

Supporting Information

Design, Synthesis, and Antifolate Activity of New Analogues of Piritrexim and Other Diaminopyrimidine Dihydrofolate Reductase Inhibitors with ω -Carboxyalkoxy or ω -Carboxy-1-alkynyl Substitution in the Side Chain

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Benzyl 4-Pentynoate. A mixture of 4-pentynoic acid (3.92 g, 40 mmol) and Cs_2CO_3 (6.5 g, 10 mmol) in anhydrous DMF (100 mL) was stirred for 15 min, and benzyl bromide (4.76 mL, 6.48 g, 40 mmol) was added. The reaction was stirred overnight, the solvent was removed by rotary evaporation under vacuum (Dry Ice/acetone trap), and the colorless residue was partitioned between EtOAc and H_2O . The organic layer was washed with brine and evaporated to a brown oil. Silica gel flash chromatography (95:5 pentane-Et₂O) afforded the ester as a colorless oil (6.98 g, 93%); ¹H NMR ($\text{DMSO}-d_6$) δ 2.37-2.60 (m, 4H, $\text{HC}\equiv\text{CCH}_2\text{CH}_2$), 2.79 (t, $J = 2.5$ Hz, $\text{HC}\equiv\text{C}$), 5.10 (s, 2H, CH_2Ph), 7.35 (s, 5H, aryl H) (data consistent with ref. 1s)

Benzyl 5-Hexynoate. This compound was obtained similarly as a colorless oil (86% yield): ¹H NMR (CDCl_3) δ 1.87 (q, 2H, $J = 7.1$ Hz, $\text{HC}\equiv\text{CCH}_2\text{CH}_2$), 1.96 (t, 1H, $J = 2.4$ Hz, $\text{HC}\equiv\text{C}$), 2.27 (dt, 2H, $J = 2.0, 6.9$ Hz, $\text{HC}\equiv\text{CCH}_2$), 2.52 (t, 2H, $J = 7.4$ Hz, CH_2COOBn), 5.12 (s, 2H, CH_2Ph), 7.31-7.37 (m, 5H, aryl H) (data consistent with ref. 2s).

Benzyl 6-Heptynoate. This compound was obtained similarly as a colorless solid (86% yield): ¹H NMR (CDCl_3) δ 1.50-1.64 (m, 2H, $\text{HC}\equiv\text{CCH}_2\text{CH}_2$), 1.70-1.86 (m, 2H, $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2$), 1.96 (t, 1H, $J = 2.6$ Hz, $\text{HC}\equiv\text{C}$), 2.17-2.27 (m, 2H, $\text{HC}\equiv\text{CCH}_2$), 2.40 (t, $J = 7.5$ Hz, CH_2COOBn), 5.13 (s, 2H, CH_2Ph), 7.35-7.38 (m, 5H, aryl).

2,4-Diamino-5-methyl-6-(2'-methoxy-5'-hydroxybenzyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (29). **Step 1.** Using the method previously reported,^{3s} 4-hydroxyanisole (12.4 g, 0.1 mol) was treated with methyl chloroformate (8.1 mL, 9.95 g, 105 mmol) in a mixture of pyridine (8.5 mL) and CH_2Cl_2 (75 mL) and the resulting methyl carbonate ester was distilled under vacuum, and the pale-green liquid boiling at 89-96 °C (0.11-0.14 mm Hg) was collected (lit.^{3s} bp 112 °C, 0.2 mm Hg) and used directly in the next step without further purification; yield 14.6 g, 80%). A portion of this distillate (10 g, 55 mmol) in CH_2Cl_2 (125 mL) was cooled to 0 °C and treated with TiCl_4 (14.3 mL,

24.6 g, 130 mmol) in CH_2Cl_2 (25 mL). Dichloromethoxymethane (5.75 mL, 7.3 g, 63.5 mmol) was then added dropwise under an inert atmosphere over a 30-min period, and the mixture was allowed to come to room temperature and stirred for another 30 min. The mixture was concentrated to half volume on a rotary evaporator and poured into a mixture of ice (125 g) and 12 N HCl (5 mL). The solution was extracted with EtOAc (2 x 100 mL). And the pooled organic layers were evaporated to dryness to obtain 2-methoxy-5-methoxycarbonyloxybenzaldehyde as a buff-colored solid (8.76 g, 76%). Without additional purification, several pooled batches of the aldehyde (42 g, 0.2 mol) were added to a solution of NaOMe prepared by dissolving metallic Na (4.6 g, 0.2 mol) in MeOH (800 mL). The resultant orange suspension was stirred for 30 min, the solvent removed by rotary evaporation to obtain the Na salt **24**, which was washed thoroughly with Et_2O and then dried a vacuum desiccator. A portion of this solid (30.6 g, 176 mmol) was taken up in dry DMF (40 mL) and treated with freshly distilled benzyl bromide (20.9 mL, 30.1 g, 176 mmol). After being stirred for 3 hr under an inert atmosphere, the initial solution became very viscous and a brown solid was observed to form. The reaction mixture was shaken vigorously with 1 M NaOH (300 mL), and the off-white solid was washed with a copious amount of warm H_2O , filtered, and dried to obtain **25** (39 g, 80%); mp 98-99 °C (lit.^{4s} 99-100 °C).

Step 2. Essentially according to Rauckman et al.^{5s}, a mixture of **25** (75 g, 0.31 g, pooled from two runs), ethyl acetoacetate (46 mL, 47.3 g, 0.36 mol), toluene (110 mL), cyclohexane (440 mL), piperidine (1.5 mL), and glacial AcOH (45 mL) was stirred under reflux for 3.5 hr and evaporated to dryness under reduce pressure. The dark-green mixture of olefins formed in the Knoevenagel reaction (56 g crude yield) was reduced catalytically in batches without further purification. A solution of the olefins (25 g) in EtOH (150 mL) was hydrogenated in a Parr apparatus at 20 psi in the presence of 5% Pd-C (0.9 g) for 3 hr, and the product was purified by flash chromatography (9:1

hexanes-EtOAc, R_f 0.22) to obtain ethyl 2-(2-methoxy-5-benzyloxyphenyl)-3-butanoate (**26**) as a pale-green oil which solidified upon standing (18 g, 24%). Starting from **26**, Steps 3-5 below were likewise carried out according to Rauckman et al.^{5s} with minor modifications,

Step 3. A mixture of **26** (12 g, 33.7 mmol) and 2,4,6-triaminopyrimidine (4.2 g, 33.7 mmol) in dry NMP (30 mL) was heated for 2 hr at 190 °C in a two-neck round-bottom flask fitted with a Dean-Stark trap. Although complete dissolution occurred initially, an off-white solid began to precipitate in the dark-colored solution after 30 min. At the end of 2 hr the reaction mixture was cooled, MeOH (45 mL) was added, and the fine white solid, consisting of crude 2,4-diamino-5-methyl-6-(2'-methoxy-5'-benzyloxybenzyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27**) was collected by suction filtration, and washed with boiling H₂O; yield 6.61 g (47%).

