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Indole-3-carbaldehydes Arylhydrazones as Multisite C-Nucleophiles in the Reactions with Quinazoline

Yu. A. Azev[a],*, O. S. Koptyaeva[a], O. S. Eltsov[a], Yu. A. Yakovleva[a], A. N. Tsmokalyuk[a], A. V. Ivoilova[a], E. A. Seliverstova[a], T. A. Pospelova[a], and V. A. Bakulev[a]

[a] *Ural Federal University, Yekaterinburg, 620002 Russia*
**e-mail: azural@yandex.ru*

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Abstract—C,C-Coupling of indole-3-carbaldehyde arylhydrazones with quinazoline in trifluoroacetic acid has occurred at position 5 or 7′ of the hydrazone molecule and has afforded the σ-adducts. The C,C-coupling has been accompanied by a change in the *E*-configuration of the C=N bond of the starting hydrazones to the *Z*-configuration in the formed quinazoline trifluoroacetyl hydrazides.

Keywords: arylhydrazones, indole-3-carbaldehydes, C,C-coupling, quinazoline, trifluoro hydrazides

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Quinazoline core is a part of natural alkaloids [1, 2]. The derivatives of quinazoline include the compounds revealing various types of biological activity, including antimicrobial, antiallergic, hypotonic, antiviral [3], antitumor [4], and radioprotective [5] ones.

The addition of C-nucleophiles at 3-methylquinazolinium iodide yielding 4-substituted 3,4-dihydroquinazolines has been reported [6]. Furthermore, it has been found that unsubstituted quinazoline reacts with indole, 5-methyl-2-phenylpyrazol-3-one, 1,3-dimethylbarbituric acid, and pyrogallol in the presence of an acid, resulting in the 4-σ-adducts [7]. The examples of quinazoline arylation with 1,3,5-trimetoxybenzene, 1-(4-metoxybenzylidene)-2-phenylhydrazine, and *o*-phenylenediamines have been described [8].

Efficient quinazoline-based drugs can be prepared via varying the substituents (pharmacophore fragments) in these compounds, which allows tuning of their physicochemical properties (hydrophilicity and lipophilicity), bioavailability, and activity.

Indole core is a constituent of tryptophane and its metabolites as well as certain natural alkaloids and antibiotics [9]. Indole derivatives have revealed antitumor, antiviral, antiinflammatory, antidepressant, and other types of activity [10].

We continue to develop methods for the synthesis of biologically active derivatives of quinoxaline [7]. At present, atom economic processes that correspond to the principles of green chemistry are the most promising [11]. The reactions of nucleophilic C–C coupling are among them, since they can proceed under conditions of acid catalysis (without the use of metal catalysts) and are theoretically waste-free [12, 13].

In this study, phenylhydrazones of indole-3-carbaldehydes **3a**–**3e** were used as nucleophiles which were prepared by short-term heating of indole-3-carbaldehydes **1a**, **1b** with phenylhydrazines **2a**–**2d** in aqueous ethanol in the presence of HCl (Scheme 1).

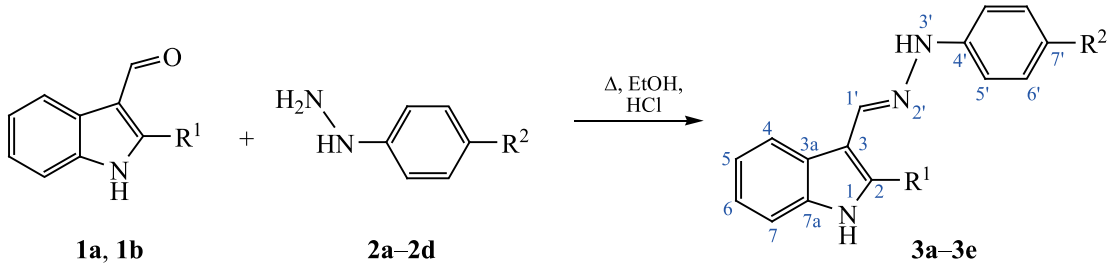
The structure of the obtained compounds was confirmed using ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and the 2D experiments: ^{1}H–^{13}C gHSQC/gHMBC and ^{1}H–^{15}N gHMBC. In the case of arylhydrazones, the *E*-configuration of the C=N bond is thermodynamically favorable, as confirmed by X-ray diffraction analysis [14, 15].

Heating of quinazoline **4** with hydrazones **3a**–**3c** in trifluoroacetic acid (TFA) gave compounds **5a**–**5c** (Scheme 2).

The structure of compounds **5a**–**5c** was confirmed by the data of ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy, mass spectrometry, and 2D correlation spectroscopy (^{1}H–^{13}C gHMBC/gHSQC and 2D ^{1}H–^{15}N gHMBC).

It was found that the C^{5} atom of the indole part of the hydrazone **3a**–**3c** molecule was added at the $C^{4'}$ atom of

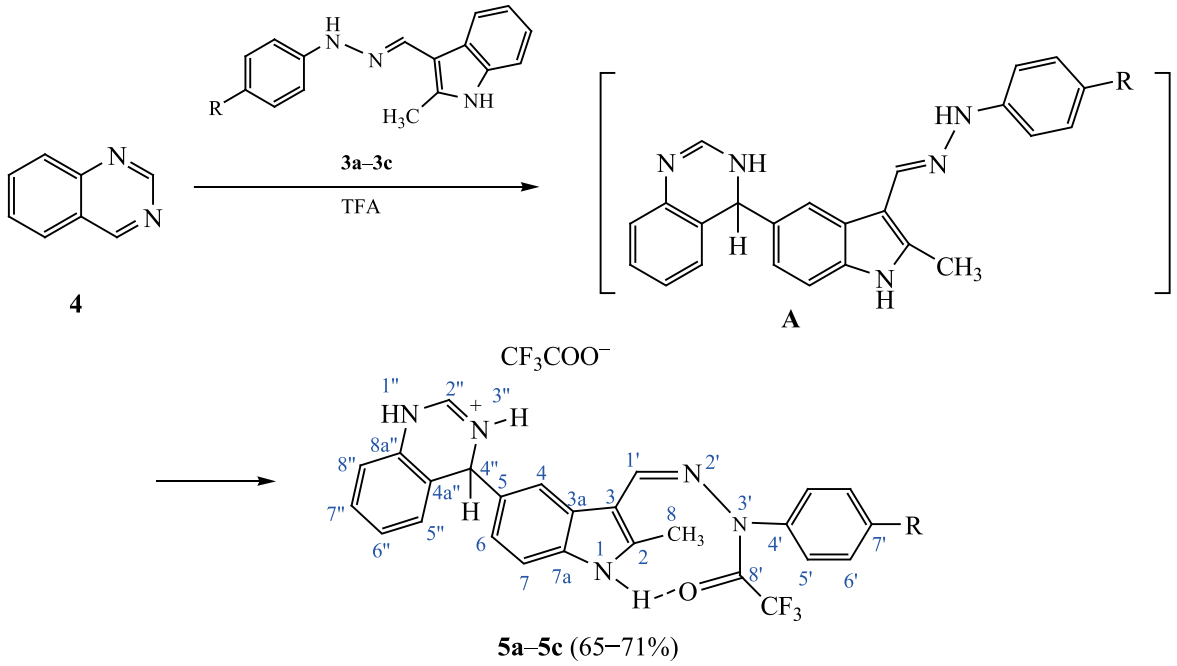
Scheme 1.



