

New Substituted Thiazol-2-ylidene-benzamides and Their Reaction with 1-Aza-2-azoniaallene Salts. Synthesis and anti-HIV Activity

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A series of *N*-(3-(substituted-alkyl- or halophenyl)-4-methylthiazol-2(3*H*)-ylidene)-substituted alkyl- or halo-benzamides **21–40** were prepared by base-catalyzed cyclization of the corresponding 1-(substituted-alkyl- or halo-benzoyl)-3-(substituted-halophenyl)thioureas **1–20**. Substituted pyrazolo[4,3-*d*]thiazol-5(6*aH*)-ylidenebenzamides **45a–d** were synthesized by cycloaddition of compound **45** with the reactive cumulene intermediates **42a–d**. All compounds were evaluated for their antiviral activity against the replication of HIV-1 and HIV-2 in MT-4. Compounds **35** and **39** showed an IC₅₀ of 2.02 $\mu\text{g mL}^{-1}$ and 0.40 $\mu\text{g mL}^{-1}$ against the HIV-2 strain ROD with CC₅₀ of $\geq 104.00 \mu\text{g mL}^{-1}$ and $> 125.00 \mu\text{g mL}^{-1}$, respectively, resulting in a selectivity index of ≥ 52 and > 313 . Based on the chemical structure of compounds **35** and **39**, these molecules can be proposed to act as NNRTIs. However, it is exceptional to observe an antiretroviral activity that is limited to HIV-2.

Key words: Anti-HIV Activity, Benzamides, Thiazolidones, Pyrazoles

Introduction

Thiazoles and thiazolidones have attracted continuing interest over the years because of their varied biological activities [1–4]. Thiazole and thiazolidone units have been incorporated into a wide variety of therapeutically interesting candidates which then exhibited a number of biological activities, such as antibacterial [5–7], anti-HIV [8], antiinflammatory [9], antiprotozoal [10, 11], anticonvulsant [12], anticancer [13, 14], and renin inhibitor properties [15]. 2-Aminothiazole analogs were reported as potential neuroprotective agents [16] for treatment of neurological diseases and modulators of transcriptional repression for treatment of Huntington's disease [17]. Further, some derivatives of thiazoles exhibited remarkable activity against the herpes simplex virus (HSV) [18]. Amin *et al.* [19] reported new substituted coumarinyl thiazolines, coumarinyl thiazolidin-4-ones and substituted chromenothiazoles and evaluated these species for anticonvulsant activity. A brief review of thiazoles associated with a large number of biological activities was presented by Siddiqui *et al.* [20].

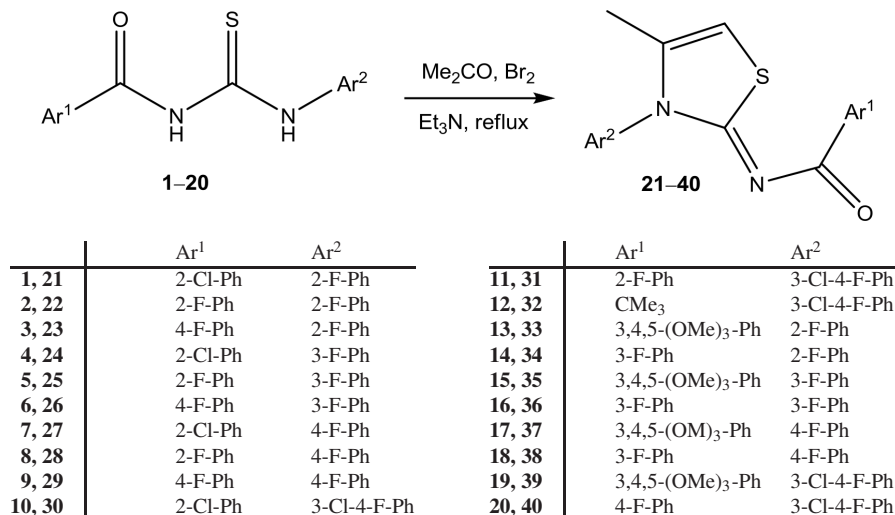
Pyrazoles and their derivatives have been reported to be potent agents for the treatment of different diseases [21,22]. Jochims *et al.* [23] have synthesized new pyrazole analogs *via* [2+3] cycloaddition reactions of olefins with the reactive intermediates 1-aza-2-azoniaallene salts (cumulene intermediates).

Prompted by the observed biological activities of the above mentioned derivatives and in continuation of our ongoing studies on *N*-(4-phenyl-3-aryylthiazol-2(3*H*)-ylidene)-substituted-benzamides [24], we report here the synthesis of some new fluoro-substituted benzamide analogs with evaluation of their anti-HIV activity as well as the synthesis of new substituted *N*-(pyrazolo[4,3-*d*]thiazol-5(6*aH*)-ylidene)benzamide derivatives.

Results and Discussion

Synthesis

Condensation of the 1-aryyl-3-arylthioureas **1–20** with α -haloketones in the presence of Et₃N for 1–2 h at r. t. afforded, after purification, the *N*-(3-(substituted-alkyl- or halophenyl)-4-methylthiazol-2(3*H*)-ylidene)-substituted alkyl- or halo-benzamides **21–40**



Scheme 1. Synthesis of *N*-(3-(substituted-alkyl- or halophenyl)-4-methylthiazol-2(3*H*)-ylidene)-substituted alkyl- or halo-benzamides.

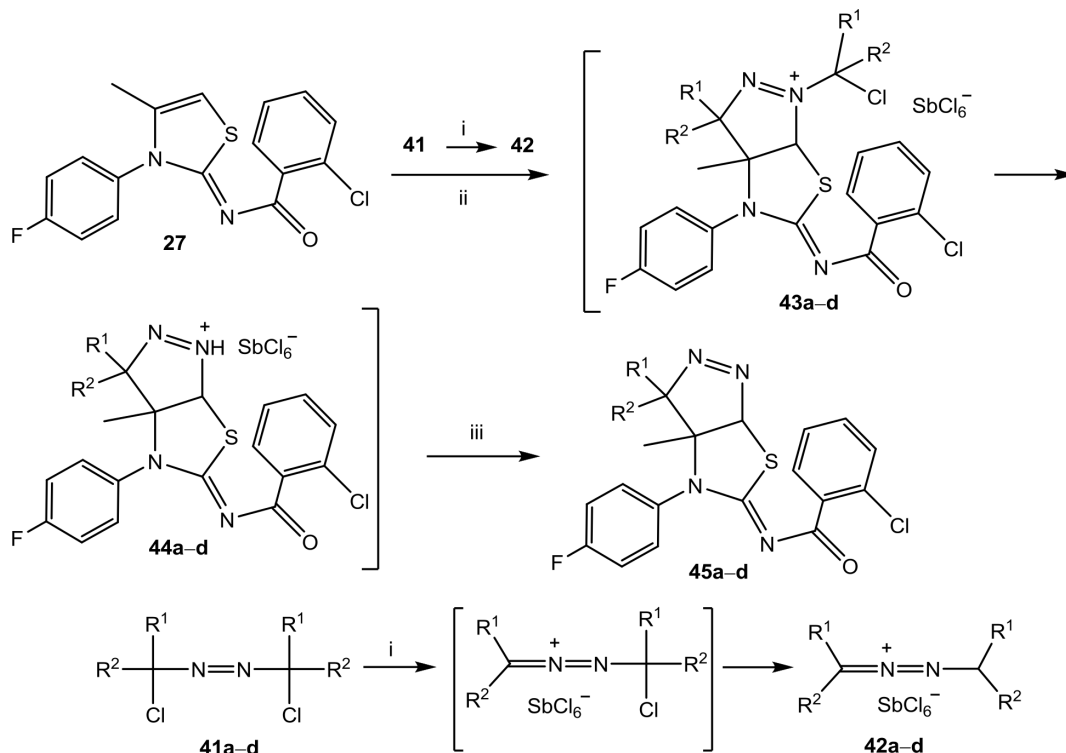
in 82–91 % yield. Compounds **1–20** were obtained according to the reported procedure [25] involving the preparation of the substituted benzoyl isothiocyanates from the reaction of halo-benzoyl chlorides, pivaloyl chloride or 3,4,5-trimethoxybenzoyl chloride with KSCN in anhydrous acetone and subsequent reaction with the respective halo-aniline (Scheme 1).

