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$POCl_3$ mediated synthesis of 2-substituted benzimidazolyl-coumarin, benzimidazolyl-indole and styrylbenzimidazole derivatives

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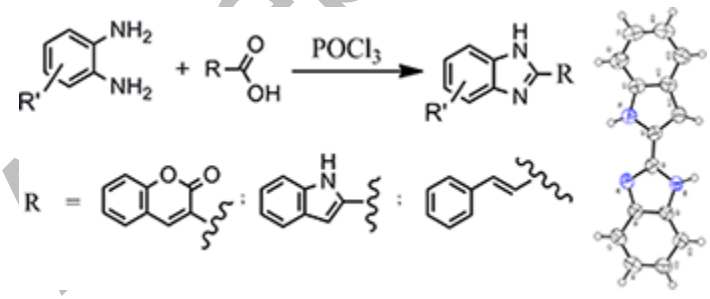
Abstract

2-substituted benzimidazolyl heterocycles and styrylbenzimidazoles have been synthesized by the reaction of substituted *o*-phenylenediamine with different heterocyclic carboxylic acids and cinnamic acid respectively in the presence of $POCl_3$ as a solvent and catalyst. The proposed reaction has prominent features of affording high yields, short reaction time as well as operational simplicity. In addition, the scope and limitations were explored and a plausible reaction mechanism was proposed. The synthesized molecules were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. Further, single crystals of 2-(1*H*-indol-2-yl)-1*H*-benzo[*d*]imidazole have been developed and its structural parameters were collected from X-ray diffraction data.



KEYWORDS: 1*H*-benzimidazoles; Benzimidazolyl heterocycles; crystal structure; $POCl_3$

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INTRODUCTION

Benzimidazole nucleus may be termed as 'Master Key', since it is an important core in several compounds acting at different targets to elicit varied pharmacological properties. **Fig. 1** reveals that a suitable substitution around the benzimidazole core nucleus has resulted in many lead compounds of diverse range of therapeutic properties.

Benzimidazole derivatives are structural isosters of naturally occurring nucleotides, which allow them to interact easily with biopolymers of the living system. In addition to the biological significance of benzimidazoles, these moieties serve as important intermediates in numerous organic reactions[1,2] and also employed as fluorescent pigments and found their applications in optical/electro devices.[3] The broad usefulness of these moieties has provoked significant efforts towards their synthesis.

Several methods have been reported for the synthesis of benzimidazoles. Conventionally, benzimidazoles are commonly prepared from the reaction of *o*-phenylenediamines with carboxylic acids, aldehydes, nitriles and orthoesters under strong dehydrating reaction conditions and in the presence of strong acids[4] or under microwave irradiation.[5] **Fig. 2** exemplifies various catalytic systems that were employed for the synthesis of 2-aryl benzimidazoles.[6-20]

Particularly, Tsay et al.[21] have synthesized a library of coumarin-benzimidazole hybrid compounds by the condensation of substituted *o*-phenylendiamine and 3-(ethoxycarbonyl)coumarins in 85% *o*-phosphoric acid for 8 h at 165 ºC with 40-67%

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yield. Bakhtiari et al.[22] have reported the synthesis of 3-(1*H*-Benzo[*d*]imidazol-2-yl)-2*H*-chromen-2-one by the reaction of *o*-phenylenediamine with coumarin-3-carboxylic acid in sulphuric acid for 8 h at reflux temperature with 55% yield. Similarly, Arora et al.[23] also synthesized the 3-(1*H*-Benzo[*d*]imidazol-2-yl)-2*H*-chromen-2-one by the reaction of *o*-phenylenediamine and coumarin-3-carboxylic acid in polyphosphoric acid for 1 h at 175 ºC with 75% yield. Further, Shingalapur et al.[24] have reported the synthesis of series of 5-(nitro/bromo)-styryl-2-benzimidazoles and studied their antitubercular and antimicrobial activities. The reported synthetic method involved the condensation of 5-(nitro/bromo)-*o*-phenylenediamine with *trans*-cinnamic acids in ethylene glycol for 6 h at around 200 ºC with 75-82% yield. However, most of these methods suffer from one or more disadvantages such as low yields, long reaction times, drastic reaction conditions, use of excessive oxidant, use of expensive catalysts, tedious work-up procedures, and co-occurrence of several side reactions which makes them undesirable under the sustainable and industrial applications. In view of ample applications of benzimidazole as a significant bioactive molecule as well as precursor for various organic transformations and for designing fluorescent materials, there is still necessary for mild, simple, less expensive and feasible reaction protocol for its synthesis.

