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Original article

Design, synthesis and evaluation of novel diaryl urea derivatives as potential antitumor agents

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ABSTRACT

A novel series of diaryl ureas containing different linker groups were designed and synthesized. Their *in vitro* antitumor activity against MX-1, A375, HepG2, Ketr3 and HT-29 was evaluated using the standard MTT assay. Compounds having a rigid linker group such as vinyl, ethynyl and phenyl showed significant inhibitory activity against a variety of cancer cell lines. Specifically, compound **23** with a phenyl linker group demonstrated broad-spectrum antitumor activity with IC_{50} values of 5.17–6.46 μM against five tested tumor cell lines. Compound **23** is more potent than reference drug sorafenib (8.27–15.2 μM), representing a promising lead for further optimization.

1. Introduction

Cellular signaling network in tumor cells is complex and redundant, therefore broad-acting and multi-targeted kinase inhibitors may be more advantageous than selective agents because of their ability to block multiple signaling pathways associated with tumor survival [1–3]. A number of multi-targeted kinase inhibitors based on different scaffolds, such as sorafenib [4], linifanib [5,6] and curcumin [7], have reached market or have been in late-stage clinical trials. These agents have demonstrated clinical benefits with manageable side effects (Fig. 1).

The antitumor activity of kinase inhibitors containing a diaryl urea scaffold has been described in literature [8–10]. These molecules possess a unique binding mode and kinase inhibition profile [11]. For example, sorafenib, a diaryl urea multi-targeted inhibitor of several kinases including Raf, VEGFR and PDGFR, was approved by Food and Drug Administration (FDA) for the treatment of advanced renal cell carcinoma (RCC) in 2005 and unresectable hepatocellular carcinoma (HCC) in 2007 [4,12].

Crystal structure of B-Raf in complex with sorafenib revealed a distinctive mode of protein–ligand interaction [13]. The diaryl urea portion of the molecule is highly conserved and shared by most type II kinase inhibitors. The *N*-methyl-4-picolinamide moiety that binds to the hinge region of the kinase is highly mobile. The pyridyl ring nitrogen atom in sorafenib forms hinge hydrogen bonding, but it is known to be less critical compared with that in other kinase inhibitors [14,15].

The interest in designing novel diaryl ureas with improved antitumor activity has been growing following the successful launch of sorafenib [16–20]. Linifanib is another potent kinase inhibitor in clinical development. As compared to the structure of sorafenib, linifanib has a more rigid structure with a 3-aminoindazole moiety at the hinge region. It has been demonstrated that a large group at the hinge region can be well tolerated [15,21–24] and there is growing interest in finding an optimal hinge binding scaffold.

To develop a new generation of more potent multi-targeted kinase inhibitors, we took advantage of the previous structure–activity relationships (SAR) of sorafenib analogs. The diaryl urea and amide groups, as key pharmacophores, were kept intact. At the same time, we planned to preserve the chloro and trifluoromethyl substituents on the distal phenyl ring, while replacing the *N*-methyl group by α-methylbenzyl and cyclic alkyl groups in order to investigate their effects on antitumor activity. We focused our main modifications on the oxygen atom and pyridyl ring of sorafenib, exploring a variety of linker groups such as vinyl, ethynyl and phenyl to connect the diaryl urea and amide moieties. A total of

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0223-5234/

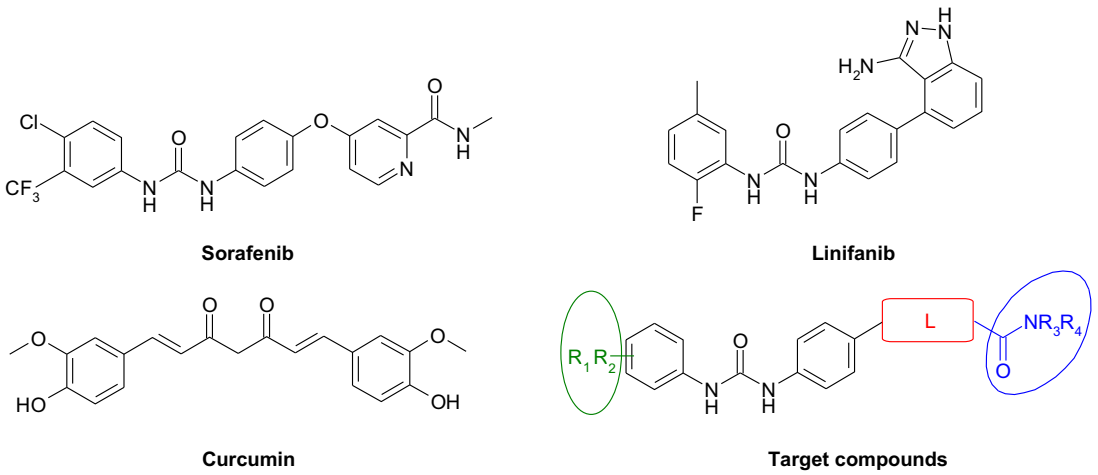


Fig. 1. Structures of known multi-targeted kinase inhibitors and target compounds.

twenty seven novel diaryl ureas were designed and synthesized. The inhibitory activity of these compounds **1**–**27** against five cancer cell lines, including human breast cancer (MX-1), human melanoma (A375), human liver cancer (HepG2), human kidney cancer (Ketr3) and human colon cancer (HT-29) cell lines, was evaluated using the standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Herein, we wish to report the synthesis and SAR of the target compounds.

2. Results and discussion

2.1. Chemistry

The intermediate amines **A1**–**A8** were synthesized following known synthetic procedures as outlined in Scheme 1. Some improvements were made, especially for **A6**. The general synthetic procedures of target compounds **1**–**27** were illustrated in Scheme 2.

2.1.1. General synthesis of intermediate *A1*–*A3*

4-Nitrobenzaldehyde was submitted to the Knoevenagel reaction with malonic acid or methylmalonic acid [25]. Condensation with corresponding amines, followed by reduction of nitro group with $SnCl_2$ gave intermediates **A1(a–d)** or **A3(a–c)**. The subsequent catalytic hydrogenation of nitro group and double bond simultaneously using 5% Pd/C gave intermediates **A2(a–d)**.

2.1.2. General synthesis of intermediate *A4*

4-Nitroacetophenone was treated with trimethyl phosphonoacetate in the presence of *N*-sodiumhexamethyldisilazane (NaHMDS) [26]. Ester saponification and amidation, followed by reduction of nitro group with $SnCl_2$ provided intermediates **A4(a–c)**.

2.1.3. General synthesis of intermediate *A5*

Treatment of *N*-Boc-4-aminophenol with methyl propiolate in the presence of a catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) [27], followed by ester saponification and amidation using (benzotriazol-1-yloxy)-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP) as a condensation reagent [28], and Boc deprotection afforded intermediates **A5(a–b)**.

2.1.4. General synthesis of intermediate *A6*

The conversion of 4-iodonitrobenzene to methyl 3-(4-nitropheny1)propiolate was accomplished according to the reported procedure [29], followed by ester saponification and amidation using BOP reagent gave amide intermediate. Herein, an improved approach for selective reduction of nitro group in compounds containing an ethynyl group was investigated. We reduced the nitro group with Fe powder in ethanol under acidic condition, which gave intermediates **A6(a–b)** in high yield (about 80%).

2.1.5. General synthesis of intermediate *A7*–*A8*

Suzuki coupling between 4-bromonitrobenzene and 3-carboxybenzeneboronic acid with $Pd(PPh_3)_4$ as a catalyst in the presence of K_2CO_3 afforded 4-nitrobiphenyl-3-carboxylic acid quantitatively [30]. 4-Biphenylcarboxylic acid was treated with ice-cold nitric acid to provide 4-nitrobiphenyl-4-carboxylic acid [31]. Condensation the two acids with the corresponding amines, followed by reduction of nitro group with 5% Pd/C gave intermediates **A7(a–b)** and **A8(b–c)**, respectively.

