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Synthesis and bioactivity of novel 2-(1,2-benzisothiazol-3-yloxy)-*N*-(1-aryl-3-cyanopyrazol-5-yl) acetamides

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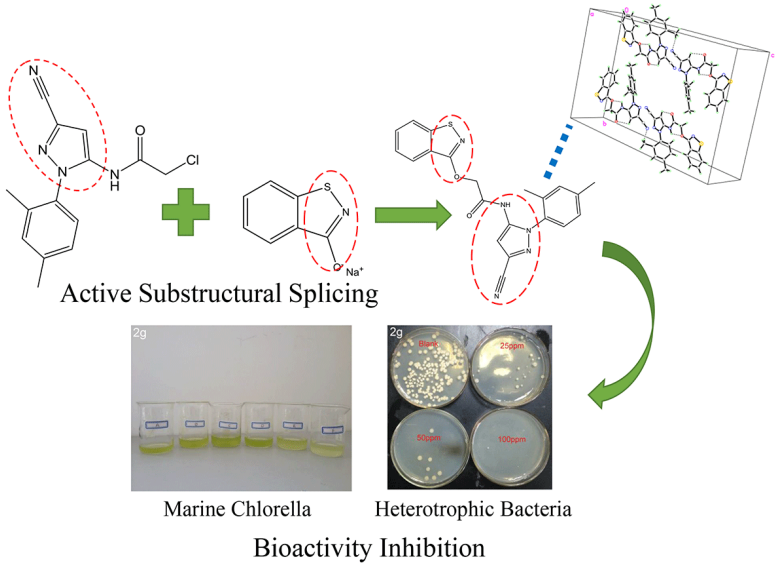
Abstract

Nine novel types of 2-(1,2-benzisothiazol-3-yloxy)-*N*-(1-aryl-3-cyanopyrazol-5-yl)-acetamides were synthesized, and their inhibition effects on selected bacteria (heterotrophic bacteria) and algae (marine chlorella) were evaluated. Results showed that 2-(1,2-benzisothiazol-3-yloxy)-*N*-(3-cyano-1-(2,4-dimethylphenyl)pyrazol-5-yl) acetamide achieved the highest yield of 81% with good bioactivity against heterotrophic bacteria and marine chlorella.



