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# REGIOSELECTIVE SYNTHESIS OF FLUORINE-CONTAINING INDAZOLONES FROM 2-ACYL-CYCLOHEXANE-1,3-DIONES

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*New regioisomeric indazolones containing fluorine atoms in the aromatic ring have been synthesized in high yield by the interaction of 2-acylcyclohexane-1,3-diones, and of their enol methyl ethers, obtained by methylating the initial β,β'-triketones with dimethyl sulfate in the presence of calcined potassium carbonate, with 4-fluorophenylhydrazine hydrochloride and with pentafluorophenylhydrazine. The structures of the synthesized compounds were confirmed by data of IR and $^{1}H$, $^{13}C$, and $^{19}F$ NMR spectra.*

**Keywords:** 2-acylcyclohexane-1,3-diones, fluorine-containing indazolones, regioselective synthesis.

At the present time methods of synthesizing various fluorine-containing polyfunctional heterocyclic structures as medicinal preparations are being developed vigorously [1, 2]. Indazoles are an important class of organic compounds, many of which possess anti-inflammatory, analgesic, antiviral, and other physiological activitities [3, 4].

The aim of the present work was to obtain new fluorine-containing indazolones from various 2-acylcyclohexane-1,3-diones.

Thanks to their polyfunctionality and depending on the structure of the acyl side chain and the cyclic portion of the molecule the 2-acylcyclohexane-1,3-diones are widely applied in the synthesis of steroids, prostaglandins, antibiotics, and other biologically active substances [5-8]. Chemical conversions of 2-acylcyclohexane-1,3-diones existing in the enolic form may also affect such reaction centers as the exo- and endocyclic carbonyl groups, and also the methylene groups adjacent to them [9].

With the aim of synthesizing new derivatives of indazolones containing a fluorine atom in position 4 of the benzene ring or a completely fluorinated benzene ring we studied the interaction of 2-acylcyclohexane-1,3-diones **1a-e** and their methyl ethers with 4-fluorophenylhydrazine and pentafluorophenylhydrazine.

The interaction of 2-acylcyclohexane-1,3-diones **1a-e** with a small excess of an equimolar mixture of 4-fluorophenylhydrazine hydrochloride and sodium hydroxide in ethanol for 8 h at room temperature led in high yield to the products of heterocyclization, indazolones **3a-e**. The intermediate hydrazones **2a-e** were not isolated.

* Dedicated to Distinguished Scientist Academician A. A. Akhrem in his 95th Year.

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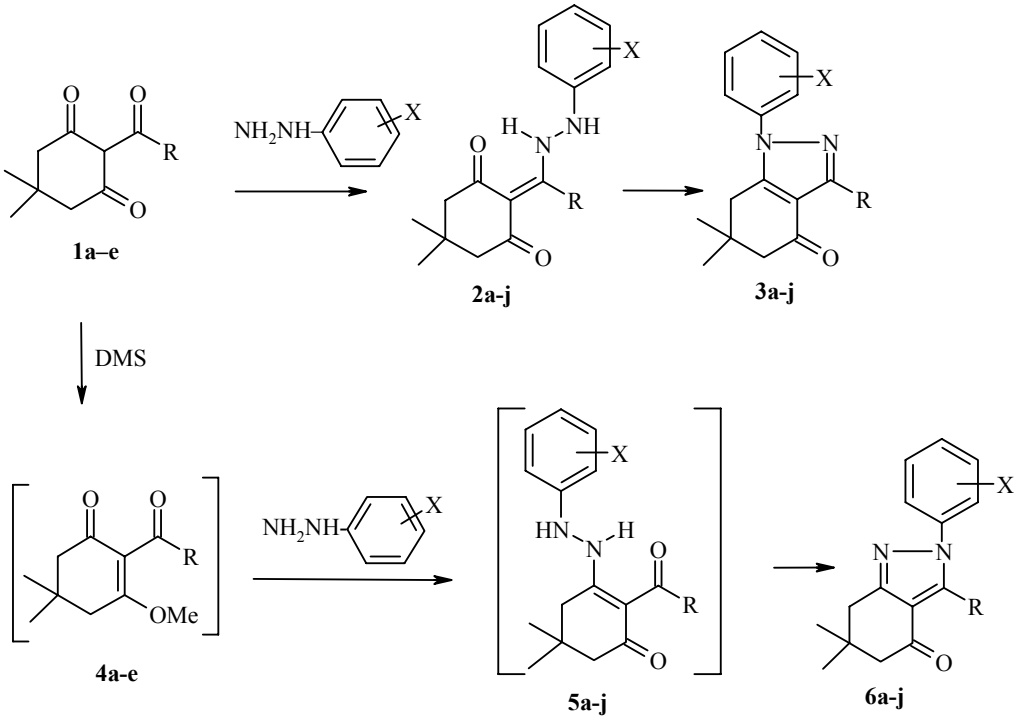
However on reacting triketones **1a,b** with a small excess of pentafluorophenylhydrazine in ethanol for 8 h at room temperature both hydrazones **2f,g** and indazolones **3f,g** were isolated by preparative TLC in yields of 79, 61 and 21, 39% respectively. Meanwhile, for compounds **1c-e** under the same conditions, only the heterocyclic products **3h-j** were isolated. Indazolones **3f,g** were obtained as the sole reaction products on boiling compounds **1a,b** in ethanol for 20 h with a small excess of pentafluorophenylhydrazine.




