Synthesis of Acyclic Nucleosides with *N*-[(Benzyloxy)(aryl)methyl] Substituents as Potential HEPT, EBPU, and TNK-651 Analogues

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The syntheses of the novel acyclic nucleosides **5a**–**5m**, carrying different *N*-[(benzyloxy)(aryl)-methyl] substituents, are described (*Scheme*). These compounds could be prepared in medium-to-good yields by either direct or silyl-assisted coupling of the electrophiles **6** with either purine or pyrimidine nucleobases, or with different imidazole derivatives. The reactivity of the positively charged electrophilic intermediates derived from **6** upon Cl^- abstraction was rationalized by *ab initio* HF/6-311G quantum-mechanic calculations. The positive charge was found to be dispersed differently, depending on the electronic properties of the aryl substituents.

Introduction. – The intensive effort to find effective chemotherapeutic agents with antiviral and anticancer activities has reaffirmed the need for efficient synthetic methods towards diverse, modified nucleosides and their analogues. The unprecedented discovery of the antiviral drug acyclovir (*Zovirax*; **1**) [1], which corresponds to 9-[(2-hydroxyethoxy)methyl]guanine, and the subsequent clarification of its behavior towards virally coded enzymes has provided a massive impetus for the further synthesis of analogous compounds and the investigation of their biochemical fates. In this respect, many variants, based on both acyclic glycones and heterocyclic bases, have been described [2]. Like acyclovir (**1**), most of the acyclic nucleosides exert their antiviral activities through conversion into phosphate esters [3][4]. However, HEPT (**2**), which corresponds to 1-[(2-hydroxyethoxy)methyl]-6-(phenylsulfanyl)thymine, does not compete with thymidine for phosphorylation by thymidine kinase [5]. Further experiments have manifested that the anti-HIV-1 activity of HEPT (**2**) is almost independent of the acyclic side chain [6]. Conspicuously, the imperative presence of an aryl residue at C(6) of **2** for the inhibition of HIV-1 reverse transcriptase (RT) has been confirmed [6]. It is well-recognized that the aryl residue at C(6) of HEPT interacts with flexible HIV-RT, thereby altering the enzyme's conformation, which eventually results in inhibition of HIV-RT activity [7]. Based on the structure, activity, and mode of action of HEPT (**2**), the analogues EBPU (**3**), *i.e.*, 1-[(benzyloxy)methyl]-5-ethyl-6-(phenylsulfanyl)pyrimidine-2,4(1*H*,3*H*)-dione [8], and TNK-651 (**4**), *i.e.*, 6-benzyl-1-[(benzyloxy)methyl]-5-(1-methylethyl)pyrimidine-2,4(1*H*,3*H*)-dione [9], were devel-

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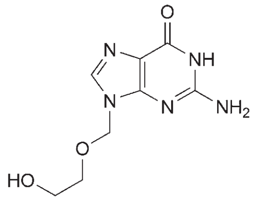
oped as potent HIV-RT inhibitors. Although compounds **2**–**4** possess acyclic nucleoside templates, they are categorized as 'non-nucleoside' transcriptase inhibitors [10].



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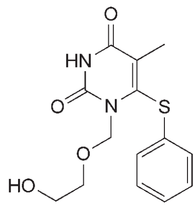

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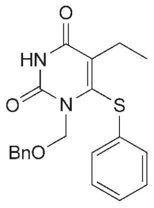

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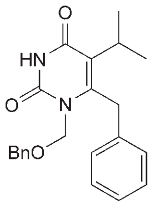

