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(6a*H*)-ylidene)benzamides **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 IC_{50} of 2.02 μg mL^{-1} and 0.40 μg mL^{-1} against the HIV-2 strain ROD with CC_{50} of $\geq$ 104.00 μg mL^{-1} and $>$ 125.00 μg mL^{-1}, respectively, resulting in a selectivity index of $\geq$ 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].

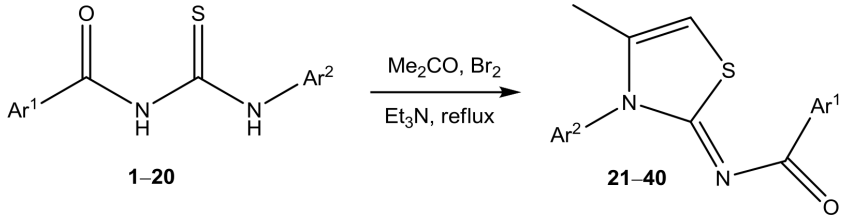
Pyrazoles and their derivatives have been reported to be potent agents for the treatment of different diseases [21, 22]. Jochims *et al.* [23] have synthesized new pyrazole analoges *via* [2+3] cycloaddition reactions of olefins with the reactive intermediates 1-aza-2-azoniallene salts (cumulene intermediates).

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

Results and Discussion

Synthesis

Condensation of the 1-aroyl-3-arylthioureas **1** – **20** with α-haloketones in the presence of Et_3N 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**



1–20 **21–40**

	Ar^1	Ar^2		Ar^1	Ar^2
1, 21	2-Cl-Ph	2-F-Ph	**11, 31**	2-F-Ph	3-Cl-4-F-Ph
2, 22	2-F-Ph	2-F-Ph	**12, 32**	CMe_3	3-Cl-4-F-Ph
3, 23	4-F-Ph	2-F-Ph	**13, 33**	3,4,5-$(OMe)_3$-Ph	2-F-Ph
4, 24	2-Cl-Ph	3-F-Ph	**14, 34**	3-F-Ph	2-F-Ph
5, 25	2-F-Ph	3-F-Ph	**15, 35**	3,4,5-$(OMe)_3$-Ph	3-F-Ph
6, 26	4-F-Ph	3-F-Ph	**16, 36**	3-F-Ph	3-F-Ph
7, 27	2-Cl-Ph	4-F-Ph	**17, 37**	3,4,5-$(OM)_3$-Ph	4-F-Ph
8, 28	2-F-Ph	4-F-Ph	**18, 38**	3-F-Ph	4-F-Ph
9, 29	4-F-Ph	4-F-Ph	**19, 39**	3,4,5-$(OMe)_3$-Ph	3-Cl-4-F-Ph
10, 30	2-Cl-Ph	3-Cl-4-F-Ph	**20, 40**	4-F-Ph	3-Cl-4-F-Ph

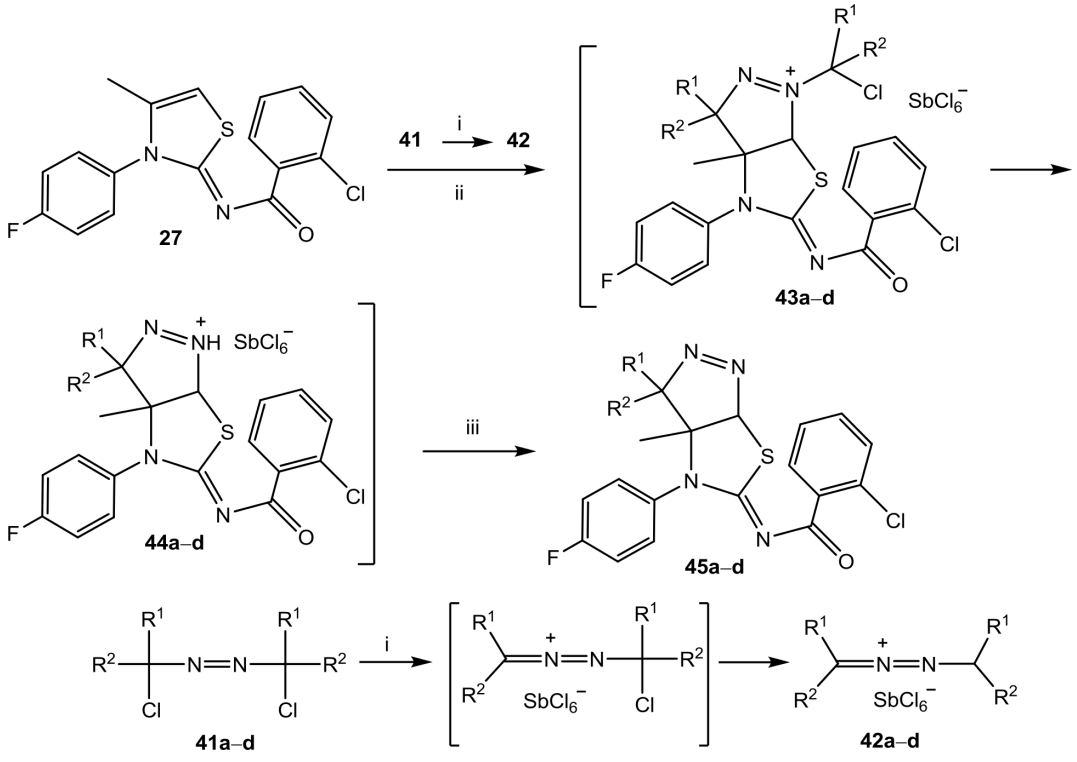
Scheme 1. Synthesis of *N*-(3-(substituted-alkyl- or halophenyl)-4-methylthiazol-2(3*H*)-ylidene)-substituted alkyl- or halobenzamides.

