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REVIEW article

Natural products and synthetic analogues in the prevention and management of urolithiasis: A comprehensive review

Bhavana KS, **Pramod N** *, **Kaif Mollick**, **Aneesa**
Dilbar Saikh, and **Sk Md Rijhwan**

Department of Pharmaceutical Chemistry, Harsha College of Pharmacy, Kambayyanapalya, Jakkanahalli post, Thymagondlu road, Nelamangala taluk, Bangalore rural-562123, Karnataka, India
* Author to whom correspondence should be addressed

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Abstract: Urolithiasis is a multifactorial renal disorder characterized by calcium oxalate crystallization, oxidative stress, inflammation, urinary supersaturation, and enzyme-mediated pathological processes. Recent developments in synthetic analogues and natural lead compounds investigated for kidney stone therapy and prevention are critically summarized in this study. Along with nephroprotective, antioxidant, anti-inflammatory, and diuretic properties, 25 natural compounds showed anti-urolithiatic efficacy mainly by suppression of calcium oxalate nucleation, aggregation, and growth. By promoting the development of less adherent calcium oxalate dihydrate and reestablishing urinary citrate and magnesium levels, several extracts also altered crystal shape. In addition, twenty-five synthesized drugs were classified according to dominating processes, such as enzyme-targeted tactics, diuretic-mediated urine regulation, antioxidant-supported crystal suppression, and direct crystallization inhibition. Strong calcium oxalate inhibitory potential was demonstrated by synthetic scaffolds such as phthalimides, barbiturates, imidazoles, benzene sulphonamides, and Schiff bases, while hybrids targeting urease and carbonic anhydrase showed low-micromolar to nanomolar enzyme inhibition, addressing urinary pH imbalance and infection-associated lithogenesis. Relationships between structure and action demonstrated how crucial heterocyclic frameworks, sulfonamide moieties, and electron-donating substituents are for increasing efficacy. The importance of multi-target techniques is shown by the fact that natural and synthetic candidates work together through complementary pathways, including crystal modification, oxidative stress attenuation, urine parameter normalization, and enzyme inhibition. To turn these candidates into successful antiurolithiatic treatments, more pharmacokinetic profiling, safety assessment, and clinical validation are necessary, even if many leads have encouraging preclinical efficacy.

Introduction

Urolithiasis is a common and recurrent urinary tract disorder characterized by the formation of calculi in the kidneys or urinary system [1]. Due to dietary practices, dehydration, metabolic disorders, and lifestyle modifications, its prevalence has significantly increased globally [1, 2]. Nearly 70 - 80% of urinary calculi are calcium oxalate stones, with calcium phosphate, uric acid, struvite, and cystine stones following [3]. The high recurrence rate of urolithiasis remains a major clinical problem despite advancements in diagnosis and surgical therapy [2]. The pathogenesis of urolithiasis involves urinary supersaturation, crystal nucleation, growth, aggregation, and retention within renal tubules [4]. Stone formation and recurrence are greatly influenced by

factors such as oxidative stress, inflammation, renal epithelium damage, hyperoxaluria, and hypercalciuria [4, 5]. In addition to the use of pharmacological medicines like citrate preparations, allopurinol, and thiazide diuretics, current therapeutic approaches mostly concentrate on stone removal using procedures including extracorporeal shock wave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy [4]. However, these methods are frequently linked to side effects, recurrence, and poor long-term effectiveness [4]. The anti-urolithiatic potential of natural medicines made from medicinal plants has been extensively studied [6]. In addition to having antioxidant, diuretic, and nephroprotective properties, phytoconstituents like flavonoids, alkaloids, saponins, terpenoids, and polyphenols show inhibitory effects on crystal nucleation and aggregation [6]. Synthetic analogues have been created concurrently to enhance pharmacokinetic characteristics, potency, and selectivity. The current review highlights the therapeutic potential and mechanisms of urinary stone inhibition of reported natural agents and synthetic analogues studied for the treatment of urolithiasis.

Natural products in urolithiasis management

Calcium oxalate nucleation and aggregation inhibitors

Cenchrus purpureus hydro-alcoholic extract inhibits CaOx nucleation/aggregation in vitro: The hydroalcoholic extract of *Pennisetum purpureum (Cenchrus purpureus)* demonstrated significant inhibitory activity against calcium oxalate crystal nucleation and aggregation in vitro, along with notable stone-dissolving potential. Phytochemical analysis confirmed the presence of bioactive constituents, supporting its anti-urolithiatic effect. However, additional in vivo studies are required to validate these findings and establish their therapeutic potential [7].

Acacia senegal exerts antioxidant/nephroprotective roles with relevance to stone formation: The extracts of *Argania spinosa* press-cake and *Acacia senegal* demonstrated inhibitory effects on calcium oxalate crystallization, with nucleation inhibition of approximately 83.8% and 43.7%, respectively. *Argania spinosa* additionally exhibited strong litholytic activity against cystine and uric acid stones, outperforming gum Arabic extract. The pronounced anti-urolithiatic effect of *Argania spinosa* may be attributed to its high phenolic acid content [8].

Assessment of anti-urolithiatic activity of some herbal fractions using in vitro techniques: In vitro evaluation demonstrated that extracts of *Trigonella foenum-graecum* and *Nigella sativa* effectively inhibited calcium oxalate crystal nucleation and promoted crystal dissolution. Using a titrimetric assay, both seed extracts showed measurable anti-urolithiatic activity, indicating the presence of bioactive constituents responsible for crystal inhibition. These findings support the potential of fenugreek and kalonji as natural anti-urolithiatic agents and provide a basis for more preclinical evaluation [9].

In vitro anti-urolithiatic activity of the leaves and flowers extracts of Paronychia argentea, a plant used in traditional medicine in Algeria. Ethanolic extracts of *Paronychia argentea* leaves and flowers were evaluated for in vitro anti-urolithiatic activity using calcium oxalate crystallization assays. Both extracts exhibited concentration-dependent inhibition of crystal formation, with the flower extract showing a maximum inhibition of 70.9% at 5.0 mg/mL. Phytochemical analysis revealed higher polyphenol content in the leaf extract and greater flavonoid content in the flower extract. These findings indicate that *P. argentea* possesses significant anti-urolithiatic potential and may be useful in preventing kidney stone formation [10].

Anti-calcifying activity of Terminalia arjuna: Crude extracts and successive solvent fractions of *Terminalia arjuna* bark were evaluated in vitro for their inhibitory effects on calcium phosphate formation and calcium oxalate monohydrate crystal growth. The extracts significantly suppressed both crystal types, with the butanol fraction showing the strongest inhibitory activity. These findings indicate that *Terminalia arjuna* bark possesses notable anti-urolithiatic potential through inhibition of calcium phosphate and calcium oxalate crystallization [11].

Inhibition of calcium oxalate crystallization in vitro by methanolic leaf extract of Murraya koenigii (L.) Spreng: The methanolic leaf extract of *Murraya koenigii* (L.) Spreng demonstrated inhibitory activity against calcium oxalate crystallization in vitro, indicating its potential as a natural anti-urolithiatic agent. These findings support additional investigation of *M. koenigii* for kidney stone management [12].

Antilithiatic activity of phlorotannin-rich extract of Sargassum wightii on calcium oxalate urolithiasis - in vitro and in vivo evaluation: Extract of *Sargassum wightii* effectively inhibited calcium oxalate crystal nucleation, aggregation, and growth in vitro, while also reducing urinary and serum supersaturation of calcium, oxalate, and magnesium. The extract showed stronger preventive activity against stone formation than dissolution of existing stones. These findings indicate the anti-urolithiatic potential of *Sargassum wightii* and support further investigation to identify its active constituents [13].

Rhus chinensis Mill.: A medicinal plant with promising inhibition of calcium oxalate crystallization, an in-vitro study: In vitro calcium oxalate crystal nucleation and aggregation were markedly prevented by the aqueous fruit pulp extract of *Rhus chinensis*, which also decreased crystal density in a concentration-dependent manner. Its activity was similar to that of the usual combination of Cystone, citric acid, and malic acid. These results support R. chinensis fruit's potential as a natural anti-urolithiatic agent by showing that organic acids in the fruit contribute to its inhibitory action on calcium oxalate crystallization [14].

Anti-urolithiatic activity of Boldoa purpurascens aqueous extract, an in vitro and in vivo study: Aqueous leaf extract of *Boldoa purpurascens* significantly inhibited calcium oxalate crystal nucleation, aggregation, and growth in vitro, while also reducing crystal density and promoting crystal dissolution. In an ethylene glycol-induced rat model, the extract lowered urinary and serum uric acid and creatinine levels and improved renal histopathology at higher doses. These findings demonstrate that *B. purpurascens* exerts crystal-inhibitory and nephroprotective effects, supporting its potential role in kidney stone prevention [15].

