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Synthesis, Antimicrobial Activity, and Molecular Docking of Benzoic Hydrazide or Amide Derivatives Containing a 1,2,3-Triazole Group as Potential SDH Inhibitors

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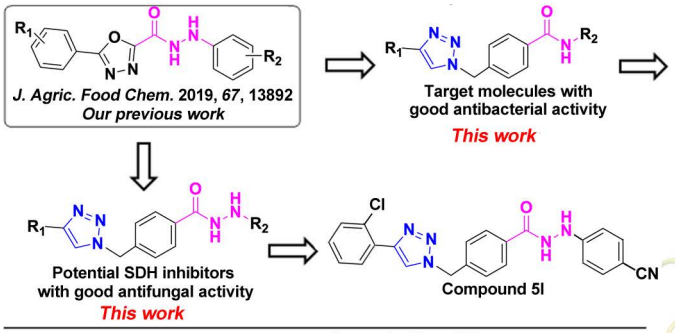
Keywords

Hydrazide | Amide | 1,2,3-Triazole | Molecular docking | SDH inhibitory activity

Main observation and conclusion

The present study was carried out in an attempt to synthesize a new class of antimicrobial agents containing a 1,2,3-triazole motif formed by classical copper catalyzed click chemistry. Antifungal bioassay results showed that five compounds **5a**, **5e**, **5h**, **5j**, and **5k** possessed a remarkable growth inhibitory activity against *Botryosphaeria dothidea*, *Rhizoctonia solani* and *Gibberella zeae* with EC_{50} values within 10.0—0.306 μg/mL. The *in vitro* efficacy was better than those of the commercial agrochemicals Azoxystrobin, Boscalid, and Fluxapyroxad. *In vivo* trials showed that compound **5l** was effective for the control of rice sheath blight and wheat scab with the effects of 75% and 95%, respectively. Antifungal mechanism studies suggested that target compounds were potential succinate dehydrogenase inhibitors (SDHIs), which were proposed by the agreeable molecular docking study and restrained SDH activity (IC_{50} = 3.95 μg/mL, **5l**). Interestingly, compounds **5r** and **5s** displayed good antibacterial activity against phytopathogens. *In vivo* screening of **5r** and **5s** against rice bacterial blight afforded a superior control effect (up to 51%) than those of commercial agents Bismerthiazol and Thiodiazole copper. The current studies could support some title compounds to be the lead compounds for exploring highly bioactive antimicrobial substrates, particularly the potential SDHIs.

Comprehensive Graphic Content



Compounds	Control effects (%)			
	Rice sheath blight		Wheat scab	
	100 μg/mL	200 μg/mL	100 μg/mL	200 μg/mL
5k	10	30	40	65
5l	65	75	45	95
Boscalid	100	100	10	15
Fluopicolide	70	85	80	85

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Background and Originality Content

As the population continues to grow, food security has once again become a rigid demand.[1-4] Among the many factors contributing to food shortages, plant microbial diseases cause a dramatic decline in crop quality and yield, as a result of which farmers suffer huge economic losses.[5-6] Pathogenic fungi, such as *Botryosphaeria dothidea* (*B. d.*), *Rhizoctonia solani* (*R. s.*), *Colletotrichum gloeosporioides* (*C. g.*) and *Gibberella zeae* (*G. z.*) are the most damaging plant parasitic organisms, which can cause serious degrees of diseases on the various types of crops; followed by pathogenic bacteria, including the disreputable strains *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), *Pseudomonas syringae* pv. *actinidiae* (*Psa*), and *Xanthomonas axonopodis* pv. *citri* (*Xac*). Currently, chemical pesticide is still the main helper for controlling plant microbial diseases, however, the progressively reduced effectiveness as well as resistance generated by pathogenic microorganisms have always plagued people and resulted in an increasing number of infections.[7-8] Furthermore, the emergence and pullulation of multidrug-resistant microbial strains have complicated the situation.[9-13] Therefore, novel and efficient pesticides with unique modes of action are urgently developed to manage plant microbial diseases.

Exploring new pesticides based on identified targets can promote and accelerate the discovery of alternatives to traditional agrochemicals. Succinate dehydrogenase (SDH), which involves in the respiration chain and Krebs cycle and catalyzes the oxidation of succinate to fumarate in the mitochondrial matrix, has been definitely recognized as one of the most important molecular targets in the development of new fungicides.[14-18] Since the first commercial SDHI carboxin was launched in 1966,[19] a total of twenty-three SDHI fungicides have been created with broad fungicidal spectrum and promising market prospects.[20-23] Careful observation found that these structures include a conserved amide moiety (−CO-NH−) as the linker to combine substituted benzoic/pyrazol/pyridyl/pyrazinyl/furyl acids and most substituted aniline/thiophenine/pyridinamine, and naturally leading to a relatively monotonous molecular skeleton.[24-25] Thereby, resistance is rapidly emerged and developed, and more than ten kinds of pathogens were reported to have high resistance to SDHIs.[26-27] To solve this problem, novel SDHIs bearing multifarious frameworks must be explored. Consequently, extensive works for the design of alternatives based on these commercial SDHIs (especially the pyrazole amides) were performed and afforded certain similar structures with admirable bioactivity.[28-41] On the other hand, fabrication of fresh molecular frameworks to break the original molecular skeleton of current SDHIs is highly approved.

Investigation reveals that triazole fungicides with their derivatives have been persistently studied in view of the versatile triazole moiety acting as a crucial bioactive nucleus.[42-47] Among these flexible and multifarious triazoles, 1,2,3-triazole which can be easily fabricated by Cu(I)-catalyzed click chemistry reaction with Huisgen 1,3-dipolecycloaddition[48-49] has aroused great interests due to its derivatives bearing diverse pharmacological activities including antibacterial,[50-51] antifungal,[52-53] anticancer,[54] antitubercular,[55] and anti-HIV[56] activities. Especially, some 1,2,3-triazole compounds (Figure 1) have been commercialized as the *β*-lactamase inhibitor (Tazobactam acid),[57] antibacterial drug (Cefatrizine),[58] anticancer drug (Carboxyamidotriazole),[59] and anticonvulsant drug (Rufinamide).[60] Notably, the incorporation of 1,2,3-triazole as the promising pharmacophore to the target compound might promote the discovery of new fungicides differentiating from the current structures of SDHIs.[61] Additionally, our previous work has discovered 1,3,4-oxadiazole-2-carbohydrazides as potential SDHIs with significant antifungal activities.[62] In this work, we reserved the carbohydrazide motif and incorporated the 1,2,3-triazole scaffold to the target compounds (Figure 1) to explore new SDHIs with prospective antifungal effects both *in vitro* and *In vivo*. Meanwhile, the broadened bioactive potentials against plant pathogenic bacteria were also screened.

Results and Discussion

Chemistry. The synthesis of 1,2,3-triazole-tailored benzoic hydrazide derivatives **5a**—**5n** was executed by four steps and illustrated in Figure 2. Initially, intermediate **4** was prepared by stepwise substitution reaction, click cyclization reaction, and hydrolysis reaction, which was then reacted with substituted phenylhydrazines under the classical condensating agent to afford the target compounds, which were confirmed by NMR, HRMS, and the crystal structure of compound **5m** (Figure 3 and Table 1). As a comparison for the bioactivity, compounds **5o**—**5s** bearing the amide bond were also constructed.

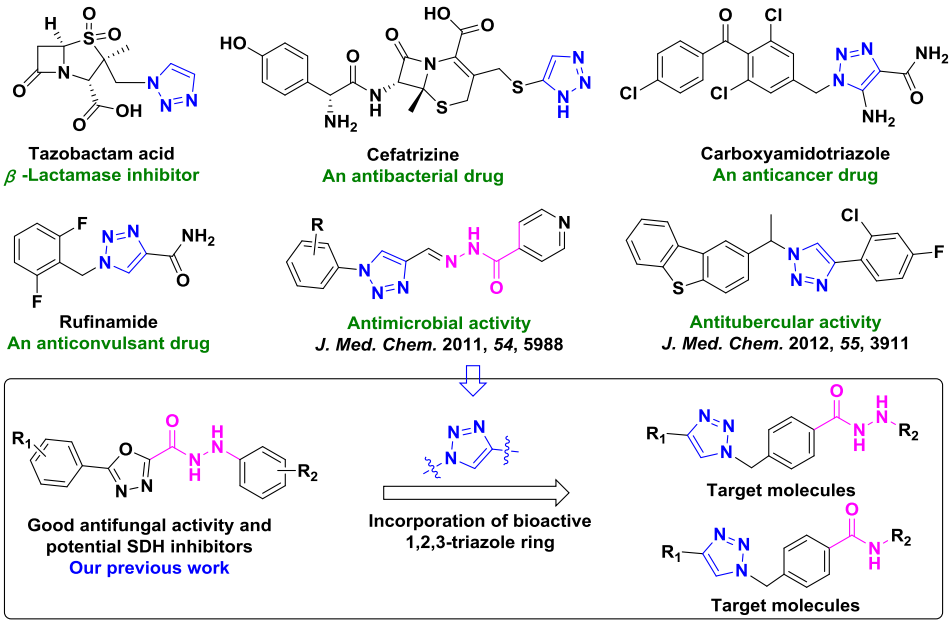

Figure 1 Commercial drugs and bioactive compounds containing the 1,2,3-triazole moiety and design strategy for title compounds.

