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# Laccase-catalyzed reaction of 3-*tert*-butyl-1*H*-pyrazol-5(4*H*)-one with substituted catechols using air as an oxidant

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ABSTRACT

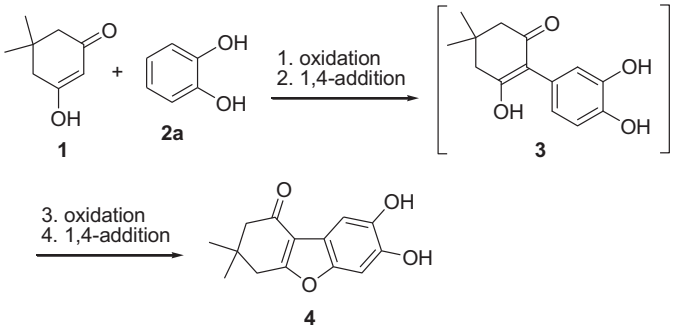
The laccase-catalyzed reaction of 3-*tert*-butyl-1*H*-pyrazol-5(4*H*)-one with a number of catechols and aerial oxygen as an oxidant selectively affords 4-substituted 3-*tert*-butyl-1*H*-pyrazol-5-ol derivatives with yields ranging from 77 to 99%.



## 1. Introduction

Pyrazolones are very well known for their analgesic, antipyretic, and antiinflammatory properties.[1,2a–d] There are also renowned for their antitumor[2e–h] and hypoglycemic[2i,j] activities. For a couple of years, the potent radical scavenger edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is in use as a neuroprotective agent for treatment of acute cerebral infarction in several countries.[3] A number of pyrazolones find use as herbicides.[4] Moreover, substituted pyrazolones have been applied for the synthesis of dyes.[5] The numerous applications for pyrazolones are the reason for the continuing interest in the development of new methods for their efficient preparation.[6]

In organic synthesis, there is an urgent need for the development of environmentally benign oxidations.[7] Molecular oxygen represents an ideal alternative to traditionally used oxidants.[8] This is why enzyme-catalyzed oxidations using aerial oxygen as the oxidant have received increasing attention.[9] Recently, there are considerable attempts to use laccases as catalysts for selective and efficient oxidations with $O_2$.[10] Laccases are produced by fungi, plants, and prokaryotes. They can easily be isolated and some laccases are even commercially available. Laccases (benzenediol: $O_2$ oxidoreductase EC 1.10.3.2.) are multicopper oxidases, which can catalyze the oxidation of a number of substrates using $O_2$ as the oxidant with simultaneous reduction of $O_2$ to give $H_2O$.[11] Apart from laccase-catalyzed oxidative couplings of electron rich phenols,[10,12] oxidative aromatizations,[10,13] and oxidative cleavages[10,14] the focus is on laccase-catalyzed oxidations of catechols and hydroquinones to the corresponding benzoquinones and their reactions with C-nucleophiles.[10,15] Typical examples include the reactions of catechols with cyclic 1,3-dicarbonyls to yield 3,4-dihydro-7,8-dihydroxy-2*H*-dibenzofuran-1-ones as the result of a domino oxidation/intermolecular 1,4-addition/oxidation/intramolecular 1,4-addition (Scheme 1).[15h] As an extension of this work, we became interested in using 1,3-dicarbonyl equivalents as substrates.




**Scheme 1.** Synthesis of 3,4-dihydro-7,8-dihydroxy-2*H*-dibenzofuran-1-one (**4**) by laccase-catalyzed domino oxidation/intermolecular 1,4-addition/oxidation/intramolecular 1,4-addition.

Here, we report on the laccase-catalyzed reaction between 3-*tert*-butyl-1*H*-pyrazol-5(4*H*)-one (**5**) and unsubstituted catechol **2a**,

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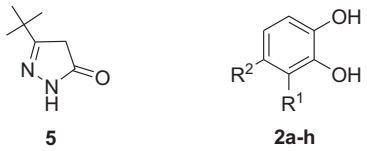
3-substituted catechols **2b**–**e** and 4-substituted catechols **2f**–**h** (Fig. 1) using air as an oxidant.

