100. Synthesis and Biological Activity of Tetrahydropyrido[2′,3′:4,5]imidazo[1,2-*c*]pyrimidine-6,8-diones

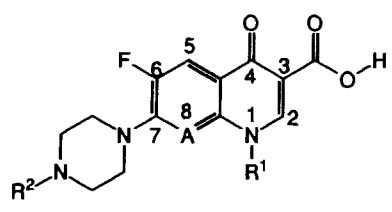
by **Jan Sraga**[1]), **Philippe Guerry**, and **Ivan Kompis***

Pharma Division, Preclinical Research, *F. Hoffmann-La Roche Ltd.*, CH-4002 Basel

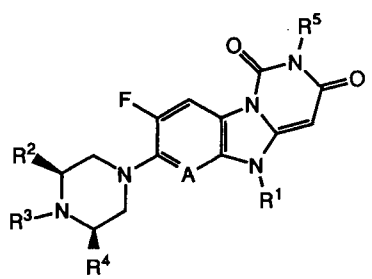
(28.III.94)

Substituted 4-oxoquinoline-3- (**1a**) and 4-oxo-1,8-naphthyridine-3- (**1b**) carboxylic acids are clinically useful antibacterial agents exerting their activity by inhibiting the subunit A of DNA gyrase. Recently, pyrimido-[1,6-*a*]benzimidazoles **2** were found to be a new class of inhibitors of this enzyme. As, in **1**, replacement of C(8) by the N-atom was shown beneficial for the biological properties, a synthesis of the corresponding aza analogues of **2** has been carried out. The synthesis, DNA gyrase inhibitory activity, and *in vitro* antibacterial activity of the target compounds **16–19** are reported.

Introduction. – Pyrimido[1,6-*a*]benzimidazoles **2** were found to be a novel class of the subunit A of DNA gyrase inhibitors [1]. They were designed in a way that the 4-oxo-pyridine-3-carboxylic-acid moiety of a quinolin-4-one was replaced by structural elements of thymine, while the relative position of all other structural features of a quinolone (*i.e.* substituents at N(1), C(6), and C(7) in **1**) was maintained. Naphthyridines, a class of compounds differing from quinolinones in that C(8) of **1** is replaced by the N-atom, have shown excellent *in vitro* and *in vivo* antibacterial activity [2] [3]. We have, therefore, synthesized the aza analogues of **2** and tested them for DNA gyrase inhibitory and *in vitro* antibacterial activity.



1a A = CH,
R^1 = cyclopropyl, R^2 = H
1b A = N,
R^1 = cyclopropyl, R^2 = H
1c A = CF,
R^1 = 2-fluoroethyl, R^2 = Me



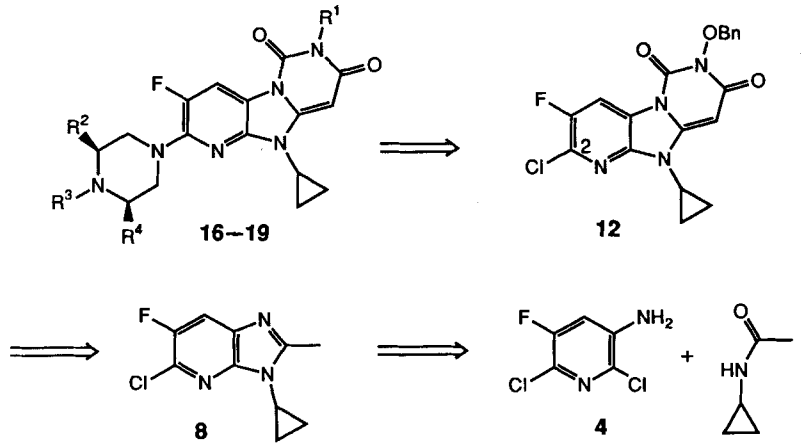
2 A = CH, R^1 = cyclopropyl,
R^2 = H;Me, R^3 = H;Me,
R^4 = H;Me, R^5 = H;OH

16–19 A = N, R^1 = cyclopropyl,
R^2 = H;Me, R^3 = H;Me,
R^4 = H;Me, R^5 = H;OH

[1]) Present address: *Synkola*, Consortium, Mlynska Dolina, CH-2, 84215 Bratislava, Slovakia.

Synthetic Strategy. – The compounds **16–19** are representatives of a hitherto unknown heterocyclic system. Their synthesis was conceived in a way to enable a broad variation of substituents by nucleophilic substitution at C(2) of tetrahydropyrido-[2′,3′:4,5]imidazo[1,2-*c*]pyrimidine-6,8-dione **12** leading to the target compounds **16–19** (*Scheme 1*). A retrosynthetic analysis of the tricyclic compound **12** indicated to disconnect first the pyrimidine-2,4-dione ring, producing the imidazo-pyridine **8**, which might be synthesized from the 3-aminopyridine **4** and an activated derivative of *N*-cyclopropylacetamide. The 3-aminopyridine **4** can be prepared by classical functional-group interconversion starting from the 2,6-dichloro-5-fluoropyridine-3-carboxamide (**3**, *cf. Scheme 2*).

