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REVIEW ARTICLE

Quinolone as a Privileged Scaffold: A Brief Overview on Early Classical and Recent Advanced Synthetic Pathways, Innovative Neuroprotective Potential, and Structure-Activity Relationships

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ABSTRACT

Neurodegenerative disorders represent the second largest group of diseases worldwide. 2(1*H*)-quinolone and its structural congener, 4(1*H*)-quinolone have recently become significant topics in the field of drug design and development of modulators of neurotransmitter systems and neuroprotective agents to tackle neurodegenerative disorders. In this review, the structural properties and the early classical as well as the recent novel synthetic strategies for 2(1*H*)-/4(1*H*)-quinolone are discussed. The neuropharmacological activity and mechanisms of action of several 2(1*H*)-/4(1*H*)-quinolinone-based compounds are demonstrated with special emphasis on the structure–activity relationships (SAR). Therefore, the perspectives elaborated in this review could guide medicinal chemists for rational design and development of novel 2(1*H*)-/4(1*H*)-quinolone therapeutic candidates targeting neurodegenerative diseases.

1 | Introduction

2(1*H*)-Quinolone and 4(1*H*)-quinolone (Figure 1) are the main structural motifs of numerous large and complicated natural products (Chu et al. 2019; Fernández-Álvaro et al. 2016; Rossiter et al. 2017). The quinolinone scaffold is a heteroaromatic, bicyclic framework, comprising a benzene ring fused with a 2/4-pyridinone motif at two adjacent carbons with the nitrogen being tethered to the benzene ring. These compounds can exist as a mixture of two rapidly interconvertible tautomeric forms (lactam; keto-NH and lactim; enol) as a result of intramolecular proton transfer between nitrogen and oxygen atoms. This tautomerism provides a rationale for the alterations in physicochemical properties, which influence the pharmacokinetic and pharmacodynamic characteristics that in turn affect the pharmacological activity and/or drug-target interaction (Horta et al. 2017; Mesiti et al. 2021; Tashima 2015). Extensive theoretical and experimental analyses for the possible tautomers indicated the dominance of the keto form (Q) over 2-hydroxyquinoline (QH) in the nonaqueous solution and in the solid state due to its existence as a stabilized hydrogen-bonded dimeric structure (Lewis et al. 1991). However, other factors, including solvent polarity (Krebs et al. 1982), steric hindrance, and substituent electronic characteristics (Volle et al. 2008), also appeared to influence the equilibrium between the two tautomeric forms. Contrarily, spectroscopic and computational

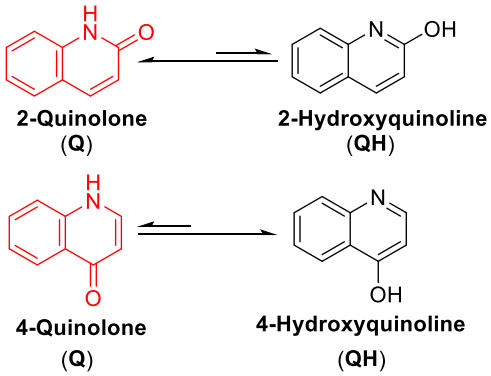


FIGURE 1 | Chemical structures and tautomeric forms of 2-(1*H*) and 4-(1*H*)-quinolones.

investigations for the tautomerism in 4-(1*H*)-quinolinone had identified the 4-hydroxy form (QH) as the major tautomer (Figure 1) (Ewing and Steck 1946; Masoud et al. 1988; Mirek and Syguła 1982; Pan et al. 2014; Pfister-Guillouzo et al. 1981). Pharmacologically, the quinolone scaffold had been considered a gold mine in terms of the discovery and development of novel derivatives against different target proteins implicated in various diseases and disorders.

Indeed, the interactions of 2-(1*H*)-quinolinone derivatives with β-adrenergic receptors (Mònica Aparici et al. 2019; Xing et al. 2019), tyrosine-protein kinases (Tintori et al. 2015), muscarinic acetylcholine receptors (Monica Aparici et al. 2017; Jones et al. 2015), poly[ADP-ribose] polymerase-1 (Chen et al. 2014; Hannigan et al. 2013; Park et al. 2010), vascular endothelial growth factor receptors (Han et al. 2012; Tang et al. 2016), and serine/threonine-protein kinases (Brnardic et al. 2007) were reported. In addition to that, 4-quinolinone analogues are well known for their ability to target gyrase and topoisomerase IV and convert them into toxic enzymes that fragment the bacterial chromosome (Aldred et al. 2014). Thus, several generations of fluorine-containing 4-quinolone antimicrobials (generally referred to as fluoroquinolones) had been discovered (Figure 2). Similarly, several 2-(1*H*)-quinolinone drugs had been marketed (Figure 2) for the treatment of chronic airway inflammations, ulcers, psychotic depression conditions, and infections with helminths (Hong et al. 2020). Furthermore, myriad 2-(1*H*)/4-(1*H*)quinolinone derivatives were reported as anti-HCV (Cannalire et al. 2016), antibacterial (Medellín-Luna et al. 2023; Moussaoui et al. 2022; Zhang et al. 2018), anti-HIV (Sekgota et al. 2017), anti-inflammatory (Upadhyay et al. 2018), antitubercular (Fan et al. 2018), anticancer (Ahadi et al. 2023; Chen et al. 2023; Sharma et al. 2013), antimalarial (Fan et al. 2018), and anti-Alzheimer candidates (Chu et al. 2019).

Over the past few decades, several reviews emphasizing the synthesis of 2-(1*H*) and/or 4-(1*H*)-quinolones along with their biological applications had been published (Dine et al. 2023; Dube et al. 2023; Elshaier et al. 2022; Sharma et al. 2024; Swedan et al. 2023). Most of them extensively discussed the development of quinolones as antimicrobials in terms of detection methods in food of animal origin (Guo et al. 2024), the synthetic routes, the spectrum of activity, pharmacokinetics and pharmacodynamics, the structure–activity relationships attributes, the resistance mechanisms, the toxicological data, and the lethality of fluoroquinolones (FQs) and the potential pathways leading to slow or quick cell death, in addition to providing suggestions for potential strategies to develop more effective quinolone antibiotics against resistant strains (Bush et al. 2020; Hong et al. 2020; Khanna et al. 2024; Liu et al. 2018; Millanao et al. 2021; Moussaoui et al. 2022; Pham et al. 2019; Sharma et al. 2022; Spencer and Panda 2023). This review is complementary to these earlier articles and provides a brief survey on the classical as well as the recently developed synthetic approaches for 2-(1*H*)/4-(1*H*)quinolone derivatives. The mode of action of several quinolinones as inhibitors for various neurological targets and the SAR of drug candidates are analyzed to underscore the essential structural features for correcting and preventing neurodegeneration.

2 | Synthetic Strategies for Functionalized 2-Quinolones

The functionalized 2-(1*H*)-quinolinones had been synthesized using traditional and innovative methodologies.

2.1 | Early Classical Methods

2.1.1 | Friedländer-Type Condensation

The 3-benzimidazol-2-yl hydroquinolin-2-one **1** (Scheme 1, **route 1**) (Renhowe et al. 2009) and 3-(4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-quinolin-2-one **2** (Scheme 1, **route 2**) (Han et al. 2012) were synthesized through one-pot base-catalyzed Friedländer-type condensation involving 2-aminobenzaldehydes **3** or **4** with ethyl 2-benzimidazol-2-yl acetate and imidazopyridine acetate, respectively.

A facile and efficient acid-catalyzed Knorr-type synthesis for substituted quinolin-2(1*H*)-one **5** (Scheme 1, **route 3**) via chemoselective intramolecular cyclization of penta-2,4-dienamide **6** mediated by concentrated H_2SO_4 was reported (Liu et al. 2012).

The 2-oxo-quinoline-3-carbaldehyde compounds **7** (Scheme 2) were synthesized in a two-step process. Initially, the Vilsmeier-Haack-Arnold condensation reaction of acetanilide derivatives **8** with *N*,*N*-dimethylformamide (DMF) in the presence of phosphorus oxychloride afforded 2-chloroquinoline-3-carbaldehyde derivatives **9**, which subsequently were hydrolyzed to the desired quinolinones by 70% acetic acid aqueous solution (Srivastava and Singh 2005; Zhang et al. 2013).

A two-step methodology was documented by E. Abdo Moustafa et al. for the synthesis 4-chloro-2-oxo-quinoline **10** (Scheme 3). First, a cyclocondensation reaction between aniline **11** and malonic acid **12** in the presence of sufficient phosphoryl chloride under reflux for a whole day yielded 2,4-dichloroquinoline **13**. Second, a regioselective oxidation of the latter product at position-2 was carried out using 6 N HCl in dioxane and produced the target compound in a good yield (Abdo Moustafa et al. 2024).

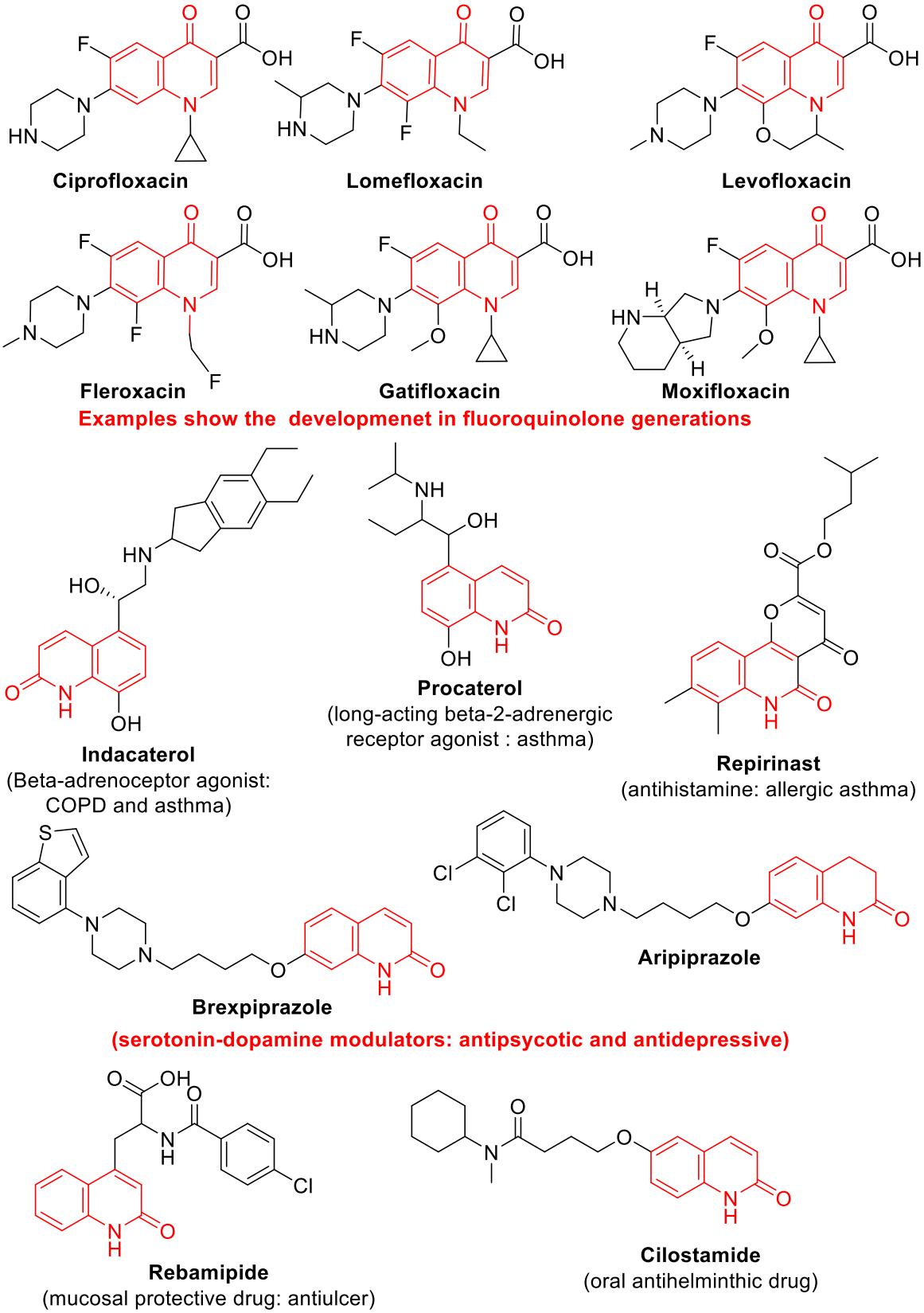
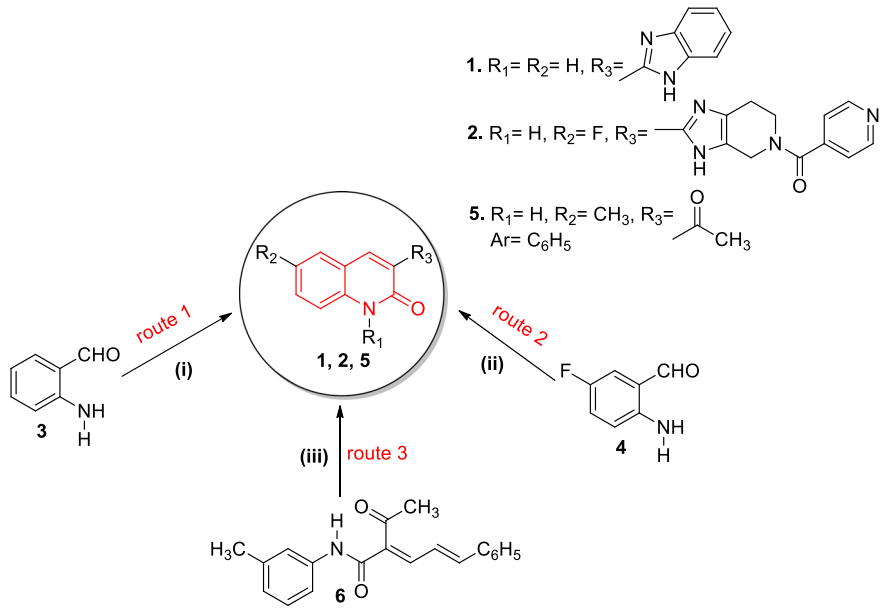


