Theor Chem Acc (2012) 131:1160
DOI 10.1007/s00214-012-1160-8

REGULAR ARTICLE

Tautomerism in drugs with benzimidazole carbamate moiety: an electronic structure analysis

Yoganjaneyulu Kasetti · Prasad V. Bharatam

Received: 23 May 2011 / Accepted: 11 October 2011 / Published online: 2 March 2012
© Springer-Verlag 2012

Abstract Several medicinally important compounds carry benzimidazole carbamate moiety. In the scientific literature, these molecules are represented in different tautomeric forms. In this report, conformational and tautomeric preferences were analyzed on the model benzimidazole carbamate (carbendazim), so as to understand the potential energy surface of the title compounds. Quantum chemical calculations have been performed using HF, B3LYP, and MP2 methods in gas phase and solvent phase on model benzimidazole carbamate to understand the conformational and tautomeric preferences. (1) PE surface of amide–imide tautomers, (2) electron distribution, (3) AIM analysis, (4) NBO charges, (5) 1,3-H shift, etc., have been investigated for carbendazim and its conformers. The molecular electrostatic potential (MESP) surfaces of carbendazim have been studied. Further to understand the polymorphism in benzimidazole carbamate, analysis of dimers of carbendazim has been carried out. The results indicate that a neglected tautomer is important and the tautomeric equilibrium is quite subtle in these systems and it should be extensively considered in all studies related to these drugs.

Keywords Benzimidazole carbamate derivatives · Ab initio study · Tautomerism · Conformational polymorphism

1 Introduction

Benzimidazole carbamate (**BC**) derivatives are important class of compounds that have extensive medicinal applications in the therapy of several parasitic infections [1–3]. Thiabendazole (**1**), is an anthelmintic drug, introduced to treat parasitic infections. However, thiabendazole is found to have toxic effects, which obligated the researchers to develop benzimidazole carbamate derivatives. Albendazole (**2**), Mebendazole (**3**), Fenbendazole (**4**), Ciclobendazole (**5**), Flubendazole (**6**), Oxibendazole (**7**) are the relatively safe benzimidazole carbamates, which are most widely used for the treatment for a variety of parasitic infections such as hydatidosis, neurocystercosis, schistosomiasis, and intestinal nematodes (Fig. 1). All these molecules are well-known anthelmintic drugs beneficial to control, prevent, and treat against diverse set of infections caused by roundworms, hookworms, whipworms, and tapeworms [4–9]. Thus, these anthelmintic drugs are used in humans and animals for the therapy of trematode, cestode, and nematode parasitic infestations [10]. Recent reports suggested that a few of these drugs found application in cancer treatment [11]. Carbendazim (**8**) and Benomyl (**9**), which also share the benzimidazole carbamate moiety, have been shown to exhibit significant activity against fungal infections (Fig. 2) [12–15].

Low aqueous solubility (<6 mg/mL) of these molecules has restricted their formulation development in the forms of suspensions, paste, powder, or intraruminal bolus, which compels the administration in larger doses to achieve the desired therapeutic response [16–20]. Solid-state researchers working in the molecular

Dedicated to Professor Eluvathingal Jemmis and published as part of the special collection of articles celebrating his 60th birthday.

Electronic supplementary material The online version of this article (doi:10.1007/s00214-012-1160-8) contains supplementary material, which is available to authorized users.

Y. Kasetti · P. V. Bharatam (✉)
Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Sector-67, S. A. S. Nagar 160 062, Punjab, India
e-mail: pvbharatam@niper.ac.in

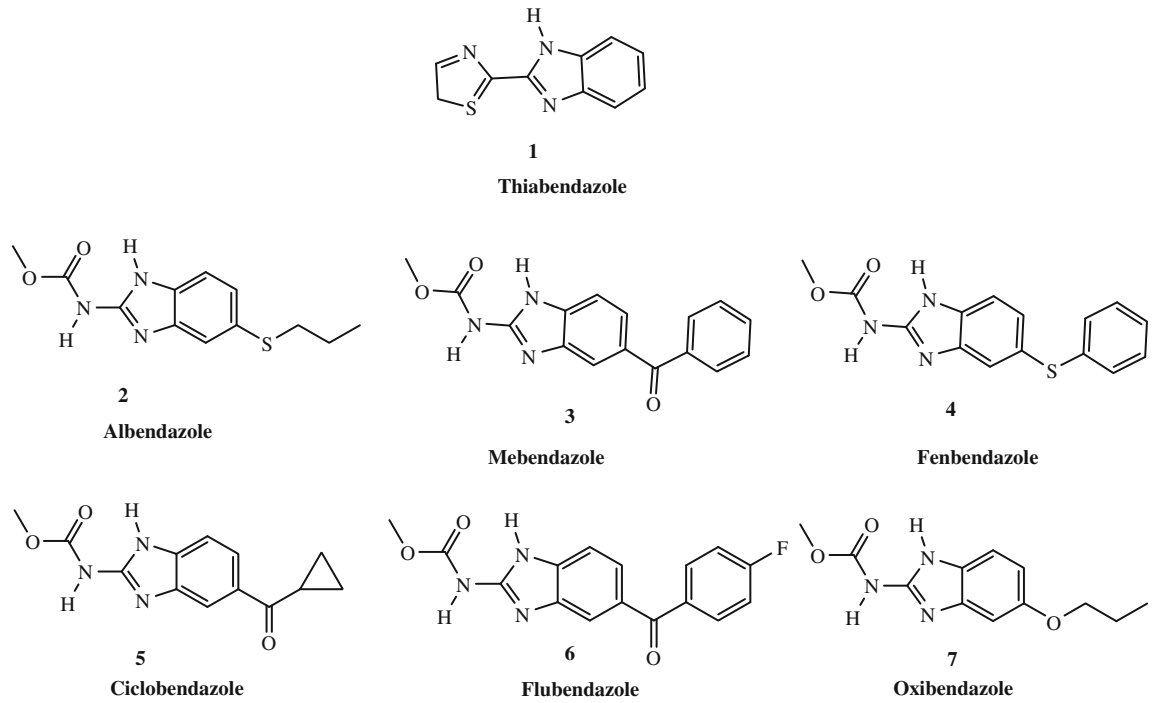

Fig. 1 Anthelmentic drugs of benzimidazole carbamates

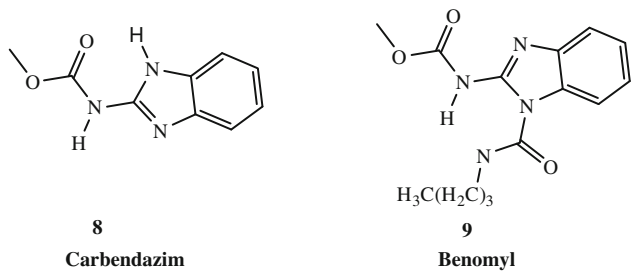

Fig. 2 Fungicidal drugs of benzimidazole carbamates

pharmaceutics are fascinated to understand the polymorphism in the **BC** molecules, so as to improve the bioavailability profile of these molecules. In order to increase the solubility of these molecules, several strategies were adopted. Derivatives of the **BC** molecules were synthesized in the form of oxidized products and in the form of prodrugs. Recently, research is focused on the active sulfoxide metabolites of albendazole (i.e., Ricobendazole (**10**)) and fenbendazole (i.e., oxefenbendazole (**11**)) (Fig. 3) [21, 22]. Phosphonooxymethyl prodrugs of benzimidazole carbamates are reported as agents with better safety profile. Basic property of benzimidazole carbamates were exploited to prepare their acidic salts such as sulfonic acid salts. Chassaing et al. [23] reported that the intramolecular hydrogen bond present in the benzimidazole carbamate between the benzimidazole NH and the carbonyl of the carbamate moiety is the probable cause of the lack of solubility of these compounds.

