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PHARMACOLOGICAL PROPERTIES OF NEW 2,3-BENZODIAZEPINE AND B-CARBOLINE DERIVATIVES

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Backround. The current strategy for the search for next-generation neurotherapeutic agents is increasingly moving away from the “one target, one ligand” paradigm in favor of the concept of polypharmacology. This approach assumes the ability of a compound to interact with multiple biological targets and may result in higher efficacy and a more favorable safety profile [1, p. 274].

In this context, the so-called "privileged" molecular structures (privileged scaffolds), capable of interacting with multiple receptor types, play a key role.

Such structures include 2,3-benzodiazepines (2,3-BZDs), which differ in their structure from the classical 1,4-BZDs. Historically, 2,3-BZDs, of which GYKI 52466 is the prototypical representative, were created as non-competitive antagonists of AMPA receptors, which gives them neuroprotective and anticonvulsant properties that are different from direct modulation of the GABAergic system [2, p. 53]. However, recent evidence suggests that their anxiolytic action may be due to interactions with a wider range of CNS targets. Another promising class of compounds are β-carboline derivatives. This versatile heterocyclic base has served as a basis for the design of ligands for many CNS targets, including the benzodiazepine site of the GABA receptor. Importantly, some β-carboline derivatives have demonstrated potent nootropic and neuroprotective activity. This makes them an extremely attractive basis for the development of agents that can not only eliminate anxiety, but also correct the associated cognitive deficit, a key drawback of classical anxiolytics [3, p. 364].

The search for anxiolytics with an improved safety profile is a key task of modern neuropsychopharmacology. Promising candidates are 2,3-benzodiazepine derivatives (MPTD-01, BS34-20) and β-carboline (Carbacetam), which in preclinical studies have demonstrated anxiolytic activity in the absence of side effects characteristic of classical 1,4-benzodiazepines.

Aim: to determine and compare the polypharmacological profiles of structurally distinct anxiolytic candidates MPTD-01, BS34-20 and Carbacetam to elucidate the molecular mechanisms of their action using *in silico* methods.

Materials and methods. The interaction of the compounds with a panel of key central nervous system targets, including GABAergic ($GABA^A$, $GABA^B$, TSPO), glutamatergic (AMPA), neuropeptide receptors, and ion channels (Nav1.2), was analyzed using molecular docking (AutoDock Vina, UCSF ChimeraX). ADMET profiling was also performed to assess the pharmacokinetic properties of the compounds.

Results. Carbaracetam demonstrated a potent multitarget profile with high predicted affinity for $GABA^A$ (-10.513 kcal/mol), the ion channel Nav1.2 (-9.420 kcal/mol), and the translocator protein TSPO (-9.053 kcal/mol), as well as significant interaction with $GABA^B$ and AMPA receptors. In contrast, 2,3-benzodiazepine derivatives (BS34-20 and MPTD-01) showed a more focused effect, consisting in a balanced modulation of $GABA^A$ (binding energy up to -8.379 kcal/mol for BS34-20) and AMPA receptors. A favorable safety profile and the ability to overcome the blood-brain barrier were predicted for all compounds.

A comprehensive *in silico* study has revealed the complex polypharmacological mechanisms of action of three novel anxiolytic compounds. The use of a multitarget approach has revealed unique pharmacological profiles that explain their therapeutic potential and favorable safety profiles. The results provide an objective, data-based basis for understanding the mechanisms of action of these structurally diverse compounds. The β-carboline derivative, Carbaracetam, has been identified as a potent multitarget compound. Calculations suggest that its high efficacy is likely due to synergistic interactions with a network of key CNS targets, including $GABA^{A}$-, $GABA^{B}$- and TSPO-receptors, as well as Nav1.2 and NMDA ion channels. This unique multi-target profile provides the molecular basis for the combination of anxiolytic, nootropic, and neuroprotective properties, which is its key mechanistic difference from classical anxiolytics. The 2,3-benzodiazepine derivatives MPTD-01 and BS34-20 achieve their "anxiety-selective" profile, presumably through a more focused, dual modulation of the GABAergic and glutamatergic systems (GABAA and AMPA receptors, respectively). This balanced mechanism likely prevents the global CNS depression characteristic of less selective drugs.

Conclusion. The obtained data indicate that the favorable therapeutic profile of the studied compounds is due not to selectivity to a single target, but to a balanced interaction with several signaling pathways. Understanding these polypharmacological profiles created the basis for further experimental validation and rational design of safer neurotherapeutic agents.

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