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Tao Wang [a] , Cai Hua Zheng [a] , Shu Liu [a] & Hong Wu He [b]

[a] College of Chemistry and Chemical Engineering, Jiangxi Normal University , Nanchang, China

[b] Key Laboratory of Pesticide and Chemical Biology, Ministry of Education of China, Institute of Organic Synthesis, Central China Normal University , Wuhan, China

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Facile Method for the Synthesis of Pyrazolo[3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones via a Tandem Aza-Wittig Reaction

Tao Wang,[1] Cai Hua Zheng,[1] Shu Liu,[1] and Hong Wu He[2]
[1]College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, China
[2]Key Laboratory of Pesticide and Chemical Biology, Ministry of Education of China, Institute of Organic Synthesis, Central China Normal University, Wuhan, China

Abstract: Fifteen novel pyrazolo[3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones (**7a–o)** were designed and have been successfully synthesized via tandem aza-Wittig and annulation reactions of the corresponding iminophosphorances **5**, phenylisocyanate, and substituted phenols in 60–77% isolated yields. Their structures were clearly verified by infrared (IR), ^{1}H NMR, electron impact–mass spectrometry (EI-MS), and elemental analysis. The results of a preliminary bioassay indicated that some compounds possess inhibition activities against the root of *Brassica napus* (rape) and *Echinochloa crusgalli* (barnyard grass) at a dosage of 100 mg/L L and 10 mg/L.

Keywords: aza-Wittig reaction, herbicidal activity, pyrazolo[3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones, synthesis

INTRODUCTION

The derivatives of pyridopyrimidines have been the focus of great interest over many years. This is due to the wide range of biological activities associated with this heterocyclic scaffold. Some of their derivatives have

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Address correspondence to Tao Wang, College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, China. E-mail: wangtao1962@sohu.com

shown remarkable biological properties such as antitumor, antiviral, antibacterial, antihypertensive, antibronchitis, antiallergic, antiarthritic, and anti-HIV activities,[1–12] whereas others exhibited good insecticidal, growth regulatory, herbicidal, and fungicidal activities.[13–15] On the other hand, heterocycles containing the pyrazole nucleus exhibit various biological activities; several of them have been used as fungicidal, bactericidal, and insecticidal agents[16–18]. The introduction of a pyrazole ring to the pyrido[4,3-d]-pyrimidine-4-one system is expected to significantly influence the biological activities. However, this heterocyclic scaffold system has been much less investigated, and there is no report on the synthesis of pyrazolo[3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones.

The aza-Wittig reactions of iminophosphoranes have received increasing attention in view of their utility in the synthesis of N-heterocyclic compounds.[19–23] Recently, we have become interested in the synthesis of new bioactive heterocycles such as pyrido[4,3-d]-pyrimidine from various iminophosphoranes, with the aim of evaluating their biological activities. Herein, we describe a facile synthesis of 2-(substituted phenoxy)-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo[3,4-b]pyrido[4,3-d]pyrimidine-4-ones via the tandem aza-Wittig and cyclization reaction. The results of bioassay indicated that these title compounds possess herbicidal activity against the roots of *Brassica napus* (rape) and *Echinochloa crusgalli* (barnyard grass).