Step 4. Without additional purification, **27** (4.36 g, 10 mmol) was added at room temperature to the pre-formed Vilsmeier reagent obtained by adding oxalyl chloride (27.2 mL, 0.32 mol) at 0 °C to a DMF (24.3 g, 0.32 mol) and CH₂Cl₂ (150 mL) and stirring this mixture for 15 hr at room temperature. After the addition of **27** to the solution of Vilsmeier reagent, the mixture was refluxed 3 hr, then chilled at 0 °C while *n*-BuNH₂ (65 mL) was added in small portions over the course of 2 hr, followed by another 1.5 hr of reflux. The reaction mixture was cooled, the finely suspended solid was filtered, washed thoroughly with EtOH and then with boiling H₂O, and finally dried in a vacuum desiccator over P₂O₅ to obtain crude 2,4-diamino-5-methyl-6-(2'-methoxy-5'-benzyloxy)-benzyl-7-chloropyrido[2,3-*d*]pyrimidine (**28**) as a white solid; yield 9.3 g (69%).

Step 5. Without further purification, chloride **28** (4.36 g, 10 mmol) and 5% Pd-C (3.2 g) were suspended in 2-methoxyethanol (800 mL), the mixture was brought to a boil, and sodium formate (4.04 g, 60 mmol) was added in small portions over a period of 4 hr. The suspension was filtered

through a pad of Celite, and the solvent evaporated under reduced pressure to afford a brown solid which was triturated with CH_2Cl_2 and filtered to obtain crude 2,4-diamino-5-methyl-6-(2'-methoxy-5'-hydroxybenzyl)pyrido[2,3-*d*]pyrimidine (**29**) as a buff-colored solid which was used directly in the next step; yield 4 g (>100%).

4-(2-Benzoyloxy-5-methoxyphenyl)-2-butanone (34). A suspension of aldehyde **33** (2.42 g, 0.01 mol) and $\text{Ph}_3\text{P}=\text{CHCOMe}$ (3.82 g, 0.012 mol) in dry benzene (15 mL) was refluxed for 18 hr under an inert atmosphere, the solvent was evaporated, and the oily residue was purified by flash chromatography on silica gel using 2:1 hexanes-EtOAc) to yield, in addition to some unreacted Wittig reagent, a mixture of the *E*- and *Z*-isomers of the desired α,β -unsaturated ketone (2.78 g, 99%). The latter was transferred without additional purification to a round-bottomed flask containing PtO_2 monohydrate (42.5 mg) and de-gassed EtOAc (10 mL). Hydrogen gas was introduced via a balloon, and reduction was allowed to proceed with stirring until it was complete (ca. 2 hr. The catalyst was removed by filtration through a Celite pad, the solvent was evaporated, and the amber-colored residue was purified by flash chromatography (silica gel, 4:1 petroleum ether-Et₂O) to obtain **34** as a colorless oil which hardened slowly on standing; yield 1.1 g (77%). Anal ($\text{C}_{18}\text{H}_{20}\text{O}_3$) C, H.

Ethyl 2-(2-Benzoyloxy-5-methoxybenzyl)-3-oxobutanoate (41). Step 1. A solution of 2-benzoyloxy-5-methoxybenzaldehyde (9.68 g 40 mmol) in MeOH-H₂O (9:1, 300 mL) was treated in small portions with NaBH_4 (4.54 g, 120 mmol) at 0-5 °C; and the reaction mixture was stirred at room temperature for 2 hr and worked up as described to obtain 2-benzoyloxy-5-methoxybenzyl alcohol (**39**) as white solid pure enough to be used directly in the next step; yield 8.7 g (89%). Recrystallization of a portion of this material from hexanes gave long needles: mp 53-54 °C (lit.^{6s} 48-49 °C).

Step 2. A solution of SOCl_2 (1.9 mL, 3.09 g, 26 mmol) in dry benzene (5 mL) was added dropwise to a stirred solution of **39** (4.5 g, 20 mmol) and pyridine (1.62 mL, 1.58 g, 20 mmol) in CH_2Cl_2 (4 mL) while keeping the temperature below 25 °C. The resulting white suspension was stirred at room temperature for 2 hr, more benzene (20 mL) was added, and the mixture was washed first with H_2O (50 mL), then 5% NaOH (50 mL), and finally brine until the pH was neutral. The organic phase was dried with CaCl_2 and the volatiles were removed by rotary evaporation, leaving 2-benzyloxy-5-methoxybenzyl chloride (**40**) as a pale-yellow oil (4.5 g, 86%) that solidified on standing and was used directly in the next step.

Step 3. Ethyl acetoacetate (22.5 mL, 22.9 g, 0.176 mol) was added dropwise to a stirred suspension of NaH (7.04 g of 60% dispersion in mineral oil, 0.176 mol) in dry THF (200 mL). The reaction mixture was then warmed to room temperature and left to stir for another 2.5 hr, whereupon the chloride **40** (42 g, 0.16 mol) was added and the mixture was refluxed overnight. The resulting yellowish-white suspension was cooled, H_2O (60 mL) was added, and the product was extracted several times into Et_2O . The combined organic layers were dried over anhydrous MgSO_4 and evaporated to dryness, and the residue was purified by silica gel flash chromatography (hexanes followed by 9:1 hexanes-EtOAc, R_f 0.15) to obtain ethyl 2-(2-benzyloxy-5-methoxy)benzyl-3-oxobutanoate (**41**) as a colorless oil (42 g, 73%); MS: calcd *m/e* 356.16 (M^+), found 356.07. Anal. ($\text{C}_{21}\text{H}_{24}\text{O}_5$) C, H.

2,4-Diamino-5-methyl-6-(2'-methoxybenzyl)pyrido[2,3-d]pyrimidine (53). **Step 1.** A mixture of 2-methoxybenzaldehyde (40.6 g, 0.3 mol), ethyl acetoacetate (48.8 g, 0.375 mol), cyclohexane (500 mL), toluene (125 mL), piperidine (1.5 mL), and glacial AcOH (4.5 mL) was refluxed for 3.5 hr, and the volatiles were removed under reduced pressure. The resulting Knoevenagel product, a syrupy liquid, was divided directly into two batches without purification, and each batch was

dissolved in EtOH (200 mL) and reduced overnight in a Parr apparatus in the presence of 10% Pd-C (1.5 g). After filtration through a Celite pad, the solvent was removed by rotary evaporation and the combined product from the two reductions was distilled *in vacuo* to obtain ethyl 2-(2-methoxybenzyl)-3-oxobutanoate (**47**) as a light-greenish oil (61.5g, 82%): bp 103-105 °C/0.005 mm Hg); MS: *m/e* calcd 251.12 (MH⁺), found, 250.90 .

