Characteristics and Statistics of Optuna Models

Table A1: **Model statistics of the highest accuracy and rate correct score found using Optuna**. Three training variations include using randomly initialized models and using KD based on the original Chemformer and the model trained on Zinc.

Training	Objective	Size	Sample Time	Val Accuracy	RCS	Percentage Invalid	Percentage Unique
RandomInit	Accuracy	11.3M	0.017 s	46.7	0.49	0.57	100
KD-Zinc	Accuracy	27.9M	0.012 s	45.2	0.65	1.95	100
KD-Chemformer	Accuracy	27.9M	0.013 s	46.1	0.63	1.99	100
RandomInit	RCS	4.0M	0.011 s	38.4	0.62	2.07	100
KD-Zinc	RCS	23.7M	0.011 s	35.4	0.73	17.08	100
KD-Chemformer	RCS	23.7M	0.011 s	35.4	0.71	16.00	100

Table A2: **Model parameters of the highest accuracy and rate correct score found using Optuna**. Three training variations include using randomly initialized models and using KD based on the original Chemformer and the model trained on Zinc.

Training	RandomInit	KD-Zinc	KD-Chem	RandomInit	KD-Zinc	KD-Chem
Objective	Accuracy	Accuracy	Accuracy	RCS	RCS	RCS
Parameter						
Size	11.3M	27.9M	27.9M	4.0M	23.7M	23.7M
Feed Forward Dimension	1024	2048	2048	1024	2048	2048
Embedding Dimension	256	512	512	256	512	512
Encoder Layers	6	6	6	2	6	6
Decoder Layers	6	2	2	2	1	1
Attention Heads	4	16	8	16	16	16
Learning Rate	0.005	0.001	0.001	0.01	0.001	0.001
Hard Label Weight	1.0	1.0	1.0	1.0	1.0	1.0
KD Temperature	0	8	8	0	8	8
Feature KD Embedding Weight	0.0	1.0	1.0	0.0	1.0	1.0
Feature KD Encoder Weight	0.0	1.0	0.5	0.0	1.0	0.5
Feature KD Decoder Weight	0.0	1.0	1.0	0.0	1.0	1.0
Response KD Weight	0.0	1.0	0.5	0.0	1.0	0.5

Beam Search Accuracy Scores

Table A3: **Single-step beam search breakdown of the top-1, top-2, top-3, top-5 and top-10 accuracies, with or without invalid SMILES.** Models are trained either from scratch (RandomInit), fine-tuned from training on Zinc (FT-Zinc), using KD on the Chemformer model (KD-Chem) or KD on the Zinc model (KD-Zinc). Hyper-parameters are either from the original publication (original), identical to the original but using retrained (baseline) or using hyper-parameters gathered from an Optuna search (opt: Acc/RCS) where specific parameters depend on the training setting. Models are then trained and evaluated on USPTO-50k and USPTO-full. Reported statistics are based on beam-search results on random split test set values.

	Accuracy				Valid Accuracy				Valid Unique Accuracy			
Training	Top 1	Top 3	Top 5	Top 10	Top 1	Top 3	Top 5	Top 10	Top 1	Top 3	Top 5	Top 10
USPTO-50k												
RandomInit-Original	50.6	60.5	62.2	63.1	50.6	60.5	62.3	63.1	50.6	61.7	62.9	63.1
FT-Zinc-Original	53.5	60.2	61.1	61.6	53.6	60.2	61.1	61.6	53.6	60.9	61.5	61.6
RandomInit-Baseline	51.3	61.2	62.7	63.7	51.4	61.2	62.8	63.7	51.4	62.2	63.5	63.7
RandomInit-OptAcc	50.9	65.6	68.5	70.2	51.0	65.6	68.6	70.2	51.0	67.1	69.5	70.2
RandomInit-OptRCS	45.8	67.8	74.0	79.5	46.0	68.0	74.2	79.5	46.0	69.1	76.0	79.5
FT-Zinc-Baseline	53.6	60.3	61.3	61.7	53.7	60.4	61.3	61.7	53.7	61.1	61.6	61.7
KD-Chemformer-OptAcc	48.5	57.1	59.1	60.4	48.7	57.2	59.2	60.4	48.7	57.9	59.8	60.4
KD-Chemformer-OptRCS	43.3	51.0	53.5	55.7	44.3	52.3	54.4	55.7	44.3	53.2	55.3	55.7
KD-Zinc-OptAcc	19.0	37.9	46.0	53.5	19.0	39.1	47.2	53.5	19.0	42.4	51.1	53.5
KD-Zinc-OptRCS	19.5	39.1	44.5	49.1	20.2	40.5	45.9	49.1	20.2	42.7	47.4	49.1
USPTO-full												
RandomInit-Baseline	46.5	64.3	69.4	72.7	46.6	64.4	69.4	72.7	46.6	64.8	69.9	72.7
RandomInit-OptAcc	40.1	58.5	64.3	68.6	40.2	58.6	64.4	68.6	40.2	59.1	65.0	68.6
RandomInit-OptAcc	29.7	46.5	52.6	57.8	29.8	46.6	52.7	57.8	29.8	47.6	54.0	57.8
FT-Zinc-Baseline	47.9	64.9	69.6	72.6	47.9	65.0	69.7	72.6	47.9	65.5	70.2	72.6

