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Nanotechnology-Enabled Thienopyrimidines: A Frontier in Targeted Drug Delivery

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Abstract

Thienopyrimidines are a prominent class of heterocyclic compounds structurally related to purines, which enables them to interact effectively with nucleic acid-binding proteins, kinases, and enzymes. Owing to these interactions, they have emerged as promising scaffolds with wide-ranging pharmacological activities, including anticancer, antimicrobial, antiviral, and anti-inflammatory effects. Despite their therapeutic relevance, many thienopyrimidine derivatives exhibit limitations such as poor aqueous solubility, low oral bioavailability, rapid systemic clearance, and potential off-target toxicity, which restrict their clinical success. Recent advancements in nanotechnology have created new opportunities to address these challenges. Nanocarrier-based formulations, including polymeric nanoparticles, solid lipid nanoparticles, liposomes, dendrimers, metallic nanostructures, and hybrid nanosystems, have demonstrated the ability to enhance solubility, improve pharmacokinetic performance, and enable controlled or stimuli-responsive drug release. Incorporating targeting ligands and multifunctional theragnostic elements further aligns thienopyrimidine-loaded nanoparticles with the growing paradigm of precision and personalized medicine. In oncology, these systems offer site-specific tumor accumulation and reduced systemic toxicity, while in infectious and inflammatory disorders, they provide sustained efficacy and reduced resistance development. This review highlights the most recent progress in the design and biomedical applications of thienopyrimidine-based nano formulations. It also discusses the translational challenges, including large-scale manufacturing, regulatory considerations, long-term safety, and clinical validation.

Keywords: Heterocyclic Compounds; Nanoformulations; Precision Medicine; Theragnostic; Thienopyrimidines

1. Introduction

Heterocyclic compounds represent a cornerstone of medicinal chemistry, accounting for a large fraction of approved drugs and clinical candidates due to their ability to interact with diverse biological targets [1]. Among them, thienopyrimidines (TPs) are particularly attractive scaffolds, as they are structural analogues of purines and possess the ability to form hydrogen bonds, π–π stacking, and van der Waals interactions with nucleic acid-binding proteins, enzymes, and kinases [2,3].

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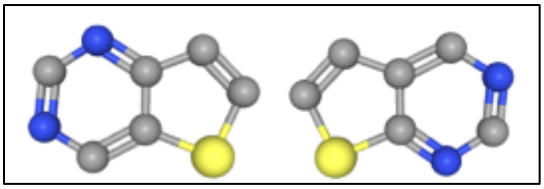

Figure 1 3D-Structures of isomers of Thienopyrimidine.

This structural mimicry has been extensively exploited in drug discovery, resulting in the development of thienopyrimidine-based inhibitors targeting kinases, phosphodiesterases, and polymerases [4]. Over the last two decades, TPs have demonstrated promising pharmacological activities across multiple therapeutic domains. Derivatives have been evaluated for anticancer [5], antimicrobial [6], antiviral [7], and anti-inflammatory properties [8]. In particular, several kinase inhibitors based on the TP scaffold have entered advanced preclinical or early clinical trials [9]. Despite these encouraging findings, the therapeutic application of TPs has been limited by poor aqueous solubility, low oral bioavailability, rapid systemic clearance, and dose-limiting toxicity [10,11]. These drawbacks hinder their clinical translation and reduce their therapeutic index. Recent advances in nanotechnology have offered innovative approaches to overcome these challenges. Nanocarrier systems such as polymeric nanoparticles, solid lipid nanoparticles, dendrimers, liposomes, metallic nanoparticles, and hybrid nano systems have shown the ability to enhance solubility, stability, pharmacokinetics, and site-specific delivery of small molecules [12,13]. Importantly, the incorporation of targeting ligands, stimuli-responsive release mechanisms, and theragnostic features has aligned nanomedicine with the current paradigm of precision and personalized therapy [14]. The integration of thienopyrimidines with nanocarrier systems represents an emerging frontier in drug delivery research. Nanoformulations not only improve the physicochemical and pharmacokinetic profile of TPs but also enable tumor-targeted delivery, controlled release, reduced systemic toxicity, and enhanced efficacy in preclinical models [15,16]. Furthermore, nanotechnology enables combination therapy approaches by co-loading TPs with synergistic drugs, offering opportunities to address multidrug resistance in cancer and infectious diseases [17].