Chenopodium album Linn. leaves prevent ethylene glycol-induced urolithiasis in rats: Methanolic and aqueous leaf extracts of *Chenopodium album* significantly reduced ethylene glycol-induced elevations of urinary and plasma calcium, phosphorus, urea, uric acid, and creatinine in rats. Treatment also lowered urinary oxalate levels, decreased renal oxalate content, and markedly reduced calcium oxalate crystal deposition in kidney tissue. Both extracts showed protective effects comparable to Cystone, mediated through inhibition of crystallization and stone dissolution, indicating the anti-urolithiatic potential of *C. album* leaves [16].

Anti-urolithiatic activity of saponin-rich fraction from the fruits of Solanum xanthocarpum Schrad. and Wendl. (Solanaceae) against ethylene glycol-induced urolithiasis in rats: Saponin-rich fraction from fruits of *Solanum xanthocarpum* significantly inhibited calcium oxalate crystal nucleation and aggregation in vitro. In ethylene glycol-induced urolithiatic rats, treatment reduced hyperoxaluria, hypercalciuria, crystalluria, and renal calcium oxalate deposition while improving antioxidant status and restoring urinary citrate and magnesium levels. Histopathological analysis confirmed reduced renal injury, and urinary glycosaminoglycan levels were increased, indicating enhanced stone-inhibitory capacity. These findings demonstrate that *S. xanthocarpum* exerts anti-urolithiatic effects through crystal inhibition and normalization of lithogenic factors [17].

Antioxidant and nephroprotective natural products

Quercetin and betulin reduce calculus formation in a rat model: Treatment with the combination of quercetin and betulin with piperine significantly reduced calcium, phosphate, and oxalate crystal formation in experimental animals and improved renal function markers, including BUN, urea, and creatinine. Histopathological evaluation revealed the absence of renal calculi and restoration of normal kidney architecture. The combination also demonstrated marked nephroprotective activity by normalizing serum parameters and protecting renal tissue. These findings suggest that quercetin and betulin, enhanced by piperine, exhibit promising anti-urolithiatic and nephroprotective potential; however, further pharmacokinetic studies are required to clarify the role of piperine as a bio-enhancer [18].

Polyherbal formulation prevents stone formation in the rat NaOx model: LACTN treatment increased urinary output, reduced calcium excretion, and improved magnesium levels in blood and urine, along with normalization of kidney function markers. It also lowered lipid peroxidation and restored antioxidant status, thereby reducing calcium oxalate supersaturation and preventing crystal formation. The findings suggest that combining multiple components in a single formulation enhances anti-urolithiatic efficacy compared to individual constituents [19].

Anti-urolithiatic effects of Punica granatum in male rats: Chloroform and methanolic extracts of *Punica granatum* significantly reduced urinary oxalate, calcium, and phosphate levels in ethylene glycol-induced urolithiatic rats, while also improving serum creatinine, urea, and uric acid. Treatment decreased renal oxalate content and markedly reduced calcium oxalate deposition with restoration of kidney histoarchitecture. Higher doses showed greater protective effects, indicating the anti-urolithiatic and nephroregenerative potential of *P. granatum* extracts [20].

In vivo investigation of the inhibitory effect of Peganum harmala L. and its major alkaloids on ethylene glycol-induced urolithiasis in rats: Extracts of *Peganum harmala* and its isolated β-carboline alkaloids (harmine and harmalacidine HCl) significantly alleviated ethylene glycol-induced urolithiasis in rats by reducing oxidative stress, inflammatory markers, and serum toxicity parameters, including BUN, creatinine, uric acid, and oxalate. Treatment improved urine output and pH while restoring antioxidant enzymes and renal histoarchitecture. These findings demonstrate that *P. harmala* and its major alkaloids exert pronounced nephroprotective and anti-urolithiatic effects, supporting their therapeutic potential in kidney stone management [21].

Evaluation of anti-urolithiatic effect of aqueous extract of Bryophyllum pinnatum (Lam.) leaves using ethylene glycol-induced renal calculi. Aqueous leaf extract of *Bryophyllum pinnatum* significantly reduced urinary oxalate levels and improved serum creatinine and blood urea in ethylene glycol-induced urolithiatic rats. Treatment also decreased kidney weight and calcium oxalate crystal deposition, as confirmed by histopathology. Preventive and curative regimens showed marked protection against renal calculi, indicating that *B. pinnatum* exhibits effective anti-urolithiatic activity in vivo [22].

Nephroprotective and diuretic effect of Nigella sativa L seeds oil on Lithiasic Wistar rats: Nigella sativa seed oil significantly reduced urinary and serum levels of calcium, phosphate, and oxalate in ethylene glycol-induced urolithiatic rats, while also increasing urine volume. Preventive administration improved serum creatinine, BUN, and uric acid levels and reduced renal histopathological damage. These findings demonstrate the nephroprotective and diuretic effects of *N. sativa* seed oil, supporting its potential role in preventing calcium oxalate stone formation [23].

Anti-urolithiatic activity of ethanol leaf extract of Ipomoea eriocarpa against ethylene glycol-induced urolithiasis in male Wistar rats: Ethanolic leaf extract of *Ipomoea eriocarpa* significantly improved urinary, serum, and renal biochemical parameters in ethylene glycol-induced urolithiatic rats under prophylactic and curative regimens. Treatment markedly reduced calcium oxalate crystal deposition and restored renal histoarchitecture. These findings indicate that *I. eriocarpa* leaf extract effectively inhibits stone formation and promotes recovery from urolithiasis [24].

Anti-urolithiatic and antioxidant activity of Hordeum vulgare seeds on ethylene glycol-induced urolithiasis in rats: Ethanolic seed extract of *Hordeum vulgare* significantly improved urinary output and reduced calcium, phosphate, uric acid, urea, magnesium, and oxalate levels in ethylene glycol-induced urolithiatic rats under preventive and curative regimens. Treatment also decreased renal deposition of stone-forming constituents and enhanced citrate excretion. In addition, the extract reduced lipid peroxidation while increasing superoxide dismutase and catalase activities, indicating antioxidant-mediated nephroprotection. These findings support the anti-urolithiatic potential of *H. vulgare* seeds [25].

Diuretic and urinary modulatory agents

Moringa oleifera leaves: in vitro plus in vivo plus in silico anti-urolithiatic activity: The study demonstrated the anti-urolithiatic potential of *Moringa oleifera* leaf extract through combined in vitro, in vivo, and in silico evaluations. The extract exhibited diuretic, antioxidant, and calcium oxalate crystal-inhibitory activities, along with improvement in serum and urinary biochemical parameters. These findings support the role of *Moringa oleifera* leaf extract as a promising natural agent for the management of urolithiasis [26].

Effect of hydro-alcoholic extract of Vernonia cinerea L. against ethylene glycol-induced urolithiasis in rats: Hydro-alcoholic whole-plant extract of *Vernonia cinerea* significantly reduced ethylene glycol-induced elevations of urinary calcium, oxalate, and phosphate, while also improving serum creatinine, urea, and uric acid levels in rats. Treatment produced dose-dependent increases in urine output and body weight, along with marked reductions in renal stone-forming constituents and histopathological damage. These findings indicate that *V. cinerea* exhibits preventive and curative anti-urolithiatic activity in vivo [27].

Curative treatment with extracts of Bombax ceiba fruit reduces risk of calcium oxalate urolithiasis in rats: Aqueous and ethanolic fruit extracts of *Bombax ceiba* significantly reduced ethylene glycol-induced hyperoxaluria and lowered urinary calcium and phosphate levels in urolithiatic rats. Treatment decreased renal deposition of stone-forming constituents, indicating regulation of endogenous oxalate synthesis and promotion of stone clearance. These findings demonstrate the curative anti-urolithiatic potential of *B. ceiba* fruit extracts [28].

Crystal morphology modifiers and litholytic agents

Effect of phenolic compounds from Bergenia ciliata Sternb. leaves on experimental kidney stones: In vitro studies showed that extracts of *Bergenia ciliata* leaves and the isolated phenolic compound (P_1) were effective in dissolving kidney stone components. Among all samples tested, P_1 demonstrated the strongest activity against calcium oxalate and calcium phosphate crystals, with greater effectiveness toward calcium phosphate. The isolated compound performed better than the ethyl acetate extract from which it was obtained, suggesting that P_1 may serve as a promising natural lead for anti-urolithiatic therapy [29].

In vitro effects on calcium oxalate crystallization kinetics and crystal morphology of an aqueous extract from Ceterach officinarum: Analysis of a potential antilithiatic mechanism: Ceterach officinarum aqueous extract exhibited strong inhibitory effects on calcium oxalate monohydrate growth and aggregation in vitro, while promoting the formation of calcium oxalate dihydrate crystals, which are less adherent to renal tubular cells. The extract also induced dose-dependent changes in crystal size and morphology, producing smaller, rounded crystals that are more easily excreted. AFM analysis confirmed adsorption of extract components on crystal surfaces, suggesting direct modulation of crystallization. These findings indicate that *C. officinarum* extract reduces lithogenic potential by altering calcium oxalate crystal growth and promoting less harmful crystal forms [30].