Step 2. A mixture of **47** (50 g, 0.2 mol) and 2,4,6-triaminopyrimidine (25 g, 0.2 mol) in dry NMP (200 mL) was heated for 3 hr at 190 °C in a two-neck round-bottom flask fitted with a Dean-Stark trap. After 30 min, an off-white solid began to form. At the end of the heating period the reaction mixture was cooled, MeOH (300 mL) was added, and the fine white solid was filtered and washed with boiling H₂O to obtain 2,4-diamino-5-methyl-6-(2'-methoxybenzyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**49**) as a white solid which was taken directly to the next step.

Step 3. Oxalyl chloride (60.5 mL, 88 g, 0.69 mol) was added to a stirred mixture of DMF (114 mL, 108 g, 1.48 mol) and CH₂Cl₂ (300 mL) at 0 °C. The mixture was brought back to room temperature and stirring was continued for 15 hr. whereupon all of lactam **49** from the preceding step was added and the mixture was refluxed for 3 hr. The mixture was chilled to 0 °C, n-BuNH₂ (145 mL) was added slowly over 2 hr. Reflux was resumed for another 1.5 hr, and after being cooled to room temperature the mixture was suction filtered. The filter cake was washed thoroughly with EtOH and then boiling H₂O, and the product was dried *in vacuo* over P₂O₅ overnight to obtain 2,4-diamino-5-methyl-6-(2'-methoxybenzyl)-7-chloropyrido[2,3-*d*]pyrimidine (**51**) as a white solid (15.1 g, 67%) which was taken directly to the next step.

Step 4. A mixture of chloride **51** (7.3 g, 22 mmol) and 5% Pd-C (7.1 g) in 2-methoxyethanol (1.5 L) was heated to reflux, and sodium formate (8.9 g, 132 mol) was added in small portions over 4 hr. The suspension was filtered through a Celite pad, the solvent was removed by rotary evaporation, and the residue was suspended in boiling H₂O, filtered, and dried under reduced pressure to obtain

2,4-diamino-5-methyl-6-(2'-methoxybenzyl)pyrido[2,3-*d*]pyrimidine (**53**) as a beige solid (5.45 g, 83%) which was taken directly to the next step.

2,4-Diamino-5-methyl-6-(5'-methoxybenzyl)pyrido[2,3-*d*]pyrimidine (54). **Step 1.** Condensation of ethyl acetoacetate with 3-methoxybenzaldehyde followed by catalytic hydrogenation as in the synthesis of **47** gave an 86% yield of ethyl 2-(3-methoxybenzyl)-3-butanoate (**48**): bp 126-128 °C/0.025 mm Hg. The keto ester was used directly in the next step.

Step 2. Condensation of **48** with 2,4,6-triaminopyrimidine as in the synthesis of **49** afforded a 47% yield of 2,4-diamino-5-methyl-6-(3'-methoxybenzyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**50**) as a white solid which was taken directly to the next step.

Step 3. Vilsmeier reaction of **50** as described for the 2'-methoxy isomer afforded a 70% yield (crude) of 2,4-diamino-5-methyl-6-(3'-methoxybenzyl)-7-chloropyrido[2,3-*d*]pyrimidine (**52**) as a white solid which was taken directly to the next step.

Step 4. Catalytic dechlorination and debenylation of **52** with sodium formate as described in for the 2'-methoxy isomer gave a 97% yield of **54** which was used without further purification.

2,4-Diamino-5-methyl-6-(2'-methoxy-5'-iodobenzyl)pyrido[2,3-*d*]pyrimidine (55). NIS (1.91 g, 10 mmol) was added to a stirred solution of **53** (2.38 g, 10 mmol) in TFA (10 mL) under an inert atmosphere, and the dark-red reaction mixture was left to stand at room temperature overnight. The reaction was quenched by repetitive addition of EtOH followed each time by rotary co-evaporation of ethyl trifluoroacetate (caution: the flask should be cooled in an ice bath to moderate the exothermic reaction of TFA with EtOH). The grayish solid remaining at the end (2.41 g, 70% crude yield) was extensively purified by silica gel flash chromatography (9:1 CHCl₃-MeOH) and recrystallization from EtOH to obtain **55** (2.24 g, 66%) as a buff-colored solid: mp 262-264 °C. Anal. (C₁₆H₁₆N₅) C, H, N.

2,4-Diamino-5-methyl-6-(2'-iodo-5'-methoxybenzyl)pyrido[2,3-*d*]pyrimidine (56). Iodination of **54** with NIS in TFA was performed essentially as in the case of **53** to obtain a cream-colored solid (2.41 g, 70%): mp 267-268 °C. Microchemical analysis indicated that when the product was still solvated with TFA despite being subjected to several cycles of EtOH co-evaporation. Anal. (C₁₆H₁₆I₂N₅·1.2CF₃COOH) C, H, N. Removal of the TFA was accomplished by stirring this material briefly with dilute NaOH, then filtering and washing it to neutrality with H₂O, ¹H NMR spectra were obtained on both the TFA solvate and the base-washed product (cf. S-20).

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IR and ^1H NMR Data for Compounds **6-14, 19-22,****25-32, 34-39, 48, 51-56, 63**

2,4-Diamino-5-methyl-6-[2'-methoxy-5'-(3-carboxypropyl)oxybenzyl]pyrido[2,3-*d*]pyrimidine (6): IR (KBr) ν 3360, 3160, 2940, 1670, 1600, 1550, 1500, 1460, 1390, 1370, 1280, 1260, 1250, 1230 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 1.83 (t, $J = 6.7$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{COOH}$), 2.30 (t, $J = 7.2$ Hz, 2H, CH_2COOH), 2.53 (s, 3H, 5-Me), 3.73 (s, 3H, OMe), 3.81 (t, $J = 6.5$ Hz, 2H, OCH_2), 3.87 (s, 2H, bridge CH_2), 6.32 (br s, NH_2 , exchangeable with D_2O), 6.43 (d, $J = 2.2$ Hz, 1H, H_6), 6.72 (dd, $J = 2.2, 8.8$ Hz, 1H, H_4), 6.86 (d, $J = 2.2$ Hz, 1H, H_3), 7.04 (br s, NH_2 , exchangeable with D_2O), 8.34 (s, 1H, pyridine H_7).

2,4-Diamino-5-methyl-6-[2'-methoxy-5'-(4-carboxybutyl)oxybenzyl]pyrido[2,3-*d*]pyrimidine (7): IR (KBr) ν 3360, 3160, 2960, 1640, 1600, 1560, 1500, 1470, 1390, 1280, 1240, 1230 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 1.61 (m, 4H, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 2.21 (t, 2H, $J = 6.6$ Hz, CH_2COOH), 2.54 (s, 3H, 5-Me), 3.75 (s, 3H, OMe), 3.81 (t, 2H, $J = 6.1$ Hz, OCH_2), 3.88 (s, 2H, bridge CH_2), 6.18 (br s, NH_2), 6.41 (d, 1H, $J = 2.6$ Hz, H_6), 6.70 (dd, 1H, $J = 2.8, 8.8$ Hz, H_4), 6.88 (d, 1H, $J = 8.8$ Hz, H_3), 6.90 (br s, NH_2), 8.35 (s, 1H, pyridine H_7).

