Microwave-assisted synthesis and regioisomeric structural elucidation of novel benzimidazo[1,2*d*][1,4]benzodiazepinone derivatives

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Abstract

The synthesis of 5*H*-benzimidazo [1,2-*d*] [1,4] benzodiazepin -6(7*H*)-ones **3a-e** from readily available 2-(2-aminophenyl)-1*H*-benzo[*d*]imidazole derivatives **2a-e** and 2-bromoacetyl bromide under microwave conditions is described. Unambiguous structural elucidation of the obtained regioisomers was finally established by means of 2D-NOESY experiment.

Keywords: Heterocycles, benzimidazoles, benzodiazepines, microwaves

Introduction

Seven-membered heterocyclic ring represents an area of considerable interest mainly due to its interesting pharmacological properties.[1,2] Among them, undoubtedly the [1,4]benzodiazepine skeleton has been one of the most studied, and commonly associated with central nervous system depressive effects.[3] The [1,4] benzodiazepine framework is nowadays linked with antitumoral activity, in such sense pyrrolo[1,4]benzodiazepine **B**,[4,5] pyrazolo[4,3-*e*] pyrrolo[1,2-*a*] [1,4]diazepinone **C**[6] and dibenzo[*b*,*e*][1,4]diazepin-11-one **D**[7] (Figure 1) have been reported to display cytotoxic activity.

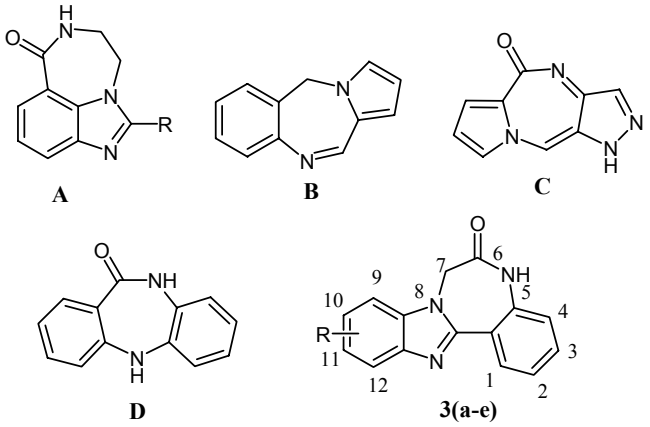


Figure 1. Citotoxyc fused 1,4-benzodiazepines **A-D** reported in literature and target benzimidazo[1,2*d*][1,4]benzodiazepinones **3a-e**.

On the other hand, the benzimidazole unit is the key building block for a variety of derivatives that are known to play crucial roles in the functions of a number of anticancer, antimicrobial and antiviral compounds among others.[8-13] However, to the best of our knowledge, there are just a few works reporting the synthesis of benzimidazole rings fused to a [1,4]benzodiazepine framework.[14,15] Skalitzky and co-workers described the synthesis of 5,6-dihydroimidazo[4,5,1-*jk*] [1,4] benzodiazepin-7(4*H*)-one derivatives **A** (Figure 1) with a potent cytotoxic activity.[16]

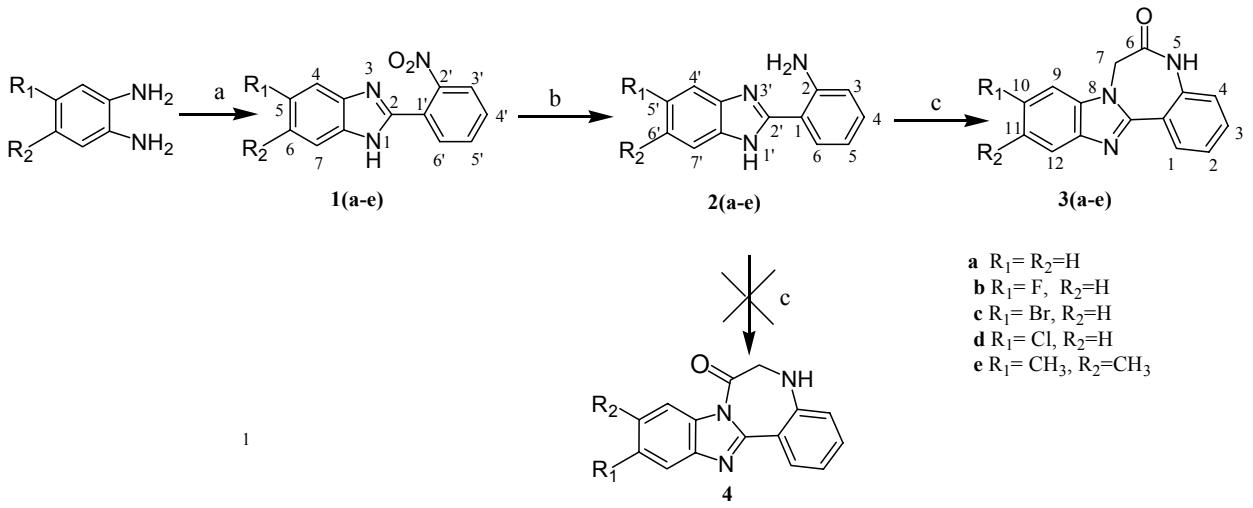
The benzimidazo-benzodiazepinone framework **3a** (R=H) was first reported by Duncan et al[14]. Years later Cherkaoui et al[15], reported just the isolation of **3a** as an intermediate in the route to triazolobenzodiazepine derivatives. This compound was obtained by a condensation reaction between 2-bromoacetyl bromide and 2-(1*H*-benzimidazol-2-yl) aniline, under drastic heating conditions and long reaction times. As a part of our medicinal chemistry project aimed at the synthesis of potential anticancer agents,[17] we are interested in to extend the studies towards the synthesis of novel 5*H*-benzimidazo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-one derivatives **3a-e** under microwave-promoted conditions.

