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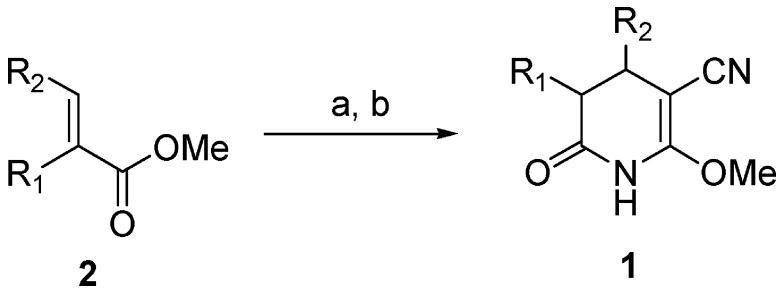

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2-Methoxy-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles: Versatile Starting Materials for the Synthesis of Libraries with Diverse Heterocyclic Scaffolds

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Heterocyclic demonstration libraries for agrochemical screening were prepared from the common intermediates 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles (**1**), using standard solution-phase techniques. A total of 18 screening libraries were prepared in good to excellent yields. Several members of these libraries were active in the first level of agrochemical screening, especially in the fungicide screen.

Introduction

Heterocyclic compounds have had an invaluable role in both drug and agrochemical discovery processes. The high incidence of heterocyclic frameworks in known pharmaceutical and agrochemical structures make them an attractive target for combinatorial synthetic approaches.[1] In particular, heterocyclic compounds such as quinazolinones, naphthyridones, pyridones, and pyridopyrimidines are especially appealing, because they exhibit a broad range of biological activities. They have extensively been reported as antitumor agents,[2,3] kinase inhibitors,[4−8] anti-inflammatory agents,[9] fungal plants inhibitors,[10,11] and antibacterial agents.[12,13] Although several synthetic approaches have been reported for the preparation of each of these heterocycles, they have not been prepared in a library format using a common intermediate in which the library diversity comes not only from the different substituents present in the scaffold but also from the scaffold itself. Our attention was drawn to 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles **1**[14,15] as attractive common starting materials for the production of small libraries of the previously mentioned heterocycles. Compounds **1** contain two points of variation (R_1 and R_2) and present multiple functionalities that can be exploited for the synthesis of a wide array of heterocycles.[16] Pyridones **1** can be easily transformed to *N*-alkyltetrahydropyridones, 2-cyanoglutarimides,[14,15] iminopyridones,[17] pyrazolo[3,4-*b*]pyridine-6-ones,[17] pyrido[2,3-*d*]pyrimidin-7-ones,[18−20] 1,6-naphthyridin-2-ones,[21] pyrano[4,3-*b*]pyridine-2-ones,[22] imidazo[1,2-*a*]pyridine-5-ones,[23] pyrido[1,2-*a*]pyrimidin-6-ones,[23] and pyrido[1,2-*a*][1,3]diazepinones,[23] as shown in Figure 1.

The rich chemistry associated with pyridones **1**, combined with the large number of substituents tolerated at the α,*β*-positions of the starting, commercially available α,*β*-unsaturated esters (**2**), the straightforward chemistry, and the simple isolation protocols, make these compounds ideally suited building blocks for the preparation of a very diverse set of the previously mentioned heterocycles. Each heterocyclic scaffold presents two sites of diversity (R_1 and R_2), and additional diversity can be realized by post-functionalization (see compounds **4** and **18**).

This paper reports the preparation of small demonstration libraries of a diverse set of heterocycles, based on the chemistry of tetrahydropyridine-3-carbonitriles (**1**) for agrochemical profiling, and the first-level screening results for these compounds.

Results and Discussion

Library Design. A goal of our library design was to maximize the diversity of the heterocyclic rings produced. We wanted each library to comply with Lipinski's rules[24] and similar rules developed for agrochemicals.[25] We also selected starting materials based on diversity, availability, and their cost.

A search of α,*β*-unsaturated esters (**2**), which are starting materials for the preparation of compounds **1** (vide infra, Scheme 1), in the Available Chemicals Directory (ACD) database[26] gave more than 200 candidates. Seventeen commercially available methyl α,*β*-unsaturated esters **2**{*1*−*17*} were selected on the basis of price, availability, and diversity (Figure 2). The diversity selection was conducted with the Selector module of the Sybyl[27] molecular modeling software. The target compounds were selected using hierarchical clustering of the Tripos 2D-fingerprints and atom pair descriptors, using the Tanimoto distances as the metric.

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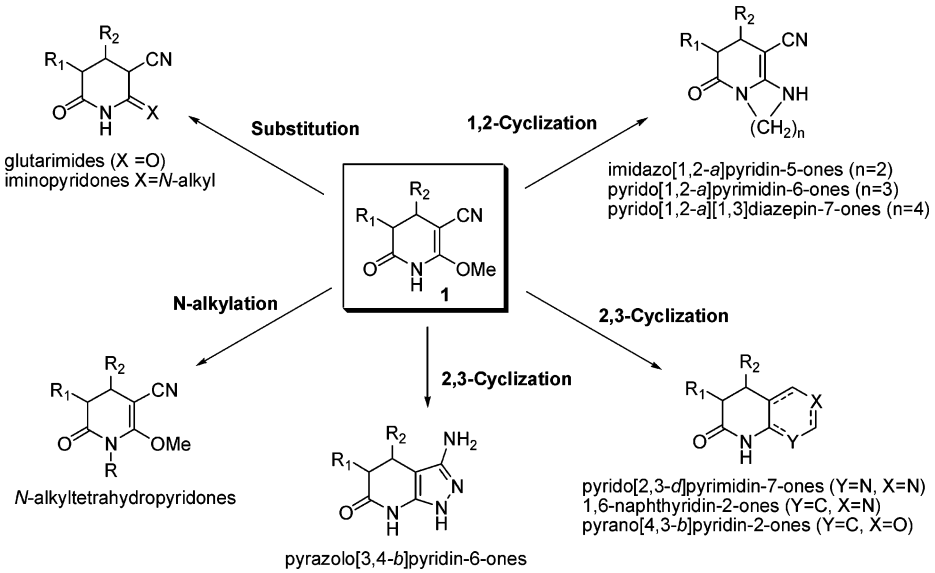
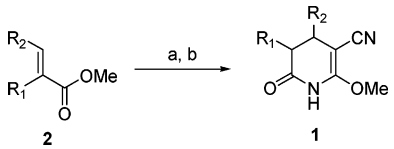


Figure 1. Examples of heterocyclic structures derived from 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles (**1**).

Scheme 1. Preparation of 2-Methoxy-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles (**1**)[a]



[a] a = NC−CH_2−CN, NaOMe, reflux. b = HCl.

Because desirable ranges of molecular weight (MW), calculated octanol−water partition coefficient (log *P*), and numbers of hydrogen-bond donors, acceptors, and rotable bonds for orally bioavailable drugs and for agrochemicals have been proposed,[24,25,28] the MW value, the number of hydrogen-bond donors and hydrogen-bond acceptors, and the log *P* value were estimated for all the neutral compounds in the libraries, using Accord for Excel functions.[29] The log *P* calculation uses the Atom/Fragment Contribution (AFC) method,[30] in which a structure is divided into fragments (atom or larger functional groups) and coefficient values of each fragment or group are summed together to yield the log *P* estimate, which is then improved by the addition of correction factors. The log *P* and MW values for the designed structures fall within these desirable ranges (Figure 3).

Chemistry. The starting building block 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles (**1**), first described by Victory and Diago, can easily be prepared by the high-yielding reaction of α,*β*-unsaturated esters (**2**) and malononitrile in NaOMe/MeOH at reflux (see Scheme 1).[14,15] The R_1 and R_2 groups of the starting α,*β*-unsaturated esters **2**{*1*−*17*} are very diverse and include silicon and phosphorus functional groups, carboxylic esters, [1,3]-dioxolane, and substituted phenyl groups (see Figure 2). The structures and isolated yields of the 17 pyridones **1**{*1*−*17*} prepared are summarized in Table 1. Compounds **1**{*1*−*17*} were used as starting materials to produce 17 diverse heterocyclic scaffolds, which are depicted in Scheme 2.

Reaction of Compounds 1 with Simple Oxygen, Nitrogen, or Carbon Nucleophiles. 1. Reaction with Oxygen Nucleophiles. Acid hydrolysis of **1** in 1.5 M HCl proceeds smoothly to afford 2-cyanoglutarimides **3**{*5*,*8*,*9*,*14*,*17*} in yields of ≥92% (see Table 1). Compounds **3** show very weak nitrile band stretching (ca. 2250 cm^{-1}), in contrast to that of the starting pyridones **1**.

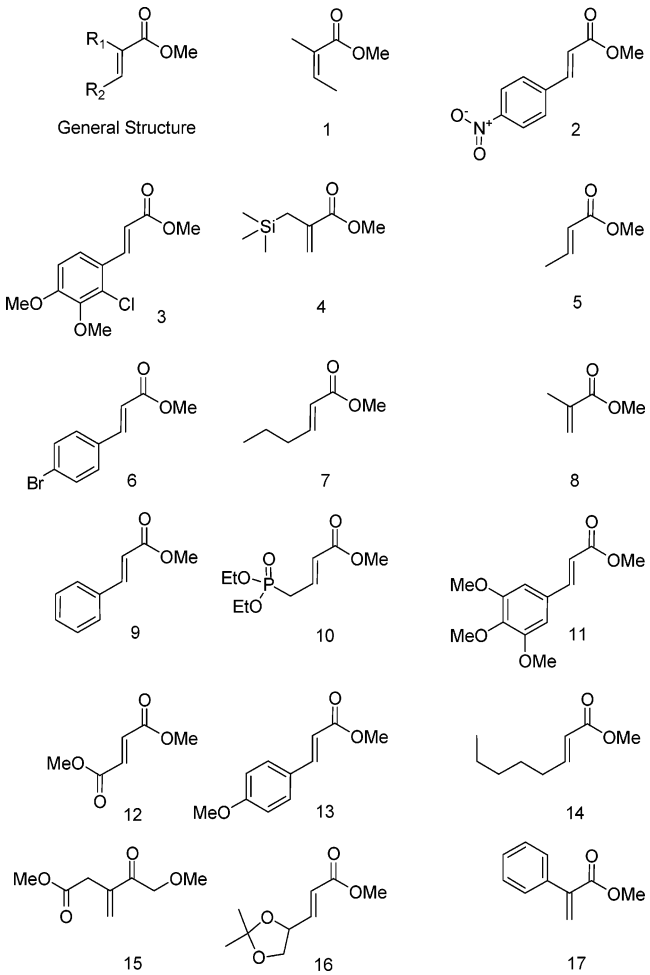


Figure 2. α,*β*-Unsaturated esters **2** used for libraries production.

2. Reaction with Nitrogen Nucleophiles. Treatment of pyridones **1** with primary or secondary amines (**20**) (Figure 4) in methanol at reflux yielded the corresponding *N*-

Table 1. Isolated Yields of Prepared Compounds[a]

	Yield from α,β-Unsaturated Ester **2** (%)																
compound	{*1*}	{*2*}	{*3*}	{*4*}	{*5*}	{*6*}	{*7*}	{*8*}	{*9*}	{*10*}	{*11*}	{*12*}	{*13*}	{*14*}	{*15*}	{*16*}	{*17*}
1	35	65	84	75	50	65	57	49	85	36	95	20	76	75	15	24	50
3					96			92	95					94			100
5	100	100	87	84	85	86	100						89				
6			41	83		63	38	60	93	82			49	76	65		
7					74			79	94								54
8	83	89	84	50	85		50										
9	97	51		43	70												
10				99		92	57	78	96				92	78	77		
12					74			79	94								54
15								74	64								
16								50	65								
17		92	90	60		92	66	63	37	90	90		87				
18			70	90		70	77	87	89	79	76		70				
19 ($n = 2$)					69			74	83								47
19 ($n = 3$)					51			45	78								14
19 ($n = 4$)					28			26	27								16

[a] Purity of each compound is >95%. Blank cells represent reagent combinations that were not attempted.