In the scientific literature, benzimidazole carbamates are represented with **A** [24] and **B** tautomeric representations (Fig. 4). Crystal structure details of most **BC** drugs suggest that **B** is the correct representation [17, 20]. Sokol et al. [25] suggested that two tautomers (**B** and **C**) are possible for carbendazim (**CM**). The energy profile of tautomeric process in this class of drugs was not explored. Pranzo et al. recently reported the crystal structure of albendazole, in which a polymorph with the tautomeric representation **C** is found to be more stable. Electronically, tautomer **A** suffers from lone pair-lone pair repulsion between imidazole nitrogen and carboxylic oxygen, whereas conformation **B** represents a tautomer, which is devoid of such repulsion, and in addition, it carries stabilizing intramolecular hydrogen bonding interaction. Structure **C** represents the imide form of benzimidazole (*N*-heterocyclic carbene) moiety; this tautomer also maintains the stable hydrogen bonding interaction. Thus, the critical phenomenon of structural tautomerism observed in the **BC** molecules prompted us to explore the PE surface of benzimidazole carbamate (**BC**) derivatives quantum chemically, to identify the conformational and tautomeric preferences of these molecules.

Understanding the atomic level information regarding the drug molecules helps the pharmaceutical scientist in the design of new molecules and development (so as to overcome the shortcomings associated with drugs) of the existing drug molecules in different areas of pharmaceutical research—(1) Molecular pharmaceutics scientists to generate new polymorphs to improve the solubility and

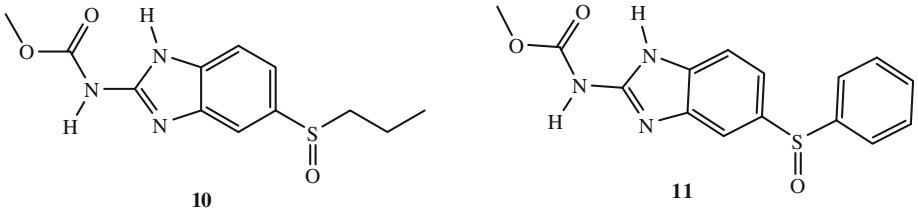

Fig. 3 Metabolites of albendazole (ricobendazole) and fenbendazole (oxefenbendazole)

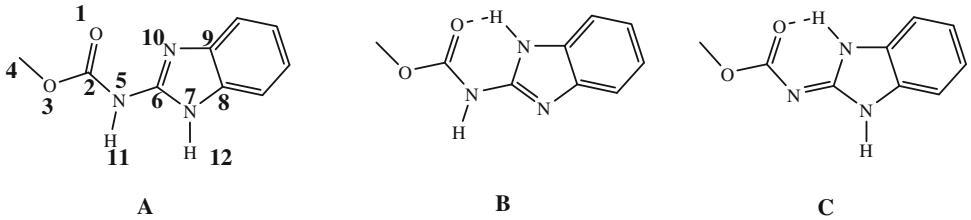

Fig. 4 Three important tautomers of benzimidazole carbamate (carbendazim)

bioavailability profile of drugs, (2) Computational chemists to understand the drug receptor interactions that help in the design of new potent molecules, (3) Medicinal chemists and pharmacologists to identify the stereo and electronic features that are responsible for drug resistance.

Several groups highlighted the role of tautomeric preferences of drugs [26–32]. Our group reported the detailed electronic structure studies, conformational and tautomeric preferences on aminoguanidine, biguanide, guanylthiourea, sulfonylurea, and guanylurea derivatives, which are therapeutically important [33–41]. Lipkowitz and McCracken performed semi-empirical (MNDO) studies on albendazole, oxibendazole, etc., to understand the conformational tautomerism in these molecules [42–45]. They suggested that the conformer **B** is the most stable molecular model, but did not consider structure **C** in the study.

In the current report, an electronic structure analysis and tautomerism details of the model benzimidiazole carbamate, Carbendazim (**CM**) are presented. To understand the influence of solvent medium on the conformational preferences, implicit solvent models were employed. To comprehend the polymorphism in **BC** molecules, analysis on the dimers has been carried out. The results indicate that the tautomerism is highly probable in this class of compounds, a tautomer which was generally ignored in the chemistry literature turns out to be quite important.

2 Methodology

Ab initio molecular orbital (MO) [46, 47] and density functional theory (DFT) [48, 49] calculations have been carried out using the GAUSSIAN03 software package [50]. Complete optimizations have been performed on various tautomers and rotamers of carbendazim (**CM-1** to **CM-9**, Fig. 5), transition states, and various dimeric arrangements of conformers of the model **BC** moiety, using HF (Hartree–Fock), B3LYP (Becke3, Lee, Yang, Parr), [51, 52] and MP2 (Moeller-Plesset perturbation) [53, 54] methods with the 6-31+G(d) basis set. 6-31+G(d) basis set incorporates the polarization function and diffuse functions, and hence it is sufficiently rigorous in tautomerism studies as evident from the published work from our group [37–39, 41]. Solvent level optimization studies have been performed using the integral equation formalism versions of the polarizable continuum model (IEFPCM; using RMIN = 0.5, OFAC = 0.8) method [55] at 6-31+ G(d) basis set to understand the influence of the solvent medium. A few representative drugs of benzimidazole carbamate derivatives have also been optimized using the B3LYP/6-31+G(d) method to understand the differences in the conformational preferences of these drugs. Intramolecular hydrogen bonding is confirmed by AIM (atoms in molecules) calculations using AIM2000 software package [56, 57]; NBO (natural bond orbital) analysis has been employed in the estimation of partial atomic charges [58, 59]. NICS (nuclear independent chemical shift) [60, 61] values were obtained using the GIAO method [62] using B3LYP/6-31+G(d) geometries to get the extent of electronic delocalization in the ring-forming conformations. The energy and geometric parameters used in the discussion are from the B3LYP/6-31+G(d) method unless otherwise specifically mentioned. MESP calculations have been carried out to know the surface properties of these compounds [63].

3 Result and discussion

3.1 Electronic structure and conformational analysis

Carbendazim (**CM**) can be taken as a representative of benzimidazole carbamate (**BC**)-based drugs. Considering the chemically feasible 3D geometries, 15 conformers and

tautomers were generated for **CM**. Semi-empirical PM3 method was initially used to optimize the generated models, high energy conformers were excluded, and nine important tautomers/conformers were selected for further accurate quantum chemical (HF, B3LYP, and MP2 methods) analysis. These studies lead to the recognition of nine important tautomers/rotamers (**CM-1** to **CM-9**) of carbendazim as specified in Table 1. Figure 5 shows the 3D