Given that microwave-assisted reactions take place at rates dramatically enhanced over classical heating, providing increased yields and lower side reactions,[18,19] we therefore decided to probe microwave stimulation as environmentally friendly protocol. The structure of the target compounds have been unequivocally established by ^{1}H NMR, ^{13}C NMR and 2D- ROESY (rotating-frame Overhauser spectroscopy) experiments.

Results and Discussion

The synthesis of 5*H*-benzimidazo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-ones **3(a-e)** has been accomplished according to the sequence displayed on scheme 1. Equimolar reaction of

commercial substituted *o*-phenylenediamines with 2-nitrobenzaldehyde in ethanol afforded the corresponding benzimidazoles **1(a-e)** in high yields (80% - 90%). Subsequent nitro group reduction of **1a-e** derivatives was efficiently accomplished using iron powder in a mixture of concentrated HCl, ethanol and water (0.25:1:1), obtaining the corresponding 2-(1*H*-benzimidazol-2-yl)aniline derivatives **2a-e** in good yields (70-80%).



Scheme 1. Reagents and conditions. (a) 2-nitrobenzaldehyde, *o*-phenylenediamine, ethanol, stirring, rt., 48 H. (b) Iron powder, solution of HCl(concd.):EtOH:H_2O (0.25:1:1) stirring, rt, 15 m. (c) 2-Bromoacetyl bromide, anhydrous THF, Na_2CO_3, microwave (300 W).

The condensation reaction between 2-(1*H*-benzimidazol-2-yl)aniline derivatives **2a-e** and 2-bromoacetyl bromide, was carried under microwave irradiation (300 W) in anhydrous THF and sodium carbonate. The reactions were successfully completed at 1 to 6 minutes when a white precipitated was formed and the presence of a new compound was corroborated by thin layer chromatography.

It should be noted that although benzimidazole precursors **2b-d** could exist under two tautomeric forms, only the single obtained benzimidazo benzodiazepine regioisomers **3b-d** were obtained. These results suggest that the thermodynamic more stable tautomer will probably determine the course of the reaction. As expected, conformational analysis carried out by *ab initio* studies on intermediate ii (scheme 2) confirmed the presence of an intramolecular hydrogen bonding between the amide and the NH of the benzimidazole ring.

Besides, the regiochemistry of the nucleophilic attack could yield either the 5*H*-benzimidazo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-ones **3a-e** or the 5,6-dihydro-7*H*-benzimidazo[1,2-*d*][1,4]benzodiazepin-7-ones **4**. However, no mixture of regioisomers was found for final products 3a-3e, as judged by TLC and ^{1}H NMR. A previous Fukui calculus (DFT at B3LYP level of theory with a set of basis 3-21G) performed in Gaussian assigned a significantly higher nucleophilicity to the aniline in **2a-e** compared to the benzimidazole. This suggested that the

obtaining of structure **3a-e** is favored over structure **4**. In fact, the following spectroscopic observations confirmed this expectation: i) the IR (KBr) spectrum of compounds **3a-e** exhibited the typical amidic carbonyl group absorption (1660-1680 cm^{-1}) in accord with amides **3a-e** rather than **4.** This may be attributed to the low amidic character exhibited by isomer **4;** ii) the ^1H NMR of **3a-e** derivatives displayed a singlet for one proton in the amidic region (δ= 10.55 -11.01 ppm) and a singlet for two protons at δ= 4.74-5.14 ppm, that can be assigned to N**H**-5 and to the methylenic protons on C-7, respectively. On the other hand, coupling between the methylene hydrogens and the NH are expected if the structure of compounds was consistent with **4.**