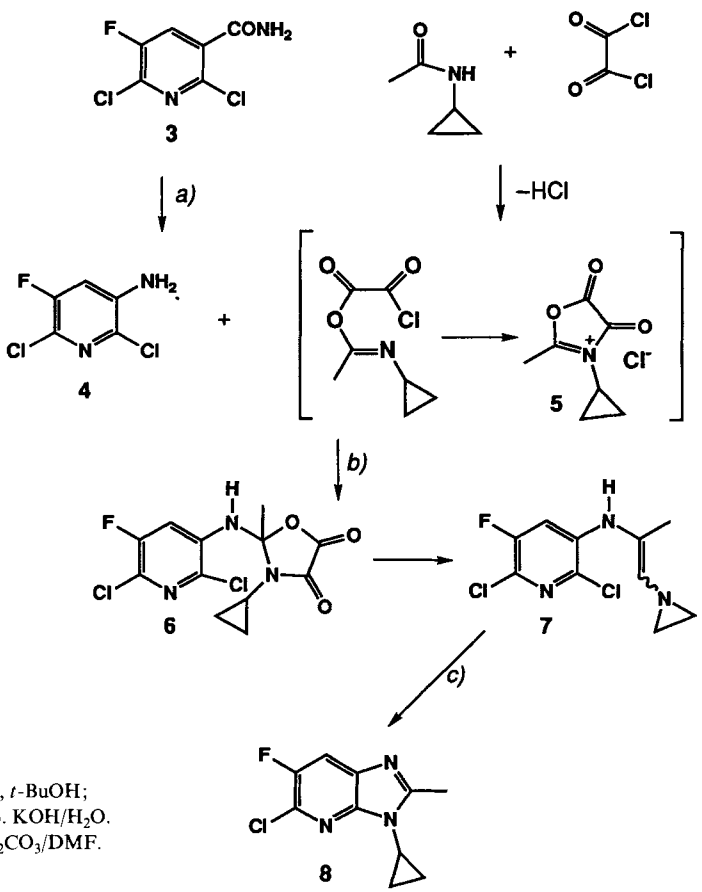
Scheme 1



Synthesis. – The starting material **3** was prepared by a three-step process from ethyl fluoroacetate, ethyl formate, and malonamide [4]. *Hoffmann* rearrangement, adopting general procedure described in [5], yielded the amine **4**.

Several attempts have been made to transform **4** to the 2-methylimidazo[4,5-*b*]pyridine **8**. Treatment of **4** with *N*-cyclopropylacetamide and an activator gave either no reaction (heat [6], $SOCl_2$ [7], $TiCl_4$ [7], Me_3OBF_4 [8]) or a complex mixture (PCl_5 [7], P_2O_5 [9]). Oxalyl chloride [10] was found to be the reagent of choice for the required transformation **4** to **8**. Reaction of *N*-cyclopropylacetamide with oxalyl chloride in Et_2O at temperatures below +3° followed by the addition of **4** and stirring at room temperature for 16 h, and by precipitation at 0° gave a crude product which was directly treated with K_2CO_3 in DMF at 140° to afford **8** in an overall yield of 61%. Attempts to characterize the crude precipitate led to the isolation of two compounds **6** (78% of the precipitate, as determined by HPLC) and **7** (14%) beside other minor compounds structures of which have not been elucidated (*Scheme 2*). Formation of the dihydro-1,3-oxazole-dione **6** can be explained by the 1,2 addition of the amine **4** onto the iminium compound **5**, one of the possible products of the reaction of *N*-cyclopropylacetamide and oxalyl chloride at low temperature [10]. Successive decarboxylation and decarbonylation of **6** would then lead to the formation of **7**. By monitoring the cyclization of **6** to **8** in DMF/K_2CO_3 at 150° with HPLC, it was possible to observe the fast transformation of **6** into **7**, followed by the ring closure to form **8**. In an attempt to avoid the drastic conditions of the ring closure, NaH

Scheme 2



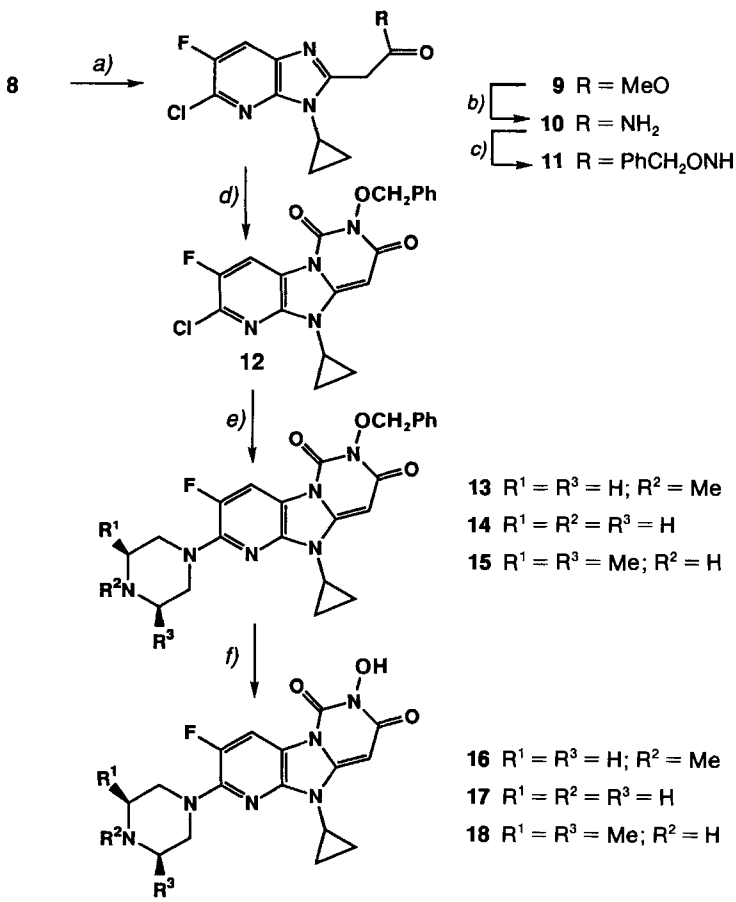
a) 1. $Pb(OAc)_4$, *t*-BuOH; 2. HCl/Et_2O; 3. KOH/H_2O. b) Et_2O. c) K_2CO_3/DMF.