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 ^{1}H and ^{13}C NMR, IR and mass spectra. The ^{1}H 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 λ_{max} = 1598 – 1664 and 1443 – 1553 cm^{-1}, attributed to the C=O and C=N groups. In the ^{1}H NMR spectra, the doublet in the region δ = 2.07 – 2.16 ppm (J = 0.9 – 1.2 Hz) was assigned to the methyl group at C-4, while the quartet in the region δ = 6.34 – 6.46 ppm was assigned to 5-H of the thiazole backbone. The ^{13}C NMR spectra of **21** – **40** contained similar resonance signals for the thiazole carbon atoms. The signals between δ_C = 175.1 and 173.4 ppm was assigned to the carbonyl carbon atoms, while the resonance in the range of δ_C = 163.7 – 165.2 ppm was assigned to C-2 (C=N). C-4 displayed a signal in the region δ_C = 151.2 – 149.3 ppm. A signal between δ_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 δ_C = 14.3 – 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 backbone at δ_H = 6.43 ppm showed a $^2J_{C,H}$ coupling with C-2 at δ_C = 105.0 ppm, in addition to a $^3J_{C,H}$ coupling with C-2 (C=N) at δ_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 $SbCl_5$ at −60 °C. At approximately −30 °C, the color changed from orange to brown, indicating that cumulates **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 CR_2Cl group at N-1′ was eliminated, leading to the protonated salts **44a** – **d**. *In situ* deprotonation of salts **44a** – **d** with aqueous $NaHCO_3$ and NH_3 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 ^{1}H and ^{13}C NMR spectra. The singlet at lower field (δ_H = 1.38 – 1.43 ppm) was attributed to the methyl proton at C-3a, while the singlet of 6a-H appeared at δ_H = 3.12 – 3.18 ppm). In the ^{13}C NMR spectra of **45a** – **d**, the C=N signals appeared at higher field (δ = 183.3, 183.6, 183.9 or 183.7 ppm, respectively), while the resonances at δ = 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** $R^1 = R^2 = Me$; **b** $R^1 = Me$, $R^2 = Et$; **c** $R^1 = Et$, $R^2 = Et$; **d** $R^1 = Me$, $R^2 = i\text{-Pr}$.

peared at δ = 87.7, 87.3, 87.0 or 75.8 ppm, respectively, and C-6a resonated at δ_C = 70.1, 69.8, 69.9 or 69.6 ppm, respectively. C-3 and C3a-*Me* carbons resonated at δ_C = 62.3–74.2 ppm and δ_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* $^2J_{C,H}$ and $^3J_{C,H}$ couplings the assignment of most of the carbon atoms. C-3 and C^5=N (δ_C = 62.3 and 183.3 ppm) were identified from their $^3J_{C,H}$ correlations to 6a-H at δ_H = 3.18 ppm, respectively, and C-3a′ (δ_C = 87.7 ppm) was identified from its $^2J_{C,H}$ correlation to 6a-H at δ_H = 3.18 ppm. The mass spectrum of **45a**, (FAB) exhibited the correct molecular ion (417/419 $[M+H]^+$).

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 results 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 $\mu g\,mL^{-1}$ and 0.40 $\mu g\,mL^{-1}$ with CC_{50} of $\geq$ 104.0 $\mu g\,mL^{-1}$ and $>$ 125.00 $\mu g\,mL^{-1}$, respectively, resulting in a selectivity index of $\geq$ 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 $IC_{50} \geq$ 12.70 $\mu g\,mL^{-1}$ and a CC_{50} = 70.13 $\mu g\,mL^{-1}$, but with a low selectivity ($SI \leq 6$).