**1**–**6 a** R = Me, **b** R = Et, **c** R = Ph, **d** R = 2-furyl, **e** R = *cyclo*-$C_3H_5$;
**2**, **3**, **5**, **6 f** R = Me, **g** R = Et, **h** R = Ph, **i** R = 2-furyl, **j** R = *cyclo*-$C_3H_5$;
**2**–**6 a**–**e** X = 4-F; **f**–**j** X = $F_5$

The condensation of 2-acylcyclohexane-1,3-diones **1a-e** with fluorine-containing phenylhydrazines therefore takes place at the exocyclic carbonyl group with subsequent intramolcular cyclization of the intermediate hydrazones **2a-j** and the formation of indazolones **3a-j**. The reaction proceeds regioselectively. In every case one regioisomer is formed, as was shown previously for the reaction of 2-acetylcyclohexane-1,3-diones with phenylhydrazines [10-13]. It should be mentioned that the formation of fluoro-substituted indazolones **3a-j** requires significantly more time than in the case of the unsubstituted derivatives.

With the aim of obtaining regioisomeric indazolones we undertook the synthesis of the corresponding enol methyl ethers of 2-acylcyclohexane-1,3-diones **4a-e**, since it is known that the reaction of enol ethers at the cyclic keto group of 2-acylcyclohexane-1,3-diones with phenylhydrazine proceeds according to a vinylogous substitution scheme [14].

A series of methods is proposed for the synthesis of methyl ethers of 2-acylcyclohexane-1,3-diones, among which are alkylation of their silver salts with methyl iodide [15], or sodium and tetrabutylammonium salts with dimethyl sulfate [16]. However the use of these methods in our case proved to be ineffective, since by the first method the methyl ethers **4b-e** were not isolated at all, apparently due to the instability of the silver

TABLE 1. IR Spectra and $^{1}H$, $^{13}C$, and $^{19}F$ NMR Spectra of the Synthesized Compounds **3a-j**, **6a-j**