[11] and Bu_4NF [12] were tested in bases. Whereas NaH showed no advantage over K_2CO_3, as far as the reaction time or the yield are concerned, Bu_4NF failed completely to give **8**.

Selective proton abstraction from the Me group of **8** was achieved with lithium bis(trimethylsilyl)amide ($LiN(Me_3Si)_2$) in THF at −75° (*Scheme 3*). Both LDA and BuLi, which have been successfully used for similar deprotonations [13] [14], proved to be nonselective. Quenching of the lithium derivative with dimethyl carbonate in the presence of a second equiv. of $LiN(Me_3Si)_2$ gave a quantitative yield of **9**.

Reaction of **9** with *O*-benzylhydroxylamine ($PhCH_2OHN_2$) provided only poor yields of **11** under a variety of conditions (base or acid catalysis in MeOH, MeCN, $CHCl_3$, or $PhCH_2ONH_2$ as a solvent). On the other hand, the corresponding amide **10** (readily available from **9** and NH_3 in MeOH in the presence of NaCN [15]) smoothly underwent transamidation with $PhCH_2ONH_2 \cdot HCl$ in EtOH/H_2O 1:1. The pyrimidine ring closure by treatment of **11** with *N,N'*-carbonyldiimidazole resulted in the key intermediate **12** in high yield. Substitution of Cl with N nucleophiles in *N*-methylpyrrolidone in the presence

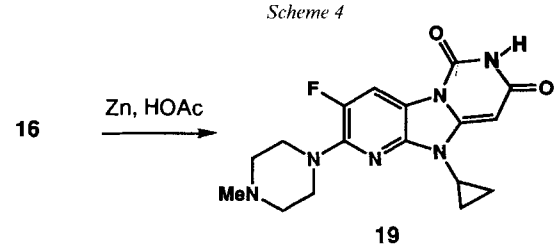
Scheme 3



a) $(Me_3Si)_2NLi$/THF, $(MeO)_2CO$. b) NH_3/MeOH. c) NH_2OCH_2Ph HCl, EtOH/H_2O 1:1. d) Im_2CO, THF. e) Substituted piperazine/*N*-methylpyrrolidone. f) H_2, Pd/C, MeOH/AcOH 3:1.

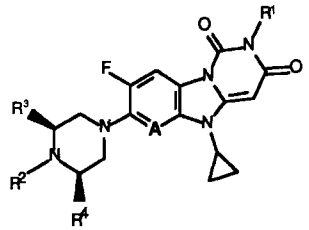
of catalytic amounts of KI, followed by hydrogenolytic removal of the $PhCH_2$ group yielded the desired *N*-hydroxypyrimidine-diones. An attempt to obtain **19** by cyclization of the amide **8** with *N,N'*-carbonyldiimidazole failed. The compound **19** was prepared by reduction of **17** with Zn in AcOH (*Scheme 4*).

Scheme 4



Biological Results and Discussion. – The results of the inhibition of the *Escherichia coli* DNA gyrase and the *in vitro* antibacterial activities [1] of compounds **16**–**19** against selected representative microorganisms are summarized in the *Table*. For comparison, the activities of ciprofloxacin (**1a**), fleroxacin (**1c**), and the pyrimidol[1,6-*a*]benzimidazoles **2** and **3** are also included.

Table. *Inhibition of* E. coli *DNA Gyrase and Antibacterial Activity of Selected Target Compounds*[a])



	A	R^1	R^2	R^3	R^4
16	N	OH	Me	H	H
17	N	OH	H	H	H
18	N	OH	H	Me	Me
19	N	H	Me	H	H
2a	CH	OH	Me	H	H
2b	CH	OH	H	H	H
2c	CH	OH	H	Me	Me
2d	CH	H	Me	H	H

Compound	MNEC[b]) [g/ml]	Minimal inhibitory concentration (MIC)[b]) [g/ml]									
		Ec(A)	*Ec*(B)	*Ec*(C)	*Ko*	*Et*	*Pa*(A)	*Pa*(B)	*Sa*	*Sh*	*Ef*
16	0.5	≤ 0.12	≤ 0.12	1	≤ 0.12	≤ 0.12	2	> 64	4	64	64
17	0.5	≤ 0.12	≤ 0.12	2	≤ 0.12	0.12	64	> 64	16	> 32	32
18	0.3	≤ 0.06	≤ 0.06	2	0.5	0.5	1	> 32	16	> 32	32
19	0.2	2	1	8	4	2	> 32	> 32	8	> 32	> 32
2a	1.0	≤ 0.06	≤ 0.06	1	0.12	0.12	1	> 32	4	32	16
2b	1.0	≤ 0.25	≤ 0.25	2	1	1	2	> 64	> 64	> 64	> 128
2c	0.5	0.12	≤ 0.06	1	1	0.25	2	> 32	4	16	> 32
2d	1.0	2	0.25	16	4	2	16	> 32	8	32	32
1a	0.05	≤ 0.03	≤ 0.03	0.06	≤ 0.03	≤ 0.03	0.06	32	1	32	4
1c	0.5	≤ 0.06	≤ 0.06	0.5	≤ 0.06	≤ 0.06	0.12	> 32	2	8	8

[a]) Organisms selected for the *Table*: *Ec*(A), *E. coli* 1346; *Ec*(B), *E. coli* B; *Ec*(C), *E. coli* K12 KEA-12; *Ko*, *Klebsiella oxytoca* 1082E; *Et*, *Enterobacter cloacae* P99; *Pa*(A), *Pseudomonas aeruginosa* 799/61; *Pa*(B), *Pseudomonas aeruginosa* 3351 (quinolone-resistant); *Sa*, *Staphylococcus aureus* 887; *Sh*, *Staphylococcus haemolyticus* 75 (quinolone-resistant); *Ef*, *Enterococcus faecalis*.