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} ($\mu g\,mL^{-1}$)[a,c]	HIV-2 (ROD) IC_{50} ($\mu g\,mL^{-1}$)[a,c]	CC_{50} ($\mu g\,mL^{-1}$)[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] IC_{50}: concentration of compound required to achieve 50 % protection of MT-4 cells from HIV-induced cytopathogenicity, as determined by the MTT method; [b] CC_{50}: 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 (^{1}H) and 150.91 MHz (^{13}C) 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 ^{1}H-^{13}C 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-aroyl-3-arylthioureas **1** – **20** (1.0 mmol) in dry acetone (20 mL) was added Et_3N (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). – ^{1}H NMR ($CDCl_3$): 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, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 174.1 (C=O); 170.2 (C=N); 157.6 (d, $^1J_{C,F}$ = 251 Hz); 136.0, 134.3, 133.6, 131.5 (d, $^3J_{C,F}$ = 8.3 Hz); 131.2, 131.0, 130.7, 126.3, 125.1, 124.8 (d, $^3J_{C,F}$ = 12.8 Hz), 124.6 (d, $^4J_{C,F}$ = 3.8 Hz), 116.8 (d, $^2J_{C,F}$ = 19.5 Hz), 104.6 (CH=C), 14.32 (CH_3). – MS (FAB): m/z = 346/348 $[M+H]^+$. – $C_{17}H_{12}ClFN_2OS$: 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}): ν = 608 (C=O), 1443 (C=N). – ^{1}H NMR ($CDCl_3$): δ = 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, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 173.4 (C=O); 169.7 (C=N); 162.3 (d, $^1J_{C,F}$ = 257 Hz); 157.6 (*d*, $^1J_{C,F}$ = 251 Hz); 134.0, 132.6 (d, $^3J_{C,F}$ = 8.3 Hz); 132.1 (d, $^4J_{C,F}$ = 0.8 Hz); 131.2 (d, $^3J_{C,F}$ = 8.8 Hz); 130.3, 125.1 (d, $^3J_{C,F}$ = 7.5 Hz); 124.7 (d, $^4J_{C,F}$ = 3.8 Hz); 123.4 (d, $^4J_{C,F}$ = 3.8 Hz); 116.8 (d, $^2J_{C,F}$ = 19.5 Hz); 116.7 (d, $^2J_{C,F}$ = 22.5 Hz); 104.4 (CH=C); 14.3 (CH_3). – MS (FAB): m/z = 330/332 $[M+H]^+$. – $C_{17}H_{12}F_2N_2OS$: 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}): ν = 602 (C=O), 1455 (C=N). – ^{1}H NMR ($CDCl_3$): δ = 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, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 173.4 (C=O); 170.0 (C=N); 165.1 (d, $^1J_{C,F}$ = 250 Hz); 157.5 (d, $^1J_{C,F}$ = 251 Hz); 134.1, 133.0 (d, $^4J_{C,F}$ = 3.0 Hz); 131.7, 131.1 (d, 2C, $^3J_{C,F}$ = 8.3 Hz); 130.2, 124.9 (d, $^4J_{C,F}$ = 3 Hz); 124.8 (d, $^3J_{C,F}$ = 6.75 Hz); 116.9 (d, $^2J_{C,F}$ = 19.5 Hz); 114.8 (d, 2C, $^2J_{C,F}$ = 21.8 Hz); 104.5 (CH=C); 14.30 (CH_3). – MS (FAB): m/z = 330/332 $[M+H]^+$. – $C_{17}H_{12}F_2N_2OS$: 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}): ν = 600 (C=O), 1461 (C=N). – ^{1}H NMR ($CDCl_3$): δ = 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, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 172.3 (C=O); 169.3 (C=N); 162.7 (*d*, $^1J_{C,F}$ = 247 Hz); 138.4 (*d*, $^3J_{C,F}$ = 9.75 Hz); 135.9, 134.4, 133.6, 131.8, 131.2, 130.9, 130.6 (*d*, $^3J_{C,F}$ = 9.0 Hz), 126.2, 123.9 (*d*, $^4J_{C,F}$ = 3.5 Hz); 116.5 (*d*, $^2J_{C,F}$ = 21 Hz); 115.9 (*d*, $^2J_{C,F}$ = 22.5 Hz); 105.0 (CH=C); 14.93 (CH_3). – MS (FAB): m/z = 346/348 $[M]^+$. – $C_{17}H_{12}ClFN_2OS$: 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}): ν = 600 (C=O), 1461 (C=N). – ^{1}H NMR ($CDCl_3$): δ = 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, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 172.4 (d, J = 3.3 Hz, C=O); 169.9 (C=N); 162.8 (d, $^1J_{C,F}$ = 247 Hz); 162.3 (d, $^1J_{C,F}$ = 251 Hz); 138.4 (d, $^3J_{C,F}$ = 9.8 Hz); 133.9, 132.7 (d, $^3J_{C,F}$ = 8.3 Hz); 132.2 (d, $^4J_{C,F}$ = 0.8 Hz); 130.7 (d, $^3J_{C,F}$ = 9.0 Hz); 125.2 (d, $^3J_{C,F}$ = 7.8 Hz); 123.9 (d, $^4J_{C,F}$ = 4.5 Hz); 123.4 (d, $^2J_{C,F}$ = 18.8 Hz); 116.7 (d, $^2J_{C,F}$ = 22.5 Hz); 116.3 (d, $^2J_{C,F}$ = 21 Hz); 115.9 (d, $^2J_{C,F}$ = 23.3 Hz); 105.1 (CH=C); 14.59 (CH_3). – MS (FAB): m/z = 330/332 $[M+H]^+$. – $C_{17}H_{12}F_2N_2OS$: 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}): ν = 606 (C=O), 1473 (C=N). – ^{1}H NMR ($CDCl_3$): δ = 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, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 170.4 (C=O); 169.9 (C=N); 164.9 (d, $^1J_{C,F}$ = 250 Hz); 162.7 (d, $^1J_{C,F}$ = 247 Hz); 138.4 (d, 1C, $^3J_{C,F}$ = 9.8 Hz); 133.9, 133.0 (d, 2C, $^3J_{C,F}$ = 8.0 Hz); 131.6, 130.3 (d, $^3J_{C,F}$ = 9.0 Hz); 124.0 (d, $^4J_{C,F}$ = 4.5 Hz); 116.6 (d, $^2J_{C,F}$ = 21.0 Hz); 115.9 (d, $^2J_{C,F}$ = 23.3 Hz); 114.8 (d, 2C, $^2J_{C,F}$ = 21.3 Hz); 105.1 (CH=C); 14.8 (CH_3). – MS (FAB): m/z = 330/332 $[M+H]^+$. – $C_{17}H_{12}F_2N_2OS$: 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}): ν = 599 (C=O), 1554 (C=N). – ^{1}H NMR ($CDCl_3$): δ = 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, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 174.0 (C=O); 170.2 (C=N); 162.6 (d, $^1J_{C,F}$ = 248 Hz); 136.0, 134.4, 133.5, 126.2,

