An efficient and versatile synthesis of 2, 2'-(alkanediyl)-bis-1H-benzimidazoles employing aqueous fluoroboric acid as catalyst: Density Functional Theory calculations and fluorescence studies

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Abstract
2,2'-((Alkanediyl)-bis-1H-benzimidazoles (simple and mixed) with variable methylene spacers were synthesized in excellent yields with aqueous fluoroboric acid (45%) (0.1 ml) as catalyst under solvent-free conditions. Their optimized structures were obtained using DFT calculations where it was seen that the s-trans orientation of the two imidazole rings was preferred for all types of bis-benzimidazole systems. The X-ray crystal structure of one such bis-benzimidazole further corroborated this fact. Finally, photophysical studies were carried out to get insight into the fluorescence characteristics of the newly synthesized bis-1H-benzimidazoles.

Keywords: 2,2'-(alkanediyl)bis-1H-benzimidazoles, 45% aqueous fluoroboric acid, Solvent-free conditions, DFT, photophysical studies

Introduction

The development of efficient approaches to chemically and biologically important products from readily available inexpensive starting materials has been an active topic in modern organic chemistry.1 The main objective of this research was to use easily available reagents and their application in an environment-friendly way to the synthesis of functionalized heterocycles that are of great interest in organic synthesis, as such motifs are ubiquitous in both natural products and biologically active pharmaceutical agents. Development of a more practical pathway is important to synthesize new heterocyclic compounds that are otherwise difficult to synthesize by conventional methodologies. We became particularly interested in the synthesis of bis-1H-benzimidazoles by solvent-free techniques that have gradually replaced the use of volatile, hazardous and toxic organic solvents over the past few decades.2 Such ecofriendly chemical processes have attained substantial interest both in the industry and in academia.3 Bis-benzimidazoles are known to offer lead inhibition of the activity of M1-RNA, the inhibitions
being caused by the unusual mechanism of the binding of these organic ligands (whose structures are not based on natural products) to the substrates.\(^3\) In continuation of our interest towards the synthesis of biologically important heterocycles,\(^4\) we envisaged the one-pot synthesis of 2, 2′-bis-1\(H\)-benzimidazoles with variable methylene spacers under solvent-free conditions in an oil-bath. This methodology is environmentally benign being solvent-free, operationally simple, employs no tedious work-up procedures, has wide general applicability, short reaction times, mild reaction conditions, large scale-ups and quite good yields. 45% Aqueous fluoroboric acid is used to the maximum extent of 0.1 ml for 2 mmol of the starting diamine. The excess acid which remains after the reaction is neutralized using saturated aqueous sodium bicarbonate solution. This reaction condition is necessarily quite mild as compared to the previous reports (although very few) of using polyphosphoric acid or aqueous hydrochloric acid as the refluxing solvent cum reagent\(^5,6\) for the synthesis of simple bis-1\(H\)-benzimidazoles. This neat reaction condition is operationally very simple rather than using high temperature and pressure autoclave,\(^7\) the setup of which is quite cumbersome in a laboratory and is also not quite easily available.

The main theme of this paper is the construction of 2, 2′-bis-1\(H\)-benzimidazoles (both simple and mixed) with variable methylene spacers in a one-pot operation under solvent-free conditions. The benzimidazole moiety is an important heterocyclic nucleus which has been extensively used in medicinal chemistry. Benzimidazoles are present in various bioactive compounds having anticancer, antihypertension and antiviral properties\(^8\) in addition being a component of Vitamin B\(_{12}\). Compounds containing the benzimidazole skeleton are significantly active against several viruses such as HIV,\(^9\) influenza,\(^10\) Herpes (HSV-1)\(^11\) and human cytomegalovirus (HCMV).\(^9\) Bis-benzimidazoles behave as DNA-minor groove binding agents having anti-tumour activity\(^12\) and can act as ligands to transition metals for modeling biological systems.\(^13\)

Fluoroboric acid (45% in water, 0.1 ml) was used as the catalyst under solvent-free conditions in an oil-bath. During the synthesis of 2, 2′-bis-1\(H\)-benzimidazoles, both simple and mixed systems were tried. Our challenge was therefore, the synthesis of the pure mixed 2, 2′-bis-1\(H\)-benzimidazoles avoiding contamination with the simultaneous inevitable formation of simple bis-benzimidazoles. A synthetic strategy has been developed for 2, 2′-bis-1\(H\)-benzimidazoles in which the two halves are different (compounds 4b, 4d, 4e, 4i, 4l), and consequently of different basicity, which could be important for biomimicry and metal ion transport.

### Results and Discussion

In order to standardize the reaction conditions for the synthesis of 2, 2′-bis-benzimidazoles, 1, 2-phenylene diamine (2 mmol) and oxalic acid (1 mmol) (Scheme 1) were heated at various temperatures with varying amount of HBF\(_4\) and the results are tabulated in Table 1. The best result was obtained with 0.1 ml of HBF\(_4\) (45% in water) for 2 hours at 150 °C (Table 1, entry 5). The yield slightly decreased on increasing the amount of HBF\(_4\), probably due to some other side reactions. On cooling to room temperature, the reaction mixture solidified and was taken out of
the oil-bath. Next, saturated aqueous NaHCO₃ solution (8 ml) was added, stirred for 10 minutes to remove the acid catalyst, filtered to separate the solid product, washed with brine and dried. The product was finally recrystallized from methanol / ethyl acetate (1:3), without any need for further purification. The yield of the product did not increase with greater amounts of fluoroboric acid and mention must be made of the fact that no reaction took place in absence of fluoroboric acid. Therefore, fluoroboric acid definitely catalyses this reaction. As only 0.1 ml of aqueous HBF₄ is used, it cannot act as a solvent.

Scheme 1. Synthesis of 2, 2'-bis-benzimidazole with fluoroboric acid under solvent-free conditions.

