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Understanding the planar conformations in diarylsubstituted heteroarenes: structural and theoretical insights

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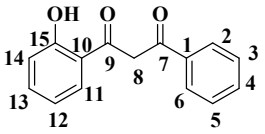
1. Synthesis and characterization of compounds 1–5

General Procedure for the Synthesis of β-Diketones (IIa-c)

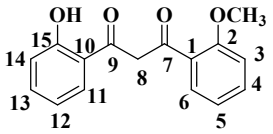
β-Diketones (IIa-c) were prepared in two steps according to a modified Baker-Venkataraman rearrangement.[1-3] In a 100 mL round bottom flask fitted with $CaCl_2$ drying tube, 0.1 mole of *o*-hydroxyacetophenone was dissolved in 30 mL of dry pyridine at room temperature. The mixture was cooled in a crushed ice box and corresponding acid chloride was added. The reaction mixture was stirred vigorously for 30 minutes keeping the flask in ice and then at ambient temperature for 30 minutes. The reaction mixture was poured with constant stirring into 500 mL ice cold 3 % HCl. The crude products (Ia-c) obtained were recrystallized from ethanol. The β-diketones IIa-c were prepared by placing 0.1 mole of the corresponding phenolic ester Ia-c in a 500 mL round bottom flask fitted with a mechanical stirrer in 150 mL of dry THF. While keeping the reaction flask in crushed ice, 1.5 mole of potassium *ter*. butoxide was added. The reaction mixture was stirred for 30 minutes in ice bath and then for 30 minutes at ambient temperature. Glacial acetic acid (15 mL) was added followed by 100 mL of water. The mixture was extracted with 3×50 mL diethyl ether. Crude product was obtained by evaporating diethylether under vacuum. The β-diketones IIa-c prepared were purified by column chromatography using ethyl acetate and petroleum ether (6:4) as eluent and recrystallized from ethanol

1-(2-Hydroxyphenyl)-3-phenylpropane-1,3-dione (IIa)



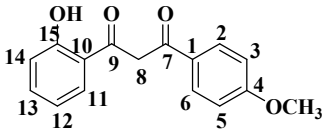
Yield: 89 %; m.p: 122-123 °C [Lit.120-122][2]; R_f: 0.65 (*n*-hexane : ethylacetate; 6 : 4); IR (ATR, $\bar{\upsilon}$): cm^{-1} 3412 (O-H stretch), 1721 (C=O stretch), 1567, 1486 (2×C=C stretch), 1249, 1024 (2×C-O stretch), 747 (C_{sp^2}-H bend). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 12.10 (1H, bs, OH), 7.95-8.20 (3H, m, H-2,6,11), 6.90-7.89 (6H, m, H-3,4,5,12,13,14), 6.85 (2H, s, H-8). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 201.3, 193.7, 162.4, 136.5, 135.5, 134.9, 133.2, 130.3, 128.6, 125.9, 121.0, 118.5, 97.5.

1-(2-Hydroxyphenyl)-3-(2-methoxyphenyl)propane-1,3-dione (IIb)



Yield: 73 %; m.p: 79-80 °C [Lit. 79.5-80][3]; R_f: 0.65 (*n*-hexane : ethylacetate; 6 : 4); IR (ATR, $\bar{\upsilon}$): cm^{-1} 3400 (O-H stretch), 1724 (C=O stretch), 1595, 1486 (2×C=C stretch), 1249, 1043 (2×C-O stretch), 747 (C_{sp^2}-H bend). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 12.00 (1H, bs, OH), 7.95-8.01 (1H, m, H-6), 7.71-7.76 (1H, m, H-11), 7.43-7.54 (2H, m, H-4,13), 7.00-7.11 (3H, m, H-3,5,14), 6.90-6.98 (1H, m, H-12), 6.63 (2H, s, H-8), 3.99 (3H, s, OCH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 188.0, 181.5, 159.4, 158.7, 136.4, 134.9, 134.0, 129.9, 125.3, 123.8, 121.0, 119.8, 118.0, 112.9, 101.4, 56.3.

