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Design, synthesis and biological evaluation of 5-amino-4-(1H-benzoimidazol-2-yl)-phenyl-1,2-dihydro-pyrrol-3-ones as inhibitors of protein kinase FGFR1

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Abstract. Fibroblast growth factor receptor 1 (FGFR1) plays an important role in tumorigenesis and is therefore an attractive target for anticancer therapy. Using molecular docking approach we have identified inhibitor of FGFR1 belonging to 5-amino-4-(1H-benzoimidazol-2-yl)-phenyl-1,2-dihydro-pyrrol-3-ones with IC_{50} value of 3.5 μM. A series of derivatives of this chemical scaffold has been synthesized and evaluated for inhibition of FGFR1 kinase activity. It was revealed that the most promising compounds 5-amino-1-(3-hydroxy-phenyl)-4-(6-methyl-1H-benzoimidazol-2-yl)-1,2-dihydro-pyrrol-3-one and 5-amino-4-(1H-benzoimidazol-2-yl)-1-(3-hydroxy-phenyl)-1,2-dihydro-pyrrol-3-one inhibit FGFR1 with IC_{50} values of 0.63 and 0.32 μM, respectively, and posses antiproliferative activity against KG1 myeloma cell line with IC_{50} values of 5.6 and 9.3 μM. Structure-activity relationships have been studied and binding mode of this chemical class has been proposed.

Keywords: protein kinase FGFR1; inhibitor; 5-amino-4-(1H-benzoimidazol-2-yl)-phenyl-1,2-dihydro-pyrrol-3-ones; virtual screening; kinase assay.

1. Introduction.

Fibroblast growth factor receptor 1 (FGFR1) is a receptor tyrosine kinase which is involved in the regulation of cell growth, cell proliferation, cell differentiation, embryonic development, angiogenesis and other important physiological functions. FGFR1 has been suggested to be important therapeutic target. For example, FGFR1 is correlated closely with the occurrence and development of lung cancer.[1-10] It was demonstrated that inhibition of FGFR1 by a specific kinase inhibitor or a dominant-negative FGFR1 construct led to significantly decreased proliferation, clonogenicity, migration, spheroid formation, and G1 cell cycle arrest in several mesothelioma cell lines.[11] FGFR1 has been shown to be involved in the pathogenesis of oral tongue squamous cell carcinomas,[12] sinonasal cancer,[13] gastric cancer,[14] pancreatic cancer,[15, 16] colorectal cancer,[17, 18] renal cell carcinoma,[19, 20] prostate cancer,[21, 22] bladder cancer[23] and acute myeloid leukemia.[24] Recently, it was reported, that oncogenic mutations of FGFR1 occurred in a subset of patients with pilocytic astrocytoma with worse outcome.[25] Experimental evidences suggest that upregulated FGFR1 expression appears to be associated with parathyroid carcinoma in hyperparathyroidism-jaw tumor (HPT-JT) syndrome.[26] High FGFR1 amplification is a frequent oncogenic alteration and an independent poor prognostic factor in resected esophageal squamous cell carcinoma.[27] The integrative genomic and transcriptomic approach indicated that FGFR1 amplification, as well as the consequent up-regulation of the protein products, plays an important role in the aetiology of uterine leiomyomas.[28] FGFR1 might be involved in endometriosis development, which could possibly serve as a novel therapeutic target and prognostic marker for this disease.[29] The activity of FGFR1, and thereby progression of the tumor growth can be reduced by administration of inhibitors. Therefore, the development of small molecule FGFR1 modulators is a significant area of medicinal chemistry research.

2. Results and Discussion.

Using high-throughput screening of in-house drug-like compound library targeting ATP-binding site of FGFR1 kinase, we have identified hit compound belonging to 5-amino-4-(1H-benzoimidazol-2-yl)-phenyl-1,2-dihydro-pyrrol-3-ones (compound **1**) with IC_{50} value of 3.5 μM (Figure 1). This compound has some chemical similarity (Tanimoto coefficient = 0.4 accordingly to FCFP4 fingerprints) with multitargeted RTK inhibitor TKI258 (dovitinib) (Figure 1).[30] TKI258 is potent ATP-competitive inhibitor of VEGFR2, FGFR1, PDGFR and is currently undergoing Phase III clinical trial in patients with renal cell carcinoma, and is undergoing Phase II clinical trial in patients with advanced breast cancer.[31]

