

ETHYL 2-(2-ACETYL-2-ETHOXYCARBONYL-1-ETHENYL)AMINO-3-DIMETHYLAMINOPROPENOATE IN THE SYNTHESIS OF HETEROCYCLIC SYSTEMS. THE SYNTHESIS OF SUBSTITUTED 3-AMINOAZOLO- AND -AZINOPYRIMIDINONES, PYRIDOPYRIDINONES AND PYRANONES

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Abstract - Ethyl 2-(2-acetyl-2-ethoxycarbonyl-1-ethenyl)amino-3-dimethylaminopropenoate (**2**) was prepared from ethyl *N*-(2-acetyl-2-ethoxycarbonyl-1-ethenyl)glycinate (**1**) and *N,N*-dimethylformamide dimethyl acetal, and used as a reagent for preparation of substituted amino azolo- and azinopyrimidin-4-ones (**16-20**), quinolizin-4-ones (**31** and **32**), 2*H*-1-benzopyran-2-ones (**33**), and isomeric naphthopyranones (**34-37**), 2*H*-pyrano[2,1-*b*]pyridine-2,5-dione (**38**), pyrano[4,5-*b*]pyran-2,5-dione (**39**) and pyrano[3,2-*c*]bezopyran-2,5-dione (**40**).

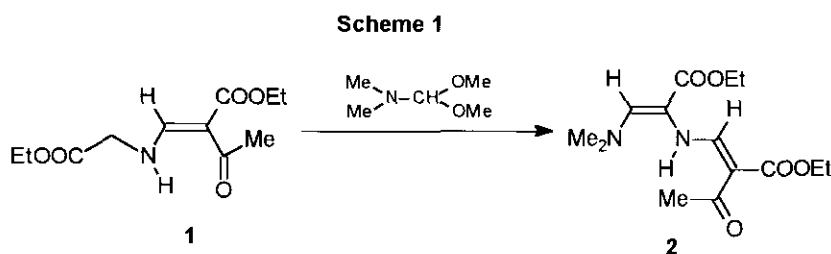
Substituted alkyl 2-acylamino-3-dimethylaminopropenoates and 2-(2,2-disubstituted ethenyl)amino-3-dimethylaminopropenoates as masked α -formyl- α -amino acid derivatives have been recently found to be versatile reagents in the synthesis of β -aryl-, β -heteroaryl-, β -arylamino-, and β -heteroarylamino- α -amino acids and their α,β -dehydro analogs.¹ They are intermediates in the synthesis of many heterocyclic systems, such as indolizines, quinolizines, pyranones, benzo- and isomeric naphthopyranones, pyranopyrimidines, azolopyrimidines and azinopyrimidines.¹

Recently, alkyl 2-(2,2-disubstituted ethenyl)amino-3-dimethylaminopropenoates, such as ethyl (*Z*)-2-[2,2-bis(ethoxycarbonyl)ethenyl]amino-3-dimethylaminopropenoate,²⁻⁴ alkyl 2-(2-benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-dimethylaminopropenoate,⁵ and methyl 2-[2,2-bis(acetyl)ethenyl]amino-3-dimethyl-

aminopropenoate⁶ have been used as reagents for preparation of various heterocyclic systems with 2,2-disubstituted 1-ethenylamino group at position 3 of a newly formed pyrimidinone^{2, 6-9} or pyridinone ring^{3,6}. Furthermore, 2,2-disubstituted 1-ethenyl groups can be applied as *N*-protecting groups in the synthesis of dehydropeptide derivatives containing *N*-terminal 3-heteroaryl-amino-2,3-dehydroalanine structural element, since they can be easily removed with hydrazine or hydroxylamine under mild conditions,¹⁰ and recently, for the synthesis of 3-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones¹¹. This latter method has been shown to be superior to the previously described methods.^{12, 13}

In this paper, we present, as an extension of our research in this area, the synthesis of ethyl 2-(2-acetyl-2-ethoxycarbonyl-1-ethenyl)amino-3-dimethylaminopropenoate (**2**) and its application for the synthesis of fused 3-amino substituted pyridinones, pyrimidinones and pyranones.

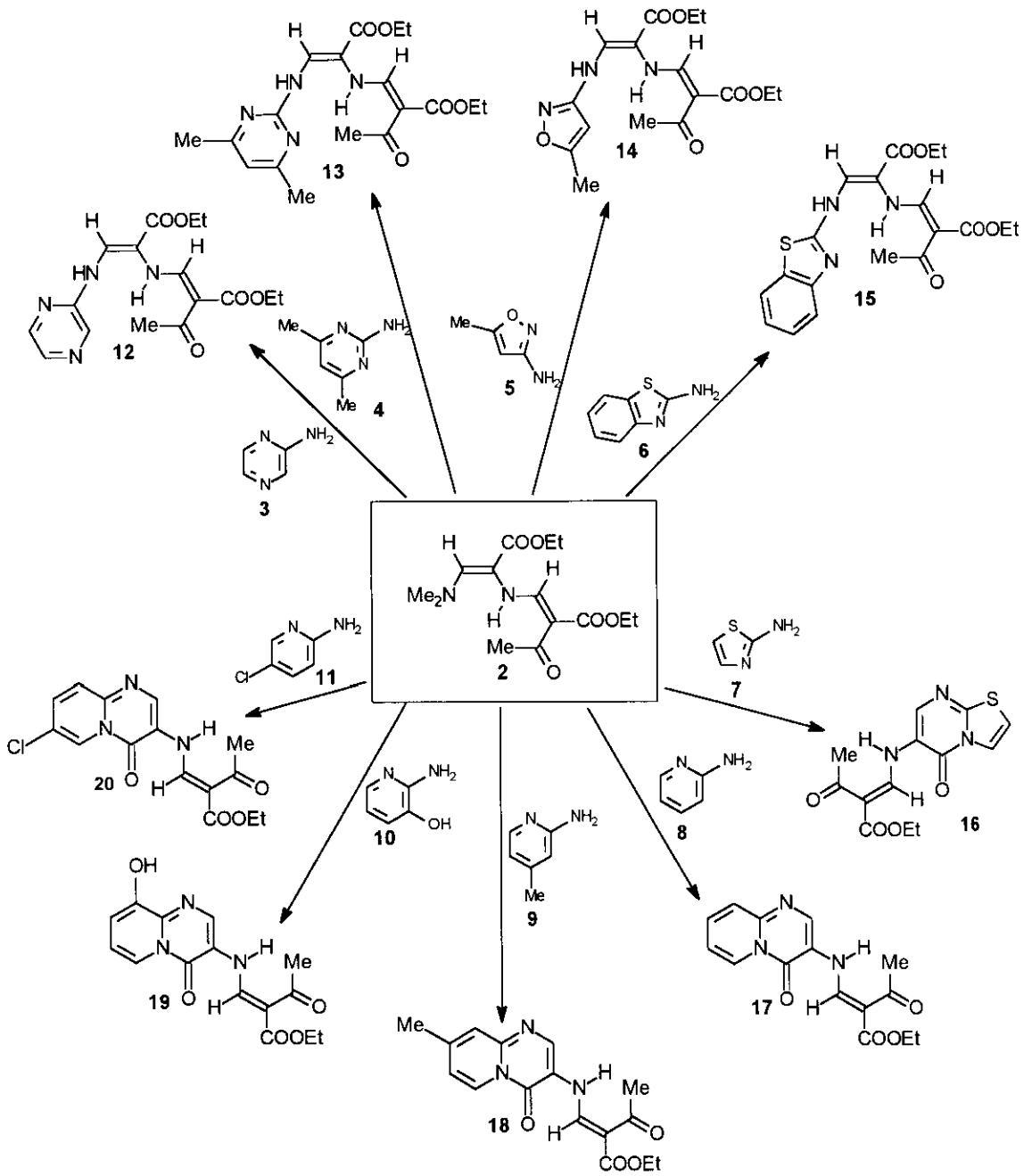
Compound (**2**) was prepared from ethyl *N*-(2-acetyl-2-ethoxycarbonyl-2-ethoxycarbonyl-1-ethenyl)-glycinate (**1**) obtained from ethyl glycinate and ethyl 2-acetyl-3-dimethylaminopropenoate¹⁰ by treatment with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) in 67% yield. (Scheme 1).



