Reactivity studies on a novel 4-(2-hydroxyphenyl)-1,3-dihydro-1,5-benzodiazepine-2-thione

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The novel 4-(2-hydroxyphenyl)-1,3-dihydro-1,5-benzodiazepine-2-thione (**4**) has been synthesised and used as precursor to the hitherto unreported 7-methylthio[1]benzopyrano[4,3-*c*][1,5]-benzodiazepine (**7**). Hydrazinolysis of **4** gave 5-(2-aminophenylamino)-3-(2-hydroxyphenyl)-1*H*-pyrazole (**9**) which with excess of *N*,*N*-dimethylformamide dimethylacetal formed the 5-(2-hydroxyphenyl-2*H*-pyrazol-3-yl)-1*H*-benzimidazole (**10**).

Keywords: benzodiazepines, fused benzopyrans, benzodiazepinethiones, dimethylformamide dimethylacetal

Since the fusion of heterocyclic rings to the *a*, *b*, *c*, or *d* sides of a benzodiazepine system has proved especially promising for the synthesis of derivatives of enhanced biological activity,[1,2] renewed interest has been directed towards fused 1,4- and 1,5-benzodiazepine chemistry.[3-5] In this field we have recently described the synthesis and studied the reactivity of the tetracyclic [1]benzopyrano[4,3-*c*][1,5]benzodiazepin-7(8*H*)-one (**3**).[6,7] These findings made us aware of the paucity of molecular features combining the chromone and the benzodiazepine moieties, and encouraged our interest to explore routes to analogs to **3** and to report here our results.

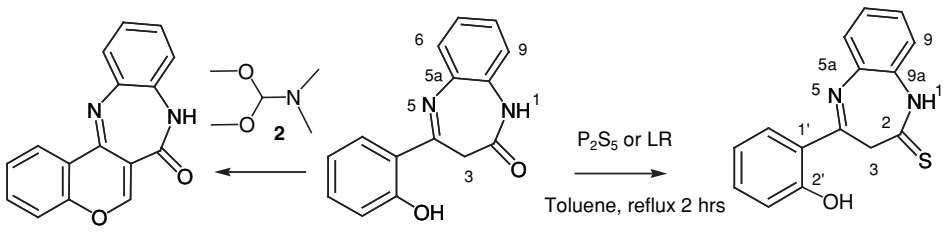
Results and discussion

The general concept we have used for the construction of the benzopyrano[4,3-*c*]benzodiazepine target-system was based on the two-step formylation/cyclisation of 1,5-benzodiazepines having an active methylene and a 2-hydroxyphenyl group at the 3- and 4- positions, respectively. *N*,*N*-Dimethylformamide dimethylacetal (DMFDMA) (**2**) has been found to be a most useful formylating agent of 4-(2-hydroxyphenyl)-1,3-dihydro-1,5-benzodiazepin-2-one (**1**), forming the 3-dimethylaminomethylene intermediate then cyclising *in situ* to **3**.[6] However, considering the relative lack of reactivity often observed for the methylene group at the 3-position, we thought it interesting to see whether suitable chemical transformation of **1** could result in a synthon of higher reactivity. Consequently, **1** was converted into the corresponding thiolactam **4** through interaction with phosphorus pentasulfide or Lawesson reagent (LR) in refluxing anhydrous toluene (Scheme 1). The structure of the obtained 4-(2-hydroxyphenyl)-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thione (**4**) was fully characterised by mass spectrometry, and both 1D and 2D NMR spectroscopical methods (see Experimental section).

