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Review Article

Diphenyl Methylene Derivatives as Emerging Drug Scaffolds: Chemistry, Pharmacology, and Future Opportunities

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ABSTRACT

Diphenylmethane and benzhydryl scaffolds are versatile structural frameworks in medicinal chemistry owing to their rigidity, lipophilicity, electronic adaptability, and potential for structural modification. Their presence in diverse bioactive molecules has stimulated interest in their application to drug discovery and pharmaceutical development. A structured literature search was conducted to examine the chemistry, structural characteristics, synthesis, functionalization, pharmacological activities, Structure-Activity Relationships (SAR), pharmacokinetic and toxicological properties, and emerging applications of diphenylmethane and related benzhydryl derivatives. Literature was identified through PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar using relevant combinations of keywords associated with diphenylmethane, diphenylmethylene, benzhydryl, medicinal chemistry, drug design, pharmacological activity, SAR, pharmacokinetics, toxicity, prodrug strategies, green synthesis, and nanotechnology. The reviewed evidence highlights conventional synthetic approaches, including Grignard reactions, Friedel-Crafts alkylation, and benzophenone reduction, as well as microwave-assisted, solvent-free, photocatalytic, electrochemical, and biocatalytic methods. Aromatic and benzylic functionalization enables substitution, cyclization, rearrangement, and metal coordination. Derivatives demonstrate antimicrobial, anticancer, anti-inflammatory, antioxidant, neuroprotective, antiviral, and enzyme-inhibitory activities. SAR studies indicate that substituent identity and position influence biological potency, while pharmacokinetic and toxicological properties vary substantially with molecular structure. Emerging applications include computational drug design, QSAR, molecular docking, prodrug development, nanotechnology, and sustainable synthesis. Diphenylmethane and benzhydryl scaffolds remain valuable platforms for therapeutic lead development. Future research should emphasise validated SAR, target-specific mechanisms, quantitative ADME-toxicity assessment, safety, selectivity, and sustainable synthesis to facilitate translational pharmaceutical development.

Keywords: Diphenyl methylene, Drug design, Neuroprotective scaffolds, Pharmacokinetics, Prodrug strategies.

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INTRODUCTION

Drug design is interdisciplinary and rapidly developing in the pharmaceutical sciences with the goal of determining and optimising the bioactive compounds with therapeutic utility. This is done by the rigorous construction, formulation and innovation of chemical substances in order to manipulate a given biological target, e.g. influence on proteins or fermentations linked with disease processes.[1,2] Diphenyl methylene scaffolds are a distinctive genre of organic frameworks with a methylene ($-CH_2-$) group in the middle and surrounded by two phenyl groups. The unique structure which gives rise exceptional chemical versatility, rigidity as well as lipophilicity not only represents a useful Dieckmann core in synthesis but also in medicinal chemistry (Figure 1).[1,3] Conjugation of the phenyl groups with the central methylene atom enables the electron delocalization, the impact of which on the reactivity and the possible interaction with the biological targets should be considered.[3,4] On account of their attractive physicochemical characteristics, the diphenyl methylene derivatives have been vastly investigated in an extensive variety of applications, as

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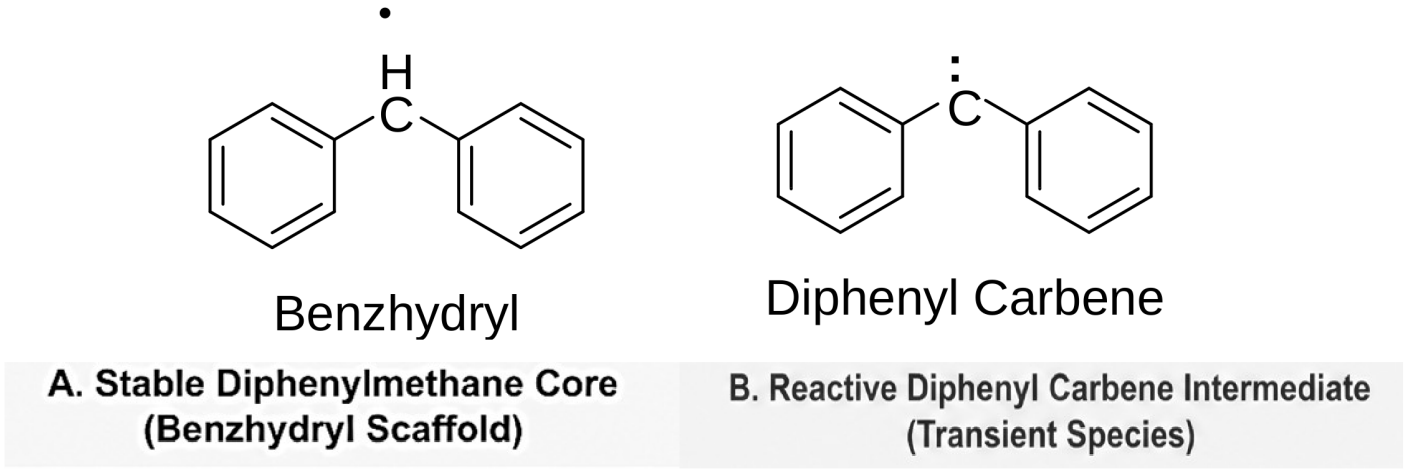


Figure 1: Distinction between the stable diphenylmethane core and the reactive diphenyl carbene intermediate. (A) Stable diphenylmethane (benzhydryl) scaffold, in which the central carbon is present as a methylene (-CH_2-) group linking two phenyl rings. (B) Reactive diphenyl carbene intermediate, a transient species characterised by a divalent carbon centre bearing a lone pair of electrons and bonded to two phenyl groups. The figure highlights the structural distinction between the stable diphenylmethane framework and the highly reactive carbene intermediate.

intermediates in organic conjugation, as ligands in coordination, and as drug or pharmacophores in drug discovery. Their occurrence in different bioactive compounds, in particular, anticancer, antimicrobial, anti-inflammatory and neuroactive bioactivities, has attracted more and more research interests by various scientists on ways to design new medicines.[5,6] The modifiability of the scaffold along with both aromatic rings and the methylene core, provides an abundant basis for structural optimisation, facilitating finely tuning of the biological activity and pharmacokinetic characteristics. Research on diphenyl methylene structures is thus ongoing in the discovery of new chemicals in various areas of therapeutic concern.[5,7]

Diphenyl methylene scaffolds the early history of research into the use of diphenyl methylene scaffolds can be traced back to the relatively early years of organic chemistry when synthetic chemists were first interested in the unusual structural characteristics of these scaffolds. These scaffolds were originally investigated as stable carbenes and reaction intermediates of dye and polymer synthesis, but now have become very common groups in medicinal and pharmaceutical chemistry.[8,9] Their chemical reactivity especially in electrophile and nucleophile substitutions reactions brought additional potentials in the synthesis of biologically active complex molecules. During the decades synthetic developments have allowed the widespread use of such diphenyl methylene functions in many heterocyclic systems and hybrid structures, often greatly extending their utility. Due to the pharmacological profile, the scaffold assumed significance as scientists started to note the occurrence of molecules with high anticancer, antibacterial and neuroprotective effects.[10] It is highly lipophilic (due to structural rigidity and the potential of being largely functionalized), which is preferential for binding a wide range of biological targets. Consequently, diphenyl methylene scaffolds have been taken to be part of leading compounds in drug discovery with their long-term relevance in academic research and innovation in pharmaceuticals.

This review provides a detailed and current examination of recent breakthroughs in chemistry and pharmacology associated with diphenyl methylene scaffolds. It covers the basic chemistry and synthesis methods, functional derivatization and the extensive biological activity explored by these substances. Particular attention is paid to their importance in the process of drug design, such as Structure-Activity Relationship (SAR) knowledge, pharmacokinetics and new therapeutic uses.[11] Indicators of future events, like green synthesis, formulations through nanotechnology and modelling techniques, also form a part of the review. The purpose of this article is to present and discuss the versatility of the scaffold, outline gaps in existing knowledge, and suggest future directions for its use to the fullest in chemical and biomedical research. The final goal is to serve as a resource for researchers, medicinal chemists, and pharmaceutical scientists involved in the development of innovative therapeutics that include diphenylmethylene structures.

