Exploring diverse frontiers: Advancements of bioactive 4-aminoquinoline-based molecular hybrids in targeted therapeutics and beyond

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Exploring Diverse Frontiers: Advancements of Bioactive 4-Aminoquinoline-based molecular hybrids in targeted therapeutics and beyond

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Abstract

Amongst heterocyclic compounds, quinoline and its derivatives are advantaged scaffolds that appear as a significant assembly motif for developing new drug entities. Aminoquinoline moiety has gained significant attention among researchers in the 21stcentury. Considering the biological and pharmaceutical importance of aminoquinoline derivatives, herein, we review the recent developments (since 2019) in various biological activities of the 4-aminoquinoline scaffold hybridized with diverse heterocyclic moieties such as quinoline, pyridine, pyrimidine, triazine, dioxine, piperazine, pyrazoline, piperidine, imidazole, indole, oxadiazole, carbazole, dioxole, thiazole, benzothiazole, pyrazole, phthalimide, adamantane, benzochromene, and pyridinone. Moreover, by gaining knowledge about SARs, structural insights, and molecular targets, this review may help medicinal chemists design cost-effective, selective, safe, and more potent 4-aminoquinoline hybrids for diverse biological activities.

Keywords: 4-Aminoquinolines, anticancer, antimalarial, antibacterial, antitubercular

1. Introduction

Derivatives of aminoquinolines evaluated for various biological activities are significant substances for developing novel drugs. As a result, these compounds have been produced as intended structures by many scientific groups worldwide, who have also assessed their biological properties [1-3]. Among them, 4-aminoquinoline is considered an important biological active moiety with numerous biological properties such as anticancer [4-6], antibacterial [7], antifungal [8], antiviral [9], anti-inflammatory [10], anti-analgesic, antileishmanial [11], anti-Alzheimer [12], antitubercular [13], and antimalarial [14,15]. Successful introduction of chloroquine, hydroxychloroquine, piperaquine, amopyroquine, and amodiaquine as antimalarial, amsacrine as antineoplastic, neratinib and pelitinib (EKB-569) as HER2 and EGFR anticancer agents, respectively, bosutinib as oral Src/Abl tyrosine kinase inhibitor, dovitinib as antitumor, aminacrine as antiseptic, antrafenine, glafenine, and floctafenine as anti-inflammatory and anti-analgesic, tacrine as anti-alzheimer, and different other properties proved the potential of the 4-aminoquinoline system [16]. The variability in the biological response profile has drawn scientists' interest, who are currently examining the 4-aminoquinoline skeleton to learn more about its various potentials as an active moiety [17,18]. **Figure 1** displays some of the 4-aminoquinoline-related drugs currently on the market.

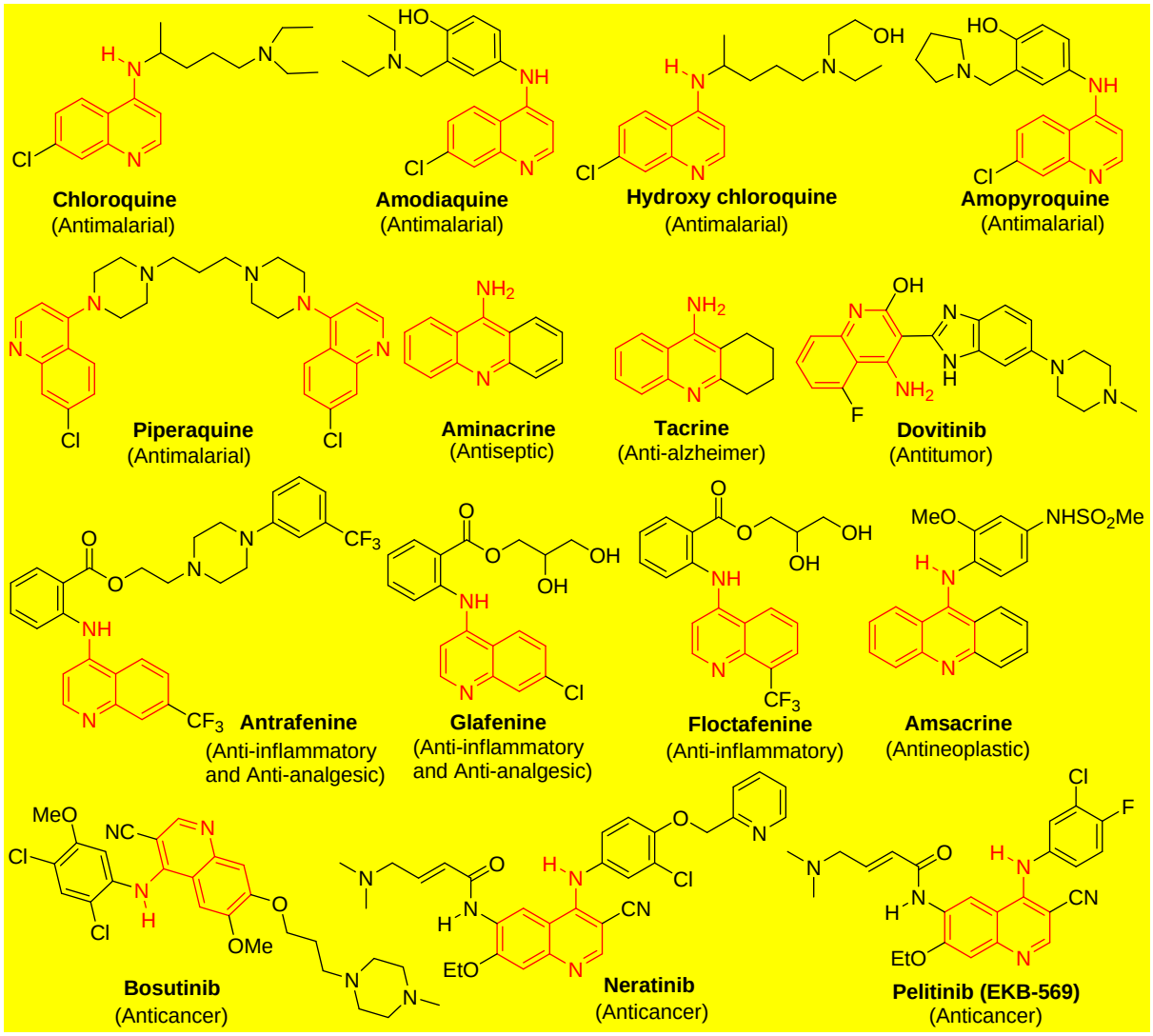


Figure 1. Marketed drugs based on 4-aminoquinoline moiety

Since Hans Andersag and colleagues discovered in 1934 chloroquine (CQ), a 4-aminoquinoline, has served as the foundation for antimalarial agents [19]. Later research revealed it also had immunomodulating, anti-tumour, anti-thrombotic, anti-infective, and metabolic properties. The mechanism of CQ and hydroxychloroquine (HCQ) in inflammatory and rheumatic illnesses has been tentatively identified over the past ten years [20]. Recently, the mechanism of CQ and HCQ as a possible COVID-19 treatment was also presented [21-23]. Several 4-aminoquinoline hybrids have been designed as the skeleton, which is considered a potential framework for constructing anticancer drugs since the approval of pelitinib for cancer therapy [24]. 4-Aminoquinoline, as an immunostimulatory drug, has drawn more attention due to its ability to inhibit the proliferation of certain cancer cells. Pathogenic microorganisms affect the quality of life. Many people worldwide die from bacterial illnesses each year [25].

Drug-drug interaction may result in additional severe side effects, and the progress of an efficient combination therapy is expensive. Due to the disparities in the pharmaceuticals'

stability, solubility, and pharmacokinetic profiles, selecting the right drugs and dosages for combination therapy can be difficult. Hence, modifying existing drugs *via* the construction of hybrid molecules would appear to be a promising approach [26,27]. Combination therapy can be overcome while overall efficacy is increased by the molecular hybridization of two or more active pharmacophores into a single molecule [28,29].

In this review, we are outlining the potential of a 4-aminoquinoline moiety, hybridized with diverse heterocyclic moieties such as quinoline, pyridine, pyrimidine, triazine, dioxine, piperazine, pyrazoline, piperidine, imidazole, indole, oxadiazole, carbazole, dioxole, thiazole, benzothiazole, pyrazole, phthalimide, adamantane, benzochromene, and pyridinone, as anticancer, antibacterial, antifungal, antiviral, anti-mycobacterial, anti-inflammatory, anti-analgesic, antileishmanial, anti-Alzheimer, antitubercular and antimalarial agent.

2. Anticancer activity of 4-aminoquinolines:

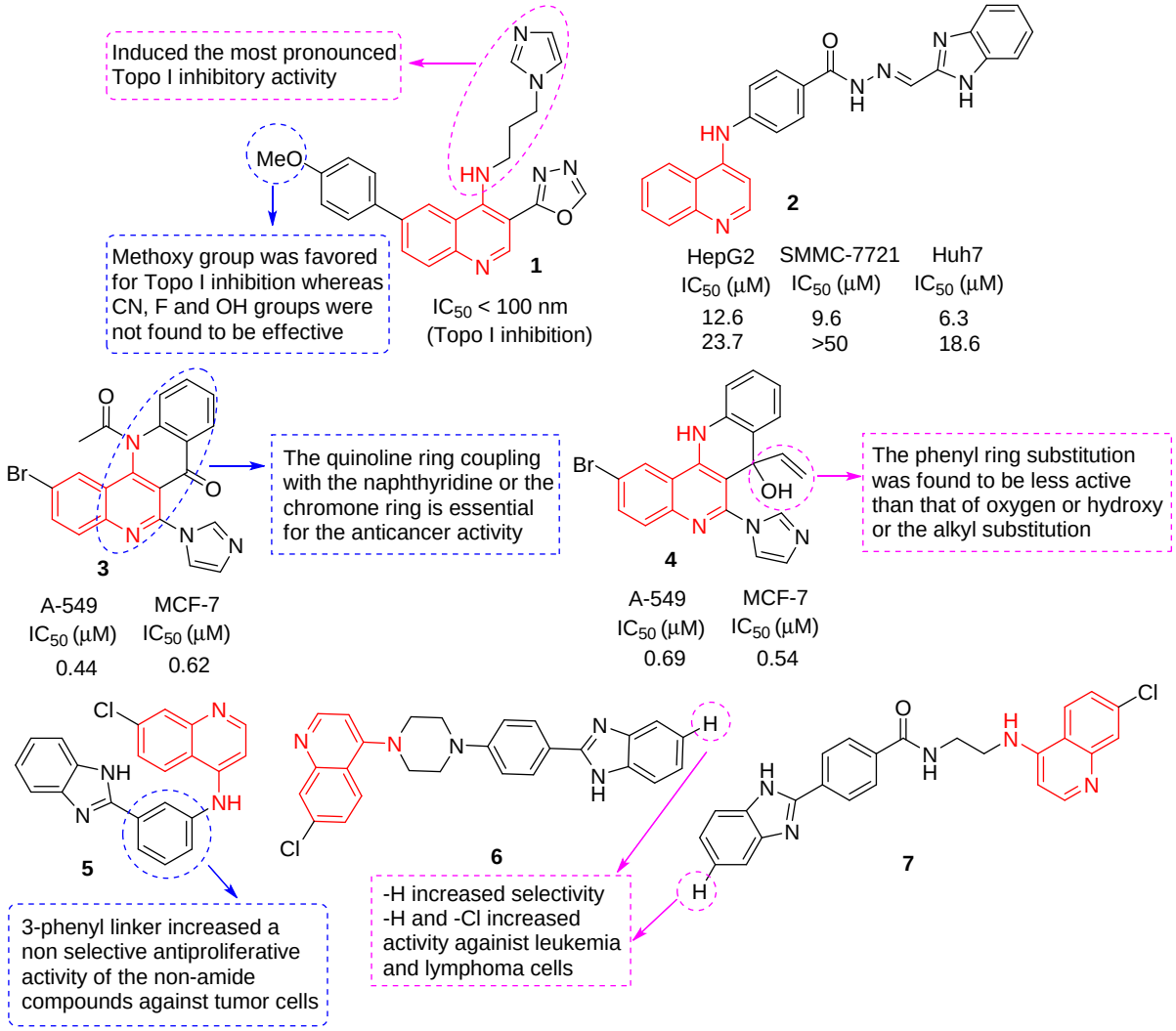
Cancer has been regarded for a long time as one of the major global public health issues, and it is currently the second leading cause of death worldwide [30,31]. The class of 4-aminoquinoline conjugated heterocyclic compounds continues to be one of the most promising for developing anticancer drugs [32,33].

2.1. Imidazole-4-aminoquinoline conjugates:

4-Aminoquinoline-based hybrids that contain imidazole units either fused or substituted directly to the 4-aminoquinoline moiety or *via* intermediate chain or linkers were reported. By combining the chemical structures of indenoisoquinolines and camptothecin (such as indotecanand indimitecan), Kundu and co-workers [34] synthesized imidazole containing 4-aminoquinoline hybrids and examined them for their ability to inhibit human Topoisomerase I in a plasmid DNA relaxation test. The assay's findings showed hybrid **1** (**Figure 2**) to be substantially potent, with an activity index similar to that of topotecan and camptothecin. Additionally, the series of hybrids' anticancer potential was assessed using various cell lines, and it was discovered that hybrid **1** significantly inhibits the growth of several cancer cell lines, including HCT116, HeLa, and MCF7, with IC_{50} values of 2.34, 2.61, and 2.74 μM. In 2020, Li and co-workers [35] developed a small library of imidazole containing 4-aminoquinoline hybrids as anticancer agents. Among them, benzimidazole conjugate **2** (**Figure 2**) demonstrated moderate activity towards the HepG2 cell line (IC_{50} = >80 μM).

In the following year, the research group of Kardile [36] furnished a new family of conformationally constrained 4-aminoquinoline hybrids containing imidazole moiety as active anticancer candidates with potent Topo I inhibitory activity. *In vitro* antiproliferative examination counter to MCF-7 and A549 cancer cells revealed that the hybrids **3** (IC_{50}= 0.62

μM (MCF-7) and 0.44 μM (A549)) and **4** (IC_{50}= 0.54 μM (MCF-7) and 0.69 μM (A549)) were the most potent agents (**Figure 2**). Very recently, Krstulovi´c and co-workers [37] examined the antiproliferative effects of novel benzimidazole-4-aminoquinoline derivatives, differed by the substitutions on benzimidazole unit and the type of linker between benzimidazole and 4-aminoquinoline moieties, against Raji, CaCo-2, THP-1, Hut78, CCRF-CEM, MCF-7 (tumour cells), and MDCK1 (non-tumour cell). The analogues having unsubstituted benzimidazole unit and varied linkers (**5-7, Figure 2**) demonstrated a strong cytotoxic effect with GI_{50} values between 0.4 and 8 μM and efficiently suppressed the cell cycle progression in the lymphoma and leukaemia cell lines.



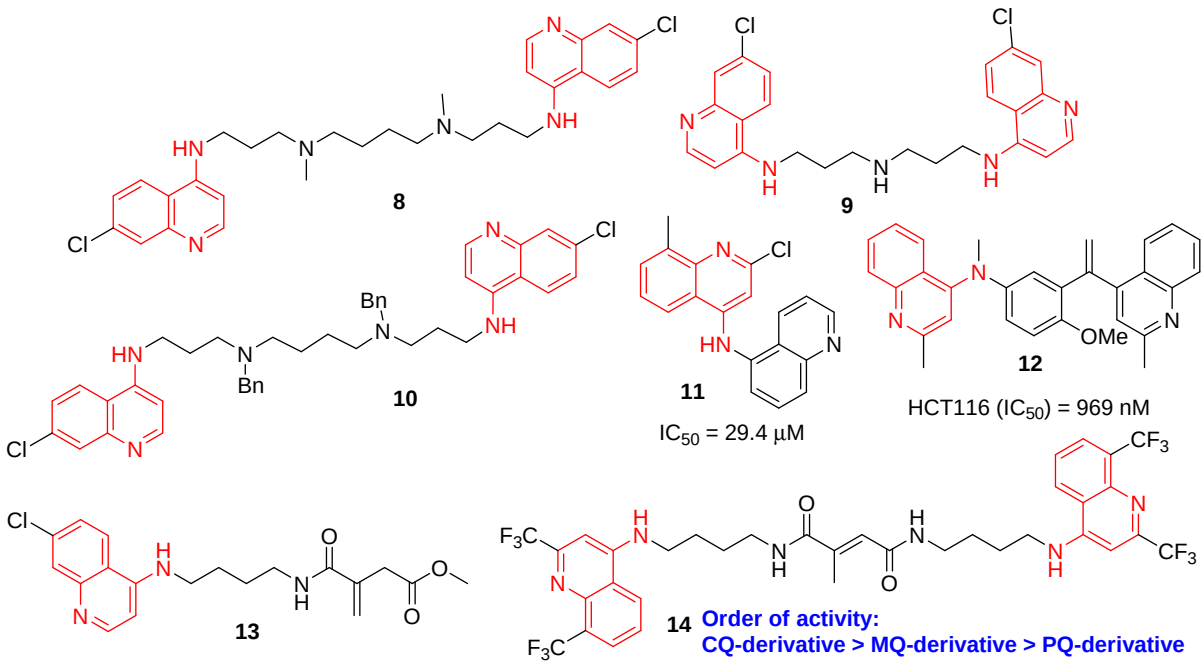
	MDCK1 GI_{50} (μM)	Hela GI_{50} (μM)	CaCo-2 GI_{50} (μM)	MCF-7 GI_{50} (μM)	CCRF-CEM GI_{50} (μM)	THP1 GI_{50} (μM)	Raji GI_{50} (μM)	HuT78 GI_{50} (μM)
5.	20.4	0.7	1.0	33.6	8.2	0.6	4.3	0.4
6.	>100	>100	>100	>100	5.0	3.2	3.8	8.1
7.	100	100	16.4	20.0	17.2	4.0	57.7	3.5

Figure 2. Anticancer activity of imidazole containing 4-aminoquinoline derivatives

2.2. Quinoline-4-aminoquinoline conjugates:

Amaravadi and co-workers [38] constructed a novel series of bisaminoquinoline derivatives with diverse linkers and examined them by employing A375P melanoma cells, and the active compounds **8–10** demonstrated logIC_{50} values of -6.57 to -6.39. It was determined that dimeric chloroquines' cytotoxicity and ROS production improved by lengthening the linkers inside their quinolone rings (**Figure 3**). A small family of novel quinoline-conjugated 4-aminoquinoline derivatives was synthesized by Vennilaet al. [39] and tested against a non-small cell lung cancer cell line, A549, by employing Pemetrexed as a standard drug. One of the derivatives, 2-chloro-8-methyl-N-(quinolin-5-yl)quinolin-4-amine (**11**), was found to be active with 29.4 μM of IC_{50} value (**Figure 3**).

An array of diverse heterocyclic-4-aminoquinoline hybrids were furnished and tested for anticancer efficacy by the research group of Khelifi [40], including the quinoline derivative (**12, Figure 3**), which demonstrated poor *in vitro* cytotoxicity with an IC_{50} 969 nM against HCT116 cell line. Currently, Perković and group [41] reported the anticancer efficacy of novel itaconic acid-based quinoline, indole, pyridine, and mefloquine hybrid compounds counter to Capan-1, LN-229, HCT 116, MCF-7, H460 (solid tumour cells), and Z-138, K-562, HL-60, DND-41(haematological cancer cells). Compared to the haematological cancer cells, solid tumour cells were more responsive. The MCF-7 breast adenocarcinoma cell line appeared to be the most sensitive. Amongst all the tested hybrids, 4-aminoquinoline-based amido-ester **13** and 4-aminoquinoline homodimer **14** demonstrated superior efficacy towards all tested cells, with the GI_{50} ranging from 0.7 to 8.6 μM (**Figure 3**).



