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Research Article

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Next-Generation Rigid Scaffolds: Lessons from Prismane and Twistane

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Abstract

Rigid polycyclic hydrocarbons represent a unique class of molecular scaffolds whose constrained three-dimensional architectures offer distinct advantages for chemical biology and drug design. Among these, prismane and twistane occupy an exceptional position due to their extreme rigidity, high geometric strain, and well-defined topological features. In contrast to classical rigid frameworks such as adamantane, prismane and twistane remain largely unexplored in biomedical research, despite their potential to access novel regions of pharmacological space.This review provides a comprehensive analysis of prismane- and twistane-based model compounds bearing diverse functional groups and halogen substituents, with a particular focus on their predicted biological activities evaluated using the Prediction of Activity Spectra for Substances (PASS) algorithm. By systematically comparing these scaffolds to the clinically validated adamantane framework, we elucidate how differences in topology, symmetry, chirality, and strain influence biological activity profiles. PASS-based structure–activity analysis reveals that selected prismane derivatives exhibit strong predicted antiprotozoal, anti-inflammatory, and neuroactive properties, while specific twistane derivatives demonstrate notable potential as DNA intercalators, neuroprotective agents, and stroke-related therapeutics. Mechanistic hypotheses are discussed in the context of rigid-scaffold interactions with ion channels, redox-sensitive pathways, neuro–immune–inflammatory signaling, and nucleic acid targets. Overall, this review positions prismane and twistane as promising next-generation rigid scaffolds for in silico-guided drug discovery. The findings highlight their value as model systems for exploring structure–activity relationships driven by molecular topology and rigidity, and underscore their potential relevance in the development of new therapeutics for neurodegenerative, inflammatory, infectious, and oncological diseases.

Keywords: Prismane, Twistane, Drugs, Antiparkinsonian, Alzheimer's Disease, Neurodegenerative Diseases

1. Introduction

Cyclobutanes constitute a distinctive class of saturated hydrocarbons characterized by four-membered carbon rings with highly strained C–C–C bond angles (≈90°), which deviate significantly from the ideal tetrahedral geometry of sp^3-hybridized carbon. This inherent angle strain imparts unique physicochemical properties, including elevated internal energy, restricted conformational flexibility, and pronounced rigidity. While simple monocyclic cyclobutanes are well known in organic chemistry, their role as structural motifs becomes particularly significant when multiple cyclobutane units are fused or embedded within polycyclic frameworks [1-4]. In this broader structural context, prismane and twistane can be viewed as advanced cyclobutane-based architectures, in which cyclobutane motifs are not isolated but integrated into rigid, three-dimensional hydrocarbon scaffolds. Prismane consists of two parallel three-membered carbon rings connected by three vertical bonds, generating a polycyclic system that incorporates multiple four-membered ring junctions with near-orthogonal bond angles. This arrangement produces an exceptionally rigid and highly strained hydrocarbon framework that serves as a canonical model for studying the consequences of enforced 90° bond angles in saturated carbon systems [5-8]. From a chemical biology and medicinal chemistry perspective, cyclobutane-based rigid frameworks such as prismane and twistane occupy

a unique position among hydrocarbon scaffolds. Their structural rigidity minimizes entropic penalties upon binding to biological targets, enforces precise spatial orientation of functional groups, and enables predictable structure–activity relationships. These features distinguish prismane- and twistane-derived compounds from more flexible aliphatic systems and from planar aromatic scaffolds, positioning them as valuable platforms for probing biological recognition processes, stereochemical selectivity, and mechanistic aspects of enzyme and receptor interactions [6-10]. Thus, in a broadened definition, cyclobutanes may be understood not only as simple four-membered rings, but also as foundational geometric motifs underlying rigid polycyclic hydrocarbons such as prismane and twistane, whose extreme angular constraints and three-dimensional architectures render them particularly attractive for applications in chemical biology, stereochemical theory, and scaffold-based drug design.The primary purpose of this review is to systematically evaluate prismane and twistane as rigid hydrocarbon model scaffolds for probing structure–activity relationships in chemical biology and medicinal chemistry. Owing to their exceptional three-dimensional rigidity, well-defined geometry, and minimal conformational freedom, prismane and twistane provide ideal reference frameworks for assessing how the spatial arrangement of functional groups influences predicted biological activity.

In this work, prismane and twistane derivatives bearing diverse functional groups—including amino, nitro, hydroxy, hydroperoxy, halogen, thiol, sulfate, phosphate, and phosphonate substituents—are employed as model structures rather than as optimized drug candidates. Their role is to serve as geometrically constrained platforms that allow the isolation of steric, electronic, and topological effects on biological activity without the confounding influence of conformational flexibility.To achieve this goal, the review applies the Prediction of Activity Spectra for Substances (PASS) algorithm to a curated set of functionalized prismane and twistane derivatives. This computational approach enables the comparative profiling of predicted biological activities across different substitution patterns and functional group classes, providing insight into how extreme rigidity and cyclobutane-rich architectures modulate pharmacological potential. Specifically, the review aims to: (i) Assess the suitability of prismane and twistane as universal rigid scaffolds for in silico biological activity prediction; (ii) Identify functional group–dependent activity trends associated with these rigid frameworks; (iii) Compare predicted biological spectra of prismane and twistane derivatives to highlight complementarities arising from their distinct topologies; (iv) Evaluate their potential relevance as conceptual models for anticancer, neuroprotective, anti-inflammatory, antimicrobial, and enzyme-modulating activities; (v) Demonstrate the utility of PASS-guided screening for prioritizing highly strained, non-classical hydrocarbon scaffolds in early-stage drug discovery.

Overall, this review positions prismane and twistane not merely as chemical curiosities, but as powerful model systems for understanding how extreme molecular rigidity and topology influence biological activity, thereby providing a conceptual foundation for future experimental, computational, and translational studies involving rigid three-dimensional scaffolds.

2. Prismane (Ladenburg's Benzene) and its Activities

Prismane (Ladenburg’s benzene) is a polycyclic hydrocarbon with the formula C6H6. It is an isomer of benzene, specifically a valence isomer. Prismane is far less stable than benzene. The carbon (and hydrogen) atoms of the prismane molecule are arranged in the shape of a six-atomtriangular prism [11-13]. According to established facts, the history of prisms began in 1869, when Albert Ladenburg proposed a triangular prismatic structure as a possible model for benzene [14]. However, the actual prism molecule was first synthesized in 1973 by Katz and Acton highlighting its unique, strained structure and role in understanding benzene's aromaticity more than a century later; the first terms appeared in the 1960s. Ladenburg proposed a prismatic (triangular prismatic) structure to explain the properties of benzene, but this proved less stable and accurate than the Kekulé ring structure [15,16]. Prismat is a valence isomer of benzene, exhibiting alternative bonding patterns between atoms with the same formula. Its strained C-C bonds (60° angles) make it highly reactive; it converts to benzene at higher temperatures, a phenomenon widely studied in physical organic chemistry (See Figure 1).

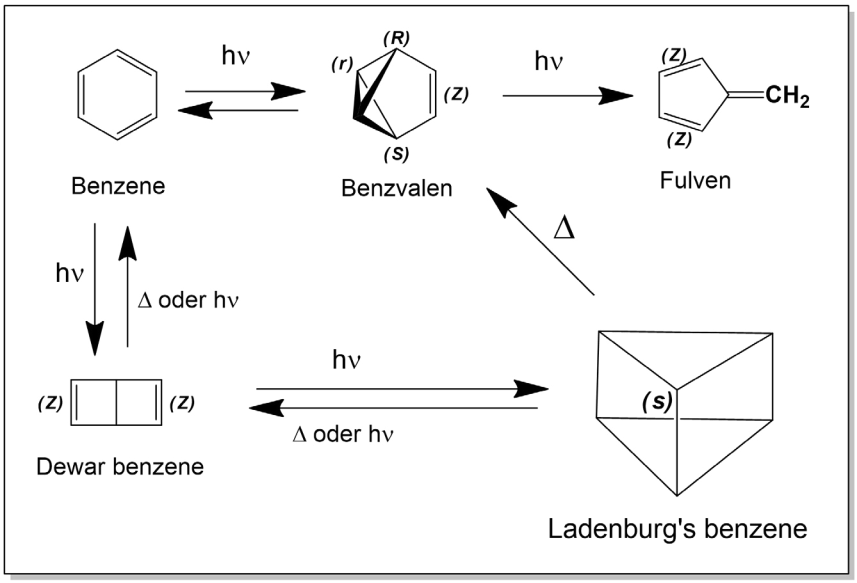

Figure 1: General scheme of the formation of Ladenburg's benzene (prismane), and comparison with the Kekulé ring structure and Dewar benzene structure

This comparison highlights how alternative bonding topologies can preserve the C_6H_6 formula while dramatically altering molecular geometry and strain. The rigid three-dimensional architecture of prismane contrasts sharply with the planar aromatic and non-planar valence isomers, underscoring the unique structural features that motivate its consideration as a scaffold in molecular design.