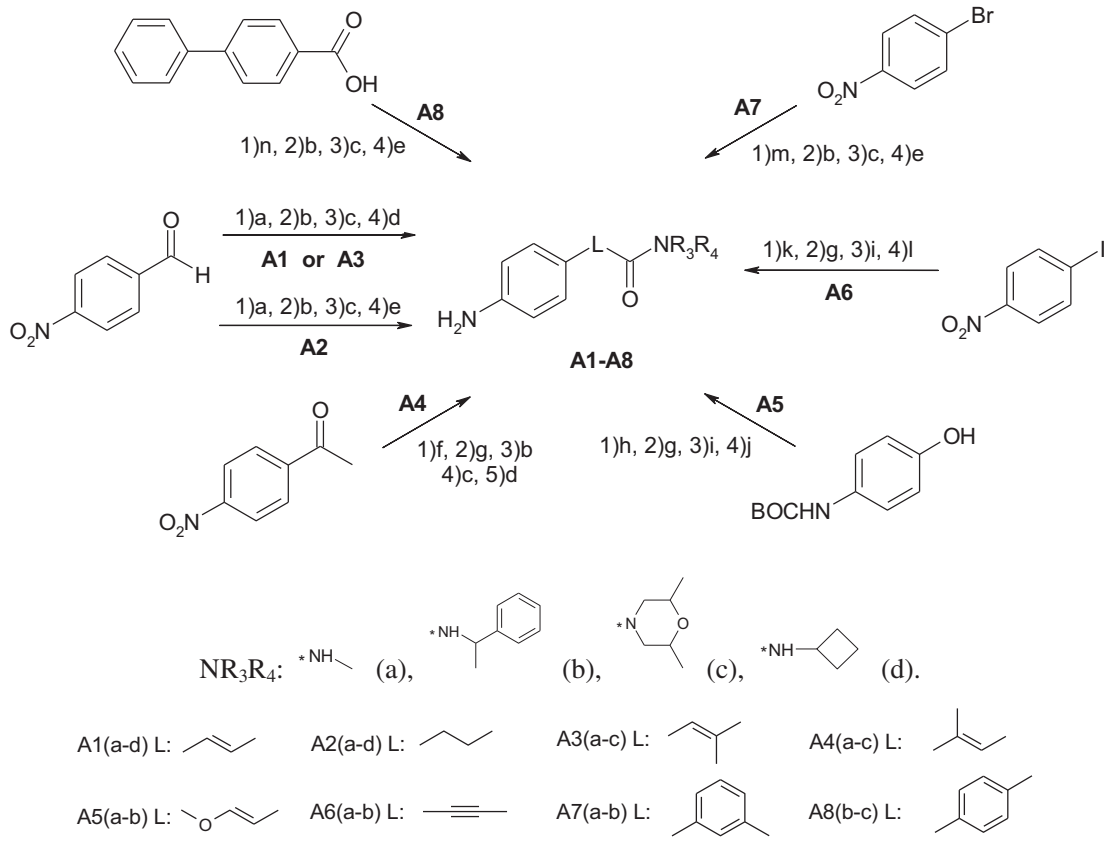
2.1.6. General synthesis of target compounds *1*–*27*

Finally, condensation of **A1**–**A8** with corresponding aryl isocyanates in anhydrous dichloromethane (DCM) afforded the desired diaryl urea derivatives **1**–**27** in 79%–91% yields [32].

2.2. Biological evaluation

The *in vitro* inhibitory activity of target compounds against MX-1, A375, HepG2, Ketr3 and HT-29 cell lines was evaluated using the MTT-based assay. The IC_{50} results of various analogs were summarized in Table 1 with sorafenib as the reference compound.

As illustrated in Table 1, most compounds bearing a rigid linker group such as vinyl (compounds **2**–**4**), ethynyl (compounds **20**–**21**) and phenyl (compounds **23**–**25**) exhibited moderate to potent activities against the tested cancer cell lines, while flexible linker group such as saturated ethyl chain (compounds **6**–**9**) and bulky linker group such as branched vinyl (compounds **10**–**15**) were all detrimental for activities. The results were consistent with several recently published articles [33–35] which suggested that a,β-unsaturated ketone may be the pharmacophore of many antitumor agents like curcumin. It was also noted that a moderate to dramatic decrease in potency was found if the vinyl group was replaced with a more electron-deficient –OCH=CH group (compounds **2** versus **17**, **3** versus **18**). These observations may be due to a combination of electronic and steric effects of the linker groups. Interestingly, most compounds that contain a rigid linker group demonstrated potent activities against both MX-1 and HT-29, especially with an



Scheme 1. General synthetic scheme for amines **A1**–**A8** with various designed linker groups. Reagents and conditions: a. malonic acid or methylmalonic acid, piperidine, pyridine, 90 °C, 4–8 h, 72%–83%; b. $SOCl_2$, reflux, 2 h; c. R_3R_4NH, TEA, DCM, rt, 4–8 h, 82%–92%; d. $SnCl_2$, 6 mol/L HCl, EtOH–H_2O, reflux, 4 h, 50%–68%; e. H_2, 5% Pd/C, THF, 6 h, 83%–94%; f. trimethyl phosphonoacetate, 1 mol/L NaHMDS/THF, toluene, rt, 10 h, 70%; g. NaOH, THF–H_2O, rt, 12 h, 87%–93%; h. methyl propiolate, DABCO, DCM, rt, 1.5 h, 89%; i. R_3R_4NH, BOP, TEA, THF, rt, 3 h, 59%–78%; j. (i) HCl/EtOAc, rt, 1 h, (ii) $NaHCO_3$, DCM, 80%–84%; k. methyl propiolate, $Pd(PPh_3)_2Cl_2$, CuI, K_2CO_3, THF, reflux, 5 h, 78%; l. Fe, 2 mol/L HCl, EtOH–H_2O, 70 °C, 4 h, 78%–83%; m. 3-carboxybenzeneboronic acid, $Pd(PPh_3)_4$, K_2CO_3, EtOH–H_2O–toluene, reflux, 48 h, 96%; n. HNO_3, 1 h, 55%.

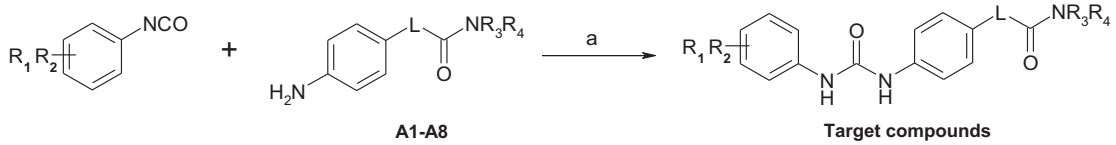
outstanding activity on HT-29 cell line with IC_{50} lying in the micromolar range, such as compounds **2**–**4**, **20**–**21**, **23**–**27**. In particular, in the phenyl series, there was a similar trend for different linking patterns of amide groups, either on *meta*-position or *para*-position of the biphenyl substructure. Compounds **26** and **27** that contain the linker as 1,4-disubstituted phenyl group exhibited superior selective anticancer activity against HT-29 with IC_{50} values of 2.05 μM and 1.90 μM, respectively, compared to sorafenib with IC_{50} value of 15.2 μM. This information could be useful in designing potent inhibitors against colon cancer.

Additionally, we found that introduction of a large substituent like *N*-methylbenzyl compared to *N*-methyl in amide moiety led to more potent inhibitors, as evidenced by compound **2** versus compound **1**, compound **20** versus compound **19**, compound **23** versus compound **22**. It was also consistent with the results that many researches have demonstrated that the large groups are well tolerated in this region to be beneficial to the activity and physicochemical properties [18,21]. Finally, the effect of the position of the electron-withdrawing substituents on the distal phenyl ring such as 4-Cl–3-CF_3 versus 2-Cl–5-CF_3 was investigated. The preliminary result showed that the position of Cl and CF_3 on the phenyl ring did not have a significant impact on activities, as exemplified by compound **2** versus compound **3**.

It is worth noting that compound **23** with a 1,3-disubstituted phenyl linker, demonstrated superior broad-spectrum antitumor activities with IC_{50} values in the micromolar range (5.17 μM–6.46 μM) against all tested five cell lines compared to the reference compound sorafenib with IC_{50} values in the range of 8.27 μM–15.2 μM. Compound **23** could become a valuable lead for further optimization.

