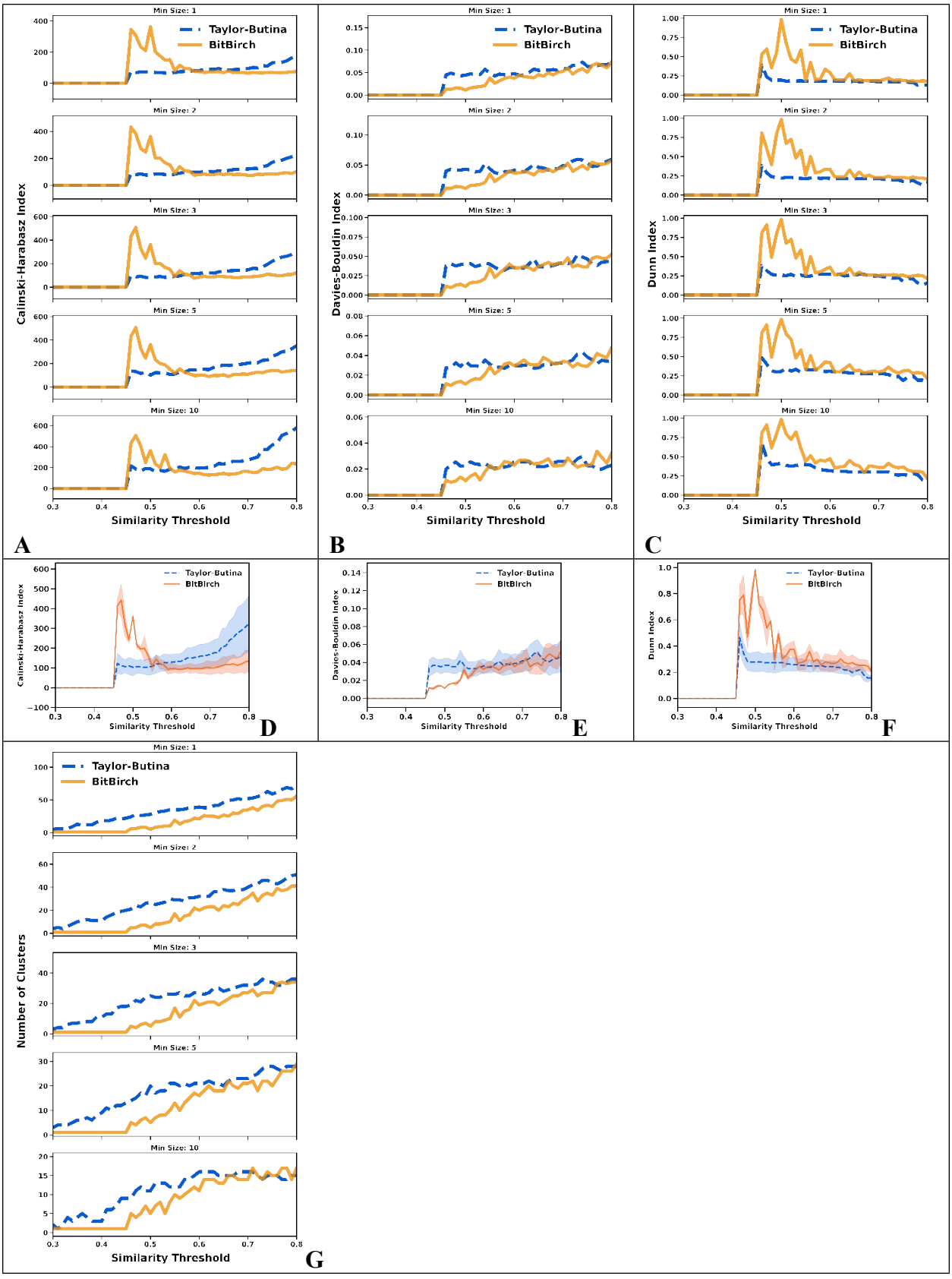
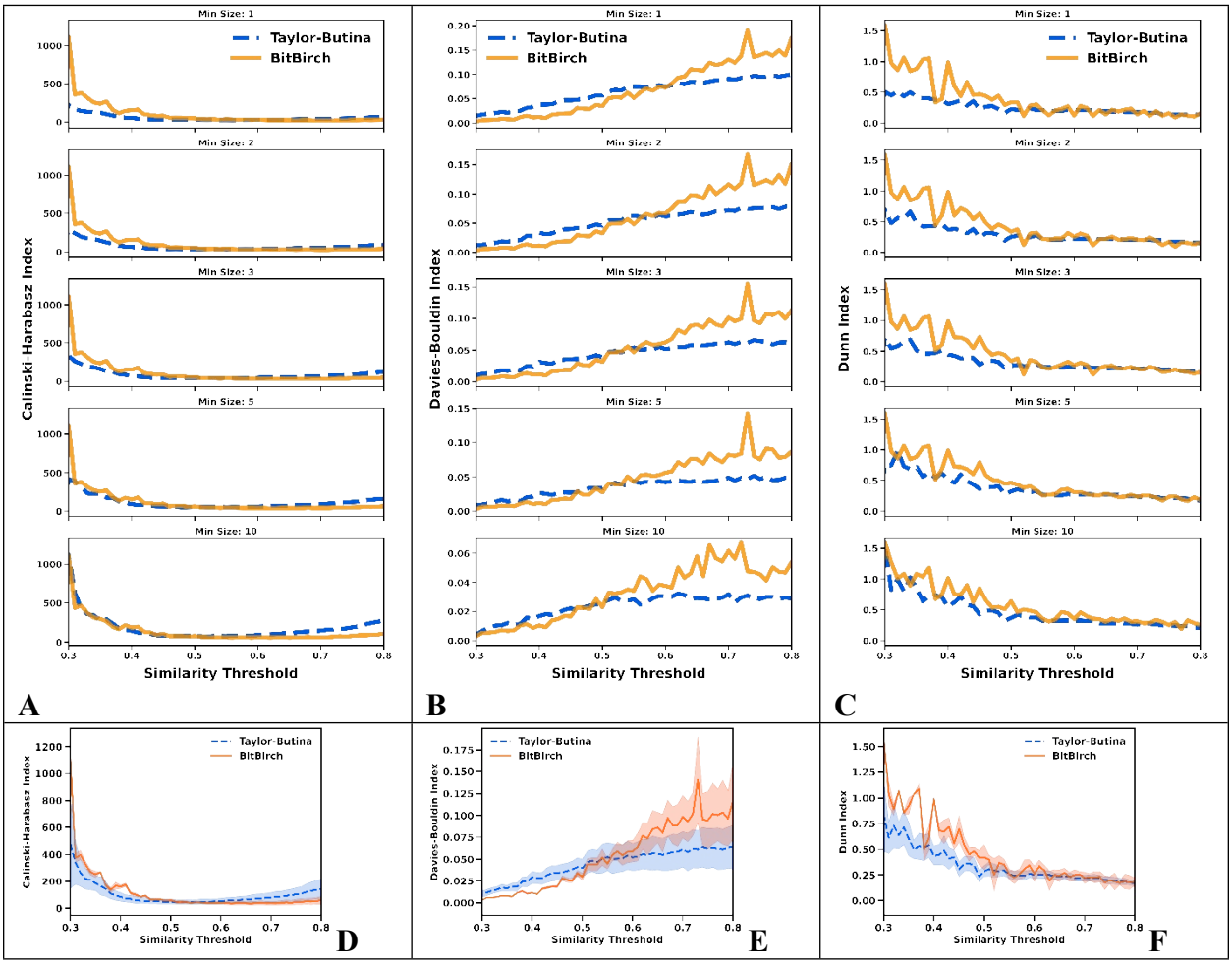

Min Size: 1
Min Size: 2
Min Size: 3
Min Size: 5
Min Size: 10
Taylor-Butina
BitBirch
Calinski-Harabasz Index
Davies-Bouldin Index
Dunn Index
Number of Clusters
Similarity Threshold
A
B
C
D
E
F
G

Figure S4.28: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [28] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



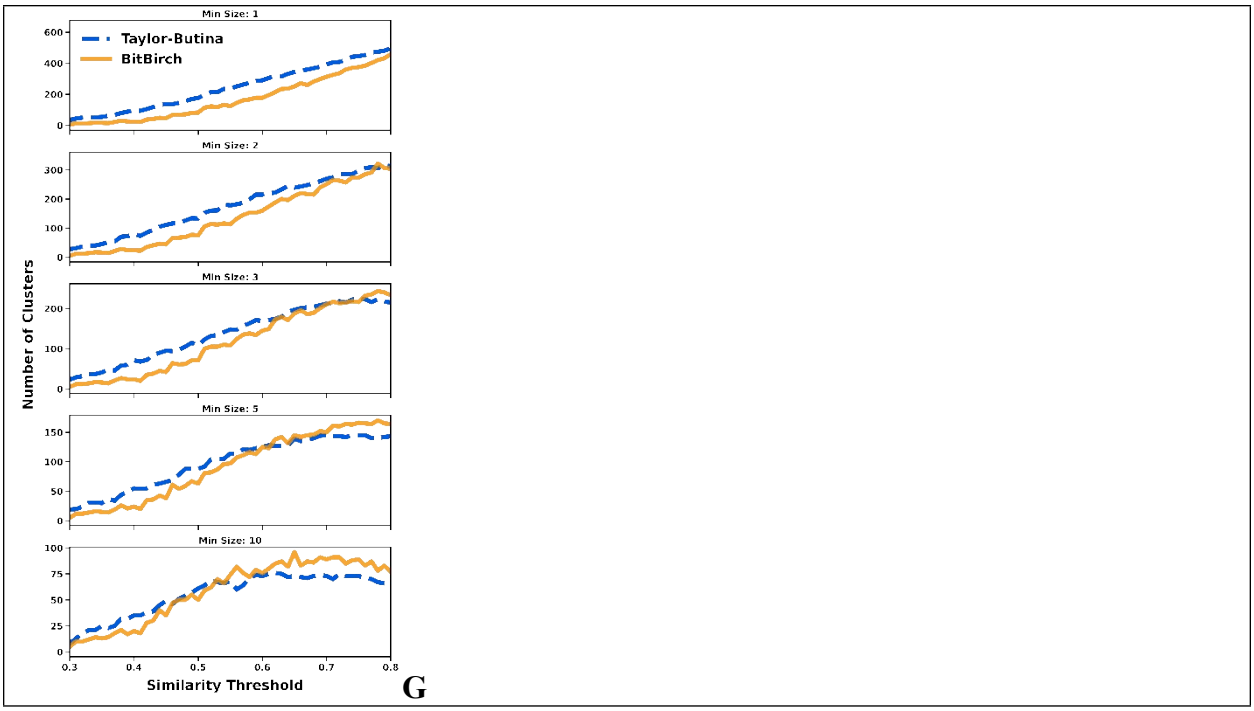
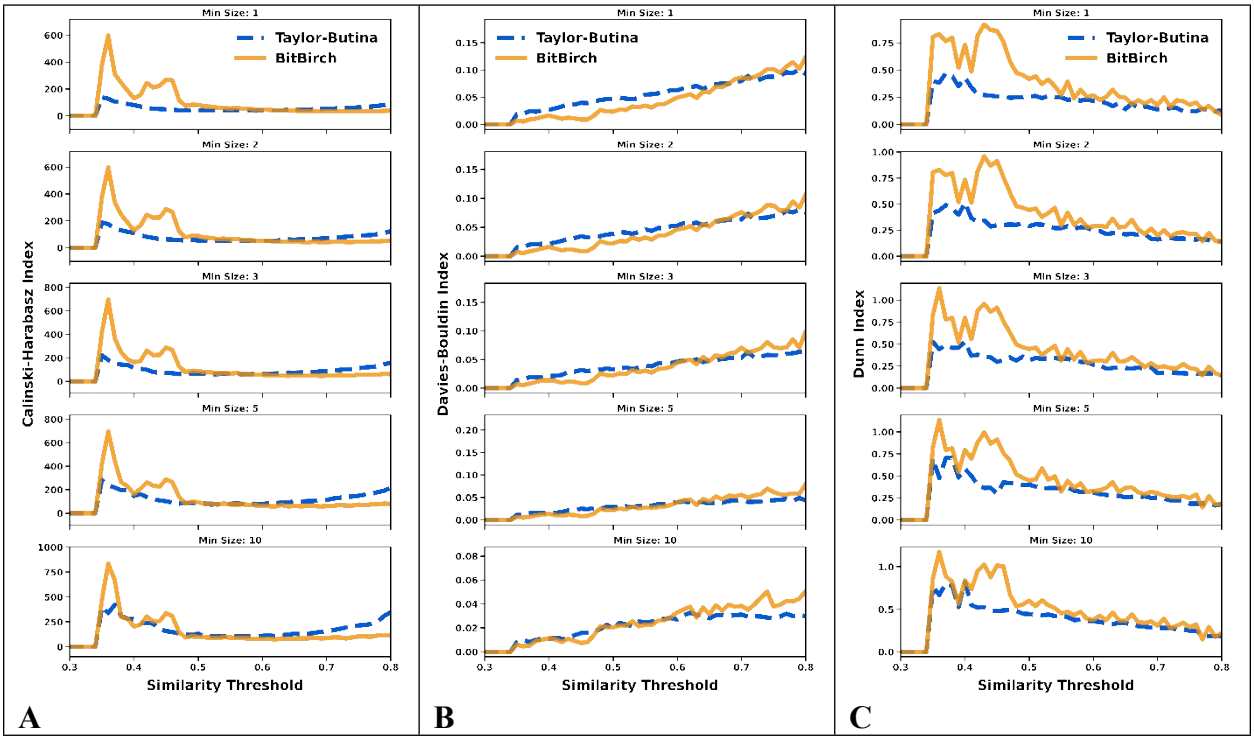


Figure S4.29: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [29] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).



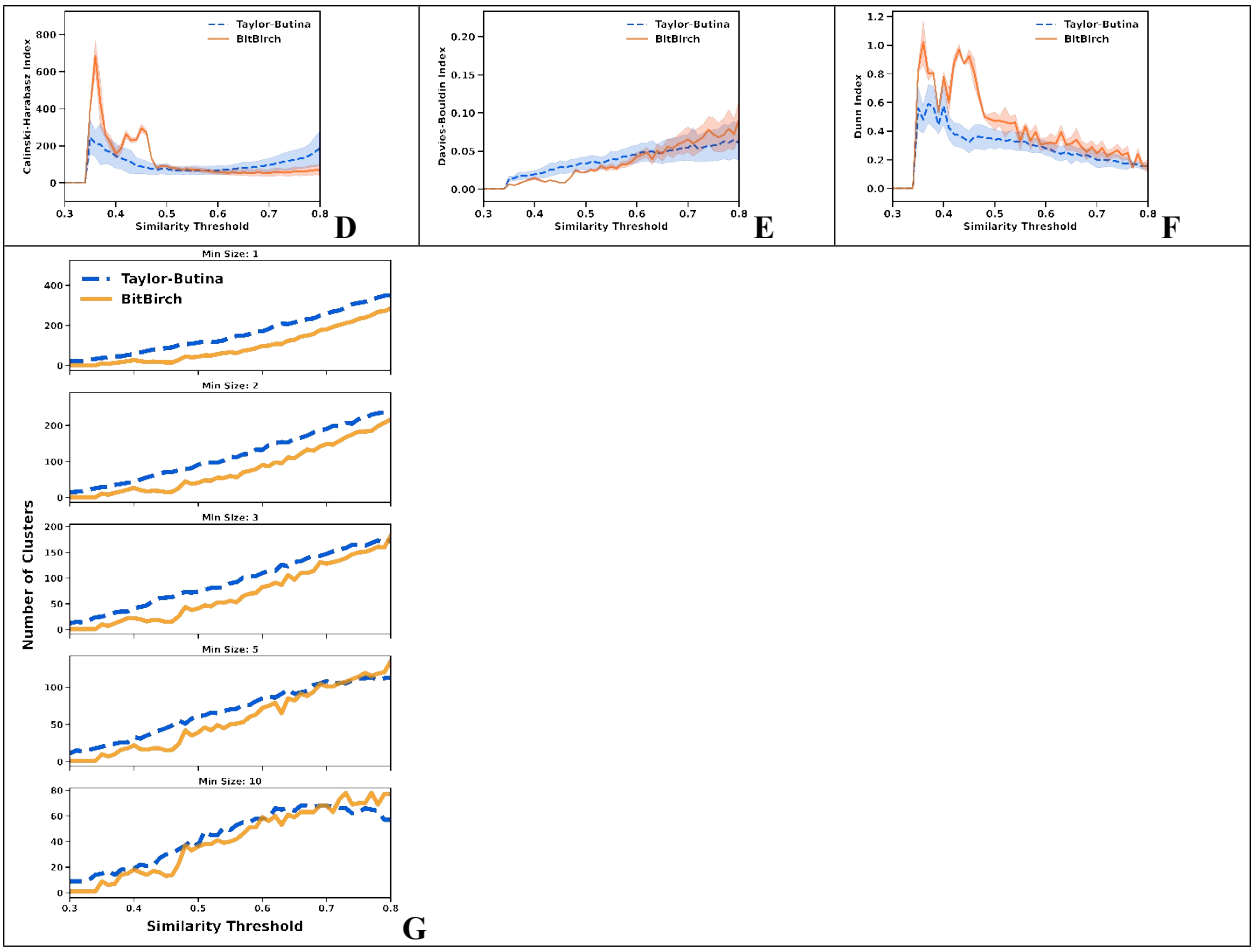


Figure S4.30: **A**: CHI, **B**: DBI, **C**: DI analysis for min_size = 1, 2, 3, 5, 10 for the [30] ChEMBL subset. Average **D**: CHI, **E**: DBI, **F**: DI values over the min_size variable. **G**: Number of clusters. BitBIRCH (orange continuous line), Taylor-Butina (blue dashed line).

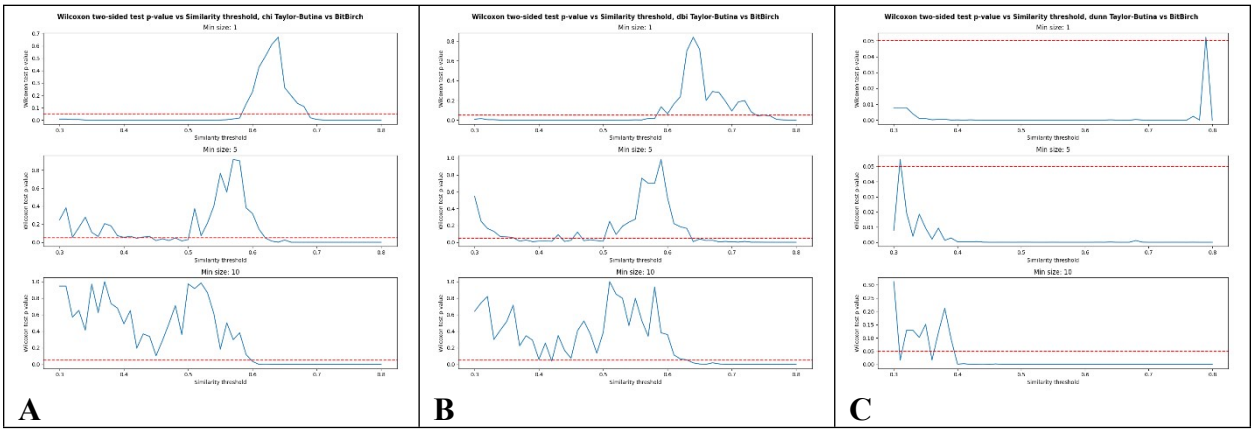


Figure S4.31: Wilcoxon two-sided (Ha: TB ≠ BB) test comparing the BitBIRCH and Taylor-Butina **A**: CHI, **B**: DBI, and **C**: DI results for different similarity thresholds and min_size (1, 5, 10) values.

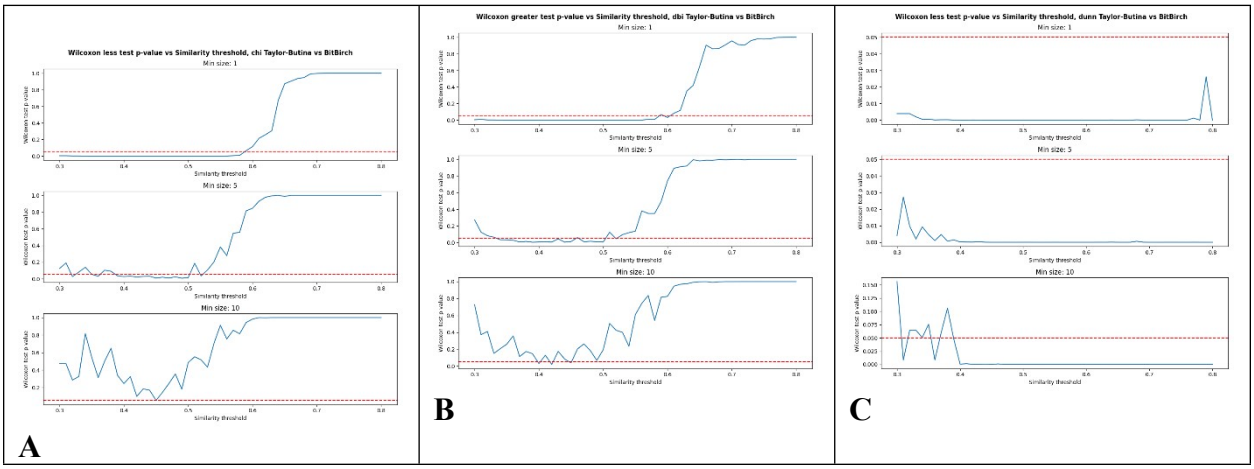


Figure S4.32: Wilcoxon one-sided test comparing the BitBIRCH and Taylor-Butina **A**: CHI (Ha: TB < BB), **B**: DBI (Ha: TB > BB), and **C**: DI (Ha: TB < BB), results for different similarity thresholds and min_size (1, 5, 10) values.

