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A facile synthesis of 4-acylamino-tetrahydroindazoles via the Ritter reaction

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ABSTRACT

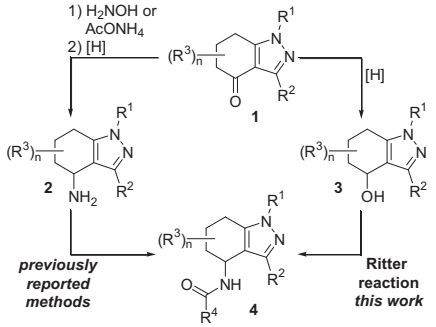
A new route toward 4-acylamino- and 4-amino-substituted tetrahydroindazoles is disclosed. The title compounds are obtained in good to excellent yields in the Ritter reaction between 4-hydroxy-tetrahydroindazoles and various nitriles. The reactivity of the tetrahydroindazole-derived carbenium ion is both sufficiently high to react with trichloroacetonitrile and sufficiently selective to resist the azide functionality within its structure. The present approach adds a method to the toolbox of tetrahydroindazole chemistry and facilitates the structural modifications of the scaffold, which has found important applications in medicinal chemistry.

1. Introduction

In recent years there has been considerable interest in the development of various molecular scaffolds for medicinal chemistry. The term Fsp^3 has been suggested, which stands for the ratio of sp^3 hybridized carbon atoms to the total carbon count.[1] It was demonstrated that for a successful drug candidate Fsp^3 approaches 0.5 and that the structure probably contains at least one chiral center. In this context tetrahydroindazoles (THIs) have proved to be particularly attractive due to the presence of both the planar pyrazole moiety and a C_4-tether, which points the substituents in distinct spatial directions. Exploration of this concept in the tetrahydroindazole series has resulted in many distinct biological activities.[2] Due to the fact that amino-substituted partially saturated heterocycles are of tremendous interest in medicinal chemistry[3] we[4] and others[5] have worked on the introduction of amino groups into the tetrahydroindazole core.

2. Results and discussion

Here we report a straightforward synthesis of 4-acylamino-4,5,6,7-tetrahydro-1*H*-indazoles **4** via the Ritter reaction. Previously known methods toward derivatives of type **4** rely on imination or oximation of the corresponding ketone **1** followed by reduction (Scheme 1). Then, a plethora of amide forming reactions would provide derivatives **4**. In our hands this approach was not general. For example, oximes derived from 1-pyridin-2-yl-THIs reacted smoothly in the aforementioned synthetic sequence. On the other hand, oximes of 1-phenyl derivatives produced a broad range of unidentified reduction byproducts (transformation **1**→**2**, Scheme 1). Moreover, structurally related oximes are reported to undergo a Beckmann rearrangement when treated with hydride containing reducing agents.[6]



Scheme 1. Synthetic approaches toward 4-acylamino-tetrahydroindazoles.

In our hands reductive amination was not very successful on either of the type **1** systems. At this point the Ritter reaction[7] was considered. We have found that 3-unsubstituted and 3-alkyl-1-aryl-4-hydroxy-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazoles undergo a Ritter reaction when treated with various nitriles in an

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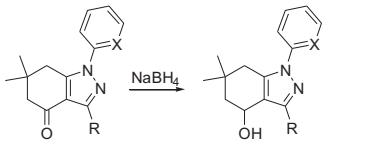
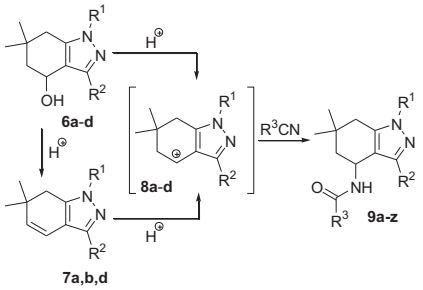
acidic medium. We began our investigations with 4-hydroxy-1-phenyl-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole (**6a**), which was obtained upon reduction of the corresponding tetrahydroindazolone **5a** with $NaBH_4$ in ethanol at ambient temperature (Scheme 2).[5b] Other 4-hydroxy-THI's **6b**–**d** were synthesized by the same procedure from previously reported starting materials.[4,8]



Scheme 2. Synthesis of 4-hydroxy-tetrahydroindazoles.

We envisaged sulfuric acid or polyphosphoric acid in acetic acid solution as a strongly ionizing medium for the Ritter reaction. Indeed, under such strongly acidic conditions **6a** smoothly underwent the aforementioned reaction with acetonitrile and produced amide **9a** (Scheme 3, Table 1). It was observed that in the absence of a nitrile 6,7-dihydroindazoles **7** were formed by deprotonation. The latter intermediates produced identical Ritter products when treated with the corresponding nitriles under strongly acidic conditions.[9] On the other hand, reaction of **6a** with MeCN or PhCN in CD_3COOD in the presence of D_2SO_4 failed to produce the expected deuteration at C(5) of the tetrahydroindazole. It can be concluded that at least in the latter cases the consumption of carbenium ion **8** by the nitrile is faster than its deprotonation–deuteration equilibrium. We have also demonstrated that the transformation **6a**+MeCN→**9a** proceeded equally well in trifluoroacetic acid as the sole reaction medium. Nevertheless, due to economical reasons this approach was not explored further as trifluoroacetic acid costs at least ten times more than AcOH and H_2SO_4. Optimization of the reaction conditions (**6a**→**9a**) revealed that 5 equiv of sulfuric acid are sufficient for an effective reaction that proceeds with full conversion in 4 h at 60 °C. Other acids were investigated, including concd phosphoric acid, concd perchloric acid, *para*-toluene sulfonic acid, and camphorsulfonic acid. These latter acids promoted amide formation sluggishly and the expected products **9** were isolated along with 6,7-dihydroindazoles **7a**–**d**.



Scheme 3. Synthesis of target compounds **9a**–**z** via the Ritter reaction.

With optimized reaction conditions in hand, a combinatorial library of 4-acylamino-tetrahydroindazoles was prepared. In a typical experiment a solution of **6a**–**d** (5 mmol) and a nitrile (1.5–20 equiv) in glacial acetic acid (5 mL) and concd H_2SO_4 (5–20 equiv) was heated at 60–70 °C for the time indicated in Table 1. After neutralization with an aqueous solution of NaOH the precipitated products **9a**–**z** were filtered and recrystallized.

More labile nitriles such as $ClCH_2CN$ and Cl_3CCN required higher loading of sulfuric acid along with a larger excess of the nitrile itself (up to 20 equiv) in order to obtain acceptable isolated yields of the target amides (e.g., **9c**, **9l**). This may reflect increased reactivity of the newly formed chloroacetate moiety, that is, predisposed to further transformations involving nucleophilic displacement and can be cleaved by various bifunctional nucleophiles.[10] It is noteworthy that even trichloroacetonitrile undergoes a Ritter reaction with 4-hydroxy-THI's. Indeed, this report represents one of the very few examples where Cl_3CCN is successfully used in the Ritter reaction.[11]

Table 1 lists many other combinations of pseudo benzylic alcohols **6** and nitriles that produce amides **9** in good to excellent yields. Among others they include the synthesis of acrylamides **9d**,**m**,**v** that are programmed for Michael additions of various nucleophiles. It is also shown that substituted benzonitriles with both electron donating (Table 1, entries 6, 24) and electron accepting groups (Table 1, entries 8, 26) produce the corresponding amides equally well under the aforementioned conditions. Last but not least, fluorine containing products are produced by reacting either tetrahydroindazole **6c** with nonfluorinated nitriles or *o*-fluorobenzonitrile with 4-hydroxy-THI's **6a**,**b**,**d**.

Next, we briefly studied the diastereoselectivity of the Ritter reaction on our substrates. Diastereomeric mixtures of azido (**12**) and amino (**13**) alcohols were obtained from compounds **10** and **11** that we reported earlier.[4] Ritter reaction of **12** and **13** with MeCN gave 75:25 and 95:5 diastereoselectivity in favor of the trans-products, respectively (Scheme 4). It is interesting to note that the azido group of **12** survives the strongly electrophilic reaction conditions.[12] The preference for *trans*-**15**,**16** can be explained by the conformation of the intermediate carbenium ion **14**, the *si*-face attack of which is partially hindered by the pseudo-axial methyl group at C(6). The relative configuration of each of the isomers in the azido series was independently established by coupling constant analysis in their ^1H NMR spectra and by positive cross-peaks in their 2D-NOESY spectra. Diastereoisomers *trans*-**15** and *cis*-**15** are separable by crystallization. The structure of *trans*-**15** was unambiguously proved by X-ray diffraction analysis (Fig. 1).[13] Coupling constant (^3J) analysis and 2D-NOESY spectrum of 7-amino-THI derivative *trans*-**16** revealed the pattern practically identical to that of *trans*-**15**. This allows us to attribute also the relative configuration of *trans*-**16**.

We have also explored the deacylation of some representative 4-acylamino-THI's. In the case of **9a**,**b** deacylation was achieved by acidic hydrolysis with HCl (Scheme 5). The corresponding amine was isolated in good yields as the tosylate salt **17**. Additionally, amide **9b** was deprotected by treatment with thiourea.[10] This approach provided product **17** in 80% yield.

In summary, we have reported a convenient synthetic approach to 4-acylamino-4,5,6,7-tetrahydroindazoles that are versatile building blocks in medicinal chemistry. The synthetic sequence includes reduction of tetrahydroindazolones to the corresponding alcohols and their Ritter reaction with various nitriles, including the relatively unreactive trichloroacetonitrile. Moreover, 4-amino-terahydroindazoles can be conveniently obtained by deprotection of the aforementioned 4-acylamino-THI's. Preliminary studies revealed that good to excellent levels of diastereoselectivity can be obtained when the Ritter reaction is performed on 7-substituted tetrahydroindazoles. It is worth mentioning that the azido group resists the presence of carbenium ion under the reported conditions. The well established reactivity of the azido and amino moieties allows the further decoration of the 4-acylamino-tetrahydroindazole core.

3. Experimental section

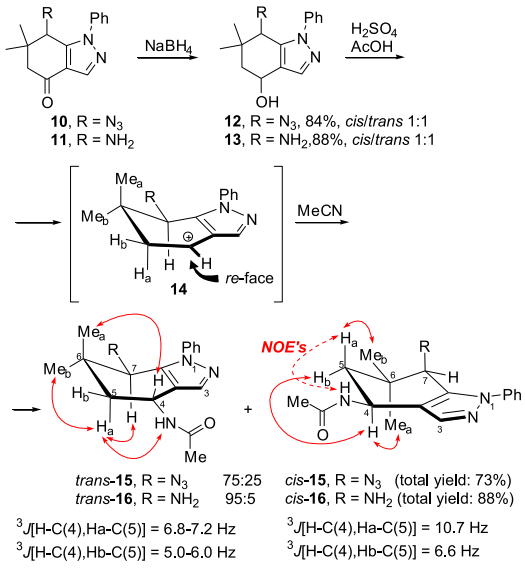
3.1. General

All reactions were carried out without a protective atmosphere of nitrogen or argon. All commercial reagents were used as