RESULTS AND DISCUSSION

In the course of our efforts to develop a new route for the synthesis of 2-substituted benzimidazoles, we here in report phosphoryl chloride mediated simple and viable method for the synthesis of 2-substituted benzimidazolyl heterocycles and styrylbenzimidazoles by utilizing the dehydrating ability of phosphoryl chloride.

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Initially, the reaction of *o*-phenylenediamine with coumarin-3-carboxylic acid was selected as a model reaction to find out a suitable reaction condition for the synthesis of 2-substituted benzimidazoles. The desired product, 3-(1*H*-benzo[*d*]imidazol-2-yl)-2*H*-chromen-2-one was obtained by the excess use of $POCl_3$ as a cyclizing agent and solvent as well at 80 ºC.

To optimize the reaction conditions, the investigator has carried out the same reaction using different solvents with different reaction time intervals. The optimized reaction conditions are given in **Table 1**. Initially, the reaction was carried out in the presence of catalytic amounts of $POCl_3$ with different solvents. Solvent screening experiments demonstrated that the role of solvent was crucial; poor yields of products were obtained when organic solvents were used in the reaction. The yield of the desired product, 3-(1*H*-benzo[*d*]imidazol-2-yl)-2*H*-chromen-2-one was improved significantly (up to 93% yield), when the reaction was conducted in the presence of $POCl_3$ only. Subsequent reaction temperature screening revealed the decreased yield of the product when the temperature was reduced and the reaction time was extended. After several trials, we found that a temperature of 80 ºC was ideal. Highest yield of the compound was obtained in 1 h. However, prolonged reaction time resulted in decreased yields.

Under the optimized conditions, a variety of substituted *o*-phenylenediamine and coumarin-3-carboxylic acid, indole-2-carboxylic acid and cinnamic acids were prepared (**Scheme 1**) to explore the scope and generality of the process. In most of the cases, good yields of products were obtained. The yields were

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better when cinnamic acid was used for the synthesis of styrylbenzimidazoles (**7a-e**). This might be due to the decreased steric hindrance.

A mechanistic rationale for the formation of **3a** is suggested in **Scheme 2**. Coumarin-3-carboxylic acid **2** forms acid chloride **II** by an intramolecular substitution via the intermediate of the dichlorophosphate ester **I**. Reaction of the acid chloride **II** with *o*-phenylenediamine **1a** leads to an intermediate *o*-amino amide **III** by a nucleophillic attack at the trigonal carbon of the acid chloride. An intramolecular nucleophillic addition followed by a proton transfer leads to a cyclic aminal **IV**. Under the reaction conditions aminal **IV** undergoes dehydration to give benzimidazole **V**. Under the acidic reaction conditions compound **V** undergoes protonation to yield protonated benzimidazole **VI** which upon neutralization with 25% ammonia gives free 3-(1*H*-benzo[*d*]imidazol-2-yl)-2*H*-chromen-2-one (**3a**).

^{1}H NMR spectra of all compounds showed a broad peak at 9.8-12.91 ppm due to amine proton of benzimdiazole. In compounds **3a-e,** a sharp singlet was observed at 9.13 ppm due to C4-H of coumarin moiety. Further, the absence of OH proton of coumarin-3-carboxylic acid and the presence of only one amine proton at 12.55 ppm confirmed the formation of benzimidazolyl coumarins. In compounds **5a-e**, in addition to amine proton of benzimidazole, a broad peak observed at 11.94 ppm was attributed to amine proton of indole moiety. In compounds **7a-e**, two doublets in the region at 7.3 ppm and 8.08 ppm were noticed due to vinylic protons. The coupling constant of these vinylic protons was found to be ~ 16 Hz which suggested that these two protons were *trans* to each other.

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Aromatic protons were observed in the expected region. ^{13}C NMR spectra of compounds **3a-e** showed a peak at 160 ppm due to carbonyl carbon atom of coumarin moiety. In compounds **3a-e**, the peak noticed at 142 ppm was attributed to C2 of benzimidazole whereas the same carbon atom was resonated around 146 ppm and around 149 ppm in compounds **5a-e** and **7a-e**, respectively. Rest of the carbon atoms were resonated in the expected region. The mass spectra of all the compounds have shown *m/z* values which corresponded to their respective molecular masses.

