Development of an Efficient, One-Pot, Multicomponent Protocol for Synthesis of 8-Hydroxy-4-Phenyl-1,2-Dihydroquinoline Derivatives

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Abstract

A one pot quick and efficient multicomponent reaction has been developed for the synthesis of a new series of functionalized 8-hydroxy-4-phenyl-1,2-dihydroquinoline derivatives using 30 mol% ammonium acetate in ethanol as solvent. This economical protocol run smoothly to give variety of quinoline derivatives in 55-98% yield from inexpensive reagents and catalyst in mild reaction conditions. Various spectroscopic techniques like FTIR, ^{1}H NMR and ^{13}C NMR, MALDI-TOF-MS and EI-MS were employed to study and confirm their structure.

Keywords: Quinoline derivatives, 8-hydroxyquinoline, economical, heterocyclic, efficient protocol.

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1. Introduction

Multicomponent reactions attracted a great attention in recent years due to their simplicity, atom economy, and greater efficiency due to reduced number of intermediate purification steps that increase the yield of target products. These reactions are very useful for generation of a variety of heterocyclic compounds in one pot through one step or by many successive steps protocol from simple and inexpensive starting materials [1-18]. Quinoline derivatives are heterocyclic compounds that are used as selective and potent drugs against many diseases. They show excellent antiviral activity against dengue Zika and avian influenza virus [19-21] and now in current year even against COVID-19 [22-24]. Modification of quinoline moiety through substitution can improve its physical and chemical properties and also pharmacological behavior. Due to its wide range of pharmaceutical applications it is very popular compound to design new drugs for treatment of multiple diseases like cancer, dengue fever, malaria, tuberculosis, fungal infections, AIDS, Alzheimer's disease and diabetes etc. [25-56]. 8-Hydroxy quinoline is a vital part of various natural and pharmaceutically active compounds exhibiting a wide-range of biological activities [57-59]. On account of their vital role as medicinal agents [60-64] (**Figure 1**), 8-hydroxyquinolines have become important synthetic targets for chemists. No doubt a diverse range of synthetic protocols including both catalytic and non-catalytic have been developed for construction of new compounds with virtually boundless combinations of functionality having quinoline and 8-hydroxy quinoline scaffold [8, 65-72]. L-proline as catalyst was reported for the synthesis of quinoline derivatives from anilines but reaction time was 8-12h [66] so we use ammonium acetate as catalyst in one pot protocol which reduced the reaction time to 20min-120min. Ammonium acetate is used as catalyst as well as reagent in synthesis of a wide range of heterocyclic compounds [73, 74]. In this paper we report a quick and efficient three component

reaction of malononitrile, 2-aminophenol and functionalized aldehydes for the synthesis of 8-hydroxy-4-phenyl-1,2-dihydroquinoline derivatives catalyzed by ammonium acetate.µ

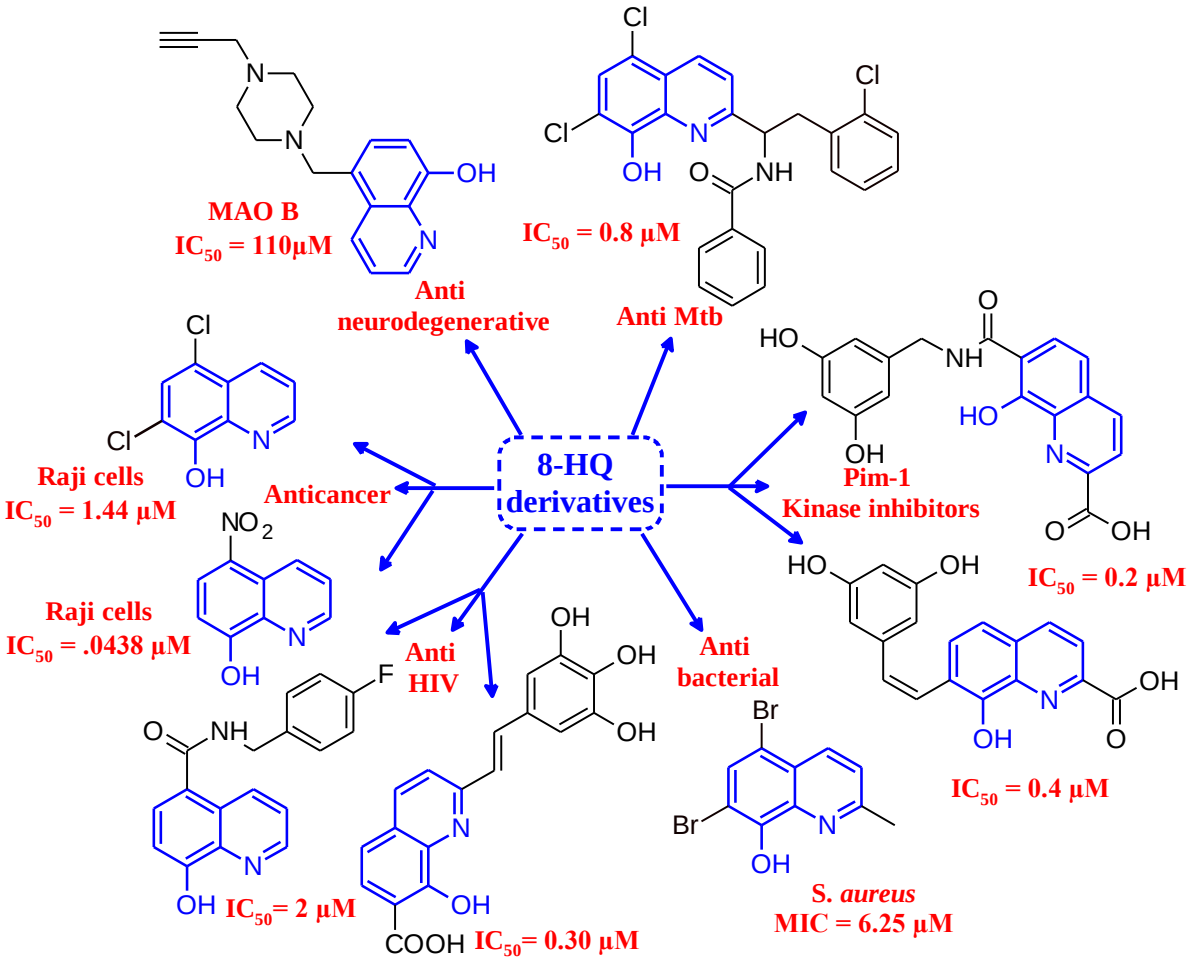
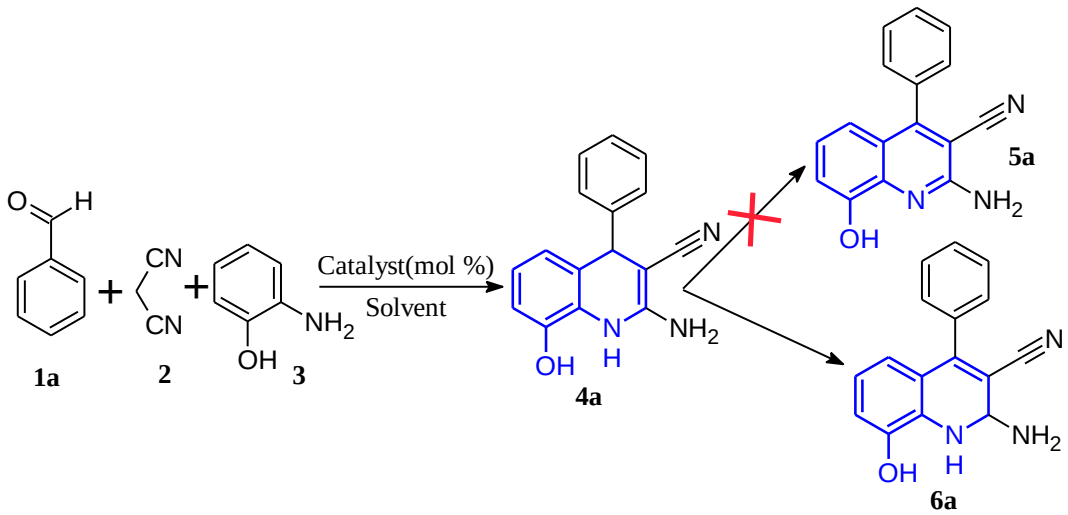


Figure. 1: 8-Hydroxy quinoline derivatives with potential pharmacological applications

2. Results and discussion

Our research work started with screening of catalyst for model reaction of benzaldehyd (**1a**) malononitrile (**2**) and 2-aminophenol (**3**) (**Scheme 1**) in the absence and presence of different catalysts. Surprisingly we did not get the product **5a** as reported [66] instead **6a** was produced in all screening protocols confirmed by ^{1}H-NMR and ^{13}C-NMR spectral analysis. To our delight according to screening results (Table 1 entry 1) without using any catalyst 43% of product was obtained in one hour at reflux temperature. This reaction proceeded through single step i.e.

benzylidenemalononitrile was not separated by the reaction of **1a** and **2** but when **3** was added, firstly intermediate was produced at room temperature then on reflux it yielded the product **6a,** that showed that 2-aminophenol itself acted as catalyst for Knoevenagel condensation of benzaldehyde and malononitrile. So to increase the yield we tried different catalyst and recorded results in **Table 1** and found that when Et_3N 10 mol% and 20 mol% (Table 1 entry 2 and 3) was used as catalyst product was obtained in 56% yield and increasing the amount of catalyst did not increase the yield of **6a**. With L. proline (Table 1 entry 4) Knoevenagel condensation reaction was not accomplished and benzaldehyde and malononitrile remained as such even after 24 hours of stirring. Then we tried different ammonium salts (Table 1 entries 5-9) as catalyst and amazingly got 68% yield of product with ammonium acetate in one hour at reflux temperature. Then we performed reaction with different quantities of ammonium acetate and best result was obtained with 30 mol% of ammonium acetate (Table 1 entry 12) which was 98% yield of product in just 20 min (5min stirring at room temperature (step 1) and 15 minutes stirring at reflux temperature(step 2)).