The structures of **21–40** were assigned on the basis of their ¹H and ¹³C NMR, IR and mass spectra. The ¹H NMR spectra of **21–40** showed similar patterns for the thiazole protons and carbon atoms. The IR spectra of **21–40** showed absorption bands in the region $\lambda_{\text{max}} = 1598\text{--}1664$ and $1443\text{--}1553\text{ cm}^{-1}$, attributed to the C=O and C=N groups. In the ¹H NMR spectra, the doublet in the region $\delta = 2.07\text{--}2.16$ ppm ($J = 0.9\text{--}1.2$ Hz) was assigned to the methyl group at C-4, while the quartet in the region $\delta = 6.34\text{--}6.46$ ppm was assigned to 5-H of the thiazole backbone. The ¹³C NMR spectra of **21–40** contained similar resonance signals for the thiazole carbon atoms. The signals between $\delta_{\text{C}} = 175.1$ and 173.4 ppm was assigned to the carbonyl carbon atoms, while the resonance in the range of $\delta_{\text{C}} = 163.7\text{--}165.2$ ppm was assigned to C-2 (C=N). C-4 displayed a signal in the region $\delta_{\text{C}} = 151.2\text{--}149.3$ ppm. A signal between $\delta_{\text{C}} = 104.4$ and 105.1 ppm was assigned to the olefinic carbon C-5, whereas the methyl carbon at C-4 was found in the region $\delta_{\text{C}} = 14.3\text{--}15.1$ ppm. Compound **21** was selected for further NMR studies. From the gradient-selected HMBC [26] spectrum of **21**, 5-H of the thiazole back-

bone at $\delta_{\text{H}} = 6.43$ ppm showed a ²*J*_{C,H} coupling with C-2 at $\delta_{\text{C}} = 105.0$ ppm, in addition to a ³*J*_{C,H} coupling with C-2 (C=N) at $\delta_{\text{C}} = 165.8$ ppm.

Next, we have selected the most potential anti-HIV-2 candidate, 2-chloro-*N*-(3-(4-fluorophenyl)-4-methylthiazol-2(3*H*)-ylidene)benzamide (**27**), for a [2+3]-cycloaddition reaction with some reactive cumulenes. Thus, the intermediates **42**, obtained from the α,α' -dichloroazo compounds **41** [23], were treated with **27** in the presence of SbCl₅ at -60 °C. At approximately -30 °C, the color changed from orange to brown, indicating that cumulenes **42a–d** underwent cycloaddition reactions with olefin **27** to give salts, presumably 1,2-pyrazolium hexachloroantimonates **43a–d**, which could not be isolated. After increasing the temperature to 23 °C, the CR₂Cl group at N-1' was eliminated, leading to the protonated salts **44a–d**. *In situ* deprotonation of salts **44a–d** with aqueous NaHCO₃ and NH₃ solution gave the desired products **45a–d** in 52–67 % yield (Scheme 2). The proposed regiochemistry of **45a–d** is plausible.

Compounds **45a–d** were identified by their ¹H and ¹³C NMR spectra. The singlet at lower field ($\delta_{\text{H}} = 1.38\text{--}1.43$ ppm) was attributed to the methyl proton at C-3a, while the singlet of 6a-H appeared at $\delta_{\text{H}} = 3.12\text{--}3.18$ ppm). In the ¹³C NMR spectra of **45a–d**, the C=N signals appeared at higher field ($\delta = 183.3$, 183.6 , 183.9 or 183.7 ppm, respectively), while the resonances at $\delta = 173.9$, 173.9 , 173.8 or 174.1 ppm were assigned to C=O, respectively. The C-3a carbons ap-



Scheme 2. Reagents and conditions: (i) SbCl_5 , CH_2Cl_2 , -60°C ; (ii) CH_2Cl_2 , -60°C to 23°C ; (iii) NaHCO_3 , NH_3 , MeCN , 0°C , 2 h. **41**–**45**: **a** $\text{R}^1 = \text{R}^2 = \text{Me}$; **b** $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Et}$; **c** $\text{R}^1 = \text{Et}$, $\text{R}^2 = \text{Et}$; **d** $\text{R}^1 = \text{Me}$, $\text{R}^2 = i\text{-Pr}$.

peared at $\delta = 87.7$, 87.3 , 87.0 or 75.8 ppm, respectively, and C-6a resonated at $\delta_{\text{C}} = 70.1$, 69.8 , 69.9 or 69.6 ppm, respectively. C-3 and C3a-Me carbons resonated at $\delta_{\text{C}} = 62.3$ – 74.2 ppm and $\delta_{\text{C}} = 11.0$ – 11.7 ppm, respectively.

Compound **45a** was selected for homo- and heteronuclear NMR studies. The gradient-selected HMBC [26] spectrum allowed *via* $^2J_{\text{C,H}}$ and $^3J_{\text{C,H}}$ couplings the assignment of most of the carbon atoms. C-3 and $\text{C}^5=\text{N}$ ($\delta_{\text{C}} = 62.3$ and 183.3 ppm) were identified from their $^3J_{\text{C,H}}$ correlations to 6a-H at $\delta_{\text{H}} = 3.18$ ppm, respectively, and C-3a' ($\delta_{\text{C}} = 87.7$ ppm) was identified from its $^2J_{\text{C,H}}$ correlation to 6a-H at $\delta_{\text{H}} = 3.18$ ppm. The mass spectrum of **45a**, (FAB) exhibited the correct molecular ion ($417/419$ $[\text{M}+\text{H}]^+$).

In-vitro anti-HIV assay

Compounds **21**–**40** and **45a–d** were evaluated for their *in-vitro* anti-HIV activity using HIV-1 (strain III_B) for HIV-1 and HIV-2 (strain ROD) in cells of human T-lymphocyte cell line (MT-4). The re-

sults are summarized in Table 1, in which the data for nevirapine (BOE/BIRG587) [27], azidothymidine (AZT) [28], dideoxycytidine (DCC) [29] and didanosine [30] were included for comparison purposes. Compound-induced cytotoxicity was also measured in MT-4 cells parallel with the antiviral activity.

Compounds **35** and **39** were found to be the only compounds from the series inhibiting HIV-2 replication in a cell culture, which showed an IC_{50} of $2.02 \mu\text{g mL}^{-1}$ and $0.40 \mu\text{g mL}^{-1}$ with CC_{50} of $\geq 104.0 \mu\text{g mL}^{-1}$ and $> 125.00 \mu\text{g mL}^{-1}$, respectively, resulting in a selectivity index of ≥ 52 and > 313 .

Based on the chemical structure of compounds **35** and **39**, these molecules can be proposed to act as NNRTIs. However, the activity spectrum that is limited to HIV-2 is completely in contrast with what was observed with NNRTIs. On the other hand, **27** showed some activity against HIV-1 (III_B strain) with $\text{IC}_{50} \geq 12.70 \mu\text{g mL}^{-1}$ and a $\text{CC}_{50} = 70.13 \mu\text{g mL}^{-1}$, but with a low selectivity ($\text{SI} \leq 6$).

In conclusion, the above data suggest that substitution of the aromatic ring of a phenyl-4-methylthiazol-

Table 1. *In-vitro* anti-HIV-1 and HIV-2 activity and cytotoxicity of compounds **21–40**.

