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SHORT REVIEW

5-Oxo-hexahydroquinoline: an attractive scaffold with diverse biological activities

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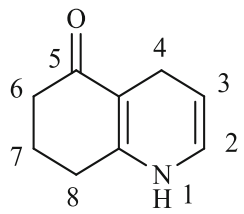
Abstract

5-Oxo-hexahydroquinoline (5-oxo-HHQ) represents a biologically attractive fused heterocyclic core. Various synthetic analogs of 5-oxo-HHQ have been synthesized and assessed for different biological activities. Some derivatives have exhibited myorelaxant, analgesic, anticancer, antibacterial, antifungal, antitubercular, antimalarial, antioxidant, anti-inflammatory, multidrug resistance reversal, anti-Alzheimer, neuroprotective, antidiabetic, antidyslipidemic and antiosteoporotic activities. This review provides a comprehensive report regarding the preparation and pharmacological characterization of 5-oxo-HHQ derivatives that have been reported so far. This information will be beneficial for medicinal chemists in the field of drug discovery to design and develop new and potent therapeutical agents bearing the 5-oxo-HHQ nucleus.

Keywords 5-Oxo-hexahydroquinoline · Biological effects · Multicomponent reaction · Medicinal chemistry · Structure–activity relationship · Anticancer

Introduction

5-Oxo-1,4,5,6,7,8-hexahyroquinoline (5-oxo-HHQ) (**1**) is a fused heterocycle which consists of a nitrogen containing doubly unsaturated six-membered nucleus, termed dihydropyridine (DHP) ring, and a cyclohexanone ring. During the last decades, compounds containing 5-oxo-HHQ core have been of great interest to the researchers due to their broad pharmacological and biological significance [1–6]. Accordingly, considerable attention has been given to the synthesis of various 5-oxo-HHQ derivatives using multicomponent reactions (MCRs) of diverse methodologies. This review provides a systematic study to assemble the chemical and pharmacological aspects of several synthesized 5-oxo-HHQ analogs reported to date.



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Synthesis of 5-oxo-HHQs and the derivatives

Multicomponent condensation reactions provide the synthesis of libraries of diverse small molecules in one-pot procedure using several condensation reagents [7, 8]. 5-Oxo-HHQs are synthesized by a type of MCR called Hantzsch reaction which is used widely for the synthesis of symmetrical and unsymmetrical DHPs. The reaction includes cyclocondensation of an aldehyde, β-ketoester, 1,3-cyclohexanedione and ammonia or ammonium acetate either in acetic acid or in refluxing ethanol (Scheme 1) [9, 10]. Some modifications for this typical method have been applied in

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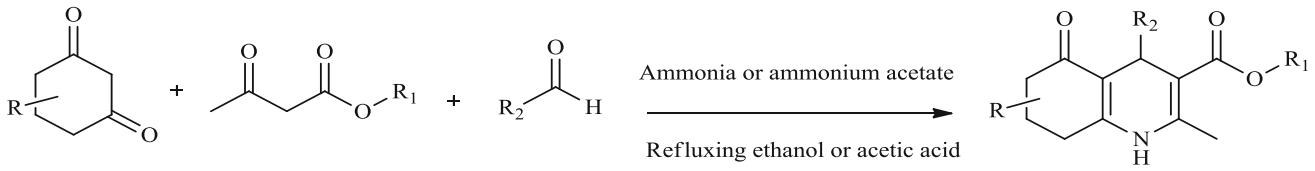
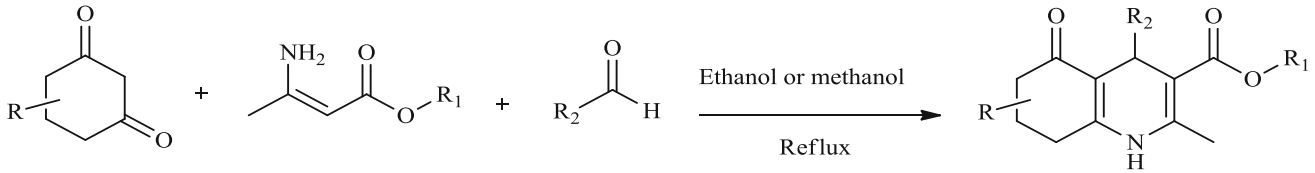
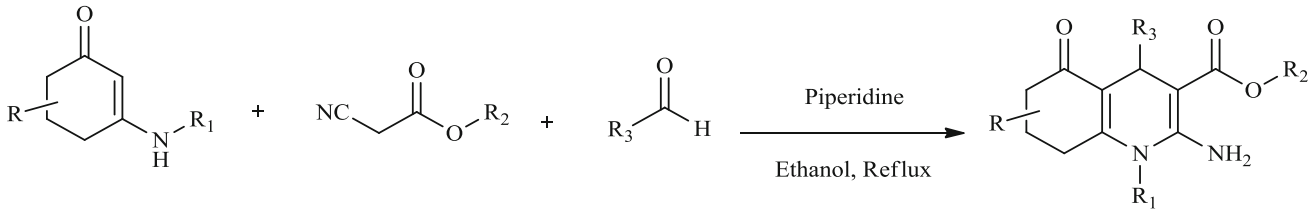


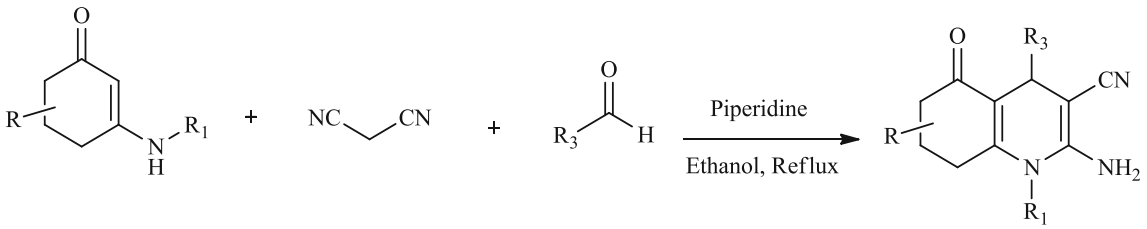
Scheme 1 Typical Hantzsch reaction for the synthesis of 3-carboxylate-substituted 5-oxo-HHQs using β-ketoester, aldehyde, 1,3-cyclohexanedione and ammonia or ammonium acetate



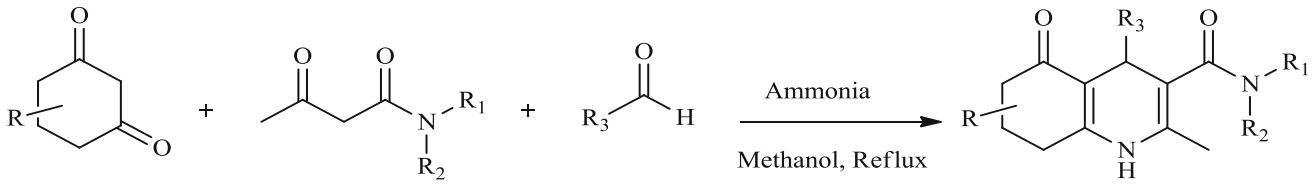
Scheme 2 Schematic representation of synthetic route for the preparation of 3-carboxylate-substituted 5-oxo-HHQs using β-aminocrotonate



Scheme 3 Synthetic route for the preparation of N-substituted 2-amino-5-oxo-HHQs bearing carboxylate moieties at C_3 position



Scheme 4 Synthetic route for the preparation of N-substituted 2-amino-5-oxo-HHQs bearing cyanide function at C_3 position



Scheme 5 Synthetic route for the preparation of 5-oxo-HHQs having carboxamide substitutions at C_3 position

order to achieve diverse biologically active HHQs with various substitutions at all positions.

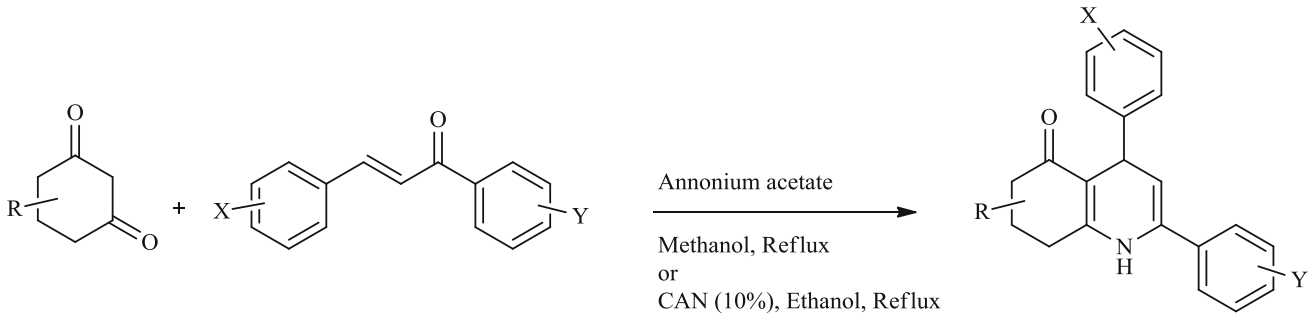
Instead of the β-ketoester compounds, β-aminocrotonate derivatives may be used for the synthesis of 5-oxo-HHQs (Scheme 2). In this case, there is no need to use ammonia as the source of nitrogen [1, 11].

N-substituted 2-amino-5-oxo-HHQs can be prepared via a one-pot three-component cyclocondensation reaction between N-substituted cyclohexane-enaminone, ethylcyanoacetate and an aldehyde in the presence of a catalytic amount of a base such as piperidine (Scheme 3) [5].

Substitution of a cyanide group at C_3 of N-substituted 2-amino-5-oxo-HHQs is also possible by the reaction of N-substituted cyclohexane-enaminone, an aldehyde and malononitrile in the presence of a catalytic amount of a base such as piperidine (Scheme 4) [5, 12].

Cyclocondensation of 1,3-cyclohexanedione, different aldehydes and ammonia with various acetoacetamides leads to 5-oxo-HHQ derivatives with different carboxamide substitutions at C_3 position of HHQ core (Scheme 5) [1, 3].

C_3-unsubstituted 5-oxo-HHQs containing aryl moieties at C_2 and C_4 positions have been obtained by proceeding



Scheme 6 Synthesis of C_3-unsubstituted 5-oxo-HHQs containing aryl moieties at C_2 and C_4 positions

through reaction of 1,3-cyclohexanedione, chalcone derivatives and ammonium acetate in methanol or ethanol as solvents (Scheme 6) [13, 14]. The reaction is also possible by a solid-state green synthetic route without using solvent and catalyst at 80 °C in high yields [15].

The traditional synthetic methods suffer from numerous disadvantages such as low yields, long reaction time, use of volatile organic solvents and harsh reaction conditions. Therefore, in recent years, an increasing focus has been put in the discovery of green synthetic approaches toward the synthesis of 5-oxo-HHQs. In this vein, new synthetic strategies using more effective energy sources and less harmful solvents as well as reproducible and biodegradable catalysts to achieve the 5-oxo-HHQ scaffold have been developed. The use of ultrasound and microwave irradiations, grinding technique, solvent-free approaches, ionic liquids, reusable nano-catalysts, organocatalyst and nano-metal organic frameworks has been reported in some studies [16–25]. Some synthetic routes reported in the literatures are summarized in Table 1.

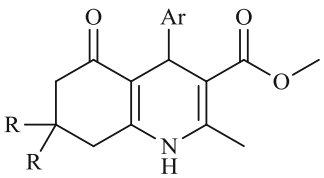
Biological activities of various functionalized 5-oxo-HHQs

Calcium channel modulatory activity

L-type calcium channel modulatory activity

L-type channels are responsible for regulating contractility in muscle cells [80]. Blockers and activators of L-type calcium channels are commonly used for treatment of cardiovascular diseases [81]. Since the discovery of the 1,4-DHPs, such as nifedipine and Bay K 8644 as potent calcium channel blockers and activators, many DHP analogs have been synthesized in order to investigate the structure–activity relationships and to find more effective compounds [82–86]. In this vein, some studies with the aim of fixing one carbonyl group in an antiperiplanar position by anellation at the DHP structure and introduction of the 1,4-DHP moiety into condensed systems have been done and revealed that 5-oxo-HHQ core, the condensed ring system of the DHP structure, could be proposed as a considerable scaffold in the field of drug discovery as potential cardiovascular agents [87–92].

U. Rose described the synthesis and calcium modulatory evaluation of some 5-oxo-HHQ derivatives. The racemic hexahydroquinolines **2** and **3** showed positive inotropic effects at the electrically stimulated left guinea pig atrium and suppressed $BaCl_2$-induced contractions of the guinea pig ileum dose dependently with activity rates comparable to those of nifedipine [88, 90, 93].



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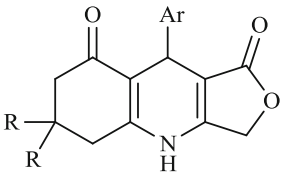

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In 2000, Şimşk et al. synthesized a series of 2,6,6-trimethyl-3-carbomethoxy(ethoxy)-4-aryl-hexahydroquinoline analogs and evaluated their calcium antagonistic activity in rat aortic rings precontracted with 30 mM K^+. It was demonstrated that substitution of the phenyl ring at C_4 position with a pyridine ring resulted in increased calcium antagonistic activity, so that compound **4** displayed the highest activity among other tested derivatives [91]. In a subsequent study, 23 compounds with 2-ethyl-3-carbmethoxy-4-aryl-5-oxo-6,6-dimethyl-hexahydroquinoline structure have been evaluated and compounds **5**, **6**, **7**, **8**, **9** and **10** showed good calcium antagonistic activity on isolated rat ileum lamb carotid artery [92]. Moreover, in 2007, Şimşk et al. reported the synthesis and evaluation of some novel 3-alkyloxycarbonyl-4-(disubstituted)aryl-5-oxo-hexahydroquinoline derivatives and found that introduction of a second electron-withdrawing substituent into the phenyl ring increased the activity. Results indicated that compound **11**, containing 5-chloro-2-nitrophenyl, was the most active compound comparable to nifedipine as the positive control [1].