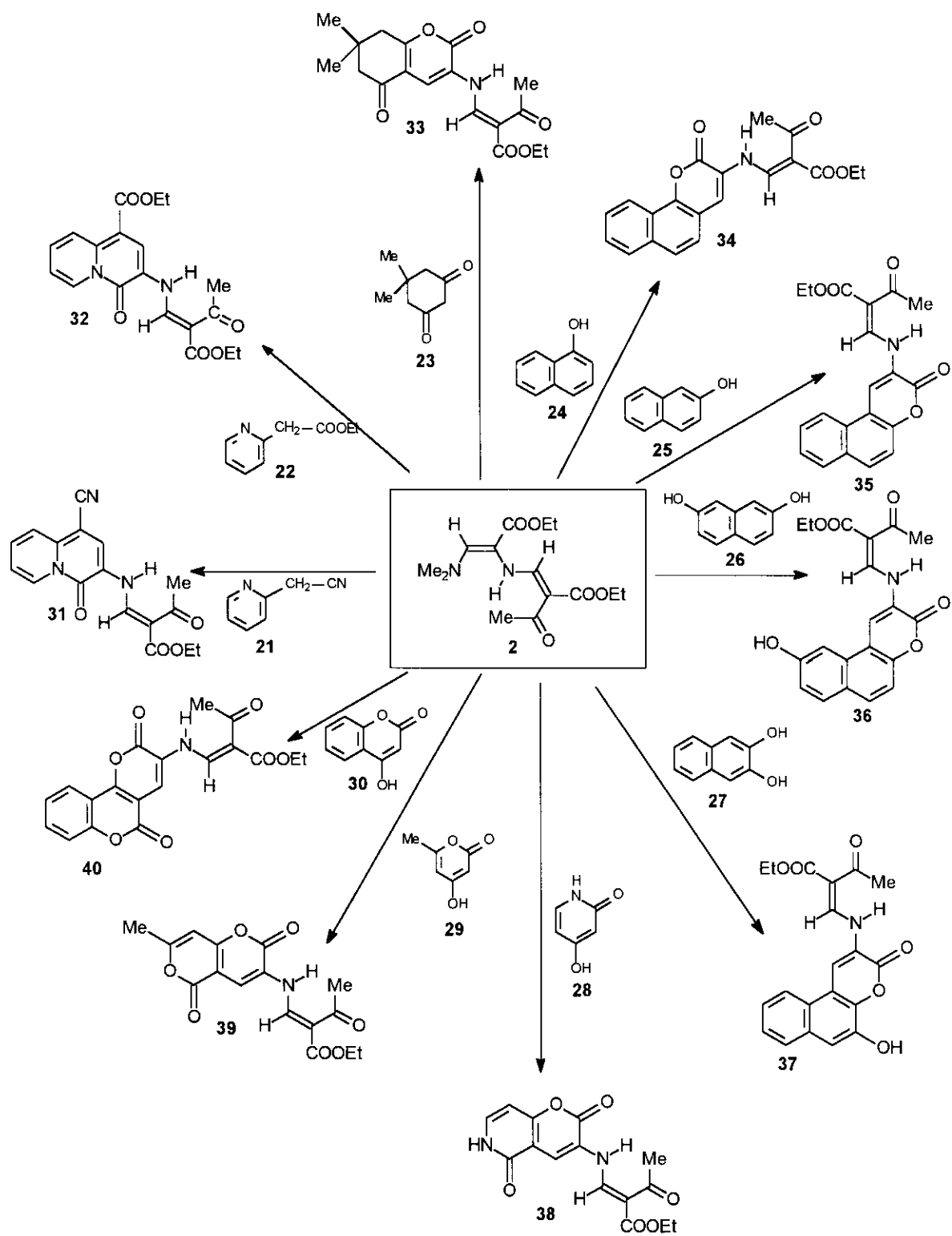
Compound (**2**) reacts with *N*- and *C*-nucleophiles in which *N,N*-dimethylamino group is substituted. The first group of amino heterocycles, such as 2-aminopyrazine (**3**), 2-amino-4,6-dimethylaminopyrimidine (**4**), 3-amino-5-methylisoxazole (**5**), and 2-aminobenzothiazole (**6**), gave by heating in acetic acid the corresponding ethyl 2-(2-acetyl-2-ethoxycarbonyl-1-ethenyl)amino-3-heteroarylaminopropenoates **12-15**. On the other hand, 2-aminothiazole (**7**), 2-aminopyridine (**8**) and its 4-methyl- (**9**), 3-hydroxy- (**10**), and 5-chloro- (**11**) derivatives afforded under analogous conditions 6-(2-acetyl-2-ethoxycarbonyl-1-ethenyl)amino-5*H*-thiazolo[2,3-*b*]pyrimidin-4-one (**16**), 3-(2-acetyl-2-ethoxycarbonyl-1-ethenyl)amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**17**), and its 8-methyl- (**18**), 9-hydroxy- (**19**), and 7-chloro- (**20**) derivatives. (Scheme 2).