1-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)propane-1,3-dione (IIc)

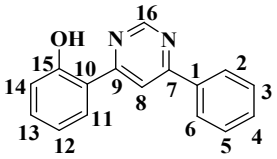


Yield: 87 %; m.p: 117-118 °C [Lit. 115-116][2]; R_f: 0.65 (*n*-hexane : ethylacetate; 6 : 4); IR (ATR, $\bar{\upsilon}$): cm^{-1} 3408 (O-H stretch), 1721 (C=O stretch), 1599, 1484 (2×C=C stretch), 1237, 1020 (2×C-O stretch), 735 (C_{sp^2}-H bend). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 11.47 (1H, bs, OH), 8.01 (2H, d, J = 9.0 Hz, H-2,6), 7.43-7.48 (1H, m, H-13), 7.33 (2H, bs, H-8), 6.93-7.01 (5H, m, H-3,5,11,12,14), 3.85 (3H, s, OCH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 187.9, 182.6, 163.5, 159.8, 136.4, 135.0, 131.2, 129.7, 126.9, 119.7, 118.0, 114.7, 94.8, 56.0.

General procedure for the synthesis of 4,6-diarylpyrimidines[4] (1 and 2)

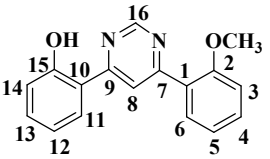
The respective β-diketone (IIa-b; 0.01mole) was taken in a round bottom flask fitted with a reflux condenser and a magnetic stirrer. Formamide (20 mL) was poured into reaction flask and the mixture refluxed for 8 hours. The colour of the reaction mixture turned dark brown. The reaction mixture was cooled down to room temperature and poured into 100 mL ethanol : water (70:30) mixture. The mixture was kept for 24 hours at room temperature; the brownish mass appeared was filtered and dried. The crude product was soxhlet extracted using *n*-hexane and recrystallized from ethanol.

2-(6-Phenylpyrimidin-4-yl)phenol (1)



Yield: 75 %; m.p: 133-134 °C ; R_f: 0.45 (*n*-hexane : ethylacetate; 6 : 4); IR (ATR, $\bar{\upsilon}$): cm^{-1} 3394 (O-H stretch), 1579 (C=N stretch), 1521, 1497 (2×C=C stretch), 1218, 1048 (2×C-O stretch), 826 (C_{sp^2}-H bend). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 13.25 (1H, bs, OH), 9.27 (1H, s, H-16), 8.71 (1H, s, H-8), 8.34-8.37 (3H, m, H-2,6,11), 7.56-7.60 (3H, m, H-3,4,5), 7.40-7.46 (1H, m, H-13), 6.98-7.02 (2H, m, H-12,14). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 164.5 (2×C), 160.4, 157.0, 136.5, 133.8, 131.8, 129.4, 129.0, 127.8, 119.7, 118.4, 118.3, 112.4.

2-(6-(2-Methoxyphenyl)pyrimidin-4-yl)phenol (2)



Yield: 69 %; m.p: 100-101 °C; R_f: 0.40 (*n*-hexane : ethylacetate; 6 : 4); IR (ATR, $\bar{\upsilon}$): cm^{-1} 3393 (O-H stretch), 2970, 2840 (2× C_{sp}3-H stretch), 1600 (C=N stretch), 1576, 1494 (2×C=C stretch), 1454 (C_{sp}3-H bend), 1248, 1022 (2×C-O stretch), 851 (C_{sp^2}-H bend). ^{1}H-NMR (300 MHz,$CDCl_3$): δ (ppm) 12.87 (1H, bs, O-H), 9.26 (1H, s, H-16), 8.63 (1H, s, H-8), 8.03 (1H, dd, J = 6.3, 1.5 Hz, H-11), 7.93 (1H, dd, J = 5.7, 1.8 Hz, H-6), 7.49-7.55 (1H, m, H-4), 7.38-7.43 (1H, m, H-13), 7.20-7.23 (1H, m, H-3), 7.09-7.14 (1H, m, H-14), 6.95-7.01 (2H, m, H-5,12), 3.91 (3H, s, OCH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 163.6, 163.3, 159.8, 158.2, 157.0, 133.6, 133.4, 131.0, 128.6, 125.9, 121.2, 119.8, 118.8, 118.4, 117.3,112.6, 56.2.