| Com-pound | IR spectrum, ν, $cm^{-1}$ | NMR spectrum, δ, ppm (*J*, Hz) | | |
|---|---|---|---|---|
| | | $^{1}H$ | $^{13}C$ | $^{19}F$ |
| 1 | 2 | 3 | 4 | 5 |
| **3a** | 1665, 1525, 1490 | 1.11 (6H, s, $2CH_3$); 2.39 (2H, s, $CH_2$); 2.54 (3H, s, $CH_3$); 2.75 (2H, s, $CH_2$); 7.19 (2H, m, $H_{Ar}$); 7.46 (2H, m, $H_{Ar}$) | 13.34, 28.40, 35.82, 37.04, 52.39, 116.32 (d, *J* = 23); 116.85, 125.65 (d, *J* = 9); 134.79, 149.01 (C–N); 149.85 (C=N); 161.91 (d, *J* = 249); 193.34 (C=O) | -113.24 (1F, m) |
| **3b** | 1670, 1520, 1500 | 1.11 (6H, s, $2CH_3$); 1.30 (3H, t, *J* = 7.5, $CH_3$); 2.40 (2H, s, $CH_2$); 2.75 (2H, s, $CH_2$); 2.95 (2H, q, *J* = 7.5, $CH_2$); 7.19 (2H, m, $H_{Ar}$); 7.47 (2H, m, $H_{Ar}$) | 12.86, 21.28, 28.40, 35.76, 37.09, 52.48, 116.30 (d, *J* = 23); 116.40, 125.71 (d, *J* = 9); 134.86, 149.14 (C–N); 155.39 (C=N); 161.89 (d, *J* = 249); 193.06 (C=O) | -113.34 (1F, m) |
| **3c** | 1670, 1520, 1480 | 1.13 (6H, s, $2CH_3$); 2.48 (2H, s, $CH_2$); 2.79 (2H, s, $CH_2$); 7.22 (2H, m, $H_{Ar}$); 7.41 (3H, m, $H_{Ar}$); 7.53 (2H, m, $H_{Ar}$); 8.14 (2H, m, $H_{Ar}$) | 28.24, 35.33, 37.31, 53.14, 115.81, 116.38 (d, *J* = 23); 126.19 (d, *J* = 9); 128.09, 128.85, 129.01, 131.66, 134.71, 150.19 (C–N); 151.68 (C=N); 162.16 (d, *J* = 249); 192.16 (C=O) | -112.60 (1F, m) |
| **3d** | 1680, 1520, 1485 | 1.13 (6H, s, $2CH_3$); 2.48 (2H, s, $CH_2$); 2.77 (2H, s, $CH_2$); 6.54 (1H, m, $H_{furan}$); 7.21 (2H, m, $H_{Ar}$); 7.53 (3H, m, $2H_{Ar}$+ $1H_{furan}$); 7.88 (1H, m, $H_{furan}$) | 28.25, 35.32, 37.07, 52.85, 111.57, 114.00, 114.90, 116.40 (d, *J* = 23); 126.49 (d, *J* = 9); 134.51, 142.45 (C–N); 143.14, 146.55, 149.78 (C=N); 162.32 (d, *J* = 250); 191.61 (C=O) | -112.27 (1F, m) |
| **3e** | 1670, 1525, 1500 | 1.00 (2H, m, $H_{cyclopropane}$); 1.05 (2H, m, $H_{cyclopropane}$); 1.11 (6H, s, $2CH_3$); 2.41 (2H, s, $CH_2$); 2.63 (1H, m, $H_{cyclopropane}$); 2.71 (2H, s, $CH_2$); 7.16 (2H, m, $H_{Ar}$); 7.42 (2H, m, $H_{Ar}$) | 8.32, 9.15, 28.42, 35.63, 37.16, 52.59, 116.28 (d, *J* = 23); 117.01, 125.75 (d, *J* = 9); 134.94, 148.89 (C–N); 155.84 (C=N); 161.93 (d, *J* = 249); 193.29 (C=O) | -113.37 (1F, m) |
| **3f** | 1690, 1545, 1490 | 1.13 (6H, s, $2CH_3$); 2.42 (2H, s, $CH_2$); 2.54 (5H, m, $CH_3$+$CH_2$) | 13.43, 28.27, 35.35, 35.87, 52.39, 113.72 (m); 117.00, 138.02 (dm, *J* = 258); 142.26 (dm, *J* = 259); 143.72 (dm, *J* = 255); 151.73 (C–N); 152.86 (C=N); 192.89 (C=O) | -145.16 (2F, m); -150.77 (1F, t, *J* = 22); -160.17 (2F, m) |
| **3g** | 1690, 1545, 1490 | 1.12 (6H, s, $2CH_3$); 1.30 (3H, t, *J* = 7.5, $CH_3$); 2.42 (2H, s, $CH_2$); 2.53 (2H, s, $CH_2$); 2.96 (2H, q, *J* = 7.5, $CH_2$) | 12.33, 21.36, 28.25, 35.37, 35.78, 52.46, 113.86 (m); 116.36, 138.00 (dm, *J* = 255); 142.21 (dm, *J* = 259); 143.79 (dm, *J* = 256); 152.93 (C–N); 157.07 (C=N); 192.64 (C=O) | -144.98 (2F, m); -150.84 (1F, t, *J* = 22); -160.18 (2F, m) |
| **3h** | 1690, 1540, 1520 | 1.16 (6H, s, $2CH_3$); 2.51 (2H, s, $CH_2$); 2.60 (2H, s, $CH_2$); 7.43 (3H, m, $H_{Ar}$); 8.10 (2H, m, $H_{Ar}$) | 28.12, 35.36, 35.70, 53.20, 113.75 (m); 116.03, 128.19, 128.93, 129.46, 130.96, 138.06 (dm, *J* = 257); 142.52 (dm, *J* = 260); 143.87 (dm, *J* = 256); 153.56 (C–N); 153.79 (C=N); 191.61 (C=O) | -144.77 (2F, m); -150.24 (1F, t, *J* = 22); -159.91 (2F, m) |
| **3i** | 1680, 1540, 1470 | 1.16 (6H, s, $2CH_3$); 2.52 (2H, s, $CH_2$); 2.59 (2H, s, $CH_2$); 6.54 (1H, m, $H_{furan}$); 7.52 (1H, m, $H_{furan}$); 7.91 (1H, m, $H_{furan}$) | 28.12, 35.34, 35.46, 52.83, 111.69, 113.54 (m); 114.89, 115.05, 138.01 (dm, *J* = 255); 142.48 (dm, *J* = 255); 143.59, 143.93 (dm, *J* = 257); 144.14 (C–N); 145.82, 153.41 (C=N); 191.11 (C=O) | -144.50 (2F, m); -149.79 (1F, t, *J* = 22); -159.85 (2F, m) |
| **3j** | 1670, 1530, 1500 | 1.02 (4H, m, $H_{cyclopropane}$); 1.13 (6H, s, $2CH_3$); 2.43 (2H, s, $CH_2$); 2.50 (2H, s, $CH_2$); 2.61 (1H, m, $H_{cyclopropane}$) | 8.29, 9.48, 28.26, 35.37, 35.64, 52.57, 113.85 (m); 117.08, 138.05 (dm, *J* = 253); 142.23 (dm, *J* = 259); 143.79 (dm, *J* = 256); 152.63 (C–N); 157.67 (C=N); 192.84 (C=O) | -145.01 (2F, m); -151.08 (1F, t, *J* = 21); -160.33 (2F, m) |

TABLE 1. (continued)