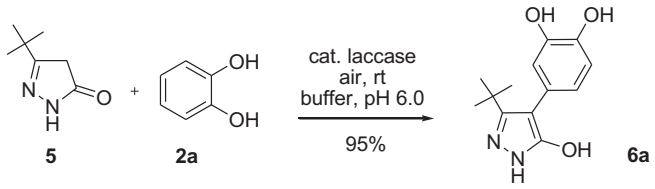



| | | | | | |
|---|---|---|---|---|---|
| **2a** | $R^1$ = H | $R^2$ = H | **2f** | $R^1$ = H | $R^2$ = $CH_3$ |
| **2b** | $R^1$ = $CH_3$ | $R^2$ = H | **2g** | $R^1$ = H | $R^2$ = $C_2H_5$ |
| **2c** | $R^1$ = $OCH_3$ | $R^2$ = H | **2h** | $R^1$ = H | $R^2$ = $NO_2$ |
| **2d** | $R^1$ = F | $R^2$ = H | | | |
| **2e** | $R^1$ = Br | $R^2$ = H | | | |

**Fig. 1.** Substrates for the laccase-catalyzed transformations.

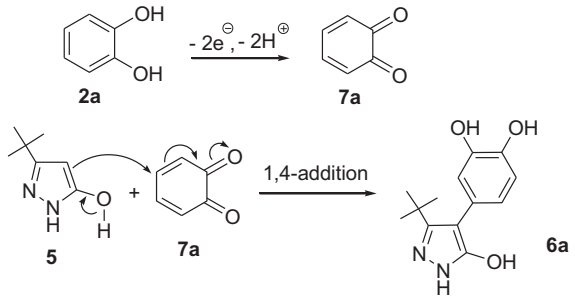
## 2. Results and discussion

First, the laccase-catalyzed reaction between 3-*tert*-butyl-1*H*-pyrazol-5(4*H*)-one (**5**) and the unsubstituted catechol (**2a**) was studied using aerial oxygen as the oxidant (Scheme 2). After some experimentation it was found that **6a** can be isolated in 95% yield when 1 equiv of **5** and 1.1 equiv of **2a** were reacted in the presence of laccase from *Agaricus bisporus* in phosphate buffer (pH 6.0) at room temperature.




**Scheme 2.** Laccase-catalyzed reaction between **5** and **2a**.

It is assumed that the first step of the transformation is the laccase-catalyzed oxidation of catechol (**2a**) with $O_2$ to *o*-benzoquinone (**7a**), which then undergoes an intermolecular 1,4-addition with the CH-acidic 3-*tert*-butyl-1*H*-pyrazol-5(4*H*)-one (**5**) as a nucleophile to yield **6a** (Scheme 3).




**Scheme 3.** Plausible reaction mechanism for the formation of **6a**.

It should be noted that the only product formed was the 1,4-adduct **6a** and that not even a trace of the expected cyclization product **8** could be observed (Fig. 2). This result is quite astonishing as the laccase-catalyzed reaction of **2a** with other CH-acidic compounds, such as 1,3-diketones and β-ketoesters, exclusively yields the corresponding cyclization products.[15] Their formation is based on a domino oxidation/intermolecular 1,4-addition/oxidation/intramolecular 1,4-addition process.

In addition, catechol (**2a**) was also reacted with other substituted pyrazolones. The results, however, were not satisfying as the formation of product mixtures, which could not be separated, was observed.

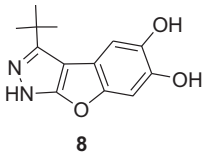
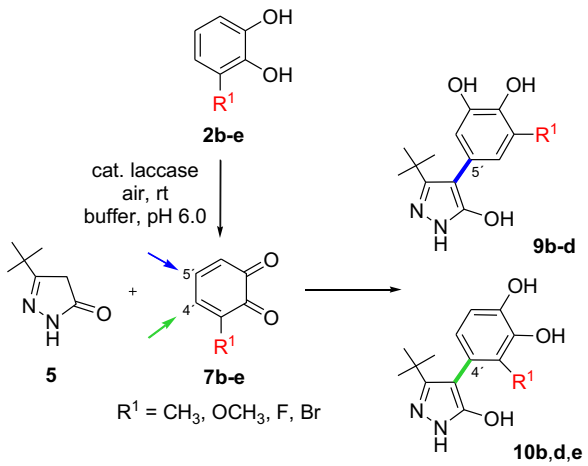



**Fig. 2.** Structure of the expected cyclization product **8** from the reaction of **5** with **2a**.

The next set of experiments was devoted to the reactions between the 3-*tert*-butyl-pyrazol-5-one (**5**) and several monosubstituted catechols **2b**–**e** (Scheme 4, Table 1, Fig. 3). Depending on whether the intermolecular 1,4-addition of the nucleophile occurs at C-4′ or C-5′ of the corresponding *o*-benzoquinone intermediates **7b**–**e** (Scheme 4), either products of type **9** or type **10** were formed. The reaction of 3-*tert*-butyl-pyrazol-5-one (**5**) with 3-methylcatechol (**2b**) delivered 98% of a 91:9 mixture of **9b** and **10b** (Table 1, entry 2). In the reaction with 3-methoxycatechol (**2c**) the 1,4-adduct **9c**, i.e., the product resulting from an attack at C-5′ of **7c**, was isolated with 80% (Table 1, entry 3). When **5** was reacted with 3-fluorocatechol (**2d**), the regioselectivity was less pronounced. Here, a 60:40 mixture of the two regioisomers **9d** and **10d** was isolated in 98% yield (Table 1, entry 4). In contrast, upon reaction of **5** with 3-bromocatechol (**2e**) the regioisomer resulting from an 1,4-attack of **5** at C-4′ of **7e** was formed exclusively. The corresponding product **10e** was obtained with 96% yield (Table 1, entry 5). The regioselectivity of these reactions may be rationalized in such a way that the 1,4-addition exclusively takes place at the more electrophilic carbon atom of the corresponding *o*-benzoquinones **7** (Scheme 4).