Further, single crystals of 2-(1*H*-indol-2-yl)-1*H*-benzo[*d*]imidazole (**5a**) were grown from its alcoholic solution. Crystal refinement data and unit cell parameters of compound **5a** are presented in **Table 2**. **Fig. 3** and **Fig. 4** illustrate the ORTEP and packing diagrams of this compound. The bond lengths and bond angles of the compound were observed to be in the expected region. The molecules in the solid state were stabilized by hydrogen bonding of N3-H3···N2 atoms. The hydrogen bonding network in compound **5a** is depicted in **Fig. 5** and the corresponding hydrogen bonding parameters are given in **Table 3**. From the data, it is evident that the indole plane was slightly deviated from the mean plane of benzimidazole by an angle of 22.37º in compound **5a**.

SUMMARY

In conclusion, a simple and practicable route for the synthesis of 2-substituted benzimidazoles has been proposed that includes condensation of *o*-aryldiamines with aromatic acid in the presence of $POCl_3$. This method has advantages

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such as the use of an inexpensive and commercially available dehydrating agent ($POCl_3$), high yields of products, short reaction times, and a simple workup procedure.

EXPERIMENTAL

General Method For The Synthesis Of Benzimidazolyl Coumarin (3a-E), Benzimidazolyl Indole (5a-E) And Styryl Benzimidazoles (7a-E)

A mixture of *o*-phenylenediamine (1mmol) and heterocyclic (coumarin and indole) or cinnamic acids (1mmol) was heated to 80 ºC in $POCl_3$ (5 mmol) for about one hour. The completion of the reaction was monitored by TLC. After the completion of reaction, the reaction mixture was poured on to crushed ice and the pH of the solution was adjusted to neutral pH using 20% NH_3 solution. The separated solid was thoroughly washed with water. Then, the solid was filtered and dried to obtain a pure product.

3-(1*H*-benzo[*d*]imidazol-2-yl)-2*H*-chromen-2-one **(3a)**: Yield: 93%; m.p: 230-232 ºC; IR (KBr, cm^{-1}): 3340 (NH), 1707 (C=O); ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 7.08 (t, 2H, J = 6.4 and 8.0 Hz, C5,C6-H of benzimidazole), 7.21 (d, 1H, J = 8.4 Hz, , C8-H of coumarin), 7.42 (t, 1H, J = 7.6 Hz, C6-H of coumarin), 7.49-7.70 (m, 3H, Ar-H) 7.98 (d, 1H, J = 7.6 Hz, C5-H of coumarin), 9.13 (s, 1H, C4-H of coumarin moiety), 12.55 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, δ): 112.80, 116.12, 116.63, 118.49, 119.02, 122.16, 122.42, 125.05, 129.57, 132.92, 134.81, 141.75, 142.86, 145.74, 153.23, 159.25; MS (*m/z*): 262 (M^+); Elemental analysis: calcd. for $C_{16}H_{10}N_2O_2$ (262.26): C, 73.27%; H, 3.84%; N, 10.68%; Found: C, 73.31%; H, 3.85%; N, 10.62%.

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2-(1*H*-indol-2-yl)-1*H*-benzo[*d*]imidazole **(5a)**: Yield: 93%; m.p: 160-162 ºC; IR (KBr, cm^{-1}): 3428 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 7.05 (t, 1H, *J* = 8 and 7.2 Hz, C5-H of benzimidazole), 7.13-7.40 (m, 3H, Ar-H), 7.45 (d, 1H, J = 8Hz, C4-H of benzimidazole), 7.63 (d, 1H, J = 8Hz, C8-H of benzimidazole), 11.93 (s, 1H, NH of indole), 12.91 (s, 1H, NH of benzimidazole); ^{13}C NMR (DMSO-d_6, 100 MHz, δ): 102.10, 111.68, 112.48, 118.99, 120.23, 121.33, 122.21, 123.11, 123.32, 128.37, 129.17, 135.26, 137.74, 144.17, 146.67; MS (*m/z*): 233 (M^+); Elemental analysis: calcd. for $C_{15}H_{11}N_3$ (233.27): C, 77.23%; H, 4.75%; N, 18.01%; Found: C, 77.19%; H, 4.73%; N, 17.96%.