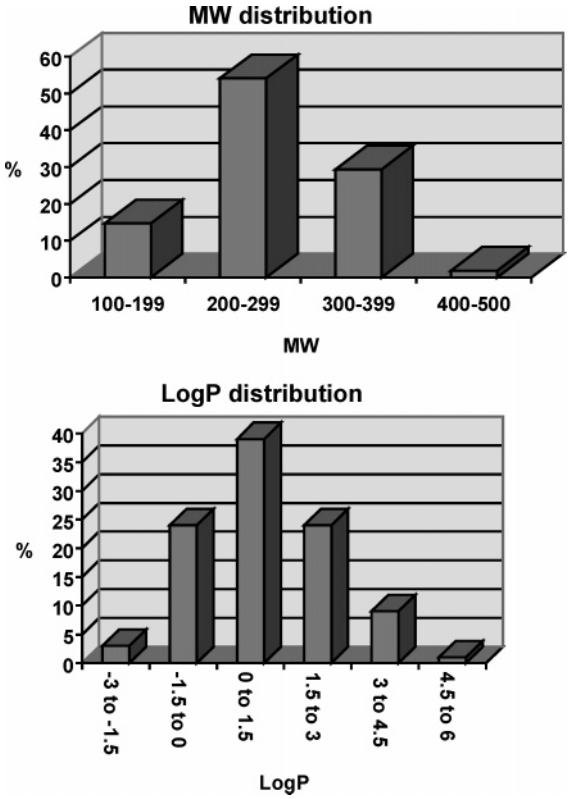


Figure 3. Log P and molecular weight (MW) distribution of designed compounds.

substituted derivatives (**4**) in isolated yields of 53−84% (Table 2). Similarly, substitution of the methoxy group present in pyridones **1** by cyanamide was performed in dioxane at reflux in the presence of a stoichiometric amount of sodium methoxide to yield the sodium salts of cyanoiminopyridones (**5**) (Scheme 3) in isolated yields of 84−100% (see Table 1). Although the neutral cyanoimino derivatives **5** can be obtained by treatment of the corresponding sodium salts with an equimolar amount of HCl in methanol, compounds **5** were tested as sodium salts.

3. Reaction with Carbon Nucleophiles. Reaction of compounds **1** with carbon nucleophiles bearing a cyano group also proceeds in high yields.[31] Treatment of pyridones **1** with malononitrile in NaOMe/MeOH afforded, after neutralization of the intermediate sodium salts, the corresponding dicyanomethylene-substituted pyridones (**6**) (Scheme 4, Table 1). The two diastereomers of compounds **6** are present in different proportions, as revealed by the ^{1}H NMR spectra. Thus, in a previous work, we assigned, in the case of **6**{*5*}, the major component to the 4*R*5*R* and 4*S*5*S* enantiomers and the minor component to the 4*R*5*S* and 4*S*5*R* pair (Scheme 5).[32] Similarly treatment of **1** with methyl cyanoacetate in the presence of sodium in dioxane with a catalytic amount of MeOH yielded derivatives **7** (see Scheme 4, Table 1) in isolated yields of 50−95%.

The presence of a 1,5-dinitrile system on the previously prepared cyanoiminopyridones **5**, dicyanomethylenepyridones **6**, and cyanomethoxycarbonylmethylene pyridones **7** as sodium salts has allowed production, in high yields, of the corresponding bicyclic heterocycles **8** and **9**, **10** and **11**, and **12**, respectively when treated with HBr in dioxane (see Scheme 2).[31] Cyclization of **5** yielded both positional isomers **8** (G_1 = Br, G_2 = NH_2) and **9** (G_1 = NH_2, G_2 = Br). When the reaction was performed at 10−15 °C, only **8** was formed; when the reaction temperature was increased to 95−100 °C, only **9** was produced. Results are summarized in Table 1. On the other hand, the 5-amino-7-bromo-substituted naphthyridines (**10**) (G_1 = Br, G_2 = NH_2) are predominantly formed when compounds **6** are treated with HBr (see Table 1). However, the proportion of **10** is dependent on the presence or absence of the substituent R_2, the nature of the solvent, and the temperature of reaction. The presence of R_2, a decrease in the polarity, and the use of low temperatures favored the formation of the 7-amino-5-bromo isomer **11** (G_1 = NH_2, G_2 = Br). Only compounds **10** were submitted for testing. Compounds **7** in acidic media (HCl, HBr, TFA, or 5:1 AcOH/TFA) yielded the pyrano[4,3-*b*]pyridines (**12**) in high yields (see Table 1).

Nucleophilic substitution of the Br atom present in **8**{*5*} (G_1 = Br, G_2 = NH_2) and **9**{*5*} (G_1 = NH_2, G_2 = Br) by amines afforded compounds **13** and **14** (see Table 2), increasing the chemical diversity of the pyrido[2,3-*d*]pyrimidines prepared.[33]

Scheme 2. Heterocyclic Scaffolds Derived from Pyridones **1**

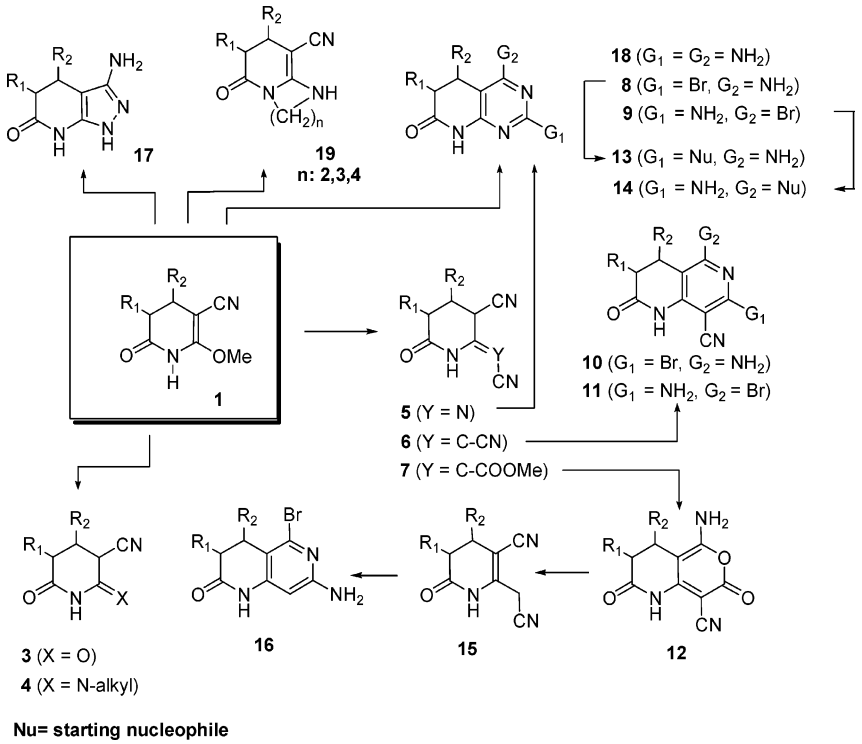


Table 2. Isolated Yields of Compounds **4**, **18**, and **19**[a]

	Yield from Amine **20** (%)									
compound	{*1*}	{*2*}	{*3*}	{*4*}	{*5*}	{*6*}	{*7*}	{*8*}	{*9*}	{*10*}
4{*5*}	84	64	73	64	60					
4{*8*}	75		50	60	53					
13{*5*}		80		100		69	88	75	76	86
14{*5*}				90						

[a] Purity of each compound is >95%. Blank cells represent reagent combinations that were not attempted.

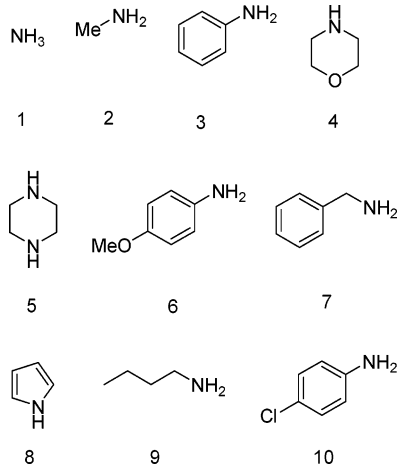
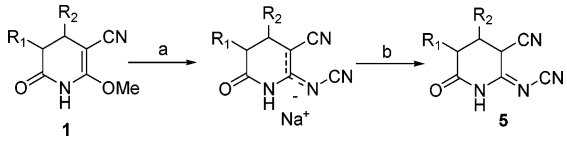


Figure 4. Amines **20** used for libraries production.

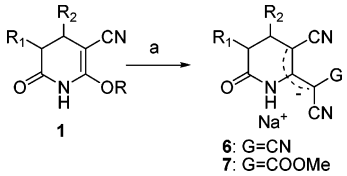
Finally, we prepared compounds **16**{*8*} and **16**{*9*}, which were obtained in 50% and 65% yield, respectively, by cyclization with HBr of the corresponding cyano methyl-substituted pyridones **15**{*8*} and **15**{*9*}, formed (74% and 64% yield) upon treatment of pyrano[4,3-*b*]pyridines **12**{*8*} and **12**{*9*} with aqueous ammonia by a ring opening−ring closure mechanism that includes a decarboxylation.[22] Compounds **12** can be easily prepared by acidic treatment of **7** (see Table 1).

Scheme 3. Preparation of Cyanoiminopyridones (**5**)[a]



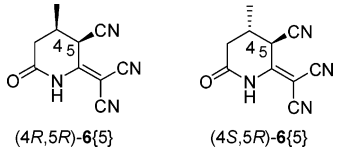
[a] a = NH_2CN, Na, MeOH (catalytic). b = HCl.

Scheme 4. Preparation of Substituted Pyridones (**6** or **7**)[a]



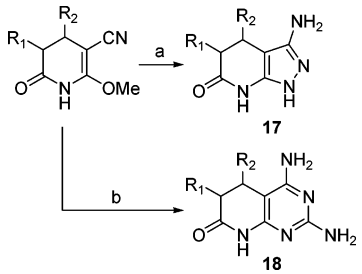
[a] NC−CH_2-G (G = CN, COOMe), NaOMe, MeOH, room temperature.

Scheme 5. Major Pair (4*R*,5*R*)/(4*S*,5*S*) and Minor Pair (4*S*,5*R*)/(4*R*,5*S*) Diastereomers of **6**{5} (Only the 5*R* Configuration is Depicted)



Reaction of Compounds 1 with Bidentate Nucleophiles. Treatment of **1** with hydrazine or guanidine yielded pyrazolo-[3,4-*b*]pyridines (**17**) or 2,4-diaminopyrido[2,3-*d*]pyrimidines (**18**, $G_1 = G_2 = NH_2$) by intramolecular cyclization of the substitution product onto the C3 cyano group, as shown in Scheme 6. These reactions proceed smoothly, giving **17** and **18** in yields of 70−92% and the results are summarized in Table 1.

Scheme 6. Preparation of Pyrazolopyridines **17** and Pyridopyrimidines **18**[a]



[a] a = N_2H_2.2HCl, NaOMe, MeOH, reflux. b = $H_2NC(NH)NH_2$, NaOMe, MeOH, reflux.

Table 3. Statistics of Biological Activity per Cluster

		Screen			
compound(s)	number of members	fungicide	herbicide	insecticide	total of actives[a]
1	17	8	1	0	9
3	5		0	0	0
4	9	0	0	0	0
5	8	0	0	0	0
6	10	6			6
7	4	0	0	0	0
8 + **9** + **13** + **14** + **18**[b]	27	3	1	0	4
10 + **16**[c]	10	5	0	0	5
12	4	0	0	0	0
17	10	1	0	0	1
19	12	0	1	2	3
total	116	23	3	2	25

[a] The term "active compound" is defined in the Experimental Section. [b] The biological results of pyridopyrimidines **8**, **9**, **13**, **14**, and **18** are combined in a single row of data. [c] The biological results of naphthyridines **10** and **16** are combined in a single row of data.

Treatment of compounds **1** with diamino alkanes yielded the corresponding bicyclic compounds **19** by a ring-opening−ring-closing mechanism.[23] Treatment of **1** with $NH_2(CH_2)_nNH_2$ (n = 2, 3, 4) proceeds by initial displacement of the 2-OMe but is followed by nucleophilic addition to the lactam carbonyl group and recyclization to easily produce imidazo[1,2-a]pyridin-5-ones (**19**, n = 2), pyrido[1,2-a]-pyrimidin-6-ones (**19**, n = 3), or pyrido[1,2-a][1,3]diazepin-7-ones (**19**, n = 4).[23] A total of 12 bicyclic derivatives **19**{*5*,*8*,*9*,*17*}, with n = 2, 3, 4, were synthesized. Results are summarized in Table 1.