**Scheme 4.** Laccase-catalyzed synthesis of **9** and **10**.

Finally, the reactions with some 4-substituted catechols, i.e., 4-methylcatechol (**2f**), 4-ethylcatechol (**2g**), and 4-nitrocatechol (**2h**), were conducted (Scheme 5, Table 2, Fig. 4). The transformations of **2f** and **2g** gave the products arising from attack of **5** at C-5′ of the *o*-benzoquinone intermediate **7**. The yield of **11f** amounted to 99% (Table 2, entry 1) and **11g** was isolated in 96% (Table 2, entry 2). However, when **5** was treated with the nitro-substituted catechol **2h**, the 1,4-addition took place at C-3′ of the intermediate **7h**. As a result, the regioselective formation of **12h** in 77% was observed.

Again, the regioselectivity of these three reactions may be rationalized in such a way that the 1,4-addition exclusively occurs at the more electrophilic carbon atom of the corresponding *o*-benzoquinones **7** (Scheme 5).

**Table 1**
Laccase-catalyzed reaction of **5** with catechol (**2a**) and 3-substituted catechols **2b**–**e** using air as an oxidant[a]

| Entry | 2 | $R^1$ | Time (h) | Product | Ratio[b] **9**:**10** | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **a** | H | 17 | **9a** | — | 95 |
| 2 | **b** | $CH_3$ | 15 | **9b**, **10b** | 91:9 | 98 |
| 3 | **c** | $OCH_3$ | 15 | **9c** | — | 80 |
| 4 | **d** | F | 15 | **9d**, **10d** | 60:40 | 98 |
| 5 | **e** | Br | 17 | **10e** | — | 96 |

[a] Reactions were performed with 1.5 mmol **5** and 1.7 mmol **2**.
[b] The ratio **9**:**10** was determined by $^1$H NMR of the crude product.

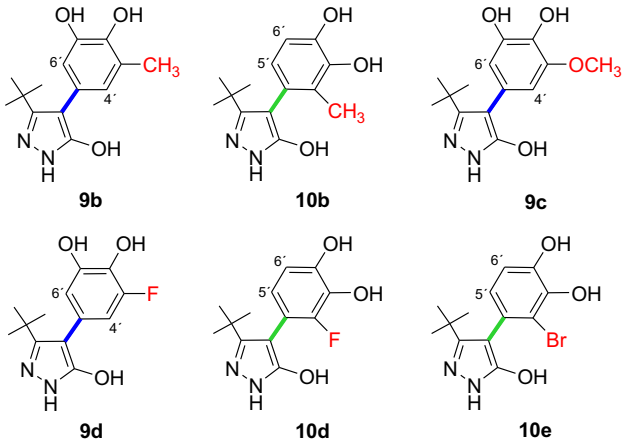
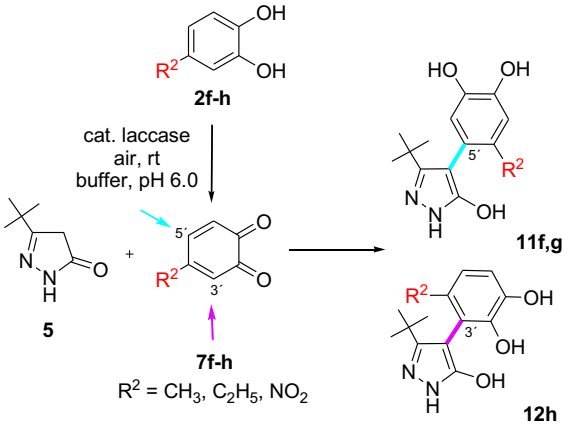



**Fig. 3.** Products of the laccase-catalyzed reaction between **5** and **2b**–**e**.




**Scheme 5.** Laccase-catalyzed synthesis of **11** and **12**.

**Table 2**
Laccase-catalyzed reaction of **5** with 4-substituted catechols **2f**–**h** using air as an oxidant[a]

| Entry | 2 | R | Time (h) | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 | **f** | $CH_3$ | 18 | **11f** | 99 |
| 2 | **g** | $C_2H_5$ | 17 | **11g** | 96 |
| 3 | **h** | $NO_2$ | 15 | **12h** | 77 |

[a] Reactions were performed with 1.5 mmol **5** and 1.7 mmol **2**.

