METHYL (*Z*)-2-[(BENZYLOXYCARBONYL)AMINO]-3-DIMETHYLAMINOPROPENOATE IN THE SYNTHESIS OF HETEROCYCLIC SYSTEMS. SYNTHESIS OF (BENZYLOXYCARBONYL)AMINO SUBSTITUTED FUSED PYRIMIDINONES

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Dedicated to the memory of the late Dr Miroslav Protiva.

Methyl (*Z*)-2-[(benzyloxycarbonyl)amino]-3-dimethylaminopropenoate (**1**) was used as a reagent for preparation of 3-[(benzyloxycarbonyl)amino] substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **17**–**21**, 4*H*-pyrimido[1,2-*b*]pyridazin-4-ones **22** and **23**, 5*H*-[1,2,4]triazolo[2,3-*a*]-pyrimidin-5-one **24**, 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **25**, and 4*H*-pyrazino[1,2-*a*]pyrimidin-4-one **26**. Removal of the benzyloxycarbonyl group by catalytical transfer hydrogenation with Pd/C in the presence of cyclohexene is selective to give 3-amino-4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones **27**–**30** in 85–92% yields, or with hydrogen bromide in acetic acid to give 3-amino-4*H*-pyrimido[1,2-*b*]pyridazin-4-one (**31**) and 6-amino-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**32**) in 80% yields.

Key words: Pyrido[1,2-*a*]pyrimidines; Pyrimido[1,2-*b*]pyridazines; 1,2,4-Triazolo[2,3-*a*]pyrimidines; Thiazolo[3,2-*a*]pyrimidines; Pyrazino[1,2-*a*]pyrimidines; Fused heterocycles.

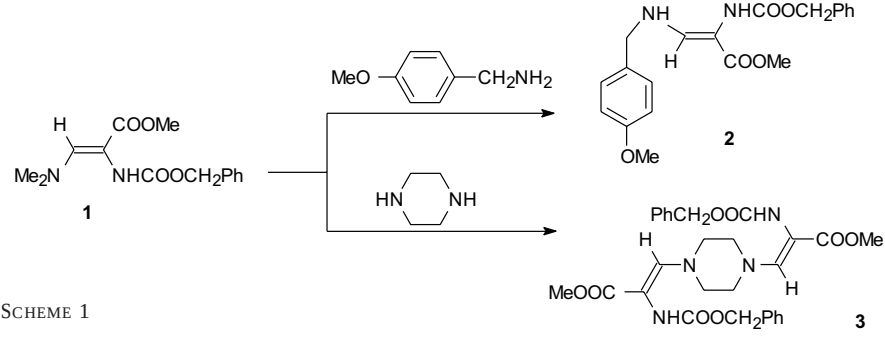
Synthesis of various derivatives of pyran-2-ones and fused pyran-2-ones has attracted great interest, since many of them have been found to be nonpeptide HIV protease inhibitors[1] and 3-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones have been recently studied as fluorescent probes for hypoxic cells in solid tumors[2,3].

Recently, we have prepared a series of substituted alkyl 2-[(2,2-disubstituted ethenyl)amino]-3-dimethylaminopropenoates as versatile reagents in the synthesis of many heterocyclic systems, such as indolizines, quinolizines, pyranones, benzo- and naphthopyranones, pyranopyrimidines, azolo- and

azinopyrimidines, with a monosubstituted amino group in the newly formed rings[4–18].

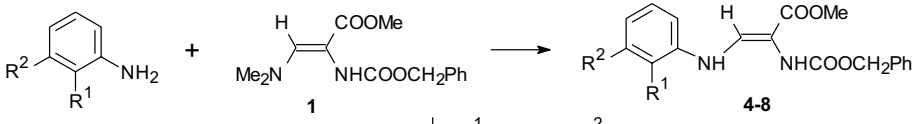
In continuation of our studies, methyl (*Z*)-2-[(benzyloxycarbonyl)-amino]-3-dimethylaminopropenoate (**1**), as a new reagent in this series, was recently prepared, and used for the synthesis of trisubstituted pyrroles, simple and fused 3-amino-2*H*-pyran-2-ones, and 1,4-dihydropyridin-4-ones[19].

In this paper, we report the reactions of methyl (*Z*)-2-[(benzyloxycarbonyl)amino]-3-dimethylaminopropenoate (**1**) with nitrogen nucleophiles. 4-Methoxybenzylamine and piperazine were transformed into methyl 2-[(benzyloxycarbonyl)amino]-3-[(4-methoxybenzyl)amino]propenoate (**2**) and dimethyl 3,3'-(piperazine-1,4-diyl)bis{2-[(benzyloxycarbonyl)amino]propenoate} (**3**) in 73 and 64% yields, respectively (Scheme 1). Aromatic amines such as aniline, 3-bromoaniline, 2-nitroaniline,



SCHEME 1

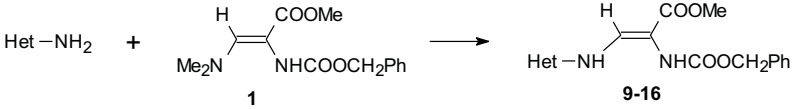
3-nitroaniline, and 1-aminonaphthalene afforded the corresponding methyl 2-[(benzyloxycarbonyl)amino]-3-(arylamino)propenoates **4**–**8** in 65–98% yields (Scheme 2). Analogously, heteroaromatic amines, such as 2-amino-6-methylpyridine, 2-amino-4,6-dimethylpyrimidine, 3-amino-5-

