Synthesis of New 2-(5-Aryl-3-styryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidines

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Abstract: A series of 2-(5-aryl-3-styryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidines was synthesized by the cyclocondensation of 5-aryl-1-carboxamidino-3-styryl-4,5-dihydro-1*H*-pyrazoles with 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones. Efficient cyclizations catalyzed by $Ti(O\textit{i}\text{-}Pr)_4$ or $BF_3{\cdot}OEt_2$ gave the desired pyrimidines in good yields. The crystal structure of ethyl 3-[2-(5-phenyl-3-styryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidin-6-yl]propanoate was determined.

Key words: 1*H*-pyrazoles, pyrimidines, homogeneous catalysis

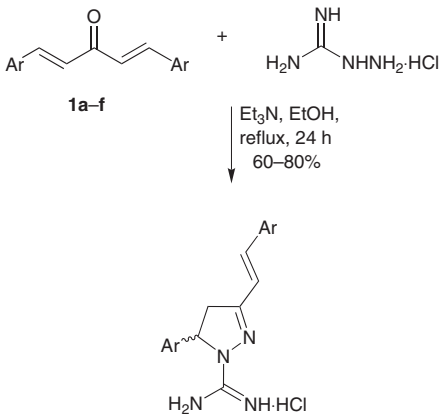
Azole rings play an important role in medicinal and material chemistry, serving as key templates central to the development of numerous novel compounds. Among the many five-membered-ring heterocycles, pyrazoles are the most studied. Nowadays much interest is devoted to polyaromatic pyrazoles owing to their important biological, photochemical, and electronic properties.[1–4]

Previously, we reported convenient synthetic approaches to trihalomethylated pyrazolylpyrimidines: (a) from 2-hydrazino-4-(trifluoromethyl)pyrimidines and 4-alkoxy-1,1,1-trihaloalk-3-en-2-ones by [3+2] cyclocondensation[5] and (b) by one-pot, two-step [3+2] and [3+3] cyclocondensations of 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones (2 equiv) with aminoguanidine.[6]

The 1,3,5-triaryl-4,5-dihydropyrazoles and 5-aryl-3-styryl-4,5-dihydropyrazole derivatives are well-known fluorescent compounds with high quantum yields, and are widely used as whitening or brightening agents,[7,8] and as fluorescence probes in some elaborated chemosensors.[9,10] The photochemical properties of polyaromatic 2-pyrazolines are determined by substituent atoms/groups on the aromatic ring attached at the 1- and 3-positions of 4,5-dihydropyrazole.[11,12] Although many studies of 4,5-dihydropyrazoles substituted with various aromatic rings at C5 and C3 have been reported in the literature, less attention has been paid to the aryl group attached to N1. The 1-substituted 3,5-diaryl-1*H*-pyrazoles found in the literature possess acetyl or phenyl attached at N1.[3,13,14]

Continuing our interest in the preparation and applications of new bi-heterocyclic systems, we now present the synthesis of 5-aryl-1-carboxamidino-3-styryl-4,5-dihydro-1*H*-pyrazole derivatives **2** from [3+2] cyclocondensation of 1,5-diarylpenta-1,4-dien-3-ones **1** and aminoguanidine hydrochloride, and their application in the synthesis of new 2-(5-aryl-3-styryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidines **4**–**15** by [3+3] cyclocondensation of 5-aryl-1-carboxamidino-3-styryl-4,5-dihydro-1*H*-pyrazoles **2** with 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones **3**, in which $Ti(O\textit{i}\text{-}Pr)_4$ or $BF_3{\cdot}OEt_2$ is used as pyrimidine cyclocondensation catalyst.

1,5-Diarylpenta-1,4-dien-3-ones **1a**–**f** were obtained by condensation of acetone with the appropriate benzaldehyde (1:3) in ethanol solution with NaOH.[15] The 5-aryl-1-carboxamidino-3-styryl-4,5-dihydro-1*H*-pyrazoles **2a**–**f** were synthesized by the reactions of 1,5-diarylpenta-1,4-dien-3-ones **1a**–**f** with aminoguanidine hydrochloride in the presence of triethylamine in ethanol, under reflux for 24 hours (Scheme 1). When the mixture had cooled to 25 °C, the unreacted starting material precipitated and was removed by filtration. Compounds **2a**–**f** were obtained as hydrochlorides, yellow solids that formed in 60–85 yield.



1, 2	a	b	c	d
Ar	Ph	2-MeC_6H_4	4-MeC_6H_4	4-$MeOC_6H_4$

1, 2	e	f
Ar	3,4-$(MeO)_2C_6H_3$	3,4,5-$(MeO)_3C_6H_2$

Scheme 1 Synthesis of 1-carboxamidino-1*H*-pyrazoles

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5-Aryl-1-carboxamidino-3-styryl-4,5-dihydro-1*H*-pyrazoles **2** crystallized with hydrochloride molecules in the unit cell. The products **2a–f** were characterized by ^{1}H, ^{13}C, and ^{35}Cl NMR spectroscopy. The chemical shifts in the ^{35}Cl NMR spectrum were between δ = –0.2 to 1.3 referenced to external $KClO_4$ at δ = 1007.0.[16] 5-Aryl-1-carboxamidino-3-styryl-4,5-dihydro-1*H*-pyrazole hydrochlorides **2a–f** are strategic 1,3-dielectrophilic amidines for heterocyclizations to different 2-(1*H*-pyrazolyl)pyrimidines.

Initially, the reactions of the 1-carboxamidino-4,5-dihydro-1*H*-pyrazole series **2** with 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones **3** (Scheme 2) were carried out in refluxing ethanol, with reaction times of 2–72 hours, depending on the pyrazole **2** used (Table 1). Under conventional ethanol reflux conditions, pyrazoles **2b**, **2c**, **2e**, and **2f** gave poor yields, even after long reaction times.

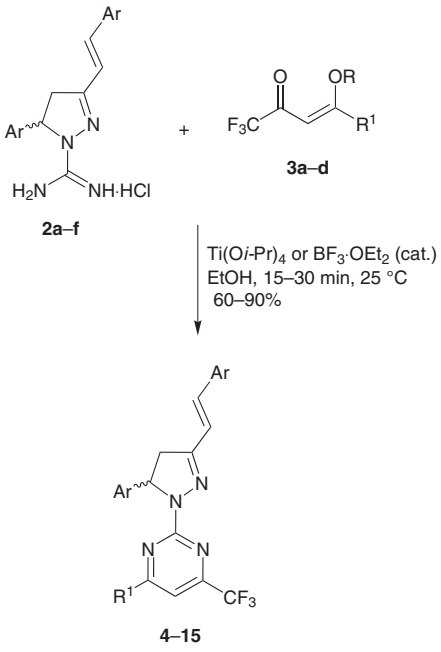
With the use of $Ti(O\textit{i}\text{-}Pr)_4$ or $BF_3{\cdot}OEt_2$ as catalysts, the reaction times were drastically reduced (Table 1).[6] For the great majority of reactions, pyrazolylpyrimidine products **4–15** precipitated, generally as crystalline yellow solids, immediately after the Lewis acid $Ti(O\textit{i}\text{-}Pr)_4$ or $BF_3{\cdot}OEt_2$ had been added; with the catalysts, better yields were obtained in shorter reaction times (15–30 min, Scheme 2, Table 1) than without a catalyst.