Compound (**2**) reacts also with several types of *C*-nucleophiles. 2-Pyridylacetonitrile (**21**) and ethyl 2-pyridylacetate (**22**) by heating in acetic acid 3-(2-acetyl-2-ethoxycarbonyl-1-ethenyl)amino-4*H*-quinolizin-4-one (**31**) and its 1-ethoxycarbonyl- derivative (**32**). 5,5-Dimethylcyclohexane-1,3-dione (**23**), yielded 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one derivative (**33**), 1-naphthol (**24**) was transformed into 2*H*-naphtho[1,2-*b*]pyran-2-one derivative (**34**), while 2-naphthol (**25**), 2,7-dihydroxynaphthalene (**27**)

Scheme 2



Scheme 3

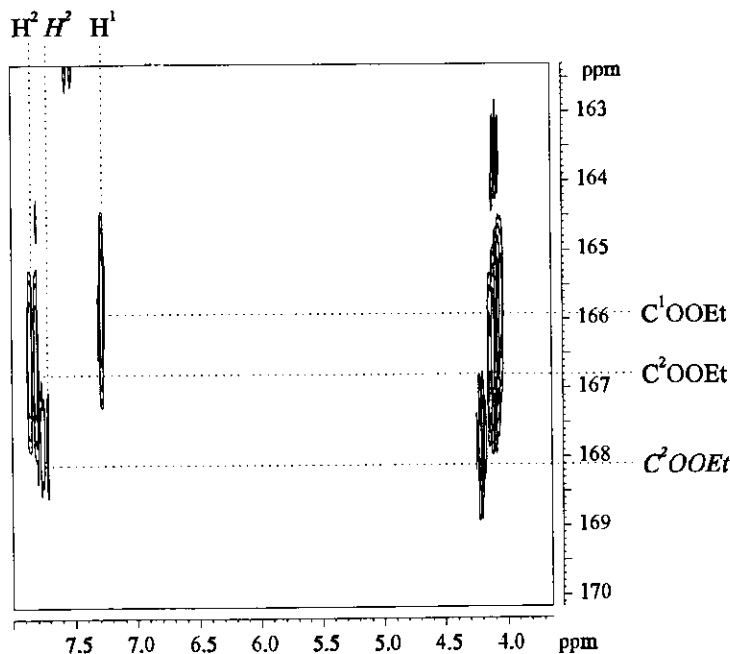


afforded derivatives of 3*H*-naphtho[2,1-*b*]pyran-3-one (**35-37**). 4-Hydroxypyridin-2(1*H*)-one (**28**) gave 2*H*-pyrano[2,1-*b*]pyridine-2,5-dione derivative (**38**), while 4-hydroxy-6-methylpyran-2-one (**29**) and 4-hydroxybenzopyran-2-one (**30**) produced 2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione (**39**) and 2*H*,5*H*-pyrano[3,2-*c*]benzopyran-2,5-dione (**40**) derivatives, respectively. (Scheme 3).

The structures of all new compounds were determined by ¹H NMR spectral characteristics and elemental analysis. The structure of compound (**2**) was determined by ¹H NMR spectra. Namely, the compound dissolved in CDCl₃ showed in ¹H NMR spectrum two sets of signals in a ratio 40 : 10, which indicates an equilibrium between two isomers. The magnitude of coupling constant $J_{\text{CHNH}} = 13.6$ Hz strongly suggests the trans (antiperiplanar) orientation of both hydrogens in respect to each other. The final proof structures was obtained by NOESY experiments in DMSO solution showing H-C₃-C₂-¹³C₁-coupling constant $^3J_{13\text{C,H}} = 3.3$ Hz, and H-C₁-C₂-¹³C₃-coupling constant $^3J_{13\text{C,H}} = 3.7$ Hz for (**2a**), and $^3J_{13\text{C,H}} = 3.3$ Hz and $^3J_{13\text{C,H}} = 9.8$ Hz for (**2b**), respectively, in ratio 90:10. The orientation in (**2a**) is therefor (*Z*, *E*), while the orientation in (**2b**) is (*Z*, *Z*). (Scheme 4, Figure 1).

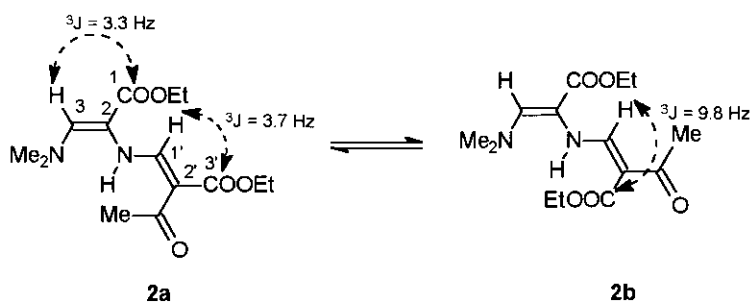
The orientation around the double bond of the group at position 3 in the pyrimidine ring of compound (**33**) was established on the basis of NOE experiment showing that the compound (**17**) exists in DMSO-*d*₆ solution in equilibrium of (**17a**) and (**17b**) in a ratio 10 : 1.4, while the compound (**33**) in equilibrium of (**33a**) and (**33b**) in a ratio of 10 : 1.5. (Scheme 4).

Figure 1

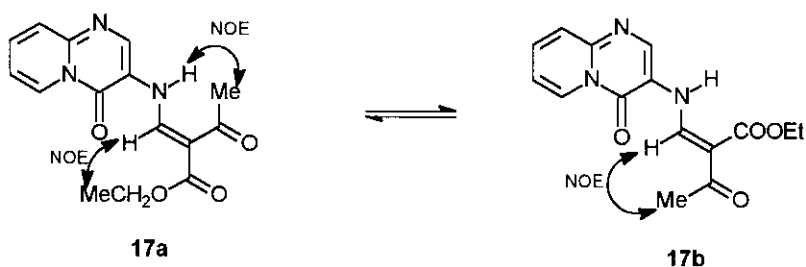


Carbonyl part of the HMBC spectrum in DMSO-*d*₆ with traces containing $^3J(\text{CO},\text{H})$ couplings. The cross peaks of the minor conformer are indicated in italics.

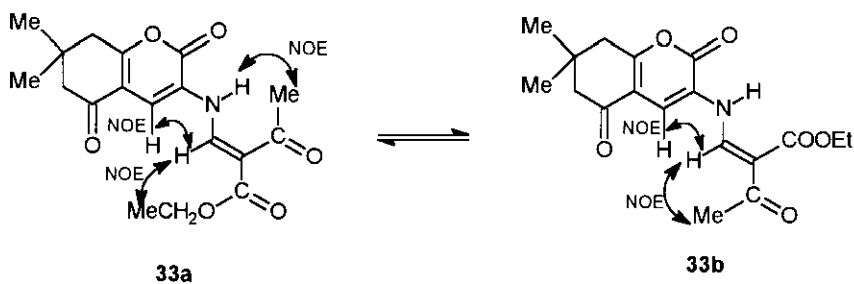
Scheme 4



2a : 2b = 90 : 10



17a : 17b = 10 : 1.4



33a : 33b = 10 : 1.5

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^1H NMR spectra were obtained on Bruker Advance DPX 300 spectrometer with TMS as the internal standard, IR spectra on Perkin-Elmer 1310 instrument and microanalyses for C, H and N on Perkin-Elmer Analyzer 2400.

