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On the reaction of some 5-polyfluoroaryl-1,2,4-oxadiazoles with methylhydrazine: synthesis of fluorinated indazoles

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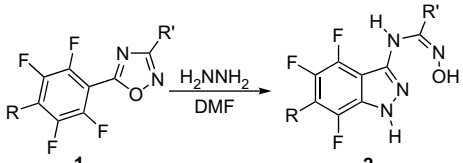
ABSTRACT

The reaction of 5-polyfluoroaryl-1,2,4-oxadiazoles with methylhydrazine has been studied and the synthesis of fluorinated *N*-methylindazoles has been realized. Rearrangement reactions showed predominantly formation of *N*(1)-methylindazole regioisomers. Starting compounds were preliminarily functionalized at the polyfluoroaryl moiety through fluorine displacement with nucleophiles (methanol, methylamine, dimethylamine), allowing the obtainment of target indazoles substituted at the C(6) position.

1. Introduction

The indazole nucleus is a pharmaceutically important and emerging heterocycle with a broad spectrum of activities, including antiinflammatory,[1] antitumor,[2] anti-HIV,[3] antimicrobial,[4] contraceptive,[5] and have also been used as nNOS inhibitors.[6] Particularly, 3-aminoindazole derivatives show potent dopamine receptor antagonist activity, useful for antipsychotic treatment,[7] and are reported as non-steroidal antiinflammatory compounds with analgesic properties.[7,8] In this context, fluorinated 3-aminoindazoles have been identified as lead compounds for the treatment of psychiatric disorders such as obsessive compulsive disorder and attention deficit disorder,[9] and are also reported as protein kinase inhibitors, especially of Aurora-2 and GSK-3, useful for the treatment of diseases associated with protein kinases, such as diabetes, cancer, and Alzheimer's disease.[10] Due to their pharmaceutical importance, the synthesis of fluorinated 3-aminoindazoles represents an interesting research field, so far limited to few examples, mostly regarding monofluorinated derivatives.

In the frame of our research on heterocycles reactivity, we have recently reported some *ANRORC-like* (*A*ddition of *N*ucleophile, *R*ing-*O*pening, *R*ing-*C*losure) rearrangements of 5-perfluoroalkyl-1,2,4-oxadiazoles as a valid approach for the obtainment of target fluorinated compounds such as 1,2,4-triazole, 1,2,4-oxadiazole, and 1,2,4-triazine.[11] Moreover, *ANRORC* rearrangement of 5-tetrafluoroaryl-1,2,4-oxadiazoles **1**, with hydrazine, leads easily to 3-amino-4,5,7-trifluoroindazoles **2** with various substituents linked to C(6) (Scheme 1).[12]



Scheme 1.

In this work we report the results concerning the reactivity of 5-polyfluoroaryl-1,2,4-oxadiazoles **3a–d** (Chart 1) with methylhydrazine, in order to evaluate the regiochemistry of the reaction with an unsymmetrical bidentate nucleophile and to generalize the ANRORC approach for the synthesis of mono-, di-, and trifluoro-3-aminoindazole derivatives.

2. Results and discussion

1,2,4-Oxadiazoles **3a–d** were obtained through the conventional amidoxime route (see Section 4).[13] In order to prevent the formation of byproducts during the rearrangements,[12] substrates bearing a fluorine atom on the 4′-position of the fluoroaryl moiety have been preliminarily reacted with oxygen or nitrogen nucleophiles (ZH in Scheme 2) such as methanol, methylmine, and

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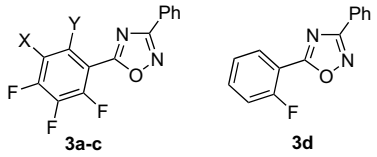
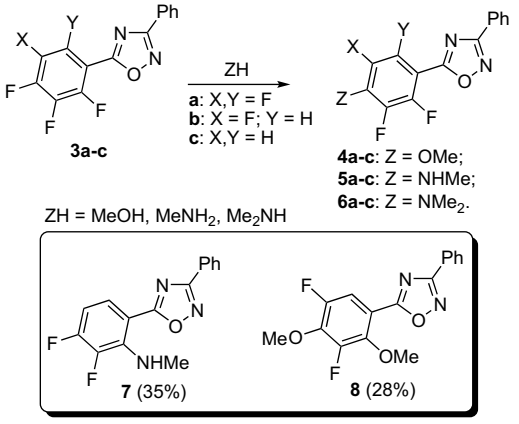


a: X = Y = F
b: X = F; Y = H
c: X = Y = H

Chart 1.

dimethylamine, under mild conditions, yielding the corresponding 4′-substituted derivatives **4**–**6** (Scheme 2). The reactions occur through an S_NAr mechanism and represent an easy and straightforward strategy to introduce different functionalities in the target indazoles. The observed substitution at the 4′-position is in agreement with previously reported S_NAr reactions on 5-pentafluorophenyl-1,2,4-oxadiazoles.[12,14] The reaction is favored by the electron-withdrawing ability of the oxadiazole ring, which activates both the *ortho* and *para* positions, the latter being preferred as the less hindered site.[12,14] On the other hand, in the case of oxadiazole **3c**, when methylamine was employed as nucleophile, preferential formation of 2′-subtituted isomer **7**, despite 4′-regioisomer **5c**, was observed (**7**/**5c** ratio 35:33); moreover, in the case of oxadiazole **3b**, with methoxide anion, subsequent attack occurs at the 2′-position, leading to the disubstituted derivative **8** (inset in Scheme 2). These results show, for the first time, the reactivity of the 2′-positions of 5-polyfluoro-1,2,4-oxadiazoles toward nucleophiles.

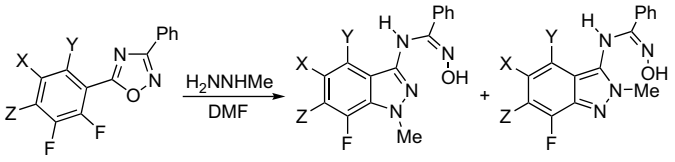


Scheme 2.

1,2,4-Oxadiazoles **4**–**6** were reacted with an excess of methylhydrazine in DMF at rt. Under these conditions, a mixture of fluorinated *N*-methylindazole regioisomers **9**–**14** was obtained (Scheme 3; Table 1). The mixtures were chromatographically resolved with the *N*(1)-methyl isomers eluting first. The regioisomers were identified, by means of ^{1}H NMR: the chemical shift of *N*-methyl singlet is deshielded in the case of *N*(2)-methyl isomer with respect to the *N*(1)-methyl one.[15] Moreover, the *H*(4) signal of *N*(1)-methyl regioisomers **11** and **13** is deshielded with respect to the *H*(4) signal of *N*(2)-methyl isomers **12** and **14** (see Section 4).[14]

In all the cases preferential formation of *N*(1)-methyl isomer was observed, and in the case of monofluorinated compound **3d**, *N*(1)-methyl isomer **15** was obtained in very high yield (95%) (Scheme 4).

In order to unequivocally confirm the proposed structure of the obtained *N*-methylindazole isomers, representative *N*-indazol-3-yl-amidoximes **9a** and **10a** were hydrolyzed to the corresponding *N*-methyl-3-aminoindazoles **16** and **21**, which were



4-6 a-c
a: X,Y = F;
b: X = F; Y = H;
c: X,Y = H.

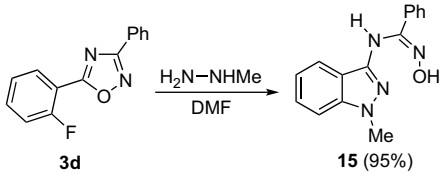
9a-c: Z = OMe;
11a-c: Z = NHMe;
13a-c: Z = NMe_2.

10a,c: Z = OMe;
12a,b: Z = NHMe;
14a-c: Z = NMe_2.

Scheme 3.

Table 1
Products distribution for reactions of compounds **4**–**6** with methylhydrazine

Substrate (% recovered)	X	Y	Z	*N*(1)-Methyl (% yield)	*N*(2)-Methyl (% yield)
4a (None)	F	F	OMe	**9a** (68)	**10a** (16)
4b (41)	F	H	OMe	**9b** (34)	—
4c (None)	H	H	OMe	**9c** (77)	**10c** (4)
5a (5)	F	F	NHMe	**11a** (60)	**12a** (10)
5b (30)	F	H	NHMe	**11b** (60)	**12b** (5)
5c (52)	H	H	NHMe	**11c** (37)	—
6a (4)	F	F	$N(Me)_2$	**13a** (68)	**14a** (17)
6b (16)	F	H	$N(Me)_2$	**13b** (50)	**14b** (13)
6c (26)	H	H	$N(Me)_2$	**13c** (39)	**14c** (20)



Scheme 4.