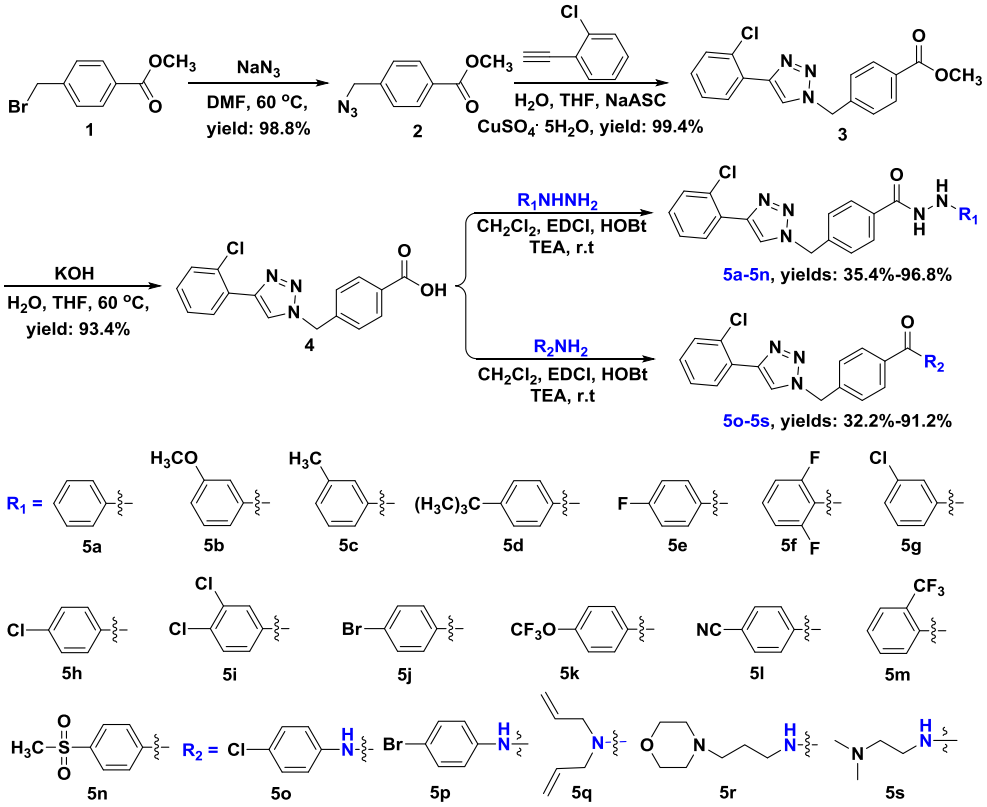

Figure 2 Synthetic route for title compounds **5a**—**5s**.

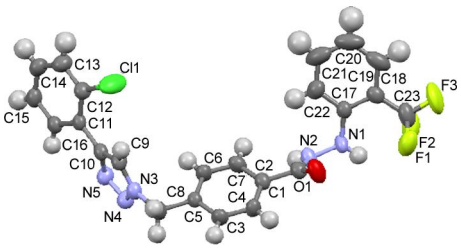

Figure 3 X-ray crystal structure of target compound **5m**.

Table 1 Crystal data and structural refinement parameters of **5m**

Compound	**5m**
Formula	$C_{23}H_{17}ClF_3N_5O$
CCDC number	2055076
Crystal system	Monoclinic
Space group	*P*2(1)/*n*
a/Å	11.0683(9)
b/Å	17.3757(13)
c/Å	11.3045(9)
α/(°)	90.00
β/(°)	97.739(10)
γ/(°)	90.00
V/Å^3	2154.3(3)
Z	4
Calculated density/(g·cm^{-3})	1.455
F (000)	968
Reflections collected/unique	10672/3798 [*R*(int) = 0.0457]
Goodness-of-fit on F^2	1.020
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0508, wR_2 = 0.1136
R indices (all data)	R_1 = 0.1131, wR_2 = 0.1362

***In vitro* antifungal activity.** Antifungal screening against *B. d.*, *R. s.*, *C. g.* and *G. z.* was carried out by the classical mycelium growth rate method, and Azoxystrobin (AS), Boscalid (BS) and Fluopyram (FP) were used as the positive agrochemicals. The preliminary screening result at 50 μg/mL (Table 2) demonstrated that compounds **5a** (-H), **5e** (4-F), **5h** (4-Cl), **5j** (4-Br), and **5k** (4-OCF_3) were bioactive against *B. d.* with the inhibitory rates within 67.5%—77.9%, which were comparative to AS (77.3%) and FP (67.9%), and superior to BS (55.8%); compounds **5h** (4-Cl), **5j** (4-Br), **5k** (4-OCF_3), and **5l** (4-CN) presented good anti-*R. s.* activity with the values of 62.2%—70.2%, which were better than AS (37.5%) and FP (18.2%), but lower than BS (83.6%); compounds **5a** (-H), **5b** (3-OCH_3), **5g** (3-Cl), and **5i** (3,4-diCl) displayed a moderate anti-*C. g.* activity with inhibitory values within 50.8%—58.3%, which were similar with that of AS (59.8%), but quite lower than BS (94.2%) and FP (94.8%); compound **5e** afforded an excellent anti-*G. z.* activity with the rate of 92.6%, which was quite better than AS (65.7%), BS (26.4%), and FP (74.2%). The EC_{50} values of bioactive compounds were determined and filled in Table 3. Clearly, compounds **5h** (4-Cl), **5j** (4-Br), **5k** (4-OCF_3), and **5l** (4-CN) provided the EC_{50} values of 2.95, 3.55, 1.55, and 3.87 μg/mL against *R. s.*, respectively, which were lower than that of BS (1.01 μg/mL). The EC_{50} of compound **5e** (4-F) against *G. z.* could reach 0.306 μg/mL, which was quite better than FP (3.47 μg/mL). Meanwhile, compounds **5e** (4-F), **5h** (4-Cl), **5j** (4-Br) and **5k** (4-OCF_3) displayed excellent activities against *B. d.* with EC_{50} of 0.404, 0.526, 1.09, and 1.03 μg/mL, respectively, which exceeded those of commercial agents AS (2.30 μg/mL) and FP (24.1 μg/mL). To visualize the inhibitory effect, the mycelium growth maps of *B. d.* on agar medium triggered by compound **5e** (0.404 μg/mL) was presented in Figure 4. Distinctly, the hypha growth and extension of *B. d.* was dramatically restricted with enhancing the concentration of compound **5e**, indicating that the designed compounds were endowed with perceptible antifungal competency. By contrast, compounds **5o**—**5p** bearing an amide bond yielded insignificant

Table 2 Antifungal activities of compounds **5a**—**5s** against pathogens *B. d.*, *R. s.*, *C. g.*, and *G. z. in vitro* at 50.0 μg/mL

No.	Inhibition rate/%			
	B. d.	*R. s.*	*C. g.*	*G. z.*
3	56.8 ± 1.5	31.0 ± 1.2	43.1 ± 2.5	0
4	48.8 ± 0.7	27.0 ± 1.2	39.4 ± 0.0	0
5a	70.5 ± 1.9	44.3 ± 2.0	58.3 ± 1.2	67.6 ± 0.3
5b	43.4 ± 1.0	49.6 ± 1.2	53.5 ± 5.7	35.2 ± 1.2
5c	14.8 ± 0.1	0	12.5 ± 1.0	0
5d	56.0 ± 0.7	28.4 ± 0.1	27.3 ± 0.1	0
5e	77.9 ± 1.0	0	0	92.6 ± 0.2
5f	22.1 ± 1.7	10.5 ± 0.1	12.5 ± 1.8	36.1 ± 1.6
5g	35.0 ± 1.0	28.2 ± 0.1	50.8 ± 2.0	53.4 ± 0.5
5h	70.5 ± 1.8	70.2 ± 0.1	49.2 ± 1.5	39.8 ± 0.2
5i	0	47.6 ± 4.3	57.6 ± 0.1	39.8 ± 0.2
5j	67.5 ± 0.6	68.2 ± 0.1	48.2 ± 1.2	57.4 ± 0.8
5k	73.8 ± 0.1	69.2 ± 1.1	48.2 ± 2.3	29.6 ± 0.6
5l	36.9 ± 6.0	62.2 ± 0.1	21.2 ± 0.1	43.7 ± 1.4
5m	21.9 ± 1.6	0	0	9.26 ± 0.17
5n	12.6 ± 0.4	16.4 ± 0.0	0	0
5o	0	0	0	0
5p	0	0	0	0
5q	29.0 ± 1.2	56.9 ± 1.2	37.0 ± 2.2	56.2 ± 5.3
5r	0	0	0	0
5s	58.5 ± 1.9	11.7 ± 1.2	42.1 ± 3.2	26.2 ± 0.9
AS	77.3 ± 0.8	37.5 ± 0.9	59.8 ± 0.8	65.7 ± 3.0
BS	55.8 ± 0.4	83.6 ± 1.0	94.2 ± 0.8	26.4 ± 2.5
FP	67.9 ± 0.4	18.2 ± 0.5	94.8 ± 0.5	74.2 ± 3.8

Table 3 EC_{50} values of target compounds **5a**, **5e**, **5h**, **5j** and **5k** against tested fungi *in vitro*

