THE HANTZSCH SYNTHESIS WITH 6-AMINOURACILS : ONE STEP SYNTHESIS OF PYRIDO [2,3-*d*] PYRIMIDINES

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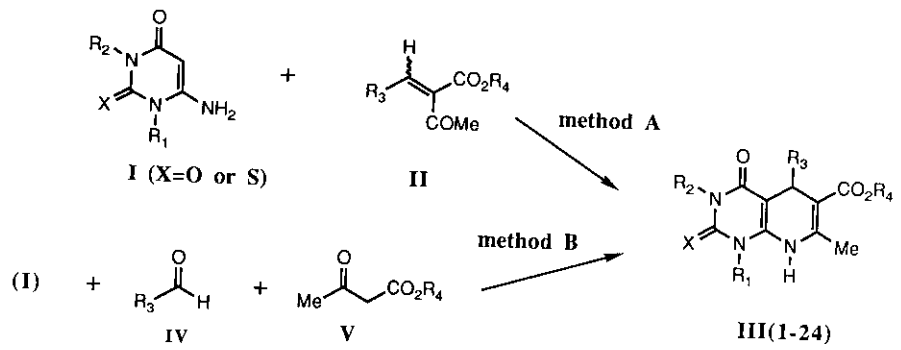
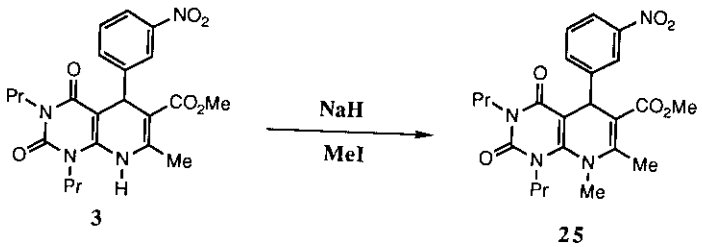
Abstract - A one-step synthesis of new pyrido [2,3-*d*] pyrimidine derivatives (**III**) was achieved through the Hantzsch synthesis using 6-aminouracils (**I**) as enamine nucleophiles.

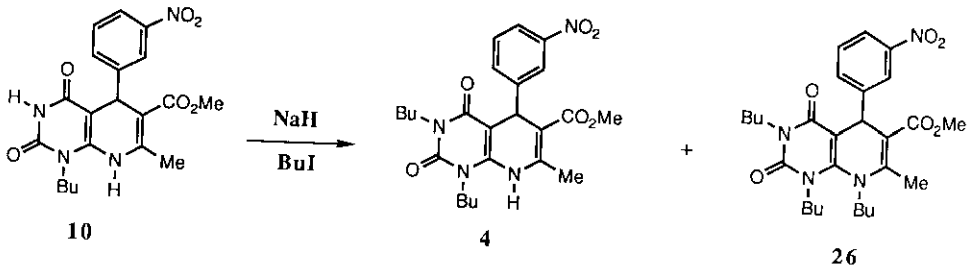
Recently, various 4-aryl-1,4-dihydropyridine derivatives [1] that operate as calcium antagonists [2] or calcium channel blockers have been synthesized as potential cardiovascular drugs.[3] In a search for new calcium antagonists, we aimed to synthesize novel bicyclic compounds which include the 4-aryl-1,4-dihydropyridine skeleton as the key component. Thus the Hantzsch synthesis [1a] was applied to 6-aminouracil derivatives (**I**) [4] which are typical heterocyclic enamines, in order to synthesize pyrido[2,3-*d*]pyrimidines (**III**) in one step [5] as shown in Scheme 1.

