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INTEGRATING QUINOLINE CHEMISTRY INTO ANTIHYPERTENSIVE DRUG DISCOVERY: PROGRESS AND PROSPECTIVES

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Abstract:

Hypertension is a major global health issue contributing to cardiovascular morbidity and mortality. Despite the availability of several antihypertensive classes - such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers, calcium channel blockers, and diuretics - limitations like poor selectivity, low bioavailability, and adverse effects persist. Quinoline-based molecules have emerged as a versatile scaffold in drug discovery due to their unique aromatic heterocyclic structure, which allows π–π stacking, hydrogen bonding, and metal chelation - crucial for interaction with the zinc-containing catalytic site of ACE. Quinoline derivatives exhibit a broad spectrum of cardiovascular actions, including ACE inhibition, calcium channel blocking, β-adrenergic antagonism, and nitric oxide modulation. This review summarizes recent advances in the chemistry, synthesis, structure - activity relationships (SAR), and molecular docking studies of quinoline-based antihypertensive agents. Challenges such as solubility, metabolic stability, and target selectivity are discussed, alongside prospects in hybrid drug design and AI-assisted QSAR modeling. The evidence supports quinoline scaffolds as promising leads for next-generation antihypertensive drugs targeting multiple mechanisms in the renin - angiotensin - aldosterone system (RAAS).

Index Terms: Quinoline derivatives; ACE inhibitors; Antihypertensive agents; SAR; Molecular docking; Hybrid Molecules; Drug Design.

1. INTRODUCTION:

Hypertension, defined as a persistent elevation in arterial blood pressure above 140/90 mmHg, affects nearly 1.3 billion people globally and represents a major risk factor for stroke, myocardial infarction, and renal disease. (Mendis et al., 2011; Campbell et al., 2015) Conventional therapeutic agents include ACE inhibitors, ARBs, β-blockers, calcium channel blockers, and diuretics (James et al., 2014; Heran et al., 2008). Although ACE inhibitors such as captopril, enalapril, and lisinopril remain first-line treatments, they exhibit limitations - most notably dry cough, angioedema, hyperkalemia, and renal impairment (Brown & Vaughan, 1998; Banerji et al., 2017; Na Takuathung et al., 2022). Moreover, nonselective inhibition of ACE's N- and C-domains leads to bradykinin accumulation, aggravating adverse effects (Fox et al., 1996; Anthony et al., 2012; Alves-Lopes et al., 2021).

The quinoline nucleus, a bicyclic aromatic compound consisting of fused benzene and pyridine rings, has attracted considerable attention as a privileged pharmacophore due to its broad biological spectrum—antimalarial, antibacterial, anticancer, and cardiovascular activities (Kumar et al., 2014; Mermer et al., 2018). The nitrogen atom in quinoline imparts electronic versatility, enabling metal chelation, hydrogen bonding, and interaction with aromatic residues in enzyme pockets.

This review explores quinoline-based antihypertensive agents, particularly ACE inhibitors, focusing on their chemistry, synthesis, structure – activity relationship (SAR), molecular docking, recent advances, and development challenges, with an outlook toward future design strategies (Acharya et al., 2024; Anthony et al., 2012).

2. CHEMISTRY AND IMPORTANCE OF THE QUINOLINE SCAFFOLD:

Chemical Structure: Benzopyridine (Fusion of Benzene and Pyridine)

The quinoline nucleus is a heterocyclic ring system. It is fundamentally composed of a benzene ring fused to a pyridine ring. Quinoline derivatives have attracted considerable attention in medicinal chemistry due to their diverse pharmacological properties and structural versatility (Kumar et al., 2014; Mermer et al., 2018).

Key Chemical Properties

The fused aromatic nature of the quinoline scaffold endows it with properties crucial for effective drug-target interaction (Anthony et al., 2012):

1. **pi-pi Interactions (Aromatic Stacking):** The aromatic nature of the quinoline ring facilitates crucial pi-pi interactions (aromatic stacking) with amino acid residues in protein binding pockets (Mermer et al., 2018).
   - In the search for SARS-CoV-2 inhibitors, virtual screening identified that quinoline-based ligands bind to viral entry proteins (Spike-ACE2 and TMPRSS2) using pi stacking interactions (Kumar et al., 2014).
   - These pi-pi interactions occur between the quinoline ring and aromatic amino acid residues present in the active site.
   - In studies targeting Acetylcholinesterase (ACE) inhibition, a quinolin-4(1H)-one moiety was shown to occupy the binding pocket and engage in strong pi-pi interactions with the Trp286 aromatic side chain (Mermer et al., 2018).
   - In ACE inhibitor studies using quinazolinone (a related heterocyclic structure), the quinazolinone moiety explored a hydrophobic binding pocket surrounded by aromatic residues like Tyr523, Phe457, Phe460, and Trp279 (Natesh et al., 2003).
2. **Hydrogen Bond Donor/Acceptor Capabilities:** The nitrogen atom and potential substituent groups on the quinoline ring allow the structure to act as both a hydrogen bond donor and acceptor, necessary for forming stable anchor points within enzyme active sites (Anthony et al., 2012; Acharya et al., 2024).
   - In docking studies of quinazolinone derivatives against ACE, key hydrogen bonds (H-bonds) were observed with residues such as Glu411 and Glu384 (Venkatesh et al., 2015).
   - The core structure of ACE inhibitors, including quinolines, must participate in various interactions, such as hydrogen bonding and ionic bonding, within the active site (Cushman et al., 1977; Ondetti et al., 1977).
3. **Metal Chelation Potential (Important for ACE Inhibition**): Angiotensin-Converting Enzyme (ACE) is a zinc metallo-endopeptidase (Acharya et al., 2003; Dive et al., 1999). Its catalytic activity relies on a divalent zinc ion Zn^{2+}. Therefore, any effective ACE inhibitor must contain a moiety capable of interacting with or chelating the Zn^{2+} ion to mimic the transition state of peptide hydrolysis.
   - ACE inhibitors typically contain moieties like sulfhydryl, carboxylate, or phosphate to connect to the Zn^{2+}ion (Cushman et al., 1977).
   - While the core quinoline scaffold itself may not be the chelating group, its derivatives are designed to contain such groups. For instance, in quinazolinone derivatives, the carbonyl moiety and linker hydroxyl group facilitate Zn^{2+}mediated interactions with critical ACE residues such as His383 and His387 (Venkatesh et al., 2015).
   - Specific quinoline-appended compounds designed as potential anti-hypertensive agents have shown significant ACE inhibition through dose-dependent inhibition (Kumar et al., 2015).

Naturally Derived Quinolines and Therapeutic Versatility

Although the provided sources do not explicitly detail the structures or full mechanism of quinine or camptothecin, they highlight that quinoline derivatives are present in bioactive natural isolates and possess significant therapeutic value (Ahmad et al., 2018; Adhitia et al., 2017).

