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

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Abstract
2,2′-(Alkanediyl)-bis-1*H*-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-1*H*-benzimidazoles.

Keywords: 2,2´-(alkanediyl)bis-1*H*-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-1*H*-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 M_1-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.

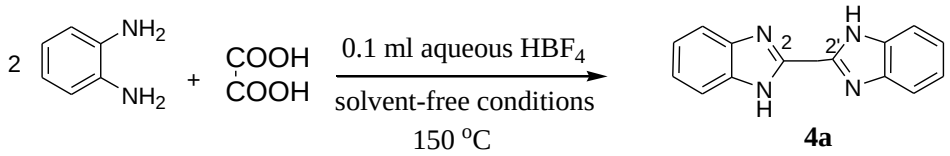
The main theme of this paper is the construction of 2, 2′-bis-1*H*-benzimidazoles (both simple and mixed) with variable methylene spacers in a one-pot operation under solvent-free conditions. The benzimidazole moiety is an important heterocyclic nucleus which has been extensively used in medicinal chemistry. 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 ºC (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 $NaHCO_3$ 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 HBF_4 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-1*H*-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-1*H*-benzimidazole obtained on using Gaussian 03 software are given below:

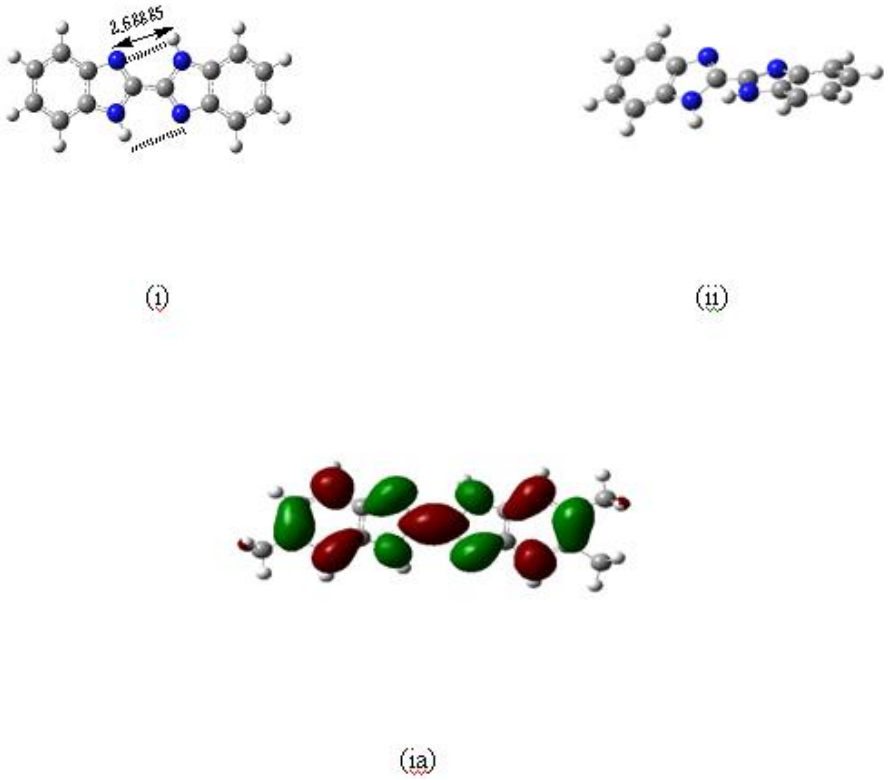


Figure 1. (i) s-trans conformer of compound **4a**; (ia) MO picture (as obtained from calculation) of compound **4e** showing the electron density of nitrogen atom pointing towards the neighbouring NH functionality thereby showing the possibility of H-bond formation in such compounds; (ii) s-cis conformer 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.

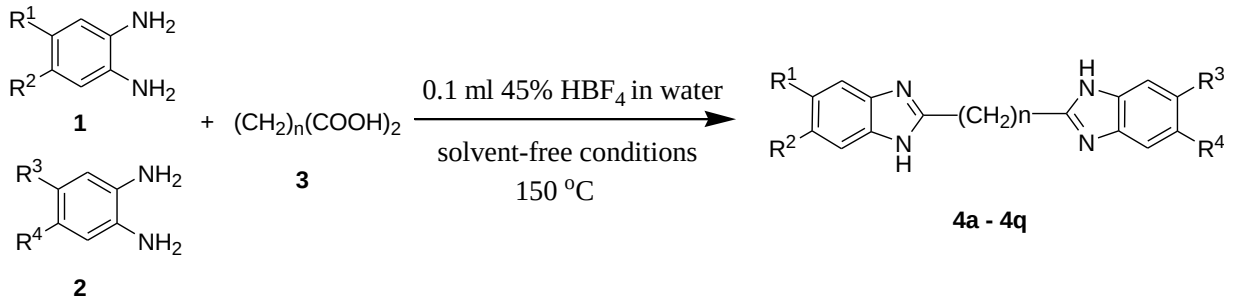
Table1. Synthesis of 2, 2′-bis-1*H*-benzimidazole under various conditions using 45 % aqueous fluoroboric acid as catalyst

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, ^{1}H NMR, ^{13}C NMR) data.

We then turned our attention towards the synthesis of mixed 2, 2′-bis-1*H*-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-1*H*-benzimidazoles with 45% aqueous HBF_4 (0.1 ml) at 150 ºC

