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Reaction of Polyfluorinated Chalcones with Guanidine

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Abstract—Reactions of polyfluorinated chalcones with guanidine in the presence of bases are accompanied by elimination of the polyfluorophenyl group. 3-(Pentafluorophenyl)-1-phenylprop-2-en-1-one and its derivatives reacted with guanidine under basic conditions to give 4-phenylpyrimidin-2-amine, polyfluorobenzenes, and Michael adducts, 3-(2-amino-4-phenylpyrimidin-5-yl)-3-(4-R-2,3,5,6-tetrafluorophenyl)-1-phenylpropan-1-ones. 1-(Pentafluorophenyl)-3-phenylprop-2-en-1-one and 1,3-bis(pentafluorophenyl)prop-2-en-1-one were converted into cinnamic acid derivatives whose reaction with guanidine afforded 2-amino-6-aryl-5,6-dihydropyrimidin-4(1*H*)-ones.

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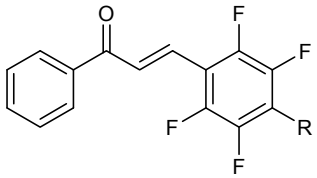
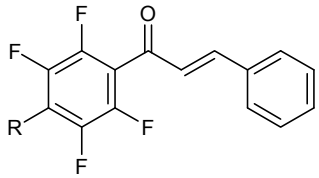
Reactions of α,β-unsaturated carbonyl compounds (including chalcones) with urea, thiourea, and guanidine were reported to produce various pyrimidine derivatives which exhibited a broad spectrum of biological activity, in particular antimicrobial [1, 2], antitumor [3], anti-inflammatory, analgesic [4–6], antiviral [7], anti-HIV [8], antioxidant [9], and other kinds of activity. Reactions of chalcones with urea derivatives follow 1,2- and/or 1,4-addition path [10]. The most interesting are products of their reactions with guanidine, 2-amino-4,6-diarylpyrimidines, which can be subjected to further functionalization via transformations of the amino group. Polyfluorinated analogs of such compounds have not been reported, though some derivatives with one or two fluorine atoms in the aromatic rings are known [11–13]. Chalcones generally react with guanidine hydrochloride in alcohols or DMF in the presence of strong bases such as aqueous alkali, sodium ethoxide, or sodium hydride [11, 12, 14, 15].

In this work we studied reactions of polyfluorinated chalcones **1a**–**1f** containing one or two polyfluorophenyl rings with guanidine hydrochloride in ethanol and DMF in the presence of bases.

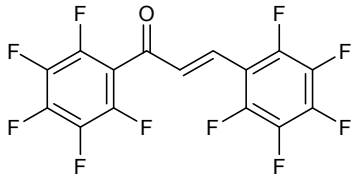
In keeping with the generally accepted mechanism [10], the reaction of chalcone **1a** with guanidine under conventional conditions (heating with an equimolar amount of guanidine hydrochloride in ethanol in the presence of sodium hydroxide) should be expected to give pyrimidine **A** (Scheme 1). However, the reaction mixture contained only decomposition products, 4-phenylpyrimidin-2-amine (**2**) and ethoxy derivative **3a**. In addition, we detected a compound which was assigned the structure of 3-(2-amino-4-phenylpyrimidin-5-yl)-3-(4-ethoxy-2,3,5,6-tetrafluorophenyl)-1-phenylpropan-1-one (**4a**) on the basis of X-ray diffraction data and ^{1}H and ^{19}F NMR spectra (Scheme 1). The polyfluorophenyl rings in **3a** and **4a** contained an ethoxy group as a result of reaction with ethanol in the presence of alkali. Chalcones **1b** and **1c** with a phenoxy or piperidino group in the fluorinated ring reacted with guanidine in alcohol in a similar way, and the products were mixtures of amine **2**, tetrafluoro-



1a–1c



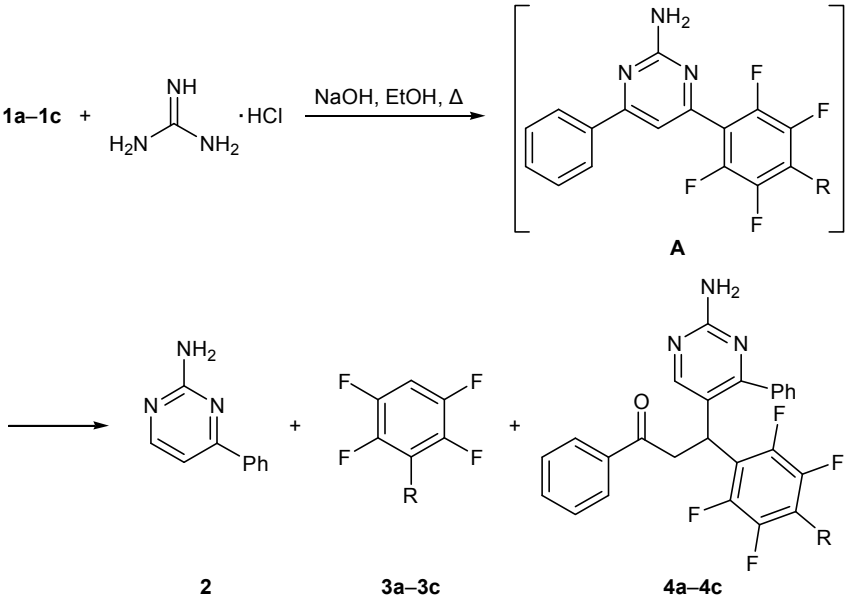
1d, **1e**



1f

R = F (**a**, **d**), PhO (**b**), $(CH_2)_5N$ (**c**, **e**).