1a, **1b** **2a–2d** **3a–3e**

R^1 = H (**1a**), Me (**1b**); R^2 = NO_2 (**2a**), Me (**2b**), F (**2c**), H (**2d**); R^1 = Me, R^2 = NO_2 (**3a**), Me (**3b**), F (**3c**), H (**3e**); R^1 = R^2 = H (**3d**).

Scheme 2.



4 **A**

5a–5c (65–71%)

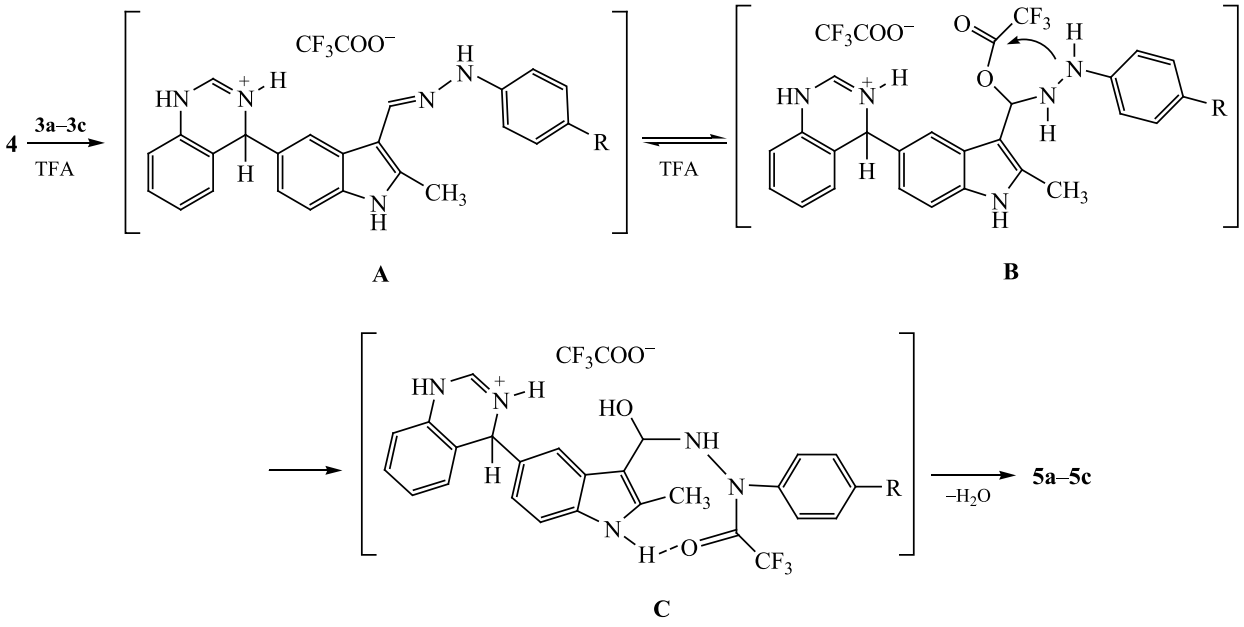
R = NO_2 (**a**), CH_3 (**b**); F (**c**).

quinazoline. That fact was confirmed by the presence of the characteristic cross peaks of the interaction between the C^{7a} atom with the broadened signal of the H^4 proton and the H^6 atom doublet in the 2D ^1H–^{13}C HMBC spectrum of compound **5a**. If the alternative addition of the nucleophile at the C^6 atom of the indole fragment took place, the interaction of the C^{7a} atom with the H^4 hydrogen atom doublet would be observed.

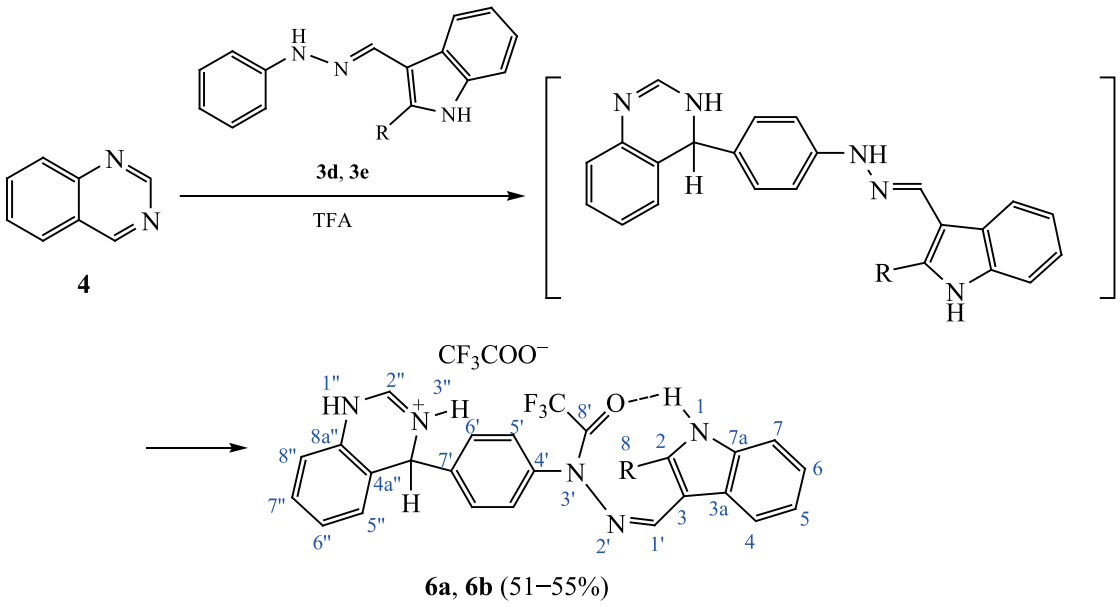
^1H NMR spectra of compounds **5a–5c** contained a characteristic singlet of the $H^{4''}$ proton (6.25–6.26 ppm) at the sp^3-hybridized $C^{4''}$ quinazoline atom, the ^{13}C NMR signal of which was observed at 54.14–54.61 ppm. The signals of the $H^{5'}$ and $H^{6'}$ protons of the aryl substituent in compounds **5** were observed as two-proton doublets revealing spin-spin interaction and recognized from the cross-interactions with the nitrogen atom in the 2D ^1H–^{15}N gHMBC spectrum.

Acylation of the intermediate **A** with TFA occurred at the $N^{3'}$ atom, as confirmed by significant downfield shift of the $N^{3'}$ atom signal in the ^{15}N NMR spectrum. The chemical shift of that nitrogen atom in the spectrum of the starting hydrazone **3a** was 155.43 ppm, compared to 215.5 ppm for the acylation product (thifluoroacetyl hydrazide **5a**). The proton signals of the NH groups of the indole and quinazoline moieties were retained in the

Scheme 3.



Scheme 4.



