CHEMICAL SCIENCES

SYNTHESIS OF NOVEL ADAMANTYL-CONTAINING QUINOLIN-2-ONE DERIVATIVES AS POTENTIAL GSK-3B INHIBITORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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Abstract

Glycogen synthase kinase-3β (GSK-3β) has recently been implicated as a critical factor in the development of Alzheimer's disease (AD). In this study, a new series of quinolin-2-one derivatives containing a 1-adamagtyl substituent was synthesized. The results of this study suggest that these new compounds may have potential as antiviral agents against Alzheimer's disease by targeting GSK-3β.

Introduction

Alzheimer's disease (AD) is a complex, chronic, aging-related neurodegenerative disorder whose pathophysiology remains incompletely understood [1]. Approximately 50 million patients worldwide suffer from the disease, and this number is projected to more than triple by 2050, creating significant financial and medical burdens for both patients and healthcare systems [2]. Despite its complexity, many hypotheses have been put forward to explain its pathophysiology, including the tau hypothesis, the cholinergic theory, the amyloid-β (Aβ) protein hypothesis, and others [3]. Galantamine, donepezil, rivastigmine, and memantine are the only FDA-approved drugs for the treatment of AD, however, all of them are primarily used for palliative care and cannot prevent or reverse the pathology of AD [4]. As a result, the development of disease-modifying therapeutics targeting tauopathy or Aβ deposition is an urgent need [5].

Tau is a binding protein responsible for the formation of microtubules and their stabilization in normal physiological conditions. Hyperphosphorylation of the tau protein renders it incapable of binding to microtubules. As a result, dissociated tau protein accumulates and forms clusters in neurons as toxic neurofibrillary tangles (NFTs), leading to neuronal death [6,7]. This pathogenic process is believed to be triggered by dysregulation and mutations in kinases and phosphatases that interact with the tau protein [8].

Dysregulation is considered a major factor initiating numerous human diseases, including immunological and neurological diseases, in addition to cancer [9]. Glycogen synthase kinase-3β (GSK-3β) has been found to be an important protein kinase in the hyperphosphorylation and pathological accumulation of tau protein [10].

Thus, GSK-3β has been proposed as a promising target for neurodegenerative diseases, among other diseases [11]. According to the "dual pathway" theory, GSK-3β has been shown to actively promote excess Aβ formation and tau protein hyperphosphorylation, key neuropathological hallmarks of Alzheimer's disease [12]. In addition, abnormal GSK-3β activity is associated with neuroinflammation and oxidative stress [13]. Accordingly, GSK-3β is involved in almost all pathological processes of Alzheimer's disease. As a result, recent studies have focused on GSK-3β inhibition as an effective strategy for the treatment of Alzheimer's disease [13].

Currently, kinase inhibitors account for 25% of all ongoing drug development research [14]. However, clinical trials of competitive ATP inhibitors often fail due to the striking similarity of their target ATP-binding sites, which increases the risk of off-target toxicity [15,16]. Due to the therapeutic importance of kinase inhibitors, several approaches have been required to overcome the kinase selectivity barrier and provide more effective targeted treatments [17]. Promising new approaches include targeting the inactive conformation of kinases and interacting with their unphosphorylated catalytic site (type II inhibitors) or developing kinase inhibitors that can bind outside the catalytic/ATP-binding site and regulate kinase activity through an allosteric mechanism [18]. For example, tideglusib is an irreversible allosteric, ATP-noncompetitive inhibitor of GSK-3β. However, tideglusib failed to achieve its primary treatment targets for patients with Alzheimer's disease, and phase II clinical trials of tideglusib as an anti-Alzheimer's drug were discontinued. To date, none of the investigated GSK-3β inhibitors have reached the market, so there is great interest in finding suitable GSK-3β inhibitors for therapeutic use as anti-Alzheimer's agents [19].

Quinolines and quinolones are heterocyclic structures that commonly act as structural building blocks for a number of complex natural products [20]. In addition, they have demonstrated a number of biological and pharmacological effects, including anti-Alzheimer's activity [21].