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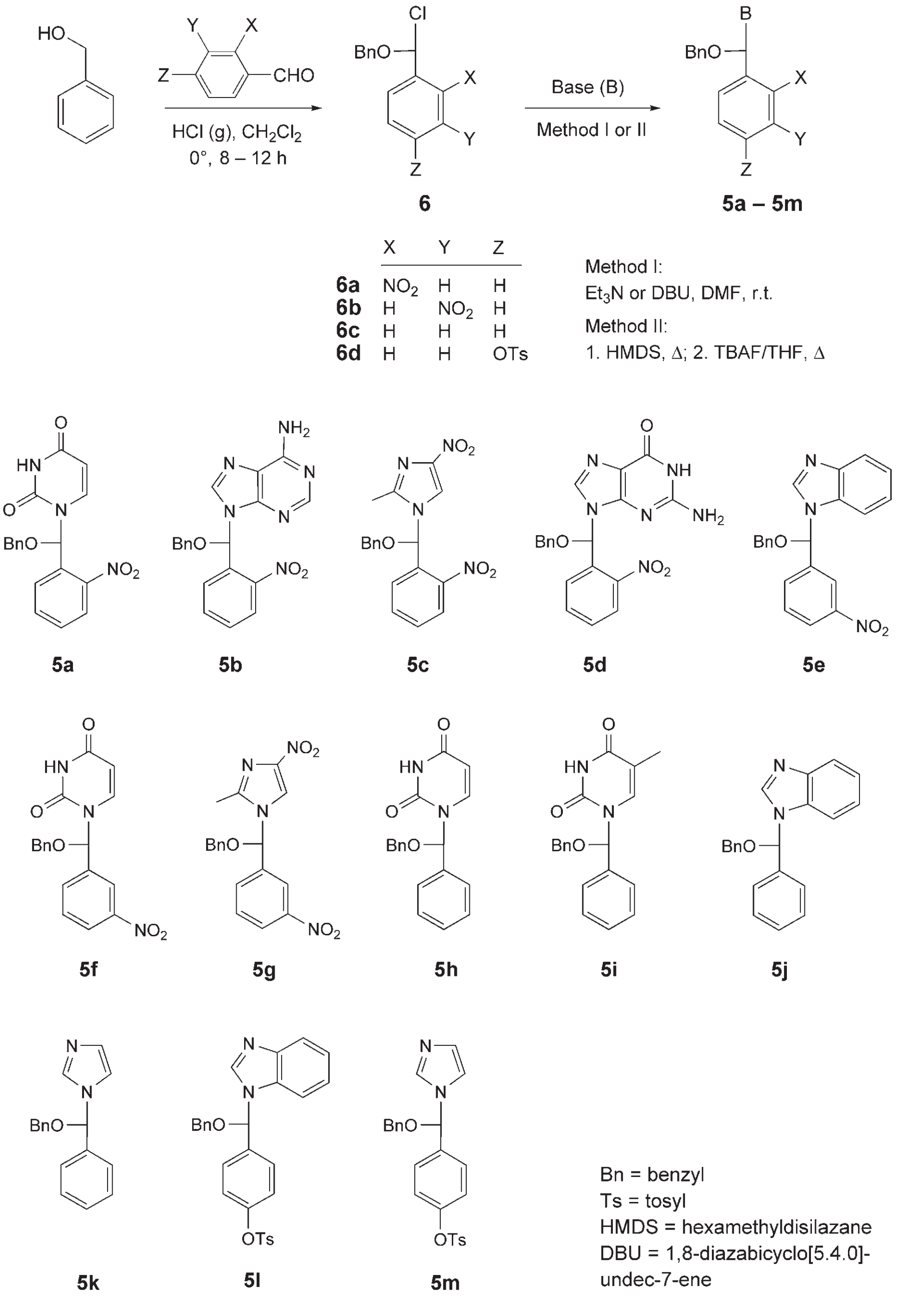
Encouraged by the success of EBPU (**3**) and TNK-651 (**4**), and in continuation of our interest in the synthesis of acyclic nucleosides [11] as part of our drug-discovery program, we, herein, report the synthesis of a series of 13 novel acyclic nucleosides of type **5** (see *Scheme* below).

Results and Discussion. – The synthesis of compounds **5a**–**5m** is outlined in the *Scheme*. The first step consisted in the preparation of the α-chloro ethers **6**. The synthesis of these key intermediates was necessary since, to our knowledge, there is no report for chlorobenzylation of an alcohol with benzaldehyde or its derivatives. In analogy to the established reaction conditions for chloromethylation of alcohols with simple aliphatic aldehydes [4a][12], we first tried to pass a gentle stream of anhydrous HCl through a solution of benzyl alcohol and 3-nitrobenzaldehyde in CH_2Cl_2 at 0°. However, after 6–8 h, there was no considerable progress in the reaction, not even when the reaction time was prolonged up to 18 h. However, by increasing the rate of HCl, compound **6b** was obtained in 75% yield after 8 h, as indicated by ^{1}H-NMR analysis.

In the above reaction, 3-nitrobenzaldehyde was chosen due to its high reactivity towards the weakly nucleophilic benzyl alcohol. However, the same procedure was found to work also with benzaldehyde proper or with Ts-protected 4-hydroxybenzaldehyde, but was inefficient for benzaldehydes with electro-donating groups such as 4-methoxybenzaldehyde. Thus, the related compounds **6a**, **6c**, and **6d** were obtained analogously, in yields of 70, 68, and 42%, respectively, within 8–12 h. Since compounds **6** were generally very sensitive to both humidity and temperature, and because they rapidly decompose on silica gel, they were used directly in the next step without further purification.

