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Design and synthesis of chloroquine analogs with anti-breast cancer property

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ABSTRACT

A series of chloroquine (CQ) analogs were designed and synthesized in a *repositioning* approach to develop compounds with high anti-breast cancer property. The compounds were then examined for their antiproliferative effects on two human breast tumor cell lines and a matching non-cancer cell line. Although many of them showed substantial antiproliferative effects on breast cancer cells examined, two compounds, 7-chloro-*N*-(3-(4-(7-(trifluoromethyl)quinolin-4-yl)piperazin-1-yl)propyl)quinolin-4-amine (**14**) and {3-[4-(7-chloro-quinolin-4-yl)-piperazin-1-yl]-propyl}-(7-trifluoromethyl-quinolin-4-yl)-amine (**26**), emerged as the most active among this series. They were particularly potent against MCF7 cells when compared to CQ and cisplatin, a widely prescribed anti-cancer drug. The results suggest that these CQ analogs could serve as bases for the development of a new group of effective cancer chemotherapeutics.

1. Introduction

Breast cancer is one of the most commonly diagnosed cancers and causes the second leading cancer deaths in women [1,2]. Although overall survival rate of breast cancer patients has substantially increased during the last decades, this is mainly due to early tumor detection [3–5]. Unfortunately, the recovery rate of advanced breast cancer by currently available treatment modalities is still unacceptably low [6]. Although chemotherapy is the mainstay of cancer therapy, most of the chemotherapy drugs cause general toxicity to any proliferating cells, which can severely limit the therapeutic value of these drugs [7]. In an attempt to overcome this problem, new anti-cancer agents with unique mechanisms of action have been developed; however, many of them have not been therapeutically useful due to low tumor selectivity [7]. This prompted us to design and synthesize novel compounds with high efficacy and specificity for the treatment of breast tumors.

A study of 68 newly approved drugs estimated that developing a single effective cancer drug takes an average of 15 years and US $800 million [8]. One approach to overcome this hurdle may be developing a new use of existing drugs [9]. This *repositioning* or *repurposing* approach can be very effective way to develop new drug, since many existing drugs have been studied for their pharmacokinetics and safety profiles and often have already been approved by regulatory agencies for human use. Therefore, a newly identified use of existing drugs can often be rapidly evaluated in phase II trials [9,10]. The efficacy and specificity of a known drug can also be improved by modifications of clinical formulations, which is termed *redirecting* [9,10]. An important facet of the *repositioning* approach is that the discovery of new targets can be parlayed directly into the generation of new chemical entities (NCEs) by structural analog derivatization that can further enhance the new mechanism or target activity. Therefore, we have applied a *repositioning* and lead optimization approach to develop effective anti-cancer agents using chloroquine (CQ) as a lead compound.

Chloroquine (Fig. 1) is a well-known anti-malarial and -rheumatoid agent, possessing a 4-aminoquinoline scaffold [11]. Based on *repositioning* concept, we have previously demonstrated that 10 μM CQ substantially increases cancer cell killing effects when used in combination with radiation or Akt inhibitors [12,13]. Importantly, the CQ-mediated enhancement of cell killing by Akt inhibitors is cancer-specific [13,14]. In continuation of our efforts to develop effective anti-cancer drugs from CQ, we designed and synthesized several CQ analogs. In this study, we introduced linear alkyl side chain and dialkyl substitution on the lateral side chain, and examined their antiproliferative effects on MDA-MB468 and MCF7 breast cancer cell lines [15]. We found that some of these compounds were indeed more effective than CQ. The lysosomotropic CQ is

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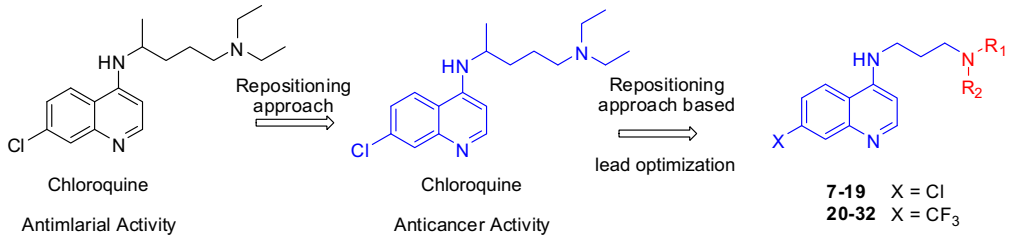


Fig. 1. Synthesis of CQ analogs to develop effective CQ-derived cancer agents.

accumulated in the lysosomes, raises intra-lysosomal pH, and interferes with autophagosome degradation in the lysosomes [11]. This unique property of CQ and its analogs may be important for the enhancement of cell killing/antiproliferative activities by cancer therapeutic agents in a variety of different tumors [11].

These findings have given impetus to our cancer drug research by further augmenting the realization that rational choice of inputs based on known CQ 4-aminoquinoline scaffold could lead to molecules with desirable anti-breast cancer property. Therefore, we designed and synthesized new molecules to further optimize CQ-based anti-cancer agents, in which we selectively modified the lateral side chain of diethyl amino functionality (Fig. 1, Scheme 1) with a variety of heterocyclic ring substitutions including piperidinyl, pyrrolidinyl, morpholinyl, piperazinyl, substituted piperazinyl, and isatin. We took this approach because the heterocyclic ring substituted CQ analogs have not yet been explored for the anti-breast cancer activity. We have found that some of them are promising as they show more effective antiproliferative activities than CQ in a cancer-specific manner.

2. Results and discussion

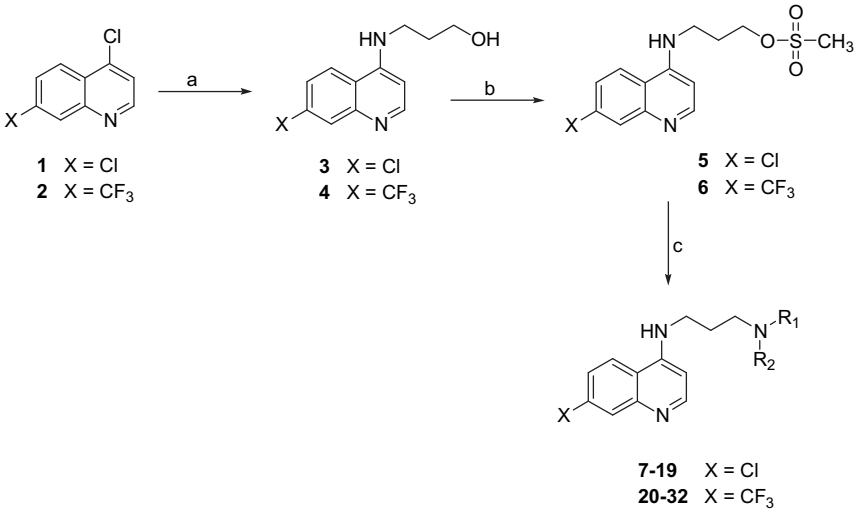
2.1. Chemistry

The target *N*-alkylated 4-aminoquinoline compounds were prepared as outlined in Scheme 1. The amino alcohol components (**3**–**4**) used in the present study were prepared by aromatic nucleophilic substitution on 4-chloro-7-substituted-quinoline with excess of propanol amine in triethyl amine as reported earlier [16]. This was followed by O-mesylation in THF at 0 °C for 4 h to furnish mesylate (**5**–**6**) in very good yield. Chemoselectivity in the mesylation of preformed alcohol (**1**–**2**) was not a problem in spite of the presence of a 4-amino (NH) group, which is poorly nucleophilic due to the conjugation of the lone pair of electrons into the quinoline nitrogen. The synthesis of *N*-alkylated 4-aminoquinoline derivatives (**7**–**32**) (Scheme 1) employed with various active amino components and sodium hydride as the base in *N*,*N*-dimethylformamide (DMF) as the solvent resulting in good yields.

It should be noted that synthesis of compounds **3**, **5**, **7**, **9**, **13**, and **20** has been reported [17–21]. However, none of these compounds has been examined for their antiproliferative activities on cancer cells.