Compound	HIV-1 (III _B) IC ₅₀ (μg mL ⁻¹) ^{a,c}	HIV-2 (ROD) IC ₅₀ (μg mL ⁻¹) ^{a,c}	CC ₅₀ (μg mL ⁻¹) ^{b,c}	SI (III _B) ^d	SI (ROD) ^d
21	> 55.65	> 55.65	55.65 ± 11.21	< 1	< 1
22	> 49.70	> 49.70	49.70 ± 10.60	< 1	< 1
23	≥ 17.20	> 17.20	17.20 ± 3.53	< 1	< 1
24	> 68.80	> 68.80	≥ 68.80	< 1	< 1
25	> 125	> 125	> 125	–	–
26	> 125	> 125	> 125	–	–
27	≥ 12.70	> 70.13	70.13 ± 7.00	≤ 6	< 1
28	> 125	> 125	> 125	–	–
29	> 125	> 125	> 125	–	–
30	> 17.63	> 17.63	17.63 ± 0.89	< 1	< 1
31	> 125	> 125	> 125	–	–
32	> 12.45	> 12.45	12.45 ± 0.73	< 1	< 1
33	> 15.23	> 15.23	15.23 ± 2.69	< 1	< 1
34	> 19.73	> 19.73	19.73 ± 8.18	< 1	< 1
35	> 104.00	2.02 ± 0.25	≥ 104.00	–	≥ 52
36	> 125	> 125	> 125	–	–
37	> 108.30	> 108.30	108.30 ± 14.39	< 1	< 1
38	> 125	> 125	> 125	–	–
39	> 125	0.40 ± 0.03	> 125	–	> 313
40	> 23.00	> 23.00	≥ 23.00	< 1	< 1
45a	> 3.34	> 3.34	≥ 3.34	< 1	< 1
45b	> 12.10	> 12.10	≥ 12.10	< 1	< 1
45c	> 6.72	> 6.72	≥ 6.72	< 1	< 1
45d	> 62.53	> 62.53	≥ 62.53	< 1	< 1
nevirapine	0.050 ± 0.011	> 4	> 4	> 80	–
AZT	0.0022 ± 0.0011	0.0009 ± 0.0005	> 25	> 11587	> 26731
ddC	0.16 ± 0.12	0.19 ± 0.11	> 20	> 127	> 108
ddI	2.09 ± 0.68	3.78 ± 1.22	> 50	> 24	> 13

^a IC₅₀: concentration of compound required to achieve 50 % protection of MT-4 cells from HIV-induced cytopathogenicity, as determined by the MTT method; ^b CC₅₀: concentration of compound that reduces the viability of mock-infected cells by 50 %, as determined by the MTT method; ^c all data represent mean values ± standard deviations for at least two separate experiments; ^d SI: selectivity index.

2(3H)-ylidene)-3,4,5-trimethoxybenzamide backbone by a *meta* halogen atom (fluorine or chlorine) may engender an inhibitory activity on HIV-2 replication that is most exceptional.

Experimental Section

General. Melting points are uncorrected and were measured on a digital Gallenkamp (SANYO) model MPD BM 3.5 apparatus. NMR spectra were recorded on 300 MHz (¹H) and 150.91 MHz (¹³C) spectrometers (Bruker AM-300, Germany) with TMS as internal standard and on the δ scale in ppm. Signal assignments for protons were identified by selective proton decoupling or by COSY spectra. Heteronuclear assignments were verified by ¹H-¹³C COSY, or HMQC experiments. FT IR spectra were recorded on a FTS 3000 MX spectrophotometer. Mass spectra (EI, 70 eV) were obtained on a GC-MS instrument (Agilent-technologies), using nitrobenzyl alcohol (NBOH) or glycerol as matrices. All compounds were purified by thick-layer chromatography using silica gel from Merck.

Synthesis of N-(3-(substituted-alkyl- or halophenyl)-4-methylthiazol-2(3H)-ylidene)-substituted alkyl- or halo-benzamides (21–40)

To a stirred solution of 1-aryl-3-arylthioureas **1–20** (1.0 mmol) in dry acetone (20 mL) was added Et₃N (1.0 mmol), followed by a dropwise addition of a bromine solution (1.0 mmol) in acetone (10 mL) under nitrogen. The reaction mixture was stirred for 1–2 h, and the progress of the reaction was monitored by TLC (hexane: ethyl acetate 4 : 1). After the reaction was completed, the mixture was filtered, and the filtrate was evaporated to dryness to give the desired products, which were purified by recrystallization from EtOH.

2-Chloro-N-(3-(2-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)benzamide (21)

From 1-(2-chlorobenzoyl)-3-(2-fluorophenyl)thiourea (**1**) (308 mg). Yield: 291 mg (88 %), m. p. 133 °C. – IR (cm⁻¹): ν = 1606 (C=O), 1458 (C=N). – ¹H NMR (CDCl₃): δ = 7.81 (dd, 1H, *J* = 1.8, 7.7 Hz, Ar-H); 7.55–7.16 (m, 7H,

Ar-H); 6.43 (q, 1H, $J = 1.2$ Hz, CH=C); 2.12 (d, 3H, $J = 1.2$ Hz, CH₃). – ¹³C NMR (CDCl₃): $\delta = 174.1$ (C=O); 170.2 (C=N); 157.6 (d, ¹ $J_{C,F} = 251$ Hz); 136.0, 134.3, 133.6, 131.5 (d, ³ $J_{C,F} = 8.3$ Hz); 131.2, 131.0, 130.7, 126.3, 125.1, 124.8 (d, ³ $J_{C,F} = 12.8$ Hz), 124.6 (d, ⁴ $J_{C,F} = 3.8$ Hz), 116.8 (d, ² $J_{C,F} = 19.5$ Hz), 104.6 (CH=C), 14.32 (CH₃). – MS (FAB): $m/z = 346/348$ [M+H]⁺. – C₁₇H₁₂ClFN₂OS: calcd. C 58.87, H 3.49, N 8.08; found C 58.57, H 3.37, N 7.40.

2-Fluoro-N-(3-(2-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)benzamide (22)

From 1-(2-fluorobenzoyl)-3-(2-fluorophenyl)thiourea (**2**) (292 mg). Yield: 300 mg (91 %), m. p. 165 °C. – IR (cm⁻¹): $\nu = 608$ (C=O), 1443 (C=N). – ¹H NMR (CDCl₃): $\delta = 77.88$ (dt, 1H, $J = 1.8, 7.8$ Hz, Ar-H); 7.55–7.02 (m, 7H, Ar-H); 6.43 (q, 1H, $J = 1.2$ Hz, CH=C); 2.16 (d, 3H, $J = 1.2$ Hz, CH₃). – ¹³C NMR (CDCl₃): $\delta = 173.4$ (C=O); 169.7 (C=N); 162.3 (d, ¹ $J_{C,F} = 257$ Hz); 157.6 (d, ¹ $J_{C,F} = 251$ Hz); 134.0, 132.6 (d, ³ $J_{C,F} = 8.3$ Hz); 132.1 (d, ⁴ $J_{C,F} = 0.8$ Hz); 131.2 (d, ³ $J_{C,F} = 8.8$ Hz); 130.3, 125.1 (d, ³ $J_{C,F} = 7.5$ Hz); 124.7 (d, ⁴ $J_{C,F} = 3.8$ Hz); 123.4 (d, ⁴ $J_{C,F} = 3.8$ Hz); 116.8 (d, ² $J_{C,F} = 19.5$ Hz); 116.7 (d, ² $J_{C,F} = 22.5$ Hz); 104.4 (CH=C); 14.3 (CH₃). – MS (FAB): $m/z = 330/332$ [M+H]⁺. – C₁₇H₁₂F₂N₂OS: calcd. C 61.81, H 3.66, N 8.48; found C 61.60, H 3.61, N 8.25.

4-Fluoro-N-(3-(2-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)benzamide (23)

From 1-(4-fluorobenzoyl)-3-(2-fluorophenyl)thiourea (**3**) (292 mg). Yield: 270 mg (82 %), m. p. 175 °C. – IR (cm⁻¹): $\nu = 602$ (C=O), 1455 (C=N). – ¹H NMR (CDCl₃): $\delta = 8.07$ –6.95 (m, 8H, Ar-H); 6.43 (q, 1H, $J = 1.2$ Hz, CH=C); 2.12 (d, 3H, $J = 1.2$ Hz, CH₃). – ¹³C NMR (CDCl₃): $\delta = 173.4$ (C=O); 170.0 (C=N); 165.1 (d, ¹ $J_{C,F} = 250$ Hz); 157.5 (d, ¹ $J_{C,F} = 251$ Hz); 134.1, 133.0 (d, ⁴ $J_{C,F} = 3.0$ Hz); 131.7, 131.1 (d, 2C, ³ $J_{C,F} = 8.3$ Hz); 130.2, 124.9 (d, ⁴ $J_{C,F} = 3$ Hz); 124.8 (d, ³ $J_{C,F} = 6.75$ Hz); 116.9 (d, ² $J_{C,F} = 19.5$ Hz); 114.8 (d, 2C, ² $J_{C,F} = 21.8$ Hz); 104.5 (CH=C); 14.30 (CH₃). – MS (FAB): $m/z = 330/332$ [M+H]⁺. – C₁₇H₁₂F₂N₂OS: calcd. C 61.81, H 3.66, N 8.48; found C 61.60, H 3.60, N 8.27.