Inhibitory effects of taraxasterol and aqueous extract of Taraxacum officinale on calcium oxalate crystallization in vitro study: Taraxasterol and the aqueous extract of *Taraxacum officinale* aerial parts significantly inhibited calcium oxalate crystallization in vitro by reducing crystal nucleation and total crystal number in a dose-dependent manner. Both treatments decreased calcium oxalate monohydrate formation while promoting the formation of calcium oxalate dihydrate crystals with reduced size, indicating a shift toward less lithogenic crystal forms. The extract showed stronger anti-crystallization activity than isolated taraxasterol, suggesting a synergistic effect of multiple phytoconstituents. These findings support the potential of *T. officinale* as a natural anti-urolithiatic agent [31].

Representative natural compounds are summarized in **Table 1**.

Table 1: Natural products with reported anti-urolithiatic activity

Ref.	Natural product	Experimental model	Major activity	Key findings
7	*Cenchrus purpureus*	In vitro	Crystal inhibition	Hydroalcoholic extract inhibited calcium oxalate nucleation and aggregation with notable stone-dissolving activity.
8	*Argania spinosa* and *Acacia senegal*	In vitro	Crystal inhibition / litholytic activity	Extracts reduced calcium oxalate crystallization, while *Argania spinosa* showed strong litholytic activity against urinary stones.
9	*Trigonella foenum-graecum* and *Nigella sativa*	In vitro	Crystal inhibition	Seed extracts inhibited calcium oxalate nucleation and promoted crystal dissolution.
10	*Paronychia argentea*	In vitro	Crystal inhibition	Ethanolic extracts showed concentration-dependent inhibition of calcium oxalate crystal formation.
11	*Terminalia arjuna*	In vitro	Anti-calcifying activity	Bark extracts suppressed calcium phosphate formation and calcium oxalate crystal growth.
12	*Murraya koenigii*	In vitro	Crystal inhibition	Methanolic leaf extract inhibited calcium oxalate crystallization in vitro.
13	*Sargassum wightii*	In vitro / in vivo	Crystal inhibition	Extract inhibited calcium oxalate nucleation, aggregation, and crystal growth.
14	*Rhus chinensis*	In vitro	Crystal inhibition	Fruit pulp extracts reduced calcium oxalate nucleation, aggregation, and crystal density.
15	*Boldoa purpurascens*	In vitro/in vivo	Crystal inhibition/ nephroprotection	Extract inhibited crystal formation and improved renal biochemical parameters.
16	*Chenopodium album*	In vivo	Anti-urolithiatic activity	Reduced urinary lithogenic factors and renal calcium oxalate deposition.
17	*Solanum xanthocarpum*	In vitro / in vivo	Crystal inhibition	Saponin-rich fraction reduced hyperoxaluria and calcium oxalate crystal deposition.
18	Quercetin and betulin	In vivo	Nephroprotective activity	Reduced crystal deposition and restored normal renal histology.
19	Polyherbal formulation (LACTN)	In vivo	Antioxidant/ nephroprotective	Improved antioxidant status and reduced calcium oxalate supersaturation.
20	*Punica granatum*	In vivo	Nephroprotective activity	Reduced urinary oxalate and restored kidney histoarchitecture.
21	*Peganum harmala*	In vivo	Antioxidant/ nephroprotective	Reduced oxidative stress and improved renal function markers.
22	*Bryophyllum pinnatum*	In vivo	Anti-urolithiatic activity	Reduced urinary oxalate levels and renal crystal deposition.
23	*Nigella sativa* seed oil	In vivo	Nephroprotective/ diuretic	Improved urine output and reduced renal damage in lithiasic rats.
24	*Ipomoea eriocarpa*	In vivo	Anti-urolithiatic activity	Improved urinary and renal biochemical parameters with reduced crystal deposition.
25	*Hordeum vulgare*	In vivo	Antioxidant/ anti-urolithiatic	Reduced oxidative stress and improved urinary stone-forming parameters.
26	*Moringa oleifera*	In vitro / in vivo / in silico	Diuretic/ crystal inhibition	Demonstrated antioxidant, diuretic, and calcium oxalate inhibitory activities.
27	*Vernonia cinerea*	In vivo	Diuretic/ anti-urolithiatic	Increased urine output and reduced urinary stone-forming constituents.
28	*Bombax ceiba*	In vivo	Urinary modulation/ stone clearance	Reduced hyperoxaluria and promoted clearance of renal stone constituents.
29	*Bergenia ciliata*	In vitro	Litholytic activity	The phenolic compound exhibited dissolution of calcium oxalate and calcium phosphate crystals.
30	*Ceterach officinarum*	In vitro	Crystal morphology modulation	Promoted calcium oxalate dihydrate formation and reduced crystal adhesion.
31	Taraxasterol and *Taraxacum officinale*	In vitro	Crystal morphology modulation	Reduced calcium oxalate monohydrate formation and promoted less lithogenic crystal forms.

Synthetic analogues for urolithiasis therapy: Considering the multifactorial pathogenesis of urolithiasis, the reported synthetic anti-urolithiatic agents were categorized based on their primary mechanism of action, including direct calcium oxalate crystallization inhibition, diuretic-mediated urinary modulation, antioxidant-supported crystal suppression, and enzyme-targeted approaches, to allow systematic comparison of diverse synthetic strategies.

Direct calcium oxalate crystallization inhibitors

Anti-urolithiatic potential of a series of phthalimide derivatives on calcium oxalate crystals: This study evaluated 15 phthalimide derivatives for their inhibition of urinary calcium oxalate crystallization using a rat urine model. All compounds reduced calcium oxalate monohydrate (COM) formation to varying degrees, but only LD-F03 affected dihydrate crystals. Among the series, LD-F10 (2-(4-methoxyphenyl)-1H-isoindole-1,3(2H)-dione) emerged as the primary lead, producing strong COM inhibition (89.0%) without promoting dihydrate crystal formation, indicating a favorable anti-urolithiatic profile. Structure-activity analysis suggested that the para-methoxy substituent enhances crystal suppression, likely through electronic and hydrogen-bonding effects. Overall, the findings highlight phthalimide scaffolds, particularly LD-F10, as promising direct inhibitors of calcium oxalate crystallization, warranting further pharmacokinetic and *in vivo* evaluation [32].

Inhibitors of calcium oxalate crystallization for the treatment of oxalate nephropathies: This work identifies OEG4-$(IP5)_2$, a divalent IP6-derived analogue, as a highly potent inhibitor of calcium oxalate crystallization with nanomolar activity. The compound disrupts early crystal formation, limits crystal-epithelial adhesion, and suppresses CaOx-induced inflammatory responses. These effects translated in vivo, where significant reductions in renal crystal deposition and tubular injury were observed in a hyperoxaluric mouse model. Overall, multivalent IP6 analogues emerge as promising synthetic leads for developing disease-modifying therapies for calcium oxalate-related nephropathies [33].

Synthesis of coumarin thiazole-based Schiff base derivatives and their evaluation as potential anti-urolithiatic agents: The synthesized coumarin-thiazole derivatives (P1 - P5) differ in their aromatic substituents (R groups) attached via a Schiff base linkage. The coumarin-thiazole Schiff base P5 (3-{2-[(4-dimethyl aminobenzylidene) amino]-thiazol-4-yl}-2H-chromen-2-one) demonstrated marked anti-urolithiatic activity by inhibiting calcium oxalate nucleation, crystallization, and aggregation, together with strong antioxidant effects. In ethylene glycol-induced urolithic rats, P5 reduced renal crystal deposition, improved biochemical markers, restored antioxidant enzymes, and protected kidney histology. Overall, P5 appears to act through combined suppression of calcium oxalate crystal formation and oxidative renal injury, supporting coumarin-thiazole Schiff bases as promising synthetic leads for anti-urolithiatic therapy [34].

Synthesis, characterization, and molecular docking studies of novel hippuric acid anhydrides as potential anti-urolithic, analgesic, and free radical scavenging agents: Anhydride-linked mutual prodrugs of hippuric acid with eleven NSAIDs (P1-P11) were synthesized and characterized to explore combined anti-urolithiatic and analgesic potential. The most active compounds were P6 (hippuric acid-ketorolac anhydride) and P9 (hippuric acid-aceclofenac anhydride), which showed the strongest in vivo anti-urolithic effects, while P8 and P9 also exhibited notable antioxidant activity, and most derivatives retained analgesic efficacy. The conjugates were stable under acidic conditions and hydrolysed preferentially at physiological pH, suggesting reduced gastric irritation with effective systemic release. Docking studies supported favourable interactions with TNF-α and COX-2. Hippuric acid-NSAID anhydrides, particularly the ketorolac (P6) and aceclofenac (P9) conjugates, emerge as promising synthetic leads combining stone-inhibitory, antioxidant, and analgesic [35].