FIGURE 2 | Examples of 2-(1*H*) and 4-(1*H*)-quinolone-containing marketed drugs.

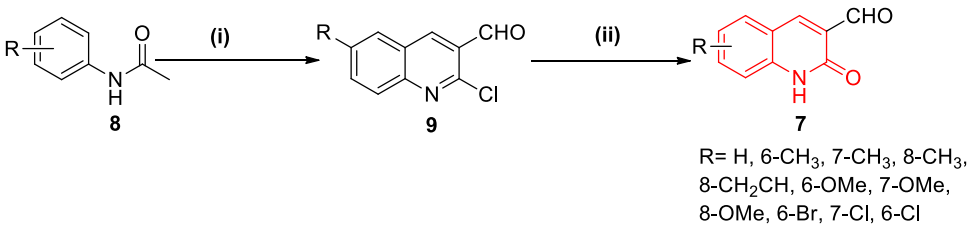
2.2 | Nonclassical Palladium-Catalyzed Recent Synthetic Routes

Wu and co-researchers reported in 2014 a concise and a broad-spectrum strategy for the synthesis of 2-quinolone derivatives via a one-pot $Pd(OAc)_2$-catalyzed cascade involving C–H bond activation, amonolysis, and a cyclization reaction of aniline with ethyl acrylate. This methodology (Scheme 4) was employed for the construction of quinolone core **14** of the anticancer agent, Tipifarnib **15,** using 4-amino-4′-chlorodiphenylmethane **16** and



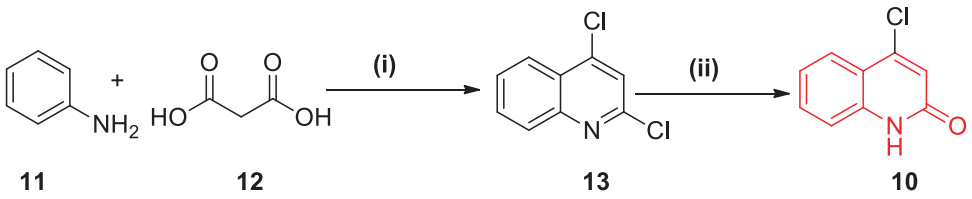
Reagents and conditions: (i) 2-benzimidazol-2-ylacetate, Piperidine, EtOH, 70 °C, (ii) imidazopyridine acetates, Piperidine, xylene, reflux, (iii) H_2SO_4 (98%)

SCHEME 1 | Synthetic routes for products 1, 2 and 5.



Reagents and conditions: (i) DMF/ $POCl_3$, 90 °C, 4-16 h, (ii) 70% AcOH aq. solution, 95 °C, 6 h

SCHEME 2 | Synthetic routes for product 7.



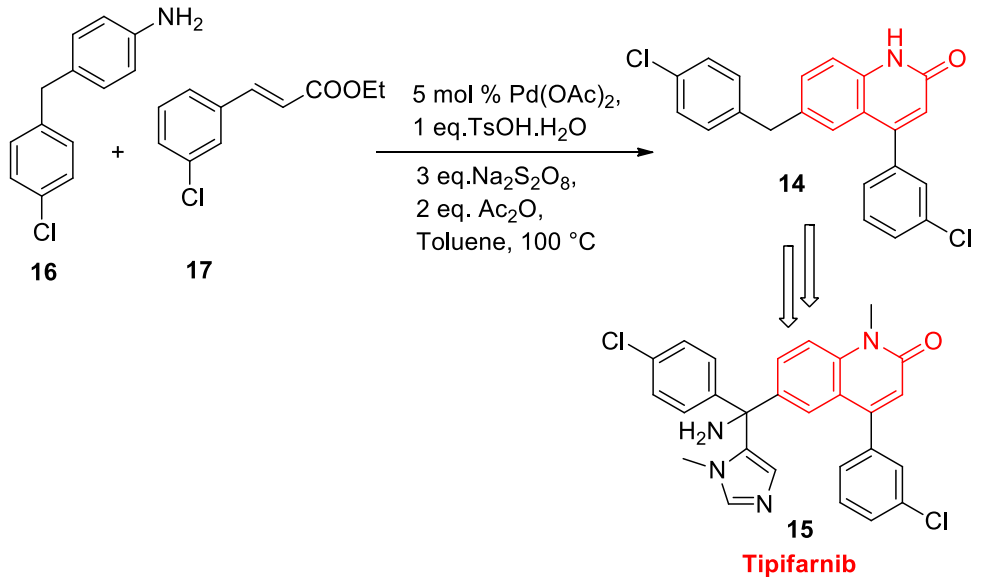
Reagents and conditions: (i) $POCl_3$, reflux 24 h, (ii) 1,4-dioxane, 6N HCl,reflux 36

SCHEME 3 | Synthetic routes for product 10.

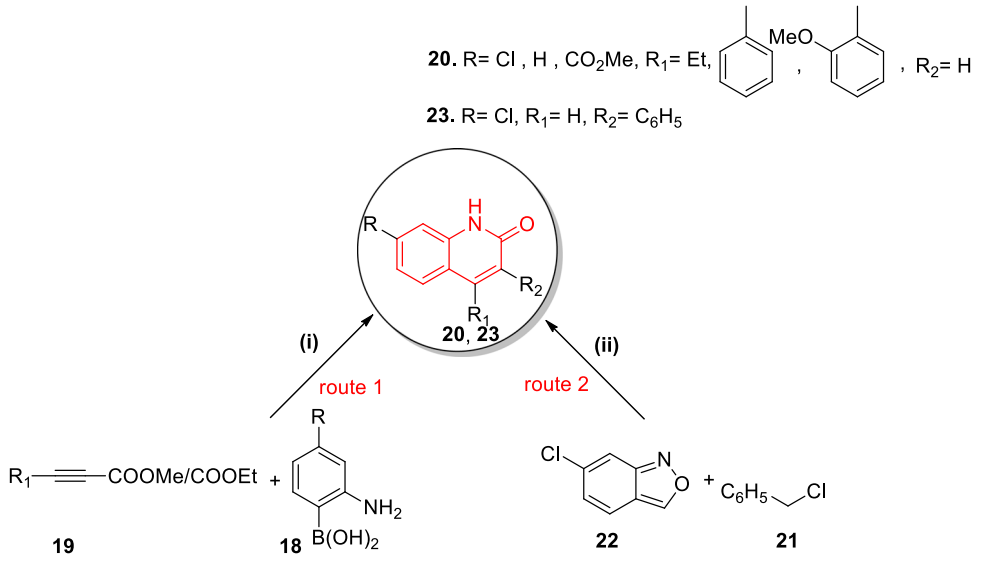
4-chlorophenyl ethyl acrylate **17** as starting materials in one step (Wu et al. 2015).

Recently, Corpas and co-workers disclosed a sequential catalytic anti-hydroarylation/cyclization reaction (Scheme 5, **route 1**) of substituted 2-aminophenyl boronic acid **18** and electron-deficient internal alkynoates **19** in the presence of $Pd(OAc)_2$/dppe, AcOH, and Ir(ppy) as photosensitizers in THF under blue light irradiation (465 nm) for the assembly of the pharmaceutically privileged 2-quinolinone derivatives **20** within 24 h (Corpas et al. 2020).

An efficient palladium-catalyzed aminocarbonylation process (Scheme 5, **route 2**) for the readily available benzyl chloride **21** with 2,1-benzisoxazole **22** as a *N*-source as well as the cyclizing agent and in the presence of the $Pd(AcO)_2$ catalyst, $Mo(CO)_6$, BINAP, Et_3N, water, and 1,2-dimethoxyethane was established for the synthesis of a variety of 3-arylquinoin-2(1*H*)-ones **23** in



SCHEME 4 | Synthetic routes for product 15.



Reagents and conditions: (i) $Pd(OAc)_2$/ dppe, AcOH, $Ir(ppy)_3$, THF: H_2O (10:1), T 25-80 °C, 24 h, blue light (465 nm), (ii) $Pd(OAc)_2$, BINAP, $Mo(CO)_6$, Et_3N, H_2O, DME, 100 °C, 26 h

SCHEME 5 | Synthetic routes for products 20 and 23.

moderate to excellent yields with good functional group tolerance (Liu et al. 2021).

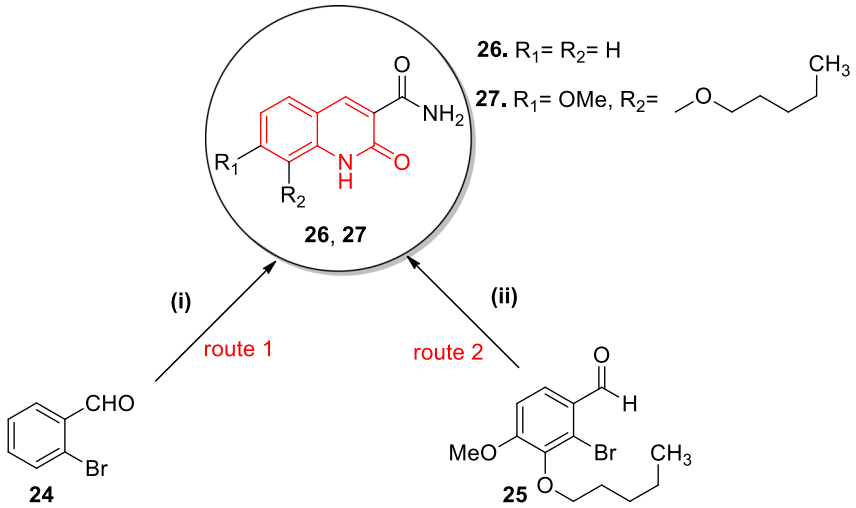
2.3 | Other Transition-Metal (Cu, Rh, Co, Au)-Catalyzed Strategies

2.3.1 | Copper-Mediated Synthesis

A single one-pot annulation of 2-bromoarylaldehydes **24** and **25** and malonamide derivatives mediated by dendritic copper powder and piperidine was developed for the construction of 3-amido-2-quinolone **26** (Scheme 6, **route 1**) (Ahn et al. 2018).

