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Posted Date: 23 February 2024

doi: 10.20944/preprints202402.1386.v1

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Article

Synthesis and PASS-Assisted Evaluation of New Heterocyclic Compounds Containing Hydroquinoline Scaffold

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Abstract: Now day; the interest for the synthesis of heterocyclic compounds containing hydroquinoline fragments has increased tremendously due to their wide variety of pharmaceutical and industrial applications. This work details the synthesis of linear and fused heterocyclic systems containing hydroquinoline fragments and the pharmacological activity spectra of the synthesized compounds was predicted by in silico method using Prediction of Activity Spectra of Substances (PASS) program. 1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbaldehyde **5a** was reacted for three hours with a system of hydroxylammonium chloride/pyridinium chloride/toluene to produce 1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-nitrile **7**. N-benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-6-carbaldehyde **6b** and iodine reacted at room temperature in aqueous ammonia water, followed by aq. treatment with Na₂S₂O₃ and produced N-benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-6-nitrile **8**. 30-60% 2-phenyl-1,3-oxazol-5(4H)-ones **9a,b**; **10a,b** were synthesized via the condensation reaction of N-alkylhydroquinoline-6-carbaldehydes **5a,b**; **6a,b** with hippuric acid in acetic acid. When activated 7-methylazolopyrimidines **11a,b** were reacted with N-alkyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-6-carbaldehydes **6a,b**, the reaction produced 60–70% yield of 7-[(E)-2,2,4-trimethylhydroquinolin-6-ylidenemethyl]azolo[1,5-a]pyrimidin-6-yl carboxylic acids **12a,b**. The condensation reaction of 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline **3h** with dimethylacetylenedicarboxylate (DMAD) and ethylacetoacetate afforded methyl (Z)-2-(5,7,7,8-tetramethyl-2-oxo-7,8-dihydrofuro[3,2-g]quinolin-3(2H)-ylidene)acetate **16** and 4,6,8,8,9-pentamethyl-8,9-dihydro-2H-pyrano[3,2-g]quinolin-2-one **17**, respectively. The condensation reaction of 6-formyl-7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline **5e** with methylene active compounds ethylcyanoacetate/dimethyl-3-oxopentanedioate/ethylacetoacetate/diethylmalonate/Meldrum's acid afforded 3-substituted dihydroquinoline containing coumarins **19** & **21**. A pentacyclic coumarin **22** was obtained via the random condensation reaction of malononitrile with **5e** in the presence of catalytic amount of piperidine in ethanol. The potential biological activities of the synthesized compounds were evaluated using PASS computer program. According to the prognosis, (E)-4-(N-alkylhydroquinolin-6-yl)-3-buten-2-ones, **13a, b** & **14** showed high probability of being active (Pa) as the Gluconate 2-dehydrogenase inhibitor, Anti-allergic, Anti-asthmatic, and Anti-arthritis with the Pa value of 0.849-0.870. It was also found out that hydroquinolinecarbonitrile compounds **7** & **8** have a propensity to act as a good progesterone antagonists, anti-allergic, anti-asthmatic, and anti-arthritis (Pa = 0.276-0.827). Among the coumarin moieties containing hydroquinolines, compounds **17**, **19a**, and **19c** were predicted to be good progesterone antagonists with the Pa values of 0.710, 0.630 and 0.615; respectively.

Keywords: heterocyclic compound; hydroquinoline; vilsmeier-haack formylation; quinoline

1. Introduction

Nowadays, heterocyclic compounds have gained a great deal of research interest because of their numerous significant medical and biological applications [1–4]. Quinoline derivatives belong to the N-containing heterocyclic compounds which are known for their applications in medicinal chemistry such as antimalarial, anti-inflammatory agents, anti-asthmatic, anti-bacterial, antihypertensive, and tyrosine kinase inhibiting agents [5–11]. Hence, the interest for 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 of great practical importance [16–18]. 2,2,4-trimethyl-1,2-*H*-dihydroquinoline is one of the most important representative, which is considered as an essential and effective anti-oxidant in rubber technologies [19]. The methods of the synthesis of 1,2-quinoline derivatives are based on the cyclization reaction, well known as Skraup reaction and various Skraup-based modification reactions such as Combes, Knorr, Doebner and Friedlander [12,17,19–21]. Tetrahydroquinoline is one of the most important simple nitrogen heterocycles, being widespread in nature and present in a broad variety of pharmacologically active compounds [22,23].

It is found out that heterocyclic compounds containing hydroquinoline derivatives are the basis for a wide range of biological activities [24–26] and also have industrial applications such as photo sensitizers 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. Even though the methods of synthesis of annulated heterocyclic systems containing 1,2-dihydro- and 1,2,3,4-tetrahydroquinoline moieties are stated in the literature, the problem of synthesizing new classes of linear and fused heterocyclic systems with hydroquinoline fragment including those containing a chiral center in a certain configuration and various substituent's, has not been completely solved.

In-silico studies are becoming more important in drug development from its 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 a wide practice as it helps in decreasing the cost/time related to drug discovery [32,33].

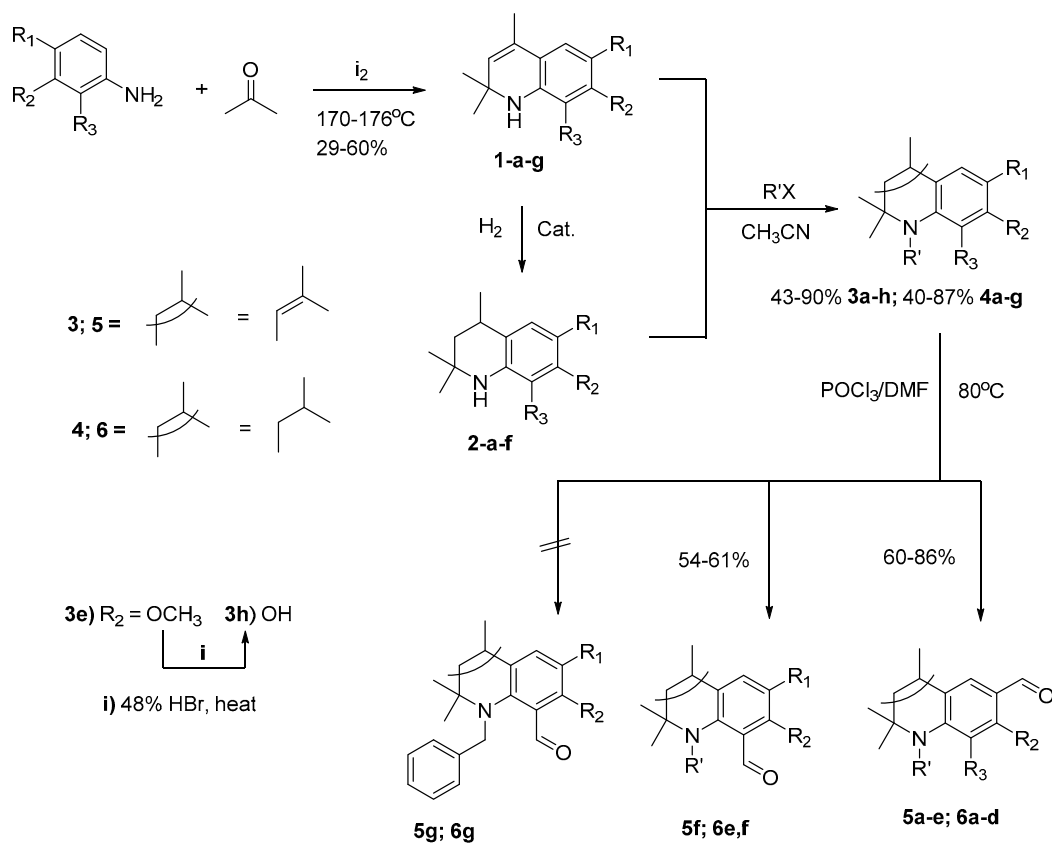
Hence, in this study, the synthesis of new heterocyclic compounds containing hydroquinoline moieties such as carbonitriles, oxazolones, pyrazolo/triazolo[1,5-*a*]pyrimidines, and coumarins based on formylhydroquinolines was described. Moreover, the pharmacological activity spectrum of the synthesized compounds were predicted by in-silico method using the prediction of activity spectrum of substances (PASS) computer program [32–34].

