Reactions of Methyl 2-(Benzyloxycarbonyl)amino-3-dimethylaminopropenoate and Related Compounds with Hydrazines. Regiospecific Synthesis of 1-Substituted-4-amino-substituted-1*H*-pyrazol-5-(2*H*)-ones

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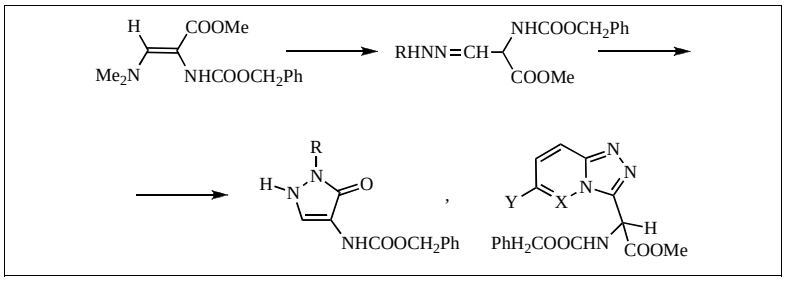
Dedicated to Professor Dr. Miha Tišler, Professor Emeritus of the University of Ljubljana, on the occasion of his 80th anniversary



In this paper the regiospecific transformations of methyl 2-(benzyloxycarbonyl)amino-3-dimethylaminopropenoate (**1**) with hydrazine, alkyl-, aryl- and heteroaryl-substituted hydrazines *via* the corresponding hydrazones **12-16** into pyrazoles **17-25** are described. Heteroaryl-substitued hydrazones **13-16** afforded by oxidation with bromine or lead tetraacetate the corresponding substituted (1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)glycinates **27-30**. Alkyl 2-(2,2-disubstituted-1-ethenyl)amino-3-dimethylaminopropenoates **31-33** gave with hydrazines alkyl 2-[2,2-(disubstituted)ethenyl]amino-3-heteroarylhydrazonopropanoates **40-48** and 2-alkyl 2,3-bis((hetero)arylhydrazono)propanoates **51-55**.

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Introduction.

Pyrazole and its derivatives are an important class of compounds since they have been claimed to be effective as germicides, antimicrobial agents, analgesics, antipyretics and antifungals [1-3]. Numerous methods for the synthesis of substituted pyrazoles are known [2-5]. One of the most frequently utilized methods is the reaction of 1,3-dicarbonyl compounds, or equivalent 1,3-bis-electrophilic reagents, with hydrazine or its derivatives. However, in the case of substituted hydrazines this type of reaction frequently results in mixtures of regioisomeric pyrazoles [6]. On the other hand, the reaction of substituted hydrazines with α,β-unsaturated ketones has been reported to lead to regioselective formation of pyrazolines which could be easily oxidized to the corresponding pyrazoles [7,8]. Several other methods for the regioselective synthesis of pyrazoles have also been published [9,10]. Hydrazines readily react with acetylenic ketones to afford pyrazoles directly [11,12]. Recently, regiospecific synthesis of 1,3,5-trisunstituted pyrazoles from acetylenic ketones and hydrazines has been reported [13].

Alkyl 2-substituted 3-(dimethylamino)propenoates and related enaminones have been used for the preparation of dihydroalanine esters and various heterocyclic systems [14], including some indole alkaloids, such as aplysinopsins and their analogs [15-18] and meridianins and their analogs [19]. Recently, applications of 3-(dimethylamino)propenoates in combinatorial synthesis have also been reported [20-22]. In several instances, substituted pyrazoles have been obtained in the reactions with hydrazines [23-30].

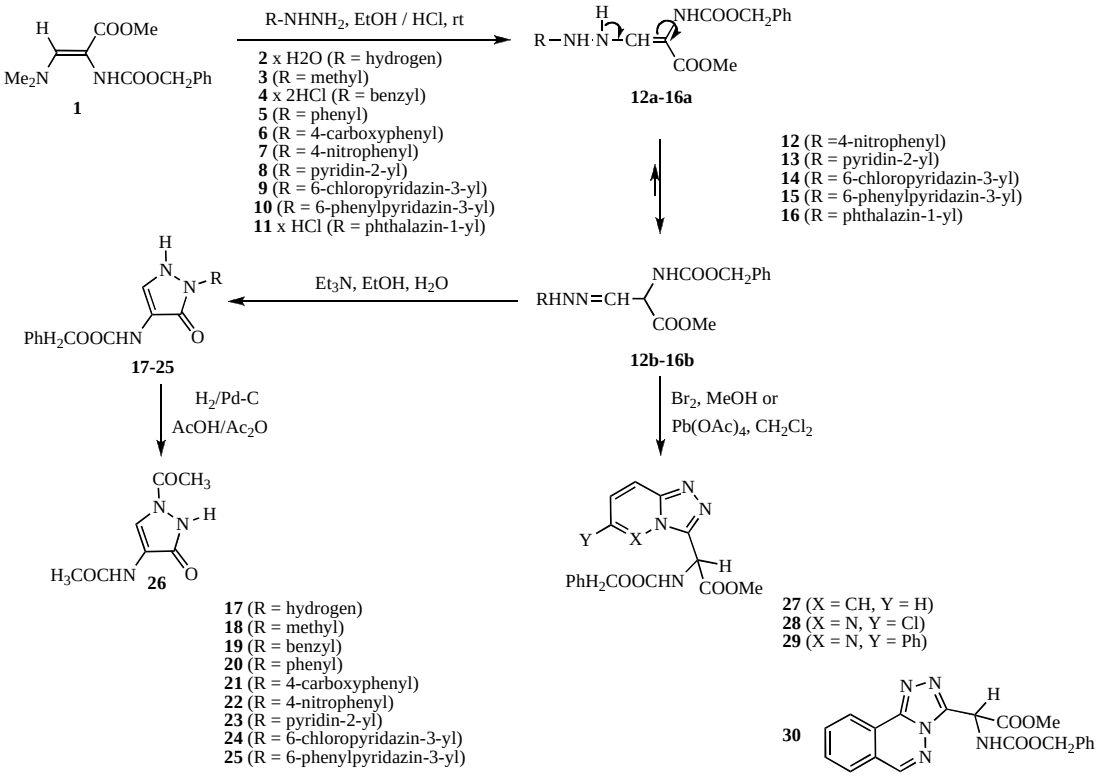
In this paper, the regiospecific transformations of methyl 2-(benzyloxycarbonyl)amino-3-dimethylaminopropenoate (**1**) with hydrazine, alkyl-, aryl- and heteroaryl-substituted hydrazines *via* the corresponding hydrazones **12-16** into pyrazoles **17-25**. Heteroaryl-substitued hydrazones **13-16** afforded by oxidation with bromine or lead tetraacetate the corresponding substituted (1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-glycinates **27-30**. Alkyl 2-(2,2-disubstituted-1-ethenyl)amino-3-dimethylaminopropenoates **31-33** gave with hydrazines alkyl 2,3-bis((hetero)arylhydrazono)propenoates **51-55**.

Results and Discussion.

When a mixture of 2-(benzyloxycarbonyl)amino-3-dimethylaminopropenoate (**1**) was stirred with an equivalent amount of heteroarylhydrazines **2-11** in ethanol in the presence of catalytic amount of hydrochloric acid at room temperature for several hours, the corresponding propenoates **12-16** were formed in 52-

97 % yield. They exist as a mixture of enehydrazino **12a**-**16a** and hydrazono derivatives **12b**-**16b**. The ratios between both forms were determined by ^{1}H nmr spectra. When compound **1** was heated with hydrazine hydrate (**2**) in ethanol for three hours the corresponding 4-(benzyloxycarbonyl)amino-1*H*-pyraz-ol-5(2*H*)-one (**17**) was directly from **1** and the corresponding heteroarylhydrazine **8** or **10** by stirring at room temperature for several hours to form hydrazones **13** or **15** as intermediates, which were cyclized without isolation with bromine in methanol in the presence of sodium acetate to give compounds **27** and **29**. The hydrazone **14** yields