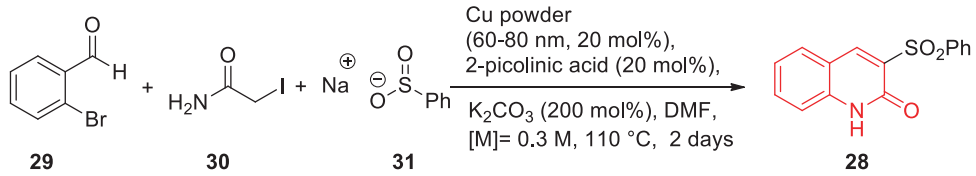
This methodology was applied for the preparation of 7-methoxy-2-oxo-8-(pentyloxy)-1,2-dihydroquinoline-3-carboxamide **27** (Scheme 6, **route 2**), which is required for the synthesis of the CB2 selective cannabinoid receptor inverse agonist (Raitio et al. 2006).

A new catalytic system employing copper powder with 2-picolinic acid was used in a highly efficient three-component annulation to access functionalized 3-sulfonyl-2-quinolone **28** (Scheme 7) from 2-bromobenzaldehyde **29**, 2-iodoacetamide **30**, and sodium sulfinate **31** as sulfur nucleophiles in dry DMF and in the presence of K_2CO_3 (Kim and Lim 2020).



Reagents and conditions: (i) Malonamide, Dendritic Cu powder, Piperidine, Dimethylacetamide, 70 - 130 °C, 48 h, (ii) Malonamide, Dendritic Cu powder, Piperidine, Dimethylacetamide, 130 °C, 24 h

SCHEME 6 | Synthetic routes for products 26 and 27.



SCHEME 7 | Synthetic routes for product 28.

2.3.2 | Rhodium (III)-Mediated Synthesis

An efficient and direct cross-coupling reaction of substituted *N*-methoxycycloalkene-1-carboxamides with aryl boronic acid pinacol esters in the presence of rhodium (III) $[Cp^*RhCl_2]_2$ catalyst and the oxidant Ag_2O was developed for the synthesis of 3,4-cycloalkylquinolin-2(1*H*)-ones (Zhu et al. 2019).

2.3.3 | Cobalt-Mediated Synthesis

Under cobalt acetate catalysis, *N*-(2-vinylphenyl)picolinamides were successfully converted to various (*NH*)-quinolin-2(1*H*)-one derivatives in excellent yields (up to 92%) (Zhu et al. 2022).

2.3.4 | Gold-Mediated Synthesis

A fast and simple $AuPPh_3Cl$/AgOTf-catalyzed intramolecular alkyne hydroarylation process of *N*-arylamides of 3-substituted propynoic acids (Ugi adducts) having an electron-rich benzene ring was developed for the efficient construction of diverse 2-quinolones bearing branched substituents on the nitrogen atom (Du et al. 2018).

2.4 | Recent Transition Metal-Free Methods

The metal-free C–H [5 + 1] carbonylative annulation of 2-alkenylanilines **32** with dioxazolones as carbonylating reagents in toluene was utilized for the synthesis of a broad range of 2-quinolinone derivatives **33** (Scheme 8, **route 1**) with excellent functionality tolerance. However, the simplest unsubstituted 2-quinolinone failed to occur using this protocol (Nan et al. 2021).

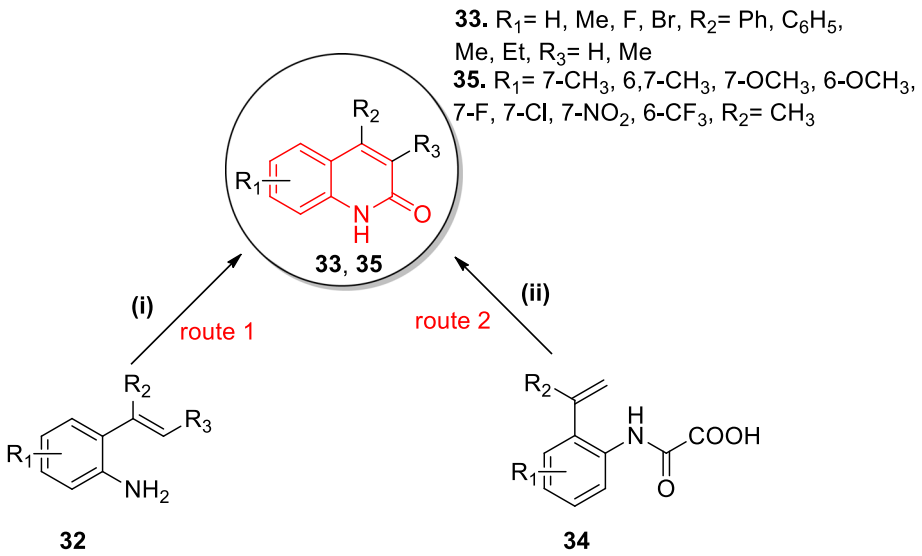
A green metal-free and chemoselective hypervalent iodine (III)-mediated intramolecular decarboxylative Heck-type lactimization of 2-vinyl-phenyloxamic acids **34** at room temperature was established for the synthesis of diverse 2-quinolinone structures **35** in moderate to excellent yields (Scheme 8, **route 2**) (Fan et al. 2018).

Recently, an innovative iodine-catalyzed intramolecular cyclization of *N*–substituted acrylamide derivatives was established for the synthesis of *N*-activated 2-quinolones (Das et al. 2024).

3 | Synthetic Strategies for 4-Quinolones

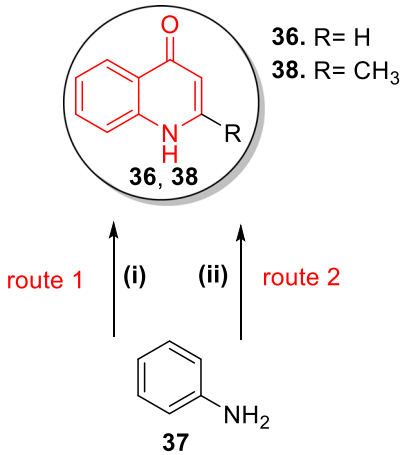
3.1 | Early Classical Methods

Several well-established methods have been employed for the synthesis of 4-quinolones. The Conrad-Limpach



Reagents and conditions: (i) 3-(*p*-tolyl)-1,4,2-dioxazol-5-one, Toluene, 120 °C, 15h, (ii) 4-F-C_6H_4-I$(OAc)_2$, $CHCl_3$, r.t., 24 h

SCHEME 8 | Synthetic routes for products 33 and 35.



Reagents and conditions: (i) 1- Ethyl 3-oxobutanoate/H_2SO_4, Δ on water bath, 2- Ph_2O, 260 °C, (ii) 1- Diethyl 2-acetylmalonate, r.t., 72 h, 2- N_2, mineral oil, 250 -265 °C, 3- aq. NaOH, Δ, acidification, 4- Δ/ decarboxylation

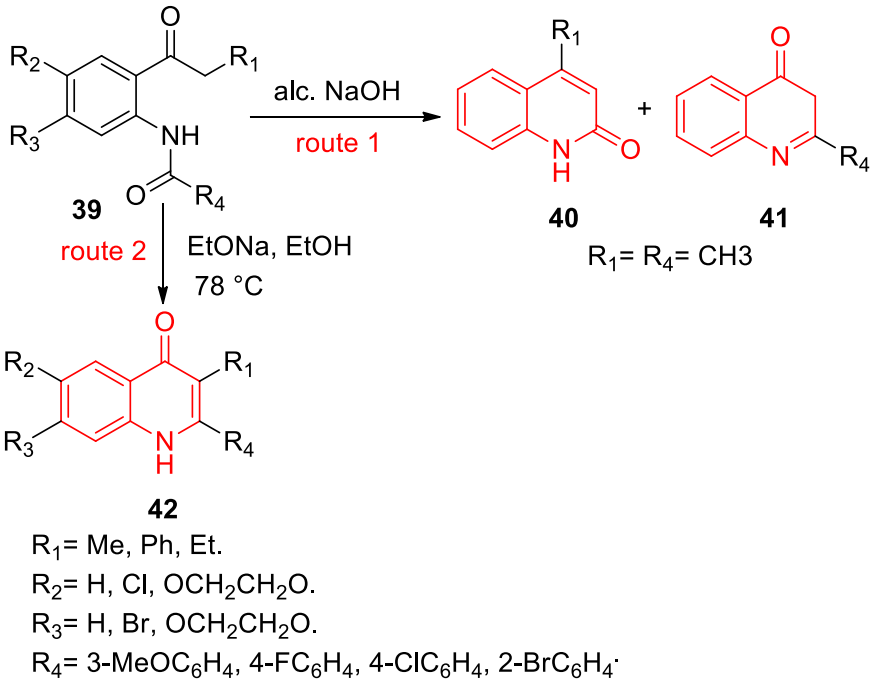
SCHEME 9 | Synthetic routes for products 36 and 38.

approach is a two-step methodology for synthesizing 4(1*H*)-quinolone **36** from ethyl acetoacetate and aniline **37** (Scheme 9, **route 1**) (Conrad and Limpach 1887). Similarly, the Gould–Jacobs reaction is a multistep process for the synthesis of 4-quinolone **38** from aniline **37** and ethoxymethylenemalonic esters (Scheme 9, **route 2**) (Gould and Jacobs 1939).

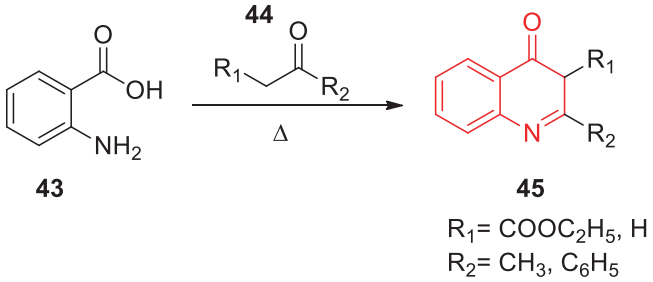
Another classical route, the Camps cyclization, involves intramolecular condensation of 2-acetamido acetophenone **39** (Scheme 10, **route 1**), in the presence of alcoholic sodium hydroxide, yielding a mixture of the isomeric products, 4-methyl-quinolin-2-one **40** and 2-methyl-quinolin-4-one **41** (Camps 1899). However, sodium ethoxide-mediated cyclization of benzamides **39** having propanoyl-, butanoyl-, or phenylacetyl substituents at the *ortho* position to the amide fragment led to the formation of quinolin-4(1*H*)-ones **42** in high yields (88%–100%) (Scheme 10, **route 2**) (Mochalov et al. 2016).

Further classical work by Niementowski includes the thermal condensation of anthranilic acid **43** and ketones (or aldehydes) **44** (Scheme 11) for the synthesis of 2,3-disubstituted-γ-quinolinone derivatives **45** (Niementowski. 1894).

Additionally, Potassium *tert*-butoxide-catalyzed, intramolecular cyclization of enamino diester was reported for the synthesis of 4-quinolinone derivative (Biere and Seelen 1976).



SCHEME 10 | Synthetic routes for products 40, 41 and 42.



SCHEME 11 | Synthetic route for product 45.

3.2 | Recent Synthetic Methods

Recent advancements in quinolone synthesis focus on increasing selectivity and environmental sustainability. Shao and coworkers reported an efficient one-pot synthesis for *N*-butyl substituted 4-quinolone **46** from easily accessible 1-(2-chlorophenyl)-3-phenylprop-2-yn-1-one **47** and functionalized alkyl amines (Scheme 12, **route 1**) (Shao et al. 2012).

