Non-Condensed Trifluoromethylated 5,5-Bicycles: Synthesis of 2-[3-Alkyl(phenyl)-1*H*-pyrazol-1-yl]-4-phenyl-5-alkylthiazole and -4,5,6,7-tetrahydrobenzothiazole Systems

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Abstract: A convenient method for the synthesis of a novel series of eighteen non-condensed 5,5-bicycles, specifically 2-[3-alkyl(phenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-4-phenyl-5-alkylthiazoles and -4,5,6,7-tetrahydrobenzothiazoles **3a**–**i** from the reaction of 3-alkyl(phenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-pyrazolethiocarboxyamide (**1**) with 2-bromoacetophenone, 2-bromopropiophenone and 2-bromocyclohexanone (**2**), is reported. The dehydration of compounds **3a**–**i** with a mixture of concentrated sulfuric acid–acetic acid (1:10 v/v) led to the corresponding 2-[3-alky(phenyl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]-4-phenyl-5-alkylthiazoles and respective 4,5,6,7-tetrahydrobenzothiazoles **4a**–**i** in good yield.

Key words: thiazoles, benzothiazoles, fluorine, heterocycles, pyrazoles, cyclizations

Thiazoles, pyrazoles and their derivatives are know to exhibit remarkable biological activities and they have been widely used in a variety of fields ranging from medicinal to agriculture applications.[1–7] Furthermore, the development of new and efficient methods for the synthesis of fluorinated N-heterocycles have attracted much attention due to their importance in biology and pharmacology research fields.[8–10]Among natural products derived from thiazole, thiamine (aneurine, vitamine B_1) is of great importance and the thiazole ring of the thiamine is responsible for its biological action. The Hantzch's synthesis is the most widely employed synthetic method to obtain thiazoles. This procedure condenses an α-halocarbonyl compound with a reactant bearing the NCS fragment such as thioamides, thioureas, or dithiocarbamic acid derivatives.[11] On the other hand, natural products containing pyrazole rings are rare. However, many synthetically produced pyrazoles are biologically active and some are used as pharmaceuticals, herbicides and insecticides. The synthesis of 1*H*-pyrazoles is well explored, where β-diketones or derivatives thereof as the 3-atom fragment are condensed with hydrazine or its derivatives to close the pyrazole ring.[1] Although many methods for the synthesis of thiazoles and pyrazoles have been reported, the synthesis of non-condensed 5,5-bicycles, such as 2-(1*H*-pyrazol-1-yl)thiazoles and 2-(1*H*-pyrazol-1-yl)-4,5,6,7-tetrahydrobenzothiazoles is little explored and it is also relatively rare to find trifluoromethylated derivatives thereof. In a search of the literature, we found just a few methods to obtain these bi-heterocyclic systems. Sing and co-workers[12] reported the synthesis of a mixture of isomeric products of 2-(3-trifluoromethylpyrazol-1-yl)- and 2-(5-trifluoromethylpyrazol-1-yl)benzothiazole from the condensation reaction between 2-chlorothiazole and the sodium salts of the pyrazoles using sodium hydride in dimethylformamide under reflux. The isomer 2-(5-trifluoromethyl-pyrazol-1-yl)benzothiazole was obtained by treating 2-hydrazinobenzothiazole with 1,1,1-trifluoropentane-2,4-dione in ethanolic HCl.[12] In 1988, Peet and co-workers reported the synthesis and the X-ray crystallographic data of 2-(5-methyl-1,2-dihydro-3*H*-pyrazol-3-one-2-yl)benzothiazole during a reinvestigation of the condensation reaction of 2-hydrazinobenzothiazole with ethyl acetoacetate.[13] In 1999, the same author reported the synthesis of a series of 5-trifluoromethylpyrazol-3-yl 5,5- and 5,6-substituted heterocycles from the reactions of (3-oxo-4,4,4-trifluorobutanoyl) heterocycles with hydrazine hydrate.[14] In the same year, Rezessy at al. reported two methods for the condensation reaction of chalcones with 2-hydrazinothiazoles and pyrazoline-1-thiocarboxyamides to give hydrazones which upon treatment with acid underwent ring closure to yield a series of five dihydropyrazolylthiazoles or giving directly 2-(3,5-diarylpyrazol-1-yl)thiazoles, respectively.[15] Recently, Saloutin at al. showed that the interaction of polyfluoro-2,3-epoxyalkanes with thiosemicarbazide afforded 2-hydrazino-1,3-thiazolines which reacted with acetylacetone to give only a single 2-(3,5-dimethylpyrazol-1-yl)-1,3-thiazoline.[16] The literature above shows that the method described by Rezessy employs 1-pyrazolthicarboxyamide as precursor for the synthesis of 2-(pyrazol-1-yl)thiazole. However, starting from chalcones, this procedure does not allow the synthesis of the interesting non-fused 5,5-bi-aromatic system, 2-(1*H*-pyrazol-1-yl)thiazole.