Scheme 1.



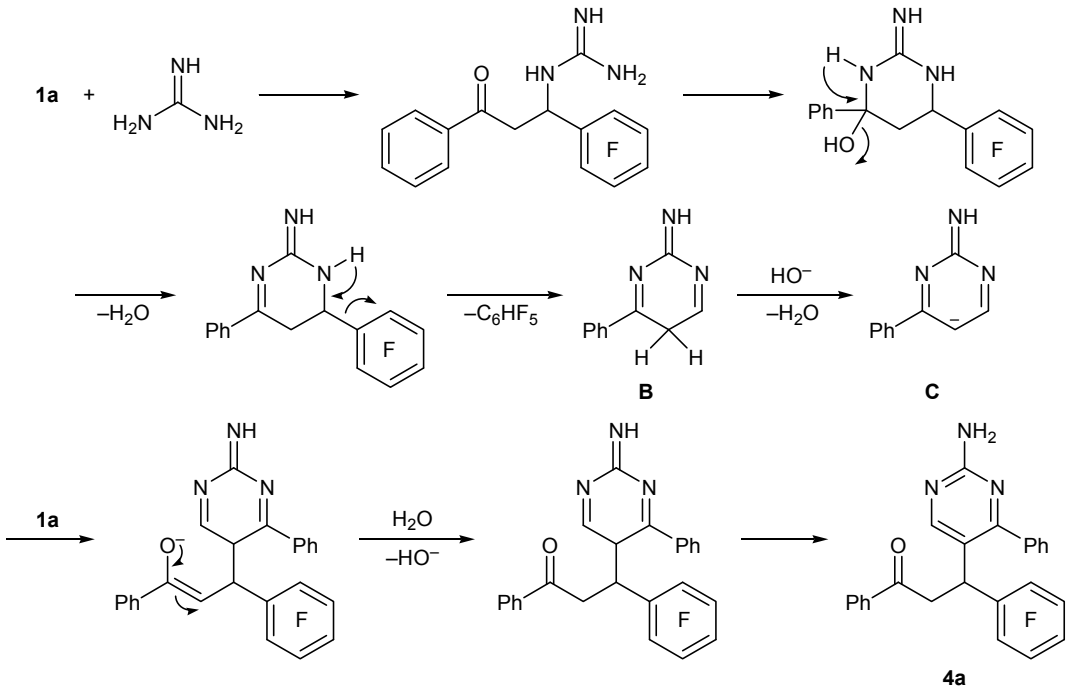
R = EtO (**a**), PhO (**b**), $(CH_2)_5N$ (**c**).

benzene **3b** or **3c**, and Michael adduct **4b** or **4c**. The fraction of the latter in the product mixture was found to correlate with the effect of the R substituent on the stability of polyfluorophenyl anion.

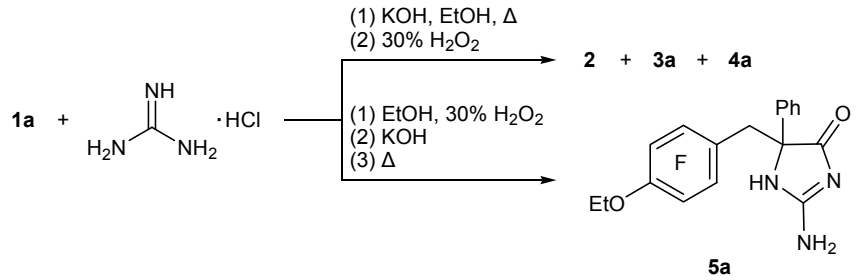
Haloform-type reaction of polyfluoroaromatic carbonyl compounds, including chalcone derivatives, by the action of charged nucleophiles with elimination of relatively stable $C_6F_5^-$ anion is well known [16, 17]. Presumably, azomethine derivatives of carbonyl compounds are also prone to behave in this way.

Formalistically, compound **4a** is the product of Michael addition to chalcone **1a** of the carbon-centered nucleophile generated from aminopyrimidine **2** by the action of alkali. However, compound **1a** failed to react

Scheme 2.



Scheme 3.

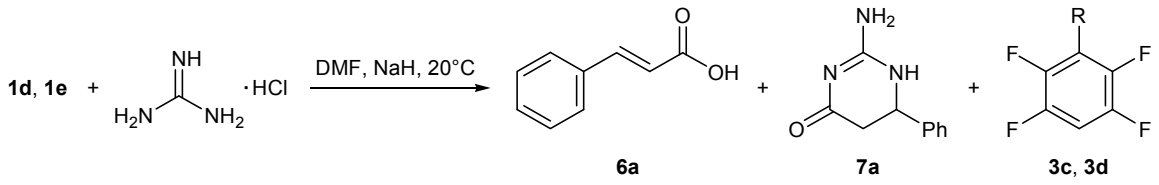


with pyrimidine **2** in the presence of alkali, and only the initial compounds were detected in the reaction mixture. On the other hand, carbon nucleophile can be formed from the precursor of **A**, dihydropyrimidine **B** possessing an acidic proton, and adduct **4a** can result from the reaction of **1a** with carbanion **C** according to Scheme 2. In order to verify this assumption we performed experiments with addition of hydrogen peroxide, by analogy with the data reported in [18] for nonfluorinated chalcone. It was found that the product composition depends on the order of addition of the reactants (Scheme 3). Heating of the reaction mixture in boiling ethanol in the presence of KOH for 2 h, followed by addition of 30% hydrogen peroxide, led to the formation of the same compounds as in the absence of oxidant. When hydrogen peroxide was added first, we obtained dihydroimidazole derivative **5a**, as reported for nonfluorinated chalcone. Compound **5a** was isolated in a poor yield from the organic part of the reaction mixture which contained mainly water-soluble compounds and was not studied in detail.