[b]) See *Exper. Part.*

At the enzyme level, replacement of C by N slightly improved the enzyme inhibitory activities for the four compounds tested. The MNEC values [16] in the range of 0.1–0.5 μg/ml displayed by the aza derivatives **16**–**19** are comparable with those of the reference compound ciprofloxacin (**1a**), fleroxacin (**1c**), and of other clinically useful antibacterials with this mode of action [17]. Their *in vitro* antibacterial activities are, however, lower than one would expect from their enzyme-inhibition data in analogy to quinolinones. This discrepancy was already observed for the C analogues **2a**–**c** which display a weak but broad antibacterial activity [1]. Introduction of N has accentuated this discrepancy. The aza analogues are still active against gram-negative bacteriae but are almost inactive against gram-positive organisms. This difference between enzyme-inhibition activity and *in vitro* antibacterial activity is very strong for **19** (R^1 = H); indeed, this compound is almost totally devoid of any antibacterial activity as was its carbon analogue **2d**.

Our thanks are due to our colleagues from Pharma Preclinical Research Drs. *H. Gmünder* and *P. Angehrn* for the determination of the MNEC values and antibacterial activities *in vitro*, respectively, Drs. *W. Arnold* (NMR), *W. Vetter, W. Meister* (MS), and *M. Grosjean* (IR) for spectral data, and *S. Müller* for elemental analysis.

Experimental Part

General. $Pb(OAc)_4$ (*Fluka*) was powdered under N_2 and stored over concentrated H_2SO_4 for at least two weeks prior to use. *N*-Cyclopropylacetamide was prepared in 81% yield following the procedures in [18] [19]. Workup of the reaction mixture was slightly modified to avoid difficulties experienced with the purification of the amide [18]: the crude product was distilled (b.p. 70°/20 Pa) before crystallization from Et_2O at −20° (m.p. 51–53°). Dry solvents were obtained by standard procedures (*t*-BuOH distilled from CaH_2, THF, and Et_2O distilled from $LiAlH_4$). The rest of the reactants and solvents were used as purchased from *Fluka*. M.p.: *Büchi 20* melting-points apparatus; uncorrected. IR Spectra [cm^{-1}]: *Nicolet* FTIR spectrometer. ^{1}H-NMR Spectra: *Bruker AC 250* (250 MHz, δ in ppm rel. to internal TMS; coupling constants J in Hz). ^{13}C-NMR Spectra: *Bruker AM 400* (100.62 MHz, δ in ppm rel. to internal TMS); MS: *MS9-ZAB* data system *SS 300 Finnigan*. HPLC: *Lichrospher® 60 RP-select B*, 5 µm.

Enzyme inhibition and *in vitro* antibacterial activity were evaluated according to the procedures described in [1]. The inhibiting activity of the compound tested is expressed as MNEC (maximal noneffective concentration), *i.e.*, the highest inhibitor concentration at which all DNA is still completely supercoiled. The *in vitro* antibacterial activity, defined as minimal inhibitory concentration (MIC), is the lowest concentration of the drug that prevented the macroscopic growth of a culture after 18 h of incubation at 35°.

2,6-Dichloro-5-fluoropyridine-3-amine (**4**). $Pb(OAc)_4$ (53.2 g, 0.12 mol) is added to a suspension of *2,6-dichloro-5-fluoropyridine-3-acetamide* (**3**; 20.9 g, 0.1 mol) in dry *t*-BuOH (400 ml), and the mixture is stirred and heated at 100° (bath temp.) for 3 h. After cooling, the solvent is evaporated and the residue extracted with Et_2O (6 × 120 ml), each portion filtered with suction through alumina (120 g, *Brockmann I*, neutral). The volume of the filtrate is reduced to *ca.* 300 ml, and anh. HCl is passed into the stirred soln. for 3 h at internal temp. below 0°. Stirring is continued for 1 h at the same temp., the precipitate is collected, washed with Et_2O, petroleum ether (30–40°), and dried. The hydrochloride is added with ice cooling and stirring to a soln. of KOH (17.0 g, 0.3 mol) in H_2O (150 ml) and the suspension extracted with Et_2O (200 and 2 × 75 ml). After drying ($MgSO_4$) and removal of the solvent *in vacuo*, the crude product is crystallized from $CHCl_3$/MeOH 4:1: 16.25 g (90%) of **4**. M.p. 146–147°. ^{1}H-NMR ($CDCl_3$): 4.25 (br. *s*, 2 H); 6.90 (*d*, J = 8, 1 H). MS: 180 (100, $M^{+\cdot}$). Anal. calc. for $C_5H_3Cl_2FN_2$ (180.997): C 33.18, H 1.67, N 15.48, Cl 39.18; found: C 33.11, H 1.71, N 15.45, Cl 39.22.