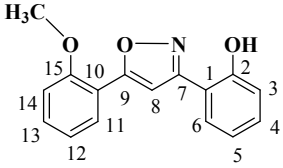
General procedure for the synthesis of 3,5-diarylisoxazoles[5] (3a, 3b and 5)

The respective β-diketone (IIb,c; 0.01 mole) was taken in a 100 mL round bottom flask fitted with a condenser and stirrer. Pyridine (60 mL) was added and warmed the mixture with stirring till complete dissolution. To the mixture, 0.015 mole of hydroxylamine hydrochloride was added and the mixture refluxed for four hours while monitoring with TLC. After complete consumption of starting materials, the reaction mixture was poured onto 200 g of crushed ice. The precipitates formed were filtered and washed with distilled water followed by 10 mL of 20 % acetic acid. The crude products were purified by column chromatography and further recrystallized from ethanol. Regioisomers 3a was eluted prior to 3b.

Procedure for the synthesis of 2-(5-(4-Hydroxyphenyl)isoxazol-3-yl)phenol[5] (4)

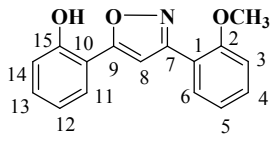
The compound 5 was taken in a 250 mL round bottom flask fitted with a reflux condenser. HBr (48 %, 50 mL) was added carefully in the reaction flask and the mixture was heated at 100 °C for 1 hour. After cooling to room temperature, glacial acetic acid (45 mL) was added with care and the mixture refluxed for twenty hours. The reaction mixture was cooled to room temperature, poured into 200 mL of ice cold water, and allowed to stay overnight. Solid appeared was filtered, washed with water, and recrystallized from ethanol.

2-(5-(2-Methoxyphenyl)isoxazol-3-yl)phenol (3a)



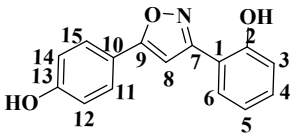
Yield: 21 %; m.p: 106-107 °C [Lit.141-143][6]; R_f: 0.82 (chloroform : methanol; 6 : 4); IR (ATR, $\bar{\upsilon}$): cm^{-1} 3250 (O-H stretch), 3086 (C_{sp^2}-H stretch), 2962, 2836 (2×C_{sp}3-H stretch), 1604 (C=N stretch), 1588, 1471 (2×C=C stretch), 1454, 1385 (C_{sp}3-H bend), 1252, 1054 (2×C-O stretch), 755 (C_{sp^2}-H bend). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 10.10 (1H, bs, OH), 7.89 (1H, dd, J = 7.8, 1.5 Hz, H-11), 7.77 (1H, dd, J = 7.8, 1.5 Hz, H-6), 7.48-7.54 (1H, m, H-4), 7.37 (1H, s, H-8), 7.30-7.36 (1H, m, H-13), 7.26 (1H, d, J = 8.4 Hz, H-14), 7.16 (1H, t, J = 7.5 Hz, H-12), 7.04 (1H, d, J = 8.1 Hz, H-3), 6.91 (1H, t, J = 7.8 Hz, H-5), 3.96 (3H, s, OCH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 165.2, 161.2, 156.3, 156.0, 132.1, 131.7, 129.1, 127.4, 121.3, 119.8, 117.1, 115.9, 115.6, 112.6, 104.7, 55.9.

2-(3-(2-Methoxyphenyl)isoxazol-5-yl)phenol (3b)



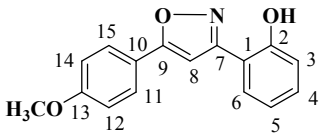
Yield: 49 %; m.p: 208-209 °C; R_f: 0.71 (chloroform : methanol; 6 : 4); IR (ATR, $\bar{\upsilon}$): cm^{-1} 3286 (O-H stretch), 3016 (C_{sp^2}-H stretch), 2970, 2836 (2×C_{sp}3-H stretch), 1608 (C=N stretch), 1568, 1495 (2×C=C stretch), 1426 (C_{sp}3-H bend), 1252, 1047 (2×C-O stretch), 748 (C_{sp^2}-H bend). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 10.62 (1H, bs, OH), 7.80-7.86 (2H, m, H-6,11), 7.46-7.52 (1H, m, H-13), 7.32-7.37 (1H, m, H-4), 7.31 (1H, s, H-8), 7.19 (1H, d, J = 8.1 Hz, H-14), 7.06-7.11 (2H, m, H-5,12), 6.96 (1H, d, J = 7.8 Hz, H-3), 3.89 (3H, s, OCH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 166.0, 160.6, 157.4, 155.1, 131.9, 131.7, 129.4, 127.2, 121.2, 119.9, 118.0, 116.9, 115.5, 112.6, 104.7, 56.1.