To examine further the behaviour of **4** towards DMFDMA, the thiolactam was firstly reacted with a slight excess of the formamide acetal for 10 min in dry hot toluene. The reaction monitored by TLC has been found to be selective in that only the tautomeric methylthioiminoether **5** has been formed (Scheme 2). Such a process in which *S*-methylation is the first reaction to take place was earlier described by Stanovnik *et al.* for the *S*-methylation of many mercapto-heterocycles.[8]

The ^{1}H NMR spectrum of compound **5** (500 MHz, $CDCl_3$), exhibited signals which can, according to chemical shifts and multiplicities, be assigned to the methyl attached to sulfur (3H singlet, 2.48 ppm), a broad singlet at 3.46 ppm integrating two protons consistent with the methylenic hydrogens, and eight aromatic protons appeared as a set of characteristic signals between 6.98 ppm and 7.80 ppm. The ^{13}C spectrum reinforced by a HMBC experiment allowed unambiguous assignments for all carbons, namely CH_3-S at 14.1 ppm, C-3 at 38.0 ppm, C-2 at 157.5 ppm, C-4 at 158.2 ppm, and aromatic carbons (see Experimental section). The mass spectrum recorded in electron impact mode showed a stable molecular ion [M^+] at *m/z* 282 and a base peak at *m/z* [M-47]$^+$, which was in accordance with the formation of a stable daughter fragment involving loss of a methylsulfide unit.[9]

The second step of the reaction involved the benzopyran ring closure *via* the transformation of the methylene group into its dimethylaminomethylene derivative followed by intramolecular condensation of the phenolic OH group. Such a strategy is widely used in heterocyclic synthesis.[10] More vigorous conditions were required to bring this reaction about. Treatment of compound **4** with a large excess of DMFDMA for two hours in hot anhydrous toluene gave, after removal of the solvent, an oily residue from which the main product (60%), isolated after crystallisation from ethanol, was identified from its spectral data as 3-(dimethylaminomethylene)-4-(2-hydroxyphenyl)-2-methylthio-1,5-benzodiazepine (**6**). Work-up of the mother liquor gave a very small amount (5%) of the corresponding cyclised form **7** (Scheme 2).



3 **1** **4**

Scheme 1

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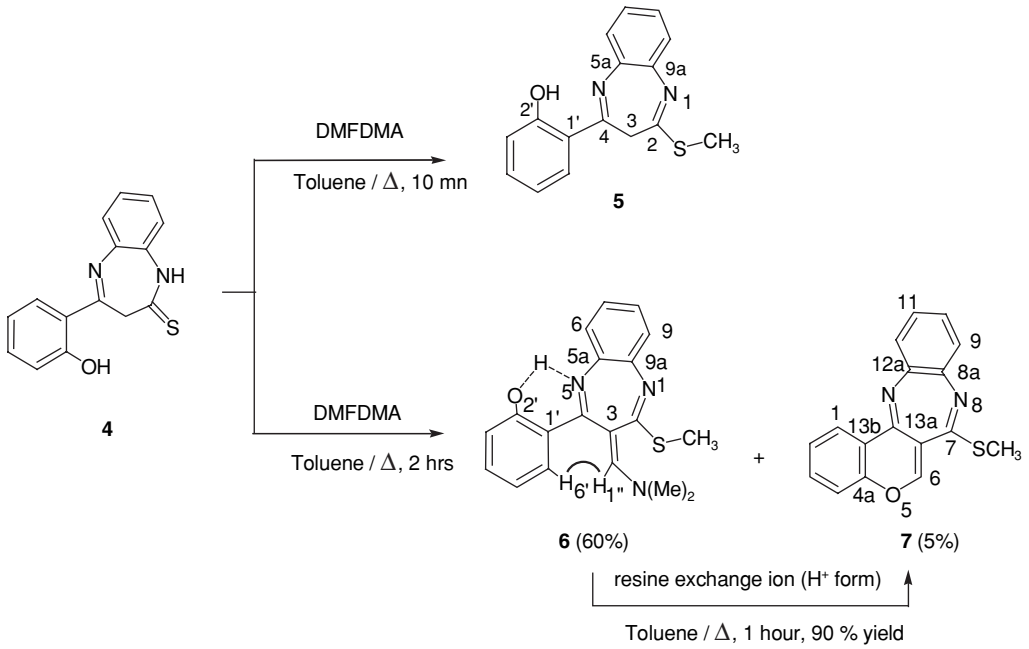
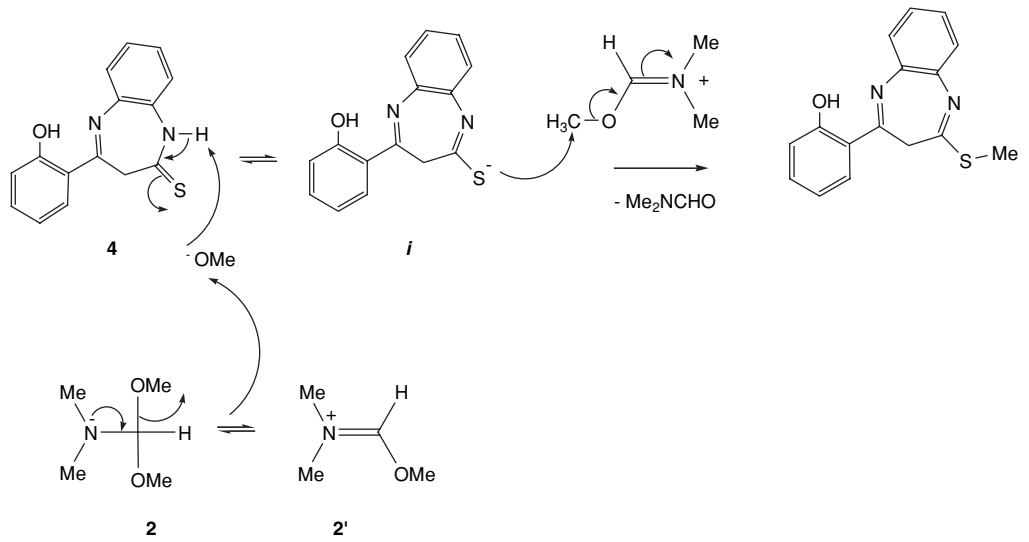


