Additional figures and tables

SMILES-based deep generative scaffold decorator for de-novo drug design

Josep Arús-Pous[§⊥*], Atanas Patronov[§], Esben Jannik Bjerrum[§], Christian Tyrchan[‖], Jean-Louis Reymond[⊥], Hongming Chen[¥], Ola Engkvist[§].

§ Molecular AI, Hit Discovery, Discovery Sciences, BioPharmaceutical R&D, AstraZeneca, Gothenburg, Sweden.

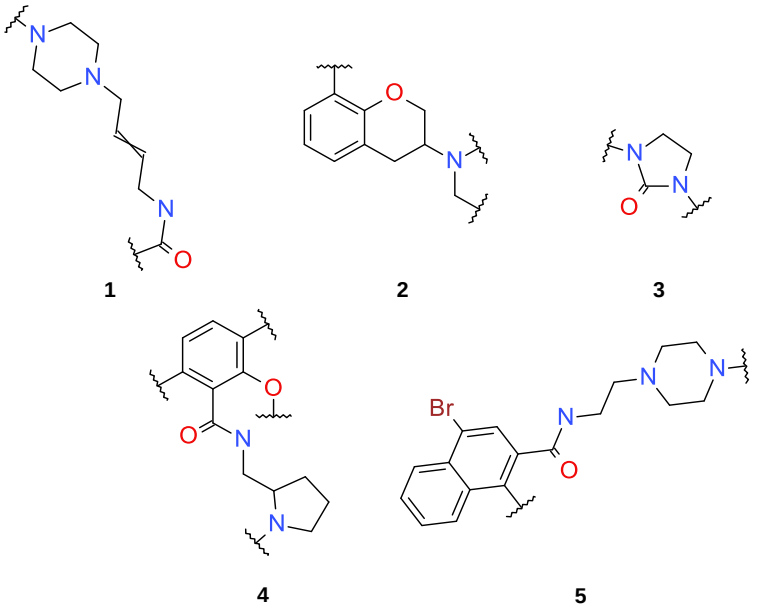
‖ Medicinal Chemistry, Respiratory Inflammation, and Autoimmune (RIA), BioPharmaceutical R&D, AstraZeneca, Gothenburg, Sweden.

⊥ Department of Chemistry and Biochemistry, University of Bern, Freiestrasse 3, 3012 Bern, Switzerland.

¥ Chemistry and Chemical Biology Centre, Guangzhou Regenerative Medicine and Health - Guangdong Laboratory, Guangzhou, China

* Corresponding author: josep.arus@dcb.unibe.ch

Additional Tables



	Generated		ChEMBL decoys			DRD2 decoys		
S	*Total*	*% act.*	*% act.*	*% diff*	*EOR*	*% act.*	*% diff*	*EOR*
1	11,628	47.2 %	0.9 %	46.3 %	52.6	4.0 %	43.2 %	11.7
2	10,483	29.9 %	8.0 %	21.9 %	3.7	19.5 %	10.4 %	1.5
3	77,548	26.1 %	0.8 %	25.3 %	32.2	15.6 %	10.5 %	1.7
4	844	25.2 %	0.4 %	24.9 %	69.3	1.0 %	24.2 %	25.1
5	182	28.0 %	9.9 %	18.1 %	2.8	15.1 %	12.9 %	1.9

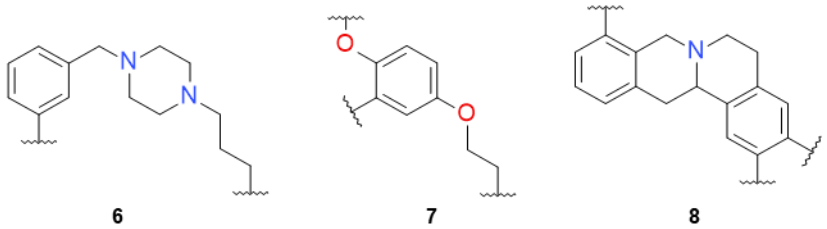
Table S1: Scaffolds obtained from the validation set of the DRD2 dataset alongside the results from the decoration process using the single-step decoration model. **Legend:** Total number of molecules sampled (Total); Percent of generated molecules that are predicted as active ($p_{active} \geq 0.5$) by the APM (% act); For both the decoys decorated with ChEMBL fragments and DRD2 fragments from the training set: Percent of predicted active decoys ($p_{active} \geq 0.5$) (% act); Difference between the generated predicted active percent and the predicted active percent of the decoys (% Diff); Enrichment Over Random ($percent_{active}/percent_{decoy}$) (EOR).

