ISSN 1070-3632, Russian Journal of General Chemistry, 2020, Vol. 90, No. 2, pp. 187–195. © Pleiades Publishing, Ltd., 2020.
Russian Text © The Author(s), 2020, published in Zhurnal Obshchei Khimii, 2020, Vol. 90, No. 2, pp. 199–209.

Completely Regioselective *N*-Tosylation of 5-Acetyl-4-aryl-6-hydroxy-3,6-dimethyl-4,5,6,7-tetrahydroindazoles

A. I. Ismiyev[a], V. V. Dotsenko[b,c,*], A. V. Bespalov[b], E. E. Netreba[d], and A. M. Maharramov[a]

[a] *Baku State University, Baku, 1148 Azerbaijan*
[b] *Kuban State University, Krasnodar, 350040 Russia*
[c] *North Caucasus Federal University, Stavropol, 355009 Russia*
[d] *Taurida Academy, Vernadsky Crimean Federal University, Simferopol, 295007 Russia*
**e-mail: victor_dotsenko_@mail.ru*

Received July 25, 2019; revised July 25, 2019; accepted August 6, 2019

Abstract—The reaction of 5-acetyl-4-aryl-6-hydroxy-3,6-dimethyl-4,5,6,7-tetrahydroindazoles *p*-toluenesulfonyl chloride in boiling acetone in the presence of triethylamine was found to occur in a completely regioselective with the exclusive formation of 5-acetyl-4-aryl-6-hydroxy-3,6-dimethyl-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydroindazoles. The experimental results were confirmed by quantum chemical calculations. In silico biological activity evaluation of the synthesized compounds was performed.

Keywords: cyclic β-hydroxy ketones, indazoles, completely regioselective tosylation, quantum chemical calculations

DOI: 10.1134/S1070363220020048

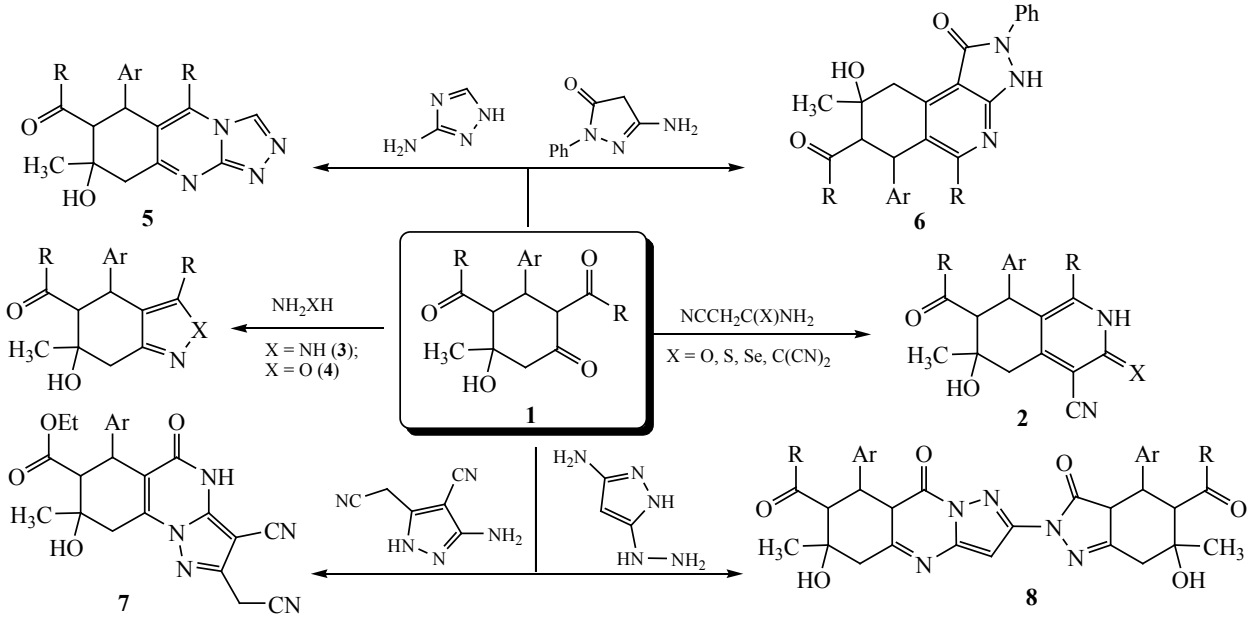
2,4-Diacyl(dialkoxycarbonyl)-3-R-5-hydroxy-5-methylcyclohexanones **1** (also referred to as cyclic β-hydroxy ketones of β-cycloketols) are promising building blocks for fine organic synthesis [1, 2]. Compounds **1** readily undergo heterocyclizations with various 1,2- and 1,3-binucleophiles to produce isoquinolines **2** [3–7], indazoles **3** [1, 8–12], 2,1-benzoxazoles **4** [1, 9–11], [1,2,4]triazolo[3,4-*b*]quinazolines **5** [13], pyrazolo[3,4-*c*]isoquinolines **6** [14], 4,5,6,7,8,9-hexahydropyrazolo[1,5-*a*]quinazolines **7** [15], and 6,7,8,8a-tetrahydropyrazolo[5,1-*b*]quinazolin-9(5*H*)-one derivatives **8** [16] (Scheme 1). Among the heterocyclic systems presented in Scheme 1, we focused on indazole derivatives **3**. The synthesis of compounds like **3** was described for the first time in the early 20th century [1, 17, 18]. Since that time, numerous data have been accumulated on the synthesis of analogous indazoles from various β-cycloketols and substituted hydrazines [8–12, 19–22]; however, their transformations and functionalizations have been explored to a much lesser extent. It should also be noted that indazole fragment is the key structural unit of many therapeutically important compounds (for reviews, see [23–26]).

In continuation of our studies in the field of β-cycloketols and their analogs [15, 27–30], we turned our attention to the regioselectivity of tosylation of indazoles **3**. A priori, the tosylation of **3** could give rise to N^1-, N^2-, and/or 6-O-tosyl derivatives (Scheme 2). Regioisomeric N^1- and N^2-substituted products could be formed assuming the possibility of prototropic tautomerism of **3**.