	MCF-7 GI_{50} (µM)	HCT 116 GI_{50} (µM)	H460 GI_{50} (µM)	LN-229 GI_{50} (µM)	Capan-1 GI_{50} (µM)	DND-41 GI_{50} (µM)	HL-60 GI_{50} (µM)	K-562 GI_{50} (µM)	Z-138 GI_{50} (µM)
13	0.8	2.0	2.0	1.1	1.3	3.1	1.9	8.1	1.9
14.	0.7	2.4	3.0	2.4	2.3	7.9	2.6	8.6	6.9

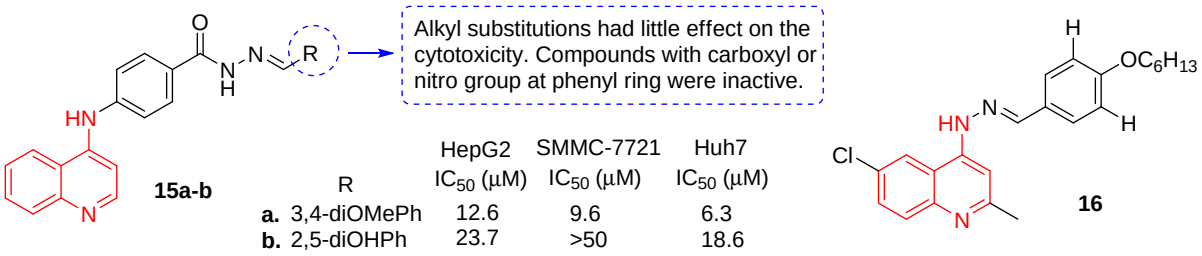
Figure 3. Anticancer properties of quinoline conjugated 4-aminoquinolines

2.3. Hydrazone-4-aminoquinoline conjugates:

Li et al. [35] furnished a range of 4-aminoquinoline-benzoylhydrazide compounds and investigated their anticancer potency to create novel 4-aminoquinoline hybrids for treating liver cancer. The IC_{50} values for the active antiproliferative analogues **15a** and **15b** towards the HepG2 cell line were determined to be 12.6 µM and 27.3 µM, respectively. The most potent analogue, **15a,** also showed cytotoxicity counter to the Huh7 and SMMC-7721 cell lines with 6.3µM and 9.6 µM of IC_{50} values, respectively. Due to their inhibition of cell migration, induction of cell cycle arrest and cell death, and anti-survival action, **15a** and **15b** were proven to suppress the growth of HepG2 cells. These findings demonstrated that **15a** might be a lead compound for developing anticancer drugs to treat hepatocellular carcinoma (**Figure 4**).

Considering the biological importance of 4-aminoquinolines, the research group of Katariya [42] constructed a family of novel hydrazone-based 4-aminoquinolines and carried out the cytotoxic examination counter to full NCI 60 human cancer cells. Nine out of sixteen analogues displayed substantial anti-proliferative efficacy at a concentration of 10 µM and were next examined at 100, 10, 1, 0.1, and 0.01 µM of five different concentrations (10-fold dilutions) with 4.67 µM to >100 µM range of LC_{50} values and 0.33 to 4.87 µM range of GI_{50} values. In addition, the significant values of LC_{50} and GI_{50} of the promising analogue **16** were

compared with the clinically used anticancer drugs chlorambucil and bendamustine, showing that the quinolyl hydrazones hold promise as potential anticancer agents (**Figure 4**).



R	HepG2 IC_{50} (μM)	SMMC-7721 IC_{50} (μM)	Huh7 IC_{50} (μM)
a. 3,4-diOMePh	12.6	9.6	6.3
b. 2,5-diOHPh	23.7	>50	18.6

Figure 4. Anticancer properties of hydrazone-based 4-aminoquinolines

2.4. Chalcone-4-aminoquinoline conjugates:

A small family of chalcone-4-aminoquinoline conjugates (*E*)-1-[3 or 4-(7-chloroquinolin-4-ylamino) phenyl]-3-(phenyl substituted) prop-2-ene-1-one (**17-18**) were furnished by Charriset al. [43] to achieve an anticancer and antimalarial dual action. The hybrids induce cell death on two humancancer cells (HL60 and Jurkat E6.1) without affecting the primary culture of human lymphocytes. It is interesting to highlight that the hybrid **17** exhibited significant anticancer activities, comparable to the reference drug doxorubicin against both cancer cells. Particularly, the action of hybrid **17** does not affect the viability of normal human leukocytes at 8 μM, showing a unique activity/toxicity profile (**Figure 5**).

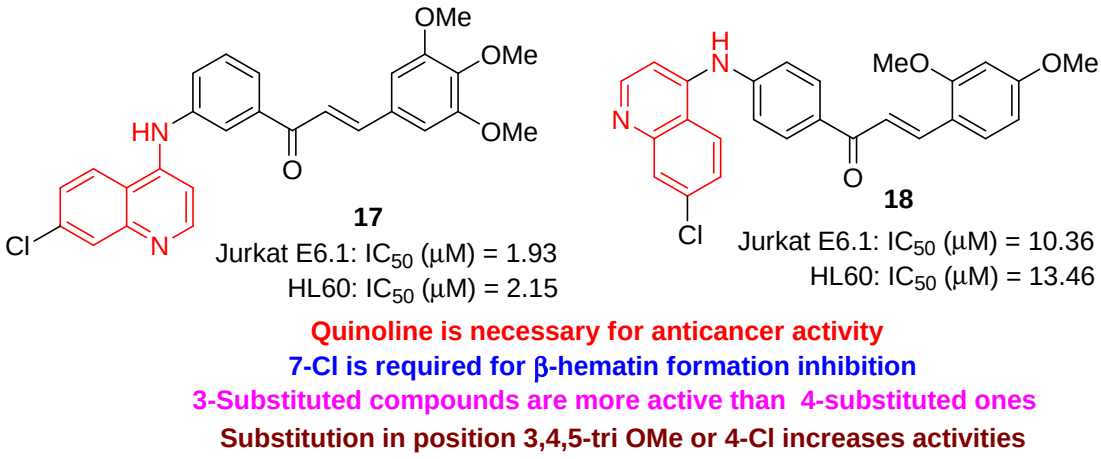
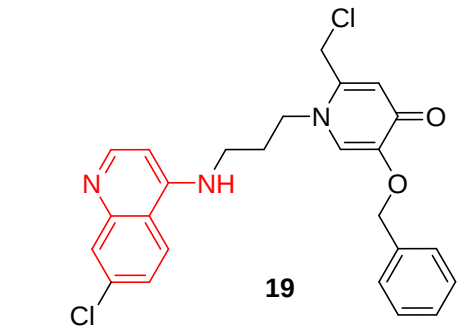


Figure 5. Anticancer properties of chalcones conjugated 4-aminoquinolines

2.5. Pyridinone-4-aminoquinoline conjugates:

Novel pyridine-linked 4-aminoquinolines were furnished by Fayyazi et al. [44] and examined for biological potency as dual VEGFR-2 and EGFR inhibitors. The preliminary examination demonstrated that the hybrids showed efficient antiproliferative activities counter to AGO1522, MCF7, HT29, and A549 cell lines. It is worth mentioning that the outcomes of cytotoxicity assay towards human carcinoma cells showed 0.8 μM for **19** counter to A549, demonstrating its higher potency in comparison to the standard drug erlotinib (**Figure 6**).



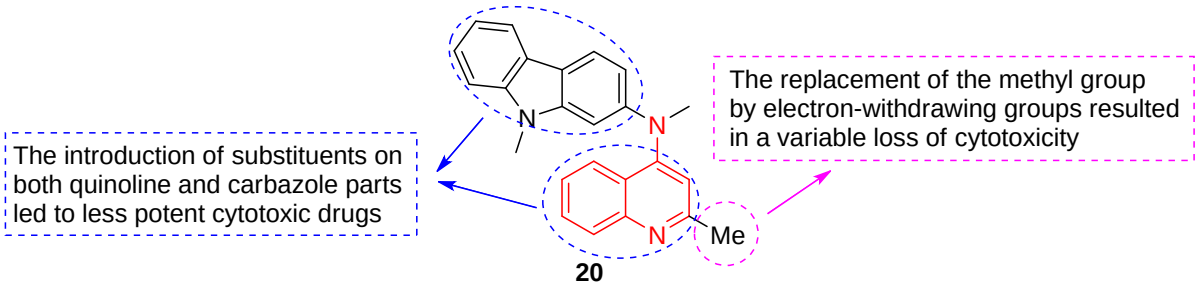
19

A549 IC_{50} (μM)	HT29 IC_{50} (μM)	MCF7 IC_{50} (μM)	AGO1522 IC_{50} (μM)
0.81	1.41	1.26	2.87

Figure 6. Anticancer properties of pyridine conjugated 4-aminoquinolines

2.6. Carbazole-4-aminoquinoline conjugates:

Several 4-aminoquinoline hybrids containing different heterocycles were constructed and examined for activity by Khelifi and co-workers [40], counting the carbazole derivative **20**, which demonstrated exceptional sub-nanomolar *in vitro* cytotoxicity counter to the colon carcinoma cell line HCT116 (IC_{50} = 0.070 nM) as well as substantial inhibitory potency towards tubulin polymerization. Remarkably, hybrid **20** demonstrated a significant sub-micromolar cytotoxicity counter to JIM-T1, K562R, K562, MiaPaca2, A2780R, and A2780 human cancer cell lines. In addition, at a concentration of 5 nM, **20** arrested the cellular cycle in the G2/M phase of the cellular cycle and induced apoptosis of HCT116 cell lines (**Figure 7**).



20

HCT116 IC_{50} (nM)	ITP IC_{50} (μM)	A2780 IC_{50} (μM)	A2780R IC_{50} (μM)	MiaPaca2 IC_{50} (μM)	K562 IC_{50} (μM)	K562R IC_{50} (μM)	JIM-T1 IC_{50} (μM)
0.070	1.13	0.53	0.54	0.47	0.60	0.28	0.36

Figure 7. Anticancer properties of carbazole conjugated 4-aminoquinolines

2.7. Dioxole/dioxine-4-aminoquinoline conjugates:

In an endeavour to develop new 4-aminoquinolines as cancer drugs, Jin and co-workers [45] synthesized a family of 4-aminoquinoline-dioxole conjugates and tested for their *in vitro* cytotoxicity counter to L-02, SGC-7901, Hela, and A-549 human cancer cells. Compared to the un-substituted analogues, all the alkyliodine substituted analogues were proved to be the

most active agents, of which analogue **21** (**Figure 8**) showed superior antitumor potency counter to L-02, SGC-7901, Hela, and A-549 cells with IC_{50} values of 54.45, 17.59, 7.62, and 5.18 µM respectively, stronger than the positive control MTX and 5-FU. The research group of Khelifi [40] synthesized and tested the anticancer activity of benzodiaxine conjugated 4-aminoquinoline (**22, Figure 8**) counter to the HCT116 cell line. Hybrid **22** demonstrated superior *in vitro* cytotoxicity counter to the HCT116 cell line (IC_{50} = 20.7 nM).

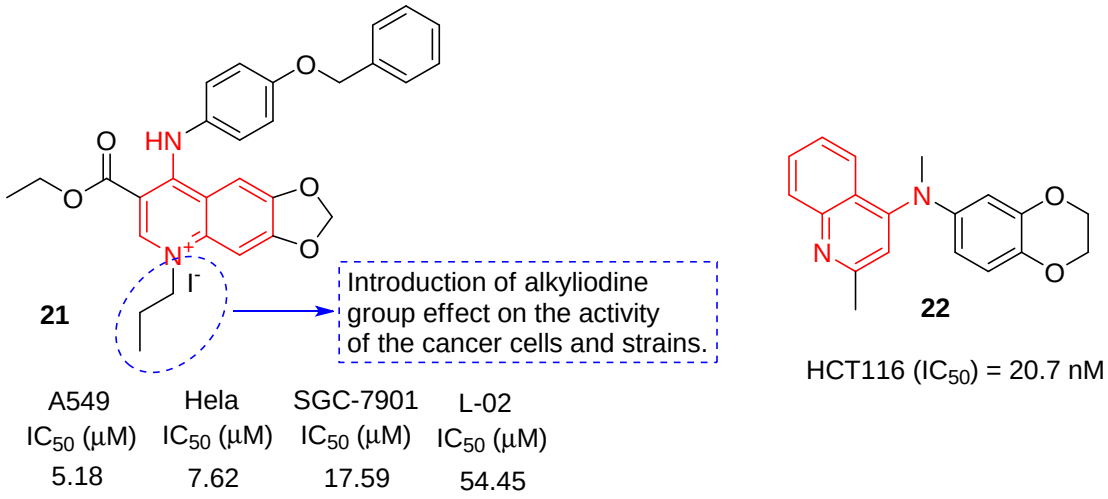


Figure 8. Anticancer properties of dioxole/dioxine conjugated 4-aminoquinolines

2.8. Triazine-4-aminoquinoline conjugates:

Bhat and co-workers [46] constructed several 1,3,5-triazine conjugated 4-aminoquinoline hybrids and tested them counter to the HepG2, HL-60, MCF-7, and HeLa cancer cells to check their anticancer effects. Remarkably, hybrid **23** demonstrated superior anticancer activity against all four cancer cells, comparable to the reference drug cisplatin against HeLa cell lines. Notably, all the tested hybrids were discovered to be nontoxic to MCF-12A. Additionally, the hybrids demonstrated stronger EGFR-TK inhibition in an enzyme-based assay when compared to erlotinib (**Figure 9**).

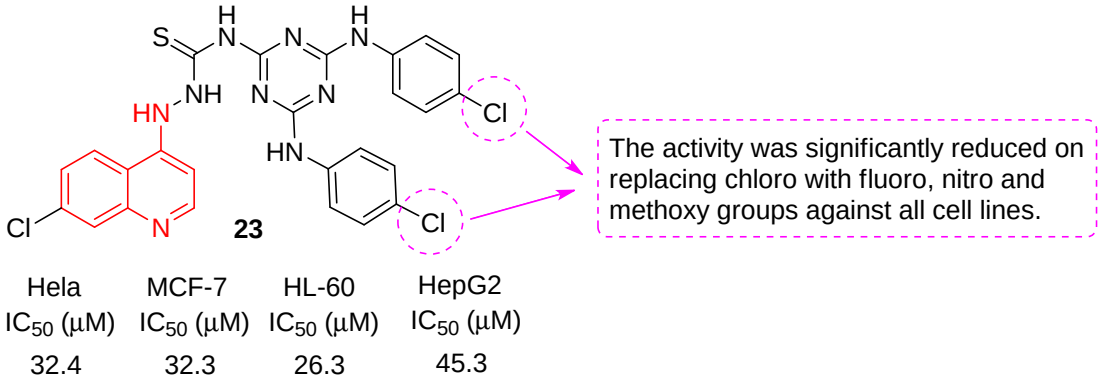


Figure 9. Anticancer properties of 1,3,5-triazine conjugated 4-aminoquinolines

2.9. Thiazole-4-aminoquinoline conjugates:

A broad range of benzothiazole-based 4-aminoquinolines were furnished by Yuan et al. [47] as Topo I inhibitors. Antiproliferative test counter to NCI-H460, T-24, HepG-2, MGC-803 (human cancer cells), and HL-7702 (normal cell) revealed that the majority hybrids were significantly potent with IC_{50} values lowed to micromole level and few of them even more active than the standard drug HCPT. Hybrid **24** (**Figure 10**) demonstrated the most promising activity with IC_{50} value <2.20 (μM) towards all cancer cells. Agarose-gel electrophoresis and spectroscopic analysis showed that hybrid **24** could interact with DNA andstrongly inhibit Topo I. A molecular modelling analysis proved that hybrid **24** interacts uniquely with Topo I and DNA. On MGC-803 xenograft nude mice, the effectiveness **24** was also assessed, and the relative tumour growth suppression was 42.4% at 12 mg/kg without obviously lowering body weight. In 2020, Li and co-workers [35] synthesized a novel thiazole containing 4-aminoquinoline hybrid **25** (**Figure 10**) as an anticancer agent, which demonstrated moderate activity towards the HepG2 cell line (IC_{50} = >80 μM).

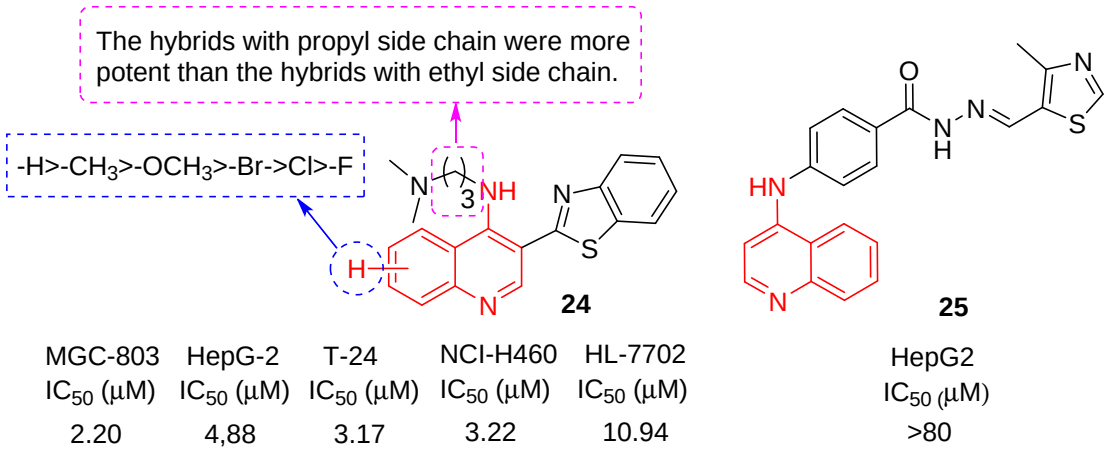


Figure 10. Anticancer properties of thiazole-4-aminoquinolines

2.10. Ursolic acid-4-aminoquinoline conjugates:

In vitro, examinations of ursolic acid conjugated 4-aminoquinoline hybrid compounds counter to the MCF-7, HeLa, and MDA-MB-231 human cancer cell lines were performed by the research group of Khwaza [48]. Hybrid **26** was potent against MCF-7 and HeLa cancer cells, whereas hybrid **27** was active towards MDA-MB-231 cancer cells. Hybrid **26** was more cytotoxic than ursolic acid, displaying 48.18 μg/ml of IC_{50}value. In addition, docking results showed that hybrid **26** performed superior docking energy and excellent binding interactions on the Epidermal Growth Factor Receptor (EGFR) than the parent compound, ursolic acid (**Figure 11**).