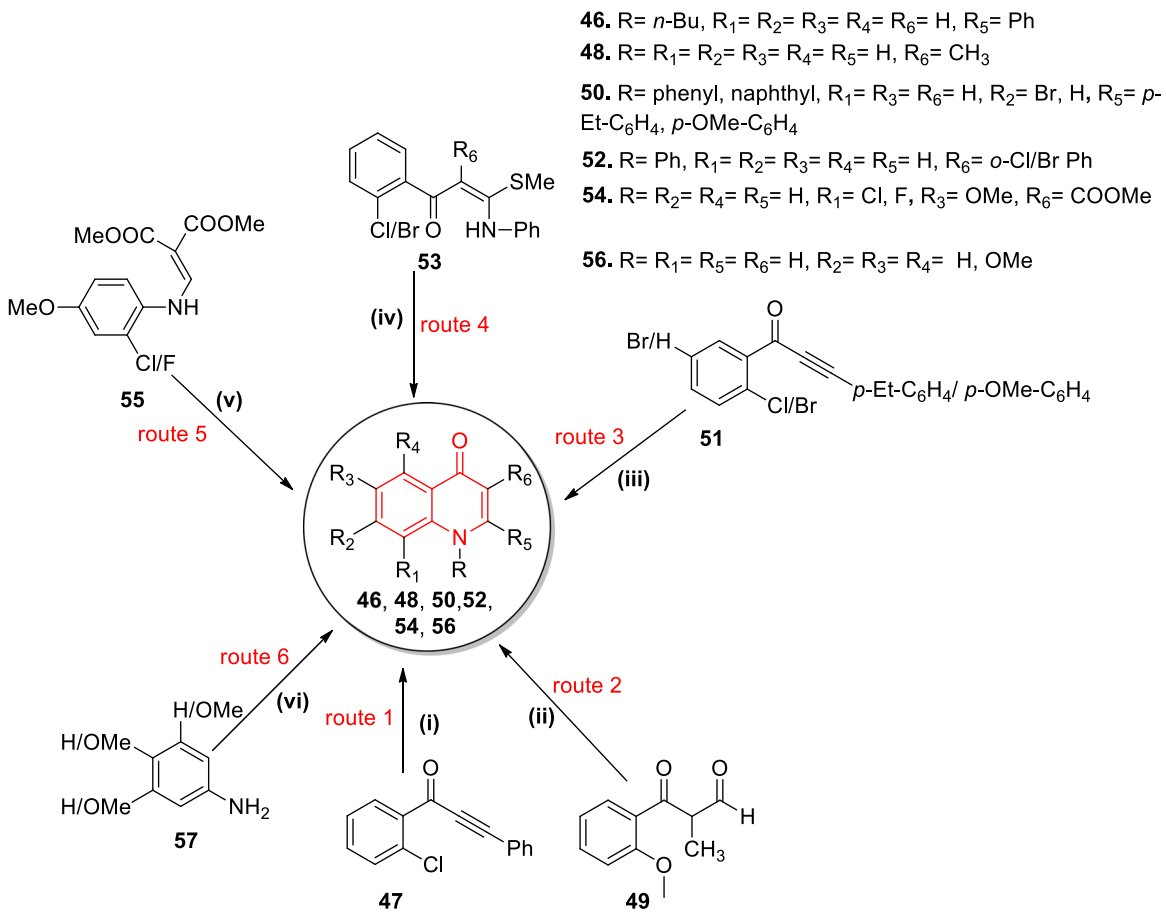
Zaho and his colleagues disclosed an effective and metal-free approach for the synthesis of 4-quinolone derivative **48** via K_2CO_3-catalyzed intramolecular cyclization of 3-(2-methoxyphenyl)-2-methyl-3-oxopropanal **49** (Scheme 12, **route 2**) (Zhao et al. 2012). While, Zhao and Xu developed an efficient one-step palladium-catalyzed tandem amination strategy for the synthesis of functionalized *N*-substituted-4-quinolone derivatives **50** in high yields (up to 93%) from *o*-haloaryl acetylenic ketones **51** and primary amines (Scheme 12, **route 3**) (Zhao and Xu 2010).

Moreover, Janni and his colleagues presented a new metal-free, base-assisted approach for synthesizing 4-quinolone derivatives **52** using ketene *S*,*N*-acetals **53** (Scheme 12, **route 4**) (Janni et al. 2016). On the other hand, Zewge et al. reported a reasonably gentle, effective, and scalable route for the preparation of 4-quinolone derivative **54** via Eaton's reagent-promoted cyclization of enamine diester **55** with various types of substitution (Scheme 12, **route 5**) (Zewge et al. 2007). Therefore, this methodology requires milder conditions than the traditional Biere and Seelen approach.

Besides, Duarte's group reported a single-step microwave-assisted synthesis of several substituted 2-methyl-4-quinolone derivatives **56** from electron-rich anilines **57** and ethyl acetoacetate in the presence of diphenyl ether as a solvent (Scheme 12, **route 6**) (Duarte et al. 2013).

Further developments include a two-step synthesis of ethyl *N*-substituted 2-carboxylate-4-quinolone **58** with good regioselectivity via a direct reductive amination reaction followed by an in situ LiHMDS-induced annulation (Scheme 13, **route 1**) (Hasan et al. 2017). Malvacio & Moyano also developed an effective microwave-assisted method for generating ethyl quinolin-4-one-3-carboxylates **61** (Scheme 13, **route 2**) by irradiating a mixture of diethyl-ethoxymethylenemalonate **62** and *p*-substituted anilines **63** in the presence of diphenyl ether (Malvacio et al. 2014). On the other hand, Xuefeng's research group reported a unique and direct protocol for synthesizing 4-quinolones **64** with high functional-group tolerance from simple and readily available anilines **65** and methyl 3-phenylpropiolate **66** under the catalysis of $Cu(OTf)_2$ (Scheme 13, **route 3**) (Xu and Zhang 2017).

Finally, a novel catalytic method was reported by Sardar et al. using an acridine-based SNS-ruthenium pincer-catalyzed dehydrogenative annulation of a wide range of alcohols with various 2′-aminoacetophenones for the synthesis of



Reagents and conditions: (i) Butan-1-amine, $K_3PO_4.3H_2O$, DMSO, 140 °C, (ii) 1- RNH_2, DMSO, 90 °C, 3 h, N_2, 2- K_2CO_3 (40%), 130 °C, 24-48 h, N_2, (iii) Phenyl or naphthyl amine, $Pd_2(dba)_3$, PPh_3, K_2CO_3, dioxane, reflux, (iv) KO^tBu, dioxane, 90 °C, 6-9 h, 9v) Eaton's Reagent, 80-90 °C, (vi) Ethyl 3-oxobutanoate, AcOH, Ph_2O, 300 W, 205-230 °C, 5 min

SCHEME 12 | Synthetic routes for products 46, 48, 50, 52, 54 and 56.

2,3-disubstituted-4-quinolones under solvent-free conditions (Sardar et al. 2023).

4 | Quinolones as Neuroprotective Agents

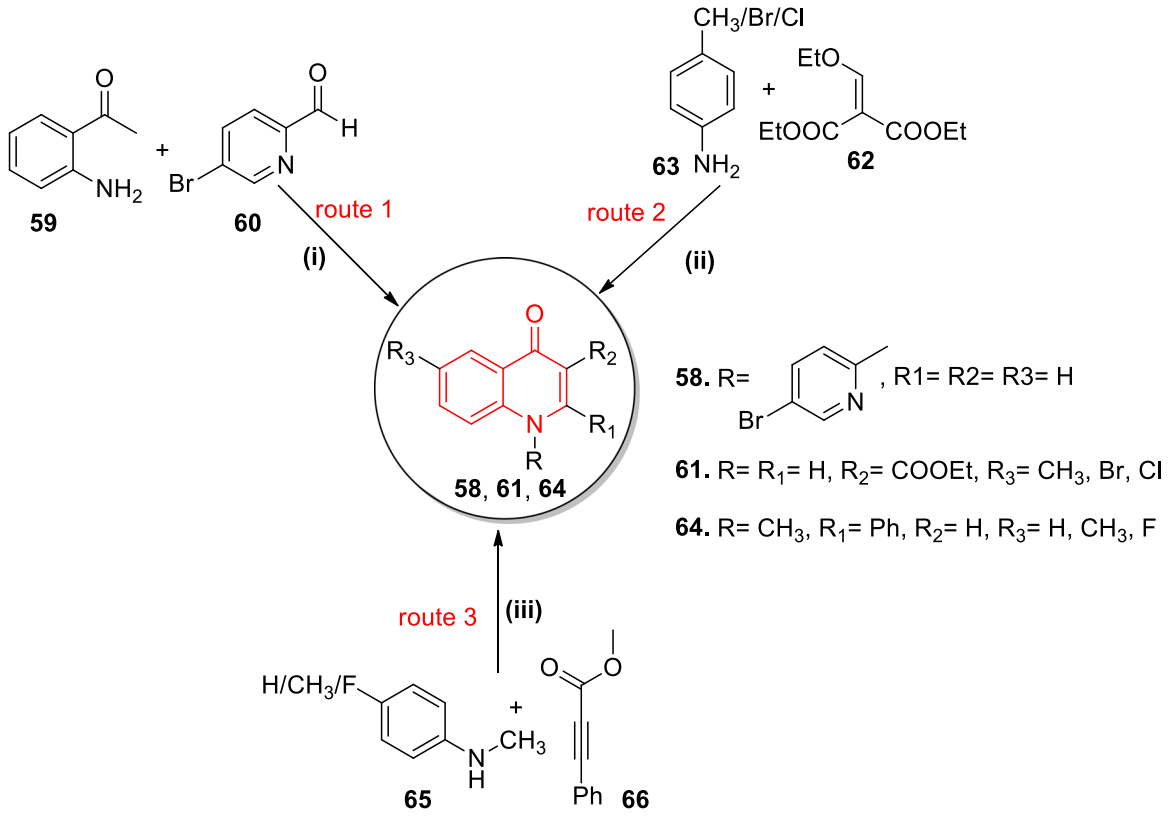
The neuroprotective potentials of quinolones are attributed to their ability to modulate various neurotransmitter systems, in addition to their antioxidant actions (Figure 3).

4.1 | Quinolones as Cholinesterase Inhibitors

Acetylcholine (Ach) is an essential neurotransmitter for improving perception and memory-related processes. Human studies demonstrated a significant decline of ACh neurotransmitter in the cortex and hippocampus of the brains affected by Alzheimer's disease (Haam and Yakel 2017). As a result, the loss of cholinergic neurotransmission is the most acceptable strategy in Alzheimer's disease etiology (Deardorff et al. 2015; El-Sayed et al. 2019; Ezzat et al. 2023; Umar and Hoda 2017). ACh is hydrolyzed by two cholinesterases: acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) (Abd El-Mageed et al. 2025). Clinical data gathered over the past ten years undeniably indicated that commercially available anti-Alzheimer cholinesterase inhibitors provide neuroprotective benefits in addition to their symptomatic relief effects (Munoz-Torrero. 2008). Therefore, cholinesterase inhibitors were projected as effective treatments for Alzheimer's disease complications (Singh et al. 2013).

In this sense, quinolone derivatives had become an active area of research for the development of AChE inhibitors (Carlier et al. 2000). For example, *N*-[(1-benzylpiperidin-4-yl)methyl]-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamide derivatives **69** and **70** (Figure 4) were prepared and assessed for their AChE and BuChE inhibitory activity by Ellman's technique, using tacrine and donepezil as reference drugs (Pudlo et al. 2014).

The results of in vitro analysis showed that compounds **69** and **70** effectively inhibited AChE with IC_{50} values of 0.11 and 0.48 μM with greater selectivity for AChE, as no BuChE inhibition was observed at 60 μM and 10 μM, respectively. SAR studies (Figure 5) proved that hydroxy or methoxy substituents on the quinolone ring enhanced the selectivity for AChE over



Reagents and conditions: (i) 1- $PhSiH_3$, Bu_2SnCl_2, THF, r.t. 16 h, 2- LiHMDS, Diethyloxalate, THF, 80 °C, (ii) DPE, Two consecutive MW irradiation cycles; 1 min at 80 °C followed by 2 min at 240 °C, (iii) $Cu(OTf)_2$, HOTf, DCE, 120 °C, air

SCHEME 13 | Synthetic routes for products 58, 61 and 64.

BuChE. Moreover, compounds containing a methylene linkage between the *N*-amide and the piperidine ring exhibited greater activity compared to those without the spacer ($n = 0$).

Molecular docking simulations against Torpedo California AChE (*t*AChE) and Human AChE (*h*AChE) using the CDocker program indicated that compound **70** showed the same pattern of binding to both proteins, wherein the quinolone moiety coupled to the peripheral anionic site via π-stacking interaction with Trp286, in addition to the establishment of two H-bonding interactions, one between the quinolone's hydroxyl group in position 4 and the hydroxyl group of amino acid residue Tyr124 and the second between the quinolone's carbonyl in position 2 and the NH of amino acid Phe295. In the catalytic pocket, the phenyl moiety exhibited a π-stacking interaction with Trp86. Moreover, the piperidinium moiety formed cation-π interactions with Tyr337 and Phe338 (Figure 6) (Pudlo et al. 2014).