RESULTS AND DISCUSSION

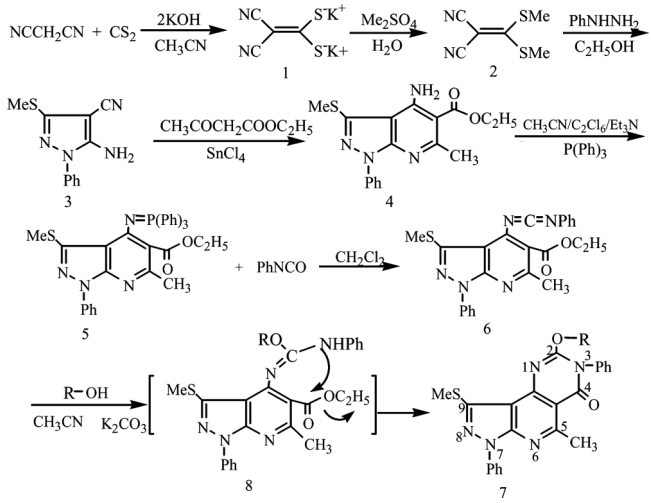
Synthesis

5-Amino-4-cyano-3-methylthio-1-phenylpyrazole **3**[24] was converted to pyrazolo[3,4-b]pyridine derivative **4** via reaction with acetoacetic ester and tin tetrachloride under heating. The iminophosphorane **5** was subsequently obtained in satisfactory yield when **4** was treated with triphenylphosphine, hexachloroethane, and Et_3N. Iminophosphorane **5** reacted with phenylisocyanate to give carbodiimide **6**. The direct reaction of carbodiimide **6** with substituted phenols did not produce 2-(substituted phenoxy)-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo[3,4-b]pyrido[4,3-d]pyrimidine-4-ones **7**. However, the reaction took place to give **7a–o** in good yields with heating for 12–14 h in the presence of a catalytic amount of K_2CO_3 (Table 1). The formation of **7** can be rationalized in terms of an initial nucleophilic addition of phenoxides to the carbodiimides **6** to give the intermediate **8**, which cyclizes to give **7a–o** (Scheme 1). Regardless of whether the substituents on the phenols were electron-withdrawing or electron-releasing groups, the cyclization was completed smoothly.

Table 1. The physical data of compounds **7**

Compound	R	Formula	Color	Mp (°C)	Reaction time (h)	Yield (%)[a]
7a	Ph	$C_{28}H_{21}N_5O_2S$	White	246–248	12	64
7b	2-ClPh	$C_{28}H_{20}ClN_5O_2S$	White	253–255	12	67
7c	4-ClPh	$C_{28}H_{20}ClN_5O_2S$	White	>280	14	60
7d	2-CH_3Ph	$C_{29}H_{23}N_5O_2S$	White	241–243	13	72
7e	4-CH_3Ph	$C_{29}H_{23}N_5O_2S$	White	265–267	12	65
7f	2-NO_2Ph	$C_{28}H_{20}N_6O_4S$	White	276–278	12	68
7g	4-NO_2Ph	$C_{28}H_{20}N_6O_4S$	White	262–264	14	66
7h	3-FPh	$C_{28}H_{20}FN_5O_2S$	White	243–245	13	74
7i	2,4-F_2Ph	$C_{28}H_{19}F_2N_5O_2S$	White	225–227	12	72
7j	4-BrPh	$C_{28}H_{20}BrN_5O_2S$	White	261–264	12	77
7k	2-Cl – 4-FPh	$C_{28}H_{19}FClN_5O_2S$	White	281–283	13	75
7l	3-Cl – 4-FPh	$C_{28}H_{19}FClN_5O_2S$	White	249–251	14	73
7m	2-Cl-5-CH_3Ph	$C_{29}H_{22}ClN_5O_2S$	White	242–245	13	69
7n	4-Cl-3-CH_3Ph	$C_{29}H_{22}ClN_5O_2S$	White	243–244	14	67
7o	2,4-Cl_2Ph	$C_{28}H_{19}Cl_2N_5O_2S$	White	277–279	13	76

[a]Yields of isolated products based on iminophosphorane **5**.



Scheme 1. Synthesis of the title compounds **7a**–**o**.

Herbicidal Activity

The herbicidal activity of all compounds **7** against *Brassica napus* (rape) and *Echinochloa crusgalli* (barnyard grass) has been investigated at the dosage of 100 mg/L and 10 mg/L using known procedure[25] compared with distilled water. The results of bioassay showed that many of them exhibit good herbicidal activity when the pyrazole ring is introduced. The inhibition rates are listed in Table 2. They showed that most of compounds **7** in Table 2 exhibit good inhibition rates (80–100%) against the root of barnyard grass at a dose of 10 mg/L. For example, **7d, 7e, 7f, 7g, 7j, 7k, 7l, 7m**, and **7o** showed >90% inhibition rate to roots of barnyard grass. Most of compounds 7 in Table 2 exhibit good inhibition rates (97–100%) against the roots of rape and barnyard grass at 100 mg/L. For example, **7a, 7b, 7c, 7e, 7g, 7h, 7i, 7j, 7k, 7l, 7m, 7n**, and **7o** showed >97% inhibition rate to roots of rape and barnyard grass.

EXPERIMENTAL

Melting points were measured on an electrothermal melting-point apparatus and are uncorrected. Mass spectra were measured on a Finnigan Trace MS 2000 spectrometer. Infrared (IR) spectra were recorded on an FTS-185 IR spectrometer as KBr pellets with absorption in centimeters^{-1}. ^{1}H NMR were recorded in dimethyl sulfoxide (DMSO)-d_6 or $CDCl_3$ as solvent on a Bruker AC-P400 spectrometer, and resonances