In previous papers a series of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones have been used as precursors of a variety of five-, six- and seven-membered halomethyl substituted heterocycles, e.g. isoxazoles,[17–20] pyrazoles,[21,22] pyrimidines,[23–25] benzodiazepines[26] and thiazines.[27]

In a recent work we reported the regiospecific synthesis of 5-trihalomethyl-4,5-dihydro-1*H*-pyrazoles (**1**) from the cyclocondensation of β-alkoxyvinyl trihalomethyl ke-

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tones with semicarbazide and thiosemicarbazide in excellent yields.[28,29] However, in an attempt to perform the dehydration of **1** under acidic conditions degradation of this compound occurred furnishing 3(4)-alkyl- and 3-aryl-substituted 5-trifluoromethyl-1*H*-pyrazole.

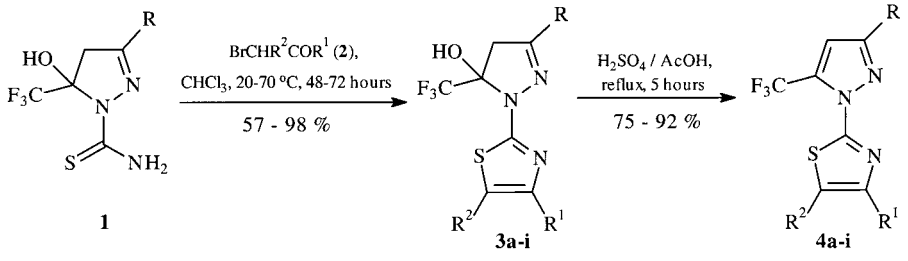
Thus, this situation prompted us to investigate the synthesis of sulfur and nitrogen containing non-condensed and especially substituted 5,5-bicycle 2-(1*H*-pyrazol-1-yl)-thiazoles **3a–f** and the respective tetrahydrobenzothiazoles derivatives **3g–i** from reaction of the thiocarboxyamide substituted compounds **1** with various 2-bromoketones **2**. In a second procedure, the acid dehydration of **3** was performed to obtain a series of pyrazolylthiazoles **4** in good yields.

In this work a series of 2-[3-alkyl(phenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-4-phenyl-5-alkylthiazoles and the respective -4,5,6,7-tetrahydrobenzothiazoles (**3a–i**) from the reactions of 3-alkyl(phenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-pyrazolethiocarboxyamide (**1**) with 2-bromoacetophenone, 2-bromopropiophenone and 2-bromocyclohexanone (**2**) in 57–98% yields was obtained. All cyclocondensation reactions of compounds **1** with 2-bromo ketones were carried out in chloroform under mild conditions for **3a–c** (20–25 °C) or under reflux for **3d–i**. The reaction times were determined as 24 hours for the reactions of **1** with 2-bromoacetophenones, 72 hours for 2-bromopropiophenones and 48 hours for 2-bromocyclohexanone. The bicycles that crystallized in the course of the reaction, were filtered off and recrystallized from hexane–chloroform (1:3) or ethanol. Although the structures of **3a–i** were determined by ^{1}H-, and ^{13}C-NMR and mass spectra as pure compounds, they are highly hygroscopic and showed unsatisfactory elemental analysis. Subsequently, **3a–i** were dehydrated to furnish another series of 2-[3-alky(phenyl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]-4-phenyl-5-alkylthiazoles and the respective -4,5,6,7-tetrahydrobenzothiazoles (**4a–i**), in good yields (75–92%). The dehydration reaction of **3a–i** was carried out with a mixture of concentrated sulfuric acid–acetic acid (1:10 v/v) for 5 hours under reflux. The reactions were neutralized and the compounds **4** were isolated by extraction with chloroform and recrystallized from methanol or ethanol. All reactions are presented in the Scheme and the most satisfactory results of these reactions, selected physical and mass data are presented in the experimental part and in Table 1 and Table 3. The ^{1}H- and ^{13}C-NMR spectral data are presented and in Table 2 and Table 4.

