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Original article

Synthesis and in vitro antitumor activity of substituted quinazoline and quinoxaline derivatives: Search for anticancer agent

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ABSTRACT

The synthesis of some 2-furano-4(3*H*)-quinazolinones, diamides (open ring quinazolines), quinoxalines and their biological evaluation as antitumor agents using National Cancer Institute (NCI) disease oriented antitumor screen protocol are investigated. Among the synthesize compounds, seventeen compounds were granted NSC code and screened at National Cancer Institute (NCI), USA for anticancer activity at a single high dose (10^{-5} M) in full NCI 60 cell panel. Among the selected compounds, 3-(2-chloro benzylideneamine)-2-(furan-2-yl) quinazoline-4(3h)-one **21** was found to be the most active candidate of the series at five dose level screening against Ovarian OVCAR-4 and Non-small cell lung cancer NCI-H522 with GI_{50} 1.82 & 2.14 μM respectively. Rational approach and QSAR techniques enabled the understanding of the pharmacophoric requirement for quinazoline, diamides and quinoxaline derivatives.

1. Introduction

Cancer is continuing to be a major health problem in developing as well as undeveloped countries [1–9]. Surpassing heart diseases, it is taking the position number one killer due to various worldwide factors. Although major advances have been made in the chemotherapeutic management of some patients, the continued commitment to the laborious task of discovering new anticancer agents remains critically important. In the course of identifying various chemical substances which may serve as leads for designing novel antitumor agents, we are particularly interested in the present work with quinazoline and quinoxaline derivatives which have been identified as a new class of cancer chemotherapeutic agents with significant therapeutic efficacy against solid tumors [7–9]. It is well known that quinazoline derivatives are potent inhibitors of epidermal growth factor receptor (EGFR) [10–18]. The epidermal growth factor receptor (EGFR) is cellular trans-membrane tyrosine kinases that is over-expressed in a significant number of human tumors (e.g., breast, ovarian, colon, and prostate), their expression levels often correlate with vascularity, and is associated with poor prognosis in patients [19–22]. Inhibitors of the EGFR PTK are therefore expected to have great therapeutic potential in the treatment of malignant and non -malignant epithelial diseases. A great number of different structural classes of tyrosine kinase inhibitors have been reported and reviewed [23–25]. The most promising small-molecule selective EGFR-TK inhibitors include quinazolines and quinoxalines. Chart 1 includes some examples that are currently approved drugs or in clinical trials [19].

In May 2003, the FDA approved gefitinib (ZD1839, Iressa) as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after chemotherapies had failed [26]. Consequently, various approaches were adopted to enhance the potency and selectivity of these inhibitors. These efforts led to discovery of lapatinib, a dual EGFR and erbB2 inhibitor, which is currently in phase III clinical trials [17]. Later, it has been reported that somatic mutations in the tyrosine kinase domain of the EGFR gene occur in a subset of patients with lung cancer who showed a dramatic response to the EGFR tyrosine kinase inhibitors gefitinib and erlotinib [27–29]. Intensive research in the area of tyrosine kinase inhibitors led to development of enormous number of active compounds [30–36]. Apart from quinazolines, quinoxalines are also proved to be selective ATP competitive inhibitors. AG 1295 (Chart 1), a quinoxaline derivatives have been shown to block selectively EGFR kinase. This molecule reverses the transformed phenotype of *sis*-trans-formed NIH 3T3 cells and slow C6 glioma-induced tumors in nude mice [37].

In view of the previous rationale and in continuation of an ongoing program aiming at finding new structure leads with potential chemotherapeutic activities [38,39], in the present study new series of quinazolinones and quinoxalines have been synthesized and screened in vitro for antitumor activity at NCI. These series

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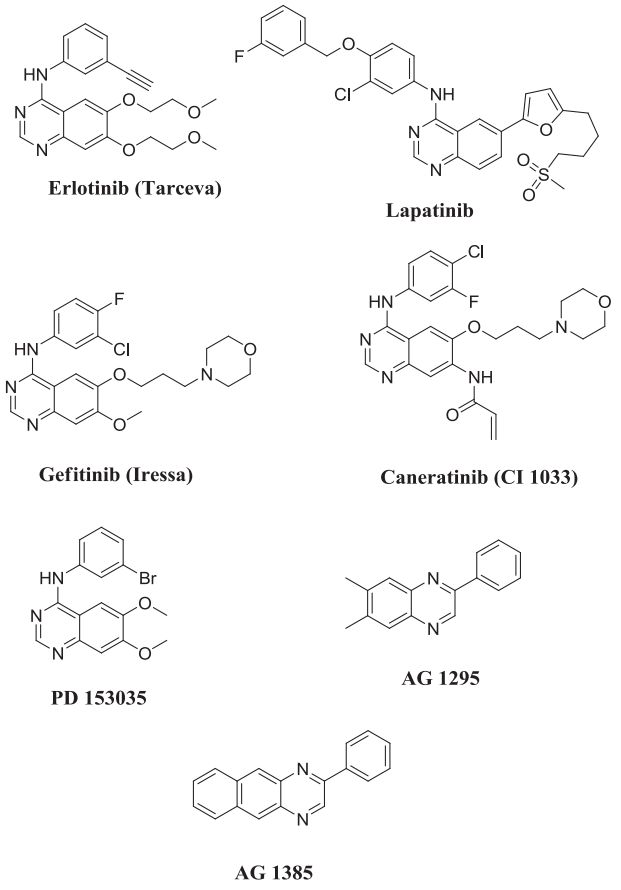


Chart 1. EGFR Tyrosine Kinase inhibitors.

comprise the derived 2,3-diubstituted quinazoline and quinoxaline pharmacophore that are structurally related to Erlotinib and Lapatinib (Fig. 1). In the present study, the substitution pattern at the 2, 3-disubstituted quinazoline and quinoxaline pharmacophore were selected so as to confer different electronic environment that would affect the lipophilicity and hence the activity of the target molecules. The objective of forming these hybrids is an attempt to reach an active antitumor agent with potentiated activity and selectivity toward cancerous cells. Moreover QSAR study was used to identify the structural features required for the antitumor properties of these new series [40–42]. However the results of this QSAR study could support the postulation that our active compounds may act on the same enzyme target where EGFR inhibitor acts confirming the molecular design of the reported class of antitumor agents.

All the synthesized compounds were submitted to National Cancer Institute (NCI) for anticancer screening. The tumor growth inhibition properties of the seventeen compounds **5**, **10**, **11**, **14**, **15**, **21**, **39**, **40**, **41**, **42**, **48b**, **48c**, **48e**, **48f**, **48g**, **48h** and **48i** with the NCI codes NSC D-752812/1, NSC D-752813/1, D-753448/1, D-753446/1, D-753445/1, D-753439/1, D-753786/1, D-753787/1, D-753788/1, D-753789/1, D-753225/1, D-753230/1, D-532226/1, D-753231/1, D-753227/1, D-753228/1 and D-753229/1 selected among **5**–**48**(**a**–**i**) by the National Cancer Institute (NCI), USA, were screened on human tumor cell lines at 10^{-5} M at the NIH, Bethesda, Maryland, USA, under the drug discovery program of the NCI. Among the selected seventeen compounds, compound **21** (NSC D-753439/1) was further screened for 5-log dose molar range as it has shown prominent cell growth inhibition at 10^{-5} M concentration against variety of cell lines.

2. Rational and design

In recent years, quinazolines have emerged as a versatile template for inhibition of a diverse range of receptor tyrosine kinases. The most widely studied of these is the epidermal growth factor receptor (EGFR), with the small-molecule inhibitor gefitinib being the first agent from this class to be approved for the treatment of non-small cell lung cancer refractory to prior chemotherapeutic intervention [43,44]. Subsequent research aimed at further exploration of the SAR of this novel template has led to discovery of highly selective compounds that target EGFR. These compounds act via competing with ATP for binding at the catalytic domain of tyrosine kinase. Later on, a great structural variety of compounds of structurally diverse classes have proved to be highly potent and selective ATP-competitive inhibitors. The ATP binding site has the following features; Adenine region- Contains two key Hydrogen bonds formed by the interaction of N-1 and N-6 amino group of the adenine ring. Many potent inhibitors use one of these Hydrogen bonds. Sugar region – A hydrophilic region, except a few e.g. EGFR. Hydrophobic pocket – Though not used by ATP but plays an important role in inhibitor selectivity. Hydrophobic channels – It is not used by ATP and may be exploited for inhibitor specificity. Phosphate binding region – This is used for improving inhibitor selectivity [45]. In this study, we present a new sub-family of compounds containing 2, 3-disubstituted quinazoline and quinoxaline core as EGFR inhibitors. Our strategy is directed toward designing a variety of ligands with diverse chemical properties hypothesizing that the potency of these molecules might be enhanced by adding alternative binding group such as furan ring at position 2-, urea, thiourea, thiosemicarbazide, phenyl hydrazine, hydroxylamine, para amino benzoic acid, sulphonamide and imines at position 3-of the quinazoline ring, substituted styryl at position 3 and thio methyl benzimidazole at position 2 of quinoxaline ring. In this way, such substitution pattern could target different regions of the ATP-binding site of the protein kinase domain to create differentially selective molecules. The design of our ligands was done based on previous Quntitive Structure Activity Relationship (QSAR) of 4-anilinoquinazolines as EGFR inhibitor [40–42]. We introduced larger moiety at 3 position of the quinazoline and quinoxalines such as substituted arylidene, sulfonamide, substituted styryl, thio methyl benzimidazole and substituted chalcone in ring opened quinazolines [N-2-(phenyl carbamoyl) phenyl) furan-2-carboxamide and 2-benzamido-N-phenylbenzamide] moiety in a fashion similar to lapatinib which binds in the ATP-binding cleft, so that the bulky group could be oriented deep in the back of the ATP binding site and makes predominantly hydrophobic interactions with the protein mimicking the 3′-chloro-4′-[(3-fluorobenzyl)oxy]aniline group of lapatinib (Fig. 2).

3. Chemistry

The reaction of anthranilic acid **1** and 2-furanocarbonylchloride **2** afforded the amide analog **3** which was then refluxed in acetic anhydride to obtain the key intermediate 2-(furan-2-yl)- 4H-3,1-benzoxazin-4-one **4** (Scheme 1).The reaction of thiosemicarbazide, urea, thiourea, phenyl hydrazine and para amino benzoic acid with 2-(furan-2-yl)-4H-3,1-benzoxazin-4-one **4** by fusion at high temperature afforded the corresponding quinazoline-4-one derivatives **6**–**10** (Scheme 1).The benzoxazine derivative **4** was also reacted with hydroxylamine hydrochloride in dry pyridine to afford compound **5**. Compound **4** was reacted with p-toludine and sulphanilamide by fusion in an attempt to obtain 3-substituted-quinazolin-4-ones in different reaction conditions, in all cases; the reaction afforded the diamides **11** (Scheme 1) and **12** (Scheme 2) instead. Attempts to cyclize the diamides **11** and **12** to the

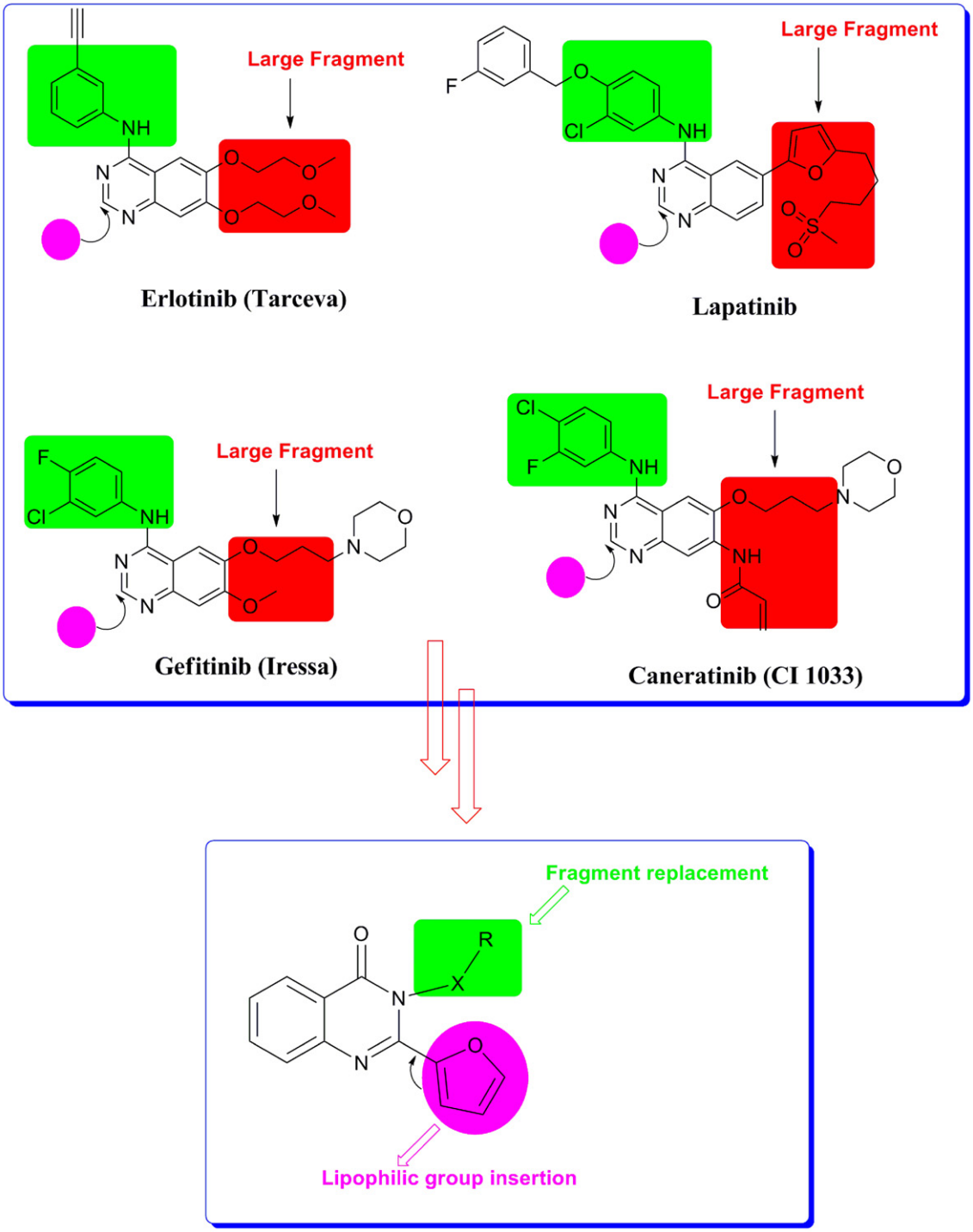


Fig. 1. Reported and proposed antitumor quinazoline derivatives.

corresponding 4-(3H)-quinazolin-4-one using variety of reaction conditions, including fusion, were not successful. Condensation of **12** with different substituted aromatic aldehydes gave corresponding chalcone derivatives of diamides **13**–**17** in acetic acid (Scheme 2). Fusion of **4** with hydrazine hydrate at 200 °C afforded compound **18**, which on further condensation with appropriate aromatic aldehydes in glacial acetic acid afforded the arylidene derivatives **19**–**34** (Scheme 3). Anthranilic acid **35** reaction with benzoyl chloride **36** yielded 2-phenyl-4H-3, 1-Benzoxazin-4 one **37** by N-acylation via dehydrative cyclization mechanism. Subsequently which was fused with p-toludine at 200 °C in an attempt to obtain 3-substituted-quinazolin-4-ones in different reaction conditions, in all cases; the reaction afforded the diamides **38** (Scheme 4) instead. Condensation of **38** with different substituted aromatic aldehydes gave corresponding chalcone derivatives of diamides **39**–**42** in acetic acid (Scheme 4). Condensation of o-phenylenediamine **43** with pyruvic acid in an aqueous medium alone yielded 3-methyl quinoxaline –2(1*H*)-one **45**. The active

