Synthesis and Bioactivity of Novel Bis-heterocyclic Compounds Containing Pyrazole and Oxadiazoline

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Nucleophilic addition of the starting material 3-aryl-1-phenyl-4-formylpyrazoles (**1~3**) and 4-substituted aryloxyacetyl hydrazine (**4a~4e**) afford hydrazone compounds containg pyrazolyl (**5a~5e**, **6a~6e**, **7a~7e**) in the ethanol. These adducts were refluxed in Ac_2O and furnished a series of novel bis-heterocyclic compounds. (**8a~8e**, **9a~9e**, **10a~10e**) via cyclic reaction. The structures of all newly synthesized compounds were established by IR, ^{1}H NMR, MS and elemental analysis. New compounds conducted preliminary tests of antibacterial activities about *Fusarium oxyaporium, Verticillium dahliae, Rhizoctonia solani, Pychium aphanidermatum, Alternaria solani, Sclerotinia sclerotiorum*. The results showed that the inhibiting rate of the bis-heterocyclic compounds **(8a~8e**, **9a~9e**, **10a~10e**) was higher than the pyrazolyl hydrazones (**5a~5e, 6a~6e, 7a~7e**) obviously.

Keywords: Pyrazole; Oxadiazoline; Synthesis; Bioactivity.

INTRODUCTION

Heterocycles are popularly known for displaying a wide range of biological properties.[1] The structural diversity and biological importance of nitrogen containing heterocycles have made them attractive synthetic targets over many years.[2]

Oxadiazoline, pyrazole and pyrazoline derivatives are in general well-known five–membered containing heterocyclic compounds. Compounds with pyrazole ring are of interest due to their broad spectrum of biological activities against NOS inhibitor,[3] monoamine oxidase inhibitor,[4] antibacterial,[5] antiamoebic.[6] Moreover, *N*-phenylpyrazole derivatives play an important role in antitumor screening[7] as well as potent antimicrobial activity.[8] Furthermore, a number of hydrazide-hydrazone derivatives also have been claimed to possess interesting bioactivity such as antibacterial-antifungal, anticonvulsant, antiinfloammatory, antimalarial, analgesic, anticancer acticities.[9] So, a few of pyrazole carbohydrazide hydrazone derivatives have also been reported, which have been synthesized in many methods.[10,11]

On the other hand, oxadiazoline are important for both chemical and biological purposes.[12,13] Oxadiazoline play a crucial role in the development of theory in heterocyclic chemistry and also are extensively used as useful synthon in organic synthesis. Also, a number of oxadiazoline have been reported to exhibit diverse pharmacological properties[14,15] and antimicrobial activity.[16] Therefore, compounds both the pyrazole and the oxadiazoline possess worthy and imperative bioactivities, which render them useful substances in organic synthesis. However, bis-heterocyclic compounds which contain pyrazole and oxadiazoline have rarely been reported. On this basis, our work has focused on the synthesis of antibacterial compounds. Therefore, due to the possible importance of these compounds and our interest in the development of heterocycle-based pyrazole, in this paper, we have synthesized a series of pyrazole carbohydrazide hydrazone derivatives (**5a~5e**, **6a~6e**, **7a~7e**) by reacting appropriately 1-phenyl-3-aryl-4-formacyl pyrazoles (**1~3**) and 4-substituted aryloxyacetyl hydrazine in ethanol, and some new bis-heterocycle derivatives (**8a~8e**, **9a~9e**, **10a~10e**) based pyrazole and oxadiazoline in one-step as illustrated in Scheme I. Specially, we have focused on the preliminary