- Antimalarial History: Quinoline structures have a history in antimalarial activities (Kumar et al., 2014).
- Source Diversity: The quinoline scaffold forms the basis of many drugs used to treat various diseases. Research efforts often focus on extracting and synthesizing novel quinoline analogues from sources like medicinal plants (Fadahunsi et al., 2022).

Quinoline as a Privileged Structure in Drug Design

The versatility and effectiveness demonstrated by quinoline-based drugs across multiple disease states confirm its status as a privileged structure in medicinal chemistry (Mermer et al., 2018; Kumar et al., 2015).

- **Antimalarial/Antimicrobial:** Quinolones are recognized as some of the most important synthetic antibacterial agents known for their excellent safety profiles and broad spectrum. They are also explored for antiviral properties (Mermer et al., 2018).
- Anticancer/Antitumor: Quinoline derivatives have shown activity as anticancer and antitumor agents (Kumar et al., 2014).
- **Cardiovascular and Antihypertensive Drugs:** Quinoline derivatives are crucial in cardiovascular drug development (Anthony et al., 2012; Acharya et al., 2024).
  - The structural versatility allows for rational drug design, leading to the development of potent and selective compounds for the management of hypertension.
  - A clinically used ACE inhibitor, Quinapril, belongs to the isoquinoline class (a structural analogue of quinoline), and its structure enhances lipophilicity and confers strong C domain selectivity in ACE inhibition (Anthony et al., 2012).
  - Quinoline-based compounds have also been studied for other cardiovascular effects, such as anti-inflammatory and anti-oxidant activity, and the ability to modulate pathways implicated in hypertension, including the renin-angiotensin-aldosterone system (RAAS) and endothelial function (Alam et al., 2013).
- **Other CNS and Metabolic Uses:** Quinoline structures are explored for activity in Alzheimer's Disease (e.g., anticholinesterase activity) and are potent alpha -glucosidase inhibitors (used for Type 2 Diabetes) (Mermer et al., 2018).

3. MECHANISMS OF ANTIHYPERTENSIVE ACTION OF QUINOLINE DERIVATIVES:

Quinoline derivatives may act through multiple molecular targets (Kumar et al., 2015; Patil et al., 2023).

- **ACE inhibition** is the most prominent and well-studied (Cushman et al., 1977; Ondetti et al., 1977; Acharya et al., 2024). The inhibitor binds in the ACE active site, coordinates the Zn^{2+} ion (often via a carboxylate, thiol, or phosphinate group) (Dive et al., 1999; Cozier et al., 2022), and interacts via hydrogen bonds and hydrophobic contacts to inhibit cleavage of angiotensin I to II (Natesh et al., 2003; Anthony et al., 2012).
- **Calcium channel blockade**: Though less common in literature for quinoline derivatives, fusing or linking quinoline onto dihydropyridine or other calcium channel blocker backbones is conceptually possible (Patil et al., 2023).
- **Adrenergic antagonism** can arise when a quinoline moiety is appended to β-blocker pharmacophores (Kumar et al., 2014).
- **NO modulation** is another approach: a quinoline derivative bearing a nitrate or oxime group may produce NO, augmenting vasodilation (Alam et al., 2013).
- Multi-target or hybrid molecules can combine one or more of these mechanisms in a single molecule, e.g. ACE inhibition + NO donation (Kumar et al., 2015; Patil et al., 2023).

Table 3.1: Summary (Anthony et al., 2012)

Mechanism	Target	Examples / Hypothetical	Key Features
ACE inhibition	Angiotensin-Converting Enzyme	Quinoline-2-carboxylic acid derivatives, quinoline-appended chalcones	Zn^{2+} binding/co-ordination, suppression of Ang II formation
Calcium channel blockade	L-type Ca^{2+} channels	4-quinolinyl dihydropyridine hybrids	Inhibition of Ca^{2+} influx → vasodilation
Adrenergic receptor antagonism	β / α receptors	Quinoline-imidazole or quinoline-propanolamine hybrids	Decrease heart rate / contractility
Endothelin receptor antagonism	ET-A / ET-B receptors	Quinoline sulfonamide derivatives	Reduce vasoconstriction mediated by endothelin
Nitric oxide (NO) modulation	eNOS / NO pathway	Quinoline-oxime, nitrate linked quinolines	Release NO → vasodilation

4.QUINOLINE-BASED ANTIHYPERTENSIVE AGENTS:

A. Quinoline-Based ACE Inhibitors

Quinoline derivatives are structurally incorporated into the family of Angiotensin-Converting Enzyme (ACE) inhibitors, which are first-line therapies for hypertension, heart failure, and myocardial infarction (Brown & Vaughan, 1998; James et al., 2014; McDonagh et al., 2021).

- **Examples and Drug Class:** A key example is Quinapril, which is classified as a dicarboxylate-containing ACE inhibitor. Structurally, Quinapril belongs to the isoquinoline class, specifically featuring a tetrahydroisoquinoline ring (Beermann, 1988; Cushman et al., 1977). Derivatives based on the quinazoline

nucleus (a fused heterocycle related to quinoline), such as quinazolinone derivatives (9a-g), have also been successfully synthesized and evaluated as potent ACE inhibitors (Venkatesh et al., 2015; Nchinda et al., 2006).

- **Mode of Action: Zn^{2+} Coordination:** ACE is a zinc metallo-endopeptidase (Acharya et al., 2003; Anthony et al., 2012). The mechanism of inhibition involves the ligand targeting the catalytic Zn^{2+} ion. Quinapril's active metabolite, quinaprilat, is one of the proline-containing inhibitors that utilize a functional group (the carboxyl moiety) to bind directly to the Zn^{2+} ion (Ondetti et al., 1977). In quinazolinone derivatives (e.g., compound 9e), the carbonyl moiety and linker hydroxyl group facilitate Zn^{2+} mediated interactions with critical active site residues His383 and His387. This binding blocks the conversion of Angiotensin I (Ang I) to the potent vasoconstrictor Angiotensin II (Ang II) (Natesh et al., 2003; Acharya et al., 2024).
- **Molecular Docking Supporting Strong Binding Affinity:** Molecular docking studies confirm the mechanism and potency of these structures:
  - Quinaprilat was predicted to be 180 times more selective for the C-domain (ACE C) of ACE than the N-domain (ACE). This selectivity is attributed to the hydrophobic tetrahydroisoquinoline moiety leading to a differential effect in the P2' position compared to drugs like enalaprilat (Anthony et al., 2012; Alves-Lopes et al., 2021).
  - Quinazolinone derivative 9e showed potent ACE inhibition in enzyme-based assays, with docking indicating shared key active site interactions (H-bonding with Glu411 and Glu384, and Zn^{2+} coordination via His383 and His387 with the standard drug Lisinopril (Venkatesh et al., 2015; Cozier et al., 2022).