133.1 (d, $^4J_{C,F}$ = 3 Hz); 131.8, 131.0, 130.8, 129.9 (d, 2C, $^3J_{C,F}$ = 8.3 Hz); 126.2, 116.6 (d, 2C, $^2J_{C,F}$ = 22.5 Hz); 104.9 (CH=C); 15.0 (CH_3). – MS (FAB): m/z = 346/348 $[M]^+$. – $C_{17}H_{12}ClFN_2OS$: 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}): ν = 605 (C=O), 1461 (C=N). – ^{1}H NMR ($CDCl_3$): δ = 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, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 172.4 (d, J = 3.0 Hz, C=O); 170.1 (C=N); 162.6 (d, $^1J_{C,F}$ = 248 Hz); 162.3 (d, $^1J_{C,F}$ = 257 Hz), 134.2, 133.1 (d, $^4J_{C,F}$ = 3.0 Hz); 132.7 (d, $^3J_{C,F}$ = 9.0 Hz); 132.1 (d, $^4J_{C,F}$ = 0.8 Hz); 129.9 (d, 2C, $^3J_{C,F}$ = 9.0 Hz); 125.2 (d, $^3J_{C,F}$ = 8.3 Hz); 123.4 (*d*, $^4J_{C,F}$ = 3.8 Hz); 116.7 (d, $^2J_{C,F}$ = 22.5 Hz); 116.6 (d, 2C, $^2J_{C,F}$ = 22.5 Hz); 104.9 (CH=C); 15.0 (CH_3). – MS (FAB): m/z = 330/332 $[M+H]^+$. – $C_{17}H_{12}F_2N_2OS$: 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}): ν = 602 (C=O), 1450 (C=N). – ^{1}H NMR ($CDCl_3$): δ = 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, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 173.8 (C=O); 169.9 (C=N); 164.9 (d, $^1J_{C,F}$ = 250 Hz); 162.6 (d, $^1J_{C,F}$ = 248 Hz); 134.1, 133.4 (d, $^4J_{C,F}$ = 3 Hz); 133.0 (d, 2C, $^3J_{C,F}$ = 8.0 Hz), 131.6, 130.2 (d, 2C, $^3J_{C,F}$ = 8.3 Hz); 116.3 (d, 2C, $^2J_{C,F}$ = 23 Hz); 114.9 (d, 2C, $^2J_{C,F}$ = 21.75 Hz); 104.4 (CH=C); 15.0 (CH_3). – MS (FAB): m/z = 330/332 $[M+H]^+$. – $C_{17}H_{12}F_2N_2OS$: 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}): ν = 660 (C=O), 1553 (C=N). – ^{1}H NMR ($CDCl_3$): δ = 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, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 174.1 (C=O); 170.2 (C=N); 158.3 (d, $^1J_{C,F}$ = 251 Hz); 135.9, 134.2, 133.5, 133.4 (d, $^4J_{C,F}$ = 3.0 Hz); 131.8, 130.7, 130.6, 128.2 (d, $^3J_{C,F}$ = 7.5 Hz); 126.3, 122.1 (d, $^2J_{C,F}$ = 19.5 Hz); 121.8, 117.4 (d, $^2J_{C,F}$ = 22.5 Hz); 105.2 (CH=C); 15.0 (CH_3). – MS (FAB): m/z = 381/383 $[M+H]^+$. – $C_{17}H_{11}FCl_2N_2OS$: 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}): ν = 618 (C=O), 1521 (C=N). – ^{1}H NMR ($CDCl_3$): δ = 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, $J_{C,F}$ = 1.2 Hz, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 172.4 (d, J = 3.0 Hz, C=O); 170.1 (C=N); 162.3 (d, $^1J_{C,F}$ = 256 Hz); 158.3 (d, $^1J_{C,F}$ = 255 Hz); 133.8, 133.4 (d, $^4J_{C,F}$ = 3.75 Hz); 132.8 (d, $^3J_{C,F}$ = 9.0 Hz); 132.1, 130.5, 128.2 (d, $^3J_{C,F}$ = 7.5 Hz); 125.0 (d, $^3J_{C,F}$ = 7.5 Hz); 123.5 (d, $^4J_{C,F}$ = 4.5 Hz); 122.1 (d, $^2J_{C,F}$ = 18.8 Hz); 117.4 (d, $^2J_{C,F}$ = 22.5 Hz); 116.7 (d, $^2J_{C,F}$ = 22.5 Hz); 104.6 (CH=C); 15.02 (CH_3). – MS (FAB): m/z = 364/366 $[M+H]^+$. – $C_{17}H_{11}ClF_2N_2OS$: 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**)*