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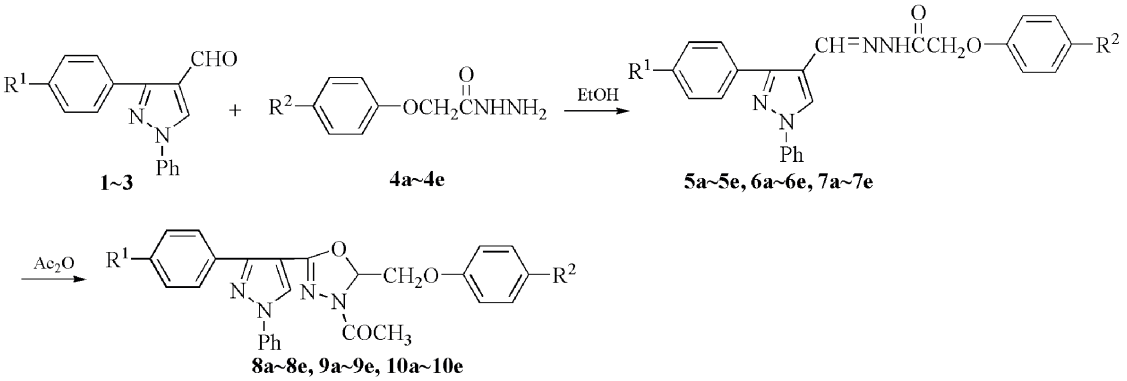
Scheme I



5a~5e, 8a~8e: R^1=OCH_3; **6a~6e, 9a~9e:** R^1=Br; **7a~7e, 10a~10e:** R^1=Cl;
4a~10a: R^2=H; **4b~10b:** R^2=CH_3; **4c~10c:** R^2=OCH_3; **4d~10d:** R^2=Br; **4e~10e:** R^2=NO_2

tests of antibacterial activities of new compounds. Our purpose is that it might be possible to develop new organic antibacterial activity compounds by satisfactory combination of pyrazole and oxadiazoline groups through appropriate molecular design and synthesis. The entire investigated compounds exhibited moderate antibacterial activityies with the percentage inhibition of six strains, while bis-heterocyclic compound showed better inhibitory activity than pyrazole carbohydrazide hydrazone derivatives.

RESULTS AND DISCUSSION

The positions of IR band provide significant indication for the formation of (**5a~5e**, **6a~6e**, **7a~7e**) and (**8a~8e**, **9a~9e**, **10a~10e**). The IR spectra of these compounds exist mainly the bands due to C=N, C=O and C-O-C functional groups. A strong band appeared at 1677-1645 cm^{-1} was assigned to C=O stretching which shifted to the low wave number owing to conjugated system. And, the absorption bands at 1577-1504 cm^{-1} was attributed to the C=N stretching vibrations. These compounds (**5a~5e**, **6a~6e**, **7a~7e**) showed sharp bands in the region 3243-3100 cm^{-1} due to N-H stretching vibrations. In addition, the absorption bands at 1231-1219 cm^{-1} was attributed to the C-O-C, which also confirmed the formation of desired oxadiazoline ring in the compounds (**8a~8e**, **9a~9e**, **10a~10e**). And the bands due to *v*(NH) stretch were absent. The data of the IR spectra of all new compounds are listed in Table 2.

Further evidence for the formation of (**5a~5e**, **6a~6e**, **7a~7e**) and (**8a~8e**, **9a~9e**, **10a~10e**) were obtained by ^{1}H NMR spectroscopy, which provided diagnostic tools for the positional elucidation of the protons. In the ^{1}H NMR spectra, phenyl protons were observed at the expected chemical shifts and integral values in all compounds. The single signal at 8.71-8.41 ppm was assigned to N-H of compounds (**5a~5e**, **6a~6e**, **7a~7e**). And, The CH=N proton of compounds showed single signal at 4.64-4.41 ppm. In addition, 8.49-8.21 ppm was due to C-H proton of pyrazole ring. As for the compounds (**8a~8e**, **9a~9e**, **10a~10e**), the signals of N-H and CH=N proton were disappeared after the ring closure, then proton belonging to the oxadiazoline ring was observed with the expected chemical shift at 8.77-8.43 ppm. The data of ^{1}H NMR spectra of all new compounds are listed in Table 2.

The MS (ESI) spectra displayed that all synthesized compounds had quasi-molecular on peaks; most of which were the base peaks. The characteristic peaks were observed in the mass spectra of the compounds. The elemental analysis date and MS data of all new compounds are listed in Table 1.