2-Chloro-N-(3-(3-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)benzamide (24)

From 1-(2-chlorobenzoyl)-3-(3-fluorophenyl)thiourea (**4**) (308 mg). Yield: 315 mg (91 %), m. p. 186 °C. – IR (cm⁻¹): $\nu = 600$ (C=O), 1461 (C=N). – ¹H NMR (CDCl₃): $\delta = 7.82$ (dd, 1H, $J = 1.8, 7.7$ Hz, Ar-H); 7.57 (q, 1H, $J = 8.1$ Hz, Ar-H); 7.34–7.12 (m, 6H, Ar-H); 6.42 (q, 1H, $J = 1.2$ Hz, CH=C); 2.16 (d, 3H, $J = 1.2$ Hz, CH₃). – ¹³C NMR (CDCl₃): $\delta = 172.3$ (C=O); 169.3 (C=N); 162.7 (d, ¹ $J_{C,F} = 247$ Hz); 138.4 (d, ³ $J_{C,F} = 9.75$ Hz); 135.9, 134.4, 133.6, 131.8, 131.2,

130.9, 130.6 (d, ³ $J_{C,F} = 9.0$ Hz), 126.2, 123.9 (d, ⁴ $J_{C,F} = 3.5$ Hz); 116.5 (d, ² $J_{C,F} = 21$ Hz); 115.9 (d, ² $J_{C,F} = 22.5$ Hz); 105.0 (CH=C); 14.93 (CH₃). – MS (FAB): $m/z = 346/348$ [M]⁺. – C₁₇H₁₂ClFN₂OS: calcd. C 58.87, H 3.49, N 8.08; found C 58.61, H 3.41, N 7.37.

2-Fluoro-N-(3-(3-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)benzamide (25)

From 1-(2-fluorobenzoyl)-3-(3-fluorophenyl)thiourea (**5**) (292 mg). Yield: 294 mg (89 %), m. p. 117 °C. – IR (cm⁻¹): $\nu = 600$ (C=O), 1461 (C=N). – ¹H NMR (CDCl₃): $\delta = 7.87$ (dt, 1H, $J = 1.8, 7.8$ Hz, Ar-H); 7.60–7.01 (m, 7H, Ar-H); 6.43 (q, 1H, $J = 1.2$ Hz, CH=C); 2.10 (d, 3H, $J = 1.2$ Hz, CH₃). – ¹³C NMR (CDCl₃): $\delta = 172.4$ (d, $J = 3.3$ Hz, C=O); 169.9 (C=N); 162.8 (d, ¹ $J_{C,F} = 247$ Hz); 162.3 (d, ¹ $J_{C,F} = 251$ Hz); 138.4 (d, ³ $J_{C,F} = 9.8$ Hz); 133.9, 132.7 (d, ³ $J_{C,F} = 8.3$ Hz); 132.2 (d, ⁴ $J_{C,F} = 0.8$ Hz); 130.7 (d, ³ $J_{C,F} = 9.0$ Hz); 125.2 (d, ³ $J_{C,F} = 7.8$ Hz); 123.9 (d, ⁴ $J_{C,F} = 4.5$ Hz); 123.4 (d, ² $J_{C,F} = 18.8$ Hz); 116.7 (d, ² $J_{C,F} = 22.5$ Hz); 116.3 (d, ² $J_{C,F} = 21$ Hz); 115.9 (d, ² $J_{C,F} = 23.3$ Hz); 105.1 (CH=C); 14.59 (CH₃). – MS (FAB): $m/z = 330/332$ [M+H]⁺. – C₁₇H₁₂F₂N₂OS: calcd. C 61.81, H 3.66, N 8.48; found C 61.60, H 3.60, N 8.27.

4-Fluoro-N-(3-(3-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)benzamide (26)

From 1-(4-fluorobenzoyl)-3-(3-fluorophenyl)thiourea (**6**) (292 mg). Yield: 277 mg (84 %), m. p. 146 °C. – IR (cm⁻¹): $\nu = 606$ (C=O), 1473 (C=N). – ¹H NMR (CDCl₃): $\delta = 8.08$ –8.05 (m, 2H, Ar-H); 7.57 (q, 1H, $J = 8.1$ Hz, Ar-H); 7.30–7.24 (m, 2H, Ar-H); 7.17 (q, 1H, $J = 8.1$ Hz, Ar-H); 7.06–6.96 (m, 2H, Ar-H); 6.44 (q, 1H, $J = 1.2$ Hz, CH=C); 2.14 (d, 3H, $J = 1.2$ Hz, CH₃). – ¹³C NMR (CDCl₃): $\delta = 170.4$ (C=O); 169.9 (C=N); 164.9 (d, ¹ $J_{C,F} = 250$ Hz); 162.7 (d, ¹ $J_{C,F} = 247$ Hz); 138.4 (d, 1C, ³ $J_{C,F} = 9.8$ Hz); 133.9, 133.0 (d, 2C, ³ $J_{C,F} = 8.0$ Hz); 131.6, 130.3 (d, ³ $J_{C,F} = 9.0$ Hz); 124.0 (d, ⁴ $J_{C,F} = 4.5$ Hz); 116.6 (d, ² $J_{C,F} = 21.0$ Hz); 115.9 (d, ² $J_{C,F} = 23.3$ Hz); 114.8 (d, 2C, ² $J_{C,F} = 21.3$ Hz); 105.1 (CH=C); 14.8 (CH₃). – MS (FAB): $m/z = 330/332$ [M+H]⁺. – C₁₇H₁₂F₂N₂OS: calcd. C 61.81, H 3.66, N 8.48; found C 61.60, H 3.60, N 8.27.

2-Chloro-N-(3-(4-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)benzamide (27)

From 1-(2-chlorobenzoyl)-3-(4-fluorophenyl)thiourea (**7**) (308 mg). Yield: 291 mg (84 %), m. p. 179 °C. – IR (cm⁻¹): $\nu = 599$ (C=O), 1554 (C=N). – ¹H NMR (CDCl₃): $\delta = 7.81$ (dd, $J = 2.1, 7.7$ Hz, Ar-H); 7.36–7.15 (m, 7H, Ar-H); 6.44 (q, 1H, $J = 1.2$ Hz, CH=C); 2.06 (d, 3H, $J = 1.2$ Hz, CH₃). – ¹³C NMR (CDCl₃): $\delta = 174.0$ (C=O); 170.2 (C=N); 162.6 (d, ¹ $J_{C,F} = 248$ Hz); 136.0, 134.4, 133.5, 126.2,

133.1 (d, $^4J_{\text{C,F}} = 3$ Hz); 131.8, 131.0, 130.8, 129.9 (d, 2C, $^3J_{\text{C,F}} = 8.3$ Hz); 126.2, 116.6 (d, 2C, $^2J_{\text{C,F}} = 22.5$ Hz); 104.9 (CH=C); 15.0 (CH₃). – MS (FAB): $m/z = 346/348$ [M]⁺. – C₁₇H₁₂ClF₂N₂OS: calcd. C 58.87, H 3.49, N 8.08; found C 58.59, H 3.38, N 7.34.

