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New Emivirine (MKC-442) Analogues Containing a Tetrahydronaphthalene at C-6 and their Anti-HIV Activity

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Summary. An 5-ethyl-2-thiouracil derivative with a 6-(tetrahydronaphthalen-1-yl)methyl substituent was synthesized by condensation of thiourea with an adequate β-ketoester which in turn was synthesized in a single step from (tetrahydronaphthalen-1-yl)acetonitrile. The latter starting material was also used to synthesize an analogously substituted tetrahydronaphthalen-1-yl substituted uracil with a locked conformation. Only the non-nucleoside derivatives prepared from the desulfurized substituted 2-thiouracil showed moderate activity against HIV whereas a corresponding non-nucleoside derivative was devoid of activity against HIV.

Keywords. Bioorganic chemistry; Drug research; HIV; Non-nucleoside reverse transcriptase inhibitors; Emivirine analogues.

Introduction

The discovery of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (*HEPT,* Fig. 1) in 1989 as a novel type of reverse transcriptase (RT) inhibitors [1] initiated extensive structure-activity relationship (SAR) studies of *HEPT*, which resulted in the development of Emivirine (6-benzyl-1-(ethoxymethyl-5-isopropyl)uracil, formerly known as MKC-442, Fig. 1) in 1993 [2–5].

Emivirine was selected for clinical trials [6] after preclinical trials had shown low toxicity of Emivirine and synergistic action with the anti-HIV drug *AZT*. The drawback of Emivirine is however the loss of activity against various resistant HIV-1 strains, especially the loss of activity with a factor of >3000 when tested against the mutated virus (Y181C). Consequently, many investigations have tried to optimize Emivirine by introducing various modifications. The more successful analogues are modified at the N-1 position or at the C-6 position of the uracil ring. The analogous with 3,5-dimethyl substituents on the phenyl ring such as GCA-186 (Fig. 1) and the introduction of the flexible thiocyclohexyl group (TNK-6123, Fig. 1) at the C-6 position has reduced the loss of activity against the mutated virus (Y181C) considerable [7]. The N-1 substituent has been optimized by the introduction of unsaturated moieties (BED-60 and AMB-A10, Fig. 1) [8]. Several of the recently described second generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) are much less affected towards RT mutations than Emivirine and this could be one of the reasons for the surprising withdrawal of Emivirine from late phase III clinical trials in January 2002. The official argument for the withdrawal was the higher potency of abacavir in a combination study [9]. However, Emivirine also activates the liver enzyme cytochrome P450, which leads to drug interactions between Emivirine and protease inhibitors [6].

Recently, various investigations have discussed the possibility of either to lock the NNRTI in the

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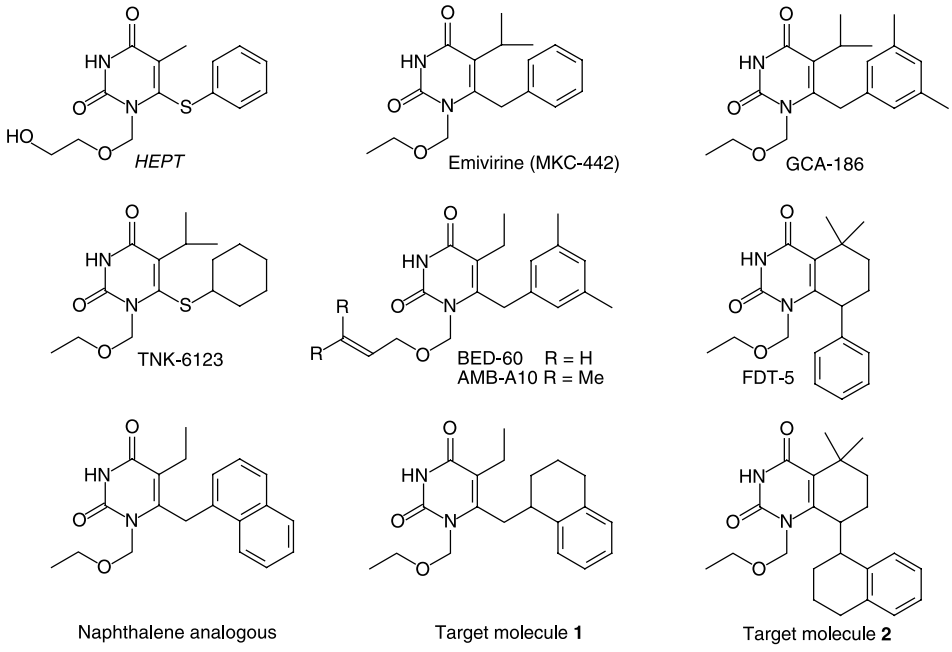


Fig. 1. Chemical structure of *HEPT,* Emivirine (MKC-442), GCA-186, TNK-6123, BED-60, AMB-A10, FDT-5, the naphthalene analogous of Emivirine, and the structure of the target molecules **1** and **2**

bioactive conformation or to have highly flexible NNRTIs, which can adopt various bioactive conformations without encountering significant energy barriers. The reduction of inactive conformations, which may have unwanted side effects and the lower entropic penalty in the binding process to RT, is advantageous to locked NNRTIs. On the other hand, a flexible NNRTI has an increased potential to rearrange and adapt to the different environments in the hydrophobic pockets of different mutants of HIV-1. However, the synthesis of different conformationally restricted analogues of Emivirine was generally not a success, as the compounds only showed moderate anti-HIV-1 activity [10, 11].

1-(Ethoxymethyl)-5-ethyl-6-(1-naphthylmethyl)-1*H*-pyrimidine-2,4-dione has previously been synthesized and shown to be by a factor of 10 less active than Emivirine towards HIV-1 wild-type (Fig. 1) [12, 13]. Because of the slightly lower activity of the naphthalene analogous we speculated that the naphthalene moiety is missing some flexibility to adapt in an ideal way in the hydrophobic pocket. A combination of the naphthalene analogous and TNK-6123 was hypothesized as an interesting new analogous of Emivirine (target molecule **1**, Fig. 1). In addition to the flexible naphthalene analogous we were also interested in the corresponding annelated analogous (target molecule **2**, Fig. 1), as previous results with annelated analogues of Emivirine had shown that additional hydrophobic contacts at the C-6 substituent were highly favourable for the anti-HIV-1 activity.