Scheme 2

The ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of compound **6** was very similar to that of the precursor **5** but revealed in particular the disappearance of the signal relative to the methylenic hydrogens at C-3 in favour of a six-proton inglet at 2.60 ppm and a one-proton singlet at 6.73 ppm, corresponding to the dimethylamino group and the methylidene proton, respectively. It seemed that the reluctance of compound **6** to cyclise to **7** could be rationalised in terms of a strong intramolecular hydrogen bond between the hydroxyl and the nitrogen at the 5-position. This fact was supported by the high δ value of the phenolic proton (~15 ppm) and the NOE observed between the methylidene proton (singlet at 6.73 ppm) and the aromatic H-6' (dd, 7.52 ppm) (see Scheme 2). This limitation, which also in part be derived from the steric hindrance of the dimethylamino group and its strong electron donating properties reducing the electrophilic character at carbon, was, however, overcome by treating compound **6** with an ion exchange resin (H^+ form), affording **7** in very good yield as a stable yellow crystalline solid. The ^{1}H spectrum (500 MHz, DMSO-d_6) of the 7-methylthio[1]benzopyrano [4,3-*c*][1,5]benzodiazepine (**7**) showed the presence of a singlet at 2.41 ppm for the S-CH_3, the eight aromatic hydrogens signals appearing between 7.05 ppm and 8.02 ppm, and the signal (s, 8.04 ppm) from H-6 of the benzopyran ring. Total NMR spectral assignments for all protons and carbons were performed by mean of 2D NMR spectroscopic techniques (see Experimental section).

Our approach to the 2-methlylthio-1,5-benzodiazepine system in compound **5** is advantageous in that it does not involve the traditional treatment of thiolactams with a base followed by the *in situ* alkylation of the generated sulfide anion.[11] As depicted in Scheme 3, the one-pot mechanism of the sulfur methylation may occur through the formation of the positively charged species **2**' involving shift of the lone electron pair on the nitrogen atom of **2** with concomitant loss of methoxide anion, which may deprotonate the amide nitrogen of the benzodiazepine-2-thione (**4**). The so-formed sulfide anion ***i*** can then attack the iminium cation **2**' at the methyl group thus forming the *S*-methylated product with release of a *N,N*-dimethylformamide molecule.[12]

