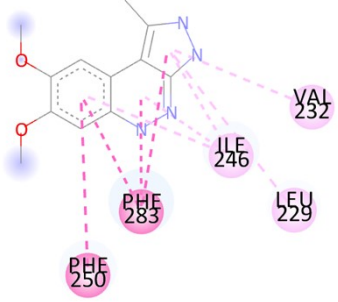
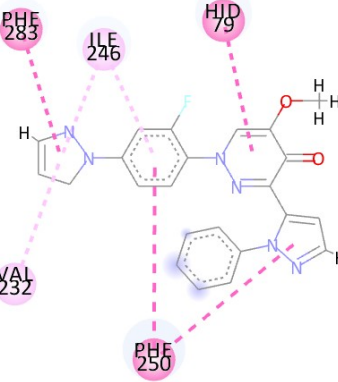
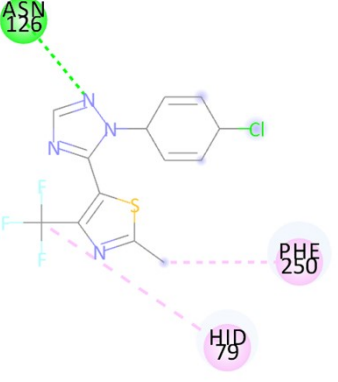


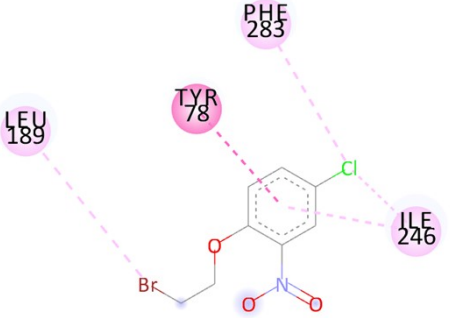
Table S1. Physicochemical properties of the hits that fit the criteria of the CNS active drug.

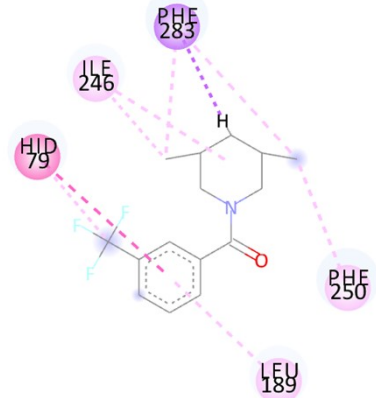
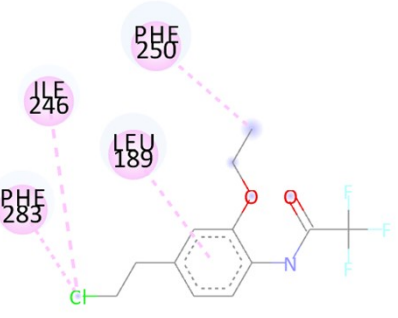
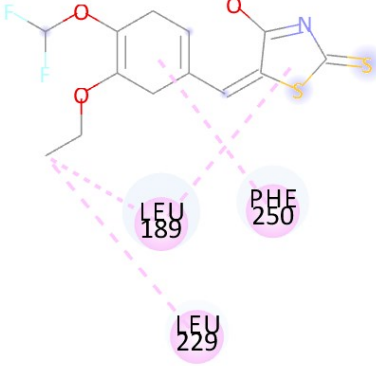
Ligand	M.wt	Log P	No. of HBA	No. of HBD	PSA	LogBB	CNS active drug	No. of RB	PFS
Zinc01397213	344.7	3.9	4.0	0	42.5	0.5	2	0	48.0
Zinc02156284	280.5	2.9	1.7	0	47.5	0	1	4	48.0
Zinc42657360	348.3	3.2	5.7	1	57.6	0	0	4	55.3
Zinc43638301	279.2	3.4	3.0	0	36.9	0.3	1	4	56.0
Zinc47464611	285.3	3.9	3.0	0	27.0	0.4	2	1	55.7
Zinc71439134	295.6	3.8	3.2	1	43.5	0.4	1	4	56.9
Zinc71759377	331.3	2.6	3.7	1	55.9	0	1	6	56.6
Zinc72553806	310.3	2.9	4.5	1	36.0	0.6	2	4	56.3
Zinc72878277	284.3	4.0	4.0	2	43.9	0.4	2	6	56.0
Zinc79055898	327.3	4.2	4.0	0	41.0	0	1	6	55.9
Zinc82446000	296.4	2.9	5.2	0	52.5	0	1	4	48.4
Zinc82779572	250.2	2.8	2.0	2	35.4	0.3	1	4	48.0
Zinc82779574	250.2	2.7	2.0	2	36.3	0.3	1	4	48.0
Zinc82779590	268.2	3.0	2.0	2	36.2	0.4	2	4	48.0