Table 1
Synthesis on 4-acylamino-tetrahydroindazoles via the Ritter reaction

Entry	Starting material **6**	R^1	R^2	R^3	Molar ratio **6**:nitrile:H_2SO_4	Reaction time, h[a]	Product (yield, %)	Melting point, °C[c]
1	**6a**	Ph	H	Me	1:5:5	4	**9a** (95)	198–199
2	**6a**	Ph	H	CH_2Cl	1:4:10	25	**9b** (69)	172–174[d]
3	**6a**	Ph	H	CCl_3	1:20:10	36[b]	**9c** (50)	145–146
4	**6a**	Ph	H	$CH{=}CH_2$	1:2:5	4	**9d** (71)	189–191
5	**6a**	Ph	H	Ph	1:3:5	4	**9e** (73)	159–160
6	**6a**	Ph	H	$C_6H_4OCH_3(m)$	1:1.5:4	15	**9f** (54)	139–140
7	**6a**	Ph	H	$C_6H_4F(o)$	1:2:5	9	**9g** (69)	68–70
8	**6a**	Ph	H	$C_6H_4NO_2(p)$	1:1.5:5	9	**9h** (72)	167–169
9	**6b**	Ph	Me	Me	1:2:5	4	**9i** (95)	196–197
10	**6b**	Ph	Me	*n*-Pr	1:5:5	4	**9j** (83)	195–197
11	**6b**	Ph	Me	CH_2Cl	1:4:8	8	**9k** (80)	156–157[d]
12	**6b**	Ph	Me	CCl_3	1:20:10	12[b]	**9l** (67)	181–182
13	**6b**	Ph	Me	$CH{=}CH_2$	1:2:5	4	**9m** (66)	149–152
14	**6b**	Ph	Me	Ph	1:3:5	4	**9n** (80)	244–245
15	**6b**	Ph	Me	$C_6H_4F(o)$	1:2:5	4	**9o** (71)	158–160
16	**6c**	Ph	CF_3	Me	1:5:5	6	**9p** (86)	178–179
17	**6c**	Ph	CF_3	CH_2Ph	1:3:5	4	**9q** (82)	157–159
18	**6d**	Py(2)	Me	Me	1:5:5	4	**9r** (95)	159–160
19	**6d**	Py(2)	Me	*n*-Pr	1:5:10	8	**9s** (76)	164–165
20	**6d**	Py(2)	Me	CH_2Cl	1:4:10	11	**9t** (76)	156–157[d]
21	**6d**	Py(2)	Me	CCl_3	1:10:5	20[b]	**9u** (62)	181–182[e]
22	**6d**	Py(2)	Me	$CH{=}CH_2$	1:2:5	4	**9v** (81)	176–177
23	**6d**	Py(2)	Me	Ph	1:2:5	4	**9w** (85)	217–218
24	**6d**	Py(2)	Me	$C_6H_4OCH_3(m)$	1:1.5:5	4	**9x** (78)	149–150
25	**6d**	Py(2)	Me	$C_6H_4F(o)$	1:2:5	8	**9y** (75)	173–174
26	**6d**	Py(2)	Me	$C_6H_4NO_2(p)$	1:2:5	4	**9z** (74)	195–196

[a] All reactions were run at 60 °C if not stated otherwise.
[b] The reaction was run at 70 °C.
[c] Products **9** were crystallized from EtOH/H_2O 1:1 if not stated otherwise.
[d] The product was crystallized from hexanes/EtOAc 2:1.
[e] The product was crystallized from EtOH/H_2O 2:1.



Scheme 4. Synthesis of 7-substituted 4-acylamino-THI's **15** and **16** via Ritter reaction.

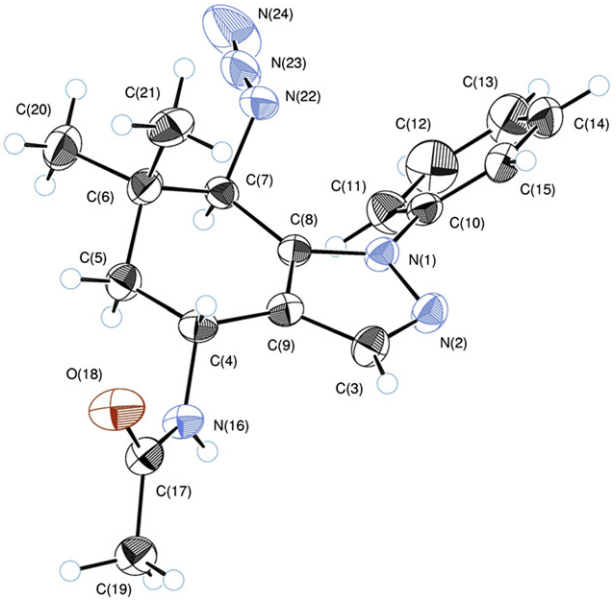
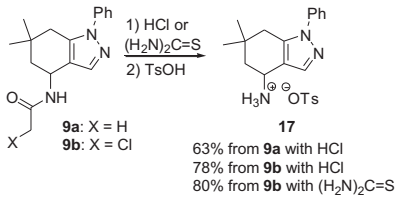


Fig. 1. ORTEP representation of *trans*-**15**.

purchased. ^1H NMR, ^{13}C NMR spectra were recorded in $CDCl_3$, C_6D_6 or DMSO-d_6 with solvent residual signal[14] as the internal standard. ^{19}F NMR spectra were recorded in $CDCl_3$ and α,α,α-trifluorotoluene was used as an external standard for these spectra; the chemical shifts were converted from α,α,α-trifluorotoluene to CCl_3F. Melting points were measured on *Fisher Digital Melting Point Analyzer Model* 355 and *Boetius* apparatus and are uncorrected. The progress of the reactions was followed by TLC (Merck, 60 F_{254}).

3.2. General procedure for synthesis of products 6a–d (method A): 6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-ol (6a)

$NaBH_4$ (0.760 g, 20.1 mmol) was added to a solution of **5a** (2.40 g, 10.0 mmol) in ethanol (30 mL). The resulting reaction mixture was stirred at ambient temperature for 12 h and concentrated under reduced pressure. The residue was partitioned between EtOAc (40 mL) and aqueous saturated solution of NH_4Cl



Scheme 5. Synthesis of 4-amino-THI **17** by deacylation of **9a** and **9b**.

(30 mL). The aqueous phase was extracted with EtOAc (2×20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue (white solid) was crystallized from EtOH/H_2O 1:1. Yield: 2.30 g (95%); mp 149–150 °C; IR (KBr) ν (cm^{-1}): 3270, 3190, 2934, 1600, 1506, 1407, 1308, 1047, 1025; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.74 (s, 1H, H–C(3)), 7.49–7.42 (m, 4H, H–C(Ph)), 7.38–7.31 (m, 1H, H–C(Ph)), 4.85 (dd, 1H, ^3J=8.5 Hz, ^3J=6.0 Hz, H–C(4)), 2.60, 2.42 (2d, AB syst., 2H, ^2J=16.0 Hz, H–C(7)), 1.96 (ddd, 1H, ^2J=13.0 Hz, ^3J=6.0 Hz, ^4J=1.3 Hz, H_a-C(5)), 1.53 (dd, 1H, ^2J=13.0 Hz, ^3J=8.5 Hz, H_b-C(5)), 1.12, 0.94 (2s, 6H, H_3C–C(6)); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 139.7, 138.7, 138.2, 129.1, 127.1, 123.3, 120.3, 63.3, 46.5, 37.0, 33.1, 30.6, 26.2; Anal. Calcd for $C_{15}H_{18}N_2O$ (242.32): C 74.35, H 7.49, N 11.56; found C 74.21, H 7.53, N 11.55.

*3.2.1. 3,6,6-Trimethyl-1-phenyl-4,5,6,7-tetrahydro-1H-indazol-4-ol (**6b**).* Product **6b** was synthesized by method A using **5b** (2.55 g, 10.0 mmol) as a starting material. Product **6b** (2.49 g, 97%) was obtained as a white solid. The spectral data of **6b** are consistent with those reported earlier.[15] Mp 174–175 °C (lit.[15]: 174–175 °C); IR (KBr) ν (cm^{-1}): 3224, 3066, 2954, 1601, 1572, 1508, 1433, 1384, 1073; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.46–7.43 (m, 4H, H–C(Ph)), 7.35–7.27 (m, 1H, H–C(Ph)), 4.86 (dd, 1H, ^3J=7.3 Hz, ^3J=6.0 Hz, H–C(4)), 2.56, 2.41 (2d, AB syst., 2H, ^2J=16.4 Hz, H–C(7)), 2.40 (s, 3H, H_3C–C(3)), 1.97 (ddd, 1H, ^2J=13.4 Hz, ^3J=6.0 Hz, ^4J=1.3 Hz, H_a-C(5)), 1.58 (dd, 1H, ^2J=13.4 Hz, ^3J=7.3 Hz, H_b-C(5)), 1.11, 0.95 (2s, 6H, H_3C–C(6)); Anal. Calcd for $C_{16}H_{20}N_2O$ (256.34): C 74.97, H 7.86, N 10.93; found C 74.72, H 8.04, N 10.97.

*3.2.2. 6,6-Dimethyl-1-phenyl-3-trifluoromethyl-4,5,6,7-tetrahydro-1H-indazol-4-ol (**6c**).* Product **6c** was synthesized by method A using **5c** (1.24 g, 4.02 mmol) as a starting material. Product **6c** (1.10 g, 88%) was obtained as colorless crystals. Mp 120–122 °C (hexane/Et_2O); IR (KBr) ν (cm^{-1}): 3495, 3385, 2960, 2875, 1635, 1600, 1500, 1470, 1450, 1390, 1385, 1370, 1330, 1290, 1260, 1245, 1165, 1130, 1035, 1015, 985, 950; ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.41–7.51 (m, 5H, H–C(Ph)), 5.01 (dd, 1H, ^3J=6.0 Hz, ^3J=7.2 Hz, H–C(4)), 2.60, 2.42 (2d, AB syst., 2H, ^2J=16.2 Hz, H–C(7)), 2.06 (br s, 1H, HO–C(4)), 1.99 (ddd, AB syst., 1H, ^2J=13.6 Hz, ^3J=6.0 Hz, ^4J=1.0 Hz, H_a-C(5)), 1.70 (dd, AB syst., 1H, ^2J=13.6 Hz, ^3J=7.2 Hz, H_b-C(5)), 1.15, 0.97 (2s, 6H, H_3C–C(6)); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 141.3, 140.1 (q, ^2J=37 Hz), 138.7, 129.4, 128.4, 124.1, 121.8 (q, ^1J=270 Hz), 117.9, 62.0, 45.2, 36.9, 32.6, 29.8, 27.1; ^{19}F ($CDCl_3$, 470 MHz) δ (ppm): −61.3; Anal. Calcd for $C_{16}H_{17}N_2OF_3$ (310.31): C 61.93, H 5.52, N 9.03; found C 62.15, H 5.49, N 8.98.

*3.2.3. 3,6,6-Trimethyl-1-pyridin-2-yl-4,5,6,7-tetrahydro-1H-indazol-4-ol (**6d**).* Product **6d** was synthesized by method A using **5d** (2.56 g, 10.0 mmol) as a starting material. Product **6d** (2.37 g, 92%) was obtained as a white solid. The spectral data of **6d** are consistent with those reported earlier.[5b] Mp 118–119 °C (lit.[5b]: 125–126 °C); IR (KBr) ν (cm^{-1}): 3455, 2987, 2948, 2924, 2866, 1585, 1474, 1444, 1387, 1368, 1057, 1045; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.38 (d, 1H, ^3J=5.6 Hz, H–C(Py)), 7.85 (d, 1H, ^3J=8.2 Hz, H–C(Py)), 7.75 (dd, 1H, ^3J=8.2 Hz, ^3J=7.2 Hz, H–C(Py)), 7.11 (dd, 1H, ^3J=7.2 Hz, ^3J=5.2 Hz, H–C(Py)), 4.82 (dd, 1H, ^3J=7.7 Hz, ^3J=6.1 Hz, H–C(4)), 2.95 (s, 2H, H–C(7)), 2.41 (s, 3H, H_3C–C(3)), 1.95 (dd, 1H, ^2J=13.3 Hz, ^3J=6.1 Hz, H_a-C(5)), 1.54 (dd, 1H, ^2J=13.3 Hz, ^3J=7.7 Hz, H_b-C(5)), 1.15, 0.97 (2s, 6H, H_3C–C(6)).

3.3. General procedure for synthesis of products 7a–d (method B): 6,6-dimethyl-1-phenyl-6,7-dihydro-1*H*-indazole (7a)

A solution of 4-hydroxy-THI **6a** (0.485 g, 2.00 mmol) in AcCl (2 mL) was heated under reflux for 2 h and poured into water. The precipitated solid was recrystallized from water/ethanol. Yield: 0.35 g (79%); mp 80–81 °C (EtOH/H_2O 1/3); IR (KBr) ν (cm^{-1}): 3034, 2960, 2946, 2934, 2885, 2857, 1601, 1561, 1507, 1424, 1387; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.52 (s, 1H, H–C(3)), 7.49–7.45 (m, 4H, H–C(Ph)), 7.40–7.32 (m, 1H, H–C(Ph)), 6.32, 5.44 (2d, 2H, ^3J=9.6 Hz, H–C(4,5)), 2.79 (s, 2H, H–C(7)), 1.09 (s, 6H, H_3C–C(6)); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 139.5, 137.5, 136.3, 133.9, 129.2, 127.0, 123.2, 117.3, 117.2, 35.9, 34.4, 28.4 (2C); Anal. Calcd for $C_{15}H_{16}N_2$ (224.30): C 80.32, H 7.19, N 12.49; found C 80.11, H 7.32, N 12.54.