METHODOLOGY

A structured literature search was conducted to identify relevant published information on the chemistry, synthesis, structural characteristics, functionalization, biological activities, Structure-Activity Relationships (SAR), pharmacokinetic properties, toxicological aspects, and emerging pharmaceutical applications of diphenylmethane/diphenylmethylene derivatives. Relevant literature was identified through searches of PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. The search was performed using combinations of keywords and Boolean operators, including "diphenylmethane," "diphenylmethylene,"

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"benzhydryl," "diphenylmethane derivatives," "medicinal chemistry," "drug design," "structure-activity relationship," "SAR," "pharmacological activity," "anticancer," "antimicrobial," "anti-inflammatory," "neuroprotective," "pharmacokinetics," "toxicity," "prodrug," "green synthesis," and "nanotechnology."

Structure and Geometry

Diphenyl methylene scaffolds the starting point of diphenyl methylene scaffolds is a central methylene (-CH_2 -) bridge connecting two phenyl rings, which imparts a characteristic structural motif that has a major steric and electronic impact. Geometry A good part of the geometry of this scaffold is dictated by the spatial positioning of the two bulky aromatic rings around the methylene carbon, which is sp^3-hybridized in most stable derivatives. Such a structure is prone to taking a non-planar, twisty form because of steric interaction between the ortho-hydrogen atoms on opposing phenyls and a dihedral angle between the planes of the two aromatic rings is often evident.[12,13] The conformational bulkiness added by the diphenyl substituent also limits intrinsic flexibility and may be of benefit in drug design because it increases specificity by boosting target selectivity and limiting the entropic cost of binding. In addition, additional functional groups electronically attached to the phenyl rings (e.g. electron-donating or electron-withdrawing groups) can greatly affect the distribution of electron density throughout the structure, affecting reactivity and biological behavior. This is because the central carbon has a sp^2-like character in some reactive intermediates (like the diphenyl carbenes), and these have a planar or nearly planar geometry, where the electrons are delocalized between the aromatic systems. It is this dual capability of conformational rigidity and electronic tunability that lends to the interest of the scaffold both in the fields of synthetic chemistry as well as drug research.

Chemical Features and Synthetic Strategies

The class of diphenyl methylene derivatives has as its core a methylene carbon flanked by two phenyl groups to provide a unique scaffold with both steric mass and conjugative capability. The aromatic rings are highly electronegative, and the methylene group is an electron donor, making the reactivity unusual. This scaffold is relatively stiff, with a torsion angle between the two phenyl rings that is freely rotatable depending upon the substitution pattern, and influences both electronic delocalization and recognition by biological systems. The introduction of substituents in the ortho-, meta- or para-positions of the phenyl rings can have a profound effect on the physical characteristics, pharmacokinetics and pharmacodynamics of the substance, including lipophilicity, electronic character as well as steric environment which may then be used to modulate the bioactivity characteristics of the substance (Figure 2).[14]

(A) Parent diphenylmethane (benzhydryl) scaffold, consisting of two phenyl rings linked through a methylene carbon. (B) Representative benzhydryl (diphenylmethane) derivatives, including diphenylmethanol, diphenylmethyl chloride, and substituted diphenylmethane analogues bearing methoxy, trifluoromethyl, and nitro groups. (C) Selected pharmacologically relevant benzhydryl-containing compounds, including diphenhydramine, cetirizine, cinnarizine, trifluoperazine, ebastine, fexofenadine, clofepramine, meclizine, fluoxetine, and tamoxifen, illustrating the incorporation of the benzhydryl/diphenylmethyl motif into diverse therapeutic agents. The figure highlights the structural diversity and pharmacological significance of the diphenylmethane/benzhydryl scaffold.

Common Synthetic Approaches

There are a number of classical and more modern methodologies to the synthesis of diphenyl methylene derivatives. A common way of preparing it is by reacting benzophenone with reducing agents like zinc amalgam in acid and this results in the formation of diphenylmethanol; this may further be used to form the methylene derivative by dehydration or halogenation and subsequent dehydrohalogenation.[15,16] The second method involves of Grignard reagents, in which phenyl magnesium bromide is reacted with formaldehyde to produce diphenylmethanol, which in further steps can be transformed into the respective methylene structure. Otherwise, diphenylmethane and its analogues can also be obtained through Friedel Crafts alkylation of benzene derivatives in the presence of formaldehyde and acidic conditions.[16] Lately, the organocatalytic and microwave-assisted methods have been integrated into these syntheses to simplify them.

Functionalization Techniques

The possibility of the presence of two reactive benzene rings and a functionalizable methylene bridge makes the species by diphenyl methylene scaffolds versatile chemically functionalized substrates. The given structural peculiarities provide a wide range of structural modifications that make them highly valuable in the design of drugs and organic synthesis since they can be adjusted to the required physicochemical and biological characteristics.[17,18] Functionalization can target either the aromatic rings or the methylene centre, depending on the desired structural and electronic outcome.

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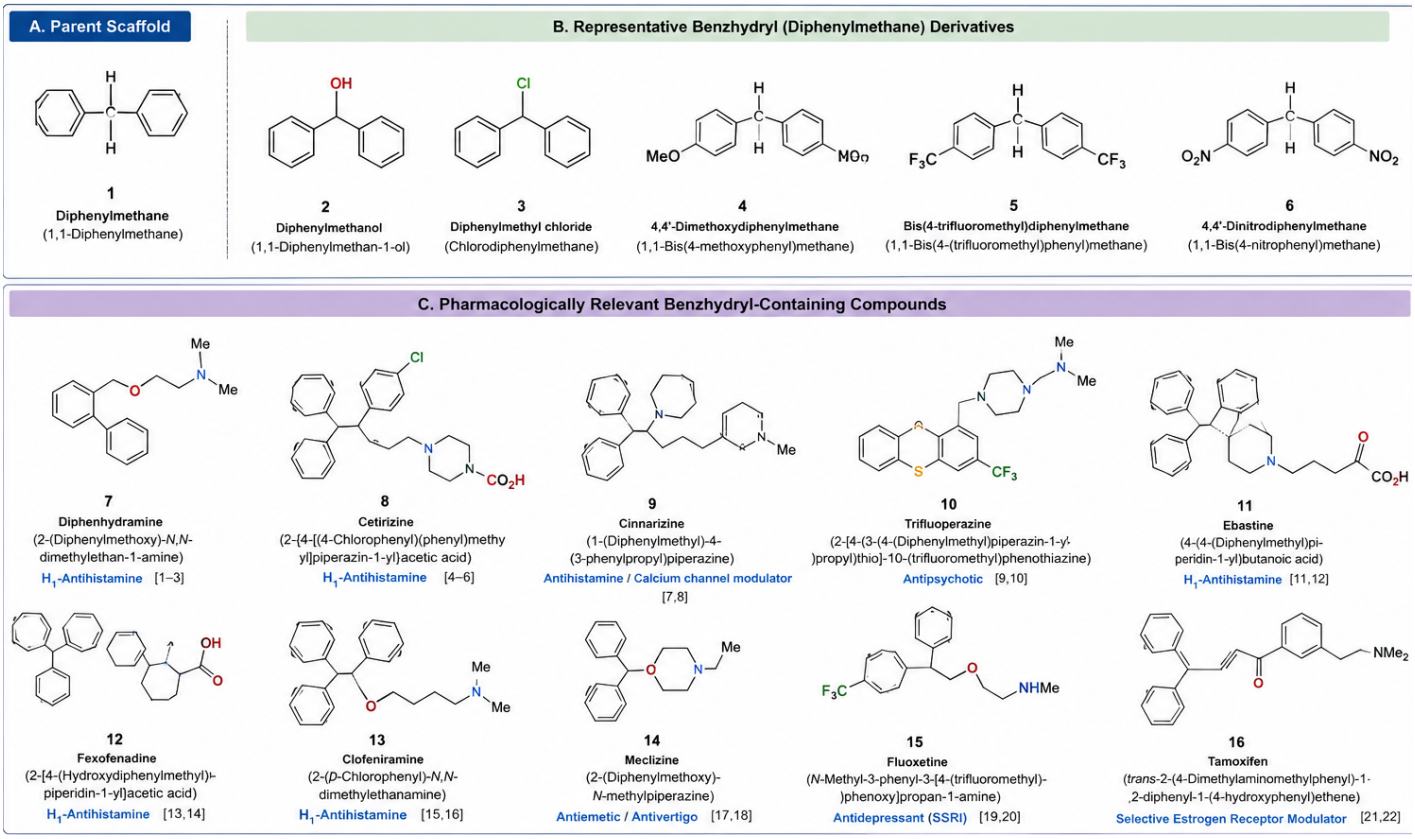