*5-Chloro-3-cyclopropyl-6-fluoro-2-methyl-3*H*-imidazo[4,5-*b*]pyridine* (**8**). A soln. of oxalyl chloride (14.0 g, 0.11 mol) in dry Et_2O (30 ml) is added dropwise with stirring, at internal temp. below +3°, to a suspension of *N*-cyclopropylacetamide (9.9 g, 0.1 mol) in Et_2O (80 ml). The stirring is continued for 6 h at ambient temp. Solid **4** (18.1 g, 0.1 mol) is added in one portion and the mixture stirred at 24° for 16 h. After standing for 1 h at 0°, the precipitate[2]) is collected, washed with Et_2O, petroleum ether, dried (25 g, m.p. dec. > 115°), and dissolved in DMF (400 ml). Anh. K_2CO_3 (55.3 g, 0.4 mol) is added and the mixture stirred at 155–160° (bath temp.) for 48 h. After cooling, the mixture is filtered through *Dicalite* (8 g), the insoluble material is washed with $CHCl_3$, until the filtrate is colorless, and the solvents are evaporated. The residue is extracted with boiling Et_2O (8 × 150 ml), each extract is

---

[2]) Isolation and characterization of the main components (composition determined by HPLC: **6**: 78%, **7**: 14%) of the precipitate: the precipitate (1 g) is suspended in AcOEt (50 ml) and stirred for 30 min at r.t. Insoluble material is filtered off with suction and washed with AcOEt (25 ml) and dried *in vacuo* to give 0.10 g (10%) of **7**. After evaporation of AcOEt, the residue is crystallized from $CHCl_3$ to give 0.52 g (52%) of **6**.

*(*RS*)-3-Cyclopropyl-2-[(2,6-dichloro-5-fluoropyridin-3-yl)amino]-4,5-dihydro-2-methyl-2*H*-oxazole-4,5-dione* (**6**): M.p. 134–135°. IR (KBr): 3476*w*, 3356*m*, 3025*w*, 1818*s*, 1749*s*, 1589*m*, 1517*s*, 1398*s*, 1299*m*, 1234*s*, 1230*s*, 1206*s*, 1202*s*. ^{1}H-NMR ($CDCl_3$): 0.90–1.15 (*m*, 4 H); 2.15 (*s*, 3 H); 2.50–2.60 (*m*, 1 H); 5.36 (*s*, 1 H); 8.31 (*d*, J = 8, 1 H). ^{13}C-NMR (100.62 MHz, (D_6)DMSO): 158.37, 153.61 (2 CO); 153.30 (CF); 136.03 (*C*NH); 135.28 (Cl*C*=CF); 127.70 (Cl*C*=CNH); 117.80 (H*C*=CF); 101.21 (N*C*(CH_3)O); 23.54, 23.57 (*C*H_3, H*C*N); 4.99, 3.21 (2 *C*H_2CHN). MS: 333.1 (65, [M − H]$^+$). Anal. calc. for $C_{12}H_{10}Cl_2FN_3O_3$ (334.134): C 43.14, H 3.02, N 12.58, Cl 21.22; found: C 43.32, H 2.95, N 12.63, Cl 21.15.

*2,6-Dichloro-*N*-[(*E*/*Z*)-2-cyclopropyl-1-methylethenyl]-5-fluoropyridine-3-amine Hydrochloride* (**7**): M.p. 230–231°. IR (KBr): 2974*m*, 2827*s*, 1648*s*, 1557*m*, 1406*s*, 1201*m*, 1122*s*. ^{1}H-NMR ((D_6)DMSO): 0.75–1.30 (*m*, 4 H); 2.08 (*s*, 1.8 H); 2.58 (*s*, 1.2 H); 2.85 (*m*, 1 H); 8.32 (*d*, J = 10, 0.6 H); 8.42 (*d*, J = 10, 0.4 H); 9.48 (*m*, 0.6 H); 10.82 (*m*, 0.4 H). MS: 261 (18, $M^{+\cdot}$). Anal. calc. for $C_{10}HN_3Cl_2F \cdot HCl$ (298.568): C 40.47, H 3.72, N 14.06; found: C 40.77, H 3.86, N 13.82.

filtered through *Dicalite* (4 g), and the solvent is removed. The crude product is crystallized from petroleum ether (90–100°): 13.98 g (61%) of **8**. M.p. 139–140°. ^{1}H-NMR ($CDCl_3$): 1.10–1.35 (*m*, 4 H); 2.70 (*s*, 3 H); 3.10–3.25 (*m*, 1 H); 7.69 (*d*, J = 8, 1 H). MS: 225 (41, M^+). Anal. calc. for $C_{10}H_9ClFN_3$ (225.654): C 53.23, H 4.02, N 18.62, Cl 15.71; found: C 53.16, H 4.00, N 18.42, Cl 15.73.

*Methyl 5-Chloro-3-cyclopropyl-6-fluoro-3*H*-imidazo[4,5-*b*]pyridine-2-acetate* (**9**). At internal temp. below −70°, a 1M soln. of $LiN(Me_3Si)_2$ in THF (85 ml, 85 mmol) is added to a stirred suspension of **8** (15.8 g, 70 mmol) in dry THF (150 ml). The mixture is stirred at −75° for 1.5 h, and additional 75 ml (75 mmol) of $LiN(Me_3Si)_2$ soln. are added dropwise. After being stirred for 0.5 h, the soln. is added fairly rapidly to a stirred soln. of $(MeO)_2CO$ (25.2 g, 0.28 mol) in dry THF (150 ml) at −70°. The soln. is stirred at −75° for 2 h and quenched with aq. NH_4Cl. The temp. is allowed to rise to −10°, the mixture is poured into 15% aq. NH_4Cl (300 ml) and extracted with AcOEt (700 ml). The org. soln. is washed with aq. NH_4Cl (3 × 100 ml), the combined aq. phases are re-extracted with AcOEt (3 × 150 ml), and the combined AcOEt soln. is washed with 10% aq. NaCl soln. After drying (Na_2SO_4) and removal of the solvent *in vacuo* the crude product is crystallized from petroleum ether (90–100°): 18.8 g (94%) of **9**. M.p. 120–121°. ^{1}H-NMR ($CDCl_3$): 1.20–1.30 (*m*, 4 H); 3.20–3.30 (*m*, 1 H); 3.79 (*s*, 3 H); 4.14 (*s*, 2 H); 7.75 (*d*, J = 8, 1 H). MS: 283 (100, M^+). Anal. calc. for $C_{12}H_{11}ClFN_3O_2$ (283.690): C 50.81, H 3.91, N 14.81, Cl 12.50; found: C 50.76, H 3.73, N 14.63, Cl 12.22.