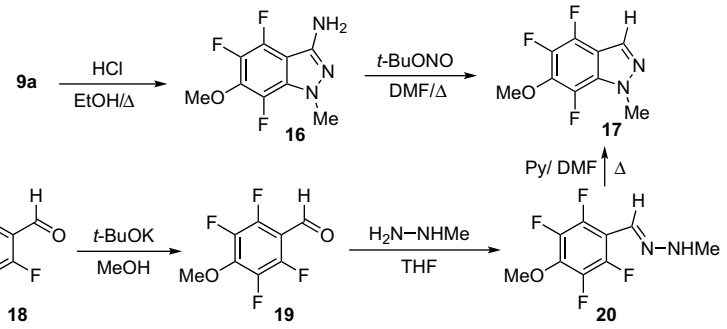
then deaminated with *t*-BuONO in DMF[16] to *N*-methylindazoles **17** and **22**, respectively. The latter derivatives were compared with those obtained from two regiocomplementary synthesis (Schemes 5 and 6).

N(1)-Methyl isomer **17** was also obtained, adapting a previously reported method,[17] through condensation reaction of 4-methoxy-tetrafluorobenzaldehyde **19** with methylhydrazine followed by base promoted cyclization of methylhydrazone **20** (Scheme 5).

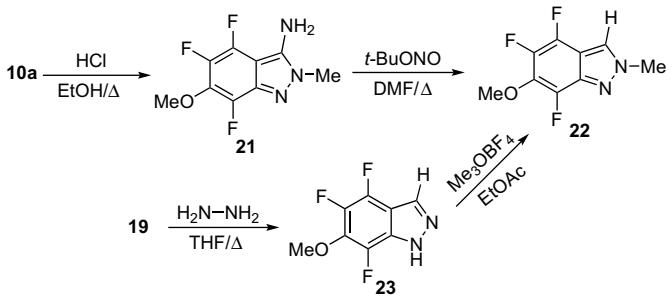
In turn, an authentic sample of *N*(2)-methyl regioisomer **22** was obtained by means of regioselective methylation of the parent indazole **23**, arising from **19**, with Me_3OBF_4 (Scheme 6).[18]

The reported results can be rationalized on the basis of two different pathways, which consider the initial nucleophilic attack occurring at either the C(5) of the oxadiazole ring (*path a*) or at the fluorine substituted 2′-position of the aryl moiety (*path b*) (Scheme 7).

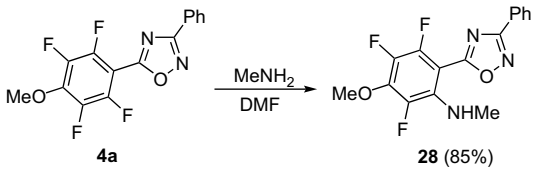
Path a is a classic *ANRORC*-like rearrangement involving the preferential attack of the less hindered unsubstituted nitrogen of the nucleophile[11d] at the C(5) of the azole ring, giving **24**, followed by oxadiazole ring-opening into **25** and final cyclization into *N*(1)-methylindazole regioisomers with nucleophilic displacement of an *o*-fluorine from the fluoroaryl moiety.[12] *Path b* considers at first nucleophilic displacement of an *o*-fluorine, in the fluoroaryl moiety, by either the NHMe end (*path b-1*) or the NH_2 (*path b-2*) end of the methylhydrazine nucleophile. Then, a nucleophilic attack of the β nitrogen of the arylhydrazine intermediate **26** on the C(5) of the oxadiazole ring leads to the formation of spiro-intermediate **27**,



Scheme 5.



Scheme 6.



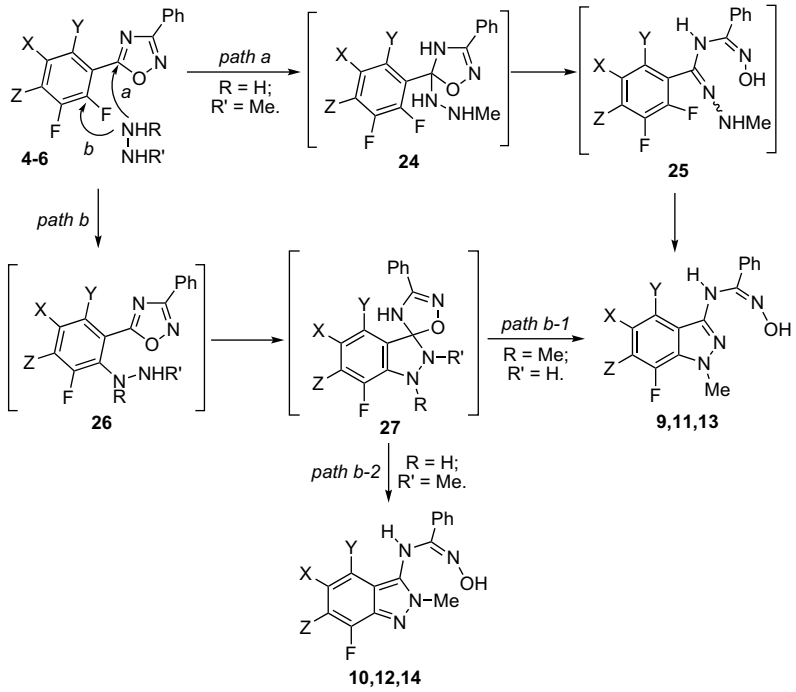
Scheme 8.

which, after ring-opening of the oxadiazolidine moiety, produces final *N*-methylindazole isomers.

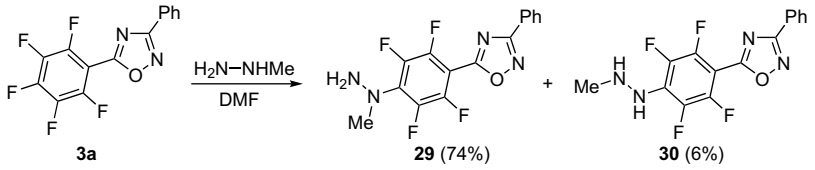
In order to asses the most electrophilic site between C(5) of oxadiazole ring and 2′-position of fluoroaryl moiety (and so the preferred reaction *path*), representative oxadiazole **4a** was reacted with methylamine in DMF at rt (Scheme 8).

2′-Substituted oxadiazole **28** was obtained in high yield from nucleophilic displacement of a 2′-fluorine, while products arising from a nucleophilic attack at the oxadiazole C(5) were not obtained. Moreover, the competition between the two different nucleophilic sites of methylhydrazine was evaluated from reaction with 1,2,4-oxadiazole **3a** in DMF with 1 equiv of nucleophile. The observed distribution of the obtained 4′-substituted methylhydrazino-regioisomers **29** and **30** confirms the preferential attack of the NHMe moiety of methylhydrazine nucleophile under the reaction conditions used (Scheme 9).

All these data suggest the preference for *path b* on rearrangement reactions (see Scheme 7) with a regioselectivity that should be affected from the balance between electrophilic character at 2′-position of the fluoroaryl moiety and accessibility of the electrophilic site.



Scheme 7.



Scheme 9.

3. Conclusions

The synthesis of fluorinated *N*-methylindazoles has been performed with a simple rearrangement of 1,2,4-oxadiazoles, with preference for *N*(1) isomer. This reactivity is not limited to highly fluorinated derivatives and has been extended to the obtainment also of 7-fluoro- and 5,7-difluoro-indazoles as well as to the synthesis of unfluorinated compound **15**. The proposed strategy represents a valid approach for the synthesis of various polysubstituted indazoles of pharmacological interest, because it allows selective introduction of fluorine atoms and preliminary functionalization of C(6) of target molecules.