Table 2. The herbicidal activity of compounds **7**

Compound	R	Percentage of relative inhibition (root/stalk)			
		Rape (dose: 100 mg/L)	Rape (dose: 10 mg/L)	Barnyard grass (dose: 100 mg/L)	Barnyard grass (dose: 10 mg/L)
7a	Ph	100/100	57.4/9.50	100/100	81.4/20.0
7b	2-ClPh	97.1/98.7	35.1/13.3	100/100	63.6/33.5
7c	4-ClPh	97.6/89.7	12.7/−7.70	97.8/92.8	51.1/46.4
7d	2-CH_3Ph	94.5/96.5	23.2/8.40	100/100	97.5/77.8
7e	4-CH_3Ph	97.5/96.5	65.1/43.2	100/100	98.6/79.6
7f	2-NO_2Ph	93.7/95.3	43.3/33.3	100/100	95.6/77.5
7g	4-NO_2Ph	98.3/93.5	32.1/23.2	100/100	94.3/75.7
7h	3-FPh	98.7/97.6	53.3/33.0	100/100	73.4/67.8
7i	2,4-F_2Ph	100/100	54.3/9.50	100/100	62.8/60.0
7j	4-BrPh	98.5/98.7	45.5/23.4	100/100	96.4/79.8
7k	2-Cl-4-FPh	100/100	76.7/28.7	100/100	98.6/88.6
7l	3-Cl-4-FPh	100/100	80.5/46.6	100/100	97.3/73.4
7m	2-Cl-5-CH_3Ph	100/100	63.1/23.3	100/100	97.5/78.8
7n	4-Cl-3-CH_3Ph	100/100	53.2/2.40	97.7/76.7	72.1/30.0
7o	2,4-Cl_2Ph 2,4-D	100/100	83.1/73.6	97.1/82.1	97.1/79.6
		98.5/91.2	98.1/91.2	97.3/33.3	95.6/30.8

are given in parts per million (d) relative to tetramethylsilane (TMS). Elementary analyses were taken on a Vario EL III elementary analysis instrument. All of the solvents and materials were reagent grade and purified as required.

Synthesis of 3-Methylthio-1-phenyl-4-amine-5-ethanoxy-6-methyl-1H-pyrazolo[3,4-b]-pyridine 4

5-Amino-3-methylthio-1-phenyl-pyrazole-4-carbonitrile **3** (0.92 g, 4 mmol) and anhydrous $SnCl_4$ (0.92 mL, 8 mmol) were added to a stirred solution of ethyl acetoacetate (0.56 g, 4.3 mmol) in anhydrous toluene (15 mL). The mixture was stirred at rt for 1 h, and then heated at reflux for 5 h. The mixture was added to sat. aq. Na_2CO_3 solution (50 mL, pH 10), and the resulting suspension was extracted with AcOEt (350 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford **4** in 63.5% yield. Colorless crystals; mp 117–118°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40 (t, 3H, $J = 7.2$ Hz, CH_3), 2.68 (s, 3H, SCH_3), 2.78 (s, 3H, CH_3), 4.37 (q, 2H, $J = 7.2$ Hz, OCH_2CH_3), 7.25–8.22 (m, 5H, C_6H_5), 7.32 (br, 2H, NH_2). Elemental anal. calcd. for $C_{17}H_{18}N_4O_2S$: C, 59.63; H, 5.30; N, 16.36. Found: C, 59.59; H, 5.23; N, 16.44.

Synthesis of Iminophosphorane 5

To a solution of **4** (5.13 g, 15 mmol) in CH_3CN (60 mL), Ph_3P (7.86 g, 30 mmol), C_2Cl_6(7.11 g, 30 mmol), and, in this order, Et_3N (8.3 ml) were added. The mixture was stirred for 6–7 h at rt Then, the solution was concentrated, and the residue was recrystallized from EtOH to give **5** in 94.3% yield. mp 152–153°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, 3H, $CH_2\underline{CH_3}$, $J = 6.8$ Hz), 2.77 (s, 3H, SCH_3), 3.05 (s, 3H, CH_3), 4.67 (q, 2H, $\underline{CH_2}CH_3$, $J = 7.2$ Hz), 7.22–7.68 (m, 20H, Ar-H). Elemental anal. calcd. for $C_{35}H_{31}N_4O_2PS$: C, 69.75; H, 5.18; N, 9.30. Found: C, 71.49; H, 5.28; N, 9.67. MS (EI, m/z, %): 602 (M^+, 43.30%), 539 (21.71%), 463 (43.86%), 262 (58.26%), 201 (45.49%), 183 (100%), 108 (40.30%), and 77 (56.03 %).