Scheme 1: Synthesis of **6a** as model reaction

Table 1. Screening of catalysts for model reaction.[a]

Entry	Conditions				Yield %[b]
	Catalyst (C)	C amount mol%	Solvent	Time	
1[c]	-	-	Ethanol	1h	43
2	Et_3N	10	Ethanol	2h	56
3	Et_3N	20	Ethanol	2h	56
4	L-Proline	20	Ethanol	24h	NR[d]
5	NH_4OAc	10	Ethanol	1h	68
6	$(NH_4)_2CO_3$	20	Ethanol: Water(4:1)	1h	37
7	NH_4Cl	20	Ethanol: Water(4:1)	24h	NR[d]
8	$(NH_4)_2SO_4$	20	Ethanol: Water(4:1)	24h	NR[d]
9	AcOH	20	Ethanol	24h	NR[d]
10	NH_4OAc	20	Ethanol	40min	83
11	NH_4OAc	25	Ethanol	30min	90
12	NH_4OAc	30	Ethanol	20min	**98**
13	NH_4OAc	35	Ethanol	20min	98

[a] Reaction conditions: **1a** (2mmol), **2** (2mmol), catalyst, Solvent (5mL) Stirred at room temperature then added **3** (2mmol) dissolved in 5mL solvent and refluxed.
[b] Isolated yield in hot reaction mixture.
[c] Without any catalyst.
[d] NR stands for no reaction.

After the selection of appropriate catalyst we further investigated different solvents for reaction (Table2 entries 1-9) and found that ethanol was the most suitable solvent for reaction as product separated during heating and no further purification was required except washing the product with hot ethanol In water and methanol(Table 2 entries 1 & 2) reaction was not proceeded while in ^{n}propanol and ^{n}butanol (Table 2 entries 4 & 5) product was separated after cooling and in very low yield i.e. 25% and 18% respectively. When THF and DMSO was used as solvent reaction

was accomplished as monitored by TLC but product was not separated even after cooling that might be due to the high solubility of products in these solvents.

Table 2. Screening of solvents for model reaction.[a]

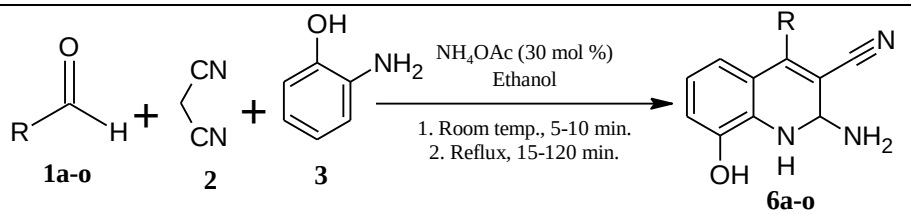
Entry	Conditions		Yield %[b]
	Solvent	Time	
1	Water	2h	NR[c]
2	Methanol	2h	NR[c]
3	Ethanol	20 min	98
4	^{n}Propanol	2h	25[d]
5	^{n}Butanol	2h	18[d]
6	DCM	40min	53
7	Ethanol: Water(1:1)	1h	70

[a] Reaction conditions: **1a** (2mmol), **2** (2mmol), catalyst (30 mol% NH_4OAc), Solvent (5mL) Stirred at room temperature then added **3** (2mmol) dissolved in 5mL solvent and refluxed.
[b] Isolated yield in hot reaction mixture.
[c] NR stands for no reaction.
[d] Product was isolated after cooling the reaction mixture at room temperature.

With optimized reaction conditions i.e. reaction of **1** and **2** at room temperature using ethanol as solvent in the presence of 30 mol% catalyst and then addition of **3** and reflux for required time, we further investigated the scope and generality of aldehydes for this multicomponent reaction and results are enlisted in **Table 3**. A variety of aldehydes non-substituted (**1a**, **1k**) and substituted with electron withdrawing groups such as NO_2 , Cl, Br, F and electron donating groups like OCH_3, CH_3 and OH reacted efficiently with 2-amino phenol(**3**) and malononitrile (**2**) and produced the corresponding 8-hydroxy-4-phenyl-1,2-dihydroquinoline derivatives in moderate to excellent yield (55-98%) under mild reaction conditions. Benzaldehyde (**1a)** produced the required products **6a** in highest yields which is 98% in just 20 minutes (1^{st} step was completed in 5 minutes and second step was completed in15 minutes). Substitution on aldehydes

effected the time of completion of reaction, for example non substituted aldehydes (**1a, 1k**) and *para* substituted aldehyde **1n** converted into products in 20 minutes while all other *para* substituted aldehydes yield product in 25 minutes, *meta* substituted aldehydes took 30-40 minutes for completion of reaction and for *ortho* substituted aldehydes longest time was required to convert the reactants into desired product (90-120 minutes). Substitution on aldehydes irrespective of electron withdrawing or electron donating groups, also effected the yield of corresponding quinoline derivatives **6,** such as *meta* substituted aldehydes like**1c, 1d, 1f, 1i, 1k** and **1l** furnished their corresponding products **6c, 6d, 6f, 6i**, **6k** and **6l** in higher yield 83%, 86%, 85%, 89%, 82% and 69% respectively as compared to *para* substituted aldehydes **1b, 1e, 1g, 1j** and **1m** which furnished the required products **6b, 6e, 6g, 6j** and **6m** in 74%, 78%, 82%, 65% and 67% yields respectively only *P*-tolualdehyde (**1n**) produced the required products **6n** in highest yields which is 96%. *Ortho* substituted aldehydes **1h** and **1o** produced the lowest yield of products which was for **6h** 58% and for **6o** 55%. Steric effect may be aroused due to steric hindrance of groups present at *ortho, meta and para* position of **1** as in *para* substituted aldehydes this effect is lowest as compared to *meta* substituted aldehydes while in *ortho* substituted aldehydes steric hindrance is highest which could be the reason of lowest yield. Some aldehydes did not gave the corresponding products, for example *para* dimethyl amino benzaldehyde only furnished the intermediate which did not get dissolved in hot ethanol and ultimately not reacted with **3** to yield product **6**, similarly heterocyclic aldehydes like 2-pyridine aldehyde, furfural aldehyde did not reacted with **2** to produce the intermediate which could yield the corresponding products.

Table 3. Substrate scope for synthesis of 8-hydroxy-4-phenyl-1,2-dihydroquinoline derivatives (**6a-o**).[a]



1a-o **2** **3** **6a-o**

Entry	Aldehyde	R	Time(min.)	Product	Yield (%)[b]
1	**1a**	-C_6H_5	20	**6a**	98
2	**1b**	*p*-OCH_3-C_6H_5	25	**6b**	74
3	**1c**	*m*-OCH_3-C_6H_5	40	**6c**	83
4	**1d**	*m*-Br-C_6H_5	35	**6d**	86
5	**1e**	*p*-NO_2-C_6H_5	25	**6e**	78
6	**1f**	*m*-NO_2-C_6H_5	30	**6f**	85
7	**1g**	*p*-Cl-C_6H_5	25	**6g**	82
8	**1h**	*o*-Cl-C_6H_5	90	**6h**	58
9	**1i**	*m*-Cl-C_6H_5	30	**6i**	89
10	**1j**	*p*-F-C_6H_5	25	**6j**	65
11	**1k**	*β*-Naphthyl	20	**6k**	82
12	**1l**	*m*-OH-C_6H_5	40	**6l**	69
13	**1m**	*p*-OH-C_6H_5	25	**6m**	67
14	**1n**	*p*-CH_3-C_6H_5	20	**6n**	96
15	**1o**	*o*-Br-C_6H_5	120	**6o**	55

[a] Reaction conditions: **1a** (5mmol), **2** (5mmol), catalyst (30 mol% NH_4OAc), Solvent (10 mL) Stirred at room temperature then added **3** (5 mmol) dissolved in 10 mL solvent and refluxed.
[b] Isolated yield in hot reaction mixture.

2.1. Structure Elucidation

Synthesis and structure of 8-hydroxyquinoline derivatives were confirmed by using different techniques like FTIR, ^{1}H-NMR, ^{13}C-NMR, MALDI-TOF-MS and EI-MS.

FTIR spectra of all synthesized compounds were recorded in 4000cm^{-1} to 600cm^{-1} domain and all spectra have prominent peaks characteristic of synthesized quinoline derivatives (**6a-6o**) (**Figures S1-S15**) such as NH_2, NH, OH, C≡N, C=C, C-N and C-O peaks in the vibrational range of 3500-1000 cm^{-1}. NH_2 stretching vibrations give rise to two bands in the region of 3500-3300 cm^{-1} one for asymmetric stretch at higher frequency and other for symmetric stretch at lower frequency while NH_2 bending vibrations appears as strong band in the region of 1600-1500 cm^{-1} [75] and NH peaks appear in the region of 3390 ± 60 cm^{-1} while C≡N showed peaks in the region of 2200-2100 cm^{-1} and stretching of OH attached with aromatic rings give rise to a broad peak from 3500-3000 cm^{-1} [76]. In all spectra of compounds **6a-o** all corresponding peaks are in accordance with the literature and proposed structure of quinoline derivatives [77-80]. All compounds showed two peaks for NH_2 stretching vibrations that is for asymmetric stretching band appear in the region of 3500-3400 cm^{-1} and symmetric stretching peak appear in the range of 3400-3300 cm^{-1} while for NH there was a single peak in all spectra in the region of 3400-3300 cm^{-1} except **6a** (**Figure 2**), **6h** and **6m** where NH peak is overlapped with NH_2 and OH peaks respectively. Aromatic C−H stretching vibrations are expected to appear in the region of 3200-3000 cm^{-1} which is characteristic region for C−H stretching vibrations [81, 82]. The aromatic C-H stretching bands of synthesized compounds are appeared in the expected region and is in good agreement with literature values [81, 82]. Most important peak for structure elucidation of carbonitrile compounds is C≡N as this group is present in target compounds so showed a strong and sharp peak in the region of 2200-2100 cm^{-1} which confirms the presence of this group in synthesized quinoline derivatives. C−N vibration are very difficult to interpret as there are a

number of possible band in this region. However by taking the help of literature [77-79] C−N bands are assigned to the bands in the range of 1165-1185 cm^{-1}. The FTIR peak observed in the range of 1640-11400 cm^{-1} assigned to C=C vibrations while bands in the range of 1525-1508 cm^{-1} to corresponding peak of NH_2 bending vibrations. C−O stretching vibration of C−OH bond appeared in the region of 1051-1025 cm^{-1}. C−X (where X = Cl, Br and F) also observed in their respective region that is C−F peak in **6j** appeared at 1231.29cm^{-1} while peak at 1093.80 and 1125.52 cm^{-1} appointed to C−Cl stretching vibrations in compounds **6g** and **6h** and C−Br peak in compounds 6d and 6o appeared at 1125.87 and 1125.89 cm^{-1} respectively. NO_2 group show two distinct peaks at 1550 and 1350 cm^{-1} assigned to asymmetric stretching and symmetric stretching vibration[76]. In reported compounds **6e** and **6f** asymmetric stretching band of NO_2 seems to be overlapped with NH_2 deformation band while NO_2 symmetric stretch is assigned to the peak appeared at 1344.97 and 1353.47cm^{-1} respectively. All the corresponding peaks of synthesized 8-hydroxy-1,2-dihydroquinoline derivatives are in accordance with literature[75-78, 82]. In ^{1}H-NMR and ^{13}C-NMR spectra of all synthesized compounds (**6a-6o**) **(Figures S16-S45)** all required signals conforming the respective proton and carbon nuclei of suggested structures are observed at agreeing chemical shifts (ppm) values which helped in unambiguous characterization of 8-hydroxy-4-phenyl-1,2-dihydroquinoline derivatives. ^{1}H-NMR spectra allows us to identify different proton's chemical shift values, as in our synthesized compounds CH present next to NH of quinoline ring showed a singlet peak in the region of 5.0-4.0 ppm while NH_2 protons appeared as singlet of integral two in the region of 5.5.5-5.1 ppm. Proton Hb showed a doublet (d) while Ha and Hc appeared as multiplet (m) signal in the range of 7.0-6.0 ppm, NH and OH groups appeared as overlapped broad peak at 6.8-6.6 ppm while aromatic protons of aldehyde benzene ring showed signals in the region of chemical shift value of 8.0-7.0 ppm for example, in ^{1}H-