More information supporting the proposed structures of compounds **3a-e** arouse from a set of two complementary experiments. First, a 2D NOESY experiment clearly showed the presence of a through-space NOE effect between the aromatic H-4 and the NH in **3d**, as shown in figure 2. Second, two complementary decoupled 1D 1H homonuclear spectra for **3d** were recorded. When the NH proton (d, 10.67 ppm) was irradiated, the H-4 signal, (dd, 7.49 ppm) collapsed, supporting the NH/H-4 connectivity. Additionally, when the 9-H nucleus was irradiated (s, 7.91 ppm) the 7-CH_2 signal (d, 4.96 ppm) collapsed, supporting the 9-H /7-CH_2 connectivity. All the above theoretical and experimental evidence support the proposed structures **3a-e**.

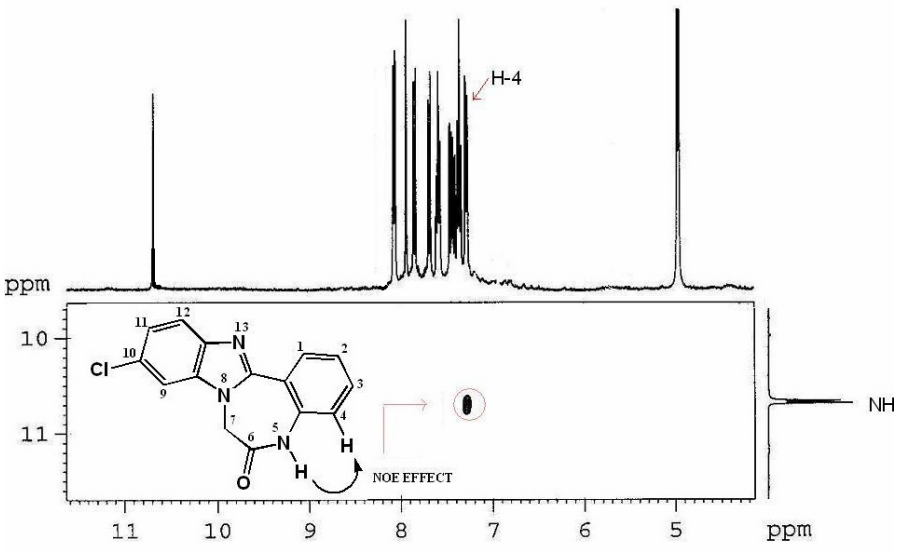
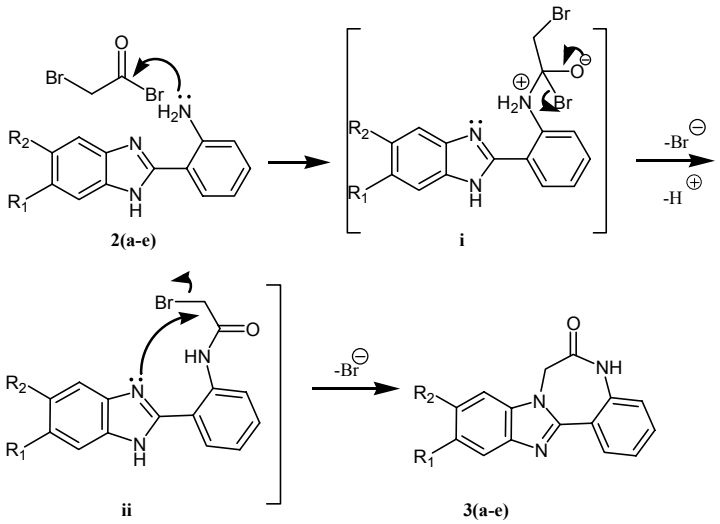


Figure 2. NOE effects between NH and H4 in a 2D-NOESY experiment.

According to the obtained results, a plausible mechanistic sequence (scheme 2), would involve a nucleophilic attack of the primary amine of the aniline **2** on the acid halide of the 2-bromoacetyl bromide, to give **ii** as an intermediate, which would undergoes a benzimidazolic nitrogen attack, followed by a cyclodehydrobromination, thereby resulting in the 5H-benzimidazo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-ones **3a-e**.



Scheme 2. Probable mechanistic sequence for the obtaining of 5H-benzimidazo[1,2-*d*][1,4]-benzodiazepin-6(7*H*)-ones **3a-3.**

The fast microwaves-promoted cyclization gave the target compounds in good yields; with reaction times between 1 and 6 minutes (Table 1).