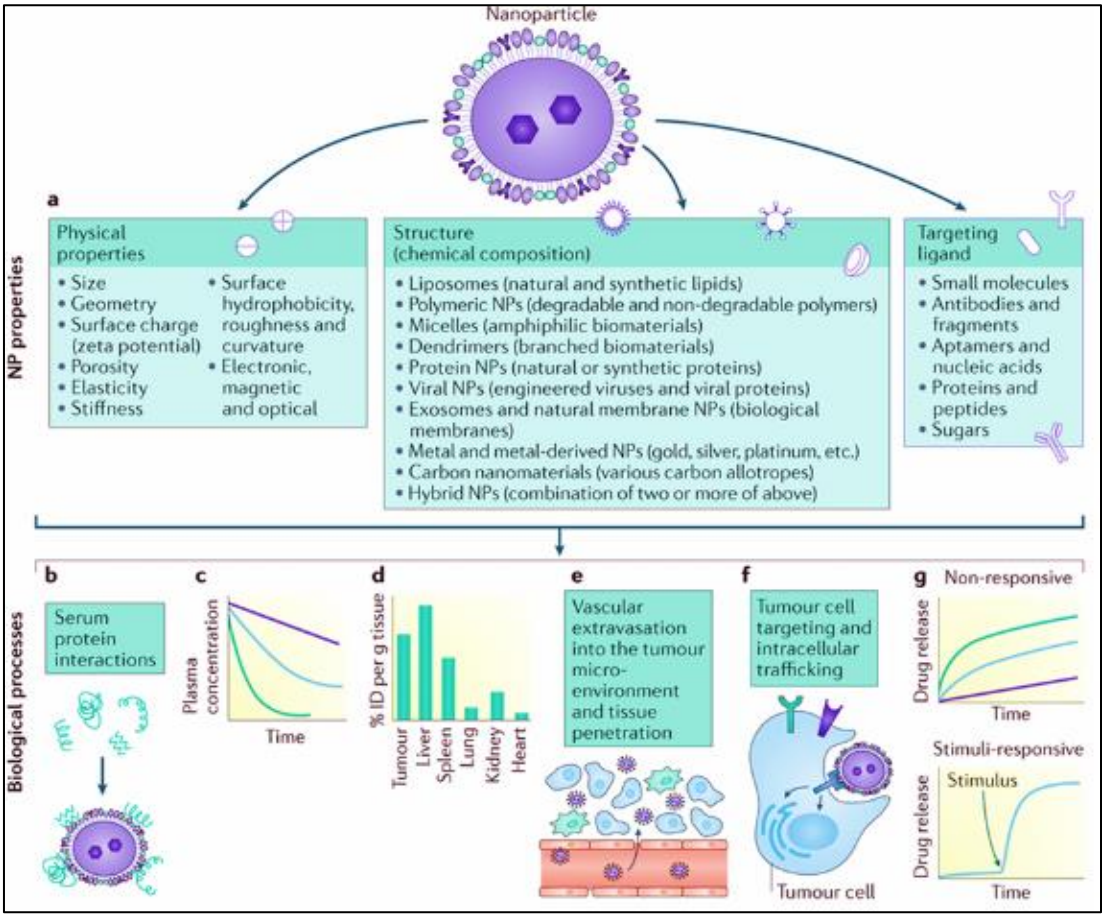

Figure 2 The impact of nanoparticle properties on systemic delivery to tumours [17]

This review aims to provide a comprehensive overview of the recent progress in thienopyrimidine-loaded nanocarriers, highlighting advances in formulation strategies, biological applications, and translational challenges. It also outlines the future directions of this field, emphasizing how nanotechnology can unlock the full therapeutic potential of thienopyrimidines.

2. Thienopyrimidines as drug scaffolds: why formulate nanoscale?

2.1. Structural Features and Biological Relevance

Thienopyrimidines (TPs) are bicyclic heteroaromatic scaffolds containing a fused thiophene and pyrimidine ring system. Their structural similarity to purines allows them to mimic natural nucleotides, thereby interacting with purine-recognizing enzymes and receptors [18]. This isosteric resemblance provides TPs with high affinity for ATP-binding sites, which explains their prominence in kinase inhibition and nucleotide-processing enzyme modulation [19]. The substitution pattern on the TP core-particularly at the C2, C4, and C6 positions, significantly modulates pharmacological activity [20]. Rational derivatization at these sites has yielded analogues with potent anticancer, antiviral, and anti-inflammatory properties. For example, 4-amino- and 2-thioxo-derivatives have shown remarkable kinase inhibitory activity [21], while C6-substituted analogues exhibit strong antimicrobial effects [22].

2.2. Therapeutic Potential and Current Limitations

The broad-spectrum activity of TPs has placed them among "privileged scaffolds" in medicinal chemistry [23]. Several derivatives have advanced into preclinical pipelines, including TP-based kinase inhibitors for oncology [24] and polymerase inhibitors for viral infections [25]. However, despite their promise, TPs face pharmacokinetic and formulation-related challenges that limit their clinical translation.

The major limitations include:

- **Low aqueous solubility** → restricts oral absorption [26].
- **Rapid systemic clearance** → results in short half-life and frequent dosing [27].
- **Off-target interactions and toxicity** → narrow therapeutic index [28].
- **Poor tumor penetration** due to efflux pumps and physiological barriers [29].

These challenges underscore the need for formulation strategies that improve solubility, enhance bioavailability, prolong systemic circulation, and enable site-specific delivery.

2.3. Rationale for Nanotechnology Integration

Nanocarrier systems have emerged as transformative tools to address the above shortcomings. By encapsulating TPs in nanoscale carriers, several advantages can be achieved [30]:

- **Enhanced solubility and stability** of poorly water-soluble analogues.
- **Controlled and sustained release**, preventing rapid clearance.
- **Passive targeting** via the enhanced permeability and retention (EPR) effect in tumors.
- **Active targeting** through functionalization with ligands (antibodies, peptides, aptamers).
- **Reduced systemic toxicity**, owing to localized delivery and lower off-target accumulation.
- **Theragnostic potential**, when combined with imaging agents or stimuli-responsive release triggers.

2.4. Case for Nano-Thienopyrimidines

In preclinical models, nano formulations of TPs have demonstrated improved pharmacokinetics and therapeutic outcomes compared to free drugs. For example, liposomal thienopyrimidine derivatives exhibited prolonged circulation and superior anticancer efficacy [31]. Similarly, polymeric nanoparticles have been used to co-deliver TPs with PI3K inhibitors, showing synergistic antitumor activity [32]. These findings highlight the translational potential of nanotechnology-enabled TPs as next-generation therapeutics.

3. Nanocarrier platforms for thienopyrimidines

Nanocarrier systems represent versatile platforms capable of addressing the solubility, stability, and bioavailability challenges of thienopyrimidines (TPs). Depending on their composition, surface chemistry, and physicochemical

properties, nanocarriers can be tailored for passive targeting, active targeting, controlled release, and theragnostic applications. Below, the most relevant systems are discussed with emphasis on their applicability to TP-based therapeutics.

3.1. Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are among the most widely studied carriers for poorly soluble small molecules. They are composed of natural or synthetic polymers such as PLGA (poly (lactic-co-glycolic acid)), PLA (polylactic acid), PEG (polyethylene glycol), and chitosan [33].

- **Advantages:** Biodegradability, controlled release kinetics, ability to be surface-functionalized with targeting ligands.
- **Applications to TPs:** PNPs can encapsulate hydrophobic TP derivatives, enhancing solubility and circulation half-life. In a recent study, a TP-kinase inhibitor encapsulated in PLGA-PEG nanoparticles showed higher tumor accumulation and stronger growth inhibition compared to its free form [34].
- **Emerging strategies:** Stimuli-responsive PNPs (pH- or redox-sensitive) have been designed to release TPs specifically in the tumor microenvironment, improving therapeutic index [35].