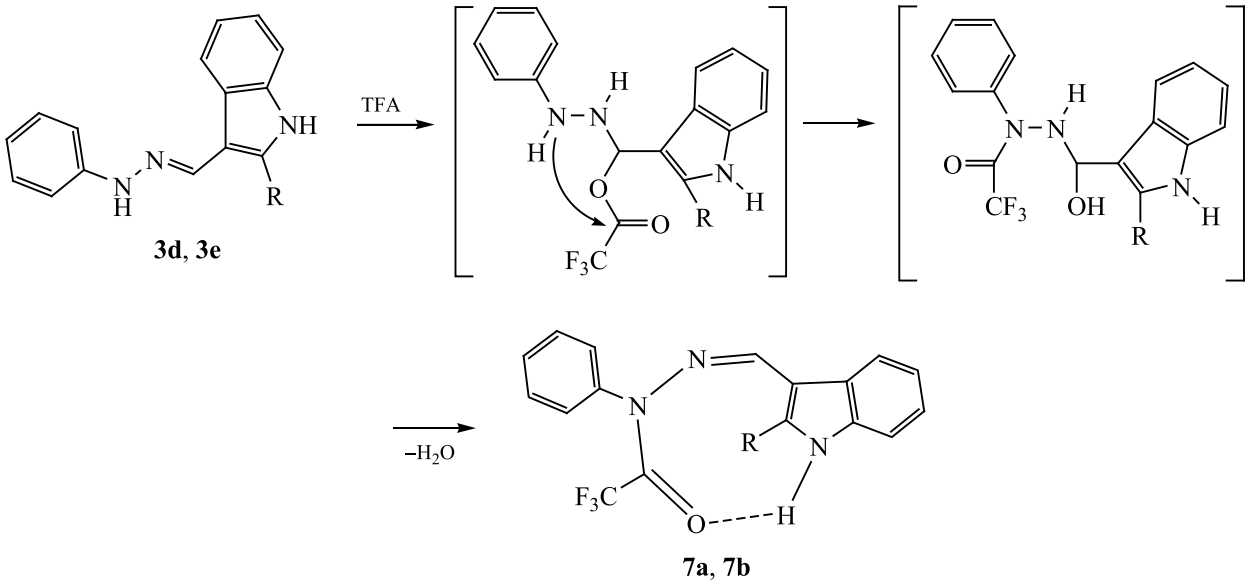
R = H (**6a**), CH_3 (**6b**).

^{1}H NMR spectra of compound **5a**. Hence, the acylation occurred at the nitrogen atom of the hydrazine fragment.

The 2D ^{1}H–^{13}C gHMBC spectra of the acylation products **5a**–**5c** contained strong cross-peaks between the quartet signal of the $C^{8'}$ atom of the trifluoroacetyl group and the broadened signal of the N^1H proton at 155.4 ppm (**5a**, J_{CF} = 36.7 Hz). Moreover, the $^{2h}J(C^{8'}H^1)$ = 3.2 Hz value resulting from the stable intramolecular N–H···O=C hydrogen bond was determined from the ^{13}C NMR spectrum without proton decoupling. Since an intramolecular hydrogen bond was formed in the molecule, it could be assumed that compounds **5c**–**5c** in DMSO-d_6 had a molecular conformation in which the C=N bond was in *Z*-configuration.

Synthesis of the trifluoroacetyl derivatives **5c**–**5c** likely occurred in several stages. Hydrazones **3a**–**3c**

Scheme 5.



R = H (**7a**), CH_3 (**7b**).

were first added at quinazoline **4** to form intermediate **A**. Further acylation of the molecule started with the addition of TFA at the C=N bond (intermediate **B**), followed by the intramolecular rearrangement affording the N-acetyl intermediate **C**. Subsequent dehydration of intermediate **C** gave compounds **5a**–**5c** with the hydrogen bond between the carbonyl group of the trifluoroacetyl fragment and the NH group of the indole moiety closing the 9-membered pseudo cycle (Scheme 3).

In contrast to compounds **3a**–**3c**, addition of hydrazines **3d**, **3e** (R^1 = H, CH_3; R^2 = H) to the quinazoline core occured at $C^{7'}$-position to yield adducts **6a**, **6b** (Scheme 4).

Mass spectra of compounds **6** contained the molecular ions corresponding to the products of addition of the hydrazone molecule at the quinazoline core. The ^{1}H NMR spectrum contained the singlet of the proton at the quinazoline sp^3-hybridized $C^{4''}$ atom, at 6.24 ppm. Two doublets of the aromatic protons at 7.61 and 7.92 ppm (**6a**) confirmed the addition of hydrazones **3d**, **3e** at compound **4** via the *para*-position of the phenyl group. Since the signal of the NH proton of the indole moiety in adducts **6** was preserved, acylation apparently took place in the hydrazine part of the molecule.

The 2D ^{1}H–^{13}C gHMBC spectra of adducts **6a**, **6b** (like those of compounds **5**) contained strong cross-peaks between the quartet signal of the $C^{8'}$ atom of trifluoroacetyl group at 155.9 ppm (**6a**, $^2J_{CF}$ = 36.3 Hz) and the broadened signal of the N^1H group proton, evidencing the formation of the intramolecular N–H···O=C hydrogen bond. The presence of the intramolecular hydrogen bond in the molecule suggested that the obtained compounds **6a**, **6b** in DMSO-d_6 took the conformation with the C=N bond in the *Z*-configuration, as in adducts **5**.

Similarly to adducts **5**, the formation of the trifluoroacetyl quinazoline derivatives **6** (Scheme 4) likely involved the stages of addition of hydrazone to quinazoline and acylation of the adduct with TFA at the $N^{3'}$H group closing the 9-membered pseudo cycle via the trifluoroacetyl group and the NH proton of the indole moiety.

Hence, the study of reactivity of indole-3-carbaldehydes phenylhydrazones **3a**–**3e** towards quinazoline **4** in acidic medium revealed two active C-nucleophilic sites in the hydrazone molecules: the $C^{7'}$ atom of the phenyl fragment and the C^5 atom of the indole moiety. Since the addition to quinazoline in the absence of a substituent in position 7′ of the phenyl fragment (compounds **3d**, **3e**) occurred via the $C^{7'}$ atom, higher nucleophilicity of that site in comparison with the C^5 atom could be suggested.

Since the C,C-coupling was accompanied by the acylation of the hydrazone NH group, we expected that heating of the starting hydrazones **3** in TFA should also lead to their acylation into hydrazide **7**; that was confirmed in the experiment: heating of hydrazones

3d, **3e** in TFA gave the trifluoroacyl derivatives **7a**, **7b** (Scheme 5).

The structure of the acylation products **7a**, **7b** was confirmed by the data of ^{1}H, ^{13}C, ^{15}N, and ^{19}F NMR spectroscopy including the 2D correlation experiments (^{1}H–^{13}C HSQC/HMBC). Since the spectra of compounds **7a**, **7b** contained the signals of the indole NH protons, the acylation evidently occurred at the hydrazine part of the molecule. The 2D ^{1}H–^{13}C HMBC spectra of the products, similarly to the cases of compounds **5** and **6**, contained strong cross-peaks between the quartet signal of the trifluoroacetyl carbon atom (155.4 ppm, $^{2}J_{CF}$ = 36.7 Hz) and the indole N^{1}H proton (11.01 ppm), marking the spin-spin interaction via the hydrogen bond.