2.1. Note on the Biological Relevance of Prismane Scaffolds

Beyond their fundamental importance in physical organic chemistry and carbon cluster science, prismane and its derivatives represent an exceptionally powerful model system for studying structure–activity relationships in chemical biology, particularly in the context of anticancer and neuroactive compounds. The prismane framework is characterized by an extreme degree of geometric rigidity, three-dimensional symmetry, and well-defined spatial orientation of substituents, properties that are highly desirable for probing biological recognition processes involving enzymes, receptors, and nucleic-acid-associated targets [17-19].

The suitability of prismane as a privileged rigid scaffold has already been demonstrated in stereochemical theory. Fujita's stereoisogram approach established prismane as an ideal promolecule for systematically analyzing geometric and stereoisomeric aspects of stereochemistry [20]. Using prismane derivatives, five fundamental types of stereoisograms (Types I–V) were rigorously derived and proven through group-theoretical methods, providing a unified framework for understanding chirality, RS-stereogenicity, pseudoasymmetry, and sclerality. Importantly, these studies highlighted the independence of chirality from RS-stereogenicity, an insight of direct relevance to biological activity, where enantiomeric and diastereomeric effects often diverge unpredictably [20,21]. From a biomedical perspective, the highly constrained prismane skeleton allows precise spatial placement of pharmacophoric groups, minimizing conformational entropy and enabling clearer correlations between molecular geometry and biological response. Such features are particularly advantageous in the design and evaluation of compounds targeting cancer-related signaling pathways and neurological disorders, where receptor selectivity, blood–brain barrier penetration, and resistance to metabolic degradation are critical. Moreover, the energy-rich yet metastable nature of prismane derivatives suggests potential for redox activity, controlled reactivity, and interaction with oxidative or stress-related cellular pathways, which are central to both oncogenesis and neurodegeneration [22-24]. Taken together, the combination of theoretical stereochemical rigor and exceptional structural rigidity makes prismane and its functionalized derivatives an outstanding platform for modeling biological activity, bridging fundamental stereochemistry with translational applications in anticancer and neuropharmacological research. Figure 2 presents a representative set of prismane (triprismane) derivatives bearing various functional groups and halogen substituents. These rigid, highly strained hydrocarbon frameworks were selected as model structures to systematically evaluate how different substituents and electronic environments influence predicted biological activity [25]. All compounds shown in Figure 2 were analyzed using the Prediction of Activity Spectra for Substances (PASS) algorithm, which enables in silico estimation of a broad range of pharmacological effects based solely on molecular structure. The PASS-based activity prediction methodology applied here has been extensively validated and previously employed for large datasets of natural products, as well as for synthetic rigid hydrocarbon scaffolds, including cyclobutanes, adamantanes, cubanes, and related polycyclic systems. In these earlier studies, PASS predictions demonstrated good qualitative agreement with experimentally observed biological activities, particularly in the areas of anticancer, neuroprotective, antiviral, anti-inflammatory, and enzyme-inhibitory effects. By extending this established computational framework to prismane derivatives, the present analysis aims to (i) assess the intrinsic biological potential of the

prismane scaffold, (ii) identify substituent patterns that enhance specific activity profiles, and (iii) compare the predicted activity landscape of prismanes with that of other rigid hydrocarbon cores. This approach allows prismanes to be positioned within a broader structure–activity context and supports their use as informative models for exploring structure-driven biological effects in chemical biology and medicinal chemistry.

3. Model Primans Used to Study Their Activity

Primans-3 (compounds **1–16**, Figure 2), primans-5 (**17–32**, Figure 3), and primans-6 (**33–48**, Figure 4) were selected as model compounds. Each series comprises derivatives bearing diverse functional groups or halogen substituents at position 1, allowing systematic evaluation of structure–activity relationships. Amino-substituted primans include **1, 17**, and **33**, while nitro-containing derivatives are **2, 18**, and **34**. Thiol groups are present in primans **3, 19**, and **35**, whereas the corresponding selenol analogues are **4, 20**, and **36**. Hydroxyl-substituted primans are **5, 21**, and **37**, and hydroperoxy derivatives are represented by **6, 22**, and **38**. Aldehyde-containing compounds include **7, 23**, and **39**, while carboxylic acid derivatives correspond to **8, 24**, and **40**. Halogenated primans were also incorporated into the dataset, including fluorinated (9, 25, 41), chlorinated (**10, 26, 42**), brominated (**11, 27, 43**), and iodinated (**12, 28, 44**) analogues. In addition, sulfate esters are present in primans **13, 29**, and **45**, while phosphate esters are represented by **14, 30**, and **46**. The phosphonic acid functionality—formally written as R–P(O)(OH)2—belongs to the broader class of organophosphorus compounds and was introduced to assess its influence on predicted biological activity. Finally, primans **16, 32**, and **48** contain a thiocyanate (–SCN) functional group.

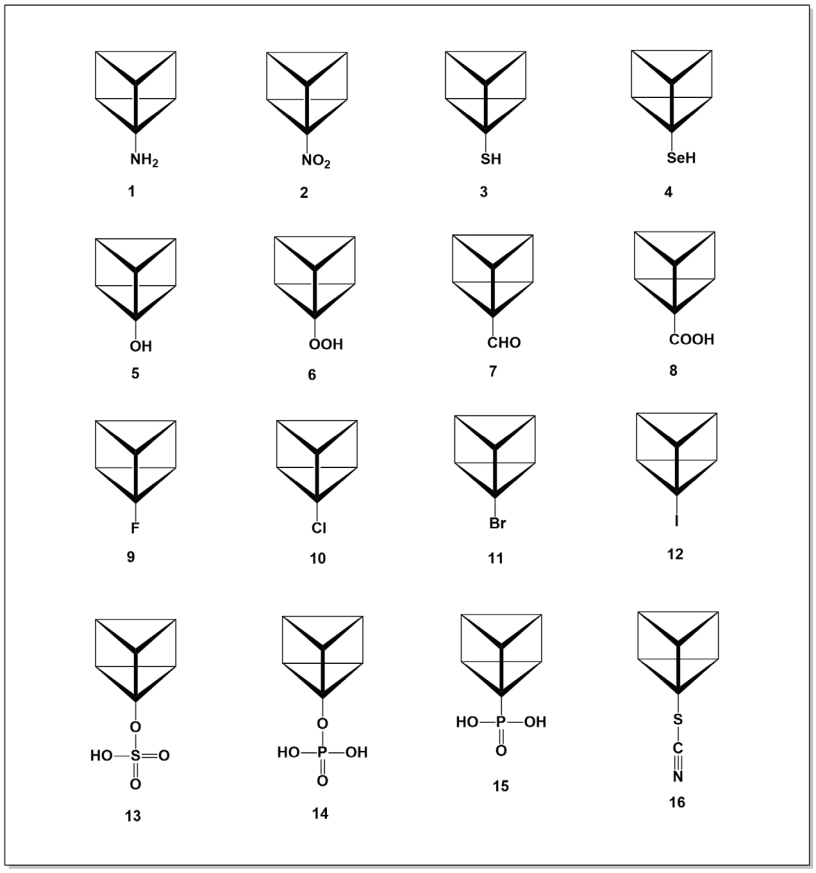

Figure 2: A set of prismane (triprismane) derivatives containing various functional groups and halogen substituents

These examples illustrate the synthetic versatility of the prismane framework, demonstrating that extensive functionalization is possible despite its high rigidity and strain. The introduction of polar groups and halogens enables systematic tuning of physicochemical properties relevant to molecular recognition and biological activity.