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All mps were determined on a Reichert Thermovar apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in DMSO-d_6 for **3a–i** and in chloroform-d_1 for **4a–i** using TMS as internal reference. Mass spectra were registered on a HP 6890 GC connected to a HP 5973 MSD and interfaced by a Pentium PC. The GC was equipped with a split–splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and the helium was used as the carrier gas. The CHN elemental analyses were performed on a Perkin Elmer 2400 CHN elemental analyzer.

2-[3-Alkyl(phenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-4-phenyl-5-alkylthiazoles and -4,5,6,7-tetrahydrobenzothiazoles (3a–i); General Procedure

In a 100 mL flask a mixture of 3-alkyl(phenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-pyrazolethiocarboxyamides (**1**) (10 mmol) and 2-bromo ketones **2** (10 mmol) in $CHCl_3$ (20 mL) was magnetically stirred at 20–25 °C. The mixtures were stirred at 20–25 °C for 24 h (**3a–c**), at reflux for 48 h (**3g–i**) or at reflux for 72 h (**3d–f**). The products precipitated immediately or if necessary, the solvent was partially evaporated under reduced pressure. The precipitated products **3a–i** were filtered off. The solids were recrystallized from hexane–$CHCl_3$ (1:3) or EtOH. Compounds **3** are highly hygroscopic.



1-4	a	b	c	d	e	f	g	h	i
R	H	CH_3	Ph	H	CH_3	Ph	H	CH_3	Ph
R^1	Ph	Ph	Ph	Ph	Ph	Ph	-$(CH_2)_4$-	-$(CH_2)_4$-	-$(CH_2)_4$-
R^2	H	H	H	CH_3	CH_3	CH_3			

Scheme

Table 1 Selected Physical and Mass Data of 2-[3-Alkyl(phenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-4-phenyl-5-alkylthiazoles and -4,5,6,7-tetrahydrobenzothiazoles (**3a–i**)

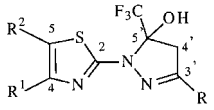
Compd.	Yield (%)[a]	Mp (°C)[b]	Molecular Formula (g/mol)	MS *m/z* (%)
3a	71	104–105	$C_{13}H_{10}N_3OF_3S$ 313.29	313 (M^+, 73), 244 (67), 202 (100), 77 (47)
3b	94	142–143	$C_{14}H_{12}N_3OF_3S$ 327.32	327 (M^+, 86), 258 (100), 216 (64), 77 (53)
3c	98	158–159	$C_{19}H_{14}N_3OF_3S$ 389.39	389 (M^+, 54), 371 (14), 320 (100), 77 (27)
3d	76	171–172	$C_{14}H_{12}N_3OF_3S$ 327.32	327 (M^+, 38), 258 (30), 216 (100), 77 (13)
3e	76	[c]	$C_{15}H_{14}N_3OF_3S$ 341.35	341 (M^+, 80), 272 (100), 230 (67), 77 (14)
3f	79	144–145	$C_{20}H_{16}N_3OF_3S$ 403.42	403 (M^+, 57), 334 (100), 292 (21), 77 (25)
3g	77	167–168	$C_{11}H_{12}N_3OF_3S$ 291.29	291 (M^+, 29), 222 (31), 180 (100), 140 (29)
3h	83	[c]	$C_{12}H_{14}N_3OF_3S$ 305.31	305 (M^+, 57), 236 (100), 194 (96), 140 (21)
3i	57	186–187	$C_{17}H_{16}N_3OF_3S$ 367.38	367 (M^+, 50), 298 (100), 256 (43), 77 (21)

[a] Yields of isolated compounds.
[b] The melting points are uncorrected.
[c] Highly hygroscopic compounds.