2.2. Antiproliferative effects of the compounds on cancer and non-cancer cells

All of the compounds synthesized were evaluated for their antiproliferative effects on two breast cancer cell lines, MDA-MB231 (p53 and pRB mutated, ER negative breast carcinoma cell line), and MCF7 (p53+/−, invasive ductal breast carcinoma) [22–25]. In addition, the cytotoxicity of all the compounds was also evaluated using MCF10A, a non-cancer breast epithelial cell line, to determine if our newly synthesized compounds have differential effects on cancer and non-cancer cells. The antiproliferative activity was measured by a sulforhodamine B (SRB) assay as described previously [14]. The reading of SRB staining is known to accurately reflect the levels of total cellular macromolecules/cell growth/proliferation. For each compound, 50% growth inhibition (GI_{50}) was



Reagent and Conditions: (a) Triethyl amine, Amino propanol, 120-130° C for 6 h (b) Triethylamine, Methane sulfonyl chloride, THF, RT, 4 h (c) Amino component, NaH, DMF reflux at 65° C, 12 h

Scheme 1. Synthesis of CQ analogs.

calculated from Sigmoidal dose-response curves that were generated with data obtained from two independent experiments carried out each in triplicate. The resultant data is presented in Table 1. The data for CQ and cisplatin were included as references.

Among the twenty six CQ analogs synthesized and examined, ten compounds showed GI_{50} in the range of 4.31–19.13 μM, ten compounds 25.72–49.37 μM, and remaining six compounds showed above 50.24 μM on the MDA-MB231 breast cancer cells (Table 1). As for MCF-7 cells, sixteen compounds showed GI_{50} in the range of 4.60–18.77 μM, ten compounds at 20.63–46.72 μM. The differences in the GI_{50} values may be attributable to such factors as the nature of the lateral side chain N-substitution at the 4-aminoquinoline ring system and the halogen substitution on the 7th position of 4-aminoquinoline ring system, and the genetic and biochemical background of the cell lines.

The structure–activity relationship (SAR) analysis appeared to suggest that compounds **7**–**19** derived from the lateral side chain of the 7-chloro-4-aminoquinoline ring system (except compound **16**) showed better antiproliferative activity than CQ on MCF7 cells. Compounds derived from the 7- trifluoromethyl-4-aminoquinoline lateral side chain substituted series (**20**–**32**) showed less antiproliferative activity than the corresponding 7-Cl derivatives. However, they are generally equivalent to or more potent than CQ on MCF7 cells, with the exception of compound **28**. Compounds **11**–**14** derived from the lateral side chain of the 7-chloro-4-aminoquinoline ring system generally showed better antiproliferative activity than CQ on MDA-MB231 cells.

Further SAR studies suggest that the introduction of a diethyl amino (**7**) group on the lateral side chain of the 7-chloro-4-aminoquinoline ring system increases in the antiproliferative activity on MCF7 cells (GI_{50} = 17.85 μM, compared to GI_{50} 38.44 μM of CQ; Table 1). The substitution of the five-membered heterocyclic ring system with a piperidinyl group (**8**) also resulted in an increase of the antiproliferative activity on MCF7 cells (GI_{50} = 21.45 μM). In contrast, substitutions with alicyclic amino functionality (i.e., the six-membered heterocyclic ring) namely piperidinyl (**9**) and morpholinyl (**10**) resulted in a decrease of antiproliferative activity on MDA-MB231 cells.

In the case of 4-methyl (**11**) and 4-phenyl (**12**) piperazinyl substituted compound, there is an increase in antiproliferative activity 1–2-fold on MDA-MB231 in comparison to morpholinyl substituted compound (**10**). Furthermore, substitution of 4-(7-chloroquinolin-4-yl)piperazin-1-yl (**13**) and 4-(7-trifluoromethyl) quinolin-4-yl)piperazin-1-yl (**14**) showed an increase in antiproliferative activity on both MDA-MB231 and MCF7 cells. However, compounds substituted with isatin ring (**15)** showed a decrease in antiproliferative effects on both MDA-MB231 and MCF7cells. The compounds derived from the 4-chloro isatin (**16**) and 6-bromo isatin (**19**) ring substitution led to the reduction of antiproliferation activity for MDA-MB231 and MCF7cells. Introduction of the 4-bromo isatin (**17**) and 6-chloro isatin (**18**) ring led to a 5-fold increase in antiproliferative activity for MCF7 cells in comparison to CQ. Among the 7-chloro substitution on 4-aminoquinoline derived analogs, the compound **14** was the most effective as its GI_{50} values were 6.33 and 5.42 μM on MDA-MB231 and MCF7cells, respectively. This data demonstrates that the antiproliferative effect of **14** on MDA-MB231 and MCF7 cells is 3.5–7.7-fold, respectively, higher than the original CQ compound (Table 1 and Fig. 2). Furthermore, compound **14** is 3.7-fold (MDA-MB231) to 5.16-fold (MCF7) more potent than cisplatin, one of the most widely prescribed anti-cancer agents. Importantly, the compound **14** is 2.03-fold (MDA-MB231) to 2.58-fold (MCF7) more active than MCF10A, the non-cancer cell control.

Compounds derived from bioisoteric replacement of 7-chloro group with 7-trifluoromethyl substitution on the 4-aminoquinoline ring system having diethyl (**20**), pyrrolidinyl (**21**), piperidinyl (**22**),

Table 1
Antiproliferative activity of CQ analogs on human breast cancer cells and non-cancer cells.

Compounds[a]	X	NR_1R_2	GI_{50} (μM)[b,c]		
			MDA-MB231	MCF7	MCF10A
7	Cl	$(CH_3CH_2)_2N$	27.81 ± 1.17	17.85 ± 0.84	65.26 ± 1.87
8	Cl	Pyrrolidin-1-yl	29.78 ± 1.21	21.45 ± 0.97	45.84 ± 1.25
9	Cl	Piperidin-1-yl	37.95 ± 1.34	17.66 ± 0.78	47.83 ± 1.45
10	Cl	Morpholinoyl	40.25 ± 1.45	17.25 ± 0.74	86.46 ± 1.89
11	Cl	4-Methylpiperazin-1-yl	19.13 ± 0.95	17.10 ± 0.72	16.66 ± 0.23
12	Cl	4-Phenylpiperazin-1-yl	15.88 ± 0.78	12.77 ± 0.64	12.60 ± 0.54
13	Cl	4-(7-Chloroquinolin-4-yl)piperazin-1-yl	7.52 ± 0.32	5.42 ± 0.21	8.72 ± 0.23
14	Cl	4-(7-Trifluoromethyl)quinolin-4-yl)piperazin-1-yl	6.33 ± 0.22	4.99 ± 0.18	12.87 ± 0.44
15	Cl	Isatin	47.57 ± 1.61	23.52 ± 0.99	35.87 ± 0.86
16	Cl	4-Chloro-isatin	55.58 ± 1.83	46.72 ± 1.45	84.76 ± 1.87
17	Cl	4-Bromo-isatin	16.83 ± 0.65	6.57 ± 0.24	20.79 ± 0.75
18	Cl	6-Chloro-isatin	15.81 ± 0.60	7.36 ± 0.32	6.88 ± 0.21
19	Cl	6-Bromo-isatin	35.04 ± 1.23	16.55 ± 0.58	19.90 ± 0.66
20	CF_3	$(CH_3CH_2)_2N$	57.05 ± 1.77	20.63 ± 0.90	45.81 ± 1.23
21	CF_3	Pyrrolidin-1-yl	70.39 ± 1.91	36.75 ± 1.21	58.65 ± 1.56
22	CF_3	Piperidin-1-yl	38.62 ± 1.33	32.61 ± 1.32	48.84 ± 1.23
23	CF_3	Morpholinoyl	79.76 ± 1.94	38.75 ± 1.41	26.48 ± 0.88
24	CF_3	4-Methylpiperazin-1-yl	43.29 ± 1.42	30.75 ± 1.32	51.68 ± 1.64
25	CF_3	4-Phenylpiperazin-1-yl	9.90 ± 0.32	8.75 ± 0.27	19.78 ± 0.88
26	CF_3	4-(7-Chloroquinolin-4-yl)piperazin-1-yl	4.31 ± 0.09	4.60 ± 0.10	8.84 ± 0.21
27	CF_3	4-(7-Trifluoromethyl)quinolin-4-yl)piperazin-1-yl	25.72 ± 1.02	17.23 ± 0.85	30.01 ± 0.65
28	CF_3	Isatin	54.13 ± 1.53	45.31 ± 1.54	46.79 ± 1.21
29	CF_3	4-Chloro-isatin	50.24 ± 1.49	18.78 ± 0.84	20.15 ± 0.77
30	CF_3	4-Bromo-isatin	49.37 ± 1.38	34.36 ± 1.01	33.66 ± 1.01
31	CF_3	6-Chloro-isatin	17.38 ± 0.76	14.30 ± 0.52	25.17 ± 1.24
32	CF_3	6-Bromo-isatin	18.88 ± 0.82	7.98 ± 0.25	14.57 ± 0.78
CQ			22.52 ± 1.44	38.44 ± 1.20	81.26 ± 1.45
Cisplatin			23.65 ± 0.23	25.77 ± 0.38	51.51 ± 0.65