No.	Pathogens	Toxic regression equation	EC_{50}/(μg·mL^{-1})
5a	*B. d.*	$y = 0.523x + 4.626$	5.19 ± 0.07
	G. z.	$y = 1.597x + 3.402$	10.0 ± 0.78
5e	*B. d.*	$y = 1.944x + 5.766$	0.404 ± 0.005
	G. z.	$y = 0.836x + 5.430$	0.306 ± 0.174
5h	*B. d.*	$y = 0.827x + 5.231$	0.526 ± 0.037
	R. s.	$y = 0.511x + 4.760$	2.95 ± 0.13
5j	*B. d.*	$y = 1.356x + 4.952$	1.09 ± 0.02
	R. s.	$y = 0.523x + 4.713$	3.55 ± 0.41
5k	*B. d.*	$y = 1.501x + 4.984$	1.03 ± 0.01
	R. s.	$y = 1.410x + 4.732$	1.55 ± 0.04
5l	*R. s.*	$y = 0.345x + 4.797$	3.87 ± 0.22
AS	*B. d.*	$y = 0.367x + 4.867$	2.30 ± 0.06
BS	*R. s.*	$y = 1.760x + 4.920$	1.01 ± 0.03
FP	*B. d.*	$y = 0.439x + 4.394$	24.1 ± 0.9
	G. z.	$y = 0.345x + 4.813$	3.47 ± 0.65

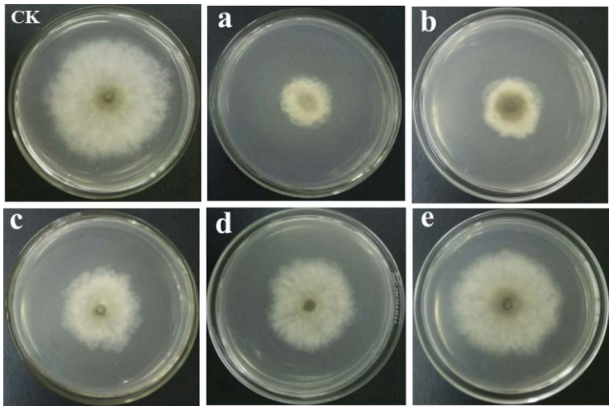

Figure 4 The mycelium growth and extension of *B. d.* after treatment with different concentrations of compound **5e** on the agar medium: CK) 0 μg/mL; a) 4.0 μg/mL; b) 2.0 μg/mL; c) 1.0 μg/mL; d) 0.5 μg/mL; e) 0.25 μg/mL.

bioactivity after replacing the hydrazide moiety; while compounds **5q** and **5s** possessing the alkylamine substituents showed moderate inhibition effect against *R. s.* (56.9%), *G. z.* (56.2%), and *B. d.* (58.5%), respectively.

The structure-activity relationship (SAR) was proposed based on the above screening results: (1) the substituent at the 4-position is beneficial to antifungal activity, such as **5a** (3-Cl, 35.0%) and **5h** (4-Cl, 70.5%) against *B. d.*; (2) multi-substituents on the benzene ring can block the inhibitory effect, illustrated by **5i** (3,4-diCl, 0 and 47.6%) and **5h** (4-Cl, 70.5% and 70.2%) against *B. d.* and *R. s.*, respectively, **5f** (2,6-diF, 22.1% and 36.1%) and **5e** (4-F, 77.9% and 92.6%) against *B. d.* and *G. z.*, respectively; (3) the type of halogen showed the order of 4-F (EC_{50} = 0.404 μg/mL, **5e**) > 4-Cl (EC_{50} = 0.526 μg/mL, **5h**) > 4-Br (EC_{50} = 1.03 μg/mL, **5j**) against *B. d.*; (4) introducing the weak electron-withdrawing group promotes the bioactivity, for example, 4-F (**5e**) on the benzene ring affords the minimum EC_{50} values of 0.404 and 0.306 μg/mL against the corresponding fungi *B. d.* and *G. z.*; (5) the amide bond significantly reduces the bioactivity, for instance, **5h** (CONHNH, 70.5%, 70.2%, 49.2%, 39.8%) and **5o** (CONH, 0), **5j** (CONHNH, 67.5%, 68.2%, 48.2%, 57.4%) and **5p** (CONH, 0). In general, the fabricated compounds bearing 1,2,3-triazole group could be considered as antifungal leads.

In vivo* antifungal activity toward *R. s.* and *G. z. *In vivo* trial against rice sheath blight (caused by *R. s.*) was evaluated by Shenyang Sinochem Agrochemicals R&D Co., Ltd. (Shenyang, China), and compounds **5k** and **5l** with good anti-*R. s.* effects (69.2% and 62.2% at 50 μg/mL *in vitro*, respectively) along with BS and FP served as the positive drugs were used (Table 4). The result showed available control effects were afforded for compound **5l** with 75% and 65% at 200 and 100 μg/mL, respectively, which were comparable to that of FP (85% and 70%). By contrast, com-

pound **5k** gave the lower efficacy (30% and 10%). Moreover, the bioassay against wheat scab (caused by *G. z.*) of **5k** and **5l** was also evaluated, which displayed good control effects of 65% and 95% at 200 μg/mL (FP gave the effect of 85%), respectively. As the dosage decreased to 100 μg/mL, the effectiveness reduced to the corresponding 40% and 45%. These outcomes suggested the designed compounds could be regarded as antifungal leads for further investigations.

Molecular docking analysis and inhibitory activity of SDH. To expound the designed compounds as potential SDHIs, molecular docking study between SDH (PDB entry: 2FBW) and compounds **5k**, **5l**, and Boscalid was performed. As displayed in Figure 5, compounds **5k** and **5l**, and commercial SDHI Boscalid located in the same binding pocket of SDH and displayed interactions with amino acid residues of SDH, indicating that the designed compounds might be potential SDHIs. For compound **5k**, the nitrogen atoms from the hydrazide group formed two hydrogen bonds with the key residue Ser39 with the bond lengths of 2.8 and 3.2 Å, respectively (Figure 5A). In comparison, two nitrogen atoms from 1,2,3,-triazole motif of compound **5l** yielded strong hydrogen bonds with the residues Trp173 (bond lengths 3.1 and 3.3 Å) and Tyr58 (bond lengths 3.1 and 3.0 Å) of SDH (Figure 5B), suggesting that 1,2,3,-triazole group could be considered as a functional tool to promote the interactions targeting SDH. Additionally, the 4-cyanophenyl moiety of compound **5l** formed an extra π–π stacking interaction with the residue Trp-32, deeply promoting the interactions with SDH. For the commercial SDHI Boscalid, two hydrogen bonds between the carbonyl group and Trp173 (bond length 3.0 Å) and Tyr58 (bond length 3.1 Å) and one hydrogen bond between the nitrogen atom of pyridinyl group and Ser39 (bond length 2.9 Å) were observed (Figure 5C). This outcome indicated that compound **5l** afforded more similarity with that of Boscalid in the binding mode with SDH, which was in agreement with the *in vivo* bioassay result that compound **5l** was more bioactive than that of compound **5k**. Furthermore, the SDH enzymatic activity in *R. s.* strain was obviously suppressed by compound **5l** with the IC_{50} value of 3.95 μg/mL (For the Boscalid, IC_{50} = 3.15 μg/mL, Table 5), confirming that title compounds could act as the potential SDHIs.

***In vitro* antibacterial activity.** The antibacterial activities of compounds **5a**—**5s** towards *Xoo*, *Xac*, and *Psa* were also evaluated

Table 4 Control effects of **5k** and **5l** against rice sheath blight and wheat scab *in vivo*

No.	Control effect/%			
	Rice sheath blight		Wheat scab	
	100 μg/mL	200 μg/mL	100 μg/mL	200 μg/mL
5k	10	30	40	65
5l	65	75	45	95
BS	100	100	10	15
FP	70	85	80	85

Table 5 SDH inhibitory effects of **5l** and Boscalid in *R. s.* strain

No.	Regression equation	*r*	IC_{50}/(μg·mL^{-1})
5l	$y = 2.743x + 3.363$	0.99	3.95 ± 0.23
Boscalid	$y = 4.776x + 2.622$	0.99	3.15 ± 0.02

to exploit other potential applications, and Bismerthiazol (BT) and Thiodiazole copper (TC) were used as positive agrochemicals. Preliminary screening results showed that target compounds afforded poor, moderate to good inhibitory effects (Table 6). At the doses of 100 and 50 μg/mL, compounds **5r** and **5s** bearing the corresponding 4-propylmorpholine and *N,N*-dimethylethanamine patterns owned the best antibacterial capacity, providing the inhibition rates of 99.4% and 68.1%, 98.6% and 30.0% against *Xoo*, 88.7% and 80.0%, 97.0% and 89.3% against *Xac*, and 50.6% and 43.7%, 55.7% and 42.3% against *Psa*, respectively. This finding indicated that the flexible alkylamine substituents might benefit the antibacterial potency. Meanwhile, compounds **5c**, **5i**, **5j**, **5m**, and **5q** gave moderate anti-*Xac* activity with the inhibitory values within 52.5%—64.0% at 100 μg/mL, while compound **5h** bearing a 4-methylsulfonyl group showed certain anti-*Psa* activity with the rate of 54.1% at 100 μg/mL. Subsequently, the EC_{50} values of highly bioactive molecules **5r** and **5s** were further screened and presented values of 28.2 and 60.7 μg/mL against *Xoo* and 34.4 and 17.9 μg/mL against *Xac*, respectively, which were comparable to the commercial agents BT and TC (Table 7).

