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Review Article

Triphenyloxazole and Its Derivatives Pharmacological Activity, ADME Behaviour, Toxicity Profiles, Computational (DFT/HF) Chemistry, Structure–Activity Relationships and Future Therapeutic Prospects- A Review

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The 1,3-oxazole nucleus, and particularly the symmetrically triaryl-substituted 2,4,5-triphenyloxazole (TPO) scaffold, occupies a distinctive place in medicinal chemistry because its rigid, planar, aromatic five-membered ring can be decorated at three positions (C-2, C-4 and C-5) to fine-tune potency, selectivity, lipophilicity and metabolic stability. This review consolidates the literature on pharmacological activities reported for triphenyl- and triaryl-oxazole derivatives anticancer, antimicrobial, antitubercular, anti-inflammatory, antidiabetic, antiparasitic, antioxidant and central-nervous-system-related effects and summarises their absorption, distribution, metabolism and excretion (ADME) behaviour and toxicity profiles. It further reviews computational-chemistry approaches used to rationalise activity, including Hartree–Fock (HF) and density-functional-theory (DFT) frontier-orbital analyses, molecular electrostatic potential (MEP) mapping, global reactivity descriptors, molecular docking and QSAR modelling. A structure–activity relationship (SAR) map links substitution patterns at the three aryl rings to the observed biological profile. The review closes with an evidence-based discussion of underexplored directions for future development of triphenyloxazole-based therapeutics.

Keywords: 2,4,5-triphenyloxazole; oxazole; SAR; ADME; toxicity; DFT; HOMO–LUMO; molecular docking; QSAR; heterocyclic medicinal chemistry.

INTRODUCTION

Five-membered oxygen-nitrogen heterocycles are one of the privileged scaffolds in medicinal chemistry. Among them, 1,3-oxazole, being a ring system in which nitrogen and oxygen are separated by one carbon atom, is a fascinating heterocycle with an aromatic system and a dipole moment due to the hydrogen-bond-accepting ability of both nitrogene and oxygen. The oxazole ring system is the core structure of more than 20 approved pharmaceuticals, including antibacterial (linezolid, furazolidone), anti-inflammatory (oxaprozin, valdecoxib), antidiabetic (aleglitazar), antiplatelet (ditazole) and tyrosine-kinase-inhibitory (mubritinib) agents, as well as a number of natural products, among them, pimprinine, hennoxazole A and telomestatin. 2,4,5-Triphenyl-1,3-oxazole (TPO) is the fully triarylated parent compound of this class of heterocycles (Fig. 1). Previously known as a scintillation fluor closely related to 2,5-diphenyloxazole (PPO) 13, TPO's molecular skeleton is now considered as a pharmacophore in medicinal chemistry. The three phenyl rings can carry various electron-withdrawing or electron-donating substituents at different positions, leading to considerable variations in hydrophobicity (log P), electronic properties and steric profiles. At the same time, the oxazole ring

system provides the molecule with a hydrogen-bond-accepting nitrogen and oxygen atoms to participate in additional hydrogen bonds or ion-pair interactions. This review highlights the accumulated experimental and computational data on triphenyl/triaryl oxazole derivatives, including: (i) chemistry and preparation methods; (ii) pharmacology; (iii) quantitative structure-activity relationships; (iv) absorption, distribution, metabolism and excretion (ADME); (v) toxicity; (vi) quantum-chemical (HF/DFT) calculations; (vii) theoretical/theoretical data; and (viii) opportunities for the emergence of new biological activity, with the inclusion of references to the literature and pharmacy in general.

2. Chemistry and Properties of Triphenyloxazole Derivatives

The 1,3-oxazole ring is a six-electron aromatic system meeting Huckel's rule. The ring oxygen atom contributes one lone pair of electrons to the conjugated π-system, while the nitrogen atom donates one electron from its p-orbital, leaving another electron pair in its orbital for hydrogen bonding interaction. According to the resonance structures, the substituents at C-2 (between oxygen and nitrogen) have the most significant effect on the electronic properties of the ring since this position is influenced by both heteroatoms. The substituents at C-4 and C-5 (on the carbon side) affect mainly the conjugation of the oxazole ring with the substituent groups. In the case of 2,4,5-triphenyloxazole and its analogs, all three phenyl rings are perpendicular to the oxazole plane at various angles, depending on the substituents. This is explained by the fact that conjugation of the aryl groups with the oxazole ring affects the degree of their planarity and, hence, the geometry of the molecule. The same effect is noted for the triazole derivatives of different heterocycles (imidazole, pyridine, etc.), for which single-crystal X-ray diffraction and quantum-chemical calculations of geometrical parameters showed that the planes of the three rings are at different angles relative to each other, on average, from 6 to 60 degrees. This is due to the balance between the tendency to increase the degree of π-conjugation between the rings and the repulsion of the ortho-hydrogen atoms of the phenyl rings. Similar effects occur when substituents with various electronic properties are attached to the phenyl rings of triphenyloxazole. Therefore, the geometry of these molecules largely depends on the nature and position of the substituents. To conclude this section, it should be noted that triphenyloxazole derivatives most often have a crystalline appearance at room temperature and are stable to light, air and moisture. However, they have low solubility in most common solvents due to their hydrophobicity. At the same time, their amphiphilic nature allows their use in various physicochemical assays, including determination of solubility, log P, membrane permeability [4,16].

2.1 Generalised Substitution Map

For medicinal-chemistry purposes, the TPO scaffold is best represented as a generalised pharmacophore bearing independent substituents R2, R4 and R5 on the three aryl rings, or alternatively at the ring carbons themselves.

