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Synthesis, Characterization and Antitumor Activity of Benzimidazole Phosphonate Derivatives

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In Loving Memory of Late Professor Doctor ""Mohamed Refaat Hussein Mahran""

Abstract

A series of Benzimidazole derivatives were obtained *via* reaction of 2-chloro-1*H*-benzo[*d*]imidazole (**1**) with morpholine, which produce benzo[*d*]imidazol-yl-morpholine **2** that react with chloroacetonitrile to give (benzo[*d*]imidazol-yl)acetonitrile **3**, by its next reaction with hydrazine hydrate afforded the key intermediate **4**, that afford thiadiazole derivatives **5** by its reaction with carbon disulfide *via* cyclization reaction. Alkylation of compound **5** with ethyl bromoacetate, afforded benzo[*d*]imidazolo derivative **6**, that react with thioglycolic acid to give thiazolidine compound in suitable conditions. Also Benzimidazole **1** reacted with various Wittig Horner reagents in DMF to afford phosphoryl and phosphonates derivatives **12a-e** in moderate yields. On the other hand, **1** react with trialkyl phosphites to yield the known phosphonates derivatives **14a-c** in high yields, also we obtained the same products by reacting **1** with dialkyl phosphites. In addition, hexaalkyltriamidophosphites were applied to **1** in ethanol to afford phosphonic diamide derivatives **17a-c** in high yields through addition-elimination reaction. Antitumor activity of the newly synthesized compounds were tested on three cell lines of breast (MCF7) and liver (HepG2) carcinoma cell lines and HCT-116 cancer cells together with human healthy cell line (BJ-1) using the MTT assay. Most compounds suppressed three cancer cells (HCT-116, HepG2 and MCF-7) and exhibited considerable anticancer properties in a dose-dependent manner
Keywords: Chloro-benzo[d]imidazole, anticancer, microwave-assisted, phosphorus Horner reagents, Heterocyclic compounds

Introduction

Benzimidazole primarily based heterocycles are structurally much like evidently taking the place of nucleotides, i.e., adenine base of the DNA [1-3]. This is regarded in addition to a factor of vitamin B. This feature substantially has been utilized in drug synthesis and medicinal chemistry, Heterocyclic compounds are considered as an extremely important class of compounds which play a key role in health care and pharmaceutical drug design [3]. Currently, a number of heterocyclic compounds are available commercially as anti-cancer drugs. Heterocyclic benzimidazole derivatives are an important class of nitrogen containing heterocycles with a wide range of medicinal properties such as serotoninergic 5-HT3 and 5-HT4 receptors in the CNS [4], antihistamine [5], anticancer [6], antibacterial [7], antifungal [8], anti-inflammatory, antianalgesic [9], antioxidant [10], antidiabetic [11], selective neuropeptide YY1 receptor antagonists [12], antimalerial, antitubercular [13], antiulcer [14], antitumor, antiproliferative and anticancer activity [15,16], where moiety plays the role of 'Master Key' [17]. Therefore, it is an imperative anchor for development of new therapeutic drugs. On the other hand, Organophosphorus chemistry has been the cutting edge subject in the past decades due to the discovery of many naturally C-P compounds which reveal anticancer, antiviral, antibacterial occurring [18], meanwhile, heterocyclic compounds gained great importance due to their pharmaceutical benefits and their diverse applications in organic synthesis. It not easy to synthesize heterocycles in which phosphonyl groups are directly linked to the carbon nucleus by the normal methods [19-22]. In this article it is easy synthesized various heterocyclic phosphonates in one step, and also series of heterocyclic phosphorus systems. We describe the synthesis of new compounds through the reactions of Benzimidazole **1** with different types of phosphonyl carbanions and phosphorus reagents including trialkyl phosphites, dialkyl phosphites or hexaalkyl triamidophosphites.

Results and Discussion:

The reaction of 2-chloro-1*H*-benzo[*d*]imidazole (**1**) with morpholine in DMSO with few drops of

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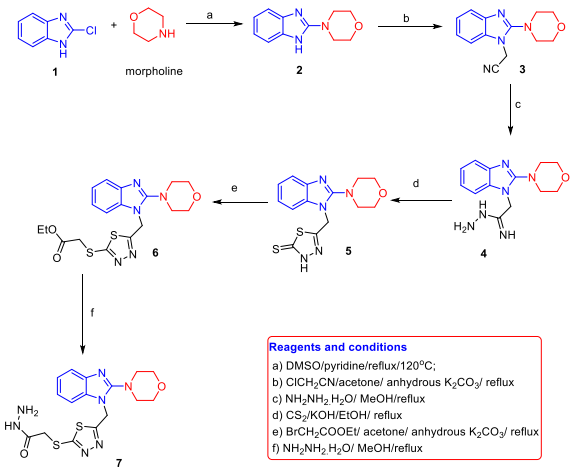
pyridine under heating afforded product **2**. Cyanomethylation of compound **2** with chloroacetonitrile in the presence of anhydrous potassium carbonate in dry acetone afforded compound **3** which react with hydrazine hydrate in methanol to give compound **4** (Scheme 1).

