REACTIONS OF URACILS, 23 (◊). SUBSEQUENT REACTIONS OF 7-ETHOXYPYRIMIDO[4,5-d]PYRIMIDINES: NUCLEOPHILIC EXCHANGE, PYRIMIDO[4,5:4',5']PYRIMIDO[1,2-a]QUINAZOLINES, BENZO[f]PYRIMIDO[4,5:4',5']PYRIMIDO[1,2-d][1,3,4]TRIAZEPINE

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Abstract

The nucleophilic substitution of 7-ethoxypyrimido[4,5-d]pyrimidines 1a-d is described to afford with ammonia 7-amino derivative 2a, with glycine ester 3a, and with (±)2-phenylethylamine 4a, while reaction with amino acid ester hydrochlorides in DMSO at 150 °C leads with remarkable ease to *syn*-elimination of ethylene to give tetraones 5a,b. DBN employed as base reacts with substitution and cleavage to pyrrolidinone-N-propylamino derivative 6. Pyridopyrimidines 1a-c and hydrazine hydrate afford the 7-hydrazino derivatives 7a-c which give with S,S-ketene acetal 8 the 7-(N-1′-pyrazolyl)-derivatives 9a-c. The 6-(2'-methoxycarbonylphenyl)-derivative 1d reacts with ammonia to the pyrimido-pyrimido carboxylate 6-ammonium betaine 10a and is converted into the tetracyclic pyrimido-pyrimido-quinazoline 10b by refluxing in DMSO. Short treatment of 1d with hydrazine gives 6-aminoquinazoline 11 as a pure product, while a prolonged heating leads to a nearly insoluble mixture of 11 and its isomer the 1,3,4-triazepine 12 as the main products and a third component in small amount, the structure of which could not be elucidated till now.

Introduction

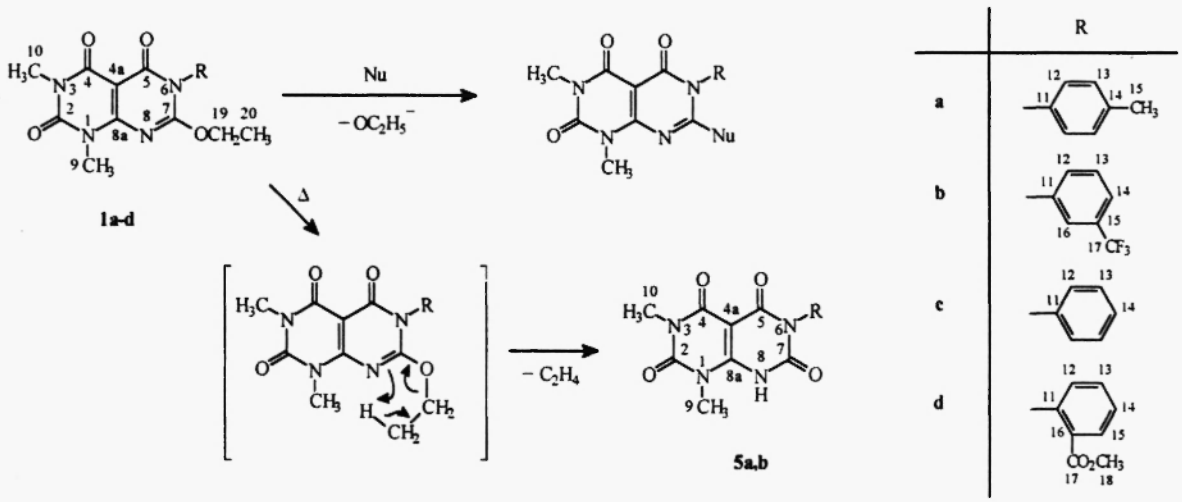
Recently (3), we have described a simple access to 7-ethoxypyrimido[4,5-d]pyrimidines 1 *via* a novel pyrimidine anellation reaction employing 6-(triphenylphosphoranylideneamino)-uracil-5-carboxylates and isocyanates (4). Due to their manifold biological activity (5,6,7,8) the derivatization of the

(◊) Part 22: Ref. (1)

bicyclic lactimethers 1, e.g. by nucleophiles, should lead to novel promising structures as potential biologically active leads.

After some preliminary nucleophilic exchange reactions with amines have been described (3), now we want to report on detailed experiments into this direction revealing once again the useful synthetic kit chemistry ('Baukastenchemie') character of the heterocyclic β-enamino esters (9). However, running these S_N-reactions it must be taken into account, that above a temperature of only 150 °C *syn*-elimination of the 7-ethoxy group as ethylene occurs spontaneously and leading predominantly to an energetically favored lactam moiety 5a,b.

S_N-reactions and *syn*-elimination of 7-ethoxypyrimido[4,5-d]pyrimidines:

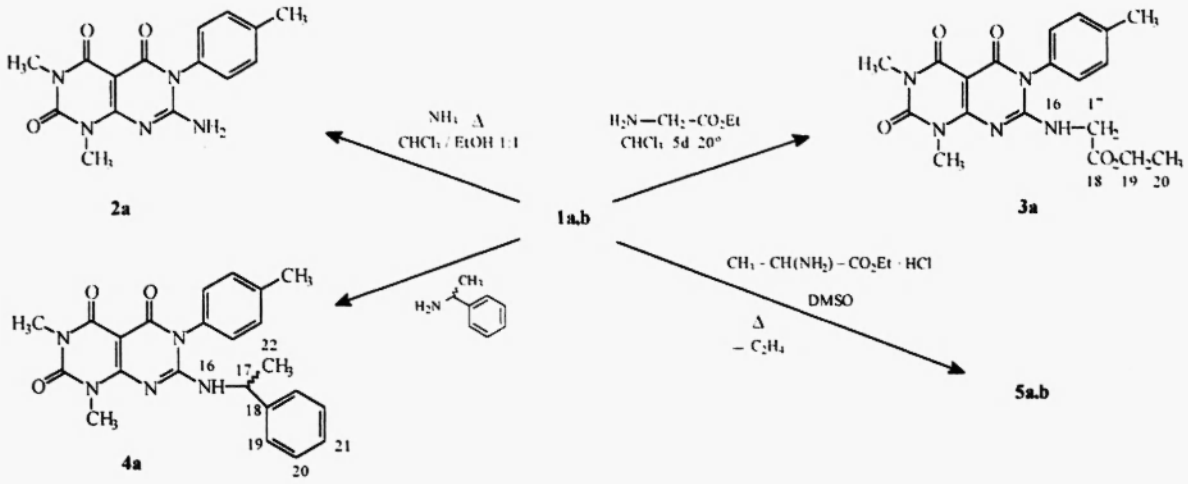


Discussion and Results

After some unsuccsessful attempts, passing of ammonia in a refluxing $CHCl_3$/EtOH solution of 1a leads in good yield to the corresponding amino derivative 2a, improving a previous approach of heterocondensed uracils *via* hydrazinolysis, diazotation and photolysis of the azido derivative (10).

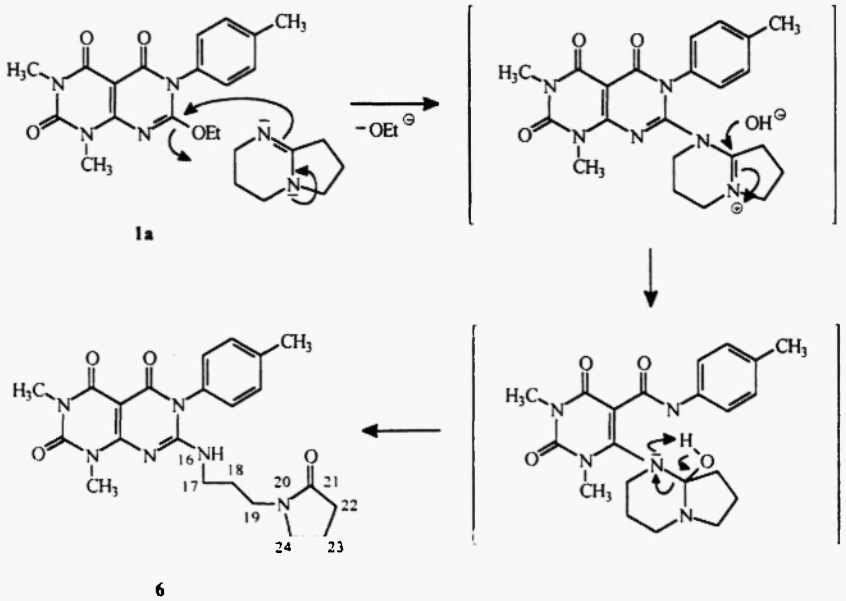
From several amino acid esters employed only glycine seems to possess a sufficient basicity for a rapid exchange; alanine and leucine ester fail while the comparably voluminous (±)2-phenylethylamine reacts smoothly to give 4a. However, treatment of the hydrochlorides of alanine ester with 1a,b in DMSO at 150 °C forms again with remarkable ease the lactam products 5a,b in a rapid *syn*-elimination of ethylene.

Substitution of the 7-ethoxy group by several amino esters:



Surprisingly, upon treatment of 1a with alanine ester hydrochloride in the presence of diazabicyclononene (DBN) for generating the free amino acid ester. the DBN substitutes the 7-ethoxy group with subsequent ring cleavage to give the pyrrolidone-N-propylamine derivate 6.

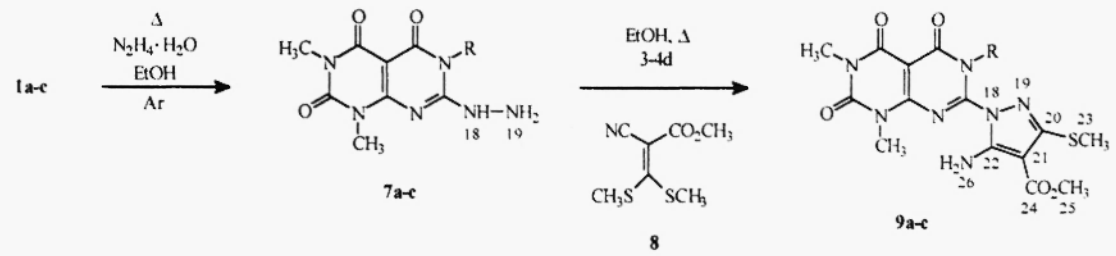
Treatment with diazabicyclononene (DBN) leads with subsequent ring cleavage to pyrrolidone-N-propylamine:



In refluxing ethanol and in an argon atmosphere 1a-c are smoothly converted with hydrazine hydrate into the 7-hydrazino derivatives 7a-c. 7a-c decompose slowly on exposure to air forming dark violet oxidation products according to previous observations of Gompper and Töpfl (11). 7a-c

react in turn with methyl 2,2-bis-methyl-mercapto-1-cyano acrylate 8, a typical ketene S,S-acetal, to afford the 7-(N-1'-pyrazolyl)-derivatives 9a-c.