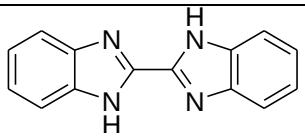
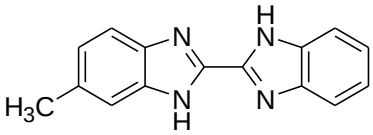
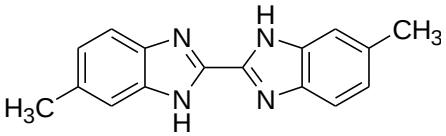
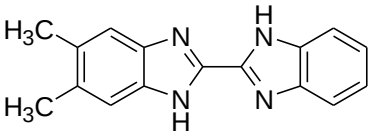
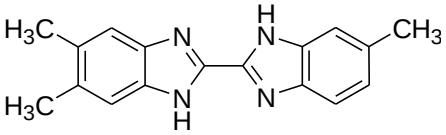
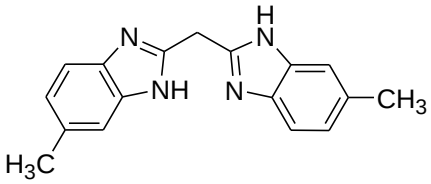
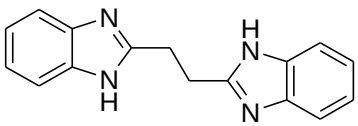
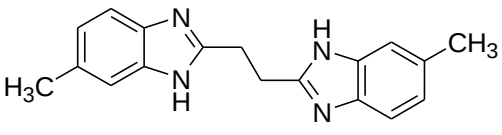
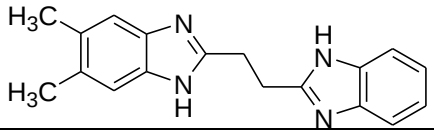
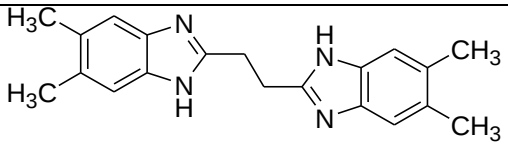
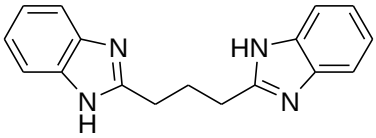
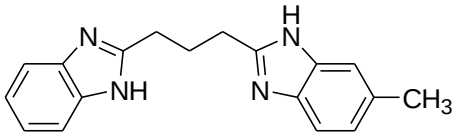
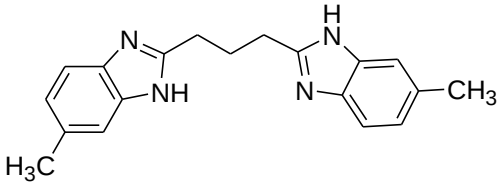
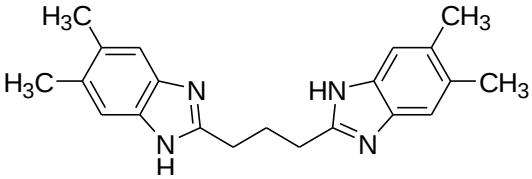
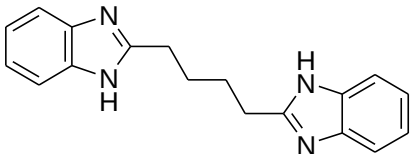
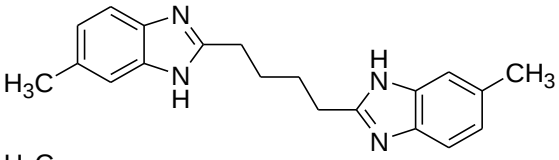
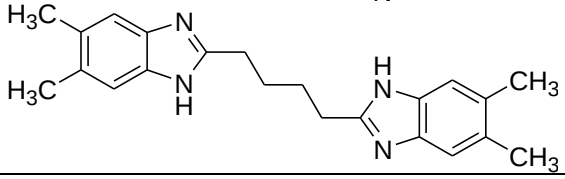
Entry (Compound No.)	Products	Time (hours)	Yield* (%)	References
1 (4a)		2	80	7
2 (4b)		2.5	70	14
3 (4c)		2.2	85	15
4 (4d)		2.5	72	□
5 (4e)		3	75	□
6 (4f)		3	95	16
7 (4g)		4	95	7
8 (4h)		3	80	5
9 (4i)		3	75	□

Table 2. Continued

Entry (Compound No.)	Products	Time (hours)	Yield* (%)	References
10 (4j)		2.5	98	16
11 (4k)		2	98	16
12 (4l)		4	77	□
13 (4m)		2	88	16
14 (4n)		2	98	□
15 (4o)		2	99	5
16 (4p)		4	82	17
17 (4q)		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-1*H*-benzimidazoles although the yields for the mixed bis-compounds (Table 2, entries 2, 4, 5, 9 and 12) were slightly lower. The mixed bis-1*H*-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 an 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-1*H*-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-1*H*-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.

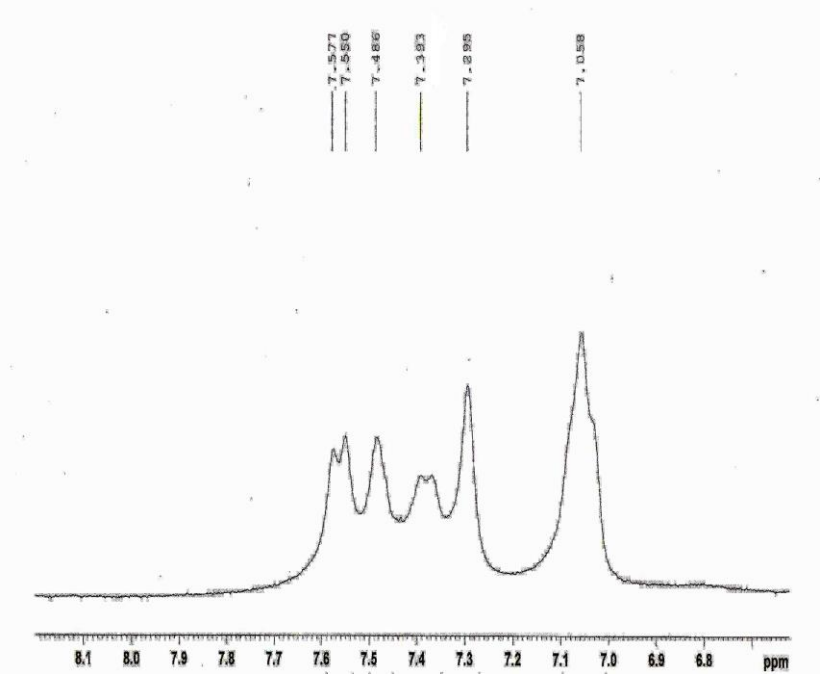
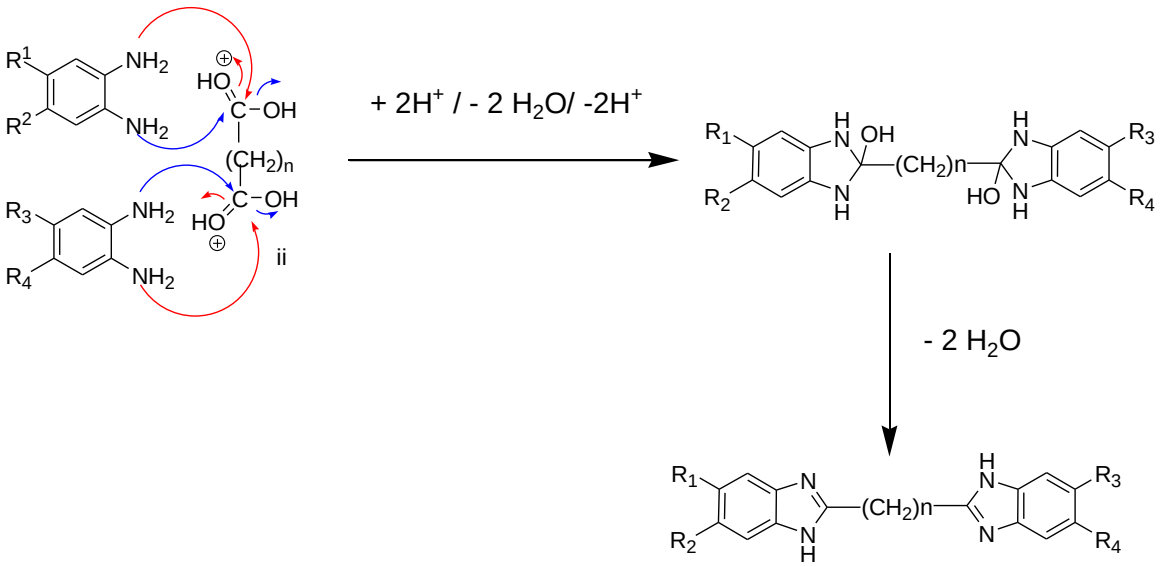


Figure 2. ^{1}H-NMR showing expanded portion of the aromatic region of compound **4c**: the pattern depicting the possible presence of two tautomers (details given in Supplementary Section) and further explained from DFT theory below.