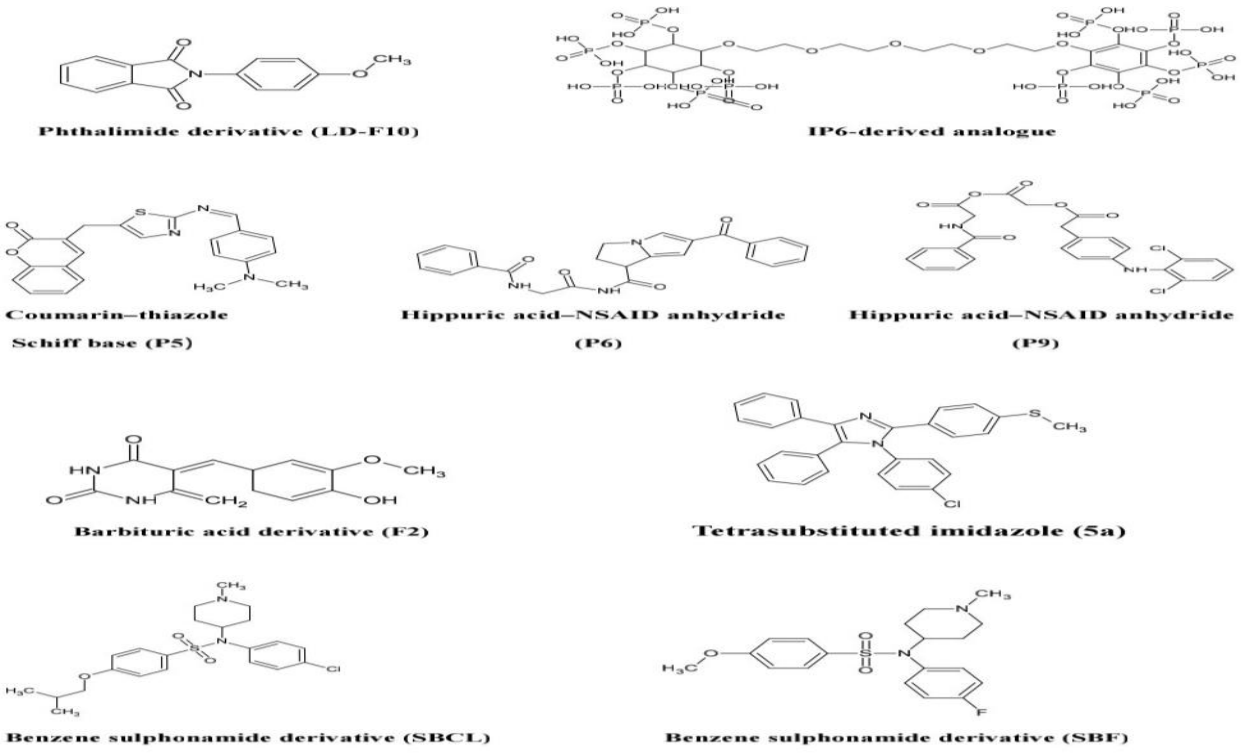
Synthesis and evaluation of pyrimidine derivatives for urolithiasis prevention activity: A series of pyrimidine (barbituric acid-based) derivatives were successfully synthesized via Knoevenagel condensation and structurally confirmed using FTIR, ^1H-NMR, and mass spectrometry. This study demonstrates that

benzylidene barbituric acid-based pyrimidine derivatives can act as direct calcium oxalate dissolution agents in vitro. Among the synthesized series, F2 (5-(4-hydroxy-3-methoxybenzylidene) barbituric acid) emerged as the lead compound, showing the highest CaOx dissolution, while F3 and F5 displayed moderate activity. Structure-activity trends revealed that electron-donating substituents, particularly hydroxyl and methoxy groups, significantly enhance anti-urolithiatic efficacy, whereas unsubstituted or chloro-substituted analogues were least effective. Overall, F2 highlights this scaffold as a simple and promising starting point for developing small-molecule calcium oxalate inhibitors for urolithiasis management [36].

One-pot synthesis and characterization of 1, 2, 4, 5-Tetrasubstituted imidazole derivatives under ultrasound-assistance and the study of their anti-urolithiasis activities (in vitro): A series of 1,2,4,5-tetrasubstituted imidazole derivatives (5a - 5g) were efficiently synthesized via a one-pot multicomponent strategy, with ultrasound irradiation offering shorter reaction times and slightly improved yields compared to conventional heating. In vitro evaluation using calcium oxalate nucleation and aggregation assays identified compound 5a (1-(4-chlorophenyl)-2-(4-(methylthio) phenyl)-4,5-diphenyl-1H-imidazole) as the lead molecule, showing the highest inhibitory activity at 200 - 250 µg/mL, surpassing the reference drug cystone in both assays, while 5g displayed moderate activity. Structure–activity trends suggested that electron-withdrawing substituents, particularly chloro groups, favour crystal inhibition. Overall, 5a highlights tetrasubstituted imidazole as a promising synthetic scaffold for developing direct calcium oxalate inhibitors in anti-urolithiatic therapy [37].

Unveiling the anti-urolithiatic potentiality of two benzene sulphonamide derivatives against ethylene glycol-induced renal calculi: This study demonstrates that benzene sulphonamide derivatives effectively attenuate ethylene glycol-induced nephrolithiasis by improving renal function, lowering serum and urinary oxalate, restoring antioxidant defences, suppressing inflammatory cytokines, and reversing histopathological damage. Among the two candidates, compound A (SBCL: N-(4-chlorophenyl)-4-isobutoxy-N-(1-methylpiperidin-4-yl) benzene sulphonamide) and compound B (SBF: N-(4-fluorophenyl)-4-methoxy-N-(4-methylpiperidin-4-yl) benzene sulphonamide) showed comparable anti-urolithiatic efficacy; however, SBCL emerged as the lead compound, exhibiting superior antioxidant and anti-inflammatory effects alongside marked reduction of renal crystal burden. Overall, SBCL represents a promising synthetic lead for calcium oxalate-associated nephrolithiasis through its combined nephroprotective, antioxidant, and anti-inflammatory actions [38].

Figure 1: Representative synthetic analogues reported for calcium oxalate crystal inhibition activity



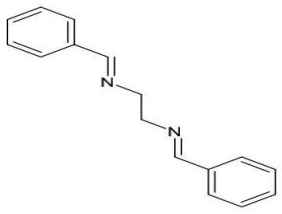
Diuretic-mediated synthetic analogues

Synthesis and characterization of Schiff base derivatives and their effect on urinary parameters of Wistar rats: A comparative analysis with different classes of diuretics: Bidentate Schiff base derivatives synthesized from ethylenediamine and substituted benzaldehydes were evaluated in Wistar rats for anti-urolithiatic potential. Compound 1 (N, N′-bis(benzylidene)ethylenediamine), compound 2 (mono-chloro benzylidene Schiff base), and compound 3 (di-chloro benzylidene Schiff base) significantly increased urine output, showed calcium-sparing diuretic effects, and reduced urinary calcium oxalate crystals, with activity comparable to hydrochlorothiazide, highlighting these analogues as promising synthetic leads for kidney stone prevention [39].

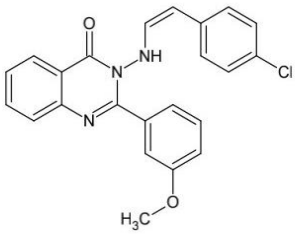
Antioxidant-supported synthetic leads

Synthesis of benzotriazole-based azetidinone derivatives and their evaluation on calcium oxalate crystallization: Benzotriazole-based synthetic derivatives were evaluated for anti-urolithiatic potential, among which *compound 5e [2-(1H-benzotriazol-1-yl)-N-(3-chloro-2-(4-aminophenyl)-4-oxoazetidin-1-yl) acetamide]* exhibited notable antioxidant activity and effectively inhibited calcium oxalate crystallization, nucleation, and aggregation. Computational studies further supported its strong radical-scavenging capacity, suggesting that oxidative stress modulation contributes to its anti-urolithiatic effect. These findings highlight compound 5e as a promising synthetic lead for nephrolithiasis management, although further in vivo validation is required [40].