2. Results and Discussion

2.1. Chemistry

K. Tian et al. previously reported that the Vilsmeier–Haack (VH) formylation reaction of 1,2,2,4-tetramethyl-1,2-dihydroquinoline bearing 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], with the objective of broadening the scope of the synthesis of formyl hydroquinolines containing electron-donating substituents on the aromatic ring; we reported that the VH formylation reaction of 7(8)-substituted-N-alkyl-1,2-dihydro- and 1,2,3,4-tetrahydroquinolines leads to the exclusive formation of 6-formyl-7(8)-substituted-N-alkyl-1,2-dihydro- and 1,2,3,4-tetrahydroquinolines.

Whereas the Vilsmeier-Haack formylation reaction of 6-substituted-N-methyl-2,2,4-trimethyl-1,2-di(1,2,3,4-tetra)hydroquinolones afforded 8-formyl-6-substituted-1,2,2,4-tetramethyl-1,2-di(1,2,3,4-tetra)hydroquinolones, our attempt that was made to formylate 6-substituted-N-benzyl-2,2,4-trimethyl-1,2-dihydro(1,2,3,4-tetrahydro)quinolines to obtain 8-formyl-6-substituted-N-benzyl-2,2,4-trimethyl-1,2-di(1,2,3,4-tetra)hydroquinolines was not succeeded (**Scheme 1** and **Table 1**). This can be explained mainly due to the steric impedence at the 8 position of the hydroquinoline ring which is introduced by the more bulky N-benzyl substituent compared to the methyl group.



Scheme 1. Synthesis of 6(8)-Formyl-N-alkyl-2,2,4-trimethyl-1,2-di(1,2,3,4-tetra)hydroquinolines **5a-f** and **6a-f** via 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
3c	CH ₃	H	CH ₃	H	5c	CH ₃		CH ₃	H
3d	Bn	H	CH ₃	H	5d	Bn		CH ₃	H
3h	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
4c	CH ₃	H	CH ₃	H	6c	CH ₃		CH ₃	H
4d	CH ₃	H	H	OCH ₃	6d	CH ₃		H	OCH ₃
3e	CH ₃	H	OCH ₃	H	-				
3f	CH ₃	OCH ₃	H	H	5f	CH ₃	OCH ₃	H	CHO
4e	CH ₃	OCH ₂ CH ₃	H	H	6e	CH ₃	OCH ₂ CH ₃	H	
4f	CH ₃	CH ₃	H	H	6f	CH ₃	CH ₃	H	
3g	Bn	CH ₃	H	H	5g	No Reaction			
4g	Bn	OCH ₃	H	H	6g	No Reaction			

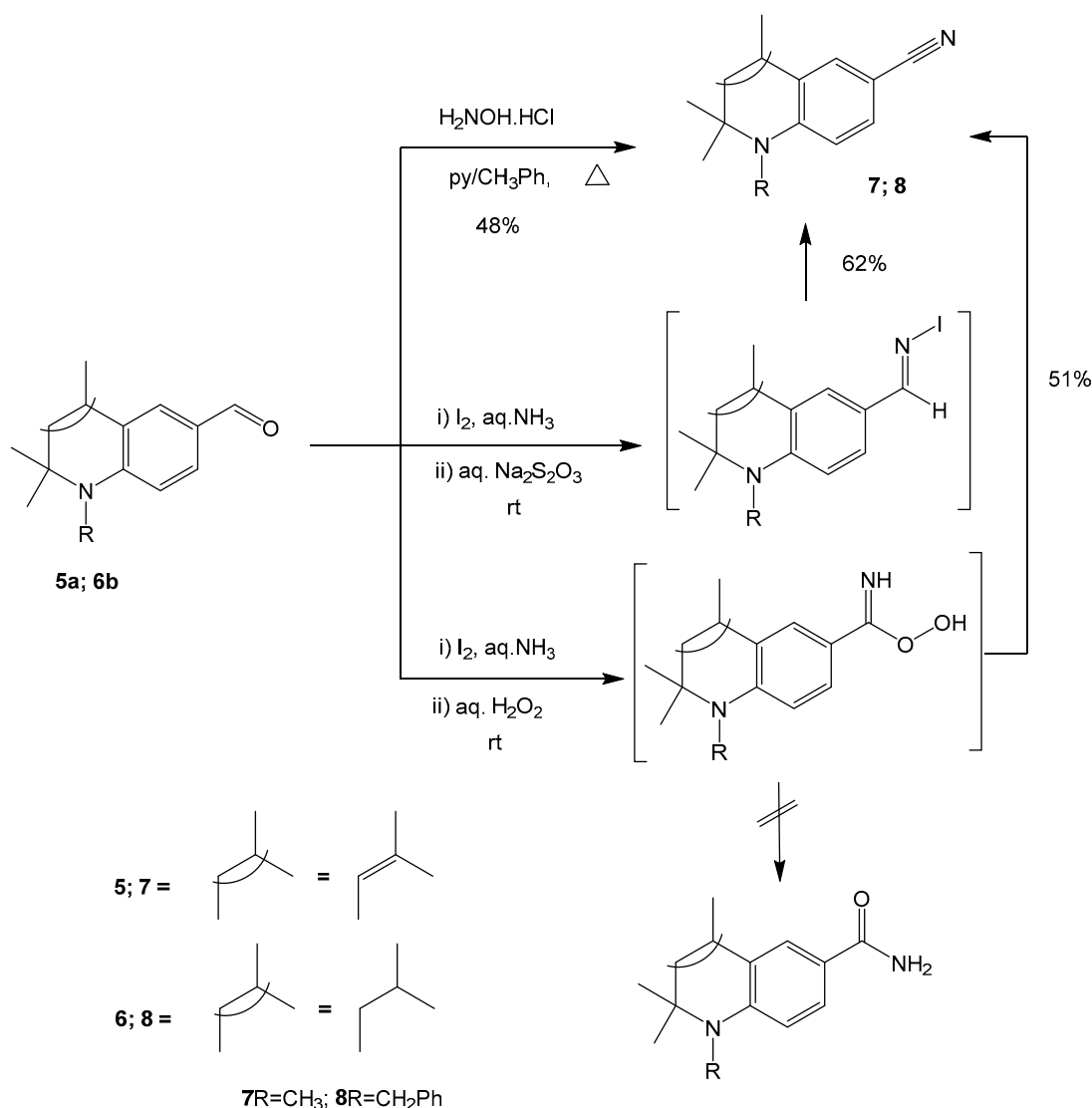
2.1.1. Synthesis of N-alkyl-2,2,4-trimethylhydroquinolin-6-yl-carbonitriles 7, 8

One of the most important functional group transformations in organic synthesis is the conversion of aldehyde functional groups into nitriles. Nitriles are 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, benzamidines, etc [38]. In the majority of cases, nitriles are obtained via the initial formation of aldoxime which is obtained by the condensation reaction of hydroxylamine hydrochloride with aldehyde which is then subjected to dehydration effected by a variety of reagents to give nitriles. There are also a few methods known for the one-step conversion of aldehydes in to nitriles without separation of the aldoxime formed [38–42].

Hence, with the objective of further functionalizing the hydroquinoline carbaldehydes, we have attempted to synthesis carbonitrile via the two adopted methodologies. First, the hydroxylammonium chloride/pyridium/toluene system with the azeotropic separation of water was employed. The pyridinium chloride formed participates in the aldoxime-nitrile conversion; thus, the presence of a dehydrating agent is not necessary. The reaction of 6-formyl-N-methyl-2,2,4-trimethyl-1,2-dihydroquinoline **5a** with $\text{H}_2\text{NOH.HCl/C}_5\text{H}_5\text{N/C}_7\text{H}_8$ were completed within 3 hours with the reaction yield of 48% to afford 1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-nitrile **7**. The disappearance of the aldehydic proton signal that typically resonates in the range of 9.88 – 10.22 ppm on the ^1H -NMR spectrum of the starting material is evidence that the reaction has gone to completion (supporting information- **Figure 1**).