2-[3-Alky(phenyl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]-4-phenyl-5-alkylthiazoles and -4,5,6,7-tetrahydrobenzothiazoles (4a–i); General procedure

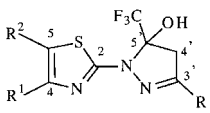
In a 50 mL flask a mixture of 2-[3-alkyl(phenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-4-phenyl-5-alkylthiazoles and -4,5,6,7-tetrahydrobenzothiazoles (**3a–i**) (3 mmol), H_2SO_4 (0.2 mL) and HOAc (20 mL) was magnetically stirred at reflux for 5 h. The mixture was poured slowly on ice–water (50 mL). Sat. aq Na_2CO_3 was added to the initial solution at r.t.. The resulting solution was extracted with $CHCl_3$ (3 × 20 mL). The combined organic fractions were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The solid products **4a–i** were recrystallized from EtOH or MeOH.

Table 2 Selected ^1H and ^{13}C MNR Spectral Data[a] of 2-[3-Alkyl-(phenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-4-phenyl-5-alkylthiazoles and -4,5,6,7-tetrahydrobenzothiazoles (**3a–i**)



Compd.	^1H NMR, δ, *J* (Hz). ^{13}C NMR, δ, *J* (Hz)
3a	7.98–7.76, 7.49–7.26 (m, 5 H, Ph), 7.53 (s, 1 H, H3′), 7.34 (s, 1 H, H5), 3.59 (d, 1H, $J_{H4a–H4b}$ = 19.2, H4′a), 3.29 (d, 1 H, $J_{H4b–H4a}$ = 19.2, H4′b). 163.6 (C2), 151.1 (C4), 145.3 (C3′), 134.7, 129.0, 128.2, 126.1 (6 C, Ph), 123.7 (q, $^1J_{C–F}$ = 284.6, CF_3), 107.1 (C5), 91.3 (q, $^2J_{C–F}$ = 33.3, C5′), 46.8 (C4′).
3b	7.98–7.90, 7.51–7.29 (m, 5 H, Ph and 1 H, OH and 1 H, H 5), 3.59 (d, 1 H, $JH_{4a–H4b}$ = 19.1, H4′a), 3.22 (d, 1 H, $JH_{4b–H4a}$ =19.1, H4′b), 2.07 (s, 3 H, CH_3′). 164.0 (C2), 163.3 (C3′), 139.6 (C4), 130.5, 129.3, 126.8, 126.1 (6 C, Ph), 122.5 (q, $^1J_{C–F}$ = 285.9, CF_3), 106.2 (C5), 93.9 (q, $^2J_{C–F}$ = 34.0, C5′), 46.3 (C4′), 16.0 (CH_3′).
3c	8.27 (s, 1 H, OH), 7.98–7.80, 7.52–7.28 (m, 10 H, 2 Ph), 7.55 (s, 1 H, H5), 4.04 (d, 1 H, $J_{H4a–H4b}$ = 19.0, H4′a), 3.74 (d, 1 H, $J_{H4b–H4a}$ = 19.0, H4′b). 163.1 (C2), 151.4 (C3′), 151.1 (C4), 134.5, 130.4, 130.2, 128.9, 128.6, 127.7, 126.4, 125.8 (12 C, 2 Ph), 123.3 (q, $^1J_{C–F}$ = 285.0, CF_3), 106.8 (C5), 92.9 (q, $^2J_{C–F}$ = 33.5, C5′), 45.0 (C4′).
3d	7.62–7.60, 7.41–7.27 (m, 5 H, Ph and s, 1 H, H3′), 3.50 (d, 1 H, $^1J_{H4a–H4b}$ = 9.5, H4′a), 3.27 (d, 1 H, $J_{H4b–H4a}$ = 19.5, H4′b), 2.39 (s, 3 H, CH_3′). 159.5 (C2), 145.4 (C4), 145.3 (C3′), 134.7, 128.4, 128.2, 127.5 (6 C, Ph), 123.5 (q, $^1J_{C–F}$ = 284.0, CF_3), 120.8 (C5), 91.0 (q, $^2J_{C–F}$ = 33.3, C5′), 46.3 (C4′), 12.2 (CH_3′).
3e	7.67–7.63, 7.48–7.34 (m, 5 H, Ph and 1 H, OH), 3.56 (d, 1 H, $J_{H4a–H4b}$ = 19.0, H4′a), 3.27 (d, 1 H, $J_{H4b–H4a}$ = 19.0, H4′b), 2.43 (s, 3 H, CH_3), 2.08 (s, 3 H, CH_3′). 159.7 (C2), 154.8 (C3′), 144.4 (C4), 134.1, 128.4, 128.3, 127.6 (6 C, Ph), 123.3 (q, $^1J_{C–F}$ = 285.2, CF_3), 120.0 (C5), 92.2 (q, $^2J_{C–F}$ = 33.2, C5′), 48.0 (C4′), 15.0 (CH_3), 12.0 (CH_3′).
3f	8.23 (s, 1 H, OH), 7.82–7.76, 7.48–7.29 (m, 10 H, 2 Ph), 4.00 (d, 1 H, $J_{H4a–H4b}$ = 18.8, H4′a), 3.74 (d, 1 H, $J_{H4b–H4a}$ = 18.8, H4′b), 2.50 (s, 3 H, CH_3′). 159.1 (C2), 151.0 (C3′), 146.1 (C4), 135.1, 130.3, 128.8, 128.2, 128.0, 127.1, 126.3 (12 C, 2 Ph), 123.3 (q, $^1J_{C–F}$ = 285.0, CF_3), 120.7 (C5), 92.8 (q, $^2J_{C–F}$ = 33.2, C5′), 44.8 (C4′), 12.1 (CH_3′).
3g	7.65 (s, 1 H, H3′), 3.57 (s, 1 H, H4′a), 3.54 (s, 1 H, H4′b), 2.54 (s, 4 H, 2 CH_2), 1.67 (s, 4 H, 2 CH_2). 165.6 (C2), 150.7 (C3′), 138.7 (C4), 123.2 (q, $^1J_{C–F}$ = 285.8, CF_3), 120.7 (C5), 91.3 (q, $^2J_{C–F}$ = 33.5, C5′), 45.0 (C4′), 24.1, 22.5, 22.4, 21.6 (4 CH_2).