S5: Local Clustering Analysis of BitBIRCH and BitBIRCH-parallel

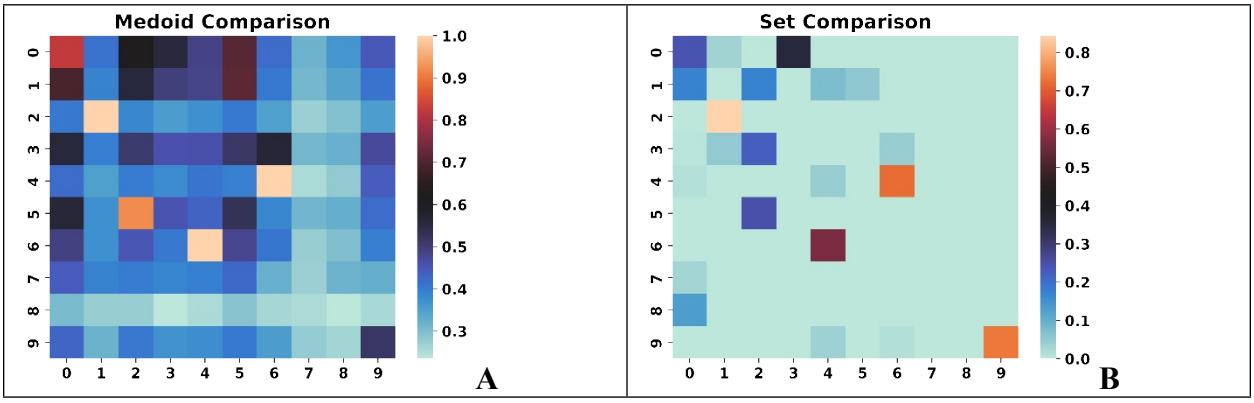


Figure S5.1: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [1] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

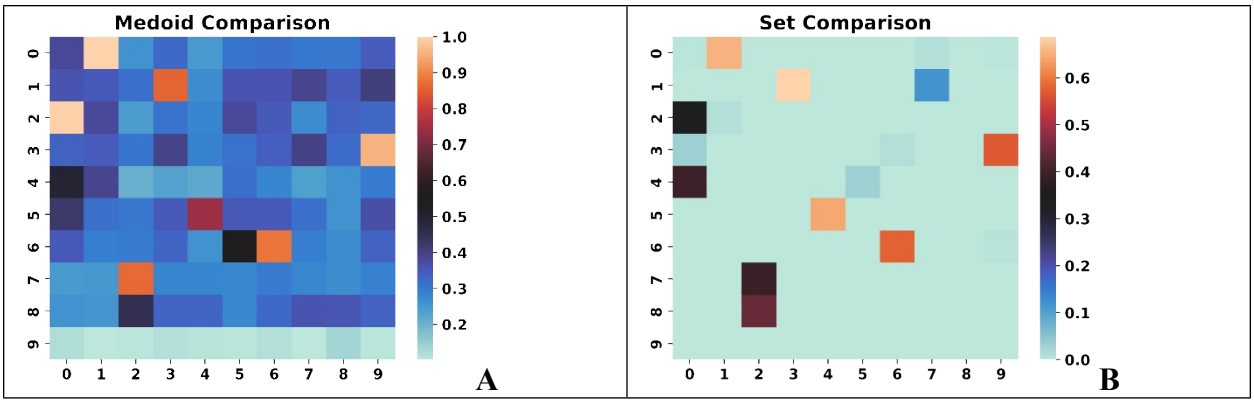


Figure S5.2: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [2] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

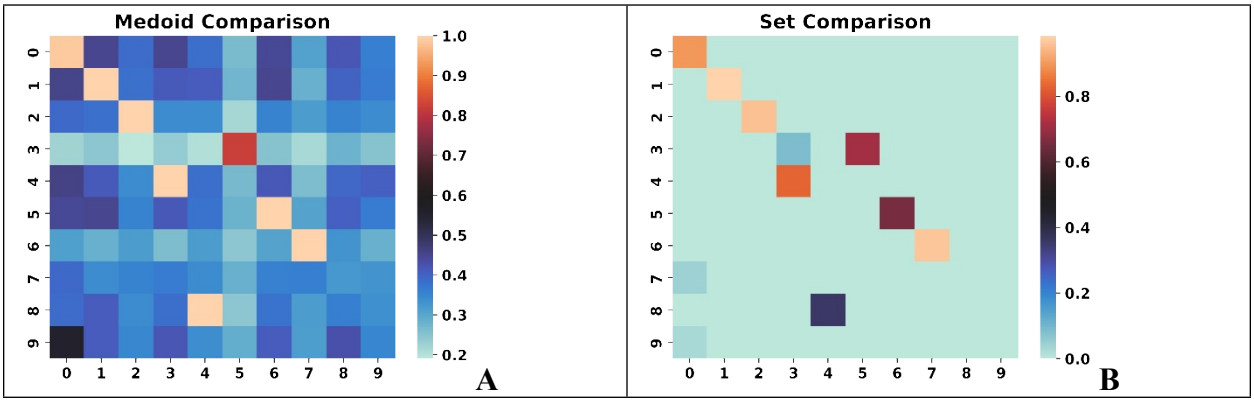


Figure S5.3: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [3] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

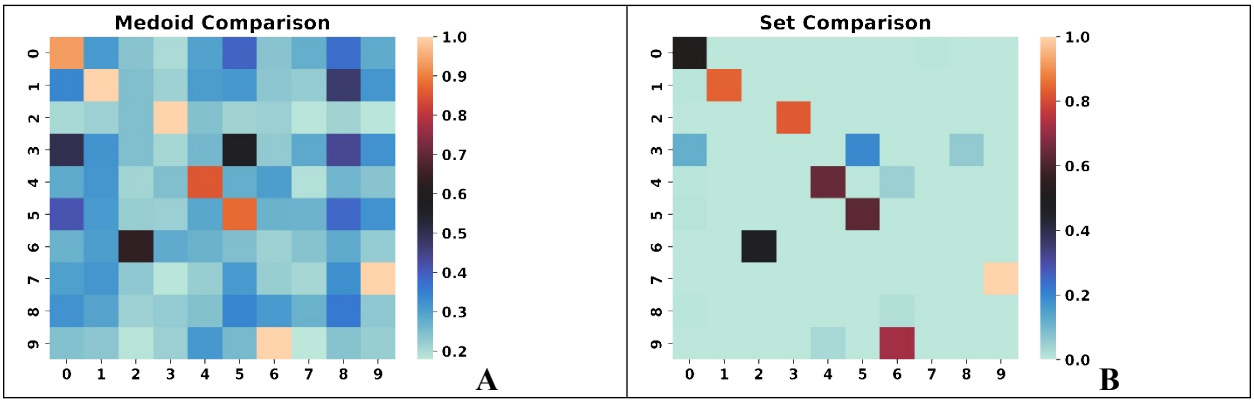


Figure S5.4: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [4] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

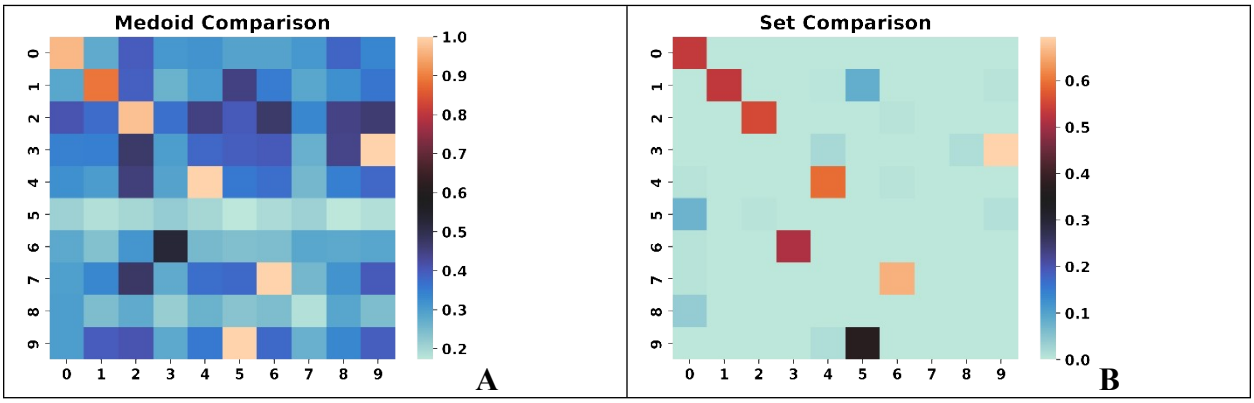


Figure S5.5: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [5] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

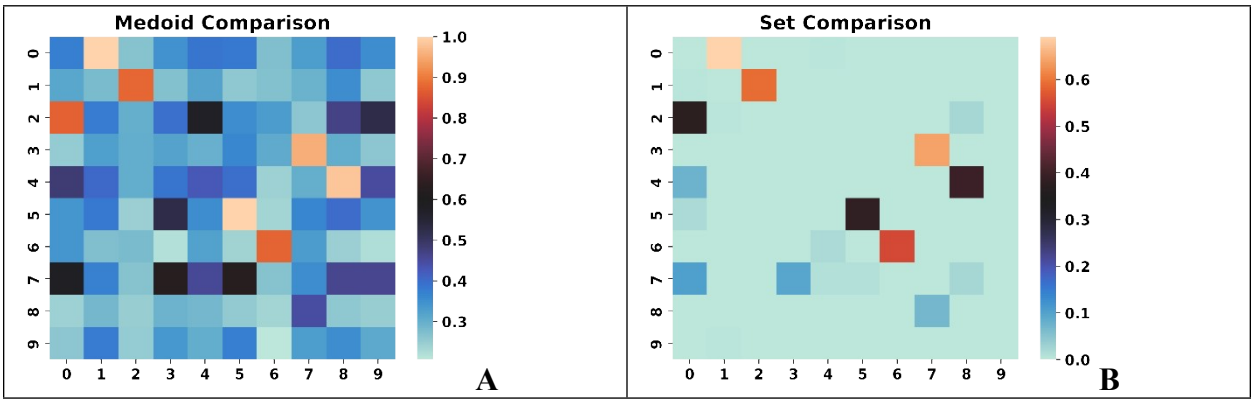


Figure S5.6: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [6] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

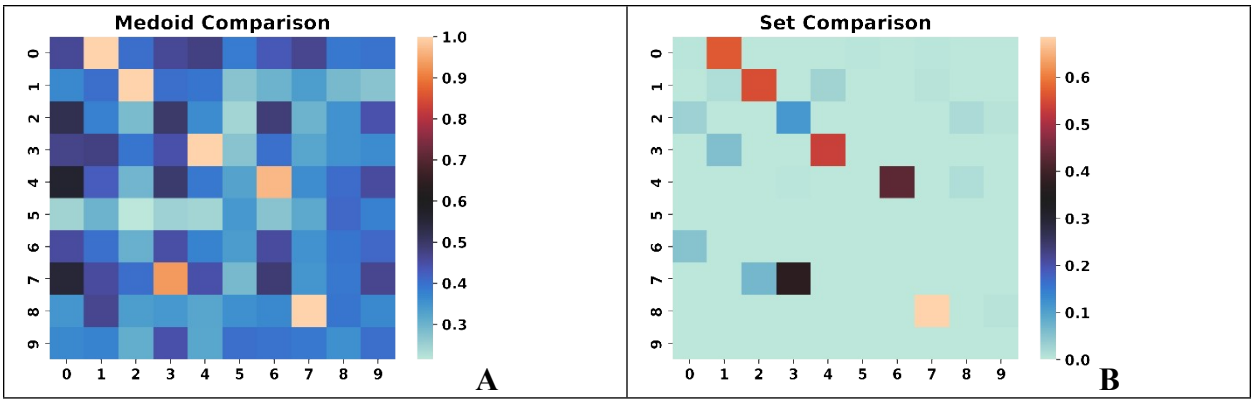


Figure S5.7: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [7] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

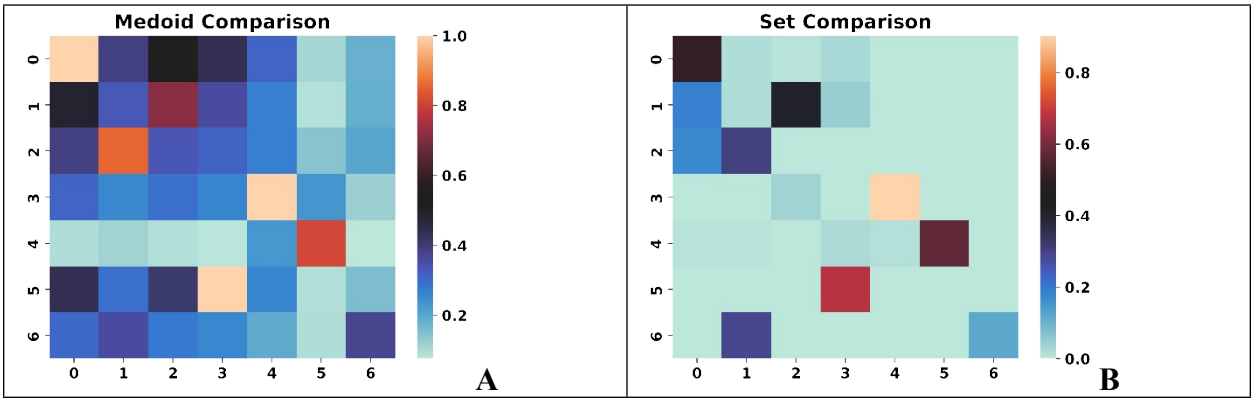


Figure S5.8: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [8] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

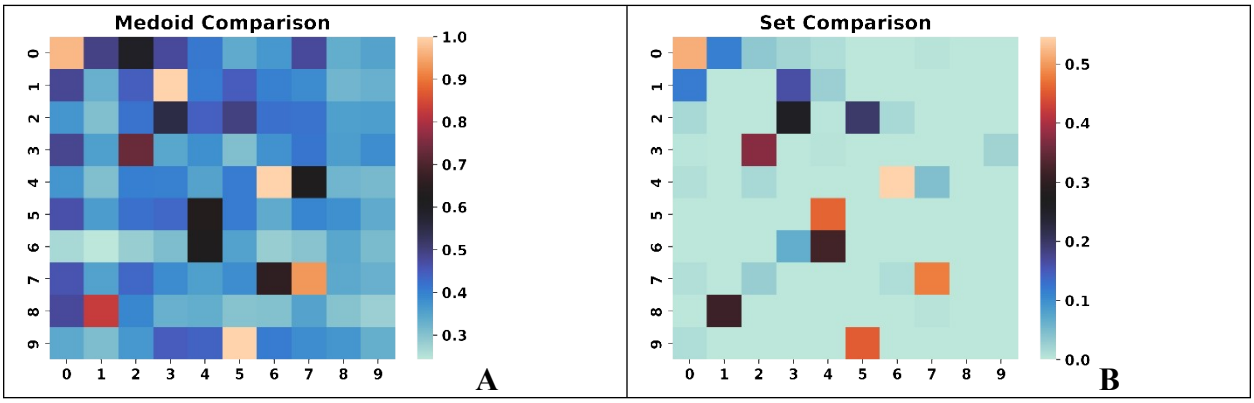


Figure S5.9: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [9] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

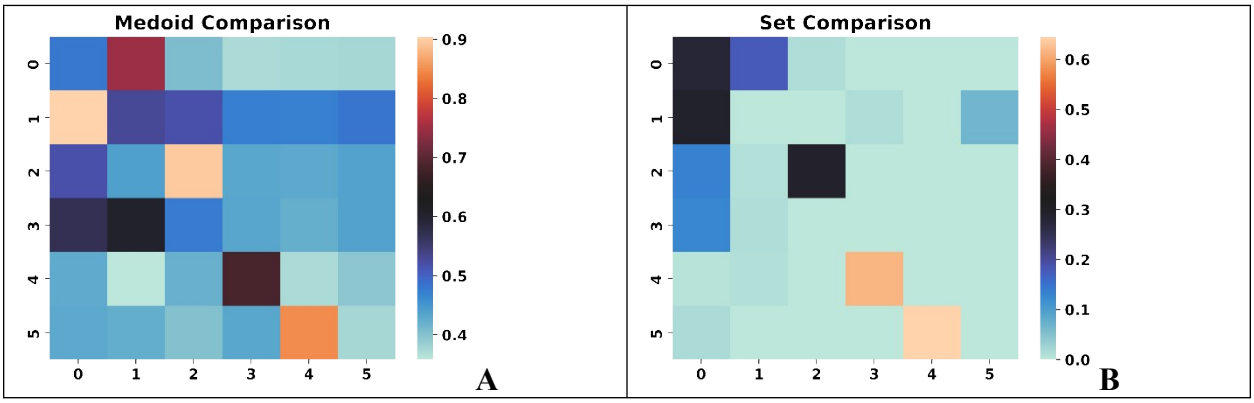


Figure S5.10: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [10] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

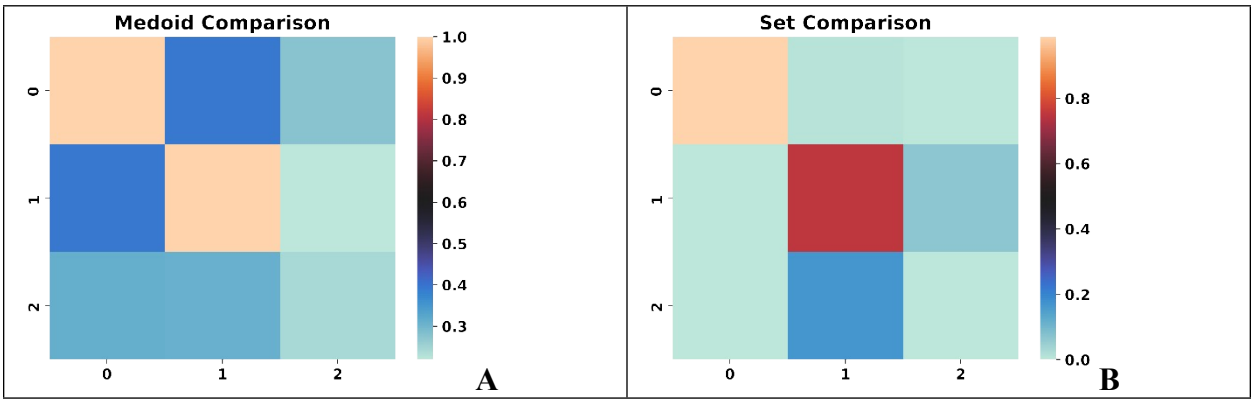


Figure S5.11: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [11] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

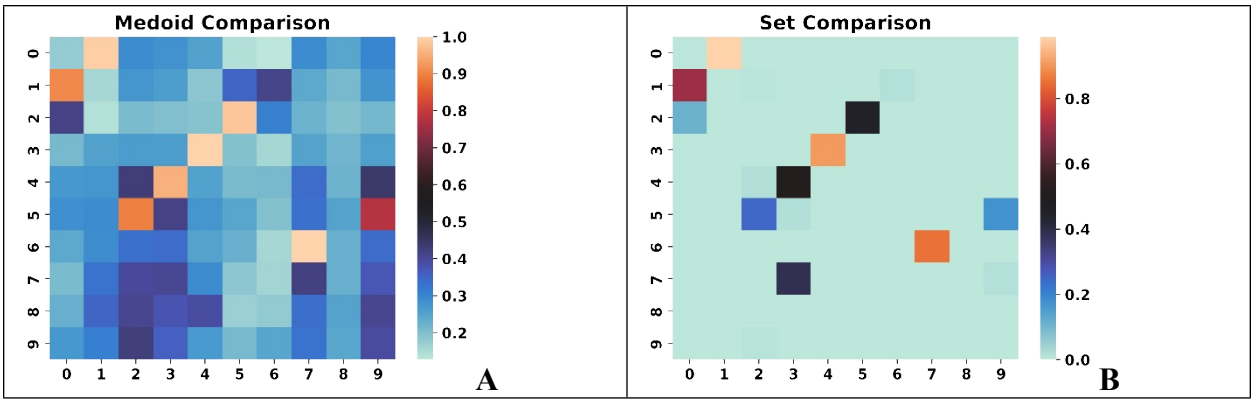


Figure S5.12: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [12] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

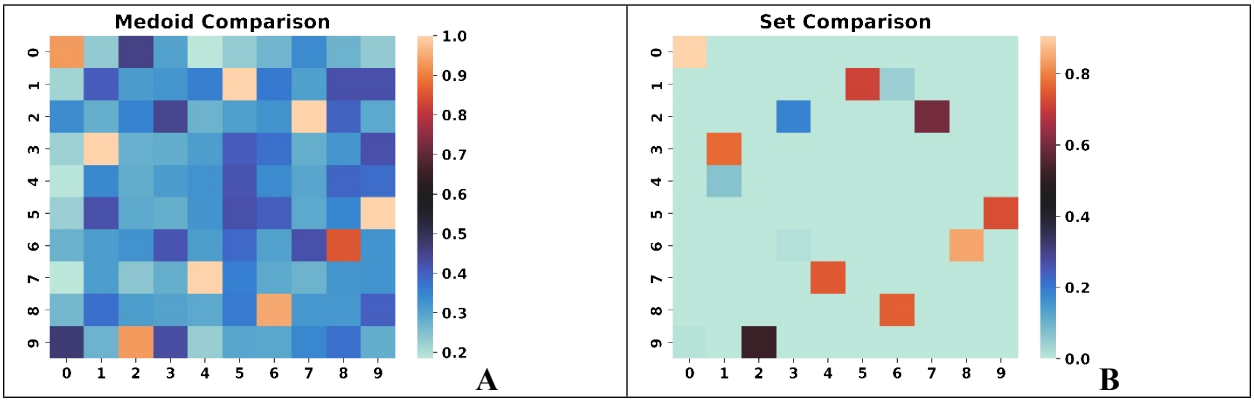


Figure S5.13: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [13] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

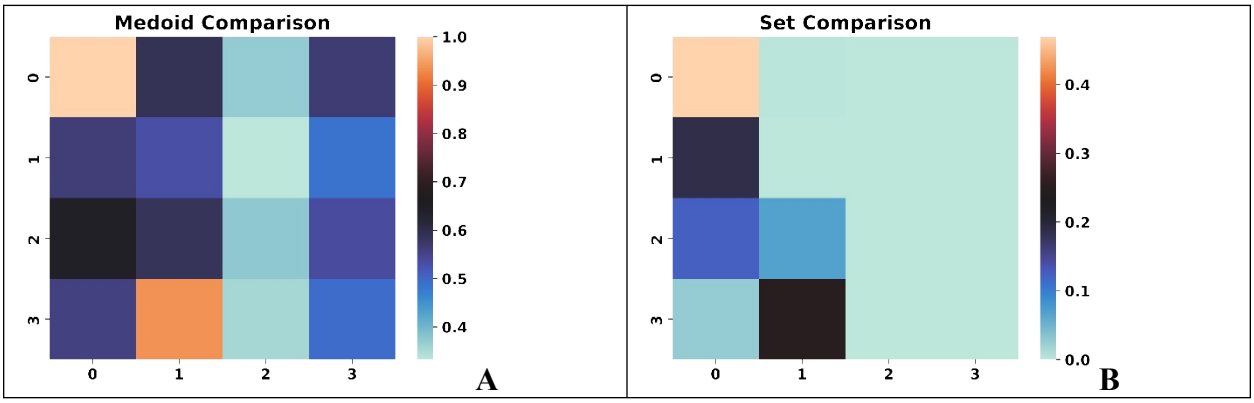


Figure S5.14: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [14] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

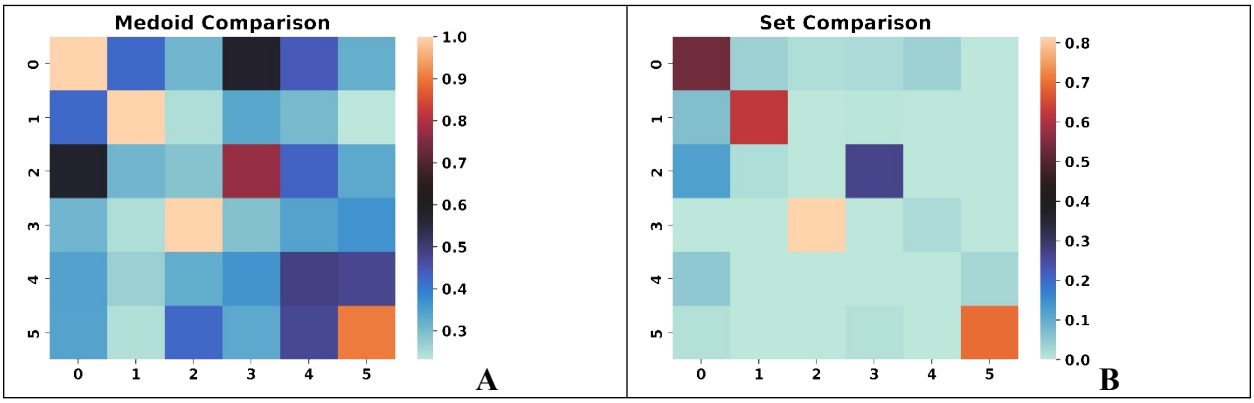


Figure S5.15: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [15] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

