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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

A synthetic approach and molecular docking study of hybrids of quinazolin-4-ones and thiazolidin-4-ones as anticancer agents

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Abstract A series of 3-(4-(2-(aryl)-4-oxothiazolidin-3-yl) phenyl-2-phenylquinazolin-4(3*H*)-one derivatives were synthesized in appreciable yield by using anthranilic acid as a starting material. The structures of synthesized compounds (QT1–QT10) were confirmed on the basis of various spectral techniques and analytical methods. These synthesized compounds were screened for their in vitro antitumor activity against the human breast cancer cell line (MCF-7), human hepatocellular cancer cell line (HepG2) using MTT assay method and doxorubicin as a standard drug. Compound 3-(4-(2-(3-chlorophenyl)-4-oxothiazolidin-3-yl) phenyl-2-phenylquinazolin-4(3*H*)-one (QT4) showed comparable cytotoxic activity against Hep-G2 cell line. Compound 3-(4-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl) phenyl-2-phenylquinazolin-4(3*H*)-one (QT5) showed comparable cytotoxic activity against MCF-7 cell line while QT6, QT7, QT8 were the less cytotoxic as they showed high IC_{50} and away from that of doxorubicin. The remaining compounds did not show significant activity against both the cell lines. To understand the interaction of series with active binding site of receptor, docking study was performed with topoisomerase-II co-crystallized with adenylyl-imidodiphosphate complex using AutoDockVina. There was a good correlation between in vitro and in silico study. Thus, this investigation leads to the identification of newer anticancer agents.

Keywords Quinazolin-4-one · Thiazolidin-4-one · MCF-7 · Hep-G2 · Molecular docking

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Introduction

Cancer is one of the deathliest diseases in the medical field intercontinental, characterized by uncontrolled, rapid, and pathological proliferation of abnormal cells. It is one of the key challenges which concern the medical territory all over the world (Jerry and Woodring 2006). It represents the second leading crusade of human mortality after cardiovascular diseases (Bandgar et al. 2010). According to information from the World Health Organization (WHO), it is estimated that there will be 12 million deaths from cancer in 2030. World statistics on cancers have revealed that hepatocarcinoma is the sixth most common malignancy, which is highly defiant to chemotherapeutic treatment resulting in increased mortality rates (Gali et al. 2014). The human liver cancer cell line HepG2, established in 1979, is the best characterized and most frequently used cell line to predict overall hepatotoxicity (Niklas et al. 2009). Breast cancer is the most commonly diagnosed malignant tumor in women and accounting for approximately 23% of all female

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cancers and the second most fatal cancer in women worldwide today (Siegel et al. 2011). To date, both of liver cancer and breast cancer are belligerent and correlated with overall poor prognosis. Therefore, the search for potent, safe, and selective anticancer compounds is a crucial aspect of modern cancer research.

Quinazoline is 1,3-diazanaphthalene, also familiar as 5,6-benzopyrimidine or benzo[a]pyrimidine, or phenmiazine (Merck Index 2001), and its 4-oxo derivative is called 4 (3*H*)-quinazolinone (Reddy et al. 2003; El-Hiti 2000; El-Hiti; Abdel-Megeed 2005). It has been stupendously utilized as a drug-like template in medicinal chemistry. Quinazolinone and their derivatives (Khan et al. 2014) are also elementary unit for approximately 150 naturally occurring alkaloids secluded from a number of families of the plant kingdom, from microorganisms and animals. 4(3*H*)-quinazolinones have been allied with a broad spectrum of pharmacological activities, such as analgesic (Aly et al. 2010), antimicrobial (Jatav et al. 2006; Tiwari et al. 2012), antitumor (El-Azab et al. 2010; Georgey and Gawad 2010), anticancer (Giri et al. 2010), anti-inflammatory (Kumar and Rajput 2009; Zayed and Hassan 2014), anticonvulsant (Kashaw et al. 2009; Zayed 2014), protein tyrosine kinase inhibitors (Sumegi et al. 2007) and, antimalarial (Zhu et al. 2010). Interest in quinazolinones as anticancer agents has further heightened since the discovery of Raltitrexed and Thymitaq and their activity as Thymidylate enzyme inhibitors (Bavetsias et al. 1997).

Thiazolidin-4-one a saturated form of thiazole with carbonyl group on fourth carbon occupies an important place in medicinal chemistry (Verma and Saraf 2008). Moreover, thiazolidin-4-one derivatives are also reported to have important biological activities such as anti-inflammatory (Taranalli et al. 2008; Hu et al. 2013), anti-tuberculosis (Karali et al. 2007), anticancer (Kaminskyy et al. 2012), antitumor (Havrylyuk et al. 2012; Wang et al. 2011), anti-HIV (Balzarini et al. 2009), antibacterial (Dwivedi et al. 2012), antifungal (Omar et al. 2010), antimicrobial (Deep et al. 2014), antioxidant (Shih and Ke 2004), antiviral (Terziog˘lu et al. 2006), antiamoebic (Mushtaque et al. 2012), anticonvulsant (Ragab et al. 1997; Velmurugan et al. 2012), anti-alzheimer (Sadashiva and Chandra 2009), diuretics (Raikwar et al. 2008), nematicidal (Srinivas et al. 2008), antihistaminic activity (Diurno et al. 1992) etc.

A comprehensive literature survey indicated that the presence of these two pharmacophore i.e., quilazoline and thiazolidinone, plays an important role in enhancement of activity. A lot of attention has been paid to the concept of hybrid synthesis rather than one active pharmacophore. It is supposed that hybrid may lead to multiple targeting effects.

In our present study, we incorporated thiazolidinone with quinazoline to target breast cancer as well as hepatic cancer cells.