[a] For chemical structures of these compounds, see Fig. 1 and Scheme 1.
[b] GI_{50} values were calculated from Sigmoidal dose–response curves (variable slope), which were generated with GraphPad Prism V. 4.02 (GraphPad Software Inc.).
[c] Values are the mean of triplicates of at least two independent experiments.

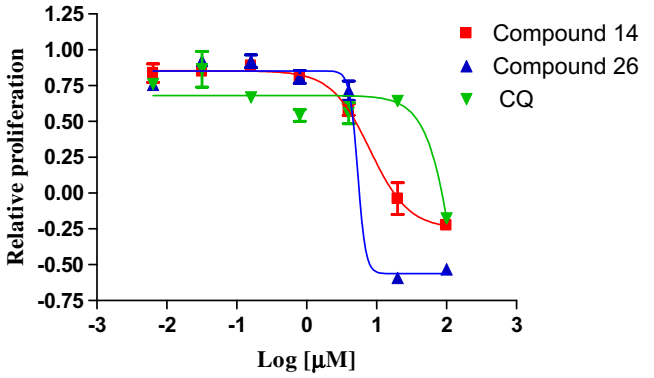


Fig. 2. Antiproliferative effects of compounds **14**, **26** and **CQ** on MCF7 breast cancer cells.

morpholinyl (**23**), isatin (**28**), 4-chloro isatin (**29**), 4-bromo isatin (**30**), 6-chloro isatin (**31**) and 6-bromo isatin (**32**) were generally not as effective as those derived from the 7-chloro substitution on 4-aminoquinoline ring system (Table 1). However, 4-(7-chloroquinolin-4-yl)piperazin-1-yl substituted compound (**26**) emerged as the most active compound in this series, as its GI_{50} values were 4.31 μM (MDA-MB231) to 4.60 μM (MCF7). Compound **26** was 1.92-fold (MCF7) to 2.05-fold (MDA-MB231) more effective on cancer cells than MCF10A non-cancer cells (Table 1). This differential effect on cancer and non-cancer cells is similar to that of compound **14**. Thus, compounds **14** and **26** are potentially very promising anti-breast cancer agents.

Compounds **7**–**10**, **13**, **14**, **16**, **17**, **22**, **24**, **25**, **26** and **31** showed less cytotoxicity on MCF10A cells in comparison to cancer cells. However, most of them may not be useful anti-cancer agents as their cytotoxic effects are generally too low, except compounds **14** and **26**.

It may be important to note that the substitution of the 4-(7-(trifluoromethyl)quinolin-4-yl)piperazin-1-yl ring system on 4-aminoquinoline lateral side chain is very effective in differential antiproliferation on cancer cells when the 7th position of the ring is a –Cl group (**14**), but not $-CF_3$ group (**27**). Conversely, the substitution of the 4-(7-chloroquine 4-yl)piperazin-1-yl ring system on 4-aminoquinoline lateral side chain showed higher differential antiproliferation effects on cancer cells when the 7th position of the ring is a $-CF_3$ group (**26**) than a –Cl group (**13**). Compounds derived from the 7-chloro-4-aminoquinoline ring system with either 4-methylpiperazin-1-yl (compound **11**), 4-phenylpiperazin-1-yl (**12**), or 4-(7-chloroqunolin-4-yl)piperazin-1-yl (**13**) showed an increase in cytotoxic activity on non-cancer cells; thus, they may not be ideal anti-cancer agents.

3. Conclusion

We here report the design, synthesis, and examination of CQ analogs in an attempt to develop effective and safe anti-breast cancer agents. At least 10 of the 26 CQ-derived compounds exhibited improved anti-cancer activity against human breast cancer cells, compared to CQ. In particular, 7-chloro-*N*-(3-(4-(7-(trifluoromethyl)quinolin-4-yl)piperazin-1-yl)propyl)quinolin-4-amine (**14**) and {3-[4-(7-chloro-quinolin-4-yl)-piperazin-1-yl]-propyl}-(7-trifluoromethyl-quinolin-4-yl)-amine (**26**) emerged as the most active compounds in this series. These two compounds are particularly promising, since they are not only much more active than CQ, but also their toxicities are at least twice more effective on cancer cells than the MCF10A non-cancer control. Our data thus demonstrates that CQ is an excellent base compound for *repositioning* toward breast cancer treatment.

4. Experimental protocols

Melting points (mp) were taken in open capillaries on the Complab melting point apparatus. Elemental analysis was performed on a Perkin–Elmer 2400 C, H, N analyzer and values were within the acceptable limit of the calculated values. The ^1H spectra were recorded on a DPX-500 MHz Bruker FT-NMR spectrometer using $CDCl_3$ and DMSO-d_6 as solvent. The chemical shifts were reported as parts per million (δ ppm) tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive). The progress of the reaction was monitored on readymade silica gel plates (Merck) using chloroform–methanol (9:1) as solvent. Iodine was used as a developing agent or by spraying with the Dragendorff's reagent. Chromatographic purification was performed over a silica gel (100–200 mesh). All chemicals and reagents obtained from Aldrich (USA) were used without further purification.

*4.1. Synthesis of 3-(7-substituted-quinolin-4-ylamino)-propanol (**3**–**4**)*

A mixture of 4-chloro-7-substituted-quinoline (20.25 mmol), propanolamine (1.96 ml, 25.75 mmol) and triethylamine (3.6 ml, 25.75 mmol) was heated slowly to 80 °C longer than 1 h while stirring. The temperature was then increased to 130–140 °C, where it was kept for 6 h while stirring continuously. The reaction mixture was cooled to room temperature, and then poured into ice-cold water and filtered. The precipitate was filtered, washed, and recrystallized using chloroform:methanol (3:1) mixture to obtain as cream-white solid.

*4.1.1. 3-(7-Chloroquinolin-4-ylamino)propanol (**3**)*

Yield 80%; mp 140–142 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 1.90 (br s, 1H, OH), 2.06–2.10 (m, 2H, CH_2), 3.32–3.38 (m, 2H, CH_2), 3.65–3.67 (m, 2H, CH_2), 6.34–6.35 (d, J = 5.0 Hz, 1H, Ar-*H*), 6.96 (br s, 1H, N*H*), 7.24–7.27 (dd, J = 10.0 Hz, 1H, Ar-*H*), 7.78 (s, 1H, Ar-*H*), 8.00–8.02 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.35–8.36 (d,J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR (500 MHz, $CDCl_3$): δ 30.95, 40.75, 59.85, 98.62, 117.73, 123.40, 124.40, 127.92, 128.31, 134.20, 149.26, 150.59, 152.00; ES-MS m/z 237 $[M + H]^+$; Anal. Calcd for $C_{12}H_{13}ClN_2O$: C, 60.89; H, 5.54; N, 11.84: found: C, 60.92; H, 5.51; N, 11.87.