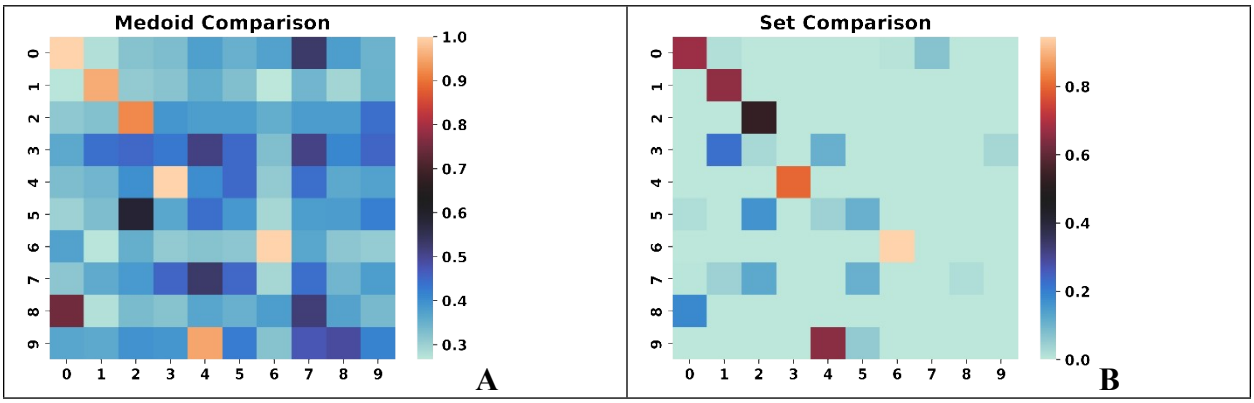


Figure S5.16: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [16] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

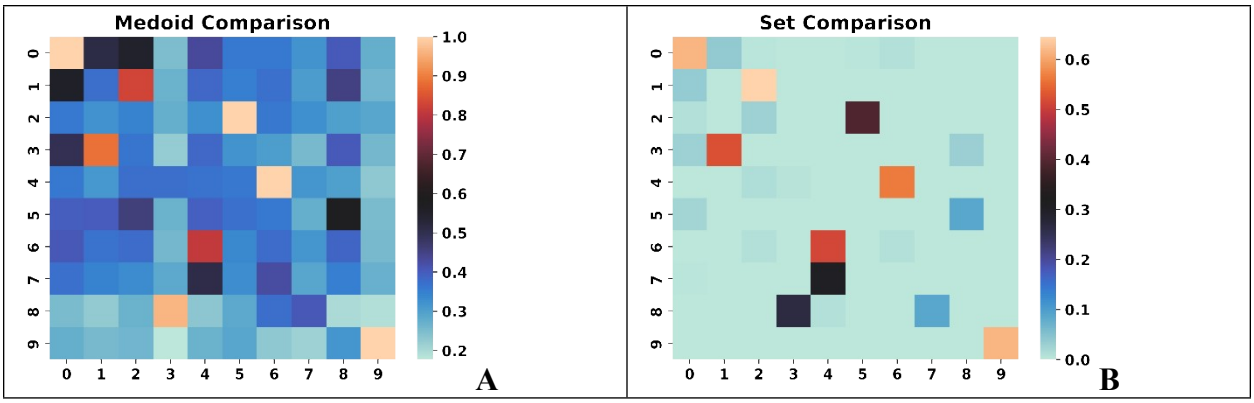


Figure S5.17: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [17] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

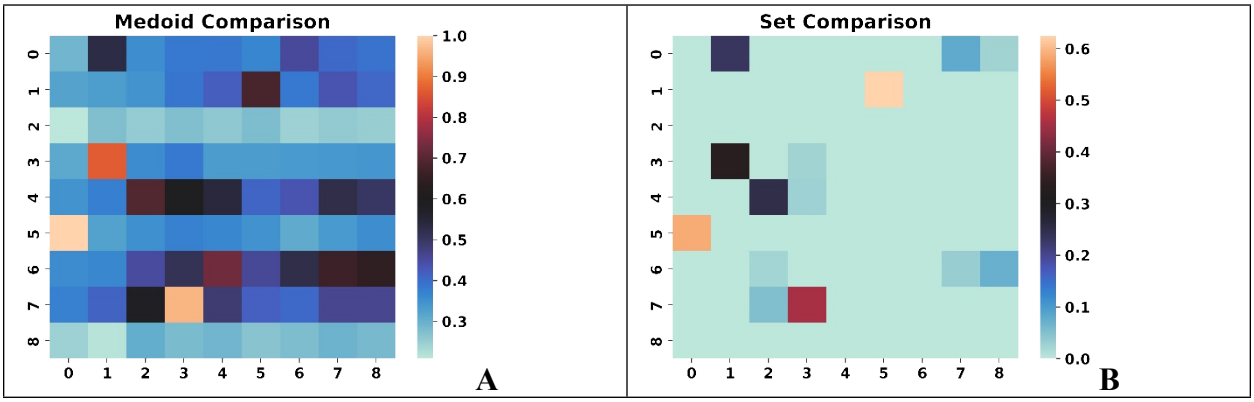


Figure S5.18: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [18] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

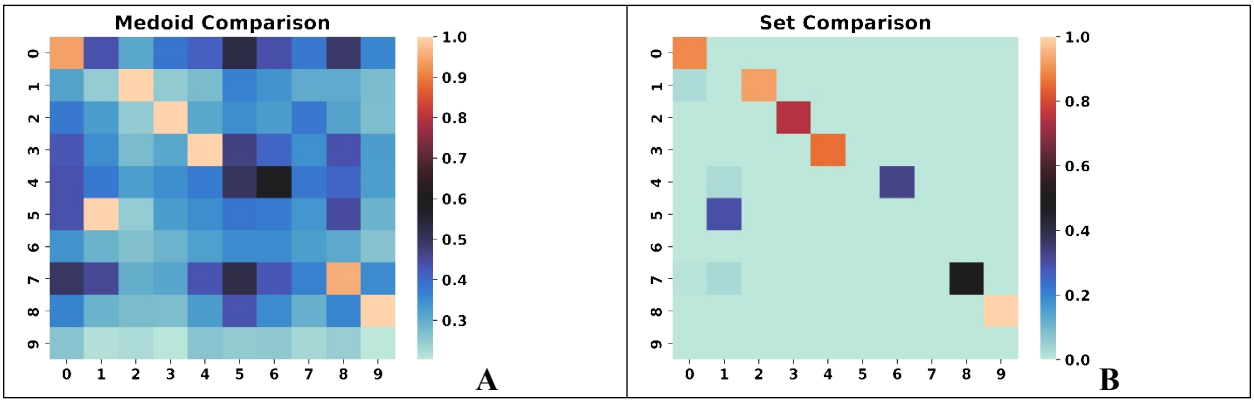


Figure S5.19: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [19] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

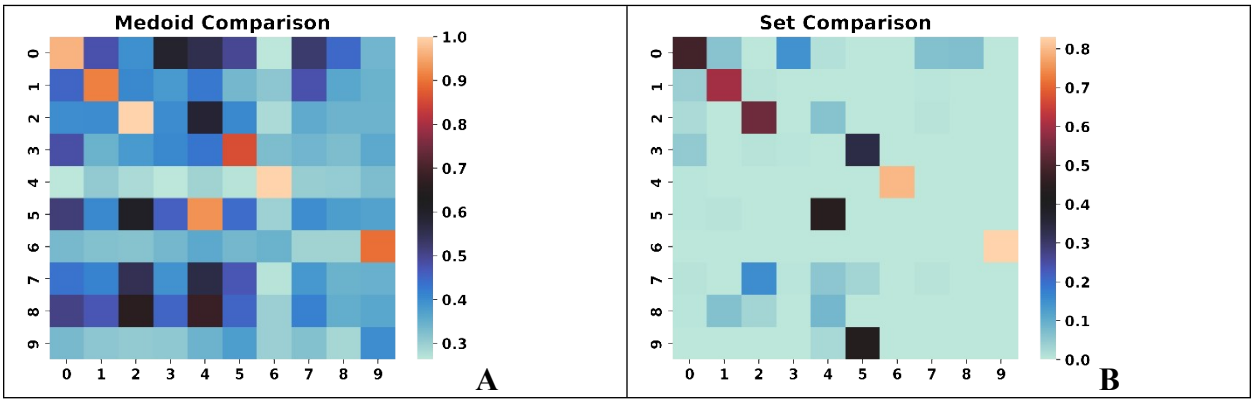


Figure S5.20: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [20] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

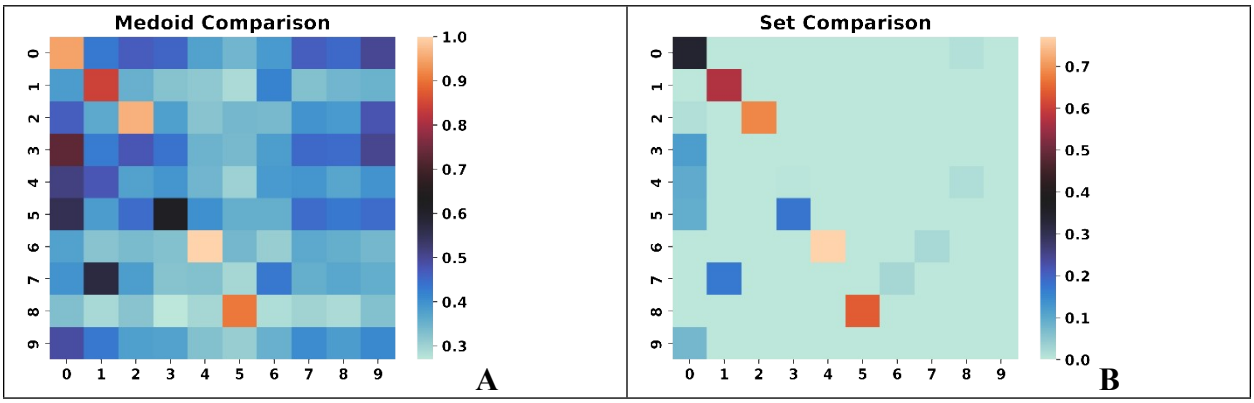


Figure S5.21: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [21] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

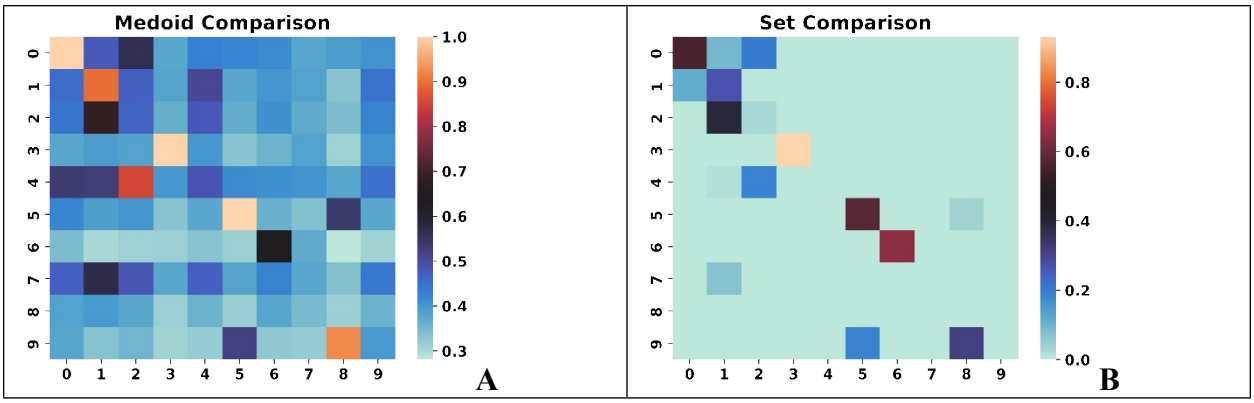


Figure S5.22: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [22] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

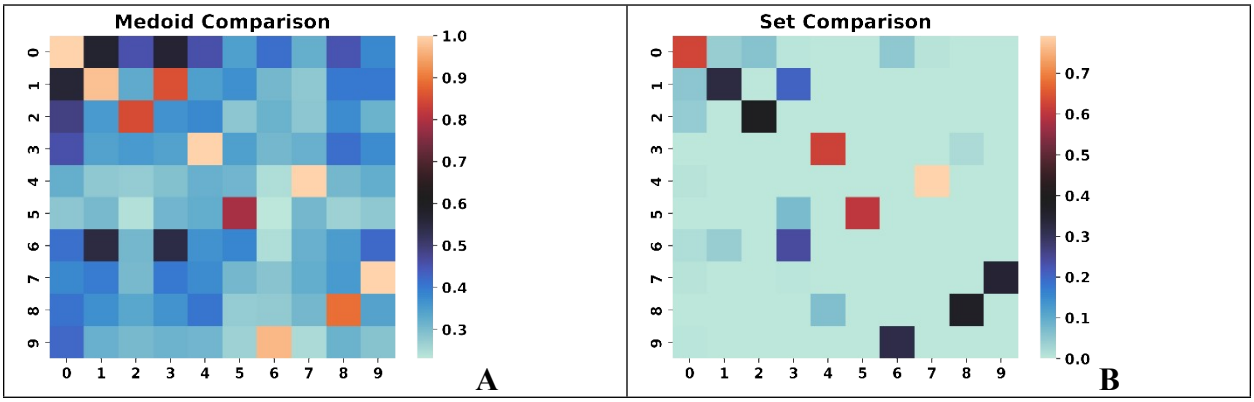


Figure S5.23: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [23] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

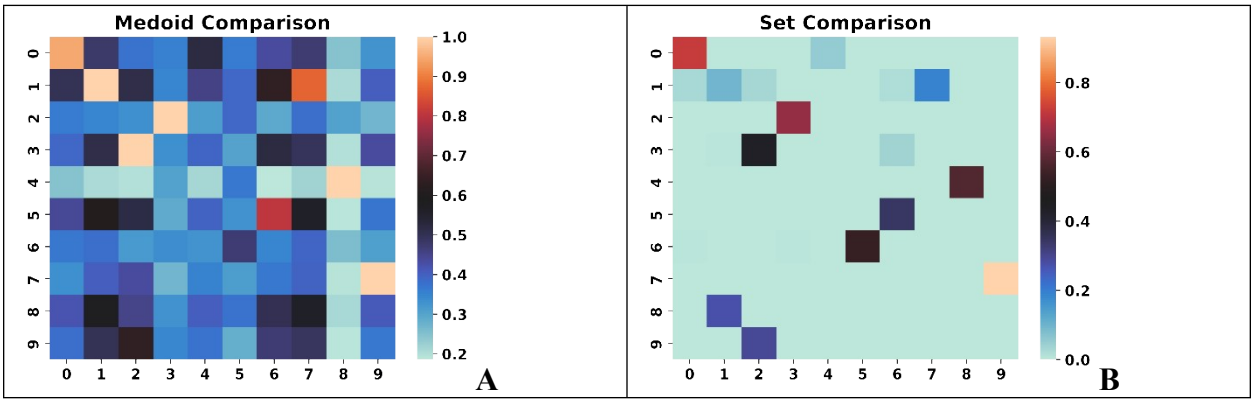


Figure S5.24: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [24] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

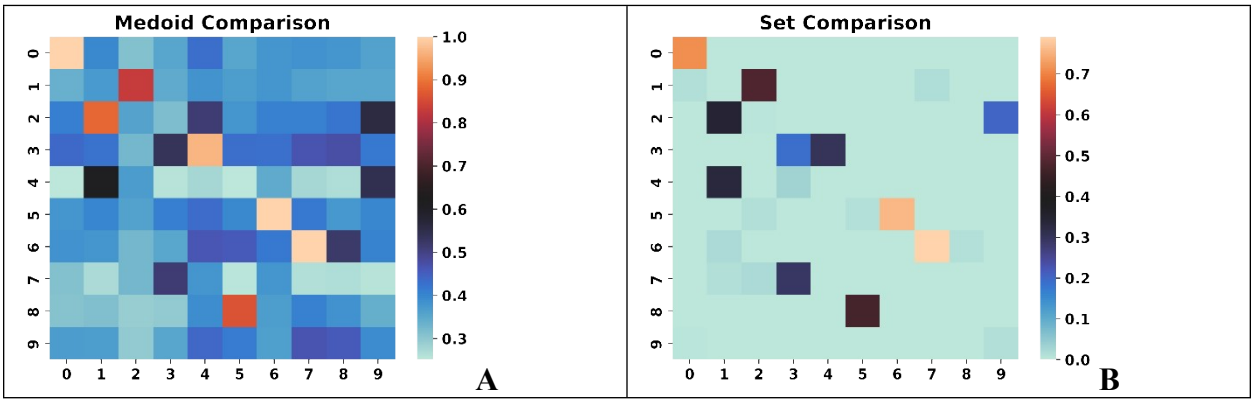


Figure S5.25: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [25] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

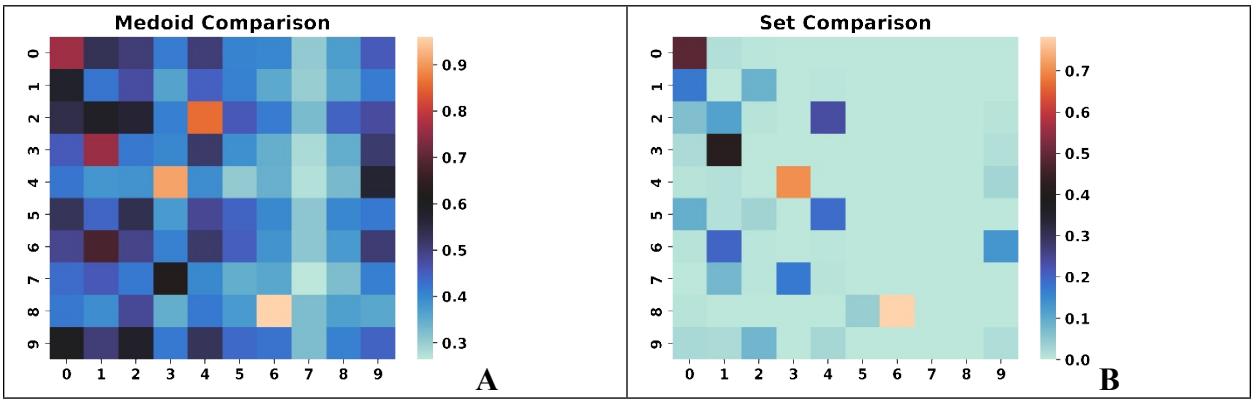


Figure S5.26: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [26] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

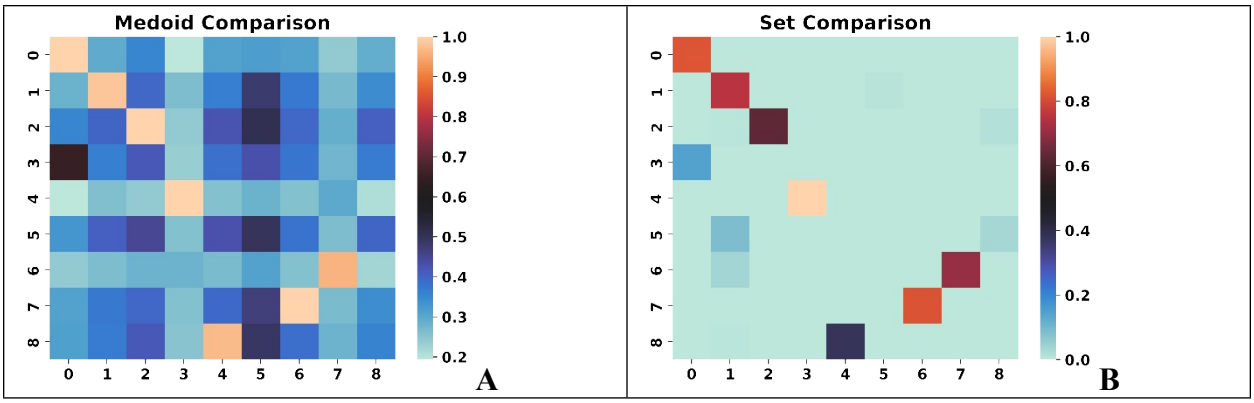


Figure S5.27: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [27] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

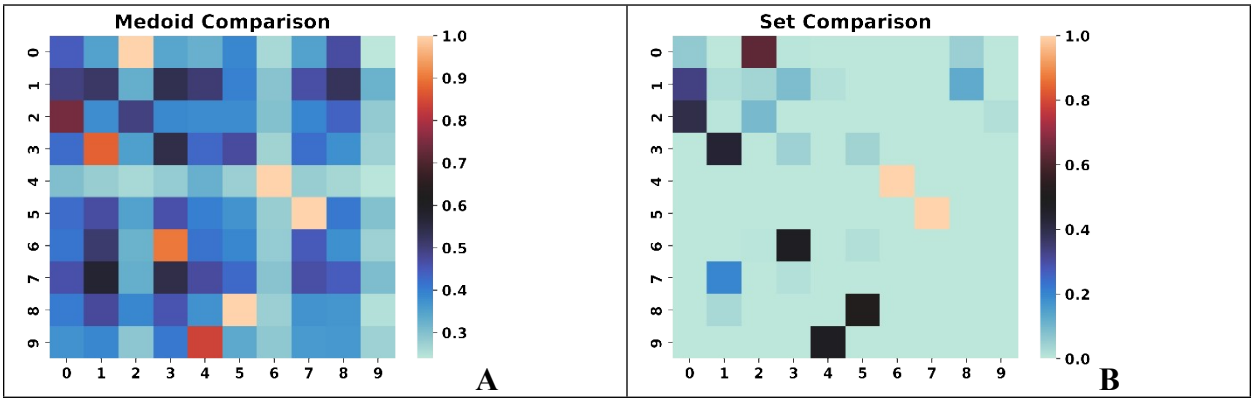


Figure S5.28: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [28] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

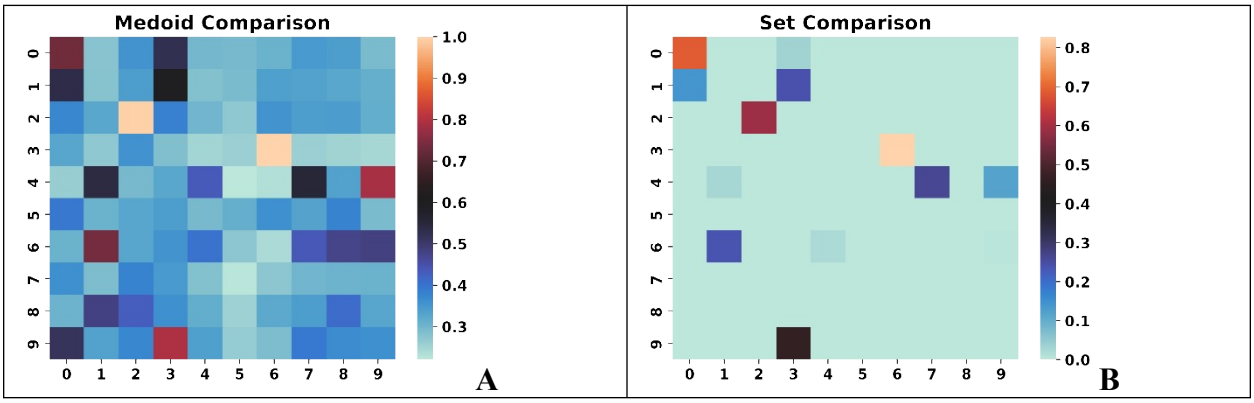


Figure S5.29: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [29] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

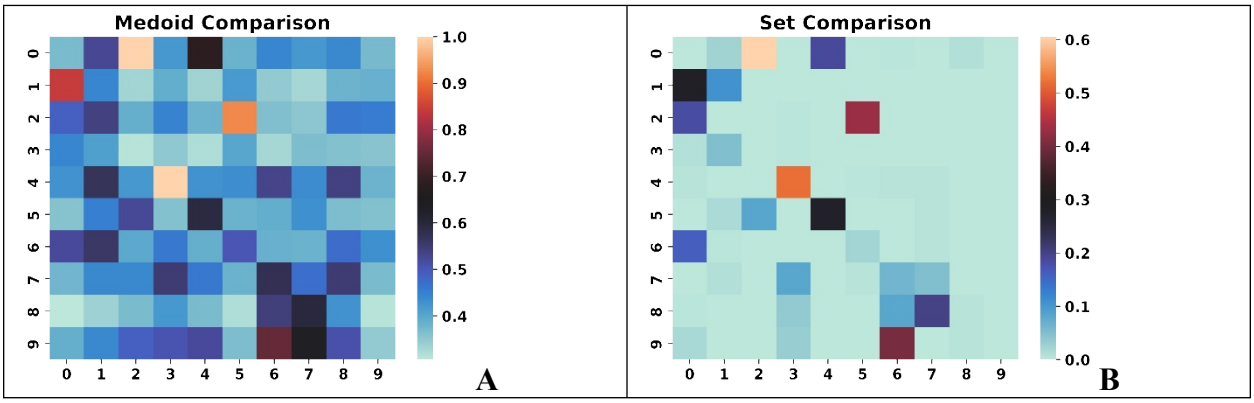


Figure S5.30: Comparison of the **A**: medoids, **B**: sets for the top populated clusters of the [30] ChEMBL subset using the BitBIRCH and BitBIRCH-parallel algorithms (similarity threshold = 0.65, min_size = 10).