*3.3.1. 3,6,6-Trimethyl-1-phenyl-6,7-dihydro-1H-indazole (**7b**).* Product **7b** was synthesized by method B using starting material **6b** (0.520 g, 2.03 mmol). Product **7b** (0.421 g, 87%) was obtained as a white solid. Mp 57–59 °C (EtOH/H_2O 1/3); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.48–7.41 (m, 4H, H–C(Ph)), 7.35–7.28 (m, 1H, H–C(Ph)), 6.28, 5.42 (2d, 2H, ^3J=9.6 Hz, H–C(4,5)), 2.75 (s, 2H, H–C(7)), 2.31 (s, 3H, H_3C–C(3)), 1.09 (s, 6H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 144.9, 139.5, 138.0, 133.2, 129.1, 126.7, 123.1, 116.9, 115.9, 36.2, 34.4, 28.5 (2C), 11.6; Anal. Calcd for $C_{16}H_{18}N_2$ (238.33): C 80.63, H 7.61, N 11.75; found C 80.30, H 7.66, N 11.64.

*3.3.2. 3,6,6-Trimethyl-1-pyridin-2-yl-6,7-dihydro-1H-indazole (**7d**).* Product **7d** was synthesized by method B using starting material **6d** (1.60 g, 6.22 mmol). Product **7d** (1.10 g, 74%) was obtained as a white solid. Mp 73–74 °C (EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.40 (ddd, 1H, J=4.9, 1.9, 0.8 Hz, H–C(Py)), 7.87 (dt, 1H, J=8.3, 0.8 Hz, H–C(Py)), 7.75 (ddd, 1H, J=8.3, 7.3, 1.9 Hz, H–C(Py)), 7.10 (ddd, 1H, J=7.3, 4.9, 1.1 Hz, H–C(Py)), 6.22, 5.44 (2d, 2H, ^3J=9.6 Hz, H–C(4,5)), 3.26 (s, 2H, H–C(7)), 2.30 (s, 3H, H_3C–C(3)), 1.17 (s, 6H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 153.2, 147.6, 145.9, 139.6, 138.1, 134.1, 120.4, 117.1, 116.1, 114.6, 37.6, 33.9, 28.8 (2C), 11.7. Anal. Calcd for $C_{15}H_{17}N_3$ (239.32): C 75.28, H 7.16, N 17.56; found C 75.30, H 7.22, N 17.54.

3.4. General procedure I for Ritter reaction: *N*-(6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-yl)-acetamide (9a)

Starting material **6a** (0.969 g, 4.00 mmol, 1 equiv) was added to a stirred solution of MeCN (1.00 mL, 20.0 mmol, 5 equiv) in glacial acetic acid (4 mL) and concd H_2SO_4 (1.10 mL, 20 mmol, 5 equiv). The resulting reaction mixture was stirred at 60 °C for 4 h (TLC control). The reaction mixture was cooled to 0 °C and poured into a vigorously stirred ~10% aqueous solution of NaOH (50–60 mL) at 0 °C. The crude product **9a** was filtered and thoroughly washed with water until the filtrate became neutral. The obtained solid was recrystallized from a mixture of EtOH/H_2O (1:1). Yield: 1.07 g (95%); IR (KBr) ν (cm^{-1}): 3265, 3068, 2963, 2905, 1645, 1634, 1601, 1554, 1510, 1455, 1396, 1383, 1371, 1293, 1276, 1178, 1141, 1130, 1066, 966; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.60 (s, 1H, H–C(3)), 7.50–7.44 (m, 4H, Ph–N(1)), 7.39–7.31 (m, 1H, Ph–N(1)), 5.73 (d, 1H, ^3J=8.3 Hz, H–N–C(4)), 5.14, (ddd, 1H, ^3J=9.8 Hz, ^3J=8.3 Hz, ^3J=7.2 Hz, H–C(4)), 2.60 (d, 1H, ^2J=16.0 Hz, H_a-C(7)), 2.43 (d, 1H, ^2J=16.0 Hz, H_b-C(7)), 2.03 (s, 3H, H–C(2′)), 2.01 (ddd, 1H,

^2J=13.0 Hz, ^3J=7.2 Hz, ^4J=1.1 Hz, H_b-C(5)), 1.35 (dd, 1H, ^2J=13.0 Hz, ^3J=9.8 Hz, H_a-C(5)), 1.10 (s, 3H, H_3C–C(5)), 0.96 (s, 3H, H_3C–C(5)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 169.7, 139.5, 139.1, 137.9, 129.1, 127.2, 123.3, 118.1, 43.5, 41.8, 36.9, 32.6, 30.8, 25.3, 23.5; Anal. Calcd for $C_{17}H_{21}N_3O$ (283.37): C 72.06, H 7.47, N 14.83; found C 72.16, H 7.38, N 14.69.

3.5. General procedure II for Ritter reaction: 2-chloro-*N*-(6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-yl)-acetamide (9b)

Starting material **6a** (0.969 g, 4.00 mmol, 1 equiv) was added to a stirred solution of $ClCH_2CN$ (1.00 mL, 16.0 mmol, 4 equiv) in glacial acetic acid (4 mL) and concd H_2SO_4 (2.20 mL, 40 mmol, 10 equiv). The resulting reaction mixture was stirred at 60 °C for 24 h (TLC control). The reaction mixture was cooled to 0 °C and poured into a vigorously stirred ~10% aqueous solution of NaOH (60 mL) at 0 °C. The crude product **9b** was filtered and thoroughly washed with water until the filtrate became neutral. The obtained solid was recrystallized from a mixture of hexanes/EtOAc (1:1). Yield: 0.87 g (69%); IR (KBr) ν (cm^{-1}): 3253, 3076, 2961, 1648, 1562, 1505, 1402, 1249, 1165, 968; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.62 (s, 1H, H–C(3)), 7.50–7.45 (m, 4H, Ph–N(1)), 7.40–7.33 (m, 1H, Ph–N(1)), 6.75 (d, 1H, ^3J=8.1 Hz, H–N–C(4)), 5.16 (ddd, 1H, ^3J=9.6 Hz, ^3J=8.1 Hz, ^3J=5.8 Hz, H–C(4)), 4.14 (d, 1H, ^2J=15.3 Hz, H_a-C(2′)), 4.08 (d, 1H, ^2J=15.3 Hz, H_b-C(2′)), 2.61 (d, 1H, ^2J=16.2 Hz, H_a-C(7)), 2.46 (d, 1H, ^2J=16.2 Hz, H_b-C(7)), 2.02 (dd, 1H, ^2J=13.0 Hz, ^3J=5.8 Hz, H_a-C(5)), 1.46 (dd, 1H, ^2J=13.0 Hz, ^3J=9.6 Hz, H_b-C(5)), 1.13 (s, 3H, H_3C–C(6)), 0.99 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.6, 139.5, 139.3, 137.9, 129.2, 127.4, 123.5, 117.2, 43.3, 42.7, 42.4, 36.9, 32.7, 30.6, 25.6; Anal. Calcd for $C_{17}H_{20}ClN_3O$ (317.81): C 64.25, H 6.34, N 13.22; found C 64.11, H 6.27, N 13.00.

3.6. General procedure III for Ritter reaction: 2,2,2-trichloro-*N*-(6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-yl)-acetamide (9c)

Starting material **6a** (0.969 g, 4.00 mmol, 1 equiv) was added to a stirred solution of Cl_3CCN (8.00 mL, 80.0 mmol, 20 equiv) in glacial acetic acid (5 mL) and concd H_2SO_4 (2.20 mL, 40 mmol, 10 equiv). The resulting reaction mixture was stirred at 70 °C for 36 h (TLC control). The reaction mixture was cooled to 0 °C and poured into a vigorously stirred ~10% aqueous solution of NaOH (70 mL) at 0 °C. The crude product **9c** was filtered and thoroughly washed with water until the filtrate became neutral. The obtained solid was recrystallized from a mixture of EtOH/H_2O (1:1). Yield: 0.77 g (50%); IR (KBr) ν (cm^{-1}): 3034, 2958, 2934, 1601, 1561, 1507, 1424, 1387, 896; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.64 (s, 1H, H–C(3)), 7.51–7.45 (m, 4H, Ph–N(1)), 7.41–7.34 (m, 1H, Ph–N(1)), 6.79 (d, 1H, ^3J=7.7 Hz, H–N–C(4)), 5.13 (ddd, 1H, ^3J=9.2 Hz, ^3J=7.7 Hz, ^3J=6.1 Hz, H–C(4)), 2.62 (d, 1H, ^2J=16.4 Hz, H_a-C(7)), 2.49 (d, 1H, ^2J=16.4 Hz, H_b-C(7)), 2.08 (ddd, 1H, ^2J=13.0 Hz, ^3J=6.1 Hz, ^4J=1.0 Hz, H_a-C(5)), 1.53 (ddd, 1H, ^2J=13.0 Hz, ^3J=9.2 Hz, H_b-C(5)), 1.15 (s, 3H, H_3C–C(6)), 1.02 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.6, 139.7, 139.1, 137.5, 129.3, 127.7, 123.6, 116.4, 92.6, 44.2, 42.6, 36.7, 32.6, 30.4, 25.7; Anal. Calcd for $C_{17}H_{18}Cl_3N_3O$ (386.70): C 52.80, H 4.69, N 10.87; found C 52.80, H 4.56, N 10.79.

3.7. Synthesis of 4-acylamino-tetrahydroindazoles via the Ritter reaction

*3.7.1. N-(6,6-Dimethyl-1-phenyl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-acrylamide (**9d**).* Product **9d** (0.839 g, 71%) was obtained as a white solid by general procedure I for Ritter reaction using acrylnitrile (2 equiv) instead of MeCN. IR (KBr) ν (cm^{-1}): 3277, 3065, 2962, 2908, 1657, 1623, 1600, 1504, 1453, 1411, 1396, 1383, 1259, 1240, 1067, 990, 967, 954; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.60 (s, 1H, H–C(3)), 7.48–7.44 (m, 4H, Ph–N(1)), 7.39–7.32 (m, 1H, Ph–N(1)), 6.33 (dd, 1H, ^3J=17.0 Hz, ^2J=1.5 Hz, H_a-C(3′)), 6.12 (dd, 1H, ^3J=17.0 Hz, ^3J=10.2 Hz, H–C(2′)), 5.84 (d, 1H, ^3J=7.3 Hz, H–N–C(4)), 5.67 (dd, 1H, ^3J=10.2 Hz, ^2J=1.5 Hz, H_b-C(3′)), 5.23 (ddd, 1H, ^3J=9.8 Hz, ^3J=7.3 Hz, ^3J=5.8 Hz, H–C(4)), 2.58 (d, 1H, ^2J=16.2 Hz, H_a-C(7)), 2.45 (d, 1H, ^2J=16.2 Hz, H_b-C(7)), 2.04 (dd, 1H, ^2J=13.0 Hz, ^3J=5.8 Hz, H_a-C(5)), 1.38 (dd, 1H, ^2J=13.0 Hz, ^3J=9.8 Hz, H_b-C(5)), 1.11 (s, 3H, H_3C–C(6)), 0.98 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.1, 139.6, 139.3, 138.1, 130.9, 129.2, 127.2, 126.7, 123.3, 117.9, 43.5, 41.9, 37.0, 32.7, 30.8, 25.4; Anal. Calcd for $C_{18}H_{21}N_3O$ (295.38): C 73.19, H 7.17, N 14.23; found C 72.91, H 7.24, N 14.17.

*3.7.2. N-(6,6-Dimethyl-1-phenyl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-benzamide (**9e**).* Product **9e** (1.01 g, 73%) was obtained as a white solid by general procedure I for Ritter reaction using benzonitrile (3 equiv) instead of MeCN. IR (KBr) ν (cm^{-1}): 3271, 2955, 1627, 1600, 1578, 1534, 1505, 1490, 1401, 1294, 1182, 1149, 1067, 968; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.81 (dd, 2H, ^3J=7.7 Hz, ^4J=0.9 Hz, Ph–C(1′)), 7.66 (s, 1H, H–C(3)), 7.54–7.41 (m, 7H, Ph–N(1), Ph–C(1′)), 7.40–7.32 (m, 1H, Ph–N(1)), 6.34 (d, 1H, ^3J=8.5 Hz, H–N–C(4)), 5.37 (ddd, 1H, ^3J=9.4 Hz, ^3J=8.5 Hz, ^3J=5.8 Hz, H–C(4)), 2.62 (dd, 1H, ^2J=16.1 Hz, ^4J=1.1 Hz, H_a-C(7)), 2.48 (d, 1H, ^2J=16.1 Hz, H_b-C(7)), 2.12 (ddd, 1H, ^2J=12.8 Hz, ^3J=5.8 Hz, ^4J=1.1 Hz, H_a-C(5)), 1.49 (dd, 1H, ^2J=12.8 Hz, ^3J=9.4 Hz, H_b-C(5)), 1.14 (s, 3H, H_3C–C(5)), 1.02 (s, 3H, H_3C–C(5)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 167.1, 139.7, 139.2, 138.2, 134.5, 131.6, 129.2, 128.6, 127.2, 126.9, 123.4, 118.0, 43.6, 42.4, 37.0, 32.8, 30.8, 25.6; Anal. Calcd for $C_{22}H_{23}N_3O$ (345.44): C 76.49, H 6.71, N 12.16; found C 76.36, H 6.81, N 11.93.