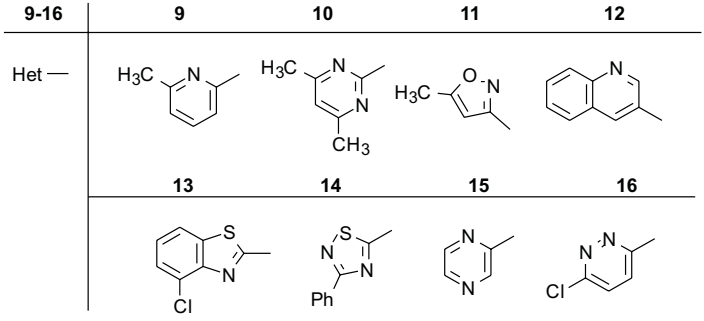


	R^1	R^2
4	H	H
5	H	Br
6	NO_2	H
7	H	NO_2
8	-CH=CH-CH=CH-	

SCHEME 2

methylisoxazole, 3-aminoquinoline, 2-amino-4-chlorobenzothiazole, 5-amino-3-phenyl-1,2,4-thiadiazole, 2-aminopyrazine, and 3-amino-6-chloropyridazine afforded by heating in acetic acid or in a mixture of acetic acid and methanol (2 : 3) methyl (*Z*)-2-[(benzyloxycarbonyl)amino]-3-(hetarylamino)propenoates **9**–**16** in 66–96% yields (Scheme 3). On the other hand, some heteroaromatic amines, such as 2-aminopyridine,



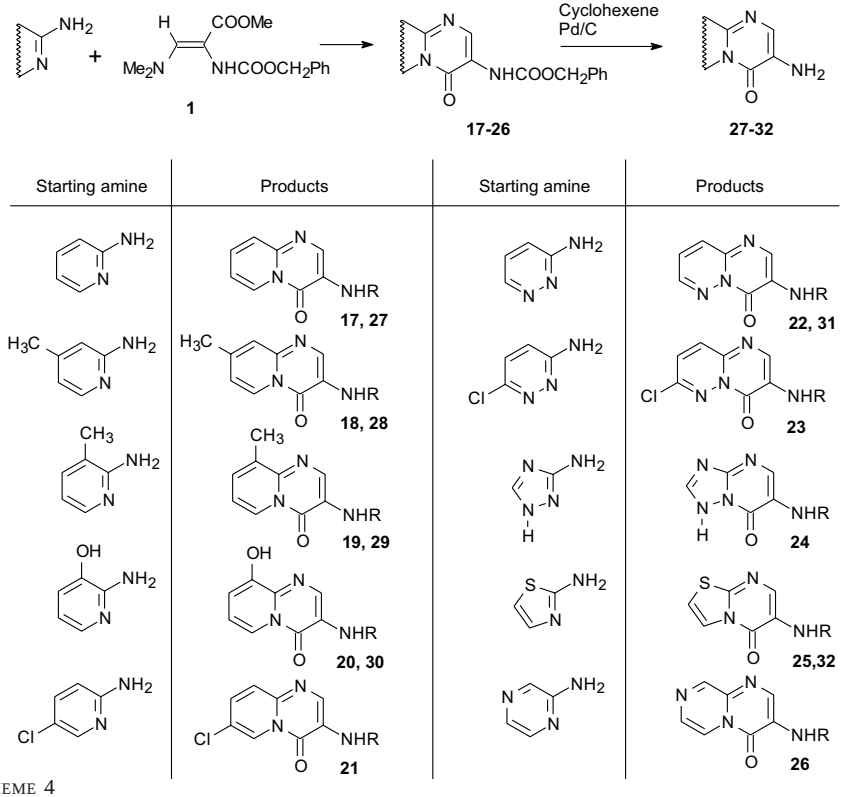


SCHEME 3

2-amino-4-methyl-, 2-amino-3-methyl-, 2-amino-3-hydroxy-, and 2-amino-5-chloropyridine, 3-aminopyridazine, 3-amino-6-chloropyridazine, 1*H*-3-amino-1,2,4-triazole, 2-aminothiazole, and 2-aminopyrazine, were transformed into the corresponding fused pyrimidin-4-ones: 3-[(benzyloxycarbonyl)amino]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**17**), and its 8-methyl (**18**), 9-methyl (**19**), 9-hydroxy (**20**), and 7-chloro (**21**) derivatives, 3-[(benzyloxycarbonyl)amino]-4*H*-pyrimido[1,2-*b*]pyridazin-4-one (**22**) and its chloro derivative (**23**), 6-[(benzyloxycarbonyl)amino]-7*H*-[1,2,4]triazolo[2,3-*a*]pyrimidin-5-one (**24**), 6-[(benzyloxycarbonyl)amino]-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**25**), and 3-[(benzyloxycarbonyl)amino]-4*H*-pyrazino[1,2-*a*]pyrimidin-4-one (**26**) in 69–96% yields (Scheme 4).

Removal of benzyloxycarbonyl group by catalytic transfer hydrogenation with Pd/C in the presence of cyclohexene turned out to be selective[20,21] (no hydrogenation of pyran-2-one, and 4*H*-pyridin-4-one ring systems has been observed) to give unsubstituted amino compounds in over 80% yields[19]. In this manner, 3-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**27**) and its

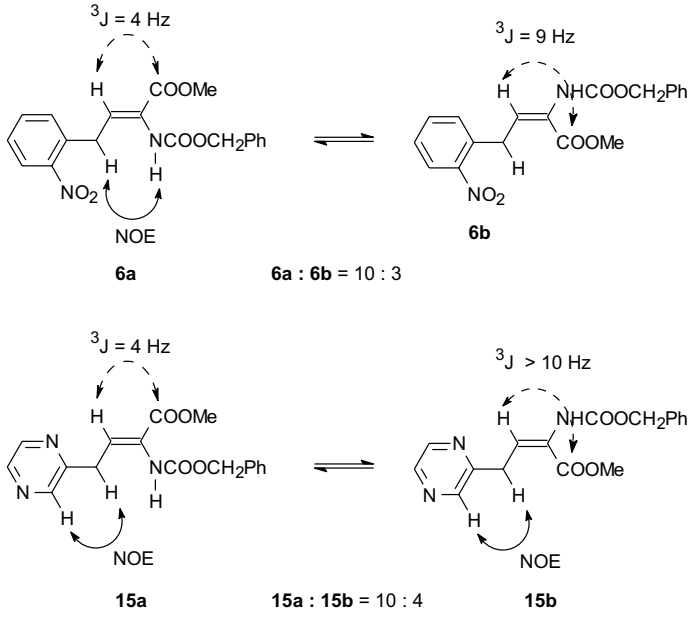
8-methyl (**28**), 9-methyl (**29**), and 9-hydroxy (**30**) derivatives were prepared in 85–92% yields (Scheme 4). Removal of benzyloxycarbonyl group in compounds **22** and **25** was achieved with hydrogen bromide in acetic acid according to the procedure used in peptide chemistry[22].