Conversion into the 7-hydrazino derivatives and further reaction to 7-(N-1'-pyrazolyl)-derivatives :

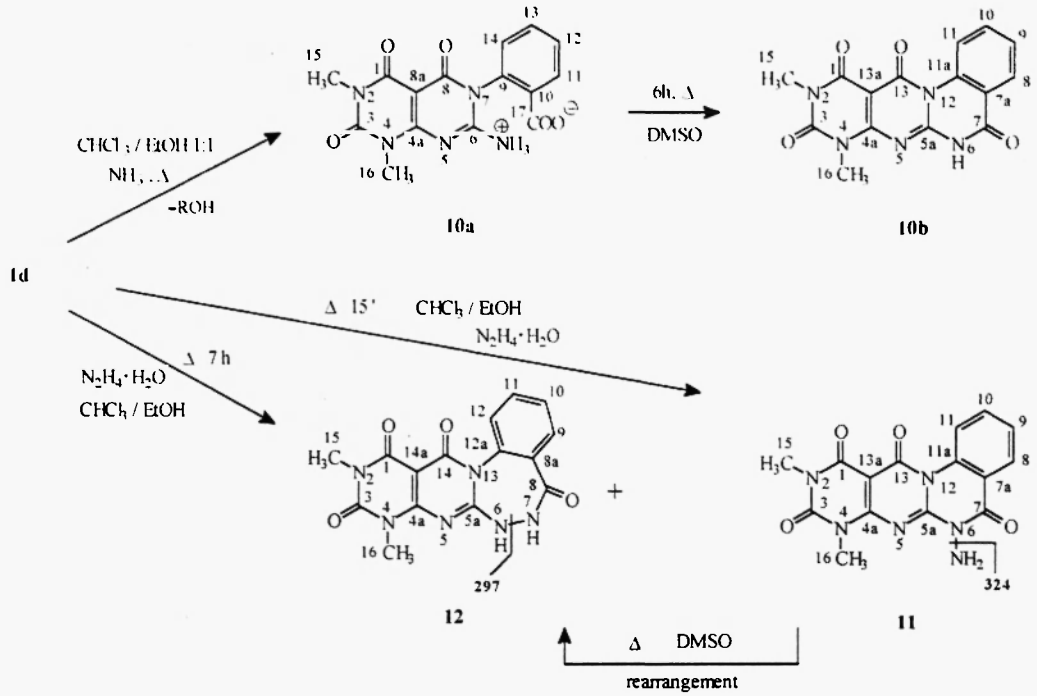


These derivatives display again an enamino ester moiety (9), so that starting originally from an uracil enamino ester this structural element was transferred over several steps ending up finally again with this rather versatile substituent pattern (9).

When the original heterocyclization reaction (3) leading to 7-ethoxypyrimido[4,5-d]pyrimidine is carried out with 2-carbomethoxyphenylisocyanate (12) the appropriate bicyclic product 1d is obtained; this is smoothly converted by treatment with gaseous ammonia in a refluxing solution of $CHCl_3$/EtOH into 6-ammonium-2,4-dimethyl-7-phenylpyrimido[4,5:4',5']pyrimido-1,3,8(2H,4H,7H)trioxo-10-carboxylate 10a. A prolonged heating in DMSO at about 120 °C leads to a novel tetracyclic pyrimido[4,5:4',5']pyrimido[1,2-a]quinazoline 10b. This is verified by the chemical shift of the NH-signals (δ = 6.95; $-NH_3^{\oplus}$ in 10a and δ = 13.05; -NH in 10b). With hydrazine hydrate 1d affords in a short reaction time of only 15 min. in good yield pure 6-amino-2,4-dimethylpyrimido[4,5:4',5']pyrimido[1,2-a]quinazoline-1,3,7,13(2H,4H,6H,12H)tetraone 11. An extended reaction time leads to a solid mixture of two isomeric tetracyclic pyrimido[4,5:4',5']pyrimido[1,2-a]quinazoline and benzo[f]pyrimido[4,5:4',5']pyrimido[1,2-d][1,3,4]triazepine 11 and 12, respectively, as the main products and a third component in a lower amount.

Because of their very poor solubility in all common solvents the determination of the constitutional formulae turned out to be rather difficult. So it is impossible to give a completely verified structure of the third component till now. In the NMR spectra the quinazoline and triazepine part of the both main products are determined by direct and long-range coupling correlations (especially to C-5a and to C-7 and C-8, respectively) using 2D-HMQC and 2D-HMBC measurements. The assignment is based on these methods, thereby 10b can be used for direct comparison possessing the same pyrimido[4,5-d]pyrimidine system and the *(ortho)*-disubstituted phenylring.

Novel tetracyclic pyrimido[4,5:4',5']pyrimido-[1,2-a]quinazolines and -[1,2-d][1,3,4]triazepines:



An important feature is the chemical shift of the 11-H in 10b and 11 at δ = 8.88-9.05 due to the deshielding effect of the adjacent 13-C=O group. The non-planar structure of the triazepinone ring in 12 results in a non-planar arrangement of the benzene ring and the 14-amide carbonyl group causing a much smaller deshielding effect for 12-H at δ = 8.45; furthermore, the NH-shifts of 12 appear at low field characteristic for guanidines and amides (δ = 10.06 and 12.06), while the signal of N-NH_2 group in 11 appears at δ = 6.28 as expected for primary amines. Comparison of the integration points to a rate of 2:1 for 11 *vs.* 12 (for the mixture prepared for 7 h) with an inclusion rate of 25% of hydrazine being in accordance with the found elemental composition.

With HR-MS a molecular peak of *m/z* = 340 u is registrated corresponding to an elemental composition $C_{15}H_{12}N_6O_4$ and a base peak of *m/z* = 297 u [M^+ - HNCO], which is in agreement with constitution of 12, while another fragmentation gives a peak at *m/z* = 325 u [M^+ - NH] and *m/z* = 324 u [M^+ - NH_2]. All these results support strongly formula 11.

In conclusion, cyclization of 1d with hydrazine hydrate leads to the primary product 11 which upon heating in DMSO is transformed into 12 in an irreversible way. The further conversion of 12 cannot be definitively answered because of the high insolubility. In protic solvents like TFA, a rapid rearrangement is observed with subsequent ring contraction 12 → 11 as it has been found ealier on other 1,3,4-benzo-triazepine-2,5-diones (13).

Experimental

The melting points are not corrected. - FT-IR spectra: Perkin-Elmer Paragon 500 (in KBr). - ^{1}H NMR: Bruker AC 200 (200 MHz), Bruker AM 250 (250.1 MHz) and Bruker DRX 500 (500.1 MHz). - ^{13}C NMR: Bruker AM 250 (62.9 MHz), Bruker AM 400 (100.6 MHz) and Bruker DRX 500 (125.8 MHz). For $CDCl_3$ as solvent δ_H = 7.24 and δ_C = 77.7; for [D_6]DMSO as solvent δ_H = 2.49 and δ_C = 39.5. - MS: MS-30 and MS-50 of Kratos (A.E.I.).