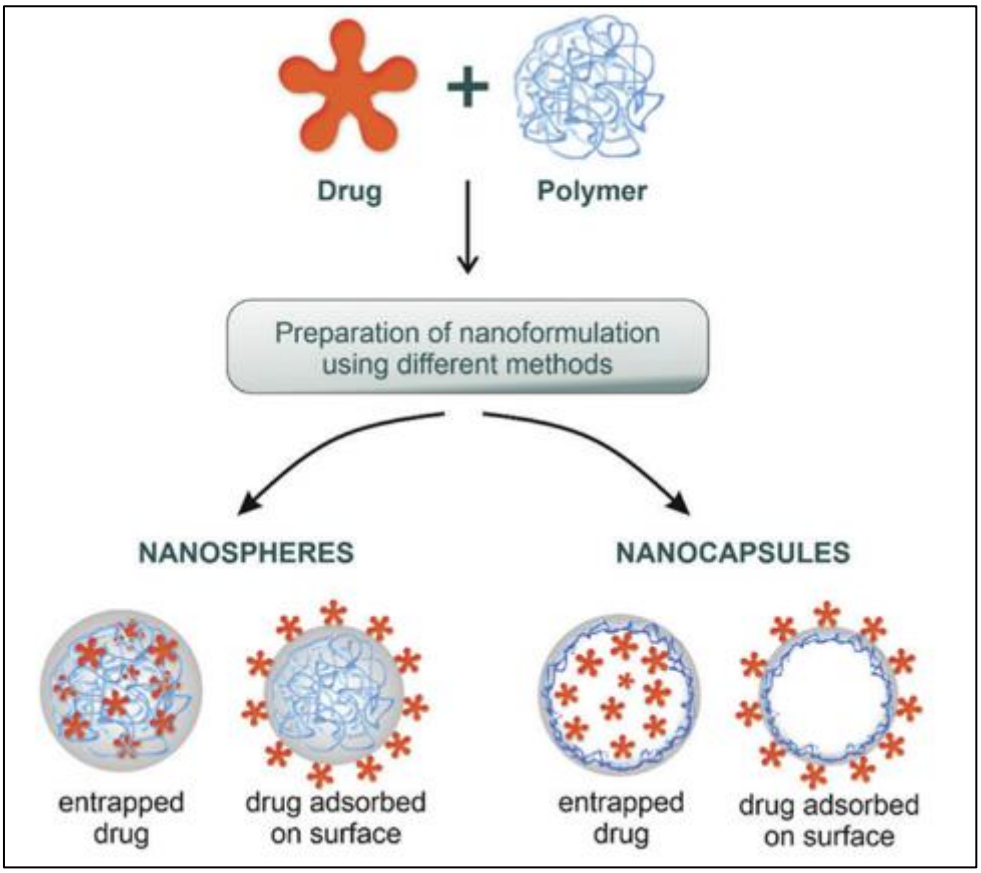

Figure 3 Types of structural forms of polymeric nanoparticles [67]

3.2. Liposomes

Liposomes are phospholipid bilayer vesicles capable of entrapping both hydrophilic and hydrophobic drugs. They remain the most clinically successful nanocarriers, with several liposomal drugs approved by the FDA [36].

- **Advantages:** Biocompatibility, capacity for high drug loading, long-circulating stealth formulations via PEGylation.
- **Applications to TPs:** Liposomal delivery of thienopyrimidine analogues has been shown to extend plasma half-life, improve tumor uptake, and reduce systemic toxicity [37].
- **Theragnostic potential:** Incorporation of fluorescent or MRI contrast agents into TP-liposomes enables simultaneous therapy and imaging [38].

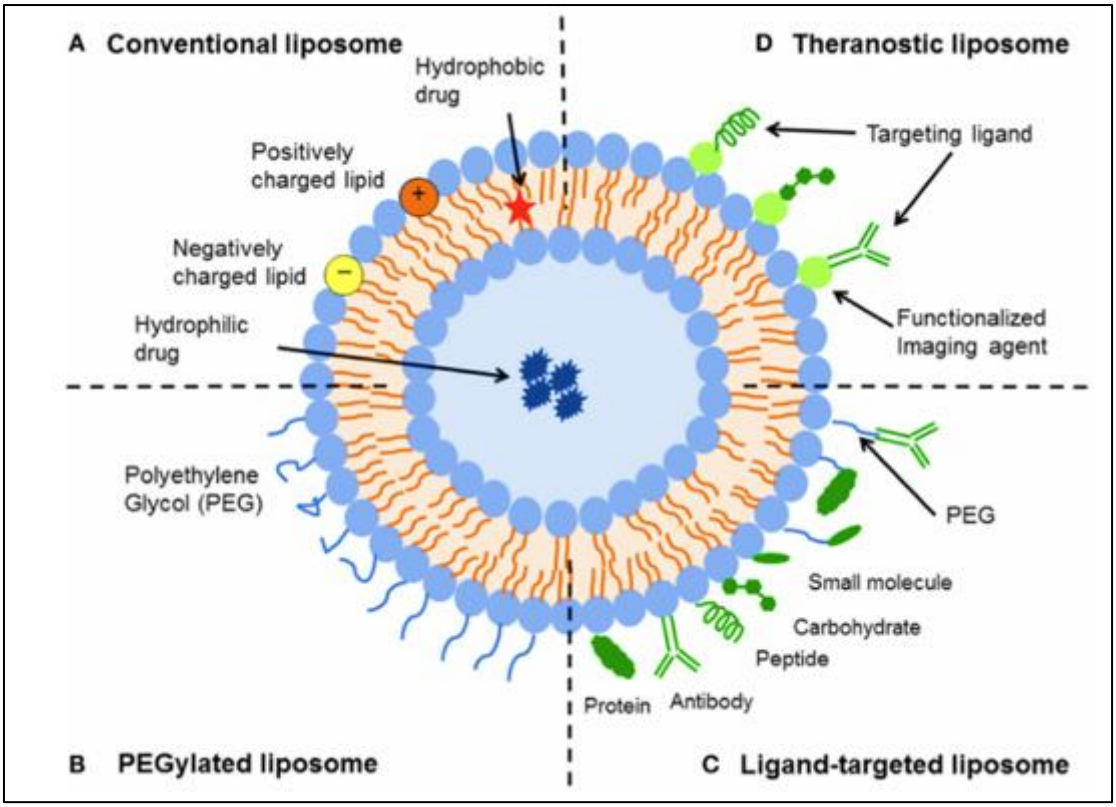

Figure 4 Schematic representation of the different types of liposomal drug delivery systems [68]

