Recent Development in the Chemistry of Bicyclic 6-6 Systems
Containing One Bridgehead Nitrogen Atom and One Extra
Heteroatom and Their Benzologs (Update II).

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I. Introduction

This chapter covers the primary chemical literature of the title bi- and tricyclic ring systems cited in Chemical Abstracts Chemical Substance Indexes up to Volume 151 from Volume 144 between 2006 and 2009. Earlier literature data were systematically treated as primary subjects in Comprehensive Heterocyclic Chemistry series (96CHC-II(8)563, 08CHC-III(12)77).

The members of these ring systems occupy valuable parts of the chemical space for drug research, as most of their derivatives have drug-like properties and their outstanding representatives play an indispensable role in medicinal chemistry. The compounds, which were introduced into the human and veterinary therapies are depicted on Figure 1. Antofloxacin is the newest member of this class, which has been applied to combat antibacterial infections since 2009 in China. Some prominent members were isolated from different natural sources, and their structures are on Figure 2.
II. Pyrido[2,1-\textit{b}][1,3]oxazines, -[1,4]thiazines and Their Benzologs

Perhydropyrido[2,1-\textit{b}][1,3]oxazin-6-ones \textit{8} and \textit{10} were obtained when they \textit{7} and \textit{9} precursors were split from resins (07JCC1060).

![Chemical structures and reactions](image)

III. Pyrido[1,2-\textit{a}]pyrimidines

\textit{A. Structure}

1. Thermodynamic Aspects

Solubility for risperidon was calculated at pH 2 and with 13 with the ACD/Solubility DB computer program to be $7.3 \times 10^{-3}$ and 9.6 mg/ml, respectively. The predicted distribution coefficient of risperidon is -1.02 and 1.82 between \textit{n}-octanol and water at pH 2 and 13, respectively, calculated by the ACD/LogD DB computer program (05JSS1195).

A charge transfer complex was formed by reacting risperidine with chloranil, and its spectral characteristic, stability constant and thermodynamic parameters were investigated (05OJC427).
Octanol-water partition coefficients of 4H-pyrido[1,2-a]pyrimidin-4-one and its 2,3-dimethyl derivative was determined by traditional shake-flask and reversed phase thin-layer chromatographic methods (08MI11).

The rate of brain penetration of risperidone was predicted by different assays (MDR1-MDCKII, PAMPA-BBB, in situ brain perfusion) (09JPS1980).

Theoretical and experimental solubility of risperidone were determined in polymeric micelles formed from di-block polyethylene glycol and random copolyesters of ε-caprolactone and trimethylene carbonate (07PHA499). The experimental partition coefficients in octanol-water system and pKₐ values of risperidone and paliperidone are 3.04, 8.24 and 2.35, 8.24, respectively (07DMD649). Risperidone and paliperidone were also included into a set of compounds to predict alkane/water partition coefficients (08JMC3720).

Pemirolast was determined in human plasma by a LC-MS method (05MI1).

Risperidone was determined by different HPLC methods in formulated products (06MI4), in biological fluids [06JCH(B)1, 06JCH(B)100, 06MI3, 06MI8, 07JC(B)20, 07MI9, 08MI1, 09DMD787]. Reversed-phase liquid chromatographic columns were classified/characterized by using different drugs, among them risperidone (06JPB751). Risperidone was determined by a flow-injection chemiluminescence method (06CPA288).

A reverse-phase HPLC method was developed for determination of 32-43 potential impurities and 44 degradation product of risperidone (08JPB165). Hydroxylated derivative on the pyridine moiety of paliperidone, 2-(9-hydroxy-2-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-3-yl)acetic acid, 9-hydroxy derivative of
compound 39, and its hydroxylated derivative on the pyridine moiety, furthermore 9-oxo derivative of risperidone were identified in human urine and feces by LC-MS/MS method as the metabolites of paliperidone (08DMD769).
HPLC methods for the separation of enantiomers of paliperidone on an α1-acid glycoprotein (06MI9) and on Chiral-AGP (07MI8) columns were developed. Water solubility of risperidone base was increased by salt formation with saccharine (08CGD3483). Dissolution of risperidone tablets were determined by HPLC (06MI4). That of sustained release paliperidone was investigated in 0.001 M HCl (06ANA181).

While A tetrazole shows asymmetric permeability in Caco-2, this phenomenon was not observed with B carboxylic acid and C nitrile derivatives (06JPS717).

Compatibility and stability of risperidone with soft-drinks were investigated by isothermal titration microcalorimetry (06JTA681).

The lipophilicity of risperidone was determined by RP-TLC using RP-18-HPTLC plates (08MI5). The retention behavior of risperidone in different normal-phase TLC (06MI1), high pressure TLC (0808JLC1913) and in supercritical fluid chromatography (08JCH(A)186) was investigated. Risperidone was determined by a TLC method in formulated products (09CHR393). A sensitive and rapid liquid chromatographic-tandem mass spectrometry methods were developed for simultaneous quantification of

\[
PDR = \frac{P_{B \to A}}{P_{A \to B}}
\]

<table>
<thead>
<tr>
<th></th>
<th>PA to B 10^{-6} (cm/s)</th>
<th>PB to A 10^{-6} (cm/s)</th>
<th>PDR</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>4.7 0.2</td>
<td>26.4 0.5</td>
<td>5.7</td>
</tr>
<tr>
<td>B</td>
<td>19.0 3.5</td>
<td>18.6 2.1</td>
<td>1.0</td>
</tr>
<tr>
<td>C</td>
<td>19.2 0.5</td>
<td>20.1 1.4</td>
<td>1.0</td>
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}
risperidone and its active metabolite 9-hydroxyrisperidone in rat plasma (07RCM920) and rat brain homogenate (07JC(B)276).

An isocratic reversed-phase HPLC method was developed for the separation of risperidone and its main metabolite, the 9-hydroxy derivative, from other psychotropic drugs (06JPB333). Risperidone and its active metabolite, 9-hydroxyrisperidone, were simultaneously determined in biological fluids by rapid and sensitive LC/tandem mass spectrometry methods (06RCM2104, 07TAL360, 08MI7, 09DMD787, 09JCH(B)2589), and by HPLC methods (07ANB235, 08CHR321, 08JCH(B)8, 09BCH929). 2,7-Dimethyl 3-{2-[4-[6-fluoro-1,2-benzisoxazol-3-yl]-1-piperidyl]ethyl-4H-pyrido[1,2-a]pyrimidin- one was used as internal standard at the determination of risperidone and paliperidone in biological samples (09BCH929). Risperidone was determined by a differential pulse polarographic method (06CCA541) in pharmaceutical formulations. Risperidone and enantiomers of 9-hydroxyriperidone were determined in human plasma by a LC-MS/MS methods (06MI5, 07JC(B)497). An optimized sample preparation and chromatography was developed to minimize matrix effects in bioanalytical LC/MS/MS assays for determination of risperidone and 9-hydroxyriperidone (07JC(B)22). The bioequivalence of risperidone tablets was studied by HPLC/MS method (06MI6). Enantiomers of 9-hydroxyriperidone was separated by both a HPLC and a capillary electrophoresis method (07JC(A)228).

Extractive colorimetric methods (08CPB1092) and spectrophotometric methods (08MI8) were developed for the determination of risperidone in pure and in its formulated product (tablet).
Retention behavior of risperidone was investigated on different plates with mixtures of phosphate buffer and six modifiers (acetone, MeCN, dioxane, EtOH, MeOH, THF) as mobile phases (07MI1).

Diverse marketed central nervous system-active drugs, among them risperidone and paliperidone, were tested in three P-glycoprotein in vitro assays and their permeability were measured in two in vitro models to predict the in vivo interactions of P-glycoprotein with drugs in the central nervous system (08DMD268).

Behavior of risperidone was characterized by liquid chromatography-electrospray ionization-mass spectrometry, ion trap mass spectrometry, gas chromatography-flame ionization detection and polarographic methods (07TAL755). An analytical method was developed for the simultaneous separation of risperidone and the enantiomers of 9-hydroxirisperidone using cyclodextrin-electrokinetic chromatography in the dual cyclodextrins mode using anionic and neutral cyclodextrins at acidic pH 2.5 (07ELP2683).

Risperidone and paliperidone were also measured, among other CNS-active drugs, on different in vitro P-glycoprotein assays to predict the in vivo interactions of P-glycoprotein with drugs in the central nervous system (08DMD268).

2. Theoretical Calculations

Quantitative structure-property relationship models that can predict the $pK_a$ values of neutral and basic drugs, including risperidon, were developed. The predicted $pK_a$ value of risperidone is 7.757 and 7.534 with a heuristic model and radial basis function neural networks, respectively (05PR1454). Its experimental $pK_a$ value is 8.30.
Risperidon is a substrate of P-glycoprotein, but it was predicted to be an inhibitor by a GRIND-based descriptor model (05MP33). Different QSAR studies were carried out to predict hERG potassium channel affinity of compounds, among them risperidone (06BMC3153, 06JCI1371, 08BMC6252, 08CHJ2125, 08QSC1305, 09EJM1926, 09JCI247) and paliperidone (08QSC1305, 09JCI247), too. A structure-based virtual screening model was developed to estimate the IC$_{50}$ value of a wide range of ligands (including risperidon too) for the hERG potassium channel (07BBR889). Predictive quantitative structure-toxicity and toxicophore models were developed for a diverse series of hERG K$^+$ channel blockers, including risperidone, too (08JGM966).

Risperidon was also included into a group of compounds to analyze the scaffold diversity of commercially available screening collection (06JCI512). An in silico P450 profiler based on pharmacophore models was developed and validated by using a set of drugs, including risperidone, too (06CDDT1). Paliperidone was also used, among other drugs to predict cytochromes P450 2D6 and 1A2 inhibition (06JMC6231).

Blood-to-plasma concentration ratio of drugs, including risperidone, was predicted well by artificial neural networks model (09EJP544).

A data set of 130 diverse compounds, including risperidone, was used to generate a renal clearance model using a classical Volsurf approach (06JCI1312). A topological substructural molecular design approach was developed to classify P-glycoprotein substrate/nonsubstrate compounds. Risperidon was also applied in this development (06JPS589).
The theoretical binding mode of compounds 57-59 obtained by docking simulations into the active site of human aldose reductase crystal structure was fully consistent with the structure – activity relationship (07JMC4917).

Different new approaches, boosted regression trees and two-step boosted regression trees (07MI7), a method based on ab initio calculated quantum chemical descriptors (08JMG1223) and biopartitioning micellar chromatography system (09JCH(A)5190) were evaluated for modeling and predicting the blood-brain barrier passage of drugs including risperidone, too. Blood-brain partitioning of risperidone and paliperidone was predicted by a chemometric method called genetic algorithm variable selection (08QSC704). A combinatorial quantitative structure-activity relationship analysis was carried out for a set of 159 compounds, including also risperidone and paliperidone, with known blood-brain permeability data (08PR1902).

Compound 156 was identified as a potential novel glycogen synthase kinase-e inhibitor hit by a sequential virtual screen (08BMC636).

Risperidone was included into a test set of compounds at the development a hologram QSAR model for the prediction of human oral bioavailability (07BMC7738).
A physiologically based modeling approach was developed for predicting metabolism, tissue distribution, and bioavailability in rat for a structurally diverse set of compounds, including risperidone and paliperidone, too (07DMD649). Risperidon was also included into a set of drugs to predict their human pharmacokinetics by physiologically based pharmacokinetics models (07DMD1766).

Multiple pharmacophore models predict that risperidone a P-glycoprotein substrate (07JCI2429).

2-Methylthio-3-phenylsulfonyl-4-imino-4H-pyrido[1,2-α]pyrimidine was selected by a virtual screening based on a ligand-based pharmacophore model as a potent serotonin 5-HT$_6$ receptor antagonist (08JCI197).

Experimental blood-brain partition coefficients for a diverse set of drug, including risperidone and paliperidone, are correlated with computed structural descriptors using CODESSA-PRO and ISIDA programs to give statistically significant QSAR models (06BMC4888). Risperidone was also included in a set of drugs to develop a QSAR model for the prediction of blood - brain barrier permeability (07JCC1252) and to develop a high-throughput screening of drug-brain tissue binding and in silico prediction for assessment of central nervous system drug delivery (07JMC4606, 09JMC1693). A supervised artificial neural network model has been developed for the accurate prediction of blood-brain barrier partition of a structural diverse set of compounds, included risperidone, too (08QSC586). Risperidone was also included intro a set of structurally diverse molecule to predict human plasma protein binding by hologram QSAR (07DLD502).
A quantitative structure-activity relations approach was used to explore relationship of drug-induced neutrophil immaturity and haematological toxicity to physicochemical characteristics of 10 antipsychotic drugs, including risperidone, too (09. Pharmacophore representation concept was used to elucidate molecular similarity of dopamine antagonists, including risperidone, too (07JCAM239).

Magnetic criteria, magnetic susceptibility isotropic and nucleus-independent chemical shifts calculated with B3LYP levels at the 6-31G** basis set were used to evaluate aromaticity of a set of 29 planar bicyclic π-electron systems: naphthalene and its mono- and di-aza- (among them 9aH-pyrido[1,2-a]pyrimidine), -phospha-derivatives (07IJQ1846).

The complexation of risperidone and paliperidone with seven cyclodextrines was studied by affinity capillary electrophoresis and NMR for acidic pH 2.5 and physiological pH 7.4 (08JCH(A)185). Melting point of risperidone was predicted using principal component-genetic algorithm–artificial neural network (08BKC833).