The 7-ethoxypyrimido[4.5-d]pyrimidines 1a-c are described in loc. cit (3).

7-Ethoxy-1,3-dimethyl-6(2'-carbomethoxyphenyl)pyrimido[4,5-d]pyrimidine-2,4,5(1H,3H,6H)-trione 1d: A suspension of 2-carbomethoxyphenylisocyanate (12) (3 g, 16.9 mmol) and of ethyl 1,3-dimethyl-6-(triphenylphosphoranylideneamino)-uracil-6-carboxylate (3) in acetonitrile (100 mL) was refluxed for 72 h. After removal of the solvent *in vacuo* the residue was treated with petroleum ether 40-60 (20 mL) until a solid had been formed. After addition of ethanol it was heated for additional 20 min. All solvents were evaporated and the residue chromatographed on silicagel (petroleum ether 40-60/acetone 2:1) to give 1.1 g (49%) of 1d, m.p. 205 °C. - IR: ν [cm^{-1}] = 3020 (CH_{ar}), 2980 (CH_{al}), 1750, 1730, 1690 (C=O), 1540 (C=C). - ^{1}H NMR ($CDCl_3$): δ = 1.20 (t, J = 7.0 Hz, 3 H, 20-H), 3.35 (s, 3 H, 10-H), 3.59 (s, 3 H, 9-H), 3.73 (s, 3 H, 18-H), 4.46 (q, J = 7.0 Hz, 2 H, 19-H), 7.22 (d, J = 8.0 Hz, 1 H, 12-H), 7.57 (t, J = 8.0 Hz, 1 H, 14-H), 7.59 (t, J = 8.0 Hz, 1 H, 13-H), 8.13 (d, J = 8.0 Hz, 1 H, 15-H). - ^{13}C NMR ($CDCl_3$): δ = 13.8 (C-20), 27.9 (C-10), 30.0 (C-9), 52.3 (C-18), 66.2 (C-19), 92.2 (C-4a), 127.1 (C-16), 129.6 (C-12), 131.8 (C-14), 131.9 (C-15), 133.8 (C-13), 134.4 (C-11), 151.4 (C-2), 157.8 (C-7, 8a), 158.6 (C-4, 5), 164.7 (C-17). - MS (70 eV); m/z: 386 [M^+]. - $C_{18}H_{18}N_4O_6$ (386.4): calcd. C 55.95, H 4.70; found C 55.90, H 4.78.

7-Amino-1,3-dimethyl-6(4'-methylphenyl)pyrimido[4,5-d]pyrimidine-2,4,6(1H,3H,7H)trione 2a: 1a (1 g, 2.9 mmol) was dissolved in $CHCl_3$ (20 mL) and EtOH (20 mL), and a moderate gas stream of NH_3 was passed into the refluxing solution for 1 h. After cooling to room temperature the precipitate was collected by filtration and dried *in vacuo* at 100 °C, to give 0.68 g 2a (73.4%), m.p. >430 °C. - IR: ν [cm^{-1}] = 3480-3160 (NH), 3060 (CH_{ar}), 2960 (CH_{al}), 1730, 1680, 1630 (C=O), 1530 (C=C). - ^{1}H NMR ([D_1]TFA / $CDCl_3$): δ = 2.56 (s, 3 H, 15-H), 3.69 (s, 3 H, 10-H), 3.82 (s, 3 H, 9-H), 7.36 (d, J = 8.0 Hz, 1 H, 12-H), 7.64 (d, J = 8.0 Hz, 1 H, 13-H). - ^{13}C NMR ([D_1]TFA / $CDCl_3$): δ = 21.6 (C-15), 30.6 (C-10), 31.8 (C-9), 86.9 (C-4a), 128.2 (C-12), 133.7 (C-13), 134.07 (C-11), 146.0 (C-14), 152.1 (C-2), 159.7 (C-7), 160.7 (C-8a), 167.4 (C-4), 168.2 (C-5). - MS (70 eV); m/z: 313 [M^+]. - $C_{15}H_{15}N_5O_3$ (313.3): calcd. C 57.50, H 4.83; found C 57.24, H 4.90.

Ethyl N[1,3-dimethyl-2,4,5(1H,2H,6H)trioxo-6(4'-methylphenyl)pyrimido[4,5-d]pyrimidine-7-yl]glycinate 3a: 1a (5 g, 14.6 mmol) was dissolved in $CHCl_3$ (100 mL) and freshly destilled ethyl glycinate (10.3 g, 100 mL) was added and stirred for 4 d at ambient temperature. The solvent was removed *in vacuo*, and the product chromatographed on silicagel (petroleum ether 40-60/acetone 2:1) to afford 3.3 g (56.7%), m.p. 240 °C. - IR: ν [cm^{-1}] = 3300, 3100 (NH), 3000 (CH_{ar}), 2940 (CH_{al}), 1745 (C=O). - ^{1}H NMR ([D_6]DMSO / $CDCl_3$): δ = 1.14 (t, *J* = 7.0 Hz, 3 H, 20-H), 2.33 (s, 3 H, 15-H), 3.11 (s, 3 H, 10-H), 3.26 (s, 3 H, 9-H), 3.89 (m, 2 H, 17-H), 4.00 (q, *J* = 7.0 Hz, 2 H, 19-H), 7.06 (d, *J* = 9.0 Hz, 2 H, 12-H), 7.19 (br, 1 H, 16-H), 7.35 (d, *J* = 9.0 Hz, 2 H, 13-H). - MS (70 eV); m/z: 399 [M^+]. - $C_{19}H_{21}N_5O_5$ (399.4): calcd. C 57.13, H 5.30, N 17.54; found C 57.48, H 5.31, N 17.39.