The exclusive formation of the monosubstituted pyrazolyl catechols **9**–**12**, which results from 1,4-addition of **5** to the corresponding *o*-benzoquinone intermediates **7** is particularly noteworthy, since the reaction between pyrazolones and catechols under electrochemical conditions delivers different products or mixtures of products in considerably lower yields.[16]

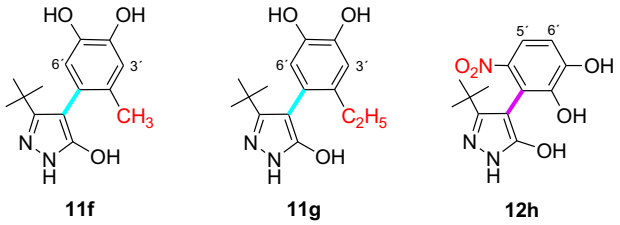



**Fig. 4.** Products from the laccase-catalyzed reaction of **5** with **2f**–**h**.

The structures of all products were unambiguously elucidated by mass spectrometry and NMR spectroscopic methods. The reactions between 3-*tert*-butyl-1*H*-pyrazol-5(4*H*)-one (**5**) and substituted catechols **2** result in the formation of different regioisomers, in which the pyrazole moiety is attached at C-3′, C-4′ or C-5′ of the catechol moiety.

In the reaction of **5** with 3-methylcatechol (**2b**) a mixture of two isomers was obtained. The $^1$H NMR spectrum of the 91:9 mixture of **9b** and **10b** shows two sets of doublets in the aromatic region. The protons at $\delta$=6.34 ppm and $\delta$=6.45 ppm reveal a small coupling constant of $J$=1.8 Hz indicating a meta coupling between these protons, which can be attributed to 4′-H and 6′-H of the major component **9b**. Furthermore, strong $^3J$ HMBC correlations from 4′-H to C-4 and from 6′-H to C-4 demonstrate that the pyrazole ring is attached at C-5′ of the catechol. The second set of doublets in $^1$H NMR spectrum of the mixture at $\delta$=6.37 ppm and $\delta$=6.55 ppm sharing a coupling constant of $J$=8.1 Hz can be attributed to the *ortho*-positioned 5′-H and 6′-H of the minor component **10b**. A $^3J$ HMBC correlation from 5′-H to C-4 indicates that the pyrazole ring is attached at C-4′ of the catechol.

In the $^1$H NMR spectrum of **9c**, two doublets (4′-H at $\delta$=6.21 ppm and 6′-H at $\delta$=6.24 ppm) with a coupling constant of $J$=1.5 Hz and HMBC correlations similar to **9b** provide evidence for the structure assigned. The structure of **10e** was proven by the occurrence of the 5′-H ($\delta$=6.53 ppm) and 6′-H ($\delta$=6.71 ppm) protons as doublets with a coupling constant of $^3J_{(5'\text{-H},6'\text{-H})}$=8.3 Hz and HMBC correlation from 5′-H to C-4.

In the reaction between **5** and **2d** a 60:40 mixture of the two regioisomers **9d** and **10d** was obtained. The structures of **9d** and **10d** were deduced by analysis of their NMR spectra. In the major component **9d**, protons 4′-H and 6′-H both appear as doublets of doublets with coupling constants for 4′-H [$^4J_{(4'\text{-H},6'\text{-H})}$=2.0 Hz, $^3J_{(4'\text{-H,F})}$=11.5 Hz] and for 6′-H [$^4J_{(4'\text{-H},6'\text{-H})}$=2.0 Hz, $^5J_{(6'\text{-H,F})}$=2.0 Hz], that clearly establish the structure assigned. In the minor component **10d**, the protons 5′-H and 6′-H also occur as doublets of doublets. Here, the coupling constants for 5′-H [$^3J_{(5'\text{-H},6'\text{-H})}$=8.3 Hz, $^4J_{(5'\text{-H,F})}$=8.0 Hz] and for 6′-H [$^3J_{(5'\text{-H},6'\text{-H})}$=8.3 Hz, $^5J_{(6'\text{-H,F})}$=1.5 Hz] prove that in **10d** the pyrazole is attached to C-4′ of the catechol ring.