The second methodology we employed was via the treatment of the respective aldehyde with iodine in aqueous ammonia water at room temperature [42]. We speculated that the reaction proceeded via the oxidation of aldimine with iodine to give an *N*-iodoaldimine intermediate, which eliminated an HI molecule in ammonia solution to afford the nitrile product. It was found out that this procedure was applicable in our case using the 6-formyl-N-benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline **6b** that afforded N-benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-6-nitrile **8** (**Scheme 2** & supporting information- **Figure 2**).

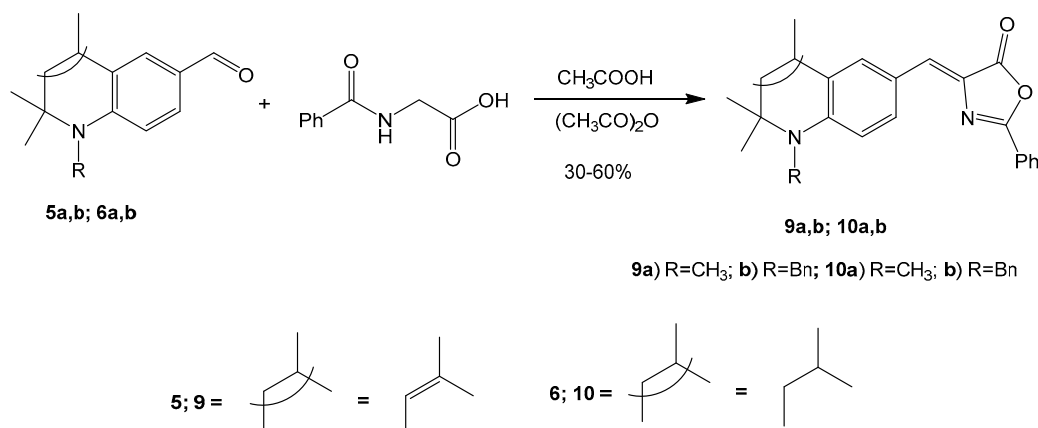
We have also made an attempt to synthesis an amide from 6-formyl-N- benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline **6b** with the treatment of aqueous hydrogen peroxide at room temperature, reportedly with the intermediate formation of peroxocarboxamic acid [43]. However, a 4 hour exposure to hydrogen 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.



Scheme 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**.

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

Benzoxazole derivatives have been reported in the literature that they possess anti-inflammatory, analgesic, anti-bacterial, trichomonacidal, anthelmintic, fungicidal, antiviral and kinase inhibition activities [44]. The method for the synthesis of 4-arylidene-2-aryloxazol-5-ones has been known for a long time and is widely used in synthetic organic chemistry, which consists in 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 **5**, **6** with hippuric acid and we obtained 2-aryl-4-arylidene-5(4H)-oxazolones **9a,b**; **10a,b** with moderate yield of 30-60% (Scheme 3). Sidhu and coworkers confirmed that the ¹H-NMR spectra of oxazolones show the deshielding influence of the cis-N=C-C₆H₅ 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 $\delta = 7.18$ -7.22 ppm, which is relatively up field than expected (nearly $\delta = 7.60$ -7.85 ppm). Hence, based on the ¹H-NMR spectral data these compounds have been assigned the (Z) configuration at the 4 position (supporting information-Figure 3-6).

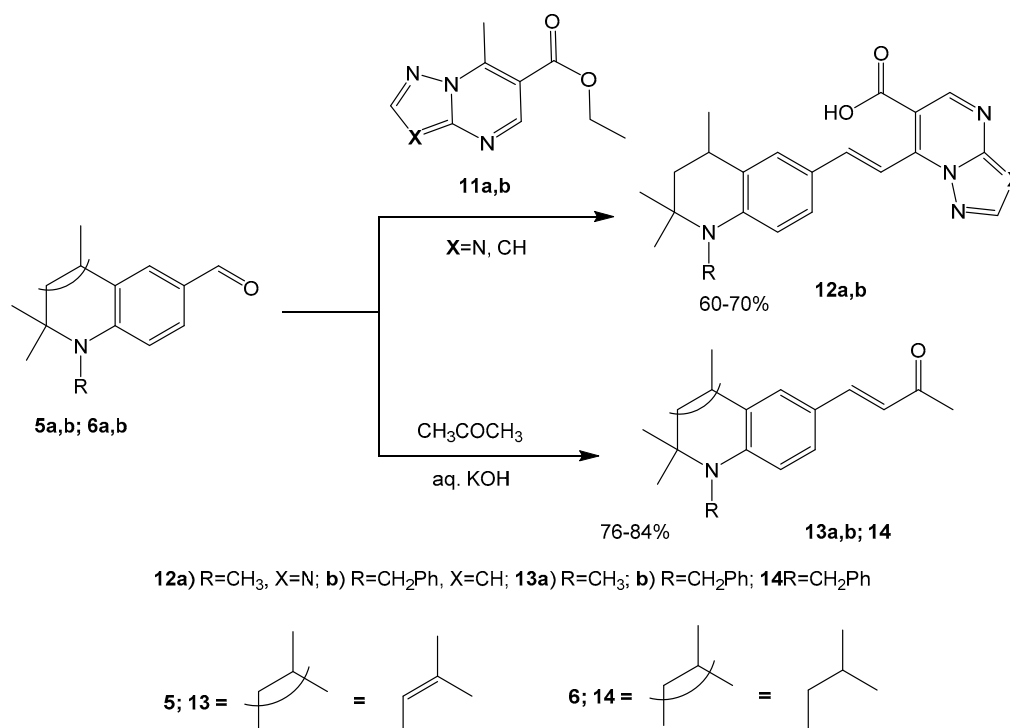


Scheme 3. Synthesis of 2-phenyl-1,3-oxazol-5(4H)-ones **9, 10**.

2.1.3. Condensation of Hydroquinolinecarbaldehydes with Reagents Containing an Activated Methyl Group 12, 13 14

In order to search for potential biologically active compounds, we extended our work with the reaction of 6-formyl-N-alkyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolines **5a,b; 6a,b** with ethyl-7-methylpyrazolo/triazolo/[1,5-a]pyrimidine-6-carboxylates **11a,b** (**Scheme 4**).

It was found out that the condensation of N-alkyl-1,2,3,4-tetrahydroquinoline-6-carbaldehydes **5a,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 condensation reaction. The downfield broad signals observed on the ¹H-NMR spectra at 13.31 and 13.50 ppm are assignable to carboxylic acid protons of **12a, b**, respectively (supporting information- **Figure 7 & 8**). 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 which are sparingly soluble in water.



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

Analysis of the ^1H NMR spectra of carboxylic acids **12**, **b** showed that they are trans isomers. This is evidenced by the fact that the coupling constant of the alkene protons which resonate as doublets at δ 8.23 and 9.05 ppm is 16 Hz; which is the typical characteristic of trans- isomer substituted alkenes. 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 (supporting information- **Figure 9**).