No	Predicted Activity, Ra	Rank	Additional Activity	Rank
1	Antiprotozoal (Plasmodium) (0,936)	Strong	Phobic disorders treatment (0,900)	Strong
2	Antiprotozoal (Plasmodium) (0,932)	Strong	Phobic disorders treatment (0,854)	Moderate
3	Phobic disorders treatment (0,871)	Moderate	Kidney function stimulant (0,806)	Weak
4	Antiparkinsonian (0,977) Alzheimer's disease treatment (0,961) Neurodegenerative diseases treatment (0,960)	Strong Strong Strong	DNA intercalator (0,994) Antioxidant (0,992) Apoptosis agonist (0,983)	Strong Strong Strong
5	Antiprotozoal (Plasmodium) (0,927)	Strong	Phobic disorders treatment (0,892)	Moderate
6	Antiprotozoal (Plasmodium) (0,966)	Strong	Phobic disorders treatment (0,838)	Moderate
7	Postmenopausal disorders treatment (0,902)	Strong	Cardiotonic (0,878)	Moderate
8	Renal disease treatment (0,960)	Strong	Heart failure treatment (0,946)	Strong
9	Anxiolytic (0,973) Antiallergic (0,957) Antipsychotic (0,952) Psychotropic (0,951)	Strong Strong Strong Strong	Antiasthmatic (0,950) Antiinflammatory (0,945) Antiarthritic (0,921) Phobic disorders treatment (0,913)	Strong Strong Strong Strong
10	Psychotropic (0,971)	Strong	Phobic disorders treatment (0,894)	Moderate
11	Phobic disorders treatment (0,886)	Moderate	Kidney function stimulant (0,727)	Weak
12	Phobic disorders treatment (0,871)	Moderate	Kidney function stimulant (0,674)	Weak
13	Antibiotic Glycopeptide-like (0,792)	Weak	Biliary tract disorders treat. (0,772)	Weak
14	Antineoplastic (liver cancer) (0,932)	Strong	Anesthetic general (0,769)	Weak
15	Antiparkinsonian (0,958) Neurodegenerative diseases treatment (0,939)	Strong Strong	Anxiolytic (0,946) Psychotropic (0,876)	Strong Moderate
16	Postmenopausal disorders treatment (0,954)	Strong	Phobic disorders treatment (0,886)	Moderate

Table 1: Predicted Biological Activity of triprimanes (1-16)

Using the PASS (*Prediction of Activity Spectra for Substances*) program, a number of intriguing and, in some cases, unexpected trends in predicted biological activity were observed [26-30]. One of the most notable findings was that primans-despite bearing chemically distinct functional groups (thiol, hydroxyl, and hydroperoxy, respectively)—exhibited identical qualitative activity spectra, with only minor differences in predicted activity intensities. This observation suggests that, within the rigid prismane framework, these substituents may occupy functionally equivalent spatial positions relative to key pharmacophoric features, leading to similar biological response profiles. Such behavior highlights the dominant role of the prismane scaffold itself in shaping activity, rather than the specific nature of certain polar substituents (the structures are shown in Figures 2-4, and the activities of these structures are shown in Tables 1-3).

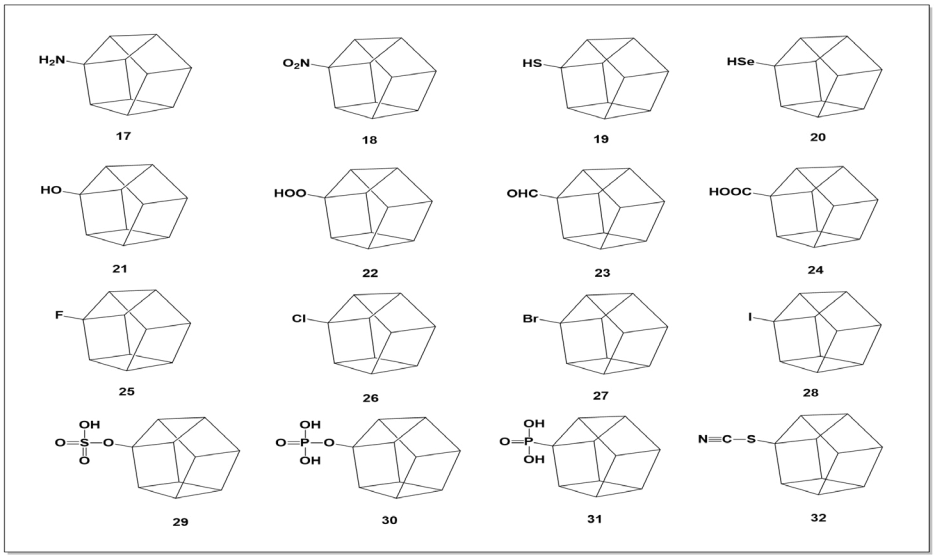

Figure 3: Pentaprismane, or -prismane ($C_{10}H_{10}$), is a highly strained, symmetrical polycyclic cage hydrocarbon consisting of two cyclopentane rings connected by five cyclobutane rings

Despite its extreme strain and compact geometry, pentaprismane can accommodate a range of substituents without loss of structural integrity. Functionalized and halogenated derivatives highlight the potential of this rigid scaffold for systematic structure–property studies and for exploring shape-driven effects in molecular and medicinal design. A pronounced antiprotozoal activity against *Plasmodium* species was predicted for several series of primans, including amino-substituted compounds **1, 17**, and **33**, nitro derivatives **2, 18**, and **34**, as well as hydroxyl- and hydroperoxy-containing analogues **5, 21, 37** and **6, 22, 38**, respectively. The consistency of this activity across multiple substitution patterns and prismane generations suggests that these compounds may interfere with conserved biochemical pathways in protozoan parasites, potentially through membrane interactions or redox-related mechanisms.

No	Predicted Activity, Ra	Rank	Additional Activity, Ra	Rank
17	Antiprotozoal (Plasmodium) (0,921)	Strong	Phobic disorders treat. (0,851)	Moderate
18	Antiprotozoal (Plasmodium) (0,917)	Strong	Phobic disorders treat. (0,798)	Weak
19	Phobic disorders treatment (0,852)	Moderate	Kidney function stimulant (0,806)	Weak
20	Antiparkinsonian (0,955) Alzheimer's disease treatment (0,938) Neurodegenerative diseases treat. (0,926)	Strong Strong Strong	DNA intercalator (0,978) Antioxidant (0,969) Apoptosis agonist (0,958)	Strong Strong Strong
21	Antiprotozoal (Plasmodium) (0,909)	Strong	Phobic disorders treat. (0,822)	Moderate
22	Antiprotozoal (Plasmodium) (0,931)	Strong	Phobic disorders treat. (0,789)	Weak
23	Postmenopausal disorders treat. (0,887)	Moderate	Cardiotonic (0,851)	Moderate
24	Renal disease treatment (0,960)	Strong	Heart failure treatment (0,946)	Strong
25	Anxiolytic (0,954) Antipsychotic (0,938)	Strong Strong	Antiasthmatic (0,929) Antiinflammatory (0,933)	Strong Strong
26	Psychotropic (0,962)	Strong	Phobic disorders treat. (0,844)	Moderate
27	Phobic disorders treatment (0,811)	Weak	Kidney function stimulant (0,727)	Weak
28	Phobic disorders treatment (0,787)	Weak	Kidney function stimulant (0,674)	Weak
29	Antibiotic Glycopeptide-like (0,792)	Weak	Biliary tract disorders treat(0,772)	Weak
30	Antineoplastic (liver cancer) (0,961)	Strong	Anesthetic general (0,876)	Moderate
31	Antiparkinsonian (0,972) Neurodegenerative diseases treat. (0,961)	Strong Strong	Anxiolytic (0,977) Psychotropic (0,894)	Strong Moderate
32	Postmenopausal disorders treat. (0,932)	Strong	Phobic disorders treat. (0,856)	Moderate