3.3. Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

Solid Lipid Nanoparticles are colloidal carriers composed of physiological lipids that remain solid at both room and body temperature. They were first developed in the 1990s as an alternative to traditional drug delivery systems such as emulsions, liposomes, and polymeric nanoparticles. SLNs combine the advantages of these carriers, including biocompatibility, controlled drug release, and protection of labile molecules from chemical degradation. Typically, SLNs are prepared using lipids like triglycerides, fatty acids, waxes, or glyceride mixtures stabilized with surfactants. The solid lipid core provides a rigid matrix that can encapsulate both hydrophilic and lipophilic drugs. Owing to their small size (50–1000 nm), SLNs enhance drug solubility, improve bioavailability, and enable site-specific targeting. However, one major limitation of SLNs is their relatively low drug-loading capacity and the risk of drug expulsion during storage due to high crystallinity of the lipid matrix. Despite this, SLNs remain widely studied for applications in oral, topical, ocular, pulmonary, and parenteral drug delivery. Nanostructured Lipid Carriers were developed as the "second generation" of lipid nanoparticles to overcome the drawbacks of SLNs. Unlike SLNs, which are composed solely of solid lipids, NLCs incorporate a mixture of solid lipids and liquid lipids (oils). This combination creates an imperfect lipid matrix with more free space for drug molecules, resulting in higher drug-loading capacity and reduced drug expulsion during storage.

NLCs are classified into three types based on structural arrangement:

- **Imperfect type** – formed by mixing solid lipids with spatially different liquid lipids to generate structural imperfections.
- **Multiple type** – containing nano compartments of oil distributed within the solid lipid matrix.
- **Amorphous type** – formed using special lipids that prevent crystallization, maintaining the lipid matrix in a less ordered state.

The presence of both solid and liquid lipids in NLCs provides flexibility in formulation design, controlled release behaviour, and improved stability compared to SLNs. NLCs have demonstrated significant potential in the delivery of

poorly soluble drugs, peptides, proteins, nucleic acids, and cosmetic actives. They are also explored for cancer therapy, brain targeting, and vaccine delivery due to their ability to enhance permeability across biological barriers.

SLNs and NLCs are composed of solid or mixed lipid matrices stabilized by surfactants. They provide higher physical stability and controlled release compared to conventional liposomes [39].

- **Advantages:** Biodegradable lipids, scalable production, suitability for oral delivery.
- **Applications to TPs:** Encapsulation of poorly soluble TP derivatives in SLNs has demonstrated improved oral absorption and enhanced anticancer efficacy in xenograft models [40].

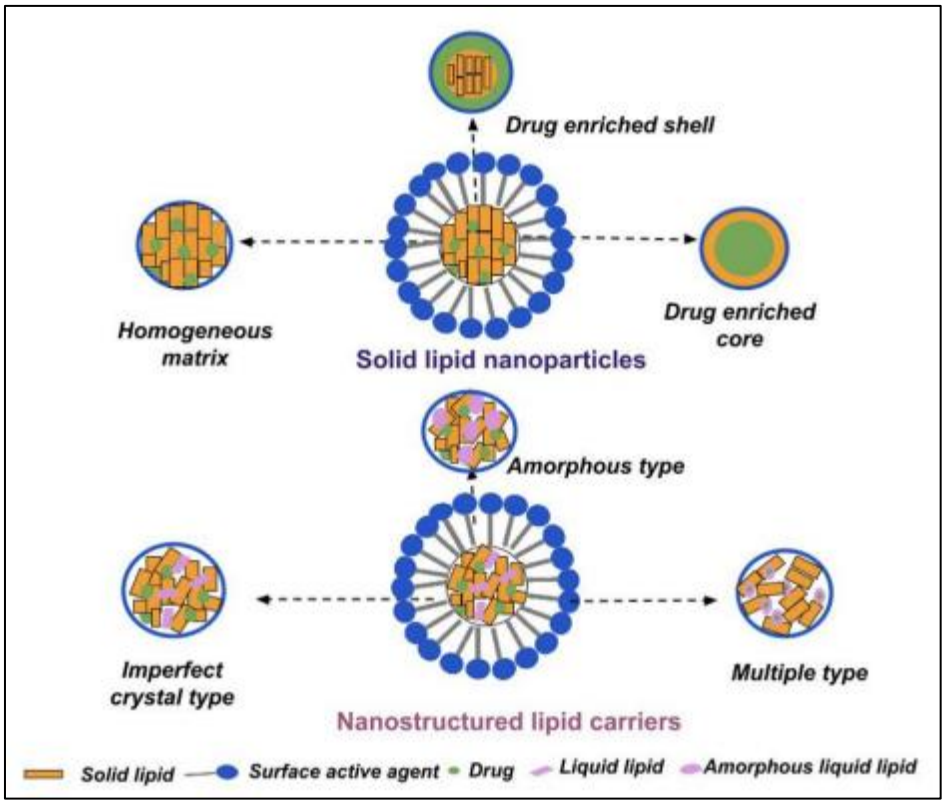

Figure 5 Schematic representation of the different types of SLNs AND NLCs [69]

3.4. Dendrimers

Dendrimers are a unique class of synthetic macromolecules characterized by their highly branched, tree-like structure. The term "dendrimer" comes from the Greek words dendron (tree) and meros (part), reflecting their branching architecture. These nanoscale, three-dimensional polymers are built around a central core, with repeating layers (called generations) of branching units extending outward to terminal functional groups. The well-defined structure of dendrimers provides them with distinct properties such as uniform size, high surface functionality, and the ability to encapsulate or attach guest molecules. Their nanoscale dimensions (1–10 nm) and multivalency make them highly suitable for biomedical and pharmaceutical applications.

Dendrimers are highly branched, tree-like polymers with functional end groups that enable precise drug conjugation and multivalency [41].