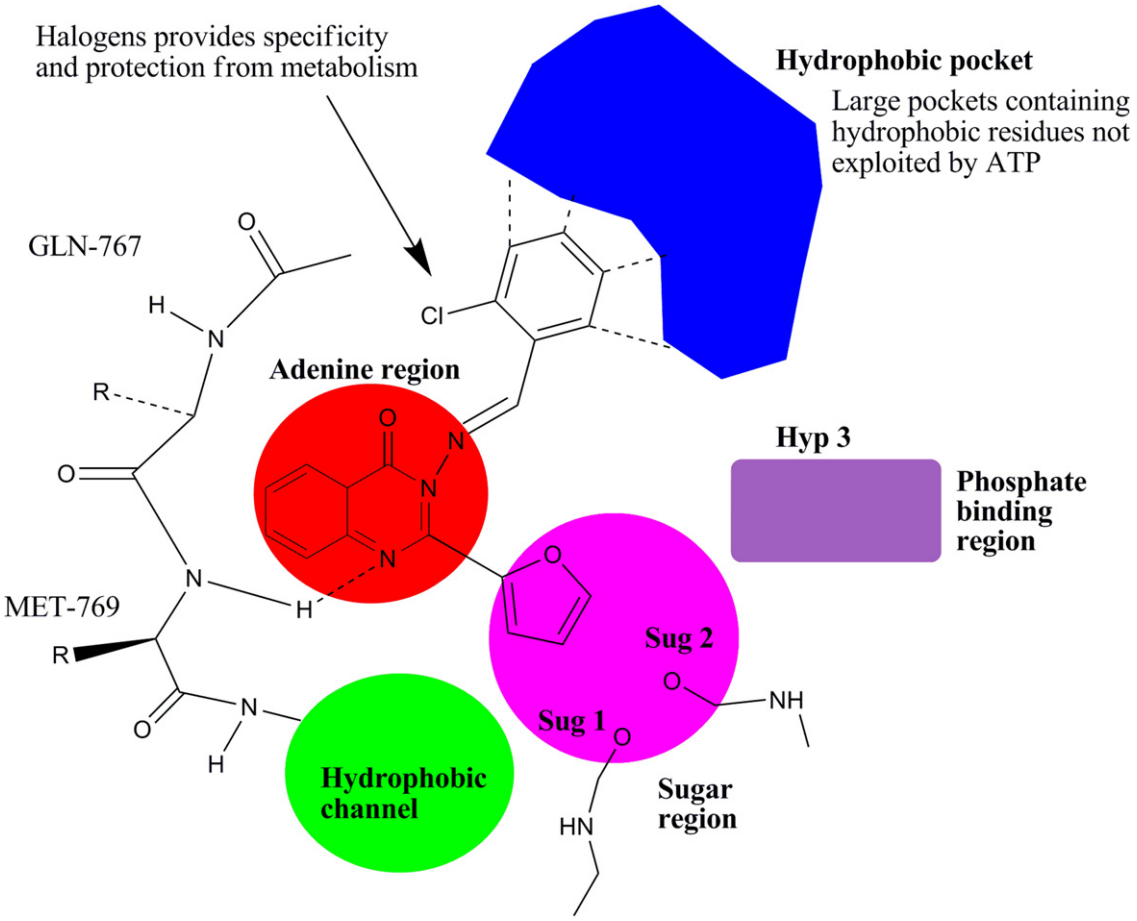


Fig. 2. Proposed hypothetical model of the highly active 2, 3-disubstituted quinazoline (Compound 21) bound to ATP binding site of EGFR protein tyrosine kinase.

methyl group of **45** condenses with different aromatic aldehydes in acetic acid and catalytic amount of H_2SO_4 to afford the **46** (**a**–**i**). Chlorination of **46** (**a**–**i**) with phosphorus oxychloride ($POCl_3$) in the presence of catalytic amount of dimethylformamide (DMF) under refluxing condition yielded the corresponding chloro compound **47** (**a**–**i**), which on reaction with thio methyl *1H*-benzimidazole gave the corresponding nucleophillic substituted product **48** (**a**–**i**) (Scheme 5). It has been seen that benzoxazinones undergo ring opening with different nucleophiles, allowing incorporation of substitution at the 3-position. It is a reported that the benzoxazinones are liable to hydrolysis by water. The actual extent to which this hydrolysis occurs varies greatly across a range of molecules. A molecule of water would be able to open the benzoxazinone ring by attacking the intracyclic carbonyl and effectively hydrolyzing the cyclic ester (Chart 2) [46].

It is also been suggested that the nature of the substitution on the benzoxazinone can modulate the reactivity of the carbonyl, in that electron-donating groups cause the carbonyl to be less electrophilic and reduce the reactivity of the benzoxazinone carbonyl to nucleophillic attack [47]. This is desirable in terms of stability on storage, or if they are to be final molecules themselves, but may be a factor when these molecules are altered for further analog production.

An alkyl chain will act as an electron donor (+I effect); suggests that the longer the chain gets, the more difficult a reaction and insertion of the group that will constitute substitution at the 3-position of the corresponding quinazoline (Chart 3).

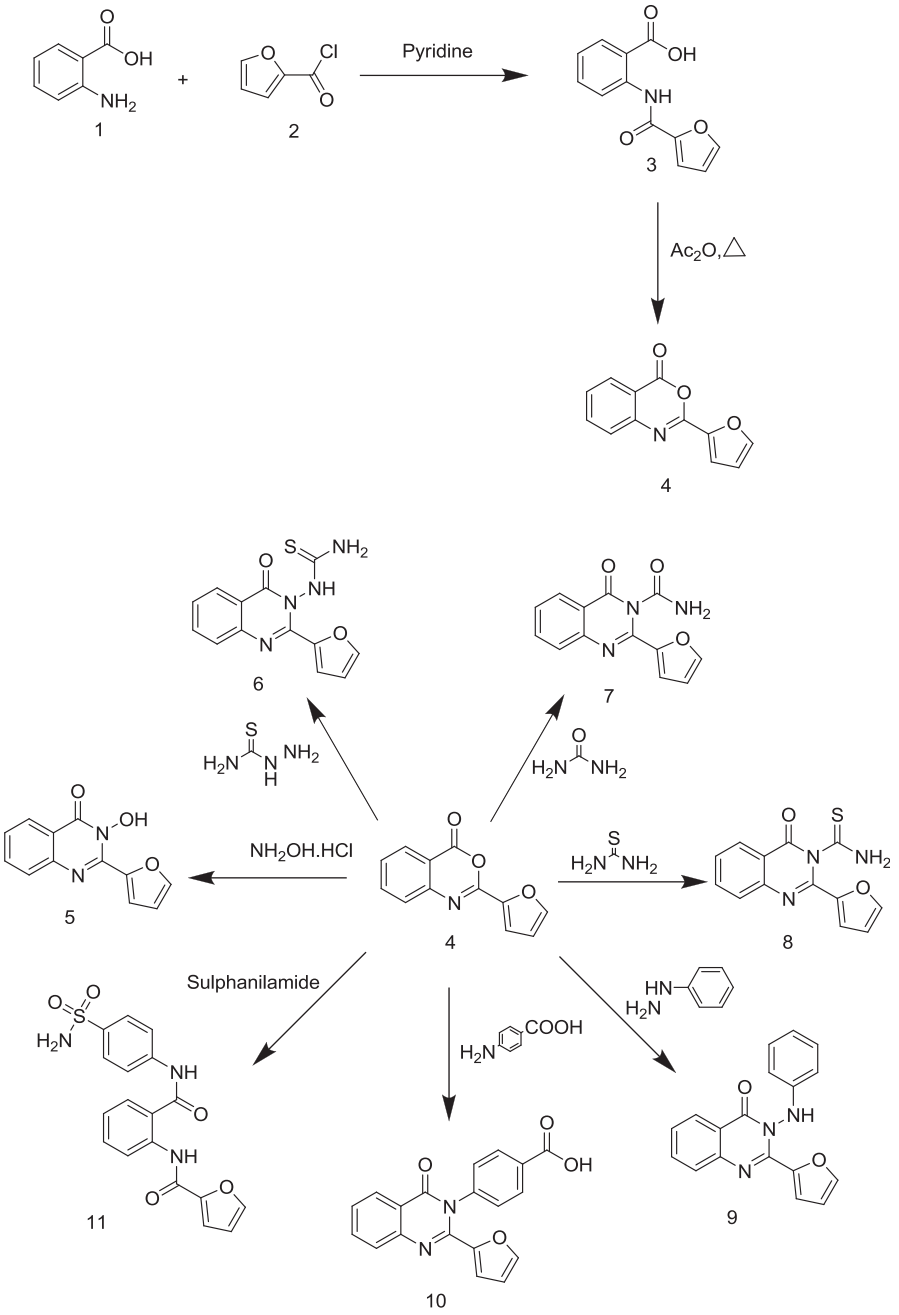
Compound **4** and **37** was reacted with p-toludine by fusion in an attempt to obtain 3-substituted-quinazolin-4-ones in different reaction conditions, in all cases; the reaction afforded the (ring open quinazolines) diamides **12** (Scheme 2) and **38** (Scheme 4) instead. The reaction mechanism of ring opening is explained in Chart 4 and 5.

4. Pharmacology

4.1. In vitro cancer screen

The screening is a two-stage process, beginning with the evaluation of all compounds against the 60 cell lines at a single dose of 10^{-5} M. The output from the single dose screen is reported as a mean graph and is available for analysis by the COMPARE program. Compounds which exhibit significant growth inhibition are evaluated against the 60 cell panel at five concentration levels. The human tumor cell lines of the cancer-screening panel are grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. For a typical screening experiment, cells are inoculated into 96 well microtiter plates in 100 μL at plating densities ranging from 5000 to 40,000 cells/well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates are incubated at 37 °C, 5% CO_2, 95% air and 100% relative humidity for 24 h prior to addition of experimental drugs.

After 24 h, two plates of each cell line are fixed *in situ* with TCA, to represent a measurement of the cell population for each cell line at the time of drug addition (Tz). Experimental drugs are solubilized in dimethyl sulfoxide at 400-fold the desired final maximum test concentration and stored frozen prior to use. At the time of drug addition, an aliquot of frozen concentrate is thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 μg/ml gentamicin. Additional four, 10-fold or ½



Scheme1. Synthetic route for the preparation of the target compounds **5**–**11**.

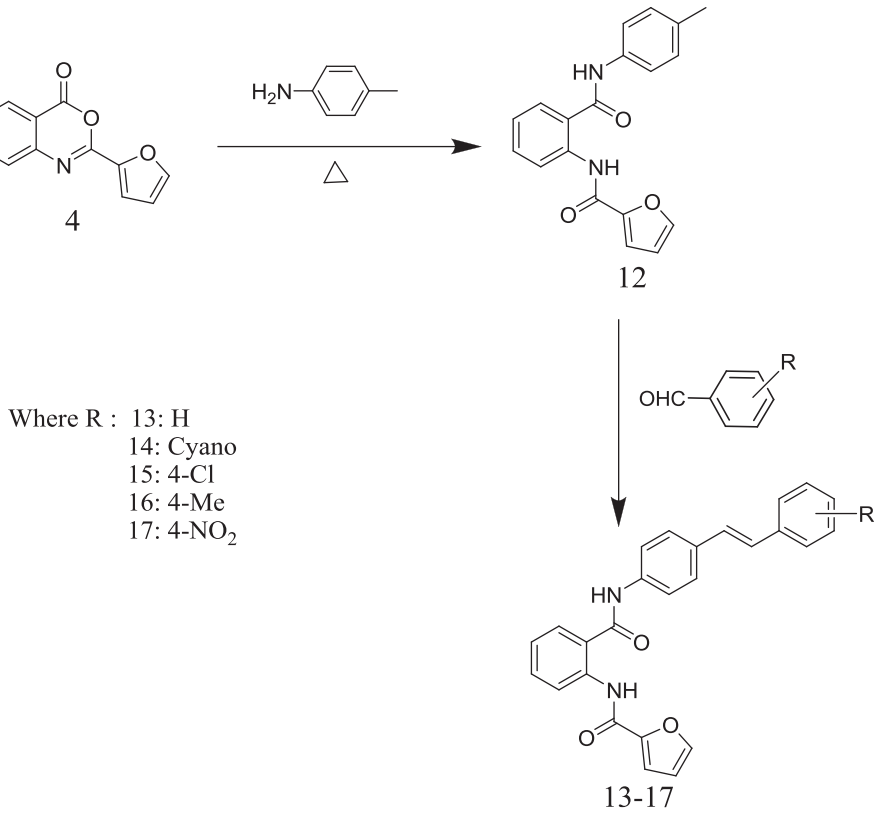
log serial dilutions are made to provide a total of five drug concentrations plus control. Aliquots of 100 μl of these different drug dilutions are added to the appropriate microtiter wells already containing 100 μl of medium, resulting in the required final drug concentrations.

Following drug addition, the plates are incubated for an additional 48 h at 37 °C, 5% CO_2, 95% air, and 100% relative humidity. For adherent cells, the assay is terminated by the addition of cold TCA. Cells are fixed *in situ* by the gentle addition of 50 μl of cold 50% (w/v) TCA (final concentration, 10% TCA) and incubated for 60 min at 4 °C. The supernatant is discarded, and the plates are washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (100 μl) at 0.4% (w/v) in 1% acetic acid is added to each well, and plates are incubated for 10 min at room temperature. After staining, unbound dye is removed by washing five times with 1% acetic acid and the plates are air dried. Bound stain is subsequently solubilized with 10 mM trizma base, and the absorbance is read on an automated plate reader at a wavelength of 515 nm. For suspension cells, the methodology is the same except that the assay is terminated by fixing settled cells at the bottom of the wells by gently adding 50 μl of 80% TCA (final concentration, 16% TCA). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth is calculated at each of the drug concentrations levels. Percentage growth inhibition is calculated as:

$$[(\mathrm{Ti}-\mathrm{Tz})/(\mathrm{C}-\mathrm{Tz})] \times 100 \text{ for concentrations for which } \mathrm{Ti} >/= \mathrm{Tz}$$

$$[(\mathrm{Ti}-\mathrm{Tz})/\mathrm{Tz}] \times 100 \text{ for concentrations for which } \mathrm{Ti} < \mathrm{Tz}.$$

Three dose response parameters are calculated for each experimental agent. Growth inhibition of 50% (GI50) is calculated from



Scheme 2. Synthetic route for the preparation of the target compounds **13**–**17**.

[(Ti−Tz)/(C−Tz)] × 100 = 50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The drug concentration resulting in total growth inhibition (TGI) is calculated from Ti = Tz. The LC50 (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment is calculated from [(Ti−Tz)/Tz] × 100 = −50. Values are calculated for each of these three parameters if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter is expressed as greater or less than the maximum or minimum concentration tested [48–50].

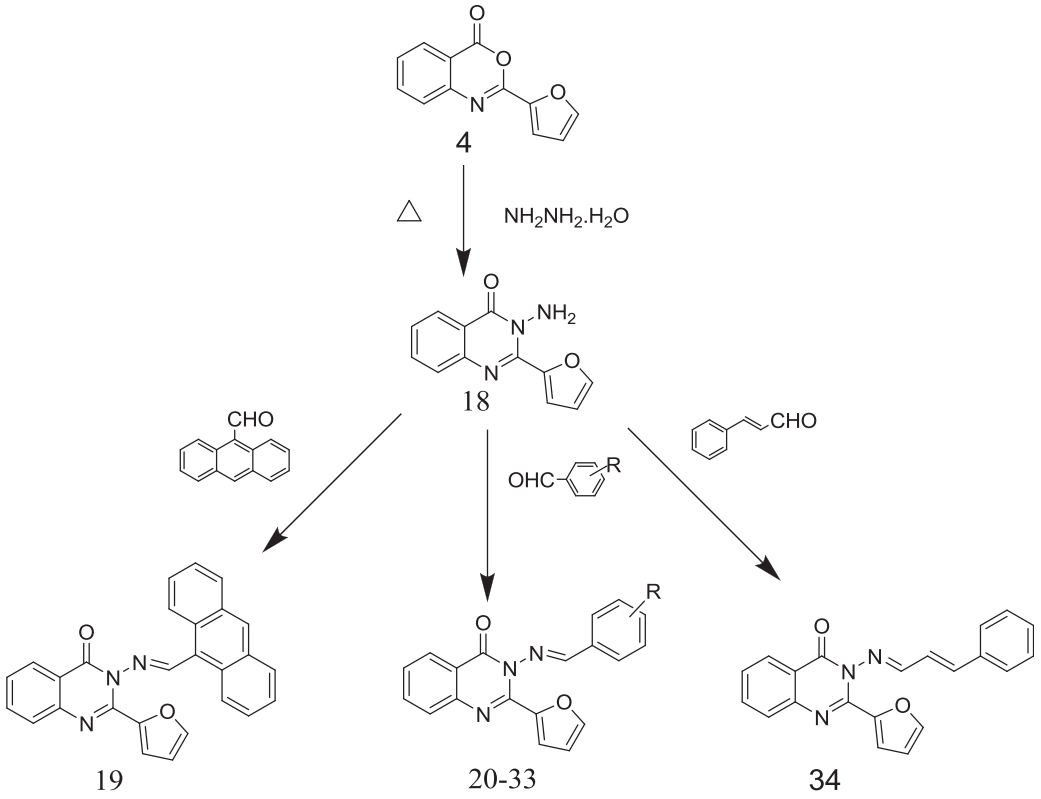
4.2. Pharmacological (in vitro anticancer activity)

The tumor growth inhibition properties of the seventeen compounds **5**, **10**, **11**, **14**, **15**, **21**, **39**, **40**, **41**, **42**, **48b**, **48c**, **48e**, **48f**, **48g**, **48h** and **48i** with the NCI codes NSC D-752812/1, NSC D-752813/1, D-753448/1, D-753446/1, D-753445/1, D-753439/1, D-753786/1, D-753787/1, D-753788/1, D-753789/1, D-753225/1, D-753230/1, D-532226/1, D-753231/1, D-753227/1, D-753228/1 and D-753229/1 selected among **5**–**48**(**a**–**i**) by the National Cancer Institute (NCI), USA, were screened on human tumor cell lines at 10^{-5} M at the NIH, Bethesda, Maryland, USA, under the drug discovery program of the NCI. Among the selected seventeen compounds, compound **21** (**NSC D-753439/1**) was further screened for 5-log dose molar range as it has shown prominent cell growth inhibition at 10^{-5} M concentration against verity of cell lines.

