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DESIGN, SYNTHESIS AND BIOLOGICAL ACTIVITY EVALUATION OF 2,5-DIPHENYL-1,3,4-OXADIAZOLE DERIVATIVES AS NOVEL INHIBITORS OF FRUCTOSE-1,6-BISPHOSPHATASE

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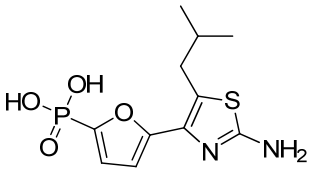
Abstract – Fructose-1,6-bisphosphatase (FBPase), an important gluconeogenic enzyme, catalyzes the hydrolysis of fructose 1,6-bisphosphate to fructose 6-phosphate. The effort to discover new FBPase inhibitors was carried out by high-throughput screening (HTS) of a library of 56,000 lead-like compounds, and a 2,5-diphenyl-1,3,4-oxadiazole (**3a**, IC_{50} = 15.45 μM) which bearing no phosphate group was identified as a potential FBPase inhibitor for the first time. Structure-activity-relationship (SAR) research of a series of analogues obtained by modifying the substituent groups and replacing the 1,3,4-oxadiazole with several other heterocycles disclosed the key structure and substituent groups related to the binding with FBPase.

INTRODUCTION

Type-2 diabetes mellitus (T2DM) is associated with an increased rate of hepatic glucose production that contributes to fasting hyperglycemia. Specifically, increased endogenous glucose production can be accounted for by increased rates of hepatic gluconeogenesis (GNG).[1] The rate of gluconeogenesis is governed by the activity of three regulatory and irreversible enzymes, phosphoenolpyruvate carboxykinase (PEPCK), fructose-1,6-bisphosphatase (FBPase), and glucose-6-phosphatase (G6Pase).[2] As a key enzyme of gluconeogenic pathways, FBPase catalyzes the hydrolysis of fructose 1,6-bisphosphate (F1,6-P2) to fructose-6-phosphate (F6-P) and inorganic phosphate,[3] which is a

rate-controlling reaction of hepatic and renal gluconeogenesis.[4] Unlike both PEPCK and G6Pase, FBPase is not only a rate-controlling enzyme within the GNG pathway but also functions only within the GNG pathway.[5] Therefore FBPase is an attractive target in the development of new anti-diabetic pharmaceuticals.

FBPase is generally considered to be regulated in vivo via the allosteric interactions of AMP.[6] Therefore the AMP-site was recognized as a specific target of FBPase inhibitor research. Several clusters of small molecules were reported as AMP-site allosteric inhibitors of FBPase. Among them, two AMP mimics **1** and **2** were highlighted.[7-9] However, there are still challenges for the AMP mimics due to the abundance of AMP-binding enzymes controlling other key biosynthetic pathways resulting in issues with specificity. Other difficulties that need to be overcome include the hydrophilic nature of AMP sites and their reliance on the negatively charged phosphate group of AMP for binding affinity.[10] Therefore, in the past decade, a lot of effort was made to discover new FBPase inhibitors structurally distinct from the AMP analogues without phosphate groups.[11-15]



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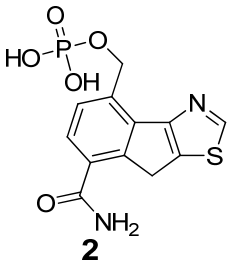

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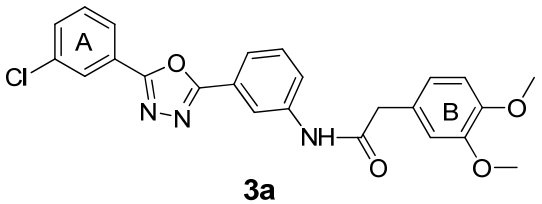
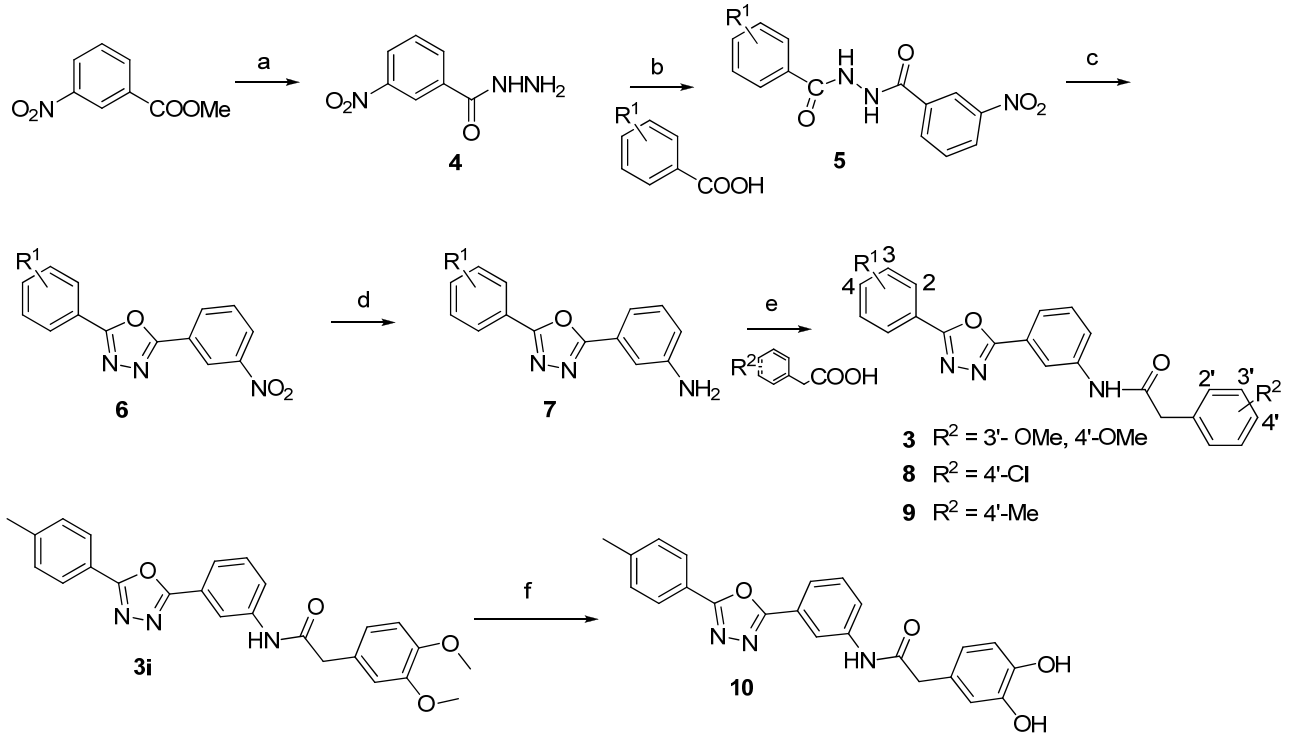


3a

In order to search for new hits with FBPase inhibitory activity, we carried out a high-throughput screening (HTS) campaign of a library of 56,000 lead-like small molecular compounds. As a result, **3a** was recognized as a lead compound with a moderate FBPase inhibitory activity (IC_{50} = 15.45 μM). The scaffold of **3a** contains three typical elements: the 1,3,4-oxadiazole ring, amide bond and other three substituted phenyl groups. Because the amide bond usually plays key roles in binding to the target sites of enzymes and usually are responsible for good pharmacokinetic and toxic properties. So at the first stage of SAR, the amide bond was reserved. Additionally, phenyl B was reserved without any modification due to the complication caused by multi-substitution. The rest areas of the structure with high modifiability, phenyl A, B and the 1,3,4-oxadiazole ring were investigated systematically.