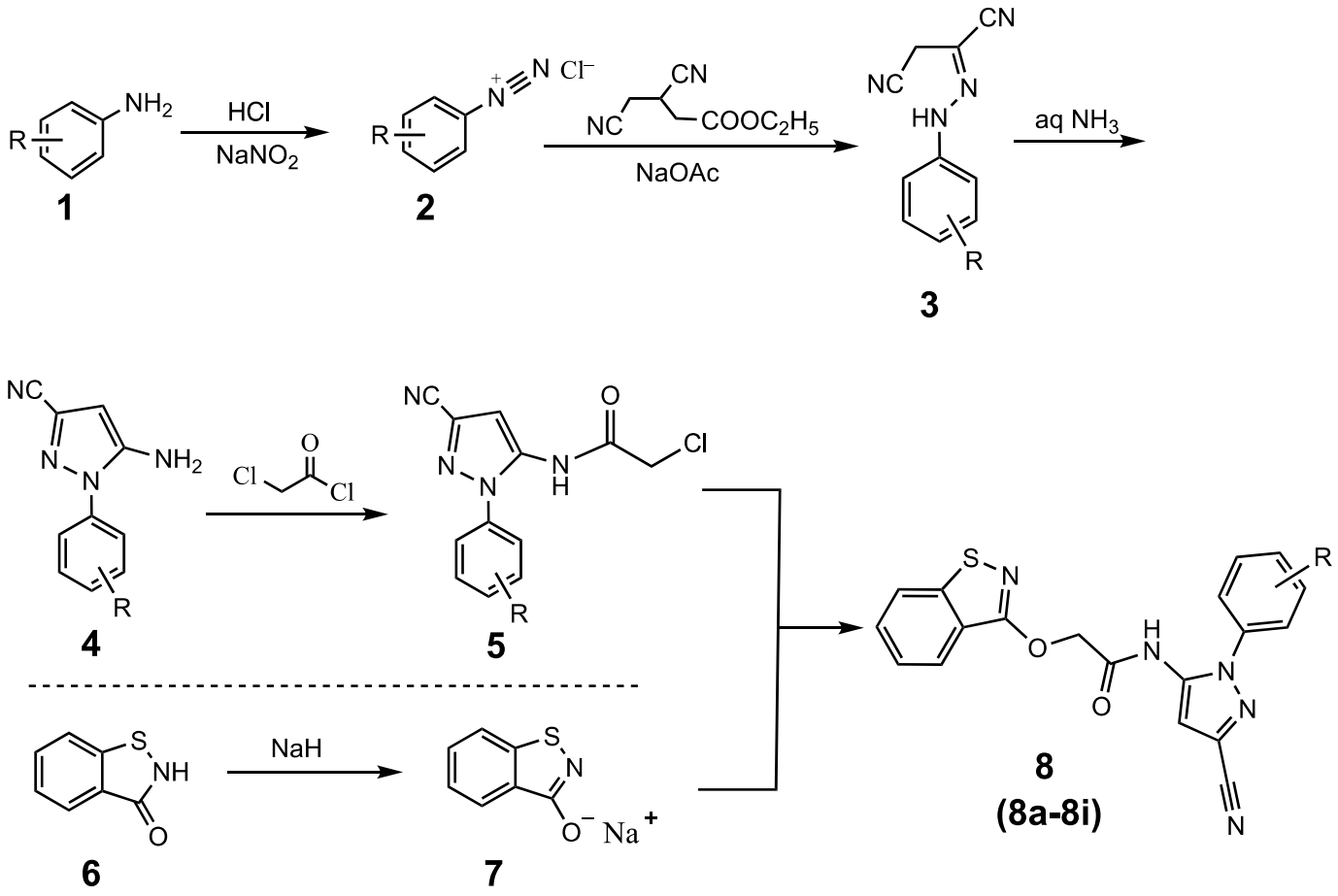
Keywords: *N*-Aryl pyrazole, isothiazolinone, synthesis, bioactivity

Introduction

Over the past years, N-arylpyrazole-containing heterocyclic scaffolds have been widely studied in many fields because of its diverse biological activities, such as antimicrobial, insecticide, and herbicidal.[1-5] Meanwhile, isothiazolone has attracted considerable interest because of its antimicrobial activity against bacteria and fungi.[6,7] Derivatives of isothiazolone also exhibit excellent performance as antibacterial and antifungal agents and enzyme inhibitors.[8-13] Multifunctional water treatment agents are currently a hot research topic.[14-15] To give the target compound excellent biological activity and a broad spectrum of activity, we introduced an N-arylpyrazole structure, following the principle of sub-structure group splicing.[16-18]

Results and Discussion

Synthesis. In connection with our research on the synthesis of novel 2-(1,2-benzisothiazol-3-yloxy)-*N*-(3-cyano-1-(substituted-phenyl)pyrazol-5-yl) acetamides aimed at achieving multi-functional antifouling agents, we describe the synthesis, one crystal structure, and potential antimicrobial activity of these compounds. Results showed them to exhibit a broad spectrum of activity against heterotrophic bacteria and chlorella. The synthesis route is shown in Scheme 1: 2-(1,2-benzisothiazol-3-yloxy)-*N*-(3-cyano-1-(substituted-phenyl)pyrazole-5-yl) acetamides (**8a–8i**) were prepared by the reaction of 3-cyano-5-amino-1-(substituted-phenyl)pyrazole chloroacetamides (**5**) and 1,2-benzisothiazol-3-one sodium salt (**7**).



Scheme 1.