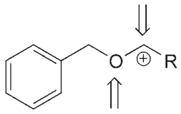
The presence of an aryl residue and of the benzyloxy O-atom at the α-chloromethyl ether moiety in compounds **6** are expected to affect the leaving-group propensity of the Cl-atom, mostly due to electronic effects, *i.e.*, the 'anomeric' effect exerted by the O-atom and aryl-substituent effects. The dispersion of the positive charge upon abstraction of Cl^- was calculated for several benzyloxy-substituted arylmethyl cations by means of *ab initio* HF/6-311G quantum-mechanic calculations. The results are summarized in the *Table*. As can be seen, a simple phenyl (C_6H_5) residue causes a considerable increase in the negative and positive charge densities on the O-atom and the benzylic C-atom, respectively. The presence of an NO_2 group in the *ortho*-, *meta*-, or

Scheme


HO
Y X Z CHO
HCl (g), CH2Cl2
0°, 8 – 12 h
Cl
BnO
X
Y
Z
6
Base (B)
Method I or II
B
5a – 5m
X Y Z
6a NO2 H H
6b H NO2 H
6c H H H
6d H H OTs
Method I:
Et3N or DBU, DMF, r.t.
Method II:
1. HMDS, Δ; 2. TBAF/THF, Δ
5a
5b
5c
5d
5e
5f
5g
5h
5i
5j
5k
5l
5m
Bn = benzyl
Ts = tosyl
HMDS = hexamethyldisilazane
DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene

para-positon of the aryl ring decreases the negative charge at the O-atom, and increases the positive one at the C-atom. So, the opposite is expected for a MeO group on aryl residue, as indeed found for a 4-MeO substituent. Hence, electron-withdrawing groups on the aryl residue induce further dispersion of the positive charge *via* the benzyloxy O-atom so that the compound has the reactivity of an aliphatic α-chloro ether. In contrast, when electron-donating groups are present on the aryl ring, the positive charge is stabilized by both the O-atom and the aryl residue. In accord with the calculated data (*Table*), we found that several *para*-methoxy derivatives of type **6** could not be obtained due to their high reactivity towards nucleophiles (unreacted benzyl alcohol), which gave rise to the corresponding acetals as the main products.

Table. *Calculated* ab initio (HF/6–311G) *Charge Densities* (in *Mulliken* units) *for Selected (Benzyloxy)(aryl)methyl Cations.*



R	O-atom	C-atom
H	– 0.44873	0.28288
C_6H_5	– 0.53866	0.40831
$2\text{-}NO_2-C_6H_4$	– 0.49585	0.53023
$3\text{-}NO_2-C_6H_4$	– 0.53703	0.42643
$4\text{-}NO_2-C_6H_4$	– 0.52810	0.42416
$4\text{-}MeO-C_6H_4$	– 0.55769	0.38761

The target compounds **5** were prepared by nucleophilic substitution of the Cl-atom of compounds **6** with the appropriate nitrogen base. Several purines, pyrimidines, and relevant isosteres thereof, including imidazole and benzimidazole derivatives, were designated for *N*-alkylation. Thereby, two different methods were applied. In the case of purine nucleobases, which are poorly soluble in organic media, *in situ* persilylation with hexamethyldisilazane (HMDS) [13] was required prior to coupling (see *Exper. Part*). For pyrimidine, imidazole, and benzimidazole derivatives, direct coupling with **6** in the presence of a base such as Et_3N or DBU (=1, 8-diazabicyclo[5.4.0]undec-7-ene) in anhydrous DMF was possible (*Scheme*).

We used different nitrogen bases to obtain a range of structurally diverse compounds. Note that the purine derivatives **5b** and **5d** were obtained as the *N*(9)-substituted compounds in yields of 63 and 52%, respectively, as deduced by ^1H- and ^{13}C-NMR. The imidazole derivatives were prepared to further widen the scope of biological activities, aiming at antifungal and chemotherapeutic properties [14]. The condensation of 1*H*-imidazole, 2-methyl-4-nitro-1*H*-imidazole, and 1*H*-benzimidazole by the direct method afforded the corresponding acyclic nucleoside derivatives in reasonable-to-good yields. Moreover, in agreement with literature data [11a][15], the *N*-alkylation of 2-methyl-4-nitro-1*H*-imidazole with **6a** and **6b** afforded mainly the respective $4\text{-}NO_2$ isomers **5c** and **5g**, rather than the $5\text{-}NO_2$ derivatives.