4.2.1. Primary single high dose (10^{-5} M) full NCI 60 cell panel in vitro assay

All the selected compounds submitted to National Cancer Institute (NCI) for in vitro anticancer assay were evaluated for their anticancer activity. Primary in vitro one dose anticancer assay was performed in full NCI 60 cell panel representing leukemia, melanoma and cancers of lung, colon brain breast, ovary, kidney and prostate in accordance with the protocol of the NCI, USA. The compounds were added at a single concentration (10^{-5} M) and the culture was incubated for 48 h. End point determinations were made with a protein binding dye, Sulforhodamine B. Results for each compound were reported as a mean graph of the percent growth of the treated cells when compared to the untreated control cells. There after obtaining the results for one dose assay, analysis of historical Development Therapeutics Programme (DTP) was performed and compound **21** (**NSC D-753439/1**) which satisfied predetermined threshold inhibition criteria was selected for NCI full panel 5 dose assay.

The tested quinazolines, diamides and quinoxalines analogs showed a distinctive pattern of selectivity. With regard to sensitivity against individual cell lines (Table 1). Compound **11** and **21** showed remarkably lowest cell growth promotion against Renal A-498 and Non-small lung HOP-62 cancer cell line with cell growth promotion of −23 and −34.84 respectively. Apart from this compound **21** also exhibited broad spectrum cell growth inhibition against Non Small Cell Lung Cancer NCI-H522 (cell growth promotion 10.38%, inhibition 89.62%), Colon HCT-116 Cancer (cell growth promotion 24.88%, inhibition 75.12%), CNS Cancer SNB-75 (cell growth promotion 32.38%, inhibition 67.62%), Melanoma LOX IMVI (cell growth promotion 34.24%, inhibition 65.76%), Ovarian OVCAR-4 Cancer cell line (cell growth promotion 4.38%, inhibition 95.62%), Renal ACHN Cancer Cell line (cell growth promotion 23.89%, inhibition 76.11%) and Breast BT -549 cancer cell line (cell growth promotion 13.63%, inhibition 86.37%) at single dose assay concentration of 10^{-5} M. The highest activity of this compound might be because of its structural resemblance with lapatinib since it contain 2-chloro benzylideneamine group at C-3 position of



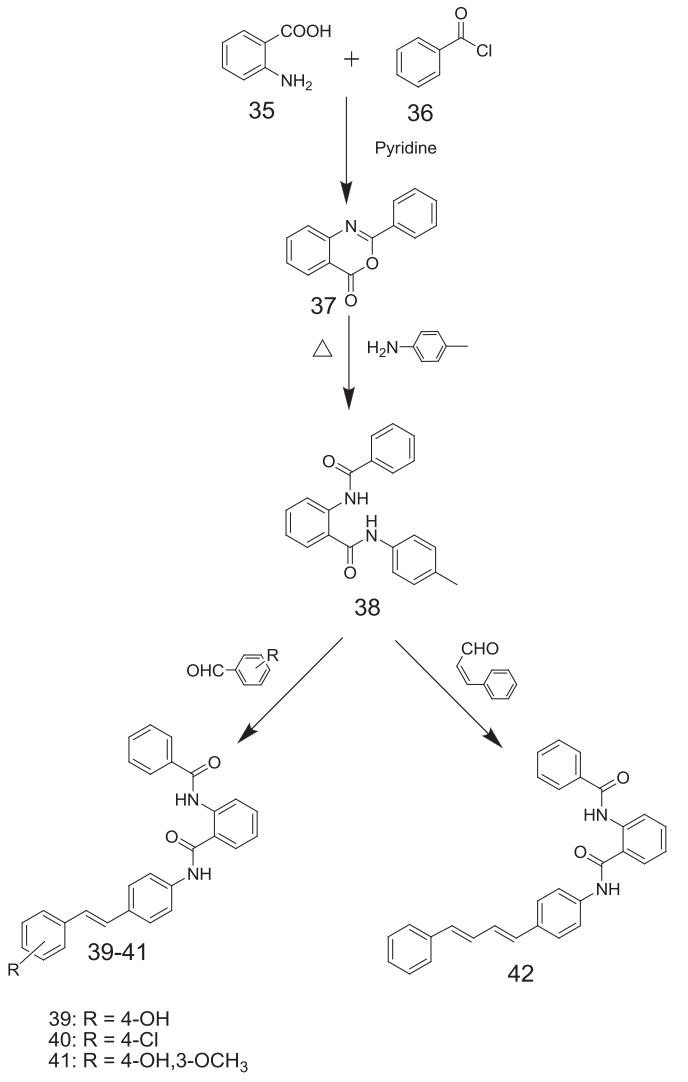
20: R= 4-Chloro
21: R= 2-Chloro
22: R= H
23: R= 3-OCH_3, 4-OH
24: R= 4-OH
25: R = 4-CH_3
26: R = 3-Bromo
27: R= 4-Cyano
28: R= 2,5-dimethoxy
29: R =4-Nitro
30: R =2-Nitro
31: R = 4-Bromo
32: R = 4-Fluro
33: R= 3-Nitro

Scheme 3. Synthetic route for the preparation of the target compounds **19**–**34**.

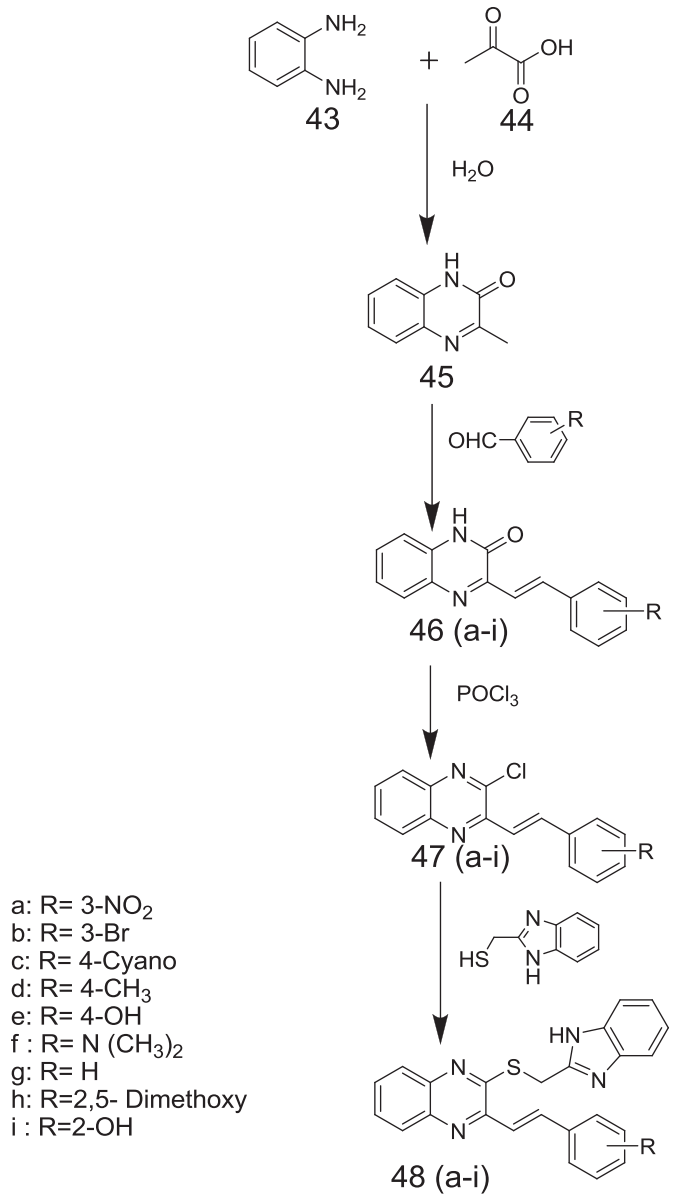
quinazoline which suppose to block the hydrophobic pocket of Tyrosine kinase (Fig. 2). The third most-highest active compound from the category of quinoxalines is no one but the **48g**, which showed significant cell growth inhibition against Ovarian OVCAR-4 (cell growth promotion 2.71%, inhibition 97.29%), Non-Small Cell Lung EKVX (cell growth promotion 22.23%, inhibition 77.77%) and Melanoma SK-MEL-5 Cancer Cell line (cell growth promotion 17.40%, inhibition 82.6%). With regard to broad spectrum antitumor activity **48g** was found to active against Ovarian, Non-Small Cell Lung, Melanoma, Colon, Renal and Breast cancer subpanel cell lines. Contrary compound **14**, **48c** has not shown any significant cell growth inhibition while **5**, **10**, **15**, **41**, **48e** and **48f** was found to be moderately active against subpanel of cell lines. From the category of diamides (open quinazolines) compound **39** was emerged as active compound which showed significant cell growth inhibition against Leukemic Cancer Cell lines K-562 (cell growth promotion 40.21%, inhibition 59.79%), Melanoma UACC-62 (cell growth promotion 40.16%, inhibition 59.84%) and Renal UO-31 (cell growth promotion 39.29%, inhibition 60.71%). Apart from this it also showed cell growth inhibition against Non Small Cell Lung, Colon, CNS, Ovarian, Prostate and Breast Cancer subpanel cell lines. Another diamides namely compound **40** and **42** showed up to 50% cell growth inhibition against Renal UO-31 while individually compound **40** also exhibited 51% cell inhibition against Colon HCT-116 Cancer cell line. Another active candidate from quinoxalines was **48i**, which significantly cell growth inhibition against Ovarian OVCAR-4 Cancer cell line (cell growth promotion 25.22%, inhibition 74.78%) and Leukemia HL-60(TB) (cell growth promotion 26.78%, inhibition 73.22%).Compound **48h**, another member of quinoxalines showed up to 44% (56.15% cell growth promotion) cell growth inhibition against Renal TK-10 Cancer cell line at single dose assay (10^{-5} M concentration) as shown in Table 1.

4.2.2. In vitro 5 dose full NCI 60 cell panel assay

All the cell lines (about 60), representing nine tumor subpanels, were incubated at five different concentrations (0.01, 0.1, 1, 10 &



Scheme 4. Synthetic route for the preparation of the target compounds **39**–**42**.



Scheme 5. Synthetic route for the preparation of the target compounds **48** (**a**–**i**).

100 μM). The outcomes were used to create log concentration Vs % growth inhibition curves and three response parameters (GI50, TGI and LC50) were calculated for each cell line. The GI50 value (growth inhibitory activity) corresponds to the concentration of the compound causing 50% decrease in net cell growth, the TGI value (cytostatic activity) is the concentration of the compound resulting in total growth inhibition and LC_{50} value (cytotoxic activity) is the concentration of the compound causing net 50% loss of initial cells at the end of the incubation period of 48 h. Compound under investigation **21** (**NSC D-753439/1**) exhibited remarkable anticancer activity against most of the tested cell lines representing nine different subpanels with GI_{50} values between "1.82–15.24 μM", except one HL-60 (TB) Cell line of Leukemia subpanel showing GI_{50} at a concentration of 23.89 μM (Table 2), whereas four cell lines of Leukemia subpanel namely K-562,MOLT-4,RPMI-8226 and SR were found to be insensitive at the highest tested concentration i.e. 100 μM therefore a sign of ">" is used as prefix to the concentration. With regard to the sensitivity against some individual cell lines (Table 2) the compound showed high activity against Ovarian OVCAR-4 and Non-small cell lung cancer NCI-H522 with GI_{50} 1.82 & 2.14 μM respectively. Obtained data revealed an obvious sensitivity profile toward ovarian subpanel (GI_{50} value ranging from 1.82 to 6.12 μM), least for OVCAR-4 and maximum for IGROV1 cell line. The criterion for selectivity of a compound depends upon the ratio obtained by dividing the full panel MID (the average sensitivity of all cell lines toward the test agent) by their individual subpanel MID (the average sensitivity of all cell lines of a particular subpanel toward the test agent). Ratios between 3 and 6 refer to moderate selectivity; ratios greater than 6 indicate high selectivity toward the corresponding cell line, while compounds not meeting either of these criteria rated non-selective [51]. As per this criterion, compound in the study was found to be moderate selective toward ovarian cancer subpanel only with selectivity ratio of 3.17, whereas it was found to be non-selective against remaining cell panel (Table 2).

5. Structure activity relationship

Structure-activity correlation of the synthesized compounds revealed that, in the diamide (open ring quinazolines) series **39**, **40**, **41** and **42** aromatic substitution, on the benzamide amide function, favors the activity. Replacement of aromatic substitution by sulphonamide ring on the benzamide amide function resulting into a potent compound. This is obvious upon comparing compound **11**

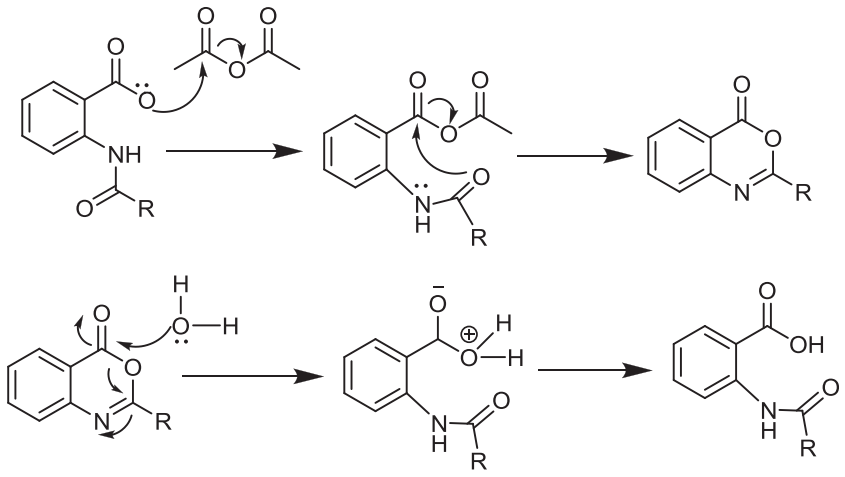


Chart 2. Ring opening of benzoxazinone by water.

(Renal A-498 cancer cell line −23% promoted) and compound **39** Renal UO-31(cell growth promotion 39.29%, inhibition 60.71%). Introduction of −OH and benzoic acid group at position 3-of quinazoline did not result into the very active compounds **5** and **10**. Introduction of 2-chloro benzylideneamine group at 3 position of quinazoline markedly increased the activity that results into the very potent and broad spectrum compound **21** (Non-small lung HOP-62 cancer cell line −34.84 promoted at one dose with GI_{50} value of 1.82 μM against Ovarian OVCAR-4 cancer cell line at five dose assay). The highest activity of this compound might be because of its structural resemblance with lapatinib since it contain 2-chloro benzylideneamine group at 3-position of quinazoline which suppose to block the hydrophobic pocket of Tyrosine kinase (Fig. 2). In quinoxaline series, styryl substitution at 3-position of quinoxaline favors the activity as well broad spectrumness rather than substituted styryl substitution. This is obvious upon comparing compound **48g** [Ovarian OVCAR-4 (cell growth promotion 2.71%, inhibition 97.29%), Non-Small Cell Lung EKVX (cell growth promotion 22.23%, inhibition 77.77%) and Melanoma SK-MEL-5 Cancer Cell line (cell growth promotion 17.40%, inhibition 82.6%)] and **48h** [44% cell growth inhibition against Renal TK-10 Cancer cell line].

6. Conclusion

All the compounds were submitted to screen for their anticancer potential at NCI on the basis of results obtained it was found that 3-(2-chloro benzylideneamine)-2-(furan-2-yl) quinazoline-4(3h)-one **21** (NSC D-753439/1) proved to be the most active member of this study. Rational approach and QSAR techniques enabled the understanding of the pharmacophoric requirement for quinazoline and quinoxaline derivatives. The overall outcome of this model revealed that: (i) the quinazoline ring is satisfactory backbone for antitumor activity, (ii) the presence of 2-chloro benzylideneamine group at 3 position of quinazoline and chalcone on the benzamide amide function of diamides (open ring quinazolines) enhances the activity as hydrophobic region, (iii) the presence of sulphonamide group is necessary as H-bond region (iv) plane styryl group at 3-position of quinoxaline improves the potency and broad spectrumness of compound as compared to substituted styryl. These preliminary encouraging results of biological screening of the tested compounds could offer an excellent framework in this field that may lead to discovery of potent antitumor agent.

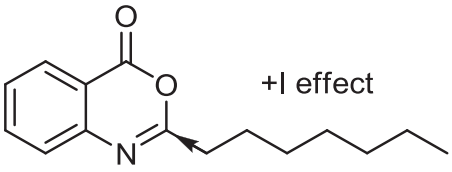


Chart 3. Impact of electron donating group at C-2 over the reactivity of benzoxazinone.