For the structure of 2, 2'-bis-1H-benzimidazole 4a, two conformers, s-cis and s-trans are possible. It is quite obvious that the s-trans conformer is the more stable one due to the presence of two five-membered intramolecular H-bonds as shown in Figure 1 (i). The stability of the s-trans conformation was proved computationally which is further corroborated from molecular orbital diagram of compound 4e as shown in Figure 1 (ia). All the time-independent computational studies reported in this work were performed using the Gaussian 03 program, within the density functional theory (DFT) framework. B3LYP hybrid functionals were used along with the 6-31G** split-valence basis set. The s-trans and s-cis conformations of 2, 2'- bis-1H-benzimidazole obtained on using Gaussian 03 software are given below:
Figure 1. (i) s-trans conformer of compound 4a; (ia) MO picture (as obtained from calculation) of compound 4e showing the electron density of nitrogen atom pointing towards the neighbouring NH functionality thereby showing the possibility of H-bond formation in such compounds; (ii) s-cis conformer of 4a from DFT calculations. Energy barrier between the 2 tautomers is 48.58 kJ/mol. Such energy barrier between the two tautomers is comparable to the results obtained earlier.
Table 1. Synthesis of 2, 2′-bis-1H-benzimidazole under various conditions using 45 % aqueous fluoroboric acid as catalyst

| Entry | (ml) | reaction condition, temperature (°C) | Time (h) | Yield * (%) |
|-------|-----|--------------------------------------|---------|-------------|
| 1     | –   | 150                                  | 10      | –           |
| 2     | 0.05| 150                                  | 10      | 40          |
| 3     | 0.05| 150                                  | 5       | 40          |
| 4     | 0.05| 150                                  | 2       | 40          |
| 5     | 0.1 | 150                                  | 2       | 80          |
| 6     | 0.2 | 150                                  | 2       | 65          |
| 7     | 0.3 | 150                                  | 2       | 50          |
| 8     | 0.1 | 150                                  | 10      | 80          |
| 9     | 0.1 | microwave oven, 150, 840 watt         | 20      | 60          |
| 10    | 0.1 | 120                                  | 2       | 40          |
| 11    | 0.1 | 90                                   | 5       | 20          |

* isolated

With the above result of optimized reaction conditions, we investigated the reactions of varieties of orthophenylene diamines with aliphatic carboxylic acids and the results are summarized in Table 2. In all the cases, the yields were very good. A total of three different orthophenylene diamines were utilized (Table 2). All the products gave satisfactory spectral (IR, 1H NMR, 13C NMR) data.

We then turned our attention towards the synthesis of mixed 2, 2′-bis-1H-benzimidazoles using varieties of dicarboxylic acids (Scheme 2, Table 2). For this purpose, again three different ortho-phenylenediamines and dicarboxylic acids with various methylene spacers were employed (Table 2).

Scheme 2. Bis-benzimidazole formation with aqueous fluoroboric acid under solvent-free conditions.
Table 2. Synthesis of 2, 2′-simple and mixed bis-1H-benzimidazoles with 45% aqueous HBF₄ (0.1 ml) at 150 ºC

| Entry (Compound No.) | Products | Time (hours) | Yield* (%) | References |
|----------------------|----------|--------------|------------|------------|
| 1 (4a)               | ![Image](image1) | 2            | 80         | 7          |
| 2 (4b)               | ![Image](image2) | 2.5          | 70         | 14         |
| 3 (4c)               | ![Image](image3) | 2.2          | 85         | 15         |
| 4 (4d)               | ![Image](image4) | 2.5          | 72         |            |
| 5 (4e)               | ![Image](image5) | 3            | 75         |            |
| 6 (4f)               | ![Image](image6) | 3            | 95         | 16         |
| 7 (4g)               | ![Image](image7) | 4            | 95         | 7          |
| 8 (4h)               | ![Image](image8) | 3            | 80         | 5          |
| 9 (4i)               | ![Image](image9) | 3            | 75         |            |
| Entry (Compound No.) | Products | Time (hours) | Yield* (%) | References |
|----------------------|----------|--------------|------------|------------|
| 10 (4j)              | ![Product Image](image1) | 2.5 | 98 | 16 |
| 11 (4k)              | ![Product Image](image2) | 2 | 98 | 16 |
| 12 (4l)              | ![Product Image](image3) | 4 | 77 | |
| 13 (4m)              | ![Product Image](image4) | 2 | 88 | 16 |
| 14 (4n)              | ![Product Image](image5) | 2 | 98 | |
| 15 (4o)              | ![Product Image](image6) | 2 | 99 | 5 |
| 16 (4p)              | ![Product Image](image7) | 4 | 82 | 17 |
| 17 (4q)              | ![Product Image](image8) | 2.3 | 80 | |

* isolated after recrystallisation
On examination of Table 2, we find that our methodology works excellent for the synthesis of both simple and mixed bis-1H-benzimidazoles although the yields for the mixed bis-compounds (Table 2, entries 2, 4, 5, 9 and 12) were slightly lower. The mixed bis-1H-benzimidazoles could be synthesized without almost any contamination of the simple benzimidazoles at the same time (HPLC data of crude 4d, 4i and 4l given in the Supplementary Section). Perhaps this is the greatest advantage of this methodology (crude NMR for compound 4i is given in the Supplementary Section: Figure A). The reaction is performed by the initial mixing of the two types of the diamines and the dicarboxylic acid followed by the addition of the catalyst. The mixture is heated for the specified time (Table 2) in a oil-bath at 150 ºC. On cooling, the crude product solidified, saturated aqueous NaHCO$_3$ solution (10 ml) was added, stirred for 10 minutes to remove the acid catalyst, filtered to separate the solid product, washed with brine and dried. The product was finally recrystallized from methanol-ethyl acetate (1:3) without any need for further purification by column chromatography (details given in the Experimental Section). The mechanism of bis-1H-benzimidazole formation goes by the usual acid catalysed initial formation of diamides followed by ring closure and elimination of water molecules (Scheme 3). The final confirmation of the formation of bis-1H-benzimidazole and its trans conformation comes from the X-ray crystal structure of compound 4n (Figure 3). The low solubility of the compound 4n did fortuitously lead to crystals (during acquisition of NMR experiment) suitable for single-crystal X-ray analysis with the solid-state structure.

![Figure 2](image-url)

**Figure 2.** $^1$H-NMR showing expanded portion of the aromatic region of compound 4c: the pattern depicting the possible presence of two tautomers (details given in Supplementary Section) and further explained from DFT theory below.
Scheme 3. Plausible mechanism for 1H-bis-benzimidazole formation.