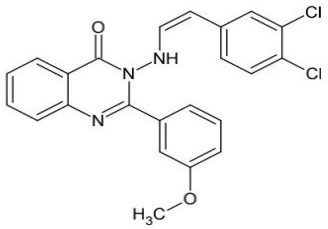
Figure 2: Representative synthetic analogues with antioxidant, nephroprotective, and urinary modulation activities against urolithiasis



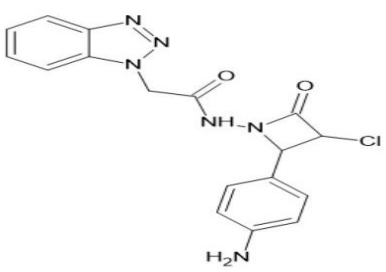
Schiff base derivative (Compound 1)



Chloro-substituted Schiff base (Compound 2)



Dichloro Schiff base derivative (Compound 3)



Benzotriazole–azetidinone derivative (5e)

Enzyme-targeted synthetic analogues

Urease inhibitors

New 4-thiazolidinone/quinoline-2-one scaffold: Design, synthesis, docking studies, and biological evaluation as potential urease inhibitors: A series of quinolinone-thiazolidinone hybrids (3a-i and 4a-c) were synthesized and evaluated as urease inhibitors, with most derivatives outperforming thiourea. The most potent compound was 3e [(Z)-ethyl-2-((Z)-2-(2-(6-bromo-2-oxo-1,2-dihydroquinolin-4-yl)hydrazono)-4-oxo-3-phenylthia zolidin-5-ylidene)acetate] (IC_{50} = 0.46 µM), followed by 3d [(Z)-ethyl-2-((Z)-2-(2-(6-chloro-2-oxo-1,2-dihydroquinolin-4-yl) hydrazono)-4-oxo-3-phenylthiazolidin-5-ylidene) acetat e] and 3b [(Z)-ethyl-2-((Z)-2-(2-(6-methyl-2-oxo-1,2-dihydroquinolin-4-yl) hydrazono)-4-oxo-3-phenyl thiazolidin-5-ylidene)acetate], showing ~10–50-fold higher activity than the standard. Docking studies supported the strong binding of these leads within the urease active site. Overall, the ester-linked thiazolidinone derivatives, particularly compound 3e, represent promising synthetic scaffolds for further optimization as potent urease inhibitors relevant to infection-associated urolithiasis [41].

Synthesis, in vitro urease inhibitory potential, and molecular docking study of benzofuran-based-thiazoldin-one analogues: A series of benzofuran-bearing thiazolidinone derivatives (1 - 14) were synthesized and evaluated for urease inhibitory activity. All compounds demonstrated appreciable inhibition with IC_{50} values ranging from 1.2 to 23.5 µM, and display improved potency compared to thiourea. N-(4-(4-chlorophenyl)-2-oxothiazolidin-3-yl)-4-fluoro-6-nitrobenzofuran-2-carboxamide (compound 1) exhibited the strongest activity. Structure-activity relationship supported by molecular docking revealed favourable binding within the urease active site, highlighting a promising urease-targeted synthetic lead for further optimization [42].

Synthesis, biological evaluation, and molecular docking study of pyrimidine-based thiazolidinone derivatives as potential anti-urease and anti-cancer agents: Pyrimidine-based thiazolidinone derivatives (1-13) were synthesized and evaluated for urease inhibition. Several analogues exhibited stronger activity than thiourea, with compounds 3, 6, 7, and 10 emerging as the most potent. (Z)-2-((5-nitropyrimidin-2-yl)imino)-3-(4-(trifluoromethyl)phenyl)thiazolidin-4-one (3), its 3-trifluoromethyl analogue (6), (Z)-3-(4-fluoro-2-hydroxyphenyl)-2-((5-nitropyrimidin-2-yl)imino) thia zolidine-4-one (7), and (Z)-3-(3-chloro-4-fluoro-phenyl)-2-((5-nitropyrimidin-2-yl)imino) thiazolidin-4-one (10) showed low-micromolar IC_{50}. Structure-activity analysis and docking studies indicated favourable hydrogen-bonding interactions within the urease active site, highlighting these scaffolds as promising urease-targeted synthetic leads for optimization [43].

Synthesis of new aryl hydrazide bearing Schiff bases/thiazolidinone: α-amylase, urease activities, and their molecular docking studies: Aryl hydrazide Schiff bases and thiazolidinone derivatives were developed as dual α-amylase/urease inhibitors. Compound 1j (4-cyano-N′-(3,4-dihydroxybenzylidene) benzohydrazide) showed the strongest α-amylase inhibition (IC_{50} = 0.80 µM), surpassing acarbose, while compound 2k (4-cyano-N-(2-(2,4-dichlorophenyl)-4-oxothiazolidin-3-yl) benzamide) emerged as the most potent urease inhibitor (IC_{50} = 4.10 µM), outperforming thiourea. SAR and docking confirmed that electron-withdrawing substituents, particularly dichloro groups, enhance enzyme binding, identifying 1j and 2k as promising synthetic leads [44].

The synthesis, in vitro bio-evaluation, and in silico molecular docking studies of pyrazoline-thiazole hybrid analogues as promising anti-α-glucosidase and anti-urease agents: A library of benzothiazole-derived pyrazoline-thiazole hybrids was synthesized and screened for dual α-glucosidase and urease inhibition. The standout lead was compound 6 [2-(3-(2,5-dichloropyridin-3-yl)-1-(4-(4-trifluoromethylphenyl) thiazol-2-yl)-4,5-dihydro-1H-pyrazol-5-yl) benzo[d]thiazole], which showed the strongest dual activity (α-glucosidase IC_{50} = 2.50 µM; urease IC_{50} = 14.30 µM), outperforming acarbose and thiourea. Its enhanced potency is attributed to the -CF_3 electron-withdrawing group that promotes favourable enzyme binding, supported by docking studies. Overall, compound 6 emerges as the primary synthetic lead for further development of dual α-glucosidase/urease inhibitors [45].

Atenolol thiourea hybrid as potent urease inhibitors: Design, biology-oriented drug synthesis, inhibitory activity screening, and molecular docking studies: A series of *atenolol–thiourea hybrids (1-23)* was designed and synthesized to target urease. Atenolol–thiourea hybrids were synthesized and evaluated as urease inhibitors, among which compound 22, N-(4-ethoxyphenyl)-N′-[2-(4-(2-hydroxy-3 (isopropylamino) propoxy) phenyl] acetamide] thiourea, emerged as the primary lead molecule. This derivative exhibited the strongest activity (IC_{50} = 11.73 µM), outperforming parent atenolol and the standard thiourea. Structure-activity analysis indicated that para-ethoxy substitution on the phenyl ring significantly enhanced inhibition, while molecular docking confirmed stable binding through hydrogen bonding and metal coordination with the urease active site. Collectively, these findings identify this atenolol-thiourea hybrid as a promising synthetic lead for further optimization toward potent urease inhibitors [46].

Novel (thio)barbituric-phenoxy-N-phenylacetamide derivatives as potent urease inhibitors: Synthesis, in vitro urease inhibition, and in silico evaluations. A series of (thio)barbituric-phenoxy-N-phenylacetamide derivatives (7a-l) were synthesized and evaluated as urease inhibitors, with all compounds showing markedly higher potency than thiourea and hydroxyurea. The most active analogue was compound 7d, N-(2,3-dichlorophenyl)-2-(4-((2,4,6-trioxotetrahydropyrimidin-5(2H)-ylidene) methyl) phenoxy) acetamide, exhibiting submicromolar inhibition (IC_{50} ≈ 0.69 µM). Docking and molecular dynamics revealed strong coordination with the bi-nickel center and key flap residues (Cys592 and His593), stabilizing the closed active-site conformation. Overall, 7d emerges as a potent synthetic lead, highlighting the barbituric-phenoxy-N-phenylacetamide scaffold as a promising platform for further development of urease inhibitors relevant to infection-associated urolithiasis [47].

Synthesis of novel 5-arylidene (thio)barbituric acid and evaluation of their urease inhibitory activity: Novel 5-arylidene (thio)barbituric acid derivatives were synthesized via Knoevenagel condensation and evaluated for urease inhibition. Among the series**,** compound 3a, methyl 2-((2,4,6-trioxotetrahydropyrimidin-5(2H)-ylidene) methyl) benzoate, emerged as the primary lead, exhibiting superior activity (IC_{50} ≈ 145 µM) compared with hydroxyurea. The corresponding ethyl analogue 3b showed moderate potency, while thio barbituric derivatives were markedly less active. These findings indicate that barbituric acid-based 5-arylidene scaffolds, particularly compound 3a, represent promising synthetic leads for further development of urease inhibitors relevant to urolithiasis-associated infections [48].

Novel coumarin derivatives as potential urease inhibitors for kidney stone prevention and antiulcer therapy: From synthesis to in vivo evaluation: A series of 4-aminocoumarin-based Schiff bases (2a - 11a) were synthesized and evaluated as urease inhibitors targeting struvite stone-associated pathways. Among all derivatives, compound 5a, (E)-4-(4-nitrobenzylideneamino)-2H-chromen-2-one, emerged as the primary lead, showing strong urease inhibition (IC_{50} = 0.322 µM, 77.7% inhibition), supported by stable Ni-O coordination and key interactions with His492, His593, and Asp494 in docking, MD, and MM-PBSA analyses. The compound effectively occupied the urease active pocket, blocking substrate access and stabilizing the enzyme in an inactive conformation. In vivo, 5a further demonstrated protective effects by reducing gastric acidity, lipid peroxidation, and ulcer severity, along with measurable inhibition of gastric ATPase. Overall, compound 5a represents a promising synthetic coumarin-Schiff base scaffold for urease inhibition, supporting its further optimization as a potential lead for urease-mediated kidney stone prevention [49].