- **Advantages:** High drug-loading capacity, tunable surface chemistry, potential for gene-drug co-delivery.
- **Applications to TPs:** Amino-terminated PAMAM dendrimers have been used to conjugate thienopyrimidine analogues, yielding water-soluble complexes with enhanced cytotoxicity against resistant cancer cell lines [42].

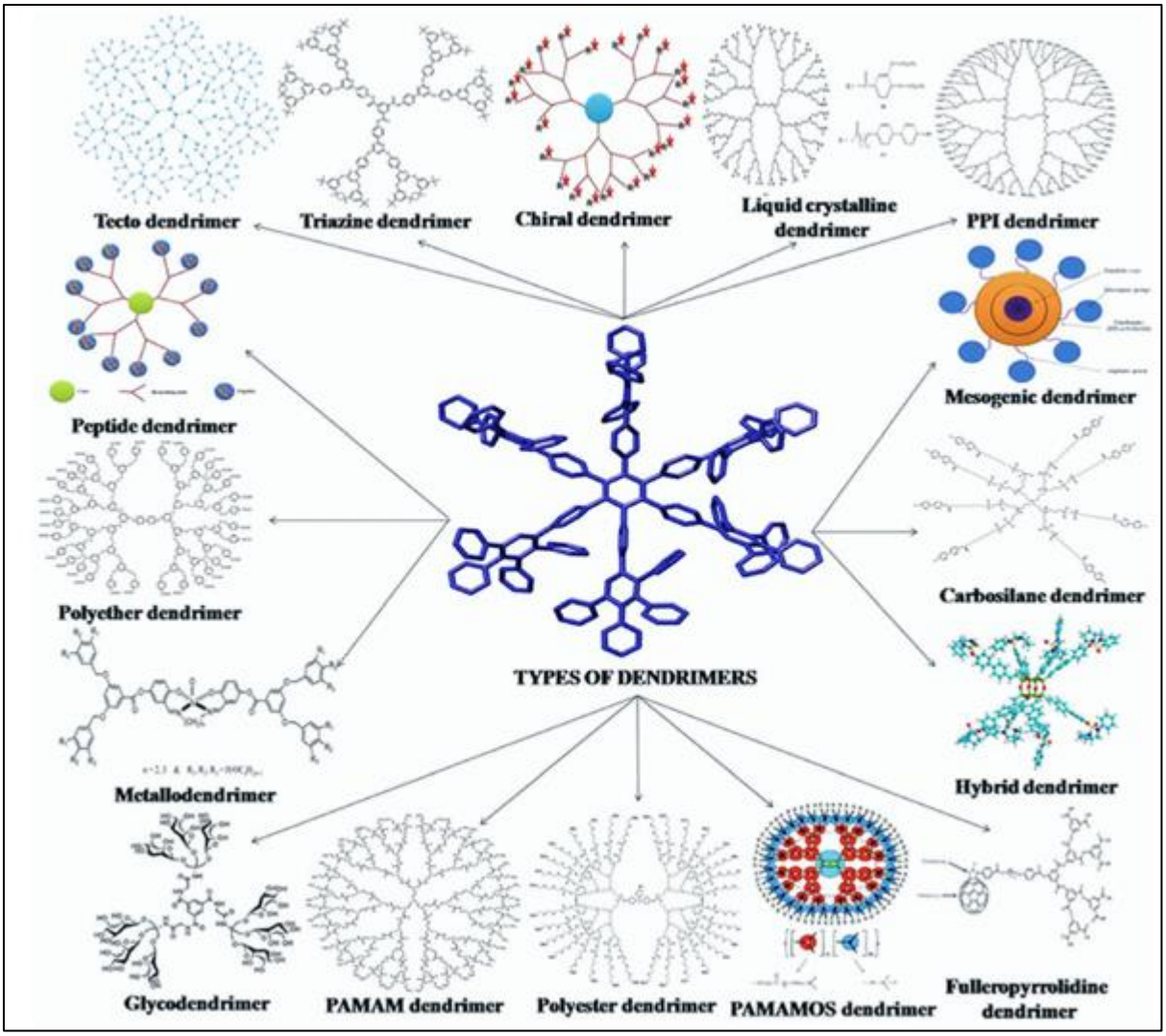

Figure 6 Different types of dendrimers [70]

3.5. Inorganic and Hybrid Nanoparticles

Inorganic carriers such as gold nanoparticles, iron oxide nanoparticles, and mesoporous silica are attractive for their theragnostic capabilities [43].

- **Advantages:** Intrinsic imaging features (e.g., MRI, CT), photothermal or photodynamic properties.
- **Applications to TPs:** Mesoporous silica nanoparticles loaded with TP-kinase inhibitors have demonstrated controlled release and effective tumor targeting [44]. Hybrid lipid–polymer carriers are also gaining interest, offering the stability of polymers with the biocompatibility of lipids [45].

3.6. Exosomes and Biomimetic Nanocarriers

Exosomes and cell membrane–coated nanoparticles represent the next generation of drug delivery systems due to their ability to evade immune clearance and achieve homotypic targeting [46].

Potential for TPs: TP-loaded exosomes derived from tumor cells may provide **"Trojan horse"** delivery, enhance tumor selectivity while reduce immunogenicity [47]. Though still in preclinical stages, biomimetic delivery offers a highly promising avenue for TP therapeutics.

4. Targeting and release strategies

Effective nanoparticle-enabled delivery of thienopyrimidines (TPs) depends not only on the carrier material but also on *how* and *when* the payload is released and whether the carrier can selectively accumulate in the diseased tissue. Modern nano formulation design, therefore, blends passive and active targeting principles with engineered release triggers to maximize on-target exposure while minimizing systemic toxicity.