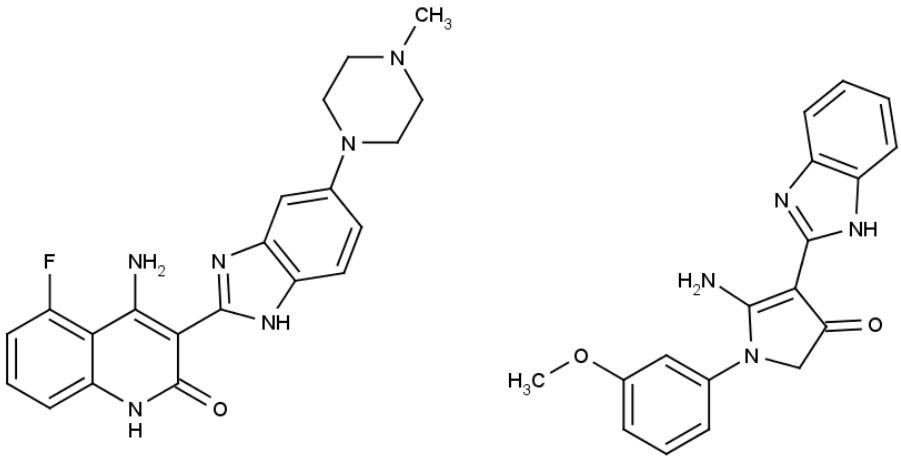
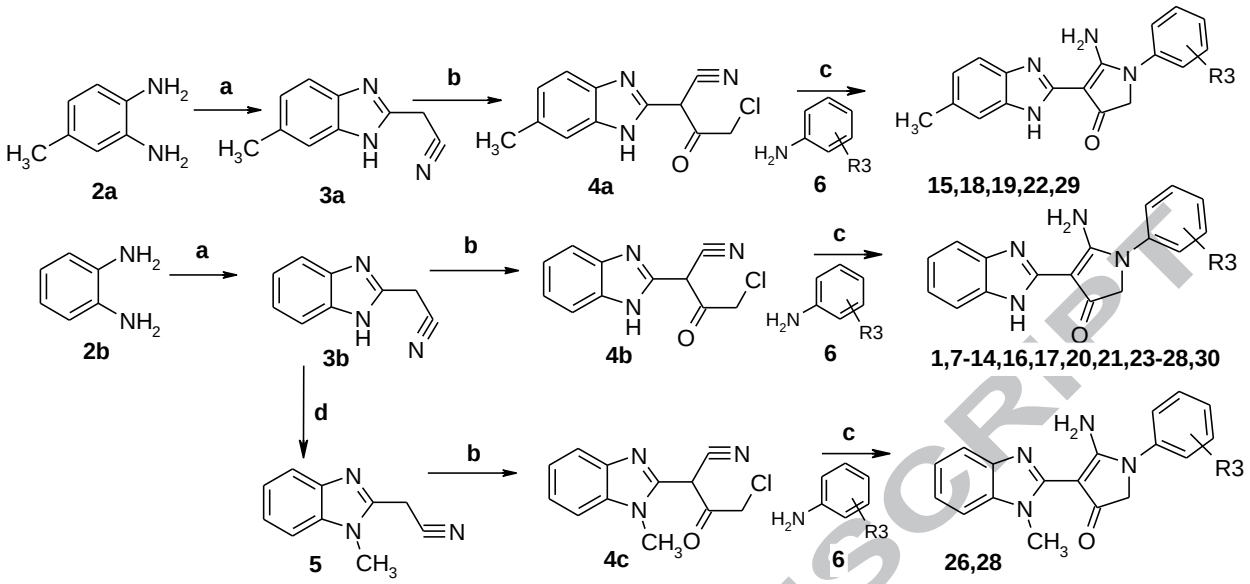


Figure 1. Chemical structures of multikinase inhibitor TKI258 and compound **1**.

In order to find more effective inhibitors of FGFR1 a series of 5-amino-4-(1H-benzoimidazol-2-yl)-phenyl-1,2-dihydro-pyrrol-3-one derivatives has been synthesized and tested (Table 1). The compounds were synthesized accordingly to Scheme 1.

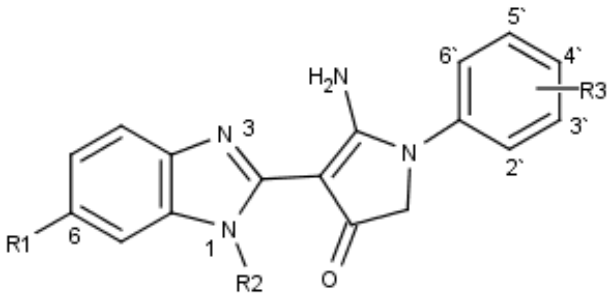


Scheme 1. The synthesis pathway for compounds **1**, **7-30**. Reagents and conditions: (a) Ethyl cyanoacetate, 175°C, 2h; (b) chloroacetyl chloride, TEA, dioxane, 5°C, then reflux 1h; (c) appropriate aniline, DMF, 130°C, 7-9h; (d) dimethylsulfate, NaOH, water.

At the first stage, o-phenyldiamines (**2a**, **b**) were converted to the benzimidazole acetonitrile intermediates (**3a**, **b**) after cyclocondensation reaction with cyanoacetic acid ethyl ester. Then, active methylene group in benzimidazole acetonitrile was acylated with chloroacetyl chloride. The intermediate benzodiazole-4-chloro-3-oxobutanenitriles (**4a, b, c**) were used for synthesis of 5-amino-4-(1H-benzoimidazol-2-yl)-phenyl-1,2-dihydro-pyrrol-3-ones (**1, 7-30**), cyclization was achieved by amination with appropriate anilines (**6**).[32, 33]

Inhibitory activity of the synthesized compounds toward FGFR1 was determined by measuring the levels of phosphorylation of the synthetic peptide kinase substrate by radiolabeled P^{32} –γ-ATP. IC_{50} values are presented in Table 1.

Table 1. Chemical structure and *in vitro* FGFR1 inhibition activity of the 5-amino-4-(1H-benzoimidazol-2-yl)-phenyl-1,2-dihydro-pyrrol-3-ones



Compound	R1	R2	R3	IC_{50}, μM[a]
1	H	H	3`-OCH_3	3.5
7	H	H	H	>30
8	H	H	3`-CH_3	>30
9	H	H	4`-CH_3	>30
10	H	H	2`-OCH_3	9.9
11	H	H	4`-OCH_3	7
12	H	H	2`-OCH_2CH_3	>30
13	H	H	2`,5`-diOCH_3	3.28
14	H	H	2`,4`-diOCH_3	>30
15	CH_3	H	2`-$OCH_3$, 5`-CH_3	11
16	H	H	2`-$OCH_3$, 5`-Cl	0.6
17	H	H	3`-Cl	1.12
18	CH_3	H	3`-Cl	1.85
19	CH_3	H	3`-F	7.3
20	H	H	2`-Cl	>30
21	H	H	2`-F	>30
22	CH_3	H	4`-Cl	28.2
23	H	H	4`-F	27
24	H	H	3`-CF_3	10
25	H	H	4`-OH	2.12
26	H	CH_3	4`-OH	27
27	H	H	3`-OH, 4`-CH_3	2.28
28	H	CH_3	3`-OH	3.8
29	CH_3	H	3`-OH	0.63
30	H	H	3`-OH	0.32