4.2 | Quinolones as Antioxidants

Mitochondrial dysfunction in neurons leads to increased production of reactive oxygen species (ROS) at levels that exceed the body's antioxidant capacity, thus causing oxidative stress. This pathological state is associated with detrimental effects to neural viability, including excitotoxicity, synaptic failure, inflammation, DNA and cell membrane damage, impairment of protein degradation systems, and apoptosis. These abnormalities play critical roles in the development of neurodegenerative disorders such as Alzheimer's (Molnar 2001) and Parkinson's disease (Coyle and Puttfarcken 1993). Therefore, antioxidant interventions had been proposed as therapeutic approaches to fight against ROS-mediated oxidative cell damage in neurodegenerative disorders (Morén et al. 2022).

Nonenzymatic antioxidants can provide protection against oxidative stress. Basically, antioxidants may produce their effects via a chain-breaking mechanism by acting as hydrogen or single-electron donors, thus scavenging harmful radicals, or by suppressing the initiation of oxidation reactions through preventing superoxide anion formation, degrading H_2O_2, and reducing or chelating metal ions.

Four hydroxy-2-phenylquinolin-4(1*H*)-one derivatives **71-74** were synthesized, and their antioxidant activities were established based on reducing ferrous ions and diminishing hydrogen peroxide and hydroxyl radical production as assessed by the ferric reducing/antioxidant power (FRAP), oxygen radical absorbance capacity (ORAC), and thiobarbituric acid-reactive substances (TBARS) assays, respectively. The in-silico evaluations of their physicochemical properties, oral bioavailability, blood–brain barrier permeation capabilities, and toxicity risks highlighted their significance as orally bioavailable and potential drug candidates in terms of drug metabolism, as well as

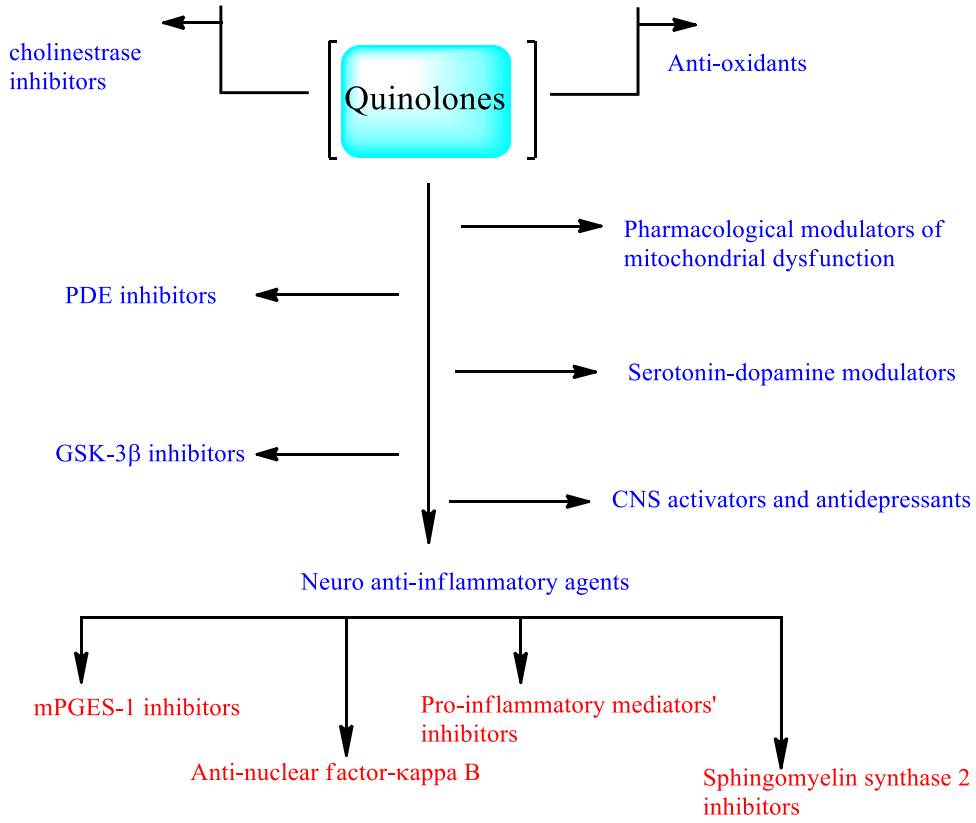


FIGURE 3 | Quinolones' categorization as neuroprotective agents.

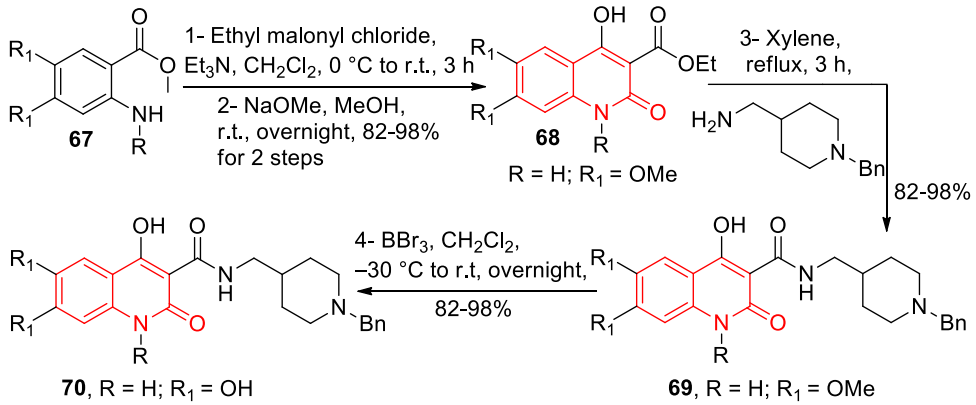


FIGURE 4 | Synthesis of 2-oxo-1,2-dihydroquinoline derivatives as cholinesterase inhibitors.

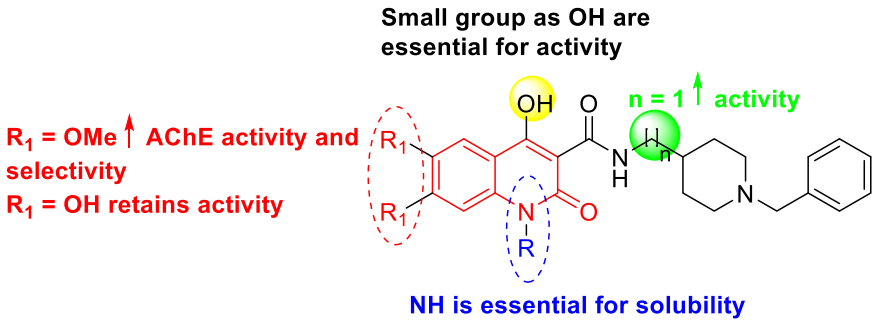


FIGURE 5 | SAR of 2-oxo-1,2-dihydroquinoline derivatives as cholinesterase inhibitors.

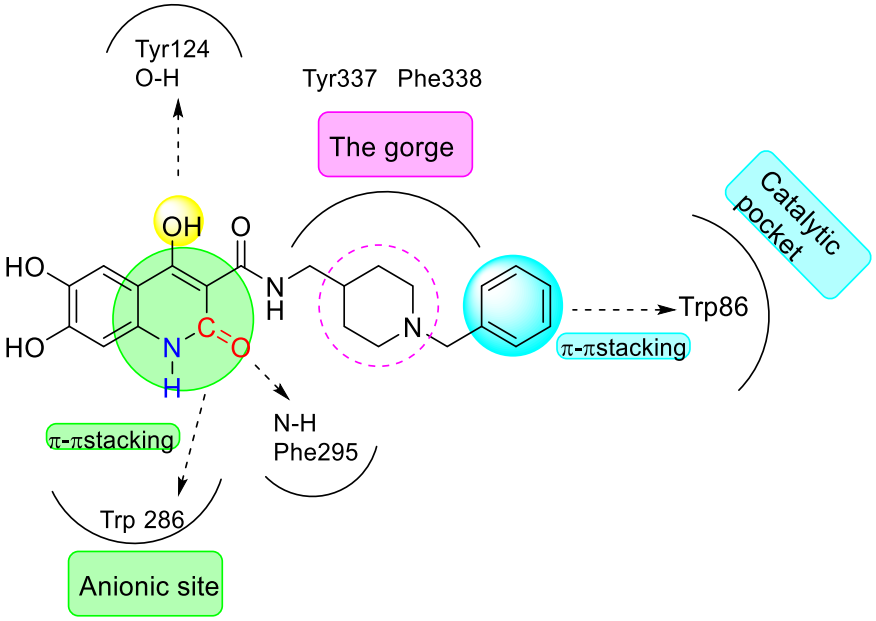


FIGURE 6 | Binding interactions of compound **70** with the AChE binding site.

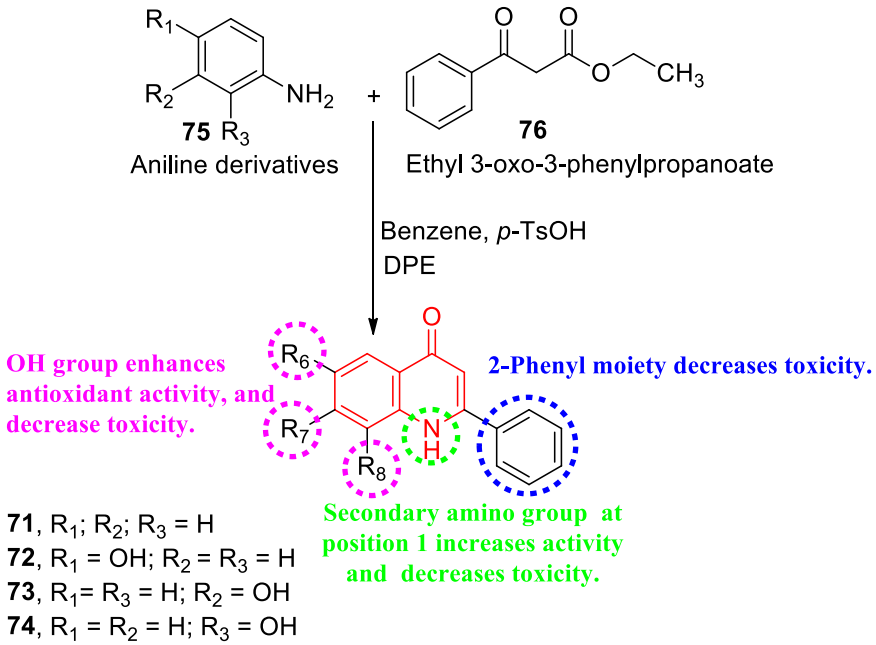


FIGURE 7 | Synthesis and SAR of 2-phenylquinolin-4(1*H*)-one derivatives of antioxidant potential.

blood-brain barrier permeation. Also, their predicted toxicity data suggested that they would be free of irritation, reproductive, tumorigenicity, and mutagenicity risks.

The SAR analyses (Figure 7), which were performed in comparison to quinoline and flavone analogues, confirmed the importance of the secondary amino group at position-1 and the hydroxyl substituents at positions -8 or -6, as shown in compounds **72** and **74,** for improving antioxidant efficiency in the FRAP and TBARS assays and the 7-substitution (as in compound **73**) in the ORAC assay. Moreover, the toxicity findings suggested that the 2-phenyl moiety, the substitution of the oxo in position 1 of the flavone with the secondary amino group, and the insertion of hydroxyl groups enhanced the safety of these 2-phenylquinolin-4(1*H*)-ones in comparison to their quinoline and flavone analogues (Greeff et al. 2012).

