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Structure–activity relationship in the 3-iodo-4-phenoxypyridinone (IOPY) series: The nature of the C-3 substituent on anti-HIV activity

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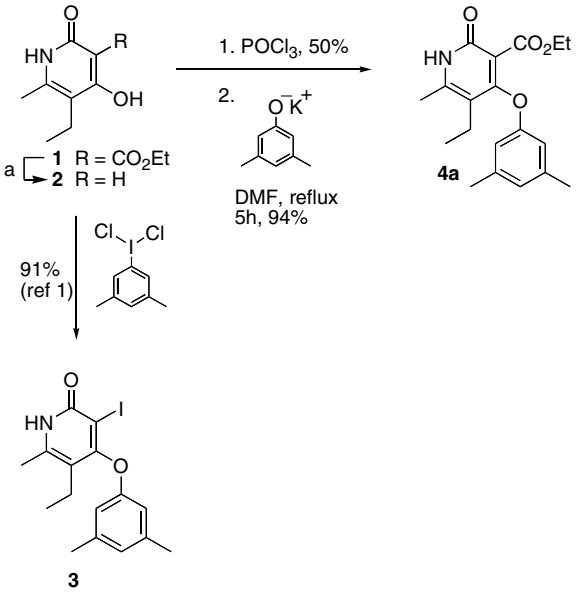
Abstract—As part of a systematic SAR study on the 3-iodo-4-phenoxypyridinone **3** (IOPY) type non-nucleoside reverse transcriptase inhibitors, the analogues **4a**–**4z** bearing different C-3 substituents were synthesized and evaluated for their anti-HIV activity against wild-type HIV-1 and four of the principal HIV mutant strains (K103N, Y181C, Y188L, and I100L). The results show that the 3-vinyl analogue **4j** is the only compound which displays anti-HIV activity comparable to IOPY **3**, and in this respect represents a possible back-up to this lead molecule.

The 3-iodo-4-phenoxypyridinone **3** (IOPY) is representative of a new family of pyridinone based non-nucleoside reverse transcriptase inhibitors (NNRTI's) which are highly active in vitro against a broad panel of HIV-1 mutant strains encountered in AIDS patients.[1] Compound **3**, obtained in high yield through reaction of 3,5-dimethyl(dichloroiodo)benzene with the 4-hydroxypyridinone **2** (Scheme 1), was originally synthesized with the idea that the iodo substituent could be used as a convenient vehicle to incorporate widely differing functionality at the C-3 position of the pyridinone ring. As reported in this communication, we have explored this option to see whether new phenoxypyridinone analogues could be identified having an anti-HIV activity profile superior to that for the lead molecule **3**. A series of 26 new 3-substituted phenoxypyridinone analogues **4a**–**4z** have been synthesized (Schemes 1–4) and evaluated for their anti-HIV activity against wild-type HIV-1 (Table 1) and four of the principal HIV



Scheme 1.

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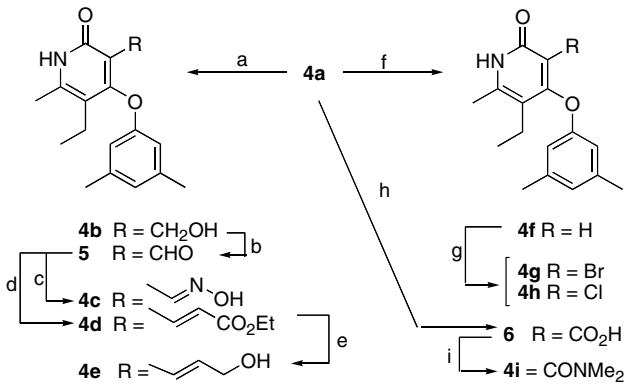
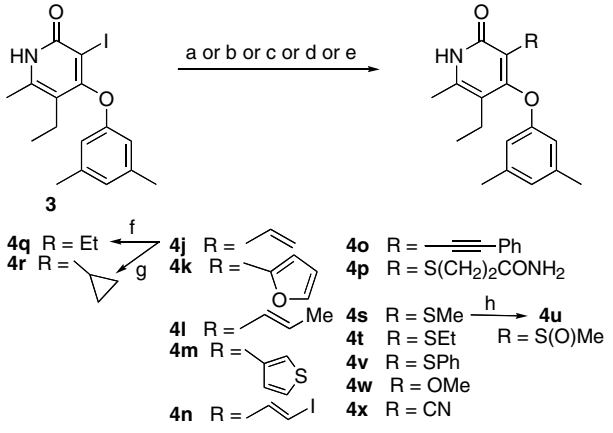
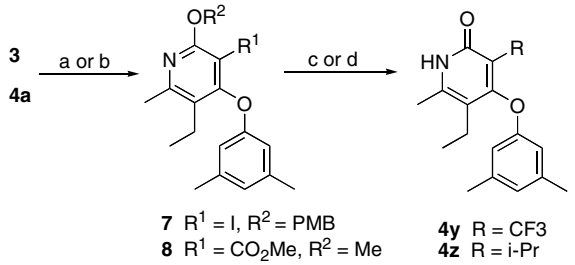


Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, 20 °C, 4 h, 60%; (b) MnO_2, CH_2Cl_2, 20 °C, 18 h, 90%; (c) NH_2OH, EtOH, rt, 2 h, 52%; (d) $Ph_3P{=}CHCO_2Et$, THF, reflux, 4 h, 65%; (e) DiBAl-H, CH_2Cl_2, −78 °C, 60%; (f) 2N HCl, reflux, 18h, 86%; (g) NBS 94% (for **4g**) or NCS 90% (for **4h**), HOAc/EtOAc 1:1, 20 °C, 1 h; (h) 3 N HCl, 20 °C, 1 h, 78%; (i) Me_2NH, DCC, HOBT, Et_3N, CH_2Cl_2, rt, 8 h, 77%.



Scheme 3. Reagents and conditions: (a) $RB(OH)_2$ or $RSnR'_3$, Pd(0), DMF or DME reflux for **4j**, **4k**, **4l**, **4m**, **4n**, **4o** and **4p**; (b) BuLi, THF, −78 °C, MeSSMe for **4s** or EtSSEt for **4t**; (c) thiophenol, DMF, K_2CO_3, reflux for **4v**; (d) 30% NaOMe in MeOH, CuI, DMF, 90 °C, 48 h, 29% for **4w**; (e) CuCN, Py, reflux for **4x**; (f) H_2, Pd/C; (g) CH_2I_2, Et_2Zn, CF_3CO_2H, CH_2Cl_2, 20 °C, 18h, 57%; (h) *m*-CPBA, CH_2Cl_2.



Scheme 4. Reagents and conditions: (a) DEAD, PPh_3, 4-MeOBnOH, THF, 20 °C, 18h, 58% for **7** from **3**; (b) DEAD, PPh_3, MeOH, THF, 20 °C, 18 h, 54% for **8** from **4a**; (c) $FSO_2CF_2CO_2Me$, CuI, DMF, 80 °C, 24 h, 87% for **4y** from **7**; (d) i—MeLi (3 equiv), THF, 0 °C 1 h then reflux 18 h then; ii—Ac_2O, reflux, 18 h, 58% (2 steps); iii—H_2, Pd/C then 3 N HCl, reflux, 18 h, 40% for **4z** from **8**.

mutant strains (K103N, Y181C, Y188L, and I100L) which confer resistance to the NNRTI's. Selected compounds were further evaluated against the two double mutant strains 100I + 103N and 103N + 181C.

To obtain analogue **4a** with an ester functionality at C-3, it proved judicious to work with pyridinone **1** (Scheme 1). Treatment of this material with $POCl_3$, followed by reaction of the derived 4-chloropyridinone intermediate with potassium 3,5-dimethylphenate in refluxing DMF, provided the target ester in 47% yield for the two steps.[1,2] Continuing with **4a** (Scheme 2), the ester function was reduced using $LiAlH_4$ (THF, 20 °C, 4 h, 60%) to give alcohol **4b**. Oxidation of **4b** using MnO_2 (CH_2Cl_2, rt, 18 h) then furnished aldehyde **5** (90% yield). This product was subsequently used to prepare oxime **4c** (NH_2OH, EtOH, rt, 2 h, 52%) and acrylate **4d** ($Ph_3P{=}CHCO_2Et$, THF, Rfx, 4 h, 65%). Selective reduction of the ester motif in **4d** (DiBAl-H, CH_2Cl_2, −78 °C, 60%) gave the C-3 allylic alcohol containing analogue **4e**.