[a] – Values are the mean of at least two independent experiments

The SAR associated with different substituents on the phenyl ring (R3) of 5-amino-4-(1H-benzoimidazol-2-yl)-phenyl-1,2-dihydro-pyrrol-3-one derivatives was investigated. Compound **7** with unsubstituted phenyl group and compounds **8** and **9** with methyl group in *meta* and *para* positions were inactive toward FGFR1. At the same time, compound **1** with methoxy group in *meta* position inhibits FGFR1 with IC_{50} value of 3.5 μM. Compounds **10** and **11** with methoxy group in *ortho* and *para* position, respectively, were less active than compound **1**. Replacing methoxy group with ethoxy in *ortho* position (**12**) resulted in a complete loss of inhibitory activity (IC_{50} >30 μM) which indicates a low tolerance to substituent size. Comparing with *meta* methoxy derivative **1**, compound **17** with meta chlorine substituent in phenyl ring was 3-fold more active FGFR1 inhibitor. On the other hand, compounds with *para* and *ortho* chlorine (**22, 20**) and *para, meta* and *ortho* fluorine (**23, 19, 21**) in phenyl ring have significantly lower activity than respective methoxy derivatives. Introduction of bulkier trifluoromethyl group in *meta* position of phenyl (**24**) led to reduction in potency comparing with *meta* halogenated phenyl derivatives (**17**, **19**), that can be explained by unfavorable steric interaction, as it has been shown for *ortho* position (**12** vs. **10**). Thus, it can be concluded that inhibitory activity of 5-amino-4-(1H-benzoimidazol-2-yl)-phenyl-1,2-dihydro-pyrrol-3-one derivatives toward FGFR1 increases with introduction of halogen or methoxy groups in *meta* position of phenyl ring. The same groups in *ortho* and *para* positions generally led to lower activity in comparison with corresponding *meta* derivatives.

The same SAR was observed for compounds with double substitution in phenyl ring. The replacement of methyl group in meta position (**15**) with methoxy group (**13**) leads to 3.3-fold higher activity (IC_{50} = 11 μM and 3.28 μM, respectively). The substitution of *meta* methoxy group (**13**) with chlorine (**16**) causes 5.5-fold increasing of inhibitory activity (IC_{50} = 0.6 μM).

Also, we have synthesized and tested a series of 5-amino-4-(1H-benzoimidazol-2-yl)-phenyl-1,2-dihydro-pyrrol-3-one derivatives containing hydroxyl group on the phenyl ring (**25-30**). Compound **25** with hydroxyl group at

para position of the phenyl ring was more efficient than analogs with methoxy group or halogen (**11**, **22**, **23**). An introduction of hydroxyl group at *meta* position of the phenyl ring leads to significant increasing of inhibitory activity toward FGFR1 (compound **30**, $IC_{50} = 0.32$ μM).

Finally, we have investigated effect of substitution of hydrogen atoms at N1 (R2) and C6 (R1) on benzimidazole heterocycle by methyl group. The presence of methyl group at the N1 position reduces inhibitory activity in 5-10 fold (**26** vs **25** and **28** vs **30**). A possible reason for this effect is the blocking of hydrogen bond donor group involved in interaction with FGFR1 ATP-binding site. Methyl group at C6 atom only slightly decreases inhibitory activity (**17** vs **18** and **29** vs **30**).

In order to clarify the relationship between chemical structure of 5-amino-4-(1H-benzoimidazol-2-yl)-phenyl-1,2-dihydro-pyrrol-3-one derivatives and inhibitory activity toward FGFR1 we have studied complexes of described compounds with ATP-binding site of FGFR1, obtained by molecular docking. The binding mode of compound **30** with FGFR1 is presented in Figure 2. Accordingly to the results of molecular modeling, dihydro-1H-pyrrol-3-one is involved in the hydrophobic interactions with amino acid residues Leu630, Val561, Ala512 in the adenine-binding region. Also, it was revealed that the carbonyl group of this heterocycle forms hydrogen bond with amino group of Ala564 which located in the hinge region.

The benzimidazole core is implicated in van der Waals contacts with Tyr563, Leu484 and Gly567 residues in hydrophobic region II and builds hydrogen bond with the carbonyl group of Ala564.

The R3 substituted phenyl ring in compound **30** is extended to a back pocket (hydrophobic region I), which is comprised of the side chains of Lys514, Ile545, Val561 and Ala640. Substituents on the phenyl ring can interact with amino acid residues in the back pocket depth, and possibly have a significant impact on binding affinity in described binding mode. The *meta* hydroxyl group of compound **30** forms hydrogen bond with carboxyl group of Asp641 side chain, which could improve the binding ability of the compound **30** with FGFR1.