Scheme 1



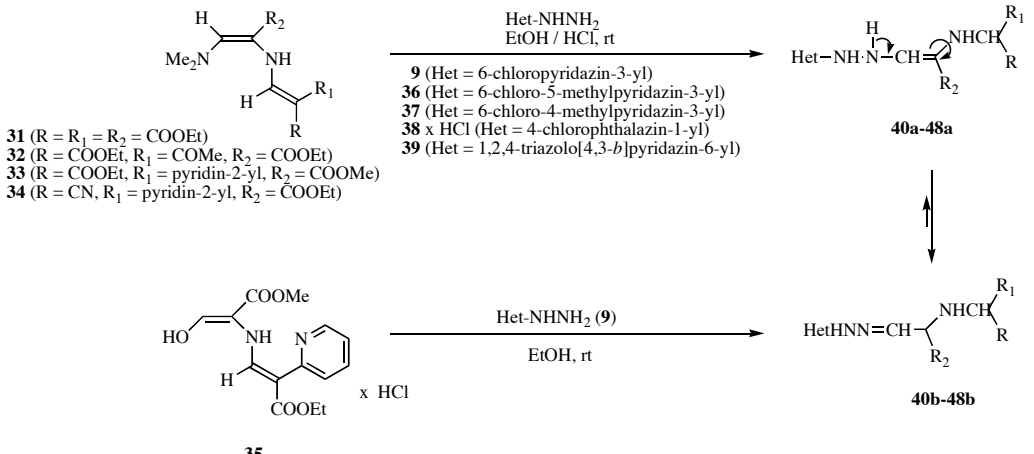
obtained in 79 % yield. Similarly, alkylhydrazines **3** and **4** and arylhydrazines **5**-**7** gave in the presence of catalytic amounts of hydrochloric acid the corresponding 4-(benzyloxycarbonyl)amino-1-alkyl- and -1-aryl-1*H*-pyrazol-5(2*H*)-ones 17-21 in 29-63 % yields. On the other hand, heterocyclic hydrazines **8-11** were heated in ethanol or methanol in the presence of triethylamine for 10 minutes to two hours to afford the corresponding 4-(benzyloxycarbonyl)amino-1-heteroaryl-1*H*-pyrazol-5(2*H*)-ones **23**-**25** in 61-79 % yields. When compound **17**, dissolved in a mixture of acetic acid and acetic anhydride, was hydrogenated over 10 % Pd/C at room temperature for 12 hours, 2-acetyl-4-acetylamino-1*H*-pyrazol-5(2*H*)-one was isolated, indicating that the benzyloxycarbonyl group was removed from the amino group followed by acetylation of the free amino group at 4-position and endocyclic NH group at 2-position.

Methyl *N*-(benzyloxycarbonyl)amino-(1,2,4-triazolo-[4,3-*x*]azin-3-yl)glycinates **27**-**30** were prepared either under the same reaction conditions compound **28**. Instead of bromine lead tetraacetate in dichloromethane was used as oxidizing agent, according to the procedures described earlier for preparation of various [1,2,4]triazolo[4,3-*b*]pyridazines [31-35]. In this manner, hydrazones **14** and **16** were transformed into **28** and **30** (Scheme 1).

Another group of hydrazones was prepared from alkyl 2-[2,2-(disubstituted)ethenyl]amino-3-(dimethylamino)propenoates **31**-**34**. When compounds **31**-**34** reacted with heteroarylhydrazines **9** and **36**-**39** in ethanol in the presence of catalytic amounts of hydrochloric acid at room temperature, the corresponding hydrazones **40**-**48** were isolated. Compound **46** was prepared also from 2-[2-ethoxycarbonyl-2-(pyridin-2-yl)amino]-3-hydroxypropenoate hydrochloride (**35**) and 6-chloro-3-hydrazinopyridazine (**9**) in 59 % yield (Scheme 2).

Treatment of alkyl 2-[2,2-(disubstituted)ethenyl]-amino-3-(dimethylamino)propenoates **31**-**33** with

Scheme 2



31 (R = R_1 = R_2 = COOEt)
32 (R = COOEt, R_1 = COMe, R_2 = COOEt)
33 (R = COOEt, R_1 = pyridin-2-yl, R_2 = COOMe)
34 (R = CN, R_1 = pyridin-2-yl, R_2 = COOEt)

9 (Het = 6-chloropyridazin-3-yl)
36 (Het = 6-chloro-5-methylpyridazin-3-yl)
37 (Het = 6-chloro-4-methylpyridazin-3-yl)
38 x HCl (Het = 4-chlorophthalazin-1-yl)
39 (Het = 1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)

40a-48a

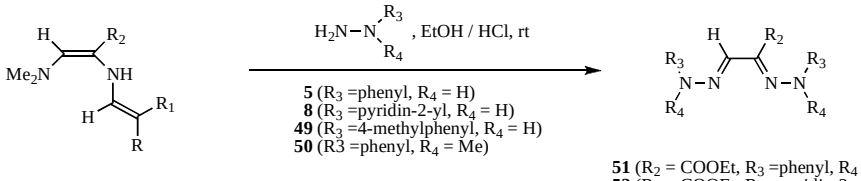
35

40b-48b

40 (R = R_1 = R_2 = COOEt, Het = 6-chloropyridazin-3-yl)
41 (R = R_1 = R_2 = COOEt, Het = 6-chloro-5-methylpyridazin-3-yl)
42 (R = R_1 = R_2 = COOEt, Het = 6-chloro-4-methylpyridazin-3-yl)
43 (R = R_1 = R_2 = COOEt, Het = 4-chlorophthalazin-1-yl)
44 (R = R_1 = R_2 = COOEt, Het = 1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)
45 (R = COOEt, R_1 = COMe, R_2 = COOEt, Het = 6-chloropyridazin-3-yl)
46 (R = COOEt, R_1 = pyridin-2-yl, R_2 = COOMe, Het = 6-chloropyridazin-3-yl)
47 (R = COOEt, R_1 = pyridin-2-yl, R_2 = COOMe, Het = 4-chlorophthalazin-1-yl)
48 (R = CN, R_1 = pyridin-2-yl, R_2 = COOEt, Het = 6-chloropyridazin-3-yl)

heteroarylhydrazines **5**, **8**, **49**, and **50** in ethanol in the presence of hydrochloric acid at room temperature for several hours afforded alkyl-2,3-bis(heteroarylhydrazono)propanoates **51**-**55** in 17-60 % yields. (Scheme 3).

Scheme 3



31 (R = R_1 = R_2 = COOEt)
32 (R = COOEt, R_1 = COMe, R_2 = COOEt)
33 (R = COOEt, R_1 = pyridin-2-yl, R_2 = COOMe)

5 (R_3 =phenyl, R_4 = H)
8 (R_3 =pyridin-2-yl, R_4 = H)
49 (R_3 =4-methylphenyl, R_4 = H)
50 (R3 =phenyl, R_4 = Me)

51 (R_2 = COOEt, R_3 =phenyl, R_4 = H)
52 (R_2 = COOEt, R_3 =pyridin-2-yl, R4 = H)
53 (R_2 = COOEt, R_3 =4-methylphenyl, R_4 = H)
54 (R_2 = COOMe, R_3 =pyridin-2-yl, R_4 = H)
55 (R_2 = COOMe, R_3 =phenyl, R_4 = Me)

The structures of new compounds were determined by spectroscopic methods and by analysis for C, H, and N. Compounds **12**-**16** exist in dimethyl sulfoxide-d_6 solution in equilibria between hydrazine forms **12a**-**16a** and hydrazone forms **12b**-**16b**. The ratios were determined by ^{1}H nmr techniques and are given in Table 2. On the other hand, compounds **40**-**48** exist exclusively in hydrazone forms **40b**-**48b**. The structures of pyrazolone derivatives **17**-**25** are unambiguous since the compounds obtained by treatment of compound **1** with hydrazine of monosubstituted hydrazine **2**-**11** (Method A) are identical with compounds obtained by cyclisation of hydrazones **12**-**16** as intermediates (Method B). No attempts were made in order to determine the tautomeric form of pyrazolone part of the molecule.