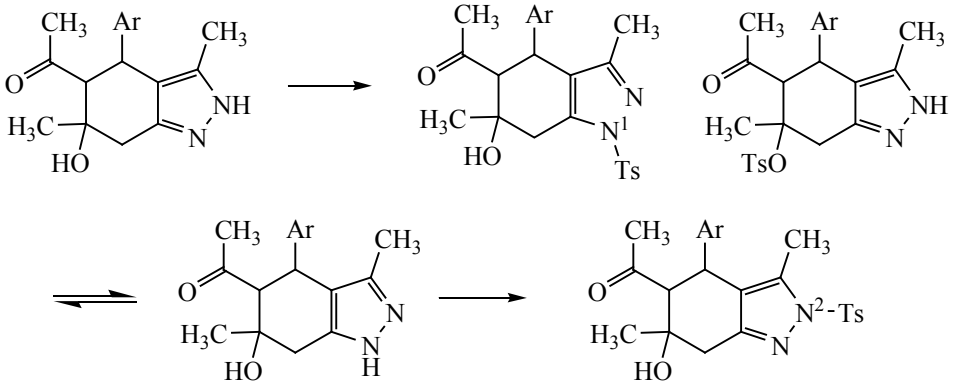
In fact, indazoles **3a**–**3e** reacted with tosyl chloride in anhydrous acetone in the presence of triethylamine as a base to afford exclusively N^1-tosyl derivatives **4a**–**4e** (Scheme 3). No O-tosylation products were detected; presumably, this reaction path is unfavorable for steric reasons. The structure of **4a**–**4e** was confirmed by NMR spectra and X-ray analysis of **4a**. It should be noted that both initial hydroxy ketone **1** [1] and its hydrazination products exist as mixtures of diastereoisomers with preferential *syn* orientation of the HO and $CH_3C(O)$ groups. According to the X-ray diffraction data, indazole **3a** [31] and its hydrochloride [32] are racemates that crystallize in centrosymmetric space groups; at least two stereochemical configurations, (4*S*,5*R*,6*S*) or (4*R*,6*R*) were reported for these compounds. The presence of diastereoisomers of **4** is responsible for doubling of some signals in their NMR spectra.

Figure 1 shows the structure of molecule **4a** determined by X-ray analysis. It was identified as 1-[6-hy-

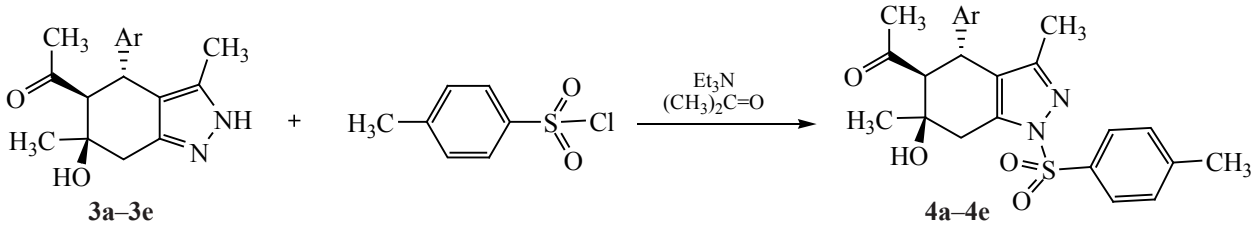
Scheme 1.



Scheme 2.



Scheme 3.



Ar = Ph (**a**), 4-$CH_3C_6H_4$ (**b**), 4-$CH_3OC_6H_4$ (**c**), 2-furyl (**d**), 4-ClC_6H_4 (**e**).

droxy-3,6-dimethyl-1-(4-methylbenzenesulfonyl)-4-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-5-yl]ethanone. The principal crystallographic data are given in Table 1, and Table 2 contains the bond lengths and bond angles in molecule **4a**. The cyclohexene ring has a half-*chair* conformation with the C^5 and C^4 atoms significantly deviating from the $C^6C^7C^2$ plane [by 0.521(5) and 0.270(5) Å, respectively] and the C^3 atom lying almost in that plane (the deviation of C^3 from the $C^6C^7C^2$ plane does not exceed 0.1 Å). The bond angles in the cyclohexene ring are

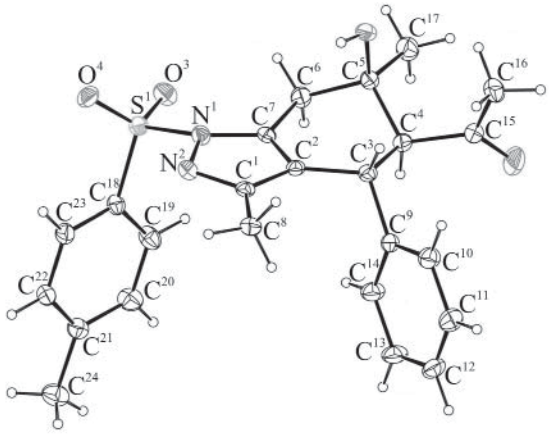


Fig. 1. Structure of the molecule of 1-[6-hydroxy-3,6-dimethyl-1-(4-methylbenzenesulfonyl)-4-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-5-yl]ethanone (**4a**) in crystal according to the X-ray diffraction data.