*3.7.3. N-(6,6-Dimethyl-1-phenyl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-3-methoxy-benzamide (**9f**).* Product **9f** (0.54 g, 54%) was obtained as a white solid by general procedure I for Ritter reaction using 3-methoxy-benzonitrile (1.5 equiv) instead of MeCN and H_2SO_4 (4 equiv). Reaction time: 15 h. IR (KBr) ν (cm^{-1}): 3339, 2960, 1641, 1602, 1581, 1527, 1505, 1485, 1406, 1295, 1236, 1046; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.64 (s, 1H, H–C(3)), 7.48–7.45 (m, 4H, Ph–N(1)), 7.44–7.41 (m, 1H, Ar–C(1′)), 7.39–7.30 (m, 3H, Ph–N(1), Ar–C(1′)), 7.07–7.00 (m, 1H, Ar–C(1′)), 6.44 (d, 1H, ^3J=8.3 Hz, H–N–C(4)), 5.34 (ddd, 1H, ^3J=9.6 Hz, ^3J=8.3 Hz, ^3J=6.0 Hz, H–C(4)), 3.85 (s, 3H, *m*-CH_3–O-Ar–C(1′)), 2.60 (d, 1H, ^2J=16.2 Hz, H_a-C(7)), 2.46 (d, 1H, ^2J=16.2 Hz, H_b-C(7)), 2.09 (dd, 1H, ^2J=12.9 Hz, ^3J=6.0 Hz, H_a-C(5)), 1.44 (dd, 1H, ^2J=12.9 Hz, ^3J=9.6 Hz, H_b-C(5)), 1.12 (s, 3H, H_3C–C(6)), 1.00 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.9, 159.8, 139.5, 139.1, 138.0, 135.9, 129.5, 129.1, 127.2, 123.2, 118.6, 117.9, 117.7, 112.3, 55.4, 43.4, 42.3, 36.9, 32.7, 30.7, 25.5; Anal. Calcd for $C_{23}H_{25}N_3O_2$ (375.46): C 73.57, H 6.71, N 11.19; found C 73.33, H 6.72, N 11.07.

*3.7.4. N-(6,6-Dimethyl-1-phenyl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-2-fluoro-benzamide (**9g**).* Product **9g** (1.00 g, 69%) was obtained as a white solid by general procedure I for Ritter reaction using 2-fluorobenzonitrile (2 equiv) instead of MeCN. Reaction time: 9 h. IR (KBr) ν (cm^{-1}): 3388, 3066, 2951, 1648, 1616, 1501, 1396, 1320, 1297, 1258, 1219, 1099, 968, 924; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.15 (dt, 1H, J=7.9 Hz, J=1.9 Hz, *o*-F–C_6H_4–C(1′)), 7.67 (s, 1H, H–C(3)), 7.52–7.43 (m, 5H, *o*-F–C_6H_4–C(1′), Ph–N(1)), 7.39–7.32 (m, 1H, Ph–N(1)), 7.30 (d, 1H, J=7.7 Hz, *o*-F–C_6H_4–C(1′)), 7.11 (dd, 1H, J=12.2 Hz, ^3J=8.3 Hz, *o*-F–C_6H_4–C(1′)), 6.91 (dd, 1H, J_{H-F}=12.2 Hz, ^3J=8.5 Hz, H–N–C(4)), 5.40 (ddd, 1H, ^3J=9.4 Hz, ^3J=8.5 Hz, ^3J=5.8 Hz, H–C(4)), 2.63 (d, 1H, ^2J=15.8 Hz, H_a-C(7)), 2.49 (d, 1H, ^2J=15.8 Hz, H_b-C(7)), 2.14 (dd, 1H, ^2J=13.0 Hz, ^3J=5.8 Hz, H_a-

C(5)), 1.53 (dd, 1H, ^2J=13.0 Hz, ^3J=9.4 Hz, H_b-C(5)), 1.14 (s, 3H, H_3C–C(6)), 1.03 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 163.0 (d, J_{C-F}=3 Hz), 160.7 (d, J_{C-F}=247 Hz), 139.7, 139.2, 138.1, 133.4 (d, J_{C-F}=9 Hz), 132.1 (d, J_{C-F}=2 Hz), 129.2, 127.2, 124.9 (d, J_{C-F}=3 Hz), 123.4, 121.1 (d, J_{C-F}=12 Hz), 117.8, 116.0 (d, J_{C-F}=25 Hz), 43.5, 42.4, 37.0, 32.7, 30.6, 25.8; Anal. Calcd for $C_{22}H_{22}N_3OF$ (363.43): C 72.71, H 6.10, N 11.56; found C 72.58, H 6.29, N 11.70.

*3.7.5. N-(6,6-Dimethyl-1-phenyl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-4-nitro-benzamide (**9h**).* Product **9h** (1.13 g, 72%) was obtained as a white solid by general procedure I for Ritter reaction using 4-nitrobenzonitrile (1.5 equiv) instead of MeCN. Reaction time: 9 h. IR (KBr) ν (cm^{-1}): 3392, 2960, 2920, 2864, 1645, 1599, 1527, 1504, 1486, 1476, 1454, 1402, 1349, 1191, 975; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.30 (d, 2H, ^3J=8.7 Hz, *p*-NO_2–C_6H_4–C(1′)), 7.98 (d, 2H, ^3J=8.7 Hz, *p*-NO_2–C_6H_4–C(1′)), 7.64 (s, 1H, H–C(3)), 7.49–7.45 (m, 4H, Ph–N(1)), 7.40–7.34 (m, 1H, Ph–N(1)), 6.50 (d, 1H, ^3J=8.1 Hz, H–N–C(4)), 5.36 (ddd, 1H, ^3J=9.6 Hz, ^3J=8.1 Hz, ^3J=5.7 Hz, H–C(4)), 2.62 (d, 1H, ^2J=16.4 Hz, H_a-C(7)), 2.49 (d, 1H, ^2J=16.4 Hz, H_b-C(7)), 2.13 (dd, 1H, ^2J=12.9 Hz, ^3J=5.7 Hz, H_a-C(5)), 1.47 (dd, 1H, ^2J=12.9 Hz, ^3J=9.6 Hz, H_b-C(5)), 1.14 (s, 3H, H_3C–C(6)), 1.02 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.0, 149.6, 140.0, 139.4, 139.3, 138.0, 129.3, 128.2, 127.4, 123.8, 123.2, 117.4, 43.3, 42.8, 37.0, 32.8, 30.8, 25.4; Anal. Calcd for $C_{22}H_{22}N_4O_3$ (390.44): C 67.68, H 5.68, N 14.35; found C 67.80, H 5.56, N 14.53.

*3.7.6. N-(3,6,6-Trimethyl-1-phenyl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-acetamide (**9i**).* Product **9i** (1.14 g, 95%) was obtained as a white solid by general procedure I for Ritter reaction using starting material **6b** (1.03 g, 4.02 mmol) and MeCN (2 equiv). IR (KBr) ν (cm^{-1}): 3248, 3058, 2948, 2369, 1636, 1560, 1507, 1381, 1292, 1109, 1039, 1014; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.45–7.39 (m, 4H, Ph–N(1)), 7.33–7.27 (m, 1H, Ph–N(1)), 5.76 (d, 1H, ^3J=8.9 Hz, H–N–C(4)), 5.16 (dt, 1H, ^3J=8.9 Hz, ^3J=6.2 Hz, H–C(4)), 2.54 (d, 1H, ^2J=16.2 Hz, H_a-C(7)), 2.37 (d, 1H, ^2J=16.2 Hz, H_b-C(7)), 2.23 (s, 3H, H_3C–C(3)), 1.99 (s, 3H, H–C(2′)), 1.95 (dd, 1H, ^2J=13.2 Hz, ^3J=6.2 Hz, H_a-C(5)), 1.37 (dd, 1H, ^2J=13.2 Hz, ^3J=8.9 Hz, H_b-C(5)), 1.06 (s, 3H, H_3C–C(6)), 0.92 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 169.3, 147.1, 140.0, 139.4, 129.2, 126.9, 123.1, 115.0, 44.0, 41.5, 37.2, 32.7, 30.4, 25.8, 23.4, 12.4; Anal. Calcd for $C_{18}H_{23}N_3O$ (297.39): C 72.70, H 7.80, N 14.13; found C 72.76, H 7.86, N 14.17.

*3.7.7. N-(3,6,6-Trimethyl-1-phenyl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-butyramide (**9j**).* Product **9j** (1.10 g, 83%) was obtained as a white solid by general procedure I for Ritter reaction using starting material **6b** (1.03 g, 4.02 mmol) and butyronitrile (5) instead of MeCN. IR (KBr) ν (cm^{-1}): 3305, 2959, 2370, 1638, 1530, 1507, 1383, 1047; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.47–7.42 (m, 4H, Ph–N(1)), 7.35–7.29 (m, 1H, Ph–N(1)), 5.49 (d, 1H, ^3J=9.2 Hz, H–N–C(4)), 5.22 (ddd, 1H, ^3J=9.2 Hz, ^3J=8.7 Hz, ^3J=6.0 Hz, H–C(4)), 2.57 (d, 1H, ^2J=16.0 Hz, H_a-C(7)), 2.41 (d, 1H, ^2J=16.0 Hz, H_b-C(7)), 2.27 (s, 3H, H_3C–C(3)), 2.19 (t, 2H, ^3J=7.9 Hz, H–C(2′)), 2.01 (dd, 1H, ^2J=13.1 Hz, ^3J=6.0 Hz, H_a-C(5)), 1.72 (sext., 2H, ^3J=7.5 Hz, H–C(3′)), 1.23 (dd, 1H, ^3J=13.1 Hz, ^3J=8.7 Hz, H_b-C(5)), 1.09 (s, 3H, H_3C–C(6)), 0.98 (t, 3H, ^3J=7.3 Hz, H–C(4′)), 0.96 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.1, 147.1, 140.2, 139.5, 129.1, 126.8, 123.3, 115.0, 44.1, 41.3, 38.9, 37.2, 32.6, 30.3, 25.9, 19.2, 13.8, 12.4; Anal. Calcd for $C_{20}H_{27}N_3O$•$0.2H_2O$ (325.45•$0.2H_2O$): C 73.00, H 8.39, N 12.77; found C 73.22, H 8.53, N 12.99.

*3.7.8. 2-Chloro-N-(3,6,6-trimethyl-1-phenyl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-acetamide (**9k**).* Product **9k** (1.07 g, 80%) was obtained as a white solid by general procedure II for Ritter reaction using starting material **6b** (1.03 g, 4.02 mmol) and H_2SO_4 (8 equiv). Reaction time: 8 h. IR (KBr) ν (cm^{-1}): 3221, 3066, 2954, 1648, 1560, 1507, 1383, 1253, 1152, 1040; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.46–7.40 (m, 4H, Ph–N(1)), 7.34–7.27 (m, 1H, Ph–N(1)), 6.67 (d, 1H, ^3J=8.7 Hz, H–N–C(4)), 5.19 (dt, 1H, ^3J=6.0 Hz, ^3J=8.7 Hz, H–C(4)), 4.09 (s, 2H, H–C(2′)), 2.58 (d, 1H, ^2J=16.2 Hz, H_a-C(7)), 2.41 (d, 1H, ^2J=16.2 Hz, H_b-C(7)), 2.24 (s, 3H, H_3C–C(3)), 2.00 (dd, 1H, ^2J=13.0 Hz, ^3J=6.0 Hz, H_a-C(5)), 1.48 (dd, 1H, ^2J=13.0 Hz, ^3J=8.7 Hz, H_b-C(5)), 1.11 (s, 3H, H_3C–C(6)), 1.00 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.1, 147.0, 140.1, 139.4, 129.0, 126.8, 123.1, 113.9, 43.5, 42.5, 42.1, 37.0, 32.5, 30.1, 25.9, 12.4; Anal. Calcd for $C_{18}H_{22}ClN_3O$ (331.84): C 65.15, H 6.68, N 12.66; found C 64.86, H 6.83, N 12.31.