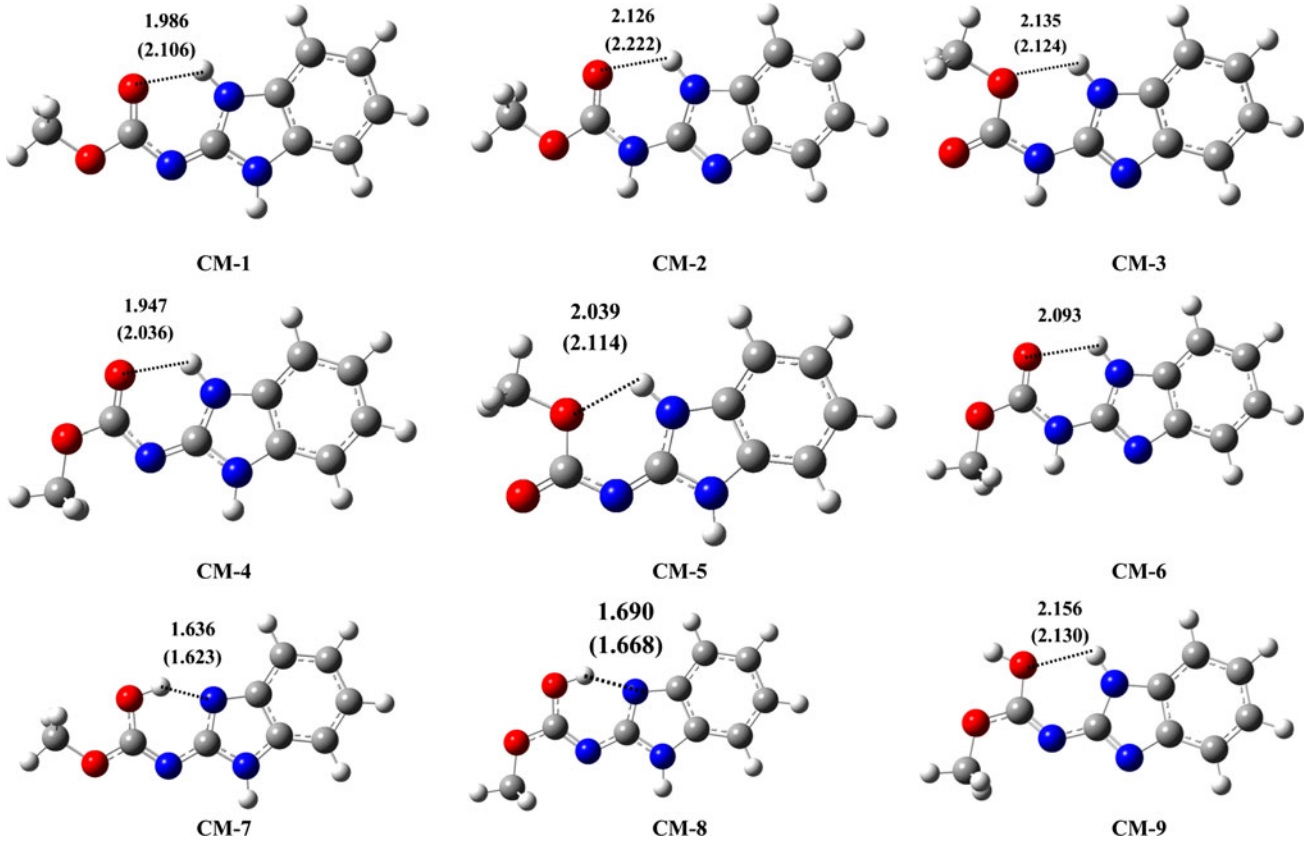

Fig. 5 Optimized 3D geometries of benzimidazole carbamate (carbendazim) **CM-1** to **CM-9**. The H-bond lengths obtained using B3LYP/6-31+G(d) method are given, data in parentheses corresponding to water medium

Table 1 Relative energies (in kcal/mol) of various tautomers of model benzimidazole carbamate moiety carbendazim (**CM**)

Conformer	Structural description	Gas phase			Solvent phase[a]	
		HF	MP2	B3LYP	Water B3LYP	Methanol B3LYP
CM-1	N5-N7 H shift (1,3-H shift tautomer of **CM-2**)	0.00	0.00	0.00	0.00	0.00
CM-2	Generally referred **CM** structure	−3.31	−5.46	−2.47	0.05	0.08
CM-3	C2-N5 rotamer of **CM-2**	0.51	−2.29	1.01	4.48	2.35
CM-4	O3-C4 rotamer of **CM-1**	2.80	2.12	2.27	3.38	1.35
CM-5	C2-N5 rotamer of **CM-1**	6.30	4.82	5.04	2.07	2.53
CM-6	O3-C4 rotamer of **CM-2**	6.18	2.89	5.27	–	6.98
CM-7	N10-N1 H shift (1,5-H shift tautomer of **CM-1**)	13.90	8.22	9.70	15.47	13.18
CM-8	1,5-H shift of **CM-4**	11.73	6.51	8.70	15.00	12.89
CM-9	1,3-H shift of **CM-4**	22.97	17.26	20.16	23.99	21.79
CM1-TS	Transition state for 1,3-H shift in **CM-2**	55.91	41.46	42.45	51.75	49.42

Basis set used for all optimizations is 6-31+G(d)

All relative energies are corrected for zero-point vibrational energy and thermal correction to Gibbs free energy

The ZPE and Gibbs free energy corrected absolute energy values are given as supporting information in Table S1 and S2

[a] Implicit solvent analysis using IEFPCM level using B3LYP/6-31+G(d) method

Table 2 Tautomeric preferences observed for the **BC** drugs in both gas phase and water phase

Drugs	ΔE_g (kcal/mol)	ΔE_w (kcal/mol)
Albendazole	2.01	−0.77
Mebendazole	3.07	0.45
Fenbendazole	2.42	−0.40
Ciclobendazole	3.06	−0.16
Flubendazole	3.32	0.41
Oxibendazole	1.87	−0.45
Ricobendazole	1.03	−2.09
Oxifenbendazole	3.76	2.31

Negative value of ΔE indicates the conformational preference toward **CM-1** type tautomer, and positive value indicates the preference toward **CM-2** type tautomer

Basis set used for all optimizations is 6-31+G(d)

All relative energies are corrected for zero-point vibrational energy and thermal correction to Gibbs free energy

The ZPE and Gibbs free energy corrected absolute energy values are given as supporting information in Table S1 and S2

Implicit solvent analysis using IEFPCM level using B3LYP/6-31+G(d) method

structures of **CM-1** to **CM-9** and Table 1 shows their relative energies both in gas phase and solvation phase.

The relative energy data given in Table 1 show that there is a tautomeric equilibrium between tautotmers **CM-1** and **CM-2**. Under gas-phase conditions, **CM-2** is favored, whereas in solvent conditions, **CM-1** is favored. **CM-1** suffers from lone pair (O_3)-lone pair (N_5) repulsion. The influence of this electrostatic repulsion gets reduced in polar solvents, and hence in solvent media, **CM-1** turned out to be marginally more stable. Because the ΔE between these two tautomers is quite low in water medium (0.05 kcal/mol), it can be concluded that all the drugs based on **BC** moiety may exist in tautomeric equilibrium in physiological conditions. This is further supported by the data given in Table 2.

The ΔE_g and ΔE_w values for Albendazole obtained using B3LYP/6-31+G(d) method, respectively, are 2.01 and −0.77 kcal/mol. Similarly, the comparative ΔE values of Mebendazole (ΔE_g, ΔE_w: 3.07, 0.45 kcal/mol), Fenbendazole (ΔE_g, ΔE_w: 2.42, −0.40 kcal/mol), Ciclobendazole (ΔE_g, ΔE_w: 3.06, 0.16 kcal/mol), Flubendazole (ΔE_g, ΔE_w: 3.32, 0.41 kcal/mol), Oxibendazole (ΔE_g, ΔE_w: 1.87, −0.45 kcal/mol), Ricobendazole (ΔE_g, ΔE_w: 1.03, −2.09 kcal/mol), and Oxifenbendazole (ΔE_g, ΔE_w: 3.76, 2.31 kcal/mol) clearly establish the existence of tautomeric equilibrium in these drugs. Recently, Pranzo et al. [18] reported about the **CM-1** type of polymorph experimentally; however, PE surface of the benzimidazole carbamates and the electronic structure distribution of these compounds were not comprehensively reported with detailed quantum chemical analysis till now. Considering the importance of the tautomerism in drug molecules in the recent past [26–41], the current results on the tautomerism of benzimidazole carbamates drugs may gain importance.