The new products were characterized on the bases of IR, NMR and mass spectral data; compound **4** afforded peaks at its IR (KBr, cm^{-1}): 3355, 3330 (NH, NH_2), and 1661 (C=N). Also, ^1H NMR (500 MHz, DMSO) revealed signals at δ 4.59 & 5.44 due to the presence of NH_2, NH groups while the other NH group appears at 14 which are exchangeable by D_2O, and 5.95 (s, 1H, $CH_2{}^b$), 5.97 (s, 1H, $CH_2{}^a$) due to the presence of nonequivalent CH_2 protons.



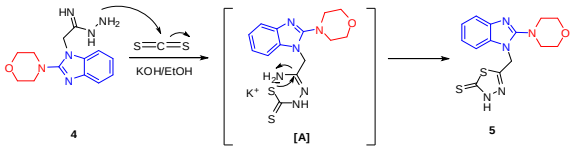
Scheme 1

Cyclization reaction of compound **4** with carbon disulfide in alcoholic potassium hydroxide at reflux temperature afforded compound **5** (Scheme 1). The suggested mechanism is depicted in scheme 2; nucleophilic attack of amino lone pair to carbon disulfide to afford dithiocarbamate potassium salt which under intramolecular cyclization gives product **5** (Scheme 2) [23]. ^1H NMR (500 MHz, DMSO) revealed disappearance of signals at δ 4.59 and 5.44 of two D_2O exchangeable NH and NH_2 with appearance of signals at δ 5.97 ppm (CH_2) and broad signal at 14.20 ppm of NH. Also, ^{13}C NMR spectrum of compound **5** revealed strong signal at δ 193.87 of C=S.

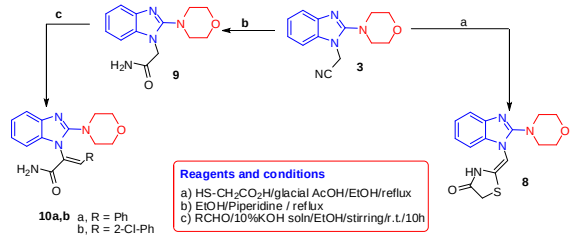
Alkylation of compound **5** with ethyl bromoacetate in acetone containing anhydrous potassium carbonate afforded ethyl 2-((5-((2-morpholino-1*H*-benzo[*d*]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)thio)acetate **6** which upon refluxing in methanol with hydrazine hydrate give acetohydrazide derivative **7** in good yield (Scheme 1).

Furthermore, compound **3** reacted with thioglycolic acid in ethanol containing glacial acetic acid at reflux temperature to afford 2-((2-morpholino-1*H*-benzo[*d*]imidazol-1-yl)methylene)thiazolidin-4-one **8** in good yield (Scheme 3).

On the other hand, refluxing compound **3** with ethanol containing piperidine afforded 2-(2-morpholino-1*H*-benzo[*d*]imidazol-1-yl)acetamide **9** which condensed with benzaldehyde or 2-cholrobenzaldehyde to give acrylamide derivatives **10a,b** (Scheme 3).

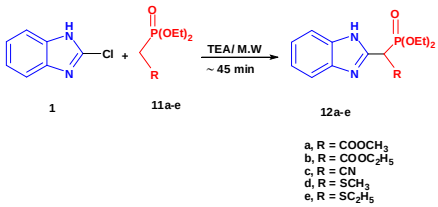


Scheme 2



Scheme 3

Treatment of 2-chloro-1*H*-benzo[*d*]imidazole (**1**) with diethylphosphonoacetates **11a** or **11b** under microwave thermal reaction in dimethylformamide (DMF), and drops of triethylamine (TEA), afforded the diethoxyphosphorylacetate substituted imidazole **12a,b** in 80 % yields (Scheme 4).



Scheme 4

The chemical structure of **12b** was in according with elemental analysis, molecular weight determination (MS) and spectroscopic data. The IR spectrum of **12b** showed absorption bands at 1750 (C=O) and 1246 (P=O, bonded), its ^1H NMR revealed the presence of two types of ethoxy group protons with different chemical shifts. The two equivalent OC_2H_5 protons coupled with phosphorus appeared as a doublet of a triplet (6H, J_{HH} = 6.3 Hz, J_{PH} = 2.8 Hz) at δ 1.21 ppm and as a doublet of a quartet (4H, J_{HH} = 6.3, J_{PH} = 4.9 Hz) at 4.18 ppm, whereas OC_2H_5 protons displayed as a triplet (3H, J_{HH} = 7.5 Hz) at 1.37 and a quartet (2H, J_{HH} = 7.5Hz) at 4.25 ppm.