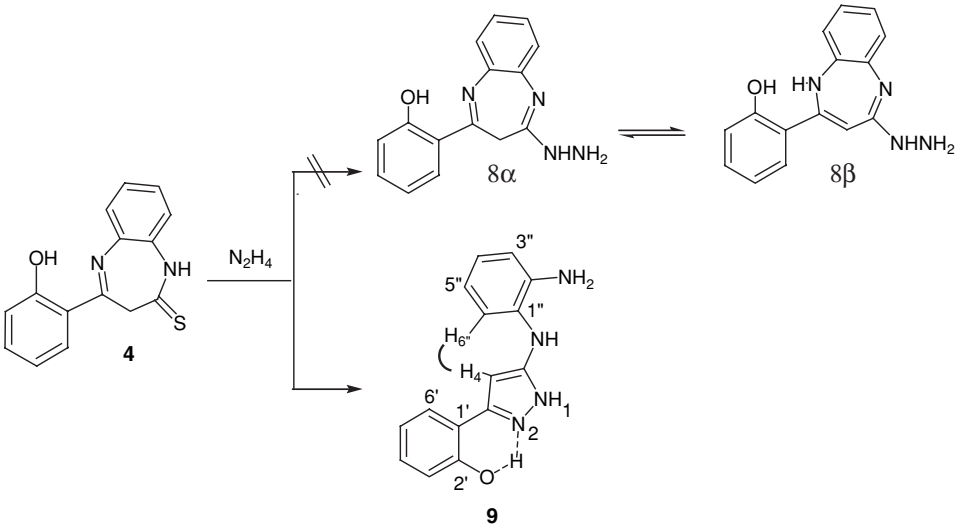


Scheme 3

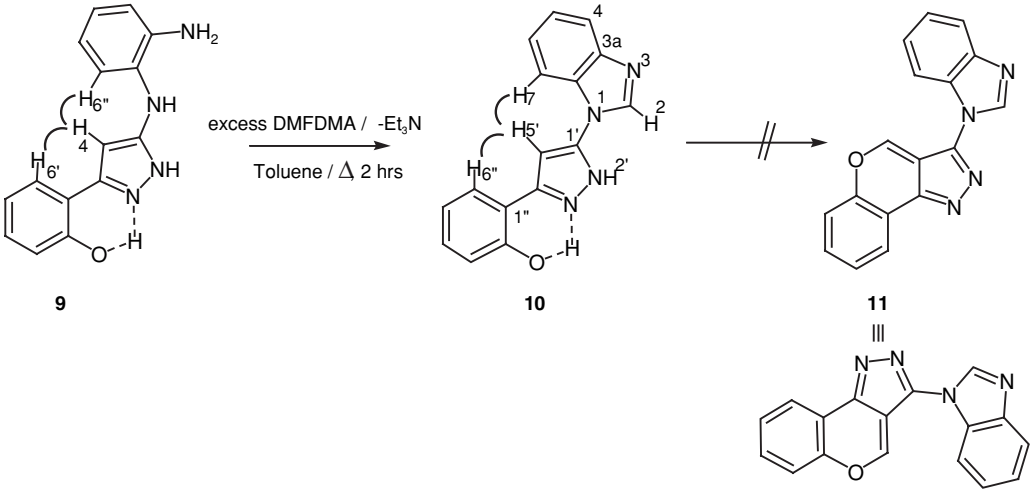
Pursuing our investigations into the reactivity of compound **4**, we aimed to form the 2-hydrazino-4-(2-hydroxyphenyl)-3*H*-1,5-benzodiazepine (**8**α). Thus,our first goal, by treatment with excess of DMFDMA, was to annelate a benzopyran and a triazole nucleus to the *a* and *c* faces of the benzodiazepine ring, respectively. In an attempt to functionalise the thiolactam moiety to form the corresponding hydrazino-amidine, compound **4** (or the iminothioether **5**) was treated for two hours with a slight excess of hydrazine hydrate in ethanol at room temperature, affording a single product **9** which was formulated as 5-(2-aminophenylamino)-3-(2-hydroxyphenyl)-1*H*-pyrazole. In fact, as formation of the tautomeric form **8**β may also be envisaged,[13] and since this and compound **9** cannot be distinguished on the base of simple spectral data (^{1}H and ^{13}C NMR); a NOESY experiment was carried out, which revealed the correlation between the pyrazolic H-4 (s, 6.40 ppm) and the aromatic H-6" (brd, 7.56 ppm) of the 2-aminophenylamino residue. This is consistent with the proposed structure **9**, rather than the hydrazino-amidine **8**β (Scheme 4). Such a ring contraction is not surprising, as rearrangement and aromatization reactions in the benzodiazepine series has been well documented;[14,15] in particular Essasi *et al.*[16] have earlier reported the formation of an analogous pyrazole system by hydrazinolysis of 4-phenyl-1,3-dihydro-1,5-benzodiazepine-2-thione.