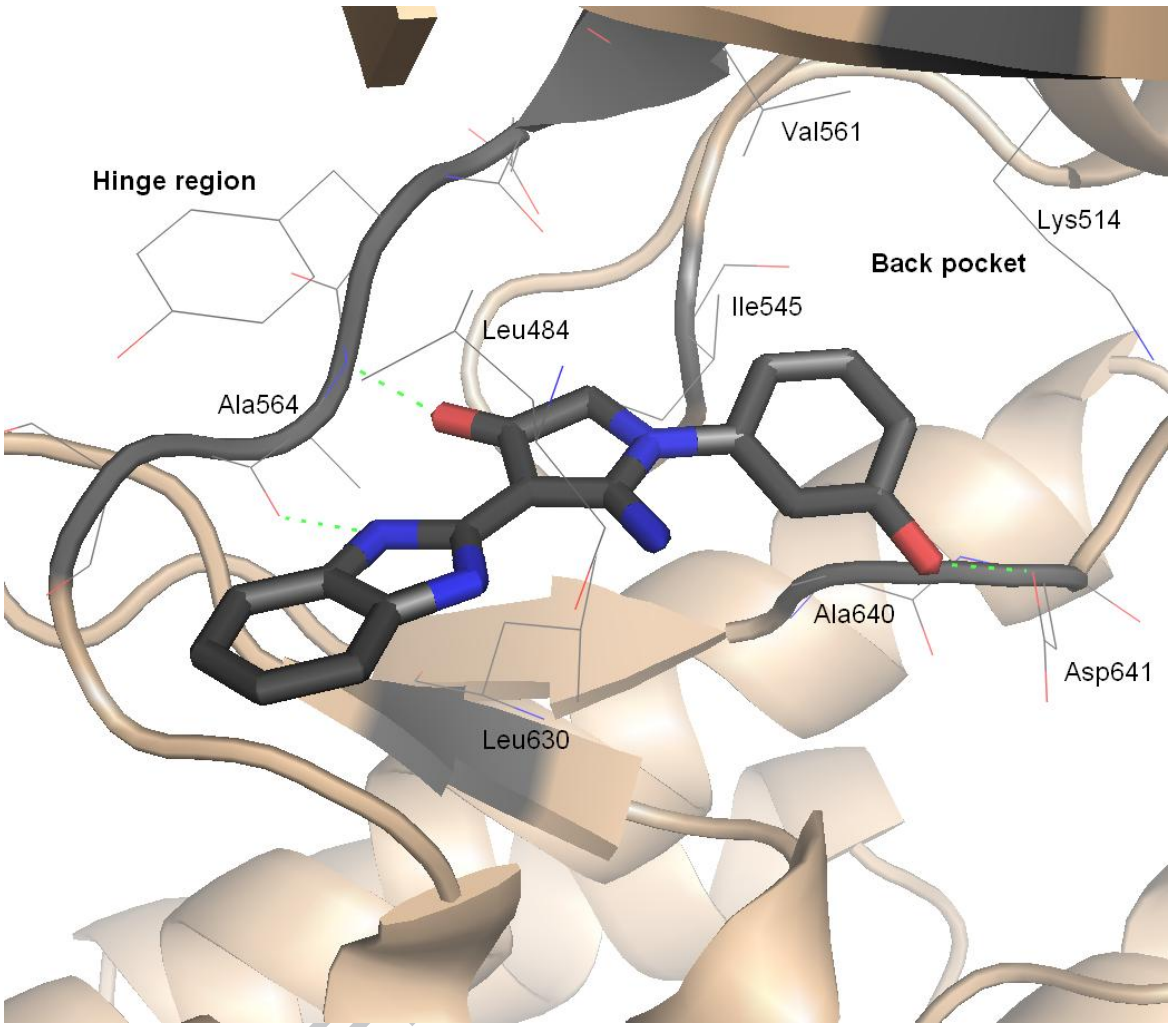


Figure 2. Binding mode of compound **30** in the active site of the CK2 catalytic subunit. Hydrogen bonds are shown by the green dotted lines.

Three compounds with submicromolar kinase inhibition activity (**16**, **29**, **30**) were tested for antiproliferative activity against KG1 myeloma cell line. This cancer cell line is characterized by constitutive activity of FGFR1[34] and is often used for investigation of FGFR1 inhibitors cytotoxicity.[35] The results of the antiproliferative activities are summarized in Table 2. Unexpectedly, compound **16** was inactive in cell line. Also, antiproliferative activity of compound **29** was higher than in **30** despite lower enzymatic potency. This fact can be explained by significant role of methyl group on the benzimidazole heterocycle for membrane permeability of investigated compounds. Also, we have tested compounds **16**, **29**, **30** for their cytotoxicity potential in "normal" non-tumorous cell line – HEK293. In this case, the compounds did not have effect on cell viability.

Table 2. Antiproliferative activities of compounds **16**, **29** and **30** against KG1 and HEK293 cell lines

Compound	KG1 cell proliferation IC_{50}, μM[a]	HEK293 cell proliferation IC_{50}, μM[a]
16	>50	>50
29	5.6	>50
30	9.3	>50

a - Values are the mean of three independent experiments, all SD within ±15 %

Two the most promising compounds (**29** and **30**) were taken for kinase selectivity analysis on the panel of 7 protein kinases (Table 3). The results of our study have shown that these compounds tend to be selective inhibitors of FGFR1.

Table 3. Residual Activity of Protein Kinases (%) in the Presence of CK2 inhibitors at 10 μM Concentration.

Compound/Kinase	FGFR1	Tie-2	c-MET	Aurora A	JNK3	CK2	ASK1
29	5	92.7	92.5	75.8	100.8	77.3	91.6
30	2.1	84.7	128.3	85.8	118	81.4	95.7

3. Conclusions

Virtual screening experiments allowed us to identify novel class of FGFR1 inhibitors, namely, 5-amino-4-(1H-benzoimidazol-2-yl)-phenyl-1,2-dihydro-pyrrol-3-ones. A series of derivatives of this chemical scaffold has been synthesized and evaluated as FGFR1 inhibitors. It was revealed that the most active compounds **29** and **30** with submicromolar IC_{50} have hydroxyl substituent in *meta* position of phenyl ring. These inhibitors posses antiproliferative activity

against KG1 myeloma cell line with IC_{50} values of 5.6 and 9.3 μM and can be promising lead compounds for further optimization as anticancer agents.

4. Experimental

4.1. Synthetic Chemistry. Starting materials and solvents were purchased from Acros Organics and were used without further purification.^{1}H NMR spectra were recorded on Varian Mercury VXR400, 400 MHz with TMS as an internal standard, DMSO-d_6 was used as solvent, chemical shifts were described as parts per million (δ) and spin multiplicities are given as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), or m (multiplet). All tested compounds displayed purity of >95 %.