As shown in Table 3, all of the tested compounds showed moderate activities against *Alternaria solani, Sclerotinia sclerotiorum*. And, the entire investigated bis-heterocyclic compounds exhibited good fungicidal activity with the percentage inhibition of six strains ranged from 45.6 to 97.5, while the most active compounds **10d** (R^1=Cl, R^2=Br) and **10e** (R^1=Cl, R^2=NO_2) among the series exhibited the excellent inhibitory activity (> 85.5%) against six strains. However, pyrazole carbohydrazide hydrazone derivatives were found to be less active among the tested compounds. Table 3 perusal of data suggests that the active

Table 1. Physical data, the elemental analysis and MS data of new compounds

Compd.	Molecule	Yield/%	m.p./°C	Elemental analysis (calcd.)/%			MS m/z (%)
				C	H	N	
5a	$C_{25}H_{22}O_3N_4$	81	192~194	70.47(70.41)	5.22(5.20)	13.11(13.14)	449 ([M+ Na]$^+$, 100)
5b	$C_{26}H_{24}O_3N_4$	87	191~192	70.83(70.89)	5.48(5.49)	12.74(12.72)	463 ([M+ Na]$^+$, 100)
5c	$C_{26}H_{24}O_4N_4$	89	183~184	68.48(68.41)	5.32(5.30)	12.24(12.27)	479 ([M+Na]$^+$, 100)
5d	$C_{25}H_{21}O_3N_4Br$	88	204~206	59.37(59.42)	4.21(4.19)	11.11(11.09)	528 ([M+ Na]$^+$, 100)
5e	$C_{25}H_{21}O_5N_5$	70	214~215	63.76(63.69)	4.48(4.49)	14.83(14.85)	494 ([M+ Na]$^+$, 100)
6a	$C_{24}H_{19}O_2N_4Br$	88	218~219	60.69(60.64)	4.05(4.03)	11.76(11.79)	498 ([M+Na]$^+$, 100)
6b	$C_{25}H_{21}O_2N_4Br$	82	225~227	61.28(61.36)	4.34(4.33)	11.46(11.45)	512 ([M+Na]$^+$, 100)
6c	$C_{25}H_{21}O_3N_4Br$	83	160~161	59.37(59.42)	4.17(4.19)	11.12(11.09)	528 ([M+Na]$^+$, 100)
6d	$C_{24}H_{18}O_2N_4Br_2$	87	206~207	52.08(52.01)	3.25(3.27)	10.15(10.11)	577 ([M+Na]$^+$, 100)
6e	$C_{24}H_{18}O_4N_5Br$	74	247~248	55.47(55.40)	3.50(3.49)	13.42(13.46)	543 ([M+Na]$^+$, 100)
7a	$C_{24}H_{19}O_2N_4Cl$	85	137~139	66.82(66.90)	4.45(4.44)	13.04(13.01),	454 ([M+Na]$^+$, 100)
7b	$C_{25}H_{21}O_2N_4Cl$	82	124~125	67.56(67.49)	4.77(4.76)	12.55(12.59)	468 ([M+Na]$^+$, 100)
7c	$C_{25}H_{21}O_3N_4Cl$	83	131~132	65.09(65.15)	4.62(4.59)	12.18(12.16)	484 ([M+Na]$^+$, 100)
7d	$C_{24}H_{18}O_2N_4ClBr$	85	189~190	56.45(56.54)	3.57(3.56)	10.96(10.99)	533 ([M+Na]$^+$, 100)
7e	$C_{24}H_{18}O_4N_5Cl$	73	213~214	60.53(60.57)	3.79(3.81)	14.74(14.72)	499 ([M+Na]$^+$, 100)
8a	$C_{27}H_{24}O_4N_4$	79	115~116	69.28(69.22)	5.17(5.16)	11.93(11.96)	491 ([M+Na]+, 100)
8b	$C_{28}H_{26}O_4N_4$	73	113~115	69.62(69.70)	5.41(5.43)	11.59(11.61)	505 ([M+Na]$^+$, 100)
8c	$C_{28}H_{26}O_5N_4$	72	118~119	67.54(67.46)	5.24(5.26)	11.27(11.24)	521 ([M+Na]$^+$, 100)
8d	$C_{27}H_{23}O_4N_4Br$	76	120~121	59.17(59.24)	4.24(4.23)	10.16(10.23)	570 ([M+Na]$^+$, 100)
8e	$C_{27}H_{23}O_6N_5$	71	>250	63.06(63.15)	4.49(4.51)	13.67(13.64)	536 ([M+Na]$^+$, 100)
9a	$C_{26}H_{21}O_3N_4Br$	68	125~127	60.28(60.36)	4.10(4.09)	10.80(10.83)	540 ([M+Na]$^+$, 100)
9b	$C_{27}H_{23}O_3N_4Br$	74	136~137	61.11(61.03)	4.34(4.36)	10.50(10.54)	554 ([M+Na]$^+$, 100)
9c	$C_{27}H_{23}O_4N_4Br$	78	225~226	59.17(59.24)	4.24(4.23)	10.26(10.23)	570 ([M+Na]$^+$, 100)
9d	$C_{26}H_{20}O_3N_4Br_2$	72	>250	52.30(52.37)	3.39(3.38)	9.43(9.40)	619 ([M+Na]$^+$, 100)
9e	$C_{26}H_{20}O_5N_5Br$	61	183~184	55.60(55.53)	3.57(3.58)	12.49(12.45)	585 ([M+Na]$^+$, 100)
10a	$C_{26}H_{21}O_3N_4Cl$	68	120~121	66.14(66.03)	4.50(4.48)	11.81(11.85)	496 ([M+Na]$^+$, 100)
10b	$C_{27}H_{23}O_3N_4Cl$	72	132~133	66.68(66.60)	4.75(4.76)	11.48(11.51)	510 ([M+Na]$^+$, 100)
10c	$C_{27}H_{23}O_4N_4Cl$	78	210~211	64.40(64.48)	4.58(4.61)	11.16(11.14)	526 ([M+Na]$^+$, 100)
10d	$C_{26}H_{20}O_3N_4ClBr$	71	196~197	65.65(56.59)	3.67(3.65)	10.22(10.15)	575 ([M+Na]$^+$, 100)
10e	$C_{26}H_{20}O_5N_5Cl$	54	225~227	60.23(60.30)	3.87(3.89)	13.56(13.52)	541 ([M+Na]$^+$, 100)