RESULTS AND DISCUSSION

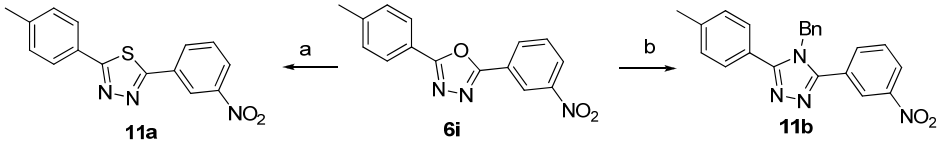
1. Chemistry. All the final products (**3**, **8, 9** and **24**) were prepared via the key nitro-containing intermediates **6** and **11**. The synthesis of 1,3,4-oxadiazole **6** was followed the classical procedures: dehydrated cyclization of dihydrazide **5** with $POCl_3$ in acetonitrile (**Scheme 1**).[16] Condensation of compounds **7** with the corresponding carboxylic acid using EDC as the condensation reagent gave **3**, **8** or **9.** The dihydroxy compound **10** was prepared by demethylation of **3i** with boron tribromide.[17]



Scheme 1

a) Dioxane, 85% hydrazine hydrate, reflux, 6 h, 99%. b) EDC, HOBt, 3-picoline, DCM, rt, 12 h, 65~75%. c) $POCl_3$, MeCN, reflux, 8 h. d) THF, MeOH, H_2O, Zn, NH_4Cl, reflux, 4 h, 76%~91%. e) EDC, HOBt, 3-picoline, DCM, 20 h, 81~90%. f) BBr_3, DCM -20 ^oC, 8 h, 92%.

The reaction of **6i** with Lawesson's reagent afforded 1,3,4-thiadiazole **11a**.[18] **11b** was produced from **6i** with benzylamine at a high temperature (**Scheme 2**).[19]

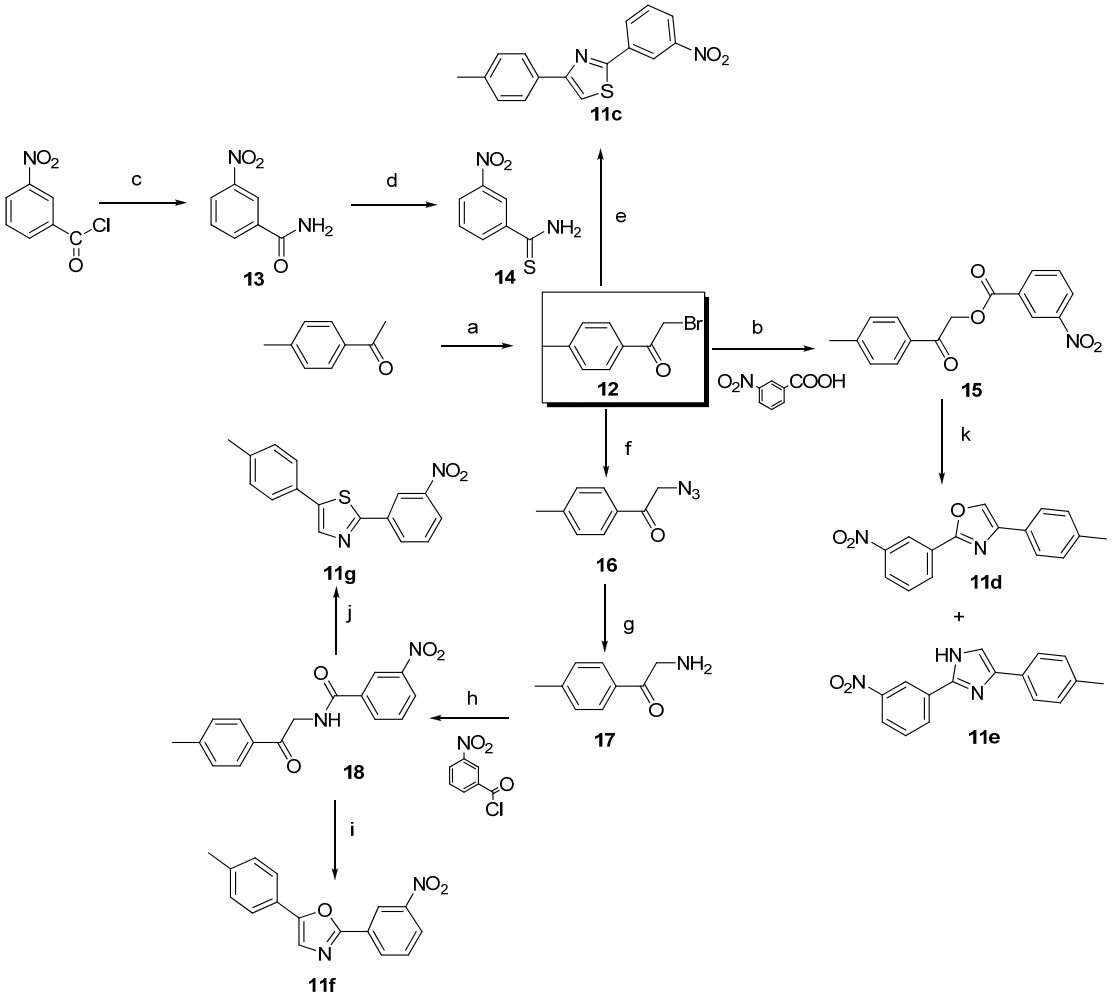


Scheme 2

a) Lawesson's reagent, THF, reflux, 5 h, 55%. b) $BnNH_2$, TsOH, mesitylene, reflux, 13 h, 46%.

The synthesis of heterocyclic rings that containing two heteroatoms (**11c~11g**) was shown in **Scheme 3**. Bromination of 4'-methylacetophenone afforded the key initial material **12**.[20] Compound **12** reacted with

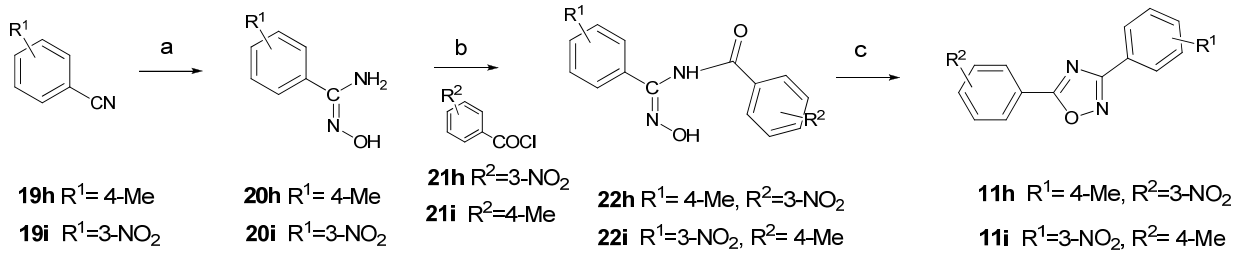
thioamide **14** to produce 2,4-diphenylthiazole **11c** in one step.[21] 2,5-diphenylthiazole **11g** and 2,5-diphenyloxazole **11f** were obtained by the reaction of **18** with Lawesson's reagent or phosphorus oxychloride, respectively.[22,23] Compound **18** was synthesized from **12** via the azide substitution, hydrogenation and acylation successively.[24] Cyclization of **15** in acetic acid with the presence of ammonium acetate yielded a mixture of **11d** (18%) and **11e** (27%).[25]



Scheme 3

a) MeOH, Br_2, HBr, 0 °C, 3 h, 92%. b) DMF, DBU, 60 °C, 3 h, 67%. c) toluene, ammonium hydroxide, 60%. d) THF, P_2S_5, reflux, 3 h, 46%. e) EtOH, reflux, 3 h, 61%. f) DMF, NaN_3, rt, 4 h, 97%. g) MeOH, concentrated hydrochloric acid, Pd/C, H_2, 1 atm, rt, overnight, 82%. h) DCM, TEA, 0 °C, 3 h, 67%. i) $POCl_3$, reflux, 3 h, 99%. j) Lawesson's reagent, THF, reflux, 3 h, 66%. k) NH_4OAc, HOAc, reflux, 6 h.