Figure 2: Representative diphenylmethane (benzhydryl) scaffolds and pharmacologically relevant derivatives.

Electrophilic Aromatic Substitution

The phenyl rings in diphenyl methylene derivatives are electron-rich and undergo classical electrophilic aromatic substitution reactions. These include:

Nitration of Diphenylmethane

$$(C_6H_5)_2CH_2+HNO_3+H_2SO_4 \rightarrow NO_2\text{-}C_6H_4\text{-}CH_2\text{-}C_6H_5+H_2O$$

Diphenylmethane is a substance that is electrophilically aromatically nitrated in the presence of a nitrating mixture of concentrated Nitric Acid (HNO_3) and sulfuric acid (H_2SO_4). A hydrogen atom of one of the phenyl rings is usually replaced by Nitro ($-NO_2$) group, the para-position (with respect to the presence of a methylene group) to the nitro group is most common because of steric and electronic considerations.[19]

Halogenation of Diphenylmethane

Halogenation Diphenylmethane can be halogenated (usually with either chlorine or bromine) at its benzylic (methylene), or at the rings of the diphenylmethane depending upon the reaction conditions. Under free-radical conditions, e.g. exposure to chlorine gas under conditions of ultraviolet light (hv) or heat, benzylic halogenation is more favorable because it results in an intermediate radical which is appreciably more stable.[20]

$$(C_6H_5)_2CH_2+Cl_2 \rightarrow (C_6H_5)_2\ CH\text{-}Cl + HCl$$

And in this reaction, one of the Hydrogen atoms of the central methylene group ($-CH_2-$) is exchanged by a chlorine atom, to form benzhydryl chloride. The halogen compound is a useful building block in organic synthesis, normally used to further synthetic transformation as a nucleophilic addition or elimination reaction.

Sulfonation of Diphenylmethane

Diphenylmethane can undergo electrophilic aromatic sulfonation in the presence of concentrated sulfuric acid or fuming sulfuric acid (oleum), resulting in the introduction of a Sulfonic Acid group ($-SO_3H$) onto one of the aromatic rings.

$$(C_6H_5)_2CH_2 + H_2SO_4 \rightarrow SO_3H\text{-}C_6H_4\text{-}CH_2\text{-}C_6H_5 + H_2O$$

Under appropriate reaction conditions, the major product is generally the para-sulfonated derivative, 4-(diphenylmethyl)benzenesulfonic acid, owing to the activating and ortho/para-directing influence of the diphenylmethyl substituent on the aromatic ring.

The reaction proceeds through an Electrophilic Aromatic Substitution (EAS) mechanism. In strongly acidic media, Sulfur Trioxide (SO_3) and protonated sulfur trioxide species are generated and act as the effective electrophilic sulfonating species. The electron-rich aromatic ring of diphenylmethane attacks the electrophile to form a resonance-stabilised σ-complex (arenium ion). Subsequent deprotonation restores

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Table 1: Representative Synthetic Methods for Diphenyl Methylene Derivatives.

Method	Starting materials/reagents	Conditions	Product	Yield (%)	References
Grignard reaction	Benzophenone + phenylmagnesium bromide	Dry ether, reflux, followed by acid quench	Diphenylmethanol	80-90	[63]
Friedel-Crafts alkylation	Benzene + formaldehyde/paraformaldehyde	HCl or $AlCl_3$ catalyst; room temperature-60 °C	Diphenylmethane	70-85	[64]
Zinc amalgam reduction	Benzophenone + Zn(Hg) + HCl	Reflux, aqueous medium	Diphenylmethane	65-80	[65,66]
Microwave-assisted Friedel-Crafts reaction	Aromatic compound + aldehyde	Solid acid catalyst; microwave irradiation; solvent-free	Diphenylmethane derivative	80-92	[65,66]
Solvent-free synthesis	Benzene + formaldehyde + solid acid catalyst	80-120 °C, 1-2 h	Diphenylmethane	75-88	[67,68]
Biocatalytic method	Benzophenone + alcohol dehydrogenase + NADH	Aqueous buffer, pH 7.0, room temperature	Diphenylmethanol	60-70	[69,70]

aromaticity and affords the corresponding arylsulfonic acid derivative. The central methylene group (-CH_2-) is not itself the site of electrophilic aromatic substitution. Rather, the diphenylmethyl substituent exerts an electron-donating influence through hyperconjugative and inductive effects, increasing the electron density of the aromatic ring and facilitating electrophilic substitution. The para position is generally favoured over the ortho position because of reduced steric hindrance between the incoming sulfonic acid group and the diphenylmethyl substituent. The resulting sulfonated diphenylmethane derivatives possess increased polarity and water compatibility compared with the parent hydrocarbon and may therefore serve as useful intermediates for the preparation of functional organic materials, dyes, surfactants, and biologically relevant compounds. Table 1 summarises selected conventional, microwave-assisted, solvent-free, and biocatalytic synthetic approaches for the preparation of diphenylmethane and related diphenylmethylene derivatives, highlighting the starting materials and reagents, reaction conditions, representative products, reported yields, and corresponding literature references.

Green and Sustainable Synthesis

Due to the growing environmental issues and the trend towards emitting eco-friendly and green methods of manufacturing substances, interest in the creation of green and eco-friendly techniques for the synthesis of diphenyl methylene derivatives has significantly grown. Conventional procedures usually imply harsh reagents, poisonous solvents, and energy-consuming processes and are more and more substituted by new and sustainable procedures that comply with the ideas of green chemistry. Table 2 summarises representative green and sustainable synthetic approaches for the preparation of diphenylmethylene and related diarylmethane derivatives, including solvent-free synthesis, microwave-assisted methods, the use of environmentally benign solvents, heterogeneous catalysis, and biocatalytic transformations. The key advantages, representative applications, and supporting literature references are also highlighted, emphasising strategies that reduce solvent use, energy consumption, chemical waste, and environmental impact.[21,22]

Solvent-Free Reactions

The non-solvent methods are one of the most efficient environmentally friendly techniques. The lack of toxic organic solvents reduces toxicity and eases the isolation of the product. Friedel-Crafts alkylation of benzene with formaldehyde under neat conditions, with the use of a solid acid catalyst like Montmorillonite K10, Amberlyst-15 or sulfonated silica, can be accomplished to give a significant yield of diphenylmethane derivatives in the absence of any solvent.[23]

Microwave-Assisted Synthesis

One of the most effective tools that is used to hasten organic reactions is microwave irradiation. It shortens the reaction time from a few hours to a few minutes, improves yield, and allows reactions to proceed at more moderate conditions. Microwave irradiation has been used to accelerate and achieve more purity of products when Friedel and Crafts reaction are performed between aromatic hydrocarbons and aldehydes; they form diphenylmethane derivatives. This method does not overheat and minimises the carbon footprint of the reaction.[24]

Use of Green Solvents

Sustainable chemistry relies on green solvents, especially water, ethanol, glycerol, ethyl lactate, and Deep Eutectic Solvents (DESs). The solvents are not toxic, biodegradable and normally have

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Table 2: Green Synthesis Approaches for Diphenyl Methylene Derivatives.