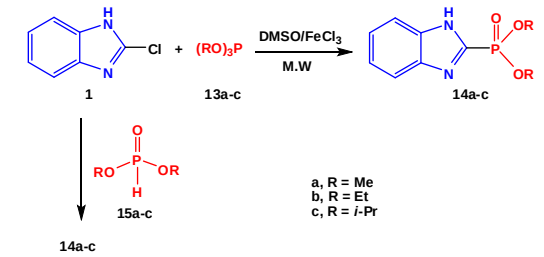
A reasonable mechanism of addition reaction of **1** with phosphonylcarbanions **11a,b** involves an initial nucleophilic attack of carbanion center in **11a,b** on the

(=C-Cl) group with concomitant elimination of the appropriate hydrogen chloride moiety.

Next, the reaction of **1** with diethylcyanomethylphosphonate **11c** was studied. When **1** was treated with **11c** in DMF containing drops of TEA in microwave, phosphonate **12c** was obtained in 75% yield. The structure of phosphonate substituted imidazole was based on the following reasons: The IR spectrum showed absorption bands at 1245 (P=O, bonded), 1050 (P-O-C) and 2250 (CN) cm^{-1}. The ^1H NMR exhibited two ethoxy groups were equivalent, whereupon the OC_2H_5 protons coupled with phosphorus were split into doublet of triplets at 1.22 and doublet of quartets at 4.24 ppm. The ^{13}C NMR appeared a doublet signal at 118.9 ppm due to the presence of CN group and a doublet at 44.5 according to the C-P (J_{PC} = 163.6).

In the same study, the reaction of **1** with Wittig-Horner reagents **11d**,**e** were studied. the obtained products are depicted in Scheme 4. They gave the corresponding phosphonates **12d** (78% yield) and **12e** (76% yield). The suggested structures are in a good agreement with their spectral and analytical data.

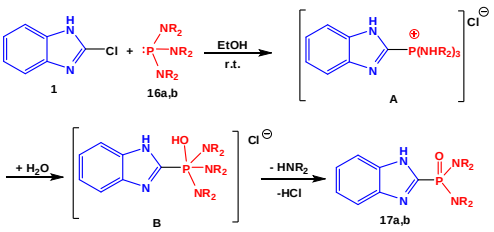
The behavior of **1** toward trialkylphosphites **13a-c** in DMSO solution containing 10% $FeCl_3$ at r.t. was studied, followed by heating under microwave irradiation to give the known imidazol-2-phosphonates **14a-c** (Scheme 5). We obtain the same products with dialkylphosphites (**15a-c**) in DMSO containing drops of piperidine with reflux in microwave for 1 hour. The products **14a-c** were known in literature [24,25,26]. These reactions provided an easy synthetic route to obtain heterocyclic phosphonates and in one step preparations.



Scheme 5

The investigation was extended to obtain more substituted heterocyclic phosphor derivatives *via* applying hexaalkyltriamidophosphites to the imidazole **1**. When **1** was treated with tris(dialkylamino)phosphines **16a-b** in boiling ethanol for 2h, *N*,*N*,*N*,*N*-tetraalkylphosphonic diamide **17a-b** were isolated in ~ 75% yield. Elemental analyses and molecular weight determinations confirmed structure **17a,b**. The ^1H NMR spectrum (DMSO) of **17a** showed the 2NMe_2 protons as two doublets centered at δ = 2.42, 2.73 ppm assigned to 12H of the two nonequivalent magnetically dimethylamino groups connected to phosphorus. The ^{13}CNMR (DMSO) spectrum of **17a** displayed the C-P signal at 161.5 ppm (J_{PC} = 178.8Hz).

A plausible explanation for the mechanism of the products **17a,b** were proposed in Scheme 6. According the products were formed through an initial addition of the aminophosphine **16a,b** to **1** giving rise to the phosphonium dipolar ion intermediates **A**, stabilization of **A** was attained by its reaction with fortuitous water to give the intermediates **B** followed by extrusion of dialkylamine moiety leading to **17a,b** [27,28].