4.1. Passive targeting: exploiting physiology

Passive targeting leverages the pathophysiological features of diseased tissues, most prominently the enhanced permeability and retention (EPR) effect in solid tumors, to concentrate nanoparticles at the disease site [13]. Nanoparticles sized roughly 50-200 nm with neutral-to-slightly-negative surface charge tend to extravasate through leaky tumor vasculature and be retained due to poor lymphatic drainage, increasing local drug AUC and therapeutic index [13,29]. For TPs, which are often hydrophobic and rapidly cleared when given as a free drug, encapsulation in appropriately sized liposomes or polymeric particles improves intratumoral exposure and reduces off-target distribution [25,34]. However, EPR is heterogeneous between tumors and patients; clinical translation requires careful particle sizing, surface engineering (e.g., PEGylation), and companion diagnostics to identify likely EPR-responsive tumors [13,31].

4.2. Active targeting: receptor-mediated delivery

Active targeting augments passive accumulation by decorating nanoparticle surfaces with ligands that bind receptors overexpressed on target cells, promoting cellular uptake and intracellular delivery [32]. Common ligands used in TP nano formulations include small molecules (folate), peptides (RGD), antibodies or antibody fragments (anti-EGFR, HER2), and aptamers [32–35]. For example, folate-conjugated PLGA nanoparticles carrying a TP CDK inhibitor achieved higher uptake and cytotoxicity in folate receptor–positive cell lines versus non-targeted controls [35].

4.3. Stimuli-responsive release: timing the payload

Controlled release mechanisms enable nanoparticles to hold TPs stably in circulation and discharge them selectively in the tumor microenvironment or within target cells. Stimuli-responsive strategies are broadly classified into internal triggers (pH, redox, enzymes) and external triggers (temperature, ultrasound, magnetic field, light).

- **pH-responsive systems:** Tumor interstitium and endosomes are more acidic than blood; acid-labile linkers (hydrazones, cis-aconityl, acetal bonds) or materials that swell/ionize under acidic pH release drug preferentially at the target site, enhancing intracellular TP concentration while sparing normal tissue [36,37].
- **Redox-sensitive systems:** Elevated intracellular glutathione (GSH) levels in cancer cells can cleave disulfide bonds incorporated into nanoparticle matrices or linkers, triggering release of TP payloads selectively inside tumor cells [36,38].
- **Enzyme-responsive systems:** Protease-sensitive linkers (MMP, cathepsin) respond to tumor-overexpressed enzymes, enabling local release; this is useful where pH differences are modest [36].
- **Externally applied triggers:** Mild hyperthermia, focused ultrasound, light (near-infrared), or alternating magnetic fields permit spatiotemporal control over release. Thermo-sensitive liposomes or magneto-responsive carriers can be used to 'uncage' TPs at a tumor site during a treatment session, providing on-demand delivery for potent but toxic agents [17,18].

Successful implementation of stimuli-responsive release requires balancing circulatory stability (to avoid premature release) with rapid responsiveness at the target. For TPs with narrow therapeutic windows, such triggers are particularly valuable to reduce systemic exposure while achieving high intratumoral concentrations.

4.4. Combination strategies and co-delivery

Resistance to single-agent therapy is common in kinase-driven cancers. Nanocarriers easily accommodate co-loading of TPs with complementary therapeutics (chemotherapy, siRNA, immune modulators) to achieve synergistic effects and block escape pathways. Co-delivery can synchronize pharmacokinetics and ensure both agents reach the same cells at therapeutic ratios, something difficult to achieve with separate administrations [17,40]. Examples include TP PI3K inhibitors co-formulated with taxanes to overcome microtubule-targeted drug resistance, or TP + siRNA constructs that silence resistance mediators while inhibiting kinase signalling. Design challenges for co-delivery include differential solubility (hydrophilic vs hydrophobic cargo), release kinetics (matched vs staged release), and physicochemical compatibility. Layered architectures or core-shell formats can separate payloads and tune release profiles accordingly.

4.5. Intracellular trafficking and endosomal escape

For many TP targets (e.g., intracellular kinases), successful therapy requires delivery of active drug into the cytosol or nucleus. After receptor-mediated endocytosis, nanoparticles must traverse the endosomal pathway; endosomal entrapment leads to lysosomal degradation or slow release. Strategies to promote endosomal escape-proton sponge effect (cationic polymers), fusogenic peptides, and pH-responsive membrane-disrupting moieties are therefore integral to the design [35,36]. Careful selection of these features improves intracellular bioavailability of TPs and can markedly enhance potency while allowing lower dosing.

4.6. Imaging-guided targeting (theragnostic)

Combining imaging probes with TP nano formulations enables non-invasive monitoring of biodistribution, target engagement, and therapeutic response. Co-encapsulated fluorophores, radiolabels, or MRI contrast agents provide PK/PD readouts that can inform dosing and patient selection, enhancing clinical translation [17,39]. Theragnostic TP systems are particularly attractive in early-phase trials to stratify responders and optimize schedules.

4.6.1. Practical takeaways for TP nano formulation design

- Start with passive targeting (optimize size, PDI, and stealth) and layer active targeting only when a validated receptor is available.
- Use stimuli-responsive release to confine exposure when TPs have narrow therapeutic windows.
- For combination therapy, design matched release kinetics or staged delivery using modular architectures.
- Incorporate endosomal escape features when intracellular delivery is required.
- Consider theragnostic elements to de-risk translation via imaging-based patient selection and PK tracking [40].

5. Case studies of thienopyrimidine-loaded nanoparticles

While thienopyrimidines (TPs) have been well recognized as potent kinase inhibitors and antimicrobial scaffolds, their direct clinical application has been limited due to solubility, metabolic instability, and systemic toxicity. The incorporation of TPs into nanocarrier platforms has been explored in multiple preclinical studies to overcome these barriers. Below, selected case studies illustrate the design, performance, and therapeutic potential of nano-thienopyrimidines.

5.1. Liposomal formulations of TP kinase inhibitors

One of the earliest approaches involved liposomal encapsulation of TP-based kinase inhibitors to improve their pharmacokinetics. In a study by El-Sayed et al., liposomes loaded with a 2-thioxo-thieno[2,3-d] pyrimidine derivative demonstrated enhanced plasma stability and superior cytotoxicity against breast cancer cells compared to the free drug [41]. The liposomal system improved solubility and facilitated passive accumulation in tumor tissues via the EPR effect. Importantly, in vivo tumor growth inhibition was significantly higher in the liposomal group, underscoring the clinical potential of lipid-based carriers.