2.2 Representative Marketed and Investigational Oxazole Drugs

Although fully triphenyl-substituted oxazoles remain predominantly a research-stage chemotype, several clinically used diaryl- and monoaryl-oxazoles validate the pharmacological relevance of the core. Oxaprozin β-(4,5-diphenyl-1,3-oxazol-2-yl) propanoic acid is an FDA-approved non-steroidal anti-inflammatory drug (NSAID) bearing two of the three aryl positions found in TPO, and serves as a useful pharmacokinetic and toxicological benchmark throughout this review [2,10,11]. Other clinically important oxazole-containing agents include valdecoxib and its prodrug parecoxib (selective COX-2 inhibitors), aleglitazar (a dual PPAR-α/γ agonist investigated for type 2 diabetes), ditazole (a platelet-aggregation inhibitor), mubritinib (a HER2/ErbB2 tyrosine-kinase inhibitor), linezolid (an oxazolidinone antibacterial acting on the 50S ribosomal subunit) and tafamidis (a transthyretin stabiliser for amyloidosis) [2,3].

2.3 Spectroscopic Signatures

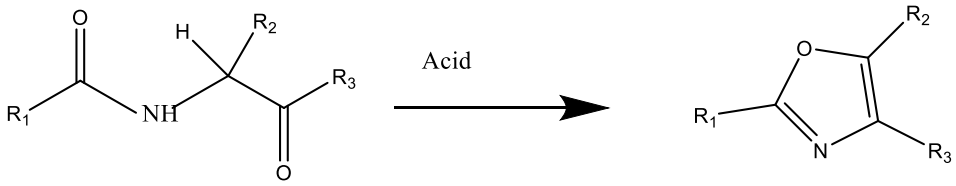
Structural confirmation of newly synthesised triaryl-oxazole derivatives typically relies on a consistent

combination of spectroscopic and analytical techniques. FT-IR spectra characteristically show C=N stretching absorption in the 1600-1650 cm-1 region and C-O-C ring stretching around 1000-1100 cm-1, distinct from the carbonyl-dominated spectra of open-chain precursor amido-ketones. 1H and 13C NMR spectra distinguish the three chemically inequivalent aryl rings by their distinct aromatic multiplet patterns and, for 13C, by the diagnostic downfield ring-carbon resonances of C-2 (typically 160-162 ppm, flanked by O and N) relative to C-4 and C-5 (typically 125-145 ppm). Single-crystal X-ray diffraction, where obtainable, provides the definitive measure of inter-ring dihedral angles and ring-puckering parameters referenced in Section 2, and is routinely used alongside Hirshfeld-surface analysis to map intermolecular contacts (C-H...O, C-H...N, π-π stacking) that influence solid-state packing, crystallinity and, indirectly, formulation behaviour [6,16].

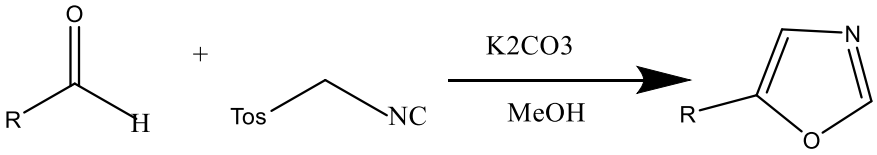
3. Synthetic Approaches

Triaryl-oxazoles are most commonly accessed via three classical routes, each amenable to combinatorial diversification of the three aryl rings:

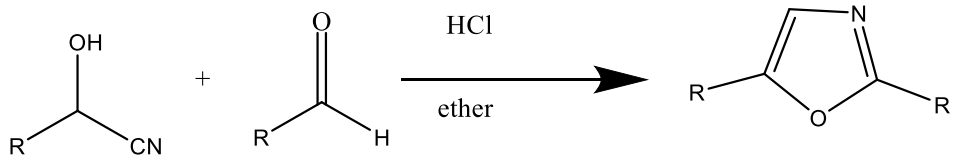
● Robinson–Gabriel cyclodehydration: cyclisation of an α-acylamino ketone (from an aroyl chloride and an α-amino ketone, or via acylation of an amino-alcohol followed by oxidation) using dehydrating agents such as POCl3, PPA, H2SO4 or, more recently, triflic anhydride or iodine-mediated oxidative systems.



● Van Leusen oxazole synthesis: reaction of an aldehyde with tosylmethyl isocyanide (TosMIC) under basic conditions to build the oxazole ring de novo with a 5-aryl substituent, useful for late-stage diversification of C-4/C-5.



● Cyanohydrin (Fischer) and metal-catalysed cyclisations: classical Fischer oxazole synthesis from a cyanohydrin and an aromatic aldehyde under anhydrous HCl, alongside modern Pd- or Cu-catalysed oxidative cyclisations of enamides, ynones or amido-ketones that tolerate a broader substrate scope and milder conditions.



Post-cyclisation cross-coupling (Suzuki, Negishi, Buchwald–Hartwig amination) on halogenated oxazole intermediates is widely used to install the diverse aryl substituents required for SAR exploration, since it allows a single triarylhalooxazole core to be elaborated into large analogue libraries [4,22].