7. Experimental

All chemicals and solvents were supplied by Merck, S.D. Fine Chemical Limited, Mumbai. All the solvents were distilled and dried before use. The reactions were monitored with the help of thin-layer chromatography using pre-coated aluminum sheets with GF_{254} silica gel, 0.2 mm layer thickness (E. Merck). Melting points of the synthesized compounds were recorded on the Veego (VMP-MP) melting point apparatus. IR spectrum was acquired on a Shimadzu Infra Red Spectrometer, (model FTIR-8400S). Both ^{1}H NMR (DMSO) and ^{13}C NMR (DMSO) spectra of the synthesized compounds were performed with Bruker Avance-II 400 NMR Spectrometer operating at 400 MHz in SAIF, Punjab University (Chandigarh). Chemical shifts were measured relative to internal standard TMS (δ: 0). Chemical shifts are reported in δ scale (ppm). Mass spectra of the synthesized compounds were recorded at MAT 120 in SAIF, Punjab University.

7.1. 2-[(furan-2-ylcarbonyl) amino] benzoic acid (3)

2-Furoyl chloride **2** (0.01 mol) was added drop wise to a stirred solution of anthranilic acid **1** (0.01 mol) in pyridine (50 ml) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was poured into cold 5% dilute HCl, solution (100 ml). The solid obtained was filtered, washed several times with water, dried and crystallized from ethanol. Yield 67%; mp 190–192 °C; IR (KBr) ν_{max} 3446, 3115, 2980, 1681, 1638, 1598, 1457 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 6.54–8.96 (m,7H, Ar–H and furan-H), 10.89 (s,1H,NHCO), 12.32 (s,1H, COOH); ^{13}C NMR (DMSO-d_6) δ ppm: 170.1, 164.9, 148.5, 143.9, 140.3, 134.1, 130.6, 124.3, 118.4, 114.8; HRMS (EI) *m/z* calcd for $C_{12}H_9NO_4$: 231.0532; found: 231.0536.

7.2. 2-(furan-2-yl)-4H-3, 1-benzoxazin-4-one (4)

A mixture of 2-[(furan-2-ylcarbonyl) amino] benzoic acid **3** (0.01 mol) and acetic anhydride (0.1 mol) was heated under reflux for 4 h. The solvent was removed under reduced pressure. The residue was triturated with petroleum ether 40–60. The separated solid was collected by filtration, washed with petroleum ether 40–60, dried and crystallized from toluene. Yield 64%; mp 161–163 °C; IR (KBr) ν_{max}

2918, 1699, 1644, 1495, 1455, 1379 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 6.63–8.21 (m, 7H, Ar–H and furan-H); ^{13}C NMR (DMSO-d_6) δ ppm: 163.5, 159.3, 142.8, 143.4, 141.6, 134.1, 128.8, 126.4, 122.2, 118.8, 108.9, 108.4; HRMS (EI) m/z calcd for $C_{12}H_7NO_3$: 213.0426; found: 213.0428.

7.3. 2-(furan-2-yl)-3-hydroxyquinazolin-4(3H)-one (**5**)

A mixture of 2-(furan-2-yl)-4*H*-3,1-benzoxazin-4-one **4** (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) in dry pyridine (30 ml) was heated under reflux for 8 h and the reaction mixture was then concentrated to half its volume. The separated solid was filtered, washed with water and crystallized with ethanol. Yield 66%; mp 223–227 °C; IR (KBr) ν_{max} 3418, 2918, 1649, 1623, 1550, 1451, 1320 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 6.51–8.72 (m, 7H, Ar–H and furan-H), 12.31 (s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ ppm: 160.2, 158.6, 142.7, 141.7, 140.7, 133.4, 128.3, 124.7, 121.8, 108.8, 108.6; HRMS (EI) m/z calcd for $C_{12}H_8N_2O_3$: 228.0535; found: 228.0539.

7.4. General procedure for the synthesis of 3(4H)-substituted 2-(furan-2-yl)-4-oxoquinazoline) (**6**–**8**)

Equimolar amount of 2-(furan-2-yl)-4*H*-3,1-benzoxazin-4-one **4** and different primary amino containing moieties like thiosemicarbazide, urea, and thiourea were fused together at 200 °C in an oil

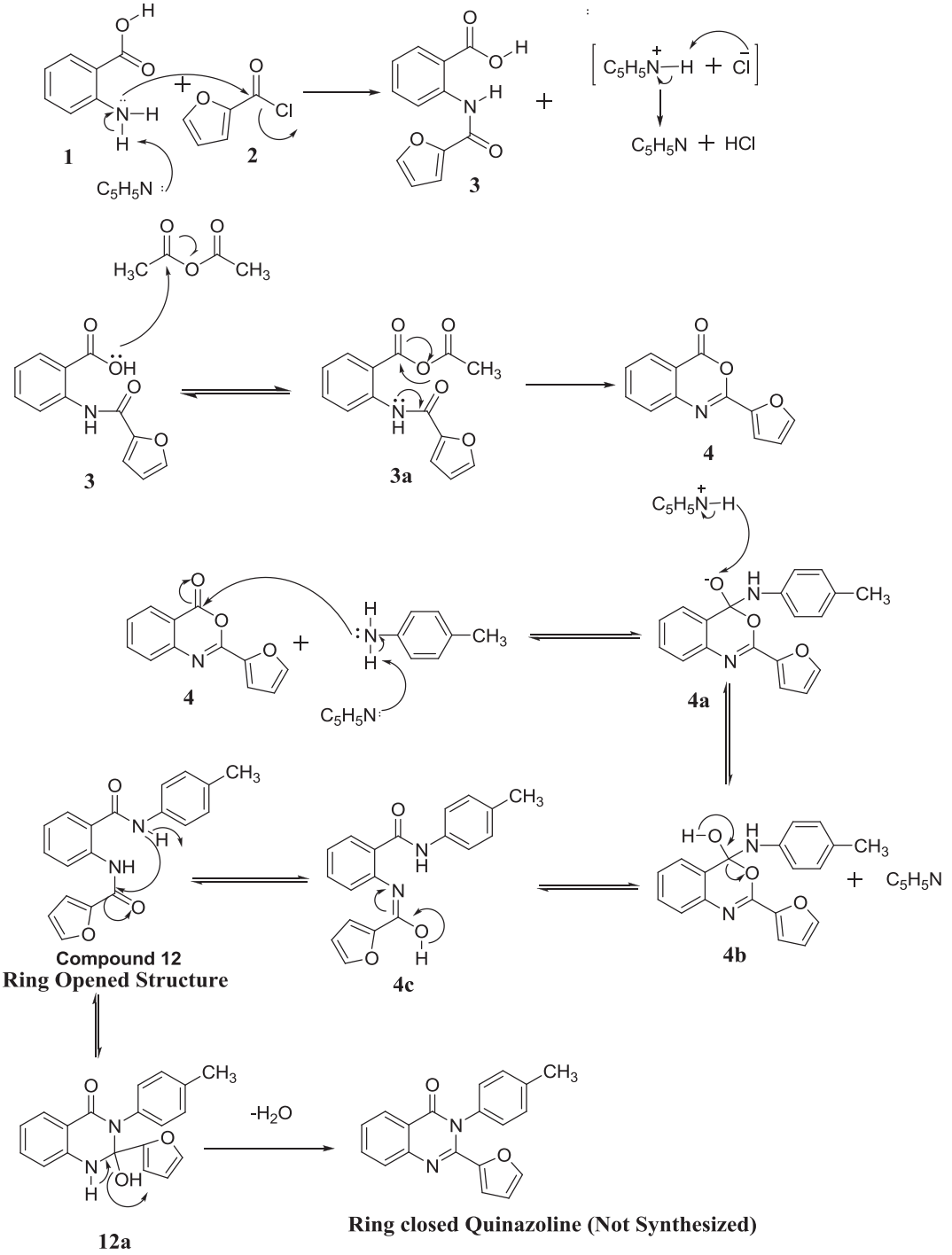


Chart 4. Reaction mechanism of ring opening of compound **12** in the synthesis of target compound **13**–**17** (Scheme 2).

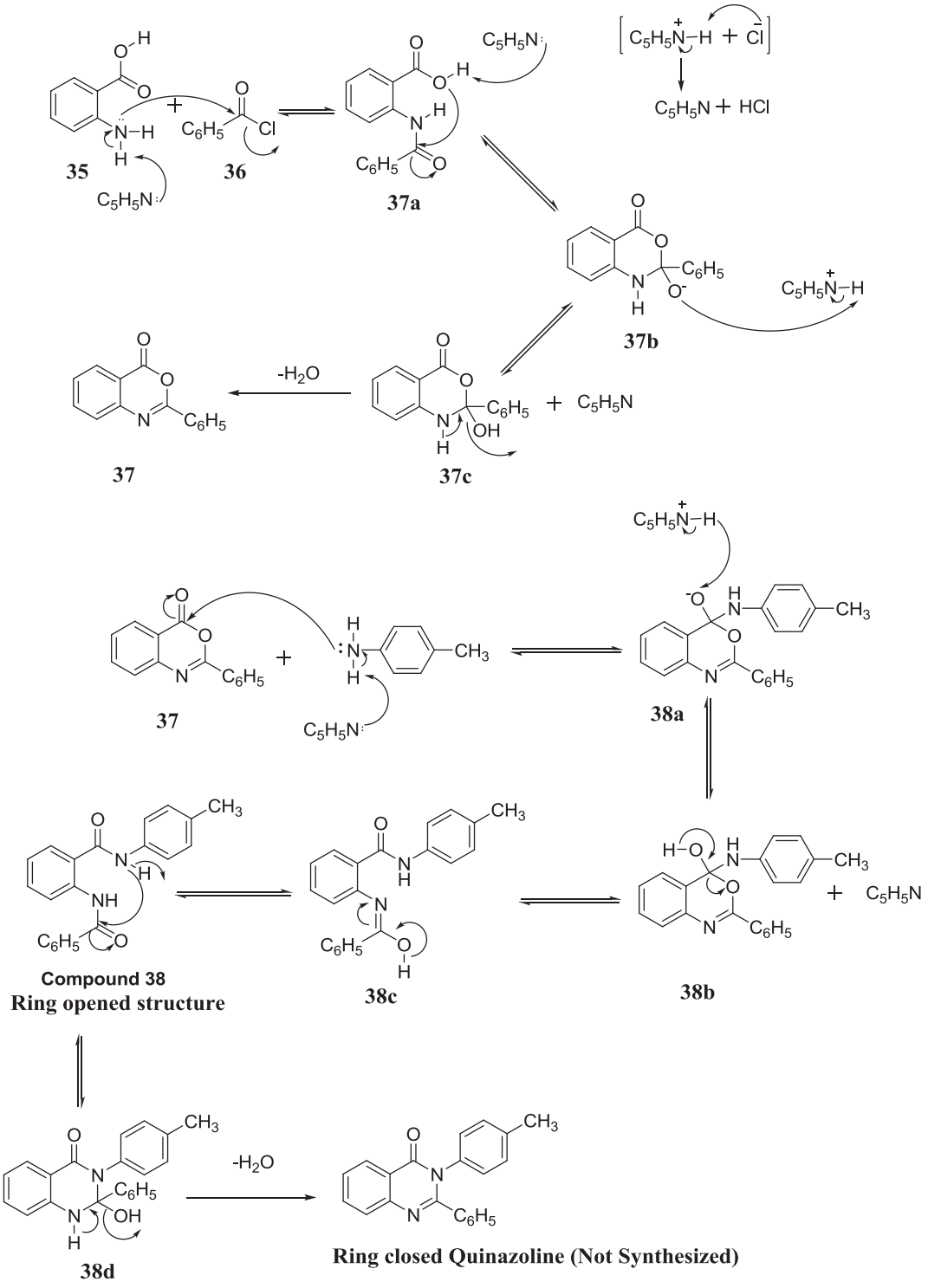


Chart 5. Reaction mechanism of ring opening of compound **38** in the synthesis of target compound **39**–**42** (Scheme 4).

bath for 1 h. The mixture was cooled and methanol was added to the mixture. The separated solid was collected by filtration, washed with methanol, dried and crystallized from ethanol.

*7.4.1. 1- (2-Furan-2-yl)-4-oxoquinazoline-3(4H)-yl) thiourea (**6**)*

This compound was prepared and purified as per the above mentioned procedure: yield 24%; mp 228–231 °C; IR (KBr) ν_{max} 3648, 2918, 1658,1632,1504,1455, 1320 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 7.11–8.80 (m, 7H, Ar–H and furan-H), 9.99 (s, 1H, NH), 12.32 (s, 2H, NH2); ^{13}C NMR (DMSO-d_6) δ ppm: 180.3, 168.5, 154.3, 143.8, 141.3, 140.7, 132.4, 128.7, 126.8, 120.6, 108.9, 108.4; HRMS (EI) m/z calcd for $C_{13}H_{10}N_4O_2S$: 286.0524; found: 286.0527.

*7.4.2. 2-(furan-2-yl)-4-oxoquinazoline-3(4H)-carboxamide (**7**)*

This compound was prepared and purified as per the above mentioned procedure: yield 18%; mp 215–218 °C; IR (KBr) ν_{max}

Table 1
Sixty human tumor cell line anticancer screening data at single dose assay (10^{-5} M concentration) as percent cell growth promotion of compound **5**, **10**, **11**, **14**, **15**, **21**, **39**, **40**, **41**, **42**, **48b**, **48c**, **48e**, **48f**, **48g**, **48h**, **48i**.