Alternatively, treatment of **4a** with aqueous acid at reflux effected ester hydrolysis and decarboxylation giving the pydridinone **4f** lacking substitution at C-3. Reaction of this aryloxypyridinone intermediate with *N*-bromosuccinimide produced the 3-bromo analogue **4g**[3] (94%) of lead compound **3**, and the corresponding reaction with NCS gave the 3-chloro compound **4h** (90%). Under mild hydrolysis conditions compound **4a** was converted to acid **6**, providing the opportunity to prepare the dimethylamide **4i** (77%).

IOPY **3**, itself, was engaged in Pd(0) coupling reactions with the requisite tributyltin or boronate reagents to prepare the C-3 vinyl (**4j**),[4] 2-furyl (**4k**), propenyl (**4l**), 3-thienyl (**4m**), β-iodovinyl (**4n**), and phenylethynyl (**4o**) compounds, as well as the extended chain amide **4p**[5] [(i) $Bu_3SnS(CH_2)_2CO_2Et$, Pd(0), DMF, 120 °C, 72 h, 50%; (ii) ester to acid (KOH, EtOH, H_2O, reflux, 2 h, 96%), and (iii) acid to amide ($SOCl_2$ then NH_3, 30% yield)] (Scheme 3). The C-3 ethyl analogue **4q** was obtained by catalytic hydrogenation of the double bond in **4j**, and the cyclopropane analogue **4r** was obtained by treatment of this vinyl analogue with CH_2I_2 and Et_2Zn (57% yield).[6] In metal–halogen exchange reactions (*n*-BuLi, THF, −78 °C, MeSSMe or EtSSEt 30–35%) compound **3** was converted to the 3-methylthio analogue **4s**[7] or to the homologous 3-ethylthio pyridinone **4t**.[8] S-Oxidation of **4s** provided the corresponding sulfoxide **4u** in excellent yield. By simply heating **3** with thiophenol (K_2CO_3 in DMF, CuCl, 140 °C, 11%) overnight the SPh analogue **4v** was also prepared. In a similar fashion, heating **3** in the presence of NaOMe/CuI or CuCN led to formation of the 3-OMe and 3-CN substituted analogues **4w**[9] and **4x**, respectively.

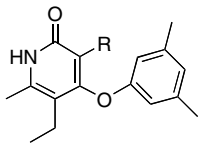
For preparation of **4y** and **4z**, it was first necessary to *O*-alkylate IOPY **3** and ester **4a**. This was readily achieved under Mitsunobu conditions.[10] Subsequent reaction of the 2-*O*-*para*-methoxybenzyl (*O*-PMB) pyridine **7** with $FSO_2CF_2CO_2Me$, CuI in DMF at 80 °C provided access to the target 3-CF_3 analogue **4y**

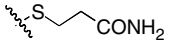
in 87% yield.[11] Reaction of the *O*-methylpyridine **8** with two equivalents of MeLi resulted in double addition to the ester function giving the expected tertiary alcohol intermediate, which was converted to the 3-isopropyl compound **4z** in three steps (acetylation/elimination (Ac_2O, reflux), reduction (H_2, Pd/C), and *O*-demethylation (3N HCl, reflux)).

As the in vitro (cell based assay) anti-HIV[12] data show (Table 1), 9 of the 26 analogues prepared displayed activity in the IC_{50} = 1–10 nM range against wild-type HIV-1, and an additional 5 compounds were active below the cut-off point of IC_{50} = 20 nM, the upper limit fixed by us for further evaluation to be considered (listed in alphabetical order; analogues with IC_{50} LAI strain > 20 nM are presented separately at the bottom of Table 1).