Ethyl *N*-(2-acetyl-2-ethoxycarbonyl-1-ethenyl)glycinate (**1**) was prepared according to the procedure described in the literature.¹⁰

The Synthesis of Ethyl 2-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-3-dimethylaminopropenoate (2). To a solution of ethyl *N*-(2-acetyl-2-ethoxycarbonyl-1-ethenyl)glycinate (**1**) (3.610 g, 15 mmol) in acetonitrile (20 mL) *N,N*-dimethylformamide dimethyl acetal (7.5 mL, 50 mmol) was added and the mixture was heated in an oil bath at reflux temperature for 1.5 hour. The reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and ethyl acetate/heptane, 2:1 as solvent). After reaction was completed, the volatile components were evaporated *in vacuo*. To the oily residue ether was added and after cooling the solid product was collected by filtration and recrystallized from diisopropyl ether to give **2**. Yield: 2.995 g (67 %), mp 83-87°; ¹H NMR (deuteriochloroform): δ 1.25, 1.29 and 1.30 (3t, *J* = 7.1 Hz, 2 x COOCH₂CH₃, *Z,E* and *Z,Z*), 2.50 (s, COCH₃), 3.02 (s, N(CH₃)₂), 4.17 and 4.19 (2q, *J* = 7.1 Hz, 2 x COOCH₂CH₃), 7.24 (s, *Z,E*-CHN(CH₃)₂), 7.25 (s, *Z,Z*-CHN(CH₃)₂), 7.96 (d, *J* = 13.6 Hz, *Z,E*-CHNH), 7.93, (d, *J* = 13.2 Hz, *Z,Z*-CHNH), 11.64 (d, *J* = 13.6 Hz, *Z,E*-CHNH), ratio (*Z, E*)-form : (*Z, Z*)-form = 80 : 20. *Anal.* Calcd for C₁₄H₂₂N₂O₅: C, 56.36; H, 7.43; N, 9.39. Found: C, 56.74; H, 7.48; N, 9.53.

The Reaction between Heterocyclic Amines (3-11) and Ethyl 2-[2-Acetyl-2-ethoxycarbonyl-1-ethenyl]amino-3-dimethylaminopropenoate (2). The Synthesis of Ethyl 2-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-3-heteroarylaminopropenoate (12-15) and Ethyl 2-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)aminoazolo- and -azinopyrimidines (16-20).

General Procedure : To a solution of a heterocyclic amine (1.5 mmol) in acetic acid (5 mL) compound (**2**) (1.5 mmol) was added and the mixture was heated under reflux for several hours. The reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and chloroform/methanol, 25:1 as solvent). After reaction was completed, acetic acid was evaporated *in vacuo* and the solid residue was recrystallized from an appropriate solvent. The following compounds were prepared in this manner:

Ethyl 2-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-3-(pyrazinyl-2)aminopropenoate (12). This compound was prepared from 2-aminopyrazine (**3**) (0.143 g), 2 hours of reflux. Yield: 0.172 g (33 %), mp 165-167° (from toluene); ¹H NMR (DMSO-d₆): δ 1.21, 1.25 and 1.29 (3t, *J* = 7.1 Hz, 2 x COOCH₂CH₃, *Z,E* and *Z,Z*), 2.43 (s, *Z,E*-Me), 2.34 (s, *Z,Z*-Me), 4.12, 4.20 and 4.26 (3q, *J* = 7.1 Hz, 2 x COOCH₂CH₃, *Z,E* and *Z,Z*), 7.98 (d, *J* = 13.4 Hz, *Z,E*-CHNH), 7.89 (d, *J* = 14.4 Hz, *Z,Z*-CHNH), 8.20 (d, *J* = 2.6 Hz, H₆), 8.36 (dd, *J* = 2.6 and 1.4 Hz, H₅), 8.40 (br s, *Z,E*-CHNHHet), 7.89 (br s, *Z,Z*-CHNHHet), 8.46 (d, *J* = 1.4 Hz, H₃), 10.26 (br s, CHNHHet), 11.46 (d, *J* = 13.4 Hz, *Z,E*-CHNH), 9.64 (d, *J* = 14.4 Hz, *Z,Z*-CHNH), ratio (*Z, E*)-form : (*Z, Z*)-form = 95 : 5. *Anal.* Calcd for C₁₆H₂₀N₄O₅: C, 55.17; H, 5.79; N, 16.08. Found: C, 55.06; H, 5.79; N, 16.03.

Ethyl 2-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-3-(4,6-dimethylpyrimidinyl-2)aminopropenoate (13). This compound was prepared from 2-amino-4,6-dimethylpyrimidine (**4**) (0.185 g), 2.5 hours of reflux. Yield: 0.079 g (14 %), mp 115-117° (from a mixture of n-heptane and ethyl acetate); ¹H NMR (DMSO-d₆): δ 1.24 and 1.29 (2t, *J*=7.1 Hz, 2 x COOCH₂CH₃), 2.36 (s, 2 x Het-CH₃), 2.39 (s, *Z,E*-Me), 2.35 (s, *Z,Z*-Me), 4.14 and 4.29 (2q, *J*=7.1 Hz, 2 x COOCH₂CH₃), 6.90 (s, *Z,E*-H₅), 6.85 (s, *Z,Z*-H₅), 8.07 (d, *J* = 13.1 Hz, *Z,E*-CHNH), 8.02 (d, *J* = 13.5 Hz, *Z,Z*-CHNH), 8.10 (d, *J* = 11.9 Hz, CHNHHet), 9.78 (d, *J* = 11.9 Hz, *Z,E*-CHNHHet), 11.42 (br d, *J* = 11.9 Hz, *Z,Z*-CHNHHet), 12.05 (d, *J* = 13.1 Hz, *Z,E*-CHNH), 10.14 (d, *J* = 13.5 Hz, *Z,Z*-CHNH), ratio (*Z, E*)-form : (*Z, Z*)-form = 92 : 8. *Anal.* Calcd for C₁₈H₂₄N₄O₅: C, 57.44; H, 6.43; N, 14.88. Found: C, 57.32; H, 6.45; N, 14.77.

Ethyl 2-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-3-(5-methylisoxazolyl-3)aminopropenoate (14).