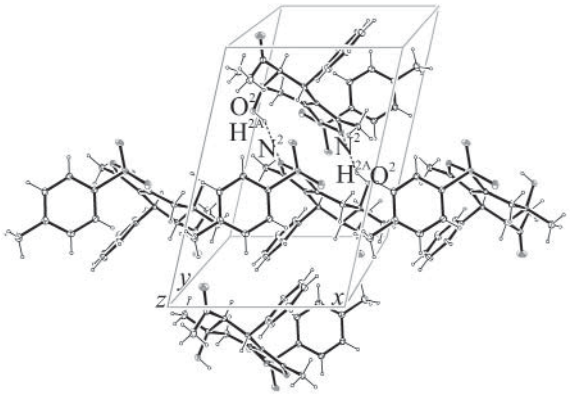


Fig. 2. A fragment of crystal packing of compound **4a**.

as follows: $C^2C^7C^6$ 125.0(3), $C^7C^6C^5$ 109.5(3), $C^6C^5C^4$ 108.6(3), $C^5C^4C^3$ 113.2(3), $C^4C^3C^2$ 110.3(3), $C^3C^2C^7$ 123.7(3)°. Due to the presence of different substituents, the cyclohexene ring is characterized by the following torsion angles: $C^7C^6C^5C^4$ 51.0(4), $C^6C^5C^4C^3$ –63.0(4), $C^5C^4C^3C^2$ 38.7(4), $C^4C^3C^2C^7$ –6.0(5), $C^3C^2C^7C^6$ –2.7(6), $C^2C^7C^6C^5$ –21.0(5)°. The substituents on C^3, C^4, and C^5 occupy equatorial positions but are oriented oppositely with respect to each other. The hydroxy group on C^5 is axial. Similar orientations of substituents were reported previously [33, 34]. The pyrazole ring in molecule **4a** is virtually planar, and deviations of atoms from the $C^7N^1C^1N^2C^2$ plane ar within 0.001–0.011 Å. The bond lengths and bond angles in the pyrazole ring conform to the corresponding reference values: N^2–C^1 1.321(4), C^1–C^2 1.424(4), C^2–C^7 1.364(4), C^7–N^1 1.388(4), N^1–N^2

Table 1. Some crystallographic parameters for compound **4a**

Parameter	Value	Parameter	Value
Formula	$C_{24}H_{26}N_2O_4S$	μ, mm^{-1}	0.179
Molecular weight	438.53	*F*(000)	464
Crystal system	Triclinic	Crystal dimensions, mm	0.37×0.30×0.20
Space group	$P1^-$	θ, deg	1.70–24.71
a, Å	8.4141(6)	Reflection indices	$-9 \le h \le 9$
b, Å	11.2364(8)		$-13 \le k \le 13$
s, Å	12.6166(9)		$-14 \le l \le 14$
α, deg	75.032(2)	Total/independent reflection number	11826/3761 (R_{int} = 0.0626)
β, deg	77.310(2)	Number of reflections with $I > 2\sigma(I)$	2599
γ, deg	77.678(2)	Number of variables	284
V, Å^3	1108.56(14)	*R* [reflections with $I > 2\sigma(I)$]	R_1 = 0.0642, wR_2 = 0.1451
Z	2	*R* (all independent reflections)	R_1 = 0.1007, wR_2 = 0.1639
d_{calc}, g/cm^3	1.314	Goodness of fit (F^2)	0.999
		$\Delta\rho_{max}/\Delta\rho_{min}$, *e*/Å^3	0.261/–0.276

Table 2. Some bond angles and bond lengths in molecule **4a**

Angle	ω, deg	Angle	ω, deg	Bond	*d*, Å
$O^4S^1O^3$	120.71(17)	$N^2C^1C^2$	111.3(3)	$S^1–O^4$	1.421(3)
$O^4S^1N^1$	106.77(15)	$N^2C^1C^8$	120.4(3)	$S^1–O^3$	1.421(3)
$O^3S^1N^1$	104.52(15)	$C^{23}C^{18}S^1$	119.8(3)	$S^1–N^1$	1.680(3)
$O^4S^1C^{18}$	108.82(17)	$C^{19}C^{18}S^1$	119.4(3)	$S^1–C^{18}$	1.745(4)
$O^3S^1C^{18}$	110.38(16)	$O^2C^5C^{17}$	105.5(3)	$O^1–C^{15}$	1.200(4)
$N^1S^1C^{18}$	104.26(15)	$O^2C^5C^6$	110.4(3)	$N^1–N^2$	1.386(4)
$N^2N^1C^7$	111.2(3)	$O^2C^5C^4$	111.3(3)	$N^1–C^7$	1.388(4)
$N^2N^1S^1$	115.6(2)	$C^2C^7N^1$	106.1(3)	$N^2–C^1$	1.321(4)
$C^7N^1S^1$	128.7(2)	$N^1C^7C^6$	128.2(3)		
$C^1N^2N^1$	105.1(3)				

Table 3. Hydrogen bonds in the crystal structure of compound **4a**

D–H···A	Symmetry operation	*d*(H···A), Å	*d*(D–H), Å	*d*(D···A), Å	ω(D–H···A)
$O_2–H^{2A}\cdots N^2$	$1 – x, 1 – y, 1 – z$	2.26(5)	0.78(5)	2.959(3)	151.0(4)

Table 4. Calculated [B3LYP/6-31G(*d*,*p*)] partial negative charges on the nitrogen atoms in molecule **3a**

Atom	Mulliken charge	Electrostatic charge
N^8	–0.387	–0.060
N^9	–0.429	–0.626

1.386(4) Å; 111.3(3)–105.1(3)° [35]. The tosyl substituent on N^1 is axial, and the methyl group on C^1 is equatorial; the S^1 atom of the tosyl group deviates from the pyrazole ring plane by 0.502(5) Å upward, whereas deviation of the methyl carbon atom (C^8) from that plane is insignificant [0.043(5) Å]. Molecules **4a** in crystal are linked through intermolecular hydrogen bonds (Table 3, Fig. 2) to form dimers with a graph set descriptor of R_2^2(**8**) [36].

In order to rationalize the observed regioselectivity of the tosylation of indazoles **3**, we performed a theoretical study of their reactivity and relative thermodynamic stability of possible products. The calculations were carried out in the framework of density functional theory (DFT) using a widely known B3LYP hybrid functional [37, 38] and split-valence 6-31G(*d*,*p*) basis set implemented in GAMESS (US) software package. The optimized structures were visualized by ChemCraft. The ground-state energies were calculated after preliminary search for most stable conformations, followed by geometry optimization. Non-specific solvation was taken into account according to the CPCM model with acetone as solvent [39].