The mechanism of formation of dihydroimidazolones [18] includes oxidation of chalcone at the double bond to epoxide, transformation of the latter into 1,2-diketone, and subsequent reaction with guanidine. Intramolecular cyclization of the resulting Schiff base is accompanied by migration of the benzyl group to the neighboring position with closure of five-membered ring.

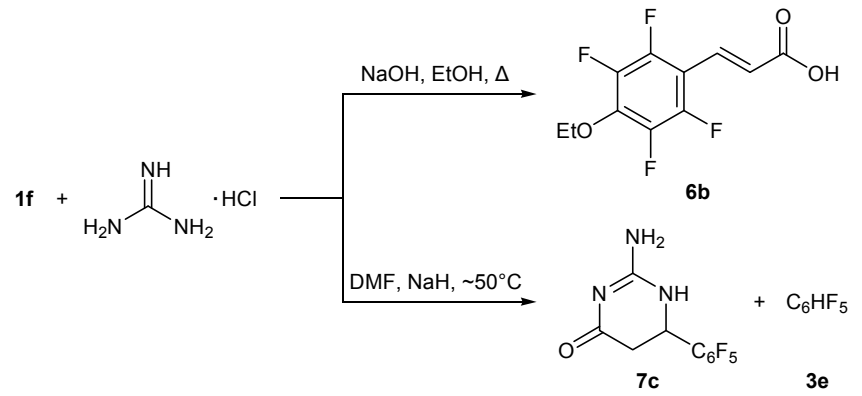
In the reaction of pentafluorophenyl ketone **1d** with guanidine in ethanol in the presence of NaOH, the major products resided in the aqueous phase, and they were not isolated by extraction with different organic solvents. Obviously, the water-soluble product was sodium cinnamate resulting from elimination of polyfluorophenyl group from **1d** under alkaline conditions. Cinnamic acid (**6a**) was detected by GC/MS together with 2,3,5,6-tetrafluorophenol (**3d**) in the reaction

Scheme 4.



R = $(CH_2)_5N$ (**c**), HO (**d**).

Scheme 5.



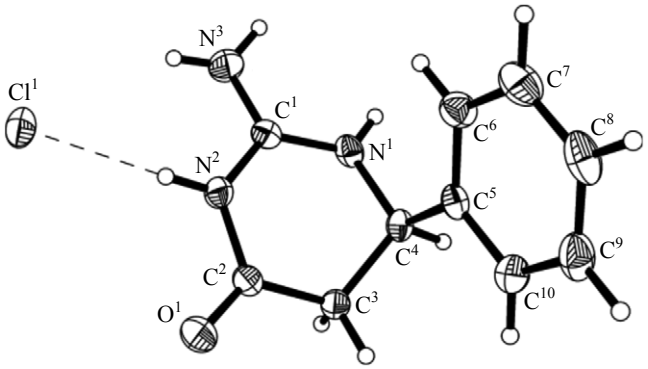


Fig. 1. Structure of the molecule of 2-amino-6-phenyl-5,6-dihydropyrimidin-4(1*H*)-one hydrochloride (**7b**) according to the X-ray diffraction data.

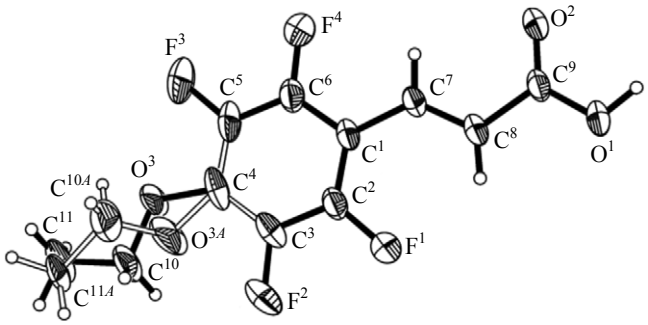


Fig. 2. Structure of the molecule of 3-(4-ethoxy-2,3,5,6-tetrafluorophenyl)prop-2-enoic acid (**6b**) according to the X-ray diffraction data.

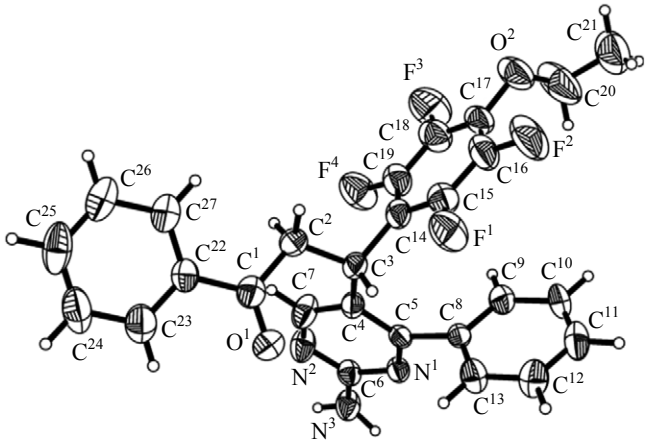


Fig. 3. Structure of the molecule of 3-(2-amino-4-phenylpyrimidin-5-yl)-3-(4-ethoxy-2,3,5,6-tetrafluorophenyl)-1-phenylpropan-1-one (**4a**) according to the X-ray diffraction data (one of the two independent molecules is shown).