Table 2: Predicted Biological Activity of fiveprimanes (17-32)

In addition, carboxylated primans **8, 24**, and **40** displayed strong predicted activity associated with the treatment of kidney-related disorders, indicating a possible role in renal modulation or nephroprotective mechanisms. Aldehyde-containing primans **7, 23**, and **39**, together with thiocyanate derivatives **16, 32**, and **48**, were predicted to possess significant activity relevant to the management of postmenopausal disorders, suggesting potential interactions with hormonal regulation or metabolic pathways. Particularly noteworthy—and of high relevance to both medicinal chemists and pharmacologists—was the observation that selenol-containing primans **4, 20**, and **36**, as well as phosphonate-bearing derivatives **15, 31**, and **47**, demonstrated strong predicted activity related to antiparkinsonian effects, Alzheimer's disease, and broader neurodegenerative disorders. Given the increasing demand for novel therapeutic strategies targeting neurodegeneration, these results are especially compelling. The combination of a rigid, strain-rich prismane core with redox-active (selenol) or phosphorus-containing functionalities may enable unique interactions with neural targets, oxidative stress pathways, or enzyme systems implicated in neurodegenerative disease progression. Overall, these PASS-based predictions underscore the value of prismane derivatives as model structures for probing structure–activity relationships in diverse therapeutic areas, particularly infectious diseases and neurodegenerative disorders. While these findings require experimental validation, they strongly support further in vitro and in vivo investigations of selected primans as promising lead structures.

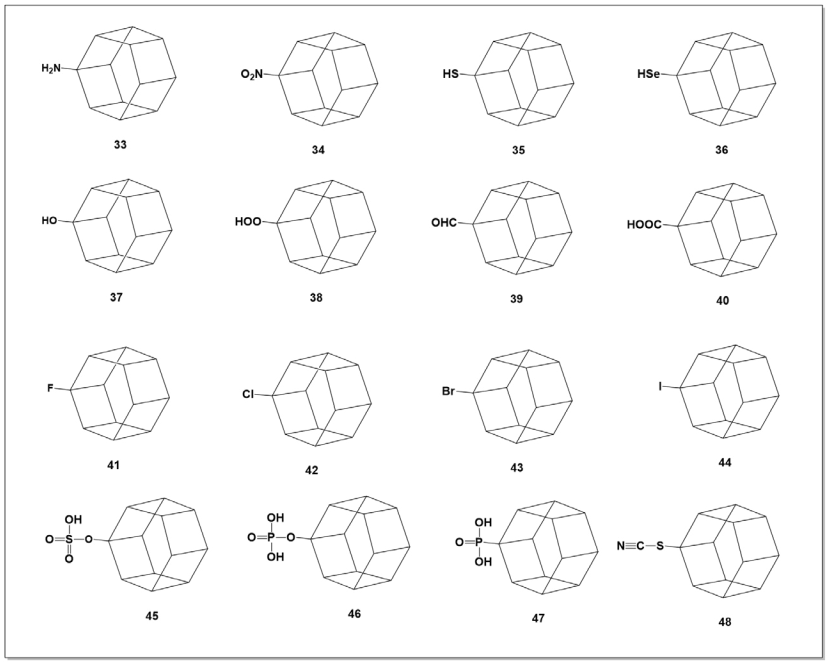

Figure 4: Hexaprismane, or [6]-prismane, is a theoretical, highly strained heptacyclic saturated hydrocarbon ($C_{12}H_{12}$) with D_6h symmetry

It consists of twelve methine units arranged in a regular hexagonal prism and can be structurally regarded as a face-to-face dimer of benzene. Computational studies predict exceptional rigidity and uniform strain distribution within the cage, making hexaprismane an extreme example of conformationally locked molecular architecture. Although not yet realized experimentally, this framework provides a valuable conceptual model for understanding the limits of rigidity and symmetry in scaffold design.

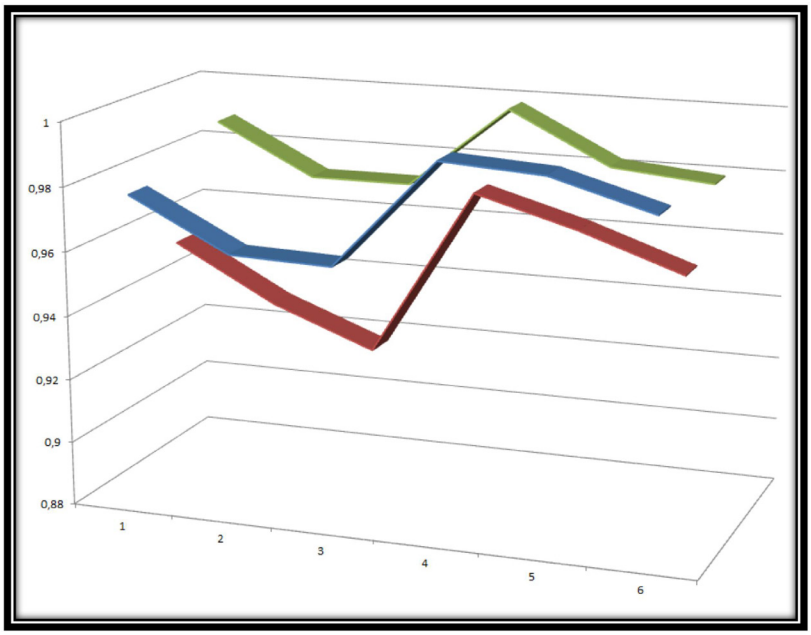

Figure 5: Comparative activity of selenium derivatives, (1*R*,2*R*,3*R*,5*S*,6*S*)-prismane-1-selenol (**4**, blue line), pentaprismane (**20**, red line), and hexaprismane (**36**, green line), based on the data presented in Tables 2–4

Activity of various prismanes (3, 5, and 6) demonstrates strong antiparkinsonian, Alzheimer's, and broader neurodegenerative effects. The observed differences in activity across the series highlight the influence of scaffold size, symmetry, and rigidity on biological response. Notably, selenium incorporation appears to enhance neuroprotective profiles, suggesting a synergistic role

between the redox-active substituent and the conformationally locked prismane frameworks. These results support rigid prismane scaffolds as promising platforms for the development of neurotherapeutic agents.

No	Predicted Activity, Ra	Rank	Additional Activity, Ra	Rank
33	Antiprotozoal (Plasmodium) (0,911)	Strong	Phobic disorders treat. (0,836)	Moderate
34	Antiprotozoal (Plasmodium) (0,904)	Strong	Phobic disorders treat. (0,854)	Moderate
35	Phobic disorders treatment (0,834)	Moderate	Kidney function stimulant (0,789)	Weak
36	Antiparkinsonian (0,988) Alzheimer's disease treatment (0,972) Neurodegenerative diseases treat. (0,972)	Strong Strong Strong	DNA intercalator (0,998) Antioxidant (0,982) Apoptosis agonist (0,979)	Strong Strong Strong
37	Antiprotozoal (Plasmodium) (0,923)	Strong	Phobic disorders treat. (0,856)	Moderate
38	Antiprotozoal (Plasmodium) (0,934)	Strong	Phobic disorders treat. (0,823)	Moderate
39	Postmenopausal disorders treat. (0,847)	Moderate	Cardiotonic (0,838)	Moderate
40	Renal disease treatment (0,941)	Strong	Heart failure treatment (0,904)	Strong
41	Anxiolytic (0,981) Antipsychotic (0,965)	Strong Strong	Antiasthmatic (0,933) Antiinflammatory (0,929)	Strong Strong
42	Psychotropic (0,971)	Strong	Phobic disorders treat. (0,868)	Moderate
43	Phobic disorders treatment (0,855)	Moderate	Kidney function stimulant (0,732)	Weak
44	Phobic disorders treatment (0,838)	Moderate	Kidney function stimulant (0,689)	Weak
45	Antibiotic Glycopeptide-like (0,748)	Weak	Biliary tract disorders treat(0,798)	Weak
46	Antineoplastic (liver cancer) (0,943)	Strong	Anesthetic general (0,733)	Weak
47	Antiparkinsonian (0,966) Neurodegenerative diseases treat. (0,953)	Strong Strong	Anxiolytic (0,953) Psychotropic (0,889)	Strong Moderate
48	Postmenopausal disorders treat. (0,949)	Strong	Phobic disorders treat. (0,896)	Moderate