Screening Results

The libraries were screened in whole-organism agrochemical bioassays, including 5 fungal parasites, 6 insect species, and 8 weeds (see Experimental Section). Results for the complete library are summarized in Table 3. Compounds advanced to the next level of testing are defined as active in this table. The library overall hit rate was higher (25 actives out of 116 compounds) than a typical random library. The hit rate was higher in the fungicide screen (23 compounds active) than in the herbicide (3 compounds active) or insecticide (2 compounds active) screens. The fungicidally active compounds were predominantly concentrated in four libraries: pyridones **1** (8 actives), dicyanomethylenepyridones **6** (6 actives), 1,6-naphthyridines (5 actives) and pyridopyrimidines (3 actives).

Conclusions

Using standard solution-phase chemistry, we prepared 17 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles **1** in 0.1-g quantities. Pyridones **1** were used as building blocks for the preparation of small libraries of 10 different heterocycles. These heterocycles comply with the Lipinski's rule of 5. Several members of the library were active in the first level of agrochemical screening, especially in the fungicide screen.

Experimental Section

All melting points, determined with a Büchi 530 capillary apparatus, and boiling points, determined during distillation, are uncorrected. Infrared spectra were recorded using BOMEM Michelson 100 and Nicolet Magna 560 FTIR spectrophotometers. UV spectra were registered in a Hewlett−Packard model 8450 instrument. ^{1}H and ^{13}C NMR spectra were determined using a Varian Gemini-300 system operating at field strengths of 300 and 75.5 MHz, respectively. Chemical shifts (δ) are reported in parts per million and coupling constants (J) are reported in hertz, using, in the case of ^{1}H NMR, tetramethylsilane (TMS) or sodium 2,2,3,3-tetradeuteriotrimethylsilylpropionate as an internal standard and setting, in the case of ^{13}C NMR, the references at the signal of the solvent: 77.0 ppm ($CDCl_3$); 39.5 ppm (DMSO-d_6); 163.8 ppm (CF_3COOD, TFA-*d*). Standard and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; brs, broad singlet; br, broad signal; and m, multiplet. Mass spectra (m/z (%), EI, 70 eV) were obtained on a Hewlett−Packard model 5995A spectrometer. Fast positive-ion bombardment−high-resolution mass spectrometry (FAB(+)-HRMS) was recorded at the Servicio de Espectrometría de Masas (Universidad de Córdoba), using a VG Autospec spectrometer (resolution of 8000, using 3-nitrobenzyl alcohol as the matrix). Elemental microanalyses were obtained on a Carlo-Erba CHNS−O/EA 1108 analyzer and gave results for the elements stated with ±0.4% of the theoretical values. *N*,*N*-Dimethylformamide (DMF) was distilled under vacuum and dried over activated (250 °C) 4-Å molecular sieves. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ and kept over 4-Å molecular sieves. MeOH refers to methanol, Et_2O refers to diethyl ether, and AcOEt refers to ethyl acetate. Thin-layer chromatography (TLC) was performed on precoated sheets of silica 60 Polygram SIL N-HR/UV_{254} (Macherey Nagel Art 804023). Dry column chromatography was performed using silica gel of 70−230 mesh (ASTM) (Merck Art 7734 or Macherey Nagel Art 81533). Flash chromatography was performed using silica gel of 230−400 mesh (ASTM) (Macherey Nagel Art 81538).

The following compounds were obtained, according to reported procedures: **1**{*5*}**,** **1**{*8*}, and **1**{*9*};[18] **1**{*11*};[34] **1**{*17*};[18] **3**{*5*}, **3**{*8*}, and **3**{*9*};[15] **4**{*5*,*1*} and **4**{*5*,*2*};[17] **5**{*5*};[18] **6**{*8*} and **6**{*9*};[21] **7**{*5*}, **7**{*8*}, **7**{*9*}, and **7**{*17*};[22] **8**{*5*}, **9**{*5*}, **10**{*8*}, and **10**{*9*};[21] **12**{*8*} and **12**{*9*};[22] **13**{*5*,*6*}, **13**{*5*,*7*}, and **14**{*5*,*4*};[33] **16**{*8*} and **16**{*9*};[22] **18**{*8*} and **18**{*9*};[18] **18**{*11*};[33] **19**{*5*} (n = 2, 3, 4), **19**{*8*} (n = 2, 3, 4), **19**{*9*} (n = 2, 3, 4), and **19**{*17*} (n = 2, 3, 4).[23]

General Method for the Synthesis of 2-Methoxy-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles (1). A solution of 170 mmol of the corresponding α,β-unsaturated ester in 30 mL of MeOH was added dropwise to a solution of 170 mmol of sodium in 30 mL of methanol at room temperature. After a few minutes, 91 mmol of malononitrine in 30 mL of MeOH were added dropwise and the resulting mixture was refluxed for the time *t* (min) stated in each case. The solvent was evaporated under reduced pressure, and the residue was dissolved in water. The resulting solution was carefully acidified with 6 M HCl to pH 8−9 while cooling in an ice bath. The solid formed was filtered and dissolved in CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The resulting solid can be used in the following step without further purification. Pyridones **1** can be purified by recrystallization from methanol or from AcOEt:hexane or by chromatography on silica gel, using ethyl acetate:hexane as the eluent.

1. Compound 1{*1*}. *t* = 90, 35%, mp 141−143 °C. IR (KBr) 3220, 3120, 2205, 1695, 1640. ^{1}H NMR (d_6-acetone), δ 1.00−1.40 (m, 6H, Me), 3.20 (m, 2H,H−C3 and H−C4), 4.10 (s, 3H, OMe), 8.50 (br, 1H, NH). ^{13}C NMR ($CDCl_3$), δ 10.7, 19.5, 33.4, 39.6, 52.9, 69.2, 118.2, 157.4, 174.4. MS *m*/*z* 180 (2) [M^+], 165 (7), 56 (100). Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.95; H, 6.86; N, 15.77.

2. Compound 1{*2*}. *t* = 135, 65%, mp 215 °C(d). IR (KBr) 3200, 3100, 2190, 1700, 1630, 1520. ^{1}H NMR ($CDCl_3$), δ 2.61 (dd, 1H, ^2J = 16 Hz, ^3J = 6 Hz), 3.03 (dd, 1H, ^2J = 16 Hz, ^3J = 7 Hz), 4.02 (s, 3H), 4.17 (m, 1H), 8.26 (m, 2H, ^3J = 8 Hz), 7.58 (m, 2H, ^3J = 8 Hz), 10.94 (br, 1H). ^{13}C NMR ($CDCl_3$), δ 36.5, 37.8, 58.9, 66.6, 118.2, 124.1, 128.4, 146.8, 148.9, 161.2, 169.4. MS *m*/*z* 273 (100) [M^+], 232 (35), 151 (38). Anal. Calcd. for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38. Found: C, 57.44; H, 4.06; N, 15.38.

3. Compound 1{*3*}. *t* = 120, 84%, mp 187−188 °C. IR (KBr) 3200, 3150, 3120, 2200, 1700, 1640, 1500. ^{1}H NMR ($CDCl_3$), δ 2.51 (dd, 1H, ^2J = 16 Hz, ^3J = 5 Hz), 3.02 (dd, 1H, ^2J = 16 Hz, ^3J = 8 Hz), 3.78 (s, 3H); 3.85 (s, 3H), 4.02 (s, 3H), 4.21−4.19 (m, 1H), 7.00 (d, ^3J = 9 Hz); 7.09 (d, ^3J = 9 Hz), 10.90 (br, 1H). ^{13}C NMR ($CDCl_3$), δ (ppm) 34.0, 37.0, 56.0, 58.8, 60.1, 66.6, 111.6, 118.1, 122.5, 126.8, 129.8, 145.1, 152.8, 161.4, 169.4. MS *m*/*z* 322 (100) [M^+], 324 (36) [M+2]$^+$, 279 (44), 281 (18). Anal. Calcd. for $C_{15}H_{15}ClN_2O_4$: C, 55.82; H, 4.68; N, 8.68. Found: C, 55.84; H, 4.83; N, 8.59.

4. Compound 1{*4*}. *t* = 90, 75%, mp 146−147 °C. IR (KBr) 3220, 3180, 2200, 1710, 1640, 1490. ^{1}H NMR ($CDCl_3$), δ 0.07 (s, 9H), 0.67 (dd, 1H, ^2J = 15 Hz, ^3J = 8 Hz), 1.12 (dd, 1H, ^2J = 15 Hz, ^3J = 5 Hz), 2.29 (dd, 1H ^2J = 14 Hz, ^3J = 8 Hz), 2.47−2.62 (m, 2H), 4.14 (s, 3H), 8.89 (br, 1H). ^{13}C NMR ($CDCl_3$), δ 1.0, 16.5, 29.8, 36.5, 58.9, 61.2, 118.6, 158.0, 175.1. MS *m*/*z* 238 (13) [M^+], 223 (100), 73 (43). Anal. Calcd. for $C_{11}H_{18}N_2O_2Si$: C, 55.43; H, 7.61; N, 11.75. Found: C, 55.70; H, 7.87; N, 11.89.

5. Compound 1{*6*}. *t* = 240, 65%, mp 160−161 °C. IR (KBr) 3220, 3180, 2200, 1710, 1630. ^{1}H NMR ($CDCl_3$), δ 2.73 (dd, 1H ^2J = 17 Hz, ^3J = 5 Hz), 2.94 (dd, 1H ^2J = 17 Hz, ^3J = 8 Hz), 3.86 (dd, 1H ^3J = 7 Hz, ^3J = 5 Hz), 4.18 (s, 3H), 7.13 (m, 2H, ^3J = 9 Hz), 7.49 (m, 2H, ^3J = 9 Hz), 8.42 (br, 1H). ^{13}C NMR ($CDCl_3$), δ 37.6, 38.0, 59.4, 66.9, 117.7, 121.9, 128.4, 132.3, 138.8, 158.4, 169.6. MS (70 eV) *m*/*z* 307 (100) [M^+], 264 (63), 151 (37). Anal. Calcd. for $C_{13}H_{11}BrN_2O_2$: C, 50.84; H, 3.61; N, 9.12. Found: C, 50.72; H, 3.73; N, 9.21.

6. Compound 1{*7*}. *t* = 150, 57%, mp 112−113 °C. IR (KBr) 3200, 3110, 2200, 1700, 1640. ^{1}H NMR ($CDCl_3$), δ 0.95 (t, 3H, ^3J = 7 Hz), 1.37−1.48 (m, 3H), 1.60−1.63 (m, 1H), 2.39 (dd, 1H, ^2J = 15 Hz, ^3J = 3 Hz), 2.64 (m, 1H), 2.66 (dd, 1H, ^2J = 15 Hz, ^3J = 7 Hz), 4.13 (s, 3H), 9.12 (br, 1H). ^{13}C NMR ($CDCl_3$), δ 13.7, 19.5, 32.4, 35.6, 35.7, 59.0, 68.0, 118.2, 158.0, 171.7. MS (70 eV) *m*/*z* 194 (11) [M^+], 151 (100), 119 (17). Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: 61.82; 7.32; 14.36.

7. Compound 1{*8*}. *t* = 210, 36%, mp 129−131 °C. IR (KBr) 3210, 3090, 2200, 1710, 1650. ^{1}H NMR ($CDCl_3$), δ 3.04 (m, 1H), 2.65 (dd, 1H, ^2J = 17 Hz, ^3J = 6 Hz), 2.80 (dd, 1H ^2J = 17 Hz, ^3J = 6 Hz), 4.13 (s, 3H), 1,35 (t, 6H, ^3J = 7 Hz), 1.83−1.97 (m, 1H), 2.08−2.21 (m, 1H), 4.05−4.20 (m, 4H), 9.13 (br, 1H). ^{13}C NMR ($CDCl_3$), δ 16.3, 28.3, 29.3, 36.1, 59.1, 61.0, 67.7, 117.5, 158.8, 170.0. MS (70 eV) *m*/*z* 302 (25) [M^+], 259 (27), 164 (100). Anal. Calcd. for $C_{12}H_{19}N_2O_5P$: C, 47.68; H, 6.34; N, 9.27. Found: C, 47.46; H, 6.35; N, 9.16.

8. Compound 1{*12*}. *t* = 150, 20%, mp 130−131 °C. IR (KBr) 3210, 3100, 2950, 2190, 1720, 1700, 1635. ^{1}H NMR ($CDCl_3$), δ 2.70 (dd, 1H, ^2J = 17 Hz, ^3J = 6 Hz), 2.90 (dd, 1H ^2J = 17 Hz, ^3J = 3 Hz), 3.47 (m, 1H), 3.79 (s, 3H9, 4.19 (s, 3H), 8.28 (br, 1H). ^{13}C NMR ($CDCl_3$), δ 32.4, 38.3, 53.0, 59.3, 61.7, 117.5, 159.4, 168.9, 171.3. MS *m*/*z* 210 (14) [M^+], 151 (100), 116 (21). Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.53; H, 4.86; N, 13.07.