3. UV Spectroscopy

Risperidone formed a charge transfer complex with 2,3-dichloro-5,6-dicyano-p-benzoquinone (06OJC139) and tetracyanoethylene (06OJC95). Their stability constants and ultraviolet spectra were determined.

4. IR and Raman Spectroscopy

Structures of 2-oxo-1,2,3,4-tetrahydropyrido[2-a]pyrimidinium chloride (08JST244) and 1-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2-a]pyrimidinium bromide (07JST107) have been confirmed by Raman and Fourier transformed infrared and NMR spectra, and DFT (B3LYP) calculations.

A FT-Raman spectroscopic method was developed for non-destructive quantitative analysis of risperidone in commercially available film-coated tablets (08JPB631)
5. NMR Spectroscopy

2-Oxo-1,2,3,4-tetrahydropyrido[2,3-a]pyrimidinium chloride (32) shows a ring-chain tautomerism in wet DMSO-\(d_6\) (08JST244).

![Chemical Structures](image)

Structures of two impurities 20 and 21, isolated from risperidone, were characterized by mass and \(^1\)H and \(^{13}\)C NMR spectroscopy (06JPB598).

\(^1\)H NMR investigations were applied to study the mechanism of racemization of enantiomers of paliperidone (09TA1125). All results confirm that racemization occurs via an imine-enamine tautomerism.

A \(^1\)H NMR NOESY experiments on 23 \(\text{cis-}5\alpha\text{H,}9\text{H-}
\text{hexahydropyrido[2,1-}b\text{-}quinoxalin}-9\text{-carboxylate}
\) showed a strong spatial relationship between 5\(\alpha\)-H and 9-H protons. This was not observed with 22 \(\text{trans-}5\alpha\text{H,}9\text{H-}
\) derivatives (06OL239).

![Chemical Structures](image)

In DMSO-\(d_6\) only the signals of the ring tautomer could be identified (05RJC527). The possible ring – chain tautomerism was not investigated in CDCl\(_3\), which usually favoured for the ring tautomers (96JOC).
The $^1$H, experimental and calculated $^{13}$C NMR spectra of compounds 97 have indicated that these compounds exist mainly in 2-hydroxy tautom form in DMSO-$d_6$ solutions (07CHE729).

$^1$H and $^{13}$C NMR spectra of 51 2-oxo-1,2,3,4-tetrahydropyrido[1,2-$a$]pyridinium chlorid revealed an ring – chain tautomerism in DMSO-$d_6$, and the ring form was the main component in the equilibrium mixture (07ARK55).

### 6. Mass Spectrometry

A tandem mass spectrometric investigation of the collosion-induced dissociation of risperidone and its 9-hydroxy metabolite was carried out. (07RCM2031). A selective and sensitive time-of-flight mass spectrometers method was validated to determine risperisdone and paliperidone in rat plasma using midazolam as an internal standard (08JLC2737). Structures of 97 2-hydroxy-4$H$-pyrido[1,2-$a$]pyridine-3carboxylates were characterized by mass spectrometric analysis, too (07CHE729).

### 7. X-Ray Investigations
X-Ray investigation of risperidone N-oxide hydrogen peroxide methanol solvate revailed, that the piperidine ring adopts a chair conformation, while the tetrahydropyridine ring has a sofa conformation (05AXE2515). Crystal structure of risperidone hydrochloride 2.5-hydrate [06AX(E)768] and crystalline form B of risperidone [06AX(E)3527] were determined by single crystal X-ray diffraction investigation. The tetrahydropyridine moiety of the bicycle adopts a sofa conformation.

Structures of 35 and 36 3-substituted 2-dimethylamino-4H-pyrido[1,2-a]pyrimidin-4-ones were confirmed by single-crystal X-ray analysis (07TL941, 07T1630).

![Chemical structures](image)

The structures of 23 disalt (09JA9174), 15 2H-pyrido[1,2-a]pyrimidine (06OM416), 9-benzoyl-7-nitro-6-phenyl-1,2,3,47,8-hexahydro-6H-pyrido[1,2-a]pyrimidine (08SL1357), 2-morpholino-9-trifluoromethylsulfonyloxy-4H-pyrido[1,2-a]pyrimidin-4-one (07OBC2670), 3-bromo-7-chloro-2-(2-methylprop-1-enyl)-4H-pyrido[1,2-a]pyrimidin-4-one (08SL2836), 3-bromo-7-chloro-2-[2,2-bis(ethoxycarbonyl)ethyl]-4H-pyrido[1,2-a]pyrimidin-4-one (08SL2836), ethyl 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-carboxylate (07CHE729), methyl 3-pivaloyloxy-7-bromo-4-oxo-4H-pyrido[1,2-
pyrimidin-2-carboxylate (08TL6556), N-(2-diethylaminoethyl)-8-methyl-2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-carboxamide (08CHE50), N-[2-methoxyphenyl)methyl]-8-methyl-2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-carboxamide (08CHE565), 9-(4-methoxybenzoyl)-1,2,3,4-tetrahydro-6H-pyrido[1,2-a]pyrimidin-6-one (07AX(E)3186), 6-imino-8-methylthio-9-benzoyl-1,2,3,4-tetrahydro-6H-pyrido[1,2-a]pyrimidine-7-carbonitrile (07SL761), and dimethyl 2-[N-cyclohexyl-N-(ethoxycarbonylcarbonyl)amino]-4H-pyrido[1,2-a]pyrimidine-3,4-dicarboxylate (07TL4195, 07T11135) were characterized by X-ray crystallography. The stereostructure of 19 (2R,6S,9aR)-4-oxoperhydropyrido[1,2-a]pyrimidine-6-carboxylate was also determined by X-ray crystallography (06OL239). Two conformers are present in the single crystal of 1-methyl-2-oxo-1,2,3,4-tetrahydropyrido[1,2-a]pyrimidinium bromide (07JST107).

Structures of two impurities of risperidone, 20 and 21 were unambiguously confirmed by single crystal X-ray diffraction investigations (06JPA598). Structures of 2-methyl-3-(2-chloroethyl)-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (06AX(E)3730), 3-ethyl-2-(4-methylthiazol-2-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (06T12064), 9-(4-methoxybenzoyl)-1,2,3,4,7,8-hexahydro-6H-pyrido[1,2-a]pyrimidin-6-one (06AX(E)3040) have been assigned by X-ray measurements.

X-ray powder diffraction study proved that polymorph A of risperidone was stable during the manufacturing process and after a storage period of 2 years (07TAL1382).

Distribution of risperidone on and in thin polymer coatings was investigated by a TOF-SIMS method (06ASS6628).

B. Reactivity
1. Ring Opening

Heating 37 4-aryl-2-hydroxy-4H-pyrido[1,2-a]pyrimidines in EtOH gave 38 ring opened products (05RCB2841)

\[
\begin{array}{c}
\text{37} \\
\text{Ar} \\
\text{(CF}_2\text{)}_2\text{H} \\
\text{N} \\
\text{O} \\
\text{38} \\
\text{Ar} \\
\text{N} \\
\end{array}
\]

2-Chloro-4H-pyrido[1,2-a]pyridine-4-one was used as precursor to synthesize 211 iminopropadienone by flash vacuum thermolysis (FVT) (2008JPC(A)9742).

2. Oxidation, Dehydrogenation

Reaction of methyl 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate with 2,3-dichloro-4,5-dicyano-1,4-benzoquinone in dioxane at 60 °C for 1h, then treatment of the reaction mixture with 5 equiv. NEt₃ for 4h gave 6,7-dihydro derivative (07WOP2007/039218). 3-Hydroxy-4-oxo-6,7-dihydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate and was dehydrogenated over 10% Pd/C catalysts by heating in o-xylene for 48 h to 3-hydroxy-4-oxo-6,7,4H-pyrido[1,2-a]pyrimidine-2-carboxylate. Dehydrogenation of N-(4-fluorobenzyl)-3-hydroxy-9-methylamino-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide trifluoroacetate over 10% Pd/C catalyst in the presence of Hüning’s base in o-xylene at 156 °C for 7 h afforded N-(4-fluorobenzyl)-3-hydroxy-9-methylamino-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide.
2-Methyl-3-(2-chloroethyl)-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one and risperidone were enzymatically hydroxylated in the position 9 by using oxidoreductase enzymes (08WOP2008/144073).

Instead of the oxidation of 9-CH₂ group of methyl 3-benzoyloxy-6,7,8,9-tetrahydro-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylate to a carbonyl group with PDC, PCC, CrO₃, MnO₂ or KMnO₄ degradation occurred (07TL6552).

Oxidation of 2-methyl-3-(2-chloroethyl)-4H-pyrido[1,2-a]pyrimodin-4-one (88) with SeO₂ in boiling pyridine yielded 89 tricyclic derivative (08TL1301).

Treatment of 2-methyl-3-vinyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one with 9-borabicyclo[3.3.1]nonane in THF at 60 °C for 3 h, then at room temperature pyridinium chlorochromate in CH₂Cl₂ was added to the reaction mixture, which was heated at 90-98 °C for 3 h gave 3-(2-oxoethyl) derivative in 53% yield (05APR1019).

Oxidation of risperidon with 30% H₂O₂ in MeOH gave 1 risperidone N-oxide hydrogen peroxide methanol solvate (05AXE2515).

6,7,8,9-Tetrahydro-2H derivative was obtained when 4-(4-fluorophenyl)-9-[3-methoxy-4-(4-methylimidazol-1-yl)benzylidene]-3,4,6,7,8,9-hexahydro-2H-pyrido[1,2-a]pyrimidin-2-one was reacted first with LDA followed by the addition of PhSeBr at -78 °C, then the reaction mixture was treated with H₂O₂ at ambient temperature (08WIO2008/153793).

3. Hydrogenation, Reduction
Catalytic reduction of 23 disalt yielded 24 ring opened disalts (09JA9174). Reduction with LiAlH₄ gave 25 2H,6H-3,4-dihydropyrido[1,2-a]pyrimidinium salt.

\[
\begin{align*}
\text{R} & \quad \text{NMe₂H}^+ \\
\text{NMe₂H}^+ & \quad \text{2 TsO}^- \\
X = H, \ 98\% & \quad \text{X₂, 52 psi, rt Pd-C, MeCN} \\
X = H, \ D & \quad \text{X₂, 52 psi, rt LiAlH₄ MeCN, rt TsO}^- \\
\text{X} & \quad \text{NMe₂H}^+ \\
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{NMe₂H}^+
\end{align*}
\]

Reductive alkylation of a 9-amino-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate with aldehydes in the presence of NaBH₃CN yielded 9-alkylamino derivatives (09BML1930).

Catalytic reduction of methyl 3-benzyloxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate, furthermore that of 9-benzylamino derivatives of 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate over Pd/C catalyst in MeOH gave 3-hydroxy and of 9-amino derivatives, respectively (07TL6552, 08JMC861).

Reductive N-methylation of a diastereomeric mixture of 9-[(S)-α-methylbenzylamino]-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylates with H₂CO in the presence of NaBH₃CN in MeOH afforded 9-methylamino derivatives (07TL6552). A diastereomeric mixture of 9-[N-methyl-N-(R)-α-methylbenzylamino]-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylates was obtained by the reduction of a diastereomeric mixture of 9-formamido derivatives with BH₃-SMe₂ in THF at 0-45 °C.

Catalytical hydrogenation of methyl 2-vinyl-3-(1,3-dioxolan-2-yl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-8-carboxylate in MeOH over 10% Pd/C catalyst provided a 2-ethyl-3-(dimethoxymethyl) derivative in 98% yield (06BMC1993). That of 2-methyl-4H-
pyrido[1,2-a]pyrimidin-4-one in 6N HCl solution over Pd/C under a 125 psi pressure for 18 h provided 6,7,8,9-tetrahydro derivative in 73% yield (05APR1019).

9-Ethylamino derivative was obtained from N-(4-fluorobenzyl)-3-hydroxy-9-amino-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide by treatment with MeCHO and NaBH₃CN in a 1:1 mixture of CH₂Cl₂ and MeOH at room temperature (07WOP2007/039218).

Reduction of 2-butyl-3-(5-indolyl)-4H-pyrido[1,2-a]pyrimidin-4-one with NaBH₃CN in glacial AcOH at ambient temperature gave 3-(5-indoliny1) derivative (08USP2008/0194616, 08WOP2008/097991). Treatment of (R)-2-butyl-3-{4-[3-pyrrolidinylamino]phenyl}-4H-pyrido[1,2-a]pyrimidin-4-one with 37% H₂CO in THF in the presence of Et₃N, NaB(O₂CMe)₃H and catalytic amount of AcOH at room temperature for 16 h gave a 7:1 mixture of 3-{4-[(1-methyl-3-pyrrolidinyl)amino]phenyl and 3-{4-[methyl(1-methyl-3-pyrrolidinylamino]phenyl derivatives.

A side-chain aromatic nitro group of 4H-pyrido[1,2-a]pyrimidin-4-ones was reduced to amino group with Zn powder in AcOH (06WOP2006/109081).

Catalytic hydrogenation of 9-benzyloxy-2-methyl-3-(2-chloroethyl)-4H-pyrido[1,2-a]pyrimidin-4-one in acidified aqueous MeOH over 5% Pd/C catalyst gave 9-hydroxy-6,7,8,9-tetrahydro derivative in 73% yield (08WOP2008/128436).