2,4-Diamino-5-methyl-6-[2'-methoxy-5'-(5-carboxypentyl)oxybenzyl]pyrido[2,3-*d*]pyrimidine (8): IR (KBr) ν 3320, 3180, 2940, 1640, 1600, 1550, 1500, 1460, 1380, 1280, 1240, 1220 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 1.27-1.67 (m, 6H, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 2.17 (t, 2H, $J = 7.1$ Hz, CH_2COOH), 2.51 (s, 3H, 5-Me), 3.77 (t, $J = 6.0$ Hz, OCH_2), 6.15 (br s, NH_2), 6.37 (d, 1H, $J = 2.7$ Hz, H_6), 6.69 (dd, 1H, $J = 2.7, 8.7$ Hz, H_4), 6.86 (d, 1H, $J = 8.7$ Hz, H_3), 6.89 (br s, NH_2), 8.33 (s, 1H, pyridine H_7).

2,4-Diamino-5-methyl-6-[2'-(3-carboxypropoxy)-5'-methoxybenzyl]pyrido[2,3-*d*]pyrimidine (9): IR (KBr) ν 3340, 3200, 2950, 1650, 1590, 1560, 1500, 1470, 1370, 1230 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 1.89 (t, $J = 6.6$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 2.33 (t, $J = 6.8$ Hz, 2H, CH_2COOH), 2.52 (s, 2H, bridge CH_2), 3.58 (s, 3H, OMe), 3.88 (t, $J = 6.6$ Hz, 2H, OCH_2), 6.20 (br s, NH_2 , exchangeable with D_2O), 6.38 (d, $J = 3$ Hz, 1H, H_6), 6.67 (dd, $J = 3.0, 8.8$ Hz, H_4), 6.85 (d, $J = 8.6$ Hz, 1H, H_3), 6.89 (br s, NH_2 , exchangeable with D_2O), 8.36 (s, 1H, pyridine H_7).

2,4-Diamino-5-methyl-6-[2'-methoxy-5'-(4-carboxy-1-butynyl)benzyl]pyrido[2,3-*d*]pyrimidine (10): IR (KBr) ν 3340, 3200, 2940, 1660, 1600, 1550, 1390, 1250 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.45 (d, t, 4H, CH_2CH_2 , partly obscured by non-deuterated DMSO), 2.50 (s, 3H, 5-Me), 3.62 (s, 3H, OMe), 3.88 (s, 3H, bridge CH_2), 6.19 (br s, NH_2), 6.77 (d, 1H, $J = 1.7$ Hz, H_6), 6.93 (br s, NH_2), 6.94 (d, 1H, $J = 8.8$ Hz, H_3), 7.20 (d, $J = 8.2$ Hz, pyridine H_7).

2,4-Diamino-5-methyl-6-[2'-methoxy-5'-(5-carboxy-1-pentynyl)benzyl]pyrido[2,3-*d*]pyrimidine (11): IR (KBr) ν 3340, 3200, 2940, 1660, 1560, 1500, 1250 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 1.69 (m, 2H, $J = 7.1$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.30 (t, 2H, $J = 7.3$ Hz, $\text{C}\equiv\text{CCH}_2$), 2.36 (t, 2H, $J = 7.1$ Hz, $\text{CH}_2\text{CH}_2\text{COOH}$), 2.52 (s, 3H, 5-Me), 3.83 (s, 3H, OMe), 3.89 (s, 2H, bridge CH_2), 6.21 (br s, NH_2), 6.82 (d, $J = 1.7$ Hz, H_6), 6.92 (br s, NH_2), 6.95 (d, 1H, $J = 8.6$ Hz, H_3), 7.23 (dd, 1H, $J = 1.6$ Hz, H_4), 8.36 (s, 1H, pyridine H_7).

2,4-Diamino-5-methyl-6-[2'-methoxy-5'-(6-carboxy-1-hexynyl)benzyl]pyrido[2,3-*d*]pyrimidine (12): IR (KBr) ν 3320, 3200, 2920, 1630, 1600, 1550, 1500, 1240 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 1.40-1.64 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$), 2.21 (t, 2H, $J = 6.7$ Hz, $\text{C}\equiv\text{CCH}_2$), 2.32 (t, 2H, $J = 6.9$ Hz, CH_2COOH), 2.50 (s, 3H, 5-Me), 3.82 (s, 3H, OMe), 3.89 (s, 2H, bridge CH_2), 6.18 (br s, NH_2), 6.78 (d, 1H, $J = 1.8$ Hz, H_6), 6.91 (br s, NH_2), 6.94 (d, 1H, $J = 8.4$ Hz, H_3), 7.20 (dd, 1H, $J = 1.8, 8.4$ Hz, H_4), 8.35 (s, 1H, pyridine H_7).

2,4-Diamino-5-methyl-6-[2'-(4-carboxy-1-butynyl)-5'-methoxybenzyl]pyrido[2,3-*d*]pyrimidine (13): IR (KBr) ν 3320, 3140, 2920, 1640, 1600, 1580, 1500, 1350, 1260 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.42 (s, 3H, 5-Me), 2.56-2.62 (m, 4H, $\text{CH}_2\text{CH}_2\text{COOH}$), 3.57 (s, 3H, OMe), 4.01 (s, 2H, bridge CH_2), 6.29 (d, 1H, $J = 1.2$ Hz, H_6), 6.46 (br s, NH_2), 6.68 (dd, 1H, $J = 1.2, 8.6$ Hz, H_4), 6.95 (br s, NH_2), 7.24 (d, 1H, $J = 8.6$ Hz, H_3), 8.30 (s, 1H, pyridine H_7).

2,4-Diamino-5-methyl-6-[2'-(4-carboxy-1-pentynyl)-5'-methoxybenzyl]pyrido[2,3-*d*]pyrimidine (14): IR (KBr) ν 3340, 3180, 2940, 1640, 1600, 1550, 1500, 1380, 1300, 1250 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 1.69 (m, 2H, $J = 7.1$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.29 (t, 2H, $J = 7.3$ Hz, $\text{C}\equiv\text{CCH}_2$), 2.42 (t, 2H, $J = 7.3$ Hz, $\text{CH}_2\text{CH}_2\text{COOH}$), 2.45 (s, 3H, 5-Me), 3.59 (s, 3H, OMe), 4.03 (s, 2H, bridge CH_2), 6.22 (br s, NH_2), 6.35 (d, 1H, $J = 1.3$ Hz, H_6), 6.70 (dd, 1H, $J = 1.3, 8.6$ Hz, H_4), 6.91 (br s, NH_2), 7.28 (d, 1H, $J = 8.6$ Hz, H_3), 8.31 (s, 1H, pyridine H_7).

2,4-Diamino-6-[2'-(3-carboxy-1-propynyl)-5H-dibenz[*b,f*]azepinyl]methylpteridine (19): IR (KBr) ν 3450, 3395, 1625, 1470, 1350 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 3.34 (s, 2H, $\text{C}\equiv\text{CCH}_2$), 5.13 (s, bridge CH_2), 6.61 (overlapping doublets, H_{10} and H_{11}), 6.89 (s, 1H, H_1), 6.94-7.20 (m, 6H, $\text{H}_{3',4',6',9'}$), 7.41 (br s, NH_2), 7.63 (br s, NH_2), 8.68 (s, 1H, pteridine H_7).