Like their precursors, 2-pyrazol-1-ylpyrimidines **4–15** were identified by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectra of products **4–15** showed sets of signals corresponding to the proposed structures. The AMX spin system of the three protons on the 4,5-dihydro-1*H*-pyrazole rings gives rise to three doublets of doublets; of these, the peaks appearing at approximately δ = 3.05–3.20 with approximate coupling constants *J* = 17.2 and 5.0 Hz, attributable to geminal and vicinal coupling, respectively, can be assigned to the *trans* H-4. The doublet of doublets at approximately δ = 3.50–3.70, with two large coupling constants around *J* = 12.0 and 17.2 Hz is assigned to the *cis* H-4. The remaining doublet of doublets at approximately δ = 5.75 with *J* = 5.2 and 12.0 Hz is due to H-5. For representative example **8**, it was possible to see the doublets from vinylic hydrogens in the styryl moiety at 6.88 ppm and 7.26 ppm with $^{3}J_{trans}$ = 16.3 Hz. The signals from H-5 on the pyrimidine ring was a singlet at 6.68 ppm; all were confirmed by HMQC experiments.

The ^{13}C NMR spectra of pyrazolylpyrimidine products **4–15** contained sets of signals corresponding to the postulated structure. The assignment of the ^{13}C chemical shifts of 2-(5-aryl-3-styryl-4,5-dihydro-1*H*-pyrazol-1-yl)pyrimidines **4–15** can be illustrated with that of representative example **8**. The 4,5-dihydro-1*H*-pyrazole carbons appeared at δ = 40.4, 58.6, and 154.8, assigned to C-4, C-5, and C-3, respectively. The carbon signals from the 4-(trifluoromethyl)pyrimidine moiety were at δ = 106.9 ($^{3}J_{CF}$ = 2.2 Hz), 120.5 (J_{CF} = 275.5 Hz), 155.9 ($^{2}J_{CF}$ = 36.7 Hz), 157.9, and 171.3. The remaining 14 carbon signals appearing in the range δ = 122.6 to 140.7 corresponded to vinyl and aryl structures.

The ^{19}F NMR spectra of the compounds **4–15** contained signals due to the trifluoromethyl groups attached to the pyrimidine rings from δ = –70.0 to –71.0 relative to the external standard $CFCl_3$.[17,18]

A single-crystal X-ray diffraction study confirmed the structure of compound **6** (Figure 1, Tables 2 and 3). In the crystal structure of **6**, the 4,5-dihydropyrazole and pyrimidine rings are almost coplanar (rms deviations of 0.0111 and 0.0056 Å, respectively, from the best-fit plane for each ring), with an angle of 7.79(16)° between the two rings (Figure 1).



3	a	b	c	d	e	f
R	Et	Me	Me	Me	Me	Me
R^1	H	Me	-$(CH_2)_2CO_2Me$	Ph	2-furyl	2-thienyl

	4	5	6	7	8
R^1	H	Me	-$(CH_2)_2CO_2Et$	Ph	Me
Ar	Ph	Ph	Ph	Ph	4-MeC_6H_4

	9	10	11	12
R^1	Ph	2-furyl	2-thienyl	Me
Ar	2-MeC_6H_4	2-MeC_6H_4	2-MeC_6H_4	4-$MeOC_6H_4$

	13	14	15
R^1	Ph	Ph	Ph
Ar	4-$MeOC_6H_4$	3,4-$(MeO)_2C_6H_3$	3,4,5-$(MeO)_3C_6H_2$

Scheme 2 Lewis acid catalyzed cyclocondensation to give 2-(5-aryl-3-styryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidines

Table 1 Comparison of Yields and Reaction Times for the Synthesis of 2-(5-Aryl-3-styryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidines by Ti(O*i*-Pr)$_4$ or $BF_3{\cdot}OEt_2$ Catalysis[a] and under Conventional Conditions[b]

Product	Conditions	Time	Yield (%)
4	Reflux	2 h	62
4	Ti(O*i*-Pr)$_4$	15 min	87
5	Reflux	4 h	73
5	Ti(O*i*-Pr)$_4$	15 min	90
6	Reflux	16 h	57
6	Ti(O*i*-Pr)$_4$	15 min	81
7	Reflux	24 h	40
7	Ti(O*i*-Pr)$_4$	15 min	77
7	$BF_3{\cdot}OEt_2$	15 min	95
9	Reflux	24 h	30
9	Ti(O*i*-Pr)$_4$	15 min	83
9	$BF_3{\cdot}OEt_2$	15 min	67
10	Reflux	24–48 h	Traces
10	Ti(O*i*-Pr)$_4$	15 min	60
12	$BF_3{\cdot}OEt_2$	15 min	95
14	Reflux	24 h	40
14	Ti(O*i*-Pr)$_4$	15 min	88
14	$BF_3{\cdot}OEt_2$	15 min	90
15	Reflux	24 h	20
15	Ti(O*i*-Pr)$_4$	30 min	66
15	$BF_3{\cdot}OEt_2$	15 min	61

[a] In dry ethanol at 25 °C under argon.
[b] In dry ethanol at reflux.

In conclusion, this work demonstrates the efficient catalysis with Ti(O-*i*-Pr)$_4$ and $BF_3{\cdot}OEt_2$, successfully decreasing the reaction times and increasing the yields of isolated products, for the cyclocondensation of 5-aryl-1-carboxamidino-3-styryl-4,5-dihydro-1*H*-pyrazoles with 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones to afford promising 2-(5-aryl-3-styryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidines.

Unless otherwise stated, all reagents and solvents were purchased from commercial sources and used without further purification (EtOH, Aldrich). Melting points were determined using open capillaries on Electrothermal Mel-Temp 3.0 apparatus and are uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz, ^{13}C at 100.62 MHz, ^{19}F at 376.30 MHz, and ^{35}Cl at 39.2 MHz); measurements were done in 5-mm sample tubes, at 300 K, with digital resolution ±0.01, and in $CDCl_3$ or DMSO-d_6 with TMS as internal standard. ^{19}F NMR spectra were calibrated relative to $CFCl_3$ using external fluorobenzene at –113.1 ppm. ^{35}Cl NMR spectra were calibrated from external $KClO_4$ at δ = 1007 (NaCl: δ = 0.0 ppm, 0.5 M solution in DMSO-d_6). The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (São Paulo University, USP, Brazil).