	Generated		ChEMBL decoys			DRD2 decoys		
S	*Total*	*Sampled*	*Total*	*Overlap*	*% overlap*	*Total*	*Overlap*	*% overlap*
1	1,728	26,759	25,724	1	0.1 %	24,793	3	0.2 %
2	1,626	61,115	59,084	8	0.5 %	58,029	19	1.1 %
3	10,666	38,074	36,554	0	0 %	34,353	0	0 %
4	262	50,163	46,531	0	0 %	45,892	2	0.8 %
5	18	1,791	841	0	0 %	810	7	38.9 %

Table S2: Additional sampling statistics for the multi-step model sample of the five validation set scaffolds. **Legend:** Total number of unique molecules obtained with each sampling approach (Total); Number of sampled molecules in total using the decorator model (Sampled); Nomber of molecules that overlap between a given decoy set and the molecules generated with a decorator (Overlap); Ratio between the overlap and the total obtained (% overlap).

	Generated		ChEMBL decoys			DRD2 decoys		
S	*Total*	*Sampled*	*Total*	*Overlap*	*% overlap*	*Total*	*Overlap*	*% overlap*
1	11,628	124,225	118,331	14	0.1 %	109,585	21	0.2 %
2	10,483	129,515	126,403	3	0.0 %	124,635	39	0.4 %
3	77,548	117,598	114,277	19	0.0 %	104,535	44	0.1 %
4	844	130,914	120,527	1	0.1 %	117,799	77	9.1 %
5	182	130,988	38,040	4	2.2 %	27,823	58	31.9 %

Table S3: Additional sampling statistics for the single-step model sample of the five validation set scaffolds. **Legend:** Total number of unique molecules obtained with each sampling approach (Total); Number of sampled molecules in total using the decorator model (Sampled); Nomber of molecules that overlap between a given decoy set and the molecules generated with a decorator (Overlap); Ratio between the overlap and the total obtained (% overlap).



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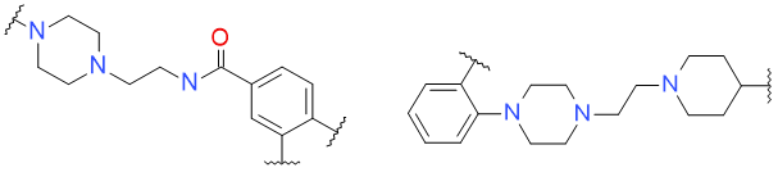

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	Generated		ChEMBL decoys			DRD2 decoys		
S	*Total*	*% act.*	*% act.*	*% diff*	*EOR*	*% act.*	*% diff*	*EOR*
6	15,885	78.1 %	48.3 %	29.7 %	1.6	64.6 %	13.5 %	1.2
7	49,799	18.2 %	1.0 %	17.2 %	18.1	10.7 %	7.5 %	1.7
8	2,194	90.2 %	44.1 %	46.1 %	2.0	48.4 %	41.8 %	1.9
9	1,525	8.8 %	2.9 %	5.8 %	3.0	6.8 %	1.9 %	1.3
10	9,278	96.4 %	89.5 %	6.9 %	1.1	92.6 %	3.8 %	1.0

Table S4: Non-dataset scaffolds obtained from a generative model (see methods) and results of the decoration of each of them using the single-step decoration model. **Legend:** Total number of molecules sampled (Total); Percent of generated molecules that are predicted as active ($p_{active} \geq 0.5$) by the APM (% act); For both the decoys decorated with ChEMBL fragments and DRD2 fragments from the training set: Percent of predicted active decoys ($p_{active} \geq 0.5$) (% act); Difference between the generated predicted active percent and the predicted active percent of the decoys (% Diff); Enrichment Over Random ($percent_{active}/percent_{decoy}$) (EOR).