General Procedure for the Preparation of 2-(Substituted Phenoxy)-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo [3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones

Phenylisocyanate (3 mmol) was added to a solution of iminophosphorane **5** (3 mmol) in dry methylene chloride (10 mL), under nitrogen at room

temperature. After the reaction mixture was left unstirred for 6–8 h, the solvent was removed under vacuum, and anhydrous ethanol (10 mL) was added to precipitate triphenylphosphineoxide. Removal of the solvent gave carbodiimides **6** [mp 161–161.3°C ^{1}H NMR (TMS, $CDCl_3$): δ 1.37 (t, 3H, $CH_2\underline{CH_3}$, $J = 6.8$ Hz), 2.77 (s, 3H, SCH_3), 3.05 (s, 3H, CH_3), 4.67 (q, 2H, $\underline{CH_2}CH_3$, $J = 7.2$ Hz), 7.24–8.38 (m, 10H, Ar-H)], which were used directly without further purification.

Substituted phenol (2 mmol) and cat. solid K_2CO_3 (0.024 g, 0.2 mmol) were added to the solution of **6** prepared previously in CH_3CN (20 mL). The mixture was stirred for 12–14 h at 75°C and filtered, the filtrate was condensed, and the residue was recrystallized from dichloromethane/petroleum ether to give pure 2-(substituted phenoxy)-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrzolo[3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones.

Data

2-Phenoxy-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo[3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones (**7a**)

Anal. calcd. (%) for $C_{28}H_{21}N_5O_2S$: C, 68.41; H, 4.31; N, 14.25. Found: C, 68.20; H, 4.64; N, 14.47. IR (KBr, ν/cm^{-1}): 3265 (Ph-H), 2919 (C-H), 1725 (C=O), 1674 (C=C), 1563 (N=C); ^{1}H NMR (DMSO-d_6, 400 MHz): 2.80 (s, 3H, SCH_3), 3.03 (s, 3H, CH_3), 7.27–8.28 (m, 15H, Ar-H); MS (EI, m/z, %): 491 ($M^+ + 1$, 2.08), 490 (M^+, 6.59), 489 ($M^+ - 1$, 16.01), 415 (23.94), 368 (35.05), 323 (53.66), 268 (28.44), 119 (32.13), 93 (52.28), 77 (100).

2-[(2-Chlorophenyl)oxy]-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo[3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones (**7b**)

Anal. calcd. (%) for $C_{28}H_{20}ClN_5O_2S$: C, 63.93; H, 3.83; N, 13.31. Found: C, 63.61; H, 3.64; N, 13.48; IR (KBr, ν/cm^{-1}): 3272 (Ph-H), 2911 (C-H), 1720 (C=O), 1663 (C=C), 1561 (N=C); ^{1}H NMR (DMSO-d_6, 400 MHz): 2.68 (s, 3H, SCH_3), 2.83 (s, 3H, CH_3), 7.17–8.29 (m, 14H, Ar-H); MS (EI, m/z, %): 526 ($M^+ + 1$, 2.22), 525 (M^+, 4.92), 415 (82.31), 382 (59.74), 368 (7.57), 323 (3.66), 268 (27.92), 119 (37.31), 93 (11.17), 77 (100).

2-[(4-Chlorophenyl)oxy]- 3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo [3,4-B]-pyrido[4,3-d]-pyrimidine-4-ones (**7c**)

Anal. calcd. (%) for $C_{28}H_{20}ClN_5O_2S$: C, 63.93; H, 3.83; N, 13.31. Found: C, 63.73; H, 3.62; N, 13.46; IR (KBr, ν/cm^{-1}): 3272 (Ph-H), 2912 (C-H),

1722 (C=O), 1671 (C=C), 1562 (N=C); ^{1}H NMR (DMSO-d_6, 400 MHz): 2.66 (s, 3H, SCH_3), 2.82 (s, 3H, CH_3), 7.19–8.30 (m, 14H, Ar-H); MS (EI, m/z, %): 526 ($M^+ + 1$, 1.02), 415 (86.36), 382 (50.94), 368 (4.59), 323 (4.69), 268 (21.02), 119 (47.30), 93 (10.11), 77 (100).

2-[(2-Methylphenyl)oxy]-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo [3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones (**7d**)

Anal. calcd. (%) for $C_{29}H_{23}N_5O_2S$: C, 68.89; H, 4.59; N, 13.85. Found: C, 68.71; H, 4.72; N, 13.66, IR (KBr, ν/cm^{-1}): 3266 (Ph-H), 2914 (C-H), 1724 (C=O), 1666 (C=C), 1562 (N=C), ^{1}H NMR (DMSO-d_6, 400 MHz): 1.58 (s, CH_3Ph), 2.76 (s, 3H, SCH_3), 2.92 (s, 3H, CH_3), 7.18–8.32 (m, 14H, Ar-H); MS (EI, m/z, %): 506 ($M^+ + 1$, 1.92), 505 (M^+ 4.02), 415 (81.32), 382 (53.93), 368 (4.39), 323 (4.62), 268 (35.03), 119 (42.33), 93 (13.21), 77 (100).