Carbonic anhydrase inhibitors

Synthesis of coumarin-sulphonamide derivatives and determination of their cytotoxicity, carbonic anhydrase inhibitory, and molecular docking studies: A series of coumarin-sulphonamide hybrids were synthesized and evaluated as carbonic anhydrase (CA) inhibitors, targeting CA IX and CA XII isoforms. Among all analogues, compound 8i [4-(((2-((1-(3-((2-oxo-2H-chromen-7-yl) oxy) propyl)-1H-1,2,3-triazol-4-yl) methoxy) naphthalen-1yl) methylene) amino) methyl) benzenesulfonamide] emerged as the primary

lead, exhibiting the strongest CA IX inhibition (Ki = 45.5 nM) along with significant CA XII inhibition. Molecular docking confirmed stable binding within the CA active site, while cellular studies demonstrated effective downregulation of CA IX/XII expression with low toxicity toward normal cells. Overall, compound 8i highlights the coumarin-sulphonamides scaffold as a promising synthetic carbonic anhydrase inhibitory framework, supporting further investigation of such analogues in CA-mediated pathological conditions, including renal stone-related processes [50].

Figure 3: Representative urease-targeted synthetic analogues investigated for anti-urolithiatic activity (Panel I)

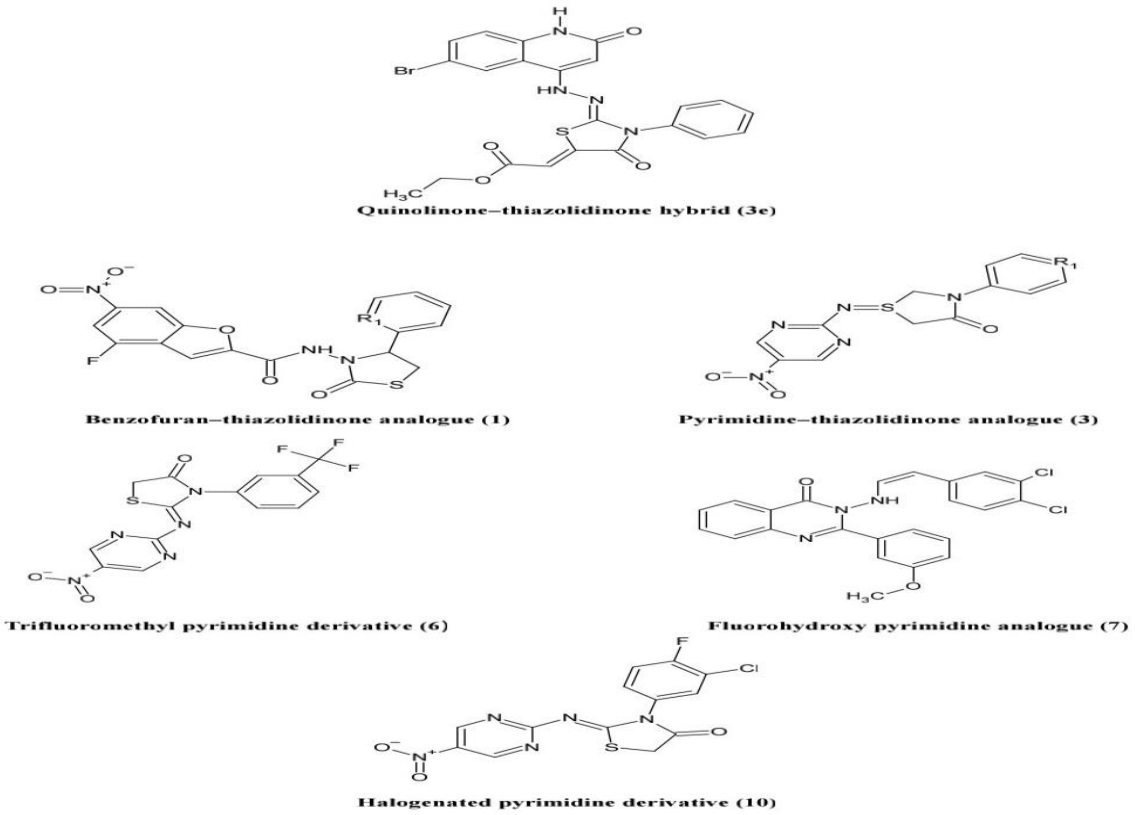
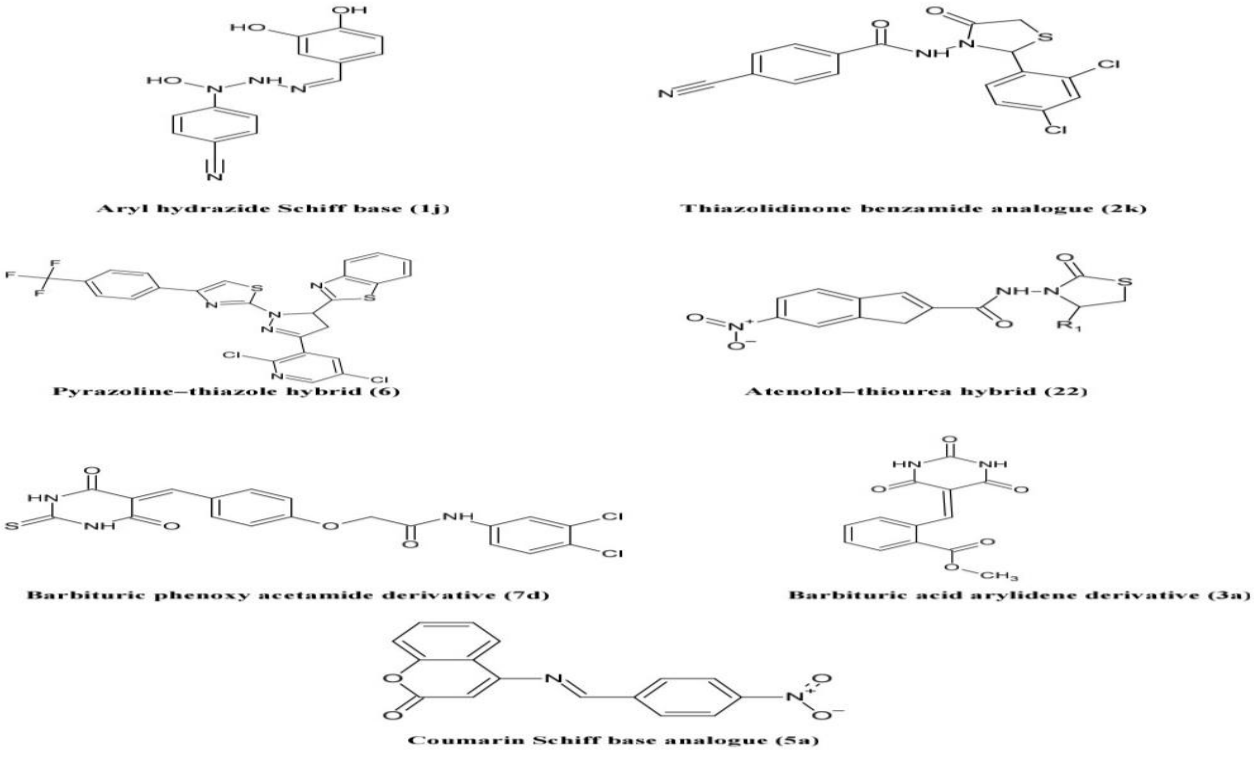


Figure 4: Representative urease-targeted synthetic analogues investigated for anti-urolithiatic activity (Panel II)



Isoxazole derivatives against carbonic anhydrase: synthesis, molecular docking, MD simulations, and free energy calculations coupled with in vitro studies: Novel isoxazole derivatives were synthesized via ultrasound-assisted cyclization and evaluated as carbonic anhydrase inhibitors using combined in vitro and in silico approaches. Among the series, AC2 [(E)-3-propyl-4-(thiophen-2-ylmethylene) isoxazol-5(4H)-one] emerged as the primary lead compound, exhibiting the strongest CA inhibition (IC_{50} = 112.3 µM), followed by AC3. Molecular docking, MD simulations, and MMPBSA analysis confirmed stable binding of AC2 within the CA active pocket through hydrogen bonding and van der Waals interactions involving key catalytic residues. These findings highlight isoxazole scaffolds, particularly AC2, as promising synthetic carbonic anhydrase inhibitory frameworks, supporting further optimization toward CA-mediated renal stone-related pathways [51].