Clinical trials have shown that 8-hydroxyquinoline derivatives, clioquinol I and PBT2 II (Fig. 2), are potent metal chelators that significantly improved cognitive function by reducing Aβ levels in cerebrospinal fluid (CSF) [22,23]. Recent studies have shown that

quinoline-2(1H)-one derivatives act as multitarget agents with ROS scavenging ability, in addition to potent cholinesterase action, possessing inhibitory activity [24]. Moreover, 2-heptyl-3-hydroxyquinol-4(1H)-one derivative protected neurons from glutamate-induced cell death in HT22 cells by preventing cellular Ca2+ uptake and glutamate-induced ROS generation [25]. Pyrazolo[3,2-c]quinol-4(5H)-one derivative improved cognitive impairment associated with Alzheimer's disease through its inhibitory effect on phosphodiesterase 9A (PDE9A) [26]. Furthermore, the FDA-approved quinolin-2(1H)-one derivative, brexipiprazole (III), is a serotonin and dopamine modulator that controls non-cognitive psychological symptoms associated with Alzheimer's disease dementia [27].

Furthermore, the 2-quinolone derivative ZINC67773573 (IV) (Fig. 2) was computationally identified as a promising candidate compound for the development of novel GSK-3β inhibitors for the treatment of Alzheimer's disease [28].

ZINC67773573 (IV) demonstrated a promising predicted binding pattern and binding affinity in molecular docking simulations, as it perfectly fit the hinge region, interacting with essential amino acids.

This binding pattern directs the hydrophobic isoindole ring at position 3 to the hydrophobic amino acid side chains [28].

A natural isatin derivative, indirubin, is a key ingredient of the traditional Chinese medicine Dang Gui Long Hui Wan, used to treat chronic myelocytic leukemia (CML) through inhibition of GSK-3β and CDK2 [29–32]. Furthermore, indirubin and its derivatives have been found to inhibit GSK-3β and further abnormal phosphorylation of tau protein in Alzheimer's disease as competitive inhibitors of ATP [33]. The isatin ring of indirubin is located in the hinge region of the GSK-3β binding site, interacting through its carbonyl and NH groups via hydrogen bonds with the essential amino acids Val135 and Asp133, respectively [32–35].