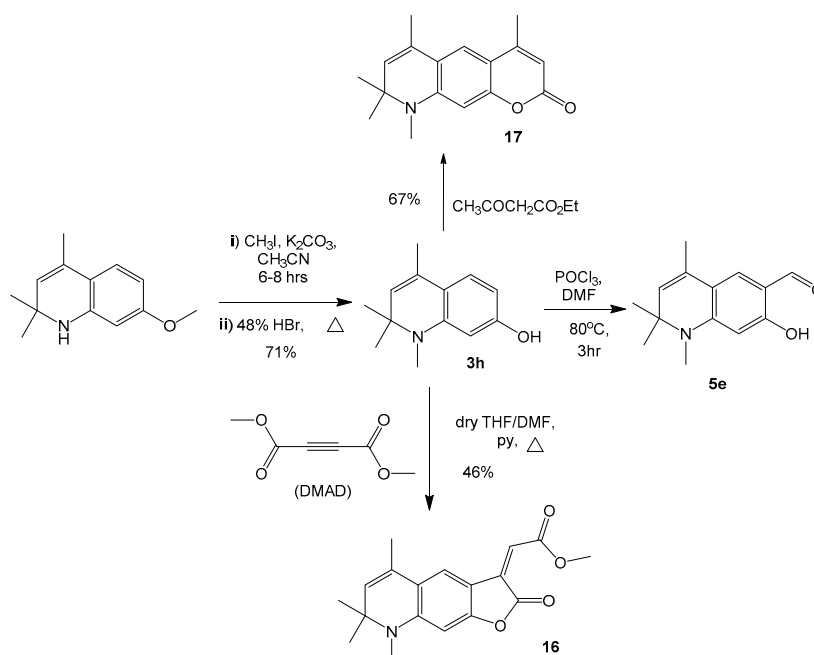
The condensation of N-alkylhydroquinoline-6-carbaldehydes **5a**, **b**; **6a**, **b** with acetone proceeds under milder conditions and leads to the previously unknown 4-(2,2,4-trimethylhydroquinoline- 6-yl)-3-buten-2-ones **13 a**, **b** and **14**, which are promising synthons for synthesizing biologically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

In the ^1H NMR spectra of compounds **13 a,b**, and **14**, the olefinic protons 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 (supporting information- **Figure 10-12**). There is the typical characteristics for 1,2-disubstituted alkenes with the 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 (**Scheme 4**).

2.1.4. Cyclizations of 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline 3h and 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbaldehyde, 5e with Methylene Active Compounds 16, 17, 19, 21, 22

Dimethylacetylenedicarboxylate (DMAD) is an electron-deficient acetylenic compound which is widely used in cyclization reactions. With phenol, DMAD usually gives adducts, which are the result of addition of the 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 fact that the product of the reaction between DMAD and various phenols is annelated α -methylene- γ -butyrolactones [47].

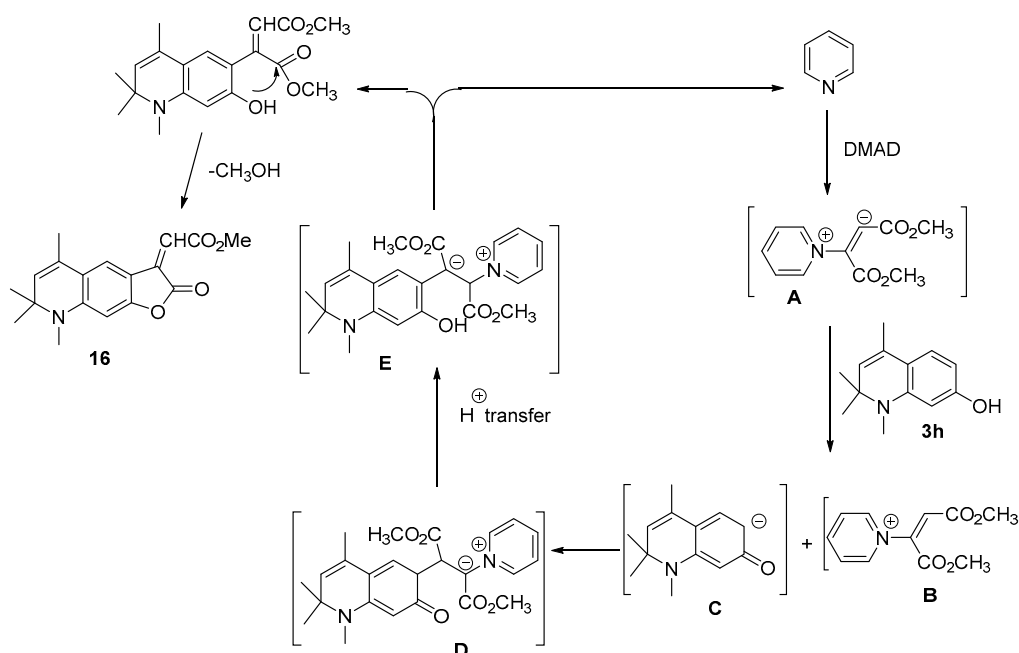
In 7-hydroxy-1,2,3,4-tetramethyl-1,2-dihydroquinoline, **3h**, positions 6 and 8 exhibit pronounced CH-acidity associated with the coordinated orientation of the -OH and disubstituted amine groups, which made it possible to hope for the preparation of the corresponding cyclic derivatives under pyridine catalysis conditions. Since position 8 is relatively sterically hindered as compared with position 6, only one cycling center remains, which is position 6.



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

The reaction of 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline **3h** with DMAD in the presence of catalytic amount of pyridine afforded **16** with 46% reaction yield. The ^1H NMR spectrum of **16** indicates a set of signals corresponding to the tricyclic structure of annulated α -methylene- γ -butyrolactone (supporting information- **Figure 13**). The plausible reaction mechanism was proposed as shown in **Scheme 6**. In the presence of pyridine, DMAD gives a betaine derivative of dimethyl maleate **A**, which is stabilized by interaction with the phenolic derivative **3h** (**B** and **C**, here in **D**).

Subsequent intramolecular proton transfer leads to an 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 dimethylmaleate fragment are spatially closed. The subsequent intramolecular transesterification leads to the elimination of methanol and the formation of lactone **16**.

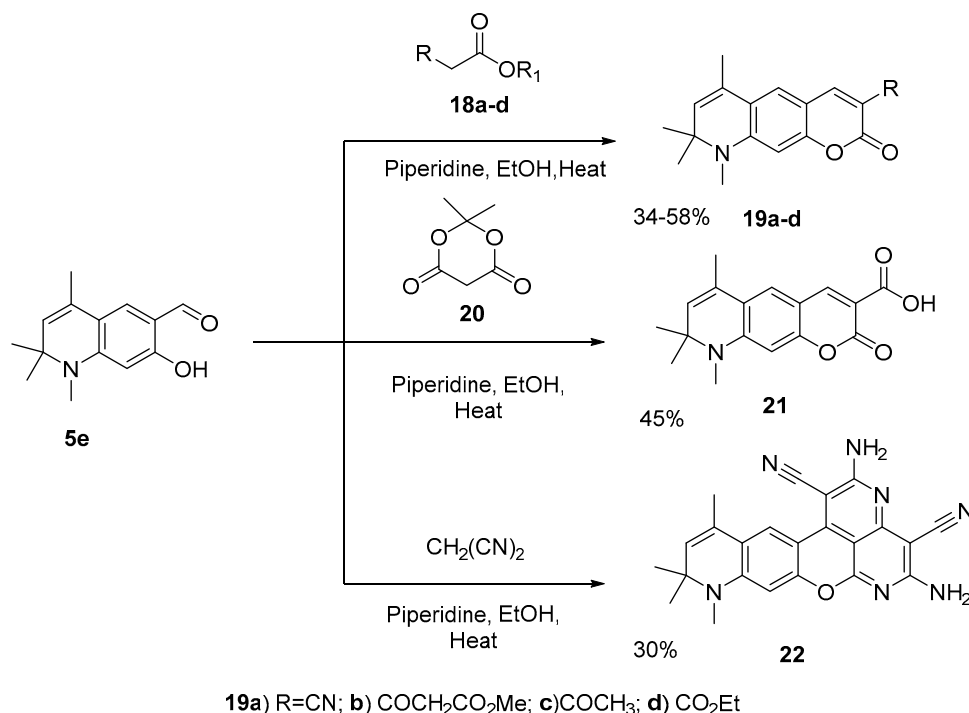


Scheme 6. Plausible reaction mechanism of methyl (Z)-2-(5,7,7,8-tetramethyl-2-oxo-7,8-dihydrofuro[3,2-g]quinolin-3(2H)-ylidene)acetate **16**.