Figure 3. Ortep plot of compound 4n showing crystallographic numbering (CCDC 762795)

A detailed analysis for the formation of the unsymmetrical bis-benzimidazoles 4i has been shown here in Figure 4. Although, statistically, the formation of all the three bis-benzimidazoles, 4i, 4j and 4g are possible, in real practice, only 4i and 4j are formed in a ratio of 5:1 from the integration ratios of the aromatic protons in the crude ¹H NMR spectra. That compound 4g was absent was proved conclusively since 4g is insoluble in DMSO-­‐d₆ and no product was present as a residue during the preparation of this crude mixture for NMR sampling.
$4i : 4j = 5:1$ from integration of crude $^1$H-NMR peaks of the aromatic protons.

**Figure 4.** Crude $^1$H-NMR spectrum of compound $4i$ (before purification by crystallization on solubility basis) showing the presence of a mixture of compound $4i$ and compound $4j$ in a ratio of 5:1 respectively.

Theoretically, there should be formation of compound $4g$ along with compound $4j$ as shown above in Figure 4, but $4g$ was not formed in this reaction. Of all the mixed bis-$^1$H-benzimidazoles prepared (compounds $4b$, $4d$, $4e$, $4i$, $4l$), only compound $4i$ was formed as a mixture of a symmetrical bis-benzimidazole and an unsymmetrical bis-benzimidazole. In case of the other four compounds $4b$, $4d$, $4e$ and $4l$, only the target unsymmetrical bis-benzimidazole
compounds resulted in somewhat lower yields than the symmetrical bis-benzimidazoles. Although this might not appear to be very sound, but the actual picture shows to be so as is evident from the crude $^1$H NMR spectra for the formation of the unsymmetrical bis-benzimidazoles (all given in the Supplementary Section). HPLC analysis were performed on crude compounds 4d, 4i and 4l (details given in supplementary section). The high insolubility of these bis-benzimidazoles stopped us from performing HPLC analyses on all such compounds particularly, the pure ones. The exact reason for the formation of the target unsymmetrical bis-benzimidazoles without the contamination of the symmetrical bis-benzimidazoles for the formation of 4b, 4d and 4e could be the high conjugative stabilization present in the products (as 4b, 4d and 4e are obtained from oxalic acid) neglecting the small difference of the electronic effects in the starting diamines; resulting in the formation of solely the unsymmetrical bis-benzimidazoles since the starting diamines are present in 1:1 ratio and there is no choice for selectivity. As expected, when 1 mol of the diamine is allowed to react with 1 mol of the diacid, quinoxaline derivative formation takes place (Scheme 4) with oxalic acid (6-membered ring) and benz-diazepine type ring formation with malonic acid (7-membered ring). With the higher methylene spacers, no quinoxaline or benz-diazepine type ring formation takes place. The reason for this could be the stability of the 6- and 7-membered rings. No quinoxaline type ring formation takes place with two equivalents of the diamine.

\[
\begin{align*}
\text{R} \quad \text{NH}_2 & \quad + \quad (\text{CH}_2)_n(\text{COOH})_2 \quad \rightarrow \quad 0.1 \text{ ml 45\% aqueous HBF}_4, \\
\text{solvent-free conditions} & \quad \text{oil-bath, 150} \degree \text{C} \\
\end{align*}
\]

R = H, n=0 [6a]$^{18}$; R= CH$_3$, n=0 [6b]$^{18}$; R= H, n=1 [6c]$^{19}$

**Scheme 4.** Quinoxaline (or benz-diazepine type) ring formation with equimolar ratios of diamine and diacid.

This could probably because of the higher rate of amide bond formation with the one amine group of a diamine than the second one. In presence of equimolar amount of diacid and diamine, single-step cyclization seems to have taken place to form the quinoxaline 6a, 6b or the benz-diazepine type derivative (1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione) 6c. The formation of the quinoxaline is evident from the IR band at 1669 cm$^{-1}$. Final confirmation for quinoxaline formation comes from an X-ray crystallography of a single crystal of 6b (Figure 5).
Figure 5. Ortep plot of 6b showing the crystallographic numbering (CCDC 744703).

DFT Calculations
Next we were interested to study the minimum energy conformers for some of the known and the unknown synthesized bis-1H-benzimidazoles at the computational level; the calculation of which resulted in some interesting outcomes. The oxalic acid derived compounds 4a – 4e were shown to exist in both the cis and trans isomers, the latter being more stable energetically. The trans isomers were always planar but the cis-form presented out-of-plane orientations thereby coming in way of the extensive delocalization of the two benzimidazole moieties. However, for the malonic 4f, succinic 4g-4j, glutaric 4k-4n and adipic acid derived compounds 4o-4q, the cis-conformer seemed to have no existence at all. Moreover in all structures - cis or trans, the isomer in which the methyl substituent was meta to NH was found to be most stable (compounds 4c, 4e, 4f, 4h and 4l).
Figure 6. B3LYP/6-31G** optimized structures of the most stable isomers of the synthesized bis-1H-benzimidazoles.
Compound 4c was obtained as a mixture of two tautomers to the extent of 51.6% (tautomer A) and 48.4% (tautomer B) as analysed from $^1$H-NMR (given in Figure 2). The possible structures of the tautomers were established in terms of energy from these density functional theory calculations.

![Possible structures of the most stable conformers of compound 4c from DFT optimization](image)

**Figure 7.** Possible structures of the most stable conformers of compound 4c from DFT optimization: the structures v to viii of compound 4c are in increasing order of energy respectively.