Additional Highest Route Statistics

Table A4: **Analysis on the number of pre-cursors and route length of the highest predicted routes.**

	Average Number of Pre-cursors	Percentage Single Pre-cursor Routes	Average Route Length
USPTO-50k	Including Template-based Model		
Template-based	3.41	1.82	3.19
Multi-expansion	3.07	1.88	2.36
	Original		
RandomInit-Original	3.05	5.42	2.93
FT-Zinc-Original	2.94	7.42	2.74
	Baselines		
RandomInit-baseline	3.06	5.22	2.95
FT-Zinc-baseline	2.86	7.80	2.67
	Optimized: Randomly Initiated		
RandomInit-OptAcc	3.16	3.32	3.06
RandomInit-OptRCS	3.09	2.62	2.76
	Optimized: KD Chemformer		
KD-Chemformer-OptAcc	2.91	7.70	2.67
KD-Chemformer-OptRCS	2.85	11.84	2.66
	Optimized: KD Zinc		
KD-Zinc-OptAcc	1.98	39.14	2.32
KD-Zinc-OptRCS	1.84	44.14	2.13
USPTO-Full	Baselines		
RandomInit-baseline	3.15	1.96	2.40
FT-Zinc-baseline	3.17	2.28	2.40
	Optimized: Randomly Initiated		
RandomInit-OptAcc	3.07	1.88	2.37
RandomInit-OptRCS	2.99	2.22	2.39

Example prediction of Zinc and Template

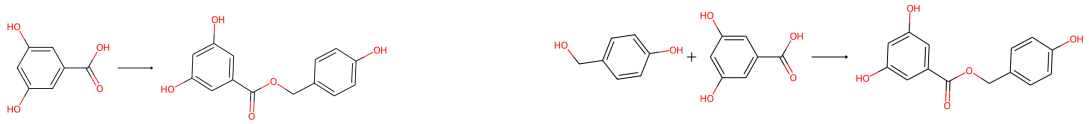

Figure A1: **Illustrative example using routes generated for target CHEMBL1668049, using either KD-Zinc (left) and template-based models (right) indicates KD-Zinc predicts only partial reactant sets.**