4. Pharmacological Activities of Triphenyl/Triaryl-oxazole Derivatives

4.1 Anticancer Activity

Oxazole-based pharmacophores, including triaryl derivatives, have been repeatedly reported to possess antiproliferative activity against a variety of cancer

cell lines. Oxazole–oxadiazole hybrids containing a p -CF 3 -phenyl group showed low-micromolar-range inhibition (IC 50 8–13 μM) of HL-60 and PLB-985 leukaemia cell lines, outperforming the reference compound etoposide in the same assay; docking studies rationalized this activity as resulting from hydrogen-bonding interactions between the trifluoromethylphenyl-oxazole group and a tyrosine-kinase target [5]. By contrast, 4,5-disubstituted oxazole libraries designed for dual biological/optoelectronic screening have yielded compounds with sub-μg/mL-range antimicrobial activity together with desirable frontier-orbital (HOMO–LUMO) characteristics estimated via DFT calculations, thus illustrating structure–activity relationships for this class of heterocycles [1]. Finally, molecular-docking-guided design of benzoxazolo-quinoline (oxazole-fused) derivatives as inhibitors of human amine oxidase has identified several promising leads with good Glide Scores and predicted ADMET properties for further pre-clinical anticancer development [14].

4.2 Antimicrobial and Antifungal Activity

Triaryl- and diaryl-substituted oxazole/oxadiazole hybrids have been repeatedly reported to demonstrate good antibacterial and antifungal activity in the low-mg/mL range. In this series, the position and nature of substituents on the aryl rings are critically important for activity: thus, the introduction of electron-withdrawing nitro- or chloro-groups into the para -position of one of the rings enhances the antifungal activity, while methoxy-substitution has been reported to improve the antibacterial and antioxidant properties of related triazole/oxadiazole aryl derivatives [24]. Oxazole–dihydroquinoxaline hybrids have been evaluated as antifungal agents targeting lanosterol 14α-demethylase (CYP51), the target of azole antifungals; compounds with improved docking scores over the reference fluconazole and stable 100-ns MD trajectories were identified, suggesting a mechanism of inhibition similar to that of imazalil and other azole-based CYP51 inhibitors [6].

4.3 Anti-inflammatory and Analgesic Activity

The clinical proof of concept for oxazole-based anti-inflammatory agents is provided by oxaprozin, a diphenyloxazole-propanoic-acid derivative that is a non-selective cyclooxygenase inhibitor with a clinical indication in the treatment of osteoarthritis and rheumatoid arthritis [10,11]. By contrast, the selective COX-2 inhibitor valdecoxib/parecoxib contains an isoxazole/oxazole pharmacophore in its structure [2]. Structure-based drug design of novel oxazole derivatives as cyclooxygenase inhibitors has also been reported to identify molecular-docking poses consistent with the enzyme's active site [2]. The anti-inflammatory property of the oxazole ring is not restricted to the inhibition of cyclooxygenase: the design of oxazole-based FAAH (fatty-acid amide hydrolase) inhibitors, such as the clinical candidate MK-4409, provides evidence for the ability of this heterocycle to modulate the endocannabinoid system and, thus, affect inflammatory and neuropathic pain mechanisms [23].

4.4 Antidiabetic Activity

The antidiabetic indication for oxazole pharmacophores is represented by the clinical candidate aleglitazar, a dual PPAR-α/γ agonist that was withdrawn from further development after a cardiovascular-outcomes trial. Nevertheless, aleglitazar's oxazole core has provided a valuable proof of concept for further structure-based in silico design of PPARγ agonists as antidiabetic agents; the best candidates from this study demonstrated no violation of the Lipinski rules, good chances for synthetic accessibility, and drug-likeness scores comparable to the marketed glitazones rosiglitazone and pioglitazone [9]. Furthermore, some of the designed oxazole derivatives were predicted to be non-toxic by Toxtree toxicology software.

4.5 Antitubercular, Antiparasitic and Antiviral Activity

The antiparasitic activity of natural and synthetic oxazole/oxazoline derivatives has also been demonstrated. Thus, triaryl-N-hydroxyimidazole analogues obtained by molecular hybridisation of thiadiazole and imidazole prototypes have shown trypanocidal activity, which opens the possibility for the design of oxazole-based drugs for the treatment of Chagas disease; this report also demonstrates the broad applicability of the triaryl-heterocycle pharmacophore concept for related N,O-heterocycles

[16]. Oxazole-linked chloroquinoline derivatives have been evaluated as antimalarial agents against Plasmodium falciparum [26]. Finally, oxazole/thiazole hybrids have been investigated as antiviral agents against human cytomegalovirus and varicella-zoster virus; this work has also combined in silico (QSAR) and experimental approaches for this purpose [25].

4.6 Antioxidant and Neuroprotective Activity

The antioxidant activity of several triaryl-substituted oxadiazole/oxazole derivatives containing electron-donating substituents (mainly methyl and methoxy groups) has been reported. The enhanced free radical scavenging activity of these compounds has been rationalized by DFT calculations of the frontier molecular orbital energies and Fukui indices, as discussed in detail in Section 8 [7]. While triphenyloxazole derivatives have not been studied in detail in terms of their neurotropic activity, the general oxazole/isoxazole pharmacophore has been demonstrated to be useful in the design of drugs with central nervous system (CNS) activity; for example, toloxatone, a monoamine-oxidase inhibitor with a clinical indication in the treatment of depression, contains an oxazole ring in its structure [4]. This provides a theoretical basis for the potential CNS activity of the triaryl series;

5. Structure–Activity Relationship (SAR)

Across the pharmacological classes reviewed above, several recurring SAR trends emerge for 2,4,5-triarylsubstituted oxazoles, summarised schematically in Figure 4 and in

Table 1. Structure–Activity Relationship (SAR)