**Photophysical studies**
Finally we studied the absorption and emission spectral characteristics of the newly synthesized compounds and their differences with the core compound 4a were determined. As is quite evident from their structures, the fluorescence spectral characteristics of compounds 4d and 4e should be different from those of compounds 4q, 4n and 4l with variable methylene spacers. To prove these points, their absorbance and emission (Figure 8) were recorded along with that of 2, 2,2´-bis-1H-benzimidazole (compound 4a).
The absorption band maxima for compound 4d ($\lambda_{abs} = 337$ nm) is red-shifted with respect to that of compound 4a ($\lambda_{abs} = 326$ nm; the absorption and emission of compound 4a are given in the supplementary section). Similar to its absorption spectrum, the fluorescence spectrum of compound 4d ($\lambda_{emi} = 380$ nm) is also red-shifted as compared to compound 4a ($\lambda_{emi} = 366$ nm). The fluorescence spectrum of compound 4d almost makes a mirror image with its absorption spectra, indicating that the molecular conformation in the first excited state ($S_1$) differs little from that in the ground state ($S_0$).\textsuperscript{20} The emission spectrum of 4d shows the same vibrational energy spacing as the absorption spectrum. The fluorescence spectrum was found to be independent of the excitation wavelengths. The absorption and emission spectra are highly structured and red-shifted as compared to compound 4a indicating better extensive conjugation between the two rings in 4d.

The absorption band maxima of compound 4e ($\lambda_{abs} = 336$ nm) is also red-shifted as compared to compound 4a. A weak shoulder in the absorption spectrum for compound 4e is present at 323 nm, whereas for compound 4a it was at 316 nm. Although the fluorescence spectrum of compound 4e makes a mirror image with its absorption spectrum, along with being red-shifted indicating more extensive conjugation , the fluorescence spectrum was not independent of the excitation wavelengths and gave two similar but different emission spectra when excited at 335 nm and 430 nm respectively i.e., it exists as a two-emitting species. Proton transfer probably takes place in the excited state, yielding a highly conjugated species that fluoresces at a longer wavelength.\textsuperscript{7,15} It cannot be due to tautomerisation, because different tautomeric forms are possible in all these bis-benzimidazole compounds.

The extensive conjugation is absent for compounds 4q, 4n and 4l; both the absorption and fluorescence band maxima are blue-shifted as compared to compound 4a. The structural nature of their absorption bands are absent in their fluorescent spectra, i.e., their absorption and emission spectra are not mirror images. The shorter wavelength absorption peak is probably due
to excitation to the second excited state (S₂), which relaxes rapidly to S₁. Emission occurs predominantly from the lowest singlet state (S₁), so emission from S₂ is not observed. The low fluorescence quantum yield values for compounds 4q, 4n and 4l also reflects that the molecules are not rigid; variable methylene spacers between the two benzimidazole moieties are present in these compounds and so are viable to free rotation. Moreover, for all the molecules the quantum yields are not close to unity, which indicates that their non-radiative decay rates are much higher than their rates of radiative decay.

Table 3. Fluorescence studies and quantum yields of compounds 4d, 4e, 4q, 4n and 4l

| Compounds | Absorption wavelength (λ<sub>abs</sub> (nm)) | Emission wavelength (λ<sub>emi</sub> (nm)) | Quantum Yield |
|-----------|---------------------------------------------|------------------------------------------|---------------|
| 4d        | 337, 355                                    | 362, 380, 399                            | 0.0073        |
| 4e        | 323, 336, 353                               | 379, 398                                 | 0.0141        |
|           | 323, 336, 353                               | 467, 497, 531                            | 0.0138        |
| 4q        | 286, 292                                    | 311                                      | 0.0044        |
| 4n        | 286, 292                                    | 311                                      | 0.0021        |
| 4l        | 277, 284                                    | 307                                      | 0.0031        |

Conclusions

From our detailed studies, we find that, fluoroboric acid (45% aqueous solution) proved to be a very efficient catalyst for the synthesis of 2,2′-bis-1H-benzimidazoles (both simple and mixed) under solvent-free conditions in an oil-bath at 150 ºC. The products could be readily purified in excellent yields without the need for column chromatography. All representative molecules were computed for their energy-minimized structures using the B3LYP/6-31G** level of theory in Gaussian 03. The fluorescence studies of a few unknown compounds were studied which proved that the absorption and emission maxima were highly dependant on the methylene spacers as expected.

Experimental Section

General. All NMR analyses were performed on a 300 MHz Bruker machine using deuterated DMSO as the solvent. The pure batch of compounds after recrystallisation was used for the determination of elemental analysis.

General method for 2, 2′-bis-1H-benzimidazole formation
Diamine 1 (1 mmol) and diamine 2 (1 mmol) were mixed together in a 25 ml round-bottomed flask and to it the diacid 3 (1 mmol) was added followed by 0.1 ml of 45 % aqueous fluoroboric
acid. The contents of the flask were heated in an oil-bath at 150 °C for the specified time (Table 3). On cooling, the crude product solidified, saturated aqueous NaHCO₃ solution (10 ml) was added, stirred for 10 minutes to remove the acid catalyst, filtered to separate the solid product, washed with brine and dried. The products were finally recrystallized from methanol-ethyl acetate (1:3) without any need for further purification by column chromatography. All the experiments were performed at least thrice to produce the same results in each case.

An important observation is that, for all the oxalic acid derived compounds 4a, 4b, 4c, 4d and 4e, the proton-nmr signals were broadened and consequently overlapping (especially the aromatic region) took place. These yellowish-green compounds were also highly fluorescent even in the minimal amount required for sampling NMR in DMSO-d₆ solvent. The broadening of signal occurs due to problems in magnetic field homogeneity. In the present case, this problem probably occurs due to the viscosity of sample. Similar signal broadening has been observed in compounds refereed in reference no. 20. Absorption and emission spectra of the representative compounds were very characteristic for each compound studied as mentioned in the main manuscript.

2, 2'-Bis-1H-benzimidazole (4a). (Table 2, entry 1): m.p. >250°C (DMSO-H₂O); ¹H-NMR (DMSO-d₆) δ 7.25 (s, 4H, C₅-H, C₆-H, C₅-H and C₆-H), 7.52 (d, J=6.3 Hz, 2H, C₇-H and C₇-H), 7.71 (d, J=6.0 Hz, 2H, C₄-H and C₄-H) and 13.52 (br s, 2H, N₁-H and N₁-H); ¹³C-NMR (75 MHz, DMSO-d₆) δ 112.2 (C₇ and C₇), 119.3 (C₄ and C₄), 122.3 (C₃ and C₃), 123.7 (C₆ and C₆), 134.9 (C₃a and C₃'a), 143.6 (C₇a and C₇a) and 143.9 (C₂ and C₂); IR (KBr): 3754, 3438, 3034, 2946, 2867, 2747, 2373, 1622, 1498, 1397, 1341, 946 and 742 cm⁻¹; Anal. calcd. for C₁₄H₁₀N₄: C: 71.78, H: 4.30, N: 23.92. Found: C: 71.70, H: 4.35, N: 23.99 %.