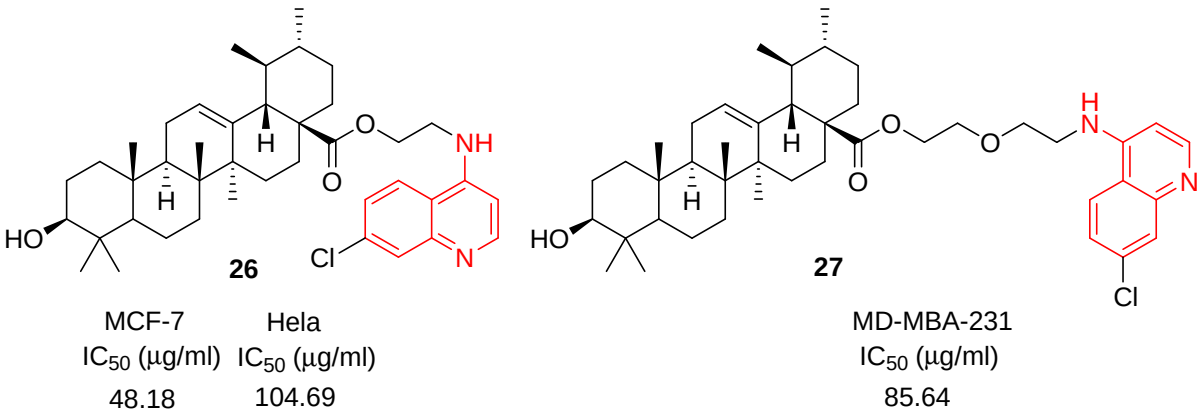


Figure 11. Anticancer properties of ursolic acid-based 4-aminoquinolines

2.11. Piperazine-4-aminoquinoline conjugates:

In the effort to develop efficient and potentially safe anticancer drugs, Solomon et al. [49] constructed a vast array of 4-aminoquinoline and 4-piperazinyl quinolone-derivedsulfonyl hybrids. The SAR revealed that the 7-chloro-4-piperazinylquinoline-derived sulfonyl hybrids displayed enhanced antigrowth activity on breast cancer cells than the 7-trifluoromethyl-4-aminoquinoline-derived sulfonyl hybrids. Most of the analogues were fairly effective on the breast cancer cells; the analogue 7-chloro-4-(4-(2,4-dinitrophenylsulfonyl)piperazin-1-yl)quinoline (**28**) was proved to be the most active agent in this series of hybrids. Data from the NCI-60 cancer panel examination showed that hybrid **28** was potent on a broad range of diverse cancers (**Figure 12**).

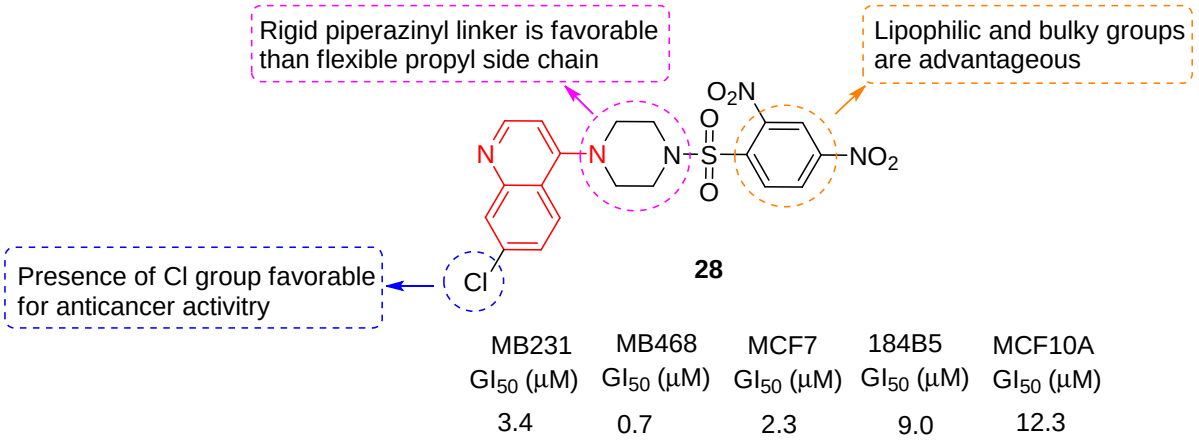
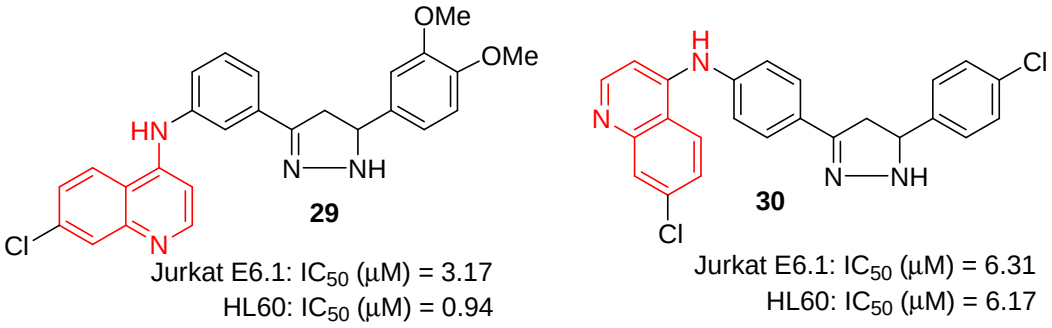


Figure 12. Anticancer properties of 4-aminoquinoline and 4-piperazinylquinoline derived sulfonyl hybrids

2.12. Pyrazoline-4-aminoquinoline conjugates:

To test the anticancer and antimalarial dual action, Charris et al. [43] also synthesized a small library of pyrazoline-4-aminoquinoline derivatives 7-Chloro-*N*-[3 or 4-(4,5-dihydro-5-(phenyl-substituted)-1H-pyrazol-3-yl] phenyl)quinoline-4-amine (**29-30**). The hybrids induce

cell death on two humancancer cells (HL60 and Jurkat E6.1) without affecting the primary culture of human lymphocytes. Remarkably, hybrid **29** exhibited significant anticancer activity amongst the series, nearly two-fold higher potent than the reference drug doxorubicin against HL60 cell lines (**Figure 13**).



Quinoline is necessary for anticancer activity
7-Cl is required for β-hematin formation inhibition
3-Substituted compounds are more active than 4-substituted ones
Substitution in position 3,4,5-tri OMe or 4-Cl increases activities

Figure 13. Anticancer properties of pyrazoline-based 4-aminoquinolines

2.13. Pyridine-4-aminoquinoline conjugates:

A small library of pyridine-based 4-aminoquinoline hybrids (**31-33**) was constructed by the research group of Khelifi [40] and examined for anticancer activity against HCT116 and ITP cancer cell lines. It is noteworthy that hybrid **33** demonstrated exceptional nanomolar *in vitro* cytotoxicity counter to the colon carcinoma cell line HCT116 (IC_{50} = 1.73 nM) as well as substantial inhibitory potency towards tubulin polymerization amongst all the tested hybrids (**Figure 14**).

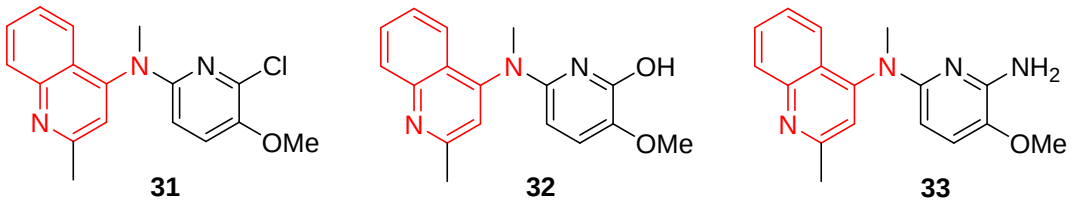
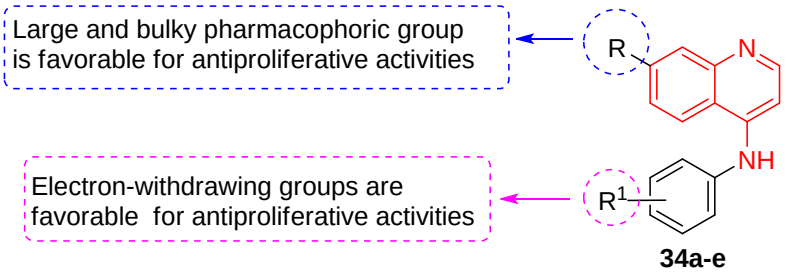


Figure 14. Anticancer properties of pyridine-based 4-aminoquinolines

2.14. Miscellaneous 4-aminoquinolines:

A broad range of novel 4-aminoquinoline analogues were furnished by Su et al. [50] and tested for their anti-proliferative efficacy. The outcomes showed that five out of forty-four analogues (**34a-e**) were potent anti-proliferative agents with <10 μM of IC_{50} values counter to seven human tumour cells, and *N*-(3-methoxyphenyl)-7-(3-phenylpropoxy) quinoline-4-amine **34d** emerged as potentially the most desirable one counter to Hela, A2780, RKO, and HCT-

116 cell lines with an IC_{50}value of 2.71, 3.46, 3.67, and 2.56 μM, respectively. In addition, analogue **34d** effectively inhibited tumour growth by approximately 82.1% in mice bearing CT25-Cl26 cells compared with the control drug (**Figure 15**).

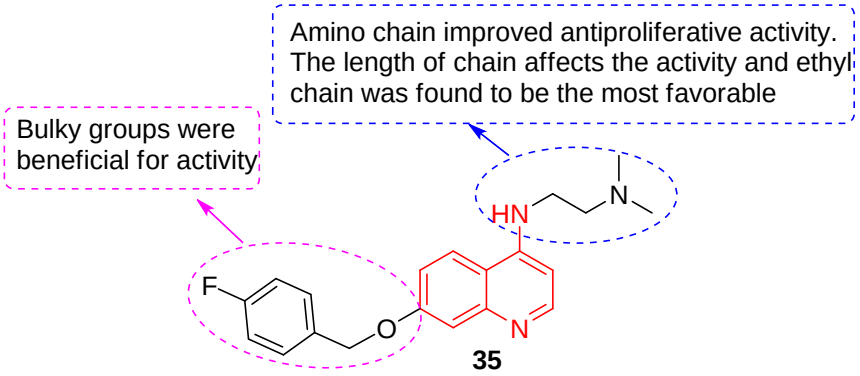


34a-e

	R	R^1	HCT116 IC_{50} (μM)	RKO IC_{50} (μM)	A2780 IC_{50} (μM)	Hela IC_{50} (μM)	BGC-823 IC_{50} (μM)	A549 IC_{50} (μM)	NCI-H1650 IC_{50} (μM)
a.	OC_8H_{17}	3-F	9.30	9.54	9.75	4.30	5.96	9.52	9.45
b.	$OCH_2C_6H_5$	3-NO_2	8.76	9.68	9.19	5.39	8.13	9.49	9.54
c.	OCH_2(4-F)C_6H_4	3-NO_2	8.17	8.70	6.51	5.79	9.45	7.30	9.35
d.	$O(CH_2)_3C_6H_5$	3-OMe	2.56	3.67	3.46	2.71	9.08	8.22	6.30
e.	$O(CH_2)_3C_6H_5$	3-NO_2	7.46	8.29	4.46	4.13	8.32	5.09	6.01

Figure 15. Antiproliferative activity of 4-aminoquinoline derivatives

The 4-aminoquinoline-based analogues were furnished by the research group of Li [51] and tested on a panel of seven cancer cells. Analog **35** outperformed the other analogues regarding its efficient antitumor activities counter to all tested cell lines. Employing a colorectal cancer xenograft model in nude mice, *in vivo* tests were conducted, and it was found that analogue **35** significantly inhibited tumour growth at a dose of 80 mg/kg. Detailed investigations also showed that **35** activated p53 transcriptional potency, which led to the induction of p53/Bax-dependent colorectal cancer cell death (**Figure 16**).



35

HCT-116 IC_{50} (μM)	RKO IC_{50} (μM)	DLD1 IC_{50} (μM)	HepG2 IC_{50} (μM)	BGC-823 IC_{50} (μM)	NCI-H1650 IC_{50} (μM)	SK-OV-3 IC_{50} (μM)
0.37	0.58	0.81	0.79	0.89	0.78	0.89

Figure 16. Anticancer activity of 4-aminoquinoline derivatives

3. Antibacterial activity of 4-aminoquinolines:

Treatment of infections has proven to be highly challenging due to antimicrobial agent resistance. Developing hybrid molecules employing the potential drugs is an important approach to constructing effective antibacterial agents [52].

3.1. Dioxole-4-aminoquinoline conjugates:

Aiming to develop novel 4-aminoquinolines as antibacterial agents, Jin and co-workers [45] synthesized a family of 4-aminoquinoline-dioxole conjugates and tested for their antibacterial activities counter to ATCC 29213 (*Escherichia coli*) and ATCC 8739 (*Staphylococcus aureus*) human bacterial clones. Compared to the un-substituted analogues, all the alkyliodine substituted analogues were proved to be the most active agents, of which analogue **36** showed superior antibacterial activity counter to both the ATCC 29213 and ATCC 8739 bacterial clones with MIC of 3.125 nmol·mL^{-1}, which was lower than the standard drugs, ciprofloxacin, and amoxicillin (**Figure 17**).

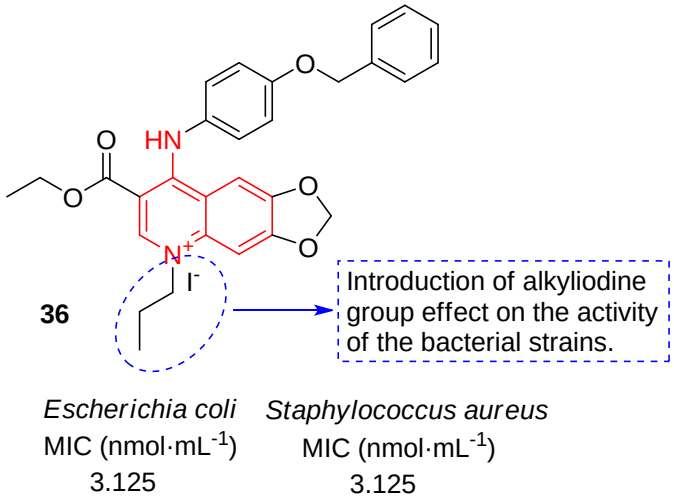
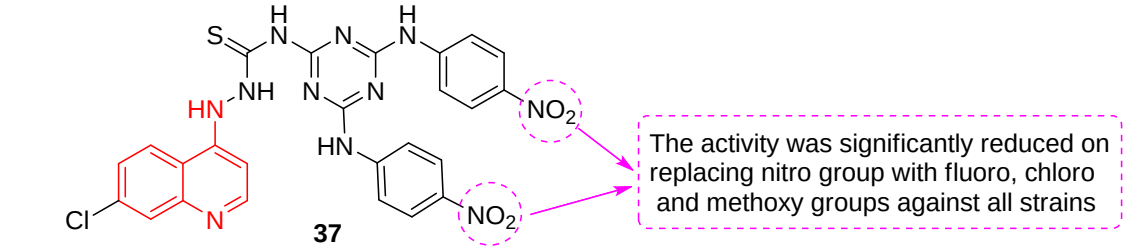


Figure 17. Antibacterial activity of dioxole-4-aminoquinoline derivatives

3.2. Triazine-4-aminoquinoline conjugates:

Bhat and co-workers [46] furnished a range of triazine-4-aminoquinoline hybrids and tested them counter to the *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus vulgaris*, *Staphylococcus aureus*, *Bacillus cereus*, and *Bacillus subtilis* clones employing cefixime as reference drug to check their antibacterial effects. Hybrid **37** demonstrated superior antibacterial activity counter to *P. vulgaris*, *P. aeruginosa*, and *S. aureus* and moderate potency counter to *E. coli*, *B. cereus*, and *B. subtilis*. Antibacterial test results revealed that the development of potential antimicrobial agents requires the presence of electron-withdrawing groups like methoxy and nitro on the fourth position of the phenylamine. All the tested analogues were discovered to be nontoxic to MCF-12A. Furthermore, the hybrids

demonstrated stronger EGFR-TK inhibition in an enzyme-based assay compared to erlotinib (**Figure 18**).

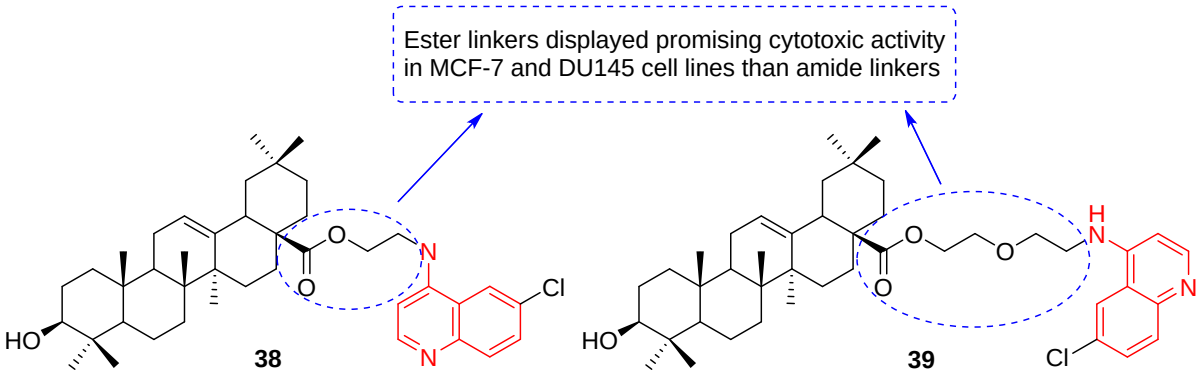


S. aureus	*B. subtilis*	*B. cereus*	*P. aeruginosa*	*E. coli*	*P. vulgaris*
MIC (nmol·mL^{-1})	MIC (nmol·mL^{-1})	MIC (nmol·mL^{-1})	MIC (nmol·mL^{-1})	MIC (nmol·mL^{-1})	MIC (nmol·mL^{-1})
3.12	25	12.5	3.12	12.5	3.12

Figure 18. Antibacterial properties of 1,3,5-triazine conjugated 4-aminoquinolines

3.3. Oleanolic acid-4-aminoquinoline conjugates:

A small family of oleanolic acid-based 4-aminoquinoline derivatives were identified as antibacterial agents by Khwazaet al. [53]. They performed their antibacterial potency with MIC of 1.25 mg/mL compared to oleanolic acid (2.5 mg/mL) towards Gram-negative bacteria, *Proteus vulgaris* (*PV*), *Escherichia coli* (*EC*), *Klebsiella oxytoca* (*KO*) and Gram-positivebacteria, *Staphylococcus aureus* (*SA*), *Bacillus subtilis* (*BS*), and *Enterococcus faecalis* (*EF*). *In vitro* tests using the cancer cells DU 145 and MCF-7 revealed that analogues **38** and **39** with ester linkers were more cytotoxic than oleanolic acid (IC_{50} □ 200 μM). Analogue **39** was more cytotoxic than analogue **38** towards both cells, indicating that the ester linker's length between oleanolic acid and 4-aminoquinoline moieties significantly affected their cytotoxic potency on the cancer cells (**Figure 19**).