Table 2 Selected ^{1}H and ^{13}C MNR Spectral Data[a] of 2-[3-Alkyl-(phenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-4-phenyl-5-alkylthiazoles and -4,5,6,7-tetrahydrobenzothiazoles (**3a**–**i**) (continued)



Compd.	^{1}H NMR, δ, *J* (Hz). ^{13}C NMR, δ, *J* (Hz)
3h	3.72 (d, 1 H, $J_{H4a–H4b}$ = 19.5, H4′a), 3.58 (d, 1 H, $J_{H4b–H4a}$ = 19.5, H4′b), 2.58 (s, 4 H, 2 CH_2), 2.17 (s, 3 H, CH_3′), 1.76 (s, 4 H, 2 CH_2). 161.1 (C2), 160.5 (C3′), 137.4 (C4), 123.2 (q, $^1J_{C–F}$ = 286.5, CF_3), 119.9 (C5), 92.6 (q, $^2J_{C–F}$ = 33.3, C5′), 46.5 (C4′), 23.7, 22.4, 22.3, 21.4 (4 CH_2), 15.8 (CH_3′).
3i	8.35 (s, 1 H, OH), 7.90–7.88, 7.52 (m, 5 H, Ph), 4.18 (d, 1 H, $J_{H4a–H4b}$ = 19.0, H4′a), 3.94 (d, 1 H, $J_{H4b–H4a}$ = 19.0, H4′b), 2.61 (s, 4 H, 2 CH_2), 1.75 (s, 4 H, 2 CH_2). 160.0 (C2), 156.0 (C3′), 139.1 (C4), 131.5, 129.2, 128.9, 127.2 (6 C, Ph), 123.0 (q, $^1J_{C–F}$ = 286.2, CF_3), 120.5 (C5), 93.1 (q, $^2J_{C–F}$ = 33.3, C5′), 43.0 (C4′), 24.2, 22.4, 22.3, 21.5 (4 CH_2).

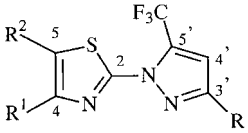
[a] The NMR spectra were recorded on a Bruker DPX-200 (^{1}H at 200.13 MHz and ^{13}C at 50.32MHz) in DMSO-d_6–TMS.