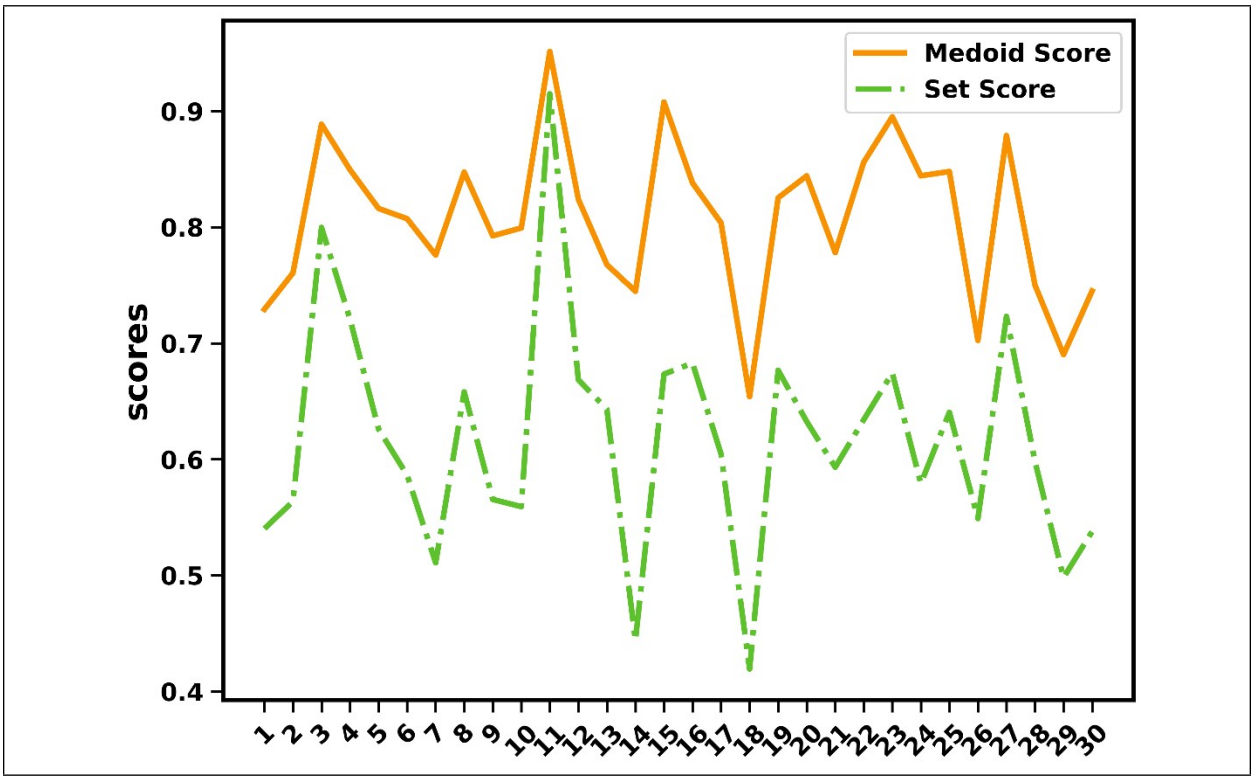


Figure S5.31: Summary of the Medoid (continuous orange line) and Set (dashed green line) scores for the 30 ChEMBL subsets for the BitBIRCH and BitBIRCH-parallel algorithms.

	CHI	DBI	DI
t-statistic	163.0	195.0	41.0
p-value	0.158	0.452	1.824e-05

Table S5.1: *t*-statistic and *p*-value for the two-sided Wilcoxon test comparing the BitBIRCH and BitBIRCH-parallel methods for the 30 ChEMBL subsets at a 0.65 similarity threshold, with min_size = 10.

We also performed a one-sided Dunn test (Ha: BB < BB-parallel), that resulted in a *t*-statistic of 41.0 and a *p*-value of 9.122e-05.

S6: Local Clustering Analysis of BitBIRCH and BitBIRCH-folded

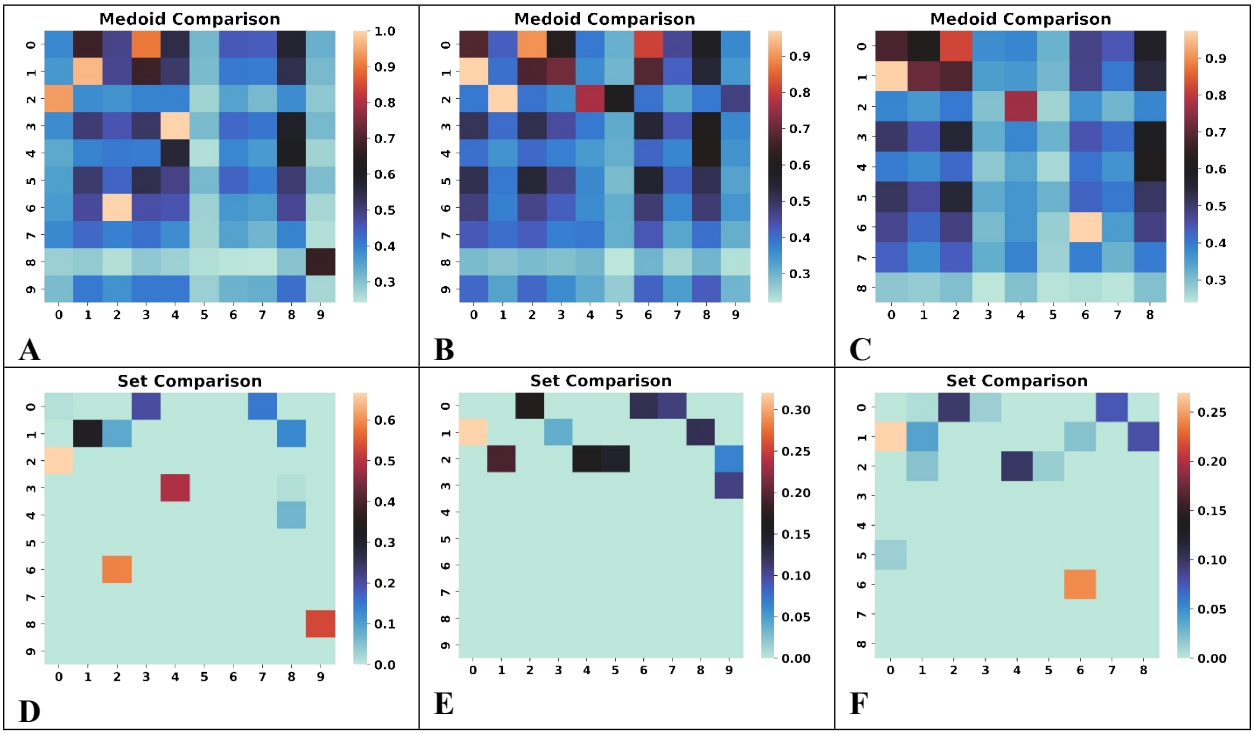


Figure S6.1: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [1] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

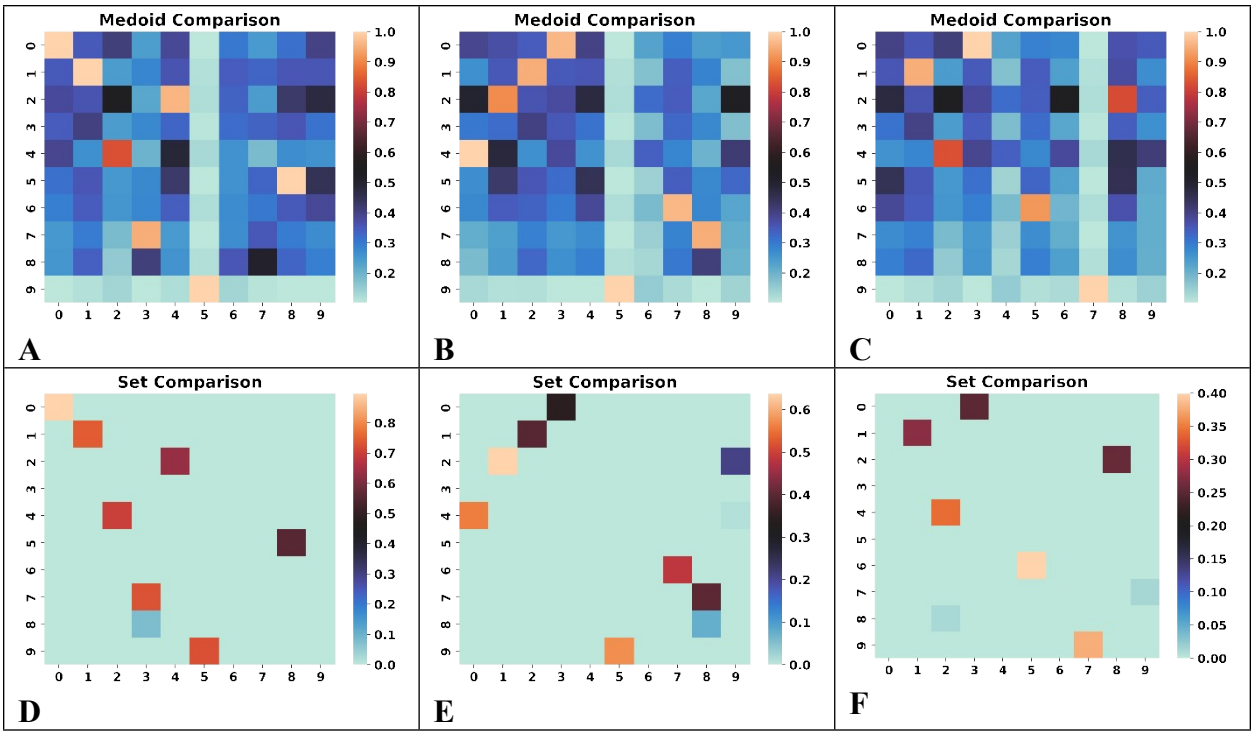


Figure S6.2: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [2] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

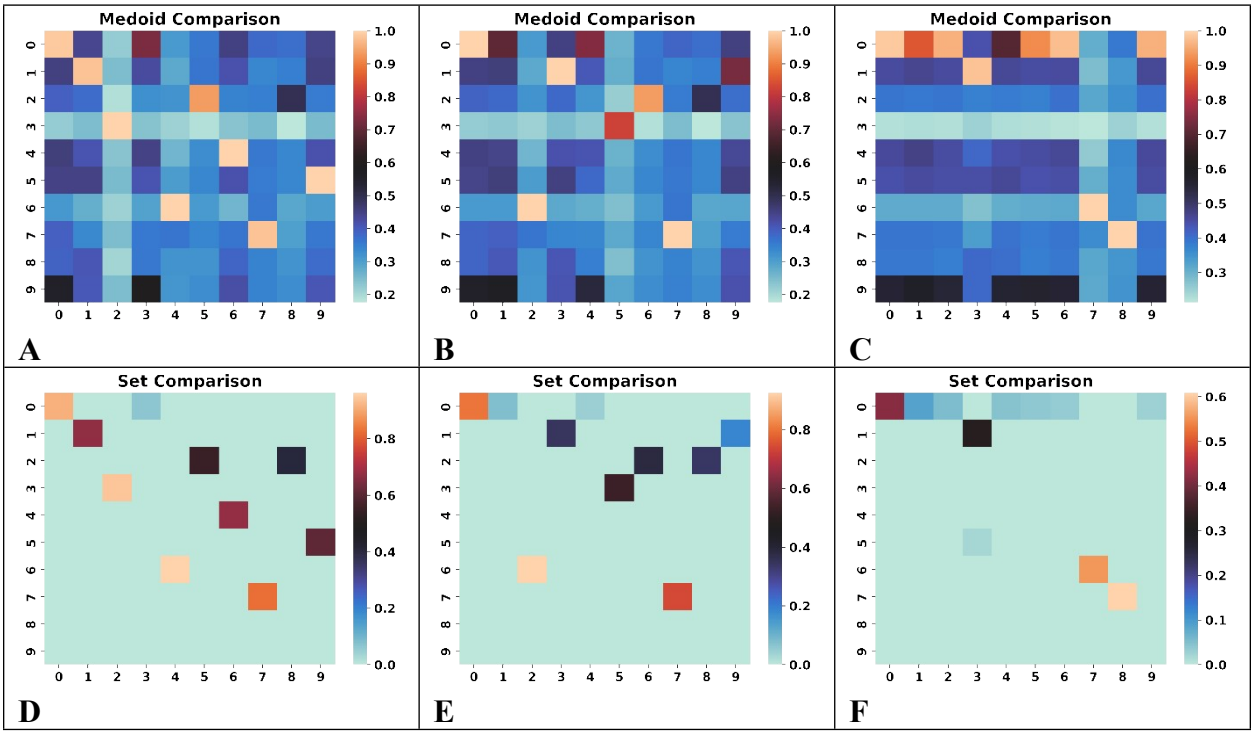


Figure S6.3: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [3] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

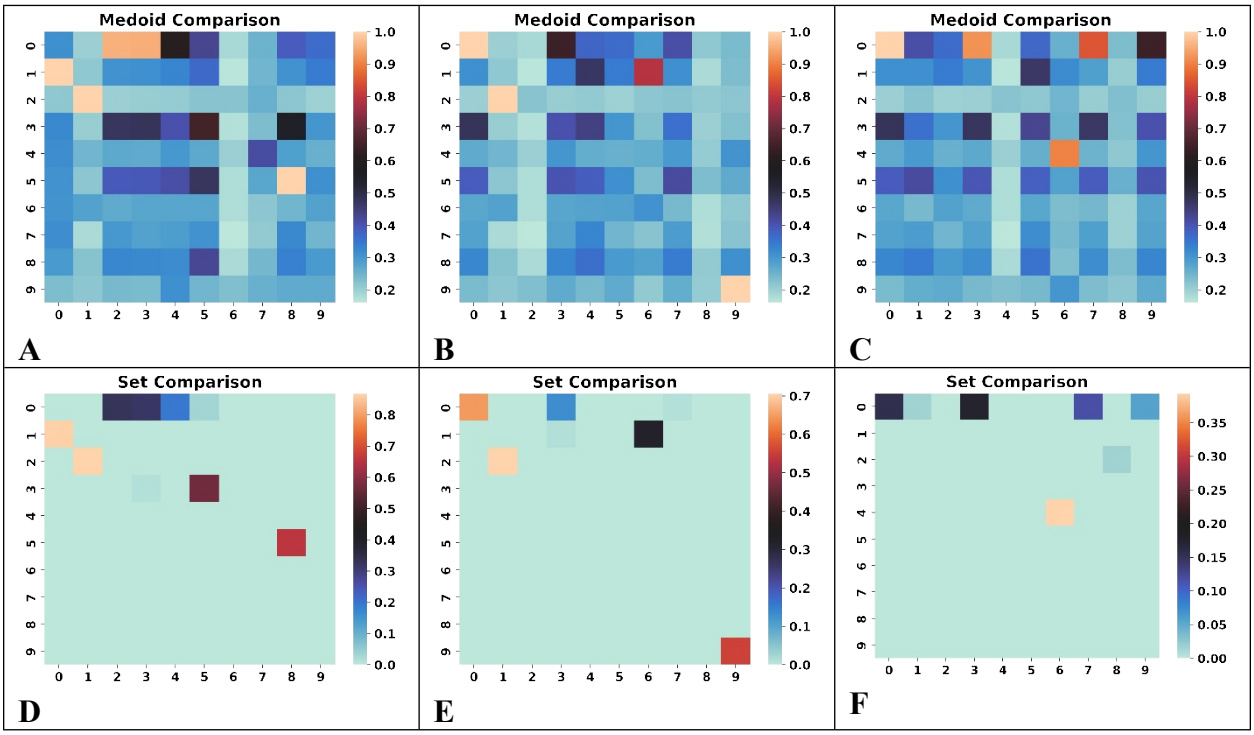
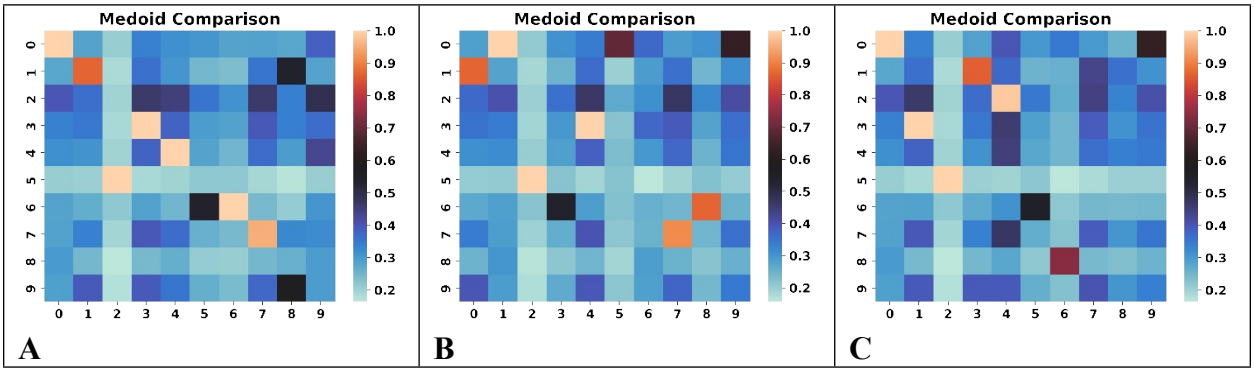


Figure S6.4: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [4] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).