	Generated		ChEMBL decoys			DRD2 decoys		
S	*Total*	*Sampled*	*Total*	*Overlap*	*% overlap*	*Total*	*Overlap*	*% overlap*
6	1,864	21,947	20,665	8	0.4 %	19,857	26	1.4 %
7	15,724	528,094	501,054	15	0.1 %	480,975	100	0.6 %
8	2,178	70,617	62,618	105	4.8 %	60,091	175	8.0 %
9	5,362	143,101	124,532	32	0.6 %	117,511	70	1.3 %
10	1,012	13,491	10,843	7	0.7 %	10,058	40	3.9 %

Table S5: Additional sampling statistics for the multi-step model sample of the five non-dataset scaffolds. **Legend:** Total number of unique molecules obtained with each sampling approach (Total); Number of sampled molecules in total using the decorator model (Sampled); Nomber of molecules that overlap between a given decoy set and the molecules generated with a decorator (Overlap); Ratio between the overlap and the total obtained (% overlap).

	Generated		ChEMBL decoys			DRD2 decoys		
S	*Total*	*Sampled*	*Total*	*Overlap*	*% overlap*	*Total*	*Overlap*	*% overlap*
6	15,885	127,281	113,932	215	1.4 %	100,916	922	5.8 %
7	49,799	126,284	124,656	17	0.0 %	123,476	79	0.1 %
8	2,194	130,970	114,531	133	6.1 %	108,146	220	10.0 %
9	1,525	130,862	114,634	6	0.4 %	108,974	31	2.0 %
10	9,278	129,861	91,142	177	1.9 %	73,660	1033	11.1 %

Table S6: Additional sampling statistics for the single-step model sample of the five non-dataset scaffolds. **Legend:** Total number of unique molecules obtained with each sampling approach (Total); Number of sampled molecules in total using the decorator model (Sampled); Nomber of molecules that overlap between a given decoy set and the molecules generated with a decorator (Overlap); Ratio between the overlap and the total obtained (% overlap).