Result and discussion

Chemistry

Quinazolin-4-one linked to thiazolidinones was synthesized by cyclo-condensation of the Schiff base with thioglycholic acid in dimethyl formamide in presence of anhydrous zinc chloride. Treatment of (0.01 mol) of anthranilic acid with (0.02 mol) of benzoyl chloride in pyridine affords 2-phenyl-4*H*-benzo[d] [1,3] oxazin-4-one(2). Fusion of benzoxazinone (2) with *p*-phenylenediamine in presence of pyridine yield 3-(4-aminophenyl)-2-phenyl- quinazolin-4(3*H*)-one. Then on reaction with substituted aromatic aldehydes converted to Schiff bases (4), which on cyclization with thioglycolic acid gave 3-(4-(2-(aryl)-4-oxothiazolidine-3-yl)phenyl-2-phenylquinazolin-4(3*H*)-one derivatives (Scheme 1). The structures were confirmed on the basis of analytical data and spectroscopic measurements.

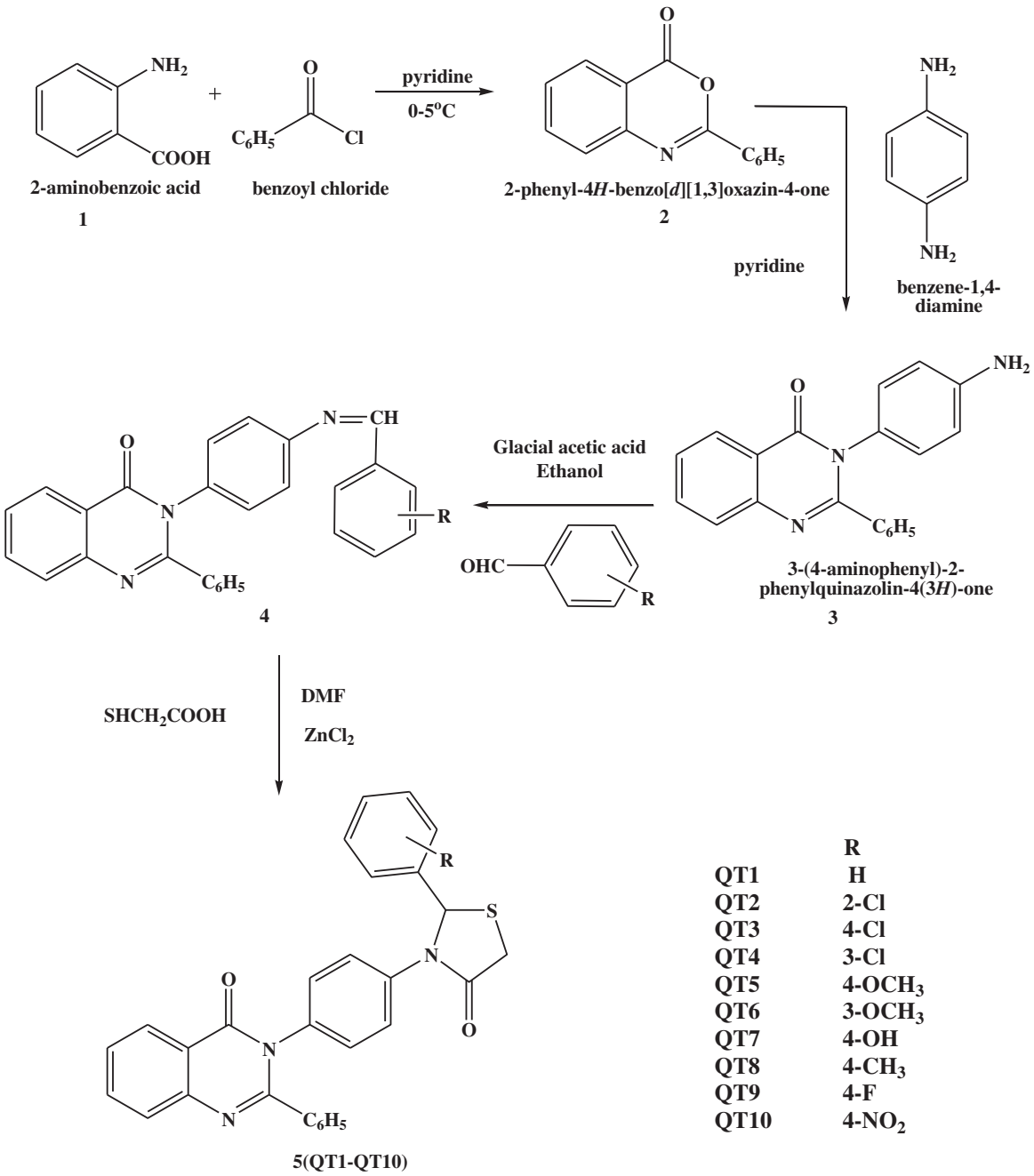
Biological screening

All the synthesized compounds were screened for their in vitro cytotoxic and growth inhibitory activities against MCF-7 and Hep-G2 cell lines using MTT assay method in comparison with the activity of the known anticancer drug doxorubicin (Table 1). The cytotoxic activities of our tested compounds were expressed as IC_{50} values (the dose that reduces survival to 50%). From the in vitro studies, it can be inferred that both position and electronegativity of the substituents on the phenyl ring plays an important role in selectivity and activity of the synthesized compounds against both hepatic as well as breast cancer cell line. It has been observed in literature that there is significant decrease in cytotoxic activity when chloro group is replaced by relatively strong electron-withdrawing substituent like fluoro group. Thus, QT9 is less effective than QT4. In the given study, a group having positive R effect and substituent specifically at *m*-position found to be most active against hepatic cell line QT4 (IC_{50}-1.79 µg/ml). On the other hand, for good activity against breast cancer cell line MCF-7, phenyl ring should be substituted at *p*-position with a group having positive R effect QT5 (IC_{50}-1.94 µg/ml).