The completely regioselective tosylation of **3a** at the N^1 atom (Figs. 3, 4) is primarily determined by the kinetic factor, i.e., by a significant difference in the partial negative charges on the N^1 and N^2 atoms (Table 4). This difference arises from the involvement of the N^2 lone electron pair (LEP) in the pyrazole aromatic system; in contrast, the LEP on N^1 appears in the pyrazole ring plane and is not involved in conjugation. Presumably, the thermodynamic factor is not crucial here, since the energy difference between the isomeric N^1- and N^2-substituted compounds is as small as 4.8 kJ/mol. Conformational analysis of product **3a** revealed two most stable conformers **3a-1** and **3a-2** (Fig. 4) with an energy difference of 0.06 kJ/mol in favor of the former, where the benzene rings are located at the same side of the tetrahydroindazole plane.

Compounds **4a**–**4e** were analyzed in silico to predict their drug-likeness, ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) parameters, biological activity, and possible targets with the aid OSIRIS Property Explorer [40], SwissADME [41], SwissTargetPrediction [42], Molinspiration Property Calculation Service [43],

and AntiBac-Pred services [44]. OSIRIS Property Explorer was used to evaluate *c*Log *P* (lipophilicity), log *S* (solubility), TPSA (Topological Polar Surface Area), risks of side effects (such as mutagenic, oncogenic, and reproductive), drug-likeness, and drug score [40]. The structures were analyzed for the conformity to "Lipinski's rule of five" (*c*Log $P \le 5.0$, MW ≤ 500, TPSA ≤ 140, number of H-bond acceptors ≤ 10, number of H-bond donors ≤ 5) [45–47]. The results are presented in Table 5.

It is seen that the *c*Log*P* values of **4a**–**4e** do not exceed 2.9, which suggests a good absorption and acceptable lipophilicity [45–47]. All compounds (except for **4b** and **4e**) are characterized by an acceptable solubility (log *S*). The molecular weights of **4a**–**4e** do not exceed 500, which meets Lipinski's rule of five. On the other hand, compound **4e** was the only one that showed a positive drug-likeness value. All compounds **4a**–**4e** exhibited a moderately high drug score (~0.3). Possible toxicological risks for the reproductive systems were predicted for all these compounds. Molinspiration Property Calculation Service predicted kinase inhibitory activity of **4a**–**4e** as the most probable biological activity (Molinspiration bioactivity score –0.42 to –0.26).

The AntiBac-Pred computations suggest probable resistance of *Staphylococcus simulans* and *Mycobacterium ulcerans* toward the examined compounds [the confidence parameters (*C*) calculated as the difference between probable activity (P_A) and probable inactivity (P_I) range from 0.28 to 0.42 and from 0.18 to 0.36, respectively]. Antibacterial activities against *Staphylococcus lugdunensis* (*C* =

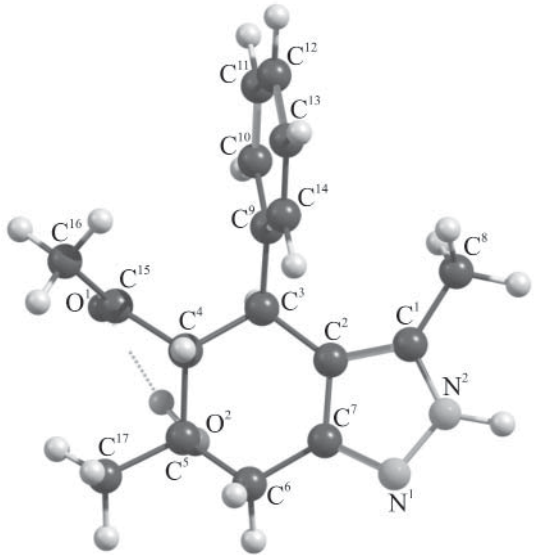
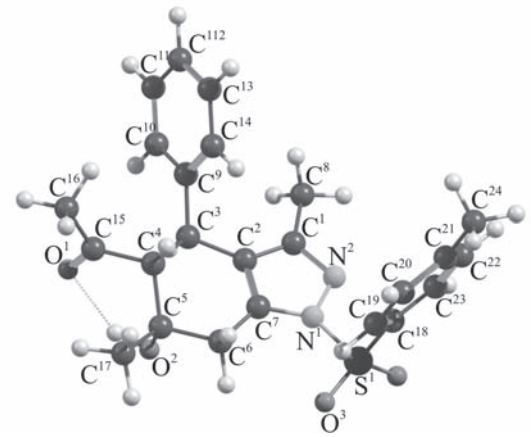


Fig. 3. Optimized structure of 1-[6-hydroxy-3,6-dimethyl-4-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-5-yl]ethanone (**3a**).

(a)



(b)

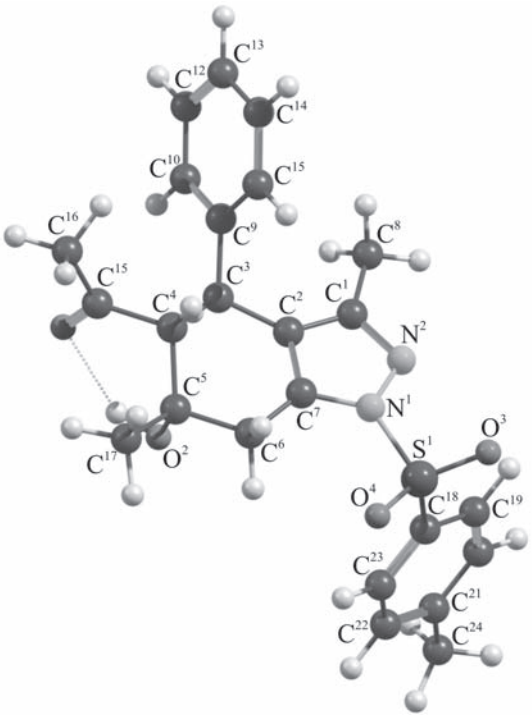


Fig. 4. Most stable conformers of compound **4a** with (a) *syn* and (b) *anti* orientation of the benzene rings.

Table 5. Toxicity risks and physicochemical characteristics of compounds **4a**–**4e** predicted by OSIRIS Property Explorer

Comp. no.	Risk[a]				Physicochemical characteristics					
	mutagenicity	oncogenicity	irritant	reproductive effects	*c*Log*P*	log*S*	MW	TPSA	drug-likeness	drug score
4a	–	–	–	+	2.27	–4.01	438	97.64	–0.14	0.31
4b	–	–	–	+	2.62	–4.36	452	97.64	–0.39	0.27
4c	–	–	–	+	2.20	–4.02	468	106.8	–0.19	0.29
4d	–	–	–	+	1.46	–3.69	428	110.7	–0.53	0.31
4e	–	–	–	+	2.88	–4.74	472	97.64	0.67	0.29

[a] "–" stands for predicted absence of toxicity, and "+" stands for possible toxicity risk.