This compound was prepared from 3-amino-5-methylisoxazole (**5**) (0.147 g), 2 hours of reflux. Yield: 0.237 g (45 %), mp 125-128° (from toluene); ¹H NMR (DMSO-d₆): δ 1.23, 1.27 and 1.29 (3t, *J*=7.0 Hz, 2 x COOCH₂CH₃, *Z,E* and *Z,Z*), 2.35 (s, *Z,E*-Het-CH₃), 2.40 (s, *Z,Z*-Het-CH₃), 2.37 (s, *Z,E*-Me), 2.34 (s, *Z,Z*-Me), 4.12, 4.16 and 4.26 (3q, *J*=7.0 Hz, 2 x COOCH₂CH₃, *Z,E* and *Z,Z*), 6.40 (s, *Z,E*-H₄), 6.06 (s, *Z,Z*-H₄), 7.65 (d, *J* = 12.3 Hz, *Z,E*-CHNHHet), 7.62 (d, *J* = 13.3 Hz, *Z,Z*-CHNHHet), 8.02 (d, *J* = 13.1 Hz, *Z,E*-CHNH), 8.00 (d, *J* = 14.3 Hz, *Z,Z*-CHNH), 9.68 (d, *J* = 12.3 Hz, *Z,E*-CHNHHet), 11.39 (d, *J* = 13.3 Hz, *Z,Z*-CHNHHet), 12.03 (d, *J* = 13.1 Hz, *Z,E*-CHNH), 10.07 (d, *J* = 14.3 Hz, *Z,Z*-CHNH), ratio (*Z, E*)-form : (*Z, Z*)-form = 72 : 28. *Anal.* Calcd for C₁₆H₂₁N₃O₆: C, 54.70; H, 6.02; N, 11.96. Found: C, 54.30; H, 5.96; N, 11.99.

Ethyl 2-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-3-(benzothiazolyl-2)aminopropenoate (15).

This compound was prepared from 2-aminobenzothiazole (**6**) (0.225 g), 2 hours of reflux. Yield: 0.048 g (8 %), mp 153-155° (from ethanol); ¹H NMR (DMSO-d₆): δ 1.25 and 1.31 (2t, *J*=7.1 Hz, 2 x COOCH₂CH₃), 2.40 (s, *Z,E*-Me), 2.35 (s, *Z,Z*-Me), 4.15, 4.24 and 4.32 (3q, *J*=7.1 Hz, 2 x COOCH₂CH₃, *Z,E* and *Z,Z*), 7.24 (ddd, *J* = 8.1, 7.8 and 1.1 Hz, H₆), 7.40 (ddd, *J* = 7.8, 8.1 and 1.3 Hz, H₅), 7.68 (dd, *J* = 7.8 and 1.3 Hz, H₇), 7.91 (dd, *J* = 7.8 and 1.1 Hz, H₄), 8.00 (br s, *Z,E*-CHNHHet), 8.10 (br s, *Z,Z*-CHNHHet), 8.13 (d, *J* = 13.1 Hz, *Z,E*-CHNH), 10.84 (br s, CHNHHet), 12.14 (d, *J* = 13.1 Hz, *Z,E*-CHNH), 10.24 (d, *J* = 14.1 Hz, *Z,Z*-CHNH), ratio (*Z, E*)-form : (*Z, Z*)-form = 88 : 12. *Anal.* Calcd for C₁₉H₂₁N₃O₅S: C, 56.56; H, 5.25; N, 10.42. Found: C, 56.23; H, 5.08; N, 10.45.

6-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-5H-thiazolo[3,2-*a*]pyrimidin-5-one (16). This compound was prepared from 2-aminothiazole (**7**) (0.150 g), 1.5 hour of reflux. Yield: 0.120 g (29 %), mp

184-188° (from toluene); $^1\text{H NMR}$ (DMSO- d_6): δ 1.28 (t, $J = 7.1$ Hz, $E\text{-COOCH}_2\text{CH}_3$), 1.33 (t, $J = 7.1$ Hz, $Z\text{-COOCH}_2\text{CH}_3$), 2.42 (s, $E\text{-Me}$), 2.37 (s, $Z\text{-Me}$), 4.17 (q, $J = 7.1$ Hz, $E\text{-COOCH}_2\text{CH}_3$), 4.27 (q, $J = 7.1$ Hz, $Z\text{-COOCH}_2\text{CH}_3$), 7.66 (d, $J = 4.9$ Hz, $E\text{-H}_7$), 7.65, (d, $J = 4.9$ Hz, $Z\text{-H}_7$), 8.13 (d, $J = 4.9$ Hz, $E\text{-H}_6$), 8.11, (d, $J = 4.9$ Hz, $Z\text{-H}_6$), 8.48 (s, $E\text{-H}_2$), 8.45, (s, $Z\text{-H}_2$), 8.64 (d, $J = 13.4$ Hz, $E\text{-CHNH}$), 8.56 (d, $J = 14.3$ Hz, $Z\text{-CHNH}$), 12.49 (d, $J = 13.4$ Hz, $E\text{-CHNH}$), 10.71 (d, $J = 14.3$ Hz, $Z\text{-CHNH}$), ratio (E)-form : (Z)-form = 87 : 13. *Anal.* Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_4\text{S}$: C, 50.81; H, 4.26; N, 13.67. Found: C, 50.92; H, 4.11; N, 13.56.

3-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-4H-pyrido[1,2-a]pyrimidin-4-one (17). This compound was prepared from 2-aminopyridine (**8**) (1.41 g), 2 hours of reflux. Yield: 0.154 g (34 %), mp 153-155° (from ethanol); $^1\text{H NMR}$ (DMSO- d_6): δ 1.29 (t, $J = 7.1$ Hz, $E\text{-COOCH}_2\text{CH}_3$), 1.34 (t, $J = 7.1$ Hz, $Z\text{-COOCH}_2\text{CH}_3$), 2.44 (s, $E\text{-Me}$), 2.39, (s, $Z\text{-Me}$), 4.19 (q, $J = 7.1$ Hz, $E\text{-COOCH}_2\text{CH}_3$), 4.29 (q, $J = 7.1$ Hz, $Z\text{-COOCH}_2\text{CH}_3$), 7.41 (ddd, $J = 7.3$, 6.7 and 1.4 Hz, H_7), 7.76 (ddd, $J = 9.1$, 1.4 and 0.8 Hz, H_9), 7.91 (ddd, $J = 6.7$, 9.1 and 1.6 Hz, H_8), 8.79 (s, $E\text{-H}_2$), 8.77 (s, $Z\text{-H}_2$), 8.75 (d, $J = 13.6$ Hz, $E\text{-CHNH}$), 8.68 (d, $J = 14.7$ Hz, $Z\text{-CHNH}$), 8.89 (ddd, $J = 7.3$, 1.6 and 0.8 Hz, H_6), 12.66 (d, $J = 13.6$ Hz, $E\text{-CHNH}$), 10.90, (d, $J = 14.7$ Hz, $Z\text{-CHNH}$), ratio (E)-form : (Z)-form = 88 : 12. *Anal.* Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_4$: C, 59.80; H, 5.02; N, 13.95. Found: C, 59.90; H, 4.86; N, 14.10.