The obtained hydrazides **7** were not involved in the C,C-coupling with quinazoline **4**: compounds **7** were isolated unchanged upon heating of quinazoline **4** with hydrazides **7a**, **7b** in TFA. Inertness of hydrazides **7** in the C,C-coupling reaction showed that the first stage of the described process occurred as the addition of hydrazones **3** to quinazoline, followed by acylation.

During the study of the hydrazones reactivity, the electron-donor properties of the considered molecules were assessed by means of voltammetry. The sensitivity of the compounds to oxidation (the hydrazones fragment NH–N=CH is readily oxidized [16]) can be used to describe their nucleophilicity.

Electrochemical oxidation of compounds **3a**–**3e** and **7a**, **7b** led to the appearance of a single strong peak in the voltammogram. The introduction of electron-donating substituents in the molecule of hydrazones **3** noticeably reduced the potential of the first oxidation wave (Table 1),

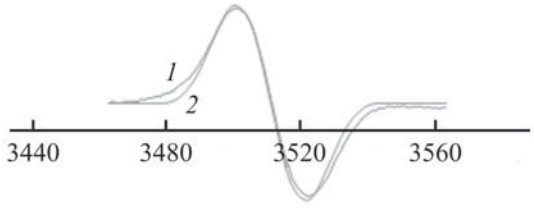


Fig. 1. Experimental (*1*) and calculated (*2*) ESR spectra of cation-radical of compound **3b** in acetonitrile.

whereas the effect of the electron-accepting substituents was the opposite. The highest oxidation potentials were observed for trifluoroacetyl hydrazides **7a**, **7b**.

Since the curves of electrochemical oxidation of the hydrazones and hydrazides were similar, it could be suggested that they reflected similar process. The wave of oxidation of the considered compounds likely corresponded to the single-electron transfer. That suggestion was confirmed by linear correlation between the oxidation potential and the calculated data on the electron affinity of cations of compounds **3** and **7** (Table 2).

The study of the reactivity features of the reactions of compound **3b** in trifluoroacetic acid revealed the electron spin resonance (ESR) signal evidencing the single-electron transfer yielding the cation-radical. It could be suggested that the donor-acceptor interaction occurs in the molecule of hydrazone **3b** in the presence of an acceptor (tetrabutylammonium fluoride), affording a cation-radical (Scheme 6). The calculated ESR spectrum of the cation-

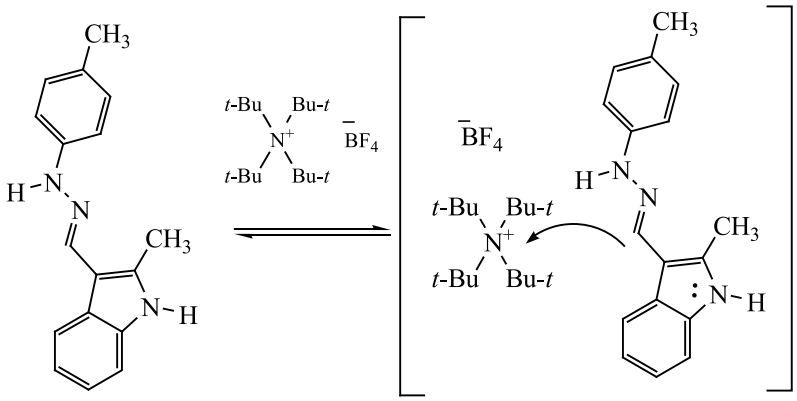
Table 1. Oxidation potentials of hydrazones **3a**–**3e** and hydrazides **7a**, **7b** in acetonitrile

R	**3a**	**3b**	**3c**	**3d**	**3e**	**7a**	**7b**
R^1	CH_3	CH_3	CH_3	H	CH_3	CH_3	CH_3
R^2	NO_2	CH_3	F	H	H	NO_2	CH_3
E_o, V	0.811	0.500	0.581	0.625	0.588	0.908	0.892

Table 2. Energy of oxidation and cations electron affinity of compounds **3a**–**3e** and **7a**, **7b** in acetonitrile

Comp. no.	E_{Ox}, V	E^{cat}_{opt}, eV	E_{opt}, eV	E^{EA}_{cat}, eV
3a	0.811	–26867.9	–26873	5.006898
3b	0.470	–22372.9	–22377.5	4.680361
3c	0.581	–24003.3	–24008	4.761995
3d	0.625	–20232.7	–20237.5	4.843629
3e	0.588	–21302.9	–21307.6	4.761995
7a	0.870	–39122	–39127.8	5.768817
7b	0.860	–34627	–34632.7	5.714394

Scheme 6.



radical of compound **3b** was in good accordance with the experimental one (Fig. 1).

It is known that the radical processes are fast and occur under mild conditions, but the C,C-coupling of hydrazones **3** with quinazoline **4** at room temperature was not observed using ^{1}H NMR spectroscopy. Characteristic NMR signals of the adducts **5** and **6** appeared in the spectrum upon keeping of the reaction mixture in a spectrometer cell during 30 h at 50°C. Evidently, the radical species did not appear at the coordinate of the considered reactions.

To elucidate the nucleophilic sites in the molecules of the studied compounds, we performed the quantum-chemical simulations and determined the localization of the electron density in the highest orbitals. Using compound **3d** as an example, we simulated the electron density in three HOMO levels with close energy eigenvalues.

Visual analysis of the obtained data (Fig. 2) revealed that the highest electron density was localized at the N^3 atom of the hydrazone **3d** molecule. That was reflected in the strongest electron-donating activity of the N sites and determined the oxidation potential of the hydrazone as well as the formation of the stable cation-radical in a solution of compound **3b**, that with the lowest oxidation potential.

The adducts at the N^3 site were not formed in the reaction (at least, they were not detected in the reaction products), due to weakness of the C–N bond. The formation of stable adducts was possible upon the interaction of quinazoline **4** with C-nucleophilic sites C^2, C^5, and $C^{7'}$ of hydrazones **3**. Localization of the electron density at the $C^{7'}$ atom and spatial availability of the latter led to the formation of the adducts at that site (Fig. 2a). Spatial shielding of the $C^{7'}$ and C^2 sites (in hydrazones **3a**–**3c**) emerged the nucleophilic properties of the C^5 atom with the highest occupancy of the HOMO-1 and HOMO-2 levels (Fig. 2b). Indeed, the C^5 and $C^{7'}$ nucleophilic sites were involved in the C,C-coupling of hydrazones **3** with quinazoline **4**.

