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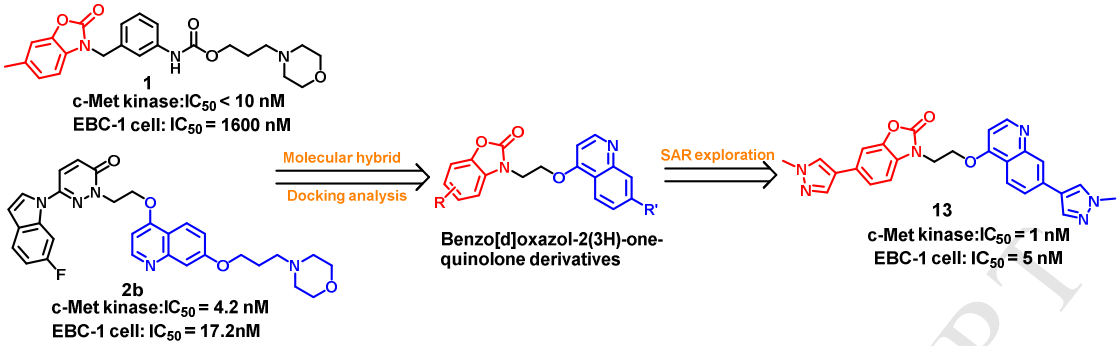
Graphical abstract



Members of a series of benzo[*d*]oxazol-2(3H)-one-quinolones were designed to serve as c-Met kinase inhibitors. The results of a SAR studies identified **13** as a highly potent inhibitor of this kinase

Highlights

- Docking studies with **1** and **7a** with c-Met protein were carried out.
- A molecular hybridization strategy was employed to design c-Met inhibitors.
- Novel benzo[*d*]oxazol-2(3H)-one-quinolone derivatives were synthesized.
- **13** displayed excellent inhibition against c-Met kinase and the EBC-1 cell line.

Title:

Design and synthesis of novel benzo[*d*]oxazol-2(3H)-one derivatives bearing 7-substituted-4-enthoxyquinoline moieties as c-Met kinase inhibitors.

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Abstract:

Analysis of the results of studies of docking **1** and **7a** with c-Met kinase led to the identification of benzo[*d*]oxazol-2(3H)-one-quinolone derivatives as potential inhibitors of this enzyme. A molecular hybrid strategy, using a 4-ethoxy-7-substituted-quinoline core and a benzo[*d*]oxazol-2(3H)-one scaffold, was employed to design members of this family for study as inhibitors of the kinase and proliferation of EBC-1 cells. Most of the substances were found to display good to excellent c-Met kinase inhibitory activities. The results of a structure-activity relationship (SAR) study led to the discovery of benzo[*d*]oxazol-2(3H)-one-quinolone **13**, which has IC_{50} values of 1 nM against c-Met kinase and 5 nM against proliferation of the EBC-1 cell line.

Key words:

c-Met/ benzo[*d*]oxazol-2(3H)-one-quinolone/ molecular hybridization / anti-cancer

1. Introduction

c-Met, encoded by Met proto-oncogene, is a receptor tyrosine kinase (RTK) whose binding with the hepatocyte growth factor (HGF) induces several complex signaling pathways that result in cell proliferation, migration and invasion [1-4]. Aberrant c-Met activation, mutation, amplification and translocation play important roles in cancer formation, progression, dissemination, as well as drug resistance [5-9]. Moreover, elevations of both c-Met and HGF are also associated with poor clinical outcomes for cancer patients [10,11]. As a result, c-Met kinase has received considerable attention as an attractive target for cancer treatment.

During the last decade, the utilization of a structure-based drug design approach [12] has led to the discovery of a number of small molecules, which possess various pharmacophores, such as triazolopyridazines [13], triazolotriazines [14], quinolones [15-20] and quinoxalines [21], that have c-Met inhibitory activities. Furthermore, a significant number of c-Met inhibitors are in clinic trails at the current time (Fig. 1).

Figure 1

The benzo[*d*]oxazol-2(3H)-one ring system is an important skeletal feature of molecules that have a diverse array of biological properties including anti-inflammatory, cytotoxicity, anti-tumor and neurological activities [22-26]. More pertinent to the current study is the report by workers at the Merck company that although benzo[*d*]oxazol-2(3H)-one **1** (Fig. 2A) is a modest c-Met inhibitor (IC_{50} = 1.6 μM) [27], it has poor cellular inhibitory activity against c-Met dependent EBC-1 cell proliferation. Based on observations made in a previous investigation of pyridazinone-quinoline derivatives, we speculated that the greatly lowered cellular activity of **1** is a consequence of the presence of the polar carbamate group [28], which is not compatible with the hydrophobic hinge pocket of the enzyme. We speculated that replacement of the carbamate by the more hydrophobic quinoline moiety (as in **2b** in Fig. 2A) would enhance both hydrogen bonding (with Met1160) and hydrophobic interactions with c-Met and lead to an improvement of cellular activity (Fig. 2A). Importantly, a quinoline moiety serving as a motif to promote hinge binding is prevalent in a number of known c-Met inhibitors (Fig. 1).

Based on the proposal made above, substances containing the benzo[d]oxazol-2(3H)-one-quinolone scaffold were designed by using a molecular hybridization strategy to be novel c-Met inhibitors (Fig. 2A). The results of studies in which **1** and **7a** are docked with c-Met kinase revealed that benzo[*d*]oxazol-2(3H)-one moiety in **7a** exactly matches the binding model established using **1**. Specifically, **7a** exists in a "U" shape conformation in the ATP binding pocket of c-Met kinase where it is sandwiched between Met 1211 and Tyr1230 (Fig. 2B). In addition, the quinoline ring nitrogen in **7a** forms a hydrogen bond with Met1160 instead of a carbonyl group, and the substituent at C7 of the quinoline moiety appears to extend into the solvent exposed region of the protein. SAR studies were explored using selected benzo[*d*]oxazol-2(3H)-one and quinolone ring substituted analogs of **7a** (see Tables 1 and 2). The results of this effort demonstrated that the benzo[*d*]oxazol-2(3H)-one-quinolone **13** is a potent c-Met inhibitor and it displays anti-proliferation activity against EBC-1 cells.

Figure 2

2. Results and Discussion

2.1 Chemistry

The routes employed to synthesize benzo[d]oxazol-2(3H)-one-quinolones **7a-7g** are outlined in Scheme 1. 6-Methylbenzo[d]oxazol-2(3H)-one, prepared from commercially available 2-amino-5-methylphenol [27], was subjected to N-alkylation with 2-bromoethoxy-(*t*-butyl-dimethylsilane) to form the corresponding N-alkylated derivative **3**. Removal of the TBS group in **3** generated alcohol **4**, which was subjected to Buchwald cross coupling with 7-substituted-4-chloroquinolines **6** to form the target benzo[d]oxazol-2(3H)-one-quinolones **7a-7g**. Intermediates **6c-6g** used in these routes were

generated by O-alkylation reactions of 4-chloroquinoline-7-ol [29] followed by amination reactions with secondary amines.

Scheme 1

The methods used to prepare benzo[d]oxazol-2(3H)-one-quinolones **7h-7i**, **11**, **12** and **13** are outlined in Scheme 2. 4-Chloro-7-methoxyquinoline or 4-chloro-7-bromoquinoline [30] were reacted with 2-*tert*-butoxyethanol to produce the corresponding O-ethoxy derivatives **9**, which were transformed to the respective alcohols **10**. Mesylation of the hydroxyl group in **10** was followed by N-alkylation reactions with substituted benzo[*d*]oxazol-2(3H)-ones **8** [27] to produce benzo-oxazole substituted quinolones **11**. Alternatively, **7h-7i** and **12a-12c** were generated by Suzuki or Buchwald cross coupling reactions of the corresponding bromo-substituted analogs **11**. Finally, the pyrazole derivative **13** was prepared by using a double Suzuki reaction of **11k** with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.