The Pechmann reaction introduces 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 **3h** with ethylacetoacetate in the presence of catalytic amount of sulphuric acid afforded 4,6,8,8,9-pentamethyl-8,9-dihydro-2H-pyrano[3,2-g]quinolin-2-one **17** in 67% yield (**scheme 5**). The ^1H -NMR spectrum of **17** indicates that there are two singlet signals at δ 6.36 & 7.16 ppm each signal integrable to one proton which are assignable to H-10 and H-5 aromatic protons, respectively. This clearly indicated that the condensation reaction occurred via position 6, not through position 8 of the aromatic ring of **3h**. If the condensation had been occurred via position 8 of the ring, there would have been two ortho-substituted aromatic protons which would result in two doublet aromatic signals with each signal integrable to one proton with the J-value of nearly 7(8) Hz. The preference of position 6 over position 8 can be rationalized due to the relative steric hindrance of position 8 over 6 of the aromatic ring of the starting material **3h** (supporting information- **Figure 14**).

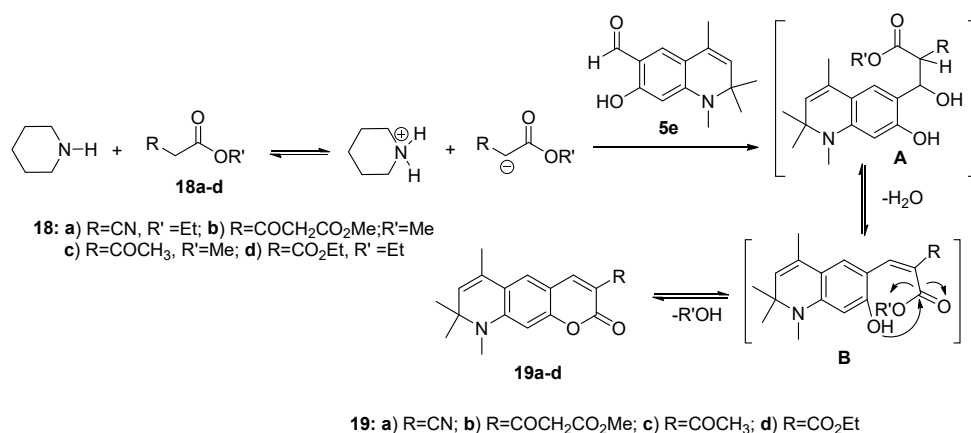
Coumarins are natural plant species with diverse biological activities including anti-inflammatory, anti-tumor, anti-oxidant, and antidiabetic. Coumarin derivatives have been also considered as neuroprotective agents against oxidative stress and free radical generation [49]. Several methods have been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

In the condensation reaction with 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbaldehyde **5e** in the presence of catalytic amount of secondary amine piperidine in ethanol, we have used methylene active compounds such as ethylcyanoacetate (**18a**), dimethyl-3-oxopentanedioate (**18b**), ethylacetoacetate (**18c**), and diethylmalonate (**18d**) (**Scheme 7**); and 34-58% yield of 3-substituted dihydroquinoline containing coumarins **19a-d** were obtained.



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

The plausible reaction mechanism of formation of 3-R-6,8,9-tetramethyl-8,9-dihydro-2H-pyrano[3,2-g]quinolin-2-one **19a-d** is shown in **Scheme 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 the arylidene derivative **B**, which is formed after dehydration of the Knoevenagel adduct **A**.



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

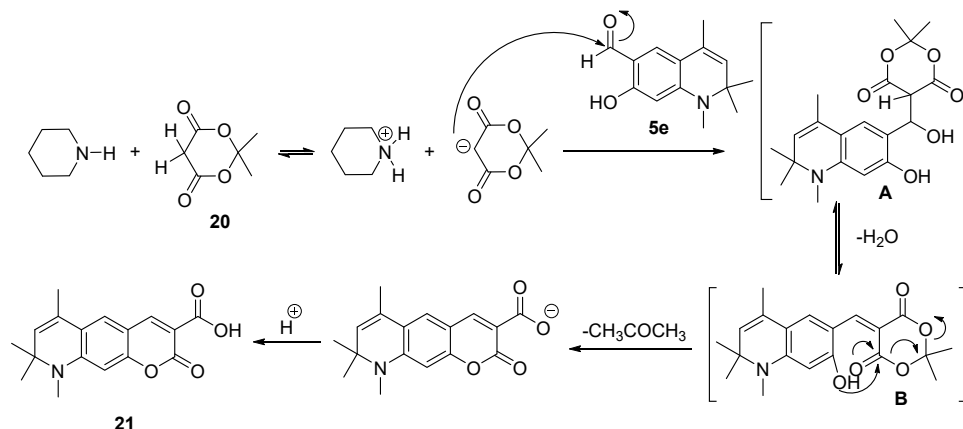
The ¹H-NMR spectrum of **19a** shows that there are two singlet signals, each integrable to one proton at the chemical shifts δ = 6.44 and 8.48 ppm which are assignable to the aromatic protons H-

10 and H-5, respectively. The downfield signal at $\delta = 7.25$ 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 a $[M]^+$ value of 280.12 (supporting information- **Figure 15**).

The ^1H -NMR spectrum of compound **19b** indicates that the singlet signal at $\delta = 8.53$ and 6.43 ppm belong to the aromatic protons H-5 and H-10, respectively. The singlet signal at $\delta = 3.96$ ppm, which is integrable to two protons, belongs to the methylene protons, whereas the singlet signals at $\delta = 3.62$ ppm and 7.46 ppm are assignable to the methoxy and olefinic (H-4) protons. The ^{13}C -NMR spectrum of **19b** shows the chemical shift values at 189.14, 168.48 and 160.07 ppm which are assignable to the carbonyl carbon of ketone, lactone and acyclic ester, respectively (Supporting information- **Figure 16 & 17**). The ^1H -NMR spectrum of compound **19c** designates that the singlet signal at $\delta = 8.47$ and 6.40 ppm belongs to the aromatic protons H-5 and H-10, respectively. The singlet signal at $\delta = 2.51$, which is integrable to three protons, belongs to the acetyl protons (supporting information- **Figure 18**).

The ^1H -NMR spectrum of compound **19d** designates that there is a triplet signal at $\delta = 1.28$ ppm with the spin-spin coupling constant value of 7.10 Hz, which is integrable to three protons belongs to the methyl protons of ethoxy group. The quartet signal at $\delta = 4.22$ ppm $J = 7.10$ Hz assignable to the methylene protons. The singlet signal at $\delta = 8.54$ and 6.37 ppm belong to the aromatic protons H-5 and H-10, respectively (supporting information- **Figure 19**).

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, the arylidene derivative **B** (**Scheme 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**. The formation of analogous compounds is described by the interaction of salicylaldehyde with acid [51].



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

The ^1H -NMR spectrum of compound **21** indicates that there is downfield singlet signal at $\delta = 7.39$ ppm which can be assignable to the olefinic proton H-4 which is beta to the electron-withdrawing carboxylic group (supporting information- **Figure 20**).