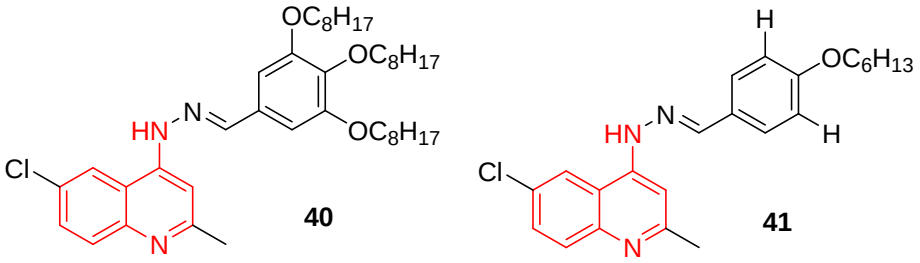
Minimum inhibitory concentration (MIC, mg/mL)

	Gram-positive					Gram-negative					
	BS	*EF*	*SE*	*SA*	*MS*	*ECL*	*PV*	*KO*	*PA*	*PM*	*EC*
38.	2.5	1.25	1.25	1.25	1.25	1.25	2.5	1.25	2.5	2.5	2.5
39.	2.5	1.25	2.5	2.5	1.25	2.5	2.5	2.5	2.5	1.25	1.25

Figure 19. Antibacterial properties of oleanolic acid-4-aminoquinolines

3.4. Hydrazone-4-aminoquinoline conjugates:

Aiming to investigate potentially better antibacterial agents, Katariya and co-workers [42] synthesized a library of novel hydrazone-based 4-aminoquinoline derivatives. It tested their antibacterial effects against Gram-positive (*B. subtilis* and *S. aureus*) and Gram-negative (*P. aeruginosa* and *E. coli*) bacterial strains. All the tested analogues with 6.25 to 100 µg/mL range of MIC values towards the screened pathogenic strains demonstrated good to excellent antibacterial potencies. The best antibacterial effect was performed against both the *S. aureus* and *P. aeruginosa* strains by **40** (MIC = 6.25 µg/mL). In the case of *E. coli* and *S. aureus* strains, analogue **41** displayed superior activity with 6.25 and 12.5 µg/mL of MIC values, respectively (**Figure 20**).



	Gram-positive		Gram-negative	
	S. aureus MIC (µg/mL)	*B. subtilis* MIC (µg/mL)	*E. coli* MIC (µg/mL)	*P. aeruginosa* MIC (µg/mL)
4.	6.25	25	12.5	6.25
5.	12.5	12.5	6.5	12.5

Figure 20. Antibacterial properties of hydrazone-based 4-aminoquinolines

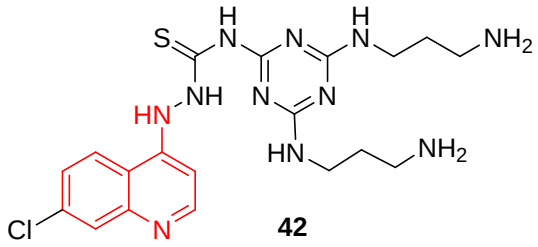
4. Antifungal activity of 4-aminoquinolines:

4-Aminoquinoline moiety commonly serves as a core fragment in a broad range of active molecules, which show widespread biological properties counting antifungal activity [54].

4.1. Triazine-4-aminoquinoline conjugates:

Bhat and co-workers [46] also tested the antifungal activities of a wide variety of novel triazine-4-aminoquinoline hybrids counter to the *Aspergillus fumigatus*, *Aspergillus niger*, and *Candida albicans* strains utilizing fluconazole as reference drug. Antifungal screening results showed that hybrid **42** containing 1,3-diaminopropane on triazinering was a significantly potent antifungal agent counter to *A. fumigates*, *A. niger* and moderately active towards *C. albicans* among all tested and compared to the hybrids containing 1,3-diaminopropane, 4-methoxyaniline, cyclohexamine groups on the triazine ring, the hybrids with morpholine, dimethylamine, diethylamine, *p*-chloroaniline, *p*-nitroaniline, and *N*-methyl piperazine on triazine ring demonstrated mild to moderate potency towards all the examined

fungal strains. All the tested analogues were discovered to be nontoxic to MCF-12A (**Figure 21**).



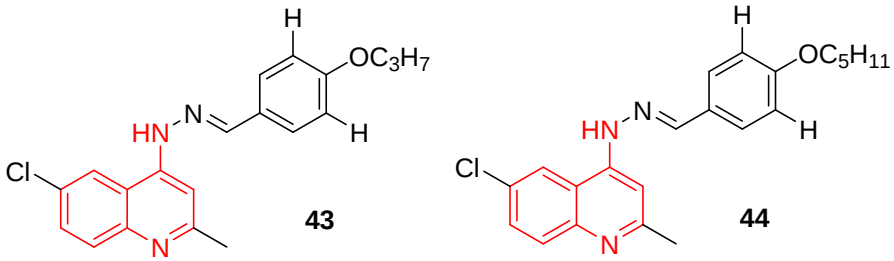
42

C. albicans MIC (μg mL^{-1})	*A. niger* MIC (μg mL^{-1})	*A. fumigatus* MIC (μg mL^{-1})
08	08	08

Figure 21. Antifungal properties of 1,3,5-triazine conjugated 4-aminoquinolines

4.2. Hydrazone-4-aminoquinoline conjugates:

Continuing their interest in screening biological activities, Katariya and co-workers [42] tested the antifungal effects of novel hydrazone-based 4-aminoquinoline hybrid compounds against *C. albicans* and *A. niger* strains. All the hybrids with a 6.25 to 100 μg/mL range of MIC values demonstrated good to excellent antimicrobial potencies towards the screened pathogenic strains. In the case of the *C. albicans* strain, analogue **43** demonstrated superior antifungal activity with 12.5 μg/mL of MIC value, while against the *A. niger* strain, the best antibacterial effect was performed by **44** (MIC = 12.5μg/mL, **Figure 22**).



43 **44**

	C. albicans MIC (μg/mL)	*A. niger* MIC (μg/mL)
43.	12.5	25
44.	25	12.5

Figure 22. Antifungal properties of hydrazone-based 4-aminoquinolines

4.3. Miscellaneous 4-aminoquinolines:

Yang's group reported antifungal evaluations of an array of 2-phenyl-4-aminoquinoline derivatives counter to three phytopathogenic fungi [55]. The screening results signified that most target analogues displayed substantial potencies counter to the tested fungi. Amongst all the target analogues, *para*-chloro substituted analogue (**45**) was found to be the most promising agent, displaying superior inhibitory potencies than the commercial fungicide azoxystrobin

agonist *A. alternate*, *P. grisea*, and *C. lunata* with EC_{50} values of 15.6, 14.4, and 13.3 µg/mL, respectively. According to the SAR results, the aniline core on the quinoline ring played an important role in an analogue's activity, and the substituent's position (on an aniline scaffold) highly influenced the potencies. In the majority of cases, the order of potency is *para- >meta- >ortho-* (**Figure 23**).

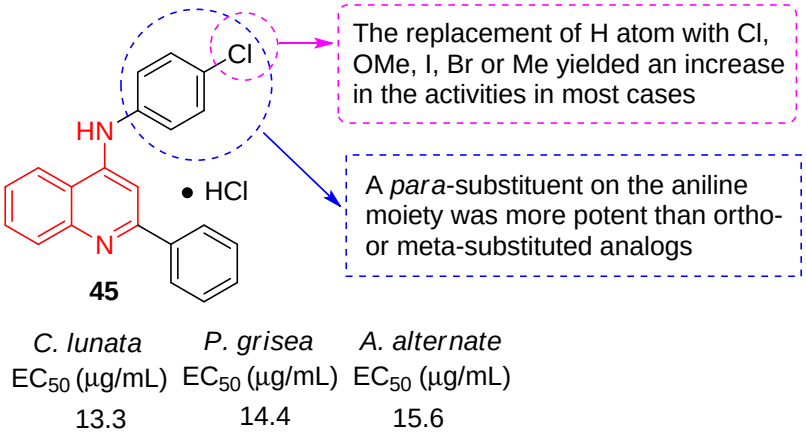


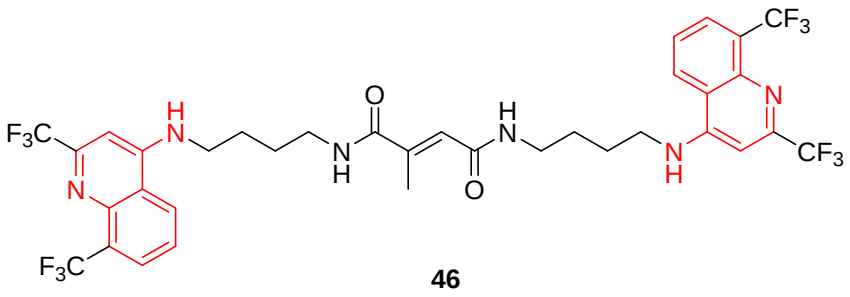
Figure 23. Antifungal activities of 2-phenyl-4-aminoquinoline derivatives

5. Antiviral activity of 4-aminoquinolines:

Currently, much research has been done on the use of 4-aminoquinoline hybrids in viral infections. Most *in vitro* investigations showed that 4-aminoquinoline hybrids have some effect against viral infections [56].

5.1. Quinoline-4-aminoquinoline conjugates:

Currently, Perkovićet al. [41] reported the antiviral effects of novel itaconic acid, a key structural moiety in various antiviral and anticancer drugs, conjugated quinoline, indole, pyridine, and mefloquine hybrid compounds counter to an array of virus families such asinfluenza B (B/Ned/537/05), influenza A/H3N2 (A/HK/7/87), influenza A/H1N1 (A/Ned/378/05), Zika virus, yellow fever virus, Punta Toro virus, standbys viru, reovirus-1, respiratory syncytial virus, Coxsackievirus B4, vesicular stomatitis virus, human coronavirus (229E), adenovirus-2, vaccinia virus, herpes simplex virus-2, and herpes simplex virus-1. Almost all hybrids were inactive, displaying EC_{50}> 100 µmol L^{-1}, except 4-aminoquinoline homodimer **46**, which demonstrated the superior antiviral activity towards Coxsackievirus B4 and Zika virus in low micromolar concentrations (EC_{50}= 0.85 µmol L^{-1}). The CC_{50} values of hybrid **46** were between 6.7 and 10 µmol L^{-1} in Hep-2 or Vero cell lines in which Coxsackievirus B4 or Zika virus replication was measured (**Figure 24**).

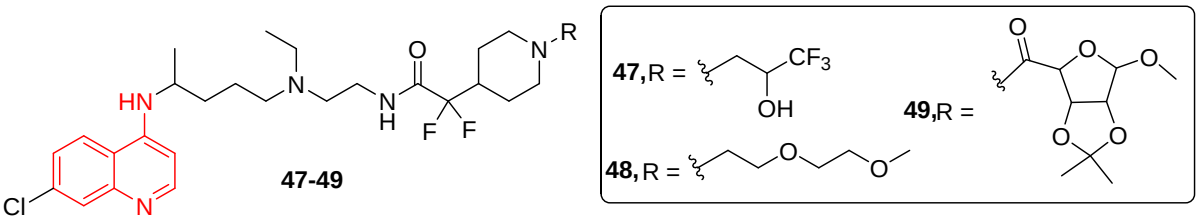


46

Figure 24. Antiviral effects of quinoline conjugated 4-aminoquinolines

5.2. Piperidine-4-aminoquinoline conjugates:

To investigate the antiviral effects on SARS CoV-2 spike glycoprotein, Song et al. [57] furnished a small library of piperidine-4-aminoquinolines (**47-49**). Huh7 cell lines infected with pseudo-virus particles (2019nCoV-S-HIV) packaged on 293 T cells were utilized to investigate the inhibitory activity of drugs against 2019nCoV-2 spike glycoprotein to discover effective inhibitors of SARS-Cov2 spike glycoprotein swiftly. Chloroquine demonstrated poor inhibitory activitytowards SARSCoV-2 spike glycoprotein with 16.66 µMof EC_{50} value, slightly lower than its cytotoxicity on Huh7 cell (CC_{50}: 26.36µM). However, hydroxychloroquine was found to be ineffective. The piperidine-4-aminoquinoline hybrids **47** and **49** displayed lower inhibitory potency with EC_{50} values>20 µM, whereas hybrid **48** showed an enhanced inhibitory activity on 2019nCoV-2 spike glycoprotein with 5.53 µM of EC_{50} value (**Figure 25**).



47-49

47, R =

48, R =

49, R =

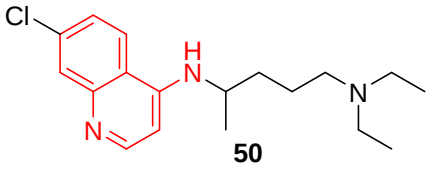
	Huh7 cell CC_{50} (µM)	2019nCoV-S-HIV EC_{50} (µM)
47.	16.68	32.75
48.	5.75	5.53
49.	16.90	25.23

Figure 25. Antiviral activity of piperidine-4-aminoquinolines

5.3. Miscellaneous 4-aminoquinolines:

Chloroquine (CQ, **50**), a safe and inexpensive drug widely used as an autoimmune and antimalarial drug for over 70 years, has recently been reported as anactive antiviral drug to treat 2019-nCoV infection [58]. A time-of-addition test in Vero E6 cell lines revealed that CQ was active during the entry and postentry stages of 2019-nCoV infection. In addition to having antiviral strength, CQ also had immune-modulating effectiveness, which worked in concert to

increase its antiviral activity *in vivo*. Following oral ingestion, CQ is broadly disseminated throughout the entire body, including the lungs.). The plasma of rheumatoid arthritis patients who received 500 mg administration showed that the EC_{90} value of CQ counter to the 2019-nCoV in Vero E6 cell lines was 6.90 M, which can be therapeutically attainable (**Figure 26**).



50

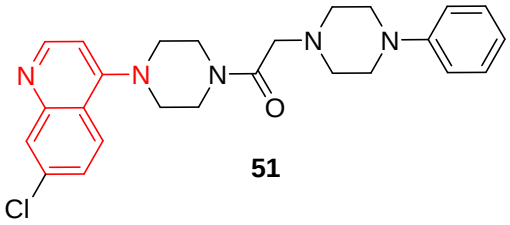
Figure 26. Antiviral activity of chloroquine

6. Anti-inflammatory activity of 4-aminoquinolines:

The development of different classes of novel medications with various biological features, such as anti-inflammatory pharmaceuticals, is greatly aided by aminoquinoline hybrids [59].

6.1. Piperazine-4-aminoquinoline conjugates:

In vitro, the anti-inflammatory activity of a series of novel 7-chloro-4-(piperazine-1-yl)quinolines was investigated by the research group of Aboutabl [60]. These analogues demonstrated substantial inhibition of NO level in RAW 264.7 cell lines. Among all, analogue1-(4-(7-chloroquinoline-4-yl)piperazin-1-yl)-2-(4-phenylpiperazin-1-yl)ethanone (**51**) showed strongest NO inhibitory potency that was accompanied by inhibition of iNOS protein expression and decreased gene expression levels of inflammatory markers. Inhibiting abdominal writhing in mice given doses of 15 and 30 mg/kg demonstrated a potential peripheral analgesic effect, and its impact was comparable to that of diclofenac sodium (**Figure 27**).



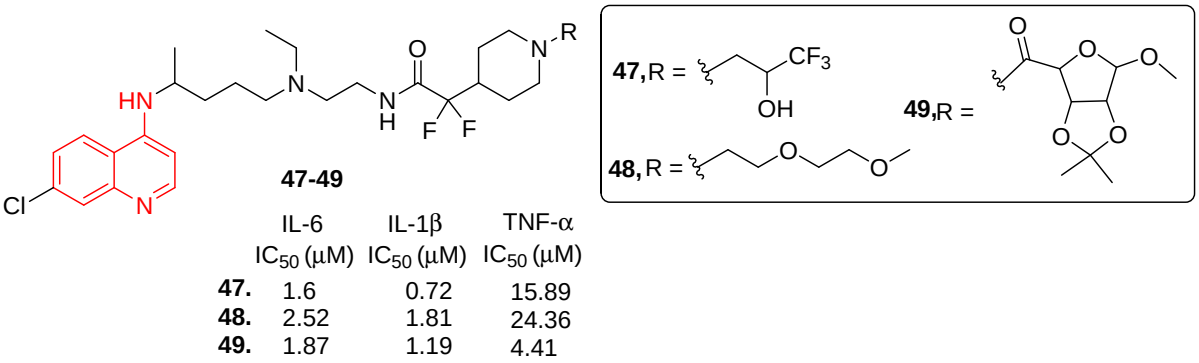
51

Figure 27. Anti-inflammatory activity of piperazine-based 4-aminoquinoline

6.2. Piperidine-4-aminoquinoline conjugates:

Macrophages are a significant source of inflammatory cytokines implicated in inflammation, immune response, and infectious processes. When activated by microbes, microbials, or macrophages, endogenous factors can provide and liberate a variety of cytokines. Song et al. [57] investigated the effect of analogues on LPS-induced cytokine production in RAW 264.7 murine macrophage cell lines. Analog **49** exerted much more potent restriction on

the production of TNF-α, IL-1β, and IL-6 (IC_{50}:4.41, 1.19, and 1.87 µM) than chloroquine (IC_{50}: 35.02, 2.72, and 14.63 µM) and hydroxychloroquine (IC_{50}: 10.03, 3.51, and 16.54 µM), while analogues **47** and **48** performed better inhibition on IL-6 and IL-1β (**Figure 28**).



	IL-6 IC_{50} (µM)	IL-1β IC_{50} (µM)	TNF-α IC_{50} (µM)
47.	1.6	0.72	15.89
48.	2.52	1.81	24.36
49.	1.87	1.19	4.41

Figure 28. Anti-inflammatory activity of piperidine-4-aminoquinolines

6.3. Thiazole-4-aminoquinoline conjugates:

Receptor-interacting protein kinase 2 (RIPK2) is a protein kinase that mediates signal transduction by NOD1 and NOD2, which play crucial roles in immunological signalling. Currently, a novel family of thiazole-based various aryl/heteroaryl-substituted 4-aminoquinolines (**52-53**) as RIPK2 inhibitors was synthesized by Fan's group [61]. In a dendrogram depiction of the human kinome phylogenetic tree, hybrid **52** demonstrated great affinity (IC_{50}: 5.1 nM) and outstanding selectivity to RIPK2. Hybrid **52** was chosen for its cellular anti-inflammatory activity due to its advantageous lipophilicity and eligible lipophilic ligand efficiency (LipE) and was found to be a powerful inhibitor of MDP-induced TNF-a release in a dose-dependent manner. Furthermore, hybrid **52** demonstrated considerable stability in human liver microsomes(**Figure 29**).