Table 1. Synthesis of compounds **8a-8i**

Compound	R	Time (h)	Yield (%)	Melting Point (℃)
8a	H	5	72	159–161
8b	2-methoxy	5	70	158–160
8c	4-methoxy	5	68	178–179
8d	4-methyl	5	69	186–188
8e	4-chloro	5	59	188–190
8f	4-bromine	5	54	199–201
8g	2,4-dimethyl	5	81	142–144
8h	2,6-dichloro	5	72	196–198
8i	2,4,6-trichloro	5	62	182–184

Compound **8g** was subjected to single crystal X-ray crystallography, and intensity data were measured using an Enraf-Nonius CAD4 four-circle diffractometer. Under the condition of 293(2)K, the MoKα ray (λ=0.71073 Å) monochromated with a graphite monochromator was irradiated in ω/2θ scanning modes and XSCANS. Diffraction data were collected between 2.2°<θ<25.4°, and 3656 diffraction points were collected and reduced, including 3063 independent diffraction points, 1534 strong points (I>2σ), and R(int)=0.056 after absorption correction, orthogonal crystal system, space group Pbca, refinement result R=0.0789, wR=0.1341 (w=1/[σ2(Fo 2) +(0.1000P)2 + 0.0000P], P = (Fo2 + 8fc 2) / 3), S = 1.008. The highest peak of residual electron density is 0.166 e/Å3, and the lowest valley is -0.218 e/Å3. SHELXS-97 program was used to identify the rough structure by a direct method, and the data were refined by the SHEXLX-97 full matrix least squares method (Fig. 2), with all non-hydrogen atoms anisotropically corrected. All hydrogen atoms underwent theoretical hydrogenation.[19,20]

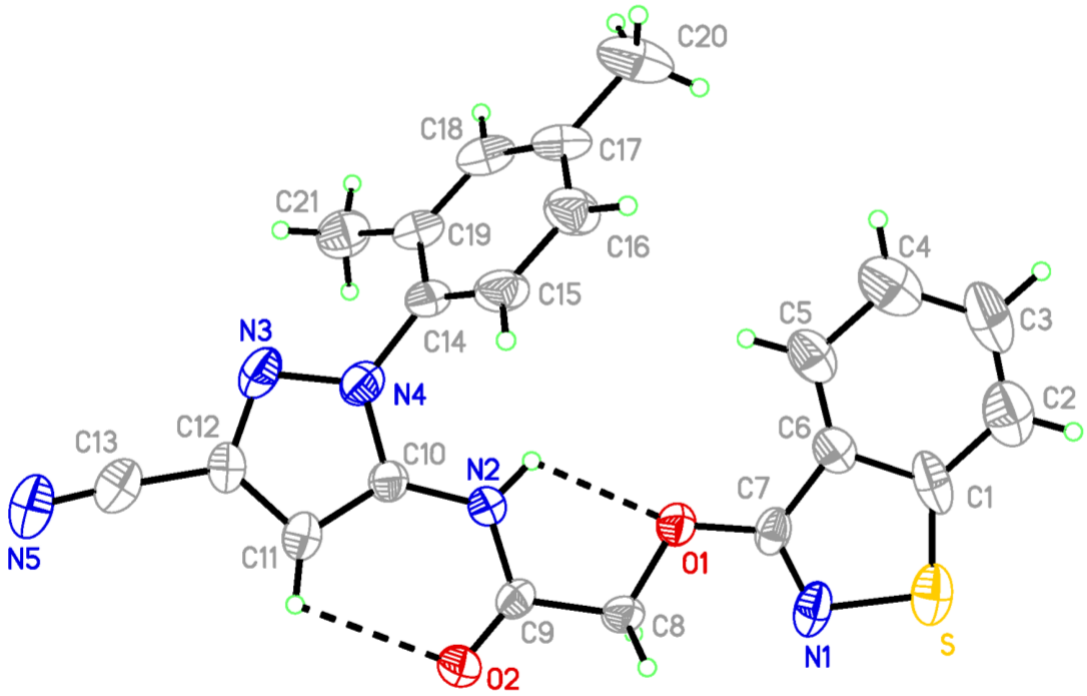


Figure 1. ORTEP diagram of **8g**. thermal ellipsoids are shown at the 30% probability level.