2-(5-(4-hydroxyphenyl)isoxazol-3-yl)phenol (4)



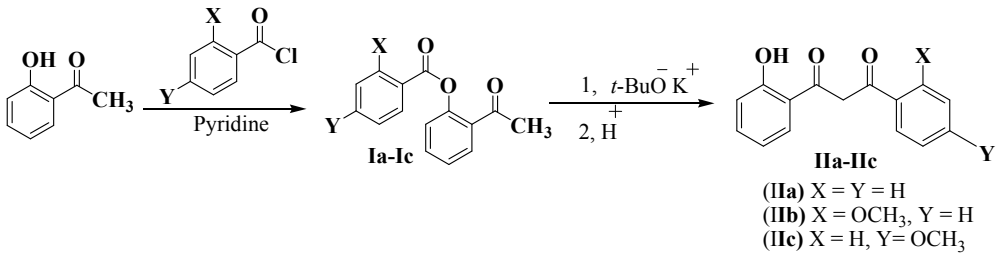
Yield: 67 %; m.p: 180-181 °C [Lit. 86-88][7]; R_f: 0.38 (petroleum ether : acetone; 6 : 4); IR (ATR, $\bar{\upsilon}$): cm^{-1} 3357 (O-H stretch), 1606 (C=N stretch), 1586, 1467 (2×C=C stretch), 1219, 1037 (2×C-O stretch), 842 (C_{sp^2}-H bend). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 10.08 (2H, s, OH), 7.73-7.76 (3H, m, H-6,11,15), 7.29 -7.35 (1H, m, H-4), 7.24 (1H, s, H-8), 7.02 (1H, d, *J* = 7.5 Hz, H-3), 6.90-6.96 (3H, m, H-5,12,14). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 169.4, 161.2, 159.8, 156.0, 131.7, 129.1, 127.8, 119.8, 118.5, 117.0, 116.4, 115.6, 99.2.

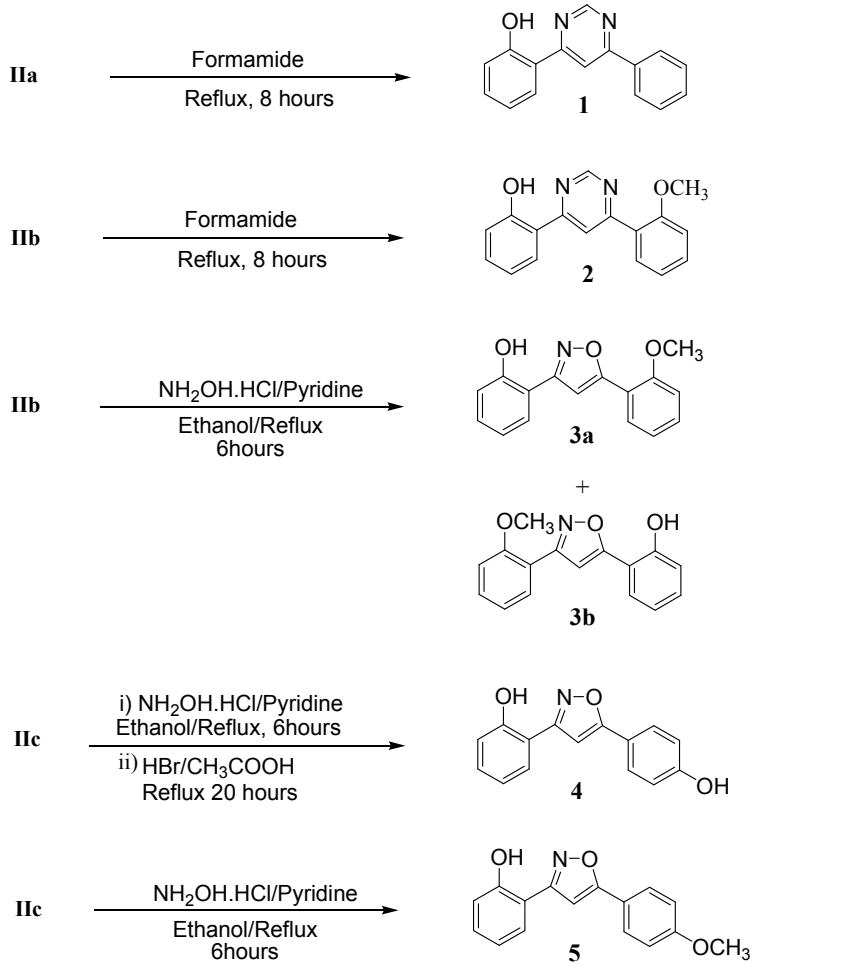
2-(5-(4-Methoxyphenyl)isoxazol-3-yl)phenol (5)



