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Synthesis and PASS-assisted evaluation of new heterocyclic compounds containing hydroquinoline scaffolds

Gizachew Mulugeta Manahelohe[1*] and Khidmet Safarovich Shikhaliev[2]

Abstract

Currently, there is a growing interest in the synthesis of heterocyclic compounds containing hydroquinoline fragments. This surge can be attributed to the broad range of pharmaceutical and industrial applications that these compounds possess. In this study, the synthesis of both linear and fused heterocyclic systems that incorporate hydroquinoline fragments was described. Furthermore, the pharmacological activity spectra of the synthesized compounds were predicted using the in silico method, employing the Prediction of Activity Spectra of Substances (PASS) program. Hydroquinolines containing the nitrile functionality **7** and **8** were synthesized through the reaction of the corresponding hydroquinolinecarbaldehyde **5a**, **6b** with hydroxylamine hydrochloride and iodine in aqueous ammonia under ambient conditions, respectively. 2-Phenyl-1,3-oxazol-5(4 H)-ones **9a**, **b** and **10a**, **b** were synthesized via the condensation of compounds **5a**, **b** and **6a**, **b** with hippuric acid in acetic acid in 30–60% yield. When the methyl activated 7-methylazolopyrimidines **11a**, **b** were reacted with N-alkyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-6-carbaldehydes **6a**, **b**, 60–70% yield of triazolo/pyrazolo[1,5-a]pyrimidin-6-yl carboxylic acids **12a**, **b** were obtained. The condensation of 7-hydroxy-1,2,3,4-tetramethyl-1,2-dihydroquinoline **3 h** with dimethylacetylenedicarboxylate (DMAD) and ethyl acetoacetate afforded cyclic products **16** and **17**, respectively. The condensation reaction of 6-formyl-7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline **5e** with methylene-active compounds such as ethyl cyanoacetate/dimethyl-3-oxopentanedioate/ethyl acetoacetate/diethylmalonate/Meldrum's acid afforded 3-substituted coumarins **19** and **21** containing dihydroquinoline moiety. The pentacyclic coumarin **22** was obtained via the tandom condensation reaction of malononitrile with **5e** in the presence of a catalytic amount of piperidine in ethanol. The biological activities of the synthesized compounds were predicted using the PASS program. Based on the prognosis, compounds **13a**, **b**, and **14** exhibited a high likelihood of being active as inhibitors of gluconate 2-dehydrogenase, as well as possessing antiallergic, antiasthmatic, and antiarthritic properties, with a probability value (Pa) ranging from 0.849 to 0.870. Furthermore, it was discovered that compounds **7** and **8** tended to act as effective progesterone antagonists and displayed antiallergic, antiasthmatic, and antiarthritic effects (Pa = 0.276–0.827). Among the hydroquinolines containing coumarin moieties, compounds **17**, **19a**, and **19c** were predicted to be potent progesterone antagonists, with Pa values of 0.710, 0.630, and 0.615, respectively.

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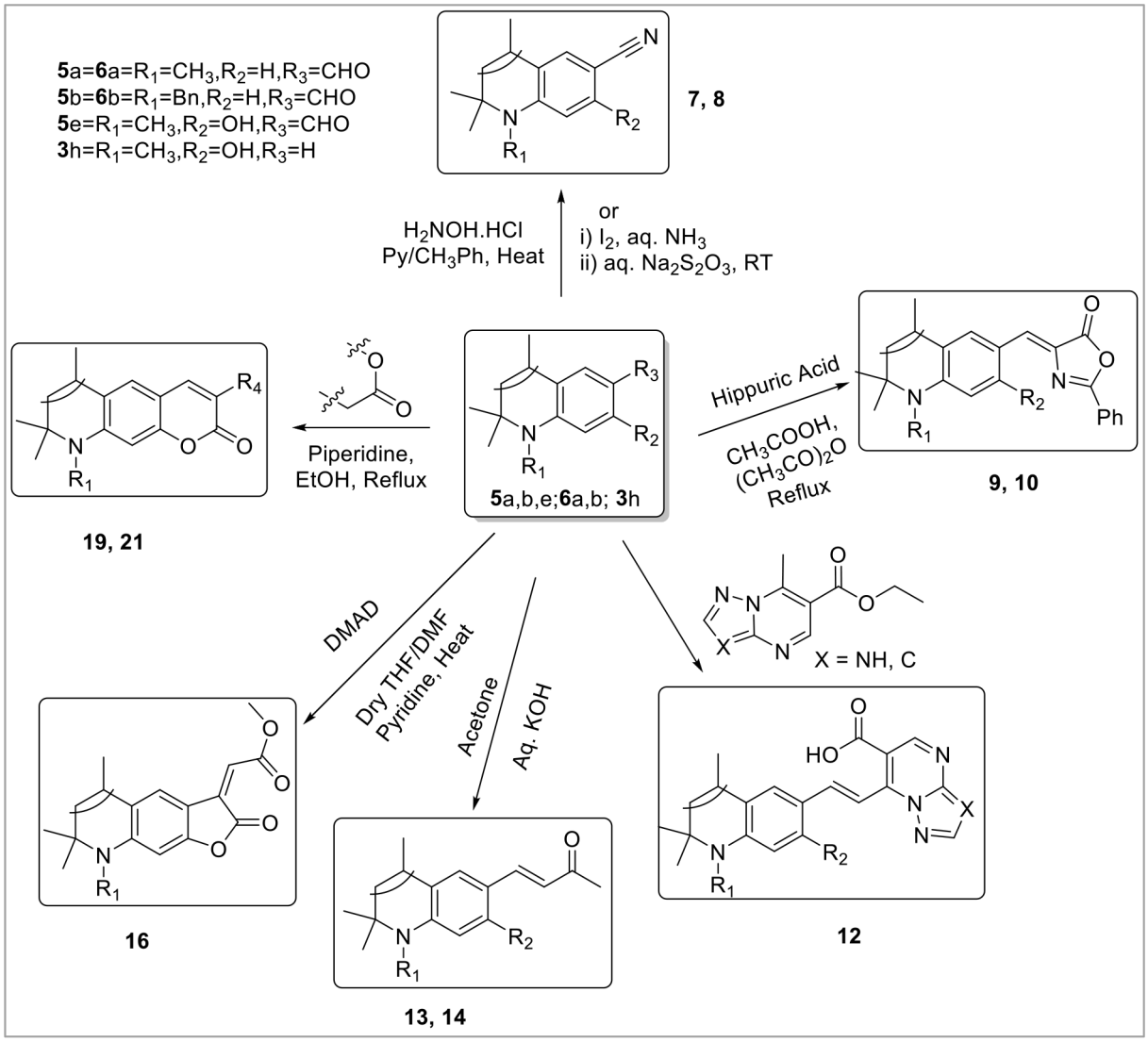
Keywords Heterocyclic compound, Hydroquinoline, Vilsmeier–Haack formylation, Quinolone

Graphical Abstract



Introduction

Currently, heterocyclic compounds have attracted a great deal of research interest because of their numerous significant medical and biological applications [1–4]. Quinoline derivatives are N-containing heterocyclic compounds that are known for their applications in medicinal chemistry as antimalarial, anti-inflammatory, anti-asthmatic, antibacterial, antihypertensive, and tyrosine kinase inhibiting agents [5–11]. Hence, interest in the synthesis of heterocyclic compounds containing a quinoline scaffold has increased tremendously [12–15].

Alkyl derivatives of 1,2-*H*-dihydroquinoline belong to a large group of quinoline derivatives and are known to have great practical importance [16–18]. 2,2,4-Trimethyl-1,2-*H*-dihydroquinoline is one of the most important representatives and is considered an essential and effective antioxidant in rubber technologies [19]. The methods used for the synthesis of 1,2-quinoline derivatives are based on cyclization reactions, well known as the Skraup reaction, and various Skraup-based modification reactions, such as Combes, Knorr, Doebner and Friedlander [20, 21]. Tetrahydroquinoline is one of the most important simple nitrogen heterocycles, being widespread and present in a broad variety of pharmacologically active compounds [22, 23].

It has been found that heterocyclic compounds containing hydroquinoline derivatives are the basis for a wide range of biological activities [24–26] and have

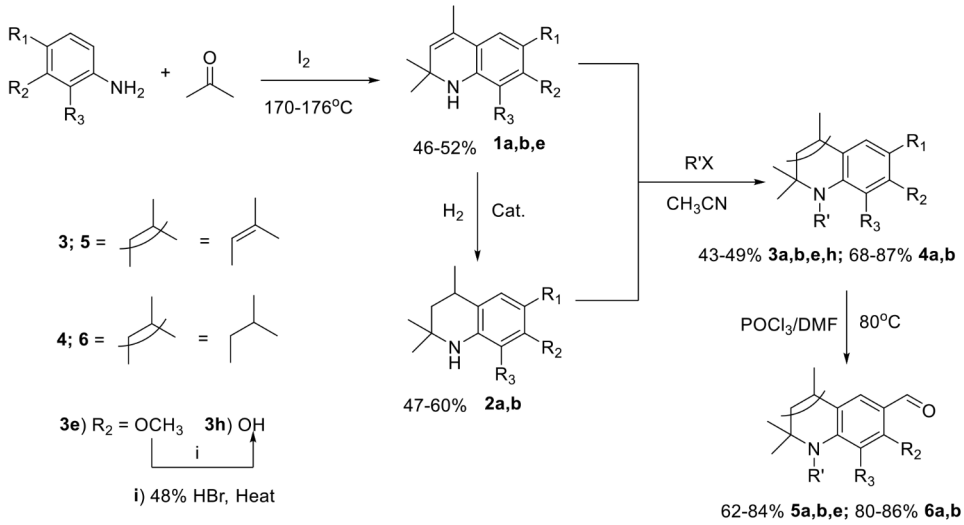


Fig. 1 Synthesis of 6(8)-Formyl-N-alkyl-2,2,4-trimethyl-1,2-di(1,2,3,4-tetra)hydroquinolines **5a, b, e** and **6a, b** via a VH formylation reaction

Table 1 Substituents of the synthesized 6(8)-formyl-N-alkyl-2,2,4-trimethyl-1,2-di(1,2,3,4-tetra)hydroquinolines **5** and **6**

Compound	*R'*	R1	R2	R3	Compound	*R'*	R1	R2	R3
3a	CH_3	H	H	H	5a	CH_3	CHO	H	H
3b	Bn	H	H	H	5b	Bn		H	H
3 h	CH_3	H	OH	H	5e	CH_3		OH	H
4a	CH_3	H	H	H	6a	CH_3		H	H
4b	Bn	H	H	H	6b	Bn		H	H
3e	CH_3	H	OCH_3	H	-	-	-	-	-

industrial applications, such as photosensitizers in solar cells [27–29] and additives to polymers [30, 31]. Hence, the construction of new heterocyclic assemblies and functionalization of hydroquinoline compounds have attracted the attention of synthetic organic chemists to further realize their versatile potential. Although methods for the synthesis of annulated heterocyclic systems containing 1,2-dihydro- and 1,2,3,4-tetrahydroquinoline moieties have been described in the literature, the problem of synthesizing new classes of linear and fused heterocyclic systems with hydroquinoline fragments, including those containing a chiral center in a certain configuration and various substituents, has not been completely solved.

