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КОМПЛЕКСНА ПРОГРАМА ОЗДОРОВЛЕННЯ: СИСТЕМНИЙ ПІДХІД ТА ІНТЕГРАТИВНА ТЕРАПІЯ ЗАХВОРЮВАНЬ ЧЕРЕЗ ТЕРАПЕВТИЧНУ КОРЕКЦІЮ ПСИХОБІОЛОГІЧНИХ КОНФЛІКТІВ
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ANXIOLYTIC POTENTIAL OF 1-METHYL/4-(*TERT*-BUTYL)-2'-(CYCLOALKYL/HETARYL)-6'*H*-SPIRO[PIPERIDINE/CYCLOALKANE-4,5'/1,5'-[1,2,4]TRIAZOLO[1,5-*C*]QUINAZOLINES]

Introduction. The landscape of anxiolytic therapy has evolved significantly, particularly in addressing post-traumatic stress reactions (PTSR). Traditional pharmacological interventions often present limitations, although recent advances in GABAergic modulation have demonstrated promising therapeutic potential, as evidenced by extensive clinical studies [1]. Research has established that the gamma-aminobutyric acid subtype A (GABA(A)) receptor serves as a critical target for most clinically effective sedative-hypnotic compounds, including general anesthetics, benzodiazepines, barbiturates, and gaboxadol (4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol) [2]. The emergence of novel delivery systems and receptor-specific compounds has revolutionized anxiety treatment approaches [3], while the integration of computational methods in drug design [4], particularly in analyzing GABA(A) receptor interactions, has enabled more precise development of potential anxiolytics. Therefore, this study investigates a series of novel spiro[1,5'/4,5'-[1,2,4]triazolo[1,5-*c*]quinazoline] derivatives, examining their binding properties and structure-activity relationships with the GABA(A) receptor complex.

The aim of the work. Systematically analyze the binding affinities of a series of compounds targeting GABA(A) receptors, identify structural characteristics that correlate with high receptor binding efficiency, and develop structure-activity

relationship (SAR) insights to guide future ligand design for pharmaceutical development.

Materials and Methods. Using CB-Dock2, an advanced protein-ligand blind docking tool [4, 5], the binding affinities of 40 novel compounds (Fig. 1) were analyzed to the α1/β3/γ2L GABA(A)R receptor (RCSB PDB ID: 6HUP [6]). The computational analysis employed curvature-based cavity detection combined with AutoDock Vina for binding prediction. All molecular structures were processed using standardized mol format inputs, while protein target was analyzed in pdb format. Diazepam served as a reference compound for comparative analysis [7].

Results. Analysis of the investigated compound series revealed a systematic structural organization based on the 5,6-dihydro[1,2,4]triazolo[1,5-*c*]quinazoline scaffold. Benzodiazepines, particularly diazepam (Valium), represent the current gold standard for GABA(A) receptor targeting [2, 7]. The novel compounds are characterized by distinct cycloalkyl rings fused to the core structure: cyclobutyl (**1**-**8**), cyclopentyl (**9**-**18**), cyclohexyl (**19**-**24**), 4-(*tert*-butyl)cyclohexyl (**25**-**30**), and 1-methylpiperidinyl (**31**-**40**) (Fig. 1). Comparative analysis revealed that the majority of synthesized compounds demonstrated superior binding affinities compared to diazepam.