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| **6a** | 1670, 1575, 1530 | 1.13 (6H, s, $2CH_3$); 2.39 (2H, s, $CH_2$); 2.57 (3H, s, $CH_3$); 2.73 (2H, s, $CH_2$); 7.20 (2H, m, $H_{Ar}$); 7.42 (2H, m, $H_{Ar}$) | 12.07, 28.51, 35.10, 36.93, 53.36, 115.98, 116.28 (d, *J* = 23); 127.13 (d, *J* = 9); 134.61, 141.77 (C–N); 156.14 (C=N); 162.29 (d, *J* = 249); 195.07 (C=O) | -112.45 (1F, m) |
| **6b** | 1680, 1560, 1520 | 1.13 (6H, s, $2CH_3$); 1.18 (3H, t, *J* = 7.5, $CH_3$); 2.40 (2H, s, $CH_2$); 2.72 (2H, s, $CH_2$); 2.92 (2H, q, *J* = 7.5, $CH_2$); 7.19 (2H, m, $H_{Ar}$); 7.41 (2H, m, $H_{Ar}$) | 13.17, 18.97, 28.52, 35.10, 36.96, 53.40, 115.12, 116.32 (d, *J* = 23); 127.59 (d, *J* = 9); 134.78, 147.93 (C–N); 156.28 (C=N); 162.50 (d, *J* = 249); 194.57 (C=O) | -112.07 (1F, m) |
| **6c** | 1680, 1560, 1530 | 1.17 (6H, s, $2CH_3$); 2.43 (2H, s, $CH_2$); 2.83 (2H, s, $CH_2$); 7.00 (2H, m, $H_{Ar}$); 7.21 (2H, m, $H_{Ar}$); 7.35 (5H, m, $H_{Ar}$) | 28.49, 34.90, 37.19, 53.77, 115.78, 115.97 (d, *J* = 23); 127.26 (d, *J* = 9); 128.00, 128.20, 129.51, 130.35, 135.29, 143.36 (C–N); 156.60 (C=N); 161.85 (d, *J* = 249); 193.49 (C=O) | -113.10 (1F, m) |
| **6d** | 1680, 1540, 1475 | 1.16 (6H, s, $2CH_3$); 2.47 (2H, s, $CH_2$); 2.79 (2H, s, $CH_2$); 6.50 (1H, m, $H_{furan}$); 7.11 (2H, m, $H_{Ar}$); 7.28 (1H, m, $H_{furan}$); 7.34 (2H, m, $H_{Ar}$); 7.63 (1H, m, $H_{furan}$) | 28.39, 34.70, 37.09, 53.77, 111.79, 115.74 (d, *J* = 23); 116.22, 127.45 (d, *J* = 9); 136.71, 142.00, 143.74, 145.22 (C–N); 156.66 (C=N); 162.27 (d, *J* = 248); 193.07 (C=O) | -112.78 (1F, m) |
| **6e** | 1685, 1530, 1445 | 0.95 (2H, m, $H_{cyclopropane}$); 1.11 (6H, s, $2CH_3$); 1.19 (2H, m, $H_{cyclopropane}$); 1.85 (1H, m, $H_{cyclopropane}$); 2.37 (2H, s, $CH_2$); 2.71 (2H, s, $CH_2$); 7.19 (2H, m, $H_{Ar}$); 7.52 (2H, m, $H_{Ar}$) | 8.22, 8.29, 28.36, 34.75, 37.18, 53.85, 115.15, 116.08 (d, *J* = 23); 127.71 (d, *J* = 9); 135.36, 147.65 (C–N); 156.46 (C=N); 162.32 (d, *J* = 249); 193.56 (C=O) | -112.44 (1F, m) |
| **6f** | 1690, 1580, 1540 | 1.14 (6H, s, $2CH_3$); 2.42 (2H, s, $CH_2$); 2.48 (3H, s, $CH_3$); 2.75 (2H, s, $CH_2$) | 10.84, 28.45, 35.09, 36.89, 53.30, 113.79 (m); 116.01, 137.97 (dm, *J* = 253); 142.40 (dm, *J* = 259); 143.79 (dm, *J* = 256); 144.96 (C–N); 157.82 (C–N); 194.68 (C=O) | -144.70 (1F, m); -150.37 (1F, t, *J* = 22); -160.24 (2F, m), |
| **6g** | 1680, 1570, 1540 | 1.15 (6H, s, $2CH_3$); 1.15 (3H, t, *J* = 7.5, $CH_3$); 2.42 (2H, s, $CH_2$); 2.75 (2H, s, $CH_2$); 2.81 (2H, q, *J* = 7.5, $CH_2$) | 12.54, 18.91, 28.44, 35.06, 53.35, 113.95 (m); 115.25, 137.90 (dm, *J* = 253); 142.48 (dm, *J* = 259); 144.11 (dm, *J* = 256); 150.77 (C–N); 158.04 (C=N); 194.24 (C=O) | -144.68 (2F, m); -150.02 (1F, t, *J* = 21); -160.20 (2F, m) |
| **6h** | 1690, 1560, 1540 | 1.18 (6H, s, $2CH_3$); 2.47 (2H, s, $CH_2$); 2.84 (2H, s, $CH_2$); 7.38 (5H, m, $H_{Ar}$) | 28.44, 34.90, 37.13, 53.67, 115.00 (m); 115.66, 126.78, 128.50, 129.17, 130.38, 137.68 (dm, *J* = 253); 142.25 (dm, *J* = 259); 143.86 (dm, *J* = 256); 147.29 (C–N); 158.26 (C=N); 193.19 (C=O) | -144.49 (2F, m); -150.56 (1F, t, *J* = 22); -160.55 (2F, m) |
| **6i** | 1690, 1550, 1475 | 1.17 (6H, s, $2CH_3$); 2.51 (2H, s, $CH_2$); 2.80 (2H, s, $CH_2$); 6.55 (1H, m, $H_{furan}$); 7.30 (1H, m, $H_{furan}$); 8.13 (1H, m, $H_{furan}$) | 28.31, 34.54, 37.02, 53.74, 112.34, 114.07, 116.87 (m); 117.55, 136.43, 137.64 (dm, *J* = 257); 142.19, 142.23 (dm, *J* = 258); 144.22 (dm, *J* = 259); 144.50, 145.24 (C–N); 158.24 (C=N); 192.67 (C=O) | -144.50 (2F, m); -149.79 (1F, t, *J* = 22); -159.85 (2F, m) |
| **6j** | 1690, 1545, 1440 | 0.96 (2H, m, $H_{cyclopropane}$); 1.12 (6H, s, $2CH_3$); 1.23 (2H, m, $H_{cyclopropane}$); 1.64 (1H, m, $H_{cyclopropane}$); 2.39 (2H, s, $CH_2$); 2.72 (2H, s, $CH_2$) | 7.34, 28.31, 34.68, 37.14, 53.80, 114.84 (m); 115.07, 137.90 (dm, *J* = 254); 142.32 (dm, *J* = 259); 143.89 (dm, *J* = 256); 150.64 (C–N); 158.20 (C=N); 193.34 (C=O) | -144.32 (2F, m); -150.64 (1F, t, *J* = 21); -160.53 (2F, m) |