SCHEME 4

The structure of compound **1** has been established previously[19]. In this paper we were interested in the orientation of groups around the C=C double bond in substituted propenoates. Two compounds were selected for this purpose: methyl 2-[(benzyloxycarbonyl)amino]-3-(2-nitroanilino)propenoate (**6**) and methyl 2-[(benzyloxycarbonyl)amino]-3-[(pyrazin-2-yl)-amino]propenoate (**15**). Both compounds show in ^{1}H NMR two sets of signals indicating that there is an equilibrium between two isomers for each compound. The coupling constant for the structural element CH–NH, $J_{CH-NH} \approx 11$ Hz, clearly indicates the *trans* (antiperiplanar) orientation of

both hydrogens. The coupling constant $^3J_{H-C=C-13C}$ = 4.0 Hz and NOE between both NH groups suggest the *Z*-orientation (**6a**), while the coupling constant $^3J_{H-C=C-13C}$ = 9.0 Hz is significant for *trans* orientation around the double bond (Fig. 1, Scheme 5). The ratio **6a** : **6b** is 10 : 3 both in chloroform and DMSO-d_6. Similar is the situation in compound **15**, in which two isomers exist in equilibrium. The magnitude of coupling constant for the CH–NH structural element, J_{CH-NH} = 11 Hz, indicates the *trans*



SCHEME 5

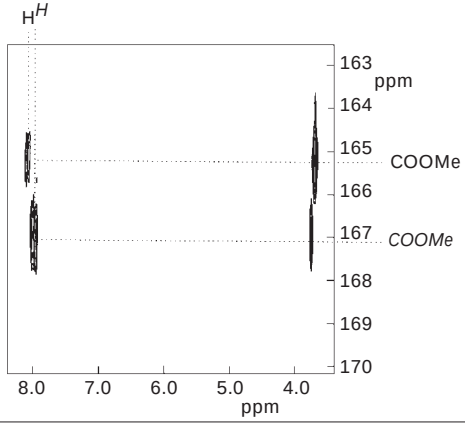


FIG. 1
Carbonyl part of the HMBC spectrum (DMSO-d_6) of methyl 2-[(benzyloxycarbonyl)-amino]-3-(2-nitroanilino)propenoate (**6**). The cross-peaks of the minor conformer are indicated in italics

(antiperiplanar) orientation of both hydrogen atoms in both isomers. The orientation of the ring against the NH group at position 3, was established on the basis of NOE, while the orientation of the groups around the double bond was established by NOESY experiments[23]. The long-range $^{13}CO–^{1}H$ coupling constants were evaluated from the antiphase splitting of cross peaks in the HMBC spectrum[24,25]. The coupling constants, $^{3}J_{H–C=C–COOMe} \approx 4$ Hz for one and $^{3}J_{H–C=C–COOMe} > 10$ Hz for the other isomer, clearly indicate that there is an equilibrium between the *Z*- and *E*-isomers **15a** and **15b**, respectively (10 : 4) (Scheme 5).

EXPERIMENTAL

Melting points were taken on a Kofler hot microstage. The ^{1}H NMR spectra (δ, ppm; *J*, Hz) were obtained on a Bruker Avance DPX 300 spectrometer, IR spectra on a Perkin–Elmer 1310 instrument and C, H and N microanalyses on a Perkin–Elmer Analyzer 2400. Mass spectra were obtained on an Autospeck Q spectrometer. Reactions were followed by TLC (Merck pre-coated plates silica gel 60 F 254, chloroform–methanol 25 : 1, if not otherwise stated).

Methyl 2-[(benzyloxycarbonyl)amino]-3-dimethylaminopropenoate (**1**) was prepared according to the procedure described in the literature[19].

Methyl 2-[(Benzyloxycarbonyl)amino]-3-[(4-methoxybenzyl)amino]propenoate (**2**)

To a solution of 4-methoxybenzylamine (0.137 g, 1.0 mmol) in acetic acid (5 ml), methyl 2-[(benzyloxycarbonyl)amino]-3-dimethylaminopropenoate (**1**; 0.278 g, 1.0 mmol) was added and the mixture was refluxed for 2.5 h. Then acetic acid was evaporated *in vacuo* and the solid residue was recrystallized from a mixture of methanol and water to give **2** (0.270 g, 73%) , m.p. 128–131 °C. For $C_{20}H_{22}N_2O_5$ (370.4) calculated: 64.85% C, 5.99% H, 7.56% N; found: 64.74% C, 6.15% H, 7.77% N. ^{1}H NMR ($CDCl_3$): 3.68 s, 3 H ($ArOCH_3$); 3.81 s, 3 H ($COOCH_3$); 4.31 d, 2 H, *J*(CH_2,NH) = 5.7 (CH_2); 5.12 s, 2 H (CH_2); 5.51 br s and 6.78 br s, 2 H (NH); 6.89 d, 2 H, *J*(2,3) = 8.1 (H-3, H-5); 7.19 d, 2 H, *J*(5,6) = 8.1 (H-2, H-6); 7.31–7.34 m, 6 H (Ph, –CH=).

Dimethyl 3,3'-(Piperazine-1,4-diyl)bis{2-[(benzyloxycarbonyl)amino]propenoate} (**3**)

To a solution of piperazine hexahydrate (0.194 g, 1.0 mmol) in a mixture of acetic acid (2 ml) and methanol (3 ml), methyl 2-[(benzyloxycarbonyl)amino]-3-dimethylaminopropenoate (**1**; 0.556 g, 2.0 mmol) was added and the mixture was refluxed for 4 h. The residue after evaporation was recrystallized from a mixture of methanol and water to give **3** (0.357 g, 64%); m.p. 193–194 °C. For $C_{28}H_{32}N_4O_8$ (552.6) calculated: 60.86% C, 5.84% H, 10.14% N; found: 60.68% C, 5.84% H, 10.15% N. ^{1}H NMR ($CDCl_3$): 3.36 s, 8 H (piperazine H); 3.67 s, 6 H (CH_3); 5.14 s, 4 H (CH_2); 5.57 br s, 2 H (NH); 7.19 s, 2 H (–CH=); 7.32–7.34 m, 10 H (Ph).