Table 2 Crystal Data and Structure Refinement for 2-(3-Aryl-5-styryl-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidine **6**

CCDC No.	283448
Formula	$C_{27}H_{25}F_3N_4O_2$
Habit	Colorless, plate
Size (mm)	0.38 × 0.34 × 0.17
Symmetry	Triclinic, *P*–1
Unit cell dimensions (Å, °)	*a* = 9.8597(3) α = 118.159(2) *b* = 12.3869(4) β = 98.876(2) *c* = 12.3975(3) γ = 104.980(2)
Volume (Å^3), *Z*	1219.81(7), 2
D_c (g·cm^{-3}), *F*(000)	1.346, 516
μ (mm^{-1})	0.102
θ range for data collection (°)	3.41 < θ < 26.99
Index ranges	–12 ≤ *h* ≤ 12 –15 ≤ *k* ≤ 15 –15 ≤ *l* ≤ 15
Reflections collected	27554
Independent reflections (R_{int})	5313 (0.0235)
Completeness to θ	99.8%
$T_{min} - T_{max}$	0.9622–0.9828
Solution	Direct methods SHELXS-97
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5313/0/340
Goodness-of-fit on F^2	1.053
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.0554, *wR*2 = 0.1568
R indices (all data)	*R*1 = 0.0757, *wR*2 = 0.1747
Largest diff. peak and hole (e·Å^3)	0.508 and –0.347

The crystal and molecular structure of **6** was determined by a single-crystal X-ray diffraction study. Data were recorded on a Bruker Kappa Apex II CCD area detector with graphite monochromatized Mo K_α radiation (λ = 0.71073 Å). The data were processed with SAINT and SADABS. The structure was solved by direct methods (SHELXS-97) and additional atoms were located in the difference Fourier map and refined on F^2 (SHELXL-97) using the SHELXTL[19] and Wingx[20] packages. The trifluoromethyl group presents rotational disorder; the three F atoms were refined in a position rotated approximately 45° from their original positions at 5.3% occupancy.

Compounds 2a–f; General Procedure

A mixture of 1,5-diarylpenta-1,4-dien-3-one **1** (4 mmol), aminoguanidine hydrochloride (10 mmol), and Et_3N (10 mmol) was refluxed in dry EtOH (25 mL) for 24 h. After the soln had been

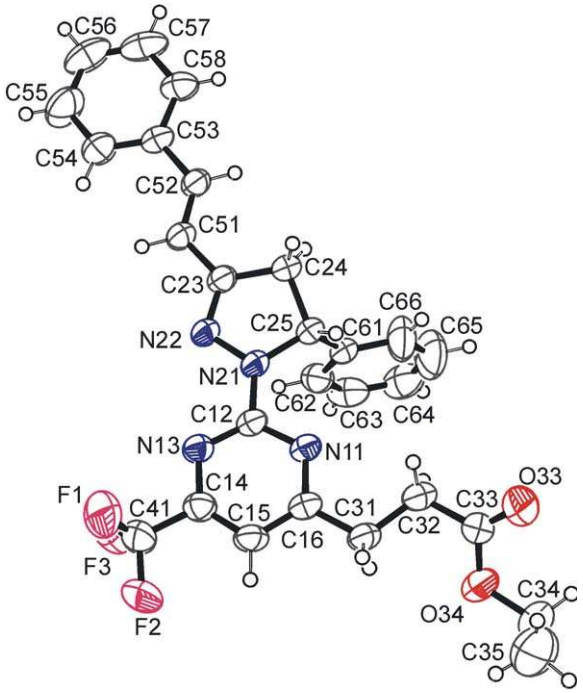


Figure 1 ORTEP representation of the X-ray crystal structure of **6** at the 50% probability level; the minor components of the disordered F atoms are omitted for clarity.

cooled, the aminoguanidine hydrochloride excess was removed by filtration. The solvent was removed in vacuo and the residue was dissolved in $CHCl_3$ and washed with deionized H_2O (3 × 30 mL). The organic layer was dried over anhyd Na_2SO_4 and the solvent was evaporated. The yellow, solid 1-carboxamidino-4,5-dihydro-1*H*-pyrazole hydrochlorides **2a–f** thus obtained (60–80% yield) were used without further purification.

1-Carboxamidino-5-phenyl-3-styryl-4,5-dihydro-1*H*-pyrazole (2a)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.0 (dd, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 5.0 Hz, 1 H, H-4 *trans*), 3.7 (dd, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 12.0 Hz, 1 H, H-4 *cis*), 5.4 (dd, $^2J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 5.0 Hz, 1 H, H-5), 6.65 (d, ^2J = 16.4 Hz, 1 H, styryl), 7.0 (d, ^2J = 16.4 Hz, 1 H, styryl), 7.25–7.50 (br m, 10 H, Ar, amidine).

^{13}C NMR (400 MHz, DMSO-d_6): δ = 39.9 (Pyr C-4), 63.5 (Pyr C-5), 122.2 (styryl CH), 127.6, 127.7, 128.5, 128.6, 128.8, 128.9 (Ar), 132.0 (styryl CH) 150.8 (Pyr C-3), 152.0 (amidine C).

^{35}Cl NMR (39.2 MHz, DMSO-d_6): δ = 1.3.

1-Carboxamidino-3-(2-methylstyryl)-5-(2-tolyl)-4,5-dihydro-1*H*-pyrazole (2b)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.35 (s, 3 H, 2-Me), 2.5 (s, 3 H, 2-Me), 3.0 (dd, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 4.0 Hz, 1 H), 3.9 (dd, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 11.0 Hz, 1 H), 6.20 (dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 4.0 Hz, 1 H), 6.90–7.55 (br m, 13 H, Ar, styryl, amidine).

^{13}C NMR (400 MHz, DMSO-d_6): δ = 19.4 (2-Me), 19.7 (2-Me), 41.8 (Pyr C-4), 59.0 (Pyr C-5), 120.0 (styryl CH), 125.7, 126.4, 126.7, 127.2, 128.5, 129.5, 130.3, 131.6, 133.8, 135.1, 136.0, 136.5, 137.3 (Ar, styryl), 153.4 (Pyr C-3), 158.2 (amidine C).

^{35}Cl NMR (39.2 MHz, DMSO-d_6): δ = 1.1.

1-Carboxamidino-3-(4-methylstyryl)-5-(4-tolyl)-4,5-dihydro-1*H*-pyrazole (2c)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.0 (s, 3 H, 4-Me), 2.1 (s, 3 H, 2-Me), 3.2 (dd, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 3.8 Hz, 1 H), 3.9 (dd, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 11.0 Hz, 1 H), 5.9 (dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 3.8 Hz, 1 H), 6.80–7.62 (br m, 13 H, Ar, styryl, amidine).

^{13}C NMR (400 MHz, DMSO-d_6): δ = 21.0 (4-Me), 21.3 (4-Me), 42.0 (Pyr C-4), 59.7 (Pyr C-5), 119.0 (styryl CH), 125.2, 125.7, 126.7, 127.2, 127.8, 129.3, 129.9, 131.6, 133.8, 134.3, 137.0, 137.5, 138.3 (Ar, styryl), 151.2 (Pyr C-3), 158.2 (amidine C).

^{35}Cl NMR (39.2 MHz, DMSO-d_6): δ = –0.2.

1-Carboxamidino-5-(4-methoxyphenyl)-3-(4-methoxystyryl)-4,5-dihydro-1*H*-pyrazole (2d)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.0 (dd, $^2J_{HH}$ = 16.8 Hz, $^3J_{HH}$ = 3.8 Hz, 1 H), 3.84 (s, 3 H, 4-MeO), 3.85 (dd, $^2J_{HH}$ = 16.8 Hz, $^3J_{HH}$ = 11.0 Hz, 1 H), 3.86 (s, 3 H, 4-MeO), 5.8 (dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 3.8 Hz, 1 H); 6.80–7.40 (m, 9 H, Ar, styryl), 7.6 (d, $^3J_{HH}$ = 16 Hz, 1 H, styryl), 7.9 (br, amidine).