Synthesis and carbonic anhydrase inhibition studies of sulfonamide-based indole-1, 2, 3-triazole chalcone hybrids: A series of indolyl chalcone-benzene sulfonamide-1,2,3-triazole hybrids were synthesized via Knoevenagel condensation followed by click chemistry and evaluated against key human carbonic anhydrase isoforms. Among all analogues, compound 6d, (E)-4-(4-((3-(3-(4-bromophenyl)-3-oxoprop-1-en-1-yl)-1H-indol-1-yl) methyl)-1H-1,2,3-triazol-1-yl) benzenesulfonamide, emerged as the primary lead, exhibiting the strongest hCA I inhibition (Ki = 18.8 nM), outperforming acetazolamide. Molecular docking confirmed zinc coordination and stable interactions with catalytic residues Thr199 and His200. Overall, this sulphonamide–triazole-chalcone scaffold, particularly compound 6d, represents a promising synthetic carbonic anhydrase inhibitory framework, supporting optimization toward CA-mediated renal stone–related pathways [52].

Novel thiopyrano [2, 3-d] thiazole-pyrazole hybrids as potential non-sulphonamide human carbonic anhydrase IX and XII inhibitors: design, synthesis, and biochemical studies: Novel thiopyrano[2,3-d] thiazole-pyrazole hybrids were synthesized via Knoevenagel condensation followed by cycloaddition and evaluated as nonsulfonamide carbonic anhydrase inhibitors. Among all analogues, compound 7e, 7-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-2-oxo-3,5,6,7-tetrahydro-2H-thiopyrano [2,3-d]thiazole-6-carbonitrile, emerged as the most potent hCA IX inhibitor (IC_{50} = 0.067 µM), while compound 7i, ethyl 7-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2-oxo-3,5,6,7-tetrahydro-2H-thiopyrano[2,3-d]thiazole-6-carboxylate, showed the highest selectivity toward hCA XII (IC_{50} = 0.123 µM), with activities comparable to acetazolamide. Molecular docking confirmed stable zinc coordination through the thiazole carbonyl and key interactions within the CA active pocket, emphasizing the role of electron-withdrawing halogen substituents. Overall, compounds 7e and 7i define a promising thiopyrano[2,3-d] thiazole-pyrazole scaffold as a nonsulfonamide carbonic anhydrase inhibitory framework, supporting optimization toward CA-mediated renal stone-related pathways [53].

Quinazolinones as competitive inhibitors of carbonic anhydrase-II (human and bovine): synthesis, in-vitro, in-silico, selectivity, and kinetics studies: A series of quinazolinone analogues (4a-p) were synthesized and evaluated against human carbonic anhydrase II (hCA-II). Among the series, compound 4g (3-amino-2-(4-bromophenyl) quinazolin-4(3H)-one) showed the strongest hCA-II inhibition (IC_{50} = 14.0 µM), while compound 4o (3-amino-2-(4-methoxyphenyl) quinazolin-4(3H)-one) also displayed comparable activity and enhanced selectivity toward hCA-II. Kinetic studies confirmed competitive inhibition, and molecular docking demonstrated effective coordination with the catalytic Zn^{2+} ion and key active-site residues. Overall, 4g and 4o highlight quinazolinones as promising synthetic scaffolds for selective hCA-II inhibition, supporting further optimization toward CA-mediated renal stone-related pathways [54].

Carbonic anhydrase inhibition activities of Schiff's bases based on quinazoline-linked benzenesulfonamide: A series of quinazoline-linked benzenesulfonamide Schiff bases (2-27) were synthesized and evaluated against human carbonic anhydrase II (hCA-II). Several derivatives displayed nanomolar inhibition; however, compound 27 [4-(2-(4-oxo-2-((2-oxo-2-(2-(1-(pyridin-3-yl) ethylidene) hydrazineyl) ethyl) thio) quinazolin-3(4H)-yl) ethyl) benzenesulfonamide] emerged as the most potent hCA-II inhibitor (Ki ≈ 10.8 NM), comparable to the reference drug. Additional analogues (2, 3, 10, 11, 16, 18, 24, and 26) also showed strong

activity, confirming the robustness of this scaffold. Structure-activity analysis highlighted pyridyl substitution as a key contributor to potency, while docking studies supported effective Zn^{2+} coordination within the catalytic site. Overall, this work identifies compound 27 as the primary lead and establishes quinazoline-sulphonamide Schiff bases as promising synthetic frameworks for selective hCA-II inhibition relevant to kidney-stone-associated pathways [55].

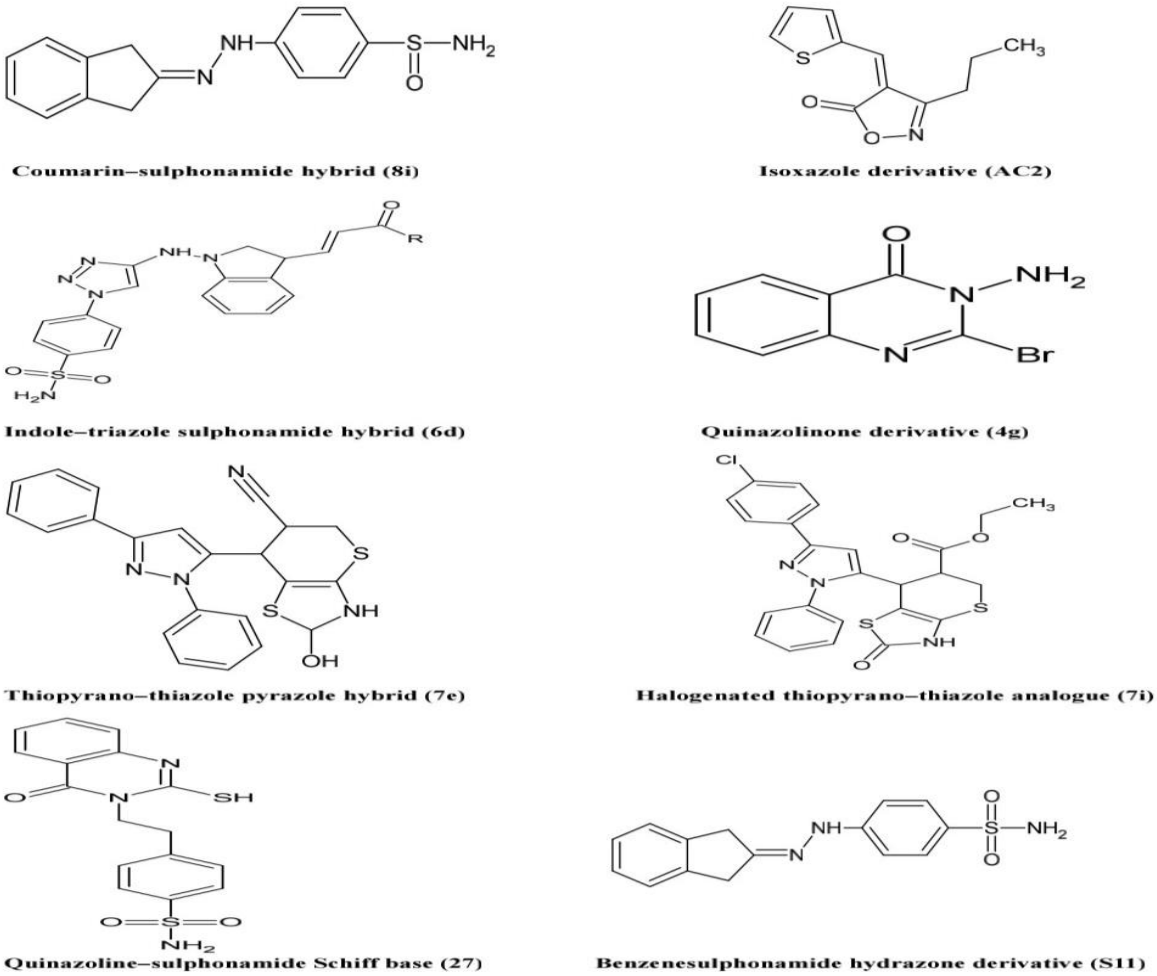
Table 2: Synthetic analogues with reported anti-urolithiatic activity