Scheme 2

2.2 SAR Development and Lead Generation

An evaluation of the inhibitory activities of the benzo[d]oxazol-2(3H)-one-quinolones **7a-i** against c-Met kinase and proliferation of EBC-1 cells was carried out. The results of this SAR exploration, focusing on the effects of quinolone C7 substituents are given in Table 1. The findings show that these substances display excellent inhibitory activities against c-Met kinase with IC_{50} values in the 3.4-11.0 nM range. The C7 substituents on the quinolone ring, which modeling studies suggested would extend into the solvent exposed region of the protein, have an obvious effect on the cellular activity as determined by using the EBC-1 cell proliferation assay. In line with this reasoning, the results (Table 1) show that introduction of hydrophilic substituents leads to a dramatic improvement in proliferation inhibition. For example, **7d-7g** containing more hydrophilic C7 substituents have cellular activities with IC_{50} values in the 120-330 nM range. In addition, **7d** in which the carbamate moiety in **1** is replaced by a quinoline moiety is a more potent cell proliferation inhibitor. Furthermore, **7g** which contains a four carbon linker, is less potent than **7e** and **7f**, indicating that a linker length of two or three carbons is optimal for inhibition. Aslo, **7h** possessing an amino side chain has a more potent cellular inhibitory activity than does **7e** which contains an alkoxy side chain. Finally, introduction of highly water soluble N-methylpyrazole substituents, produces **7i**, which displays the most potent cell proliferation inhibitory activity (IC_{50} = 35 nM) of substances in this family. Notably, **7i** has the nearly the same anti-proliferation inhibitory activity as does Crizotinib and a 10 fold lower ratio of cellular to enzymatic IC_{50} values than this reference substances.

Table 1

An additional SAR study was carried out to explore the effects of substituents on the benzo[*d*]oxazol-2(3H)-one moiety in the benzo[d]oxazol-2(3H)-one-quinolones. The results (Table 2) show that **7a**, **11b**, **11d** and **12b**, each of which contains a C6 substituent, exhibit better inhibitory activities against c-Met kinase than do **11a**, **11c**, **11e** and **12c**, which possess C5 substituents. Interestingly, the results of the docking studies also showed that the space available for a benzo[*d*]oxazol-2(3H)-one C5 substituent in the ATP binding site of c-Met protein is limited. As a result, according to the results of docking studies with **12b** and **12c** (Fig. 3), introduction of a

C5 substituent promotes a shift of the position of binding an inhibitor, which causes weakening of the π-π stacking interactions with Tyr1230 of c-Met. Furthermore, the results show that substances possessing both sterically and electron donating groups (e. g., **7a** with methyl and **11g** with amino group), display more potent enzymatic inhibitory activities than do analogs with electron withdrawing groups (e. g., **11b** with a fluoride group and **11d** with a methyl formate group). Also, **12a** containing a sterically bulky electron donating group has a highly decreased inhibitory activity. In general, the findings show that substitution on the benzo[*d*]oxazol-2(3H)-one moiety leads to no significant improvement in cellular activity for substances in the family that do not possess a hydrophilic C7 substituent that is needed in the solvent-exposed region of the protein. Moreover, only **11g** and **12b** with an amino or N-methylpyrazole substituent at C6 of the benzo[*d*]oxazol-2(3H)-one moiety display moderate EBC-1 cellular inhibition.

Table 2

Figure 3

Based on the results of the SAR study presented above, we designed the benzo[d]oxazol-2(3H)-one-quinolone **13** (Fig. 4), which contains two N-methylpyrazole substituents that combine the favorable effects seen by introducing substituents on both the benzo[*d*]oxazol-2(3H)-one scaffold and quinolone moiety. Significantly, biological evaluation showed that **13** is an excellent c-Met inhibitor on both the enzymatic and EBC-1 cellular levels (IC_{50} = 1 and 5 nM, respectively). The results of a docking study with **13** revealed that both N-methylpyrazole groups extend into hydrophilic regions of the kinase where they enjoy favorable hydrophilic interactions (SI, Figure S1).

Figure 4

3. Conclusions

In conclusion, by using a molecular hybridization strategy, novel benzo[*d*]oxazol-2(3H)-one derivatives bearing 7-substituted-4-enthoxyquinoline moiety were designed to serve as c-Met inhibitors. In accord with reasoning developed by analysis of the results of docking studies, replacement of the carbamate group in **1** with a quinolone motif to enhance hinge region binding, and introduction of a hydrophilic C7 substituent on quinolone to promote favorable interactions with water leads to benzo[d]oxazol-2(3H)-one-quinolones that have significantly improved c-Met kinase and cell proliferation inhibitory activities. Finally, biological evaluation of **13,** which contains two N-methylpyrazole groups selected by combining the favorable substitution patterns seen with both the benzo[*d*]oxazol-2(3H)-one and quinolone fragments, showed that it is an excellent c-Met inhibitor on both enzymatic and EBC-1 cellular levels. Further evaluation and optimization of the drug-like properties of **13** are currently under investigation.

4. Experimental Section

4.1 General Information

^{1}H NMR and ^{13}C NMR spectral data were recorded on with Varian Mercury 500, 400 or 300 NMR spectrometer and Chemical shifts (δ) were reported in parts per million (ppm), and the signals were described as brs (broad singlet), d (doublet), dd (doublet of doublet), m (multiple), q (quarter), s (singlet), and t (triplet). Coupling constants (*J* values) were given in Hz.

Low-resolution mass spectra (ESI)was obtained using Agilent HPLC-MS (1260-6120B) and all final compounds had purity >95% determined by using High Pressure Liquid Chromatography (HPLC) using a ZorbaxEclipase XDB-C18 column eluting with a mixture of MeCN/Water (V:V = 70: 30).

4.2 The Procedure for Preparation of 3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-methylbenzo[d]oxazol-2(3H)-one ***(3)***

A solution of triphosgene (1.93 g, 6.5 mmol) in anhydrous THF (40 mL) was added to a solution of 2-amino-5-methylphenol (10 g, 8.1 mmol) and Et_3N (2.3 mL) in anhydrous THF (40 mL) at 0 °C. The resulting solution was stirred at room temperature (RT) for overnight and was diluted with water (10 mL). After 30 min, the reaction mixture was concentrated in vacuo and the residue was extracted with ethyl acetate (50 mL×3). The combined organic layer was washed by saturated sodium chloride solution for three times, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 6-methylbenzo[d]oxazol-2(3H)-one as an off-white solid. Yield 83% (1.93g). MS (ESI): 150.1 $[M+H]^+$.

A solution of 6-methylbenzo[d]oxazol-2(3H)-one (0.74 g, 5.0 mmol) in DMF (30 mL) was added with (2-bromoethoxy)(*tert*-butyl)dimethylsilane (1.43 g, 6.0 mmol) and Cs_2CO_3 (1.95 g, 6.0 mmol). The reaction mixture was stirred at 50 °C. After 5 h, the mixture was poured into water (60 mL) and then was extracted with ethyl acetate (20 mL×3). The combined organic layer was washed by water for two times and saturated sodium chloride solution for one time, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **3** as a white solid. Yield 85% (1.31 g) .^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 0.6 Hz, 1H), 6.95 (d, *J* = 1.0 Hz, 2H), 3.90 (d, *J* = 8.5 Hz, 4H), 2.38 (d, *J* = 0.4 Hz, 3H), 0.81 – 0.78 (m, 9H), -0.06 – -0.09 (m, 6H). MS (ESI): 308.2 $[M+H]^+$.

4.3 The Procedure for Preparation of 3-(2-hydroxyethyl)-6-methylbenzo[d]oxazol-2(3H)-one **(4)**

A solution of **3** (0.92 g, 3.0 mmol) in THF (30 mL) and water (10 mL) was added with 3N HCl (5 mL) and the mixture was stirred at RT for 1h. The reaction mixture was concentrated in vacuo and the residue was extracted with ethyl acetate (20 mL×3). The combined organic layer was washed by 20 mL of 1N NaOH for two times and saturated sodium chloride solution for one time, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **4** as a white solid. Yield 75% (0.43 g).^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.95 (s, 2H), 3.95 – 3.88 (m, 4H), 2.89 (t, *J* = 4.8 Hz, 1H), 2.35 (s, 3H). MS (ESI): 194.1 $[M+H]^+$.

4.4 The General Procedure for Preparation of **6c-g**

The mixture of dibromo aliphatic analogue (25.0 mmol) and 4-chloroquinolin-7-ol (895 mg, 5.0 mmol) in DMF (20 mL) was added with K_2CO_3 (3.45 g, 25.0 mmol) and stirred at 50 °C for 5 h. Then the reaction mixture was cooled to room temperature and quenched with water (20 mL). The mixture was extracted with ethyl acetate (30 mL×3). The combined organic layer was

washed by saturated sodium chloride solution for three times, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product **5** was reacted further directly without the purification.