Table 1. Reaction time and yields of the cyclization reaction

Compound	Reaction time (min)	Yield (%)
3a	1	70
3b	6	57
3c	5	55
3d	5	48
3e	2	50

As a result, we have developed a rapid, simple microwave-promoted synthesis of novel 5*H*-benzimidazo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-one derivatives. The structures of the obtained regioisomers were deduced and supported from the inspections of complete spectroscopic data.

Experimental Section

General. All organic solvents used for the synthesis were of analytical grade. Melting points were determined on a Stuart Scientific SMP3 apparatus and are uncorrected. IR spectra were recorded on a Brucker Vector 22 spectrophotometer using KBr discs. ^{1}H and ^{13}C NMR spectra were obtained on a Brucker APC-200 spectrometer using tetramethylsilane as internal reference.

Column chromatography was performed on Merck silica gel 60 (70-230 mesh). Thin layer chromatographic separations were performed on Merck Kiesselgel 60 (70-230 mesh). Elemental analyses were carried out on a FISONS EA 1108 CHNS-O analyzer. The microwave reactions were carried out in a CEM Discover microwave reactor and irradiated at for the period shown in the table. The reaction temperature was maintained by modulating the power level of the reactor. Yield values are given for pure products.

General synthetic procedure for 2-(2-nitrophenyl)-1*H*-benzo[*d*]imidazole derivatives 1a-e

A solution of 2-nitrobenzaldehyde (1 equiv.) in ethanol (60 mL) and the corresponding *o*-phenylenediamine (1 equiv.) is stirred at 80 ºC for 24 hours. The reaction mixture is then poured into water. The precipitate is then purified by recrystallization from ethanol, isolating the corresponding benzimidazoles **3(a-e)**. Compound **1a** has been previously described.[20]

6-Fluoro-2-(2'-nitrophenyl)-1*H*-benzo[*d*]imidazole (1b). Prepared from 4-fluor-1,2-phenylenediamine (500 mg, 3.96 mmol) and 2-nitrobenzaldehyde (600 mg, 3.96 mmol). Yield = 75%; mp: 197 – 198 ºC (Ethanol); IR (KBr) cm^{-1}: 3207 (NH), 1529(NO_2), 1341 (NO_2), ^{1}H NMR (200 MHz, DMSO-d_6) δ: 13.16 (1H, s, NH), 8.05 (dd, 1H, J_1 = 7.8, J_2 = 1.5 H-3´), 7.95 (dd, 1H, J_1 = 7.7, J_2 = 1.6, H-6´), 7.87 (td, 1H, J_1 = 7.5, J_2 = 1.4, H-5´), 7.79 (dd, 1H, J_1 = 7.8, J_2 = 1.7, H-7), 7.63 (m, 1H, H-4´), 7.45 (dd, 1H, J_1 = 8.0, J_2 = 2.5 H-4), 7.12 (td, 1H, J_1 = 7.4, J_2 = 1.5, H-5).^{13}C NMR (50 MHz, DMSO-d_6) δ: 161.1 (d, J_1= 236 Hz, 6), 156.4 (6), 153.9 (2), 148.7 (2'), 148.6 (3a), 2x132.6 (7a, 5'), 131.0 (4'), 130.9 (3'), 124.3 (6'), 123.8 (1'), 111.0 (d, J_2= 25 Hz, 5), 110.5 (5), 101.8, (d, J_2= 25 Hz, 7) 101.3 (7). Anal. Calcd. for $C_{13}H_8FN_3O_2$ (MW: 257.22): C, 60.70; H, 3.13; N, 16.34. Found: C, 60.82; H, 3.23; N, 15.99.

6-Bromo-2-(2'-nitrophenyl)-1*H*-benzo[*d*]imidazole (1c). Prepared from 4-bromo-1,2-phenylenediamine (500 mg, 2.67 mmol) and 2-nitrobenzaldehyde (403 mg, 2,67 mmol). Yield = 64%; mp: 147 – 149 ºC (Ethanol); IR (KBr) cm^{-1}: 3423 (NH), 1527(NO_2), 1347 (NO_2), ^{1}H NMR (200 MHz, DMSO-d_6) δ: 13.24 (s, 1H, NH), 8.02 (d, 1H, J = 8.0, H-3´), 7.93 (d, 1H, J = 7.7, H-6´), 7.84 (td, 1H, J_1 = 7.5, J_2 = 1.1, H-5´), 7.74 (td, 1H, J_1 = 7.8, J_2 = 1.3, H-4´), 7.65 (s, 1H, H-7), 7.59 (d, 1H, J = 8.5, H-4), 7.23 (dd, 1H, J_1 = 8.5, J_2 = 1.8, H-5). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 149.4 (2), 149.3 (2'), 2x 138.1 (3a, 7a), 133.4 (5'), 131.7 (4'), 131.6 (6'), 124.9 (3'), 2x 124.4 (5, 1'), 123.3 (4), 2x 117.3 (6, 7). Anal. Calcd. for $C_{13}H_8BrN_3O_2$ (MW: 318.13): C, 49.08; H, 2.53; N, 13.21. Found: C, 49.18; H, 2.69; N, 13.48.