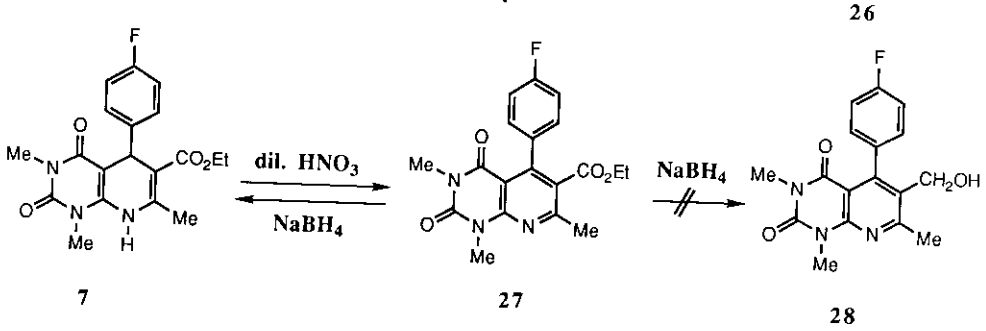
6-Aminouracils (**I**) [4] were refluxed with 2-arylmethyleneacetoacetates (**II**)[6] in an appropriate solvent such as MeOH, EtOH or iso-PrOH to afford the desired pyrido[2,3-*d*]pyrimidines (**III**) in good to excellent yields (method A). The 2-arylmethyleneacetoacetates (**II**) were prepared from arylaldehydes (**IV**) and acetoacetates (**V**) [7] by means of the Knoevenagel condensation. [6] The pyridopyrimidines (**III**) were also prepared by the one-pot condensation of **I**, **IV** and **V** (method B) under conditions similar to those used for method A. These methods were applicable to the 3-unsubstituted uracils (**I**, R_2=H) as exemplified by the synthesis of compounds (**8**), (**9**), (**10**), and (**13**), but not to the 1,3-unsubstituted aminouracils. It seems that the 1,3-unsubstituted aminouracils exist in the dihydroxypyrimidine form, lacking reactivity as enamines. The thia-analogues (**11**, **18**) were similarly obtained from thiouracils (**I**, X=S) [4] by method A or B.



Scheme 1





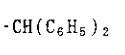
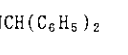


Scheme 2

Table I. Pyrido[2,3-d]pyrimidines(III)

Compd. No.	R_1	R_2	R_3	R_4	X	Method[a]	Yield (%)	mp (°C)	Recrystn. solvent[b]	Formula	Analysis(%) Calcd.(Found) C	H	N
1	Me	Me	3-NO_2-C_6H_4	Me	O	A	87.4	273-274	A-D	$C_{18}H_{16}N_4O_6$	55.96	4.70	14.50
											(55.94	4.65	14.77)
2	Me	Me	3-NO_2-C_6H_4	Et	O	A	74.8	256-258	D	$C_{19}H_{20}N_4O_6$	57.00	5.03	13.99
											(56.81	5.02	13.67)
3	Pr	Pr	3-NO_2-C_6H_4	Me	O	A	77.9	192-193	I	$C_{22}H_{26}N_4O_6$	59.72	5.92	12.66
											(59.75	5.92	12.65)
4	Bu	Bu	3-NO_2-C_6H_4	Me	O	B	19.8	160-161	I-L	$C_{24}H_{30}N_4O_6$	61.26	6.43	11.91
											(61.57	6.59	11.84)
5	Me	Bu	3-NO_2-C_6H_4	Me	O	A	60.7	170-171	I	$C_{21}H_{24}N_4O_6$	58.87	5.65	13.08
											(59.04	5.75	13.05)
6	Me	Me	3,4-$(OMe)_2$-C_6H_3	Me	O	A	84.6	213-215	F-H	$C_{20}H_{23}N_3O_6$	59.84	5.78	10.67
											(59.65	5.66	10.42)
7	Me	Me	4-F-C_6H_4	Et	O	A	86.2	240-241	C-B	$C_{19}H_{20}N_3O_4F$	61.12	5.40	11.25
											(60.97	5.37	11.19)
8	Me	H	3-NO_2-C_6H_4	Me	O	A	66.6	290-291	F	$C_{17}H_{16}N_4O_6$	54.84	4.33	15.05
											(55.15	4.62	14.79)
9	Me	H	3-NO_2-C_6H_4	Et	O	A	75.5	298-299	G-H	$C_{18}H_{18}N_4O_6$	55.96	4.70	14.50
											(55.71	4.76	14.58)
10	Bu	H	3-NO_2-C_6H_4	Me	O	A	64.6	250-252	C-I	$C_{20}H_{22}N_4O_6$	57.97	5.35	13.52
											(58.08	5.36	13.58)
11	Me	Me	3-NO_2-C_6H_4	Me	S	A	72.5	118-120	B-J	$C_{18}H_{18}N_4O_5S$	53.74	4.51	13.92
											(53.63	4.49	13.81)
12	Me	Me	3-NO_2-C_6H_4	$(CH_2)_2N(Me)CH_2C_6H_5$	O	B	22.9	148-149	I	$C_{27}H_{29}N_5O_6$	62.42	5.63	13.48
											(62.47	5.61	13.40)
13	Me	H	3-NO_2-C_6H_4	$(CH_2)_2N(Me)CH_2C_6H_5$	O	B	27.8	232-234	I	$C_{26}H_{27}N_5O_6$	61.77	5.38	13.85
											(61.48	5.28	13.52)
14	Me	Me	2,3-Cl_2-C_6H_3	$(CH_2)_2N(Me)C_6H_5$	O	B	45.1	202-204	C-I	$C_{27}H_{28}N_4O_4Cl$	59.67	5.19	10.31
											(59.20	5.15	10.25)
15	Me	Me	2,3-Cl_2-C_6H_3	$(CH_2)_2$-N⟨⟩-$NCH(C_6H_5)_2$	O	B	29.3	224-226	A-J	$C_{36}H_{37}N_5O_4Cl_2$	61.19	5.28	9.91
											(61.48	5.50	9.60)