Table 1 Summary of synthetic routes reported in the literatures

Substrates	Energy supply	Solvent	Catalyst	Temp/Power	Time	Yield (%)	Compound	References
Dimedone, propionic (or isobutyric) aldehyde, 2-cyanothioacetamide, *N*-methylmorpholine, alkyl halides	–	Ethanol	–	20 °C	4 h and then 3 h	68–90	2-Alkylthio-7,7-dimethyl-5-oxo-4-ethyl(isopropyl)-3-cyano-hexahydroquinolines	[26]
Dimedone, arylidenemalononitrile, ammonium acetate	Heat	Acetic acid	–	Reflux	5 h	63–72	2-Amino-7,7-dimethyl-5-oxo-4-ary-hexahydroquinoline-3-carbonitrile	[27]
Arylidenemalononitrile, enhydrazinoketone	Heat	Ethanol	–	Reflux	5 min–8 h	58–84	2-Amino-4-aryl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitriles containing different amine substituents on 1 position	[27]
Cyanothioacetamide, 1,3-cyclohexanedione, 4-chlorobenzaldehyde	–	Ethanol	Piperidin	20 °C	6 h	66	4-(4-Chlorophenyl)-3-cyano-5-oxo-hexahydroquinoline-2-thiol	[28]
Benzylidenemalononitrile, *N*-hetaryl-substituted enaminoketones	–	Ethanol	Piperidin	Reflux	15–20 min	85–95	2-Amino-5-oxo-hexahydroquinoline-3-carbonitriles with different aromatic substitutions at 1 and 4 positions	[38]
Aryl aldehyde, ethylacetoacetate, 1,3-cyclohexanedione, ammonium acetate	Heat	–	$[MoO_2(L)(MeOH)]$ in molten tetra-butylammonium bromide (TBAB)	110 °C	7–15 min	84–92	Ethyl-1,4,5,6,7,8-hexahydro-2-methyl-5-oxo-4-aryl quinoline-3-carboxylates	[29]
Aromatic aldehydes, malononitrile, cyclicβ-enaminoketones	Heat	Water	Tetrabutylammonium fluoride (TBAF)	Reflux	30–300 min	88–96	2-Amino-5-oxo-hexahydroquinoline-3-carbonitriles with different aromatic substitutions at 1 and 4 positions	[30]
N–*N*-diethyl aminoacetamide, 4,4(5,5)-dimethyl-1,3-cyclohexanedione, aromatic aldehyde, ammonia	Heat	Methanol	–	Reflux	4–5 h	Not reported	*N*,*N*-diethyl-2,6,6- or 2,7,7-trimethyl-5-oxo-4-(disubstituted phenyl)-hexahydroquinoline-3-carboxamides	[31]
Aldehyde, ammonium acetate, dimedone, ethyl acetoacetate	–	Ethanol	Threo-(1S,2S)-2-amino-1-(4´-nitrophenyl)-1,3-propanediol (ANP)	RT	4–5 h	75–95	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[32]

Table 1 continued

Substrates	Energy supply	Solvent	Catalyst	Temp/Power	Time	Yield (%)	Compound	References
5-(Trifluoromethyl)-1,3-cyclohexanedione, acetoacetate ester, aryl aldehyde, ammonium acetate	Heat	Trifluoroethanol	–	50 °C	25 min	72–99	2-Methyl-5-oxo-7-trifluoromethyl-4-aryl-hexahydroquinoline-3-carboxylic acid ethyl ester	[33]
5-(Trifluoromethyl)-1,3-cyclohexanedione, aryl aldehyde, ammonium acetate	Heat	Trifluoroethanol	–	50 °C	50 min	79	9-(4-Fluorophenyl)-3,6-bis(trifluoromethyl)-hexahydroacridine-1,8(2H,5H)-dione	[33]
Cyanoselenoacetamide with aromatic aldehydes, cyclohexane-1,3-dione, *N*-methylmorpholine	–	Ethanol	–	20 °C	15 min	22–80	*N*-methylmorpholinium 4-aryl-3-cyano-5-oxo-hexahydroquinoline-2-selenolates	[34]
Aryl aldehyde, dimedone, ammonium acetate, ethyl acetoacetate	Heat	Ethanol/H_2O	AgI nanoparticles	Reflux	45–75 min	80–94	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[35]
Dimedone, malononitrile or ethyl cyanoacetate, 4-(piperidin-1-ylsulfonyl)aniline or 4-(morpholin-4-ylsulfonyl)aniline, aromatic aldehyde	Heat	Ethanol	Ammonium chloride	70 °C	200–360 min	52–70	2-Amino-7,7-dimethyl-5-oxo-4-aryl-1-[4-(piperidin-1-ylsulfonyl)phenyl]-hexahydroquinoline-3-carbonitrile or ethyl 2-amino-7,7-dimethyl-5-oxo-4-aryl1-[4-(piperidin-1-ylsulfonyl)phenyl]-hexahydroquinoline-3-carboxylate	[36]
Dimedone, malononitrile or ethyl cyanoacetate, 4-(piperidin-1-ylsulfonyl)aniline or 4-(morpholin-4-ylsulfonyl)aniline	Ultrasonic irradiation	Ethanol	Ammonium chloride	70 °C	38–65 min	81–96	2-Amino-7,7-dimethyl-5-oxo-4-aryl-1-[4-(piperidin-1-ylsulfonyl)phenyl]-hexahydroquinoline-3-carbonitrile or ethyl 2-amino-7,7-dimethyl-5-oxo-4-aryl1-[4-(piperidin-1-ylsulfonyl)phenyl]-hexahydroquinoline-3-carboxylates	[36]
5,5-Dimethyl-3-((3-methyl-4-phenyl-1H-pyrazol-5-yl)amino) cyclohex-2-enone, arylidenemalononitrile	Heat	Ethanol	Piperidine	Reflux	3 h	83–89	2-Amino-7,7-dimethyl-1-(3-methyl-4-phenyl-1H-pyrazol-5-yl)-5-oxo-4-aryl-hexahydroquinoline-3-carbonitriles	[37]

Table 1 continued

Substrates	Energy supply	Solvent	Catalyst	Temp/Power	Time	Yield (%)	Compound	References
Ethyl 5-((5,5-dimethyl-3-oxocyclohex-1-en-1-yl)amino)-3-phenyl-1H-pyrazole-4-carboxylate, arylidenemalononitrile	Heat	Ethanol	Piperidine	Reflux	3 h	81–87	Octahydropyrazolo [4′,3′:5,6]pyrimido[1,2-a]quinoline-6-carbonitriles	[37]
Aryl aldehyde, ammonium acetate, dimedone, ethyl acetoacetate	Mild Heat	Perfluorodecalin	Hafnium (IV) bis(perfluorooctane sulfonyl)imide complex [$Hf(NPf)_4$]	60 °C	2–8 h	83–95	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[38]
Aryl aldehydes, dimedone, ethyl acetoacetate, ammonium acetate	Heat	Solvent-free	Silica gel-supported polyphosphoric acid (PPA-SiO_2)	80 °C	40–60 min	85–92	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[39]
Isatin, malononitrile, 3-anilino-5,5-dimethylcyclohex-2-en-1-one enaminone	–	THF	Ethylenediamine diacetate (EDDA)	RT	7 h	72	Spirooxindole bearing 5-oxo-hexahydroquinolins	[40]
Aromatic aldehyde, malononitrile, dimedone, ammonium acetate	MWI	Solvent-free	–	–	6–8 min	80–94	2-Amino-7,7-dimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carbonitriles	[41]
1,3-Cyclohexanedione, arylaldehyde, β-ketoester, ammonium acetate	–	Ethanol	Ceric ammonium nitrate (CAN)	RT	25 min–1.5 h	88–98	Ethyl 2-methyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[42]
Aromatic and aliphatic aldehydes, dimedone, ethyl acetoacetate, ammonium acetate	Heat	Ethanol	Montmorillonite K10 clay	80 °C	20–100 min	34–97	Ethyl 2-methyl-5-oxo-hexahydroquinoline-3-carboxylate derivatives containing aromatic/aliphatic moieties on position 4	[43]
1,3-Diaryl-2-propen-1-one, dimedone, ammonium acetate	Heat	Solvent-free	–	80 °C	2–5 h	82–92	7,7-Dimethyl-5-oxo-2,4-diaryl-hexahydroquinolines	[15]
Aryl aldehyde, PEG 4000-bound acetoacetate 1,3-cyclohexanedione, ammonium acetate	MWI	Solvent-free	Polyphosphoric acid	400 W	3–4 min	90–95	Ethyl 2-methyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates[a]	[44]
Aldehyde, dimedone, beta-ketoesters, ammonium acetate	Grinding	Solvent-free	–	RT	12–45 min	56–95	Methyl/Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[18]

Table 1 continued

Substrates	Energy supply	Solvent	Catalyst	Temp/Power	Time	Yield (%)	Compound	References
Aldehyde, dimedone, malononitrile or ethyl cyanoacetate, ammonium acetate	Grinding	Solvent-free	–	RT	15–25 min	65–88	2-Amino-4-phenyl-7,7-dimethyl-5-oxo-hexahydroquinolines bearing CN or COOET at position 3	[18]
Aryl aldehyde, dimedone, ethyl acetoacetate, ammonium acetate	MWI	Acetonitrile	Glycine	180 W 80 °C	1–3 min	90–98	Ethyl 2-methyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[45]
5,5-Dimethyl-1,3-cyclohexadione or 1,3-cyclohexadione, aromatic aldehyde, methyl acetoacetate, ammonium acetate	Mild heat	Few drops of ethanol	Silica sulfuric acid	50 °C	3.0–5.5 h	83–95	Methyl 4-(4-aryl)-2-methyl-5-oxo-hexahydroquinoline-3-carboxylates	[46]
5,5-Dimethyl-3-aminocyclohex-2-enone, aromatic aldehyde, acyl acetonitrile	Heat	1-Butyl-3-methylimidazolium bromide ([bmim]Br)	–	80 °C	4–8 h	90–96	5-Oxo-hexahydroquinoline-3-carbonitriles containing different aromatic substitutions at 1, 2 and 4 positions	[47]
Aromatic aldehyde, 1,3-cyclohexanediones, β-ketoesters, anhydrous ammonium carbonate	MWI	Water	–	300 W 60 °C	5 min	89–96	Methyl/ethyl 4-(4-aryl)-2-methyl-5-oxo-hexahydroquinoline-3-carboxylates	[48]
Aryl aldehydes, dimedone, malononitrile, ammonium acetate	Mild heat	Solvent-free	Melamine trisulfonic acid (MTSA)	60 °C	2.5–3.5 h	85–95	2-Amino-4-phenyl-3-cyano-7,7-dimethyl-5-oxo-hexahydroquinoline derivatives	[49]
Aromatic aldehydes, alkyl acetoacetate, ethyl acetoacetate, ammonium acetate	Heat	Solvent-free	FeF_3	75–80 °C	1 h	85–95	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[50]
Aromatic aldehydes, dimedone, methyl acetoacetate, ammonium acetate	–	Water	Triton X-100	RT	25–130 min	87–98	Methyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[51]
Dimedone, arylaldehyde, β-ketoester, ammonium acetate	Mild heat	Solvent-free	Ionic liquid 1,3-disulfonic acid imidazolium hydrogen sulfate {[Dsim]HSO_4}	50 °C	25–40 min	88–96	Methyl/Ethyl 2,7,7-methyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[52]

Table 1 continued

Substrates	Energy supply	Solvent	Catalyst	Temp/Power	Time	Yield (%)	Compound	References
Dimedone, aryl aldehyde, methyl/ethyl acetoacetates, ammonium acetate	Mild heat	Solvent-free	Ionic liquid sulfonic acid-functionalized pyridinium chloride [pyridine-SO_3H]Cl	50 °C	5–13 min	96–76	Methyl/Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[53]
Aromatic aldehydes, malononitrile, dimedone, arylamines	Heat	Solvent-free	Zirconium hydrogenphosphate $Zr(HPO_4)_2$ H_2O	80 °C	2 h	95–98	2-Amino-7,7-dimethyl-5-oxo-1,4-diaryl-hexahydroquinoline-3-carbonitrile derivatives	[54]
Dimedone, ethyl acetoacetate, ammonium acetate, various aromatic and aliphatic aldehydes	–	Water	2-methyl pyridinium trifluoromethane-sulfonate ([2-MPyH]OTf)	RT	1–15 min	92–98	Ethyl 2,7,7-trimethyl-5-oxo -hexahydroquinoline-3-carboxylates containing different aromatic/aliphatic substitutions on 4 position	[17]
Dimedone, an aldehyde, methyl/ethyl acetoacetates, ammonium acetate	–	Water	Dispersed magnetic nanoparticles (DMNPs) of γ-Fe_2O_3	RT	2–3 h	90–96	Methyl/Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[55]
4-(Prop-2-ynyloxy)benzaldehyde or 3-methoxy-4-(prop-2-ynyloxy)benzaldehyde, substituted aryl azide, dimedone or cyclohexane-1,3-dione, ethyl acetoacetate, ammonium acetate	Ultrasonic irradiation	PEG 400	$CuSO_4 \cdot 5H_2O$ and sodium ascorbate	RT	25–45	86–93	1,2,3-Triazole-linked pentasubstituted 5-oxo-HHQs	[56]
4-(Prop-2-ynyloxy)benzaldehyde or 3-methoxy-4-(prop-2-ynyloxy)benzaldehyde, substituted aryl azide, dimedone or cyclohexane-1,3-dione, ethyl acetoacetate, ammonium acetate	MWI	PEG 400	PEG 400	50 °C	10–18	90–95	1,2,3-Triazole-linked pentasubstituted 5-oxo-HHQs	[56]
Aromatic aldehydes, 1,3-dione, b-ketoester and ammonium acetate	–	Solvent-free	Nano-ionic liquid and 1-methylimidazolium trinitromethanide {[HMIM]$C(NO_2)_3$	RT	5–33 min	90–98	Methyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates and methyl 4-(4-aryl)-2-methyl-5-oxo-hexahydroquinoline-3-carboxylates	[57]

Table 1 continued

Substrates	Energy supply	Solvent	Catalyst	Temp/Power	Time	Yield (%)	Compound	References
Aromatic aldehyde, dimedone, enaminone, ammonium acetate	Mild heat	Water	Brønsted acidic hydrogensulfate ionic liquid immobilized SBA-15 [MPIm][HSO_4]@SBA-15	45 °C	2–3 h	88–96	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[58]
Dimedone, 1,3-diphenyl-2-propen-1-one derivatives, ammonium acetate	Heat	Solvent-free	Silica-supported perchloric acid ($HClO_4$–SiO_2)	80 °C	2–3 h	85–96	7,7-Dimethyl-5-oxo-2,4-diphenyl-hexahydroquinoline derivatives	[59]
Cyclic enaminoketones, malononitrile, aromatic aldehydes	Ultrasonic irradiation	Ethanol	ZnO nanoparticles	80 °C	27–55 min	88–93	2-Amino-5-oxo-hexahydroquinoline-3-carbonitriles with different substitutions on 4 and 7 positions	[60]
Dimedone, aryl aldehyde, acetoacetanilide, ammonium acetate	Grinding	Ethanol	p-toluenesulfonic acid (p-TSA)	RT	10–25	72–84	4-Aryl-2,7,7-trimethyl-5-oxo-*N*-phenyl-hexahydroquinoline-3-carboxamides	[61]
2-(3-Methylthienylidene)malononitrile, 5,5-dimethyl-3-arylamino-2-cyclohexanone	Heat	Solvent-free	–	200 °C	1 h	72–80	2-Amino-1-aryl-7,7-dimethyl-4-hetaryl-5-oxo-hexahydroquinoline-3-carbonitriles	[25]
Aromatic aldehyde, dimedone, ethyl acetoacetate, ammonium acetate	Mild heat	Solvent-free	Ionic liquid 1-butyl-3-sulfonic acid imidazolium chloride, [Bsim]Cl	60 °C	4–10 min	89–94	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[62]
Aromatic aldehydes, dimedone, ethyl acetoacetate, ammonium acetate		Solvent-free	acidic ionic liquids [NMP][H_2PO_4], [NMP][HSO_4], [Et_3N-H][HSO_4], [L-Pro_2][SO_4], [L-Pro][NO_3]	RT	7–16 min	90–95	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[63]
Dimedone, arylaldehyde, β-ketoester, ammonium acetate	Mild heat	Solvent-free	Silica-bonded imidazolium-sulfonic acid chloride (SBISAC)	50 °C	5–12 min	85–93	Methyl/Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[64]