In silico studies are becoming increasingly important in drug development from the initial stage to the approval of the drug. Using in silico tools to predict the biological activity and/or ADMET target for novel compounds has been widely used, as it helps in decreasing the cost and time related to drug discovery [32, 33].

Hence, in this study, the synthesis of new heterocyclic compounds containing hydroquinoline moieties such as carbonitriles, oxazolones, pyrazolo/triazolo[1,5-a]pyrimidines, and coumarins based on formylhydroquinolines was described (Fig. 1). Moreover, the pharmacological activity spectrum of the synthesized compounds was predicted by the in silico method using the Prediction of Activity Spectrum of Substances (PASS) computer program [34].

Results and discussion

Chemistry

K. Tianet et al. previously reported that the Vilsmeier-Haack (VH) formylation reaction of 1,2,2,4-tetramethyl-1,2-dihydroquinoline bearing an unsubstituted benzene ring proceeded with the formation of 1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbaldehyde as the only product [35]. In our previous publication [36] and PhD dissertation [37], we reported the synthesis of the starting materials hydroquinolinecarbaldehydes.

Hence in this work, the starting materials namely- N-alkyl-1,2-di (1,2,3,4-tetera)hydrohydroquinoline-6-carbaldehydes **5a**, **b**, **e** and **6a**, **b** and 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline **3 h** (Fig. 1; Table 1) were used to synthesize the desired compounds due to their structural favorability to synthesis the intended cyclic compounds.

Synthesis of N-alkyl-2,2,4-trimethylhydroquinolin-6-yl-carbonitriles **7** *and* **8**

One of the most important functional group transformations in organic synthesis is the conversion of aldehyde

functional groups into nitriles. Nitriles are a very versatile functional group that can be used as a starting material for the synthesis of a variety of biologically active compounds, such as thiazole derivatives, oxazolines, imidazoles, triazolopyrimidines, and benzamidines [38]. In the majority of cases, nitriles are obtained via the initial formation of aldoxime, which is obtained by the condensation of hydroxylamine hydrochloride with an aldehyde, which is then subjected to dehydration by a variety of reagents to give nitriles. There are also a few methods known for the one-step conversion of aldehydes into nitriles without separating the formed aldoxime [38–42].

Consequently, to further functionalize hydroquinoline carbaldehydes, we have endeavored to synthesize carbonitrile groups using two different methodologies. Initially, we employed a hydroxylamine hydrochloride, pyridine and toluene system with the azeotropic separation of water. The formation of pyridinium chloride facilitates aldoxime–nitrile conversion, making the presence of a dehydrating agent unnecessary. The reaction between 6-formyl-N-methyl-2,2,4-trimethyl-1,2-dihydroquinoline **5a** and $H_2NOH\ HCl/C_5H_5N/C_7H_8$ was completed within 3 h, yielding 48% 1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-nitrile **7** (Fig. 2). The absence of the aldehydic proton signal, which typically resonates between 9.88 and 10.22 ppm in the ^{1}H-NMR spectrum of the starting material, serves as evidence that the reaction has reached its completion (Figure S1). The second methodology we employed was the treatment of the respective aldehyde with iodine in aqueous ammonia at room temperature [42]. We speculated that the reaction proceeded via the oxidation of an aldimine with iodine to give an *N*-iodoaldimine intermediate, which eliminated an HI molecule in an ammonia solution to afford the nitrile product. This procedure was applicable in our case using 6-formyl-N-benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline **6b**, which afforded N-benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-6-nitrile **8** (Figure S2).

We have also attempted to synthesize an amide from 6-formyl-N-benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline **6b** via treatment with aqueous hydrogen peroxide at room temperature, reportedly resulting in the

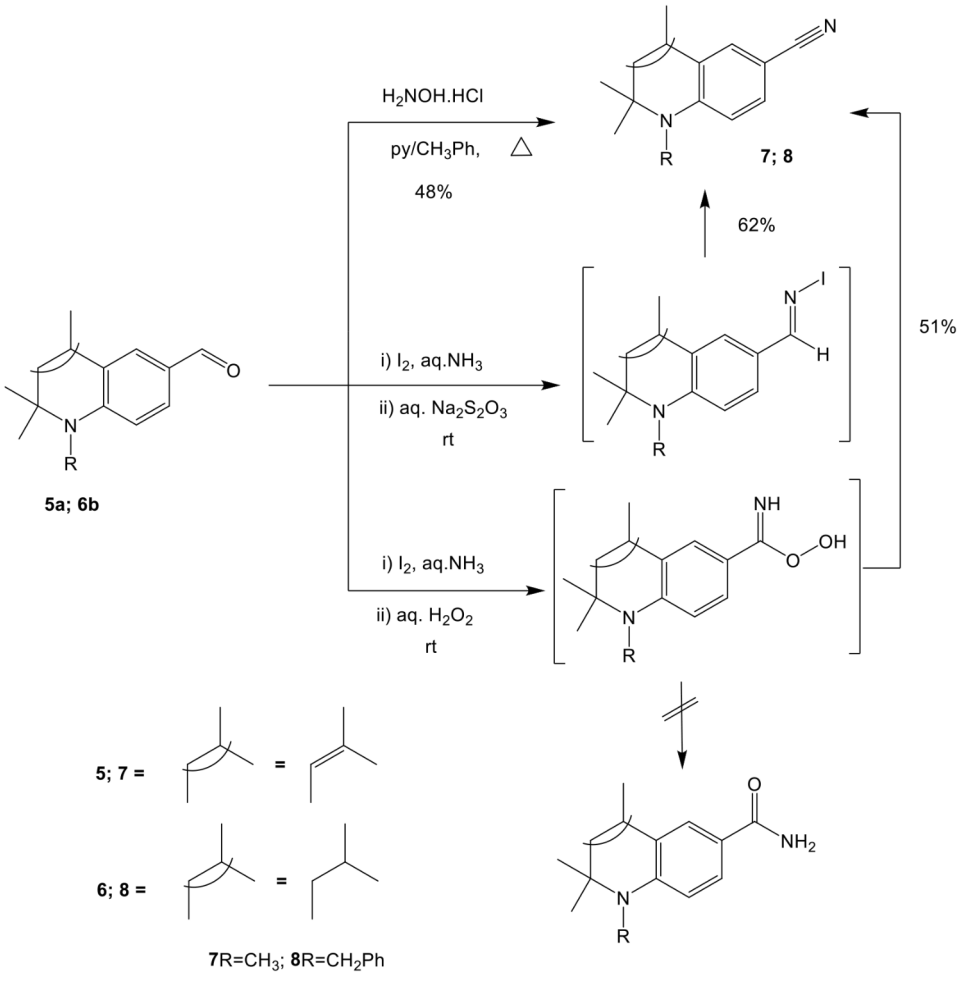


Fig. 2 Synthesis of 1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbonitrile **7** and 1-benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-6-carbonitrile **8**

intermediate formation of peroxocarboxamic acid [43]. However, a 4-h exposure to hydrogen peroxide at room temperature did not lead to the formation of the expected corresponding amide, yet the isolated compound was identified as the previously obtained nitrile **8**. This might be due to the antioxidant properties of the tetrahydroquinoline fragment.

Synthesis of 2-Phenyl-1,3-oxazol-5(4H)-ones **9** *and* **10**

Benzoxazole derivatives have been reported in the literature to possess anti-inflammatory, analgesic, antibacterial, trichomonacidal, anthelmintic, fungicidal, antiviral, and kinase inhibitory effects [44]. The method for the synthesis of 4-arylidene-2-aryloxazol-5-ones has been widely used in synthetic organic chemistry and consists of the condensation of aromatic/heterocyclic/aldehydes with hippuric acid or its heteroanalogues in glacial acetic acid in the presence of anhydrous sodium acetate [45]. In our case, we used a solution of acetic anhydride in acetic acid for the condensation of hydroquinolinecarbaldehydes **5a**, **b** and **6a**, **b** with hippuric acid, and we obtained 2-aryl-4-arylidene-5(4 H)-oxazolones **9a** and **b** and **10a** and **b** in moderate yields of 30–60% (Fig. 3 and Figure S3-S6). Sidhu and coworkers confirmed that the ^{1}H-NMR spectra of oxazolones show the deshielding influence of the cis-N=C-C_6H_5 moiety on the olefinic hydrogen atom, which shifts more downfield than when the olefinic hydrogen is cis to the carbonyl group [45]. In our case, the olefinic protons were found to resonate in the chemical shift range of δ=7.18–7.22 ppm, which is relatively more upfield than expected (nearly δ=7.60–7.85 ppm). Hence, based on the ^{1}H-NMR spectral data, these compounds were assigned the (Z) configuration at position 4.

Condensation of Hydroquinoline Carbaldehydes with Reagents Containing an Activated Methyl Group **12, 13, 14**

To search for potential biologically active compounds, we extended our work by reacting 6-formyl-N-alkyl-2,2,4-trimethyldihydroquinolines **5a**, **b**; **6a**, **b** with ethyl-7-methylpyrazolo/triazolo/[1,5-a]pyrimidine-6-carboxylates **11a**, **b** (Fig. 4).

The condensation of N-alkyl-1,2,3,4-tetrahydroquinoline-6-carbaldehydes **6a**, **b** with 7-methylazolopyrimidines **11a**, **b** occurs in the presence of the strong base potassium tert-butoxide, and the reaction product is accompanied by the hydrolysis of the ester group under the action of the water released during the condensation reaction. The broad downfield signals observed in the ^{1}H-NMR spectra at 13.31 and 13.50 ppm are assigned to the carboxylic acid protons of **12a** and **b**, respectively. The resulting 7-[(E)-2,2,4-trimethylhydroquinolin-6-ylidenemethyl]triazolo/pyrazolo[1,5-a]pyrimidin-6-yl carboxylic acids **12a**, **b** are red crystalline compounds that are sparingly soluble in water.

Analysis of the ^{1}H NMR spectra of carboxylic acids **12a** and **b** showed that they are trans isomers. This is evidenced by the fact that the coupling constant of the olefinic protons, which resonate as doublets at δ 8.23 and 9.05 ppm, is 16 Hz, which is a typical characteristic of trans-substituted alkenes (Figure S7-S8). The ^{13}C NMR spectrum of **12b** shows a signal at 166.78 ppm, which is assignable to the carbonyl carbon atom of the carboxylic acid functional group (Figure S9).

The condensation of N-alkylhydroquinoline-6-carbaldehydes **5a**, **b**, **6a**, and **b** with acetone proceeds under milder conditions and leads to the previously unknown 4-(2,2,4-trimethylhydroquinoline-6-yl)-3-buten-2-ones **13a**, **b** and **14**, which are promising synthons for synthesizing biologically active heterocyclic systems.

In the ^{1}H NMR spectra of compounds **13a**, **b**, and **14**, olefinic proton signals are observed in the form of two doublets in the regions of 6.50–6.54 and 7.44–7.49 ppm, and the value of the coupling constant is 16.4 Hz. These are the typical characteristics of 1,2-disubstituted alkenes with a trans configuration. On this basis, the compounds obtained were assigned the structure (E)-4-(1,2,2-trimethylhydroquinolin-6-yl)but-3-en-2-ones (Figure S10-S12).