The IC_{50} for the standard drug was found to be 0.09 µg/ml. QT4 and QT5 exhibited excellent cytotoxicity. QT6, QT7, QT8 showed less cytotoxic activity. Other compounds were found to be ineffective against both cancer cell lines.

Molecular docking study

After in vitro evaluation, it was thought worthy to study the interaction of synthesized compounds QT1 to QT10 with topoisomerase-II using molecular docking. The purpose of the study was to screen the synthesized compounds in vitro



Scheme 1 Synthesis of 3-(4-(2-(aryl)-4-oxothiazolidin-3-yl)phenyl-2-phenylquinazolin-4(3H)-ones

as well as in silico. Considering 1ZXM as target, the compounds were docked to get the best in silico confirmations (Shukla et al. 2013).

In the present study, H-bonding and free-binding energy say, dock score were considered for the analysis. In silico study revealed all the synthesized compounds to have good binding energy in the range of −9.5 to −10.3 kcal/mol. Among the series, compounds QT4 and QT5 possessed best dock score of −10.3 kcal/mol and −10.2 kcal/mol, respectively, and also comparable to the standard doxorubicin (−10.2 kcal/mol). It was observed that the presence of chloro group at meta position may become more selective towards the topoisomerase-II activity. The main amino acids which played a vital role in interaction are Tyr72, Gln310, Gln59 and Arg241. The data of dock score and interactive amino acids of all the synthesized compounds is provided in (Table 2). The interactions with the target receptor shown by QT4, QT5, and doxorubicin are displayed, respectively, (Figs. 1, 2, and 3). The electrostatic potential surface diagram for receptor with the overlay of all

Table 1 Results of in vitro cytotoxic activity of the synthesized compounds and doxorubicin on human breast carcinoma cell line (MCF-7) and human hepatocellular carcinoma cell line (Hep-G2)

Sr. No.	Compounds	IC_{50} (μg/ml) MCF-7	IC_{50} (μg/ml) Hep-G2
1	**QT4**	–	1.79
2	**QT5**	1.94	–
3	**QT6**	8.57	–
4	**QT7**	8.54	–
5	**QT8**	8.78	–
6	Doxorubicin	0.09	0.09

the synthetic ligands at their binding pose is shown on Fig. 4. From the docking study, we predicted that the compounds QT4 and QT5 have comparable anticancer activity with respect to doxorubicin while QT7 and QT8 also possessed good anticancer activity than other compounds of the series.

Conclusion

In this study, a series of 3-(4-(2-(aryl)-4-oxothiazolidin-3-yl)phenyl-2-phenylquinazolin-4(3*H*)-one derivatives were synthesized and characterized. Compound QT4 showed comparable cytotoxic activity against Hep-G2 cell line and compound QT5 showed comparable cytotoxic activity against MCF-7 cell line while QT7 and QT8 also possessed good anticancer activity than other compounds of the series.

The most significant finding came out from this study was the role of electronegativity and position of substituents for their selectivity and potency. This can be further exploited for the exploration of more potent-specific chemotherapeutic agents against liver and breast tumors. Also, molecular docking studies helped further to establish the in vitro results through binding energy calculations and binding mode predictions.

Experimental

Chemistry

All the chemicals and reagents were of analytical grade and used without further purification. Melting points of the synthesized compounds were determined by Decibel melting point apparatus and were uncorrected. All reactions were monitored by thin-layer chromatography (TLC) using silica gel G. The plates were developed by exposing to iodine chamber. Infrared spectra were recorded by Perkin Elmer IR spectrophotometer using KBr pellets. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) were recorded on BrukerAvance II 400 NMR Spectrophotometer. Chemical shifts are expressed as δ values (ppm), downfield from tetramethylsilane used as internal standard. Elemental analyses were carried out on Carlo Erba1106 CHN Analyzer. Mass spectra of the compounds were carried out on API-4000 Quadrupole Mass Spectrometer.

Table 2 Amino-acid interactions and the binding scores of the docked compounds

Sr. No.	Compounds	Dock score	No. of H-bond	Amino acid
1	**QT1**	−9.7	–	–
2	**QT2**	−9.8	–	–
3	**QT3**	−9.5	1	Tyr72
4	**QT4**	**−10.3**	1	Tyr72
5	**QT5**	**−10.2**	1	Tyr72
6	**QT6**	−9.9	1	Gln310
7	**QT7**	−10.1	1	Tyr72
8	**QT8**	−10.1	–	–
9	**QT9**	−9.8	1	Tyr72
10	**QT10**	−9.6	1	Gln59
11	Doxorubicin	**−10.2**	2	Gln59, Arg241

Bold values represent the highest dock scorer among the series with respect to standard

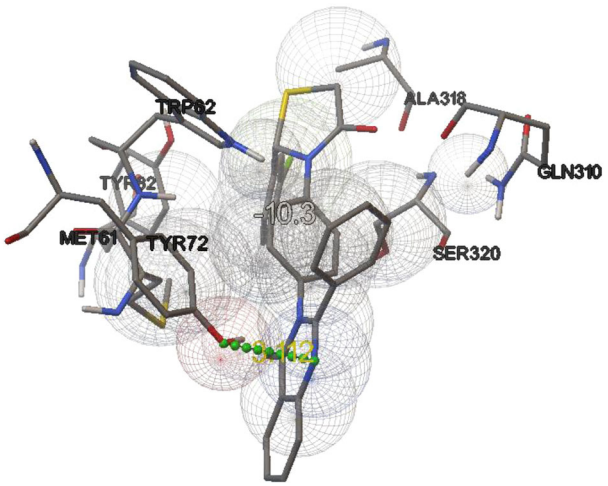


Fig. 1 Binding pose for compound QT4 within the ATPase domain of topoisomerase-II showing hydrogen bonding in dashed *green line* (Color figure online)

Synthesis of 2-phenyl-4H-benzo[d] [1,3] oxazin-4-one (2)