(*E*)-2-styryl-1*H*-benzo[*d*]imidazole **(7a)**: Yield: 91%; m.p: 114-116 ºC; IR (KBr, cm^{-1}): 3423 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 7.32 (d, 1H,*J* = 16.8 Hz, H2 of vinylic proton), 7.37-7.70 (m, 9H, Ar-H), 8.08 (d, 1H, *J* = 16.8 Hz, H1 of vinylic proton), 9.81 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, δ): 112.54, 114.13, 120.19, 124.63, 127.75, 129.23, 130.30, 134.06, 134.65, 139.99, 149.08; MS (*m/z*): 219 $(M-H)^+$; Elemental analysis: calcd. for $C_{15}H_{12}N_2$ (220.27): C, 81.79%; H, 5.49%; N, 12.72%; Found: C, 81.83%; H, 5.53%; N, 12.69%.

Characterizations of the all the remaining synthesized compounds are given in the supplementary file.

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Table 1. Optimized reaction conditions for the synthesis of 2-substituted benzimidazoles.

Compound	**$POCl_3$ in equivalents**	**Solvent**	**Time**	**Yield (%)**
3a	0.2	Ethanol	6 h (Reflux)	10
3a	0.5	Ethanol	6 h (Reflux)	15
3a	1	Ethanol	6 h (Reflux)	18
3a	5	Ethanol	6 h (Reflux)	24
3a	5	1,4-Dioxane	6 h (Reflux)	21
3a	5	DMSO	6 h (Reflux)	18
3a	5	---	6 h (Reflux)	78
3a	5	---	2 h (80 ºC)	82
3a	5	---	1 h (80 ºC)	93

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Table 2. The crystallographic data and refinement parameters of compound **5a**.

Parameter	**5a**
Empirical formula	$C_{15}H_{11}N_3$
Crystal system	Monoclinc
Space group	*P 1 21/c 1*
Unit cell dimensions	a = 14.1835(10) (Å)
	b = 9.1141(6) (Å)
	c = 9.5262(6) (Å)
	α = 90°
	β = 108.015(5)°
	γ = 90°
Limiting indices	-19<=h<=18, -9<=k<=12, -12<=l<=13
Volume	1171.08(13) (Å3)
Z, Calculated density	4, 1.329 mg/m^3
Reflections collected	11287
No. of independent reflections	3112 [R(int) = 0.0239]
Data/Restraints/Paramaeters	3112 / 0 / 164
Final R indices [I > 2σ(I)]	R1 = 0.0518, wR2 = 0.1307
R indices (all data)	R1 = 0.1072, wR2 = 0.1630
CCDC number	1425672

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Table 3. Hydrogen bonding parameters in compound **5a**.

D–H···A	*d*(D–H)	*d*(H···A)	D(D···A)	∠DHA
N3–H3···N2	0.860	2.076	2.897	159.60

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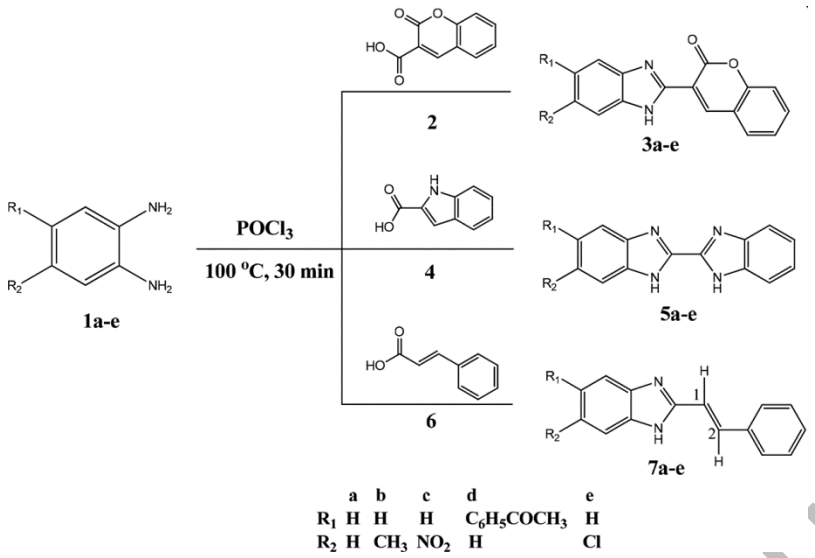
Scheme 1. Synthesis of 2-substituted benzimidazoles



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Scheme 2. Plausible mechanism for the formation of **3a**