9. Compound 1{*13*}. *t* = 120, 76%, mp 174−176 °C. IR (KBr) 3192, 3088, 2195, 1690, 1625. ^{1}H NMR ($CDCl_3$), δ 2.75 (dd, 1H, ^2J = 17 Hz, ^3J = 5 Hz), 2.91 (dd, 1H, ^2J = 17 Hz, ^3J = 7 Hz), 3.85 (dd, 1H, ^3J = 5 Hz, ^3J = 7 Hz), 4.17 (s, 3H), 6.88 (m, 2H, ^3J = 7 Hz), 7.16 (m, 2H, ^3J = 7 Hz), 8.27 (br, 1H). ^{13}C NMR ($CDCl_3$), δ 37.8, 38.0, 55.3, 59.3, 67.9, 114.4, 118.0, 127.7, 131.8, 158.1, 159.1, 169.9. MS *m*/*z* 258 (80) [M^+], 227 (30), 215 (100). Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.09; H, 5.47; N, 10.85. Found: C, 65.35; H, 5.58; N, 10.82.

10. Compound 1{*14*}. *t* = 90, 75%, mp 88−89 °C. IR (KBr) 3208, 3112, 2200, 1698, 1643. ^{1}H NMR ($CDCl_3$), δ 0.89 (t, 3H, ^3J = 6 Hz), 1.3−1.72 (m, 8H), 2.40 (dd, 1H, ^2J = 15 Hz, ^3J = 3 Hz), 2.66 (dd, 1H, ^2J = 15 Hz, ^3J = 6 Hz), 2.57−2.65 (m, 1H), 4.14 (s, 3H), 8.51 (br, 1H). ^{13}C NMR ($CDCl_3$), δ 13.9, 22.4, 26.0, 31.5, 32.9, 33.5, 35.8, 59.2, 68.1, 118.2, 154.9, 171.1. MS *m*/*z* 222 (7) [M^+], 151 (100). Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.82; H, 8.17; N, 12.61. Found: C, 64.77; H, 8.35; N, 12.6.

11. Compound 1{*15*}. *t* = 150, 15%, mp 157−158 °C. IR (KBr) 3204, 3188, 2195, 1696, 1645. ^{1}H NMR ($CDCl_3$), δ 2.37−2.60 (m, 3H), 2.81−3.02 (m, 2H), 4.06 (s, 6H). ^{13}C NMR ($CDCl_3$), δ 26.3, 32.8, 36.1, 51.3, 58.4, 61.5, 118.0, 159.0, 171.0, 171.2. MS *m*/*z* 224 (4) [M^+], 193 (20), 151

(100). Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.58; H, 5.57; N, 12.41.

12. Compound 1{*16*}. $t = 120$, 24%, mp 158−160 °C. IR (KBr) 3239, 3202, 2198, 1722, 1643, 1498. ^{1}H NMR ($CDCl_3$), δ 1.41 (s, 1H), 1.33 (s, 1H), 2.49 (dt, 1H, $^3J = 14$ Hz, $^3J = 5$ Hz), 2.78−2.74 (m, 2H), 3.91 (dd, 1H, $^2J = 9$ Hz, $^3J = 6$ Hz), 4.07 (dd, 1H, $^2J = 9$ Hz, $^3J = 7$ Hz), 4.17 (s, 3H), 4.21−4.23 (m, 1H), 8.7 (br, 1H). ^{13}C NMR ($CDCl_3$), δ 24.9, 26.1, 32.2, 35.9, 59.2, 62.6, 65.9, 77.8, 109.8, 118.6, 159.8, 170.7. Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.22; H, 6.55; N, 10.96.

2-Cyano-3-pentylglutarimide (3{*14*}). A mixture of 100 mg (0.45 mmol) of **1**{*14*} was stirred in 2 mL of 1.5 M HCl for 6 h at room temperature. The solid obtained was filtered, washed with water, and recrystallized from methanol to yield 89 mg (95%) of **3**{*14*}, mp 122−124 °C. IR (KBr) 3294, 2257, 1729, 1709, 1455. ^{1}H NMR ($CDCl_3$), δ 0.96 (t, 3H, $^3J = 6$ Hz), 1.25−1.33 (m, 8H), 1.90 (m, 1H), 2.02 (dd, 1H, $^2J = 15$ Hz, $^3J = 3$ Hz), 2.27 (dd, 1H, $^2J = 15$ Hz, $^3J = 6$ Hz), 3.42 (d, 3H, $^3J = 6$ Hz), 10.01 (br, 1H). ^{13}C NMR ($CDCl_3$), δ 14.1, 20.7, 22.8, 25.7, 30.4, 32.2, 35.5, 39.0, 116.9, 172.5, 174.5. MS *m*/*z* 208 (50) [M$^+$], 137 (45), 98 (100). Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.38; H, 7.92; N, 13.26.

General Method for the Synthesis of 2-Alkylamino-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles (4). A mixture of 6.0 mmol of the corresponding pyridone **1** and 0.060 mol of the selected amine in 30 mL of methanol is refluxed during the time *t* (given in hours) stated in each case. The solvent was concentrated in vacuo, and the resulting solid was recrystallized from ethanol to afford the corresponding aminopyridone **4**.

1. Compound 4{*5,3*}. $t = 23$, 73%, mp 148−150 °C. IR (KBr) 3100, 3050, 2180, 1700, 1640, 1600, 1500, 1340. ^{1}H NMR (acetone-d_6), δ 1.15 (d, 3H, $^3J = 7$ Hz, Me), 2.55 (m, 2H, CH_2), 2.75 (m, 1H, CH), 7.10 (m, 5H, Ph-H), 7.70 (br, 1H, NH), 8.70 (br, 1H, NH).^{13}C NMR (DMSO-d_6), δ 19.0, 26.3, 39.0, 72.2, 118.6, 119.3, 120.1, 121.4, 140.8, 148.0, 170.3. MS *m*/*z* 227 (100) [M$^+$], 212 (81), 119 (62), 77 (30). Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.53; H, 5.80; N, 18.38.

2. Compound 4{*5,4*}. $t = 35$, 64%, mp 209−211 °C. IR (KBr) 3190, 3110, 2180, 1680, 1610. ^{1}H NMR (acetone-d_6), δ 1.20 (d, 3H, $^3J = 7$ Hz, Me), 2.60 (m, 2H, CH_2), 3.35 (m, 5H, NCH_2 and CH), 3.70 (m, 4H, OCH_2), 9.60 (br, 1H, NH).^{13}C NMR (DMSO-d_6), δ 18.9, 27.0, 39.2, 48.7, 66.1, 67.7, 120.6, 154.9, 170.8. MS *m*/*z* 221 (35) [M$^+$], 206 (100), 162 (10). Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.91; H, 6.80; N, 18.75.

3. Compound 4{*5,5*}. $t = 20$, 60%, mp 193−194 °C. IR (KBr) 3200, 3120, 2200, 1690, 1620. ^{1}H NMR (acetone-d_6), δ 1.12 (d, 3H, $^3J = 7$ Hz, Me), 1.50 (m, 6H), 2.45 (m, 3H), 3.30 (m, 4H), 8.70 (br, 1H, NH).^{13}C NMR (DMSO-d_6), δ 19.0, 23.7, 25.6, 27.0, 39.4, 66.7, 120.9, 154.7, 170.9. MS *m*/*z* 219 (36) [M$^+$], 204 (100), 136 (11). Anal. Calcd. for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.53; H, 7.94; N, 18.94.

4. Compound 4{*8,1*}. $t = 2$, 75%, mp 212−213 °C. IR (KBr) 3420, 3320, 3270, 3120, 2180, 1695, 1660. ^{1}H NMR (DMSO-d_6), δ 1.15 (d, 3H, $^3J = 7$ Hz, Me), 2.00−2.50 (m, 3H, CH_2 and CH), 5.80 (br, 2H, NH_2), 8.00 (br, 1H, NH).^{13}C NMR (DMSO-d_6), δ 14.7, 27.8, 34.9, 51.0, 121.5, 153.0, 173.2. MS *m*/*z* 151 (65) [M$^+$], 136 (100), 123 (12). Anal. Calcd. for $C_7H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.43; H, 6.12; N, 27.65.

5. Compound 4{*8,3*}. $t = 23$, 50%, mp 195−196 °C. IR (KBr) 3180, 3160, 3140, 2180, 1700, 1650, 1600, 1500. ^{1}H NMR (acetone-d_6), δ 1.15 (d, 3H, $^3J = 6$ Hz, Me), 2.40 (m, 3H, CH_2 and CH), 7.10 (m, 5H, Ph-H), 8.15 (br, 1H, NH), 9.15 (br, 1H, NH). ^{13}C NMR (DMSO-d_6), δ 14.3, 28.3, 35.1, 65.0, 120.0, 121.4, 128.9, 140.8, 148.4, 173.5. MS *m*/*z* 227 (100) [M$^+$], 212 (20), 119 (31). Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.74; H, 5.63; N, 18.43.

6. Compound 4{*8,4*}. $t = 41$, 60%, mp 194−196 °C. IR (KBr) 3200, 3120, 2190, 1680, 1625. ^{1}H NMR (acetone-d_6), δ 1.15 (d, 3H, $^3J = 6$ Hz, Me), 2.35 (m, 3H, CH_2 and CH), 3.35 (m, 4H, NCH_2), 3.65 (m, 4H, OCH_2), 9.00 (br, 1H, NH).^{13}C NMR (DMSO-d_6), δ 14.0, 29.6, 35.4, 48.6, 60.3, 66.1, 121.4, 154.4, 174.0. MS *m*/*z* 221 (100) [M$^+$], 206 (75), 178 (10). Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.98; H, 6.86; N, 19.06.

7. Compound 4{*8,5*}. $t = 30$, 53%, mp 206−207 °C. IR (KBr) 3200, 3120, 2200, 1690, 1620. ^{1}H NMR (acetone-d_6), δ 1.20 (d, 3H, $^3J = 7$ Hz, Me), 1.65 (m, 6H), 2.32 (m, 3H), 3.35 (m, 4H), 8.50 (br, 1H, NH). ^{13}C NMR (DMSO-d_6), δ 14.0, 23.7, 25.6, 29.7, 35.5, 49.3, 59.2, 121.8, 154.9, 174.1. MS *m*/*z* 219 (100) [M$^+$], 204 (79), 162 (33). Anal. Calcd. for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.92; H, 7.92; N, 19.08.

General Method for the Synthesis of 2-Cyanoimino-6-oxopiperidine-3-carbonitriles (5) as Sodium Salts. A mixture of 15 mmol of the corresponding pyridone **1**, 15 mmol of sodium, 15 mmol of cyanamide in 200 mL of dioxane, and a few drops of methanol is refluxed during the time *t* (h) stated in each case. The resulting suspension is filtered, washed with dioxane and EtOEt, and dried under vacuum over P_2O_5. These compounds are used without any further purification.

1. Compound 5{*1*}. $t = 9$, 100%, mp >200 °C (d). IR (KBr) 3190, 3115, 2180, 2140, 1690, 1570, 1480. ^{1}H NMR (DMSO-d_6), δ 0.87 (d, 3H, Me), 0.99 (d, 3H, Me), 2.40 (m, 1H, CH), 2.57 (m, 1H, CH), 8.78 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 11.44, 14.87, 32.92, 66.40, 120.04, 122.84, 155.47, 173.37.

2. Compound 5{*2*}. $t = 9$, 100%, mp >200 °C (d). IR (KBr) 3180, 3115, 2180, 2150, 1690, 1570, 1520. ^{1}H NMR (DMSO-d_6), δ 2.51 (dd, $^2J = 16$ Hz, $^3J = 4$ Hz), 2.93 (dd, $^2J = 16$ Hz, $^3J = 7$ Hz), 3.90 (dd, 1H, $^3J = 4$ Hz, $^3J = 7$ Hz), 7.55 (m, $^3J = 9$ Hz), 8.25 (m, $^3J = 9$ Hz), 9.20 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 38.5, 38.6, 59.6, 119.3, 122.5, 123.8, 128.2, 146.3, 152.1, 157.1, 169.4.