	5	10	11	14	15	21	39	40	41	42	48b	48c	48e	48f	48g	48h	48i
Leukemia																	
CCRF-CEM	98.16	87.86	98.87	96.43	103	83.12	40.37	52.41	79.93	53.89	99.77	93.78	77.99	81.79	89.58	81.59	41.14
HL-60(TB)	95.84	94.52	93.06	84.98	96.67	89.12	50.34	94.11	97.49	92.43	96.53	94.70	84.38	87.19	77.83	91.21	26.78
K-562	105.54	98.25	95.39	94.72	95.66	101.3	40.21	57.81	96.88	62.47	79.20	99.20	107	105	61.44	90.78	77.33
MOLT-4	101.31	91.05	87.33	99.10	100	99.12	44.21	59.17	86.81	77.32	84.40	88.59	75.47	84.64	63.07	69.92	57.51
RPMI-8226	NT	NT	117.5	108	120	92.65	53.22	56.24	79.36	63.43	108	102	85.51	100	47.73	77.53	63.38
SR	94.70	92.85	101.4	109	109	94.12	94.97	81.19	106.41	70.89	97.29	97.73	99.18	79.22	83.80	81.40	44.46
Non-Small Cell Lung Cancer																	
A549/ATCC	113.82	104.77	106.3	101	102	38.12	75.71	70.02	99.78	91.49	100	93.12	85.66	97.05	64.03	90.64	77.16
EKVX	109.13	98.39	97.23	88.81	80.41	64.12	85.24	86.68	100	87.70	79.01	99.04	92.68	92.96	22.23	81.90	60.40
HOP-62	112.74	107.05	106	111	104	−34.84	95.55	105	94.69	93.96	97.73	99.49	101	100	88.30	87.33	73.71
NCI-H226	97.88	78.42	114.6	107	105	53.52	79.29	85.77	95.46	84.69	96.35	95.59	99.33	105	65.68	87.18	79.35
NCI-H23	105.41	98.82	110.8	94.62	95.98	64.87	91.38	73.51	105	91.39	93.86	105	102	102	52.23	92.16	76.93
NCI-H322M	97.18	97.61	119.5	102	110	36.23	71.88	89.27	91.92	81.13	95.01	120	NT	97.59	86.40	94.87	80.01
NCI-H460	108.52	95.38	115.5	116	107	28.38	92.10	72.92	107	94.36	NT	104	95.51	104	70.22	94.48	80.34
NCI-H522	NT	109.67	90.78	106	114	10.38	69.87	70.95	99.45	70.10	NT	NT	NT	NT	NT	NT	NT
Colon Cancer																	
COLO 205	107.29	103.97	NT	124	128	32.76	101	124	115	121	119	105	119	110	75.70	104	96.37
HCC-2998	119.50	120.31	103.3	105	96.83	34.89	94.19	78.38	99.70	93.69	99.44	NT	123	90.32	86.35	NT	102
HCT-116	105.94	99.69	109.7	103	108	24.88	70.71	49.35	92.70	84.74	78.83	88.47	89.77	87.81	35.79	73.92	65.39
HCT-15	108.36	93.69	105.5	104	109	62.36	57.75	65.81	98.82	73.53	101	114	96.67	93.83	96.13	103	74.29
HT 29	103.19	92.00	99.28	108	103	52.78	97.64	89.94	121	111	94.19	89.43	86.49	101	50.17	80.40	83.56
KM 12	110.22	104.99	108.4	107	110	26.67	67.28	64.38	106	93.79	90.27	104	98.91	104	79.70	97.42	77.92
SW-620	107.69	106.15	101.9	106	106	34.38	101	99.16	109	107	NT	98.13	95.64	102	83.03	96.03	93.22
CNS Cancer																	
SF-268	106.30	106.85	98.43	104	107	72.86	69.03	82.84	108	98.17	94.82	109	91.53	107	88.12	99.47	81.66
SF-295	117.66	108.58	103.8	114	122	52.12	97.53	52.07	162	58.93	100	127	82.46	104	58.32	110	93.22
SF-539	95.42	104.20	86.82	102	97.41	24.89	81.74	91.80	110	102	101	125	111	85.81	97.75	94.92	97.28
SNB-19	101.58	91.35	110.7	111	107	62.14	86.41	74.25	104	90.58	94.19	100	97.81	96.81	82.87	98.90	76.60
SNB-75	86.97	89.20	87.71	80	71.39	32.38	99.47	84.55	85.88	82.74	NT	NT	93.68	NT	NT	NT	NT
U251	110.85	102.8	99.55	100	107	37.22	103	60.68	103	95.87	90.27	107	95.56	102	79.81	104	83.34
Melanoma																	
LOX IMVI	107.97	98.82	101.6	109	94.63	34.24	69.03	74.93	92.00	84.87	91.83	100	95.29	103	56.83	93.90	78.17
MALME-3M	122.97	102.96	118.8	108	115	78.64	97.53	91.75	101	78.99	86.98	90.35	86.88	102	63.63	108	83.19
M14	89.53	103.37	113.1	112	107	87.98	81.74	78.50	92.83	83.75	102	99.32	100	92.21	76.83	99.58	70.20
MDA-MB-435	124.51	112.17	107.2	108	101	90.21	86.41	82.15	107	90.52	90.95	109	96.11	102	88.93	105	81.04
SK-MEL-2	103.59	93.19	115.3	116	136	67.89	99.47	90.64	104	96.46	NT	NT	NT	NT	NT	NT	NT
SK-MEL-28	109.58	115.08	107.1	113	111	38.98	103	101	115	107	86.57	88.08	102	124	94.52	118	95.95
SK-MEL-5	111.56	94.96	108.4	103	105	48.82	76.71	82.15	86.16	77.57	96.24	101	95.26	97.96	17.40	75.46	68.43
UACC-257	112.27	107.43	100.1	103	112	82.72	94.49	94.73	104	103	93.79	113	117	102	67.72	111	81.10
UACC-62	92.42	84.67	107	99	101	62.82	40.16	79.67	98.83	84.87	79.86	100	96.99	84.34	61.37	80.62	58.04
Ovarian Cancer																	
IGROV1	103.91	91.67	117	110	117	71.23	85.60	89.85	96.30	78.34	101	103	71.03	116	87.44	79.39	59.92
OVCAR-3	114.53	105.38	108	107	109	27.98	89.47	86.93	107	88.79	92.52	110	102	107	65.02	107	81.53
OVCAR-4	114.55	100.60	98.00	100	101	4.38	82.05	85.63	NT	NT	NT	NT	107	NT	**2.71**	NT	25.22
OVCAR-5	100.49	98.22	99.82	105	108	37.89	96.06	123	116	99.95	94.90	104	102	102	95.41	101	86.09
OVCAR-8	110.28	104.87	103	106	100	26.87	86.46	88.85	105	104	97.32	103	100	108	82.17	92.09	75.12
NCI/ADR-RES	112.30	102.28	111	109	104	12.24	71.73	95.06	117	112	89.75	103	100	106	53.22	95.82	82.43
SK-OV-3	106.84	107.59	110	111	116	25.85	92.69	95.35	96.53	87.56	NT	NT	NT	NT	73.61	85.70	NT
Renal Cancer																	
786-0	104.23	105.17	108	115	103	26.39	81.43	75.14	95.86	84.31	95.67	90.69	94.31	90.32	76.68	90.52	89.92
A-498	97.65	106.88	−23	94.62	69.42	36.82	85.08	NT	NT	NT	NT	105	88.72	88.48	71.11	95.89	92.56
ACHN	98.81	101.24	101	104	100	23.89	58.96	82.68	97.71	87.29	102	100	93.62	103	76.83	94.36	69.99
CAKI-1	102.81	102.24	100	83.31	89.89	62.86	70.25	90.60	95.90	83.56	69.32	111	76.71	107	77.88	83.86	56.68
RXF-393	117.15	109.93	113	114	117	82.73	97.37	82.15	95.14	98.83	105	107	106	99.96	97.82	87.00	87.29
SN 12C	98.60	99.34	105	104	103	36.81	80.93	79.73	96.62	87.79	88.36	94.09	94.78	100	74.42	88.34	78.21
TK-10	98.03	94.73	102	126	127	73.98	100	123	97.64	114	103	86.49	107	113	44.74	56.15	43.48
UO-31	68.92	68.61	104	84.80	83.88	62.12	39.29	52.88	68.52	49.85	63.70	86.51	85.96	84.96	58.60	60.33	49.71
Prostate Cancer																	
PC-3	91.05	86.25	118	109	115	78.23	61.81	65.20	94.13	75.75	125	103	96.98	119	NT	113	63.90
DU-145	122.21	111.42	113	104	112	56.23	100	107	108	111	97.76	103	97.51	95.35	74.33	98.54	76.88
Breast Cancer																	
MCF7	103.51	63.47	95.61	98.40	98.82	63.86	77.81	82.72	96.33	100	61.74	101	89.91	77.51	40.30	82.73	51.80
MDA-MB-231/ATCC	93.48	83.73	102	94.46	102	52.12	76.35	81.11	96.74	87.48	93.29	97.02	95.18	89.23	77.23	96.56	53.69
HS 578T	NT	NT	118	100	113	83.85	104	67.95	100	80.44	NT	107	110	119	90.10	87.08	48.80
BT -549	103.70	100.59	111	109	127	13.63	65.95	76.41	95.53	86.19	NT	NT	NT	NT	NT	NT	NT
T-47D	106.81	83.00	103	103	106	62.59	66.17	82.14	89.85	86.44	NT	NT	NT	NT	34.60	63.43	NT
MDA-MB-468	115.34	101.43	106	108	108	78.92	77.87	83.46	95.39	81.99	101	104	114	109	39.93	98.24	59.53

NT- Not Tested, 30-40% growth inhibition, 40-50% growth inhibition, 50-70% growth inhibition, 70-90% growth inhibition, 90-100% growth inhibition, Highly potent compound.

3130, 2933, 1655, 1641, 1558, 1460, 1449 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 7.43–8.10 (m, 7H, Ar–H and furan-H), 12.39 (s, 2H, NH2); ^{13}C NMR (DMSO-d_6) δ ppm: 170.8, 158.4, 156.4, 143.7, 141.3, 140.7, 133.4, 127.3, 126.6, 118.8, 108.9, 108.6; HRMS (EI) *m/z* calcd for $C_{13}H_9N_3O_3$: 255.0644; found: 255.0646.

*7.4.3. 2-(furan-2-yl)-4-oxoquinazoline-3(4H)-carbothioamide (**8**)*

This compound was prepared and purified as per the above mentioned procedure: yield 23%; mp 222–224 °C; IR (KBr) ν_{max} 3124, 2916, 1675, 1642, 1549, 1458, cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 7.38–7.98 (m, 7H, Ar–H and furan-H), 12.17 (s, 2H, NH_2); ^{13}C

Table 2
NCI in vitro testing result of compound 21 (NSC D-753439/1) at five dose level in μM.

Panel	Cell Line	GI_{50}			TGI	LC_{50}
		Concentration per cell line	Subpanel MID[b]	Selectivity ratio (MID[a]: MID[b])		
Leukemia	CCRF-CEM	11.8	72.63	0.170	> 100	> 100
	HL-60(TB)	23.8			> 100	> 100
	K-562	> 100			> 100	> 100
	MOLT-4	> 100			> 100	> 100
	RPMI-8226	> 100			> 100	> 100
	SR	> 100			> 100	> 100
Non-Small Cell Lung Cancer	A549/ATCC	4.78	4.65	2.65	> 100	> 100
	EKVX	7.23			> 100	> 100
	HOP-62	3.56			13.7	> 100
	NCI-H226	4.12			> 100	> 100
	NCI-H23	7.87			> 100	> 100
	NCI-H322M	4.11			76.86	> 100
	NCI-H460	3.45			8.41	> 100
	NCI-H522	2.14			6.45	82.9
Colon Cancer	COLO 205	4.96	4.49	2.75	34.1	> 100
	HCC-2998	5.68			> 100	> 100
	HCT-116	3.32			23.6	> 100
	HCT-15	5.73			> 100	> 100
	HT 29	3.42			> 100	> 100
	KM 12	3.65			25.4	> 100
	SW-620	4.68			12.7	> 100
CNS Cancer	SF-268	6.84	4.65	2.65	> 100	> 100
	SF-295	3.26			> 100	> 100
	SF-539	3.28			21.2	> 100
	SNB-19	6.34			12.8	> 100
	SNB-75	4.10			7.51	> 100
	U251	4.12			32.3	> 100
Melanoma	LOX IMVI	4.54	6.94	1.78	> 100	> 100
	MALME-3M	7.23			> 100	> 100
	M14	10.8			> 100	> 100
	MDA-MB-435	8.23			16.96	> 100
	SK-MEL-2	6.86			> 100	> 100
	SK-MEL-28	4.45			18.6	> 100
	SK-MEL-5	5.56			31.8	> 100
	UACC-257	8.34			> 100	> 100
	UACC-62	6.38			> 100	> 100
Ovarian Cancer	IGROV1	6.12	3.89	3.17	> 100	> 100
	OVCAR-3	4.12			6.87	> 100
	OVCAR-4	1.82			6.48	> 100
	OVCAR-5	5.12			> 100	> 100
	OVCAR-8	3.98			25.8	> 100
	NCI/ADR-RES	2.45			8.78	52.7
	SK-OV-3	3.68			14.8	> 100
Renal Cancer	786–0	3.94	6.41	1.92	14.9	> 100
	A-498	5.76			16.7	> 100
	ACHN	3.12			> 100	> 100
	CAKI-1	7.99			34.8	> 100
	RXF-393	11.6			42.6	> 100
	SN 12C	4.89			> 100	> 100
	TK-10	7.84			> 100	> 100
	UO-31	6.12			> 100	> 100
Prostate Cancer	PC-3	8.23	6.30	1.96	> 100	> 100
	DU-145	4.38			> 100	> 100
Breast Cancer	MCF7	5.29	7.23	1.70	> 100	> 100
	MDA-MB-231/ATCC	3.13			7.84	> 100
	HS 578T	15.2			> 100	> 100
	BT -549	2.92			6.8	72.4
	T-47D	6.89			> 100	> 100
	MDA-MB-468	9.96			> 100	> 100
MID[a]		12.36				

MID[a] = Average sensitivity of all cell line in μM.
MID[b] = Average sensitivity of all cell line of a particular subpanel in μM.

NMR (DMSO-d_6) δ ppm: 180.4, 172.4, 158.2, 143.7, 141.3, 140.7, 132.6, 128.8, 126.6, 118.7, 108.8, 108.2; HRMS (EI) m/z calcd for $C_{13}H_9N_3O_2S$: 271.0415; found: 271.0418.

7.5. 2-(furan-2-yl)-3-(phenylamino) quinazolin-4(3H)-one (**9**)

A mixture of 2-(furan-2-yl)-3-hydroxyquinazolin-4(3*H*)-one **4** (0.01 mol) and phenyl hydrazide (0.01 mol) in ethanol (20 ml) was heated under reflux for 10 h. The reaction mixture was concentrated, cooled and the separated solid was crystallized out from acetone to afford compound **9**.Yield 68%; mp 158–162 °C; IR (KBr) ν_{max} 3114, 2913, 1673, 1640, 1543, 1458 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 7.28–8.10 (m, 12H, Ar–H and furan-H), 10.37(s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 163.8, 158.6, 148.5, 142.7, 141.6, 140.6, 133.2, 132.4, 129.2, 127.9, 126.8, 121.6, 118.8, 108.8, 108.4; HRMS (EI) m/z calcd for $C_{18}H_{13}N_3O_2$: 303.1008; found: 303.1011.

7.6. 4-[2-(furan-2-yl)-4-oxoquinazolin-3(4H)-yl] benzoic acid (**10**)

Equimolar amount of 2-(furan-2-yl)-4*H*-3, 1-benzoxazin-4-one **4** and p-amino benzoic acid was fused together at 200 °C in an oil bath for 1 h. The mixture was cooled and methanol was added to the mixture. The separated solid was collected by filtration, washed with methanol, dried and crystallized from acetic acid. Yield 56%; mp 184–186 °C; IR (KBr) ν_{max} 3450, 2851, 1668, 1614, 1502, 1438, 1374 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 6.99 (t, 1H, $J = 4.0$ Hz, furan-H), 7.19–8.68 (m, 10H, Ar–H and furan-H), 11.68(s, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ ppm: 168.8, 161.8, 158.6, 143.6, 142.1, 141.8, 138.4, 132.4, 130.5, 128.3, 126.8, 124.8, 124.3, 118.6, 108.8, 108.3; HRMS (EI) m/z calcd for $C_{19}H_{12}N_2O_4$: 332.0797; found: 332.0799.

7.7. N-{2-[(4-sulfamoylphenyl) carbamoyl] phenyl} furan-2-carboxamide (**11**)

Equimolar amount of 2-(furan-2-yl)-4*H*-3, 1-benzoxazin-4-one **4** and sulphanilamide were fused together at 200 °C in an oil bath for 1 h. The mixture was cooled and methanol was added to the mixture. The separated solid was collected by filtration, washed with methanol, dried and crystallized from 1,4 dioxane. Yield 72%; mp 188–189 °C; IR (KBr) ν_{max} 3350, 2913, 1676, 1624,1606, 1505, 1453, 1328,1140 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 3.43 (s, 2H, NH_2), 7.68 (d, 1H, $J = 8.0$ Hz, Ar–H), 6.57–7.98 (m, 10H, Ar–H and furan-H) 10.53 (s,1H,–NHCO–), 11.71(s,1H,–CONH–); ^{13}C NMR (DMSO-d_6) δ ppm; 168.5, 163.7, 146.7, 142.8, 141.4, 136.4, 135.5, 130.2, 128.7, 127.6, 124.4, 122.3, 118.6, 116.3, 114.4, 112.3; HRMS (EI) m/z calcd for $C_{18}H_{15}N_3O_5S$: 385.0732; found: 385.0735.

7.8. N-(2-(p-tolyl carbamoyl) phenyl) furan-2-carboxamide (**12**)

Method A: A mixture of 2-furanyl-4*H*-3, 1-benzoxazin-4-one 4 and 4-methyl aniline was fused together equimolarly at 200 °C in an oil bath for 1 h. The mixture was cooled and methanol was added to the mixture. The separated solid was collected by filtration, washed with methanol, dried and crystallized from acetic acid.

Method B: A mixture of 2-furanyl-4*H*-3, 1-benzoxazin-4-one 4 (0.01 mol) and 4-methyl aniline (0.01 mol) in dry pyridine (50 ml) was heated under reflux for 8 h. Subsequently, mixture was poured into water (containing few drops of HCl) solid thus separated was filtered, washed repeatedly with water. It was dried and crystallized from acetic acid. Yield 52%; mp 141–142 °C; IR (KBr) ν_{max} 3111, 2951, 1687,1632,1458, 1442 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 3.69 (s,3H, CH_3), 7.45 (d,1H, $J = 8.0$ Hz, Ar–H), 6.55–8.06 (m,10H, Ar–H and furan-H), 10.26 (s,1H,–NHCO–), 11.72(s,1H,–CONH–); ^{13}C NMR (DMSO-d_6) δ ppm: 168.8, 163.4, 146.5, 142.6, 138.7, 136.8, 134.4, 132.8, 128.4, 126.6, 124.4, 122.5, 120.5, 118.4, 116.7, 112.6, 23.6; HRMS (EI) m/z calcd for $C_{19}H_{16}N_2O_3$: 320.1161; found: 320.1165.

7.9. General procedure for the synthesis of N-(2-(4- substituted styryl phenyl carbamoyl) phenyl) furan-2-carboxamides (**13**–**17**)

A mixture of 2-(furan-2-yl)-3-(4-methylphenyl)quinazolin-4 (3H)-one **12** (0.01 mol) and substituted aromatic aldehydes in equimolar quantities (0.01 mol) in glacial acetic acid (50 ml) with few drops of concentrated sulphuric acid was heated under reflux for 4 h. Subsequently, mixture was poured into water and the residual solid was filtered, washed repeatedly with water. It was dried and crystallized from ethanol.