Although the main aim of this work was to gain access to the benzopyrano[4,3-*c*]benzodiazepine system we were interested to see how compound **9** would behave towards excess of DMFDMA, when reaction at both the 4-position and the free amino group, to the corresponding *N,N*-dimethylaminomethylene and *N,N*-(dimethylaminomethylene)amino functionalities, respectively, followed by intramolecular cyclisations, could be expected to generate the 7-(1*H*-benzimidazol-1-yl)[1]benzopyrano[4,3-*c*]pyrazole (**11**). Unfortunately, repeated attempts proved unsuccessful, and 5-(2-hydroxyphenyl-2*H*-pyrazol-3-yl)-1*H*-benzimidazole (**10**) was always isolated as the major product whatever the reaction conditions tried. Indeed the observed NOE cross-peaks between the pyrazole proton H-5' (s, 7.15 ppm) and both H-6" (d, 7.71 ppm) and H-7 (d, 8.07 ppm) in structure **10**, placed the aromatic hydroxy group (δ 13.16 ppm) close to the pyrazole sp^2-hybridised nitrogen; establishment of strong intramolecular H-bonding can account for the marked stability of this compound (Scheme 5).

In conclusion, the thionation of compound **1** afforded the corresponding benzodiazepinethione **4** which exhibited an enhanced reactivity, allowing a versatile access to novel fused 7-methylthio[1]benzopyrano[4,3-*c*][1,5]benzodiazepine (**7**). On hydrazinolysis of compound **4** a ring contraction afforded 5-(2-aminophenylamino)-3-(2-hydroxyphenyl)-1*H*-pyrazole (**9**). Despite the failure to transform **9** into the corresponding



Scheme 4



Scheme 4

7-(1*H*-benzimidazol-1-yl)benzopyrano[4,3-c]pyrazole (**11**) in so far as it possesses several reactive sites, a number of synthetic routes to other heterocycles are now under investigation.

Experimental

Melting points were taken on a Buchi-510 capillary apparatus. IR spectra were recorded with a Perkin-Elmer Spectrum BX FT-IR apparatus, as films on NaCl. ^{1}H (500.13 MHz), ^{13}C (125.77 MHz) and two-dimensional NMR experiments were performed with an Avance-500 Bruker spectrometer. Chemical shifts are measured in ppm on the δ scale. Mass spectra were obtained with an Automass Multi Thermo Finnigan (electron impact mode, 70 eV) spectrometer. All the reactions were followed by TLC using aluminium sheets of Merck silica gel 60 F_{254}, 0.2 mm, Merck silica gel 60 (40–63 μm) was used for column chromatography. Elemental analyses were performed at the Institut de Chimie des Substances Naturelles, CNRS de Gif-sur-Yvette, France.

The benzopyrano-benzodiazepinone **1** was prepared following our previously described procedure,[6] using the two-step formylation/cyclisation reaction between 4-(2-hydroxyphenyl)-1,5-benzodiazepin-2-one[17] and excess of DMFDMA.