2-[(4-Methylphenyl)oxy]-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo [3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones (**7e**)

Anal. calcd. (%) for $C_{29}H_{23}N_5O_2S$: C, 68.89; H, 4.59; N, 13.85. Found: C, 68.71; H, 4.72; N, 13.66; IR (KBr, ν/cm^{-1}): 3262 (Ph-H), 2913 (C-H), 1721 (C=O), 1670 (C=C), 1558 (N=C), ^{1}H NMR (DMSO-d_6, 400 MHz): 1.58 (s, CH_3Ph), 2.76 (s, 3H, SCH_3), 2.92 (s, 3H, CH_3), 7.22–8.34 (m, 14H, Ar-H); MS (EI, m/z, %): 506 ($M^+ + 1$, 1.32), 505 (M^+, 3.32), 415 (82.22), 382 (51.33), 368 (11.19), 323 (4.32), 268 (31.43), 119 (48.43), 93 (12.24), 77 (100).

2-[(2-Nitrophenyl)oxy]-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo [3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones (**7f**)

Anal. calcd. (%) for $C_{28}H_{20}N_6O_4S$: C, 62.68; H, 3.76; N, 15.66. Found: C, 62.43; H, 3.56; N, 15.87, IR (KBr, ν/cm^{-1}): 3258 (Ph-H), 2927 (C-H), 1726 (C=O), 1670 (C=C), 1561 (N=C), ^{1}H NMR (DMSO-d_6, 400 MHz): 2.68 (s, 3H, SCH_3), 2.88 (s, 3H, CH_3), 7.08–8.29 (m, 14H, Ar-H); MS (EI, m/z, %): 537 ($M^+ + 1$, 3.12), 536 (M^+, 6.59), 535 ($M^+ - 1$, 16.01), 415 (76.39), 382 (56.74), 219 (32.29), 119 (22.76), 93(16.76), 77 (100).

2-[(4-Nitrophenyl)oxy]-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo [3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones (**7g**)

Anal. calcd. (%) for $C_{28}H_{20}N_6O_4S$: C, 62.68; H, 3.76; N, 15.66. Found: C, 62.43; H, 3.56; N, 15.87, IR (KBr, ν/cm^{-1}): 3264 (Ph-H), 2919 (C-H), 1723

(C=O), 1664 (C=C), 1553 (N=C), ^{1}H NMR (DMSO-d_6, 400 MHz): 2.68 (s, 3H, SCH_3), 2.86 (s, 3H, CH_3), 7.16–8.28 (m, 14H, Ar-H); MS (EI, m/z, %): 537 ($M^+ + 1$, 3.72), 536 (M^+, 10.50), 535(M^+, −1 19.11), 415 (78.38), 382 (55.64), 219 (31.22), 119 (25.26), 93(19.79), 77 (100).

2-[(3-Fluorophenyl)oxy]-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo [3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones (**7h**)

Anal. calcd. (%) for $C_{28}H_{20}FN_5O_2S$: C, 66.00; H, 3.96; N, 13.74. Found: C, 66.23; H, 4.03; N, 13.57, IR (KBr, ν/cm^{-1}): 3262 (Ph-H), 2925 (C-H), 1724 (C=O), 1677 (C=C), 1566 (N=C), ^{1}H NMR (DMSO-d_6, 400 MHz): 2.72 (s, 3H, SCH_3), 2.99 (s, 3H, CH_3), 7.07–8.30 (m, 14H, Ar-H); MS (EI, m/z, %): 512 ($M^+ + 3$, 4.32), 511 ($M^+ + 2$, 7.87), 510 ($M^+ + 1$, 43.32), 494 (32.69), 474 (38.05), 398 (15.68), 219 (32.12), 119 (24.72), 101 (49.80), 93 (6.41), 77 (100).

2-[(2,4-Difluorophenyl)oxy]-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo [3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones (**7i**)

Anal. calcd. (%) for $C_{28}H_{19}F_2N_5O_2S$: C, 63.75; H, 3.63; N, 13.28. Found: C, 63.54; H, 3.46; N, 13.10, IR (KBr, ν/cm^{-1}): 3265 (Ph-H), 2926 (C-H), 1730 (C=O), 1680 (C=C), 1568 (N=C), ^{1}H NMR (DMSO-d_6, 400 MHz): 2.58 (s, 3H, SCH_3), 3.07 (s, 3H, CH_3), 6.97–8.32 (m, 13H, Ar-H); MS (EI, m/z, %): 529 ($M^+ + 3$, 7.19), 528 ($M^+ + 2$, 24.12), 527 ($M^+ + 1$, 55.11), 494 (38.27), 474 (31.08), 398 (19.62), 219 (34.09), 119 (21.77), 101 (44.00), 93 (6.32), 77 (100).