3-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-8-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (18). This compound was prepared from 2-amino-4-methylpyridine (**9**) (0.162 g), 2.5 hours of reflux. Yield: 0.331 g (70 %), mp 188-189° (from ethanol); $^1\text{H NMR}$ (DMSO- d_6): δ 1.29 (t, $J = 7.2$ Hz, $E\text{-COOCH}_2\text{CH}_3$), 1.34 (t, $J = 7.2$ Hz, $Z\text{-COOCH}_2\text{CH}_3$), 2.44 (s, $E\text{-Me}$), 2.39 (s, $Z\text{-Me}$), 2.47 (s, Het-CH_3), 4.18 (q, $J = 7.2$ Hz, $E\text{-COOCH}_2\text{CH}_3$), 4.28 (q, $J = 7.2$ Hz, $Z\text{-COOCH}_2\text{CH}_3$), 7.28 (dd, $J = 7.5$ and 1.9 Hz, $E\text{-H}_7$), 7.27, (dd, $J = 7.5$ and 1.9 Hz, $Z\text{-H}_7$), 7.59 (d, $J = 1.9$ Hz, H_9), 8.73 (s, $E\text{-H}_2$), 8.70 (s, $Z\text{-H}_2$), 8.73 (d, $J = 13.6$ Hz, $E\text{-CHNH}$), 8.66, (d, $J = 14.7$ Hz, $Z\text{-CHNH}$), 8.89 (d, $J = 7.5$ Hz, $E\text{-H}_6$), 8.86 (d, $J = 7.5$ Hz, $Z\text{-H}_6$), 12.65 (d, $J = 13.6$ Hz, $E\text{-CHNH}$), 10.87, (d, $J = 14.7$ Hz, $Z\text{-CHNH}$), ratio (E)-form : (Z)-form = 88 : 12. *Anal.* Calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.65; H, 5.21; N, 13.49.

3-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one (19). This compound was prepared from 2-amino-3-hydroxypyridine (**10**) (0.165 g), 3 hours of reflux. Yield: 0.149 g (32 %), mp 209-211° (from i-propanol); $^1\text{H NMR}$ (DMSO- d_6): δ 1.29 (t, $J = 7.1$ Hz, $E\text{-COOCH}_2\text{CH}_3$), 1.34 (t, $J = 7.1$ Hz, $Z\text{-COOCH}_2\text{CH}_3$), 2.44 (s, $E\text{-Me}$), 2.39 (s, $Z\text{-Me}$), 4.19 (q, $J = 7.1$ Hz, $E\text{-COOCH}_2\text{CH}_3$), 4.29 (q, $J = 7.1$ Hz, $Z\text{-COOCH}_2\text{CH}_3$), 7.19 (dd $J = 7.7$ and 1.2 Hz, H_8), 7.28 (dd, $J =$

7.1 and 7.7 Hz, H₇), 8.51 (dd, $J = 7.1$ and 1.2 Hz, H₆), 8.73 (s, *E*-H₂), 8.71 (s, *Z*-H₂), 8.75 (d, $J = 13.5$ Hz, *E*-CHNH), 8.68, (d, $J = 14.5$ Hz, *Z*-CHNH), 12.65 (d, $J = 13.5$ Hz, *E*-CHNH), 10.92, (d, $J = 14.5$ Hz, *Z*-CHNH), ratio (*E*)-form : (*Z*)-form = 86 : 14. *Anal.* Calcd for C₁₅H₁₅N₃O₅: C, 56.78; H, 4.76; N, 13.24. Found: C, 57.07; H, 4.68; N, 13.01.

3-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-7-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (20). This compound was prepared from 2-amino-5-chloropyridine (**11**) (0.192 g), 2.5 hours of reflux. Yield: 0.252 g (50 %), mp 206-209° (from a mixture of ethanol and toluene); ¹H NMR (DMSO-*d*₆): δ 1.29 (t, $J = 7.2$ Hz, *E*-COOCH₂CH₃), 1.34 (t, $J = 7.2$ Hz, *Z*-COOCH₂CH₃), 2.44 (s, *E*-Me), 2.39 (s, *Z*-Me), 4.19 (q, $J = 7.2$ Hz, *E*-COOCH₂CH₃), 4.29 (q, $J = 7.2$ Hz, *Z*-COOCH₂CH₃), 7.79 (dd, $J = 9.0$ and 0.8 Hz, *E*-H₉), 7.77 (dd, $J = 9.0$ and 0.8 Hz, *Z*-H₉), 7.94 (dd, $J = 9.0$ and 2.3 Hz, H₈), 8.74 (d, $J = 13.6$ Hz, *E*-CHNH), 8.67 (d, $J = 12.4$ Hz, *Z*-CHNH), 8.81 (s, *E*-H₂), 8.78, (s, *Z*-H₂), 8.89 (dd, $J = 2.3$ and 0.8 Hz, *E*-H₆), 8.86, (dd, $J = 2.3$ and 0.8 Hz, *Z*-H₆), 12.65 (d, $J = 13.6$ Hz, *E*-CHNH), 10.87 (d, $J = 12.4$ Hz, *Z*-CHNH), ratio (*E*)-form : (*Z*)-form = 87 : 13. *Anal.* Calcd for C₁₅H₁₄N₃O₄Cl: C, 53.66; H, 4.20; N, 12.52. Found: C, 53.27; H, 3.96; N, 12.26.

The Synthesis of 4*H*-Quinolizin-4-one Derivatives (**31**, **32**) and Fused 2*H*-Pyran-2-ones (**34-40**).

General Procedure : To a solution of a compound with an active methylene group (1.5 mmol) in the acetic acid (5 mL) the compound (**2**) (1.5 mmol) was added and the mixture was heated under reflux for several hours. The reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and chloroform/methanol, 25:1 as solvent). After reaction was completed, acetic acid was evaporated *in vacuo* and the solid residue was recrystallized from an appropriate solvent. The following compounds were prepared in this manner:

3-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-1-cyano-4*H*-quinolizin-4-one (31). This compound was prepared from 2-pyridylacetonitrile (**21**) (0.177 g), 0.5 hour of reflux. Yield: 0.298 g (61 %), mp 233-235° (from a mixture of ethanol and toluene); ¹H NMR (DMSO-*d*₆): δ 1.31 (t, $J = 7.1$ Hz, *E*-COOCH₂CH₃), 1.34 (t, $J = 7.1$ Hz, *Z*-COOCH₂CH₃), 2.45 (s, *E*-Me), 2.41 (s, *Z*-Me), 4.21 (q, $J = 7.1$ Hz, *E*-COOCH₂CH₃), 4.29 (q, $J = 7.1$ Hz, *Z*-COOCH₂CH₃), 7.48 (ddd, $J = 7.3$, 7.0 and 1.4 Hz, H₇), 7.88 (ddd, $J = 7.0$, 8.7 and 1.2 Hz, H₈), 7.98 (dd, $J = 8.7$ and 1.4 Hz, *E*-H₉), 7.96, (dd, $J = 8.7$ and 1.4 Hz, *Z*-H₉), 8.66 (d, $J = 13.4$ Hz, *E*-CHNH), 8.63, (d, $J = 14.0$ Hz, *Z*-CHNH), 8.65 (s, *E*-H₂), 8.61, (s, *Z*-H₂), 9.13 (dd, $J = 7.3$ and 1.2 Hz, *E*-H₆), 9.10 (dd, $J = 7.3$ and 1.2 Hz, *Z*-H₆), 12.84 (d, $J = 13.4$ Hz, *E*-CHNH), 11.12 (d, $J = 14.0$ Hz, *Z*-CHNH), ratio (*E*)-form : (*Z*)-form = 86 : 14. *Anal.* Calcd for

$C_{17}H_{15}N_3O_4$: C, 62.76; H, 4.65; N, 12.92. Found: C, 63.04; H, 4.53; N, 12.85.