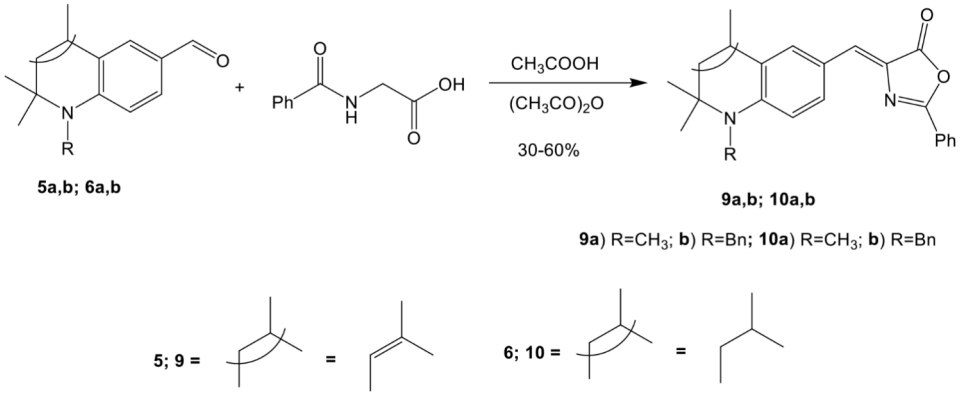


Fig. 3 Synthesis of 2-phenyl-1,3-oxazol-5(4 H)-ones **9** and **10**

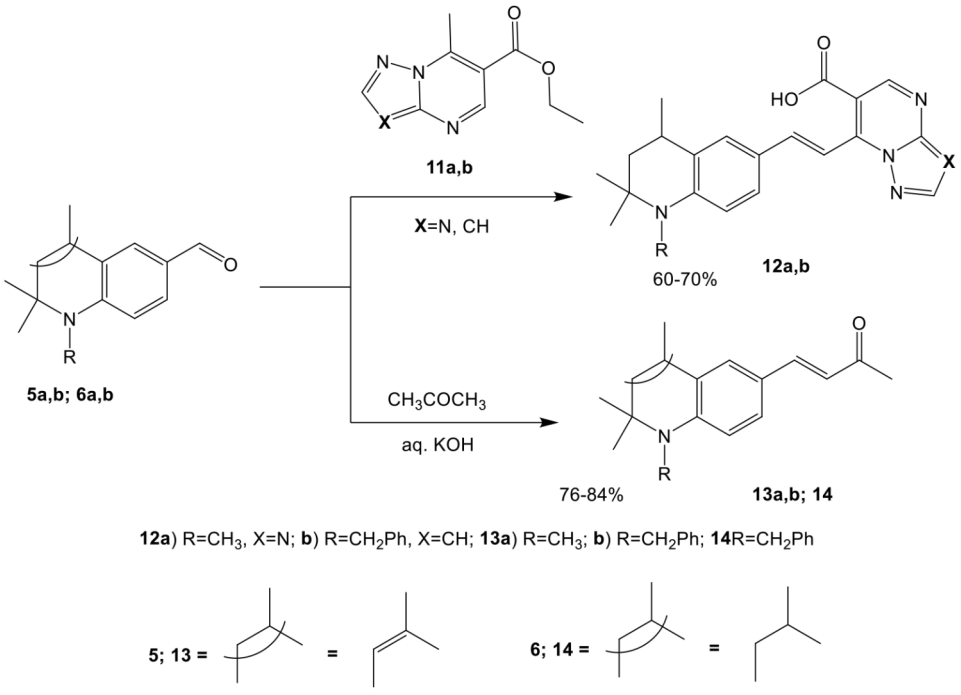


Fig. 4 Synthesis of triazolo/pyrazolo[1,5-a]pyrimidin-6-yl carboxylic acids **12a**, **b**

***Cyclizations of 7-Hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline* 3 h *and 7-Hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbaldehyde* 5e*, with Methylene-active compounds* 16, 17, 19, 21, *and* 22**

Dimethylacetylenedicarboxylate (DMAD) is an electron-deficient acetylenic compound that is widely used in cyclization reactions. With phenol, DMAD usually forms adducts, which are the result of the addition of a hydroxyl group under both basic and acid catalysis. However, with pyridine in the presence of sufficiently strong CH-acids, DMAD forms stable 1,4-diionic compounds of the betaine type [46]. The formation of such compounds leads to the reaction between DMAD and various phenols being terminated by α-methylene-γ-butyrolactones [47].

7-Hydroxy-1,2,3,4-tetramethyl-1,2-dihydroquinoline, **3 h**, at positions 6 and 8, exhibits pronounced CH acidity associated with the coordinated orientation of the –OH and disubstituted amine groups, which made it possible to prepare the corresponding cyclic derivatives under pyridine catalysis conditions. Since position 8 is relatively sterically hindered compared with position 6, only one cycling center remains, which is position 6 (Fig. 5).

The reaction of 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline **3 h** with DMAD in the presence of a catalytic amount of pyridine resulted in the formation of compound **16** with a reaction yield of 46%. The ^{1}H NMR spectrum of compound **16** displays a series of signals that correspond to the tricyclic structure of annulated α-methylene-γ-butyrolactone (Figure S13). A plausible reaction mechanism has been proposed, as depicted in Fig. 6. In the presence of pyridine, DMAD forms a betaine derivative of dimethyl maleate A, which is stabilized through interaction with the phenolic derivative **3 h**.

Subsequent intramolecular proton transfer leads to intermediate **E**, which decomposes with the regeneration of pyridine and the formation of a compound in which the phenolic hydroxyl group and one of the ester groups of the dimethyl maleate fragment are spatially closed. The subsequent intramolecular transesterification leads to the elimination of methanol and the formation of lactone **16**.

The Pechmann reaction is one of the most significant and simple methods for the synthesis of a variety of coumarin derivatives [48]. Pechmann condensation of 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline **3 h** with ethyl acetoacetate in the presence of a catalytic amount of sulfuric acid afforded 4,6,8,8,9-pentamethyl-8,9-dihydro-2 H-pyrano[3,2-g]quinolin-2-one **17** in 67% yield. The ^{1}H-NMR spectrum of **17** indicates that there are two singlet signals at δ 6.36 and 7.16 ppm, in which each signal is attributed to one proton that is assignable to the H-10 and H-5 aromatic protons, respectively. This indicated that the condensation reaction occurred at position 6, not at position 8 of the aromatic ring of **3 h**. If the condensation had occurred via position 8 of the ring, there would have been two ortho-substituted aromatic protons, which would have resulted in two doublet aromatic signals with each signal integrable to one proton with a J-value of nearly 7(8) Hz. The preference of position 6 over position 8 can also be rationalized by the

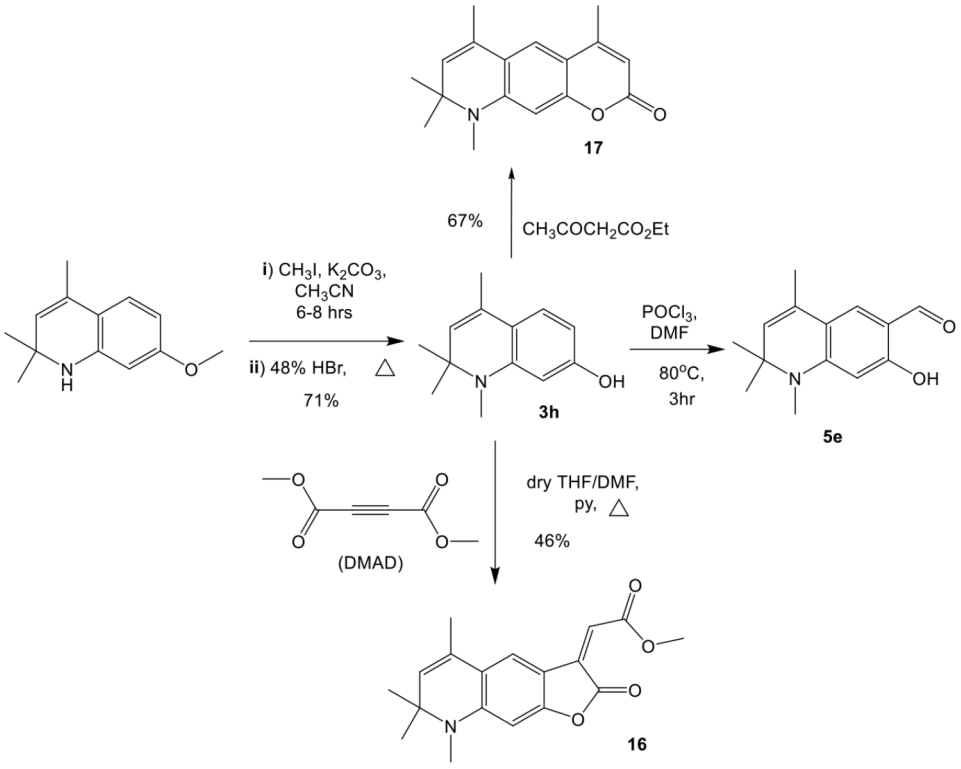


Fig. 5 Synthesis of methyl (Z)-2-(5,7,7,8-tetramethyl-2-oxo-7,8-dihydrofuro[3,2-g]quinolin-3(2 H)-ylidene)acetate **16** and 4,6,8,8,9-pentamethyl-8,9-dihydro-2 H-pyrano[3,2-g]quinolin-2-one **17**

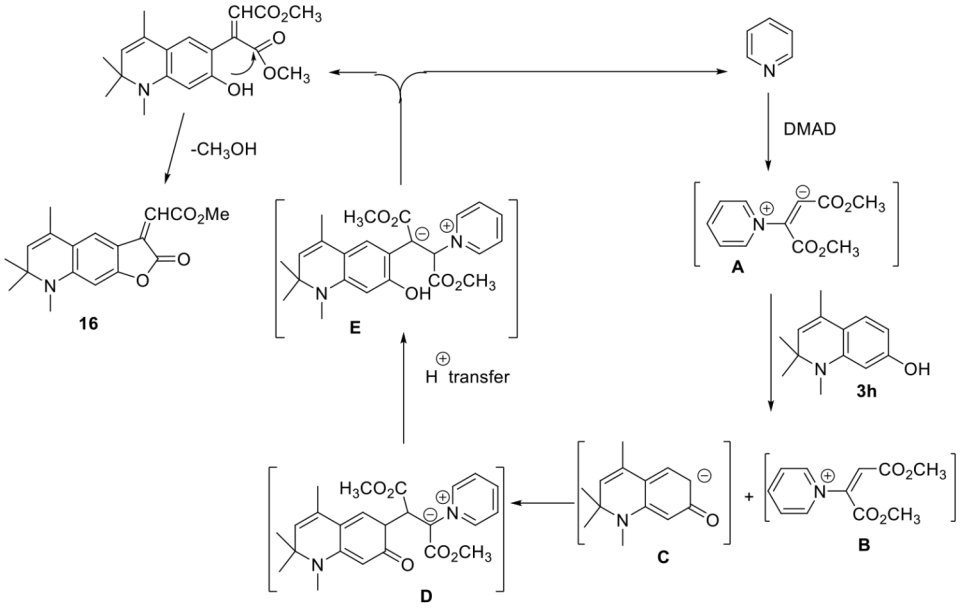


Fig. 6 Plausible reaction mechanism of methyl (Z)-2-(5,7,7,8-tetramethyl-2-oxo-7,8-dihydrofuro[3,2-g]quinolin-3(2 H)-ylidene)acetate **16**

relative steric hindrance of position 8 over position 6 of the aromatic ring of starting material **3 h** (Figure S14).