6-Methyl-2, 2'-bis-1H-benzimidazole (4b). (Table 2, entry 2): m.p. >250°C (DMSO-H₂O); ¹H-NMR (DMSO-d₆) δ 7.06 (s, 1H, C₅-H), 7.24-7.40 (m, 3H, C₇-H, C₅-H and C₆-H), 7.54 (br s, 2H, C₄-H and C₇-H), 7.69 (br s, 1H, C₄-H) and 13.35-13.46 (m, 2H, N₁-H and N₁-H); ¹³C-NMR (DMSO-d₆) δ 21.4 (C₆-CH₃), 111.8 (C₇), 112.2 (C₇), 118.8 (C₄), 119.0 (C₆), 122.3 (C₃), 123.7 (C₅ and C₆), 131.0 (C₆), 133.0 (C₃a), 135.0 (C₇a), 142.0 (C₇a), 143.6 (C₂) and 144.0 (C₂); IR (KBr): 3045, 2944, 2864, 1738, 1588, 1399, 1338, 949, 802 and 742 cm⁻¹; Anal. calcd. for C₁₄H₁₂N₄: C: 72.56, H: 4.87, N: 22.57. Found: C: 72.55, H: 4.84, N: 22.52 %.

5(6), 5'(6')-Dimethyl-2, 2'-bis-1H-benzimidazole (4c). (Table 2, entry 3): ¹H-NMR (DMSO-d₆) δ 2.40 [s, {3.096H (CH₃) and 2.904H (CH'₃)}], 7.06 [br s, {1.032H (H₃) and 0.968H (H'₃)}], 7.30 [s, 1.032H (H₆)], 7.38 [d, J=6.6 Hz, 0.968H (H₆)], 7.49 [s, 0.968H (H₆)], 7.56 [d, J=8.1 Hz, 1.032H (H₆)] and 13.30 [br s, {1.032H (NH) and 0.968H (NH')}], ¹³C-NMR (DMSO-d₆) δ 21.4 (CH₃ and CH'₃), 111.7 (C₆-H₅ and C₆-H₆), 118.7 (C₆-H₅ and C₆-H₆), 124.0 (C₆-H₇, C₆-H₇, C₆-H₈ and C₆-H₉), 133.0 (C₃a, C₇a, C₃a, C₇a, C₃a, C₇a, C₃a and C₇a) and 143.7 (C₂ and C₂); IR (KBr): 2923, 2661, 1590, 1399, 1335, 956 and 800 cm⁻¹. MS: m/z (%): 262.1 (M⁺, 100), 263.1 (M⁺+1, 20), 264.1 (M⁺+2, 2); Anal. calcd. for C₁₆H₁₄N₄: C: 73.26, H: 5.38, N: 21.36. Found: C: 73.40, H: 5.36, N: 21.57 %.
5, 6-Dimethyl-2, 2'-bis-1H-benzimidazole (4d). (Table 2, entry 4): m.p. >250°C (DMSO-H2O); 1H-NMR (DMSO-d6) δ 2.29 (s, 6H, C5-CH3 and C6-CH3), 7.24 (br s, 3H, C7-H, C5-H, and C6-H), 7.44-7.68 (m, 3H, C4-H, C4'-H and C7'-H) and 13.17-13.37 (m, 2H, N1-H and N1'-H); 13C-NMR (DMSO-d6) δ 20.1 (C5-CH3 and C6-CH3), 112.0 (C7 and C7'), 119.0 (C4 and C4'), 122.3 (C3), 123.7 (C6), 130.8 (C8), 132.4 (C5), 133.4 (C3a), 142.3 (C3a), 143.0 (C7a), 143.3 (C2), 143.9 (C7a) and 144.2 (C2); IR (KBr): 2920, 2664, 1584, 1395, 1327, 1001, 953, 847 and 737 cm⁻¹; MS: m/z (%): 262.1 (M⁺, 100), 263.1 (M+1, 20), 264.1 (M+2, 2); Anal. calcd. for C16H14N4; C: 73.26, H: 5.38, N: 21.36. Found; C: 73.44, H: 5.23, N: 21.50 %.

5, 6'-Trimethyl-2, 2'-methanediyldi-bis-1H-benzimidazole (4e). (Table 2, entry 5): m.p. >250°C (DMSO-H2O); 1H-NMR (DMSO-d6) δ 2.30 (s, 6H, C5-CH3 and C6-CH3), 2.40 (s, 3H, C6-CH3), 7.06 (br s, 1H, C5-H), 7.29 (br s, C7-H and C7'-H ), 7.46 (br s, 1H, C4-H), 7.55 (br s, 1H, C4-H) and 13.16-13.25 (m, 2H, N1-H and N1'-H); 13C-NMR (DMSO-d6) δ 20.1 (C5-CH3 and C6-CH3), 21.4 (C6-CH3), 111.8 (C6, C7, C4 and C7'), 119.0 (C5, C6, C5' and C6'), 135.0 (C3a, C7a, C3a and C7a), 143.1 (C2) and 143.3 (C2); IR (KBr): 2921, 2738, 1586, 1394, 1330, 1003, 955, 852 and 801 cm⁻¹; MS: m/z (%): 276.1 (M⁺, 100), 277.1 (M+1, 21), 278.1 (M+2, 2); Anal. calcd. for C17H16N4; C: 73.89, H: 5.84, N: 20.27. Found; C: 73.49, H: 5.63, N: 20.43 %.

6'-Dimethyl-2, 2'-methanediyldi-bis-1H-benzimidazole (4f). (Table 2, entry 6): m.p. >250°C (DMSO-H2O); 1H-NMR (DMSO-d6) δ 2.35 (s, 6H, C5-CH3 and C6-CH3), 4.36 (s, 2H, C2-CH2), 6.92 (d, J=8.1 Hz, 2H, C5-H and C5'-H), 7.24 (s, 2H, C7-H and C7'-H), 7.33 (d, J=7.8 Hz, 2H, C4-H and C4'-H) and 12.22 (br s, 2H, N1-H and N1'-H); 13C-NMR (DMSO-d6) : sensitivity very poor; IR (KBr): 2916, 2864, 1625, 1542, 1446, 1277, 1030, 805 and 760 cm⁻¹; Anal. calcd. for C17H16N4; C: 73.89, H: 5.84, N: 20.27. Found; C: 73.87, H: 5.80, N: 20.27 %.