2-[(4-Bromophenyl)oxy]-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo [3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones (**7j**)

Anal. calcd. (%) for $C_{28}H_{20}BrN_5O_2S$: C, 58.95; H, 3.53; N, 12.28. Found: C, 58.78; H, 3.34; N, 12.02, IR (KBr, ν/cm^{-1}): 3263 (Ph-H), 2924 (C-H), 1728 (C=O), 1675 (C=C), 1565 (N=C), ^{1}H NMR (DMSO-d_6, 400 MHz): 2.68 (s, 3H, SCH_3), 3.00 (s, 3H, CH_3), 6.98–8.22 (m, 14H, Ar-H); MS (EI, m/z, %): 570 ($M^+ + 1$, 5.62), 415 (67.76), 382 (72.90), 368 (5.56), 323 (4.06), 268 (26.21), 119 (52.33), 93 (11.12), 77 (100).

2-[(2-Chloro-4-fluorophenyl)oxy]-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo[3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones (**7k**)

Anal. calcd. (%) for $C_{28}H_{19}FClN_5O_2S$: C, 61.82; H, 3.52; N, 12.87. Found: C, 61.69; H, 3.33; N, 12.69, IR (KBr, ν/cm^{-1}): 3268 (Ph-H),

2924 (C-H), 1729 (C=O), 1678 (C=C), 1566 (N=C), ^{1}H NMR (DMSO-d_6, 400 MHz): 2.56 (s, 3H, SCH_3), 2.97 (s, 3H, CH_3), 6.98–8.23 (m, 13H, Ar-H); MS (EI, m/z, %): 544 ($M^+ + 1$, 2.72), 543 (M^+ 6.59), 415 (54.73), 382 (63.60), 368 (7.58), 323 (8.16), 268 (21.25), 119 (72.35), 93 (14.22), 77 (100).

2-[(3-Chloro-4-fluorophenyl)oxy]-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo[3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones (**7l**)

Anal. calcd. (%) for $C_{28}H_{19}FClN_5O_2S$: C, 61.82; H, 3.52; N, 12.87. Found: C, 61.66; H, 3.31; N, 12.73, IR (KBr, ν/cm^{-1}): 3266 (Ph-H), 2922 (C-H), 1726 (C=O), 1675 (C=C), 1564 (N=C), ^{1}H NMR (DMSO-d_6, 400 MHz): 2.56 (s, 3H, SCH_3), 3.02 (s, 3H, CH_3), 6.97–8.24(m, 13H, Ar-H); MS (EI, m/z, %): 544 ($M^+ + 1$, 3.79), 543 (M^+, 9.74), 415 (59.61), 382 (62.63), 368 (6.98), 323 (7.31), 268 (22.45), 119 (79.25), 93 (12.52), 77 (100).

2-[(2-Chloro-5-methylphenyl)oxy]-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo[3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones (**7m**)

Anal. calcd. (%) for $C_{29}H_{22}ClN_5O_2S$: C, 64.50; H, 4.11; N, 12.97. Found: C, 64.46; H, 4.30; N, 13.16, IR (KBr, ν/cm^{-1}): 3266 (Ph-H), 2926 (C-H), 1728 (C=O), 1677 (C=C), 1565 (N=C), ^{1}H NMR (DMSO-d_6, 400 MHz): 1.60 (s, CH_3Ph), 2.78 (s, 3H, SCH_3), 3.02 (s, 3H, CH_3), 7.17–8.35 (m, 13H, Ar-H); MS (EI, m/z, %): 539 ($M^+ + 1$, 2.72), 443 (100), 410 (71.21), 382 (48.62), 368 (7.77), 323 (6.16), 268 (16.65), 219 (14.65), 119 (24.76), 93 (13.45), 77 (98.38).