Coumarins are natural plant species with diverse biological activities, including anti-inflammatory, antitumor, antioxidant, and antidiabetic effects. Coumarin derivatives are also considered neuroprotective agents against oxidative stress and free radical generation [49]. Several methods have been employed for the synthesis of coumarins, such as Von Pechmann, Perkin, Knoevenagel, Reformatsky, Wittig, and Claisen rearrangement reactions [50].

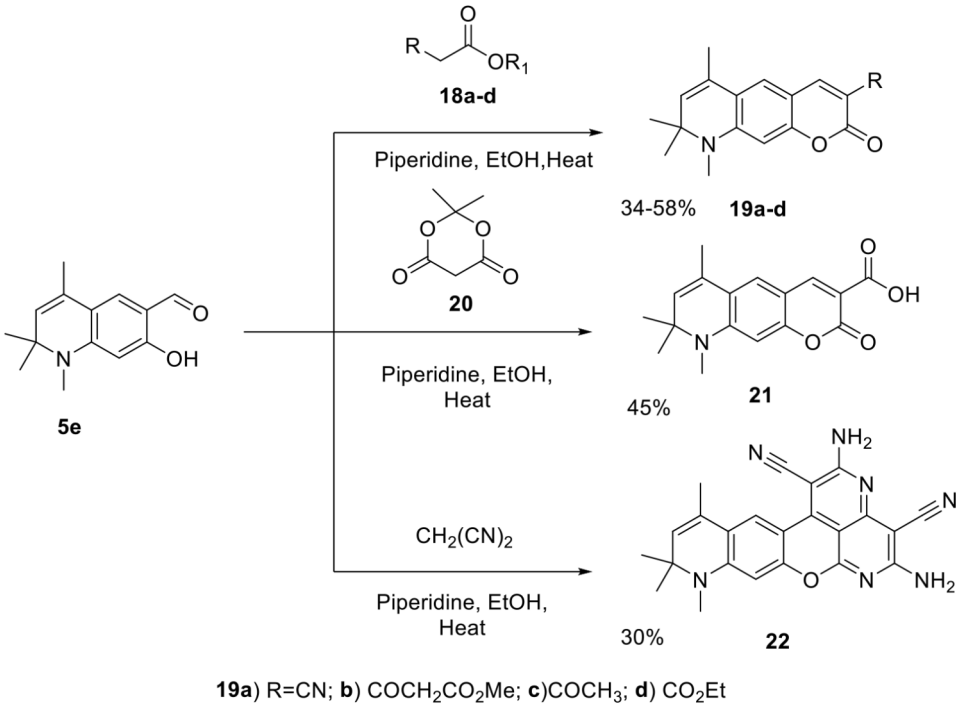


Fig. 7 Condensation reaction of 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbaldehyde **5e** with methylene-active compounds

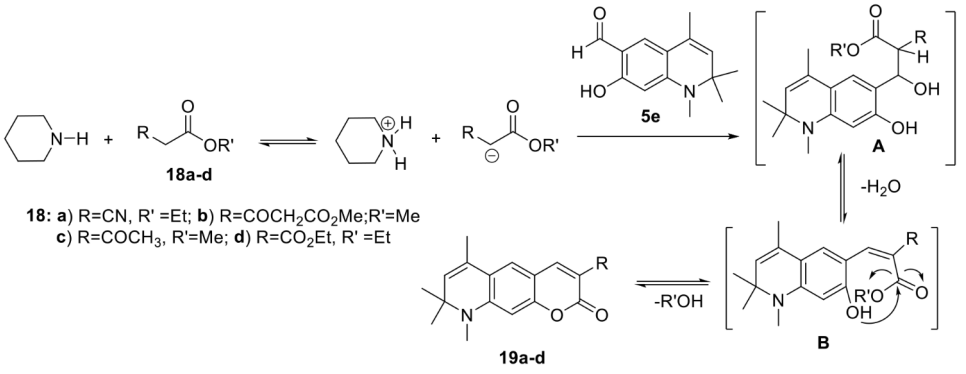


Fig. 8 Plausible reaction mechanism for the formation of 3-R-6,8,8,9-tetramethyl-8,9-dihydro-2 H-pyrano[3,2-g]quinolin-2-one **19a-d**

The condensation reaction of 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbaldehyde **5e** with methylene-active compounds, such as ethyl cyanoacetate (**18a**), dimethyl-3-oxopentanedioate (**18b**), ethyl acetoacetate (**18c**), and diethylmalonate (**18d**), in the presence of a catalytic amount of piperidine in ethanol afforded 3-substituted dihydroquinoline containing coumarins **19a-d** in 34–58% yields, as shown in Fig. 7.

A plausible reaction mechanism for the formation of 3-R-6,8,8,9-tetramethyl-8,9-dihydro-2 H-pyrano[3,2-g] quinolin-2-one **19a-d** is shown in Fig. 8. Common to all methylene-active compounds **18a-d** is the presence of an ester functional group, which enters into the intramolecular transesterification reaction of arylidene derivative **B**, which is formed after dehydration of Knoevenagel adduct **A**.

The ^{1}H-NMR spectrum of **19a** shows that there are two singlets, each corresponding to one proton at δ=6.44 and 8.48 ppm, which are attributed to the aromatic protons H-10 and H-5, respectively. The downfield signal at δ=7.25 ppm belongs to the olefinic proton H-4, which is beta to the electron-withdrawing cyano group. The mass spectrum of compound **19a** indicates that it has an $[M]^{+}$ value of 280.12 (Figure S15).

The ^{1}H-NMR spectrum of compound **19b** indicates that the signals at δ=8.53 and 6.43 ppm are attributed to the aromatic protons H-5 and H-10, respectively. The singlet signal at δ=3.96 ppm, which is attributed

to two protons, is attributed to the methylene protons, whereas the singlet signals at δ=3.62 ppm and 7.46 ppm are attributed to the methoxy and olefinic (H-4) protons (Figure S16). The ^{13}C-NMR spectrum of **19b** shows chemical shifts at 189.14, 168.48, and 160.07 ppm, which are assigned to the carbonyl carbon of ketone, lactone, and acyclic ester, respectively (Figure S17). The ^{1}H-NMR spectrum of compound **19c** indicated that the signals at δ=8.47 and 6.40 ppm were attributed to the aromatic protons H-5 and H-10, respectively. The singlet signal at δ=2.51, which is integrable to three protons, belongs to the acetyl protons (Figure S18).

The ^{1}H-NMR spectrum of compound **19d** indicates that there is a triplet signal at δ=1.28 ppm with a spin–spin coupling constant of 7.10 Hz, which is attributed to three protons that belong to the methyl protons of the ethoxy group. The quartet signal at δ=4.22 ppm and *J*=7.10 Hz is assignable to the methylene protons. The signals at δ=8.54 and 6.37 ppm are attributed to the aromatic protons H-5 and H-10, respectively (Figure S19).

Another highly reactive methylene compound is Meldrum's acid **20**, which we also used in the Knoevenagel condensation reaction with 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbaldehyde **5e**. In this case, arylidene derivative **B** (Fig. 9) undergoes the following transformation: the intramolecular nucleophilic attack of the phenol hydroxyl group on the carbonyl group of Meldrum's acid leads to the elimination of the acetone molecule and, after protonation, to the formation of acid **21**. K. A. Undale et al. reported the analogous synthesis of 3-carboxy coumarins by the potassium phosphate-catalyzed reaction of salicylaldehyde with Meldrum's acid [51].

The ^{1}H-NMR spectrum of compound **21** indicates that there is a downfield singlet signal at δ=7.39 ppm, which can be assigned to the olefinic proton H-4, which is beta to the electron-withdrawing carboxylic group (Figure S20).

Unlike other methylene-active compounds, malononitrile ($CH_2(CN)_2$) is capable of undergoing cascade condensation reactions with salicylaldehyde and its analogs. At the first stage of the cascade, 2-imino-2 H-chromene-3-carbonitrile is formed, the analog of which is intermediate **C** (Fig. 10). At an equimolar ratio of reactants and under conditions of catalysis with metal halides [52] or ion-exchange resins [53], this primary condensation product can be isolated; however, with an excess of malononitrile, it enters into further condensation.

2-Imino-2 H-chromene-3-carbonitrile, or its analog C, contains an electrophilic carbon atom at position 4, which reacts with N- and S-nucleophiles under mild conditions [54]. With an excess of malononitrile under basic catalysis, this reaction center enters into a Knoevenagel condensation with a C-nucleophile, which is the bridging carbon atom of malononitrile. As a result, intermediate D is formed, the further transformation of which requires the transformation of the nitrile group, for example, into an amidine group, which occurs when piperidine is the catalyst of the transformation.

However, the third equivalent of malononitrile [55] can act as a nucleophile, under the action of which F is formed, the next participant in the domino reaction, which is oxidized under the action of intermediate C or atmospheric oxygen to tetracyclic intermediate G, which is close to the final pentacyclic product **22**. Previously, a similar scheme was proposed for the interaction of salicylaldehyde with an excess of malononitrile [56].

The molecular ion peak [M]+at *m*/*z* 408, which was expected in the mass spectrum of compound **22**, was not observed. However, there are notable peaks at *m*/*z* (rel. intensity, %) 31(60), 44(100), 197(30), and 394(53). The heaviest peak at *m*/*z* 394 corresponds to [M-14]+. The broad singlet signal at δ=7.28 ppm in the ^{1}H-NMR spectrum of compound **22**, which can be attributed to a total of four protons, is attributed to the two amine groups (Figure S21).