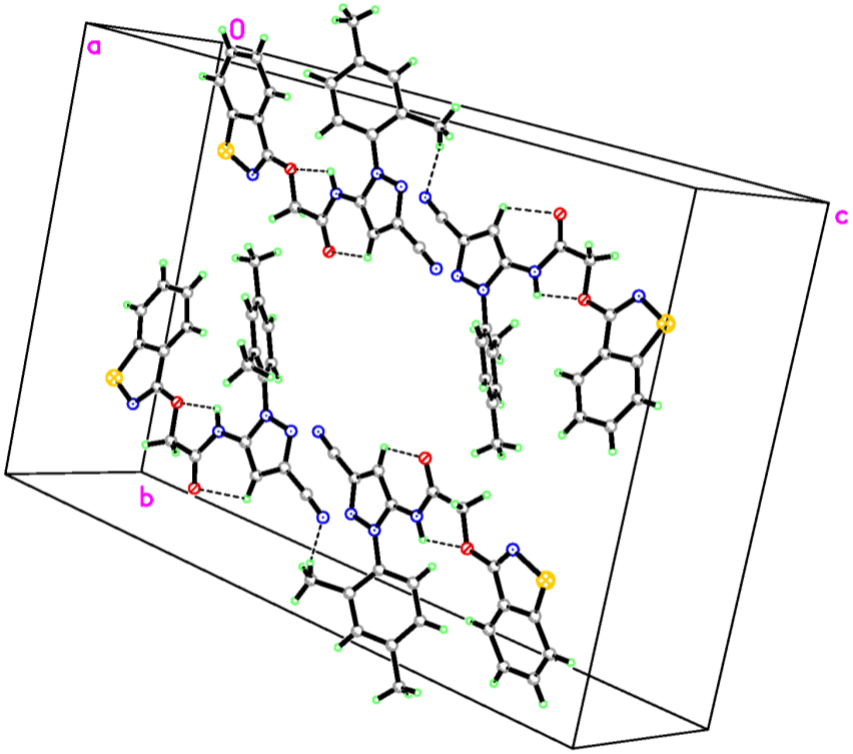


Figure 2. Crystal packing of **8g**.

Table 2. Crystal data and structure refinement of compound **8g**

Empirical formula	$C_{21}H_{17}N_5O_2S$
CCDC number	980925
Formula weight (g/mol)	403.46
Crystal size (mm)	0.30×0.20×0.10
Crystal system	Orthorhombic
Space group	Pbca
a (Å)	7.1230 (14)
b (Å)	18.236(4)
c (Å)	30.579(6)
V (Å3)	3972.1 (14)
Z	8
Crystal density	1.349
λ(MoKa) (Å)	0.71073
F(000)	1680
Theta range for data collection	2.2°to 25.4°
h, k and l ranges	0≤h≤8, 0≤k≤21, 0≤l≤36
Reflections measured	3656
Independent reflections	3603
Observed reflection (I > 2σ(I))	1534
Rint	0.056
Final R* indices (I > 2σ(I))	R=0.079, wR = 0.165
Goodness-of-fit	1.008