Table 3: Predicted Biological Activity of -primanes (33-48)

4. Proposed Mechanistic Hypotheses for the Neurodegenerative Activity of Prismane Derivatives

The strong predicted antiparkinsonian, anti-Alzheimer's, and general neuroprotective activities observed for selected prismane derivatives—particularly the selenol-containing primans 4, 20, and 36 and the phosphonate-bearing compounds 15, 31, and 47—may be rationalized through several complementary mechanistic hypotheses. First, the rigid, highly strained three-dimensional prismane scaffold imposes a fixed spatial orientation of substituents, which may facilitate selective interactions with neuronal enzymes, receptors, or transport proteins. Unlike flexible aliphatic systems, prismane derivatives present functional groups in well-defined geometries, potentially enhancing binding specificity and reducing off-target interactions. This rigidity is particularly relevant for neurological targets, where subtle stereoelectronic effects often govern ligand recognition [31]. Second, selenol-substituted primans may exert neuroprotective effects through redox-modulating mechanisms. Selenium-containing compounds are well known for their involvement in antioxidant defense, often mimicking or modulating the activity of glutathione peroxidases and thioredoxin reductases [32-34]. In the context of neurodegeneration—where oxidative stress, mitochondrial dysfunction, and reactive oxygen species (ROS) play central pathogenic roles—selenol groups may contribute to ROS scavenging, metal chelation, or regulation of redox-sensitive signaling pathways. The rigid prismane core may further stabilize such redox-active substituents, enhancing their functional persistence in biological environments [32,35].

Third, phosphonate-containing primans are structurally reminiscent of biologically relevant phosphate esters and may act as bioisosteres of endogenous phosphorylated metabolites [36-38]. This structural similarity suggests potential interactions with enzymes involved in phosphorylation-dependent signaling cascades, such as kinases or phosphatases, which are critically implicated in Alzheimer's disease and Parkinson's disease pathology [39-42]. Moreover, phosphonate groups are known to improve metabolic stability and blood–brain barrier permeability in certain contexts, potentially enhancing central nervous system exposure [43-45].

Additionally, both selenium- and phosphorus-containing primans may influence neuroinflammatory pathways, which are increasingly recognized as central contributors to neurodegenerative disease progression. Modulation of microglial activation, cytokine signaling, or NF-κB-related pathways could underlie the predicted neuroprotective effects observed in the PASS analysis. Finally, the high strain energy and unique topology of the prismane skeleton may enable interactions with hydrophobic domains of membrane proteins or lipid bilayers, potentially affecting neurotransmitter release, synaptic plasticity, or membrane-associated enzymatic processes. Such interactions may be particularly relevant in Parkinson's disease, where dopaminergic neuron membrane integrity and mitochondrial membrane function are compromised

[46-48]. Taken together, these hypotheses suggest that the neurodegenerative activity predicted for selected prismane derivatives likely arises from a multifactorial mechanism, combining scaffold-driven spatial precision with redox activity, phosphorylation mimicry, and modulation of oxidative and inflammatory pathways. While these interpretations remain speculative and require experimental validation, they provide a coherent framework for prioritizing prismane-based compounds in future in vitro neuroprotection assays, enzyme inhibition studies, and in vivo models of neurodegeneration.

5. Comparison with Adamantane- and Memantine-Based Neuroprotective Mechanisms

The predicted antiparkinsonian, anti-Alzheimer's, and neuroprotective activities of selected prismane derivatives gain additional significance when considered in the context of clinically established adamantane-based drugs, most notably amantadine and memantine. Both compounds share a rigid, cage-like hydrocarbon scaffold that has proven particularly effective in targeting central nervous system (CNS) pathways, thereby providing a useful mechanistic benchmark for evaluating prismane-based systems [48-50]. Adamantane derivatives exert their neuropharmacological effects primarily through modulation of ion channels and neurotransmitter systems. Amantadine is known to enhance dopaminergic signaling and inhibit NMDA-type glutamate receptors, contributing to its clinical efficacy in Parkinson's disease. Memantine, a second-generation amino-adamantane, functions as a low-to-moderate affinity, uncompetitive NMDA receptor antagonist, preferentially blocking pathological glutamate overactivation while preserving physiological synaptic transmission [51-53]. This mechanism reduces excitotoxic neuronal damage, a hallmark of Alzheimer's disease and other neurodegenerative disorders.

In comparison, prismane derivatives share key structural features with adamantanes, including high rigidity, saturated carbon frameworks, and three-dimensional cage-like geometry. However, prismane scaffolds are more strained and geometrically constrained, resulting in a distinct spatial presentation of functional groups. This difference may lead to altered binding modes at ion channels, receptors, or enzyme active sites, potentially enabling interactions inaccessible to the more flexible adamantane skeleton. Notably, the strong predicted neurodegenerative activity of selenol- and phosphonate-substituted primans suggests mechanistic extensions beyond classical NMDA receptor antagonism. While amino-adamantanes rely primarily on ion-channel modulation, prismane derivatives may combine receptor-level effects with redox regulation and metabolic pathway interference. Selenium-containing primans, for example, may introduce antioxidant and mitochondrial-protective properties absent in memantine, while phosphonate-bearing primans may act as phosphate bioisosteres, influencing kinase- or phosphatase-mediated signaling involved in tau phosphorylation and synaptic dysfunction [54-56]. Furthermore, the rigid cubic-like topology of prismane may enhance selectivity toward pathological receptor states, analogous to memantine's voltage-dependent NMDA blockade, but through alternative steric or electrostatic mechanisms. PASS predictions indicating strong activity against Parkinson's disease, Alzheimer's disease, and general neurodegeneration suggest that prismane derivatives may operate as multimodal neuroprotective agents, in contrast to the more target-focused adamantane drugs. Importantly, unlike adamantane derivatives—whose clinical activity is largely confined to amino-substituted frameworks—prismane derivatives exhibit predicted neuroactivity across a broader range of functional groups, including selenols, phosphonates, and hydroxylated variants. This observation supports the notion that the prismane scaffold itself plays an active role in shaping biological response, rather than merely serving as a passive hydrophobic carrier. In summary, while adamantane- and memantine-based drugs validate the therapeutic relevance of rigid hydrocarbon cages in neurodegenerative disease, prismane derivatives represent a next-generation extension of this concept. Their enhanced rigidity, higher strain energy, and expanded functional-group compatibility may enable novel mechanisms of neuroprotection, potentially combining NMDA modulation, redox homeostasis, mitochondrial stabilization, and phosphorylation control within a single molecular framework. These features position prismane scaffolds as promising candidates for further experimental investigation alongside established adamantane pharmacophores [57].

5.1. Interrelationship of the Predicted Disease Activities

At first glance, the spectrum of predicted activities observed for fluoride-containing Primant-3—including anxiolytic, antiallergic, antipsychotic, psychotropic, antiasthmatic, anti-inflammatory, antiarthritic, and phobic disorder–related effects—may appear unusually broad. However, accumulating evidence from neurobiology, immunology, and psychoneuroimmunology indicates that these disease categories are not independent, but instead are biologically interconnected through shared molecular and signaling pathways.

5.2. Neuroinflammation as a Central Link

A key unifying mechanism linking psychiatric, neurological, allergic, and inflammatory disorders is chronic low-grade inflammation, particularly neuroinflammation. Disorders such as anxiety, phobic disorders, psychosis, and mood dysregulation are now recognized to involve dysregulated cytokine signaling, microglial activation, and oxidative stress within the central nervous system [58-60]. Elevated levels of pro-inflammatory mediators (e.g., TNF-α, IL-1β, IL-6) have been documented both in psychiatric conditions and in systemic inflammatory diseases such as asthma and arthritis [61-63]. Accordingly, compounds with predicted anti-inflammatory and immunomodulatory activity may exert secondary benefits on neuropsychiatric symptoms by reducing inflammatory signaling at both peripheral and central levels. This provides a plausible mechanistic explanation for the convergence of anxiolytic, antipsychotic, and anti-inflammatory activities predicted for Primant-3.