General procedure of synthesis of benzoimidazol-2-yl acetonitriles (**3a**, **3b**). The mixture of appropriate o-phenylenediamine (**2a**, **2b**) with 1.5 equivalent of cyanoacetic acid ethyl ester was heated on an oil bath for 1-2 h at 175^{o}C, the evolved ethanol being allowed to escape. After the mixture has been cooled to 100^{o}C dioxane was added. Then the reaction mixture was cooled down to room temperature, precipitate was filtered, washed by ethanol, water and dried. Yield of compounds was 65-70%.

The synthesis of N1-methylbenzoimidazol-2-yl acetonitrile (**5**). The 1.2 equivalent of dimethylsulfate was added by drop wise to solution benzimidazol-2-yl acetonitrile (**3b**), 1.1 equivalent sodium hydroxide in water at 30^{o}C for 1h. Then the reaction mixture was cooled down to room temperature, precipitate was filtered, washed by water and dried. Yield of compound was 78%.

General procedure of the synthesis of 2-(1H-benzoimidazol-2-il)-4-chloro-3-oxo-butyronitriles (**4a**, **4b**, **4c**). The benzimidazol-2-yl acetonitriles (**3a**, **3b**, **5**) from previous synthesis stage were mixed with 1.1 equivalent of triethylamine in dioxane and after pre-cooling to 5^{o}C was added 1.1 equivalent of chloroacetyl chloride. The reaction mixture was reflux for 1 h. Then the reaction mixture was cooled down to room temperature, precipitate was filtered, washed with water and dried. Yield of compounds was 70-85%.

General procedure of the synthesis of 5-amino-4-(1H-benzoimidazol-2-yl)-phenyl-1,2-dihydro-pyrrol-3-one derivatives (**1, 7-30**). The 2-(1H-benzoimidazol-2-il)-4-chloro-3-oxo-butyronitrile from previous synthesis stage was solved in DMF with 1.5 equivalent of appropriate aniline and was heated at 130^{o}C for 7-9 h. Then the reaction mixture was poured in tenfold water volume excess. The precipitate was filtered and washed by isopropanol. All compounds didn't require additional purification. Yield of compounds was 50-90%.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(3-methoxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**1**). Yield 72% (yellow crystal powder); m.p. 247°C. LC-MS m/z 321 [M+H^{+}], R_t = 2.02 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.84 (s, 3H), 4.39 (s, 2H), 6.93 (d, 1H, J= 8.1), 7.02 (d, 1H, J= 8.1), 7.03 (s, 1H), 7.02 (m, 2H), 7.40 (t, 1H J= 7.8), 7.72 (m, 2H), 8.67 (s, 2H), 13.95 (bs, 1H). Anal. Calc. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.44; H, 5.00; N, 17.46.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-phenyl-1,2-dihydro-3*H*-pyrrol-3-one (**7**). Yield 72% (grey crystal powder); m.p. 257°C. LC-MS m/z 291 [M+H^{+}], R_t = 2.09 min. ^{1}H NMR (DMSO-d_6) δ 4.27 (s, 2H), 7.01 (m, 2H), 7.23 (t, 1H J= 6.6), 7.42 (m, 1H), 7.46 (m, 5H), 8.01 (s, 1H), 8.95 (s, 1H), 11.57 (s, 1H). Anal. Calc. for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N,19.30%. Found: C, 70.31; H, 4.83%; N, 19.31.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(3-methylphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**8**). Yield 71% (white crystal powder); m.p. 187°C. LC-MS m/z 305 [M+H^{+}], R_t = 2.14 min. ^{1}H NMR (DMSO-d_6) δ 2.40 (s, 3H), 4.22 (s, 2H), 7.02 (m, 3H), 7.22 (d, 1H J= 7.8), 7.27 (s, 1H), 7.31 (t, 1H J= 6.8), 7.44 (m, 2H), 7.75 (bs, 1H), 9.00 (bs, 1H), 11.32 (bs, 1H). Anal. Calc. for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41. Found: C, 71.01; H, 5.28; N, 18.39.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(4-methylphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**9**). Yield 71% (yellow crystal powder); m.p. 292°C (dec.). LC-MS m/z 305 [M+H^{+}], R_t = 2.14 min. ^{1}H NMR (DMSO-d_6) δ 2.36 (s, 3H), 4.19 (s, 2H), 7.02 (m, 2H), 7.24 (d, 2H J= 7.8), 7.29 (d, 2H J= 7.8), 7.46 (m, 2H), 7.75 (s, 1H),

9.00 (s, 1H), 11.32 (s, 1H). Anal. Calc. for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41. Found: C, 71.03; H, 5.29; N, 18.38.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(2-methoxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**10**). Yield 72% (yellow crystal powder); m.p. 282°C. LC-MS m/z 321 [M+H$^+$], R_t = 2.08 min. ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H), 4.09 (s, 2H), 7.01 (m, 2H), 7.06 (t, 1H J= 7.8), 7.15 (d, 1H, CH J= 8.3), 7.46 (m, 3H), 7.75 (s, 1H), 8.96 (s, 1H), 11.46 (s, 1H). Anal. Calc. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.47; H, 5.02; N, 17.48.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(4-methoxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**11**). Yield 72% (brown crystal powder); m.p. 257°C. LC-MS m/z 321 [M+H$^+$], R_t = 2.08 min. ^{1}H NMR (DMSO-d_6) δ 3.82 (s, 3H), 4.39 (s, 2H), 7.11 (d, 2H, CH J= 8.2), 7.38 (m, 2H), 7.43 (d, 2H, CH J= 8.2), 7.72 (m, 2H), 8.48 (s, 2H), 13.77 (s, 1H). Anal. Calc. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.48; H, 5.02; N, 17.47.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(2-ethoxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**12**). Yield 72% (yellow crystal powder); m.p. 218°C. LC-MS m/z 335 [M+H$^+$], R_t = 2.09 min. ^{1}H NMR (DMSO-d_6) δ 1.38 (t, 3H J= 8.3), 4.16 (m, 4H), 7.11 (m, 4H), 7.36 (m, 2H), 7.66 (m, 3H), 8.94 (s, 1H), 11.42 (s, 1H). Anal. Calc. for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 16.76. Found: C, 68.22; H, 5.42; N, 16.74.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(2,5-dimethoxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**13**). Yield 72% (light beige crystal powder); m.p. 244°C. LC-MS m/z 351 [M+H$^+$], R_t = 2.06 min. ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H), 3.92 (s, 3H), 4.16 (s, 2H), 6.89 (d, 1H, CH J= 7.8), 6.98 (s, 2H), 7.02 (d, 1H, CH J= 7.8), 7.24(m, 2H), 7.75 (m, 2H), 9.12 (m, 2H), 8.78 (s, 1H), 14.17 (s, 1H). Anal. Calc. for $C_{19}H_{18}N_4O_3$: C, 68.13; H, 5.18; N, 15.99. Found: C, 68.10; H, 5.17; N, 15.97.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(2,4-dimethoxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**14**). Yield 72% (yellow crystal powder); m.p. 247°C. LC-MS m/z 351 [M+H$^+$], R_t = 2.05 min. ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H), 3.88