2,4-Diamino-6-[2'-(4-carboxy-1-butynyl)-5H-dibenz[*b,f*]azepinyl]methylpteridine (20): IR (KBr) ν 3440, 3400, 1635, 1450, 1380, 1200 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.56 and 2.60 (2 x t, 4H, $J = 9.6$ Hz, $\text{C}\equiv\text{CCH}_2\text{CH}_2$), 5.20 (s, 2H, bridge CH_2), 6.75 (d, $J = 12$ Hz, H_{10} or H_{11}), 6.86 (d, 1H, $J = 12$ Hz, H_{10} or H_{11}), 6.98 (s, 1H, H_1), 7.01-7.20 (m, 6H, $\text{H}_{3',4',6',9'}$), 7.37 (br s, NH_2), 7.58 (br s, NH_2), 8.82 (s, 1H, pteridine H_7).

2,4-Diamino-6-[2'-(5-carboxy-1-hexynyl)-5H-dibenz[*b,f*]azepinyl]methylpteridine (21): IR (KBr) ν 3460, 3410, 1620, 1480, 1350, cm^{-1} ; ^1H NMR (DMSO- d_6) δ 1.22 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.90 (t, 2H, $J = 11.7$ Hz, CH_2COOH), 2.50 (t, $J = 11.7$ Hz, $\text{C}\equiv\text{CCH}_2$), 5.03 (s, 2H, bridge CH_2), 6.56

(1H, d, $J = 12$ Hz, H_{10} or H_{11}), 6.60 (d, 1H, H_{10} or H_{11}), 6.83 (s, 1H, H_1), 6.95-7.20 (m, 6H, $H_{3,4,6,9}$), 7.51 (br s, NH_2), 7.53 (br s, NH_2), 8.66 (s, 1H, pteridine H_7).

2,4-Diamino-5-[3'-(4-carboxy-1-butynyl)-4'-bromo-5'-methoxybenzyl]pyrimidine (22): IR (KBr) ν 3400sh, 3220, 3100br, 1675, 1595, 1575, 1540, 1470, 1410, 1355, 1255 cm^{-1} ; 1H NMR (DMSO- d_6) δ 2.58 (m, CH_2CH_2 , partially overlapped by DMSO), 3.50 (s, 2H, bridge CH_2), 3.74 (s, 3H, OMe), 5.70 (br s, NH_2 , exchangeable with D_2O), 6.06 (br s, NH_2 , exchangeable with D_2O), 6.79 (s, 1H, aryl H), 6.94 (s, 1H, aryl H), 7.50 (s, 1H, pyrimidine H_5 , not exchangeable with D_2O).

2-Methoxy-5-benzyloxybenzaldehyde (25): 1H NMR (DMSO- d_6) δ 3.9 (s, 3H, OMe), 5.1 (s, 2H, OCH_2Ph), 7.15-7.4 (m, 8H, aryl H), 10.3 (s, 1H, $CH=O$).

Ethyl 2-(2-Methoxy-5-benzyloxy)-3-butanoate (26): IR (thin film) ν 3000, 2940, 1740, 1720, 1500, 1230 cm^{-1} ; 1H NMR (DMSO- d_6) δ 1.09 (t, 3H, $J = 7.1$ Hz, CH_2CH_3), 2.07 (s, 2H, CH_2CO), 2.83-3.06 (m, 2H, CH_2CH), 3.71 (s, 3H, OCH_3), 3.88 (t, 1H, $J = 6.6$ Hz, CH_2CHCO), 4.02 (q, 2H, $J = 7.1$ Hz, CH_2CH_3), 4.99 (s, CH_2Ph), 6.76-6.84 (m, 3H, aryl H), 7.29-7.39 (m, 3H, aryl H).

2,4-Diamino-5-methyl-6-[2'-methoxy-5'-(3-carbethoxypropyl)oxybenzyl]pyrido[2,3-*d*]pyrimidine (30): IR (KBr) ν 3520, 3340, 3160, 2980, 1730, 1660, 1620, 1560, 1500, 1470, 1390, 1290, 1250, 1220 cm^{-1} ; 1H NMR (DMSO- d_6) δ 1.10 (t, 3H, $J = 7.1$ Hz, CH_2CH_3), 1.85 (m, 2H, $J = 6.7$ Hz, $CH_2CH_2CH_2$), 2.35 (t, 3H, $J = 7.2$ Hz, CH_2COOEt), 2.51 (s, 3H, 5-Me), 3.73 (s, 3H, OMe), 3.80 (t, 2H, $J = 6.3$ Hz, OCH_2), 3.87 (s, 2H, bridge CH_2), 3.92 (q, 2H, $J = 7.1$ Hz, CH_2CH_3), 6.12 (br s, NH_2), 6.35 (d, 1H, $J = 2.7$ Hz, H_6), 6.68 (dd, 1H, $J = 2.7, 8.8$ Hz, H_4), 6.86 (d, 1H, $J = 8.8$ Hz, H_3), 6.88 (br s, NH_2), 8.32 (s, 1H, pyridine H_7).

2,4-Diamino-5-methyl-6-[2'-methoxy-5'-(4-carbethoxybutyl)oxybenzyl]pyrido-[2,3-*d*]pyrimidine (31): IR (KBr) ν 3340, 3180, 2950, 1730, 1640, 1590, 1550, 1500, 1480, 1220 cm^{-1} ; 1H NMR (DMSO- d_6) δ 1.13 (t, 3H, $J = 7.1$ Hz, CH_2CH_3), 1.59-1.62 (m, 4H, $OCH_2CH_2CH_2$), 2.28 (t, 2H, $J =$

5.8 Hz, CH_2COOEt), 2.53 (s, 3H, 5-Me), 3.73 (s, 3H, OMe), 3.79 (t, 2H, $J = 6.6$ Hz, OCH_2), 3.88 (s, 2H, bridge CH_2), 3.95 (q, 2H, $J = 7.1$ Hz, CH_2CH_3), 6.36 (br s, NH_2), 6.39 (d, 1H, $J = 2.8$ Hz, H_6), 6.70 (dd, 1H, $J = 2.8, 8.8$ Hz, H_4), 6.86 (s, 1H, $J = 8.9$ Hz, H_3), 7.11 (br s, NH_2), 8.34 (s, 1H, pyridine H_7).