Scheme 6

In Vitro Antiproliferative activity

Sixteen compounds were examined *in vitro* for their activity against HCT-116, HepG2 and MCF-7 human cancer cells and one human healthy cell line (BJ-1) using the LDH assay. The percentages of dead cells were calculated and compared to those of the control. Activities of these compounds against the three carcinoma cell lines were compared to the activity of doxorubicin. All compounds suppressed three cancer cells (HCT-116, HepG2 and MCF-7) in a dose-dependent manner (**Fig. 1 - 3**). In case of HCT-116 human colorectal carcinoma cells: both Figure 1 and Table 1 show that seven compounds (**5**, **7**, **8**, **4**, **3**, **12c**, and **12d** respectively) have comparable cytotoxic activities; the rest of the compounds have moderate cytotoxic activity against HCT-116 relative to that of doxorubicin. In case of MCF-7 human breast cancer cells: fourteen compounds (**12c**, **10a**, **3**, **4**, **8**, **9**, **5**, **7**, **17b**, **14b**, **12a**, **12b**, **14a** and **17a**, respectively) have comparable cytotoxic activities; two of the compounds (**12d** and **12e**) have weak cytotoxic activities against MCF-7 relative to the reference drug (**Figure 2** &**Table 1**). In case of HepG2 human liver cancer cells: fourteen compounds (**12c**, **17b**, **17a**, **14b**, **5**, **8**, **14a**, **7**, **4**, **10a**, **3**, **9**, **12b** and **12a**, respectively) have superior cytotoxic activities; one compound **12d** has comparable cytotoxic activity; one compound **12e** has weak cytotoxic activity against HepG2 relative to that of doxorubicin (**Figure 3** &**Table 1**). In case of the non-tumor fibroblast-derived cell line (BJ): both Figure **4** and Table **1** showed that all the compounds have less cytotoxic activities against the healthy cells relative to that of doxorubicin.

By comparing the cytotoxicity results on all cancer types relative to normal cell line, one can conclude that's: six compounds **3**,**4**,**5**,**7**,**8**,**9** are having good cytotoxic activities on the three human cancer types; eight compounds (**14a**, **14b**, **17a**,**17b**, **12a**,**12b**, **12c** and **10a**) are having good cytotoxicity on both human liver and breast cancer types rather than on the human colon cancer type; one compound **12d** have good cytotoxic activity on both human liver and colon cancer types rather than human breast cancer type.

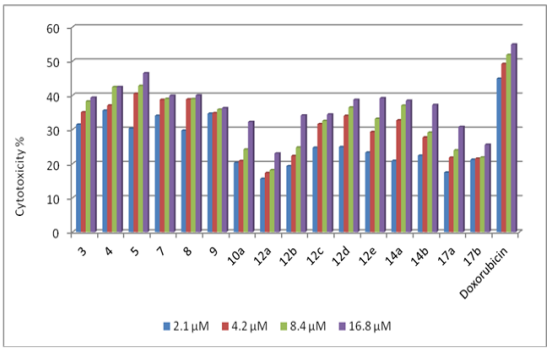


Figure 1 Dose dependent antiproliferative data of the sixteen compounds against HCT-116 cancer cells according to the LDH assay after 48 h of exposure

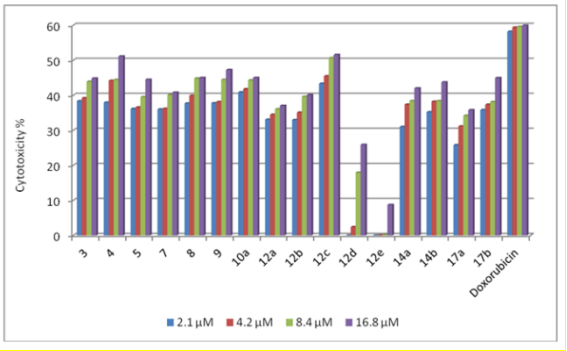


Figure 2 Dose dependent antiproliferative data of the sixteen compounds against MCF-7 cancer cells according to the LDH assay after 48 h of exposure.

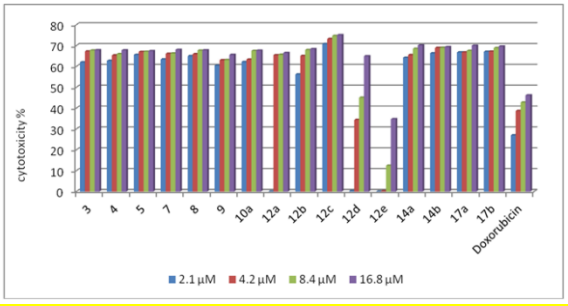


Figure 3 Dose dependent antiproliferative data of the sixteen compounds against HepG2 cancer cells according to the LDH assay after 48 h of exposure.

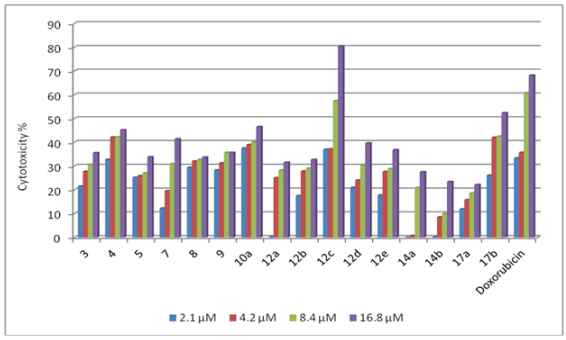


Figure 4 Dose dependent antiproliferative data of the sixteen compounds against BJ-1 normal cells according to the LDH assay after 48 h of exposure.