(s, 3H), 4.06 (s, 2H), 6.53 (d, 1H, CH J= 7.8), 6.59 (s, 2H), 7.08 (m, 2H), 7.23 (d, 1H, CH J= 7.8), 7.59 (m, 3H), 8.78 (s, 1H), 11.47 (s, 1H). Anal. Calc. for $C_{19}H_{18}N_4O_3$: C, 68.13; H, 5.18; N, 15.99. Found: C, 68.11; H, 5.18; N, 15.96.

5-amino-1-(2-methoxy-5-methylphenyl)-4-(6-methyl-1*H*-benzimidazol-2-yl)-1,2-dihydro-3*H*-pyrrol-3-one (**15**). Yield 71% (brown crystal powder); m.p. 242°C. LC-MS m/z 349 [$M+H^+$], R_t = 2.14 min. ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H), 2.46 (s, 3H), 3.82 (s, 3H), 4.22 (s, 2H), 7.11 (d, 2H J= 7.8), 7.18 (d, 2H J= 7.8), 7.27 (m, 2H), 7.49 (s, 1H), 7.57 (d, 1H J= 7.8), 8.15 (s, 1H), 8.50 (s, 1H), 11.46 (s, 1H). Anal. Calc. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.92; H, 5.77; N, 16.06.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(5-chloro-2-methoxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**16**). Yield 73% (yellow crystal powder); m.p. 284°C. LC-MS m/z 355 [$M+H^+$], R_t = 2.11 min. ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 3H), 4.21 (s, 2H), 7.17 (d, 1H, CH J= 8.8), 7.31 (m, 2H), 7.42 (d, 1H, CH J= 8.8), 7.49 (s, 1H), 7.73 (m, 2H), 8.75 (s, 2H), 14.02 (s, 1H). Anal. Calc. for $C_{18}H_{15}ClN_4O_2$: C, 60.94; H, 4.26; Cl, 9,99; N, 15.79. Found: C, 60.90; H, 4.25; Cl, 9,97; N, 15.76.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(3-chlorophenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**17**). Yield 73% (grey crystal powder); m.p. 234°C. LC-MS m/z 325 [$M+H^+$], R_t = 2.11 min. ^{1}H NMR (DMSO-d_6) δ 4.30 (s, 2H), 7.09 (m, 2H), 7.31 (d, 1H, CH J= 7.1), 7.41 (d, 1H, CH J= 7.6), 7.49 (m, 4H), 8.29 (s, 1H), 8.99 (s, 1H), 11.60 (s, 1H). Anal. Calc. for $C_{17}H_{13}ClN_4O$: C, 62.87; H, 4.03; Cl, 10,92; N, 17.25. Found: C, 62.84; H, 4.02; Cl, 10,90; N, 17.23.

5-amino-1-(3-chlorophenyl)-4-(6-methyl-1*H*-benzimidazol-2-yl)-1,2-dihydro-3*H*-pyrrol-3-one (**18**). Yield 70% (grey crystal powder); m.p. 258°C. LC-MS m/z 339 [$M+H^+$], R_t = 2.16 min. ^{1}H NMR (DMSO-d_6) δ 2.41 (s, 3H), 4.26 (s, 2H), 6.83 (m, 1H), 7.27 (m, 3H), 7.39 (d, 1H, CH J= 7.8), 7.46 (d, 1H, CH J= 8.1), 7.50 (d, 1H, CH J= 8.1), 7.51 (s, 1H), 8.18 (s, 1H), 9.03 (s, 1H), 11.43 (s, 1H). Anal. Calc. for $C_{18}H_{15}ClN_4O$: C, 63.81; H, 4.46; Cl, 10,46; N, 16.54. Found: C, 63.80; H, 4.45; Cl, 10,44; N, 16.51.