Results and Discussion

The synthesis strategies for obtaining the target molecule **1** and **2** are outlined in Fig. 2. Both target molecules could be obtained from key intermediate (1,2,3,4-tetrahydronaphthalen-1-yl)acetonitrile (**5**), which could be obtained from the commercially available 1-tetralone (**3**). The synthesis of target molecule **1** was considered to be straightforward by using the β-ketoester procedure, developed in our group, to synthesize Emivirine [14]. The synthesis of target molecule **2** involves two key synthetic steps, the first being the α-alkylation of (1,2,3,4-tetrahydronaphthalen-1-yl)acetonitrile (**5**), and the second the ring closing step to the annelated uracil derivative.

The synthesis of (1,2,3,4-tetrahydronaphthalen-1-yl)acetonitrile (**5**) was achieved in two steps from 1-tetralone (Scheme 1). The *Horner-Emmons* reaction of 1-tetralone (**3**) and the sodium salt of diethyl cyanomethylphosphonate gave (3,4-dihydro-2*H*-naphthalen-1-ylidene)acetonitrile (**4**) in 82% yield and the following hydrogenation of **4**, first at a pressure of 10 bar and then at 70 bar, gave (1,2,3,4-tetrahydronaphthalen-1-yl)acetonitrile (**5**) in 99% yield

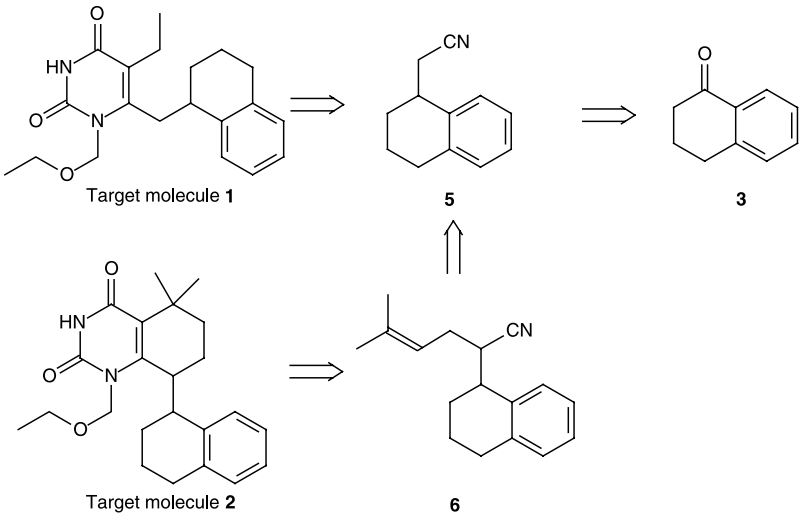
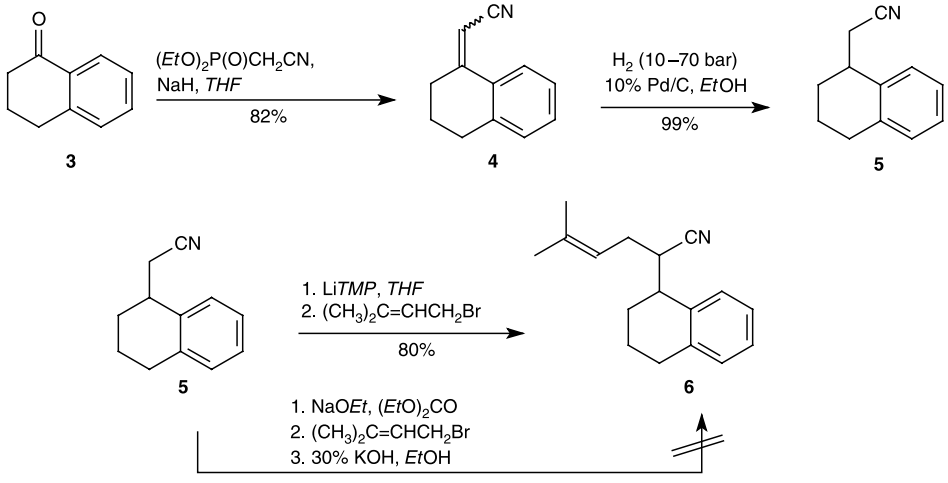


Fig. 2. Retrosynthesis of target compounds **1** and **2** both obtained from key intermediate **5**