NMR spectrum of **6a** (**Figure 3A**) it is clear that there is a peak of H_d at 4.5ppm while H_b due to coupling with neighboring *ortho* protons(H_a, H_c) showed a doublet with J= 8.1Hz at 6.65 ppm. Signals of protons H_a, H_c and H_{e-g} due to the presence of *ortho* as well as *meta* protons appeared as multiplet in the range of 6.32-6.26 ppm and 7.32-7.15 ppm respectively. NH_2 peak appeared as singlet at 5.23 ppm while NH and OH as overlapped broad peak at 6.79 ppm. In all synthesized quinoline derivatives carbon bonded to NH_2 (C2) group resonated at chemical shift value of 60-55 ppm while carbon atom attached with nitrile group is evident in the region of 102-100 ppm and carbon bonded to OH group which is C7 appeared in the region of 149-150 ppm. In addition, carbon C6 that is attached to nitrogen of pyridine ring also resonate at 149-150 ppm. Carbon of nitrile group (C12) appear at 129-136 ppm while C14 aldehyde ring carbon attached to quinoline ring showed a signal in the region of 142-148 ppm. Carbon of OCH_3 group (C21) in compounds **6b** and **6c** showed a signal at 55.5 and 55.4 ppm while carbon attached to methoxy group in these compounds resonated at 158.3 and 160.9 ppm respectively. Signals at 21.1 ppm in ^{13}C NMR spectra of compounds **6n** confirm the presence of CH_3 carbon nuclei while carbon attached to CH_3 group appear at 136.0 ppm. C−F carbon in compounds **6j** showed a doublet with coupling constant 240.75 ppm which is in accordance to literature [83]. C−F of compound **6j** showed two signals at 162.96 and 159.75 ppm. In exemplary ^{13}C-NMR spectrum of **6a** (**Figure 3B**) C≡N signal appeared at 129.9 ppm while carbons attached with NH_2, CN and OH groups showed peaks at 56.9, 100.5 and 149.4 ppm respectively.

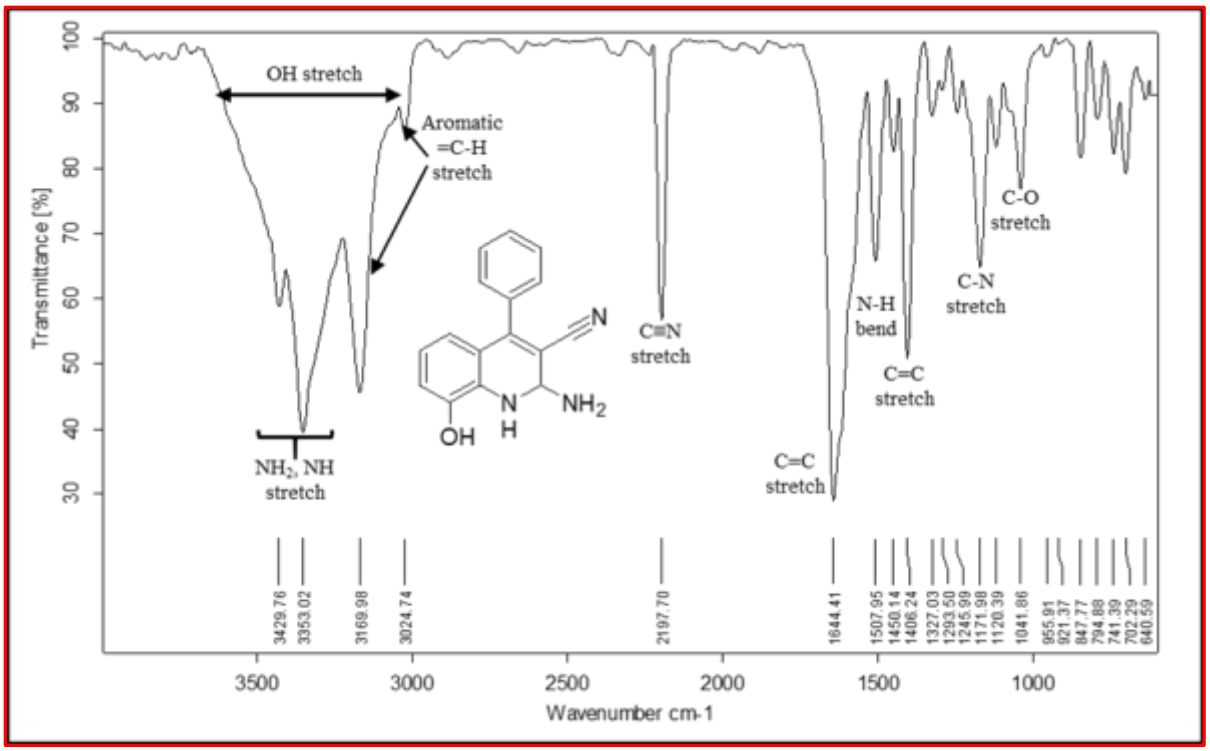


Figure 2: FTIR spectrum of 6a

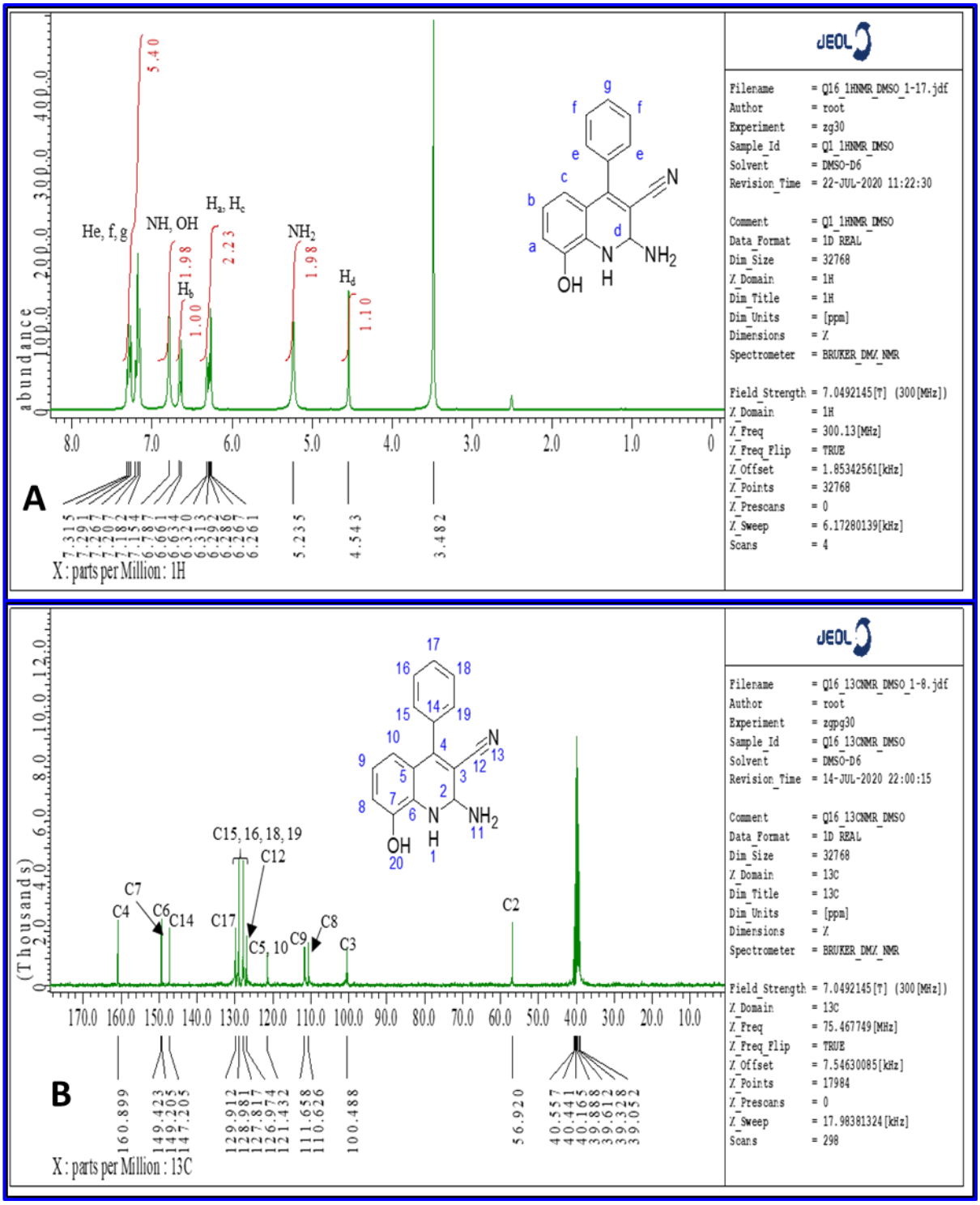


Figure 3: A) ^{1}HNMR spectrum of 6a B) ^{13}CNMR spectrum of 6a

Mass of the synthesized compounds were determined by MALDI-TOF-MS by using Alpha-Cyano-4-hydroxycinnamic acid (α-CHCA) as matrix in positive ion, reflectron mode and EI-MS

by using positive ion mode. MALDI-TOF uses soft ionization method to generate ions and is well known as a high throughput technique[84]. Previously it was mostly used for compounds with higher molecular weight but now a days it is also employed for compounds with low molecular weight with great success[85, 86]. Surprisingly $[M-H]^+$, $M^{+\cdot}$, $[M-H_2]^+$, and $[M-H-H_2]^+$ peaks also produced in addition to $[M+H]^+$ peaks in almost all investigated compounds(**Table 4**) (**Figures S46-S60**). $[M-H-H_2]^+$ peak observed as most intense peak in most of the spectra which may appear due to the removal of hydrogen molecule from $[M-H]^+$ ion and $[M-H]^+$ ion may be produced due to; a) transfer of hydrogen atom from radical cation of analyte or b) by hydride removal from neutral molecule of analyte, or c) removal of H_2 from protonated molecule of analyte [87-90]. $M^{+\cdot}$ ion may be observed due to removal of electron from parent molecule by photoionization process and $[M-H_2]^+$ by removal of H_2 from molecular ion. All these mechanisms may occur simultaneously or not depending on the structure of analyte molecule[91]. MALD-TOF-MS spectrum of **6a** (**Figure 4A**) showed $[M-H]^+$ peak at 262.72 m/z while EI-MS spectrum of **6a** (**Figure 4B**) showed molecular ion ($M^{+\cdot}$) peak at 263.2 m/z ratio which confirmed the mass of **6a.**