Fom 1-(3-Chloro-4-fluorophenyl)-3-pivaloylthiourea (**12**) (289 mg). Yield: 265 mg (81 %), m. p. 124 °C. – IR (cm^{-1}): ν = 609 (C=O), 1502 (C=N). – ^{1}H NMR ($CDCl_3$): δ = 7.41 – 7.28 (m, 2H, Ar-H); 7.21 (s, 1H, Ar-H); 6.34 (s, 1H, CH=C); 2.08 (s, 3H, CH_3); 1.11 (s, 9H, CMe_3). – ^{13}C NMR ($CDCl_3$): δ = 174.6 (C=O); 169.0 (C=N); 158.1 (d, $^1J_{C,F}$ = 251 Hz); 128.2 (d, $^3J_{C,F}$ = 7.5 Hz); 121.7 (d, $^2J_{C,F}$ = 18.5 Hz); 117.1 (d, $^2J_{C,F}$ = 22.5 Hz); 104.3 (CH=C); 40.7, 27.5 (CMe_3); 15.1 (CH_3). – MS (FAB): m/z = 326/328 $[M+H]^+$. – $C_{15}H_{16}ClFN_2OS$: 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}): ν = 664 (C=O), 1479 (C=N). – ^{1}H NMR ($CDCl_3$): δ = 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, OCH_3); 3.77 (s, 6H, 2 × OCH_3); 3.23 (d, 3H, J = 1.2 Hz, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 173.6 (C=O); 169.6 (C=N); 157.7 (d, $^1J_{C,F}$ = 251 Hz); 152.5 (2C); 140.8, 133.9, 132.0, 131.2 (d, $^3J_{C,F}$ = 7.5 Hz); 130.5, 125.1 (d, $^3J_{C,F}$ = 12.8 Hz); 124.6 (d, $^4J_{C,F}$ = 3.8 Hz); 116.7 (d, $^2J_{C,F}$ = 19.5 Hz), 106.2 (2C); 104.3 (CH=C); 60.8 (OCH_3); 55.8 (2C, 2 × OCH_3); 14.3 (CH_3). – MS (FAB): m/z = 402/404 $[M+H]^+$. – $C_{20}H_{19}FN_2O_4S$: 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). – ^{1}H NMR ($CDCl_3$): 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, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 173.3 (C=O); 169.6 (C=N); 162.4 (d, ^1J = 256 Hz); 157.9 (d, $^1J_{C,F}$ = 251 Hz); 134.0, 132.6 (d, $^3J_{C,F}$ = 8.8 Hz); 132.2 (d, $^4J_{C,F}$ = 0.8 Hz); 131.1 (d, ^3J = 9.0 Hz); 130.3, 125.1 (d, $^3J_{C,F}$ = 7.5 Hz); 124.6 (d, $^4J_{C,F}$ = 3.0 Hz); 123.3 (d, $^4J_{C,F}$ = 3.8 Hz); 116.9 (d, $^2J_{C,F}$ = 21.0 Hz); 116.6 (d, ^2J = 22.5 Hz); 105.1 (CH=C); 15.0 (CH_3). – MS (FAB): m/z = 330/332 $[M+H]^+$. – $C_{17}H_{12}F_2N_2OS$: 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). – ^{1}H NMR ($CDCl_3$): 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, OCH_3); 3.67 (s, 6H, 2 × OCH_3); 2.10 (d, 3H, J = 1.2 Hz, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 172.4 (C=O); 169.5 (C=N); 162.7 (d, $^1J_{C,F}$ = 247 Hz); 152.5 (2C); 140.7, 138.6 (d, $^3J_{C,F}$ = 9.75 Hz); 133.9, 132.0, 130.5 (d, $^3J_{C,F}$ = 8.25 Hz), 123.9 (d, $^4J_{C,F}$ = 3.8 Hz); 116.5 (d, $^2J_{C,F}$ = 21.5 Hz); 115.2 (d, $^2J_{C,F}$ = 22.5 Hz); 106.2 (2C); 104.3 (CH=C); 60.7 (OCH_3); 55.7 (2C, 2 × OCH_3); 14.2 (CH_3). – MS (FAB): m/z = 402/404 $[M+H]^+$. – $C_{20}H_{19}FN_2O_5S$: 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). – ^{1}H NMR ($CDCl_3$): 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, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 173.7 (C=O); 169.2 (C=N); 162.6 (d, $^1J_{C,F}$ = 257 Hz); 157.9 (d, $^1J_{C,F}$ = 257 Hz); 134.1, 132.5 (d, $^3J_{C,F}$ = 8.8 Hz); 132.1 (d, $^4J_{C,F}$ = 3.75 Hz); 131.2 (d, $^3J_{C,F}$ = 8.8 Hz); 130.4, 125.2 (d, $^3J_{C,F}$ = 8.8 Hz); 124.7 (d, $^4J_{C,F}$ = 0.8 Hz); 123.4 (d, $^4J_{C,F}$ = 3 Hz); 116.9 (d, $^2J_{C,F}$ = 18.8 Hz); 116.6 (d, $^2J_{C,F}$ = 21.0 Hz); 104.8 (CH=C); 15.0 (CH_3). – MS (FAB): m/z = 330/332 $[M+H]^+$. – $C_{17}H_{22}FN_2O_5S$: 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). – ^{1}H NMR ($CDCl_3$): 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, OCH_3); 3.79 (s, 6H, 2 × OCH_3); 2.11 (d, 3H, J = 1.2 Hz, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 173.0 (C=O); 169.9 (C=N); 162.6 (d, $^1J_{C,F}$ = 248 Hz); 152.5 (2C); 140.8, 134.1, 133.3 (d, $^4J_{C,F}$ = 3.0 Hz); 132.1, 130.2 (d, $^3J_{C,F}$ = 8.3 Hz); 116.3 (d, $^2J_{C,F}$ = 23.0 Hz); 106.1 (2C); 104.5 (CH=C); 60.9 (OCH_3); 55.77 (2C, 2 × OCH_3); 15.0 (CH_3). – MS (FAB): m/z = 402/404 $[M+H]^+$. – $C_{20}H_{19}FN_2O_5S$: 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). – ^{1}H NMR ($CDCl_3$): 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, OCH_3); 3.79 (s, 6H, 2 × OCH_3); 2.11 (d, 3H, J = 1.2 Hz, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 173.0 (C=O); 169.9 (C=N); 162.6 (d, $^1J_{C,F}$ = 248 Hz); 152.5 (2C); 140.8, 134.1, 133.3 (d, $^4J_{C,F}$ = 3.0 Hz); 132.1, 130.2 (d, $^3J_{C,F}$ = 8.3 Hz); 116.3 (d, $^2J_{C,F}$ = 23.0 Hz); 106.1 (2C); 104.5 (CH=C); 60.9 (OCH_3); 55.77 (2C, 2 × OCH_3); 15.0 (CH_3). – MS (FAB): m/z = 402/404 $[M+H]^+$. – $C_{17}H_{12}F_2N_2OS$: 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). – ^{1}H NMR ($CDCl_3$): 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, OCH_3); 3.82 (s, 6H, 2 × OCH_3); 2.14 (d, 3H, J = 1.2 Hz, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 173.6 (C=O); 169.9 (C=N); 158.2 (d, $^1J_{C,F}$ = 251 Hz); 152.6 (2C); 140.9, 133.6 (d, $^4J_{C,F}$ = 3.8 Hz); 133.5, 131.8, 131.0, 128.2 (d, $^3J_{C,F}$ = 7.5 Hz); 121.8 (d, $^2J_{C,F}$ = 18.8 Hz); 117.1 (d, $^2J_{C,F}$ = 21.7 Hz); 106.1 (2C); 104.8 (CH=C); 60.9 (OCH_3); 55.8 (2C, 2 × OCH_3); 15.0 (CH_3). – MS (FAB): m/z = 436/438 $[M+H]^+$. – $C_{20}H_{18}ClFN_2O_4S$: 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(3H)-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). – ^{1}H 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, $^1J_{C,F}$ = 250 Hz); 158.2 (d, $^1J_{C,F}$ = 255 Hz); 134.1, 133.5 (d, $^4J_{C,F}$ = 3.8 Hz); 133.0 (d, 2C, $^3J_{C,F}$ = 8.3 Hz); 131.7, 130.5, 128.3 (d, $^3J_{C,F}$ = 7.5 Hz); 122.1 (d, $^2J_{C,F}$ = 18.8 Hz); 117.4 (d, $^2J_{C,F}$ = 22.5 Hz); 114.6 (d, 2C, $^2J_{C,F}$ = 21.8 Hz); 105.1 (CH=C); 15.0 (CH_3). – MS (FAB): m/z = 364/366 $[M+H]^+$. – $C_{17}H_{11}ClF_2N_2OS$: 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(6aH)-ylidene)benzamides (**45a – 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 × 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-3a,4-dihydro-3H-pyrazolo[4,3-d]thiazol-5(6aH)-ylidene)benzamide (**45a**)*