Table 3. Selected Bond Distances (Å) and Bond Angles (°) of **8g**

Bond	Dist.	Bond	Dist.	Bond	Dist.
S-C1	1.646(5)	C2-C3	1.376(7)	C12-C13	1.436(6)
S-N1	1.671(3)	N4-N3	1.361(4)	C14-C15	1.355(5)
O1-C7	1.343(4)	N4-C10	1.371(5)	C14-C19	1.390(5)
O1-C8	1.448(4)	N4-C14	1.441(5)	C15-C16	1.391(5)
N1-C7	1.287(5)	C3-C4	1.418(7)	C16-C17	1.385(5)
C1-C2	1.398(6)	N5-C13	1.148(5)	C17-C18	1.373(6)
C1-C6	1.445(5)	C4-C5	1.411(5)	C17-C20	1.512(6)
N2-C9	1.368(4)	C10-C11	1.365(5)	C18-C19	1.395(5)
N2-C10	1.388(4)	C11-C12	1.370(5)	C19-C21	1.493(5)
C5-C6	1.364(5)	C6-C7	1.419(5)	C8-C9	1.498(5)
O2-C9	1.212(4)	C12-N3	1.334(5)		
Angle	(°)	Angle	(°)	Angle	(°)
C1-S-N1	93.9(2)	C5-C6-C1	124.3(4)	C11-C12-C13	127.6(4)
C7-O1-C8	114.8(3)	C7-C6-C1	105.5(4)	N5-C13-C12	176.1(5)
C7-N1-S	110.6(3)	N1-C7-O1	122.3(4)	C12-N3-N4	103.0(3)
C2-C1-C6	115.8(5)	N1-C7-C6	118.0(4)	C15-C14-C19	122.2(4)
C2-C1-S	132.3(5)	O1-C7-C6	119.6(4)	C15-C14-N4	117.6(4)
C6-C1-S	111.9(3)	O1-C8-C9	110.1(3)	C19-C14-N4	120.3(4)
C9-N2-C10	122.8(3)	O2-C9-N2	123.6(3)	C14-C15-C16	120.6(4)
C3-C2-C1	120.9(6)	O2-C9-C8	120.1(4)	C17-C16-C15	119.4(4)
N3-N4-C10	111.5(3)	N2-C9-C8	116.2(3)	C18-C17-C16	118.4(4)
N3-N4-C14	121.5(3)	C11-C10-N4	107.0(3)	C18-C17-C20	121.4(4)
C10-N4-C14	127.1(3)	C11-C10-N2	132.8(4)	C16-C17-C20	120.2(5)
C2-C3-C4	121.9(5)	N4-C10-N2	120.2(3)	C17-C18-C19	123.5(4)
C5-C4-C3	118.8(5)	C10-C11-C12	104.5(4)	C14-C19-C18	115.8(4)
C6-C5-C4	118.1(5)	N3-C12-C11	114.0(4)	C14-C19-C21	124.3(4)
C5-C6-C7	130.1(4)	N3-C12-C13	118.4(4)	C18-C19-C21	119.9(4)

Table 4. Intramolecular and intermolecular hydrogen bonds of **8g**

D–H…A	d(D–H)	d(H…A)	d(D…A)	∠DHA
N2-H2A··O1	0.86	2.18	2.604 (3)	110
C11-H11A· ·O2	0.93	2.45	2.869 (5)	107
C21-H21C··N5 i	0.96	2.59	3.535 (5)	168

Symmetry codes: (i) x−1/2, −y+1/2, −z.

Figs. 1 and 2 correspond to compound **8g**, Tables 2 and 3 provide detailed information on the parameters of the compound and the major bond lengths and bond angles. Table 4 shows the hydrogen bonds in the crystal structure. The C-C bonds have lengths of 1.355(5)–1.512(6) Å, which are typical C-C bond lengths and consistent with the literature. Due to the conjugation effect of the pyrazole ring, the C14–N4 bond is long (1.441(5) Å), which is between a standard C–N single bond (1.471 Å) and a C=N double bond (1.273 Å). The range of the bond angles between the atoms on the benzene ring is between 115.8(5)° and 124.3(4)°, but the average value is 120°, indicating that the benzene ring is a stable coplanar six-membered ring. The intermolecular hydrogen bonds N-H··O and C-H··O form a twisted five-membered ring and a six-membered ring, respectively, and the intermolecular hydrogen bond C-H·· N causes the molecule to form a multi-layered structure.

Crystallographic data for the structure reported in this paper have been deposited n the Cambridge data center with deposition number CCDC 980925.

Biological assay: Batch antimicrobial experiments were conducted in six parallel samples, and the average results are listed in Table 6. Heterotrophic bacteria and marine chlorella were selected as typical targets for their normal existence in bodies of water, and are important parameters reflecting water quality. The results showed that the target compounds exert good inhibition against the tested organisms.