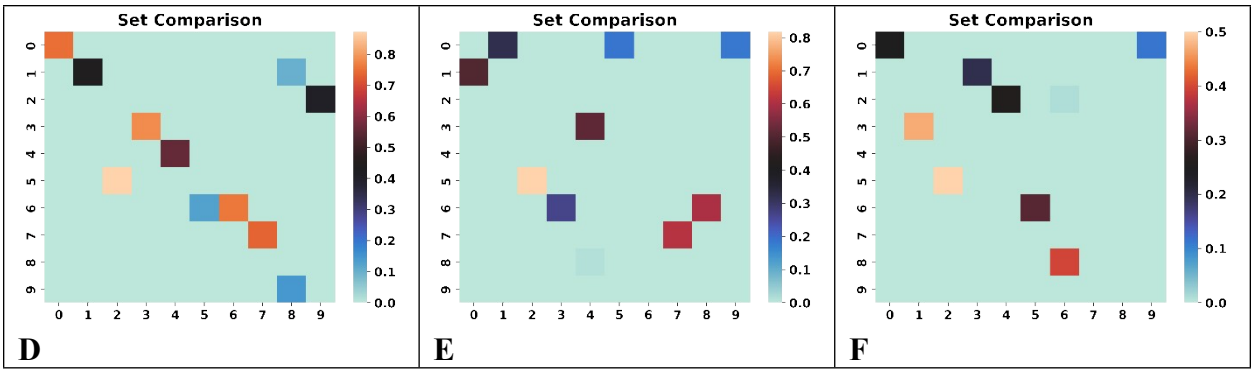


Figure S6.5: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [5] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

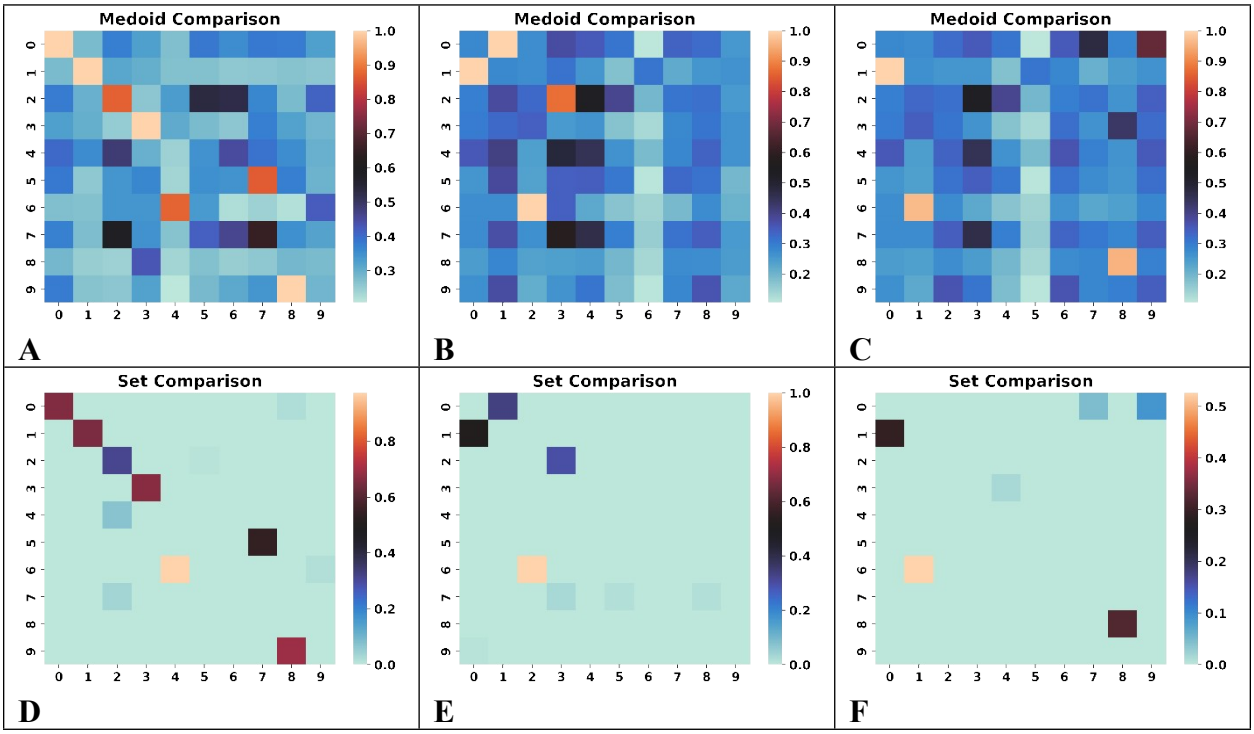


Figure S6.6: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [6] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

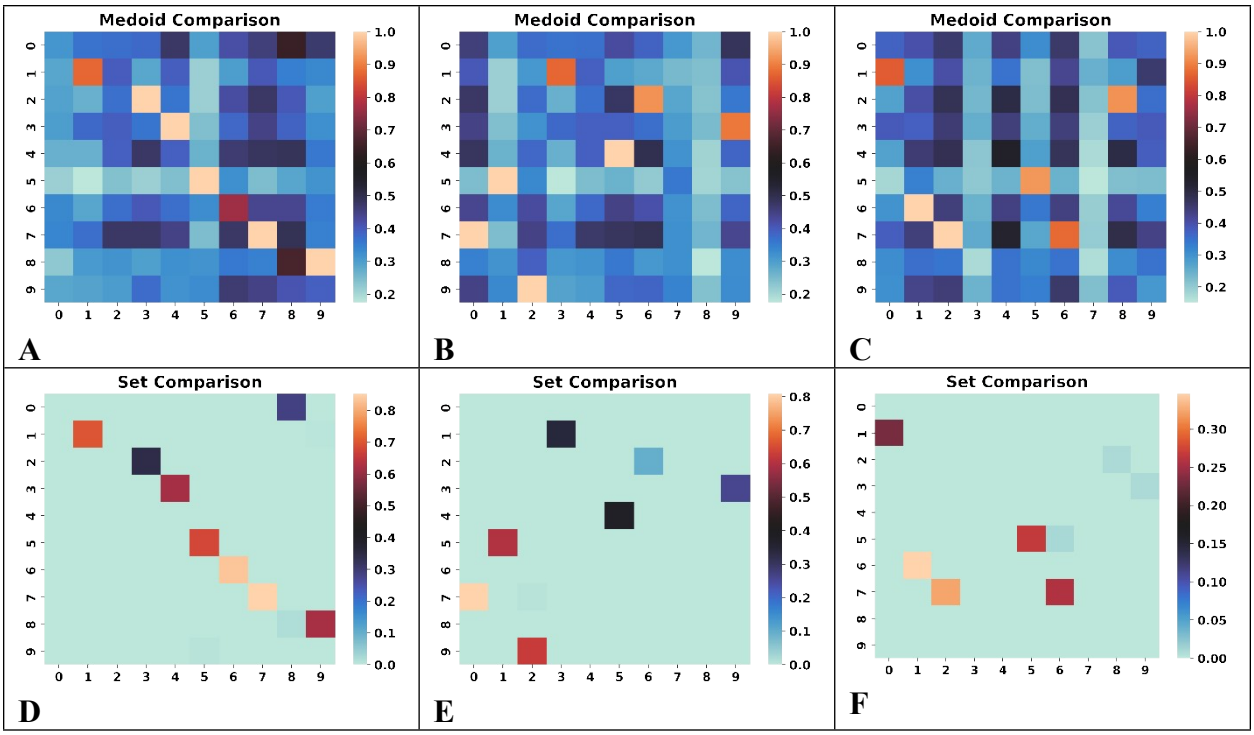


Figure S6.7: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [7] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

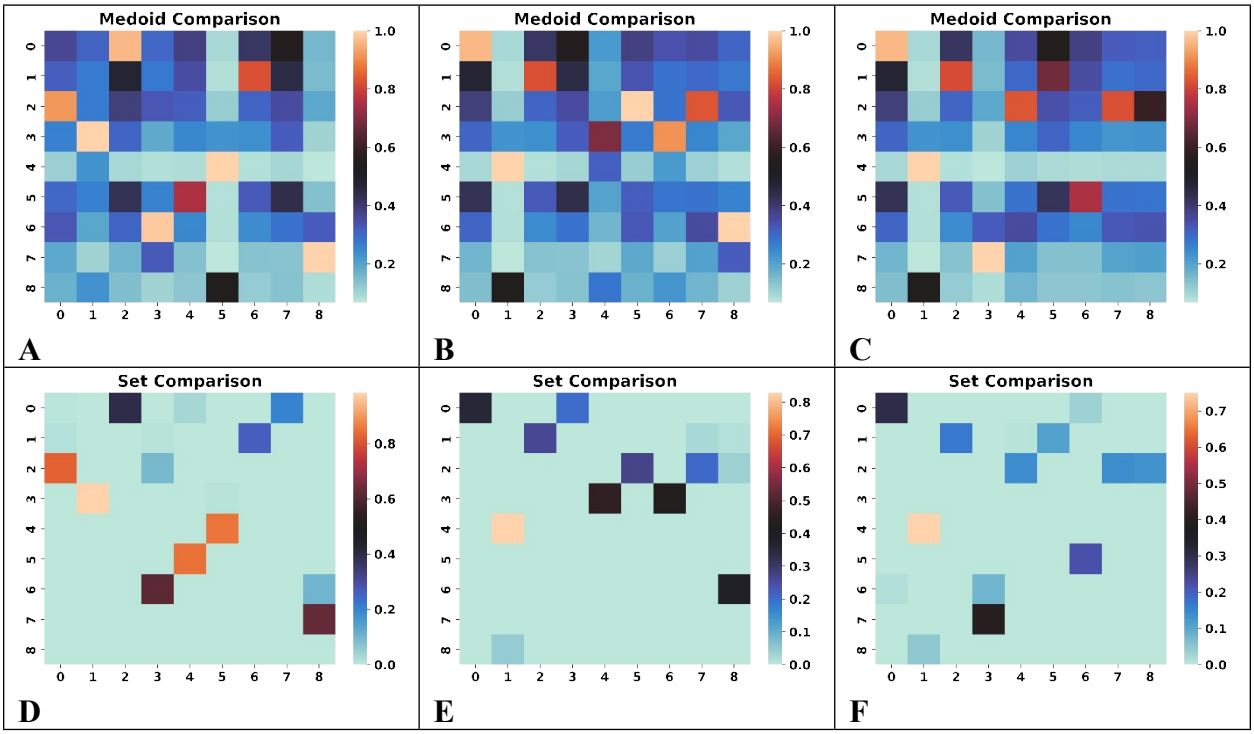


Figure S6.8: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [8] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

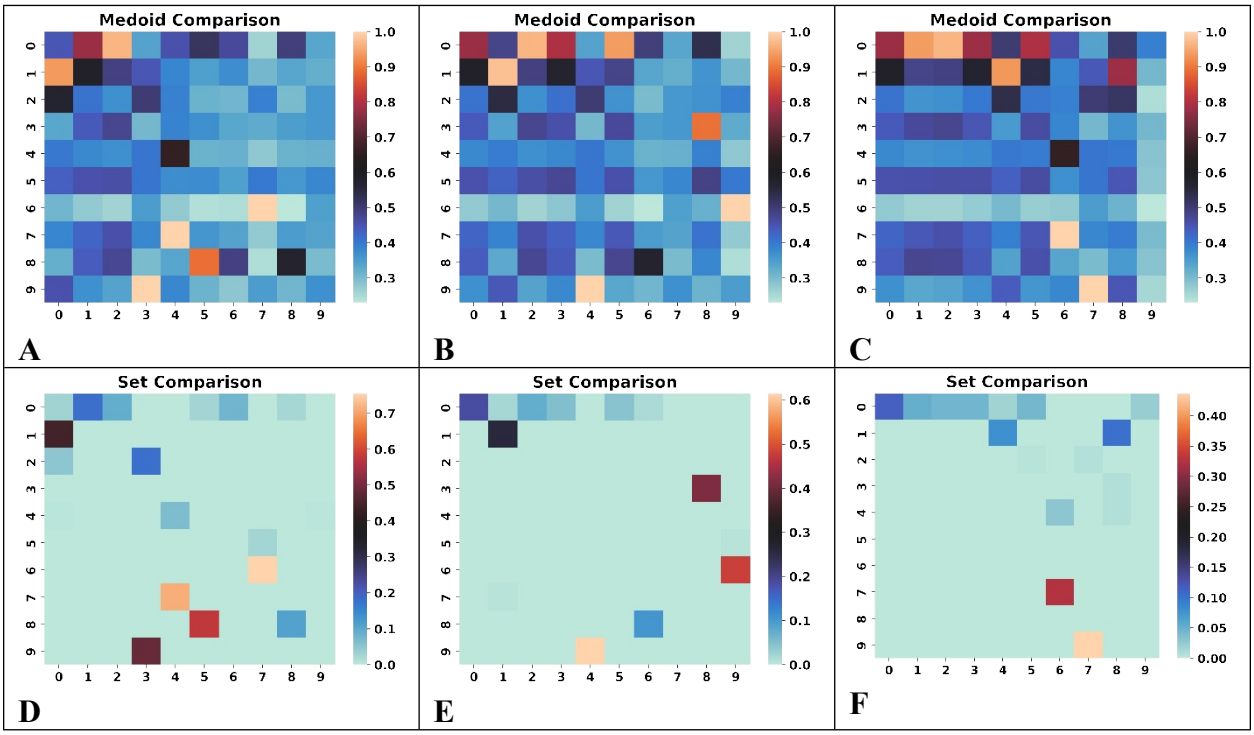
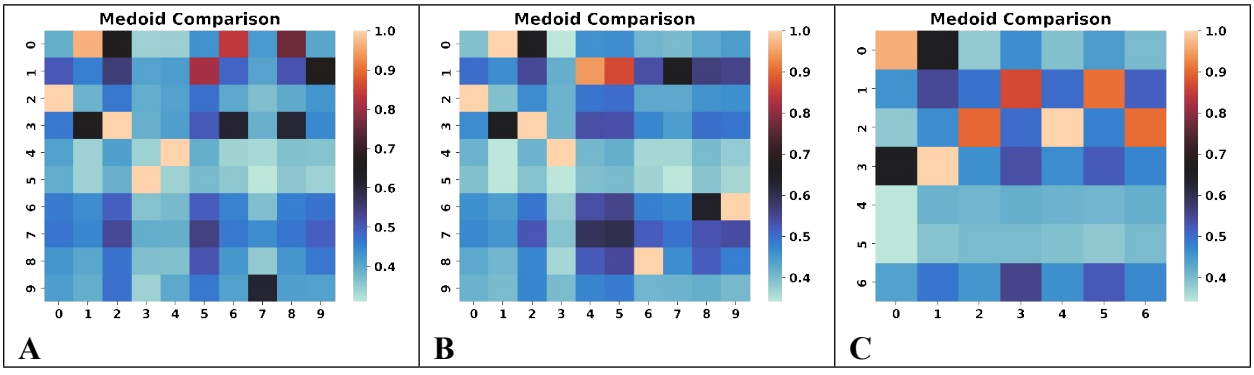


Figure S6.9: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [9] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).



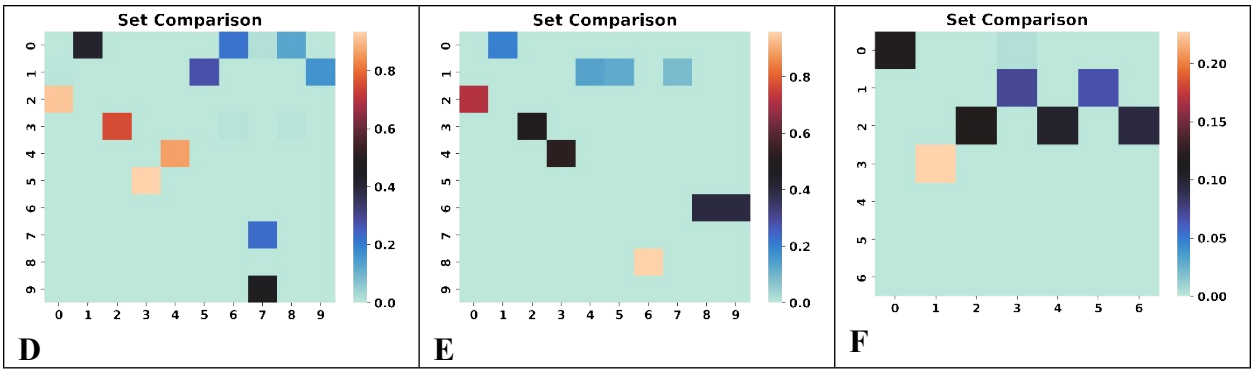


Figure S6.10: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [10] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

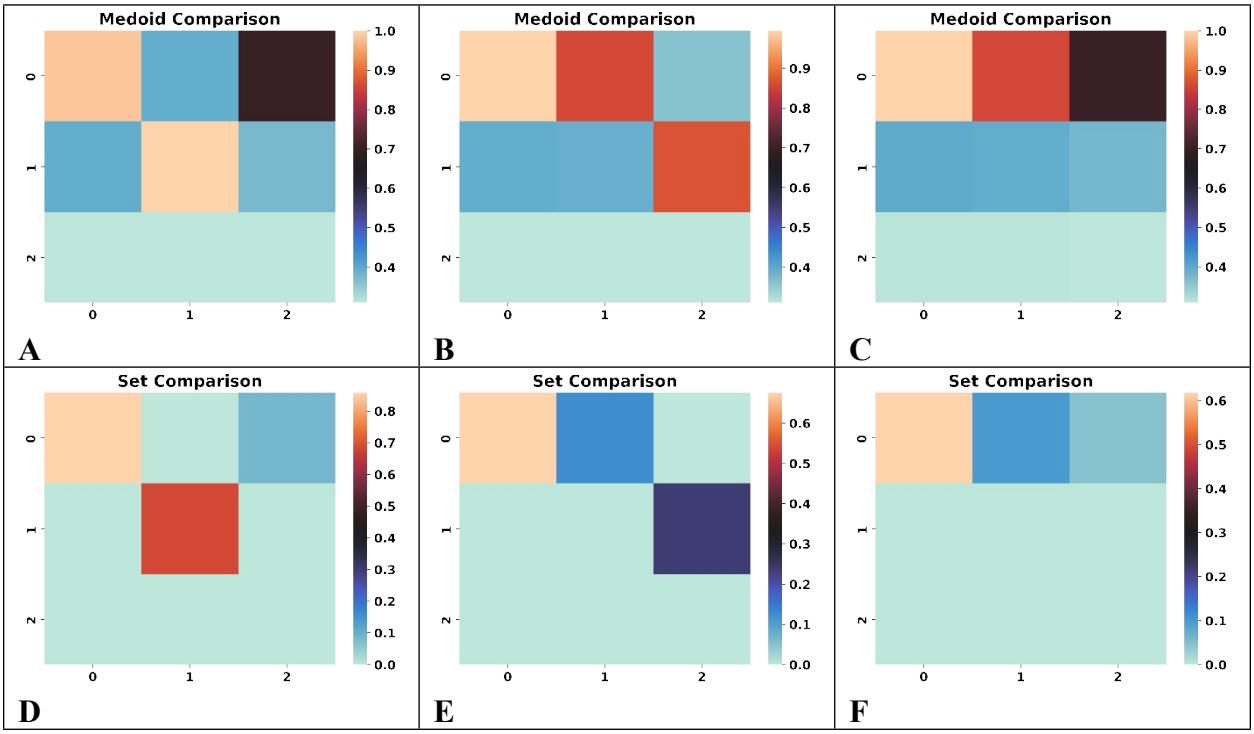


Figure S6.11: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [11] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

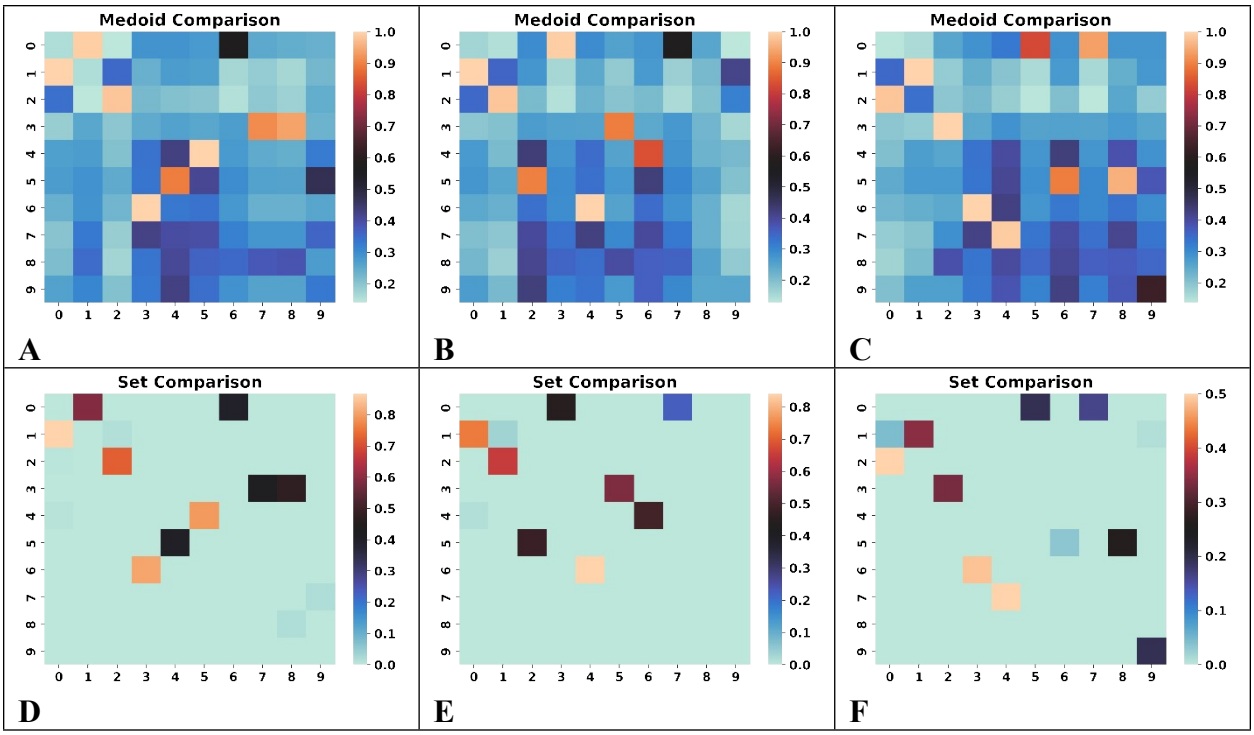


Figure S6.12: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [12] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

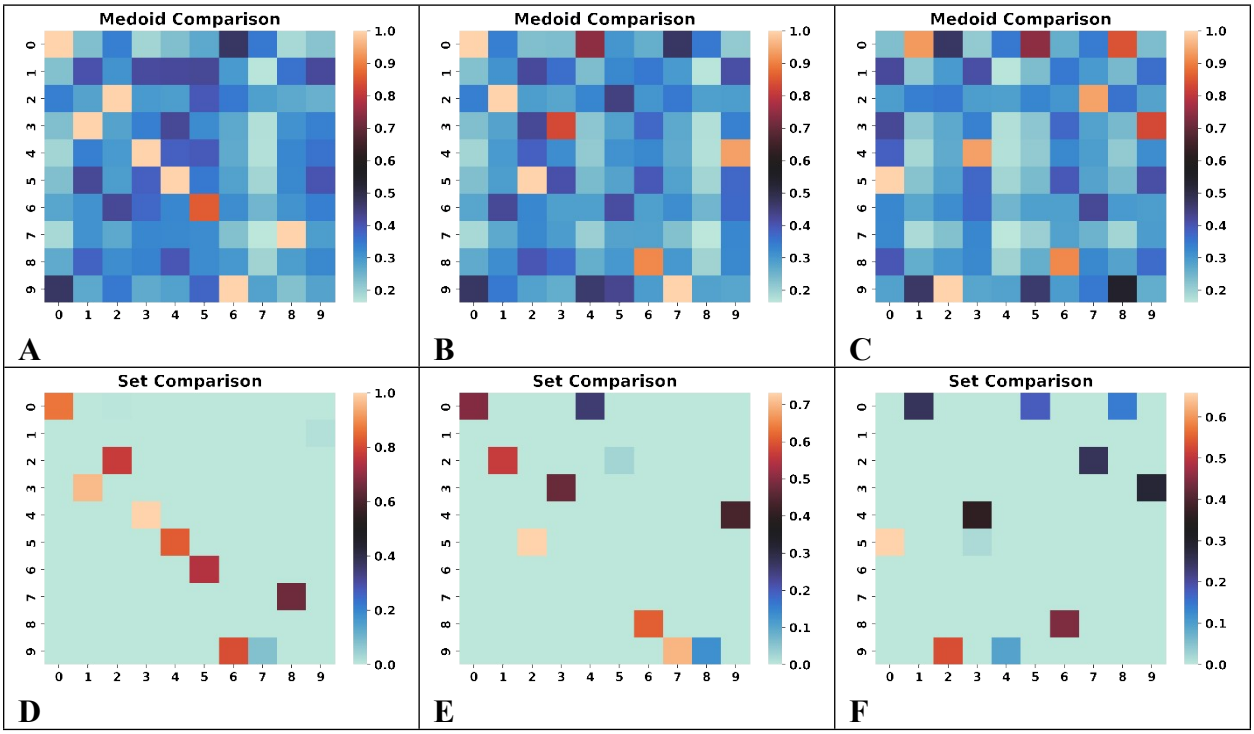


Figure S6.13: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [13] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