Table 3 Selected Physical and Mass Data of 2-[3-Alky(phenyl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]-4-phenyl-5-alkylthiazoles and -4,5,6,7-tetrahydrobenzothiazoles (**4a**–**i**)

Compd.	Yield (%)[a]	Mp (°C)[b]	Molecular Formula[c] (g/mol)	MS *m/z* (%)
4a	91	oil	$C_{13}H_8N_3F_3S$ 295.28	295 (M^+, 100), 250 (20), 134 (18), 77(5)
4b	75	98-99	$C_{14}H_{10}N_3F_3S$ 309.30	309 (M^+, 100), 240 (14), 134 (49), 77 (14)
4c	92	145–146	$C_{19}H_{12}N_3F_3S$ 371.37	371 (M^+, 100), 338 (76), 134 (83), 77 (24)
4d	89	100–101	$C_{14}H_{10}N_3F_3S$ 309.30	309 (M^+, 100), 250 (19), 147 (44), 77 (8)
4e	77	95–96	$C_{15}H_{12}N_3F_3S$ 323.33	323(M^+, 100), 290 (09), 147 (26), 77 (6)
4f	87	165–166	$C_{20}H_{14}N_3F_3S$ 385.40	385 (M^+, 100), 352 (7), 148 (27), 77 (16)
4g	82	oil	$C_{11}H_{10}N_3F_3S$ 273.27	273 (M^+, 100), 245 (82), 215 (14), 137 (20)
4h	87	75–76	$C_{12}H_{12}N_3F_3S$ 287.30	287(M^+, 100), 268 (7), 259 (47), 138 (17)
4i	81	106–107	$C_{17}H_{14}N_3F_3S$ 349.37	349 (M^+, 100), 320 (20), 288 (14), 138 (34)

[a] Yields of isolated compounds.
[b] The melting points are uncorrected.
[c] Satisfactory elemental analysis found: C, H, N ±0.45, except for: **4a** H ± 0.80, N ± 0.95; **4e** C ± 0.87; **4g** C ± 0.94, N ± 0.83.

Table 4 Selected ^{1}H and ^{13}C MNR Spectral Data[a] of 2-[3-Alky(phenyl)-5-trifluoromethyl-1H-pyrazol-1-yl]-4-phenyl-5-alkylthiazoles and -4,5,6,7-tetrahydrobenzothiazoles (**4a**–**i**)