mixture obtained from **1d** and guanidine hydrochloride in DMF in the presence of sodium hydride (Scheme 4). In addition, we isolated from that mixture 2-amino-6-phenyl-5,6-dihydropyrimidin-4(1*H*)-one (**7a**) which was identified by comparing its melting point and ^{1}H NMR spectrum with those of a sample described in [19], as well as by X-ray analysis of its hydrochloride **7b** (Fig. 1). The formation of **7a** may be rationalized by elimination of polyfluorophenyl residue from initial chalcone **1d** to give cinnamoyl cation and subsequent Michael addition of guanidine, followed by lactam ring closure. Likewise, piperidino-substituted chalcone **1e** reacted with guanidine hydrochloride in DMF/NaH to afford a mixture of **7a** and **3c**.

In the reaction of decafluorochalcone **1f** with guanidine in ethanol in the presence of NaOH we isolated only 4-ethoxy-2,3,5,6-tetrafluorocinnamic acid (**6b**) (Scheme 5, Fig. 2). Chalcone **1f** reacted with guanidine in DMF/NaH in a way similar to compounds **1d** and **1e**, with formation of cyclic amino ketone **7c** and pentafluorobenzene (**3e**) (Scheme 5).

The melting points and ^{1}H and ^{19}F NMR spectra of **2** and **3a** were consistent with the data of [20–22]. The structure of the newly synthesized compounds was determined on the basis of spectral and analytical data. The structure of **4a** was unambiguously proved by X-ray analysis (Fig. 3). The bond lengths in the 2-aminopyrimidine fragment of **4a** were similar to the corresponding bond lengths in the crystal structure of *tert*-butyl 4-{[2-amino-4-(2-hydroxyphenyl)pyrimidin-5-yl]methyl}piperazine-1-carboxylate [23]. The dihedral angles between the tetrafluorophenyl ring and phenyl ring in position *4* of the pyrimidine ring in the two independent molecules of **4a** are 23.7 and 20.8°, which favors C–F $\cdots\pi$ interactions [the shortest distance between fluorine atoms and the centroid of the 4-phenyl ring is 3.613(3) and 3.482(2) Å]. Molecules **4a** are linked to form dimers through hydrogen bonds N^3–H $\cdots$ N^{1A} and N^{3A}–H $\cdots$ N^1 [H $\cdots$ N 2.18(4), 2.24(4) Å, ∠NHN 164(3), 157(3)°].

The geometric parameters of molecule **6b** coincide with those of (*E*)-3-(pentafluorophenyl)prop-2-enoic acid [24]. Molecules **6b** in crystal are also linked to dimers through hydrogen bonds O^1–H $\cdots$ O^2 [H $\cdots$ O 1.72(5) Å, ∠OHO 176(4)°].

The tetrahydropyrimidine ring in the cation of salt **7b** adopts a distorted *boat* conformation with the N^1 and C^4 atoms deviating by 0.318 and 0.770 Å toward one side of the plane formed by the other ring atoms and axial orientation of the phenyl substituent. Analogous conformation and bond lengths were found in the crystal structure of 5-cyano-8-methyl-4-oxo-1,3-diazaspiro[5.5]undecan-2-iminium chloride [25]. Molecules **7b** in crystal are linked through intermolecular hydrogen bonds N–H $\cdots$ Cl [2.21(2), 2.28(3) Å, ∠177(2),

176(2)°] and N–H···O [2.21(2) Å, 139(2)°] to form bands parallel to the crystallographic *a* axis.

The ^{19}F NMR spectrum of **4a** displayed two signals with equal intensities at δ_F 4.38 and 18.52 ppm, corresponding to 2,3,5,6-tetrafluoro substitution. The ^{1}H NMR spectrum of **4a** contained signals typical of ethoxy protons and *ABX* spin system of the CH_2CH fragment, a two-proton singlet from the amino group, multiplets from aromatic protons in two phenyl rings, and a broadened singlet belonging to 6-H of the pyrimidine ring. The ^{1}H and ^{19}F NMR spectra of **4b** and **4c** were similar to those of **4a**.

In summary, we have found that polyfluorinated chalcones react with guanidine hydrochloride in ethanol or DMF in the presence of strong bases (NaOH or NaH). The reactions of 3-(polyfluorophenyl)-1-phenylprop-2-en-1-ones are accompanied by elimination of the polyfluorophenyl fragment from the initially formed unstable 2-amino-4,6-diarylpyrimidines or their dihydropyrimidine precursors to afford a mixture of 4-phenylpyrimidin-2-amine, the corresponding polyfluorobenzene, and Michael adduct. Under analogous conditions, 1-(polyfluorophenyl)-3-phenylprop-2-en-1-ones and 1,3-bis(pentafluorophenyl)prop-2-en-1-one are likely to lose the polyfluorophenyl group even in the first step to give cinnamic acid derivatives, and addition of guanidine to the latter and subsequent intramolecular cyclization of the adduct yield 2-amino-6-aryl-5,6-dihydropyrimidin-4(1*H*)-ones **7**. Compound **7a** can also be formed through the corresponding diaryl-substituted pyrimidine and dihydropyrimidine as shown in Scheme 2.