Methyl 2-[(Benzyloxycarbonyl)amino]-3-(arylamino)propenoates (**4**–**8**). General Procedure

To a solution of aromatic amine (1.0 mmol) in a mixture of ethanol (5 ml) and concentrated hydrochloric acid (0.1 ml), methyl 2-[(benzyloxycarbonyl)amino]-3-dimethylaminopropenoate (**1**; 0.278 g, 1.0 mmol) was added and the mixture was refluxed for several hours. The solid residue after evaporation was recrystallized from an appropriate solvent.

Methyl 2-[(Benzyloxycarbonyl)amino]-3-anilinopropenoate (**4**)

Reaction time 2 h. Yield 95%; m.p. 125–127 °C (methanol–water). For $C_{18}H_{18}N_2O_4$ (326.4) calculated: 66.25% C, 5.56% H, 8.58% N; found: 66.24% C, 5.47% H, 8.79% N. ^{1}H NMR ($CDCl_3$): 3.77 s, 3 H (CH_3); 5.17 s and 5.19 s, 2 H (CH_2); 5.91 br s and 6.53 br s, 1 H (NH); 6.94–7.03 m, 3 H (Ph); 7.26–7.39 m, 7 H (CH_2**Ph**, Ph); 7.71 d, 1 H, *J*(CH–NH) = 12.2 (–CH=); 7.97 br s and 9.59 br s, 1 H (CHN**H**); *Z*/*E* = 86 : 14.

Methyl 2-[(Benzyloxycarbonyl)amino]-3-(3-bromoanilino)propenoate (**5**)

Reaction time 2 h. Yield 98%; m.p. 153–155 °C (methanol–water). For $C_{18}H_{17}BrN_2O_4$ (405.3) calculated: 53.35% C, 4.23% H, 6.91% N; found: 53.56% C, 4.25% H, 6.80% N. ^{1}H NMR ($CDCl_3$): 3.79 s, 3 H (CH_3); 5.17 s and 5.19 s, 2 H (CH_2); 6.64 br s, 1 H (NH); 6.86 m, 1 H (Ph); 7.08–7.17 m, 3 H (Ph); 7.36–7.40 m, 5 H (CH_2**Ph**); 7.57 d, 1 H, *J*(CH–NH) = 12.4 (–CH=); 8.21 br s, 1 H (CHN**H**); *Z*/*E* = 88 : 12.

Methyl 2-[(Benzyloxycarbonyl)amino]-3-(2-nitroanilino)propenoate (**6**)

Reaction time 30 min. Yield 65%; m.p. 145–148 °C (ethanol). For $C_{18}H_{17}N_3O_6$ (371.4) calculated: 58.22% C, 4.61% H, 11.32% N; found: 58.47% C, 4.60% H, 11.19% N. ^{1}H NMR ($CDCl_3$): 3.81 s and 3.95 s, 3 H (CH_3); 5.18 s and 5.25 s, 2 H (CH_2); 6.38 br s and 6.43 br s, 1 H (NH); 7.02 ddd, 1 H, *J*(3,4) = 8.6, *J*(4,5) = 7.2, *J*(4,6) = 1.1 (H-4); 7.31–7.42 m, 6 H (Ph, H-6); 7.60 ddd, 1 H, *J*(3,5) = 1.5, *J*(4,5) = 7.2, *J*(5,6) = 8.7 (H-5); 7.84 d, 1 H, *J*(CH–NH) = 11.7 (–CH=); 8.24 dd, 1 H, *J*(3,4) = 8.6, *J*(3,5) = 1.5 (H-3); 10.30 br s and 11.74 br s, 1 H (CHN**H**); *Z*/*E* = 76 : 24.

Methyl 2-[(Benzyloxycarbonyl)amino]-3-(3-nitroanilino)propenoate (**7**)

Reaction time 20 min. Yield 69%; m.p. 153–155 °C (methanol–water). For $C_{18}H_{17}N_3O_6$ (371.4) calculated: 58.22% C, 4.61% H, 11.32% N; found: 58.26% C, 4.62% H, 11.32% N. ^{1}H NMR ($CDCl_3$): 3.82 s, 3 H (CH_3); 5.18 s and 5.21 s, 2 H (CH_2); 6.78 br s, 1 H (NH); 7.23 d, 1 H, *J*(5,6) = 8.7 (H-6); 7.34–7.46 m, 6 H (Ph, H-5); 7.58 d, 1 H, *J*(CH–NH) = 11.7 (–CH=); 7.79–7.81 m, 2 H (H-2, H-4); 8.68 br s, 1 H (CHN**H**;, *Z*/*E* = 92 : 8.

Methyl 2-[(Benzyloxycarbonyl)amino]-3-(1-naphthylamino)propenoate (**8**)

To a solution of 1-aminonaphthalene (0.144 g, 1.0 mmol) in acetic acid (5 ml), compound (**1**; 0.278 g, 1.0 mmol) was added and the mixure was refluxed for 30 min. The solid residue after evaporation was recrystallized from a mixture of methanol and water to give **8** (0.327 g, 87%); m.p. 123–125 °C. For $C_{22}H_{20}N_2O_4$ (376.4) calculated: 70.20% C, 5.36% H, 7.44% N; found: 70.52% C, 5.56% H, 7.70% N. ^{1}H NMR ($CDCl_3$): 3.80 s, 3 H (CH_3); 5.19 s

and 5.27 s, 2 H (CH_2); 5.98 br s and 6.78 br s, 1 H (NH); 7.11 d and 7.20 d, 1 H, *J*(4,5) = 7.1 (H-4); 7.36–7.54 m, 9 H (Ph, H-3, H-5, H-6, H-7); 7.78 d and 7.93 d, 1 H, *J*((*Z*)-CH–NH) = 11.7, *J*((*E*)-CH–NH) = 12.3 (–CH=); 7.83–7.85 m, 1 H (H-2); 8.03 d, 1 H, *J*(7,8) = 7.9 (H-8); 8.95 br s and 10.48 br s, 1 H (CHN**H**); *Z*/*E* = 74 : 26.