To a stirred solution of anthranilic acid (0.01 mol) in pyridine (25 ml), benzoyl chloride (0.02 mol) was added dropwise, maintaining temperature near 0–5 °C for about 1 h. The reaction mixture was stirred for another 2 h at room temperature until a solid product was formed. The reaction mixture was neutralized with saturated sodium carbonate

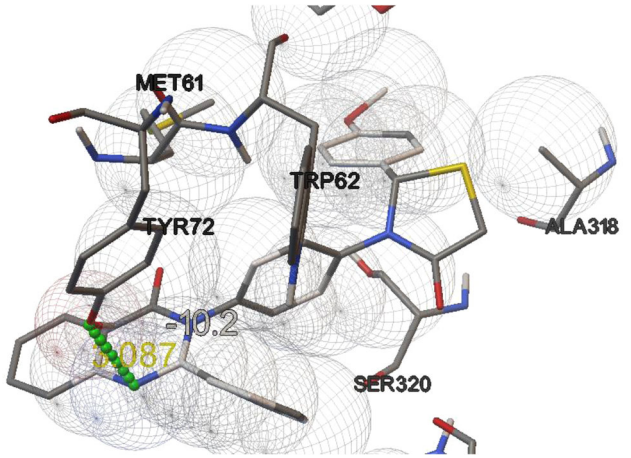


Fig. 2 Binding pose for compound QT5 within the ATPase domain of topoisomerase-II showing hydrogen bonding in dashed *green line* (Color figure online)

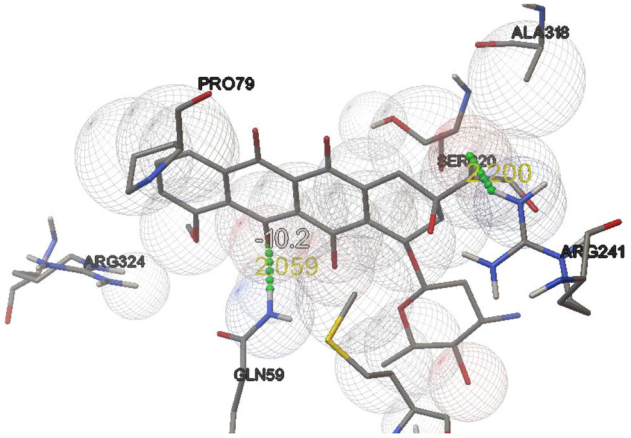


Fig. 3 Binding pose for compound doxorubicin within the ATPase domain of topoisomerase-II showing hydrogen bonding in dashed *green line* (Color figure online)

solution and the separated pale yellow solid was filtered (Salih 2008).

Synthesis of 3-(4-aminophenyl)-2-phenylquinazolin-4(3H)-one (3)

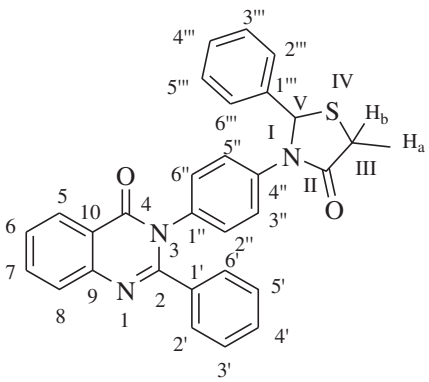
To a stirred solution of 2-phenyl-4*H*-benzo[d] [1,3] oxazin-4-one (0.01 mol) in pyridine, *p*-phenylenediamine (0.01 mol) was added. The reaction mixture was stirred and refluxed for 14 h. The completion of reaction was monitored by TLC. After the completion of the reaction it was poured in iced water, filtered, and dried. The product was recrystallized from ethanol.

Synthesis of Schiff bases (4)

3-(4-aminophenyl)-2-phenylquinazolin-4(3*H*)-one (0.01 mol) and substituted benzaldehyde were dissolved in ethanol (30 ml) by the addition of few drops of glacial acetic acid. The reaction mixture was refluxed for 6 h on a water bath and poured into ice cold water. The separated solid was filtered, washed, and recrystallized from ethanol.

*Synthesis of 3-(4-(2-(aryl)-4-oxothiazolidine-3-yl)phenyl-2-phenylquinazolin-4(3*H*)-one derivatives (5)*

Schiff bases (0.01 mol) were dissolved in dry DMF, containing a pinch of anhydrous zinc chloride and thioglycolic acid (0.01 mol) and refluxed for 8 h. The reaction mixture was cooled and then poured into ice cold water. The separated solid was filtered, and recrystallized from ethanol (Jain et al. 2011).



*3-(4-(4-oxo-2-phenylthiazolidin-3yl)phenyl)-2-phenylquinazolin-4(3H)-one (**QT1**)*

Yield 48%; mp > 300 °C; IR (KBR) ν_{max} 3060 (CH aromatic), 1721 (C=O), 1602.53 (C=N), 1327.02 (C–N); ^{1}H NMR (300 MHz, DMSO-d$_6$) $\delta = 3.33$ (1H, dd, H-III$_b$), 3.43 (1H, dd, H-III$_a$), 5.92 (1H, s, H-V), 7.05–7.15 (7H, m, H-2‴ to H-6‴, H-3″, H-5″), 7.23–7.29 (3H, m, H-3′, H-4′, H-5′), 7.41–7.51 (3H, m, H-6, H-7, H-8), 7.71–7.90 (5H, m, H-2′, H-6′, H-2″, H-6″, H-5); ^{13}C NMR (DMSO-d$_6$) $\delta = 171.2$ (N–CO–C), 164.1 (N=C–N), 160.9 (N–CO–C), 151.3 (C–N), 139.2 (C-1‴) 137.3 (C–N), 133.5 (C-7), 130.2 (C-4′), 129.1 (C-2′, C-6′), 128.9 (C-3′, C-5′) 128.8 (C-5, C-2‴, C-6‴), 128.7 (C1′, C-3‴), 128.4 (C–N), 127.7 (C-5‴), 127.4 (C-6), 127.2 (C-4‴), 122.4 (C-8), 121.8 (C-2″, C-3″, C-5″, C-6″), 120.9 (C-10), 65.6 (N–C–S), 33.6 (CH$_2$); MS: $m/z =$ 475.14; Anal. Calcd for: $C_{29}H_{21}N_3O_2S$: C, 73.24; H, 4.45; N, 8.84 %. Found C, 73.20; H, 4.42; N, 8.80%.