EXPERIMENTAL

The analytical and spectral studies were performed at the Joint Chemical Service Center, Siberian Branch, Russian Academy of Sciences. The ^{1}H and ^{19}F NMR spectra were recorded on Bruker AV-300 (300.13 MHz for ^{1}H and 282.37 MHz for ^{19}F) and Bruker AV-400 instruments (400.13 MHz for ^{1}H). The ^{1}H chemical shifts were determined relative to the residual proton signals of deuterated solvents ($CHCl_3$, δ 7.24 ppm; DMSO-d_5, δ 2.50 ppm; acetone-d_5, δ 2.04 ppm). The ^{19}F chemical shifts were measured relative to C_6F_6 as internal standard. GC/MS analyses were obtained on an Agilent Technologies 6890N gas chromatograph coupled with an Agilent 5973N mass-selective detector [electron impact, 70 eV; ion source temperature 230°C; HP-5MS capillary column, 30 m × 0.25 mm × 0.25 μm; carrier gas helium, 1 mL/min; oven temperature programming from 50°C (2 min) to 280°C at a rate of 10 deg/min and 30 min at 280°C; injector temperature 280°C]. The high-resolution mass spectra were recorded on a DFS instrument with direct sample admission into the ion source (electron impact, 70 eV).

Single crystals of **4a**, **6b**, and **7b** were obtained by crystallization from ethanol. The X-ray diffraction experiments were performed at 200 K on a Bruker Kappa Apex II diffractometer (MoK_α radiation, graphite monochromator). Corrections for absorption were applied empirically using SADABS program. The structures were solved by the direct method and were refined in anisotropic approximation for non-hydrogen atoms using SHELX97 package. The positions of amino and hydroxy hydrogen atoms were refined in isotropic approximation, and of the other hydrogens, according to the riding model. The crystallographic data for compounds **4a**, **6b**, and **7b** were deposited to the Cambridge Crystallographic Data Centre.

Compound **4a**. Orthorhombic crystals system, space group $Pna2_1$; $C_{27}H_{21}F_4N_3O_2$, M 495.47; a = 12.7084(6), b = 13.5958(7), c = 27.745(2) Å; V = 4793.9(4) Å^3; Z = 8; d_{calc} = 1.373 g/cm^3. Number of independent reflections 9114 (θ_{max} = 25.7°), including 5938 reflections with $I > 2\sigma(I)$. Final divergence factor R = 0.0460 (for F_o), S = 1.006. CCDC entry no. 1442487.

Compound **6b**. Triclinic crystal system, space group P-1; $C_{11}H_8F_4O_3$, M 264.17; a = 7.9786(4), b = 8.4651(4), c = 9.1297(4) Å; α = 95.434(2), β = 108.876(2), γ = 109.826(2)°; V = 534.20(4) Å^3; Z = 2; d_{calc} = 1.642 g/cm^3. Number of independent reflections 3230 (θ_{max} = 30°), including 2424 reflections with $I > 2\sigma(I)$. Final divergence factor R = 0.0686 (for F_o), S = 0.992. The ethoxy group is disordered by two positions with a population ratio of 0.637(9):0.363(9). CCDC entry no. 1442488.

Compound **7b** (**7a** hydrochloride). Monoclinic crystal system, space group $P2_1/n$; $C_{10}H_{12}ClN_3O$, M 225.68; a = 6.6615(1), b = 23.5775(6), c = 6.8587(2) Å; β = 102.635(1)°; V = 1051.15(4) Å^3; Z = 4; d_{calc} = 1.426 g/cm^3. Number of independent reflections 2827 (θ_{max} = 29°), including 2563 reflections with $I > 2\sigma(I)$. Final divergence factor R = 0.0346 (for F_o), S = 1.137. CCDC entry no. 1442489.

Initial polyfluorinated chalcones **1a**, **1d**, **1f** [26] and **1b**, **1c**, **1e** [17] were synthesized according to known methods. The reaction mixtures were analyzed by ^{1}H and ^{19}F NMR.

Reaction of 3-(pentafluorophenyl)-1-phenylprop-2-en-1-one (1a) with guanidine. *a*. Chalcone **1a**, 0.3 g (1.0 mmol), was added to a solution of 0.095 g (1.0 mmol) of guanidine hydrochloride and 0.12 g (3.0 mmol) of sodium hydroxide in 7 mL of ethanol, and the mixture was heated for 2.5 h under reflux with stirring. The mixture was cooled to room temperature, poured onto ice, and extracted with ethyl acetate. The extract was washed with water, dried over $CaCl_2$, and evaporated under reduced pressure on a rotary evaporator. The product was 0.16 g of a mixture of compounds **2**, **3a**, and **4a** at a ratio of 60:16:24.

3-Ethoxy-1,2,4,5-tetrafluorobenzene (3a) was identified by ^{1}H and ^{19}F NMR spectroscopy [22]. Mixture **2**/**3a**/**4a** was subjected to alumina column chromatography to isolate 0.13 g of a ~1:1 mixture of 4-phenylpyrimidin-2-amine (**2**) and 3-(2-amino-4-phenylpyrimidin-5-yl)-3-(4-ethoxy-2,3,5,6-tetrafluorophenyl)-1-phenylpropan-1-one (**4a**). Recrystallization of that mixture from benzene gave 0.05 g (29%) of **2** which was identified by the melting point, mp 164–166°C (mp 165–166°C [20]) and ^{1}H NMR spectrum [21]. The mother liquor obtained after separation of **2** was evaporated. The residue, 0.08 g, was a mixture of **2** and **4a** at a ratio of 1:1.2. When benzene was allowed to slowly evaporate from the mother liquor, crystals of **4a** suitable for X-ray analysis separated. Yield 18% (^{1}H NMR), the product was identified in the mixture by the NMR data. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.34 t (3H, $OCH_2C\mathbf{H}_3$, J = 7.0 Hz); 3.66, 3.76, and 5.12 (1H each, CH_2CH, *ABX*, J = 17.5, 8.5, 7.2 Hz); 4.19 q (2H, OCH_2, J = 7.0 Hz), 5.44 br.s (2H, NH_2), 7.28–7.35 m (2H, H_{arom}), 7.37–7.48 m (5H, H_{arom}), 7.52–7.59 m (1H, H_{arom}), 7.83–7.90 m (2H, H_{arom}), 8.34 br.s (1H, H_{arom}). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: 4.38 m (3-F, 5-F), 18.55 m (2-F, 6-F).