From **41a** (549 mg). Yield 467 mg (56 %), m. p. 168 – 171 °C. – ^{1}H NMR ($CDCl_3$): δ = 7.78 – 7.21 (m, 8H, H_{arom}); 3.18 (s, 1H, H-6a); 1.43 (s, 3H, C^{3a}-*Me*); 1.38 (s, 6H, C^3-*Me*$_2$). – ^{13}C NMR ($CDCl_3$): δ = 183.3 (C^5=N); 173.7 (C=O); 151.4 (d, $J_{C4,F}$ = 248 Hz, $C^4_{arom\text{-}F}$); 138.8 (d, $J_{C1,F}$ = 3.3 Hz; $C^1_{arom\text{-}F}$); 136.9, 135.8, 134.2, 131.0, 128.5, 126.4 ($C_{arom\text{-}Cl}$); 117.2 (d, $J_{C2\text{-}F,C6\text{-}F}$ = 8.5 Hz, $C^{2,6}_{arom\text{-}F}$); 115.6 ($J_{C3\text{-}F,C5\text{-}F}$ = 22.0 Hz, $C^{3,5}_{arom\text{-}F}$);), 87.7 (C-3a); 70.1 (C-6a); 62.3 (C-3); 19.9 (C^3-*Me*$_2$); 11.2 (C^{3a}-*Me*). – MS (FAB): m/z = 417/419 $[M+H]^+$. – $C_{20}H_{18}ClFN_4OS$: 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)-3,3a-dimethyl-3a,4-dihydro-3H-pyrazolo[4,3-d]thiazol-5(6aH)-ylidene)benzamide (**45b**)*