Compd.	^{1}H NMR, δ, *J* (Hz). ^{13}C NMR, δ, *J* (Hz)
4a	7.93–7.89, 7.47–7.24 (m, 5 H, Ph), 7.72 (s, 1 H, H3′), 7.33 (s, 1 H, H5), 6.88 (s, 1 H, H4′). 158.7 (C2), 152.8 (C4), 141.0 (C3′), 133.7, 128.8, 128.4, 126.0 (6 C, Ph), 119.5 (q, $^1J_{C–F}$ = 269.0, CF_3), 132.1 (q, $^2J_{C–F}$ = 42.2, C5′), 111.7 (C4′) , 110.5 (C5).
4b	7.93–7.89, 7.46–7.24 (m, 5 H, Ph), 7.29 (s, 1 H, H5), 6.67 (s, 1 H, H4′), 2.36 (s, 3 H, CH_3′). 158.8 (C2), 152.6 (C4), 150.8 (C3′), 133.8, 128.7, 128.3, 126.0 (6 C, Ph), 132.4 (q, $^2J_{C–F}$ = 41.6, C5′), 122.2 (q, $^1J_{C–F}$ = 269.0, CF_3), 111.9 (C5), 109.9 (C4), 13.4 (CH_3′).
4c	7.92–7.81, 7.40–7.26 (m, 10 H, 2 Ph), 7.19 (s, 1 H, H5), 7.13 (s, 1 H, H4′). 158.8 (C2), 152.7 (C4), 152.6 (C3′), 133.8, 130.5, 129.4, 128.8, 128.7, 128.4, 126.0, 125.9 (12 C, 2 Ph), 133.0 (q, $^2J_{C–F}$ = 41.9, C5′), 119.4 (q, $^1J_{C–F}$ = 269.3, CF_3), 110.3 (C5), 109.1 (C4′).
4d	7.75–7.68, 7.48–7.34 (m, 5 H, Ph and s, 1 H, H3′), 6.84 (s, 1 H, H4′), 2.60 (s, 3 H, CH_3). 155.0 (C2). 148.4 (C4), 141.2 (C3′), 133.7, 128.8, 128.4, 126.0 (6 C, Ph), 132.4 (q, $^2J_{C–F}$ = 42.0, C5′), 127.3 (C5), 120.0 (q, $^1J_{C–F}$ = 269.0, CF_3), 111.8 (C4′), 13.1 (CH_3).
4e	7.67–7.62, 7.39–7.24 (m, 5 H, Ph), 6.55 (s, 1 H, H4′), 2.51 (s, 3 H, CH_3), 2.26 (s, 3 H, CH_3′). 154.6 (C2), 150.5 (C3′), 147.7 (C4), 134.6, 128.4, 128.2, 127.6 (6 C, Ph), 132.3 (q, $^2J_{C–F}$ = 41.6, C5′), 119.5 (q, $^1J_{C–F}$ = 268.5, CF_3), 126.4 (C5), 111.4 (C4′), 13.4 (CH_3′), 12.7 (CH_3).
4f	7.88–7.83, 7.77–7.72, 7.50–7.23 (m, 10 H, 2 Ph), 7.14 (s, 1 H, H4′), 2.61 (s, 3 H, CH_3). 154.7 (C2), 152.4 (C3′), 147.9 (C4), 134.6, 130.8, 129.2, 128.8, 128.4, 128.2, 127.6, 126,0 (12 C, 2 Ph), 133.0 (q, $^2J_{C–F}$ = 41.7, C5′), 119.4 (q, $^1J_{C–F}$ = 269.3, CF_3), 126.7 (C5), 108.7 (C4′), 12.8 (CH_3).
4g	7.54 (s, 1 H, H3′), 6.74 (s, 1 H, H4′), 2.68 (s, 4 H, 2 CH_2), 1.80 (s, 4 H, 2 CH_2). 155.5 (C2), 148.2 (C4), 140.5 (C3′), 132.0 (q, $^2J_{C–F}$ = 41.6, C5′), 119.4 (q, $^1J_{C–F}$ = 269.0, CF_3), 128.4 (C5), 110.9 (C4′), 26.7, 23.2, 23.0, 22.7 (4 CH_2).
4h	6.61 (s, 1 H, H4′), 2.74 (t, 4 H, 2 CH_2), 2.33 (s, 3 H, CH_3′), 1.87 (t, 4 H, 2 CH_2). 155.5 (C2), 150.3 (C3′), 148.0 (C4), 132.3 (q, $2J_{C–F}$ = 41.2, C5′), 119.4 (q, $1J_{C–F}$ = 269.1, CF_3), 127.7 (C5), 110.9 (C4′), 26.7, 23.2, 23.0, 22.7 (4 CH_2), 13.3 (CH_3′).
4i	7.87–7.82, 7.47–7.38 (m, 5 H, Ph), 7.11 (s, 1 H, H4′), 2.77 (s, 4 H, 2 CH_2), 1.88 (s, 4 H, 2 CH_2). 155.2 (C2), 151.8 (C3′), 147.8 (C4), 130.4, 128.8, 128.4, 125.9 (6 C, Ph), 132.5 (q, $^2J_{C–F}$ = 41.6, C5′), 118.9 (q, $^1J_{C–F}$ = 269.1, CF_3), 127.8 (C5), 107.8 (C4′), 26.7, 23.2, 23.0, 22.7 (4 CH_2).

[a] The NMR spectra were recorded on a Bruker DPX-200 (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz) in chloroform-d_1–TMS.