*5-Chloro-3-cyclopropyl-6-fluoro-3*H*-imidazo[4,5-*b*]pyridine-2-acetamide* (**10**). NaCN (340 mg, 7 mmol) and **9** (18.5 g, 65.2 mmol) are added to a 9M soln. of NH_3 in MeOH (220 ml), and the mixture is kept at 45–50° (bath temp.) for 1 h, before it is left to stand overnight at 24°. H_2O (150 ml) is added, the precipitate collected, washed with H_2O, ice-cold MeOH, Et_2O, and dried *in vacuo*. Crude **10** (16.8 g, 95%) is used in the next step. M.p. 230–232° ($CHCl_3$). ^{1}H-NMR ((D_6)DMSO): 1.00–1.25 (*m*, 4 H); 3.20–3.40 (*m*, 1 H); 3.95 (*s*, 2 H); 7.24 (br. *s*, 1 H); 7.70 (br. *s*, 1 H); 8.14 (*d*, J = 8, 1 H). MS: 268 (68, M^+). Anal. calc. for $C_{11}H_{10}ClFN_4O$ (268.679): C 49.17, H 3.75, N 20.85, Cl 13.20; found: C 48.86, H 3.75, N 20.60, Cl 13.25.

N*-Benzyloxy-5-chloro-3-cyclopropyl-6-fluoro-3*H*-imidazo[4,5-*b*]pyridine-2-acetamide* (**11**). A mixture of **10** (16.8 g, 65.5 mmol), *O*-benzylhydroxylamine hydrochloride (40.0 g, 0.25 mol), EtOH (230 ml), and H_2O (230 ml) is stirred at 73° (bath temp.) for 48 h. Most of EtOH is removed destilled off, H_2O (300 ml) is added, the crystals are collected and washed with H_2O and Et_2O. After drying *in vacuo*, crude **11**, 16.9 g (69%) is used in the next step. M.p. 167–168° (AcOEt/petroleum ether). ^{1}H-NMR ($CDCl_3$): 1.10–1.35 (*m*, 4 H); 3.15–3.30 (*m*, 1 H); 3.99 (*s*, 2 H); 4.94 (*d*, 2 H); 7.10–7.40 (*m*, 5 H); 7.60 (*d*, J = 8, 1 H); 10.54 (*s*, 1 H). MS: 374 (88, M^+). Anal. calc. for $C_{18}H_{16}ClFN_4O$ (374.803): C 57.68, H 4.30, N 14.95, Cl 9.46; found: C 57.42, H 4.40, N 14.74, Cl 9.23.

7-(Benzyloxy)-2-chloro-10-cyclopropyl-3-fluoro-6,7,8,10-tetrahydropyrido[2′,3′:4,5]imidazo[1,2-c]pyrimidine-6,8-dione (**12**). A soln. of **11** (15.0 g, 40.0 mmol) and 1,1′-carbonyldiimidazole (13.0 g, 80 mmol) in THF (200 ml) is stirred at 65–70° for 1 h. The mixture is kept at 0° for 2 h, crystals are collected, washed with ice-cold THF, Et_2O, and dried *in vacuo* to give 14.7 g (85%) of **12**. M.p. 254–256° ($CHCl_3$/MeOH). ^{1}H-NMR ((D_6)DMSO): 0.95–1.05 (*m*, 2 H); 1.15–1.25 (*m*, 2 H); 3.00–3.10 (*m*, 1 H); 5.09 (*s*, 2 H); 5.57 (*s*, 1 H); 7.40–7.50 (*m*, 3 H); 7.50–7.60 (*m*, 2 H); 8.35 (*d*, J = 8, 1 H). MS: 400 (2.4, M^+). Anal. calc. for $C_{19}H_{14}ClFN_4O_3$ (400.797): C 56.94, H 3.52, N 13.98, Cl 8.85; found: C 56.64, H 3.46, N 13.72, Cl 8.53.

7-(Benzyloxy)-10-cyclopropyl-3-fluoro-2-(4-methylpiperazin-1-yl)-6,7,8,10-tetrahydropyrido[2′,3′:4,5]imidazo[1,2-c]pyrimidine-6,8-dione (**13**). A soln. of **12** (401 mg, 1 mmol), 1-methylpiperazine (1.0 g, 10 mmol), and KI (33 mg, 0.2 mmol) in *N*-methylpyrrolidone (5 ml) is stirred at 120° for 12 h. Volatiles are removed *in vacuo* (50°/*ca.* 30 Pa), and the residue is dissolved in CH_2Cl_2 (50 ml). After washing with sat. aq. $NaHCO_3$ soln. (2 × 15 ml), the aq. solns. are re-extracted with CH_2Cl_2 (2 × 15 ml) and the combined org. phases are washed with 5% NaCl. After drying (Na_2SO_4) and evaporation *in vacuo*, the crude product is dried *in vacuo* (6 Pa) and crystallized from MeOH: 317 mg (76%) of **13**. M.p. 227–229°. ^{1}H-NMR ($CDCl_3$): 1.05–1.25 (*m*, 4 H); 2.36 (*s*, 3 H); 2.50–2.60 (*m*, 2 H); 2.85–2.95 (*m*, 1 H); 3.50–3.60 (*m*, 4 H); 5.20 (*s*, 2 H); 5.53 (*s*, 1 H); 7.30–7.40 (*m*, 3 H); 7.50–7.60 (*m*, 2 H); 8.04 (*d*, J = 12, 1 H). MS: 464 (62, M^+). Anal. calc. for $C_{24}H_{25}FN_6O_3$ (464.501): C 62.06, H 5.15, N 18.09; found: C 61.82, H 5.15, N 17.97.