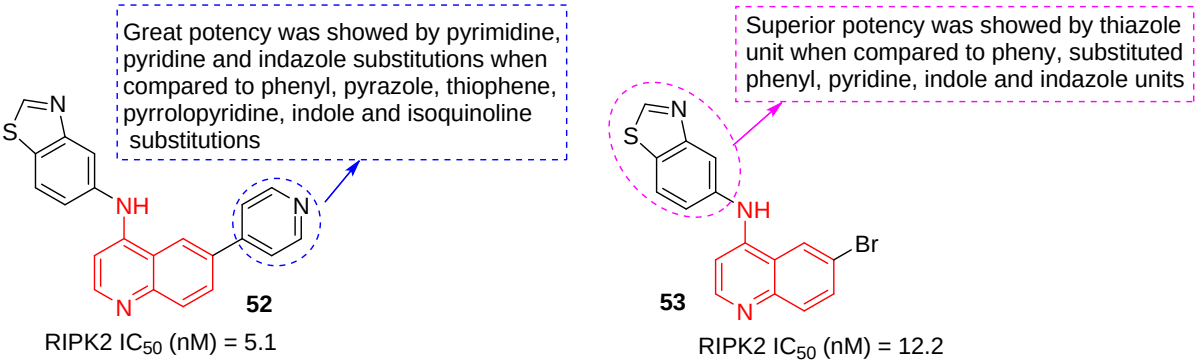
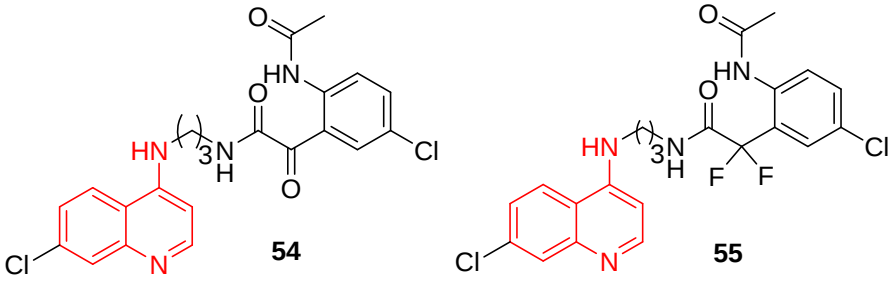


Figure 29. Anti-inflammatory activity of thiazole-based 4-aminoquinoline

6.4. Miscellaneous 4-aminoquinolines:

To achieve antimalarial and anti-inflammatory dual action, Boechat's group in 2020 [62] synthesized a library of novel 4-aminoquinoline compounds. The anti-inflammatory effect of potent antimalarial agents was investigated by NO and TNFα formed from macrophages

stimulated by LPS. All the screened analogues demonstrated cytotoxicity in concentrations >25 µM in a resazurin cell viability test with the J774A.1 macrophage cell. Interestingly, only chlorinated analogues **54** and **55** dose-dependently reduced NO production and inhibited TNFα production by LPS-stimulated J774A.1 macrophages (**Figure 30**).



% Viability Concentration

	0	12.5 µM	25 µM	50 µM	100 µM
2.	100%	100%	100%	82.7%	10.7%
3.	100%	100%	95.5%	87.55%	10.4%

Figure 30. Anti-inflammatory activity of 4-aminoquinolines

7. Anti-analgesic activity of 4-aminoquinolines:

7.1. Piperazine-4-aminoquinoline conjugates:

Aboutabl and co-workers [60] also investigated the peripheral and central analgesic effects of novel 7-chloro-4-(piperazine-1-yl)quinoline derivatives. Analog 1-(4-(7-chloroquinoline-4-yl)piperazin-1-yl)-2-(4-phenylpiperazin-1-yl)ethanone (**51**) exhibited an analgesic effect starting from 15 min post administration and reached its peak at 45 min which was substantially superior to tramadol hydrochloride indicating its potential as a central analgesic drug. It also demonstrated a 34, 50, and 64% suppression of oedema at 1, 2, and 3 hours after the carrageenan challenge, respectively, and a substantial drop in serum NO and COX-2 levels (**Figure 31**).

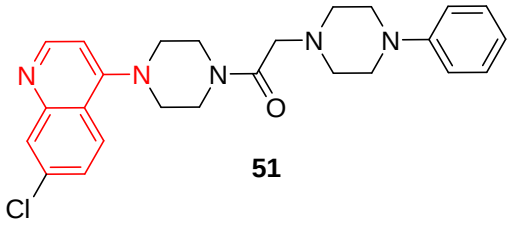


Figure 31. Anti-analgesic activity of piperazine-based 4-aminoquinoline

8. Antileishmanial activity of 4-aminoquinolines:

Leishmania, one of the most deadly neglected tropical diseases, is endemic in many regions of the world andposes a serious threat to public health. Visceral leishmaniasis, causedby *Leishmania chagasi, L. infantum and L. donovani*, is fatal if untreated [63].

8.1. Triazole-4-aminoquinoline conjugates:

Triazole and quinoline derivatives are renowned *N*-heterocycles with various pharmacological activities, but their antileishmanial efficacy is still underutilized. To contribute to investigations involving these intriguing chemical groups, Glanzmann et al. [64] provided a small library of hybrids derived from 1,2,3-triazole and 4-aminoquinoline, and biological evaluations employing *L. amazonensis* species were performed. The results showed that the hybrid **56** had the best antileishmanial action among the screened compounds, with IC_{50} values of ~1 µM towards intramacrophage amastigotes of *L. amazonensis* and higher selectivity index, being 16-fold more potent to parasites than to the host cell (**Figure 32**).

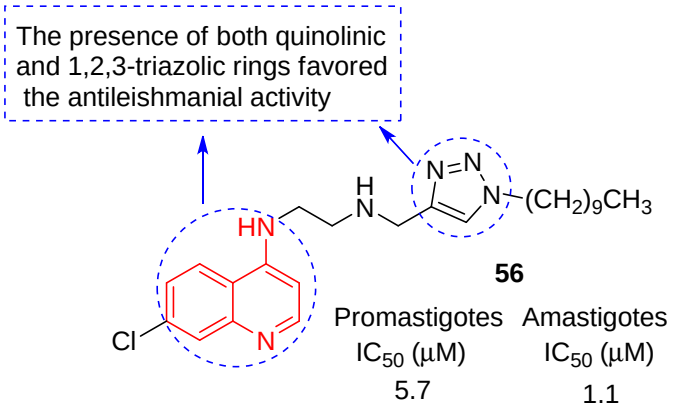
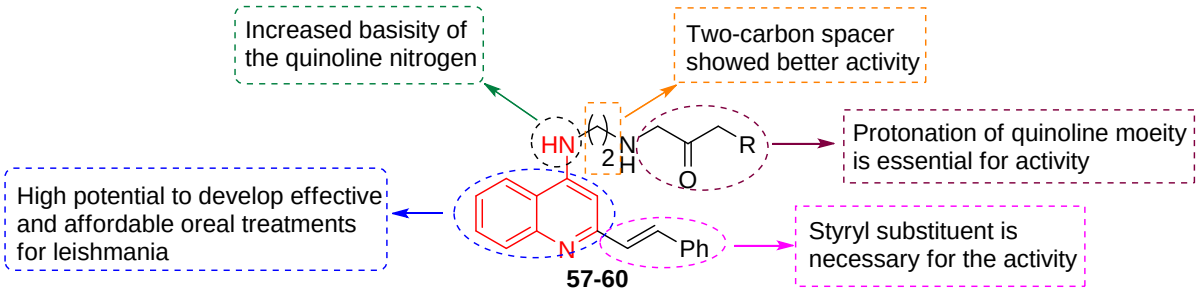


Figure 32. Antileishmanial activity of 1,2,3-triazole-4-aminouinolines against *L. amazonensis*

8.2. Miscellaneous 4-aminoquinolines:

Antileishmanial activity of a novel family of quinolines, containing a styryl unit at C-2 and divers amino chains at C-4, were screened by Staderini et al. [65] counter to axenic and intracellular *Leishmania pifanoi* amastigotes and *Leishmania donovani* promastigotes. Amongst, the analogues **57-60** were the most promising agents with IC_{50} values of 1.1 µM, 1.6 µM, 0.9 µM, and 1.2 µM, respectively, towards *L. pifanoi* amastigotes and 1.6 µM,3.4 µM, 2.1 µM, and 8.4 µM, respectively towards *L. donovani* promastigotes, and were proved to be non-cytotoxic towards mammalian macrophage cell lines with a good selectivity index. Further investigation of these hybrids revealed leishmanicidal effectiveness by interfering with the parasite's mitochondrial function, resulting in bioenergetic collapse due to ATP exhaustion (**Figure 33**).



	L. donovani promastigotes IC_{50} (µM)	*L. pifanoi* amastigotes IC_{50} (µM)
57.	1.6	1.1
58.	3.4	1.6
59.	2.1	0.9
60.	8.4	1.2

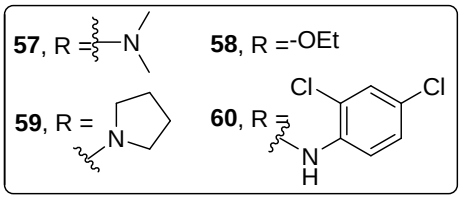


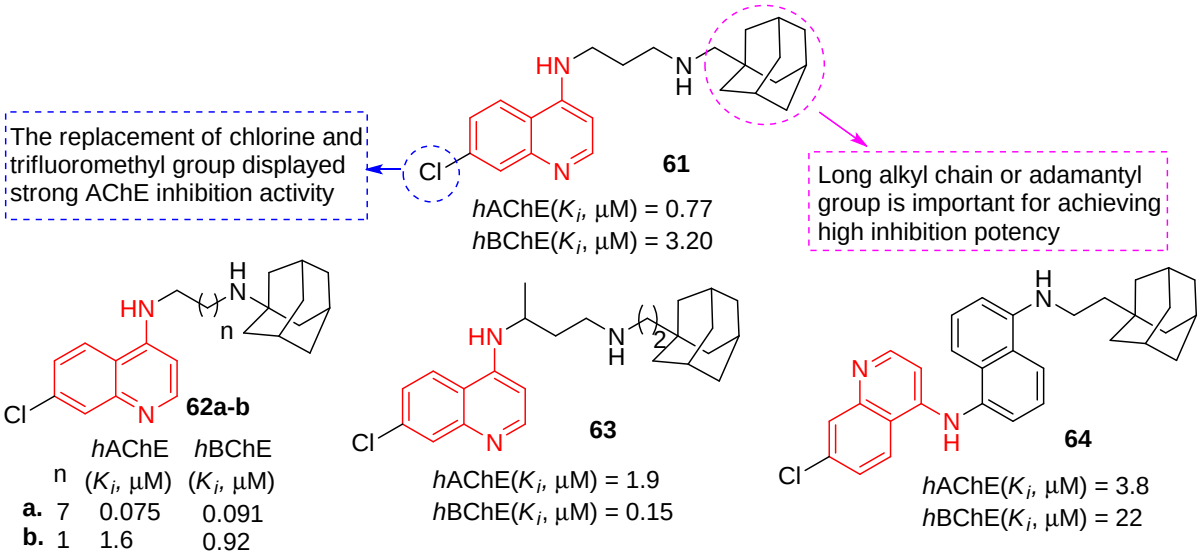
Figure 33. Antileishmanial activity of 4-aminostyrylquinolines

9. The anti-Alzheimer activity of 4-aminoquinolines:

Alzheimer's disease (AD) is a widely recognized multifactorial and complicated neurodegenerative disease, mainly affecting people over sixty, characterized by cholinergic neuron loss in the brain. Attempts to discover drugs to treat Alzheimer's disease have been impeded by unsuccessful clinical trials over the past two decades [66-70].

9.1. Adamantane-4-aminoquinoline conjugates:

Considering that acetylcholinesterase (AChE) inhibition is a significant mode of action expected of a potential drug used to treat AD symptoms, different substituted 4-aminoquinoline hybrids were synthesized by Bosak et al. in 2019 [71] and examined for AD *in vitro* against AChE and butyrylcholinesterase (BChE). Adamantane-based 4-aminoquinoline hybrid **62** was discovered to be a good anti-AChE and anti-BChE agent with K*i* values of 0.77 and 3.20 µM, respectively (**Figure 34**). Continuing their research on the ChE inhibitory activity of 4-aminoquinolines, Komatovi´c et al. [72] currently synthesized a novel series of adamantine-based 4-aminoquinolines (**62-64**). According to the inhibition study results, all the hybrids were effective inhibitors of BChE and AChE, with *Ki* ranging from 0.075 to 25 µM. Hybrid **62a** was the most effective inhibitor against both BChE and AChE, with a *Ki* value of 0.091 and 0.075 µM, respectively. The screened hybrids showed a modest selectivity between the two ChEs; the most selective for AChE was hybrid **64**, which showed a 5.8 times higher preference, whereas hybrid **63** was a 10 times more active inhibitor of BChE (**Figure 34**).

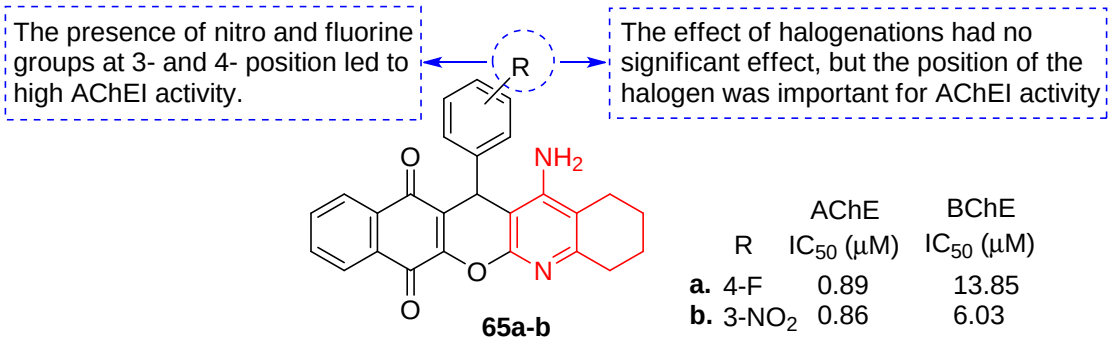


	n	*h*AChE (K_i, µM)	*h*BChE (K_i, µM)
a.	7	0.075	0.091
b.	1	1.6	0.92

Figure 34. Anti-Alzheimer's activity of adamantine-4-aminoquinolines

9.2. Benzochromene-4-aminoquinoline conjugates:

Various benzochromenoquinolinones containing different substituents on phenyl ring were developed as anti-AD agents by the research group of Mahdavi [73]. All the furnished hybrids were investigated for their ChE and β-secretase 1 (BACE1) inhibitory potencies and metal-chelating and neuroprotective activities. Most hybrids displayed better AChE inhibition, with IC_{50}values between 0.86 and 27.52 µM. Two of them (**65a** and **65b)** were found to be promising agents against BChE (IC_{50}: 13.85 and 6.03 µM, respectively) and AChE (IC_{50}: 0.89 and 0.86µM, respectively). Interestingly, hybrid **65b** inhibited BACE1 with an IC_{50} 19.60 µM and exhibited metal chelating ability toward Zn^{2+}, Fe^{2+}, and Cu^{2+} (**Figure 35**).



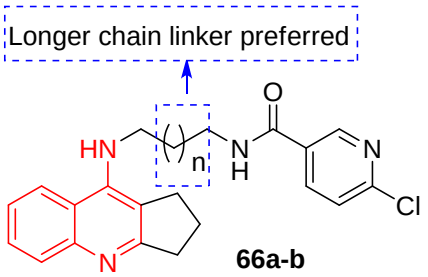
	R	AChE IC_{50} (µM)	BChE IC_{50} (µM)
a.	4-F	0.89	13.85
b.	3-NO_2	0.86	6.03

Figure 35. Anti-Alzheimer's activity of benzochromeno-4-aminoquinolines

9.3. Pyridine-4-aminoquinoline conjugates:

A small library of Pyridine-based cyclopenta-4-aminoquinoline analogues as anti-AChE and anti-BChE agents was reported by Czarnecka and co-workers [74]. Against BChE, all the tested hybrids were proved to be potent inhibitory agents with 42 to 662 nM range of IC_{50} values, whereas only half of the tested hybrids containing alkyl spacers with 6 to 9 carbons

in the chain were discovered to be active anti-AChE inhibitors with <100 nM of IC_{50} values. Among them, hybrids **66a** and **66b** demonstrated the most promising inhibition activities towards AChE (IC_{50}: 0.067 and 0.073 µM, respectively) and BChE (IC_{50}: 0.15 and 0.042 µM, respectively). According to the docking study results, the amide nitrogen atom of **66a** formed a hydrogen bond with the hydroxyl group of Tyr121 towards AChE, while for **66b** with BChE, a hydrogen bond was with the main chain of Tyr332 in anionic site (**Figure 36**).



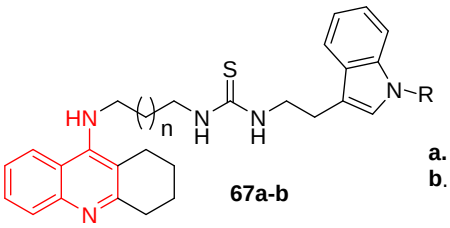
66a-b

	n	AChE IC_{50} (µM)	BChE IC_{50} (µM)
a.	4	0.067	0.153
b.	6	0.073	0.042

Figure 36. Anti-Alzheimer's activity of pyridine-4-aminoquinolines

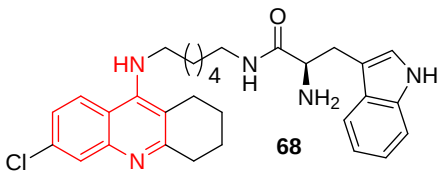
9.4. Indole-4-aminoquinoline conjugates:

Aiming to develop potentially better anti-AChE and anti-BChE agents, Hamulakova and co-workersin 2021 [75] synthesized a novel class of indole-4-aminoquinole derivatives and examined their anti-*h*AChE and anti-*h*BChE properties. In this investigation, significant anti-*h*AChE (IC_{50} values range between 25 and 160 nM) and anti-*h*BChE (IC_{50} values range between 39 and 160 nM) properties were recorded for all the tested hybrids. Against *h*BChE, the best inhibitory effect with 25 nM of IC_{50} value was recorded for hybrid **67a** containing four-methylene spacer and unsubstituted indole moiety, while hybrid **67b** having six-methylene spacer and methoxy group on indole nitrogen displayed better anti-*h*BChE activity with an IC_{50} 39 nM (**Figure 37**). In the same year, Mezeiova et al. [76] examined the cholinesterase inhibitory activities of a novel family of huprineY-tryptophan heterodimers (**68-69**). The most potent agent from these analogues was hybrid **68**, displaying the AChE (IC_{50}= 6.31 nM) and human BChE (IC_{50}= 9.07 nM) inhibition potency.



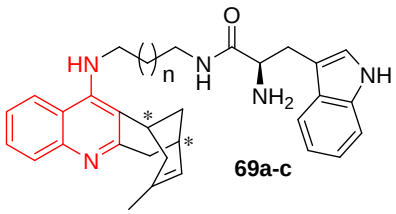
67a-b

	n	R	*h*AChE IC_{50} (nM)	*h*BChE IC_{50} (nM)
a.	2	H	25	76
b.	3	OMe	70	39



68

*h*AChE (IC_{50}) = 6.31 nM
*h*BChE (IC_{50}) = 9.07 nM



69a-c

	n	*h*AChE IC_{50} (nM)	*h*BChE IC_{50} (nM)
a.	3	22.7	68.3
b.	4	11.7	45.7
c.	5	12.1	84.5

Figure 37. Anti-Alzheimer's activity of indole-4-aminoquinolines

9.5. Miscellaneous 4-aminoquinoline:

In 2019, Zhu et al. [77] furnished a novel class of 4-Nphenylaminoquinoline hybrids to test their inhibitory activity on both BChE and AChE. Against AChE, all the tested hybrids displayed moderate to good IC_{50} values ranging from 0.65 to 11.84 µM. Only two of them (**70a** and **70b**) inhibited AChE (IC_{50} = 0.86 µM and 1.86 µM, respectively) and BChE (IC_{50} = 2.65 µM and 2.78 µM, respectively). Among them, hybrid **70a** greatly affected both BChE and AChE (**Figure 38**). In the same year, a novel family of quinoline-ferulic acid derivatives was constructed by Mo et al. [78] and examined as cholinesterase inhibitors. The majority of hybrids demonstrated superior inhibitory activities against both BChE and AChE. Towards AChE, hybrid **71a** was the most promising inhibitor with an IC_{50} of 0.62 µM, whereas hybrid **71b** was proved to be the most effective inhibitor, showing 0.10 µM of IC_{50} value against BChE among all the tested hybrids (**Figure 38**).