7.9.1. N-(2-(4-styryl phenyl carbamoyl) phenyl) furan-2-carboxamide (**13**)

This compound was prepared and purified as per the above mentioned procedure: yield 40%; mp 231–233 °C; IR (KBr) ν_{max} 3241, 2821, 1660, 1649, 1454, 1412 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 7.72 (d, 1H, $J = 16.6$ Hz, olefinic CH), 6.74–8.70 (a set of signals, 17 H, Ar–H, furan-H and olefinic CH), 10.19 (s, 1H,–NHCO–), 12.08 (s, 1H,–CONH–); ^{13}C NMR (DMSO-d_6) δ ppm:168.7, 163.2, 146.7, 144.4, 138.5, 136.5, 134.7, 132.8, 129.8, 128.8, 128.5, 126.9, 126.2, 124.5, 122.7, 120.8, 118.6, 114.4, 112.4; HRMS (EI) m/z calcd for $C_{26}H_{20}N_2O_3$: 408.1474; found: 408.1476.

7.9.2. N-(2-(4-(4 – cyano styryl) phenyl carbamoyl) phenyl) furan-2-carboxamide (**14**)

This compound was prepared and purified as per the above mentioned procedure: yield 46%; mp 204–208 °C; IR (KBr) ν_{max} 3238, 2818, 2215, 1665, 1641, 1460, 1421, 1416 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 7.67 (d, 2H, $J = 16.6$ Hz, olefinic CH), 6.31–8.25 (a set of signals, 16H, Ar–H, furan-H and olefinic CH), 10.27 (s, 1H,–NHCO–), 11.89 (s, 1H,–CONH–); ^{13}C NMR (DMSO-d_6) δ ppm: 168.2, 163.1, 146.7, 144.9, 142.3, 136.6, 135.5, 132.1, 129.7, 128.7, 128.5, 126.7, 126.2, 125.2, 124.6, 120.5, 119.6, 118.4, 114.2, 111.8; HRMS (EI) m/z calcd for $C_{27}H_{19}N_3O_3$: 433.1426; found:433.1429.

7.9.3. N-(2-(4-(4 – chloro styryl) phenyl carbamoyl) phenyl) furan-2-carboxamide (**15**)

This compound was prepared and purified as per the above mentioned procedure: yield 32%; mp 190–193 °C; IR (KBr) ν_{max} 3237, 2833, 1660, 1638, 1575, 1406, 777 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 7.52 (d, 2H, $J = 16.6$ Hz, olefinic CH), 6.83–8.45 (a set of signals, 16H, Ar–H, furan-H and olefinic CH), 9.48 (s, 1H,–NHCO–), 12.17 (s, 1H,–CONH–); ^{13}C NMR (DMSO-d_6) δ ppm: 168.1, 163.4, 149.2, 144.2, 138.4, 136.3, 134.7, 133.3, 132.1, 130.1, 128.9, 128.2, 126.4, 126.1, 125.3, 122.5, 121.5, 118.2, 114.3, 111.4; HRMS (EI) m/z calcd for $C_{26}H_{19}ClN_2O_3$: 442.1084; found: 442.1088.

7.9.4. N-(2-(4-(4 – methyl styryl) phenyl carbamoyl) phenyl) furan-2-carboxamide (**16**)

This compound was prepared and purified as per the above mentioned procedure: yield 23%; mp 221–224 °C; IR (KBr) ν_{max} 3203, 2910, 1633, 1456 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 3.37(s, 3H, CH_3), 7.45 (d, 2H, $J = 16.6$ Hz, olefinic CH), 6.81–8.48 (a set of signals, 16H, Ar–H, furan-H and olefinic CH), 9.41 (s, 1H,–NHCO–), 12.10 (s, 1H,–CONH–); ^{13}C NMR (DMSO-d_6) δ ppm: 168.1, 163.9, 149.1, 142.6, 138.8, 138.1, 137.6, 135.8, 134.2, 129.8, 128.8, 128.6, 128.1, 126.3, 126.3, 124.7, 122.1, 120.2, 118.6, 114.6, 111.4, 23.3; HRMS (EI) m/z calcd for $C_{27}H_{22}N_2O_3$: 422.1630; found: 422.1633.

7.9.5. N-(2-(4-(4-nitro styryl) phenyl carbamoyl) phenyl) furan-2-carboxamide (**17**)

This compound was prepared and purified as per the above mentioned procedure: yield 21%; mp 238–240 °C; IR (KBr) ν_{max}

3301,2902,1647,1560, 1556, 1401, 1353, cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 7.71 (d, 2H, J = 16.6 Hz, olefinic CH), 6.75–8.72 (a set of signals, 16H, Ar–H, furan-H and olefinic CH), 10.29 (s, 1H,–NHCO–), 12.11 (s, 1H,–CONH–); ^{13}C NMR (DMSO-d_6) δ ppm: 168.5, 163.7, 146.4, 144.2, 142.6, 142.3, 136.8, 136.3, 132.6, 129.3, 128.6, 126.4, 126.7, 125.3, 122.7, 122.2, 121.5, 118.2, 114.3, 111.6; HRMS (EI) m/z calcd for $C_{26}H_{19}N_3O_5$: 453.1325; found: 453.1328.

7.10. 3-amino-2-(furan-2-yl) quinazolin-4(3H)-one (**18**)

3-amino-2-(furan-2-yl) quinazolin-4(3*H*)-one (0.01 mol) **4** was heated to melt and excess of hydrazine hydrate was added. The mixture was fused together at 200 °C in an oil bath for 1 h. The separated solid was cooled and acetone was added to the mixture. The separated solid was collected by filtration, washed with methanol, dried and crystallized from acetone. Yield 42%; mp 197–199 °C; IR (KBr) ν_{max} 3390, 2980, 1656, 1638, 1579, 1472, 1450 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 5.18 (s, 2H, NH_2), 7.86 (t, 1H, J = 4.0 Hz, furan-H), 6.61–7.98 (m, 6H, Ar–H and furan-H); ^{13}C NMR (DMSO-d_6) δ ppm: 164.8, 158.9, 146.6, 142.2, 141.6, 132.8, 126.3, 125.8, 116.2, 108.4, 108.2; HRMS (EI) m/z calcd for $C_{12}H_9N_3O_2$: 227.0695; found: 227.0699.

7.11. General procedure for the synthesis of 2-(furan-2-yl)-3-substituted arylideneamino-3, 4 dihydro-quinazoline-4-ones (**19**–**34**)

Equimolar amount of 3-amino-2-(furan-2-yl) quinazolin-4(3*H*)-one **18** (0.01 mol) and the appropriate aromatic aldehydes (0.015 mol) in glacial acetic acid was heated under reflux for 4 h. The separated solid was poured into water, filtered, washed with water and crystallized from ethanol to give required products.

7.11.1. 3-(anthracene-9-yl methylene amino)-2-(furan-2-yl) quinazoline-4(3H) one (**19**)

This compound was prepared and purified as per the above mentioned procedure: yield 62%; mp 289–291 °C; IR (KBr) ν_{max} 3050, 1684, 1582, 1530, 1448 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 6.54–8.65 (m, 16H, Ar–H and furan-H), 8.77 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ ppm: 169.7, 160.2, 144.5, 142.6, 141.2, 140.4, 132.4, 130.3, 128.6, 128.4, 127.6, 126.2, 124.2, 120.2, 108.9, 108.4; HRMS (EI) m/z calcd for $C_{27}H_{17}N_3O_2$: 415.1321; found: 415.1323.

7.11.2. 3-(4-chloro benzylideneamine))-2-(furan-2-yl) quinazoline-4(3H) one (**20**)

This compound was prepared and purified as per the above mentioned procedure: yield 48%; mp 210–212 °C; IR (KBr) ν_{max} 2931, 1648, 1502, 1355, 560 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 7.16–7.94 (m, 11H, Ar–H), 8.78 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ ppm: 169.4, 160.5, 144.1, 142.3, 140.4, 138.2, 132.4, 131.3, 129.4, 128.7, 127.1, 125.3, 120.4, 108.6, 108.4; HRMS (EI) m/z calcd for $C_{19}H_{12}ClN_3O_2$: 349.0618; found: 349.0621.

7.11.3. 3-(2-chloro benzylideneamine))-2-(furan-2-yl) quinazoline-4(3H) one (**21**)

This compound was prepared and purified as per the above mentioned procedure: yield 53%; mp 201–204 °C; IR (KBr) ν_{max} 2920, 1650, 1488, 1399, 554 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 7.09 (t, 1H, J = 4.0 Hz, furan-H), 7.50–8.25 (m, 10H, Ar–H and furan-H), 8.79 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ ppm: 169.1, 160.4, 144.2, 142.3, 141.8, 140.3, 134.6, 132.2, 132.1, 131.4, 130.4, 127.4, 127.1, 125.6, 125.9, 120.3, 108.8, 108.9; HRMS (EI) m/z calcd for $C_{19}H_{12}ClN_3O_2$: 349.0618; found:349.0622.

7.11.4. 3-(benzylideneamino))-2-(furan-2-yl) quinazoline-4(3H) one (**22**)

This compound was prepared and purified as per the above mentioned procedure: yield 51%; mp 206–207 °C; IR (KBr) ν_{max} 2927, 1682, 1536, 1394 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 6.60 (t, 1H, J = 4.0 Hz, furan-H), 7.10–8.26 (m, 11 H, Ar–H and furan-H), 8.78 (s, 1H, N=CH); ^{13}C NMR(DMSO-d_6) δ ppm: 169.9, 160.4, 144.1, 141.3, 140.1, 132.7, 132.4, 131.3, 129.4, 128.1, 127.7, 125.1, 120.9, 108.8, 108.4; HRMS (EI) m/z calcd for $C_{19}H_{13}N_3O_2$: 315.1008; found: 315.1010.

7.11.5. 3-(4-hydroxy-3-methoxy benzylideneamino))-2-(furan-2-yl) quinazoline-4(3H) one (**23**)

This compound was prepared and purified as per the above mentioned procedure: yield 32%; mp 270–273 °C; IR (KBr) ν_{max} 3344, 2944, 1674, 1470, 1379 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 3.94 (s, 3H, OCH_3), 7.51–8.15 (m, 10H, Ar–H and furan-H), 8.89 (s, 1H, N=CH), 11 (s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ ppm: 169.8, 160.5, 156.2, 152.1, 148.2, 143.3, 142.3, 140.8, 132.3, 131.6, 128.2, 126.3, 122.2, 120.2, 118.2, 114.4, 108.4, 108.1, 54.4; HRMS (EI) m/z calcd for $C_{20}H_{15}N_3O_4$: 361.1063; found: 361.1066.

7.11.6. 3-(4-hydroxy benzylideneamino))-2-(furan-2-yl) quinazoline-4(3H) one (**24**)

This compound was prepared and purified as per the above mentioned procedure: yield 38%; mp 199–202 °C; IR (KBr) ν_{max} 3330, 2921, 1641, 1466 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 6.56–8.70 (m, 11H, Ar–H and furan-H), 8.78 (s, 1H, N=CH), 11.99 (s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ ppm: 170.7, 160.4, 148.4, 142.4, 140.6, 132.6, 130.6, 128.6, 126.2, 126.1, 120.8, 118.2, 108.4, 108.2; HRMS (EI) m/z calcd for $C_{19}H_{13}N_3O_3$: 331.0957; found: 331.0960.

7.11.7. 3-(4-methyl benzylideneamino))-2-(furan-2-yl) quinazoline-4(3H) one (**25**)

This compound was prepared and purified as per the above mentioned procedure: yield 32%; mp 218–220 °C; IR (KBr) ν_{max} 2919, 1650, 1460, 1413 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 2.48 (s, 3H, CH_3), 6.56–7.87 (m, 11H, Ar–H and furan-H), 8.87 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ ppm: 169.8, 160.9, 146.8, 143.6, 142.4, 140.8, 132.2, 130.4, 128.4, 126.2, 125.8, 125.6, 120.4, 108.4, 108.2, 22.5; HRMS (EI) m/z calcd for $C_{20}H_{15}N_3O_2$: 329.1164; found: 329.1168.

7.11.8. 3-(3-bromo benzylideneamino))-2-(furan-2-yl) quinazoline-4(3H) one (**26**)

This compound was prepared and purified as per the above mentioned procedure: yield 38%; mp 213–214 °C; IR (KBr) ν_{max} 2927, 1677, 1521, 11456, 670 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 6.57–7.96 (m, 11H, Ar–H and furan-H), 8.86 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ ppm: 169.6, 160.6, 144.9, 143.8, 142.6, 140.6, 136.4, 132.6, 131.6, 129.4, 128.6, 127.7, 127.5, 125.3, 122.5, 120.5, 108.6, 108.4; HRMS (EI) m/z calcd for $C_{19}H_{12}BrN_3O_2$: 393.0113 found: 393.0116.

7.11.9. 3-(4-cyano benzylideneamino))-2-(furan-2-yl) quinazoline-4(3H) one (**27**)

This compound was prepared and purified as per the above mentioned procedure: yield 62%; mp 222–225 °C; IR (KBr) ν_{max} 3057, 2226, 1684, 1534, 1393 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 6.60 (t, 1H, J = 4.0 Hz, furan-H), 7.10–8.26 (m, 10H, Ar–H and furan-H), 8.79 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ ppm: 169.9, 160.6, 144.2, 142.8, 141.6, 136.2, 133.2, 131.2, 127.3, 126.8, 126.4, 116.6, 114.4, 108.4, 108.2; HRMS (EI) m/z calcd for $C_{20}H_{12}N_4O_2$: 340.0960; found: 340.0964.

7.11.10. 3-(2, 5-dimethoxy benzylideneamino))-2-(furan-2-yl) quinazoline-4(3H) one (**28**)

This compound was prepared and purified as per the above mentioned procedure: yield 28%; mp 251–254 °C; IR (KBr) ν_{max}

2958, 1685, 1489, 1395 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 3.96 (s, 6H, OCH_3), 7.10–8.26 (m, 10H, Ar–H and furan-H), 8.88 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ ppm: 169.2, 160.4, 152.3, 148.4, 142.3, 142.4, 141.4, 140.2, 132.2, 127.4, 126.6, 120.4, 116.4, 114.2, 112.4, 108.4, 108.1, 58.2; HRMS (EI) *m/z* calcd for $C_{21}H_{17}N_3O_4$: 375.1219; found: 375.1221.

*7.11.11. 3-(4-nitro benzylideneamino))-2-(furan-2-yl) quinazoline-4(3H) one (**29**)*

This compound was prepared and purified as per the above mentioned procedure: yield 30%; mp 246–250 °C; IR (KBr) ν_{max} 3013, 1669, 1478, 1386, 1391 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 7.90 (t, 1H, $J = 4.0$ Hz, furan-H), 6.65–7.83 (m, 10H, Ar–H and furan-H), 8.82 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ ppm: 169.8, 160.9, 152.4, 146.6, 144.2, 142.4, 138.6, 132.2, 128.2, 126.2, 124.4, 124.1, 108.8, 108.2; HRMS (EI) *m/z* calcd for $C_{19}H_{12}N_4O_4$: 360.0859; found: 360.0862.

*7.11.12. 3-(2-nitro benzylideneamino))-2-(furan-2-yl) quinazoline-4(3H) one (**30**)*

This compound was prepared and purified as per the above mentioned procedure: yield 32%; mp 250–252 °C; IR (KBr) ν_{max} 3025, 1670, 1465, 1362, 1342 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 6.70–7.83 (m, 11H, Ar–H and furan-H), 8.62 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ ppm: 169.4, 160.1, 150.6, 146.2, 143.6, 142.4, 140.4, 136.4, 132.6, 132.4, 128.2, 127.5, 125.2, 124.2, 120.2, 108.6, 108.4; HRMS (EI) *m/z* calcd for $C_{19}H_{12}N_4O_4$: 360.0859; found: 360.0861.

*7.11.13. 3-(4-bromo benzylideneamino))-2-(furan-2-yl) quinazoline-4(3H) one (**31**)*

This compound was prepared and purified as per the above mentioned procedure: yield 42%; mp 262–265 °C; IR (KBr) ν_{max} 2917, 1667, 1520, 1453, 669 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 7.16–7.94 (m, 11H, Ar–H and furan-H), 8.75 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ ppm: 169.8, 160.4, 144.2, 143.2, 140.2, 133.4, 132.8, 130.4, 128.4, 127.4, 126.2, 124.3, 120.4, 108.9, 108.6; HRMS (EI) *m/z* calcd for $C_{19}H_{12}BrN_3O_2$: 393.0113; found: 393.0116.

*7.11.14. 3-(4-fluro benzylideneamino))-2-(furan-2-yl) quinazoline-4(3H) one (**32**)*

This compound was prepared and purified as per the above mentioned procedure: yield 24%; mp 201–204 °C; IR (KBr) ν_{max} 2939, 1655, 1467, 1376, 1010 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 6.55–7.94 (m, 11H, Ar–H and furan-H), 8.74 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ ppm: 168.6, 166.8, 158.4, 143.4, 140.2, 132.6, 130.6, 128.2, 126.8, 126.6, 120.8, 114.2, 108.8, 108.4; HRMS (EI) *m/z* calcd for $C_{19}H_{12}FN_3O_2$: 333.0914; found: 333.0918.