5.3. Shared Neurotransmitter and Immune Pathways

Psychotropic, antipsychotic, anxiolytic, and phobia-related activities are closely linked through dopaminergic, glutamatergic,

GABAergic, and serotonergic systems, which are themselves modulated by inflammatory and oxidative processes [64-67]. For example: (i) Dopamine dysregulation is implicated in psychosis, anxiety, and motivation-related disorders; (ii) Glutamate excitotoxicity contributes to both psychiatric and neurodegenerative pathology; (iii) Immune mediators influence synaptic plasticity and neurotransmitter release.

In parallel, allergic and asthmatic diseases share overlapping pathways involving mast cells, histamine release, and leukotriene signaling, which are increasingly recognized to interact with CNS function and behavior (the so-called neuroimmune axis). Thus, predicted antiallergic and antiasthmatic activities may not be independent from psychotropic or anxiolytic effects, but rather reflect modulation of common regulatory networks [68-70].

5.4. Systemic Inflammation and Comorbidity

Clinical and epidemiological studies consistently demonstrate high comorbidity between [71-73]: (i) Inflammatory diseases (asthma, arthritis); (ii) Psychiatric disorders (anxiety, depression, psychosis; (iii) stress-related and phobic conditions. Systemic inflammation can exacerbate psychiatric symptoms, while chronic psychological stress can intensify immune dysregulation. Therefore, a compound predicted to act at the intersection of immune regulation, CNS signaling, and inflammatory control may reasonably show activity across these domains [74-76].

5.5. Concluding Perspective

In summary, the disease categories associated with Primant-3 are biologically related through shared inflammatory, neuroimmune, and neurotransmitter-based mechanisms. The predicted activity profile is therefore coherent rather than contradictory, reflecting modulation of interconnected systems rather than isolated pharmacological effects. This integrated activity spectrum supports the inclusion of fluoride-containing Primant-3 as a high-priority candidate for preclinical investigation, particularly in studies addressing the interface between inflammation, immune regulation, and CNS function.

6.0. Fluorine-Containing Compounds are the Future of Medicine.

Over the last two decades, fluorine substitution has become one of the defining structural features of modern pharmaceuticals. Consequently, approximately half of the most successful drugs (blockbuster drugs) contain at least one fluorine atom. During the past 15 years, fluorine chemistry has evolved from a specialized subfield of organic chemistry into a major multidisciplinary research area, contributing to advances in health, food, and energy-related industries [77-79]. The remarkable electronic, physical, and biological properties of organofluorine compounds, along with their distinctive reactivity compared with non-fluorinated analogues, are widely exploited for technological innovation. In particular, the exceptional NMR properties of fluorine nuclei have enabled significant progress in diagnostic technologies, including magnetic resonance imaging (MRI), as well as in peptide and protein engineering. The latter relies on the design of tailor-made fluorinated amino acids and their strategic incorporation into peptide chains to achieve detailed three-dimensional insight into peptide–receptor interactions [80-83].

Positron emission tomography (PET), employing the ^{18}F radionuclide, represents another important technological advance enabled by fluorine chemistry. Nevertheless, the most prominent application of fluorine remains the design of new pharmaceutical agents and formulations. Remarkably, fluorine-containing compounds account for more than 50% of blockbuster drugs, generating considerable interest within the organic chemistry community. Indeed, medicinal applications of novel organic molecules have long served as a major driving force for the development of new organic methodologies [84-87]. Accordingly, chemists closely follow advances in pharmaceutical research, with particular attention to molecular design strategies and therapeutic targets. We were very discouraged by the fact that-fluoride-containing prismane (**9**, Figure 2) demonstrated remarkable activity across eight different activities, including anxiolytic, antiallergic, antipsychotic, psychotropic, antiasthmatic, antiinflammatory, antiarthritic, and phobic disorders, which was not observed for - (**25**) or -prismanes (**41**). Comparative activity is presented in Figure 6.

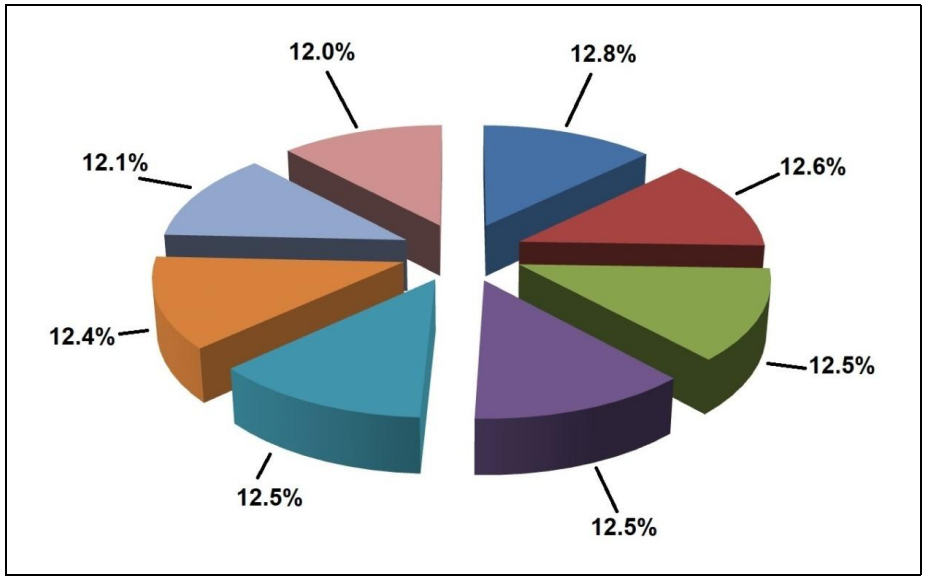

Figure 6: Percentage distribution of the eight biological activities exhibited by the [3]-fluoride-containing prismane (9) across distinct therapeutic areas, including anxiolytic (12.8%), antiallergic (12.6%), antipsychotic (12.5%), psychotropic (12.5%), antiasthmatic (12.5%), anti-inflammatory (12.4%), antiarthritic (12.1%), and phobic (12.0%) activities

The near-uniform distribution of activity suggests a broad and balanced pharmacological profile rather than dominance of a single therapeutic effect. This multimodal behavior may reflect the influence of fluorine substitution on target engagement and bioavailability within the rigid prismane scaffold.

6.1. Interpretation of Pass Predictions

The high PASS probabilities observed for fluoride-containing Primant-3 suggest that this compound may interact with fundamental regulatory pathways rather than single disease-specific targets. Such a profile is characteristic of pleiotropic or multi-target agents, which are increasingly valued in the context of complex, multifactorial disorders. Importantly, these predictions do not imply confirmed clinical efficacy, but rather identify Primant-3 as a promising lead structure for further experimental validation. The convergence of neuropsychiatric, anti-inflammatory, and immunomodulatory activities highlights its potential relevance for diseases characterized by neuroimmune and inflammatory overlap, including anxiety disorders with somatic components, stress-associated inflammatory conditions, and chronic inflammatory diseases with neuropsychiatric comorbidity.

6.2. The Neuro–Immune–Inflammatory Axis as a Unifying Framework

The convergence of predicted neuropsychiatric, anti-inflammatory, antiallergic, and immunomodulatory activities observed for several primane derivatives—particularly fluoride-containing Primant-3—can be rationalized within the framework of the neuro–immune–inflammatory axis. This axis describes the bidirectional and tightly regulated communication between the central nervous system, the immune system, and inflammatory signaling networks [88-91]. Peripheral immune activation leads to the release of cytokines, chemokines, and lipid mediators that can cross the blood–brain barrier or signal through vagal and humoral pathways, thereby influencing neurotransmitter balance, synaptic plasticity, and neuronal excitability. Conversely, central nervous system signaling modulates immune responses through neuroendocrine pathways, including the hypothalamic–pituitary–adrenal (HPA) axis and autonomic regulation. Dysregulation of this axis has been implicated in a wide spectrum of disorders, ranging from anxiety, psychosis, and neurodegenerative diseases to asthma, arthritis, and allergic conditions [92-96]. Compounds capable of modulating inflammatory mediators, oxidative stress, and neuronal signaling simultaneously may therefore exert pleiotropic biological effects across multiple disease categories. Within this conceptual model, primane derivatives with high predicted activity across neuropsychiatric and inflammatory domains may act as multi-target regulators of the neuro–immune–inflammatory interface, providing a mechanistic basis for their broad predicted pharmacological profiles.