Green approach	Description	Advantages	Representative example/application	References
Solvent-free synthesis	Reactions performed without conventional organic solvents, frequently using solid acid catalysts	Reduced VOC emissions, simplified work-up, reduced chemical waste	Solvent-free Friedel-Crafts-type synthesis of diphenylmethane derivatives	[71,72]
Microwave-assisted synthesis	Microwave irradiation used to accelerate condensation or Friedel-Crafts reactions	Short reaction times, energy efficiency, potentially improved yields/selectivity	Microwave-assisted synthesis of diarylmethane derivatives	[73,74]
Green solvents	Replacement of conventional hazardous solvents with water, ethanol, glycerol, ionic liquids, or deep eutectic solvents	Reduced environmental impact and improved solvent sustainability	Synthesis using aqueous or bio-derived solvent systems	[75]
Heterogeneous catalysis	Use of recyclable solid catalysts such as zeolites, clays, or metal-organic frameworks	Catalyst recovery, simplified purification, reduced waste	Catalytic C-C bond-forming synthesis of diarylmethane derivatives	[76]
Biocatalytic methods	Enzymes or whole cells used to perform selective transformations	High selectivity, mild conditions, reduced environmental burden	Enzymatic reduction of carbonyl-containing precursors	[77,78]

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renewable sources. Both aqueous-phase Grignard reactions and Grignard reactions with ethanol have been reported as synthesising diphenylmethanol and diphenylmethanol derivatives with a better environmental profile. Reactions carried out in ionic liquids or supercritical CO_2 are also recyclable and relatively low-toxicity.[25,26]

Catalysis with Recyclable and Heterogeneous Catalysts

The use of heterogeneous catalysts that can be easily recovered and reused is central to green synthetic design. Zeolites, clay-supported acids, biochar, Metal-Organic Frameworks (MOFs), and magnetic nanocatalysts. Catalysts such as $FeCl_3$ supported on silica, Cu- or Zn-doped oxides, or biogenic catalysts (e.g., from plant ash) provide good yields under mild conditions and can be reused for multiple cycles.[27]

Electrochemical and Photocatalytic Methods

Electrosynthesis and photocatalysis represent cutting-edge technologies for sustainable chemistry:

- **Electrochemical oxidation/reduction** of benzophenone or diphenylmethanol can produce desired methylene derivatives without external reagents.[28]
- **Photo- and redo** catalysis photocatalysis with visible light and organic dyes or semiconductor materials enables the formation of C-C and C-X bonds under ambient conditions with little waste.[29]

Reactivity and Chemical Modifications

The chemical reactivity of diphenyl methylene scaffolds is highly diverse due to two phenyl rings being essentially electron-rich and a methylene linker in the centre. These structural characteristics enable many similar chemical manipulations, e.g. electrophilic and nucleophilic substitutions, cyclization reactions, rearrangements, and coordination with transition metals.[30] The reactions do not only increase the chemical diversity of the scaffold but also enlarge its use in the field of pharmacology, catalysis and materials science.

Electrophilic and Nucleophilic Substitutions

A diphenyl methylene derivative has very reactive phenyl rings to Electrophilic Aromatic Substitution reaction (EAS), as the methylene bridge exerts an electron donating effect. Other typical EAS reactions e.g. nitration, sulfonation, halogenation and Friedel-Crafts reaction involving alkylation/acylation are found to be largely in the para-position of the rings. Nitration of

which with nitric acid and concentrated sulfuric acid produces mono- or di-nitro diphenylmethane derivatives, and sulfonation to p-sulfodiphenylmethane, which is an ingredient in detergent additives. Conversely, by installing electron-withdrawing groups on the phenyl rings (e.g., nitro groups), the phenyl rings will be subject so-called nucleophilic aromatic substitution reaction (S-N-Ar) so that nucleophiles such as amines or alkoxides can be introduced.[31,32] This amphiphilicity as both electrophilic as well as nucleophilic creates much synthetic versatility in the design of complex compounds.

Cyclization and Rearrangement Reactions

Diphenyl methylene compounds are easily cyclized under appropriate conditions to give polycyclic structures like fluorenes. Examples include fluorene which is formed in a series of protonation, rearrangement, and cyclization starting with acid-catalysed intramolecular cyclization of diphenylmethanol derivatives. The transformation has high interest when used in the synthesis of fluorescent materials, organic semiconductors and the pharmacophores. Diphenyl methylene derivatives may also react by rearrangement, e.g. via the Wagner-Meerwein rearrangement, especially in the presence of acid or heat. The rearrangements have the ability to create the structurally varied complex carbocation intermediates, which are then functionalized or fusion of rings further adding to the complexity of the structures.[33]

Coordination Chemistry and Metal Complex Formation

Diphenylmethane-based compounds containing suitable donor groups can serve as ligands in coordination chemistry. In these systems, coordination to a metal centre generally occurs through heteroatom donor sites, such as nitrogen, oxygen, or sulfur, introduced into the diphenylmethane framework. The aromatic rings themselves do not normally coordinate to metal ions simply because they are present; rather, coordination depends on the nature, electronic properties, and spatial arrangement of the available donor atoms.[34] Functionalized diphenylmethane derivatives can coordinate with a variety of transition-metal ions, including Cu (II), Ni (II), Pd (II), and Pt (II), when appropriate donor atoms are present. Schiff bases and related N-, O-, or S-donor ligands derived from diphenylmethane frameworks are of particular interest because they can form stable chelate complexes through coordination of their donor atoms to the metal centre.[34,35] The resulting coordination geometry and complex stability depend on factors such as the denticity of the ligand, donor-atom characteristics, metal oxidation state, ligand-field effects, and steric environment.

For example, aminated diphenylmethane-derived Schiff bases have been investigated as ligands for Cu (II) and Zn (II) complexes. Such complexes have been reported in studies evaluating their potential biological properties, including antimicrobial, antioxidant, and anticancer activities. The structural rigidity and aromatic character of diphenylmethane-derived ligands can provide a suitable framework for positioning donor groups around a metal centre. Depending on ligand design, these complexes may therefore have applications in homogeneous catalysis, materials chemistry, supramolecular chemistry, and medicinal inorganic chemistry.[36] However, the coordination behaviour should be interpreted primarily in terms of the specific donor atoms and ligand architecture rather than attributing metal binding to the diphenylmethane core alone.

Recent Advances in Medicinal Chemistry

Pharmacological Activity

Diphenylmethane and benzhydryl derivatives have been investigated for a broad range of pharmacological activities, including antimicrobial, anticancer, anti-inflammatory, antioxidant, neuroprotective, and enzyme-inhibitory effects. The biological activity of these compounds depends strongly on the substitution pattern, physicochemical properties, molecular conformation, and interactions with specific biological targets. Some of the major areas of therapy within which these scaffolds have offered promise are listed below.