Table. 4: Observed MALDI-TOF-MS peaks of compounds **6a-o**

Compound	$M^{+\cdot}$	$[M+H]^+$	$[M-H]^+$	$[M-H_2]^+$	$[M-H-H_2]^+$
6a	-	-	262.72	261.75	260.69
6b	293.24	-	292.36	291.23	-
6c	-	-	292.72	291.05	290.71
6d	341.46	342.25	340.42	-	338.39
6e	308.61	-	307.66	-	305.66
6f	308.19	-	-	306.68	305.76
6g	297.17	-	-	295.06	294.67
6h	-	298.23	296.22	-	-

6i	297.05	298.11	296.58		294.54
6j	281.41	-	280.42	-	-
6k	-	-	312.09	311.04	310.72
6l	279.23	280.24	-	-	2276.37
6m	279.49	-	-	277.44	276.43
6n	277.38	-	276.03	-	274.78
6o	341.21	342.53	340.61	-	338.87

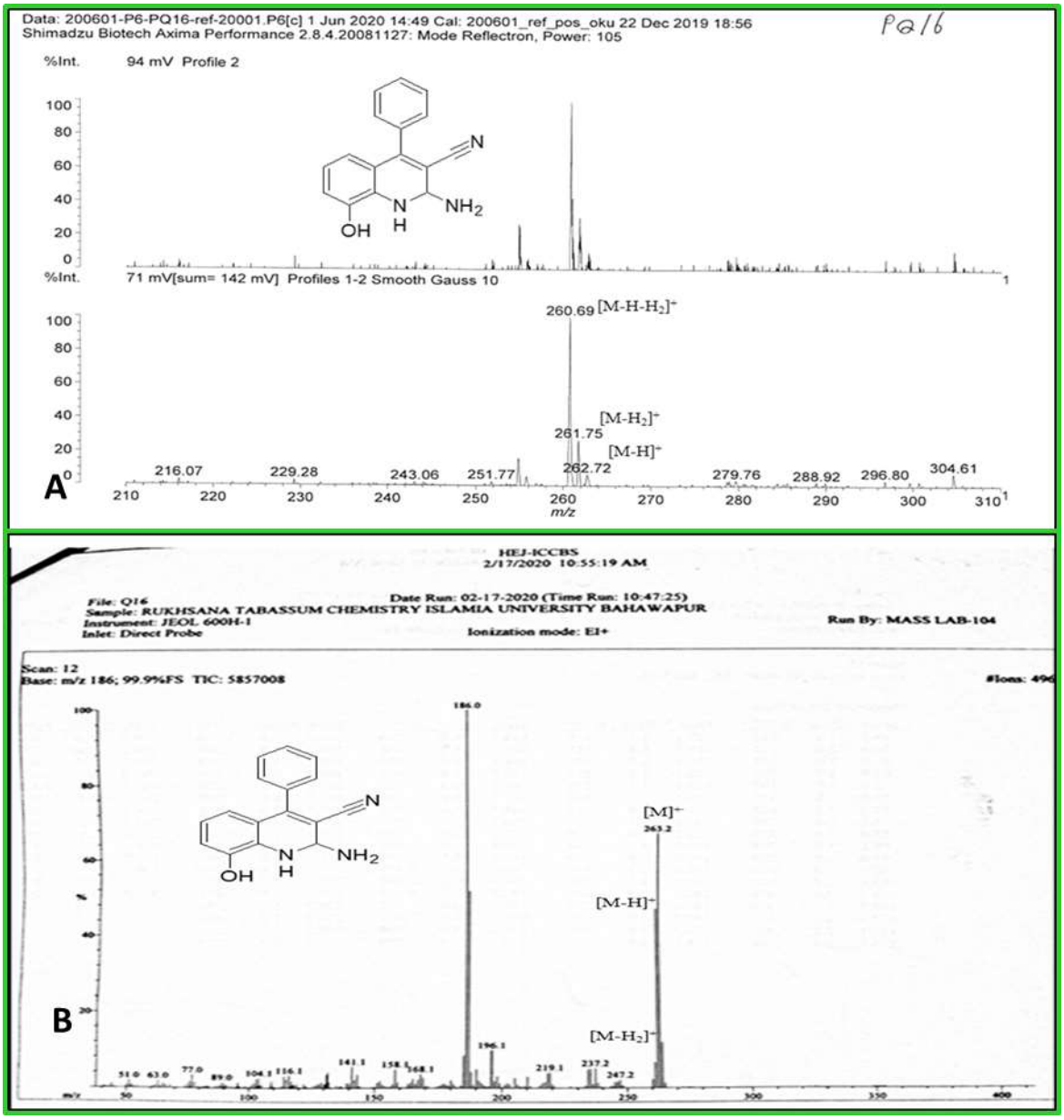
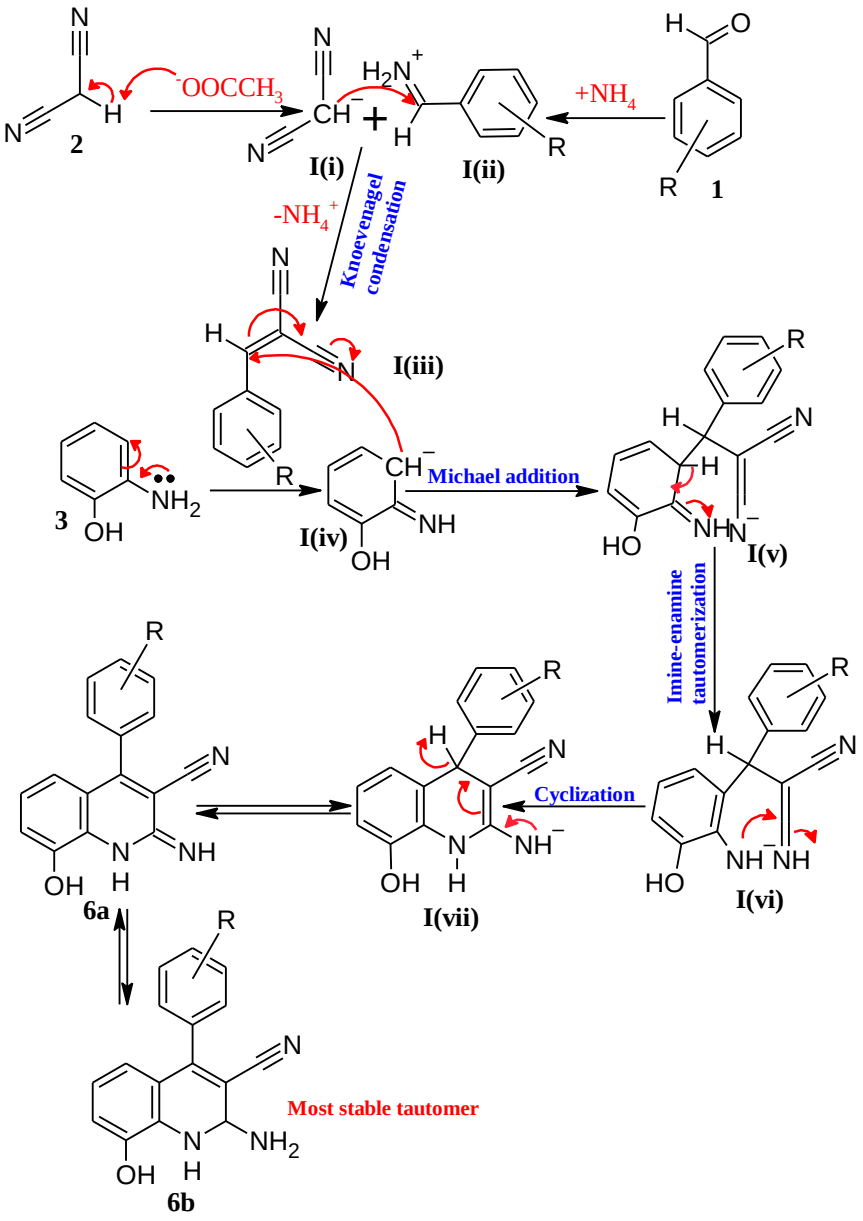


Figure 4: Mass spectra of 6a A) MALDI-TOF-MS B) EI-MS

2.1. Proposed mechanism

Based on the experimental results and previous literature [74, 92, 93] a proposed mechanism of the reaction was shown in **Scheme 2**. According to proposed mechanism acetate ion facilitate the removal of H from **2** to yield **I(i)** while ammonium ion catalyzed the formation of iminium ion (**I(ii)**) which due to higher reactivity than carbonyl group expedite the Knoevenagel condensation between **I(i)** and **I(ii)** followed by elimination of ammonium ion to yield benzylidenemalononitrile (**I(iii)**). Then benzylidenemalononitrile through Michael addition with intermediate **I(iv)** produced **I(v)** which by imine-enamine tautomerization and cyclization yielded **I(vi)** and **I(vii)** respectively. Intermediate **I(vii)** might exhibit in three possible tautomeric forms out of which **6b** is the most stable as indicated by NMR and mass spectral analysis.



Scheme 2: Proposed mechanism for the synthesis of compound **6**

3. Conclusion

In summary, we successfully synthesized 8-hydroxy-4-phenyl-1,2-dihydroquinoline derivatives (6a-o) by a convenient one pot, three component reaction in 55-98% yield. The reaction proceed though Knoevenagel condensation, Michael addition, rearrangements and cyclization. It is worth mentioning that this protocol proceeded without the use of toxic solvents, co-catalysts, precious metals, inert atmosphere and harsh reaction conditions. This one pot atom economic method

furnished excellent yield of corresponding products with a wide range of substituted aldehydes and thus provided high substrate scope under mild reaction conditions. Furthermore, all synthesized compounds were characterized by various techniques including FTIR, ^{1}H-NMR, ^{13}C-NMR, MALDI-TOF-MS and EI-MS which confirmed their synthesis. Additionally, significance of this protocol to a variety of substrates and bio screening of synthesized compounds are in progress in our laboratory.