Table 6. ADMET parameters and biological activity of compounds **4a**–**4e** predicted by SwissADME and SwissTargetPrediction

Comp. no.	Hastrointestinal absorption	BBB permeability	Cytochrome P450 inhibition[a]					Possible targets	Bioavailability index
			CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4		
4a	High	No	–	+	–	–	+	A GPCR[b]	0.55
4b	High	No	–	+	–	–	+	A GPCR[b]	0.55
4c	High	No	–	+	–	–	+	Enzymes	0.55
4d	High	No	–	+	–	–	+	–	0.55
4e	High	No	–	+	+	–	+	Enzymes A GPCR[b]	0.55

[a] "+" and "–" stand for the presence or absence of effect, respectively.
[b] A GPCR denotes class A G-protein-conjugated receptors.

0.24–0.33) and *Staphylococcus sciuri* (*C* = 0.29–0.32 for **4a**–**4c**) were predicted.

According to the SwissADME prediction, all compounds **4a**–**4e** are characterized by high gastrointestinal absorption and the lack of BBB (blood–brain barrier) permeability, as well as by possible inhibitory activity against proteins of the cytochrome P450 family (CYP) (Table 6). As the SwissTargetPrediction data showed, the most probable targets of all compounds (except for **4d** for which no appropriate targets were found) are a number of enzymes and class A G-protein-conjugated receptors. The bioavailability index for all compounds is equal to 0.55, in keeping with Lipinski's rule of five [48].

In summary, the tosylation of indazoles obtained from cyclic β-hydroxy ketones and hydrazine gives the corresponding *N*[1]-tosyl derivatives with complete regioselectivity. Theoretical study of the reactivity of the initial indazoles and thermodynamic stability of the tosylation products confirmed the predominant reaction direction and revealed the determining effect of the kinetic factor. In silico evaluation of biological activity of the synthesized *N*-tosylindazoles showed that these compounds meet the bioavailability criterion and are promising candidates for further in vitro and in vvo screening.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer (300 and 75 MHz, respectively) in $CDCl_3$ or DMSO-d_6 using the residual proton and carbon signals of the solvent as reference. The IR spectra were measured in KBr on a Varian 3600 FT-IR Excalibur Series spectrometer. The elemental analyses were obtained using a Carlo Erba 1106 CHN analyzer. The melting points were measured on a Koefler hot stage and are uncorrected. The purity of the isolated compounds was checked by TLC on Silufol UV-254 plates using acetone–hexane (1 : 1) as eluent; spots were visualized by treatment with iodine vapor or under UV light.

1-[4-Aryl-6-hydroxy-3,6-dimethyl-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-indazol-5-yl)-ethanones 4a–4e (*general procedure*). A mixture of tetrahydroindazole **3a**–**3e** (50 mmol), 9.53 g (50 mmol) of *p*-toluenesulfonyl chloride, and 10 mL of triethylamine in 300 mL of anhydrous acetone was refluxed for 6–8 h (TLC). The mixture was cooled and diluted with 300 mL of cold distilled water, the resulting suspension was kept for 24 h, and the precipitate was filtered off and recrystal-

lized from ethanol. Compounds **4a**–**4e** were isolated as white finely crystalline powders.

1-[6-Hydroxy-3,6-dimethyl-1-(4-methylbenzenesulfonyl)-4-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-5-yl]ethanone (4a). Yield 65%, mp 178°C, stereoisomer ratio ~3 : 1. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: major stereoisomer: 1.39 s (3H, CH_3), 1.50 s (3H, CH_3), 1.68 s (3H, CH_3), 2.41 s (3H, CH_3), 2.91–3.05 m (2H, 5-H, 7-H, overlapped), 3.29 d (1H, 7-H, ^2J = 17.9 Hz), 3.70 br.s (1H, OH), 4.02 d (1H, 4-H, ^3J = 10.6 Hz), 7.07 d (2H, H_{arom}, ^3J = 7.7 Hz), 7.28–7.33 m (5H, H_{arom}), 7.86 d (2H, $MeC_6\mathbf{H}_4$, ^3J = 8.1 Hz); minor stereoisomer: 1.32 s (3H, CH_3), 1.66 s (3H, CH_3), 2.71 d (1H, 7-H, ^2J = 16.7 Hz), 3.55 br.s (1H, OH), 4.09 d (1H, 4-H, ^3J = 11.5 Hz), 7.80 d (2H, $MeC_6\mathbf{H}_4$, ^3J = 8.3 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: major stereoisomer: 13.3, 21.6, 28.3, 34.7, 37.4, 41.7, 62.7, 71.2, 119.4, 127.5, 128.0, 129.1, 129.9, 135.0, 140.1, 140.8, 145.2, 152.4, 162.2, 216.3; minor stereoisomer, 11.9, 28.2, 37.0, 41.6, 63.1, 71.3, 118.9, 127.4, 129.8, 139.7, 140.9, 145.6, 152.6, 162.1, 216.2. Found, %: C 65.70; H 6.06; N 6.37. $C_{24}H_{26}N_2O_4S$. Calculated, %: C 65.73; H 5.98; N 6.39.