^{13}C NMR (400 MHz, DMSO-d_6): δ = 56.4 (4-MeO), 56.8 (4-MeO), 43.0 (Pyr C-4), 59.8 (Pyr C-5), 118.8 (styryl CH), 123.7, 124.4, 125.5, 126.2, 128.0, 128.6, 131.3, 133.0, 133.8, 135.2, 136.0, 146.0, 146.3 (Ar, styryl), 150.5 (Pyr C-3), 159.2 (amidine C).

^{35}Cl NMR (39.2 MHz, DMSO-d_6): δ = –0.3.

1-Carboxamidino-5-(3,4-dimethoxyphenyl)-3-(3,4-dimethoxystyryl)-4,5-dihydro-1*H*-pyrazole (2e)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.0 (dd, $^2J_{HH}$ = 17 Hz, $^3J_{HH}$ = 4.2 Hz, 1 H), 3.6 (dd, $^2J_{HH}$ = 17 Hz, $^3J_{HH}$ = 12 Hz, 1 H), 3.78 (s, 3 H, MeO), 3.8 (s, 3 H, MeO), 3.85 (s, 6 H, MeO), 4.7 (br, amidine), 5.6 (dd, $^2J_{HH}$ = 12 Hz, $^3J_{HH}$ = 4.2 Hz, 1 H); 6.6–7.0 (m, 8 H, Ar, styryl).

^{13}C NMR (400 MHz, DMSO-d_6): δ = 43.3 (Pyr C-4), 55.9 (MeO), 55.95 (MeO), 56.1 (MeO), 60.8 (Pyr C-5), 109.1, 109.3, 111.2, 111.8, 117.0, 117.8, 121.5 (styryl), 128.1, 131.4, 139.5, 149.0, 149.3, 150.7, 137.3 (Ar, styryl), 153.4 (Pyr C-3), 157.6 (amidine C).

^{35}Cl NMR (39.2 MHz, DMSO-d_6): δ = –0.2.

1-Carboxamidino-5-(3,4,5-trimethoxyphenyl)-3-(3,4,5-trimethoxystyryl)-4,5-dihydro-1*H*-pyrazole (2f)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.1 (dd, $^2J_{HH}$ = 17 Hz, $^3J_{HH}$ = 4.0 Hz, 1 H), 3.7 (dd, $^2J_{HH}$ = 17 Hz, $^3J_{HH}$ = 12 Hz, 1 H), 3.78 (s, 3 H, MeO), 3.8 (s, 6 H, 2 × MeO), 3.85 (s, 3 H, MeO), 3.9 (s, 6 H, MeO), 5.45 (dd, $^2J_{HH}$ = 12 Hz, $^3J_{HH}$ = 4 Hz, 1 H), 5.8 (br, amino-hydrogens), 6.6 (s, 2 H, Ar), 6.63 (d, $^3J_{HH}$ = 16.8 Hz, 1 H, styryl), 6.73 (s, 2 H, Ar), 7.3 (d, $^3J_{HH}$ = 16.8 Hz, 1 H, styryl).

^{13}C NMR (400 MHz, DMSO-d_6): δ = 43.0 (Pyr C-4), 55.9 (MeO), 56.0 (MeO), 56.3 (MeO), 56.6 (MeO), 60.1 (Pyr C-5), 109.1, 109.3, 111.2, 111.8, 117.0, 117.8 (Ar), 121.5 (styryl), 128.1, 131.4 (Ar), 139.5 (styryl), 148.3, 149.0, 150.7 (Ar), 151.9 (Pyr C-3), 157.9 (amidine C).

^{35}Cl NMR (39.2 MHz, DMSO-d_6): δ = 0.8.

Compounds 4–15; General Procedure

To a mixture of pyrazole hydrochloride **2** (1.2 mmol) and 4-alkoxy-1,1,1-trifluoroalk-3-en-2-one **3** (1 mmol) in dry EtOH (3–5 mL) was added a catalytic amount (3 drops) of BF_3·OEt_2 or Ti(O*i*-Pr)$_4$. A yellow solid separated out, and after the mixture had stirred for 15 min, the product was isolated by filtration, washed with cold EtOH (2 × 5 mL), and crystallized from $CHCl_3$; this afforded pure 2-(4,5-dihydro-1*H*-pyrazol-1-yl)pyrimidines **4–15**.

Table 3 Bond Lengths (Å) and Angles (°) for 2-(3-Aryl-5-styryl-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidine **6**

F(1)–C(41)	1.334(4)
F(2)–C(41)	1.322(3)

Table 3 Bond Lengths (Å) and Angles (°) for 2-(3-Aryl-5-styryl-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidine **6** (continued)

F(3)–C(41)	1.319(3)
N(11)–C(16)	1.329(2)
N(11)–C(12)	1.352(2)
C(12)–N(13)	1.338(2)
C(12)–N(21)	1.364(2)
N(13)–C(14)	1.333(2)
C(14)–C(15)	1.362(3)
C(14)–C(41)	1.511(3)
C(15)–C(16)	1.399(3)
C(16)–C(31)	1.498(3)
N(21)–N(22)	1.384(2)
N(21)–C(25)	1.472(2)
N(22)–C(23)	1.292(2)
C(23)–C(51)	1.442(2)
C(23)–C(24)	1.505(3)
C(24)–C(25)	1.537(2)
C(33)–O(33)	1.200(3)
C(33)–O(34)	1.319(3)
C(34)–C(35)	1.453(5)
C(34)–O(34)	1.464(3)
C(16)–N(11)–C(12)	116.46(16)
N(13)–C(12)–N(11)	127.03(16)
N(13)–C(12)–N(21)	118.87(16)
N(11)–C(12)–N(21)	114.10(16)
C(14)–N(13)–C(12)	113.90(16)
N(13)–C(14)–C(15)	124.90(19)
N(13)–C(14)–C(41)	114.12(18)
C(15)–C(14)–C(41)	120.97(19)
C(14)–C(15)–C(16)	116.49(17)
N(11)–C(16)–C(15)	121.20(17)
N(11)–C(16)–C(31)	118.96(17)
C(15)–C(16)–C(31)	119.83(16)
C(12)–N(21)–N(22)	121.95(15)
C(12)–N(21)–C(25)	124.45(15)
N(22)–N(21)–C(25)	113.41(13)
C(23)–N(22)–N(21)	107.39(15)

Table 3 Bond Lengths (Å) and Angles (°) for 2-(3-Aryl-5-styryl-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidine **6** (continued)

N(22)–C(23)–C(51)	120.97(17)
N(22)–C(23)–C(24)	113.87(16)
C(51)–C(23)–C(24)	125.14(16)
C(23)–C(24)–C(25)	102.09(14)
H(24A)–C(24)–H(24B)	109.2
N(21)–C(25)–C(61)	112.74(15)
N(21)–C(25)–C(24)	100.63(14)
C(61)–C(25)–C(24)	112.16(15)
C(16)–C(31)–C(32)	115.33(16)