2,4-Diamino-5-methyl-6-[2'-methoxy-5'-(5-carbethoxypropyl)oxybenzyl]pyrido[2,3-*d*]-pyrimidine (32): IR (KBr) ν 3340, 3160, 960, 1730, 1660, 1620, 1550, 1500, 1460, 1380, 1280, 1240, 1220 cm^{-1} ; 1H NMR (DMSO- d_6) δ 1.13 (t, 3H, $J = 7.0$ Hz, CH_2CH_3), 1.25-1.67 (m, 6H, $OCH_2CH_2CH_2CH_2$), 2.25 (t, 2H, $J = 6.2$ Hz, CH_2COOEt), 2.51 (s, 3H, 5-Me), 3.73 (s, 3H, OMe), 3.77 (t, 2H, $J = 6.2$ Hz, OCH_2), 3.86 (s, 2H, bridge CH_2), 3.95 (q, 2H, $J = 7.0$ Hz, CH_2CH_3), 6.14 (br s, NH_2), 6.36 (d, 1H, $J = 2.8$ Hz, H_6), 6.69 (dd, 1H, $J = 2.9, 9.0$ Hz, H_4), 6.86 (d, 1H, $J = 8.8$ Hz, H_3), 6.89 (br s, NH_2), 8.33 (s, 1H, pyridine C_7).

4-(2-Benzyloxy-5-methoxyphenyl)-2-butanone (34): IR (KBr) ν 1700, 1590, 1495, 1290, 1210 cm^{-1} ; 1H NMR (DMSO- d_6) δ 2.0 (s, 3H, CH_3), 2.69 (m, 4H, CH_2CH_2), 3.65 (s, 3H, OMe), 5.03 (s, 2H, OCH_2), 6.65-6.72 (m, 2H, aryl H), 6.90 (d, 1H, $J = 8.8$ Hz, H_3), 7.29-7.43 (m, 5H, aryl H).

(Z)-4-Chloro-2-[(2-benzyloxy-5-methoxy)benzyl]-3-propen-2-one (35a): 1H NMR (DMSO- d_6) δ 2.25 (s, 3H, CH_3), 3.57 (s, 2H, CH_2), 3.63 (s, 3H, OMe), 5.04 (s, 2H, CH_2), 6.46 (d, 1H, $J = 2.9$ Hz, H_6), 6.67 (dd, 1H, $J = 2.9, 8.8$ Hz, H_4), 6.92 (s, 1H, $J = 8.8$ Hz, H_3), 7.29-7.45 (m, 5H, aryl H), 10.11 (s, 1H, $CH=O$).

(E)-4-Chloro-2-[(2-benzyloxy-5-methoxy)benzyl]-3-propen-2-one (35b): 1H NMR (DMSO- d_6) δ 2.68 (s, 3H, CH_3), 3.61 (s, 3H, OCH_3), 3.65 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 6.36 (d, 1H, $J = 2.9$ Hz, H_6), 6.65 (dd, 1H, $J = 2.6, 8.8$ Hz, H_4), 6.90 (d, 1H, $J = 8.8$ Hz, H_3), 7.29-7.46 (m, 5H, aryl H), 10.04 (d, 1H, $CH=O$).

5-[(2'-Benzyloxy-5'-methoxy)benzyl]-3-cyano-4-methyl-2-pyridone (36): IR (KBr) ν 2220, 1640, 1615, 1500, 1205, 1050 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.20 (s, 3H, CH_3), 3.64 (s, 3H, OMe), 3.69 (s, 2H, bridge CH_2), 5.04 (s, 2H, OCH_2), 6.57 (d, 1H, $J = 2.9$ Hz, pyridone C_6), 6.72 (dd, 1H, $J = 2.9, 8.9$ Hz, H_4), 6.98 (d, 1H, $J = 8.9$ Hz, H_3), 7.34 (m, 5H, aryl H), 12.20 (br s, lactam NH).

2-Chloro-5-[(2'-benzyloxy-5'-methoxy)benzyl]-3-cyano-4-methylpyridine (37): ^1H NMR (CDCl_3) δ 2.39 (s, 3H, 4- CH_3), 3.74 (s, 3H, OMe), 3.92 (s, 2H, bridge CH_2), 4.96 (s, 2H, OCH_2Ph), 6.54 (d, 1H, $J = 2.8$ Hz, H_6), 6.73 (dd, 1H, $J = 2.9, 8.9$ Hz, H_4), 6.87 (d, 1H, $J = 8.9$ Hz, H_3), 7.23-7.38 (m, 5H, aryl H), 8.18 (s, 1H, pyridine H_6).

2,4-Diamino-5-methyl-6-(2'-benzyloxy-5'-methoxybenzyl)pyrido[2,3-*d*]pyrimidine (38): IR (KBr) ν 3330, 3320, 2940, 2900, 2110, 1650, 1620, 1540, 1490, 1450, 1370, 1200 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.58 (s, 3H, 5-Me), 3.67 (s, 3H, OMe), 4.01 (s, 2H, bridge CH_2), 5.14 (s, 2H, OCH_2Ph), 6.44 (br s, NH_2 , exchangeable with D_2O), 6.50 (1H, $J = 2.6$ Hz, H_6), 6.77, dd, 1H, $J = 2.8, 8.8$ Hz, H_4), 7.04 (d, 1H, $J = 8.8$ Hz, H_3), 7.13 (br s, NH_2 , exchangeable with D_2O), 7.41-7.42 (m, 5H, aryl H), 8.41 (s, 1H, pyridine H_7).

2-Benzyloxy-5-methoxybenzyl alcohol (39): IR (KBr) ν 3300, 1580, 1500, 1270, 1205 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 6.37 (s, 3H, OMe), 4.51 (s, 2H, CH_2OH), 5.02 (br s, 3H, CH_2Ph overlapping OH exchangeable with D_2O), 6.67 (dd, 1H, $J = 2.9, 8.8$ Hz, H_4), 6.89 (d, 1H, $J = 8.8$ Hz, H_3), 6.96 (d, 1H, $J = 2.8$ Hz, H_6), 7.26-7.43 (m, 5H, aryl H).

2-Benzyloxy-5-methoxybenzyl chloride (40): IR (KBr) ν 1590, 1500, 1290, 1225 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.77 (s, 3H, OMe), 4.67 (s, 2H, CH_2Cl), 5.09 (s, 2H, OCH_2Ph), 6.77-6.97, m, 3H, aryl H), 7.31-7.47 (m, 5H, aryl H); ^1H NMR (DMSO- d_6) δ 3.68 (s, 3H, OMe), 4.70 (s, 2H, CH_2Cl),

5.11 (s, 2H, OCH₂Ph), 6.83 (dd, 1H, $J = 3.0, 9.2$ Hz, H₄), 7.00-7.04 (m, 2H, aryl H), 7.29-7.48 (m, 5H, aryl H).

Ethyl 2-(2-Benzyloxy-5-methoxy)benzyl-3-oxobutanoate (41): IR (thin film) ν 3300, 1580, 1500, 1270, 1205 cm⁻¹; ¹H NMR (CDCl₃) δ 3.67 (s, 3H, OMe), 4.51 (s, 2H, CH₂OH), 1.18 (t, 3H, $J = 7.4$ Hz, CH₂CH₂), 2.10 (s, 3H, COCH₃), 3.03-3.26 (m, 2H, CH₂CH), 3.90 (t, 1H, $J = 7.3$ Hz, CH₂CH), 4.09 (q, 2H, $J = 7.4$ Hz, CH₂CH₃), 5.04 (s, 2H, OCH₂Ph), 6.67-6.85 (m, 3H, aryl H), 7.31-7.44 (m, 3H, aryl H).