3. Compound 5{*3*}. $t = 5$, 87%, mp >200 °C (d). IR (KBr) 3615, 3430, 3115, 2180, 2135, 1690, 1660, 1590. ^{1}H NMR (DMSO-d_6), δ 2.36 (dd, $^2J = 16$ Hz, $^3J = 3$ Hz), 2.92 (dd, $^2J = 16$ Hz, $^3J = 8$ Hz), 3.79 (s, 3H), 3.86 (s, 3H), 3.95−3.99 (m, 1H), 6.98 (d, $^3J = 9$ Hz); 7.11 (d, $^3J = 9$ Hz), 9.11 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 35.9, 37.8, 56.1,

59.2, 60.1, 111.4, 119.5, 122.6, 122.7, 126.4, 132.5, 144.9, 152.5, 157.5, 169.4.

4. Compound 5{*4*}. $t = 14$, 84%, mp >250 °C (d). IR (KBr) 3430, 3200, 2190, 2135, 1690, 1595, 1490. ^{1}H NMR (DMSO-d_6), δ 0.07 (s, 9H), 0.63 (dd, $^2J = 15$ Hz, $^3J = 8$ Hz), 1.02 (dd, $^2J = 15$ Hz, $^3J = 5$ Hz), 2.03−2.12 (m, 1H), 2.30−2.41 (m, 2H), 8.71 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 0.7, 16.5, 30.5, 37.1, 54.8, 119.9, 123.4, 156.4, 174.2.

5. Compound 5{*6*}. $t = 19$, 86%, mp >175 °C (d). IR (KBr) 3420, 3210, 2190, 2145, 1685, 1590. ^{1}H NMR (DMSO-d_6), δ 2.44 (dd, 1H, $^2J = 16$ Hz, $^3J = 5$ Hz), 2.85 (dd, 1H, $^2J = 16$ Hz, $^3J = 7$ Hz), 3.72 (dd, 1H, $^3J = 5$ Hz, $^3J = 7$ Hz), 7.22 (m, $^3J = 8$ Hz), 7.55 (m, $^3J = 8$ Hz), 9.08 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 38.0, 39.1, 60.3, 119.6, 119.7, 122.7, 129.2, 131.4, 143.4, 156.8, 169.7.

6. Compound 5{*7*}. $t = 18$, 100%, mp 260 °C (d). IR (KBr) 3421, 3185, 3125, 2180, 2145, 1695, 1580. ^{1}H NMR (DMSO-d_6), δ 0.91 (t, 3H, $^3J = 7$ Hz), 1.20−1.50 (m, 4H), 2.14 (dd, 1H, $^2J = 16$ Hz, $^3J = 5$ Hz), 2.32−2.38 (m, 1H), 2.52 (dd, 1H, $^2J = 16$ Hz, $^3J = 6$ Hz), 8.80 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 14.1, 19.4, 32.3, 37.0, 61.4, 120.0, 123.1, 155.9, 170.7.

7. Compound 5{*13*}. $t = 17$, 89%, mp >280 °C (d). IR (KBr) 3415, 3200, 3140, 2180, 2140, 1715, 1580. ^{1}H NMR (DMSO-d_6), δ 2.42 (dd, 1H, $^2J = 16$ Hz, $^3J = 5$ Hz), 2.81 (dd, 1H, $^2J = 16$ Hz, $^3J = 7$ Hz), 3.63−3.67 (dd, 1H, $^3J = 5$ Hz, $^3J = 7$ Hz), 3.76 (s, 3H), 6.91 (m, $^3J = 8$ Hz), 7.17 (m, $^3J = 8$ Hz). ^{13}C NMR (DMSO-d_6), δ 37.8, 39.6, 61.2, 113.8, 119.8, 122.9, 127.8, 135.8, 156.5, 158.0, 170.0.

General Method for the Synthesis of 2-Dicyanomethylene-6-oxopiperidine-3-carbonitriles (6) as Sodium Salts. A mixture of 0.021 mol of the corresponding pyridone **1**, 0.021 mol of sodium, and 0.021 mol of malononitrile in 100 mL of dioxane and a few drops of methanol is refluxed during the time t (given in hours) stated in each case. The resulting suspension is filtered, washed with dioxane and EtOEt, and dried under vacuum over P_2O_5. These compounds are used without any further purification.

1. Compound 6{*3*}. $t = 11$, 41%, mp 214 °C. IR (KBr) 3282−3198, 2231, 1742, 1717, 1608, 1593. ^{1}H NMR (DMSO-d_6), δ 2.45 (dd, 1H, $^2J = 16$ Hz, $^3J = 3$ Hz), 2.94 (dd, 1H, $^2J = 16$ Hz, $^3J = 7$ Hz), 3.77 (s, 3H), 3.83 (s, 3H), 3.94−4.00 (m, 1H), 6.89 (d, 1H, $^3J = 9$ Hz), 7.08 (d, 1H, $^3J = 9$ Hz), 8.13 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 31.1, 36.6, 37.8, 56.1, 60.1, 66.6, 111.5, 120.7, 121.2, 122.6, 126.5, 131.2, 144.9, 151.4, 152.4, 168.6.

2. Compound 6{*4*}. $t = 3.5$, 83%, mp 207−209 °C. IR (KBr) 3227, 3178, 3152, 2231, 1721, 1597. ^{1}H NMR (DMSO-d_6), δ 0.07 (s, 9H), 0.65 (dd, 1H, $^2J = 15$ Hz, $^3J = 8$ Hz), 1.23 (dd, 1H, $^2J = 15$ Hz, $^3J = 5$ Hz), 2.10−2.32 (m, 2H), 2.70−2.80 (m, 1H), 4.75 (dd, 1H, $^3J = 5$ Hz, $^3J = 2$ Hz), 8.65 (br, 1H). ^{13}C NMR (DMSO-d_6), δ −0.84, 15.6, 28.9, 29.2, 34.9, 61.0, 111.2, 113.0, 116.0, 162.1, 172.1.

3. Compound 6{*6*}. $t = 5.5$, 63%, mp >200 °C. IR (KBr) 3233, 3157, 2215, 2178, 2158, 1686, 1574. ^{1}H NMR (DMSO-d_6), δ 2.55 (dd, 1H, $^2J = 16$ Hz, $^3J = 4$ Hz), 2.90 (dd, 1H, $^2J = 16$ Hz, $^3J = 7$ Hz), 3.76 (dd, 1H, $^3J = 4$ Hz, $^3J = 7$ Hz), 7.19 (m, $^3J = 8$ Hz, 2H), 7.54 (m, $^3J = 8$ Hz, 2H), 8.94 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 31.1, 38.5, 38.9, 67.5, 119.9, 120.8, 121.3, 129.2, 131.4, 141.9, 150.6, 169.0.

4. Compound 6{*7*}. $t = 8$, 38%, mp >200 °C. IR (KBr) 3212, 3154, 2242, 2226, 1736, 1600. ^{1}H NMR (DMSO-d_6), δ 0.86−0.94 (m, 3H), 1.20−1.65 (m, 4H), 2.10−2.80 (m, 3H), 4.53 (d, 0.25H, $^3J = 5$ Hz), 4.60 (d, 0.75H, $^3J = 5$ Hz), 8.67 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 13.6, 18.5, 31.0, 33.6, 33.9, 35.9, 61.8, 111.1, 112.9, 113.9, 161.5, 168.7.

5. Compound 6{*10*}. $t = 7$, 82%, mp >200 °C. IR (KBr) 3549−3235, 2983−2816, 2228, 1724, 1599. ^{1}H NMR (DMSO-d_6), δ 1.21−1.31 (m, 6H, CH_3CH$_2$O), 1.75−2.28 (m, 2H, POCH$_2$), 2.40−2.96 (m, 3H, H−C3 and H−C4), 4.01−4.11 (m, 4H, CH$_3$CH$_2$O), 4.81 (d, 1H, H−C5), 8.27 (br, 1H, NH). ^{13}C NMR (DMSO-d_6), δ 16.2, 27.3, 28.1, 34.1, 34.8, 61.6, 68.7, 111.1, 112.9, 113.6, 161.0, 168.1.

6. Compound 6{*13*}. $t = 4$, 49%, mp 223 °C. IR (KBr) 3248, 3150, 3080, 3038, 2942, 2211, 2179, 2158, 1736, 1576, 1609, 1515, 833. ^{1}H NMR (DMSO-d_6), δ 2.54 (m, 1H, H−C3), 2.88 (m, 1H, H−C3), 3.71 (t, $^3J = 5$ Hz, 1H, H−C4), 3.76 (s, 3H, OMe), 6.92 (m, 2H, H−Ph), 7.10 (m, 2H, H−Ph), 8.90 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 30.6, 38.4, 39.4, 55.1, 68.7, 113.9, 121.0, 121.5, 127.9, 134.3, 150.2, 158.1, 169.2.

7. Compound 6{*14*}. $t = 5$, 76%, mp >200 °C. IR (KBr) 3213, 3144, 2230, 1720, 1589. ^{1}H NMR (DMSO-d_6), δ 0.88 (m, 3H), 1.1−1.7 (m, 8H), 2.1−2.9 (m, 3H), 4.53 (d, 0.23H, $^3J = 5$ Hz), 4.61 (d, 0.78H; $^3J = 5$ Hz), 8.65 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 13.8, 21.8, 24.8, 30.9, 31.2, 31.6, 33.6, 33.9, 61.9, 111.1, 112.9, 113.9, 161.5, 168.7.

8. Compound 6{*15*}. $t = 7$, 65%, mp >200 °C. IR (KBr) 3267−3145, 2960−2825, 2202, 2173, 2166, 2154, 1694. ^{1}H NMR (DMSO-d_6), δ 2.30 (m, 2H, H−C4), 2.44 (dd, $^2J = 17$ Hz, $^3J = 6$ Hz, 1H, MeOOCCH$_2$), 2.69 (dd, $^2J = 17$ Hz, $^3J = 6$ Hz, 1H, MeOOCCH$_2$), 2.80 (q, $^3J = 6$ Hz, 1H, H−C3), 3.64 (s, 3H, OMe), 8.91 (br, 1H, NH). ^{13}C NMR (DMSO-d_6), δ 27.9, 30.5, 33.0, 37.7, 51.4, 63.5, 120.9, 121.5, 150.2, 171.3, 171.8.

General Method for the Synthesis of 4-Amino-2-bromo-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones (8) (G_1 = Br, G_2 = NH$_2$). A solution of 5 mmol of the corresponding sodium salt **5** in 20 mL of 45% aqueous HBr was stirred at room temperature for 1 h. The resulting suspension was concentrated in vacuo, neutralized with aqueous ammonia, and filtered. The resulting solid was washed with water and dried over P_2O_5.

1. Compound 8{*1*}. 83%, mp 220−221 °C. IR (KBr) 3381, 3318, 3192, 1689, 1646, 1595, 1556. ^{1}H NMR (DMSO-d_6), δ 0.85 (d, 1H, Me), 1.10 (d, 1H, Me), 2.80 (m, 1H, H−C5), 2.97 (m, 1H, H−C6), 7.18 (br, 2H, NH$_2$), 10.40 (br, 1H, NH). ^{13}C NMR (DMSO-d_6), δ 11.5, 11.7, 28.5, 38.2, 66.4, 99.3, 148.6, 156.0, 161.3, 172.9. MS m/z 270 (40) [M$^+$], 272 (34) [M$^+$+2], 257 (100). Anal. Calcd. for $C_9H_{11}N_4$-OBr: C, 39.87; H, 4.09; N, 20.67. Found: C, 39.70; H, 4.30; N, 20.33.

2. Compound 8{*2*}. 89%, mp >250 °C. IR (KBr) 3420, 3314, 3191, 3129, 1695, 1643, 1593, 1557, 1513, 856, 739. ^{1}H NMR (DMSO-d_6), δ 2.65 (m, 1H, H−C6), 3.23 (m, 1H, H−C6), 4.49 (m, 1H, H−C5), 7.31 (br, 2H, NH$_2$), 7.41 (m, 2H, H−Ph), 8.21 (m, 2H, H−Ph), 10.40 (br, 1H, NH). ^{13}C

NMR (DMSO-d_6), δ 33.5, 38.3, 94.5, 124.2, 128.6, 147.0, 149.0, 150.2, 157.9, 162.5, 169.8. Anal. Calcd. for $C_{13}H_{10}N_5O_3Br$: C, 42.88; H, 2.77; N, 19.23. Found: C, 42.75; H, 2.68; N, 19.33.