b. Chalcone **1a**, 0.3 g (1.0 mmol), was added to a solution of 0.14 g (1.5 mmol) of guanidine hydrochloride and 2 mL of 50% aqueous potassium hydroxide in 10 mL of ethanol. The mixture was heated for 2 h under reflux with stirring, 0.34 mL of 30% hydrogen peroxide was added, and the mixture was heated for 1 h under reflux, cooled, and treated as described in *a*. The product was 0.18 g of a mixture containing compounds **2**, **3a**, and **4a** at a ratio of 33:47:20.

c. A solution of 0.6 g (2.0 mmol) of chalcone **1a**, 0.28 g (3.0 mmol) of guanidine hydrochloride, and 0.68 mL of 30% hydrogen peroxide in 20 mL of ethanol was heated to the boiling point, 4 mL of 50% aqueous potassium hydroxide was added, and the mixture was heated for 2 h under reflux with stirring, cooled, and treated as described in *a*. The residue, 0.29 g (a multicomponent mixture, according to the ^{1}H and ^{19}F NMR data), was washed with 5 mL of chloroform–hexane (1:1) to isolate 0.13 g (18%) of 2-amino-5-(4-ethoxy-2,3,5,6-tetrafluoro-benzyl)-5-phenyl-1*H*-imidazol-4(5*H*)-one (**5a**) as colorless crystals with mp 272–274°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30 t (3H, $OCH_2C\mathbf{H}_3$, J = 7.0 Hz), 3.34 and 3.40 (1H each, CH_2, *AB*, J = 14.1 Hz), 4.25 q (2H, OCH_2, J = 7.0 Hz), 6.91 br.s (1H, NH_2), 7.27–7.30 m (1H, H_{arom}), 7.23–7.37 m (2H, H_{arom}), 7.49–7.52 m (2H, H_{arom}), 7.64 br.s (1H, NH_2), 8.42 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 15.17, 31.78, 68.92, 70.79, 108.59, 125.36, 127.38, 128.05, 135.93, 139.44, 139.62, 141.07, 144.42, 146.04, 170.66, 186.94. ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: 4.33 m (3-F, 5-F), 22.22 m (2-F, 6-F). Found: m/z 381.1103 $[M]^+$. $C_{18}H_{15}F_4N_3O_2$. Calculated: M 381.1109.

Reaction of 3-(pentafluorophenyl)-1-phenylprop-2-en-1-one (1a) with 4-phenylpyrimidin-2-amine (2). Chalcone **1a**, 0.09 g (0.3 mmol), was added to a solution of 0.05 g (0.3 mmol) of pyrimidine **2** and 0.036 g (0.9 mmol) of sodium hydroxide in 3 mL of ethanol. The mixture was heated for 2.5 h under reflux with stirring, cooled, and poured onto ice, the precipitate was treated with ethyl acetate, the extract was washed with water, dried over $CaCl_2$, and evaporated under reduced pressure on a rotary evaporator, and the residue was analyzed by ^{1}H and ^{19}F NMR. No compound **4a** was detected in the product mixture.

Reaction of 1-phenyl-3-(2,3,5,6-tetrafluoro-4-phenoxyphenyl)prop-2-en-1-one (1b) with guanidine. Chalcone **1b**, 0.3 g (0.8 mmol), was added to a solution of 0.08 g (0.8 mmol) of guanidine hydrochloride and 0.1 g (2.4 mmol) of sodium hydroxide in 7 mL of ethanol. The mixture was heated for 3.5 h under reflux with stirring, cooled to room temperature, and poured onto ice. The precipitate was treated with ethyl acetate, the extract was washed with water and dried over $CaCl_2$, the solvent was removed on a rotary evaporator, and the residue, 0.25 g (a mixture of compounds **2**, **3b**, and **4b** at a ratio of 7:29:64), was analyzed by ^{1}H and ^{19}F NMR. The product mixture was washed with hexane–chloroform (2:1) to isolate 0.07 g (32%) of 3-(2-amino-4-phenylpyrimidin-5-yl)-1-phenyl-3-(2,3,5,6-tetrafluoro-4-phenoxyphenyl)-propan-1-one (**4b**) as colorless crystals with mp 156–158°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.67–

3.87 m (2H, CH_2), 5.15–5.31 m (3H, CH, NH_2), 6.83–6.91 m (2H, H_{arom}), 7.08 m (1H, H_{arom}), 7.26–7.36 m (4H, H_{arom}), 7.38–7.48 m (5H, H_{arom}), 7.57 m (1H, H_{arom}), 7.86–7.94 m (2H, H_{arom}), 8.37 br.s (1H, H_{arom}). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: 7.29 m (3-F, 5-F), 19.99 m (2-F, 6-F). Found: *m/z* 543.1559 $[M]^+$. $C_{31}H_{21}F_4N_3O_2$. Calculated: *M* 543.1564.