2-(5-Phenyl-3-styryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidine (4)

Mp 170–172 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.22 (dd, $^2J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 4.6 Hz, 1 H, Pyr H-4 *trans*), 3.74 (dd, $^2J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 11.6 Hz, 1 H, Pyr H-4 *cis*), 5.69 (dd, $^3J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 4.6 Hz, 1 H, Pyr H-5), 6.77 (d, $^3J_{HH}$ = 16.40 Hz, 1 H, styryl CH), 6.86 (d, $^3J_{HH}$ = 4.8 Hz, 1 H, Pyrim H-5), 7.26–7.47 (m, 11 H, Ar, styryl), 8.6 (d, $^3J_{HH}$ = 4.8 Hz, 1 H, Pyrim H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.07 (Pyr C-4), 62.11 (Pyr C-5), 107.0 (Pyrim C-5), 120.3 ($^1J_{CF}$ = 275 Hz, CF_3), 121.2 (styryl CH=), 125.4, 126.3, 127.0, 127.6, 128.6, 128.9, 135.94 (Ar), 136.5 (styryl CH=), 141.7 (Ar), 155.0 (Pyr C-3), 156.2 ($^2J_{CF}$ = 36.5 Hz, Pyrim C-4), 158.0 (Pyrim C-2), 160.7 (Pyrim C-6).

^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –70.5.

MS (EI, 70 eV): *m*/*z* (%) = 394 (88) [M$^+$], 289 (41), 252 (92), 143 (100), 115 (40).

Anal. Calcd for $C_{22}H_{17}F_3N_4$: C, 67.00; H, 4.34; N, 14.21. Found: C, 67.25; H, 4.50; N, 14.35.

6-Methyl-2-(5-phenyl-3-styryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidine (5)

Mp 150–153 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48 (s, 3 H, Me), 3.2 (dd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 4.7 Hz, 1 H, Pyr H-4 *trans*), 3.71 (dd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 11.9 Hz, 1 H, Pyr H-4 *cis*), 5.69 (dd, $^3J_{HH}$ = 11.9 Hz, $^3J_{HH}$ = 4.7 Hz, 1 H, Pyr H-5), 6.75 (d, $^3J_{HH}$ = 16.4 Hz, 1 H, styryl CH), 6.75 (s, 1 H, Pyrim H-5), 7.19–7.46 (m, 11 H, Ar, styryl CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7 (Me), 40.8 (Pyr C-4), 62.1 (Pyr C-5), 107.0 ($^3J_{CF}$ = 2.7 Hz, Pyrim C-5), 120.53 ($^1J_{CF}$ = 274 Hz, CF_3), 121.5 (styryl CH), 126.4, 126.9, 127.5, 128.5, 128.8, 128.9, 136.0 (Ar), 136.1 (styryl CH), 142.0 (Ar), 154.7 (Pyr C-3), 155.9 ($^2J_{CF}$ = 35.2 Hz, Pyrim C-4), 157.9 (Pyrim C-2), 171.2 (Pyrim C-6).

^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –70.43.

MS (EI, 70 eV): *m*/*z* (%) = 408 (91.5) [M$^+$], 389 (8), 303 (17), 278 (90), 266 (100), 202 (27), 143 (78), 115 (29).

Anal. Calcd for $C_{23}H_{19}F_3N_4$: C, 67.64; H, 4.69; N, 13.62. Found: C, 67.80; H, 4.60; N, 13.85.

Ethyl 3-[2-(5-Phenyl-3-styryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidin-6-yl]propanoate (6)

Mp 196–197 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, $^3J_{HH}$ = 6.80 Hz, 3 H, Me), 2.63 (m, 2 H, CH_2), 2.99 (m, 2 H, CH_2), 3.16 (dd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 4.8 Hz, 1 H, Pyr H-4 *trans*), 3.69 (dd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 11.9 Hz, 1 H, Pyr H-4 *cis*), 4.09 (m, $^3J_{HH}$ = 6.8 Hz, 2 H, CH_2), 5.65 (dd, $^3J_{HH}$ = 11.9 Hz, $^3J_{HH}$ = 4.8 Hz, 1 H, Pyr H-5), 6.73 (d, $^3J_{HH}$ = 16.4 Hz, 1 H, styryl CH), 6.79 (s, 1 H, Pyrim H-5), 7.26–7.47 (m, 11 H, Ar, styryl CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (Me), 31.5 (CH_2), 32.4 (CH_2), 40.9 (Pyr C-4), 60.4 (CH_2), 62.3 (Pyr C-5), 106.5 (Pyrim C-5, $^3J_{CF}$ = 2.2 Hz), 120.5 (CF_3, $^1J_{CF}$ = 275.5 Hz), 121.4 (styryl CH), 126.2, 127.0, 127.5, 128.6, 128.9, 136.0 (Ar), 136.4 (styryl CH), 142.1 (Ar), 155.0 (Pyr C-3), 156.4 ($^2J_{CF}$ = 35.4 Hz, Pyrim C-4), 157.6 (Pyrim C-2), 172.3 (CO_2Et), 172.4 (Pyrim C-6).

^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –70.46.

MS (EI, 70 eV): *m*/*z* (%) = 494 (90) [M$^+$], 449 (22), 306 (39), 278 (100), 230 (40), 143 (80), 115 (25).

Anal. Calcd for $C_{27}H_{25}F_3N_4O_2$: C, 65.58; H, 5.10; N, 11.33. Found: C, 65.58; H, 5.10; N, 11.33.

6-Phenyl-2-(5-phenyl-3-styryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidine (7)
Mp 164–167 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.19 (dd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 5.2 Hz, 1 H, Pyr H-4 *trans*), 3.72 (dd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 12.0 Hz, 1 H, Pyr H-4 *cis*), 5.76 (dd, $^3J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 5.2 Hz, 1 H, Pyr H-5), 6.74 (d, $^3J_{HH}$ = 16.4 Hz, 1 H, styryl), 7.23–7.50 (m, 14 H, Ar, styryl CH, Pyrim H-5), 7.82 (m, 2 H, Pyrim 6-Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.1 (Pyr C-4), 62.6 (Pyr C-5), 103.2 ($^3J_{HH}$ = 2.2 Hz, Pyrim C-5), 120.7 ($^1J_{CF}$ = 275.5 Hz, CF_3), 121.6 (styryl CH), 126.0, 126.9, 127.3, 127.6, 127.5, 128.7, 128.7, 128.8, 131.3, 136.0 (Ar), 136.1 (styryl CH), 136.2, 142.5 (Ar), 154.6 (Pyr C-3), 157.3 ($^2J_{CF}$ = 35.1 Hz, Pyrim C-4), 158.3 (Pyrim C-2), 167.3 (Pyrim C-6).

MS (EI, 70 eV): *m*/*z* (%) = 470 (70) [M$^+$], 365 (23), 340 (100), 328 (83), 264 (25), 128 (56), 115 (45), 103 (59).

Anal. Calcd for $C_{28}H_{19}Cl_2F_3N_4$: C, 62.35; H, 3.55; N, 10.39. Found: C, 62.50; H, 3.75; N, 10.70.