2.3. Docking analysis

In order to understand the mode of binding for these novel diaryl ureas, the most promising compound **23** was docked into the crystal structure published for B-Raf (1UWH) [36] using Discovery Studio 2.0 software (Accelrys, Inc.) (Fig. 2). The docking model suggested a mode of binding with matching hydrogen bonds to the backbone NH and C=O of Cys531 in the hinge region through the amide moiety, and to the Asp593/Glu500 pair in the catalytic region through the urea moiety. Furthermore, a π-stacking interaction of the phenyl ring of α-methylbenzyl with



Scheme 2. General synthetic route of target compounds **1**–**27**. Reagent and condition: a. anhydrous DCM, Ar, rt, 12 h.

Table 1
Structures and inhibitory activity of target compounds against MX-1, A375, HepG2, Ketr3 and HT-29 cancer cell lines *in vitro*.

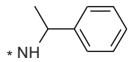
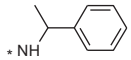
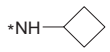
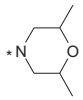
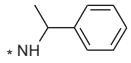
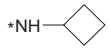
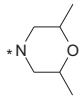
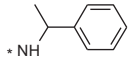
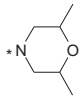
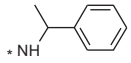
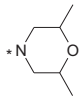
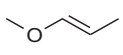
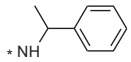
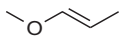
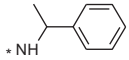
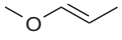
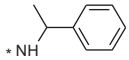
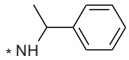
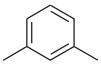
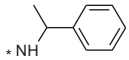
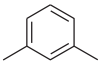
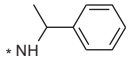
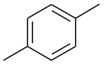
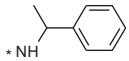
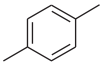
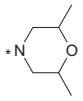
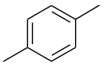
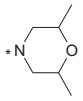
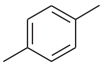
Compd.	R_1R_2	NR_3R_4	L	IC_{50} (μmol/L)				
				MX-1	A375	HepG2	Ketr3	HT-29
1	4-Cl–3-CF_3			13.8	20.9	20.4	21.2	11.7
2	4-Cl–3-CF_3			3.13	20.8	12.2	21.2	1.06
3	2-Cl–5-CF_3			1.89	40.9	35.9	14.3	4.19
4	4-Cl–3-CF_3			4.53	15.4	7.51	17.3	4.43
5	4-Cl–3-CF_3			12.8	>50	45.9	>50	9.10
6	4-Cl–3-CF_3			20.4	25.2	21.0	24.0	20.6
7	4-Cl–3-CF_3			>50	>50	>50	>50	26.5
8	4-Cl–3-CF_3			24.0	>50	>50	>50	21.3
9	4-Cl–3-CF_3			>50	>50	>50	>50	>50
10	4-Cl–3-CF_3			>50	>50	44.3	>50	>50
11	4-Cl–3-CF_3			>50	>50	>50	>50	>50
12	4-Cl–3-CF_3			>50	>50	>50	>50	>50
13	4-Cl–3-CF_3			>50	>50	>50	>50	>50
14	4-Cl–3-CF_3			>50	>50	>50	>50	>50
15	4-Cl–3-CF_3			>50	46.2	>50	>50	26.2
16	4-Cl–3-CF_3			18.8	36.8	24.2	>50	>50
17	4-Cl–3-CF_3			13.7	20.7	14.1	14.5	>50

Table 1 (*continued*)

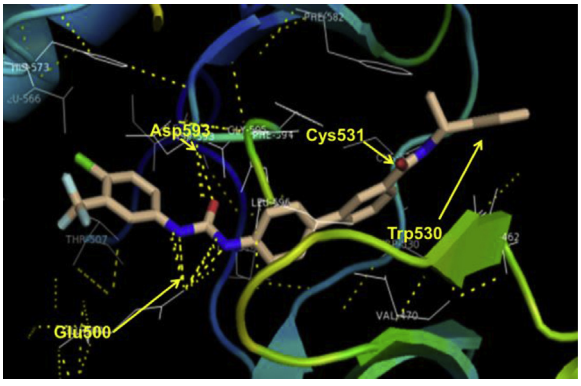
Compd.	R_1R_2	NR_3R_4	L	IC_{50} (μmol/L)				
				MX-1	A375	HepG2	Ketr3	HT-29
18	2-Cl–5-CF_3			16.1	16.0	11.9	16.4	>50
19	4-Cl–3-CF_3			26.4	>50	23.3	24.7	14.0
20	4-Cl–3-CF_3			12.8	16.8	20.5	21.4	4.92
21	2-Cl–5-CF_3			16.1	30.5	19.0	23.2	3.17
22	4-Cl–3-CF_3			>50	46.5	37.1	39.3	29.3
23	4-Cl–3-CF_3			5.24	5.17	5.67	6.46	6.32
24	4-Cl–3-CF_3			4.63	12.8	16.8	19.3	5.96
25	2-Cl–5-CF_3			17.7	16.9	18.4	16.8	6.57
26	4-Cl–3-CF_3			>50	>50	31.1	41.9	2.05
27	2-Cl–5-CF_3			>50	>50	>50	>50	1.90
Sorafenib				8.27	9.17	8.67	18.8	15.2

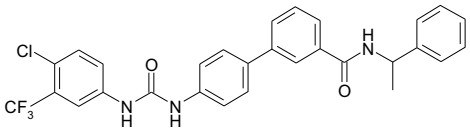
Trp530 can be observed, which could provide additional binding affinity.

The docking model indicates that an appropriate linker group such as 1,3-disubstituted phenyl would allow each fragment of the molecule to nicely fit into the desired pockets, which may explain the potent antitumor activity of compound **23** observed.

2.4. Kinase inhibitory activity

To investigate the possible mechanism of action responsible for the observed antitumor activities and to verify the docking analysis above, compound **23** was selected to be initially screened for B-Raf and C-Raf inhibitory activities





Compound 23

Fig. 2. Docking model of compound **23** (yellow) in B-Raf. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in vitro by employing the standardized ADP-Glo assay methodology.

As shown in Table 2, compound **23** is very weak against B-Raf and C-Raf kinases with IC_{50} more than 50 μM. The inconsistency between the enzyme inhibitory activity and cellular efficiency against five tested cell lines suggested that this compound may exert antitumor activity by inhibiting other receptor tyrosine kinases rather than Raf kinase. This structural modification might have switched the binding affinity to other biomolecular targets involved in cellular signaling pathways. It is worthy of further research to explore the exact target(s) and details on the mechanism of action for this novel target compounds in the future.

3. Conclusion

We herein described the design and synthesis of a novel series of diaryl ureas with the goal to develop a new generation of potent multi-targeted antitumor agents. All target compounds were evaluated for their inhibitory activities on a series of human cancer cell lines including MX-1, A375, HepG2, Ketr3 and HT-29. Our modifications were focused on the variation of the linker groups between diaryl urea and amide moieties. We concluded that most compounds containing a rigid linker group such as vinyl, ethynyl and phenyl showed potent activities against both MX-1 and HT-29 cell lines with IC_{50} values at the micromolar level. Compound **23** with a 1,3-disubstituted phenyl linker group exhibited potent broad-spectrum activities against tumor cell lines with IC_{50} values less or equal to 6 μM. It was also noteworthy that 1,4-disubstituted phenyl analogs **26** and **27** bearing a large polar amide displayed selective inhibition against HT-29 cell line, approximately eight-fold more potent than sorafenib.

Finally, the lack of Raf kinase inhibitory activity of compound **23** suggested that other mechanism of action accounts for its significant broad-spectrum antitumor activity. Efforts to identify molecular targets of compound **23** and further optimization are ongoing and will be reported in due course.

4. Experimental protocols

Melting points were determined with a Yanaco MP-J3 micro melting point apparatus and were uncorrected. The NMR spectra were obtained on Mercury-300, 400 MHz and Bruker AV500-III spectrometers with tetramethylsilane (TMS) as the internal standard. High-resolution mass spectra (HRMS) were taken in electrospray ionization (ESI) mode on an Agilent 1100 series LC/MSD mass spectrometer. IR spectra were run on Nicolet 5700 spectrometer (Thermo). All reagents and solvents were purchased from commercial sources unless otherwise indicated. TLC was carried out on silica gel plates (GF_{254}) with visualization of components by UV light (254 nm) or exposure to I_2. Column chromatography was carried out on silica gel (200–300 mesh).