2-Fluoro-N-(3-(4-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)benzamide (28)

From 1-(2-fluorobenzoyl)-3-(4-fluorophenyl)thiourea (**8**) (292 mg). Yield: 297 mg (87 %), m. p. 103 °C. – IR (cm⁻¹): $\nu = 605$ (C=O), 1461 (C=N). – ¹H NMR (CDCl₃): $\delta = 7.89$ –7.01 (m, 8H, Ar-H); 6.43 (q, 1H, $J = 0.9$ Hz, CH=C); 2.09 (d, 3H, $J = 0.9$ Hz, CH₃). – ¹³C NMR (CDCl₃): $\delta = 172.4$ (d, $J = 3.0$ Hz, C=O); 170.1 (C=N); 162.6 (d, $^1J_{\text{C,F}} = 248$ Hz); 162.3 (d, $^1J_{\text{C,F}} = 257$ Hz); 134.2, 133.1 (d, $^4J_{\text{C,F}} = 3.0$ Hz); 132.7 (d, $^3J_{\text{C,F}} = 9.0$ Hz); 132.1 (d, $^4J_{\text{C,F}} = 0.8$ Hz); 129.9 (d, 2C, $^3J_{\text{C,F}} = 9.0$ Hz); 125.2 (d, $^3J_{\text{C,F}} = 8.3$ Hz); 123.4 (d, $^4J_{\text{C,F}} = 3.8$ Hz); 116.7 (d, $^2J_{\text{C,F}} = 22.5$ Hz); 116.6 (d, 2C, $^2J_{\text{C,F}} = 22.5$ Hz); 104.9 (CH=C); 15.0 (CH₃). – MS (FAB): $m/z = 330/332$ [M+H]⁺. – C₁₇H₁₂F₂N₂OS: calcd. C 61.81, H 3.66, N 8.48; found C 61.63, H 3.55, N 8.19.

4-Fluoro-N-(3-(4-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)benzamide (29)

From 1-(4-fluorobenzoyl)-3-(4-fluorophenyl)thiourea (**9**) (292 mg). Yield: 300 mg (91 %), m. p. 184 °C. – IR (cm⁻¹): $\nu = 602$ (C=O), 1450 (C=N). – ¹H NMR (CDCl₃): $\delta = 8.07$ –7.35 (m, 4H, Ar-H); 7.28 (dt, 2H, $J = 2.1$, 7.8 Hz, Ar-H); 7.02–6.95 (m, 2H, Ar-H); 6.42 (q, 1H, $J = 1.2$ Hz, CH=C); 2.07 (d, 3H, $J = 1.2$ Hz, CH₃). – ¹³C NMR (CDCl₃): $\delta = 173.8$ (C=O); 169.9 (C=N); 164.9 (d, $^1J_{\text{C,F}} = 250$ Hz); 162.6 (d, $^1J_{\text{C,F}} = 248$ Hz); 134.1, 133.4 (d, $^4J_{\text{C,F}} = 3$ Hz); 133.0 (d, 2C, $^3J_{\text{C,F}} = 8.0$ Hz); 131.6, 130.2 (d, 2C, $^3J_{\text{C,F}} = 8.3$ Hz); 116.3 (d, 2C, $^2J_{\text{C,F}} = 23$ Hz); 114.9 (d, 2C, $^2J_{\text{C,F}} = 21.75$ Hz); 104.4 (CH=C); 15.0 (CH₃). – MS (FAB): $m/z = 330/332$ [M+H]⁺. – C₁₇H₁₂F₂N₂OS: calcd. C 61.81, H 3.66, N 8.48; found C 61.58, H 3.60, N 8.30.

3-Chloro-N-(3-(3-chlorophenyl)-4-methylthiazol-2(3H)-ylidene)-4-fluorobenzamide (30)

From 1-(3-chloro-4-fluorophenyl)-3-(2-chlorobenzoyl)thiourea (**10**) (343 mg). Yield: 285 mg (83 %), m. p. 174 °C. – IR (cm⁻¹): $\nu = 660$ (C=O), 1553 (C=N). – ¹H NMR (CDCl₃): $\delta = 7.82$ (dd, 1H, $J = 2.1$, 7.7 Hz, Ar-H); 7.39–7.19 (m, 6H, Ar-H); 6.45 (q, 1H, $J = 0.9$ Hz, CH=C); 2.11 (d, 3H, $J = 0.9$ Hz, CH₃). – ¹³C NMR (CDCl₃): $\delta = 174.1$ (C=O); 170.2 (C=N); 158.3 (d, $^1J_{\text{C,F}} = 251$ Hz); 135.9, 134.2, 133.5, 133.4 (d, $^4J_{\text{C,F}} = 3.0$ Hz); 131.8, 130.7, 130.6, 128.2 (d, $^3J_{\text{C,F}} = 7.5$ Hz); 126.3, 122.1 (d, $^2J_{\text{C,F}} = 19.5$ Hz); 121.8, 117.4 (d, $^2J_{\text{C,F}} = 22.5$ Hz); 105.2 (CH=C); 15.0 (CH₃). – MS (FAB): $m/z = 381/383$ [M+H]⁺. –

C₁₇H₁₁ClCl₂N₂OS: calcd. C 53.56, H 2.91, N 7.35; found C 53.29, H 2.85, N 7.12.

N-(3-(3-Chloro-4-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)-2-fluorobenzamide (31)

From 1-(3-chloro-4-fluorophenyl)-3-(2-fluorobenzoyl)thiourea (**11**) (326 mg). Yield: 305 mg (78 %), m. p. 187 °C. – IR (cm⁻¹): $\nu = 618$ (C=O), 1521 (C=N). – ¹H NMR (CDCl₃): $\delta = 77.88$ (dt, 1H, $J = 1.8$, 7.8 Hz, Ar-H); 7.46 (dd, 1H, $J = 2.4$, 6.3 Hz, Ar-H); 7.42–7.02 (m, 5H, Ar-H); 6.43 (q, 1H, $J = 1.2$ Hz, CH=C); 2.10 (d, 3H, $J_{\text{C,F}} = 1.2$ Hz, CH₃). – ¹³C NMR (CDCl₃): $\delta = 172.4$ (d, $J = 3.0$ Hz, C=O); 170.1 (C=N); 162.3 (d, $^1J_{\text{C,F}} = 256$ Hz); 158.3 (d, $^1J_{\text{C,F}} = 255$ Hz); 133.8, 133.4 (d, $^4J_{\text{C,F}} = 3.75$ Hz); 132.8 (d, $^3J_{\text{C,F}} = 9.0$ Hz); 132.1, 130.5, 128.2 (d, $^3J_{\text{C,F}} = 7.5$ Hz); 125.0 (d, $^3J_{\text{C,F}} = 7.5$ Hz); 123.5 (d, $^4J_{\text{C,F}} = 4.5$ Hz); 122.1 (d, $^2J_{\text{C,F}} = 18.8$ Hz); 117.4 (d, $^2J_{\text{C,F}} = 22.5$ Hz); 116.7 (d, $^2J_{\text{C,F}} = 22.5$ Hz); 104.6 (CH=C); 15.02 (CH₃). – MS (FAB): $m/z = 364/366$ [M+H]⁺. – C₁₇H₁₁ClF₂N₂OS: calcd. C 53.56, H 2.91, N 7.35; found C 53.29, H 2.85, N 7.12.

N-(3-(3-Chloro-4-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)pivalamide (32)

From 1-(3-Chloro-4-fluorophenyl)-3-pivaloylthiourea (**12**) (289 mg). Yield: 265 mg (81 %), m. p. 124 °C. – IR (cm⁻¹): $\nu = 609$ (C=O), 1502 (C=N). – ¹H NMR (CDCl₃): $\delta = 7.41$ –7.28 (m, 2H, Ar-H); 7.21 (s, 1H, Ar-H); 6.34 (s, 1H, CH=C); 2.08 (s, 3H, CH₃); 1.11 (s, 9H, CMe₃). – ¹³C NMR (CDCl₃): $\delta = 174.6$ (C=O); 169.0 (C=N); 158.1 (d, $^1J_{\text{C,F}} = 251$ Hz); 128.2 (d, $^3J_{\text{C,F}} = 7.5$ Hz); 121.7 (d, $^2J_{\text{C,F}} = 18.5$ Hz); 117.1 (d, $^2J_{\text{C,F}} = 22.5$ Hz); 104.3 (CH=C); 40.7, 27.5 (CMe₃); 15.1 (CH₃). – MS (FAB): $m/z = 326/328$ [M+H]⁺. – C₁₅H₁₆ClF₂N₂OS: calcd. C 55.13, H 4.93, N 8.57; found C 54.89, H 4.82, N 8.32.