6-Methyl-2-[3-(4-methylstyryl)-5-(4-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-(trifluoromethyl)pyrimidine (8)
Mp 176–178 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, 4-Me), 2.42 (s, 3 H, Pyrim 6-Me), 2.47 (s, 3 H, 4-Me), 3.02 (dd, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 5.2 Hz, 1 H, Pyr H-4 *trans*), 3.66 (dd, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 12.1 Hz, 1 H, Pyr H-4 *cis*), 5.81 (dd, $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 5.2 Hz, 1 H, Pyr H-5), 6.68 (s, 1 H, Pyrim H-5), 6.88 (d, $^3J_{HH}$ = 16.3 Hz, 1 H, styryl), 7.01–7.16 (m, 7 H, Ar), 7.26 (d, $^3J_{HH}$ = 16.3 Hz, 1 H, styryl), 7.49 (m, 1 H, Ar).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3 (Me), 19.8 (Me), 24.8 (Pyrim 6-Me), 40.4 (Pyr C-4), 58.6 (Pyr C-5), 106.9 (Pyrim C-5), 120.5 ($^1J_{CF}$ = 275.5 Hz, CF_3), 122.6, 124.7, 125.6, 126.5, 126.7, 127.3, 128.6, 130.2, 130.7, 133.5, 134.8 (Ar), 136.0 (styryl CH), 140.7 (Ar), 154.8 (Pyr C-3), 155.9 ($^2J_{CF}$ = 35.2 Hz, Pyrim C-4), 157.9 (Pyrim C-2), 171.3 (Pyrim C-6).

MS (EI, 70 eV): *m*/*z* (%) = 436 (100) [M$^+$], 421 (81), 345 (61), 303 (26), 280 (95), 258 (36), 215 (14), 157 (92), 128 (37), 115 (83).

Anal. Calcd for $C_{25}H_{23}F_3N_4$: C, 68.79; H, 5.31; N, 12.84. Found: C, 68.90; H, 5.35; N, 12.80.

2-[3-(2-Methylstyryl)-5-(2-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-6-phenyl-4-(trifluoromethyl)pyrimidine (9)
Mp 199–201 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, 5-aryl Me), 2.47 (s, 3 H, styryl Me), 3.0 (dd, $^2J_{HH}$ = 16.9 Hz, $^3J_{HH}$ = 5.5 Hz, 1 H, Pyr H-4 *trans*), 3.69 (dd, $^2J_{HH}$ = 16.9 Hz, $^3J_{HH}$ = 12.2 Hz, 1 H, Pyr H-4 *cis*), 5.85 (dd, $^3J_{HH}$ = 12.2 Hz, $^3J_{HH}$ = 5.5 Hz, 1 H, Pyr H-5), 6.87 (d, $^2J_{HH}$ = 16.3 Hz, 1 H, styryl), 7.05–7.32 (m, 13 H, aryl, styryl CH, Pyrim H-5), 7.69 (m, 2 H, Pyrim 6-Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5 (Me), 19.8 (Me), 40.2 (Pyr C-4), 59.3 (Pyr C-5), 103.3 ($^3J_{CF}$ = 2.4 Hz, Pyrim C-5), 120.7 ($^1J_{CF}$ = 275.5 Hz, CF_3), 122.6 (styryl CH), 124.6, 125.6, 126.5, 126.8, 127.3, 127.4, 128.6, 128.7, 130.3, 130.6, 131.3, 133.5 (aryl, styryl CH), 134.3, 134.8, 136.0, 136.3, 140.6, 154.8 (aryl, Pyr C-3), 157.3 ($^2J_{CF}$ = 34.4 Hz, Pyrim C-4), 158.2 (Pyrim C-2), 167.4 (Pyrim C-6).

MS (EI, 70 eV): *m*/*z* (%) = 498 (50) [M$^+$], 483 (38), 407 (20), 342 (44), 223 (22), 157 (27), 130 (49), 115 (100), 91 (52).

Anal. Calcd for $C_{28}H_{21}F_3N_4$: C, 72.28; H, 5.05; N, 11.24. Found: C, 72.5; H, 5.1; N, 11.1.

6-(2-Furyl)-2-[3-(2-methylstyryl)-5-(2-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-(trifluoromethyl)pyrimidine (10)
Mp 245–246 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, 5-aryl Me), 2.57 (s, 3 H, styryl Me), 3.07 (dd, $^2J_{HH}$ = 16.9 Hz, $^3J_{HH}$ = 5.5 Hz, 1 H, Pyr H-4 *trans*), 3.75 (dd, $^2J_{HH}$ = 16.9 Hz, $^3J_{HH}$ = 12.0 Hz, 1 H, Pyr H-4 *cis*), 5.89 (dd, $^3J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 5.5 Hz, 1 H, Pyr H-5), 6.51 (d, $^3J_{HH}$ = 1.8 Hz, 1 H, Furyl H-4), 6.93 (d, $^2J_{HH}$ = 16.2 Hz, 1 H, styryl), 7.10–7.25 (m, 9 H, Ar, Pyrim H-5), 7.34 (d, $^2J_{HH}$ = 16.2 Hz, 1 H, styryl), 7.55 (s, 1 H, Furyl H-3), 7.58 (1 H, Furyl H-5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4 (Me), 19.7 (Me), 40.3 (Pyr C-4), 59.0 (Pyr C-5), 101.5 (Pyrim C-5), 112.5 (Furyl), 113.4 (Furyl), 120.5 ($^1J_{CF}$ = 275.5 Hz, CF_3), 122.6 (styryl CH), 124.6, 125.7, 126.5, 126.8, 127.3, 128.6, 130.3, 130.6, 133.5, 134.3, 134.8 (Ar), 136.0 (styryl CH), 140.6 (Furyl), 145.3 (Furyl), 151.4 (Ar), 154.8 (Pyr C-3), 157.1 ($^2J_{CF}$ = 37.8 Hz, Pyrim C-4), 158.1 (Pyrim C-2), 158.3 (Pyrim C-6).

MS (EI, 70 eV) *m*/*z* (%) = 488 (84) [M$^+$], 473 (59), 397 (35), 332 (100), 244 (30), 213 (23), 157 (80), 115 (95).

Anal. Calcd for $C_{28}H_{23}F_3N_4O$: C, 68.84; H, 4.75; N, 11.47. Found: C, 68.6; H, 4.60; N, 11.50.