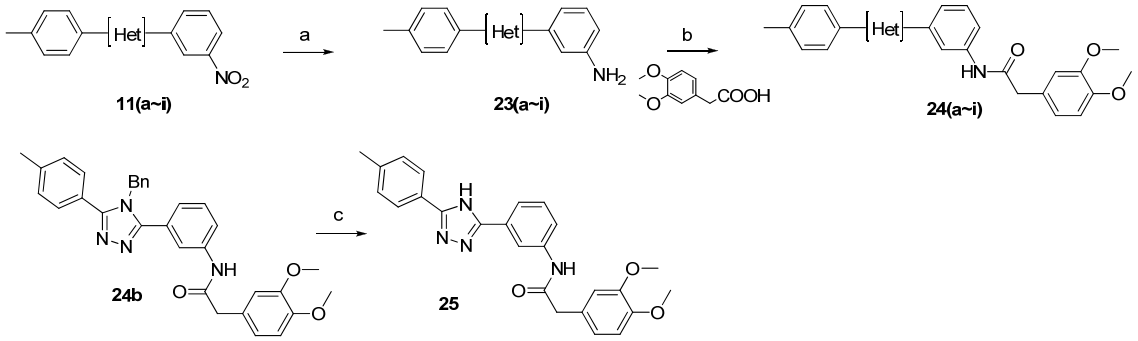
The analogue 3,5-diphenyl-1,2,4-oxadiazole (**11h** and **11i**) was synthesized by a common procedure as shown in **Scheme 4**. A nucleophilic addition of hydroxylamine to the cyano afforded **20** in a high yield. Condensation of **20** with benzoyl chloride in 2-picoline produced the precipitate **22**. The dehydrative cyclization of **22** was easily accomplished in refluxing toluene to give **11h** and **11i**.[26,27]



Scheme 4

a) EtOH, K_2CO_3, hydroxylamine hydrochloride, reflux, 8 h, 90%. b) 2-picoline, 0 °C~rt, overnight, 45%. c) toluene, reflux, 3 h, 93%.

In order to avoid the possible hydrogenation of the heterocyclic rings, the reduction of NO_2 group (**6** and **11**) to NH_2 group (**7** and **23**) was carried out in the presence of zinc and ammonium chloride.[28] Similar to the preparation of **3**, **24** was obtained via the condensation of compounds **23** with (3,4-dimethoxyphenyl)acetic acid using EDC as the condensation reagent. Debenzylation of **24b** in hydrogen with Pd/C as the catalyst gave **25** (**Scheme 5**).



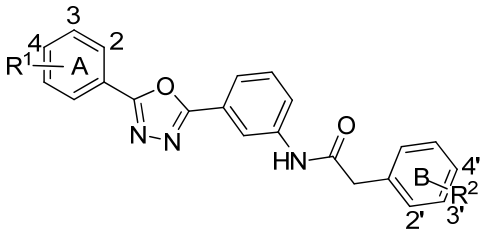
Scheme 5

a) THF, MeOH, H_2O, Zn, NH_4Cl, reflux, 4 h, 76%~91%. b) EDC, HOBt, 3-picoline, DCM, 20 h, 81~90%. C) Pd/C, H_2, 2.5 MPa, rt, 4 h, 99%.

2. In vitro biological evaluation. All the compounds were evaluated in the enzyme inhibition assay against FBPase by a method reported by Doris Rittmann.[29] Initially, in order to enhance the activity against FBPase, we investigated the substituent groups on phenyl A and B. Due to the conjugated system constituted by three aromatic rings, the inductive effect of the substituent groups on ring A had significant effect on activity (Table 1). Removing of the methyl group at C-4 (**3b**) resulted in the elimination of the activity. However, the C-3 position of ring A showed some tolerance of electron-withdrawing groups. 3-Br substituted **3c** showed an enhanced threefold (IC_{50} = 4.92 μM) activity than the lead compound **3a** (IC_{50} = 15.45 μM). Methoxycarbonyl substituted **3f** also kept a similar activity to **3a**. However, the introduction of more electron-withdrawing group cyano (**3d**) and trifluoromethyl (**3e**) led to the elimination of the activity. Moreover, we still investigated effects of the substituent groups at C-4 and C-2 position. Similar to **3b**, the electron-withdrawing 4-Cl (**3g**) or 4-F (**3h**) substituted compound didn't show

significant inhibitory activity to the enzyme. In contrast, by introducing electron-donating methyl at C-4 position, we obtained **3i** (IC_{50} = 4.51 μM) with an improved threefold activity than **3a**. A bigger and more hydrophobic isopropyl (**3j,** IC_{50} = 7.24 μM) at C-4 showed a decreased activity. In addition, the combination of the optimized group at C-3 and C-4 position (**3k**, **3l**) didn't display an encouraging result. Modification of C-2 on ring A gave two compounds (**3m**, **3n**), which showed no significant inhibition activity against FBPase. When it comes to the substituents on phenyl B, the comparison of **3i** with **8** and **9** showed the importance of 3',4'-dimethoxy unit for the inhibitory activity. Remarkably, when the 3',4'-dimethoxy group was replaced by 3',4'-dihydroxy group (**10**), the activity reduced by half (IC_{50} = 9.21 μM). The result revealed that a hydrogen-bonding acceptor on ring B is essential for the binding with FBPase instead of a hydrogen-bonding donor. The result convinced the importance of 4-methyl group on phenyl A ring and 3,4-dimethoxy substituent on phenyl B ring, which were reserved in the following SAR research.

Table 1. Inhibitory activity of 2,5-diphenyl-1,3,4-oxadiazole derivatives against FBPase

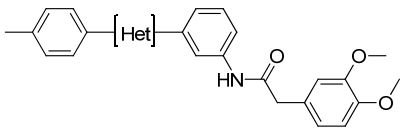


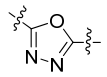
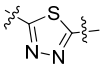
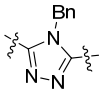
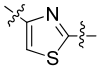
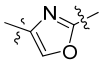
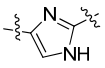
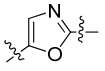
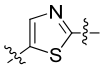
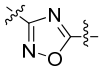
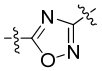
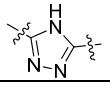
Compounds	R^1	R^2	FBPase, IC_{50} (μM)
3a	3-Cl	3'-OMe, 4'-OMe	15.45±0.23
3b	H	3'-OMe, 4'-OMe	>40
3c	3-Br	3'-OMe, 4'-OMe	4.92±0.35
3d	3-CN	3'-OMe, 4'-OMe	>40
3e	3-CF_3	3'-OMe, 4'-OMe	>40
3f	3-CO_2Me	3'-OMe, 4'-OMe	11.92±0.61
3g	4-Cl	3'-OMe, 4'-OMe	>40
3h	4-F	3'-OMe, 4'-OMe	>40
3i	**4-Me**	**3'-OMe, 4'-OMe**	**4.51±0.22**
3j	4-*i*-Pr	3'-OMe, 4'-OMe	7.24±0.65
3k	3-Cl, 5-Cl	3'-OMe, 4'-OMe	>40
3l	3-Cl, 4-Me	3'-OMe, 4'-OMe	6.61±0.11
3m	2-OMe	3'-OMe, 4'-OMe	>40

3n	2-Cl	3'-OMe, 4'-OMe	>40
8	4-Me	4'-Cl	>40
9	4-Me	4'-Me	>40
10	4-Me	3'-OH, 4'-OH	9.21±0.27

On the reservation of 4-methyl at phenyl A and 3,4-dimethoxy at phenyl B, we tried to replace the 1,3,4-oxadiazole unit with typical bioisosteres: a class of five-membered heterocycles (**24a**~**24i**, **25**). The IC_{50} value of these compounds in **Table 2** demonstrated that none of them could provide a similar affinity with the enzyme as 1,3,4-oxadiazole (**Table 1**). Whether the oxygen atom was replaced with sulfur (**24a**) or nitrogen (**24b**, **25**) the activity diminished dramatically. Transposition of the nitrogen atom on oxadiazole ring also caused the lost of activity (**24h**, **24i**). Furthermore, all the heterocyclic rings that containing two heteroatoms (**24c**~**24g**) didn't show activities against FBPase. The results demonstrated the key role of 1,3,4-oxadiazole moiety for the inhibition against the enzyme.

Table 2. Inhibitory activity of various diphenyl heterocyclic compounds against FBPase



Compounds	Het	FBPase, IC_{50} (μM)
3i		4.51±0.22
24a		>40
24b		>40
24c		>40
24d		>40
24e		>40
24f		>40
24g		>40
24h		>40
24i		>40
25		>40

CONCLUSION

In this paper we reported a series of compounds with a novel scaffold as inhibitors against fructose 1,6-bisphosphatase. The substituent groups on phenyl A and phenyl B and a class of heterocyclic bioisosteres were synthesized and evaluated systematically. Some of these compounds showed moderate to good inhibitory activity against FBPase. The two most potent compounds **3i** (IC_{50} = 4.51 μM) and **3c** (IC_{50} = 4.92 μM) showed improved threefold FBPase inhibitory activity than the lead compound **3a**. The SAR research demonstrated the characteristics of the substituents at different positions essential to the activities and the key role of the 1,3,4-oxadiazole ring. These novel 2,5-diphenyl-1,3,4-oxadiazole derivatives could be promising lead compounds for the development of a new class of FBPase inhibitors. Further SAR research and evaluation of new derivatives are still in progress.