7-(Benzyloxy)-10-cyclopropyl-3-fluoro-2-(piperazin-1-yl)-6,7,8,10-tetrahydropyrido[2′,3′:4,5]imidazo[1,2-c]-pyrimidine-6,8-dione (**14**). Compound **14** was obtained from **12** and piperazine in analogy to the preparation of **13**. M.p. 215–217° (MeOH). ^{1}H-NMR ($CDCl_3$): 1.08–1.24 (*m*, 4 H); 1.91 (br. *s*, 1 H); 2.82–2.95 (*m*, 1 H); 3.00–3.08 (*m*, 4 H); 3.45–3.58 (*m*, 4 H); 5.20 (*s*, 2 H); 5.54 (*s*, 1 H); 7.35–7.44 (*m*, 3 H); 7.58–7.70 (*m*, 2 H); 8.04 (*d*, J = 12, 1 H). MS: 450 (36, M^+). Anal. calc. for $C_{23}H_{23}FN_6O_3$ (450.474): C 61.32, H 5.15, N 18.66; found: C 61.16, H 5.16, N 18.44.

*7-(Benzyloxy)-10-cyclopropyl-2-(*cis*-3,5-dimethylpiperazin-1-yl)-3-fluoro-6,7,8,10-tetrahydropyrido[2′,3′:4,5]-imidazo[1,2-c]pyrimidine-6,8-dione* (**15**). Compound **15** was obtained from **12** and *cis*-3,5-dimethylpiperazine in analogy to the preparation of **13**. M.p. 241–243° (EtOH). ^{1}H-NMR ($CDCl_3$): 1.05–1.25 (*m*, 4 H); 1.14 (*d*, J = 6,

6 H); 2.45–2.60 (*m*, 2 H); 2.85–2.95 (*m*, 1 H); 2.95–3.15 (*m*, 2 H); 3.90–4.05 (*m*, 2 H); 5.20 (*s*, 2 H); 5.54 (*s*, 1 H); 7.35–7.45 (*m*, 3 H); 7.60–7.70 (*m*, 2 H); 8.03 (*d*, J = 12, 1 H). MS: 478 (64, M^{+}). Anal. calc. for $C_{25}H_{27}FN_6O_3$ (478.528): C 62.75, H 5.69, N 17.56; found: C 62.76, H 5.48, N 17.46.

10-Cyclopropyl-3-fluoro-7-hydroxy-2-(4-methylpiperazin-1-yl)-6,7,8,10-tetrahydropyrido[2',3':4,5]imidazo-[1,2-c]pyrimidine-6,8-dione (**16**). A soln. of **13** (232 mg, 0.5 mmol) in MeOH (15 ml) and AcOH (5 ml) is hydrogenated over 5% Pd/C (25 mg). The precipitate is dissolved by addition of AcOH, the catalyst is filtered off, and the solvents are evaporated *in vacuo*. The residue is dissolved in H_2O (20 ml), rapidly filtered, and the pH of the filtrate is adjusted to 7–8 with sat. aq. $NaHCO_3$ soln. The precipitate is collected, washed successively with H_2O, THF, Et_2O, and dried *in vacuo* to give 170 mg (91%) of **16**: M.p. 269–273° (dec.). ^{1}H-NMR ((D$_6$)DMSO): 1.02–1.16 (*m*, 4 H); 2.23 (*s*, 3 H); 2.42–2.48 (*m*, 2 H); 2.94–3.02 (*m*, 1 H); 3.35–3.45 (*m*, 2 H); 5.41 (*s*, 1 H); 7.99 (*d*, J = 12, 1 H); 10.57 (br. *s*, 1 H). MS: 374 (11, M^{+}). Anal. calc. for $C_{17}H_{19}FN_6O_3$ (374.376): C 54.54, H 5.12, N 22.45; found: C 54.23, H 5.21, N 22.25.

10-Cyclopropyl-3-fluoro-7-hydroxy-2-(piperazin-1-yl)-6,7,8,10-tetrahydropyrido[2',3':4,5]imidazo[1,2-c]-pyrimidine-6,8-dione (**17**). Compound **17** was obtained by hydrogenation of **13** in analogy to the preparation of **16**. M.p. 288–290° (dec.). ^{1}H-NMR ((D$_6$)DMSO): 1.00–1.22 (*m*, 4 H); 2.73–2.82 (*m*, 4 H); 2.98–3.05 (*m*, 1 H); 3.30–3.42 (*m*, 4 H); 5.40 (*s*, 1 H); 7.96 (*d*, J = 11, 1 H). MS: 361.2 (100, $[M+H]^{+}$). Anal. calc. for $C_{16}H_{17}FN_6O_3$ (360.349): C 53.33, H 4.76, N 23.32; found: C 53.38, H 4.77, N 23.14.