6-Chloro-2-(2'-nitrophenyl)-1*H*-benzo[*d*]imidazole (1d). Prepared from 4-chloro-1,2.phenylenediamine (500 mg, 3.51 mmol) and 2-nitrobenzaldehyde (518 mg, 3.51 mmol). Yield = 72%; mp: 108–109 ºC (Ethanol); IR (KBr) cm^{-1}: 3422 (NH), 1526, 1349 (NO_2), ^{1}H NMR (200 MHz, DMSO-d_6) δ: 13.15 (1H, s, NH), 8.02 (1H, d, J = 8.0, H-3´), 7.93 (1H, d, J = 7.6, H-6´), 7.84 (1H, t, J = 7.5, H-5´), 7.79 (1H, s, H-7), 7.75 (1H, t, J_1 = 8.0, J_2 = 1.1, H-4´), 7.55 (1H, d, J = 8.6, H-4), 7.35 (1H, dd, J_1 = 8.5, J_2 = 1.6, H-5). ^{13}C NMR (50 MHz DMSO-d_6) δ: 149.4 (2), 149.2 (2'), 2x 138.1 (3a, 7a), 133.3 (5'), 131.7 (4'), 131.6 (6), 125.9 (3'), 124.9 (6'), 2x 124.4 (5, 1'), 2 x 115.2 (4, 7). Anal. Calcd. for $C_{13}H_8ClN_3O_2$ (MW: 273.67): C, 57.05; H, 2.95; N, 15.35. Found: C, 57.40; H, 2.65; N, 15.24.

5,6-Dimethyl-2-(2'-nitrophenyl)-1*H*-benzo[*d*]imidazole (1e). Prepared from 4,5-dimethyl-1,2-phenylenediamine (500 mg, 3.67 mmol) and 2-nitrobenzaldehyde (555 mg, 3.67 mmol). Yield = 91%; mp: 190–191ºC (Ethanol); IR (KBr) cm-1: 3395 (NH), 1526 (NO_2), 1347 (NO_2), ^{1}H NMR (200 MHz-DMSO-d_6) δ: 12.93 (s, 1H, NH), 7.93 (t, 2H, J = 8.6, H-3′,6′), 7.79 (t, 1H, J = 7.4, H-5′), 7.67 (t, 1H, J = 7.6, H-4′), 7.39 (s, 1H, H-7), 7.28 (s, 1H, H-4), 2.32 (s, 6H, 2x CH_3) . ^{13}C NMR (50 MHz, DMSO-d_6) δ: 149.4 (2), 146.7 (2'), 138.1 (3a), 132.9 (7a), 131.1 (5'), 131.0 (3'), 2 x 124.9 (5, 6), 124.6 (1'), 2 x 119.7 (4, 4'), 112.0 (7), 2x20.5 (8, 9).Anal Calcd for $C_{15}H_{13}N_3O_2$ (MW: 267.28): C, 67.40; H, 4.90; N, 15.72. Found: C, 67.21; H, 4.96; N, 15.60.

General synthetic procedure for 2-(1*H*-benzimidazol-2-yl) aniline derivatives 2a-e

Iron powder (500 mg, 9 mmol) is added to a solution of the corresponding benzimidazole (1 equiv.) in a solution of HCl(concd.):EtOH:H_2O (0.25:1:1) (50 mL). The mixture is stirred at room temperature by 15 minutes and then neutralized with solid $NaHCO_3$. The crude is extracted with ethyl acetate (25 mLx3), evaporated under vacuum and dried with anhydrous Na_2SO_4 to yield the reduced derivative. Compound **2a** has been previously described.[21]