4. Experimental

4.1. General methods and materials

Melting points were determined on a Reichart-Thermovar hot-stage apparatus and are uncorrected. IR spectra (Nujol) were determined with a Shimadzu FTIR-8300 instrument; ^{1}H NMR and ^{19}F NMR spectra were recorded on a BRUKER 300 Avance spectrometer with TMS or $CFCl_3$, respectively, as an internal standard. GC–MS determinations were carried out on a VARIAN STAR 3400 CX/SATURN 2000 system. Flash chromatography was performed by using silica gel (Merck, 0.040–0.063 mm) and mixtures of ethyl acetate and petroleum ether (fraction boiling in the range of 40–60 °C) in various ratios. Compounds **3a**–**c**[13] (obtained in 78%, 80%, and 73% yields, respectively) and **4a**, **5a**, **6a**[12] were obtained as previously reported.

4.2. Synthesis of 5-(2-fluorophenyl)-3-phenyl-1,2,4-oxadiazole 3d

A mixture of benzamidoxime (1.0 g, 7.35 mmol), pyridine (0.059 mL, 8 mmol), and 2-fluorobenzoylchloride (8 mmol) in anhydrous toluene (100 mL) was heated to reflux for 4 h. After removal of the solvent, the residue was chromatographed (ethyl acetate/petroleum ether 1:20) giving oxadiazole **3d** (68%): *5-(2-fluorophenyl)-3-phenyl-1,2,4-oxadiazole* **3d**. Mp 94–95 °C (petroleum ether); R_f=0.70 (silica gel, ethyl acetate/petroleum ether 1:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.38 (m, 2H, ArH, overlapped signals), 7.52–7.61 (m, 4H, ArH, overlapped signals), 8.18–8.24 (m, 3H, ArH, overlapped signals); ^{19}F NMR (282 MHz, $CDCl_3$) δ −111.38 (s, 1F); FTIR (Nujol) 1617 cm^{-1}. GC–MS (*m*/*z*): 240 (M^+, 100%). Anal. Calcd for $C_{14}H_9FN_2O$: C, 69.99; H, 3.78; N, 11.66. Found: C, 69.90; H, 3.90; N, 11.50.

4.3. Reaction of oxadiazoles 3b,c with methanol. General procedure

Oxadiazole **3** (1 mmol) was dissolved in a solution of *t*-BuOK (1.2 mmol) in dry MeOH (20 mL). After stirring for 24 h at rt, the solvent was evaporated, the residue treated with water (100 mL), filtered, and crystallized from an appropriate solvent, or chromatographed giving **4b** and **4c**.

4.3.1. Reaction of *3b* with methanol

Chromatography of the residue gave **4b** (57%, from ethyl acetate/petroleum ether 1:50), and **8** (28%, from ethyl acetate/petroleum ether 1:20).

*4.3.1.1. 5-(2,3,5-Trifluoro-4-methoxy-phenyl)-3-phenyl-1,2,4-oxadiazole **4b**.* Mp 80–82 °C (petroleum ether); R_f=0.60 (silica gel, ethyl acetate/petroleum ether 1:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (s, 3H, O*CH*$_3$), 7.49–7.56 (m, 3H, ArH), 7.73–7.81 (m, 1H, *H*(6)), 8.15–8.19 (m, 2H, ArH); ^{19}F NMR (282 MHz, $CDCl_3$) δ −134.78 (m, 1F), −136.23 (m, 1F), −152.46 (m, 1F); FTIR (Nujol) 1636 cm^{-1}. GC–MS (*m*/*z*): 306 (M^+, 100%). Anal. Calcd for $C_{15}H_9F_3N_2O_2$: C, 58.83; H, 2.96; N, 9.15. Found: C, 59.00; H, 2.90; N, 9.20.

*4.3.1.2. 5-(3,5-Difluoro-2,4-dimethoxy-phenyl)-3-phenyl-1,2,4-oxadiazole **8**.* Mp 115–117 °C (petroleum ether); R_f=0.45 (silica gel, ethyl acetate/petroleum ether 1:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (s, 3H, *p*-O*CH*$_3$), 4.16 (s, 3H, *o*-O*CH*$_3$), 7.51–7.54 (m, 3H, ArH), 7.73 (dd, 1H, J_1=2.8 Hz, J_2=13.4 Hz, H(6)), 8.15–8.19 (m, 2H, ArH); ^{19}F NMR (282 MHz, $CDCl_3$) δ −135.53 (d, 1F, *J*=5.6 Hz), −146.52 (br s, 1F); FTIR (Nujol) 1596 cm^{-1}. GC–MS (*m*/*z*): 318 (M^+, 100%). Anal. Calcd for $C_{16}H_{12}F_2N_2O_3$: C, 60.38; H, 3.80; N, 8.80. Found: C, 60.40; H, 3.70; N, 8.60.

4.3.2. Reaction of *3c* with methanol

*4.3.2.1. 5-(2,3-Difluoro-4-methoxy-phenyl)-3-phenyl-1,2,4-oxadiazole **4c**.* Yield: 59%. Mp 135–138 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (s, 3H, O*CH*$_3$), 6.93 (ddd, 1H, J_1=1.8 Hz, J_2=7.2 Hz, J_3=9.0 Hz, *H*(5)), 7.50–7.55 (m, 3H, ArH), 7.96 (ddd, 1H, J_1=2.1 Hz, J_2=7.2 Hz, J_3=9.0 Hz, *H*(6)), 8.16–8.19 (m, 2H, ArH); ^{19}F NMR (282 MHz, $CDCl_3$) δ −135.73 (d, 1F, *J*=16.9 Hz), −161.03 (d, 1F, *J*=16.9 Hz); FTIR (Nujol) 1624 cm^{-1}. GC–MS (*m*/*z*): 288 (M^+, 100%). Anal. Calcd for $C_{15}H_{10}F_2N_2O_2$: C, 62.50; H, 3.50; N, 9.72. Found: C, 62.60; H, 3.40; N, 9.80.

4.4. Reaction of oxadiazoles 3b,c with amines in DMF. General procedure

To a mixture of oxadiazoles **3b**,**c** (1 mmol) in dry DMF (2 mL), the appropriate amine (1.1 mmol) was slowly added. After stirring for 3 h at rt, the mixture was diluted with water (50 mL) and the formed precipitate filtered and crystallized from an appropriate solvent, or chromatographed giving desired compounds **5b**,**c** and **6b**,**c**.

4.4.1. Reaction of *3b* with methylamine

4.4.1.1. 5-[2,3,5-Trifluoro-4-(N-methylamino)-phenyl]-3-phenyl-1,2,4-oxadiazole 5b. Yield: 93%. Mp 146–149 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.10 (s, 3H, NH*CH*$_3$), 6.76 (s, 1H, N*H*CH$_3$, exch. with D_2O), 7.64–7.72 (m, 4H, ArH, overlapped signals), 8.08–8.12 (m, 2H, ArH); ^{19}F NMR (282 MHz, $CDCl_3$) δ −138.60 (d, 1F, *J*=16.9 Hz), −140.53 (m, 1F), −158.79 (m, 1F); FTIR (Nujol) 3392, 1635 cm^{-1}. GC–MS (*m*/*z*): 305 (M^+, 100%). Anal. Calcd for $C_{15}H_{10}F_3N_3O$: C, 59.02; H, 3.30; N, 13.77. Found: C, 59.10; H, 3.40; N, 13.70.

*4.4.2. Reaction of **3c** with methylamine*

Chromatography of the residue gave **7** (35%, from ethyl acetate/petroleum ether 1:50), recovered **3c** (25%, from ethyl acetate/petroleum ether 1:20), and **5c** (33%, from ethyl acetate/petroleum ether 1:5).

*4.4.2.1. 5-[2,3-Difluoro-4-(N-methylamino)-phenyl]-3-phenyl-1,2,4-oxadiazole **5c**.* Mp 165–166 °C (EtOH); R_f=0.35 (silica gel, ethyl acetate/petroleum ether 1:5); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.91 (d, 3H, J=5.0 Hz, NHCH_3), 6.74–6.80 (m, 1H, H(5)), 7.05 (br q, 1H, NHCH$_3$, exch. with D_2O, J=5.0 Hz), 7.63–7.68 (m, 3H, ArH), 7.86–7.91 (m, 1H, H(6)), 8.11–8.14 (m, 2H, ArH); ^{19}F NMR (282 MHz, $CDCl_3$) δ −137.07 (m, 1F), −165.81 (m, 1F); FTIR (Nujol) 3363, 1685, 1635 cm^{-1}. GC–MS m/z 287 (M^+, 100%). Anal. Calcd for $C_{15}H_{11}F_2N_3O$: C, 62.72; H, 3.86; N, 14.63. Found: C, 62.70; H, 3.90; N, 14.50.