1-[6-Hydroxy-3,6-dimethyl-1-(4-methylbenzenesulfonyl)-4-(4-methylphenyl)-4,5,6,7-tetrahydro-1*H*-indazol-5-yl]ethanone (4b). Yield 62%, mp 173°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.28 s (3H, CH_3), 1.34 s (3H, CH_3), 2.02 s (3H, CH_3), 2.22 s (3H, CH_3), 2.37 s (3H, CH_3), 2.81 d (1H, 5-H, ^3J = 10.7 Hz), 3.15 br.s (2H, 7-H), 4.17 d (1H, 4-H, ^3J = 10.7 Hz), 4.94 br.s (1H, OH), 6.99 d (2H, 4-$C_6\mathbf{H}_4$, ^3J = 7.5 Hz), 7.05 d (2H, 4-$C_6\mathbf{H}_4$, ^3J = 7.5 Hz), 7.42 d (2H, *m*-H, Ts, ^3J = 7.8 Hz), 7.79 d (2H, *o*-H, Ts, ^3J = 7.8 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 12.9, 20.6, 21.1, 28.0, 30.7, 38.7, 38.9, 65.0, 69.4, 120.7, 127.3, 128.4, 129.2, 130.2, 134.6, 136.0, 137.9, 141.7, 145.4, 152.3, 210.1. Found, %: C 66.34; H 6.36; N 6.15. $C_{25}H_{28}N_2O_4S$. Calculated, %: C 66.35; H 6.24; N 6.19.

1-[6-Hydroxy-3,6-dimethyl-4-(4-methoxyphenyl)-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-indazol-5-yl]ethanone (4c). Yield 59%, mp 184°C, stereoisomer ratio ~4 : 1. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: major stereoisomer: 1.37 s (3H, CH_3), 1.52 s (3H, CH_3), 1.71 s (3H, CH_3), 2.40 s (3H, CH_3), 2.89–3.02 m (2H, 5-H, 7-H, overlapped), 3.26 d (1H, 7-H, ^2J = 18.1 Hz), 3.69 br.s (1H, OH), 3.78 s (3H, OCH_3), 3.98 d (1H, 4-H, ^3J = 10.7 Hz), 6.82 d (2H, *m*-H, 4-$MeOC_6H_4$, ^3J = 8.3 Hz), 6.99 d (2H, *o*-H, 4-$MeOC_6H_4$, ^3J = 8.3 Hz), 7.31 d (2H, *m*-H, Ts, ^3J = 8.0 Hz), 7.85 d (2H, *o*-H, Ts, ^3J = 8.0 Hz); minor stereoisomer, 1.31 s (3H, CH_3), 1.69 s (3H, CH_3), 1.86 s (3H, CH_3), 2.68 d (1H, 7-H, ^2J = 16.2 Hz), 3.54 br.s (1H, OH), 4.04 d (1H, 4-H, ^3J = 11.1 Hz), 7.79 d (2H, *o*-H, Ts, ^3J = 8.7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: major stereoisomer: 13.4, 21.6, 28.3, 34.7, 37.4, 40.9, 55.1, 62.7, 71.2, 114.4, 119.7, 127.5, 129.9, 131.9, 135.0, 140.6, 145.2, 152.5, 158.8, 162.2, 216.5; minor stereoisomer: 11.8, 21.6, 28.4, 37.0, 40.7, 63.2, 71.2, 114.3, 119.1, 127.6, 129.0, 129.8, 132.6, 139.7, 142.3, 152.0, 158.6, 162.3, 216.4. Found, %: C 64.04; H 6.06; N 6.00. $C_{25}H_{28}N_2O_5S$. Calculated, %: C 64.08; H 6.02; N 5.98.

1-[4-(Furan-2-yl)-6-hydroxy-3,6-dimethyl-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-indazol-5-yl]ethanone (4d). Yield 57%, mp 136°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.39 s (3H, CH_3), 1.66 s (3H, CH_3), 1.86 s (3H, CH_3), 2.40 s (3H, CH_3), 2.97 d (1H, 7-H, ^2J = 17.9 Hz), 3.16–3.28 m (2H, 5-H, 7-H), 3.64 br.s (1H, OH), 4.20 d (1H, 4-H, ^3J = 10.7 Hz), 6.15–6.16 m (1H, 3-H, Fu), 6.31–6.32 m (1H, 4-H, Fu), 7.31 d (2H, *m*-H, Ts, ^3J = 7.9 Hz), 7.36–7.37 m (1H, 5-H, Fu), 7.85 d (2H, *o*-H, Ts, ^3J = 7.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.3, 21.6, 28.3, 33.7, 34.9, 37.3, 58.9, 71.0, 108.3, 110.5, 117.3, 127.6, 129.9, 135.0, 140.6, 142.3, 145.2, 152.0, 162.3, 215.9. Found, %: C 61.60; H 5.76; N 6.52. $C_{22}H_{24}N_2O_5S$. Calculated, %: C 61.67; H 5.65; N 6.54.

1-[4-(4-Chlorophenyl)-6-hydroxy-3,6-dimethyl-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-indazol-5-yl]ethanone (4e). Yield 65%, mp 181°C, stereoisomer ratio ~3 : 1. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: major stereoisomer: 1.27 s (3H, CH_3), 1.36 s (3H, CH_3), 2.04 s (3H, CH_3), 2.39 s (3H, CH_3), 2.82 d (1H, 5-H, ^3J = 11.2 Hz), 3.14 br.s (2H, 7-H), 4.24 d (1H, 4-H, ^3J = 11.2 Hz), 5.00 br.s (1H, OH), 7.16 d (2H, ClC_6H_4, ^3J = 8.3 Hz), 7.32 d (2H, ClC_6H_4, ^3J = 8.3 Hz), 7.43 d (2H, *m*-H, Ts, ^3J = 8.3 Hz), 7.78 d (2H, *o*-H, Ts, ^3J = 8.3 Hz); minor stereoisomer: 1.18 s (3H, CH_3), 1.82 s (3H, CH_3), 2.00 s (3H, CH_3), 2.61 d (1H, 7-H, ^2J = 16.6 Hz), 2.77 br.s (2H, 7-H), 4.28 d (1H, 4-H, ^3J = 11.0 Hz), 4.85 br.s (1H, OH), 7.76 d (2H, *o*-H, Ts, ^3J = 8.3 Hz). Found, %: C 60.88; H 5.45; N 6.00. $C_{24}H_{25}ClN_2O_4S$. Calculated, %: C 60.94; H 5.33; N 5.92.