Table 1 continued

Substrates	Energy supply	Solvent	Catalyst	Temp/Power	Time	Yield (%)	Compound	References
Aromatic aldehydes, dimedone, β-ketoester, ammonium acetate	Heat	Solvent-free	Silica-coated magnetic nanoparticle immobilized ionic liquid $\{Fe_3O_4@Si_2@(CH_2)_3ImC(CN)_3$	80–85 °C	20–45 min	78–95	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[65]
1,3-Diaryl-2-propen-1-ones, dimedone, ammonium acetate	Heat	Solvent-free	Triethylamine	80 °C	20–55 min	84–97	2,4-Diaryl-5-oxo-hexahydroquinolines	[66]
Dimedone, aryl aldehyde, beta-ketoester, ammonium acetate	Heat	Solvent-free	$ZrOCl_2{\cdot}8H_2O$	85 °C	40–180 s	75–96	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[67]
Aromatic aldehydes, dimedone, ammonium acetate, ethyl or methyl acetoacetate	–	Ethanol	Fe_3O_4@chitosan	RT	30–140 min	98–84	Ethyl/methyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[68]
Aromatic aldehydes, dimedone, ethyl acetoacetate, ammonium acetate	–	Solvent-free	Ionic liquid 2-ethyl imidazolium hydrogen sulfate, [2-Eim] HSO_4	RT	7–11 min	90–95	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[69]
5,5-Dimethylcyclohexane-1,3-dione, aromatic aldehyde, malononitrile, ammonium acetate	MWI	Ethanol	Triethylamine	100 W	12 min RT	92–98	2-Amino-7,7-dimethyl-5-oxo-4-ary-hexahydroquinoline-3-carbonitriles	[23]
Aldehydes, dimedone, ethyl acetoacetate, ammonium acetate	–	Solvent-free	ionic liquid, 1-sulpopyridinium chloride	110 °C	25–35 min	84–93	Ethyl 2,7,7-trimethyl-5-oxo-hexahydroquinoline-3-carboxylates bearing various moieties on 4 position	[70]
Aldehyde, dimedone, ethyl/methyl acetoacetate, ammonium acetate	Heat	Solvent-free	Chitosan	60 °C	5–19 min	45–91	Ethyl/methyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[22]
1,3-Cyclic di-ketone, aromatic aldehyde, malononitrile, ammonium acetate	Mild heat	Solvent-free	Nano-Fe_3O_4@TDI@TiO_2	70 °C	14–40 min	82–95	2-Amino-5-oxo-hexahydroquinoline-3-carbonitriles with different substitutions on 4 and 7 positions	[71]

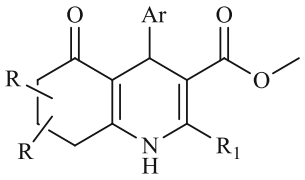
Table 1 continued

Substrates	Energy supply	Solvent	Catalyst	Temp/Power	Time	Yield (%)	Compound	References
Dimedone, aryl Aldehyde, ethyl acetoacetate, ammonium acetate	Mild heat	Solvent-free	Nano-Mn-[4-nitrophenyl-salicylaldimine-methyl pyranopyrazole]Cl_2 (nano-[Mn–4NSMP]Cl_2)	50 °C	4–24 min	52–96	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[24]
Aryl aldehydes, 1,3-cyclohexadione or dimedone, β-ketoesters and ammonium acetate	Heat	Solvent-free	Nano 4,4′ (butane-1,4-diyl)bis(1-sulfo-1,4-diazabicyclo[2.2.2]octane-1,4-diium)tetrachloride (NS-C_4(DABCO-$SO_3H)_2$)·4Cl)	100 °C	2–50 min	80–100	Ethyl/methyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates or ethyl/methyl 4-(4-aryl)-2-methyl-5-oxo-hexahydroquinoline-3-carboxylates	[72]
Ethylacetoacetate, aldehyde, dimedone and ammonium acetate	–	Solvent-free	Nano-silica-bonded sulfuric acid supported on KIT-5 (SO_3H-KIT-5)	90 °C	60–85 min	63–91	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl/alkyl-hexahydroquinoline-3-carboxylates	[73]
Aromatic aldehyde, dimedone, ethyl acetoacetate, ammonium acetate	Heat	Ethanol/H_2O	KH_2PO_4	120 °C	5 h	24–95	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[74]
Aromatic aldehyde, dimedone, ammonium acetate	Heat	Ethanol/H_2O	KH_2PO_4	100 °C	5 h	85–96	Acridine-1,8-diones	[74]
Aryl aldehydes, dimedone, ethyl acetoacetate, ammonium acetate	–	Solvent-free	Tris(hydroxymethyl)methyl ammonium acetate supported on graphene oxide	RT	15–30 min	70–98	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[75]
Dimedone or cyclohexane-1,3-dione, Aromatic aldehydes, malononitrile, ammonium acetate	Heat	Solvent-free	Sulfamic acid-functionalized nano-titanium dioxide (n-TiO_2–$NHSO_3H$)	80 °C	20–50 min	85–97	2-Amino-1-aryl-7,7-dimethyl-4-aryl-5-oxo-hexahydroquinoline-3-carbonitriles	[76]

Table 1 continued

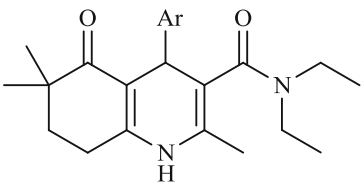
Substrates	Energy supply	Solvent	Catalyst	Temp/Power	Time	Yield (%)	Compound	References
Aromatic aldehydes, dimedone, ammonium acetate, ethylacetoacetate	MWI	Solvent-free	Nano-$Ni_{0.35}Cu_{0.25}Zn_{0.4}Fe_2O_4$	400 W	2–4 min	80–97	Ethyl 2,7,7-trimethyl-5-oxo-hexahydroquinoline-3-carboxylates with various aromatic and hetero aromatic moieties on 4 position	[77]
Aromatic aldehydes, dimedone, methyl acetoacetate, ammonium acetate	Heat	Solvent-free	Mesoporous vanadium ion-doped titania nanoparticles	RT and then 80 °C	10–20 min	65–94	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[20]
Aromatic aldehydes, malononitrile, cyclicβ-enaminoketones	Heat	H_2O/Ethanol	Crown ether complex cation ionic liquids (CECILs)	Reflux	10–20 min	85–91	2-Amino-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitriles with different substitutions at positions 1, 4 and 7	[78]
Dimedone, ammonium acetate, aryl aldehydes, malononitrile	Heat	Ethanol	*N*-(3-silyl propyl) diethylene triamine *N*,*N*′,*N*″-tri-sulfonic acid immobilized on $Fe_{3-x}Ti_xO_4$ magnetic nanoparticles	75 °C	$T_1 = 40$ min $T_2 = 10$–25 min	83–93	2-Amino-7,7-dimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carbonitriles	[79]
Aldehydes, dimedone, ethyl acetoacetate, ammonium acetate	Heat	Ethanol	Carbon microsphere-supported metallic copper nanoparticles (Cu-NP/C)	Reflux	2 h	82–94	Ethyl 2,7,7-trimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carboxylates	[21]

[a]The obtained solid from MWI rout was then added to a NaOEt (1 N)/EtOH solution to yield the final products at room temperature overnight



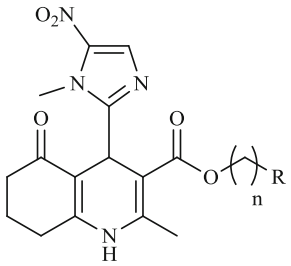
4 R = 6,6-dimethyl; $R_1 = CH_2CH_3$, Ar = pyridyl, % Reversal of contraction = 20.5 % (10^{-6} M)
5, R = 6,6-dimethyl; $R_1 = CH_2CH_3$, Ar = 3-bromophenyl, 61.5 % (10^{-4} M)
6, R = 6,6-dimethyl; $R_1 = CH_2CH_3$, Ar = 3-fluorophenyl, 72.6 % (10^{-4} M)
7, R = 6,6-dimethyl; $R_1 = CH_2CH_3$, Ar = 2-fluorophenyl, 56.9% (10^{-4} M)
8, R = 6,6-dimethyl; $R_1 = CH_2CH_3$, Ar = trifluoromethyl, 63.9 % (10^{-4} M)
9, R = 6,6-dimethyl; $R_1 = CH_2CH_3$, Ar = 4-fluorophenyl, 63.4 % (10^{-4} M)
10, R = 6,6-dimethyl; $R_1 = CH_2CH_3$, Ar = 2,6-dichlorophenyl, 75.8 % (10^{-4} M)
11, R = 7,7-dimethyl; $R_1 = CH_3$, Ar = 5-chloro-2-nitrophenyl, E_{max} = 99.94

A number of diethylaminocarbonyl-5-oxo-hexahydroquinoline derivatives have been synthesized and evaluated by Kısmetli et al. for calcium antagonistic activity on isolated rat ileum and lamb carotid artery. The results indicated that in isolated rat ileum, compounds **12**, **13** and **14** were found to be more active than nicardipine at a concentration of 10^{-5} mol/L and in lamb carotid artery studies, at the concentration 10^{-4} mol/L compounds **14** and **15** showed greater inhibition than nicardipine [94].



12, Ar = 3-fluorophenyl, 59.4 % (10^{-5} M in rat ileum)
13, Ar = 2,6-dichlorophenyl, 100 % (10^{-5} M in rat ileum)
14, Ar = 3,4-dichloropheny, 71.2 % (10^{-5} M in rat ileum) and 31.2 % (10^{-4} M in lamb carotid artery)
15, Ar = 2-nitrophenyl, 27.6 % (10^{-4} M in lamb carotid artery)

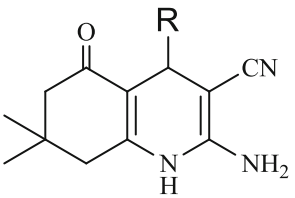
2-Methyl-4-(1-methyl-5-nitro-2-imidazolyl)-5-oxo-hexahydroquinolines bearing alkyl, cycloalkyl and aryl carboxylates at C_3 position (**16**) were synthesized by Miri et al. All compounds exhibited calcium antagonist activity on guinea pig ileum longitudinal smooth muscle, and some of the compounds showed agonistic effect on guinea pig auricle [11].



16

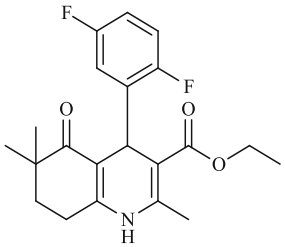
R = Methyl, Isopropyl, Cyclopropyl, Cyclopentyl, Cyclohexyl, Phenyl.
n = 0, 1, 2
Calcium channel antagonist activity; IC_{50} = 1.10 x10^{-6} - 9.01x10^{-7} M
Calcium channel agonist activity' ED_{130} = 1.91 x10^{-6} - 9.952 x10^{-7} M

The synthesis and evaluation of various 6-amino-1,4-dihydropyridines, such as ethyl 6-amino-4-aryl-5-cyano-1,4-dihydro-2-methyl-3-pyridinecarboxylic acids and 2-amino-7,7-dimethyl-5-oxo-4-aryl-hexahydroquinoline-3-carbonitriles, were described by León et al. [95]. 5-Oxo-HHQs **17** and **18** were the best blockers of the Ca^{2+} overload induced by depolarization with high K^+ of SH-SY5Y neuroblastoma cells, with values of 63.8% and 50.4%, respectively.



17, R= 4-flurophenyl
% Blockade [Ca^{2+}] uptake = 63.9 % (3 x 10^{-7} M)
18, R= pyridine
% Blockade [Ca**2+**] uptake = 50.4 % (3 x 10**-7** M)

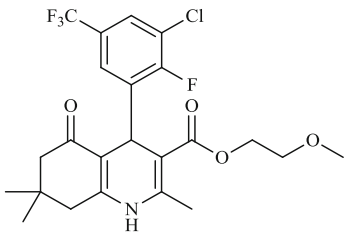
Gupta and Misra [31] focused on difluoro-substituted hexahydroquinolines bearing 6,6- or 7,7-dimethyl substitutions while containing methyl/ethyl carboxylates and carboxamide moieties at C_3 position. The most potent compound was **19** (86.8%), whereas nicardipine exhibited 69.6% inhibition of barium chloride-induced contraction. Derivatives containing 6,6-dimethyl were more active than the 7,7-dimethyl analogs, and carboxamide analogs exhibited less activity than compounds with carboxylate moieties.



19

% Inhibition = 86.8 % (10^{-5} M, on isolated rat ileum precontracted with $BaCl_2$)

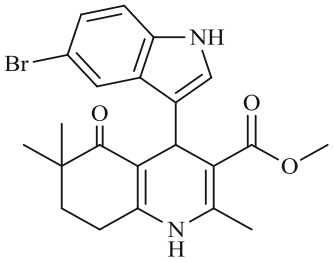
Bülbül et al. [96] explored relaxant responses (Emax) of a series of HHQs with various carboxylates including methyl, ethyl, isobutyl, tertbutyl, allyl, benzyl and 2-methoxyethyl carboxylates on isolated strips of rabbit sigmoid colon circular smooth muscle and demonstrated that 5-oxo-HHQ derivatives containing 2-methoxyethyl carboxylate such as compound **20** were the most active compounds.



20

E_{max}= 44.99 (on isolated strips of rabbit sigmoid colon circular smooth muscle)

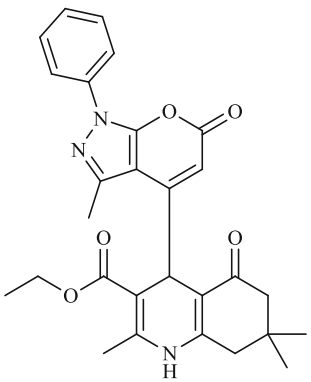
El-Khouly et al. [97] screened several 4-indolylhexahydroquinolines for their spasmolytic activities on isolated rat ileum. The obtained results indicated that introduction of the indolyl ring did not lead to significant activity; however, inserting bromine on the indole ring, as in compound **21**, improved the mentioned activity. Moreover, it was observed that compounds bearing methyl substituent instead of the ethyl group in ester function are more active analogs.



21

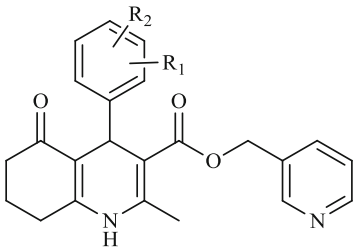
% Inhibition =71.20 % (on isolated rat ileum, 10-7 M)

Very recently, Kumar et al. [98] introduced compound **22** as a potent positive inotrope agent by performing in vivo evaluations. Furthermore, docking analysis revealed that the compound binds with the calcium channels even more toughly than Bay K 8644. The active site of the receptor contains residues LEU 26, VAL 27, LEU 29, VAL 31 and TYR 33 of chain A and VAL 56, TYR 59, LEU 60, LEU 159, LEU 162, TYR 163 and PHE 166 of chain B, which make good contacts with the ligand. A hydrogen bond between the hydroxyl group of TYR 163 and carbonyl oxygen of the ligand is also formed.