antibacterial compounds could be related to substituent. It indicated that compounds which substituted electron-withdrawing groups possess reasonable good antibacteria activity as compared to that of electron-donating group. The preliminary fungicidal activities of these novel compounds evidenced that the presence of bromine and nitro groups in the aromatic ring of 5-position and chlorine group in the aromatic ring at the 3-position of the pyrazoline nucleus gave rise to an increased antibacterial activities. All in all, we founded that compounds carrying two heterocyclic moieties are more active than those carrying single pyrazole moiety in our work. Moreover, bis-heterocyclic compounds containing both pyrazoline and oxadiazoline are important compounds containing bioactivity that are worthy of doing research.

EXPERIMENTAL

General method

Melting points were taken on a Yanaco MP-S3 microscopic melting point apparatus. The IR spectra were recorded in KBr pellets on a Brucker Equinox-55 FT-IR apparatus. The ^{1}H NMR spectra were recorded on an INOVA-400 (using TMS as internal standard, DMSO-d_6 as solvent). Mass spectra were recorded on an HP 1100 LC-MS (ESI). Elemental analyses were performed on Perkin-Elmer 2400 CHN analyzer. All reagents were commercial products of analytical grade and can be used directly without purification except where they especially noted.

1. Compound 1~3 were prepared according to the reported method[17,18]

1: Yield 81%, m.p. 136~138 ºC (lit[18]: m.p. 141~143

Table 2. IR, ^{1}H NMR data of new compounds

Compd.	IR (KBr) ν/cm^{-1}	^{1}H NMR (DMSO-d_6, 400 MHZ) δ
5a	3161 (s, -NH-), 3042 (w, Ar-H), 1666 (s, C=O), 1540 (s, C=N)	8.43 (s, 1H, -NH-CO-), 8.41 (s, 1H, pyrazole-H), 6.94~8.42 (m, 14H, ph-H), 4.64 (s, 1H, -CH=N-), 3.34 (s, 2H, -CH_2O-), 2.50 (3H, s, -OCH_3)
5b	3195 (s, -NH-), 3048 (w, Ar-H), 1671 (s, C=O), 1503 (s, C=N)	8.43 (s, 1H, -NH-CO-), 8.29 (s, 1H, pyrazole-H), 6.71~7.52 (m, 13H, ph-H), 4.64 (s, 1H, -CH=N-), 3.31 (s, 2H, -CH_2O-), 3.79 (3H, s, -OCH_3), 2.48 (s, 3H, -CH_3)
5c	3174 (s, -NH-), 3054 (w, Ar-H), 1645 (s, C=O), 1504 (s, C=N)	8.47 (s, 1H, -NH-CO-), 8.49 (s, 1H, pyrazole-H), 7.26~8.10 (m, 13H, ph-H), 4.53 (s, 1H, -CH=N-), 3.83 (s, 2H, -CH_2O-), 3.56 (3H, s, -OCH_3), 3.42 (3H, s, -OCH_3)
5d	3190 (s, -NH-), 3047 (w, Ar-H), 1661 (s, C=O), 1508 (s, C=N)	8.64 (s, 1H, -NH-CO-), 8.27 (s, 1H, pyrazole-H), 6.75~7.89 (m, 13H, ph-H), 4.51 (s, 1H, -CH=N-), 3.57 (s, 2H, -CH_2O-), 3.34 (3H, s, -OCH_3)
5e	3243 (s, -NH-), 3042 (w, Ar-H), 1666 (s, C=O), 1514 (s, C=N)	8.71 (s, 1H, -NH-CO-), 8.41 (s, 1H, pyrazole-H), 6.73~7.68 (m, 13H, ph-H), 4.55 (s, 1H, -CH=N-), 3.61 (s, 2H, -CH_2O-), 3.34 (3H, s, -OCH_3)
6a	3195 (s, -NH-), 3043 (w, Ar-H), 1648 (s, C=O), 1577 (s, C=N)	8.57 (s, 1H, -NH-CO-), 8.21 (s, 1H, pyrazole-H), 6.79~7.32 (m, 14H, ph-H), 4.41 (s, 1H, -CH=N-), 3.20 (s, 2H, -CH_2O-)