*7.11.15. 3-(3-nitro benzylideneamino))-2-(furan-2-yl) quinazoline-4(3H) one (**33**)*

This compound was prepared and purified as per the above mentioned procedure: yield 30%; mp 244–246 °C; IR (KBr) ν_{max} 3003, 1672, 1468, 1393, 1360 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 6.65–7.91 (m, 11H, Ar–H and furan-H), 9.19 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ ppm: 169.6, 160.4, 156.4, 150.0, 146.6, 144.2, 141.6, 136.2, 134.8, 132.6, 128.6, 127.4, 126.6, 126.2, 122.8, 122.5, 108.8, 108.2; HRMS (EI) *m/z* calcd for $C_{19}H_{12}N_4O_4$: 360.0859; found: 360.0863.

*7.11.16. 3-(3-phenyl allyllidene amino))-2-(furan-2-yl) quinazoline-4(3H) one (**34**)*

This compound was prepared and purified as per the above mentioned procedure: yield 28%; mp 283–284 °C; IR (KBr) ν_{max} 2939, 1649, 1521, 1468, 1386 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 6.55–8.32 (a set of signals, 14H, Ar–H, furan-H and olefinic CH=CH), 8.88 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ ppm: 169.4, 160.4, 158.6, 146.6, 144.2, 140.4, 138.4, 136.2, 134.1, 132.4, 128.6, 128.2, 127.8, 127.4, 126.8, 126.6, 120.8, 108.4, 108.2; HRMS (EI) *m/z* calcd for $C_{21}H_{15}N_3O_2$: 341.1164; found: 341.1167.

*7.12. Synthesis of 2-phenyl-4H-benzo[d] [1,3] oxazine-4-one (**37**)*

Anthranilic acid **35** (0.1 mol) was dissolved in minimum volume of dry pyridine (30 mL) by shaking. To this solution an ice-cold solution of benzoyl chloride **36** (0.2 mol) taken in dry pyridine (30 mL), was added slowly with constant stirring. When the addition was completed (the operation of addition required half an hour), the resultant solution was subjected to vigorous stirring for 1 h mechanically subsequently, it was left as such for 1 h at room temperature and treated with a solution of sodium bicarbonate (10%). Addition of sodium bicarbonate solution was continued till the effervescence due to the evolution of carbon-dioxide ceased. The separated solid was allowed to settle down and filtered off. It was washed with cold water repeatedly till there was no smell of pyridine and unreacted benzoyl chloride. The crude benzo-oxazine was dried in vacuum overnight and recrystallization from diluted ethanol afforded analytically pure sample of 2-phenyl benzo[d] [1,3] oxazin-4-one **37** as white crystalline mass. Yield 82%; mp 109–112 °C; IR (KBr) ν_{max} 2910, 1765,1610,1510,1256 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 7.60–8.21 (m, 9H, Ar–H); ^{13}C NMR (DMSO-d_6) δ ppm: 162.6, 158.4, 148.2, 134.6, 132.8, 129.9, 128.8, 128.2, 128.2, 127.4, 122.8, 118.6.

*7.13. 2-benzamido-N-p-tolylbenzamide (**38**)*

Method A: A mixture of 2-phenyl-benzo[d] [1,3] oxazine-4-one 37 and 4-methyl aniline was fused together at 200 °C in an oil bath for 1 h. The mixture was cooled and methanol was added to the mixture. The separated solid was collected by filtration, washed with methanol, dried and crystallized from acetic acid.

Method B: A mixture of 2-phenyl-benzo[d] [1,3] oxazine-4-one 37 (0.01 mol) and 4-methyl aniline (0.01 mol) in dry pyridine (50 ml) was heated under reflux for 10 h. Subsequently, mixture was poured into water (containing few drops of HCl) solid thus separated was filtered, washed repeatedly with water. It was dried and crystallized from acetic acid. Yield 71%; mp 206–208 °C; IR (KBr) ν_{max} 2940, 1760, 1624, 1518, 1370, 1265 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 2.33 (s, 3H, CH3), 7.14–7.98 (m, 13H, Ar–H), 10.22 (s, 1H,–NHCO–), 12.11 (s, 1H,–CONH–); ^{13}C NMR (DMSO-d_6) δ ppm: 164.8, 161.4, 150.2, 138.6, 132.2, 130.1, 129.7, 129.4, 128.9, 128.8, 128.4, 127.6, 127.4, 126.4, 126.2, 24.4; HRMS (EI) *m/z* calcd for $C_{21}H_{18}N_2O_2$: 330.1368; found: 330.1371.

*7.14. General procedure for the synthesis of 2-benzamido-N-(substituted styryl phenyl) benzamide (**39**–**42**)*

A mixture of 2-benzamido-*N*-p-tolylbenzamide **38** (0.01 mol) and substituted aromatic aldehydes in equimolar quantities (0.01 mol) in glacial acetic acid (50 ml) with few drops of concentrated sulphuric acid was heated under reflux for 4 h. Subsequently, mixture was poured into water and the residual solid was filtered, washed repeatedly with water. It was dried and crystallized from ethanol.

*7.14.1. 2-benzamido-N-(4-(4-hydroxy styryl) phenyl) benzamide (**39**)*

This compound was prepared and purified as per the above mentioned procedure: yield 44%; mp 258–261 °C; IR (KBr) ν_{max} 3561, 3223, 2921, 1670, 1667, 1445 cm^{-1}; ^1H NMR (DMSO-d_6)

δ ppm: 6.68 (d, 2H, J = 15.8 Hz, olefinic CH) 6.89–8.45 (a set of signals, 18H, aromatic protons and olefinic CH), 10.20 (s, 1H,–NHCO–), 10.84 (s, 1H, OH), 12.07 (s, 1H,–CONH–); ^{13}C NMR (DMSO-d_6) δ ppm: 169.8, 166.6, 158.4, 138.5, 136.2, 134.6, 132.8, 132.4, 131.6, 130.4, 129.6, 128.8, 128.4, 127.8, 127.4, 126.2, 125.2, 122.4, 120.6, 118.6, 116.4; HRMS (EI) m/z calcd for $C_{28}H_{22}N_2O_3$: 434.1630; found: 434.1633.

*7.14.2. 2-benzamido-N-(4-(4-chloro styryl) phenyl) benzamide (**40**)*

This compound was prepared and purified as per the above mentioned procedure: yield 38%; mp 240–244 °C; IR (KBr) ν_{max} 3253, 2971, 1676, 1445,743 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 6.71 (d, 2H, J = 15.8 Hz, olefinic CH) 7.05–8.38 (a set of signals, 14H, aromatic protons and olefinic CH); 10.51 (s, 1H,–NHCO–), 12.00 (s, 1H,–CONH–); ^{13}C NMR (DMSO-d_6) δ ppm: 168.2, 166.8, 138.9, 138.4, 136.8, 135.4, 133.4, 132.4, 132.2, 130.1, 129.8, 128.6, 128.1, 127.6, 127.4, 127.2, 126.4, 124.2, 122.6, 118.8; HRMS (EI) m/z calcd for $C_{28}H_{21}ClN_2O_2$: 452.1292; found: 452.1295.

*7.14.3. 2-benzamido-N-(4-(4-hydroxy-3-methoxy styryl) phenyl) benzamide (**41**)*

This compound was prepared and purified as per the above mentioned procedure: yield 46%; mp 248–251 °C; IR (KBr) ν_{max} 3565, 3240, 2941, 1667, 1430 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 3.89 (d, 3H, OCH_3), 6.56 (s, 2H, J = 15.8 Hz, olefinic CH), 7.08–8.39 (a set of signals, 17H, aromatic protons and olefinic CH), 9.78 (s, 1H,–NHCO–), 10.56 (s, 1H, OH), 12.04 (s, 1H,–CONH–); ^{13}C NMR (DMSO-d_6) δ ppm: 168.6, 166.6, 148.8, 148.6, 138.8, 137.6, 135.6, 134.4, 132.4, 130.4, 129.12, 128.9, 128.6, 126.7, 126.5, 125.2, 124.4, 123.4, 122.6, 121.4, 118.6, 116.2, 108.4, 54.6; HRMS (EI) m/z calcd for $C_{29}H_{24}N_2O_4$: 464.1736; found: 464.1739.

*7.14.4. 2-benzamido-N-(4-(4-phenyl buta-1, 3-dienyl) phenyl) benzamide (**42**)*

This compound was prepared and purified as per the above mentioned procedure: yield 38%; mp 261–264 °C; IR (KBr) ν_{max} 3240, 2951, 1670, 1569, 1445 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 6.70 and 6.89 (d, 2H, J = 15.8 Hz, olefinic CH), 7.11–8.37 (a set of signals, 21H, aromatic protons and olefinic CH), 10.34 (s, 1H,–NHCO–), 12.09 (s, 1H,–CONH–); ^{13}C NMR (DMSO-d_6) δ ppm: 168.8, 166.5, 136.8, 136.2, 135.4, 134.4, 133.4, 132.2, 132.8, 130.0, 129.9, 129.8, 126.6, 126.4, 125.1, 124.6, 122.6, 120.6, 120.6; HRMS (EI) m/z calcd for $C_{30}H_{24}N_2O_2$: 444.1838; found: 444.1841.

*7.15. 3-methylquinoxalin-2(1H)-one (**45**)*

To a solution of o-phenylenediamine **43** (50 mM) in H_2O (60 ml) was added to a solution of pyruvic acid **44** (50 mM) in H_2O (20 ml). The mixture was stirred at RT for 10 min. At the end of this period, the separated product was filtered, washed with water and recrystallized from hot water. Yield 88%; mp 181–182 °C; IR (KBr) ν_{max} 3325, 2980, 1660, 1640, 1568, 1502, 1458 1370 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 2.41 (s, 3H, CH3), 7.2–8.6 (m, 4H, Ar–H), 12.35 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.2, 156.8, 134.6, 132.4, 130.4, 128.6, 124.7, 116.2, 22.4.

*7.16. General procedure for the synthesis of 3-(4-substituted styryl) quinoxalines-2(1H)-ones **46** (**a**–**i**)*

In the three necked round bottom flask, equipped with a mechanical stirrer, thermometer socket and condenser and, a mixture of compound(3-methyl quinoxaline-2(1H)-one **45**, (10 mM), substituted aromatic aldehydes (11 mM) in acetic acid with catalytic amount of sulphuric acid was refluxed (118°c) for 1 h. Latter the reaction mass was cooled to RT, the separated solid was filtered, washed with water and dried to obtained next compounds by using different aldehydes. The acetic acid mother liquor on dilution with water gave a gummy solid, which was extracted into chloroform (50 ml) the chloroform layer was separated and evaporated to obtain a residue, which on recrystallization from acetone gave purified compound **46** (**a**–**i**).

*7.16.1. 3- (3-nitro styryl) quinoxalin-2 (1H)-one (**46a**)*

This compound was prepared and purified as per the above mentioned procedure: yield 70%; mp 287–290 °C; IR (KBr) ν_{max} 3310, 2945, 1662, 1642, 1540, 1510, 1524, 1452, 1353 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 6.21 (d, 1H, J = 15.2 Hz, olefinic CH), 7.28–8.50 (a set of signals, 8H, aromatic protons and olefinic CH), 12.60 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.2, 158.6, 149.9, 139.2, 138.8, 136.2, 134.6, 132.7, 130.5, 130.1, 126.9, 124.5, 124.2, 123.4, 122.3, 118.2; HRMS (EI) m/z calcd for $C_{16}H_{11}N_3O3$: 293.0800; found: 293.0804.

*7.16.2. 3- (3-bromo styryl) quinoxalin-2 (1H)-one (**46b**)*

This compound was prepared and purified as per the above mentioned procedure: 3-Bromo Benzaldehyde yield 73%; mp 237–240 °C; IR (KBr) ν_{max} 3320, 2975, 1670, 1640, 1580, 1512, 1461, 660 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 5.80 (d, 1H, J = 15.2 Hz, olefinic CH), 7.20–8.10 (a set of signals, 8H, aromatic protons and olefinic CH), 12.40 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.4, 158.8, 139.4, 138.5, 136.6, 132.4, 131.4, 130.8, 129.5, 129.2, 128.7, 126.6, 124.6, 124.2, 122.1, 116.4; HRMS (EI) m/z calcd for $C_{16}H_{11}BrN_2O$: 326.0055; found: 326.0058.

*7.16.3. 3- (4-cyano styryl) quinoxalin-2 (1H)-one (**46c**)*

This compound was prepared and purified as per the above mentioned procedure: yield 69%; mp 242–244 °C; IR (KBr) ν_{max} 3310, 2985, 2215, 1660, 1648, 1508, 1570, 1448 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 6.10 (d, 1H, J = 15.2 Hz, olefinic CH), 7.10–8.25 (a set of signals, 8H, aromatic protons and olefinic CH), 12.10 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.5, 158.9, 140.6, 139.3, 133.5, 132.6, 131.3, 130.2, 128.3, 126.4, 124.6, 122.2, 119.7, 112.9, 114.3; HRMS (EI) m/z calcd for $C_{17}H_{11}N_3O$: 273.0902; found: 273.0905.

*7.16.4. 3- (4-methyl styryl) quinoxalin-2 (1H)-one (**46d**)*

This compound was prepared and purified as per the above mentioned procedure: yield 65%; mp 234–236 °C; IR (KBr) ν_{max} 3314, 2990, 1665, 1639, 1509, 1580, 1456 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 5.60 (d, 1H, J = 15.2 Hz, olefinic CH), 7.09–8.30 (a set of signals, 8H, aromatic protons and olefinic CH), 12.23 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.6, 158.3, 140.2, 138.8, 134.6, 133.5, 132.6, 130.1, 128.4, 128.1, 126.3, 124.2, 122.2, 114.1, 23.2; HRMS (EI) m/z calcd for $C_{17}H_{14}N_2O$: 262.1106; found: 262.1109.

*7.16.5. 3- (4-hydroxy styryl) quinoxalin-2 (1H)-one (**46e**)*

This compound was prepared and purified as per the above mentioned procedure: yield 78%; mp 248–249 °C; IR (KBr) ν_{max} 3410, 3335, 2920, 1664, 1641, 1553, 1502, 1458 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 4.78 (s, 1H, OH), 6.30 (d, 1H, J = 15.2 Hz, olefinic CH), 7.21–8.41 (a set of signals, 8H, aromatic protons and olefinic CH), 12.00 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.8, 158.6, 155.6, 140.2, 135.6, 132.6, 130.4, 128.2, 127.9, 126.8, 125.6, 122.4, 116.9, 116.4; HRMS (EI) m/z calcd for $C_{16}H_{12}N_2O_2$: 264.0899; found: 264.0903.

*7.16.6. 3- (4-dimethylamino styryl) quinoxalin-2 (1H)-one (**46f**)*

This compound was prepared and purified as per the above mentioned procedure: yield 63%; mp 240–244 °C; IR (KBr) ν_{max} 3323, 2967, 1665, 1644, 1578, 1509, 1457, 1372 cm^{-1}; ^{1}H NMR

(DMSO-d_6) δ ppm: 3.08 (s, 6H, CH_3), 5.30 (d, 1H, J = 15.2 Hz, olefinic CH), 6.88–8.10 (a set of signals, 8H, aromatic protons and olefinic CH), 12.18 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.6, 158.6, 154.2, 140.2, 136.6, 133.6, 130.2, 128.4, 126.5, 122.4, 116.7, 112.4, 38.2; HRMS (EI) m/z calcd for $C_{18}H_{17}N_3O$: 291.1372; found: 291.1376.

*7.16.7. 3- styryl quinoxalin-2 (1H)-one (**46g**)*

This compound was prepared and purified as per the above mentioned procedure: yield 73%; mp 228–231 °C; IR (KBr) ν_{max} 3340, 2985, 1650, 1638, 1518, 1503, 1462 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 5.89 (d, 1H, J = 15.2 Hz, olefinic CH), 7.20–8.25 (a set of signals, 9H, aromatic protons and olefinic CH), 12.21 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.8, 158.2, 140.2, 136.1, 134.6, 132.5, 130.2, 129.8, 128.8, 126.6, 125.8, 124.4, 122.4, 116.4; HRMS (EI) m/z calcd for $C_{16}H_{12}N_2O$: 248.0950; found: 248.0954.

*7.16.8. 3- (2, 5-dimethoxy styryl) quinoxalin-2 (1H)-one (**46h**)*

This compound was prepared and purified as per the above mentioned procedure: yield 66%; mp 224–227 °C; IR (KBr) ν_{max} 3345, 2987, 1666, 1648, 1588, 1510, 1461 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 3.89 (s, 6H, OCH_3), 6.30 (d, 1H, J = 15.2 Hz, olefinic CH), 7.34–8.45 (a set of signals, 7H, aromatic protons and olefinic CH), 12.16 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.8, 158.4, 156.6, 152.8, 140.6, 132.6, 130.3, 128.9, 125.6, 123.4, 116.8, 115.1, 114.6, 110.4, 58.4, 54.2; HRMS (EI) m/z calcd for $C_{18}H_{16}N_2O_3$: 308.1161; found: 308.1163.