Table I. (continued)

Compd. No.	R_1	R_2	R_3	R_4	X	Method[a]	Yield (%)	mp (°C)	Recrystn. solvent[b]	Formula	Analysis(%) Calcd.(Found) C	H	N
16	Me	Me	2-Cl-C_6H_4	$(CH_2)_2N(CHMe_2)_2$	O	B	12.7	193-195	I	$C_{25}H_{33}N_4O_4Cl$	61.40	6.80	11.46
											(61.27	6.87	11.43)
17	Me	Me	3-NO_2-C_6H_4		O	B	54.9	224-225	E	$C_{30}H_{33}N_6O_6Cl$	59.16	5.46	13.80
											(59.17	5.47	14.08)
18	Me	Me	2,3-Cl_2-C_6H_3	$(CH_2)_2N(Me)CH_2C_6H_5$	S	B	27.0	175-177	I-K	$C_{27}H_{28}N_4O_3Cl_2S$	57.96	5.04	10.01
											(57.83	4.76	10.23)
19	Me	Me			O	B	13.5	189-191	C-L	$C_{36}H_{37}N_7O_5$	66.76	5.76	15.14
											(66.53	5.88	14.76)
20	Me	Me	2-Cl-C_6H_4		O	B	42.7	208-209	L	$C_{23}H_{27}N_4O_5Cl$	58.17	5.73	11.80
											(58.01	5.93	11.63)
21	Me	Me	cyclohexyl	Me	O	A	32.3	214-215	B-J	$C_{18}H_{25}N_3O_4$	62.23	7.25	12.09
											(62.00	7.23	11.78)
22	Me	Me	2-Cl-C_6H_4	$(CH_2)_2N(Me)CH_2C_6H_5$	O	B	46.6	175-176	I	$C_{27}H_{29}N_4O_4Cl$	63.71	5.74	11.01
											(63.51	5.70	10.92)
23	Me	Pr	2-Cl-C_6H_4	$(CH_2)_2N(CHMe)_2$	O	B	10.4	128-131	I-K	$C_{27}H_{35}N_4O_4Cl$	62.96	6.85	10.88
											(62.68	7.20	11.01)
24[c]	Me	Pr	2-Cl-C_6H_4		O	B	29.1	208-212	D-H	$C_{38}H_{42}N_5O_4Cl$	61.58	5.98	9.45
											(61.10	5.92	9.29)

[a] See Experimental. [b] A. CH_2Cl_2; B. $CHCl_3$; C. MeOH; D. EtOH; E. iso-PrOH; F. DMSO; G. DMF; H. H_2O; I. AcOEt; J. iso-Pr_2O; K. hexane; L. Et_2O. [c] Dihydrochloride.