4. Reactivity of the Ring Carbon Atoms

Reaction of anhydro-(2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidinium)hydroxyde and EtOAc in benzene in the presence of catalytic amount of piperidine and AcOH at room temperature overnight afforded 3-acetyl-2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one in 80% yield (06MI10).
Condensation of \textbf{22} 2,4-dimethylpyrido[1,2-\textit{a}]pyrimidinium salt with \textbf{23} methosulphates in Ac\textsubscript{2}O in the presence of Et\textsubscript{3}N at ambient temperature gave \textbf{24} dyes (07DP466).

Reactions of 3-unsubstituted 4\textit{H}-pyrido[1,2-\textit{a}]pyrimidin-4-ones with Br\textsubscript{2} (05APR1019, 08SL2836, 08USP2008/0194616, 08WOP2008/097991) and NBS yielded 3-bromo derivatives (07WOP2007/002701, 08BMCL688, 08USP2008/0194616, 08WOP2008/097991). 3-Bromo-2-propoxy-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidin-4-one was prepared from the 3-unsubstituted bicycle with NBS in CHCl\textsubscript{3} (08USP2008/0194616, 08WOP2008/097991).

Bromination of methyl 3-benzyloxy-6,7,8,9-tetrahydro-4-oxo-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidine-2-carboxylate and methyl 9-methyl-3-benzyloxy-4-oxo-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidine-2-carboxylate with NBS under radical conditions in CCl\textsubscript{4} gave 9-bromo (07TL6552, 08JMC861) and 9-bromomethyl (09BML1930) derivatives, respectively. 9-Bromo derivative was reacted with secondary amines in DMF and (\textit{S})-(\textit{S})-1-phenylethylamine to yield 3-hydroxy-9-disubstituted amines (08JMC861) and 9\textit{a}-diastereomers of methyl 9-[(\textit{S})-\textit{α}-methylbenzylamino]-3-hydroxy-6,7,8,9-tetrahydro-4-
oxo-4H-pyrido[1,2-\textit{a}]pyrimidine-2-carboxylate (07TL6552), respectively. Polar protic solvents (MeOH-H\textsubscript{2}O, 7:3) and low temperature (-30 °) increased the diastereoselectivity. Reaction of methyl 9-bromomethyl-3-benzoyloxy-4-oxo-4H-pyrido[1,2-\textit{a}]pyrimidine-2-carboxylate under Staudinger conditions with NaN\textsubscript{3} followed by treatment with Pb\textsubscript{3} afforded 9-aminomethyl derivative, which contained a small amount of 9-[(benzoylamino)methyl] impurity, formed during this reaction by migration of the benzoate from position 3 to the newly formed amino group (09BML1930). 9-Bromomethyl group was reacted with morpholine and 4-acetylpiperazine, too.

Reactions of anhydro-(2-hydroxy-4-oxo-4H-pyrido[1,2-\textit{a}]pyrimidinium)hydroxyde (50) with SO\textsubscript{2}Cl\textsubscript{2}, Br\textsubscript{2} in AcOH, and I\textsubscript{2} gave 51 3-chloro, 53 3-bromo and 55 3-iodo derivatives (05MI2, 07HC19). Treatment of either 50 or 55 with Br\textsubscript{2} in boiling dioxane yielded 54 3,3-dibromo derivative. Heating 50 and 51 in a mixture of PCl\textsubscript{5} and POCl\textsubscript{3} at 200-220 °C provided 52 2,3-dichloro derivative, which could be converted back into 51 by heating in 6 N HCl.
Vielsmeier-Haack formylation of a 3-unsubstituted 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-8-carboxamide with a mixture of (COCl)₂ and DMF in CH₂Cl₂ at 0 °C gave 3-formyl derivative which was condensed with 2-[1-(4-methoxybenzyl)tetrazol-5-yl]acetic acid in the presence of piperidine in boiling pyridine to provide a 3-{2-[1-(4-methoxybenzyl)tetrazol-5-yl]vinyl derivative in 71% yield (07BMC7087).

Vielsmeier-Haack formylation of a 2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one with POCl₃ and DMF at 80 °C gave 2-chloro-3-formyl derivative (06BMC1993). Chloro atom was changed for secondary amino group with secondary amines in the presence of NEt₃ in MeOH at ambient temperature in good yields (07T1630). Reaction of the formyl group with (tert-butoxycarbonylmethylene)triphenylphosphorane yielded a 3-[(1E)-(3-tert-butoxy-3-oxoprop-1-en-1-yl)-2-chloro derivative (06BMC1993). The formyl group was converted into a 1,3-dioxolan-2-yl moiety by treatment with HOCH₂CH₂OH in boiling toluene in the presence of Amberlyst® 15. 3-Formyl group was prepared from the 3-(1,3-dioxolan-2-yl) group by treatment with AcOH in aqueous acetone.

Dropwise treatment of a solution of 7-chloro- and 7-bromo-2-chloromethyl-4H-pyrido[1,2-a]pyrimidin-4-ones in conc H₂SO₄ with 65% HNO₃ at 0° C provided 3-nitro derivatives in good yields (08H(75)925).

Bromination of N-[(4-fluorophenyl)methyl]-3-pivaloyloxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide in a 3:1 mixture of MeCN and AcOH with NBS for 4 days provided 7-bromo derivative (07WOP2007/039218).
Bromination of 14 4-oxo-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidine-2-carboxylate did not occur with Br\textsubscript{2}, but 15 addition product was obtained with NBS in a mixture of AcOH and MeCN. Treatment of 15 with Et\textsubscript{3}N gave 16 7-bromo derivative (08TL6556).

Heating compounds 36 in MeCN in the presence of PPTS or AcOH gave mixtures of 40 2-amino-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidin-4-ones and 41 pyrrolo[3,4-\textit{c}]pyrrole-1-carboxylates (07T1630). Similar reaction mixtures were obtained when one-pot three component reaction mixtures containing 39 3-formyl derivative, \(\alpha\)-amino acid methyl ester and \(N\)-phenylmaleimide were heated under similar reaction conditions.

Beside 2\textit{H}-pyrrolidine derivatives compound 40 was also obtained from 43 and one-pot three component reactions of 39 3-formyl derivative, \(\alpha\)-amino acid methyl ester and 42 acetylene derivatives (2007TL941).
Reaction of 34 2-methylthio-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitriles with amines, H$_2$NNH$_2$·H$_2$O, NH$_2$OH and acetamidine·HCl yielded 35 2-amino derivatives, and 36-38 tricyclic compounds, respectively (08MI10).

Oxidative Heck-type alkenylation of 39 1,2,3,4-tetrahydro-6H-pyrido[1,2-a]pyrimidin-6-one leaded to exclusive formation of 40 7-(2-substituted vinyl) derivatives (09OL2639). Similar reaction with 2-vinylpyridine failed. It is likely, that palladation is followed by formation a stable chelate 41, involving the pyridine lone pair and the adjacent π-bond, which prevented the further reaction. $^1$H NMR spectra indicated that in DMSO-$d_6$ cca. 16% of 42 formed from 40 in the presence of 20 mol % of Pd(OAc)$_2$. 

27
Hydrolysis of 8-iodo derivative of 60 tetrahydropyrido[1,2-α]pyrimidinium mesylate afforded 61 8-iodo-1,2,3,4-tetrahydro-6H-pyrido[1,2-α]pyrimidin-6-one (07OL5175). Under similar reaction conditions 9-iodo derivative of 60 yielded a mixture of 9-iodo derivative of 61 and the deiodinated 1,2,3,4-tetrahydro-6H-pyrido[1,2-α]pyrimidin-6-one. 7-Iodo derivative 60 (7-I) gave only the deiodinated 1,2,3,4-tetrahydro-6H-pyrido[1,2-α]pyrimidin-6-one. Iodo atom of 7-, 8-, and 9-iodo derivatives 60 was easily changed for aryl groups in Suzuki-Miyaura coupling, and the quaternary salts were hydrolyzed to 62 aryl substituted 1,2,3,4-tetrahydro-6H-pyrido[1,2-α]pyrimidin-6-ones.

Reaction of 2-chloro-3-bromo-4H-pyrido[1,2-α]pyrimidin-4-one with NaOMe in boiling MeOH and with primary and secondary amines in boiling EtOH yielded 2-alkoxy and 2-amino derivatives, respectively (08USP2008/0194616, 08WOP2008/097991).

5. Reactivity of the Ring Nitrogen Atom
It was assumed, that the reaction of \textit{anhydro-(2-hydroxy-4-oxo-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidinium)hydroxyde} and ClCH$_2$CN under phase transfer conditions afforded mesoionic tricyclic compound (05MI2, 07HC19).

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1- Allyl derivative was prepared in 58\% yield when 1,2,3,4-tetrahydro-6\textit{H}-pyrido[1,2-\textit{a}]pyrimidin-6-one was treated with NaH, then with allyl bromide in boiling THF for 5 h (09OL2639).

6. Reactivity of Substituent Attached to a Ring Carbon Atom

Phase transfer alkylation of \textit{anhydro-(2-hydroxy-4-oxo-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidinium)hydroxyde} with MeI, EtI, PrBr, CH$_2$=CHCH$_2$Br, ClCH$_2$CO$_2$Me, BrCH$_2$CO$_2$Et, ClCO$_2$Et, epichlorohydrin, and 2-(2-bromoethyl)isoindole-1,3-(2\textit{H})-dione in the presence of K$_2$CO$_3$ and Bu$_4$NBr in boiling acetone for 4-8 h provided 2-O-alkylated products (05MI2, 07HC19). Reaction of \textit{anhydro-(2-hydroxy-4-oxo-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidinium)hydroxyde} with PrBr in the presence of Cs$_2$CO$_3$ in boiling acetone gave 2-propoxy derivative (08WOP/2008097991). When \textit{anhydro-(2-hydroxy-4-oxo-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidinium)hydroxyde} was heated with (COCl)$_2$ under reflux for 1 h 2-chloro-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidin-4-one was obtained in 44\% yield.

Reaction of 2,9-dihydroxy-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidin-4-one and POCl$_3$ for 48 h at reflux gace 9-hydroxy-2-chloro derivatives in 60\% yield (07OBC2670). The 2-chloro atom was changed for morpholino group when the chloro derivative was reacted with morpholine.
in boiling EtOH for 18 h in 97% yield. 2-Morpholino-9-hydroxi-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidin-4-one was reacted with (CF\textsubscript{3}SO\textsubscript{2})\textsubscript{2}O in CH\textsubscript{2}Cl\textsubscript{2} in the presence of NEt\textsubscript{3} at (-30)-(-20) °C to give 9-trifluorosuylfonyloxy derivative, which was involved in Suzuki reactions with (het)arylboronic acids in the presence of Pd(Ph\textsubscript{3})\textsubscript{4} in dioxane at 95 °C for 48 h provided 9-(het)aryl derivatives. Suzuki reaction of 2-substituted 3-bromo-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidin-4-ones with (het)arylboronic acids in the presence of Pd(Ph\textsubscript{3})\textsubscript{4} and 2M Na\textsubscript{2}CO\textsubscript{3} in boiling 1,2-dimethoxyethane for 16 h provided 3-(het)aryl derivatives (08USP2008/0194616, 08WOP2008/097991).

Suzuki-Miyaura reactions of 20 2-chloro-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidin-4-ones afforded 21 2-\{[1-(\textit{tert}-butoxycarbonyl)piperidin-4-yl]methyl\}-, 22 2-aryl derivatives (06BMC1993, 06BMC8506). Reaction of methyl 7-bromo-3-pivaloyloxy-4-oxo-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidine-2-carboxylate and (2-morpholin-4-ylphenyl)boronic acid in the presence of

![Scheme 1](image-url)
Pd(OAc)$_2$, dicyclohexyl(2’,6’-dimethoxybiphenyl-2-yl)phosphine and K$_3$PO$_4$ in BuOH at 90 °C for 10 min gave 7-(2-morpholin-4-ylphenyl derivative) (07WOP2007/039218). Stille reactions gave 23 2-vinyl and 24 2-[1-tert-butoxycarbonyl-1,2,5,6-tetrahydropiridin-4-yl] derivatives (Scheme 1) (06BMC1993). Stille reaction of 3-bromo-2-methyl-6,7,8,9-tetrahydro-4$H$-pyrido[1,2-$a$]pyrimidin-4-one with tributyl(vinyl)stannane in the presence of P(PPh$_3$)$_4$ in toluene at 100-105 °C for 15 h afforded 3-vinyl derivative in 83% yield (05APR1019).

Bromination of 3-substituted 2-ethyl-4$H$-pyrido[1,2-$a$]pyrimidin-4-ones with NBS in $\alpha,\alpha,\alpha$-trifluorotoulene at 90 °C for 3 days, and in boiling CCl$_4$ in the presence of benzooylperoxide gave 2-(1-bromoethyl) derivatives (07WOP2007/002701, 08BMCL688). 2-(1-Bromoethyl) derivatives were reacted with phthalimide in the presence of K$_2$CO$_3$ in DMF to give 2-(1-phthalimidoethyl) derivatives, which were converted into 2-(1-aminoethyl) derivatives by treatment with H$_2$NNH$_2$·H$_2$O in boiling EtOH overnight. Addition of ethylsulfonylethene to amino group of 2-(1-aminoethyl) derivatives afforded 2-(1-(2-(ethylsulfonyl)ethylamino)ethyl) derivatives, which were N-acylated with 2-[4-fluoro-3-(trifluoromethyl)phenyl]acetic acid in the presence of EDC, HOBt, and $N$-methylmorpholine in DMF. A 2-(1-aminoethyl) derivative was also obtained from a 2-{1-[N-(benzyloxycarbonyl)amino]ethyl} derivative by treatment with BBr$_3$ in CH$_2$Cl$_2$ (07WOP2007/002701).