*4.1.2. 3-(7-Trifluoromethyl-quinolin-4-ylamino)-propan-1-ol (**4**)*

Yield 79%; mp 122–124 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 1.90 (br s, 1H, OH), 2.07–2.11 (m, 2H, CH_2), 3.47–3.51 (m, 2H, CH_2), 3.98–4.02 (m, 2H, CH_2), 6.16 (br s, 1H, N*H* D_2O exchangeable), 6.44–6.45 (d,J = 5.0 Hz, 1H, Ar-*H*), 8.39–8.41 (m, 2H, Ar-*H*), 8.49 (s, 1H, Ar-*H*), 8.57–8.58 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR (500 MHz, $CDCl_3$): δ 30.14, 39.77, 58.51, 98.81, 118.31, 120.35, 122.40, 122.62, 126.72, 128.31, 146.89, 149.68, 151.45; ES-MS m/z 271 $[M + H]^+$; Anal. Calcd for $C_{13}H_{13}F_3N_2O$: C, 57.78; H, 4.85; N, 10.37; found: C, 57.82; H, 4.88; N, 10.32.

*4.2. Synthesis of 3-(7-substituted-quinolin-4-ylamino)-propyl methanesulfonate (**5**–**6**)*

A solution of compound 3-(7-Substituted-quinolin-4-ylamino)-propanol (12.70 mmol) in anhydrous THF (25 ml) under a nitrogen atmosphere was added triethylamine (15.25 mmol). The mixture was cooled to below 0 °C. Methanesulfonyl chloride (0.9 ml, 12.70 mmol) was added slowly, while maintaining the temperature below 5 °C, and the mixture was stirred in an ice bath 1 h. After dilution with saturated $NaHCO_3$ solution (50 ml, 2×) the reaction was extracted with ether. The organic extracts were dried over

Na_2SO_4, filtered, and evaporated to leave compounds **3** and **4** as a white solid.

*4.2.1. 3-(7-Chloroquinolin-4-ylamino)propyl methanesulfonate (**5**)*

Yield 75%; mp 124–126 °C; ^{1}H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ 2.09–2.13 (m, 2H, CH_2), 3.08 (s, 3H, SO_2CH_3), 3.38–3.42 (m, 2H, CH_2), 4.32–4.34 (m, 2H, CH_2), 6.38–6.39 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.13 (br s, 1H, N*H*), 7.30–7.31 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.74 (s, 1H, Ar-*H*), 8.15–8.17 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.37–8.38 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR (DMSO-d_6 + $CDCl_3$): δ 27.90, 37.17, 38.64, 68.34, 98.81, 117.86, 123.96, 124.50, 127.84, 134.26, 149.24, 150.52, 151.93; ES-MS m/z 315 $[M + H]^+$; Anal. Calcd for $C_{13}H_{15}ClN_2O_3S$: C, 49.60; H, 4.80; N, 8.90; found: C, 49.56; H, 4.85; N, 8.92.

*4.2.2. Methanesulfonic acid 3-(7-trifluoromethyl-quinolin-4-ylamino)-propyl ester (**6**)*

Yield 73%; mp 82–84 °C; ^{1}H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ 2.11–2.16 (m, 2H, CH_2), 3.01 (s, 3H, SO_2CH_3), 3.42–3.45 (m, 2H, CH_2), 4.32–4.35 (m, 2H, CH_2), 6.48–6.49 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.29 (br s, 1H, N*H* D_2O exchangeable), 7.50–7.52 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.05 (s, 1H, Ar-*H*), 8.34–8.36 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.46–8.47 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR (DMSO-d_6 + $CDCl_3$): δ 32.55, 41.94, 44.34, 72.99, 104.51, 124.11, 125.92, 127.89, 128.44, 131.15, 135.14, 152.11, 155.30, 156.63; ES-MS m/z 350 $[M + H]^+$; Anal. Calcd for $C_{14}H_{15}F_3N_2O_3S$: C, 48.27; H, 4.34; N, 8.04; found: C, 48.22; H, 4.37; N, 8.07.

4.3. General synthetic procedure for 7-substituted-N-(3-(alkyl/heteroalkyl/aryl)propyl) quinolin-4-amine

To a mixture of 3-(7-substituted-quinolin-4-ylamino)-propyl methanesulfonate (3.81 mmol), active amine compound (3.81 mmol) and triethylamine (0.4 ml, 3.81 mmol) in 20 ml of anhydrous DMF were stirred at 50–60 °C for 72 h. The reaction mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was taken up in dichloromethane. The organic layer was washed with 5% aq. $NaHCO_3$, followed by brine wash. The organic layer was dried over anhydrous Na2SO4 and solvent was removed under reduced pressure. The crude product was chromatographed on silica gel, eluting with chloroform–methanol.

*4.3.1. 7-Chloro-N-(3-(diethylamino)propyl)quinolin-4-amine (**7**)*

Yield 65%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06–1.09 (m, 6H, N(CH_2CH_3)$_2$), 1.87–1.91 (m, 2H, CH_2), 2.60–2.64 (m, 4H, N(CH_2CH_3)$_2$), 2.65–2.67 (m, 2H, CH_2), 3.72–3.75 (m, 2H, CH_2), 6.25–6.26 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.29–7.31 (dd, J = 5.0 Hz, J = 10.0 Hz, 1H, Ar-*H*), 7.68–7.69 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.91 (s, 1H, Ar-*H*), 8.16 (br s, 1H, N*H* D_2O exchangeable), 8.53–8.54 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 11.55, 24.23 (2C), 47.03 (2C), 53.55, 68.14, 98.21, 122.16, 125.38, 128.50, 132.44, 134.58, 150.70, 151.86, 152.01; ES-MS m/z 293 $[M + H]^+$; Anal. Calcd for $C_{16}H_{22}ClN_3$: C, 65.85; H, 7.60; N, 14.40; found: C, 65.80; H, 7.55; N, 14.37.

*4.3.2. 7-Chloro-N-(3-(pyrrolidin-1-yl)propyl)quinolin-4-amine (**8**)*

Yield 66%; mp 86–88 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.83–1.94 (m, 2H, CH_2), 2.59–2.64 (m, 4H, CH_2), 2.73–2.77 (m, 2H, CH_2), 3.39–3.44 (m, 4H, CH_2), 2.51–2.54 (m, 2H, CH_2), 6.23–6.24 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.25–7.27 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.57–7.60 (dd, J = 5.0 Hz, J = 10.0 Hz, 1H, Ar-*H*), 7.89 (s, 1H, Ar-*H*), 8.23 (br s, 1H, N*H* D_2O exchangeable), 8.42–8.43 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 23.74 (2C), 25.30, 44.22, 54.14 (2C), 55.98, 98.38, 117.66, 121.93, 124.88, 128.10, 134.68, 148.32, 150.95, 151.80; ES-MS m/z 291 $[M + H]^+$; Anal. Calcd for $C_{16}H_{20}ClN_3$: C, 66.31; H, 6.96; N, 14.50; found: C, 66.29; H, 6.92; N, 14.53.

*4.3.3. 7-Chloro-N-(3-(piperidin-1-yl)propyl)quinolin-4-amine (**9**)*

Yield 56%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38–1.42 (m, 2H, CH_2 piperidinyl), 1.68–1.72 (m, 4H, CH_2 piperidinyl), 1.89–1.92 (m, 2H, CH_2), 2.33–2.39 (m, 4H, CH_2 piperidinyl), 2.51–2.54 (m, 2H, CH_2), 3.29–3.32 (m, 2H, CH_2), 6.26–6.27 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.29–7.31 (dd, J = 5.0 Hz, J = 10.0 Hz, 1H, Ar-*H*), 7.81 (br s, 1H, N*H* D_2O exchangeable), 7.83–7.85 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.41 (s, 1H, Ar-*H*), 8.44–8.45 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 23.99, 24.32, 26.10 (2C), 44.46, 54.92 (2C), 59.43, 98.34, 117.59, 122.53, 124.44, 128.77, 134.54, 149.06, 150.71, 152.07; ES-MS m/z 305 $[M + H]^+$; Anal. Calcd for $C_{17}H_{22}ClN_3$: C, 67.20; H, 7.30; N, 13.83; found: C, 67.22; H, 7.35; N, 13.87.