Scheme 3. Plausible mechanism for 1*H*- bis-benzimidazole formation.

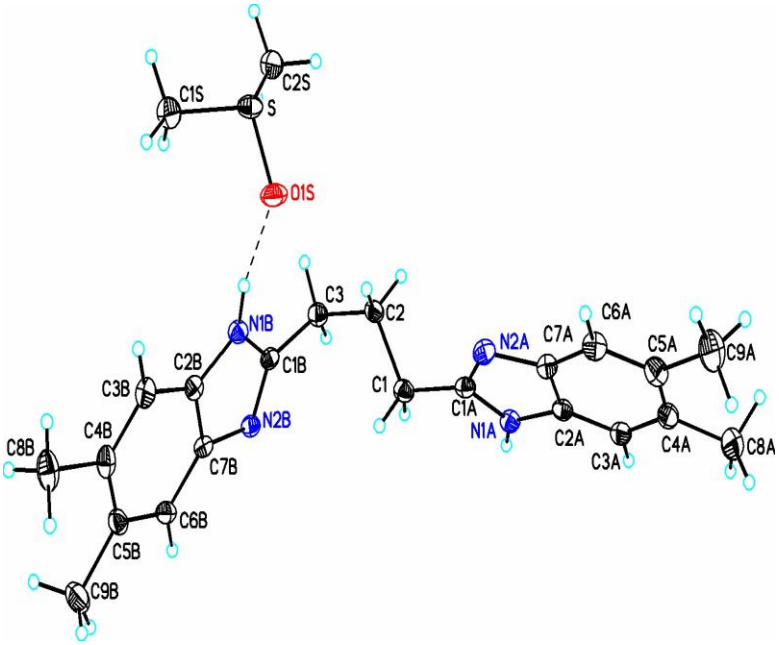
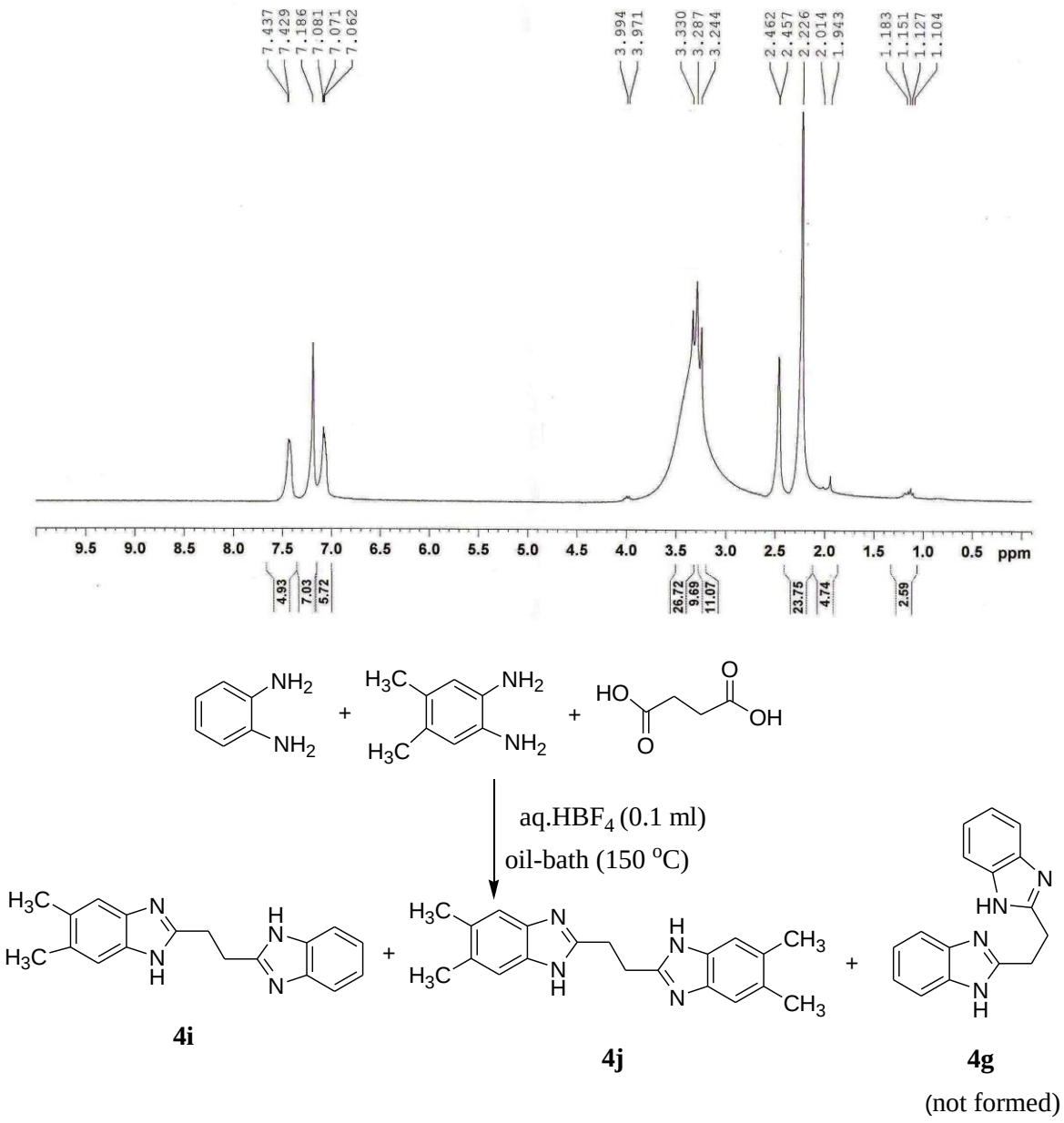


Figure 3. Ortep plot of compound **4n** showing crystallographic numbering (CCDC 762795)

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 ^{1}H NMR spectra.. That compound **4g** was absent was proved conclusively since **4g** is insoluble in DMSO-d_6 and no product was present as a residue during the preparation of this crude mixture for NMR sampling.