***In vivo* antibacterial activity toward rice bacterial blight.** *In vivo* antibacterial activity of compounds **5r** and **5s** against rice bacterial blight (caused by *Xoo*) was performed (Table 8 and Figure 6). Interestingly, although the *in vitro* activity of **5s** was weaker than that of **5r**, compound **5s** showed excellent *in vivo* bactericidal activity in potted rice with curative and protective activities of 51.05% and 49.25%, respectively. This effect was better than those of compound **5r** (42.48% and 46.99%), BT (37.40% and 40.79%), and TC (32.33% and 39.09%), demonstrating that the amide series compounds could be regarded as antibacterial leads.

Conclusions

In conclusion, a type of benzoic hydrazide or amide derivatives containing a valuable 1,2,3-triazole motif was developed and biologically screened against plant pathogens. Antifungal bioassays indicated that target compounds were extremely bioactive against the notorious strains *B. d.*, *G. z.*, and *R. s.* with the minimal EC_{50} values of 0.404, 0.306, and 1.55 μg/mL, respectively. *In vivo* assays confirmed that compound **5l** was effective for the control of rice sheath blight and wheat scab with the corresponding efficiencies of 75% and 95%. The subsequent molecular docking studies showed that the five-membered 1,2,3,-triazole ring of **5l** could form strong hydrogen bonds with the amino acid residues

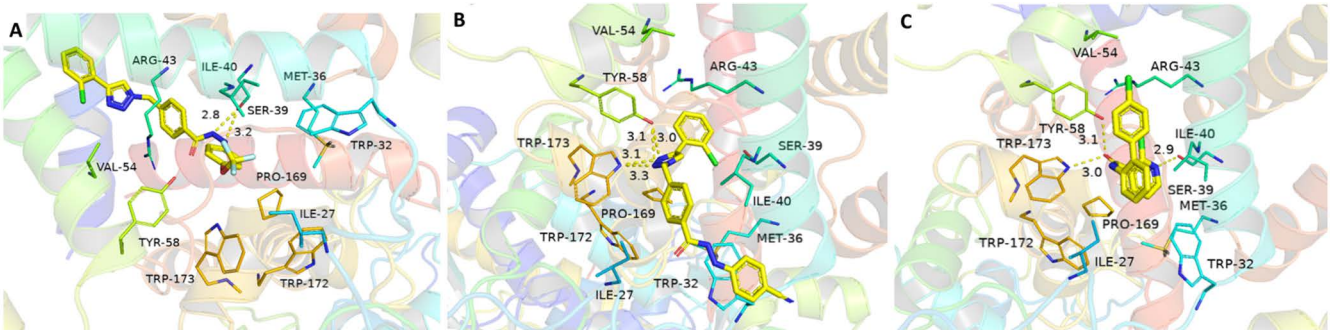

Figure 5 Molecular docking and binding sites of compounds **5k** (A), **5l** (B), and Boscalid (C) with SDH (PDB entry: 2FBW).

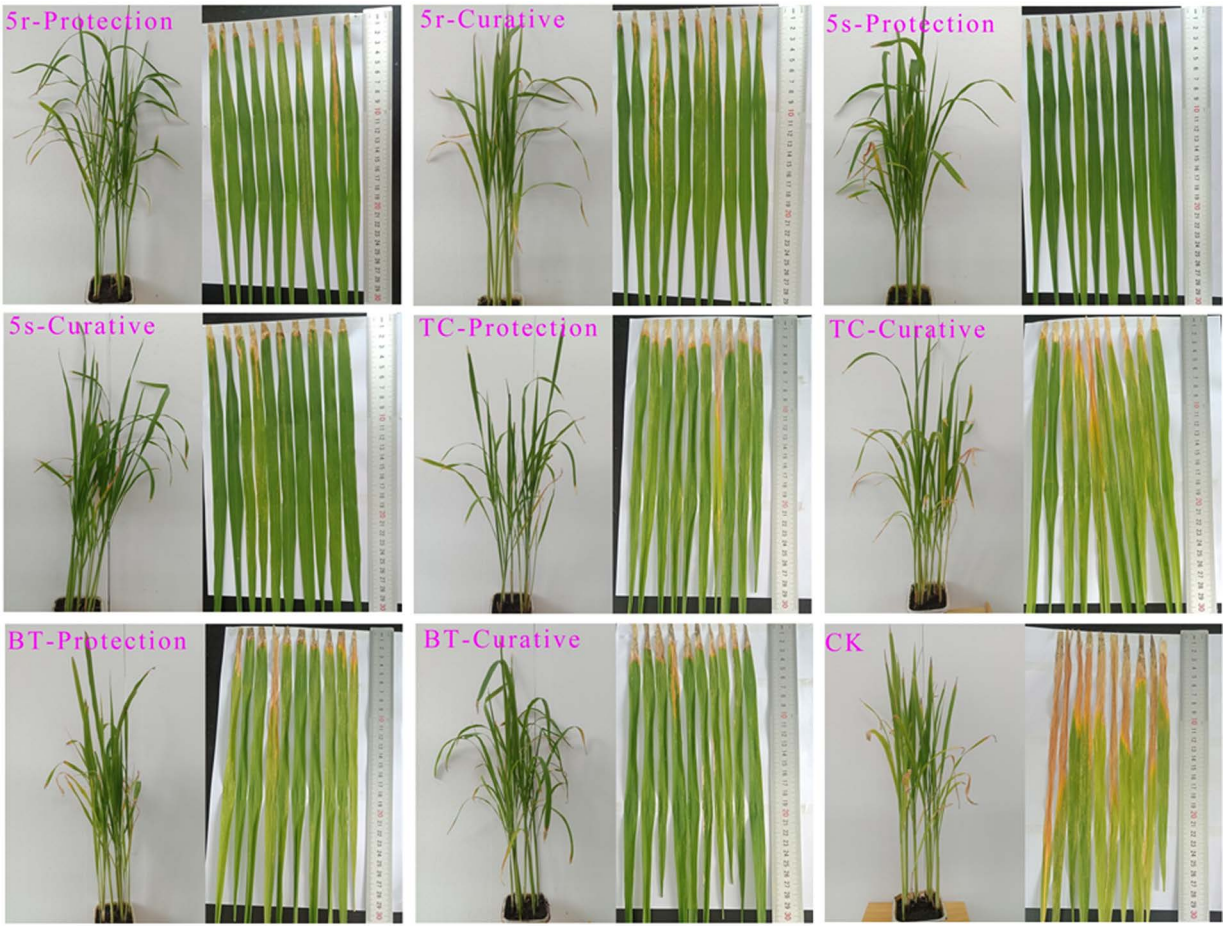

Figure 6 Control effects of **5r**, **5s**, BT, and TC against rice bacterial blight under greenhouse conditions at 200 μg/mL.

Table 6 Preliminary inhibitory effects of target compounds **5a**—**5s** against *Xoo*, *Xac*, and *Psa*

No.	***Xoo***, Inhibition/%		***Xac***, Inhibition/%		***Psa***, Inhibition/%	
	100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL
3	28.3 ± 5.0	19.3 ± 1.5	52.8 ± 4.1	24.6 ± 1.1	23.0 ± 0.7	17.2 ± 1.4
4	26.6 ± 5.0	17.0 ± 4.6	35.9 ± 2.5	26.2 ± 1.1	16.0 ± 1.0	0
5a	34.8 ± 2.7	14.4 ± 5.6	39.6 ± 5.2	26.8 ± 3.9	34.6 ± 4.4	13.4 ± 4.3
5b	39.6 ± 4.8	30.9 ± 3.6	44.1 ± 5.8	33.8 ± 3.3	45.4 ± 3.0	32.6 ± 1.5
5c	27.6 ± 1.7	18.4 ± 2.2	53.6 ± 0.9	34.2 ± 4.0	47.5 ± 3.7	31.8 ± 7.1
5d	38.3 ± 8.1	16.9 ± 5.2	39.0 ± 4.8	24.8 ±3.4	43.9 ± 3.9	17.6 ± 5.5
5e	19.4 ± 6.1	9.66 ± 1.2	34.9 ± 3.8	22.0 ± 3.4	41.0 ± 3.7	29.4 ± 6.8
5f	12.5 ± 1.8	0	45.8 ± 5.6	36.6 ± 6.6	30.5 ± 9.7	22.2 ± 2.7
5g	38.7 ± 6.6	28.4 ± 3.7	47.0 ± 5.7	30.6 ± 6.5	31.5 ± 0.4	25.4 ± 6.4
5h	29.0 ± 4.1	20.1 ± 2.5	48.1 ± 2.8	39.3 ± 1.1	54.1 ± 0.4	46.0 ± 4.1
5i	22.6 ± 4.1	15.7 ± 7.8	53.7 ± 2.1	44.1 ± 5.9	34.2 ± 1.3	20.5 ± 3.5
5j	40.6 ± 4.4	27.3 ± 1.5	55.2 ± 2.6	40.6 ± 7.6	42.9 ± 3.0	21.9 ± 2.0
5k	47.8 ± 2.1	30.2 ± 3.3	13.8 ± 1.0	0	0	0
5l	17.4 ± 4.4	12.1 ± 2.9	42.4 ± 7.1	31.3 ± 1.5	25.1 ± 6.5	14.0 ± 4.5
5m	37.8 ± 1.7	20.6 ± 7.4	52.5 ± 5.2	41.4 ± 3.4	45.4 ± 3.5	36.0 ± 1.1
5n	17.5 ± 1.3	0	38.4 ± 4.2	27.2 ± 4.4	32.2 ± 2.0	12.9 ± 3.4
5o	39.8 ± 1.1	25.2 ± 0.2	34.7 ± 1.4	27.6 ± 5.7	26.6 ± 4.3	21.1 ± 7.4
5p	24.5 ± 4.5	10.9 ± 2.6	27.7 ± 1.9	13.8 ± 6.2	16.6 ± 3.3	9.56 ± 1.76
5q	44.9 ± 1.8	22.7 ± 6.8	64.0 ± 6.4	57.7 ± 2.8	49.5 ± 2.2	39.1 ± 4.5
5r	**99.4 ± 0.4**	68.1 ± 9.5	**88.7 ± 3.5**	**80.0 ± 3.7**	50.6 ± 6.8	43.7 ± 3.4
5s	**98.6 ± 0.5**	30.0 ± 4.1	**97.0 ± 1.7**	**89.3 ± 0.8**	55.7 ± 4.3	42.3 ± 6.3
TC	51.0 ± 2.1	38.8 ± 2.3	57.9 ± 2.7	36.2 ± 0.3	57.3 ± 0.8	46.6 ± 2.0
BT	100 ± 1.2	100 ± 0.4	99.8 ± 0.3	49.5 ± 2.2	24.7 ± 0.2	0