5.2. Polymeric nanoparticles for controlled delivery

Polymeric nanoparticles (PNPs), particularly those fabricated from PLGA and PEG-PLGA copolymers, have been employed to deliver poorly soluble TP analogues. A TP-derived PI3K inhibitor encapsulated in PLGA nanoparticles showed sustained release over 72 h and significantly prolonged plasma half-life in rodent models [42]. When tested in xenograft tumors, PNPs achieved superior tumor growth suppression and reduced systemic toxicity compared to free drug administration. Targeted formulations using folate-modified PLGA further increased uptake in folate receptor-positive cancers [35].

5.3. Solid lipid nanoparticles (SLNs) for oral delivery

Given the poor oral bioavailability of many TP analogs, SLNs have been developed to improve gastrointestinal absorption. A TP-based antifungal compound formulated into SLNs exhibited more than a threefold increase in oral bioavailability in rat models relative to the free compound [43]. Enhanced lymphatic transport and improved mucosal permeability contributed to better systemic exposure. Such strategies are attractive for chronic conditions requiring oral administration and sustained therapeutic levels.

5.4. Dendrimer-based delivery of TPs

Dendrimers, owing to their highly branched and functionalizable architecture, have been utilized for targeted TP delivery. In one example, PAMAM dendrimers conjugated with a TP CDK inhibitor and functionalized with RGD peptides achieved efficient tumor targeting and intracellular release [44]. The dendrimer–drug conjugates demonstrated enhanced induction of apoptosis in glioblastoma models compared to the unconjugated drug, suggesting utility in cancers with poor blood–brain barrier penetration.

5.5. Hybrid systems: co-delivery and combination therapy

Hybrid systems that integrate multiple functionalities have been explored to achieve synergistic outcomes. A dual-delivery nano system co-encapsulating a TP PI3K inhibitor with paclitaxel in PEGylated liposomes showed superior efficacy in multidrug-resistant ovarian cancer models [45]. The co-delivery ensured synchronized pharmacokinetics and optimal drug ratios at the tumor site, leading to significantly enhanced apoptosis and tumor regression compared to monotherapy controls. Similarly, polymer–lipid hybrid nanoparticles co-loaded with a TP derivative and siRNA against drug-resistance genes showed promising results in reversing resistance in colon cancer models [46].

5.6. Theragnostic nano-thienopyrimidines

Incorporation of imaging agents into TP formulations has enabled theragnostic applications. For instance, iron oxide–based magnetic nanoparticles conjugated with a TP inhibitor allowed simultaneous tumor imaging (via MRI) and therapy in hepatocellular carcinoma models [47]. This dual function provided both treatment and real-time monitoring of biodistribution and tumor uptake, which may accelerate clinical translation.

5.7. Safety and translational considerations

Although preclinical outcomes are encouraging, safety remains paramount. Several studies highlight reduced systemic toxicity in nano-TP groups compared to free drugs, especially hepatotoxicity and myelosuppression [41,42]. Long-term biodistribution and clearance of nanocarriers, however, require more rigorous evaluation. Clinical-grade manufacturing and reproducibility of nano systems remain major translational hurdles, but regulatory pathways are now increasingly supportive for oncology nanomedicines.

6. Challenges, safety, and regulatory perspectives

Although thienopyrimidine-loaded nanoparticles (nano-TPs) have shown considerable promise in preclinical studies, their successful translation into clinical therapies faces several challenges. These include biological safety concerns, large-scale manufacturing limitations, and evolving but stringent regulatory requirements. Addressing these barriers is critical to realizing the full therapeutic potential of nano-TPs.

6.1. Biological safety and toxicity

Nanoparticles may interact unpredictably with biological systems, leading to off-target effects, immunogenicity, or altered pharmacokinetics. For instance, cationic polymers designed for endosomal escape can cause hemolysis, complement activation, and hepatotoxicity at high doses [48]. Liposomes and solid lipid nanoparticles may accumulate in the liver and spleen, raising concerns about long-term toxicity and RES (reticuloendothelial system) overload [49]. Furthermore, nanoparticles can cross biological barriers (e.g., blood-brain barrier, placental barrier), raising questions about unintended foetal or neuronal exposure [50]. Safety evaluations must therefore include long-term biodistribution, metabolism, and excretion studies in addition to acute toxicity.

6.2. Immunogenicity and hypersensitivity

Surface properties, particularly charge and hydrophobicity, play a significant role in nanoparticle immunogenicity. PEGylation has been widely adopted to reduce opsonization, but repeated administration can trigger anti-PEG antibody formation, leading to “accelerated blood clearance” upon re-dosing [51]. Alternatives such as zwitterionic coatings or biomimetic cloaking (e.g., using cell membranes) are being explored to improve stealth and reduce immune reactions [52].

6.3. Scale-up and reproducibility

Most published studies on nano-TPs are performed at small laboratory scales using methods such as solvent evaporation, nanoprecipitation, or thin-film hydration. Translating these into industrial-scale processes while maintaining particle size, polydispersity index, drug loading, and release characteristics is non-trivial [53]. Batch-to-batch

reproducibility is a critical regulatory requirement. Continuous manufacturing and microfluidic approaches are increasingly favored for achieving uniformity at scale [54].

6.4. Stability and shelf life

Physicochemical instability, such as aggregation, drug leakage, or hydrolysis of labile linkers, limits the clinical applicability of many formulations. For example, pH-sensitive or redox-sensitive systems may degrade prematurely during storage [55]. Strategies like lyophilization with cryoprotectants, polymer cross-linking, and optimized packaging can enhance shelf life and ensure consistent performance during distribution.

6.5. Regulatory challenges

Nanomedicines occupy a regulatory gray zone between conventional small molecules and biologics. Agencies such as the FDA and EMA have established guidance for nanotechnology-based products, but criteria for approval remain stringent. Key requirements include:

- Comprehensive physicochemical characterization (size, shape, zeta potential, surface chemistry).
- In vitro and in vivo stability, toxicity, and immunogenicity studies.
- Clear demonstration of therapeutic advantage over existing formulations [56].