N-(3-(2-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)-3,4,5-trimethoxybenzamide (33)

From 1-(2-fluorobenzoyl)-3-(3,4,5-trimethoxybenzoyl)thiourea (**13**) (364 mg). Yield: 364 mg (84 %), m. p. 152 °C. – IR (cm⁻¹): $\nu = 664$ (C=O), 1479 (C=N). – ¹H NMR (CDCl₃): $\delta = 7.58$ –7.51 (m, 1H, Ar-H); 7.44 (dt, 1H, $J = 1.8$, 7.8 Hz, Ar-H); 7.39–7.31 (m, 4H, Ar-H); 6.43 (q, 1H, $J = 1.2$ Hz, CH=C); 3.86 (s, 3H, OCH₃); 3.77 (s, 6H, 2 × OCH₃); 3.23 (d, 3H, $J = 1.2$ Hz, CH₃). – ¹³C NMR (CDCl₃): $\delta = 173.6$ (C=O); 169.6 (C=N); 157.7 (d, $^1J_{\text{C,F}} = 251$ Hz); 152.5 (2C); 140.8, 133.9, 132.0, 131.2 (d, $^3J_{\text{C,F}} = 7.5$ Hz); 130.5, 125.1 (d, $^3J_{\text{C,F}} = 12.8$ Hz); 124.6 (d, $^4J_{\text{C,F}} = 3.8$ Hz); 116.7 (d, $^2J_{\text{C,F}} = 19.5$ Hz), 106.2 (2C); 104.3 (CH=C); 60.8 (OCH₃); 55.8 (2C, 2 × OCH₃); 14.3 (CH₃). – MS (FAB): $m/z = 402/404$ [M+H]⁺. – C₂₀H₁₉FN₂O₄S: calcd. C 59.69, H 4.76, N 6.96; found C 59.44, H 4.66, N 6.34.

2-Fluoro-N-(3-(3-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)benzamide (34)

From 1-(3-fluorobenzoyl)-3-(2-fluorophenyl)thiourea (**14**) (292 mg). Yield: 254 mg (87 %), m. p. 117 °C. – IR (cm⁻¹): ν = 609 (C=O), 1467 (C=N). – ¹H NMR (CDCl₃): δ = 7.31–7.69 (m, 8H, Ar-H); 6.43 (q, 1H, J = 1.2 Hz, CH=C); 2.12 (d, 3H, J = 1.2 Hz, CH₃). – ¹³C NMR (CDCl₃): δ = 173.3 (C=O); 169.6 (C=N); 162.4 (d, ¹ $J_{C,F}$ = 256 Hz); 157.9 (d, ¹ $J_{C,F}$ = 251 Hz); 134.0, 132.6 (d, ³ $J_{C,F}$ = 8.8 Hz); 132.2 (d, ⁴ $J_{C,F}$ = 0.8 Hz); 131.1 (d, ³ J = 9.0 Hz); 130.3, 125.1 (d, ³ $J_{C,F}$ = 7.5 Hz); 124.6 (d, ⁴ $J_{C,F}$ = 3.0 Hz); 123.3 (d, ⁴ $J_{C,F}$ = 3.8 Hz); 116.9 (d, ² $J_{C,F}$ = 21.0 Hz); 116.6 (d, ² J = 22.5 Hz); 105.1 (CH=C); 15.0 (CH₃). – MS (FAB): m/z = 330/332 [M+H]⁺. – C₁₇H₁₂F₂N₂OS: calcd. C 61.81, H 3.66, N 8.48; found C 61.67, H 3.60, N 8.22.

N-(3-(3-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)-3,4,5-trimethoxybenzamide (35)

From 1-(3-fluorophenyl)-3-(3,4,5-trimethoxybenzoyl)thiourea (**15**) (364 mg). Yield: 390 mg (90 %), m. p. 172 °C. – IR (cm⁻¹): ν = 613 (C=O), 1509 (C=N). – ¹H NMR (CDCl₃): δ = 77.56 (q, 1H, J = 8.1 Hz, Ar-H); 7.37 (s, 2H, Ar-H); 7.29–7.20 (m, 1H, Ar-H); 7.14 (dt, 1H, J = 2.1, 8.1 Hz, Ar-H); 6.42 (q, 1H, J = 1.2 Hz, CH=C); 3.87 (s, 3H, OCH₃); 3.67 (s, 6H, 2 × OCH₃); 2.10 (d, 3H, J = 1.2 Hz, CH₃). – ¹³C NMR (CDCl₃): δ = 172.4 (C=O); 169.5 (C=N); 162.7 (d, ¹ $J_{C,F}$ = 247 Hz); 152.5 (2C); 140.7, 138.6 (d, ³ $J_{C,F}$ = 9.75 Hz); 133.9, 132.0, 130.5 (d, ³ $J_{C,F}$ = 8.25 Hz); 123.9 (d, ⁴ $J_{C,F}$ = 3.8 Hz); 116.5 (d, ² $J_{C,F}$ = 21.5 Hz); 115.2 (d, ² $J_{C,F}$ = 22.5 Hz); 106.2 (2C); 104.3 (CH=C); 60.7 (OCH₃); 55.7 (2C, 2 × OCH₃); 14.2 (CH₃). – MS (FAB): m/z = 402/404 [M+H]⁺. – C₂₀H₁₉FN₂O₅S: calcd. C 59.69, H 4.76, N 6.96; found C 59.37, H 4.64, N 6.75.

3-Fluoro-N-(3-(3-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)benzamide (36)

From 1-(3-fluorobenzoyl)-3-(3-fluorophenyl)thiourea (**16**) (400 mg). Yield: 261 mg (79 %), m. p. 166 °C. – IR (cm⁻¹): ν = 605 (C=O), 1588 (C=N). – ¹H NMR (CDCl₃): δ = 77.68–7.26 (m, 8H, Ar-H); 6.43 (q, 1H, J = 0.9 Hz, CH=C); 2.11 (d, 3H, J = 0.9 Hz, CH₃). – ¹³C NMR (CDCl₃): δ = 173.7 (C=O); 169.2 (C=N); 162.6 (d, ¹ $J_{C,F}$ = 257 Hz); 157.9 (d, ¹ $J_{C,F}$ = 257 Hz); 134.1, 132.5 (d, ³ $J_{C,F}$ = 8.8 Hz); 132.1 (d, ⁴ $J_{C,F}$ = 3.75 Hz); 131.2 (d, ³ $J_{C,F}$ = 8.8 Hz); 130.4, 125.2 (d, ³ $J_{C,F}$ = 8.8 Hz); 124.7 (d, ⁴ $J_{C,F}$ = 0.8 Hz); 123.4 (d, ⁴ $J_{C,F}$ = 3 Hz); 116.9 (d, ² $J_{C,F}$ = 18.8 Hz); 116.6 (d, ² $J_{C,F}$ = 21.0 Hz); 104.8 (CH=C); 15.0 (CH₃). – MS (FAB): m/z = 330/332 [M+H]⁺. – C₁₇H₁₂FN₂O₅S: calcd. C 61.81, H 3.66, N 8.48; found C 61.63, H 3.59, N 8.29.

N-(3-(4-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)-3,4,5-trimethoxybenzamide (37)

From 1-(4-fluorobenzoyl)-3-(3,4,5-trimethoxybenzoyl)thiourea (**17**) (364 mg). Yield: 381 mg (88 %), m. p. 180 °C. – IR (cm⁻¹): ν = 599 (C=O), 1498 (C=N). – ¹H NMR (CDCl₃): δ = 7.39–7.35 (m, 4H, Ar-H); 7.28 (dt, 2H, J = 2.1, 8.3 Hz, Ar-H); 6.41 (q, 1H, J = 1.2 Hz, CH=C); 3.86 (s, 3H, OCH₃); 3.79 (s, 6H, 2 × OCH₃); 2.11 (d, 3H, J = 1.2 Hz, CH₃). – ¹³C NMR (CDCl₃): δ = 173.0 (C=O); 169.9 (C=N); 162.6 (d, ¹ $J_{C,F}$ = 248 Hz); 152.5 (2C); 140.8, 134.1, 133.3 (d, ⁴ $J_{C,F}$ = 3.0 Hz); 132.1, 130.2 (d, ³ $J_{C,F}$ = 8.3 Hz); 116.3 (d, ² $J_{C,F}$ = 23.0 Hz); 106.1 (2C); 104.5 (CH=C); 60.9 (OCH₃); 55.77 (2C, 2 × OCH₃); 15.0 (CH₃). – MS (FAB): m/z = 402/404 [M+H]⁺. – C₂₀H₁₉FN₂O₅S: calcd. C 59.69, H 4.76, N 6.96; found C 59.39, H 4.68, N 6.80.