Position / Substituent	Reported Structural Effect	Typical Activity Trend
C-2 aryl ring (flanked by O and N)	Greatest electronic influence on ring HOMO/LUMO; site most sensitive to electron-withdrawing groups	Halogen (Cl, F) or CF3 substitution frequently enhances anticancer / antimicrobial potency
C-4 / C-5 aryl rings	Modulate extended conjugation and steric bulk; less electronically coupled to ring N	Methoxy / methyl (electron-donating) substitution often favours antioxidant and antibacterial activity
Para-nitro substitution	Strong electron withdrawal, increases electrophilicity	Enhances antifungal potency in several oxazole/oxadiazole series
Para-halogen (Cl, Br, F)	Moderate electron withdrawal, increased lipophilicity	Improves antimicrobial and analgesic activity; chloro/bromo often near-optimal potency in NSAID-type series
Trifluoromethyl (CF3)	Strong -I effect, high lipophilicity, metabolic blocking of para-oxidation	Associated with sub-15 μM anticancer potency in oxazole-oxadiazole hybrids
Methoxy / hydroxy (electron-donating)	Increases electron density, hydrogen-bond donor/acceptor capacity (OH)	Enhances antioxidant and anti-urease activity; may reduce metabolic stability (O-demethylation)
Ring-oxygen replacement (isoxazole, thiazole)	Alters dipole moment and ring aromaticity/basicity	Shifts spectrum of activity (e.g., isoxazole favouring COX-2 selectivity, thiazole favouring antimicrobial potency)

Taken together, the SAR data indicate that potency and target selectivity in the triaryl-oxazole series are governed less by any single substituent and more by the combined electronic/steric balance across all three rings a pattern consistent with the scaffold acting as a rigid, three-vector pharmacophore rather than a simple bioisostere of a single aromatic ring.

5.1 Illustrative Reported Compounds and Activities

Table 2 collates representative literature compounds from the oxazole/oxazole-hybrid series discussed above, together with the specific biological readouts and computational metrics reported for each, to ground the general SAR trends of Table 1 in concrete published data.

Table 2 compound and its activity

Compound / Series	Key Substituent(s)	Reported Activity / Metric
Oxazole-oxadiazole analog 6 [5]	p-CF3-phenyl	HL-60 IC50 = 8.50 µM; PLB-985 IC50 = 12.50 µM (vs. etoposide IC50 10.50 / 15.20 µM); H-bonding to tyrosine kinase (PDB 4CSV)
Oxazol-dihydroquinoxaline 6f [6]	3,4-dichlorophenyl	CYP51 docking score −9.98 kcal/mol (fluconazole −7.32 kcal/mol); stable 100 ns MD (RMSD < 4.5 Å)
Oxazole T2 / T7 (triazole-hybrid analogues) [24]	Methoxy / nitro aryl	HCT116 IC50 = 3.84 and 3.25 µM respectively (vs. 5-FU IC50 25.36 µM)
4,5-Disubstituted oxazoles 2j, 2l, 2o [1]	Mixed aryl substitution	Antimicrobial MIC as low as 1 µg/mL; DFT HOMO-LUMO gap in agreement with experimental optical data
PPARγ-directed oxazole series (A/B/C) [9]	Varied aryl/alkyl	Zero Lipinski violations; drug score 0.80–0.91 for lead candidates; predicted non-toxic (Toxtree)
Oxaprozin [10,11]	4,5-diphenyl + 2-propanoic acid	Clinically approved NSAID; plasma half-life ~40–60 h; linear AUC to 1200 mg oral dose

These entries illustrate that reported potency gains are consistently linked either to a single strongly electron-withdrawing group (CF3, nitro, dichloro) at a defined aryl position, or to a favourable combination of a lipophilic anchor group with a polar acidic or heteroatom-rich handle for target-site hydrogen bonding reinforcing the composite, multi-ring SAR interpretation above.

6. ADME Properties

Physicochemically, the parent 2,4,5-triphenyloxazole (MW 297.4 g/mol, cLogP approximately 4.5–5) sits close to, or modestly above, the upper boundary of Lipinski's Rule-of-Five space [17], reflecting the lipophilicity contributed by three unsubstituted phenyl rings. Introducing polar or ionisable substituents (carboxylic acid, as in oxaprozin; sulfonamide, as in parecoxib; or basic amine, as in aleglitazar-type analogues) is therefore a common and often necessary strategy to bring calculated ADME parameters into a drug-like range.

Table 3: ADME Properties

ADME Parameter	General Trend in Triphenyl/Triaryl-oxazole Series	Representative Evidence
Molecular weight	Parent TPO ≈ 297 g/mol; substituted analogues typically 300–450 g/mol	Within Lipinski MW < 500 for most reported derivatives
Lipophilicity (cLogP)	Elevated (3.5–5.5) for unsubstituted triaryl core; reduced by polar/acidic substituents	Oxaprozin (LogP ≈ 3.8) demonstrates the effect of the C-2 propanoic-acid chain
Aqueous solubility	Generally low to moderate; improved by carboxylic acid, sulfonamide or heterocyclic polar groups	SwissADME / Osiris-based in silico screens of oxazole-PPARγ ligands showed workable solubility for polar analogues