Reaction of 3-amino-4$H$-pyrido[1,2-$a$]pyrimidin-4-one (33) with NaNO$_2$ in 6M HCl at 0 °C gave 34 diazonium chloride, which was converted into 35 3-azido derivative by treatment with aqueous NaN$_3$ solution (08AJC107).
Hydroxy group of a 3-substituted 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-8-carboxamide was changed for different piperidine groups by treatment first with (PhO)₂P(Ο)Cl in the presence of Hüning’s base at 0 °C in a solvent, then with different piperidine derivatives at 80 °C (07BMC7087). That of a methyl 3-hydroxy-6,7,8,9-tetrahydro-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylate was acylated with (PhCO)₂O in the presence of pyridine (07TL6552, 08JMC861) and Ac₂O in the presence of Et₃N and DMAP (07TL6552).

Reaction of 9-hydroxy-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones with 3,4-dihydro-2H-pyran in the presence of PhSO₃H in CHCl₃ at room temperature gave protected 9-(2-pyranyloxy) derivatives (09WOP2009/015828). The hydroxyl group was liberated from the 9-(2-pyranyloxy) group by treatment with conc. HCl in MeOH.

9-Amino group of a 9-[(R)-α-methylbenzylamino]-6,7,8,9-tetrahydro-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylate was formylated with a mixture of HCO₂H and Ac₂O in the presence of Et₃N (07TL6552). Acylation of the amino group of 9(S)-amino-6,7,8,9-tetrahydro-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylate was carried out with the enantiomers of α-methoxy-α-trifluoromethylphenylacetic acids in the presence of EDC, HOBt and DIPEA in DMF (07TL6552). The absolute configuration of tetrahydropyrido-pyrimidine in position 9 was determined by comparison of the chemical shifts of the resulting diastereomers, and by molecular mechanics and semiempirical (AM1) calculations.
Heating 3-benzyl-2-dimethoxymethyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one in 10% aqueous H$_2$SO$_4$ solution at 50 °C for 50 min gave 2-formyl derivative in 89% yield (06WOP2006/008523). The formyl derivative was reacted with EtMgBr at -78 °C for 1 h in THF to afforded 2-(1-hydroxypropyl) derivative, which was treated first with (MeCO)$_2$O in the presence of 2,6-lutidine in CH$_2$Cl$_2$, then with 2-(dimethylamino)ethylamine under microwave conditions providing 2-{1-(2-dimethylamino)ethylamino}propyl} derivative in 4% yield. The secondary amino group was acylated with 4-chlorobenzoyl chloride in CH$_2$Cl$_2$ in the presence of aqueous solution of K$_2$CO$_3$.

![Chemical Structures](image)

Reaction of 51 aldehyde with 52 CH active compounds in the presence of a base in a solvent afforded 53 condensation products, sometimes as mixtures of $E$ and $Z$ isomers (07T4548).

2-Amino derivative was obtained from a 2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one derivative in the reaction with $p$TsCl in the presence of DMAP in CH$_2$Cl$_2$, followed by 3,4-dimethoxybenzylamine in dioxane at 50 °C for 3 h and finally the treatment of the obtained 2-[(3,4-dimethoxybenzyl)amino] derivative with CF$_3$CO$_2$H at 60 °C for 0.5 h (09WOP2009/034976).

Heating 2,9-dihydroxy-4H-pyrido[1,2-a]pyrimidin-4-one in POCl$_3$ under reflux for 48 h furnished 2-chloro-9-hydroxy derivative in 60% yield (06WOP2006/109081,
Chloro atom was changed for morpholino group by reacting with morpholine in boiling EtOH for 18 h in 97% yield. 9-Hydroxy group was reacted with (CF₃CO)₂ in CH₂Cl₂ in the presence of NEt₃ at -20 °C to give 9-triflate in 90% yield. Suzuki-Miyaura reaction of 9-triflate with 3-phenylphenylboronic acid (06WOP2006/109084) and with (06WOP2006/109081) in the presence of a palladium catalyst [Pd(PPh₃)₄ and PdCl₂dppf] and a base (K₂CO₃ and Cs₂CO₃) in dioxane or THF at 80-95 °C for 18-48 h yielded 9-aryl derivatives. Under microwave conditions reaction time was only 30 min. Suzuki-Miyaura reaction of 3-bromo-4H-pyrido[1,2-a]pyrimidin-4-ones with 4-cyanophenyl boronic acid in the presence of Pd(dppf)₂Cl₂, Na₂CO₃ in THF under microwave conditions in THF at 150 °C for 10 min yielded 3-(4-cyanophenyl) derivatives (07WOP2007/002701, 08BMCL688). Reaction of 7-iodo-4H-pyrido[1,2-a]pyrimidin-4-one derivatives with (2-fluoro-3-chlorobenzyl)zinc chloride in the presence (2-MePh)₃P and Pd(dba)₂ in THF at 70 °C, with isothiazolidine 1,1-dioxide and tetrahydro-2H-[1,2]thiazine 1,1-dioxide in the presence of Cu(I)I, MeNHCH₂CH₂NHMe and K₂CO₃ in DMF at 80 °C gave 7-(2-fluoro-3-chlorophenyl)methyl, 7-(1,1-dioxoisothiazolidin-2-yl) and 7-(1,1-dioxo-tetrahydro-2H-[1,2]thiazin-2-yl) derivatives, respectively (08WOP2008/077188). N-(4-Fluorobenzyl)-7-trifluoroacetamido-3-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide was obtained, when 7-bromo-3-benzyloxy derivative was reacted with trifluoroacetamide in the presence of Cu(I)I, MeNHCH₂CH₂NHMe and K₂CO₃ in DMF at 80 °C in 31% yield.
Reaction of 33 aldehyde and 34 phenylalanine ester at 85 °C, then treatment of the reaction mixture with DMAD or DBZA at ambient temperature afforded a complex reaction mixture containing 37 cycloadducts and 38 3-unsubstituted 4H-pyrido[1,2-a]pyrimidin-4-one (07TL941). Treatment of the cold reaction mixture with methyl propiolate provided 39 cycloadduct together with 38 and 2-benzyl-1H-pyrroline-3,4-dicarboxylate. When the reaction mixtures of 33 aldehyde and different amino acid methyl esters were treated with ethyl or methyl propiolate at 85 °C for 20-66 h 38 was obtained in 57-98% yield together with diethyl and dimethyl 2-substituted 1H-pyrroline-
3,4-dicarboxylates, respectively. When PPTS additive was added to the reaction mixture somewhat shorter reaction period (2-45 h) could be applied.

Reaction mixture of 33 aldehyde and 34 phenylalanine ester was reacted with 35 olefinic dipolarophiles at room temperature and 50 °C for 19-48 h gave diastereomeric mixtures of 53, 54 and 55 4H-pyrido[1,2-a]pyrimidin-4-ones (06H(70)647). When the obtained mixtures were treated with PPTS in toluene afforded 2-dimethylamino-4H-pyrido[1,2-a]pyrimidin-4-one (38) in 78-90% yields. When the reaction mixtures of 33, 34 and 35 were heated in the presence of 2 equiv. of PPTS 2-dimethylamino-4H-pyrido[1,2-a]pyrimidin-4-one (38) could be isolated from the reaction mixture 78-85% yields besides mixture of diastereomeric trimethyl 2-benzyl-2,3-dihydropyrrolidine-2,3,4-tricarboxylates.
Cyclocondensation reactions of 35 imines, formed in situ from 33 aldehyde and 34 \( \alpha \)-amino acid methyl esters, with \( N \)-phenylmaleimide resulted in the formation of mixtures of 36-38 diastereomeric adducts with the preference of 36 (2007T1630). In all cases the cycloadditions gave excellent yields and endo-selectivity. Reaction periods were usually 1, 27 and 32 h in MePh, MeCN and DME, respectively. In EtOH only 36 (\( R = \text{Me}, R^1 = \text{Ph} \)) was obtained after 45 h reaction period in 43% yield. Increasing the reaction temperature usually slightly increased the yield of 37. When 34 (\( R = \text{NMe}_2, R^1 = \text{'Pr} \)) was applied the diastereomeric ratio of 36 and 37 (\( R = \text{NMe}_2, R^1 = \text{'Pr} \)) was 43-38 : 57-62. In this case, the ratio of 37 versus 36 increased when the reaction temperature was
increased. Applying glycine methyl ester (34, R¹ = H) the ratio of 36 endo and 38 (R = NMe₂, R¹ = H) exo products was 82 to 18.

Condensations of 3-acetyl-2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one with aromatic aldehydes in the presence of catalytic amounts of piperidine and AcOH in boiling benzene for 2 h provided 3-(3-aryl-1-oxo-allyl)-2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-ones (40) in 82-85% yields (06MI10). Cyclocondenzations of compounds 40 with H₂NNH₂·H₂O, HONH₂·HCl, CH₂(CN)₂ and heating in the presence of 40 % KOH yielded 41-43 3-substituted 4H-pyrido[1,2-a]pyrimidin-4-ones and 44 tricyclic derivatives, respectively.

Cyclocondensation of 134 2-phenoxy-3-formyl-4H-pyrido[1,2-a]pyrimidin-4-one and 135 5-aminopyrazole in refluxing DMF gave 136 tetracyclic derivatives (06MI6).
Reaction of 7-chloro- and 7-bromo-2-chloromethyl-3-nitro-4H-pyrido[1,2-a]pyrimidin-4-ones with diethyl oxomalonate in DMF at -20 °C for 30 min, than TDAE was added to the reaction mixtures and they were stirred at this temperature for an additional 2 h, followed by gradual heating to room temperature for 2 h to give diethyl 2-[(7-halo-3-nitro-4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)methylene]malonates in 19-24% yields (08H(75)925).

At room temperature amine salt was obtained from 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylate and EtNH$_2$ in EtOH (08CHE565). Reaction of 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylates and alkylamines, benzylamines and aniline in boiling EtOH and DMF afforded the corresponding amines in good yields (08CHE50, 08CHE565). Reaction of methyl 3-benzyloxy- and 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylates with 4-fluorobenzylamine in MeOH at 60-65 °C gave $N$-(4-fluorobenzyl-3-hydroxy-2-carboxamides (08JMC861, 09BML1930). In a four component Ugi condensation between 43 3-formyl-4H-pyrido[1,2-a]pyrimidin-4-one, 44 amine, 45 carboxylic acid and 46 isonitrile the expected 47 product formed only in trace amount (07TL2563).
After drop-wise addition of TMSCl to a reaction mixture of 7-bromo-2-chloromethyl-4H-pyrido[1,2-α]pyrimidin-4-one and 4-methoxycarbonyl benzaldehyde, the reaction mixture was heated in a pressure tube on a water bath to yield compound 123 (07S3163).

Under S_{RN1} conditions (inert atmosphere, photostimulation), the reaction of 146 2-chloromethyl-4H-pyrido[1,2-α]pyrimidin-4-one with anions formed from 2-nitropropane and malonates gave 147 ethylenic derivative resulting from a consecutive C-alkylation and HNO_2 elimination and 148 alkylated malonates, respectively (08SL2836). Both reactions were strongly inhibited by TEMPO, a free radical scavenger. Reactions of 146 and sodium salt of thiophenol and arylsulfinic acids yielded 149 S-alkylated derivatives in S_{N2} reactions, as addition of TEMPO did not decreased the yields significantly.

9-Amino-2-hetaryl-6,7,8,9-tetrahydro-4H-pyrido[1,2-α]pyrimidin-4-ones were obtained from 9-(1,3-dioxo-2,3-dihydro-1H-isindol-2-yl) derivatives with H_2NNH_2·H_2O in boiling EtOH (07WOP2007/057790, 08EPP1939187, 08WOP2008/078196). The amino
group was reacted with PhNCO, PhO₂CCl (07WOP2007/057790), and with different hetaroyl chlorides (08EPP1939187, 08WOP2008/078196) in the presence of NEt₃. Treatment of 3-benzyloxyamino-4H-pyrido[1,2-a]pyrimidin-4-ones with HBr in AcOH at 50-60 °C for 2 h afforded 3-amino derivatives (08H(75)2477). Amino group was reacted with different sugars in refluxing MeOH in the presence of small amount of AcOH to give N-glycosides in 62-100% yields.

Different N-benzyl derivatives of 3-benzoxyloxy- and 3-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamides were obtained by the treatment of methyl 3-benzoxyloxy-(07WOP2007/039218, 08JMC861) and 3-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylates with benzylamines in MeOH at 65 °C (07WOP2007/039218, 08JMC861, 08WOP2008/077188). N-[(4-Fluorophenyl)methyl] 2-carboxamide was also obtained when methyl 3-pivaloyloxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylate was reacted first with [(4-fluorophenyl)methyl]amine, and the obtained 3-pivaloyloxy-2-amide was hydrolyzed with 0.1 M aqueous NaOH (07WOP2007/039218, 08JMC861). 9-Amino derivative was obtained from N-(4-fluorobenzyl)-3-hydroxy-9-(benzyloxycarbonylamino)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide by treatment with 30% HBr in AcOH at ambient temperature for 2 h (08JMC861, 09BML1930). 9-Alkylamino group of N-(4-fluorobenzyl)-3-hydroxy-9-alkylamino-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamides was acylated with methylsulfonylacetyl chloride and N,N-(diethylamino)(oxy)acetyl chloride (08JMC861) furthermore with acyl chlorides and methyl oxalyl chloride (09BML1930). Hydroxy group of methyl 3-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylates was reacted with pivaloyl chloride, benzyl bromide, tBu,Me₂SiCl in the presence of a base to yield 3-pivaloyloxy,
3-benzyloxy and 3-\(t\)-butyldimethylsilyloxy derivatives, respectively. 3-Hydroxy derivatives were liberated from 3-methylsulfonyloxy-, 3-benzyloxy- and 3-\(t\)-butyldimethylsilyloxy-4\(H\)-pyrido[1,2-\(a\)]pyrimidin-4-ones by treatment with NaOH in MeOH, with Me\(_3\)SiI in MeCN under N\(_2\) at room temperature and under acidic and basic conditions, respectively.