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Abbreviations

8-HQ = 8-Hydroxyquinoline

MAO = Monoamineoxidase

Raji cells = Cell line derived from a human B cell lymphoma

HIV = Human immunodeficiency virus

Mtb = *Mycobacterium tuberculosis*

S. aureus = *Staphylococcus aureus*

MIC = Minimal inhibitory concentration

IC_{50} = Half maximal inhibitory concentration

4. Experimental

General information

All reagents were from Sigma Aldrich, Merck, Alfa Aesar and BDH and were used without further purification. Melting points were on Stuart SMP10 and are uncorrected. Silica gel plates were used to monitor the progress of reaction by TLC using acetone: n-hexane solvent system

(7:3) which were visualized under UV. FTIR spectra were recorded on Bruker Tensor 27 FTIR spectrophotometer using KBr discs. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker DMZ NMR spectrophotometer operating at 300 MHz. Mass spectra were recorded by MALDI-TOF-MS

technique on Shimadzu Biotech Axima Performance mass spectrometer using Alpha-Cyano-4-hydroxycinnamic acid (α-CHCA) as matrix in positive ion, reflectron mode. EI-MS spectra were recorded in positive ion mode using JEOL-600H-1 mass spectrometer.

General procedure for the synthesis of 8-hydroxy-4-phenylquinoline derivatives (6a-o)

To a 10 ml solution of malononitrile **2** (0.33g, 5.0 mmol) and ammonium acetate (0.116g, 30 mol %) in ethanol, respective benzaldehyde **1** (5.0 mmol) was added and stirred at room temperature for 5-10 minutes. Intermediate benzylidenemalononitrile was obtained as solid product which was then heated at 70℃ which helped to dissolve intermediate in ethanol. After getting clear solution of reaction mixture, solution of 2-amino phenol (0.545g, 5.0 mmol) in 10 mL ethanol was added in it and refluxed for 15-120 minutes. The solid thus obtained was filtered and washed with hot ethanol to obtain highly pure corresponding product **6a-o** in 55-98% yield.

2-amino-8-hydroxy-4-phenyl-1,2-dihydroquinoline-3-carbonitrile (**6a**)

Dark yellow solid, Yield: 98%, m.p: 218-220°C, Rf: 0.64 (Acetone: n-hexane (7:3)), FTIR (KBr disc, cm^{-1}): 3429.76, 3353.01 (NH_2, NH stretch), 3500-31 (OH), 3169.98 (Ar CH), 3024.74 (Ar CH), 2197.70 (C≡N), 1644.41 (C=C), 1507.95 (NH_2 bend), 1406.24 (C=C), 1171.98 (C−N), 1041.90 (C−O), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.32-7.15 (m, 5H, He, Hf, Hg), 6.79 (s, 2H, NH, OH), 6.65 (d, J = 8.1 Hz, 1H, Hb), 6.32-6.26 (m, 2H, Ha, Hc), 5.23 (s, 2H, NH_2), 4.54 (s, 1H, Hd), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 160.9 (C4), 149.4 (C7), 149.2 (C6), 147.2 (C14), 129.9 (C12), 129.0 (C16, C18), 127.8 (C15, C19), 127.0 (C17), 121.4 (C5, C10), 111.7 (C9),

110.6 (C8), 100.5 (C3), 56.9 (C2), MALDI-TOF-MS m/z: $[M-H]^+$, required for $C_{16}H_{12}N_3O^+$: 262.097, found: 262.72 EI-MS m/z: $M^{+\cdot}$ required for $C_{16}H_{13}N_3O^{+\cdot}$: 263.11, found: 263.2.

2-amino-8-hydroxy-4-(4-methoxyphenyl)-1,2-dihydroquinoline-3-carbonitrile (6b)

Dark yellow solid, Yield: 74%, m.p: 214-216°C, Rf: 0.69 (Acetone: n-hexane (7:3)), FTIR (KBr disc, cm^{-1}): 3447.91, 3366.47, 3314.98 (NH_2, NH stretch), 3229.85, 3187.3196, 3036.44 (Ar CH), 3012.07, 2955.86, 2903.02 (CH_3 stretch), 2188.67 (C≡N), 1636.15 (C=C), 1510.03 (NH_2 bend), 1414.22 (C=C), 1250.27 (C−N), 1031.74 (C−O), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.07 (d, *J* = 8.5 Hz, 2H, He), 6.85 (d, *J* = 8.5 Hz, 2H, Hf), 6.73 (s, 2H, NH, OH), 6.61 (d, *J* = 8.3 Hz, 1H, Hb), 6.30-6.23 (m, 2H, Ha, Hc), 5.22 (s, 2H, NH_2), 4.48 (s, 1H, Hd), 3.71 (s, 3H, OCH_3), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 160.7 (C4), 158.3(C17), 149.3 (C7), 149.1(C6), 139.3 (C14), 129.9 (C12), 128.9 (C15, C19), 121.5 (C10), 115.7 (C5), 114.3 (C16, C18), 111.6 (C9), 110.9 (C8), 100.4 (C3), 57.2 (C2), 55.5 (C21), MALDI-TOF-MS m/z: $[M-H]^+$, required for $C_{17}H_{14}N_3O_2^+$: 292.11, found: 292.63.

2-amino-8-hydroxy-4-(3-methoxyphenyl)-1,2-dihydroquinoline-3-carbonitrile (6c)

Yellow solid, Yield: 83%, m.p: 188-190°C, Rf: 0.61 (Acetone: n-hexane (7:3)), FTIR (KBr disc, cm^{-1}): 3460.94, 3377.73, 3337.81 (NH_2, NH stretch), 3009.90 (Ar CH), 2941.36, 2903.02 (CH_3 stretch), 2192.05 (C≡N), 1638.99 (C=C), 1511.91 (NH_2 bend), 1407.62 (C=C), 1270.5110 (C−N), 1044.98 (C−O), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.21 (t, *J* = 8.1 Hz, 1H, Hf), 6.78-6.65 (m, 6H, He, Hg, Hh, Hb, NH, OH), 6.30-6.22 (m, 2H, Ha, Hc), 5.24 (s, 2H, NH_2), 4.49 (s, 1H, Hd), 3.74 (s, 3H, OCH_3), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 160.9 (C18), 159.8(C4), 149.4 (C7), 149.2 (C6), 148.8 (C14), 130.1 (C12), 129.8 (C16), 121.4 (C5, C10), 120.0 (C15), 113.9 (C17), 111.8 (C19), 111.6 (C9), 110.4 (C8), 100.4 (C3), 56.7 (C2), 55.4 (C21), MALDI-TOF-MS m/z: $[M-H]^+$, required for $C_{17}H_{14}N_3O_2^+$: 292.11, found: 292.72.

2-amino-4-(3-bromophenyl)-8-hydroxy-1,2-dihydroquinoline-3-carbonitrile (6d)

Off white solid, Yield: 86%, m.p: 220-223°C, Rf: 0.65 (Acetone: n-hexane (7:3)), FTIR (KBr disc, cm^{-1}): 3461.42, 3378.56, 3336.89(NH_2, NH stretch), 3242.74, 3190.21, 3068.68 (Ar CH), 2192.58 (C≡N), 1639.21 (C=C), 1513.09 (NH_2 bend), 1413.58 (C=C), 1174.24 (C−N), 1125.87 (C−Br) 1035.80 (C−O), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.39 (d, *J* = 8.1 Hz, 1H, Hg), 7.32-7.24 (m, 2H, He, Hf), 7.19 (s, 1H, Hh), 6.88 (s, 2H, NH, OH), 6.65 (d, *J* = 8.3 Hz, 1H, Hb), 6.32-6.24 (m, 2H, Ha, Hc), 5.29 (s, 2H, NH_2), 4.58 (s, 1H, Hd), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 161.0 (C4), 150.0 (C7), 149.5 (C6), 149.4 (C14), 131.3 (C12), 130.4 (C17), 129.9 (C15), 129.9 (C18), 127.0 (C19), 122.3 (C16), 121.2 (C10), 111.7 (C9), 109.7 (C8), 100.4 (C3), 56.3 (C2), MALDI-TOF-MS m/z: $[M-H]^+$, required for $C_{16}H_{11}BrN_3O^+$: 340.00, found: 340.42.

2-amino-8-hydroxy-4-(4-nitrophenyl)-1,2-dihydroquinoline-3-carbonitrile (6e)

Yellow solid, Yield: 78%, m.p: 195-197°C, Rf: 0.64 (Acetone: n-hexane (7:3)), FTIR (KBr disc, cm^{-1}): 3478.24, 3433.18, 3386.56, 3338.31 (NH_2, NH stretch), 3108.20 (Ar CH), 2189.28 (C≡N), 1643.83 (C=C), 1573.82 (NO_2 asym. stretch), 1514.42 (NH_2 bend), 1412.37 (C=C), 1344.97 (NO_2 sym. stretch), 1174.53 (C−N), 1122.60 (C−N), 1043.36 (C−O), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.18 (d, J = 8.3 Hz, 2H, Hf), 7.43 (d, *J* = 8.3 Hz, 2H, He), 6.95 (s, 2H, NH, OH), 6.63 (d, *J* = 8.3 Hz, 1H, Hb), 6.30-6.26 (m, 2H, Ha, Hc), 5.31 (s, 2H, NH_2), 4.75 (s, 1H, Hd), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 161.0 (C4), 154.7 (C17), 149.7 (C7), 149.4 (C6), 146.6 (C14), 129.9 (C12), 129.1 (C15, C19), 124.5 (C16, C18), 121.0 (C10), 111.7 (C9), 109.0 (C8), 100.5 (C3), 55.7 (C2), MALDI-TOF-MS m/z: $[M-H]^+$, required for $C_{16}H_{11}N_4O_3^+$: 307.08, found: 307.66 .

2-amino-8-hydroxy-4-(3-nitrophenyl)-1,2-dihydroquinoline-3-carbonitrile (6f)

Yellow solid, Yield: 85%, m.p: 235-237°C, Rf: 0.71(Acetone: n-hexane (7:3)), FTIR (KBr disc, cm^{-1}): 3456.25, 3407.14, 3360.42 (NH_2, NH stretch), 3219.53, 3102.23, 3049.04 (Ar CH), 2182.19 (C≡N), 1648.94(C=C), 1578.20 (NO_2 asym. stretch), 1523.17, 1448.58 (NH_2 bend), 1401.14 (C=C), 1353.47 (NO_2 sym. stretch), 1176.40 (C−N), 1051.95 (C−O), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.06-8.01 (m, 2H, Hg, Hh), 7.62 (dd, *J* = 20.7, 7.9 Hz, 2H, He, Hf), 6.98 (s, 2H, NH, OH), 6.68 (d, *J* = 8.1 Hz, 1H, Hb), 6.36-6.33 (m, 2H, Ha, Hc), 5.31 (s, 2H, NH_2), 4.82 (s, 1H, Hd), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 161.1 (C4), 149.6 (C18), 149.5 (C7), 149.4 (C6), 148.4 (C14), 134.7 (C12), 130.6 (C15), 130.0 (C16), 122.2 (C17, C19), 121.2 (C10), 111.9 (C9), 109.3 (C8), 100.6 (C3), 56.1 (C2), MALDI-TOF-MS m/z: $[M]^+$, calcd for $C_{16}H_{12}N_4O_3^+$: 308.09, found: 308.19.