Alkylation of **3** with methyl iodide in the presence of NaH in DMF gave the 8-methyl derivative (**25**) in 42.4 % yield. Alkylation of the 3-unsubstituted compound (**10**) with butyl iodide in the presence of two equivalents of NaH afforded both the 3-alkylated (**4**) and 3,8-dialkylated compounds (**26**) in 26.3% and 27.2% yield, respectively. Oxidation of **7** with nitric acid gave the corresponding pyridine derivative (**27**), while reduction of **27** with $NaBH_4$ in *tert*-BuOH/MeOH, the method reported by Soai *et al.* [8] for reducing simple pyridine esters to the corresponding alcohols, led back to the dihydropyridine (**7**) in 46.4 % yield, rather than the expected alcohol(**28**). On the other hand, application of the same procedure to diethyl 2,6-dimethyl-4-phenyl-3,5-pyridine-dicarboxylate [9] which is a fully substituted pyridine ester without a fused ring was not successful in reducing it either to the dihydropyridine or the alcohol, only the starting material being recovered. Soai's method therefore, as well as being useful for reducing simple pyridine esters to alcohols, also seems to be useful for reducing pyridines to their dihydropyridine equivalents when another aromatic ring is fused to the pyridine skeleton, as in our 5-aryl-pyridopyrimidine-6-carboxylate case.

Antihypertensive activity of **III** was evaluated in conscious spontaneously hypertensive rats (SHR) after oral administration. [10] Some of the compounds which possess aminoethyl ester groups had only moderate antihypertensive activity but the effects were longer-lasting compared with the case of nifedipine [3] as shown in Table II.

Table II. Effects of Pyrido[2,3-d]pyrimidines (**III**) on Systolic Blood Pressure in Spontaneously Hypertensive Rats(SHR).

Compd.	Dose (mg/kg, p.o.)	Antihypertensive action	
		Maximum [a] (mmHg)	Duration [b] (h)
14	50	-35	5-8
15	30	-18	5-8
16	50	-24	8-24
18	50	-22	5-8
22	50	-32	8-24
Nifedipine	10	-45	< 5

[a] Antihypertensive activity is shown as maximum reductions in blood pressure from the basal values.

[b] The duration of action is shown in hours during which a statiscally significant reduction was observed.

EXPERIMENTAL

Melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. *Infrared(Ir)* spectra were taken on a Hitachi IR-260-10 spectrophotometer. Proton nuclear magnetic resonance(^{1}H-Nmr) spectra were recorded on a Varian EM-390 (90 MHz) spectrometer in the solvent indicated. Chemical shifts are given in ppm relative to Me_4Si as the internal standard. The following abbreviations are used: s=singlet ; d=doublet ; t=triplet ; q=quartet ; m=multiplet ; br=broad. Column chromatography was performed on E. Merck 70-230 mesh silica gel.

Synthesis of Pyrido[2,3-*d*]pyrimidines (III, Table I)

Typical examples are given to illustrate the general procedures for methods A and B.

Method A

Methyl 1,2,3,4,5,8-hexahydro-1,3,7-trimethyl-5-(3-nitrophenyl)-2,4-dioxopyrido[2,3-*d*]-pyrimidine-6-carboxylate (1)

A mixture of methyl 2-(3-nitrobenzylidene)acetoacetate (4.65 g, 18.7 mmol), 6-amino-1,3-dimethyluracil(2.89 g, 18.6 mmol) and EtOH (30 ml) was refluxed with stirring for 3 h. The mixture was concentrated *in vacuo* and the crystals obtained were recrystallized from CH_2Cl_2-EtOH to give **1** (6.10 g, 87.4 %) as colorless crystals, mp 273-274 °C. Ir(Nujol): 3280, 1700 cm^{-1}. Nmr(DMSO-d_6) δ : 2.48 (3H, s), 3.10 (3H, s), 3.46 (3H, s), 3.58 (3H, s), 5.04 (1H, s), 7.37-8.07 (4H, m), 8.77 (1H, s). *Anal.* Calcd for $C_{18}H_{18}N_4O_6$: C, 55.96; H, 4.70; N, 14.50. Found: C, 55.94; H, 4.65; N, 14.77.