The mixture of **5** (4.0 mmol) and secondary amine (20.0 mmol) in DMF (20 mL) was added K_2CO_3 (20.0 mmol) and stirred at 50 °C for 5 h. Then the reaction mixture was cooled to room temperature and quenched with water. The mixture was extracted with ethyl acetate (30 mL×3). The combined organic layer was washed by saturated sodium chloride solution for three times, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **6c-6g**.

4.4.1. 4-chloro-7-(3-(pyrrolidin-1-yl)propoxy)quinoline (**6c**).
Yellow solid (80 %, 2 steps).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.8 Hz, 1H), 8.10 (d, *J* = 9.1 Hz, 1H), 7.42 (s, 1H), 7.33 (d, *J* = 4.6 Hz, 1H), 7.30 (s, 1H), 4.19 (t, *J* = 6.3 Hz, 2H), 2.72 – 2.63 (m, 2H), 2.55 (s, 4H), 2.14 – 2.04 (m, 2H), 1.80 (s, 4H). MS (ESI): 291.1 $[M+H]^+$.

4.4.2. 4-chloro-7-(3-(4-methylpiperazin-1-yl)propoxy)quinoline (**6d**).
Yellow solid (76%, 2 steps).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.6 Hz, 1H), 8.10 (d, *J* = 8.9 Hz, 1H), 7.41 (s, 1H), 7.33 (d, *J* = 4.5 Hz, 1H), 7.29 (s, 1H), 4.18 (t, *J* = 6.3 Hz, 2H), 2.58 (d, *J* = 7.1 Hz, 2H), 2.55 (s, 8H), 2.29 (s, 3H), 2.05 (s, 2H). MS (ESI): 320.2 $[M+H]^+$.

4.4.3. 4-(3-((4-chloroquinolin-7-yl)oxy)propyl)morpholine (**6e**).
Yellow solid (81%, 2 steps).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.8 Hz, 1H), 8.10 (d, *J* = 9.2 Hz, 1H), 7.41 (d, *J* = 2.5 Hz, 1H), 7.33 (d, *J* = 4.8 Hz, 1H), 7.30 – 7.26 (m, 1H), 4.18 (t, *J* = 6.3 Hz, 2H), 3.75 – 3.70 (m, 4H), 2.59 – 2.53 (m, 2H), 2.52 – 2.44 (m, 4H), 2.05 (dt, *J* = 13.5, 6.5 Hz, 2H). MS (ESI): 307.1 $[M+H]^+$.

4.4.4. 4-(2-((4-chloroquinolin-7-yl)oxy)ethyl)morpholine (**6f**).
Yellow solid (75% ,2 steps).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, *J* = 4.8 Hz, 1H), 8.11 (d, *J* = 9.2 Hz, 1H), 7.41 (d, *J* = 2.5 Hz, 1H), 7.35 (d, *J* = 4.8 Hz, 1H), 7.33 – 7.29 (m, 1H), 4.29 (d, *J* = 5.6 Hz, 2H), 3.80 – 3.73 (m, 4H), 2.89 (t, *J* = 5.6 Hz, 2H), 2.69 – 2.56 (m, 4H). MS (ESI): 293.2 $[M+H]^+$.

4.5 The General Procedure for Preparation of **7a-7g**.

A solution of the corresponding compound **6** (1 mmol) in dry toluene (20 mL) was added with **4** (252 mg, 1.3 mmol), $Pd(OAc)_2$ (22 mg, 10 mol%), SPhos (82 mg, 20 mol%) and Cs_2CO_3 (651 mg, 2 mmol) . The mixture was stirred at 110 °C under argon atmosphere for 12 h and then cooled to room temperature. The solution was removed in vacuo, and the residue was extracted with ethyl acetate (20 mL×3). The combined organic layer was washed by saturated sodium chloride solution for three times, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **7a-7g**.

4.5.1. 3-(2-((7-methoxyquinolin-4-yl)oxy)ethyl)-6-methylbenzo[d]oxazol-2(3H)-one (**7a**).
White solid (60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, *J* = 5.3 Hz, 1H), 7.88 (d, *J* = 9.2 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.11 – 7.01 (m, 4H), 6.59 (d, *J* = 5.3 Hz, 1H), 4.49 (t, *J* = 5.1 Hz, 2H), 4.35 (t, *J* = 5.1 Hz, 2H), 3.92 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.06 (s), 160.84 (s), 154.71 (s), 151.56 (s), 151.18 (s), 142.80 (s), 133.02 (s), 128.85 (s), 124.22 (s), 122.97 (s), 118.60 (s), 115.56 (s), 110.97 (s), 108.01 (s), 107.14 (s), 99.22 (s), 65.43 (s), 55.46 (s), 41.53 (s), 21.42 (s). MS (ESI): 351.2 $[M+H]^+$. Purity: >95%.

4.5.2. 3-(2-((7-(2-methoxyethoxy)quinolin-4-yl)oxy)ethyl)-6-methylbenzo[d]oxazol-2(3H)-one (**7b**).
White solid (56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 5.4 Hz, 1H), 7.89 (dd, *J* = 9.2, 6.2 Hz, 1H), 7.35 (d, *J* = 2.1 Hz, 1H), 7.15 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.04 (d, *J* = 3.9 Hz, 3H), 6.61 (d, *J* = 5.4 Hz, 1H), 4.50 (t, *J* = 5.1 Hz, 2H), 4.36 (t, *J* = 5.1 Hz, 2H), 4.28 – 4.21 (m, 2H), 3.84 – 3.78 (m, 2H), 3.47 (s, 3H), 2.39 (s, 3H). MS (ESI): 395.3 $[M+H]^+$. Purity: >95%.

4.5.3.6-methyl-3-(2-((7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)ethyl)benzo[d]oxazol-2(3H)-one (**7c**).
White solid (40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 5.2 Hz, 1H), 7.91 (d, *J* = 9.1 Hz, 1H), 7.35 (s, 1H), 7.09 (dt, *J* = 6.4, 2.9 Hz, 4H), 6.62 (d, *J* = 5.3 Hz, 1H), 4.52 (t, *J* = 5.1 Hz, 2H), 4.38 (t, *J* = 5.1 Hz, 2H), 4.17 (t, *J* = 6.3 Hz, 2H), 3.79 – 3.70 (m, 4H), 2.60 – 2.56 (m, 2H), 2.51 (s, 4H), 2.42 (s, 3H), 2.11 – 2.02 (m, 2H). MS (ESI): 448.3 $[M+H]^+$. Purity: >95%.

4.5.4.6-methyl-3-(2-((7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)ethyl)benzo[d]oxazol-2(3H)-one (**7d**).
White solid (45%). ^{1}H NMR (400 MHz, DMSO) δ 8.54 (d, *J* = 5.4 Hz, 1H), 7.90 (d, *J* = 9.2 Hz, 1H), 7.25 – 7.14 (m, 2H), 7.11 – 7.02 (m, 2H), 6.93 (dd, *J* = 8.2, 0.9 Hz, 1H), 6.85 (d, *J* = 5.5 Hz, 1H), 4.56 (t, *J* = 4.9 Hz, 2H), 4.39 (t, *J* = 4.9 Hz, 2H), 4.15 (t, *J* = 6.1 Hz, 2H), 2.88 (s, 4H), 2.75 – 2.65 (m, 4H), 2.55 (s, 3H), 2.37 (s, 3H), 2.12 – 2.00 (m, 2H), 1.25 (d, *J* = 6.4 Hz, 1H). MS (ESI): 477.3 $[M+H]^+$. Purity: >95%.

4.5.5.6-methyl-3-(2-((7-(3-morpholinopropoxy)quinolin-4-yl)oxy)ethyl)benzo[d]oxazol-2(3H)-one (**7e**).
White solid (53%).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 5.3 Hz, 1H), 7.81 (d, *J* = 9.2 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 7.03 – 6.95 (m, 4H), 6.52 (d, *J* = 5.3 Hz, 1H), 4.42 (t, *J* = 5.1 Hz, 2H), 4.28 (t, *J* = 5.1 Hz, 2H), 4.08 (t, *J* = 6.3 Hz, 2H), 3.70 – 3.63 (m, 4H), 2.49 (d, *J* = 7.0 Hz, 2H), 2.41 (d, *J* = 4.3 Hz, 4H), 2.33 (s, 3H), 1.95 (dd, *J* = 14.0, 7.0 Hz, 2H).^{13}C NMR (151 MHz, $CDCl_3$) δ 160.81 (s), 160.39 (s), 154.71 (s), 151.58 (s), 142.81 (s), 133.02 (s), 128.87 (s), 124.21 (s), 122.94 (s), 118.81 (s), 115.51 (s), 110.99 (s), 108.02 (s), 107.85 (s), 99.18 (s), 67.01 (s), 66.29 (s), 65.42 (s), 55.53 (s), 53.76 (s), 41.54 (s), 26.29 (s), 21.43 (s). MS (ESI): 464.2 $[M+H]^+$. Purity: >95%.