*4.3.4. 7-Chloro-N-(3-morpholinopropyl)quinolin-4-amine (**10**)*

Yield 67%; mp 118–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.93–1.97 (m, 2H, CH_2), 2.59 (s, 4H, N(CH_2CH_2)$_2$O), 2.63–2.66 (m, 2H, CH_2), 3.40–3.43 (m, 2H, CH_2), 3.87 (s, 4H, N(CH_2CH_2)$_2$O), 6.36–6.37 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.20 (br s, 1H, N*H* D_2O exchangeable), 7.38–7.41 (dd, J = 5.0 Hz, J = 10.0 Hz, 1H, Ar-*H*), 7.82–7.84 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.97 (s, 1H, Ar-*H*), 8.53–8.54 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 23.36, 44.12, 54.04 (2C), 59.01, 68.17 (2C), 98.64, 117.47, 121.78, 124.90, 128.81, 134.75, 149.17, 150.40, 152.21; ES-MS m/z 307 $[M + H]^+$; Anal. Calcd for $C_{16}H_{20}ClN_3O$: C, 62.84; H, 6.59; N, 13.74; found: C, 62.79; H, 6.62; N, 13.70.

*4.3.5. 7-Chloro-N-(3-(4-methylpiperazin-1-yl)propyl)quinolin-4-amine (**11**)*

Yield 59%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48–1.52 (m, 2H, CH_2), 2.29–2.35 (m, 2H, CH_2), 2.38–2.44 (m, 2H, CH_2), 2.53 (s, 3H, N-CH_3), 4.37–4.40 (s, 8H, N(CH_2CH_2)$_2$N), 6.12–6.14 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.27 (br s, 1H, N*H* D_2O exchangeable), 7.29 (s, 1H, Ar-*H*), 7.82–7.83 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.95 (s, 1H, Ar-*H*), 8.47–8.48 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 29.37, 34.19, 44.24, 45.79, 54.25 (4C), 101.01, 117.93, 125.52, 125.63, 128.75, 134.65, 150.84, 151.94, 153.10; ES-MS m/z 319 $[M + H]^+$; Anal. Calcd for $C_{17}H_{23}ClN_4$: C, 64.04; H, 7.27; N, 17.57; found: C, 64.09; H, 7.30; N, 17.52.

*4.3.6. 7-Chloro-N-(3-(4-phenylpiperazin-1-yl)propyl)quinolin-4-amine (**12**)*

Yield 53%; mp 110–112 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.01–2.07 (m, 2H, CH_2), 2.65–2.70 (m, 2H, CH_2), 2.71 (s, 4H, N(CH_2CH_2)$_2$N-Ar), 3.27–3.36 (m, 2H, CH_2), 3.41 (s, 4H, N(CH_2CH_2)$_2$N-Ar), 6.33 (br s, 1H, N*H* D_2O exchangeable), 6.35–6.36 (d, J = 5.0 Hz, 1H, Ar-*H*), 6.94–6.97 (m, 2H, Ar-*H*), 7.00–7.01 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.21–7.22 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.33–7.38 (m, 2H, Ar-*H*), 7.81–7.83 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.95 (s, 1H, Ar-*H*), 8.52–8.53 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 23.65, 37.44, 44.25 (2C), 49.42 (2C), 53.64, 58.59, 98.56, 116.24, 117.44, 120.25, 122.08, 124.84, 127.56, 128.63, 129.95, 134.73, 149.06, 150.52, 151.12, 152.13; ES-MS m/z 382 $[M + H]^+$; Anal. Calcd for $C_{22}H_{25}ClN_4$: C, 69.37; H, 6.62; N, 14.71; found: C, 69.41; H, 6.66; N, 14.75.

*4.3.7. 7-Chloro-N-(3-(4-(7-chloroquinolin-4-yl)piperazin-1-yl) propyl)quinolin-4-amine (**13**)*

Yield 61%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.01–2.03 (m, 2H, CH_2), 2.69–2.74 (m, 2H, CH_2), 2.94 (s, 4H, N(CH_2CH_2)$_2$N-Ar), 3.42 (s, 4H, N(CH_2CH_2)$_2$N-Ar), 3.43–3.46 (m, 2H, CH_2), 6.36–6.37 (d, J = 5.0 Hz, 1H, Ar-*H*), 6.88–6.89 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.08 (br s, 1H, N*H*), 7.25–7.26 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.29 (s, 1H, Ar-*H*), 7.42–7.44 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.71–7.72 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.78–7.80 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.93–7.95 (d, J = 10.0 Hz, 1H, Ar-*H*),

8.50–8.51 (d, J = 5.0 Hz, 1H, Ar-*H*), 8.78–8.79 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 30.36, 43.83, 46.07, 52.23 (2C), 53.42 (2C), 98.70, 108.87, 117.40, 121.86, 124.78, 126.32, 128.67, 128.96, 130.89, 132.45, 134.74, 135.01, 149.01, 150.39, 152.05, 152.08, 156.70, 167.77; ES-MS m/z 467 $[M + H]^+$; Anal. Calcd for $C_{25}H_{25}Cl_2N_5$: C, 64.38; H, 5.40; N, 15.02; found: C, 64.35; H, 5.37; N, 14.99.

4.3.8. 7-Chloro-N-(3-(4-(7-(trifluoromethyl)quinolin-4-yl) piperazin-1-yl)propyl)quinolin-4-amine (**14**)

Yield 61%; mp 121–123 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.05–2.07 (m, 2H, CH_2), 2.79–2.81 (m, 2H, CH_2), 2.95 (s, 4H, N(CH_2CH_2)$_2$N-Ar), 3.41 (s, 4H, N(CH_2CH_2)$_2$N-Ar), 3.46–3.49 (m, 2H, CH_2), 6.40–6.41 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.01 (br s, 1H, N*H* D_2O exchangeable), 7.02–7.03 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.30–7.32 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.68–7.70 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.82–7.83 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.97–7.98 (d, J = 5.0 Hz, 1H, Ar-*H*), 8.16–8.17 (d, J = 5.0 Hz, 1H, Ar-*H*), 8.41 (s, 1H, Ar-*H*), 8.55–8.56 (d, J = 5.0 Hz, 1H, Ar-*H*), 8.91–8.92 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 23.95, 43.90, 52.25 (2C), 53.44 (2C), 58.30, 98.76, 110.15, 117.41, 121.06, 121.68, 124.85, 124.91 (2C), 125.16, 127.96, 128.88, 134.78, 148.81, 149.14, 150.32, 152.21, 152.32 (2C), 156.31; ES-MS m/z 501 $[M + H]^+$; Anal. Calcd for $C_{26}H_{25}ClF_3N_5$: C, 62.46; H, 5.04; N, 14.01; found: C, 62.49; H, 5.07; N, 14.06.

4.3.9. (3-(7-Chloroquinolin-4-ylamino)propyl)isatin (**15**)

Yield 61%; mp 87–89 °C; ^{1}H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ 2.09–2.11 (m, 2H, CH_2), 3.33–3.39 (m, 2H, CH_2), 3.82–3.85 (m, 2H, CH_2), 6.34–6.35 (d, J = 5.0 Hz, 1H, Ar-*H*), 6.97 (br s, 1H, N*H*), 7.02–7.05 (m, 2H, Ar-*H*), 7.25–7.27 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.45–7.49 (m, 2H, Ar-*H*), 7.63–7.65 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.06–8.08 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.34–8.35 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR (DMSO-d_6 + $CDCl_3$): δ 25.81, 38.09, 40.65, 98.86, 110.65, 117.69, 117.83, 123.64, 123.69 (2C), 124.48, 124.97, 127.91, 134.24, 138.38, 150.37, 150.79, 151.94, 158.62, 183.51; ES-MS m/z 366 $[M + H]^+$; Anal. Calcd for $C_{20}H_{16}ClN_3O_2$: C, 65.67; H, 4.41; N, 11.49; found: C, 65.71; H, 4.39; N, 11.52.

4.3.10. 4-Chloro-(3-(7-chloroquinolin-4-ylamino)propyl)isatin (**16**)

Yield 59%; mp 227–229 °C; IR (KBr, cm^{-1}): 1725, 1625; ^{1}H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ 1.58–1.62 (m, 2H, CH_2), 2.18–2.25 (m, 2H, CH_2), 3.31–3.40 (m, 2H, CH_2), 6.35 (br s, 1H, N*H*), 6.37–6.38 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.11–7.12 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.31–7.32 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.45–7.49 (m, 2H, Ar-*H*), 7.69–7.70 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.79–7.81 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.45–8.46 (d, J = 5.0 Hz, 1H, Ar-*H*); ES-MS m/z 401 $[M + H]^+$; Anal. Calcd for $C_{20}H_{15}Cl_2N_3O_2$: C, 60.01; H, 3.78; N, 10.50; found: C, 60.03; H, 3.75; N, 10.44.