Methyl 2-[(Benzyloxycarbonyl)amino]-3-hetarylaminopropenoates (**9**–**16**). General Procedure

To a solution of heterocyclic amine (1.0 mmol) in 5 ml acetic acid (compounds **9**–**14**) or 5 ml of a 2 : 3 mixture of acetic acid and methanol (compounds **15**–**16**) compound **1** (0.278 g, 1.0 mmol) was added and the mixture was refluxed for several hours. The solid residue after evaporation was recrystallized from an appropriate solvent.

Methyl 2-[(Benzyloxycarbonyl)amino]-3-[(6-methyl-2-pyridyl)amino]propenoate (**9**)

Reaction time 3.5 h. Yield 66%; m.p. 173–175 °C (ethanol–water). For $C_{18}H_{19}N_3O_4$ (341.4) calculated: 63.33% C, 5.61% H, 12.31% N; found: 63.32% C, 5.64% H, 12.11% N. ^{1}H NMR ($CDCl_3$): 2.67 s, 3 H (CH_3); 3.79 s, 3 H ($COOCH_3$); 5.19 s, 2 H (CH_2); 6.53 d, 1 H, *J*(4,5) = 7.9 (H-5); 6.60 br s, 1 H (NH); 6.72 d, 1 H, *J*(3,4) = 7.5 (H-3); 7.33–7.39 m, 5 H (Ph); 7.45 dd, 1 H, *J*(3,4) = 7.5, *J*(4,5) = 7.9 (H-4); 8.27 d, 1 H, *J*(CH–NH) = 11.9 (–CH=); 8.44 br s, 1 H (CHN**H**).

Methyl 2-[(Benzyloxycarbonyl)amino]-3-[(4,6-dimethylpyrimidin-2-yl)amino]-propenoate (**10**)

Reaction time 2.5 h. Yield 83%; m.p. 154–156 °C (methanol–water). For $C_{18}H_{20}N_4O_4$ (356.4) calculated: 60.66% C, 5.66% H, 15.72% N; found: 60.60% C, 5.69% H, 15.82% N. ^{1}H NMR ($CDCl_3$): 2.38 s, 6 H (CH_3); 3.80 s, 3 H ($COOCH_3$); 5.19 s, 2 H (CH_2); 6.52 br s, 1 H (NH); 6.59 s, 1 H (H-5); 7.31–7.37 m, 5 H (Ph); 8.37 d, 1 H (–CH=); 8.53 br s, 1 H, *J*(CH–NH) = 11.9 (CHN**H**).

Methyl 2-[(Benzyloxycarbonyl)amino]-3-[(5-methylisoxazol-3-yl)amino]propenoate (**11**)

Reaction time 1.5 h. Yield 92%; m.p. 165–167 °C (methanol–water). For $C_{16}H_{17}N_3O_5$ (331.3) calculated: 58.00% C, 5.17% H, 12.68% N; found: 57.72% C, 4.97% H, 12.87% N. ^{1}H NMR ($CDCl_3$): 2.36 s, 3 H (CH_3); 3.77 s, 3 H ($COOCH_3$); 5.15 s and 5.17 s, 2 H (CH_2); 5.75 s, 1 H (H-4); 6.73 br s, 1 H (NH); 7.34–7.36 m, 5 H (Ph); 7.61 d, 1 H, *J*(CH–NH) = 11.8 (–CH=), 8.39 br s, 1 H (CHN**H**); *Z*/*E* = 94 : 6.

Methyl 2-[(Benzyloxycarbonyl)amino]-3-[(quinolin-3-yl)amino]propenoate (**12**)

Reaction time 3 h. Yield 94%; m.p. 170–173 °C (methanol–water). For $C_{21}H_{19}N_3O_4$ (374.4) calculated: 66.83% C, 5.07% H, 11.13% N; found: 66.47% C, 5.00% H, 11.26% N. ^{1}H NMR ($CDCl_3$): 3.83 s, 3 H ($COOCH_3$); 5.19 s and 5.23 s, 2 H (CH_2); 6.07 br s and 6.77 br s, 1 H (NH); 7.34–7.44 m, 5 H (Ph); 7.48–7.59 m and 7.68–7.74 m, 5 H (Het); 7.93 d and 8.03 d, 1 H, *J*(CH–NH) = 8.0 (–CH=); 8.56 br s and 9.86 br s, 1 H (CHN**H**); 8.64–8.67 m, 1 H (H-2); *Z*/*E* = 87 : 13.

Methyl 2-[(Benzyloxycarbonyl)amino]-3-[(4-chlorobenzothiazol-2-yl)amino]-propenoate (**13**)

Reaction time 3 h. Yield 89%; m.p. 183–185 °C (methanol–water). For $C_{19}H_{16}ClN_3O_4S$ (417.9) calculated: 54.61% C, 3.86% H, 10.06% N; found: 54.42% C, 3.72% H, 10.01% N. ^{1}H NMR ($CDCl_3$): 3.84 s, 3 H ($COOCH_3$); 5.18 s and 5.21 s, 2 H (CH_2); 6.94 br s, 1 H (NH); 7.14 dd, 1 H, *J*(5,6) = 7.9, *J*(6,7) = 7.9 (H-6); 7.36–7.42 m, 6 H (Ph, H-7); 7.50 dd, 1 H, *J*(5,6) = 7.9, *J*(5,7) = 1.0 (H-5); 7.82 d, 1 H, *J*(CH–NH) = 10.2 (C**H**NH); 9.89 br s, 1 H (CHN**H**); *Z*/*E* = 96 : 4.