4.5.6. 6-methyl-3-(2-((7-(2-morpholinoethoxy)quinolin-4-yl)oxy)ethyl)benzo[d]oxazol-2(3H)-one (**7f**).
White solid (57%).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, *J* = 5.3 Hz, 1H), 7.88 (d, *J* = 9.1 Hz, 1H), 7.48 – 7.40 (m, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.09 (dd, *J* = 9.3, 2.5 Hz, 1H), 6.60 (d, *J* = 5.3 Hz, 1H), 4.49 (t, *J* = 5.1 Hz, 2H), 4.35 (t, *J* = 5.1 Hz, 2H), 4.31 – 4.20 (m, 2H), 3.81 – 3.70 (m,

4H), 2.87 (dd, *J* = 11.6, 6.0 Hz, 2H), 2.67 – 2.56 (m, 4H), 2.38 (d, *J* = 6.6 Hz, 3H), 1.75 (s, 3H). LCMS (ESI): 450.2 $[M+H]^+$. Purity: >95%.

4.5.7. 6-methyl-3-(2-((7-(4-morpholinobutoxy)quinolin-4-yl)oxy)ethyl)benzo[d]oxazol-2(3H)-one (**7g**).

White solid (50%).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, *J* = 5.3 Hz, 1H), 7.88 (d, *J* = 9.2 Hz, 1H), 7.30 (s, 1H), 7.13 – 6.97 (m, 4H), 6.59 (d, *J* = 5.2 Hz, 1H), 4.49 (d, *J* = 4.8 Hz, 2H), 4.35 (t, *J* = 4.9 Hz, 2H), 4.11 (t, *J* = 6.4 Hz, 2H), 3.72 (d, *J* = 4.3 Hz, 4H), 2.45 (d, *J* = 4.6 Hz, 6H), 2.40 (s, 3H), 1.95 – 1.83 (m, 2H), 1.73 (s, 2H). MS (ESI): 478.3 $[M+H]^+$. Purity: >95%.

4.6 The General Procedure for Preparation of **11**.

A solution of 2-(*tert*-butoxy)ethanol (708 mg, 6 mmol) in DMF (40 mL) was added with NaH (480 mg, 12 mmol). After stirred for 15 minutes, 7-substitued-4-chloroquinoline (4 mmol) was added to the mixture and then stirred at 40 °C for overnight. The reaction mixture was quenched with water and extracted with ethyl acetate (30 mL×3). The combined organic layer was washed by saturated sodium chloride solution for three times, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **9**.

Compound **9** (2.0 mmol) was dissolved in TFA (10ml), and the solution was stirred at RT for 1 hour. Then the mixture was concentrated in vacuo and the residue was extracted with ethyl acetate (20 mL×3). The combined organic layer was washed by 10% NaOH solution for two times and saturated sodium chloride solution for one time, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give **10**.

10 (2.0 mmol) was dissolved in toluene (20 mL) and the solution was cooled to 0 °C. The mixture was slowly added with Et_3N (4.0 mmol) and methanesulfonyl chloride (0.19 mL, 2.4 mmol), respectively. The reaction mixture was stirred at room temperature for 30 minutes and then quenched with water. The mixture was extracted with ethyl acetate (30 mL×3). The combined organic layer was washed by saturated sodium chloride solution for three times, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was further reacted directly for next step without further purification.

The crude product above (2.0 mmol) was dissolved in DMF (20mL). The corresponding benzo[*d*]oxazol-2(3H)-one (2.4 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) was added to the solution. The reaction mixture was stirred at 50 °C for 5 h and then cooled to room temperature. The mixture was diluted with water (40 mL) and then was extracted with ethyl acetate (20 mL×3). The combined organic layer was washed by saturated sodium chloride solution for three times, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **11**.

4.6.1. 3-(2-((7-methoxyquinolin-4-yl)oxy)ethyl)-5-methylbenzo[d]oxazol-2(3H)-one (**11a**).

White solid (36%, 4 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, *J* = 5.3 Hz, 1H), 7.89 (d, *J* = 9.2 Hz, 1H), 7.32 (s, 1H), 7.08 (d, *J* = 7.7 Hz, 2H), 7.01 (s, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.60 (d, *J* = 5.3 Hz, 1H), 4.48 (d, *J* = 5.1 Hz, 2H), 4.35 (d, *J* = 5.0 Hz, 2H), 3.92 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.45 (s), 162.21 (s), 156.23 (s), 153.05 (s), 152.63 (s), 142.10 (s), 135.32 (s), 132.48 (d, *J* = 30.6 Hz), 124.55 (s), 124.36 (s), 119.99 (s), 116.96 (s), 111.30 (s), 110.65 (s), 108.56 (s), 100.64 (s), 67.11 (s), 56.90 (s), 42.84 (s), 22.92 (s). MS (ESI): 351.1

$[M+H]^+$.. Purity: >95%.

4.6.2. 6-fluoro-3-(2-((7-methoxyquinolin-4-yl)oxy)ethyl)benzo[d]oxazol-2(3H)-one (**11b**).
White solid (30%, 4 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, *J* = 5.3 Hz, 1H), 7.85 (d, *J* = 9.2 Hz, 1H), 7.34 (s, 1H), 7.09 (d, *J* = 8.5 Hz, 2H), 7.01 (t, *J* = 8.6 Hz, 2H), 6.61 (d, *J* = 5.2 Hz, 1H), 4.51 (d, *J* = 5.0 Hz, 2H), 4.38 (d, *J* = 4.7 Hz, 2H), 3.94 (d, *J* = 6.7 Hz, 3H). MS (ESI): 355 .1$[M+H]^+$. Purity: >95%.

4.6.3. 5-fluoro-3-(2-((7-methoxyquinolin-4-yl)oxy)ethyl)benzo[d]oxazol-2(3H)-one (**11c**).
White solid (20%, 4 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.88 (d, *J* = 9.1 Hz, 1H), 7.34 (s, 1H), 7.14 (s, 2H), 6.96 (s, 1H), 6.85 (s, 1H), 6.62 (s, 1H), 4.51 (s, 2H), 4.36 (s, 2H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.16 (s), 160.75 (s), 154.72 (s), 151.48 (s), 151.13 (s), 138.53 (s), 122.74 (s), 118.77 (s), 115.43 (s), 110.94 (d, *J* = 9.4 Hz), 108.98 (d, *J* = 24.6 Hz), 108.77 (s), 107.16 (s), 99.21 (s), 97.28 (s), 97.09 (s), 65.43 (s), 55.49 (s), 41.82 (s). MS (ESI): 355.0 $[M+H]^+$. Purity: >95%.

4.6.4. methyl 3-(2-((7-methoxyquinolin-4-yl)oxy)ethyl)-2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxylate (**11d**).
White solid (17%, 4 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, *J* = 5.3 Hz, 1H), 8.03 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.89 (d, *J* = 1.4 Hz, 1H), 7.82 (d, *J* = 9.2 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 7.08 (dd, *J* = 9.2, 2.6 Hz, 1H), 6.61 (d, *J* = 5.3 Hz, 1H), 4.53 (t, *J* = 4.9 Hz, 2H), 4.41 (t, *J* = 4.9 Hz, 2H), 3.94 (d, *J* = 3.3 Hz, 3H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.52 (s), 162.53 (s), 162.10 (s), 155.76 (s), 152.92 (s), 152.55 (s), 143.68 (s), 136.64 (s), 127.88 (s), 126.60 (s), 124.11 (s), 120.18 (s), 116.81 (s), 112.93 (s), 109.33 (s), 108.55 (s), 100.63 (s), 66.75 (s), 56.91 (s), 53.85 (s), 43.28 (s). MS (ESI): 395.1 $[M+H]^+$. Purity: >95%.

4.6.5. methyl 3-(2-((7-methoxyquinolin-4-yl)oxy)ethyl)-2-oxo-2,3-dihydrobenzo[d]oxazole-5-carboxylate (**11e**).
White solid (16%, 4 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 – 8.63 (m, 1H), 7.97 – 7.89 (m, 2H), 7.33 (d, *J* = 2.5 Hz, 1H), 7.28 (s, 1H), 7.25 (d, *J* = 2.1 Hz, 1H), 7.05 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.62 (dd, *J* = 5.3, 2.8 Hz, 1H), 4.53 (t, *J* = 5.1 Hz, 2H), 4.49 – 4.41 (m, 2H), 3.98 (d, *J* = 4.2 Hz, 3H), 3.92 (d, *J* = 1.5 Hz, 3H). MS (ESI): 395.2 $[M+H]^+$. Purity: >95%.