2-[3-(2-Methylstyryl)-5-(2-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-6-(2-thienyl)-4-(trifluoromethyl)pyrimidine (11)
Mp 261–263 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, Ar Me), 2.59 (s, 3 H, styryl Me), 3.04 (dd, $^2J_{HH}$ = 16.8 Hz, $^3J_{HH}$ = 5.2 Hz, 1 H, Pyr H-4 *trans*), 3.76 (dd, $^2J_{HH}$ = 16.8 Hz, $^3J_{HH}$ = 12.0 Hz, 1 H, Pyr H-4 *cis*), 5.93 (dd, $^3J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 5.2 Hz, 1 H, Pyr H-5), 6.94 (d, $^3J_{HH}$ = 16.2 Hz, 1 H, styryl), 7.06–7.25 (m, 9 H, Ar, Pyrim H-5), 7.32 (d, $^3J_{HH}$ = 16.2 Hz, 1 H, styryl), 7.46 (d, $^3J_{HH}$ = 4.8 Hz, 1 H, thienyl H-3), 7.58 (dd, 1 H, thienyl H-4), 7.63 (d, 1 H, thienyl H-5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7 (Me), 19.8 (Me), 40.2 (Pyr C-4), 59.3 (Pyr C-5), 101.8 (Pyrim C-5), 120.6 ($^1J_{CF}$ = 275.5 Hz, CF_3), 122.6 (styryl CH), 124.4, 125.7, 126.5, 126.7, 127.2, 128.2 (Ar), 128.4 (thienyl), 128.7 (Ar), 130.5 (thienyl), 130.6 (Ar), 130.9 (thienyl), 133.6 (Ar), 134.1 (thienyl), 134.8 (Ar), 136.1 (styryl CH), 140.4, 142.0 (Ar), 155.0 (Pyr C-3), 157.1 ($^2J_{CF}$ = 36.8 Hz, Pyrim C-4), 158.0 (Pyrim C-2), 161.8 (Pyrim C-6).

MS (EI, 70 eV): *m*/*z* (%) = 504 (5) [M$^+$], 491 (58), 475 (65), 399 (23), 357 (15), 334 (50), 244 (22), 157 (66), 128 (42), 115 (100).

Anal. Calcd for $C_{28}H_{23}F_3N_4S$: C, 66.65; H, 4.59; N, 11.10. Found: C, 66.60; H, 4.55; N, 10.96.

2-[5-(4-Methoxyphenyl)-3-(4-methoxystyryl)-4,5-dihydro-1*H*-pyrazol-1-yl]-6-methyl-4-(trifluoromethyl)pyrimidine (12)
Mp 200–201 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.4 (s, 3 H, Pyrim 6-Me), 3.10 (dd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 4.4 Hz, 1 H, Pyr H-4 *trans*), 3.59 (dd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 11.8 Hz, 1 H, Pyr H-4 *cis*), 3.68 (s, 3 H, 4-OMe), 3.75 (s, 3 H, 4-OMe), 5.57 (dd, $^3J_{HH}$ = 11.80 Hz, $^3J_{HH}$ = 4.4 Hz, 1 H, Pyr H-5), 6.64 (d, $^2J_{HH}$ = 15 Hz, 1 H, styryl), 6.66 (s, 1 H, Pyrim H-5), 6.73 (m, 2 H, Ar), 6.82 (m, 2 H, Ar), 7.17 (m, 2 H, Ar), 7.20 (d, $^2J_{HH}$ = 15 Hz, 1 H, styryl), 7.33 (m, 2 H, Ar).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8 (Pyrim 6-Me), 40.7 (Pyr C-4), 55.2 (Pyr C-5), 61.4 (4-OMe), 106.7 ($^3J_{CF}$ = 2.7 Hz, Pyrim C-5), 113.8, 114.4 (Ar), 119.5 (styryl CH), 120.6 ($^1J_{CF}$ = 275.4 Hz, CF_3), 127.9, 128.3, 128.9, 134.3 (Ar), 135.7 (styryl CH), 155.0 (Pyr C-3), 155.8 ($^2J_{CF}$ = 35.8 Hz, Pyrim C-4), 157.9 (Pyrim C-2), 158.9, 160.3 (Ar), 171.2 (Pyrim C-6).

MS (EI, 70 eV): *m*/*z* (%) = 468 (100) [M$^+$], 437 (79), 361 (11), 308 (34), 260 (10), 202 (14), 161 (19), 131 (47), 115 (31).

Anal. Calcd for $C_{25}H_{23}F_3N_4O_2$: C, 64.10; H, 4.95; N, 11.96. Found: C, 64.25; H, 5.10; N, 12.10.

2-[5-(4-Methoxyphenyl)-3-(4-methoxystyryl)-4,5-dihydro-1*H*-pyrazol-1-yl]-6-phenyl-4-(trifluoromethyl)pyrimidine (13)
Mp 188–190 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.14 (dd, $^2J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 5.1 Hz, 1 H, Pyr H-4 *trans*), 3.73 (dd, $^2J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 12.0 Hz, 1 H, Pyr H-4 *cis*), 3.84 (s, 3 H, styryl 4-OMe), 3.93 (s, 3 H, 4-OMe), 6.12 (dd, $^3J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 5.1 Hz, 1 H, Pyr H-5), 6.8–7.0 (m, 4 H, Ar), 7.09 (d, $^2J_{HH}$ = 16.6 Hz, 1 H, styryl), 7.15–7.27 (m, 4 H, Ar), 7.28 (s, 1 H, Pyrim H-5), 7.33–7.45 (m, 2 H, Ar), 7.46 (d, $^2J_{HH}$ = 16.6 Hz, 1 H, styryl), 7.54 (m, 1 H, Ar), 7.85 (m, 2 H, Pyrim 6-Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.1 (Pyr C-4), 55.3 (OMe), 55.5 (OMe), 57.1 (Pyr C-5), 102.7 (Pyrim C-5), 110.4, 110.8, 120.7, 120.6 (Ar), 120.7 ($^1J_{CF}$ = 275.5 Hz, CF_3), 122.0 (styryl CH), 125.0, 126.4, 127.0, 127.3, 128.4, 128.6, 129.8, 130.2 (Ar), 130.8 (styryl CH), 131.2, 136.2 (Ar), 156.1 (Pyr C-3), 156.2, 157.0 (Ar), 157.2 ($^2J_{CF}$ = 35.0 Hz, Pyrim C-4), 158.1 (Pyrim C-2), 166.9 (Pyrim C-6).

^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –69.84.

MS (EI, 70 eV): *m*/*z* (%) = 530 (100) [M$^+$], 499 (75), 423 (10), 370 (46), 358 (23), 223 (22), 173 (23), 131 (53), 115 (32), 91 (82).

Anal. Calcd for $C_{30}H_{25}F_3N_4O_2$: C, 67.92; H, 4.75; N, 10.56. Found: C, 68.5; H, 5.00; N, 10.8.