2-(6'-Fluoro-1*H*-benzimidazol-2'-yl)aniline (2b). Prepared from 6-fluoro-2-(2-nitrophenyl)-1*H*-benzo[*d*]imidazole (385 mg, 1.50 mmol) and Fe^0 (500 mg, 9 mmol). Yield: 55%; mp: 179–181 ºC (Ethanol); IR (KBr) cm^{-1}: 3382 (NH), 3178 (NH_2), 3153 (NH_2). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 12.37 (b.s., 1H, NH), 7.72 (dd, 1H, J_1 = 7.9, J_2 = 1.2, H-4'), 7.41 (dd, 1H, J_1 = 8.0, J_2 = 1.2 H-7′), 7.16 (d, 1H, J = 8.0, H-5′), 7.05 (d, 1H, J = 7.5, H-3), 6.87 (t; 1H, J_1 = 7.2, J_2 = 2.5, H-5), 6.76 (d, 1H, J = 7.9, H-6), 6.60 (t, 1H, J = 7.7, H-4), 3.24 (b.s., 2H, NH_2). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 161.7 (d, J_1= 260Hz, 6'), 156.5 (6'), 151.8 (2'), 2x 147.6 (3a', 7a'), 130.0 (4), 126.9 (6), 2 x 123.1 (5, 4'), 116.0 (7'), 115.0 (3), 110.9 (d, J_2= 37 Hz, 5'), 110.2 (5'), 102.8(d, J_2= 37 Hz, 7'), 102.1(7')Anal. Calcd. for $C_{13}H_{10}FN_3$ (MW: 227.24): C, 68.71; H, 4.44; N, 18.49. Found: C, 68.35; H, 4.48; N, 18.11

2-(6'-Bromo-1*H*-benzimidazol-2'-yl)aniline (2c). Prepared from 6-bromo-2-(2-nitrophenyl)-1*H*-benzo[*d*]imidazole (420 mg, 1.32 mmol) and Fe^0(500 mg, 9 mmol). Yield: 51%; mp: 153–155 ºC (Ethanol); IR (KBr) cm^{-1}: 3422 (NH_2), 3383 (NH_2), 1618 (C-N). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 12.79 (b.s., 1H, NH), 7.82 (d, 1H, J = 7.8, H-5′), 7.63 (s, 1H, H-7′), 7.35 (m, 2H, H-3′,4′), 7.17 (t, 3H, J = 7.3, H-5 and NH_2), 6.84 (d, 1H, J = 8.3, H-6), 6.65 (t, 1H, J = 7.5 and H-4). ^{13}C NMR (50 MHz DMSO-d_6) δ:148.1 (2'), 146.8 (2), 2x130.8 (3a', 7a'), 127.2 (4), 124.9 (5'), 120.4 (6), 116.2 (4'), 2 x 115.2 (5, 7'), 113.4 (1), 112.4 (3), 109.4 (6'). Anal. Calcd. for $C_{13}H_{10}BrN_3$ (MW: 288.14): C, 54.19; H, 3.50; N, 14.58. Found: C, 54.46; H, 3.71; N, 14.29.

2-(6'-Chloro-1*H*-benzimidazol-2'-yl)aniline (2d). Prepared from 6-chloro-2-(2-nitrophenyl)-1*H*-benzo[*d*]imidazole (450 mg, 1.64 mmol) and Fe^0(500 mg, 9 mmol). Yield: 58%; mp: 165–167 ºC (Ethanol); IR (KBr) cm^{-1}: 3372 (NH_2), 3324 (NH_2), 1617 (C-N). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 12.47 (b.s., 1H, NH), 7.72 (d, 1H, J = 8.5, H-7′), 7.45 (d, 1H, J = 8.3, H-4′), 7.33 (d, 1H, J = 8.7, H-5′), 7.19 (d, 1H, J = 8.8, H-3), 7.06 (t, 1H, J_1 = 8.1, J_2 = 1.4, H-5), 6.79 (b.s, 2H, NH_2), 6.76 (d, 1H, J = 8.2, H-6′), 6.60 (t, 1H, J_1 = 8.1, J_2 = 1.1, H-4). ^{13}C NMR (50 MHz DMSO-d_6) δ: 147.7 (2'), 2x130.2 (3a', 7a'), 127.1 (2), 124.5 (4), 120.4 (5'), 119.2 (4'), 116.1

(6'), 2x115.2 (4, 7'), 113.2 (5), 111.8 (1), 110.0 (3). Anal. Calcd. for $C_{13}H_{10}ClN_3$ (MW: 243.69): C, 64.07; H, 4.14; N, 17.24. Found: C, 64.26; H, 4.15; N, 17.28.