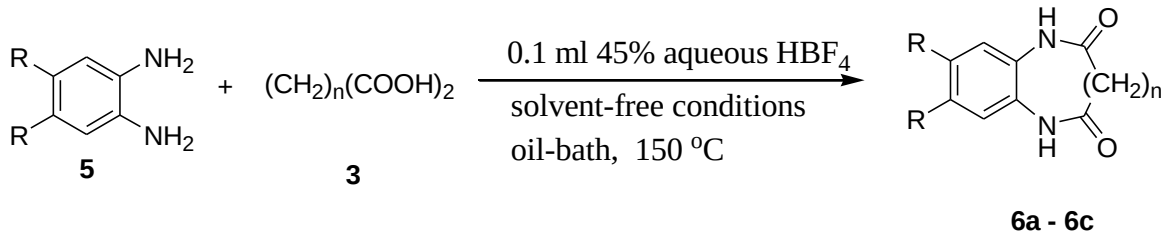


4i : 4j = 5:1 from integration of crude ^{1}H-NMR peaks of the aromatic protons.

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.



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).

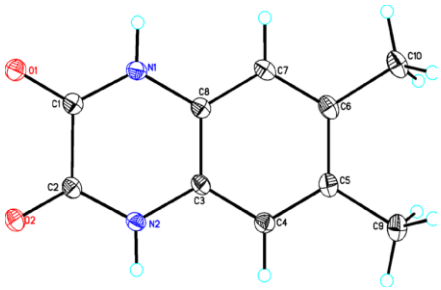


Figure 5. Ortep plot of **6b** showing the crystallographic numbering (CCDC 744703).

DFT Calculations

Next we were interested to study the minimum energy conformers for some of the known and the unknown synthesized bis-1*H*-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 entensive 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**).

4d

4e

4f

4h

4l

4q

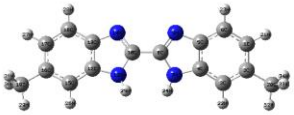
Figure 6. B3LYP/6-31G** optimized structures of the most stable isomers of the synthesized bis-1*H*-benzimidazoles.

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.

v(tautomer A)

vi

vii(tautomer B)



viii

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-1*H*-benzimidazole (compound **4a**)**.**

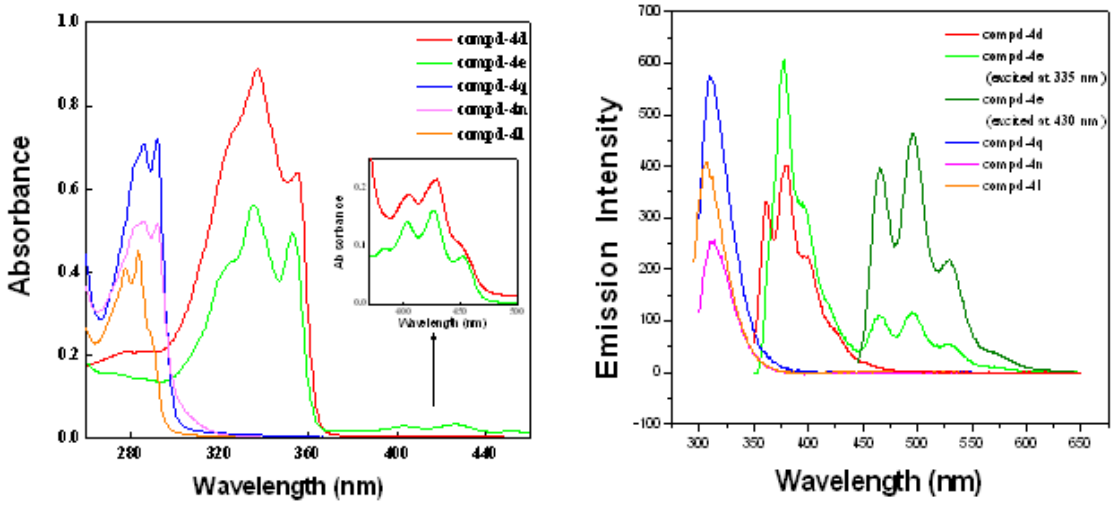


Figure 8. Absorption and Emission graphs of compounds **4d**, **4e**, **4q**, **4n** and **4l**

The absorption band maxima for compound **4d** (λ_{abs} = 337 nm) is red-shifted with respect to that of compound **4a** (λ_{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** (λ_{emi} = 380 nm) is also red-shifted as compared to compound **4a** (λ_{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).[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** (λ_{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.[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 (S_2), which relaxes rapidly to S_1. Emission occurs predominantly from the lowest singlet state (S_1), so emission from S_2 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_{abs} (nm)	Emission wavelength λ_{emi} (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-1*H*-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-1*H*-benzimidazole formation

Diamine **1** (1 mmol) and diamine **2** (1mmol) 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 ºC for the specified time (Table 3). 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 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-d_6 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-1*H*-benzimidazole (4a). (Table 2, entry 1): m.p. >250˚C (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 7.25 (s, 4H, C_5-H, C_6-H, $C_{5'}$-H and $C_{6'}$-H), 7.52 (d, J=6.3 Hz, 2H, C_7-H and $C_{7'}$-H), 7.71 (d, J=6.0 Hz, 2H, C_4-H and $C_{4'}$-H) and 13.52 (br s, 2H, N_1-H and $N_{1'}$-H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 112.2 (C_7 and $C_{7'}$), 119.3 (C_4 and $C_{4'}$), 122.3 (C_5 and $C_{5'}$), 123.7 (C_6 and $C_{6'}$), 134.9 (C_{3a} and $C_{3'a}$), 143.6 (C_{7a} and $C_{7'a}$) and 143.9 (C_2 and $C_{2'}$); IR (KBr): 3754, 3438, 3034, 2946, 2867, 2747, 2373, 1622, 1498, 1397, 1341, 946 and 742 cm^{-1}; Anal. calcd. for $C_{14}H_{10}N_4$; C: 71.78, H: 4.30, N: 23.92. Found; C: 71.70, H: 4.35, N: 23.99 %.