*4.4.2.2. 5-[3,4-Difluoro-2-(N-methylamino)-phenyl]-3-phenyl-1,2,4-oxadiazole **7**.* Mp 136–139 °C (EtOH); R_f=0.55 (silica gel, ethyl acetate/petroleum ether 1:50); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.29–3.33 (m, 3H, NHCH_3), 6.87 (ddd, 1H, J_1=7.0 Hz, J_2=9.0 Hz, J_3=10.0 Hz, H(5)), 7.63–7.71 (m, 3H, ArH), 7.77 (br s, 1H, NHCH$_3$, exch. with D_2O), 7.86 (ddd, 1H, J_1=2.0 Hz, J_2=6.0 Hz, J_3=9.0 Hz, H(6)), 8.22–8.25 (m, 2H, ArH); ^{19}F NMR (282 MHz, $CDCl_3$) δ −132.89 (m, 1F), −160.46 (m, 1F); FTIR (Nujol) 3320, 1631 cm^{-1}. GC–MS (m/z): 287 (M^+, 100%). Anal. Calcd for $C_{15}H_{11}F_2N_3O$: C, 62.72; H, 3.86; N, 14.63. Found: C, 62.60; H, 3.80; N, 14.70.

*4.4.3. Reaction of **3b** with dimethylamine*

*4.4.3.1. 5-[2,3,5-Trifluoro-4-(N,N-dimethylamino)-phenyl]-3-phenyl-1,2,4-oxadiazole **6b**.* Yield: 80%. Mp 119–121 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88 (t, 6H, J=3.4 Hz, N(CH_3)$_2$), 7.29–7.35 (m, 3H, ArH), 7.42 (ddd, 1H, J_1=2.7 Hz, J_2=7.6 Hz, J_3=15.4 Hz, H(6)), 7.94–7.98 (m, 2H, ArH); ^{19}F NMR (282 MHz, $CDCl_3$) δ −128.05 (m, 1F), −140.02 (m, 1F), −148.31 (m, 1F); FTIR (Nujol) 1630 cm^{-1}. GC–MS (m/z): 319 (M^+, 100%). Anal. Calcd for $C_{16}H_{12}F_3N_3O$: C, 60.19; H, 3.79; N, 13.16. Found: C, 60.10; H, 3.90; N, 13.30.

*4.4.4. Reaction of **3c** with dimethylamine*

*4.4.4.1. 5-[2,3-Difluoro-4-(N,N-dimethylamino)-phenyl]-3-phenyl-1,2,4-oxadiazole **6c**.* Yield: 73%. Mp 121–122 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 6H, N(CH_3)$_2$), 6.64 (ddd, 1H, J_1=1.8 Hz, J_2=8.1 Hz, J_3=9.3 Hz, H(5)), 7.49–7.54 (m, 3H, ArH), 7.80 (ddd, 1H, J_1=2.1 Hz, J_2=7.5 Hz, J_3=9.3 Hz, H(6)), 8.15–8.19 (m, 2H, ArH); ^{19}F NMR (282 MHz, $CDCl_3$) δ −137.31 (m, 1F), −154.08 (m, 1F); FTIR (Nujol) 1627 cm^{-1}. GC–MS (m/z): 301 (M^+, 100%). Anal. Calcd for $C_{16}H_{13}F_2N_3O$: C, 63.78; H, 4.35; N, 13.95. Found: C, 63.80; H, 4.50; N, 13.90.

4.5. Reaction of 1,2,4-oxadiazoles 4–6 with methylhydrazine in DMF. General procedure

To a mixture of oxadiazoles **3d**, **4**–**6** (1 mmol) in dry DMF (2 mL), a large excess of methylhydrazine (3 mL; 0.3 mL in the case of derivatives **4a**, **5a**, and **6a**) was slowly added. After stirring for 24 h at rt (3 h in the case of derivatives **4a**, **5a** and **6a**), the mixture was diluted with 1 M HCl (50 mL) and the formed precipitate extracted with EtOAc (200 mL). The organic layer was dried over Na_2SO_4 and evaporated. Chromatography of the residue gave *N*-methylindazolyl-*N*′-hydroxy-benzamidines **9**–**15**.

*4.5.1. Reaction of oxadiazole **3d** with methylhydrazine in DMF*

Chromatography of the residue gave **15** (95%, from ethyl acetate/petroleum ether 1:1).

*4.5.1.1. (Z)-N-(1-Methyl-1H-indazol-3-yl)-N′-hydroxy-benzamidine **15**.* Yield: 95%. Mp 224–225 °C (EtOH); R_f=0.55 (silica gel, ethyl acetate/petroleum ether 1:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.79 (s, 3H, N(1)CH_3), 7.05 (ddd, 1H, J_1=1.0 Hz, J_2=6.6 Hz, J_3=6.9 Hz, H(5)), 7.24–7.29 (m, 3H, ArH), 7.32–7.41 (m, 3H, ArH, overlapped signals), 7.48 (d, 1H, J=8.4 Hz, H(7)); 7.67 (d, 1H, J=6.6 Hz, H(4)), 8.42 (s, 1H, NH, exch. with D_2O), 10.54 (s, 1H, OH, exch. with D_2O); FTIR (Nujol) 3331, 3145, 1630, 1617 cm^{-1}. GC–MS (m/z): 266 (M^+, 2%), 250 (M^+−16, 71%), 104 (100%). Anal. Calcd for $C_{14}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.50; H, 5.50; N, 21.00.

*4.5.2. Reaction of oxadiazole **4a** with methylhydrazine in DMF*

Chromatography of the residue gave **9a** (68%, from ethyl acetate/petroleum ether 1:5) and **10a** (16%, from ethyl acetate/petroleum ether 1:2).

*4.5.2.1. (Z)-N-(4,5,7-Trifluoro-6-methoxy-1-methyl-1H-indazol-3-yl)-N′-hydroxy-benzamidine **9a**.* Mp 169–172 °C (EtOH); R_f=0.45 (silica gel, ethyl acetate/petroleum ether 1:5); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.91 (s, 3H, OCH_3), 4.05 (s, 3H, N(1)CH_3), 7.24–7.31 (m, 3H, ArH), 7.33–7.41 (m, 2H, ArH), 8.43 (s, 1H, NH, exch. with D_2O), 10.53 (s, 1H, OH, exch. with D_2O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −154.84 (t, 1F, J=19.7 Hz), −161.56 (d, 1F, J=20.1 Hz), −165.39 (d, 1F, J=19.5 Hz); FTIR (Nujol) 3328, 3202, 1628 cm^{-1}. GC–MS (m/z): 350 (M^+, 4%), 334 (M^+−16, 43%), 104 (100%). Anal. Calcd for $C_{16}H_{13}F_3N_4O_2$: C, 54.86; H, 3.74; N, 15.99. Found: C, 54.90; H, 3.70; N, 16.10.

*4.5.2.2. (Z)-N-(4,5,7-Trifluoro-6-methoxy-2-methyl-2H-indazol-3-yl)-N′-hydroxy-benzamidine **10a**.* Mp 180–183 °C (EtOH); R_f=0.25 (silica gel, ethyl acetate/petroleum ether 1:2); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.98 (s, 3H, OCH_3), 4.09 (s, 3H, N(2)CH_3), 7.29–7.34 (m, 5H, ArH, overlapped signals), 8.83 (s, 1H, NH, exch. with D_2O), 10.64 (s, 1H, OH, exch. with D_2O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −155.36 (t, 1F, J=19.6 Hz), −156.89 (d, 1F, J=20.3 Hz), −162.83 (d, 1F, J=19.2 Hz); FTIR (Nujol) 3318, 1670, 1632 cm^{-1}. GC–MS (m/z): 350 (M^+, 2%), 334 (M^+−16, 36%), 104 (100%). Anal. Calcd for $C_{16}H_{13}F_3N_4O_2$: C, 54.86; H, 3.74; N, 15.99. Found: C, 54.70; H, 3.70; N, 16.00.

*4.5.3. Reaction of oxadiazole **4b** with methylhydrazine in DMF*

Chromatography of the residue gave recovered **4b** (41%, from ethyl acetate/petroleum ether 1:20) and **9b** (34%, from ethyl acetate/petroleum ether 1:5).