Analysis of the structure of hydrazones **3** suggested that the localization of the negative charge at the positions C^5 and $C^{7'}$ of the hydrazones was due to the conjugation of the π-electrons of the aromatic nuclei with the electrons of the amino groups of molecules **3**. Deactivation of both nucleophilic sites in the molecule of hydrazide **7** was due to the effect of the electron-accepting trifluoroacetyl group. Calculation of the eigenvalues of energy (eV)

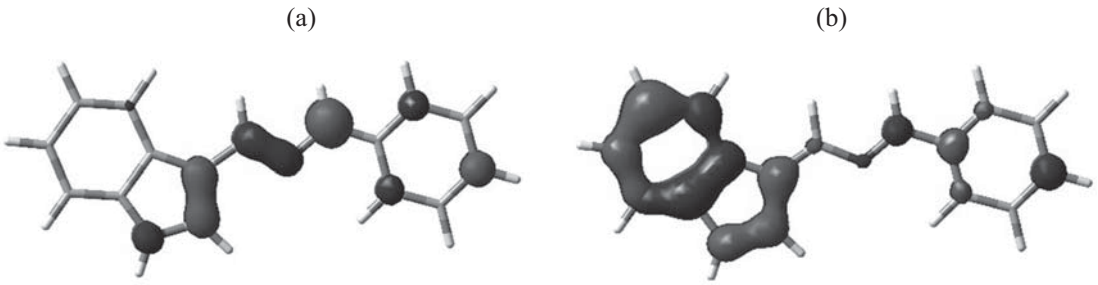


Fig. 2. Electron density distribution in the molecule of compound **3b:** (a) HOMO, (b) HOMO-1, HOMO-2.

and occupancy of the molecular orbitals (Fig. 3) in the molecule of the trifluoroacetyl derivative **7a** showed that the HOMO energy of that molecule was significantly lower than that of the non-acylated compound **3d**:

Localization of the electron density at the C^5 and $C^{7'}$ atoms of compounds **7a**, **7b** was not revealed (Fig. 3), explaining the inertness of molecules **7a**, **7b** as C-nucleophiles.

Trifluoroacetyl hydrazides **7** showed the highest oxidation potentials (Table 1) among the considered compounds, meaning that the electron-donor properties of those derivatives were less prominent in comparison with hydrazones **3**. That was likely the reason of the inertness of compounds **7a**, **7b** towards C,C-coupling with quinazoline **4**.

In summary, phenylhydrazones of indole-3-carbaldehydes were multisite C-nucleophiles which could be used in the C,C-coupling reactions for the preparation of various derivatives of quinazoline promising in view of their biological activity. The C,C-coupling of the hydrazones was accompanied by the acylation of the NH group of the hydrazone fragment with TFA, changing the *E*-configuration of the C=N hydrazone bond to the *Z*-configuration.

EXPERIMENTAL

Commercial chemicals (Sigma Aldrich, Merck) were used as received. The reactions progress was monitored by TLC on silica gel plates (Merck).

^1H, ^{19}F, ^{13}C, and ^{15}N NMR spectra of the solutions in DMSO-d_6 were recorded using Bruker AVANCE NEO-600 and AVANCE-400 spectrometers. ^1H and ^{19}F chemical shifts were measured with respect to the internal references—tetramethylsilane and trichlorofloromethane, respectively and those of ^{13}C were determined with reference to the solvent signal (DMSO-d_6). Mass spectra (EI) were registered using a MicrOTOF-Q instrument (Bruker Daltonics), ionization potential being 75 eV at 250°C. High-resolution mass spectra (electrospray ionization) were obtained using an Agilent 6545 Q-TOF LC-MS instrument (Agilent Technologies, USA).

Cyclic voltammetry measurements were performed using a μAutolab Type III potentiostat-galvanostat (Metrohm, Switzerland) in a standard three-electrode cell (working electrode: glassy carbon disk pressed in fluoroplastic, d = 2.5 mm, Metrohm, Switzerland; auxiliary electrode: glassy carbon rod, Metrohm, Switzerland; reference electrode: silver chloride, Metrohm, Switzerland; background electrolyte: tetrabutylammonium tetrafluoroborate, "special pure" grade, Panreac, Spain in acetonitrile, "special pure" grade, Kriokhrom, Russia). Cyclic voltammograms were recorded in a linear mode with potential scanning rate 100 mV/s.

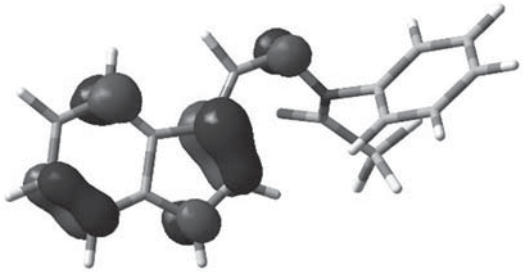


Fig. 3. Electron density distribution in the molecule of compound **7a** (HOMO).

Electron affinity energy of cations of the studied hydrazones in gas phase was determined accounting for solvation in acetonitrile. The simulation was performed in the scope of the density functional theory using the B3LYP exchange-correlation potential in the 6-31G++(d, p) basis set [17,18] implemented in GAUSSIAN09 software [19]. The coefficient of determination for the linear regression of the electron affinity with respect to oxidation potential (R^2) equaled 0.84.

Quantum-chemical simulation of the ESR spectrum of the compound **3b** cation-radical was performed via DFT with geometry optimization using the B3LYP method in the 6-31+G(d) basis set. The superfine interaction constants were calculated via the UB3LYP method in the IGLO-III basis [20]. The simulations were performed using ORCA 4.01 software [21]. Simulation of the ESR spectra was performed using EasySpin software [22].

Compound **3d** was prepared as described elsewhere [23].

Synthesis of hydrazones 3a–3c, 3e (*general procedure*). A solution of 0.5 mmol of 2-methyl-1*H*-indole-3-carbaldehyde **1a**, **1b** in 3 mL of ethanol was added to a solution of 0.5 mmol of the corresponding hydrazine **2a–2d** and 0.02 mL of conc. HCl in 3 mL of water. The obtained mixture was refluxed during 3–5 min and cooled. The hydrazone precipitate was filtered off and dried.

2-Methyl-3-{(*E*)-[2-(4-nitrophenyl)hydrazinylidene]methyl}-1*H*-indole (3a). Yield 59%, mp 288–289°C. ^1H NMR spectrum (600 MHz), δ, ppm: 2.54 s (3H, CH_3), 7.09 br. s (2H, $H^{4'}$), 7.12–7.15 m (2H, H^5, H^6), 7.33–7.37 m (1H, H^7), 8.12–8.17 m (3H, H^4, $H^{5'}$), 8.34 s (1H, $H^{1'}$), 10.98 s (1H, $N^{3'}H$), 11.47 s (1H, N^1H).

^{13}C NMR spectrum (151 MHz), δ_C, ppm: 108.08 (C^3), 110.56 ($C^{5'}$), 111.41 (C^7), 120.86 (C^5), 121.11 (C^4), 122.23 (C^6), 125.68 (C^{3a}), 126.93 ($C^{6'}$), 136.18 (C^{7a}), 137.38 ($C^{7'}$), 139.65 (C^2), 140.25 ($C^{1'}$), 151.31 ($C^{4'}$). ^{15}N NMR spectrum (61 MHz), δ_N, ppm: 144.79 (N^1), 155.43 ($N^{3'}$), 303.13 ($N^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 294 (100) $[M]^+$, 157 (86), 130 (64). Mass spectrum (HRMS ESI-MS), *m/z*: 295.1203 $[M + H]^+$ (calculated for $C_{16}H_{15}N_4O_2$: 295.1190).