B. Quinoline-Derived Calcium Channel Blockers (CCBs)

Quinoline structures can serve as cores for or substituents on calcium channel blockers (CCBs), which lower blood pressure by inhibiting the flow of calcium ions into vascular smooth muscles, leading to dilation of the arteries (Patil et al., 2023).

- **Quinoline Fused or Substituted Analogs of Dihydropyridines:** Research has focused on synthesizing dihydropyrimidine (DHPM) analogues (which are bioisosters of the classic CCB Nifedipine) by using heterocyclic aldehydes (Patil et al., 2023).
- **Mechanism:** Compounds synthesized using 2-chloroquinoline-3-carbaldehyde exhibited high-efficiency CCB activity, as demonstrated by the inhibition of potassium chloride-induced smooth muscle contractions. The most promising compounds showed antihypertensive activity comparable to the reference drug Nifedipine (Patil et al., 2023).
- **SAR: Electron-Donating Groups on Quinoline Improve Activity:** The synthesis route allowed for varied substitutions. The substitution with heterocyclic rings (like quinolone) at the C4 position of the DHPM ring seemed to slightly enhance both the antihypertensive and the CCB activity. Generally, the biological activity of these analogues depends on the hydrophilic, lipophilic, electronic, and steric properties of the substituents (Patil et al., 2023).

C. Quinoline-β Blocker Hybrids

The combination of the quinoline scaffold with the characteristic beta-blocking structural motif is a strategy for achieving dual activity (Kumar et al., 2014).

- **Quinoline Moiety Linked with Propanolamine or Imidazoline**: Synthesis has been reported for 8-substituted quinoline derivatives containing the 2-hydroxypropyloxyquinoline moiety, a structure typically associated with aryloxypropanolamine beta-blocking properties (Kumar et al., 2015).
- **Mechanism: Block beta 1-receptors right arrow Decrease Heart Rate and Contractility:** While the sources do not specify selective beta-1 blocking, they confirm that beta -blockers decrease peripheral vascular resistance and inhibit the tonic effect of Ang II on the sympathetic nervous system without increasing heart rate (Matchar et al., 2008).
- **Benefit: Dual Action (beta-blocking + Vasodilation):** The antihypertensive effects of compounds such as 8-(3'-(4"-phenylpiperazino)-2'-hydroxypropyloxy) quinoline (Compound 20) were observed to significantly antagonize the pressor response elicited by adrenaline. This pharmacological profile suggested that their antihypertensive effects are directly correlated to the presence of beta-blocking properties. The hybrid nature combines the core quinoline ring with the propanolamine/aminoethane side chain (Kumar et al., 2015).

D. Quinoline–NO Donor Hybrids

This class leverages the quinoline scaffold in combination with functional groups that enhance vasodilation by releasing Nitric Oxide (NO) or affecting related pathways (Alam et al., 2013).

- **Mechanism:**

  Enhance Vasodilation through Endothelial NO Signalling: While no source explicitly details a quinoline hybrid containing a nitrate or oxime group (NO donor), the principle of sulfhydryl-containing ACE inhibitors is analogous:

- Sulfhydryl-containing ACE inhibitors (like Captopril) are known for their ability to stimulate nitric oxide activity (NO) and reduce oxidative stress in hypertensive patients. This effect helps decrease systemic vascular resistance (Na Takuathung et al., 2022; ISIS Collaborative Group, 1995).
- ACE inhibition, generally, alters the formation and degradation of vasoactive substances, including bradykinin, which is involved in vasodilation. The sulfhydryl group specifically confers properties like free-radical scavenging (Brown & Vaughan, 1998).

- **Advantage: Synergistic Effect, Reducing Oxidative Stress: The synergistic effect stems from the dual action: ACE in**
- Blocks vasoconstriction (Ang II), while the NO-donating/sulfhydryl group enhances vasodilation and provides cardiovascular protection by balancing the nitric oxide/oxidative stress pathways.

E. Natural Quinoline Alkaloids

The quinoline scaffold is fundamentally derived from natural sources, making plant-derived compounds an important area of research (Mermer et al., 2018; Mendis et al., 2011).

- **Example: Quinine and its Analogues (Mild Vasodilators):** Although specific mechanisms detailing quinine as a mild vasodilator are not provided in the sources, the importance of the quinoline nucleus derived from natural products is confirmed. The quinoline nucleus is confirmed to form the basis of many drugs used in the treatment of various diseases.
- **Phytochemical Derivatives with Potential Antihypertensive Properties:**
- Quinoline derivatives are prominent components of bioactive natural isolates, including several marine alkaloids.
- Novel peptides derived from food sources, which are often sought as safer alternatives to synthetic drugs, frequently contain aromatic amino acids (like Trp, Tyr, Phe) which exploit pi-pi stacking interactions often facilitated by the structural characteristics associated with the quinoline scaffold (Pan et al., 2012; Ma et al., 2023; Pearman et al., 2025).
- Specific quinoline-appended chalcone derivatives (e.g., ADMQ) synthesized based on bioactive heterocyclic scaffolds have been confirmed to possess significant antihypertensive activity via ACE inhibition (Kumar et al., 2015).

Table. 5.1: Summary Table of Quinoline-Based Antihypertensive Agents

Drug/Class Type	Quinoline Scaffold Feature	Mechanism of Action	Key Structural/Binding Insight
A. ACE Inhibitors	Isoquinoline (Quinapril), Quinazolinone derivatives	Inhibits ACE, blocking Ang I → Ang II conversion.	**Zn^{2+} Coordination:** Quinaprilat uses a carboxyl moiety to chelate the Zn2+ ion. **Selectivity:** Quinaprilat is highly C-domain selective due to its tetrahydroisoquinoline ring filling the P2' subsite.
B.Calcium Channel Blockers (CCBs)	2-Chloroquinoline-3-carbaldehyde (as aldehyde precursor)	Inhibits calcium ion influx into vascular smooth muscles.	**Nifedipine Bioisosteres:** Quinoline-derived dihydropyrimidine (DHPM) analogues show comparable CCB activity to Nifedipine. **SAR:** Heterocyclic substitution at C4 of DHPM enhances activity.
C.Beta-Blocker Hybrids	Aryloxypropanolamine attached to quinoline (e.g., 8-substituted quinolines)	Blocks beta-receptors, counteracting pressor responses elicited by adrenaline.	**Dual Action:** Antihypertensive activity is strongly correlated with the presence of beta-blocking aryloxypropanolamine properties.
D.NO Donor Hybrids	Sulfhydryl group (e.g., Captopril, often structurally compared to quinoline derivatives)	Enhances vasodilation via NO signaling pathways; reduces oxidative stress.	**Synergy:** The sulfhydryl (-SH) group confers secondary benefits like **free-radical scavenging** and NO stimulation,

			augmenting the cardiovascular effects beyond simple ACE inhibition.
E. Natural Alkaloids	Quinoline (core scaffold)	General antihypertensive properties through interaction with pathways like RAAS.	**Privileged Structure:** Quinoline is a highly attractive nucleus found in bioactive natural isolates; derivatives show antihypertensive effects through ACE inhibition and are tested as potent agents.