Table 7 EC_{50} values of target compounds **5r** and **5s** against *Xoo* and *Xac in vitro*

No.	*Xoo*			*Xac*		
	Toxic regression equation	*r*	EC_{50}/(μg·mL^{-1})	Toxic regression equation	*r*	EC_{50}/(μg·mL^{-1})
5r	$y = 5.930x - 3.602$	0.99	28.2 ± 0.1	$y = 1.485x + 2.718$	0.99	34.4 ± 1.3
5s	$y = 6.331x - 6.289$	0.99	60.7 ± 0.8	$y = 2.235x + 2.200$	1	17.9 ± 0.2
TC	$y = 4.105x - 2.740$	1	76.8 ± 2.2	$y = 1.706x + 1.885$	0.97	67.0 ± 0.5
BT	$y = 5.069x - 2.625$	0.93	31.9 ± 3.6	$y = 1.893x + 1.776$	0.98	50.5 ± 2.1

Table 8 *In vivo* control effects of **5r** and **5s** against rice bacterial blight at 200 μg/mL

No.	Curative activity (14 days after spraying)			Protective activity (14 days after spraying)		
	Morbidity/%	Disease index/%	Control efficiency[b]/%	Morbidity/%	Disease index/%	Control efficiency[b]/%
5r	100	48.57	42.48B	100	44.76	46.99A
5s	100	41.33	51.05A	100	42.86	49.25A
BT	100	52.86	37.40B	100	50.00	40.79B
TC	100	57.14	32.33B	100	51.43	39.09B
CK[a]	100	84.44	—	100	84.44	—

[a] Negative control. [b] Statistical analysis was conducted via the ANOVA method under a condition of equal variances assumed ($P > 0.05$) and equal variances not assumed ($P < 0.05$). Different uppercase letters indicate the values of control efficiency with significant difference among different treatment groups at $P < 0.05$.

Trp173 and Tyr58 of SDH, which yielded the similar binding sites with the commercial SDHI Boscalid, suggesting the designed compounds were potential SDHIs, consequently validated by the highly restrained SDH activity (IC_{50} = 3.95 μg/mL, **5l**). Antibacterial results manifested that the amide series compounds **5r** and **5s** could not only significantly suppress the growth of *Xoo* and *Xac in vitro*, but also display appreciable *in vivo* efficacy against rice bacterial blight disease. This study could support some of the hydrazide series compounds as the potential SDHIs and the amide series compounds as the antibacterial leads.

Experimental

Instruments

Using the DMSO-d_6 or $CDCl_3$ as the solvent, and TMS as the internal standard, ^{1}H NMR and ^{13}C NMR spectra were generated from the Varian Mercury 500 MHz or a Bruker Biospin AG-400 spectrometer. The mass spectra were analyzed by Agilent mass spectrometer. The melting points were measured by the SGW® X-4B, Shanghai Yidian Physical Optical Instrument Co., Ltd.

Antifungal activity assay

Compared with the commercially available SDHIs Azoxystrobin, Boscalid and Fluxapyroxad, the synthesized compounds were screened for their antifungal activities *in vitro* against *B. d.*, *R. s.*, *C. g.*, *G. z.* following our previously reported method.[62] The *in vivo* fungicidal activities of the synthesized compounds against *R. s.* and *G. z.* were carried out by Shenyang Sinochem Agrochemicals R&D Co. Ltd.

Molecular docking study towards SDH

All reported SDHs are highly reserved in their spatial structure, subunit and electron transport pathway, as well as the ubiquinone binding site in the prokaryotes and eukaryotes. For these reasons, avian (Gallus gallus) respiratory complex II with carboxin bound (PDB code: 2FBW) was chosen for the molecular docking study.[33,63] The 3D structures of the title compounds (**5k** and **5l**) with good antifungal activity and positive control Boscalid were constructed by Sybyl X 2.0. Molecular docking studies were also performed using the Sybyl X 2.0. All the water molecules and ligand were eliminated from this crystal complex protein and the polar hydrogens were added to the protein.[28,64] The results indicated that the combination of **5l** with SDH was superior to that of **5k**, and the hydrogen bonds formed were nearly consistent with that of Boscalid.

SDH inhibitory assay

The SDH enzyme activity affected by **5l** was determined by spectrophotometer using the SDH Activity Detection Kit (Solabio, BC0955). *R. s.* was treated by compound **5l** with different concentrations and grew in potato dextrose medium on a constant temperature shaker (180 r/min, 28 °C) for two weeks, while Boscalid and DMSO were used as the controls at the same conditions. The fungal hyphae was collected by vacuum filtration, then washed with water and PBS (10 mmol/L, pH 7.2) 2—3 times, respectively, and stored in an refrigerator under −80 °C after freeze-drying. After that, the samples were ground in a tissue grinder and then subjected to SDH enzyme activity test by using the Assay Kit.

Antibacterial activity assay

The experimental procedures of *in vitro* and *in vivo* antibacterial bioassays were performed by our previously reported methods.[65-67]

Synthetic procedure and characterization data

Synthesis of intermediate 2 (methyl 4-(azidomethyl)benzoate). Sodium azide (7.10 g, 0.11 mol), methyl 4-(bromomethyl)-benzoate (5.00 g, 21.83 mmol) and *N,N*-dimethylformamide (DMF, 14 mL) were added into a 25 mL round-bottom flask. Then the mixture system was reacted at 60 °C for 4 h. After that, the mixture was added with 60 mL ethyl acetate. The organic layer was washed with saturated NH_4Cl, water, dried with anhydrous sodium sulfate, filtered, followed by the removal of the solvent under vacuum. The residue was further purified by column chromatography on a silica gel using petroleum ether and ethyl acetate (12 : 1, *V*/*V*) as the eluent to afford the intermediate **2,** a white solid, yield 98.8%.

Synthesis of intermediate 3 (methyl 4-((4-(2-chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)benzoate). Intermediate **2** (4.00 g, 20.92 mmol) and 1-chloro-2-ethynylbenzene (2.60 g, 19.02 mmol) were dissolved in 10 mL dry THF, then 10 mL water was added. Then $CuSO_4 \cdot 5H_2O$ (0.48 g, 1.90 mmol) and sodium ascorbate (0.75 g, 3.80 mmol) were firstly dissolved in water (8.0 mL) and added

into the above reaction system. The mixture was stirred for 14 h at room temperature. After that, the mixture was added with 60 mL ethyl acetate. The organic layer was washed with water, brine, dried with sodium sulfate, filtered, followed by removal of the solvent under vacuum. The residue was further purified by column chromatography on a silica gel using petroleum ether and ethyl acetate (20 : 1, *V*/*V*) as the eluent to afford the intermediate **3**.

Methyl 4-((4-(2-chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-benxzoate (3). A white solid, yield 99.4%; m. p. 209.1—209.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.23 (dd, *J* = 7.9, 1.7 Hz, 1H, 2-Cl-phenyl-H), 8.15 (s, 1H, triazole-H), 8.03–8.00 (m, 2H, benzene-H), 7.40 (dd, *J* = 8.0, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.36—7.33 (m, 2H, benzene-H), 7.33—7.31 (m, 1H, 2-Cl-phenyl-H), 7.24 (ddd, *J* = 9.1, 6.6, 1.3 Hz, 1H, 2-Cl-phenyl-H), 5.65 (s, 2H, CH_2), 3.89 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 166.5, 144.6, 139.6, 131.2, 130.6, 130.4, 130.3, 129.8, 129.2, 129.1, 127.8, 127.3, 123.4, 53.8, 52.4.

Synthesis of intermediate 4 (4-((4-(2-chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)benzoic acid). Intermediate **3** (4.30 g, 13.12 mmol) dissolved in 20 mL dry THF and KOH (1.10 g, 19.68 mmol) dissolved in water (20.0 mL) were separately added into the reaction bottle. The mixture was heated to 60 °C for 10 h. After that, the solvent was removed under vacuum, followed by adding a small amount of water. The pH of the solution was adjusted to 3—4 with dilute hydrochloric acid. Then the system was cooled in an ice bath for 30 min and subsequently resulted in the formation of abundant white precipitates. Finally, the precipitates were filtered and dried to afford the desired product **4**.