Table 1: The antiproliferative IC_{50} of the sixteen compounds against the four cell lines according to the LDH assay

Compound Code	IC_{50} (µM) ± SD			
	HCT-116	HepG-2	MCF-7	BJ-1
3	6.0 ± 1.2	1.7 ± 0.1	2.7 ± 0.1	13.7 ± 2.1
4	5.7 ± 1.1	1.7 ± 0.1	2.8 ± 0.2	9.9 ± 1.2
5	5.2 ± 1.1	1.6 ± 0.1	2.9 ± 0.2	15.5 ± 1.1
7	5.4 ± 1.1	1.7 ± 0.2	2.9 ± 0.2	13.6 ± 1.3
8	5.4 ± 1.1	1.6 ± 0.1	2.8 ± 0.1	12.8 ± 1.4
9	6.0 ± 1.1	1.7 ± 0.1	2.8 ± 0.1	11.8 ± 1.1
10a	10.1 ± 1.2	1.7 ± 0.1	2.6 ± 0.2	10.5 ± 1.1
12a	12.1 ± 2.1	3.2 ± 0.2	3.2 ± 0.2	14.8 ± 1.2
12b	9.4 ± 1.3	1.9 ± 0.1	3.2 ± 0.2	14.5 ± 1.5
12c	6.6 ± 1.1	1.5 ± 0.1	2.4 ± 0.2	7.3 ± 1.1
12d	6.2 ± 1.1	6.1 ± 0.9	23.4 ± 3.2	13.9 ± 2.3
12e	7.2 ± 1.4	24.2 ± 3.1	96 ± 4.2	14.5 ± 2.4
14a	6.4 ± 1.1	1.6 ± 0.1	3.4 ± 0.2	20.0 ± 2.3
14b	7.6 ± 1.1	1.6 ± 0.1	3.0 ± 0.2	42.0 ± 3.9
17a	9.7 ± 1.2	1.6 ± 0.2	4.1 ± 0.2	22.6 ± 2.5
17b	9.8 ± 1.3	1.6 ± 0.1	2.9 ± 0.1	9.9 ± 1.2
Doxorubicin	4.3 ± 0.5	5.4 ± 0.3	1.8 ± 0.2	6.9 ± 0.3

Experimental

Chemistry

Melting points were determined with an open capillary tube on an Electrothermal (variable heater) melting point apparatus and are uncorrected. IR spectra (KBr) were recorded on a Shimadzu FT-IR 8400S spectrophotometer. Reactions were monitored using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck) utilizing various solvents for elution. The chemical structures of the synthesized compounds were characterized by nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) recorded on a JEOL NMR spectrometer (500 MHz, 125 MHz for ^{1}H and ^{13}C, respectively). Chemical shifts are reported in parts per million (ppm) using the deuterated solvent peak as an internal standard.

The purity of all new samples was verified by microchemical analysis (C/H/N) carried out at the Microanalysis Laboratory, Cairo University, Cairo, Egypt. The microwave oven used is a Milestone Italy (model: StartSynth, Reactor: Pack2B Basic Single Vessel Kit).

Synthesis of 4-(1H-benzo[d]imidazol-2-yl)morpholine (2)

3.3 mmol of morpholine was added to 3.03 mmol of 2-cholorobenzimidazole in 5mL of DMSO and 1mL of pyridine. The mixture was heated in sand bath for 12h (TLC monitoring). After cooling, the crude product poured on acidified water then filtered, washed with EtOH/H_2O to get crude product.

Compound **2** was separated as dark brown solid. (0.4 g, 60%); mp107-109 ^oC (EtOH); ^1H NMR (500 MHz, DMSO): δ = 3.63-3.67 (m, 2H, morpholine CH_2), 3.76-3.80 (m, 4H, morpholine $2CH_2$), 3.85-3.89 (m, 2H, morpholine CH_2), 7.81 (d, J = 5.2 Hz, 2H, $CH_{arom.}$), 7.92 (d, J = 6.7 Hz, 2H, CH_{arom}), 8.3 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (125 MHz, DMSO): δ = 163.9, 139.1, 138.1, 121.0, 120.2, 115.1, 113.1 (7 benzoimidazol C), 66.8, 49.2 (4 morpholino C); MS (m/z): M^+ 203 (25%); IR (KBr, cm^{-1}): 3125 (NH(br)), 1630 (C=N); Anal. calcd. for $C_{11}H_{13}N_3O$ (203.25): C, 65.01; H, 6.45; N, 20.68; Found: C, 65.15; H, 6.29; N, 20.51.