7-(1'Phenylethyl)amino-1,3-dimethyl-6-(4'methylphenyl)pyrimido[4,5-d]pyrimidine-2,4,5=(1H,3H,6H)trione 4a: 1a (2 g, 5.8 mmol) was suspended in α(±)phenylethylamine (10 mL) and heated slowly up to 90 °C. After 1.5 h the reaction mixture was let come to ambient temperature and treated with boiling diethyl ether (50-100 mL), filtered and the residue was recrystallized from EtOH/$CHCl_3$/n-hexane (3:2:1) to give 1.7 g (69%), m.p. 220 °C. - IR: ν [cm^{-1}] = 3260 (NH), 3040 (CH_{ar}), 2920 (CH_{al}), 1750, 1680 (C=O), 1520 (C=C). - ^{1}H NMR ([D_6]DMSO): δ = 1.42 (d, *J* = 6 Hz, 3 H, 22-H), 2.38 (s, 3 H, 15-H), 3.29 (s, 3 H, 10-H), 3.42 (s, 3 H, H-9), 5.06 (q, *J* = 6 Hz, 1 H, 17-H), 5.08 (br, 1 H, 16-H), 6.99-7.39 (m, 9 H, H_{ar}). - ^{13}C NMR ($CDCl_3$): δ = 21.30 (C-15), 22.46 (C-22), 27.74 (C-10), 29.75 (C-9), 52.08 (C-17), 89.76 (C-4a), 125.52 (C-21), 127.73 (C-19), 128.50 (C-12, 20), 130.31 (C-13), 131.51 (C-11), 140.67 (C-14), 142.61 (C-18), 151.68 (C-2), 153.52 (C-7), 158.34 (C-8a), 158.70 (C-4), 159.12 (C-5). - MS (70 eV); m/z: 417 [M^+]. - $C_{23}H_{23}N_5O_3$ (417.5): calcd. C 66.17, H 5.55, N 16.78; found C 65.21, H 5.67, N 16.25.

Pyrimido[4,5-d]pyrimidine-2,4,5,7(1H,3H,6H,8H)tetraones 5a,b; General Procedure:

A suspension of 1a,b (1-2 g) in DMSO (10-20 mL) was heated for 5 h to 150 °C. After cooling down, the product was filtered off and washed several times with EtOH.

1,3-Dimethyl-6-(4'-methylphenyl)pyrimido[4,5-d]pyrimidine-2,4,5,7(1H,3H,6H,8H)tetraone 5a: from 3 mmol 1a yield 0.58 g (22%), m.p. 335 °C. - IR: ν [cm^{-1}] = 3410 (NH), 3060 (CH_{ar}), 2980 (CH_{al}), 1758, 1722, 1695, 1677 (C=O), 796 (1,4-disubst. phenyl ring). - ^{1}H NMR ([D_6]DMSO): δ = 2.33 (s, 3 H, 15-H), 3.18 (s, 3 H, 10-H), 3.47 (s, 3 H, 9-H), 7.04 (d, *J* = 9.0 Hz, 1 H, 12-H), 7.24 (d, *J* = 9.0 Hz, 1 H, 13-H). - ^{13}C NMR ([D_6]DMSO): δ = 20.46 (C-15), 27.51 (C-10), 30.58 (C-9), 86.77 (C-4a), 128.49 (C-12), 129.25 (C-13), 132.38 (C-11), 137.64 (C-14), 149.74 (C-7), 149.98 (C-2),

152.94 (C-8a), 157.60 (C-4), 158.45 (C-5). - MS (70 eV): m/z: 314 [M^+]. - $C_{15}H_{14}N_4O_4$ (314.3): calcd. C 57.32, H 4.49, N 21.98; found C 57.11, H 4.15, N 21.92.

1,3-Dimethyl-6(3'trifluormethylphenyl)pyrimido[4,5-d]pyrimidine-2,4,5,7(1H,3H,6H,8H)tetraone 5b: from 5 mmol 1b yield 0.31 g (16.7%), m.p. 298 °C. - IR: ν [cm^{-1}] = 3450 (NH), 3080 (CH_{ar}), 2980 (CH_{al}), 1770, 1730, 1705, 1687 (C=O). - ^{1}H NMR ([D_6]DMSO): δ = 3.15 (s, 3 H, 10-H), 3.46 (s, 3 H, 9-H), 7.55-7.85 (m, 4 H, H_{ar}), 8.03 (s, 1 H, 8-H). - MS (70 eV); m/z: 368 [M^+]. - $C_{15}H_{11}F_3N_4O_4$ (368.3): calcd. C 48.92, H 3.01, N 15.21; found C 48.13, H 3.33, N 14.92.

7[3'(2-Oxopyrrolidine-1-yl)propyl]amino-1,3-dimethyl-6-(4'-methylphenyl)pyrimido[4,5-d]=pyrimidine-2,4,5(1H,3H,6H)trione 6 on trying the nucleophilic exchange with ethyl glycinate hydrochloride and DBN: 1a (1 g, 2.9 mmol) and ethyl glycinate hydrochloride (0.4 g, 2.9 mmol) were refluxed in triethylamine (40 mL) for 4 h; then 1,5-diazabicyclo[4,3,0]non-5-ene (DBN) was added and the refluxing was maintained for additional 20 min. The volatile components were removed in high vacuum and the product was recrystallized from ethanol to afford 0.42 g (33%), m.p. 185 °C. - IR: ν [cm^{-1}] = 3240 (NH), 2980 (CH_{ar}), 2940 (CH_{al}), 1730, 1690, 1670 (C=O). - ^{1}H NMR ($CDCl_3$): δ = 1.55-2.29 (m, 3 H, 18-, 22-, 23-H), 2.40 (s, 3 H, 15-H), 3.08-3.54 (m, 3 H, 17-, 19-, 24-H), 3.32 (s, 3 H, 10-H), 3.54 (s, 3 H, 9-H), 6.27 (t, J = 6.0 Hz, 1 H, 16-H), 7.08 (d, J = 8.0 Hz, 1 H, 12-H), 7.33 (d, J = 8.0 Hz, 1 H, 13-H). - ^{13}C NMR ($CDCl_3$): δ = 17.87 (C-18), 21.20 (C-15), 26.41 (C-23), 27.67 (C-10), 29.58 (C-9), 30.62 (C-22), 38.45 (C-17), 39.35 (C-19), 47.40 (C-24), 89.24 (C-4a), 128.31 (C-12), 131.15 (C-13), 131.41 (C-11), 140.20 (C-14), 151.77 (C-2), 154.49 (C-7), 158.51 (C-8a), 159.16 (C-4), 159.28 (C-5), 175.95 (C-21). - MS (70 eV); m/z: 438 [M^+]. - $C_{22}H_{26}N_6O_4$ (438.2): calcd. C 60.26, H 5.98, N 19.17; found C 58.09, H 6.60, N 18.24.