*3.7.9. 2,2,2-Trichloro-N-(3,6,6-trimethyl-1-phenyl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-acetamide (**9l**).* Product **9l** (1.08 g, 67%) was obtained as a white solid by general procedure III for Ritter reaction using starting material **6b** (1.03 g, 4.02 mmol). Reaction time: 12 h. IR (KBr) ν (cm^{-1}): 3267, 2952, 1696, 1507, 1078; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.48–7.42 (m, 4H, Ph–N(1)), 7.37–7.30 (m, 1H, Ph–N(1)), 6.74 (d, 1H, ^3J=8.5 Hz, H–N–C(4)), 5.15 (ddd, 1H, ^3J=5.8 Hz, ^3J=8.1 Hz, ^3J=8.5 Hz, H–C(4)), 2.61 (d, 1H, ^2J=16.2 Hz, H_a-C(7)), 2.45 (d, 1H, ^2J=16.2 Hz, H_b-C(7)), 2.29 (s, 3H, H_3C–C(3)), 2.07 (dd, 1H, ^2J=13.2 Hz, ^3J=5.8 Hz, H_a-C(5)), 1.56 (dd, 1H, ^2J=13.2 Hz, ^3J=8.1 Hz, H_b-C(5)), 1.11 (s, 3H, H_3C–C(6)), 1.00 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.0, 147.1, 140.4, 139.2, 129.2, 127.1, 123.3, 113.3, 92.7, 44.1, 42.9, 37.0, 32.5, 29.8, 26.3, 12.4; Anal. Calcd for $C_{18}H_{20}Cl_3N_3O$ (400.73): C 53.95, H 5.03, N 10.49; found C 53.93, H 4.93, N 10.45.

*3.7.10. N-(3,6,6-Trimethyl-1-phenyl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-acrylamide (**9m**).* Product **9m** (0.893 g, 66%) was obtained as a white solid by general procedure I for Ritter reaction using starting material **6b** (1.03 g, 4.02 mmol) and acrylonitrile (2 equiv) instead of MeCN. IR (KBr) ν (cm^{-1}): 3434, 3050, 2956, 2370, 2345, 1656, 1558, 1251; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.47–7.41 (m, 4H, Ph–N(1)), 7.34–7.28 (m, 1H, Ph–N(1)), 6.32 (d, 1H, ^3J=16.8 Hz, H_a-C(3′)), 6.11 (dd, 1H, ^3J=16.8 Hz, ^3J=10.2 Hz, H–C(2′)), 5.74 (d, 1H, ^3J=8.9 Hz, H–N–C(4)), 5.67 (d, 1H, ^3J=10.2 Hz, H_b-C(3′)), 5.28 (ddd, 1H, ^3J=8.9 Hz, ^3J=8.7 Hz, ^3J=6.2 Hz, H–C(4)), 2.58 (d, 1H, ^2J=16.2 Hz, H_a-C(7)), 2.40 (d, 1H, ^2J=16.2 Hz, H_b-C(7)), 2.23 (s, 3H, H_3C–C(3)), 2.02 (dd, 1H, ^2J=13.3 Hz, ^3J=6.2 Hz, H_a-C(5)), 1.45 (dd, 1H, ^2J=13.3 Hz, ^3J=8.7 Hz, H_b-C(5)), 1.08 (s, 3H, H_3C–C(6)), 0.96 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.9, 147.3, 140.1, 139.4, 130.8, 129.2, 126.9, 126.7, 123.2, 114.8, 43.9, 41.6, 37.2, 32.7, 30.3, 25.9, 12.4; Anal. Calcd for $C_{19}H_{23}N_3O \cdot 1.5H_2O$ ($309.41 \cdot 1.5H_2O$): C 67.83, H 7.79, N 12.49; found C 67.58, H 7.71, N 12.59.

*3.7.11. N-(3,6,6-Trimethyl-1-phenyl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-benzamide (**9n**).* Product **9n** (1.16 g, 80%) was obtained as a white solid by general procedure I for Ritter reaction using starting material **6b** (1.03 g, 4.02 mmol) and benzonitrile (3 equiv) instead of MeCN. IR (KBr) ν (cm^{-1}): 3299, 3057, 2949, 2926, 1630, 1531, 1507, 1375, 1291, 1177, 1024, 1045, 920; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.79 (d, 1H, ^3J=7.3 Hz, Ph–C(1′)), 7.54–7.44 (m, 7H, Ph–N(1, 1′)), 7.38–7.32 (m, 1H, Ph–N(1)), 6.24 (d, 1H, ^3J=8.7 Hz, H–N–C(4)), 5.43 (dt, 1H, ^3J=6.2 Hz, ^3J=8.7 Hz, H–C(4)), 2.62 (d, 1H, ^2J=15.8 Hz, H_a-C(7)), 2.45 (d, 1H, ^2J=15.8 Hz, H_b-C(7)), 2.29 (s, 3H, H_3C–C(3)), 2.11 (dd, 1H, ^2J=13.1 Hz, ^3J=6.2 Hz, H_a-C(5)), 1.56 (dd, 1H, ^2J=13.1 Hz, ^3J=8.7 Hz, H_b-C(5)), 1.12 (s, 3H, H_3C–C(6)), 1.01 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.7, 147.2, 140.2, 139.4, 134.5, 131.5, 129.1, 128.7, 126.9, 126.8, 123.2, 114.9, 44.0, 42.0, 37.2, 32.7, 30.3, 26.0, 12.5; Anal. Calcd for $C_{23}H_{25}N_3O$ (359.46): C 76.85, H 7.01, N 11.69; found C 76.53, H 7.34, N 11.54.

*3.7.12. 2-Fluoro-N-(3,6,6-trimethyl-1-phenyl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-benzamide (**9o**).* Product **9o** (1.08 g, 71%) was

obtained as a white solid by general procedure I for Ritter reaction using starting material **6b** (1.03 g, 4.02 mmol) and 2-fluorobenzonitrile (2 equiv) instead of MeCN. IR (KBr) ν (cm^{-1}): 3247, 2957, 2930, 2368, 1648, 1508, 1220, 1103, 1069; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.16 (dd, 1H, ^3J=7.7 Hz, ^4J=1.7 Hz, H–C(Ar)), 7.51–7.43 (m, 5H, H–C(Ar)), 7.36–7.29 (m, 2H, H–C(Ar)), 7.12 (dd, 1H, ^3J=12.2 Hz, ^3J=8.3 Hz, H–C(Ar)), 6.81 (d, 1H, ^3J=9.0 Hz, H–N–C(4)), 5.45 (ddd, 1H, ^3J=9.2 Hz, ^3J=8.3 Hz, ^3J=6.0 Hz, H–C(4)), 2.62 (d, 1H, ^3J=16.3 Hz, H_a-C(7)), 2.45 (d, 1H, ^2J=16.3 Hz, H_b-C(7)), 2.29 (s, 3H, H_3C–C(3)), 2.14 (dd, 1H, ^2J=13.2 Hz, ^3J=6.0 Hz, H_a-C(5)), 1.59 (dd, 1H, ^3J=13.2 Hz, ^3J=8.3 Hz, H_b-C(5)), 1.12 (s, 3H, H_3C–C(6)), 1.02 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 162.6 (d, J_{C-F}=3 Hz), 160.5 (d, J_{C-F}=247 Hz), 147.3, 140.1, 139.6, 133.3 (d, J_{C-F}=9 Hz), 132.1 (d, J_{C-F}=2 Hz), 129.1, 126.8, 124.9 (d, J_{C-F}=3 Hz), 123.2, 121.0 (d, J_{C-F}=12 Hz), 116.0 (d, J_{C-F}=25 Hz), 114.6, 43.9, 42.2, 37.3, 32.6, 30.1, 26.2, 12.5; Anal. Calcd for $C_{23}H_{24}N_3O$ (377.45): C 73.19, H 6.41, N 11.13; found C 72.94, H 6.53, N 10.90.

*3.7.13. N-(6,6-Dimethyl-1-phenyl-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-4-yl)acetamide (**9p**).* Product **9p** (1.21 g, 86%) was obtained as a white solid by general procedure I for Ritter reaction using starting material **6c** (1.24 g, 4.00 mmol). Reaction time: 6 h. IR (KBr) ν (cm^{-1}): 3450, 2960, 2930, 1655, 1650, 1645, 1600, 1540, 1500, 1470, 1450, 1395, 1375, 1285, 1260, 1235, 1170, 1130, 1015; ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.45–7.52 (m, 5H, H–N(Ph)), 5.67 (d, 1H, ^3J=8.3 Hz, H–N–C(4)), 5.28 (ddd, 1H, ^3J=9.0 Hz, ^3J=8.3 Hz, ^3J=5.5 Hz, H–C(4)), 2.58, 2.42 (2d, AB syst., 2H, ^2J=16.2 Hz, H–C(7)), 2.07 (dd, 1H, ^2J=13.1 Hz, ^3J=5.5 Hz, H_a-C(5)), 2.01 (s, 3H, H–C(2′)), 1.50 (dd, 1H, ^2J=13.1 Hz, ^3J=9.0 Hz, H_b-C(5)), 1.11, 0.99 (2s, 6H, H_3C–C(6)); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 169.3, 142.1, 138.8 (q, ^2J=37 Hz), 138.5, 129.4, 128.5, 124.1, 121.5 (q, ^1J=270 Hz), 115.1, 43.7, 41.3, 36.9, 32.4, 30.2, 25.8, 23.3; ^{19}F NMR ($CDCl_3$, 470 MHz) δ (ppm): −61.6; Anal. Calcd for $C_{18}H_{20}F_3N_3O$ (351.37): C 61.53, H 5.74, N 11.96; found C 61.32, H 5.39, N 11.62.

*3.7.14. N-(6,6-Dimethyl-1-phenyl-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-4-yl)-2-phenylacetamide (**9q**).* Product **9q** (1.40 g, 82%) was obtained as a white solid by general procedure I for Ritter reaction using starting material **6c** (1.24 g, 4.00 mmol) and phenylacetonitrile (3 equiv) instead of MeCN. IR (KBr) ν (cm^{-1}): 3425, 2960, 1685, 1670, 1650, 1645, 1600, 1560, 1540, 1500, 1455, 1395, 1385, 1340, 1260, 1235, 1170, 1130, 1015; ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.49–7.46 (m, 2H, H–C(Ph)), 7.42–7.39 (m, 3H, H–C(Ph)), 7.36–7.33 (m, 2H, H–C(Ph)), 7.29–7.25 (m, 3H, H–C(Ph)), 5.49 (d, 1H, ^3J=8.3 Hz, H–N–C(4)), 5.28 (ddd, 1H, ^3J=9.0 Hz, ^3J=8.4 Hz, ^3J=5.9 Hz, H–C(4)), 3.65, 3.61 (2d, AB syst., 2H, ^2J=16.4 Hz, H–C(2′)), 2.50, 2.37 (2d, AB syst., 2H, ^2J=16.2 Hz, H–C(7)), 2.01 (dd, 1H, ^2J=13.3 Hz, ^3J=5.9 Hz, H_a-C(5)), 1.40 (dd, 1H, ^2J=13.3 Hz, ^3J=8.4 Hz, H_b-C(5)), 0.98, 0.95 (2s, 6H, H_3C–C(6)); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 170.0, 142.1, 139.8 (q, ^2J=37 Hz), 138.5, 134.5, 129.7, 129.4, 129.0, 128.5, 127.4, 124.1, 121.4 (q, ^1J=270 Hz), 114.7, 43.9, 43.6, 41.3, 36.8, 32.2, 29.8, 26.1; ^{19}F NMR ($CDCl_3$, 470 MHz) δ (ppm): −61.4; Anal. Calcd for $C_{24}H_{24}F_3N_3O$ (427.46): C 67.43, H 5.66, N 9.83; found C 67.42, H 5.49, N 9.69.