EXPERIMENTAL

General. ^{1}H (400 and 500 MHz) and ^{13}C (100 and 125 MHz) NMR spectra were recorded on a JEOL-400 or Bruker AM-500 Fourier transform spectrometer. The chemical shifts were reported (δ in ppm) using the δ = 7.26, 2.5 signals of $CDCl_3$, DMSO-d_6 (^{1}H NMR), and using the δ = 77.23, 39.51 signals of $CDCl_3$, DMSO-d_6 (^{13}C NMR) as internal standards. High-resolution mass data were obtained on a Micromass Tof II spectrometer.

General procedure A, synthesis of dihydrazide 5. 3-Nitrobenzohydrazide (**4**, 10 mmol), substituted benzoic acid (10 mmol), EDC (13 mmol) and HOBt (13 mmol) were suspended in anhydrous DCM (25 mL). To this mixture, 3-picoline (14 mmol) was added. After stirring at room temperature for 12 h, the reaction mixture was filtered. The filter cake was washed with 5% HCl and water successively, dried in oven and used without any purification.

General procedure B, synthesis of 6. Dihydrazide **5** (10 mmol) was suspended in anhydrous MeCN (20 mL). To this mixture $POCl_3$ (2 mL) was added. After stirring at reflux for 8 h, the reaction mixture was evaporated in vacuo. The resultant residue was then purified by column chromatography (DCM / hexane = 1:1).

General procedure C, synthesis of 7 or 23. Nitro compounds **6** or **11** (10 mmol), zinc dust (50 mmol), ammonium chloride (100 mmol) were suspended in a mixed solution of MeOH (15 mL), THF (15 mL) and water (15 mL). The mixture was heated to reflux for 4 h. After filtration, the filtration was concentrated in vacuo and purified by column chromatography (DCM / EtOAc= 5:1).

General procedure D, synthesis of 3 or 24. Amino compounds **7** or **23** (2 mmol), substituted phenylacetic acid (2 mmol), EDC (2.5 mmol) and HOBt (2.5 mmol) were dissolved in anhydrous DCM (10 mL). To this solution 3-picoline (3 mmol) was added. After stirring at room temperature for 20 h, the reaction mixture was diluted with DCM (10 mL), and then washed with 5% HCl, water, 5% NaOH and

saturated aqueous $NaHCO_3$ successively. After dried over anhydrous Na_2SO_4, the organic phase was evaporated in vacuo and then purified by column chromatography (DCM / EtOAc / MeOH = 25: 5: 1).

***N*-(3-(5-(3-Chlorophenyl)-1,3,4-oxadiazol-2-yl)phenyl)-2-(3,4-dimethoxyphenyl)acetamide (3a). Synthesized according to the General procedure D.** White solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.63 (s, 2H), 3.75 (s, 3H), 3.78 (s, 3H), 6.89-6.94 (m, 2H), 6.99 (s, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.84~7.88 (m, 2H), 8.07 (d, J = 7.5 Hz, 1H), 8.12 (s, 1H), 8.46 (s, 1H), 10.44 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.8, 164.3, 163.9, 148.6, 147.7, 140.1, 134.1, 131.8, 131.5, 130.0, 128.0, 126.1, 125.3, 123.5, 122.4, 121.5, 121.1, 116.8, 113.2, 113.1, 111.9, 55.5, 55.4, 42.9; HRMS (ESI): Calcd for $C_{24}H_{21}ClN_3O_4$ $[M+H]^+$, 450.1215; Found, 450.1218.

2-(3,4-Dimethoxyphenyl)-*N*-(3-(5-phenyl-1,3,4-oxadiazol-2-yl)phenyl)acetamide (3b). Synthesized according to the General procedure D. White solid; mp 152-154 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.62 (s, 2H), 3.73 (s, 3H), 3.76 (s, 3H), 6.87~6.92 (m, 2H), 6.98 (s, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.63-7.64 (m, 3H), 7.79 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 7.6 Hz, 1H), 8.09 (d, J = 6.2 Hz, 2H), 8.45 (s, 1H), 10.38 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.8, 164.0, 163.9, 148.6, 147.7, 140.1, 132.0, 129.9, 129.4 (2C), 128.0, 126.6 (2C), 123.7, 123.3, 122.3, 121.3, 121.1, 116.7, 113.1, 111.9, 55.5, 55.4, 42.9; HRMS (ESI): Calcd for $C_{24}H_{22}N_3O_4$ $[M+H]^+$, 416.1610; Found, 416.1642.

***N*-(3-(5-(3-Bromophenyl)-1,3,4-oxadiazol-2-yl)phenyl)-2-(3,4-dimethoxyphenyl)acetamide (3c). Synthesized according to the General procedure D.** White solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.73 (s, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 6.85-6.89 (m, 3H), 7.36 (t, J = 7.9 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.90 (s, 1H), 8.01 (d, J = 7.9 Hz, 1H), 8.18 (s, 1H), 8.21 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 164.5, 163.3, 149.4, 148.5, 138.7, 134.7, 130.6, 129.8, 129.6, 129.0, 126.5, 125.4, 124.0, 123.3, 123.1, 122.7, 121.7, 117.9, 112.5, 111.6, 55.9 (2C), 44.2; HRMS (ESI): Calcd for $C_{24}H_{21}BrN_3O_4$ $[M+H]^+$, 494.0715; Found, 494.0718.

***N*-(3-(5-(3-Cyanophenyl)-1,3,4-oxadiazol-2-yl)phenyl)-2-(3,4-dimethoxyphenyl)acetamide (3d). Synthesized according to the General procedure D.** White solid; mp 186-187 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.61 (s, 2H), 3.73 (s, 3H), 3.76 (s, 3H), 6.87-6.92 (m, 2H), 6.97 (s, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.82-7.85 (m, 3H), 8.10 (d, J = 7.5 Hz, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.45 (s, 1H), 8.52 (s, 1H), 10.41 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.8, 164.4, 162.6, 148.6, 147.7, 140.1, 135.3, 131.0, 130.7, 130.2, 130.0, 128.0, 124.6, 123.5, 122.5, 121.6, 121.1, 117.8, 116.9, 113.1, 112.7, 111.9, 55.5, (2C), 42.9; HRMS (ESI): Calcd for $C_{25}H_{21}N_4O_4$ $[M+H]^+$, 441.1557; Found, 441.1532.

2-(3,4-Dimethoxyphenyl)-*N*-(3-(5-(3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)phenyl)acetamide (3e). Synthesized according to the General procedure D. White solid; mp 177-179 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.74 (s, 2H), 3.88 (s, 3H), 3.89 (s, 3H), 6.87-6.89 (m, 3H), 7.45 (t, J = 8.0 Hz, 1H), 7.66

(t, *J* = 7.8 Hz, 1H), 7.74 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 2H), 7.84 (d, *J* = 7.7 Hz, 1H), 8.18 (s, 1H), 8.29 (d, *J* = 7.7 Hz, 1H), 8.5 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 164.7, 163.5, 149.4, 148.6, 138.7, 131.7 (q), 130.0, 129.9, 129.8, 128.3, 128.2, 126.4, 124.5, 124.0, 123.7 (q), 123.3, 122.7, 121.7, 118.0, 112.5, 111.7, 55.9 (2C), 44.3; HRMS (ESI): Calcd for $C_{25}H_{21}F_3N_3O_4$ $[M+H]^+$, 484.1479; Found, 484.1449.

Methyl 3-(5-(3-(2-(3,4-dimethoxyphenyl)acetamido)phenyl)-1,3,4-oxadiazol-2-yl)benzoate (3f). Synthesized according to the General procedure D. White solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.61 (s, 2H), 3.73 (s, 3H), 3.76 (s, 3H), 3.87 (s, 3H), 6.87-6.92 (m, 2H), 6.98 (s, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 8.41 (s, 1H), 8.59 (s, 1H), 10.43 (s, 1H); HRMS (ESI): Calcd for $C_{26}H_{23}N_3NaO_6$ $[M+Na]^+$, 496.1485; Found, 496.1541.