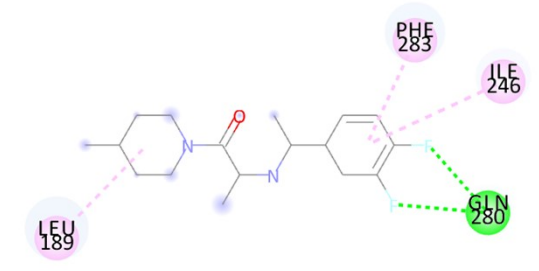
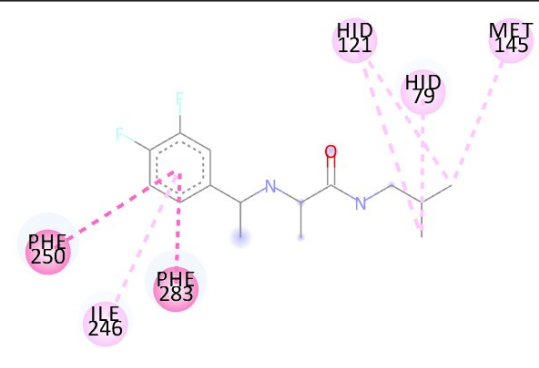
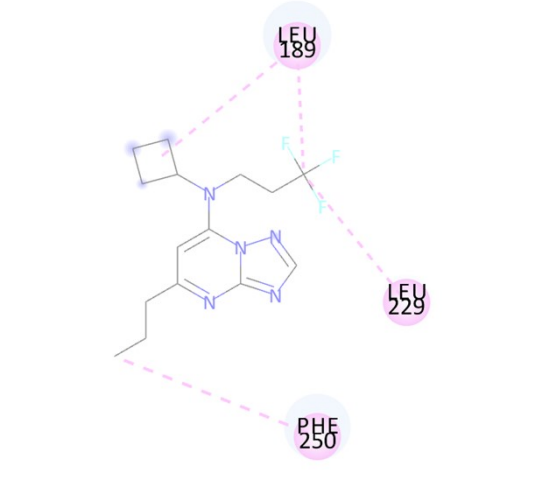
*M.wt: Molecular weight, Log P: Octanol/Water partition coefficient, No. of HBA: Number of hydrogen bond acceptor, No. of HBD: Number of hydrogen bond donor, PSA: Polar surface area, LogBB: Blood/Brain partition coefficient, No. of RB: Number of rotatable bond, PFS: Pharmacophore fit score.

Table S2. Amino acids involved in the interactions between PDE10A and the ligands

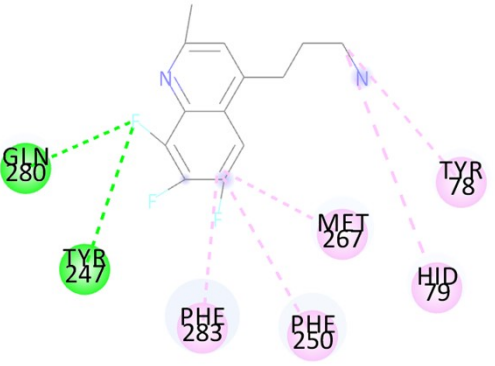
Ligand	Hydrophobic Interactions	Hydrogen Bond Interactions	π -Stacking Interactions	2D Image
Co-crystallised ligand (JY4)	LEU229, VAL232 and ILE246	-	PHE250 with dimethoxybenzene PHE283 with pyrazole, tetrahydropyridazine and dimethoxybenzene	
TAK063 (standard)	VAL232 and ILE246	-	HID79 with pyridazine PHE250 with fluorobenzene and pyrazole PHE283 and pyrazole	
Zinc01397213	HID79 and PHE250	ASN126 N of triazole	-	