5. STRUCTURE–ACTIVITY RELATIONSHIP (SAR) INSIGHTS IN ACE INHIBITOR DESIGN:

Structure–Activity Relationship (SAR) studies are essential for the rational design of new-generation ACE inhibitors, particularly those targeting domain selectivity or those built upon complex scaffolds like quinoline derivatives (Acharya et al., 2003; Anthony et al., 2012; Dive et al., 1999). The activity is governed by optimizing four major requirements: the zinc-chelating group, the hydrophobic groups fitting the S1 and S2 pockets, the functional groups stabilizing the S1 pocket, and crucial functional groups interacting with the domain-specific S2 pocket (Acharya et al., 2024; Cozier et al., 2022).

Substitution Patterns and Their Effects on Potency and Selectivity

1. Zinc-Chelating Groups and Basic Potency

Potency initiation relies heavily on the group coordinating the divalent zinc ion Zn^{2+} at the catalytic site (Natesh et al., 2003; Anthony et al., 2012). Clinically effective ACE inhibitors utilize one of three primary Zn^{2+} binding motifs:

- **Sulfhydryl (-SH):** Found in Captopril. This group is critical for ACE inhibition. Sulfhydryl-containing ACE inhibitors offer the additional advantage of stimulating nitric oxide activity and acting as free-radical scavengers, potentially reducing oxidative stress in hypertensive patients (Cushman et al., 1977; Alam et al., 2013).
- **Carboxylate (-COOH):** Found in dicarboxylate derivatives like Lisinopril and Enalaprilat. This moiety interacts directly with the Zn^{2+} metal ion (Beermann, 1988; Brown & Vaughan, 1998).
- **Phosphinate/Phosphonate (-P):** Found in Fosinopril. Phosphonyl substitution (as seen in the natural product K-26) is a critical determinant of activity, resulting in a significantly enhanced increase in ACE inhibition when compared to its carboxyl analogues (Dive et al., 1999; Cozier et al., 2022).

2. Substitution at P2 and S2 Subsites (Domain Selectivity)

The S2 subsite, located adjacent to the zinc ion, is critical for conferring selectivity because the amino acid residues lining this pocket are non-conserved between the ACE-N and ACE-C domains. Bulky groups at this site are paramount for improving selectivity for receptor subtypes (Natesh et al., 2004; Alves-Lopes et al., 2021).

- **N-Domain Selective Substitutions (nACE):**
  - The substitution must exploit the specific residues Arg381 and Tyr369 in the nACE S2 subsite, which are replaced by Glu403 and Phe391 in cACE (Dive et al., 1999).
  - The incorporation of acidic functional groups (e.g., Aspartic acid (Asp), Glutamate (Glu), or Asparagine (Asn)at the P2 position promotes N-selectivity. The P2 Aspartate group in RXP407 forms a salt bridge with Arg381 and a hydrogen bond with Tyr369, which is critical for its high N-domain selectivity (2000-fold) (Dive et al., 1999).
- **C-Domain Selective Substitutions (cACE):**
  - The goal is to exploit the hydrophobic S2 residue Phe391 and the negatively charged Glu403 (Anthony et al., 2012; Venkatesh et al., 2015).
  - The inclusion of bulky hydrophobic groups, such as the P2 phenylalanine (Phe) group in RXPA380, allows for specific hydrophobic interactions with Phe391 in cACE, conferring 2000-fold C-selectivity. The phenyl ring of keto-ACE derivatives also orients for a stacking interaction with Phe391 in ACE-C (Cushman et al., 1977; Alves-Lopes et al., 2021).
  - Generally, large P2 ‘groups contribute to ACE-C selectivity.

3. Hydroxyl or Carboxyl Groups (Solubility and H-Bond Formation)

Hydroxyl (-OH) and carboxyl (-COOH) groups are critical for stabilizing the ligand-receptor complex through polar interactions and enhancing solubility (Pan et al., 2012; Ma et al., 2018).

- **Hydrogen Bond Formation:** Compounds that exhibit high ACE inhibitory activity often rely on strong hydrogen bonding and hydrophobicity to orient the ligand optimally in the active site.
  - For phenolic acid-derived inhibitors, hydroxyl groups may serve as good hydrogen donors to chelate with Zn2+ in the active site (Ma et al., 2023).
  - In hybrid quinazolinone inhibitors, the linker hydroxyl group formed H-bonds with Glu411 and Glu384 (Venkatesh et al., 2015).
  - The carboxy group of proline in Lisinopril showed H-bonding interactions with sidechain residues Glu281, Lys511, and Tyr520 (Natesh et al., 2003).
- **Aromatic Substitution (2- or 4-position):** In phenolic acids, substitution in positions 3 and 4 in the benzene ring is beneficial for increasing ACE-inhibitory activity (Pan et al., 2012).

4. Bulky and Hydrophobic Groups (P1 and P2 ')

The P1 and P2 ' positions are typically occupied by hydrophobic groups, which are critical for potency and stabilizing the peptide backbone mimic within the binding channel (Anthony et al., 2012; Manikandan et al., 2017).

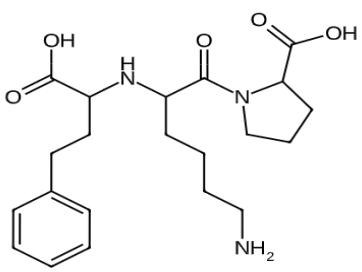
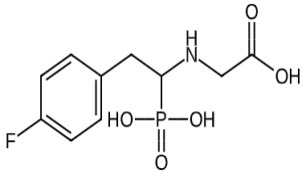
- **P1 and P2 'Hydrophobicity:** Amino acid residues at the P1 site require side chains containing many hydrophobic groups. The binding surface of the carboxy- terminal proline moieties of inhibitors is composed of a hydrophobic patch formed by residues like F457 / F435, F527 / F505, Y520 / Y498, and Y523 / Y501 (Anthony et al., 2012; Manikandan et al., 2017).
- **Stereochemistry and Bulk:** Stereochemistry is vital for efficient ACE inhibition. In the design of dual inhibitors (e.g., ACE/ECE-1), the R configuration of the P1 'residue, combined with long and bulky P1 'side chains, was shown to control inhibitor selectivity against Neprilysin (NEP) (Alves-Lopes et al., 2021).