***N*-(3-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)phenyl)-2-(3,4-dimethoxyphenyl)acetamide (3g). Synthesized according to the General procedure D.** White solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.62 (s, 2H), 3.75 (s, 3H), 3.78 (s, 3H), 6.88-6.92 (m, 2H), 6.99 (s, 1H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.81-7.85 (m, 2H), 8.12 (d, *J* = 8.4 Hz, 2H), 8.48 (s, 1H), 10.44 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.8, 164.1, 163.2, 148.5, 147.7, 140.1, 136.7, 130.0, 129.6 (2c), 128.4 (2c), 128.0, 123.6, 122.3, 122.2, 121.4, 121.1, 116.7, 113.1, 111.9, 55.5 (2c), 42.9; HRMS (ESI): Calcd for $C_{24}H_{20}ClN_3O_4$ $[M+H]^+$, 450.1215; Found, 450.1257.

2-(3,4-Dimethoxyphenyl)-*N*-(3-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)phenyl)acetamide (3h). Synthesized according to the General procedure D. White solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.73 (s, 2H), 3.87 (s, 3H), 3.89 (s, 3H), 6.85-6.88 (m, 3H), 7.19 (t, *J* = 8.5 Hz, 2H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 8.08-8.11 (m, 2H), 8.17 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 165.1, 164.0, 163.2, 163.1, 148.5, 147.7, 140.1, 129.9, 129.3, 128.0, 123.6, 122.3, 121.3, 121.1, 120.0, 116.8, 116.7, 116.6, 113.1, 111.8, 55.5, 55.4, 42.9; HRMS (ESI): Calcd for $C_{24}H_{21}FN_3O_4$ $[M+H]^+$, 434.1516; Found, 434.1537.

2-(3,4-Dimethoxyphenyl)-*N*-(3-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)phenyl)acetamide (3i). Synthesized according to the General procedure D. White solid; mp 169-170 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.41 (s, 3H), 3.62 (s, 2H), 3.74 (s, 3H), 3.77 (s, 3H), 6.88~6.93 (m, 2H), 6.93 (s, 1H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 7.5 Hz, 2H), 8.44 (s, 1H), 10.43 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.8, 164.1, 163.7, 148.6, 147.6, 142.2, 140.1, 130.0 (2C), 128.0, 126.6 (2C), 123.8, 122.2, 121.3, 121.1 (2C), 120.6, 116.7, 113.1, 111.9, 55.5, 55.5, 42.9, 21.1; HRMS (ESI): Calcd for $C_{25}H_{24}N_3O_4$ $[M+H]^+$, 430.1761; Found, 430.1756.

2-(3,4-Dimethoxyphenyl)-*N*-(3-(5-(4-isopropylphenyl)-1,3,4-oxadiazol-2-yl)phenyl)acetamide (3j). Synthesized according to the General procedure D. White solid; mp 138-140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (d, *J* = 6.9 Hz, 6H), 2.93-3.02 (m, 1H), 3.72 (s, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 6.81-6.89 (m, 3H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.89 (s, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 164.8, 164.0, 153.2, 149.3, 148.5, 138.6, 129.7, 127.1 (2C), 127.0 (2C), 126.5, 124.3, 122.5, 121.6, 121.5, 121.0, 117.8, 112.5, 111.2, 55.8, 55.7, 44.2, 34.2, 23.6 (2C); HRMS (ESI): Calcd for $C_{27}H_{28}N_3O_4$ $[M+H]^+$, 458.2080; Found, 458.2082.

***N*-(3-(5-(3,5-Dichlorophenyl)-1,3,4-oxadiazol-2-yl)phenyl)-2-(3,4-dimethoxyphenyl)acetamide (3k). Synthesized according to the General procedure D.** White solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.59 (s, 2H), 3.72 (s, 3H), 3.75 (s, 3H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.96 (s, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.84~7.86 (m, 2H), 7.92 (s, 1H), 8.08 (s, 1H), 8.09 (s, 1H), 8.42 (s, 1H), 10.38 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.8, 164.5, 161.9, 148.5, 147.7, 140.1, 135.2 (2C), 131.3, 130.0, 128.0, 126.5, 125.1 (2C), 123.4, 122.6, 121.7, 121.1, 116.8, 113.1, 111.8, 55.5, 55.4, 42.9. HRMS (ESI): Calcd for $C_{24}H_{20}Cl_2N_3O_4$ $[M+H]^+$, 484.0831; Found, 484.0871.

***N*-(3-(5-(3-Chloro-4-methylphenyl)-1,3,4-oxadiazol-2-yl)phenyl)-2-(3,4-dimethoxyphenyl)acetamide (3l). Synthesized according to the General procedure D.** White solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.72 (s, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 6.83-6.88 (m, 3H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.77-7.79 (m, 2H), 7.83 (dd, J_1 = 1.5 Hz, J_2 = 7.9 Hz, 1H), 8.01 (d, *J* = 1.4 Hz, 1H), 8.07 (s, 1H), 8.18 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 164.2, 163.6, 149.3, 148.5, 140.3, 138.7, 135.1, 131.5, 129.7, 127.2, 126.6, 124.9, 124.1, 123.2, 122.6 (2C), 121.6, 117.9, 112.5, 111.6, 55.8 (2C), 44.1, 20.2; HRMS (ESI): Calcd for $C_{25}H_{23}ClN_3O_4$ $[M+H]^+$, 464.1377; Found, 464.1377.

2-(3,4-Dimethoxyphenyl)-*N*-(3-(5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenyl)acetamide (3m). Synthesized according to the General procedure D. White solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.59 (s, 2H), 3.71 (s, 3H), 3.74 (s, 3H), 3.92 (s, 3H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.96 (s, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.91 (d, *J* = 6.8 Hz, 1H), 8.41 (s, 1H), 10.39 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.8, 163.8, 162.8, 157.5, 148.6, 147.7, 140.1, 133.6, 130.2, 130.0, 128.0, 123.8, 122.1, 121.2, 121.1, 120.8, 116.7, 113.1, 112.7, 112.2, 111.9, 56.1, 55.5 (2C), 42.9; HRMS (ESI): Calcd for $C_{25}H_{24}N_3O_5$ $[M+H]^+$, 446.1716; Found, 446.1731.

***N*-(3-(5-(2-Chlorophenyl)-1,3,4-oxadiazol-2-yl)phenyl)-2-(3,4-dimethoxyphenyl)acetamide (3n). Synthesized according to the General procedure D.** White solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.63 (s, 2H), 3.75 (s, 3H), 3.78 (s, 3H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.99 (s, 1H), 7.56~7.63 (m, 2H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.75~7.80 (m, 2H), 7.88 (d, *J* = 8.1 Hz, 1H), 8.12 (d, *J* = 7.7

Hz, 1H), 8.46 (s, 1H), 10.45 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.9, 164.3, 162.2, 148.5, 147.7, 140.2, 133.3, 131.8, 131.3, 131.2, 130.1, 128.0, 127.9, 123.5, 122.5, 122.4, 121.4, 121.1, 116.8, 113.1, 111.8, 55.5 (2C), 42.9; HRMS (ESI): Calcd for $C_{24}H_{21}ClN_3O_4$ $[M+H]^+$, 450.1215; Found, 450.1212.

3-Nitrobenzohydrazide (4). Methyl 3-nitrobenzoate (18.1 g, 0.1 mol) was dissolved in dioxane (50 mL). To this solution, 85% hydrazine hydrate (23.5 g, 0.4 mol) was added. After stirring at reflux for 6 h, the reaction mixture was concentrated in vacuo to give **4** as a yellow solid without any purification.

***N'*-(4-Methylbenzoyl)-3-nitrobenzohydrazide (5i), synthesized according to the General procedure A.** White solid; Yield: 67%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H), 7.32 (d, J = 7.2 Hz, 2H), 7.84-7.86 (m, 3H), 8.36 (d, J = 7.6 Hz, 1H), 8.44 (d, J = 8.0 Hz, 1H), 8.75 (s, 1H), 10.56 (s, 1H), 10.88 (s, 1H); Calcd for $C_{15}H_{14}N_3O_4$ $[M+H]^+$, 300.0979; Found, 300.0976.