7-Hydrazinopyrimido[4,5-d]pyrimidines 7a-c; General Procedure:

The 7-ethoxypyrimido[4,5-d]pyrimidines were refluxed with an twofold molar excess of hydrazine hydrate in an argon atmosphere. After filtration of the reaction mixture the residue was treated several times with ethanol and dried *in vacuo*.

7-Hydrazino-1,3-dimethyl-6(4'-methylphenyl)pyrimido[4,5-d]pyrimidine-2,4,5(1H,3H,6H)trione 7a: from 1a (10 g, 29.2 mmol) and hydrazine hydrate (2 g, 40 mmol) after refluxing in ethanol (150 mL) for 45 min. yield 8.45 g (88%), m.p. 307-310 °C. - IR: ν [cm^{-1}] = 3365, 3327, 3234 (NH), 1727, 1686, 1646 (C=O), 800 (1,4-disubst. phenyl ring). - ^{1}H NMR ([D_6]DMSO): δ = 2.35 (s, 3 H, 15-H), 3.13 (s, 3 H, 10-H), 3.48 (s, 3 H, 9-H), 7.03 (d, J = 7.5 Hz, 2 H, 12-H), 7.27 (d, J = 7.5 Hz, 2 H, 13-H). - ^{13}C NMR ([D_6]DMSO): δ = 20.8 (C-15), 27.1 (C-10), 29.3 (C-9), 87.2 (C-4a), 128.6 (C-12), 130.3 (C-13), 131.4 (C-11), 138.6 (C-14), 151.4 (C-2), 156.3 (C-7), 157.9 (C-5), 158.6 (C-8a),

158.8 (C-4). - MS (70 eV); m/z: 328 [M^+]. - $C_{15}H_{16}N_6O_3$ (328.3): calcd. C 54.87, H 4.91, N 25.60; found C 54.44, H 4.98, N 25.71.

7-Hydrazino-1,3-dimethyl-6(3'-trifluormethylphenyl)pyrimido[4,5-d]pyrimidine-2,4,5(1H,3H,6H)-trione 7b: from an ethanolic suspension of 1b (1.0 g, 2.5 mmol) and hydrazine hydrate (0.2 g, 3.5 mmol) after refluxing for 30 min. yield 0.68 g (71%), m.p. 326 °C. - IR: ν [cm^{-1}] = 3383, 3336, 3234 (NH), 1726, 1693, 1637 (C=O). - ^{1}H NMR ([D_6]DMSO): δ = 3.13 (s, 3 H, 10-H), 3.47 (s, 3 H, 9-H), 7.49 (d, *J* = 7.5 Hz, 1 H, 14-H), 7.57 (s, 1 H, 16-H), 7.69 (t, *J* = 7.5 Hz, 1 H, 13-H), 7.74 (d, *J* = 7.5 Hz, 1 H, 12-H). - ^{13}C NMR ([D_6]DMSO): δ = 27.1 (C-10), 29.3 (C-9), 86.5 (C-4a), 125.2 (C-17), 126.2 (C-16), 126.3 (C-14), 130.2 (C-15), 130.5 (C-12), 133.5 (C-13), 136.2 (C-11), 151.5 (C-2), 157.2 (C-7), 157.8 (C-5), 158.6 (C-8a), 159.1 (C-4). - MS (70 eV); m/z: 382 [M^+]. - $C_{15}H_{13}F_3N_6O_3$ (382.3): calcd. C 47.13, H 3.43, N 21.98; found C 46.82, H 3.45, N 21.92.

7-Hydrazino-1,3-dimethyl-6-phenyl-pyrimido[4,5-d]pyrimidine-2,4,5(1H,3H,6H)trione 7c: from 1c (14.6 g, 45 mmol) and hydrazine hydrate (4 g, 80 mmol) suspended in ethanol (200 mL) after refluxing for 30 min. yield 10.6 g (75%), m.p. 318-323 °C. - IR: ν [cm^{-1}] = 3373, 3331, 3241 (NH), 1729, 1686, 1650 (C=O), 755, 697 (monosubst. phenyl ring). - ^{1}H NMR ([D_6]DMSO): δ = 3.14 (s, 3 H, 10-H), 3.49 (s, 3 H, 9-H), 7.16 (d, *J* = 7.5 Hz, 1 H, 12-H), 7.39 (t, *J* = 7.5 Hz, 1 H, 14-H), 7.47 (t, *J* = 7.5 Hz, 1 H, 13-H). - ^{13}C NMR ([D_6]DMSO): δ = 27.0 (C-10), 29.2 (C-9), 87.1 (C-4a), 128.8 (C-13, 14), 129.6 (C-12), 134.1 (C-11), 151.4 (C-2), 153.7 (C-7), 158.6 (C-8a), 160.4 (C-4), 161.2 (C-5). - MS (70 eV); m/z: 314 [M^+]. - $C_{14}H_{14}N_6O_3$ (314.3): calcd. C 53.50, H 4.49, N 26.74; found C 53.65, H 4.43, N 26.35.