Anticancer Activity

Several diphenylmethane and benzhydryl derivatives have been investigated for their potential anticancer properties (Figure 3). Reported mechanisms include modulation of signalling pathways, inhibition of enzymes involved in tumour-cell proliferation, induction of apoptosis, and interference with cellular proliferation and survival pathways. However, anticancer activity should be interpreted in relation to the experimental model used, including the specific cancer cell line, assay methodology, exposure time, and concentration range.[37,38] Where available, quantitative parameters such as IC_{50} values, together with selectivity or cytotoxicity data from nonmalignant cells, provide a more informative assessment of the therapeutic potential of individual derivatives.[38,39]

Antimicrobial and Antiviral Applications

Diphenylmethane-derived compounds have demonstrated activity against a variety of bacterial and fungal pathogens (Figure 4). Reported antibacterial activity has been investigated against organisms including *Staphylococcus aureus*, Methicillin-Resistant *Staphylococcus aureus* (MRSA), *Bacillus subtilis*, and *Escherichia coli*. Certain derivatives have also demonstrated antifungal activity against pathogenic fungi, including *Candida albicans*. The antimicrobial effects of these compounds may arise through several mechanisms, depending on the molecular structure and biological target. These mechanisms may include disruption of microbial membrane integrity, interference with essential

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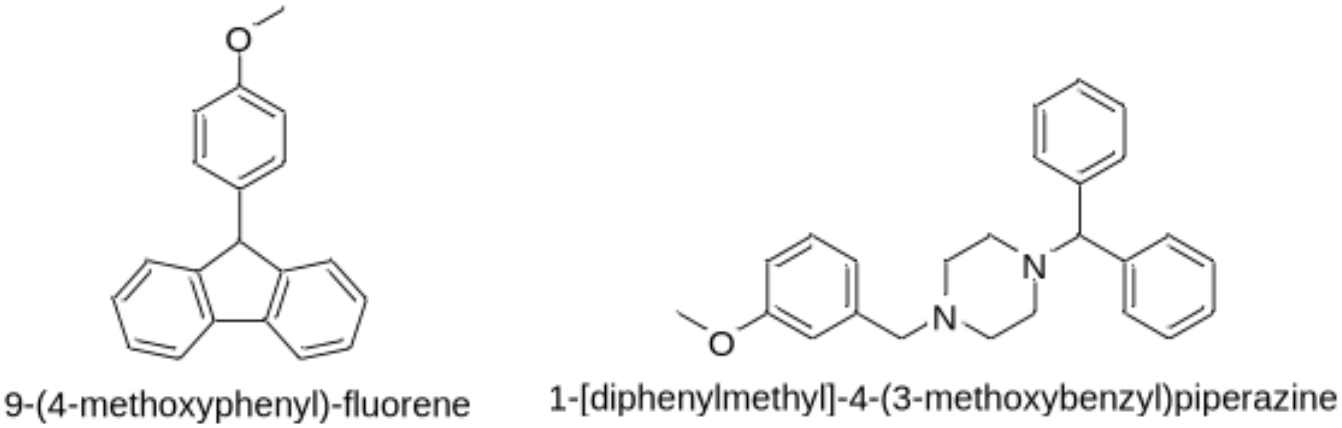


Figure 3: Chemical structures of 9-(4-methoxyphenyl)-fluorene and 1-[(diphenylmethyl)]-4-(3-methoxybenzyl) piperazine.

enzymes, inhibition of bacterial fatty-acid biosynthesis, and other target-specific interactions. Quantitative measures such as Minimum Inhibitory Concentration (MIC) should be used where available to facilitate meaningful comparison of antimicrobial potency.[40,41] Some of the derivatives in the antiviral sphere have also demonstrated an inhibition ability to RNA viruses (such as influenza virus, hepatitis virus) through interference with the mechanism of viral replication. Their structural property of lipophilicity helps in the process of membrane permeability, an important aspect in intracellular targeting of viruses. The possibility of resistance to newer drugs such as traditional antibiotics and antivirals necessitates the use of diphenyl methylene derivatives as an interesting scaffold in the design of new-generation antimicrobial drugs.[42,43]

Anti-inflammatory and Analgesic Properties

Diphenylmethane-based compounds have also been investigated for anti-inflammatory effects in cellular and experimental models. Depending on the chemical structure, reported effects may involve modulation of inflammatory mediators and signalling pathways, including pathways associated with cytokine production and inflammatory enzyme activity. Such findings should be interpreted according to the experimental model and should not be generalised to the entire diphenylmethane class.[44] Moreover, central analgesia is found with specific derivatives, which may affect opioid or cannabinoid receptors (Figure 5). Their properties predispose diphenyl methylene compounds as potential in the creation of safe and effective anti-inflammatory medications.[44,45]

Neuroprotective and CNS Effects

Hydroxylated and other appropriately functionalized diphenylmethane derivatives have been investigated for antioxidant activity, including their ability to scavenge reactive oxygen species or reactive radical species. Some derivatives have additionally

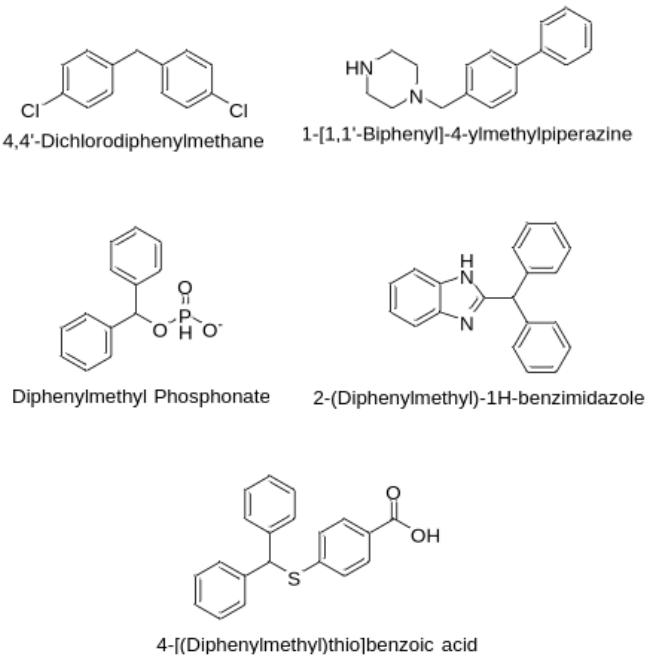


Figure 4: Chemical Structure of 4,4′-Dichlorodiphenylmethane, 1-[1,1′-Biphenyl]-4-ylmethylpiperazine, Diphenylmethyl Phosphonate, 2-(Diphenylmethyl)-1H-benzimidazole, 4-[(Diphenylmethyl) this] benzoic acid.

been evaluated in models of neuronal oxidative stress and neuroprotection (Figure 6). The presence of electron-donating substituents, particularly phenolic hydroxyl groups, can influence radical-scavenging activity; however, the biological outcome depends on the complete molecular structure and experimental conditions. Therefore, antioxidant activity should preferably be reported using the specific assay and quantitative endpoint employed rather than through generalised statements regarding substituent effects.[46]

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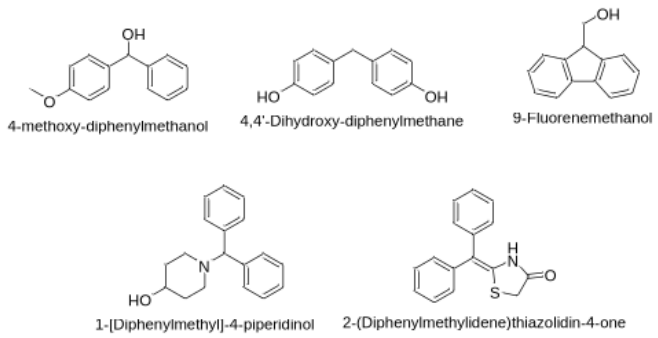


Figure 5: Chemical structures of 4-methoxy-diphenylmethanol, 4,4'-dihydroxy-diphenylmethane, 9-fluorenemethanol, 1-[diphenylmethyl]-4-piperidinol, and 2-(diphenylmethylidene) thiazolidin-4-one.