2-[(4-Chloro-3-methylphenyl)oxy]-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrzolo [3,4-b]-pyrido[4,3-d]-pyrimidine-4-ones (**7n**)

Anal. calcd. (%) for $C_{29}H_{22}ClN_5O_2S$: C, 64.50; H, 4.11; N, 12.97. Found: C, 64.30; H, 4.34; N, 13.19, IR (KBr, ν/cm^{-1}): 3262 (Ph-H), 2921 (C-H), 1729 (C=O), 1674 (C=C), 1562 (N=C), ^{1}H NMR (DMSO-d_6, 400 MHz): 1.60 (s, CH_3Ph), 2.77 (s, 3H, SCH_3), 3.04 (s, 3H, CH_3), 7.24–8.37 (m, 13H, Ar-H); MS (EI, m/z, %): 539 ($M^+ + 1$, 1.82), 443 (100), 410 (62.69), 382 (52.85), 368 (8.89), 323 (6.10), 268 (11.48), 219 (10.25), 119 (20.79), 93 (10.86), 77 (92.53).

2-[(2,4-Dichlorophenyl)oxy]-3,7-dihydro-3,7-diphenyl-5-methyl-9-methylthio-pyrazolo [3,4-b]-pyrido[4,3-b]-pyrimidine-4-ones (**7o**)

Anal. calcd. (%) for $C_{28}H_{19}Cl_2N_5O_2S$: C, 60.00; H, 3.42; N, 12.50. Found: C, 60.22; H, 3.64; N, 12.77, IR (KBr, ν/cm^{-1}): 3266 (Ph-H), 2926 (C−H), 1727 (C=O), 1674 (C=C), 1562 (N=C), ^{1}H NMR (DMSO-d_6, 400 MHz): 2.82 (s, 3H, SCH_3), 3.02 (s, 3H, CH_3), 7.14–8.36 (m, 13H, Ar-H); MS (EI, m/z, %): 561 ($M^+ + 2$, 11.32), 560 ($M^+ + 1$, 32.16), 494 (29.29), 474 (57.85), 398 (21.22), 219 (37.49), 119 (27.76), 101 (47.66), 93 (4.36), 77 (100).

Herbicidal Testing

Herbicidal testing of the newly synthesized compounds **7** was carried out in a plant growth room (temperature $23 \pm 1°C$, RH $60 \pm 5\%$, light intensity 10 Klux, photoperiod 8 h/day). Twenty seeds of each weed species including rape and barnyard grass were chosen for testing. Seedlings were grown in the 9-cm-diameter test plate of containing two pieces of filter paper and 9 mL solution of the tested compound (100 mg/L and 10 mg/L, respectively). Distilled water and 2,4-dichlorophenoxyl acetic acid (2,4-D), a commercially available herbicide in the market, were used as comparison compounds. The herbicidal activity was assessed as the inhibition rate in comparison with the distilled water. The herbicidal rating score was based on visual observation, ranging from 0% to 100%: 0% means no effect, 100% means complete killing.

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REFERENCES

1. Tomita, K.; Chiba, K.; Kashimoto, S. Novel compound, process for producing the same, and antitumor agent. PCT Int. Appl. WO 9534559, 1995; *Chem. Abstr.* **1995**, *124*, 289559a.
2. Bar, T.; Zimmermann, P.; Boer, R.; Gekeler, V. Pyridopyrimidines. PCT Int. Appl. WO 9719946, 1997; *Chem. Abstr.* **1997**, *127*, 81463u.
3. Broom, A. D.; Shim, J. L.; Anderson, G. L. Pyrido[2,3-d]pyrimidines,. IV: Synthetic studies leading to various oxopyrido[2,3-d]pyrimidines. *J. Org. Chem.* **1976**, *41*, 1095–1098.