*3.7.15. N-(3,6,6-Trimethyl-1-pyridin-2-yl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-acetamide (**9r**).* Product **9r** (1.13 g, 95%) was obtained as a white solid by general procedure I for Ritter reaction using starting material **6d** (1.03 g, 4.00 mmol). IR (KBr) ν (cm^{-1}): 3307, 3279, 2952, 1659, 1639, 1595, 1563, 1557, 1486, 1471, 1445, 1378, 1090, 1042; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.39 (ddd, 1H, ^3J=4.9 Hz, ^4J=1.6 Hz, ^5J=1.0 Hz, Py–N(1)), 7.83 (ddd, 1H, ^3J=8.5 Hz, ^4J=1.0 Hz, ^5J=1.0 Hz, Py–N(1)), 7.76 (ddd, 1H, ^3J=8.5 Hz, ^3J=7.2 Hz, ^4J=1.6 Hz, Py–N(1)), 7.12 (ddd, 1H, ^3J=7.2 Hz, ^3J=4.9 Hz, ^4J=1.0 Hz, Py–N(1)), 5.64 (d, 1H, ^3J=9.2 Hz, H–N–C(4)), 5.16 (ddd, 1H, ^3J=9.2 Hz, ^3J=9.0 Hz, ^3J=6.0 Hz, H–C(4)), 2.95 (d, 1H, ^2J=17.7 Hz, H_a-C(7)), 2.87 (d, 1H, ^2J=17.7 Hz, H_b-C(7)), 2.24 (s, 3H, H–C(2′)), 2.03 (s, 3H, H_3C–C(3)), 1.89 (ddd, 1H, ^2J=13.0 Hz, ^3J=6.0 Hz, ^4J=0.9 Hz, H_a-C(5)), 1.29 (dd, 1H, ^2J=13.0 Hz, ^3J=9.0 Hz, H_b-C(5)) 1.09 (s, 3H, H_3C–C(6)), 0.95 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 169.2, 153.0, 148.2, 147.5, 141.8, 138.3, 120.6, 116.3, 114.8, 43.9, 41.3, 38.8, 32.2, 30.6, 25.8, 23.4, 12.6; Anal. Calcd for $C_{17}H_{22}N_4O$ (298.38): C 68.43, H 7.43, N 18.78; found C 68.44, H 7.49, N 18.74.

*3.7.16. N-(3,6,6-Trimethyl-1-pyridin-2-yl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-butyramide (**9s**).* Product **9s** (0.992 g, 76%) was obtained as a white solid by general procedure I for Ritter reaction using starting material **6d** (1.03 g, 4.00 mmol), H_2SO_4 (10 equiv) and butyronitrile (5 equiv) instead of MeCN. Reaction time: 8 h. IR (KBr) ν (cm^{-1}): 3232, 3063, 2957, 2927, 2871, 1639, 1584, 1557, 1486, 1470, 1443, 1382, 1366, 1216, 1058, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.39 (ddd, 1H, ^3J=4.9 Hz, ^4J=1.6 Hz, ^5J=1.0 Hz, Py–N(1)), 7.84 (ddd, 1H, ^3J=8.3 Hz, ^4J=1.0 Hz, ^5J=1.0 Hz, Py–N(1)), 7.76 (ddd, 1H, ^3J=8.3 Hz, ^3J=7.2 Hz, ^4J=1.6 Hz, Py–N(1)), 7.13 (ddd, 1H, ^3J=7.2 Hz, ^3J=4.9 Hz, ^4J=1.0 Hz, Py–N(1)), 5.67 (d, 1H, ^3J=9.0 Hz, H–N–C(4)), 5.17 (dt, 1H, ^3J=9.0 Hz, ^3J=6.0 Hz, H–C(4)), 2.93, 2.87 (2d, AB syst., 2H, ^2J=17.9 Hz, H–C(7)), 2.25 (s, 3H, H_3C–C(3)), 2.23–2.15 (m, 2H, H–C(2′)), 1.90 (dd, 1H, ^2J=13.0 Hz, ^3J=6.0 Hz, H_a-C(5)), 1.70 (sext., 2H, ^3J=7.5 Hz, H–C(3′)), 1.29 (dd, 1H, ^2J=13.0 Hz, ^3J=9.0 Hz, H_b-C(5)), 1.08 (s, 3H, H_3C–C(6)), 0.97 (t, 3H, ^3J=7.5 Hz, H–C(4′)), 0.95 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.2, 152.9, 148.2, 147.5, 141.9, 138.3, 120.7, 116.4, 114.9, 43.9, 41.1, 38.8, 38.7, 32.2, 30.5, 25.9, 19.2, 13.8, 12.6; Anal. Calcd for $C_{19}H_{26}N_4O$ (326.44): C 69.91, H 8.03, N 17.16; found C 69.89, H 8.08, N 17.24.

*3.7.17. 2-Chloro-N-(3,6,6-trimethyl-1-pyridin-2-yl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-acetamide (**9t**).* Product **9t** (1.01 g, 76%) was obtained as a white solid by general procedure II for Ritter reaction using starting material **6d** (1.03 g, 4.00 mmol). Reaction time: 11 h. IR (KBr) ν (cm^{-1}): 3246, 3073, 2951, 2899, 2870, 1604, 1583, 1564, 1557, 1538, 1482, 1446, 1430, 1382, 1371, 1252; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.39 (ddd, 1H, ^3J=4.9 Hz, ^4J=1.7 Hz, ^5J=0.9 Hz, Py–N(1)), 7.85 (ddd, 1H, ^3J=8.3 Hz, ^4J=0.9 Hz, ^5J=0.9 Hz, Py–N(1)), 7.77 (ddd, 1H, ^3J=8.3 Hz, ^3J=7.2 Hz, ^4J=1.7 Hz, Py–N(1)), 7.13 (ddd, 1H, ^3J=7.2 Hz, ^3J=4.9 Hz, ^4J=0.9 Hz, Py–N(1)), 6.63 (d, 1H, ^3J=8.9 Hz, H–N–C(4)), 5.19 (ddd, 1H, ^3J=8.9 Hz, ^3J=8.7 Hz, ^3J=6.0 Hz, H–C(4)), 4.11 (s, 2H, H–C(2′)), 3.00 (d, 1H, ^2J=17.7 Hz, H_a-C(7)), 2.93 (d, 1H, ^2J=17.7 Hz, H_b-C(7)), 2.25 (s, 3H, H_3C–C(3)), 1.97 (ddd, 1H, ^2J=13.0 Hz, ^3J=6.0 Hz, ^4J=0.8 Hz, H_a-C(5)), 1.47 (dd, 1H, ^3J=13.0 Hz, ^3J=8.7 Hz, H_b-C(5)), 1.13 (s, 3H, H_3C–C(6)), 1.00 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.1, 153.1, 148.1, 147.5, 142.0, 138.3, 120.7, 115.5, 114.8, 43.5, 42.6, 42.0, 38.8, 32.1, 30.3, 26.2, 12.6; Anal. Calcd for $C_{17}H_{21}ClN_4O$ (332.83): C 61.35, H 6.36, N 16.83; found C 61.39, H 6.33, N 16.83.

*3.7.18. 2,2,2-Trichloro-N-(3,6,6-trimethyl-1-pyridin-2-yl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-acetamide (**9u**).* Starting material **6d** (1.03 g, 4.00 mmol, 1 equiv) was added to a stirred solution of Cl_3CCN (4.00 mL, 40.0 mmol, 10 equiv) in glacial acetic acid (5 mL) and concd H_2SO_4 (1.10 mL, 20 mmol, 5 equiv). The resulting reaction mixture was stirred at 70 °C for 20 h (TLC control). The reaction mixture was cooled to 0 °C and poured into a vigorously stirred ~10% aqueous solution of NaOH (60 mL) at 0 °C. The crude product **9u** was filtered and thoroughly washed with water until the filtrate became neutral. The obtained white solid was recrystallized from a mixture of EtOH/H_2O (2:1). Yield: 1.00 g (62%). IR (KBr) ν (cm^{-1}): 3302, 2965, 2928, 2356, 2343, 1704, 1681, 1595, 1582, 1520, 1485, 1471, 1445, 1430, 1382, 1371, 1078, 1041; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.40 (br d, 1H, ^3J=4.9 Hz, Py–N(1)), 7.85

(br d, 1H, ^3J=8.3 Hz, Py–N(1)), 7.77 (ddd, 1H, ^3J=8.3 Hz, ^3J=7.3 Hz, ^4J=1.7 Hz, Py–N(1)), 7.15 (ddd, 1H, ^3J=7.3 Hz, ^3J=4.9 Hz, ^4J=0.9 Hz, Py–N(1)), 6.74 (d, 1H, ^3J=8.7 Hz, H–N–C(4)), 5.13 (ddd, 1H, ^3J=8.7 Hz, ^3J=8.3 Hz, ^3J=6.0 Hz, H–C(4)), 2.99 (s, 2H, H–C(7)), 2.29 (s, 3H, H_3C–C(3)), 2.02 (dd, 1H, ^2J=13.0 Hz, ^3J=6.0 Hz, H_a-C(5)), 1.53 (dd, 1H, ^2J=13.0 Hz, ^3J=8.3 Hz, H_b-C(5)), 1.14 (s, 3H, H_3C–C(6)), 1.02 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.1, 153.1, 148.2, 147.6, 142.2, 138.4, 120.9, 114.9, 114.8, 92.8, 44.1, 42.9, 38.7, 32.1, 30.1, 26.6, 12.7; Anal. Calcd for $C_{17}H_{19}Cl_3N_4O$ (401.72): C 50.83, H 4.77, N 13.95; found C 50.86, H 4.63, N 13.82.

*3.7.19. N-(3,6,6-Trimethyl-1-pyridin-2-yl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-acrylamide (**9v**).* Product **9v** (1.00 g, 81%) was obtained as a white solid by general procedure I for Ritter reaction using starting material **6d** (1.03 g, 4.00 mmol) and acrylonitrile (2 equiv) instead of MeCN. IR (KBr) ν (cm^{-1}): 3237, 3066, 2950, 2932, 1651, 1621, 1593, 1583, 1549, 1486, 1470, 1446, 1427, 1382, 1366, 1320, 1307, 1249, 1147, 1134, 1088, 1069, 1053, 1042, 988, 971; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.39 (ddd, 1H, ^3J=4.9 Hz, ^4J=1.7 Hz, ^5J=0.9 Hz, Py–N(1)), 7.82 (ddd, 1H, ^3J=8.3 Hz, ^4J=0.9 Hz, ^5J=0.9 Hz, Py–N(1)), 7.75 (ddd, 1H, ^3J=8.3 Hz, ^3J=7.2 Hz, ^4J=1.7 Hz, Py–N(1)), 7.12 (ddd, 1H, ^3J=7.2 Hz, ^3J=4.9 Hz, ^4J=0.9 Hz, Py–N(1)), 6.33 (dd, 1H, ^3J=17.0 Hz, ^2J=1.9 Hz, H_a-C(3′)), 6.19 (dd, 1H, ^3J=17.0 Hz, ^3J=10.0 Hz, H–C(2′)), 6.10 (d, 1H, ^3J=9.4 Hz, H–N–C(4)), 5.67 (dd, 1H, ^3J=10.0 Hz, ^2J=1.9 Hz, H_b-C(3′)), 5.18 (dt, 1H, ^3J=9.4 Hz, ^3J=6.2 Hz, H–C(4)), 2.89 (s, 2H, H–C(7)), 2.19 (s, 3H, H_3C–C(3)), 1.83 (dd, 1H, ^2J=13.0 Hz, ^3J=6.2 Hz, H_a-C(5)), 1.11 (dd, 1H, ^2J=13.0 Hz, ^3J=9.4 Hz, H_b-C(5)), 1.03 (s, 3H, H_3C–C(6)), 0.91 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.9, 153.0, 148.5, 147.6, 142.0, 138.4, 130.9, 126.6, 120.7, 116.2, 114.7, 43.5, 41.2, 38.8, 32.3, 30.6, 25.7, 12.7. Anal. Calcd for $C_{18}H_{22}N_4O$ (310.18): C 69.65, H 7.14, N 18.05; found C 69.77, H 7.15, N 18.15.

*3.7.20. N-(3,6,6-Trimethyl-1-pyridin-2-yl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-benzamide (**9w**).* Product **9w** (1.23 g, 85%) was obtained as a white solid by general procedure I for Ritter reaction using starting material **6d** (1.03 g, 4.00 mmol) and benzonitrile (2 equiv) instead of MeCN. IR (KBr) ν (cm^{-1}): 3291, 3060, 2946, 2927, 2914, 1629, 1582, 1530, 1487, 1470, 1445, 1429, 1382, 1268, 1319, 1301, 1286, 1178, 1148, 1075, 1042; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.41 (br d, 1H, ^3J=4.9 Hz, Py–N(1)), 7.85–7.82 (m, 3H, Py–N(1), H–C(Ph)), 7.75 (ddd, 1H, ^3J=8.3 Hz, ^3J=7.2 Hz, ^4J=1.7 Hz, Py–N(1)), 7.53–7.41 (m, 3H, H–C(Ar)), 7.13 (ddd, 1H, ^3J=7.2 Hz, ^3J=4.9 Hz, ^4J=1.0 Hz, Py–N(1)), 6.39 (d, 1H, ^3J=8.9 Hz, H–N–C(4)), 5.38 (ddd, 1H, ^3J=9.0 Hz, ^3J=8.9 Hz, ^3J=6.0 Hz, H–C(4)), 2.96 (s, 2H, H–C(7)), 2.24 (s, 3H, H_3C–C(3)), 1.99 (dd, 1H, ^2J=13.0 Hz, ^3J=6.0 Hz, H_a-C(5)), 1.37 (dd, 1H, ^2J=13.0 Hz, ^3J=9.0 Hz, H_b-C(5)), 1.10 (s, 3H, H_3C–C(6)), 0.99 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.7, 153.1, 148.3, 147.5, 141.9, 138.3, 134.5, 131.5, 128.6, 126.8, 120.6, 116.4, 114.8, 43.7, 41.8, 38.8, 32.2, 30.5, 26.0, 12.7; Anal. Calcd for $C_{22}H_{24}N_4O$ (360.45): C 73.31, H 6.71, N 15.54; found C 73.37, H 6.73, N 15.59.