X-Ray analysis of compound 4a. The X-ray diffraction data for compound **4a** were obtained at 296(2) K on a Bruker APEX-II automated three-circle diffractometer (MoK_α radiation, λ 0.71073 Å, graphite monochromator, CCD detector, ω-scanning, 2θ = 49.42°). The structure was solved by the direct method using SHELXL-2014

[49] and WINGX [50] and was refined against F^2 by the full-matrix least-squares method in anisotropic approximation for non-hydrogen atoms. Hydrogen atoms were placed in geometrically calculated positions (or their positions were determined by difference electron density synthesis) which were refined according to the riding model ($U_{iso} = nU_{eq}$, $n = 1.5$ for methyl groups, $n = 1.2$ for other hydrogens). The molecular structures were plotted usng Platon [51] and Ortep-3 [52]. The coordinates of atoms and other crystallographic parameters of compound **4a** were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1874578).

FUNDING

This study was performed under financial support by the Ministry of Science and Higher Education of the Russian Federation (project no. 0795-2020-0010, V.V. Dotsenko).

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Kriven'ko, A.P. and Sorokin, V.V., *Zameshchennye tsiklogeksanolony* (Substituted Cyclohexanolones), Saratov: Saratov. Univ., 1999, p. 20.
2. Ismiev, A.I., Magerramov, A.M., Sukach, V.A., and Vovk, M.V., *Zh. Org. Farm. Khim*., 2016, vol. 14, no. 4(56), p. 16.
3. Ozols, A.I., Pelcher, Yu.Ê., Kalme, Z.A., Popelis, Yu.Yu., Turovskis, I.V., and Duburs, G.Ya., *Chem. Heterocycl. Compd*., 1996, vol. 32, no. 1, p. 52. https://doi.org/10.1007/BF01169354
4. Dyachenko, V.D., Sukach, S.M., and Dyachenko, A.D., *Chem. Heterocycl. Compd*., 2015, vol. 51, no. 1, p. 51. https://doi.org/10.1007/s10593-015-1658-9
5. Dyachenko, V.D. and Karpov, E.N., *Russ. J. Org. Chem*., 2014, vol. 50, no. 12, p. 1787. https://doi.org/10.1134/S1070428014120136
6. Sukach, S.M. and Dyachenko, V.D., *Russ. J. Org. Chem*., 2015, vol. 51, no. 7, p. 1020. https://doi.org/10.1134/S1070428015070210
7. Dyachenko, V.D. and Sukach, S.M., *Chem. Heterocycl. Compd*., 2010, vol. 46, no. 12, p. 1467. https://doi.org/10.1007/s10593-011-0693-4
8. Gein, V.L., Nosova, N.V., Potemkin, K.D., Aliev, Z.G., and Kriven'ko, A.P., *Russ. J. Org. Chem*., 2005, vol. 41, no. 7, p. 1016. https://doi.org/10.1007/s11178-005-0287-7
9. Sorokin, V.V., Grigor'ev, A.V., Ramazanov, A.K., and Krivenko, A.P., *Chem. Heterocycl. Compd*., 1999, vol. 35, no. 6, p. 671. https://doi.org/10.1007/BF02251624
10. Smirnova, N.O., Plotnikov, O.P., Vinogradova, N.A., Sorokin, V.V., and Kriven'ko, A.P., *Pharm. Chem. J*., 1995, vol. 29, no. 1, p. 49. https://doi.org/10.1007/BF02219464
11. Hote, B.S. and Lokhande, P.D., *Synth. Commun*., 2014, vol. 44, no. 10, p. 1492. https://doi.org/10.1080/00397911.2013.862724
12. Gein, V.L., Gein, N.V., Potemkin, K.D., and Kriven'ko, A.P., *Russ. J. Gen. Chem*., 2004, vol. 74, no. 10, p. 1564. https://doi.org/10.1007/s11176-005-0056-x
13. Poplevina, N.V., Kuznetsova, A.A., and Krivenko, A.P., *Chem. Heterocycl. Compd*., 2010, vol. 46, no. 9, p. 1148. https://doi.org/10.1007/s10593-010-0644-5
14. Dyachenko, V.D. and Sukach, S.M., *Russ. J. Gen. Chem*., 2012, vol. 82, no. 2, p. 305. https://doi.org/10.1134/S1070363212020211
15. Semenova, A.M., Oganesyan, R.V., Dotsenko, V.V., Chigorina, E.A., Aksenov, N.A., Aksenova, I.V., and Netreba, E.E., *Russ. J. Gen. Chem*., 2019, vol. 89, no. 1, p. 19. https://doi.org/10.1134/S1070363219010043
16. Etman, H.A., Sadek, M.G., and Khalil, A.G.M., *Res. J. Pharm. Biol. Chem. Sci*., 2015, vol. 6, no. 2, p. 247.
17. Rabe, P. and Elze, F., *Justus Liebigs Ann. Chem*., 1902, vol. 323, p. 83. https://doi.org/10.1002/jlac.19023230104
18. Rabe, P. and Elze, F., *Justus Liebigs Ann. Chem*., 1904, vol. 332, p. 1. https://doi.org/10.1002/jlac.19043320102
19. Finar, I.L., *J. Chem. Soc*., 1961, no. 2, p. 674. https://doi.org/10.1039/JR9610000674
20. Gein, V.L., Zorina, A.A., Nosova, I.V., Voronina, E.V., Vakhrin, M.I., and Kriven'ko, A.I., *Pharm. Chem. J*., 2007, vol. 41, no. 6, p. 319. https://doi.org/10.1007/s11094-007-0072-8
21. Gein, V.L., Yankin, A.N., Nosova, N.V., Levandovskaya, E.B., Novikova, V.V., and Rudakova, I.P., *Russ. J. Gen. Chem*., 2019, vol. 89, no. 6, p. 1169. https://doi.org/10.1134/S1070363219060112
22. Gein, V.L., Nosova, N.V., Vagapov, A.V., Dozmorova, N.V., and Yankin, A.N., *Russ. J. Gen. Chem*., 2019, vol. 89, no. 7, p. 1353. https://doi.org/10.1134/S1070363219070016
23. Denya, I., Malan, S.F., and Joubert, J., *Expert Opin. Ther. Pat*., 2018, vol. 28, no. 6, p. 441. https://doi.org/10.1080/13543776.2018.1472240