Yield: 23 %; m.p: 139-140 °C [Lit. 137-138.5][8]; R_f: (chloroform : methanol; 6 : 4); IR (ATR, $\bar{\upsilon}$): cm^{-1} 3192 (O-H stretch), 3054 (C_{sp^2}-H stretch), 2945, 2841 (2×C_{sp}3-H stretch), 1598 (C=N stretch), 1582, 1477 (2×C=C stretch), 1451 (C_{sp^3}-H bend), 1245, 1032 (2×C-O stretch), 826 (C_{sp^2}-H bend). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 10.08 (1H, bs, OH), 7.85 (2H, d, *J* = 8.7 Hz, H-11,15), 7.74 (1H, dd, *J* = 6.3, 1.5 Hz, H-6), 7.31-7.36 (1H, m, H-4), 7.30 (1H, s, H-8), 7.08 (2H, d, *J* = 8.7 Hz, H-12,14), 7.02 (1H, d, *J* = 7.8 Hz, H-3), 6.91-6.96 (1H, m, H-5), 3.83 (3H, s, OCH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 169.0, 161.3, 161.2, 156.0, 131.7, 129.1, 127.2, 119.8, 117.0, 115.5, 115.1, 99.0, 55.8.

2. Scheme S1





Scheme S1. Synthesis of diarylsubstituted hetarenes **1**–**5**

3. Figure S1

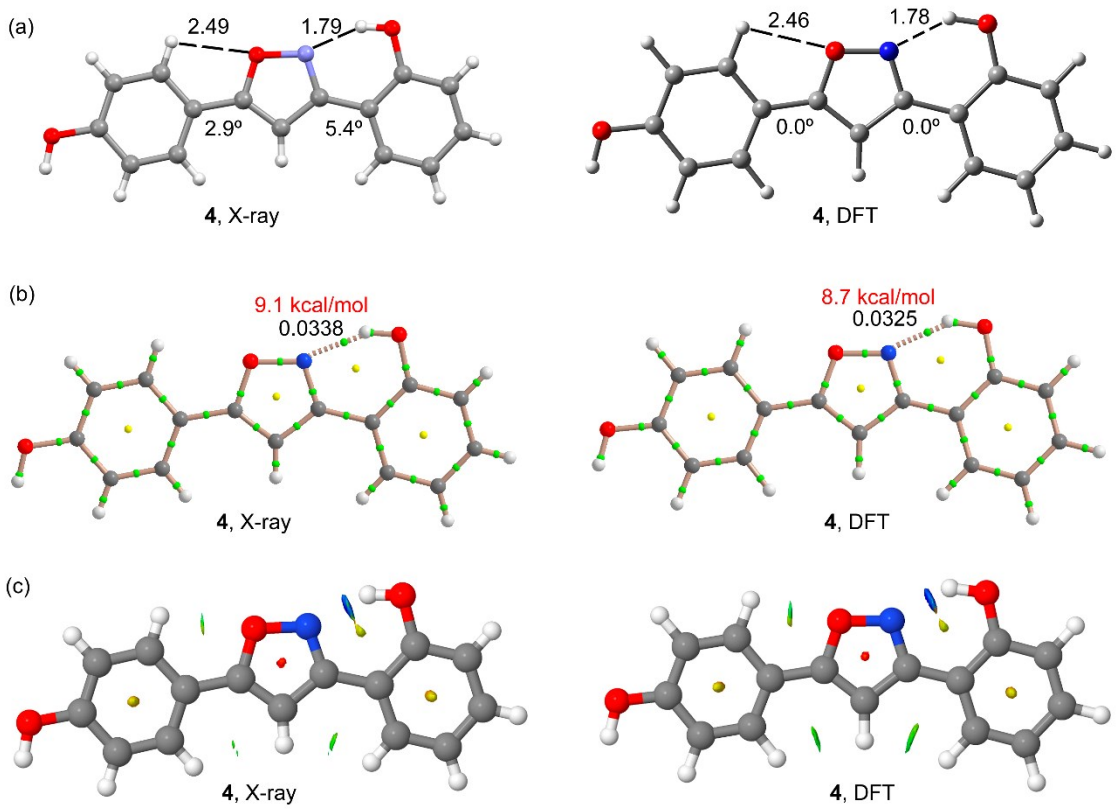


Figure S1. (a) X-ray structure (left) and DFT-optimized geometry (right) of compound **4**, distances in Å. The torsion angels between the rings are given in degrees. (b) AIM distribution of bond and ring critical points (green and yellow spheres, respectively) and bond paths in the X-ray (left) and optimized (right) structures of compound **4**. The values of the Lagrangian kinetic energy density at the bond CPs are given in a.u. (in black) and the dissociation energy of the hydrogen bond are given in red. (c) NCIplot of the X-ray (left) and optimized (right) structures of compound **4**.