6-Methyl-2, 2'-bis-1*H*-benzimidazole (**4b**). (Table 2, entry 2): m.p. >250˚C (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 2.40 (br s, 3H, C_6-C$\underline{H}_3$), 7.06 (s, 1H, C_5-H), 7.24-7.40 (m, 3H, C_7-H, $C_{5'}$-H and $C_{6'}$-H), 7.54 (br s, 2H, $C_{4'}$-H and $C_{7'}$-H), 7.69 (br s, 1H, C_4-H) and 13.35-13.46 (m, 2H, N_1-H and $N_{1'}$-H); ^{13}C-NMR (DMSO-d_6) δ 21.4 (C_6-$\underline{C}H_3$), 111.8 (C_7), 112.2 ($C_{7'}$), 118.8 (C_4), 119.0 ($C_{4'}$), 122.3 (C_5), 123.7 ($C_{5'}$ and $C_{6'}$), 131.0 (C_6), 133.0 (C_{3a}), 135.0 ($C_{3'a}$), 142.0 (C_{7a}), 143.6 ($C_{7'a}$), 143.9 ($C_{2'}$) and 144.0 (C_2); IR (KBr): 3045, 2944, 2864, 1738, 1588, 1399, 1338, 949, 802 and 742 cm^{-1}; Anal. calcd. for $C_{15}H_{12}N_4$; 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-1*H*-benzimidazole (4c). (Table 2, entry 3): ^{1}H-NMR (DMSO-d_6) δ 2.40 [s, {3.096H (C$\underline{H}_3$) and 2.904H (C$\underline{H}'_3$)}], 7.06 [br s,{1.032H (H_c) and 0.968H (H'_c)}], 7.30 {s, 1.032H (H_a)}, 7.38 {d, J=6.6 Hz, 0.968H ($H_{b'}$)}, 7.49 {s, 0.968H ($H_{a'}$)}, 7.56{d, J=8.1 Hz, 1.032H (H_b)} and 13.30 [br s, {1.032H (N$\underline{H}$) and 0.968H (N$\underline{H}'$)}]; ^{13}C-NMR (DMSO-d_6) δ 21.4 ($\underline{C}H_3$ and $\underline{C}H'_3$), 111.7 ($\underline{C}$-H_a and $\underline{C}$-$H_{a'}$), 118.7 ($\underline{C}$-H_b and $\underline{C}$-$H_{b'}$), 124.0 ($\underline{C}$-H_c, $\underline{C}$-$H_{c'}$, $\underline{C}$-CH_3 and $\underline{C}$-CH'_3), 133.0 (C_{3a}, C_{7a}, $C_{3'a}$, $C_{7'a}$, $C_{3a'}$, $C_{7a'}$, $C_{3'a'}$ and $C_{7'a'}$) and 143.7 (C_2 and $C_{2'}$); 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 $C_{16}H_{14}N_4$; 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-1*H*-benzimidazole (4d). (Table 2, entry 4): m.p. >250˚C (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 2.29 (s, 6H, C_5-C<u>H</u>$_3$ and C_6-C<u>H</u>$_3$), 7.24 (br s, 3H, C_7-H, $C_{5'}$-H, and $C_{6'}$-H), 7.44-7.68 (m, 3H, C_4-H, $C_{4'}$-H and $C_{7'}$-H) and 13.17-13.37 (m, 2H, N_1-H and $N_{1'}$-H); ^{13}C-NMR (DMSO-d_6) δ 20.1 (C_5-<u>C</u>H$_3$ and C_6-<u>C</u>H$_3$), 112.0 (C_7 and $C_{7'}$), 119.0 (C_4 and $C_{4'}$), 122.3 ($C_{5'}$), 123.7 ($C_{6'}$), 130.8 (C_6), 132.4 (C_5), 133.4 ($C_{3'a}$), 142.3 (C_{3a}), 143.0 ($C_{7'a}$), 143.3 ($C_{2'}$), 143.9 (C_{7a}) and 144.2 (C_2); 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 $C_{16}H_{14}N_4$; C: 73.26, H: 5.38, N: 21.36. Found; C: 73.44, H: 5.23, N: 21.50 %.

5, 6, 6'-Trimethyl-2,2'-bis-1*H*-benzimidazole (4e). (Table 2, entry 5): m.p. >250˚C (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 2.30 (s, 6H, C_5-C<u>H</u>$_3$ and C_6-C<u>H</u>$_3$), 2.40 (s, 3H, $C_{6'}$-C<u>H</u>$_3$), 7.06 (br s, 1H, $C_{5'}$-H), 7.29 (br s, C_7-H and $C_{7'}$-H), 7.46 (br s, 1H, C_4-H), 7.55 (br s, 1H, $C_{4'}$-H) and 13.16-13.25 (m, 2H, N_1-H and $N_{1'}$-H); ^{13}C-NMR (DMSO-d_6) δ 20.1 (C_5-<u>C</u>H$_3$ and C_6-<u>C</u>H$_3$), 21.4 ($C_{6'}$-<u>C</u>H$_3$), 111.8 (C_4, C_7, $C_{4'}$ and $C_{7'}$), 119.0 (C_5, C_6, $C_{5'}$ and $C_{6'}$), 135.0 (C_{3a}, C_{7a}, $C_{3'a}$ and $C_{7'a}$), 143.1 (C_2) and 143.3 ($C_{2'}$); 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 $C_{17}H_{16}N_4$; C: 73.89, H: 5.84, N: 20.27. Found; C: 73.49, H: 5.63, N: 20.43 %.

6, 6'-Dimethyl-2, 2'-methanediyl-bis-1*H*-benzimidazole (4f). (Table 2, entry 6): m.p. >250˚C (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 2.35 (s, 6H, C_6-C<u>H</u>$_3$ and $C_{6'}$-C<u>H</u>$_3$), 4.36 (s, 2H, C_2-C<u>H</u>$_2$), 6.92 (d, *J*=8.1 Hz, 2H, C_5-H and $C_{5'}$-H), 7.24 (s, 2H, C_7-H and $C_{7'}$-H), 7.33 (d, *J*=7.8 Hz, 2H, C_4-H and $C_{4'}$-H) and 12.22 (br s, 2H, N_1-H and $N_{1'}$-H); ^{13}C-NMR (DMSO-d_6) : sensitivity very poor; IR (KBr): 2916, 2864, 1625, 1542, 1446, 1277, 1030, 805 and 760 cm^{-1}; Anal. calcd. for $C_{17}H_{16}N_4$; 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-1*H*-benzimidazole (4g). (Table 2, entry 7): Melting point >250˚C (DMSO-H_2O); ^{1}H-NMR and ^{13}C-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 $C_{16}H_{14}N_4$; C: 73.26, H: 5.38, N: 21.36. Found; C: 73.25, H: 5.32, N: 21.37 %.