2,4-Diamino-5-methyl-6-(2'-benzyloxy-5'-methoxybenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (42): ¹H NMR (DMSO-*d*₆) δ 2.32 (s, 3H, 5-Me), 3.55 (s, 3H, OMe), 3.81 (s, 2H, bridge CH₂), 5.08 (s, 2H, OCH₂Ph), 6.33 (s, 1H, aryl H), 6.64-6.97 (m, 6H, aryl H), 7.33-7.48 (m, 5H, aryl H).

2,4-Diamino-5-methyl-6-(2'-benzyloxy-5'-methoxybenzyl)-7-choropyrid[2,3-d]pyrimidine (43): ¹H NMR (DMSO-*d*₆) δ 2.50 (s, 3H, 5-Me), 3.53 (s, 3H, OMe), 4.08 (s, 2H, bridge CH₂), 5.14 (s, 2H, OCH₂Ph), 6.05 (s, 1H, $J = 3.6$ Hz, H₆), 6.40 (br s, NH₂), 6.91 (dd, 1H, $J = 3.6, 8.8$ Hz, H₄), 6.99 (d, 1H, $J = 8.8$ Hz, H₃), 7.04 (br s, NH₂), 7.31-7.48 (m, 5H, aryl H).

2,4-Diamino-5-methyl-6-[2'-(carbethoxypropyloxy)-5'-methoxybenzyl]pyrido[2,3-d]pyrimidine (45): IR (KBr) ν 3200, 3140, 1720, 1620, 1570, 1540, 1490, 1450, 1380, 1210 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.27 (t, 3H, $J = 7.1$ Hz, CH₂CH₃), 1.92 (m, 2H, $J = 6.8$ Hz, CH₂CH₂CH₂), 2.37 (t, 2H, $J = 7.3$ Hz, CH₂COOEt), 2.54 (s, 3H, 5-Me), 3.59 (s, 3H, OMe), 3.90 (s, 2H, bridge CH₂), 3.99 (t, 2H, partly overlapped by adjacent signals, OCH₂CH₂), 4.03 (q, 2H, $J = 7.1$ Hz, CH₂CH₃), 6.45 (d, 1H, $J = 2.6$ Hz, H₆), 6.61 (br s, NH₂), 6.69 (dd, 1H, $J = 2.8, 8.8$ Hz, H₄), 6.85 (d, 1H, $J = 8.8$ Hz, H₃), 7.32 (br s, NH₂), 8.35 (s, 1H, pyridine H₇).

Ethyl 2-(3-Methoxybenzyl-3-butanoate (48): IR (thin film) ν 2980, 2940, 1740, 1720, 1600, 1590, 1490, 1460, 1260, 1220 cm⁻¹; ¹H NMR (CDCl₃) δ 1.25 (t, 2H, $J = 7.1$ Hz, CH₂CH₃), 2.23

(s, 3H, COCH₃), 3.15 (d, 2H, $J = 7.6$ Hz, CH₂CH), 3.81 (overlapping s and m, 3H, OMe and CH₂CH), 4.17 (q, 2H, $J =$ CH₂CH₃), 6.76-6.80 (m, 2H, aryl H), 7.21-7.29 (m, 1H, aryl H).

2,4-Diamino-5-methyl-6-(2'-methoxybenzyl)-7-chloropyrido[2,3-*d*]pyrimidine (51): ¹H NMR (DMSO-*d*₆) δ 2.46 (s, 3H, 5-Me), 3.81 (s, 3H, OMe), 4.00 (s, 2H, bridge CH₂), 6.37 (br s, NH₂), 6.45-6.49 (m, 1H, aryl H), 6.70-6.73 (m, 1H, aryl H), 6.94-7.14 (overlapping br s and m, 4H, NH₂, aryl H).

2,4-Diamino-5-methyl-6-(3'-methoxybenzyl)-7-chloropyrido[2,3-*d*]pyrimidine (52): ¹H NMR (DMSO-*d*₆) δ 2.56 (s, 3H, 5-Me), 3.68 (s, 3H, OMe), 4.14 (s, 2H, bridge CH₂), 6.38 (br s NH₂), 6.59-6.76 (m, 3H, aryl H), 7.06 (br s, NH₂), 7.13-7.21 (m, 1H, aryl H).

2,4-Diamino-5-methyl-6-(2'-methoxybenzyl)pyrido[2,3-*d*]pyrimidine (53): IR (thin film) ν 2980, 2940, 1740, 1710, 1600, 1590, 1500, 1470, 1250 cm⁻¹; ¹H NMR (CDCl₃) δ 1.22 (t, $J = 7.0$ Hz, 3H, CH₂CH₃), 2.18 (s, 3H, COCH₃), 3.13 (m, 2H, CH₂CH), 3.82 (overlapping s and m, 3H, OMe and CH₂CH), 4.10 (q, $J = 7.0$ Hz, CH₂CH₃), 6.80, 6.87 (m, 2H, aryl H), 7.09-7.24 (m, 2H, aryl H).

2,4-Diamino-5-methyl-6-(3'-methoxybenzyl)pyrido[2,3-*d*]pyrimidine (54): ¹H NMR (DMSO-*d*₆) δ 2.53 (s, 3H, 5-Me), 3.68 (s, 3H, OMe), 3.98 (s, 2H, bridge CH₂), 6.20 (br s, NH₂), 6.65-6.76 (m, 3h, aryl H), 6.90 (br s, NH₂), 7.13-7.21 (m, 1H, aryl H), 8.43 (s, 1H, pyridine H₇).

2,4-Diamino-5-methyl-6-(2'-methoxy-5'-iodobenzyl)pyrido[2,3-*d*]pyrimidine (55): IR (KBr) ν 3500, 3340, 3100, 1640, 1620, 1590, 1550, 1520, 1490, 1460, 1250 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 2.50 (s, 3H, 5-Me), 3.77 (s, 3H, OMe), 3.86 (s, 2H, bridge CH₂), 6.16 (br s, NH₂, exchangeable with D₂O), 6.81 (d, $J = 8.8$ Hz, 1H, H₃), 6.90 (br s, NH₂, exchangeable with D₂O), 7.10 (d, $J =$ H₆), 7.48 (dd, $J = 2.2, 8.8$ Hz, 1H, H₄), 8.32 (s, 1H, pyridine H₇).