Synthesis of 2-(2-Morpholino-1H-benzo[d]imidazol-1-yl)acetonitrile (3)

In 10mL acetone, 3.3 mmol of Chloroacetonitrile was added to 3.3 mmol of compound 2 then anhydrous potassium carbonate (3.3 mmol) in acetone (15mL) was added and the mixture was refluxed for 10h (TLC monitoring). The reaction was poured onto ice water to get a precipitate, filtered, dried the recrystallized to obtain compound **3**.

Product **3** was separated as yellow crystals, (0.49 g, 62 %); mp148-150 ^oC (EtOH); ^1H NMR (500 MHz, DMSO): δ = 3.65-3.69 (m, 2H, morpholine CH_2), 3.76-3.80 (m, 4H, morpholine $2CH_2$), 3.96-4.00 (m, 2H, morpholine CH_2), 4.85 (s, 1H, $CH_2{}^b$), 5.54 (s, 1H, $CH_2{}^a$), 7.20 (d, J = 4.3 Hz, 2H, CH_{arom}),7.52 (d, J = 6.6 Hz, 2H, CH_{arom}); ^{13}C-NMR: (125 MHz, DMSO) δ = 163.66, 141.75, 132.35, 123.06, 120.81, 119.24, 108.38 (7 benzoimidazol C), 158.01 (C=NH), 65.78, 49.77 (4 morpholino C), 39.2 (CH_2-N); MS (m/z): M^+ 242 (25%); IR (KBr, cm^{-1}): 2190 (CN), 1663 (C=NH); Anal. calcd. for $C_{13}H_{14}N_4O$ (242.28): C, 64.45; H, 5.82; N, 23.13; Found: C, 64.61; H, 5.64; N, 22.97.

Synthesis of 2-(2-Morpholino-1H-benzo[d]imidazol-1-yl)acetimidohydrazide (4)

0.01 mol of hydrazine hydrate was added dropwise to 0.01 mol of compound **3** in 20 mL methanol. The reaction mixture was refluxed for 6h, then cooling to obtain the crude product of compound **4** which then filtrate, wash with EtOH/H_2O mixture.

Product **4** was separated as yellow crystals (0.58 g, 65 %). mp198-200 ^oC (EtOH); ^1H NMR (500 MHz, DMSO): δ = 3.67-3.71 (m, 2H, morpholine CH_2), 3.73-3.81 (m, 2H, morpholine CH_2), 3.91-4.00 (m, 4H, morpholine $2CH_2$), 4.59 (br (s), 2H, NH_2), 5.95 (s, 1H, $CH_2{}^b$), 5.97 (s, 1H, $CH_2{}^a$), 7.20 (d, J = 4.9 Hz, 2H, CH_{arom}), 7.57 (d, J = 6.7 Hz, 2H, $CH_{arom.}$), 7.95 (br (s), 1H, NH), 12.00 (br, 1H, NH, D_2O exchangeable); ^{13}C-NMR: (125 MHz, DMSO); δ = 160.39, 140.49, 134.41, 123.02, 122.47, 119.50, 109.54 (7 benzoimidazol C), 159.42 (C=NH), 65.78, 49.77 (4 morpholino C), 49.36 (CH_2-N). IR (KBr, cm^{-1}): 3355, 3330 (NH, NH_2), 1661 (C=N). MS (m/z): M^+ 274 (25%); Anal. calcd. for $C_{13}H_{18}N_6O$ (274.33): C, 56.92; H, 6.61; N, 30.64; Found: C, 57.11; H, 6.44; N, 30.49.

Synthesis of 5-((2-Morpholino-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazole-2(3H)-thione (5)

Carbon disulfide (6 mmol) was added to ice cold solution of compound **4** (3.3mmol) and 3.3 mmol of KOH in 15mL ethanol, then the mixture was stirred at r.t. for 3h then refluxed for 11h (TLC monitoring). The mixture was cooled, acidified with conc. HCl (1mL) to get the crude product which filtered, washed with water, dried and crystallized.

Product **5** was separated as brown crystals, (0.78 g, 71%). mp 215-217 ^oC (acetone); ^1H NMR (500 MHz, DMSO): δ 3.58-3.62 (m, 2H, morpholine CH_2), 3.77-3.81 (m, 4H, morpholine $2CH_2$), 4.21-4.25 (m, 2H, morpholine CH_2), 5.56 (s, 1H, $CH_2{}^b$), 6.09 (s, 1H, $CH_2{}^a$), 7.26 (d, J = 8.2 Hz, 2H, CH_{arom}), 7.55 (s, 1H, CH_{arom}), 7.71 (s, 1H, CH_{arom}), 12.00 (br, 1H, NH, exchangeable with D_2O); ^{13}C NMR (125 MHz, DMSO): δ = 193.87 (C=S), 161.28, 141.04, 136.50, 122.48, 118.95, 110.09 (7 benzoimidazol C), 156.26 (thiadiazole C=N), 65.78, 49.77 (4 morpholino C); 50.43(CH_2-N); IR (KBr, cm^{-1}): 3180 (NH), 1650, 1630 (2C=N), 1210 (C=S); MS (m/z): M^+ 333 (35%); Anal. calcd. for $C_{14}H_{15}N_5OS_2$ (333.43): C, 50.43; H, 4.53; N, 21.00; Found: C, 50.57; H, 4.35; N, 20.84.