In the case of the pyrimidines used, it is interesting to note that solely *N*(1)-alkylated, but no or only trace amounts of *N*(1),*N*(3)-dialkylated products were observed [11a,d]. This is most probably due to the intrinsic steric hindrance present in the electrophiles **6**. The mono-alkylated products could be readily identified by means of ^{1}H-NMR spectroscopy, with a typical down-field NH signal for **5a**, **5f**, **5h**, and **5i**. All compounds were fully characterized (m.p., IR, ^{1}H- and ^{13}C-NMR, MS, elemental analysis). In the ^{1}H-NMR spectra, the two diastereoisotopic benzylic H-atoms resonated separately at δ(H) 4–5 ppm as two *doublet*s, with a coupling constant of 10–12 Hz (see *Exper. Part*). However this was restricted to the products with a functional group on the aryl residue; the other compounds (**6h**–**k**) gave rise to a benzylic *singlet*.

The biological properties of the new compounds are currently under investigation and will be reported in due course.

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Experimental Part

1. *General.* All chemicals were obtained from *Fluka* or *Merck*, except 4-formylphenyl 4-methylbenzenesulfonate, which was prepared according to a literature procedure [16]. Solvents were purified and dried by standard procedures, and stored over 3-Å molecular sieves. Reactions were followed by TLC using *SILG/UV 254* silica-gel plates. Column chromatography (CC) was performed on silica gel *60* (0.063–0.200 mm, 70–230 mesh; *ASTM*). Melting points (M.p.): *Büchi-510* apparatus; in open capillaries (uncorrected). IR Spectra: *Shimadzu FT-IR-8300* spectrophotometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker Avance-DPX-250* spectrometer; at 250/62.5 MHz, resp., δ in ppm, J in Hz. GC/MS: *Shimadzu GC/MS-QP 1000-EX* apparatus; in m/z (rel. %). Elemental analyses (CHNS) were performed on a *Perkin-Elmer 240-B* micro-analyzer.

2. *General Procedure for the Synthesis of Compounds* **6a**–**d**[1]). In a three-neck, round-bottom 200-ml flask equipped with a thermometer and a gas inlet and outlet was placed a mixture of benzyl alcohol (10.8 g, 0.1 mol) and appropriate benzaldehyde (0.12 mol) in anh. CH_2Cl_2 (100 ml). After cooling in an ice bath, a fast stream of HCl gas was passed through the reaction mixture, which was stirred at 0° for 8–12 h. The mixture was then transferred to a conical flask containing anh. $CaCl_2$ (20 g), and shaken vigorously for 30 min. The resulting suspension was flash-filtered, and the filtrate was concentrated under reduced pressure below 50°. The resulting crude, oily (benzyloxy)(aryl)methylchlorides **6** were used in the next step without further purification or characterization. They could be stored at –30° for three months without remarkable loss in reactivity.

3. *General Procedure for the Synthesis of Compounds* **5**. 3.1. *Direct Condensation* (Method I). To a soln. of the appropriate nucleobase (10 mmol) in anh. DMF (50 ml) was added either anh. Et_3N (1.52 g, 15 mmol) or DBU (2.31 g, 15 mmol). The ice-cooled mixture was treated with the appropriate chloride **6** (15 mmol), and stirred at r.t. for 12 h (TLC control). The solvent was evaporated under reduced pressure, and the residue was dissolved in $CHCl_3$ (200 ml) and washed with H_2O (3×100 ml). The org. layer was dried (10 g of Na_2SO_4) and concentrated to afford the crude product.

3.2. *Silyl-Assisted Condensation* (Method II) [13]. In a 500-ml round-bottom flask, a mixture of the appropriate purine nucleobase (10 mmol), $(NH_4)_2SO_4$ (10 mg, 0.076 mmol), and hexamethyldisilazane (HMDS; 100 ml) was heated at reflux, until a clear soln. was obtained (*ca.* 6 and 10 h for adenine and guanine, resp.). The solvent was removed at reduced pressure, the residue was immediately diluted with freshly dist., anh. THF (300 ml), and an anh. benzene soln. (25 ml) containing both Bu_4NF (TBAF; 2.62 g, 10 mmol) and the appropriate electrophile **6** (15 mmol) was added over 20 min. Then, the mixture was heated at reflux for 12 h (TLC control). The solvent was evaporated at reduced pressure, the residue

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[1]) Caution! This reaction must be conducted in an efficient fume hood cupboard. Benzyloxy(aryl)-methyl chlorides are potential carcinogens [17].

was dissolved in $CHCl_3$ (200 ml), and washed with H_2O (3 × 100 ml). The org. layer was dried (10 g of Na_2SO_4) and concentrated to afford the crude product.