From **41b** (633 mg). Yield: 534 mg (62 %), m. p. 154 – 157 °C. – ^{1}H NMR ($CDCl_3$): δ = 7.74 – 7.17 (m, 8H, H_{arom}); 3.15 (s, 1H, H-6a); 1.62 (q, 2H, J = 7.1 Hz, C^3-*CH*$_2$CH$_3$); 1.45 (s, 3H, C^{3a}-*Me*); 1.31 (s, 6H, C^2-*Me*); 0.98 (t, 3H, C^3-CH$_2$*CH*$_3$). – ^{13}C NMR ($CDCl_3$): δ = 183.6 (C^5=N); 173.9 (C=O); 151.0 (d, $J_{C4,F}$ = 250 Hz, $C^4_{arom\text{-}F}$); 138.9 (d, $J_{C1,F}$ = 3.2 Hz; $C^1_{arom\text{-}F}$); 137.0, 135.6, 134.5, 131.2, 128.4, 126.6 ($C_{arom\text{-}Cl}$); 116.9 (d, $J_{C2\text{-}F,C6\text{-}F}$ = 8.3 Hz, $C^{2,6}_{arom\text{-}F}$); 115.2 ($J_{C3\text{-}F,C5\text{-}F}$ = 22.2 Hz, $C^{3,5}_{arom\text{-}F}$);), 87.3 (C-3a); 69.8 (C-6a); 68.7 (C-3); 24.0 (C^3-*CH*$_2$CH$_3$); 11.0 (C^3-*Me*); 7.2 (C^3-CH$_2$*CH*$_3$). – MS (FAB): m/z = 431/433 $[M+H]^+$. – $C_{21}H_{20}ClFN_4OS$: 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)-3a-methyl-3a,4-dihydro-3H-pyrazolo[4,3-d]thiazol-5(6aH)-ylidene)benzamide (**45c**)*