4-((4-(2-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)benzoic acid (4). A white solid, yield: 93.4%, m.p. 208.5—209.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.04 (s, 1H, COOH), 8.82 (s, 1H, triazole-H), 8.09 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-phenyl-H), 7.96 (d, *J* = 8.3 Hz, 2H, benzene-H), 7.56 (dd, *J* = 7.9, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.48—7.44 (m, 2H, benzene-H), 7.44 (d, *J* = 2.5 Hz, 1H, 2-Cl-phenyl-H), 7.41—7.35 (m, 1H, 2-Cl-phenyl-H), 5.80 (s, 2H, CH_2); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 167.4, 143.3, 141.3, 131.0, 130.8, 130.7, 130.3, 130.0, 129.5, 128.4, 128.0, 125.2, 53.0.

Synthesis of title compound 5a (4-((4-(2-chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*'-phenylbenzohydrazide). Intermediate **4** (0.20 g, 0.64 mmol), EDCI (0.24 g, 1.27 mmol) and HOBT (0.09 g, 0.64 mmol) were dissolved in 8 mL CH_2Cl_2 and triethylamine (0.13 g, 1.27 mmol). Then the reaction was stirred at room temperature for 10 min, followed by adding phenylhydrazine hydrochloride (0.11 g, 0.76 mmol). The mixture was stirred for another 12—24 h at room temperature. After that, the solvent was removed under vacuum followed by adding 40 mL ethyl acetate. The organic layer was washed with water, brine, dried with sodium sulfate, filtered, followed by removal of the solvent under vacuum. The pure product **5a** could be obtained by column chromatography using petroleum ether and ethyl acetate (1 : 1) as eluent. The synthesis of **5b—5s** was carried out by the same method for **5a**.

4-((4-(2-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*'-phenylbenzohydrazide (5a). A yellow solid, yield: 86.4%, m.p. 200.2—200.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.37 (s, 1H, CONH), 8.82 (s, 1H, triazole-H), 8.09 (d, *J* = 7.7 Hz, 1H, 2-Cl-phenyl-H), 7.98—7.89 (m, 3H, CO-benzene-H & CONHNH), 7.58 (d, *J* = 7.9 Hz, 1H, 2-Cl-phenyl-H), 7.49 (d, *J* = 6.6 Hz, 2H, CO-benzene-H), 7.45 (d, *J* = 7.7 Hz, 1H, 2-Cl-phenyl-H), 7.39 (t, *J* = 7.6 Hz, 1H, 2-Cl-phenyl-H), 7.14 (t, *J* = 7.7 Hz, 2H, benzene-H), 6.78 (d, *J* = 7.2 Hz, 2H, benzene-H), 6.71 (t, *J* = 7.3 Hz, 1H, benzene-H), 5.79 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.4, 149.9, 143.4, 140.0, 133.3, 130.8, 130.7, 130.0, 129.6, 129.2, 128.4, 128.3, 128.0, 125.2, 119.1, 112.8, 53.0. HRMS (ESI) $[M-H]^-$ calcd for $C_{22}H_{17}ON_5Cl$: 402.1116, found: 402.1125.

4-((4-(2-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*'-(3-methoxyphenyl)benzohydrazide (5b). A white solid, yield: 42.1%, m.p. 134.0—134.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.37 (d, *J* = 2.9 Hz, 1H, CONH), 8.84 (s, 1H, triazole-H), 8.09 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-phenyl-H), 7.98–7.92 (m, 2H, CO-benzene-H), 7.91 (s, 1H, CONHNH), 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.51—7.47 (m, 2H, CO-benzene-H), 7.45 (dd, *J* = 7.7, 1.4 Hz, 1H, 2-Cl-phenyl-H),7.42—7.33 (m, 1H, 2-Cl-phenyl-H), 7.04 (t, *J* = 8.0 Hz, 1H, 3-OCH_3-phenyl-H), 6.37 (dd, *J* = 7.7, 1.6 Hz, 1H, 3-OCH_3-phenyl-H), 6.34—6.26 (m, 2H, 3-OCH_3-phenyl-H), 5.79 (s, 2H, CH_2), 3.66 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.0, 160.1, 151.0, 142.9, 139.6, 132.8, 130.4, 130.3, 129.7, 129.6, 129.5, 129.1, 128.0, 127.8, 127.6, 124.7, 105.1, 104.1, 98.2, 54.8, 52.5. HRMS (ESI) $[M-H]^-$ calcd for $C_{23}H_{19}O_2N_5Cl$: 432.1222, found: 432.1230.

4-((4-(2-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*'-(*m*-tolyl)benzohydrazide (5c). A yellow solid, yield: 96.8%, m.p. 187.8—188.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.37 (s, 1H, CONH), 8.84 (s, 1H, triazole-H), 8.10 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-phenyl-H), 7.93 (d, *J* = 8.3 Hz, 2H, CO-benzene-H), 7.85 (s, 1H, CONHNH), 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.49 (d, *J* = 8.3 Hz, 2H, CO-benzene-H), 7.45 (dd, *J* = 7.7, 1.4 Hz, 1H, 2-Cl-phenyl-H), 7.42—7.35 (m, 1H, 2-Cl-phenyl-H), 7.02 (t, *J* = 7.8 Hz, 1H, 3-CH_3-phenyl-H), 6.58 (d, *J* = 7.6 Hz, 2H, 3-CH_3-phenyl-H), 6.53 (d, *J* = 7.6 Hz, 1H, 3-CH_3-phenyl-H), 5.79 (s, 2H, CH_2), 2.19 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 165.9, 149.59, 142.9, 139.59, 137.9, 132.9, 130.4, 130.3, 129.6, 129.5, 129.1, 128.7, 128.0, 127.9, 127.6, 124.7, 119.6, 112.9, 109.7, 52.6, 21.3. HRMS (ESI) $[M-H]^-$ calcd for $C_{23}H_{19}ON_5Cl$: 416.1273, found: 416.1284.

***N*'-(4-(*tert*-Butyl)phenyl)-4-((4-(2-chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)benzohydrazide (5d).** A white solid, yield: 46.7%, m.p. 191.3—191.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.38 (d, *J* = 2.9 Hz, 1H, CONH), 8.84 (s, 1H, triazole-H), 8.10 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-phenyl-H), 7.92 (d, *J* = 8.3 Hz, 2H, CO-benzene-H), 7.78 (d, *J* = 2.9 Hz, 1H, CONHNH), 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.51—7.47 (m, 2H, CO-benzene-H), 7.46 (dd, *J* = 7.7, 1.4 Hz, 1H, 2-Cl-phenyl-H), 7.43—7.37 (m, 1H, 2-Cl-phenyl-H), 7.16 (d, *J* = 8.7 Hz, 2H, 4-$C(CH_3)_3$-phenyl-H), 6.72 (d, *J* = 8.7 Hz, 2H, 4-$C(CH_3)_3$-phenyl-H), 5.79 (s, 2H, CH_2), 1.21 (s, 9H, 4-$C(CH_3)_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.0, 147.2, 142.9, 141.0, 139.5, 132.9, 130.4, 130.4, 129.6, 129.5, 129.1, 128.0, 127.8, 127.6, 125.4, 124.7, 112.2, 52.6, 33.7, 31.4. HRMS (ESI) $[M-H]^-$ calcd for $C_{26}H_{25}ON_5Cl$: 458.1742, found: 458.1752.

4-((4-(2-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*'-(4-fluorophenyl)benzohydrazide (5e). A yellow solid, yield: 51.9%, m.p. 175.1—175.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.41 (d, *J* = 3.2 Hz, 1H, CONH), 8.83 (s, 1H, triazole-H), 8.09 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-phenyl-H), 7.94 (s, 1H, CONHNH), 7.92 (d, *J* = 2.1 Hz, 2H, CO-benzene-H), 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.48 (dd, *J* = 4.9, 3.5 Hz, 2H, CO-benzene-H), 7.45 (dd, *J* = 7.7, 1.4 Hz, 1H, 2-Cl-phenyl-H), 7.42—7.36 (m, 1H, 2-Cl-phenyl-H), 7.03—6.94 (m, 2H, 4-F-phenyl-H), 6.82—6.75 (m, 2H, 4-F-phenyl-H), 5.79 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.4, 156.4 (d, $^1J_{C\text{-}F}$ = 233.4 Hz), 146.5 (d, $^4J_{C\text{-}F}$ = 1.7 Hz), 143.3, 140.0, 133.2, 130.8, 130.7, 130.0, 129.6, 129.3, 128.4, 128.3, 128.1, 125.2, 115.7 (d, $^2J_{C\text{-}F}$ = 22.3 Hz), 114.0 (d, $^3J_{C\text{-}F}$ = 7.6 Hz), 53.0. ^{19}F NMR (377 MHz, DMSO-d_6) δ: −126.35. HRMS (ESI) $[M-H]^-$ calcd for $C_{22}H_{16}ON_5ClF$: 420.1022, found: 420.1031.