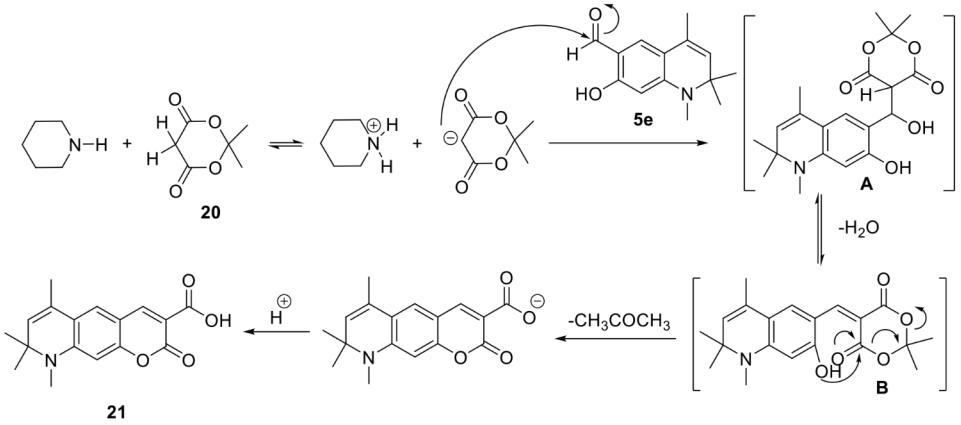


Fig. 9 Plausible reaction mechanism for the formation of 6,8,8,9-tetramethyl-2-oxo-8,9-dihydro-2 H-pyrano[3,2-g]quinoline-3-carboxylic acid **21**

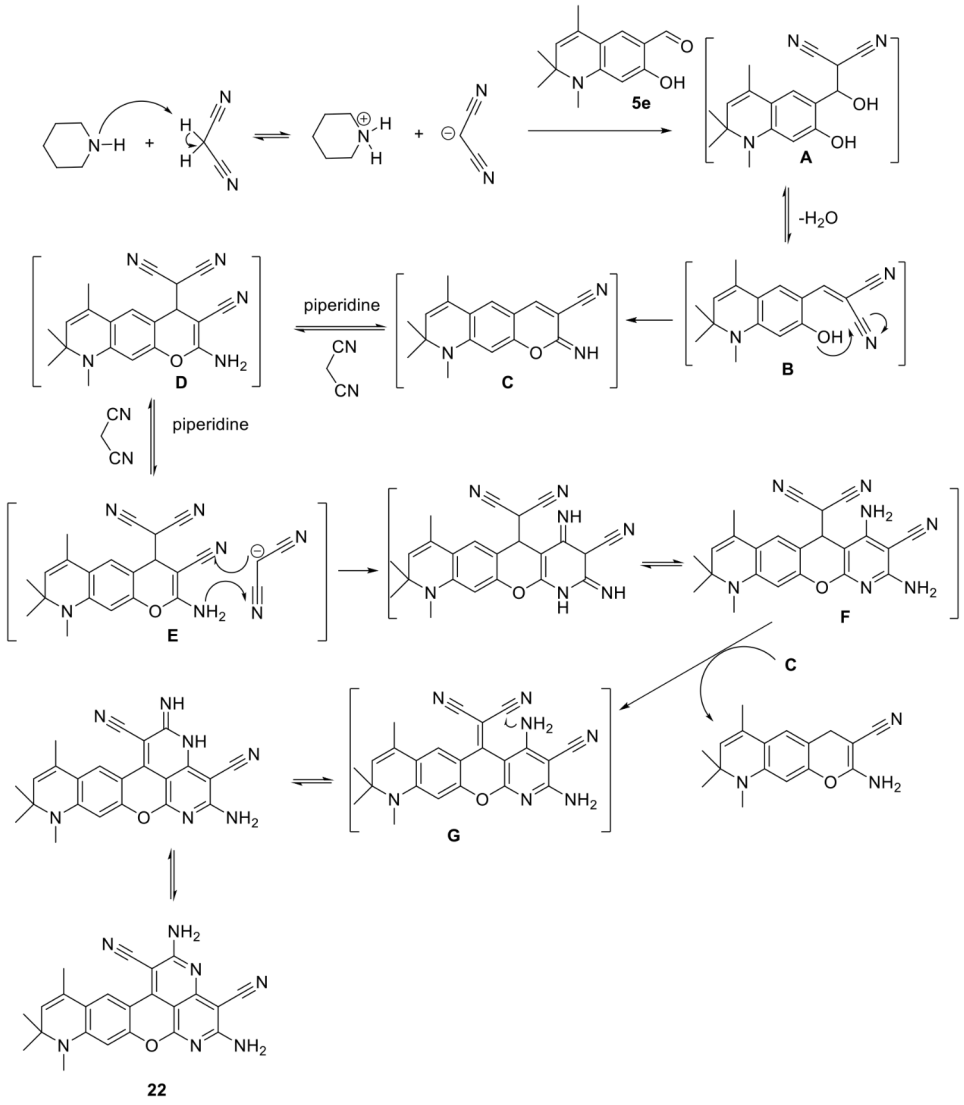


Fig. 10 Plausible reaction mechanism for the formation of 2,5-diamino-9,10,10,12-tetramethyl-9,10-dihydropyrido[4′,3′,2′:8,1]isochromeno[4,3-g]quinoline-1,4-dicarbonitrile **22**

In silico *studies*

PASS predicted activity spectrum of the synthesized compounds

The predicted PASS activity spectra of the test compounds (Table 2) showed that 4-aryl-substituted 3-buten-2-one compounds **13a**, **13b**, and **14** likely exhibit gluconate 2-dehydrogenase (acceptor) inhibitor activity, with Pa values ranging from 0.849 to 0.870. Whereas hydroquinoline carbonyl-containing compounds **7** and **8** have a propensity to act as good antiallergic, antiasthmatic, antiarthritic, and progesterone antagonists (Pa values of 0.276–0.827), phenyloxazolones **9**, **10(a, b)** have a low probability of being pharmaceutically active. Coumarins containing compounds **17**, **19a**, and **19c** were predicted to be good progesterone antagonists, with Pa values of 0.710, 0.63, and 0.615, respectively.

Experimental section

General

The starting materials of hydroquinolinecarbaldehydes were synthesized via the Vilsmeier–Haack formylation reaction of the corresponding N-alkylhydroquinolines. All other reacting materials were commercially accessible from Sigma–Aldrich suppliers. In this study, analytical grade reagents and solvents were used, except for the solvents THF and DMF, where further purifications were conducted. The reaction progress and purity of the individual synthesized compounds were monitored using precoated silica gel TLC plates (Merck TLC Silica gel 60 F254 plates, chloroform eluent, methanol, hexane, and ethyl acetate in various proportions), and visualization of the spots was carried out using a UV lamp. The ^{1}H and ^{13}C NMR spectra were recorded in deuterated dimethyl

Table 2 PASS-predicted activity of the test compounds

Compound	Probability of a Compound Being Active (Pa) or Inactive (Pi)									
	Antiallergic		Antiasthmatic		Antiarthritic		Progesterone Antagonist		Gluconate 2-Dehydrogenase (Acceptor) Inhibitor	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
7	0.546	0.025	0.471	0.032	0.422	0.071	0.827	0.001	-	-
8	0.691	0.009	0.63	0.013	0.626	0.025	0.276	0.003	-	-
9a	-	-	-	-	-	-	0.367	0.003	-	-
9b	0.509	0.027	0.385	0.053	0.455	0.06	0.18	0.004	-	-
10a	-	-	-	-	-	-	0.266	0.003	-	-
10b	0.287	0.101	-	-	0.311	0.126	0.212	0.007	-	-
12a	-	-	-	-	-	-	0.142	0.005	-	-
12b	0.571	0.018	0.533	0.023	0.616	0.026	0.06	0.017	-	-
13a	0.311	0.088	0.257	0.117	0.488	0.051	0.515	0.002	0.87	0.005
13b	0.707	0.008	0.694	0.009	0.771	0.01	0.217	0.004	0.869	0.005
14	0.543	0.022	0.462	0.033	0.641	0.023	0.145	0.005	0.849	0.008
16	0.556	0.02	0.42	0.042	0.379	0.088	0.506	0.002	0.441	0.254
17	0.423	0.046	0.267	0.11	0.29	0.139	0.71	0.002	-	-
19a	0.305	0.09	-	-	0.248	0.172	0.63	0.002	-	-
19b	0.247	0.134	-	-	-	-	0.394	0.003	-	-
19c	0.392	0.055	0.231	0.139	-	-	0.615	0.002	-	-
19d	0.227	0.109	-	-	-	-	0.429	0.003	-	-
21	0.28	0.106	-	-	0.21	0.205	0.493	0.002	-	-
22	-	-	-	-	0.372	0.091	0.305	0.003	-	-

sulfoxide (DMSO-d6) at 500.13 and 125.03 MHz, respectively, on a Bruker DRX instrument. Chemical shifts (δH) are recorded relative to the internal standard, tetramethyl silane (TMS) (see also Supplementary Materials). Mass spectra were recorded using Agilent Technologies LCMS6230B (CA; USA (chemical ionization, 200 eV)) and GCMS7890B (CA, USA) (carrier gas, EI, energy of ionization 70 eV) instruments. Melting points (mp) were measured uncorrected using a Stuart SMP30 (Hanan Advanced Technology Group Co., Ltd., Jinan; China) melting point instrument.

*Synthesis of 1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbonitrile***7**

1,2,2,4-Tetramethyl-1,2-dihydroquinoline-6-carbaldehyde 5a (2.0 g, 9.28 mmol) was added to a flask containing a solution of hydroxylamine hydrochloride (0.65 g, 9.28 mmol) in 2 mL of pyridine with continuous stirring. After 5 min of stirring using a magnetic stirrer, 10 mL of toluene was added, and the mixture was refluxed with a Dean–Stark trap. Upon completion of the process (TLC, hexane/ethyl acetate 8:2), the reaction mixture was cooled and filtered from the precipitate of pyridinium chloride, the filtrate was washed with distilled water and dried over anhydrous sodium sulfate, and the toluene was removed on a rotary evaporator. The product was recrystallized from aqueous acetonitrile.

Yield: 48%, Mp. 80–82 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.32 (s, 6 H, $(CH_3)_2$); 1.91 (s, 3 H, CH_3-C4); 2.81 (s, 3 H, N-CH_3); 5.43 (s, 1H, CH-C3); 6.54 (d, 1H, *J*=8.67, H-8); 7.23 (d, 1H, *J*=2.03, H-5); 7.41 (dd, 1H, *J*=8.62, *J*=2.04, H-7).

*Synthesis of 1-benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-6-carbonitrile***, 8**

a. Hydroquinolinecarbaldehyde **6b** (5 mmol) was treated with iodine (5.5 mmol) in a mixture of aqueous ammonia (25% 30 mL) and THF (5 mL) at room temperature for 8 h. During the reaction, the solution gradually became colorless as the iodine was consumed. An aqueous solution of $Na_2S_2O_3$ (1 M, 10 mL) was added dropwise to the reaction mixture, which was then stirred for 3 h and extracted with methylene chloride. The organic phase was washed with water, dried, and evaporated. The residue was recrystallized from aqueous acetonitrile.
b. Hydroquinolinecarbaldehyde **6b** (5 mmol) was treated with iodine (5.5 mmol) in a mixture of aqueous ammonia (25% 30 mL) and THF (5 mL) at room temperature for 8 h. During the reaction, the solution gradually became colorless as the iodine was consumed. An aqueous solution of H_2O_2 (35%, 3 mL) was added dropwise to the reaction mixture, which was then stirred for 4 h and extracted with methylene chloride. The organic phase was washed with water, dried, and evaporated. The residue was recrystallized from aqueous acetonitrile.

Yields: 62% (Method A) and 51% (Method B), Mp. 115–117 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.26 (s, 6 H, $(CH_3)_2$); 1.34 (d, 3 H, *J*=6.60, CH_3-C4); 1.63 (t, 1H, *J*=13.01, CH_{2A}-C3); 1.92 (dd, 1H, *J*=13.14, *J*=4.61, CH_{2B}-C3); 2.95 (m, 1H, CH-C4); 4.36 (d, 1H, *J*=18.12, Bn-Ha); 4.83 (d, 1H, *J*=17.99, Bn-Hb); 6.24 (d, 1H, *J*=8.78, arom.); 7.15–7.45 (m, 7 H, arom.).