Reaction of 1-phenyl-3-[2,3,5,6-tetrafluoro-4-(piperidin-1-yl)phenyl]prop-2-en-1-one (1c) with guanidine. Chalcone **1c**, 0.3 g (0.8 mmol), was added to a solution of 0.08 g (0.8 mmol) of guanidine hydrochloride and 0.1 g (2.4 mmol) of sodium hydroxide in 7 mL of ethanol. The mixture was heated for 3.5 h under reflux with stirring, cooled, and treated as described above for the reaction with **1b**. The product, 0.24 g of a mixture of **2**, **3c**, and **4c** at a ratio of 37:46:17, was subjected to alumina column chromatography. Elution with hexane–chloroform (1:1) gave 0.03 g (16%) of 1-(2,3,5,6-tetrafluorophenyl)piperidine (**3c**) whose ^{19}F NMR spectrum was identical to that of a sample described in [27]. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.66 m (6H, CH_2), 3.18 m (4H, CH_2), 6.61 m (1H, H_{arom}). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: 10.54 m (2-F, 6-F), 20.66 m (3-F, 5-F). Found: *m/z* 232.0747 $[M - H]^+$. $C_{11}H_{11}F_4N$. Calculated: *M* 233.0822.

We failed to separate compounds **2** and **4c** by chromatography.

Reaction of 1-(pentafluorophenyl)-3-phenylprop-2-en-1-one (1d) with guanidine. *a*. Chalcone **1d**, 1.0 g (3.4 mmol), was added to a solution of 0.64 g (6.7 mmol) of guanidine hydrochloride and 0.32 g (13.4 mmol) of sodium hydride in 10 mL of DMF. The mixture was stirred for 1.5 h at 50°C, cooled, poured onto ice, and treated with ethyl acetate. The undissolved material at the phase boundary was filtered off. We thus isolated 0.1 g (16%) of 2-amino-6-phenyl-5,6-dihydropyrimidin-4(1*H*)-one (**7a**) which was identical to a sample described in [19] in ^1H NMR data and melting point (mp 255–257°C; 257.3°C [19]). The extract was washed with water and dried over $CaCl_2$, the solvent was removed under reduced pressure on a rotary evaporator, and the residue, 0.29 g, was analyzed by NMR and GC/MS.

b. Chalcone **1d**, 0.3 g (1.0 mmol), was added to a solution of 0.095 g (1.0 mmol) of guanidine hydrochloride and 0.12 g (3.0 mmol) of sodium hydroxide in 6 mL of ethanol. The mixture was heated for 5 h under reflux with stirring, cooled, poured onto ice, and treated first with diethyl ether and then with methylene chloride. The extracts were combined, washed with water, and dried over $CaCl_2$, and the solvent was removed under reduced pressure on a rotary evaporator. According to the ^1H NMR data, the residue, 0.03 g, contained mainly cinnamic acid (**6a**).

Reaction of 3-phenyl-1-[2,3,5,6-tetrafluoro-4-(piperidin-1-yl)phenyl]prop-2-en-1-one (1e) with guanidine. Chalcone **1e**, 0.6 g (3.4 mmol), was added to a solution of 0.32 g (6.7 mmol) of guanidine hydrochloride and 0.16 g (13.4 mmol) of sodium hydride in 6 mL of DMF. The mixture was stirred for 1 h at 50°C, cooled, and poured onto ice, and the precipitate was treated with ethyl acetate. The extract was washed with water and dried over $CaCl_2$, and the solvent was removed under reduced pressure on a rotary evaporator to leave 0.18 g (34%) of compound **3c**. A solid separated from the aqueous phase and was filtered off, washed with a small amount of water, and dried in air. We thus isolated 0.07 g (11%) of compound **7a**.

Reaction of 1,3-bis(pentafluorophenyl)prop-2-en-1-one (1f) with guanidine. *a*. Chalcone **1f**, 0.3 g (0.8 mmol), was added to a solution of 0.07 g (0.8 mmol) of guanidine hydrochloride and 0.09 g (2.3 mmol) of sodium hydroxide in 6 mL of ethanol. The mixture was heated for 1 h under reflux with stirring, cooled, and treated as described above. We isolated 0.15 g (75%) of 3-(4-ethoxy-2,3,5,6-tetrafluorophenyl)prop-2-enoic acid (**6b**) as colorless crystals with mp 129–131°C. ^1H NMR spectrum (acetone-d_6), δ, ppm: 1.40 t (3H, $OCH_2C\mathbf{H}_3$, J = 7.0 Hz), 4.41 q (2H, OCH_2, J = 7.0 Hz), 6.63 and 7.58 (1H each, CH=CH, *AB*, J = 16.3 Hz), 7.92 br.s (1H, OH). ^{19}F NMR spectrum (acetone-d_6), δ_F, ppm: 5.38 m (3-F, 5-F), 20.87 m (2-F, 6-F).

b. Chalcone **1f**, 0.5 g (1.3 mmol), was added to a solution of 0.25 g (2.6 mmol) of guanidine hydrochloride and 0.12 g (5.2 mmol) of sodium hydride in 10 mL of DMF. The mixture was stirred for 10 min at 50°C, cooled, and poured onto ice, and the oily material was extracted into ethyl acetate. The extract was washed with water and dried over $CaCl_2$, and the solvent was removed under reduced pressure on a rotary evaporator. The residue was 0.20 g of 2-amino-6-(pentafluorophenyl)-5,6-dihydropyrimidin-4(1*H*)-one (**7c**) which was identified by NMR data. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.50, 2.65, and 5.10 (1H each, *ABX*, CH_2CH, J = 6.7, 9.5, 16.4 Hz), 5.77 br.s (2H, NH_2), 6.95 br.s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: –0.13 m (2F), 6.71 m (1F), 19.94 m (2F).