These data indicated that for wild-type RT the shape, volume, and the polar nature of the substituent at C-3 are important for activity. In the direction of increasing volume, this effect can be seen by comparing the IC_{50} values for compounds **4f** (3-H), **4x** (CN), **4h** (Cl), **4g** (Br), and **3** (I). Compound **4f**, lacking substitution at C-3, and the C-3 cyano substituted analogue **4x** are, respectively, 300- and 63-fold less active than the more bulky or globular iodo substituted lead compound **3**. The chloro substituted analogue remains slightly, but measurably less active than **3**, whereas the bromo substituted analogue is essentially equipotent to this lead compound. The 3-SMe (**4s**), OMe (**4w**), CF_3 (**4y**), vinyl (**4j**), and Et (**4q**) substituted compounds also display activities very close to IOPY **3**. From these data it would appear that these substituents, which are similar in their bulk or size, are optimal in terms of their interaction within the hydrophobic pocket of RT. Indeed, for the larger or more extended SEt analogue **4t**, vinyl iodide **4n** the propenyl substituted compound **4l**, and the phenylacetylene derivative **4o** a decrease in activity is observed. Indeed, compound **4o** is inactive. However, this view is lacking in precision as compound **4v** substituted by a SPh motif is highly active, as is compound **4p** which can be looked upon as an analogue of **4t** in which a polar amide function is added at the end of the linear chain. Heterocyclic motifs at C-3, as in the furan analogue **4k** and thiophene **4m** as well as certain small polar substituents at C-3 (cf. **4n**, **4u**, and to a lesser extent **4c**), also interact favorably with the hydrophobic pocket, but

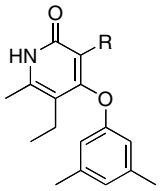
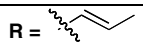
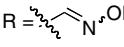
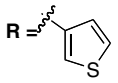
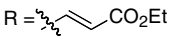
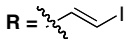
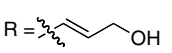
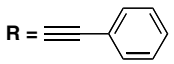
Table 1. Activity (IC_{50}, nM) versus HIV-1[12] for compounds **4a**–**z**



Compound	R	LAI	SI[a]	103N	181C	188L	100I	100I + 103N	103N + 181C
4b	CH_2OH	19.9	5012						
4g	Br	1.99	90,119	39.8	63.1	631		63.1	158
4h	Cl	6.3	10,000	19.9	100	398	31.6		
4j		3.1	6309	3.1	19.9	12.5	6.3		200
4k		15.8	126						
4p		12.5	1995	316	794	2511	158		
4q	Et	3.1	3162	39.8	39.8	63.1	12.5		
4r		6.3	1259	199	158	158	39.8		
4s	SMe	1.99	25,119	31.6	31.6	125	19.9	63.1	31.6
4u		15.8	6309						
4v	SPh	10.0	5012	794	158	794	125	1584	1584
4w	OMe	2.5	39,811	79.4	158	794	31.6	316	501
4y	CF_3	3.1	12,589	12.5	50.1	199	31.6		
4z		19.9	5012	39.8	39.8	31.6	12.5		
3	I	1.25	9000	3.16	19.9	50.1	6.31	19.9	39.8
EFV[b]		1.0	10,000	39.8	1.99	158	3.98	1,000	39.8

(*continued on next page*)

Table 1 (*continued*)

			IC_{50} LAI (nM)			IC_{50} LAI (nM)
	**4a**	R = CO_2Et	631	**4l**		39.8
	4c		31.6	**4m**		50.1
	4d		6310	**4n**		100
	4e		63.1	**4o**		15,848
	4f	R = H	398	**4t**	R = SEt	125
	4i	R = $CONMe_2$	5020	**4x**	R = CN	79.4

[a] Selectivity index or ratio of CC_{50} to IC_{50} relative to LAI (fold).
[b] EFV, efavirenz.

a considerable loss in activity was observed for the ester analogue **4a**, the corresponding dimethylamide **4i**, and the conjugated ester analogue **4d**.

These results on wild-type HIV suggest that the eight analogues **4g**, **4h**, **4j**, **4q**, **4r**, **4s**, **4w**, and **4y** are viable alternatives to IOPY **3** for lead development. However, further evaluation of these compounds against the four mutant strains brought to light a number of limitations. Indeed, with the exception of the 3-vinyl analogue **4j** all these analogues were less active than IOPY **3** against one or several of the mutant strains. This may result from a weaker interaction with Gly 190 and/or Val 189, which are a key feature in the binding of the iodine atom in **3**,[13] and/or from steric clashes with the 181C and 188L residues as observed in related non-nucleoside RT inhibitors.[14] Noteworthy is the increased sensitivity of the C-3 vinyl analogue **4j** over IOPY **3** and the clinically used reference compound efavirenz against the important Y188L mutant. However, a diminished level of sensitivity relative to the two control compounds was observed for the double mutant K103N + Y181C. Globally, IOPY **3** remains the most attractive pyridinone based NNRTI developed to date. This does not preclude, however, that in subsequent in vivo evaluation the vinyl analogue **4j**, or one of the other C-3 modified 4-aryloxypyridinones, may prove attractive for further development.