The structures of **11f** are proven by the two singlets of the protons 3′-H and 6′-H ($\delta$=6.54 ppm and $\delta$=6.46 ppm) and the strong $^3J_{(H,C)}$ HMBC correlations between 6′-H and C-4 and 3′-H and the carbon of the methyl group. The structure elucidation of **11g** is similar to **11f**: two singlets for 3′-H at $\delta$=6.57 ppm and for 6′-H at $\delta$=6.44 ppm and $^3J_{(H,C)}$ HMBC correlations between 6′-H and C-4 and 3′-H and the $CH_2$ of the ethyl group. The structure of **12h** follows from the two doublets at $\delta$=7.37 ppm and at $\delta$=6.84 ppm, which were assigned to 5′-H and 6′-H, respectively. The vicinal coupling constant between 5′-H and 6′-H amounts to $J$=9.0 Hz.

## 3. Conclusions

A simple to execute and efficient method for the synthesis of 4-substituted 3-*tert*-butyl-1*H*-pyrazol-5-ols has been developed. It relies on the laccase-catalyzed oxidation of a catechol to the corresponding *o*-benzoquinone which in turn undergoes an

intermolecular 1,4-addition with the 3-*tert*-butyl-1*H*-pyrazol-5(4*H*)-one as a nucleophile. The reactions can be performed under mild reaction conditions with air as the oxidant and the products are formed with yields ranging between 77 and 99%. Depending on the substituent on the catechol moiety, different regioisomers are formed.

## 4. Experimental section

### 4.1. General

All chemicals and the laccase from *A. bisporus* (ASA Spezialenzyme) were purchased from commercial suppliers. Solvents used in extraction and purification were distilled prior to use. The pH of the buffer was adjusted using a pH 330/SET-1 pH-meter. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 $F_{245}$ aluminum plates (Merck) with visualization under UV light and by immersion in ethanolic vanillin solution followed by heating. Flash chromatography was carried out on silica gel MN 60, 0.04–0.053 mm (Macherey & Nagel). Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were measured on a Perkin–Elmer Spectrum One (FT-IR spectrometer). $^1$H and $^{13}$C NMR spectra were recorded at 300 (75) MHz on a Varian Unity Inova instrument using DMSO-$d_6$ as a solvent. The chemical shifts were referenced to the solvent signals at $\delta$ H/C 2.49/39.50 ppm (DMSO-$d_6$) relative to TMS as internal standards. Coupling constants $J$ [Hertz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet) and m (multiplet). Low resolution electron spray ionisation mass spectra (ESI-LRMS) and exact electron spray ionisation mass spectra (HRMS) were recorded on a Bruker Daltonics (micro TOFQ) instrument. The intensities are reported as percentages relative to the base peak ($I$=100%).

### 4.2. General procedure for the laccase-catalyzed reaction of catechols with 3-*tert*-butyl-1*H*-pyrazol-5(4*H*)-one

3-*tert*-Butyl-1*H*-pyrazol-5(4*H*)-one (**5**) (1.5 mmol) and catechol **2** (1.7 mmol) were dissolved in 80 mL 0.2 M phosphate buffer (pH 6.0). Laccase from *A. bisporus* (50 mg, 6 U/mg) was added and the mixture was vigorously stirred under air at room temperature until the substrates had been fully consumed, as judged by TLC. This mixture was acidified with 2 M HCl to pH ~4, saturated with NaCl and filtered on a Buchner funnel. The filter cake was washed with 15% sodium chloride solution (75 mL) and water (5 mL). The crude products obtained after drying exhibit a purity of 90–95% (NMR). Analytically pure products were obtained by recrystallization of the crude products.

*4.2.1. 4′-(3-tert-Butyl-5-hydroxy-1H-pyrazol-4-yl)benzene-1′,2′-diol (**6a**).* Reaction of **5** (210 mg, 1.5 mmol) and **2a** (187 mg, 1.7 mmol) according to the general procedure gave **6a** (355 mg, 95%) as a brown solid; mp 298–303 °C (dec); $R_f$ 0.24 ($CH_2Cl_2$/MeOH=8.5:1.5); IR (ATR) $\tilde{\nu}$ 3236, 2959, 1581, 1515, 1480, 1429, 1364, 1309, 1240, 1114, 812, 788 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.12 (s, 9H, $^t$Bu), 6.42 (dd, $^3J$=8.1 Hz, $^4J$=1.8 Hz, 1H, 5′-H), 6.56 (d, $^4J$=2.1 Hz, 1H, 3′-H), 6.66 (d, $^3J$=8.1 Hz, 1H, 6′-H), 8.68 (br s, 1H, OH), 8.75 (br s, 1H, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 30.1 ($CH_3$-$^t$Bu), 32.1 (C-$^t$Bu), 102.9 (C-4), 114.9 (C-6′), 119.0 (C-3′), 122.5 (C-5′), 125.2 (C-4′), 143.8 (C-1′), 144.3 (C-2′), 147.7 (C-3), 159.3 (C-5); MS (ESI) $m/z$ (%) 249.1 (100) [M+H]$^+$, 271.1 (3) [M+Na]$^+$; HRMS (ESI) calculated for $C_{13}H_{16}N_2O_3$ 248.1161, found 248.1153.