Table 6. Comparison of the bioactivity of synthesized compounds **8** against heterotrophic bacteria and marine chlorella

Compound	Inhibition rate of heterotrophic bacteria (%)			Inhibition rate of Marine Chlorella (%)
	100ppm	50ppm	25ppm	
8a	91.3	85.3	62.1	60.29
8b	94.3	86.9	75.5	65.81
8c	94.5	90.2	81.2	65.305
8d	100	98.2	80.7	67.955
8e	98.9	88.4	58.9	68.48
8f	95.2	85.2	67.8	72.5
8g	97.7	90.2	68.5	71.02
8h	96.2	81.6	64.3	73.99
8i	100	95.3	81.9	74.01
BIT-20	80.1	42.8	22.5	53.5

Conclusions

This study demonstrated the synthesis and antimicrobial activities of 2-(benzisothiazol-3-yloxy)-N-(3-cyano-1-aryl-5-yl) acetamides. Bioactivity testing showed that the compounds exert satisfactory inhibition effects against heterotrophic bacteria and marine chlorella, with rates more than 58.9% and 60.29% for heterotrophic bacteria and marine chlorella at a dosage of 25 ppm, respectively. The highest yield obtained was 81%, indicating that compounds with an aryl-pyrazole and a benzisothiazolone spliced together have high biological activities and low toxicities and represent a new direction for further structural optimization and biological studies on such synthetic acetamides.

Experimental Section

General. All chemicals used in this study were commericallly available. Melting points were recorded on a X-4 binocular spectra melting apparatus. IR spectra in KBr were recorded on a PerkinElmer PE-683 IR spectrometer. The ^{1}H NMR spectra were determined using TMS as an internal reference with a Avance Bruker-500 instrument operating at 500 MHz or an Avance Bruker-300 instrument operating at 400 MHz. Elemental analyses were performed by an Elementer Vario EL III elementary analysis instrument. Compounds were synthesized in accordance the method described in our previous work.[21]

Benzisothiazolinone sodium salt. A mixture of benzisothiazol-3(8*H*)-one (**6)** (0.01 mol) and NaH (0.011 mol) in MeOH (40 mL) was stirred and heated at refluxed for 2 h. The remaining MeOH was evaporated under negative pressure. The crude product was washed with MeOH and dried to obtain benzisothiazolin-3-one sodium salt (**7**) as a white solid, mp >300 ℃.

3-Cyano-5-amino-1-(substituted-phenyl)pyrazoles. Ethyl 2,3-dicyanopropanoate (0.01 mol), NaOAc (0.03 mol), and EtOH (50 mL) were mixed in a 150 mL round-bottomed flask. Then, the mixture was added to a substituted aniline diazonium salt within 20 min and stirred at 5 ℃ for 8 h, after which, the mixture was extracted with CH_2Cl_2 (3 x 30 mL). Ammonia was then added to the combined organic extracts to adjust the pH to 9–10. After addition, the mixture was stirred at rt for 3 h. The organic phase was washed and then concentrated. After cooling, the crude product precipitated, was filtered off, washed with EtOH, dried, and then recrystallized from toluene to afford the 3-cyano-5-amino-1-(substituted-phenyl)pyrazole (**4**).

3-Cyano-5-amino-1-(substituted-phenyl)pyrazole chloroacetamide. Chloroacetyl chloride (0.015 mol) was added dropwise to a CH_2Cl_2 solution of 3-cyano-5-amino-1-(substituted-phenyl)pyrazole (0.01 mol in 30 mL) at 0–5 ℃, and the mixture obtained was stirred at rt for 8 h with Et_3N (0.015 mol) as an acid acceptor. After the reaction, the remaining CH_2Cl_2 was evaporated under reduced pressure to obtain crude 3-cyano-5-amino-1-(substituted-phenyl)pyrazole chloroacetamide (**5**).