salts, and by the second the desired methyl ethers **4a-e** were synthesized in low yield. It turned out that the enol methyl ethers of 2-acylcyclohexane-1,3-diones **4a-e** are unstable compounds and are readily hydrolyzed to the initial triketones in the process of isolation and storage.

It was shown by us that the optimum variant is to carry out the alkylation of 2-acylcyclohexane-1,3-diones **1a-e** with dimethyl sulfate in the presence of calcined potassium carbonate. The enol ethers obtained were used in the reaction without isolation in order to avoid loss due to their instability. Reactions were effected by the interaction of the enol methyl ethers **4a-e** with 4-fluorophenylhydrazine hydrochloride or with pentafluorophenylhydrazine by stirring at room temperature in ethanol for 5 h. As was expected the interaction of ethers **4a-e** with phenylhydrazines proceeded by a vinylogous substitution mechanism with the formation of hydrazones **5a-j**, subsequent intramolcular cyclization of which led to indazolones **6a-j**, regioisomeric with indazolones **3a-j**.

The structures of the synthesized compounds **2f,g**, **3a-j**, and **6a-j** were confirmed by data of elemental analysis, IR, mass, and $^{1}H$, $^{13}C$, and $^{19}F$ NMR spectra (Tables 1, 2). Indazolones **3f,g** and hydrazones **2f,g** are readily distinguished spectrally. In the $^{1}H$ NMR spectra of the latter two additional signals are present for the NH group protons at δ 6.33 and 6.60 (N–H, singlet) and at 14.63 and 14.67 ppm (singlet of N–H protons bonded with a strong intramolcular bond to C=O) respectively. In the IR spectra of hydrazones **2f,g** a low

TABLE 2. Characteristics of the Synthesized Compounds **3a-j**, **6a-j**

| Compound | Empirical formula | Found, % / Calculated, % | | | mp., °C | Mass-spectrum *m/z*, $[M]^+$ | Yield, % |
|---|---|---|---|---|---|---|---|
| | | C | H | N | | | |
| **3a** | $C_{16}H_{17}FN_2O$ | 70.73 / 70.57 | 6.31 / 6.29 | 10.35 / 10.29 | 110-112 | 272 | 85 |
| **3b** | $C_{17}H_{19}FN_2O$ | 71.48 / 71.31 | 6.75 / 6.69 | 9.87 / 9.78 | 108-110 | 286 | 76 |
| **3c** | $C_{21}H_{19}FN_2O$ | 75.25 / 75.43 | 5.68 / 5.73 | 8.31 / 8.38 | 181-184 | 334 | 86 |
| **3d** | $C_{19}H_{17}FN_2O_2$ | 70.23 / 70.36 | 5.19 / 5.28 | 8.51 / 8.64 | 160-163 | 324 | 76 |
| **3e** | $C_{18}H_{19}FN_2O$ | 72.57 / 72.46 | 6.51 / 6.42 | 9.45 / 9.39 | 159-162 | 298 | 87 |
| **3f** | $C_{16}H_{13}F_5N_2O$ | 55.69 / 55.82 | 3.73 / 3.81 | 8.06 / 8.14 | 77-80 | 344 | 85 |
| **3g** | $C_{17}H_{15}F_5N_2O$ | 56.81 / 56.99 | 4.12 / 4.22 | 7.75 / 7.82 | 59-61 | 358 | 83 |
| **3h** | $C_{21}H_{15}F_5N_2O$ | 62.16 / 62.07 | 3.78 / 3.72 | 6.96 / 6.89 | 175-177 | 406 | 80 |
| **3i** | $C_{19}H_{13}F_5N_2O_2$ | 57.43 / 57.58 | 3.26 / 3.31 | 6.98 / 7.07 | 168-171 | 396 | 88 |
| **3j** | $C_{18}H_{15}F_5N_2O$ | 58.54 / 58.38 | 4.01 / 4.08 | 7.49 / 7.56 | 172-175 | 370 | 87 |
| **6a** | $C_{16}H_{17}FN_2O$ | 70.43 / 70.57 | 6.22 / 6.29 | 10.22 / 10.29 | 83-86 | 272 | 68 |
| **6b** | $C_{17}H_{19}FN_2O$ | 71.29 / 71.31 | 6.61 / 6.69 | 9.67 / 9.68 | 91-94 | 286 | 67 |
| **6c** | $C_{21}H_{19}FN_2O$ | 75.21 / 75.43 | 5.65 / 5.73 | 8.28 / 8.38 | 172-175 | 334 | 73 |
| **6d** | $C_{19}H_{17}FN_2O_2$ | 70.47 / 70.36 | 5.35 / 5.28 | 8.71 / 8.64 | 121-124 | 324 | 72 |
| **6e** | $C_{18}H_{19}FN_2O$ | 72.63 / 72.46 | 6.54 / 6.42 | 9.47 / 9.39 | 67-70 | 298 | 69 |
| **6f** | $C_{16}H_{13}F_5N_2O$ | 55.98 / 55.82 | 3.87 / 3.81 | 8.28 / 8.14 | 115-118 | 344 | 70 |
| **6g** | $C_{17}H_{15}F_5N_2O$ | 57.14 / 56.99 | 4.31 / 4.22 | 7.89 / 7.82 | 56-59 | 358 | 71 |
| **6h** | $C_{21}H_{15}F_5N_2O$ | 62.20 / 62.07 | 3.81 / 3.72 | 6.95 / 6.89 | 127-130 | 406 | 75 |
| **6i** | $C_{19}H_{13}F_5N_2O_2$ | 57.41 / 57.58 | 3.20 / 3.31 | 6.96 / 7.07 | 101-104 | 396 | 74 |
| **6j** | $C_{18}H_{15}F_5N_2O$ | 58.25 / 58.38 | 3.95 / 4.08 | 7.47 / 7.56 | 98-101 | 370 | 72 |