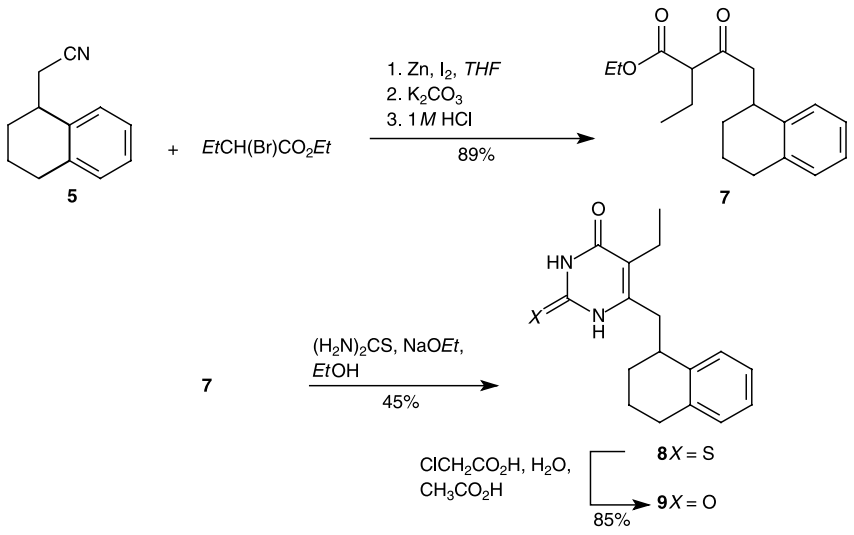


Scheme 1

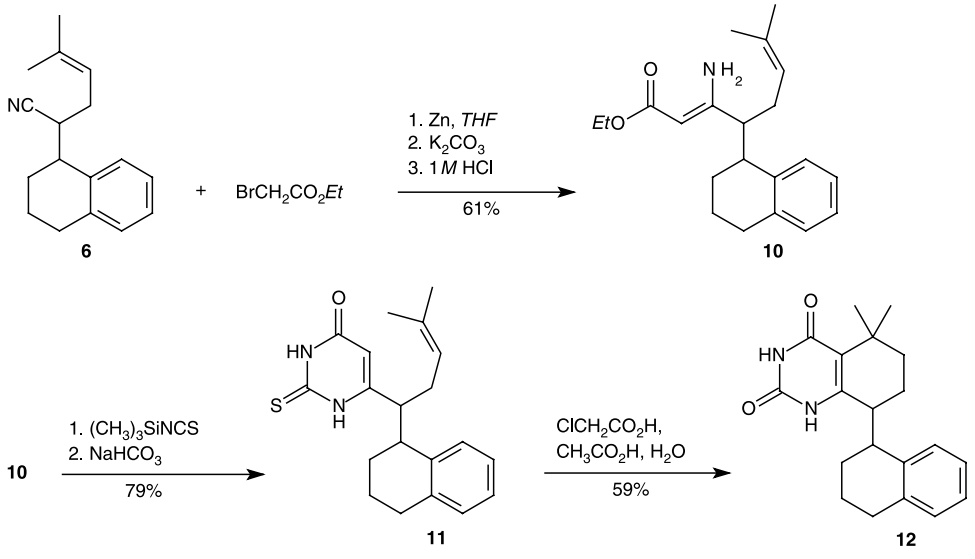
[15]. To ensure mono-alkylation of compound **5**, the alkylation was initially attempted by introducing an ethoxycarbonyl group prior to the alkylation with 4-bromo-2-methylbut-2-ene (Scheme 1). Previous results with benzylic cyanides had demonstrated the usefulness of this method [10, 11]. However, the full recovery of compound **5** showed that the α-protons of **5** were not sufficient acidic to be deprotonated by ethoxide in diethyl carbonate. Instead the α-alkylation of **5** to **6** was accomplished selectively in 80% yield from the deprotonation of **5** with lithium 2,2,6,6-tetramethylpiperidide (Li*TMP*) [16] and subsequent reaction with 4-bromo-2-methylbut-2-ene (Scheme 1).

The *Blaise* reaction of **5** with activated zinc and ethyl 2-bromobutanoate provided the β-keto ester **7** in 89% yield. The ring closure with thiourea and ethoxide provided the thiouracil **8** in 45% yield, and the following desulfurization in aqueous chloroacetic acid/acetic acid gave the corresponding uracil derivative **9** in 85% yield (Scheme 2).

In the *Blaise* reaction of **6**, the enamine **10** proved stable in 1 *M* HCl and was isolated in 61% yield. The enamine was ring closed with trimethylsilyl isothiocyanate to the thiouracil derivative **11** in 79% yield [11]. The subsequent desulfurization with aqueous chloroacetic acid/acetic acid also favoured a ring closure from C-5 of the uracil ring to the double bond, which gave **12** in 59% yield. The diastereomeric ratio of **12** was determined by NMR to $\sim$1:1 (Scheme 3).



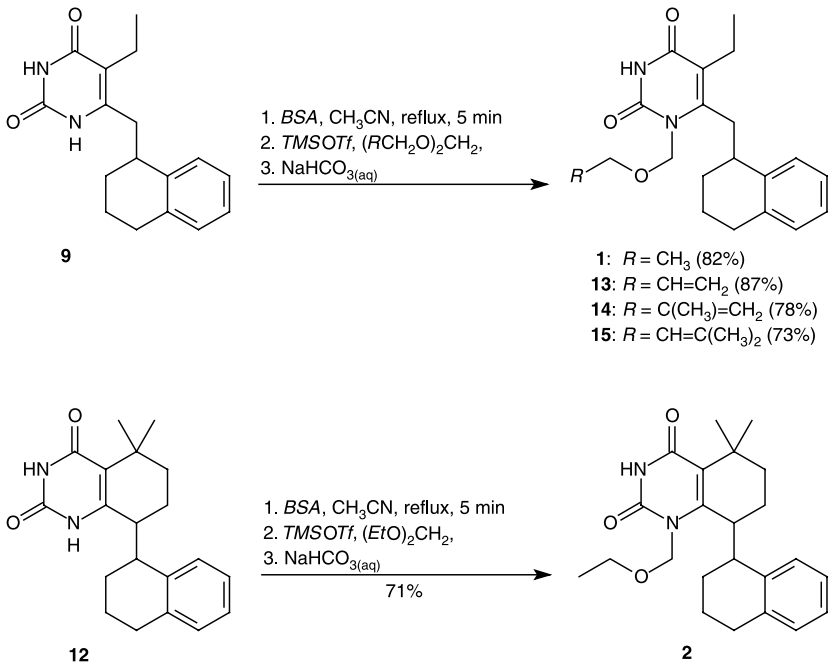
Scheme 2



Scheme 3

The uracil derivatives **9** and **12** were silylated with *N*,*O*-bis(trimethylsilyl)acetamide (*BSA*) and were selectively at low temperature alkylated on N-1 by the use of the *Lewis* acid trimethylsilyl triflate (*TMSOTf*) and formaldehyde diethyl acetal [8, 17] (Scheme 4). The target molecules **1** and **2** were obtained in 82% and 71% yield. Compound **9** was alkylated at N-1 with three additional formaldehyde acetals [8, 17], which gave the analogues **13**–**15** in 87, 78, and 73%.