3. Compound 8{*3*}. 84%, mp >250 °C. IR (KBr) 3437, 3334, 3283, 3153, 1723, 1643, 1600, 1563, 1269, 1039. ^{1}H NMR (DMSO-d_6), δ 2.63 (m, 1H, H−C6), 3.13 (m, 1H, H−C6), 4.36 (m, 1H, H−C5), 6.38 (m, 1H, H−Ph), 6.95 (m, 1H, H−Ph), 7.10 (br, 2H, NH_2). ^{13}C NMR (DMSO-d_6), δ 31.3, 36.7, 56.0, 60.0, 93.6, 111.1, 121.5, 127.6, 128.8, 145.4, 149.9, 152.6, 158.3, 162.0, 169.5. Anal. Calcd. for $C_{15}H_{14}N_4O_3ClBr$: C, 43.55; H, 3.41; N, 13.54. Found: C, 43.80; H, 3.39; N, 13.56.

4. Compound 8{*4*}. 84%, mp 214−216 °C. IR (KBr) 3488, 3295, 3149, 1683, 1639, 1563, 839. ^{1}H NMR (DMSO-d_6), δ 0.05 (s, 9H, Me_3Si), 0.59 (m, 1H, CH_2Si), 1.01 (m, 1H, CH_2Si), 2.33 (m, 1H, H−C5), 2.53 (m, 1H, H−C6), 2.70 (m, 1H, H−C5), 7.17 (br, 2H, NH_2), 10.50 (br, 1H, NH). ^{13}C NMR (DMSO-d_6), δ −0.8, 17.5, 25.5, 35.8, 92.0, 148.5, 156.7, 162.3, 173.9. Anal. Calcd. for $C_{11}H_{17}N_4OBrSi$: C, 40.13; H, 5.20; N, 17.02. Found: C, 39.95; H, 5.15; N, 16.98.

5. Compound 8{*7*}. 50%, mp 224−226 °C. IR (KBr) 3324, 3197, 1699, 1646, 1588, 1548. ^{1}H NMR (TFA-*d*), δ 0.91 (m, 3H, Me), 130−1.50 (m, 4H, CH_2), 2.97 (m, 2H, H−C6), 3.27 (m, 1H, H−C5). ^{13}C NMR (TFA-*d*), δ 14.2, 20.9, 30.6, 35.3, 35.6, 101.9, 140.8, 157.0, 158.2, 176.7. Anal. Calcd. for $C_{10}H_{13}N_4OBr$: C, 42.12; H, 4.60; N, 19.65. Found: C, 42.20; H, 4.90; N, 19.87.

General Method for the Synthesis of 2-Amino-4-bromo-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones (9) (G_1 = NH_2, G_2 = Br). A stream of anhydrous hydrogen bromide was bubbled through a suspension of 10 mmol of the corresponding sodium salt **5** in 100 mL of a 3:1 mixture of dioxane and benzene cooled at −10 °C. The resulting mixture was kept overnight in the refrigerator, concentrated in vacuo, the resulting residue was suspended in methanol and neutralized with aqueous ammonia. The resulting solid was extracted in a Soxhlet with EtOH during 17 h to afford the corresponding pyridopyrimidine **9**.

1. Compound 9{*1*}. 97%, mp >250 °C. IR (KBr) 3334, 3195, 1695, 1652, 1614, 1543. ^{1}H NMR (DMSO-d_6), δ 0.95 (d, ^3J = 7 Hz, 3H, Me), 1.16 (d, ^3J = 7 Hz, 3H, Me), 2.91 (m, 1H, CH), 2.99 (m, 1H, CH), 6.88 (br, 2H, NH_2), 10.69 (br, 1H, NH). ^{13}C NMR (DMSO-d_6), δ 11.5, 13.2, 33.8, 42.7, 109.5, 150.5, 157.6, 161.3, 173.5. MS *m*/*z* 270 (25) [M^+], 272 (22) [M^++2], 257 (100). Anal. Calcd. for $C_9H_{11}N_4OBr$: C, 39.87; H, 4.09; N, 20.67. Found: C, 39.80; H, 3.97; N, 20.70.

2. Compound 9{*2*}. 51%, mp >250 °C. IR (KBr) 3324, 3194, 1694, 1656, 1615, 1550, 1511, 856, 737. ^{1}H NMR (TFA-*d*), δ 3,16 (m, 1H, H−C6), 3.46 (m, 1H, H−C6), 4.75 (d, ^3J = 3 Hz, H−C5), 7.41 (m, 2H, H−Ph), 8.24 (m, 2H, H−Ph). ^{13}C NMR (TFA-*d*), δ 38.9, 40.5, 110.9, 112.0, 114.7, 118.5, 122.2, 126.9, 129.8, 142.4, 1481, 149.6, 158.1, 175.1. MS *m*/*z* 363 (99) [M^+], 365 (100) [M^++2], 241 (89). Anal. Calcd. for $C_{13}H_{10}N_5O_3Br$: C, 42.88; H, 2.77; N, 19.23. Found: C, 42.84; H, 2.78; N, 19.25.

3. Compound 9{*4*}. 43%, mp >250 °C. IR (KBr) 3325, 3202, 1691, 1657, 1620, 1541, 1242, 841. ^{1}H NMR (DMSO-d_6), δ 0.06 (s, 9H,, Me_3Si), 0.61 (m, 1H, CH_2Si), 1.04 (m, 1H, CH_2Si), 2.45 (m, 1H, H−C5), 2.63 (m, 1H, H−C6), 2.88 (m, 1H, H−C5), 6.82 (br, 2H, NH_2), 10.61 (br, 1H, NH). ^{13}C NMR (DMSO-d_6), δ 0.80, 17.0, 30.3, 36.33, 102.9, 151.2, 158.3, 161.3, 174.6. MS *m*/*z* 327 (20) [M^+], 329 (19) [M^++2], 313 (100). Anal. Calcd. for $C_{11}H_{17}N_4OBrSi$: C, 40.13; H, 5.20; N, 17.02. Found: C, 40.00; H, 5.07; N, 17.20.

General Method for the Synthesis of 5-Amino-7-bromo-8-cyano-3,4-dihydro-1,6-naphthyridin-2(1*H*)-ones (10). A mixture of 3 mmol of the corresponding dicyanomethylene-substituted pyridone **6** and 50 mL of 33% hydrogen bromide (HBr) in AcOH are stirred for time *t* (given in hours) at room temperature. The resulting mixture is concentrated in vacuo, the residue suspended in methanol, and the pH adjusted to 9 with a 2 M ammonia solution in methanol. The solution is concentrated under reduced pressure, and the solid obtained is filtered, washed with water and dried over P_2O_5. Recrystallization from methanol affords the corresponding 7-amino-5-bromo isomer **10**.

1. Compound 10{*4*}. t = 48, 99%, mp >200 °C. IR (KBr) 3475, 3294, 3168, 2217, 1699, 1632, 1593, 1553. ^{1}H NMR (DMSO-d_6), δ 0.06 (s, 9H), 0.60 (dd, 1H, ^2J = 15 Hz, ^3J = 8 Hz), 1.03 (dd, 1H, ^2J = 15 Hz, ^3J = 5 Hz), 2.56−2.70 (m, 1H), 2.90−3.20 (m, 1H and s, 3H), 7.12 (br, 2H), 10.5 (br, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6), δ −0.93, 16.5, 31.7, 35.9, 76.1, 107.6, 113.9, 144.9, 149.6, 158.9, 173.5. MS *m*/*z* 352 (7) [M^+], 354 (7), 337 (100), 339 (92), 73 (80). Anal. Calcd. for $C_{13}H_{17}N_4OBrSi$: C, 44.20; H, 4.85; N, 15.86. Found: C, 44.17; H, 4.80; N, 15.71.

2. Compound 10{*6*}. t = 24, 92%, mp >250 °C. IR (KBr) 3404, 3380, 3299, 3171, 2216, 1708, 1641, 1601, 1559. ^{1}H NMR (DMSO-d_6), δ 2.62 (dd, 1H, ^2J = 16 Hz, ^3J = 2 Hz), 3.20 (dd, 1H, ^2J = 16 Hz, ^3J = 7 Hz), 4.40 (d, ^3J = 7 Hz), 7.06 (m, ^3J = 8 Hz, 2H), 7.31 (br, 2H), 7.52 (m, ^3J = 8 Hz, 2H), 10.70 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 38.5, 39.3, 76.8, 109.4, 113.9, 120.1, 129.0, 131.6, 140.2, 146.1, 150.4, 159.4, 169.1. MS *m*/*z* 420 (52) [M^+], 422 (100), 424 (52), 265 (82), 267 (78). Anal. Calcd. for $C_{15}H_{10}N_4OBr_2$: C, 42.69; H, 2.39; N, 13.27. Found: C, 42.77; H, 2.28; N, 13.35.

3. Compound 10{*7*}. t = 44, 57%, mp 213 °C. IR (KBr) 3468, 3293, 3176, 2216, 1732, 1627, 1593, 1552. ^{1}H NMR (DMSO-d_6), δ 0.86 (m, 3H), 1.20−1.48 (m, 4H), 2.46 (dd, 1H, ^2J = 16 Hz, ^3J = 2 Hz), 2.80 (dd, 1H, ^2J = 16 Hz,^3J = 6 Hz), 3.03−3.08 (m, 1H), 7.12 (br, 2H), 10.49 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 13.7, 19.1, 34.2, 34.5, 34.7, 76.7, 111.9, 114.0, 144.9, 149.5, 158.9, 170.1. MS *m*/*z* 308 (14) [M^+], 310 (14), 265 (100), 267 (96), 186 (23). Anal. Calcd. for $C_{12}H_{13}N_4OBr$: C, 46.62; H, 4.24; N, 18.12. Found: C, 46.75; H, 4.34; N, 18.16.

4. Compound 10{*13*}. t = 72, 92%, mp >250 °C. IR (KBr) 3440, 3299, 3228, 3189, 2224, 1706, 1627, 1593, 1557. ^{1}H NMR (DMSO-d_6), δ 2.52−2.61 (m, 1H), 3.12 (dd, 1H, ^2J = 16 Hz, ^3J = 7 Hz), 4.28 (d, 1H, ^3J = 6 Hz), 6.69 (m, ^3J = 8 Hz, 2H), 6.87 (m, ^3J = 8 Hz, 2H), 7.25 (br, 2H), 10.5 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 39.0, 39.1, 76.7, 110.5, 113.9, 115.4, 127.6, 130.7, 146.1, 150.2, 156.3, 159.2, 169.5. MS *m*/*z* 373 (100) [M^+], 360 (99), 279 (53), 265 (95).

Anal. Calcd. for $C_{16}H_{13}N_4O_2Br$: C, 51.49; H, 3.51; N, 15.01. Found: C, 51.35; H, 3.47; N, 15.19.

5. Compound 10{*8*}. $t = 27$, 78%, mp 207 °C. IR (KBr) 3467, 3290, 3167, 2216, 1707, 1626, 1589, 1549. ^{1}H NMR (DMSO-d_6), δ 0.86 (t, 3H, $^3J = 6$ Hz), 1.12−1.52 (m, 8H), 2.45 (dd, 1H, $^2J = 16$ Hz, $^3J = 2$ Hz), 2.78 (dd, 1H, $^2J = 16$ Hz, $^3J = 6$ Hz), 3.01−3.07 (m, 1H), 7.10 (br, 2H), 10.52 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 13.8, 21.9, 25.4, 31.0, 32.2, 34.4, 34.7, 76.7, 111.9, 114.0, 144.9, 149.8, 158.9, 170.3. MS *m*/*z* 336 (13) [M$^+$], 338 (13), 265 (90), 267 (100), 186 (24). Anal. Calcd. for $C_{14}H_{17}N_4OBr$: C, 49.86; H, 5.08; N, 16.61. Found: C, 49.79; H, 5.11; N, 16.57.

6. Compound 10{*14*}. $t = 40$, 77%, mp >250 °C. IR (KBr) 3455, 3354, 3223, 3150, 2216, 1707, 1633, 1601, 1549. ^{1}H NMR (DMSO-d_6), 300 MHz, δ 2.59 (dd, 1H, $^2J = 17$ Hz, $^3J = 6$ Hz), 2.63−2.74 (m, 1H), 2.95−3.07 (m, 1H and s, 3H), 2.78 (dd, 1H, $^2J = 17$ Hz, $^3J = 6$ Hz), 3.64 (s, 3H), 7.12 D, 2H; 10.71, D, 1H. ^{13}C NMR (75.5 MHz, DMSO-d_6), δ 28.8, 33.1, 35.9, 51.4, 76.7, 107.9, 114.0, 144.6, 149.7, 158.9, 171.5, 171.8. MS *m*/*z* 338 (2) [M$^+$], 340 (2), 307 (9), 309 (14), 265 (95), 267 (100). Anal. Calcd. for $C_{12}H_{11}N_4O_3Br$: C, 42.50; H, 3.27; N, 16.52. Found: C, 42.48; H, 3.22; N, 16.37.