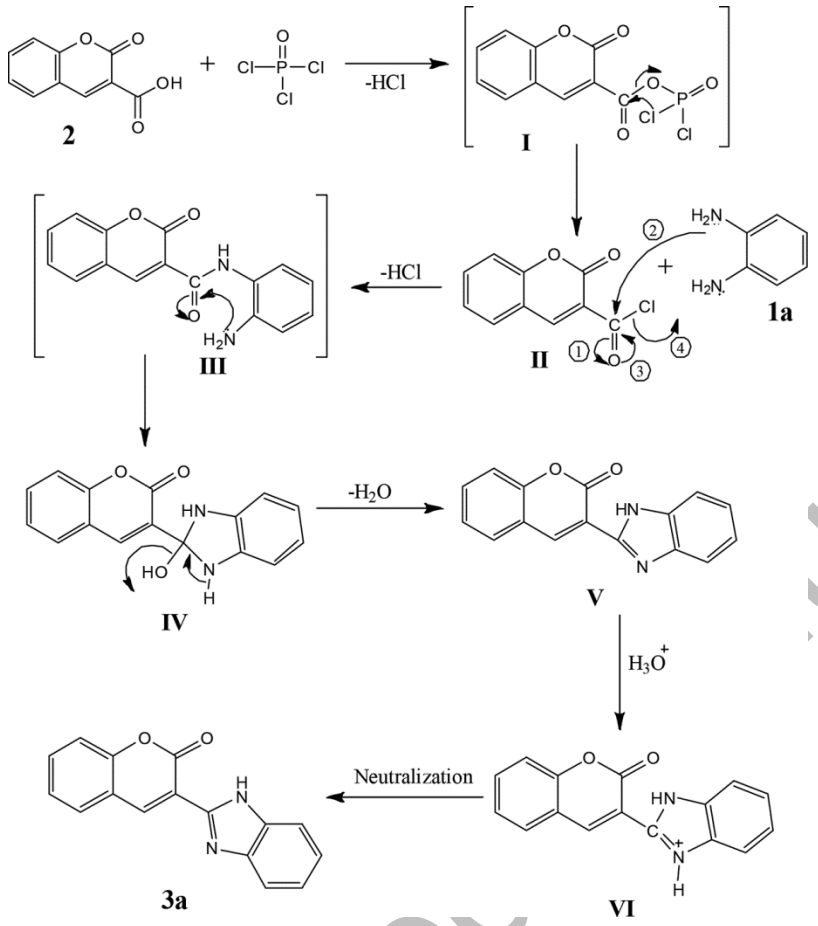

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Figure 1. A multifunctional nucleus, benzimidazole

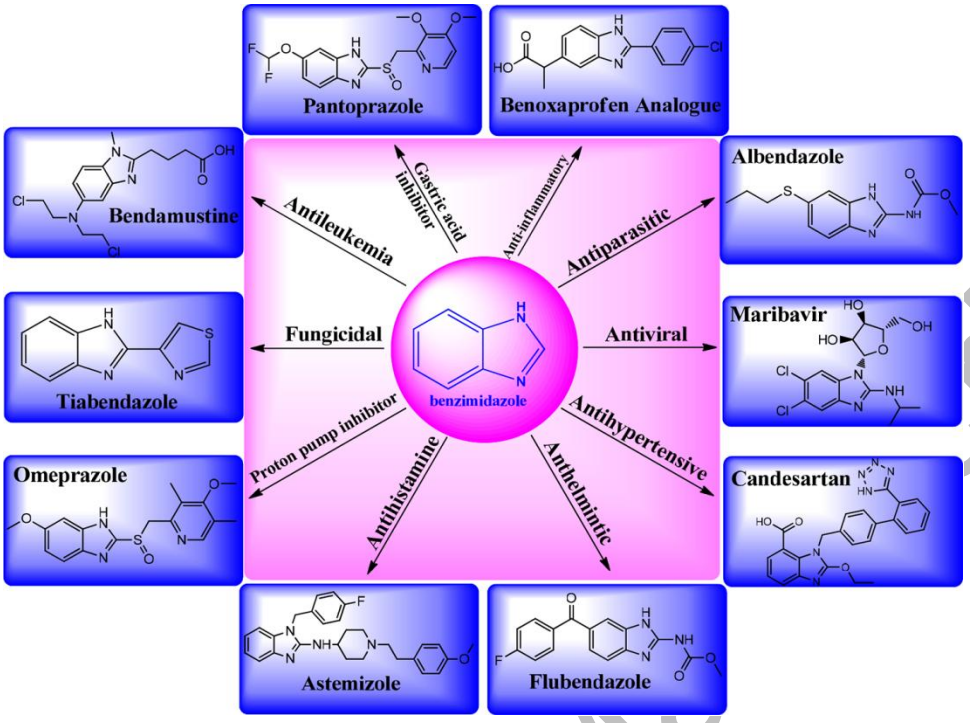

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Figure 2. Various catalytic systems used for the synthesis of 2-aryl benzimidazoles