2-Methyl-3-{(*E*)-[2-(4-methylphenyl)hydrazinylidene]methyl}-1*H*-indole (3b). Yield 61%, mp 143–144°C. ^{1}H NMR spectrum (600 MHz), δ, ppm: 2.21 s (3H, CH_3), 2.51 s (3H, C^2CH_3), 6.94 d (2H, $H^{4'}$, J = 7.9 Hz), 7.03 d (2H, $H^{5'}$, J = 8.1 Hz), 7.10 d. d (2H, H^5, H^6, J = 5.9, 3.1 Hz), 7.31 d. d (1H, H^7, J = 5.6, 3.4 Hz), 8.15 s (2H, $H^{1'}$, H^4), 9.64 br. s (1H, $N^{3'}H$), 11.23 s (1H, N^1H). ^{13}C NMR spectrum (151 MHz), δ_C, ppm: 108.79 (C^3), 111.14 (C^7), 111.85 ($C^{5'}$), 120.25 (C^5), 121.02 (C^4), 121.77 (C^6), 125.88 (C^{3a}), 126.24 ($C^{7'}$), 129.96 ($C^{6'}$), 134.61 ($C^{1'}$), 136.08 (C^{7a}), 136.76 (C^2), 144.58 ($C^{4'}$). ^{15}N NMR spectrum (61 MHz), δ_N, ppm: 140.1 ($N^{3'}$), 140.5 (N^1), 311.7 ($N^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 263 (100) $[M]^+$, 157 (68), 130 (41). Mass spectrum (HRMS ESI-MS), *m/z*: 264.1506 $[M + H]^+$ (calculated for $C_{17}H_{18}N_3$: 264.1495).

2-Methyl-3-{(*E*)-[2-(4-fluorophenyl)hydrazinylidene]methyl}-1*H*-indole (3c). Yield 68%, mp 133–134°C. ^{1}H NMR spectrum (600 MHz), δ, ppm: 2.51 s (3H, CH_3), 6.98–7.02 m (2H, H^5, H^6), 7.05–7.11 m (4H, $H^{5'}$, $H^{6'}$), 7.29–7.33 m (1H, H^7), 8.11–8.14 m (1H, H^4), 8.15 s (1H, $H^{1'}$), 9.75 s (1H, N^3H), 11.23 s (1H, N^1H). ^{13}C NMR spectrum (151 MHz), δ_C, ppm: 108.65 (C^3), 111.16 (C^7), 111.83 ($C^{5'}$), 120.98 (C^5), 121.81 (C^4), 122.34 (C^6), 125.84 (C^{3a}), 126.75 ($C^{7'}$), 128.40 ($C^{6'}$), 135.17 ($C^{1'}$), 136.07 (C^{7a}), 136.98 (C^2), 143.52 ($C^{4'}$). ^{19}F NMR spectrum (565 MHz): δ_F –127.76 ppm. ^{15}N NMR spectrum (61 MHz), δ_N, ppm: 142.2 ($N^{3'}$), 147.4 (N^1), 315.2 ($N^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 267 (100) $[M]^+$, 157 (69), 130 (51). Mass spectrum (HRMS ESI-MS), *m/z*: 268.1255 $[M + H]^+$ (calculated for $C_{16}H_{15}FN_3$: 268.1245).

2-Methyl-3-[(*E*)-(2-phenylhydrazinylidene]-1*H*-indole (3e). Yield 59%, mp 192–193°C (mp 192–193°C [21]). ^{1}H NMR spectrum (600 MHz), δ, ppm: 2.49 s (3H, CH_3), 6.67 t. t (1H, H^p, J = 7.3, 1.2 Hz), 7.03 d. d (2H, H^o, J = 8.5, 1.2 Hz), 7.08–7.12 m (2H, H^5, H^6), 7.21 d. d (2H, H^m, J = 8.5, 7.3 Hz), 7.31 m (1H, H^7), 8.15 m (1H, H^4), 8.17 s (1H, $H^{1'}$), 9.78 br. s (1H, $N^{3'}H$), 11.23 s (1H, N^1H). ^{13}C NMR spectrum (151 MHz), δ_C, ppm: 136.06 (C^2), 118.04 (C^3), 129.91 (C^{3a}), 130.99 (C^4), 127.76 (C^5), 127.49 (C^6), 127.78 (C^7), 132.84 (C^{7a}), 139.22 ($C^{1'}$), 139.44 (C^i), 124.4 (C^o), 129.27 (C^m), 127.67 (C^p), 115.98 (CF_3), 155.28 (C=O). ^{15}N NMR spectrum (61 MHz), δ_N, ppm: 126.8 (N^1), 305 ($N^{3'}$), 218.5 ($N^{3'}$). Mass spectrum, *m/z* (I_{rel}, %): 249 (100) $[M]^+$.

Synthesis of trifluoroacetyl hydrazides 5a–5c (*general procedure*). A mixture of 0.5 mmol of quinazoline **4** and 0.5 mmol of the corresponding hydrazone **3a–3c** in 3 mL of TFA was refluxed during 65–70 h. The solvent was evaporated off; the residue was suspended in 2 mL of water, filtered off, and dried.

4-(2-Methyl-3-{(*Z*)-[2-(4-nitrophenyl)-2(2,2,2-trifluoroacetyl)hydrazinylidene]methyl}1*H*-indol-5-yl)-1,4-dihydroquinazolin-3-ium 2,2,2-trifluoroacetate (5a). Yield 68%, mp 143–144°C. ^{1}H NMR spectrum (600 MHz), δ, ppm: 2.29 s (3H, H^8), 6.26 s (1H, $H^{4''}$), 7.13 d (1H, $H^{5''}$, J = 7.6 Hz), 7.20 d (1H, $H^{8''}$, J = 7.9 Hz), 7.24 t (1H, $H^{6''}$, J = 7.5 Hz), 7.37 t (1H, $H^{7''}$, J = 7.6 Hz), 7.50 d (2H, H^7, J = 8.0 Hz), 7.53 s (1H, H^4), 7.55 d (1H, H^6, J = 8.1 Hz), 7.76 s (1H, $H^{1'}$), 7.87 d (2H, $H^{5'}$, J = 9.0 Hz), 8.41 d (2H, $H^{6'}$, J = 8.9 Hz), 8.56 s (1H, $H^{2''}$), 11.12 s (2H, N^1H, $N^{3''}H$), 12.39 s (1H, COOH). ^{13}C NMR spectrum (151 MHz), δ_C, ppm: 12.22 (C^8), 54.61 ($C^{4''}$), 116.39 (CF_3, J = 288.7 Hz), 117.61 ($C^{8''}$), 119.67 (C^3), 121.93 ($C^{4a''}$), 124.75 ($2C^{5'}$), 125.51 ($2C^{6'}$), 127.62 (C^6), 127.86 ($C^{6''}$), 128.60 ($C^{5''}$), 128.72 (C^7), 129.86 ($C^{8a''}$), 130.05 ($C^{7''}$), 130.24 (C^{3a}), 130.46 (C^4), 133.64 (C^{7a}), 137.63 (C^2), 141.26 ($C^{1'}$), 142.44 (C^5), 144.73 ($C^{4'}$), 146.25 ($C^{7'}$), 149.20 ($C^{2''}$), 155.83 ($COCF_3$, ^2J = 36.3 Hz), 158.39 q (COOH, ^2J = 31.6 Hz). ^{19}F NMR spectrum (565 MHz), δ_F, ppm: –73.53, –74.00. ^{15}N NMR spectrum (61 MHz), δ_N, ppm: 126.1 ($N^{1''}$, $N^{3''}$), 215.5 (N^1, $N^{3'}$), 304.2 ($N^{2'}$), 369.2 (NO_2). Mass spectrum, *m/z* (I_{rel}, %): 520 (15) $[M]^+$, 390 (31), 131 (100). Mass spectrum (HRMS ESI-MS), *m/z*: 521.1565 $[M + H]^+$ (calculated for $C_{26}H_{20}F_3N_6O_3$: 521.1543).