*10-Cyclopropyl-2-(*cis*-3,5-dimethylpiperazin-1-yl)-3-fluoro-7-hydroxy-6,7,7,8,10-tetrahydropyrido[2',3':4,5]-imidazo[1,2-c]pyrimidine-6,8-dione* (**18**). Compound **18** was obtained by hydrogenation of **15** in analogy to the preparation of **16**. M.p. 265° (dec.). ^{1}H-NMR ((D$_6$)DMSO): 1.01 (*d*, J = 6, 6 H); 1.00–1.25 (*m*, 4 H); 2.34–2.49 (*m*, 2 H); 2.78–2.95 (*m*, 1 H); 2.95–3.05 (*m*, 1 H); 3.72–3.85 (*m*, 2 H); 5.40 (*s*, 1 H); 7.98 (*d*, J = 12, 1 H). MS: 389.5 (100, $[M+H]^{+}$). Anal. calc. for $C_{18}H_{21}FN_6O_3$ (388.403): C 55.66, H 5.45, N 21.64; found: C 55.67, H 5.35, N 21.32.

10-Cyclopropyl-3-fluoro-2-(4-methylpiperazin-1-yl)-6,7,8,10-tetrahydropyrido[2',3':4,5]imidazo[1,2-c]pyri-midine-6,8-dione (**19**). A mixture of **16** (375 mg, 1 mmol), Zn (3.0 g, 46 mmol), and AcOH (25 ml) is kept in an ultrasonic bath at 40° for 65 h. After filtration and evaporation, the residue is treated with 5% aq. $NaHCO_3$ (15 ml) and extracted with CH_2Cl_2 (3 × 30 ml). The org. soln. is washed with H_2O (5 ml), dried, the solvent is removed *in vacuo* and the residue crystallized from MeOH. M.p. 272–275° (dec.). ^{1}H-NMR ($CDCl_3$): 1.07–1.33 (*m*, 4 H); 2.39 (*s*, 3 H); 2.53–2.70 (*m*, 4 H); 2.86–2.98 (*m*, 1 H); 3.50–3.66 (*m*, 4 H); 5.49 (*s*, 1 H); 8.02 (*d*, J = 12, 1 H); 9.15 (br. *s*, 1 H). MS: 358 (78, M^{+}). Anal. calc. for $C_{17}H_{19}FN_6O_2$ (358.377): C 56.98, H 5.34, N 23.45; found: C 56.49, H 5.15, N 23.10.

REFERENCES

[1] C. Hubschwerlen, P. Pflieger, J. L. Specklin, K. Gubernator, H. Gmünder, P. Angehrn, I. Kompis, *J. Med. Chem.* **1992,** *35,* 1385.

[2] D. T. W. Chu, P. B. Fernandes, *Adv. Drug. Res.* **1991,** *21,* 71.

[3] J. P. Sanchez, J. M. Domagala, S. E. Hagen, C. L. Heifetz, M. P. Hutt, J. B. Nichols, A. K. Trehan, *J. Med. Chem.* **1988,** *31,* 983.

[4] T. Miyamoto, H. Egawa, J. I. Matsumoto, *Chem. Pharm. Bull.* **1987,** *35,* 2280.

[5] H. E. Baumgarten, H. L. Smith, A. Staklis, *J. Org. Chem.* **1975,** *40,* 3554.

[6] L. Kaczmarek, P. Nantka-Namirski, E. Moryl, E. Chojnacka-Wojcik, *Pol. J. Pharmacol. Pharm.* **1990,** *42,* 79.

[7] G. V. Boyd, 'Recent Advances in the Synthesis of Amidines', in 'The Chemistry of Amidines and Imidates', Eds. S. Patai and Z. Rappoport, Wiley, Chichester, 1991, pp. 334–351, and ref. cit. therein.

[8] L. Weintraub, S. R. Oles, N. Kalish, *J. Org. Chem.* **1968,** *33,* 1679.

[9] L. Andersen, F. E. Nielsen, E. B. Pedersen, *Chem. Scr.* **1988,** *28,* 191.

[10] A. J. Speziale, L. R. Smith, *J. Org. Chem.* **1963,** *28,* 1805.

[11] D. T. W. Chu, P. B. Fernandes, R. E. Maleczka, Jr., C. W. Nordeen, A. G. Pernet, *J. Med. Chem.* **1987,** *30,* 504.

[12] D. Bouzard, P. Di Cesare, M. Essiz, J. P. Jacquet, P. Remuzon, *Tetrahedron Lett.* **1988,** *29,* 1931.

[13] R. C. F. Jones, M. W. Anderson, M. J. Smallridge, *Tetrahedron Lett.* **1988,** *29,* 5001.

[14] M. W. Anderson, M. J. Begley, R. C. F. Jones, J. Saunders, *J. Chem. Soc., Perkin Trans. 1* **1984,** 2599.

[15] T. Högberg, P. Ström, M. Ebner, S. Rämsby, *J. Org. Chem.* **1987,** *52,* 2033.

[16] R. Otter, N. R. Cozzarelli, *Methods Enzymol.* **1983,** *100,* 171.

[17] L. P. Elwell, L. M. Walton, J. M. Besterman, A. Hudson, 'Use of an In Vitro DNA Strand-Breakage Assay to Monitor Compound Interactions with DNA Gyrase' in 'The 4-Quinolones', Ed. G. C. Crumplin, Springer Verlag, London, 1990, pp. 87–102.

[18] L. A. Paquette, J. R. Malpass, G. R. Krow, *J. Am. Chem. Soc.* **1970,** *92,* 1980.

[19] M. Bouzoubaa, G. Leclerc, S. Rakhit, G. Andermann, *J. Med. Chem.* **1985,** *28,* 896.