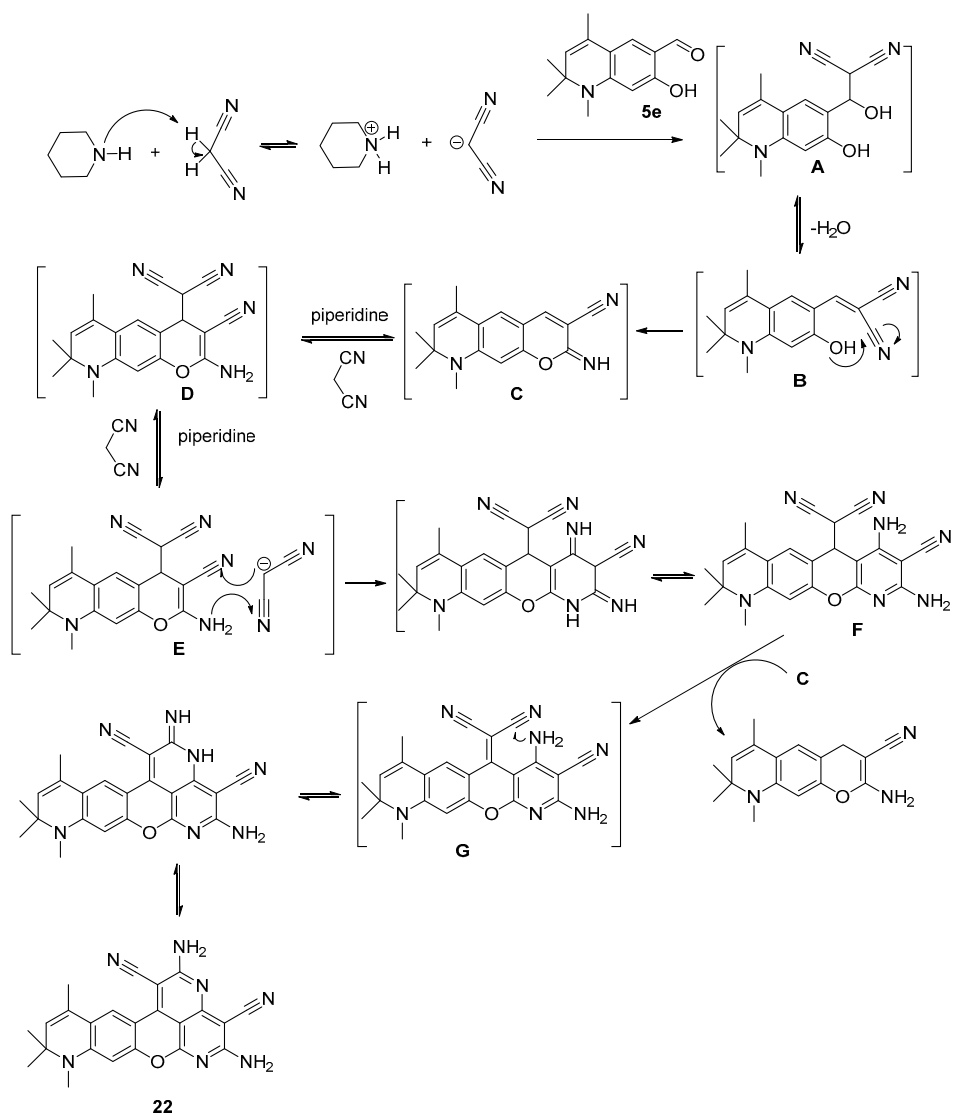
Unlike other methylene active compounds, malononitrile ($\text{CH}_2(\text{CN})_2$) is capable of undergoing a cascade condensation reactions with salicylaldehyde and its analogues. At the first stage of the cascade, 2-imino-2H-chromene-3-carbonitrile is formed; who's analog is the intermediate **C**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

2-Imino-2H-chromene-3-carbonitrile or its analogue **C** contains an electrophilic carbon atom in position 4, which reacts with N- and S-nucleophiles under mild conditions [54]. With an excess of

malononitrile under the conditions of 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, an 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 ammonium acetate is the catalyst of the transformation.

However, the third equivalent of malononitrile [55] can act as such 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 the tetracyclic intermediate G, which is closed into 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 on 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 value of the heaviest peak at m/z 394 corresponds to $[M-14]^+$. The broad singlet signal at $\delta = 7.28$ ppm in the $^1\text{H-NMR}$ spectrum of compound **22**, which can be integrated to a total of four protons, is attributed to the two amine groups (supporting information- **Figure 21**).



Scheme 10. Plausible reaction mechanism of 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**.

2.2. In-silico studies

2.2.1. PASS the predicted activity spectrum of test synthesized compounds

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

Table 2. PASS the predicted activity of 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	-	-

3. Experimental Section

3.1. General

The starting materials hydroquinolinecarbaldehydes are synthesized via the Vilsmeier-Haack formylation reaction of the respective N-alkylhydroquinolines. All other reacting materials were

commercially accessible from Sigma-Aldrich suppliers. In this study, analytical grade reagents and solvents were employed except for the solvents THF and DMF where further purifications were done. 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, eluent chloroform, methanol, hexane, ethyl acetate in various proportions) and visualization of the spots was carried out using a UV lamp. The ^1H and ^{13}C NMR spectra were recorded in deuterated dimethyl sulfoxide (DMSO- d_6) 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). Mass spectra were recorded using Agilent Technologies LCMS6230B (chemical ionization, 200 eV) and GCMS7890B instruments (carrier gas, EI, energy of ionization 70 eV). Melting points (mp) were measured uncorrected using a Stuart SMP30 melting point instrument.

3.2. 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 minutes of stirring on 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 mass was cooled, filtered off from the precipitate of pyridine hydrochloride, the filtrate was washed with distilled water, dried over anhydrous sodium sulfate, and toluene was removed on a rotary evaporator. The product was recrystallized from aqueous acetonitrile.

Yield: 48%, Mp. 80-82 °C. ^1H NMR (DMSO- d_6 , 500.13 MHz, δ (ppm), J (Hz)): 1.32 (s, 6H, $(\text{CH}_3)_2$); 1.91 (s, 3H, $\text{CH}_3\text{-C}_4$); 2.81 (s, 3H, N- CH_3); 5.43 (s, 1H, CH- C_3); 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).

3.3. 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 hours. During the reaction, the solution gradually became colorless as the iodine was consumed. An aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (1M, 10 ml) was added dropwise to the reaction mixture, stirred for 3 hours, 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 hours. 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, stirred for 4 hours, 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. ^1H NMR (DMSO- d_6 , 500.13 MHz, δ (ppm), J (Hz)): 1.26 (s, 6H, $(\text{CH}_3)_2$); 1.34 (d, 3H, $J=6.60$, $\text{CH}_3\text{-C}_4$); 1.63 (t, 1H, $J=13.01$, $\text{CH}_{2\text{A}}\text{-C}_3$); 1.92 (dd, 1H, $J=13.14$, $J=4.61$, $\text{CH}_{2\text{B}}\text{-C}_3$); 2.95 (m, 1H, CH- C_4); 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, 7H, arom.).

3.4. Synthesis of 2-phenyl-1,3-oxazol-5(4H)-ones 9, 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 hours, poured into crushed ice, and stirred for 30 minutes. The product was extracted with chloroform, washed, and the chloroform was evaporated using a rotary evaporator, and the residue was recrystallized from isopropanol.

3.4.1. (Z)-2-Phenyl-4-((1,2,2,4-tetramethyl-1,2-dihydroquinolin-6-yl)methylene)oxazol-5(4H)-one (9a)

Yield: 60%, Mp. 180-182 °C. ¹H NMR (DMSO-d₆, 500.13 MHz, δ (ppm), J (Hz)): 1.37 (s, 6H, C(CH₃)₂); 2.02 (s, 3H, CH₃-4); 2.91 (s, 3H, N-CH₃); 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, 7H, arom.)

3.4.2. (Z)-4-((1-Benzyl-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)methylene)-2-phenyloxazol-5(4H)-one (9b)

Yield: 30%, Mp. 130-132 °C. ¹H NMR (DMSO-d₆, 500.13 MHz, δ (ppm), J (Hz)): 1.41 (s, 6H, C(CH₃)₂); 2.08 (s, 3H, CH₃-4); 4.73 (s, 2H, CH₂-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, 12H, arom.)

3.4.3. (Z)-2-Phenyl-4-((1,2,2,4-tetramethyl-1,2,3,4-tetrahydroquinolin-6-yl)methylene)oxazol-5(4H)-one (10a)

Yield: 41%, Mp. 140-142 °C. ¹H NMR (DMSO-d₆, 500.13 MHz, δ (ppm), J (Hz)): 1.25 (s, 3H, C(CH₃)_{2A}), 1.32 (s, 3H, C(CH₃)_{2B}); 1.39 (d, J=6.56, 3H, CH₃-4); 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, 3H, N-CH₃); 6.67 (d, J=8.86, 1H, arom.); 7.22 (s, 1H, CH-methylene); 7.55-8.20 (m, 7H, arom.)

3.4.4. (Z)-4-((1-Benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolin-6-yl)methylene)-2-phenyloxazol-5(4H)-one (10b)

Yield: 47%, Mp. 195-197°C. ¹H NMR (DMSO-d₆, 500.13 MHz, δ (ppm), J (Hz)): 1.29 (s, 3H, C(CH₃)_{2A}); 1.32 (s, 3H, C(CH₃)_{2B}); 1.44 (d, J=6.54, 3H, CH₃-4); 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-3); 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, 12H, arom.)