Methyl 2-[(Benzyloxycarbonyl)amino]-3-[(3-phenyl-1,2,4-thiadiazol-5-yl)amino]-propenoate (**14**)

Reaction time 2.5 h. Yield 96%; m.p. 178–180 °C (methanol–water). For $C_{20}H_{18}N_4O_4S$ (410.5) calculated: 58.53% C, 4.42% H, 13.65% N; found: 58.80% C, 4.39% H, 13.98% N. ^{1}H NMR ($CDCl_3$): 3.87 s, 3 H ($COOCH_3$); 5.19 s and 5.22 s, 2 H (CH_2); 7.26 br s, 1 H (NH); 7.38–7.44 m, 5 H (CH_2Ph); 7.45–7.46 m, 3 H (Ph); 7.69 d, 1 H, *J*(CH–NH) = 10.9 (–CH=); 8.23–8.26 m, 2 H (Ph); 10.21 br s, 1 H (CHN**H**); *Z*/*E* = 91 : 9.

Methyl 2-[(Benzyloxycarbonyl)amino]-3-[(pyrazin-2-yl)amino]propenoate (**15**)

Reaction time 3.5 h. Yield 80%, m.p. 150–152 °C (methanol–water). For $C_{16}H_{16}N_4O_4$ (328.3) calculated: 58.53% C, 4.91% H, 17.06% N; found: 58.56% C, 4.85% H, 17.28% N. ^{1}H NMR ($CDCl_3$): 3.82 s, 3 H ($COOCH_3$); 5.17 s and 5.21 s, 2 H (CH_2); 6.91 br s, 1 H (NH); 7.35–7.42 m, 5 H (Ph); 8.09 d, 1 H, *J*(3,5) = 2.3 (H-3); 8.14–8.17 m, 3 H (H-5, H-6, –CH=); 9.22 br s, 1 H (CHN**H**).

Methyl 2-[(Benzyloxycarbonyl)amino]-3-[(6-chloropyridazin-3-yl)amino]-propenoate (**16**)

Reaction time 6.5 h. Yield 93%, m.p. 199–201 °C (methanol–water). For $C_{16}H_{15}ClN_4O_4$ (362.8) calculated: 52.97% C, 4.17% H, 15.44% N; found: 52.77% C, 3.81% H, 15.59% N. ^{1}H NMR ($CDCl_3$): 3.81 s, 3 H ($COOCH_3$); 5.19 s, 2 H (CH_2); 6.91 d, 1 H, *J*(4,5) = 9.1 (H-4); 6.99 br s, 1 H (NH); 7.32 d, 1 H, *J*(4,5) = 9.1 (H-5); 7.35–7.41 m, 5 H (Ph); 8.27 d, 1 H, *J*(CH–NH) = 11.1 (–CH=); 9.40 br s, 1 H (CHN**H**).

(Benzyloxycarbonyl)amino Substituted Fused Pyrimidinones **17**–**26**. General Procedure

To a solution of heterocyclic amine (1.0 mmol) in acetic acid (5 ml), compound **1** (0.278 g, 1.0 mmol) was added and the mixture was refluxed for several hours or (compounds **23** and **26**) after 1 h of reflux, sodium acetate (0.08 g, 1 mmol) was added and the mixture was refluxed for additional 4 h. After reaction was completed, acetic acid was evaporated *in vacuo* and the solid residue was recrystallized from an appropriate solvent.

3-[(Benzyloxycarbonyl)amino]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**17**)

Reaction time 2.5 h. Yield 82%; m.p. 146–148 °C (methanol–toluene). For $C_{16}H_{13}N_3O_3$ (295.3) calculated: 65.08% C, 4.44% H, 14.23% N; found: 65.27% C, 4.51% H, 14.24% N.

^{1}H NMR ($CDCl_3$): 5.25 s, 2 H (CH_2); 7.10 ddd, 1 H, *J*(6,7) = 7.7, *J*(7,8) = 7.5, *J*(7,9) = 1.2 (H-7); 7.36-7.44 m, 5 H (Ph); 7.57 s, 1 H (H-2); 7.61 ddd, 1 H, *J*(6,8) = 1.2, *J*(7,8) = 7.5, *J*(8,9) = 9.0 (H-8); 7.66 dd, 1 H, *J*(7,9) = 1.2, *J*(8,9) = 9.0 (H-9); 8.92 dd, 1 H, *J*(6,7) = 7.7, *J*(6,8) = 1.2 (H-6); 9.24 s, 1 H (NH).

3-[(Benzyloxycarbonyl)amino]-8-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**18**)

Reaction time 2.5 h. Yield 89%; m.p. 178–179 °C (ethanol–toluene). For $C_{17}H_{15}N_3O_3$ (309.3) calculated: 66.01% C, 4.89% H, 13.58% N; found: 66.19% C, 4.80% H, 13.98% N. ^{1}H NMR ($CDCl_3$): 2.46 s, 3 H (CH_3); 5.24 s, 2 H (CH_2); 6.94 dd, 1 H, *J*(6,7) = 7.4, *J*(7,9) = 1.9 (H-7); 7.32–7.44 m, 7 H (Ph, NH, H-9); 8.82 d, 1 H, *J*(6,7) = 7.4 (H-6); 9.18 s, 1 H (H-2).

3-[(Benzyloxycarbonyl)amino]-9-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**19**)

Reaction time 2 h. Yield 69%; m.p. 154–156 °C (methanol–toluene). For $C_{17}H_{15}N_3O_3$ (309.3) calculated: 66.01% C, 4.89% H, 13.58% N; found: 65.93% C, 5.05% H, 13.43% N. ^{1}H NMR ($CDCl_3$): 2.60 s, 3 H (CH_3); 5.25 s, 2 H (CH_2); 7.01 dd, 1 H, *J*(6,7) = 7.2, *J*(7,8) = 6.8 (H-7); 7.26–7.46 m, 6 H (Ph, H-8); 7.50 br s, 1 H (NH); 8.83 d, 1 H, *J*(6,7) = 7.2 (H-6); 9.25 s, 1 H (H-2).