*4.5.3.1. (Z)-N-(5,7-Difluoro-6-methoxy-1-methyl-1H-indazol-3-yl)-N′-hydroxy-benzamidine **9b**.* Mp 163–166 °C (EtOH); R_f=0.43 (silica gel, ethyl acetate/petroleum ether 1:5); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.83 (s, 3H, OCH_3), 4.01 (s, 3H, N(1)CH_3), 7.25–7.32 (m, 3H, ArH), 7.36–7.39 (m, 2H, ArH), 7.46 (d, 1H, J=11.4 Hz, H(4)), 8.61 (s, 1H, NH, exch. with D_2O), 10.64 (s, 1H, OH, exch. with D_2O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −137.66 (m, 1F), −154.92 (br s, 1F); FTIR (Nujol) 3332, 1629 cm^{-1}. GC–MS (m/z): 332 (M^+, 2%), 316 (M^+−16, 46%), 104 (100%). Anal. Calcd for $C_{16}H_{14}F_2N_4O_2$: C, 57.83; H, 4.25; N, 16.86. Found: C, 57.90; H, 4.30; N, 16.70.

*4.5.4. Reaction of oxadiazole **4c** with methylhydrazine in DMF*

Chromatography of the residue gave **9c** (77%, from ethyl acetate/petroleum ether 1:5) and **10c** (4%, from ethyl acetate/petroleum ether 1:2).

*4.5.4.1. (Z)-N-(7-Fluoro-6-methoxy-1-methyl-1H-indazol-3-yl)-N′-hydroxy-benzamidine **9c**.* Mp 158–161 °C (EtOH); R_f=0.40 (silica gel, ethyl acetate/petroleum ether 1:5); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 (s, 3H, OCH_3), 3.94 (s, 3H, N(1)CH_3), 7.01 (dd, 1H, J_1=6.9 Hz, J_2=8.7 Hz, H(5)), 7.25–7.32 (m, 3H, ArH), 7.37–7.40 (m, 2H, ArH), 7.46

(d, 1H, J=8.7 Hz, H(4)), 8.51 (s, 1H, NH, exch. with D_2O), 10.59 (s, 1H, OH, exch. with D_2O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −164.44 (m, 1F); FTIR (Nujol) 3338, 1674, 1647 cm^{-1}. GC–MS (m/z): 314 (M^+, 1%), 298 (M^+−16, 38%), 104 (100%). Anal. Calcd for $C_{17}H_{15}FN_4O$: C, 61.14; H, 4.81; N, 17.83. Found: C, 61.10; H, 4.80; N, 17.90.

4.5.4.2. (Z)-N-(7-Fluoro-6-methoxy-2-methyl-2H-indazol-3-yl)-N′-hydroxy-benzamidine ***10c***. Mp 184–185 °C (EtOH); R_f=0.35 (silica gel, ethyl acetate/petroleum ether 1:2); ^1H NMR (300 MHz, DMSO-d_6) δ 3.86 (s, 3H, OCH_3), 4.03 (s, 3H, N(2)CH_3), 6.84 (dd, 1H, J_1=6.9 Hz, J_2=9.0 Hz, H(5)), 7.03 (d, 1H, J=9.0 Hz, H(4)), 7.23–7.29 (m, 3H, ArH), 7.36–7.39 (m, 2H, ArH), 8.75 (s, 1H, NH, exch. with D_2O), 10.71 (s, 1H, OH, exch. with D_2O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −163.38 (m, 1F); FTIR (Nujol) 3350, 3095, 1635 cm^{-1}. GC–MS (m/z): 314 (M^+, 1%), 298 (M^+−16, 52%), 104 (100%). Anal. Calcd for $C_{16}H_{15}FN_4O_2$: C, 61.14; H, 4.81; N, 17.83. Found: C, 61.30; H, 4.70; N, 17.90.

4.5.5. Reaction of oxadiazole ***5a*** *with methylhydrazine in DMF*

Chromatography of the residue gave recovered **5a** (5%, from ethyl acetate/petroleum ether 1:20), **11a** (60%, from ethyl acetate/petroleum ether 1:5), and **12a** (10%, from ethyl acetate/petroleum ether 1:2).

4.5.5.1. (Z)-N-[4,5,7-Trifluoro-6-(N-methylamino)-1-methyl-1H-indazol-3-yl]-N′-hydroxy-benzamidine ***11a***. Mp 208 °C dec (EtOH); R_f=0.35 (silica gel, ethyl acetate/petroleum ether 1:5); ^1H NMR (300 MHz, DMSO-d_6) δ 3.00 (s, 3H, NHCH_3), 3.84 (s, 3H, N(1)CH_3), 5.70 (s, 1H, NHCH$_3$, exch. with D_2O), 7.23–7.32 (m, 3H, ArH), 7.38–7.40 (m, 2H, ArH), 8.24 (s, 1H, NH, exch. with D_2O), 10.49 (s, 1H, OH, exch. with D_2O); ^{19}F NMR (DMSO-d_6) δ −153.20 (t, 1F, J=19.8 Hz), −160.27 (d, 1F, J=20.1 Hz), −163.58 (d, 1F, J=17.0 Hz); FTIR (Nujol) 3370, 3340, 1672, 1623 cm^{-1}. GC–MS (m/z): 349 (M^+, 6%), 333 (M^+−16, 45%), 104 (100%). Anal. Calcd for $C_{16}H_{14}F_3N_5O$: C, 55.01; H, 4.04; N, 20.05. Found: C, 55.10; H, 4.00; N, 20.20.

4.5.5.2. (Z)-N-[4,5,7-Trifluoro-6-(N-methylamino)-2-methyl-2H-indazol-3-yl]-N′-hydroxy-benzamidine ***12a***. Mp 176–178 °C (EtOH); R_f=0.25 (silica gel, ethyl acetate/petroleum ether 1:2); ^1H NMR (300 MHz, DMSO-d_6) δ 2.94 (s, 3H, NHCH_3), 4.09 (s, 3H, N(2)CH_3), 5.34 (s, 1H, NHCH$_3$, exch. With D_2O), 7.26–7.37 (m, 5H, ArH, overlapped signals), 8.71 (s, 1H, NH, exch. with D_2O), 10.59 (s, 1H, OH, exch. with D_2O); ^{19}F NMR (DMSO-d_6) δ −153.69 (t, 1F, J=19.6 Hz), −158.27 (d, 1F, J=20.0 Hz), −162.43 (d, 1F, J=16.8 Hz); FTIR (Nujol) 3330, 1635 cm^{-1}. GC–MS (m/z): 349 (M^+, 1%), 333 (M^+−16, 47%), 104 (100%). Anal. Calcd for $C_{16}H_{14}F_3N_5O$: C, 55.01; H, 4.04; N, 20.05. Found: C, 55.10; H, 4.00; N, 20.20.

4.5.6. Reaction of oxadiazole ***5b*** *with methylhydrazine in DMF*

Chromatography of the residue gave recovered **5b** (30%, from ethyl acetate/petroleum ether 1:20), **11b** (60%, from ethyl acetate/petroleum ether 1:5), and **12b** (5%, from ethyl acetate/petroleum ether 1:2).

4.5.6.1. (Z)-N-[5,7-Difluoro-6-(N-methylamino)-1-methyl-1H-indazol-3-yl]-N′-hydroxy-benzamidine ***11b***. Mp 184–186 °C (EtOH); R_f=0.41 (silica gel, ethyl acetate/petroleum ether 1:5); ^1H NMR (300 MHz, DMSO-d_6) δ 2.98–3.02 (m, 3H, NHCH_3), 3.77 (s, 3H, N(1)CH_3), 5.37–5.41 (m, 1H, NHCH$_3$, exch. with D_2O), 7.14 (d, 1H, J=12.0 Hz, H(4)), 7.24–7.29 (m, 3H, ArH), 7.30–7.39 (m, 2H, ArH), 8.36 (s, 1H, NH, exch. with D_2O), 10.53 (s, 1H, OH, exch. with D_2O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −137.84 (d, 1F, J=12.0 Hz), −158.70 (br s, 1F); FTIR (Nujol) 3452, 3332, 3100, 1653, 1629 cm^{-1}. GC–MS (m/z): 331 (M^+, 1%), 315 (M^+−16, 47%), 104 (100%). Anal. Calcd for $C_{16}H_{15}F_2N_5O$: C, 58.00; H, 4.56; N, 21.14. Found: C, 58.00; H, 4.50; N, 21.10.