Both **CM-1** and **CM-2** are characterized by intramolecular hydrogen bonds. Indeed, AIM calculations also confirmed the presence of intramolecular hydrogen bond in these species. For example in **CM-1**, a bond critical point was observed between O1 and H11–N10 indicating the presence of a hydrogen bond, which is characterized by charge density $\rho = 0.02704$, density laplacian $\nabla^2\rho = 0.09449$, and ellipticity $\varepsilon = 0.1003E + 00$. A ring critical point was also observed corresponding to the six-membered ring that is formed due to intramolecular hydrogen bond and is characterized by density $0.1656E - 01$. The energy difference between **CM-2** and **CM-1** is only about 2.47 kcal/mol in gas-phase conditions. The estimated barrier for the unimolecular 1,3-H shift is quite high (44.92 kcal/mol) in **CM-1**, and hence, it is not a favorable process under regular room temperature conditions. However, the estimated barrier for the unimolecular 1,3-H shift via water-assisted mechanism (explicit one water molecule) is found to be 12.92 kcal/mol suggesting that 1,3-H shift through water is a favorable process for the interconversion of **CM-1** to **CM-2** and vice versa.

To elucidate the origin of the tautomeric preferences in this class of drugs, calculations have been carried out on the base moiety carbamate guanidine (**CG**, Fig. 6, Table 3). **CG-1** has been found to be most stable in gas phase (by 6.19 kcal/mol) as well as in solvent phase (by 8.57 kcal/mol) conditions. This clearly points out that on a simple guanidine, the carbamate substituent prefers to be on the imine nitrogen than the amine nitrogen. The marginal preference for **CM-2** over **CM-1** (in gas phase in comparison with the strong preference for **CG-1** over **CG-2** indicates that the aromatic ring in the imidazole ring of carbendazim is playing a role in shifting the tautomeric preferences in carbendazim, the **CM-2** carries aromatic stabilization, whereas in **CG**, this component is absent. To further verify this aspect, tautomerization in carbamate imidazoles (**CI**, Fig. 6) has been studied. The energy difference between **CI-1** and **CI-2** is 4.86 kcal/mol favoring **CI-2**. However, the energy difference is reduced to 0.42 kcal/mol favoring **CI-2** under solvent conditions. Table 3 shows tautomerization energies associated with **CG** and **CI**. NICS studies were performed to understand the aromaticity of benzimidazole, imidazole, and the delocalization of guanidine derivatives. After tautomerism (in **CM-1**), the aromatic character in five-membered ring (on *N*-heterocyclic carbene unit) is reduced. The NICS value for the five-membered ring in **CM-1** (5.78) is relatively smaller than that in **CM-2** (8.03) (See supporting information, Table S10). These data support that in

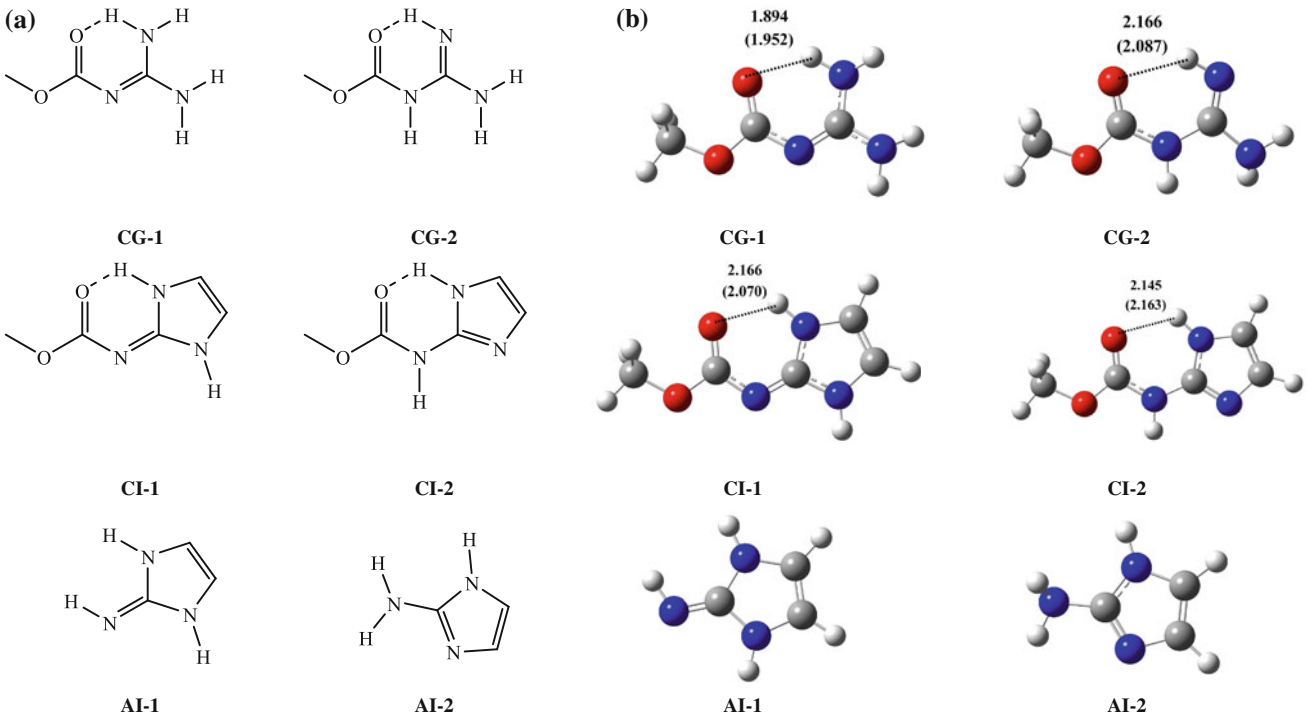

Fig. 6 **a** 2D Structures **b** Optimized 3D geometries of carbamate guanidine (**CG**), carbamate imidazole (**CI**), and amino imidazole (**AI**), intramolecular hydrogen bond distances are given in Å units. The H-bond lengths obtained using B3LYP/6-31+G(d) method are given, data in parentheses corresponding to water medium

Table 3 Tautomeric preferences observed for the Carbamate guanidine (**CG**) and Carbamate imidazole (**CI**) isomers, in both gas phase and water phase

Molecule	ΔE_g (kcal/mol)	ΔE_w (kcal/mol)	NBO charge on central nitrogen in **CM-1** type isomer
Carbamate guanidine	−6.19	−8.57	−0.661
Carbamate imidazole	4.86	0.42	−0.658
Carbendazim	2.47	−0.05	−0.644

Negative value of ΔE indicates the conformational preference toward **CM-1** type, and positive value indicates the conformational preference toward **CM-2** type isomer

Basis set used for all optimizations is 6-31+G(d)

All relative energies are corrected for zero-point vibrational energy and thermal correction to Gibbs free energy

The ZPE and Gibbs free energy corrected absolute energy values are given as supporting information in Table S1 and S2

Implicit solvent analysis using IEFPCM level using B3LYP/6-31+G(d) method

carbendazim, the tautomerization tilts the balance toward **CM-1** but the aromatic character of the five-membered ring tilts the balance toward **CM-2**; overall, **CM-2** is marginally more stable.

On the PE surface of **CM**, one more low energy structure could be identified. This is also characterized by intramolecular hydrogen bond. **CM-3** is an isomer of **CM-2** in which the OMe group of carbamate is involved in intramolecular hydrogen bond. This structure may also be possible under equilibrium conditions because this tautomer is only about 1.01 kcal/mol unstable. Similarly, **CM-4** is a conformer of **CM-1**, which is only about 2.27 kcal/mol less stable than **CM-1**. These data clearly indicate that the carbendazim may adopt any of the low-lying energy states **CM-1** to **CM-4** under equilibrium conditions. **CM-5** and **CM-6** are other alternative structures whose energies lie within 6 kcal/mol with reference to **CM-1**. **CM-7** is an enol tautomer stabilized through strong intramolecular hydrogen bond. This may be obtained by 1,5-H shift in **CM-1**. This tautomer is 10 kcal/mol less stable than **CM-1**. But this particular tautomer may not be observable owing to the fact that there are alternatively many other stable possibilities, i.e., **CM-1** to **CM-4**.