4-(2-Methyl-3-{(*Z*)-[2-(4-methylphenyl)-2(2,2,2-trifluoroacetyl)hydrazinylidene]methyl}-1*H*-indol-5-yl)-1,4-dihydroquinazolin-3-ium 2,2,2-trifluoroacetate (5b). Yield 71%, mp 118–119°C. ^{1}H NMR spectrum (400 MHz), δ, ppm: 2.15 s (3H, H^8), 2.39 s (3H, $H^{7'}$), 6.25 s (1H, $H^{4''}$), 7.13 d (1H, $H^{5''}$, J = 8.0 Hz), 7.20 d (1H, $H^{8''}$, J = 8.0 Hz), 7.24 t (1H, $H^{6''}$, J = 8.0 Hz), 7.42–7.30 m (4H, $H^{4,6,7,7''}$), 7.87 d (2H, $H^{5'}$, J = 8.0 Hz), 7.60 s (1H, $H^{1'}$), 8.41 m (2H, $H^{6'}$), 8.55 s (2H, $H^{2''}$), 11.06 s (2H, N^1H, $N^{3''}H$), 12.35 s (1H, COOH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 11.24 (C^8), 20.57 ($C^{8'}$), 54.14

($C^{4''}$), 111.33 (CF_3, J = 284.6 Hz), 117.10 (C^3), 117.39 ($2C^{5'}$), 117.79 ($C^{8''}$), 121.45 ($C^{4a''}$), 122.55 (C^6), 124.36 ($2C^{6'}$), 126.64 ($C^{6''}$), 127.35 ($C^{5''}$), 128.15 (C^7), 129.33 ($C^{8a''}$), 129.71 (C^{3a}), 130.44 ($C^{7''}$), 130.97 (C^{7a}), 132.98 (C^4), 136.19 (C^2), 136.95 ($C^{1'}$), 137.35 (C^5), 138.86 ($C^{4'}$), 141.84 ($C^{2''}$), 148.70 ($C^{7'}$), 155.67–154.96 m ($COCF_3$), 158.13–157.77 m (COOH). ^{19}F NMR spectrum (376 MHz), δ_F, ppm: –73.65, –74.00. ^{15}N NMR spectrum (61 MHz), δ_N, ppm: 128.3 ($N^{1''}$, $N^{3''}$), 221.7 (N^1, $N^{3'}$), 300.6 ($N^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 489 (38) $[M]^+$, 359 (32), 131 (100). Mass spectrum (HRMS ESI-MS), *m/z*: 490.1872 $[M + H]^+$ (calculated for $C_{27}H_{23}F_3N_5O$: 490.1849).

2-Methyl-4-{3-[2-(4-fluorophenyl)-2(2,2,2-trifluoroacetyl)hydrazinylidene]methyl}-1*H*-indol-5-yl)-1,4-dihydroquinazolin-3-ium 2,2,2-trifluoroacetate (5c). Yield 65%, mp 123–124°C. ^{1}H NMR spectrum (400 MHz), δ, ppm: 2.16 s (3H, H^8), 6.25 s (1H, $H^{4''}$), 7.13 d (1H, $H^{5''}$, J = 8.0 Hz), 7.20 d (1H, $H^{8''}$, J = 8.0 Hz), 7.25 t (1H, $H^{6''}$, J = 8.0 Hz), 7.44–7.35 m (4H, $H^{4,6,7,7''}$), 7.55–7.50 d. d (2H, $H^{6'}$, J = 14.4, 2.8 Hz), 7.56 d (2H, $H^{5'}$, J = 8.0 Hz), 7.63 s (1H, $H^{1'}$), 8.55 s (2H, $H^{2''}$), 11.08 s (2H, N^1H, $N^{3''}H$), 12.32 s (1H, COOH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 11.14 (C^8), 54.14 ($C^{4''}$), 116.19 (CF_3, J = 286.3 Hz), 117.10 ($C^{8''}$), 117.54 (C^3), 121.44 ($C^{4a''}$), 126.43–126.97 m ($2C^{6'}$, $2C^{5'}$), 127.43 (C^6), 127.72–127.83 m ($C^{5''}$, $C^{6''}$), 128.16 (C^7), 129.35 ($C^{8a''}$), 129.56 ($C^{7''}$), 129.88 (C^{3a}), 130.33 (C^4), 130.89–131.03 m ($C^{7'}$), 133.03 ($C^{4'}$), 135.77 (C^{7a}), 136.49 (C^2), 139.16 ($C^{1'}$), 141.86 (C^5), 148.69 ($C^{2''}$), 154.97–155.64 m ($COCF_3$), 157.59–158.18 m (COOH). ^{19}F NMR spectrum (376 MHz), δ_F, ppm: –73.55, –74.01, –114.01. ^{15}N NMR spectrum (61 MHz), δ_N, ppm: 127.5 ($N^{1''}$, $N^{3''}$), 218.1 (N^1, $N^{3'}$), 302.5 ($N^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 493 (35) $[M]^+$, 363 (18), 131 (100). Mass spectrum (HRMS ESI-MS), *m/z*: 494.1619 $[M + H]^+$ (calculated for $C_{26}H_{19}F_4N_5O$: 494.1598).

Trifluoroacetyl hydrazides 6a, **6b** (*general procedure*). A mixture of 0.5 mmol of quinazoline **4** and 0.5 mmol of the corresponding hydrazone **3d**, **3e** in 3 mL of TFA was refluxed during 65–70 h. The solvent was evaporated off in vacuum; the residue was suspended in 2 mL of water, filtered off, and dried.