Additional figures

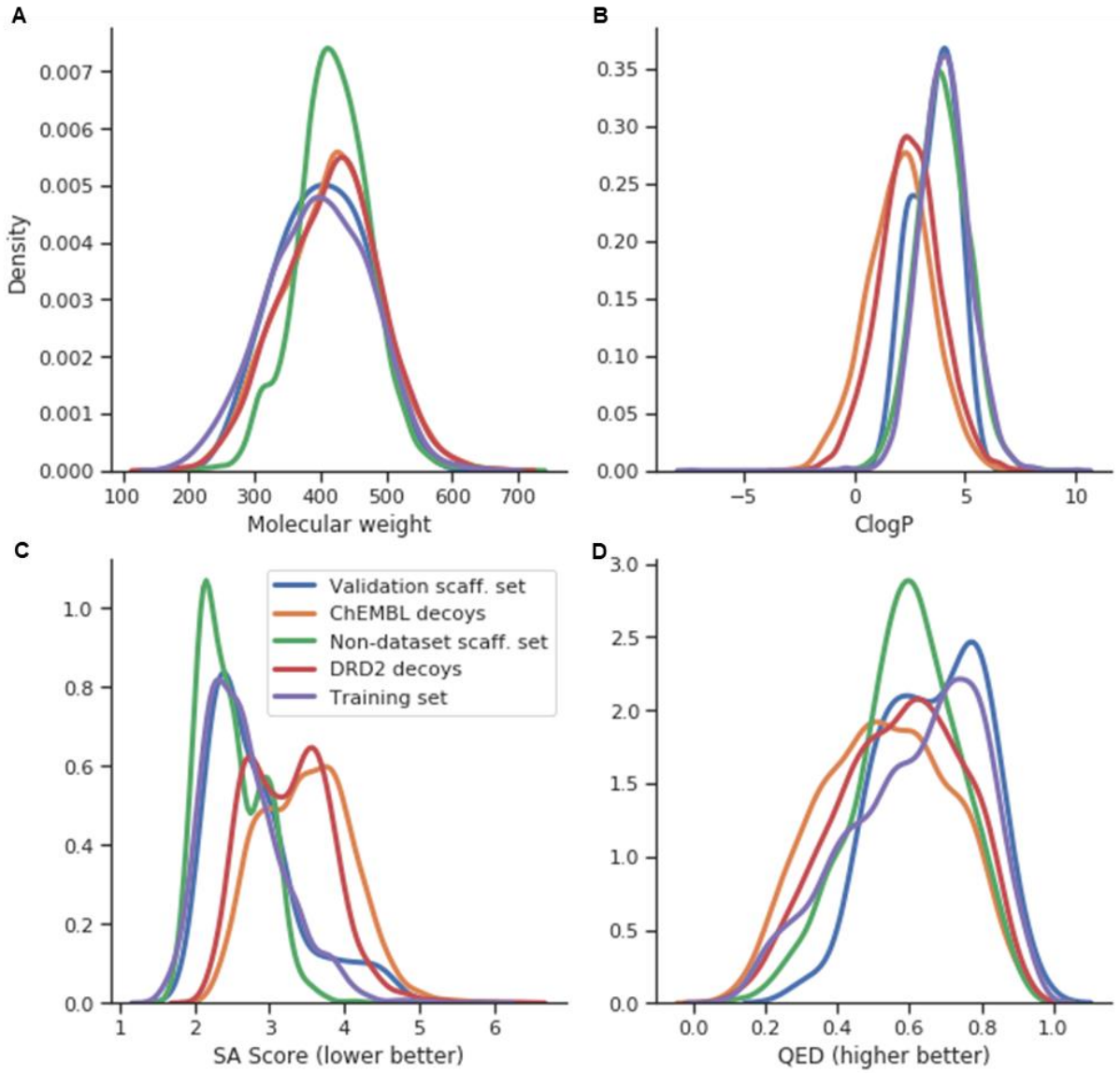

Figure S1: Histograms of different descriptors calculated in three sets of molecules obtained from the DRD2 multi-step decorator model: Generated molecules from validation set scaffolds (blue), generated molecules from non-dataset scaffolds (green), training set molecules (purple) and the two decoy sets (ChEMBL – orange, DRD2 – red). A) Molecular weight (Da); B) ClogP; C) Synthetic Accessibility Score; D) Quantitative Estimate of Drug Likeness (QED).