2, 2'-(1, 2-Ethanediyl) bis-1H-benzimidazole (4g). (Table 2, entry 7): Melting point >250°C (DMSO-H2O); 1H-NMR and 13C-NMR could not be obtained since the compound was insoluble in all possible NMR solvents; IR (KBr): 2747, 1540, 1439, 1274, 1030, 919, 874 and 745 cm⁻¹; Anal. calcd. for C16H14N4; C: 73.26, H: 5.38, N: 21.36. Found; C: 73.25, H: 5.32, N: 21.37 %.

6'-Dimethyl-2, 2'-(1, 2-ethanediyl) bis-1H-benzimidazole (4h). (Table 2, entry 8): m.p. >250°C (DMSO-H2O); 1H-NMR (DMSO-d6) δ 2.34 (s, 6H, C5-CH3 and C6-CH3), 3.29 (s, 4H, C2-CH2 and C2'-CH2), 6.89 (d, J=8.1 Hz, 2H, C5-H and C5'-H), 7.21 (s, 2H, C7-H and C7'-H) and 7.30 (d, J=8.1 Hz, 2H, C4-H and C4'-H); 13C-NMR (DMSO-d6) δ 21.3 (C6-CH3 and C6'-CH3), 26.7 (C2-CH2 and C2'-CH2), 114.0 (C7 and C7'), 114.5 (C4 and C4'), 112.7 (C5, C6, C5' and C6'), 130.3 (C3a, C7a C3a and C7a) and 153.7 (C2 and C2); IR (KBr): 3028, 2865, 1735, 1542, 1426, 1283, 1149, 1023 and 796 cm⁻¹; Anal. calcd. for C18H18N4; C:74.46, H: 6.25, N: 19.30. Found; C: 74.40, H: 6.25, N: 19.27 %.

5, 6-Dimethyl-2, 2'-(1, 2-ethanediyl) bis-1H-benzimidazole (4i). (Table 2, entry 9): m.p. 250°C (DMSO-H2O); 1H-NMR (DMSO-d6) δ 2.23 (s, 6H, C5-CH3 and C6-CH3), 3.30 (t, J=12.9 Hz, 4H, C2-CH2 and C2'-CH2), 7.07 (dd, J=6.0 Hz, 3.3 Hz, 2H, C5-H and C5'-H), 7.19 (s, 2H, C4-H and C4'-H) and 7.43 (dd, J=6.0 Hz, 3.0 Hz, 2H, C4-H and C4'-H); 13C-NMR (DMSO-d6) δ: 20.0 (C5-CH3 and C6-CH3), 26.7 (C2-CH2), 26.8 (C2'-CH2), 114.7 (C4, C7, C4' and C7'), 121.3 (C5' and C5'), 129.5 (C5 and C6), 137.3 (C3a and C7a), 138.8 (C3a and C7a), 153.1 (C2') and 154.2 (C2);
IR (KBr): 3381, 2923, 1542, 1499, 1022 and 741 cm⁻¹; MS: m/z (%): 290.2 (M⁺, 100), 291.2 (M+1, 22), 292.2 (M+2, 2); Anal. calcd. for C₁₅H₁₈N₄: C: 74.46, H: 6.25, N: 19.30. Found: C: 74.39, H: 6.30, N: 19.09 %.

5, 6, 5', 6'-Tetramethyl-2, 2'-1H-benzimidazole (4j). (Table 2, entry 10): m.p. >250°C (DMSO-H₂O); ¹H-NMR (DMSO-d₆) δ 2.23 (s, 12H, C₅-H₃, C₆-H₆, C₅-H₃ and C₆-H₆), 3.25 (s, 4H, C₂-H₂ and C₂-H₂), 7.19 (s, 4H, C₄-H, C₇-H, C₄-H and C₇-H), and 12.0 (br s, 2H, N₁-H and N₁-H); ¹³C-NMR (DMSO-d₆) δ 20.0 (C₅-H₃, C₆-H₆, C₅-H₃ and C₆-H₆), 26.8 (C₂-H₂ and C₂-H₂), 129.4 (C₄, C₅, C₆, C₇, C₃a, C₇a, C₄, C₅, C₆, C₇, C₅a and C₇a), 153.1 (C₂ and C₂); IR (KBr): 2928, 1540, 1451, 1306, 1013, 848 and 765 cm⁻¹; Anal. calcd. for C₂₀H₂₂N₄: C: 75.44, H: 6.96, N: 17.60. Found: C: 75.44, H: 6.97, N: 17.58 %.

2, 2'-(1, 3-Propanediyl)bis-1H-benzimidazole (4k). (Table 2, entry 11): m.p. 260°C (DMSO-H₂O); ¹H-NMR (DMSO-d₆) δ 2.25 (t, J = 7.2 Hz, 2H, C₂-H₂ and C₂-H₂), 2.88 (t, J = 7.5 Hz, 4H, C₂-H₂ and C₂-H₂), 7.06-7.09 (m, 4H, C₅-H, C₆-H, C₅-H and C₆-H), and 7.42-7.44 (m, 4H, C₄-H, C₇-H, C₄-H and C₇-H); ¹³C-NMR (DMSO-d₆) δ 25.8 (C₂-H₂ and C₂-H₂), 28.0 (C₂-H₂ and C₂-H₂), 114.5 (C₄, C₇, C₄ and C₇), 121.2 (C₅, C₆, C₅ and C₆), 139.0 (C₃a, C₇a, C₃a and C₇a) and 154.6 (C₂ and C₂); IR (KBr): 3385, 2849, 1591, 1531, 1479, 1312, 1198 and 924 cm⁻¹; Anal. calcd. for C₁₇H₁₆N₄: C: 73.89, H: 5.84, N: 20.27. Found: C: 73.80, H: 5.83, N: 20.26 %.