5-amino-1-(3-fluorophenyl)-4-(6-methyl-1*H*-benzimidazol-2-yl)-1,2-dihydro-3*H*-pyrrol-3-one (**19**). Yield 70% (grey crystal powder); m.p. 264°C. LC-MS m/z 323 [M+H$^+$], R_t = 2.10 min. ^{1}H NMR (DMSO-d_6) δ 2.42 (s, 3H), 4.28 (s, 2H), 6.86 (d, 1H, CH J= 5.9), 7.05 (t, 1H J= 7.8), 7.31 (m, 4H), 7.50 (q, 1H, CH J= 6.8), 8.15 (s, 1H), 9.04 (s, 1H), 11.43 (s, 1H). Anal. Calc. for $C_{18}H_{15}FN_4O$: C, 67.07; H, 4.69; N, 17.38. Found: C, 67.03; H, 4.68; N, 17.35.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(2-chlorophenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**20**). Yield 70% (white crystal powder); m.p. 269°C. LC-MS m/z 325 [M+H$^+$], R_t = 2.13 min. ^{1}H NMR (DMSO-d_6) δ 4.18 (s, 2H), 7.22 (m, 2H), 7.47 (m, 2H), 7.62 (m, 2H), 7.73 (m, 2H), 7.50 (q, 1H, CH J= 6.8), 8.18 (s, 1H), 9.18 (s, 1H), 11.46 (s, 1H). Anal. Calc. for $C_{17}H_{13}ClN_4O$: C, 62.87; H, 4.03; Cl, 10,92; N, 17.25. Found: C, 62.85; H, 4.02; Cl, 10,92; N, 17.22.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(2- fluorophenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**21**). Yield 70% (beige crystal powder); m.p. 263°C. LC-MS m/z 325 [M+H$^+$], R_t = 2.10 min. ^{1}H NMR (DMSO-d_6) δ 4.22 (s, 2H), 7.32 (m, 4H), 7.48 (q, 1H, CH J= 6.8), 7.59 (t, 1H J= 7.8), 7.74 (m, 2H), 9.08 (s, 2H), 11.57 (s, 1H). Anal. Calc. for $C_{17}H_{13}FN_4O$: C, 66.23; H, 4.25; N, 18.17. Found: C, 66.20; H, 4.24; N, 18.15.

5-amino-1-(4-chlorophenyl)-4-(6-methyl-1*H*-benzimidazol-2-yl)-1,2-dihydro-3*H*-pyrrol-3-one (**22**). Yield 70% (beige crystal powder); m.p. 291°C. LC-MS m/z 339 [M+H$^+$], R_t = 2.15 min. ^{1}H NMR (DMSO-d_6) δ 2.41 (s, 3H), 4.26 (s, 2H), 6.83 (m, 1H), 7.27 (m, 3H), 7.39 (d, 1H, CH J= 7.8), 7.46 (d, 1H, CH J= 8.1), 7.50 (d, 1H, CH J= 8.1), 7.51 (s, 1H), 8.18 (s, 1H), 9.03 (s, 1H), 11.43 (s, 1H). Anal. Calc. for $C_{18}H_{15}ClN_4O$: C, 63.81; H, 4.46; Cl, 10,46; N, 16.54. Found: C, 63.79; H, 4.46; Cl, 10.43; N, 16.51.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(4-fluorophenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**23**). Yield 77% (yellow crystal powder); m.p. 292°C (dec.). LC-MS m/z 309 [M+H$^+$], R_t = 2.12 min. ^{1}H NMR (DMSO-d_6) δ 2.42 (s, 3H), 4.31 (s, 2H), 6.89 (d, 2H J= 7.8), 7.33 (s, 1H), 7.41 (d, 2H J= 7.8), 7.51 (d, 2H J= 8.3), 7.56 (d,

2H J= 8.3), 8.15 (s, 1H), 8.88 (s, 1H), 11.56 (s, 1H). Anal. Calc. for $C_{17}H_{13}FN_4O$: C, 66.23; H, 4.25; N, 18.17. Found: C, 66.21; H, 4.24; N, 18.14.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydro-3*H*-pyrrol-3-one (**24**). Yield 70% (white crystal powder); m.p. 242°C. LC-MS m/z 359 [M+H$^+$], R_t = 2.10 min. ^{1}H NMR (DMSO-d_6) δ 4.28 (s, 2H), 7.03 (m, 2H), 7.46 (m, 2H), 7.57 (d, 1H, CH J= 7.8), 7.64 (t, 1H, CH J= 7.6), 7.76 (s, 1H, CH), 8.17 (s, 1H), 9.08 (s, 1H), 11.43 (s, 1H). Anal. Calc. for $C_{18}H_{13}F_3N_4O$: C, 60.34; H, 3.66; N, 15.64. Found: C, 60.31; H, 3.65; N, 15.62.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(4-hydroxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**25**). Yield 70% (light grey crystal powder); m.p. 238°C. LC-MS m/z 307 [M+H$^+$], R_t = 2.02 min. ^{1}H NMR (DMSO-d_6) δ 4.19 (s, 2H), 6.86 (d, 2H, CH J= 7.8), 7.09 (m, 2H), 7.16 (d, 2H, CH J= 7.8), 7.48 (m, 2H), 7.50 (d, 1H, CH J= 8.1), 7.51 (s, 1H), 8.23 (s, 1H), 9.38 (s, 1H), 11.41 (s, 1H). Anal. Calc. for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.62; H, 4.60; N, 18.26.

5-amino-1-(4-hydroxyphenyl)-4-(1-methyl-1*H*-benzimidazol-2-yl)-1,2-dihydro-3*H*-pyrrol-3-one (**26**). Yield 70% (brown crystal powder); m.p. 163°C. LC-MS m/z 321 [M+H$^+$], R_t = 2.01 min. ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H), 4.12 (s, 2H), 6.86 (d, 2H, CH J= 7.8), 7.11 (m, 2H), 7.22 (d, 2H, CH J= 7.8), 7.41 (m, 1H), 7.48 (m, 1H), 7.61 (s, 1H), 8.73 (s, 1H), 9.58 (s, 1H), 11.37 (s, 1H). Calc. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.45; H, 5.02; N, 17.47.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(3-hydroxy-4-methylphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**27**). Yield 78% (orange crystal powder); m.p. >300°C(dec.). LC-MS m/z 321 [M+H$^+$], R_t = 2.03 min. ^{1}H NMR (DMSO-d_6) δ 2.17 (s, 3H), 4.16 (s, 2H), 6.74 (d, 1H, CH J= 7.8), 6.82 (s, 1H), 7.01 (m, 2H), 7.11 (d, 1H, CH J= 7.8), 7.46 (m, 2H), 7.84 (s, 1H), 9.01 (s, 1H), 9.03 (s, 1H), 9.58 (s, 1H), 11.51 (s, 1H). Calc. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.46; H, 5.03; N, 17.46.