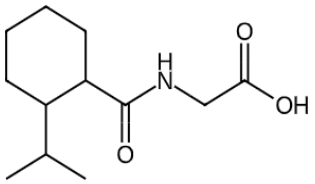
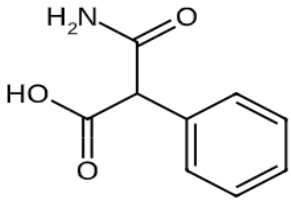
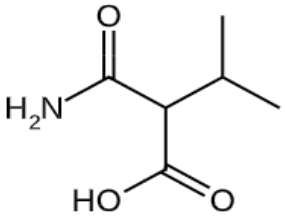
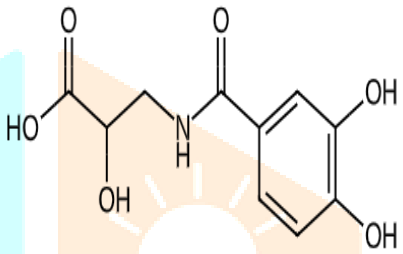
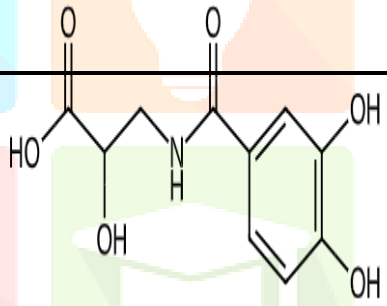
5. Electron-Withdrawing Groups (EWGs)

The effect of substituents like electron-withdrawing groups (-Cl, -NO_2) is context-dependent, sometimes aiding binding affinity through specific electronic or halogen interactions, but other times proving detrimental due to steric clash or charge repulsion (Manikandan et al., 2017; Venkatesh et al., 2015).

- **Detrimental Effects:** In one study using quinazolinone ACE inhibitors, substitution of a nitro group (NO_2) was detrimental to activity because it was oriented near Glu143 (Venkatesh et al., 2015).
- **Beneficial Effects (EDGs):** In contrast, SAR studies on quinazolinone ACE inhibitors suggested that substitution of an electron donating group on the quinazolinone ring resulted in higher percentage of ACE inhibitory activity (Venkatesh et al., 2015).
- **Halogen/Hydrophobicity:** The presence of a highly electronegative group, such as the trifluoromethyl group (CF_3) on Captopril analogues, improved potency significantly. This is attributed to the increased hydrophobicity and stereoelectronic effects, enhancing attractive interactions with the hydrophobic binding subsite of ACE. Halogen bonding interactions were also noted to aid stability in protein-ligand complexes (Cushman et al., 1977).

Table 6.1: SAR Summary Table

Feature / Modification (location)	Example structure	Potency / Selectivity effect	Key ACE residues / sub-pockets
Zn^{2+}-chelating group (P1)		**Thiol of captopril chelates Zn^{2+} (R-S) and gives strong inhibition (class L)**	**His383, His387, Glu411**
Phosphinate chelator (P1)		**Fosinoprilat's phosphinate binds Zn^{2+} and shows C-domain selectivity**	**His383, His387, Glu411**

Bulky/hydrophobic P2′ (cACE-selective)		**Cyclohexane side-chain of fosinoprilat fits the lipophilic cACE S2′ pocket, ↑ cACE selectivity**	**Val380 (cACE) vs. Ser357/Thr358 (nACE)**
Aromatic P2 (cACE potency)		**Phe-like P2 of RXPA380 stacks with Phe391 in cACE S2, enhancing binding**	**Phe391 (cACE)**
Hydrophobic P1 (S1 pocket)		**Aliphatic side-chain fits S1 (Phe512/Val518), raising overall potency**	
Phenolic-OH (Zn-chelating/H-bond)		**3,4-dihydroxy-phenyl acid (e.g., caffeic acid) supplies additional H-bonds and modest Zn interaction**	
Substitu-EDG at 3/4 of aromatic ring		**Electron-donating groups at positions 3/4 improve ACE binding (observed for 7a)**	

6. PHARMACOLOGICAL EVALUATION:

The evaluation of novel antihypertensive compounds progresses rigorously from bench-top biochemical assays to advanced in vivo animal models to confirm potency, efficacy, mechanism of action, and preliminary safety (Morris et al., 2009; Dive et al., 1999; Heran et al., 2008).

Outline of Common Assays

A. In Vitro ACE Inhibition Assay

The foundational assessment for potential ACE inhibitors involves quantifying the compound's ability to suppress the enzymatic activity of ACE.

- **Methodology:** The most commonly employed method is a high-throughput colorimetric assay. This assay uses the synthetic substrate Hippuryl-L-Histidyl-L-Leucine (HHL) (Pan et al., 2012).
- **Principle:** ACE hydrolyzes HHL to produce hippuric acid (HA). The amount of HA released is directly proportional to ACE activity (Almquist et al., 1980).
- **Detection:** Released HA is transformed into a yellow color upon mixing with pyridine and benzene sulfonyl chloride, which is then measured colorimetrically at 410 nm. Compounds inhibiting ACE block this hydrolysis, leading to a diminished yellow color formation (Pan et al., 2012).
- **Enzyme Source:** The enzyme source may be kidney cortex plasma membrane preparations or commercial ACE preparations (Anthony et al., 2012).
- **Peptide Isolation:** For food-derived peptides, targeted purification steps are critical prior to in vitro assaying. Techniques like ACE gel affinity chromatography (ACE–Sepharose 4B) are utilized to specifically enrich the active ACE inhibitory peptides (ACEIPs) and remove non-target substances (Pan et al., 2012; Ma et al., 2018).

B. In Vivo Antihypertensive Models

Animal models are indispensable for evaluating the systemic effects of lead compounds, particularly their impact on blood pressure (BP) and cardiovascular function (Heran et al., 2008; McDonagh et al., 2021).

- **Spontaneously Hypertensive Rats (SHRs):** The SHR model is the most widely used animal model for investigating agents aimed at treating human essential hypertension.

  - **Measurements:** BP is measured automatically using the non-invasive tail-cuff method (Heran et al., 2008).
  - **Acute Tests:** Assess the immediate reduction in Systolic Arterial Pressure (SBP) following a single dose, typically over a period of hours (e.g., 6 hours) (Kumar et al., 2015).
  - **Therapeutic Tests:** Assess prolonged efficacy and safety, often involving oral administration daily for 7 consecutive days, with BP measured daily (Qin et al., 2023).
- **Normotensive Anesthetized Rats:** These animals are used to evaluate the hypotensive activity of novel compounds and their effect on the pressor response to endogenous vasoconstrictors like adrenaline and noradrenaline (Kumar et al., 2014).
- **Other Models:** While the SHR is dominant, other models (like those representing severe lung injury or chronic kidney disease) are used in studies involving domain-selective inhibitors (Alves-Lopes et al., 2021).

Toxicity and Safety Profiles of Potent Compounds

A major focus in drug development is minimizing the adverse effects historically associated with traditional ACE inhibitors, such as persistent dry cough (RR = 2.66) and angioedema. Novel compounds are evaluated in silico for ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) properties and tested in vivo for clinical safety (Fox et al., 1996; Na Takuathung et al., 2022).