24. Cerecetto, H., Gerpe, A., González, M., Aran, V.J., and de Ocariz, C.O., *Mini-Rev. Med. Chem*., 2005, vol. 5, no. 10, p. 869. https://doi.org/10.2174/138955705774329564
25. Cankařová, N., Hlaváč, J., and Krchňák, V., *Org. Prep. Proced. Int*., 2010, vol. 42, no. 5, p. 433. https://doi.org/10.1080/00304948.2010.513898
26. Schmidt, A., Beutler, A., and Snovydovych, B., *Eur. J. Org. Chem*., 2008, vol. 2008, no. 24, p. 4073. https://doi.org/10.1002/ejoc.200800227
27. Ismiyev, A.I., Maharramov, A.M., Aliyeva, R.A., Askerov, R.K., Mahmudov, K.T., Kopylovich, M.N., Naili, H., and Pombeiro, A.J.L., *J. Mol. Struct*., 2013, vol. 1032, p. 83. https://doi.org/10.1016/j.molstruc.2012.08.006
28. Magerramov, A.M., Ismiev, A.I., Kadyrova, N.A., Gadzhieva, K.É., Askerov, R.K., and Potekhin, K.A., *J. Struct. Chem*., 2013, vol. 54, no. 6, p. 1137. https://doi.org/10.1134/S002247661306019X
29. Dotsenko, V.V., Krivokolysko, S.G., Polovinko, V.V., and Litvinov, V.P., *Chem. Heterocycl. Compd*., 2012, vol. 48, p. 309. https://doi.org/10.1007/s10593-012-0991-5
30. Maharramov, A.M., Ismiyev, A.I., Allahverdiyev, M.A., Maleev, A.V., and Potekhin, K.A., *J. Struct. Chem*., 2016, vol. 57, no. 4, p. 764. https://doi.org/10.1134/S002247661604020X
31. Maharramov, A.M., Ismiyev, A.I., Rashidov, B.A., and Aliyev, I.V., *Acta Crystallogr., Sect. E*, 2011, vol. 67, no. 5, p. o1127. https://doi.org/10.1107/S1600536811013195
32. Maharramov, A.M., Ismiyev, A.I., Rashidov, B.A., Askerov, R.K., and Khrustalev, V.N., *Acta Crystallogr., Sect. E*, 2010, vol. 66, no. 7, p. o1848. https://doi.org/10.1107/S1600536810024281
33. Hema, R., Parthasarathi, V., Ravikumar, K., Sridhar, B., and Pandiarajan, K., *Acta Crystallogr., Sect. E*, 2006, vol. 62, p. o656. https://doi.org/10.1107/S1600536806001486
34. Maharramov, A.M., Ismiyev, A.I., and Rashidov, B.A., *Acta Crystallogr., Sect. E*, 2011, vol. 67, p. o480. https://doi.org/10.1107/S160053681100242X
35. *Structure Correlation*, Burgi, H.-B. and Dunitz, J.D., Eds., Weinheim: VCH, 1994, vol. 2, p. 741. https://doi.org/10.1002/9783527616091
36. Bernstein, J., Davis, R.E., Shimoni, L., and Chang, N.L., *Angew. Chem., Int. Ed. Engl*., 1995, vol. 34, no. 15, p. 1555. https://doi.org/10.1002/anie.199515551
37. Becke, A.D., *J. Chem. Phys*., 1993, vol. 98, no. 7, p. 5648. https://doi.org/10.1063/1.464913
38. Lee, C., Yang, W., and Parr, R.G., *Phys. Rev. B*, 1988, vol. 37, no. 2, p. 785. https://doi.org/10.1103/PhysRevB.37.785
39. Tomasi, J., Mennucci, B., and Cammi, R., *Chem. Rev*., 2005, vol. 105, p. 2999. https://doi.org/10.1021/cr9904009
40. Sander, T., OSIRIS Property Explorer. Idorsia Pharmaceuticals Ltd., Switzerland. https://www.organic-chemistry.org/prog/peo/.
41. Daina, A., Michielin, O., and Zoete, V., *Sci. Rep*., 2017, vol. 7, article no. 42717. https://doi.org/10.1038/srep42717
42. Gfeller, D., Grosdidier, A., Wirth, M., Daina, A., Michielin, O., and Zoete, V., *Nucleic Acids Res*., 2014, vol. 42, no. 1, p. 32. https://doi.org/10.1093/nar/gku293
43. Molinspiration Property Calculation Service. Molinspiration Cheminformatics, Slovak Republic, 2002. www.molinspiration.com
44. Way2Drug, AntiBac-Pred. Laboratory for Structure-Function Based Drug Design, Institute of Biomedical Chemistry (IBMC), Moscow, Russia. http://way2drug.com/antibac/.
45. Lipinski, C.A., Lombardo, F., Dominy, B.W., and Feeney, P.J., *Adv. Drug Delivery Rev*., 1997, vol. 23, nos. 1–3, p. 4. https://doi.org/10.1016/S0169-409X(96)00423-1
46. Lipinski, C.A., *Drug Discovery Today: Technol*., 2004, vol. 1, no. 4, p. 337. https://doi.org/10.1016/j.ddtec.2004.11.007
47. Lipinski, C.A., Lombardo, F., Dominy, B.W., and Feeney, P.J., *Adv. Drug Delivery Rev*., 2012, vol. 64, p. 4. https://doi.org/10.1016/j.addr.2012.09.019
48. Martin, Y.C., *J. Med. Chem*., 2005, vol. 48, no. 9, p. 3164. https://doi.org/10.1021/jm0492002
49. Sheldrick, G.M., *Acta. Crystallogr., Sect. C*, 2015, vol. 71, p. 3. https://doi.org/10.1107/S2053229614024218
50. Farrugia, L.J., *J. Appl. Crystallogr*., 1999, vol. 32, no. 4, p. 837. https://doi.org/10.1107/S0021889899006020
51. Spek, A.L., *J. Appl. Crystallogr*., 2003, vol. 36, part 1, p. 7. https://doi.org/10.1107/S0021889802022112
52. Farrugia, L.J., *J. Appl. Crystallogr*., 1997, vol. 30, no. 5, p. 565. https://doi.org/10.1107/S0021889897003117