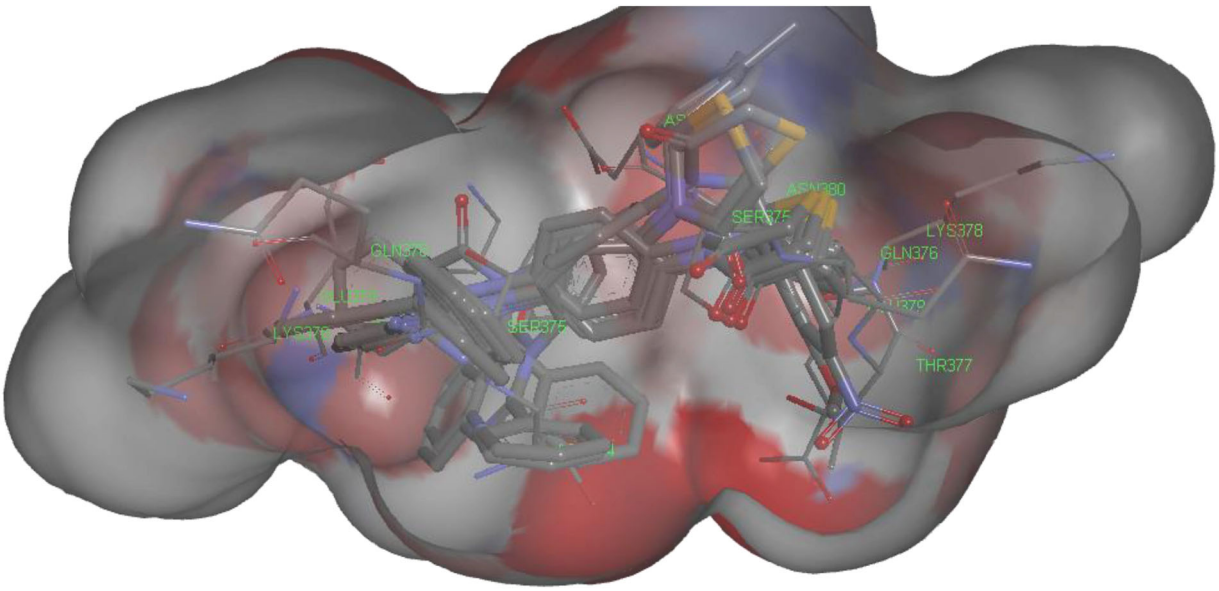


Fig. 4 Electrostatic potential surface diagram for receptor protein (PDB ID: 1ZXM) with the overlay of ligands at their binding pose

*3-(4-(2-(2-chlorophenyl)-4-oxothiazolidin-3yl)phenyl)-2-phenylquinazolin-4(3H)-one (**QT2**)*

Yield 52%; mp > 300 °C; IR (KBR) ν_{max} 3059.76 (CH aromatic), 1719.74 (C=O), 1602.67 (C=N), 1306.71 (C–N), 790 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.35 (1H, dd, H-III$_b$), 3.47 (1H, dd, H-III$_a$), 5.95 (1H, s, H-V), 7.00–7.15 (6H, m, H-3‴ to H-6‴, H-3″, H-5″), 7.29 (3H, m, H-3′, H-4′, H-5′), 7.41–7.52 (3H, m, H-6, H-7, H-8), 7.69–7.89 (5H, m, H-2′, H-6′, H-2″, H-6″, H-5); ^{13}C NMR (DMSO-d_6) δ = 171.4 (N–CO–C), 165.0 (N=C–N), 161.0 (N–CO–C), 151.5 (C–N), 137.5 (C–N), 134.1 (C–Cl), 130.2 (C-6‴), 130.1 (C-4′), 129.4 (C-2′, C-6′), 129.0 (C-3′, C-5′), 128.9 (C-5, C-2‴, C-6‴), 128.8 (C-1′), 128.8 (C-3‴), 128.6 (C-4‴), 128.5 (C–N), 127.9 (C-5‴), 127.5 (C-6), 127.1 (C-4‴), 126.8 (C-5‴), 122.2 (C-8), 121.6 (C-2″, C-3″, C-5″, C-6″), 120.4 (C-10), 56.6 (N–C–S), 33.4 (CH_2); MS: m/z = 509.10; Anal. Calcd for: $C_{29}H_{20}ClN_3O_2S$: C, 68.30; H, 3.95; N, 8.24%. Found C, 68.27; H, 3.92; N, 8.19%.