To explore the biological activity against AD, Mezeiova et al. [79] constructed a novel class of 4-aminoquinolines having various methylene linkers between diversely substituted amino/imino methylated phenolic ring and 4-aminoquinoline moiety and tested them as neuroprotective analogues for AD *in vitro*. The analogues demonstrated inhibitory potency in the micromolar range towards BChE (amines) and AChE (amines and imines). The most active analogues were non-cytotoxic and did not stimulate pro-inflammatory potency in glial cells. According to the SAR results, reducingimines (**72**) to amines (**73**) was crucial for enhanced potency against BChE. It is interesting to highlight that analogue **73a** displayeda potential anti-inflammatory effect by reducing the microglial release of NO at a concentration that is 15-fold higher than the IC_{50} towards AChE (1.97µM) and equivalent to the IC_{50} towards BChE (30.32µM) (**Figure 38**).

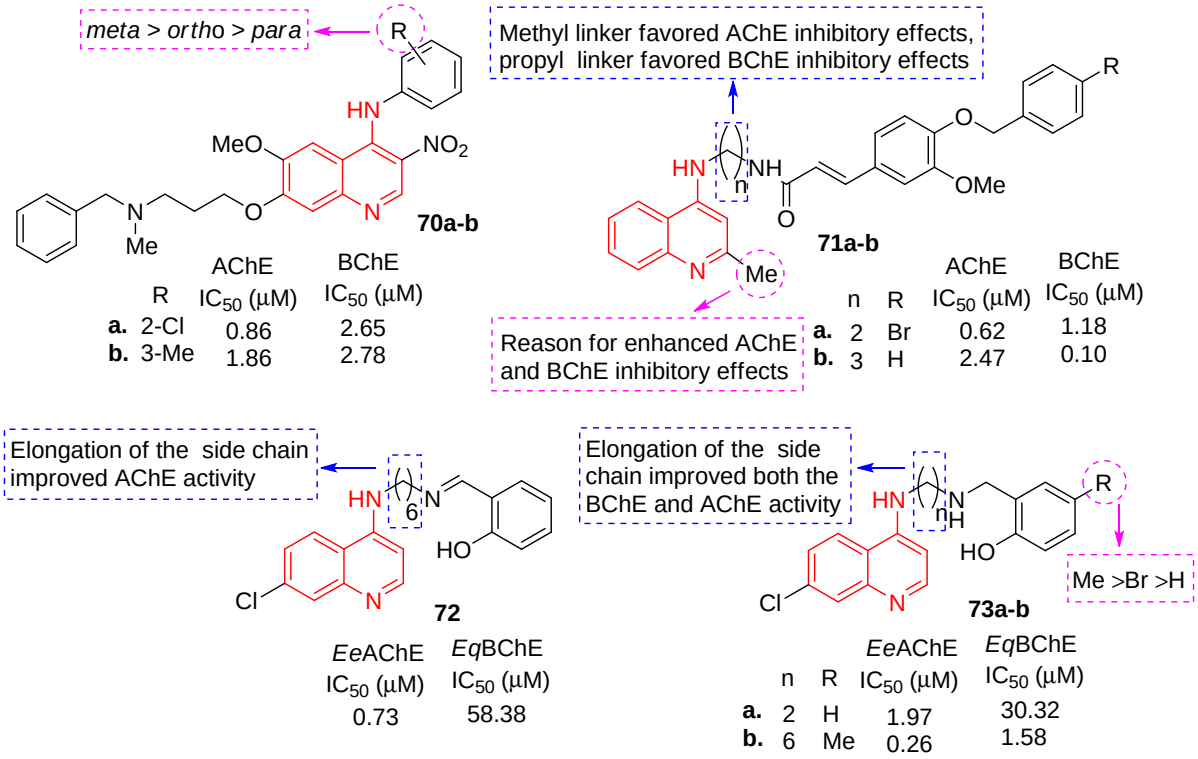


Figure 38. Anti-Alzheimer's activity of various 4-aminoquinolines

In 2020, the inhibitory effects of a novel family of 4-amino-2,3-polymethylene-quinolines counter to AChE and BChE were investigated by Makhaeva's group [80]. All the hybrids effectively inhibited AChE (IC_{50} = 1.90-45.0 μM) and BChE (IC_{50} = 0.084-4.27 μM). Among them, hybrids **74a** and **74b** demonstrated better inhibitory effects against hAChE, displaying 4.03 and 1.90 μM of IC_{50} values, respectively, and hBuChE with 0.419 and 0.084 μM of IC_{50} values, respectively (**Figure 39**). The same research group in the same year [81] also examined the inhibitory effects of another class of 4-amino-2,3-polymethylene-quinoline derivatives against AChE and BChE. The screened analogues were found to be potent inhibitory agents against AChE (IC_{50}=0.131-9.01 μM) and BChE (IC_{50}= 0.0431-0.924 μM) but demonstrated selectivity against BChE. Amongst, analogues **75a** and **75b** were proved to be the most promising agents against hAChE (with IC_{50}: 0.668 and 0.131 μM, respectively) and hBuChE (with IC_{50}: 0.0617 and 0.068 μM, respectively) (**Figure 39**).

Against BChE and AChE, the inhibitory effects of *O*-and *N*-phosphorylatedtacrine derivatives were examined by Przybyłowska's group in 2022 [82]. All the screened compounds were potent with 6.11 to 676.7 nM ranges of IC_{50} values towards AChE and 1.969 to 186.2 nM ranges of IC_{50} values towards BuChE. With the pIC_{50} of 0.786 nM, **76a** was discovered to be the most effective analogue towards AChE, while analogue **76b** displayed the best inhibitory activity with the pIC_{50} of 0.913nM towards BChE. According to the molecular docking results,

analogue **76a** showed lower docking energies of 10.7 and –12.5 kcal/mol for BChEand AChE, respectively (**Figure 39**).

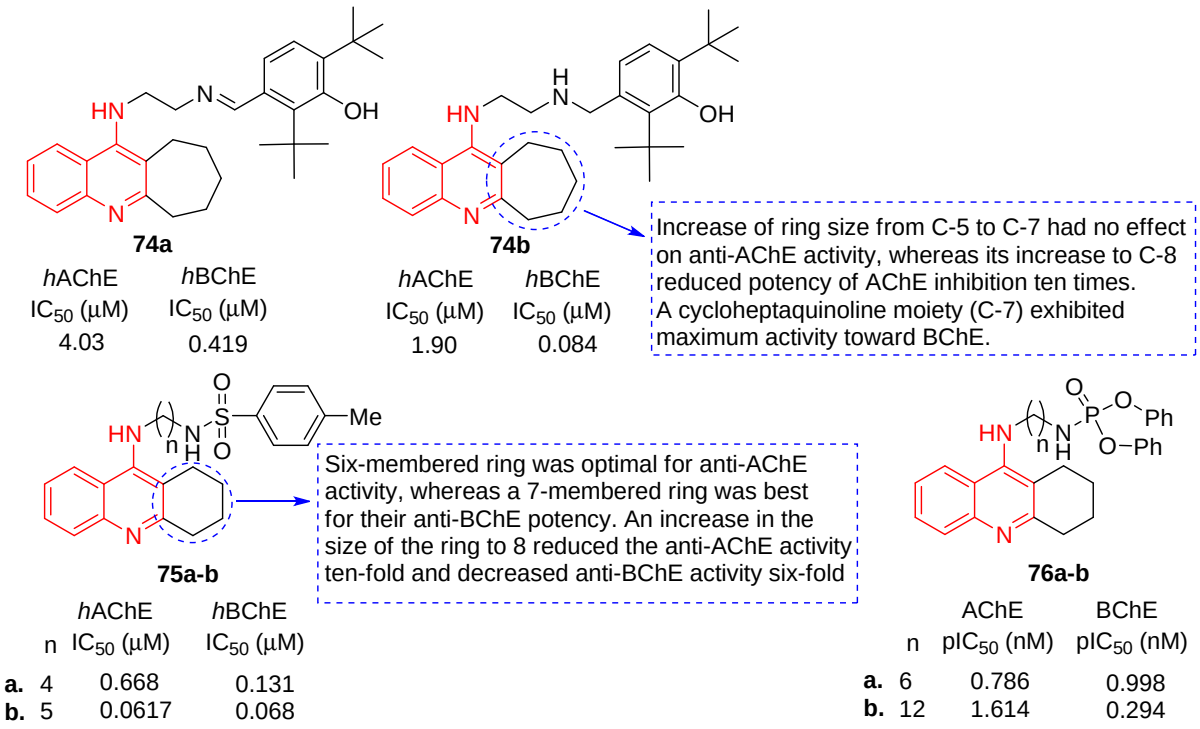


Figure 39. Anti-Alzheimer's activity of various 4-aminoquinolines

10. Antitubercular activity of 4-aminoquinolines:

Tuberculosis is an infectiousillness caused by *Mycobacterium tuberculosis* (Mtb), responsible for the largest deaths worldwide each year [83,84].

10.1. Quinoline-4-aminoquinoline conjugates:

Against the Mtb clone H37Rv, Patel and co-workers recently conducted an investigation of *in vitro* antitubercular activity of the synthesized 4-aminoquinoline hybrids containing quinoline and pyridine moiety [85]. The antituberculosis test results showed that the quinoline-4-aminoquinoline hybrids containing –CONHNH– linkage (**77a** and **77b**) demonstrated higher antitubercular potency towards *M. tuberculosis* with MIC values of 42 μM (at 98% inhibition) and 38 μM (at 99% inhibition), respectively as compared to the standard rifampicin (MIC: 48 μM at 98% inhibition) (**Figure 40).**

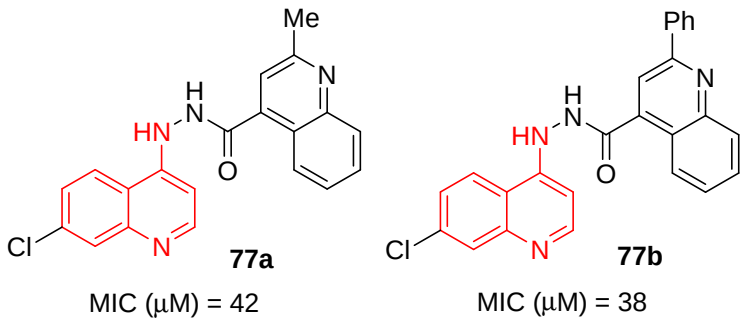


Figure 40. Antitubercular activity of quinoline-4-aminoquinolines

10.2. Oxadiazole-4-aminoquinoline conjugates:

In vitro, the antitubercular activity of a broad range of different substituted 1,2,4-oxadiazol-3-ylmethyl-piperazin-1-yl-quinolines towards Mtb WT H37Rv was tested by the research group of Shruthi [86]. Of the twenty-one tested analogues, 7-chloroquinoline hybrid **(78**) was proved to be the most effective antitubercular agent (MIC = 0.5 µg/ml), and the hybrids containing 3-pyridine substituent at 7-position of quinoline moiety (**79-81**) were also significant with 0.25 µg/ml of MIC value (**Figure 41).**

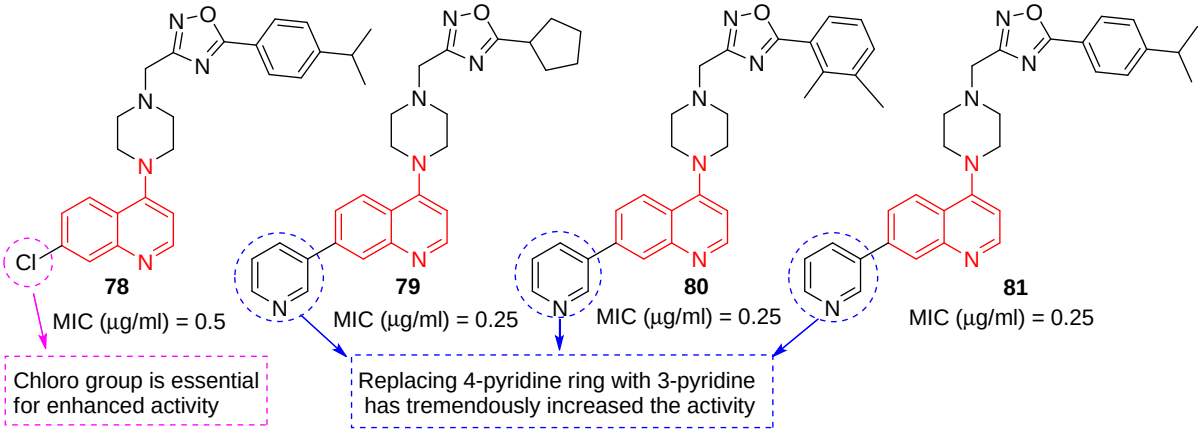


Figure 41. Antitubercular activity of oxadiazole-4-aminoquinolines

10.3. Hydrazone-4-aminoquinoline conjugates:

Alegaonet al. [87] constructed a vast array of semicarbazone and thiosemicarbazone-based 4-aminoquinoline derivatives to examine *In vitro* antitubercular activity against Mtb H37Rv. The study outcomes suggested that most tested hybrids were sensitive to Mtb, and all demonstrated Mtb inhibition with an acceptable range of MIC values (1.5 to 50 µM). From the results, it was observed that among the thirty-six tested hybrids, semicarbazone derivatives **82** and **83** were proved to be the most effective antitubercular agents with 1.5 µM of MIC value when compared to reference isoniazid (MIC = 1.56 µM). The SAR revealed that the semicarbazone derivatives were more potent than thiosemicarbazone derivatives. Among thiosemicarbazones, the electron-donating group (-Me and -OMe) substituted hybrids were more potent than the electron-withdrawing group (F, Br, and NO_2) substituted counterparts (**Figure 42).**

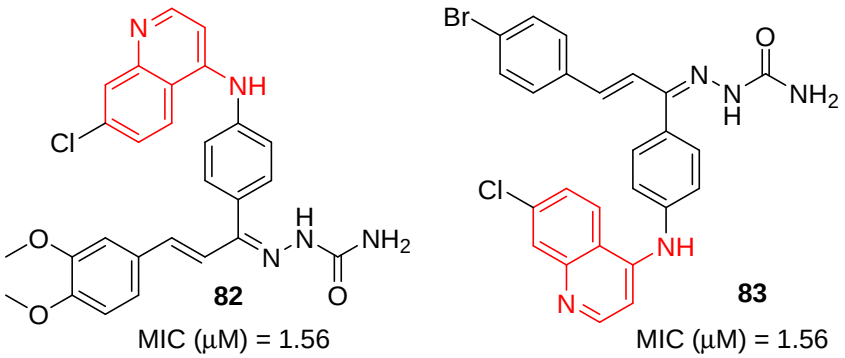


Figure 42. Antitubercular activity of hydrazone-4-aminoquinolines

10.4. Triazole-4-aminoquinoline conjugates:

Quinoline-isoniazid analogues are promising antitubercular agents. A wide variety of 1,2,3-triazole-based 4-aminoquinoline derivatives were synthesized by Alcarazand co-workers [88] and evaluated for their antitubercular activity against Mtb H37Rv. All the screened 4-aminoquinoline hybrids, except **84** and **85** (MIC = 50 µg/ml), were found to be inactive Mtb inhibitors with >200 µg/ml of MIC value (**Figure 43).**

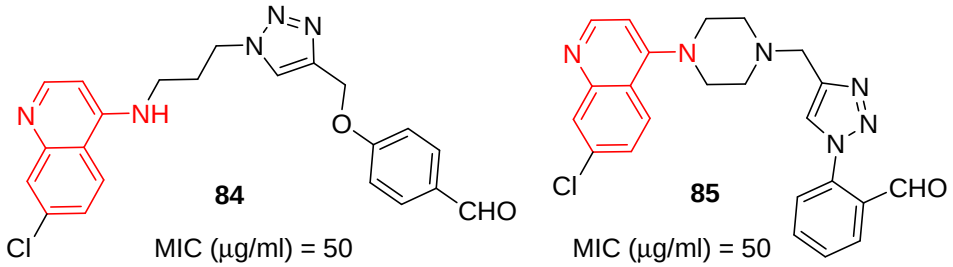


Figure 43. Antitubercular activity of triazole-4-aminoquinolines

10.5. Benzothiazole-4-aminoquinoline conjugates:

A novel family of benzothiazole-urea-quinoline derivatives was furnished successfully by Moodley's group [89] and examined for antitubercular efficacy towards Mtb H37Rv. Seventeen out of twenty-five screened hybrids possessed < 62.6 µM MIC values, and thirteen of them showed potential antitubercular activities with MIC values ranging between 1 and 10 µM, while hybrid **86**, being the most potent, displayed sub-micromolar activity (MIC = 0.968 µM) in the CAS test. Furthermore, cytotoxicity towards the HepG2 cell (cell viability above 75%) in eleven of the seventeen hybrids, at their respective MIC concentrations, was noticed, with **86** showing 100% cell viability (**Figure 44).**

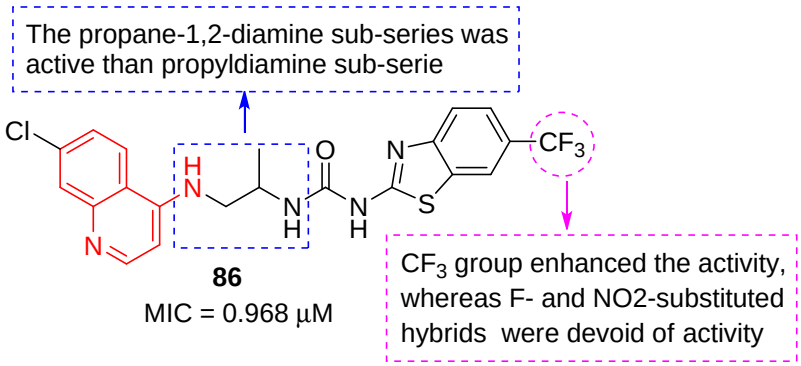


Figure 44. Antitubercular activity of benzothiazole-4-aminoquinolines

10.6. Phthalimide-4-aminoquinoline conjugates:

Rani and co-workers [90] furnished alibrary of 4-aminoquinoline-isoindoline-dione-isoniazid hybridsto examine their anti-mycobacterial effects counter to the mc^{2}6230 cone of *M. tuberculosis* and cytotoxicity towards Vero cell lines. Most hybrids displayed superior potencies with a 3.125 to 12.5 µg/mL range of MIC_{99} values and were proved to be non-cytotoxic. The carbon chain lengths enhanced the anti-mycobacterial activity, as evidenced in the hybrids **87a** and **87b** with MIC_{99} of 12.5 and 3.1 µg/mL, respectively. Without depending on alkyl chain length, the enhanced activity (MIC_{99} = 3.1 µg/mL) with no cytotoxicity ($IC_{50} \geq$ 100 µg/mL) was observed in the case of hybrid **88** when the position of isoniazid switched with quinoline diamines around isoindoline moiety. Introducing a piperazine ring instead of alkyl amine, as in hybrid **89,** also resulted in good anti-mycobacterial activity. The hybrids lacking either quinoline or isoniazid moiety in their structural unit failed to inhibit the growth of *M. tuberculosis* (**Figure 45)**.