Synthesis of ethyl 2-((5-((2-morpholino-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)thio)acetate (6)

A suspension of compound **5** (3.3 mmol) and anhydrous potassium carbonate (3.3mmol) in dry acetone (20mL) was stirred at r.t. for 1h followed by addition of ethyl bromoacetate (3.3mmol). The reaction mixture was refluxed for 7h. After cooling with ice water (10mL), the precipitate product was filtered, dried and crystallized.

Product **6** was separated as yellow crystals, (0.89 g, 65%). mp 168-170 ^oC (EtOH); ^1H NMR (500 MHz, DMSO): δ 1.06 (t, 3H, CH_3), 3.49-3.53 (m, 2H,

morpholine CH_2), 3.76-3.80 (m, 4H, morpholine $2CH_2$), 3.95-3.99 (m, 2H, morpholine CH_2), 4.20 (s, 2H, S-CH_2), 4.21-4.25 (q, 2H, CH_2), 5.72 (s, 1H, CH_2^b), 5.93 (s, 1H, CH_2^a), 7.28 (d, J = 7.4 Hz, 2H, CH_{arom}), 7.57 (s, 1H, CH_{arom}), 7.61 (s, 1H, CH_{arom}); ^{13}C NMR (125 MHz, DMSO): δ = 168.6, 165.5 (2 thiadiazole C=N); 165.1 (C=O), 161.2, 141.0, 135.6, 122.4, 120.5, 118.9, 107.6 (7 benzoimidazol C), 65.7, 49.7 (4 morpholino C), 61.6 (OCH_2-CH_3), 48.0 (CH_2-N), 30.80 (CH_2-S), 13.96 (O-CH_2-CH_3). IR (KBr, cm^{-1}): 1740 (C=O), 1630, 1620 (2 C=N); MS (m/z): M^+ 419 (21%); Anal. calcd. for $C_{18}H_{21}N_5O_3S_2$ (419.52): C, 51.53; H, 5.05; N, 16.69; Found: C, 51.36; H, 4.86; N, 16.83.

Synthesis of 2-((5-((2-Morpholino-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)thio)acetohydrazide (7)

A solution of compound **6** (3.3 mmol) and hydrazine hydrate (6 mmol) in methanol (20mL) was refluxed for 8h, cool, and excess solvent evaporate under vacuum and the crude product was separated by filtration, and the crystallized product **7** was separated as buff crystals (0.79 g, 60%); mp116-118ºC (EtOH). ^{1}H NMR (500 MHz, DMSO): δ = 3.68-3.72 (m, 2H, morpholine CH_2), 3.76-3.80 (m, 4H, morpholine $2CH_2$), 3.81-3.85 (m, 2H, CH_2), 3.95- 3.99 (m, 2H, morpholine CH_2), 4.20 (s, 2H, S-CH_2), 4.60 (br (s), 2H, NH_2), 4.99 (s, 1H, CH_2^b), 5.47 (br(s), 1H, NH, exchangeable with D_2O), 6.04 (s, 1H, CH_2^a), 7.22-7.30 (m, 2H, CH_{arom}), 7.57 (s, 1H, CH_{arom}), 7.61 (s, 1H, CH_{arom}). ^{13}C NMR (125 MHz, DMSO): δ= 170.7 (C=O), 168.6, 164.9 (2 thiadiazole C=N), 161.2, 141.0, 135.6, 122.4, 120.5, 118.9, 107.6 (7 benzoimidazol C); 65.7, 49.7 (4 morpholino C), 48.0 (CH_2-N); 31.5 (CH_2-S); MS (m/z): M^+ 405 (25%); IR (KBr, cm^{-1}): 3481, 3268 (NH, NH_2), 1750 (C=O), 1630, 1570 (C=N); Anal. calcd. for $C_{16}H_{19}N_7O_2S_2$ (405.50): C, 47.39; H, 4.72; N, 24.18. Found: C, 47.58; H, 4.55; N, 24.02.

Synthesis of (E)-2-((2-morpholino-1H-benzo[d]imidazol-1-yl)methylene)thiazolidin-4-one (8)

Thioglycolic acid (3.3 mmol) was added dropwise to a solution of compound **3** (3.3 mmol) in 10mL absolute ethanol and glacial acetic acid (3mL). The mixture was stirred under reflux for 6h, then poured onto ice water to get precipitate which collected by filtration, washed several times with cooled water, dried, and crystallized.