4.3.11. 4-Bromo-(3-(7-chloroquinolin-4-ylamino)propyl)isatin (**17**)

Yield 58%; mp 86–88 °C; IR (KBr, cm^{-1}): 1722, 1621; ^{1}H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ 2.09–2.11 (m, 2H, CH_2), 3.42–3.46 (m, 2H, CH_2), 3.83–3.91 (m, 2H, CH_2), 6.35–6.36 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.11–7.12 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.32–7.39 (m, 2H, Ar-*H*), 7.75–7.76 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.90–7.92 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.04–8.05 (d, J = 5.0 Hz, 1H, Ar-*H*), 8.35–8.36 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 25.72, 38.29, 40.64, 98.92, 109.74, 116.41, 120.50, 123.76, 124.41 (2C), 127.84 (2C), 127.93, 134.16, 138.50, 150.33, 151.98, 152.53, 157.86, 181.00; ES-MS m/z 446 $[M + H]^+$; Anal. Calcd for $C_{20}H_{15}BrClN_3O_2$: C, 54.02; H, 3.40; N, 9.45; found: C, 54.06; H, 3.44; N, 9.49.

4.3.12. 6-Chloro-(3-(7-chloroquinolin-4-ylamino)propyl)isatin (**18**)

Yield 57%; mp 119–121 °C; IR (KBr, cm^{-1}): 1727, 1628; ^{1}H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ 1.63–1.69 (m, 2H, CH_2), 2.08–2.15 (m, 2H, CH_2), 3.36–3.44 (m, 2H, CH_2), 6.08 (br s, 1H, N*H*), 6.39–6.40 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.12–7.13 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.36–7.37 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.54–7.62 (m, 2H, Ar-*H*), 7.71–7.72 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.90–7.92 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.49–8.50 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 25.61, 34.26, 48.71, 93.86, 111.22, 112.59, 116.79, 119.77, 120.87, 121.99, 124.05, 126.16, 127.69, 130.39, 140.39, 144.63, 146.99, 154.44, 163.05, 176.59; ES-MS m/z 401 $[M + H]^+$; Anal. Calcd for $C_{20}H_{15}Cl_2N_3O_2$: C, 60.01; H, 3.78; N, 10.50; found: C, 59.98; H, 3.75; N, 10.47.

4.3.13. 6-Bromo-(3-(7-chloroquinolin-4-ylamino)propyl)isatin (**19**)

Yield 60%; mp 76–78 °C; IR (KBr, cm^{-1}): 1732, 1632; ^{1}H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ 2.07–2.11 (m, 2H, CH_2), 3.35–3.39 (m, 2H, CH_2), 3.82–3.85 (m, 2H, CH_2), 6.39–6.40 (d, J = 5.0 Hz, 1H, Ar-*H*), 6.99–7.01 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.28 (br s, 1H, N*H*), 7.30–7.32 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.44–7.46 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.70 (s, 1H, Ar-*H*), 8.11–8.13 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.35 (s, 1H, Ar-*H*),8.49–8.50 (d, J = 5.0 Hz, 1H, Ar-*H*); ES-MS m/z 401 $[M + H]^+$; Anal. Calcd for $C_{20}H_{15}BrClN_3O_2$: C, 54.02; H, 3.40; N, 9.45; found: C, 54.08; H, 3.44; N, 9.49.

4.3.14. N,N-diethyl-N′-(7-trifluoromethyl-quinolin-4-yl)-propane-1,3-diamine (**20**)

Yield 51%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.99–1.13 (m, 6H, N(CH_2CH_3)$_2$), 1.92–1.96 (m, 2H, CH_2), 2.64–2.67 (m, 2H, CH_2), 2.69–2.72 (m, 4H, N(CH_2CH_3)$_2$), 3.39–3.42 (m, 2H, CH_2), 6.37–6.38 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.54–7.56 (dd, J = 5.0 Hz, J = 10.0 Hz, 1H, Ar-*H*), 7.87–7.89 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.30 (s, 1H, Ar-*H*), 8.35 (br s, 1H, N*H* D_2O exchangeable), 8.59–8.61 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 11.58 (2C), 24.17, 44.84, 47.10 (2C), 53.70, 99.19, 121.00 (2C), 121.93, 125.23, 127.42, 127.46, 147.78, 150.48, 152.42; ES-MS m/z 326 $[M + H]^+$; Anal. Calcd for $C_{17}H_{22}F_3N_3$: C, 62.75; H, 6.82; N, 12.91; found: C, 62.78; H, 6.79; N, 12.95.

4.3.15. (3-Pyrrolidin-1-yl-propyl)-(7-trifluoromethyl-quinolin-4-yl)-amine (**21**)

Yield 55%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.81–1.87 (m, 6H, CH_2), 2.59–2.64 (m, 4H, CH_2), 2.77–2.79 (m, 2H, CH_2), 3.36–3.39 (m, 2H, CH_2), 6.35–6.36 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.51–7.53 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.76–7.78 (dd, J = 5.0 Hz, J = 10.0 Hz, 1H, Ar-*H*), 8.23 (s, 1H, Ar-*H*), 8.41 (br s, 1H, N*H* D_2O exchangeable), 8.56–8.57 (d, J = 5.0 Hz, 1H, Ar-*H*); ES-MS m/z 324 $[M + H]^+$; Anal. Calcd for $C_{17}H_{20}F_3N_3$: C, 63.14; H, 6.23; N, 13.00; found: C, 63.11; H, 6.25; N, 13.02.

4.3.16. (3-Piperidin-1-yl-propyl)-(7-trifluoromethyl-quinolin-4-yl)-amine (**22**)

Yield 56%; mp 118–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58–1.62 (m, 2H, CH_2 piperidinyl), 1.70–1.78 (m, 4H, CH_2 piperidinyl), 1.94–1.97 (m, 2H, CH_2), 2.49–2.52 (m, 4H, CH_2 piperidinyl), 2.58–2.62 (m, 2H, CH_2), 3.37–3.40 (m, 2H, CH_2), 6.39–6.40 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.56–7.58 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.06–8.08 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.12 (br s, 1H, N*H* D_2O exchangeable), 8.29 (s, 1H, Ar-*H*), 8.59–8.60 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 23.27, 24.34, 26.00 (2C), 44.77, 55.02 (2C), 59.65, 100.10, 119.30, 120.95, 121.22, 121.50, 122.30, 127.43, 148.74, 150.57, 152.44; ES-MS m/z 338 $[M + H]^+$; Anal. Calcd for $C_{18}H_{22}F_3N_3$: C, 64.08; H, 6.57; N, 12.45; found: C, 64.12; H, 6.60; N, 12.49.

4.3.17. (3-Morpholin-4-yl-propyl)-(7-trifluoromethyl-quinolin-4-yl)-amine (**23**)

Yield 62%; mp 120–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.97–2.02 (m, 2H, CH_2), 2.61 (s, 4H, N(CH_2CH_2)$_2$O), 2.65–2.68 (m, 2H, CH_2), 3.42–3.45 (m, 2H, CH_2), 3.85 (s, 4H, N(CH_2CH_2)$_2$O), 6.44–6.45 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.43 (br s, 1H, N*H* D_2O exchangeable), 7.62–7.63 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.01–8.03

(d, J = 10.0 Hz, 1H, Ar-*H*), 8.28 (s, 1H, Ar-*H*), 8.62–8.63 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 23.23, 44.27, 54.06 (2C), 59.08, 67.02 (2C), 99.62, 119.65, 119.68, 120.78, 121.64, 127.73, 127.76, 147.75, 150.23, 152.48; ES-MS m/z 340 $[M + H]^+$; Anal. Calcd for $C_{17}H_{20}F_3N_3O$: C, 60.17; H, 5.94; N, 12.38; found: C, 60.12; H, 5.91; N, 2.40.