Ref.	Synthetic Scaffold / class	Primary activity	Lead compound	Key findings
32	Phthalimide derivatives	Crystal inhibition	LD-F10	Strongly inhibited calcium oxalate monohydrate crystal formation without promoting dihydrate crystals.
33	IP6-derived analogues	Crystal inhibition	OEG4-$(IP5)_2$	Reduced crystal formation, epithelial adhesion, and renal crystal deposition in vivo.
34	Coumarin-thiazole Schiff bases	Crystal inhibition	P5	Suppressed calcium oxalate nucleation and aggregation with antioxidant and nephroprotective effects.
35	Hippuric acid–NSAID anhydrides	Anti-urolithiatic/antioxidant	P6 and P9	Demonstrated anti-urolithiatic, antioxidant, and analgesic activities with favourable docking interactions.
36	Barbituric acid–based pyrimidines	Crystal dissolution	F2	Exhibited the highest calcium oxalate dissolution activity among synthesized derivatives.
37	Tetrasubstituted imidazoles	Crystal inhibition	5a	Showed strong inhibition of calcium oxalate nucleation and aggregation in vitro.
38	Benzene sulphonamide derivatives	Nephroprotective activity	SBCL	Reduced oxidative stress, inflammation, and renal crystal deposition.
39	Schiff base derivatives	Diuretic/ urinary modulation	Compounds 1-3	Increased urine output and reduced urinary calcium oxalate crystal formation.
40	Benzotriazole azetidinone derivatives	Antioxidant/ crystal inhibition	5e	Inhibited calcium oxalate crystallization and exhibited strong antioxidant activity.
41	Quinolinone-thiazolidinone hybrids	Urease inhibition	3e	Displayed potent urease inhibition with strong active-site binding interactions.
42	Benzofuran-thiazolidinone analogues	Urease inhibition	Compound 1	Showed higher urease inhibitory activity than thiourea.
43	Pyrimidine-thiazolidinone derivatives	Urease inhibition	Compounds 3, 6, 7, and 10	Exhibited low micromolar urease inhibitory activity with favourable docking interactions.
44	Aryl hydrazide Schiff bases/thiazolidinones	Urease inhibition	2k	Demonstrated potent urease inhibitory activity enhanced by dichloro substitution.
45	Pyrazoline-thiazole hybrids	Dual enzyme inhibition	Compound 6	Exhibited strong α-glucosidase and urease inhibitory activity.
46	Atenolol-thiourea hybrids	Urease inhibition	Compound 22	Showed enhanced urease inhibition compared with thiourea and parent atenolol.
47	(Thio)barbituric phenoxy acetamides	Urease inhibition	7d	Demonstrated submicromolar urease inhibitory activity with stable enzyme binding.
48	5-Arylidene (thio)barbituric acids	Urease inhibition	3a	Showed improved urease inhibition compared with hydroxyurea.
49	Coumarin Schiff bases	Urease inhibition	5a	Exhibited potent urease inhibition supported by docking and in vivo studies.
50	Coumarin-sulphonamide hybrids	Carbonic anhydrase inhibition	8i	Potently inhibited CA IX and CA XII isoforms with low cellular toxicity.

51	Isoxazole derivatives	Carbonic anhydrase inhibition	AC2	Demonstrated stable carbonic anhydrase binding and favourable inhibitory activity.
52	Indole-triazole sulphonamide hybrids	Carbonic anhydrase inhibition	6d	Exhibited strong hCA-I inhibitory activity through zinc coordination interactions.
53	Thiopyrano-thiazole pyrazole hybrids	Carbonic anhydrase inhibition	7e and 7i	Showed potent inhibition of hCA IX and hCA XII isoforms.
54	Quinazolinone derivatives	Carbonic anhydrase inhibition	4g and 4o	Demonstrated selective inhibition of hCA-II with effective zinc coordination.
55	Quinazoline-sulphonamide Schiff bases	Carbonic anhydrase inhibition	27	Exhibited potent nanomolar hCA-II inhibitory activity.
56	Benzenesulfonamide hydrazones	Carbonic anhydrase inhibition	S11	Displayed strong hCA-II inhibition surpassing acetazolamide.

Synthesis of 4-(2-substituted hydrazinyl) benzenesulfonamides and their carbonic anhydrase inhibitory effects: A series of 4-(2-substituted hydrazinyl)benzenesulfonamides (S1-S11) were synthesized via microwave-assisted condensation and evaluated against human carbonic anhydrase II (hCA-II). All derivatives exhibited strong nanomolar inhibition; however, S11 (4-{2-(1,3-dihydro-2H-inden-2-ylidene) hydrazino}benzenesulfonamide) emerged as the primary lead, displaying the highest hCA-II potency (Ki ≈ 1.72 nM), surpassing acetazolamide. Structure-activity trends indicated that the indanone-derived hydrazone moiety significantly enhances enzyme binding, consistent with sulphonamide-mediated Zn^{2+} coordination at the catalytic site. Overall, this study identifies S11 as a highly promising synthetic scaffold for selective hCA-II inhibition, supporting further optimization of benzenesulfonamide–hydrazone hybrids for carbonic-anhydrase–driven renal stone pathways [56].

Figure 5: Representative carbonic anhydrase-targeted synthetic analogues investigated for anti-urolithiatic activity



Structure-activity relationships

The structure-activity relationship (SAR) analysis of synthetic analogues reported for anti-urolithiatic activity revealed that heterocyclic scaffolds play an important role in improving crystal inhibition and enzyme-targeted activity. Through better molecular interactions with crystal surfaces and enzymatically active sites, pharmacologically active heterocycles like thiazole, imidazole, pyrazole, quinazoline, pyrimidine, benzofuran, and coumarin greatly increased anti-urolithiatic potential, according to several studies [34, 37, 41, 42, 54]. Electron-withdrawing substituents, particularly halogens, nitro groups, and trifluoromethyl groups, were frequently associated with improved inhibitory activity. These substitutions likely enhance hydrophobic interactions and binding affinity within enzyme active sites, thereby improving biological potency. Halogenated derivatives of quinazoline, coumarin, pyrazole, and thiazolidinone analogues exhibited comparatively stronger urease and carbonic anhydrase inhibitory activities than unsubstituted analogues [40, 45, 49, 53]. In addition, methoxy-substituted aromatic rings also contributed positively in several analogues, possibly due to enhanced electronic stabilization and hydrogen-bonding interactions [45, 55]. Sulphonamide-containing analogues demonstrated particularly significant activity against carbonic anhydrase enzymes. The sulphonamide pharmacophore effectively coordinates with the catalytic zinc ion present within the enzyme active site, thereby enhancing inhibitory potency. Structural orientation and aromatic substitutions further influenced enzyme selectivity and binding affinity [50, 52, 55, 56]. The hybridization of two pharmacologically active scaffolds within a single molecule was another significant SAR finding. Several coumarin-thiazole, quinazoline-sulphonamide, pyrazoline-thiazole, and benzofuran-thiazolidinone hybrids showed enhanced inhibitory effects compared to simpler analogues, suggesting synergistic interactions between structural pharmacophores [34, 42, 45, 55]. Moreover, increased aromaticity and molecular planarity may also influence biological activity by stabilizing ligand-enzyme interactions. Stronger interactions with calcium oxalate crystal surfaces and enzyme binding sites may also result from increased aromaticity and molecular planarity. Additionally, it was discovered that hydrogen bond donor and acceptor groups, such as hydroxyl, amino, carbonyl, and Schiff base functions, affect biological activity via maintaining ligand-enzyme connections [35, 39, 44, 55]. These functional groups increased crystal inhibition and enzyme-targeted activity by facilitating intermolecular interactions. Overall, the evidence that is currently available indicates that the use of heterocyclic nuclei, electron-withdrawing substituents, sulphonamide pharmacophores, and hybrid scaffold strategies greatly enhances anti-urolithiatic activity and may offer helpful direction for the future development and optimization of novel synthetic analogues for the treatment of urolithiasis.

Future perspectives and challenges: Several natural compounds and synthetic analogues have shown encouraging anti-urolithiatic action in experiments, but their clinical application is currently limited by a number of issues. With little data from human clinical trials, the majority of research is limited to in vitro assessments and animal models. Major issues with natural products continue to include variability in phytochemical composition, poor bioavailability, lack of standardization, and inadequate toxicity profiling. Similar to this, more optimization is needed to enhance selectivity, pharmacokinetic characteristics, and long-term safety despite notable advancements in the creation of synthetic analogues that target calcium oxalate crystallization and stone-associated enzymes. Sophisticated computational techniques, structure-based drug design, and hybrid scaffold methodologies may aid the creation of more effective anti-urolithiatic drugs [57, 58]. Furthermore, incorporating innovative medication delivery methods and conducting thorough mechanistic studies could enhance treatment efficacy even more.

Conclusion: This review demonstrates that synthetic analogues and natural compounds provide viable therapeutic approaches for the treatment of kidney stones. In addition to restoring urinary biochemical equilibrium and offering antioxidant-mediated kidney protection, natural extracts and phytoconstituents primarily work by preventing calcium oxalate nucleation, aggregation, and growth. Simultaneously, synthetic

drugs enable focused intervention through enzyme inhibition, antioxidant-mediated protection, manipulation of urine parameters, and direct crystal inhibition. When taken as a whole, these strategies emphasize the value of multi-target therapy over single-mechanism therapy for successful stone prevention and recurrence control. Despite the fact that many candidates show promising preclinical efficacy, insufficient pharmacokinetic characterization, safety assessment, and human investigations continue to impede their clinical translation. To close the gap between experimental results and therapeutic application, future research should prioritize lead optimization, mechanistic integration, and carefully planned clinical studies. Overall, the development of safer and more potent anti-urolithiatic treatments may be greatly aided by ongoing research into natural compounds and well-crafted synthetic counterparts.

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