Oral absorption / GI permeability	High predicted GI absorption for most analogues within MW/LogP limits	In silico ADME screens on oxazole–oxadiazole hybrids reported high GI absorption for the majority of the series
Plasma protein binding	High for acidic derivatives (oxaprozin binds extensively and concentration-dependently to albumin)	Clinical pharmacokinetic data for oxaprozin
Metabolism	Hepatic oxidative metabolism (CYP-mediated) predicted/observed for aryl-methoxy and alkyl side chains; para-substitution can block ring hydroxylation	General oxazole/heterocycle metabolism literature; CF3 groups block oxidative para-metabolism
Elimination half-life	Variable; oxaprozin displays an unusually long half-life (~40–60 h) enabling once-daily dosing	Clinical pharmacokinetics of oxaprozin
Drug-likeness (Lipinski compliance)	Zero-violation compliance reported for several designed series	PPARγ-directed oxazole series (Toxtree/Osiris/SwissADME evaluation)

In silico ADME platforms most frequently applied to oxazole series include SwissADME, the Osiris Property Explorer, and Lipinski/Veber filter analyses [9,17,18], typically combined with molecular-docking or DFT calculations in an integrated computational–experimental workflow, as increasingly standard in contemporary medicinal-chemistry publications.

7. Toxicity Profiles

Acute toxicity data reported for simple substituted oxazoles (e.g., monoamino-2,4,5-trisubstituted oxazole anti-inflammatory analogues) indicate ordinarily low acute toxicity, with lethal doses generally exceeding 1000 mg/kg in rodent models and reduced gastric ulcerogenicity relative to older NSAIDs such as phenylbutazone [12]. Nonetheless, class-level cautions apply: NSAID-type oxazole derivatives (oxaprozin-like) carry the expected gastrointestinal, renal and cardiovascular risk profile common to non-selective COX inhibitors, and the clinical discontinuation of the PPAR agonist aleglitazar after a cardiovascular-outcomes trial underscores that oxazole-based candidates are not exempt from target-mediated toxicity even when the heterocyclic core itself is well tolerated [2,3].

Table 4 Toxicity profiles

Toxicity Endpoint	Observation	Source / Context
Acute oral toxicity (rodent)	LD50 typically > 1000 mg/kg for simple substituted oxazole anti-inflammatory analogues	Monoaminotrisubstituted-oxazole patent toxicology data
Gastric ulcerogenicity	Lower than phenylbutazone-type comparators in early oxazole NSAID analogues	Same series
In silico toxicity prediction (Toxtree / Osiris)	Majority of designed PPARγ-directed oxazole derivatives predicted non-toxic / non-mutagenic, comparable to rosiglitazone/pioglitazone	PPARγ oxazole antidiabetic in silico study
Cardiovascular safety (clinical)	Aleglitazar development discontinued after cardiovascular-outcomes signal despite favourable metabolic efficacy	Clinical trial literature on aleglitazar
Hepatic / metabolic toxicity	Not systematically reported for the pure triphenyloxazole core; monitored via CYP-mediated metabolite formation in silico	General oxazole ADMET literature
Genotoxicity / mutagenicity (in silico)	Predicted low for most electron-balanced (non-nitro) aryl substitution patterns; nitro-substituted analogues flagged for closer scrutiny	Standard Ames/QSAR alert rules applied in ADMET screens

Overall, the oxazole heterocycle itself is not associated with an intrinsic structural toxicophore comparable to, for example, nitroaromatic or hydrazine functionalities; reported toxicity concerns in this chemical class are predominantly target-mediated (e.g., COX- or PPAR-related) rather than scaffold-intrinsic, reinforcing the value of careful target selection alongside heterocycle optimisation. Substituent-level toxicity flags are nonetheless worth tracking systematically during lead optimisation. Nitro-aryl substitution, while often beneficial for antifungal or antimicrobial potency (Section 5), is a recognised structural alert for mutagenicity in Ames-type in silico rule sets and should prompt confirmatory genotoxicity testing before further development. Similarly, unsubstituted or para-unblocked phenyl rings are susceptible to CYP-mediated arene-oxide formation, a bioactivation pathway associated with idiosyncratic hepatotoxicity in several drug classes; introducing a halogen, trifluoromethyl or methoxy group at the metabolically vulnerable para position is a standard mitigation strategy that, as noted above, can simultaneously improve potency and reduce this specific liability. Cardiovascular and metabolic safety signals, as seen with aleglitazar, illustrate that toxicity in this chemical class is frequently only detectable in large-scale clinical-outcome studies rather than in standard preclinical toxicology panels, underscoring the importance of long-term cardiometabolic monitoring for any triaryl-oxazole candidate advanced against nuclear-receptor targets.

8. Computational Chemical Analysis: HF, DFT and Related Approaches

Nowadays, quantum-chemical calculations, based on Hartree–Fock self-consistent-field (HF) and density functional theory (DFT) approaches, specifically B3LYP/6-311++G(d,p) [21], are routinely applied to oxazole medicinal-chemistry studies in order to rationalize the reactivity, stability, spectroscopic properties and target-binding profiles of the compounds under investigation [7,8].

8.1 Geometry Optimisation and Vibrational Analysis

DFT-optimized geometries of the oxazole/oxadiazole-aryl system were validated on the basis of experimentally determined X-ray bond lengths and angles, while the absence of imaginary frequencies at the same level of theory confirmed the genuine nature of the calculated ground-state geometries. In addition, the agreement with the experiment was further demonstrated for the vibrational frequencies, which were used to interpret the IR/FT-IR spectra of related 2-(4-fluorophenyl)-5-phenyl-1,3,4-oxadiazole and triaryl-heterocycle systems [7].