*Synthesis of 2-Phenyl-1,3-oxazol-5(4H)-ones***9***and***10***(general procedure)*

A solution of the corresponding hydroquinolinecarbaldehyde **5** or **6** (3.4 mmol) in 3 mL of acetic acid was added dropwise to a stirred solution of hippuric acid (3.4 mmol), acetic anhydride (20 mL), and acetic acid. The reaction mixture was stirred at 70 °C for 3 h, poured into crushed ice, and stirred for 30 min. The product was extracted with chloroform and washed, the chloroform was evaporated using a rotary evaporator, and the residue was recrystallized from isopropanol.

(Z)-2-Phenyl-4-((1,2,2,4-tetramethyl-1,2-dihydroquinolin-6-yl)methylene)oxazol-5(4 H)-one (**9a**) Yield: 60%, Mp. 180–182 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.37 (s, 6 H, $C(CH_3)_2$); 2.02 (s, 3 H, CH_3-4); 2.91 (s, 3 H, N-CH_3); 5.48 (s, 1H, CH-3); 6.64 (d, 1H, *J*=8.8, arom.); 7.21 (s, 1H, CH-methylene); 7.60–8.20 (m, 7 H, arom.).

(Z)-4-((1-Benzyl-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)methylene)-2-phenyloxazol-5(4 H)-one (**9b)** Yield: 30%, Mp. 130–132 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.41 (s, 6 H, $C(CH_3)_2$); 2.08 (s, 3 H, CH_3-4); 4.73 (s, 2 H, CH_2-Bn); 5.57 (s, 1H, CH-3); 6.33 (d, *J*=8.86, 1H, arom.); 7.18 (s, 1H, CH-methylene); 7.21–8.20 (m, 12 H, arom.)

(Z)-2-Phenyl-4-((1,2,2,4-tetramethyl-1,2,3,4-tetrahydroquinolin-6-yl)methylene)oxazol-5(4 H)-one (**10a**) Yield: 41%, Mp. 140–142 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.25 (s, 3 H, $C(CH_3)_{2\ A}$), 1.32 (s, 3 H, $C(CH_3)_{2B}$); 1.39 (d, *J*=6.56, 3 H, CH_3-4); 1.45 (t, *J*=13.12, 1H, CH_{2A}-3); 1.89 (dd, *J*=13.12, *J*=4.20, 1H, CH_{2B}-3); 2.85 (m, 1H, CH-4); 2.92 (s, 3 H, N-CH_3); 6.67 (d, *J*=8.86, 1H, arom.); 7.22 (s, 1H, CH-methylene); 7.55–8.20 (m, 7 H, arom.).

(Z)-4-((1-Benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolin-6-yl)methylene)-2-phenyloxazol-5(4 H)-one (**10b**) Yield: 47%, Mp. 195–197 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.29 (s, 3 H, $C(CH_3)_{2\ A}$); 1.32 (s, 3 H, $C(CH_3)_{2B}$); 1.44 (d, *J*=6.54, 3 H, CH_3-4); 1.69 (t, *J*=13.05, 1H, CH_{2A}-3); 1.96 (dd, *J*=13.18, *J*=4.47, 1H, CH_{2B}-3); 3.03 (m, 1H, CH-4); 4.48 (d, *J*=18.19, 1H, CH_{2A}-Bn); 4.88 (d, *J*=18.21, 1H, CH_{2B}-Bn); 6.33 (d, *J*=8.91, 1H, arom.); 7.18 (s, 1H, CH-methylene); 7.20–8.30 (m, 12 H, arom.).

*Synthesis of (E)-7-[2,2,4-trimethylhydroquinolin-6-ylidenemethyl]triazolo(pyrazolo)[1,5-a]pyrimidin-6-ylcarboxylic acid***12***(general procedure)*

A mixture of 2 mmol of 6-formyltetrahydroquinoline (6a, b), 2 mmol of 7-methylazolopyrimidine (**11a**, **b)**, 2.2 mmol of potassium tert-butoxide, and 20 mL of methanol was refluxed for 6 h, cooled, and poured into 100 mL of 10% acetic acid solution. The precipitate formed was filtered off, washed with water, and after drying, it was recrystallized from ethanol.

(E)-7-(2-(1,2,2,4-Tetramethyl-1,2,3,4-tetrahydroquinolin-6-yl)vinyl)- [1, 2, 4]triazolo[1,5-a]pyrimidine-6-carboxylic acid (**12a**) Yield: 67%, Mp. 255–257 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.04 (d, 3 H, *J*=6.7, CH_3); 1.23 (s., 3 H, CH_3); 1.31 (s, 3 H, CH_3); 1.39–1,48 (m, 1H, CH_{2a}); 1,88 (dd, 1H, *J*=13.0, *J*=4.2 CH_{2b}); 2.80–2.86 (m, 1H, CH); 2,88 (s, 3H, N-CH_3); 6.45 (d, 1H, *J*=8.5, CH arom.); 7.42–7.46 (m, 2 H, CH arom.); 8.23 (d, 1H, *J*=16.0, CH vinyl); 8,81 (s, 1H, CHtriazol.); 9,05 (d, 1H, *J*=16.0, CH vinyl); 9,14 (s, 1H, CH pyrim.); 13,31 (s, 1H, COOH).

(E)-7-(2-(1-Benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolin-6-yl)vinyl)pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**12b**) Yield: 60%, Mp. 291–293 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.29 (s, 6 H, $(CH_3)_2$); 1.41 (d, 3 H, *J*=6.7, CH_3); 1.68 (t, 1H, *J*=12.8, CH_{2A}); 1.94 (dd, 1H, *J*=12.9, *J*=4.7, CH_{2B}); 3.02 (p, 1H, *J*=5.8, CH-4); 4.41 (d, 1H, *J*=18.0, Bn-CH_{2a}); 4.81 (d, 1H, *J*=18.0, Bn-CH_{2b}); 6.32 (d, 1H, *J*=8.6, CH arom.); 6.80 (d, 1H, *J*=2.4, CHpyraz.); 7.20–7.28 (m, 7 H arom.); 7.50 (s, 1H, CH arom.); 8.23 (d, 1H, *J*=16.0, CH vinyl); 8.43 (d, 1H, *J*=2.4, CH pyriaz.);8.87 (s, 1H, CH pyrim.); 9.05(d, 1H, *J*=16.0, CH vinyl); 13.50 (s, 1H, COOH).

^{13}C NMR (DMSO-d6, 125.03 MHz, δ(ppm): 19.69 (1C, CH_3); 24.90 (1C, CH_3); 26.65 (1C, CH_3); 28.75 (1C, CH); 45.58 (1C, CH_2); 48.38 (1C, CH_2); 55.14 (1C, $C(CH_3)_2$); 96.86 (1C, CHpyraz.); 109.20 (1C, C-6pyrim.); 110.27 (1C, CHbenz.); 112.63 (1C, CHvinyl); 123.42 (1C, CHbenz.); 125.96 (2C, o-CH phenyl); 126.46 (1C, p-CH phenyl); 126.57 (1C, Cpyraz-pyrim.); 126.96 (1C, Cbenz); 126.96 (1C, Cbenz); 127.72 (1C, C-COOH); 128.65 (2C, m-CHphenyl); 128.99 (1C, CHbenz); 139.60 (1C, CHpyraz.); 144.55 (1C, Cphenyl); 146.96 (1C, Cbenz); 147.57 (1C, Cbenz-pyr.); 149.64 (1C, CHvinyl; 150.12 (1C, Cpyrim.); 166.78 (1C, COOH).

*Synthesis of (E)-4-(2,2,4-trimethylhydroquinolin-6-yl)-3-buten-2-ones***13***and***14**

To a solution of 2 mol of the corresponding N-alkylhydroquinoline-6-carbaldehyde, **5**,**6**,15 mL of acetone was slowly added to a stirring solution of 1 g of potassium hydroxide in 20 mL of water. The solution was stirred at room temperature for 5 h. The precipitate formed was

filtered off, washed with water, dried, and recrystallized from a mixture of acetone and water (1:1).

(E)-4-(1,2,2,4-Tetramethyl-1,2-dihydroquinolin-6-yl) but-3-en-2-one (**13a**) Yield: 76%, Mp. 68–70°C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.30 (s, 6H, $(CH_3)_2$); 1.96 (s, 3H, CH_3-C'4); 2.26 (s, 3H, CH_3-CO-); 2.81 (s, 3H, N-CH_3); 5.40 (s, 1H, CH-DHQ); 6.52 (d, 1H, *J*=8.67, H'-8); 6.55 (d, 1H, *J*=16.14, CH-C3); 7.28 (d, 1H, *J*=2.14, H'5); 7.39 (dd, 1H, *J*=8.56, *J*=2.14, H'7); 7.49 (d, 1H, *J*=16.17, CH-C4).

(E)-4-(1-Benzyl-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)but-3-en-2-one (**13b**) Yield: 80%, Mp. 70–72 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.35 (s, 6 H, $(CH_3)_2$); 2.01 (s, 3 H, CH_3-C'4); 2.23 (s, 3 H, CH_3-CO-); 4.60 (s, 2 H, N-CH_2); 5.49 (s, 1H, CH-C'3); 6.22 (d, 1H, *J*=8.67, H'8); 6.50 (d, 1H, *J*=16.15, H-3); 7.15–7.35 (m, 7 H, arom.); 7.44 (d, 1H, *J*=16.17, H-4).

(E)-4-(1-Benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolin-6-yl)but-3-en-2-one (**14**) Yield: 84%, Mp. 100–102 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.25 (s, 3 H, $(CH_3)_{2\ A}$); 1.26 (s, 3 H, $(CH_3)_{2B}$); 1.37 (d, 3 H, *J*=6.59, CH_3-C'4); 1.62 (t, 1H, *J*=12.97, CH_{2A}-C'3); 1.91 (dd, 1H, *J*=13.05, *J*=4.61, CH_{2B}-C'3); 2.23 (s, 3 H, CH_3-CO-); 2.97 (m, 1H, CH-C'4); 4.33 (d, 1H, *J*=18.09, Bn-Ha); 4.80 (d, 1H, *J*=18.06, Bn-Hb); 6.21 (d, 1H, *J*=8.72, Arom.); 6.50 (d, 1H, *J*=16.12, H-3); 7.15–7.40 (m, 7 H, arom.); 7.45 (d, 1H, *J*=16.27, H-4).

*Synthesis of Methyl (Z)-2-(5,7,7,8-Tetramethyl-2-oxo-7,8-dihydrofuro[3,2-g]quinoline-3(2 H)-ylidene)acetate***16**

To a stirred solution of 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbaldehyde **5e** (5 mmol) and dimethylacetylenedicarboxylate (5 mmol), ml of anhydrous THF/DMF (4:1) was added dropwise to pyridine (0.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 min, and the mixture was refluxed until the reaction was complete. The solvent was removed on a rotary evaporator, and the residue was separated by column chromatography using n-hexane/ethyl acetate (4:1) as the eluent.

Yield: 46%, Mp. 195–197 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.35 (s, 6 H, $C(CH_3)_2$); 1.93 (s, 3 H, CH_3-5); 2.87 (s, 3 H, N-CH_3); 3.91 (s, 3 H, CH_3O-); 5.50 (s, 1H, CH-6); 6.38 (s, 1H, H-9); 6.43 (s, 1H, H-4); 7.63 (s, 1H, CH-2).