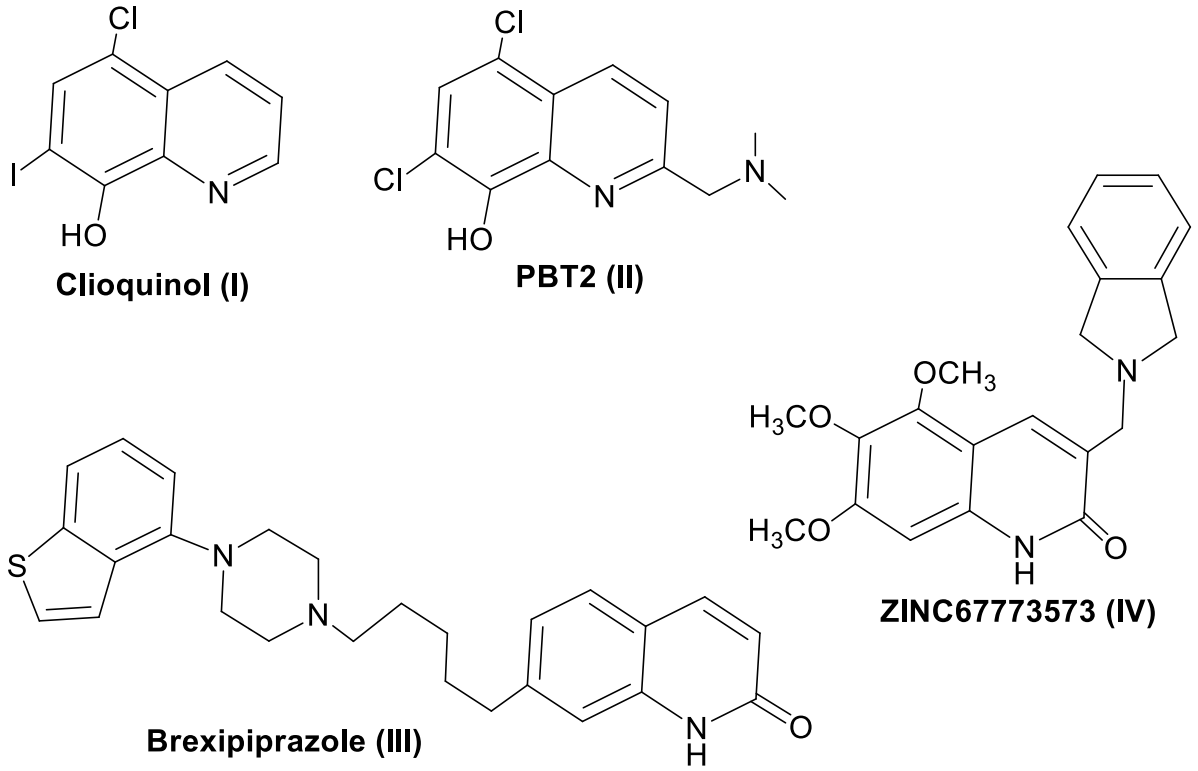
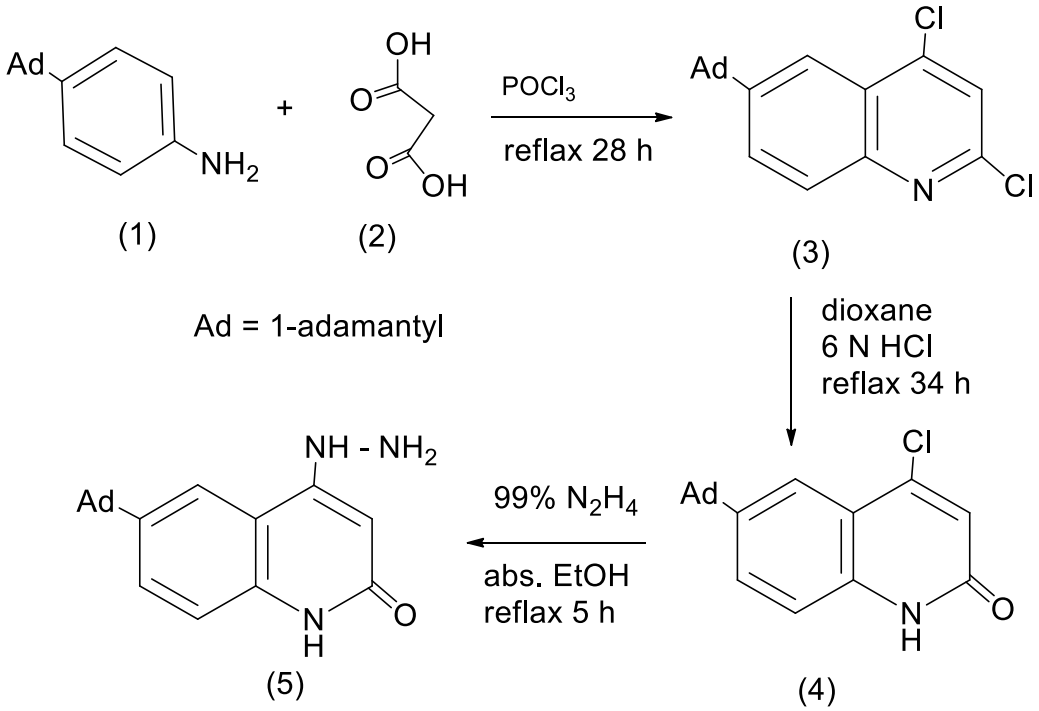


Fig. 2. Structures of some compounds with anti-Alzheimer's activity and containing quinoline and quinolone fragments.

The physiological activity of framework hydrocarbon derivatives, primarily adamantane derivatives, has been extensively studied. The activity of these compounds is due to the pronounced lipophilic nature of the compact framework hydrocarbon fragment. Therefore, the aim of this study was to attempt to impart greater lipophilicity to known anti-priposomal drugs, which, in our opinion, could improve their pharmacological activity.

