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Synthesis and integrated *in silico* and *in vivo* evaluation of 1,3,4-oxadiazole–piperazine–naphthalene conjugates as diuretics

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ABSTRACT 5-(Naphthalen-1-ylmethyl)-1,3,4-oxadiazole-2-thiol **(8)** and 2-chloro-1-(piperazin-1yl)ethan-1-one derivatives **(4a-j)** were used in a stepwise procedure to synthesise a series of 3-(5-(naphthalen-2-ylmethyl)-1,3,4-oxadiazol-2-yl)-1-(4-phenylpiperazin-1-yl)propan-1-one derivatives **(9a-j)**. Based on the findings from *in vivo* diuretic tests conducted on an experimental rat animal model, compounds **9b, 9c, 9d, 9e, 9h,** and **9j** were found to have excellent diuretic capability. The data from *in silico* investigations conducted with Auto Dock (1.5.7) software further supported the findings from the *in vivo* study. Human carbonic anhydrase II protein (PDB ID: 3HS4) and human NKCC1 K289NA492E protein (NKCC1, PDB ID: 7S1Y) were the two target proteins with which the synthesized molecules docked. Using pkCSM software, the absorption, distribution, metabolism, and excretion properties of the produced compounds were also ascertained, confirming that they are suitable candidates for oral absorption. All the data from *in silico* and *in vivo* investigations combined to show that all of the synthesised compounds had higher diuretic activity than the standard drug furosemide.

KEYWORDS 1,3,4-Oxadiazole, Piperazine, Naphthalene, Human Carbonic Anhydrase-II, Diuretic activity, Urine excretion.