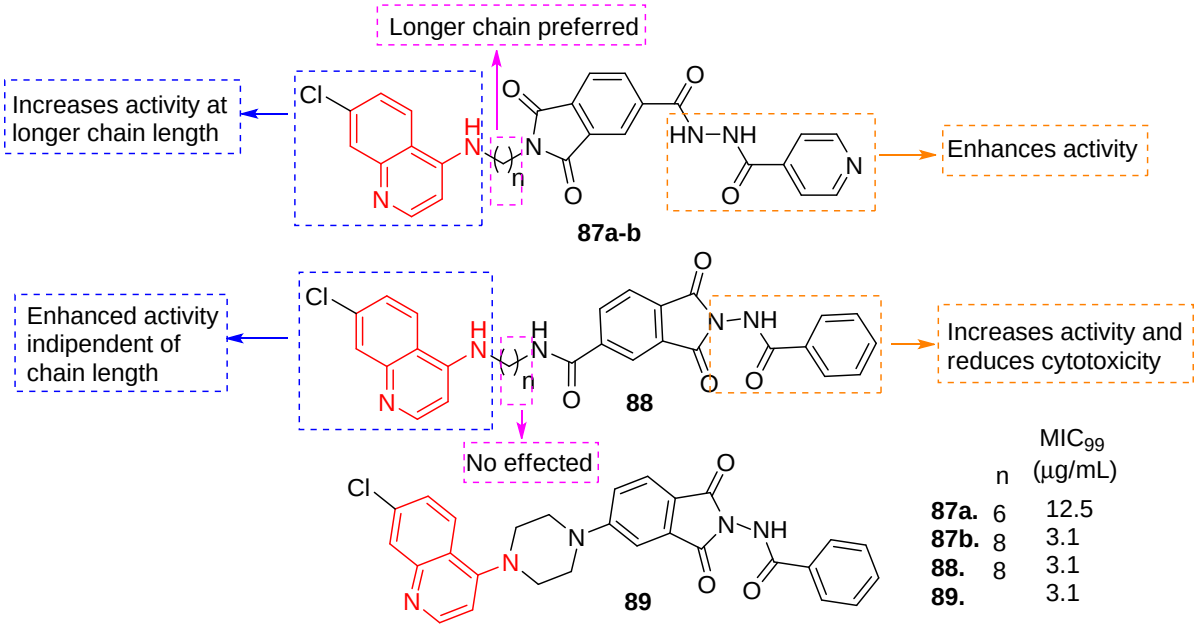


Figure 45. Antitubercular effects of 4-aminoquinoline-isoindoline-dione-isoniazid triads

10.7. The metal complex-4-aminoquinoline conjugates:

Anti-mycobacterial effects of novel cationic and neutral Rh(III) and Ir(III) 4-aminoquinoline-benzimidazole hybridcomplexes on *M. tuberculosis* 41 H37Rv utilizing Rifampicinas reference drug were examined by the research group of Baartzes [91]. The majority of hybrid complexes demonstrated moderate to good potency. All the neutral CˆN-coordinated Rh(III) and Ir(III) species (**90** and **91**) outperformed the cationic NˆN-coordinated Rh(III) and Ir(III) species (**92** and **93**). When comparing the activity of Rh(III) and Ir(III) species, the neutral Ir(III) species (**91**) was found to be more potent than the neutral Rh(III) species (**90**), while the cationic Rh(III) species (**92**) was proved to be promising agents than the cationic Ir(III) species (**93**). Among all the screened hybrid complexes, un-substituted neutral CˆN-coordinated Ir(III) species (**91**) was the most promising anti-mycobacterial agent with 0.488 µM of MIC_{90} value. Against the CHO cell line, all the tested complexes were low to no cytotoxic (**Figure 46)**.

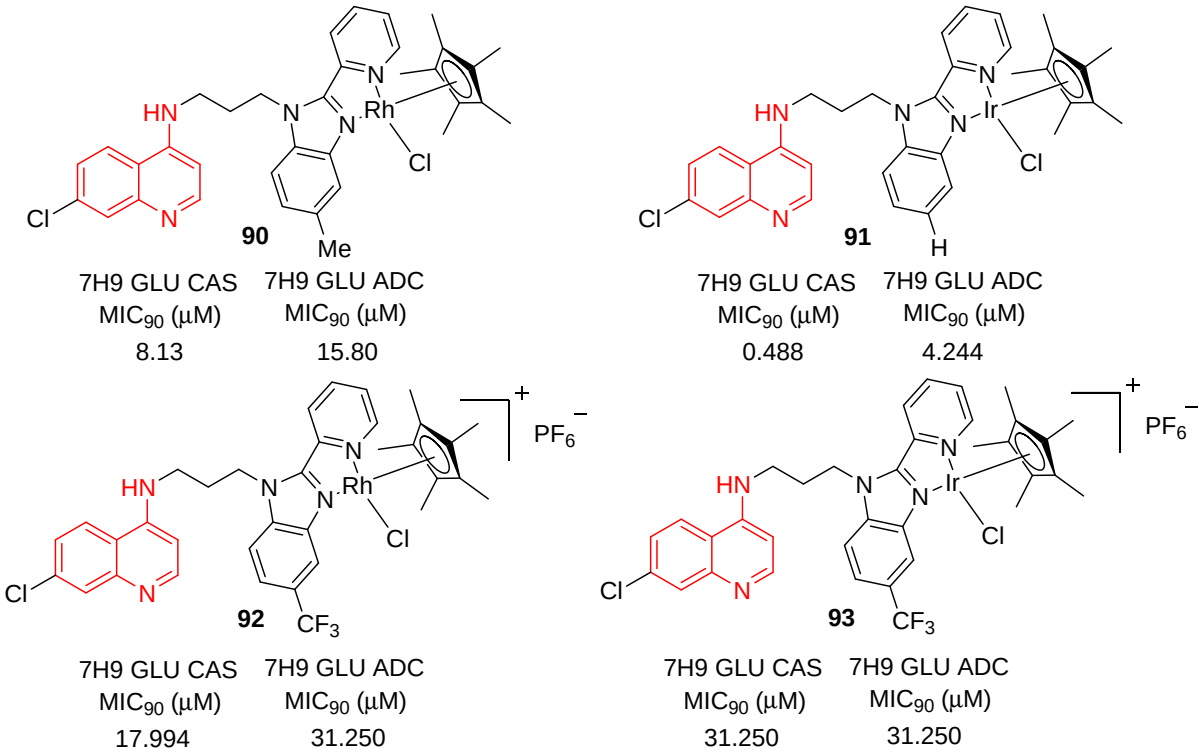


Figure 46. Antitubercular effects of Ir/Rh-complex-4-aminoquinolines

11. Antimalarial activity of 4-aminoquinolines:

Amongst available antimalarial agents, the 4-aminoquinoline hybrids were the most potential antimalarial drugs for more than five decades, and their chemistry, SARs, molecular docking, toxicity and physicochemical properties have been broadly studied [92-100].

11.1. *Pyrimidine-4-aminoquinoline conjugates:*

Against W2 (CQ^R) and D6 (CQ^S) *P. falciparum* strains, Mauryaet al. [101] examined the antimalarial efficacy of pyrimidine-based 4-aminoquinolines having pyridyl (**94-95**) and thiophenol (**96-97**) unit at the –NH group. Amongst, **97** showed 22-fold higher activity against the W2 strain than CQ (IC_{50}:0.4215µM), and **94** displayed higher activity against the D6 strain. The most active compounds were significantly non-cytotoxic against Vero cell lines (**Figure 47**). *In vitro*, Tripathi's [102] hybrid **99** demonstrated 2.8 and 47.3-fold enhanced activity than the standard drugs ART and CQ, respectively, with an IC_{50} of 4.7 nM towards the Dd2 (CQ^R) strain. Two potent analogues, **98** and **99**, were further investigated *in vivo* counter to a mouse model of *P. berghei* malaria, and **99** was found to be more potent than **98** (**Figure 47**). Against the NF54 (CQ^S) strain, Kayamba's [103] hybrid **100** with 1,4-diamine butyl spacer between pyrimidine and chloroquine units and 4-hydroxyphenyl rings on pyrimidine moiety displayed superior potency (IC_{50}: 0.32 µM), with a favourable safety profile of 9.79 to HEK293 cell lines (**Figure 47**).

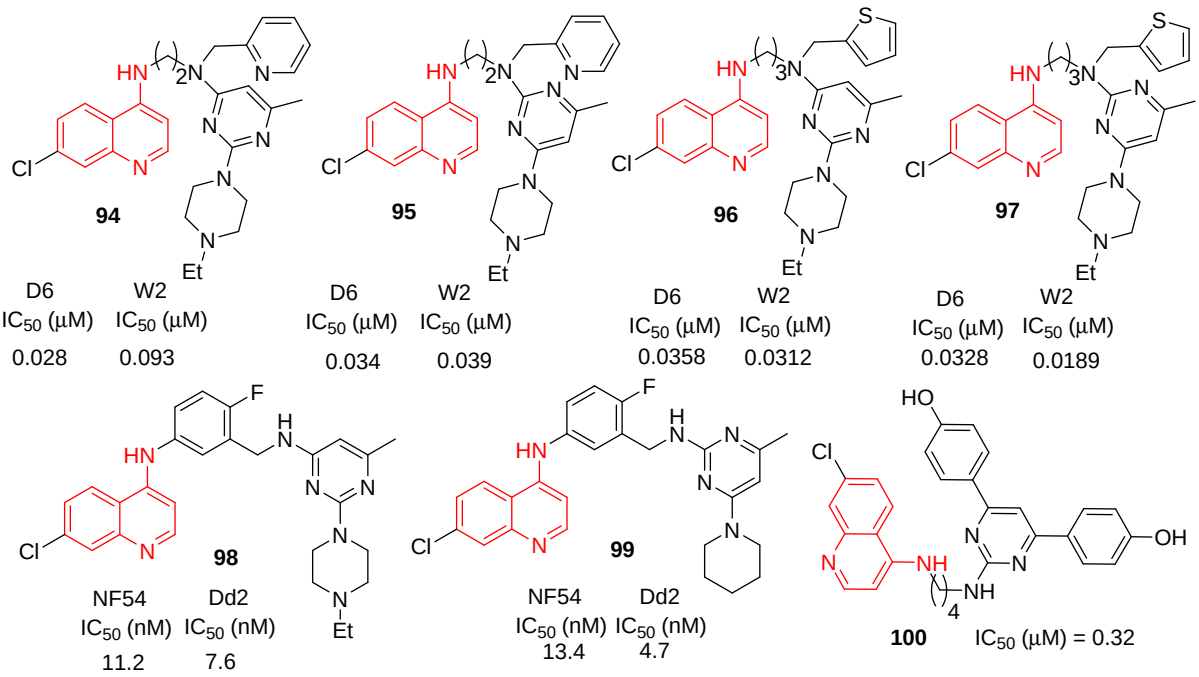


Figure 47. Antimalarial properties of 4-aminoquinoline-pyrimidines

11.2. Pyridine-4-aminoquinoline conjugates:

Remarkable antimalarial activity with 0.033 to <10 µM range of IC_{50} values against *P. falciparum* Dd2 strain has been demonstrated by pyridine conjugated 4-aminoquinoline hybrids of Huang's group [104]. In comparison to standard CQ, hybrid **101** was discovered to be the most effective agent against the Dd2 strain among the series (**Figure 48**). Similar to this, de Silva and his group [105] constructed 4-aminoquinolines substituted with a pyridine ring

and tested them for *in vitro* efficacy against the *P. falciparum* W2 strain and *in vivo* activity against the mice infected with *P. berghei*. With 8.4 μM of IC_{50}value, hybrid **102** was proved to be an effective anti-*P. falciparum* drug showed superior activity against the mice infected with *P. berghei* five days after infection (**Figure 48**).

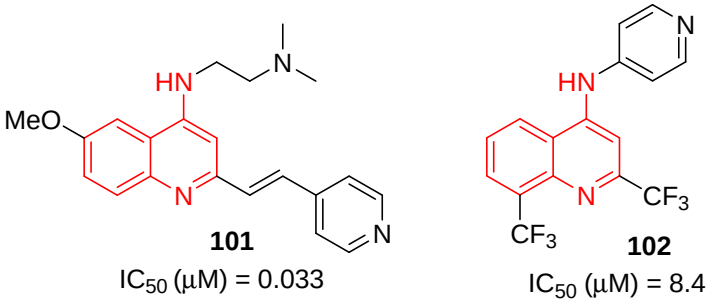


Figure 48. Antimalarial efficacy of 4-aminoquinoline-pyridines

11.3. Phthalimide-4-aminoquinoline conjugates:

Rani's group [106] examined anti-*P. falciparum* efficacy of C-5-substituted isoindoline-1,3-dione-4-aminoquinoline hybrids against W2 *P. falciparum* strain. With a diethylamino group on dioxoisoindoline moiety, **103** (IC_{50}: 0.097 μM) was discovered to be a promising non-cytotoxic drug with a selective index of > 2000 (**Figure 49**). The same group [107] examined anti-*P. falciparum* efficacy of cycloalkyl amine substituted 1,3-dioxoisoindoline-4-aminoquinoline hybrids against W2 strain. With a selectivity index > 4200, **104** with propylamine linker between quinoline and dioxoisoindoline units and a hydroxyethyl piperazine group on dioxoisoindoline ring emerged as the most potent analogue (IC_{50}: 0.006 μM) against W2 strain (**Figure 49**). Similar to this, Shaliniet al. [108] investigated the anti-*P. falciparum* effects of naphthalimide hybridized 4-aminoquinoline derivatives towards W2 strain. With a selectivity index >4000, **105** containing propylamine linker between quinoline and naphthalimide units and a hydroxyethyl piperazine group on naphthalimide ring was a promising candidate (IC_{50}: 15.445 nM) in the series (**Figure 49**). The same research team [109] testedanti-*P. falciparum* activity of another family of amide-linked naphthalimide-4-aminoquinoline hybrids against 3D7 and W2 strains. Among all, hybrid **106** was proved to be the most potent for both strains (**Figure 49**).

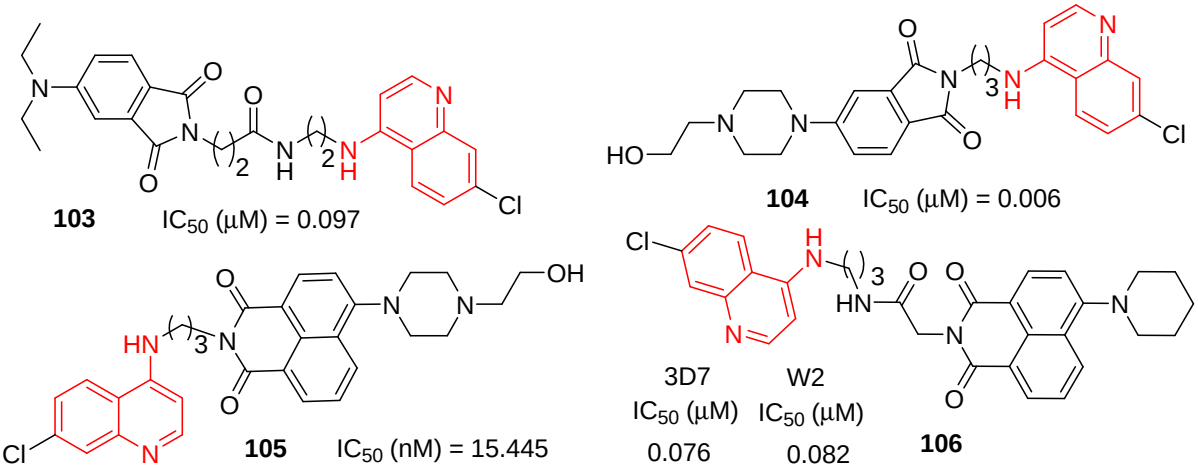


Figure 49. Antimalarial properties of 4-aminoquinoline-phthalimides

11.4. Triazole-4-aminoquinoline conjugates:

In the search for new antimalarial agents, triazole-based aminoquinoline hybrids are desirable lead molecules [110]. Triazole-tethered 4-aminoquinoline derivative **107**, synthesized by Rossier's group [111], was discovered to be 30-40 times more active than the cobalt complex counterpart against both the K1 and NF54 strains (**Figure 50**). One of the screened compounds of de Silva's group [105], **108** bearing methyl substituent on triazole nuclei, showed superior *in vitro* activity (IC_{50}: 0.083 μM) and emerged as the most promising agent against the mice infected with *P. berghei* on the 5th day after infection with favourable SI (132) and low cytotoxicity (IC_{50}: 127 μM) (**Figure 50)**. Among the Wadi's hybrids [112], the most active compound **109** towards 3D7 strain with 40.00 nM of IC_{50} value was screened further counter to *P. falciparum* RKL-9 (CQ^R) strain and was determined to be substantially higher active (IC_{50}: 2.94 nM) than standard CQ (**Figure 50)**. Sharma and his group [113] also investigated anti-*P. falciparum* effects of triazole-tethered tetrahydro-carboline-4-aminoquinoline hybrid compounds towards W2 strain, and **110** was discovered as the most promising candidate amongst (IC_{50}: 0.49 μM) with a SI > 300 on Vero cell (**Figure 50)**.

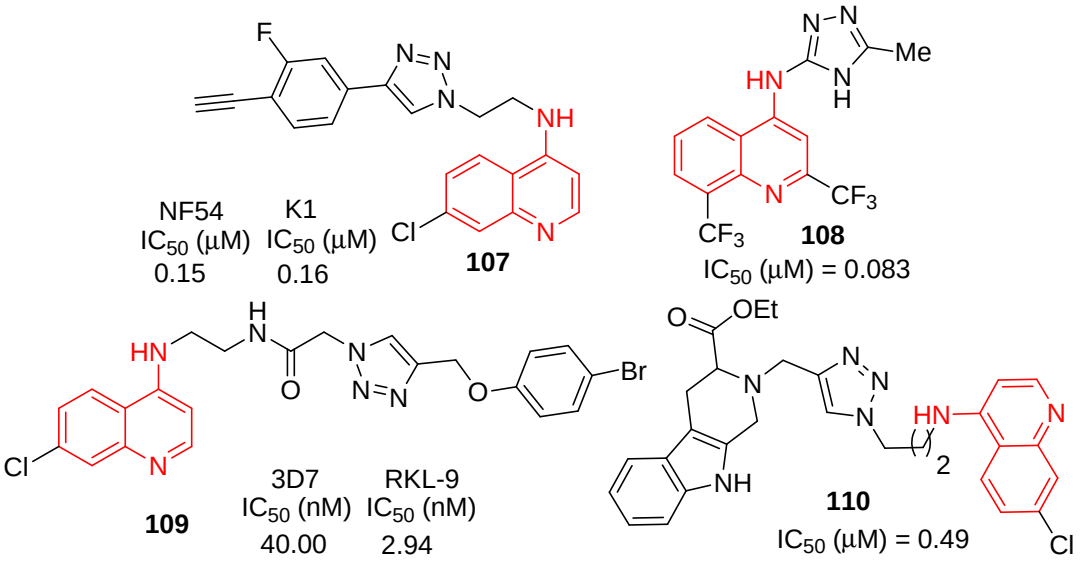


Figure 50. Antimalarial properties of 4-aminoquinoline-triazoles

11.5. Pyrazole-4-aminoquinoline conjugates:

Pyrazole-incorporated hybrids are simple and effective scaffolds that considerably produce extremely effective and low-toxic antimalarial drugs [114,115]. For the first time, Shamsuddin's group tested the antimalarial potency of pyrano[2,3c]pyrazole-4-aminoquinoline hybrids against CQ^S (3D7) and CQ^R (K1) *P. falciparum* clones. The 4-aminoquinoline and pyranopyrazole pharmacophores were responsible for enhanced antimalarial activity demonstrated by the hybrid **111**, which included an alkyl group in the *para* position of the phenyl ring (**Figure 51**) [116].