7. Twistane and its Biological Activity

Twistane represents a topologically distinct yet conceptually related rigid hydrocarbon scaffold, in which cyclobutane-like subunits are fused into a conformationally locked, helical architecture. Although twistane does not contain an isolated cyclobutane ring, its carbon framework is composed of interconnected four-membered-ring junctions that impose severe geometric constraints. These constraints result in intrinsic chirality and exceptional rigidity, distinguishing twistane from other diamondoid hydrocarbons. Importantly, the absence of conformational flexibility makes twistane an ideal model system for probing stereochemical and topological effects that arise independently of substituent-induced asymmetry [97-99]. Twistane (tricyclo[4.4.0.0^{3},^{8}] decane, see Figure 7) is a saturated tricyclic hydrocarbon with the molecular formula $C_{10}H_{16}$ and is a constitutional isomer of

adamantane. In contrast to the highly symmetrical and achiral adamantane framework, twistane is inherently chiral and exists as a pair of enantiomers ((+) and (–) forms). Its carbon skeleton is forced into a twisted, boat-like conformation, leading to higher internal strain than adamantane due to deviations from the ideal tetrahedral bond angle (~109.5°) [100,101]. Twistane was first synthesized and structurally characterized by Whitlock in 1962 and has since attracted sustained interest as a model compound in theoretical chemistry, stereochemistry, and topology-driven structure–property relationships [102,103]. On the basis of its unique architecture, extended structures such as polywistane nanotubes—one-dimensional, helical, rigid polymers—have also been proposed theoretically. Given that twistane is an isomer of adamantane, it is instructive to compare their biological relevance. Adamantane derivatives—most notably amantadine (1-aminoadamantane), memantine (1-amino-3,5-dimethyladamantane), and rimantadine—are well-established pharmacophores used clinically for the treatment of Parkinson's disease, Alzheimer's disease, and, historically, influenza A. These compounds exert their biological effects primarily through ion-channel modulation (e.g., NMDA receptor antagonism in the case of memantine and M2 proton channel blockade in influenza A viruses) [49,50]. In contrast, twistane itself has not been used as a therapeutic agent; however, its rigid, chiral, and strain-rich framework makes it an attractive model scaffold for exploring structure–activity relationships in comparison to adamantane-based drugs.

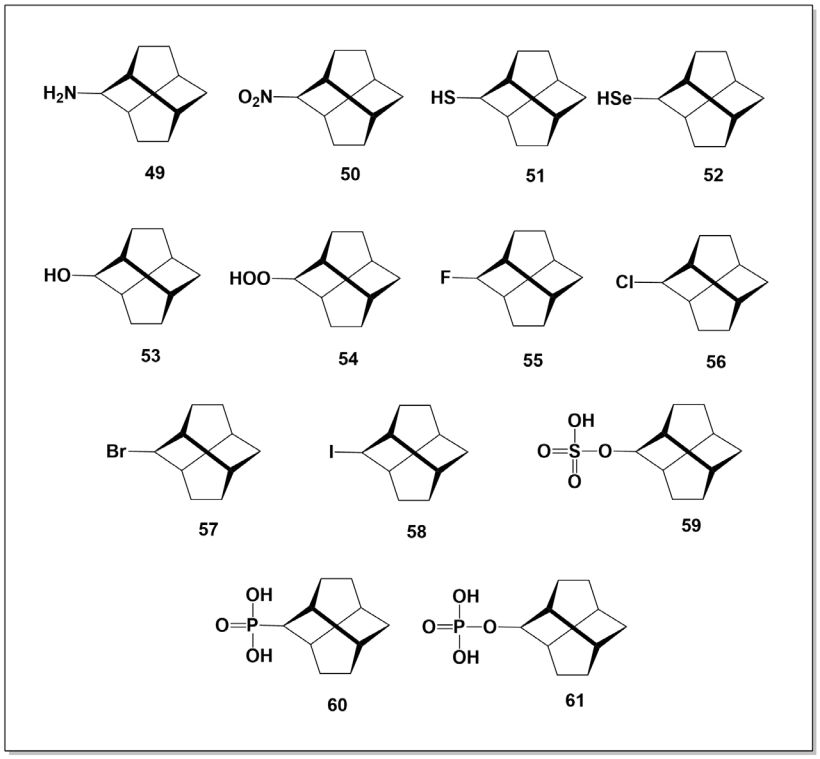

Figure 7: Twistane is an isomer of adamantane and a conceptually related rigid hydrocarbon framework

Various functionalized and halogenated derivatives of twistane highlight the potential of this structure for systematic structure–property studies. The chiral, conformationally locked architecture of twistane offers defined three-dimensional vectors for substituent presentation, which is advantageous for probing steric and electronic effects in biological systems. As such, twistane represents a valuable complementary scaffold to adamantane in the design of rigid, shape-driven molecules for medicinal chemistry. Motivated by these considerations, we employed PASS-based in silico screening to investigate the potential biological activities of a series of twistane derivatives bearing various functional groups and halogen substituents (structures shown in Figure 7; predicted activities summarized in Table 5). Among the screened compounds, two twistane derivatives exhibited particularly notable predicted activities. Selenotwistane (52), identified as (1R,3R,6S,8S)-tricyclo[4.4.0.0^{3},^{8}]decane-2-selenol, demonstrated a very high predicted probability of activity as a DNA intercalator (Pa = 0.980). DNA intercalators are molecules capable of inserting between adjacent base pairs of double-stranded DNA, inducing structural distortions that interfere with replication, transcription, and DNA repair. Such mechanisms underlie the biological activity of several important anticancer agents (e.g., doxorubicin, actinomycin D) and antibiotics, as well as fluorescent probes used in molecular biology. While most known DNA intercalators are planar aromatic systems, the high predicted activity of a rigid, nonplanar twistane-based selenol is unexpected and suggests an alternative mode of DNA interaction, potentially involving redox activity or selenium-mediated binding.

No	Predicted Activity, Ra	Rank	Additional Activity, Ra	Rank
49	Phobic disorders treatment (0,910)	Strong	Acute neurologic disorders trea (0,742)	Moderate
50	Phobic disorders treatment (0,870)	Moderate	Antiviral (Arbovirus) (0,706)	Moderate
51	Phobic disorders treatment (0,836)	Moderate	Kidney function stimulant (0,749)	Weak
52	DNA intercalator (0,980)	Strong	Antioxidant (0,979)	Strong
53	Alzheimer's disease treatment (0,768) Neurodegenerative diseases treat. (0,752)	Weak Weak	Phobic disorders treatment (0,862) Kidney function stimulant (0,805)	Moderate Weak
54	Antiprotozoal (Plasmodium) (0,926)	Strong	Antineoplastic (0,774)	Moderate
55	Phobic disorders treatment (0,903)	Strong	Antidiabetic (type 2) (0,848)	Moderate
56	Phobic disorders treatment (0,895)	Moderate	Antiglaucomic (0,828)	Strong
57	Phobic disorders treatment (0,855)	Moderate	Kidney function stimulant (0,692)	Strong
58	Antineoplastic (0,945)	Strong	Angiogenesis inhibitor (0,888)	Moderate
59	Alzheimer's disease treatment (0,736) Neurodegenerative diseases treat. (0,729)	Weak Weak	Biliary tract disorders treat. (0,830)	Moderate
60	Stroke treatment (0,953)	Moderate	Phobic disorders treatment (0,794)	Weak
61	Neuroprotector (0,900)	Strong	Anesthetic general (0,818)	Moderate

Table 5: Predicted Biological Activity of twistanes (49-61)