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3. *3-Bromo-4-(3,5-dimethylphenoxy)-5-ethyl-6-methyl-2(1H)-pyridinone* **4g**. Step 1: following the procedure described by Bishop et al. (*J. Chem. Soc.* **1952**, *437*), a mixture of 3,5-dimethylphenol (610 mg, 5 mmol) and KOH (280 mg, 5 mmol) in EtOH (15 mL) was heated at reflux for 10 min. The solvent was then removed and the residue was dissolved in DMF (15 mL) and 3-carbethoxy 4-chloro-5-ethyl-6-methyl-2(1*H*)-pyridinone[2] (244 mg, 1 mmol) was added. After heating at reflux for 5 h, water (30 mL) was added and the mixture was extracted with EtOAc (3× 20 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated. Silica-gel column chromatography of the residue (CH_2Cl_2/EtOH; 97:3) provided **4a** as yellow solid (310 mg, 94%): mp 202–204 °C ^1H NMR ($CDCl_3$) δ 13.15 (1H, br s), 6.66 (1H, s), 6.53 (2H, s), 3.95 (2H, q, J = 7.0 Hz), 2.37 (3H, s), 2.34 (2H, q, J = 7.2 Hz), 2.25 (6H, s), 0.99 (6H, m). Step 2: compound **4a** (200 mg, 0.61 mmol) was dissolved in 2 N aqueous HCl (10 mL) and heated at reflux for 18 h. After cooling to room temperature, the mixture was poured into ice water, basified using NH_4OH (28%), and extracted with EtOAc (3× 20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to give compound **4f** (133 mg, 86%) as a white solid which was dissolved in HOAc (2 mL) and EtOAc (2 mL). At room temperature, and in the dark, *N*-bromosuccinimide (44 mg, 0.19 mmol) was added in one portion. After stirring for 1 h at room temperature, the mixture was poured into water (5 mL) and the pH of the solution was adjusted to ca. 7 with NH_4OH (28%). The combined organic layers obtained by extraction with EtOAc (3× 10 mL) were dried over $MgSO_4$ and evaporated to give a solid residue. Compound **4g** was obtained as white microcrystals (61 mg, 94%) after silica-gel flash chromtography (CH_2Cl_2/EtOH; 98:2): mp 240–242 °C ^1H NMR ($CDCl_3$) δ 13.45 (1H, br s), 6.68 (1H, s), 6.47 (2H, s), 2.44 (3H, s), 2.35 (2H, q, J = 7.3 Hz), 2.26 (6H, s), 0.99 (3H, t, J = 7.3 Hz) MS (ES): *m*/*z* 334.1 and 336.1 (M−H).
4. *4-(3,5-Dimethylphenoxy)-3-ethenyl-5-ethyl-6-methyl-2(1H)-pyridinone* **4j**. Step 1: dichloro-3,5-dimethyliodobenzene (obtained by the procedure described by Lucas et al. (*Org. Synth.* **1955**, *3*, 482)) (3.75 g; 12.4 mmol) was suspended in water (50 mL) containing sodium carbonate (1.31 g; 12.4 mmol) and stirred for 30 min at room temperature. To this mixture a solution of 5-ethyl-6-methyl-4-hydroxy-2(1*H*)-pyridinone **2** (see Ref. 2) (1.9 g; 12.4 mmol) in water (50 mL) containing also sodium carbonate (1.31 g; 12.4 mmol) was added. After stirring for 1 h at 20 °C, the