From **41c** (717 mg). Yield: 596 mg (67 %), m. p. 169 – 172 °C. – ^{1}H NMR ($CDCl_3$): δ = 7.78 – 7.11 (m, 8H, $H_{arom.}$); 3.12 (s, 1H, H-6a); 1.59 (2 × q, 4H, J = 7.0 Hz, C^3-*CH*$_2$CH$_3$); 1.38 (s, 3H, C^{3a}-*Me*); 1.01 (2 × t, 3H, C^3-CH$_2$*CH*$_3$). – ^{13}C NMR ($CDCl_3$): δ = 183.9 (C^5=N); 173.8 (C=O); 151.2 (d, $J_{C4,F}$ = 249 Hz, $C^4_{arom\text{-}F}$); 138.7 (d, $J_{C1,F}$ = 3.1 Hz; $C^1_{arom\text{-}F}$); 137.6, 135.5, 133.9, 130.9, 128.5, 126.9 ($C_{arom\text{-}Cl}$); 116.5 (d, $J_{C2\text{-}F,C6\text{-}F}$ = 8.0 Hz, $C^{2,6}_{arom\text{-}F}$); 115.0 ($J_{C3\text{-}F,C5\text{-}F}$ = 21.9 Hz, $C^{3,5}_{arom\text{-}F}$); 87.0 (C-3a); 73.4 (C-3); 69.9 (C-6a); 21.1 (2 × C^3-*CH*$_2$CH$_3$); 11.7 (C^3-*Me*); 7.0 (2 × C^3-CH$_2$*CH*$_3$). – MS (FAB): m/z = 445/447 $[M+H]^+$. – $C_{22}H_{22}ClFN_4OS$: 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-3,3a-dimethyl-3a,4-dihydro-3H-pyrazolo[4,3-d] thiazol-5(6aH)-ylidene)-benzamide (**45d**)*

From **41d** (714 mg). Yield: 463 mg (52 %), m. p. 159 – 161 °C. – ^{1}H NMR ($CDCl_3$): δ = 7.74 – 7.17 (m, 8H, $H_{arom.}$); 3.15 (s, 1H, H-6a); 2.02 (m, 1H, C^3-C*H*Me$_2$); 1.35 (s, 3H, C^{3a}-*Me*); 1.12 (m, 6H, C^3-CH*Me*$_2$). – ^{13}C NMR ($CDCl_3$): δ = 183.7 (C^5=N); 174.1 (C=O); 151.1 (d, $J_{C4,F}$ = 249 Hz, $C^4_{arom\text{-}F}$); 138.9 (d, $J_{C1,F}$ = 3.0 Hz; $C^1_{arom\text{-}F}$); 136.8, 135.5, 133.7, 131.2, 127.7, 126.8 ($C_{arom\text{-}Cl}$); 116.8 (d, $J_{C2\text{-}F,C6\text{-}F}$ = 8.3 Hz, $C^{2,6}_{arom\text{-}F}$); 115.9 ($J_{C3\text{-}F,C5\text{-}F}$ = 21.7 Hz, $C^{3,5}_{arom\text{-}F}$); 75.8 (C-3a); 74.2 (C-3); 69.6 (C-6a); 31.0 (C^3 – *C*HMe$_2$); 16.3 (C^3-CH*Me*$_2$); 11.6 (C^3-*Me*). – MS (FAB): m/z = 445/447 $[M+H]^+$. – $C_{22}H_{22}ClFN_4OS$: calcd. C 59.39, H 4.98, N 12.59; found C 59.04, H 4.83, N 12.23.

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