A second compound of particular interest is (1*R*,3*R*,6*S*,8*S*)-tricyclo[4.4.0.0^{3,8}]decan-2-yl phosphonic acid (**60**), which showed strong predicted activity related to stroke treatment. Pharmacological management of stroke encompasses multiple therapeutic strategies, including modulation of thrombosis, neuroprotection, control of inflammation, and prevention of secondary neuronal damage. Phosphonic acid derivatives are known to interact with enzymes, receptors, and metal ions involved in vascular and neuronal processes. The predicted activity profile of twistane-phosphonic acid (**60**) suggests potential relevance as a multifunctional agent targeting vascular, inflammatory, and neuroprotective pathways. While these findings remain computational predictions, they position twistane-based phosphonates as promising candidates for further preclinical evaluation. Overall, these results highlight twistane as a valuable rigid and chiral scaffold for chemical biology and medicinal chemistry. When combined with appropriate functional groups, twistane derivatives may exhibit biological activity profiles that are complementary to, or distinct from, those of classical adamantane-based drugs. PASS-guided screening thus supports the use of twistane not as a replacement for established pharmacophores, but as an advanced model system for exploring topology-driven bioactivity and identifying unconventional leads for anticancer and neurovascular therapy. As summarized in Table 6, adamantane, prismane, and twistane represent three rigid hydrocarbon scaffolds occupying distinct regions of structural and biological space, differing markedly in symmetry, strain, chirality, and pharmacological precedent.

Feature	Adamantane	Prismane-3	Twistane
Chemical formula	$C_{10}H_{16}$	C_6H_6 (parent prismane); substituted derivatives	$C_{10}H_{16}$
Topological class	Diamondoid (tetrahedral network)	Polycyclic strained prism	Twisted tricyclic cage
Primary ring motifs	Fused cyclohexanes	Fused cyclobutanes (triangular prism)	Interconnected four-membered ring junctions
Geometric strain	Low (near ideal sp^3 angles)	Very high (≈90° bond angles)	Moderate–high (distorted tetrahedral angles)
Conformational flexibility	Rigid but symmetric	Extremely rigid	Extremely rigid
Chirality	Achiral	Achiral (parent), chiral upon substitution	Intrinsically chiral
Symmetry	Very high (T_d)	Moderate	Low
Occurrence in nature	Rare (mostly synthetic; diamondoid analogues known)	Detected in marine sediments and petroleum	Not known naturally
Synthetic accessibility	High	Moderate–challenging	Moderate
Known clinical drugs	Yes (amantadine, memantine, rimantadine)	None	None
Primary medical relevance	Neurodegenerative diseases, antiviral therapy	Emerging: oncology, neurodegeneration (in silico)	Emerging: oncology, stroke, neuroprotection (in silico)
Dominant biological mechanisms	Ion-channel modulation (NMDA, M2)	Predicted: redox, immune-inflammatory modulation	Predicted: DNA interaction, neurovascular regulation
Role in PASS modeling	Reference pharmacophore	High-strain comparator scaffold	Chiral rigid comparator scaffold
Bioisosteric potential	Proven benzene surrogate	Extreme rigidity model	Chirality-driven SAR model
Key advantage	Clinically validated scaffold	Maximum strain → unique bioactivity space	Intrinsic chirality without substituents
Key limitation	Overexplored chemical space	Synthetic difficulty	No clinical precedent

Table 6: Comparison of Rigid Hydrocarbon Scaffolds Used in Chemical Biology and Medicinal Chemistry

8. Natural Twistane-Containing Angucyclinones

Recent genomic analysis of the type II polyketide synthase biosynthetic gene cluster from the marine Streptomyces phaeochromogenes XSA2 by researchers at Shandong University (Qingdao, China) led to the discovery of pheomycin A, a secondary metabolite featuring a unique phthalide moiety linked to a rare twistane skeleton previously unknown in natural products. Bioinformatic insights enabled the proposal of a plausible biosynthetic pathway for the construction of this unusual framework [104]. This discovery strongly suggests that twistane-based architectures may represent an underexplored class of natural product scaffolds, and that further examples are likely to emerge from bacteria, fungi, and marine invertebrates as genome mining and metabolomic approaches continue to expand.

9. Conclusion

Rigid hydrocarbon scaffolds occupy a central yet still underexploited position in modern chemical biology and drug design. This review demonstrates that prismane and twistane represent fundamentally distinct rigid frameworks whose extreme geometric constraint, topological definition, and absence of conformational flexibility allow biological effects to be studied in a uniquely controlled manner. In contrast to flexible or semi-rigid pharmacophores, these scaffolds enable the disentanglement of topology-driven activity from conformational or substituent-driven effects. PASS-based in silico analysis reveals that functionalized prismanes and twistanes display rich and differentiated predicted biological activity profiles, including antiprotozoal, anti-inflammatory, neuroactive, psychotropic, and antineurodegenerative effects. Particularly noteworthy is the emergence of strong predicted activity for Parkinson's disease, Alzheimer's disease, stroke, and neurodegenerative disorders in selected derivatives, highlighting a convergence between neuropharmacology, inflammation, and immune regulation. These findings parallel, yet clearly extend beyond, the established pharmacological paradigms of adamantane derivatives such as amantadine and memantine, suggesting that alternative rigid topologies can access complementary or enhanced biological mechanisms. Mechanistically, the observed activity profiles support the hypothesis that rigid polycyclic scaffolds interact preferentially with ion channels, redox-sensitive enzymes, neuro–immune–inflammatory signaling pathways, and nucleic acid targets. The unique strain, chirality, and electronic distribution inherent to prismane and twistane may further promote selective target engagement and reduced off-target flexibility, features that are highly desirable in rational drug design. In summary, prismane and twistane should be regarded not merely as theoretical curiosities or structural isomers of adamantane, but as versatile and informative model systems for probing

structure–activity relationships governed by molecular rigidity and topology. Their integration with computer-aided prediction tools such as PASS provides a powerful strategy for prioritizing novel bioactive scaffolds prior to synthesis and experimental evaluation. Continued exploration of these frameworks is expected to yield valuable insights and potentially new therapeutic leads for neurodegenerative, inflammatory, infectious, and oncological diseases.

9.1. Future Perspectives

The results summarized in this review highlight rigid prismane and twistane scaffolds as promising platforms for the next generation of structure-guided drug discovery. Their extreme conformational rigidity, defined topology, and tunable functionalization make them particularly attractive for computer-aided drug design (CADD), where minimizing conformational noise is essential for reliable activity prediction, docking, and pharmacophore modeling.

Future work should prioritize the experimental validation of the most promising PASS-predicted activities, especially those related to neurodegenerative diseases, neuroinflammation, and immune–neurological crosstalk. In particular, prismane and twistane derivatives exhibiting strong predicted antiparkinsonian, anti-Alzheimer's, anxiolytic, and anti-inflammatory activity warrant focused in vitro and in vivo evaluation. These studies could clarify whether their mechanisms parallel known adamantane-based NMDA receptor antagonism, ion-channel modulation, or whether they engage alternative targets such as redox enzymes, neuroimmune mediators, or mitochondrial pathways.From a medicinal chemistry perspective, systematic exploration of substitution patterns, stereochemistry, and heteroatom incorporation will be critical to optimize pharmacokinetic properties and reduce potential toxicity associated with highly strained hydrocarbons. Advances in synthetic methodology, including selective functionalization and scalable routes to substituted prismanes and twistanes, will play a decisive role in enabling translational research. At a broader level, rigid polycyclic scaffolds such as prismane and twistane offer a conceptual bridge between theoretical stereochemistry, computational prediction, and practical drug discovery. Their use as proligand and promolecule models provides an opportunity to refine stereochemical descriptors, improve activity prediction algorithms, and develop topology-aware SAR frameworks. As interest grows in precision medicine and multitarget therapeutics, these scaffolds may contribute to the rational design of drugs that act along the neuro–immune–inflammatory axis, addressing complex disorders where single-target approaches have proven insufficient. In conclusion, the integration of rigid prismane and twistane frameworks with modern computational tools, synthetic chemistry, and biological validation represents a fertile and largely unexplored direction in chemical biology and medicinal chemistry, with significant potential for both fundamental insight and therapeutic innovation.

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