3-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-1-ethoxycarbonyl-4H-quinolizin-4-one (32). This compound was prepared from ethyl 2-pyridylacetate (**22**) (0.248 g), 3.5 hours of reflux. Yield: 0.073 g (13 %), mp 158-160° (from a mixture of ethanol and water); 1H NMR (DMSO- d_6): δ 1.31 and 1.38 (2t, $J = 7.1$ Hz, 2 x $COOCH_2CH_3$), 2.45 (s, E -Me), 2.41 (s, Z -Me), 4.20 and 4.37 (2q, $J = 7.1$ Hz, 2 x $COOCH_2CH_3$), 7.47 (ddd, $J = 7.3, 6.7$ and 1.3 Hz, E -H₇), 7.45 (ddd, $J = 7.3, 6.7$ and 1.3 Hz, Z -H₇), 7.85 (ddd, $J = 6.7, 9.3$ and 1.3 Hz, E -H₈), 7.82 (ddd, $J = 6.7, 9.3$ and 1.3 Hz, Z -H₈), 8.46 (s, E -H₂), 8.42 (s, Z -H₂), 8.64 (d, $J = 13.6$ Hz, E -CHNH), 8.59 (d, $J = 14.6$ Hz, Z -CHNH), 9.06 (dd, $J = 9.3$ and 1.3 Hz, H₉), 9.18 (dd, $J = 7.3$ and 1.3 Hz, E -H₆), 9.16 (dd, $J = 7.3$ and 1.3 Hz, Z -H₆), 12.75 (d, $J = 13.6$ Hz, E -CHNH), 11.08 (d, $J = 14.6$ Hz, Z -CHNH), ratio (E)-form : (Z)-form = 88 : 12. *Anal.* Calcd for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.05; H, 5.45; N, 7.73.

3-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-2H-1-benzopyran-2-one (33). This compound was prepared from 5,5-dimethylcyclohexane-1,3-dione (**23**) (0.210 g), 2.5 hours of reflux. Yield: 0.271 g (52 %), mp 163-165° (from a mixture of ethanol and water); 1H NMR (DMSO- d_6): δ 1.07 (s, 7,7- CH_3), 1.28 (t, $J = 7.1$ Hz, E - $COOCH_2CH_3$), 1.31 (t, $J = 7.1$ Hz, Z - $COOCH_2CH_3$), 2.43 (s, E -Me), 2.39 (s, Z -Me), 2.45 and 2.81 (2s, 6- CH_2 , 8- CH_2), 4.19 (q, $J = 7.1$ Hz, E - $COOCH_2CH_3$), 4.27 (q, $J = 7.1$ Hz, Z - $COOCH_2CH_3$), 7.78 (s, E -H₄), 7.71 (s, Z -H₄), 8.47 (d, $J = 13.1$ Hz, E -CHNH), 8.41 (d, $J = 14.9$ Hz, Z -CHNH), 12.33 (d, $J = 13.1$ Hz, E -CHNH), 10.62 (d, $J = 14.9$ Hz, Z -CHNH), ratio (E)-form : (Z)-form = 87 : 13. *Anal.* Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.23; H, 6.12; N, 4.00.

3-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-2H-naphtho[1,2-*b*]pyran-2-one (34). This compound was prepared from 1-naphthol (**25**) (0.216 g), 2 hours of reflux. Yield: 0.022 g (4 %), mp 181-183° (from a mixture of ethanol and toluene); 1H NMR (DMSO- d_6): δ 1.33 (t, $J = 7.0$ Hz, E - $COOCH_2CH_3$), 1.40 (t, $J = 7.0$ Hz, Z - $COOCH_2CH_3$), 2.47 (s, E -Me), 2.43 (s, Z -Me), 4.24 (q, $J = 7.0$ Hz, E - $COOCH_2CH_3$), 4.31 (q, $J = 7.0$ Hz, Z - $COOCH_2CH_3$), 7.66-7.76 (m, H₈, H₉), 7.75 (d, $J = 8.5$ Hz, H₆), 7.89 (d, $J = 8.5$ Hz, H₅), 8.04 (dd, $J = 6.3$ and 1.7 Hz, H₇), 8.33 (dd, $J = 9.5$ and 2.4 Hz, H₁₀), 8.34 (s, H₄), 8.57 (d, $J = 13.1$ Hz, E -CHNH), 8.53 (d, $J = 13.8$ Hz, Z -CHNH), 12.53 (d, $J = 13.1$ Hz, E -CHNH), 10.88 (d, $J = 13.8$ Hz, Z -CHNH), ratio (E)-form : (Z)-form = 82 : 18. *Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.43; H, 4.85; N, 3.97.

2-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-3H-naphtho[2,1-b]pyran-3-one (35). This compound was prepared from 2-naphthol (**25**) (0.216 g), 3.5 hours of reflux. Yield: 0.022 g (4 %), mp 215-217° (from a mixture of ethanol and toluene); ¹H NMR (DMSO-d₆): δ 1.35 (t, *J* = 7.1 Hz, COOCH₂CH₃), 2.47 (s, *E*-Me), 2.45 (s, *Z*-Me), 4.27 (q, *J* = 7.1 Hz, *E*-COOCH₂CH₃), 4.31 (q, *J* = 7.1 Hz, *Z*-COOCH₂CH₃), 7.62 (d, *J* = 9.0 Hz, H₆), 7.61-7.80 (m, H₈, H₉), 8.06 (d, *J* = 7.8 Hz, H₇), 8.12 (d, *J* = 9.0 Hz, H₅), 8.78 (d, *J* = 8.4 Hz, H₁₀), 8.84 (d, *J* = 13.4 Hz, *E*-CHNH), 9.01 (s, *E*-H₁), 8.96 (s, *Z*-H₁), 12.66 (d, *J* = 13.4 Hz, *E*-CHNH), 11.02 (d, *J* = 14.4 Hz, *Z*-CHNH), ratio (*E*)-form : (*Z*)-form = 83 : 17. *Anal.* Calcd for C₂₀H₁₇NO₅: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.24; H, 4.84; N, 3.99.