4.3.18. [3-(4-Methyl-piperazin-1-yl)-propyl]-(7-trifluoromethyl-quinolin-4-yl)-amine (**24**)

Yield 62%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.94–1.99 (m, 2H, CH_2), 2.38 (s, 3H, N-CH_3), 2.65 (s, 8H, N(CH_2CH_2)$_2$N), 2.67–2.72 (m, 2H, CH_2), 3.37–3.40 (m, 2H, CH_2), 6.39–6.40 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.53–7.55 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.70 (br s, 1H, N*H* D_2O exchangeable), 8.06–8.07 (d, J = 5.0 Hz, 1H, Ar-*H*), 8.25 (s, 1H, Ar-*H*), 8.58–8.59 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 23.30, 44.52, 46.34, 53.57 (2C), 55.28 (2C), 58.73, 99.46, 119.34, 120.80, 122.30, 123.02, 125.18, 127.47, 147.68, 150.41, 152.44; ES-MS m/z 353 $[M + H]^+$; Anal. Calcd for $C_{18}H_{23}F_3N_4$: C, 61.35; H, 6.58; N, 15.90; found: C, 61.32; H, 6.54; N, 15.86.

4.3.19. [3-(4-Phenyl-piperazin-1-yl)-propyl]-(7-trifluoromethyl-quinolin-4-yl)-amine (**25**)

Yield 60%; mp 127–129 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.98–2.02 (m, 2H, CH_2), 2.59–2.63 (m, 2H, CH_2), 2.71 (s, 4H, N(CH_2CH_2)$_2$N-Ar), 3.43 (s, 4H, N(CH_2CH_2)$_2$N-Ar), 3.39–3.42 (m, 2H, CH_2), 6.33 (br s, 1H, N*H* D_2O exchangeable), 6.44–6.45 (d, J = 5.0 Hz, 1H, Ar-*H*), 6.96–6.97 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.00–7.02 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.43–7.45 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.49 (s, 1H, Ar-*H*), 7.53–7.55 (dd, J = 5.0, 10.0 Hz, 1H, Ar-*H*), 7.72–7.73 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.99–8.01 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.26 (s, 1H, Ar-*H*), 8.61–8.62 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 23.77, 44.33, 49.44 (2C), 53.65 (2C), 58.58, 99.57, 116.24 (2C), 119.63, 119.65, 120.27, 120.77, 121.91, 128.81 (2C), 132.47, 147.67, 150.33, 151.09, 152.41, 167.78; ES-MS m/z 415 $[M + H]^+$; Anal. Calcd for $C_{23}H_{25}F_3N_4$: C, 66.65; H, 6.08; N, 13.52; found: C, 66.61; H, 6.05; N, 13.49.

4.3.20. {3-[4-(7-Chloro-quinolin-4-yl)-piperazin-1-yl]-propyl}-(7-trifluoromethyl-quinolin-4-yl)-amine (**26**)

Yield 56%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.07–2.09 (m, 2H, CH_2), 2.80–2.82 (m, 2H, CH_2), 2.90 (s, 4H, N(CH_2CH_2)$_2$N-Ar), 3.40 (s, 4H, N(CH_2CH_2)$_2$N-Ar), 3.49–3.53 (m, 2H, CH_2), 6.49–6.50 (d, J = 5.0 Hz, 1H, Ar-*H*), 6.93–6.94 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.13 (br s, 1H, N*H* D_2O exchangeable), 7.48–7.49 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.52–7.54 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.98–8.00 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.00–8.02 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.10 (s, 1H, Ar-*H*), 8.26 (s, 1H, Ar-*H*), 8.64–8.65 (d, J = 5.0 Hz, 1H, Ar-*H*), 8.82–8.83 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 23.88, 44.03, 52.27 (2C), 53.51 (2C), 58.35, 99.76, 108.91, 119.61, 120.72, 121.53, 121.90, 124.58, 125.08, 126.37, 127.80, 127.84, 129.09, 135.06, 147.78, 150.14, 150.27, 152.09, 152.50, 156.64; ES-MS m/z 501 $[M + H]^+$; Anal. Calcd for $C_{26}H_{25}ClF_3N_5$: C, 62.46; H, 5.04; N, 14.01; found: C, 62.40; H, 5.07; N, 13.98.

4.3.21. (7-Trifluoromethyl-quinolin-4-yl)-{3-[4-(7-trifluoromethyl-quinolin-4-yl)-piperazin-1-yl]-propyl}-amine (**27**)

Yield 62%; mp 125–127 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.00–2.05 (m, 2H, CH_2), 2.73–2.76 (m, 2H, CH_2), 2.84 (s, 4H, N(CH_2CH_2)$_2$N-Ar), 3.40 (s, 4H, N(CH_2CH_2)$_2$N-Ar), 3.41–3.46 (m, 2H, CH_2), 6.41–6.42 (d, J = 5.0 Hz, 1H, Ar-*H*), 6.94–6.95 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.14 (br s, 1H, N*H* D_2O exchangeable), 7.44–7.45 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.62–7.64 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.94–7.96 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.09–8.11 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.36 (s, 1H, Ar-*H*), 8.50 (s, 1H, Ar-*H*), 8.56–8.57 (d, J = 5.0 Hz, 1H, Ar-*H*), 8.83–8.84 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 23.93, 43.72, 52.18 (2C), 53.32 (2C), 58.03, 99.44, 99.71, 121.70, 122.04, 122.87,. 122.92, 125.12, 127.47, 127.76, 127.79, 128.76, 147.47, 147.63, 148.01, 148.72, 150.19, 151.89, 152.22, 152.35, 156.51; ES-MS m/z 535 $[M + H]^+$; Anal. Calcd for $C_{27}H_{25}F_6N_5$: C, 60.78; H, 4.72; N, 13.13; found: C, 60.72; H, 4.69; N, 13.09.

4.3.22. (3-(7-Trifluoromethyl-quinolin-4-ylamino)propyl)isatin (**28**)

Yield 72%; mp 138–140 °C; IR (KBr, cm^{-1}): 1738, 1619; ^{1}H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ 2.07–2.10 (m, 2H, CH_2), 3.45–3.49 (m, 2H, CH_2), 3.87–3.90 (m, 2H, CH_2), 6.25 (br s, 1H, N*H* D_2O exchangeable), 6.49–6.50 (d, J = 5.0 Hz, 1H, Ar-*H*), 6.92–6.93 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.16–1.79 (dd, J = 5.0, 10.0 Hz, 1H, Ar-*H*), 7.53–7.64 (m, 4H, Ar-*H*), 8.11–8.13 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.22 (s, 1H, Ar-*H*); ^{13}C NMR (DMSO-d_6 + $CDCl_3$): δ 25.60, 37.21, 38.89, 99.58, 110.04, 117.73, 120.36, 121.44, 124.33, 125.83, 127.26, 127.46, 128.79, 138.60, 147.89, 149.16, 150.09, 152.12, 159.13, 167.79, 182.83; ES-MS m/z 400 $[M + H]^+$; Anal. Calcd for $C_{21}H_{16}F_3N_3O2$: C, 63.16; H, 4.04; N, 10.52; found: C, 63.20; H, 4.07; N, 10.54.

4.3.23. 4-Chloro-(3-(7-trifluoromethyl-quinolin-4-ylamino)-propyl)isatin (**29**)

Yield 69%; mp 135–137 °C; IR (KBr, cm^{-1}): 1725, 1625; ^{1}H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ 2.10–2.13 (m, 2H, CH_2), 3.37–3.41 (m, 2H, CH_2), 4.32–4.35 (m, 2H, CH_2), 6.41–6.42 (d, J = 5.0 Hz, 1H, Ar-*H*), 6.94–6.95 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.05 (br s, 1H, N*H* D_2O exchangeable), 7.31–7.34 (dd, J = 5.0, 10.0 Hz, 1H, Ar-*H*), 7.43–7.45 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.04 (s, 1H, Ar-*H*), 7.56–7.58 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.20–8.22 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.46–8.47 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR (DMSO-d_6 + $CDCl_3$): δ 25.88, 37.21, 68.22, 109.11, 114.70, 119.20, 121.17, 123.15, 123.35, 124.84, 125.31, 126.71, 126.74, 132.78, 138.97, 147.70, 150.17, 152.20, 152.26, 157.91, 180.43; ES-MS m/z 435 $[M + H]^+$; Anal. Calcd for $C_{21}H_{15}ClF_3N_3O_2$: C, 58.14; H, 3.49; N, 9.69; found: C, 58.11; H, 3.52; N, 9.72.