*Synthesis of 4,6,8,8,9-pentamethyl-8,9-dihydro-2 H-pyrano[3,2-g]quinolin-2-one***17**

A mixture of 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline **3 h** (1 mmol) and ethylacetoacetate (1.2 mmol) was heated to 80 °C in the presence of sulfuric acid (2 mL) until reaction completion. After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature and extracted with ethyl acetate (2X). The solution was concentrated, and the crude product was recrystallized from ethanol to afford pure 4-substituted hydroquinoline containing coumarin 4,6,8,8,9-pentamethyl-8,9-dihydro-2 H-pyrano[3,2-g]quinolin-2-one **17**.

Yield: 68%, Mp. 170–172 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.32 (s,6 H, $(CH_3)_2$); 1.98 (s, 3 H. C_6-CH_3); 2.35 (s, 3 H, C_4-CH_3); 2.83 (s, 3 H, N-CH_3); 5.46 (s, 1H, H-10); 5.94 (s, 1H, H-3); 6.36 (s, 1H, H-10 (arom.); 7.16 (s, 1H, H-5 (arom.)).

*General procedure for the synthesis of 6,8,8,9-tetramethyl-8,9-dihydropyrano[3,2-g]quinolin-2-ones***19, 21,** *and***22**

A mixture of 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbaldehyde **5e** (8.65 mmol), the corresponding active methylene compounds **18**, **20** and malononitrile (8.64 mmol/ 25.95 mmol in the case of synthesis **21**), and a few drops of piperidine in 10 mL of ethanol was boiled until the end of the reaction, after which the reaction mixture was cooled to room temperature and poured into 5 mL of chilled water. The resulting precipitate was filtered off and recrystallized from ethanol.

6,8,8,9-etramethyl-2-oxo-8,9-dihydro-2 H-pyrano[3,2-g]quinoline-3-carbonitrile (**19a**) Yield: 51%, Mp. 190–192 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.38 (s, 6 H, $C(CH_3)_2$); 1.94 (s, 3 H, CH_3-6); 2.94 (s, 3 H, N-CH_3); 5.54 (s, 1H, CH-7); 6.44 (s, 1H, H-10); 7.25 (s, 1H, H-5); 8.48 (s, 1H, H-4).

Methyl-3-oxo-3-(6,8,8,9-tetramethyl-2-oxo-8,9-dihydro-2 H-pyrano[3,2-g]quinolin-3-yl)propanoate (**19b**) Yield: 58%, Mp. 179–181 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.39 (s, 6 H, $C(CH_3)_2$); 1.95 (s, 3 H, CH_3-6); 2.95 (s, 3 H, N-CH_3); 3.62 (s, 3 H, CH_3O-); 3.96 (s, 2 H, CH_2); 5.53 (s, 1H, CH-7); 6.43 (s, 1H, H-10); 7.46 (s, 1H, CH-5); 8.53 (s, 1H, H-4).

^{13}C NMR (DMSO-d6, 125.03 MHz, δ(ppm): 18.19, 28.67, 28.74, 32.04, 48.11, 51.74, 58.41, 95.14, 107.83, 113.42, 119.97, 124.73, 125.09, 130.30, 148.15, 151.40, 158.81, 160.02, 168.48, 189.14.

3-Acetyl-6,8,8,9-tetramethyl-8,9-dihydro-2 H-pyrano[3,2-g]quinolin-2-one (**19c**) Yield: 39%, Mp. 200–202 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.38 (s, 6 H, $C(CH_3)_2$); 1.94 (s, 3 H, CH_3-6); 2.51 (s, 3 H, CH_3-CO-); 2.93 (s, 3 H, N-CH_3); 5.51 (s, 1H, CH-7); 6.40 (s, 1H, H-10); 7.42 (s, 1H, H-5); 8.47 (s, 1H, H-4).

Ethyl 6,8,8,9-tetramethyl-2-oxo-8,9-dihydro-2 H-pyrano[3,2-g]quinoline-3-carboxylate (**19d**) Yield: 34%, Mp. 130–132 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.28 (t, 3 H, *J*=7.1, CH_3CH_2O-); 1.37 (s, 6 H, C(CH3)2); 1.94 (s, 3 H, CH_3-6); 2.91 (s, 3 H, N-CH_3); 4.22 (q, 2 H, *J*=7.1, CH_3CH_2O-); 5.58 (s, 1H, CH-7); 6.37 (s, 1H, H-10); 7.41 (s, 1H, CH-5); 8.54 (s, 1H, H-4).

6,8,8,9-. Tetramethyl-2-oxo-8,9-dihydro-2 H-pyrano[3,2-g]quinoline-3-carboxylic acid (**21**) Yield: 45%, Mp. > 250 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.36 (s, 6 H, $C(CH_3)_2$); 1.94 (s, 3 H, CH_3-6); 2.90 (s, 3 H, N-CH_3); 5.49 (s, 1H, CH-7); 6.39 (s, 1H, H-10); 7.39 (s, 1H, CH-5); 8.51 (s, 1H, H-4).

2,5-. Diamino-9,10,10,12-tetramethyl-9,10-dihydropyrido[4′,3′,2′:8,1]isochromeno[4,3-g]quinoline-1,4-dicarbonitrile (**22**) Yield: 30%, Mp. > 250 °C. ^{1}H NMR (DMSO-d6, 500.13 MHz, δ(ppm), *J* (Hz)): 1.38 (s, 6 H, $C(CH_3)_2$); 1.95 (s, 3 H, CH_3-12); 2.89 (s, 3 H, N-CH_3); 5.51 (s, 1H, CH-11); 6.37 (s, 1H, H-8); 7.28 (bro. s, 4 H, 2xNH2); 8.44 (s, 1H, H-13). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 394 $[M-14]^+$ (53), 197 (30), 44 (100), 31 (60).

In silico *PASS prediction*

Prediction of the activity spectra of substances (PASS) was used to predict the pharmacological activities of the synthesized compounds. The synthesized compounds were first converted into the SMILES format using ChemBioDraw 14.0 by PerkinElmer, Inc., and then predicted using the PASS online web tool http://www.way2drug.com/PASSOnline/predict.php (Way2Drug.com © 2011–2024 • Version 2.0), URL accessed on the 20th of July 2023). PASS indicates the probable activity (Pa) and probable inactivity (Pi) of 'drug-like' substances.

Conclusion

In this study, heterocyclic compounds containing hydroquinoline fragments, such as carbonitriles, oxazolones, azolo[1,5-a]pyrimidines, and coumarins, were synthesized.

The potential biological activities of the synthesized compounds were predicted using the PASS program. According to the prognosis, compounds **13a**, **13b**, and **14** are most likely to have inhibitory effects on gluconate dehydrogenase, as well as antiarthritic, antiallergic, and antiasthmatic effects. It was also found that hydroquinoline carbonyl compounds **7** and **8** tend to act as good progesterone antagonists and have antiallergic, antiasthmatic, and antiarthritic effects, with Pa values ranging from 0.276 to 0.827. Among the coumarin moieties containing hydroquinolines, compounds **17**, **19a**, and **19c** were predicted to be good progesterone antagonists, with Pa values of 0.710, 0.630, and 0.615, respectively.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13065-024-01267-3.

Supplementary Material 1

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Author contributions
GMM developed the methodology, performed the experimental section, collected data, interpreted data, and wrote the draft manuscript. KSS conceptualized the study, validated the work, supplied the necessary reagents and materials, and supersized the entire work. All authors have read and agreed to the published version of the manuscript.

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Data availability
All spectra for the compounds' characterization are provided as Additional material. Similarly, the raw data are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Kabir E. Uzzaman M. A review on biological and medicinal impact of heterocyclic compounds. Results Chem. 2022;4:100606. https://doi.org/10.1016/j.rechem.2022.
2. Al-Mulla. A. A review: Biological Importance of Heterocyclic compounds. Der Pharma Chem. 2017;13(9):141–7. http://www.derpharmachemica.com/archive.html.
3. Qadir T, Amin A, Sharma PK, Jeelani I, Abe H. A review on medicinally important heterocyclic compounds. Open Med Chem J. 2022;16(1):1–16. https://doi.org/10.2174/18741045-v16-e2202280.
4. Mermer A, Keles T. Sirin Y. recent studies of nitrogen containing heterocyclic compounds as novel antiviral agents: a review. Bioorg Chem. 2021;114:105076. https://doi.org/10.1016/j.bioorg.2021.
5. Chen YL, Fang KC, Sheu JY, Hsu SL. Tzeng CC. Synthesis and antibacterial evaluation of certain quinolone derivatives. J Med Chem. 2001;44:105076. https://doi.org/10.1021/jm0100335.
6. Yadav P. Shah K. Quinolines, a perpetual, multipurpose scaffold in medicinal chemistry. Bioorg. Chem. 2021;109:104639. https://doi.org/10.1016/j.bioorg.2021.104639.
7. Matada BS, Pattanashettar R. Yernale NG. A comprehensive review on the biological interest of quinoline and its derivatives. Bioorg Med Chem. 2021;32:115973. https://doi.org/10.1016/j.bmc.2020.115973.
8. Dib K. Ennibi OK, Alaoui, K, Cherrah Y, Filali-Maltouf A. Antibacterial activity of plant extracts against periodontal pathogens: a systematic review. J Herb Med. 2021;29:100493. https://doi.org/10.1016/j.hermed.2021.100493.
9. Tiglani D, Salahuddin S, Mazumder A, Kumar R, Mishra S. Synthetic approaches and biological activities of quinoline derivatives: a review. Int J Pharm Res. 2021;13(01):4605–13. https://doi.org/10.31838/ijpr/2021.13.01.582.
10. Mishra S, Salahuddin, Kumar R, Majumder A, Kumar A, Singh C, Tiglani D. Updates on synthesis and biological activities of quinoline derivatives: a review. Int J Pharm Res. 2021;13. https://doi.org/10.31838/ijpr/2021.13.01.472.