4.6.6. 6-methoxy-3-(2-((7-methoxyquinolin-4-yl)oxy)ethyl)benzo[d]oxazol-2(3H)-one (**11f**).
White solid (37%, 4 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, *J* = 5.4 Hz, 1H), 7.89 (d, *J* = 9.1 Hz, 1H), 7.34 (s, 1H), 7.08 (t, *J* = 9.1 Hz, 2H), 6.85 (s, 1H), 6.79 (d, *J* = 8.9 Hz, 1H), 6.61 (d, *J* = 5.2 Hz, 1H), 4.50 (t, *J* = 5.1 Hz, 2H), 4.35 (t, *J* = 5.1 Hz, 2H), 3.92 (s, 4H), 3.81 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.06 (s), 160.81 (s), 156.33 (s), 154.78 (s), 151.57 (s), 151.17 (s), 143.36 (s), 124.78 (s), 122.93 (s), 118.61 (s), 115.54 (s), 109.38 (s), 108.52 (s), 107.16 (s), 99.23 (s), 97.75 (s), 65.45 (s), 56.06 (s), 55.46 (s), 41.55 (s). MS (ESI): 367.1 $[M+H]^+$. Purity: >95%.

4.6.7. 6-amino-3-(2-((7-methoxyquinolin-4-yl)oxy)ethyl)benzo[d]oxazol-2(3H)-one (**11g**).
White solid (40%, 4 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.93 (d, *J* = 9.0 Hz, 1H), 7.36 (s, 1H), 7.13 (s, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.63 (s, 2H), 6.56 (s, 1H), 4.49 (d, *J* = 5.3 Hz, 2H), 4.32 (d, *J* = 5.3 Hz, 2H), 3.93 (s, 3H). MS (ESI): 352.1 $[M+H]^+$. Purity: >95%.

4.6.8. 3-(2-((7-bromoquinolin-4-yl)oxy)ethyl)-6-methylbenzo[d]oxazol-2(3H)-one (**11h**).
White solid (21%, 4 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, *J* = 5.1 Hz, 1H), 8.18 (s, 1H), 7.87 (d, *J* = 9.0 Hz, 1H), 7.53 (d, *J* = 9.5 Hz, 1H), 7.04 (s, 3H), 6.72 (d, *J* = 5.3 Hz, 1H), 4.52 (t, *J* = 5.0 Hz, 2H), 4.37 (t, *J* = 5.1 Hz, 2H), 2.39 (d, *J* = 6.6 Hz, 3H). MS (ESI): 399.1, 401.0 $[M+H]^+$. Purity: >95%.

4.6.9. 6-bromo-3-(2-((7-methoxyquinolin-4-yl)oxy)ethyl)benzo[d]oxazol-2(3H)-one (**11i**).
White solid (35%, 4 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, *J* = 5.3 Hz, 1H), 7.82 (d, *J* = 9.2 Hz, 1H), 7.37 (ddd, *J* = 9.3, 5.7, 2.3 Hz, 3H), 7.13 – 7.02 (m, 2H), 6.60 (t, *J* = 5.7 Hz, 1H), 4.49 (dd, *J* = 9.0, 3.9 Hz, 2H), 4.35 (t, *J* = 5.0 Hz, 2H), 3.92 (s, 3H). MS (ESI): 415.0, 417.1 $[M+H]^+$. Purity: >95%.

4.6.10. 5-bromo-3-(2-((7-methoxyquinolin-4-yl)oxy)ethyl)benzo[d]oxazol-2(3H)-one (**11j**).
White solid (31%, 4 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, *J* = 5.3 Hz, 1H), 7.62 (d, *J* = 9.2 Hz, 1H), 7.43 (ddd, *J* = 9.3, 5.7, 2.3 Hz, 3H), 7.11 – 7.02 (m, 2H), 6.54 (t, *J* = 5.7 Hz, 1H), 4.47 (dd, *J* = 9.0, 3.9 Hz, 2H), 4.33 (t, *J* = 5.0 Hz, 2H), 3.97 (s, 3H). MS (ESI): 415.0, 417.0 $[M+H]^+$. Purity: >95%.

4.6.11. 6-bromo-3-(2-((7-bromoquinolin-4-yl)oxy)ethyl)benzo[d]oxazol-2(3H)-one (**11k**).
White solid (27%, 4 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, *J* = 5.1 Hz, 1H), 8.20 (s, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.41 (s, 1H), 7.39 (s, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.72 (d, *J* = 5.3 Hz, 1H), 4.52 (t, *J* = 4.9 Hz, 2H), 4.39 (d, *J* = 5.2 Hz, 2H). MS (ESI): 463.1 $[M+H]^+$. Purity: >95%.

4.7 The General Procedure for Preparation of 6-methyl-3-(2-((7-((3-morpholinopropyl)amino)quinolin-4-yl)oxy)ethyl)benzo[d]oxazol-2(3H)-one (**7h**).

A solution of **11h** (400 mg, 1.0 mmol) in toluene (20 mL) was added with 3-morpholinopropan-1-amine (288 mg, 2.0 mmol) , $Pd(OAc)_2$ (22 mg, 10 mol%), SPhos (82 mg, 20 mol%) and Cs_2CO_3 (651mg, 2.0mmol). The reaction was stirred for 12 h at 110 °C under argon atmosphere and then cooled to room temperature. The mixture was concentrated in vacuo and the residue was extracted with ethyl acetate (20 mL×3). The combined organic layer was washed by saturated sodium chloride solution for three times, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **7h** as a gray solid. Yield 25% (115 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, *J* = 5.4 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.03 (d, *J* = 3.0 Hz, 3H), 6.94 (d, *J* = 2.1 Hz, 1H), 6.78 (dd, *J* = 9.0, 2.3 Hz, 1H), 6.45 (d, *J* = 5.4 Hz, 1H), 4.46 (t, *J* = 5.1 Hz, 2H), 4.33 (t, *J* = 5.0 Hz, 2H), 3.79 – 3.71 (m, 4H), 3.31 (t, *J* = 6.3 Hz, 2H), 2.53 (d, *J* = 6.5 Hz, 2H), 2.49 (d, *J* = 4.1 Hz, 4H), 2.39 (s, 3H), 1.86 (s, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 162.38 (s), 156.18 (s), 152.74 (s), 152.45 (s), 151.41 (s), 144.21 (s), 134.37 (s), 130.24 (s), 125.64 (s), 123.98 (s), 118.93 (s), 114.53 (s), 112.37 (s), 109.48 (s), 105.55 (s), 99.13 (s), 68.53 (s), 66.68 (s), 59.14 (s), 55.19 (s), 44.56 (s), 43.00 (s), 31.13 (s), 26.25 (s), 22.87 (s). MS (ESI): 463.2 $[M+H]^+$. Purity: >95%.

4.8 The General Procedure for Preparation of 6-methyl-3-(2-((7-(1-methyl-1H-pyrazol-4-yl)quinolin-4-yl)oxy)ethyl)benzo[d]oxazol-2(3H)-one (**7i**).

A solution of **11h** (400 mg, 1.0 mmol) was dissolved in tulene (20mL) in a 50ml over-dried flask and was added with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (270mg, 1.3mmol), $Pd(dppf)_2Cl_2$ (81.6mg, 10mol%) and Cs_2CO_3 (651mg, 2.0mmol). The mixture was stirred for 12 h at 100 °C under argon atmosphere. Then the reaction mixture was cooled to room temperature and was concentrated in vacuo. The residue was extracted with ethyl acetate (10 mL×3). The combined organic layer was washed by saturated sodium chloride solution for three times, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **7i** as a pale yellow solid. Yield 55% (220 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 5.4 Hz, 1H), 8.13 (s, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.90 (s, 1H), 7.79 (s, 1H), 7.61 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.06 (t, *J* = 4.6 Hz, 3H), 6.69 (d, *J* = 5.4 Hz, 1H), 4.54 (t, *J* = 5.1 Hz, 2H), 4.39 (t, *J* = 5.1 Hz, 2H), 3.98 (s, 3H), 2.40 (s, 3H).^{13}C NMR (126 MHz, DMSO) δ 161.04 (s), 154.57 (s), 151.85 (s), 149.25 (s), 142.54 (s), 136.83 (s), 134.69 (s), 132.54 (s), 128.97 (d, *J* = 12.5 Hz), 124.42 (s), 124.24 (s), 122.76 (s), 122.63 (d, *J* = 29.8 Hz), 121.66 (s), 119.09 (s), 110.44 (s), 109.26 (s), 101.18 (s), 66.04 (s), 48.82 (s), 41.49 (s), 21.06 (s). MS (ESI): 401.2 $[M+H]^+$. Purity: >95%.