2-(3-Nitrophenyl)-5-*p*-tolyl-1,3,4-oxadiazole (6i), synthesized according to the General procedure B. White solid; Yield: 86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 7.36 (d, J = 6.8 Hz, 2H), 7.76 (s, 1H), 8.04 (d, J = 7.3 Hz, 2H), 8.40 (d, J = 7.3 Hz, 1H), 8.50 (d, J = 7.1 Hz, 1H), 8.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 162.4, 148.7, 142.9, 132.4, 130.4, 129.9 (2C), 127.1 (2C), 125.9, 125.7, 121.6, 120.6, 21.7; HRMS (ESI): Calcd for $C_{15}H_{12}N_3O_3$ $[M+H]^+$, 282.0873; Found, 282.0869.

3-(5-*p*-Tolyl-1,3,4-oxadiazol-2-yl)aniline (7i). Synthesized according to the General procedure C. White solid; Yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.82 (s, 2H), 6.77 (s, 1H), 7.19-7.42 (m, 5H), 7.93 (d, J = 7.6 Hz, 2H); HRMS (ESI): Calcd for $C_{15}H_{13}N_3NaO$ $[M+Na]^+$, 274.0956; Found, 274.0999.

2-(4-Chlorophenyl)-*N*-(3-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)phenyl)acetamide (8). Synthesized according to the General procedure D. White solid; mp 211-213 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.40 (s, 3H), 3.69 (s, 2H), 7.35~7.38 (m, 4H), 7.43 (d, J = 8.0 Hz, 2H), 7.54 (t, J = 8.0 Hz, 1H), 7.77~7.81 (m, 2H), 7.97 (d, J = 8.1 Hz, 2H), 8.41 (s, 1H), 10.47 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.2, 164.1, 163.7, 142.2, 140.0, 134.7, 131.4, 131.1 (2C), 130.0 (2C), 129.5, 128.2 (2C), 126.5 (2C), 123.8, 122.2, 121.4, 120.6, 116.7, 42.4, 21.1; HRMS (ESI): Calcd for $C_{23}H_{19}ClN_3O_2$ $[M+H]^+$, 404.1166; Found, 404.1277.

2-*p*-Tolyl-*N*-(3-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)phenyl)acetamide (9). Synthesized according to the General procedure D. White solid; mp 195-197 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.27 (s, 3H), 2.47 (s, 3H), 3.62 (s, 2H), 7.13 (d, J = 7.7 Hz, 2H), 7.23 (d, J = 7.7 Hz, 2H), 7.53 (t, J = 7.9 Hz, 1H), 7.78 (d, J = 7.7 Hz, 2H), 7.81 (d, J = 7.7 Hz, 2H), 7.97 (d, J = 7.9 Hz, 2H), 8.42 (s, 1H), 10.42 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.2, 164.5, 164.2, 142.7, 141.5, 140.5, 136.1, 133.1, 130.4 (2C), 129.4 (2C), 129.3 (2C), 127.0 (2C), 124.2, 122.6, 121.7, 121.0, 117.1, 43.4, 21.6, 21.1; HRMS (ESI): Calcd for $C_{24}H_{22}N_3O_2$ $[M+H]^+$, 384.1712; Found, 384.1751.

2-(3,4-Dihydroxyphenyl)-*N*-(3-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)phenyl)acetamide (10). 3a (0.1 g, 0.23 mmol) was dissolved in DCM (10 mL) and cooled to -20 °C. To the solution was added the solution of BBr_3 (1 mmol) in DCM (1 mL). After stirring at -20 °C for 8 h, the solution was washed by water and dry over anhydrous Na_2SO_4. The resultant solution was then evaporated in vacuo to give **10**. White solid; Yield: 0.09 g (92%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.61 (s, 2H), 3.73 (s, 3H), 3.76 (s, 3H), 6.88~6.92 (m, 2H), 6.97 (s, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 7.1 Hz, 1H), 8.45 (s, 1H), 10.34 (s, 1H), 10.46 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.8, 163.5, 163.3, 156.3, 148.6, 147.7, 140.1, 133.4, 129.9, 128.7, 128.0, 123.6, 122.3, 121.1 (2C), 119.7, 117.1, 116.7, 113.2, 111.9, 109.5, 55.5 (2C), 42.9; HRMS (ESI): Calcd for $C_{24}H_{21}N_3O_5$ $[M+Na]^+$, 454.1379; Found, 454.1399.

2-(3-Nitrophenyl)-5-*p*-tolyl-1,3,4-thiadiazole (11a). 6i (1.62 g, 5.42 mmol) and Lawesson's reagent (2.42 g, 6 mmol) were suspended in anhydrous THF (20 mL). The mixture was heated to reflux for 6 h. The reaction mixture was cooled to rt and then filtrated. The cake was collected, washed with EtOH and ether and dried in oven to give **11a.** Yellow solid; Yield: 0.88g (55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.70 (t, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 8.34 (d, *J* = 8.1 Hz, 1H), 8.38 (d, *J* = 8.1 Hz, 2H), 8.79 (s, 1H); HRMS (ESI): Calcd for $C_{15}H_{12}N_3O_2S$ $[M+H]^+$; 298.0650; Found, 298.0677.

4-Benzyl-3-(3-nitrophenyl)-5-*p*-tolyl-4*H*-1,2,4-triazole (11b). To a mixture of $BnNH_2$ (5 mL), TsOH (0.25 g) and mesitylene (25 mL), **6i** (1.7 g, 6.0 mmol) was added. The mixture was heated to reflux for 13 h. After cooled to rt, the mixture was filtrated. The filter cake was collected and dissolved in DCM (30 mL). After removing the insoluble solid by filtration, the filtrate was concentrated and purified by column chromatography (DCM / EtOAc = 10:1) to give **11b**. White solid; Yield: 1.03 g (46%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H), 5.33 (s, 2H), 6.90 (d, *J* = 4.9 Hz, 2H), 7.24~7.30 (m, 5H), 7.52 (d, *J* = 6.4 Hz, 2H), 7.57 (s, 1H), 7.95 (s, 1H), 8.24 (d, *J* = 7.3 Hz, 1H), 8.38 (s, 1H); HRMS (ESI): Calcd for $C_{22}H_{19}N_4O_2$ $[M+H]^+$, 371.1508; Found, 371.1535.

2-(3-Nitrophenyl)-4-*p*-tolylthiazole (11c). 14 (0.2 g, 1.1 mmol) and **12** (0.22 g, 1.1 mmol) were dissolved in EtOH (10 mL). The solution was then heated to reflux for 3 h. After cooling to rt, white precipitate emerged immediately. The precipitate was filtered and dried in oven to give **11c**. White solid; Yield: 0.2 g (61%). HRMS (ESI): Calcd for $C_{16}H_{13}N_2O_2S$ $[M+H]^+$, 296.0698; Found, 296.0677.

2-(3-Nitrophenyl)-4-*p*-tolyloxazole (11d) and 2-(3-nitrophenyl)-4-*p*-tolyl-1*H*-imidazole (11e). The solution of **15** and ammonium acetate in acetic acid was refluxed for 6 h and then poured into ice water before a mass of light yellow precipitate appeared. The solid was collected by filtration and purified by column chromatography (hexane / EtOAc = 10 / 1) to give **11d** (White solid; Yield: 0.1 g, 18%) and **11e**

(White solid; Yield: 0.15 g, 26.8%). **11d**: HRMS (ESI): Calcd for $C_{16}H_{13}N_2O_3$ $[M+H]^+$, 281.0926; Found 281.0885. **11e**: HRMS (ESI): Calcd for $C_{16}H_{14}N_3O_2$ $[M+H]^+$, 280.1086; Found: 280.1092.

2-(3-Nitrophenyl)-5-*p*-tolyloxazole (11f). 18 (0.3 g, 1 mmol) was refluxed in $POCl_3$ (10 mL) for 3 h. After evaporating in vacuo the resultant residue was diluted with DCM (10 mL) and then poured into ice water. The DCM phase was separated and washed with saturated aqueous $NaHCO_3$. After drying over anhydrous Na_2SO_4, the solution was evaporated in vacuo to give **11f**. White solid; Yield: 0.28 g (99%). Calcd for $C_{16}H_{13}N_2O_3$ $[M+H]^+$, 281.0926; Found: 281.0913.