*3-(4-(2-(4-chlorophenyl)-4-oxothiazolidin-3yl)phenyl)-2-phenylquinazolin-4(3H)-one (**QT3**)*

Yield 49%; mp > 300 °C; IR (KBR) ν_{max} 3058.82(CH aromatic), 1723.53 (C=O), 1606.02 (C=N), 1323.80 (C–N), 750–698 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.39 (1H, dd, H-III$_b$), 3.40 (1H, dd, H-III$_a$), 5.92 (1H, s, H-V), 7.01 (2H, dd, H-2‴, H-6‴), 7.15 (2H, dd, H-3‴, H-5′ ″), 7.20–7.25 (2H, m, H-3″, H-5″), 7.30–7.49 (6H, m, H-6 to H-8, H-3′ to H-5′), 7.61–7.90 (5H, m, H-2′, H-6′, H-2″, H-6″, H-5); ^{13}C NMR (DMSO-d_6) δ = 171.6 (N–CO–C), 165.2 (N=C–N), 161.3 (N–CO–C), 151.6 (C–N), 137.8 (C–N), 137.3 (C-1‴), 133.2 (C-7), 132.7 (C–Cl), 130.2 (C-2‴, C-6‴), 130.0 (C-4′), 129.2 (C-2′, C-6′), 128.9 (C-3′, C-5′), 128.8 (C-5‴), 128.8 (C-3‴), 128.7 (C-5), 128.6 (C-1′), 128.4 (C–N), 127.3 (C-6), 122.1 (C-8), 121.4 (C-2″, C-3″, C-5″, C-6″), 120.2 (C-10), 66.1 (N–C–S), 33.2 (CH_2); MS: m/z = 509.10; Anal. Calcd for: $C_{29}H_{20}ClN_3O_2S$: C, 68.32; H, 3.98; N, 8.22%. Found C, 68.30; H, 3.95; N, 8.16%.

*3-(4-(2-(3-chlorophenyl)-4-oxothiazolidin-3yl)phenyl)-2-phenylquinazolin-4(3H)-one (**QT4**)*

Yield 56%; mp > 300 °C; IR (KBR) ν_{max} 3060.02 (CH aromatic), 1724.25 (C=O), 1605.48 (C=N), 1327.31 (C–N), 830 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.38 (1H, dd, H-III$_b$), 3.45 (1H, dd, H-III$_a$), 5.96 (1H, s, H-V), 6.95–7.08 (6H, m, H-2‴, H-4‴ to H-6‴, H-3″,H-5″), 7.31 (3H, m, H-3′, H-4′, H-5′), 7.43–7.51 (3H, m, H-6, H-7, H-8), 7.63–7.91 (5H, m, H-2′, H-6′, H-2″, H-6″, H-5); ^{13}C NMR (DMSO-d_6) δ = 171.3 (N–CO–C), 165.0 (N=C–N), 161.1 (N–CO–C), 151.3 (C–N), 140.6 (C-1‴), 137.6 (C–N), 134.2 (C–Cl), 133.1 (C-7), 130.1 (C-5‴), 129.9 (C-4′), 129.6 (C-2′, C-6′), 129.1 (C-3′, C-5′), 128.9 (C-5), 128.8 (C-1′), 128.6 (C-2‴), 128.5 (C–N), 127.5 (C-6), 127.3 (C-4‴), 126.9 (C-6‴), 122.5 (C-8), 121.2 (C-2″), 121.1 (C-3″, C-5″, C-6″), 120.5 (C-10), 65.1 (N–C–S), 33.5 (CH_2); MS: m/z = 509.10; Anal. Calcd for: $C_{29}H_{20}ClN_3O_2S$: C, 68.35; H, 3.92; N, 8.19%. Found C, 68.27; H, 3.90; N, 8.13%.

*3-(4-(2-(4-methoxyphenyl)-4-oxothiazolidin-3yl)phenyl)-2-phenylquinazolin-4(3H)-one (**QT5**)*

Yield 59.41%; mp > 300 °C; IR (KBR) ν_{max} 3060.01(CH aromatic), 1715.10 (C=O), 1607.49 (C=N), 1305.12 (C–N), 1280–1253 (C–O–C);^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 3.40$ (1H, dd, H-III$_b$), 3.48 (1H, dd, H-III$_a$), 3.73 (3H,s, OCH_3), 5.97 (1H, s, H-V), 6.65 (2H, dd, H-3‴, H-5‴), 6.95 (2H, dd, H-2‴, H-6‴), 7.10–7.15 (2H, m, H-3″, H-5″), 7.32–7.45 (6H, m, H-6 to H-8, H-3′ to H-5′), 7.63–7.92 (5H, m, H-2′, H-6′, H-2″, H-6″, H-5);^{13}C NMR (DMSO-d_6) $\delta = 171.7$ (N–CO–C), 165.1 (N=C–N), 161.2 (N–CO–C), 159.1 (C-OCH_3), 151.7 (C–N), 137.4 (C–N), 133.1 (C-7), 131.5 (C-1‴), 130.1 (C-4′), 129.8 (C-2‴), 129.8 (C-6‴), 129.3 (C-2′, C-6′), 128.9 (C-3′, C-5′), 128.8 (C-1′, C-5), 128.6 (C–N), 127.7 (C-6), 122.5 (C-8), 121.2 (C-2″), 121.1 (C-3″, C-5″, C-6″), 120.5 (C-10), 114.2 (C-5‴), 114.2 (C-3‴),65.6 (N–C–S), 55.9 (CH_3), 33.5 (CH_2); MS: $m/z = 505.15$; Anal. Calcd for: $C_{30}H_{23}N_3O_3S$: C, 71.27; H, 4.59; N, 8.37%. Found C, 71.22; H, 4.53; N, 8.33%.

*3-(4-(2-(3-methoxyphenyl)-4-oxothiazolidin-3yl)phenyl)-2-phenylquinazolin-4(3H)-one (**QT6**)*