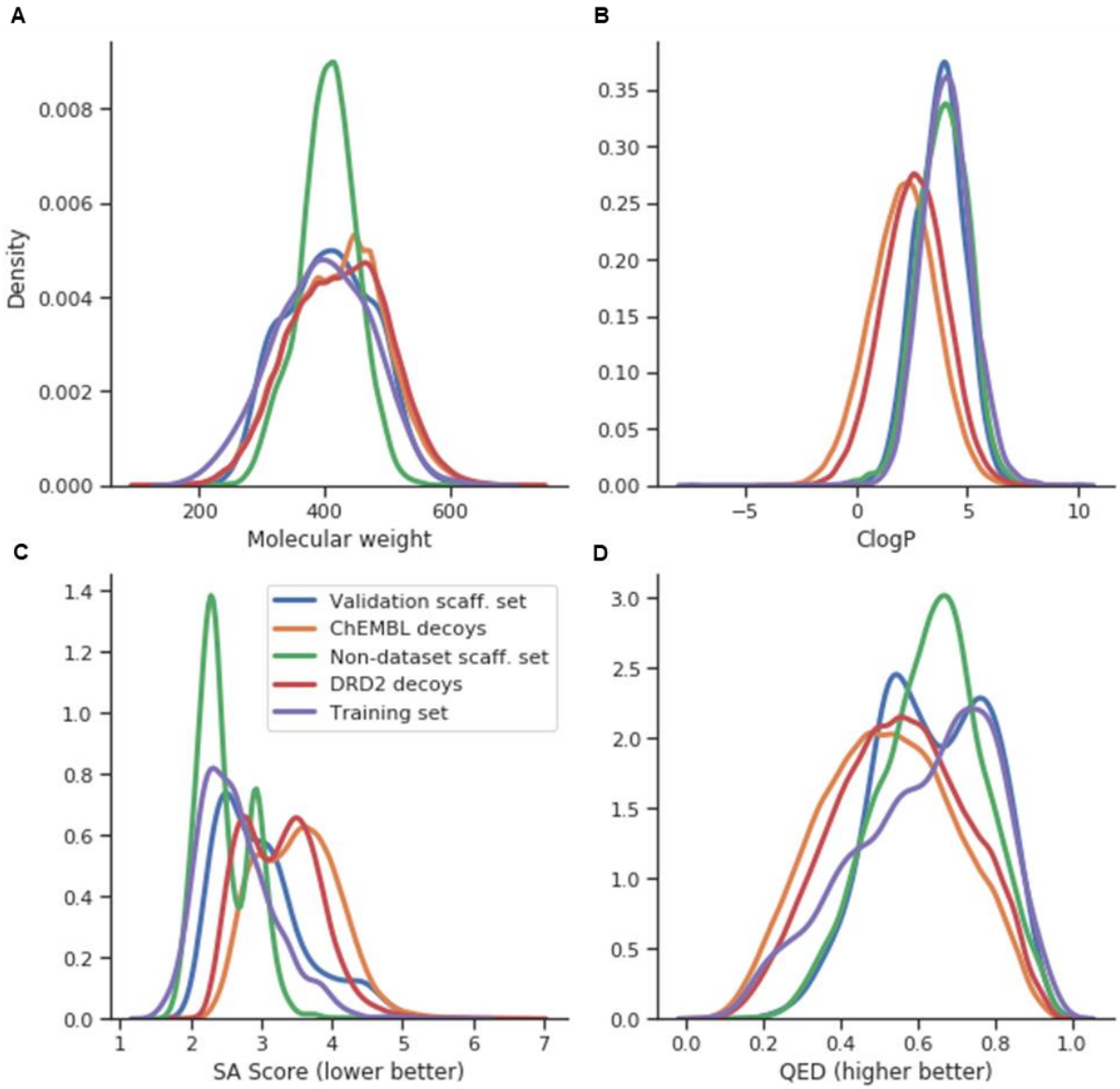

Figure S2: Histograms of different descriptors calculated in three sets of molecules obtained from the DRD2 single-step decorator model: Generated molecules from validation set scaffolds (blue), generated molecules from non-dataset scaffolds (green), training set molecules (purple) and the two decoy sets (ChEMBL – orange, DRD2 – red). A) Molecular weight (Da); B) ClogP; C) Synthetic Accessibility Score; D) Quantitative Estimate of Drug Likeness (QED).