2-(3-Nitrophenyl)-5-*p*-tolylthiazole (11g). The mixture of **18** (0.3 g, 1.0 mmol) and Lawesson's reagent (0.8 g, 2.0 mmol) in dry THF (15 mL) was refluxed for 3 h. After being evaporated in vacuo the resultant residue was purified by column chromatography (hexane / EtOAc = 10/1) to give **11g**. White solid; Yield: 0.2 g (66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 7.25 (d, J = 7.8 Hz, 2H), 7.51 (d, J = 6.3 Hz, 2H), 7.63-7.66 (m, 1H), 8.00 (s, 1H), 8.24-8.30 (m, 2H), 8.79 (s, 1H).

5-(3-Nitrophenyl)-3-*p*-tolyl-1,2,4-oxadiazole (11h). To a solution of **20h** (0.8 g, 5.3 mmol) in 2-picoline (6 mL) was added 3-nitrobenzoyl chloride (6.4 mmol) at 0~5 °C. After stirring at rt overnight, a mass of precipitate emerged. The solid was collected by filtration and then refluxed in toluene for 3 h. The reaction mixture was then concentrated in vacuo and was washed with hexane. The resultant solid was dried in oven to give **11h.** White solid; Yield: 0.65 g (43%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (s, 3H), 7.26-7.29 (m, 2H), 7.75 (t, J = 7.7Hz, 1H), 7.99 (d, J = 7.7 Hz, 2H), 8.41(d, J = 7.8 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 169.1, 148.4, 141.8, 133.4, 130.3, 129.5 (2C), 127.3 (2C), 126.8, 125.7, 123.3, 123.0, 122.9; HRMS (ESI): Calcd for $C_{15}H_{12}N_3O_3$ $[M+H]^+$, 282.0879; Found, 282.0877.

3-(3-Nitrophenyl)-5-*p*-tolyl-1,2,4-oxadiazole (11i). White solid; **11i** was synthesized from 3-nitrobenzonitrile according to the synthesis method of **11h**.

2-Bromo-1-*p*-tolylethanone (12). To the solution of 4-methylacetophenone (2.68 g, 20 mmol) in MeOH was added two drops of hydrobromic acid. A solution of bromine (1 mL, 20 mmol) in MeOH (10 mL) was added dropwise. After stirring at rt for 3 h, the reaction mixture was concentrated to afford **9**. Yellow solid; Yield: 3.7 g (92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 4.37 (s, 2H), 2.37 (s, 3H).

3-Nitrobenzamide (13). To 30% ammonium hydroxide (60 mL) was added a solution of 3-nitrobenzoyl chloride (2.5 g, 15 mmol) in toluene (20 mL). White precipitate emerged immediately. The resultant precipitate was filtered and dried in oven to give **10**. White solid; Yield: 1.5g (60%).

3-Nitrobenzothioamide (14). 13 (0.4 g, 2.4 mmol) and P_2S_5 (0.54 g, 2.4 mmol) were dissolved in THF (20 mL). The solution was then heated to reflux for 3 h. After cooling to rt the reaction mixture was concentrated in vacuum and then purified by column chromatography (hexane / DCM = 1 / 1) to give **14**.

Yellow solid; Yield: 0.2 g (46%). HRMS (ESI): Calcd for $C_7H_7N_2O_2S$ $[M+H]^+$, 183.0228; Found, 183.0200.

2-Oxo-2-*p*-tolylethyl 3-nitrobenzoate (15). 3-Nitrobenzoic acid (2.17 g, 13 mmol), **12** (2.5 g, 12.5 mmol) and DBU (1.9 g, 12.5 mmol) were dissolved in DMF. After heating at 60 °C for 3 h, the reaction mixture was poured into water (100 mL), extracted by Et_2O, and dried over anhydrous Na_2SO_4. Purification by column chromatography (hexane / EtOAc = 10 / 1) afforded **15**. White solid; Yield: 2.5 g (67%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.91 (s, 1H), 8.40 (d, J = 8.0 Hz, 2H), 7.96 (s, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.63 (s, J = 8.0 Hz, 1H), 7.25 (s, J = 8.0 Hz, 1H), 5.56 (s, 2H), 2.38 (s, 3H). HRMS (ESI): Calcd for $C_{16}H_{14}NO_5$ $[M+H]^+$, 300.0872; Found, 300.0833.

2-Azido-1-*p*-tolylethanone (16). To a solution of **12** (1 g, 5 mmol) in DMF (20 mL) was added NaN_3 (1 g, 15 mmol). After stirring at rt for 4 h, water (100 mL) was added to reaction mixture, and the mixture was extracted by EtOAc, dried over anhydrous Na_2SO_4 and evaporated in vacuo to give a light yellow liquid **16**. Yield: 0.85 g (97 %).

2-Amino-1-*p*-tolylethanone (17). 10% Pd/C (0.08 g, moisture: 50%) was suspended in a solution of **16** (0.85 g, 4.9 mmol) in a mixture of concentrated hydrogen chloride (2 mL) and MeOH (20 mL). After stirring at rt in hydrogen atmosphere overnight, the reaction mixture was filtered. The resultant filtration was evaporated in vacuo and recrystallized from EtOAc (20 mL) to give **17**. White solid; Yield: 0.6 g (82%).

3-Nitro-*N*-(2-oxo-2-*p*-tolylethyl)benzamide (18). To a mixture of **17** (4 mmol) and triethylamine (0.9 mL, 6 mmol) in DCM (20 mL) was added dropwise the solution of 3-nitrobenzoyl chloride (4 mmol) in DCM (20 mL) at 0-5 °C. After stirring at 0-5 °C overnight, the reaction mixture was washed with 10% aqueous Na_2CO_3, 1N HCl and brine successfully and then dried over anhydrous Na_2SO_4. The resultant solution was evaporated in vacuo and purified by column chromatography (hexane / EtOAc = 5 / 1) to give **18**. White solid; Yield: 0.8 g (67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 4.96 (d, J = 4.4 Hz, 2H), 7.34 (d, J = 8.0 Hz, 1H), 7.41 (brs, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 2H), 8.22 (d, J = 8.4 Hz, 1H), 8.39 (d, J = 8.4 Hz ,1H), 8.74 (s, 1H).

***N'*-Hydroxy-4-methylbenzimidamide (20h).** 4-Methylbenzonitrile (3.6 g, 30.7 mmol), K_2CO_3 (4.4 g, 31.9 mmol) and hydroxylamine hydrochloride (3 g, 43.1 mmol) were suspended in EtOH (50 mL). The mixture was then heated to reflux for 8 h. After cooling to rt, the mixture was filtered and then evaporated in vacuo and purified by column chromatography (DCM / EtOAc = 5/1) to give **20h**. White solid; Yield: 3.69 g (80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.29 (s, 3H), 5.78 (s, 2H), 7.16 (d, J = 8.0 Hz, 2H), 7.57(d, J = 8.0 Hz, 2H), 9.61 (brs, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 150.9, 138.3, 130.6, 129.4, 129.2, 128.7, 125.4, 20.9. HRMS (ESI): Calcd for $C_8H_{11}N_2O$ $[M+H]^+$, 151.0866; Found, 151.0813.

2-(3,4-Dimethoxyphenyl)-*N*-(3-(5-*p*-tolyl-1,3,4-thiadiazol-2-yl)phenyl)acetamide (24a). Synthesized according to the General procedure D. White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43(s, 3H), 3.73 (s, 2H), 3.90 (s, 3H), 3.92 (s, 3H), 6.85 (s, 1H), 6.89~6.91 (m, 2H), 7.29~7.32 (m, 3H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.99 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.8, 167.8, 167.3, 148.6, 147.7 141.6, 140.2, 131.7, 130.0 (2C), 129.9, 128.1, 127.6 (2C), 126.8, 122.4, 121.7, 121.1, 117.6, 113.1, 111.9, 55.5 (2C), 42.9, 21.0; HRMS (ESI): Calcd for $C_{25}H_{24}N_3O_3S$ $[M+H]^+$, 446.1533; Found, 446.1532.

***N*-(3-(4-Benzyl-5-*p*-tolyl-4*H*-1,2,4-triazol-3-yl)phenyl)-2-(3,4-dimethoxyphenyl)acetamide (24b). Synthesized according to the General procedure D.** White solid; mp 82-84 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.34 (s, 3H), 3.57 (s, 2H), 3.72 (s, 3H), 3.74 (s, 3H), 5.37 (s, 2H), 6.72 (d, *J* = 6.5 Hz, 2H), 6.83-6.95 (m, 3H), 7.16-7.18 (m, 3H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 7.5 Hz, 2H), 8.01 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.7, 155.3, 154.9, 148.6, 147.7, 139.8, 139.7, 136.1, 129.5 (2C), 129.4, 128.8 (2C), 128.6 (2C), 128.2, 127.8, 127.6, 125.7 (2C), 124.5, 122.9, 121.2, 120.6, 119. 6, 113.1, 111.9, 55.6, 55.5, 47.7, 42.9, 20.9; HRMS (ESI): Calcd for $C_{32}H_{31}N_4O_3$ $[M+H]^+$, 519.2396; Found, 519.2413.