The five synthesized naphthalene analogues of Emivirine were evaluated for activity against wild-type HIV-1 and against the Y181C mutant (Table 1). The annelated compound **2** did not show any activity. The flexible analogues **1** and **13**–**15** were found only to be active against wild-type HIV-1, but showed reduced activity compared to Emivirine with a factor of approximately 100. All five compounds showed a higher cytotoxicity compared to Emivirine. Furthermore, the introduction of different unsaturated N-1 substituents had no effect on the anti-HIV-1 activity, but increased the cytotoxicity by a factor of approximately 3.



Scheme 4

Table 1. Inhibitory and cytotoxic concentrations against HIV-1 in MT-4 cells

Compd	HIV-1 III (wild-type)			N119 (Y181C)
	$EC_{50}/\mu M$[a]	$CC_{50}/\mu M$[b]	SI[c]	$EC_{50}/\mu M$[a]
1	4	96	2	>100
13	4	32	8	>100
14	3	40	13	>100
15	4	30	8	>100
2	>100	33	–	>100
MKC-442	0.02	>100	>5000	44

[a] Inhibitory concentration of compounds achieving 50% inhibition of HIV multiplication in MT-4 infected cells
[b] Cytotoxic concentration of compound required to reduce the viability of normal uninfected MT-4 cells by 50%
[c] Selectivity index: ratio CC_{50}/EC_{50}. The symbol (>) indicates that CC_{50} was not reached at the highest concentration test

Experimental

NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C with *TMS* as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). MALDI mass spectra were recorded on an IonSpec Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. Melting points were determined on a *Büchi* melting point apparatus. Elemental analyses were performed at *H.C. Ørsted* Institute, University of Copenhagen; the found values agreed favourably with the calculated ones. The progress of reactions was monitored by TLC (DC-alufolio 60 F_{254}) from Merck. For column chromatography Merck silica gel (0.040–0.063 mm) was used.

Solvents for chromatography were bought as HPLC grade or distilled prior to use. Acetonitrile was dried and stored over 3 Å sieves. *THF* was distilled from Na/benzophenone. Petroleum ether: bp 60–80°C. Zn was activated by washing Zn dust, <10 micron, sequentially with $3 \times 50\,cm^3$ 4 *M* HCl, H_2O, *Et*OH, and dry diethyl ether.

(3,4-Dihydro-2H-naphthalene-1-ylidene)acetonitrile (**4**)
NaH, 60% in mineral oil (4.5 g, 113 mmol) was washed with cyclohexane prior to its suspension in dry 200 cm^3 *THF*. Diethylcyanomethyl phosphonate (20 g, 113 mmol) in 50 cm^3 dry *THF* was added dropwise over 10 min. The clear solution was cooled to 0°C, and 15.2 g, 1-tetralone (104 mmol) were added dropwise over 10 min. The reaction mixture became very viscous and after stirring for additional 10 min the reaction mixture was left standing at room temperature overnight. H_2O (50 cm^3) was added, and the phases were separated. The H_2O phase was extracted with 100 cm^3 diethyl ether. The combined organic phases were washed with 50 cm^3 brine, dried ($MgSO_4$), and evaporated under reduced pressure. Compound **4** was purified by vacuum distillation (bp 98–100°C/0.02 mbar; Ref. [15] 115–117°C/0.03 torr). Yield 14.4 g (82%).

rac-(1,2,3,4-Tetrahydronaphthalen-1-yl)acetonitrile (**5**)
Compound **4** (7.8 g, 46 mmol) and 0.8 g 10% Pd/C in 75 cm^3 absolute *Et*OH was hydrogenated under pressure (10 bar to 70 bar) for 30 min. Pd/C was removed by filtration through a silica gel pad, and evaporation under reduced pressure gave

5 as a pale green oil. Yield 7.81 g (99%); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.77$–1.93, 2.00–2.10 (4H, m, $2 \times CH_2$), 2.53–2.85 (4H, m, $2 \times CH_2$), 3.17–3.21 (1H, m, CH) 7.08–7.22 (4H, m, Ar) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 19.3$, 24.6, 28.0, 29.2 ($4 \times CH_2$), 34.6 (CH), 118.8 (CN), 126.0, 126.8, 127.9, 129.5, 136.5, 137.0 ($6 \times C_{arom}$) ppm; MS (EI): $m/z = 169$ (M^+).

rac-5-Methyl-2-(1,2,3,4-tetrahydronaphthalen-1-yl)hex-4-ene (**6**, $C_{17}H_{21}N$)

*t-Bu*Li in hexanes (21 mmol) was added dropwise to a solution of 3.9 cm^3 2,2,6,6-tetramethylpiperidine (23 mmol) in 40 cm^3 dry *THF* at −15°C in an atmosphere of N_2. The mixture was stirred 30 min at −5°C and then cooled to −78°C. Compound **5** (3.0 g, 17.5 mmol) in 10 cm^3 dry *THF* was added dropwise at −78°C and the resulting mixture was stirred at −5°C for 20 min, then recooled to −78°C, and 4.35 g 4-bromo-2-methylbut-2-ene (29 mmol) was added. The reaction mixture was warmed to room temperature in 6 h. The reaction was quenched by addition of 50 cm^3 H_2O, and the mixture was stirred vigorously for 10 min. The phases were separated and the H_2O phase was extracted with 2×100 cm^3 diethyl ether. The combined organic phases were washed with 50 cm^3 brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (CH_2Cl_2 in petroleum ether (60–80°C), 1:2, *v*:*v*) to give 3.35 g **6** (80%) as a clear colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.56$, 1.66, 1.72, 1.75 (6H, $4 \times$ s, C$(CH_3)_2$), 1.77–2.14, 2.22–2.52, 2.71–2.89 (8H, m, $4 \times CH_2$), 2.97–3.03 (1H, m, ArC*H*) 2.97–3.03 (0.5H, m, CHCN), 3.21 (0.5H, q, $J = 5.9$ Hz, CHCN), 5.17–5.24 (1H, m, =CH), 7.11–7.25 (4H, m, Ar) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 17.9$, 18.0, 20.5, 20.6, 25.5, 25.8, 25.8, 25.9, 26.7, 29.0, 29.3, 29.4, 37.5, 38.4, 38.7, 39.0 ($2 \times CH$, $4 \times CH_2$, $2 \times CH_3$), 119.4, 119.5, 121.2, 122.0, 125.8, 125.9, 126.6, 126.7, 127.8, 127.9, 129.5, 129.6, 135.5, 135.7, 135.9, 136.2, 137.9, 138.1 ($6 \times C_{arom}$, *C*H=*C*$(CH_3)_2$, CN) ppm; MS (MALDI, peak matching): $m/z = 262.1569$ ($M + Na^+$, calcd.: 262.1566).