Results and discussion

A new series of quinolin-2-one derivatives were prepared using 4-hydrazinoquinolin-2(1H)-one (5). The synthesis of the key intermediate 5 was accomplished in a three-step procedure as shown in Scheme 1. The first step of the reaction sequence involved the one-step synthesis of 2,4-dichloroquinoline (3) in 82% yield by a cyclocondensation reaction between 4-(1-adamantyl)aniline (1) and malonic acid (2) in the presence of excess phosphoryl chloride under reflux for 28 h according to modified procedures described by Mohan [36]. The second step involved regioselective oxidation of 2,4-dichloroquinoline (3) at position 2 by treatment with 6 N HCl in dioxane [37,38] to form 4-chloro-2-oxo-6-(1-adamantyl)quinoline (4) in good yield of 87%. In the final step, the chlorine-containing product (4) was treated with excess hydrazine hydrate in ethanol [39,40] at reflux for 5 h to afford the desired 4-hydrazinyl-6-(1-adamantyl)quinolin-2(1H)-one (5) in 73% yield.



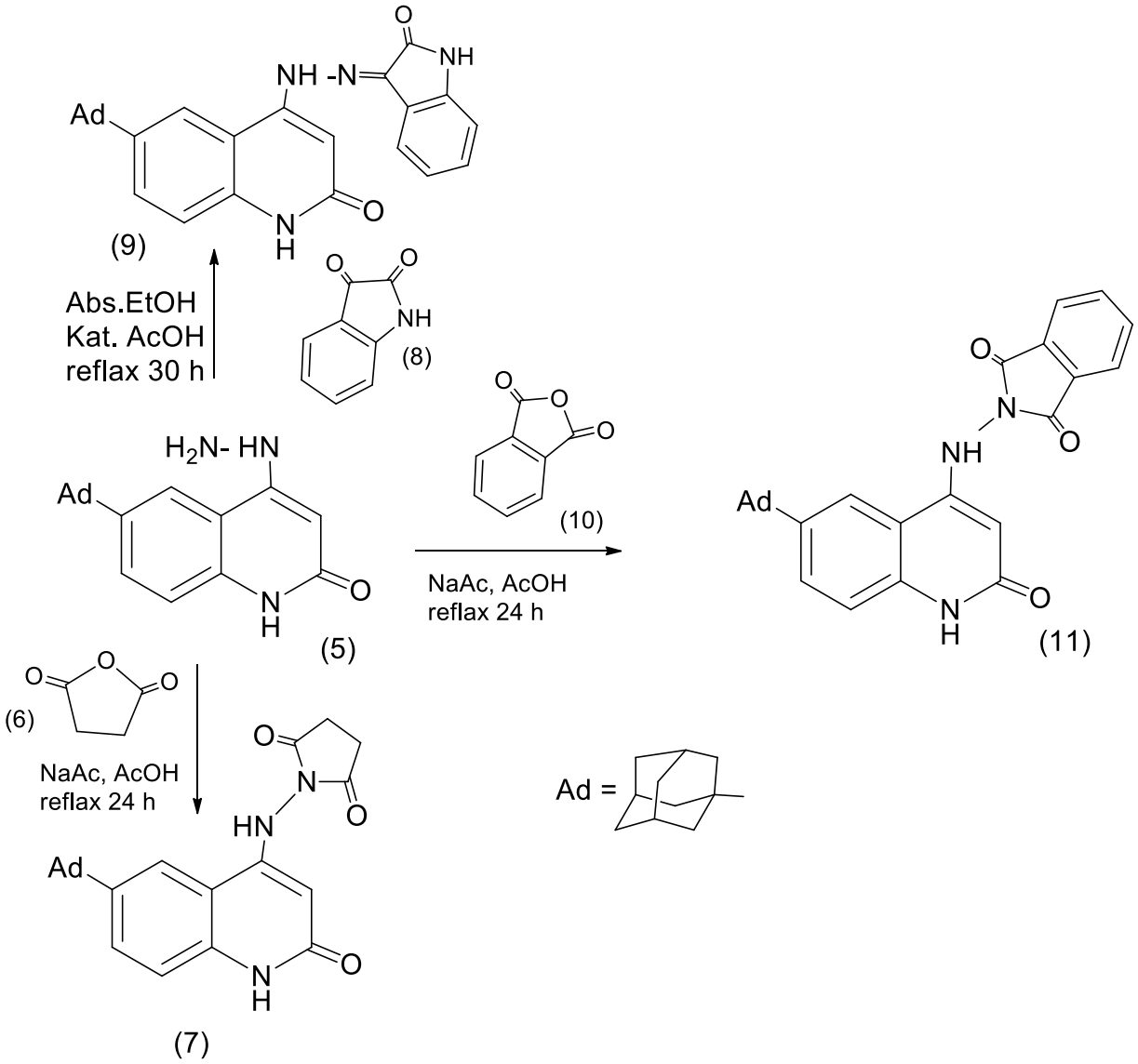
Scheme 1. Reagents and conditions: POCl3, reflux for 28 h, 1,4-dioxane, 6 N HCl, reflux for 34 h, 99% NH2-NH2, absolute EtOH, reflux for 5 h.