22

Synthesis and myorelaxant activity of several 5-oxo-HHQ derivatives bearing bulky 3-pyridylmethyl carboxylate at C_3 (**23**) have been performed by Şafak et al. The results indicated that all compounds made concentration-dependent relaxation on isolated rabbit gastric fundus [99].



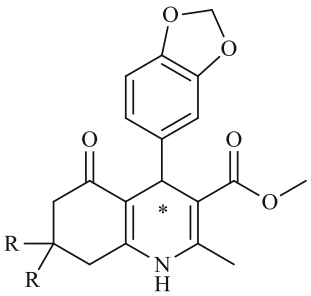
23

R_1 , R_2 : 2,3-Cl_2; 2-F, 3-Cl; 2,3-F_2; 2-Cl, 3-CF_3; 2-F, 3-CF_3

E_{max}= 71.73-100.00 (on isolated strips of rabbit gastric fundus smooth muscle)

Stereoselective calcium channel modulatory activity of 5-oxo-HHQs

5-Oxo-HHQ derivatives have a critical asymmetric center at C_4 position of DHP ring. As C_4 position of HHQ core is chiral, this case causes activity differences depending on the isomers as it was reported for asymmetric DHP analogs; one enantiomer may show agonist activity, while the other one may serve as an antagonist. Calcium agonist and antagonists bind to the same receptor and replace each other in a competitive manner [100]. Nifedipine (antagonist) and Bay K 8644 (agonist) bind a specific DHP receptor, but Bay K 8644 affects opposite to those of nifedipine [101–103]. The R-enantiomer of 5-oxo-4-phenyl-1,4,5,7-tetrahydrofuropyridine-3-carboxylate bearing 4-oxo-2-phenyl-4H-thiochromen-8-yl moiety at C_4 was found to be an agonist, while the S-enantiomer was found to be antagonist. Moreover, S-enantiomer is 50-fold more active than R-enantiomer [104]. Rose and Drage [89] reported the synthesis of enantiomerically pure HHQs of the structural type **24** and proved that the two enantiomers demonstrated calcium antagonistic activities on smooth muscles; however, the S-enantiomer was the tenfold more potent than the R-enantiomer. Furthermore, R-enantiomer exhibited positive inotropic effects on electrically stimulated atria.

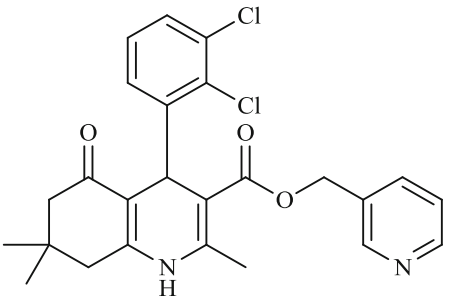


24

T-type and N-type calcium channel inhibitory activity: analgesia activity

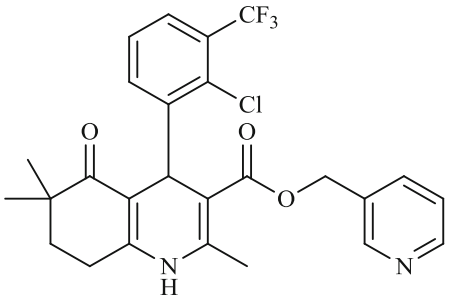
Cav3.2 (T-type) and Cav2.2 (N-type) calcium channels, the most important members of voltage-gated calcium channels, are responsible for the processing of peripheral nociceptive information [105]. N-type channels are highly expressed in afferent nerve terminals and control neurotransmitters' (such as glutamate and substance P) releases. However, T-type channels are expressed both along the afferent fiber and in a subset of nerve terminals and these channels both regulate afferent fiber excitability and appear to contribute to low-threshold neurotransmitter release. T-type calcium channel activity is increased in afferent fibers in several chronic pain conditions such as diabetic neuropathy, spinal nerve injury and irritable bowel syndrome [106–110]. It is reported that also Cav3.3 sub-type (L-type) involved in peripheral pain signaling [111].

Bladen et al. optimized the reported L-type inhibitors with 5-oxo-HHQ scaffold by adding dimethyl groups, changing carboxylate moieties at C_3 position and altering the substituents on the phenyl ring. It was discovered that modification of carboxylate moiety not only regulates the blocking affinity for both L-type and T-type channels but also allows for the development of HHQs with 30-fold selectivity for T-type channels over the L-type. Compounds **25** and **26** were introduced as selective T-type calcium channel blockers that reduce inflammatory and neuropathic pain in mouse models. The two compounds exhibited high affinity to Cav3.2 channels and preferential inhibition over Cav1.2 [112, 113]. **27** was a broad spectrum inhibitor of voltage-gated calcium channels that inhibited both Cav1.2 L- and Cav3.2 T-type calcium channels equipotently. Moreover, **27** effectively inhibited Cav3.3 (T-type) and Cav2.2 (N-type) [114].



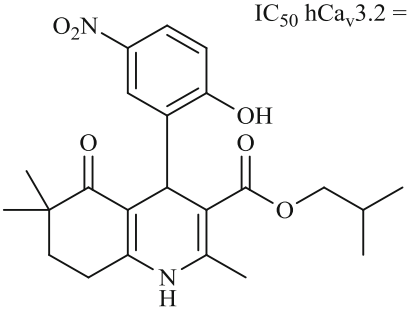
25

Inhibition $rCa_v1.2$ = 40 % (10 μM)
IC_{50} $hCa_v3.1$ = 3.2 μM
IC_{50} $hCa_v3.2$ = 257 nM



26

IC_{50} $rCa_v1.2$ = >30 μM
IC_{50} $hCa_v3.1$ = 3.2 μM
IC_{50} $hCa_v3.2$ = 1.5 μM



27

IC_{50} $rCa_v1.2$ = 4.0 μM
IC_{50} hCav3.1 = 2.4 μM
IC_{50} $hCa_v3.2$ = 3.2 μM

Structure–activity relationships of HHQs as modulators of calcium channels

According to the data presented in above sections, a structure–activity relationship (SAR) can be deduced for 5-oxo-HHQs as modulators of calcium channels (Fig. 1):

1. Nitrogen atom should be unsubstituted in the HHQ nucleus.
2. The substituents at C_2 position should be small groups such as methyl or ethyl or primary amine.
3. The compounds having carboxylate groups at the 3-position are the most effective compounds. The methyl esters were found to be more active than ethyl esters. It is reported that compounds bearing 2-methoxyethyl carboxylates are also effective inhibitors; however, inserting tertbutyl, isobutyl, allyl, benzyl and hexyl esters would reduce the activity. Converting linear carboxylate group to annulated one caused the furoquinoline derivatives to be less active than their hexahydroquinoline analogs. Carboxylate groups can be replaced by other electron-withdrawing groups such as nitrile or carboxamides. Methyl pyridine carboxylate function allows for the development of selective inhibitors of T-type channels.
4. As the C_4 position of 5-oxo-HHQ core is chiral and DHP receptors are stereoselective, one enantiomer may serve as the more potent calcium channel antagonist. The aryl group on C_4 position is the basic requirement for optimal activity. In addition, replacing phenyl ring with pyridyl or nitroimidazole moieties leads to active compounds. Type and position of the substitution on the benzene ring is of great importance. *Ortho* and *meta* electron-withdrawing substitutions including NO_2, F, Cl, Br and CF_3 are preferred.
5. 5-Oxo-HHQ derivatives containing 6,6-dimethyl are reported to be more active than the 7,7-dimethyl analogs.

Anticancer activities

Development of new synthetic cytotoxic agents by medicinal chemists is an ongoing approach for cancer treatment [115]. 5-Oxo-HHQ derivatives fused or hybridized with various biologically active cytotoxic structures have demonstrated potent anticancer and antitumor activity.

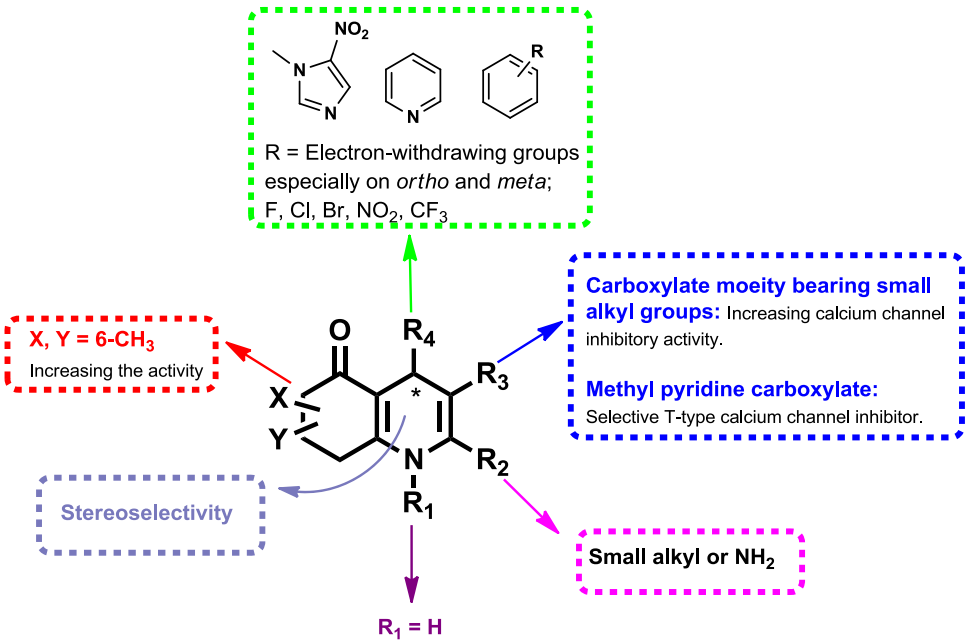
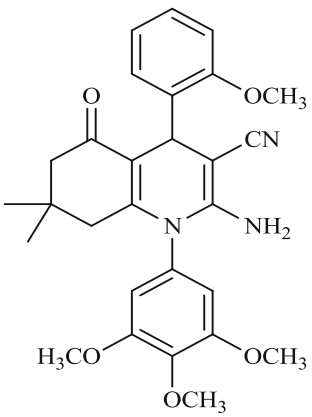


Fig. 1 Outline of structure–activity relationships of 5-oxo-HHQs as calcium channel modulators

Taking into account that trimethoxybenzene moiety has been reported to be crucial to obtain relevant cytotoxic and antitubulin responses [116, 117], Alqasoumi et al. reported the synthesis and cytotoxicity evaluation of many new hybrid compounds comprising 5-oxo-HHQ pharmacophore, bearing cyanide substituent at C_3 position with different moieties at C_4 position and 3,4,5-trimethoxyphenyl at nitrogen atom of HHQ core as potential tubulin inhibitors. 2-Amino-7,7-dimethyl-5-oxo-4-(2-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)-hexahydroquinoline-3-carbonitrile (**28**) showed the highest potency against Ehrlich ascites carcinoma (EAC) cell line with an IC_{50} value of 13.0 μM, which was better than that of doxorubicin as the reference drug. Unexpectedly, molecular docking analysis revealed that this compound did not exert its cytotoxic activity through the inhibition of the tubulin polymerization [2].



28

Some studies focused on synthesis and evaluation of the cytotoxicity and radioprotective activity of novel series of 5-oxo-HHQ derivatives bearing a sulfonamide moiety [118–122]. As several compounds containing sulfonamide group were found to possess potent carbonic anhydrase inhibitory activity [123], docking analysis was performed to confirm the potential inhibitory effect of the most potent compounds on this enzyme. Some considerable structural modifications are depicted in Figs. 2 and 3. Cytotoxicity estimation of the compounds on EAC cell line revealed that compound **29** bearing phenyl and NH_2 groups at C_4 and C_2, respectively, did not show cytotoxicity. However, replacing NH_2 with acetamide (**30**), phenylurea (**31**), phenylthiourea (**32**) and imino-phenyl-dihydropyrimidine-thione ring (**33**) would enhance the cytotoxic potential (Fig. 2) [121]. In addition, compounds bearing substituted 4-phenyl moiety with chloro (**34**), nitro (**35**) or bromo (**36**) groups, especially at the *para* position, showed remarkable in vitro cytotoxic activity (Fig. 3) [118]. In another study, the cytotoxicity of HHQs with 2,4-dichlorophenyl group at C_4 was evaluated and it was revealed that phenylacetamide (**38**), benzenesulfonamide (**39** and **40**) substitutions at C_2 and fusing DHP ring with 4-imino-phenyl-dihydropyrimidine-thione and 4-amino-dihydropyrimidin-one rings (**41** and **42**) would greatly improve the activity (Fig. 3) [119]. Later in 2012, Ghorab et al. [124] reported novel quinoline and pyrimidoquinoline derivatives, containing 4-bromophenyl substitution on nitrogen atom of central core (such as compounds **43**, **44** and **45**) as potential cytotoxic agents (on MCF-7 cells) with synergistic effects of γ-radiation.