REFERENCES

1. Ballell, L., Robert, A.F., Chung, G.A.C., and Young, R.J., *Bioorg. Med. Chem. Lett*., 2007, vol. 17, p. 1736.
2. Rao, M.S., Ehso, N., Sergeant, C., and Dembinski, R., *J. Org. Chem*., 2003, vol. 68, p. 6788.
3. Miyazaki, Y., Matsunaga, S., Tang, J., Maeda, Y., Nakano, M., Philippe, R.J., Shibahara, M., Liu, W., Sato, H., Wang, L., and Notle, R.T., *Bioorg. Med. Chem. Lett*., 2005, vol. 15, p. 2203.
4. Breault, G.A. and Pease, J.E., Int. Patent Appl. no. WO 2000012485, 2000; *Chem. Abstr*., 2000, vol. 132, no. 194385.
5. Venu, T.D., Khanu, S.A., Firdouse, A., Manuprasad, B.K., Shashikanth, S., Mohamed, R., and Vishwanth, B.S., *Bioorg. Med. Chem. Lett*., 2008, vol. 18, p. 4409.
6. Nofal, Z.M., Fahmy, H.H., Zarea, E.S., and El-Eraky, W., *Acta Polon. Pharm. Drug Res*., 2011, vol. 68, p. 507.
7. Chamakura, V.N.S.V., Ramasamy, K.S., Girardet, J.L., Gunic, E., Lai, V., Zhong, W., An, H., and Hong, Z., *Bioorg. Chem*., 2007, vol. 35, 25.
8. Malik, V., Singh, P., and Kumar, S., *Tetrahedron*, 2006, vol. 62, p. 5944.
9. Biagi, G., Costantini, A., Costantino, L., Giorgi, I., Livi, O., Pecorari, P., Rinaldi, M., and Scartoni, V., *J. Med. Chem*., 1996, vol. 39, p. 2529.
10. Kanagarajan, V., Thanusu, J., and Gopalakrishnan, M., *J. Korean Chem. Soc*., 2009, vol. 53, p. 731.
11. Bukhari, M.H., Ahmad, M., Hussain, T., Umar, S., and Ahmad, N., *Med. Chem. Res*., 2013, vol. 22, p. 5248.
12. Sharma, M., Chauhan, K., Shivahare, R., Vishwakarma, P., Suthar, M.K., Sharma, A., Gupta, S., Saxena, J.K., Lal, J., Chandra, P., Kumar, B., and Chauhan, P.M., *J. Med. Chem*., 2013, vol. 56, p. 4374.
13. Patle, S.K., Kawathekar, N., Zaveri, M., and Kamaria, P., *Med. Chem. Res*., 2013, vol. 22, p. 1756.
14. Tyagi, V., Khan, S., Shivahare, R., Srivastava, K., Gupta, S., Kidwai, S., Srivastava, K., Puri, S.K., and Chauhan, P.M., *Bioorg. Med. Chem. Lett*., 2013, vol. 23, p. 291.
15. Nagle, P.S., Pawar, Y.A., Sonawane, A.E., Bhosale, S.M., and More, D.H., *J. Pharm. Res*., 2011, vol. 4, p. 3915.
16. Gerasimova, T.N. and Fokin, E.P., *Russ. Chem. Rev*., 1980, vol. 49, no. 6, p. 558.
17. Orlova, N.A., Maior, E.F., and Gerasimova, T.N., *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 1989, no. 3, p. 117.
18. Varga, L., Nagy, T., Kovesdi, I., Benet-Buchholz, J., Dorman, G., Urge, L., and Darvas, F., *Tetrahedron*, 2003, vol. 59, p. 655.
19. Mirza-Aghayan, M., Baie Lashaki, T., Rahimifard, M., Boukherroub, R., and Tarlani, A.A., *J. Iran. Chem. Soc*., 2011, vol. 8, p. 280.
20. Breuker, K. and Van der Plas, H.C., *J. Org. Chem*., 1979, vol. 44, p. 4677.
21. Bejugam, M., Hosahalli, S., and Mahalingam, N., Int. Patent no. WO 2014125426, 2014.
22. James, J.H., Peach, M.E., and Williams, Ch.R., *J. Fluorine Chem*., 1985, vol. 27, p. 91.
23. Gajera, N.N., Patel, M.C., Jotani, M.M., and Tiekink, E.R.T., *Acta Crystallogr., Sect. E*, 2013, vol. 69, p. o1577.
24. Goud, B.S., Reddy, P.K., Panneerselvam, K., and Desiraju, G.R., *Acta Crystallogr., Sect. C*, 1995, vol. 51, p. 683.
25. Balalaie, S., Moghimi, H., Bararjanian, M., Rominger, F., Bijanzadeh, H.R., and Sheikhahmadi, M., *J. Heterocycl. Chem*., 2013, vol. 50, p. 1304.
26. Filler, R., Beaucaire, V.D., and Kang, H.H., *J. Org. Chem*., 1975, vol. 40, p. 935.
27. Rodionov, P.P. and Shein, S.M., *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 1971, no. 3, p. 86.