3-Fluoro-N-(3-(4-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)benzamide (38)

From 1-(3-fluorobenzoyl)-3-(4-fluorophenyl)thiourea (**18**) (292 mg). Yield: 271 mg (82 %), m. p. 174 °C. – IR (cm⁻¹): ν = 660 (C=O), 1467 (C=N). – ¹H NMR (CDCl₃): δ = 7.39–7.35 (m, 4H, Ar-H); 7.28 (dt, 2H, J = 2.1, 8.3 Hz, Ar-H); 6.41 (q, 1H, J = 1.2 Hz, CH=C); 3.86 (s, 3H, OCH₃); 3.79 (s, 6H, 2 × OCH₃); 2.11 (d, 3H, J = 1.2 Hz, CH₃). – ¹³C NMR (CDCl₃): δ = 173.0 (C=O); 169.9 (C=N); 162.6 (d, ¹ $J_{C,F}$ = 248 Hz); 152.5 (2C); 140.8, 134.1, 133.3 (d, ⁴ $J_{C,F}$ = 3.0 Hz); 132.1, 130.2 (d, ³ $J_{C,F}$ = 8.3 Hz); 116.3 (d, ² $J_{C,F}$ = 23.0 Hz); 106.1 (2C); 104.5 (CH=C); 60.9 (OCH₃); 55.77 (2C, 2 × OCH₃); 15.0 (CH₃). – MS (FAB): m/z = 402/404 [M+H]⁺. – C₁₇H₁₂F₂N₂OS: calcd. C 61.81, H 3.66, N 8.48; found C 61.60, H 3.60, N 8.27.

N-(3-(3-Chloro-4-fluorophenyl)-4-methylthiazol-2(3H)-ylidene)-3,4,5-trimethoxybenzamide (39)

From 1-(3-chloro-4-fluorophenyl)-3-(3,4,5-trimethoxybenzoyl)thiourea (**19**) (400 mg). Yield: 376 mg (86 %), m. p. 137 °C. – IR (cm⁻¹): ν = 608 (C=O), 1543 (C=N). – ¹H NMR (CDCl₃): δ = 7.57 (dd, 1H, J = 2.7, 6.3 Hz, Ar-H); 7.39–7.24 (m, 4H, Ar-H); 6.42 (q, 1H, J = 1.2 Hz, CH=C); 3.87 (s, 3H, OCH₃); 3.82 (s, 6H, 2 × OCH₃); 2.14 (d, 3H, J = 1.2 Hz, CH₃). – ¹³C NMR (CDCl₃): δ = 173.6 (C=O); 169.9 (C=N); 158.2 (d, ¹ $J_{C,F}$ = 251 Hz); 152.6 (2C); 140.9, 133.6 (d, ⁴ $J_{C,F}$ = 3.8 Hz); 133.5, 131.8, 131.0, 128.2 (d, ³ $J_{C,F}$ = 7.5 Hz); 121.8 (d, ² $J_{C,F}$ = 18.8 Hz); 117.1 (d, ² $J_{C,F}$ = 21.7 Hz); 106.1 (2C); 104.8 (CH=C); 60.9 (OCH₃); 55.8 (2C, 2 × OCH₃); 15.0 (CH₃). – MS (FAB): m/z = 436/438 [M+H]⁺. – C₂₀H₁₈ClFN₂O₄S: calcd. C 54.98, H 4.15, N 6.41; found C 54.77, H 4.03, N 6.20.

N-(3-(3-Chloro-4-fluorophenyl)-4-methylthiazol-2(3*H*)-ylidene)-3-fluorobenzamide (**40**)

From 1-(3-chloro-4-fluorophenyl)-3-(4-fluorobenzoyl)-thiourea (**20**) (326 mg). Yield: 324 mg (83 %), m. p. 185 °C. – IR ($^{-1}$): ν = 604 (C=O), 1506 (C=N). – ^1H NMR (CDCl_3): δ = 8.08–8.01 (m, 2H, Ar-H); 7.46 (dd, 1H, J = 2.4, 6.3 Hz, Ar-H); 7.40–6.94 (m, 4H, Ar-H); 6.44 (q, 1H, J = 1.2 Hz, CH=C); 2.13 (d, 3H, J = 1.2 Hz, CH_3). – ^{13}C NMR (CDCl_3): δ = 172.4 (C=O); 170.1 (C=N); 164.8 (d, $J_{\text{C,F}}$ = 250 Hz); 158.2 (d, $J_{\text{C,F}}$ = 255 Hz); 134.1, 133.5 (d, $J_{\text{C,F}}$ = 3.8 Hz); 133.0 (d, 2C, $J_{\text{C,F}}$ = 8.3 Hz); 131.7, 130.5, 128.3 (d, $J_{\text{C,F}}$ = 7.5 Hz); 122.1 (d, $J_{\text{C,F}}$ = 18.8 Hz); 117.4 (d, $J_{\text{C,F}}$ = 22.5 Hz); 114.6 (d, 2C, $J_{\text{C,F}}$ = 21.8 Hz); 105.1 (CH=C); 15.0 (CH_3). – MS (FAB): m/z = 364/366 [$\text{M}+\text{H}$] $^{+}$. – $\text{C}_{17}\text{H}_{11}\text{ClF}_2\text{N}_2\text{OS}$: calcd. C 55.97, H 3.04, N 7.68; found C 55.79, H 2.98, N 7.50.

*General procedure for the preparation of substituted (pyrazolo[4,3-*d*]thiazol-5(6*aH*)-ylidene)benzamides (45*a–d*)*

To a stirred, cooled (–60 °C) solution of the required azo compound **41a–d** (3.0 mmol) and thiazolylidene-benzamide (**27**) (694 mg, 2.0 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise a solution of SbCl_5 (3.0 mmol) in dry CH_2Cl_2 (30 mL). Stirring was continued at –60 °C for 1 h, then at 0 °C for 1 h and finally at 23 °C for 10 min, followed by addition of pentane (50 mL). The precipitated solid was dissolved in MeCN (40 mL), cooled to 0 °C, followed by addition of aqueous NaHCO_3 solution (2.52 g, 30 mmol in 30 mL of water) and NH_3 solution (2 mL). The mixture was stirred at r.t. for 2 h, then the organic solvents were evaporated, and the residue was extracted with CHCl_3 (3 $\times$ 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was recrystallized from EtOH or CHCl_3 -pentane.

2-Chloro-N-(4-(4-fluorophenyl)-3,3,3a-trimethyl-3*a*,4-dihydro-3*H*-pyrazolo[4,3-*d*]thiazol-5(6*aH*)-ylidene)benzamide (**45a**)

From **41a** (549 mg). Yield 467 mg (56 %), m. p. 168–171 °C. – ^1H NMR (CDCl_3): δ = 7.78–7.21 (m, 8H, H_{arom}); 3.18 (s, 1H, H-6*a*); 1.43 (s, 3H, $\text{C}^{3\text{a}}\text{-Me}$); 1.38 (s, 6H, $\text{C}^3\text{-Me}_2$). – ^{13}C NMR (CDCl_3): δ = 183.3 ($\text{C}^5\text{=N}$); 173.7 (C=O); 151.4 (d, $J_{\text{C}_4,\text{F}}$ = 248 Hz, $\text{C}^4_{\text{arom-F}}$); 138.8 (d, $J_{\text{C}_1,\text{F}}$ = 3.3 Hz; $\text{C}^1_{\text{arom-F}}$); 136.9, 135.8, 134.2, 131.0, 128.5, 126.4 ($\text{C}_{\text{arom-Cl}}$); 117.2 (d, $J_{\text{C}_2,\text{F};\text{C}_6,\text{F}}$ = 8.5 Hz, $\text{C}^{2,6}_{\text{arom-F}}$); 115.6 ($J_{\text{C}_3,\text{F};\text{C}_5,\text{F}}$ = 22.0 Hz, $\text{C}^{3,5}_{\text{arom-F}}$); 87.7 (C-3*a*); 70.1 (C-6*a*); 62.3 (C-3); 19.9 ($\text{C}^3\text{-Me}_2$); 11.2 ($\text{C}^{3\text{a}}\text{-Me}$). – MS (FAB): m/z = 417/419 [$\text{M}+\text{H}$] $^{+}$. – $\text{C}_{20}\text{H}_{18}\text{ClF}_2\text{N}_4\text{OS}$: calcd. C 57.62, H 4.35, N 13.44; found C 57.38, H 4.29, N 13.21.