Hernández-Ayala and his coworkers used the CADMA-Chem protocol to design and build a library of 8536 quinoline derivatives generated by substituting the seven positions on the quinoline ring with –OH, $–NH_2$, –SH, –COH, $–COCH_3$, and $–COOCH_3$ groups. The ADME parameters, synthetic accessibility (SA), and toxicity parameters for all of the designed derivatives were estimated. The authors developed the selection and elimination scores (S^S and S^E, respectively) as filters to identify the most promising derivatives, which are expected to demonstrate less toxicity, enhanced bioavailability, and easy synthesis as well as to be orally bioactive. At this point, 25

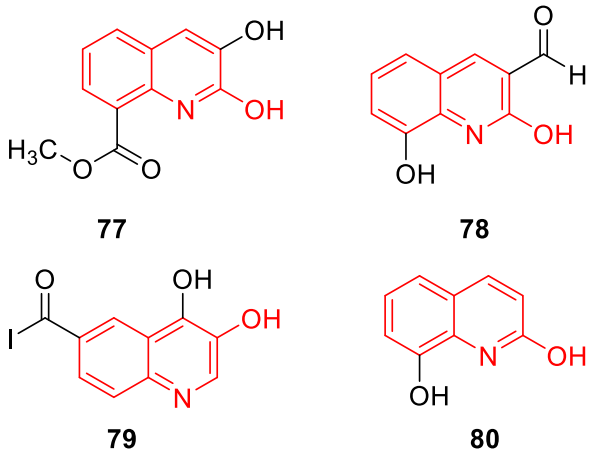


FIGURE 8 | Structures of 2-quinolinones represented by their enol forms as potential antioxidants.

compounds were chosen, among which four 2-quinolinones (represented by their enol forms) **77**-**80** (Figure 8) were included in this set of potential drugs. The ionization potential (IP) and bond dissociation energies (BDE) parameters, which are correlated to the compound's capability to scavenge a free radical by a single electron transfer (SET) or a hydrogen atom transfer (HAT) mechanism, respectively, were calculated for all the promising compounds. The oxidant target was hydroperoxide (H_2O_2) radical, whereas trolox, α-tocopherol, and vitamin C were used as reference antioxidants for comparison. The calculated values of IP and BDE indicated that seven molecules would be expected to be potent antioxidants. Among them, the four 2-hydroxyquinolines were predicted to be more powerful antioxidants than α-tocopherol through both mechanisms. Also, in comparison to Trolox, compounds **77**, **78,** and **79** would presumably be better radical scavengers via both SET and HAT mechanisms, whereas compound **80** was predicted to be equipotent as an electron donor, but it is better as an H-atom donor. Last, as compared to ascorbate compounds, **78** and **79** were among the five best compounds in this study as radical scavengers by the HAT mechanism, but they would be less efficient in the SET mechanism (Hernández-Ayala et al. 2023).

4.3 | Quinolones as Phosphodiesterase (PDE) Inhibitors

PDEs constitute a superfamily of enzymes that are present in all tissues to catalyze the hydrolysis of the 3′ phosphate bond of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). These nucleotides act as key secondary messengers in various intracellular processes such as proliferation, differentiation, apoptosis, inflammation, and metabolism, as well as neurobehavioral functions including cognition and memory. Several clinical studies indicated that inhibition of PDE activity can be effective for treatment of neurodevelopmental disorders (Matsumoto et al. 2006).

PDE10A is a member of the PDE family that is distinguished by its striatal predominance and its regulatory role over neurotransmitters in medium-sized spiny neurons. Because Parkinson's disease (PD) is caused by a dopamine deficit that impacts striatal pathways, PDE10A inhibitors could treat the condition via modifying D1 and D2 receptor signaling (Ahmad et al. 2024). Therefore, a constellation of 192 quinoline and 46 quinazoline alkaloids was selected for comprehensive in silico molecular docking evaluations against the PDE10A, followed by pharmacological and pharmacokinetic studies to prioritize the central nervous system (CNS) active drug criteria within this library. The results of these investigations indicated that four quinolinone alkaloids (**81**-**84)** exhibited strong docking scores along with desirable pharmacokinetics and drug-likeness as compounds. The molecular interactions of these ligands with PDE10A are summarized in (Figure 9). The 4-quinolinone CJ-13536 **81** showed a docking score of −7.2160 Kcal/mol against the receptor protein relative to −6.9536 by papaverine **85**, the used standard. This ligand displayed a polar interaction by forming a single H-bond with amino acid residue Ser677, in addition to a hydrophobic π-π interaction with residue Phe729. Considering 2-Undecyl-4(1*H*)-quinolone **82**, its docking score value against PDE10A was −6.9234 Kcal/mol. It established a H-bond with the accessible residue Ser677 and a hydrophobic π-H binding with the residue Ile692. Furthermore, it formed a 6-ring π-π contact with the crucial residue, PHE729 (Huang et al. 2022). Despite the fact that the latter interactions are not involved in binding with cAMP and cGMP, they were displayed by several PDE10A inhibitors, including papaverine **85**. Last, this ligand was stabilized in the PDE10A active pocket via a hydrophobic interaction with amino acid residue Ile692.

The 2-quinolinone, Huajiaosimuline **83,** showed a docking score of −6.9002, in addition to establishing two H-bonds with His525 and Met713 residues and a π-π interaction with the amino acid Phe729. The 3-Prenyl-4-prenyloxyquinolin-2-one **84** was the second efficient 2-quinolinone inhibitor with a high docking score of −7.2807 Kcal/mol via forming hydrophobic contact with the amino acid residue Phe729. Of note, the oxygen atoms of the 3,4-dimethoxybenzyl group of papaverine **85** formed two hydrogen bonds with His525 and His567, which were observed in Huajiaosimuline **83**. Also, the significant Phe729 was found in the interaction profiles of papaverine **85** and the studied alkaloids: CJ-13536 **81**, Huajiaosimuline **83,** and 3-Prenyl-4-prenyloxyquinolin-2-one **84**. Although the oxygen atom of the 3-methoxybenzyl group in papaverine **85** showed the H-bonding interaction with the His567 residue, none of the studied alkaloids displayed this interaction. Collectively, based on these docking results, the authors created a common pharmacophore predominantly focusing on compound **81** (CJ-13536) and identified the essential pharmacophoric motifs for inhibiting PDE10A to include the aromatic quinoline core, which is capable of establishing π-π stacking and hydrophobic interactions to enhance the binding affinity, a sulfur atom for augmenting the compound's H-bonding capabilities and potentially improving the selectivity and potency, in addition to a hydrogen bonding acceptor site (C = O) to interact with H-bonding donors in the active pocket (Ahmad et al. 2024).

Furthermore, analyses of the drug likeness and BBB permeability characteristics of the quinolinone alkaloids **81**-**84** indicated their BBB permeability and adherence to the Lipinski's criterion for CNS active drugs. P-glycoprotein (Pgp) is another important characteristic of brain medication since many medications are pumped out by this efflux transporter

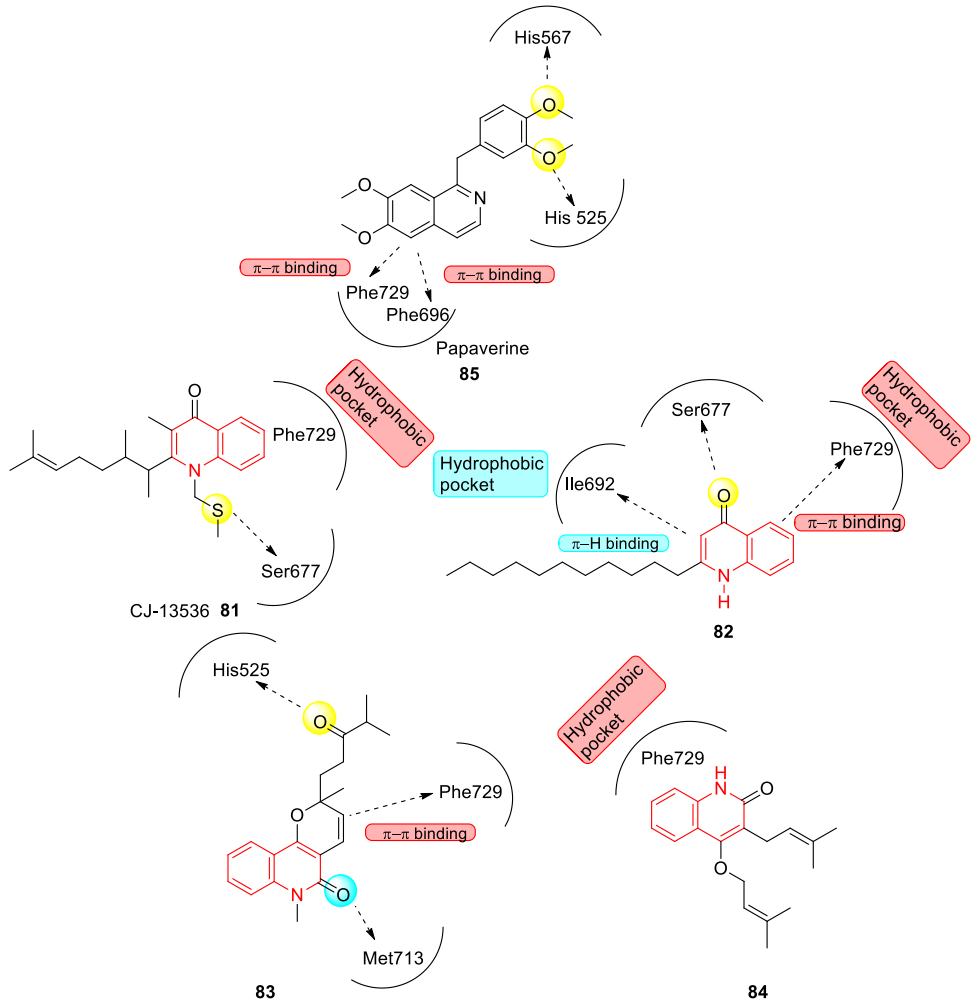


FIGURE 9 | Binding interactions of papaverine **85** and quinolinones **81-84** with PDE10A protein.

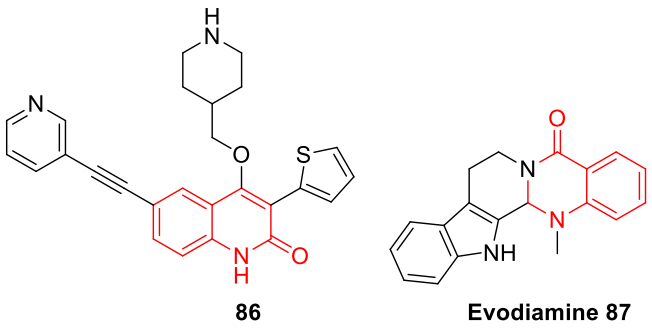


FIGURE 10 | The quinolin-2(1*H*)-one **86** derivative and evodiamine **87** as PDE2 inhibitor and mitochondrial dysfunction modulator, respectively.

in the brain, which serves as a protective mechanism. CJ-13536 **81** and Huajiaosimuline **83** were non-Pgp substrates, and so they are considered to be among the top alkaloids. At somewhat lower dosages, these alkaloids can enhance the therapeutic efficacy for neurodegenerative diseases such as Parkinson's disease. Moreover, these quinolinone alkaloids would not be carcinogenic, immunotoxic, mutagenic, or cytotoxic, suggesting that they would be safe choices (Ahmad et al. 2024).

PDE2 is another isoform belonging to the phosphodiesterase family that is mostly expressed in limbic and cortical brain regions in the CNS, which are associated with memory and learning (Zhang et al. 2017). Several in vivo studies performed on rodents demonstrated that PDE2 inhibition improved learning and memory in a variety of cognitive tests due to an increase in cAMP or cGMP levels or both (Lueptow et al. 2016; Zhang et al. 2017).

Compound **86** (Figure 10) was recognized by MERCK SHARP & DOHME as a 2-quinolone-containing potent PDE2 inhibitor with an IC_{50} value less than 0.1 nM (DeLeon et al. 2014).

4.4 | Quinolones as Modulators of Mitochondrial Dysfunctions

Mitochondria are one of the major sources of intracellular reactive oxygen species (ROS) and play vital roles in maintaining neuronal integrity and responsiveness (Sheng and Cai 2012; Shigenaga et al. 1994; Zhang et al. 2018). ROS that is produced in the electron transport chain can cause mitochondrial respiratory chain malfunction, mitochondrial enlargement, and matrix metalloproteinase (MMP) dissipation (P. Srivastava et al. 2014). In Alzheimer's disease (AD),

mitochondrial dysfunction progressively causes neural death in a variety of ways and exacerbates the occurrence and progression of the disease. As a result, it has been suggested that treating damaged mitochondria may be a promising step in treating AD (Jin et al. 2021).