3.5. 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 hours, cooled, and poured into 100 ml of 10% acetic acid solution. The precipitate formed was filtered off, washed with water, and after drying, was recrystallized from ethanol.

3.5.1. (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. ¹H NMR (DMSO-d₆, 500.13 MHz, δ (ppm), J (Hz)): 1.04 (d, 3H, J=6.7, CH₃); 1.23 (s, 3H, CH₃); 1.31 (s, 3H, CH₃); 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-CH₃); 6.45 (d, 1H, J=8.5, CH arom.); 7.42-7.46 (m, 2H, 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).

3.5.2. (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. ¹H NMR (DMSO-d₆, 500.13 MHz, δ (ppm), J (Hz)): 1.29 (s, 6H, (CH₃)₂); 1.41 (d, 3H, J=6.7, CH₃); 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); 4.41 (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, 7H arom.); 7.50 (s, 1H, CH arom.); 8.23 (d, 1H, J=16.0, CH vinyl); 8.43 (d, 1H, J=2.4, CH pyraz.); 8.87 (s, 1H, CH pyrim.); 9.05 (d, 1H, J=16.0, CH vinyl); 13.50 (s, 1H, COOH).

^{13}C NMR (DMSO- d_6 , 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); 45,58 (1C, CH_2); 55,14 (1C, $\text{C}(\text{CH}_3)_2$); 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, $\text{C}=\text{COOH}$); 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).

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

To a solution of 2 mol of the corresponding N-alkylhydroquinoline-6-carbaldehyde, **5,6** in 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 water (1:1).

3.6.1. (E)-4-(1,2,2,4-Tetramethyl-1,2-dihydroquinolin-6-yl)but-3-en-2-one (13a)

Yield: 76%, Mp. 68-70 °C. ^1H NMR (DMSO- d_6 , 500.13 MHz, δ (ppm), J (Hz)): 1.30 (s, 6H, $(\text{CH}_3)_2$); 1.96 (s, 3H, $\text{CH}_3\text{-C}'4$); 2.26 (s, 3H, $\text{CH}_3\text{-CO-}$); 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).

3.6.2. (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. ^1H NMR (DMSO- d_6 , 500.13 MHz, δ (ppm), J (Hz)): 1.35 (s, 6H, $(\text{CH}_3)_2$); 2.01 (s, 3H, $\text{CH}_3\text{-C}'4$); 2.23 (s, 3H, Bn); 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, 7H, arom.); 7.44 (d, 1H, $J=16.17$, H-4).

3.6.3. (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. ^1H NMR (DMSO- d_6 , 500.13 MHz, δ (ppm), J (Hz)): 1.25 (s, 3H, $(\text{CH}_3)_{2A}$); 1.26 (s, 3H, $(\text{CH}_3)_{2B}$); 1.37 (d, 3H, $J=6.59$, $\text{CH}_3\text{-C}'4$); 1.62 (t, 1H, $J=12.97$, $\text{CH}_{2A}\text{-C}'3$); 1.91 (dd, 1H, $J=13.05$, $J=4.61$, $\text{CH}_{2B}\text{-C}'3$); 2.23 (s, 3H, $\text{CH}_3\text{-CO-}$); 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, 7H, arom.); 7.45 (d, 1H, $J=16.27$, H-4).

3.8. Synthesis of methyl (Z)-2-(5,7,7,8-tetramethyl-2-oxo-7,8-dihydrofuro[3,2-g]quinoline-3(2H)-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) in ml of anhydrous THF/DMF (4:1) was added dropwise 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, the residue was separated by column chromatography using n-hexane/ethyl acetate (4:1) as an eluent.

Yield: 46%, Mp. 195-197 °C. ^1H NMR (DMSO- d_6 , 500.13 MHz, δ (ppm), J (Hz)): 1.35 (s, 6H, $\text{C}(\text{CH}_3)_2$); 1.93 (s, 3H, $\text{CH}_3\text{-5}$); 2.87 (s, 3H, N- CH_3); 3.91 (s, 3H, $\text{CH}_3\text{O-}$); 5.50 (s, 1H, CH-5); 6.38 (s, 1H, H-8); 6.43 (s, 1H, H-3); 7.63 (s, 1H, CH-2).

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

A mixture of 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline **3h** (1 mmol) and ethylacetoacetate (1.2mmol) 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 ethylacetate (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-2H-pyrano[3,2-g]quinolin-2-one **17**.

Yield: 68%, Mp. 170-172 °C. ¹H NMR (DMSO-d₆, 500.13 MHz, δ(ppm), J (Hz)): 1.32 (s, 6H, C(CH₃)₂); 1.98 (s, 3H, C₆-CH₃); 2.35 (s, 3H, C₄-CH₃); 2.83 (s, 3H, N-CH₃); 5.46 (s, 1H, H-8); 5.94 (s, 1H, H-3); 6.36 (s, 1H, H-10 (arom.)); 7.16 (s, 1H, H-5 (arom.))

3.10. 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 compound **18**, **20** (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.

3.10.1. 6,8,8,9-Tetramethyl-2-oxo-8,9-dihydro-2H-pyrano[3,2-g]quinoline-3-carbonitrile (**19a**)

Yield: 51%, Mp. 190-192 °C. ¹H NMR (DMSO-d₆, 500.13 MHz, δ(ppm), J (Hz)): 1.38 (s, 6H, C(CH₃)₂); 1.94 (s, 3H, CH₃-6); 2.94 (s, 3H, N-CH₃); 5.54 (s, 1H, CH-7); 6.44 (s, 1H, H-10); 7.25 (s, 1H, H-4); 8.48 (s, 1H, H-5).

3.10.2. Methyl 3-oxo-3-(6,8,8,9-tetramethyl-2-oxo-8,9-dihydro-2H-pyrano[3,2-g]quinolin-3-yl)propanoate (**19b**)

Yield: 58%, Mp. 179-181 °C. ¹H NMR (DMSO-d₆, 500.13 MHz, δ(ppm), J (Hz)): 1.39 (s, 6H, C(CH₃)₂); 1.95 (s, 3H, CH₃-6); 2.95 (s, 3H, N-CH₃); 3.62 (s, 3H, CH₃O-); 3.96 (s, 2H, CH₂); 5.53 (s, 1H, CH-7); 6.43 (s, 1H, H-10); 7.46 (s, 1H, CH-4); 8.53 (s, 1H, H-5).

¹³C 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

3.10.3. 3-Acetyl-6,8,8,9-tetramethyl-8,9-dihydro-2H-pyrano[3,2-g]quinolin-2-one (**19c**)

Yield: 39%, Mp. 200-202 °C. ¹H NMR (DMSO-d₆, 500.13 MHz, δ(ppm), J (Hz)): 1.38 (s, 6H, C(CH₃)₂); 1.94 (s, 3H, CH₃-6); 2.51 (s, 3H, CH₃-CO-); 2.93 (s, 3H, N-CH₃); 5.51 (s, 1H, CH-7); 6.40 (s, 1H, H-10); 7.42 (s, 1H, H-4); 8.47 (s, 1H, H-5).

3.10.4. Ethyl 6,8,8,9-tetramethyl-2-oxo-8,9-dihydro-2H-pyrano[3,2-g]quinoline-3-carboxylate (**19d**)

Yield: 34%, Mp. 130-132 °C. ¹H NMR (DMSO-d₆, 500.13 MHz, δ(ppm), J (Hz)): 1.28 (t, 3H, J=7.1, CH₃CH₂O-); 1.37 (s, 6H, C(CH₃)₂); 1.94 (s, 3H, CH₃-6); 2.91 (s, 3H, N-CH₃); 4.22 (q, 2H, J=7.1, CH₃CH₂O-); 5.58 (s, 1H, CH-7); 6.37 (s, 1H, H-10); 7.41 (s, 1H, CH-4); 8.54 (s, 1H, H-5).