Table 1
Experimental and Analytical Data

Compound	Yield (%)	mp (°C)	Molecular formula Analyses	MS
12	55	164-167 from ethanol	$C_{18}H_{18}N_4O_6$ Calcd: C, 55.96; H, 4.70; N, 14.50 Found:C, 55.82; H, 4.89; N, 14.24	-
13	80	114-117 from methanol/water	$C_{17}H_{18}N_4O_4$ Calcd: C, 59.64; H, 5.30; N, 16.37 Found:C, 59.75; H, 5.50; N, 16.59	-

Table 1 (continued)

Compound	Yield (%)	mp (°C)	Molecular formula Analyses	MS
14	97	161-163 from methanol/water	$C_{16}H_{16}ClN_5O_4$ Calcd: C, 50.87; H, 4.27; N, 18.54 Found:C, 50.79; H, 4.17; N, 18.63	-
15	78	188-190 from methanol/water	$C_{22}H_{21}N_5O_4$ Calcd: C, 63.00; H, 5.05; N, 16.70 Found:C, 62.61; H, 5.14; N, 16.54	-
16	77	202-204 from methanol	$C_{20}H_{19}N_5O_4$ Calcd: C, 61.06; H, 4.87; N, 17.80 Found:C, 61.00; H, 5.03; N, 17.65	-
17	79	229-232 from ethanol	$C_{11}H_{11}N_3O_3$ Calcd: C, 56.65; H, 4.75; N, 18.02 Found:C, 56.61; H, 4.79; N, 18.28	-
18	59	210-212 from ethanol	$C_{12}H_{13}N_3O_3$ Calcd: C, 58.29; H, 5.30; N, 16.99 Found:C, 58.45; H, 5.25; N, 17.29	-
19	29	204-206 from ethanol	$C_{18}H_{17}N_3O_3$ Calcd: C, 66.89; H, 5.30; N, 13.00 Found:C, 67.15; H, 5.21; N, 13.02	-
20	53	216-219 from ethanol	$C_{17}H_{15}N_3O_3$ Calcd: C, 66.01; H, 4.89; N, 13.58 Found:C, 66.11; H, 4.62; N, 13.59	-
21	63	270-275 from ethanol	$C_{18}H_{15}N_3O_5$ Calcd: C, 61.19; H, 4.28; N, 11.89 Found:C, 61.35; H, 4.33; N, 11.81	-
22	70	225-227 from ethanol/*N*,*N*-dimethylformamide	$C_{17}H_{14}N_4O_5$ Calcd: C, 57.63; H, 3.98; N, 15.81 Found:C, 57.52; H, 3.87; N, 15.82	-
23	78	183-185 from ethanol	$C_{16}H_{14}N_4O_3$ Calcd: C, 61.93; H, 4.55; N, 18.06 Found:C, 61.60; H, 4.46; N, 17.94	-
24	79	240-243 from methanol	$C_{15}H_{12}N_5O_3Cl$ Calcd: C, 52.11, H, 3.50; N, 20.26 Found:C, 52.02; H, 3.21; N, 19.98	-
25	61	>280 from ethanol/*N*,*N*-dimethylformamide	$C_{21}H_{17}N_5O_3$ Calcd: C, 65.11; H, 4.42; N, 18.08 Found:C, 64.76; H, 4.34; N, 18.00	-
26	91	230-233 from methanol	$C_7H_9N_3O_3$ Calcd: C, 45.90; H, 4.95; N, 22.94 Found:C, 45.64; H, 4.90; N, 22.72	-
27	40	153-156 from methanol/water	$C_{17}H_{16}N_4O_4$ Calcd: C, 60.00; H, 4.74; N, 16.46 Found:C, 60.37; H, 5.03; N, 16.62	-
28	83 [a] 69 [b]	145-147 from methanol	$C_{16}H_{14}ClN_5O_4$ Calcd: C, 51.14; H, 3.76; N, 18.64 Found:C, 50.94; H, 3.41; N, 18.49	-
29	45	182-185 from methanol	$C_{22}H_{19}N_5O_4$ Calcd: C, 63.30; H, 4.59; N, 16.78 Found:C, 62.97; H, 4.59; N, 16.53	-
30	68	204-207 from ethanol/toluene	$C_{20}H_{17}N_5O_4$ Calcd: C, 61.38; H, 4.38; N, 17.89 Found:C, 61.35; H, 4.33; N, 17.62	-
40	70	176-177 from toluene/ethyl acetate	$C_{17}H_{22}N_5O_6Cl$ Calcd: C, 47.72; H, 5.18; N, 16.73 Found:C, 47.99; H, 5.18; N, 16.40	-
41	73	174-175 from methanol/n-heptane	$C_{18}H_{24}N_5O_6Cl$ Calcd: C, 48.93; H, 5.47; N, 15.85 Found:C, 48.86; H, 5.50; N, 15.93	441 [h]
42	52	132-134 from ethanol	C18H24N5O6Cl Calcd: C, 48.93; H, 5.47; N, 15.85 Found:C, 49.05; H, 5.62; N, 15.93	-

Table 1 (continued)

Compound	Yield (%)	mp (°C)	Molecular formula Analyses	MS
43	71	243-236	$C_{21}H_{24}N_5O_6Cl$	-
		from methanol/toluene	Calcd: C, 52.78; H, 5.06; N, 14.65	
			Found:C, 52.70; H, 4.87; N, 14.54	
44	64	105-107	$C_{18}H_{23}N_7O_6$	434 [i]
		from	Calcd: C, 49.88; H, 5.35; N, 22.62	
		ethanol/*N*,*N*-dimethylformamide	Found:C, 49.48; H, 5.28; N, 22.63	
45	80	164-167	$C_{16}H_{20}ClN_5O_5$	-
		from toluene	Calcd: C, 48.31; H, 5.07; N, 17.60	
			Found:C, 47.89; H, 5.01; N, 17.59	
46	57 [c]	137-143	$C_{18}H_{19}ClN_6O_4$	-
	59 [d]	from ethanol	Calcd: C, 51.62; H, 4.57; N, 20.06	
			Found:C, 51.38; H, 4.39; N, 20.17	
47	28	157-165	$C_{22}H_{21}ClN_6O_4$	468 [h]
		from ethanol	Calcd:[e] C, 55.29; H, 4.64; N, 17.58	469 [i]
			Found: C, 55.02; H, 4.55; N, 17.54	
48	77	170-172	$C_{17}H_{16}ClN_7O_2$	-
		from ethanol	Calcd: C, 52.92; H, 4.18; N, 25.41	
			Found:C, 52.84; H, 4.30; N, 25.39	
51	59 [f]	224-226	$C_{17}H_{18}N_4O_2$	-
	29 [g]	from ethanol/n-heptane	Calcd: C, 65.79; H, 5.85; N, 18.05	
			Found:C, 65.67; H, 5.77; N, 18.29	
52	59	227-229	$C_{15}H_{16}N_6O_2$	-
		from	Calcd: C, 57.68; H, 5.16; N, 26.91	
		ethanol/*N*,*N*-dimethylformamide	Found:C, 57.41; H, 5.12; N, 26.70	
53	54	185-187	$C_{19}H_{22}N_4O_2$	338 [h]
		from ethanol/dimethyl sulfoxide	Calcd: C, 67.44; H, 6.55; N, 16.65	
			Found:C, 67.22; H, 6.75; N, 16.49	
54	19	205-213	$C_{14}H_{14}N_6O_2$	298 [h]
		from ethanol	Calcd: C, 56.37; H, 4.73; N, 28.17	
			Found:C, 56.23; H, 4.84; N, 28.05	
55	17	120-122	$C_{18}H_{20}N_4O_2$	-
		from ethanol	Calcd: C, 66.65; H, 6.22; N, 17.27	
			Found:C, 66.53; H, 6.38; N, 17.27	

[a] From compound **14**, by method A; [b] From compound **14**, by method B; [c] From compound **33**; [d] From compound **35**;[e] Calcd. for **47** + ½ H_2O; [f] From compound **31**; [g] From compound **32**; [h] M^+ (M/Z).

Table 2

^{1}H NMR Data

Compound	MHz Solvent	(tetramethylsilane)
12	300 dimethyl sulfoxide-d_6	δ 3.56, 3.71 (3H, 2s, COO*Me*, hydrazine, hydrazone), 4.91 (0.8H, dd, CHC*H*NH, hydrazone), 5.06, 5.08 (2H, 2s, CH_2, hydrazine, hydrazone), 7.03 (2H, d, H_2', H_6'), 7.31-7.41 (6H, m, Ph, NH-CH-C*H*=, hydrazone), 8.10 (2H, d, H_3', H_5'), 8.17 (1H, d, CH-N*H*COOCH$_2$Ph, hydrazone), 11.14 (1H, s, Het-N*H*-N=, hydrazone), $J_{NHCHCH=}$ = 5.3 Hz (hydrazone), $J_{NHCHCH=}$ = 7.9 Hz (hydrazone), $J_{CHNHCOOCH2Ph}$ = 7.9 Hz (hydrazone), $J_{H2'H3'} = J_{H5'H6'}$ = 9.2 Hz The ratio hydrazone:hydrazine = 61:39
13	300 dimethyl sulfoxide-d_6	δ 3.56, 3.71 (3H, 2s, COO*Me*, hydrazine, hydrazone), 4.86 (0.8H, dd, NH-C*H*-CH=, hydrazone), 5.08, 5.13 (2H, 2s, CH_2, hydrazine, hydrazone), 6.75 (1H, ddd, H_5'), 7.04 (1H, d, H_3'), 7.30 (0.2H, d, Het-NH-NH-C*H*=, hydrazine), 7.32-7.40 (5.8H, m, Ph, NH-CH-C*H*=, hydrazone), 7.59 (1H, ddd, H_4'), 7.90 (0.2H, br.s, N*H*COOCH$_2$Ph, hydrazine), 8.08 (1H, dd, H_6'), 8.13 (0.8H, d, CH-N*H*COOCH$_2$Ph, hydrazone), 10.71 (0.8H, s, Het-N*H*-N=, hydrazone), $J_{NHCHCH=}$ = 5.5 Hz (hydrazone), $J_{NHCHCH=}$ = 7.9 Hz (hydrazone), $J_{CHNHCOOCH2Ph}$ = 7.8 Hz (hydrazone), $J_{HetNHNHCH=}$ = 14.9 Hz (hydrazine), $J_{H3'H4'}$ = 8.3 Hz, $J_{H3'H5'}$ = 0.7 Hz, $J_{H4'H5'}$ = 7.1 Hz, $J_{H4'H6'}$ = 1.8 Hz, $J_{H5'H6'}$ = 5.0 Hz The ratio hydrazone:hydrazine = 74:16