6b	3199 (s, -NH-), 3048 (w, Ar-H), 1645 (s, C=O), 1510 (s, C=N)	8.49 (s, 1H, -NH-CO-), 8.34 (s, 1H, pyrazole-H), 7.31~7.42 (m, 13H, ph-H), 4.52 (s, 1H, -CH=N-), 3.29 (s, 2H, -CH_2O-), 2.46 (s, 3H, -CH_3)
6c	3174 (s, -NH-), 3054 (w, Ar-H), 1645 (s, C=O), 1527 (s, C=N)	8.49 (s, 1H, -NH-CO-), 8.35 (s, 1H, pyrazole-H), 7.23~7.80 (m, 13H, ph-H), 4.55 (s, 1H, -CH=N-), 3.24 (s, 2H, -CH_2O-), 3.68 (s, 3H, -OCH_3)
6d	3183 (s, -NH-), 3061 (w, Ar-H), 1668 (s, C=O), 1536 (s, C=N)	8.46 (s, 1H, -NH-CO-), 8.35 (s, 1H, pyrazole-H), 6.85~7.83 (m, 13H, ph-H), 4.62 (s, 1H, -CH=N-), 3.31 (s, 2H, -CH_2O-)
6e	3198 (s, -NH-), 3042 (w, Ar-H), 1677 (s, C=O), 1529 (s, C=N)	8.47 (s, 1H, -NH-CO-), 8.41 (s, 1H, pyrazole-H), 6.87~7.69 (m, 13H, ph-H), 4.54 (s, 1H, -CH=N-), 3.29 (s, 2H, -CH_2O-)
7a	3174 (s, -NH-), 3059 (w, Ar-H), 1676 (s, C=O), 1534 (s, C=N)	8.43 (s, 1H, -NH-CO-), 8.26 (s, 1H, pyrazole-H), 6.80~7.02 (m, 14H, ph-H), 4.64 (s, 1H, -CH=N-), 3.34 (s, 2H, -CH_2O-)
7b	3195 (s, -NH-), 3048 (w, Ar-H), 1645 (s, C=O), 1504 (s, C=N)	8.49 (s, 1H, -NH-CO-), 8.34 (s, 1H, pyrazole-H), 7.31~7.42 (m, 13H, ph-H), 4.52 (s, 1H, -CH=N-), 3.29 (s, 2H, -CH_2O-), 2.46 (s, 3H, -CH_3)
7c	3174 (s, -NH-), 3054 (w, Ar-H), 1645 (s, C=O), 1507 (s, C=N)	8.49 (s, 1H, -NH-CO-), 8.35 (s, 1H, pyrazole-H), 7.23~7.80 (m, 13H, ph-H), 4.55 (s, 1H, -CH=N-), 3.24 (s, 2H, -CH_2O-), 3.68 (s, 3H, -OCH_3)
7d	3183 (s, -NH-), 3061 (w, Ar-H), 1668 (s, C=O), 1526 (s, C=N)	8.46 (s, 1H, -NH-CO-), 8.35 (s, 1H, pyrazole-H), 6.85~7.83 (m, 13H, ph-H), 4.62 (s, 1H, -CH=N-), 3.31 (s, 2H, -CH_2O-)
7e	3198 (s, -NH-), 3042 (w, Ar-H), 1677 (s, C=O), 1539 (s, C=N)	8.53 (s, 1H, -NH-CO-), 8.33 (s, 1H, pyrazole-H), 6.87~7.69 (m, 13H, ph-H), 4.54 (s, 1H, -CH=N-), 3.29 (s, 2H, -CH_2O-)
8a	3059 (w, Ar-H), 1666 (s, C=O), 1538 (s, C=N), 1256 (s, C-O-C)	8.69 (s, 1H, oxadiazole-H), 7.97 (s, 1H, pyrazole-H), 7.34~7.86 (m, 14H, ph-H), 3.81 (s, 2H, -CH_2O-), 3.34 (3H, s, -OCH_3), 2.23 (s, 3H, -$COCH_3$)
8b	3048 (w, Ar-H), 1671 (s, C=O), 1522 (s, C=N), 1220 (s, C-O-C)	8.61 (s, 1H, oxadiazole-H), 7.99 (s, 1H, pyrazole-H), 7.48~8.09 (m, 13H, ph-H), 3.83 (s, 2H, -CH_2O-), 3.34 (3H, s, -OCH_3), 3.29 (s, 3H, -CH_3), 2.26 (s, 3H, -$COCH_3$)
8c	3033 (w, Ar-H), 1647 (s, C=O), 1525 (s, C=N), 1221 (s, C-O-C)	8.63 (s, 1H, oxadiazole-H), 7.87 (s, 1H, pyrazole-H), 7.12~7.86 (m, 13H, ph-H), 3.92 (s, 2H, -CH_2O-), 3.75 (3H, s, -OCH_3), 3.61 (3H, s, -OCH_3), 2.16 (s, 3H, -$COCH_3$)
8d	3059 (w, Ar-H), 1675 (s, C=O), 1521 (s, C=N), 1225 (s, C-O-C)	8.61 (s, 1H, oxadiazole-H), 8.24 (s, 1H, pyrazole-H), 7.27~7.83 (m, 13H, ph-H), 3.75 (s, 2H, -CH_2O-), 3.42 (3H, s, -OCH_3), 2.32 (s, 3H, -$COCH_3$)
8e	3071 (w, Ar-H), 1676 (s, C=O), 1513 (s, C=N), 1256 (s, C-O-C)	8.77 (s, 1H, oxadiazole-H), 8.06 (s, 1H, pyrazole-H), 7.19~7.92 (m, 13H, ph-H), 3.95 (s, 2H, -CH_2O-), 3.41 (3H, s, -OCH_3), 2.26 (s, 3H, -$COCH_3$)