4-(4-{2-[(*Z*)-1*H*-Indol-3-ylmethylidene]-1-(2,2,2-trifluoroacetyl)hydrazinyl}phenyl)-1,4-dihydroquinazolin-3-ium 2,2,2-trifluoroacetate (6a). Yield 51%,mp 112–113°C. ^{1}H NMR spectrum (600 MHz), δ, ppm: 6.24 s (1H, $H^{4''}$), 7.07 d (1H, $H^{5''}$, J = 7.4 Hz), 7.20–7.24 m (2H, $H^{6''}$, $H^{7''}$), 7.37 t (1H, H^5, J = 7.7 Hz), 7.41 d (1H, H^4, J = 6.7 Hz), 7.43–7.45 m (2H, $H^{6,7}$), 7.61 d (2H, $H^{5'}$, J = 8.4 Hz), 7.69 d (2H, $H^{8''}$, J = 7.6 Hz), 7.92 d (2H, $H^{6'}$, J = 8.4 Hz), 7.98 s (1H, $H^{1'}$), 8.57 s (1H, $H^{2''}$), 8.80 s (1H, H^2), 11.18 s (2H, N^1H, $N^{3''}H$), 12.37 s (1H, COOH). ^{13}C NMR spectrum (151 MHz), δ_C, ppm: 54.61 ($C^{4''}$), 116.39 (CF_3, J = 288.7 Hz), 117.59 ($C^{8''}$), 119.17 (C^3), 121,42 ($C^{6'}$), 122.42 (C^{4a}), 126.86 (C^7), 127.83 ($C^{6''}$), 128.22 ($C^{7'}$), 128.60 ($C^{5'}$), 128.73 ($C^{5''}$), 129.34 ($C^{7''}$), 129.48 (C^4), 129.82 (C^{8a}), 130.07 (C^{3a}), 131.90 (C^{7a}), 132.0 ($C^{4'}$), 139.89 (C^7), 140.54 (C^5), 141.1 (C^6), 149.14 ($C^{2''}$), 156.00 ($COCF_3$, ^2J = 36.3 Hz), 158.44 q (COOH, ^2J = 30.7 Hz). ^{19}F NMR spectrum (376 MHz), δ_F, ppm: –73.50, –74.12. ^{15}N NMR spectrum (61 MHz), δ_N, ppm: 126.9 ($N^{1'}$, $N^{3''}$), 218.6 (N^1, $N^{3'}$), 301.6 ($N^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 461 (20) $[M]^+$, 369 (11), 131 (100).

4-(4-{2-[(*Z*)-(2-Methyl-1*H*-indol-3-yl)methylidene]-1-(2,2,2-trifluoacetyl)hydrazinyl}phenyl)-1,4-dihydroquinazolin-3-ium 2,2,2-trifluoroacetate (6b). Yield 55%, mp 121–122°C. ^{1}H NMR spectrum (400 MHz), δ, ppm: 2.21 s (3H, CH_3), 6.28 s (1H, $H^{4''}$), 7.11 d (1H, CH_{Ar}, J = 7.4 Hz), 7.24 m (2H, CH_{Ar}), 7.38 t (1H, CH_{Ar}, J = 7.7 Hz), 7.44 s (5H, $4CH_{indole} + CH_{Ar}$), 7.63 s (3H, CH_{Ar}), 7.64 s (1H, $H^{1'}$), 8.57 s (1H, $H^{2''}$), 11.03 m (2H, NH), 12.37 br. s (1H, COOH). ^{13}C NMR spectrum (151 MHz), δ_C, ppm: 11.34 (CH_3), 55.96 ($C^{4''}$), 115.33 (CF_3, J = 147.38 Hz), 118.06 ($C^{8''}$), 119.17 (C^3), 123.08 ($C^{6'}$), 124.11 (C^{4a}), 124.53 (C^7), 127.50 ($C^{6''}$), 127.67 ($C^{7'}$), 127.74 ($C^{5'}$), 127.78 ($C^{5''}$), 127.95 ($C^{7''}$), 129.85 (C^{8a}), 130.97 (C^4), 132.86 (C^{7a}), 136.05 (C^{3a}), 138.50 ($C^{4'}$), 138.87 (C^7), 138.87 (C^5), 144.98 (C^6), 146.48 ($C^{2''}$), 155.30 ($COCF_3$, J = 36.5 Hz), 158.17 q (COOH, ^2J = 30.9 Hz). ^{19}F NMR spectrum (376 MHz), δ_F, ppm: –73.72, –74.07. Mass spectrum, *m/z* (I_{rel}, %): 475 (27) $[M]^+$, 345 (25), 131 (100).

Compounds 7a, **7b** (*general procedure*). A solution of 0.3 mmol of hydrazone **3d**, **3e** in 2 mL of TFA was heated during 45–50 h. The solvent was evaporated off in vacuum; the residue was suspended in 2 mL of water and adjusted to pH = 7–8 with aqueous ammonia. The precipitate was filtered off, washed with 2 mL of water, and dried.

2,2,2-Trifluoro-*N*′-[(*Z*)-1*H*-indol-3-ylmethylidene]-*N*-phenylacetohydrazide (7a). Yield 55%, mp 154–155°C. ^{1}H NMR spectrum (600 MHz), δ, ppm: 7.34 t. t (1H, H^n, J = 7.5, 1.0 Hz), 7.39 m (1H, H^6), 7.43–7.46 m (2H, H^5, H^6), 7.54 d. d (2H, H^m, J = 8.6, 7.5 Hz), 7.70 m (1H, H^4), 7.85 d. d (2H, H^z, H^o, J = 8.6, 1.0 Hz), 7.97 s

(1H, $H^{1'}$), 8.78 s (1H, H^2), 11.15 s (1H, N^1H). ^{13}C NMR spectrum (151 MHz), δ_C, ppm: 116.08 (CF_3, J = 288.6 Hz), 118.22 (C^o), 120.64 (C^3), 126.19 (C^2), 126.49 (C^n), 127.57 (C^6), 128.18 (C^5), 128.18 (C^7), 129.08 (C^4), 129.64 (C^m), 131.36 (C^{7a}), 139.39 (C^i), 139.7 ($C^{1'}$), 155.52 (C=O, J = 36.2 Hz). ^{19}F NMR spectrum (470 MHz): δ_F –74.52 ppm. Mass spectrum, *m/z* (I_{rel}, %): 331 (100) $[M]^+$, 262 (44).

2,2,2-Trifluoro-*N′*-[(*Z*)-(2-methyl-1*H*-indol-3-yl)-methylidene]-*N*-phenylacetohydrazide (7b). Yield 64%, mp 164–165°C. ^1H NMR spectrum (500 MHz), δ, ppm: 2.21 s (3H, CH_3), 7.43–7.47 m (5H, H^4, H^5, H^6, H^7, H^p), 7.52 d. d (2H, H^o, J = 8.5, 1.4 Hz), 7.57 d. d (2H, H^m, J = 8.5, 7.2 Hz), 7.63 s (1H, $H^{1'}$), 10.99 s (1H, N^1H). ^{13}C NMR spectrum (151 MHz), δ_C, ppm: –115.98 (CF_3, J = 288.8 Hz), 118.04 (C^3), 124.4 (C^o), 127.49 (C^6), 127.67 (C^p), 127.76 (C^5), 127.78 (C^7), 129.27 (C^m), 130.99 (C^4), 136.06 (C^2), 132.84 (C^{7a}), 139.22 ($C^{1'}$), 139.44 (C^i), 155.28 (C=O, J = 36.2 Hz). ^{19}F NMR spectrum (376 MHz): δ_F –74.45 ppm. Mass spectrum, *m/z* (I_{rel}, %): 345 (80) $[M]^+$, 276 (100).

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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