Table 2 (continued)

Compound	MHz Solvent	(tetramethylsilane)
14	300 dimethyl sulfoxide-d_6	δ 3.56, 3.70 (3H, 2s, COO*Me*, hydrazine, hydrazone), 4.92 (0.8H, dd, NH-C*H*-CH=, hydrazone), 5.04, 5.07 (2H, 2s, CH_2, hydrazine, hydrazone), 7.10 (0.2H, d, Het-NH-NH-C*H*=, hydrazine), 7.32-7.40 (5H, m, Ph), 7.47 (1H, d, H_4'), 7.49 (0.8H, d, NH-CH-C*H*=, hydrazone), 7.63 (1H, d, H_5'), 7.97 (0.2H, br.s, N*H*COOCH$_2$Ph, hydrazine), 8.16 (0.8H, d, CH-N*H*COOCH$_2$Ph, hydrazone), 8.70, 9.45 (0.4H, 2br.s, Het-N*H*-NH-CH=, Het-NH-N*H*-CH=, hydrazine), 11.57 (0.8H, s, Het-N*H*-N=, hydrazone), $J_{NHCHCH=}$ = 5.2 Hz (hydrazone), $J_{NHCHCH=}$ = 7.9 Hz (hydrazone), $J_{CHNHCOOCH2Ph}$ = 7.9 Hz (hydrazone), $J_{HetNHNHCH=}$ = 9.3 Hz (hydrazine), $J_{H4'H5'}$ = 9.5 Hz The ratio hydrazone:hydrazine = 80:20
15	300 dimethyl sulfoxide-d_6	δ 3.72 (3H, s, COO*Me*), 4.94 (1H, dd, NH-C*H*-CH=), 5.09 (2H, s, CH_2), 7.32-7.39 (5H, m, Ph), 7.41-7.53 (5H, m, 3H(Ph), H_4', NH-CH-C*H*=), 7.99-8.06 (3H, m, 2H(Ph), H_5'), 8.18 (1H, d, CH-N*H*COOCH$_2$Ph), 11.50 (1H, s, Het-N*H*-N=), $J_{NHCHCH=}$ = 5.3 Hz (hydrazone), $J_{NHCHCH=}$ = 7.9 Hz (hydrazone), $J_{CHNHCOOCH2Ph}$ = 7.9 Hz (hydrazone)
16	300 dimethyl sulfoxide-d_6	δ 3.60, 3.72 (3H, 2s, COO*Me*, hydrazine, hydrazone), 4.92 (1H, m, NH-C*H*-CH=, hydrazone), 5.12 (2H, s, CH_2), 7.26-7.43 (5H, m, Ph), 7.57-8.01 (4H, m, H_5', H_6', H_7', H_8'), 8.13 (1H, s, H_4'), 8.23 (1H, d, NH-CH-C*H*=, hydrazone), 8.35 (1H, d, CH-N*H*COOCH$_2$Ph, hydrazone), 12.38 (1H, s, Het-N*H*-N=, hydrazone), $J_{NHCHCH=}$ = 5.2 Hz (hydrazone), $J_{NHCHCH=}$ = 7.1 Hz (hydrazone), $J_{CHNHCOOCH2Ph}$ = 7.5 Hz (hydrazone) The ratio hydrazone:hydrazine = 60:40
17	300 dimethyl sulfoxide-d_6	δ 4.98 (2H, s, CH_2), 7.23-7.32 (6H, m, Ph, CH), 7.82 (1H, s, N*H*COOCH$_2$Ph), 9.48, 11.15 (2H, 2br.s, 2 × NH)
18	300 dimethyl sulfoxide-d_6	δ 3.46 (3H, s, Me), 5.07 (2H, s, CH_2), 7.13, 7.94 (1H, br.s, CH), 7.34-7.39 (5H, m, Ph), 8.39 (1H, s, N*H*COOCH$_2$Ph), 10.50 (1H, s, NH)
19	300 dimethyl sulfoxide-d_6	δ 5.02, 5.07 (4H, 2s, 2 × CH_2), 7.14-7.38 (11H, m, 2 × Ph, CH), 8.41 (1H, s, N*H*COOCH$_2$Ph), 10.70 (1H, s, NH)
20	300 dimethyl sulfoxide-d_6	δ 5.11 (2H, s, CH_2), 7.24-7.48 (9H, m, 8H(Ph), CH), 7.70-7.73 (2H, m, 2H(Ph)), 8.58 (1H, br.s, N*H*COOCH$_2$Ph), 11.16 (1H, br.s, NH)
21	300 dimethyl sulfoxide-d_6	δ 5.10 (2H, s, CH_2), 7.36-7.40 (5H, m, Ph) 7.58 (1H, s, CH), 7.92 (2H, d, H_2', H_6'), 8.01 (2H, d, H_3', H_5'), 8.60 (1H, br.s, N*H*COOCH$_2$Ph), 11.65 (1H, br.s, NH), 12.73 (1H, br.s, COOH), $J_{H2'H3'}$ = $J_{H5'H6'}$ = 8.8 Hz
22	300 dimethyl sulfoxide-d_6	δ 5.12 (s, 2H, CH_2), 7.37-7.41 (m, 5H, Ph), 7.68 (s, 1H, CH), 8.08 (d, 2H, $J_{H2'H3'}$ = $J_{H5'H6'}$ = 9.4 Hz, H_2', H_6'), 8.35 (d, 2H, $J_{H2'H3'}$ = $J_{H5'H6'}$ = 9.0 Hz, H_3', H_5'), 8.71 (br.s, 1H, NHCbz), 9.32 (br.s, H, NH)
23	300 dimethyl sulfoxide-d_6	δ 5.11 (s, 2H, C*H*$_2$), 7.28-7.40 (m, 7H, Ph, H_3', H_5'), 7.74 (s, 1H, C*H*), 7.99 (ddd, 1H, $J_{H4'H5'}$ = 8.3 Hz, $J_{H3'H4'}$ = 9.4 Hz, $J_{H4'H6'}$ = 1.5 Hz, H_4'), 8.18 (br.s, 1H, N*H*Cbz), 8.46 (d, 1H, $J_{H5'H6'}$ = 4.4 Hz, H_3', H_5'), 8.76 (br.s, 1H, N*H*)
24	300 dimethyl sulfoxide-d_6	δ 5.11 (s, 2H, C*H*$_2$), 7.35-7.40 (m, 5H, Ph), 7.94 (br.s, 1H, C*H*), 8.03 (d, 1H, $J_{H4'H5'}$ = 9.4 Hz, H_5'), 8.66 (d, 1H, $J_{H4'H5'}$ = 9.4 Hz, H_4'), 8.84 (s, 1H, N*H*Cbz), 12.15 (br.s, 1H, N*H*)
25	300 dimethyl sulfoxide-d_6	δ 5.12 (s, 2H, C*H*$_2$), 7.40 (br.s, 5H, Ph), 7.56 (br.s 3H, Ph), 7.93 (s, 1H, C*H*), 8.15-8.17 (m, 2H, Ph), 8.41 (d, 1H, $J_{H4'H5'}$ = 9.0 Hz, H_4'), 8.63 (br.s, 1H, N*H*Cbz), 8.84 (br.s, 1H, H_5'), N*H* exchanged
26	300 dimethyl sulfoxide-d_6	δ 2.05, 2.44 (6H, 2s, 2 × Me), 8.29 (1H, s, CH), 9.83, 11.69 (2H, 2s, 2 × NH)
27	300 deuteriochloroform	δ 3.82 (3H, s, COO*Me*), 5.15 (2H, s, CH_2), 6.00 (1H, d, C*H*NH), 6.32 (1H, d, CHN*H*), 6.92 (1H, deg dd, H_6), 7.29-7.34 (6H, m, 6H(Ph), H_7), 7.79 (1H, d, H_8), 8.36 (1H, d, H_5), J_{CHNH} = 6.8 Hz, J_{H5H6} = 6.0 Hz, J_{H6H7} = 6.4 Hz, J_{H7H8} = 9.4 Hz
28	300 deuteriochloroform	δ 3.76 (3H, s, COOMe), 5.13 (2H, s, CH2), 6.19 (1H, d, CHNH), 6.34 (1H, d, CHNH), 7.17 (1H, d, H7), 7.34 (5H, br.s, Ph), 8.10 (1H, d, H8), J_{CHNH} = 8.5 Hz, J_{H7H8} = 9.5 Hz
29	300 deuteriochloroform	δ 3.76 (3H, s, COOMe), 5.14 (2H, s, CH2), 6.23 (1H, d, CHNH), 6.48 (1H, d, CHNH), 7.29-7.36 (5H, m, Ph), 7.55-7.57 (3H, m, Ph), 7.64 (1H, d, H7), 7.95-8.02 (2H, m, Ph), 8.19 (1H, d, H8), J_{CHNH} = 7.8 Hz, J_{H7H8} = 9.8 Hz
30	300 dimethyl sulfoxide-d6	δ 3.73 (3H, s, COOMe), 5.11 (2H, s, CH2), 6.07 (1H, d, CHNH), 7.29-7.37 (5H, m, Ph), 7.98 (1H, ddd, H9), 8.08 (1H, ddd, H8), 8.26 (1H, d, H7), 8.53 (1H, d, CHNH), 8.55 (1H, d, H10), 9.15 (1H, s, H6), JCHNH = 8.4 Hz, J_{H7H8} = 7.4 Hz, J_{H7H9} = 1.5 Hz, J_{H8H9} = 8.9 Hz, J_{H8H10} = 1.1 Hz, J_{H9H10} = 7.9 Hz
40	300 dimethyl sulfoxide-d6	δ 1.17, 1.18, 1.24 (9H, 3t, 3 × CH_2CH_3), 4.15, 4.16, 4.22 (6H, 3q, 3 × CH_2CH_3), 5.88 (1H, dd, CH-NH-CH=), 7. 38, 7.68 (2H, 2d, H4', H5'), 7.65 (1H, d, CH=N-NH), 8.10 (1H, d, CH-NH-CH=), 9.63 (1H, dd, CH-NH-CH=), 11.70 (1H, s, Het-NH-N=), JCH_2CH_3 = 7.0 Hz, J_{CHNHCH}= = 14.2 Hz, J_{CHNHCH}= = 7.8 Hz, J_{NHCHCH}= = 4.3 Hz, $J_{H4'H5'}$ = 9.4 Hz
41	300 deuteriochloroform	δ 1.27, 1.35, 1.37 (9H, 3t, 3 × CH_2CH_3), 2.40 (3H, s, Het-Me), 4.20, 4.31, 4.33 (6H, 3q, 3 × CH_2CH_3), 4.90 (1H, dd, CH-NH-CH=), 7.53 (1H, s, H4'), 7.50 (1H, d, CH=N-NH), 8.15 (1H, d, CH-NH-CH=), 9.98 (1H, dd, CH-NH-CH=), 11.60 (1H, s, Het-NH-N=), JCH_2CH_3 = 7.1 Hz, J_{CHNHCH}= = 14.0 Hz, J_{CHNHCH}= = 7.1 Hz, J_{NHCHCH}= = 3.8 Hz