Methyl group of methyl 7-methyl-3-(\(t\)-butyl, dimethylsilyloxy)-4-oxo-4\(H\)-pyrido[1,2-\(a\)]pyrimidine-2-carboxylate was brominated with NBS in boiling CCl\(_4\) in the presence of \(t\)-butyl peroxide to afford 7-bromomethyl derivative. The 7-bromomethyl derivative was reacted with morpholine in an 1 : 1 mixture of CH\(_2\)Cl\(_2\)-MeOH at ambient temperature and with P(OEt)\(_3\) in boiling MePh to give 7-morpholinomethyl and 7-(EtO)\(_2\)(O)PCH\(_2\) derivatives, respectively. The 7-(EtO)\(_2\)(O)PCH\(_2\) group was hydrolyzed by treatment with Me\(_3\)SiI in MeCN at 0 °C temperature to a phosphonic acid.
Scheme 4.

Ester group of 70 4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylate was converted into different five-membered heterocyclic group to give 73-77, as it is depicted on Scheme 4 (08WOP2008/077188). Esterification of 78 (R\(^1\) = H) carboxylic acid with 79 amidoximes provided compounds 80, which were cyclized by heating in toluene to yield 81 derivatives. Compounds 80 and 84 were prepared starting from 78 (R\(^1\) = H) carboxylic
acid and 79 amidoximes, furthermore 78 (R₁ = Me, R₂ = H) and 82 amino alcohol, respectively, as it is depicted on Scheme 5.

Scheme 5.

Hydrolysis of ethyl 7-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylate with 1 N NaOH at room temperature for 16 h yielded 3-carboxylic acid, which was coupled with an aromatic acid in CH₂Cl₂ in the presence of HATU give a 3-carboxamide in 24% yield (06WOP2006/116713). A 8-carboxylic acid was obtained from a 4-oxo-4H-pyrido[1,2-a]pyrimidin-8-carboxylate by hydrolysis with aqueous NaOH solution (06BMC1993). A 8-carboxamide was prepared by reacting the 8-carboxylic acid with 2-amino-4-tert-butylthiazol in the presence of Huning’s base and N,N-bis-(2-oxo-3-oxazolidinyl)phosphinic acid chloride in CH₂Cl₂.

Heating a tert-butyl (2-vinyl-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)acrylate in dioxane in the presence of 4 N HCl for 15 h gave a 2-chloroethyl-3-acrylic acid in 62% yield.
(06BMC1993). (4-oxo-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidin-3-yl)acrylic acids were obtained from \textit{tert}-butyl esters by treatment with an acid (TFA, HCl) (06BMC1993, 06BMC8506).

Chloro atom of 2-chloromethyl-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidin-4-one was substituted with 4-substituted phenols in DMF in the presence of Cs\textsubscript{2}CO\textsubscript{3} at 60 °C for 18 h (06WOP2006/072828) and with 1-(2-fluorophenyl)piperazine in DMF in the presence of Et\textsubscript{3}N at ambient temperature overnight (07WOP2006/110868).

Reaction of 2-methyl-3-(1,3-dioxobutyl)-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidin-4-ones with H\textsubscript{2}NNH\textsubscript{2}·H\textsubscript{2}O in boiling EtOH, and with HONH\textsubscript{2}·HCl in refluxing MeOH gave 3-(5-methylimidazol-2-yl) and 3-(3-methyl-1,2-oxazol-5-yl) derivatives, respectively (05MI3).

Same products were obtained with these reagents from 2-methyl-3-[3-(2-pyridylamino)-1-oxobut-2-enyl]- and 2-methyl-3-{3-(5-methyl-2-pyridyl)amino}-1-oxobut-2-enyl]-4\textit{H}-pyrido[1,2-\textit{a}]pyrimidin-4-ones, too.

Hydroxy group of paliperidone was acylated with different aromatic carboxylic chlorides and it was reacted with phenyl chloroformate, and alkyl chloroformates (08WOP2008/128436).

7. Reactivity of Substituent Presents in a Side Chain

Treatment of 14 diaacetox derivative of 1,2,3,4-tetrahydro-6\textit{H}-pyrido[1,2-\textit{a}]pyrimidines with Na in MeOH yielded trihydroxy derivatives in 92% yield (07MIP2).
At the synthesis of a library of heterocyclic compounds a 1,2,3,4-tetrahydro-1,4-benzothiazine derivative was N(4)-alkylated with 2-chloromethyl-4H-pyrido[1,2-a]pyrimidin-4-one in the presence of K₂CO₃ in MeCN (06IVU119).

2-Butyl-4-chloro-5-formyl-1H-imidazole was N(1)-alkylated with 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one and its 6,7,8,9-tetrahydro derivative in DMF in the presence of powdered K₂CO₃ in 78% and 56% yields, respectively (07MD269).

Reductive amination of 22 aldehyde with 23 piperazine in the presence of NaBH₃CN yielded 24 3-{2-[4-(2,4-difluorobenzoyl)piperazin-1-yl]ethyl}tetrahydropyrido[1,2-a]pyrimidin-4-one (Scheme 2). The keto group of compound 24 was reacted with NH₂OH·HCl, and the treatment of 25 oxime with KOH provided risperidone (05APR1019).
Reactions of 56 oxirane with primer amines and anhydro-(2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidinium)hydroxyde (50) gave the corresponding 57 and 58 2-(3-substituted 2-hydroxypropyl) derivatives, respectively (05MI2, 07HC19).

6-Phenylpirazin-3(2H)-one was N(3)-alkylated with 2-chloromethyl-4H-pyrido[1,2-a]pyrimidin-4-one in 46% yield (0606IVU24).

Chloro atom of 3-(4-chlorophenyl)-4H-pyrido[1,2-a]pyrimidin-4-ones was replaced with different primary amines in the presence of (2-biphenyl)di-tert-butylphosphine, Pd(OAc)$_2$ and NaOtBu in toluene at 100 °C yielded 3-[4-(substituted amino)phenyl] derivatives (08USP2008/0194616, 08WOP2008/097991). Similarly 3-[5-(1-tert-butoxycarbonyl-3-pyrrolidinyl)-3-pyridinyl]-4H-pyrido[1,2-a]pyrimidin-4-one was obtained from 3-(5-chloro-3-pyridinyl) derivative. Amino group of a 3-(4-aminophenyl)-4H-pyrido[1,2-a]pyrimidin-4-one was acylated with N-tert-butoxycarbonyl-L-proline in the presence of EDCI and HOBt in CH$_2$Cl$_2$ at 0 °C. Side chain N-(tert-butoxycarbonyl) groups were eliminated by stirring with 4 M hydrochloric acid in a solvent and by treatment with CF$_3$CO$_2$H in CH$_2$Cl$_2$ at room temperature. Treatment of 3-(4-methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-ones with 1.0 M BBr$_3$ in CH$_2$Cl$_2$ dropwise at -78 °C yielded 3-4-hydroxyphenyl derivatives. Hydroxy group was reacted with (CF$_3$SO$_2$)$_2$O in the presence of Et$_3$N CH$_2$Cl$_2$ at 0 °C and with (S)-(1-tert-
butoxycarbonyl)-3-hydroxypyrrolidine in the presence of Ph₃P and EtO₂CN=NCO₂Et in at ambient temperature in THF to give 3-[(4-trifluorosulfonyloxy)phenyl] and 3-{4-[1-(tert-butoxycarbonyl)-3-pyrrolidinyloxy]phenyl} derivatives, respectively.

Chloro atom of 3-(2-chloroethyl)-4H-pyrido[1,2-a]pyrimidin-4-ones (03MIP1, 03MIP4, 06USA2006/012206, 06WOP2006/061373, 09USA2009/0270369) and their 6,7,8,9-tetrahydro derivatives (09USA2009/0270369, 09WOP2009/015828, 09WOP2009/016653) was replaced by secondary cyclic amines to give 3-{2-aminoethyl} derivatives. 3-(2-Bromoethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one was reacted with 1-[bis(4-fluorophenyl)methyl]piperazine in DMF in the presence of powered K₂CO₃ to yield 3-(2-substituted ethyl) derivative (06BML3932). A hydroxymethyl group attached to phenyl group in position 2 of 4H-pyrido[1,2-a]pyrimidin-4-one was converted into a bromomethyl group by treatment with CBr₄ and PPh₃ (06BMC8506). Bromo atom was replaced by different secondary amines. A side chain piperazino group was N(4)-alkylated with Br(CH₂)₂OH and BrCH₂CO₂Bu. Treatment of a side chain 4-allylpiperazino group with N,N-dimethylbarbituric acid, and Pd(PPh₃)₃ in CH₂Cl₂ gave piperazino group.

Demethylation of 55 methoxy derivatives by treatment with BBr₃ in CH₂Cl₂ at -10 °C gave the appropriate hydroxy derivatives (07JMC4917)

Reaction of ¹¹CH₂O with 45 4H-pyrido[1,2-a]pyrimidin-4-one in aqueous formic acid at gave radiolabeled compound 46 with 99% chemical and radiochemical (06BMC4526).
A side-chain aromatic amino group was diazotated by treatment with t-butyl nitrite in the presence of HBF₄ in EtOH, then the filtered diazonium salt was treated with Cu(NO₂)₂ and cuprous oxide in water at ambient temperature for 1 h to give deaminated by product and hydroxy derivative in 17% and 19% yields, respectively (06WOP109081). A side-chain aromatic amino group were acylated with ClCH₂COCl and Br(CH₂)₂COCl, and the products were reacted with different amines.

Thermal cyclization of 40 3-formyl-2-amino derivatives furnished 41 tricyclic compounds (06H(70)181). That of compound 40 (R = H) gave a 4:3 mixture of compounds 41 (R = H) and 42. Similar reaction of 43 cyclic amino ester failed probably due to steric reason. The ester group in 40 seems to be essential for cyclization, as 3-formyl-2-(dibenzylamino) and -2-pyrrolino-4H-pyrido[1,2-a]pyrimidin-4-ones did not happened even at more harsh reaction conditions.
Competitive thermal ene reaction and Diels-Alder reactions of 63 acrylates and 70 (R = H) in boiling xylene afforded 64 and 71 tricyclic compounds, respectively (07T4548). Similarly 74 4H-pyrido[1,2-a]pyrimidin-4-ones gave 75 tetracyclic compounds, and 65 acrylate provided a mixture of 66 tricyclic, 69 tetracyclic and 67 pentacyclic derivatives. Heating 70 (R = Me) diester yielded a mixture of 72 tricyclic and 73 tetracyclic compounds.

4-Methoxybenzyl group of 3-{2-[1-(4-methoxybenzyl)tetrazol-5-yl]vinyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-8-carboxamides was removed by with TFA in anisole at 60-80 °C to yield 3-[2-(tetrazol-5-yl)vinyl derivatives (07BMC7087). A side chain hydroxyl group was converted into an aminocarbonyloxy group by treatment first with
CCl₃CONCO at 0 °C in EtOAc, followed by the treatment with HCO₂Na in aqueous MeOH at ambient temperature. Side chain hydroxyl groups were reacted with ω-dimethylaminoalkylamines in the presence of CDI in CH₂Cl₂ to yield N-(ω-dimethylaminoalkyl)aminocarboxyloxy groups. The dimethylamino group was quaternized by MeI, 2-iodoacetamide and tert-butyl bromoacetate. A side chain methoxycarbonyl and tert-butoxycarbonyl group was converted into a carboxyl group by treatment with aqueous NaOH solution and 4 N HCl in dioxane, respectively. N-(2-dimethylaminoethyl)aminocarbonyl group was obtained from a side chain carboxyl group by treatment with 2-dimethylaminoethylamine in the presence of EDC and HOBT in a mixture of DMF and CH₂Cl₂.

8. Rearrangement, Ring Transformation

Heating 6-methyl-2-phenyl- and 2,6-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-ones in Ph₂O under reflux for 5 h (06WOP2006/086381, 07WOP2007/052120, 08USA2008/0107623, 08USA2008/0107624, 08USA2008/0107625) and 300 °C for 1 h (08TL3380), respectively, gave 7-methyl-2-phenyl- and 2,7-dimethyl-1,4-dihydro-1,8-naphthyridin-4-ones in 92% yield.

Heating 3-azido-4H-pyrido[1,2-a]pyrimidin-4-one in boiling Ac₂O for 3 h afforded 3-(diacetylamino)imidazo[1,2-a]pyridine in 815 yield (08AJC107).

9. Miscellaneous

3,4-Dihydro-2H-pyrido[1,2-a]pyrimidine was investigated as catalyst for acyl transfer reaction, together with other similar bi- and tricyclic compounds containing amidine moiety (06TL4347).
Enantiomers of 212 2-[(1-aminoethyl)-4H-pyrido[1,2-a]pyrimidin-4-ones were separated on a Chiralpak AD-H column (07WOP2007/002701, 08BMCL688). Those of 9-hetaroyl-2-(pyrimidin-4-yl)-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones and a 9-methyl-9-(2-methoxynicotinoyl) derivative were separated on a Chiralcel OD-I column by chiral preparative HPLC (07WOP2007/057790, 08EPP1939187, 08WOP2008/078196).