2-amino-4-(4-chlorophenyl)-8-hydroxy-1,2-dihydroquinoline-3-carbonitrile (6g)

Light yellow solid, Yield: 82%, m.p: 228-231°C, Rf: 0.70 (Acetone: n-hexane (7:3)), FTIR (KBr disc, cm^{-1}): 3446.95, 3367.26, 3314.64 (NH_2, NH stretch), 3229.62, 3187.99, 3040.58 (Ar CH), 2189.90 (C≡N), 1634.8708 (C=C), 1514.58 (NH_2 bend), 1414.14 (C=C), 1185.70 (C−N), 1093.80 (C−Cl), 1026.53 (C−O), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.34 (d, *J* = 8.3 Hz, 2H, Hf), 7.18 (d, *J* = 8.3 Hz, 2H, He), 6.85 (s, 2H, NH, OH), 6.62 (d, *J* = 8.3 Hz, 1H, Hb), 6.32-6.27 (m, 2H, Ha, Hc), 5.26 (s, 2H, NH_2), 4.58 (s, 1H, Hd), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 160.9(C4), 149.3 (C7, C6), 146.1 (C14), 131.6 (C12), 129.9 (C17), 129.7 (C16, C18), 128.9 (C15, C19), 121.3 (C10), 111.7 (C9), 110.0 (C8), 100.5 (C3), 56.5 (C2), MALDI-TOF-MS m/z: $[M]^+$, required for $C_{16}H_{12}ClN_3O^+$: 297.07, found: 297.17.

2-amino-4-(2-chlorophenyl)-8-hydroxy-1,2-dihydroquinoline-3-carbonitrile (6h)

White solid, Yield: 58%, m.p: 196-199°C, Rf: 0.66 (Acetone: n-hexane (7:3)), FTIR (KBr disc, cm^{-1}): 3477.12, 3378.93 (NH_2 stretch), 3219.14, 3051.65 (Ar CH), 2182.67 (C≡N), 1647.30

(C=C), 1511.02 (NH_2 bend), 1401.93 (C=C), 1177.08 (C−N), 1125.52 (C−Cl), 1038.82 (C−O), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.39 (d, *J* = 7.7 Hz, 1H, Hh), 7.30-7.16 (m, 3H, He, Hf, Hg), 6.87 (s, 2H, NH, OH), 6.61 (d, *J* = 8.3 Hz, 1H, Hb), 6.30 (dd, *J* = 10.5, 2.0 Hz, 2H, Ha, Hc), 5.27 (s, 2H, NH_2), 5.09 (s, 1H, Hd), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 161.2 (C4), 149.54 (C7), 149.46 (C6), 143.7 (C14), 132.3 (C12), 131.1 (C19), 130.1 (C17), 129.2 (C18), 128.8 (C15), 128.2 (C16), 121.1 (C10), 111.7 (C9), 109.4 (C8), 100.5 (C3), 55.5 (C2), MALDI-TOF-MS m/z: $[M-H]^+$, required for $C_{16}H_{11}ClN_3O^+$: 296.06, found: 296.22.

3.4.9. 2-amino-4-(3-chlorophenyl)-8-hydroxy-1,2-dihydroquinoline-3-carbonitrile (6i)

Off white solid, Yield: 89%, m.p: 222-224°C, Rf: 0.67 (Acetone: n-hexane (7:3)), FTIR (KBr disc, cm^{-1}): 3461.95, 3378.58, 3332.95 (NH_2, NH stretch), 3232.42, 3188.15, 3072.15 (Ar CH), 2193.12 (C≡N), 1637.79 (C=C), 1513.14 (NH_2 bend), 1414.94 (C=C), 1174.52 (C−N), 1125.91 (C−Cl), 1034.60 (C−O), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.34-7.13 (m, 4H, He, Hf, Hg, Hh), 6.88 (s, 2H, NH, OH), 6.66 (d, *J* = 8.3 Hz, 1H, Hb), 6.34-6.28 (m, 2H, Ha, Hc), 5.28 (s, 2H, NH_2), 4.60 (s, 1H, Hd), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 161.0 (C4), 149.7 (C7), 149.43 (C6), 149.40 (C14), 133.6 (C12), 130.9 (C18), 129.9 (C16), 127.5 (C17), 127.0 (C19), 126.6 (C15), 121.2 (C10), 111.8 (C9), 109.8 (C8), 100.5 (C3), 56.3 (C2), MALDI-TOF-MS m/z: $[M-H]^+$, calcd for $C_{16}H_{11}ClN_3O^+$: 296.06, found: 296.58 EI-MS m/z: $M^{+\cdot}$ required for $C_{16}H_{12}ClN_3O^{+\cdot}$: 297.07, found: 297.2.

2-amino-4-(4-fluorophenyl)-8-hydroxy-1,2-dihydroquinoline-3-carbonitrile (6j)

Off white solid, Yield: 65%, m.p: 215-218°C, Rf: 0.69(Acetone: n-hexane (7:3)), FTIR (KBr disc, cm^{-1}): 3450.07, 3368.91, 3317.09 (NH_2, NH stretch), 3232.29, 3189.48, 3050.86 (Ar CH), 2189.07 (C≡N), 1637.51 (C=C), 1509.25 (NH_2 bend), 1414.28 (C=C), 1231.29 (C−F), 1176.64 (C−N), 1030.38 (C−O), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.22-7.08 (m, 4H, He, Hf), 6.81 (s,

2H, NH, OH), 6.63 (d, *J* = 8.1 Hz, 1H, Hb), 6.29 (t, *J* = 8.7 Hz, 2H, Ha, Hc), 5.24 (s, 2H, NH_2), 4.58 (s, 1H, Hd), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 163.0 (C17, *J*= 242.66), 160.8 (C4), 159.8(C17, *J*= 242.66), 149.4 (C7), 149.3 (C6), 143.38 (C14), 143.35 (C5), 129.9 (C12), 129.7 (C15), 129.6 C19), 121.3 (C10), 15.5 (C16, C18), 111.7 (C9), 110.4 (C8), 100.5 (C3), 56.9 (C2), MALDI-TOF-MS m/z: $[M-H]^+$, required for $C_{16}H_{11}FN_3O^+$: 280.09, found: 280.42.

2-amino-8-hydroxy-4-(naphthalen-2-yl)-1,2-dihydroquinoline-3-carbonitrile (6k)

Off white solid, Yield: 82%, m.p: 260-262°C, Rf: 0.67 (Acetone: n-hexane (7:3)), FTIR (KBr disc, cm^{-1}): 3447.88, 3366.88, 3313.35 (NH_2, NH stretch), 3227.30, 3184.84, 3051.86 (Ar CH), 2188.97 (C≡N), 1636.44 (C=C), 1509.66 (NH_2 bend), 1413.05 (C=C), 1168.79 (C−N), 1032.80 (C−O), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.90-7.82 (m, 3H, Hf, Hh), 7.74 (s, 1H, He), 7.50-7.46 (m, 2H, Hg), 7.25 (dd, *J* = 8.5, 1.7 Hz, 1H, Hi), 6.85 (s, 2H, NH, OH), 6.65 (d, *J* = 9.0 Hz, 1H, Hb), 6.27 (dd, *J* = 5.7, 2.1 Hz, 2H, Ha, Hb), 5.26 (s, 2H, NH_2), 4.72 (s, 1H, Hd), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 160.8 (C4), 149.4 (C7), 149.3 (C6), 144.4 (C14), 133.3 (C12), 132.5 (C17), 130.1 (C22), 129.9 (C18), 128.9 (C21), 128.1 (C15), 128.0 (C16), 126.7 (C19), 126.5 (C20), 126.2 (C23), 125.8 (C5), 121.4 (C10), 111.7 (C9), 110.2 (C8), 100.5 (C3), 56.8 (C2), MALDI-TOF-MS m/z: $[M-H]^+$, required for $C_{20}H_{14}N_3O^+$: 312.11, found: 312.09.

2-amino-8-hydroxy-4-(3-hydroxyphenyl)-1,2-dihydroquinoline-3-carbonitrile (6l)

Off white solid, Yield: 69%, m.p: 217-220°C, Rf: 0.67(Acetone: n-hexane (7:3)), FTIR (KBr disc, cm^{-1}): 3414.20, 3353.32 (NH_2, NH stretch), 3138.79, 3037.49 (Ar CH), 2182.38 (C≡N), 1643.03 (C=C), 1512.23, 1479.26 (NH_2 bend), 1409.92 (C=C), 1169.48 (C−N), 1045.31 (C−O), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.08 (t, *J* = 7.8 Hz, 1H, Hf), 6.76 (s, 2H, NH, OH), 6.67-6.54 (m, 4H, He, Hg, Hh, Hb), 6.31-6.23 (m, 2H, Ha, Hc), 5.22 (s, 2H, NH_2), 4.42 (s, 1H, Hd), 3.52, ^{13}C-NMR (75 MHz, DMSO-d_6) δ 160.8 (C16), 157.9 (C4), 149.4 (C7), 149.2 (C6), 148.7 (C14),

129.8 (C18, C12), 121.5 (C10), 118.6 (C19), 114.5 (C17), 114.1 (C15), 111.6 (C9), 110.7 (C8), 100.4 (C3), 56.9 (C2), MALDI-TOF-MS m/z: $[M]^+$, required for $C_{16}H_{13}N_3O_2^+$: 279.10, found: 279.23.

2-amino-8-hydroxy-4-(4-hydroxyphenyl)-1,2-dihydroquinoline -3-carbonitrile (6m)

Light yellow solid, Yield: 67%, m.p: 264-266°C, Rf: 0.65 (Acetone: n-hexane (7:3)), FTIR (KBr disc, cm^{-1}): 3454.63, 3396.53, 3325.57 (NH_2, NH stretch), 3200.75, 3103.26, 3042.21(Ar CH), 2182.58 (C≡N), 1651.23 (C=C), 1509.34 (NH_2 bend), 1398.19 (C=C), 1168.60 (C−N), 1036.17 (C−O), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.32 (s, 1H, OH), 6.97 (d, *J* = 8.3 Hz, 2H, He), 6.72-6.61 (m, 5H, Hf, NH, OH, Hb), 6.31-6.23 (m, 2H, Ha, Hc), 5.19 (s, 2H, NH_2), 4.43 (s, 1H, Hd), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 160.7 (C17), 156.4 (C4), 149.3 (C7), 149.0 (C6), 137.7 (14), 129.9 (C12), 128.8 (C15, C19), 121.5 (C10), 115.9 (C5), 115.7 (C16, C18), 111.6 (C9), 111.3 (C8), 100.4 (C3), 57.4 (C2), MALDI-TOF-MS m/z: $[M]^+$, required for $C_{16}H_{13}N_3O_2^+$: 279.10, found: 279.29.