2-(5',6'-Dimethyl-1*H*-benzimidazol-2'-yl)aniline (2e). Prepared from 5,6-dimethyl-2-(2-nitrophenyl)-1*H*-benzo[*d*]imidazole (510 mg, 1.91 mmol) and Fe^0(500 mg, 9 mmol). Yield: 67%; mp: 183–185 ºC (Ethanol); IR (KBr) cm^{-1}: 3360 (NH_2), 3336 (NH_2), 1623 (C-N). ^1H NMR (200 MHz, DMSO-d_6) δ: 12.31(1H, s, NH), 7.79 (d, 1H, J_1 = 7.9, J_2 = 1.4, H-3), 7.40 (1H, s, H-7′), 7.25 (1H, s, H-4′), 7.22-7.14 (b.s, 2H, NH_2), 7.10 (dd, 1H, J_1 = 7.0, J_2 = 1.5, H-5), 6.80 (dd, 1H, J_1 = 8.2, J_2 = 1.1, H-6), 6.63 (t, 1H, J_1 = 7.0, J_2 = 1.2, H-4), 2.32 (s, 6H, 2x CH_3). ^{13}C NMR (50 MHz DMSO-d_6) δ: 168.5 (2'), 142.4 (2), 2x 136.6 (3a', 7a'), 2x 132.0 (5', 6'), 130.5 (4), 125.1 (6), 122.5 (5), 121.55 (1), 2x 119.7 (4', 7'), 110.5 (3), 20.6 (8), 20.4 (9). Anal. Calcd. for $C_{15}H_{15}N_3$ (MW: 237.30): C, 75.92; H, 6.37; N, 17.71. Found: C, 76.17; H, 6.67; N, 17.16.

General synthetic procedure for 5*H*-benzimidazo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-one derivatives 3a-e

A solution of 2-bromoacetyl bromide (1.5 equiv.) in anhydrous THF (30 mL) containing Na_2CO_3 (2 equiv.) and the corresponding 2-(1*H*-benzimidazol-2-yl) aniline derivative (1 equiv.) is heated under microwave irradiation (300W). The reaction mixture is then filtered and the solvent removed under vacuum. The obtained crude is precipitated in an ethanol-water (1:10) mixture.

5*H*-Benzimidazo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-one (3a). Prepared from 2-(1*H*-benzimidazol-2-yl)aniline (400 mg, 1.68 mmol) and bromoacetyl bromide (508 mg, 2.52 mmol). Yield: 70%; mp: 260–262 ºC ; IR (KBr) cm^{-1}: 3215 (NH), 1686 (C=O); ^1H NMR (200 MHz, DMSO-d_6) δ: 10.67 (s, 1H, NH), 8.10 (d, 1H, J = 7.8, H-12), 7.84 (d, 1H, J = 8.3, H-9), 7.75 (d, 1H, J = 7.2, H-1), 7.59 (t, 1H, J = 8.4, H-11), 7.37 (t, 1H, J = 7.5, H-10), 7.30 (m, 3H, H-2,3,4), 4.96 (s, 2H, CH_2). ^{13}C NMR (50 MHz DMSO-d_6) δ: 168.4 (6), 151.0 (13), 143.7 (4a), 136.8 (8a), 135.2 (12a), 131.8 (3), 130.6 (1), 125.2 (2), 123.1 (11), 123.0 (10), 122.5 (4), 121.3 (12), 119.7 (13a), 110.6 (9), 47.3 (7). Anal. Calcd. for $C_{15}H_{11}N_3O$ (MW: 249.27): C, 72.28; H, 4.45; N, 16.86; Found: C, 71.90; H, 4.97; N, 16.63.

10-Fluoro-5*H*-benzimidazo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-one (3b). Prepared from 2-(6-fluoro-1*H*-benzo[*d*]imidazol-2-yl)aniline (310 mg, 1.36 mmol) and bromoacetyl bromide (412 mg, 2.04 mmol). Yield: 57%; mp: 239–242 ºC; IR (KBr) cm^{-1}: 3245 (NH), 1681 (C=O); ^1H NMR (200 MHz, DMSO-d_6) δ: 11.01 (s, 1H, NH), 8.20 (d, 1H, J = 9.0, H-12), 8.01 (td, 1H, J_1 = 7.9, J_2 = 1.7, H-11), 7.88 (m, 1H, H-9), 7.75 (td, 1H, J_1 = 7.9, J_2 = 1.1, H-1), 7.47 (m, 2H, H-2,3) 7.38 (d, 1H, J = 8.3, H-4) 5.14 (s, 2H, CH_2). ^{13}C NMR (50 MHz DMSO-d_6) δ: 168.1, (6), 163.5 (d, J_1= 311 Hz, 10), 157.3 (10), 139.7 (13), 132.3 (4a), 130.9 (12a), 124.3 (8a), 124.0 (3), 123.7 (1), 122.2 (12), 121.5(2), 118.3(4), 115.2(13a), 114.1(d, J_2= 25 Hz, 11), 113.6(11), 111.3 (d, J_2= 25 Hz, 9), 110.8 (11), 48.5 (7). Anal. Calcd. for $C_{15}H_{10}FN_3O$ (MW: 267.26): C, 67.41; H, 3.77; N, 15.75; Found: C, 67.69; H, 4.05; N, 15.52.