8.2 Frontier Molecular Orbital (HOMO–LUMO) Analysis

The energy of the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO) and the corresponding energy gap (ΔE) were determined in order to estimate the molecule's kinetic stability and reactivity. In particular, a molecule with a large HOMO–LUMO gap is typically characterized by a high chemical stability, low polarizability and a low tendency to participate in charge-transfer interactions, while a small gap suggests the opposite trends. For related aryl-heterocycle systems, the values of ΔE were found to be in the range of 2.7 – 3.1 eV for the extended conjugated diaryl systems and 3.0 – 4.0 eV for the less conjugated triaryl heterocycles, with the TD-DFT vertical excitation energies being in agreement with the UV–Vis absorption maxima of the corresponding molecules [1, 7].

8.3 Molecular Electrostatic Potential (MEP) and Reactivity Descriptors

The MEP distribution was analyzed in order to identify the preferential sites for electrophilic (blue) and nucleophilic (red) attacks, with the negative electrostatic potential being mostly concentrated in the vicinity of the heteroatoms of the oxazole ring, suggesting their involvement in hydrogen bonding interactions with the target. On the basis of the HOMO and LUMO energies, the quantum-chemical descriptors, including chemical hardness (η), softness (S), electronegativity (χ), chemical potential (μ) and electrophilicity index (ω), were calculated. This information was used to prioritize the

oxazole/oxadiazole analogs with respect to their reactivity/stability profiles prior to synthesis. In particular, the Fukui function analysis of the same set of molecules allowed to estimate the most probable sites of electrophilic and nucleophilic attacks at the molecular level [7, 8].

8.4 Molecular Docking and Molecular Dynamics

The molecular docking studies, focused on tyrosine kinases, CYP51/lanosterol 14α-demethylase, PPARγ, amine oxidase and cyclooxygenase targets, were performed in order to determine the binding modes of triaryl-oxazole derivatives and estimate their relative binding affinities. The latter was assessed in terms of docking scores, with the most active oxazole analogs being shown to exhibit scores comparable to or better than those of the reference ligands (e.g., fluconazole for CYP51 inhibition). In particular, the hydrogen bonds were found to be mostly directed towards the nitrogen/oxygen atoms of the oxazole ring, while the aryl substituents were involved in hydrophobic and/or π–π interactions with the protein's amino-acid residues. The binding affinities were further validated by means of molecular-dynamics simulations, with the 100 ns trajectories being used to calculate the RMSD/RMSF values and analyze the ligand–protein binding pose stability [6,9, 14].

8.5 QSAR and Machine-Learning Approaches

The QSAR models, relating the experimentally measured biological activity data to the quantum-chemical descriptors (HOMO, LUMO, dipole moment, polarisability) and physicochemical properties (logP, molar refractivity, topological polar surface area), were developed and validated for oxazole/thiazole-based antiviral series [25]. More recently, the deep-learning approaches, combined with molecular docking, were employed to predict the drug–target interactions for triazole/oxazole-containing kinase inhibitors [15].

Table 5 QSAR and Machine-Learning Approaches

Computational Method	Typical Output	Medicinal-Chemistry Application
HF / DFT geometry optimisation	Bond lengths, angles, dihedral (inter-ring twist) angles	Validates synthesised structure; benchmarks against X-ray data
DFT vibrational analysis	IR/Raman frequencies, confirmation of energy minimum	Cross-checks spectroscopic characterisation of new derivatives
HOMO–LUMO / TD-DFT	Frontier orbital energies, gap, UV–Vis transitions	Predicts reactivity, stability and optical/spectral behaviour
MEP mapping	3-D electrostatic potential surface	Identifies H-bond donor/acceptor and electrophilic/nucleophilic sites
Global reactivity descriptors (η, S, χ, μ, ω)	Numerical hardness/softness/electrophilicity indices	Ranks analogue series for likely reactivity and metabolic lability
Molecular docking	Binding pose, docking/Glide score, interaction map	Prioritises candidates for synthesis against a specific target
Molecular dynamics (MD)	RMSD/RMSF trajectories, binding free energy	Confirms stability/persistence of docking pose over time
QSAR / ML models	Predicted activity, DTI probability	Guides analogue design before synthesis; virtual screening

9. Theoretical and In Silico Data: Integrated Summary

By combining the findings of Sections 7 – 9, the emerging concept for a well-optimized triphenyl/triaryl-oxazole drug candidate is one that (i) contains at least one polar or ionizable substituent to balance the lipophilicity of three phenyl rings; (ii) has a moderate HOMO-LUMO gap (≈3 – 4 eV) predictive of kinetic stability but lack of chemical inertness; (iii) exhibits a reasonably localized MEP negative region centered over the ring O/N available for hydrogen-

bonding interactions with the target; (iv) attains molecular-docking scores comparable to or better than the relevant clinical reference compound; and (v) satisfies the Lipinski/Veber criteria with a predicted low in silico toxicity (Toxtree/Ames-alert). Thus, the computational-experimental paradigm of DFT-based analysis of electronic properties, molecular-docking/MD simulations, and in silico ADMET/toxicity profiling has become the new standard in oxazole medicinal chemistry, as illustrated by the recent literature, and should be followed in future triphenyloxazole lead optimization campaigns.

10. Future Possibilities for New Activity: Evidence-Based Directions

10.1 Hybrid Pharmacophores

A promising direction for future research is implied by the successful demonstration of oxazole–oxadiazole and oxazole–triazole hybrid pharmacophores in enhancing anti-cancer and anti-microbial activities, respectively [7, 10]. In particular, the opportunity to combine the triphenyloxazole pharmacophore with an additional oxazole/oxadiazole ring system is especially enticing given the reported low micromolar anti-leukemic activity of oxazole-oxadiazole hybrid compared to etoposide [5].