Table 6.1: Summary of Toxicity and Safety Profiles of Potent Compounds

Safety/Toxicity Aspect	Finding and Significance
Known Class Risks	ACE inhibitors significantly increase the risk of dry cough (RR= 2.66), hypotension (RR = 1.98), dizziness (RR = 1.46), and hyperkalemia (RR = 1.24) compared to placebo.
New Hybrid Safety (7a, 7g)	Successive dosing of compounds 7a and 7g (phenolic/dipeptide/borneol hybrids) in SHRs showed no effect on the body weight of the rats, suggesting favourable preliminary safety.
Peptide ADMET Profile	Sea cucumber peptides (e.g., HDWWKER) exhibited favorable ADMET properties, including predictions of low acute oral toxicity in rats, non-carcinogenicity, and low CYP450 inhibitory potentials, indicating minimal interference with major metabolic pathways.
Organ Protection	The potent hybrid ACEI 221s (2,9) demonstrated capacity to protect cardiac function and relieve the development of cardiac fibrosis and pathological damage (e.g., reduction of myocardial fiber degeneration and necrosis) in SHRs.
Drug-Likeness/Toxicity	Synthetic compounds 5a-e were predicted to conform to Lipinski's drug rules. Furthermore, naturally derived macrocycles cyclopentadecanone and oxacycloheptadecan-2-one was predicted

	to be non-toxic; oxacycloheptadecan-2-one specifically showed higher stability in the ligand–ACE complex than Lisinopril.
Selective Cytotoxicity	Certain indoline derivatives (5c, 5h, 5l) demonstrated selective cytotoxicity, inhibiting cancer cell proliferation (MCF-7) while showing no activity on normal breast epithelial cells (MCF-10).
Prodrug Activity	Compounds 7a and 7g exhibited moderate in vitro activity but potent and long-lasting in vivo antihypertensive effects, suggesting they are most likely acting as prodrugs.

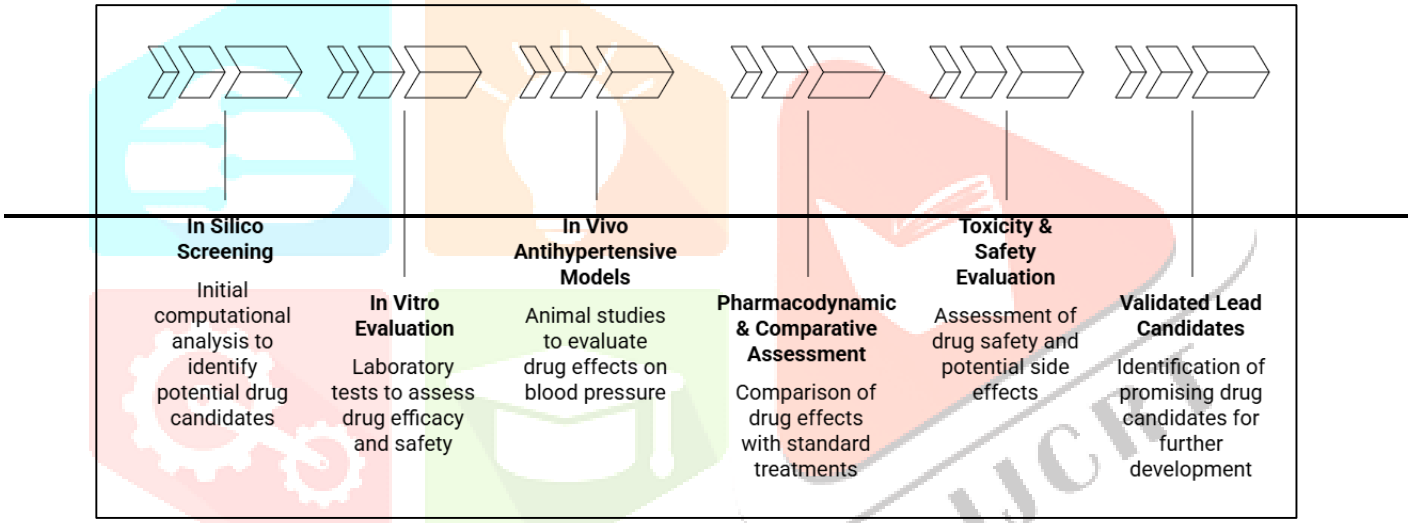


Fig.7.1 Drug Development Process

7. RECENT ADVANCES AND COMPUTATIONAL STUDIES IN ANTIHYPERTENSIVE DRUG DESIGN:

The development of new antihypertensive agents, particularly those based on the quinoline scaffold, is increasingly driven by sophisticated computational strategies and modern synthetic methodologies (Acharya et al., 2003; Anthony et al., 2012; Patil et al., 2023). Recent advances focus on addressing the limitations of first-generation drugs, such as non-selectivity and adverse effects, through precise molecular design and sustainable manufacturing (Alves-Lopes et al., 2021; Na Takuathung et al., 2022).

1. Advanced Computational Approaches

Computer-Aided Drug Discovery (CADD) techniques, which rely on the knowledge of the target protein structure, have become indispensable, providing rapid, accurate, and cost-effective analyses of large compound libraries (Morris et al., 2009; Dive et al., 1999).

A. Molecular Docking and Dynamics (MD) Simulation

Molecular docking is the cornerstone of structure-based drug design, used to predict the optimal binding pose and interaction energy between a small molecule (ligand) and a protein (receptor) at the nanoscale.

1. **Prediction and Validation:** Docking allows researchers to elucidate the inhibitor's mode of action, characterize ligand behaviour at the protein binding site, and calculate interaction energies (Morris et al., 2009). For instance, it was used to analyze the binding of phenolic acid/dipeptide/borneol hybrids (compounds 7a and 7g) to ACE, supporting their in vitro results (Ma et al., 2018).

2. **Addressing Reliability Challenges:** A significant trend involves improving the reliability of docking protocols. Because ACE binding sites (nACE and cACE) have large dimensions, docking often yields non-reliable solutions. Advanced approaches recommend the use of structural information from existing Protein Data Bank (PDB) complexes (Natesh et al., 2003; Cozier et al., 2022), particularly through Interaction Fingerprints (IFPs) analysis, to define mandatory constraints (such as specific hydrogen bond constraints with residues like K489/K511 and A334/A356) during docking calculations. This guarantees reliable poses that match crystallographic data, especially when designing domain-selective inhibitors.
3. **Molecular Dynamics (MD):** MD simulations are used to validate interactions by providing a deeper understanding of the binding process, complex stability, and conformational changes within the system over time. MD is crucial for stabilizing ligand–ACE complexes, such as confirming the stability of novel macrocyclic ACE inhibitors (Ahmad et al., 2019; Fadahunsi et al., 2022).