Table 2 (continued)

Compound	MHz Solvent	(tetramethylsilane)
42	300 dimethyl sulfoxide-d_6	δ 1.25, 1.40, 1.49 (9H, 3t, 3 × CH_2CH_3), 2.50 (3H, s, Het-*Me*), 3.59, 4.20, 4.20 (6H, 3q, 3 × CH_2CH_3), 5.70 (1H, dd, C*H*-NH-CH=), 7.46 (1H, s, H_5'), 7.54 (1H, d, C*H*=N-NH), 8.15 (1H, d, CH-NH-C*H*=), 9.51 (1H, dd, CH-N*H*-CH=), 10.55 (1H, s, Het-N*H*-N=), $J_{CH_2CH_3}$ = 7.0 Hz, $J_{CHNHCH=}$ = 13.9 Hz, $J_{CHNHCH=}$ = 7.8 Hz, $J_{NHCHCH=}$ = 4.2 Hz
43	300 dimethyl sulfoxide-d_6	δ 1.12, 1.15, 1.25 (9H, 3t, 3 × CH_2CH_3), 3.88, 4.10, 4.10 (6H, 3q, 3 × CH_2CH_3), 5.40 (1H, dd, C*H*-NH-CH=), 7.10-8.05 (6H, m, Ph, C*H*=N-NH), 8.35 (1H, d, CH-NH-C*H*=), 9.60 (1H, dd, CH-N*H*-CH=), 11.90 (1H, s, Het-N*H*-N=), $J_{CH_2CH_3}$ = 7.1 Hz, $J_{CHNHCH=}$ = 14.0 Hz, $J_{CHNHCH=}$ = 7.6 Hz
44	300 dimethyl sulfoxide-d_6	δ 1.12, 1.17, 1.23 (9H, 3t, 3 × CH_2CH_3), 4.08, 4.17, 4.22 (6H, 3q, 3 × CH_2CH_3), 5.40 (1H, dd, C*H*-NH-CH=), 6.77, 7.26 (2H, 2d, H_7', H_8'), 7.63 (1H, d, C*H*=N-NH), 8.08 (1H, d, CH-NH-C*H*=), 9.58 (1H, dd, CH-N*H*-CH=), 10.80 (1H, s, Het-N*H*-N=), $J_{CH_2CH_3}$ = 7.1 Hz, $J_{CHNHCH=}$ = 14.0 Hz, $J_{CHNHCH=}$ = 7.9 Hz, $J_{NHCHCH=}$ = 4.8 Hz, $J_{H_7'H_8'}$ = 9.9 Hz
45	300 dimethyl sulfoxide-d_6	δ 1.20, 1.21, 1.24, 1.29, 1.30 (6H, 5t, 2 × CH_2CH_3), 2.30, 2.31, 2.32, 2.38 (3H, 4s, CO*Me*), 4.08, 4.11, 4.23, 4.30, 4.36, (4H, 5q, 2 × CH_2CH_3), 5.44 (1H, dd, C*H*-NH-CH=), 7.44 (1H, d, H_4'), 7.63 (1H, d, C*H*=N-NH), 7.73 (1H, d, H_5'), 8.14 (1H, d, CH-NH-C*H*=), 11.29 (1H, dd, CH-N*H*-CH=), 11.71 (1H, s, Het-N*H*-N=), $J_{CH_2CH_3}$ = 7.2 Hz, $J_{CHNHCH=}$ = 13.6 Hz, $J_{CHNHCH=}$ = 7.5 Hz, $J_{NHCHCH=}$ = 4.1 Hz, $J_{H4'H5'}$ = 9.4 Hz
46	300 deuteriochloroform	δ 1.31 (3H, t, $COOCH_2CH_3$), 3.87 (3H, s, CO*Me*), 4.24 (2H, q, $COOCH_2CH_3$), 4.92 (1H, dd, *CH*-NH-CH=), 7.00 (1H, ddd, H_5'), 7.33 (1H, d, H_5), 7.52 (1H, d, H_4), 7.64 (1H, ddd, H_4'), 7.69 (1H, d, *CH*=N-NH), 7.99 (1H, d, CH-NH-*CH*=), 8.31 (1H, ddd, H_3'), 8.46 (1H, ddd, H_6'), 11.13 (1H, br.s, Het-*NH*-N=), 11.41 (1H, dd, CH-*NH*-CH=), J_{CH2CH3} = 7.1Hz, $J_{CHNHCH=}$ = 12.6 Hz, $J_{CHNHCH=}$ = 7.7 Hz, $J_{NHCHCH=}$ = 4.6 Hz, $J_{H3'H4'}$ = 8.5 Hz, $J_{H3'H5'}$ = 1.1 Hz, $J_{H3'H6'}$ = 1.0 Hz, $J_{H4'H5'}$ = 7.4 Hz, $J_{H4'H6'}$ = 2.0 Hz, $J_{H5'H6'}$ = 5.0 Hz, J_{H4H5} = 9.4 Hz
47	300 deuteriochloroform	δ 1.34 (3H, t, $COOCH_2CH_3$), 3.87 (3H, s, CO*Me*), 4.26 (2H, q, $COOCH_2CH_3$), 5.00 (1H, br.s, C*H*-NH-CH=), 6.99 (1H, ddd, H_5'), 7.64 (1H, ddd, H_4'), 7.74-7.80 (1H, m, H_7), 7.81-7.84 (1H, m, H_6), 7.86 (1H, d, C*H*=N-NH), 7.87-7.95 (1H, m, H_8), 8.02 (1H, d, CH-NH-C*H*=), 8.26 (1H, ddd, H_3'), 8.28-8.33 (1H, m, H_5), 8.44 (1H, ddd, H_6'), J_{CH2CH3} = 7.2Hz, $J_{CHNHCH=}$ = 12.8 Hz, $J_{NHCHCH=}$ = 4.2 Hz, $J_{H3'H4'}$ = 8.9 Hz, $J_{H3'H5'}$ = 1.1 Hz, $J_{H3'H6'}$ = 1.0 Hz, $J_{H4'H5'}$ = 7.4 Hz, $J_{H4'H6'}$ = 2.0 Hz, $J_{H5'H6'}$ = 5.0 Hz
48	300 deuteriochloroform	δ 1.39 (3H, t, $COOCH_2CH_3$), 4.37 (2H, q, $COOCH_2CH_3$), 4.90 (1H, dd, *CH*-NH-CH=), 7.08 (1H, ddd, H_5'), 7.29 (1H, d, CH-NH-*CH*=), 7.40 (1H, d, H_5), 7.50 (1H, ddd, H_3'), 7.57 (1H, d, H_4), 7.72 (1H, ddd, H_4'), 7.75 (1H, d, *CH*=N-NH), 8.34 (1H, ddd, H_6'), 10.89 (1H, dd, CH-*NH*-CH=), 11.33 (1H, br.s, Het-*NH*-N=), J_{CH2CH3} = 7.2 Hz, $J_{CHNHCH=}$ = 12.2 Hz, $J_{CHNHCH=}$ = 7.2 Hz, $J_{NHCHCH=}$ = 4.5 Hz, $J_{H3'H4'}$ = 8.3 Hz, $J_{H3'H5'}$ = 1.1 Hz, $J_{H3'H6'}$ = 0.9 Hz, $J_{H4'H5'}$ = 7.4 Hz, $J_{H4'H6'}$ = 1.9 Hz, $J_{H5'H6'}$ = 4.9 Hz, J_{H4H5} = 9.4 Hz
51	300 dimethyl sulfoxide-d_6	δ 1.31 (3H, t, CH_2CH_3), 4.25 (2H, q, CH_2CH_3), 6.90-7.45 (10H, m, 2 × Ph), 8.30 (1H, s, H_3), 10.80, 11.20 (1H, 2s, 2 × Ph-N*H*), $J_{CH_2CH_3}$ = 7.1 Hz
52	300 dimethyl sulfoxide-d_6	δ 1.32 (3H, t, CH_2CH_3), 4.28 (2H, q, CH_2CH_3), 6.88-8.37 (8H, m, 2 × Py), 8.38 (1H, s, H_3), 11.44, 13.35 (2H, 2s, 2 × Het-N*H*), $J_{CH_2CH_3}$ = 7.1 Hz
53	300 dimethyl sulfoxide-d_6	δ 1.30 (3H, t, CH_2CH_3), 2.25, 2.29 (6H, 2s, 2 × Ar-*Me*), 4.25 (2H, q, CH_2CH_3), 6.59-7.25 (10H, m, 2 × Ph), 8.20 (1H, s, H_3), 10.70, 12.13 (2H, 2s, 2 × Ar-N*H*), $J_{CH_2CH_3}$ = 7.1 Hz
54	300 dimethyl sulfoxide-d_6	δ 3.81 (3H, s, CO*Me*), 6.92, 7.09 (2H, 2ddd, 2 × H_5), 7.15, 7.49 (2H, 2d, 2 × H_3), 7.79, 7.86 (2H, 2ddd, 2 × H_4), 8.23, 8.34 (2H, 2d, 2 × H_6), 8.38 (1H, s, CH), 11.44, 13.36 (2H, 2s, 2 × Het-*NH*), J_{H3H4} = 8.3 Hz, J_{H3H5} = 0.8 Hz, J_{H4H5} = 7.2 Hz, J_{H4H6} = 1.9 Hz, J_{H5H6} = 4.9 Hz
55	300 dimethyl sulfoxide-d_6	δ 3.35, 3.38 (6H, 2s, 2 × Me), 3.87 (3H, s, CO*Me*), 6.37-6.47 (2H, m, 2H(Ph)), 6.68-6.80 (8H, m, 8H(Ph)), 7.47 (1H, s, CH)