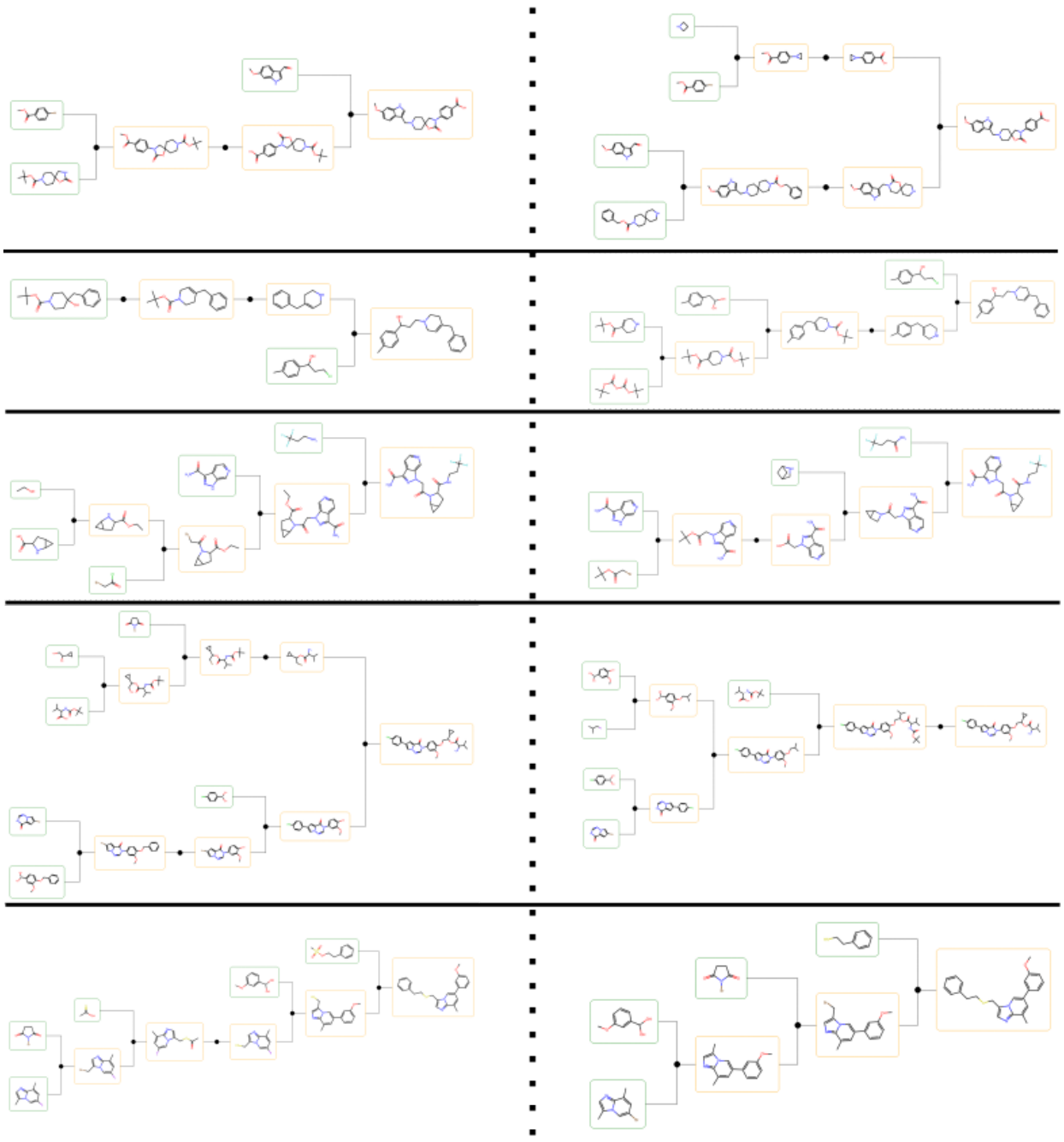

Figure A2: **Examples to illustrate the differences in routes generated from the optimized KD Chemformer OptRCS (left) and the template-based model (right).** Molecules highlighted in green are building blocks, molecules on the right of a route are the target molecules and any other molecules are treated as intermediates. Routes selected

Alternative Weights

Table A5: **Single-step model full training model statistics based on the Transformer.** Models are trained either from scratch (RandomInit), fine-tuned from training on Zinc (FT-Zinc), using KD on the Chemformer model (KD-Chem) or KD on the Zinc model (KD-Zinc). Hyper-parameters are either from the original publication (original), identical to the original but using the lowest validation loss weights (baseline) or using hyper-parameters gathered from an Optuna search (opt: Acc/RCS) where specific parameters depend on the training setting. Models are then trained and evaluated on USPTO-50k and USPTO-full. Reported statistics are based on beam-search results on random split test set values.

Training	Size	Sample Time (s)	Top 1 Accuracy	Top 10 Accuracy	Percentage Invalid	Percentage Unique	CO_2 Emissions (g)
USPTO-50k				Original			
RandomInit	44.7M	18.06	50.6	63.1	0.93	21.90	2.30
FT-Zinc	44.7M	17.47	53.5	61.6	0.68	18.06	1.28
				Baselines			
RandomInit	44.7M	23.36	44.1	76.8	3.03	63.98	1.21
FT-Zinc	44.7M	16.77	48.3	79.7	1.46	55.73	0.68
				Optimized: Randomly Initiated			
Opt: Acc	11.3M	11.08	45.5	79.1	2.84	62.54	0.97
Opt: RCS	4.0M	4.25	45.7	79.2	2.55	62.53	0.39
				Optimized: KD Chemformer			
Opt: Acc	27.9M	9.63	44.0	71.6	6.58	62.38	0.77
Opt: RCS	23.7M	5.77	34.3	57.0	29.03	80.92	0.30
				Optimized: KD Zinc			
Opt: Acc	27.9M	6.08	18.8	58.3	7.62	65.20	0.44
Opt: RCS	23.7M	5.63	15.0	46.3	23.73	77.67	0.39

Table A6: **Multi-step retrosynthesis search.** Translating effects of single-step models to multi-step search.

	Median	Average over search			Average per molecule		
Training	Search Time (s)	Search Time (h)	CO_2 emissions (g)	Percentage Solved (%)	# Solved Routes	Policy Probability	# Model Calls
USPTO-50k	Including Template-based Model						
Template-based	26.01	40	0.25	67.3	20.74	0.17	446
Multi-expansion	382.08	495	2482.29	89.0	159.17	0.19	1832
	Original						
RandomInit	25.48	62	196.34	61.5	132.92	0.48	1384
FT-Zinc	19.16	47	123.46	56.2	125.21	0.53	1259
	Baselines						
RandomInit	104.68	198	770.49	85.6	123.76	0.21	1599
FT-Zinc	81.71	165	632.99	84.1	143.69	0.22	1620
	Optimized: Randomly Initiated						
Opt: Acc	126.12	233	581.31	81.6	119.96	0.22	1680
ROpt: RCS	60.49	115	262.30	84.4	133.27	0.22	1718
	Optimized: KD Chemformer						
Opt: Acc	42.00	86	306.91	79.7	110.35	0.22	1273
Opt: RCS	23.97	47	161.99	74.2	69.95	0.18	736
	Optimized: KD Zinc						
Opt: Acc	22.24	44	159.06	77.3	61.65	0.14	608
Opt: RCS	13.36	29	99.03	67.1	36.96	0.13	364