intensity absorption band is observed for conjugated carbonyl (1640 and 1660 $cm^{-1}$ respectively), intense absorption bands for the C=C bond (1640 and 1650 $cm^{-1}$ respectively), and for C–N at 1530 $cm^{-1}$ [17]. In the mass spectra of compounds **2f,g** peaks for the molecular ions were absent, but characteristic peaks were present arising from the fission of water (*m/z* 344 $[M-H_2O]^+$ and 358 $[M-H_2O]^+$ for compounds **2f,g** respectively).

The regioisomeric indazolones **3a-j** and **6a-j** differed in their physicochemical properties. The IR spectra of compounds **3a-j** were characterized by the presence of intense absorption bands in the regions 1670-1690 (conjugated carbonyl), 1520-1545 (C=C) and 1480-1500 $cm^{-1}$ (C=N), but in the IR spectra of regioisomers **6a-j** there were intense absorption bands at 1680-1690 (conjugated carbonyl), in the 1545-1590 region (C=C), and in the 1540 $cm^{-1}$ region (C=N). These absorption regions in the IR spectra of compounds **3a-j** and **6a-j** are in good agreement with the data of IR spectra given in the literature for regioisomeric indazolones obtained from 2-acetylcyclohexane-1,3-diones [10-13] and 2-acetylcyclohexane-1,3-dione ether [14]. In the $^{13}C$ NMR spectra of indazolones **3a-j** and **6a-j**, in addition to the carbon signals of methyl, methylene, and methine groups, carbon signals were present in the region δ 191-196 (C=O), and carbon signals of C–N and C=N groups in the region of δ 143-158 ppm. The presence of fluorine is confirmed by the signal of the fluorine atom in the $^{19}F$ NMR spectra at δ from –112 to –113 ppm for compounds **3a-e** and **6a-e** and three signals for fluorine atoms in the regions δ -145, -150, and -160 ppm for compounds **3f-j** and **6f-j.** Peaks were observed for the molcular ions in the mass spectra of all compounds **3a-j** and **6a-j.**

Thanks to the regioselectivity of the reaction of 2-acylcyclohexane-1,3-diones **1a-e** and their enol methyl ethers **4a-e** with phenylhydrazines containing fluorine atoms in various positions of the benzene ring, new regioisomeric fluorine-containing indazolones have been obtained by us in preparative yield.

## EXPERIMENTAL

The $^1H$, $^{13}C$, and $^{19}F$ NMR spectra were recorded on a Bruker AVANCE 500 spectrometer (500, 125, and 470 MHz respectively) in $CDCl_3$, internal standard was TMS (for $^1H$ and $^{13}C$ NMR spectra) and trichlorofluoromethane ($^{19}F$ NMR spectra). The IR spectra were recorded on a UR-20 instrument in KBr disks. The mass spectra (EI, 70 eV) were obtained on a Hewlett-Packard 5890 gas chromatograph with a HP 5972 mass selective detector. Melting points were determined on a Boetius type heating block. A check on the progress of reactions was effected by TLC on Silufol UV-254 plates (ether–hexane, 3:1). The synthesized compounds **2f,g**, **3a-j**, and **6a-j** were isolated by preparative TLC on Fluka $HF_{254}$ silica gel (ether–hexane, 1:1).