4.1. General procedure for the preparation of target compounds *1*–*27*

The intermediate amine with designed linker (0.5 mmol) was dissolved in anhydrous DCM (3 mL). Temperature was maintained at 0 °C, then a DCM (1 mL) solution of corresponding aryl isocyanate (0.55 mmol) was added drop wise with constant stirring under argon atmosphere. The reaction mixture was stirred at room temperature for 12 h and then filtered. The resulting solid was washed with ethyl acetate (EtOAc) and dried under vacuum for 4 h to afford diaryl ureas **1**–**27**.

Table 2
Raf kinase inhibitory activity of compound **23** *in vitro*.

Compd.	IC_{50} (nM)	
	B-Raf	C-Raf
23	>50,000	>50,000
Sorafenib	43.04	21.98

4.1.1. 1-(4-((E)-2-(methylcarbamoyl)vinyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (*1*)

A mixture of 4-nitrobenzaldehyde (23 mmol), malonic acid (25 mmol) and catalytic amounts of piperidine in anhydrous pyridine (12 mL) was stirred at 90 °C for 4 h. After cooling, the resulting solution was poured into ice water, acidified to pH 1–2 with concentrated HCl and the solid formed was filtered and dried to obtain 3-(4-nitrophenyl)acrylic acid (82.6%). Then the acid (10 mmol) was slowly added to thionyl chloride (10 mL) at 0 °C, the mixture was stirred at refluxing temperature for 2 h. After cooled to room temperature, the reaction mixture was diluted with toluene (30 mL), and concentrated to near dryness *in vacuo* to obtain oily residue. To a solution of corresponding amine (11 mmol) in DCM (40 mL) containing triethylamine (TEA) (22 mmol), a DCM (10 mL) solution of the oily residue was added at 0 °C and then the mixture was stirred at room temperature for 8 h. After removal of the solvent under reduced pressure, the resulting residue was recrystallized from EtOAc and dried to give (*E*)-*N*-substituted-3-(4-nitrophenyl)acrylamide (82.3%–92.3%). To a solution of the amide (1.5 mmol) in 6 mL ethanol (EtOH) was added $SnCl_2$ (4.5 mmol) in 6 mol/L HCl (6 mL), and the mixture was heated to reflux for 4 h. The reaction mixture was poured into saturated solution of $NaHCO_3$ and extracted with DCM (2 × 30 mL), after which the organic layer was washed with saturated brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from EtOAc and dried to give intermediates **A1(a–d)** in yields of 64.4%, 56.4%, 54.8%, 63.6% respectively. Finally, following the general procedure for the preparation of target compounds to give compounds **1**–**5**.

Off white solid, yield: 83.5%, mp > 250 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.70 (d, 3H, J = 4.2 Hz, CH_3), 6.51 (d, 1H, J = 16.2 Hz, CH=CH), 7.36 (d, 1H, J = 15.3 Hz, CH=CH), 7.50 (brs, 4H, ArH), 7.62–7.64 (m, 2H, ArH), 7.97 (d, 1H, J = 4.8 Hz, ArH), 8.11 (s, 1H, CONH), 9.03 (s, 1H, NHCONH), 9.20 (s, 1H, NHCONH). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{16}ClF_3N_3O_2$ 398.0801, found 398.0812.

4.1.2. 1-(4-((E)-2-(1-phenylethylcarbamoyl)vinyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (*2*)

Off white solid, yield: 86.9%, mp > 250 °C. IR (KBr, cm^{-1}): 3293.7, 3064.7, 2979.5, 2931.3, 1704.5, 1653.0, 1592.3, 1484.1, 1418.7, 1178.4, 1032.5, 827.9, 698.7. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.39 (d, 3H, J = 7.2 Hz, CH_3), 5.01–5.06 (m, 1H, NHCH), 6.58 (d, 1H, J = 15.6 Hz, CH=CH), 7.21–7.37 (m, 6H, ArH, CH=CH), 7.46–7.53 (m, 4H, ArH), 7.62 (brs, 2H, ArH), 8.11 (s, 1H, CONH), 8.47 (d, 1H, J = 7.8 Hz, ArH), 9.03 (s, 1H, NHCONH), 9.20 (s, 1H, NHCONH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 22.47, 47.89, 116.78, 116.84, 118.55, 120.17, 121.42, 122.41, 123.12, 124.13, 126.61, 126.84, 128.23, 128.87, 131.99, 138.43, 139.17, 140.40, 144.64, 152.19, 164.23. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{22}ClF_3N_3O_2$ 488.1239, found 488.1262.

4.1.3. 1-(4-((E)-2-(1-phenylethylcarbamoyl)vinyl)phenyl)-3-(2-chloro-5-(trifluoromethyl)phenyl)urea (*3*)

Off white solid, yield: 90.9%, mp > 250 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.40 (d, 3H, J = 6.9 Hz, CH_3), 5.01–5.06 (m, 1H, NHCH), 6.59 (d, 1H, J = 15.6 Hz, CH=CH), 7.21–7.38 (m, 7H, Ar, CH=CH), 7.48–7.54 (m, 4H, ArH), 7.72 (d, 1H, J = 8.7 Hz, ArH), 8.48 (d, 1H, J = 8.1 Hz, ArH), 8.63 (s, 1H, CONH), 8.66 (s, 1H, NHCONH), 9.73 (s, 1H, NHCONH). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{22}ClF_3N_3O_2$ 488.1239, found 488.1265.

*4.1.4. 1-(4-((E)-2-(cyclobutylcarbamoyl)vinyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**4**)*

Off white solid, yield: 87.3%, mp 239–241 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.63–1.64 (m, 2H, cyclobutyl-CH_2), 1.88–2.00 (m, 2H, cyclobutyl-CH_2), 2.17–2.20 (m, 2H, cyclobutyl-CH_2), 4.26–4.32 (m, 1H, NHCH), 6.45 (d, 1H, J = 15.6 Hz, CH=CH), 7.33 (d, 1H, J = 15.6 Hz, CH=CH), 7.46–7.52 (m, 4H, ArH), 7.59–7.62 (m, 2H, ArH), 8.10 (s, 1H, CONH), 8.27 (d, 1H, J = 7.6 Hz, ArH), 9.05 (s, 1H, NHCONH), 9.23 (s, 1H, NHCONH). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{20}ClF_3N_3O_2$ 438.1191, found 438.1199.

*4.1.5. 1-(4-((E)-2-(2,6-dimethylmorpholinocarbamoyl)vinyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**5**)*

Off white solid, yield: 90.0%, mp > 250 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.11 (d, 6H, J = 5.4 Hz, 2 × CH_3), 2.27–2.35 (m, 1H, CHCH$_3$), 2.68–2.76 (m, 1H, CHCH$_3$), 3.46 (brs, 2H, NCH_2), 4.21–4.37 (m, 2H, NCH_2), 7.14 (d, 1H, J = 15.6 Hz, CH=CH), 7.45 (d, 1H, J = 15.6 Hz, CH=CH), 7.50 (d, 2H, J = 8.7 Hz, ArH), 7.59–7.67 (m, 4H, ArH), 8.08 (d, 1H, J = 1.8 Hz, ArH), 9.04 (s, 1H, NHCONH), 9.19 (s, 1H, NHCONH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 18.37, 50.39, 71.66, 115.81, 116.87, 118.28, 121.93, 123.18, 124.13, 126.84, 128.92, 129.12, 131.99, 139.16, 140.56, 141.49, 152.18, 164.39. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{24}ClF_3N_3O_3$ 482.1453, found 482.1442.

*4.1.6. 1-(4-(2-(Methylcarbamoyl)ethyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**6**)*

To a tetrahydrofuran (THF) (20 mL) solution of the (*E*)-*N*-substituted-3-(4-nitrophenyl)acrylamide (5 mmol) which was obtained in the synthesis of intermediate **A1**, was added 5% Pd/C (50 mg), and the mixture was vigorously stirred under hydrogen atmosphere for 6 h. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*, the resulting solid formed was washed with diethyl ether and dried to give intermediates **A2(a–d)** in yields of 89.0%, 83.9%, 82.5%, 88.8% respectively. Finally, following the general procedure for the preparation of target compounds to give compounds **6–9**.