Subsequently, hydrazide (5) was used to synthesize various functional derivatives of quinolin-2-one through reactions with various electrophilic reagents (Scheme 2).

The reaction of hydrazide (5) with 1H-indole-2,3-dione (8) yielded hydrazone (9). Thus, ^{1}H NMR spectra revealed the presence of three NH groups resonating at δH values in the ranges of 11.35–11.45, 11.45–11.48, and 13.34–13.38 ppm. ^{13}C NMR spectra revealed the presence of two amide carbonyl groups in the ranges of δC = 162.68–162.74 and 163.80–168.5 ppm.

Theoretically, product (9) can exist as Z or E stereoisomers, or as a mixture of the two isomers, depending on the structure and reaction conditions, which can be thermodynamically or kinetically controlled.

The geometry around the (HC=N-) bond was defined as the E-configuration based on data presented by Wardell and co-workers [41], who showed that 4-hydrazinoquinoline hydrazones adopt an E-configuration around HC=N in their crystal structures, with the amine hydrogen pointing toward the quinoline the remainder. Additionally, a previous study [42], supported by X-ray diffraction analysis, showed that azomethine protons were detected at δH values in the range of 7.46–8.80 for E-isomers. Additionally, the CH=hydrazone carbon atoms were observed at ^{13}C NMR chemical shift values in the range of 139.79–144.78, which corresponds to the values reported for similar types of E-hydrazones (141.62–148.96 ppm) [43], whereas this carbon in the Z-isomers was in the high-field range (δC around 136 ppm) [44].



Scheme.2. Reagents and conditions: absolute ethanol, 5 drops of glacial acetic acid, reflux 30 h, filtration. Anhydrous sodium acetate, glacial acetic acid, reflux 24 h.

Moreover, minimization calculations for the two possible geometric isomers (E and Z) of these Schiff bases revealed a relatively higher stability of the E-isomers compared to their Z-analogs, which may suffer from undesirable steric interactions between the phenyl proton in the ortho position and the NH proton.

With regard to the stereochemical determination of the C—N geometry in derivatives (9), the following facts and observations must be taken into account. Firstly, previous theoretical and experimental studies have shown that under thermodynamic conditions (heat treatment), isatin arylhydrazones almost always exist in the more stabilized Z-forms, which are capable of forming an intramolecular hydrogen bond [45,46] between the hydrazide hydrogen and the lactam oxygen of the oxoindole ring [N–H–O–C], whereas the E-isomers formed at 20 °C were considered less stable isomers because they could not form such hydrogen bonding. Secondly, geometric Z–E isomerization around the C–N double bond in isatin hydrazones occurs only through a photochemical reaction [47], and the less stabilized E-structures slowly thermally isomerize back to the more preferred Z-isomers [48].