rac-Ethyl 2-ethyl-3-oxo-4-(1,2,3,4-tetrahydronaphthalen-1-yl)butanoate (**7**)

Activated Zn (5.4 g, 83 mmol) and a crystal of iodine were stirred in 50 cm^3 dry *THF*. The mixture was heated to reflux and 1.42 g **5** (8.3 mmol) were added. Ethyl 2-bromobutanoate (3.1 cm^3, 21 mmol) was added during 45 min (effervescence observed) in small portions. The green/brown reaction mixture was refluxed for additional 4 h and then after cooling quenched with 75 cm^3 sat. aq. K_2CO_3. The mixture was stirred vigorously for 2 days, which resulted in a two-phase system. The upper organic layer was decanted from the lower viscous aqueous phase, which was washed and decanted with additional *THF* (4×50 cm^3). The combined organic phases were stirred with 50 cm^3 1 *M* HCl for 2 h. The organic solvent was removed by evaporated under reduced pressure. The remaining H_2O phase was extracted with 3×50 cm^3 CH_2Cl_2. The combined organic phases were washed with 2×30 cm^3 sat. aq. $NaHCO_3$ and 30 cm^3 brine and then dried ($MgSO_4$) followed by evaporation under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate in petroleum ether (60–80°C), 10–30%, *v*:*v*) to give 2.13 g **7** (89%) as a clear colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.88$–0.97 (3H, m, $CHCH_2CH_3$), 1.25, 1.26 (3H, $2 \times$ t, $J = 7.2$ Hz, OCH_2CH_3), 1.57–1.65, 1.72–1.80, 1.83–1.94 (6H, $3 \times$ m, $3 \times CH_2$), 2.45–2.53, 2.73–2.98 (4H, $2 \times$ m, $2 \times CH_2$), 3.34, 3.35 (1H, $2 \times$ t, $J = 7.2$ Hz, CHCO), 3.45–3.50 (1H, m, ArC*H*), 4.13–4.22 (2H, m, OCH_2), 7.04–7.11 (4H, m, Ar) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 11.9$, 12.0, 19.5, 19.6, 21.4, 21.6, 27.9, 28.2, 29.5, 29.5, 32.6, 32.7, 43.7, 49.5, 49.9, 60.7, 60.9, 61.1, 61.3 ($2 \times CH$, $6 \times CH_2$, $2 \times CH_3$), 125.8, 125.8, 128.2, 128.2, 129.2, 129.2, 137.1, 137.2, 139.6, 139.6, 169.6, 204.1, 204.4 ($6 \times$ Ar, $2 \times$ CO) ppm; MS (MALDI, peak matching): $m/z = 311.1616$ ($M + Na^+$, calcd.: 311.1618).

rac-5-Ethyl-6-(1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one (**8**)

Thiourea (6.65 g, 87 mmol) and 2.10 g **7** (7.28 mmol) were added to an ethanolic solution of sodium ethoxide prepared from 2.0 g Na (87.4 mmol) and 120 cm^3 absolute ethanol. The reaction mixture was refluxed for 10 h and then evaporated under reduced pressure. The yellow solid obtained was dissolved in 40 cm^3 H_2O and neutralised with 4 *M* HCl. The H_2O phase was extracted with 3×50 cm^3 CH_2Cl_2. The combined organic phases were washed with 30 cm^3 brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate in petroleum ether (60–80°C), 10–50%, *v*:*v*) and then recrystallised from ethyl acetate in petroleum ether to give 0.98 g **8** (45%) as a white solid, mp 186–189°C (ethyl acetate in petroleum ether (60–80°C)). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.88$ (3H, t, $J = 7.1$ Hz, CH_3), 1.50–1.82 (4H, m, $2 \times CH_2$), 2.13–2.27 (2H, m, CH_2), 2.57–2.84 (4H, m, $2 \times CH_2$), 3.15–3.19 (1H, m, CH), 7.04–7.12 (3H, m, Ar), 7.31–7.34 (1H, m, Ar), 12.22, 12.36 (2H, $2 \times$ br s, $2 \times$ NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.0$, 17.7, 18.8, 26.2, 28.9, 35.7, 35.9 (CH_3, $5 \times CH_2$, CH), 117.5, 125.3, 125.9, 128.6, 128.9, 136.5, 138.4, 149.3, 161.2 ($8 \times$ Ar, CO), 174.1 (CS) ppm; MS (MALDI, peak matching): $m/z = 323.1192$ ($M + Na^+$, calcd.: 323.1189).

rac-5-Ethyl-6-(1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-1H-pyrimidine-2,4-dione (**9**, $C_{17}H_{20}N_2O_2$)

Compound **8** (0.50 g, 1.66 mmol) was refluxed in an aq. solution of chloroacetic acid (20%, 100 cm^3) and acetic acid (80 cm^3) for 2 days. The reaction mixture was cooled to 0°C, where a white precipitate formed. The precipitate was filtered off and washed with 4×20 cm^3 H_2O to give 400 mg **9** (85%) as a white solid, mp >250°C (H_2O/chloroacetic acid/acetic acid). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.87$ (3H, t, $J = 7.3$ Hz, CH_3), 1.54–1.88 (4H, m, $2 \times CH_2$), 2.14 (1H, m, CH_2CHHCH_2), 2.19 (1H, m, CH_2CHHCH_2), 2.55 (1H, dd, $J = 10.1$ and 13.4 Hz, C-6C*H*H), 2.62–2.80 (3H, m, CH, CH_2), 3.17 (1H, dd, $J = 4.9$ and 10.1 Hz, C-6CH*H*), 7.04–7.12 (3H, m, Ar), 7.28–7.31 (1H, m, Ar), 10.70, 10.96 (2H, $2 \times$ br s, $2 \times$ NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.6$, 17.6, 18.8, 26.1, 28.9, 35.4, 36.3 (CH_3, $5 \times CH_2$ and CH),