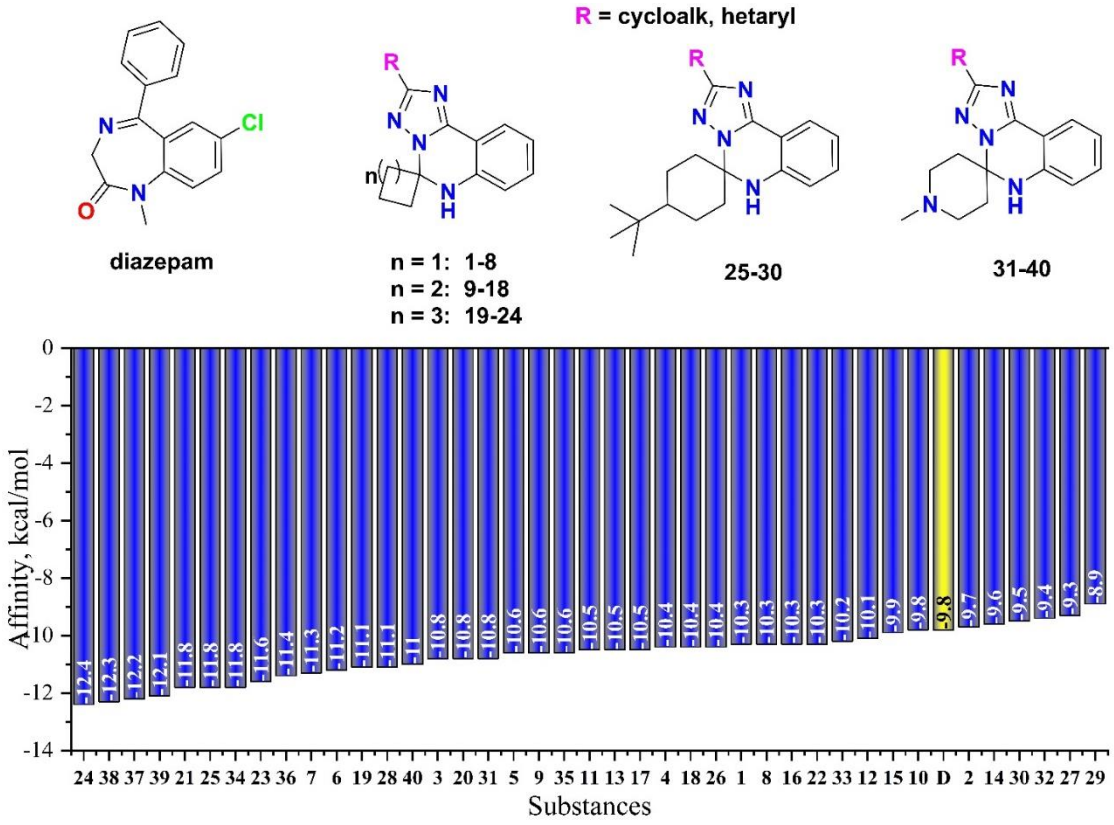

Fig. 1. **Chemical structures of studied substances, and calculated affinity of compounds towards α1/β3/γ2L GABA(A)R receptor (PDB ID: 6HUP), where is d is diazepam**

High-affinity compounds (binding energies -12.4 to -11.8 kcal/mol) encompassed **24**, **37**-**39**, **21**, **25**, and **34**. These molecules consistently exhibited larger cyclic systems, aromatic or heterocyclic R-groups, and enhanced structural flexibility in their linking groups. Moderate-affinity compounds (binding energies -11.3 to -10.8 kcal/mol), including **7**, **6**, **19**, **28**, **40**, **3**, **20**, and **31**, demonstrated intermediate-sized ring systems with varied substituent patterns. Lower-affinity compounds (binding energies -10.6 to -9.8 kcal/mol) predominantly featured smaller ring systems and more rigid structural configurations.

Spatial arrangement emerged as a crucial determinant of binding efficiency, with enhanced conformational flexibility correlating strongly with improved binding properties. This observation suggests that molecular adaptability plays a critical role in optimizing receptor interactions. Compound **24** achieved the highest binding energy (-12.4 kcal/mol), likely due to its optimal electronic and spatial characteristics. Compounds **37** and **38** demonstrated comparable performance, sharing key structural features that facilitate high-affinity binding. In contrast, compounds **27** and **29** exhibited relatively weak binding, attributable to suboptimal spatial arrangements and insufficient molecular bulk for stabilizing hydrophobic interactions.

Structural rigidity, when appropriately balanced with molecular flexibility, proved crucial for maintaining favorable binding interactions. Compounds featuring larger ring systems consistently demonstrated superior affinity (-12.4 to -11.8 kcal/mol), while the presence of strategically positioned hydrogen bond donors and acceptors enhanced specific binding interactions. Notably, electron-rich heterocycles, such as furan and thiophene, generally reduced binding affinity through unfavorable electronic distribution patterns.

Conclusions. This comprehensive investigation establishes the significant potential of the studied spiro[1,5'/4,5'-[1,2,4]triazolo[1,5-*c*]quinazoline] derivatives as GABA(A) receptor ligands. The elucidated structure-activity relationships provide crucial insights for future anxiolytic drug design, particularly in developing compounds with enhanced receptor specificity and minimized adverse effects. The identified optimal structural features, including the incorporation of larger cyclic systems and strategic placement of electronic modulating groups, offer clear direction for subsequent molecular optimization.

The computational analysis revealed, that compounds incorporating 6-7 membered rings with spiro/fused configurations demonstrated superior binding characteristics, suggesting a promising direction for future drug development. The balance between molecular flexibility and structural rigidity emerged as a critical

factor in determining binding affinity, with optimal performers exhibiting carefully tuned conformational freedom.

Several key limitations warrant consideration in future investigations. First, the computational predictions require experimental validation through binding assays and functional studies. Second, the current model does not fully account for the dynamic nature of protein-ligand interactions in physiological conditions. Future research directions should encompass: experimental validation of the computational findings through *in vitro* and *in vivo* studies, namely investigation of receptor subtype selectivity, analysis of pharmacokinetic properties, and assessment of potential metabolic interactions.

The development of these novel anxiolytics holds particular significance for individuals affected by trauma-related anxiety disorders, potentially offering improved therapeutic options with enhanced efficacy and reduced side effects. The integration of these findings with broader therapeutic strategies may contribute significantly to advancing the field of anxiety treatment [8].

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