6-Methyl-2, 2'-(1,3-Propanediyl)bis-1H-benzimidazole (4l). (Table 2, entry 12): m.p. 174°C softens and 180°C melts (DMSO-H₂O); ¹H-NMR (DMSO-d₆) δ 2.44-2.48 (m, 2H, C₂-H₂ and C₂-H₂), 2.56 (s, 3H, C₆-H₃), 3.08 (d, J = 5.7 Hz, 4H, C₂-H₂ and C₂-H₂), 7.11 (d, J = 7.8 Hz, 1H, C₅-H), 7.28-7.31 (m, 2H, C₅-H and C₆-H), 7.43 (s, 1H, C₇-H), 7.53 (d, J = 7.8 Hz, 1H, C₄-H), 7.65 (br s, 2H, C₄-H and C₇-H) and 12.37 (br s, 2H, N₁-H and N₁-H); ¹³C-NMR (DMSO-d₆) δ 21.3 (C₆-H₃), 25.9 (C₂-H₂ and C₂-H₂), 121.3 (C₄, C₇, C₄ and C₇), 122.6 (C₅, C₅ and C₆), 130.3 (C₃a, C₆ and C₃a), 154.4 (C₇a and C₇a) and 154.7 (C₂ and C₂); IR (KBr): 2950, 1541, 1443, 1273, 1024, 801 and 738 cm⁻¹; MS: m/z (%): 290.2 (M⁺, 100), 291.2 (M+1, 22), 292.2 (M+2, 2); Anal. calcd. for C₁₈H₁₈N₄: C: 74.46, H: 6.25, N: 19.30. Found: C: 74.35, H: 6.43, N: 19.08 %.

6, 6'-Dimethyl-2, 2'-(1,3-Propanediyl)bis-1H-benzimidazole (4m). (Table 2, entry 13): m.p. 122°C decomposes (DMSO-H₂O); ¹H-NMR (DMSO-d₆) δ 2.22-2.24 (m, 2H, C₂-H₂ and C₂-H₂), 2.84 (t, J = 6.6 Hz, 4H, C₂-H₂ and C₂-H₂), 6.89 (d, J = 7.5 Hz, 2H, C₅-H and C₅-H), 7.21 (s, 2H, C₇-H and C₇-H) and 7.30 (d, J = 8.1 Hz, 2H, C₄-H and C₄-H); ¹³C-NMR (DMSO-d₆) δ 21.3 (C₆-H₃ and C₆-H₃), 25.8 (C₂-H₂ and C₂-H₂), 28.0 (C₂-H₂ and C₂-H₂), 113.9 (C₇ and C₇), 114.4 (C₄ and C₄), 122.6 (C₅ and C₅), 130.2 (C₆ and C₆), 137.5 (C₇a and C₇a), 138.8 (C₃a and C₃a) and 154.3 (C₂ and C₂); IR (KBr): 3382, 2927, 1537, 1447, 1279 and 802 cm⁻¹; Anal. calcd. for C₁₉H₂₀N₄: C: 74.97, H: 6.62, N: 18.41. Found: C: 74.95, H: 6.63, N: 18.38 %.

5, 6, 5', 6'-Tetramethyl-2, 2'-(1,3-Propanediyl) bis-1H-benzimidazole (4n). (Table 2, entry 14): m.p. 250°C decomposes (DMSO-H₂O); ¹H-NMR (DMSO-d₆) δ 2.14-2.19 (m, 2H, C₂-H₂ and C₂-H₂), 2.23 (s, 12H, C₅-H₃, C₆-H₆, C₅-H₃ and C₆-H₆), 2.81 (t, J = 7.2 Hz, 4H, C₂-H₂ and C₂-H₂), and 7.19 (s, 4H, C₄-H, C₇-H, C₄-H and C₇-H); ¹³C-NMR (DMSO-d₆) δ 20.0 (C₅-H₃, C₆-H₆, C₅-H₃ and C₆-H₆), 25.9 (C₂-H₂ and C₂-H₂), 28.0 (C₂-H₂ and C₂-H₂), 114.6 (C₄, C₇,
C₄ and C₇), 129.5 (C₅, C₆, C₅ and C₆), 137.2 (C₃a, C₇a, C₃a and C₇a) and 153.7 (C₂ and C₂); IR (KBr): 2927, 1540, 1451, 1310, 1154, 1005 and 846 cm⁻¹; MS: m/z (%): 332.2 (M⁺, 100), 333.2 (M⁺+ 1, 25), 334.2 (M⁺+2, 3). Anal. calcd. For C₂H₂₄N₄; C: 75.87, H: 7.28, N: 16.85. Found: C: 75.49, H: 7.33, N: 16.50 %.

2, 2'-(1, 4-Butanediyl) bis-1H-benzimidazole (4o). (Table 2, entry 15): m.p. 257°C (DMSO·H₂O); ¹H-NMR (DMSO-d₆) δ 1.82 (s, 4H, C₂-H₂-C₂H₂ and C₂-H₂-C₂H₂), 2.68 (s, 4H, C₂-H₂ and C₂-H₂), 7.06-7.09 (m, 4H, C₅-H, C₆-H, C₅-H and C₆-H) and 7.42-7.45 (m, 4H, C₄-H, C₇-H, C₄-H and C₇-H) and 9.75 (br s, 2H, N₁-H and N₁-H); ¹³C-NMR( DMSO-d⁶) δ 27.3 (C₂-H₂-C₂H₂ and C₂-H₂-C₂H₂), 28.3 (C₂-H₂-C₂H₂ and C₂-H₂-C₂H₂), 114.5 (C₄, C₇, C₄ and C₇), 121.3 (C₃, C₆, C₅ and C₆), 138.7 (C₃a, C₇a, C₇a and C₇a) and 155.0 (C₂ and C₂); IR (KBr): 3049, 2934, 1620, 1533, 1418, 1263, 1004 and 742 cm⁻¹; Anal. calcd. for C₁₈H₁₈N₄; C: 74.46, H: 6.25, N, 19.30. Found: C: 74.40, H: 6.23, N, 19.31 %.