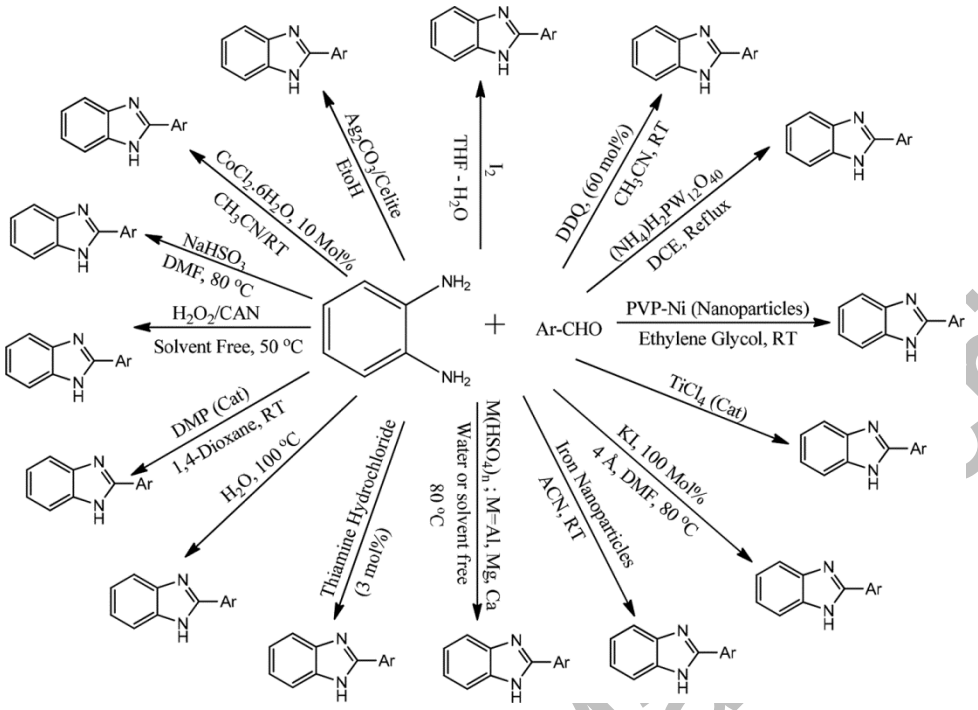

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Figure 3. ORTEP diagram of compound **5a**.

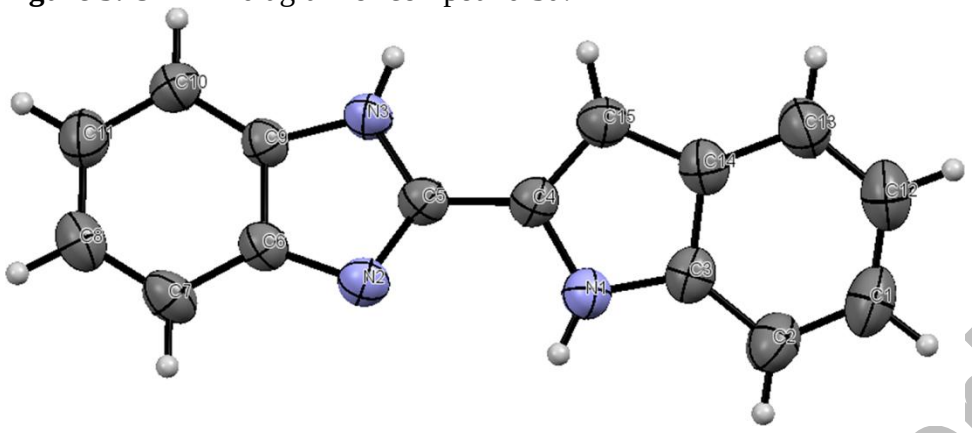

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Figure 4. Packing diagram of compound **5a**.