2,4-Diamino-5-methyl-6-(2'-iodo-5'-methoxybenzyl)pyrido[2,3-*d*]pyrimidine (56): IR (KBr) ν 3500, 3340, 3100, 1640, 1620, 1590, 1550, 1520, 1490, 1460, 1250 cm^{-1} ; TFA solvate: ^1H NMR (DMSO- d_6) δ 2.56 (s, 3H, 5-Me), 3.65 (s, 3H, OMe), 4.06 (s, 2H, bridge CH_2), 6.46 (d, $J = 2.1$ Hz, 1H, $\text{H}_{6'}$), 6.67 (dd, $J = 2.8, 8.8$ Hz, 1H, $\text{H}_{4'}$), 7.77 (d, 1H, $J = 8.8$ Hz, $\text{H}_{3'}$), 8.05 (br s, NH_2), 8.31 (s, 1H, pyridine H_7), 9.16 (br s, protonated pyridine nitrogen); free base after removal of TFA: ^1H NMR (DMSO- d_6) δ 2.51 (s, 3H, 5-Me), 3.63 (s, 3H, OMe), 3.99 (s, 2H, bridge CH_2), 6.43 (d, $J = 3.0$ Hz, $\text{H}_{6'}$), 6.64 (dd, $J = 3.2, 8.8$ Hz, 1H, $\text{H}_{4'}$), 6.74 (br s, NH_2), 7.49 (br s, NH_2), 7.75 (d, $J = 8.8$ Hz, 1H, $\text{H}_{3'}$), 8.23 (s, 1H, pyridine H_7).

2,4-Diamino-6-(2'-trifluoromethylsulfonyloxy)-5*H*-dibenzazepin-5-yl)methylpteridine (63): ^1H NMR (DMSO- d_6) δ 5.13 (s, 2H, bridge CH_2), 6.61 (overlapping doublets, 2H, $\text{H}_{10'}$ and $\text{H}_{11'}$), 6.89 (d, 1H, $J = 9.8$ Hz, $\text{H}_{3'}$), 6.94 (d, 1H, $J = 9.8$ Hz, $\text{H}_{4'}$), 7.01 (s, 1H, $\text{H}_{1'}$), 7.11-7.35 (m, 4H, $\text{H}_{6'.9'}$), 7.33 (br s, NH_2), 7.62 (br s, NH_2), 8.68, (s, 1H, pteridine H_7).

Table 3. Calculated intermolecular/intramolecular interaction energies of **10** and **13** in the ternary complex with NADPH and *P. carinii* DHFR after a molecular dynamics simulation (1 nanosec) and energy minimization

Ligands	Interaction energies (kcal/mol)	
	10	13
Inhibitor	-214.48	-196.87
NADPH	-520.79	-480.88
13 active-site residues	-1104.4	-1052.3
Ile7	-22.21	-25.70
Leu25	-4.44	-2.24
Glu32	-85.62	-77.45
Ile33	-20.92	-17.57
Phe36	-28.87	-27.61
Lys37	-20.29	-14.39
Ser64	-20.42	-16.60
Ile65	-9.10	-15.64
Pro66	+5.28	+3.64
Phe69	-13.84	-17.95
Leu72	-15.84	-19.37
Arg75	-113.52	-120.06
Ile123	-19.34	-23.61
Entire complex	-12151.76	-11745.28

Cmpd	Empirical Formula	Microchemical Analyses			Found, %		
		C	H	N	C	H	N
6	C ₂₀ H ₂₃ N ₅ O ₄ ·0.9AcOH·H ₂ O	55.77	6.14	14.92	55.77	6.09	15.20
7	C ₂₁ H ₂₅ N ₅ O ₄ ·AcOH·0.5H ₂ O	57.48	6.30	14.58	57.35	6.21	14.78
8	C ₂₂ H ₂₇ N ₅ O ₄ ·0.6AcOH·0.4H ₂ O	59.45	6.49	14.94	59.16	6.20	15.24
9	C ₂₀ H ₂₃ N ₅ O ₄ ·1.1H ₂ O	57.57	6.09	16.78	57.56	6.07	16.71
10	C ₂₁ H ₂₁ N ₅ O ₃ ·0.6AcOH·1.5H ₂ O	58.65	5.87	15.41	58.61	<u>5.31</u>	15.45
11	C ₂₂ H ₂₃ N ₅ O ₃ ·AcOH·0.05H ₂ O	61.80	5.86	15.02	61.54	5.53	15.31
12	C ₂₃ H ₂₅ N ₅ O ₃ ·1.75AcOH·0.1H ₂ O	60.47	6.17	13.30	60.35	6.16	13.41
13	C ₂₁ H ₂₁ N ₅ O ₃ ·1.2AcOH·0.8H ₂ O	58.80	5.79	14.66	58.86	<u>5.10</u>	14.73
14	C ₂₂ H ₂₃ N ₅ O ₃ ·0.45AcOH·H ₂ O	61.39	6.11	15.33	61.40	5.91	15.23
19	C ₂₅ H ₁₉ N ₇ O ₂ ·0.8NH ₃ ·4.5H ₂ O	55.17	5.64	20.08	55.25	<u>4.86</u>	20.04
20	C ₂₆ H ₂₁ N ₇ O ₂ ·2.6AcOH·0.6H ₂ O	59.43	5.22	15.55	59.41	<u>4.68</u>	15.55
21	C ₂₇ H ₂₃ N ₇ O ₂ ·1.9AcOH·0.5H ₂ O	61.59	5.30	16.32	61.27	5.58	16.68
22	C ₁₇ H ₁₇ BrN ₄ O ₃ ·2H ₂ O	46.27	4.80	12.70	46.17	4.61	12.51
30	C ₂₂ H ₂₇ N ₅ O ₄	62.10	6.40	16.46	61.81	6.15	16.29
31	C ₂₃ H ₂₉ N ₅ O ₄ ·1.4H ₂ O	59.44	6.90	15.07	59.17	6.60	14.98
32	C ₂₄ H ₃₁ N ₅ O ₄ ·0.35H ₂ O	62.69	6.95	15.23	62.77	6.91	15.03
35a	C ₁₉ H ₁₉ ClO ₃ ^b	68.98	5.79		68.99	5.83	
35b	C ₁₉ H ₁₉ ClO ₃ ^c	68.98	5.79		68.92	5.87	
36	C ₂₂ H ₂₀ N ₂ O ₃	73.32	5.59	7.77	73.04	5.32	7.64
37	C ₂₂ H ₁₉ ClN ₂ O ₂ ^d	69.75	5.05	7.39	69.66	5.20	7.29
38	C ₂₃ H ₂₃ N ₅ O ₂ ·0.25H ₂ O	68.05	5.72	17.27	67.96	5.72	17.27
41	C ₂₁ H ₂₄ O ₅	70.77	6.79		70.50	6.98	
45	C ₂₂ H ₂₇ N ₅ O ₄ ·0.35H ₂ O	61.20	6.47	16.22	61.23	6.44	16.28
55	C ₁₆ H ₁₆ IN ₅ O	45.62	3.83	16.63	45.46	3.85	16.38
56	C ₁₆ H ₁₆ IN ₅ O·1.2TFA	39.60	3.11	12.55	39.87	2.74	12.81

^aUnderlined numbers indicate a deviation of >0.4 from the calculated H value. ^bCl: calcd 10.72, found 10.45. ^cCl: calcd: 10.72, found 10.66. ^dCl: calcd 9.36, found 9.31.