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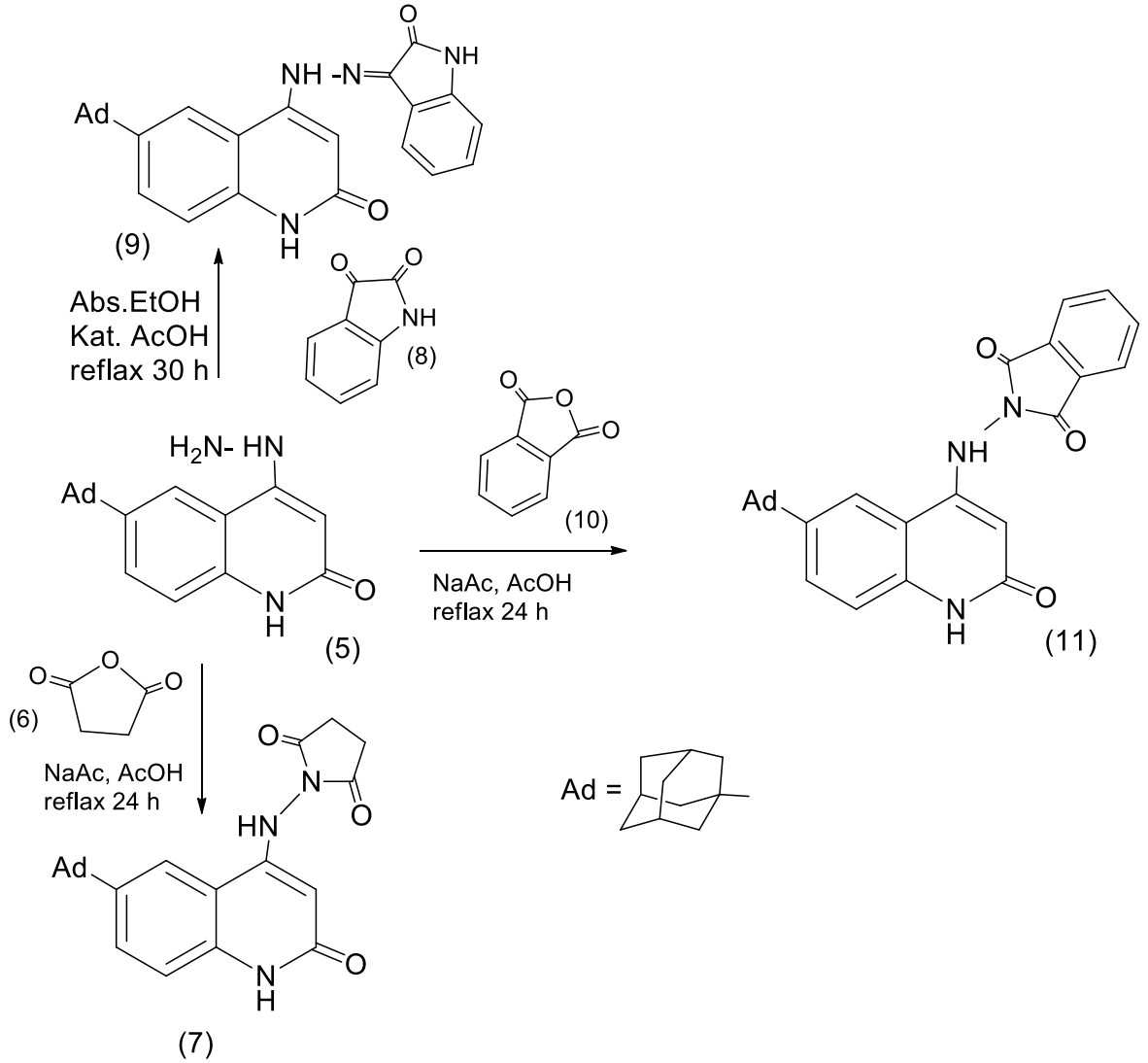
These reported ^{1}H NMR shift values are consistent with those reported for a similar type of Z-Schiff base derived from isatin (13.95 ppm) [45]. Therefore, the Z-configuration was assigned to product (9). This assignment is supported by energy minimization calculations, which indicated higher energies of the E-isomers compared to their Z-isomer counterparts. The higher energies of the E-isomers may be due to the presence of a destabilizing steric hindrance between the 4-H-oxoindole ring and the NH-hydrazide, and this eliminates the E-structure from consideration.