2-(3,4-Dimethoxyphenyl)-*N*-(3-(4-*p*-tolylthiazol-2-yl)phenyl)acetamide (24c). Synthesized according to the General procedure D. White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.70 -7.66 (m , 3H), 7.39 -7.36 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.90 (m, 2H), 6.84 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.72 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 167.1, 156.4, 149.5, 148.7, 138.4, 138.1, 134.4, 131.7, 129.6, 129.4 (2C), 126.7, 126.4 (2C), 122.6, 121.8, 121.4, 117.5, 112.6, 112.2, 111.8, 55.9 (2C), 44.4, 21.3. HRMS (ESI): Calcd for $C_{26}H_{25}N_2O_3S$ $[M+H]^+$, 445.1586; Found: 445.1555.

2-(3,4-Dimethoxyphenyl)-*N*-(3-(4-*p*-tolyloxazol-2-yl)phenyl)acetamide (24d). Synthesized according to the General procedure D. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.73 (s, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 6.84 (s, 1H), 6.92 (m, *J* = 7.5 Hz, 2H), 7.42 (m, *J* = 8.0 Hz, 1H), 7.38-7.42 (m, 2H), 7.68 (d, *J* = 7.9 Hz, 2H), 7.79-7.83 (m, 3H), 7.91 (s, 1H), 7.93 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 161.2, 149.6, 148.7, 142.1, 138.1, 138.0, 133.1, 129.5, 129.4, 128.1, 126.5, 125.5, 122.3, 121.8, 121.7, 117.4, 112.5, 111.8, 55.9 (2C), 44.4, 20.8. HRMS (ESI): Calcd for $C_{26}H_{25}N_2O_4$ $[M+H]^+$, 429.1814; Found: 429.1817.

2-(3,4-Dimethoxyphenyl)-*N*-(3-(4-*p*-tolyl-1*H*-imidazol-2-yl)phenyl)acetamide (24e). Synthesized according to the General procedure D. White solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.51 (s, 2H), 3.75 (s, 3H), 3.79 (s, 3H), 6.66-6.79 (m, 3H), 7.05-7.11 (m, 4H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.47-7.50 (m, 3H), 7.87 (s, 1H), 8.19 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 161.2, 149.2, 148.4,

146.6, 137.9, 136.7 (2C), 130.9, 129.4, 129.3(2C), 126.6 (2C), 124.7, 121.7, 121.6, 120.1, 117.1, 112.4, 111.5, 55.8 (2C) , 43.9, 21.2. HRMS (ESI): Calcd for $C_{26}H_{26}N_3O_3$ $[M+H]^+$, 428.1974; Found: 428.1979.

2-(3,4-Dimethoxyphenyl)-*N*-(3-(5-*p*-tolyloxazol-2-yl)phenyl)acetamide (24f). Synthesized according to the General procedure D. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.72 (s, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 6.85 (s, 1H), 6.89 (m, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.35 (s, 1H), 7.38-7.42 (m, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.96 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 160.2, 151.7, 149.5, 148.6, 138.6, 138.2, 129.6 (2C), 128.0 (2C), 126.4 (2C), 125.0, 124.2, 122.6, 122.1, 121.8, 121.6, 117.1, 112.4, 111.7, 55.9 (2C), 44.4, 21.4. HRMS (ESI): Calcd for $C_{26}H_{25}N_2O_4$ $[M+H]^+$, 429.1736; Found: 429.1716.

2-(3,4-Dimethoxyphenyl)-*N*-(3-(5-*p*-tolylthiazol-2-yl)phenyl)acetamide (24g). Synthesized according to the General procedure D. White solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.71 (s, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 6.84 (s, 1H), 6.89 (m, 2H), 7.21 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.87 (s, 1H), 7.94 (s, 1H). HRMS (ESI): Calcd for $C_{26}H_{25}N_2O_3S$ $[M+H]^+$, 445.1586; Found: 445.1576.

2-(3,4-Dimethoxyphenyl)-*N*-(3-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)phenyl)acetamide (24h). Synthesized according to the General procedure D. White solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.40 (s, 3H), 3.62 (s, 2H), 3.74 (s, 3H), 3.77 (s, 3H), 6.88-6.92 (m, 3H), 6.99 (s, 1H), 7.40 (d, *J* = 6.5 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 6.5 Hz, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.98 (d, *J* = 6.5 Hz, 2H), 8.55 (s, 1H), 10.45 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 175.2, 170.0, 168.2, 148.6, 147.7, 141.6, 140.2, 130.1, 129.8 (2C), 128.0 (2C), 127.0 (2C), 123.8, 123.4, 122.4, 121.2, 117.9, 113.1, 111.8, 55.5 (2C), 43.0, 21.1; HRMS (ESI): Calcd for $C_{25}H_{24}N_3O_4$ $[M+H]^+$, 430.1767; Found, 430.1761.

2-(3,4-Dimethoxyphenyl)-*N*-(3-(5-*p*-tolyl-1,2,4-oxadiazol-3-yl)phenyl)acetamide (24i). Synthesized according to the General procedure D. White solid; mp 178-180 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.44 (s, 3H), 3.60 (s, 2H), 3.73 (s, 3H), 3.76 (s, 3H), 6.87-6.92 (m, 2H), 6.97 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 2H), 8.42 (s, 1H), 10.36 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 175.4, 169.7, 168.1, 148.6, 147.7, 143.7, 140.0, 130.0 (2C), 129.6, 128.1, 127.8 (2C), 126.6, 121.8, 121.7, 121.1, 120.6, 117.5, 113.1, 111.9, 55.5, 55.4, 42.9, 21.1; HRMS (ESI): Calcd for $C_{25}H_{24}N_3O_4$ $[M+H]^+$, 430.1767; Found, 430.1761.

2-(3,4-Dimethoxyphenyl)-*N*-(3-(5-*p*-tolyl-4*H*-1,2,4-triazol-3-yl)phenyl)acetamide (25). The triazole **22b** (0.12 g, 0.28 mmol) and 10% Pd/C (moisture: 50%, 20 mg) were suspended in MeOH (10 mL), the mixture was hydrogenated at 2.5 MPa for 24 h. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to give **23**. mp 208-211 ^{o}C; Yield: 98 mg (99%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.36 (s, 3H), 3.65 (s, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 6.85-6.92 (m, 4H), 6.99 (s, 1H), 7.33

(d, J = 8.0 Hz, 2H), 7.42 (t, J = 7.9 Hz, 1H), 7.74 (t, J = 7.8 Hz, 1H), 7.97 (d, J = 8.0 Hz, 2H), 8.36 (s, 1H), 10.37 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.5, 148.5, 147.6, 139.7, 139.3, 129.4 (2C), 129.1, 128.9, 128.3, 125.9 (2C), 121.1, 121.0, 120.7, 119.9, 116.8, 113.1, 113.0, 111.9, 111.8, 55.5 (2C), 42.9, 20.9; HRMS (ESI): Calcd for $C_{25}H_{25}N_4O_3$ $[M+H]^+$, 429.1927; Found, 429.1923.

Biological activity against fructose-1,6-diphosphatase (FBPase). FBPase recombinant protein was expressed and purified according to previous report.[29] FBPase activity was measured in a coupled spectrophotometric assay containing 5 mM $MgCl_2$, 66.7 mM KCl, 66.7 mM MOPS pH 7.5, 0.25 mM $NADP^+$, yeast glucose-6-phosphate-dehydrogenase (0.4 U/mL), yeast phosphoglucoisomerase (0.7 U/mL) and 325 nmol/L FBPase. Fructose 6-phosphate formed by the reaction of FBPase was converted to glucose 6-phosphate and subsequently to 6-phosphogluconate by coupling to phosphoglucoisomerase and glucose-6-dehydrogenase and the concomitant formation of NADPH was detected at 340 nm.

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