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer in such solvents as dimethyl sulfoxide-d_6 and deuteriochloroform with tetramethylsilane as the internal standard, MS spectra on an AutoSpecQ spectrometer and elemental analyses for C, H and N on a Perkin-Elmer CHN Analyser 2400. Experimental and analytical data are given in Tables 1 and 2.

The following compounds were prepared according to the procedures described in the literature: methyl 2-(benzyloxycarbonyl)amino-3-dimethylaminopropenoate (**1**) [36], ethyl (*Z*)-2-[2,2-bis(ethoxycarbonyl)ethenyl]amino-3-dimethylaminopropenoate (**31**) [37], ethyl 2-(2-acetyl-2-ethoxycarbonyl-1-ethenyl)amino-3-dimethylaminopropenoate (**32**) [38], methyl (*Z*)-2-[(*E*)-2-ethoxycarbonyl-2-(pyridin-2-yl)ethenyl]amino-3-dimethyl-aminopropenoate (**33**) [39], ethyl (*Z*)-2-[(*E*)-2-cyano-2-(pyrid-2-yl)ethenyl]amino-3-dimethylaminopropenoate (**34**) [40], and methyl 2-[2-ethoxycarbonyl-2-(pyridin-2-yl)ethenyl]amino-3-dimethylaminopropenoate [40].

General Procedure for the Preparation of Methyl 2-(Benzyloxycarbonyl)amino-3-heteroarylhydrazono-propanoates **12**-**16**.

To a suspension of compound **1** (1 mmol, 278 mg) in ethanol (3-4 mL) a catalytic amount of hydrochloric acid (0.1 mL, 36%) and the corresponding heteroarylhydrazine **7**-**11** (1 mmol) were added. The reaction mixture was stirred at room temperature for several hours and the product was isolated by an appropriate method.

Methyl 2-(Benzyloxycarbonyl)amino-3-(4-nitrophenyl)hydrazonopropanoate (**12**).

This compound was prepared from compound **1** (1 mmol, 278 mg) and 4-nitrophenylhydrazine (**7**) (1 mmol, 154 mg), 12 hours. The volatile compounds were evaporated *in vacuo*, a mixture of ether (2 mL) and ethanol (2 mL) was added to the oily residue and the precipitate, formed after cooling, was collected by filtration. Ethanol (5 mL) was used for crystallization.

Methyl 2-(Benzyloxycarbonyl)amino-3-(pyridin-2-yl)hydrazonopropanoate (**13**).

This compound was prepared from compound **1** (1 mmol, 278 mg) and 2-hydrazinopyridine (**8**) (1 mmol, 109 mg), 2.5 hours. Water (5 mL) was added to the reaction mixture, the suspension was stirred for a while, and the precipitate was collected by filtration. The mixture of methanol (2 mL) and water (2 mL) was used for crystallization.

Methyl 2-(Benzyloxycarbonyl)amino-3-(6-chloropyridazin-3-yl)hydrazonopropanoate (**14**).

This compound was prepared from compound **1** (1 mmol, 278 mg) and 6-chloro-3-hydrazinopyridazine (**9**) (1 mmol, 144 mg), 2 hours. Water (5 mL) was added to the reaction mixture, the suspension was stirred for a while, and the precipitate was collected by filtration. The mixture of methanol (2 mL) and water (2 mL) was used for crystallization.

Methyl 2-(Benzyloxycarbonyl)amino-3-(6-phenylpyridazin-3-yl)hydrazonopropanoate (**15**).

This compound was prepared from compound **1** (1 mmol, 278 mg) and 3-hydrazino-6-phenylpyridazine (**10**) (1 mmol, 144 mg), 5 hours. Water (5 mL) was added to the reaction mixture, the suspension was stirred for a while, and the precipitate was collected by filtration. The mixture of methanol (2 mL) and water (2 mL) was used for crystallization.

Methyl 2-(Benzyloxycarbonyl)amino-3-(phthalazin-1-yl)-hydrazonopropanoate (**16**).

This compound was prepared from compound **1** (1 mmol, 278 mg) and 1-hydrazinophthalazine hydrochloride (**11**) (1 mmol, 196 mg), 12 hours. The precipitated product was collected by filtration. Methanol (5 mL) was used for crystallization.

Benzyl *N*-(3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)carbamate (**17**).