*4.2.2. 5′-(3-tert-Butyl-5-hydroxy-1H-pyrazol-4-yl)-3′-methylbenzene-1′,2′-diol (**9b**) and 4′-(3-tert-butyl-5-hydroxy-1H-pyrazol-4-yl)-3′-methylbenzene-1′,2′-diol (**10b**).* Reaction of **5** (210 mg, 1.5 mmol) and **2b** (211 mg, 1.7 mmol) according to the general procedure gave **9b** and **10b** as a 91:9 regioisomeric mixture (387 mg, 98%) and as a brown solid; mp 293–295 °C (dec); $R_f$ 0.27 ($CH_2Cl_2$/MeOH=8.5:1.5); IR (ATR) $\tilde{\nu}$ 3211, 2963, 2343, 1591, 1504, 1314, 1229, 1170, 1078, 1027, 971, 834 cm$^{-1}$; **9b**:[17] $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.12 (s, 9H, $^t$Bu), 2.08 (s, 3H, $CH_3$), 6.34 (d, $J$=1.8 Hz, 1H, 4′-H), 6.45 (d, $J$=1.8 Hz, 1H, 6′-H), 7.99 (br s, 1H, OH), 8.97 (br s, 1H, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 16.1 ($CH_3$), 30.1 ($CH_3$-$^t$Bu), 32.1 (C-$^t$Bu), 103.1 (C-4), 116.4 (C-6′), 123.4 (C-3′), 124.3 (C-5′), 124.5 (C-4′), 141.8 (C-2′), 143.9 (C-1′), 147.6 (C-3), 159.3 (C-5); **10b**:[17] $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.06 (s, 9H, $^t$Bu), 1.84 (s, 3H, $CH_3$), 6.37 (d, $J$=8.1 Hz, 1H, 5′-H), 6.55 (d, $J$=8.1 Hz, 1H, 6′-H); MS (ESI) $m/z$ (%) 263.1 (100) [M+H]$^+$, 285.1 (9) [M+Na]$^+$; HRMS (ESI) calculated for $C_{14}H_{18}N_2O_3$ 262.1317, found 262.1312.

*4.2.3. 5′-(3-tert-Butyl-5-hydroxy-1H-pyrazol-4-yl)-3′-methoxybenzene-1′,2′-diol (**9c**).* Reaction of **5** (210 mg, 1.5 mmol) and **2c** (238 mg, 1.7 mmol) according to the general procedure gave **9c** (334 mg, 80%) as a dark brown solid; mp 283–288 °C (dec); $R_f$ 0.28 ($CH_2Cl_2$/MeOH=8.5:1.5); IR (ATR) $\tilde{\nu}$ 2959, 2328, 2115, 1734, 1586, 1516, 1423, 1352, 1224, 1099, 818, 734 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.14 (s, 9H, $^t$Bu), 3.69 (s, 3H, $OCH_3$), 6.21 (d, $J$=1.5 Hz, 1H, 4′-H), 6.24 (d, $J$=1.5 Hz, 1H, 6′-H), 8.06 (s, 1H, OH) 8.73 (s, 1H, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 30.1 ($CH_3$-$^t$Bu), 32.1 (C-$^t$Bu), 55.8 ($OCH_3$), 103.2 (C-4), 107.1 (C-4′), 112.5 (C-6′), 124.3 (C-5′), 132.7 (C-2′), 144.9 (C-1′), 147.5 (C-3′), 159.1 (C-5); MS (ESI) $m/z$ (%) 279.1 (100) [M+H]$^+$, 301.1 (24) [M+Na]$^+$; HRMS (ESI) calculated for $C_{14}H_{18}N_2O_4$ 278.1267, found 278.1259.