6, 6'-Dimethyl-2, 2'-(1, 2-ethanediyl) bis-1*H*-benzimidazole (4h). (Table 2, entry 8): m.p. >250˚C (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 2.34 (s, 6H, C_6-C<u>H</u>$_3$ and $C_{6'}$-C<u>H</u>$_3$), 3.29 (s, 4H, C_2-C<u>H</u>$_2$ and $C_{2'}$-C<u>H</u>$_2$), 6.89 (d, *J*=8.1 Hz, 2H, C_5-H and $C_{5'}$-H), 7.21 (s, 2H, C_7-H and $C_{7'}$-H) and 7.30 (d, *J*=8.1 Hz, 2H, C_4-H and $C_{4'}$-H); ^{13}C-NMR (DMSO-d_6) δ 21.3 (C_6-<u>C</u>H$_3$ and $C_{6'}$-<u>C</u>H$_3$), 26.7 (C_2-<u>C</u>H$_2$ and $C_{2'}$-<u>C</u>H$_2$), 114.0 (C_7 and $C_{7'}$), 114.5 (C_4 and $C_{4'}$), 112.7 (C_5, C_6, $C_{5'}$ and $C_{6'}$), 130.3 (C_{3a} , C_{7a} $C_{3'a}$ and $C_{7'a}$) and 153.7 (C_2 and $C_{2'}$); IR (KBr): 3028, 2865, 1735, 1542, 1426, 1283, 1149, 1023 and 796 cm^{-1}; Anal. calcd. for $C_{18}H_{18}N_4$; 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-1*H*-benzimidazole (4i). (Table 2, entry 9): m.p. 250˚C (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 2.23 (s, 6H, C_5-C<u>H</u>$_3$ and C_6-C<u>H</u>$_3$), 3.30 (t, *J*=12.9 Hz, 4H, C_2-C<u>H</u>$_2$ and $C_{2'}$-C<u>H</u>$_2$), 7.07 (dd, *J*=6.0 Hz, 3.3 Hz, 2H, $C_{5'}$-H and $C_{6'}$-H), 7.19 (s, 2H, C_4-H and C_7-H) and 7.43 (dd, *J*=6.0 Hz, 3.0 Hz, 2H, $C_{4'}$-H and $C_{7'}$-H); ^{13}C-NMR (DMSO-d_6) δ: 20.0 (C_5-<u>C</u>H$_3$ and C_6-<u>C</u>H$_3$), 26.7 (C_2-<u>C</u>H$_2$), 26.8 ($C_{2'}$-<u>C</u>H$_2$), 114.7 (C_4, C_7, $C_{4'}$ and $C_{7'}$), 121.3 ($C_{5'}$ and $C_{6'}$), 129.5 (C_5 and C_6), 137.3 ($C_{3'a}$ and $C_{7'a}$), 138.8 (C_{3a} and C_{7a}), 153.1 ($C_{2'}$) and 154.2 (C_2);

IR (KBr): 3381, 2923, 1542, 1449, 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 $C_{18}H_{18}N_4$; 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'-(1, 2-ethtanediyl) bis-1*H*-benzimidazole (4j). (Table 2, entry 10): m.p. >250˚C (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 2.23 (s, 12H, C_5-C<u>H</u>$_3$, C_6-C<u>H</u>$_3$, $C_{5'}$-C<u>H</u>$_3$ and $C_{6'}$-C<u>H</u>$_3$), 3.25 (s, 4H, C_2-C<u>H</u>$_2$ and $C_{2'}$-C<u>H</u>$_2$), 7.19 (s, 4H, C_4-H, C_7-H, $C_{4'}$-H and $C_{7'}$-H), and12.0 (br s, 2H, N_1-H and $N_{1'}$-H); ^{13}C-NMR (DMSO-d_6) δ 20.0 (C_5-<u>C</u>H$_3$, C_6-<u>C</u>H$_3$, $C_{5'}$-<u>C</u>H$_3$ and $C_{6'}$-<u>C</u>H$_3$), 26.8 (C_2-<u>C</u>H$_2$ and $C_{2'}$-<u>C</u>H$_2$), 129.4 (C_4, C_5, C_6, C_7, C_{3a}, C_{7a}, $C_{4'}$, $C_{5'}$, $C_{6'}$, $C_{7'}$, $C_{3'a}$ and $C_{7'a}$), 153.1 (C_2 and $C_{2'}$); IR (KBr): 2928, 1540, 1451, 1306, 1013, 848 and 765 cm^{-1}; Anal. calcd. for $C_{20}H_{22}N_4$; 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-1*H*-benzimidazole (4k). (Table 2, entry 11): m.p. 260˚C (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 2.25 (t, J = 7.2 Hz, 2H, C_2-CH$_2$-C<u>H</u>$_2$), 2.88 (t, J = 7.5 Hz, 4H, C_2-C<u>H</u>$_2$ and $C_{2'}$-C<u>H</u>$_2$), 7.06-7.09 (m, 4H, C_5-H, C_6-H, $C_{5'}$-H and $C_{6'}$-H), and 7.42-7.44 (m, 4H, C_4-H, C_7-H, $C_{4'}$-H and $C_{7'}$-H); ^{13}C-NMR (DMSO-d_6) δ 25.8 (C_2-CH$_2$-<u>C</u>H$_2$), 28.0 (C_2-<u>C</u>H$_2$ and $C_{2'}$-<u>C</u>H$_2$), 114.5 (C_4, C_7, $C_{4'}$ and $C_{7'}$), 121.2 (C_5 , C_6 , $C_{5'}$ and $C_{6'}$), 139.0 (C_{3a} , C_{7a} , $C_{3a'}$ and $C_{7a'}$) and 154.6 (C_2 and $C_{2'}$); IR (KBr): 3385, 2849, 1591, 1531, 1479, 1312, 1198 and 924 cm^{-1}; Anal. calcd. for $C_{17}H_{16}N_4$; 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-1*H*-benzimidazole (4l). (Table 2, entry 12): m.p. 174˚C softens and 180˚C melts (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 2.44-2.48 (m, 2H, C_2-CH$_2$-C<u>H</u>$_2$), 2.56 (s, 3H, C_6-C<u>H</u>$_3$), 3.08 (d, J=5.7 Hz, 4H, C_2-C<u>H</u>$_2$ and $C_{2'}$-C<u>H</u>$_2$), 7.11(d, J=7.8 Hz, 1H, C_5-H), 7.28-7.31 (m, 2H, $C_{5'}$-H and $C_{6'}$-H), 7.43 (s, 1H, C_7-H), 7.53 (d, J=7.8 Hz, 1H, C_4-H), 7.65 (br s, 2H, $C_{4'}$-H and $C_{7'}$-H) and 12.37 (br s, 2H, N_1-H and $N_{1'}$-H); ^{13}C-NMR (DMSO-d_6) δ 21.3 (C_6-<u>C</u>H$_3$), 25.9 (C_2-CH$_2$-<u>C</u>H$_2$), 28.1 (C_2-<u>C</u>H$_2$ and $C_{2'}$-<u>C</u>H$_2$), 121.3 (C_4, C_7, $C_{4'}$ and $C_{7'}$), 122.6 (C_5, $C_{5'}$ and $C_{6'}$), 130.3 (C_{3a}, C_6 and $C_{3'a}$), 154.4 (C_{7a} and $C_{7'a}$) and 154.7 (C_2 and $C_{2'}$); 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 $C_{18}H_{18}N_4$; 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-1*H*-benzimidazole (4m). (Table 2, entry 13): m.p. 122˚C decomposes (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 2.22-2.24 (m, 2H, C_2-CH$_2$-C<u>H</u>$_2$), 2.84 (t, J = 6.6 Hz, 4H, C_2-C<u>H</u>$_2$ and $C_{2'}$-C<u>H</u>$_2$), 6.89 (d, J = 7.5 Hz, 2H, C_5-H and $C_{5'}$-H), 7.21 (s, 2H, C_7-H and $C_{7'}$-H) and 7.30 (d, J = 8.1 Hz, 2H, C_4-H and $C_{4'}$-H); ^{13}C-NMR (DMSO-d_6) δ 21.3 (C_6-<u>C</u>H$_3$ and $C_{6'}$-<u>C</u>H$_3$), 25.8 (C_2-CH$_2$-<u>C</u>H$_2$), 28.0 (C_2-<u>C</u>H$_2$ and $C_{2'}$-<u>C</u>H$_2$), 113.9 (C_7 and $C_{7'}$), 114.4 (C_4 and $C_{4'}$), 122.6 (C_5 and $C_{5'}$), 130.2 (C_6 and $C_{6'}$), 137.5 (C_{7a} and $C_{7'a}$), 138.8 (C_{3a} and $C_{3'a}$) and 154.3 (C_2 and $C_{2'}$); IR (KBr): 3382, 2927, 1537, 1447, 1279 and 802 cm^{-1}; Anal. calcd. for $C_{19}H_{20}N_4$; 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-1*H*-benzimidazole (4n). (Table 2, entry 14): m.p. 250˚C decomposes (DMSO-H_2O) ; ^{1}H-NMR (DMSO-d_6) δ 2.14-2.19 (m, 2H, C_2-CH$_2$-C<u>H</u>$_2$), 2.23 (s, 12H, C_5-C<u>H</u>$_3$, C_6-C<u>H</u>$_3$, $C_{5'}$-C<u>H</u>$_3$ and $C_{6'}$-C<u>H</u>$_3$), 2.81 (t, J=7.2 Hz, 4H, C_2-C<u>H</u>$_2$ and $C_{2'}$-C<u>H</u>$_2$), and 7.19 (s, 4H, C_4-H, C_7-H, $C_{4'}$-H and $C_{7'}$-H); ^{13}C-NMR (DMSO-d_6) δ 20.0 (C_5-<u>C</u>H$_3$, C_6-<u>C</u>H$_3$, $C_{5'}$-<u>C</u>H$_3$ and $C_{6'}$-<u>C</u>H$_3$), 25.9 (C_2-CH$_2$-<u>C</u>H$_2$), 28.0 (C_2-<u>C</u>H$_2$ and $C_{2'}$-<u>C</u>H$_2$), 114.6 (C_4, C_7,