To a solution of compound **1** (1 mmol, 278 mg) in ethanol (5 mL) hydrazine hydrate (**2**) (99%, 3 mmol, 0.146 mL) was added and the mixture was refluxed for 3 hours. The volatile compounds were evaporated *in vacuo*, ethanol (5 mL) was added and the precipitate was collected by filtration.

General Procedure for the Preparation of 4-(Benzyloxycarbonyl)amino-1-akyl and 1-aryl-1*H*-pyrazol-5(2*H*)-ones **18**-**21**.

To a solution of compound **1** (1 mmol, 278 mg) in ethanol (5 mL) a catalytic amount of hydrochloric acid (0.1 mL, 36%) and the corresponding alkylhydrazine **3**, **4** (1 mmol) or arylhydrazine **5**, **6** (1 mmol) were added. The reaction mixture was refluxed for several hours. The volatile compounds were evaporated *in vacuo*, ethanol (5 mL) was added and the precipitate was collected by filtration.

Benzyl *N*-(2-methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-carbamate (**18**).

This compound was prepared from compound **1** (1 mmol, 278 mg) and methylhydrazine (**3**) (1 mmol, 46 mg), 1 hour.

Benzyl *N*-(2-benzyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-carbamate (**19**).

This compound was prepared from compound **1** (1 mmol, 278 mg) and benzylhydrazine dihydrochloride (**4**) (1 mmol, 160 mg), 3 hours.

Benzyl *N*-(2-phenyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-carbamate (**20**).

This compound was prepared from compound **1** (1 mmol, 278 mg) and phenylhydrazine (**5**) (1 mmol, 108 mg), 4 hours.

Benzyl *N*-[2-(4-carboxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl]carbamate (**21**).

This compound was prepared from compound **1** (1 mmol, 278 mg) and 4-carboxyphenylhydrazine (**6**) (1 mmol, 152 mg), 4 hours.

Preparation of Benzyl *N*-(2-heteroaryl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)carbamates **22**-**25**.

Method A.

To a suspension of compound 1 (0.5 mmol, 139 mg) in ethanol (3 mL) a catalytic amount of hydrochloric acid (0.1 mL, 36%) and the corresponding heteroarylhydrazine **7**, **8**, **10** (0.5 mmol) was added. The reaction mixture was stirred at room temperature for several hours. Afterwards water (3 mL) and triethylamine (1 mL) were added and the mixture was refluxed (stirred at room temperature for compound **22**) for several minutes. The reaction mixture was neutralized with 10% hydrochloric acid and the formed precipitate was collected by filtration.

Method B.

The solution of methyl 2-(benzyloxycarbonyl)amino-3-(6-chloropyridazin-3-yl)hydrazonopropanoate **14** (0.5 mmol, 181 mg) in the mixture of methanol (3 mL), water (3 mL) and triethylamine (1 mL) was refluxed for 2 hours. The volatile compounds were evaporated *in vacuo*, the oily residue was neutralized with 10% hydrochloric acid and the precipitate was collected by filtration.

Benzyl *N*-[2-(4-nitrophenyl)-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl]carbamate (**22**).

This compound was prepared by method A, from compound **1** (0.5 mmol, 139 mg) and 4-nitrophenylhydrazine (**7**) (0.5 mmol,

77 mg), 1.5 hours, after addition of water and triethylamine stirred at room temperature for 10 minutes. The mixture of ethanol (2 mL) and *N*,*N*-dimethylformamide (1 mL) was used for crystallization.

Benzyl *N*-[2-(pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl]carbamate (**23**).

This compound was prepared by method A, from compound **1** (0.5 mmol, 139 mg) and 2-hydrazinopyridine (**8**) (0.5 mmol, 55 mg), 4 hours, after addition of water and triethylamine refluxed for 30 minutes. The formed precipitate was washed with ethanol (2 mL).

Benzyl *N*-[2-(6-chloropyridazin-3-yl)-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl]carbamate (**24**).

This compound was prepared by method B. Methanol (3 mL) was used for crystallization.

Benzyl *N*-[2-(6-phenylpyridazin-3-yl)-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl]carbamate (**25**).

This compound was prepared by method A, from compound **1** (0.5 mmol, 139 mg) and 6-phenyl-3-hydrazinopyridazine (**10**) (0.5 mmol, 72 mg), 2 hours, after addition of water and triethylamine refluxed for 15 minutes. The mixture of ethanol (2 mL) and *N*,*N*-dimethylformamide (1 mL) was used for crystallization.

N-(1-Acetyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)acetamide (**26**).

To a solution of compound **17** (0.6 mmol, 150 mg) in a mixture of acetic acid (5 mL) and acetic anhydride (3 mL) 10% Pd/C catalyst (30 mg) was added. The mixture was hydrogenated (hydrogen pressure = 3 atm) at room temperature for 12 hours. The catalyst was removed from reaction mixture by filtration. The volatile compounds were evaporated *in vacuo*, methanol (3 mL) was added and the precipitate was collected by filtration.

Preparation of Methyl *N*-(Benzyloxycarbonyl)amino-(1,2,4-triazolo[4,3-*x*]azin-3-yl)glycinates **27**-**30**.

Method A.

To a suspension of compound **1** (1 mmol, 139 mg) in methanol (5 mL) a catalytic amount of hydrochloric acid (0.1 mL, 36%) and the corresponding heteroarylhydrazine **8**, **10** (1 mmol) were added. The reaction mixture was stirred at room temperature for several hours. Afterwards methanol (additional 5 mL) and sodium acetate (3 mmol, 369 mg) were added. While stirring the solution of bromine in methanol (0.026 mL Bromine/2.5 mL Methanol) was added dropwise in a period of 15 minutes and the reaction mixture was stirred at room temperature for several hours. The volatile compounds were evaporated *in vacuo*, aqueous sodium bicarbonate (10 mL) was added to the residue, and the mixture was extracted with chloroform (3x 15 mL). The organic phases were collected, dried over anhydrous sodium sulfate, filtered, and the volatile compounds were evaporated *in vacuo*. The residue was treated with ether (10 mL) and precipitate collected by filtration.

Method B.

To a stirred mixture of methyl 2-(benzyloxycarbonyl)amino-3-(6-chloropyridazin-3-yl)hydraz-onopropanoate (**14**) (0.5 mmol, 181 mg), sodium acetate (1.5 mmol, 123 mg), and methanol (5 mL) the solution of bromine in methanol (0.026 mL Bromine/2.5 mL Methanol) was added dropwise in a periode of 15 minutes. The solution was stirred at room temperature for 4.5 hours. The volatile compounds were evaporated *in vacuo*, aqueous sodium bicarbonate (10 mL) was added to the residue and the mixture was extracted with chloroform (3x 15 mL). The organic phases were collected, dried over anhydrous sodium sulfate, filtered, and the volatile compounds were evaporated *in vacuo*. The mixture of ether (5 mL) and *i*-propyl alcohol (5 mL) was added to the residue and the precipitate was collected by filtration.

Method C.

To a solution of corresponding methyl 2-(benzyloxy-carbonyl)amino-3-heteroaryl-hydrazonopropanoate **14**, **16** (0.5 mmol) in dichloromethane (6 mL) lead tetraacetate (0.8 mmol, 350 mg) was added. After stirring at room temperature for several hours the precipitate was collected by filtration and washed with dichloromethane. The volatile compounds were evaporated *in vacuo*, the residue was treated with ethanol (5 mL) (with the mixture of ethanol (2.5 mL) and ether (2.5 mL) for compound **30**), and the precipitate was collected by filtration.

Methyl *N*-(Benzyloxycarbonyl)amino-(1,2,4-triazolo[4,3-*a*]-pyridin-3-yl)glycinate (**27**).

This compound was prepared by method A, from compound **1** (1 mmol, 278 mg) and 2-hydrazinopyridine (**8**) (1 mmol, 109 mg), 2 hours, after addition of Bromine/Methanol stirred for 48 hours. The mixture of methanol (2 mL) and water (2 mL) was used for crystallization.

Methyl *N*-(Benzyloxycarbonyl)amino-(6-chloro-1,2,4-triazolo-[4,3-*b*]pyridazin-3-yl)glycinate (**28**).

This compound was prepared by method B, and also by method C, from compound **14** (0.5 mmol, 189 mg), 5 hours. Methanol (5 mL) was used for crystallization.

Methyl *N*-(Benzyloxycarbonyl)amino-(6-phenyl-1,2,4-triazolo-[4,3-*b*]pyridazin-3-yl)glycinate (**29**).

This compound was prepared by method A, from compound 1 (1 mmol, 278 mg) and 3-hydrazino-6-phenylpiridazine (**10**) (1 mmol, 186 mg), 2 hours, after addition of Bromine/Methanol stirred for 4 days. Methanol (5 mL) was used for crystallization.