Ethyl 1,2,3,4,5,8-hexahydro-1,7-dimethyl-5-(3-nitrophenyl)-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylate (9)

A mixture of ethyl 2-(3-nitrobenzylidene)acetoacetate (8.14 g, 30.9 mmol), 6-amino-1-methyluracil (5.24 g, 37.1 mmol) and EtOH (50 ml) was refluxed with stirring for 15 h. The precipitated crystals were collected by filtration and recrystallized from DMF-H_2O to give **9** (9.02 g, 75.5 %) as colorless prisms, mp 298-299 °C. Ir(Nujol): 3350, 3185, 1695 cm^{-1}. Nmr(DMSO-d_6) δ : 1.14 (3H, t, J=7 Hz), 2,46 (3H, s), 3.40 (3H, s), 4.01 (2H, q, J=7 Hz), 5.00 (1H, s), 7.40-8.05 (4H, m), 8.73 (1H, s). *Anal.* Calcd for $C_{18}H_{18}N_4O_6$: C, 55.96; H, 4.70; N, 14.50. Found: C, 55.71; H, 4.76; N, 14.58.

Method B

2-(*N*-Benzyl-*N*-methylamino)ethyl 5-(2-chlorophenyl)-1,2,3,4,5,8-hexahydro-1,3,7-trimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylate (22)

A mixture of 2-chlorobenzaldehyde (2.36g, 16.8 mmol), 2-(*N*-benzyl-*N*-methylamino)ethyl acetoacetate (4.19 g, 16.8 mmol), 6-amino-1,3-dimethyluracil (2.86 g, 18.5 mmol) and iso-PrOH (20 ml) was refluxed with stirring for 8 h. The hot mixture was diluted with $CHCl_3$ (30 ml) and filtered to remove the unreacted aminouracil. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica gel (80 g) using $CHCl_3$-MeOH (20:1, v/v) as eluant to give **22** as crystals. Recrystallization from AcOEt gave colorless prisms (3.99 g, 46.6 %), mp 175-176 °C. Ir(Nujol): 3310, 1700 cm^{-1}. Nmr($CDCl_3$) δ : 2.16 (3H, s), 2.22 (3H, s), 2.60 (2H, t, *J*=6 Hz), 3.25 (3H, s), 3.34 (3H, s), 3.46 (3H, s), 4.15 (2H, t, *J*=6 Hz), 5.47 (1H, s), 6.87-7.35 (9H, m), 7.43 (1H, br s). *Anal.* Calcd for $C_{27}H_{29}N_4O_4Cl$: C, 63.71; H, 5.74; N, 11.01. Found: C, 63.51; H, 5.70; N, 10.92.

Methyl 1,2,3,4,5,8-hexahydro-7,8-dimethyl-5-(3-nitrophenyl)-1,3-dipropyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylate (25)

To a stirred suspension of NaH (60 % dispersion in oil, 0.14 g, 3.5 mmol) in DMF(5 ml) was added **3** (1.33 g, 3.0 mmol) in DMF(10 ml). After being stirred at room temperature for 30 min, methyl iodide (0.59 g, 4.2 mmol) was added. The mixture was stirred at room temperature for 20 h, diluted with water and extracted with $CHCl_3$. The extract was washed with brine, dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (70 g) using hexane-AcOEt (1:1, v/v) as eluant to yield **25** (0.81 g, 59.1 %). Recrystallization from Et_2O-hexane gave yellow prisms (0.58 g, 42.4 %), mp 97-98 °C. Ir(Nujol): 1725, 1675, 1605 cm^{-1}. Nmr($CDCl_3$) δ : 0.53 (3H, t, *J*=7.2 Hz), 0.92 (3H, t, *J*=7.2 Hz), 1.19 (2H, m), 1.60 (3H, s), 1.56-1.85 (2H, m), 2.54 (3H, s), 3.64 (2H, t, *J*=7.2 Hz), 3.67 (3H, s), 4.08(2H, t, *J*=7.2 Hz), 4.40 (1H, s), 7.35 (1H, t, *J*=17.6 Hz), 7.46-7.52 (1H, m), 7.93-7.96 (1H, m), 8.01-8.06 (1H, m). *Anal.* Calcd for $C_{23}H_{28}N_4O_6$: C, 60.52; H, 6.18; N, 12.27. Found: C, 61.02; H, 6.22; N, 12.43.