4. Figure S2

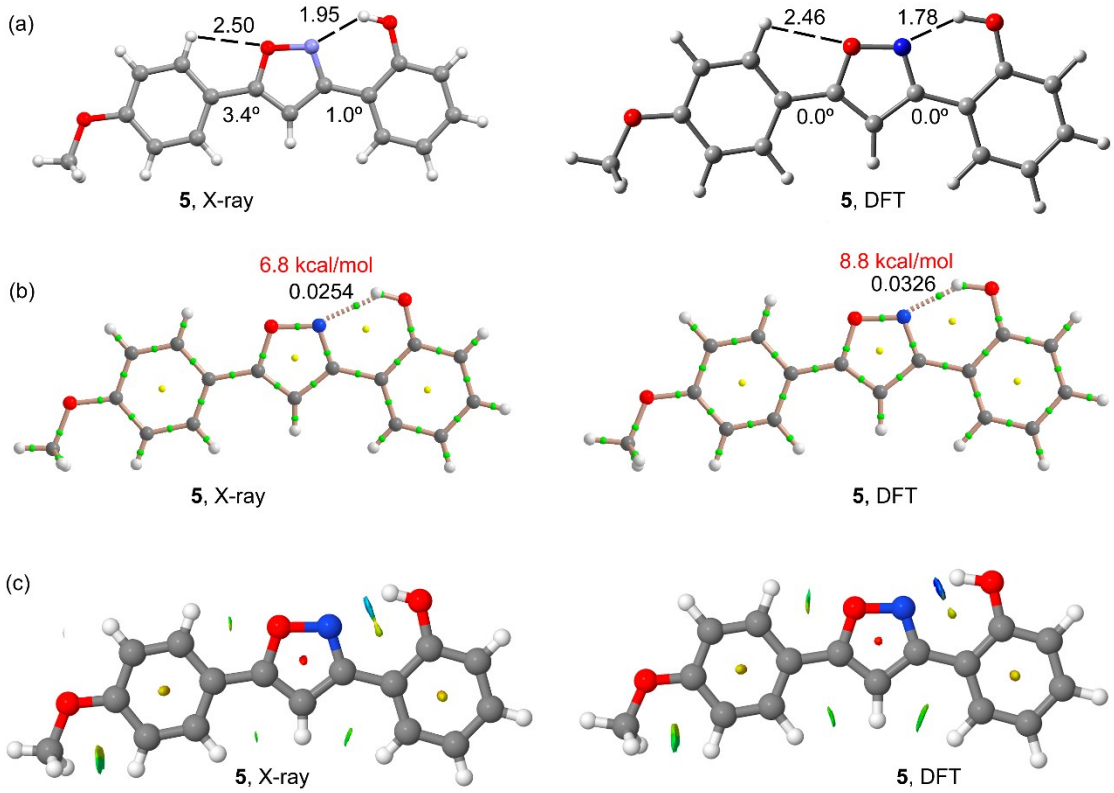


Figure S2. (a) X-ray structure (left) and DFT-optimized geometry (right) of compound **5**, distances in Å. The torsion angels between the rings are given in degrees. (b) AIM distribution of bond and ring critical points (green and yellow spheres, respectively) and bond paths in the X-ray (left) and optimized (right) structures of compound **5**. The values of the Lagrangian kinetic energy density at the bond CPs are given in a.u. (in black) and the