*3.7.21. 3-Methoxy-N-(3,6,6-trimethyl-1-pyridin-2-yl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-benzamide (**9x**).* Product **9x** (1.22 g, 78%) was obtained as a white solid by general procedure I for Ritter reaction using starting material **6d** (1.03 g, 4.00 mmol) and 3-methoxy-benzonitrile (1.5 equiv) instead of MeCN. IR (KBr) ν (cm^{-1}): 3278, 2959, 2929, 2869, 2835, 1637, 1609, 1583, 1550, 1487, 1445, 1390, 1381, 1369, 1323, 1301, 1243, 1142, 1133, 1088, 1059, 1039, 989; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.39 (br d, 1H, ^3J=4.9 Hz, Py–N(1)), 7.81 (br d, 1H, ^3J=8.1 Hz, Py–N(1)), 7.72 (ddd, 1H, ^3J=8.3 Hz, ^3J=7.2 Hz, ^4J=1.7 Hz, Py–N(1)), 7.46 (dd, 1H, ^4J=2.5 Hz, ^4J=1.0 Hz, H–C(Ar)), 7.39 (dt, 1H, ^3J=7.7 Hz, ^3J=1.0 Hz, H–C(Ar)), 7.31 (t, 1H, ^3J=7.7 Hz, H–C(Ar)), 7.11 (ddd, 1H, ^3J=7.2 Hz, ^3J=4.9 Hz, ^4J=1.0 Hz, Py–N(1)), 7.03 (ddd, 1H, ^3J=7.9 Hz, ^4J=2.5 Hz, ^4J=1.0 Hz, H–C(Ar)), 6.55 (d, 1H, ^3J=9.0 Hz, H–N–C(4)), 5.33 (ddd, 1H, ^3J=9.2 Hz, ^3J=9.0 Hz, ^3J=6.0 Hz, H–C(4)), 3.84 (s, 3H, *m*-CH_3–O–C_6H_4–C(1′)), 2.93 (s, 2H, H–C(7)), 2.21 (s, 3H, H_3C–C(3)), 1.92 (dd, 1H, ^2J=13.0 Hz, ^3J=6.0 Hz, H_a-C(5)), 1.23 (dd, 1H, ^2J=13.0 Hz, ^3J=9.2 Hz, H_b-C(5)), 1.06 (s, 3H, H_3C–C(6)), 0.95 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.5, 159.9, 153.1, 148.5, 147.6, 142.0, 138.4, 136.0, 129.6, 120.6, 118.7, 117.7, 116.4, 114.7, 112.4, 55.5, 43.5, 41.8, 38.8, 32.3, 30.6, 25.9, 12.8; Anal. Calcd for $C_{23}H_{26}N_4O_3$ (390.48): C 70.75, H 6.71, N 14.35; found C 70.46, H 6.67, N 14.29.

*3.7.22. 2-Fluoro-N-(3,6,6-trimethyl-1-pyridin-2-yl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-benzamide (**9y**).* Product **9y** (1.14 g, 75%) was obtained as a white solid by general procedure I for Ritter reaction using starting material **6d** (1.03 g, 4.00 mmol) and 2-fluorobenzonitrile (2 equiv) instead of MeCN. Reaction time: 8 h. IR (KBr) ν (cm^{-1}): 3238, 2949, 1638, 1616, 1583, 1552, 1536, 1484, 1448, 1382, 1322, 1225; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.41 (br s, 1H, H–C(Ar)), 8.14 (td, 1H, J=8.0 Hz, J=1.9 Hz, H–C(Ar)), 7.89 (br d, 1H, J=7.7 Hz, H–C(Ar)), 7.78 (t, 1H, J=8.0 Hz, H–C(Ar)), 7.51–7.44 (m, 1H, H–C(Ar)), 7.30 (d, 1H, J=8.0 Hz, H–C(Ar)), 7.16–7.08 (m, 2H, H–C(Ar)), 6.78 (dd, 1H, $J_{H\text{-}F}$=12.2 Hz, ^3J=9.0 Hz, H–N–C(4)), 5.45 (ddd, 1H, ^3J=9.0 Hz, ^3J=8.7 Hz, ^3J=6.0 Hz, H–C(4)), 2.99 (s, 2H, H–C(7)), 2.29 (s, 3H, H_3C–C(3)), 2.09 (dd, 1H, ^3J=13.2 Hz, ^3J=6.0 Hz, H_a-C(5)), 1.57 (dd, 1H, ^3J=13.2 Hz, ^3J=8.7 Hz, H_b-C(5)), 1.15 (s, 3H, H_3C–C(6)), 1.05 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 162.6 (d, J_{C-F}=3 Hz), 160.5 (d, J_{C-F}=247 Hz), 153.1, 148.2, 147.5, 141.9, 138.1, 133.3 (d, J_{C-F}=9 Hz), 132.1 (d, J_{C-F}=2 Hz), 126.8, 124.9 (d, J_{C-F}=3 Hz), 121.0 (d, J_{C-F}=11 Hz), 120.6, 116.0 (d, J_{C-F}=25 Hz), 114.9, 43.5, 41.7, 38.6, 32.0, 30.1, 26.2, 12.3; Anal. Calcd for $C_{22}H_{23}N_4OF$ (378.44): C 69.82, H 6.13, N 14.80; found C 69.79, H 6.18, N 14.86.

*3.7.23. 4-Nitro-N-(3,6,6-trimethyl-1-pyridin-2-yl-4,5,6,7-tetrahydro-1H-indazol-4-yl)-benzamide (**9z**).* Product **9z** (1.20 g, 74%) was obtained as a white solid by general procedure I for Ritter reaction using starting material **6d** (1.03 g, 4.00 mmol) and 4-nitrobenzonitrile (2 equiv) instead of MeCN. IR (KBr) ν (cm^{-1}): 3216, 2956, 2926, 1633, 1598, 1583, 1529, 1484, 1447, 1390, 1382, 1368, 1346, 1321, 1047; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.42 (br d, 1H, ^3J=4.7 Hz, Py–N(1)), 8.29, 8.04 (2d, 4H, ^3J=8.7 Hz, *p*-O_2N–C_6H_4–C(1′)), 7.79 (br d, 1H, ^3J=8.3 Hz, Py–N(1)), 7.76 (ddd, 1H, ^3J=6.5 Hz, ^3J=8.3 Hz, ^4J=1.7 Hz, Py–N(1)), 7.15 (dd, 1H, ^3J=6.5 Hz, ^3J=4.7 Hz, ^4J=1.0 Hz, Py–N(1)), 6.68 (d, 1H, ^3J=9.0 Hz, H–N(4)), 5.34 (ddd, 1H, ^3J=9.4 Hz, ^3J=9.0 Hz, ^3J=6.2 Hz, H–C(4)), 2.94 (s, 2H, H–C(7)), 2.19 (s, 3H, H_3C–C(3)), 1.95 (dd, 1H, ^2J=13.0 Hz, ^3J=6.2 Hz, H_a-C(5)), 1.26 (dd, 1H, ^2J=13.0 Hz, ^3J=9.4 Hz, H_b-C(5)), 1.09 (s, 3H, H_3C–C(6)), 0.96 (s, 3H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.6, 152.9, 149.6, 148.2, 147.7, 142.2, 140.0, 138.5, 128.2, 123.9, 120.9, 115.8, 114.8, 43.5, 42.3, 38.7, 32.3, 30.6, 25.8, 12.8; Anal. Calcd for $C_{22}H_{23}N_5O_3$ (405.45): C 65.17, H 5.72, N 17.27; found C 65.10, H 5.68, N 17.23.

3.8. Synthesis of a 3:1 mixture of (±)-(4*RS*,7*RS*)-(*trans*-15) and (±)-(4*SR*,7*RS*)-*N*-(7-azido-6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-yl)-acetamide (*cis*-15)

$NaBH_4$ (0.760 g, 20.0 mmol) was added to a solution of **10** (2.81 g, 10.0 mmol) in ethanol (30 mL) and water (5 mL). The resulting reaction mixture was stirred at ambient temperature for 60 h. Then it was diluted with water (100 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. Product **12** was obtained as a 1:1 mixture of diastereoisomers and was used in the next step without purification. Yield of crude **12** (oil): 2.38 g (84%). MeCN (1.31 mL, 25 mmol, 5 equiv) was added to a solution of crude

azido alcohol **12** (1.42 g, 5.01 mmol, 1 equiv) in glacial acetic acid (5 mL) and concd H_2SO_4 (1.40 mL, 25.0 mmol, 5 equiv). The resulting reaction mixture was stirred at 65–70 °C for 8 h (TLC control). The reaction mixture was cooled to 0 °C and poured into a vigorously stirred ~10% aqueous solution of NaOH (50–60 mL) at 0 °C. The precipitate was filtered and thoroughly washed with water until the filtrate became neutral. Drying in the air provided 1.19 g (73%) of a 3:1 mixture of *trans*-**15** and *cis*-**15** as a solid material. In order to separate the diastereoisomers the mixture was crystallized from a mixture of EtOAc (30 mL) and hexanes (30 mL). The first precipitate after 2 h at ambient temperature followed by 2 h at 4 °C provided pure diastereoisomer *trans*-**15** (0.67 g). The filtrate was precipitated with hexanes and kept for 24 h at 4 °C. It gave a mixture of disasteroisomers, which was filtered (100 mg). The second filtrate was concentrated to a volume of 5 mL and kept for 12 h at 4 °C. This provided the minor diastereoisomer *cis*-**15** (50 mg). Data for (±)-(4*RS*,7*RS*)-*N*-(7-azido-6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-yl)-acetamide (*trans*-**15**): mp 210–212 °C. IR (KBr) ν (cm^{-1}): 3238, 3069, 2964, 2939, 2870, 2100, 1638, 1566, 1504, 1407, 1323; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.62 (s, 1H, H–C(3)), 7.53–7.40 (m, 5H, H–C(Ph)), 5.75 (br d, 1H, ^3J=8.1 Hz, H–N–C(4)), 5.19 (dt, 1H, ^3J=8.1 Hz, ^3J=6.0 Hz, H–C(4)), 4.21 (s, 1H, H–C(7)), 2.13 (dd, 1H, ^2J=14.1 Hz, ^3J=6.0 Hz, H_a-C(5)), 1.99 (s, 3H, H–C(2′)), 1.58 (dd, 1H, ^2J=14.1 Hz, ^3J=6.0 Hz, H_b-C(5)), 1.10, 1.08 (2s, 6H, H_3C–C(6)); ^1H NMR (300 MHz, C_6D_6) δ (ppm): 7.58 (s, 1H, H–C(3)), 7.52 (d, 2H, ^3J=8.5 Hz, H–C(Ph)), 7.13 (t, 2H, ^3J=8.5 Hz, H–C(Ph)), 7.01 (t, 1H, ^3J=8.5 Hz, H–C(Ph)), 5.23 (ddd, 1H, ^3J=7.5 Hz, ^3J=6.8 Hz, ^3J=6.0 Hz, H–C(4)), 4.59 (br d, 1H, ^3J=7.5 Hz, H–N–C(4)), 3.97 (s, 1H, H–C(7)), 1.85 (dd, 1H, ^2J=13.9 Hz, ^3J=6.0 Hz, H_a-C(5)), 1.55 (s, 3H, H–C(2′)), 1.16 (dd, 1H, ^2J=13.9 Hz, ^3J=6.8 Hz, H_b-C(5)), 0.76, 0.65 (2s, 6H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 169.4, 139.4, 138.0, 136.7, 129.4, 128.3, 124.5, 119.4, 62.9, 41.2, 40.8, 38.2, 27.4, 23.4 (2C); Anal. Calcd for $C_{17}H_{20}N_6O$ (324.38): C 62.95, H 6.21, N 25.91; found C 62.71, H 6.42, N 26.14. Data for (±)-(4*SR*,7*RS*)-*N*-(7-azido-6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-yl)-acetamide (*cis*-**15**): mp 167–168 °C. IR (KBr) ν (cm^{-1}): 3241, 3068, 2959, 2926, 2877, 2093, 1634, 1557, 1504, 1406, 1236. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.65 (br s, 1H, H–C(3)), 7.53–7.48 (m, 4H, H–C(Ph)), 7.48–7.41 (m, 1H, H–C(Ph)), 5.73 (br d, 1H, ^3J=7.9 Hz, H–N–C(4)), 5.15 (ddd, 1H, ^3J=10.7 Hz, ^3J=7.9 Hz, ^3J=6.6 Hz, H–C(4)), 4.00 (s, 1H, H–C(7)), 2.05 (s, 3H, H–C(2′)), 1.93 (dd, 1H, ^2J=13.6 Hz, ^3J=6.6 Hz, H_a-C(5)), 1.54 (dd, 1H, ^2J=13.6 Hz, ^3J=10.7 Hz, H_b-C(5)), 1.17, 1.01 (2s, 6H, H_3C–C(6)). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 169.2, 139.1, 137.8, 136.5, 129.6, 128.1, 124.1, 120.8, 60.5, 40.1, 37.8, 37.6, 26.6, 23.5, 22.6. Anal. Calcd for $C_{17}H_{20}N_6O$ (324.38): C 62.95, H 6.21, N 25.91; found C 62.66, H 6.50, N 25.99.