4-((4-(2-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*'-(2-fluoro-6-methylphenyl)benzohydrazide (5f). A white solid, yield: 87.4%, m.p. 194.5—195.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.48 (d, *J* = 1.7 Hz, 1H, CONH), 8.84 (s, 1H, triazole-H), 8.20 (s, 1H, CONHNH), 8.10 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-phenyl-H), 7.95 (d, *J* = 8.3 Hz, 2H, CO-benzene-H), 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.53—7.48 (m, 2H, CO-benzene-H), 7.48—7.43 (m, 1H, 2-Cl-phenyl-H), 7.42—7.35 (m, 1H, 2-Cl-phenyl-H), 7.13 (ddd, *J* = 11.3, 8.8, 5.0 Hz, 1H, 2,6-2F-phenyl-H), 6.61—6.44 (m, 2H, 2,6-2F-phenyl-H), 5.80 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.5, 159.5 (dd, $^1J_{C\text{-}F}$ = 237.5, 1.2 Hz), 146.7 (dd, $^1J_{C\text{-}F}$ = 235.1, 2.0

Hz), 143.3, 140.2, 139.1 (dd, $^{3}J_{C\text{-}F}$ =13.0, 10.8 Hz), 132.9, 130.8, 130.7, 130.0, 130.0, 129.6, 128.5, 128.4, 128.1, 125.2, 116.3 (dd, $^{2}J_{C\text{-}F}$ = 20.3, 10.3 Hz), 104.3 (dd, $^{2}J_{C\text{-}F}$ = 24.4, 7.2 Hz), 100.6 (dd, $^{2}J_{C\text{-}F}$ = 28.9, 3.8 Hz), 53.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ: −117.9, −138.4. HRMS (ESI) $[M-H]^-$ calcd for $C_{22}H_{15}ON_5ClF_2$: 438.0928, found: 438.0938.

***N*'-(3-Chlorophenyl)-4-((4-(2-chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)benzohydrazide (5g).** A yellow solid, yield: 67.0%, m.p. 195.2—195.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.44 (d, *J* = 2.5 Hz, 1H, CONH), 8.83 (s, 1H, triazole-H), 8.25 (d, *J* = 2.5 Hz, 1H, CONHNH), 8.09 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-phenyl-H), 7.94 (d, *J* = 8.3 Hz, 2H, CO-benzene-H), 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.49 (d, *J* = 8.4 Hz, 2H, CO-benzene-H), 7.45 (dd, *J* = 7.6, 1.4 Hz, 1H, 2-Cl-phenyl-H), 7.42—7.36 (m, 1H, 2-Cl-phenyl-H), 7.16 (t, *J* = 8.0 Hz, 1H, 3-Cl-phenyl-H), 6.77—6.73 (m, 2H, 3-Cl-phenyl-H), 6.72 (t, *J* = 1.9 Hz, 1H, 3-Cl-phenyl-H), 5.80 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.4, 151.5, 143.3, 140.2, 134.0, 133.0, 130.9, 130.8, 130.7, 130.0, 129.6, 128.5, 128.4, 128.1, 125.2, 118.6, 112.0, 111.4, 53.0. HRMS (ESI) $[M-H]^-$ calcd for $C_{22}H_{16}ON_5Cl_2$: 436.0726, found: 436.0739.

4-((4-(2-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*'-(4-cyanophenyl)benzohydrazide (5h). A white solid, yield: 80.1%, m.p. 167.6—168.1 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.44 (d, *J* = 2.8 Hz, 1H, CONH), 8.84 (s, 1H, triazole-H), 8.15 (d, *J* = 2.8 Hz, 1H, CONHNH), 8.09 (dd, *J* = 7.8, 1.7 Hz, 1H, 2-Cl-phenyl-H), 7.97—7.88 (m, 2H, CO-benzene-H), 7.58 (dd, *J* = 8.0, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.48 (dd, *J* = 6.1, 4.2 Hz, 2H, CO-benzene-H), 7.45 (dd, *J* = 7.7, 1.4 Hz, 1H, 2-Cl-phenyl-H), 7.40 (dd, *J* = 7.4, 1.9 Hz, 1H, 2-Cl-phenyl-H), 7.21—7.11 (m, 2H, 4-Cl-phenyl-H), 6.83—6.69 (m, 2H, 4-Cl-phenyl-H), 5.79 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.0, 148.5, 142.9, 139.7, 132.6, 130.4, 130.3, 129.6, 129.5, 129.1, 128.6, 128.0, 127.9, 127.6, 124.7, 121.9, 113.8, 52.5. HRMS (ESI) $[M-H]^-$ calcd for $C_{22}H_{16}ON_5Cl_2$: 436.0726, found: 436.0736.

4-((4-(2-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*'-(3,4-dichlorophenyl)benzohydrazide (5i). A yellow solid, yield: 81.6%, m.p. 216.7—217.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.49 (d, *J* = 1.7 Hz, 1H, CONH), 8.83 (s, 1H, triazole-H), 8.39 (d, *J* = 1.9 Hz, 1H, CONHNH), 8.10 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-phenyl-H), 7.94 (d, *J* = 8.3 Hz, 2H, CO-benzene-H), 7.57 (dd, *J* = 7.9, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.50 (d, *J* = 8.3 Hz, 2H, CO-benzene-H), 7.46 (td, *J* = 7.6, 1.4 Hz, 1H, 2-Cl-phenyl-H), 7.40 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-phenyl-H), 7.36 (d, *J* = 8.8 Hz, 1H, 3,4-2Cl-phenyl-H), 6.92 (d, *J* = 2.6 Hz, 1H, 3,4-2Cl-phenyl-H), 6.76 (dd, *J* = 8.8, 2.6 Hz, 1H, 3,4-2Cl-phenyl-H), 5.80 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.4, 150.2, 143.4, 140.2, 132.8, 131.7, 131.1, 130.8, 130.7, 130.0, 129.6, 128.5, 128.4, 128.0, 125.2, 119.9, 113.7, 113.1, 53.0. HRMS (ESI) $[M-H]^-$ calcd for $C_{22}H_{15}ON_5Cl_3$: 470.0337, found: 470.0345.

***N*'-(4-Bromophenyl)-4-((4-(2-chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)benzohydrazide (5j).** A yellow solid, yield: 35.4%, m.p. 166.4—167.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.42 (s, 1H, CONH), 8.83 (s, 1H, triazole-H), 8.15 (s, 1H, CONHNH), 8.09 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-phenyl-H), 7.92 (d, *J* = 8.3 Hz, 2H, CO-benzene-H), 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.51—7.47 (m, 2H, CO-benzene-H), 7.45 (dd, *J* = 7.6, 1.4 Hz, 1H, 2-Cl-phenyl-H), 7.42—7.36 (m, 1H, 2-Cl-phenyl-H), 7.33—7.24 (m, 2H, 4-Br-phenyl-H), 6.78—6.68 (m, 2H, 4-Br-phenyl-H), 5.77 (d, *J* = 12.8 Hz, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.4, 149.3, 143.3, 140.1, 133.1, 131.8, 130.8, 130.7, 130.0, 130.0, 129.6, 128.5, 128.3, 128.1, 125.2, 114.8, 109.9, 53.0. HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{18}ON_5BrCl$: 482.0378, found: 482.0374.

4-((4-(2-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*'-(4-(trifluoromethoxy)phenyl)benzohydrazide (5k). A white solid, yield: 96.5%, m.p. 161.9—162.6 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.46 (d, *J* = 2.7 Hz, 1H, CONH), 8.84 (s, 1H, triazole-H), 8.22 (d, *J* = 2.7 Hz, 1H, CONHNH), 8.10 (dd, *J* = 7.8, 1.7 Hz, 1H, 2-Cl-phenyl-H), 7.95—7.90 (m, 2H, CO-benzene-H), 7.58 (dd, *J* = 8.0, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.52—7.48 (m, 2H, CO-benzene-H), 7.48–7.44 (m, 1H, 2-Cl-phenyl-H), 7.42—7.36 (m, 1H, 2-Cl-phenyl-H), 7.14 (d, *J* = 8.9 Hz, 2H, 4-OCF_3-phenyl-H), 6.85—6.78 (m, 2H, 4-OCF_3-phenyl-H), 5.79 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.5, 149.2, 143.3, 140.9, 140.1, 133.1, 130.2, 130.1, 130.0, 130.0, 129.6, 128.4, 128.3, 128.1, 125.2, 122.4, 120.8 ($^{1}J_{C\text{-}F}$ = 255.4 Hz), 113.4, 53.0. ^{19}F NMR (471 MHz, DMSO-d_6) δ: −57.2. HRMS (ESI) $[M-H]^-$ calcd for $C_{23}H_{16}O_2N_5ClF_3$: 486.0939, found: 486.0946.

4-((4-(2-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*'-(4-cyanophenyl)benzohydrazide (5l). A white solid, yield: 93.2%, m.p. 114.3—114.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.55 (s, 1H, CONH), 8.84 (s, 2H, triazole-H & CONHNH), 8.09 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-phenyl-H), 7.94 (d, *J* = 8.3 Hz, 2H, CO-benzene-H), 7.59—7.57 (m, 1H, 2-Cl-phenyl-H), 7.55 (dd, *J* = 5.7, 3.9 Hz, 2H, 4-CN-phenyl-H), 7.50 (d, *J* = 8.4 Hz, 2H, CO-benzene-H), 7.46 (td, *J* = 7.6, 1.4 Hz, 1H, 2-Cl-phenyl-H), 7.43—7.36 (m, 1H, 2-Cl-phenyl-H), 6.88—6.73 (m, 2H, 4-CN-phenyl-H), 5.80 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.0, 153.0, 142.9, 139.9, 133.5, 132.3, 130.4, 130.3, 129.6, 129.5, 129.1, 128.1, 128.0, 127.6, 124.7, 120.1, 111.9, 99.1, 52.5. HRMS (ESI) $[M-H]^-$ calcd for $C_{23}H_{16}ON_6Cl$: 427.1069, found: 427.1079.