Figure 7 shows the molecular electrostatic potential (MESP) of **CM-1** and **CM-2**. The electrostatic potential of **CM-1** shows the concentration of electron density at N5. Clearly, there is a large difference in the MESP of **CM-2** with respect to that of **CM-1**. In **CM-1**, negative–negative–positive electrostatic potentials due to the O–N–NH unit are noticeable, whereas in **CM-2**, alternate negative–positive–negative electrostatic potentials due to the O-NH-N unit are evident. This factor also must be contributing to the marginally greater stability of **CM-1**.

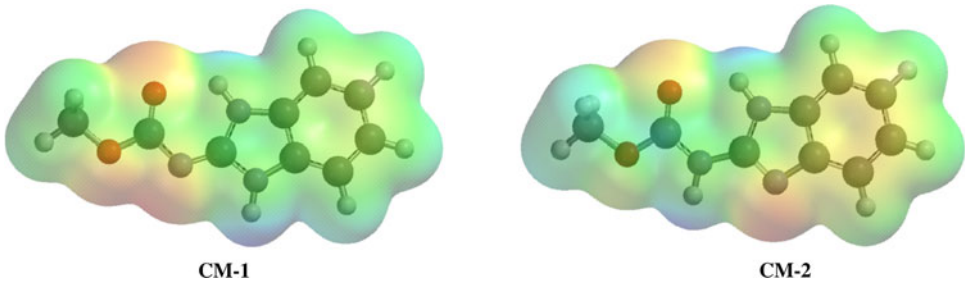

Fig. 7 Molecular electrostatic potential (MESP) surfaces of carbendazim **CM-1** and **CM-2** plotted onto a surface of constant electron density (0.002 e/au3)

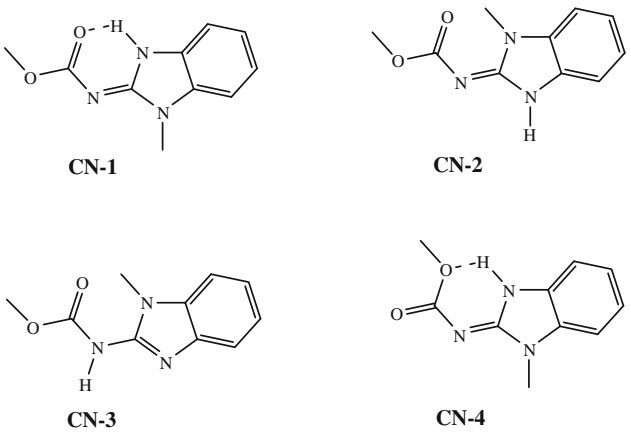

Fig. 8 2D Structures of tautomers of NSC135301

Machatha et al. [64] reported the X-ray crystal structure of carbendazim hydrochloride dehydrate. The calculated protonation energy of **CM-1** is 221.42 kcal/mol. The protonation energy of **CM-1** is quite comparable to that of simple guanidine (235.0 kcal/mol), **CG-1** (220.58 kcal/mol) and **CI** (217.27 kcal/mol). It may be presumed that the tautomerism between **CM-1** and **CM-2** may take place through this protonated species because unimolecular tautomerism can be ruled out in the case of **BM** drugs. Deprotonation is also a possible reaction on benzimidazole ring of carbendazim. This is evidenced by the fact that albendazole is described as an amphoteric species [65]. The Gibbs free energies due to deprotonation of H11 and H12 in **CM-1**, respectively, are 327.75 and 321.99 kcal/mol at the B3LYP/6-31+G(d) level, which is slightly smaller than the deprotonation energy of acetic acid (332.66 kcal/mol). The above-reported data on protonation and deprotonation are in tune with the amphoteric character of this class of compounds.

To understand the conformational and tautomeric preferences in *N*-substituted benzimidazole derivatives, quantum chemical studies were performed using B3LYP/6-

Table 4 Relative energies (gas phase) of dimeric **CM**s (**D1**–**D8**) and their stabilization energies obtained using B3LYP/6-31+G (d) method

Dimer	Relative energy (kcal/mol)[a]			Molecular unit	Stabilization energy (kcal/mol)[b]
	Gas phase	Solvent phase[c]			
		Water	Methanol		
D1	0.00	0.00	0.00	**CM-1**	7.02
D2	−0.14	0.80	0.64	**CM-2**	2.22
D3	6.87	4.45	4.71	**CM-5**	10.22
D4	7.06	5.19	5.31	**CM-3**	1.97
D5	7.63	5.47	6.48	**CM-2**	−5.56
D6	11.01	–	8.06	**CM-4**	0.55
D7	11.99	–	42.67	**CM-3**	−2.96
D8	21.80	15.35	15.56	**CM-6**	−4.24
D9	23.76	27.30	27.01	**CM-7**	2.66
HD1	2.01	–	–	**CM-7**	−2.44

The ZPE and Gibbs free energy corrected absolute energy values are given as supporting information in Table S3

All relative energies are corrected for zero-point vibrational energy and thermal correction to Gibbs free energy