3.9. Synthesis of a 95:5 mixture of (±)-(4*RS*,7*RS*)-(*trans*-16) and (±)-(4*SR*,7*RS*)-*N*-(7-amino-6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-yl)-acetamide (*cis*-16)

$NaBH_4$ (0.31 g, 8.19 mmol) was added to a solution of **11** (1.02 g, 3.96 mmol) in ethanol (30 mL) and THF (10 mL). The resulting reaction mixture was stirred at ambient temperature for 72 h. Then it was evaporated under reduced pressure and the residue was partitioned between aqueous solution of K_2CO_3 (20 mL, pH 12) and EtOAc (15 mL). The aqueous phase was extracted additionally with EtOAc (2×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. Product **13** was obtained as a 1:1 mixture of diastereoisomers and was used in the next step without purification. Yield of crude **13** (oil): 0.90 g (88%). MeCN (0.91 mL, 17.5 mmol, 5 equiv) was added to a solution of crude amino alcohol **13** (0.90 g, 3.5 mmol, 1 equiv) in glacial acetic acid (4 mL) and concd H_2SO_4 (0.93 mL, 17.5 mmol, 5 equiv). The resulting reaction mixture was stirred at 60–70 °C for 6 h (TLC control). The reaction mixture was cooled to 0 °C and poured into a vigorously stirred ~10% aqueous solution of NaOH (40–50 mL) at 0 °C. The resulting suspension was adjusted to pH 12 and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. Yield of crude **16** (solid): 1.00 g (96%). The crude product revealed dr 95:5 by ^1H NMR spectroscopic analysis. The crude product was recrystallized from a mixture of EtOAc (10 mL) and DCM (15 mL). Yield of **16**: 0.92 g (88%) as a 95:5 mixture of *trans*-**16** and *cis*-**16**. Mp 207–209 °C; IR (KBr) ν (cm^{-1}): 3400, 3247, 3067, 2965, 1637, 1560, 1507, 1400, 1370, 1300. Signals of *trans*-**16** are described form the spectrum of the mixture: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.61 (d, 2H, ^3J=8.4 Hz, H–C(Ph)), 7.57 (s, 1H, H–C(3)), 7.48 (t, 2H, ^3J=8.4 Hz, H–C(Ph)), 7.39 (t, 1H, ^3J=7.4 Hz, H–C(Ph)), 5.59 (br d, 1H, ^3J=8.3 Hz, H–N–C(4)), 5.18 (ddd, 1H, ^3J=8.3 Hz, ^3J=7.0 Hz, ^3J=6.0 Hz, H–C(4)), 3.76 (s, 1H, H–C(7)), 2.11 (dd, 1H, AB syst., ^2J=13.8 Hz, ^3J=6.0 Hz, H_a-C(5)), 2.02 (s, 3H, H–C(2′)), 1.53 (dd, 1H, AB syst., ^2J=13.8 Hz, ^3J=7.0 Hz, H_b-C(5)), 1.08, 0.98 (2s, 6H, H_3C–C(6)); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 169.5, 142.3, 140.4, 137.8, 129.3, 127.7, 124.1, 118.3, 53.6, 42.0, 41.1, 36.5, 27.4, 23.3, 21.9; Anal. Calcd for $C_{17}H_{22}N_4O$ (298.38): C 68.43, H 7.43, N 18.78; found C 68.19, H 7.62, N 19.11.

3.10. 6,6-Dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-yl-ammonium toluene-4-sulfonate (17)

Method A. A solution of **9a** (1.00 g, 3.53 mmol) in EtOH (6 mL) and 36% aqueous solution of HCl (6 mL) was heated under reflux for 11 h. The reaction mixture was poured onto ice (20 g) and neutralized with a 10% aqueous solution of NaOH until pH 10. The aqueous phase was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue (0.80 g) was redissolved in EtOAc (20 mL) and mixed with a solution of *para*-toluene sulfonic acid monohydrate (0.630 g, 3.31 mmol) in EtOAc (6 mL) at ambient temperature. The resulting turbid solution was kept for 4 h at 4 °C and the precipitate was filtered and dried in the air. Yield: 0.92 g (63%).

Method B. Equivalent to Method A, but starting material **9b** was used. Final precipitation of tosylate salt for 48 h at 4 °C provides 78% yield of product **17**.

Method C. Thiourea (0.250 g, 3.28 mmol, 1.3 equiv) was added to a solution of **9b** (0.790 g, 2.49 mmol) in ethanol (20 mL). The resulting reaction mixture was heated under reflux for 23 h and then cooled to 4 °C and kept at this temperature over a weekend. The precipitated 2-amino-thiazol-4-ol (0.22 g) was filtered and discarded. The filtrate was evaporated under reduced pressure and the residue was partitioned between water (10 mL), which was adjusted to pH 10 with 10% aqueous solution of NaOH and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue (0.60 g) was redissolved in EtOAc (10 mL) and mixed with solution of *para*-toluene sulfonic acid monohydrate (0.480 g, 2.52 mmol) in EtOAc (6 mL) at ambient temperature. The resulting turbid solution was kept for 12 h at 4 °C and the white precipitate was filtered and dried in the air. Yield: 0.83 g (80%). Mp 202–204 °C; IR (KBr) ν (cm^{-1}): 3441, 3024, 2955, 2709, 2619, 1600, 1505, 1392, 1236, 1164, 1123, 1029, 1005; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.04 (s, 1H, H–C(3)), 7.67 (s, 2H, ^3J=8.3 Hz, H–C(Ar)), 7.46–7.31 (m, 5H, H–C(Ph)), 7.08 (d, 2H, ^3J=8.3 Hz, H–C(Ar)), 4.28 (dd, 1H, ^3J=10.7 Hz, ^3J=6.2 Hz, H–C(4)), 2.54, 2.27 (2 d, AB syst., 2H, ^2J=16.6 Hz, H–C(7)), 2.25 (s, 3H, H_3C–C(Ar)), 1.85 (dd, 1H, ^2J=13.2 Hz, ^3J=6.2 Hz, H_a-C(5)), 1.68 (dd, 1H, ^2J=13.2 Hz, ^3J=10.7 Hz, H_b-C(5)), 1.00, 0.72 (2s, 6H, H_3C–C(6)); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 145.5, 139.5, 139.1, 137.9,

137.8, 129.5, 128.2, 127.4, 125.5, 123.0, 114.1, 42.8, 40.6, 35.8, 32.2, 30.6, 24.3, 20.8; Anal. Calcd for $C_{22}H_{27}N_3O_3S$ (413.53): C 63.90, H 6.58, N 10.16; found C 63.73, H 6.77, N 10.01.

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Supplementary data

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References and notes

1. (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752–6756; (b) Marson, C. M. *Chem. Soc. Rev.* **2011**, *40*, 5514–5533.
2. (a) Thangadurai, A.; Minu, M.; Wakode, S.; Agrawal, S.; Narasimhan, B. *Med. Chem. Res.*, in press. (b) For a mini-review on biological activities of THI, see the introduction part in Ref. 4.
3. Grygorenko, O. O.; Radchenko, D. S.; Volochnyuk, D. M.; Tolmachev, A. A.; Komarov, I. V. *Chem. Rev.* **2011**, *111*, 5506–5568.
4. Strakova, I.; Kumpiņa, I.; Rjabovs, V.; Lugiņina, J.; Belyakov, S.; Turks, M. *Tetrahedron: Asymmetry* **2011**, *22*, 728–739.
5. (a) Guo, S.; Song, Y.; Huang, Q.; Yuan, H.; Wan, B.; Wang, Y.; He, R.; Beconi, M. G.; Franzblau, S. G.; Kozikowski, A. P. *J. Med. Chem.* **2010**, *53*, 649–659; (b) Pevarello, P.; Villa, M.; Varasi, M.; Isacchi, A. Int. Pat. Appl. WO0069846, 2000 *Chem. Abstr.* **2000**, *133*, 362767; (c) McQuaid, L. A.; Latz, J. E.; Clemens, J. A.; Fuller, R. W.; Wong, D. T.; Mason, N. R. *J. Med. Chem.* **1989**, *32*, 2388–2396; (d) Avenell, K. Y.; Boyfield, I.; Hadley, M. S.; Johnson, C. N.; Nash, D. J.; Riley, G. J.; Stemp, G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2715–2720; (e) Massaroli, G. G.; Del Corona, L.; Signorelli, G. *Boll. Chim. Farm.* **1969**, *108*, 706–722; (f) Scuri, R. *Farmaco Prat.* **1970**, *25*, 568–579.
6. Cho, H.; Iwama, Y.; Sugimoto, K.; Mori, S.; Tokuyama, H. *J. Org. Chem.* **2010**, *75*, 627–636.
7. (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045–4048; (b) Ritter, J. J.; Kalish, J. *J. Am. Chem. Soc.* **1948**, *70*, 4048–4050; (c) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213–325; (d) Gridnev, I. D.; Gridneva, N. A. *Russ. Chem. Rev.* **1995**, *64*, 1021–1034.
8. (a) Khlebnicova, T. S.; Isakova, V. G.; Lakhvich, F. A. *Doklady NAS Belarus* **2007**, *51*, 55–58; (b) Strakova, I.; Turks, M.; Strakovs, A. *Tetrahedron Lett.* **2009**, *50*, 3046–3049.
9. *N*-(3,6,6-Trimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-yl)-acetamide (**9i**) (1.16 g, 78%) was obtained upon treatment of 3,6,6-trimethyl-1-phenyl-6,7-dihydro-1*H*-indazole (**7b**) (1.19 g, 5 mmol) and MeCN (1.30 mL, 25 mmol, 5 equiv) in the mixture consisting of glacial AcOH (5 mL) and concd H_2SO_4 (1.33 mL, 25 mmol, 5 equiv) at 60 °C for 9 h.
10. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: 1999, pp 555–556; (b) Jirgensons, A.; Kauss, V.; Kalvinsh, I.; Gold, M. R. *Synthesis* **2000**, 1709–1712; (c) de Koning, P. D.; Gladwell, I. R.; Morrison, N. A.; Moses, I. B.; Panesar, M. S.; Pettman, A. J.; Thomson, N. M.; Yazbeck, D. R. *Org. Process Res. Dev.* **2011**, *15*, 871–875.
11. (a) Mondal, D.; Bellucci, L.; Lepore, S. D. *Eur. J. Org. Chem.* **2011**, 7057–7061; (b) Noort, D.; van der Marel, G. A.; Mulder, G. J.; van Boom, J. H. *Synlett* **1992**, 224–226; (c) Song, X.; Hollingsworth, R. I. *Synlett* **2006**, 3451–3454; (d) Cannon, G. W.; Grebber, K. K.; Hsu, Y.-K. *J. Org. Chem.* **1953**, *18*, 516–520.
12. (a) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W. K.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183–10194; (b) Wiberg, N.; Schmid, K. H. *Angew. Chem.* **1964**, *76*, 381; (c) Pritzkow, W.; Pohl, G. *J. Prakt. Chem.* **1963**, *20*, 132–141.
13. Crystallographic data of *trans*-**15** have been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication CCDC-855820.
14. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512–7515.
15. Strakova, I.; Gudriniece, E.; Linabergs, J. *Latv. PSR Zin. Akad. Vestis, Kim. Ser.* **1969**, 574–578; *Chem. Abstr.* **1970**, *73*, 77133k.