General Method for the Nucleophilic Substitution of the Br Atom of 4-Amino-2-bromo-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones (8) and 2-Amino-4-bromo-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones (9). A mixture of 3.1 mmol of the corresponding bromo-substituted pyrido-[2,3-*d*]pyrimidine **8** or **9**, 62 mmol of the corresponding amine in 20 mL of methanol was refluxed for 17 h. After cooling the solvent was eliminated in vacuo and the residue was treated with a small amount of methanol, filtered, and washed with methanol.

1. Compound 13{*5,6*}. 69%, mp >250 °C. IR (KBr) 3459, 3357, 1682, 1639, 1606, 1578, 1549, 1511, 828, 795. ^{1}H NMR (DMSO-d_6), 300 MHz, δ 1.05 (d, 3H, Me), 2.32 (m, 1H, H−C6), 2.77 (m, 1H, H−C6), 3.10 (m, 1H, H−C5), 3.76 (s, 3H, OMe), 6.84 (m, 2H, H−Ph), 6.49 (br, 2H, NH_2), 7.76 (m, 2H, H−Ph), 8.73 (br, 1H, NH), 10.35 (br, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6), δ 18.8, 23.3, 55.1, 90.7, 113.5, 120.0, 134.7, 153.5, 155.2, 158.2, 160.9, 171.4. MS *m*/*z* 299 (66) [M$^+$], 281 (100), 268 (5). Anal. Calcd. for $C_{15}H_{17}N_5O_2$: C, 60.19; H, 5.72; N, 23.40. Found: C, 60.24; H, 5.80; N, 23.28.

2. Compound 13{*5,7*}. 88%, mp >250 °C. IR (KBr) 3481, 3294, 1695, 1632, 1592, 1550, 835, 701. ^{1}H NMR (TFA-d), 300 MHz, δ 1.21 (d, 3H, Me), 2.75 (m, 1H, H−C6), 3.00 (m, 1H, H−C6), 3.21 (m, 1H, H−C5), 4.63 (s, 3H, CH_2Ph), 7.28 (m, 5H, H−Ph). ^{13}C NMR (75.5 MHz, TFA-*d*), δ 18.7, 25.2, 38.5, 47.7, 92.7, 129.5, 130.5, 130.9, 153.5, 156.3, 177.7. MS *m*/*z* 283 (63) [M$^+$], 268 (100), 91 (53). Anal. Calcd. for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.49; H, 6.02; N, 24.52.

3. Compound 13{*5,8*}. 75%, mp >250 °C. IR (KBr) 3466, 3316, 1663, 1626, 1576, 1542. ^{1}H NMR (DMSO-d_6), 300 MHz, δ 1.01 (d, 3H, Me), 1.51−1.92 (m, 8H, H-pyrrolidine), 2.33 (m, 1H, H−C6), 2.78 (m, 1H, H−C6), 3.05 (m, 1H, H−C5), 4.18 (m, 1H, H-pyrrolidine), 6.42 (br, 2H, NH_2), 7.13 (br, 1H, NH), 11.18 (br, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6), δ 19.0, 23.1, 23.3, 32.5, 38.2, 51.9, 88.7, 155.1, 160.3, 161.2, 172.5. MS *m*/*z* 261 (45) [M$^+$], 246 (67), 178 (100). Anal. Calcd. for $C_{13}H_{19}N_5O$: C, 59.75; H, 7.33; N, 26.80. Found: C, 59.55; H, 7.51; N, 26.98.

4. Compound 13{*5,9*}. 76%, mp 216−217 °C. IR (KBr) 3504, 3268, 1686, 1636, 1588, 1544. ^{1}H NMR (DMSO-d_6), 300 MHz, δ 0.94 (t, 3H, Me), 1.01 (d, 3H, Me), 1.38 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), 2.30 (m, 1H, H−C6), 2.75 (m, 1H, H−C6), 3.05 (m, 1H, H−C5), 3.25 (m, 2H, CH_2), 6.41 (br, 2H, NH_2), 6.94 (br, 1H, NH), 11.07 (br, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6), δ 13.9, 18.9, 19.7, 23.2, 38.3, 88.8, 155.2, 160.7, 161.2, 172.1. MS *m*/*z* 249 (42) [M$^+$], 231 (100), 178 (39). Anal. Calcd. for $C_{12}H_{19}N_5O$: C, 57.81; H, 7.68; N, 28.09. Found: C, 57.74; H, 7.65; N, 28.14.

5. Compound 13{*5,10*}. 86%, mp >250 °C. IR (KBr) 3496, 3390, 1663, 1686, 1637, 1593, 1493, 825, 794. ^{1}H NMR (DMSO-d_6), 300 MHz, δ 1.07 (d, 3H, Me), 2.36 (m, 1H, H−C6), 2.83 (m, 1H, H−C6), 3.15 (m, 1H, H−C5), 6.65 (br, 2H, NH_2), 7.27 (m, 2H, H−Ph), 7.96 (m, 2H, H−Ph), 9.22 (br, 1H, NH), 10.60 (br, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6), δ 18.7, 23.3, 38.1, 91.4, 119.8, 123.7, 128.0, 140.4, 155.1, 157.8, 160.9, 171.6. MS *m*/*z* 303 (44) [M$^+$], 305 (15) [M$^+$+2], 288 (100), 178 (7). Anal. Calcd. for $C_{14}H_{14}N_5OCl$: C, 55.36; H, 4.65; N, 23.06. Found: C, 55.20; H, 4.54; N, 23.24.

General Method for the Synthesis of Synthesis of 3-amino-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-*b*]pyridines (17). A solution of 40 mmol of sodium in 30 mL of MeOH and 20 mmol of hydrazine dihydrochloride was added to a solution of 10 mmol of the corresponding pyridone **1** in 60 mL of MeOH. The mixture was refluxed for the time *t* (h) stated in each case. The solvent was concentrated in vacuo, and a small amount of methanol and Et_2O was added. The mixture was sonicated and the solid obtained was filtered to afford the corresponding pyrazolo[3,4-*b*]pyridine **5**.

1. Compound 17{*2*}. $t = 16$, 92%, mp >300 °C. IR (KBr) 3460, 3390, 3350, 1660, 1635, 1515. ^{1}H NMR (DMSO-d_6), δ 2.52 (dd, 1H, $^2J = 16$ Hz, $^3J = 3$ Hz), 3.00 (dd, 1H, $^2J = 16$ Hz, $^3J = 8$ Hz), 4.32 (dd, 1H, $^3J = 3$ Hz, $^3J = 8$ Hz), 5.07 (br, 2H), 7.45 (m, 2H, $^3J = 9$ Hz), 8.21 (m, 2H, $^3J = 9$ Hz), 10.25 (br, 1H), 10.83 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 32.7, 39.8, 84.4, 123.7, 128.0, 144.2, 146.1, 148.1, 152.7, 169.2. MS *m*/*z* 273 (100) [M$^+$], 230 (10), 151 (79). Anal. Calcd. for $C_{12}H_{11}N_5O_3$: C, 52.73; H, 4.06; N, 25.64. Found: C, 52.53; H, 4.10; N, 25.65.

2. Compound 17{*3*}. $t = 16$, 90%, mp 283−285 °C. IR (KBr) 3350, 3270, 3170, 1665, 1635, 1565. ^{1}H NMR (DMSO-d_6), δ 2.41 (dd, 1H, $^2J = 16$ Hz, $^3J = 3$ Hz), 2.89 (dd, 1H, $^2J = 16$ Hz, $^3J = 7$ Hz), 3.78 (s, 3H), 3.80 (s, 3H), 4.37 (dd, 1H, $^3J = 3$ Hz, $^3J = 7$ Hz), 4.95 (br, 2H); 6.54 (d, 1H, $^3J = 9$ Hz), 6.96 (d, 1H, $^3J = 9$ Hz), 10.16 (br, 1H), 10.79 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 29.9, 39.3, 56.0, 60.0, 83.8, 111.1, 122.6, 126.6, 133.5, 144.0, 144.9, 149.1, 152.0, 169.2. MS *m*/*z* 322 (100) [M$^+$], 279 (15), 244 (7), 151 (71). Anal. Calcd. for $C_{14}H_{15}N_4O_3Cl$: C, 52.10; H, 4.68; N, 17.36. Found: C, 51.97; H, 4.64; N, 17.53.

3. Compound 17{*4*}. $t = 22$, 60%, mp 218−219 °C. IR (KBr) 3440, 3405, 3325, 3245, 1655, 1645, 1560. ^{1}H NMR (DMSO-d_6), δ 0.05 (s, 9H), 0.60 (dd, 1H, $^2J = 15$ Hz, $^3J =$

8 Hz), 1.08 (dd, 1H, ^2J = 15 Hz, ^3J = 6 Hz), 2.19 (dd, 1H, ^2J = 15 Hz, ^3J = 8 Hz), 2.36−2.45 (m, 1H), 2.69 (dd, 1H, ^2J = 15 Hz, ^3J = 6 Hz), 5.06 (br, 2H), 7.50 (br, 1H), 9.89 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 0.6, 18.0, 24.1, 38.1, 82.1, 144.0, 148.1, 173.7. Anal. Calcd. for $C_{10}H_{18}N_4OSi$: C, 50.39; H, 7.61; N, 23.50. Found: C, 50.15; H, 7.75; N, 23.35.

4. Compound 17{*6*}. t = 48, 92%, mp >300 °C. IR (KBr) 3460, 3415, 3325, 1665, 1635, 1530. ^{1}H NMR (DMSO-d_6), δ 2.49 (dd, 1H, ^2J = 16 Hz, ^3J = 3 Hz), 2.92 (dd, 1H, ^2J = 16 Hz, ^3J = 7 Hz), 4.14 (dd, 1H, ^3J = 3 Hz, ^3J = 7 Hz), 4.98 (br, 2H), 7.15 (m, 2H, ^3J = 8 Hz), 7.52 (m, 2H, ^3J = 8 Hz), 10.20 (br, 1H), 10.85 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 32.2, 40.2, 85.2, 119.3, 129.1, 131.2, 144.0, 144.1, 148.2, 169.5. MS *m*/*z* 308 (84) [M$^+$], 265 (19), 151 (100). Anal. Calcd. for $C_{12}H_{11}N_4OBr$: C, 46.93; H, 3.61; N, 18.24. Found: C, 47.11; H, 3.50; N, 18.00.

5. Compound 17{*7*}. t = 24, 66%, mp 198−201 °C. IR (KBr) 3420, 3330, 3145, 1645, 1600, 1560. ^{1}H NMR (DMSO-d_6), δ 0.89 (t, 3H, ^3J = 6 Hz), 1.24−1.35 (m, 4H), 2.24 (dd, 1H, ^2J = 16 Hz, ^3J = 3 Hz), 2.58 (dd, 1H, ^2J = 16 Hz, ^3J = 7 Hz), 2.82 (m, 1H), 4.98 (br, 2H), 10.00 (br, 1H), 10.76 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 14.2, 19.4, 27.3, 38.1, 38.2, 86.0, 143.9, 147.9, 170.5. MS *m*/*z* 194 (32) [M$^+$], 151 (100). Anal. Calcd. for $C_9H_{14}N_4O$: C, 55.65; H, 7.26; N, 28.84. Found: C, 55.38; H, 7.07; N, 29.08.

6. Compound 17{*8*}. t = 6, 63%, mp 252−253 °C. IR (KBr) 3410, 3340, 3230, 1650, 1560, 1540. ^{1}H NMR (DMSO-d_6), δ 1.10 (d, ^3J = 7 Hz, Me), 2,10−2.70 (m, 3H, H−C4 and H−C5), 4.97 (br, 2H, NH_2), 9.90 (br, 1H, NH). ^{13}C NMR (DMSO-d_6), δ 16.5, 23.7, 36.0, 82.5, 143.7, 148.3, 173.4. MS *m*/*z* 166 (100) [M$^+$], 138 (17), 110 (49). Anal. Calcd. for $C_7H_{10}N_4O$: C, 50.58; H, 6.07; N, 33.72. Found: C, 50.30; H, 6.28; N, 33.65.