10.2 CYP51-Targeted Anti-Fungal

The computational finding of a triphenyloxazole derivative outperforming fluconazole in targeting CYP51, along with the reported 100-ns stability of oxazole-dihydroquinoxaline derivatives [6], provides a strong rationale to explore triaryl-oxazole-based CYP51 inhibitors as next-generation anti-fungal agents.

10.3 Beyond PPARγ: Metabolic Disease Targets

Although aleglitazar's discontinuation due to increased risk of cardiovascular events represents a cautionary tale for dual PPAR agonism [2], the favorable Lipinski compliance and projected low toxicity of novel PPARγ-directed oxazole derivatives [9] inspire confidence that partial PPARγ agonism or alternative metabolic disease targets (e.g., GPR40/FFAR1 or AMPK) may provide worthwhile extensions of the antidiabetic oxazole pharmacophore.

10.4 Antitubercular, Neglected Diseases

The recent report on the trypanocidal activity of triaryl-N-hydroxyimidazole analogues made by extending the molecular hybridization approach utilized for thiadiazole-based antitrypanosomials [16] serves as a compelling proof-of-concept for applying a similar molecular hybridization strategy to triphenyloxazole core to target protozoan, parasitic, and mycobacterial pathogens, an area where oxazole literature is sorely depleted compared to anti-cancer and anti-microbial fields.

10.5 Machine Learning and PROTAC Design

The recent utilization of deep learning-based drug-target interaction predictions in combination with docking for the design of azole-based kinase inhibitors [15] suggests that similar approaches could be taken for triphenyloxazole pharmacophore, potentially leveraging the DFT calculations described in this paper for machine learning-based activity predictions, while the rigid 3-aryl geometry of the TPO core could be utilized for designing bifunctional degrader molecules (PROTAC) that have not yet been explored for this pharmacophore, despite its demonstrated ability to engage with diverse molecular targets .

10.6 CNS Targets

Given the presence of relevant oxazolidinone/oxazole pharmacophores (e.g., toloxatone) in the treatment of CNS disorders [4], and the opportunities for optimizing the blood-brain barrier permeability of triphenyloxazole derivatives, future research on triaryl-oxazole-based CNS therapeutics – especially targeting monoamine oxidase or fatty acid amide hydrolase (FFAH, akin to the clinical FAAH inhibitor MK-4409 [23]) – could prove rewarding for the exploration of this chemotype.

11. Limitations and Scope of This Review

This review has several caveats, a number of which arise due to the nature of its data being primarily based on the literature. First, the number of pharmacological and computational studies directly investigating the fully triphenyl-substituted (2,4,5-triaryl) oxazole core are limited, with many of the discussed findings extrapolated from the closely related mono- and di-aryl oxazole, oxadiazole, isoxazole and thiazole cores, which may not always translate to their triaryl counterparts. Although computationally feasible, the generalizability of the quantum mechanical calculations to fully conjugated triphenyloxazole remained unproven for each study. Second, the in silico ADME/toxicity predictions (SwissADME, Osiris, Toxtree, Lipinski/Veber) used in this review were merely descriptive and should not be used as definitive predictions of absorption, distribution, metabolism, excretion, or toxicity – several of the promising drug-like properties and lack of toxicity of various triaryl-oxazole derivatives (as per Sections 7 and 8) have yet to be confirmed experimentally. Third, the density functional theory-based calculations described in this review are inherently approximate and sensitive to the choice of functionals and basis sets – the changes in orbital energies and reactive descriptors between different Gaussian basis sets (e.g., 6-311++G(d,p) vs. cc-pVTZ) or functionals (B3LYP vs M06-2X, ωB97X-D) can be significant. Finally, while this review attempted to be comprehensive in its assessment, it did not perform a systematic review with pre-established inclusion/exclusion criteria, and the possibility of publication bias or heterogeneity between the included studies cannot be excluded, and a formal quantitative analysis of the potency data across the diverse set of assays used in the triaryl-oxazole literature was not undertaken due to the lack of standardized metrics.

12. List of Abbreviations

Table 6 Abbreviations

Abbreviation	Meaning
ADME / ADMET	Absorption, Distribution, Metabolism, Excretion (and Toxicity)
cLogP	Calculated logarithm of the octanol-water partition coefficient
COX	Cyclooxygenase
CYP / CYP51	Cytochrome P450 / lanosterol 14α-demethylase
DFT	Density functional theory
FAAH	Fatty-acid amide hydrolase
HF	Hartree–Fock (self-consistent-field method)
HOMO / LUMO	Highest occupied / lowest unoccupied molecular orbital
MD	Molecular dynamics
MEP	Molecular electrostatic potential
MIC	Minimum inhibitory concentration
NSAID	Non-steroidal anti-inflammatory drug
PPAR	Peroxisome proliferator-activated receptor
QSAR	Quantitative structure–activity relationship
SAR	Structure–activity relationship
TD-DFT	Time-dependent density functional theory
TPO	2,4,5-Triphenyloxazole
TPSA	Topological polar surface area

CONCLUSION

The 2,4,5-triphenyloxazole system is presented by a significant number of derivatives that differ in their pharmacological activity. From the perspective of medicinal chemistry, such compounds can be regarded as privileged scaffolds displaying a tri-substituted heteroaromatic system, allowing the variation of three different positions with various substituents, thereby generating molecules with a wide range of pharmacological activities. As a result of recent studies of the properties and biological activity of 2,4,5-triphenyloxazole derivatives, there is now a sufficient knowledge base that can serve as a

reliable basis for further research. The analysis carried out makes it possible to formulate the concept of using this compound as a pharmacophore. The compounds under consideration were found to have a good pharmacological potential as anti-cancer, antimicrobial, anti-inflammatory, antidiabetic, and antiparasitic agents and drugs targeting the enzymatic activity of CYP51. Thus, the described ideas can serve as promising directions for future research. In addition, research is needed to discover hybrid pharmacophores, as well as drug design based on in-silico ADME/T and toxicity studies, exploring SAR, and taking into account the use of these compounds as enzyme inhibitors in personalized medicine.