9a	3053 (w, Ar-H), 1659 (s, C=O), 1534 (s, C=N), 1220 (s, C-O-C)	8.49 (s, 1H, oxadiazole-H), 7.86 (s, 1H, pyrazole-H), 7.19~7.76 (m14H, ph-H), 3.31 (s, 2H, -CH_2O-), 2.17 (s, 3H, -$COCH_3$)
9b	3069 (w, Ar-H), 1649 (s, C=O), 1513 (s, C=N), 1229 (s, C-O-C)	8.47 (s, 1H, oxadiazole-H), 7.92 (s, 1H, pyrazole-H), 7.28~7.79 (m, 13H, ph-H), 3.35 (s, 2H, -CH_2O-), 2.14 (s, 3H, -$COCH_3$), 2.55 (s, 3H, -CH_3)
9c	3042 (w, Ar-H), 1647 (s, C=O), 1546 (s, C=N), 1231 (s, C-O-C)	8.52 (s, 1H, oxadiazole-H), 7.98 (s, 1H, pyrazole-H), 7.17~7.76 (m, 13H, ph-H), 3.32 (s, 2H, -CH_2O-), 3.82 (3H, s, -OCH_3), 2.18 (s, 3H, -$COCH_3$)
9d	3068 (w, Ar-H), 1671 (s, C=O), 1529 (s, C=N), 1222 (s, C-O-C)	8.49 (s, 1H, oxadiazole-H), 8.03 (s, 1H, pyrazole-H), 7.16~7.71 (m, 13H, ph-H), 3.35 (s, 2H, -CH_2O-), 2.20 (s, 3H, -$COCH_3$)
9e	3073 (w, Ar-H), 1676 (s, C=O), 1526 (s, C=N), 1219 (s, C-O-C)	8.53 (s, 1H, oxadiazole-H), 7.97 (s, 1H, pyrazole-H), 7.21~7.73 (m, 13H, ph-H), 3.34 (s, 2H, -CH_2O-), 2.19 (s, 3H, -$COCH_3$)
10a	3051 (w, Ar-H), 1668 (s, C=O), 1548 (s, C=N), 1235 (s, C-O-C)	8.55 (s, 1H, oxadiazole-H), 7.86 (s, 1H, pyrazole-H), 7.23~7.81 (m, 14H, ph-H), 3.31 (s, 2H, -CH_2O-), 2.19 (s, 3H, -$COCH_3$)
10b	3059 (w, Ar-H), 1644 (s, C=O), 1523 (s, C=N), 1228 (s, C-O-C)	8.57 (s, 1H, oxadiazole-H), 7.82 (s, 1H, pyrazole-H), 7.27~7.75 (m, 13H, ph-H), 3.31 (s, 2H, -CH_2O-), 2.17 (s, 3H, -$COCH_3$), 2.59 (s, 3H, -CH_3)
10c	3062 (w, Ar-H), 1654 (s, C=O), 1531 (s, C=N), 1221 (s, C-O-C)	8.53 (s, 1H, oxadiazole-H), 7.88 (s, 1H, pyrazole-H), 7.15~7.72 (m, 13H, ph-H), 3.27 (s, 2H, -CH_2O-), 3.87 (3H, s, -OCH_3), 2.15 (s, 3H, -$COCH_3$)
10d	3064 (w, Ar-H), 1661 (s, C=O), 1522 (s, C=N), 1222 (s, C-O-C)	8.48 (s, 1H, oxadiazole-H), 7.93 (s, 1H, pyrazole-H), 7.11~7.74 (m, 13H, ph-H), 3.25 (s, 2H, -CH_2O-), 2.27 (s, 3H, -$COCH_3$)
10e	3078 (w, Ar-H), 1665 (s, C=O), 1524 (s, C=N), 1224 (s, C-O-C)	8.43 (s, 1H, oxadiazole-H), 7.91 (s, 1H, pyrazole-H), 7.20~7.67 (m, 13H, ph-H), 3.24 (s, 2H, -CH_2O-), 2.29 (s, 3H, -$COCH_3$)