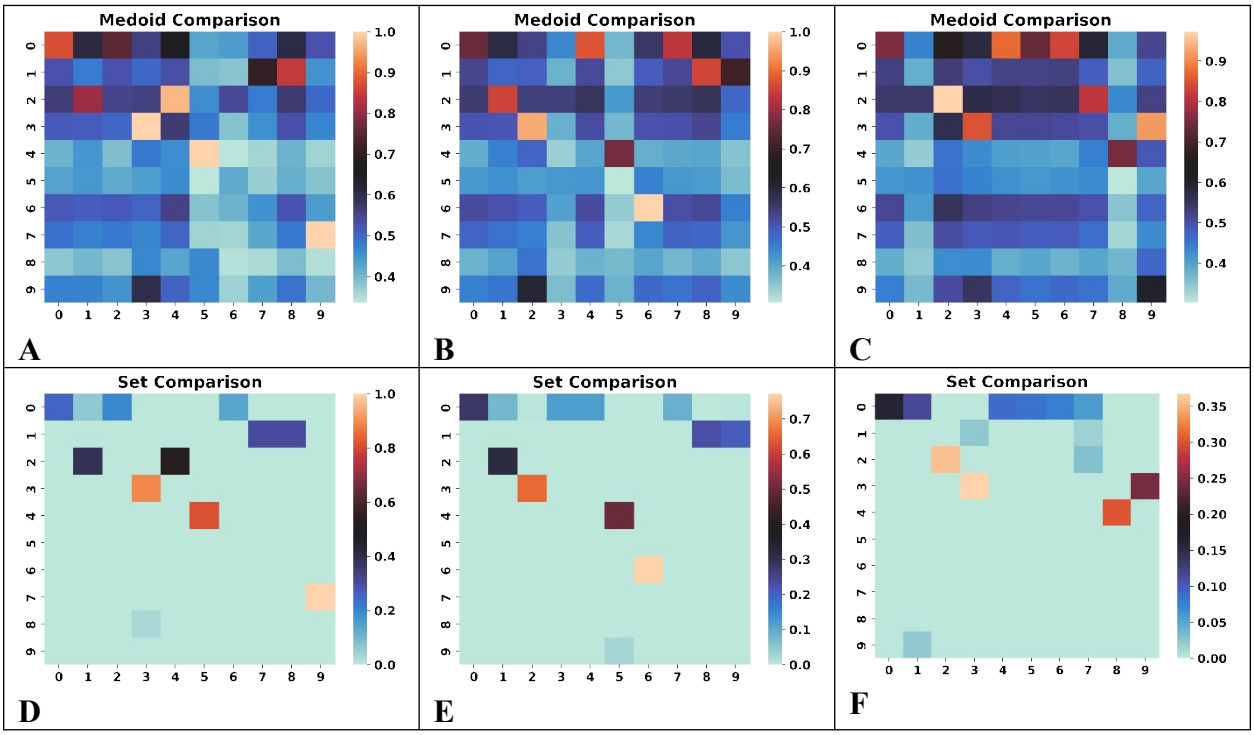
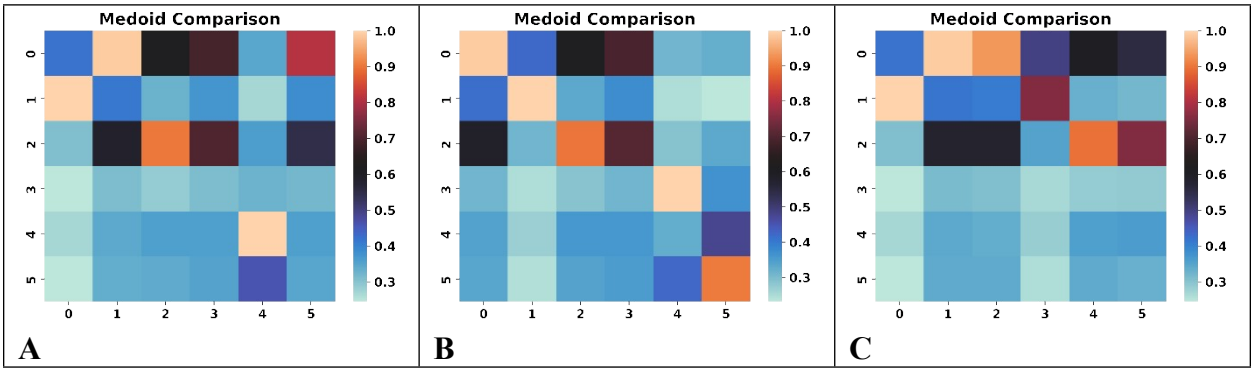


Figure S6.14: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [14] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).



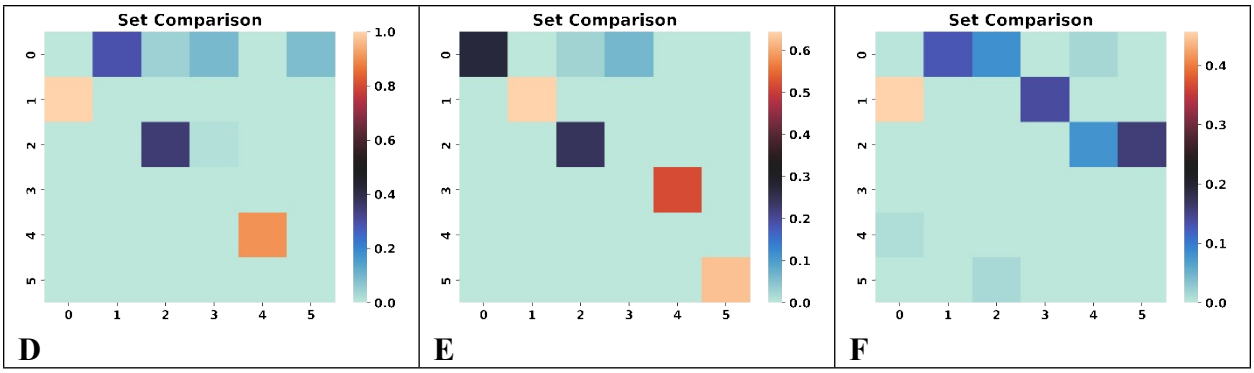


Figure S6.15: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [15] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

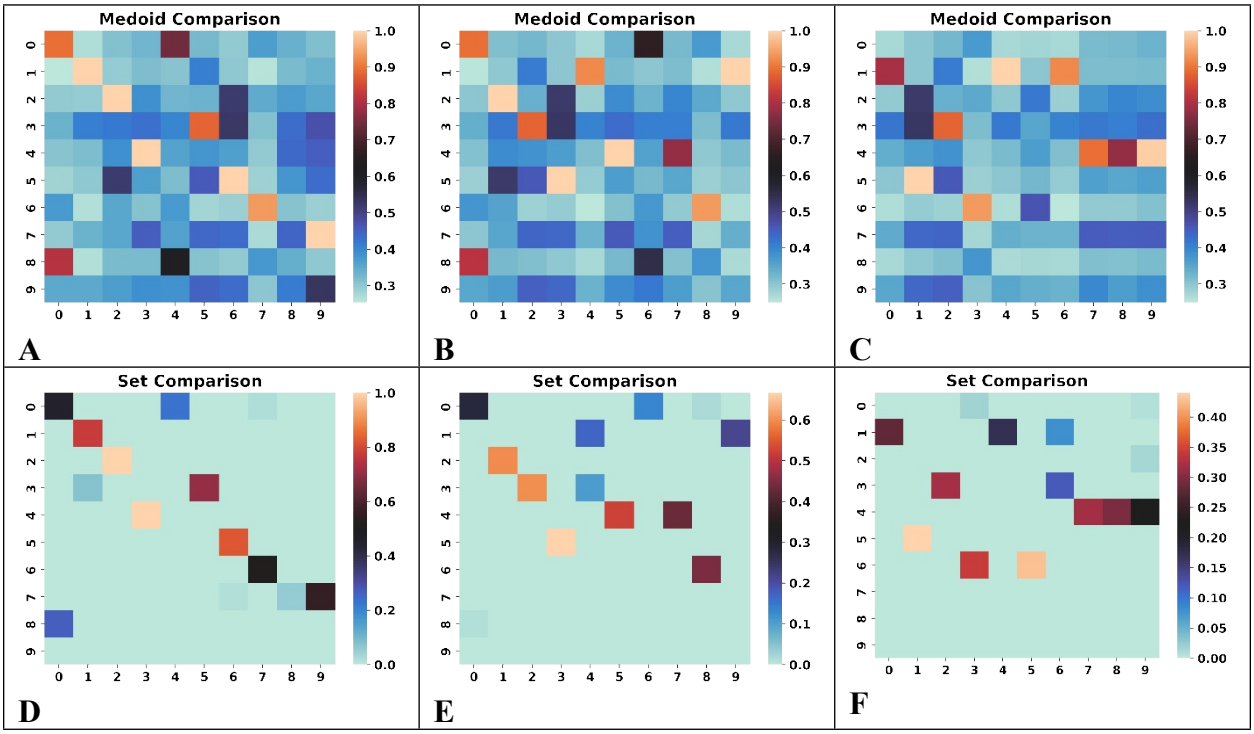


Figure S6.16: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [16] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

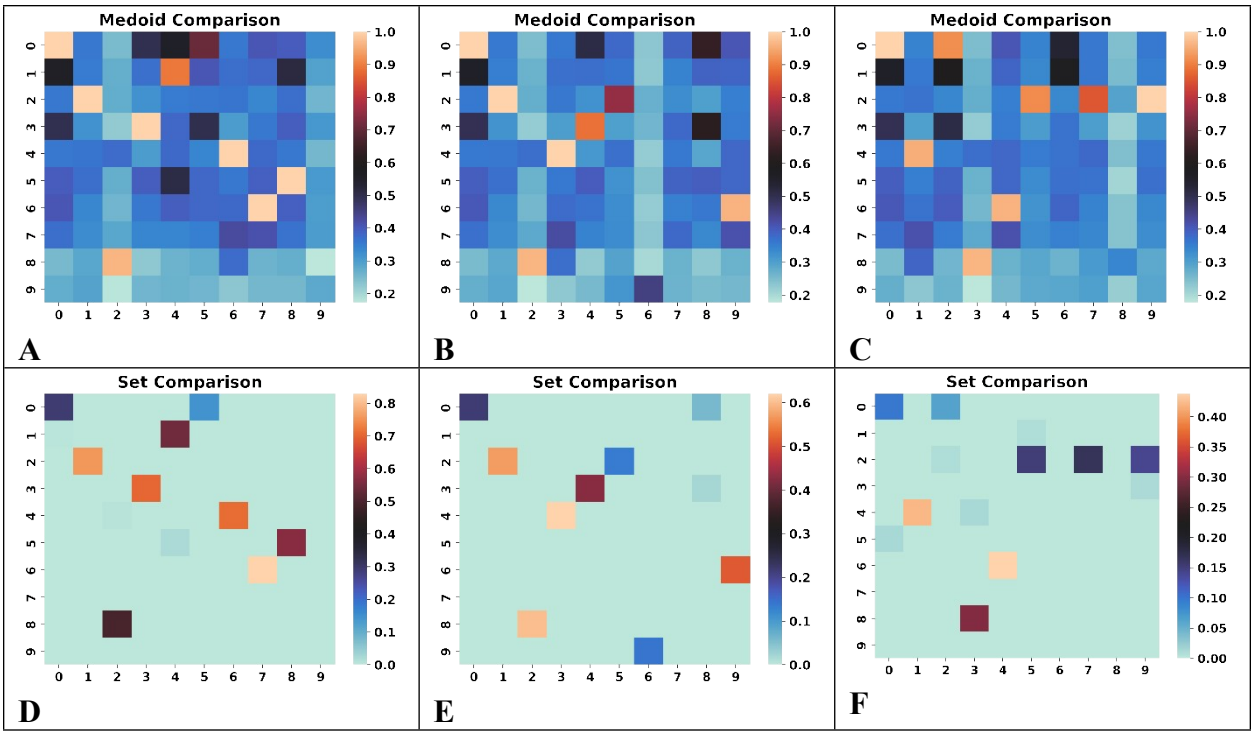


Figure S6.17: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [17] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

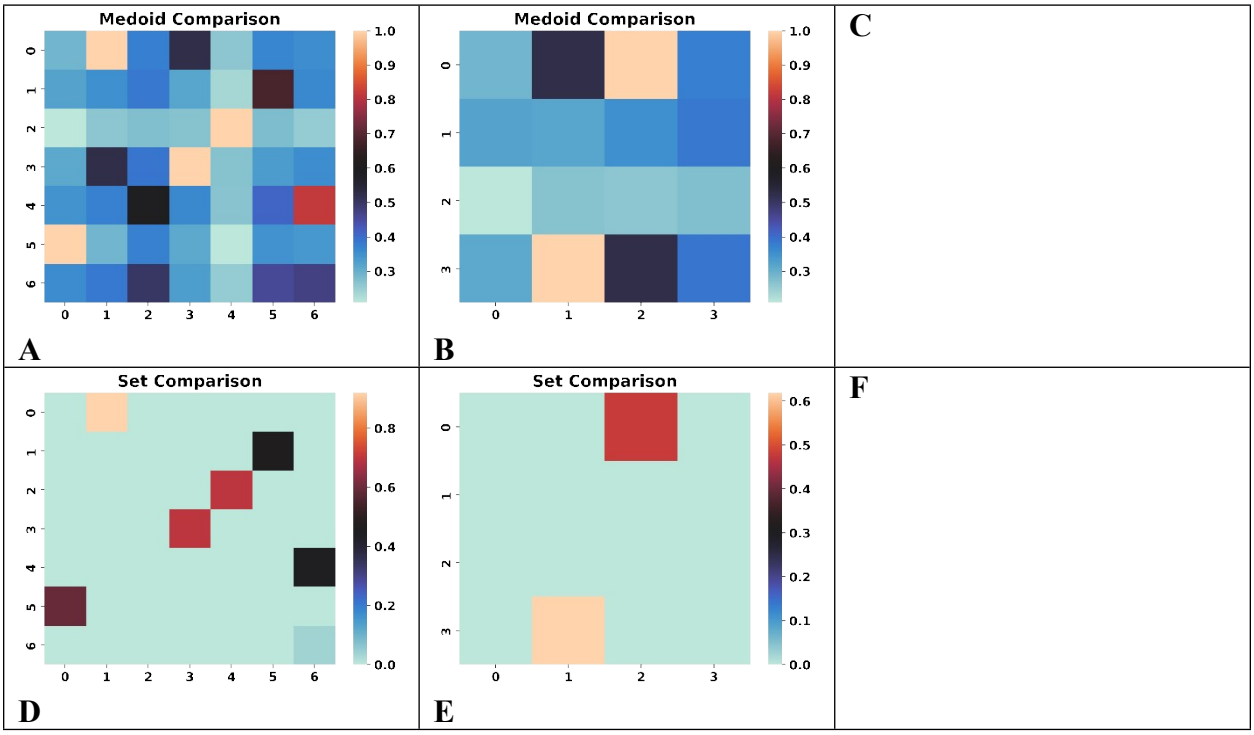


Figure S6.18: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [18] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

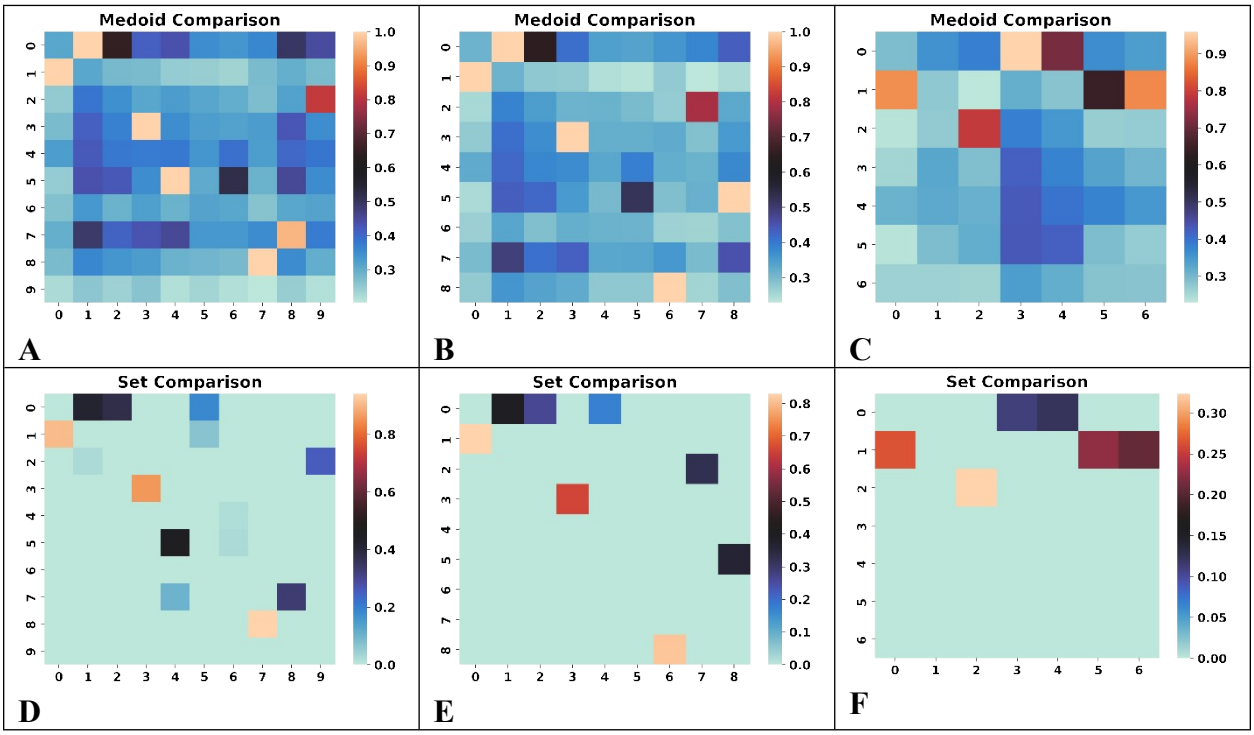
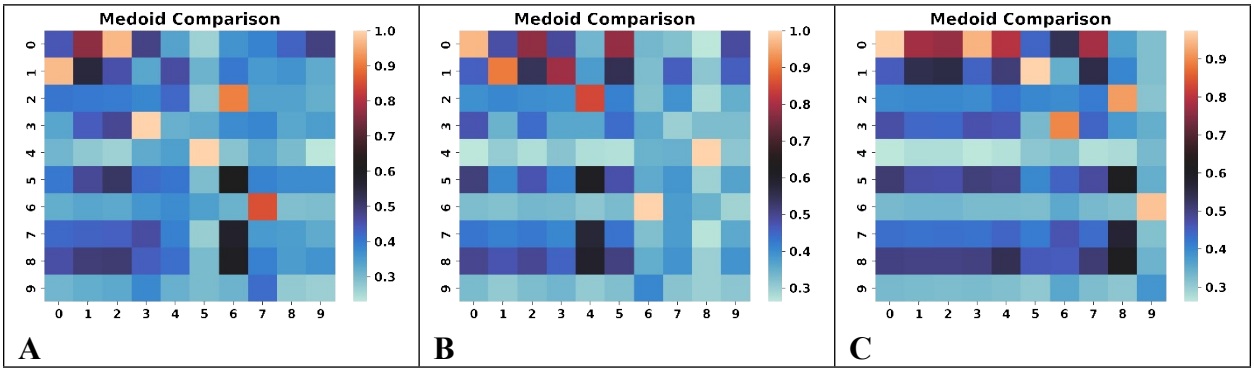


Figure S6.19: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [19] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).



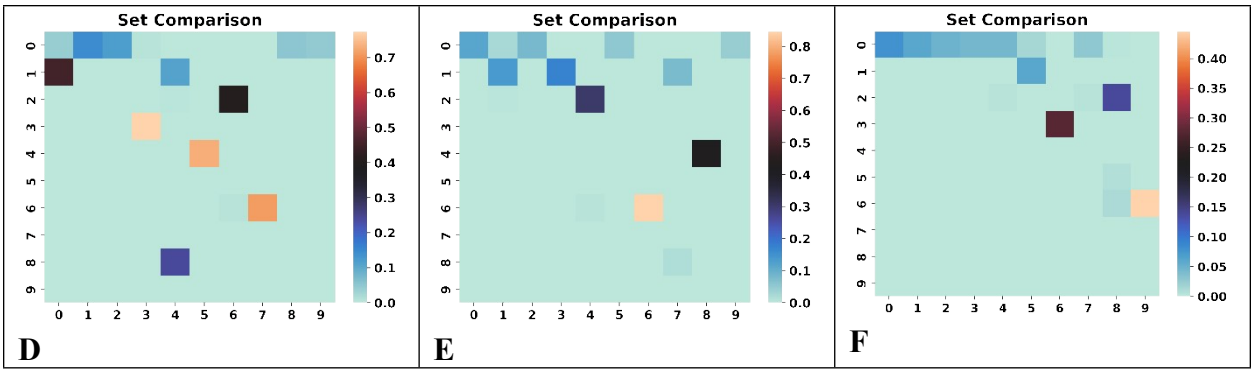


Figure S6.20: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [20] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

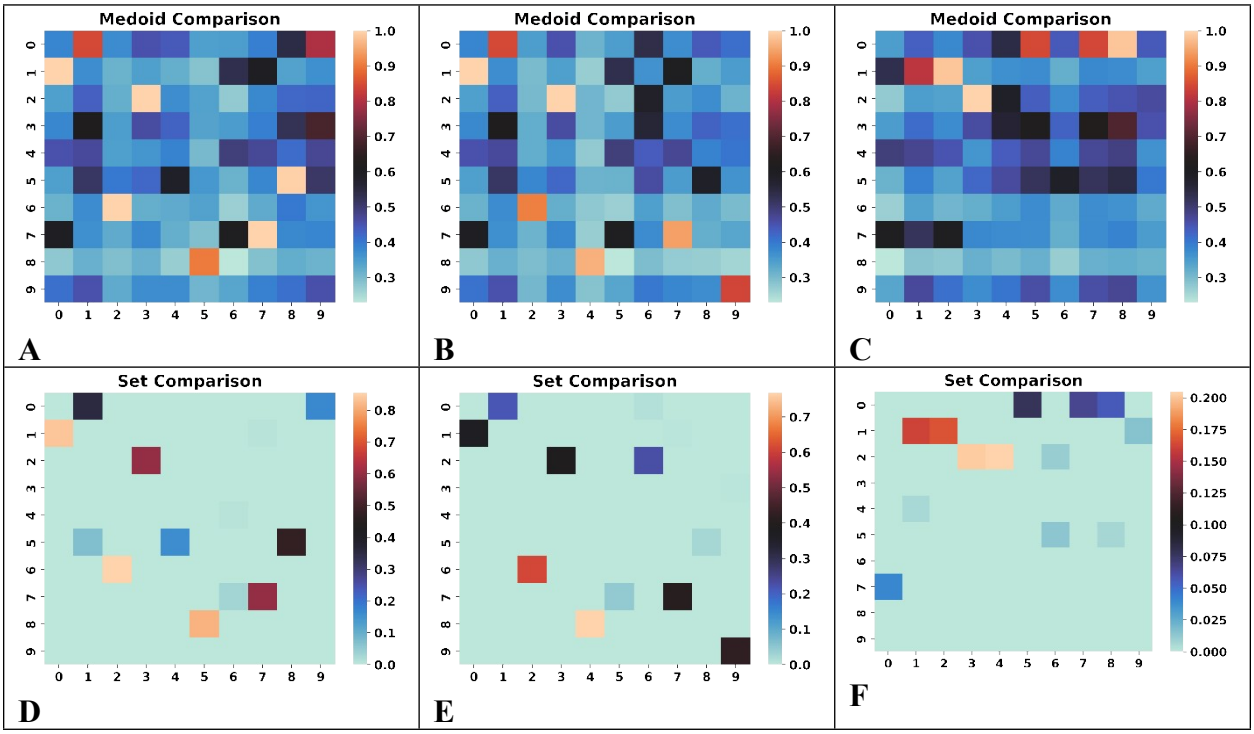


Figure S6.21: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [21] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