5-amino-1-(3-hydroxyphenyl)-4-(1-methyl-1*H*-benzimiazol-2-yl)-1,2-dihydro-3*H*-pyrrol-3-one (**28**). Yield 73% (brown crystal powder); m.p. 172°C. LC-MS m/z 321 [M+H$^+$], R_t = 1.73 min. ^{1}H NMR (DMSO-d_6) δ 4.00 (s, 3H), 4.16

(s, 2H), 6.70 (d, 1H, CH J= 6.8), 6.81 (s, 1H), 6.82 (d, 1H, CH J= 7.2), 7.11 (m, 2H), 7.25 (t, 1H J= 7.4), 7.35 (m, 1H), 7.47 (m, 1H), 8.95 (s, 2H), 9.63 (s, 1H). Calc. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.49; H, 5.00; N, 17.44.

5-amino-1-(3-hydroxyphenyl)-4-(6-methyl-1*H*-benzimidazol-2-yl)-1,2-dihydro-3*H*-pyrrol-3-one (**29**). Yield 71% (brown crystal powder); m.p. 278°C. LC-MS m/z 321 [$M+H^+$], R_t = 1.79 min. ^{1}H NMR (DMSO-d_6) δ 2.37 (s, 3H), 4.29 (s, 2H), 6.73 (d, 1H, CH J= 7.2), 6.87 (m, 3H), 7.27 (d, 1H, CH J= 8.5), 7.32 (t, 1H J= 8.3), 7.39 (d, 1H, CH J= 7.8), 8.02 (bs, 1H), 8.91 (bs, 1H), 9.85 (bs, 1H), 11.60 (bs, 1H). ^{13}C NMR (DMSO-d_6) δ 22.00, 59.43, 88.39, 111.43, 113.94, 114.63, 130.69, 139.16, 159.08, 165.73, 186.30; Calc. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.48; H, 5.01; N, 17.45.

5-amino-4-(1*H*-benzimidazol-2-yl)-1-(3-hydroxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**30**). Yield 73% (rose crystal powder); m.p. 234°C. LC-MS m/z 307 [$M+H^+$], R_t = 1.70 min. ^{1}H NMR (DMSO-d_6) δ 4.20 (s, 2H), 6.69 (d, 1H, CH J= 7.6), 6.82 (s, 1H), 6.83 (d, 1H, CH J= 7.8), 7.00 (m, 2H), 7.24 (t, 1H J= 7.6), 7.41 (m, 1H), 7.46 (m, 1H), 7.94 (s, 1H), 8.88 (bs, 1H), 9.63 (bs, 1H), 11.53 (bs, 1H). ^{13}C NMR (DMSO-d_6) δ 59.54, 96.23, 111.51, 113.99, 114.69, 130.68, 139.11, 159.08, 165.71, 186.44; Calc. for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.63; H, 4.60; N, 18.27.

4.2. Kinase assay. The FGFR1 kinase assays with recombinant cytoplasmic domain of the FGFR1 tyrosine kinase (Millipore, Cat. N. 14-582) were performed in a total volume of 30 µl containing 10 mM MOPS (pH 7.2), 0.1 mM sodium orthovanadate, 0.2 mM EDTA, 0.002 % Brij 35, 0.2 mg/ml BSA, 0.02 % β-mercaptoethanol, 250 µM of peptide substrate (KKKSPGEYVNIEFG, GenScript), various concentrations of inhibitor dissolved in DMSO (final DMSO concentration in probe less than 1%) and 10 mU of enzyme. The reaction was initiated by the addition of ATP (50 µM ATP, 25 mM MgAc containing 0.1 µCi of [γ-32P]ATP per probe) and samples incubated at 30°C for 25 min. The reaction was terminated by the addition of 5% phosphoric acid and the precipitation of material onto

phosphocellulose filters "Whatman P81". Filters were washed three times with 0.75 % phosphoric acid and the incorporation of [^{32}P] into the peptide substrate was determined by counting the radioactivity retained on the filters in a PerkinElmer scintillation counter. Kinase residual activity was expressed in percentages with respect to DMSO control. The concentration of compound that inhibited enzymatic activity by 50% (IC_{50}) was determined graphically.

Inhibition of selectivity panel kinases was perfomed according to enzyme provider protocols (Millipore). ATP concentration in reaction mixture was 100 μM.

4.3. Molecular docking. Ligands for the docking were prepared with Vega ZZ.[36] Docking was carried out in crystal structure of FGFR1 (pdb bank code 3GQI) by Autodock 4.2 with default parameters.[37] Docking results were analyzed with AutoDockTools-1.5.6.[37]

4.4. Cellular Proliferation Assay. KG1 and HEK293 cell viability was examined using a standard MTT assay.[38] Cells were grown in DMEM containing 10% fetal bovine serum (FBS), 100 mg/mL penicillin, and 100 mg/mL streptomycin in humidified air at 37^{o}C with 5% CO_2. Viable cells were seeded into 96-well tissue plate at 2X10^5 cells/mL preincubated for 24 hours and treated with the synthesized compounds (compounds in DMSO solution, final DMSO concentration less than 0.5%) at various concentrations. After 72 h treatment, the cells were incubated with 15 μl MTT (3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyl-tetrazolium bromide from Sigma) solution (5 mg/mL) for 4 h at 37^{o}C, 5% CO_2. The formazan precipitates were dissolved in 200 μl DMSO and the absorbance at 540 nm of each well was measured by spectrofluorometer MR 700 (Dynatech). The cell viability was expressed as a percentage relative to the untreated control cells.

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