Supporting Information:

A Flexible Data-Free Framework for Structure-Based De Novo Drug Design with Reinforcement Learning

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Fragment Recombination Rules

We adopted the fragment recombination rules as described in the original BRICS[1] paper, which consists of two main steps: First, heavy atoms are classified based on their atomic types, bonding information, and valency. Specific numbers are assigned to each category. Subsequently, the rules for fragment recombination are defined based on chemical reversibility and synthetic feasibility.

We have provided a script called *prepare_building_blocks.py* on GitHub for classifying heavy atoms (https://github.com/Brian-hongyan/3D-MCTS). The table below lists the recombination rules based on BRICS:

Table S1. Recombination Rules according classifications of connection heavy atoms

Class	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1		√	√		√					√						
2	√													√		
3	√			√		√		√					√	√	√	√
4		√			√						√					
5	√			√		√		√				√	√	√	√	√
6		√			√					√			√	√	√	√
7							√									
8		√			√				√	√	√		√	√	√	√
9								√					√	√	√	√
10	√					√		√					√	√	√	√
11				√				√					√	√	√	√
12					√											
13			√		√	√		√	√	√	√			√	√	√
14		√	√		√	√		√	√	√	√		√	√	√	√
15			√		√	√		√	√	√	√		√	√		√
16			√		√	√		√	√	√	√		√	√	√	√

The numbers represent classification of heavy atoms. A checkmark in the table indicates that the corresponding two categories meet the recombination rules.

References

1.   J. Degen, C. Wegscheid-Gerlach, A. Zaliani and M. Rarey, *Chemmedchem*, 2008, **3**, 1503-1507.