6, 6'-Dimethyl-2, 2'- (1,4-butandiyldi) bis-1H-benzimidazole (4p). (Table 2, entry 16): m.p. >250 °C (DMSO-H₂O); ¹H-NMR (DMSO-d₆) δ 1.77 (br s, 4H, C₂-H₂-C₂H₂ and C₂-H₂-C₂H₂), 2.33 (s, 6H, C₃-Ch₃ and C₆-Ch₃), 2.78 (br s, 4H, C₂-H₂ and C₂-H₂) 6.87 (dd, J=8.1, 1.2 Hz, 2H, C₅-H and C₅-H), 7.19 (br s, 2H, C₇-H and C₇-H) and 7.28 (dd, J=8.1 Hz, 2H, C₄-H and C₄-H); ¹³C-NMR (DMSO-d₆) δ 21.3 (C₆-Ch₃ and C₆-Ch₃), 27.3 (C₂-H₂-C₂H₂ and C₂-H₂-C₂H₂), 28.3 (C₂-H₂ and C₂-H₂), 122.5 (C₄, C₅, C₇, C₄', C₃ and C₇), 130.1 (C₆ and C₆), 137.0 (C₃a, C₇a, C₃a and C₇a) and 154.6 (C₂ and C₂); IR (KBr): 3380, 2933, 1538, 1448, 1282, 1016 and 800 cm⁻¹; Anal. calcd. for C₂₀H₂₂N₄; C: 75.44, H: 6.96, N: 17.60. Found: C: 75.42, H: 6.95, N: 17.56%.

5, 6, 5', 6'-Tetramethyl-2, 2'- (1,4-butanediyl) bis-1H-benzimidazole (4q). (Table 2, entry 17): m.p. >250 °C (DMSO-H₂O); ¹H-NMR (DMSO-d₆) δ 1.76 (br s, 4H, C₂-H₂-C₂H₂ and C₂-H₂-C₂H₂), 2.11 (s, 12H, C₃-Ch₃, C₆-Ch₃, C₅-Ch₃ and C₆-Ch₃), 2.76 (br s, 4H, C₂-H₂ and C₂-H₂) and 7.17 (s, 4H, C₄-H, C₇-H, C₄-H and C₇-H); ¹³C-NMR (DMSO-d₆) δ 20.0 (C₃-Ch₃, C₆-Ch₃, C₅-Ch₃ and C₆-Ch₃), 27.3 (C₂-H₂-C₂H₂ and C₂-H₂-C₂H₂), 28.3 (C₂-H₂ and C₂-H₂), 114.6 (C₄, C₇, C₄ and C₇), 129.4 (C₅, C₆, C₅ and C₆), 137.3 (C₃a, C₇a, C₇a and C₇a) and 154.1 (C₂ and C₂); IR (KBr): 2934, 1704, 1540, 1451, 1307, 1002 and 853 cm⁻¹; MS: m/z (%): 346.2 (M⁺, 100), 347.2 (M⁺+1, 25), 348.2 (M⁺+2, 3). Anal. calcd. For C₂₂H₂₆N₄; C: 76.27, H: 7.56, N: 16.17. Found: C: 76.39, H: 7.43, N: 16.09%.

1,4-Dihydro-quinoxalene-2,3-dione (6a). m.p. >250°C (DMSO-H₂O); ¹H-NMR (DMSO-d₆) δ 7.01-7.10 (m, 4H, C₅-H, C₆-H, C₇-H and C₈-H) and 11.87 (s, 2H, N₁-H and N₁-H); ¹³C-NMR (DMSO-d₆) δ 115.2 (C₅ and C₈), 123.1 (C₆ and C₇), 125.7 (C₄a and C₈a) and 155.2 (C₂ and C₃); IR (KBr): 3047, 2965, 2876, 2776, 1681, 1388, 856, 752 and 706 cm⁻¹; Anal. calcd. for C₈H₆N₂O₂; C: 59.26, H: 3.73, N: 17.28, O: 19.73. Found: C: 59.20, H: 3.74, N: 17.22, O: 19.73%.

6,7-Dimethyl-1,4-dihydro-quinoxalene-2,3-dione (6b). m.p.>250°C (DMSO-H₂O); ¹H-NMR (DMSO-d₆) δ 2.46 (s, 6H, C₆-Ch₃ and C₇-Ch₃), 7.17 (s, 2H, C₃-H, and C₈-H) and 12.08 (s, 2H, N₁-H and N₁-H); ¹³C-NMR (DMSO-d₆) δ 19.1 (C₆-Ch₃ and C₇-Ch₃), 115.8 (C₅ and C₈), 123.4 (C₆ and C₇), 131.2 (C₄a and C₈a) and 155.3 (C₂ and C₃); IR (KBr): 3161, 2944, 1689, 1390, 873,
684 and 576 cm\(^{-1}\); Anal. calcd. for C\(_{10}\)H\(_{10}\)N\(_2\)O\(_2\); C: 63.15, H: 5.30, N: 14.73, O: 16.82. Found; C: 63.16, H: 5.35, N: 14.72, O: 16.80 %.

1,5-Dihydro-benzo[b][1,4]diazepine-2,4-dione (6c). m.p. >250°C (DMSO-H\(_2\)O); \(^1\)H-NMR (DMSO-\(d_6\)) \(\delta\) 3.13 (s, 2H, C\(_3\)-H), 7.07-7.14 (m, 4H, C\(_6\)-H, C\(_7\)-H, C\(_8\)-H and C\(_9\)-H) and 10.35 (br s, 2H, N\(_1\)-H and N\(_5\)-H); \(^{13}\)C-NMR (DMSO-\(d_6\)) \(\delta\) 45.1 (C\(_3\)), 122.3 (C\(_7\) and C\(_8\)), 124.9 (C\(_6\) and C\(_9\)), 129.8 (C\(_5a\) and C\(_9a\)) and 165.9 (C\(_2\) and C\(_4\)); IR (KBr): 3058, 1702, 1671, 1500, 1427, 1348, 819 and 769 cm\(^{-1}\); Anal. calcd. for C\(_9\)H\(_8\)N\(_2\)O\(_2\); C: 61.36; H: 4.58; N: 15.90, O: 18.16 . Found; C: 61.33; H: 4.53; N: 15.91, O: 18.14 %.

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21. All detailed spectral data and details of DFT calculations are given in the Supplementary Section.