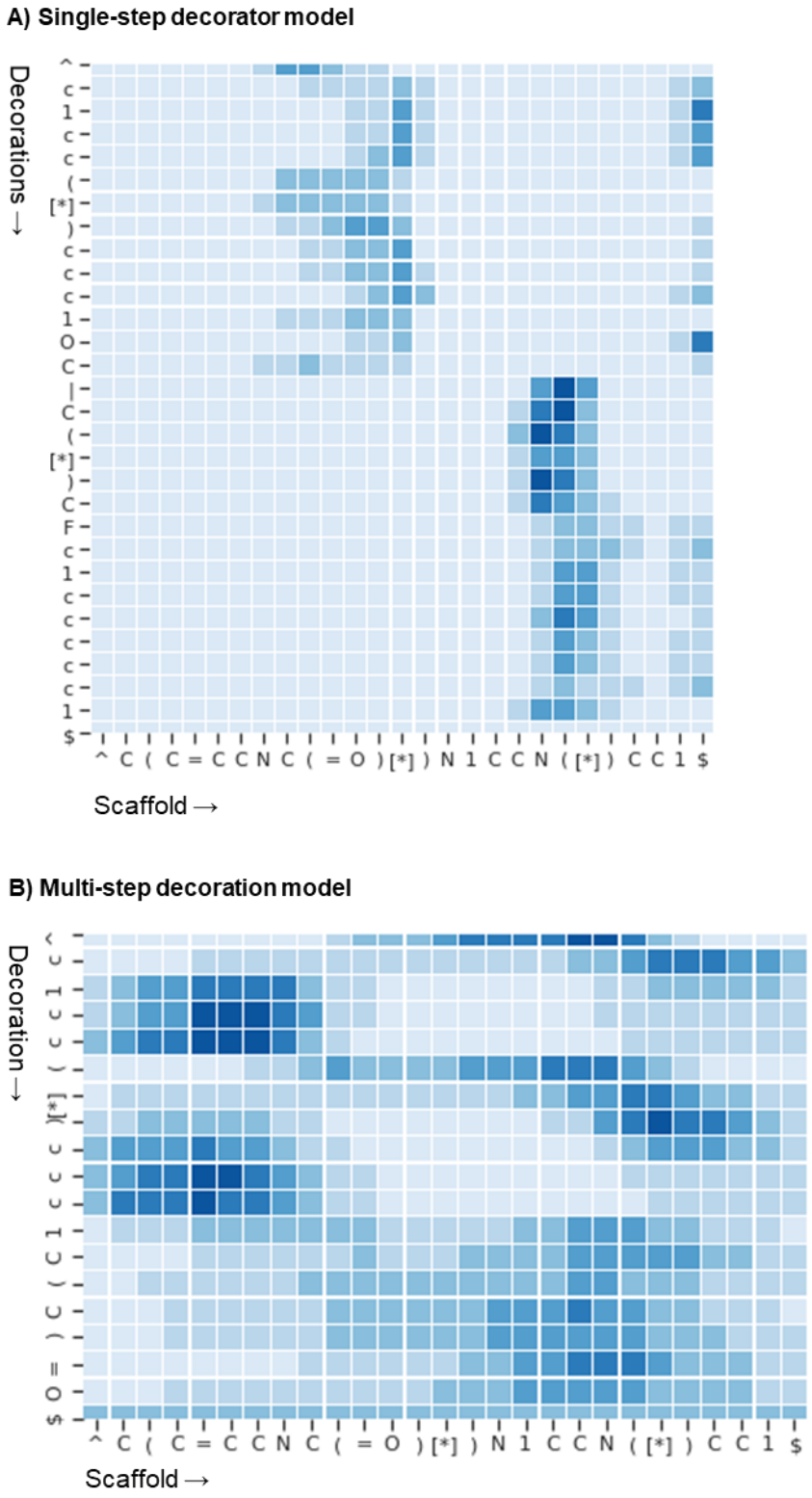

Figure S3: Attention weight heat maps for the same randomized SMILES of the scaffold (1) for the single-step (A) and multi-step (B) decoration DRD2 models. Notice how in the single-step model, attention weights usually are focused around the attachment point of the decoration being generated. On the other hand, the multi-step model attention weights have no human-discernible pattern.

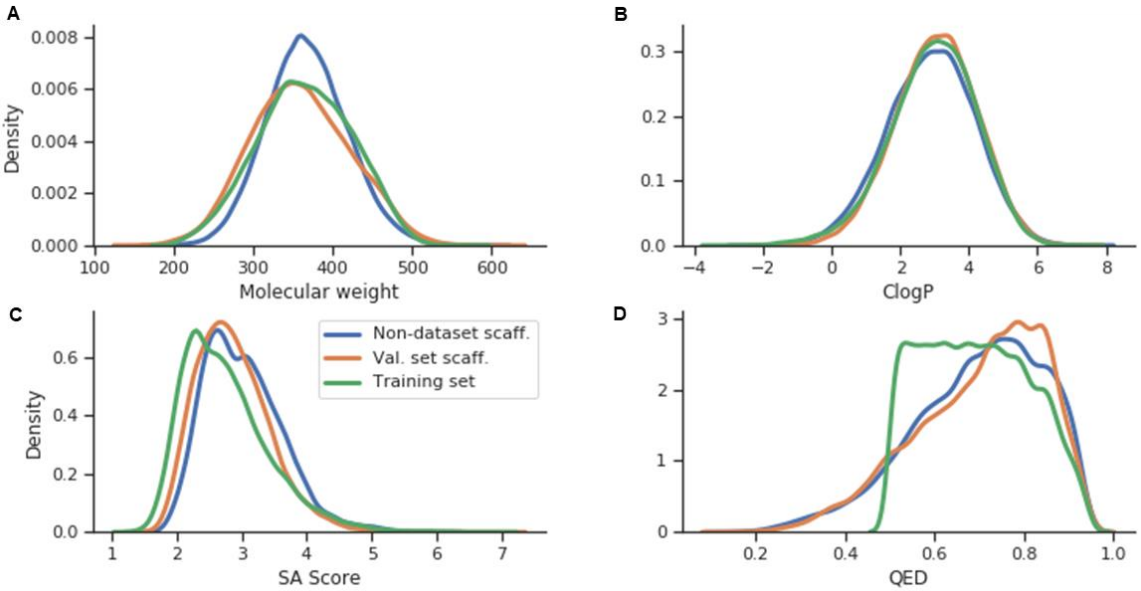

Figure S4: Histograms of different descriptors calculated in three sets of molecules obtained from the ChEMBL single-step decorator model: Generated molecules from non-dataset scaffolds (blue), generated molecules from validation set scaffolds (orange) and training set molecules (green). A) Molecular weight (Da); B) ClogP; C) Synthetic Accessibility Score; D) Quantitative Estimate of Drug Likeness (QED). Notice that one of the filtering conditions of the ChEMBL subset was that the molecules had $QED > 0.5$.