4.9 General Procedure for Preparation of 3-(2-((7-methoxyquinolin-4-yl)oxy)ethyl)-6-morpholinobenzo[d]oxazol-2(3H)-one (**12a**).

11i (415mg, 1.0mmol) was dissolved in toluene (20mL) in a 50ml over-dried flask and was added with morpholine (174mg, 2.0mmol) , $Pd(OAc)_2$ (22mg, 10mol%), SPhos (84mg, 20mol%) and Cs_2CO_3 (651mg, 2.0mmol). The mixture was stirred for 12 h at 110 °C under argon atmosphere. Then the reaction mixture was cooled to room temperature and was concentrated in vacuo. The residue was extracted with ethyl acetate (20 mL×3). The combined organic layer was washed by saturated sodium chloride solution for three times, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **12a** as a brown solid. Yield 53% (223mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, *J* = 5.3 Hz, 1H), 7.90 (d, *J* = 9.1 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.12 – 7.03 (m, 2H), 6.85 (d, *J* = 2.1 Hz, 1H), 6.78 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.60 (d, *J* = 5.3 Hz, 1H), 4.50 (t, *J* = 5.1 Hz, 2H), 4.34 (t, *J* = 5.1 Hz, 2H), 3.92 (s, 3H), 3.89 – 3.84 (m, 4H), 3.14 – 3.06 (m, 4H). MS (ESI): 422 $[M+H]^+$. Purity: >95%.

4.10 General Procedure for Preparation of **12b-12c**.

11i or **11j** (1.0mmol) was dissolved in 1,4-dioxane (20mL) in a 50ml over-dried flask and was added with the corresponding boric acid (1.3mmol) , $Pd(dppf)_2Cl_2$ (82mg, 10mol%) and Cs_2CO_3 (651mg, 2.0mmol). The mixture was stirred for 12 h at 100 °C under argon atmosphere. Then the reaction mixture was cooled to room temperature and was concentrated. The residue was extracted with ethyl acetate (10 mL×3). The combined organic layer was washed by saturated sodium chloride solution for three times, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **12b-12c.**

4.10.1.
3-(2-((7-methoxyquinolin-4-yl)oxy)ethyl)-6-(1-methyl-1H-pyrazol-4-yl)benzo[d]oxazol-2(3H)-on e (**12b**).

White solid (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, *J* = 10.8, 5.3 Hz, 1H), 7.88 (d, *J* = 9.2 Hz, 1H), 7.71 (s, 1H), 7.58 (s, 1H), 7.33 – 7.27 (m, 3H), 7.15 (d, *J* = 8.1 Hz, 1H), 7.07 (dd, *J* = 9.1,

2.5 Hz, 1H), 6.60 (d, *J* = 5.2 Hz, 1H), 4.51 (t, *J* = 5.0 Hz, 2H), 4.37 (t, *J* = 5.0 Hz, 2H), 3.94 (s, 3H), 3.91 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 161.13 (s), 160.88 (s), 154.56 (s), 151.48 (s), 151.07 (s), 145.57 (s), 143.29 (s), 136.58 (s), 129.60 (s), 128.29 (s), 126.87 (s), 122.91 (s), 122.52 (s), 121.12 (s), 118.72 (s), 108.67 (s), 107.65 (s), 107.06 (s), 99.25 (s), 65.45 (s), 55.48 (s), 41.65 (s), 39.16 (s). MS (ESI): 417.2 $[M+H]^+$. Purity: >95%.

4.10.2.
3-(2-((7-methoxyquinolin-4-yl)oxy)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)benzo[d]oxazol-2(3H)-one (**12c**).
White solid (65%). ^{1}H NMR (300 MHz, DMSO) δ 8.60 (d, *J* = 5.2 Hz, 1H), 8.09 (s, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.72 (s, 1H), 7.29 (d, *J* = 1.8 Hz, 2H), 7.25 (d, *J* = 2.4 Hz, 1H), 6.90 – 6.85 (m, 2H), 4.53 (d, *J* = 4.3 Hz, 2H), 4.41 (d, *J* = 4.7 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 161.02 (s), 160.67 (s), 154.63 (s), 151.62 (s), 151.18 (s), 141.22 (s), 136.55 (s), 131.90 (s), 129.22 (s), 126.88 (s), 122.85 (s), 122.50 (s), 120.03 (s), 118.64 (s), 115.44 (s), 110.56 (s), 107.16 (s), 105.90 (s), 99.23 (s), 65.87 (s), 55.44 (s), 41.50 (s), 39.17 (s). MS (ESI): 417.1 $[M+H]^+$. Purity: >95%.

4.11 General Procedure for Preparation of 6-(1-methyl-1H-pyrazol-4-yl)-3-(2-((7-(1-methyl-1H-pyrazol-4-yl)quinolin-4-yl)oxy)ethyl)benzo[d]oxazol-2(3H)-one (**13**).

11k (464mg, 1.0mmol) was dissolved in 1,4-dioxane (20mL) in a 50ml over-dried flask and was added with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (540mg, 2.6mmol) , $Pd(dppf)_2Cl_2$ (164mg, 20mol%) and Cs_2CO_3 (1.3g, 4.0mmol). The mixture was stirred for 12 h at 100 °C under argon atmosphere. Then the reaction mixture was cooled to room temperature and was concentrated. The residue was extracted with ethyl acetate (10 mL×3). The combined organic layer was washed by saturated sodium chloride solution for three times, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **13** as a pale yellow solid. Yield 42% (196mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, *J* = 5.1 Hz, 1H), 8.08 (s, 1H), 7.99 (d, *J* = 8.7 Hz, 1H), 7.89 (s, 1H), 7.74 (d, *J* = 4.4 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.39 – 7.30 (m, 2H), 7.17 (d, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 5.2 Hz, 1H), 4.54 (t, *J* = 4.9 Hz, 2H), 4.40 (t, *J* = 5.0 Hz, 2H), 3.97 (s, 3H), 3.95 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 162.55 (s), 156.22 (s), 152.63 (s), 150.39 (s), 144.58 (s), 138.32 (s), 137.77 (s), 135.89 (s), 130.88 (s), 129.53 (d, *J* = 11.2 Hz), 128.65 (s), 125.74 (s), 124.20 (s), 123.69 (d, *J* = 24.2 Hz), 123.53 – 122.72 (m), 122.59 (s), 120.73 (s), 110.18 (s), 108.95 (s), 101.70 (s), 66.94 (s), 42.93 (s), 40.21 (s), 30.99 (s). MS (ESI): 467.1 $[M+H]^+$. Purity: >95%.

4.12 ELISA Kinase Assay

The effects of indicated compound on the activities of c-Met kinases were determined using enzyme-linked immunosorbent assays (ELISAs) with purified recombinant proteins. Briefly, 20 μg/mL poly $(Glu,Tyr)_{4:1}$ (Sigma, St. Louis, MO, USA) was pre-coated in 96-well plates as a substrate. A 50-μL aliquot of 10 μmol/L ATP solution diluted in kinase reaction buffer (50 mmol/L HEPES [pH 7.4], 50 mmol/L $MgCl_2$, 0.5 mmol/L $MnCl_2$, 0.2 mmol/L Na_3VO_4, and 1 mmol/L DTT) was added to each well; 1 μL of various concentrations of indicated compound diluted in 1% DMSO (v/v) (Sigma) were then added to each reaction well. DMSO (1%, v/v) was used as the negative control. The kinase reaction was initiated by the addition of purified c-Met

tyrosine kinase proteins diluted in 49 μL of kinase reaction buffer. After incubation for 60 min at 37 °C, the plate was washed three times with phosphate-buffered saline (PBS) containing 0.1% Tween 20 (T-PBS). Anti-phosphotyrosine (PY99) antibody (100 μL; 1:500, diluted in 5 mg/mL BSA T-PBS) was then added. After a 30-min incubation at 37 °C, the plate was washed three times, and 100 μL horseradish peroxidase-conjugated goat anti-mouse IgG (1:2000, diluted in 5 mg/mL BSA T-PBS) was added. The plate was then incubated at 37 °C for 30 min and washed 3 times. A 100-μL aliquot of a solution containing 0.03% H_2O_2 and 2 mg/ml o-phenylenediamine in 0.1 mol/L citrate buffer (pH 5.5) was added. The reaction was terminated by the addition of 50 μL of 2 mol/L H_2SO_4 as the color changed, and the plate was analyzed using a multi-well spectrophotometer (SpectraMAX 190, Molecular Devices, Sunnyvale, CA, USA) at 490 nm. The inhibition rate (%) was calculated using the following equation: [1 − (A490/A490 control)] × 100%. The IC_{50} values were calculated from the inhibition curves in two separate experiments.4.6 Western Blot Analysis

4.13 Cell Proliferation Assay

Cells were seeded in 96-well tissue culture plates. On the next day, cells were exposed to various concentrations of compounds and further cultured for 72h. Finally, cell proliferation was determined using sulforhodamine B (SRB; Sigma, St. Louis, MO, USA) assay.IC_{50} values were calculated by concentration‐response curve fitting using a SoftMax pro-based four-parameter method.