4.5.6.2. (Z)-N-[5,7-Difluoro-6-(N-methylamino)-2-methyl-2H-indazol-3-yl]-N′-hydroxy-benzamidine ***12b***. Mp 183–186 °C (EtOH); R_f=0.28 (silica gel, ethyl acetate/petroleum ether 1:2); ^1H NMR (300 MHz, DMSO-d_6) δ 2.92–2.95 (m, 3H, NHCH_3), 3.94 (s, 3H, N(2)CH_3), 5.06–5.08 (m, 1H, NHCH$_3$, exch. with D_2O), 6.70 (d, 1H, J=11.1 Hz, H(4)), 7.22–7.30 (m, 3H, ArH), 7.34–7.37 (m, 2H, ArH), 8.61 (s, 1H, NH, exch. with D_2O), 10.63 (s, 1H, OH, exch. with D_2O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −136.95 (d, 1F, J=11.1 Hz), −157.86 (br s, 1F); FTIR (Nujol) 3586, 3340, 1653, 1647, 1630 cm^{-1}. GC–MS (m/z): 331 (M^+, 5%), 315 (M^+−16, 41%), 104 (100%). Anal. Calcd for $C_{16}H_{15}F_2N_5O$: C, 58.00; H, 4.56; N, 21.14. Found: C, 58.10; H, 4.7; N, 21.00.

4.5.7. Reaction of oxadiazole ***5c*** *with methylhydrazine in DMF*

Chromatography of the residue gave recovered **5c** (52%, from ethyl acetate/petroleum ether 1:20) and **11c** (37%, from ethyl acetate/petroleum ether 1:5).

4.5.7.1. (Z)-N-[7-Fluoro-6-(N-methylamino)-1-methyl-1H-indazol-3-yl]-N′-hydroxy-benzamidine ***11c***. Mp 196–198 °C (EtOH); R_f=0.38 (silica gel, ethyl acetate/petroleum ether 1:5); ^1H NMR (300 MHz, DMSO-d_6) δ 2.82 (s, 3H, NHCH_3), 3.78 (s, 3H, N(1)CH_3), 5.62 (s, 1H, NHCH$_3$, exch. with D_2O), 6.59 (dd, 1H, J_1=7.5 Hz, J_2=8.4 Hz, H(5)), 7.24–7.31 (m, 4H, ArH, overlapped signals), 7.37–7.40 (m, 2H, ArH), 8.31 (s, 1H, NH, exch. with D_2O), 10.53 (s, 1H, OH, exch. with D_2O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −167.61 (m, 1F); FTIR (Nujol) 3436, 3320, 3147, 1648, 1629 cm^{-1}. GC–MS (m/z): 313 (M^+, 1%), 297 (M^+−16, 46%), 104 (100%). Anal. Calcd for $C_{16}H_{16}F\,N_5O$: C, 61.33; H, 5.15; N, 22.35. Found: C, 61.40; H, 5.10; N, 22.50.

4.5.8. Reaction of oxadiazole ***6a*** *with methylhydrazine in DMF*

Chromatography of the residue gave recovered **6a** (4%, from ethyl acetate/petroleum ether 1:20), **13a** (68%, from ethyl acetate/petroleum ether 1:5), and **14a** (17%, from ethyl acetate/petroleum ether 1:2).

4.5.8.1. (Z)-N-[4,5,7-Trifluoro-6-(N,N-dimethylamino)-1-methyl-1H-indazol-3-yl]-N′-hydroxy-benzamidine ***13a***. Mp 174–176 °C (EtOH); R_f=0.51 (silica gel, ethyl acetate/petroleum ether 1:5); ^1H NMR (300 MHz, DMSO-d_6) δ 2.94 (s, 6H, N(CH_3)$_2$), 3.89 (s, 3H, N(1)CH_3), 7.28–7.30 (m, 3H, ArH), 7.38–7.41 (m, 2H, ArH), 8.35 (s, 1H, NH, exch. with D_2O), 10.50 (s, 1H, OH, exch. with D_2O); ^{19}F NMR ($CDCl_3$) δ −146.88 (t, 1F, J=19.1 Hz), −154.66 (d, 1F, J=20.2 Hz), −156.93 (d, 1F, J=18.3 Hz); FTIR (Nujol) 3391, 1652 cm^{-1}. GC–MS (m/z): 363 (M^+, 3%), 347 (M^+−16, 38%), 104 (100%). Anal. Calcd for $C_{17}H_{16}F_3N_5O$: C, 56.20; H, 4.44; N, 19.28. Found: C, 56.10; H, 4.50; N, 19.40.

4.5.8.2. (Z)-N-[4,5,7-Trifluoro-6-(N,N-dimethylamino)-2-methyl-2H-indazol-3-yl]-N′-hydroxy-benzamidine ***14a***. Mp 175–178 °C (EtOH); R_f=0.36 (silica gel, ethyl acetate/petroleum ether 1:2); ^1H NMR (300 MHz, DMSO-d_6) δ 2.83 (s, 6H, N(CH_3)$_2$), 4.05 (s, 3H, N(1)CH_3), 7.29–7.33 (m, 5H, ArH, overlapped signals), 8.77 (s, 1H, NH, exch. with D_2O), 10.62 (s, 1H, OH, exch. with D_2O); ^{19}F NMR ($CDCl_3$) δ −148.96 (t, 1F, J=19.7 Hz), −155.78 (d, 1F, J=20.7 Hz), −157.28 (d, 1F, J=18.3 Hz); FTIR (Nujol) 3350, 3187, 1670, 1653, 1628 cm^{-1}. GC–MS (m/z): 363 (M^+, 4%), 347 (M^+−16, 42%), 104 (100%). Anal. Calcd for $C_{17}H_{16}F_3N_5O$: C, 56.30; H, 4.6; N, 19.28. Found: C, 56.20; H, 4.44; N, 19.20.

4.5.9. Reaction of oxadiazole ***6b*** *with methylhydrazine in DMF*

Chromatography of the residue gave recovered **6b** (16%, from ethyl acetate/petroleum ether 1:20), **13b** (50%, from ethyl acetate/petroleum ether 1:5), and **14b** (13%, from ethyl acetate/petroleum ether 1:2).

4.5.9.1. (Z)-N-[5,7-Difluoro-6-(N,N-dimethylamino)-1-methyl-1H-indazol-3-yl]-N′-hydroxy-benzamidine ***13b***. Mp 140–142 °C (EtOH); R_f=0.47 (silica gel, ethyl acetate/petroleum ether 1:5); ^1H NMR

(300 MHz, DMSO-d_6) δ 2.90 (s, 6H, N(CH_3)$_2$), 3.81 (s, 3H, N(1)CH_3), 7.25–7.39 (m, 6H, ArH, overlapped signals), 8.50 (s, 1H, N*H*, exch. with D_2O), 10.58 (s, 1H, O*H*, exch. with D_2O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −129.38 (d, 1F, J=8.5 Hz), −147.10 (br s, 1F); FTIR (Nujol) 3171, 1628 cm^{-1}. GC–MS (*m*/*z*): 345 (M^+, 2%), 329 (M^+−16, 33%), 104 (100%). Anal. Calcd for $C_{17}H_{17}F_2N_5O$: C, 59.12; H, 4.96; N, 20.28. Found: C, 59.10; H, 4.80; N, 20.40.

4.5.9.2. (Z)-N-[5,7-Difluoro-6-(N,N-dimethylamino)-2-methyl-2H-indazol-3-yl]-N′-hydroxy-benzamidine ***14b***. Mp 180–181 °C (EtOH); R_f=0.29 (silica gel, ethyl acetate/petroleum ether 1:2); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.83 (s, 6H, N(CH_3)$_2$), 4.00 (s, 3H, N(2)CH_3), 6.79 (dd, 1H, J_1=1.0 Hz, J_2=11.1 Hz, *H*(4)), 7.27–7.30 (m, 3H, ArH), 7.37–7.40 (m, 2H, ArH), 8.68 (s, 1H, N*H*, exch. with D_2O), 10.67 (s, 1H, O*H*, exch. with D_2O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −128.83 (d, 1F, J=11.1 Hz), −146.63 (br s, 1F); FTIR (Nujol) 3260, 1653, 1637 cm^{-1}. GC–MS (*m*/*z*): 345 (M^+, 6%), 329 (M^+−16, 38%), 104 (100%). Anal. Calcd for $C_{17}H_{17}F_2N_5O$: C, 59.12; H, 4.96; N, 20.28. Found: C, 59.20; H, 5.10; N, 20.20.