1,3-Dimethyl-6(4'-methylphenyl / 3'-trifluormethylphenyl / phenyl)-7[5'-amino-4'-carbomethoxy-3-methylthiopyrazol-1-yl]pyrimido[4,5-d]pyrimidine-2,4,5(1H,3H,6H)trione 9a,b,c; General Procedure:

The 7-hydrazinopyrimido[4,5-d]pyrimidines 7a,b,c (7-16 mmol) were suspended in EtOH (300 mL) and after addition of equimolar amounts of methyl 2,2-bis-methylmercapto-1-cyanoacrylate 8 the reaction mixture was refluxed for 3-4 d. After evaporation of half of the volume the precipitate was filtered off and treated as described below.

9a: from 7a (2.3 g, 7 mmol) was obtained after recrystallization from DMF yield 0.84 g (25%), m.p. 289 °C. - IR: ν [cm^{-1}] = 3420, 3320 (NH), 3060 (CH_{ar}), 2940 (CH_{al}), 1740, 1690 (C=O). - ^{1}H NMR ([D_1]TFA / $CDCl_3$): δ = 1.89 (s, 3 H, 23-H), 2.26 (s, 3 H, 15-H), 3.22 (s, 3 H, 10-H), 3.44 (s, 3 H, 9-H), 3.66 (s, 3 H, 25-H), 7.14-7.65 (m, 4 H, H_{ar}). - ^{13}C NMR ([D_6]DMSO): δ = 14.60 (C-23), 20.75 (C-15), 29.10 (C-10), 30.94 (C-9), 52.60 (C-25), 93.34 (C-4a), 94.35 (C-21), 127.37 (C-12), 130.51

(C-13), 132.87 (C-14), 140.90 (C-11); 150.62 (C-8a), 151.99 (C-20), 155.60 (C-22), 156.68 (C-7), 157.86 (C-5), 161.32 (C-4), 161.90 (C-2). - MS (70 eV): m/z: 483 [M^+]. - $C_{21}H_{21}N_7O_5S$•1DMF (556.6): calcd. C 51.79, H 5.07, N 20.19; found C 51.29, H 5.12, N 19.75.

9b: from 7b (4.6 g, 12 mmol) after heating in a solvent mixture (5 mL DMF, 2 mL H_2O, 30 mL EtOH) then filtration, washing with EtOH and drying *in vacuo*, yield 1.53 g (24%), m.p. 298-300 °C. - IR: ν [cm^{-1}] = 3605, 3480, 3420, 3308 (NH), 3070 (CH_{ar}), 2970 (CH_{al}), 1740, 1699, 1654, 1622 (C=O). - ^{1}H NMR ([D_1]TFA / $CDCl_3$): δ = 1.78 (s, 3 H, 23-H), 3.48 (s, 3 H, 10-H), 3.78 (s, 3 H, 9-H), 3.96 (s, 3 H, 25-H), 7.30-7.88 (m, 4 H, H_{ar}). - ^{13}C NMR ([D_6]DMSO): δ = 12.5 (C-23), 27.3 (C-10), 30.2 (C-9), 50.0 (C-25), 86.5 (C-4a), 92.3 (C-21), 124.4 (C-17), 125.4 (C-16), 125.9 (C-14), 129.7 (C-12), 131.2 (C-15), 133.3 (C-13), 136.8 (C-11), 147.3 (C-20), 151.1 (C-22), 151.6 (C-2), 153.1 (C-8a), 154.1 (C-7), 157.9 (C-5), 158.3 (C-4), 163.7 (C-24). - MS (70 eV); m/z: 537 [M^+]. - $C_{21}H_{18}F_3N_7O_5S$ (537.1): calcd. C 46.93, H 3.38, N 18.27; found C 46.81, H 3.78, N 18.37.

9c: from 7c (5.0 g, 16 mmol) after heating the residue in 10-20 mL DMSO, filtration and washing with EtOH and H_2O and drying *in vacuo*, yield 5.8 g (77%), m.p. 315 °C. - IR: ν [cm^{-1}] = 3605, 3485, 3416, 3295 (NH), 1738, 1690, 1646, 1622 (C=O), 755, 693 (monosubst. phenyl ring). - ^{1}H NMR ([D_6]DMSO): δ = 1.88 (s, 3 H, 23-H), 3.22 (s, 3 H, 10-H), 3.43 (s, 3 H, 9-H), 3.64 (s, 3 H, 25-H), 7.35-7.95 (m, 6 H, 26-H, H_{ar}). - ^{13}C NMR ([D_6]DMSO): δ = 12.5 (C-23), 27.5 (C-10), 30.6 (C-9), 50.2 (C-25), 86.7 (C-4a), 92.1 (C-21), 128.1 (C-14), 128.4 (C-13), 128.8 (C-12), 135.2 (C-11), 147.4 (C-20), 150.0 (C-22), 152.1 (C-2), 153.3 (C-8a), 157.7 (C-7), 158.6 (C-4), 162.8 (C-5), 163.7 (C-24). - MS (70 eV); m/z: 469 [M^+]. - $C_{20}H_{19}N_7O_5S$•H_2O (487.5): calcd. C 49.26, H 4.37, N 20.11; found C 49.37, H 4.29, N 19.89.

Pyrimido[4,5:4',5']pyrimido-[1,2-a]quinazolines and -[1,2-d][1,3,4]triazepines 10a, 10b, 11, 12: *6-Ammonium-2,4-dimethyl-7-phenylpyrimido[4,5:4',5']pyrimido-1,3,8(2H,4H,7H)trioxo-10-carboxylate* 10a: 1d (0.92 g, 2.4 mmol) was dissolved in $CHCl_3$ (20 mL) and ethanol (20 mL) was added for better solution. Into the refluxing solution a moderate gas stream of NH_3 was passed for 5 h. After cooling down to ambient temperature, the precipitate was collected by filtration and washed with ether to give 0.66 g (84%), m.p. >400 °C. After heating in DMSO at 120 °C for 6 h 10a gives completely *2,4-dimethylpyrimido[4,5:4',5']pyrimido[1,2-a]quinazoline-1,3,7,13(2H,4H,6H,12H)-tetraone* 10b by cyclization. - IR: ν [cm^{-1}] = 3160 (NH), 1730, 1680, 1640 (C=O). - MS (70 eV); m/z: 325 [M^+]. - $C_{15}H_{11}N_5O_4$ (325.3): calcd. C 55.39, H 3.41, N 21.53; found C 54.84, H 3.53, N 21.47.