Off white solid, yield: 81.2%, mp 185–186 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.31 (t, 2H, J = 7.2 Hz, CH_2CH_2), 2.55 (d, 3H, J = 4.5 Hz, CH_3), 2.74 (t, 2H, J = 7.2 Hz, CH_2CH_2), 7.10 (d, 2H, J = 8.4 Hz, ArH), 7.34 (d, 2H, J = 8.4 Hz, ArH), 7.59–7.60 (m, 2H, ArH), 7.71 (brs, 1H, ArH), 8.09 (s, 1H, CONH), 8.73 (s, 1H, NHCONH), 9.11 (s, 1H, NHCONH). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{18}ClF_3N_3O_2$ 400.2520, found 400.2515.

*4.1.7. 1-(4-(2-(1-Phenylethylcarbamoyl)ethyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**7**)*

Off white solid, yield: 88.9%, mp 218–219 °C. IR (KBr, cm^{-1}): 3321.9, 3086.1, 2968.8, 2929.0, 1708.4, 1632.3, 1549.1, 1484.8, 1420.1, 1174.7, 1030.8, 824.9, 698.4. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.29 (d, 3H, J = 6.9 Hz, CH_3), 2.38 (t, 2H, J = 7.2 Hz, CH_2CH_2), 2.75 (t, 2H, J = 7.2 Hz, CH_2CH_2), 4.87–4.92 (m, 1H, NHCH), 7.09 (d, 2H, J = 8.1 Hz, ArH), 7.20–7.30 (m, 5H, ArH), 7.34 (d, 2H, J = 8.4 Hz, ArH), 7.61–7.62 (m, 2H, ArH), 8.09 (s, 1H, CONH), 8.22 (d, 1H, J = 7.8 Hz, ArH), 8.75 (s, 1H, NHCONH), 9.12 (s, 1H, NHCONH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 22.39, 30.48, 37.09, 47.54, 116.59, 118.62, 121.44, 122.09, 122.92, 124.16, 125.88, 126.42, 126.81, 128.10, 131.95, 135.17, 137.02, 139.44, 144.65, 152.39, 170.39. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{24}ClF_3N_3O_2$ 490.1504, found 490.1488.

*4.1.8. 1-(4-(2-(Cyclobutylcarbamoyl)ethyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**8**)*

Off white solid, yield: 88.3%, mp > 250 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.55–1.63 (m, 2H, cyclobutyl-CH_2), 1.74–1.84 (m, 2H, cyclobutyl-CH_2), 2.09–2.11 (m, 2H, cyclobutyl-CH_2), 2.27 (t, 2H, J = 7.2 Hz, CH_2CH_2), 2.72 (t, 2H, J = 7.2 Hz, CH_2CH_2), 4.11–4.20 (m, 1H, NHCH), 7.10 (d, 2H, J = 8.1 Hz, ArH), 7.34 (d, 2H, J = 8.1 Hz, ArH), 7.57–7.60 (m, 2H, ArH), 8.02 (d, 1H, J = 7.5 Hz, ArH), 8.09 (s, 1H, CONH), 8.76 (s, 1H, NHCONH), 9.14 (s, 1H, NHCONH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 14.62, 30.26, 30.40, 37.09, 43.74, 116.57, 116.63, 118.65, 122.09, 122.91, 128.47, 131.95, 135.28, 136.99, 139.44, 152.39, 170.15. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{22}ClF_3N_3O_2$ 440.1347, found 440.1335.

*4.1.9. 1-(4-(2-(2,6-Dimethylmorpholinocarbamoyl)ethyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**9**)*

Off white solid, yield: 80.3%, mp 202–203 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.03–1.07 (m, 6H, 2 × CH_3), 2.13–2.21 (m, 1H, CHCH$_3$), 2.55–2.74 (m, 6H, CH_2CH_2, NCH_2), 3.18–3.22 (m, 1H, CHCH$_3$), 3.70–4.25 (m, 2H, NCH_2), 7.14 (d, 2H, J = 8.4 Hz, ArH), 7.34 (d, 2H, J = 8.4 Hz, ArH), 7.57–7.64 (m, 2H, ArH), 8.08 (s, 1H, ArH), 8.75 (s, 1H, NHCONH), 9.12 (s, 1H, NHCONH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 18.36, 50.32, 71.31, 116.59, 118.65, 121.48, 122.13, 122.96, 124.19, 126.53, 126.83, 128.78, 131.99, 135.24, 137.07, 139.47, 152.42, 170.39. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{26}ClF_3N_3O_3$ 484.1609, found 484.1618.

*4.1.10. 1-(4-((E)-2-(methylcarbamoyl)propen-1-yl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**10**)*

Intermediates **A3(a–c)** were prepared using methylmalonic acid instead of malonic acid as the staring material in a series of reactions as described for intermediate **A1**, with the yields of 61.3%, 53.2%, 67.9% respectively. Finally, following the general procedure for the preparation of target compounds to give compounds **10–12**.

Off white solid, yield: 82.7%, mp 224–225 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.01 (d, 3H, J = 1.2 Hz, CH=CCH$_3$), 2.67 (d, 3H, J = 4.5 Hz, NHCH$_3$), 7.12 (s, 1H, CH=CCH$_3$), 7.35 (d, 2H, J = 8.7 Hz, ArH), 7.50 (d, 2H, J = 8.7 Hz, ArH), 7.61–7.63 (m, 2H, ArH), 7.92 (d, 1H, J = 4.2 Hz, ArH), 8.10 (s, 1H, CONH), 8.98 (s, 1H, NHCONH), 9.19 (s, 1H, NHCONH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 14.27, 26.22, 116.80, 116.84, 118.31, 123.11, 130.02, 130.08, 130.80, 131.76, 131.98, 138.70, 139.23, 152.28, 169.36. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{18}ClF_3N_3O_2$ 412.1034, found 412.1023.

*4.1.11. 1-(4-((E)-2-(1-phenylethylcarbamoyl)propen-1-yl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**11**)*

Off white solid, yield: 86.0%, mp 179–180 °C. IR (KBr, cm^{-1}): 3325.4, 3125.3, 3064.8, 2976.8, 1703.0, 1643.3, 1593.0, 1541.4, 1482.2, 1420.2, 1181.8, 1030.5, 829.6, 699.5. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.43 (d, 3H, J = 7.2 Hz, CHCH$_3$), 2.04 (d, 3H, J = 0.9 Hz, CH=CCH$_3$), 5.03–5.08 (m, 1H, NHCH), 7.18–7.24 (m, 2H, ArH, CH=CCH$_3$), 7.30–7.38 (m, 6H, ArH), 7.52 (d, 2H, J = 8.4 Hz, ArH), 7.60–7.63 (m, 2H, ArH), 8.11 (s, 1H, CONH), 8.34 (d, 1H, J = 8.1 Hz, ArH), 8.99 (s, 1H, NHCONH), 9.20 (s, 1H, NHCONH). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{24}ClF_3N_3O_2$ 502.1331, found 502.1368.

*4.1.12. 1-(4-((E)-2-(2,6-dimethylmorpholinocarbamoyl)propen-1-yl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**12**)*

Off white solid, yield: 90.3%, mp 230–232 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.09 (d, 6H, J = 6.3 Hz, 2 × CH_3), 2.00 (d, 3H, J = 0.9 Hz, CH=CCH$_3$), 2.48–2.50 (m, 1H, CHCH$_3$), 3.33–3.45 (m, 1H, CHCH$_3$), 3.46–3.52 (m, 2H, NCH_2), 3.95–4.05 (m, 2H, NCH_2), 6.42 (s, 1H, CH=CCH$_3$), 7.33 (d, 2H, J = 8.4 Hz, ArH), 7.48 (d, 2H, J = 8.7 Hz, ArH), 7.60–7.62 (m, 2H, ArH), 8.09 (d, 1H, J = 1.8 Hz, ArH), 8.96 (s, 1H, NHCONH), 9.17 (s, 1H, NHCONH). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{26}ClF_3N_3O_3$ 496.1609, found 496.1585.