4.5.10. Reaction of oxadiazole ***6c*** *with methylhydrazine in DMF*

Chromatography of the residue gave recovered **6c** (26%, from ethyl acetate/petroleum ether 1:20), **13c** (39%, from ethyl acetate/petroleum ether 1:5), and **14c** (20%, from ethyl acetate/petroleum ether 1:2).

4.5.10.1. (Z)-N-[7-Fluoro-6-(N,N-dimethylamino)-1-methyl-1H-indazol-3-yl]-N′-hydroxy-benzamidine ***13c***. Mp 158–160 °C (EtOH); R_f=0.42 (silica gel, ethyl acetate/petroleum ether 1:5); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.88 (s, 6H, N(CH_3)$_2$), 3.82 (s, 3H, N(1)CH_3), 6.81 (dd, 1H, J_1=7.5 Hz, J_2=9.0 Hz, *H*(5)), 7.27–7.40 (m, 6H, ArH, overlapped signals), 8.44 (s, 1H, N*H*, exch. with D_2O), 10.57 (s, 1H, O*H*, exch. with D_2O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −152.20 (br s, 1F); FTIR (Nujol) 3342, 3200, 1633 cm^{-1}. GC–MS (*m*/*z*): 327 (M^+, 1%), 311 (M^+−16, 43%), 104 (100%). Anal. Calcd for $C_{17}H_{18}FN_5O$: C, 62.37; H, 5.54; N, 21.39. Found: C, 62.40; H, 5.40; N, 21.70.

4.5.10.2. (Z)-N-[7-Fluoro-6-(N,N-dimethylamino)-2-methyl-2H-indazol-3-yl]-N′-hydroxy-benzamidine ***14c***. Oil; R_f=0.26 (silica gel, ethyl acetate/petroleum ether 1:2); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.80 (s, 6H, N(CH_3)$_2$), 4.01 (s, 3H, N(2)CH_3), 6.70 (dd, 1H, J_1=7.5 Hz, J_2=9.0 Hz, *H*(5)), 6.96 (d, 1H, J=9.0 Hz, *H*(4)), 7.25–7.29 (m, 3H, ArH), 7.36–7.39 (m, 2H, ArH), 8.68 (s, 1H, N*H*, exch. with D_2O), 10.67 (s, 1H, O*H*, exch. with D_2O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −151.37 (br s, 1F); FTIR (Nujol) 3451, 3294, 1639, 1618 cm^{-1}. GC–MS (*m*/*z*): 327 (M^+, 4%), 311 (M^+−16, 31%), 104 (100%). Anal. Calcd for $C_{17}H_{16}F\ N_5O$: C, 62.37; H, 5.54; N, 21.39. Found: C, 62.40; H, 5.60; N, 21.30.

4.6. Hydrolysis of fluorinated *N*-indazolyl-*N*′-hydroxy-benzamidines 9a and 10a. General procedure

To a mixture of **9a** or **10a** (1.0 mmol) in ethanol (10 mL), concd hydrochloric acid (0.5 mL) was added. The solution was refluxed for 24 h. After removal of the solvent, the residue was treated with water (50 mL), neutralized by the addition of solid $NaHCO_3$, and extracted with EtOAc (200 mL). The organic layer was dried over Na_2SO_4 and evaporated. Crystallization of the residue from H_2O/EtOH (1:1) gave the corresponding fluorinated 3-aminoindazoles **16** or **21**, respectively.

4.6.1. 3-Amino-4,5,7-trifluoro-6-methoxy-1-methyl-1H-indazole ***16***

Yield: 84%. Mp 137–139 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.83 (s, 3H, OCH_3), 4.05 (s, 3H, N(1)CH_3), 5.50 (s, 2H, NH_2, exch. with D_2O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −155.46 (t, 1F, J=19.7 Hz), −161.13 (d, 1F, J=20.1 Hz), −167.79 (d, 1F, J=19.5 Hz); FTIR (Nujol) 3450, 3299, 3202, 1666, 1654, 1629 cm^{-1}. GC–MS (*m*/*z*): 231 (M^+, 100%). Anal. Calcd for $C_9H_8F_3N_3O$: C, 46.76; H, 3.49; N, 18.18. Found: C, 46.80; H, 3.50; N, 18.10.

4.6.2. 3-Amino-4,5,7-trifluoro-6-methoxy-2-methyl-2H-indazole ***21***

Yield: 38%. Mp 125–127 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.98 (s, 3H, OCH_3), 4.12 (s, 3H, N(2)CH_3), 4.27 (s, 2H, NH_2, exch. with D_2O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −155.94 (t, 1F, J=19.8 Hz), −154.72 (d, 1F, J=21.1 Hz), −165.36 (d, 1F, J=19.4 Hz); FTIR (Nujol) 3454, 3376, 1681, 1654, 1617 cm^{-1}. GC–MS (*m*/*z*): 231 (M^+, 100%). Anal. Calcd for $C_9H_8F_3N_3O$: C, 46.76; H, 3.49; N, 18.18. Found: C, 46.90; H, 3.40; N, 18.10.

4.7. Deamination reaction of compounds 16 and 21. General procedure

To a solution of amine **16** or **21** (1 mmol) in DMF (5 mL) a solution of *t*-BuONO (2 mmol) in dry DMF (2 mL) was slowly added. After 2 h at 83 °C under good stirring, the mixture was treated with water (50 mL) and extracted with EtOAc (200 mL). The organic layer was dried over Na_2SO_4 and evaporated. Chromatography of the residue (from ethyl acetate/petroleum ether 1:5) gave fluorinated indazole **17** or **22**.

4.7.1. 4,5,7-Trifluoro-6-methoxy-1-methyl-1H-indazole ***17***

Yield: 55%. Mp 77–78 °C (petroleum ether); R_f=0.75 (silica gel, ethyl acetate/petroleum ether 1:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (s, 3H, OCH_3), 4.13 (s, 3H, N(1)CH_3), 8.05 (s, 1H, *H*(3)); ^{19}F NMR (282 MHz, $CDCl_3$) δ −150.77 (t, 1F, J=19.7 Hz), −160.10 (d, 1F, J=20.1 Hz), −164.25 (d, 1F, J=16.9 Hz); FTIR (Nujol) 3130, 1665, 1648 cm^{-1}. GC–MS (*m*/*z*): 216 (M^+, 100%). Anal. Calcd for $C_9H_7F_3N_2O$: C, 50.01; H, 3.26; N, 12.96. Found: C, 50.0; H, 3.40; N, 13.10.

4.7.2. 4,5,7-Trifluoro-6-methoxy-2-methyl-2H-indazole ***22***

Yield: 57%. Mp 119–120 °C (petroleum ether); R_f=0.45 (silica gel, ethyl acetate/petroleum ether 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (s, 3H, OCH_3), 4.22 (s, 3H, N(2)CH_3), 8.01 (d, 1H, J=2.4 Hz, *H*(3)); ^{19}F NMR (282 MHz, $CDCl_3$) δ −151.37 (t, 1F, J=18.8 Hz), −154.59 (d, 1F, J=20.8 Hz), −163.25 (d, 1F, J=16.3 Hz); FTIR (Nujol) 3113, 1585 cm^{-1}. GC–MS (*m*/*z*): 216 (M^+, 100%). Anal. Calcd for $C_9H_7F_3N_2O$: C, 50.01; H, 3.26; N, 12.96. Found: C, 49.80; H, 3.40; N, 12.90.

4.8. Reaction of pentafluorobenzaldehyde 18 with methanol. General procedure

Pentafluorobenzaldehyde **18** (980 mg, 5 mmol) was added to a solution of *t*-BuOK (616 mg, 5.5 mmol) in methanol (20 mL). After 1 h at rt, the solvent was removed. Chromatography of the residue (from ethyl acetate/petroleum ether 1:50) gave *2,3,5,6-tetrafluoro-4-methoxy-benzaldehyde* **19**. Yield: 60%; oil; R_f=0.80 (silica gel, ethyl acetate/petroleum ether 1:50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21–4.23 (m, 3H, OCH_3), 10.20 (s, 1H, C(O)*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ −149.21 (d, 2F, J=15.0 Hz), −161.10 (d, 2F, J=15.0 Hz); FTIR (Nujol) 1700 cm^{-1}. GC–MS (*m*/*z*): 208 (M^+, 100%). Anal. Calcd for $C_8H_4F_4O_2$: C, 46.17; H, 1.94. Found: C, 46.20; H, 2.00.