111.7, 125.4, 125.9, 128.6, 128.8, 136.5, 138.7, 148.7, 151.0, 164.3 (8 × Ar, 2 × CO) ppm; MS (MALDI, peak matching): $m/z = 307.1420$ ($M + Na^+$, calcd.: 307.1417).

rac-Ethyl 3-Amino-4-(1,2,3,4-tetrahydronaphthalen-1-yl)but-2-enoate (**10**, $C_{21}H_{29}NO_2$)

Activated Zn (8.0 g, 122 mmol) was suspended in 100 cm^3 dry *THF*. The solution was heated to reflux where 3.20 g **6** (13.0 mmol) were added. Ethyl 2-bromoacetate (3.6 cm^3, 32 mmol) was added in small portions (effervescence observed) over 45 min. The green/brown reaction mixture was refluxed for additional 1.5 h and then quenched after cooling with 75 cm^3 sat. aq. K_2CO_3. The solution was stirred vigorously overnight, which resulted in a two-phase system. The upper organic layer was decanted from the lower viscous aqueous phase, which was washed and decanted with additional *THF* (3 × 100 cm^3). The combined organic phases were washed with 50 cm^3 brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (CH_2Cl_2 in petroleum ether (60–80°C), 2:1, *v*:*v*) to give 2.60 g **10** (61%) as a clear colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.26$, 1.27 (3H, 2 × t, $J = 7.2$ Hz, CH_2CH_3), 1.50, 1.52, 1.63, 1.66 (6H, 4 × s, $C(CH_3)_2$), 1.65–1.95 (4H, m, 2 × CH_2), 2.12–2.55 (3H, m, ArCH, CH_2), 2.70–2.81 (2H, m, CH_2), 2.89–2.95, 3.04–3.10 (1H, m, ArCHC*H*), 4.10, 4.11 (2H, 2 × q, $J = 7.2$ Hz, CH_2CH_3), 4.58, 4.60 (1H, 2 × s, =CHCO), 5.03–5.09 (1H, m, CH_2CH=), 7.04–7.23 (4H, m, Ar) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 14.5$, 17.8, 17.8, 19.4, 20.6, 24.8, 25.3, 25.7, 26.7, 28.8, 29.6, 30.1, 40.5, 41.7, 50.5, 51.4 (2 × CH, 5 × CH_2, 3 × CH_3), 83.9, 84.3 (=*C*HCO), 121.7, 121.7, 125.1, 125.5, 126.0, 126.2, 128.0, 129.2, 129.5, 129.5, 133.1, 133.5, 137.8, 137.9, 138.1, 138.7 (6 × Ar and *C*H=*C*$(CH_3)_2$), 165.4, 165.6, 170.3 and 170.5 (=CNH_2 and CO) ppm; MS (MALDI, peak matching): $m/z = 350.2095$ ($M + Na^+$, calcd.: 350.2091).

rac-6-[4-Methyl-1-(1,2,3,4-tetrahydronaphthalen-1-yl)pent-3-enyl]-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one (**11**)

Compound **10** (2.01 g, 6.15 mmol) and 13.6 cm^3 trimethylsilyl isothiocyanate (92 mmol) were refluxed for 3.5 h. The cooled reaction mixture was quenched by the addition of 60 cm^3 sat. aq. $NaHCO_3$ in small portions. The mixture was extracted with 3 × 75 cm^3 CH_2Cl_2. The combined organic phases were washed with 2 × 25 cm^3 sat. aq. $NaHCO_3$, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (3% *Et*OH/CH_2Cl_2, *v*:*v*) to give 1.65 g **11** (79%) as an orange solid, mp 105–110°C. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.52$, 1.55, 1.63, 1.66 (6H, 4 × s, $C(CH_3)_2$), 1.69–1.94, 2.32–2.38 (6H, m, 3 × CH_2), 2.75–2.80 (3H, m, ArCH and CH_2), 3.15–3.17 (1H, m, ArCHC*H*), 4.96–5.01 (1H, m, =CH), 5.78, 5.81 (1H, 2 × s, 5H), 7.08–7.26 (4H, m, Ar), 9.67, 11.00 (2H, 2 × br s, 2 × NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 17.9$, 19.2, 20.4, 24.6, 24.9, 25.7, 28.5, 29.4, 29.7, 39.9, 41.0, 47.9, 48.0 (2 × CH, 4 × CH_2, 2 × CH_3), 104.4, 104.5 (C5), 119.9, 120.3, 125.7, 125.8, 126.5, 127.0, 127.5, 127.7, 129.4, 129.4, 129.9, 134.8, 135.3, 136.6, 136.8, 137.8, 137.9, 158.5, 158.8, 161.6, 161.8 (8 × Ar, *C*H=*C*$(CH_3)_2$, CO), 175.3, 175.6 (CS) ppm; MS (MALDI, peak matching): $m/z = 363.1514$ ($M + Na^+$, calcd.: 363.1502).

rac-5,5-Dimethyl-8-(1,2,3,4-tetrahydronaphthalen-1-yl)-5,6,7,8-tetrahydro-1H-quinazoline-2,4-dione (**12**)