*4.1.13. 1-(4-((E)-1-(methylcarbamoyl)propen-2-yl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**13**)*

18-Crown-6 (5 mmol) was added to a solution of trimethyl phosphonoacetate (11 mmol) in toluene (20 mL) under argon atmosphere, then a 1 mol/L NaHMDS/THF solution (20 mL) was added and the obtained mixture was stirred at room temperature for 1 h. Under ice-cooling, 4-nitroacetophenone (10 mmol) was added and the mixture was stirred for 10 h. After the reaction was complete, the solid formed was filtered, washed with cold water and dried to give (*E*)-methyl-3-(4-nitrophenyl)-2-butenoate (69.7%). To a THF (6 mL) solution of the intermediate methyl ester (2 mmol) was added 1 mol/L NaOH (10 mL). The reaction mixture was stirred at room temperature for 12 h, then chilled in ice and acidified with concentrated HCl to pH 1–2. The solid formed was filtered, washed with water and dried to afford (*E*)-3-(4-nitrophenyl)-2-butenoic acid as a white solid (91.1%). Then, amidation of carboxyl group and reduction of nitro group following the synthetic methods as described for **A1** to give intermediates **A4(a–c)** in yields of 50.0%, 67.9%, 58.2% respectively. Finally, following the general procedure for the preparation of target compounds to give compounds **13**–**15**.

Off white solid, yield: 84.6%, mp 224–225 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.46 (s, 3H, NHC$\underline{H_3}$), 2.65 (d, 3H, J = 4.2 Hz, C$\underline{H_3}$C=CH), 6.17 (d, 1H, J = 0.6 Hz, CH_3C=C$\underline{H}$), 7.45 (d, 2H, J = 8.7 Hz, ArH), 7.50 (d, 2H, J = 8.7 Hz, ArH), 7.62–7.70 (m, 2H, ArH), 7.90 (d, 1H, J = 4.8 Hz, ArH), 8.11 (s, 1H, CONH), 8.99 (s, 1H, NHCO$\underline{NH}$), 9.21 (s, 1H, $\underline{NH}$CONH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.25, 25.34, 116.77, 116.81, 118.28, 119.00, 123.09, 126.39, 131.96, 135.78, 139.22, 139.49, 146.80, 152.25, 166.69. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{19}H_{18}ClF_3N_3O_2$ 412.1034, found 412.1011.

*4.1.14. 1-(4-((E)-1-(1-phenylethylcarbamoyl)propen-2-yl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**14**)*

Off white solid, yield: 82.0%, mp 212–214 °C. IR (KBr, cm^{-1}): 3324.4, 3063.3, 2979.0, 1698.8, 1638.7, 1592.1, 1539.6, 1483.4, 1419.2, 1172.5, 1030.5, 835.0, 698.5. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.39 (d, 3H, J = 6.9 Hz, NHC$\underline{H_3}$), 2.45 (s, 3H, C$\underline{H_3}$C=CH), 4.97–5.02 (m, 1H, NHC$\underline{H}$), 6.29 (d, 1H, J = 1.2 Hz, CH_3C=C$\underline{H}$), 7.21–7.33 (m, 5H, ArH), 7.46 (d, 2H, J = 9.3 Hz, ArH), 7.50 (d, 2H, J = 9.3 Hz, ArH), 7.60–7.63 (m, 2H, ArH), 8.12 (s, 1H, CONH), 8.40 (d, 1H, J = 7.8 Hz, ArH), 9.00 (s, 1H, NHCO$\underline{NH}$), 9.21 (s, 1H, $\underline{NH}$CONH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.22, 22.54, 47.60, 116.78, 117.62, 118.25, 119.03, 123.13, 125.94, 126.01, 126.45, 126.58, 128.07, 128.24, 132.00, 135.76, 139.24, 139.59, 144.86, 147.49, 152.27, 165.23. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{26}H_{24}ClF_3N_3O_2$ 502.1454, found 502.1464.

*4.1.15. 1-(4-((E)-1-(2,6-dimethylmorpholinocarbamoyl)propen-2-yl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**15**)*

Off white solid, yield: 90.8%, mp 240–241 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.07–1.12 (m, 6H, 2 × CH_3), 2.16 (s, 3H, C$\underline{H_3}$C=CH), 2.26–2.34 (m, 1H, C$\underline{H}$CH$_3$), 2.68–2.76 (m, 1H, C$\underline{H}$CH$_3$), 3.45–3.46 (m, 2H, NCH$_2$), 3.79–4.34 (m, 2H, NCH$_2$), 6.43 (s, 1H, CH_3C=C$\underline{H}$), 7.46–7.53 (m, 4H, ArH), 7.62–7.63 (m, 2H, ArH), 8.09 (s, 1H, ArH), 9.00 (s, 1H, NHCO$\underline{NH}$), 9.20 (s, 1H, $\underline{NH}$CONH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 18.12, 51.14, 71.49, 116.78, 117.98, 118.23, 119.93, 122.36, 123.10, 126.46, 127.58, 131.96, 134.69, 139.02, 141.21, 143.81, 152.25, 166.03, 166.27. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{24}H_{26}ClF_3N_3O_3$ 496.1589, found 496.1586.

*4.1.16. 1-(4-((E)-2-(methylcarbamoyl)vinyloxy)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**16**)*

Methyl propiolate (7 mmol), *N*-Boc-4-aminophenol (7 mmol) and DABCO (0.7 mmol) were dissolved in DCM (10 mL). The reaction mixture was stirred at room temperature for 1.5 h, and then the solvent was concentrated under reduced pressure. The oily residue was recrystallized from diethyl ether to give (*E*)-methyl-3-(4-nitrophenoxy)acrylate (89.3%), then treated it (3 mmol) as described for the synthesis of the acid in intermediate **A4** to give (*E*)-3-(4-nitrophenoxy)acrylic acid (82.4%). A mixture of the acid (1 mmol), BOP (1.1 mmol) and TEA (2.2 mmol) in THF (6 mL) was stirred at room temperature for 5 min, then a THF (1 mL) solution of corresponding amine (1.1 mmol) was added and the mixture was stirred for 3 h. After removal of the solvent under reduced pressure, the resulting residue was poured into water and extracted with DCM (2 × 20 mL), then the organic layer was washed with saturated brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (light petroleum/EtOAc = 1:1) on silica gel to give (*E*)-*N*-substituted-3-(4-nitrophenoxy)acrylamide as a white solid (59.4%–78.0%). The amide (1 mmol) was deprotected by stirring in 7 mol/L HCl/EtOAc (3 mL) at room temperature for 1 h. The solid formed was filtrated and put into DCM (20 mL) immediately, then washed with saturated solution of $NaHCO_3$ to pH 8–9, concentrated to give intermediates **A5(a–b)** in yields of 84.3% and 80.3% respectively. Finally, following the general procedure for the preparation of target compounds to give compounds **16**–**18**.

Off white solid, yield: 84.6%, mp 218–219 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.62 (d, 3H, J = 4.8 Hz, CH_3), 5.58 (d, 1H, J = 12.0 Hz, OCH=C$\underline{H}$), 7.08 (d, 2H, J = 8.7 Hz, ArH), 7.46 (d, 2H, J = 9.0 Hz, ArH), 7.53 (d, 1H, J = 12.0 Hz, O$\underline{CH}$=CH), 7.60–7.62 (m, 2H, ArH), 7.76 (d, 1H, J = 7.2 Hz, ArH), 8.09 (s, 1H, CONH), 8.88 (s, 1H, NHCO$\underline{NH}$), 9.15 (s, 1H, $\underline{NH}$CONH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 25.30, 104.88, 116.72, 116.76, 118.16, 120.23, 123.01, 131.90, 135.71, 139.31, 150.65, 152.40, 154.50, 165.32. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{18}H_{16}ClF_3N_3O_3$ 414.0827, found 414.0808.

*4.1.17. 1-(4-((E)-2-(1-phenylethylcarbamoyl)vinyloxy)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**17**)*

Off white solid, yield: 90.6%, mp 196–197 °C. IR (KBr, cm^{-1}): 3295.1, 3067.0, 2975.7, 1695.1, 1664.6, 1602.7, 1551.9, 1428.1, 1421.4, 1174.0, 1031.4, 834.1, 698.8. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.34 (d, 3H, J = 7.2 Hz, CH_3), 4.94–4.99 (m, 1H, NHC$\underline{H}$), 5.64 (d, 1H, J = 12.0 Hz, OCH=C$\underline{H}$), 7.08 (d, 2H, J = 8.7 Hz, ArH), 7.21–7.30 (m, 5H, ArH), 7.46 (d, 2H, J = 9.0 Hz, ArH), 7.57 (d, 1H, J = 12.0 Hz, O$\underline{CH}$=CH), 7.60–7.62 (m, 2H, ArH), 8.09 (d, 1H, J = 1.8 Hz, $\underline{NH}$CH), 8.25 (d, 1H, J = 8.1 Hz, ArH), 8.90 (s, 1H, NHCO$\underline{NH}$), 9.18 (s, 1H, $\underline{NH}$CONH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 22.37, 47.57, 104.68, 116.74, 118.43, 120.20, 122.99, 125.91, 126.52, 128.15, 131.90, 135.83, 139.31, 144.64, 150.50, 152.39, 155.22, 163.97. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{25}H_{22}ClF_3N_3O_3$ 504.1296, found 504.1277.