3-[(Benzyloxycarbonyl)amino]-9-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**20**)

Reaction time 2.5 h. Yield 90%; m.p. 227–229 °C (methanol–toluene). For $C_{16}H_{13}N_3O_4$ (311.3) calculated: 61.73% C, 4.21% H, 13.50% N; found: 61.63% C, 4.37% H, 13.35% N. ^{1}H NMR ($CDCl_3$): 5.26 s, 2 H (CH_2); 7.01–7.26 m, 2 H (H-7, H-8); 7.35–7.44 m, 5 H (Ph); 7.51 s, 1 H (NH); 8.44 dd, 1 H, *J*(6,7) = 6.0, *J*(6,8) = 2.6 (H-6); 9.17 s, 1 H (H-2).

3-[(Benzyloxycarbonyl)amino]-7-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**21**)

Reaction time 3 h. Yield 92%; m.p. 189–191 °C (methanol–toluene). For $C_{16}H_{12}ClN_3O_3$ (329.7) calculated: 58.28% C, 3.67% H, 12.74% N; found: 58.28% C, 3.62% H, 12.34% N. ^{1}H NMR ($CDCl_3$): 5.25 s, 2 H (CH_2); 7.36–7.42 m, 5 H (Ph); 7.49 dd, 1 H, *J*(6,8) = 1.9, *J*(8,9) = 9.4 (H-8); 7.54 br s, 1 H (NH); 7.59 dd, 1 H, *J*(6,9) = 0.8, *J*(8,9) = 9.4 (H-9); 8.93 dd, 1 H, *J*(6,8) = 1.9, *J*(6,9) = 0.8 (H-6); 9.23 s, 1 H (H-2).

3-[(Benzyloxycarbonyl)amino]-4*H*-pyrimido[1,2-*b*]pyridazin-4-one (**22**)

Reaction time 3.5 h. Yield 93%; m.p. 187–190 °C (methanol–toluene). For $C_{15}H_{12}N_4O_3$ (296.3) calculated: 60.81% C, 4.08% H, 18. 91% N; found: 60.77% C, 4.18% H, 19.03% N. ^{1}H NMR ($CDCl_3$): 5.26 s, 2 H (CH_2); 7.30 dd, 1 H, *J*(7,8) = 4.1, *J*(8,9) = 9.3 (H-8); 7.37–7.42 m, 5 H (Ph); 7.77 br s, 1 H (NH); 7.87 dd, 1 H, *J*(7,9) = 1.8, *J*(8,9) = 9.3 (H-9); 8.62 dd, 1 H, *J*(7,8) = 4.1, *J*(7,9) = 1.8 (H-7); 9.22 s, 1 H (H-2).

3-[(Benzyloxycarbonyl)amino]-7-chloro-4*H*-pyrimido[1,2-*b*]pyridazin-4-one (**23**)

Yield 50%; m.p. 182–184 °C (methanol–toluene). For $C_{15}H_{11}ClN_4O_3$ (330.7) calculated: 54.47% C, 3.35% H, 16.94% N; found: 54.27% C, 3.14% H, 17.11% N. ^{1}H NMR ($CDCl_3$): 5.26 s, 2 H (CH_2); 7.37–7.42 m, 5 H (Ph); 7.26 d, 1 H, *J*(8,9) = 9.4 (H-8); 7.76 br s, 1 H (NH); 7.78 d, 1 H, *J*(8,9) = 9.4 (H-9); 9.18 s, 1 H (H-2).

6-[(Benzyloxycarbonyl)amino]-5*H*-[1,2,4]triazolo[2,3-*a*]pyrimidin-5-one (**24**)

Reaction time 2.5 h. Yield 84%; m.p. 215–217 °C (methanol–toluene). For $C_{13}H_{11}N_5O_3$ (285.3) calculated: 54.74% C, 3.89% H, 24.55% N, found: 54.70% C, 3.87% H, 24.57% N. ^{1}H NMR ($(CD_3)_2SO$): 5.13 s, 2 H (CH_2); 7.33–7.41 m, 5 H (Ph); 8.23 s, 1 H (H-2); 8.28 s, 1 H (H-6); 8.76 br s, 1 H (NH); 13.41 br s, 1 H (NH).

6-[(Benzyloxycarbonyl)amino]-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**25**)

Reaction time 2.5 h. Yield 96%; m.p. 183–184 °C (methanol–toluene). For $C_{14}H_{11}N_3O_3S$ (301.3) calculated: 55.81% C, 3.68% H, 13.95% N; found: 55.80% C, 3.52% H, 14.00% N. ^{1}H NMR ($CDCl_3$): 5.23 s, 2 H (CH_2); 7.04 d, 1 H, *J*(2,3) = 4.9 (H-2); 7.33–7.43 m, 6 H (Ph, NH); 7.93 d, 1 H, *J*(2,3) = 4.9 (H-3); 8.92 s, 1 H (H-7).

3-[(Benzyloxycarbonyl)amino]-4*H*-pyrazino[1,2-*a*]pyrimidin-4-one (**26**)

Yield 51%; m.p. 192–195 °C (methanol–toluene). For $C_{15}H_{12}N_4O_3$ (296.3) calculated: 60.81% C, 4.08% H, 18.91% N; found: 60.54% C, 3.84% H, 19.07% N. ^{1}H NMR ($CDCl_3$): 5.27 s, 2 H (CH_2); 7.37–7.43 m, 5 H (Ph); 7.68 br s, 1 H (NH); 8.04 d, 1 H, *J*(7,9) = 1.2 (H-9); 8.56 dd, 1 H, *J*(7,9) = 1.2, *J*(6,7) = 4.9 (H-7); 9.06 d, 1 H, *J*(6,7) = 4.9 (H-6); 9.34 s, 1 H (H-2).

Amino Substituted Fused Pyrimidinones **27**–**32**

Method A. A solution of compounds **17**–**19** or **20** in ethanol was mixed with cyclohexene (in excess) and commercial 10% Pd/C catalyst (catalyst–substrate ratio 1 : 2 to 1 : 5 by weight). The mixture was refluxed for 30–90 min. The reaction was followed by TLC (chloroform–methanol 5 : 1). The catalyst was removed by filtration of a warm mixture. The filtrate was evaporated *in vacuo* and the solid residue was recrystallized from an appropriate solvent.