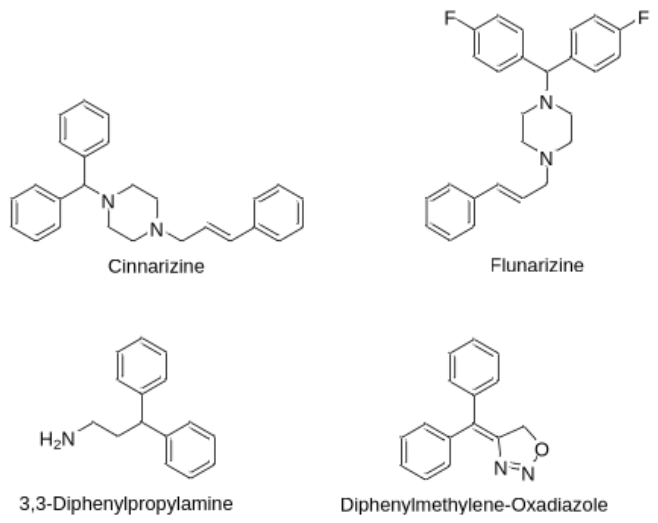


Figure 6: Chemical structures of Cinnarizine, Flunarizine, 3,3-Diphenylpropylamine, and Diphenylmethylene-Oxadiazole.

Structure Activity Relationship Studies

Structure-Activity Relationship (SAR) studies of diphenylmethane and benzhydryl derivatives demonstrate that biological activity is highly dependent on the nature, position, and combination of substituents, as well as on the biological target and assay system. Therefore, generalised statements regarding the effect of electron-donating or electron-withdrawing substituents should be interpreted cautiously and should be supported by quantitative potency data.[47] A representative example is provided by diphenylmethane derivatives investigated as anti-HIV-1 agents. However, systematic halogen substitution produced substantial changes in antiviral potency. The parent 4-methyl derivative showed an EC_{50} of 4.8 μM, whereas replacement of the methyl group by chlorine gave a 4-chloro analogue with an EC_{50} of 1.2 μM. Further chlorination produced compounds with EC_{50} values of 0.62, 0.38, and 0.31 μM, demonstrating that appropriate halogen substitution can markedly improve antiviral potency. Importantly, the Corresponding Cytotoxicity values (CC_{50}) ranged from 15 to 88 μM for these analogues, indicating that potency should be considered together with cellular selectivity rather than interpreted solely from EC_{50} values. Diphenylmethane substitution has also been investigated in oestrogen-receptor-directed medicinal chemistry. Nanjyo *et al.* developed diphenylmethane-based Selective Estrogen Receptor Down-Regulators (SERDs) and evaluated their activity quantitatively using a luciferase-based assay, with EC_{50} and E_{max} used as measures of potency and efficacy, respectively. This study provides direct evidence that systematic modification of a diphenylmethane framework can produce substantial changes in oestrogen-receptor-directed activity.[47] The importance of substituent pattern is also demonstrated in diphenylmethane-based antibacterial agents targeting FabI. In one representative series, the unsubstituted lead MN02 showed MIC values of 4.0 μg/mL against *Staphylococcus aureus* and 8.0 μg/mL against MRSA. Structural modification produced compounds with substantially improved activity; for example, RK09 and RK10 showed *S. aureus* MIC values of 2.84 and 1.32 μg/mL, respectively, while RK10 exhibited an MIC of 2.70 μg/mL against MRSA and 1.32 μg/mL against *Bacillus subtilis*. RK10 also showed activity against *Escherichia coli* with an MIC of 47.64 μg/mL. These results illustrate that the position and identity of substituents can influence antibacterial activity in a target-dependent manner. A further example is provided by diphenylmethane derivatives investigated as efflux-pump inhibitors against drug-resistant *E. coli*. Diphenylmethane-based compounds were quantitatively evaluated using IC_{50} assays, and the parent diphenylmethane derivative showed concentration-dependent effects on bacterial efflux mechanisms. In combination studies, several derivatives substantially altered the IC_{50} values of co-administered antibiotics, demonstrating that scaffold modification can influence both intrinsic activity and pharmacological modulation of antibacterial agents. Benzhydryl-containing medicinal chemistry provides additional evidence that relatively small structural changes can markedly affect receptor affinity. For example, the benzhydryl piperazine derivative LDK1229 was reported as a CB_1 receptor inverse agonist with a K_i of 220 nM and greater selectivity for CB_1 than CB_2.[48] This finding illustrates the contribution of the benzhydryl pharmacophore to receptor recognition while also emphasising that biological activity depends on the complete molecular architecture rather than on the diphenylmethane unit alone.

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Impact of Substituents on Bioactivity

The bioactivity of the diphenylmethylene scaffold is strongly dependent on the nature, position and electronic properties of substituents. An example of this was a serendipitous discovery by para-substituted derivatives of high lipophilicity with fluorine or chlorine that exhibit improved antimicrobial and anticancer properties, possibly as a result of greater lipophilicity and membrane surface permeability. Ortho- or meta- substituents may have a deactivating effect by affecting the molecule's conformation and steric profile, which may not present a favorable steric blocking.[49] An electron-donating group would tend to enhance antioxidant and neuroprotective conditions as they successfully stabilize free radicals, whereas an electron-withdrawing group can increase the anti-inflammatory and anti-cancer situations by boosting the interactions with nucleophilic centers on the biological targets. Multilocus activity emanates also due to dual substitution or heterocyclic ring fusion, which gives the possibility of developing drugs that address multiple targets.[50,51] All the above implies that it is necessary and judicious to alter substituents in the therapeutic profile of diphenyl methylene-based compounds. Table 3 summarises representative quantitative Structure-Activity Relationship (SAR) findings for diphenylmethane- and benzhydryl-containing compounds evaluated against diverse biological targets. It highlights the effects of specific structural modifications on biological activity, including antiviral, antibacterial, cannabinoid receptor, and Trace Amine-Associated Receptor 1 (TAAR1) activities. Reported potency parameters, including EC_{50}, MIC, and K_i values, are provided alongside the corresponding SAR observations to illustrate how substitution patterns and scaffold modifications influence biological potency and target recognition.

Pharmacokinetics and Toxicological Aspects

The pharmacokinetic and toxicological characteristics of diphenylmethane- and benzhydryl-containing compounds are strongly influenced by lipophilicity, molecular size, ionisation state, aromatic substitution, plasma-protein binding, metabolic stability, and the presence of additional heteroatom-containing functional groups. These properties can substantially influence absorption, tissue distribution, central nervous system penetration, metabolism, and elimination. Importantly, pharmacokinetic behaviour should be evaluated on an individual-compound basis rather than generalised to the entire diphenylmethane scaffold.

Pharmacokinetic Characteristics of Representative Benzhydryl-Containing Drugs

Several clinically used drugs containing a benzhydryl/diphenylmethyl structural motif provide useful pharmacological benchmarks for understanding the ADME behaviour of this chemical framework. Diphenhydramine, a first-generation H1-antihistamine, is a highly lipophilic compound that is rapidly absorbed following oral administration. Reported pharmacokinetic data indicate an oral bioavailability of approximately 72%, a large apparent volume of distribution of approximately 17 L/kg, and extensive plasma-protein binding. Diphenhydramine undergoes substantial hepatic metabolism, predominantly involving CYP450 enzymes, and its terminal elimination half-life in adults is approximately 9 h. Only a small proportion of the administered dose is excreted unchanged in urine. Cetirizine, a second-generation H1-antihistamine containing a diphenylmethyl-related pharmacophore, provides a contrasting example of how incorporation of polar functional groups can alter pharmacokinetic behaviour. Following repeated administration of 10 mg once daily, the reported mean C_{max} is approximately 311 ng/mL, while plasma-protein binding is approximately 93%. Approximately 70% of administered radioactivity is recovered in urine and 10% in faeces, with approximately 50% of the administered radioactivity recovered in urine as unchanged drug. The mean elimination half-life is approximately 8.3 h.[52] These findings indicate that cetirizine undergoes substantially less hepatic metabolism than highly lipophilic first-generation antihistamines such as diphenhydramine. Cinnarizine represents another clinically used benzhydryl-containing drug and demonstrates the importance of lipophilicity and prolonged terminal elimination. In a pharmacokinetic study involving healthy volunteers receiving a 75-mg oral dose, cinnarizine reached a mean C_{max} of 275±36 ng/mL at approximately 3.0±0.5 h, with an AUC of 4437±948 ng·hr/mL and a terminal elimination half-life of 23.6±3.2 h. Repeated administration resulted in measurable drug accumulation, with an observed accumulation factor of approximately 2.79. These clinically established examples demonstrate that structurally related benzhydryl-containing compounds can exhibit substantially different ADME profiles. Therefore, the pharmacokinetic behaviour of novel diphenylmethane derivatives should not be predicted solely from the presence of the diphenylmethane core.