10a: - ^{1}H NMR ([D_6]DMSO): δ = 3.17 (s, 3 H, 15-H), 3.42 (s, 3 H, 16-H), 6.95 (br, 3 H, NH_3^+), 7.43 (t, *J* = 8.0 Hz, 1 H, 12-H), 7.62 (t, *J* = 8.0 Hz, 1 H, 13-H) 8.03 (d, *J* = 8.0 Hz, 1 H, 11-H), 8.88

(d, J = 8.0 Hz, 1 H, 14-H). - ^{13}C NMR ([D$_6$]DMSO): δ = 28.1 (C-15), 29.9 (C-16), 88.3 (C-8a), 121.7 (C-14), 122.4 (C-10), 126.5 (C-12), 127.1 (C-11), 131.9 (C-13), 138.3 (C-9), 152.3 (C-3), 155.4 (C-6), 157.9 (C-4a), 159.6 (C-1), 160.4 (C-8), 168.6 (C-17).

10b: - ^{1}H NMR ([D$_6$]DMSO): δ = 3.20 (s, 3 H, 15-H), 3.47 (s, 3 H, 16-H), 7.60 (t, J = 8.0 Hz, 1 H, 9-H), 7.86 (t, J = 8.0 Hz, 1 H, 10-H) 8.18 (d, J = 8.0 Hz, 1 H, 8-H), 9.05 (d, J = 8.0 Hz, 1 H, 11-H), 13.05 (br, 1 H, NH). - ^{13}C NMR ([D$_6$]DMSO): δ = 28.4 (C-15), 30.3 (C-16), 91.2 (C-13a), 120.6 (C-7a), 122.2 (C-11), 127.7 (C-9), 128.1 (C-8), 134.9 (C-10), 137.5 (C-11a), 151.2 (C-5a), 151.8 (C-3), 157.5 (C-4a), 158.4 (C-13), 159.0 (C-1), 161.2 (C-7).

6-Amino-2,4-dimethylpyrimido[4,5:4',5']pyrimido[1,2-a]quinazoline-1,3,7,13(2H,4H,6H,12H)tetraone 11: 1d (1 g, 2.6 mmol) was dissolved in a mixture of EtOH (90 mL) and $CHCl_3$ (30 mL), then hydrazine hydrate (1 g, 20 mmol) was added and the reaction mixture was heated up to gentle reflux (ca. 70 °C) for 15 min. The precipitate was filtered off, washed with ethanol and then with diethyl ether and dried *in vacuo* at 120 °C, yield 0.64 g (72.6%) of a white powder, m.p. 362-364 °C. - IR: ν [cm^{-1}] = 3437, 3370, 3280 (NH), 1748, 1690, 1640 (C=O). - ^{1}H NMR ([D$_6$]DMSO): δ = 3.23 (s, 3 H, 15-H), 3.58 (s, 3 H, 16-H), 6.28 (s, 2 H, NH_2), 7.65 (td, J = 7.5, 1.3 Hz, 1 H, 9-H), 7.89 (td, J = 7.5, 1.9 Hz, 1 H, 10-H), 8.25 (dd, J = 7.5, 1.9 Hz, 1 H, 8-H), 9.02 (d, J = 7.5 Hz, 1 H, 11-H). - ^{13}C NMR ([D$_6$]DMSO): δ = 28.1 (C-15), 30.3 (C-16), 91.0 (C-13a), 118.6 (C-7a), 121.6 (C-11), 127.8 (C-8), 128.5 (C-9), 134.8 (C-10), 135.9 (C-11a), 147.7 (C-5a), 151.7 (C-3), 156.7 (C-4a), 156.9 (C-7), 158.1 (C-13), 158.9 (C-1). - MS (70 eV); m/z: 340 [M$^+$]. - $C_{15}H_{12}N_6O_4$ (340.1): calcd. C 52.94, H 3.55, N 24.70; found C 51.83, H 3.62, N 25.24.

11 in mixture with its isomer *benzo[f]2,4-dimethylpyrimido[4,5:4',5']pyrimido[1,2-d][1,3,4]triazepine-1,3,8,14(2H,4H,7H,13H)tetraone* 12: from 1d under the same conditions as for the pure product 11 with a reaction time of 7 h, equal yield of 73% of a white powder, m.p. 362-398 °C.

12: - IR: ν [cm^{-1}] = 3380, 3280 (NH), 1750, 1680, 1640 (C=O). - ^{1}H NMR ([D$_6$]DMSO): δ = 3.17 (s, 3 H, 15-H), 3.44 (s, 3 H, 16-H), 7.21 (t, J = 7.5 Hz, 1 H, 10-H), 7.58 (t, J = 7.5 Hz, 1 H, 11-H), 7.67 (d, J = 7.5 Hz, 1 H, 9-H) 8.45 (d, J = 7.5 Hz, 1 H, 12-H), 10.06 (s, 1H, 6-H)*, 12.06 (s, 1H, 7-H) *. - ^{13}C NMR ([D$_6$]DMSO): δ = 27.9 (C-15), 30.3 (C-16), 91.0 (C-14a), 121.9 (C-12), 123.2 (C-8a), 124.1 (C-10), 128.8 (C-9), 132.4 (C-11), 137.6 (C-12a), 151.9 (C-3), 152.1 (C-5a), 157.6 (C-4a), 159.1 (C-1), 159.4 (C-14), 167.5 (C-8). * exchangeable.

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