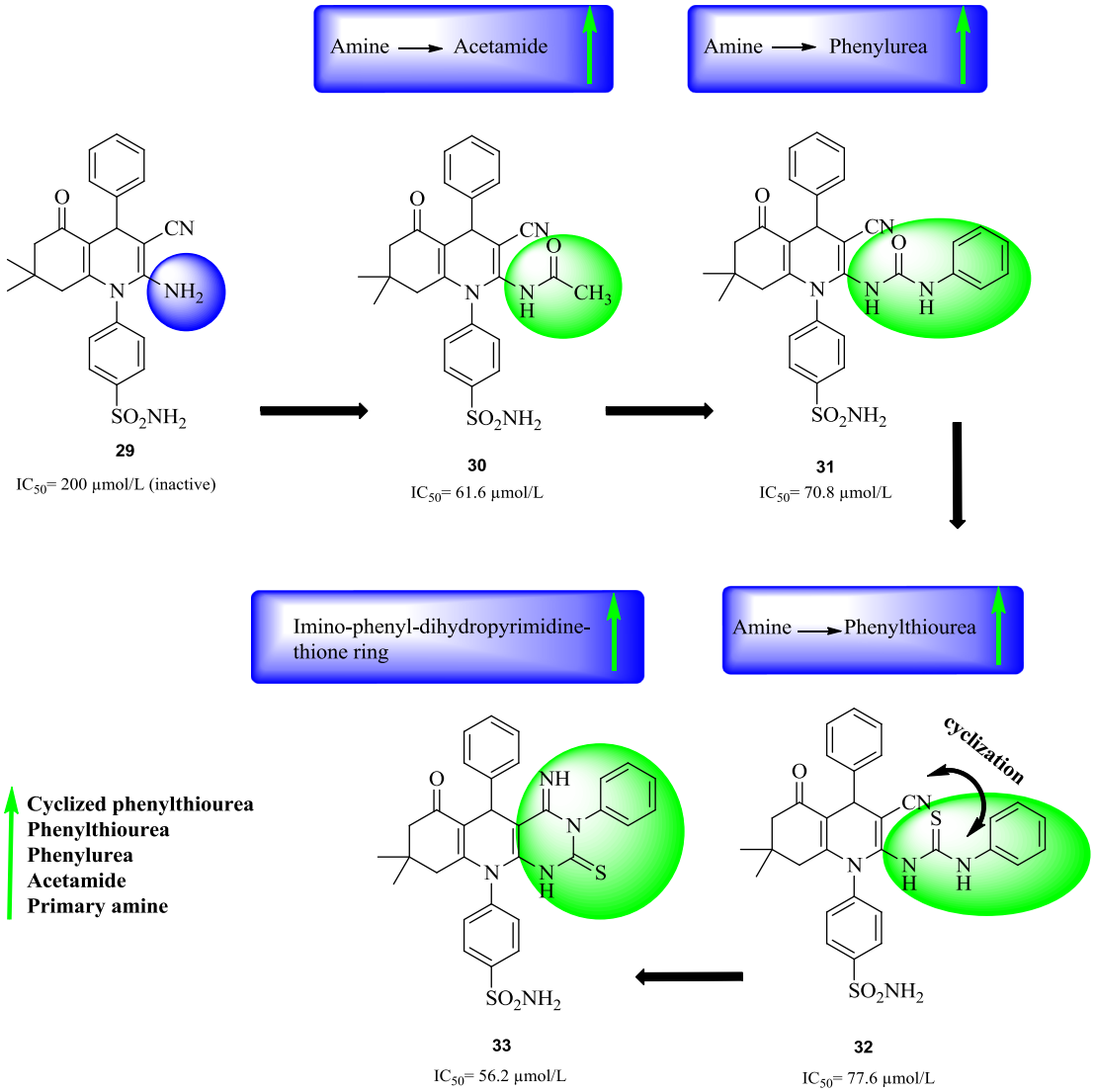


Fig. 2 Illustration of structural modifications on C_2 position of 5-oxo-HHQ core studied by Ghorab et al. Upside green arrows demonstrate positive influence on activity

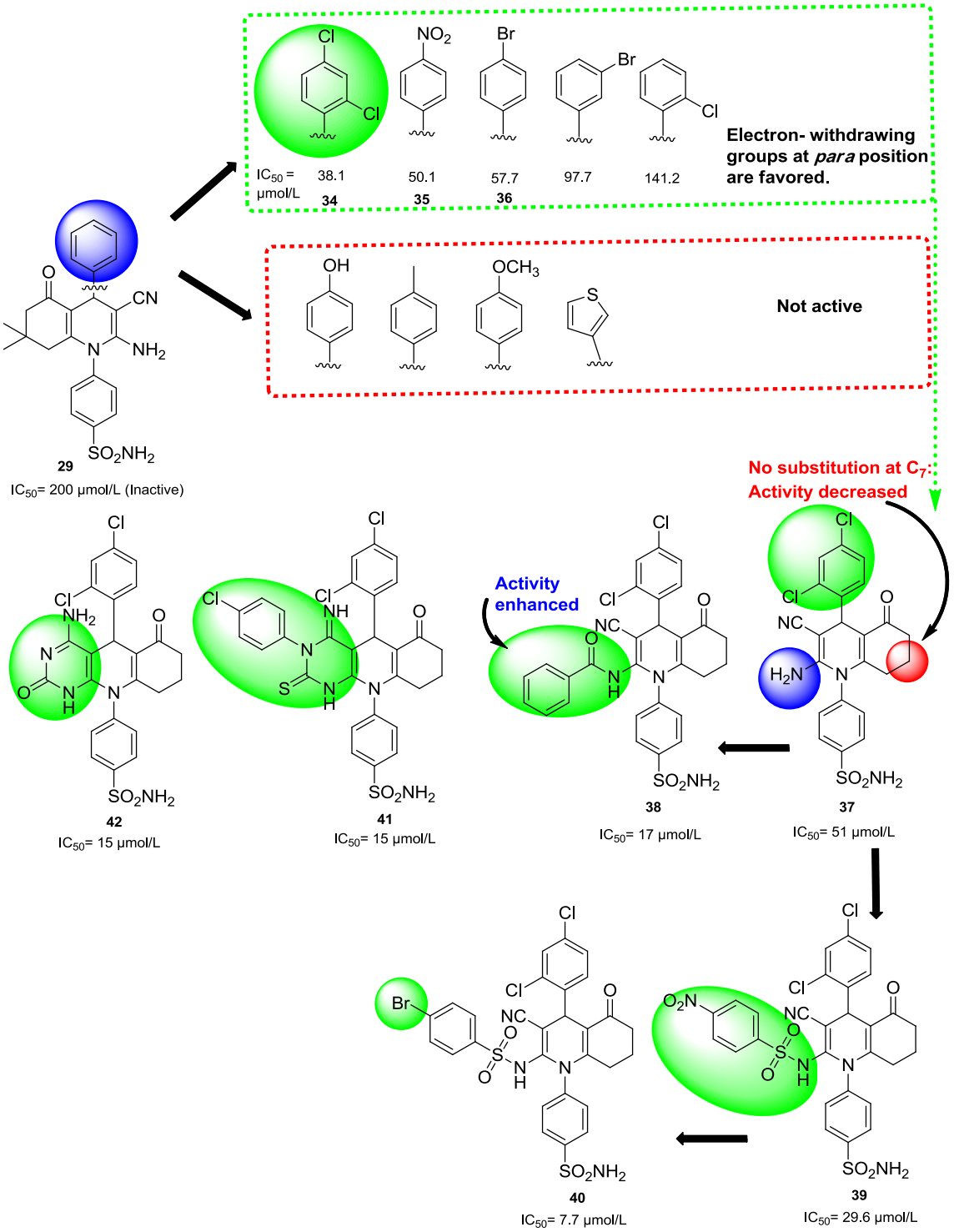
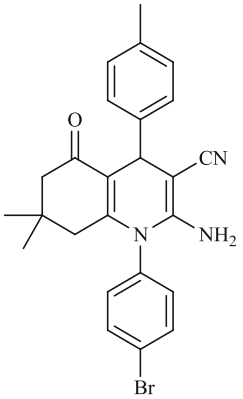
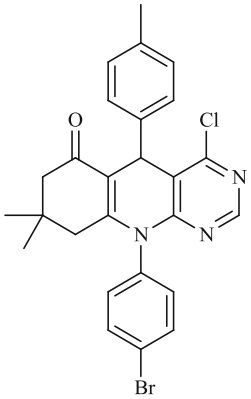


Fig. 3 Illustration of some structural modifications on C_2 and C_4 positions of 5-oxo-HHQ core studied by Ghorab et al.



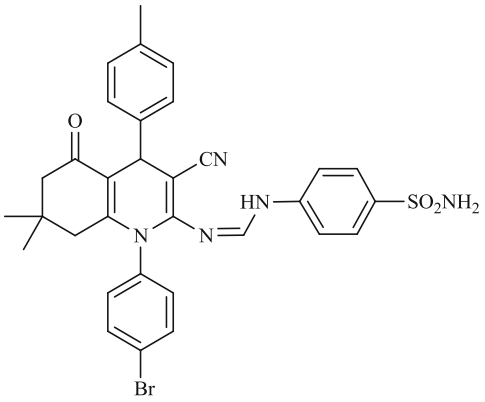
43

IC_{50}= 8.5 µM



44

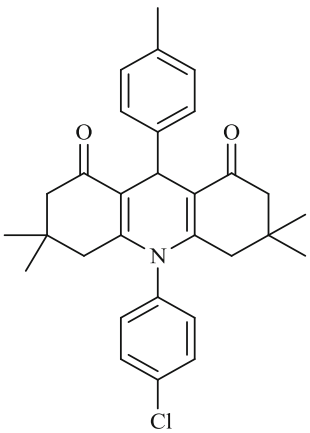
IC_{50}= 23.5 µM



45

IC_{50}= 23.7 µM

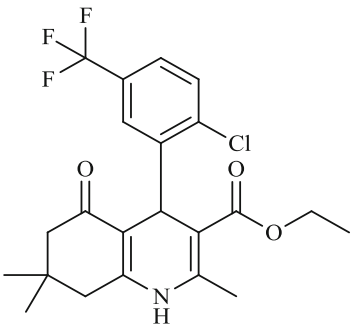
10-(4-Chlorophenyl)-9-(4-methylphenyl)-3,3,6,6-tetramethyl-decahydroacridin-1,8dione (**46**) was screened against hepatocellular carcinoma cells (HepG2) and exhibited an IC_{50} value of 4.4 mg/mL [125].



46

IC_{50}= 4.4 mg/ml

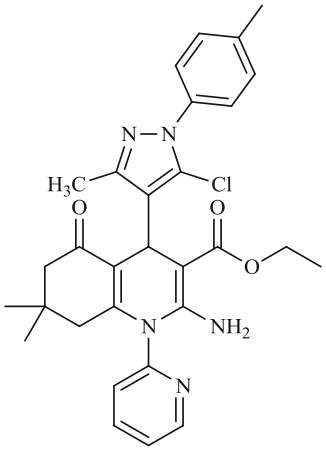
Paidepala et al. [126] reported catalyst-free efficient synthesis of 5-oxo-HHQ using polyethylene glycol (PEG) as a solvent and evaluated their cytotoxicity. Compound **47** was found to display promising cytotoxicity against three human cancer cell lines including MCF-7, human cervical cancer cells (HeLa) and human neuroblastoma cells (SK-NSH).



47

IC_{50}= 6.87, 9.23, 6.69 (µM)
against MCF-7, HeLa and SK-N-SH

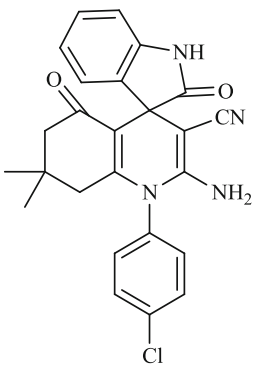
Sangani et al. [127] synthesized pyrazole–quinoline–pyridine hybrids and showed that some of them have excellent anticancer activity against A549 (human lung adenocarcinoma) and HepG2 cancer cells. Compound **48** showed good cytotoxic potential on the two cell lines, and it was found to be the most effective inhibitor of epidermal growth factor receptor (EGFR).



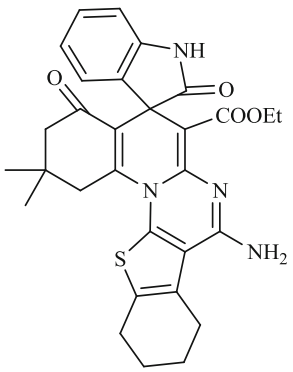
48

IC_{50}s (μM) = 0.51 (EGFR), 0.18 (A549), 4.04 (Hep G2)

The synthesis and cytotoxic screening of new spirocyclic 2-oxindole derivatives of 2-amino-hydroquinolin-5-one have been reported. It was noted that substituting the cyanide function at C_3 with an ester moiety improved the cytotoxic activity. Moreover, compounds **49** and **50** were found to be the most active members that demonstrated apoptotic inhibition of the proliferation of MCF-7 cells through DNA fragmentation, induction of the tumor suppressor protein p53, induction of caspase-9, and finally the inhibition of angiogenesis by decreasing vascular endothelial growth factor expression and secretion [128].

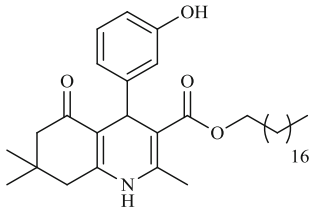


49



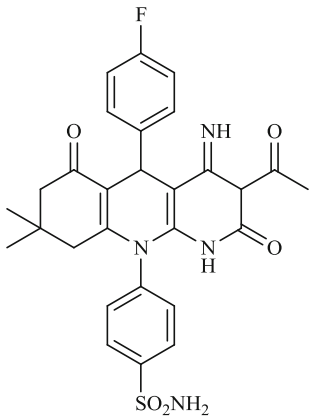
50

Costa Cabrer et al. [129] described the synthesis and antiproliferative activity of novel hybrid 3-substituted polyhydroquinoline–fatty acids. The most potent compound, the stearic fatty alkyl derivative (**51**), which contains 3-hydroxyphenyl at C_4, reduced glioma cell viability by 40% at 5 μM.



51

It has been shown very recently that compound **52** bearing a benzenesulfonamide moiety is a potent cytotoxic agent against MCF-7 cell line with an IC_{50} value of 0.041 μM, comparable to that of the reference drug doxorubicin (IC_{50} = 0.040 μM) [130].



52

IC_{50}= 0.041 μM

Structure–activity relationships of HHQs as anticancer agents

According to the above mentioned studies, a SAR could be proposed for 5-oxo-HHQ derivatives as cytotoxic agents as follows:

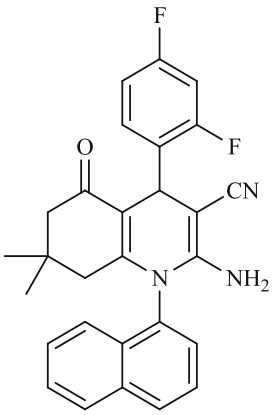
1. It can be stated that aromatic substitutions on nitrogen atom of HHQ core, such as 3,4,5-trimethoxyphenyl, benzenesulfonamide, 4-chlorophenyl, 4-bromophenyl and pyridine, would improve the cytotoxicity.
2. The derivatives having NH_2 group at C_2 position of the central core are effective compounds. Replacing NH_2 with acetamide, benzamide, benzenesulfonamide, phenylthiourea and dioxopyrrolidin moieties causes a noticeable increase in the cytotoxicity of 5-oxo-HHQs. Moreover, fusing DHP ring with some pyrimidine deriva-

tives such as 4-imino-phenyl-dihydropyrimidine-thione and 4-amino-dihydropyrimidin-one rings would improve the cytotoxicity.

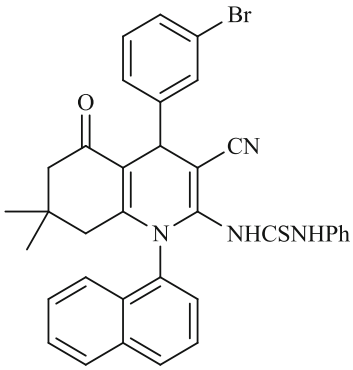
3. Nitrile and alkyl ester moieties are preferred at C_3 position (COOEt > CN). Introducing amide or carboxyl functional groups at this position would diminish the activity [120].
4. Generally, it can be deduced that placing electron-withdrawing groups such as Cl, Br and NO_2 on *para* position of 4-phenyl ring would improve cytotoxic activity.
5. Introducing methyl substitutions on 6-position of HHQ nucleus led to an increase in the activity.

Antibacterial, antifungal, antitubercular and antimalarial activities

Abdel-Gawad et al. reported the synthesis and biological activity evaluation of a new series of *N*-naphthyl substituent hydroquinolines and pyrimidoquinolines and stated that compounds **53**, **54** and **55** demonstrated remarkable antifungal activities against *Saccharomyces cerevisiae* compared with fungicide mycostatine. They also proved that these structures are radio resistant and sterilization by gamma irradiation may prove to be applicable [131]. In a subsequent study, the team synthesized and evaluated some novel thieno-quinoline, quinolino-thieno-pyrimidine and pyrido-thieno-quinoline analogs and found **56** and **57** to be nearly as active as mycostatine [132].