2-amino-8-hydroxy-4-(4-methylphenyl)-1,2-dihydroquinoline-3-carbonitrile (6n)

Light orange solid, Yield: 96%, m.p: 216-218°C, Rf: 0.70 (Acetone: n-hexane (7:3)), FTIR (KBr disc, cm^{-1}): 3453.1240, 3453.1240, 3371.9891, 3317.5286 (NH_2, NH stretch), 3231.94, 3187.58, 3034.65 (Ar CH), 2922.98 (CH_3 stretch), 2190.15 (C≡N), 1637.29 (C=C), 1512.01 (NH_2 bend), 1412.23 (C=C), 1174.58 (C−N), 1031.78 (C−O), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.07 (dd, *J* = 15.4, 8.1 Hz, 4H, He, Hf), 6.76 (s, 2H, NH, OH), 6.62 (d, *J* = 8.3 Hz, 1H, Hb), 6.28 (td, *J* = 8.3, 2.1 Hz, 2H, Ha, Hc), 5.04-5.42 (2H, NH_2), 4.49 (s, 1H, Hd), 2.25 (s, 3H, CH_3), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 160.8 (C4), 149.4 (7), 149.1 (C6), 144.3 (C14), 136.0 (C12), 129.9 (C5), 129.5 (C15, C19), 127.7 (C16, C18), 121.4 (C10), 111.6 (C9), 110.8 (C8), 100.4 (C3), 57.1 (C2),

21.1 (C21) MALDI-TOF-MS m/z: $[M-H]^+$, required for $C_{17}H_{14}N_3O^+$: 276.11, found: 276.03 EI-MS m/z: $M^{+\cdot}$ required for $C_{17}H_{15}N_3O^{+\cdot}$: 277.12, found: 277.2.

2-amino-4-(2-bromophenyl)-8-hydroxy-1,2-dihydroquinoline-3-carbonitrile (6o)

Off white solid, Yield: 55%, m.p: 195-197°C, Rf: 0.72 (Acetone: n-hexane (7:3)), FTIR (KBr disc, cm^{-1}): 3461.54, 3378.56, 3336.85 (NH_2, NH stretch), 3233.97, 3189.03, 3068.35 (Ar CH), 2192.58 (C≡N), 1639.28 (C=C), 1513.09 (NH_2 bend), 1413.49 (C=C), 1174.30 (C−N), 1035.17 (C−O), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.56 (d, *J* = 7.5 Hz, 1H, Hh), 7.30-7.11 (m, 3H, He, Hf, Hg), 6.88 (s, 2H, NH, OH), 6.63 (d, *J* = 7.5 Hz, 1H, Hb), 6.32 (d, *J* = 7.7 Hz, 2H, Ha, Hc), 5.20 (d, *J* = 43.3 Hz, 3H, NH2, Hd), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 161.1 (C4), 149.5 (C7, C6), 145.5 (C14), 133.2 (C12), 131.4 (C16), 129.2 (C19), 129.1 (C18), 128.8 (C17), 122.8 (C15), 121.0 (C10), 111.8 (C9), 109.6 (C8), 100.6 (C3), 55.9 (C2), MALDI-TOF-MS m/z: $[M+H]^+$, required for $C_{16}H_{11}BrN_3O^+$: 340.00, found: 340.61.

References

1. H. Christopher, G. Vijay, *Curr. Med. Chem.* **2003**, 10, 51
2. A. Dömling, *Chem. Rev.* **2006**, 106, 17
3. M. Ghandi, N. Zarezadeh, A. Taheri, *Tetrahedron Lett.* **2011**, 52, 1228
4. K. Lu, T. Luo, Z. Xiang, Z. You, R. Fathi, J. Chen, Z. Yang, *J. Comb. Chem.* **2005**, 7, 958
5. M. Murakami, *Angew. Chem. Int.* **2003**, 42, 718
6. C. Simon, T. Constantieux, J. Rodriguez, *Eur. J. Org. Chem.* **2004**, 2004, 4957
7. I. Ugi, B. Werner, A. Dömling, *Molecules* **2003**, 8, 53
8. J. Zhu, *Eur. J. Org. Chem.* **2003**, 2003, 1133
9. A. Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012**, 112, 3083
10. S. Zhi, X. Ma, W. Zhang, *Org. Biomol. Chem.* **2019**, 17, 7632
11. D. Paprocki, A. Madej, D. Koszelewski, A. Brodzka, R. Ostaszewski, *Frontiers in Chemistry* **2018**, 6

12. C. G. Neochoritis, T. Zarganes-Tzitzikas, K. Katsampoxaki-Hodgetts, A. Dömling, *Journal of Chemical Education* **2020**, 97, 3739
13. R. C. Cioc, E. Ruijter, R. V. A. Orru, *Green Chem.* **2014**, 16, 2958
14. R. P. Gore, A. P. Rajput, *Drug Invention Today* **2013**, 5, 148
15. C. Cimarelli, *Molecules* **2019**, 24, 2372
16. S. G. Cedric, V. R. Felipe, R. R. Kamilla, E. K. Arthur, *Current Organic Synthesis* **2019**, 16, 855
17. A. Chaudhary, *Molecular Diversity* **2020**,
18. J. E. Biggs-Houck, A. Younai, J. T. Shaw, *Current Opinion in Chemical Biology* **2010**, 14, 371
19. C. De la Guardia, D. E. Stephens, H. T. Dang, M. Quijada, O. V. Larionov, R. Lleonart, *Molecules* **2018**, 23, 672
20. Y. Han, H. T. Pham, H. Xu, Y. Quan, T. Mesplède, *J. Med. Virol.* **2019**, 91, 1182
21. J. Kos, C. F. Ku, I. Kapustikova, M. Oravec, H.-J. Zhang, J. Jampilek, *ChemistrySelect* **2019**, 4, 4582
22. A. K. Singh, A. Singh, A. Shaikh, R. Singh, A. Misra, *Diabetes Metab. Syndr.* **2020**, 14, 241
23. J. Gao, Z. Tian, X. Yang, *Biosci. trends* **2020**, 14, 72
24. L. Dong, S. Hu, J. Gao, *Drug Discov. Ther.* **2020**, 14, 58
25. R. Ghahremanzadeh, S. Ahadi, G. I. Shakibaei, A. Bazgir, *Tetrahedron Lett.* **2010**, 51, 499
26. C. Praveen, P. DheenKumar, D. Muralidharan, P. T. Perumal, *Bioorg. Med. Chem. Lett.* **2010**, 20, 7292
27. O. Afzal, S. Kumar, M. R. Haider, M. R. Ali, R. Kumar, M. Jaggi, S. Bawa, *Eur. J. Med. Chem.* **2015**, 97, 871
28. E. D. AlFadly, P. A. Elzahhar, A. Tramarin, S. Elkazaz, H. Shaltout, M. M. Abu-Serie, J. Janockova, O. Soukup, D. A. Ghareeb, A. F. El-Yazbi, R. W. Rafeh, N.-M. Z. Bakkar, F. Kobeissy, I. Iriepa, I. Moraleda, M. N. S. Saudi, M. Bartolini, A. S. F. Belal, *Eur. J. Med. Chem.* **2019**, 167, 161

29. L. Bonilla-Ramirez, A. Rios, M. Quiliano, G. Ramirez-Calderon, I. Beltrán-Hortelano, J. F. Franetich, L. Corcuera, M. Bordessoulles, A. Vettorazzi, A. López de Cerain, I. Aldana, D. Mazier, A. Pabón, S. Galiano, *Eur. J. Med. Chem.* **2018**, 158, 68

30. V. Calvillo-Páez, R. R. Sotelo-Mundo, M. Leyva-Peralta, J. C. Gálvez-Ruiz, D. Corona-Martínez, R. Moreno-Corral, R. Escobar-Picos, H. Höpfl, O. Juárez-Sánchez, K. O. Lara, *Chem.-Biol. Interact.* **2018**, 286, 34

31. K. Chalupova, J. Korabecny, M. Bartolini, B. Monti, D. Lamba, R. Caliandro, A. Pesaresi, X. Brazzolotto, A.-J. Gastellier, F. Nachon, J. Pejchal, M. Jarosova, V. Hepnarova, D. Jun, M. Hrabinova, R. Dolezal, J. Zdarova Karasova, M. Mzik, Z. Kristofikova, J. Misik, L. Muckova, P. Jost, O. Soukup, M. Benkova, V. Setnicka, L. Habartova, M. Chvojkova, L. Kleteckova, K. Vales, E. Mezeiova, E. Uliassi, M. Valis, E. Nepovimova, M. L. Bolognesi, K. Kuca, *Eur. J. Med. Chem.* **2019**, 168, 491

32. R. M. R. J. Da Silva, M. O. Gandi, J. S. Mendonça, A. S. Carvalho, J. P. Coutinho, A. C. C. Aguiar, A. U. Krettli, N. Boechat, *Bioorg. Med. Chem.* **2019**, 27, 1002

33. M. F. El Shehry, M. M. Ghorab, S. Y. Abbas, E. A. Fayed, S. A. Shedid, Y. A. Ammar, *Eur. J. Med. Chem.* **2018**, 143, 1463

34. H. M. Faidallah, A. S. Girgis, A. D. Tiwari, H. H. Honkanadavar, S. J. Thomas, A. Samir, A. Kalmouch, K. A. Alamry, K. A. Khan, T. S. Ibrahim, A. M. M. Al-Mahmoudy, A. M. Asiri, S. S. Panda, *Eur. J. Med. Chem.* **2018**, 143, 1524

35. Y.-L. Fan, X.-W. Cheng, J.-B. Wu, M. Liu, F.-Z. Zhang, Z. Xu, L.-S. Feng, *Eur. J. Med. Chem.* **2018**, 146, 1

36. Y.-L. Fan, J.-B. Wu, X.-W. Cheng, F.-Z. Zhang, L.-S. Feng, *Eur. J. Med. Chem.* **2018**, 146, 554

37. M. K. Ibrahim, M. S. Taghour, A. M. Metwaly, A. Belal, A. B. M. Mehany, M. A. Elhendawy, M. M. Radwan, A. M. Yassin, N. M. El-Deeb, E. E. Hafez, M. A. ElSohly, I. H. Eissa, *Eur. J. Med. Chem.* **2018**, 155, 117