ºC);

2: Yield 88%, m.p. 140~142 ºC (lit[18]: m.p. 138~139 ºC);

3: Yield 89%, m.p. 141~143 ºC (lit[18]: m.p. 139~141 ºC);

2. Compounds 4a-4e were prepared according to the reported method[19]

4a: Yield 71%, m.p. 112~ 113 ºC; (lit[19]: 111~112 ºC);

4b: Yield 73%, m.p. 137~138 ºC; (lit[19]: 134~136 ºC);

4c: Yield 80%, m.p. 141~142 ºC; (lit[19]: 135~136 ºC);

4d: Yield 74%, m.p. 172~173 ºC; (lit[19]: 171~172 ºC);

4e: Yield 68%, m.p. 189~191 ºC;

3. General procedure for the preparation of hydrazone compounds containg pyrazolyl (5a~5e, 6a~6e, 7a~7e)

4-Substituted aryloxyacetyl hydrazine **4a~4e** (5.5 mmol) and 1-phenyl-3-aryl-4-formylpyrazoles (**1**~**3**) (5.0 mmol) in ethanol (30 mL) was refluxed (incorporating) in the presence of a catalytic amount of glacial acetic acid (TLC, 1:1 EtOAc–petroleum ether) for 3~3.5 h. The solution was filtered and concentrated under reduced pressure to afford crude produce, which was recrystallized from DMF as colorless crystals.