10-Bromo-5*H*-benzimidazo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-one (3c). Prepared from 2-(6-bromo-1*H*-benzimidazol-2-yl)aniline (350 mg, 1.25 mmol) and bromoacetyl bromide (368 mg, 1.82 mmol). Yield: 55%; mp: 279–281 ºC; IR (KBr) cm^{-1}: 3420 (NH), 1686 (C=O); ^1H NMR

(200 MHz, DMSO-d_6) δ: 10.57 (s, 1H, NH), 8.09 (d, 1H, J = 8.0, H-12), 7.79 (d, 1H, J = 8.1, H-11), 7.70 (s, 1H, H-9), 7.50 (m, 2H, H-1,3), 7.42 (t, 1H, J = 7.7, H-2), 7.46 (d, 1H, J = 7.3, H-4); 4.74 (s, 2H, CH_2). ^{13}C NMR (50 MHz DMSO-d_6) δ: 167.0 (6), 137.0 (13), 131.3 (4a), 129.9 (12a), 126.5 (8a), 126.3 (3), 124.4 (1), 123.9 (11), 121.8 (2), 120.9 (12), 119.8 (4), 116.0 (10), 113.0 (13a), 110.7 (9), 46.9 (7).Anal. Calcd. for $C_{15}H_{10}BrN_3O$ (MW: 328.16): C, 54.90; H, 3.07; N,12.80; Found: C, 54.80; H, 3.06; N, 12.61.

10-Chloro-5*H*-benzimidazo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-one (3d). Prepared from 2-(6-chloro-1*H*-benzimidazol-2-yl)aniline (530 mg, 2.17 mmol) and bromoacetyl bromide (658 mg, 3.26 mmol). Yield: 48%; mp: 309–311 ºC; IR (KBr) cm^{-1}: 3200 (NH), 1692 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6) δ: 10.67 (s, 1H, NH), 8.05 (d, 1H, J = 7.4, H-12), 7.91 (s 1H, H-9), 7.80 (d, 1H, J = 7.6, H-11), 7.70 (d, 1H, J = 7.6, H-1), 7.60 (td, 1H, J_1 = 7.6, J_2 = 1.2, H-2), 7.51 (m, 1H, H-3), 7.49 (dd, 1H, J_1 = 7.9, J_2= 2,1, H-4), 4.96 (s, 2H, 5-CH_2). ^{13}C NMR (50 MHz DMSO-d_6) δ: 167.5 (6), 136.5 (13), 131.8 (4a), 130.1 (12a), 125.8 (3), 125.5 (1), 124.6 (11), 122.0 (2), 121.2(12), 120.3(4), 119.6 (4), 115.2 (10), 113.5 (13a), 112.2 (9), 47.1 (7). Anal. Calcd. for $C_{15}H_{10}ClN_3O$ (MW: 283.71); C, 63.50; H, 3.55; N, 14.81; Found: C, 63.76; H, 3.76; N, 14.55.

10,11-Dimethyl-5*H*-benzimidazo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-one (3e). Prepared from 2-(5,6-dimethyl-1*H*-benzimidazol-2-yl)aniline (425 mg, 1.79 mmol) and bromoacetyl bromide (542 mg, 2.69 mmol). Yield: 50%; mp: 286–288 ºC; IR (KBr) cm^{-1}: 3206 (NH), 1677 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6) δ: 10.55 (s, 1H, NH), 8.02 (d, 1H, J = 7.7, H-1), 7.55 (s, 1H, H-9), 7.51 (td, 1H, J_1 = 8.0, J_2 = 1.2, H-3), 7.47 (s, 1H, H-12), 7.30 (t, 1H, J = 7.6, H-2), 7.24 (d, 1H, J = 8.1, H-4), 4.86 (s, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.22 (s, 3H, CH_3). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 168.5 (6), 142.4 (13a), 136.6 (4a), 133.8 (12a), 132.0 (8a), 2x 131.4 (10, 11), 130.5 (3), 2x 125.1 (1, 2), 122.5 (4), 121.5 (12), 119.7 (9), 110.5 (13a), 47.3 (7), 20.6 (15), 20.4 (14).

Anal. Calcd. for $C_{17}H_{15}N_3O$ (MW: 277.32); C, 73.63; H, 5.45; N, 15.15; Found: C, 73.90; H, 5.11; N, 14.81.

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