Zinc02156284	LEU189, ILE246 and PHE283	-	TYR78 with chlorobenzene	 <p>Molecular interaction diagram for Zinc02156284. The central molecule is a chlorobenzene derivative with a bromomethyl group and a nitro group. Interactions are shown with residues: TYR78 (red), LEU189 (blue), PHE283 (green), and ILE246 (purple). Dashed lines indicate interactions between the tyrosine side chain and the aromatic ring, and between the other residues and the bromine and nitro groups.</p>
Zinc42657360	LEU229 and ILE246	THR187 and ASP228 with OH ASN126 with fluorine	TYR78 with pyrimidine PHE283 with cyclopentathiothiophene	 <p>Molecular interaction diagram for Zinc42657360. The central molecule is a complex heterocyclic structure containing a pyrimidine ring and a cyclopentathiothiophene ring. Interactions are shown with residues: TYR78 (red), PHE283 (green), LEU229 (blue), THR187 (purple), ASP228 (orange), and ASN126 (yellow). Dashed lines indicate interactions between the tyrosine side chain and the pyrimidine ring, and between the other residues and various parts of the heterocyclic structure.</p>
Zinc43638301	TYR78, LEU189 and LEU229	-	-	 <p>Molecular interaction diagram for Zinc43638301. The central molecule is a pyridine derivative with a sulfur atom and a trifluoromethyl group. Interactions are shown with residues: TYR78 (red), LEU189 (blue), and LEU229 (purple). Dashed lines indicate interactions between the tyrosine side chain and the pyridine ring, and between the other residues and the sulfur and trifluoromethyl groups.</p>

Zinc47464611	HID79, LEU189, ILE246, PHE250 and PHE283	-	HID79 with trifluoromethyl benzene	 <p>Molecular interaction diagram for Zinc47464611. The ligand is a benzene ring with a trifluoromethyl group (-CF₃) and a hydrogen atom. Interactions are shown with residues HID79, ILE246, PHE283, PHE250, and LEU189. Dashed lines indicate hydrogen bonds between the ligand and the residues.</p>
Zinc71439134	LEU189, ILE246, PHE250 and PHE283	-	-	 <p>Molecular interaction diagram for Zinc71439134. The ligand is a benzene ring with a chlorine atom (-Cl), a trifluoromethyl group (-CF₃), and a methoxy group (-OCH₃). Interactions are shown with residues ILE246, PHE283, LEU189, and PHE250. Dashed lines indicate hydrogen bonds between the ligand and the residues.</p>
Zinc71759377	LEU189, LEU229 and PHE250	-	-	 <p>Molecular interaction diagram for Zinc71759377. The ligand is a benzene ring with a trifluoromethoxy group (-OCF₃), a propoxy group (-OCH₂CH₂CH₃), and a thiazole ring. Interactions are shown with residues LEU189, PHE250, and LEU229. Dashed lines indicate hydrogen bonds between the ligand and the residues.</p>

Zinc72553806	LEU189, ILE246 and PHE283	GLN280 with fluorine	-	
Zinc72878277	HID79, HID121, MET145 and ILE246	-	PHE250 and PHE283 with difluorobenzene	
Zinc79055898	LEU189, LEU229 and PHE250	-	-	

Zinc82446000	TYR78, LEU189 and ILE246	HID121 with sulphur	PHE250 with thiazole	<p>The diagram shows a thiazole ring system with a methyl group and a thiazolidine ring. Interactions are indicated by dashed lines: HID121 (green) interacts with the sulfur atom of the thiazole ring; PHE250 (pink) interacts with the oxygen atom of the thiazolidine ring; TYR78 (pink) interacts with the nitrogen atom of the thiazolidine ring; LEU189 (pink) interacts with the methyl group; and ILE246 (pink) interacts with the thiazolidine ring.</p>
Zinc82779572	LEU189 and ALA190	-	-	<p>The diagram shows a quinoline ring system with two fluorine atoms and a propylamine side chain. Interactions are indicated by dashed lines: LEU189 (pink) interacts with the quinoline ring; and ALA190 (pink) interacts with the nitrogen atom of the propylamine side chain.</p>
Zinc82779574	HID79 and LEU189	-	HID79 with quinoline	<p>The diagram shows a quinoline ring system with two fluorine atoms and a propylamine side chain. Interactions are indicated by dashed lines: LEU189 (pink) interacts with the quinoline ring; and HID79 (pink) interacts with the nitrogen atom of the propylamine side chain.</p>

Zinc82779590	TYR78, HID79, PHE250, MET267 and PHE283	TYR247 and GLN280 with fluorine	-	 <p>The diagram illustrates the chemical structure of Zinc82779590, a 6-fluoro-1-methyl-2-(propylamino)quinoline. The structure is shown with several amino acid residues interacting with it. Green dashed lines indicate interactions with GLN280 and TYR247. Pink dashed lines indicate interactions with PHE283, PHE250, MET267, TYR78, and HID79. The quinoline ring has a methyl group at position 1, a propylamino group at position 2, and a fluorine atom at position 6. The amino acid residues are represented by colored circles: GLN280 and TYR247 are green, while PHE283, PHE250, MET267, TYR78, and HID79 are pink.</p>
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