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References

(1) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II*, Vol. 3; Elsevier Science: NY, **1996**, .
(2) Lednicer, D.; Mitscher, L. A. *Organic Chemistry of Drugs Synthesis*, Vol. 1-3; Wiley Interscience: New York, **1977**.
(3) De Arriba, A. F.; Gómez-Casajús, L. A.; Cavalcanti, F.; Almansa, C.; García-Rafanell, J.; Forn, J. *Eur. J. Pharmacol.* **1996**, *318*, 341.
(4) De Arriba, A. F.; Gómez-Casajús, L. A.; Cavalcanti, F.; Almansa, C.; García-Rafanell, J.; Forn, J. *J. Med. Chem.* **1997**, *40*, 547.
(5) Harper, R. W.; Jackson, W. T.; Froelich, L. L.; Boyd, R. J.; Aldridge, T. E.; Herron, D. K. *J. Med. Chem.* **1994**, *37*, 2411.
(6) Ishii, S.; Yagi, K.; Umehara, T.; Kudo, M.; Nawamaki, T.; Watanabe, S. Jpn. Kokai Tokkyo Koho JP 02, 129, 171 **1990**; *Chem. Abstr*. **1990**, *113*, 172014a.
(7) Buntain, I. G.; Hatton, L. R.; Hawkins, D. W.; Pearson, C. J.; Roberts, D. A. Eur. Pat. Appl. EP 295 117, **1988**; *Chem. Abstr*. **1990**, *112*, 35845n.
(8) Nenajdenko, V. G.; Sanin, A. V.; Balenkova, E. S. *Molecules* **1997**, *2*, 186.
(9) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.
(10) Denisova, A. B.; Glukhareva, T. V.; Mokrushin, V. S.; Bakulev, V. A. *Chem. Heterocycl. Compd. (N. Y.)* **1999**, *35*, 123.
(11) Metzger, J. V. *Comp. Heterocycl. Chem.* **1984**, *6*, 294.
(12) Sing, S. P.; Kumar, D.; Kapoor, J. K. *J. Chem. Research (S)* **1993**, 163.
(13) Peet, N. P.; Sunder, S.; Barbuch, R. J.; Whalon, M. R. *J. Heterocycl. Chem.* **1988**, *25*, 543.
(14) Singh, S. P.; Kumar, D.; Jones, B. G.; Threadgill, M. D. *J. Fluorine Chem.* **1999**, *94*, 1999.
(15) Rezessy, B.; Zubovics, Z.; Kovács, J.; Tóth, G. *Tetrahedron* **1999**, *55*, 5909.
(16) Saloutina, L. V.; Zapevalov, A. Ya.; Kodess, M. I.; Saloutin, V. I.; Aleksandrov, G. G.; Chupakhin, O. N. *J. Fluorine Chem.* **2000**, *104*, 155.
(17) Martins, M. A. P.; Flores, A. F. C.; Freitag, R. A.; Zanatta, N. *J. Heterocycl. Chem.* **1995**, *32*, 731.
(18) Zoch, A. N.; Clar, G.; Zanatta, N.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **1995**, *32*, 739.
(19) Martins, M. A. P.; Flores, A. F. C.; Freitag, R.; Zanatta, N. *J. Heterocycl. Chem.* **1996**, *33*, 1223.
(20) Martins, M. A. P.; Siqueira, G. M.; Bastos, G. P.; Bonacorso, H. G.; Zanatta, N. *J. Heterocycl. Chem.* **1996**, *33*, 1619.
(21) Braibante, M. E. F.; Clar, G.; Martins, M. A. P. *J. Heterocycl. Chem.* **1993**, *30*, 1159.
(22) Martins, M. A. P.; Freitag, R.; Zanatta, N. *Synthesis* **1995**, 1491.
(23) Pacholski, I. L.; Blanco, I.; Zanatta, N.; Martins, M. A. P. *J. Braz. Chem. Soc.* **1991**, *2*, 118; *Chem. Abstr.* **1994**, *120*, 323443n.
(24) Madruga, C. C.; Clerici, E.; Martins, M. A. P.; Zanatta, N. *J. Heterocycl. Chem.* **1995**, *32*, 735.
(25) Zanatta, N.; Cortelini, M. F. M.; Carpes, M. J. S.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **1997**, *34*, 509.
(26) Bonacorso, H. G.; Bittencourt, S. R. T.; Wastowski, A. D.; Wentz, A. P.; Zanatta, N.; Martins, M. A. P. *Tetrahedron Lett.* **1996**, *37*, 9155.
(27) Bonacorso, H. G.; Bittencourt, S. R. T.; Lourega, R. V.; Flores, A. F. C.; Zanatta, N.; Martins, M. A. P. *Synthesis* **2000**, 1431.
(28) Bonacorso, H. G.; Oliveira, M. R.; Wentz, A. P.; Wastowski, A. D.; Oliveira, A. B.; Höerner, M.; Zanatta, N.; Martins, M. A. P. *Tetrahedron* **1999**, *55*, 345.
(29) Bonacorso, H. G.; Wastowski, A. D.; Zanatta, N.; Martins, M. A. P.; Naue, J. A. *J. Fluorine Chem.* **1998**, *92*, 23.