**2-Acylcyclohexane-1,3-diones 1a-e** were obtained by O–C isomerization of the appropriate enol acylates of dimedone under the action of acetone cyanohydrin by the method of [18, 19]. The enol acylates of dimedone were obtained by the O-acylation of dimedone with carboxylic acid chlorides by the method of [20] and were used for subsequent O–C isomerization without isolation. Acyldimedones **1a-c** were synthesized in 86, 90, and 84% yield respectively, their constants were identical to those described in [20].

**2-(2-Furoyl)-5,5-dimethylcyclohexane-1,3-dione (1d).** Yield 88%; mp 41-44°C (ether–hexane). IR spectrum, ν, $cm^{-1}$: 1680, 1570, 1470. $^1H$ NMR spectrum, δ, ppm: 1.13 (6H, s, $2CH_3$); 2.44 (2H, s, $CH_2$); 2.61 (2H, s, $CH_2$); 6.57 (1H, m, $H_{furan}$); 7.67 (1H, m, $H_{furan}$); 7.78 (1H, m, $H_{furan}$); 17.42 (1H, br. s, OH). Mass spectrum, *m/z*: 234 $[M]^+$. Found, %: C 66.98; H 6.11. $C_{13}H_{14}O_4$. Calculated, %: C 66.66; H 6.02.

**2-Cyclopropanecarbonyl-5.5-dimethylcyclohexane-1,3-dione (1e).** Yield 95%; mp 57-60°C (ether–hexane). IR spectrum, ν, $cm^{-1}$: 1660, 1550, 1450. $^1H$ NMR spectrum, δ, ppm: 1.09 (6H, s, $2CH_3$); 1.12 (2H, m, $CH_{2cyclopropane}$); 1.30 (2H, m, $CH_{2cyclopropane}$); 2.40 (2H, s, $CH_2$); 2.53 (2H, s, $CH_2$); 3.59 (1H, m, $H_{cyclopropane}$); 18.51 (1H, br. s, OH). Mass spectrum, *m/z*: 208 $[M]^+$. Found, %: C 69.11; H 7.67. $C_{12}H_{16}O_3$. Calculated, %: C 69.21; H 7.74.

**1-(4-Fluorophenyl)-3,6,6-trimethyl-6,7-dihydro-1H-indazol-4(5H)-one (3a), 3-Ethyl-1-(4-fluorophenyl)-6,6-dimethyl-6,7-dihydro-1H-indazol-4(5H)-one (3b), 1-(4-Fluorophenyl)-6,6-dimethyl-3-phenyl-**

**6,7-dihydro-1H-indazol-4(5H)-one (3c), 1-(4-Fluorophenyl)-3-(2-furyl)-6,6-dimethyl-6,7-dihydro-1H-indazol-4(5H)-one (3d), and 3-Cyclopropyl-1-(4-fluorophenyl)-6,6-dimethyl-6,7-dihydro-1H-indazol-4(5H)one (3e)** (Table 1). 4-Fluorophenylhydrazine hydrochloride (1.1 mmol) and sodium hydroxide (1.1 mmol) were added with stirring to a solution of the appropriate triketone **1a-e** (1 mmol) in ethanol (5 ml). The reaction mixture was stirred for 8 h at room temperature. After removing the solvent on the rotary evaporator the residue was dissolved in chloroform (50 ml). The solution was washed with dilute HCl (3×15 ml), with water (2×15 ml), and dried over anhydrous magnesium sulfate. After removing the chloroform on the rotary evaporator the product was isolated by preparative TLC as orange-red crystals.

**3,6, 6-Trimethyl-1-pentafluorophenyl-6,7-dihydro-1H-indazol-4(5H)-one (3f), 3-Ethyl-6,6-dimethyl-1-pentafluorophenyl-6,7-dihydro-1H-indazol-4(5H)-one (3g), 6,6-Dimethyl-1-pentafluorophenyl-3-phenyl-6,7-dihydro-1H-indazol-4(5H)-one (3h), 3-(2-Furyl)-6,6-dimethyl-1-pentafluorophenyl-6,7-dihydro-1H-indazol-4(5H)-one (3i), and 3-Cyclopropyl-6,6-dimethyl-1-pentafluorophenyl-6,7-dihydro-1H-indazol-4(5H)-one (3j).** A solution of the appropriate triketone **1a-e** (1 mmol) and pentafluorophenylhydrazine (1.1 mmol) in ethanol (5 ml) was stirred for 8 h at room temperature. The solvent was removed on the rotary evaporator and the residue dissolved in chloroform (50 ml). The solution was washed with dilute HCl (3×15 ml), with water (2×15 ml), and dried over anhydrous magnesium sulfate. After removing the chloroform on the rotary evaporator the product was isolated by preparative TLC. In the case of compounds **1c-e** only indazolones **3g-j** were isolated, but in the case of compound **1a** hydrazone **2f** (79%) and indazolone **3f** (21%), and in the case of compound **1b** hydrazone **2g** (61%) and indazolone **3g** (39%) were obtained. The interaction of triketones **1a,b** with pentafluorophenylhydrazine on boiling for 20 h gave the desired indazolones **3f,g** as the sole products. Compounds **3a-j** were isolated as orange-red crystals.