11. Kaur T. Bhandari DD. Annotated review on various Biological activities of Quinoline Molecule. Biointerface Res Appl Chem. 2023;13:355. https://doi.org/10.33263/BRIAC134.355.
12. Patel A, Patel S, Mehta M, Patel Y, Patel R, Shah D, Patel D, Shah U, Patel M, Patel S, et al. A review on synthetic investigation for quinoline- recent green approaches. Green Chem Lett Rev. 2022;15:337–72. https://doi.org/10.1080/17518253.2022.2064194.
13. Marella A, Tanwar OP, Saha R, Ali MR, Srivastava S, Akhter M, Shaquiquzzaman M, Alam MM. Quinoline: a versatile heterocyclic. Saudi Pharm J. 2013;21:1–12. https://doi.org/10.1016/j.jsps.2012.03.002.
14. Yang JM, Wu L, Fang D, Cao J, Zhou YJ, Wang XS. Iodine-catalyzed Povarov reaction for synthesis of cyclobuta[c]quinoline derivatives. Res Chem Intermed. 2014;40:1103–13. https://doi.org/10.1007/s11164-013-1024-4.
15. Ghoshal A. Yugandhar D, Nanubolu, JB, Srivastava AK. An efficient one-pot synthesis of densely functionalized fused-quinolines via sequential Ugi4CC and acid-mediated povarov-type reaction. ACS Comb Sci. 2017;19:600–8. https://doi.org/10.1021/acscombsci.7b00095.
16. Medvedeva SM, Plaksina ME, Shikhaliev KS. The synthesis of 6-R-2,2,4-trimethyl-1,2-dihydroquinoline- and 6-R-4-R'-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-8-carboxylic acids—the structural analogs of helquinoline. J Org Pharm Chem. 2017;13:21–5. https://doi.org/10.24959/ophcj.15.847.
17. Durgadas SK, Chatare V, Mukkanti K, Pal S. Ceric Ammonium Nitrate: an efficient Catalyst for one-Pot synthesis of 2,2,4-Trimethyl-1,2-dihydroquinolines. Lett Org Chem. 2010;7:306–10. https://doi.org/10.2174/157017810791130586.
18. Patel MM, Patel LJ. Design, synthesis, molecular docking, and antibacterial evaluation of some novel flouroquinolone derivatives as potent antibacterial agent. Sci World J. 2014;2014(897187). https://doi.org/10.1155/2014/897187.
19. Nowicki J, Jaroszewska K, Nowakowska-Bogdan. E, Szmatoła M, Iłowska J. Synthesis of 2,2,4-trimethyl-1,2- H -dihydroquinoline (TMQ) over selected organosulfonic acid silica catalysts: selectivity aspects. Mol Catal. 2018;454:94–103. https://doi.org/10.1016/j.mcat.2018.05.016.
20. Dadhania H, Raval D. Dadhania A. A highly efficient and Solvent-Free Approach for the synthesis of Quinolines and Fused Polycyclic quinolines Catalyzed by Magnetite nanoparticle-supported Acidic Ionic Liquid. Polycycl Aromat Compd. 2021;41:440–53. https://doi.org/10.1080/10406638.2019.1595057.
21. Dabiri M, Azimi SC, Bazgir A. An efficient and rapid approach to quinolines via Friedländer synthesis catalyzed by silica gel supported sodium hydrogen sulfate under solvent-free conditions. Monatshefte Für Chem -Chem Mon. 2007;138:659–61. https://doi.org/10.1007/s00706-007-0678-2.
22. Muthukrishnan I, Sridharan V. Menéndez JC. Progress in the Chemistry of Tetrahydroquinolines. Chem Rev. 2019;119:5057–191. https://doi.org/10.1021/acs.chemrev.8b00567.
23. Katritzky AR, Rachwal S. Rachwal B. recent progress in the synthesis of 1,2,3,4-tetrahydroquinolines. Tetrahedron. 1996;52:15031–70. https://doi.org/10.1016/S0040-4020(96)00911-8.
24. Saadeh HA, Sweidan KA. Mubarak MS. recent advances in the synthesis and biological activity of 8-hydroxyquinolines. Molecules. 2020;25:4321. https://doi.org/10.3390/molecules25184321.
25. Kljun J, León. IE, Peršič Š, Cadavid-Vargas JF, Etcheverry SB, He W, Bai Y, Turel I. Synthesis and biological characterization of organoruthenium complexes with 8-hydroxyquinolines. J Inorg Biochem. 2018;186:187–96. https://doi.org/10.1016/j.jinorgbio.2018.05.009.
26. Heiskanen JP, Omar WAE, Ylikunnari MK, Haavisto KM, Juan MJ, Hormi OEO. Synthesis of 4-alkoxy-8-hydroxyquinolines. J Org Chem. 2007;72:920–2. https://doi.org/10.1021/jo062175i.
27. Zhang L, Wen G, Xiu Q, Guo L, Deng J. Zhong C. Synthesis and photovoltaic properties of polymeric metal complexes containing 8-hydroxyquinoline as dye sensitizers for dye-sensitized solar cells. J Coord Chem. 2012;65:1632–44. https://doi.org/10.1080/00958972.2012.677532.
28. Chen R, Yang X, Tian H, Wang X, Hagfeldt A, Sun L. Effect of tetrahydroquinoline dyes structure on the performance of organic dye-sensitized solar cells. Chem Mater. 2007;19:4007–15. https://doi.org/10.1021/cm070617g.
29. Tian H, Yang X, Cong J, Chen R, Teng C, Liu J, Hao Y, Wang L, Sun L. Effect of different electron donating groups on the performance of dye-sensitized solar cells. Dye Pigment. 2010;84:62–8. https://doi.org/10.1016/j.dyepig.2009.06.014.
30. Abd El-Ghaffar. MA, Shaffei KA, Abdelwahab N. Evaluation of some conducting polymers as novel antioxidants for rubber vulcanizates. Int J Polym Sci. 2014;2014:893542. https://doi.org/10.1155/2014/893542.
31. Šmejkal F. Číhová A, Popl M, Novák J. The analysis of polymeric 2,2,4-trimethyl-1,2-dihydroquinoline. Die Angew Makromol Chem. 1980;88:135–47. https://doi.org/10.1002/apmc.1980.050880111.
32. Saldanha L, Langel. Ü, Vale N. In Silico studies to support vaccine. Dev Pharm. 2023;15:654. https://doi.org/10.3390/pharmaceutics15020654.
33. Ratra S, Pant B, Roy K, Manohar S, Kumar P, Singh S, Tumba K, Kumari K, Singh P. A review on synthesis of antiviral drugs, in silico studies and their toxicity. J Indian Chem Soc. 2023;100:100936. https://doi.org/10.1016/j.jics.2023.100936.
34. Matin MM, Bhattacharjee. SC, Chakraborty P, Alam MS. Synthesis, PASS predication, *in vitro* antimicrobial evaluation and pharmacokinetic study of novel n-octyl glucopyranoside esters. Carbohydr Res. 2019;485:107812. https://doi.org/10.1016/j.carres.2019.107812.
35. Tian K, Hu D, Hu R, Wang S, Li S, Li Y, Yang G. Multiple fluorescence ΔCIE and ΔRGB codes for sensing volatile organic compounds with a wide range of responses. Chem Commun. 2011;47:10052. https://doi.org/10.1039/c1cc13056k.
36. Manahelohe GM. Potapov AY, Shikhaliev KS. Synthesis of new hydroquinolinecarbaldehydes. Russ Chem Bull. 2016;65:1145–7. https://doi.org/10.1007/s11172-016-1427-7.
37. Manahelohe GM. Synthesis of New Heterocyclic Systems based on Formyl Hydroquinoline. Ph.D. Dessertation, Voronezh State University, Moscow, Russian Federation. 2015.
38. Wang EC, Lin GJ. ChemInform Abstract: a New One-Pot Method for the Conversion of aldehydes into Nitriles using. Hydroxyamine Phthalic Anhydride ChemInform. 2010;29:4047–50. https://doi.org/10.1002/chin.199833138.
39. Wang EC, Lin GJ. A new one pot method for the conversion of aldehydes into nitriles using hydroxyamine and phthalic anhydride. Tetrahedron Lett. 1998;39:4047–50. https://doi.org/10.1016/S0040-4039(98)00654-6.
40. Sampath Kumar HM. Subba Reddy BV, Tirupathi Reddy P, Yadav JS. Efficient one-pot preparation of nitriles from aldehydes using N- methyl-pyrrolidone. Synthesis 1999;586–587. https://doi.org/10.1055/s-1999-3450
41. Sosnovsky G, Krogh JA. Umhoefer SG. A one-flask conversion of aldehydes to nitriles using hydroxylamine hydrochloride and selenium dioxide. Synthesis 1979;*1979*:722–724. https://doi.org/10.1055/s-1979-28813
42. Talukdar S, Hsu JL, Chou TC. Fang JM. Direct transformation of aldehydes to nitriles using iodine in ammonia water. Tetrahedron Lett. 2001;42:1103–5. https://doi.org/10.1016/S0040-4039(00)02195-X.
43. Shie JJ, Fang JM. Direct conversion of aldehydes to amides, tetrazoles, and triazines in aqueous media by one-pot tandem reactions. J Org Chem. 2003;68:1158–60. https://doi.org/10.1021/jo026407z.
44. El-Hady HA, Abubshait SA. Synthesis and anticancer evaluation of imidazolinone and benzoxazole derivatives. Arab J Chem. 2017;10:3725–31. https://doi.org/10.1016/j.arabjc.2014.05.006.
45. Rao YS. Filler R. Geometric Isomers of 2-Aryl(Aralkyl)-4-arylidene(alkylidene)-5(4 *H*)-oxazolones. Synthesis 1975; *1975*:749–764. https://doi.org/10.1055/s-1975-23919
46. Yavari I, Anary-Abbasinejad M, Alizadeh A. A simple synthesis of stable 1,4-Diionic Pyridinium Betaines. ChemInform. 2003;34:749–64. https://doi.org/10.1002/chin.200308130.
47. Yavari I, Hossaini Z. Synthesis of fused α-methylene-γ-butyrolactone derivatives through pyridine-induced addition of phenols to dimethyl acetylenedicarboxylate. Tetrahedron Lett. 2006;47:4465–8. https://doi.org/10.1016/j.tetlet.2006.04.042.
48. De SK. Gibbs RA. An efficient and practical Procedure for the synthesis of 4-Substituted coumarins. Synthesis. 2005;2005:1231–3. https://doi.org/10.1055/s-2005-865282.
49. Hirbod K, Jalili-Baleh L, Nadri H, Ebrahimi SES, Moradi A, Pakseresht B, Foroumadi A, Shafiee A. Khoobi M. Coumarin derivatives bearing benzoheterocycle moiety: synthesis, cholinesterase inhibitory, and docking simulation study. Iran. J Basic Med Sci. 2017;20:631–8. https://doi.org/10.22038/ijbms.2017.8830.
50. Alheety KA, Jamel NM. Ahmed BJ. Synthesis of coumarin by Pechman reaction—A. Rev J Pharm Sci Res. 2019;11:3344–7.
51. Undale KA, Gaikwad DS, Shaikh TS, Desai UV, Pore DM. Potassium phosphate catalyzed efficient synthesis of 3-carboxycoumarins. Indian J Chem -Sect B Org Med Chem. 2012;51:1039–42.
52. Prajapati D. Sandhu JS. Cadmium iodide as a new catalyst for Knoevenagel condensations. J Chem Soc Perkin Trans 1. 1993;6:739–40. https://doi.org/10.1039/p19930000739.

53. Mhiri C. El Gharbi R, Le Bigot Y. Polymer supported reagents: novel methodology for selective and general synthesis of iminocoumarins. Synth Commun. 1999;29:3385–99. https://doi.org/10.1080/00397919908085966.
54. Brahmachari G, Das S. Sodium Formate-Catalyzed One-Pot synthesis of Benzopyranopyrimidines and 4-Thio-substituted 4H-Chromenes via Multicomponent reaction at Room temperature. J Heterocycl Chem. 2015;52:653–9. https://doi.org/10.1002/jhet.2123.
55. Evdokimov NM, Kireev AS, Yakovenko AA, Antipin. MY, Magedov IV, Kornienko A. Convenient one-step synthesis of a medicinally relevant benzopyranopyridine system. Tetrahedron Lett. 2006;47:9309–12. https://doi.org/10.1016/j.tetlet.2006.10.110.
56. Evdokimov NM, Kireev AS, Yakovenko AA, Antipin MY, Magedov IV, Kornienko A. One-step synthesis of Heterocyclic Privileged Medicinal scaffolds by a Multicomponent reaction of Malononitrile with aldehydes and thiols. ChemInform. 2007;38:3443–53. https://doi.org/10.1002/chin.200736125.

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