*1-[(Benzyloxy)(2-nitrophenyl)methyl]pyrimidine-2,4(1*H*,3*H*)-dione* (**5a**). Purified by CC (SiO_2; AcOEt/hexane 1:2). Yield: 2.25 g (64%). Colorless crystals. TLC (EtOH): R_f 0.74. M.p. 192°. IR (KBr): 3200*s*; 3000–3100*m*, 2900*m*, 1660*s*. ^1H-NMR ($CDCl_3$): 4.60 (*d*, $J = 10.9$, 1 H of PhCH_2); 4.75 (*d*, $J = 10.9$, 1 H of PhCH_2); 5.65 (*d*, $J = 7.8$, H–C(5) of uracil); 7.12 (*d*, $J = 7.8$, H–C(6) of uracil); 7.30 (*s*, OCHN); 7.38–7.71(*m*, 8 arom. H); 7.88 (*d*, $J = 6.8$, arom. H); 9.14 (*s*, NH, exchangeable with D_2O). ^{13}C-NMR ($CDCl_3$): 73.78 (CH_2); 82.76 (CH); 103.85 (C(5) of uracil); 125.84; 128.06; 128.78; 129.06; 130.87; 131.30; 133.48; 136.02; 140.07; 142.24; 149.19; 151.19 (C(2)); 163.27 (C(4) of uracil). MS: 353 (10.3, M^+). Anal. calc. for $C_{18}H_{15}N_3O_5$ (353.33): C 61.19, H 4.28, N 11.89; found: C 61.25, H 4.22, N 11.90.

*9-[(Benzyloxy)(2-nitrophenyl)methyl]-9*H*-purin-6-amine* (**5b**). Purified by CC (SiO_2; AcOEt/hexane 1:1). Yield: 2.36 g (63%). Colorless crystals. TLC (EtOH): R_f 0.80. M.p. 170°. IR (KBr): 3100–3300*s*, 3000–3100*m*, 2900*m*, 1600*s*. ^1H-NMR ((D_6)DMSO): 2.10 (*s*, NH_2, exchangeable with D_2O); 4.60 (*d*, $J = 11.0$, 1 H of PhCH_2); 4.75 (*d*, $J = 11.0$, 1 H of PhCH_2); 5.63 (*s*, OCHN); 7.38–7.71 (*m*, 9 arom. H); 7.89 (*s*, H–C(2) of adenine); 8.54 (*s*, H–C(8) of adenine). ^{13}C-NMR ((D_6)DMSO): 73.24 (CH_2); 81.14 (CH); 119.67; 125.74; 128.45; 128.57; 128.79; 128.91; 130.82; 132.13; 133.76; 136.16; 139.16; 148.37; 150.90; 154.06; 156.16. MS: 376 (17.3, M^+). Anal. calc. for $C_{19}H_{16}N_6O_3$ (376.37): C 60.63, H 4.28, N 22.33; found: C 60.55, H 4.22, N 22.40.

*1-[(Benzyloxy)(2-nitrophenyl)methyl]-2-methyl-4-nitro-1*H*-imidazole* (**5c**). Purified by CC (SiO_2; AcOEt/hexane 1:1). Yield: 2.5 g (68%). Pale-yellow crystals. TLC (EtOH): R_f 0.70. M.p. 130°. IR (KBr): 3000–3100*m*, 2900*m*, 1500–1600*m*. ^1H-NMR ($CDCl_3$): 2.34 (*s*, Me); 4.52 (*d*, $J = 10.9$, 1 H of PhCH_2); 4.65 (*d*, $J = 10.9$, 1 H of PhCH_2); 6.98 (*s*, OCHN); 7.18–7.67 (*m*, 8 arom. H); 8.01 (*d*, $J = 7.0$, arom. H); 10.33 (*s*, H–C(5) of imidazole). ^{13}C-NMR ($CDCl_3$): 14.12 (Me); 74.11 (CH_2); 83.15 (CH); 116.67; 124.66; 128.22; 128.55; 128.79; 128.94; 131.07; 132.23; 133.86; 136.26; 140.19; 148.77; 150.90 (C(2) of imidazole). MS: 368 (12.3, M^+). Anal. calc. for $C_{18}H_{16}N_4O_5$ (368.34): C 58.69, H 4.38, N 15.21; found: C 58.72, H 4.35, N 15.23.