*7.16.9. 3- (2 hydroxy styryl) quinoxalin-2 (1H)-one (**46i**)*

This compound was prepared and purified as per the above mentioned procedure: yield 72%; mp 243–246 °C; IR (KBr) ν_{max} 3421, 3321, 2965, 1678, 1641, 1584, 1511, 1450 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 4.89 (s, 1H, OH), 5.75 (d, 1H, J = 15.2 Hz, olefinic CH), 7.12–8.30 (a set of signals, 8H, aromatic protons and olefinic CH), 12.12 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 163.4, 158.2, 154.6, 134.6, 132.6, 130.4, 129.4, 128.4, 126.2, 124.5, 124.6, 123.3, 120.7, 120.5, 118.4, 114.1; HRMS (EI) m/z calcd for $C_{16}H_{12}N_2O_2$: 264.0899; found: 264.0901.

*7.17. General procedure for the synthesis of 2- chloro-3-substituted styryl quinoxalines **47** (**a**–**i**)*

A mixture of 3-(4-substituted styryl) quinoxalines-2(1H)-ones **46** (**a**–**i**) (50 mM), $POCl_3$ (100 ml) and DMF (0.3 ml), was refluxed at 105°c for 45 min. The reaction mixture was then cooled to RT and treated with ice water. The separated solid was filtered washed with water and dried to obtained crude solid. A portion of this solid was recrystallized from hexane to obtained pure compound **47** (**a**–**i**).

*7.17.1. 2-chloro-3-(3-nitro styryl) quinoxaline (**47a**)*

This compound was prepared and purified as per the above mentioned procedure: yield 45%; mp 179–182 °C; IR (KBr) ν_{max} 3021, 1639, 1556, 1510, 1456, 1353, 890,784 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 7.08 (d, 1H, J = 15.2 Hz, olefinic CH), 7.50–8.50 (a set of signals, 8H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 159.5, 149.6, 148.2, 141.2, 140.2, 138.3, 134.6, 132.4, 130.6, 130.2, 129.6, 129.5, 128.2, 124.5, 124.2, 122.5; HRMS (EI) m/z calcd for $C_{16}H_{10}ClN_3O_2$: 311.0462; found: 311.0465.

*7.17.2. 2-chloro-3-(3-bromo styryl) quinoxaline (**47b**)*

This compound was prepared and purified as per the above mentioned procedure: yield 38%; mp 148–150 °C; IR (KBr) ν_{max} 3058,1639,1505,1460, 884, 780, 650 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 6.85 (d, 1H, J = 15.2 Hz, olefinic CH), 7.10–8.20 (a set of signals, 8H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 159.3, 149.2, 143.4, 140.2, 138.2, 132.4, 130.7, 130.6, 130.0, 129.8, 129.3, 129.1, 128.4, 128.1, 124.3, 122.1; HRMS (EI) m/z calcd for $C_{16}H_{10}BrClN_2$: 343.9716; found: 343.9719.

*7.17.3. 2-chloro-3-(4-cyano styryl) quinoxaline (**47c**)*

This compound was prepared and purified as per the above mentioned procedure: yield 44%; mp 137–139 °C; IR (KBr) ν_{max} 3075, 2215, 1638, 1504, 1452, 873, 610 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 6.90 (d, 1H, J = 15.2 Hz, olefinic CH), 7.40–8.45 (a set of signals, 8H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 159.8, 149.5, 142.4, 140.4, 139.4, 133.3, 132.4, 131.2, 131.5, 130.4, 129.8, 128.4, 125.6, 119.4, 113.8; HRMS (EI) m/z calcd for $C_{17}H_{10}ClN_3$: 291.0563; found: 291.0566.

*7.17.4. 2-chloro-3-(4-methyl styryl) quinoxaline (**47d**)*

This compound was prepared and purified as per the above mentioned procedure: yield 38%; mp 143–147 °C; IR (KBr) ν_{max} 3071, 1375, 1636, 1508, 1452, 1372, 860, 620 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 5.94 (d, 1H, J = 15.2 Hz, olefinic CH), 7.18–8.20 (a set of signals, 8H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 159.2, 149.4, 143.3, 141.4, 140.2, 138.2, 132.4, 130.6, 130.2, 129.4, 128.9, 128.5, 127.4, 123.3, 23.3; HRMS (EI) m/z calcd for $C_{17}H_{13}ClN_2$: 280.0767; found: 280.0770.

*7.17.5. 2-chloro-3-(4-hydroxyl styryl) quinoxaline (**47e**)*

This compound was prepared and purified as per the above mentioned procedure: yield 52%; mp 145–147 °C; IR (KBr) ν_{max} 3440, 3062, 1642, 1504, 1458, 895, 640 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 5.35 (s, 1H, OH), 5.80 (d, 1H, J = 15.2 Hz, olefinic CH), 6.90–8.10 (a set of signals, 8H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 160.8, 149.5, 147.5, 142.3, 138.4, 132.6, 131.4, 131.2, 130.5, 130.1, 129.2, 127.8, 124.4, 114.2: HRMS (EI) m/z calcd for $C_{16}H_{11}ClN_2O$: 282.0560; found: 282.0564.

*7.17.6. 2-chloro-3-(4-dimethyl amino styryl) quinoxaline (**47f**)*

This compound was prepared and purified as per the above mentioned procedure: yield 51%; mp 137–140 °C; IR (KBr) ν_{max} 3050, 1642, 1504, 1461, 1370, 900, 680 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 3.06 (s, 6H, CH_3), 6.90 (d, 1H, J = 15.2 Hz, olefinic CH), 7.12–8.30 (a set of signals, 8H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 159.8, 152.5, 148.2, 140.3, 138.2, 132, 130.5, 130.2, 129.4, 128.3, 125.4, 124.2, 118.4, 44.2; HRMS (EI) m/z calcd for $C_{18}H_{16}ClN_3$: 309.1033; found: 309.1037.

*7.17.7. 2-chloro-3-(styryl) quinoxaline (**47g**)*

This compound was prepared and purified as per the above mentioned procedure: yield 39%; mp 128–130 °C; IR (KBr) ν_{max} 3050, 1638, 1510, 1453, 873,760 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 6.80 (d, 1H, J = 15.2 Hz, olefinic CH), 7.35–8.30 (a set of signals, 8H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 159.6, 149.3, 141.3, 140.8, 138.5, 134.2, 131.5, 131.2, 130.3, 128.8, 128.4, 127.9, 127.5, 120.4; HRMS (EI) m/z calcd for $C_{16}H_{11}ClN_2$: 266.0611; found: 266.0614.

*7.17.8. 2-chloro-3-(2, 5-dimethoxy styryl) quinoxaline (**47h**)*

This compound was prepared and purified as per the above mentioned procedure: yield 47%; mp 161–164 °C; IR (KBr) ν_{max} 3090, 1648, 1509, 1459, 880, 780 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm: 3.85 (s, 6H, OCH_3), 6.80 (d, 1H, J = 15.2 Hz, olefinic CH), 7.20–8.10 (a set of signals, 7H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 159.3, 154.2, 152.4, 148.2, 140.2, 138.2, 130.4, 130.1, 128.2, 127.4, 127.1, 124.2, 116.3, 115.4, 114.3, 110.6, 52.4, 55.8; HRMS (EI) m/z calcd for $C_{18}H_{15}ClN_2O_2$: 326.0822; found: 326.0825.

*7.17.9. 2-chloro-3-(2-hydroxy styryl) quinoxaline (**47i**)*

This compound was prepared and purified as per the above mentioned procedure: yield 53%; mp 132–133 °C; IR (KBr) ν_{max}

3440, 1641, 1510, 1455, 3078, 895, 745 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 5.14 (s, 1H, OH), 6.89 (d, 1H, J = 15.2 Hz, olefinic CH), 7.26–8.40 (a set of signals, 8H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 159.4, 156.6, 148.2, 140.4, 138.6, 132.4, 131.8, 131.4, 130.6, 130.2, 129.4, 128.6, 124.3, 115.2; HRMS (EI) m/z calcd for $C_{16}H_{11}ClN_2O$: 282.0560; found: 282.0562.

*7.18. General procedure for the synthesis of 2-((1H-benzimidazole-2-yl) methyl thio)-3-(3-substituted styryl) quinoxalines **48** (**a**–**i**)*

A mixture of 1H-benzimidazole-2-ylmethanethiol (11 mM), triethylamine (20 mM) and 2- chloro-3-substituted styryl quinoxalines **47** (**a**–**i**) (10 mM) in methanol was refluxed for 8 h. It was then cooled to RT the separated solid was filtered, washed and recrystallized with ethanol to obtain **48** (**a**–**i**).

*7.18.1. 2-((1H-benzo[d] imidazol-2-yl) methylthio) 3-(3-nitrostyryl) quinoxaline (**48a**)*

This compound was prepared and purified as per the above mentioned procedure: yield 73%; mp 226–230 °C; IR (KBr) ν_{max} 3400, 3084, 1599,1550, 1527,1461,1350, 849, 739 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 4.99 (s, 2H, CH_2), 5.27 (s, H, NH), 7.23–8.45 (a set of signals, 12H, aromatic protons and olefinic CH), 7.06 (d, 1H, J = 15.2 Hz, olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.7, 152.3, 148.4, 144.3, 143.4, 142.4, 138.4, 135.4, 134.4, 132.4, 131.8, 131.5, 129.4, 129.3, 126.4, 123.4, 123.2, 123.1, 120.7, 116.2, 34.3; HRMS (EI) m/z calcd for $C_{24}H_{17}N_5O_2S$: 439.1103; found: 439.1107.

*7.18.2. 2-((1H-benzo[d]imidazol-2-yl) methylthio) 3-(3-bromo styryl) quinoxaline (**48b**)*

This compound was prepared and purified as per the above mentioned procedure: yield 69%; mp 234–238 °C; IR (KBr) ν_{max} 3400, 3055, 1625, 1522, 1454, 870, 846, 747 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 4.93 (s, 2H, CH_2), 5.45 (s, H, NH), 6.80 (d, 1H, J = 15.2 Hz, olefinic CH), 7.20–8.02 (a set of signals, 12H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.5, 152.1, 144.4, 142.2, 140.2, 138.4, 136.5, 132.4, 130.6, 131.9, 131.8, 129.5, 129.2, 129.1, 128.4, 126.4, 124.4, 124.2, 116.2, 34.2; HRMS (EI) m/z calcd for $C_{24}H_{17}BrN_4S$: 475.0357; found: 475.0359.

*7.18.3. 2-((1H-benzo[d]imidazol-2-yl) methylthio) 3-(4-cyano styryl) quinoxaline (**48c**)*

This compound was prepared and purified as per the above mentioned procedure: yield 55%; mp 266–268 °C; IR (KBr) ν_{max} 3400, 3000, 2224, 1628, 1522, 1455, 821, 758 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 4.80 (s, H, NH), 5.10 (s, 2H, CH_2), 6.87 (d, 1H, J = 15.2 Hz, olefinic CH), 7.34–8.05 (a set of signals, 12H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.4, 152.8, 146.4, 143.4, 142.6, 142.2, 138.4, 132.2, 131.3, 131.8, 131.4, 129.3, 128.6, 128.2, 123.5, 123.2, 116.6, 114.5, 112.4, 34.5; HRMS(EI) m/z calcd for $C_{25}H_{17}N_5S$: 419.1205; found: 419.1208.

*7.18.4. 2-((1H-benzo[d]imidazol-2-yl) methylthio) 3-(4-methyl styryl) quinoxaline (**48d**)*

This compound was prepared and purified as per the above mentioned procedure: yield 45%; mp 207–210 °C; IR (KBr) ν_{max} 3423, 3053, 1618, 1542,1452, 856, 750 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 3.42 (s, 2H, CH_2), 4.94 (s, H, NH), 6.67 (d, 1H, J = 15.2 Hz, olefinic CH), 7.15–8.04 (a set of signals, 12H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.7, 152.3, 146.5, 144.5, 142.4, 140.1, 138.4, 137.2, 132.1, 131.6, 131.2, 129.9, 128.4, 128.1, 124.5, 124.0, 114.2, 34.4, 21.3; HRMS (EI) m/z calcd for $C_{25}H_{20}N_4S$: 408.1409; found: 408.1412.

*7.18.5. 2-((1H-benzo[d]imidazol-2-yl) methylthio) 3-(4-hydroxyl styryl) quinoxaline (**48e**)*

This compound was prepared and purified as per the above mentioned procedure: yield 55%; mp 214–218 °C; IR (KBr) ν_{max} 3580, 3417, 3010, 1626, 1505, 1451, 834,751 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 4.93 (s, 2H, CH_2), 5.10 (s, H, OH), 5.21 (s, H, NH), 6.68 (d, 1H, J = 15.2 Hz, olefinic CH), 7.26–8.41 (a set of signals, 12H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.6, 158.3, 148.2, 146.2, 142.4, 140.2, 138.2, 132.4, 131.5, 131.2, 130.8, 130.4, 130.3, 128.4, 123.6, 123.4, 123.1, 114.2, 34.2; HRMS (EI) m/z calcd for $C_{24}H_{18}N_4OS$: 410.1201; found: 410.1203.

*7.18.6. 2-((1H-benzo[d]imidazol-2-yl) methylthio) 3-(4-dimethyl amino styryl) quinoxaline (**48f**)*

This compound was prepared and purified as per the above mentioned procedure: yield 49%; mp 274–276 °C; IR (KBr) ν_{max} 3427, 3020, 1601, 1502, 154, 1370,810,753 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 3.09 (s, 3H, CH_3), 3.49 (s, 2H, CH_2), 5.10 (s, H, NH), 6.60 (d, 1H, J = 15.2 Hz, olefinic CH), 6.88–8.55 (a set of signals, 12H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.6, 152.4, 150.2, 146.8, 144.2, 142.4, 138.2, 132.4, 129.8, 129.4, 129.3, 127.8, 126.4, 123.6, 123.2, 114.1, 110.4, 44.2, 34.2; HRMS (EI) m/z calcd for $C_{26}H_{25}N_5S$: 437.1674; found: 437.1677.

*7.18.7. 2-((1H-benzo[d]imidazol-2-yl) methylthio) 3-(styryl) quinoxaline (**48g**)*

This compound was prepared and purified as per the above mentioned procedure: yield 37%; mp 216–220 °C; IR (KBr) ν_{max} 3436, 3054, 1625, 1522, 1451, 847, 745 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 5.21 (s, 2H, CH_2), 5.61 (s, H, NH), 6.61 (d, 1H, J = 15.2 Hz, olefinic CH), 6.99–8.28 (a set of signals, 13H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.8, 152.4, 148.4, 142.4, 140.5, 138.4, 136.3, 132.4, 131.8, 131.4, 129.8, 129.2, 128.6, 128.5, 126.4, 124.5, 124.0, 114.5, 34.6; HRMS (EI) m/z calcd for $C_{24}H_{18}N_4S$: 394.1252; found: 394.1256.

*7.18.8. 2-((1H-benzo[d]imidazol-2-yl) methylthio) 3-(2, 5-dimethoxy styryl) quinoxaline (**48h**)*

This compound was prepared and purified as per the above mentioned procedure: yield 62%; mp 207–210 °C; IR (KBr) ν_{max} 3400, 3054, 1620, 1510, 1451, 842,761, cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 3.89 (s, 6H, OCH_3), 4.60 (s, 2H, CH_2), 5.44 (s, H, NH), 6.81 (d, 1H, J = 15.2 Hz, olefinic CH), 7.14–8.28 (a set of signals, 11H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.5, 156.4, 152.4, 150.4, 149.4, 146.4, 142.4, 141.2, 138.4, 129.9, 129.6, 129.2, 128.4, 123.6, 123.2, 116.6, 116.3, 114.3, 110.2, 56.4, 55.1, 34.4; HRMS (EI) m/z calcd for $C_{26}H_{22}N_4O_2S$: 454.1463; found: 454.1467.

*7.18.9. 2-((1H-benzo[d]imidazol-2-yl) methylthio) 3-(2-hydroxy styryl) quinoxaline (**48i**)*

This compound was prepared and purified as per the above mentioned procedure: yield 68%; mp 201–204 °C; IR (KBr) ν_{max} 3420, 3150, 1612, 1523, 1452, 873, 751 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm: 3.76 (s, 2H, CH_2), 4.34 (s, H, NH), 4.89 (s, H, OH), 6.64 (d, 1H, J = 15.2 Hz, olefinic CH), 6.95–8.45 (a set of signals, 12H, aromatic protons and olefinic CH); ^{13}C NMR (DMSO-d_6) δ ppm: 161.5, 158.1, 150.4, 148.4, 146.2, 140.5, 138.4, 129.8, 129.4, 129.3, 128.4, 127.2, 124.4, 123.6, 123.3, 118.3, 114.4, 34.1; HRMS (EI) m/z calcd for $C_{24}H_{18}N_4OS$: 410.1201; found: 410.1204.

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