4-(2-Hydroxyphenyl)-1,3-dihydro-1,5-benzodiazepine-2-thione (**4**): 4-(2-Hydroxyphenyl)-1,3-dihydro-1,5-benzodiazepin-2-one (**1**) 2 g (8 mmol) was dissolved in anhydrous toluene (150 ml), and P_4S_{10} (3.5 g, 2 eq.) was added, under vigorous stirring. After refluxing the mixture for 2 h, the suspension was filtered, then washed several times with water. Crystallisation from methanol and ethyl acetate (2 : 1 v/v) gave the pure benzodiazepinethione **4**.

Compound **4** formed a woolly pale yellow solid, m.p. 290 C; yield 60 %. IR (cm^{-1}) $\nu_{C=S}$ 1060, $\nu_{C=N}$ 1590, ν_{N-H} 3207, ν_{0-H} 3446. ^{1}H NMR (DMSO-d_6): δ 3.98 (brs, 2H, H-3), 6.98 (dd, 1H, H-3'), 7.03 (ddd, 1H, H-5'), 7.35–7.42 (m, 3H, (H-7, H-8, H-9) 7.48 (ddd, 1H, H-4'), 7.52 (m, 1H, H-6), 8.02 (dd, 1H, H-6'), 12.72 (s, 1H, NH), 13.81 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ 46.6 (C-3), 117.5 (C-3'), 117.8 (C-1'), 118.0 (C-5'), 122.4 (C-9), 126.2 (C-7), 127.0 (C-8), 127.8 (C-6), 130.1 (C-6') 132.1 (C-9a), 134.2 (C-4'), 137.7 (C-5a), 161.5 (C-2'), 163.4 (C-4), 192.9 (C-2). MS (EI): *m/z*, (%): 268 (93) [M$^{+\cdot}$], 235 (100), 210 (83), 182 (73), 58 (74). Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44; O, 5.96; S, 11.95. Found: C, 67.04; H, 4.45; N, 10.65; O, 5.53; S, 11.87 %.

2-Methylthio-4-(2-hydroxyphenyl)-3H-1,5-benzodiazepine (**5**): Compound **4** (536 mg, 2 mmol) in anhydrous toluene (25 ml) containing DMFDMA (0.3 ml, 1.2 eq). was heated at 100 °C and stirred for 10 min. The volatile components were evaporated *in vacuo* and the oily orange residue was crystallised from methanol to afford the methylthio derivative **5**.

Compound **5** formed yellow crystals (70%); m.p. 127 °C. IR (cm^{-1}) $\nu_{C=N}$= 1593, ν_{0-H}= 3433. ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H, SMe), 3.46 (brs, 2H, H-3), 6.98 (brdd, 1H, H-5'), 7.05 (brd, 1H, H-3'), 7.28 (ddd, 1H, H-7), 7.33 (ddd, 1H, H-8), 7.42 (ddd, 1H, H-4'), 7.44–7.49 (m, 2H, (H-6, H-9)), 7.80 (dd, 1H, H-6'), 14.5 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3-S), 38.0 (C-3), 117.8 (C-1'), 118.5 (C-3'), 118.8 (C-5'), 125.1 (C-7), 126.5 (C-8), 128.1 (C-6), 128.6 (C-9), 128.8 (C-6'), 133.8 (C-4'), 136.8 (C-5a), 141.4 (C-9a), 157.5 (C-2), 158.2 (C-4). MS (EI): *m/z*, (%): 282 (68) [M$^{+\cdot}$], 235 (100), 89 (69). Anal. Calcd. for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92; O, 5.67; S, 11.36. Found: C, 67.98; H, 5.09; N, 9.86; O, 5.46; S, 11.28 %.

Synthesis of compounds **6** *and* **7**: To the diazepinethione **4** (1.072 g, 4 mmol) in dry toluene (75 ml) was added DMFDMA (3.2 ml, –6 eq), and the solution was heated at 100 °C for 2 h. Removal of the volatile components under reduced pressure gave a brownish red oily residue which was dissolved in ethanol (50 ml). Crystallisation of the major product **6** (810 mg, 60%) occurred upon standing at room temperature for 2–3 h. The remaining ethanolic mother liquor was concentrated to half of its original volume, water (10 ml) was added, and the solution then left to stand overnight, to afford a small quantity of compound **7** (62 mg, 5 %).