53



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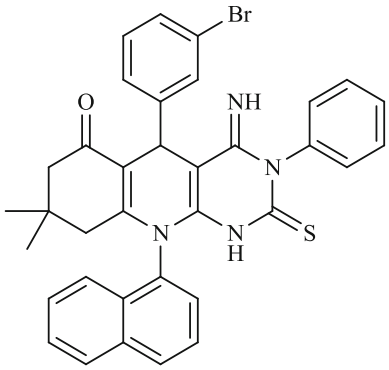

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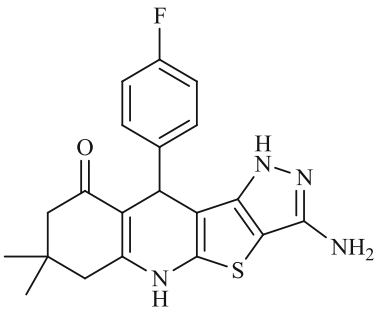
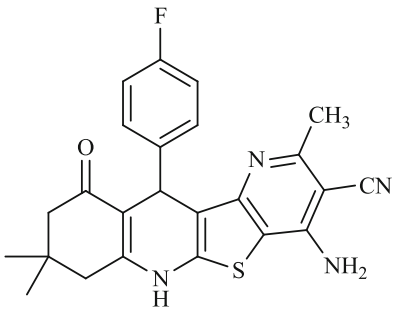
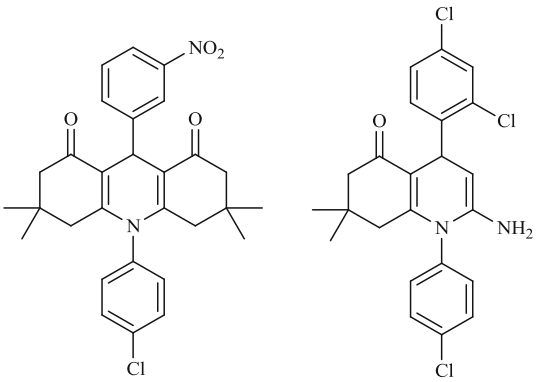


56



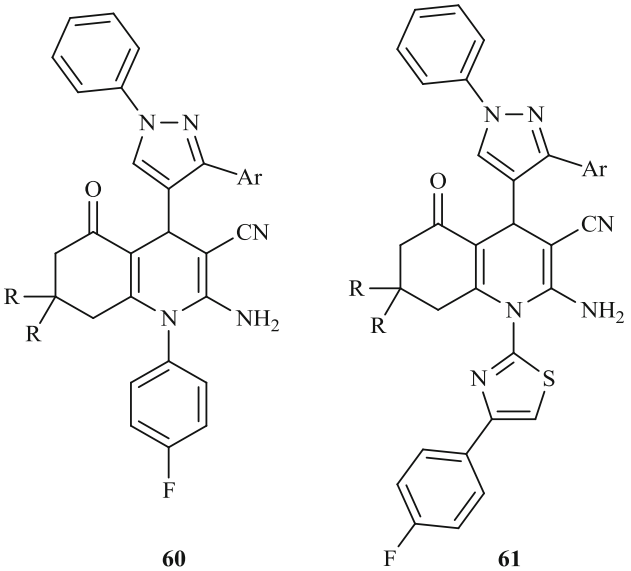
57

Sabbagh et al. [125] identified decahydroacridin-1,8-dione **58** bearing a 3-nitrophenyl group and 5-oxo-HHQ **59** having a 2,4-dichlorophenyl moiety as highly active compounds against Gram-positive and Gram-negative bacteria based upon using the disk diffusion method.



58 59

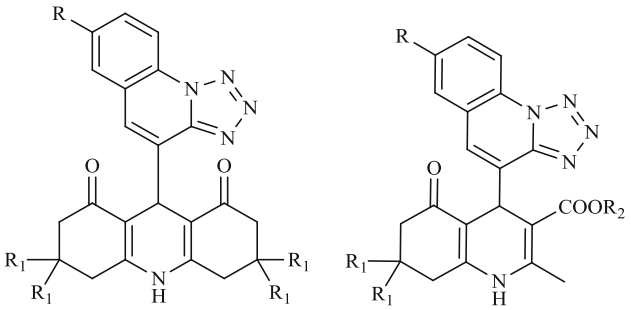
Thirty-two new *N*-(hetero) aryl-substituted 5-oxo-HHQ compounds containing 4-functionally substituted 1,3-diaryl pyrazole ring at C_4 position of HHQ core (**60** and **61**) were synthesized by Thumar et al. Most of the synthesized compounds were found to be highly active against six bacterial pathogens, including: *Bacillus subtilis*, *Clostridium tetani*, *Streptococcus pneumoniae*, *Salmonella typhi*, *Vibrio cholerae*, *Escherichia coli*, and antifungal activity, against *Candida albicans*. The best antibacterial activities were obtained against *Clostridium tetaniand* and *Bacillus subtilis* [133].



60 61

Ar	**R**
C_6H_5	H or CH3
4-Br-C_6H_4	
4-Cl-C_6H_4	
4-F-C_6H_4	
4-OCH_3-C_6H_4	
4-CH_3-C_6H_4	
4-NO_2-C_6H_4	
2-Thienyl	

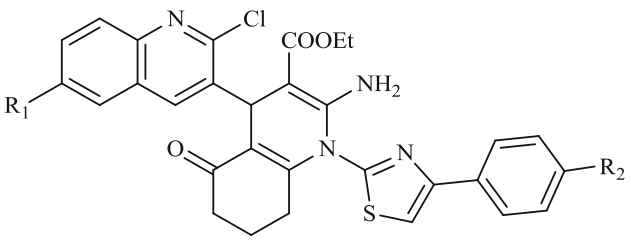
Ladani et al. [134] described the synthesis and antimicrobial activity of several polyhydroquinolines bearing the tetrazolo-quinolone moiety at C_4 position. The results revealed that some of the derivatives (**62** and **63**) possess high fungicidal activity against *R. oryzae* comparable to griseofulvin.



62 63

R = H, CH_3, OCH_3
R_1 = H, CH_3
R_2 = CH_3, C_2H_3

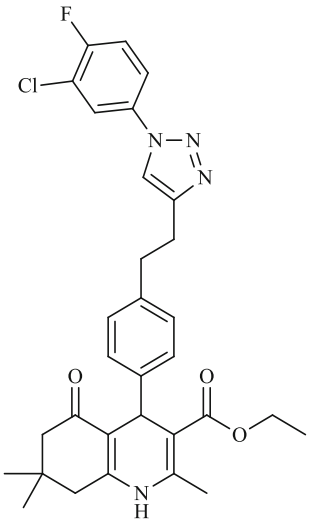
Some novel biquinoline derivatives (**64**) bearing a thiazole moiety were prepared by Shan et al., and the compounds were tested for their antibacterial (against *E. Coli*, *B. subtilis* and *Staphylococcus aureus*) and antifungal (against *A. niger*, *F. oxysporum* and *R. oryzae*) activities. Most of the compounds displayed moderate activity against all the mentioned strains [135].



64

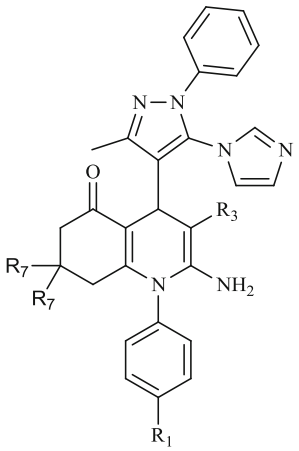
R_1 = H, CH_3, OCH_3, Cl
R_2 = H, OH, Cl

Singh et al. [56] investigated the antibacterial and antifungal activity of some novel 1,2,3-triazole-linked 5-oxo-HHQ and reported compound **65** as the best antifungal and antibacterial derivative with an MIC of 64 mg/mL against the Gram-positive bacterial strains *B. subtilis* and *S. aureus* as compared with the standard ciprofloxacin and 55.8% inhibition of mycelial growth against the fungal strain *Aspergillus flavus* and 51.1% against *Aspergillus nigeras* compared with the standard fluconazole.



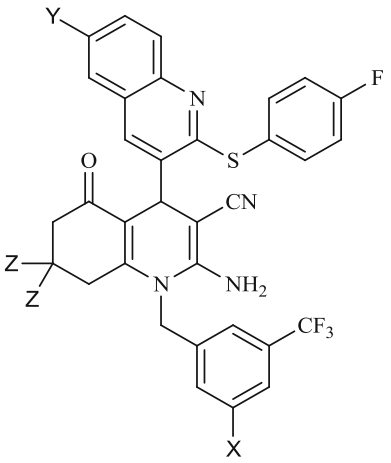
65

In an attempt to involve biologically active polyhydroquinoline, pyrazole and imidazole in one molecule, Kalaria et al. [5] designed and synthesized a new library of polyhydroquinoline derivatives. Compounds were evaluated for their in vitro antibacterial, antifungal, antimalarial and antitubercular activities. In this regard, **66**, **67**, **68** and **69** were introduced, respectively, as the strongest antibacterial, antifungal, antitubercular and antimalarial agents of the series in comparison with the standard drugs.



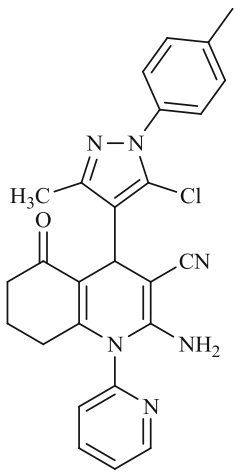
66, R_1= OH, R_3= COOEt, R_7= CH_3
67, R_1= H, R_3= $CONH_2$, R_7= CH_3
68, R_1= H, R_3= CN, R_7= CH_3
69, R_1= OH, R_3= $CONH_2$, R_7= H

Kanani and Patel [136] synthesized a new category of biquinoline derivatives and proved that compounds **70** and **71** exhibited excellent antimicrobial activity. Furthermore, compound **72** with 91% inhibition at 6.25 μg/mL against *M. tuberculosis H37Rv* was found to be a potent antitubercular agent.



70, X= H, Y= CH_3, Z= CH_3
71, X= CF_3, Y= OCH_3, Z= H
72, X= H, Y=O CH_3, Z= CH_3

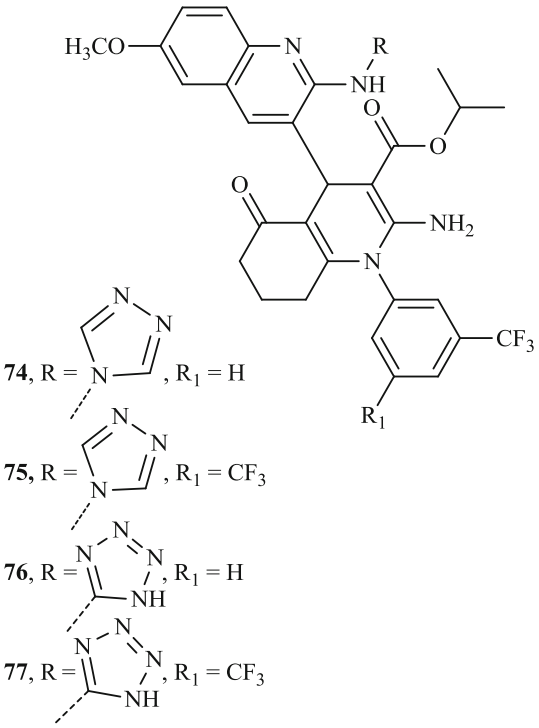
Sangani et al. studied the inhibitory effect of some pyrazole–quinoline–pyridine hybrids against β-ketoacyacyl carrier protein synthase II (FabH) of *E. coli* which is the essential enzyme for fatty acid biosynthesis. The most active compound was reported to be 5-oxo-hexahydroquinoline-3-carbonitrile derivative **73** which exhibited MIC of 1.56 μg/mL against *E. coli* (more effective than penicillin G and comparable to kanamycin B) and inhibited FabH with IC_{50} value of 3.1 μM [127].



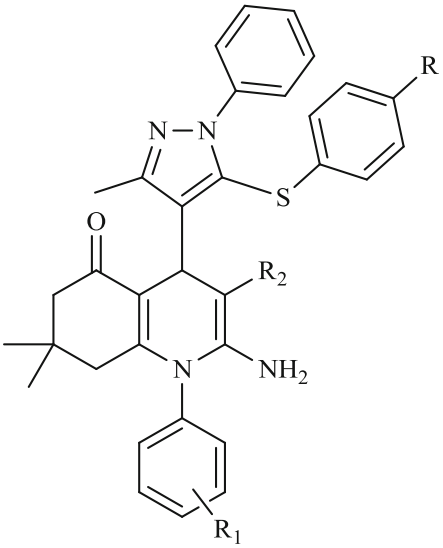
73

Gohil et al. [137] synthesized a new series of triazole/tetrazole hybrids-based biquinoline derivatives bearing aromatic trifluoromethyl moiety at $N-1$ position as antimicrobial and antitubercular agents. Compounds **74**, **75**, **76** and

77 were found to be the most potent antimicrobial and antituberculosis members.

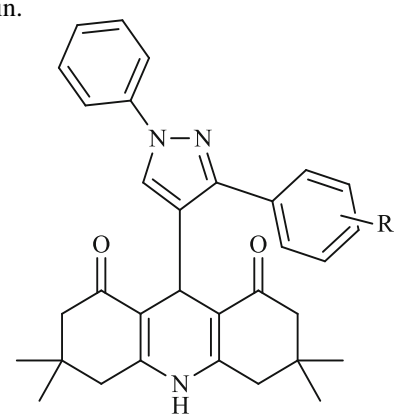


Sapariya et al. prepared some 5-(phenylthio) pyrazole-hexahydroquinoline derivatives and evaluated the synthesized compounds for the in vitro antibacterial, antitubercular and antimalarial activities. Most of the derivatives displayed remarkable antibacterial activities. The results suggested that compound **85** could be a promising candidate for a new class of antimicrobial agents in future. Compounds **81**, **82** and **83** were found to be superior antituberculosis agents against *M. tuberculosis* H37Rv with 94%, 95% and 91% inhibitory activity at 250 μg/mL concentration, respectively. The compounds **78**, **79**, **80**, **83**, **84** and **85** with IC_{50} in the range of 0.042–0.097 μg/mL exhibited noticeable antimalarial activity against *P. falciparum* as compared to quinine with IC_{50} of 0.268 μg/mL [138].