*4.2.4. 5′-(3-tert-Butyl-5-hydroxy-1H-pyrazol-4-yl)-3′-fluorobenzene-1′,2′-diol (**9d**) and 4′-(3-tert-butyl-5-hydroxy-1H-pyrazol-4-yl)-3′-fluorobenzene-1′,2′-diol (**10d**).* Reaction of **5** (210 mg, 1.5 mmol) and **2d** (218 mg, 1.7 mmol) according to the general procedure gave **9d** and **10d** as a 60:40 regioisomeric mixture (390 mg, 98%) and as a light brown solid; mp >330 °C (dec); $R_f$ 0.25 ($CH_2Cl_2$/MeOH=8.5:1.5); IR (ATR) $\tilde{\nu}$ 2964, 1583, 1514, 1480, 1461, 1430, 1348, 1252, 1219, 1026, 998, 835, 796 cm$^{-1}$; **9d**:[18] $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.13 (s, 9H, $^t$Bu), 6.39 (dd, $^3J_{(H,F)}$=11.5, $^4J_{(H,H)}$=2.0 Hz, 1H, 4′-H), 6.46 (dd, $^4J_{(H,H)}$=2.0, $^5J_{(H,F)}$=2.0 Hz, 1H, 6′-H), 8.83 (br s, 1H, OH), 9.38 (br s, 1H, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 30.1 ($CH_3$-$^t$Bu), 32.1 (C-$^t$Bu), 102.1 (C-4), 109.5 (d, $^2J_{(C,F)}$=18.5 Hz, C-4′), 114.8 (d, $^4J_{(C,F)}$=1.3 Hz, C-6′), 124.6 (d, $^3J_{(C,F)}$=9.9 Hz, C-5′), 131.7 (d, $^2J_{(C,F)}$=14.3 Hz, C-2′), 146.6 (d, $^3J_{(C,F)}$=6.6 Hz, C-1′), 147.9 (C-3), 151.3 (d, $^1J_{(C,F)}$=236.6 Hz, C-3′), 159.1 (C-5); **10d**:[18] $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.09 (s, 9H, $^t$Bu), 6.43 (dd, $^3J_{(H,H)}$=8.3, $^4J_{(H,F)}$=8.0 Hz, 1H, 5′-H), 6.56 (dd, $^3J_{(H,H)}$=8.3, $^5J_{(H,F)}$=1.5 Hz, 1H, 6′-H), 8.83 (br s, 1H, OH), 9.38 (br s, 1H, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 29.7 ($CH_3$-$^t$Bu), 31.9 (C-$^t$Bu), 95.9 (C-4), 110.3 (d, $^5J_{(C,F)}$=2.0 Hz, C-6′), 112.9 (d, $^2J_{(C,F)}$=15.6 Hz, C-4′), 122.4 (d, $^4J_{(C,F)}$=3.4 Hz, C-5′), 133.1 (d, $^2J_{(C,F)}$=15.2 Hz, C-2′), 146.5 (d, $^3J_{(C,F)}$=5.4 Hz, C-1′), 148.8 (C-3), 150.6 (d, $^1J_{(C,F)}$=236.4 Hz, C-3′), 159.6 (C-5); MS (ESI) $m/z$ (%) 267.1 (100) [M+H]$^+$, 268.1 (14) [M+Na]$^+$; HRMS (ESI) calculated for $C_{13}H_{15}FN_2O_3$ 266.1067, found 266.1060.

*4.2.5. 3′-Bromo-4′-(3-tert-butyl-5-hydroxy-1H-pyrazol-4-yl)benzene-1′,2′-diol (**10e**).* Reaction of **5** (210 mg, 1.5 mmol) and **2e** (321 mg, 1.7 mmol) according to the general procedure gave **10e** (470 mg, 96%) as a brown solid; mp 240–242 °C (dec); $R_f$ 0.27 ($CH_2Cl_2$/MeOH=8.5:1.5); IR (ATR) $\tilde{\nu}$ 2965, 2118, 1596, 1476, 1419, 1366, 1300, 1251, 1214, 905, 850, 801 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.07 (s, 9H, $^t$Bu), 6.53 (d, $J$=8.3 Hz, 1H, 5′-H), 6.71 (d, $J$=8.3 Hz, 1H, 6′-H), 8.88 (br s, 1H, OH), 9.60 (br s, 1H, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 29.7 ($CH_3$-$^t$Bu), 31.9 (C-$^t$Bu), 102.5 (C-4), 113.2 (C-6′), 115.2 (C-3′), 123.5 (C-5′), 126.6 (C-4′), 142.7 (C-2′), 144.8

(C-1′), 147.8 (C-3), 159.0 (C-5); MS (ESI) *m/z* (%) 329.0 (100) $[M+H]^+$, 359.0 (5) $[M+Na]^+$; HRMS (ESI) calculated for $C_{13}H_{15}BrN_2O_3$ 326.0266, found 326.0267.