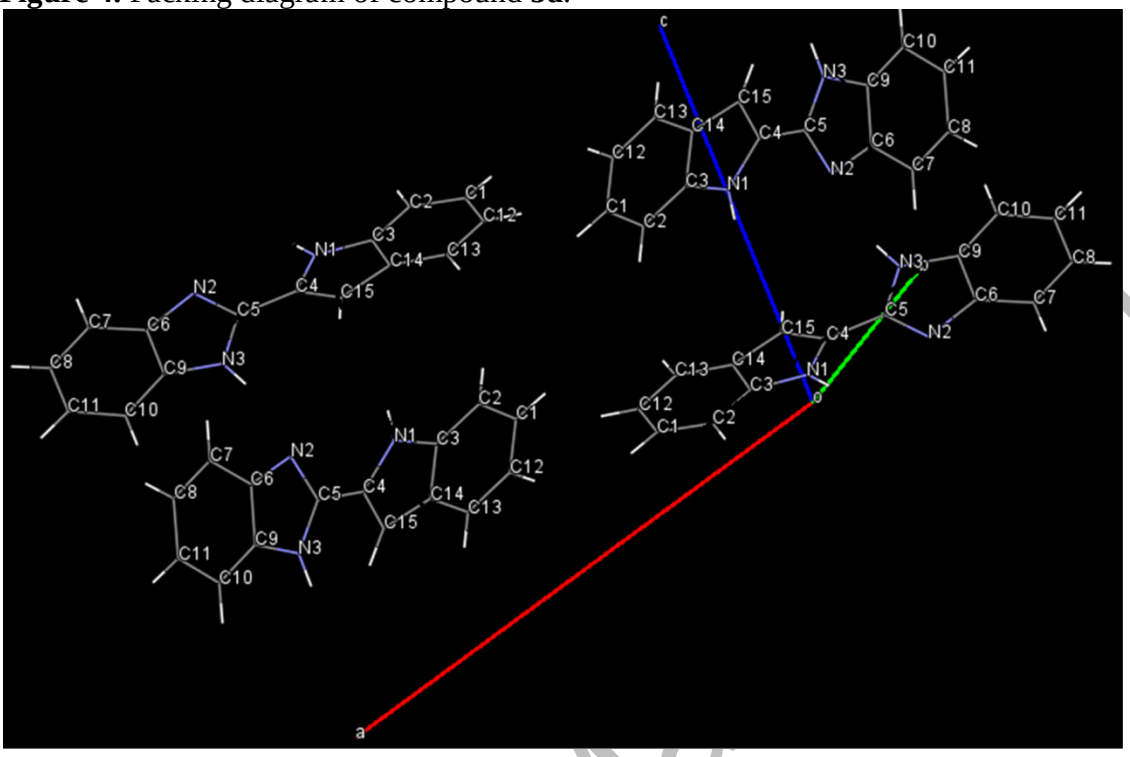

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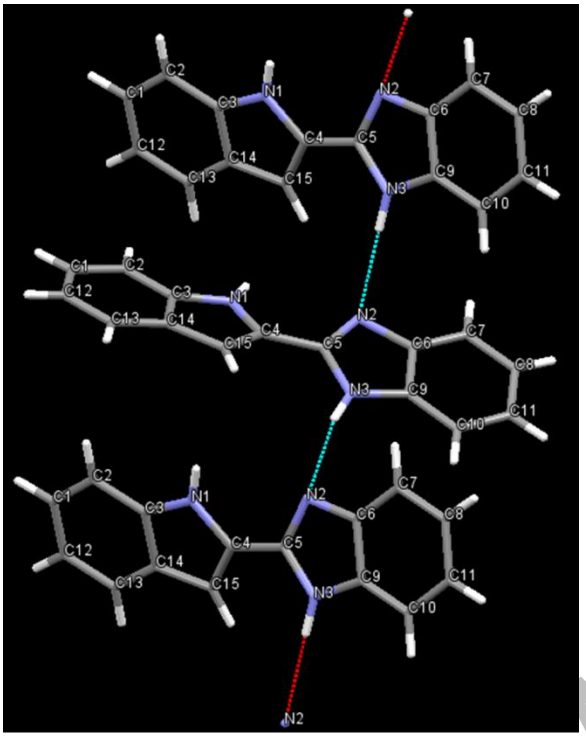
Figure 5. Hydrogen bonding network in compound **5a**.



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