*4.1.18. 1-(4-((E)-2-(1-phenylethylcarbamoyl)vinyloxy)phenyl)-3-(2-chloro-5-(trifluoromethyl)phenyl)urea (**18**)*

Off white solid, yield: 87.1%, mp 200–201 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.34 (d, 3H, J = 7.2 Hz, CH_3), 4.95–4.99 (m, 1H, NHC$\underline{H}$), 5.66 (d, 1H, J = 12.3 Hz, OCH=C$\underline{H}$), 7.10 (d, 2H, J = 9.0 Hz, ArH), 7.21–7.30 (m, 6H, ArH), 7.40–7.51 (m, 3H, ArH, O$\underline{CH}$=CH), 7.70 (d, 1H, J = 8.4 Hz, ArH), 8.26 (d, 1H, J = 8.4 Hz, ArH), 8.58 (s, 1H, NHCO$\underline{NH}$), 8.62 (d, 1H, J = 1.8 Hz, $\underline{NH}$CH), 9.60 (s, 1H, $\underline{NH}$CONH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 22.38, 47.59, 104.75, 118.57, 119.96, 125.92, 126.53, 128.16, 130.31, 135.62, 136.89, 144.64, 150.62, 152.01, 155.18, 163.98. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{25}H_{22}ClF_3N_3O_3$ 504.1296, found 504.1273.

*4.1.19. 1-(4-(2-(Methylcarbamoyl)ethynyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**19**)*

To a THF (30 mL) solution of 4-iodonitrobenzene (10 mmol) and methyl propiolate (40 mmol) were added $Pd(PPh_3)_2Cl_2$ (140 mg), CuI (76 mg) and K_2CO_3 (20 mmol). The obtained mixture was heated to reflux for 5 h. Subsequently, the solvent was concentrated under reduced pressure, the residue was poured into

water and extracted with DCM (2 × 30 mL), then the organic layer was washed with saturated brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (light petroleum/EtOAc = 6:1) on silica gel to give methyl 3-(4-nitrophenyl)propiolate (78.1%), then treated it (1.5 mmol) as described for the synthesis of the amide in intermediate **A5** to provide *N*-substituted-3-(4-nitrophenyl)propiolamide as a white solid (69.3%–74.1%). To a solution of the amide (0.5 mmol) in EtOH (5 mL) and 2 mol/L HCl (2 mL) was added Fe (3.5 mmol), then the mixture was stirred at 70 °C for 4 h. The reaction mixture was concentrated to near dryness under reduced pressure, the oily residue was poured into water and extracted with DCM (2 × 20 mL), then the organic layer was washed with saturated brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (light petroleum/EtOAc = 1:1) on silica gel to give intermediates **A6(a–b)** in yields of 78.2% and 83.3% respectively. Finally, following the general procedure for the preparation of target compounds to give compounds **19**–**21**.

Off white solid, yield: 80.4%, mp 221–223 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.56 (d, 3H, J = 4.5 Hz, CH_3), 7.18 (d, 2H, J = 8.4 Hz, ArH), 7.34–7.37 (m, 3H, ArH), 7.69 (d, 1H, J = 8.7 Hz, ArH), 7.88–7.95 (m, 1H, ArH), 8.57 (s, 1H, CONH), 8.64 (s, 1H, NHCONH), 9.51 (s, 1H, NHCONH). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{14}ClF_3N_3O_2$ 396.1288, found 396.1298.

4.1.20. 1-(4-(2-(1-Phenylethylcarbamoyl)ethynyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**20**)

Off white solid, yield: 84.8%, mp 217–218 °C. IR (KBr, cm^{-1}): 3349.3, 3123.9, 2977.9, 2932.2, 2204.0, 1718.6, 1634.9, 1528.6, 1483.6, 1420.7, 1176.2, 1030.9, 833.0, 698.6. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.37 (d, 3H, J = 6.9 Hz, CH_3), 4.95–5.00 (m, 1H, NHCH), 7.21–7.33 (m, 5H, ArH), 7.50 (d, 2H, J = 8.7 Hz, ArH), 7.52 (d, 2H, J = 8.7 Hz, ArH), 7.63 (s, 2H, ArH), 8.10 (s, 1H, CONH), 9.19 (s, 1H, NHCONH), 9.23 (d, 1H, J = 8.4 Hz, ArH), 9.29 (s, 1H, NHCONH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 22.06, 48.39, 83.39, 83.73, 112.85, 116.95, 118.38, 121.41, 122.60, 123.23, 124.12, 126.02, 126.55, 128.29, 132.02, 133.07, 139.03, 141.08, 143.98, 151.61, 152.12. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{20}ClF_3N_3O_2$ 486.1411, found 486.1400.

4.1.21. 1-(4-(2-(1-Phenylethylcarbamoyl)ethynyl)phenyl)-3-(2-chloro-5-(trifluoromethyl)phenyl)urea (**21**)

Off white solid, yield: 82.1%, mp 215–216 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.38 (d, 3H, J = 7.2 Hz, CH_3), 4.95–5.00 (m, 1H, NHCH), 7.22–7.40 (m, 6H, ArH), 7.52 (d, 2H, J = 8.7 Hz, ArH), 7.57 (d, 2H, J = 8.7 Hz, ArH), 7.72 (d, 1H, J = 8.4 Hz, ArH), 8.61 (s, 1H, CONH), 8.71 (s, 1H, NHCONH), 9.23 (d, 1H, J = 8.4 Hz, ArH), 9.85 (s, 1H, NHCONH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 22.06, 48.39, 83.45, 83.64, 113.09, 116.95, 118.26, 119.63, 122.41, 125.11, 125.63, 126.02, 128.04, 128.29, 130.43, 133.19, 136.64, 140.82, 143.97, 151.59, 151.82. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{20}ClF_3N_3O_2$ 486.1411, found 486.1412.

4.1.22. 1-(4-(3-(Methylcarbamoyl)phenyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**22**)

4-Bromonitrobenzene (9.6 mmol) and 3-carboxybenzeneboronic acid (10.8 mmol) were dissolved in a solution of toluene (40 mL), EtOH (40 mL) and water (5 mL), then K_2CO_3 (29.3 mmol) and $Pd(PPh_3)_4$ (200 mg) were added. The reaction mixture was heated to reflux for 48 h under argon atmosphere. After cooled to room temperature, the resulting solution was diluted with EtOAc (100 mL), then extracted with water (3 × 50 mL). The aqueous extracts were combined and acidified to pH 1–2 with concentrated HCl to afford an off white precipitate, which was washed with water and dried to give 4-nitrobiphenyl-3-carboxylic acid as a white solid (96.1%). Then, amidation of carboxyl group and reduction of nitro group following the synthetic methods as described for **A2** to give intermediates **A7(a–b)** in yields of 87.6% and 93.9% respectively. Finally, following the general procedure for the preparation of target compounds to give compounds **22** and **23**.

Off white solid, yield: 80.2%, mp > 250 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.81 (d, 3H, J = 4.2 Hz, CH_3), 7.48–7.66 (m, 7H, ArH), 7.69–7.76 (m, 2H, ArH), 8.09 (d, 2H, J = 10.8 Hz, ArH), 8.53 (s, 1H, CONH), 9.03 (s, 1H, NHCONH), 9.26 (s, 1H, NHCONH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 26.26, 116.69, 118.90, 121.47, 122.32, 123.09, 124.18, 124.66, 125.69, 127.19, 128.64, 128.94, 132.01, 133.35, 135.13, 139.05, 139.32, 139.75, 152.36, 166.56. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{18}ClF_3N_3O_2$ 448.1034, found 448.1045.