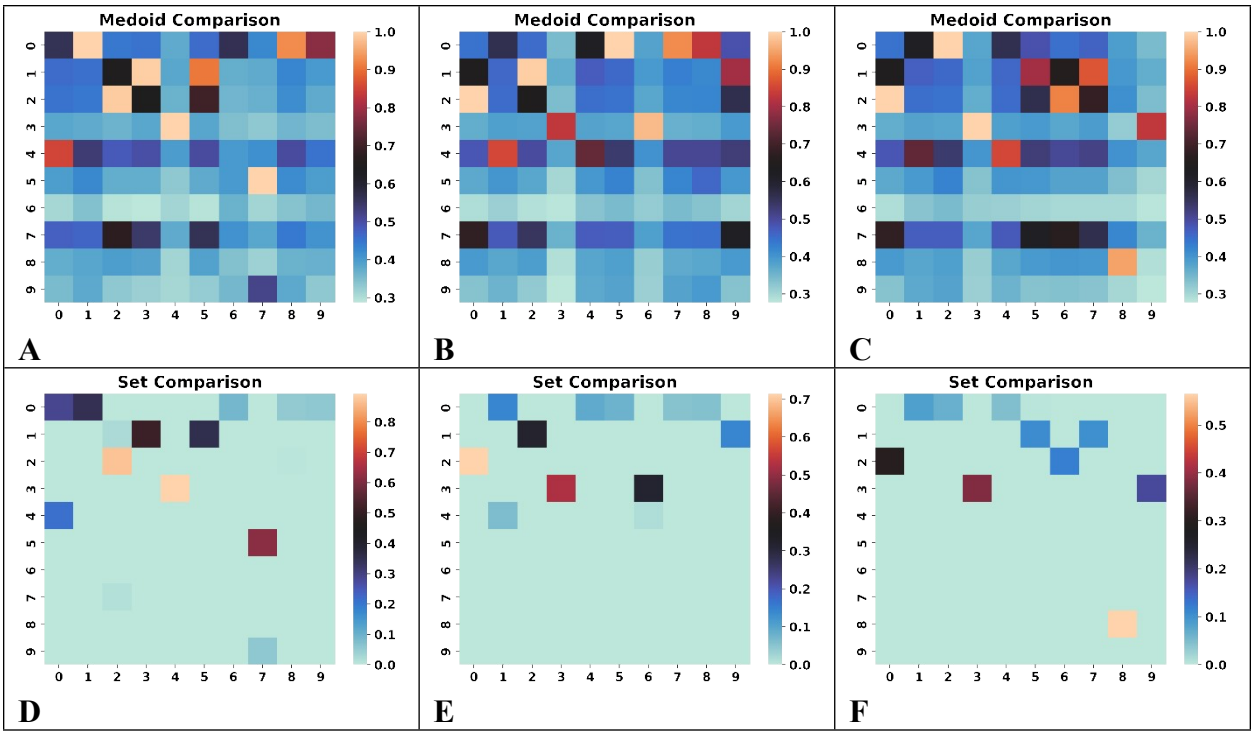


Figure S6.22: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [22] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

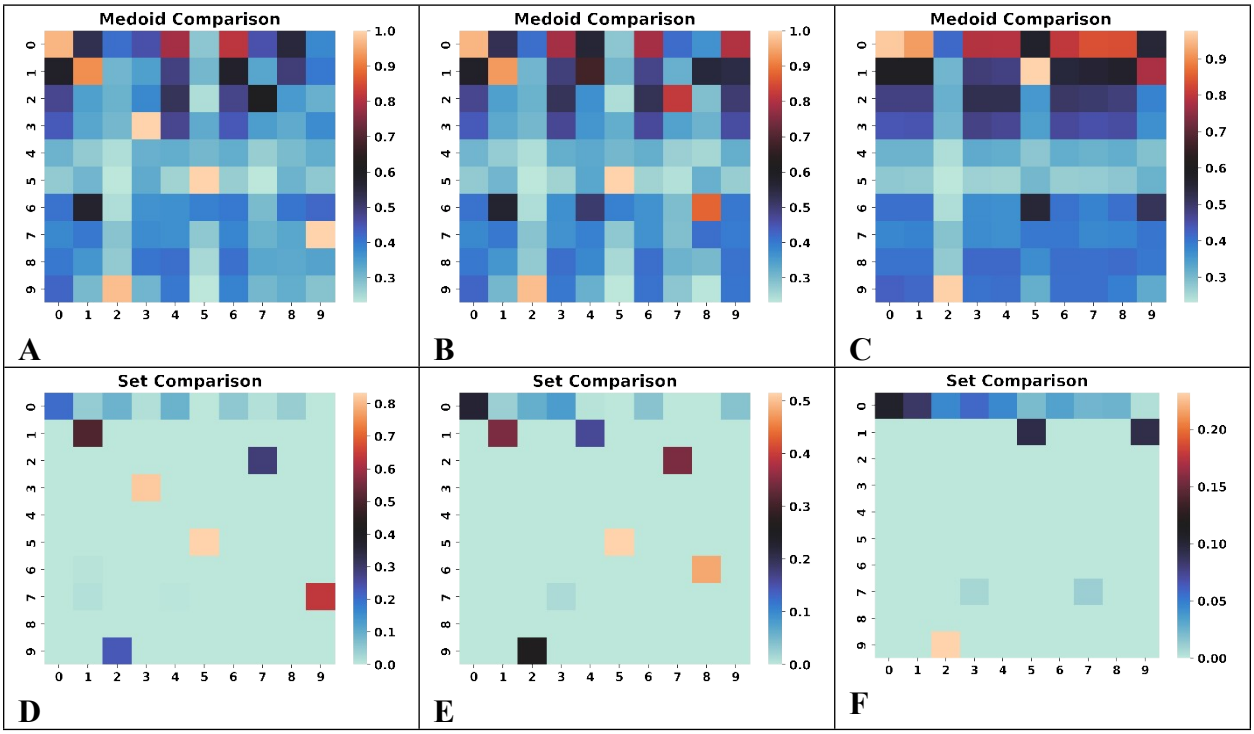


Figure S6.23: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [23] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

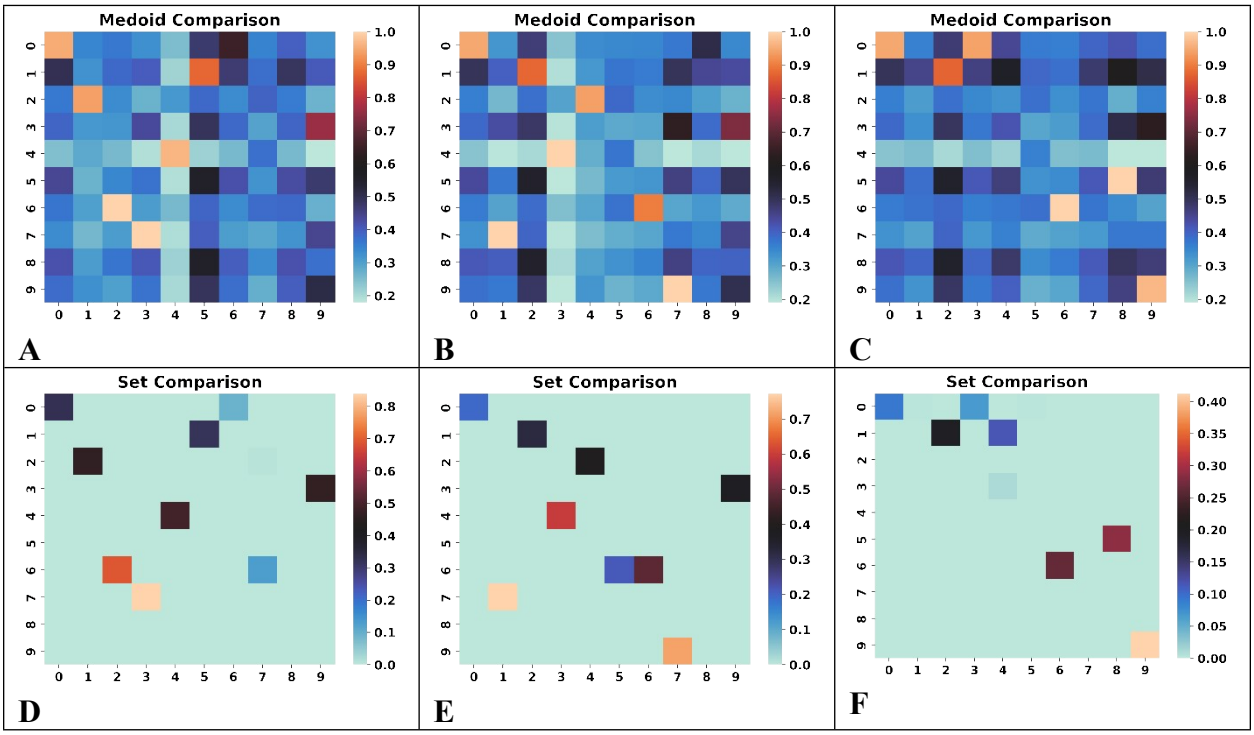
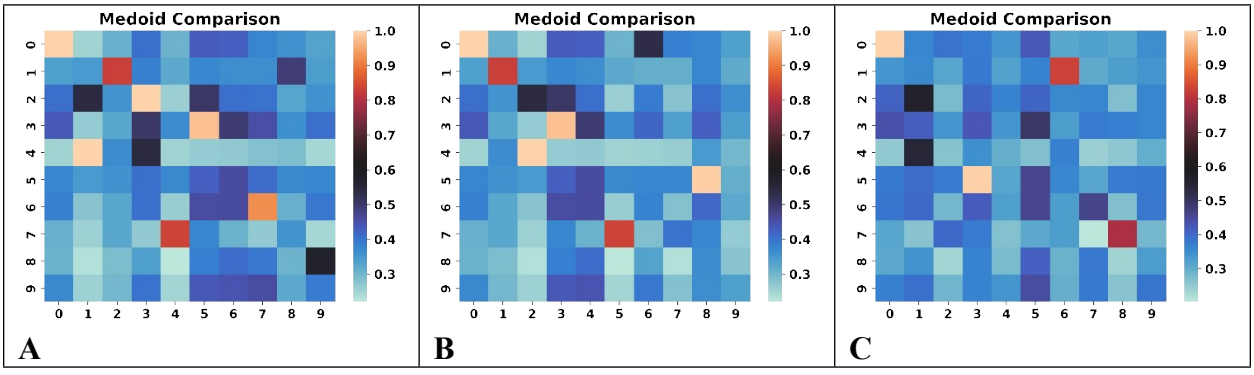


Figure S6.24: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [24] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).



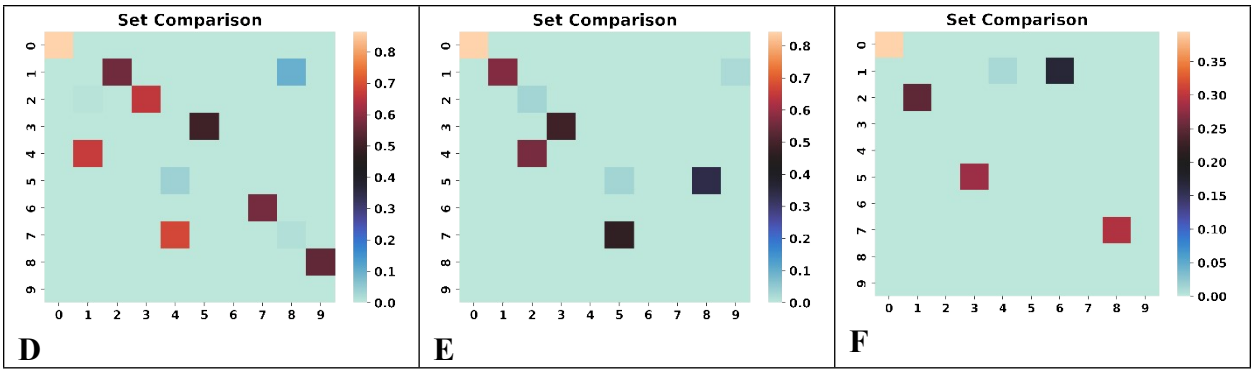


Figure S6.25: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [25] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

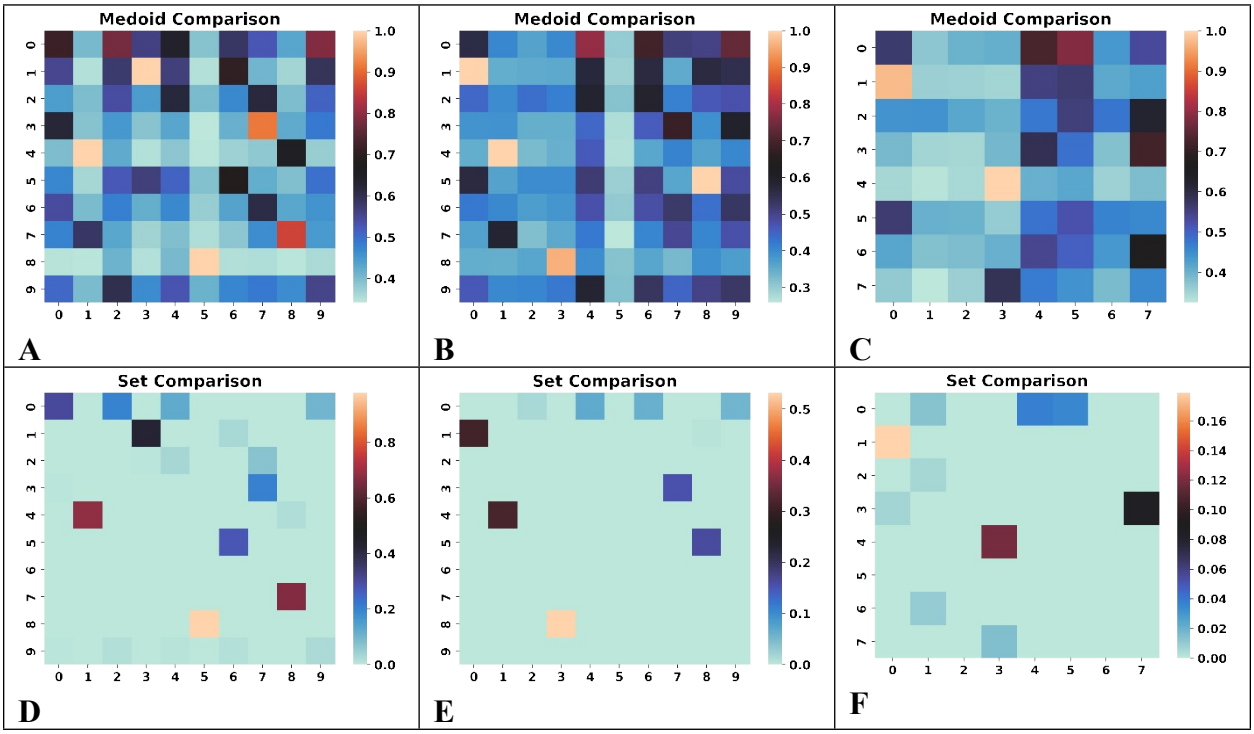


Figure S6.26: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [26] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

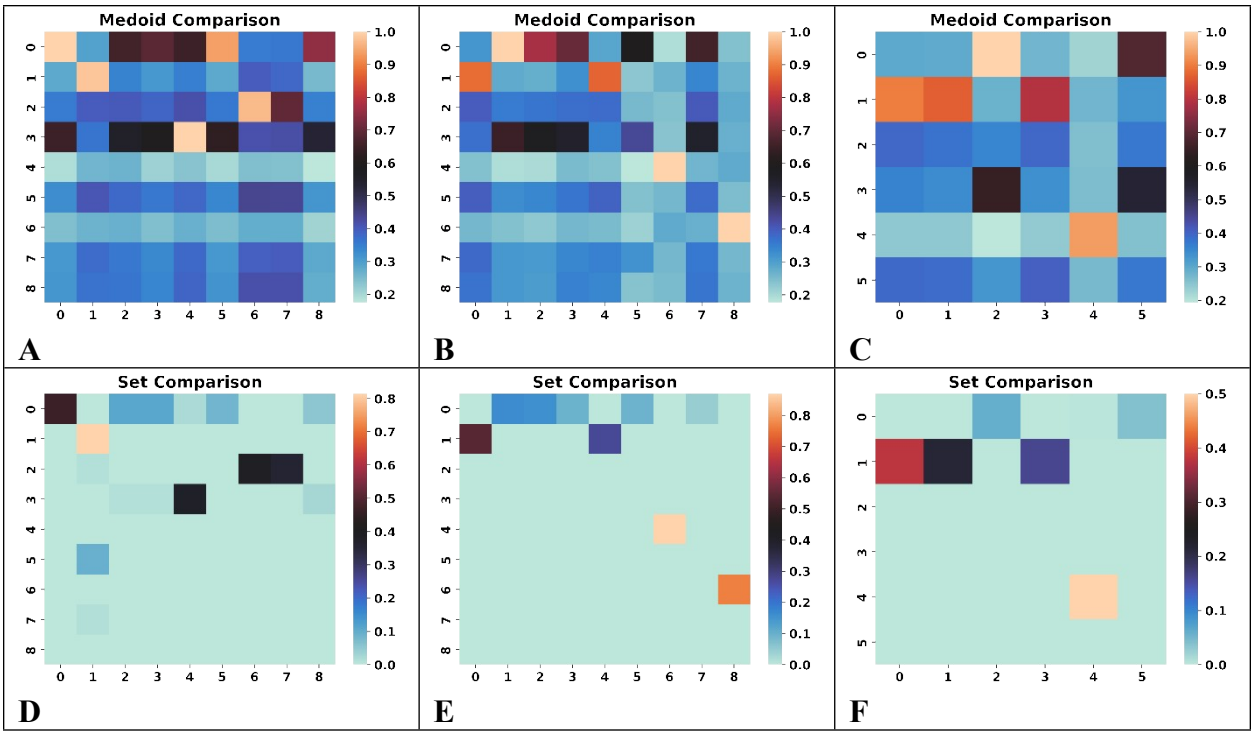


Figure S6.27: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [27] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

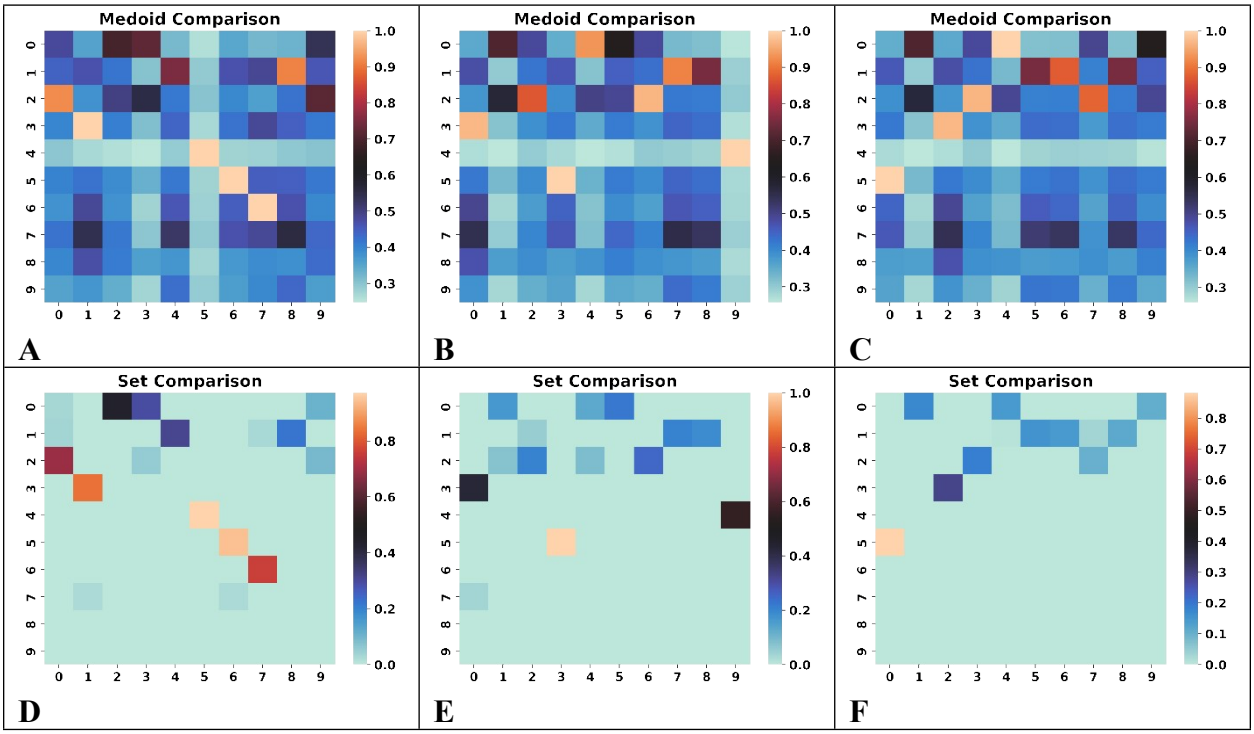


Figure S6.28: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [28] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).