3.10.5. 6,8,8,9-Tetramethyl-2-oxo-8,9-dihydro-2H-pyrano[3,2-g]quinoline-3-carboxylic acid (**21**)

Yield: 45%, Mp. >250 °C. ¹H NMR (DMSO-d₆, 500.13 MHz, δ(ppm), J (Hz)): 1.36 (s, 6H, C(CH₃)₂); 1.94 (s, 3H, CH₃-6); 2.90 (s, 3H, N-CH₃); 5.49 (s, 1H, CH-7); 6.39 (s, 1H, H-10); 7.39 (s, 1H, CH-4); 8.51 (s, 1H, H-5).

3.10.6. 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. ¹H NMR (DMSO-d₆, 500.13 MHz, δ(ppm), J (Hz)): 1.38 (s, 6H, C(CH₃)₂); 1.95 (s, 3H, CH₃-12); 2.89 (s, 3H, N-CH₃); 5.51 (s, 1H, CH-11); 6.37 (s, 1H, H-8); 7.28 (bro. s, 4H, 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).

3.11. In Silico PASS Prediction

Prediction of 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 and then predicted using the PASS online web tool/ <http://www.way2drug.com/PASSOnline/predict.php/>. PASS indicates the probable activity (Pa) and probable inactivity (Pi) of 'drug-like' substances.

4. Conclusion

In this study, heterocyclic compounds containing hydroquinoline fragment such as carbonitriles, oxazolones, azolo[1,5-a]pyrimidines and coumarins were synthesized. A three hours reflux of 1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbaldehyde **5a** with a system of hydroxylammonium chloride/pyridinium chloride/toluene afforded 1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-nitrile **7** in moderate yield. N-benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-6-carbaldehyde **6b** and iodine reacted at room temperature in aqueous ammonia water, followed by aqueous treatment with Na₂S₂O₃ and produced N-benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-6-nitrile **8** in 62%. 30-60% 2-phenyl-1,3-oxazol-5(4H)-ones **9a,b**; **10a,b** were synthesized via the condensation reaction of N-alkylhydroquinoline-6-carbaldehydes **5a,b**; **6a,b** with hippuric acid in acetic acid. When activated 7-methylazolopyrimidines **11a,b** were reacted with N-alkyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-6-carbaldehydes **6a,b**, the reaction produced 60–70% yield of 7-[(E)-2,2,4-trimethylhydroquinolin-6-ylidenemethyl]azolo[1,5-a]pyrimidin-6-yl carboxylic acids **12a,b**.

The condensation reaction of 7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline **3h** with dimethylacetylenedicarboxylate (DMAD) and ethylacetoacetate afforded methyl (Z)-2-(5,7,7,8-tetramethyl-2-oxo-7,8-dihydrofuro[3,2-g]quinolin-3(2H)-ylidene)acetate **16** and 4,6,8,8,9-pentamethyl-8,9-dihydro-2H-pyrano[3,2-g]quinolin-2-one **17**, respectively. The condensation reaction of 6-formyl-7-hydroxy-1,2,2,4-tetramethyl-1,2-dihydroquinoline **5e** with methylene active compounds ethylcyanoacetate/dimethyl-3-oxopentanedioate/ethylacetoacetate/diethylmalonate/Meldrum's acid afforded 3-substituted dihydroquinoline containing coumarins **19** - **21**. The reaction of **5e** with malononitrile afforded a pentacyclic compound **22**.

The potential biological activities of the synthesized compounds were evaluated using the PASS computer program. According to the prognosis, the (E)-4-(N-methyl(benzyl)-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)but-3-en-2-ones **13 a, b** and (E)-4-(1-benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolin-6-yl)but-3-en-2-one **14** are most likely to have inhibitory activity against gluconate dehydrogenase, as well as anti-arthritis, anti-allergic, and anti-asthmatic properties. It was also found out that hydroquinolinecarbonitrile compounds **7** & **8** have a tendency to act as a good progesterone antagonists, anti-allergic, anti-asthmatic, and anti-arthritis with the Pa values ranging from 0.276 to 0.827. Among the coumarin moieties containing hydroquinolines, compounds **17**, **19a**, and **19c** were predicted to be a good progesterone antagonists with the Pa values of 0.710, 0.630 and 0.615; respectively.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. A separate [Supporting Information](#) consisting of the spectroscopic data of the synthesized compounds is provided with this manuscript. **Figure 1.** ¹H-NMR spectrum of 1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbonitrile **7**. **Figure 2.** ¹H-NMR spectrum of 1-benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-6-carbonitrile **8**. **Figure 3.** ¹H-NMR spectrum of (Z)-2-phenyl-4-((1,2,2,4-tetramethyl-1,2-dihydroquinolin-6-yl)methylene)oxazol-5(4H)-one **9a**. **Figure 4.** ¹H-NMR spectrum of (Z)-4-((1-benzyl-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)methylene)-2-phenyloxazol-5(4H)-one **9b**. **Figure 5.** ¹H-NMR spectrum of (Z)-2-phenyl-4-((1,2,2,4-tetramethyl-1,2,3,4-tetrahydroquinolin-6-yl)methylene)oxazol-5(4H)-one **10a**. **Figure 6.** ¹H-NMR spectrum of (Z)-4-((1-benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolin-6-yl)methylene)-2-

phenyloxazol-5(4H)-one **10b**. **Figure 7.** ^1H -NMR spectrum of (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**. **Figure 8.** ^1H -NMR spectrum of (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**. **Figure 9.** ^{13}C -NMR spectrum of (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**. **Figure 10.** ^1H -NMR spectrum of (E)-4-(1,2,2,4-tetramethyl-1,2-dihydroquinolin-6-yl)but-3-en-2-one **13a**. **Figure 11.** ^1H -NMR spectrum of (E)-4-(1-benzyl-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)but-3-en-2-one **13b**. **Figure 12.** ^1H -NMR spectrum of (E)-4-(1-benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolin-6-yl)but-3-en-2-one **14**. **Figure 13.** ^1H -NMR spectrum of methyl (Z)-2-(5,7,7,8-tetramethyl-2-oxo-7,8-dihydrofuro[3,2-g]quinolin-3(2H)-ylidene)acetate **16**. **Figure 14.** ^1H -NMR spectrum of 4,6,8,8,9-pentamethyl-8,9-dihydro-2H-pyrano[3,2-g]quinolin-2-one **17**. **Figure 15.** ^1H -NMR Spectrum of 6,8,8,9-tetramethyl-2-oxo-8,9-dihydro-2H-pyrano[3,2-g]quinoline-3-carbonitrile **19a**. **Figure 16.** ^1H -NMR spectrum of methyl 3-oxo-3-(6,8,8,9-tetramethyl-2-oxo-8,9-dihydro-2H-pyrano[3,2-g]quinolin-3-yl)propanoate **19b**. **Figure 17.** ^{13}C -NMR Spectrum of methyl 3-oxo-3-(6,8,8,9-tetramethyl-2-oxo-8,9-dihydro-2H-pyrano[3,2-g]quinolin-3-yl)propanoate **19b**. **Figure 18.** ^1H -NMR Spectrum of 3-acetyl-6,8,8,9-tetramethyl-8,9-dihydro-2H-pyrano[3,2-g]quinolin-2-one **19c**. **Figure 19.** ^1H -NMR Spectrum of ethyl 6,8,8,9-tetramethyl-2-oxo-8,9-dihydro-2H-pyrano[3,2-g]quinoline-3-carboxylate **19d**. **Figure 20.** ^1H -NMR Spectrum of 6,8,8,9-tetramethyl-2-oxo-8,9-dihydro-2H-pyrano[3,2-g]quinoline-3-carboxylic acid **21**. **Figure 21.** ^1H -NMR Spectrum 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**.

Data Availability Statement: The data used to support the findings of this study are included within the supplementary information file.

Acknowledgments: The authors acknowledge the Ministry of Education and Science of the Russian Federation for financial support (Project No. 4.2100.2014/K).

Conflicts of Interest: The authors declare that there are no conflicts of interest.

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