3-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-9-hydroxy-3H-naphtho[2,1-b]pyran-3-one (36). This compound was prepared from 2,7-dihydroxynaphthalene (**26**) (0.240 g), 2 hours of reflux. Yield: 0.044 g (8 %), mp 248-250° (from a mixture of ethanol and toluene); ¹H NMR (DMSO-d₆): δ 1.34 (t, *J* = 7.1 Hz, COOCH₂CH₃), 2.46 (s, *E*-Me), 2.44 (s, *Z*-Me), 4.27 (q, *J* = 7.1 Hz, *E*-COOCH₂CH₃), 4.37 (q, *J* = 7.1 Hz, *Z*-COOCH₂CH₃), 7.20 (dd, *J* = 8.8 and 2.2 Hz, H₈), 7.34 (d, *J* = 8.9 Hz, H₆), 7.88 (d, *J* = 8.8 Hz, H₇), 7.96 (d, *J* = 2.2 Hz, H₁₀), 7.97 (d, *J* = 8.9 Hz, H₅), 8.81 (s, *E*-H₁), 8.70 (s, *Z*-H₁), 8.82 (d, *J* = 13.2 Hz, *E*-CHNH), 8.75 (d, *J* = 14.0 Hz, *Z*-CHNH), 10.13 (br s, OH), 12.64 (d, *J* = 13.2 Hz, *E*-CHNH), 10.95 (d, *J* = 14.0 Hz, *Z*-CHNH), ratio (*E*)-form : (*Z*)-form = 87 : 13. *Anal.* Calcd for C₂₀H₁₇NO₆: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.53; H, 4.61; N, 3.82.

3-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-5-hydroxy-3H-naphtho[2,1-b]pyran-3-one (37). This compound was prepared from 2,3-dihydroxynaphthalene (**27**) (0.240 g), 1 hour of reflux. Yield: 0.094 g (17 %), mp 245-247° (from a mixture of ethanol and *N,N*-dimethylformamide); ¹H NMR (DMSO-d₆): δ 1.34 (t, *J* = 7.1 Hz, COOCH₂CH₃), 2.47 (s, *E*-Me), 2.44 (s, *Z*-Me), 4.27 (q, *J* = 7.1 Hz, *E*-COOCH₂CH₃), 4.33 (q, *J* = 7.1 Hz, *Z*-COOCH₂CH₃), 7.41 (s, *E*-H₆), 7.40 (s, *Z*-H₆), 7.49-7.55 (m, H₈, H₉), 7.82 (dd, *J* = 6.2 and 2.5 Hz, H₇), 8.62 (dd, *J* = 6.2 and 3.4 Hz, H₁₀), 8.83 (d, *J* = 13.1 Hz, *E*-CHNH), 8.80 (d, *J* = 13.6 Hz, *Z*-CHNH), 8.96 (s, *E*-H₁), 8.91 (s, *Z*-H₁), 10.62 (br s, OH), 12.66 (d, *J* = 13.1 Hz, *E*-CHNH), 11.03 (d, *J* = 13.6 Hz, *Z*-CHNH), ratio (*E*)-form : (*Z*)-form = 84 : 16. *Anal.* Calcd for C₂₀H₁₇NO₆: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.31; H, 4.75; N, 3.85.

3-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-5,6-dihydro-2H-pyrano[2,1-b]pyridine-2,5-dione (38). This compound was prepared from 2,4-dihydropyridine (**28**) (0.167 g), 1 and half hour of reflux. Yield: 0.210 g (44 %), mp 255-257° (from a mixture of *i*-propanol and toluene); ¹H NMR (DMSO-d₆): δ 1.29 (t, *J* = 7.1 Hz, COOCH₂CH₃), 2.43 (s, Me), 4.23 (q, *J* = 7.1 Hz, COOCH₂CH₃), 6.42 (d, *J* = 7.3 Hz,

H₇), 7.58 (d, $J = 7.3$ Hz, H₈), 7.94 (s, H₄), 8.48 (br s, CHNH), 10.62 (br s, OH or NH), 12.41 (br s, CHNH). *Anal.* Calcd for C₁₅H₁₄N₂O₆: C, 56.60; H, 4.43; N, 8.80. Found: C, 56.27; H, 4.52; N, 8.72.

3-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione (39).

This compound was prepared from 4-hydroxy-6-methylpyran-2-one (**29**) (0.188 g), half an hour of reflux. Yield: 0.475 g (95 %), mp 160-163° (from a mixture of ethanol and water); ¹H NMR (DMSO-*d*₆): δ 1.29 (t, $J = 7.1$ Hz, *E*-COOCH₂CH₃), 1.31 (t, $J = 7.1$ Hz, *Z*-COOCH₂CH₃), 2.34 (s, Het-CH₃), 2.43 (s, *E*-Me), 2.39 (s, *Z*-Me), 4.20 (q, $J = 7.1$ Hz, *E*-COOCH₂CH₃), 4.27 (q, $J = 7.1$ Hz, *Z*-COOCH₂CH₃), 6.71 (s, H₈), 7.94 (s, *E*-H₄), 7.86 (s, *Z*-H₄), 8.52 (d, $J = 13.0$ Hz, *E*-CHNH), 8.45 (d, $J = 13.8$ Hz, *Z*-CHNH), 10.62 (br s, OH or NH), 12.44 (d, $J = 13.0$ Hz, *E*-CHNH), 10.71 (d, $J = 13.8$ Hz, *Z*-CHNH), ratio (*E*)-form : (*Z*)-form = 84 : 16. *Anal.* Calcd for C₁₆H₁₅NO₇: C, 57.66; H, 4.54; N, 4.20. Found: C, 57.47; H, 4.40; N, 4.26.

3-(2-Acetyl-2-ethoxycarbonyl-1-ethenyl)amino-2*H*,5*H*-pyrano[3,2-*c*]benzopyran-2,5-dione (40).

This compound was prepared from 4-hydroxybenzopyran-2-one (**30**) (0.243 g), half an hour of reflux. Yield: 0.150 g (27 %), mp 178-181° (from a mixture of ethanol and toluene); ¹H NMR (DMSO-*d*₆): δ 1.31 (t, $J = 7.1$ Hz, *E*-COOCH₂CH₃), 1.33 (t, $J = 7.1$ Hz, *Z*-COOCH₂CH₃), 2.45 (s, *E*-Me), 2.41 (s, *Z*-Me), 4.22 (q, $J = 7.1$ Hz, *E*-COOCH₂CH₃), 4.29 (q, $J = 7.1$ Hz, *Z*-COOCH₂CH₃), 7.49-7.57 (m, H₈, H₁₀), 7.77 (ddd, $J = 7.2$, 7.3 and 1.4 Hz, H₉), 8.00 (dd, $J = 7.8$ and 1.4 Hz, H₇), 8.08 (s, *E*-H₄), 8.01 (s, *Z*-H₄), 8.59 (d, $J = 12.9$ Hz, *E*-CHNH), 8.52 (d, $J = 13.6$ Hz, *Z*-CHNH), 12.50 (d, $J = 12.9$ Hz, *E*-CHNH), 10.82 (d, $J = 13.6$ Hz, *Z*-CHNH), ratio (*E*)-form : (*Z*)-form = 86 : 14. *Anal.* Calcd for C₁₉H₁₅NO₇: C, 61.79; H, 4.09; N, 3.79. Found: C, 61.73; H, 3.98; N, 3.83.

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