2-[5-(3,4-Dimethoxyphenyl)-3-(3,4-dimethoxystyryl)-4,5-dihydro-1*H*-pyrazol-1-yl]-6-phenyl-4-(trifluoromethyl)pyrimidine (14)
Mp 206–209 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.2 (dd, $^2J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 4.9 Hz, 1 H, Pyr H-4 *trans*), 3.72 (dd, $^2J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 11.8 Hz, 1 H, Pyr H-4 *cis*), 3.83 (s, 6 H, styryl 3,4-OMe), 3.9 (s, 3 H, 5-Ar OMe), 3.92 (s, 3 H, 5-Ar OMe), 5.71 (dd, $^3J_{HH}$ = 11.8 Hz, $^3J_{HH}$ = 4.9 Hz, 1 H, Pyr H-5), 6.72 (d, $^2J_{HH}$ = 16.3 Hz, 1 H, styryl), 6.81 (m, 1 H, Ar), 6.86 (m, 1 H, Ar), 6.92 (m, 1 H, Ar), 7.01 (m, 1 H, Ar), 7.06 (m, 1 H, Ar), 7.28 (m, 1 H, Ar), 7.3 (d, $^2J_{HH}$ = 16.3 Hz, 1 H, styryl), 7.31 (s, 1 H, Pyrim H-5), 7.4–7.5 (m, 3 H, Pyrim 6-Ph), 7.92 (m, 2 H, Pyrim 6-Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.1 (Pyr C-4), 55.7, 55.8, 55.9, 56.0 (3,4-OMe), 62.3 (Pyr C-5), 103.1 (Pyrim C-5), 108.7, 109.7, 111.2, 111.4, 118.3, 119.7 (styryl CH), 120.7 ($^1J_{CF}$ = 276 Hz, Pyrim C-4), 120.9, 127.4, 128.7, 129.2, 131.3, 135.2, 135.8, 136.3 (styryl CH), 148.4, 149.1, 149.3, 150.0, 154.9 (Pyr C-3), 157.2 ($^2J_{CF}$ = 37 Hz, Pyrim C-4), 158.3 (Pyrim C-2), 167.3 (Pyrim C-6).

^{19}F NMR (376.3 MHz, $CDCl_3$): δ = –71.32.

Anal. Calcd for $C_{32}H_{29}F_3N_4O_4$: C, 65.08; H, 4.95; N, 9.49. Found: C, 65.21; H, 4.95; N, 9.10.

6-Phenyl-4-(trifluoromethyl)-2-[5-(3,4,5-trimethoxyphenyl)-3-(3,4,5-trimethoxystyryl)-4,5-dihydro-1*H*-pyrazol-1-yl]pyrimidine (15)
Mp 214–217 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.22 (dd, $^2J_{HH}$ = 17.40 Hz, $^3J_{HH}$ = 5.40 Hz, 1 H, Pyr H-4 *trans*), 3.74 (dd, $^2J_{HH}$ = 17.40 Hz, $^3J_{HH}$ = 11.80 Hz, 1 H, Pyr H-4 *cis*), 3.80 (s, 3 H, OMe), 3.82 (s, 6 H, OMe), 3.88 (s, 3 H, OMe), 3.90 (s, 6 H, OMe), 5.68 (dd, $^3J_{HH}$ = 11.80 Hz, $^3J_{HH}$ = 5.40 Hz, 1 H, Pyr H-5), 6.60 (m, 2 H, Ar), 6.69 (d, $^2J_{HH}$ = 13.80 Hz, 1 H, styryl), 6.73 (m, 2 H, Ar), 7.27–7.51 (m, 5 H, Ar, styryl, Pyrim H-5), 7.90 (m, 2 H, Ar).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.1 (Pyr C-4), 56.1 (OMe), 56.1 (OMe), 60.8 (OMe), 60.9 (OMe), 63.0 (Pyr C-5), 103.1 (Ar), 103.4 (Pyrim C-5), 104.1 (Ar), 120.7 ($^1J_{CF}$ = 275.5 Hz, CF_3), 121.0 (styryl CH), 127.4, 128.7, 131.5, 131.6 (Ar), 135.9 (styryl CH), 136.3, 137.4, 138.3, 139.0, 153.5, 153.5 (Ar), 154.6 (Pyr C-3), 157.31 ($^2J_{CF}$ = 33.9 Hz, Pyrim C-4), 158.3 (Pyrim C-2), 167.4 (Pyrim C-6).

^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –69.89.

Anal. Calcd for $C_{34}H_{33}F_3N_4O_6$: C, 62.76; H, 5.11; N, 8.61. Found: C, 62.65; H, 4.91; N, 8.77.

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References

(1) Chimenti, F.; Bolasco, A.; Manna, F.; Secci, D.; Chimenti, P.; Befani, O.; Turini, P.; Giovannini, V.; Mondovi, B.; Cirilli, R.; La Torre, F. *J. Med. Chem.* **2004**, *47*, 2071.
(2) Meier, H.; Hormaza, A. *Eur. J. Org. Chem.* **2003**, 3372.
(3) Lévai, A. *J. Heterocycl. Chem.* **2002**, *39*, 1.
(4) Palaska, E.; Aytemir, M.; Uzbay, I. T.; Erol, D. *Eur. J. Med. Chem.* **2001**, *36*, 539.
(5) Zanatta, N.; Flores, D. C.; Madruga, C. C.; Faoro, D.; Flores, A. F. C.; Bonacorso, H. G.; Martins, M. A. P. *Synthesis* **2003**, 894.
(6) (a) Bonacorso, H. G.; Wentz, A. P.; Zanatta, N.; Martins, M. A. P. *Synthesis* **2001**, 1505. (b) Bonacorso, H. G.; Martins, D. B.; Martins, M. A. P.; Zanatta, N.; Flores, A. F. C. *Synthesis* **2005**, 809.
(7) Huang, Y. R.; Katzenellenbogen, J. A. *Org. Lett.* **2000**, *2*, 2833.
(8) Fu, H.; Xiao, D.; Xie, R.; Ji, X.; Yao, J.-N. *Can. J. Chem.* **2003**, *81*, 7.
(9) Fahrni, C. J.; Yang, L.; VanDerveer, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 3799.
(10) Xiao, D.; Xi, L.; Yang, W.; Fu, H.; Shuai, Z.; Fang, Y.; Yao, J. *J. Am. Chem. Soc.* **2003**, *125*, 6740.
(11) Wha, O. h. S.; Ri Zhang, D.; Soo Kang, Y. *Mater. Sci. Eng., C* **2004**, *24*, 131.
(12) Zhang, X. H.; Lai, W. Y.; Gao, Z. Q.; Wong, T. C.; Lee, C. S.; Kwong, H. L.; Lee, S. T.; Wu, S. K. *Chem. Phys. Lett.* **2000**, *320*, 77.

(13) Lévai, A.; Patonay, T.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S. *J. Heterocycl. Chem.* **2002**, *39*, 751.
(14) (a) Azarifar, D.; Shaebanzadeh, M. *Molecules* **2002**, *7*, 885. (b) Vijayabaskar, V.; Perumal, S.; Selvaraj, S.; Lycka, A.; Murugan, R.; Balasubramanian, M. *Magn. Reson. Chem.* **1999**, *37*, 133.
(15) Nauduri, D.; Reddy, G. B. S. *Chem. Pharm. Bull.* **1998**, *46*, 1254.
(16) Dove, M. F. A.; Sanders, J. C. P.; Appelman, E. H. *Magn. Reson. Chem.* **1995**, *33*, 44.
(17) Sevenard, D. V.; Khomutov, O. G.; Koryakova, O. V.; Sattarova, V. V.; Kodess, M. I.; Stelten, J.; Loop, I.; Lork, E.; Pashkevich, K. I.; Röschenthaler, G.-V. *Synthesis* **2000**, 1738.
(18) Berger, S.; Braun, S.; Kalinowski, H.-O. *NMR Spectroscopy of the Non-metallic Elements*; Wiley: Chichester, **1997**, 398–400.
(19) *SHELXTL 6.14*; Bruker AXS Inc.: Madison WI, **2003**.
(20) Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837.