$C_{4'}$ and $C_{7'}$), 129.5 (C_5, C_6, $C_{5'}$ and $C_{6'}$), 137.2 (C_{3a}, C_{7a}, $C_{3'a}$ and $C_{7'a}$) and 153.7 (C_2 and $C_{2'}$); 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 $C_{21}H_{24}N_4$; 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-1*H*-benzimidazole (4o). (Table 2, entry 15): m.p. 257˚C (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 1.82 (s, 4H, C_2-CH_2-C<u>H</u>$_2$ and $C_{2'}$-CH_2-C<u>H</u>$_2$), 2.68 (s, 4H, C_2-C<u>H</u>$_2$ and $C_{2'}$-C<u>H</u>$_2$), 7.06-7.09 (m, 4H, C_5-H, C_6-H, $C_{5'}$H and $C_{6'}$H) and 7.42-7.45 (m, 4H, C_4-H, C_7-H, $C_{4'}$-H and $C_{7'}$-H) and 9.75 (br s, 2H, N_1-H and $N_{1'}$-H); ^{13}C-NMR(DMSO-d^6) δ 27.3 (C_2-CH_2-C<u>H</u>$_2$ and $C_{2'}$-CH_2-C<u>H</u>$_2$), 28.3 (C_2-C<u>H</u>$_2$ and $C_{2'}$-C<u>H</u>$_2$), 114.5 (C_4, C_7, $C_{4'}$ and $C_{7'}$), 121.3 (C_5, C_6, $C_{5'}$ and $C_{6'}$), 138.7 (C_{3a}, C_{7a}, $C_{3'a}$ and $C_{7'a}$) and 155.0 (C_2 and $C_{2'}$); IR(KBr): 3049, 2934, 1620, 1533, 1418, 1263, 1004 and 742 cm^{-1}; Anal. calcd. for $C_{18}H_{18}N_4$; 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-butanediyl) bis-1*H*-benzimidazole (4p). (Table 2, entry 16): m.p. >250˚ C (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 1.77 (br s, 4H, C_2-CH_2-C<u>H</u>$_2$ and $C_{2'}$-CH_2-C<u>H</u>$_2$), 2.33 (s, 6H, C_6-C<u>H</u>$_3$ and $C_{6'}$-C<u>H</u>$_3$), 2.78 (br s, 4H, C_2-C<u>H</u>$_2$ and $C_{2'}$-C<u>H</u>$_2$) 6.87 (dd, *J*=8.1, 1.2 Hz, 2H, C_5-H and $C_{5'}$-H), 7.19 (br s, 2H, C_7-H and $C_{7'}$-H) and 7.28 (d, *J*=8.1 Hz, 2H, C_4-H and $C_{4'}$-H); ^{13}C-NMR (DMSO-d_6) δ 21.3 (C_6-C<u>H</u>$_3$ and $C_{6'}$-C<u>H</u>$_3$), 27.3 (C_2-CH_2-C<u>H</u>$_2$ and $C_{2'}$-CH_2-C<u>H</u>$_2$), 28.3 (C_2-C<u>H</u>$_2$ and $C_{2'}$-C<u>H</u>$_2$), 122.5 (C_4, C_5, C_7, $C_{4'}$, $C_{5'}$ and $C_{7'}$), 130.1 (C_6 and $C_{6'}$), 137.0 (C_{3a}, C_{7a}, $C_{3'a}$ and $C_{7'a}$) and 154.6 (C_2 and $C_{2'}$); IR (KBr): 3380, 2933, 1538, 1448, 1282, 1016 and 800 cm^{-1}; Anal. calcd. for $C_{20}H_{22}N_4$; 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-1*H*-benzimidazole (4q). (Table 2, entry 17)**:** m.p. > 250˚C (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 1.76 (br s, 4H, C_2-CH_2-C<u>H</u>$_2$ and $C_{2'}$-CH_2-C<u>H</u>$_2$), 2.22 (s, 12H, C_5-C<u>H</u>$_3$, C_6-C<u>H</u>$_3$, $C_{5'}$-C<u>H</u>$_3$ and $C_{6'}$-C<u>H</u>$_3$), 2.76 (br s, 4H, C_2-C<u>H</u>$_2$ and $C_{2'}$-C<u>H</u>$_2$) and 7.17 (s, 4H, C_4-H, C_7-H, $C_{4'}$-H and $C_{7'}$-H); ^{13}C-NMR (DMSO-d_6) δ 20.0 (C_5-C<u>H</u>$_3$, C_6-C<u>H</u>$_3$, $C_{5'}$-C<u>H</u>$_3$ and $C_{6'}$-C<u>H</u>$_3$), 27.3 (C_2-CH_2-C<u>H</u>$_2$ and $C_{2'}$-CH_2-C<u>H</u>$_2$), 28.3 (C_2-C<u>H</u>$_2$ and $C_{2'}$-C<u>H</u>$_2$), 114.6 (C_4, C_7, $C_{4'}$ and $C_{7'}$), 129.4 (C_5, C_6, $C_{5'}$ and $C_{6'}$), 137.3 (C_{3a}, C_{7a}, $C_{3'a}$ and $C_{7'a}$) and 154.1 (C_2 and $C_{2'}$); 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 $C_{22}H_{26}N_4$; C: 76.27, H: 7.56, N: 16.17. Found: C: 76. 39, H: 7.43, N: 16.09%.