*2-Amino-9-[(benzyloxy)(2-nitrophenyl)methyl]-1,9-dihydro-6*H*-purin-6-one* (**5d**). Purified by CC (SiO_2; AcOEt/EtOH 10:1). Yield: 2.04 g (52%). Yellow crystals. TLC (EtOH): R_f 0.60. M.p. 206°. IR (KBr): 3100–3300*s*, 3000–3100*m*, 2900*m*, 1600*s*. ^1H-NMR ($CDCl_3$): 3.38 (*s*, NH_2, exchangeable with D_2O); 4.56 (*d*, $J = 11.2$, 1 H of PhCH_2); 4.53 (*d*, $J = 11.2$, 1 H of PhCH_2); 6.63 (*s*, OCHN); 7.18–7.9 (*m*, 9 arom. H); 8.04 (*s*, H–C(8) of guanine); 10.85 (*s*, NH, exchangeable with D_2O). ^{13}C-NMR ($CDCl_3$): 73.30 (CH_2); 81.45 (CH); 119.25; 125.66; 128.34; 128.77; 128.79; 128.96; 130.60; 132.63; 133.79; 136.26; 139.22; 148.65; 151.12; 154.11 (C(8) of guanine); 156.22 (C(2) of guanine). MS: 316 (14.7, M^+). Anal. calc. for $C_{19}H_{16}N_6O_4$ (392.37): C 58.16, H 4.11, N 21.42; found: C 58.10, H 4.15, N 21.36.

*1-[(Benzyloxy)(3-nitrophenyl)methyl]-1*H*-benzimidazole* (**5e**). Purified by CC (SiO_2; AcOEt). Yield: 1.70 g (48%). Yellow oil. TLC (EtOH): R_f 0.36. IR (film): 3000–3100*m*, 2900*m*, 1600*s*. ^1H-NMR ($CDCl_3$): 4.40 (*d*, $J = 10.7$, 1 H of PhCH_2); 4.51 (*d*, $J = 10.7$, 1 H of PhCH_2); 6.97 (*s*, OCHN); 7.14–7.87 (*m*, 13 arom. H); 8.05 (*s*, H–C(2) of benzimidazole). ^{13}C-NMR ($CDCl_3$): 72.58 (CH_2); 83.06 (CH); 111.98; 120.88; 123.69; 124.34; 125.71; 128.18; 128.81; 128.94; 129.00; 130.78; 131.94; 133.04; 133.62; 135.79; 142.67; 143.79; 148.69. MS: 359 (11.1, M^+). Anal. calc. for $C_{21}H_{17}N_3O_3$ (359.38): C 70.18, H 4.77, N 11.69; found: C 70.22, H 4.73, N 11.75.

*1-[(Benzyloxy)(3-nitrophenyl)methyl]pyrimidine-2,4(1*H*,3*H*)-dione* (**5f**). Purified by CC (SiO_2; AcOEt/hexane 1:2). Yield: 2.08 g (59%). Colorless crystals. TLC (EtOH): R_f 0.26. M.p. 154°. IR (KBr): 3200*s*, 3000–3100*m*, 2900*m*, 1660*s*. ^1H-NMR ($CDCl_3$): 4.38 (*d*, $J = 11.9$, 1 H of PhCH_2); 4.62 (*d*, $J = 11.9$, 1 H of PhCH_2); 5.65 (*d*, $J = 7.7$, H–C(5) of uracil); 6.54 (*s*, OCHN); 7.07–7.67 (*m*, 8 arom. H); 7.74 (*d*, $J = 7.7$, H–C(6) of uracil); 8.06 (*s*, arom. H); 8.90 (*s*, NH, exchangeable with D_2O). ^{13}C-NMR ($CDCl_3$): 73.73 (CH_2); 82.69 (CH); 103.88 (C(5)); 125.87; 128.06; 128.82; 129.12; 130.80; 131.39; 134.46; 136.22; 140.17; 142.33; 149.56; 151.34; 163.36. MS: 353 (13.0, M^+). Anal. calc. for $C_{18}H_{15}N_3O_5$ (353.33): C 61.19, H 4.28, N 11.89; found: C 61.14, H 4.24, N 11.92.