4.9. Reaction of 2,3,5,6-tetrafluoro-4-methoxy-benzaldehyde 19 with methylhydrazine

To a solution of **19** (300 mg, 1.44 mmol) in THF (10 mL) an excess of methylhydrazine (80 μL, 1.5 mmol) was added. After stirring for 5 h at rt, the solvent was removed, and the residue was tritured with petroleum ether and filtered, giving methylhydrazone **20**. *E-Methylhydrazone of 2,3,5,6-Tetrafluoro-4-methoxy-benzaldehyde* **20**. Yield: 76%. Mp 103–105 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6)

δ 2.89 (s, 3H, NHCH_3), 4.08 (s, 3H, OCH_3), 7.20 (s, 1H, C(N)*H*), 8.24 (s, 1H, *NH*CH$_3$, exch. with D_2O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −149.59 (d, 2F, J=16.9 Hz), −162.31 (d, 2F, J=16.9 Hz); FTIR (Nujol) 3342, 1653 cm^{-1}. GC–MS (m/z): 236 (M$^+$, 100%). Anal. Calcd for $C_9H_8F_4N_2O$: C, 45.77; H, 3.41; N, 11.86. Found: C, 45.80; H, 3.40; N, 11.90.

4.10. Reaction of 2,3,5,6-tetrafluoro-4-methoxy-benzaldehyde 19 with hydrazine

To a solution **19** (570 mg, 2.75 mmol) in THF (10 mL) an excess of hydrazine (3 mL) was added. The mixture was then heated to reflux for 4 h. After removal of the solvent, the residue was treated with water (30 mL) and extracted with EtOAc (150 mL). The organic layer was dried over Na_2SO_4 and evaporated. Chromatography of the residue (from ethyl acetate/petroleum ether 1:1) gave fluorinated indazole **23**.

*4.10.1. 4,5,7-Trifluoro-6-methoxy-1H-indazole **23***

Yield: 19%. Mp 181–182 °C (EtOH); R_f=0.65 (silica gel, ethyl acetate/petroleum ether 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (s, 3H, OCH_3), 8.16 (d, 1H, J=3.3 Hz, H(3)); ^{19}F NMR (282 MHz, $CDCl_3$) δ −155.94 (t, 1F, J=19.2 Hz), −156.84 (d, 1F, J=21.1 Hz), −163.59 (d, 1F, J=17.7 Hz); FTIR (Nujol) 3124, 3089, 3041 cm^{-1}. GC–MS (m/z): 202 (M$^+$, 100%). Anal. Calcd for $C_8H_5F_3N_2O$: C, 47.54; H, 2.49; N, 13.86. Found: C, 47.50; H, 2.60; N, 13.80.

4.11. Synthesis of 4,5,7-trifluoro-6-methoxy-1-methyl-1*H*-indazole 17

A solution of **20** (100 mg, 0.424 mmol) in DMF/pyridine 1:1 mixture (4 mL) was heated to reflux for 5 h. The mixture was treated with water (20 mL), neutralized with HCl 1 M, and extracted with EtOAc (100 mL). The organic layer was dried over Na_2SO_4 and evaporated. Chromatography of the residue (from ethyl acetate/petroleum ether 1:5) gave fluorinated 1-methyl-1*H*-indazole **17** (20 mg, 22%).

4.12. Methylation of 4,5,7-trifluoro-6-methoxy-1*H*-indazole 23

To a solution of **23** (35 mg, 0.17 mmol) in EtOAc (5 mL), Me_3OBF_4 (33 mg, 0.22 mmol) was added. After 6 h at rt, the mixture was diluted with EtOAc (50 mL), treated with saturated $NaHCO_3$ (25 mL). The organic layer was recovered, dried over Na_2SO_4, and evaporated. Chromatography of the residue (from ethyl acetate/petroleum ether 1:5) gave fluorinated 2-methyl-2*H*-indazole **22** (23 mg, 64%).

4.13. Reaction of oxadiazole 4a with methylamine in DMF

To a mixture of oxadiazole **4a** (312 mg, 1 mmol) in dry DMF (2 mL), methylamine (1.1 mmol) was slowly added. After stirring for 1 h at rt, the mixture was diluted with water (50 mL) and the formed precipitate filtered and crystallized from EtOH giving compound **28**.

*4.13.1. 5-[2,3,5-Trifluoro-4-methoxy-6-(N-methylamino)-phenyl]-3-phenyl-1,2,4-oxadiazole **28***

Yield: 85%. Mp 94–96 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.10–3.14 (m, 3H, NHCH_3), 4.16 (s, 3H, OCH_3), 7.46 (s, 1H, N*H*CH$_3$, exch. with D_2O), 7.64–7.70 (m, 3H, ArH), 8.18–8.20 (m, 2H, ArH); ^{19}F NMR (282 MHz, $CDCl_3$) δ −141.60 (m, 1F), −145.53 (m, 1F), −161.43 (m, 1F); FTIR (Nujol) 3289, 1649 cm^{-1}. GC–MS (m/z): 335 (M$^+$, 100%). Anal. Calcd for $C_{16}H_{12}F_3N_3O_2$: C, 57.32; H, 3.61; N, 12.53. Found: C, 57.40; H, 3.50; N, 12.60.

4.14. Reaction of oxadiazole 3a with methylhydrazine in DMF

To a mixture of oxadiazole **3a** (150 mg, 0.48 mmol) in dry DMF (2 mL), methylhydrazine (1 equiv) was added. After stirring for 1 h at rt, the mixture was diluted with water (30 mL) and extracted with EtOAc (200 mL). The organic layer was dried over Na_2SO_4 and evaporated. Chromatography of the residue gave recovered oxadiazole **3a** (20 mg, 13%, from ethyl acetate/petroleum ether 1:20), 5-[2,3,5,6-tetrafluoro-4-(*N*-methylhydrazino)-phenyl]-3-phenyl-1,2,4-oxadiazole **29** (100 mg, from ethyl acetate/petroleum ether 1:5), and an unresolvable mixture of **29** and 5-[2,3,5,6-tetrafluoro-4-(*N*′-methyl-hydrazino)-phenyl]-3-phenyl-1,2,4-oxadiazole **30** (36 mg, from ethyl acetate/petroleum ether 1:5). Mixture composition was determined by means of ^{1}H NMR from integration of –N(NH$_2$)CH_3 methyl signal at 3.29 ppm for **29** and –NHNHCH_3 methyl signal at 2.64 ppm for **30**, giving a **29**/**30** ratio 69:31.

*4.14.1. 5-[2,3,5,6-Tetrafluoro-4-(N-methyl-hydrazino)-phenyl]-3-phenyl-1,2,4-oxadiazole **29***

Total yield: 74%. Mp 140–143 °C (EtOH); R_f=0.45 (silica gel, ethyl acetate/petroleum ether 1:5); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.29 (t, 3H, N(NH$_2$)CH_3, J=3.0 Hz), 5.12 (s, 2H, NH_2, exch. with D_2O), 7.65–7.71 (m, 3H, ArH), 8.11–8.13 (m, 2H, ArH); FTIR (Nujol) 3380, 3289, 1646 cm^{-1}. GC–MS (m/z): 338 (M$^+$, 100%). Anal. Calcd for $C_{15}H_{10}F_4N_4O$: C, 53.26; H, 2.98; N, 16.56. Found: C, 53.40; H, 3.00; N, 16.40.

*4.14.2. 5-[2,3,5,6-Tetrafluoro-4-(N′-methyl-hydrazino)-phenyl]-3-phenyl-1,2,4-oxadiazole **30***

Total yield: 6%; R_f=0.40 (silica gel, ethyl acetate/petroleum ether 1:5); ^{1}H NMR (300 MHz, DMSO-d_6, data from **29**+**30** mixture) δ 2.64 (d, 3H, NHNHCH_3, J=5.7 Hz), 5.08 (br q, 1H, NH*NH*CH$_3$, J=5.7 Hz), 7.62–7.70 (m, 3H, ArH), 8.13–8.15 (m, 2H, ArH), 8.35 (br s, 1H, *NH*NHCH$_3$, exch. with D_2O).

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