Diastereomeric mixtures of methyl 9-[(S)- and 9-[(R)-(α-methylbenzylamino)-3-hydroxy-6,7,8,9-tetrahydro-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylates and 9-N-methyl-9-[(S)-α-methylbenzylamino] derivative were separated by preparative RP-HPLC (07TL6552).

Purification of paliperidone by crystallization was patented (228WOP2008/021346). Polimorphs of paliperidone were patented (228WOP2008/021342).

Copper(II) complexes 39 and 40 were obtained from 37 and 38 4H-pyrido[1,2-a]pyrimidines with Cu(QAc)2 dihydrate in aqueous acetone in 85-93% yields (05RCB2841).

C. Synthesis
1. By Formation of One Bond α to the Bridgehead Nitrogen Atom [6+0(α)]

When 2-(3-hydroxypropyl)amino]pyridine was reacted with SOBr₂ at 0 °C for 0.5 h in CH₂Cl₂, then the evaporated residue was treated with 3 M NaOH 3,4-dihydro-2H-pyrido[1,2-a]pyrimidine was obtained (08JOC6899).

\[
\begin{align*}
\text{29} & \quad \xrightarrow{0.1 \text{ M HCl, dioxane, } \mu w, 140 \degree \text{C}} \quad \text{30} \quad + \quad \text{31} \\
\text{1) MsCl, Et₃N, CH₂Cl₂,} & \quad 2) \Delta, 2 \text{h, THF} \quad \text{32} \\
\end{align*}
\]

Reaction of 29 (Ar = H) 6-fluoro-2-(3-hydroxypropylamino)pyridine, prepared from 2,6-difluoropyridine and 3-hydroxypropylamine, in acidified dioxane at 140 °C under microwave irradiation afforded 30 pyridone which was accompanied by 31 (Ar = H) bicyclic compound (07OL5175). 1,2,3,4-Tetrahydro-6H-pyrido[1,2-a]pyrimidin-6-one was obtained from 30 pyridone under Mitsunobu cyclodehydration conditions in 83% yield. When 29 (Ar = H) pyridine was reacted first with MsCl, then the mesylated product was heated in THF 32 (Ar = H) mesylate formed, which was hydrolyzed into 31 (Ar = H) 1,2,3,4-tetrahydro-6H-pyrido[1,2-a]pyrimidin-6-one in 85% yield. In similar reaction sequence 2-[N-benzyl,N-(3-hydroxypropyl)amino] derivative of 29 (Ar = H) and 5-aryl derivatives 29 (Ar = 4-MeOPh, 4-NO₂Ph) gave 1-benzyl derivative of 31 and 7-aryl derivatives of 31 (Ar = 4-MeOPh, 4-NO₂Ph) in 86% and 73-86% yields, respectively. 7-, 8- and 9-Iodo-1,2,3,4-tetrahydro-4H-pyrido[1,2-a]pyrimidinium
mesylates were prepared similarly from 3-, 4- and 5-iodo derivatives of 6-fluoro-2-(3-hydroxypropylamino)pyridine.

Heating 44 3-[(2-pyridylamino)methylidene]-4,5-dihydropyran-ones in boiling POCl₃ gave 45 3-(2-chloroalkyl)-4H-pyrido[1,2-α]pyrimidin-4-ones (07T8157).

\[
\begin{align*}
\text{N} & \text{N} \\
\text{R} & \text{R} \\
\text{O} & \text{O} \\
\text{R} & \text{R} \\
\text{R} & \text{R} \\
\text{N} & \text{N} \\
\text{R} & \text{R} \\
\end{align*}
\]

Cyclization of 9 enamine by heating in 1 mol KOH solution afforded 10 pemirolast potassium (03M11).

Heating 2-[(3-hydroxypropyl)amino]-3,4,5,6-tetrahydropyridine hydrochloride in SOCl₂ at 65 °C for 1 h gave 3,4,6,7,8,9-hexahydro-2H-pyrido[1,2-α]pyrimidine in 44% yield

Condensation of \(N\)-(2-pyridyl)-2-cyanoacetamide (39) and 3-methylbutanal in the presence of pyrididine yielded 40 2-amino-3 substituted 4H-pyrido[1,2-α]pyrimidin-4-one (07RJO83)
Heating 48 ethyl malonamate in tetraline provided 49 anhydro-(1-substituted 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidinium)hydroxyde (09WOP2009/099929).

2. By Formation of One Bond $\beta$ to the Bridgehead Nitrogen Atom [6+0($\beta$)]

3. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [6+0($\gamma$)]

4. By Formation of Two Bond from [3+3] Atom Fragments

Reaction of 2-dimethylaminopyridine and 1,3-bis(trifluoromethanesulfonyloxy)propane provided 23 disalt in 98% yield (09JA9174). Reactions of 2-aminopyridines and 15 enone
Mannich bases in acidified EtOH yielded 16 3-aryloyl-3,3-dihydro-2H-pyrido[1,2-\(a\)]pyrimidinium salts (09EJM2877).

Cyclocondensation of 7 (R = Ph) Baylis-Hillman acetate and 8 (Ar = Ph) ketene aminal in different solvents (THF, DMF, MeCN) gave a mixture of isomeric 9 (Ar = R = Ph) 6-phenyl and 10 (Ar = R = Ph) 8-phenyl derivatives of 9-benzoyl-7-nitro-1,2,3,4,7,8-hexahydro-6H-tetrahydropyrido[1,2-\(a\)]pyrimidine (08SL1357). At lower reaction temperature (0 °C) the ratio of 6-phenyl isomer was higher than at room temperature. In CH\(_2\)Cl\(_2\) at 0 °C regioselectively only 9 (Ar = R = Ph) 6-phenyl isomer formed, while at ambient temperature a 6 : 1 mixture of 9 (Ar = R = Ph) 6-phenyl and 10 (Ar = R = Ph) 8-phenyl derivatives was obtained. Reactions of 7 (R = 2-furanyl) and 8 in CH\(_2\)Cl\(_2\) at 0 °C afforded only 9 (R = 2-furanyl) compounds in 75-90% yields.

Reaction of 12 2\(H\)-3,4-dihydropyrene and 13 2-arylmethyleneperhydropyrimidine in CH\(_2\)Cl\(_2\) in the presence of Et\(_3\)N at ambient temperature afforded 14 9-aryloyl-7-nitro-1,2,3,4-tetrahydro-6\(H\)-pyrido[1,2-\(a\)]pyrimidines (07MIP2).
Cyclocondensation of 2-methylaminopyridine and 3-bromopropionic acid in MeCN at ambient temperature for 2 days gave 1-methyl-2-oxo-1,2,3,4-tetrahydropyrido[1,2-a]pyrimidinium bromide in 84% yield (07JST107). That of 2-aminopyridine and 3-chloropropionic acid yielded 2-oxo-1,2,3,4-tetrahydropyrido[2-a]pyrimidinium chloride (08JST244).

Cyclocondensations of 2-aminopyridine and its 5-methyl derivative and N-aryl-3-oxobutanethioamides at 100-105 °C for 1-2 h gave 4H-pyrido[1,2-a]pyrimidine-4-thione and its 7-methyl derivative in 47% and 43% yields, respectively (07RJO1548).

Reaction of 2-aminopyridine and 15 allene in boiling MeOH gave 17 2H-pyrido[1,2-a]pyrimidin-2-one (07T10511). In the initial step the pyridine nitrogen attacked on the allenic moiety, followed by the cyclization of the formed 16 to yield 17.

Reactions of 21 2-aminotetrahydropyridine with 22 and 23 3-ethoxyacrylonitriles provided 24 and 25 2-amino-7,8-dihydro- and 2-imino-1,2,7,8-tetrahydro-6H-pyrido[1,2-a]pyrimidine-6-thiones, respectively (08MI9).
Thermal reaction of 2-aminopyridine and diethyl malonate at 100-110 °C for about 6 h gave a mixture of anhydro-(2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidinium)hydroxyde and 4-hydroxy-1,8-naphthyridin-2(1H)-one (05MI2, 07HC19). The yield of naphthyridinone was higher when the reaction was carried out at higher reaction temperature (180-200 °C). 2,9-Dihydroxy-4H-pyrido[1,2-a]pyrimidin-4-one was obtained in the reaction of 3-hydroxy-2-aminopyridine with diethyl malonate at 170 °C for 18 h and with bis(2,4,6-trichlorophenyl) malonate in boiling bromobenzene for 3 h in 82% and 98% yield, respectively (07OBC2670). When 2-aminopyridine and bis(2,4,6-trichlorophenyl) malonate was reacted in boiling POCl₃ for 48 h 2-chloro-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one was the product in 32% yield. Cyclocondensation of a 2-aminopyridines and bis(2,4,6-trichlorophenyl) malonate in high boiling solvent (toluene, xylene) afforded 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidin-4-one derivatives (07BMC7087, 09WOP2009/034976). Heating an 1 : 2 ratio of 2-aminopyridine and bis(2,4,6-trichlorophenyl) 2-phenylmalonate at 250 °C for 15 min under solvent-free microwave reactor afforded 2-hydroxy-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one in 82% yield (07TL8250).
Thermal reaction of 2-aminopyridines and triethyl methanetricarboxylate was studied in different high boiling solvents (07CHE729). The amount of side products, formed from ester by amidation with the respective 2-aminopyridine, were minimized using a two fold excess of methanetricarboxylate in boiling xylene to give the best yields of esters. From 6-methyl-2-aminopyridine only a mixture of (R = 6-Me) amide and non-cyclized product was obtained.
1-Substituted *anhydro*(2-hydroxy-4-oxo-4\(^H\)-pyrido[1,2-\(a\)]pyrimidinium)hydroxyde (R\(^1\) = H, Ph) were prepared in the reaction of 2-(substituted amino)pyridines with diethyl 2-phenylmalonate, bis(2,4,6-trichlorophenyl) malonate and malonic acid (09WOP2009/099929).

Cyclocondensation of 45 2-(substituted amino)pyridine and 46 cyanoacetate in boiling xylene yielded 47 Zwitter ionic bicycle (09WOP2009/099929).

Reaction of 101 2-aminopyridines and dimethyl diacetoxyfumarate in the presence of an acid (AcOH, pTSA) in MeOH afforded 102 methyl 3-hydroxy-4-oxo-4\(^H\)-pyrido[1,2-
\(a\)]pyrimidine-2-carboxylates in poor yields (08WOP2008/077188).

Cyclocondensation of 2-aminopyridines and \(\beta\)-oxo esters under acidic conditions [in boiling toluene in the presence of \(p\)-TsOH under a water separator (05APR1019), in PPA at 110 °C (06WOP2006/086381, 07WOP2007/052120, 07WOP2007/002701, 08BMCL688, 08H(75)925, 08SL2836, 08TL3380, 08USA2008/0107623,
in boiling AcOH (08USP2008/0194616, 08WOP2008/097991) afforded 2-substituted and 2,3-disubstituted 4H-pyrido[1,2-a]pyrimidin-4-ones. That of 3-methyl-2-aminopyridine (06USA206/0122206, 06WOP2006/061373) and 3-benzyloxy-2-aminopyridine (08WOP2008/128436) with 2-acetylbutyrolactone in POCl₃ at 90-100 °C for 5-18 h gave 2,9-dimethyl- and 2-methyl-9-benzyloxy-3-(2-chloroethyl)-4H-pyrido[1,2-a]pyrimidin-4-ones, respectively, in 31-35% yields. That of 5-fluoro-2-aminopyridine and ethyl (R)-4-(benzyloxy carbamoylamino)-3-oxopentanoate in AcOH at 90 °C overnight afforded 7-fluoro-2-[(1-benzyloxy carbamoylamino)ethyl]-4H-pyrido[1,2-a]pyrimidin-4-one in 28% yield (07WOP2007/002701).

Cyclocondensation of 2-aminopyridine with 30 indole (06HCA2774) and 31 pyrimidine (07HCA1737) in boiling AcOH yielded 32 and 33 4H-pyrido[1,2-a]pyrimidin-4-ones, respectively.