*4.2.6. 4′-(3-tert-Butyl-5-hydroxy-1H-pyrazol-4-yl)-5′-methylbenzene-1′,2′-diol (**11f**).* Reaction of **5** (210 mg, 1.5 mmol) and **2f** (211 mg, 1.7 mmol) according to the general procedure gave **11f** (389 mg, 99%) as a light brown solid; mp 296–298 °C (dec); $R_f$ 0.22 ($CH_2Cl_2$/MeOH=8.5:1.5); IR (ATR) $\tilde{\nu}$ 3422, 2965, 2663, 1594, 1512, 1460, 1435, 1367, 1288, 1231, 1165, 882, 821, 775 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.08 (s, 9H, $^t$Bu), 1.85 (s, 3H, $CH_3$), 6.46 (s, 1H, 3′-H), 6.54 (s, 1H, 6′-H), 8.50 (br s, 1H, OH), 8.56 (br s, 1H, OH); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$ 19.3 ($CH_3$), 29.7 ($CH_3$-$^t$Bu), 31.9 (C-$^t$Bu), 101.5 (C-4), 116.6 (C-6′), 119.7 (C-3′), 124.1 (C-4′), 128.5 (C-5′), 142.0 (C-2′), 143.9 (C-1′), 147.6 (C-3), 159.2 (C-5); MS (ESI) *m/z* (%) 263.1 (100) $[M+H]^+$, 285.1 (18) $[M+Na]^+$; HRMS (ESI) calculated for $C_{14}H_{18}N_2O_3$ 262.1317, found 262.1309.

*4.2.7. 4′-(3-tert-Butyl-5-hydroxy-1H-pyrazol-4-yl)-5′-ethylbenzene-1′,2′-diol (**11g**).* Reaction of **5** (210 mg, 1.5 mmol) and **2g** (235 mg, 1.7 mmol) according to the general procedure gave **11g** (399 mg, 96%) as a light brown solid; mp 287–292 °C (dec); $R_f$ 0.23 ($CH_2Cl_2$/MeOH=9:1); IR (ATR) $\tilde{\nu}$ 3350, 2965, 2663, 1596, 1511, 1445, 1367, 1291, 1256, 1222, 1130, 1165, 881, 815, 774 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 0.98 (t, 3H, $CH_3$-Et), 1.07 (s, 9H, $^t$Bu), 2.21 (q, 2H, $CH_2$-Et), 6.44 (s, 1H, 3′-H), 6.57 (s, 1H, 6′-H), 8.51 (br s, 1H, OH), 8.57 (br s, 1H, OH); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$ 14.9 ($CH_3$-Et), 25.3 ($CH_2$-Et), 29.8 ($CH_3$-$^t$Bu), 32.0 (C-$^t$Bu), 101.2 (C-4), 114.8 (C-6′), 119.7 (C-3′), 123.4 (C-4′), 134.6 (C-5′), 142.0 (C-2′), 144.2 (C-1′), 147.5 (C-3), 159.4 (C-5); MS (ESI) *m/z* (%) 277.1 (100) $[M+H]^+$, 299.1 (26) $[M+Na]^+$; HRMS (ESI) calculated for $C_{15}H_{20}N_2O_3$ 276.1474, found 276.1466.

*4.2.8. 3′-(3-tert-Butyl-5-hydroxy-1H-pyrazol-4-yl)-4′-nitrobenzene-1′,2′-diol (**12h**).* Reaction of **5** (210 mg, 1.5 mmol) and **2h** (264 mg, 1.7 mmol) according to the general procedure gave **12h** (340 mg, 77%) as a light yellow solid; mp >330 °C (dec); $R_f$ 0.22 ($CH_2Cl_2$/MeOH=8:2); IR (ATR) $\tilde{\nu}$ 3248, 2968, 1600, 1574, 1525, 1494, 1462, 1337, 1308, 1282, 1226, 1148, 1099, 965, 824, 761 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.06 (s, 9H, $^t$Bu), 6.84 (d, $J$=9 Hz, 1H, 6′-H), 7.37 (d, $J$=9 Hz, 1H, 5′-H), 8.73 (br s, 1H, OH), 10.48 (br s, 1H, OH); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$ 29.2 ($CH_3$-$^t$Bu), 31.9 (C-$^t$Bu), 93.0 (C-4), 113.0 (C-6′), 116.0 (C-5′), 117.3 (C-3′), 143.2 (C-4′), 145.2 (C-2′), 148.5 (C-3), 149.7 (C-1′), 158.7 (C-5); MS (ESI) *m/z* (%) 294.1 (100) $[M+H]^+$, 316.1 (28) $[M+Na]^+$; HRMS (ESI) calculated for $C_{13}H_{15}N_3O_5$ 293.1012, found 293.1004.

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## Supplementary data

$^1H$ NMR and $^{13}C$ NMR spectra of all compounds. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.03.023.

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17. The NMR data of **9b** and **10b** were taken from the NMR spectra of the 91:9 regioisomeric mixture of **9b** and **10b**.
18. The NMR data of **9d** and **10d** were taken from the NMR spectra of the 60:40 regioisomeric mixture of **9d** and **10d**.