Yield 62.5%; mp > 300 °C; IR (KBR) ν_{max} 3063.29 (CH aromatic), 1721.12 (C=O), 1604.68 (C=N), 1323.75 (C–N) 1250 (C–O–C); ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 3.46$ (1H, dd, H-III$_b$), 3.50 (1H, dd, H-III$_a$), 3.76 (3H,s, OCH_3), 5.97 (1H, s, H-V), 6.57–6.62 (3H, m, H-2‴, H-4‴, H-6‴), 7.03–7.08 (3H, m, H-5‴,H-3″, H-5″), 7.28–7.51 (6H, m, H-6 to H-8, H-3′ to H-5′), 7.62–7.89 (5H, m, H-2′, H-6′, H-2″, H-6″, H-5); ^{13}C NMR (DMSO-d_6) $\delta = 171.5$ (N–CO–C), 165.2 (N=C–N), 161.3 (N–CO–C), 160.6 (C–OCH_3), 151.5 (C–N), 140.2 (C-1‴), 137.6 (C–N), 133.2 (C-7), 131.2 (C-4′), 129.9 (C-2′, C-6′), 129.7 (C-5‴), 129.0 (C-3′, C-5′), 128.9 (C-5), 128.7 (C-1′), 128.5 (C–N), 127.3 (C-6), 122.7 (C-8), 121.4 (C-2″, C-3″, C-5″, C-6″), 121.1 (C-6‴),120.5 (C-10), 112.8 (C-2‴), 112.7 (C-4‴), 65.9 (N–C–S), 55.8 (CH_3), 33.6 (CH_2); MS: $m/z = 505.15$; Anal. Calcd for: $C_{30}H_{23}N_3O_3S$: C, 71.25; H, 4.61; N, 8.31%. Found C, 71.20; H, 4.55; N, 8.29%.

*3-(4-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3yl)phenyl)-2-phenylquinazolin-4(3H)-one (**QT7**)*

Yield 54.32%; mp > 300 °C; IR (KBR) ν_{max} 3470–3320 (O–H), 3064.42 (CH aromatic), 1724.21 (C=O), 1602.62 (C=N), 1327.40 (C–N); ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 3.42$ (1H, dd, H-III$_b$), 3.49 (1H, dd, H-III$_a$), 5.94 (1H, s, H-V), 6.61 (2H, dd, H-3‴, H-5‴), 6.89 (2H, dd, H-2‴, H-6‴), 7.08–7.15 (2H, m, H-3″, H-5″), 7.30–7.46 (6H, m, H-6 to H-8, H-3′ to H-5′), 7.69–7.90 (5H, m, H-2′, H-6′, H-2″, H-6″, H-5), 10.1 (1H, s, OH); ^{13}C NMR (DMSO-d_6) $\delta = 171.2$ (N–CO–C), 165.4 (N=C–N), 161.4 (N–CO–C), 156.9 (C–OH), 151.3 (C–N), 137.6 (C–N), 133.1 (C-7), 131.8 (C-1‴), 130.2 (C-2‴), 130.2 (C-6‴), 130.1 (C-4′), 129.8 (C-2′,C-6′), 128.8 (C-3′, C-5′),128.7 (C-5, C-1′), 128.4 (C–N), 127.7 (C-6), 122.4 (C-8), 121.3 (C-2″, C-3″, C-5″, C-6″), 120.6 (C-10), 115.8 (C-3‴), 115.8 (C-5‴), 65.1 (N-C-S), 33.5 (CH_2); MS: $m/z = 491.13$; Anal. Calcd for: $C_{29}H_{21}N_3O_3S$: C, 70.86; H, 4.31; N, 8.55%. Found C, 70.82; H, 4.27; N, 8.51%.

*3-(4-(4-oxo-2-p-tolylthiazolidin-3yl)phenyl)-2-phenylquinazolin-4(3H)-one (**QT8**)*

Yield 57.2%; mp > 300 °C; IR (KBR) ν_{max} 3060.34 (CH aromatic), 1721.08 (C=O), 1601.32 (C=N), 1306.79 (C–N); ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 2.35$ (3H, s, CH_3), 3.48 (1H, dd, H-III$_b$), 3.51 (1H, dd, H-III$_a$), 5.89 (1H, s, H-V), 6.94–7.01 (4H, m, H-2‴, H-3‴ H-5‴, H-6‴), 7.05–7.12 (2H, m, H-3″, H-5″), 7.26–7.50 (6H, m, H-6 to H-8, H-3′ to H-5′), 7.61–7.88 (5H, m, H-2′, H-6′, H-2″, H-6″, H-5); ^{13}C NMR (DMSO-d_6) $\delta = 172.1$ (N-CO-C), 165.6 (N=C–N), 161.3 (N–CO–C), 151.6 (C–N), 137.3 (C–N), 136.8 (C-4‴), 136.2 (C-1‴), 133.5 (C-7), 131.1 (C-4′), 130.0 (C-2′, C-6′), 129.2 (C-3′, C-5′), 129.0 (C-3‴, C-5‴), 128.9 (C-1′), 128.8 (C-5), 128.7 (C-6‴, C-2‴), 128.5 (C–N), 127.3 (C-6), 122.6 (C-8), 121.8 (C-2″, C-3″, C-5″, C-6″), 120.5 (C-10), 65.1 (N–C–S), 33.5 (CH_2), 24.3 (CH_3); MS: $m/z = 489.15$; Anal. Calcd for: $C_{30}H_{23}N_3O_2S$: C, 73.60; H, 4.74; N, 8.58%. Found C, 73.52; H, 4.69; N, 8.52%.

*3-(4-(2-(4-fluorophenyl)-4-oxothiazolidin-3yl)phenyl)-2-phenylquinazolin-4(3H)-one (**QT9**)*

Yield 53%; mp > 300 °C; IR (KBR) ν_{max} 3061.36 (CH aromatic), 1713.93 (C=O), 1603.02 (C=N), 1307.22 (C–N), 1235 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 3.39$ (1H, dd, H-III$_b$), 3.46(1H, dd, H-III$_a$), 5.93 (1H, s, H-V), 6.85 (2H, dd, H-3‴, H-5‴), 7.04 (2H, dd, H-2‴, H-6‴), 7.10–7.16 (2H, m, H-3″, H-5″), 7.39–7.50 (6H, m, H-6 to H-8, H-3′ to H-5′), 7.65–7.93 (5H, m, H-2′, H-6′, H-2″, H-6′′, H-5); ^{13}C NMR (DMSO-d_6) $\delta = 171.8$ (N–CO–C), 165.3 (N=C–N), 161.6 (N–CO–C), 161.3 (C–F), 151.5 (C–N), 137.6 (C–N), 134.8 (C-1‴), 133.8 (C-7), 131.0 (C-4′), 130.4 (C-2‴, C-6‴), 130.2 (C-2′, C-6′), 129.1 (C-3′, C-5′), 128.7 (C-5, C-1′), 128.6 (C–N), 127.5 (C-6), 122.2 (C-8), 121.3 (C-2″, C-3″, C-5″, C-6″), 120.7 (C-10), 115.4 (C-3‴), 115.4 (C-3‴), 65.1 (N–C–S), 33.5 (CH_2); MS: $m/z = 493.15$; Anal, Calcd for: $C_{29}H_{20}FN_3O_2S$: C, 70.57; H, 4.08; N, 8.51%. Found C, 70.51; H, 4.01; N, 8.47%.