**5,5-Dimethyl-2-[1-(2-pentafluorophenylhydrazono)ethyl]cyclohexane-1,3-dione (2f).** Bright-yellow crystals, yield 79%; mp 136-139°C. IR spectrum, ν, $cm^{-1}$: 1640, 1590, 1530. $^1$H NMR spectrum, δ, ppm: 1.05 (6H, s, $2CH_3$); 2.38 (2H, s, $CH_2$); 2.42 (2H, s, $CH_2$); 2.76 (3H, s, $CH_3$); 6.33 (1H, br. s, NH); 14.63 (1H, br. s, NH). $^{13}$C NMR spectrum, δ, ppm (*J*, Hz): 16.41, 28.21, 30.37, 50.71, 53.28, 107.68, 120.71 (m); 137.28 (dm, *J* = 250); 138.24 (dm, *J* = 250); 139.36 (dm, *J* = 246); 172.84 (C=N); 196.48 (C=O); 196.80 (C=O). $^{19}$F NMR spectrum, δ, ppm (*J*, Hz): -156.04 (2F, m); -162.03 (2F, m); -162.85 (1F, t, *J* = 22). Mass spectrum, *m/z*: 344 $[M-H_2O]^+$. Found, %: C 53.16; H 4.23; N 7.85. $C_{16}H_{15}F_5N_2O_2$. Calculated, %: C 53.04; H 4.17; N 7.73.

**5,5-Dimethyl-2-[1-(2-pentafluorophenylhydrazono)propyl]cyclohexane-1,3-dione (2g).** Bright-yellow crystals, yield 61%; mp 147-149°C. IR spectrum, ν, $cm^{-1}$: 1660, 1580, 1530. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.05 (6H, s, $2CH_3$); 1.24 (3H, t, *J* = 7.4, $CH_3$); 2.40 (4H, s, $CH_2$); 3.30 (2H, q, *J* = 7.4, $CH_2$); 6.60 (1H, br. s, NH); 14.67 (1H, br. s, NH). $^{13}$C NMR spectrum, δ, ppm (*J*, Hz): 11.91, 21.95, 28.18, 30.27, 51.19, 53.46, 106.65, 120.84 (m); 137.20 (dm, *J* = 251); 138.23 (dm, *J* = 251); 139.36 (dm, *J* = 247); 177.94 (C=N); 196.37 (C=O); 197.78 (C=O). $^{19}$F NMR spectrum, δ, ppm (*J*, Hz): -155.93 (2F, m); -162.10 (2F, m); -163.06 (1F, t, *J* = 22). Mass spectrum, *m/z*: 358 $[M-H_2O]^+$. Found, %: C 54.38; H 4.60; N 7.51. $C_{17}H_{17}F_5N_2O_2$. Calculated, %: C 54.26; H 4.55; N 7.44.

**2-(4-Fluorophenyl)-3,6,6-trimethyl-6,7-dihydro-2H-indazol-4(5H)-one (6a), 3-Ethyl-2-(4-fluorophenyl)-6,6-dimethyl-6,7-dihydro-2H-indazol-4(5H)-one (6b), 2-(4-Fluorophenyl)-6,6-dimethyl-3-phenyl-6,7-dihydro-2H-indazol-4(5H)-one (6c), 2-(4-Fluorophenyl)-3-(2-furyl)-6,6-dimethyl-6,7-dihydro-2H-indazol-4(5H)-one (6d), 3-Cyclopropyl-2-(4-fluorophenyl)-6,6-dimethyl-6,7-dihydro-2H-indazol-4(5H)-one (6e), 3,6,6-Trimethyl-2-pentafluorophenyl-6,7-dihydro-2H-indazol-4(5H)-one (6f), 3-Ethyl-6,6-dimethyl-2-pentafluorophenyl-6,7-dihydro-2H-indazol-4(5H)-one (6g), 6,6-Dimethyl-2-pentafluoro-phenyl-3-phenyl-6,7-dihydro-2H-indazol-4(5H)-one (6h), 3-(2-Furyl)-6,6-dimethyl-2-pentafluorophenyl-6,7-dihydro-2H-indazol-4(5H)-one (6i), and 3-Cyclopropyl-6,6-dimethyl-2-pentafluorophenyl-6,7-dihydro-2H-indazol-4(5H)-one (6j).** Calcined $K_2CO_3$ (6 mmol) and dimethyl sulfate (1 mmol) were added to a solution of the appropriate triketone (**1a-e**) (1 mmol) in absolute toluene (20 ml). The reaction mixture was

boiled for 10 h, the solid was filtered off, and washed with toluene. After removing the toluene on the rotary evaporator the residue was dissolved in ethanol (5 ml), and 4-fluorophenylhydrazine hydrochloride (1 mmol) and sodium hydroxide (1 mmol) were added to the solution. The reaction mixture was stirred for 5 h at room temperature. After removing the ethanol on the rotary evaporator, the residue was dissolved in chloroform (50 ml), the solution was washed with dilute HCl (3×15 ml), with water (2×15 ml), and dried over anhydrous magnesium sulfate. After removing the chloroform on the rotary evaporator indazolones **6a-e** were isolated by preparative TLC. To obtain indazolones **6f-j** pentafluorophenylhydrazine (1mmol) was used in place of 4-fluorophenylhydrazine (1 mmol) and sodium hydroxide (1 mmol). Compounds **6a-j** were isolated as orange-red crystals.

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