Methyl *N*-(Benzyloxycarbonyl)amino-(1,2,4-triazolo[4,3-*a*]-phthalazin-1-yl)glycinate (**30**).

This compound was prepared by method C, from compound **16** (0.5 mmol, 197 mg), 2 hours. The mixture of ethanol (3 mL) and toluene (2 mL) was used for crystallization.

General Procedure for the Preparation of Alkyl 2-[2,2-(Disubstituted)ethenyl]amino-3-heteroarylhydrazono-propanoates **40**-**48**.

To a suspension of compound **31**-**34** (1 mmol) in ethanol (3-4 mL) a catalytic amount of hydrochloric acid (0.1 mL, 36%) and the corresponding heteroarylhydrazine **9**, **36**-**39** (1 mmol) were added. The reaction mixture was stirred at room temperature for several hours and the product was isolated by an appropriate method.

Ethyl 2-[2,2-Bis(ethoxycarbonyl)ethenyl]amino-3-(6-chloro-pyridazin-3-yl)hydrazonopropanoate (**40**).

This compound was prepared from compound **31** (1 mmol, 328 mg) and 6-chloro-3-hydrazinopyridazine (**9**) (1 mmol, 144

mg), 1 hour. The volatile compounds were evaporated *in vacuo*, the mixture of toluene (2 mL) and ethyl acetate (2 mL) was added and the precipitate was collected by filtration.

Ethyl 2-[2,2-Bis(ethoxycarbonyl)ethenyl]amino-3-(6-chloro-5-methylpyridazin-3-yl)hydrazonopropanoate (**41**).

This compound was prepared from compound **31** (1 mmol, 328 mg) and 6-chloro-3-hydrazino-5-methylpyridazine (**36**) (1 mmol, 158 mg), 2.5 hours. The volatile compounds were evaporated *in vacuo*, the mixture of methanol (2 mL) and n-heptane (2 mL) was added and the precipitate was collected by filtration.

Ethyl 2-[2,2-Bis(ethoxycarbonyl)ethenyl]amino-3-(6-chloro-4-methylpyridazin-3-yl)hydrazonopropanoate (**42**).

This compound was prepared from compound **31** (1 mmol, 328 mg) and 6-chloro-3-hydrazino-4-methylpyridazine (**37**) (1 mmol, 158 mg), 2.5 hours. The volatile compounds were evaporated *in vacuo*, ethanol (4 mL) was added and the precipitate was collected by filtration.

Ethyl 2-[2,2-Bis(ethoxycarbonyl)ethenyl]amino-3-(4-chlorophthalazin-1-yl)hydrazonopropanoate (**43**).

This compound was prepared from compound **31** (1 mmol, 328 mg) and 4-chloro-1-hydrazinophthalazine hydrochloride (**38**) (1 mmol, 186 mg), 2 hours. The volatile compounds were evaporated *in vacuo*, the mixture of methanol (2 mL) and toluene (2 mL) was added and the precipitate was collected by filtration.

Ethyl 2-[2,2-Bis(ethoxycarbonyl)ethenyl]amino-3-(1,2,4-triazolo-[4,3-*b*]pyridazin-6-yl)hydrazonopropanoate (**44**).

This compound was prepared from compound **31** (1 mmol, 328 mg) and 6-hydrazino-1,2,4-triazolo[4,3-*b*]pyridazine (**39**) (1 mmol, 150 mg), 30 minutes. The volatile compounds were evaporated *in vacuo*, the mixture of ethanol (3 mL) and *N*,*N*-dimethyl formamide (1 mL) was added and the precipitate was collected by filtration.

Ethyl 2-(2-Acetyl-2-ethoxycarbonylethenyl]amino-3-(6-chloropyridazin-3-yl)hydrazonopropanoate (**45**).

This compound was prepared from compound **32** (1 mmol, 298 mg) and 6-chloro-3-hydrazinopyridazine (**9**) (1 mmol, 144 mg), 3 hours. Afterwards water (2 mL) was added and the precipitate was collected by filtration. Toluene (4 mL) was used for crystallization.

Methyl 2-[2-Ethoxycarbonyl-2-(pyridin-2-yl)ethenyl]amino-3-(6-chloropyridazin-3-yl)hydrazonopropanoate (**46**).

This compound was prepared from compound **33** (1 mmol, 320 mg) and 6-chloro-3-hydrazinopyridazine (**9**) (1 mmol, 144 mg), 3.5 hours. The formed precipitate was collected by filtration and washed with ethanol (4 mL).

Compound **46** was prepared also from methyl 2-[2-ethoxycarbonyl-2-(pyridin-2-yl)ethenyl]amino-3-hydroxypropenoate hydrochloride (**35**) (0.5 mmol, 164 mg) and 6-chloro-3-hydrazinopyridazine (**9**) (0.5 mmol, 72 mg) which were suspended in ethanol (2 mL) and the mixture was stirred at room temperature for 3.5 hours. The formed precipitate was collected by filtration and washed with ethanol (4 mL).

Methyl 2-[2-Ethoxycarbonyl-2-(pyridin-2-yl)ethenyl]amino-3-(4-chlorophthalazin-1-yl)hydrazonopropanoate (**47**).

This compound was prepared from compound **33** (1 mmol, 320 mg) and 4-chloro-1-hydrazinophthalazine hydrochloride (**38**) (1 mmol, 186 mg), 1 hour. The formed precipitate was collected by filtration and washed with ethanol (4 mL).

Ethyl 2-[2-Cyano-2-(pyridin-2-yl)ethenyl]amino-3-(6-chloropyridazin-3-yl)hydrazonopropanoate (**48**).

This compound was prepared from compound 34 (1 mmol, 286 mg) and 6-chloro-3-hydrazinopyridazine (**9**) (1 mmol, 144 mg), 30 minutes. The formed precipitate was collected by filtration and washed with ethanol (4 mL).

General Procedure for the Preparation of Alkyl 2,3-Bis((hetero)arylhydrazono)propanoates **51**-**55**.

To a suspension of compound **31**-**33** (0.5 mmol) in ethanol (2-3 mL) a catalytic amount of hydrochloric acid (0.1 mL, 36%) and the corresponding (hetero)arylhydrazine **5**, **8**, **49**, **50** (1 mmol) were added. The reaction mixture was stirred at room temperature from few minutes to several hours and the product was isolated by an appropriate method.

Ethyl 2,3-Bis(phenylhydrazono)propanoate (**51**).

This compound was prepared from compound **31** (0.5 mmol, 164 mg) and phenylhydrazine (**5**) (1 mmol, 108 mg), 1 hour. The volatile compounds were evaporated *in vacuo*, the mixture of ethanol (2 mL) and *n*-heptane (2 mL) was added and the precipitate was collected by filtration. Compound 51 was prepared also from compound **32** (0.5 mmol, 149 mg) and phenylhydrazine (**5**) (1 mmol, 108 mg), 48 hours. Afterwards water (2 mL) was added and the precipitate was collected by filtration. The mixture of ethanol (2 mL) and *n*-heptane (2 mL) was used for crystallization.

Ethyl 2,3-Bis(pyridin-2-ylhydrazono)propanoate (**52**).

This compound was prepared from compound **31** (0.5 mmol, 164 mg) and 2-hydrazinopyridine (**8**) (1 mmol, 109 mg), 3 hours. The volatile compounds were evaporated *in vacuo*, the mixture of ethanol (3 mL) and *N*,*N*-dimethyl formamide (1 mL) was added and the precipitate was collected by filtration.

Ethyl 2,3-Bis(4-methylphenylhydrazono)propanoate (**53**).

This compound was prepared from compound **31** (0.5 mmol, 164 mg) and 4-methylphenylhydrazine (**49**) (1 mmol, 122 mg), 1 hour. The volatile compounds were evaporated *in vacuo*, the mixture of ethanol (3 mL) and dimethyl sulfoxide (1 mL) was added and the precipitate was collected by filtration.

Methyl 2,3-Bis(pyridin-2-ylhydrazono)propanoate (**54**).

This compound was prepared from compound **33** (0.5 mmol, 160 mg) and 2-hydrazinopyridine (**8**) (1 mmol, 109 mg), 10 minutes. The formed precipitate was collected by filtration and washed with ethanol (2 mL).

Methyl 2,3-Bis(1-methyl-1-phenylhydrazono)propanoate (**55**).

This compound was prepared from compound **33** (0.5 mmol, 160 mg) and 1-methyl-1-phenylhydrazine (**50**) (1 mmol, 147 mg), 5 hours. The formed precipitate was collected by filtration and washed with ethanol (2 mL).

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