4. Grivsky, E. M.; Lee, S.; Sigel, C.W.; Duch, D. S. Synthesis and antitumor activity of 2,4-diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido[2,3-d]-pyrimidine. *J. Med. Chem.* **1980**, *23* (3), 327–329.
5. Motoo, H.; Yashio, P.; Isuneo, I. Pyrimidine derivative, JP1143895, 1989; *Chem. Abstr.* **1990**, *112*, 7859b.
6. Huryn, D. M.; Okabe, M. AIDS-driven nucleoside chemistry. *Chem. Rev.* **1992**, *92*, 1745.
7. Kuyper, L. F.; Garvey, J. M.; Baccanari, D. P.; Champness, J. N.; Stammers, D. K.; Beddell, C. R. Pyrrolo[2,3-*d*]pyrimidines and pyrido[2,3-d]pyrimidines as conformationally restricted analogues of the antibacterial agent trimethoprim. *Bioorg. Med. Chem.* **1996**, *4* (4), 593–602; *Chem. Abstr.* **1996**, 125, 86587.
8. Blankley, C. J.; Doherty, A. M.; Hamby, J. M. 6-Aryl pyrido[2,3-d]pyrimidines and naphthyridines for inhibiting protein tyrosine kinase mediated cellular proliferation. PCT Int. Appl. WO 9615128, 1996; *Chem. Abstr.* **1996**, *125*, 114688k.
9. Furuya, S.; Ohtaki, T. Pyridopyrimidine derivatives: Their production and use. Eur. PCT Pat. Appl. EP 608565, 1994; *Chem. Abstr.* **1994**, *121*, 205395w.
10. Takayama, K.; Hisamidi, H.; Iwata, M. Pyrido[2,3-d]pyrimidine derivatives and medicinal compositions thereof. PCT Int. Appl. WO 9719078, 1997; *Chem. Abstr.* **1997**, *127*, 65784u.
11. Degraw, J. I.; Colwell, W. T.; Sirtonok, F. M. Antiinflammatory and antineoplastic 5-deazaaminopterins and 5,10-dideazaaminopterins. US patent 5536724, 1996; *Chem. Abstr.* **1993**, *120*, 245139b.
12. Joseph, I. D.; Pamela, H. G.; Willian, T. C.; Francis, M. S. Synthesis and antifolate properties of 5,10-ethano-5,10-dideazaaminopterin. *J. Med. Chem.* **1992**, *35*, 320.
13. Heckler, R. E.; Jourdan, G. P. Condensed pyrimidine derivates. Eur. Pat. Appl. EP 414386, 1991; *Chem. Abstr.* **1991**, *115*, 71360.
14. Rouchaud, J.; Neus, O.; Eelen, H. Soil metabolism of flupyrsulfuron in winter wheat crops. *Weed Res.* **2002**, *42* (1), 14–25.
15. Yamada, H. Pyrimidine derivative. EP0665224, 1994; *Chem. Abstr.* **1994**, *121*, 230784e.
16. Waldrep, T. W.; Becl, J. R.; et al. Synthesis and herbicidal activity of 1-aryl-5-halo and 1-aryl-5-(trifluoromethyl)-1H-pyrazole-4-carboxamides. *J. Agric. Food Chem.* **1990**, *38* (2), 541–544.
17. Usui, Y.; Tsutsumi, Y.; Go, A.; Yamada, S. Sulfoamoyltriazole derivative and microbicide containing the same active ingredient. JP7215971, 1995; *Chem. Abstr.* **1995**, *124*, 72564p.
18. Drabek, J. New pesticidal 4-benzyl-oximino-methyl-5-aryloxy-pyrazole derivatives, especially used for control of insects and acarids on plants. DE4200742, 1992; *Chem. Abstr.* **1992**, *117*, 171437m.
19. Bonini, C.; Auria, M. D.; Funicello, M.; Romaniello, G. Novel *N*-(2-benzo[*b*]thienyl)iminophosphoranes and their use in the synthesis of benzo[*b*]thieno[2,3-*b*]pyridines. *Tetrahedron.* **2002**, *58*, 3507–3512.

20. Zhao, M.-X.; Wang, M.-X.; Yu, C.-Y.; Huang, Z.-T.; et al. A direct retro-Reformatsky fragmentation: Formal ring enlargement of cyclic ketones for novel and practical synthesis of heterocyclic enamines. *J. Org. Chem.* **2004**, *69* (3), 997–1000.
21. Csámpai, A.; Túrós, G.; Kudar, V.; Simon, K.; Oeynhausen, H.; Wamhoff, H.; Sohár, P. Ethyl α-(triphenylphosphoranylidene)amino-β-ferrocenylacrylate as a starting material for [2 + 2] cycloadditions, including the aza-Wittig reaction. *Eur. J. Org. Chem.* **2004**, *4*, 717–723.
22. Kurosawa, W.; Kan, T.; Fukuyama, T. Stereocontrolled total synthesis of (−)-ephedradine A (orantine). *J. Am. Chem. Soc.* **2003**, *125*, 8112.
23. Yadav, J. S.; Srinivas, C. Ring expansion approach for the synthesis of the (3*S*,4*S*)-hexahydroazepine core of balanol and ophiocordin. *Tetrahedron.* **2003**, *59*, 10325.
24. Wang, H.-Q.; Liu, H.; Liu, Z.-J. Synthesis and biological activity of 1-[2-(2,4-dichlorophenoxyl)acetyl]-5-amino-1H-pyrazole derivatives. *Chin. J. Org. Chem.* **2004**, *24*, 797.
25. Yang, G.-F. Xu, L.; Lu, A.-H. Synthesis and bioactivity of novel triazolo [1,5-*a*]pyrimidine derivatives[3]. *Heteroat. Chem.* **2001**, *12*, 491.