2-Chloro-N-(3-ethyl-4-(4-fluorophenyl)-3,3*a*-dimethyl-3*a*,4-dihydro-3*H*-pyrazolo[4,3-*d*]thiazol-5(6*aH*)-ylidene)benzamide (**45b**)

From **41b** (633 mg). Yield: 534 mg (62 %), m. p. 154–157 °C. – ^1H NMR (CDCl_3): δ = 7.74–7.17 (m, 8H, H_{arom}); 3.15 (s, 1H, H-6*a*); 1.62 (q, 2H, J = 7.1 Hz, $\text{C}^3\text{-CH}_2\text{CH}_3$); 1.45 (s, 3H, $\text{C}^{3\text{a}}\text{-Me}$); 1.31 (s, 6H, $\text{C}^2\text{-Me}_2$); 0.98 (t, 3H, $\text{C}^3\text{-CH}_2\text{CH}_3$). – ^{13}C NMR (CDCl_3): δ = 183.6 ($\text{C}^5\text{=N}$); 173.9 (C=O); 151.0 (d, $J_{\text{C}_4,\text{F}}$ = 250 Hz, $\text{C}^4_{\text{arom-F}}$); 138.9 (d, $J_{\text{C}_1,\text{F}}$ = 3.2 Hz; $\text{C}^1_{\text{arom-F}}$); 137.0, 135.6, 134.5, 131.2, 128.4, 126.6 ($\text{C}_{\text{arom-Cl}}$); 116.9 (d, $J_{\text{C}_2,\text{F};\text{C}_6,\text{F}}$ = 8.3 Hz, $\text{C}^{2,6}_{\text{arom-F}}$); 115.2 ($J_{\text{C}_3,\text{F};\text{C}_5,\text{F}}$ = 22.2 Hz, $\text{C}^{3,5}_{\text{arom-F}}$); 87.3 (C-3*a*); 69.8 (C-6*a*); 68.7 (C-3); 24.0 ($\text{C}^3\text{-CH}_2\text{CH}_3$); 11.0 ($\text{C}^3\text{-Me}$); 7.2 ($\text{C}^3\text{-CH}_2\text{CH}_3$). – MS (FAB): m/z = 431/433 [$\text{M}+\text{H}$] $^{+}$. – $\text{C}_{21}\text{H}_{20}\text{ClF}_2\text{N}_4\text{OS}$: calcd. C 58.53, H 4.68, N 13.00; found C 58.21, H 4.59, N 12.74.

2-Chloro-N-(3,3-diethyl-4-(4-fluorophenyl)-3*a*-methyl-3*a*,4-dihydro-3*H*-pyrazolo[4,3-*d*]thiazol-5(6*aH*)-ylidene)benzamide (**45c**)

From **41c** (717 mg). Yield: 596 mg (67 %), m. p. 169–172 °C. – ^1H NMR (CDCl_3): δ = 7.78–7.11 (m, 8H, H_{arom}); 3.12 (s, 1H, H-6*a*); 1.59 (2 $\times$ q, 4H, J = 7.0 Hz, $\text{C}^3\text{-CH}_2\text{CH}_3$); 1.38 (s, 3H, $\text{C}^{3\text{a}}\text{-Me}$); 1.01 (2 $\times$ t, 3H, $\text{C}^3\text{-CH}_2\text{CH}_3$). – ^{13}C NMR (CDCl_3): δ = 183.9 ($\text{C}^5\text{=N}$); 173.8 (C=O); 151.2 (d, $J_{\text{C}_4,\text{F}}$ = 249 Hz, $\text{C}^4_{\text{arom-F}}$); 138.7 (d, $J_{\text{C}_1,\text{F}}$ = 3.1 Hz; $\text{C}^1_{\text{arom-F}}$); 137.6, 135.5, 133.9, 130.9, 128.5, 126.9 ($\text{C}_{\text{arom-Cl}}$); 116.5 (d, $J_{\text{C}_2,\text{F};\text{C}_6,\text{F}}$ = 8.0 Hz, $\text{C}^{2,6}_{\text{arom-F}}$); 115.0 ($J_{\text{C}_3,\text{F};\text{C}_5,\text{F}}$ = 21.9 Hz, $\text{C}^{3,5}_{\text{arom-F}}$); 87.0 (C-3*a*); 73.4 (C-3); 69.9 (C-6*a*); 21.1 (2 $\times$ $\text{C}^3\text{-CH}_2\text{CH}_3$); 11.7 ($\text{C}^3\text{-Me}$); 7.0 (2 $\times$ $\text{C}^3\text{-CH}_2\text{CH}_3$). – MS (FAB): m/z = 445/447 [$\text{M}+\text{H}$] $^{+}$. – $\text{C}_{22}\text{H}_{22}\text{ClF}_2\text{N}_4\text{OS}$: calcd. C 59.39, H 4.98, N 12.59; found C 59.11, H 4.90, N 12.31.

2-Chloro-N-(4(4-fluorophenyl)-3-isopropyl-3,3*a*-dimethyl-3*a*,4-dihydro-3*H*-pyrazolo[4,3-*d*]thiazol-5(6*aH*)-ylidene)benzamide (**45d**)

From **41d** (714 mg). Yield: 463 mg (52 %), m. p. 159–161 °C. – ^1H NMR (CDCl_3): δ = 7.74–7.17 (m, 8H, H_{arom}); 3.15 (s, 1H, H-6*a*); 2.02 (m, 1H, $\text{C}^3\text{-CHMe}_2$); 1.35 (s, 3H, $\text{C}^{3\text{a}}\text{-Me}$); 1.12 (m, 6H, $\text{C}^3\text{-CHMe}_2$). – ^{13}C NMR (CDCl_3): δ = 183.7 ($\text{C}^5\text{=N}$); 174.1 (C=O); 151.1 (d, $J_{\text{C}_4,\text{F}}$ = 249 Hz, $\text{C}^4_{\text{arom-F}}$); 138.9 (d, $J_{\text{C}_1,\text{F}}$ = 3.0 Hz; $\text{C}^1_{\text{arom-F}}$); 136.8, 135.5, 133.7, 131.2, 127.7, 126.8 ($\text{C}_{\text{arom-Cl}}$); 116.8 (d, $J_{\text{C}_2,\text{F};\text{C}_6,\text{F}}$ = 8.3 Hz, $\text{C}^{2,6}_{\text{arom-F}}$); 115.9 ($J_{\text{C}_3,\text{F};\text{C}_5,\text{F}}$ = 21.7 Hz, $\text{C}^{3,5}_{\text{arom-F}}$); 75.8 (C-3*a*); 74.2 (C-3); 69.6 (C-6*a*); 31.0 ($\text{C}^3\text{-CHMe}_2$); 16.3 ($\text{C}^3\text{-CHMe}_2$); 11.6 ($\text{C}^3\text{-Me}$). – MS (FAB): m/z = 445/447 [$\text{M}+\text{H}$] $^{+}$. – $\text{C}_{22}\text{H}_{22}\text{ClF}_2\text{N}_4\text{OS}$: calcd. C 59.39, H 4.98, N 12.59; found C 59.04, H 4.83, N 12.23.

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