dissociation energy of the hydrogen bond are given in red. (c) NCIplot of the X-ray (left) and optimized (right) structures of compound **5**.

5. Figure S3

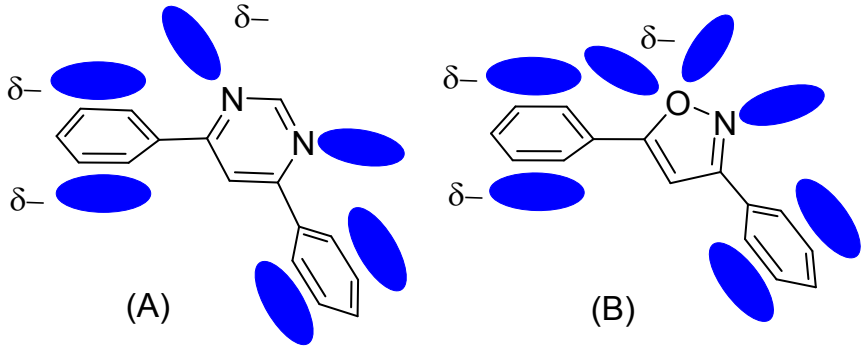


Fig. S3 Showing repulsive interactions between the lone pair of a hetero atom and the negative π cloud of the terminal ring.

6. Figure S4

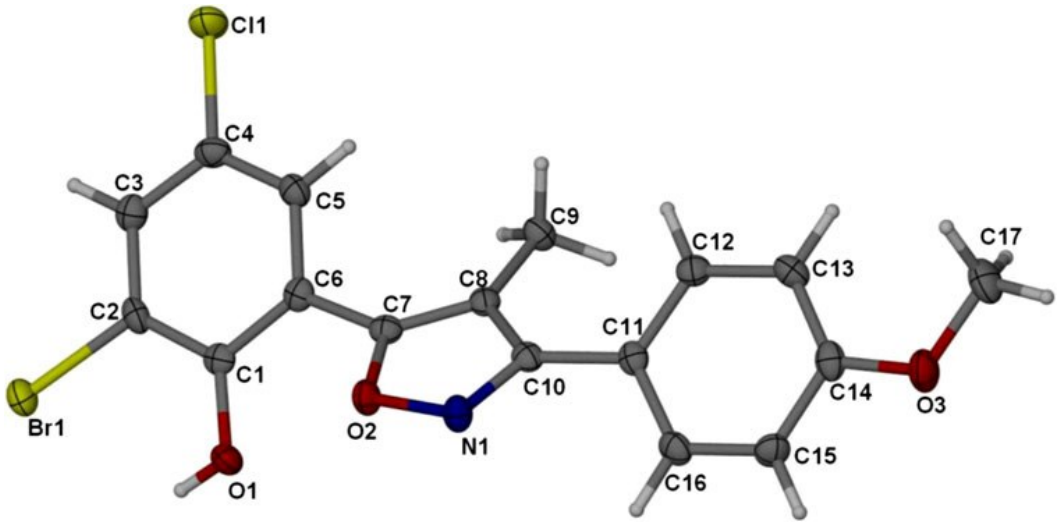


Fig. S4 The molecular structure of non-planar diaryl substituted heteroarene

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