Synthesis of 2-(1,2-benzisothiazol-3-yloxy)-*N*-(3-cyano-1-(substituted-phenyl)pyrazol-5-yl) acetamides (2). With KI as a catalyst, a benzisothiazolone sodium salt (**7**) (0.006 mol) was reacted with a solution of 3-cyano-5-amino-1-(substituted-phenyl)pyrazole chloroacetamide in DMF (40 mL), at 100 ℃ for 4 h. The solutioin was concentrated and poured into H_2O, and a solid was precipitated, filtered off, washed, and dried. The product (**8a-i**) was purified by column chromatography.

2-(1,2-Benzisothiazol-3-yloxy)-*N*-(3-cyano-1-phenylpyrazol-5-yl) acetamide (8a). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.15 (s, 2H, CH_2), 7.15 (s, 1H, C–H), 7.08～7.88 (m, 9H, Ar–H), 8.60 (s, 1H, N–H); IR (KBr) v: 3177(N–H), 3058(C–H), 2246(C≡N), 1724(C=O), 1596(C=N), 1546(C=C), 1262(C–N), 645(C–S) cm^{-1} . Anal. Calcd. (%) for $C_{19}H_{13}N_5O_2S$: C, 60.79; H, 3.49; N, 18.66. Found (%): C, 61.01; H, 3.35; N, 18.68.

2-(1,2-Benzisothiazol-3-yloxy)-*N*-(3-cyano-1-(2-methoxyphenyl)pyrazol-5-yl) acetamide (8b). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.84(s, 3H, CH_3O), 5.17 (s, 2H, CH_2), 7.14 (s, 1H, C–H), 6.78～7.87 (m, 8H, Ar–H), 8.31 (s, 1H, N–H); IR (KBr) v: 3295(N–H), 3170(C–H), 2241(C≡N), 1713(C=O), 1596(C=N), 1557(C=C), 1321(C–N), 647(C–S) cm^{-1} . Anal. Calcd. (%) for $C_{20}H_{15}N_5O_3S$: C, 59.25; H, 3.73; N, 17.27. Found (%): C, 59.28; H, 3.61; N, 17.29.

2-(1,2-Benzisothiazol-3-yloxy)-*N*-(3-cyano-1-(4-methoxyphenyl) pyrazol-5-yl) acetamide (8c). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.85(s, 3H, CH_3O), 5.14 (s, 2H, CH_2), 6.99 (s, 1H, C–H), 7.01～7.82 (m, 8H, Ar–H), 8.34 (s, 1H, N–H); IR (KBr) v: 3383(N–H), 3167(C–H), 2241(C≡N), 1717(C=O), 1597(C=N), 1557(C=C), 1323(C–N), 1225(C–F), 647(C–S) cm^{-1}. Anal. Calcd. (%) for $C_{20}H_{15}N_5O_3S$: C, 59.25; H, 3.73; N, 17.27. Found (%): C, 59.20; H, 3.62; N, 17.35.

2-(1,2-Benzisothiazol-3-yloxy)-*N*-(3-cyano-1-(4-methylphenyl)pyrazol-5-yl) acetamide (8d). ^{1}H NMR ($CDCl_3$, 500

MHz) δ: 2.39 (s, 3H, CH_3), 5.15 (s, 2H, CH_2), 7.18 (s, 1H, C–H), 6.86～7.88 (m, 8H, Ar–H), 8.51 (s, 1H, N–H); IR (KBr) v: 3401(N–H), 3171(C–H), 2241(C≡N), 1725(C=O), 1589(C=N), 1556(C=C), 1324(C–N), 646(C–S) cm^{-1}. Anal. Calcd. (%) for $C_{20}H_{15}N_5O_2S$: C, 61.68; H, 3.88; N, 17.98. Found (%): C, 61.59; H, 3.77; N, 17.83.