spectra confirmed the formation of symmetrical pyrrolidine-2,5-dione rings, showing characteristic carbon resonances at δ = 166.10 and 174.40 ppm, which can be assigned to the two equivalent carbon atoms of dione in compounds (7) and Subsequently, the synthesis of the hybrid quinolinone-pyrrolidinedione derivatives, conjugates (7) and (11), was easily achieved by refluxing a mixture of hydrazide (5) with phthalic anhydride 12 or succinic anhydride 10 in acetic acid containing sodium acetate for 24 h. From a mechanistic point of view [49, 50], these reactions involved ring opening via nucleophilic attack of the hydrazinyl amino group on one of the carbonyl groups to form monoamide monoacid intermediates, which then underwent intramolecular cyclization to yield pyrrolidinion derivatives (7) and (13), as evident from their ^{1}H NMR spectra, which showed only two singlet signals assigned to the two NH groups resonating at δH values of 9.64 and 11.21 ppm. for derivative (11) and at 9.37 and 11,13 for derivative (7).

Furthermore, ^{13}C NMR spectra confirmed the formation of symmetrical pyrrolidine-2,5-dione rings, showing characteristic carbon resonances at δ = 166.10 and 174.40 ppm, which can be assigned to the two equivalent carbon atoms of dione in compounds (7) and (11), respectively.



Scheme.2. Reagents and conditions: absolute ethanol, 5 drops of glacial acetic acid, reflux 24–48 h, filtration. Anhydrous sodium acetate, glacial acetic acid, reflux 24 h.

Experimental

2,4-Dichloroquinoline (3) [36], 4-Chloroquinolin-2(1H)-one (4) [37,38], 4-Hydazinylquinolin-2(1H)-one (5) [39,40] were obtained according to the described procedures. Chemical reagents were commercially available and used as is, without further purification unless otherwise noted. Moisture-sensitive reactions were carried out under a dry argon atmosphere in pre-baked glassware. Thin-layer chromatography was performed on silica gel thin-layer chromatography plates with a fluorescent indicator at 254 nm (Fluka). Flash column

chromatography was performed using silica gel 60 Å (BDH, 40–63 μm). Mass spectra were obtained on a Bruker ion-trap mass spectrometer. All NMR spectra were recorded on a Bruker 400 MHz spectrometer using $CDCl_3$ or DMSO-d6 as solvent.

Reverse-phase HPLC analysis of the compounds was performed on a Beckman HPLC system with an autosampler. Chromatographic separation was performed on a C18 column (2.0 mm × 150 mm, 5 μm). The mobile phase was used for isocratic elution at a flow rate of 0.2 mL/min. The injection volume was 20 μL and the UV detector was set at 260 nm.

General procedure for the synthesis of compound (9).

A mixture of hydrazide (5) (1 mmol) and (1 mmol) 1H-indole-2,3-dione (8) in absolute ethanol (15 mL) containing 5 drops of glacial acetic acid was refluxed for 30 h. The resulting precipitate was filtered off and washed with hot ethanol, yielding the corresponding pure hydrazone derivative (9).

6-(1-Adamantyl)-(Z)-4-[2-(2-oxoindolin-3-ylidene)hydrazinyl]quinolin-2(1H)-one (9). Light brown powder, yield 97%; mp.: 352–354 ◦C; IR (υ max, cm-1): 3368 and 3132 (3NH), 3075 (CH-Ar.), 2994 (CH aliph.), 1690 (C=O), 1651 (C=O); ^{1}H NMR (DMSO-d6, 400 MHz. δ): 1.48, 1.68, 1.92 (m, 15H Ad), 6.53 (s, 1H, C3 H-quinolone), 6.97 (d, J=7.8 Hz, 1H, Ar-H), 7.11 (t, J=7.5 Hz, 1H, Ar-H), 7.29–7.39 (m, 3H, Ar-Hs), 7.54–7.60 (m, 2H, Ar-Hs), 7.67 (d, J = 7.4 Hz, 1H, Ar-H), 11.35 (s, 1H, NH exchanged for D_2O), 11.45 (s, 1H, NH exchanged for D_2O), 13.38 (s, 1H, NH exchanged for D_2O); ^{13}C NMR (DMSO-d6100 MHz, δ): 29.0, 31.6, 37.5, 45.3, 97.36 (C3) 111.52, 111.73, 116.67, 120.34, 120.51, 120.63, 122.28, 122.95, 131.05, 131.55, 134.55, 139.95, 141.86, 146.44 (C–N-NH), 162.74 (C–O), 164.14 (C–O); MS (*m/z*, %): 438.60 (M^+, 12.52), 129.90 (100).