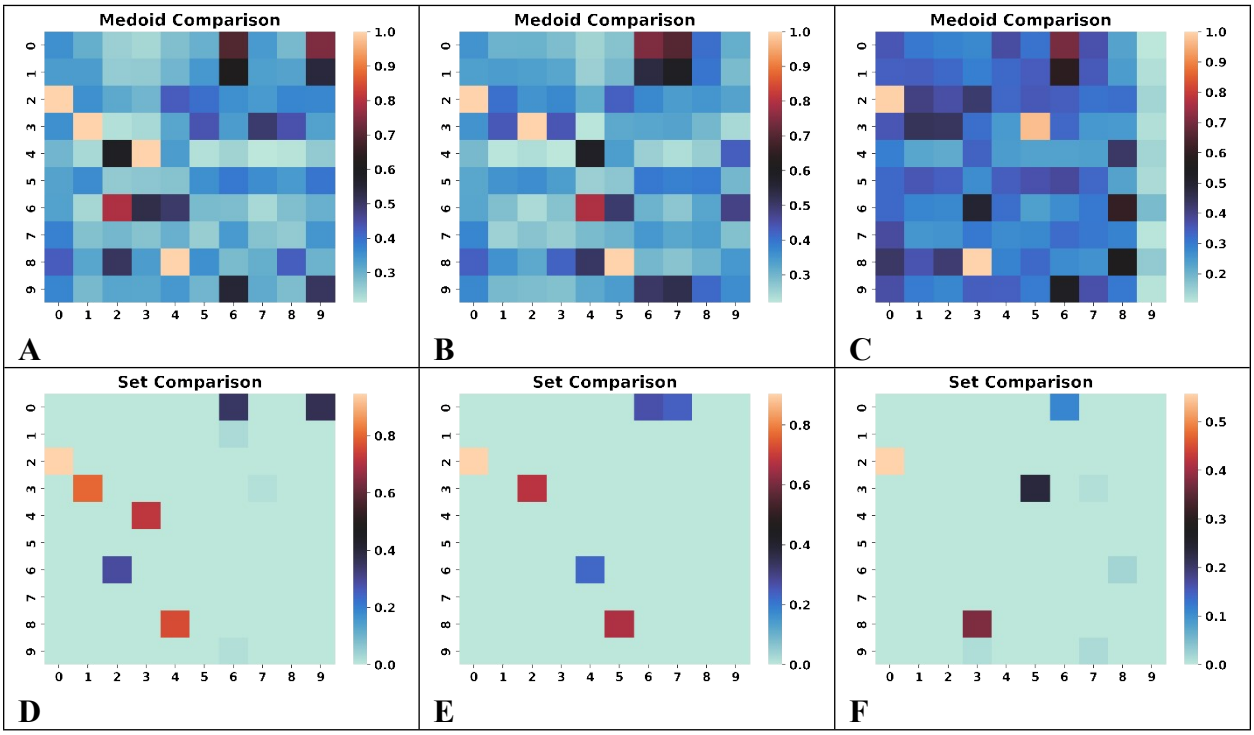
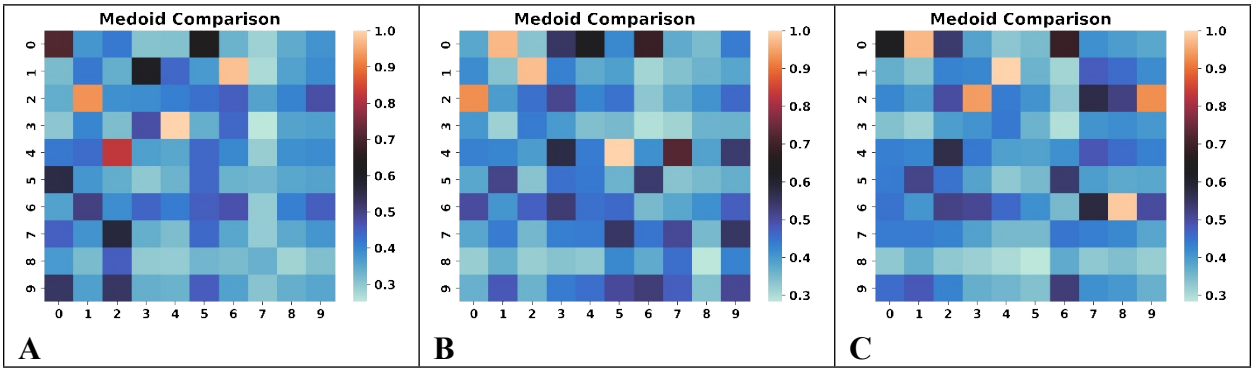


Figure S6.29: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [29] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).



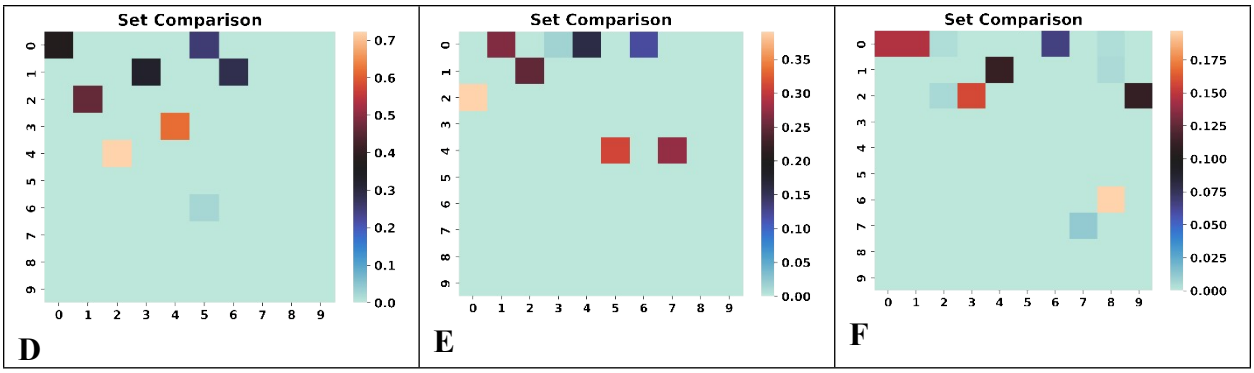
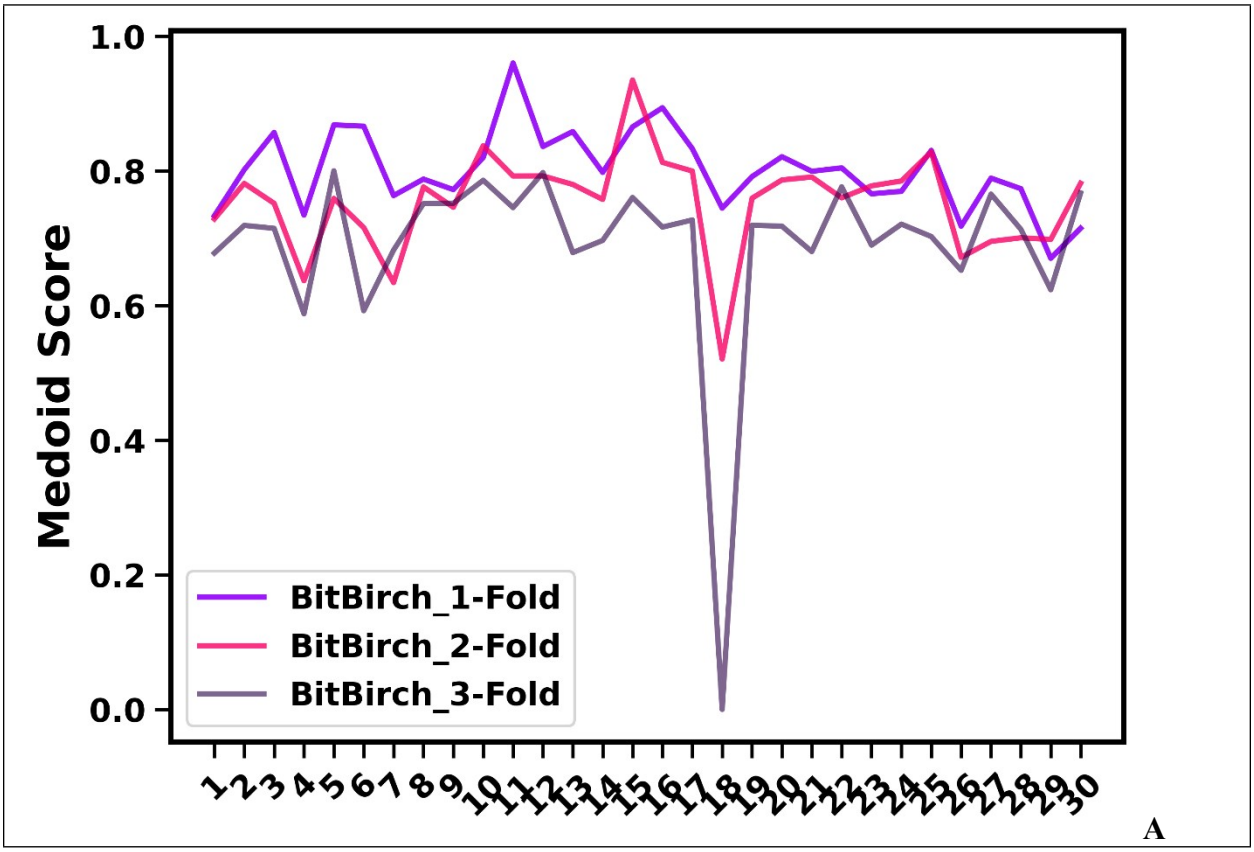


Figure S6.30: Comparison of the **A, B, C**: medoids, **D, E, F**: sets for the top populated clusters of the [30] ChEMBL subset using the BitBIRCH and BitBIRCH-folded (**A**, **D**: 1- fold, **B**, **E**: 2-fold, **C**, **F**: 3-fold) algorithms (similarity threshold = 0.65, min_size = 10).



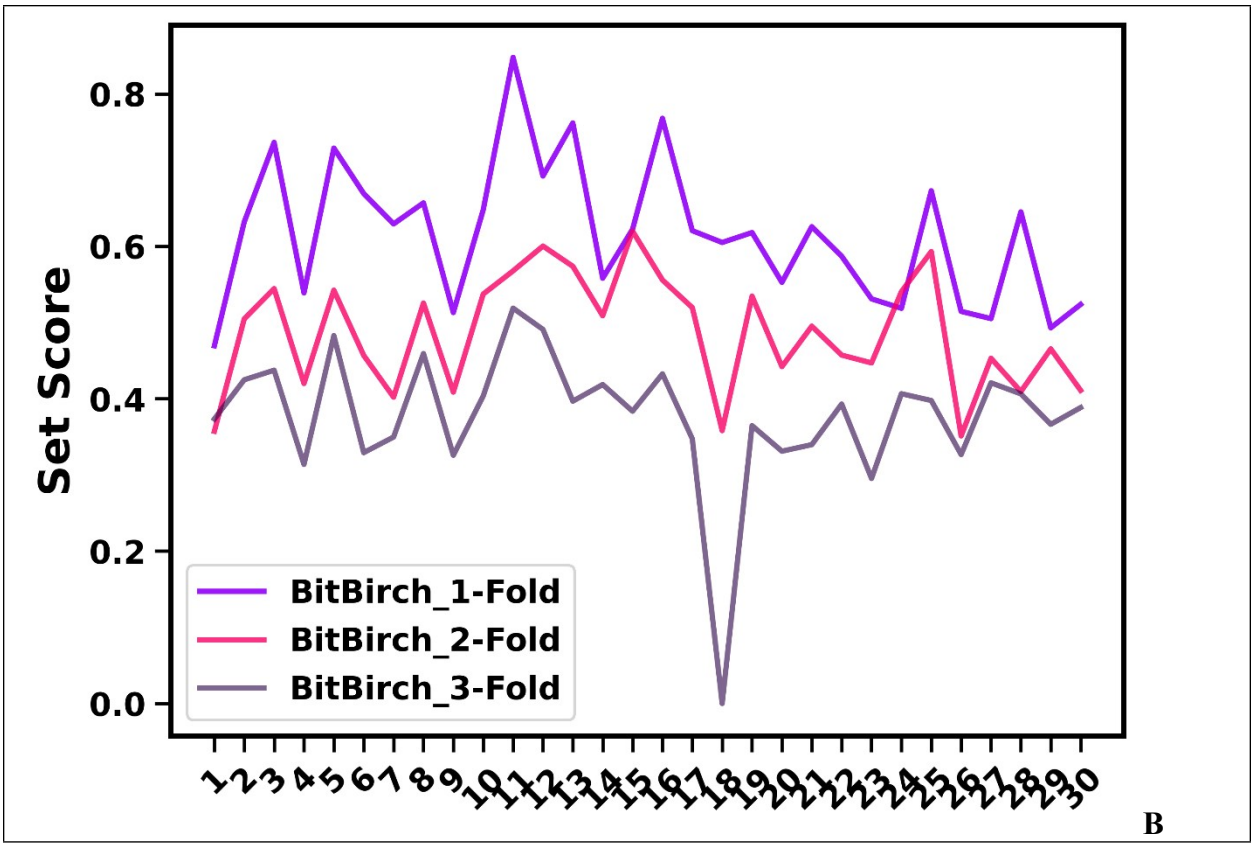


Figure S6.31: Summary of the Medoid (A) and Set (B) scores for the 30 ChEMBL subsets for the BitBIRCH and BitBIRCH-folded algorithms.

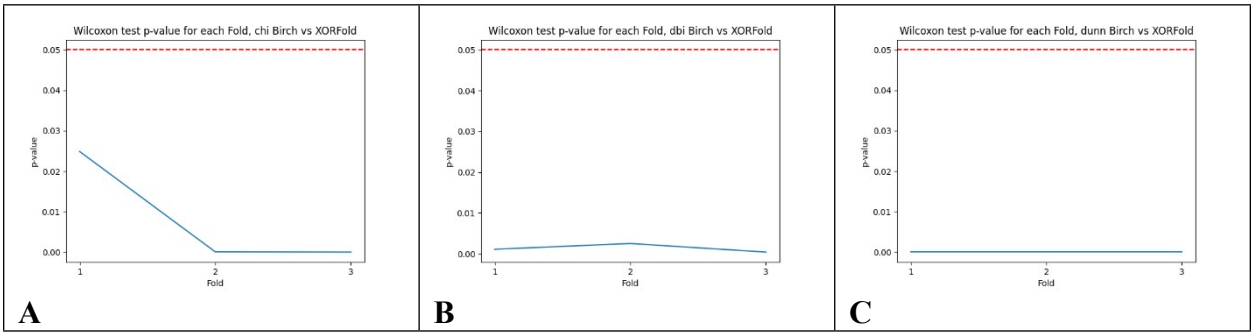


Figure S6.32: Wilcoxon two-sided tests results comparing the BitBIRCH and BitBIRCH-folded methods for the **A**: CHI (Ha: BB < BB-fold), **B**: DBI (Ha: BB > BB-fold) , and **C**: DI (Ha: BB > BB-fold).

S7: Different similarity indices

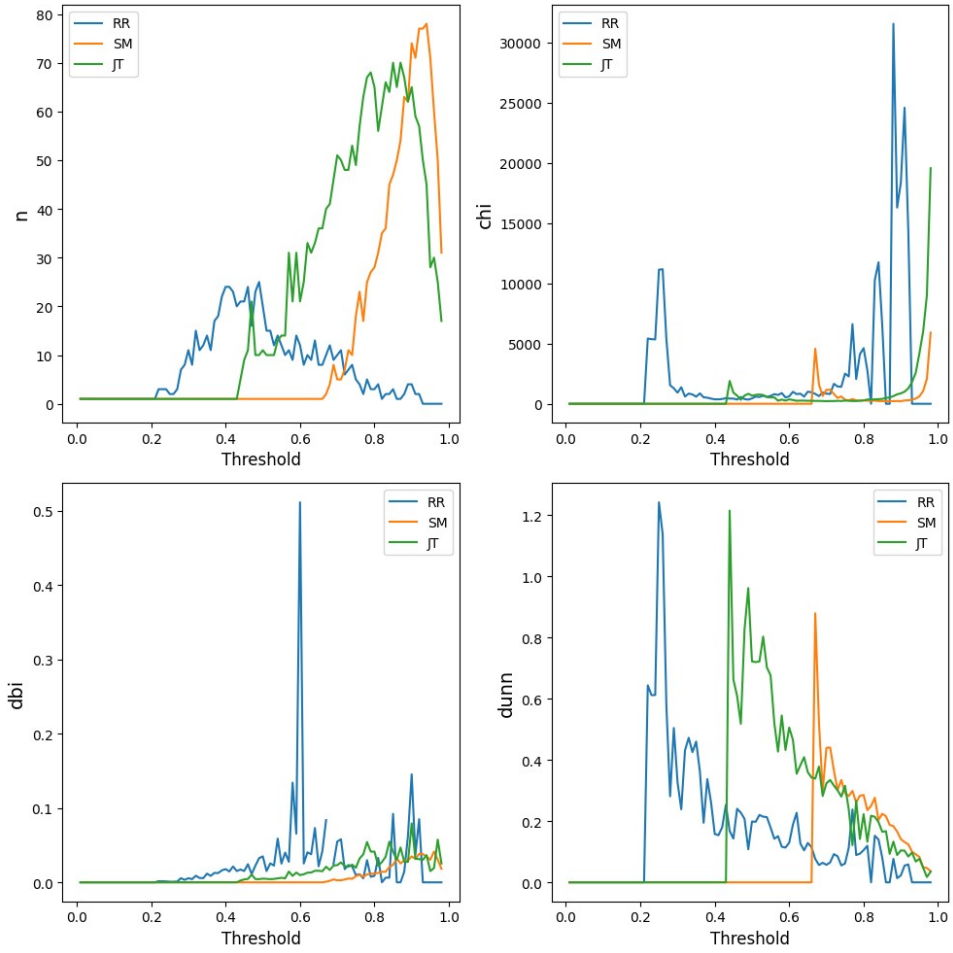


Figure S7.1: Analysis of various iSIM indices, Russel-Rao, Sokal-Michener, and Jaccard-Tanimoto, in BiBIRCH for the library CHEMBL_233_Ki (3142 molecules). *Top-left*: Change in number of clusters with similarity threshold. *Top-right*: CHI vs similarity threshold. *Bottom-left*: DBI vs similarity threshold. *Bottom-right*: Dunn vs similarity threshold.

As indicated in the main text, BitBIRCH can seamlessly accommodate other iSIM indices as well, like Russe-Rao and Sokal-Michener. Fig. S7.1 shows that RR is the least stable of the methods, usually tending to prefer lower similarity thresholds and behaving markedly different from JT and SM. Notice that for the number of clusters found in the data, JT and SM provide consistent results (albeit, as expected, with SM requiring slightly bigger thresholds), while RR fails to find more than 40 clusters in any instance. Interestingly, the index that shows the better agreement between

the similarity metrics is Dunn, which shows the same pattern for each of them, with the expected preference of lower thresholds for RR, intermediate for JT, and bigger thresholds for SM.

S8: Different types of fingerprints

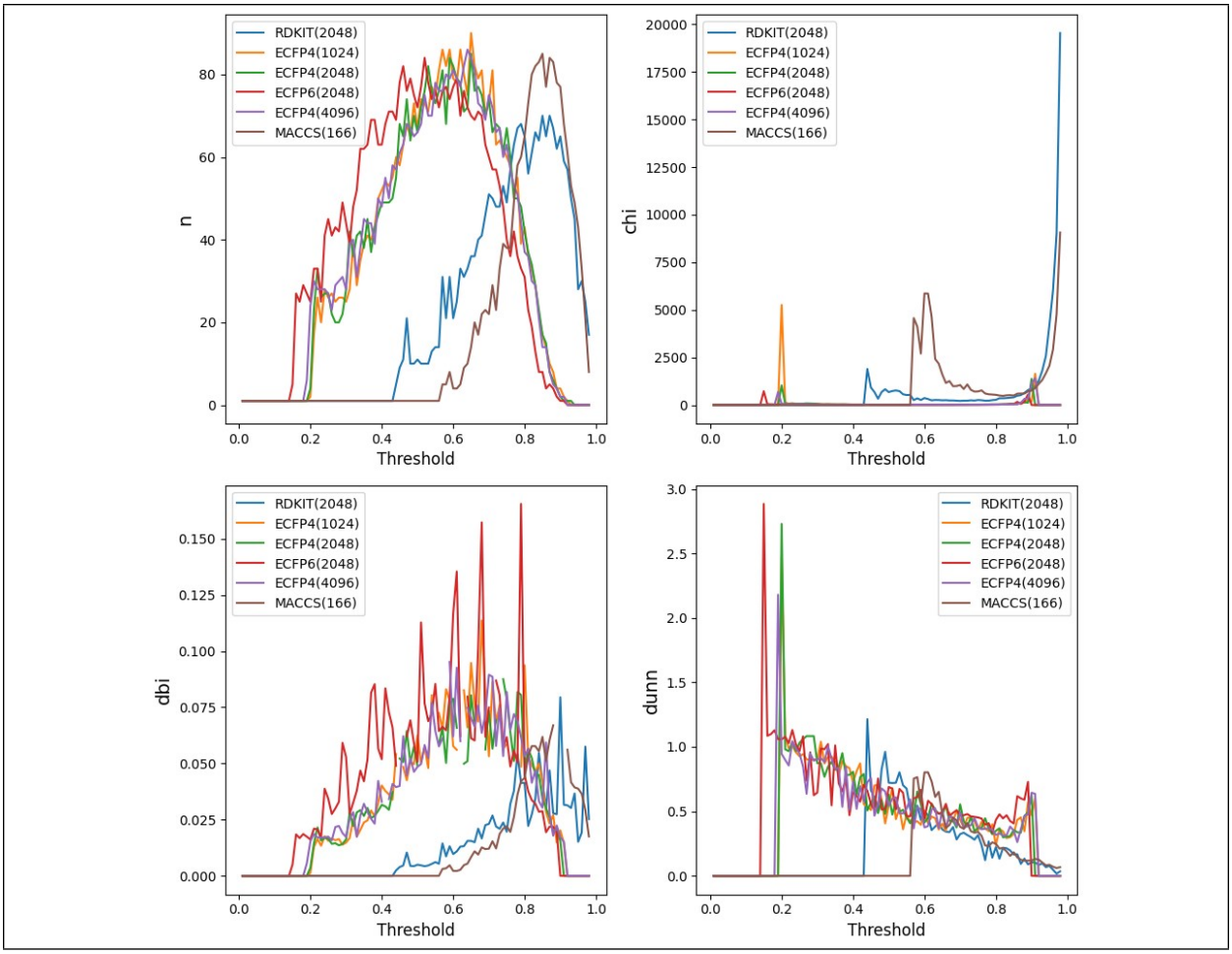


Figure S8.1: BitBIRCH results for the CHEMBL_233_Ki (3142 molecules) library with RDKit, MACCS, and ECFP fingerprints with 2048, 166, 1024, 2048, and 4096 bits. *Top-left*: Change in number of clusters with similarity threshold. *Top-right*: CHI vs similarity threshold. *Bottom-left*: DBI vs similarity threshold. *Bottom-right*: Dunn vs similarity threshold.

BitBIRCH can be used with arbitrary fingerprint types. As shown in Fig. S8.1, RDKit and MACCS have remarkably similar trends, despite the gap in number of bits (2048 and 166, respectively). On the other hand, reassuringly, all the ECFP flavors show a very consistent behavior from 1024 to 4096 bits.

S9: Ultra large libraries

The billion molecules were obtained from several randomly selected tranches with more than 1 million molecules from the ZINC22-2D database (https://cartblanche.docking.org/tranches/2d). From each selected tranche, $\lfloor n\_molecules \,/\, 1{,}000{,}000 \rfloor$ subsets were taken in order of apparition. The remaining molecules from each tranche were not included in our study. All subsets were included, except for H27, H28 and H29, only the subsets to complete the billion were used.

Table S9.1: Used tranches from the ZINC22 database codes, number of molecules in each tranche and number of 1 million subsets used.

ZINC22 Tranche	Number of molecules	Number of subsets used (1 mill. molecules each)
H15M000	1,487,831	1
H17M100	1,094,594	1
H18P090	2,524,328	2
H20P000	2,925,212	2
H20P140	7,022,735	7
H21P260	10,716,148	10
H22P470	2,835,583	2
H22P190	25,318,774	25
H22P100	19,790,141	19
H23P000	13,076,376	13
H23P280	27,504,053	27
H24P130	53,244,587	53
H25P410	26,304,860	26
H26P470	17,859,872	17
H26M200	12,760,298	12
H26P320	125,434,222	125
H27P210	275,242,750	267*
H28P280	373,968,228	340*
H29P600	70,902,324	51*
TOTAL	---	1000