4.3.24. 4-Bromo-(3-(7-trifluoromethyl-quinolin-4-ylamino)-propyl)isatin (**30**)

Yield 57%; mp 88–90 °C; IR (KBr, cm^{-1}): 1737, 1615; ^{1}H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ 1.87–1.91 (m, 2H, CH_2), 3.17–3.20 (m, 2H, CH_2), 3.62–3.65 (m, 2H, CH_2), 6.18–6.19 (d, J = 5.0 Hz, 1H, Ar-*H*), 6.53 (br s, 1H, N*H* D_2O exchangeable), 6.60–6.61 (d, J = 5.0 Hz, 1H, Ar-*H*), 6.87–6.88 (d, J = 5.0 Hz, 1H, Ar-*H*), 6.98–6.99 (d, J = 5.0 Hz, 1H, Ar-*H*), 7.24–7.26 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.85 (s, 1H, Ar-*H*), 7.90–7.92 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.25–8.26 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR (DMSO-d_6 + $CDCl_3$): δ 25.12, 37.94, 39.38, 99.49, 109.38, 116.14, 119.22 (2C), 120.83 (2C), 120.99 (2C), 122.54, 126.72 (2C), 128.05, 138.16, 149.68, 151.97, 157.76, 180.51; ES-MS m/z 479 $[M + H]^+$; Anal. Calcd for $C_{21}H_{15}BrF_3N_3O_2$: C, 52.74; H, 3.16; N, 8.79; found: C, 52.69; H, 3.12; N, 8.77.

4.3.25. 6-Chloro-(3-(7-trifluoromethyl-quinolin-4-ylamino)-propyl)isatin (**31**)

Yield 58%; mp 116–118 °C; IR (KBr, cm^{-1}): 1735, 1633; ^{1}H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ 2.10–2.14 (m, 2H, CH_2), 3.38–3.41 (m, 2H, CH_2), 3.81–3.85 (m, 2H, CH_2), 6.43–6.44 (d, J = 5.0 Hz, 1H, Ar-*H*), 6.94–6.95 (d, J = 5.0 Hz, 1H, Ar-*H*), 6.96 (br s, 1H, N*H* D_2O exchangeable), 7.03–7.05 (d, J = 10.0 Hz, 1H, Ar-*H*), 7.52–7.55 (dd, J = 5.0, 10.0 Hz, 1H, Ar-*H*), 7.56–7.58 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.04 (s, 1H, Ar-*H*), 8.22–8.24 (d, J = 10.0 Hz, 1H, Ar-*H*), 8.44–8.45 (d, J = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR (DMSO-d_6 + $CDCl_3$): δ 25.64, 38.38, 39.60, 99.91, 11.45, 116.21, 119.20, 121.21 (2C), 123.38 (2C), 123.62, 126.06, 126.75, 144.09, 147.78, 150.18, 151.87, 152.25, 158.69, 182.07; ES-MS m/z 435 $[M + H]^+$; Anal. Calcd for $C_{21}H_{15}ClF_3N_3O_2$: C, 58.14; H, 3.49; N, 9.69; found: C, 58.18; H, 3.44; N, 9.72.

*4.3.26. 6-Bromo-(3-(7-trifluoromethyl-quinolin-4-ylamino)-propyl)isatin (**32**)*

Yield 59%; mp 116–118 °C; IR (KBr, cm^{-1}): 1729, 1628; ^1H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ 2.10–2.13 (m, 2H, CH_2), 3.45–3.48 (m, 2H, CH_2), 3.86–3.89 (m, 2H, CH_2), 6.13 (br s, 1H, N*H* D_2O exchangeable), 6.49–6.50 (d, *J* = 5.0 Hz, 1H, Ar-*H*), 7.29–7.32 (dd, *J* = 5.0, 10.0 Hz, 1H, Ar-*H*), 7.42–7.43 (d, *J* = 5.0 Hz, 1H, Ar-*H*), 7.59–7.61 (d, *J* = 10.0 Hz, 1H, Ar-*H*), 8.07–8.09 (d, *J* = 10.0 Hz, 1H, Ar-*H*), 8.21 (s, 1H, Ar-*H*), 8.69–8.70 (d, *J* = 5.0 Hz, 1H, Ar-*H*); ^{13}C NMR (DMSO-d_6 + $CDCl_3$): δ 24.99, 36.29, 39.01, 99.69, 113.75, 115.83, 120.42, 120.68, 121.32, 122.89, 127.59 (2C), 128.79 (2C), 133.93, 149.10, 150.90, 151.26, 152.11, 159.13, 191.56; ES-MS *m*/*z* 479 $[M + H]^+$; Anal. Calcd for $C_{21}H_{15}BrF_3N_3O_2$: C, 52.74; H, 3.16; N, 8.79; found: C, 52.70; H, 3.12; N, 8.73.

4.4. Cell lines

The human MDA-MB231 and MCF-7 breast cancer cell lines were maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum (Hyclone, Logan UT) and 2 mM L-glutamine. MCF10A immortalized breast cells were maintained in mammary epithelial basal medium supplemented with an MEGM mammary epithelial singlequot kit (Cambrex). Cells were grown at 37 °C with 5% CO_2, 95% air under the humidified conditions.

4.5. Reagents

Chloroquine diphosphate and cisplatin were purchased from Sigma–Aldrich Canada Ltd. (Oakaville, ON, Canada). All the compounds were dissolved in 10–20 mM dimethyl sulfoxide (DMSO) and stored at −20 °C until use. The stock solution was diluted in culture medium (0.1–100 μM) immediately before use. The final concentration of DMSO in the SRB-based cytotoxicity assays did not exceed 0.1%. To rule out that the DMSO concentration used may affect cell proliferation, culture medium containing equivalent concentration of DMSO was used as a negative control in all experiments. In all studies, the concentration of DMSO used did not notably show any antiproliferative effect.

4.6. SRB assay

Antiproliferative effects were determined by a Sulphorhodamine B (SRB)-based protocol [22–25]. For a typical screening experiment, 5000–10,000 cells were inoculated into 100 μl medium per well of a 96-well microtiter plate as described previously [24,25]. Briefly, after the inoculation, the microtiter plate was incubated at 37 °C, 5% CO_2, 95% air and 100% relative humidity for 24 h, prior to addition of experimental drugs. Some of the sample wells were fixed with 25 μl of 50% tricholoroacetic acid (TCA) as a control of the cell population for each cell line at the time of drug addition (Tz). An aliquot of the frozen stock was thawed and diluted to the desired final maximum test-concentration with complete medium. Two–ten-fold serial dilutions were made to provide a total of seven drug concentrations (and a control [C]). Following addition of drugs, the culture plate was incubated for additional 48 h. Cells were fixed *in situ* by slowly adding 25 μl of ice-cold 50% (w/v) TCA (final concentration, 10% TCA), and were then incubated for 60 min at 4 °C. The supernatant was discarded, and the plate was washed five times with tap water, followed by air-dry. 50 μl of SRB solution at 0.4% (w/v) in 1% acetic acid was added to each well, and the plate was incubated for >30 min at room temperature. Unbound SRB was removed by five washes with tap water, followed by air-drying. The cells "stained" with SRB were solubilized with 10 mM trizma base, and the absorbance was read on an automated plate reader at a wavelength of 515–564 nm. The relative growth rate (%) was calculated for each of the compound concentrations according to the following formula:

$$(\mathrm{Ti} - \mathrm{Tz})/(C - Tz) \times 100$$

In the formula, time zero (Tz), control growth (C), and OD for different concentration of tested compounds (Ti). The GI_{50} for each compound was obtained from a non-linear Sigmoidal dose-response (variable slope) curve which is fitted by GraphPad Prism v.4.03 software. Values were calculated for each of these parameters if the level of activity was reached. However, if the effect was not reached or was exceeded, the value for that parameter was expressed as greater or less than the maximum or minimum concentration tested.

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