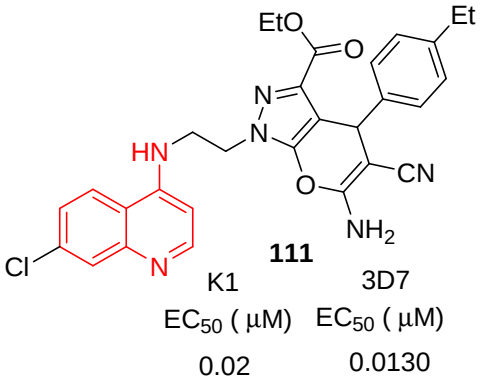


Figure 51. Antimalarial activity of 4-aminoquinolines hybridized with pyrano[2,3c]pyrazole

11.6. The metal complex-4-aminoquinoline conjugates:

In 2019, Stringer and co-workers conducted anti-*P. falciparum* screening of cationic 1,3,5-triaza-phosphaadamantane (PTA) Ir(III) and Ru(II) (**112-113**) [117], Rh(III) half-sandwich (**114**) [118] and Ferroquine-derived (**115**) [119] 4-aminoquinoline complexes against K1 (CQ^R) and NF54 (CQ^S) strains. Amongst Ir(III) and Ru(II) species, non-benzylated compounds were less potent than the benzyl-PTA counterparts against both strains. Towards

the K1 strain, all the Ru(II) species displayed reduced potency compared to the Ir(III) species. Against the NF54 strain, complex **112** (IC_{50}: 0.11 μM) of the Ir(III) series and complex **113** (IC_{50}: 0.10 μM) of the Ru(II) series were the most active candidates. Rh(III) complex **114** was active with a low nM range against the NF54 strain but disclosed cross-resistance against the K1 strain (IC_{50}: > 1000 nM). Among the Ferroquine-derived complexes, **115** was the most promising agent against NF54 and K1 strains with inhibitory concentrations of 0.305 μM and 0.328 μM, respectively (**Figure 52**)

In 2021, Pereira et al. [120] investigated anti-*P. falciparum* efficacy of multitarget metallic hybrid of CQ and primaquine (PQ) linked by Au^{I} (**116**) against the 3D7 strain. The CQPQ-Au^{I} complex was 50-fold more potent than PQ (IC_{50}: 1.1173 μM) and almost equipotent to CQ (IC_{50}: 0.018 μM). Against the W2 strain, the CQPQ-Au^{I} complex was as potent as PQ (IC_{50}: 0.1823 μM) and at very least twice as potent as CQ (IC_{50}: 0.460 μM) (**Figure 52)**. The following year, Sovari and his group [121] identified triazole-4-aminoquinoline conjugated tricarbonyl rhenium metalspecies as effective antimalarial agents against *P. falciparum* NF54 and K1 strains. The hybrid complex **117** was found to be the most promising agent with the submicromolar range inhibitory potencies against both strains (**Figure 52)**.

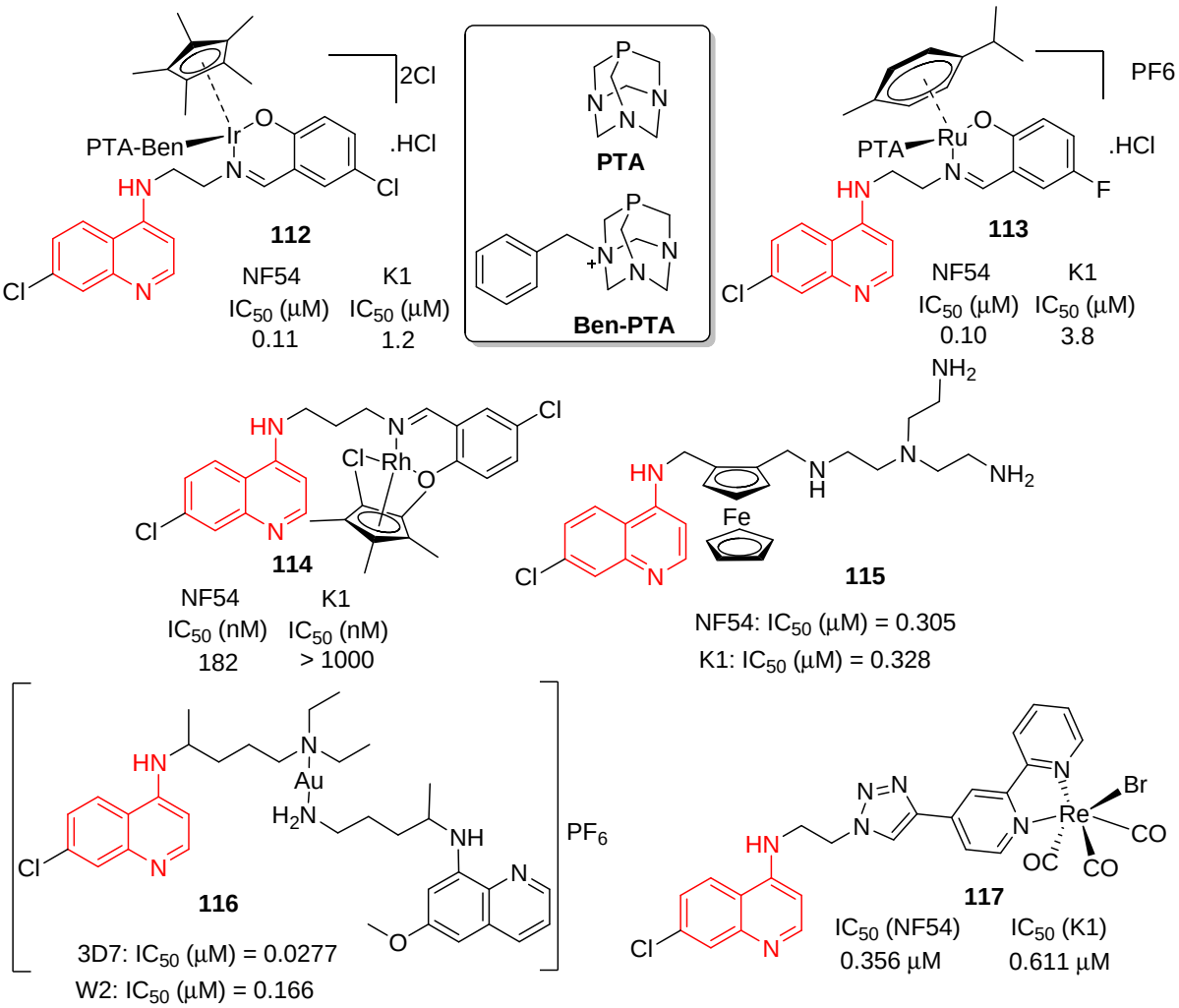


Figure 52. Antimalarial properties of various metal complex-4-aminoquinolines

11.7. Miscellaneous 4-aminoquinolines:

Aiming to develop effective antimalarial agents, Van de Walle and co-workers [122] tested anti-*P. falciparum* activity of piperidine-based 4-aminoquinoline hybrids towards K1 and NF54 strains. In the series, hybrid **118** was found to be equipotent to CQ (IC_{50}: 0.011 μM) against NF54 strain and more active against K1 strain than CQ (IC_{50}: 0.167 μM) (**Figure 53**). Of the twenty-two hybrids tested by Vinindwa's group [123], chalcone-4-aminoquinoline molecular hybrids, **119a-b**, having a propyl linker were more active than the ethyl linker counterparts against the NF54 strain (**Figure 53**). When comparing the antimalarial activity of triazolopyrimidine-based 4-aminoquinoline hybrids furnished by Chowdhary and his group [124], analogue **120** with an octylamine linker between 4-aminoquinoline and triazolopyrimidine units was found to be the most potent candidate against both the W2 and 3D7 strains with IC_{50} values of 0.20 and 0.17 μM, respectively. It is worth mentioning that **120** showed a 3-fold enhanced activity than CQ against the W2 strain (**Figure 53)**.

Harmine-based 4-aminoquinolines were examined by Poje's group [125] for their antimalarial efficacy towards *P. falciparum* CQ-sensitive 3D7 and CQ-resistant 7G8, K1, and Dd2 strains. The most effective hybrid, **121**, showed 5.5-fold enhanced activity than CQ against the 3D7 strain and 15.9-fold higher activity against all the CQ^R strains than CQ with high SI (4450) (**Figure 53)**. Srbljanovic and co-workers [126] recognized thiophene and benzothiophene-based 4-aminoquinoline molecular hybrids as effective anti-*P. falciparum* agents against 3D7 and Dd2 strains. Only one of the tested hybrids, **122**, demonstrated comparable potency (IC_{50}: 18.77 nM) to CQ against the 3D7 strain, whereas all of them were more potent against the Dd2 strain than CQ with lower IC_{50} values (**Figure 53)**.

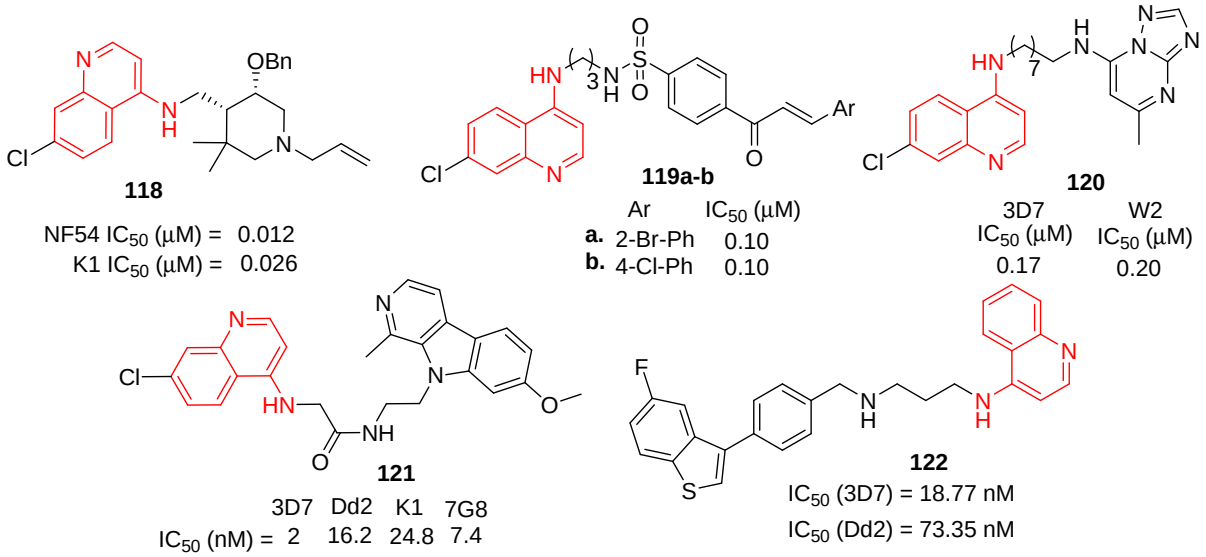


Figure 53. Antiplasmodial potency of 4-aminoquinolines hybridized with piperidine, chalcones, triazolopyrimidine, harmine, and thiophene

Ionic liquids produced from benchmark antimalarials are emerging as a unique approach to cost-effective drug rescue. The laureate salt of CQ (**123**) synthesized by Silva et al. [127] was a promising ionic liquid against the *P. falciparum* Dd2 and 3D7 strains with IC_{50} values of 110 and 4 nM, respectively (**Figure 54)**. Among the series of Kalita's group [128], the inhibitory activity of hybrid **124** with *ortho*-hydroxy phenyl ring (IC_{50}: 0.0008 μM) was comparable to CQ against 3D7 and RKL9 strains (**Figure 54)**. Benzenesulfonamide-based 4-aminoquinoline hybrid **125** with the 2-naphthyl ring on the benzenesulfonamide unit emerged as the most promising candidate against the 3D7 strain (IC_{50} = 0.89 μM) among the series of Silveira et al. (**Figure 54)** [129].

Remarkable antimalarial activities with <1 μM of IC_{50} value were noticed against W2 strain in the case of 4-aminoquinolines incorporated with imines and hydrazones synthesized by the research group of Marinho [130]. Hybrid **126** (IC_{50} = 0.215 μM) among the hydrazone

series and **127** (IC_{50} = 0.145 μM) of the imine series were proved to be more active agents against the W2 strain (**Figure 54)**. The hybrids containing methyl group at 4-aminoquinoline nuclei were constructed by Tiwari et al. [131] and examined for their anti-*P. falciparum* efficacy against K1 and 3D7 strains. The most promising agent, **128**, demonstrated lower IC_{50} values of 0.06 and 0.04 μM against K1 and 3D7 strains, respectively (**Figure 54**). Neto and his group [132] identified dual hybrid 4-aminoquinolines as potential antimalarial agents. Of them, hybrid **129** showed nearly comparable activity to CQ (IC_{50} = 0.026 μM) against the 3D7 strain, and hybrid **130** displayed 4-fold higher potency against the Dd2 strain (IC_{50}= 0.201 μM) than the reference CQ (IC_{50} 0.828 μM) (**Figure 54)**.

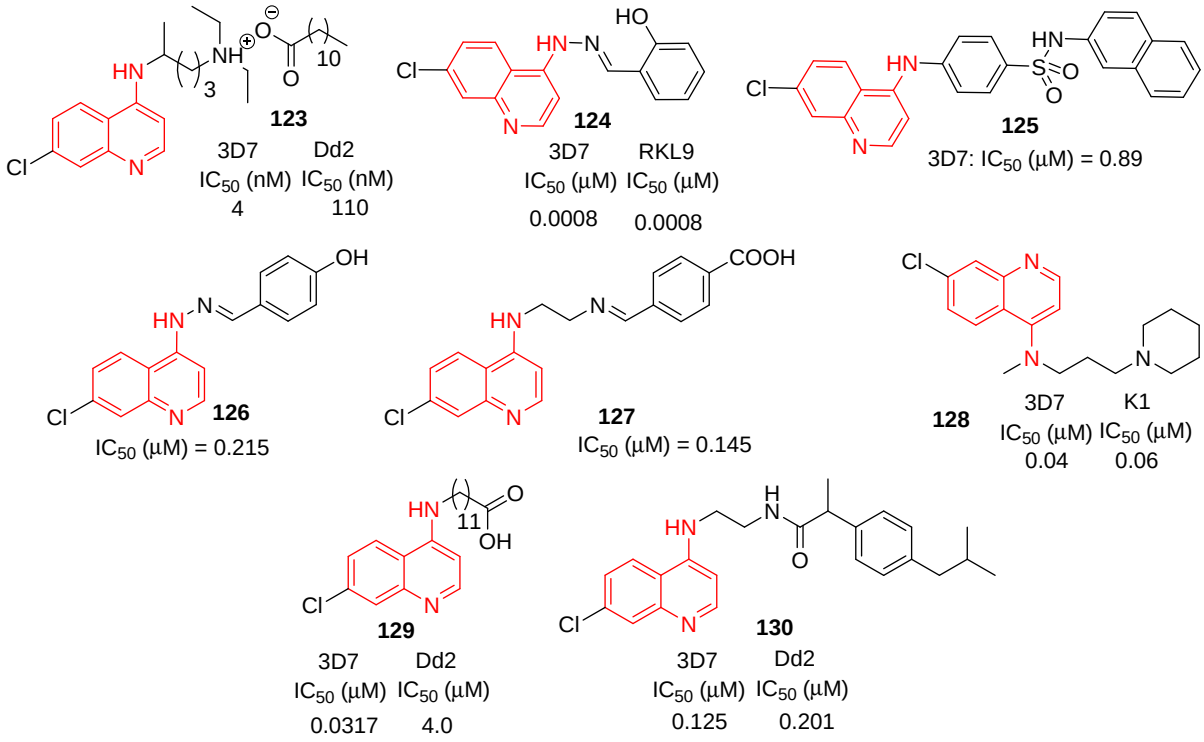


Figure 54. Antimalarial propertiesof 4-aminoquinolines

12. Conclusion

In conclusion, the drugs based on 4-aminoquinoline moiety are well-known and have been in use over the past decades in the treatment of cancer, bacterial, fungal, viral, inflammatory, analgesic, leishmanial, Alzheimer, tubercular, and malarial diseases. A wide variety of heterocycles such asquinoline, pyridine, pyrimidine, triazine, dioxine, piperazine, pyrazoline, piperidine, imidazole, indole, oxadiazole, carbazole, dioxole, thiazole, benzothiazole, pyrazole, phthalimide, adamantane, benzochromene, pyridinone and others fused to or substituted directly to the 4-aminoquinoline moiety or through intermediate chain or linker were engaged in developing various biologically potential drugs were thoroughly discussed. The hybrids' potency is determined by the type, position, and nature of the

substituents connected to the 4-aminoquinoline unit. The high potency of 4-aminoquinoline hybrids is demonstrated by their inhibitory activities in nanomolar and low micromolar concentrations against a broad range of infective agents, including resistant strains.

Towards all the tested cancer calls, hybrid **20** (against MiaPaca2, A2780R, A2780, JIM-T1, K-562, K562R, and HCT116) and hybrid **38** (against BGC-823, DLD1, HepG2, NCI-H1650, RKO, SK-OV-3, and HCT116) were displayed <1 μM IC_{50} values. Hybrids **38** and **39** against Gram-positive bacterial strains *E. faecalis* and *M. smegmatis* (MIC: 1.25 mg/mL), **42** against fungal strains *A. fumigatus, A. niger,* and *C. albicans*, (MIC: 08μg/mL), **47** against IL-1β(IC_{50}: 0.72 μM), **48** against the 2019nCoV-S-HIV virus (EC_{50}: 5.53 μM), **59** against *L. pifanoi* amastigotes (IC_{50}: 0.9 μM), **62a** against AChE (*Ki*: 0.075 μM) and BChE (*Ki*: 0.091 μM), **86** against Mtb H37Rv (MIC: 0.968 μM), and **124** against *P. falciparum* 3D7 and RKL9 (IC_{50}: 0.0008 μM) strains were found to be most potent agents among all the tested hybrids. As a result, additional research into the 4-aminoquinoline core may be fruitful and beneficial. Based on these findings, it has been concluded that 4-aminoquinoline offers a wide range of biological potential, which has piqued the interest of researchers.

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