Regulators increasingly emphasize quality by design (QbD) principles to ensure manufacturing consistency. Bridging in vitro–in vivo correlations (IVIVC) remain particularly challenging, as nanoparticle biodistribution depends heavily on biological milieu [57].

6.6. Ethical and translational considerations

Beyond technical issues, ethical considerations arise regarding patient safety in early-phase trials. Given that many nano-TPs are designed for oncology, where patient populations are vulnerable, trial designs must balance innovation with caution [58]. Cost of production is another concern; complex formulations may not be feasible for widespread use in low- and middle-income settings, limiting global accessibility.

6.7. Strategies to overcome barriers

- **Improved preclinical models:** Using patient-derived xenografts and 3D tumor spheroids better predicts clinical performance than conventional 2D cultures.
- **Biomimetic systems:** Cloaking nanoparticles with exosomes, platelets, or leukocyte membranes improves biocompatibility and reduces clearance [59].
- **Adaptive clinical trial designs:** Seamless Phase I/II designs may accelerate clinical evaluation while ensuring safety monitoring.
- **Standardization:** Adoption of harmonized guidelines for nanoparticle characterization and safety testing (e.g., ISO/TC 229 standards) is crucial.

7. Future directions and perspectives

The convergence of thienopyrimidine (TP) chemistry with nanotechnology provides a fertile ground for innovation in drug delivery and precision medicine. While significant progress has been achieved in enhancing solubility, stability, and tumor targeting, the next generation of research will likely focus on smart, multifunctional systems that integrate therapeutic, diagnostic, and adaptive features. Several emerging directions are particularly relevant.

7.1. Stimuli-responsive nanoformulations

Conventional TP-loaded nanoparticles rely primarily on passive release, which may result in premature drug leakage. Future systems are expected to adopt stimulus-responsive mechanisms, where release is triggered by tumor-associated cues such as acidic pH, high glutathione levels, or specific enzymes [60]. For example, redox-sensitive polymer–TP conjugates could release the drug selectively in the tumor microenvironment, reducing systemic toxicity. External triggers such as light, ultrasound, or magnetic fields can further enhance spatiotemporal control.

7.2. Integration with immunotherapy

Cancer immunotherapy has revolutionized oncology, but many tumors remain resistant due to immunosuppressive microenvironments. Nano-TPs may be engineered to synergize with immune checkpoint inhibitors by simultaneously

inhibiting oncogenic kinases and modulating tumor immunity [61]. For instance, co-delivery of TP kinase inhibitors with siRNA targeting PD-L1 in nanocarriers could both suppress tumor growth and enhance immune activation. Such combinatorial nano therapies may overcome resistance and improve survival outcomes.

7.3. Theragnostic and real-time monitoring

The development of theragnostic nano-TPs capable of combining therapy and imaging will be instrumental in personalized medicine. By integrating contrast agents (e.g., MRI, PET, or fluorescence labels), clinicians could monitor biodistribution and therapeutic response in real time [62]. Such systems not only improve treatment precision but also accelerate regulatory approval by providing robust pharmacokinetic and pharmacodynamic data.

7.4. Artificial intelligence (AI)-driven nano design

AI and machine learning are increasingly applied to drug discovery and nanomedicine. Predictive models can optimize nanoparticle size, surface charge, and drug release profiles to maximize tumor penetration and therapeutic index [63]. For nano-TPs, AI-guided molecular docking and pharmacophore modelling may also identify new TP analogues with enhanced nanocarrier compatibility, accelerating rational design cycles.

7.5. Personalized and precision nano therapy

Future oncology is expected to be highly personalized, with therapies tailored to patient-specific genomic and proteomic signatures. Nano-TPs could be designed to target patient-specific kinase mutations or combined with liquid biopsy data to adapt dosing regimens dynamically [64]. Integration with microfluidics and organ-on-chip technologies could enable rapid preclinical testing of individualized formulations.

7.6. Overcoming multidrug resistance (MDR)

Resistance to kinase inhibitors remains a major clinical challenge. Multifunctional nano-TPs capable of co-delivering TPs with efflux pump inhibitors or gene-silencing agents represent a promising approach [65]. Hybrid systems incorporating TP derivatives with CRISPR-Cas9 components to edit resistance genes are a particularly exciting avenue under early investigation.

7.7. Expanding beyond oncology

Although oncology remains the primary focus, TP scaffolds also show promise in antiviral, antimicrobial, and anti-inflammatory applications. Nanoformulations could enhance systemic delivery of TPs targeting viral polymerases or microbial kinases [66]. This broadens the clinical relevance of nano-TPs and may accelerate translation into diverse therapeutic areas.

7.8. Roadmap to clinical translation

To accelerate progress, several strategies should be prioritized:

- Development of scalable and GMP-compliant manufacturing platforms.
- Establishment of standardized assays for nanoparticle characterization and toxicity testing.
- Early collaboration with regulatory bodies to streamline approval processes.
- Multidisciplinary consortia combining chemistry, nanotechnology, oncology, and AI expertise.

8. Conclusion

Thienopyrimidines have emerged as versatile scaffolds with significant therapeutic potential, particularly as kinase inhibitors in oncology and beyond. However, their limited solubility, poor pharmacokinetics, and systemic toxicity have long restricted their clinical utility. The advent of nanotechnology has transformed this landscape, enabling the design of advanced delivery systems that not only improve the bioavailability of thienopyrimidines but also allow precise targeting, controlled release, and reduced off-target effects. Nano-thienopyrimidines exemplify the next generation of drug delivery platforms, combining the pharmacological strength of thienopyrimidines with the versatility of nanocarriers. These systems have shown promise in overcoming multidrug resistance, enhancing tumor penetration, and even integrating diagnostic capabilities for real-time treatment monitoring. As the field progresses, a shift toward multifunctional, patient-tailored, and clinically translatable nanoplatforms will be critical. The journey from preclinical promise to clinical success will require addressing challenges related to safety, large-scale manufacturing, and regulatory approval. With continued advances in materials science, computational modelling, and precision medicine,

nano-thienopyrimidines are poised to play a transformative role in targeted therapy. Ultimately, their development represents a paradigm shift toward smarter, safer, and more effective treatments, bridging the gap between innovative chemistry and modern nanomedicine.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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