[a] Relative energies of **D1**–**D9**

[b] Gas-phase stabilization energy due to dimer formation from various **CM**s

[c] Implicit solvent analysis using IEFPCM level using B3LYP/6-31+G(d) method

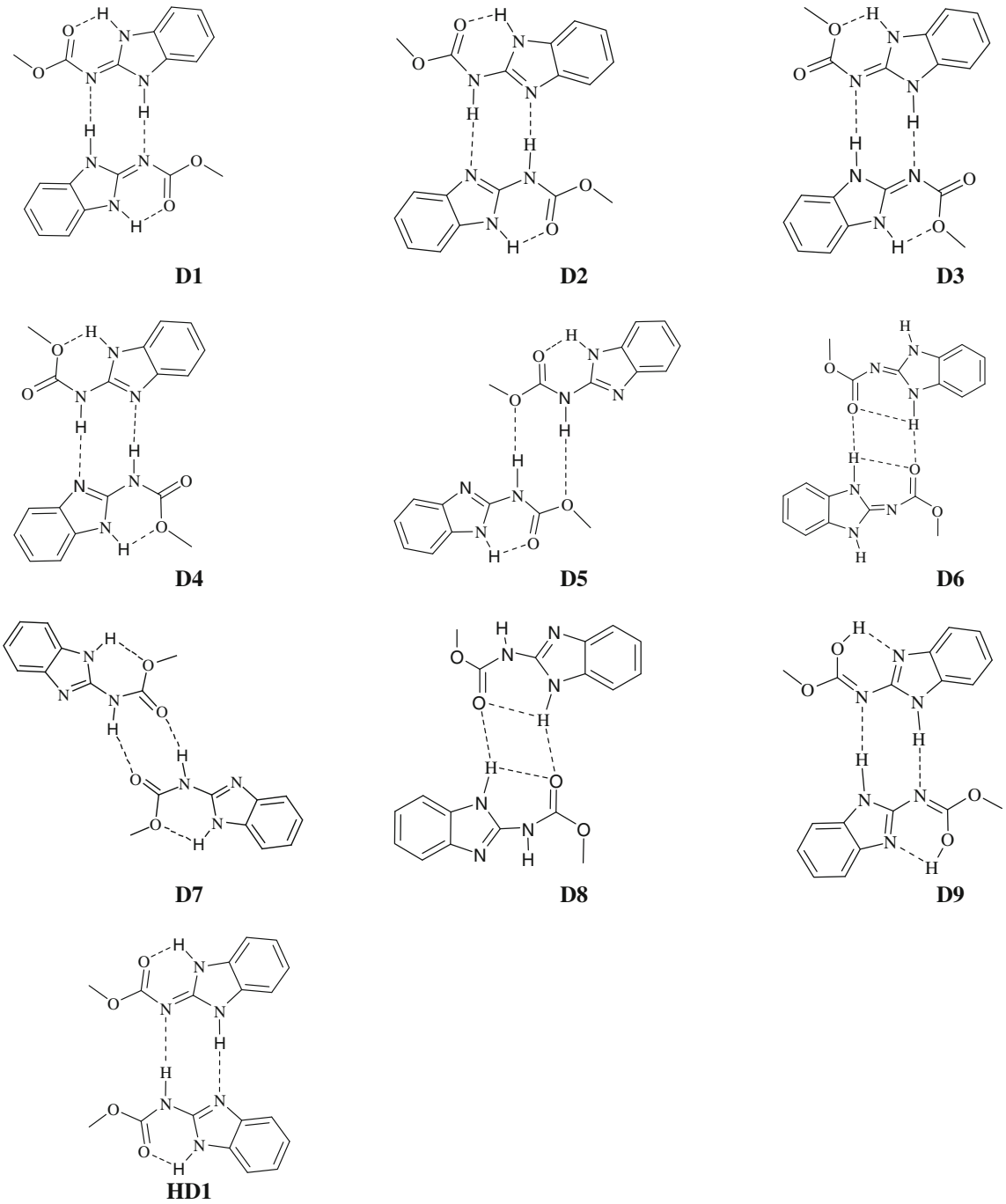

Fig. 9 Various dimeric arrangements of **D1**to **D9** with possible intermolecular interactions

31+G(d) method on NSC135301 (Fig. 8) [66]. **CN-1** was found to be more stable among possible tautomers of NSC135301, i.e., **CN-1** to **CN-4**. Both **CN-1** and **CN-4** are characterized by intramolecular hydrogen bonds. Optimized 3D geometries and the relative energy data of NSC135301 are given in supporting information (Figure S1 and Table S11).

3.2 Intermolecular interactions in carbendazim dimers and their possible contribution to polymorphism

Polymorph is 'a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state' [67]. Sokol et al. [25] reported the structure of

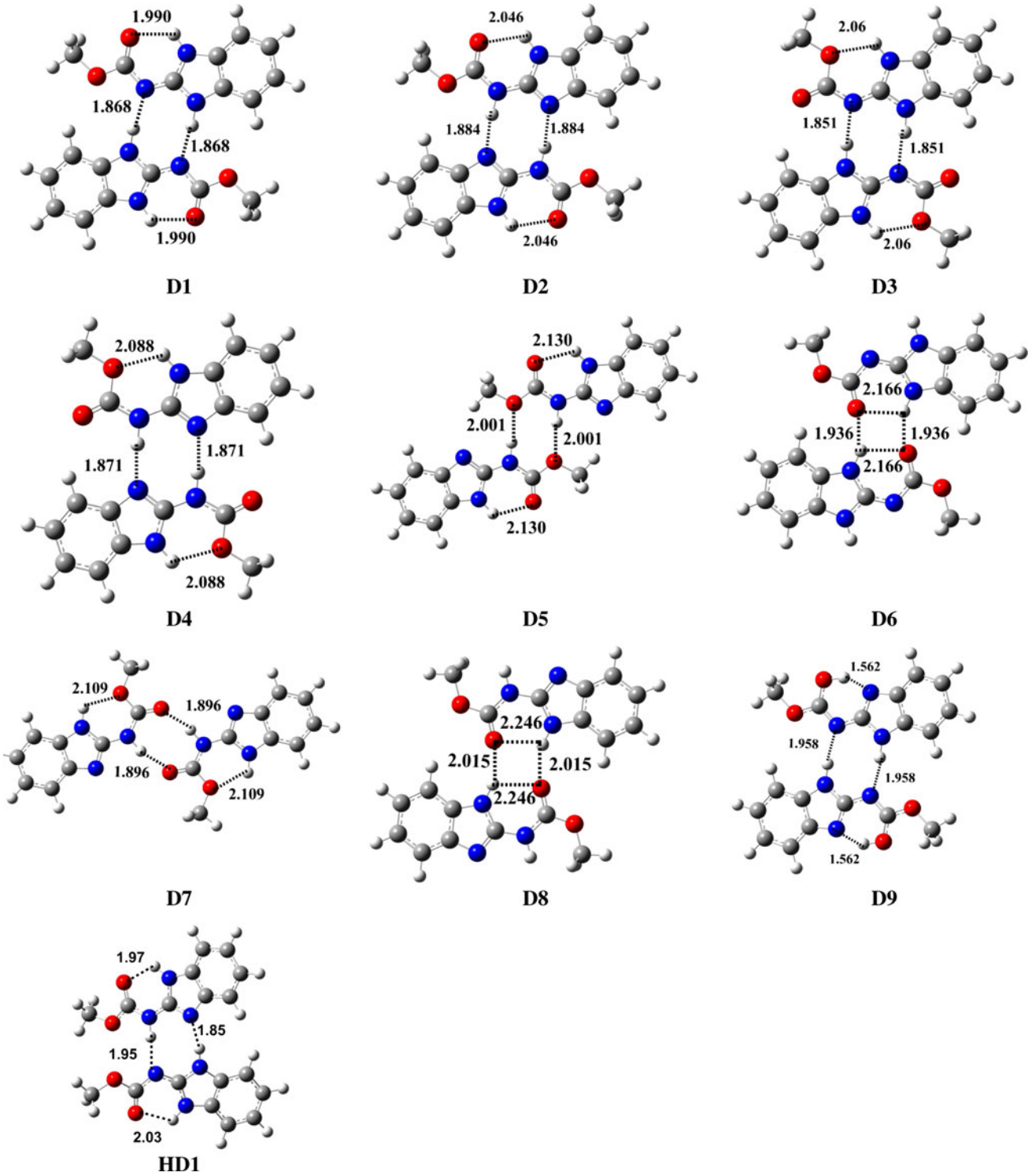

Fig. 10 Optimized 3D structures of **D1** to **D9** with inter and intramolecular hydrogen bond distances given in Å

dimer of ethyl-2-benzimidazole carbamate, in which anti-parallel arrangement of the monomeric units has shown a dimeric state with two intermolecular hydrogen bonds. Pranzo et al. [18] reported that albendazole polymorph form I is more soluble (commercial) than form II (recrystallized in DMF; dimethyl formamide). They also reported that a polymorph of albendazole with **C** tautomer is relatively more preferable, over a polymorph with **B** tautomer for albendazole. Mebendazole is known to exist in three polymorphic forms (A, B, and C), with polymorph

C being most efficacious [19, 68, 69]. Polymorph B is reported to be toxic. Martins et al. [17] reported that the intermolecular contacts influence the conformational and geometric features of polymorph C of mebendazole. Ferreira et al. [20] reported that mebendazole (form A) can exist as a network of dimers in solid state and suggested that the dimeric state is similar to a dimer of **CM-2**. Similar dimeric structures are also possible for the tautomers **CM-2** to **CM-7**. The polymorphic states of **BM** drugs are expected to emerge from the various tautomers of these drugs and their dimeric states. To estimate the energy factors associated with the dimers of **CM-1** to **CM-7**, quantum chemical analysis using B3LYP/6-31+G(d) level has been carried out. Table 4 lists the energies of stabilization due to dimer formation (**D1-D9**) and the relative energies of the dimers, the 2D and 3D structures of the dimers **D1-D9** are shown in Figs. 9 and 10, respectively. **D1** is the most stable dimer and **D2** is next best with a relative energy of 0.80 kcal/mol in aqueous phase. **D1** is a dimer from the monomeric unit **CM-1** and **D-2** is a dimer from the monomeric unit **CM-2**. Both of them are characterized by two intermolecular hydrogen bonds. The presence of inter and intramolecular hydrogen bonds in **D1** is confirmed by performing AIM analysis. The charge density $\rho = 0.0363$, density laplacian $\nabla^2\rho = 0.0986$, and the ellipticity $\varepsilon = 0.0609$ at the intermolecular BCP in **D1** are clearly indicative of a typical hydrogen bond.