4. General procedure for the preparation of 3-(substituted)aryl-4-(3-acetyl-2-aryloxylmethylene-1,3,4-oxadiazoline-5)-1-phenyl-2-pyrazoline (8a~8e, 9a~9e, 10a~10e)

A solution of the corrsponding hydrazone (**5a~5e**, **6a~6e**, **7a~7e**) (2 mmol) in acetic anhydride was refluxed for 1 h. the completion was monitored by (TLC, 1:1 MeOH-CCl_3H). The solution was filtered and poured into iced water to give the crude product. The solid subsequently was washed by water, then recrystallized from acetone to give compound as colorless crystals.

5. Fungicidal evaluation (5a~5e, 6a~6e, 7a~7e, 8a~8e, 9a~9e, 10a~10e)

The antibacterial activities of the synthesized compounds, which against six strains such as *Fusarium oxyaporium*, *Verticillium dahliae*, *Rhizoctonia solani*, *Pychium aphanidermatum*, *Alternaria solani*, *Sclerotinia sclerotiorum*, were carried out by the reported method.[11,12,20] Compounds 500 mg (anhydrous), which dissolved in 150.0 mL of sterilized DMF, were diluted with sterilized DMF to make 500 mg/L sample solutions. 2 mL of sterilized sample solution were mixed with 18 mL PDA to make 50 mg/L test culture medium. The center of medium containing the test

Table 3. Fungicidal activities of new compounds

Compd.	Inhibition rate /%					
	Fusarium oxyaporium	*Verticillium dahliae*	*Rhizoctonia solani*	*Pychiumaph anidermatum*	*Alternaria solani*	*Sclerotinia sclerotiorum*
5a	32.06	19.76	1.00	8.97	50.77	57.03
5b	38.35	30.92	30.64	6.79	64.16	60.89
5c	38.84	27.70	23.42	7.68	63.89	60.86
5d	69.31	49.32	56.20	55.32	76.79	75.27
5e	69.93	45.62	53.40	39.76	74.34	74.53
6a	44.46	31.45	6.77	16.47	50.85	54.36
6b	51.55	45.41	16.06	52.67	57.92	67.85
6c	60.02	47.01	48.40	31.35	53.35	59.98
6d	61.56	64.46	50.36	60.25	73.55	71.77
6e	63.67	61.96	56.91	63.80	71.52	70.34
7a	32.06	38.73	9.52	29.55	48.71	57.00
7b	29.47	47.63	13.25	29.80	56.16	64.20
7c	28.26	47.06	35.07	28.57	55.53	63.41
7d	69.54	66.80	43.76	65.76	75.53	74.63
7e	67.39	68.61	55.53	59.98	73.62	71.31
8a	81.70	62.65	55.85	76.61	45.31	74.46
8b	85.59	69.17	77.45	80.26	80.03	83.18
8c	92.23	73.03	80.97	80.76	82.50	84.38
8d	94.75	77.74	79.32	87.01	89.05	89.13
8e	97.31	78.12	92.89	90.11	87.68	89.71
9a	94.18	71.17	86.39	77.76	83.50	71.76
9b	92.27	74.54	91.37	82.68	84.47	74.74
9c	94.34	71.78	92.05	87.88	82.83	73.45
9d	94.27	78.76	97.26	85.00	88.12	89.65
9e	95.86	74.36	97.84	85.80	89.92	89.62
10a	88.67	76.45	84.92	85.29	81.98	86.12
10b	92.51	79.17	89.31	90.16	94.58	92.88
10c	91.36	76.34	89.67	76.36	93.61	94.76
10d	91.85	86.38	95.18	92.86	97.36	96.83
10e	95.74	88.52	96.06	91.64	97.49	96.49

compounds delivered approximately 500 mm external diameter of bacilli cells in every three repetition. The samples were incubated aseptically at 26 °C for 48 ~ 72 h. By comparison, the medium without any test compound/DMF (sterilized) was also inoculated with the test organism to check whether the media supports the growth of the antibacterial activities or not.

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