B. QSAR Modeling and AI-Based Optimization

The complexity of biological systems is increasingly being tackled using advanced machine learning (ML) and quantitative structure-activity relationship (QSAR) models:

1. **QSAR for Screening:** QSAR models exploit relationships between molecular descriptors and biological activity to predict potential novel compounds (Ma et al., 2023). QSAR modelling integrated with molecular docking has been successfully used to screen high ACE inhibitory activity peptides from hydrolysates of Qula casein (Adhitia et al., 2017).
2. **Machine Learning (ML) Integration:** ML approaches are now widely utilized in CADD, specifically for rigorous SAR investigation and model construction. Studies use ML algorithms (like Random Forest or Extremely Gradient Boost) coupled with advanced descriptors (like Mordred) to build robust QSAR models that predict the bioactivity class of ACE inhibitors with high accuracy.
3. **Scaffold and SAR Analysis:** ML allows for the comprehensive analysis of chemical space and scaffold diversity (e.g., Murcko scaffold analysis) (Ma et al., 2023). This analysis helps identify favorable scaffolds and reveals activity cliffs, providing valuable guidance for optimizing medicinal chemistry and performing lead optimization on active compounds (Fadahunsi et al., 2022).
4. **Novel Targets and Optimization:** Computational analysis guided by structures (e.g., cryo-electron microscopy structures of full-length ACE) have facilitated the identification of allosteric binding sites on ACE, opening new avenues for developing next-generation allosteric inhibitors with potentially higher specificity and the ability to fine-tune enzyme activity without complete inhibition (Acharya et al., 2024).
5. **ADMET Screening:** Predicting Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) in silico is a required step for modern drug candidates.

- **Risk Reduction:** ADMET prediction, typically performed using online servers, serves as a crucial selection criterion to reduce the risk of failure in later developmental stages (Daina et al., 2017).
- **Key Drug-Likeness Criteria:** Candidates are screened for pharmacokinetic properties, including adherence to Lipinski's rules (drug-likeness), low potential for CYP450 inhibition (suggesting minimal metabolic interference), and predictions of low acute oral toxicity and non-carcinogenicity (Daina et al., 2017; Ma et al., 2023; Pearman et al., 2025).

2. Hybrid Molecules (Quinoline + Other Pharmacophores)

A significant trend in drug design is molecular hybridization, where pharmacophores from known, active compounds are chemically linked to yield new molecules with synergistic effects, multi-target activity, and potentially fewer side effects (Qin et al., 2023). Quinoline's versatile structure makes it an excellent component for hybrid scaffolds (Kumar et al., 2015; Venkatesh et al., 2015).

3. Green and Sustainable Synthesis Methods for Quinoline Analogs

Due to global emphasis on environmental protection, organic synthesis techniques prioritize sustainability, particularly reducing hazardous solvents and enhancing energy efficiency (Mermer et al., 2018; Patil et al., 2023).

- **Microwave-Assisted Synthesis:** This is highlighted as an eco-friendly and efficient technique (Mermer et al., 2018; Patil et al., 2023).
  - **Advantages:** Microwave irradiation significantly accelerates reactions (up to 100 times faster than conventional heating), requires minimal solvent consumption, results in high yield and purity, and minimizes environmental impact (Mermer et al., 2018; Patil et al., 2023).
  - **Application:** This technique has been used for the synthesis of quinolone-triazole hybrids, demonstrating its utility in synthesizing complex heterocyclic drug candidates. It is also employed in the eco-friendly synthesis of pyrrolo [1,2-a] quinoline derivatives using a one-pot reaction (Mermer et al., 2018; Patil et al., 2023).

- **One-Pot Reactions:** The use of one-pot synthesis, such as the 1,3-dipolar cycloaddition reaction used for pyrrolo [1,2-a] quinoline derivatives, achieves targeted moieties efficiently with lower solvent usage and reduced reaction time, aligning with green chemistry principles (Patil et al., 2023).

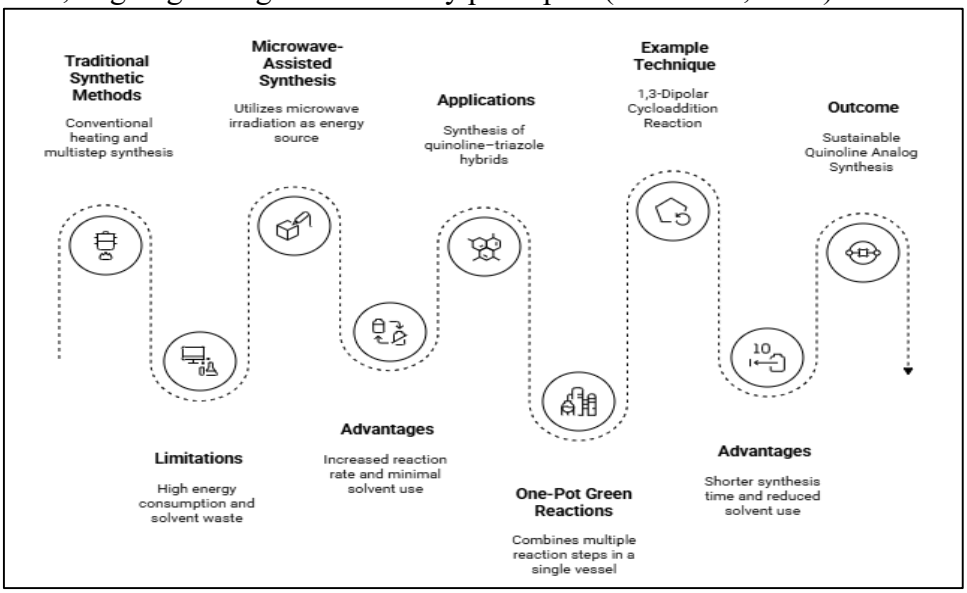


Fig 7.2: Evolution of Quinoline Synthesis Methods

8. SCOPE FOR DEVELOPING MULTI-TARGET QUINOLINE-BASED ANTIHYPERTENSIVES:

The future of antihypertensive drug development, particularly utilizing the versatile quinoline scaffold, is heavily focused on addressing the limitations of first-generation compounds through advanced design principles.

The current clinical paradigm acknowledges that single, conventional ACE inhibitors cannot completely prevent and cure hypertension. This realization drives the trend toward designing safer and multi-functional ACE inhibitors that target multiple pathways related to blood pressure regulation and cardiovascular pathology (Brown & Vaughan, 1998; Matchar et al., 2008; James et al., 2014). The quinoline scaffold is ideally positioned for this due to its structural versatility.