Transformation of **6** *into* **7**: Compound **6** (404 mg, 1.2 mmol) was dissolved in dry toluene (25 ml). An ion exchange resin (100 mg, H^+ form) was added and the mixture was stirred at 100 °C for 1 h. The catalyst was filtered off and the solvent evaporated *in vacuo*. The orange oily residue dissolved in 25 ml of ethanol gave 315 mg (90 %) of **7**.

3-(Dimethylaminomethylene)-4-(2-hydroxyphenyl)-2-methylthio-1,5-benzodiazepine (**6**): yellow crystals; m. p. 138 °C. IR (cm^{-1}) $\nu_{C=N}$ 1593, $\nu_{C=C}$ 1452, ν_{O-H} 3435. ^{1}H NMR (DMSO-d_6): δ 2.47 (s, 3H, SMe), 2.60 (s, 6H, NMe_2), 6.73 (s, 1H, H-1"), 6.85 (ddd, 1H, H-5), 6.98 (dd, 1H, H-3'), 7.16 (ddd, 1H, H-8), 7.21 (ddd, 1H, H-7), 7.28 (dd, 1H, H-6), 7.31 (ddd, 1H, H-4'), 7.33 (dd,1H, H-9), 7.52 (dd, 1H, H-6'), 14.80 (brs, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 14.9 (CH_3-S), 42.3 (NMe_2), 101.3 (C-3), 118.0 (C-3'), 118.4 (C-5'), 119.0 (C-1'), 124.5 (C-8), 125.9 (C-7), 127.5 (C-9), 127.8 (C-6) 130 (C-6'), 133 (C-4'), 139.2 (C-9a), 141.5 (C-1"), 142.8 (C-5a), 162.1 (C-2'), 165.6 (C-4), 166.6 (C-2); MS (EI): *m/z* (%): 337 (25) [M$^{+\cdot}$], 283 (100), 102 (55), 42 (78). Anal. Calcd. for $C_{19}H_{19}N_3OS$: C, 67.63; H, 5.68; N, 12.45; O, 4.74; S, 9.50 Found: C, 67.26; H, 5.78; N, 12.62; O, 4.84; S, 9.60 %.

7-Methylthio[1]benzopyrano[4,3-c][1,5]benzodiazepine (**7**): Dark yellow needles, m.p. 117 °C. IR (cm^{-1}): $\nu_{C=N}$ 1634, $\nu_{C=C}$ 1458. ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H, Me-S), 7.05–7.17 (m, 4H, (H-9, H-10, H-11, H-12), 7.27 (brd, 1H, H-4), 7.34 (brdd, 1H, H-2), 7.54 (ddd, 1H, H-3), 8.02 (dd, 1H, H-1), 8.04 (s, 1H, H-6). ^{13}C NMR (DMSO-d_6): δ 14.4 (Me-S), 117.3 (C-4), 119.0 (C-6a), 124.3 (C-13b), 125.1 (C-1), 126.0 (C-2), 127.3, 127.6, 130.7, 132.2 (C-9, C-10, C-11, C-12), 132.4 (C-3), 139.6, 140.1 (C-8a, C-12a), 149.5 (C-13a), 150.9 (C-6), 153.9 (C-4a), 159.9 (C-7). MS (EI): *m/z* (%) 292 (100) [M+.], 190 (60). Anal. Calcd. for $C_{17}H_{12}N_2OS$: C, 69.84; H, 4.14; N, 9.58; O, 5.47; S, 10.97. Found: C, 69.42; H, 4.38; N, 9.41; O, 5.88; S, 10.39 %.