38. F. Jafari, H. Baghayi, P. Lavaee, F. Hadizadeh, F. Soltani, H. Moallemzadeh, S. Mirzaei, S. M. Aboutorabzadeh, R. Ghodsi, *Eur. J. Med. Chem.* **2019**, 164, 292

39. S. Li, L. Hu, J. Li, J. Zhu, F. Zeng, Q. Huang, L. Qiu, R. Du, R. Cao, *Eur. J. Med. Chem.* **2019**, 162, 666

40. W. Luo, J.-W. Lv, T. Wang, Z.-Y. Zhang, H.-Y. Guo, Z.-Y. Song, C.-J. Wang, J. Ma, Y.-p. Chen, *Bioorg. Med. Chem.* **2019**, 28, 115190
41. S. K. Marvadi, V. S. Krishna, D. Sriram, S. Kantevari, *Eur. J. Med. Chem.* **2019**, 164, 171
42. S. K. Marvadi, V. S. Krishna, D. Sriram, S. Kantevari, *Bioorg. Med. Chem. Lett.* **2019**, 29, 529
43. A. Mrozek-Wilczkiewicz, K. Malarz, M. Rejmund, J. Polanski, R. Musiol, *Eur. J. Med. Chem.* **2019**, 171, 180
44. R. D. Overacker, S. Banerjee, G. F. Neuhaus, S. Milicevic Sephton, A. Herrmann, J. A. Strother, R. Brack-Werner, P. R. Blakemore, S. Loesgen, *Bioorg. Med. Chem.* **2019**, 27, 3595
45. J. Ramprasad, V. Kumar Sthalam, R. Linga Murthy Thampunuri, S. Bhukya, R. Ummanni, S. Balasubramanian, S. Pabbaraja, *Bioorg. Med. Chem. Lett.* **2019**, 29, 126671
46. A. G. Ribeiro, S. M. V. d. Almeida, J. F. de Oliveira, T. R. C. d. L. Souza, K. L. d. Santos, A. P. d. B. Albuquerque, M. C. d. B. L. Nogueira, L. B. d. Carvalho Junior, R. O. d. Moura, A. C. da Silva, V. R. A. Pereira, M. C. A. B. d. Castro, M. d. C. A. d. Lima, *Eur. J. Med. Chem.* **2019**, 182, 111592
47. T. G. Shruthi, S. Eswaran, P. Shivarudraiah, S. Narayanan, S. Subramanian, *Bioorg. Med. Chem. Lett.* **2019**, 29, 97
48. T. Stringer, L. Wiesner, G. S. Smith, *Eur. J. Med. Chem.* **2019**, 179, 78
49. T. Su, J. Zhu, R. Sun, H. Zhang, Q. Huang, X. Zhang, R. Du, L. Qiu, R. Cao, *Eur. J. Med. Chem.* **2019**, 178, 154
50. M. Taha, S. Sultan, S. Imran, F. Rahim, K. Zaman, A. Wadood, A. Ur Rehman, N. Uddin, K. Mohammed Khan, *Bioorg. Med. Chem.* **2019**, 27, 4081
51. K. D. Upadhyay, N. M. Dodia, R. C. Khunt, R. S. Chaniara, A. K. Shah, *ACS Med. Chem. Lett.* **2018**, 9, 283
52. P. Villa, N. Arumugam, A. I. Almansour, R. Suresh Kumar, S. M. Mahalingam, K. Maruoka, S. Thangamani, *Bioorg. Med. Chem. Lett.* **2019**, 29, 729
53. Z. Wang, J. Hu, X. Yang, X. Feng, X. Li, L. Huang, A. S. C. Chan, *J. Med. Chem.* **2018**, 61, 1871

54. G.-F. Zhang, X. Liu, S. Zhang, B. Pan, M.-L. Liu, *Eur. J. Med. Chem.* **2018**, 146, 599
55. G.-F. Zhang, S. Zhang, B. Pan, X. Liu, L.-S. Feng, *Eur. J. Med. Chem.* **2018**, 143, 710
56. J. Zhu, L.-N. Wang, R. Cai, S.-Q. Geng, Y.-F. Dong, Y.-M. Liu, *Bioorg. Med. Chem. Lett.* **2019**, 29, 1325
57. C. Crifar, A. A. Dörr, W. D. Lubell, *Tetrahedron Lett.* **2015**, 56, 3451
58. J. Achan, A. O. Talisuna, A. Erhart, A. Yeka, J. K. Tibenderana, F. N. Baliraine, P. J. Rosenthal, U. D'Alessandro, *Malar. J.* **2011**, 10, 144
59. C. Gómez, V. Kouznetsov, *Recent Developments on Antimicrobial Quinoline Chemistry*, in *Microbial pathogens and strategies for combating them: science, technology and education*, A. Mendez-Vilas, Editor. 2013, FORMATEX Publisher.
60. Y. n. Song, H. Xu, W. Chen, P. Zhan, X. Liu, *MedChemComm* **2015**, 6, 61
61. S. N. Al-Busafi, F. E. O. Suliman, Z. R. Al-Alawi, *Res. Rev. J. Chem.* **2014**, 3, 1
62. H. Jiang, J. E. Taggart, X. Zhang, D. M. Benbrook, S. E. Lind, W.-Q. Ding, *Cancer Lett* **2011**, 312, 11
63. P. Shah, L. F. Abadi, S. Gaikwad, D. Chaudhari, V. Kushwah, S. Jain, K. K. Bhutani, S. Kulkarni, I. P. Singh, *ChemistrySelect* **2018**, 3, 10727
64. K.-H. Lam, R. Gambari, K. K.-H. Lee, Y.-X. Chen, S. H.-L. Kok, R. S.-M. Wong, F.-Y. Lau, C.-H. Cheng, W.-Y. Wong, Z.-X. Bian, A. S.-C. Chan, J. C.-O. Tang, C.-H. Chui, *Bioorganic & Medicinal Chemistry Letters* **2014**, 24, 367
65. J. B. Bharate, R. A. Vishwakarma, S. B. Bharate, *RSC Adv.* **2015**, 5, 42020
66. A. Khalafi-Nezhad, S. Sarikhani, E. S. Shahidzadeh, F. Panahi, *Green Chem.* **2012**, 14, 2876
67. K. Kobayashi, S. Fujita, S. Fukamachi, H. Konishi, *Synthesis* **2009**, 2009, 3378
68. Y.-M. Ren, C. Cai, R.-C. Yang, *RSC Adv.* **2013**, 3, 7182
69. S. J. Tu, B. Jiang, R. H. Jia, J. Y. Zhang, Y. Zhang, C. S. Yao, F. Shi, *Org. Biomol. Chem.* **2006**, 4, 3664
70. Z. Fan, S. Yang, X. Peng, C. Zhang, J. Han, J. Chen, H. Deng, M. Shao, H. Zhang, W. Cao, *Tetrahedron* **2019**, 75, 868
71. A. Thanetchaiyakup, H. Rattanarat, N. Chuanopparat, P. Ngernmeesri, *Tetrahedron Lett.* **2018**, 59, 1014

72. R. Pagadala, S. Maddila, S. B. Jonnalagadda, *Green Chemistry Letters and Reviews* **2014**, 7, 131
73. R. Tayebee, A. Gohari, *Eurasian chem. commun.* **2020**, 2, 581
74. S. Kanakaraju, B. Prasanna, S. Basavoju, G. V. P. Chandramouli, *Arab. J. Chem.* **2017**, 10, S2705
75. V. Thanikachalam, V. Periyanayagasamy, J. Jayabharathi, G. Manikandan, H. Saleem, S. Subashchandrabose, Y. Erdogdu, *Spectrochim. Acta A* **2012**, 87, 86
76. N. P. G. Roeges, *A Guide to the Complete Interpretation of Infrared Spectra of Organic Structures*. 1994, New York: Wiley
77. R. F. Fernandes, P. H. F. Stroppa, G. R. Ferreira, A. D. da Silva, H. G. M. Edwards, L. F. C. de Oliveira, *Vib. Spectrosc.* **2016**, 86, 128
78. J. Mirek, Z. H. Urbanek, *Spectrochim. Acta A* **1981**, 37, 305
79. T. D. Le, N. N. Pham, T. C. Nguyen, *J. Chem.* **2018**, 2018, 4301847
80. T. Ren, J. Wang, G. Li, H. Cheng, Y. Li, *Spectrochimica acta. Part A, Molecular and biomolecular spectroscopy* **2014**, 129, 7
81. Ö. Dereli, S. Sudha, N. Sundaraganesan, *J. Mol. Struct.* **2011**, 994, 379
82. J. Mohan, *Organic spectroscopy: principles and applications*. 2000, India: Narosa Publishing House.
83. R. J. Spear, D. A. Forsyth, G. A. Olah, *J. Am. Chem. Soc.* **1976**, 98, 2493
84. J. H. Lee, H. S. Choi, K. A. Nasr, M. Ha, Y. Kim, J. V. Frangioni, *Anal. Chem.* **2011**, 83, 5283
85. S. Zhang, J. a. Liu, Y. Chen, S. Xiong, G. Wang, J. Chen, G. Yang, *J. Am. Soc. Mass Spectrom.* **2010**, 21, 154
86. P. J. Trim, M. F. Snel, *Methods (San Diego, Calif.)* **2016**, 104, 127
87. C. Kang, Y. Zhou, Z. Du, Z. Bian, J. Wang, X. Qiu, L. Gao, Y. Sun, *Int. J. Mass Spectrom.* **2013**, 48, 1318
88. H. Awad, M. J. Stoudemayer, L. Usher, I. J. Amster, A. Cohen, U. Das, R. M. Whittal, J. Dimmock, A. El-Aneed, *Int. J. Mass Spectrom.* **2014**, 49, 1139
89. X. Lou, A. J. H. Spiering, B. F. M. de Waal, J. L. J. van Dongen, J. A. J. M. Vekemans, E. W. Meijer, *Int. J. Mass Spectrom.* **2008**, 43, 1110

90. S. Sioud, N. Kharbatia, M. H. Amad, Z. Zhu, C. Cabanetos, A. Lesimple, P. Beaujuge, *Rapid Commun. Mass Spectrom.* **2014**, 28, 2389
91. J. L. Bronzel Jr, C. D. F. Milagre, H. M. S. Milagre, *J Mass Spectrom.* **2017**, 52, 752
92. Swathi Bandaru, R. K. Majji, S. Bassa, P. N. Chilla, R. Yellapragada, S. Vasamsetty, R. K. Jeldi, R. B. Korupolu, P. D. Sanasi, *Green Sustain. Chem.* **2016**, 6, 101
93. H. Sheibani, K. Saidi, M. Abbasnejad, A. Derakhshani, I. Mohammadzadeh, *Arab. J. Chem.* **2016**, 9, S901