1. **Molecular Hybridization for Synergy:** Molecular hybridization is a key strategy where pharmacophores from known active compounds are linked to create new molecules with synergistic effects and potentially fewer side effects (Anthony et al., 2012).
   - **ACE Inhibitor/ beta -Blocker Hybrids:** A critical area of development involves designing compounds possessing both ACE inhibitory activity and beta -blocker activity. This is expected to produce next-generation drugs that are safer and more effective, especially for conditions like chronic heart failure (CHF). Quinazoline derivatives have already been designed using this approach, intending to combine ACE inhibition with beta -blocker activity (McDonagh et al., 2021; Venkatesh et al., 2015).
   - **Natural Product Integration:** Novel peptidomimetics based on the quinoline/heterocyclic core, like those utilizing borneol (to enhance cellular uptake/tissue penetration) and phenolic acids (for Zn^{2+} chelation and antioxidant activity), exemplify the synthesis of multi-functional compounds. These strategies leverage synergistic hypotensive effects to overcome the adverse profiles of current ACE inhibitors. The compound 221s (2,9) synthesized via multi-molecule synergy (tanshinol, borneol, and ACEI nucleus), demonstrates this potential by regulating the RAAS and enhancing NO production (Ma et al., 2018; Fadahunsi et al., 2022., Qin et al., 2023).
2. **Multipotency Beyond Hypertension:** Future quinoline research will integrate antihypertensive activity with benefits in co-morbidities. For instance, quinoline-appended chalcone derivatives have already been investigated for dual anti-hypertensive (ACE inhibition) and antitumor/anticancer properties (Kumar et al., 2015). Furthermore, multi-target quinoline hybrids are being synthesized to target alpha -glucosidase for Type 2 diabetes alongside cardiovascular effects (Mermer et al., 2018).

Potential Combination Therapy or Dual Inhibition (e.g., ACE + NEP Inhibitors)

The future of RAAS modulation lies in fine-tuning inhibition via dual or triple peptidase inhibitors (Vaso peptidase inhibitors) and selective domain targeting (Alves-Lopes et al., 2021).

1. **Evolution of Dual Inhibition:** While dual ACE and Neprilysin (NEP) inhibitors (e.g., omapatrilat) proved more clinically efficacious than single ACE inhibition, their development was halted due to a higher incidence of angioedema. This increase in adverse effects is strongly attributed to the elevated bradykinin (BK) levels resulting from concurrent ACE and NEP inhibition (Alves-Lopes et al., 2021; Na Takuathung et al., 2022).

2. **Domain-Selective Dual Inhibition:** Research has pivoted toward developing sophisticated dual inhibitors that minimize BK accumulation by exploiting the dual-domain nature of ACE (Dive et al., 1999; Natesh et al., 2004):

- **ACE/ECE-1 Inhibitors:** A critical strategy is the development of dual C-domain ACE/Endothelin Converting Enzyme-1 (ECE-1) inhibitors. This approach effectively lowers plasma concentrations of vasoconstrictors Ang II and Endothelin-I (ET-I) without increasing BK levels, as the N-domain (ACE-N) remains active to degrade BK. A dual C-domain ACE/ECE-1 inhibitor (FII) has already demonstrated promising results in lowering mean arterial BP in SHR models (Fadahunsi et al., 2022).
- **Selective cACE / NEP Combinations:** New research suggests that a selective C-domain ACE inhibitor combined with a NEP inhibitor (e.g., Lis-W and sacubitril) could treat hypertension and heart failure by enhancing natriuretic peptide levels while preserving BK metabolism and avoiding increased vascular permeability, offering a potential path forward for ACE / NEP therapy without the angioedema risk (Alves-Lopes et al., 2021).

Other Dual Targets: There is potential for developing an ACE-chymase dual inhibitor, as combined inhibition showed improved efficacy compared to ACE inhibitor monotherapy in animal models. ACE inhibition can induce an increase in chymase activity in cardiac interstitial fluid, providing a different mechanism for Ang II accumulation that dual inhibitors could address (Brown & Vaughan, 1998).

Integration of Computational Design + Experimental Validation

The future success of developing selective, multi-target quinoline derivatives relies absolutely on the integration of computational design methods (CADD) with thorough experimental validation (Morris et al., 2009; Ma et al., 2023).

1. **Structural Biology and Target Mapping:**

- **High-Resolution Structures:** The availability of high-resolution crystal structures of the individual ACE domains (nACE and cACE) and the recently elucidated structure of the full-length ACE via cryo-EM are critical resources. These structures provide the molecular details necessary for designing domain-selective inhibitors like RXP407 (N-domain selective) and RXPA380 (C-domain selective) (Acharya et al., 2024; Cozier et al., 2022; Natesh et al., 2003; Dive et al., 1999).
- **Allosteric Site Identification:** Computational analysis of the dynamics observed in the cryo-EM structures has led to the identification of allosteric binding sites on ACE. This opens new avenues for developing allosteric inhibitors with potentially higher specificity and the ability to fine-tune enzyme activity without complete inhibition (Acharya et al., 2024).

2. **Computational Optimization and Screening:**

- **Advanced Docking:** CADD tools (molecular docking, MD simulations, QSAR) are used to characterize ligand behaviour and are essential for a complete structural picture of the mode of action. Future docking protocols will integrate mandatory constraints (derived from structural analysis) to overcome issues with large binding site dimensions and ensure reliable poses for selective design.
- **AI and Machine Learning (ML):** ML approaches are being actively used to investigate SAR, analyze scaffold diversity (e.g., Murcko scaffolds), and predict bioactivity. This includes using algorithms like Random Forest and Extremely Gradient Boost to enhance QSAR models, contributing to the advancement of drug discovery and optimization of ACE inhibitors (Ma et al., 2023).
- **The Need for More Data:** Despite these advances, there is a recognized need for more and better crystal structures of human ACE and its binding complexes with various ACE inhibitors to further refine computational models and virtual screening (Morris et al., 2009; Cozier et al., 2022).

3. **Experimental Validation of Novel Leads:**

- Computational findings must be verified experimentally. The feasibility of combined targeted affinity purification and CADD approaches is validated by successful short-term in vivo antihypertensive activity assays in spontaneously hypertensive rats (SHRs) (Heran et al., 2008; Qin et al., 2023).
- Final drug development goals for highly selective quinoline analogs include confirming PK / PD parameters and initiating clinical trials (Beermann, 1988; Packer et al., 1999).

CONCLUSION:

The quinoline scaffold is highly valued as a privileged structure for developing antihypertensive agents due to its structural versatility, enabling diverse mechanisms for blood pressure (BP) control. Quinoline derivatives, such as the isoquinoline Quinapril, function as ACE inhibitors by coordinating the catalytic Zn^{2+} ion, thereby blocking the conversion of Angiotensin I to the vasoconstrictor Angiotensin II (Ang II). The structure's inherent characteristics, such as the tetrahydroisoquinoline ring in Quinapril, contribute to strong C-domain selectivity, which is key to controlling BP while potentially reducing BK -mediated side effects (e.g., cough and angioedema) associated with non-selective inhibition. The promise of quinoline as a versatile scaffold lies in its high binding affinity—as evidenced by lead candidates (e.g., compound 5b) showing better affinity for ACE than Lisinopril—and its suitability for multi-target design, including hybrids with beta -blocking or CCB activities. However, effective clinical translation necessitates overcoming critical limitations, including poor pharmacokinetic (PK) profiles (rapid renal clearance) observed in highly selective compounds, and ensuring the designed agents achieve the required domain selectivity to mitigate adverse effects and fully realise their therapeutic potential in chronic hypertension management.

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