78, R = 4-Cl, R_1 = 4-F, R_2 = CN
79, R = 4-Cl, R_1 = 4-F, R_2 = $CONH_2$
80, R = 4-CH_3, R_1 = 4-F, R_2 = CN
81, R = 4-CH_3, R_1 = 4-F, R_2 = COOEt
82, R = 4-CH_3, R_1 = 2,4-F, R_2 = COOEt
83, R = 4-Cl, R_1 = 2,4-F, R_2 = $CONH_2$
84, R = 4-F, R_1 = 4-F, R_2 = CN
85, R = 4-F, R_1 = 4-CF_3, R_2 = CN

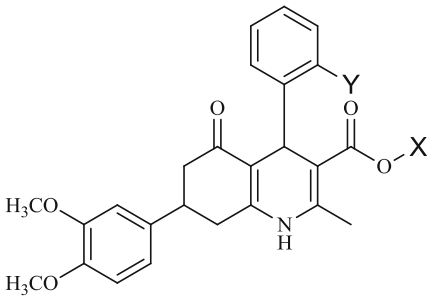
Bhatt et al. [139] synthesized some derivatives containing 1,3-diphenyl pyrazole moieties and showed that compounds **86**, **87**, **88** and **89** presented broad spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria as compared with the reference drug ciprofloxacin. Moreover, compound **88** was found to have promising antifungal activity against *A. clavatus* and *C. albicans* which is noticeably higher than that of the standard drugs nystatin and griseofulvin.



86, R = 4-CH_3
87, R = 3-CH_3
88, R = 3-Br
89, R = 2,5-dimethoxy

Some 4-indolyl-5-oxo-hexahydroquinoline derivatives possessing various alkyl carboxylate groups were synthesized by Baydar et al. and were tested against *Mycobacterium tuberculosis* H37Rv. It was concluded that introduction of ethyl or isopropyl carboxylates moieties at C_3 position would enhance the activity. Molecular docking analysis of compounds with M. *tuberculosis* enoyl reductase (InhA) revealed that InhA might be the possible target enzyme as compounds were well accommodated in the enzyme's active site [140].

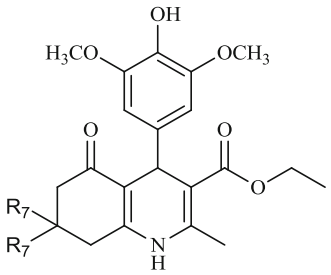
Vanaerschot et al. [6] screened 3825 compounds from the Genomics Institute of Novartis Research Foundation malaria box and identified three lead compounds having HHQ scaffold (**90**, **91** and **92**) as potent gametocytocidal inhibitors. It was proved that the compounds were potent in vitro transmission blockers. In vivo studies demonstrated the ability of lead HHQs to suppress plasmodium berghei blood-stage parasite proliferation.



90 (GNF-Pf-5640), X= isopropyl, Y= CH_3
91 (GNF-Pf-5660), X= ethyl, Y= Cl
92 (GNF-Pf-5668), X= propyl, Y= F

Antioxidant activity

A series of 5-oxo-hexahydroquinoline-3-carboxylates bearing different substitutions at 4-phenyl were tested for their antioxidant activity by 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2-azino bis (3-ethylenzothiazoline-sulfonic acid) diammonium salt ($ABST^+$) radical scavenging assays. It was reported that insertion of methoxy groups at the phenyl ring improved the antioxidant activity. Compounds **93** and **94** were found to be as the most potent derivatives [49].



93
R_7= H, DPPH IC_{50} = 14.89 (μM), ABST+ IC_{50} = 1.74 (μM)
94
R_7= CH_3, DPPH IC_{50} = 7.48 (μM), ABST+ IC_{50} = 0.87 (μM)

Montes-Avila et al. studied DPPH radical scavenging activity of some hydropyridines (dihydropyridines, polyhydroquinolines and polyhydroacridine derivatives) and concluded that polyhydroquinolines were the most active compounds among the studied hydropyridines. A schematic of SAR representation of these compounds is illustrated in Fig. 4. In particular, **95** and **96** having 5-oxo-HHQ scaffold were the most potent derivative and exhibited 53.5 and 55.1% DPPH scavenging activity at 100 μg/mL, while **97** possessing hexahydroacridine-dione structure showed 30.0% DPPH scavenging activity at the same concentration [141].

Structure–activity relationships of HHQs as antioxidant agents

Considering the above-mentioned studies, a brief SAR can be presented for 5-oxo-HHQ derivatives as antioxidants as follows:

1. 5-Oxo-HHQs bearing carboxylate moiety on C_3 demonstrate antioxidant activity and modification of the nucleus to DHP or hydroacridine diminishes the activity.
2. Hydroxyl and alkoxy substituents at 3, 4 and 5 positions of the C_4-phenyl ring lead to derivatives with enhanced antioxidant activity.

Singh et al. [56] obtained novel 1,2,3-triazole-linked 5-oxo-HHQ via an eco-friendly one-pot five-component synthesis procedure under ultrasonic and microwave irradiation in PEG 400. The antioxidant activity was evaluated using DPPH assay, and compounds **98–101** showed good antioxi-

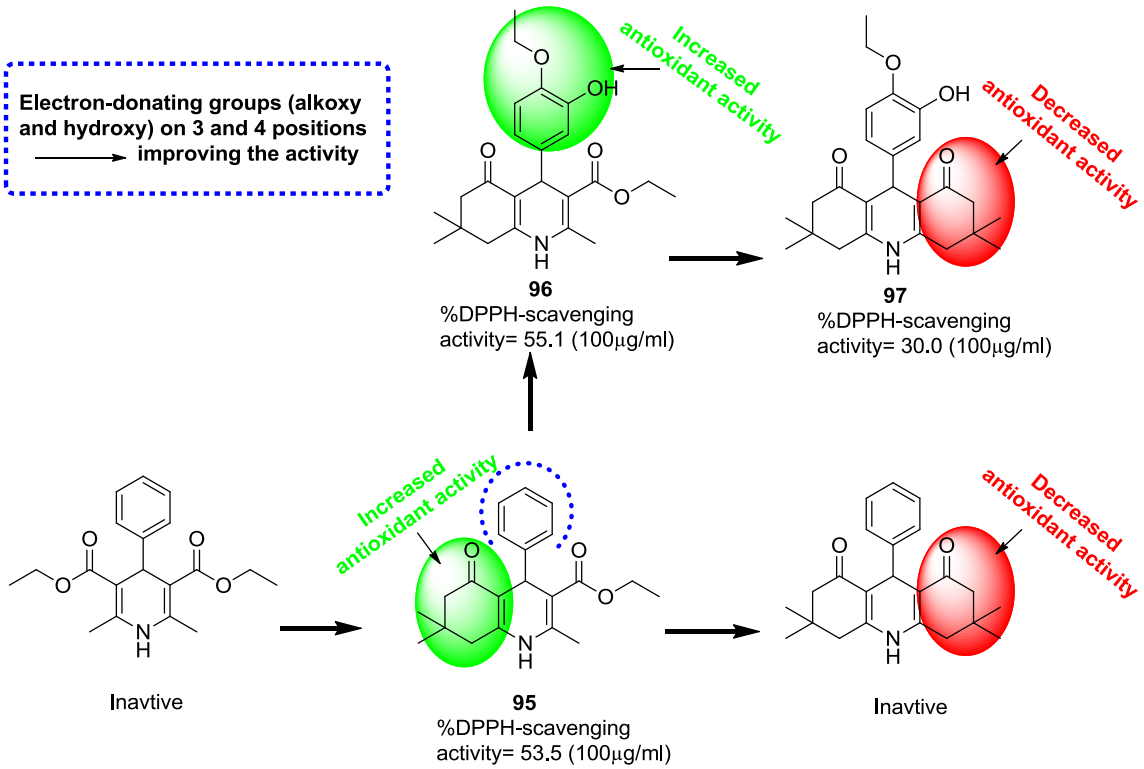
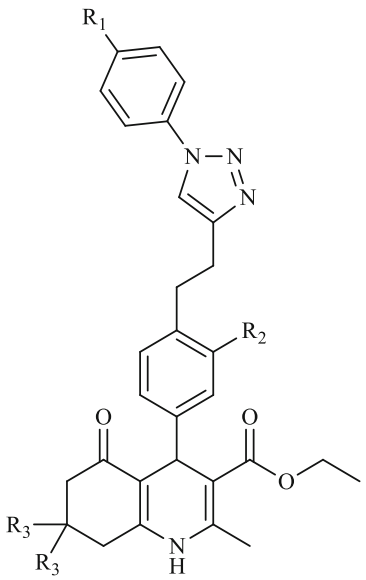


Fig. 4 Schematic of structure–activity relationship of 5-oxo-HHQ s as antioxidant agents

dant activity at 0.8 µmol/mL concentration as compared with the standard BHT. It was observed that the antioxidant activity enhanced due to the presence of R_2=OCH_3 at the phenyl ring.



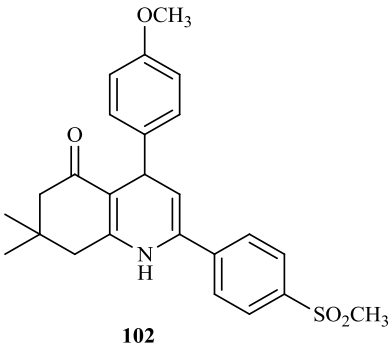
98, $R_1 = NO_2$, $R_2 = H$, $R_3 = CH_3$
99, $R_1 = CH_3$, $R_2 = OCH_3$, $R_3 = CH_3$
100, $R_1 = OCH_3$, $R_2 = OCH_3$, $R_3 = CH_3$
101, $R_1 = Br$, $R_2 = OCH_3$, $R_3 = CH_3$

COX-2 inhibitory and anti-inflammatory activities

Cyclooxygenase (COX), also known as prostaglandin synthase (PGH), is a potent mediator of inflammation which catalyzes the first step of the biosynthesis of PGG2 from arachidonic acid to generate PGH2 [142]. It is well established that there are at least two COX isozymes, COX-1 and COX-2. COX-1 is mainly associated with prostaglandin production in gastric mucosa, but COX-2 is upregulated in response to inflammatory stimuli and is involved in pathologic processes [143]. Generally, nonsteroidal anti-inflammatory drugs inhibit both COXs and, consequently, lead to undesirable side effects [144].

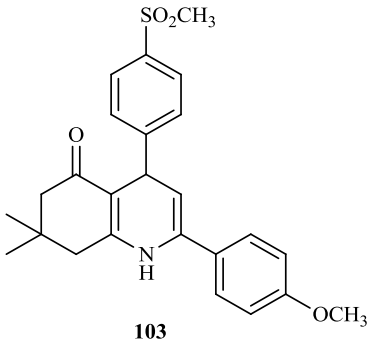
A new class of 5-oxo-HHQ derivatives possessing a SO_2Me pharmacophore at the *para* position of the C_2 or C_4 phenyl ring was designed and assessed as selective cyclooxygenase-2 (COX-2) inhibitors by Zarghi et al. The obtained results indicated that compounds having a $MeSO_2$ group at the *para* position of the C_2 phenyl ring were more selective COX-2 inhibitors compared to their corresponding regioisomers bearing a $MeSO_2$ at the *para* position of C_4 phenyl ring. Furthermore, introduction of a methoxy function at the *para* position of the C_2 or C_4 phenyl ring enhanced the potency and COX-2 selectivity. Accordingly, compounds **102** and **103** were presented as the most potent COX-2 inhibitors with high COX-2 selectivity index. In contrast, incorporation of Cl, Br or NO_2 at C_2 phenyl and C_4 phenyl

decreased COX-2 inhibitory potency and selectivity. Molecular docking study of compound **102** in active site of COX-2 indicated that the SO_2Me moiety on the C_2 phenyl ring accommodated into the secondary COX-2 binding site [13]. Later in 2015, they reported 4-(4-(methylsulfonyl)phenyl)-5-oxo-hexahydroquinoline derivatives containing alkyl substituents at C_2 position and alkyl carboxylates at C_3 position of 5-oxo-HHQ core. Compound **104** with IC_{50} value of 0.30 μM had the strongest COX-2 inhibitory activity. It was proved that placing larger groups such as propyl and phenyl at C_2 position led to significant loss in activities. Modification of ethylcarboxylate to the large-sized benzylcarboxylate group would diminish the activity [145]. Very recently, Akbari et al. [146] modeled COX-2 inhibitory activities of the above-mentioned 5-oxo-HHQs by quantitative structure–activity relationship using step-wise multiple linear regression method. According to QSAR models results, BEHm6 (highest eigenvalue n. 6 of Burden matrix/weighted by atomic masses), Mor03u (signal 03/unweighted) and IVDE (mean information content on the vertex degree equality) were important factors controlling the COX-2 inhibitory activity.



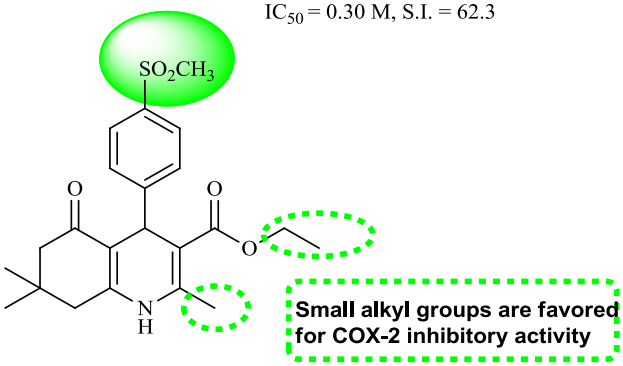
102

IC_{50} = 0.17 M, S.I. = 97.6



103

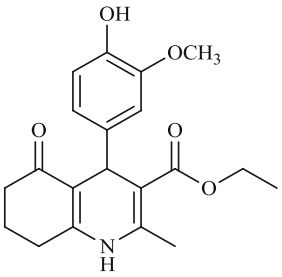
IC_{50} = 0.30 M, S.I. = 62.3



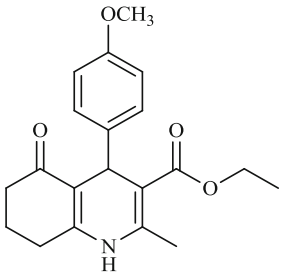
104

IC_{50} =0.30 μM, S.I. = 92.0

Teng et al. [147] reported the synthesis and endometritis anti-inflammatory activity (carrageenan-induced paw edema) of 4-aryl-5-oxo-hexahydroquinoline derivatives and find out compounds **105** and **106** with electron-donating groups at the 4-phenyl ring demonstrated potent activities.

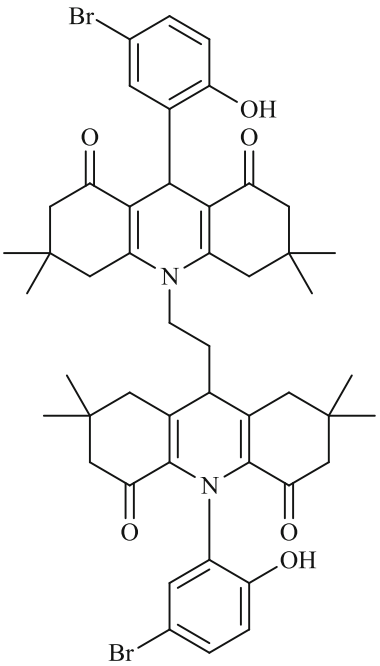


105
ED_{50} = 61.2 mg/kg



106
ED_{50} = 57.2 mg/kg

Abd-Allah et al. [148] studied the anti-inflammatory activity of novel hydroacridines by the carrageenan-induced paw edema standard method in rats and revealed that electron-donating alkyl groups in hydroacridines could increase their anti-inflammatory activity. The highly alkylated bishydroacridine-1,8-dione **107** exhibited high anti-inflammatory potency more than standard employed indomethacin.