Compound **11** (0.30 g, 0.88 mmol) was refluxed in an aq. solution of chloroacetic acid (20%, 60 cm^3) and acetic acid (60 cm^3) for 3 days. The reaction mixture was evaporated under reduced pressure. The residue was dissolved in 150 cm^3 CH_2Cl_2. The organic phase was washed with 50 cm^3 H_2O, 3 × 25 cm^3 sat. aq. $NaHCO_3$, and 25 cm^3 brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (0–5% *Et*OH/CH_2Cl_2, *v*:*v*) to give 168 mg **12** (59%, ~1:1 mixture of diastereoisomers). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.17$, 1.29, 1.31 (6H, 3 × s, 2 × CH_3), 1.38–1.99, 2.13–2.17 (8H, m, 4 × CH_2), 2.71–2.73 (2H, m, CH_2), 2.98–3.02 (1H, m, CH), 3.36–3.41, 3.46–3.50 (1H, m, CH), 7.02–7.16 (4H, m, Ar), 8.41, 9.28, 9.32, 9.63 (2H, 4 × br s, 2 × NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 19.6$, 21.3, 22.3, 22.6, 24.6, 26.1, 26.8, 27.1, 28.0, 28.3, 29.9, 30.2, 32.2, 32.3, 37.7, 38.5, 39.1, 40.5, 41.3, 42.7 (2 × CH_3, 5 × CH_2, 2 × CH and C), 117.4, 117.4, 125.8, 126.0, 126.6, 126.7, 127.9, 127.9, 129.2, 130.0, 136.7, 137.0, 138.3, 138.9, 150.7, 150.8, 151.1, 151.7, 163.6, 163.8 (8 × Ar and 2 × CO) ppm; MS (MALDI, peak matching): $m/z = 347.1742$ ($M + Na^+$, calcd.: 347.1730).

General Procedure for N-1 Alkylations of ***9*** *and* ***12***

The 5,6-disubstituted uracil derivative (**9**, **12**, 0.2 mmol) was stirred in 5 cm^3 dry CH_3CN under N_2, *N*,*O*-bis-(trimethylsilyl) acetamide (*BSA*, 0.6 mmol) was added, and the suspension was refluxed for 1–5 min until a clear solution was obtained. The solution was cooled to −35°C, and the appropriate alkylating agent (0.6 mmol, in 1 cm^3 CH_3CN) and *TMSOTf* (0.25 mmol, in 1 cm^3 CH_3CN) were added. The reaction mixture was allowed to warm to room temperature in 1 h. The reaction was monitored by TLC (ethyl acetate in petroleum ether (60–80°C, 3:1, *v*:*v*) and quenched (2 h–3 days according to TLC) with 1 cm^3 sat. aq. $NaHCO_3$, and evaporated under reduced pressure. The residue was dissolved in 20 cm^3 CH_2Cl_2 and 5 cm^3 sat. aq. $NaHCO_3$. The aq. phase was extracted with 2 × 15 cm^3 CH_2Cl_2. The combined organic phases were washed with 10 cm^3 brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (gradient of ethyl acetate in petroleum ether (60–80°C), 20–70%, *v*:*v*) to afford **1**, **2**, **13**–**15**.

rac-1-Ethoxymethyl-5-ethyl-6-(1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-1H-pyrimidine-2,4-dione (**1**)

The reaction was finished after 2 h at room temperature, and compound **1** was obtained as a clear colourless oil in 82% yield after purification. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.05$, 1.17 (6H, 2 × t, $J = 7.4$ and 7.0 Hz, 2 × CH_3), 1.81–1.93, 2.26–2.33, 2.80–2.89, 3.12–3.17, 3.53–3.62 (13H, 5 × m, 6 × CH_2, CH), 4.77 (1H, d, $J = 10.6$ Hz, NC*H*H), 5.30 (1H,

d, $J = 10.6$ Hz, NCH*H*), 6.90 (1H, d, $J = 7.2$ Hz, Ar), 7.02–7.16 (3H, m, Ar), 9.61 (1H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.4$, 15.0, 19.1, 19.3, 28.4, 29.1, 34.9, 37.5 ($2 \times CH_3$, $5 \times CH_2$, CH), 64.8 (OCH_2CH_3), 72.6 (NCH_2), 116.7, 125.7, 126.8, 128.3, 129.5, 136.7, 137.3, 150.5, 152.0, 163.3 ($8 \times$ Ar, $2 \times$ CO) ppm; MS (MALDI, peak matching): $m/z = 365.1845$ ($M + Na^+$, calcd.: 365.1836).

rac-1-Allyloxymethyl-5-ethyl-6-(1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-1H-pyrimidine-2,4-dione (**13**)
The reaction was finished after 1 day at room temperature, and compound **13** was obtained as a clear colourless oil in 87% yield after purification. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.05$ (3H, t, $J = 7.4$ Hz, CH_3), 1.78–1.95, 2.26–2.33, 2.77–2.90, 3.12–3.21 (11H, $4 \times$ m, $5 \times CH_2$, CH), 4.07 (2H, d, $J = 5.3$, CH_2), 4.77 (1H, d, $J = 11.0$ Hz, NC*H*H), 5.32 (1H, d, $J = 11.0$ Hz, NCH*H*), 5.16 (1H, td, $J = 1.3$ and 10.5 Hz, $=CH_{cis}H$), 5.26 (1H, td, $J = 1.5$ and 17.5 Hz, $=CHH_{trans}$), 5.78–5.81 (1H, m, C*H*=CH_2), 6.90 (1H, d, $J = 7.7$ Hz, Ar), 7.01–7.16 (3H, m, Ar), 9.79 (1H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.4$, 19.0, 19.2, 28.4, 29.1, 34.9, 37.5 (CH_3, $5 \times CH_2$, CH), 70.4 (OCH_2CH=), 72.4 (NCH_2), 116.8, 117.6, 125.7, 126.8, 128.3, 129.5, 133.6, 136.7, 137.2, 150.4, 152.0, 163.3 ($8 \times$ Ar, CH=CH_2, $2 \times$ CO) ppm; MS (MALDI, peak matching): $m/z = 377.1848$ ($M + Na^+$, calcd.: 377.1836).