precipitate was filtered off, washed with water, dried thoroughly under vacuum at room temperature, and then suspended in DMF (20 mL). The mixture was refluxed for l h and the solvent was evaporated under vacuum. Purification by silica-gel flash chromatography (CH_2Cl_2/EtOH; 98:2) provided 4-(3,5-dimethylphenoxy)-5-ethyl-3-iodo-6-methyl-2(1*H*)-pyridinone **3** (4.3 g, 91%) as colorless microcrystals; mp 240 °C. ^{1}H NMR ($CDCl_3$) δ 13.35 (1H, br s), 6.68 (1H, s), 6.46 (2H, s), 2.44 (3H, s), 2.35 (2H, q, J = 7.3 Hz), 2.26 (6H, s), 0.96 (3H, t, J = 7.2 Hz). Step 2: to a mixture of compound **3** (1.0 g, 2.6 mmol) and palladium tetrakistriphenylphosphine (300 mg, 10% mol) in toluene (15 mL) at room temperature was added tributyl(vinyl) tin (0.91 mL, 3.1 mmol), and the mixture was refluxed for 12 h. Water (8 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. The solvent was removed and the residue was purified by flash chromatography (neutral alumina; CH_2Cl_2/EtOH (98:2)) to give the title compound **4j** as colorless microcrystals (520 mg, 70%); mp 208 °C. ^{1}H NMR ($CDCl_3$) δ 12.28 (1H, br s), 6.40–6.70 (4H, m), 5.32 (1H, dd, J = 10.3 and 4.4 Hz), 3.73 (3H, s),. 2.39 (3H, s), 2.20–2.35 (8H, m), 0.97 (3H, t, J = 7.4 Hz) MS (ES): *m/z* 282.2 (M−H).

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7. *4-(3,5-Dimethylphenoxy)-5-ethyl-6-methyl-3-methylsulfanyl-2(1H)-pyridinone* **4s**. *n*-Butyllithium (1.6 M in hexane, 2.44 mL, 3.9 mmol) was added dropwise at −78 °C to a solution of **3** (575 mg, 1.5 mmol) in THF (25 mL) under nitrogen. The mixture was stirred at −78 °C for 20 min. and dimethyl disulfide (0.67 mL, 7.5 mmol) in THF (3 mL) was added dropwise. The mixture was stirred at room temperature for 2 h and methanol (20 mL) was added. The mixture as then concentrated under vacuum and the residue was purified by silica-gel flash chromtography (CH_2Cl_2/EtOH; 97:3) providing compound **4s** as a yellow solid (156 mg, 35%) mp 186–188 °C ^{1}H NMR ($CDCl_3$) δ 13.33 (1H, br s), 7.25 (1H, s), 6.44 (2H, s), 2.42 (3H, s), 2.34 (3H, s), 2.31 (2H, q, J = 7.3 Hz), 2.25 (6H, s), 0.98 (3H, t, J = 7.3 Hz) MS (ES): *m/z* 302.1 (M−H).
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9. *4-(3,5-Dimethylphenoxy)-5-ethyl-3-methoxy-6-methyl-2(1H)-pyridinone* **4w**. To a solution of copper(I) iodide (2 g, 10.53 mmol) in DMF (15 mL) was added at room temperature iodopyridinone **3** (1.5 g, 3.9 mmol) then sodium methoxide (7.5 mL, 30% w/w solution in MeOH). The mixture was stirred at 90 °C in a oil bath for 48 h, followed by addition of H_2O and extraction with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was silica-gel column chromatographed (CH_2Cl_2/*i*-PrOH; 97:3) as the eluent. Crystallization from acetone/MeOH (80/20) gave pyridinone **4w** (0.32 g, 29%) as a white solid: mp 178 °C. ^{1}H NMR ($CDCl_3$) δ 13.1 (1H, br s), 6.69 (1H, s), 6.56 (2H, s), 3.73 (3H, s), 2.38 (5H, m), 2.29 (6H, s), 1.04 (3H, t, J = 7.4 Hz) Anal. Calcd for ($C_{17}H_{21}NO_3$): C, 71.06; H, 7.37; N, 4.87. Found: C, 70.76; H, 7.42; N,4.82.
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12. All compounds were tested for potency (IC_{50}, nM) to achieve 50% protection of MT-4 cells from HIV-1 cytopathicity as determined by the MTT method: Pauwels, R.; Balzarini, J.; Baba, M.; Snoek, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. *J. Virol. Methods* **1988**, *20*, 309, Unless noted otherwise, the LAI strain of HIV-1 was the infecting virus. Other infecting mutant (in the reverse transcriptase) strains of virus are characterized in the tables by the mutated amino acid position and the one letter codes. For instance, 181C refers to replacement of tyrosine at position 181 with cysteine. All determinations are average values for three or more tests.
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