General procedures for the synthesis of compounds (7) and (11).

To a solution of hydrazide (5) (10 mmol) in glacial acetic acid (25 mL) and anhydrous sodium acetate (10 mmol), the corresponding anhydride (6) or (10) (10 mmol) was added. The reaction mixture was heated under reflux for 24 h. The solution was cooled to room temperature and poured onto ice water, yielding the corresponding derivatives (7) and (11), respectively. The resulting solids were washed with hot glacial acetic acid to obtain pure products.

1-[(6-(1-adamantyl)-2-Oxo-1,2-dihydroquinolin-4-yl)amino]pyrrolidine-2,5-dione (7). Beige powder, yield 80%; mp: 353–355 °C; IR spectrum (υmax, cm^{-1}): 3352 and 3287 (2NH), 3098 (CH-Ar), 2994 (CH aliphatic), 1713 and 1643 (C=O). ^{1}H NMR (DMSO-d6, 400 MHz, δ): 1.48, 1.68, 1.92 (m, 15H Ad), 1.98 and 2.88 (2 s, 4H, cis/trans conformers of pyrrolidine 2CH2), 5.41 and 5.49 (2 s, 1H, cis/trans conformers C3 H-quinolone), 7.14 and 7.20 (2 t, J = 8.0, 7.3 Hz, 1H, Ar-H), 7.26 and 7.31 (2 d, J = 7.8, 7.9 Hz, 1H, Ar-H), 7.48 and 7.53 (2 t, J = 7.7, 7.3 Hz, 1H, Ar-H), 7.94 (d, J= 7.6 Hz, 1H, Ar-H), 8.84 and 9.37 (2 s, 1H, cis/trans NH conformers substituted with D_2O), 10.96 and 11.13 (2 s, 1H, cis/trans NH conformers substituted with D_2O). ^{13}C NMR (DMSO-d6, 100 MHz, δ): 29.0, 31.6, 37.5, 45.3, 27.08 (pyrrolidine CH2), 94.47 (C3 H-quinolone), 112.19, 116.16, 121.48, 122.67, 131.19, 139.54, 150.13, 163.08 (C–O), 175.40 (C = O); MS (*m/z*, %): 391.52 (M^+, 14.54), 43.10 (100).

2-[(6-(1-adamantyl)-2-Oxo-1,2-dihydroquinolin-4-yl)amino]isoindolin-1,3-dione (11). White crystals, yield 94%; mp: 328–330 °C; IR spectrum (υ max, cm^{-1}): 3480 and 3310 (2NH), 3086 (CH-Ar), 2997 (CH aliphatic), 1790, 1732 and 1651 (C=O). ^{1}H NMR (DMSO-d6, 400 MHz, δ): 1.48, 1.68, 1.92 (m, 15H Ad), 5.43 (s, 1H, C3 H-quinolone), 7.25 (t, J = 7.6 Hz, 1H, Ar-H), 7.34 (d, J = 8.1 Hz, 1H, Ar-H), 7.56 (t, J = 7.5 Hz, 1H, Ar-H), 7.96–8.03 (m, 5H, Ar-Hs), 9.64 (s, 1H, NH exchanged for D2O), 11.21 (s, 1H, NH exchanged for D2O); ^{13}C NMR (DMSO-d6, 100 MHz, δ): 29.0, 31.6, 37.5, 45.3, 94.50 (C3 H-quinolone), 112.05, 116.28, 121.65, 122.53, 124.29, 129.91, 131.39, 135.78, 139.63, 150.85, 162.91 (C– O), 166.10 (2C = O). MS (*m/z*, %): 439.52 (M^+, 15.74), 43.10 (100).

Conclusion

Novel adamantyl-containing quinolin-2-one derivatives have been obtained as potential GSK-3β inhibitors for the treatment of Alzheimer's disease.

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