Stabilization energy due to the formation of **D1** is 7.02 kcal/mol, and the stabilization energy due to the formation of **D2** is 2.2 kcal/mol. This is the only parameter which differentiates **D1** and **D2**. On this count, it may be considered that formation of **D1** is thermodynamically preferred over the formation of **D2**. Interconversion between **D1** and **D2** may lead to two different polymorphic states of **BM** drugs. However, owing to minor changes between **D1** and **D2** and to the greater similarities in terms of geometric, thermodynamic parameters, as well as intermolecular interactions, it may not be easy to determine the polymorphic states arising from **D1** and **D2**. Since the stabilization energy in **D1** formation is relatively more favorable, it may be safely concluded that the tautomer **CM-1** is the preferred tautomer of **CM** and other **BM** drugs in solid state.

D3 is a dimer from the monomeric unit **CM-5,** and **D4** is a dimer from the monomeric unit **CM-3**. They are relatively less stable but the formation of these dimers also is thermodynamically quite feasible because of the strong stabilization energies. These dimeric structures can lead to clearly identifiable polymorphs. The dimers **D5-D9** are less stable on a relative energy scale, and these structures cannot be expected in solid-state conditions. Heterodimer (**HD-1**) was constructed from the monomers **CM-1** and **CM-2** to check the possibility of existence of heterodimer. The stabilization energy of the complex is suggesting that the heterodimer complex is 2.44 kcal/mol (Table 4) unstable with respect to the addition of individual monomeric energies of both **CM-1** and **CM-2**.

4 Conclusions

Quantum chemical exploration of the carbendazim was performed, so as to understand tautomeric preferences of benzimidazole carbamate derivatives. Quantum chemical analysis revealed that the tautomer represented by **CM-1** structure is important. This representation was not considered in previous studies. In gas phase, **CM-1** structure is marginally less stable, whereas in solvent conditions, **CM-1** is marginally favoured and in solid-state conditions also **CM-1** structure is marginally preferred. Thus, tautomeric preferences of the benzimidazole carbamate drugs are quite environment-dependent. The preference for the **CM-1** tautomer originates from the guanidinic structure; the preference toward **CM-2** tautomer is associated with aromatic character of cyclic guanidine units. Stabilization energy due to dimer formation is 7.02 kcal/mol from **CM-1** and 2.22 kcal/mol from **CM-2**. This understanding can help in the design of new polymorphic forms, which will provide desired solubility and bioavailability properties.

Acknowledgments PVB thanks Nano mission, the Department of Science and Technology (DST), New Delhi, for financial support. YK thanks the Council of Scientific and Industrial research (CSIR), New Delhi, for Senior Research Fellowship.

References

1. Griffith RK (2002) In: Abraham DJ (ed) Anthelmintics. Burger's medicinal chemistry, drug discovery and development 6th edn, vol 5. Wiley, New York, pp 1089–1096
2. Hebden SP (1961) The anthelmintic activity of thiabendazole (M.K.360). Aust Vet J 37:264–269
3. Franz KH (1963) Clinical trials with thiabendazole against human strongyloidiasis. Am J Trop Med Hyg 12:211–214
4. Cook GC (1990) Use of benzimidazole chemotherapy in human helminthiasis: indications and efficacy. Parasitol Today 6: 133–136
5. Marriner S (1986) Anthelmintic drugs. Vet Rec 118:181–184
6. Gyurik RJ, Theodorides VJ (1975) Methyl 5-propylthio-2-benzimidazolcarbamate. US patent, ed.: SmithKline Corporation
7. Al-Badr AA, Tariq M (1987) Analytical profiles of mebendazole. In: Florey K (ed) Analytical profiles of drug substances. Academic Press, New York, pp 291–325
8. Cabié A, Bouchaud O, Houzé S, Khuong MA, Ruggeri C, Ancelle T, Matheron S, Coulaud JP (1996) Albendazole versus thiabendazole as therapy for trichinosis: a retrospective study. Clin Infect Dis 22:1033–1035
9. Theodorides VJ, Gyurik RJ, Kingsbury WD, Parish RC (1976) Anthelmintic activity of albendazole against liver flukes,