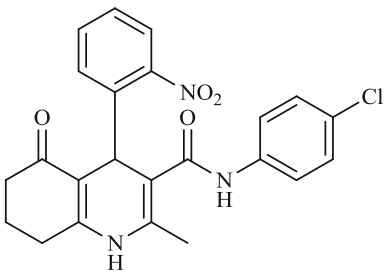


107
% of Oedema Inhibition (20 mg/kg) = 57.53

P-gp-mediated multidrug resistance (MDR) reversal activity

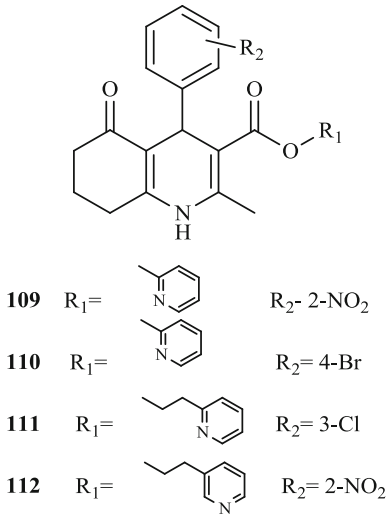
Multidrug resistance (MDR) is a major impediment to successful chemotherapy, which may occur due to the over-expression of ATP-binding cassette membrane transporter family members including P-glycoprotein (P-gp), the breast cancer resistance protein and the multidrug resistance-associated protein 1 in cancer cells [149]. The over-expression of P-gp, in cancer cells, leads to reduced accumulation of chemotherapeutic drugs and results in ineffective chemotherapy. Consequently, discovering small molecules as P-gp inhibitors seems to be a promising approach for overcoming MDR in cancer cells. P-gp substrates include amphipathic compounds, lipid soluble compounds and compounds with aromatic rings [150, 151].

In this direction, Shahraki et al. [3] synthesized several 5-oxo-HHQ derivatives containing nitrophenyl moieties at C_4 and different carboxamide substituents at C_3 and evaluated them for their ability to inhibit P-gp using a flow cytometry assay to measure the amount of rhodamine 123 (Rh123) accumulations in uterine sarcoma cells that over-express P-gp (MES-SA/DX5). Compounds with 2-nitrophenyl moiety, such as **108** with 4.6-fold Rh123 accumulation relative to the negative control at 25 μM, demonstrated good activity.



108

Our team extended the work to synthesize and screen twenty-five analogs bearing different pyridyl methyl carboxylates at C_3 and different substituents at C_4 as P-gp inhibitors. Derivatives having phenyl moiety with electron-withdrawing substitution (such as nitro, cyano, chloro and bromo moieties) at C_4 position of HHQ core presented the highest P-gp inhibitory activity. Compounds **109** and **110** which showed 6.2- and 7.4-fold Rh123 accumulation relative to the negative control at 25 μM, respectively, were even more potent than verapamil as the positive control (5.5-fold Rh123 accumulation relative to the negative control) [152]. In a subsequent study, we studied the inhibitory activity of 5-oxo-HHQ derivatives containing 2-pyridyl ethyl carboxylate, 2-pyridyl propyl carboxylate and 3-pyridyl propyl carboxylate moieties at C_3. Accordingly, compounds **111** and **112** were among the most promising modulators of P-gp transporter [153].



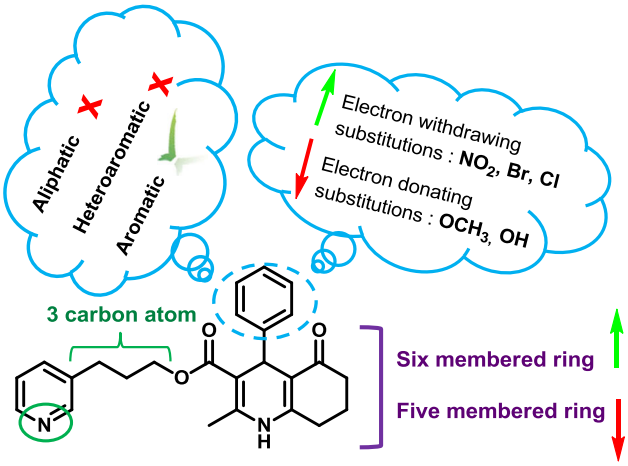


Fig. 5 Structure–activity relationship and the effect of substituted moieties on MDR reversal activity of 5-oxo-HHQs. Upside and downside arrows demonstrate that the substitutions have a positive and negative influence on activity, respectively. Cross sign indicates lack of the activity

Structure–activity relationships of 5-oxo-HHQs as MDR reversal agents

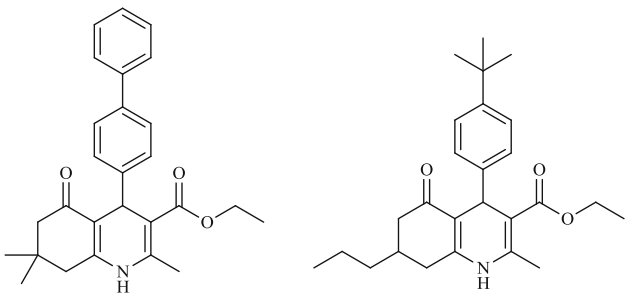
According to the above-mentioned studies, a SAR could be proposed for 5-oxo-HHQ derivatives as MDR reversal agents as follows (Fig. 5):

1. Derivatives bearing the pyridyl alkyl carboxylate moieties at position 3 are better inhibitors of P-gp than the compounds having carboxamide substituents, and more lipophilic pyridyl ethyl carboxylate and pyridyl propyl carboxylate substituents are better P-gp modulators than pyridyl methyl carboxylate substituents. 3-Pyridyl propyl carboxylate substitution led to the most active derivatives.
2. Introducing alkyl and hetero aromatic moieties at the C_4 position would diminish the activity, while aromatic moieties with electron-withdrawing substitutions such as NO_2 (as a hydrogen bond acceptor function), Cl and Br (due to their lipophilicity) would improve the MDR reversal activity.
3. Converting six-membered cyclohexenone ring to five-membered would reduce the activity.

Transforming growth factor β inhibitory activity

Transforming growth factor β (TGFβ) is a cytokine that regulates many cellular functions including cell proliferation, apoptosis, differentiation, angiogenesis and wound healing [154, 155]. The TGFβ pathway is a promising therapeutic target for a variety of diseases such as cancer, fibrosis and autoimmune diseases. TGFβ signaling occurs following initial binding of TGFβ superfamily ligands to the TGFβ receptor type II (TGFβR2) that recruits and phosphorylates TGFβ receptor type I (TGFβR1). The type I receptor then phosphorylates SMADs which bind the coSMAD SMAD4. SMAD/coSMAD complexes mount up in the nucleus, act as transcription factors and contribute to the regulation of target gene expression [156, 157].

Willems et al. [158] screened a mouse embryonic stem cell (ESC)-based differentiation assay against a small molecule library and introduced **113** as the first selective TGFβ inhibitor (IC_{50} = 0.4–0.8 μM), which induced proteasomal degradation of the TGFβR2 and inhibited TGFβ-induced mesoderm formation from mouse ESCs during early differentiation. In the subsequent study, they reported the synthesis and structure–activity relationship (SAR) studies of 50 selected 1,4-DHPs based on the "hit" compound **113**. Applying SAR-optimized substitution pattern on TGFβ inhibition, compound **114** was discovered as the most potent derivative (IC_{50} = 170 nM), which is almost as potent as the reported TGFβR1 inhibitor SB-431542 (IC_{50} = 66 nM) [159].

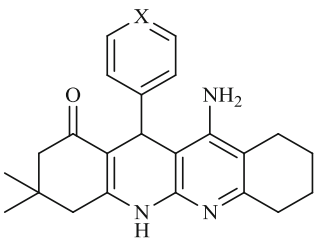


113 114

Anti-Alzheimer and neuroprotective activities

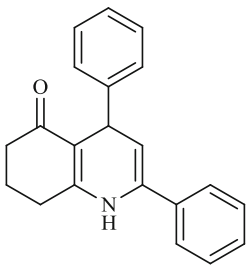
Alzheimer's disease (AD) is a neurodegenerative disease with diverse etiologies including amyloid-β (Aβ) deposits, tau protein aggregation, oxidative stress, or low levels of acetylcholine that are thought to play significant roles in the disease [160, 161]. Using acetylcholinesterase inhibitors and, consequently, increasing the acetylcholine levels in the brain is the primary therapeutic methodology in management of AD [162]. Moreover, regulating the entrance of Ca^{2+} through calcium channels could be a good strategy to prevent cell death, as Ca^{2+} overload and dysfunction, involved in the pathogenesis of AD, augments Aβ formation and cell death [163, 164].

León et al. [165] discovered a series of new tacrine–HHQ hybrids (**115**–**119**) that inhibited acetylcholinesterase, calcium entry, and showed neuroprotection profile. Compounds **115**–**119** were introduced as a new family of molecules for the management of AD.



115, X = C-H, IC_{50} EeAChE= 0.32 (μM) , IC_{50} hAChE= 0.71 (μM)
% Protection at 0.3 μM= 40.7, % blockade calcium at 0.3 μM= 24.63
116 X = C-F, IC_{50} EeAChE= 0.54 (μM) , IC_{50} hAChE= 1.60 (μM)
% Protection at 0.3 μM= 41.7, % blockade calcium at 0.3 μM= 32.88
117, X = C-Me, IC_{50} EeAChE= 0.23 (μM) , IC_{50} hAChE= 0.67 (μM)
% Protection at 0.3 μM= 46.4, % blockade calcium at 0.3 μM= 30.95
118, X = C-OMe, IC_{50} EeAChE= 0.22 (μM) , IC_{50} hAChE= 037 (μM)
% Protection at 0.3 μM= 44.1, % blockade calcium at 0.3 μM= 31.04
119, X = N, IC_{50} EeAChE= 0.6 (μM) , IC_{50} hAChE= 2.8 (μM)
% Protection at 0.3 μM= 49.7, % blockade calcium at 0.3 μM= 45.11

The diaryl-HHQ **120** displayed moderate neuroprotective and antioxidant activity and was also a potent inhibitor of calcium entry [14].

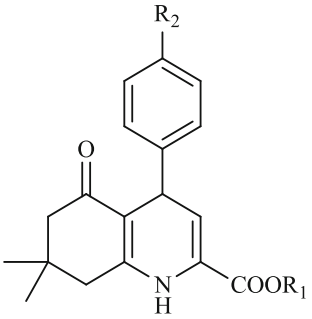


120
% Blockade Ca^{2+} increase at 10 μM= 41.2
% Protection in neuroblastoma cells at 5 μM= 28.23

Antidiabetic and antidyslipidemic activities

Non-insulin-dependent diabetes mellitus (Type-2 diabetes) is primarily characterized by insulin resistance and abnormal insulin secretion which causes hyperglycemia [166]. Dyslipidemia is connected to insulin insensitivity and associated with increased atherosclerosis susceptibility [167].

A series of 2,4-disubstituted polyhydroquinoline derivatives have been synthesized and evaluated for their antidiabetic and antidyslipidemic activity in various in vivo and in vitro models by A. Kumar. Some derivatives such as **121**, **122** and **123** exhibited antihyperglycemic activity in sucrose-loaded model (SLM) and streptozotocin (STZ-S)-induced β-cell-damaged diabetic model of Sprague–Dawley strain male albino rats comparable to the standard drugs with remarkable lipid and triglyceride modulating activity in C57BL/KsBom-db mouse (db/db). Compound **123** was a potent protein tyrosine phosphatase 1B (PTP-1B) inhibitor, whereas compounds **121** and **122** having carboxylic group inhibited the glycogen phosphorylase more efficiently than PTP-1B [4].

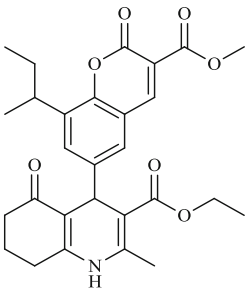


121 R_1= H, R_2= OCH_3
122 R_1= H, R_2 = Cl
123 R_1= Ethyl, R_2= F

Antiosteoporotic activity

Applying the molecular hybridization approach, Sashidhara et al. [168] discovered compound **124** as a potent antiosteoporotic agent which increased bone mass density and volume, expression of osteogenic genes, bone formation rate, mineral apposition rate, improved the trabecular microarchitecture and decreased bone turn over markers in an ovariectomized rodent model for postmenopausal osteoporosis. It was also proved that coumarin–HHQ were more effective than individual coumarins or nifedipine and benzofuran–HHQ hybrids. Very recently, the team designed some benzofuran–HHQ hybrids and evaluated them for bone anabolic activities. Compound **125** was introduced as the most promising derivative, and it was stated that benzofuran–HHQ hybrids were more active than their individuals.

Compound **125** significantly stimulate bone morphogenic protein-2 and osteoblast differentiation, increase alkaline phosphatase activity and enhance osteoblasts by improving mineralization activity in extracellular matrix. Furthermore, the compound triggers the regeneration and healing properties in bone compared to the vehicle-treated group in a drill hole fracture (defect) model [169].



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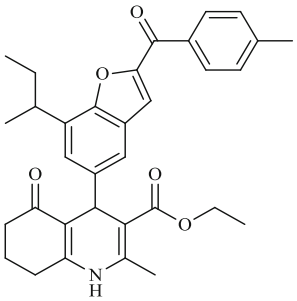

125

Conclusions

So far, several derivatives of 5-oxo-HHQ scaffold have been synthesized and numerous studies have been done on the biological effects of such compounds. The 5-oxo-HHQ derivatives display versatile biological and pharmacological activities, i.e., cardiovascular, myorelaxant, analgesia, anticancer, antibacterial, antifungal, antitubercular, antimalarial, antioxidant, anti-inflammatory, MDR reversal, neuroprotective, antidiabetic, antidyslipidemic and antiosteoporotic activities. Studies on the pharmacological activities of 5-oxo-HHQ derivatives along with the chemistry involved in those activities, which are compiled in this review, would be helpful in designing and developing new therapeutic agents.

According to reported various biological effects and structural diversity of 5-oxo-HHQs, some general considerations seem to come out. While the presence of hydrogen on N_1 and small groups on C_2 and C_3 positions of 5-oxo-HHQ core for calcium channel and COX-2 inhibitory activities are requirements, most of the cytotoxic derivatives have bulky and fused substitutions on these positions. It is well established that C_4-aryl or C_4-heteroaryl is a necessity in all reported biological activities and by placing various substitutions on these groups the biological effect could be improved or diminished. As an example, placing alkoxy and hydroxyl moieties on 4-phenyl improves the antioxidant potential of 5-oxo-HHQs, whereas in the case of MDR reversal activity this action reduces the effect.

Cytotoxic activity as well as MDR reversal potential of 5-oxo-HHQ derivatives may bring about new horizons in cancer treatment. In vivo studies reveal some derivatives are promising antimalarial, antidiabetic, antidyslipidemic and antiosteoporotic agents. We believe that 5-oxo-HHQs deserve more investigation, above all in the field of interaction with receptors and therapeutical targets as well as in their use as the scaffold for the preparation of antimalarial, antidiabetic, antidyslipidemic, antiosteoporotic and anti MDR agents.

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Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

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