1,4-Dihydro-quinoxaline-2,3-dione (6a). m.p. >250˚C (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 7.01-7.10 (m, 4H, C_5-H, C_6-H, C_7-H and C_8-H) and 11.87 (s, 2H, N_1-H and N_4-H); ^{13}C-NMR (DMSO-d_6) δ 115.2 (C_5 and C_8), 123.1 (C_6 and C_7), 125.7 (C_{4a} and C_{8a}) and 155.2 (C_2 and C_3); IR (KBr): 3047, 2965, 2876, 2776, 1681, 1388, 856, 752 and 706 cm^{-1}; Anal. calcd. for $C_8H_6N_2O_2$; 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-quinoxaline-2,3-dione (6b). m.p.>250˚C (DMSO-H_2O); ^{1}H-NMR (DMSO-d_6) δ 2.46 (s, 6H, C_6-C<u>H</u>$_3$ and C_7-C<u>H</u>$_3$), 7.17 (s, 2H, C_5-H, and C_8-H) and 12.08 (s, 2H, N_1-H and N_4-H); ^{13}C-NMR (DMSO-d_6) δ 19.1 (C_6-C<u>H</u>$_3$ and C_7-C<u>H</u>$_3$), 115.8 (C_5 and C_8), 123.4 (C_6 and C_7), 131.2 (C_{4a} and C_{8a}) and 155.3 (C_2 and C_3); IR (KBr): 3161, 2944, 1689, 1390, 873,

684 and 576 cm^{-1}; Anal. calcd. for $C_{10}H_{10}N_2O_2$; 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_2O); ^{1}H-NMR (DMSO-d_6) δ 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) δ 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 $C_9H_8N_2O_2$; 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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References and Notes

1. (a) Tietze, L. F.; Hautner, F. *In Stimulating Concepts in Chemistry*; Voegtle, F. Stoddart, J. F.; Shibasaki, M. Eds.; Wiley-VCH: Weinheim, 2000, p39. (b) Nicolaou, K. C.; Yue, E. W.; Oshima, T. In *The New Chemistry*; N. Hall, Ed.; Cambridge University Press: Cambridge, 2001; p186. (c) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (d) *New Avenues to Efficient Chemical Synthesis. Emerging Technologies*; Seeberger, P. H.; Blume,T. Eds.; Springer: Heidelberg, 2007; Ernst Schering Foundation Symposium Proceedings 2006-3. (e) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
2. Tanaka, K.*Solvent-free Organic Synthesis*, Wiley-VCH, 2003.
3. Anastas, P.T.; Warner, J.C. *Green Chemistry, Theory and Practice*, Oxford University Press: Oxford, 1998.
4. (a) Mukhopadhyay, C.; Tapaswi, P. K. *Tetrahedron Lett*. **2008**, *49*, 6237; (b) Mukhopadhyay, C.; Datta, A.; Banik, B. K. *Heterocycl*. **2007**, *1*, 181.
5. Wang, L. L. Y.; Joullie, M. M. *J. Am. Chem. Soc.* **1957**, *79***,** 5708.
6. Matthews, C. J.; Leese, T. A.; Clegg, W.; Elsegood, M. R. J.; Horsburgh, L.; Lockhart, J. C. *Inorg. Chem.* **1996,** *35*, 7563.
7. Dudd, L. M.; Venardou, E.; Garcia-Verdugo, E.; Licence, P.; Blake,A. J.; Wilson, C.; Poliakoff, M. *Green Chem.* **2003**, *5*, 187.
8. Horton, D. A.; Bourne, G. T.; Sinythe, M. L. *Chem. Rev*. **2003**, *103*, 893.

9. Porcari, A. R.; Devivar, R. V.; Kucera, L. S.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1998**, *41*, 1252.
10. Tamm, I. *Science* **1957**, *126*, 1235.
11. Walker, J. A.; Koszalka, G. W.; Chamberlain, S. D.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1998**, *41*, 1242.
12. Mann, J.; Baron, A.; Opoku-Boahen, Y.; Johansson, E.; Parkinson, G.; Kelland, L. R.; Neidle, S. *J. Med. Chem*. **2001**, *44***,** 138.
13. Bouman, E.; Driessen, W. L. Reedijk, J. *Cord. Chem. Rev*. **1990**, *104*, 143.
14. Lane, E. S. *J. Chem. Soc.* **1955**, 534.
15. Dall'Oglio, E.; Caro, M. B.; Gesser, J. C.; Zucco, C.; Rezende, M. C. *J. Braz. Chem. Soc.* **2002**, *13*, 251.
16. Alpan, A. S.; Zencir, Z.; Zupko, I.; Coban, G.; Rethy, B.; Gunes, H. S.; Topcu, Z. *Journal of Enzyme Inhibition and Medicinal Chemistry* **2009**, *24*, 844.
17. Song, L. Q.; Tan, G. Z.; Xu, X. L. *Hecheng Huaxue* **2001**, *9*, 175.
18. Landge, S. M.; Torok, B.*Catalysis Lett.* **2008**, *122*, 338.
19. Lakhrissi, B.; Massoui, M.; Goethais, G.; Martin, P.; Gode, P.; Villa, P.; Keita, A.; Essassi, E. M. *Journal Marocain de Chimie Heterocyclique* **2002**, *1*, 31.
20. Kumar, A.;.Sinha, H. K.; Dogra, S. K. *Can. J. Chem.* **1989**, *67*, 1200.
21. All detailed spectral data and details of DFT calculations are given in the Supplementary Section.