*1-[(Benzyloxy)(3-nitrophenyl)methyl]-2-methyl-4-nitro-1*H*-imidazole* (**5g**). Purified by CC (SiO_2; AcOEt/hexane 1:1). Yield: 2.09 g (57%). Pale-yellow crystals. TLC (EtOH): R_f 0.69. M.p. 135°. IR (KBr): 3000–3100*m*, 2900*m*, 1500–1600*m*. ^1H-NMR ($CDCl_3$): 2.25 (*s*, Me); 4.55 (*d*, $J = 12.0$, 1 H of PhCH_2); 4.79 (*d*, $J = 12.0$, 1 H of PhCH_2); 6.34 (*s*, OCHN); 7.09–7.67 (*m*, 8 arom. H); 8.20 (*s*, arom. H);

10.04 (*s*, H–C(5) of imidazole). ^{13}C-NMR (CDCl$_3$): 14.26 (Me); 74.32 (CH$_2$); 83.40 (CH); 116.65; 124.74; 128.24; 128.61; 128.81; 128.96; 131.11; 132.28; 133.92; 136.33; 140.24; 148.88; 150.91. MS: 368 (19.2, *M*$^+$). Anal. calc. for $C_{18}H_{16}N_4O_5$ (368.11): C 58.69, H 4.38, N 15.21; found: C 58.61, H 4.29, N 15.18.

*1-[(Benzyloxy)(phenyl)methyl]pyrimidine-2,4(1*H,*3*H*)-dione* (**5h**). Purified by CC (SiO$_2$; AcOEt/hexane 2:1). Yield: 1.07 g (64%). Colorless crystals. TLC (EtOH): *R*$_f$ 0.59. M.p. 170°. IR (KBr): 3200*s*, 3000–3100*m*, 2900*m*, 1660*s*. ^{1}H-NMR (CDCl$_3$): 4.94 (*s*, PhC*H*$_2$); 5.74 (*d*, *J* = 7.8, H–C(5) of uracil); 7.20 (*s*, OCHN); 7.32 (*d*, *J* = 7.8, H–C(6) of uracil); 7.40–7.71 (*m*, 10 arom. H); 9.50 (*s*, NH, exchangeable with D$_2$O). ^{13}C-NMR (CDCl$_3$): 72.23 (CH$_2$); 85.11 (CH); 101.30 (C(5)); 126.52; 127.27; 127.58; 127.93; 128.33; 128.51; 137.12; 142.28; 142.48; 142.38; 163.75. MS: 308 (14.8, *M*$^+$). Anal. calc. for $C_{18}H_{16}N_2O_3$ (308.33): C 70.12, H 5.23, N 9.09; found: C 70.14, H 5.18, N 9.15.

*1-[(Benzyloxy)(phenyl)methyl]-5-methylpyrimidine-2,4(1*H,*3*H*)-dione* (**5i**). Purified by CC (SiO$_2$; AcOEt/hexane 1:1). Yield: 1.30 g (40%). Colorless crystals. TLC (EtOH): *R*$_f$ 0.62. M.p. 178°. IR (KBr): 3200*s*, 3000–3100*m*, 2900*m*, 1640*s*. ^{1}H-NMR (CDCl$_3$): 2.11 (*s*, Me); 5.01 (*s*, PhCH$_2$O); 6.99 (*s*, OCHN); 7.40–7.71 (*m*, 10 arom. H); 7.82 (*s*, H–C(6) of thymine); 9.23 (*s*, NH, exchangeable with D$_2$O). ^{13}C-NMR (CDCl$_3$): 11.80 (Me); 72.21 (CH$_2$); 84.12 (CH); 111.24 (C(5)); 120.63; 127.32; 127.60; 127.92; 128.35; 128.56; 137.24; 142.26; 142.51; 142.35; 163.11. MS: 322 (16.5, *M*$^+$). Anal. calc. for $C_{19}H_{18}N_2O_3$ (322.36): C 70.79, H 5.63, N 8.69; found: C 70.85, H 5.65, N 8.60.

*1-[(Benzyloxy)(phenyl)methyl]-1*H*-benzimidazole* (**5j**). Purified by CC (SiO$_2$; AcOEt/hexane 1:5). Yield: 1.35 g (43%). Yellow oil. TLC (EtOH): *R*$_f$ 0.5. IR (film): 3000–3100*m*, 2900*m*, 1600*s*. ^{1}H-NMR (CDCl$_3$): 5.45 (*s*, PhC*H*$_2$); 6.74 (*s*, OCHN); 7.01–7.92 (*m*, 14 arom. H); 8.33 (*s*, H–C(2) of benzimidazole). ^{13}C-NMR (CDCl$_3$): 71.22 (CH$_2$); 84.23 (CH); 115.11; 120.88; 123.69; 124.34; 125.55; 128.23; 128.75; 128.84; 129.12; 130.58; 131.36; 133.59; 133.68; 142.64; 148.69. MS: 314 (23.4, *M*$^+$). Anal. calc. for $C_{21}H_{17}N_3O_3$ (314.38): C 80.23, H 5.77, N 8.91; found: C 80.22, H 5.63, N 8.88.