4.14 Docking Studies

The crystal structure of the PF- 04217903 with c-Met complex (code ID: 3ZXZ) was downloaded from the Protein Data Bank. Subsequently, the waters were deleted, hydrogen atoms were added to the protein .The 3D Structures of the compound 2 and 7a were built and minimized by molecular mechanics.

The conformation analysis was conducted using AutoDock4.2. 100 conformations for each provided by the Lamarckian Genetic Algorithm and analyzed of the predicted energy. The image files were generated using pymol system.

Acknowledgments

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Table, Figure and Scheme Captions

Table 1. SAR study probing effects of C7 substituents on quinolone moiety.

Table 2. SAR study of the effects of C5 and C6 substituents on benzo[d]oxazol-2(3H)-one scaffold.

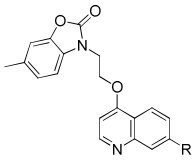
Figure 1. Representative small-molecule c-Met inhibitors with quinoline pharmacophores.

Figure 2. A. Strategy used to design benzo[d]oxazol-2(3H)-one-quinolone derivatives as c-Met kinase inhibitors. B. Predicted interactions of **1** (green) and **7a** (yellow) with the residues in the ATP binding pocket of c-Met protein. (The docking study was performed using AutoDock Tools-1.5 and a triazolopyridazines-Met crystal complex (PDB code: 3ZC5) was used.)

Figure 3. Predicted binding modes of **12b** (green) and **12c** (yellow) with the c-Met protein. Introduction of C5 substitution leads to a shift in the benzo[d]oxazol-2(3H)-one molecule, weakening π-π stacking interactions with Tyr1230 (shown in line).

Figure 4. The design of lead compound **13**.

Scheme 1. Synthesis of **7a-7g**.[α]
Scheme 2. Synthesis of **7h-7i, 11, 12 and 13**.[α]



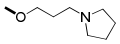
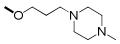
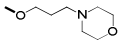
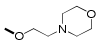
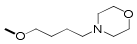
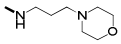
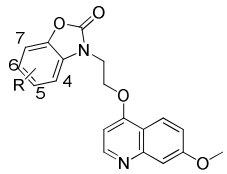
Compound	R	c-Met IC_{50}(nM)	EBC-1[a] IC_{50}(μM)
7a		7.6	>0.50
7b		3.5	>0.50
7c		5.9	>0.50
7d		5.1	0.17
7e		3.8	0.17
7f		3.8	0.12
7g		11.0	0.33
7h		6.0	0.058
7i		3.4	0.035
Crizotinib		1.0	0.053

Table 1. SAR study probing effects of C7 substituents on quinolone moiety.



Compound	R	c-Met IC_{50} (nM)	EBC-1[a] IC_{50} (μM)
7a	6-Me	7.6	>0.5
11a	5-Me	19.5	>0.5
11b	6-F	42.3	>0.5
11c	5-F	105.1	>0.5
11d	6-COOMe	33.5	>0.5
11e	5-COOMe	93.6	>0.5
11f	6-OMe	15.7	>0.5
11g	6-NH_2	9.8	0.16
12a	6- 	47.8	>0.5
12b	6- 	5.6	0.1
12c	5- 	18.9	>0.5
Crizotinib		0.9	0.044

Table 2. SAR study of the effects of C5 and C6 substituents on benzo[d]oxazol-2(3H)-one scaffold.

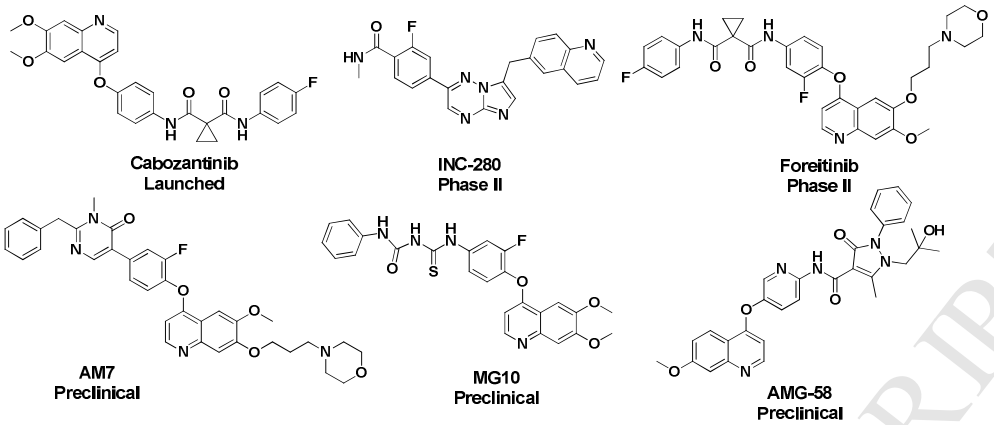
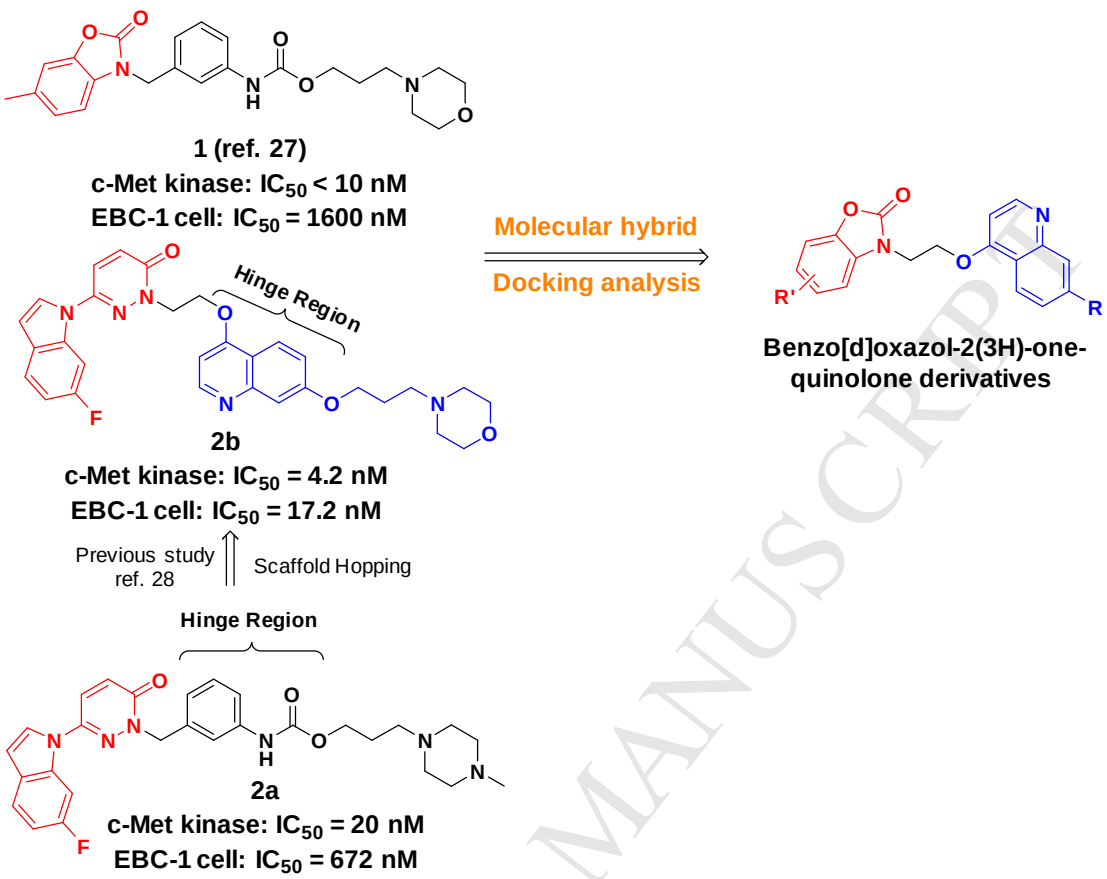


Figure 1.Representative small-molecule c-Met inhibitors with quinoline pharmacophores.