tapeworms, lung and gastrointestinal roundworms. Cell Mol Life Sci 32:702–703
10. Njoroge E, Mbithi P, Wachira T, Gathuma J, Gathura P, Maitho TE, Magambo J, Zeyhle E (2005) Comparative study of albendazole and oxfendazole in the treatment of cystic echinococcosis in sheep and goats. Intern J Appl Res Vet Med 3:97–101
11. Pourgholami MH, Akhter J, Wang L, Lu Y, Morris DL (2005) Antitumor activity of albendazole against the human colorectal cancer cell line HT-29: in vitro and in a xenograft model of peritoneal carcinomatosis. Cancer Chemother Pharmacol 55:425–432
12. Kim MN, Park HY (2003) Antifungal activity of methyl-2-benzimidazole carbamate. Mycobiology 31:81–85
13. Davidse LC (1986) Benzimidazole fungicides: mechanism of action and biological impact. Annu Rev Phytopathol 24:43–65
14. Rathinasamy K, Panda D (2008) Kinetic stabilization of microtubule dynamic instability by benomyl increases the nuclear transport of p53. Biochem Pharmacol 76:1669–1680
15. Kus C, Altanlar N (2003) Synthesis of some new benzimidazole carbamate derivatives for evaluation of antifungal activity. Turk J Chem 27:35–40
16. Wu Z, Razzak M, Tucker IG, Medlicott NJ (2005) Physicochemical characterization of ricobendazole: I. solubility, lipophilicity, and ionization characteristics. J Pharm Sci 94:983–993
17. Martins FT, Neves PP, Ellena J, Camí GE, Brusau EV, Narda GE (2009) Intermolecular contacts influencing the conformational and geometric features of the pharmaceutically preferred mebendazole polymorph C. J Pharm Sci 98:2336–2344
18. Pranzo MB, Cruickshank D, Coruzzi M, Caira MR, Bettini R (2010) Enantiotropically related albendazole polymorphs. J Pharm Sci 99:3731–3742
19. Brusau EV, Camí GE, Narda GE, Cuffini S, Ayala AP, Ellena J (2008) Synthesis and characterization of a new mebendazole salt: mebendazole hydrochloride. J Pharm Sci 97:542–552
20. Ferreira FF, Antonio SG, Rosa PCP, Paiva Santos CO (2010) Crystal structure determination of mebendazole form A using high resolution synchrotron X ray powder diffraction data. J Pharm Sci 99:1734–1744
21. Mahler G, Davyt D, Gordon S, Incerti M, Nunez I, Pezaroglo H, Scarone L, Serra G, Silvera M, Manta E (2008) Synthesis of albendazole metabolite: characterization and HPLC determination. J Chem Educ 85:1652
22. Soria-Arteche O, Castillo R, Hernández-Campos A, Hurtado-de la Peña M, Navarrete-Vázquez G, Medina-Franco JL, Gómez-Flores K (2005) Studies on the selective S-oxidation of albendazole, fenbendazole, triclabendazole, and other benzimidazole sulfides. J Mex Chem Soc 49:353–358
23. Chassaing C, Berger M, Heckeroth A, Ilg T, Jaeger M, Kern C, Schmid K, Uphoff M (2008) Highly water-soluble prodrugs of anthelmintic benzimidazole carbamates: synthesis, pharmacodynamics, and pharmacokinetics. J Med Chem 51:1111–1114
24. http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=2082
25. Sokol VI, Davidov VV, Porai-Koshits MA, Zaitsev BE, Palishkin MV, Sheban GV, Pakhomov VI, Kukalenko SS (1988) Crystal and molecular structure of N-(2-benzimidazolyl)-O-alkyl carbamates. Russ Chem Bull 37:1148–1153
26. Hernández B, Luque FJ, Orozco M (1996) Tautomerism of xanthine oxidase substrates hypoxanthine and allopurinol. J Org Chem 61:5964–5971
27. Martin YC (2010) Overview of the perspectives devoted to tautomerism in molecular design. J Comput Aided Mol Des 24: 473–474
28. Pospisil P, Ballmer P, Scapozza L, Folkers G (2003) Tautomerism in computer-aided drug design. J Recept Signal Transduct 23:361–371
29. Rosenberg LS, Schulman SG (1978) Tautomerism of singly protonated chloroquine and quinacrine. J Pharm Sci 67:1770–1772
30. Katritzky A, Hall C, El-Gendy B, Draghici B (2010) Tautomerism in drug discovery. J Comp Aided Mol Des 24: 475–484
31. Wojnarowska Z, Wlodarczyk P, Kaminski K, Grzybowska K, Hawelek L, Paluch M (2010) On the kinetics of tautomerism in drugs: new application of broadband dielectric spectroscopy. The J Chem Phys 133:94507
32. Jayaram PN, Roy G, Mugesh G (2008) Effect of thione—thiol tautomerism on the inhibition of lactoperoxidase by anti-thyroid drugs and their analogues. J Chem Sci 120:143–154
33. Sundriyal S, Khanna S, Saha R, Bharatam PV (2008) Metformin and glitazones: does similarity in biomolecular mechanism originate from tautomerism in these drugs? J Phys Org Chem 21: 30–33
34. Lammertsma K, Prasad BV (1993) Nitro $\rightleftharpoons$ aci-nitro tautomerism. J Am Chem Soc 115:2348–2351
35. Lammertsma K, Prasad BV (1994) Imine $\rightleftharpoons$ enamine tautomerism. J Am Chem Soc 116:642–650
36. Lammertsma K, Bharatam PV (2000) Keto $\rightleftharpoons$ Enol, Imine $\rightleftharpoons$ Enamine, and Nitro $\rightleftharpoons$ aci-Nitro tautomerism and their interrelationship in substituted nitroethylenes. Keto, imine, nitro, and vinyl substituent effects and the importance of H-bonding. J Org Chem 65:4662–4670
37. Bharatam PV, Iqbal P, Malde A, Tiwari R (2004) Electron delocalization in aminoguanidine: a computational study. J Phys Chem A 108:10509–10517
38. Bharatam PV, Patel DS, Iqbal P (2005) Pharmacophoric features of biguanide derivatives: an electronic and structural analysis. J Med Chem 48:7615–7622
39. Mehdi A, Adane L, Patel DS, Bharatam PV (2010) Electronic structure and reactivity of guanylthiourea: a quantum chemical study. J Comp Chem 31:1259–1267
40. Kasetti Y, Patel NK, Sundriyal S, Bharatam PV (2010) Conformational polymorphism in sulfonylurea drugs: electronic structure analysis. J Phys Chem B 114:11603–11611
41. Patel DS, Bharatam PV (2011) Divalent N(I) compounds with two lone pairs on nitrogen. J Phys Chem A 115:7645–7655
42. McCracken RO, Lipkowitz KB (1990) Experimental and theoretical studies of albendazole, oxibendazole, and tioxidazole. J Parasitol 76:180–185
43. Lipkowitz KB, McCracken RO (1991) A molecular modeling approach to in vivo efficacy of triclabendazole. J Parasitol 77: 998–1005
44. McCracken RO, Lipkowitz KB (1989) Experimental and theoretical studies of anthelmintics: oxfendazole and its imidazo [1, 2-a] pyridine-2-carbamate isomer. Int J Parasitol 19:363–368
45. Lipkowitz KB, McCracken RO (1993) Molecular modeling: a tool for predicting anthelmintic activity in vivo. Parasitol Res 79:475–479
46. Pople JA, Beveridge DL (1970) Approximate molecular orbital theory. McGraw Hill, New York
47. Hehre WJ, Radom L, Schleyer PvR, Pople JA (1985) Ab initio molecular orbital theory. Wiley, New York
48. Parr RG, Yang W (1989) Density functional theory of atoms and molecules. O.U.P, New York
49. Bartolotti LJ, Fluchick K (1996) In: Lipkowitz KB, Boyd DB (eds) Reviews in computational chemistry. VCH Publishers, New York
50. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery JA Jr, Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C,

Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA (2003) Gaussian 03, Revision B.04. Gaussian, Inc., Pittsburgh

51. Becke AD (1993) Density-functional thermochemistry. III. The role of exact exchange. Chem Phys 98:5648–5652
52. Lee C, Yang W, Parr RG (1988) Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. Phys Rev B 37:785–789
53. Møller C, Plesset MS (1934) Note on an approximation treatment for many-electron systems. Phys Rev 46:618–622
54. Krishnan R, Frisch MJ, Pople JA (1980) Contribution of triple substitutions to the electron correlation energy in fourth order perturbation theory. J Chem Phys 72:4244–4245
55. Cancès MT, Mennucci B, Tomasi J (1997) Evaluation of solvent effects in isotropic and anisotropic dielectrics, and in ionic solutions with a unified integral equation method: theoretical bases, computational implementation and numerical applications. J Chem Phys 107:3032–3041
56. Bader RFW (1991) A quantum theory of molecular structure and its applications. Chem Rev 91:893–928
57. Biegler-König F, Schönbohm J, Bayles D (2001) J Comp Chem 22:545–559. http://www.aim2000.de. [11 April 2011]
58. Reed AE, Weinstock RB, Weinhold F (1985) Natural population analysis. J Chem Phys 83:735–746
59. Reed AE, Curtiss LA, Weinhold F (1988) Intermolecular interactions from a natural bond orbital, donor-acceptor viewpoint. Chem Rev 88:899–926
60. Schleyer PvR, Maerker C, Dransfeld A, Jiao H (1996) Nucleus independent chemical shifts: a simple and efficient aromaticity probe. J Am Chem Soc 118:6317–6318
61. Jiao H, Schleyer PvR, Mo Y, McAllister MA, Tidwell TTJ (1997) Magnetic evidence for the aromaticity and antiaromaticity of charged fluorenyl, indenyl, and cyclopentadienyl systems. J Am Chem Soc 119:7075–7083
62. London F (1937) Quantum theory of interatomic currents in aromatic compounds. J Phys Radium 8:397–409
63. Hehre WJA (2001) Guide to molecular mechanics and quantum chemical calculations. Wavefunction: Irvine
64. Machatha SG, Sanghvi T, Yalkowsky SH (2005) Structure determination and characterization of carbendazim hydrochloride dihydrate. AAPS PharmSciTech 6:115–119
65. Jung H, Medina L, Garcia L, Fuentes I, Moreno-Esparza R (1998) Absorption studies of albendazole and some physicochemical properties of the drug and its metabolite albendazole sulphoxide. J Pharm Pharmacol 50:43–48
66. http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=00282132
67. Bernstein J (2002) Polymorphism in molecular crystals, vol 14. Oxford University Press, USA
68. Blaton NM, Peeters OM, De Ranter CJ (1980) (5-benzoyl-1H-benzimidazol-2-yl)-carbamic acid methyl ester hydrobromide (mebendazole. HBr), $C_{16}H_{14}BrN_3O_3$. Cryst Struct Comm 9: 181–186
69. Caira MR, Dekker TG, Liebenberg W (1998) Structure of a 1:1 complex between the anthelmintic drug mebendazole and propionic acid. J Chem Crystallogr 28:11–15