Evodiamine **87** (Figure 10), a natural quinolone alkaloid, is derived from the fruits of *Evodia rutaecarpa* and is used in traditional Chinese medicine. Evodiamine **87** has several pharmacological properties, including neuroprotective effects. Evodiamine **87** (5–40 μM) protected neural HT22 cells by restoring mitochondrial functions and reducing intracellular ROS caused by glutamate-induced oxidative stress. In D-galactose/$AlCl_3$-induced AD in rats, oral evodiamine treatments of 40 mg/kg for 42 days reduced cognitive impairment, decreased ROS levels, and increased superoxide dismutase (SOD) and glutathione peroxidase (GPx) levels in the cerebral cortex (Jin et al. 2021; Zhang et al. 2018). As mentioned previously, Alzheimer's patients have neurobiological abnormalities, including decreased acetylcholine (Ach) and choline acetyltransferase (ChAT) and increased acetylcholinesterase (AchE) (Craig et al. 2011; Schliebs and Arendt 2006). Clinical studies revealed that 6 weeks of evodiamine treatment significantly lowered AchE levels and increased Ach and ChAT levels in serum, the cerebral cortex, and the hypothalamus of AD-like animals (Zhang et al. 2018). During these studies, there were no significant alterations in the brain, spleen, or kidney across all groups, indicating the safe profile of evodiamine.

4.5 | Quinolones as Glycogen Synthase Kinase-3β (GSK-3β) Inhibitors

Tau is a microtubule (MT) bundle inducer and a stabilizing protein mainly expressed in the cytoplasm of neurons. Tau hyperphosphorylation results in the loss of its MT-binding ability and causes its detachment from MTs. Once detached, tau protein accumulates and forms insoluble intracellular aggregates or neurofibrillary tangles (NFTs) in neural cells, which are one of the major pathological features of AD. These NFTs are toxic and cause neuron death and cognitive dysfunction.

Glycogen synthase kinase 3β (GSK-3β) plays a critical role as a protein kinase in the hyperphosphorylation and unreasonable build-up of tau protein (F. Hernández et al. 2002). Consequently, current studies have concentrated on GSK-3β inhibition as a successful treatment approach for neurological disorders and AD (M. Xu et al. 2019).

The 2-quinolone derivative, ZINC67773573 **88,** was computationally identified as a promising lead GSK-3β inhibitor based on its ability to fit well and interact with key amino acids Val135 and Asp133 in the hinge region. This binding pattern aligned the hydrophobic isoindoline ring at position 3 with the hydrophobic side chains of amino acids Ile62, Val70, Pro136, and Leu188 (Figure 12) (El Kerdawy et al. 2019).

A novel series of quinolin-2-one derivatives **89-91** that maintains the necessary pharmacophoric parameters for GSK-3β inhibition based on the hit ZINC67773573 **88** was synthesized and evaluated as GSK-3β inhibitors using the ATP-Glo test. The results demonstrated the outstanding inhibitory activity of compounds **89**, **90,** and **91** (IC_{50} ranged from 4.68 ± 0.59 to 8.27 ± 0.60 nM) as compared to the reference medication staurosporine ($IC_{50} = 6.12 \pm 0.74$ nM) (Abdo Moustafa et al. 2024).

Compound **88**, which showed superior GSK-3β inhibitory efficacy in vitro and no cytotoxicity to hepatic and brain cell lines, was further tested for its ability to improve memory impairment in a scopolamine-treated AD animal model and showed promise in reducing scopolamine's cognitive deficits (El Kerdawy et al. 2019).

These compounds are characterized by the presence of a hydrophilic tail (the peripheral substituted phenyl group on the azomethine carbon) that accesses and binds with the enzyme's polar region, thus increasing the compounds' efficacy (El Kerdawy et al. 2019; Abdo Moustafa et al. 2024). These Schiff bases showed a consistent binding pattern with the quinolin-2(1*H*)-one ring being well accommodated in the hinge region and establishing H-bonding interactions with Asp133 and Val135 using the NH and CO groups as well as hydrophobic interactions with the side chains of adjacent amino acids through the benzene ring of the bicyclic core. Additionally, compounds **89** and **91** were engaged in additional contact with the nucleotide-binding loop amino acid Arg141 guanidine group, which caps the end of the pocket by hydrogen bonding, through the action of their peripheral substituted phenyl group. This extra interaction may explain their high binding scores and enhanced biological activity (Figure 11). These inhibitors complied with Lipinski's rule of five and had acceptable BBB and CNS penetration using ADME predictions (Abdo Moustafa et al. 2024).

4.6 | Quinolones as Serotonin-Dopamine Modulators

The symptoms of schizophrenia arise from disturbances in neurotransmission involving certain receptors and enzymes, mainly within the dopaminergic, glutamatergic, serotoninergic, and adrenergic systems. Nowadays, there are two quinolin-2(1*H*)-one drugs: aripiprazole and brexpiprazole (Figure 2), which have mutli-pharmacological profiles (Kondej et al. 2018; Maeda et al. 2014). Depending upon the signaling readout and cell type interrogated, aripiprazole can behave as a full agonist, a partial agonist, or an antagonist at the D2 receptor as well as an antagonist or a partial agonist to α-arrestin-2 recruitment and as a partial agonist for serotonin 5-HT_{1A} and 5-HT_{2A}. Therefore, it has clinical applications in several psychotic disorders, including schizophrenia, obsessive-compulsive disorder, autism, major depression, and bipolar disorder.

Similarly, brexpiprazole, which was developed by Otsuka Pharmaceutical Co. Ltd. (Tokyo, Japan) in collaboration with H. Lundbeck A/S (Valby, Denmark), has been licensed by the FDA in 2015 for the treatment of schizophrenia and major depressive disorder due to its ability to act as a partial agonist of serotonin 5-HT_{1A} and dopamine D_2 and D_3 receptors, an antagonist at noradrenergic α1B and α2C, and an antagonist of serotonergic 5-HT_{2A}, 5-HT_{2B}, and 5-HT_7 (Diefenderfer and Iuppa 2017). Additionally, a 12-week randomized clinical trial indicated that administration of brexpiprazole, 2 or 3 mg, to patients with Alzheimer's dementia significantly improved agitation.

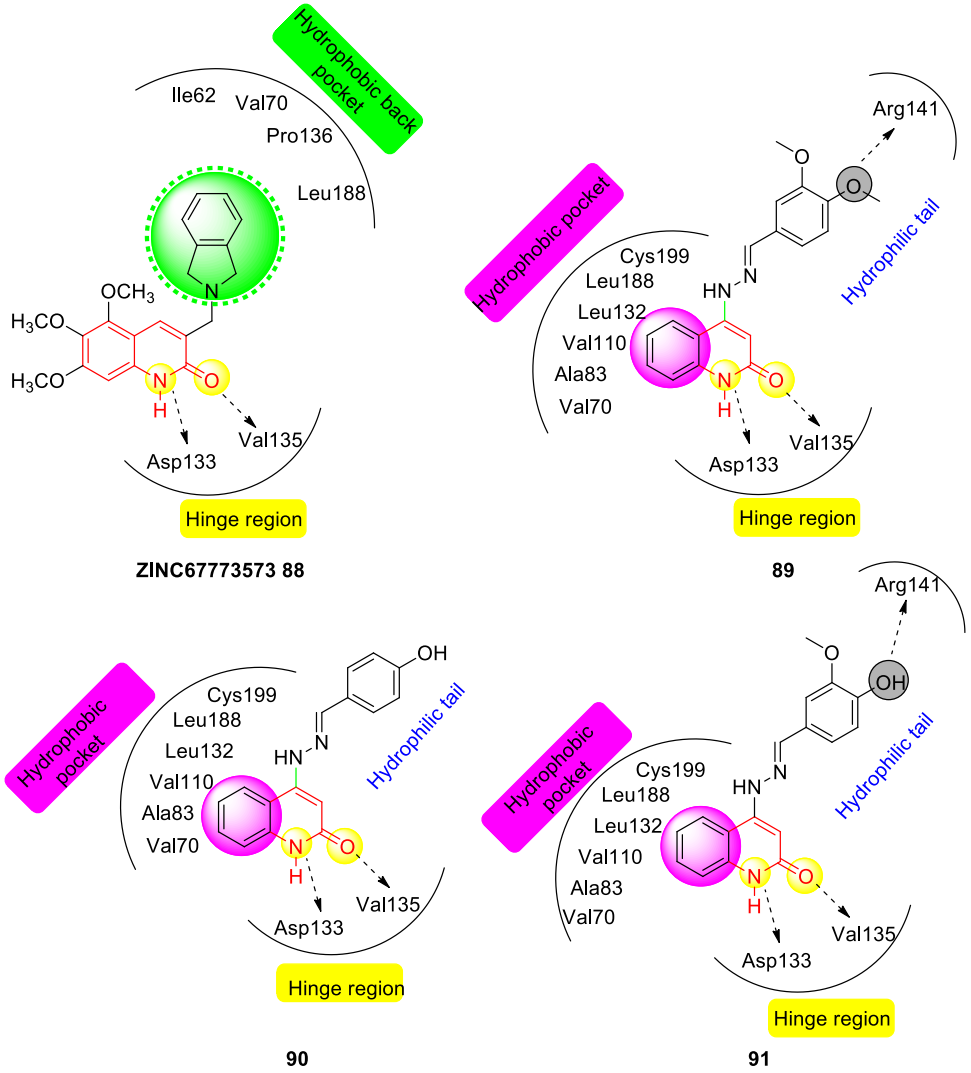


FIGURE 11 | Binding interactions of quinolin-2-one derivatives **88** and **89-91** in the GSK-3β binding site.

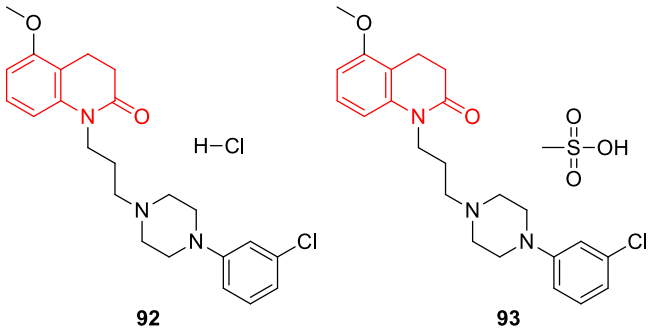


FIGURE 12 | Quinolin-2(1H)-one derivatives as CNS activators and antidepressants.

4.7 | Quinolones as CNS Activators and Antidepressants

Sigma (σ) receptors are protein receptors that are present in the central nervous system (CNS) and are involved in the regulation of neurosteroids, noradrenaline, dopamine, serotonin, acetylcholine, and glutamic acid neurotransmitter systems. These receptors have been proposed as potential targets for the diagnosis and treatment of various CNS disorders (Piechal et al. 2021). For example, the antidepressant and the nervous system stimulating activities, including reducing the sleeping time of mice anesthetized with halothane as well as accelerating the recovery from coma induced by cerebral concussion in mice by 2(1*H*)-quinolinone hydrochloride salt **92** and its mesylate analogue **93** (Figure 12), were attributed to their σ receptor agonistic activities (Oshiro et al. 2000).

4.8 | Quinolones as Neuro Anti-Inflammatory Agents

4.8.1 | Quinolones as Microsomal Prostaglandin E Synthase 1 (mPGES-1) Inhibitors

Prostaglandin E (PGE) is a well-known family of naturally occurring lipid mediators that includes two types of prostanoids: PGE1 and PGE2. The clinical importance of PGE2 relies on its crucial roles in the propagation of inflammatory responses and the development and maintenance of hyperalgesia and allodynia (Funk 2001). The biosynthesis of PGE2 from membrane phospholipids involves a series of enzymes,

including phospholipase A2 (PLA_2), cyclooxygenases COX-1 and COX-2, and microsomal prostaglandin E2 synthase-1 (mPGES-1). Both COX-2 and mPGES-1 are inducible, and they are released in response to inflammatory stimuli. Also, it was proposed that mPGES-1 might be an accelerator of neuronal death in inflammatory brain diseases such as Parkinson's disease (PD) via enhancing the accumulation of PGE2. Accordingly, inhibition of mPGES-1 was proposed as a promising strategy for suppression of increased PGE2 levels to treat human stroke and Parkinson's disease (Ikeda-Matsuo et al. 2019).

Through the optimization of the lead mPGES-1 inhibitor 1*H*-imidazo[4,5-*c*] quinolin-4(5*H*)-one derivative **94** at positions C-7 and C-8, Tomoya Shiro et al. were able to identify compounds **95** and **96** as the most potent mPGES-1 inhibitors (Shiro et al. 2013).