*3-(4-(2-(4-nitrophenyl)-4-oxothiazolidin-3yl)phenyl)-2-phenylquinazolin-4(3H)-one (**QT10**)*

Yield 61%; mp > 300 °C; IR(KBR) ν_{max} 3058.82 (CH aromatic), 1715.50 (C=O), 1603.43 (C=N), 1549, 1340 (NO_2) 1309.79 (C–N); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.31 (1H, dd, H-III$_b$), 3.42 (1H, dd, H-III$_a$), 5.98 (1H, s, H-V), 7.07–7.10 (2H, m, H-3″, H-5″), 7.32 (2H, dd, H-2‴, H-6‴), 7.36–7.48 (6H, m, H-6 to H-8, H-3′ to H-5′), 7.60–7.87 (5H, m, H-2′, H-6′, H-2″, H-6″, H-5), 8.07 (2H, dd, H-3‴, H-5‴); ^{13}C NMR (DMSO-d_6) δ = 171.6 (N–CO–C), 165.1 (N=C–N), 161.5 (N–CO–C), 151.3 (C–N), 146.8 (C–NO_2), 145.3 (C-1‴), 137.5 (C–N), 133.4 (C-7), 130.6 (C-4′), 129.9 (C-2′, C-6′), 129.7 (C-2‴, C-3′, C-5′, C-6‴), 128.9 (C-1′), 128.6 (C-5), 128.5 (C–N), 127.2 (C-6), 122.5 (C-8), 121.6 (C-2″, C-3″, C-5″, C-6″), 121.0 (C-3‴, C-5‴), 120.6 (C-10), 65.6 (N–C–S), 33.8 (CH_2); MS: *m/z* = 493.15; Anal. Calcd for: $C_{29}H_{20}N_4O_4S$: C, 66.91; H, 3.87; N, 10.76%. Found C, 66.86; H, 3.82; N, 9.45%.

Pharmacological screening

Cell culture and treatment

All reagents were handled in a sterile fume hood. Evaluation of anticancer activity was carried out in human breast cancer cell lines, MCF-7, human hepatocellular carcinoma cell lines, Hep-G2 purchased from National Cancer Center for Cell Science, Pune, India. The cells were cultured in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum at 37 °C in an atmosphere containing 5% CO_2. Unless otherwise mentioned, all the chemicals used in this study were from Sigma-Aldrich.

MTT assay

The effect of newly synthesized compounds on cell growth inhibition using MTT, a tetrazolium dye (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) assay. This assay quantifies the viable cells by observing the reduction of tetrazolium salt, MTT to purple formazan crystals by the live cells. Based on absorbance of the cell sample after the test is carried out, cell viable can be measured. Drug stock solutions were prepared in dimethyl sulfoxide (DMSO) (µg/ml) and further dilutions (0.01, 0.1, 0.5, 1, 2, 5, 10, 100 µg/ml) were prepared in medium. Cells were cultured at a density of 5×10^3cells /well in 96-well plates at 37 °C in 5.0 % CO_2 atmosphere and allowed to attach for 24 h. The cells were treated in triplicate with graded concentration of sample and reference drug doxorubicin at 37 °C for 24 h. A 20 µl aliquot of MTT solution was added directly to all the appropriate wells. Following 4 h incubation at 37 °C, the media was removed and formazan crystals, which results from the reduction of MTT by active cell were dissolved in 1000 µl DMSO and vigorously mixed to dissolve the reacted dye. The absorbance of each well was read on microplate reader (BIORAD) at 570/630 nm. The spectrometer was calibrated to zero absorbance using culture medium without cells (Slater et al. 1963; van de Loosdrecht et al. 1994; Alley et al. 1988). The relative cell viability (%) related to control well containing cell culture medium without drug was calculated by

$$\%\,\text{cell viablity} = \frac{[A]\text{test}}{[A]\text{control}} \times 100$$

The half maximal inhibitory concentration (IC_{50}) i.e., the concentration of a drug required for 50% inhibition of proliferation of MCF-7 and Hep-G2 cells in vitro. The calculations for IC_{50} were done and the values were reported as µg/ml.

Table 3 Coordinates of x, y and z of Grid Box of pdb ID: 1ZXM

Center_x	49.574
Center_y	3.731
Center_z	22.202
Size_x	30
Size_y	30
Size_z	30

Molecular modeling

AutoDockVina helps the ligand to dock into cavity of action site. The structure of topoisomerase-II co-crystallized with Adenylyl-imidodiphosphate complex (PDB id: 1ZXM) was downloaded from Protein Data Bank (www.rcsb.org). Polar hydrogen atoms were added and water molecules, which did not participate in interactions were removed. Structure of ligands were drawn in MarvinSketch and saved in pdb format, which were further converted into pdbqt format using AutoDockVina. Energy minimization was performed using MMFF94 force field. Then docking was performed according to specified conditions of grid box as given in (Table 3). The results were found in the form of most favorable free energy of binding in kcal/mol (Trott and Olson 2010).

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Conflict of interest The authors declare that they have no competing interests.

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