2-(1,2-Benzisothiazol-3-yloxy)-*N*-(3-cyano-1-(4-chlorophenyl) pyrazol-5-yl) acetamide (8e). ^1H NMR ($CDCl_3$, 500 MHz) δ: 5.16 (s, 2H, CH_2), 7.18 (s, 1H, C–H), 6.99～7.84 (m, 8H, Ar–H), 8.58 (s, 1H, N–H); IR (KBr) v: 3386(N–H), 3078(C–H), 2242(C≡N), 1712(C=O), 1589(C=N), 1557(C=C), 1334(C–N), 1120(C–F), 647(C–S) cm^{-1} . Anal. Calcd. (%) for $C_{19}H_{12}ClN_5O_2S$: C, 55.68; H, 2.95; N, 17.09. Found (%): C, 55.75; H, 2.90; N, 17.14.

2-(1,2-Benzisothiazol-3-yloxy)-*N*-(3-cyano-1-(4-bromophenyl)pyrazol-5-yl)acetamide (8f). ^1H NMR (CDCl3, 500 MHz) δ: 5.15 (s, 2H, CH2), 7.19 (s, 1H, C–H), 6.98～7.85 (m, 8H, Ar–H), 8.60 (s, 1H, N–H); IR (KBr) v: 3259(N–H), 3057(C–H), 2374(C≡N), 1674(C=O), 1597(C=N), 1539 (C=C), 1290(C–N), 1066 (C–Br), 650(C–S) cm-1. Anal. Calcd. (%) for C19H12BrN5O2S: C, 50.23; H, 2.66; N, 15.42. Found (%): C, 50.34; H, 2.53; N, 15.38.

2-(1,2-Benzisothiazol-3-oxy)-*N*-(3-cyano-1-(2,4-dimethylphenyl)pyrazole-5-yl) acetamide (8g). ^1H NMR ($CDCl_3$, 500 MHz) *δ*: 2.02 (s, 6H, CH_3), 5.11 (s, 2H, CH_2), 7.12 (s, 1H, C–H), 6.74～7.85 (m, 7H, Ar–H), 8.46 (s, 1H, N–H); IR (KBr) *v*: 3386(N–H), 3169(C–H), 2243(C≡N), 1716(C=O), 1595(C=N), 1558(C=C), 1323(C–N), 648(C–S) cm^{-1}. Anal. Calcd. (%) for $C_{21}H_{17}N_5O_2S$: C, 62.52; H, 4.25; N, 17.36. Found (%): C, 62.42; H, 4.18; N, 17.43.

2-(1,2-Benzisothiazol-3-yloxy)-*N*-(3-cyano-1-(2,6-dichlorophenyl)pyrazol-5-yl) acetamide (8h). ^1H NMR ($CDCl_3$, 500 MHz) *δ*: 5.16 (s, 2H, CH_2), 7.22 (s, 1H, C–H), 7.11～7.86 (m, 7H, Ar–H), 8.77 (s, 1H, N–H); IR (KBr) *v*: 3202(N–H), 3056(C–H), 2242(C≡N), 1689(C=O), 1596(C=N), 1560(C=C), 1259 (C–N), 1146(C–Cl), 649(C–S) cm^{-1}. Anal. Calcd. (%) for $C_{19}H_{11}Cl_2N_5O_2S$: C, 51.36; H, 2.50; N, 15.76. Found (%): C, 51.30; H, 2.54; N, 15.82.

2-(1,2-Benzisothiazol-3-yloxy)-*N*-(3-cyano-1-(2,4,6-dichlorophenyl)pyrazol-5-yl) acetamide (8i). ^1H NMR ($CDCl_3$, 500 MHz) *δ*: 5.18 (s, 2H, CH_2), 7.25 (s, 1H, C–H), 7.11～7.86 (m, 6H, Ar–H), 8.75(s, 1H, N–H); IR (KBr) *v*: 3246(N–H), 3078(C–H), 2247(C≡N), 1718(C=O), 1654(C=N), 1556(C=C), 1388(C–N), 1168(C–Cl), 651(C–S) cm^{-1}. Anal. Calcd. (%) for $C_{19}H_{10}Cl_3N_5O_2S$: C, 47.67; H, 2.11; N, 14.63. Found (%): C, 47.72; H, 2.18; N, 14.58.

Acknowledgements

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