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Table 3: Quantitative SAR Examples of Diphenylmethane and Benzhydryl Derivatives Reported in Medicinal Chemistry Studies.

Biological target/activity	Representative structural modification	Quantitative activity	Key SAR observation
Anti-HIV-1	4-Me diphenylmethane derivative	EC_{50}=4.8 μM; CC_{50}= 72 μM	Baseline activity of the 4-methyl analogue
Anti-HIV-1	4-Cl analogue	EC_{50}=1.2 μM; CC_{50}=23 μM	Chlorine substitution improved antiviral potency
Anti-HIV-1	4-Cl + 2-Cl analogue	EC_{50}=0.62 μM; CC_{50}=28 μM	Additional ortho chlorination further improved potency
Anti-HIV-1	4-Cl + 2-Cl + 5-Cl analogue	EC_{50}=0.38 μM; CC_{50}=15 μM	Multiple halogen substitution produced submicromolar activity
Anti-HIV-1	4-Cl + 2-Cl + 6-Cl analogue	EC_{50}=0.31 μM; CC_{50}=49 μM	Further positional modification produced the highest potency in this subset
FabI antibacterial activity	MN02 diphenylmethane lead	MIC=4.00 μg/mL (*S. aureus*); 8.00 μg/mL (MRSA)	Parent scaffold displays measurable antibacterial activity
FabI antibacterial activity	RK10 derivative	MIC=1.32 μg/mL (*S. aureus*); 2.70 μg/mL (MRSA)	Substitution pattern produced the most potent antibacterial analogue in the series
CB_1 receptor	LDK1229, benzhydryl piperazine	K_i=220 nM	Benzhydryl-containing architecture supported CB_1 recognition and inverse agonism
mTAAR1 agonism	SG2 diphenylmethane lead	EC_{50}=240 nM	Baseline agonist activity
mTAAR1 agonism	Methyl-substituted analogue 7	EC_{50}=134 nM	Addition of a methyl group produced approximately a 2-fold potency improvement

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Metabolism and Elimination

Benzhydryl-containing compounds may undergo hepatic oxidative metabolism, including hydroxylation, N-dealkylation, O-dealkylation, and other phase-I reactions, followed by conjugation reactions where appropriate. Diphenhydramine, for example, undergoes substantial hepatic metabolism and is predominantly eliminated as metabolites, whereas cetirizine undergoes relatively limited oxidative metabolism and is eliminated largely through the renal route. The extent of hepatic metabolism is therefore highly dependent on the complete chemical structure. Introduction of polar functional groups can increase renal elimination, whereas increased lipophilicity may favour extensive tissue distribution and hepatic metabolism. These properties should be considered during medicinal-chemistry optimisation because excessive lipophilicity may increase nonspecific protein binding and tissue accumulation, whereas excessive polarity may reduce membrane permeability.

Toxicological and Hepatotoxicological Considerations

Toxicological evaluation of diphenylmethane and benzhydryl derivatives should include both acute and repeated-dose toxicity, together with assessment of organ-specific toxicity and clinically relevant safety endpoints. Diphenhydramine provides an important clinical safety benchmark. Despite extensive use over several decades, it has not been associated with clinically apparent acute liver injury in the LiverTox database and is considered an unlikely cause of clinically significant drug-induced liver injury. Cetirizine has been associated with rare cases of clinically apparent acute liver injury. Reported cases have included cholestatic hepatitis and hepatocellular jaundice, with onset ranging from approximately 1 to 40 weeks after treatment. A published case recorded ALT of 215 U/L, alkaline phosphatase of 260 U/L, and total bilirubin of 9.7 mg/dL at the time cetirizine was discontinued; subsequent laboratory abnormalities were consistent with a prolonged cholestatic pattern.[53,54] These clinical examples demonstrate that the presence of a benzhydryl/diphenylmethyl framework does not itself predict hepatotoxicity. Rather, toxicity is determined by the complete molecular structure, dose, exposure duration, metabolism, metabolites, patient characteristics, and interactions with other drugs. For experimental diphenylmethane derivatives, acute toxicity should preferably be reported using established endpoints such as LD_{50}, while repeated-dose studies should report NOAEL, LOAEL, changes in liver enzymes, renal biomarkers,

Table 4: Representative Pharmacokinetic and Toxicological Data for Clinically Used Benzhydryl/Diphenylmethyl-Containing Drugs.

Compound	Pharmacological class	Representative ADME data	Elimination / half-life	Toxicological evidence
Diphenhydramine	First-generation H1 antihistamine	Oral bioavailability ≈ 72%; Vd ≈ 17 L/kg; extensive plasma-protein binding	t½ ≈ 9 h; primarily eliminated as metabolites; ~2% excreted unchanged in urine	No clinically apparent acute liver injury established despite extensive clinical use
Cetirizine	Second-generation H1 antihistamine	C_{max} ≈ 311 ng/mL after repeated 10 mg dosing; protein binding ≈ 93%	Mean t½ ≈ 8.3 h; ~70% radioactivity recovered in urine; ~50% as unchanged drug	Rare clinically apparent liver injury; reported cholestatic/hepatocellular injury
Cinnarizine	Antihistamine/calcium-channel-modulating drug	C_{max}=275±36 ng/mL; tax=3.0±0.5 h; AUC=4437±948 ng·hr/mL after 75 mg	Terminal t½=23.6±3.2 h; accumulation factor ≈ 2.79 after repeated dosing	Safety should be interpreted in relation to dose and prolonged exposure
Novel diphenylmethane derivatives	Experimental	Compound-dependent	Compound-dependent	Acute and repeated-dose toxicity should be evaluated using LD_{50}/NOAEL, organ biomarkers and histopathology

haematological parameters, histopathological findings, and organ weights where available. Because LD_{50} values are highly dependent on species, route of administration, formulation, and experimental protocol, values obtained from different studies should not be directly pooled or compared without considering these variables. Table 4 summarises selected pharmacokinetic, ADME, elimination, and toxicological characteristics of clinically used benzhydryl/diphenylmethyl-containing drugs, including diphenhydramine, cetirizine, and cinnarizine. Key parameters such as oral bioavailability, volume of distribution, plasma-protein binding, maximum plasma concentration, area under the curve, and elimination half-life are presented where available. They also provide representative toxicological evidence and highlight the importance of evaluating dose, duration of exposure, metabolic disposition, and organ-specific toxicity when assessing newly developed diphenylmethane derivatives.

Applications in Drug Design and Development

Interests on diphenyl methylene and derivatives have been concerned with modern applications on drug design and development, because of their flat, rigid structures, hydrophobic nature, and capacity to interact with a broad range of biological targets. Their aromatic structure is distinguished by being able to undergo π-π interactions, hydrogen bonding (via substituent), and hydrophobic recognition of sites on an enzyme or receptor. Such compounds can frequently be used as the pharmacophores or radicals of anti-inflammatory, anticancer, antimicrobial, CNS-active substances. Their structural versatility allows medicinal chemists to modify side chains or introduce functional groups to fine-tune biological activity, improve metabolic stability, and optimise pharmacokinetics.[55,56] Computational drug design, including docking and QSAR studies, frequently incorporates diphenyl methylene scaffolds to identify potent lead molecules.