4.1.23. 1-(4-(3-(1-Phenylethylcarbamoyl)phenyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**23**)

Off white solid, yield: 78.8%, mp 240–242 °C. IR (KBr, cm^{-1}): 3226.5, 3180.9, 3109.3, 3059.3, 1730.1, 1613.5, 1554.6, 1486.8, 1427.4, 1322.2, 1139.0, 1034.4, 877.1, 836.3, 777.7, 698.5. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.51 (d, 3H, J = 6.9 Hz, CH_3), 5.15–5.21 (m, 1H, NHCH), 7.22–7.24 (m, 1H, ArH), 7.30–7.39 (m, 3H, ArH), 7.52–7.67 (m, 5H, ArH), 7.81–7.83 (m, 2H, ArH), 7.95 (d, 1H, J = 8.7 Hz, ArH), 8.12–8.35 (m, 3H, ArH), 8.90 (d, 1H, J = 8.1 Hz, ArH), 9.12 (s, 1H, CONH), 9.37 (s, 1H, NHCONH), 9.51 (s, 1H, NHCONH). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{29}H_{24}ClF_3N_3O_2$ 538.1589, found 538.1559.

4.1.24. 1-(4-(4-(1-Phenylethylcarbamoyl)phenyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**24**)

To ice-cold nitric acid (15 mL) was added 4-biphenylcarboxylic acid (20 mmol) slowly, the reaction mixture was stirred under ice cooling for 1 h. The mixture was poured into ice water and then filtered. The collected solid was suspended in EtOH and heated to reflux for 2 h. The mixture was filtered at a high temperature, then the solid was washed with EtOH and dried to give 4-nitrodiphenyl-4-carboxylic acid (55.1%). Then, amidation of carboxyl group and reduction of nitro group following the synthetic methods as described for **A2** to give intermediates **A8(b–c)** in yields of 89.2% and 85.2% respectively. Finally, following the general procedure for the preparation of target compounds to give compounds **24**–**27**.

Off white solid, yield: 79.7%, mp 203–204 °C. IR (KBr, cm^{-1}): 3320.5, 3062.6, 3031.1, 2977.1, 1651.7, 1633.7, 1598.5, 1547.5, 1484.3, 1419.8, 1317.6, 1128.4, 1033.5, 829.2, 697.6. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.49 (d, 3H, J = 6.8 Hz, CH_3), 5.17–5.20 (m, 1H, NHCH), 7.20–7.23 (m, 1H, ArH), 7.30–7.32 (m, 2H, ArH), 7.40 (d, 2H, J = 7.2 Hz, ArH), 7.58 (d, 2H, J = 8.4 Hz, ArH), 7.62–7.64 (m, 2H, ArH), 7.68 (d, 2H, J = 8.8 Hz, ArH), 7.73 (d, 2H, J = 8.0 Hz, ArH), 7.95 (d, 2H, J = 8.0 Hz, ArH), 8.11 (s, 1H, CONH), 8.21 (d, 1H, J = 8.0 Hz, ArH), 9.01 (s, 1H, NHCONH), 9.20 (s, 1H, NHCONH). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{29}H_{24}ClF_3N_3O_2$ 538.1589, found 538.1559.

4.1.25. 1-(4-(4-(1-Phenylethylcarbamoyl)phenyl)phenyl)-3-(2-chloro-5-(trifluoromethyl)phenyl)urea (**25**)

Off white solid, yield: 79.6%, mp > 250 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.50 (d, 3H, J = 7.2 Hz, CH_3), 5.18–5.22 (m, 1H, NHCH), 7.21–7.24 (m, 1H, ArH), 7.32–7.37 (m, 3H, ArH), 7.42 (d, 2H, J = 8.0 Hz, ArH), 7.60 (d, 2H, J = 8.4 Hz, ArH), 7.71–7.77 (m, 5H, ArH), 7.98 (d, 2H, J = 8.0 Hz, ArH), 8.66 (s, 2H, CONH, NHCONH), 8.83 (d, 1H, J = 8.0 Hz, ArH), 9.73 (s, 1H, NHCONH). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{29}H_{24}ClF_3N_3O_2$ 538.1589, found 538.1571.

4.1.26. 1-(4-(4-(2,6-Dimethylmorpholinocarbamoyl)phenyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (**26**)

Off white solid, yield: 86.2%, mp 236–237 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.05–1.12 (m, 6H, 2 × CH_3), 2.87–2.90 (m, 1H, CHCH$_3$), 3.54–3.56 (m, 4H, 2 × NCH_2), 4.27–4.29 (m, 1H, CHCH$_3$),

7.47 (d, 2H, J = 8.0 Hz, ArH), 7.59 (d, 2H, J = 8.4 Hz, ArH), 7.62–7.65 (m, 2H, ArH), 7.67 (d, 2H, J = 8.4 Hz, ArH), 7.72 (d, 2H, J = 8.4 Hz, ArH), 8.13 (d, 1H, J = 2.0 Hz, ArH), 9.01 (s, 1H, NHCONH), 9.23 (s, 1H, NHCONH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 18.45, 52.54, 71.16, 116.73, 118.90, 121.44, 122.31, 123.06, 124.15, 126.00, 126.54, 127.12, 127.82, 131.98, 132.94, 133.93, 139.19, 139.30, 140.84, 152.32, 168.60. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{27}H_{26}ClF_3N_3O_3$ 532.1609, found 532.1659.

4.1.27. 1-(4-(4-(2,6-Dimethylmorpholinocarbamoyl)phenyl) phenyl)-3-(2-chloro-5-(trifluoromethyl)phenyl)urea (**27**)

Off white solid, yield: 87.7%, mp > 250 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.05–1.12 (m, 6H, 2 × CH_3), 2.81–2.86 (m, 1H, CHCH$_3$), 3.55–3.60 (m, 4H, 2 × NCH_2), 4.38–4.40 (m, 1H, CHCH$_3$), 7.39 (d, 2H, J = 8.4 Hz, ArH), 7.48 (d, 2H, J = 8.0 Hz, ArH), 7.60 (d, 2H, J = 8.4 Hz, ArH), 7.69 (d, 2H, J = 8.8 Hz, ArH), 7.73 (d, 2H, J = 8.0 Hz, ArH), 8.66 (s, 2H, ArH, NHCONH), 9.72 (s, 1H, NHCONH). HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{27}H_{26}ClF_3N_3O_3$ 532.1609, found 532.1655.

4.2. Inhibitory activity assay in vitro

The inhibitory activity of target compounds **1**–**27** was evaluated with MX-1, A375, HepG2, Ketr3 and HT-29 cell lines by the standard MTT assay *in vitro*, with sorafenib as the positive control. These cancer cells were maintained in dulbecco's modified eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 100 IU/mL penicillin, and 100 μg/mL streptomycin in a humidified incubator with 5% CO_2 at 37 °C.

Cancer cells were plated at a density of 2000 cells/well in 96 well plates and then incubated at 37 °C for 24 h in a humidified atmosphere with 5% CO_2 prior to treatment of various concentrations of test compounds. After 120 h, the MTT assay was performed to evaluate cell viability. Each well was supplemented with 200 μL of a 0.5 mg/mL MTT solution and incubated for 4 h at 37 °C. The supernatant was carefully removed from each well and 200 μL of dimethyl sulfoxide (DMSO) was added to each well to dissolve the formazan crystals which were formed by the cellular reduction of MTT. After mixing with a mechanical plate mixer, the absorbance of each well was measured by a microplate reader using a test wavelength of 570 nm. The results were expressed as the IC_{50} which was the average of three determinations.

4.3. Kinase assay in vitro

The Raf kinase assays were detected using ADP-Glo™ assay kit, which was performed by HD Biosciences Co., Ltd.

The Raf kinase assay was performed in duplicate in a reaction mixture of final volume of 10 μL containing kinase, substrate, ATP and compounds. The assay was started by incubating the reaction mixture in a 384-well assay plate at 30 °C for 1 h. The reaction was then terminated by the addition of 10 μL of ADP-Glo reagent. The plate was shaken and then incubated for 40 min at 27 °C. 20 μL of kinase detection reagent was added; the plate was shaken and incubated for further 30 min at the same temperature. Finally, read the assay plate on Envision. The results were expressed as the IC_{50}.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.03.020.

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