rac-5-Ethyl-1-(2-methylallyloxymethyl)-6-(1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-1H-pyrimidine-2,4-dione (**14**)
The reaction was finished after 3 days at room temperature, and compound **14** was obtained as a clear colourless oil in 78% yield after purification. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.05$ (3H, t, $J = 7.4$ Hz, CH_2CH_3), 1.69 (3H, s, $=CCH_3$), 1.82–1.92, 2.26–2.33, 2.81–2.91, 3.15–3.23 (11H, $4 \times$ m, $5 \times CH_2$, CH), 3.98 (2H, s, CH_2), 4.80 (1H, d, $J = 11.4$ Hz, NC*H*H), 4.86 (1H, s, =C*H*H), 4.93 (1H, s, =CH*H*), 5.33 (1H, d, $J = 11.4$ Hz, NCH*H*), 6.91 (1H, d, $J = 7.1$ Hz, Ar), 7.02–7.16 (3H, m, Ar), 9.56 (1H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.4$, 19.0, 19.2, 19.4, 28.4, 29.1, 34.9, 37.5 ($2 \times CH_3$, $5 \times CH_2$, CH), 72.6, 73.5 (NCH_2, OCH_2C=), 112.5, 116.8, 125.7, 126.8, 128.3, 129.6, 136.7, 137.3, 141.3, 150.4, 151.9, 163.2 ($8 \times$ Ar, C=CH_2, $2 \times$ CO) ppm; MS (MALDI, peak matching): $m/z = 391.2007$ ($M + Na^+$, calcd.: 391.1992).

rac-5-Ethyl-1-(3-methyl-but-2-enyloxymethyl)-6-(1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-1H-pyrimidine-2,4-dione (**15**)
The reaction was finished after 3 h at room temperature, and compound **15** was obtained as a clear colourless oil in 73% yield after purification. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.04$ (3H, t, $J = 7.4$ Hz, CH_2CH_3), 1.63, 1.71 (6H, $2 \times$ s, $=C(CH_3)_2$), 1.80–1.95, 2.25–2.32, 2.80–2.90, 3.11–3.20 (11H, $4 \times$ m, $5 \times CH_2$, CH), 4.04 (2H, d, $J = 6.8$ Hz, CH_2), 4.80 (1H, d, $J = 10.8$ Hz, NC*H*H), 5.25 (1H, t, $J = 6.8$ Hz, =CH), 5.31 (1H, d, $J = 10.8$ Hz, NCH*H*), 6.89 (1H, d, $J = 7.2$ Hz, Ar), 7.01–7.15 (3H, m, Ar), 9.59 (1H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.4$, 18.0, 19.0, 19.2, 25.8, 28.4, 29.1, 34.9, 37.5 ($3 \times CH_3$, $5 \times CH_2$, CH), 65.9 (OCH_2CH=), 72.4 (NCH_2), 116.7, 120.0, 125.7, 126.7, 128.3, 129.5, 136.6, 137.3, 138.1, 150.5, 151.9, 163.2 ($8 \times$ Ar, CH=C, $2 \times$ CO) ppm; MS (MALDI, peak matching): $m/z = 405.2160$ ($M + Na^+$, calcd.: 405.2149).

rac-1-Ethoxymethyl-5,5-dimethyl-8-(1,2,3,4-tetrahydronaphthalen-1-yl)-5,6,7,8-tetrahydro-1H-quinazoline-2,4-dione (**2**)
The reaction was finished after 2 h at room temperature, and compound **2** was obtained as a clear colourless oil in 71% yield after purification. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.03$, 1.08 (3H, $2 \times$ t, $J = 7.1$ Hz, CH_2CH_3), 1.33, 1.37, 1.38, 1.56 (6H, $4 \times$ s, $2 \times CH_3$), 1.53–2.06 (8H, m, $4 \times CH_2$), 2.70–2.74, 2.83–2.89 (2H, m, CH_2), 2.99–3.11, 3.52–3.55 (2H, m, $2 \times$ CH), 3.25–3.43 (2H, m, CH_2CH_3), 4.12, 5.38 (2H, $2 \times$ d, $J = 11.2$ and 10.3 Hz, NCH_2), 6.77, 7.25 (1H, $2 \times$ d, $J = 7.7$ Hz, Ar), 6.93–6.99 7.04–7.20 (3H, m, Ar), 9.28, 9.42 (1H, $2 \times$ br s, NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 14.8$, 15.0, 18.9, 21.8, 22.9, 25.7, 27.2, 27.6, 28.3, 28.5, 28.5, 28.9, 29.5, 30.1, 32.9, 33.6, 35.2, 35.4, 37.3, 40.3, 40.8, 42.6, 64.1, 64.5, 71.7, 72.5 ($3 \times CH_3$, $7 \times CH_2$, $2 \times$ CH, C), 118.6, 119.2, 125.3, 126.3, 126.3, 126.4, 127.0, 128.8, 129.3, 129.3, 136.6, 137.1, 137.4, 139.4, 151.3, 151.5, 152.2, 153.7, 162.5, 162.6 ($8 \times$ Ar, $2 \times$ CO) ppm; MS (MALDI, peak matching): $m/z = 405.2150$ ($M + Na^+$, calcd.: 405.2149).

Viruses and Cells
The inhibitory activity against HIV-1 infection was evaluated using MT-4 cells [18] as target cells and the HIV-1 strain HTLV-IIIB [19] and the NNRTI resistant strain N119 [20] as infectious virus. The virus was propagated in H9 [18] cells at 37°C, 5% CO_2 using RPMI 1640 with 10% heat-inactivated fetal calf serum (FCS) and antibiotics (growth medium). Culture supernatant was filtered (0.45 nm), aliquoted, and stored at −80°C until use. Both HIV-1 strains were obtained from the NIH AIDS Research and Reference Program.

Inhibition of HIV-1 Replication
Compounds were examined for possible antiviral activity against both strains of HIV-1 using MT-4 cells as target cells. MT-4 cells were incubated with virus (0.005 MOI) and growth medium containing the test dilutions of compounds for six days in parallel with virus-infected and uninfected control cultures without compound added. Expression of HIV in the cultures was indirectly quantified using the MTT assay [21]. Compounds mediating less than 30% reduction of HIV expression were considered without biological activity. Compounds were tested in parallel for cytotoxic effect in uninfected MT-4 culture containing the test dilutions of compound as described above. A 30% inhibition of cell growth relative to control cultures was considered significant. The 50% inhibitory concentration (EC_{50}) and 50% cytotoxic concentration (CC_{50}) were determined by interpolation from the plots of percent inhibition versus concentration of compound.

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