SAR studies (Figure 13) revealed the superiority of C-7 position substitution to C-8 position on the imidazoquinoline core with bromine and phenyl being the best substituents. Where the C-7 brominated derivative **94** ($IC_{50} = 9.1$ nM) exhibited higher inhibitory activity than the C-7 chlorinated analogue ($IC_{50} = 27$ nM) or the unsubstituted derivative ($IC_{50} = 891$ nM), thus indicating the crucialness of hydrophobicity or bulkiness of the substituents for enhancing the mPGES-1 inhibitory activity. Also, introducing a second *ortho*-substituent (F) on the phenyl group at the C(2)-position as in compound **96** enhanced the inhibitory activity ($IC_{50} = 4.1$ nM) approximately twofold compared to the mono-chlorine derivative **95** ($IC_{50} = 7.9$ nM). Furthermore, compound **96** demonstrated almost 700-fold selectivity for mPGES-1 with no inhibition against COX-1, COX-2, thromboxane synthase (TXS), or leukotriene C4 synthase. In addition to that, it displayed an acceptable in vitro ADME profile with good metabolic stability (MS), no cytochrome P (CYP) inhibition, good membrane permeability (Pe), and sufficient solubility. The in vivo rate PK studies confirmed the suitability of quinolinone **96** for oral administration (Shiro et al. 2013).

4.8.2 | Quinolones as Anti-Nuclear Factor-Kappa B (NF-kB)

The transcription factor nuclear factor Kappa light chain enhancer of activated B cells (NF-kB) is a family of transcriptional factors involved in the regulation of the immune proinflammatory responses throughout the body. Under homeostatic conditions, the NF-kB pathway is inactivated; however, bacterial or viral toxins, proinflammatory cytokines, chemical or physical stressors, and damaged or dying cells can canonically activate it. Within neurons, this activation may produce neuroprotective or neurodegenerative effects depending on the cell type. In microglia, NF-κB signaling is associated with neuroinflammation. In Alzheimer's disease (AD), the accumulation of the amyloid beta aggregates, tau tangle, and neurofibrillary tangles was found to be mediated by NF-κB activation in microglia. Consequently, microglia-specific NF-κB inhibition is a potential avenue for future neurotherapeutic development (Anilkumar and Wright-Jin 2024).

A study conducted by Giusti and coworkers in 2019 indicated that the fluoroquinolinones, ciprofloxacin and levofloxacin (Figure 2), suppressed LPS-induced NF-kB activation in microglial cells, which might contribute to their neuroinflammatory effects (Zusso et al. 2019).

4.8.3 | Quinolones as Pro-Inflammatory Mediators' Inhibitors

It is widely acknowledged that inflammation involves the activation of myriad signaling pathways with excessive release of pro-inflammatory mediators, among which are TNF-α, IL-6, and nitric oxide (NO) (Dang et al. 2008). In Alzheimer's disease, the neuronal death is triggered by the release of such pro-inflammatory cytokines (Von Bernhardi et al. 2010). As a result, many research and development investigations focused on the development of potent and specific inhibitors for these pro-inflammatory mediators (Z. Liu et al. 2014).

Yong Qu et al. *s*ynthesized and resolved by chiral HPLC eight enantiopure isomers of yaequinolone alkaloids. Moreover, they designed, synthesized, and characterized additional 34 racemic analogues, which were modified at the 4-aryl, the N-position, and the pyran. All the synthesized compounds were evaluated as anti-inflammatory agents by assessing their inhibitory efficiencies against nitric oxide production. From the synthesized series, the non-racemic compounds (-) **97** and (-) **98** showed significant inhibition of NO production with IC_{50} values lower than 0.1 μM as

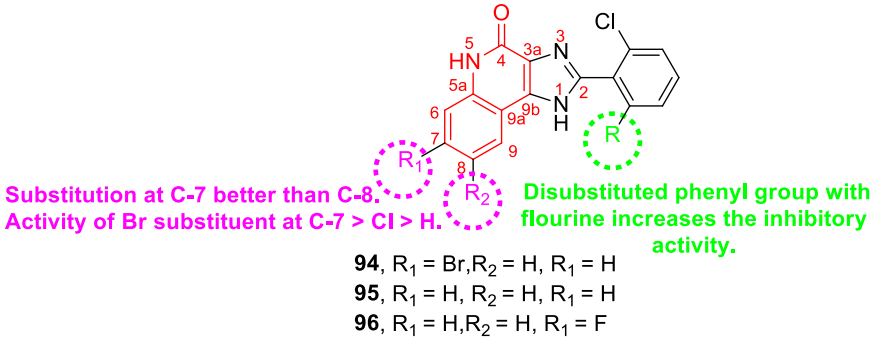


FIGURE 13 | The SAR analyses of 1,5-dihydro-4*H*-imidazo[4,5-*c*]quinolin-4-one derivatives as mPGES-1 inhibitors.

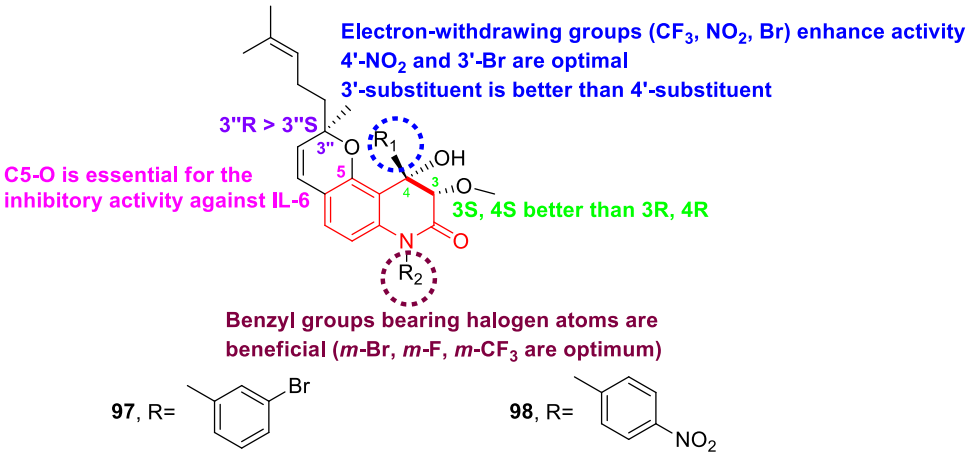
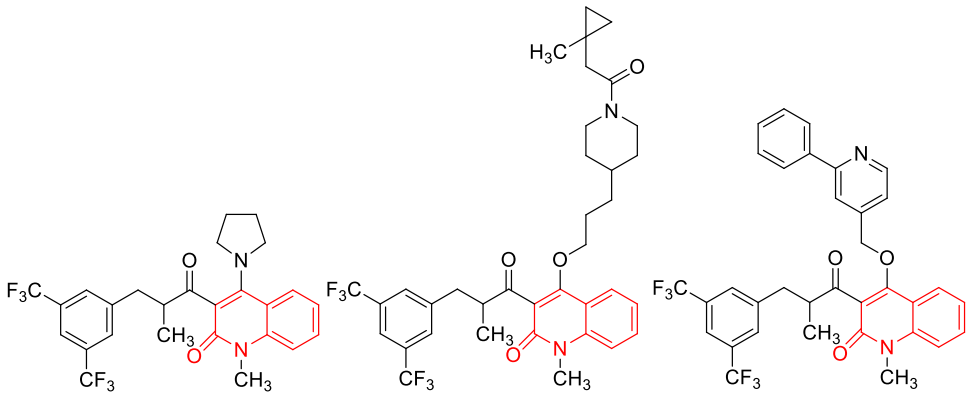


FIGURE 14 | SAR of 2*H*-pyrano[2,3-*f*] quinolin-8(7*H*)-one derivatives as pro-inflammatory mediators' inhibitors.



	99	**100**	**101**
SM2 IC_{50} (nM)	950	6.5	16
SM1 IC_{50} (nM)	> 100,000	1000	14,000
Ratio of SM1 IC_{50} / SM2 IC_{50}	> 100	150	880

FIGURE 15 | 3-(3-(3,5-Bis(trifluoromethyl)phenyl)-2-methylpropanoyl)-1-methyl-4-substituted quinolin-2(1*H*)-one derivatives as sphingomyelin synthase 2 inhibitors.

compared to 25 μM by indomethacin, and hence they were further evaluated for TNF-α and IL-6 release levels in LPS-stimulated RAW 264.7 cells via ELISA. The results revealed a marked reduction of IL-6 levels at a 0.05 μM concentration (Qu et al. 2023).

The anti-inflammatory potential of these compounds was found to be dependent on the absolute configuration where the *R*-configuration at the C3″ position in enantiomers (-)-**97** (3*S*, 4*S*, 3″ *R*) and (-)-**98** (3 *R*, 4 *R*, 3″ *R*) greatly influenced the NO inhibitory activity.

Also, the SAR studies (Figure 14) showed that substitution of the 4-phenyl moiety with electron-withdrawing groups such as 4′-CF_3, 4′-NO_2, and 3′-Br significantly improved the activity. Additionally, tethering halogen-bearing benzyl moieties to the *N*-position contributed to the noncovalent intermolecular interaction between the target protein and halogenated ligand (J. Ren et al. 2014).

4.8.4 | Quinolones as Sphingomyelin Synthase 2 Inhibitors

Sphingomyelin synthase is a membrane-bound enzyme that catalyzes the biosynthesis of sphingomyelin, which is necessary for maintaining the fluidity of plasma membrane microdomains. Recent studies have highlighted its critical role in neuroinflammatory disorders, including Alzheimer and Parkinson diseases (Lee et al. 2020).

Literature revealed that 3,5-bis(trifluoromethyl)phenyl) dimethylquinolin-2-one derivative **99** inhibited sphingomyelin synthase 2 (SMS2) with an IC_{50} of 950 nM and more than 100-fold selectivity for SMS2 over SMS1. This compound was subjected to further structural modification to boost SMS2 inhibitory action, which led to the identification of the 2-quinolone derivatives **100** and **101** (Figure 15) with sufficient potency and selectivity through modifying the substituents at the 4-position (Adachi et al. 2017).

5 | Conclusion

This comprehensive review underscores the prominent role of 2(1*H*)- and 4(1*H*)-quinolone scaffolds in modern neurotherapeutic drug discovery. Numerous derivatives of quinolones exhibit diverse and potent neuroprotective effects through multiple mechanisms, including cholinesterase inhibition, antioxidant activity, phosphodiesterase (PDE) inhibition, GSK-3β inhibition, serotonin-dopamine modulation, and anti-inflammatory actions.

Among the key compounds highlighted, the 2-oxo-1,2-dihydroquinoline derivative **70** demonstrated selective acetylcholinesterase inhibition with sub-micromolar potency and promising SAR features. Antioxidant efficacy was established for derivatives **71–74**, particularly compound **74**, which showed enhanced radical scavenging and favorable ADME-Tox profiles. Four 2-quinolinones (**77–80**) exhibited superior antioxidant activity compared to standard references, suggesting their utility as multitarget agents. Compounds such as CJ-13536 (**81**) and Huajiaosimuline (**83**) emerged as potent PDE10A inhibitors with strong docking profiles and desirable CNS pharmacokinetics. The 2-quinolone derivative ZINC67773573 (**88**) and its optimized analogues **89–91** exhibited excellent GSK-3β inhibitory activities (IC_{50} < 10 nM), while Evodiamine (**87**) demonstrated multitargeted neuroprotective effects including mitochondrial stabilization and cholinergic enhancement.

Collectively, these findings affirm the privileged status of the quinolone framework in neuroprotective drug design and support continued investigation into structurally optimized derivatives as promising therapeutic candidates for neurodegenerative disorders.

Author Contributions

Esraa Abdo Moustafa: writing – original draft. **Nahed Nasser Eid El-Sayed:** writing – review and editing, supervision. **Heba Abdelrasheed Allam:** writing – review and editing, supervision. **Marwa A. Fouad:** writing – review and editing. **Ahmed M. El Kerdawy:** writing – review and editing. **Manal Abdel Fattah Ezzat:** writing – review and editing, supervision.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

This review article is based on publicly available data, which is cited appropriately within the manuscript. Readers can access these sources through the references provided.

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