Methyl 1,3,8-tributyl-1,2,3,4,5,8-hexahydro-7-methyl-5-(3-nitrophenyl)-2,4-dioxopyrido-[2,3-*d*]pyrimidine-6-carboxylate(26) and methyl 1,3-dibutyl-1,2,3,4,5,8-hexahydro-7-methyl-5-(3-nitrophenyl)-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylate (4)

The pyridopyrimidine (**10**) (1.04 g, 2.5 mmol) in DMF (10 ml) was added dropwise to a stirred suspension of NaH (60 % dispersion in oil, 0.22 g, 5.5 mmol) in DMF (10 ml). After stirring at room temperature for 40 min, butyl iodide (0.68 ml, 6.0 mmol) was added. The mixture was stirred at room temperature for 6 h, diluted with

water and extracted with $CHCl_3$. The extract was washed with brine, dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (60 g). The eluate with hexane-AcOEt (4:1, v/v) gave **26** (0.36 g, 27.2 %) as an oil. Nmr ($CDCl_3$) δ : 0.73 (3H, t, *J*=7.4 Hz), 0.84 (3H, t, *J*=7.2 Hz), 0.98 (3H, t, *J*=7.2 Hz), 1.05-2.21 (14H, m), 2.55 (3H, s), 3.66 (2H, t, *J*=7.2 Hz), 3.66 (3H, s), 4.11 (2H, t, *J*=7.2Hz), 4.39 (1H, s), 7.35 (1H, t, *J*=7.8 Hz), 7.42-7.49 (1H, m), 7.89-8.08 (2H, m). The eluate with hexane-AcOEt(1:2, v/v) gave **4** (0.31g, 26.3 %), mp 162-163 °C. *Anal.* Calcd for $C_{24}H_{30}N_4O_6$: C, 61.26; H, 6.43; N, 11.91. Found: C, 61.33; H, 6.66; N, 11.64.

Ethyl 5-(4-fluorophenyl)-1,2,3,4-tetrahydro-1,3,7-trimethyl-2,4-dioxopyrido[2,3-*d*]-pyrimidine-6-carboxylate (27)

A mixture of **7** (3.73 g, 10 mmol), HNO_3 (d=1.38, 15 ml) and water (100 ml) was stirred at 95-100 °C for 3 h and cooled. The resulting precipitate was filtered and washed with water to yield **27** (3.58 g, 96.5 %). Recrystallization from acetone-MeOH gave colorless prisms (2.96 g, 79.7 %), mp 184-185 °C. Ir(Nujol): 1710, 1665, 1640 cm^{-1}. Nmr(DMSO-d_6) δ : 0.88 (3H, t, *J*=7.2 Hz), 2.55 (3H, s), 3.14 (3H, s), 3.61 (3H, s), 3.95 (2H, q, *J*=7.2 Hz), 7.16-7.22 (4H, m). *Anal.* Calcd for $C_{19}H_{18}N_3O_4F$: C, 61.45; H, 4.89; N, 11.31. Found: C, 61.52; H, 4.93; N, 11.32.

Reduction of 27 with $NaBH_4$

MeOH (5 ml) was added dropwise to a refluxing mixture of **27** (1.11 g, 3.0 mmol), $NaBH_4$ (0.28 g, 7.4 mmol) and *tert*-BuOH (25 ml) over a period of 10 min. After the addition was complete, the mixture was refluxed for another 3.5 h and then cooled. After 6 N HCl (2 ml) was added, the mixture was extracted with CH_2Cl_2 and worked up to give an oil. The oil was subjected to column chromatography on silica gel (50 g). The eluate with hexane-AcOEt(2:1, v/v) gave the starting material (0.33 g, 29.7 %) as crystals and the eluate with hexane-AcOEt (1:1, v/v) gave **7**. Recrystallization of **7** from MeOH-$CHCl_3$ gave colorless prisms (0.52 g, 46.4 %), mp 239-240 °C. Ir(Nujol): 3300, 3240, 1705, 1660 cm^{-1}. Nmr(DMSO-d_6) δ : 1.13 (3H, t, *J*=7.2 Hz), 2.42 (3H, s), 3.10 (3H, s), 3.43 (3H, s), 4.01 (2H, q, *J*=7.2 Hz), 4.92 (1H, s), 6.94-7.09 (2H, m), 7.16-7.29 (2H, m), 8.69 (1H, br s). *Anal.* Calcd for $C_{19}H_{20}N_3O_4F$: C, 61.12; H, 5.40; N, 11.25. Found: C, 61.14; H, 5.46; N, 11.12.

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