4-((4-(2-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*'-(2-(trifluoromethyl)phenyl)benzohydrazide (5m). A white solid, yield: 51.1%, m.p. 156.1—156.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.57 (s, 1H, CONH), 8.83 (s, 1H, triazole-H), 8.10 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-phenyl-H), 7.96 (d, *J* = 8.3 Hz, 2H, CO-benzene-H), 7.71 (s, 1H, CONHNH), 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.52—7.48 (m, 3H, CO-benzene-H & 2-Cl-phenyl-H), 7.46 (dd, *J* = 7.7, 1.4 Hz, 1H, 2-CF_3-phenyl-H), 7.44—7.41 (m, 1H, 2-Cl-phenyl-H), 7.39 (dd, *J* = 7.5, 1.8 Hz, 1H, 2-CF_3-phenyl-H), 6.97 (d, *J* = 8.4 Hz, 1H, 2-CF_3-phenyl-H), 6.88 (t, *J* = 7.5 Hz, 1H, 2-CF_3-phenyl-H), 5.80 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO) δ: 166.4, 146.8, 143.3, 140.2, 134.0, 132.9, 130.8, 130.7, 130.0 130.0, 129.6, 128.5, 128.4, 128.1, 126.6 ($^{3}J_{C\text{-}F}$ = 5.4 Hz), 125.2, 125.1 ($^{1}J_{C\text{-}F}$ = 273.7 Hz), 118.8, 113.5, 112.4 ($^{2}J_{C\text{-}F}$ = 31.0 Hz), 53.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ: −60.7. HRMS (ESI) $[M-H]^-$ calcd for $C_{23}H_{16}ON_5ClF_3$: 470.0990, found: 470.0999.

4-((4-(2-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*'-(4-(methylsulfonyl)phenyl)benzohydrazide (5n). A white solid, yield: 90.2%, m.p. 125.1—125.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.57 (d, *J* = 1.5 Hz, 1H, CONH), 8.84 (s, 1H, triazole-H), 8.81 (d, *J* = 1.3 Hz, 1H, CONHNH), 8.09 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-phenyl-H), 7.95 (d, *J* = 8.3 Hz, 2H, CO-benzene-H), 7.66 (d, *J* = 8.8 Hz, 2H, NH-phenyl-H), 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.51 (d, *J* = 8.4 Hz, 2H, CO-benzene-H), 7.46 (td, *J* = 7.6, 1.4 Hz, 1H, 2-Cl-phenyl-H), 7.42—7.37 (m, 1H, 2-Cl-phenyl-H), 6.93—6.83 (m, 2H, NH-phenyl-H), 5.80 (s, 2H, CH_2), 3.08 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.0, 153.6, 142.9, 139.9, 132.4, 130.4, 130.3, 129.6, 129.6, 129.3, 129.1, 128.8, 128.1, 128.0, 127.6, 124.8, 111.3, 52.6, 44.3. HRMS (ESI) $[M-H]^-$ calcd for $C_{23}H_{19}O_3N_5ClS$: 480.0892, found: 480.0904.

***N*-(4-Chlorophenyl)-4-((4-(2-chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)benzamide (5o).** A white solid, yield: 32.2%, m.p. 216.6—217.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.38 (s, 1H, CONH), 8.83 (s, 1H, triazole-H), 8.09 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-phenyl-H), 7.95 (d, *J* = 8.3 Hz, 2H, CO-benzene-H), 7.83—7.76 (m, 2H, 4-Cl-phenyl-H), 7.57 (dd, *J* = 7.9, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.51 (d, *J* = 8.3 Hz, 2H, CO-benzene-H), 7.46 (td, *J* = 7.6, 1.4 Hz, 1H, 2-Cl-phenyl-H), 7.43—7.37 (m, 3H, 2-Cl-phenyl-H & 4-Cl-phenyl-H), 5.81 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 165.7, 143.3, 140.0, 138.5, 135.0, 130.8, 130.7, 130.0, 130.0, 129.6, 129.0, 128.7, 128.4, 128.1, 127.8, 125.2, 122.3, 53.0. HRMS (ESI) $[M-H]^-$ calcd for $C_{22}H_{15}ON_4Cl_2$: 421.0617, found: 421.0629.

***N*-(4-Bromophenyl)-4-((4-(2-chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)benzamide (5p).** A light yellow solid, yield: 54.9%, m.p. 220.0—220.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.37 (s, 1H, CONH), 8.83 (s, 1H, triazole-H), 8.09 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-

phenyl-H), 7.95 (d, *J* = 8.4 Hz, 2H, CO-benzene-H), 7.77—7.71 (m, 2H, 4-Br-phenyl-H), 7.57 (dd, *J* = 7.9, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.55—7.48 (m, 4H, CO-benzene-H & 4-Br-phenyl-H), 7.46 (td, *J* = 7.6, 1.4 Hz, 1H, 2-Cl-phenyl-H), 7.43—7.36 (m, 1H, 2-Cl-phenyl-H), 5.78 (d, *J* = 18.8 Hz, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 165.7, 143.3, 140.1, 139.0, 135.0, 131.9, 130.8, 130.7, 130.0, 129.6, 128.7, 128.4, 128.1, 125.2, 122.6, 115.9, 53.0. HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{17}ON_4BrCl$: 467.0269, found: 467.0266.

***N,N*-Diallyl-4-((4-(2-chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)benzamide (5q).** A light green oil, yield: 91.2%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.22 (dd, *J* = 7.9, 1.7 Hz, 1H, 2-Cl-phenyl-H), 8.18 (s, 1H, triazole-H), 7.47—7.42 (m, 2H, CO-benzene-H), 7.40 (dd, *J* = 8.0, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.37—7.31 (m, 2H, CO-benzene-H), 7.30 (s, 1H, 2-Cl-phenyl-H), 7.27—7.21 (m, 1H, 2-Cl-phenyl-H), 5.77 (d, *J* = 60.9 Hz, 2H, , CH_2-$\underline{CH}$=CH_2), 5.61 (s, 2H, CH_2), 5.26—5.11 (m, 4H, CH_2-CH=$\underline{CH_2}$), 3.95 (d, *J* = 124.7 Hz, 4H, $\underline{CH_2}$-CH=CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 171.0, 144.5, 136.6, 136.4, 133.0, 132.5, 131.2, 130.2, 129.7, 129.1, 129.1, 127.8, 127.4, 127.2, 123.4, 117.8, 117.7, 53.7, 50.7, 47.1. HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{22}ON_4Cl$: 393.1477, found: 393.1466.

4-((4-(2-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*-(3-morpholinopropyl)benzamide (5r). A light yellow solid, yield: 91.0%, m.p. 121.1—121.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.23 (dd, *J* = 7.9, 1.7 Hz, 1H, 2-Cl-phenyl-H), 8.15 (s, 1H, triazole-H), 7.98 (s, 1H, CONH), 7.82 (d, *J* = 8.2 Hz, 2H, CO-benzene-H), 7.42 (dd, *J* = 8.0, 1.2 Hz, 1H, 2-Cl-phenyl-H), 7.36 (dd, *J* = 10.5, 4.6 Hz, 3H, 2-Cl-phenyl-H & CO-benzene-H), 7.29—7.23 (m, 1H, 2-Cl-phenyl-H), 5.65 (s, 2H, CH_2), 3.72—3.64 (m, 4H, morpholine-H), 3.55 (dd, *J* = 11.5, 5.9 Hz, 2H, CONH-CH_2), 2.52 (dd, *J* = 16.5, 10.4 Hz, 6H, morpholine-H & N-CH_2), 1.83—1.74 (m, 2H, CONH-$CH_2\underline{CH_2}$). ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 166.6, 144.6, 135.2, 131.2, 130.2, 129.8, 129.2, 129.0, 127.9, 127.8, 127.2, 123.3, 66.9, 58.4, 53.8, 53.7, 40.4, 24.2. HRMS (ESI) $[M-H]^-$ calcd for $C_{23}H_{25}O_2N_5Cl$: 438.1691, found: 438.1701.

4-((4-(2-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*-(2-(dimethylamino)ethyl)benzamide (5s). A white solid, yield: 77.9%, m.p. 131.2—131.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 8.79 (s, 1H, triazole-H), 8.41 (t, *J* = 5.6 Hz, 1H, CONH), 8.08 (dd, *J* = 7.8, 1.8 Hz, 1H, 2-Cl-phenyl-H), 7.84 (d, *J* = 8.3 Hz, 2H, CO-benzene-H), 7.57 (dd, *J* = 7.9, 1.3 Hz, 1H, 2-Cl-phenyl-H), 7.46 (dd, *J* = 7.5, 1.4 Hz, 1H, 2-Cl-phenyl-H), 7.43 (dd, *J* = 4.9, 3.4 Hz, 2H, CO-benzene-H), 7.41—7.36 (m, 1H, 2-Cl-phenyl-H), 5.76 (d, *J* = 2.0 Hz, 2H, CH_2), 3.34 (d, *J* = 6.0 Hz, 2H, CONH$\underline{CH_2}$), 2.40 (t, *J* = 6.8 Hz, 2H CONHCH$_2\underline{CH_2}$), 2.18 (s, 6H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 166.1, 143.3, 139.4, 134.8, 130.8, 130.7, 123.0, 129.6, 128.2, 128.1, 128.0, 125.1, 58.6, 53.0, 45.6, 37.8. HRMS (ESI) $[M+H]^+$ calcd for $C_{20}H_{23}ON_5Cl$: 384.1586, found: 384.1576.

Supporting Information

Supplementary materials include ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and HRMS spectra of intermediates **2**—**4**, title compounds **5a**—**5s** (Figures S1 to S65).

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