Prodrug Strategies

Prodrug strategies involve chemically modifying an active drug molecule to improve properties such as solubility, stability, bioavailability, or targeted delivery. Diphenyl methylene-containing compounds can be adapted into prodrugs by masking reactive functional groups (e.g., hydroxyl, amine, or carboxyl) with diphenyl methylene or similar moieties. These prodrugs are designed to undergo enzymatic or chemical transformation within the body to release the active form at the desired site of action.[57,58] For instance, conjugating diphenyl methylene structures to therapeutic agents can reduce premature metabolism or enhance membrane permeability. Such strategies are crucial in overcoming challenges like poor oral absorption, rapid clearance, or toxicity associated with parent drugs.[57]

Diphenyl Methylene as Lead Compounds

Diphenyl methylene structures are often explored as lead compounds due to their pharmacologically privileged scaffold. Their hydrophobic and rigid framework can mimic natural ligands or modulate protein-ligand interactions effectively. A great number of synthetic analogues exhibiting the diphenyl methylene core have potential activity in various biological tests, anticancer, antiviral, and neuroprotective activity. The facility of structural modification enables an extensive range of derivatives to be generated by researchers in terms of SAR (structure activity relationship). They are also planar aromatic and help in the intercalation of DNA to be used in the development of anticancer drugs.[59] The presence of a diphenyl methylene group could also

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be lipophilic anchor to enhance cell membrane behavior and enhance cellular retention.

Emerging Trends and Future Perspectives

Diphenyl methylene is one of the most common structural motifs with a central carbon that is flanked by two phenyl rings and it also has gained much interest in the field of modern chemical research because of its synthetic kinetics and electrical versatility. Its classically commendable role has been in organic intermediates; it has recently grown to enter novel realms like medicinal chemistry, and material science and catalysis. Among the essential upcoming trends is the growing of the derivatives of diphenyl methylene as pharmacophores with high-ranking bioactivity. They have found the potential in anti-inflammatory, anticancer and antimicrobial drugs discovery by means of computational drug design and Quantitative Structure-Activity Relationship (QSAR) studies and so synthetic chemists are designing a wider range of analogues through green and sustainable procedures.[60]

The derivatives of diphenyl methylene are under study as the candidates of the optical, electronic and photophysical properties in the field of materials chemistry and can be used in such fields as Organic Light-Emitting Diodes (OLEDs), molecular sensors, nonlinear optical materials. Due to this, researchers are functionalizing the phenyl rings with electron withdrawing or donating groups to tune properties such fluorescence, charge mobility, and stability. Moreover, the catalytic use is developing, with diphenyl methylene scaffolds serving as ligands or intermediates in organocatalyzed reactions as well as metal-based reactions, providing stereo- and regioselective control in complex synthesis.[60,61] From a future perspective, the field is moving toward sustainable synthesis approaches such as microwave-assisted reactions, solvent-free conditions, and the use of biocatalysts to reduce environmental impact. Integration with computational techniques like molecular docking, Density Functional Theory (DFT), and AI-driven molecular design is expected to significantly accelerate the identification of novel diphenyl methylene-based molecules with optimised properties.[47,62] Additionally, interdisciplinary collaborations between chemists, materials scientists, and pharmaceutical researchers are anticipated to unlock new functionalities and real-world applications. Diphenyl methylene chemistry stands at the cusp of transformation, with its future shaped by innovation in synthesis, application, and design methodologies.

CONCLUSION

Diphenylmethane and benzhydryl scaffolds constitute versatile structural platforms with applications across synthetic chemistry, medicinal chemistry, pharmacology, and materials science. Their chemical properties can be readily modified through substitution of the aromatic rings and functionalization of the benzylic position, enabling systematic optimisation of physicochemical and biological properties. A range of conventional and contemporary synthetic approaches has been developed for the preparation of these compounds, including Grignard reactions, Friedel-Crafts alkylation, reduction of benzophenone derivatives, microwave-assisted synthesis, solvent-free reactions, photocatalytic methods, electrochemical approaches, and biocatalytic strategies. The increasing adoption of sustainable synthetic methods provides opportunities to reduce solvent consumption, energy requirements, and chemical waste. Pharmacological investigations have identified diverse biological activities among appropriately substituted diphenylmethane and benzhydryl derivatives, including antimicrobial, anticancer, anti-inflammatory, antioxidant, neuroprotective, and enzyme-inhibitory effects. However, these activities are highly dependent on the molecular structure, biological target, experimental model, and assay conditions. Quantitative SAR data indicate that changes in substituent identity and position can substantially influence potency and selectivity; therefore, generalised substituent-activity relationships should be interpreted cautiously. Pharmacokinetic and toxicological properties are likewise strongly influenced by molecular structure. Clinically used benzhydryl-containing compounds demonstrate that relatively small structural differences can produce substantial changes in absorption, distribution, metabolism, and elimination. Accordingly, future development of novel derivatives should consider potency, selectivity, metabolic stability, tissue distribution, pharmacokinetic exposure, and safety simultaneously rather than focusing exclusively on biological activity. Emerging approaches involving green chemistry, computational drug design, Quantitative Structure-Activity Relationship (QSAR) modelling, molecular docking, Artificial Intelligence (AI), prodrug development, and advanced drug-delivery technologies may further expand the pharmaceutical potential of this scaffold. Integration of experimental medicinal chemistry with computational and translational approaches could facilitate the identification of derivatives with improved efficacy, selectivity, pharmacokinetic properties, and safety. Diphenylmethane and benzhydryl frameworks remain valuable chemical platforms for the development of bioactive molecules and functional materials. Future research should prioritise experimentally validated SAR, quantitative ADME-Tox characterisation, target-specific mechanistic studies, and sustainable synthetic strategies to translate promising derivatives from chemical discovery toward practical pharmaceutical and technological applications.

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ABBREVIATIONS

AChE: Acetylcholinesterase; **ADME:** Absorption, Distribution, Metabolism, and Excretion; **AI:** Artificial Intelligence; **BBB:** Blood-Brain Barrier; **CC_{50}:** 50% Cytotoxic Concentration; **CNS:** Central Nervous System; **COX-2:** Cyclooxygenase-2; **CYP450:** Cytochrome P450; **DFT:** Density Functional Theory; **DNA:** Deoxyribonucleic Acid; **EC_{50}:** Half-Maximal Effective Concentration; **EDG:** Electron-Donating Group; **EE:** Encapsulation Efficiency; **EMA:** European Medicines Agency; **EWG:** Electron-Withdrawing Group; **GABA:** Gamma-Aminobutyric Acid; **GI:** Gastrointestinal; **HCT-116:** Human Colorectal Carcinoma Cell Line; **HepG2:** Human Hepatocellular Carcinoma Cell Line; **HPLC:** High-Performance Liquid Chromatography; **IC_{50}:** Half-Maximal Inhibitory Concentration; **K_i:** Inhibition Constant; **KI:** Kinase Inhibitor; **LC-MS:** Liquid Chromatography-Mass Spectrometry; **MAO:** Monoamine Oxidase; **MCF-7:** Michigan Cancer Foundation-7 Human Breast Adenocarcinoma Cell Line; **MIC:** Minimum Inhibitory Concentration; **NADH:** Reduced Form of Nicotinamide Adenine Dinucleotide; **NOAEL:** No-Observed-Adverse-Effect Level; **NSAIDs:** Nonsteroidal Anti-Inflammatory Drugs; **OLEDs:** Organic Light-Emitting Diodes; **PI3K:** Phosphoinositide 3-Kinase; **PK:** Pharmacokinetics; **QSAR:** Quantitative Structure-Activity Relationship; **RNA:** Ribonucleic Acid; **ROS:** Reactive Oxygen Species; **SAR:** Structure-Activity Relationship; **SH-SY5Y:** Human Neuroblastoma Cell Line; **TiO_2:** Titanium Dioxide; **TNF-α:** Tumour Necrosis Factor-Alpha; **USFDA:** United States Food and Drug Administration; **Vd:** Volume of Distribution; **VOCs:** Volatile Organic Compounds.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declare that they have not used artificial intelligence (AI) tools for writing and editing the manuscript, and no images were manipulated using AI.

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Not applicable

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