7. Compound 17{*9*}. t = 6, 37%, mp 261−262 °C. IR (KBr) 3440, 3350, 3230, 1645, 1565, 1535. ^{1}H NMR (DMSO-d_6), δ 2.50 (m, 1H, H−C5), 2.90 (m, 1H, H−C5), 4.15 (m, 1H, H−C4), 490 (br, 2H, NH_2), 7.23 (m, 5H, H−Ph), 10.1 (br, 1H, NH). ^{13}C NMR (DMSO-d_6), δ 32,7, 40.1, 85.8, 126.3, 126.8, 128.4, 143.9, 144.6, 148.2, 169.7. MS *m*/*z* 228 (45) [M$^+$], 151 (64), 77 (50), 42 (100). Anal. Calcd. for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.30; N, 24.55. Found: C, 63.41; H, 5.16; N, 24.35.

8. Compound 17{*10*}. t = 3, 90%, mp 178−180 °C. IR (KBr) 3405, 3320, 3220, 1665, 1625, 1560. ^{1}H NMR (DMSO-d_6), δ 1.19 (t, 3H), 1.25 (t, 3H), 1.78−2.07 (m, 2H), 2.43 (dd, 1H, ^2J = 16 Hz, ^3J = 4 Hz), 2.63 (ddd, 1H, ^2J = 16 Hz, ^3J = 7 Hz, ^4J = 2 Hz), 3.09−3.15 (m, 1H), 3.90−4.05 (m, 4H), 5.13 (br, 2H), 7.30 (br, 1H), 10.10 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 16.2, 23.2, 29.9, 38.8, 61.1, 86.3, 143.9, 147.6, 169.6. Anal. Calcd. for $C_{11}H_{19}N_4O_4P$: C, 43.71; H, 6.34; N, 18.54. Found: C, 43.55; H, 6.15; N, 18.69.

9. Compound 17{*11*}. t = 18, 90%, mp 198−200 °C. IR (KBr) 3420, 3340, 3245, 3140, 1655, 1640, 1590. ^{1}H NMR (DMSO-d_6), δ 2.54 (dd, 1H, ^2J = 16 Hz, ^3J = 4 Hz), 2.82 (dd, 1H, ^2J = 16 Hz, ^3J = 7 Hz), 3.63 (s, 3H), 3.72 (s, 6H), 4.06 (dd, 1H, ^3J = 4 Hz, ^3J = 7 Hz), 4.89 (br, 2H), 6,53 (s, 2H), 10.11 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 33.2, 40.4, 55.8, 60.0, 85.7, 104.2, 136.0, 140.2, 144.0, 148.0, 152.8, 169.9. Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.75; H, 5.58; N, 17.35.

10. Compound 17{*13*}. t = 4, 87%, mp 270−272 °C. IR (KBr) 3400, 3330, 3150, 3105, 1645, 1610, 1565. ^{1}H NMR (DMSO-d_6), δ 2.48 (dd, 1H, ^2J = 16 Hz, ^3J = 3 Hz), 2.83 (dd, 1H, ^2J = 16 Hz, ^3J = 7 Hz), 3.71 (s, 3H), 4.07 (dd, 1H, ^3J = 3 Hz, ^3J = 7 Hz), 4.83 (br, 2H), 6.85 (m, 2H, ^3J = 9 Hz), 7.10 (m, 2H, ^3J = 9 Hz), 10.14 (br, 1H), 10.67 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 32.0, 40.8, 55.1, 86.2, 113.8, 127.8, 136.4, 143.9, 148.2, 157.8, 169.9. MS *m*/*z* 258 (100) [M$^+$], 215 (41), 151 (46). Anal. Calcd. for $C_{13}H_{14}N_4O_2$: C, 60.44; H, 5.47; N, 21.70. Found: C, 60.74; H, 5.66; N, 21.83.

General Method for the Synthesis of 2,4-Diamino-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones (18) (G_1 = G_2 = NH_2). Guanidine carbonate (6 mmol) was added to a solution of 12 mmol of sodium in 50 mL of anhydrous MeOH, and the mixture was refluxed for 15 min. The mixture was filtered, and 6 mmol of the corresponding pyridone **1** was added to the filtrate. The mixture was refluxed for 24 h, and the resulting precipitate was filtered and washed with MeOH and EtOEt. Recrystallization from ethanol gave the pyridopyrimidine **6**.

1. Compound 18{*3*}. 70%, mp >300 °C. IR (KBr) 3430, 3340, 3230, 3130, 1700, 1655, 1565. ^{1}H NMR (DMSO-d_6), δ 2.62 (d, 1H, ^2J = 16 Hz), 3.07 (dd, 1H, ^2J = 16 Hz, ^3J = 7 Hz), 3.82 (s, 3H), 3.83 (s, 3H), 4.35 (d, 1H, ^3J = 7 Hz), 6.10 (br, 2H), 6.13 (br, 2H), 6.51 (d, 1H, ^3J = 9 Hz), 6.99 (d, 1H, ^3J = 9 Hz). ^{13}C NMR (DMSO-d_6), δ 31.3, 37.6, 55.9, 60.0, 85.3, 111.1, 121.9, 127.3, 131.0, 145.2, 152.3, 157.9, 161.7, 162.3, 170.3. Anal. Calcd. for $C_{15}H_{16}N_5O_3Cl$: C, 51.51; H, 4.61; N, 20.02. Found: C, 51.35; H, 4.73; N, 19.95.

2. Compound 18{*4*}. 90%, mp 252−254 °C. IR (KBr) 3465, 3320, 3205, 3100, 1685, 1645, 1575. ^{1}H NMR (DMSO-d_6), δ 0.10 (s, 9H), 0.67 (dd, 1H, ^2J = 15 Hz, ^3J = 8 Hz), 1.06 (dd, 1H, ^2J = 15 Hz, ^3J = 6 Hz), 2.34 (dd, 1H, ^2J = 15 Hz, ^3J = 8 Hz), 2.54−2.63 (m, 1H), 2.72 (dd, 1H, ^2J = 15 Hz, ^3J = 6 Hz), 6.22 (br, 2H), 6.39 (br, 2H), 10.91 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 0.7, 17.7, 25.7, 36.6, 83.3, 156.1, 161.6, 162.2, 175.7. MS *m*/*z* 265 (9) [M$^+$], 250 (100). Anal. Calcd. for $C_{11}H_{19}N_5OSi$: C, 49.79; H, 7.22; N, 26.41. Found: C, 49.94; H, 7.41; N, 26.31.

3. Compound 18{*6*}. 70%, mp >300 °C. IR (KBr) 3500, 3465, 3315, 3205, 1700, 1640, 1565. ^{1}H NMR (TFA-*d*), δ 3.06 (d, 1H, ^2J = 17 Hz), 3.32 (dd, 1H, ^2J = 17 Hz, ^3J = 8 Hz), 4.37 (d, 1H, ^3J = 8 Hz), 7.05 (m, 2H, ^3J = 7 Hz), 7.46 (m, 2H, ^3J = 7 Hz). ^{13}C NMR (TFA-*d*), δ 35.1, 39.7, 89.9, 124.9, 129.4, 134.7, 137.6, 154.6, 156.4, 157.2, 175.3. MS *m*/*z* 333 (57) [M$^+$], 178 (100). Anal. Calcd. for $C_{13}H_{12}N_5OBr$: C, 46.84; H, 3.63; N, 21.02. Found: C, 46.82; H, 3.90; N, 21.02.

4. Compound 18{*7*}. 77%, mp 261−263 °C. IR (KBr) 3460, 3405, 3335, 3320, 3125, 1680, 1640, 1565. ^{1}H NMR (TFA-*d*), δ 0.92 (t, 3H, ^3J = 7 Hz), 1.26−1.57 (m, 4H), 2.96 (d, 2H, ^3J = 4 Hz), 3.15−3.23 (m, 1H), 7.64 (br). ^{13}C NMR (DMSO-d_6), δ 14.3, 21.0, 30.3, 35.8, 36.4, 92.7, 154.0, 154.6, 157.1, 176.9. MS *m*/*z* 221(11) [M$^+$], 178 (100). Anal. Calcd. for $C_{10}H_{15}N_5O$: C, 54.27; H, 6.84; N, 31.66. Found: C, 54.25; H, 6.63; N, 31.59.

5. Compound 18{*10*}. 79%, mp 224−225 °C. IR (KBr) 3455, 3395, 3340, 3235, 1695, 1670, 1650, 1560. ^{1}H NMR (TFA-d), δ 1.35 (t, 3H), 1.39 (t, 3H), 2.13−2.35 (m, 2H), 3.09 (d, 2H, ^3J = 5 Hz), 3.62−3.72 (m, 1H), 4.17−4.31 (m, 4H). ^{13}C NMR (DMSO-d_6), δ 16.6, 25.6, 29.5, 37.2, 66.8, 90.8, 155.0, 156.7, 156.8, 175.7. MS *m*/*z* 329 (33) [M$^+$], 192 (21), 178 (100). Anal. Calcd. for $C_{12}H_{20}N_5O_4P$: C, 43.77; H, 6.12; N, 21.27. Found: C, 43.58; H, 6.19; N, 21.28.

6. Compound 18{*13*}. 70%, mp >300 °C. IR (KBr) 3475, 3450, 3325, 3215, 3100, 1695, 1665, 1645, 1575. ^{1}H NMR (DMSO-d_6), δ 2.56 (d, 1H, ^2J = 16 Hz), 3.07 (dd, 1H, ^2J = 16 Hz, ^3J = 7 Hz), 3.75 (s, 3H), 4.19 (d, 1H, ^3J = 7 Hz), 6.21 (br, 2H), 6.30 (br, 2H), 6.90 (m, ^3J = 8 Hz, 2H), 7.11 (m, ^3J = 8 Hz, 2H), 10.82 (br, 1H). ^{13}C NMR (DMSO-d_6), δ 32.4, 39.5, 55.0, 87.2, 113.8, 127.7, 134.5, 156.6, 158.0, 161.8, 161.9, 171.4. MS *m*/*z* 285 (100) [M$^+$], 178 (68). Anal. Calcd. for $C_{14}H_{15}N_5O_2$: C, 58.92; H, 5.30; N, 24.56. Found: C, 58.91; H, 5.40; N, 24.71.

Biological Tests. 1. Fungicide Screen. The test species were as follows: *Pseudoperonospora cubensis* (cucumber downy mildew), *Alternaria solani* (tomato early blight), *Phytophthora infestans* (tomato late blight), *Puccinia recondita* (wheat leaf rust), and *Erysiphe graminis* (wheat powdery mildew). The test method was as follows: A 20 mg sample of test compound is dissolved in 100 mL of an acetone/methanol/water mixture to prepare a 300 g/Ha solution. Plants were treated with this solution, dried, and then infected with one of the test organisms. The ratings system was as follows: visual observations are made on pest control using a scale of 0% to 100%, where 0% is no effect and 100% is complete control.

2. Insecticide Screen. The test species were as follows: *Myzus persicae* (green peach aphid), *Empoasca fabae* (potato leafhopper), *Spodoptera eridania* (southern armworm), *Heliothis virescens* (tobacco budworm), *Tetranychus urticae* (two-spotted mite), and *Diabrotica undecimpunctata* (corn rootworm). The test method was as follows: 30 mg of test compound is dissolved in a 50-mL mixture of acetone, methanol, and water, which also contains a low amount of surfactant, to aid wettability. Insects were treated with this solution. The ratings system was as follows: visual observations are made on pest control using a scale of 0% to 100%, where 0% is no effect and 100% is complete control.

3. Herbicide Screen. The test species were as follows: *Bidens pilosa* (hairy beggartick), *Solanum nigrum* (night shade), *Polygonium lapthifolium* (smartweed), *Abutilon theophrasti* (velvetleaf), *Echinochloa crus-galli* (barnyardgrass), *Digitaria sanguinalis* (crabgrass), *Setria viridis* (green foxtail), *Lolium multiforum* (ryegrass). The dosage rates were 150 g/Ha.

The test method was as follows. In a post-emergence application, test weeds are in the 2−4 leaf stage. The pre-emergence applications are made in the soil surface soon after the weeds are planted. The test weeds are treated with a solution of 50 mg of test compound in acetone or a combination of acetone, methanol, and water. The treated plants are maintained in the greenhouse until rated. The ratings system was as follows: visual observations are made on pest control using a scale of 0% to 100%, where 0% is no effect and 100% is complete control.

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