5-(2-Aminophenylamino)-3-(2-hydroxyphenyl)-1H-pyrazole (**9**): To a stirred solution of compound **4** (1.072 g, 4 mmol) in ethanol (50 ml) was added hydrazine monohydrate (0.2 ml, ~1.2 equiv). After heating for 10–20 min the initially yellowish solution became progressively discoloured. Stirring at room temperature was continued for 2 h until completion of the reaction. The mixture was poured into ice-cold water, then extracted with ethyl acetate (3 × 25 ml), the combined extracts were washed with water and dried. Evaporation of the solvent gave a white semi-solid, which crystallised when triturated with ethanol and water.

Pyrazole **9**: colourless crystals (65%), m.p. 156 °C. IR (cm^{-1}) $\nu_{C=N}$ 1590, ν_{NH} 3207, ν_{OH} 3368. ^{1}H NMR (DMSO-d_6 + TFA-*d*): δ 6.40 (s, 1H, H-4), 6.87 (brdd, 1H, H-5'), 6.98 (brd, 1H, H-3'), 7.04 (brdd, 1H, H-4"), 7.20 (brdd, 1H, H-4'), 7.29 (brdd, 1H, H-5"), 7.35 (brd, 1H, H-3"), 7.56 (brd, 1H, H6"), 7.64 (dd, 1H, H6'). ^{13}C NMR (DMSO-d_6 + TFA-*d*): δ 92.1 (C-4), 115.1 (C-1'), 116.4 (C-3'), 119.3 (C-5'), 120.4 (C-6"), 122.2 (C-4"), 123.0 (C-2"), 129.9 (C-4'), 135.9 (C-1"), 142.6 (C-3), 149.8 (C-5), 154.7 (C-2'). MS (EI): *m/z* (%) 266 (100) [M$^+$], 91 (65), 65 (86). Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04; O, 6.01. Found: C, 67.42; H, 5.32; N, 20.88; O, 6.18 %.

In spite of its low solubility, recording a sample of compound **9** in pure DMSO-d_6 was required to show up the set of four broad singlets relative to exchangeable protons (NH_2, 2 × NH and OH) at 10.18 ppm, 11.33 ppm, 11.98 ppm and 12.40 ppm.

5-[(2-Hydroxyphenyl)-2H-pyrazol-3-yl]-1H-benzimidazole (**10**): Pyrazole **9** (800 mg, 3 mmol) and DMFDMA (2 ml, 5 equiv) in anhydrous toluene (50 ml) were stirred at 100 °C for 2 h. Although the reactant was not completely consumed the reaction was stopped owing to the formation of a complex mixture of several decomposition products as evidenced by TLC analysis. The volatile components were evaporated *in vacuo* and the separation of the major product **10** was achieved by column chromatography on silica gel using ethyl acetate as eluent. Owing to the complexity of the chromatographed crude, slight contamination of **10** could not be avoided.

Benzimidazole (**10**): Colourless crystals (30 %), m.p. 175 °C. IR (cm^{-1}) $\nu_{C=N}$ 1620, ν_{N-H} 3200, ν_{OH} 3340. ^{1}H NMR (DMSO-d_6): δ 6.91(brdd, 1H, H-5"), 7.01 (brd, 1H, H-3"), 7.15 (s, 1H, H-5'), 7.22 (brdd, 1H, H-4"), 7.31 (brdd, 1H, H-5), 7.37 (brdd, 1H, H-6), 7.71 (d, 1H, H-6"), 7.75 (d, 1H, H-4), 8.07 (d, 1H, H-7), 8.73 (s, 1H, H-2), 10.50 (brs, 1H, NH), 13.16 (brs, 1H, OH). ^{13}C NMR (DMSO-d_6): δ 95.1 (C-5'), 112.6 (C-7), 115.5 (C-1"), 116.4 (C-3"), 119.3 (C-5"), 129.7 (C-4), 122.5 (C-5), 123.6 (C-6), 127.6 (C-6"), 119.7 (C-4"), 132.2 (C-7a), 141.1 (C-4'), 142.1 (C-2), 143.5 (C-3a), 145.7 (C-1'), 154.3 (C-2"). MS (EI): *m/z* (%) 276 (100) [M$^+$].

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