3-Amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**27**)

This compound was prepared from 3-[(benzyloxycarbonyl)amino]-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one (**17**; 0.295 g, 1.0 mmol), 30 min reflux. Yield 85%; m.p. 176–179 °C (washed with methanol) (ref.[13]: 176–178 °C). For $C_8H_7N_3O$ (161.2) calculated: 59.62% C, 4.38% H, 26.07% N; found: 59.55% C, 4.46% H, 26.15% N. ^{1}H NMR ($CDCl_3$): 4.04 s, 2 H (NH_2); 7.01 ddd, 1 H, *J*(6,7) = 7.2, *J*(7,8) = 6.8, *J*(7,9) = 1.5 (H-7); 7.38 ddd, 1 H, *J*(6,8) = 1.5, *J*(7,8) = 6.8, *J*(8,9) = 9.0 (H-8); 7.52 dd, 1 H, *J*(7,9) = 1.5, *J*(8,9) = 9.0 (H-9); 8.01 s, 1 H (H-2); 8.88 dd, 1 H, *J*(6,7) = 7.2, *J*(6,8) = 1.5 (H-6).

3-Amino-8-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**28**)

This compound was prepared from 3-[(benzyloxycarbonyl)amino]-8-methyl-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one (**18**; 0.174 g, 0.7 mmol), 1.5 h reflux. Yield 92%; m.p. 223–225 °C (ethanol) (ref.[13]: 225–226 °C). For $C_9H_9N_3O$ (175.2) calculated: 61.70% C, 5.18% H, 23.99% N; found: 61.72% C, 5.25% H, 24.00% N. ^{1}H NMR ($CDCl_3$): 3.94 s, 2 H (NH_2); 6.84 dd, 1 H, *J*(6,7) = 7.4, *J*(7,9) = 1.7 (H-7); 7.28 d, 1 H, *J*(7,9) = 1.7 (H-9); 7.97 s, 1 H (H-2); 8.79 d, 1 H, *J*(6,7) = 7.4 (H-6).

3-Amino-9-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**29**)

This compound was prepared from 3-[(benzyloxycarbonyl)amino]-9-methyl-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one (**19**; 0.128 g, 0.4 mmol), 30 min reflux. Yield 89%; m.p. 183–185 °C (washed with methanol). For $C_9H_9N_3O$ (175.2) calculated: 61.70% C, 5.18% H, 23.99% N; found: 61.47% C, 5.45% H, 24.04% N. ^{1}H NMR ($(CD_3)_2SO$): 5.15 s, 2 H (NH_2); 7.02 dd, 1 H, *J*(6,7) = 7.2, *J*(7,8) = 6.8 (H-7); 7.34 d, 1 H, *J*(7,8) = 6.8 (H-8); 7.93 s, 1 H (H-2); 8.66 d, 1 H, *J*(6,7) = 7.2 (H-6).

3-Amino-9-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**30**)

This compound was prepared from 3-[(benzyloxycarbonyl)amino]-9-hydroxy-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one (**20**; 0.118 g, 0.4 mmol), 30 min reflux. Yield 89%; m.p. 206–209 °C (ethanol) (ref.[13]: 213–215 °C); MS: 177 (M^+). For $C_8H_7N_3O_2$ (177.2) calculated: 54.24% C, 3.98% H, 23.72% N; found: 53.55% C, 3.89% H, 24.07% N. ^{1}H NMR ($(CD_3)_2SO$): 5.19 s, 2 H (NH_2); 6.74 d, 1 H, *J*(7,8) = 7.5 (H-8); 6.98 dd, 1 H, *J*(6,7) = 7.2, *J*(7,8) = 7.5 (H-7); 7.89 s, 1 H (H-2); 8.28 d, 1 H, *J*(6,7) = 7.2 (H-6).

Method B. A mixture of *N*-(benzyloxycarbonyl)amine **22** or **25** (1 mmol) and a 33% solution of hydrogen bromide in acetic acid (5 ml) was stirred at 40 °C until evolution of carbon dioxide ceased (30 min). The products were purified by ion exchange chromatography in the following manner: the reaction mixture was diluted with 20 ml of water, poured on a stabilized column (Dowex® 50 W, 80 g), washed consecutively with water (500 ml), methanol (500 ml), and then the product was eluted with 2 M methanolic NH_3 (300 ml). Fractions containing the product were combined, solvent evaporated *in vacuo* and the solid residue recrystallized from an appropriate solvent.

3-Amino-4*H*-pyrimido[1,2-*b*]pyridazin-4-one (**31**)

This compound was prepared from 3-[(benzyloxycarbonyl)amino]-4*H*-pyrimido[1,2-*b*]-pyridazin-4-one (**22**; 0.306 g, 1 mmol). Yield 84%; m.p. 253–256 °C (ethanol–toluene). For $C_7H_6N_4O$ (162.2) calculated: 51.85% C, 3.73% H, 34.55% N; found: 51.73% C, 3.68% H, 34.35% N. ^{1}H NMR ($CDCl_3$): 5.60 s, 2 H (NH_2); 7.21 dd, 1 H, *J*(7,8) = 4.1, *J*(8,9) = 9.4 (H-8); 7.76 dd, 1 H, *J*(7,9) = 1.9, *J*(8,9) = 9.4 (H-9); 7.81 s, 1 H (H-2); 8.58 dd, 1 H, *J*(7,8) = 4.1, *J*(7,9) = 1.9 (H-7).

6-Amino-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**32**)

This compound was prepared from 6-[(benzyloxycarbonyl)amino]-5*H*-thiazolo[3,2-*a*]-pyrimidin-5-one (**25**; 0.301 g, 1 mmol). Yield 81%; m.p. 165–168 °C (ethanol–toluene) (ref.[18]: 169–172 °C). For $C_6H_5N_3OS$ (167.2) calculated: 43.11% C, 3.01% H, 25.13% N; found: 42.96% C, 2.92% H, 25.31% N. ^{1}H NMR ($CDCl_3$): 4.88 s, 2 H (NH_2); 7.43 d, 1 H, *J*(2,3) = 4.9 (H-2); 7.52 s, 1 H (H-7); 7.91 d, 1 H, *J*(2,3) = 4.9 (H-3).

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