The fragment 14 ( CN(C)C(=N)N ) represents 1,1-dimethylguanidine structure. Guanidine fragments can be found among acyclic guanidine-containing BACE1 inhibitors in the studies reported by Boy et al. [70] and Gerritz et al. [71]. The guanidine fragment extracted by the workflow is slightly different from the guanidine fragments found in these two studies.

The guanidine groups in these studies contain a guanidine base that has one alkyl side chain, while the extracted fragment carries two alkyl 38 side chains (dimethyl). Although the extracted fragment is not fully identical with the guanidine bases in these studies, this fragment still denotes an important moiety since acyclic guanidine-containing BACE1 inhibitors comprise a large corpus of the studies focused on discovering BACE1 targeting agents.

Moreover, as mentioned in Subsection 2.2.1, cyclic guanidines (aminohydantoins, iminohydantoins)

are also common structural cores among BACE1 inhibiting compounds [35–37], and fragment 4 may also be

pointing to the cyclic guanidine fragment present in iminohydantoins. Altogether, the ability of the workflow to find and highlight the guanidine moiety as an important fragment, which is used widely as a common motif across BACE1 inhibitors, once more marks the workflow’s success in finding meaningful chemical fragments. As it can be seen in Figure A6 (fragments 16, 18, 19, and 20), discussed in Subsection 2.2.1,

the workflow was also able to extract fragments that carry an aminohydantoin moiety (the aminohydantoin core is shown in purple in Figure C11) for the BACE Regression task as well.

In the BACE Regression task, fragment 4 (Figure A6), which bears an isoindole scaffold, is included within the molecules found in the patented study of Abdel-Magid [70], who has introduced new chemical compounds that have BACE-inhibiting effects.

Additionally, in the study of Thompson et al. [71], from which a patent has also been issued [72], a series of diaminopropane analogs (highlighted in green on fragments 8, 9, and 10 in Figure A6) have been introduced as potential BACE1 inhibitors. The 39 extra bulky size of the rings within these derivatives allows them to be well-positioned in the ligand-binding regions of the enzyme. Furthermore,

(1,1-dimethylguanidine)

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the workflow was also able to extract fragments that carry an aminohydantoin moiety (the aminohydantoin core is shown in purple in Figure C11) for the BACE Regression task as well.