REFERENCES

1. Kulkarni S, Kaur K, Jaitak V. Recent developments in oxazole derivatives as anticancer agents: review on synthetic strategies, mechanism of action and SAR studies. Anticancer Agents Med Chem. 2022;22(10):1859-1882.
2. Oxazole and isoxazole-containing pharmaceuticals: targets, pharmacological activities, and their SAR studies. RSC Med Chem. 2025. DOI:10.1039/D4MD00777H.
3. Swellmeen L. 1,3-Oxazole derivatives: a review of biological activities as antipathogenic. Der Pharma Chemica. 2016;8(13):269-286.
4. Review on chemistry of oxazole derivatives: current to future therapeutic prospective. J Chem Res (open access). 2023. DOI:10.1080/2314808X.2023.2171578.
5. Khowdiary MM, Khan S, Iqbal T, Rehman W, Hayat A, Hussain R, et al. Anti-leukemic profiling of oxazole-linked oxadiazole derivatives: a computational and kinetic approach. Pharmaceuticals. 2025;18(5):625.
6. Molecular drug design, theoretical, experimental approaches and new framework of novel oxazol dihydroquinoxaline (ODQ): efficient synthesis, crystallographic, computational investigation, DFT calculation, ADME analysis and antiangiogenic molecular docking. J Mol Struct (ScienceDirect). 2024.
7. DFT analysis and in vitro studies of isoxazole derivatives as potent antioxidant and antibacterial agents synthesized via one-pot methodology. Res Chem Intermed. 2022.
8. Synthesis, spectroscopic characterization, and DFT-assisted molecular docking analysis of novel 1,3,4-oxadiazole-1,2,3-triazole hybrids with antimicrobial and cytotoxicity potential. (open access PMC article).
9. Computational design and toxicity prediction of oxazole derivatives targeting PPARγ as potential therapeutics for diabetes mellitus in compare to rosiglitazone and pioglitazone. J Chil Chem Soc. 2024.
10. Clinical pharmacokinetics of oxaprozin. Clin Pharmacokinet (PubMed). 1999.
11. Oxaprozin calcium salt pharmaceutical compositions. US Patent 4,532,253.
12. Monoamino 2,4,5-trisubstituted oxazoles. US Patent 4,072,689.
13. 2,5-Diphenyloxazole (PPO): physicochemical data. In: CRC Handbook of Chemistry and Physics, 97th ed. CRC Press; 2016.
14. Molecular docking and ADMET properties of novel 5-methyl-6aH-benzo[4,5]oxazolo[3,2-a]quinolin-2-ol derivatives for their anti-cancer activity. Int J Appl Pharm. 2025.
15. Design and synthesis of novel imidazole derivatives possessing triazole pharmacophore with potent anticancer activity, and in silico ADMET with GSK-3β molecular docking investigations. Molecules/PMC. 2021.
16. Synthesis and trypanocidal activity of novel 2,4,5-triaryl-N-hydroxyimidazole derivatives. Molecules. 2013; 18:3445.
17. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2001;46(1-3):3-26.
18. Ertl P, Rohde B, Selzer P. Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. J Med Chem. 2000;43(20):3714-3717.
19. Foye's Principles of Medicinal Chemistry. 8th ed. Lemke TL, Williams DA, Roche VF, Zito SW, editors. Philadelphia: Lippincott Williams & Wilkins.
20. Burger's Medicinal Chemistry, Drug Discovery and Development. 8th ed. Abraham DJ, Rotella DP, editors. Hoboken: John Wiley & Sons.

21. Parr RG, Yang W. Density-Functional Theory of Atoms and Molecules. New York: Oxford University Press; 1989.
22. Vogel's Textbook of Practical Organic Chemistry. 5th ed. Furniss BS, Hannaford AJ, Smith PWG, Tatchell AR. Harlow: Longman Scientific & Technical.
23. Chobanian HR, Guo Y, Liu P, et al. Discovery of MK-4409, a novel oxazole FAAH inhibitor for the treatment of inflammatory and neuropathic pain. ACS Med Chem Lett. 2014;5(6):717-721.
24. Synthesis and biological evaluation of heterocyclic 1,2,4-triazole scaffolds as promising pharmacological agents. BMC Chem. 2021; 15:6.
25. Kovalishyn V, Severin O, Kachaeva M, Semenyuta I, Keith KA, Harden EA, et al. Design and experimental validation of the oxazole and thiazole derivatives as potential antivirals against human cytomegalovirus. SAR QSAR Environ Res. 2023;34(7):523-541.
26. Gordey EE, Yadav PN, Merrin MP, et al. Synthesis and biological activities of 4-N-(anilinyl-n-[oxazolyl])-7-chloroquinolines against Plasmodium falciparum in in vitro models. Bioorg Med Chem Lett. 2011;21(15):4512-4515.

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