A:



B:

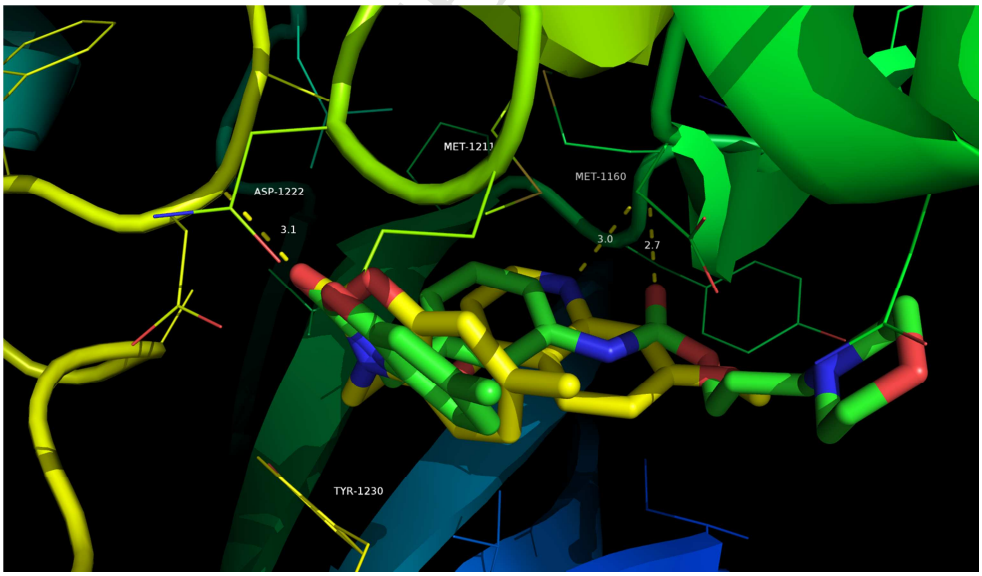


Figure 2. A. Strategy used to design benzo[d]oxazol-2(3H)-one-quinolone derivatives as c-Met kinase inhibitors. B. Predicted interactions of **1** (green) and **7a** (yellow) with the residues in the ATP binding pocket of c-Met protein. (The docking study was performed using AutoDock Tools-1.5 and a triazolopyridazines-Met crystal complex (PDB code: 3ZC5) was used.)

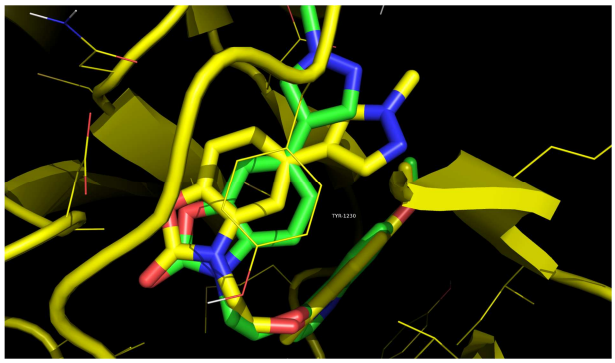


Figure 3. Predicted binding modes of **12b** (green) and **12c** (yellow) with the c-Met protein. Introduction of C5 substitution leads to a shift in the benzo[d]oxazol-2(3H)-one molecule, weakening π-π stacking interactions with Tyr1230 (shown in line).

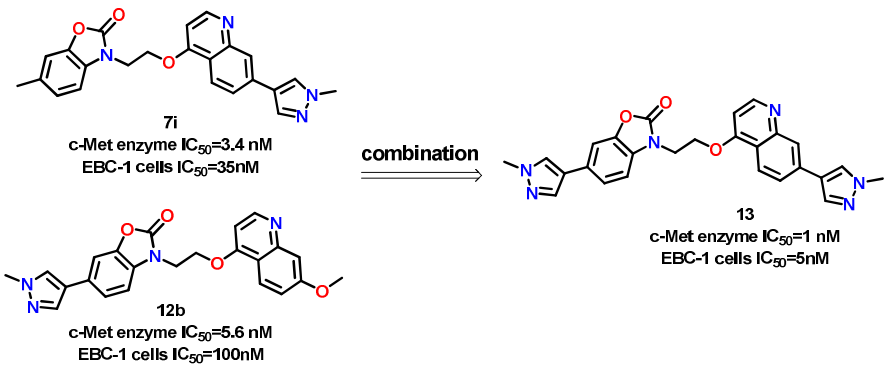
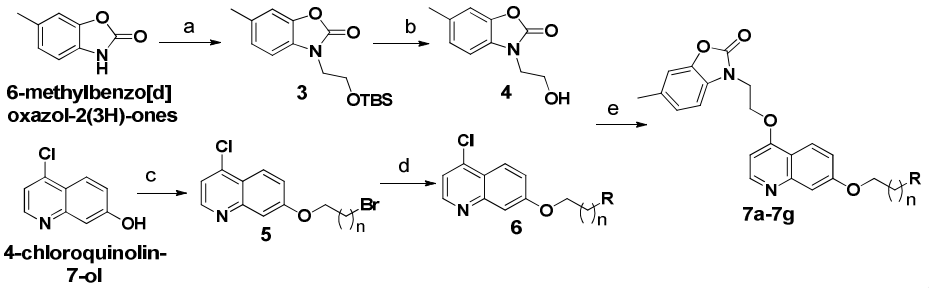


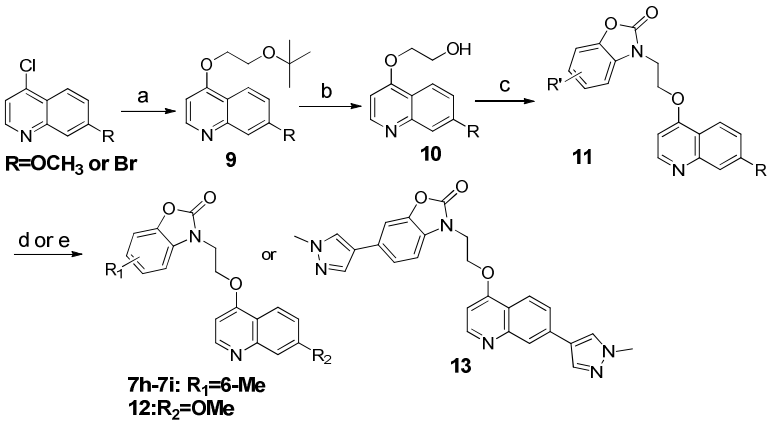
Figure 4. The design of lead compound **13**.

Scheme 1. Synthesis of **7a-7g**.[α]



[α] Reagents and conditions: (a) (2-bromoethoxy) (tert-butyl) dimethylsilane, Cs_2CO_3, DMF, 50 ^{0}C; (b) 3N HCl, THF:H_2O = 3:1, rt, overnight; (c) $Br(CH_2)nBr$, Cs_2CO_3, DMF, 50 ^{o}C; (d) secondary amines, K_2CO_3, DMF, 50 ^{o}C; (e) $Pd(OAc)_2$, SPhos, Cs_2CO_3, Toluene, 110 ^{o}C, 5h.

Scheme 2. Synthesis of **7h-7i, 11, 12 and 13**. [α]



[α]Reagents and conditions: (a) 2-(tert-butoxy)ethanol, NaH, DMF, 40 ^{o}C, overnight; (b) TFA, rt , 30-60 min; (c) (i) MsCl, Et_3N, THF, 0 ^{o}C, 30 min; (ii) **8**, Cs_2CO_3, DMF, 50 ^{o}C, 5h; (d) Boric acid ester, $Pd(dppf)_2Cl_2$, Cs_2CO_3, 1,4-dioxane, 100 ^{o}C, overninght; (e) amines, $Pd(OAc)_2$, SPhos, Cs_2CO_3, toluene, 110 ^{o}C, 5h.