*1-[(Benzyloxy)(phenyl)methyl]-1*H*-imidazole* (**5k**). Purified by CC (SiO$_2$; AcOEt/hexane 2:1). Yield: 1.27 g (47%). Pale-yellow oil. TLC (EtOH): *R*$_f$ 0.25. IR (film): 3000–3100*m*, 2900*m*, 1600*s*. ^{1}H-NMR (CDCl$_3$): 5.15 (*s*, PhC*H*$_2$); 6.93 (*s*, OCHN); 7.12–7.36 (*m*, 12 arom H, 2 H of imidazole); 7.69 (*s*, H–C(2) of imidazole). ^{13}C-NMR (CDCl$_3$): 70.35 (CH$_2$); 84.45 (CH); 112.36; 123.45; 125.36; 127.66; 128.18; 128.34; 128.46; 128.58; 137.35; 137.53; 139.15. MS: 264 (25.1, *M*$^+$). Anal. calc. for $C_{17}H_{16}N_2O$ (264.32): C 77.25, H 6.10, N 10.60; found: C 77.31, H 6.12, N 10.53.

*4-[1*H*-Benzimidazol-1-yl(benzyloxy)methyl]phenyl 4-Methylbenzenesulfonate* (**5l**). Purified by CC (SiO$_2$; AcOEt/hexane 1:2). Yield: 1.65 g (34%). Yellow oil. TLC (EtOH): *R*$_f$ 0.31. IR (film): 3000–3100*m*, 2900*m*, 1600*s*. ^{1}H-NMR (CDCl$_3$): 2.43 (*s*, Me); 4.50 (*d*, *J* = 11.7, 1 H of PhC*H*$_2$); 4.85 (*d*, *J* = 11.7, 1 H of PhC*H*$_2$); 6.60 (*s*, OCHN); 6.96 (*d*, *J* = 8.6, 2 arom. H); 7.21–7.63 (*m*, 13 arom. H); 7.83 (*d*, *J* = 8.6, 2 arom. H); 8.21 (*s*, H–C(2) of benzimidazole). ^{13}C-NMR (CDCl$_3$): 24.36 (Me); 68.32 (CH$_2$); 87.94 (CH); 115.38; 115.79; 123.45; 123.65; 127.34; 127.87; 128.22; 128.55; 128.97; 130.42; 130.65; 134.56; 136.15; 138.32; 138.56; 142.58; 143.91; 146.12; 150.23. MS: 484 (12.4, *M*$^+$). Anal. calc. for $C_{28}H_{24}N_2O_4S$ (484.57): C 69.40, H 4.99, N 5.78, S 6.62; found: C 69.48, H 5.05, N 5.83, S 6.60.

*4-[(Benzyloxy)(1*H*-imidazol-1-yl)methyl]phenyl 4-Methylbenzenesulfonate* (**5m**). Purified by CC (SiO$_2$; AcOEt/hexane 1:3). Yield: 1.82 g (42%). Yellow oil. TLC (EtOH): *R*$_f$ 0.55. IR (film): 3000–3100*m*, 2900*m*, 1600*s*. ^{1}H-NMR (CDCl$_3$): 2.40 (*s*, Me); 4.49 (*d*, *J* = 11.8, 1 H of PhC*H*$_2$); 4.85 (*d*, *J* = 11.8, 1 H of PhC*H*$_2$); 5.02 (*s*, OCHN); 6.74–7.53 (*m*, 15 arom. H, 2 H of imidazole); 7.66 (*s*, H–C(2) of imidazole). ^{13}C-NMR (CDCl$_3$): 24.43 (Me); 67.05 (CH$_2$); 85.34 (CH); 115.75; 120.01; 127.43; 128.02; 128.23; 128.76; 128.85; 128.95; 129.23; 130.12; 136.06; 137.21; 142.79;148.33; 150.23. MS: 434 (13.5, *M*$^+$). Anal. calc. for $C_{24}H_{22}N_2O_4S$ (434.51): C 66.34, H 5.10, N 6.45, S 7.36; found: C 66.42, H 5.05, N 6.40, S 7.43.

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