Cyclocondensation of 11 enamine and 2-aminopyridines in boiling AcO₂H afforded 12 3-substituted 4H-pyrido[1,2-a]pyrimidin-4-ones (09ARK137).
Reaction of 5-methyl-2-aminopyridine and diethyl ethoxymethylenemalonate in MeCN in the presence of DBU under microwave irradiation at 150 °C for 20 min gave ethyl 7-methyl-4-oxo-4\(H\)-pyrido[1,2-\(a\)]pyrimidine-3-carboxylate in 58% yield (06WOP2006/116713). Cyclocondenzation of 2-amino-3-hydroxypyridine and bis(2,4,6-trichlorophenyl) malonate in boiling bromobenzene for 3 h afforded 2,9-dihydroxy-4\(H\)-pyrido[1,2-\(a\)]pyrimidin-4-one in 98% yield (06WOP2006/109084).

\[
\begin{align*}
\text{R} & = \text{H, Me} \\
\begin{array}{c}
\text{NH}_2 \\
\text{R}
\end{array} & + & \begin{array}{c}
\text{O} \\
\text{Me} \\
\text{O}
\end{array} & \text{Me} & \text{Me}
\end{align*}
\]

\[
\text{R} = \begin{array}{c}
\text{NHAc} \\
\text{N}
\end{array} & + & \begin{array}{c}
\text{O} \\
\text{N}
\end{array} & \text{Me} & \text{Me}
\]

Reaction of 2-aminopyridines and compound 40 in boiling BuOH provided a mixture of 2-acetamidopyridines, 41 and 42 3-substituted-2-methyl-4\(H\)-pyrido[1,2-\(a\)]pyrimidine-4-ones (05MI3).

\[
\begin{align*}
\text{R} & = \text{H, Me} \\
\begin{array}{c}
\text{O} \\
\text{N}
\end{array} & \text{Me} & \text{Me}
\end{align*}
\]

\[
\text{R} = \text{NHAc} & + \text{N}
\]

Reaction of 51 pyridine N-oxide with DMAD in the presence of \(p\)TsOH in CHCl\(_3\) yielded 52 methyl 3-hydroxy-4-oxo-4\(H\)-pyrido[1,2-\(a\)]pyrimidine-2-carboxylate (07WOP2007/039218).
Michael addition of compound 36 to the ylidenic bond in compounds 35, leading to the formation of acyclic intermediates 37 which cyclized into 6-imino-1,2,3,4,6,7-hexahydro-8H-pyrido[1,2-a]pyrimidin-7-carbonitriles 38 via nucleophilic attack of an NH group on a cyano group, followed by tautomerization to 39 6-amino-1,2,3,4-tetrahydro-8H-pyrido[1,2-a]pyrimidine-7-carbonitriles (05CHE1525).

Cyclocondenzations of bis(methylthio)methylenemalonitrile and 2-(aroylmethylene)piperidines in boiling xylene for 4-8 h gave 6-imino-8-methylthio-9-aroyl-1,2,3,4-tetrahydro-6H-pyrido[1,2-a]pyrimidine-7-carbonitriles in 82-100 yields (07SL761). Reactions of 51 2-aminopyridines and 52 3-oxopropanethioamides in boiling AcOH gave 53 2-methyl-4H-pyrido[1,2-a]pyrimidine-4-thiones (07RJO276).

Reaction of 2-aminopyridine and 40 furo[2,3-b]quinoxaline in boiling AcOH provided 41 2H-pyrido[1,2-a]pyrimidin-2-one (05AFF151).
Reaction of 2-methylaminopyridine and 3-bromopropionic acid in MeCN at ambient temperature for 2 days gave 1-methyl-2-oxo-1,2,3,4-tetrahydropyrido[1,2-a]pyrimidinium bromide in 84% yield (07ARK55). Similar reaction of 2-aminopyridine and 3-chloropropionic acid for 10 days provided 2-oxo-1,2-dihydropyrido[1,2-a]pyrimidinium chloride in 73% yield.

Cyclocondensation of 2-aminopyridine, its 3- and 6-hydroxy derivatives with β-oxo esters in PPA at 100 °C for 1 h afforded 2-substituted 4H-pyrido[1,2-a]pyrimidin-4-ones in 35-97% yields (07JMC4917). Reaction of 2-amino-3-hydroxypyridine and 2-unsubstituted β-oxo esters in refluxing xylene for 16 h gave 3-unsubstituted 9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-ones in 8-76% yields (09WOP2009/063901).

Methyl 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-8-carboxylate was prepared in the reaction of bis(2,4,6-trichlorophenyl) malonate and methyl 2-aminopyridine-4-carboxylate in boiling toluene for 1h in 51% yield (06BMC1993).

Cyclocondensation of 2-aminopyridines and 2-methyl-3,3-bis(methylthio)acrylate in EtOH in the presence of NaOEt and benzene in the presence of Et3N afforded 32 2-ethoxy- and 34 2-methylthio-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitriles, respectively (08MI10).
Scheme 1.

3-Amino-4H-pyrido[1,2-a]pyrimidin-4-ones (8) were prepared by parallel solid-phase and solution-phase synthesis (Scheme 1) (06JCO95). Polymer-bound (Z)-2-benzylxycarbonylamino-3-(dimethylamino)prop-2-enoate (2) was reacted with 2-aminopyridine gave polymer-bound 3-amino-4H-pyrido[1,2-a]pyrimidin-4-ones, and 8 were cleaved by treatment with an 1:1 mixture TFA – CH₂Cl₂ at ambient temperature. The purity of 8 bicycles were 78-83%. Better yields were achieved by using parallel
solution-phase synthesis reacting 2-aminopyridines with 4 (Z)-2-benzoxycarbonylamino-3-(dimethylamino)prop-2-enoate and 5 (Z)-2-acetylamino-3-(dimethylamino)prop-2-enoate.

Cyclocondensation of 2-aminopyridine with 9 3-dimethylaminoacrylate in boiling AcOH afforded 10 3-benzyloxyamino-4H-pyrido[1,2-a]pyrimidin-4-ones (08H(75)2477).

Reaction of 2-aminopyridine with 143 α,β-unsaturated ketones in boiling AcOH yielded 145 2,4-disubstituted 2H-pyrido[1,2-a]pyrimidines and 146 7,8,9,10-tetrahydro-6H-pyrido[1,2-a]quinazolines, respectively (06IJH39).

Base catalyzed cyclocondensation of 2-iminopiperidine hydrochloride with 11 β-oxo ester yielded 12 tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one under microwave conditions (06WOP2006/008523). That of 2-amino-3,4,5,6-tetrahydropyridine and 111 β-oxo esters yielded 112 2,3-disubstituted 4H-pyrido[1,2-a]pyrimidin-4-ones (06WOP2006/041968). Similarly 45 6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones were prepared from 43 amidine and 44 β-oxo esters (07WOP2007/057790, 08EPP1939187, 08WOP2008/078196). Starting from 2-amino-3-methyl-3-(1,3-dioxo-
2,3-dihydro-1H-isoindol-2-yl)-3,4,5,6-tetrahydropyridine and 44 (R = N) β-oxo ester yielded 2-(4-pyrimidinyl)-9-methyl-9-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (08EPP1939187, 08WOP2008/078196).

\[
\text{NH}_2 \quad \text{EtO}_2\text{C} \quad \text{Ph} \quad \text{NaOEt, EtOH} \quad 1\text{ h, 120 }^\circ\text{C, mw} \quad \text{11} \quad \text{72%}
\]

\[
\text{NH}_2 \quad \text{CO}_2\text{Me} \quad \text{NaOMe, MeOH} \quad 1\text{ h, 120 }^\circ\text{C, mw} \quad \text{112} \quad R = \text{Ph, cycloC}_6\text{H}_{11}
\]

\[
\text{NH}_2 \quad \text{EtO}_2\text{C} \quad \text{Ph} \quad \text{NaOMe, MeOH} \quad \Delta, 12 \text{ h} \quad \text{45} \quad X = \text{CH} 34\%
\]

Methoxy group of 2-(2-methoxyphenyl)-3-substituted 4H-pyrido[1,2-a]pyrimidin-4-ones were demethylated by treatment with BBr\textsubscript{3} in CH\textsubscript{2}Cl\textsubscript{2} (06WOP2006/041968).

Reaction of 13 organorhenium(I) derivative with 2-aminopyridine (5 mol equiv.) in CH\textsubscript{2}Cl\textsubscript{2} at room temperature for 3 h gave 14 pyrido[1,2-a]pyridinium salt (06OM416).

15 Base was liberated from 14 by treatment with MeONa in THF.
While the reaction of 2-aminopyridine and its 3-, 4-, and 5-methyl derivatives with 16 gave 17 bicycles, its 6-methyl derivative yielded only 18 condensation product (04RCB2060).

Reaction of 2-aminopyridine and 28 4-methoxy-1,1,1-trichloro-3-buten-2-ones in boiling EtOH provided 29 2-substituted 4H-pyrido[1,2-a]pyrimidin-4-ones (06JHC231).

Cyclocondensation of 2-aminopyridine and 30 enamo ester in boiling AcOH gave 31 4H-pyrido[1,2-a]pyrimidin-4-one (05H(66)207). Under similar conditions 3-benzoyl-4H-pyrido[1,2-a]pyrimidin-4-one (43) was prepared in the reaction of 2-aminopyridine and 42 benzoyl derivative (05JCM440).
\[
\text{NH}_2 + \text{EtO}\overset{\Delta, \text{AcOH,} 2 \text{ h}}{\longrightarrow} \text{EtO} + \text{N-Ph} \\
\]

\[
\text{NH}_2 + \text{Me}_2\text{N} \overset{\Delta, \text{AcOH,} 3 \text{ h}}{\longrightarrow} \text{Ph} + \text{EtO}
\]

32 6H-Pyrido[1,2-\(a\)]pyrimidin-6-ones were prepared in the reaction of 2-phenylethynylpyrimidine and 31 dimethyl malonates in diglyme in the presence of NaH at 150 °C (06H(67)523).

\[
\text{R} - \text{CO}_3\text{Me} + \text{Ph} \quad \overset{\text{NaH} (4 \text{ equiv.})}{\longrightarrow} \quad \text{R} - \text{CO}_3\text{Me}
\]

31

\[
\text{R} = \text{Me}, 48\%
\text{R} = \text{allyl}, 30\%
\]

Reactions of 133 acrylamides and 134 2-(aroylmethylene)perhydropyrimidine in the presence of Et\(_3\)N in MeCN afforded 124 1,2,3,4,7,8-hexahydro-6H-pyrido[1,2-\(a\)]pyrimidin-6-ones (09MIP2).

\[
\text{R} = \text{Ph}, 4-\text{MeOPh}; \quad \text{Ar} = \text{Ph}, 4-\text{ClPh}, 4-\text{FPh}, 4-\text{MeOPh};
\]

Reaction of 2-aminopyridine and 33 2-arylmethylene-\(\beta\)-oxo esters in boiling benzene usually yielded a mixture of 34 and 35 4H-pyrido[1,2-\(a\)]pyrimidines (05RCB2841).
Reaction of 2-aminotetrahydropyridine and 88 2-hydroxy-3-benzyloxyfumarete in MeOH in the presence of DBU yielded 89 3-benzyloxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate (07TL6552).

Heating a mixture of 90 3-formylchromanone and 91 pyridinone in the presence of TMSCl in DMF in a sealed tube on water bath yielded 92 4H-pyrido[1,2-a]pyrimidin-4-one (08S1069).

Cyclocondenzation of acrylaldehyde and 11 piperidine afforded 12 6H-1,2,3,4,7,8-hexahydropyrido[1,2-a]pyrimidine (06WOP2006/056108).
Reaction of 13 acrylates and 14 piperidines in the presence of AcOH catalyst gave 15 hexahydropyrido[1,2-\(a\)]pyrimodin-6-ones (07MIP4).

5. By Formation of Two Bond from [4+2] Atom Fragments

Compound 13, prepared from 3-amino-3-phenylpropionic acid with SOCl\(_2\), was reacted with 2-piperidone under reflux in toluene for 2 h. to afforded 14 hexahydro-4\(H\)-pyrido[1,2-\(a\)]pyrimidin-4-one (05MCR347).

Reaction of diethyl malonate and 33 pyrimidine in the presence of piperidine in boiling EtOH yielded 34 6-oxo-6\(H\)-pyrido[1,2-\(a\)]pyrimidine-7-carboxylate (06WOP2006/033422).
Cyclocondensation of 61 pyridine-2-thiones with 62 arylidenemalononitriles in boiling dioxane in the presence of few drops of piperidine afforded 63 6H-pyrido[1,2-a]pyrimidine-6-thiones (06JSF293).

6. By Formation of Two Bond from [5+1] Atom Fragments

By the reaction of 24 ketimines with 2 mol equiv. of 25 isocyanates 26 4H-pyrido[1,2-a]pyrimidin-4-ones were obtained in excellent yields (06OBC203). The reaction did not occur with cyclohexylisocyanate, and (2,6-dimethylphenyl)isocyanate gave only 6% of 25 (R = Me, R1 = cyclohexyl). Only 22% of 25 (R = Me, R1 = Ph) was obtained from 24 (R = Me, R1 = Ph), when 1 equiv. of tosylisocyanate was applied. Reaction of 24 ketimine (R = Me, R1 = Ph) and phenylisocyanate in boiling toluene for 24 h provided a mixture of 25 4H-pyrido[1,2-a]pyrimidin-4-one (R = Me, R1 = Ph) (29%) and 26 pyridine (70%). 26 Pyridine could be cyclized into 25 4H-pyrido[1,2-a]pyrimidin-4-one (R = Me, R1 = Ph). Reaction of with 24 ketimine [R = R1 = -(CH=CH)2-] in boiling toluene for 1 h gave 75% of 1,2,3,4-tetrahydro-11H-pyrido[2,1-b]quinazolin-11-one.
Cyclocondensation of 64 pyridine-2-thiones with malononitrile in boiling dioxane in the presence of few amounts of NEt₃ gave 63 6H-pyrido[1,2-a]pyrimidine-6-thiones (06JSF293).

7. By Formation of Three Bond from [3+2+1] Atom Fragments

6-Amino-8-aryl-9-nitro-1,2,3,4-tetrahydro-8H-pyrido[1,2-a]pyrimidine-7-carbonitriles (39) were prepared by one-pot reaction of 2-nitromethyleneepiperidine (36), CH₂(CN)₂ and aromatic aldehydes in boiling EtOH in the presence of piperidine for 4 h (05CHE1525).
Three-component reactions of Meldrum’s acid, aldehyde and 111 ketene aminal in the presence of NEt₃ boiling MeCN gave 112 1,2,3,4,7,8-hexahydro-6H-pyrido[1,2-a]pyrimidin-6-ones (06SL1835, 07MIP58). In the case of 111 (R¹ = iPr and hexyl) longer reaction period (24-96 h) was necessary for good yields. When ketone (as carbonyl reactant) or dialkyl malonates (instead of Meldrum’s acid) were used, the reactions were usually very slow and resulted in a complicated mixture of products.

Tree-component reactions of malononitril, aromatic aldehydes and 113 perhydropiperidines yielded 114 9-substituted 6-amino-8-aryl-1,2,3,4-tetrahydro-8H-pyrido[1,2-a]pyrimidine-7-carbonitriles (07MIP3).

One-pot, three-component reactions of 121 isocyanides, 122 dialkyl acetylenedicarboxylate and 123 N-(2-pyridylamines under mild reaction conditions
yielded 124 2-amino-4H-pyrido[1,2-α]pyrimidine-3,4-dicarboxylates (07TL4195, 07T11135).

R = tBu, cyclohexyl; \( R^1 = \text{Me, Et} \); \( R^2 = \text{OEt, CO}_2\text{Et} \); \( R^3 = \text{H, 7(5)-Me, 8(4)-Me} \)

8. **By Formation of Three Bond from [4+1+1] Atom Fragments**

3-Ethyl-2-hetaryl-4H-pyrido[1,2-α]pyrimidin-4-ones (103) were obtained by [2+2] carbonylative cycloaddition of 101 imines with allyl bromide under CO pressure in the presence of Pd(OAc)$_2$, PPh$_3$ and Et$_3$N in THF (06T12064). In the first step 102 β-lactams formed, which then rearranged into 103 4H-pyrido[1,2-α]pyrimidin-4-ones on the action of NEt$_3$. The proposed reaction mechanism is depicted in Scheme 1.

9. **Ring Transformation**
Rearrangement of N-(2-pyridyl)-3-oxoheptanamide in cc H₂SO₄ at ambient temperature for 48 h afforded 2-butyl-4H-pyrido[1,2-a]pyrimidin-4-one in 29% yield (08USP2008/0194616, 08WOP2008/097991).

Reaction of 88 furochromone-6-aldehyde and 2-aminopyridine in alcoholic KOH yielded 89 3-substituted 9aH-pyrido[1,2-a]pyrimidine (09BML2420).

Heating 90 bicyclic 1,2,4-oxadiazoline in o-xylene yielded 91 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate (07TL6552).

Diastereomeric mixtures of 101 betaine, obtained in the reaction of 2-aminopyridines and methylglyoxal, was identified as high-affinity inhibitors of cystic fibrosis transmembrane conductance regulator chloride channels (07MI4).
Rh(II)-mediated dipolar cycloaddition of 101 isomünchnone dipole, formed in situ from 100 pyrimidin-2-one in the presence of rhodium(II) acetate dimer in boiling benzene, with dipolarophiles gave 102 oxygen-bridged bicyclic compounds, which could be transformed into 103 1,4,7,8-tetrahydro-6H-pyrido[1,2-a]pyrimidin-6-ones by treatment with TsOH (07JOC9998). Dimethyl acetylenedicarboxylate yielded compound 104.

10. Rearrangement

Rearrangement/cyclization of 10 pyridine-N-oxides, obtained in the reaction of 2-aminopyridine N-oxides and DMAD in CHCl₃, by heating in boiling o-xylene gave 11 3-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidin-2-carboxylates, which were purified through ester formation (07WOP2007/039218, 08TL6556). 9-Benzylxoyamino derivative of 11
(R = NHCO₂CH₂Ph) was obtained from 13 pyridine-N-oxide in the reaction of DMAD in the presence of pTsOH in boiling CHCl₃ (08TL6556).

11. Miscellaneous

The tandem-cyclization of 17 β-amino acid containing dipeptides in boiling toluene in the presence of p-TsOH afforded 18 (6S,9aR)-perhydropyrido[1,2-a]pyrimidine-6-carboxylates in high diastereoselectivity (06OL239).

Cyclohydrocarbonylation of 20 dipeptide catalyzed by Rh-BIPHEPHOS complex gave 21 4-oxoperhydropyrido[1,2-a]pyrimidine-6-carboxylate with high regioselectively (07JOC1871).
Perhydropyrido[1,2-\(a\)]pyrimidin-6-one 18 was obtained when its 7 precursor was split from resin (07JCC1060).

**D. Applications and Important Compounds**

3-Aroyl-3,3-dihydro-2\(H\)-pyrido[1,2-\(a\)]pyrimidinium perchlorates (16) exhibited promising nitric oxide synthases inhibitory activities (09EJM2877). Compound 44 is a potent phosphoinositide 3-kinase \(\gamma\) (PI3K\(\gamma\)) inhibitor (06EJM558). R107474 is a potent and relatively selective \(\alpha_2\)-adrenoceptor antagonist (06BMC4526). Its radiolabeled derivative might be a suitable PET ligand for human use.
Compound 102 had a high passive permeability, the highest bioavailability of compounds 100, 101, and 102; and a high colonic bioavailability relative to risperidone (06JPS883).

Pyridopyrimidinone 103 (TGX-221) is a phosphoinositide 3-kinase β specific inhibitor (08BJ383), which exhibits antithrombotic activity (06CCT339, 08MI3), and inhibits platelet aggregation and platelet-granulocyte binding (08MI4). 3,8-Dibromo-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one was identified as selective hit in a neural cell model of Huntington disease (07NCB99).

4-Oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamides 155 (09BML1930), 6,7,8,9-tetrahydro-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamides 156 and 157 (08JMC861),
and their derivatives (09DND873) exhibited a good pharmacological profile and they are potent and orally active HIV-1 integrase inhibitors.

\[
\begin{align*}
\text{125} & \quad \text{126}
\end{align*}
\]

4\(H\)-Pyrido[1,2-\(a\)]pyrimidin-4-ones 125 and 126 were identified as inhibitors of cancerous Wnt/β-catenin pathway (09NCB100).

7-Dimethyl-3-nitro-4\(H\)-pyrido[1,2-\(a\)]pyrimidin-4-one has a good immunopharmacological profile on different in vitro and in vivo models, and it exhibited antihistaminic, anti-inflammatory and bronchorelaxant activities (08MI2).

A novel polymorph of risperidone (02MIP1) was patented. Polymorphic forms of paliperidone were also patented (09USA2009/0061005, 09WOP2009/016653). Different 4\(H\)-pyrido[1,2-\(a\)]pyrimidin-4-ones were patented as effective compounds inhibiting neuronal cell death (07USA2007/0027164) and as a part of recording layers of optical recording materials (07JP2007001095).

\[
\begin{align*}
R = H, R^1 = H, OH \\
R = OH, R^1 = H \\
R^2 = OH, R^3 = H, OH
\end{align*}
\]

4\(H\)-Pyrido[1,2-\(a\)]pyrimidin-4-ones 56 exhibited selective aldose reductase inhibitory activity (07JMC4917).

Pemirolast was also used to develop an electrophysiologic method for predicting corneal epithelial breakdown by antiallergic eye drops (08MI7). Ophthalmic compositions
(Chem. Abstr. 151, 470200 (2009) and antiallergic tablets (09MIP3) of pemrolast were patented.

A composition comprising ocaperidone, an antipsychotic drug, as an active substance and an effective amount of water-soluble polymers to increase solubility of ocaperidone was patented (06EUP1690540). Different salts (e.g. with pyroglutamic acid, N-(2-carboxyphenyl)glycine acid, orotic acid, galactic acid) of ocaperidone were patented (06WOP2006/090285). The highly soluble 123 4H-pyrido[1,2-a]pyrimidin-4-one (D13-9001) has good potency in vitro and displayed excellent MexAB-OprM specific efflux pump inhibitory activity in vivo in a rat pneumonia model of Pseudomonas aeruginosa (07BMC7087).

2-Piperidino-4H-pyrido[1,2-a]pyrimidin-4-one exhibited in vitro inhibitory activities on human platelet aggregation induced in platelet-rich plasma by adenosine diphosphate, collagen and A23187 (07JMC2886).
Diastereomeric mixtures of 101 betaines, obtained in the reaction of 2-aminopyridines and methylglyoxal, were identified as high-affinity inhibitors of cystic fibrosis transmembrane conductance regulator chloride channels (07MI4).

3,4-Dihydro-2H-pyrido[1,2-a]pyrimidine could be used as acid scavenger in the esterification and amination of alkyl and aryl carboxylic acids and also in glycosylation of 2-amino-2-deoxy sugar (01MI1), but it did not show activity as an acylation catalyst . . . (07OL37).

IV. Benzologs of pyrido[1,2-a]pyrimidines

A. Structure

1. Thermodynamic Aspects

2. Theoretical Calculations

3. UV Spectroscopy

4. IR and Raman Spectroscopy

5. NMR Spectroscopy

6. Mass Spectrometry
7. X-Ray Investigations

B. Reactivity

1. Ring Opening

2. Oxidation, Dehydrogenation

3. Hydrogenation, Reduction

4. Reactivity of the Ring Carbon Atoms

5. Reactivity of the Ring Nitrogen Atom

6. Reactivity of Substituent Attached to a Ring Carbon Atom

7. Reactivity of Substituent Presents in a Side Chain

8. Rearrangement, Ring Transformation

9. Miscellaneous
C. Synthesis

1. By Formation of One Bond $\alpha$ to the Bridgehead Nitrogen Atom \([6+0(\alpha)]\)

2. By Formation of One Bond $\beta$ to the Bridgehead Nitrogen Atom \([6+0(\beta)]\)

3. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom \([6+0(\gamma)]\)

4. By Formation of Two Bond from \([3+3]\) Atom Fragments


\[ \begin{align*}
\text{R} &= \text{H, Cl, CN, CH}_2\text{CO}_2\text{H, CH}_2\text{CH}_2\text{CO}_2\text{H, 1-piperazinil, 4-methyl-1-piperazinil, 4-morpholinyl} \\
\text{R}^1 &= \text{H, 4-Me, 2-Cl, 3-Cl, 3-CO}_2\text{H, 3-CO}_2\text{Me, 2,3-(OMe)}_2
\end{align*} \]

Heating mixtures of 90 3-formylchromanone and 93 quinazolinones in the presence of TMSCl in DMF in a sealed tube on water bath yielded 94 11H-pyrido[2,1-b]quinazolin-11-ones (08S1069).

5. By Formation of Two Bond from \([4+2]\) Atom Fragments
Compound 113, prepared from anthranilic acid with SOCl₂, was reacted with 2-piperidone to give 114 tetrahydro-11\textit{H}-pyrido[2,1-\textit{b}]quinazolin-11-one (05MCR347). Tricyclic compound 114 was also prepared under solvent free conditions from 2-piperidone and anthranilic acid on silica gel by microwave irradiation.

6. By Formation of Two Bond from [5+1] Atom Fragments

7. By Formation of Three Bond from [3+2+1] Atom Fragments

8. By Formation of Three Bond from [4+1+1] Atom Fragments

9. Ring Transformation
Rh(II)-mediated dipolar cycloaddition of 201 isomünchnone dipole, formed in situ from 200 pyrimidin-2-one in the presence of rhodium(II) acetate dimer in boiling benzene, with 2-cyclohexen-1-one gave 202 1,4,7,8-tetrahydro-6H-pyrimido[1,2-a]isoquinoline-6,11-dione (07JOC9998).

10. Miscellaneous

Cyclization of 20 dipeptide in boiling toluene in the presence of p-TsOH catalyst gave a nearly 1:1 mixture of 21 tetrahydro and 22 hexahydropyrido[2,1-b]quinazoline-9-carboxylate. When the cyclization was carried out in CH2Cl2 with BF3·OEt2 a 4:1 diastereomeric mixture of 22 and 23 hexahydropyrido[2,1-b]quinazoline-9-carboxylates were obtained. The diastereomers were separated by preparative HPLC (06OL239).

D. Applications and Important Compounds
A diastereomeric mixture of 102 betaine, prepared by the reaction of 1-aminoisoquinoline and methylglyoxal, was identified as high-affinity inhibitors of cystic fibrosis transmembrane conductance regulator chloride channels (07MI4).

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AcOH</td>
<td>Acetic acid</td>
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<tr>
<td>CDI</td>
<td>1,1’-Carbonylbis -1H-imidazole</td>
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<tr>
<td>CTAB</td>
<td>Cetyltrimethylammonium bromide</td>
</tr>
<tr>
<td>DBZA</td>
<td>Dibenzoylacetylene</td>
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<tr>
<td>DIAD</td>
<td>Diisopropyl azodiucarboxylate</td>
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<td>DIBAL-H</td>
<td>Diizobutylaluminum hydride</td>
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<td>DIPEA</td>
<td>N,N-Diisopropylethylamine</td>
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<td>DMAD</td>
<td>Dimethyl acetylenedicarboxylate</td>
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<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
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<td>EDCI EDC</td>
<td>1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride</td>
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<td>PPTS</td>
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<td>pTsCl</td>
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<td>QSAR</td>
<td>Quantitative structure-activity relationships</td>
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<tr>
<td>TDAE</td>
<td>Tetrakis(dimethylamino)ethylene</td>
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<tr>
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<td>2,2,6,6-Tetramethyl-1-piperidinyloxy</td>
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<td>TFA</td>
<td>Trifluoroacetic acid</td>
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<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
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<td>TMSCl</td>
<td>Chlorotrimethylsilane</td>
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<tr>
<td>TsOH</td>
<td>$p$-Toluenesulfonic acid monohydrate</td>
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