Product **8** was separated as brown crystals, (0.65 g, 63%). mp >270 ºC (ethanol). ^{1}H NMR (500 MHz, DMSO): δ = 3.45-3.49 (m, 4H, morpholine $2CH_2$), 3.76-3.84 (m, 4H, morpholine $2CH_2$), 4.05-4.09 (m, 2H, cyclic CH_2), 5.74 (s, 1H, CH), 7.23 (d, J = 7.2 Hz, 2H, CH_{arom}), 7.62 (d, J = 1.6 Hz, 2H, CH_{arom}), 8.10 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO): δ = 174.0 (C=O); 158.5, 143.4, 127.6, 122.6, 122.1, 116.8, 112.5 (7 benzoimidazol C), 133.9, 31.5 (2 thiazole C), 115.1 (exocyclic C=C of thiazole), 65.7, 49.7 (4 morpholino C). MS (m/z): M^+ 316 (25%); IR (KBr, cm^{-1}): 3280 (NH), 1645 (C=O), 1660 (C=N); Anal. calcd. for $C_{15}H_{16}N_4O_2S$ (316.38): C, 56.95; H, 5.10; N, 17.71; Found: C, 57.09; H, 4.92; N, 17.54.

Synthesis of 2-(2-morpholino-1H-benzo[d]imidazol-1-yl)acetamide (9)

Piperidine (3.3 mmol) was added dropwise to a solution of compound **3** (3.3mmol) in ethanol (20mL). The mixture was stirred under reflux for 11h, then poured onto ice water to collect a precipitate by filtration.

Product **9** was separated as brown crystals, (0.57 g, 67%); mp 88-90 ºC (EtOH). ^{1}H NMR (500 MHz, DMSO): δ = 3.51-3.81 (m, 8H, morpholine CH_2), 5.31-5.35 (m, 2H, CH_2), 7.10 (br (s), 2H, NH_2), 7.38 (d, J = 8.7 Hz, 2H, $CH_{arom.}$), 7.92 (d, J = 17.6 Hz, 2H, $CH_{arom.}$); ^{13}C NMR (125 MHz, DMSO): δ = 170.6 (C=O), 161.1, 141.1, 134.1, 121.3, 120.6, 119.0, 107.8 (7 benzoimidazol C), 65.7, 49.7 (4 morpholino C), 51.8 (CH_2-N); MS (m/z): M^+ 260 (15%); IR (KBr, cm^{-1}): 3357 (NH_2), 1681 (C=O), 1665 (C=N); Anal. calcd. for $C_{13}H_{16}N_4O_2$ (260.30): Calced., C, 59.99; H, 6.20, N, 21.52; Found: C, 60.16; H, 6.01; N, 21.37.

General procedures for preparation of compounds 10a,b

3.3 mmol of benzaldehyde or 2-chlorobenzaldehyde was added to a solution of 3.3 mmol of compound **8** in 10% NaOH solution (8mL) and 20mL ethanol. The mixture was stirred at r.t. for 6h, then kept overnight at r.t. to get a precipitate which was collected by filtration and crystallized from ethanol to afford **10a,b**.

Synthesis of 2-(2-Morpholino-1H-benzo[d]imidazol-1-yl)-3-phenylacrylamide (10a)

Product **10a** was separated as brown crystals, (0.81 g, 71%); mp 241-243 ºC (EtOH). ^{1}H NMR (500 MHz, DMSO): δ = 3.76-3.82 (m, 8H, morpholine CH_2), 7.15-7.26 (m, 5H, $CH_{arom.}$), 7.32-7.36 (m, 2H,$CH_{arom.}$), 7.46 (s, 2H, NH_2), 7.79-7.83 (m, 2H,$CH_{arom.}$), 7.99 (s, 1H, CH);^{13}C NMR (125 MHz, DMSO): δ= 171.9 (C=O), 155.3, 143.6, 133.2, 122.6, 120.7, 117.1, 109.4 (7 benzoimidazol C), 135.0, 130.5, 129.67, 129.1, 127.8, 125.8 (6 benzene C), 135.0, 109.1 (C=C), 65.7, 49.7 (4 morpholino C); MS (m/z): M^+ 348 (19%); IR (KBr, cm^{-1}): 3325 (NH_2), 1685 (C=O), 1660 (C=N); Anal. calcd. for $C_{20}H_{20}N_4O_2$ (348.41): C, 68.95; H, 5.79; N, 16.08; Found: C, 69.11; H, 5.59; N, 15.92.

Synthesis of 3-(2-Chlorophenyl)-2-(2-morpholino-1H-benzo[d]imidazol-1-yl)acrylamide (10b)

Product **10b** was separated as pale yellow crystals, (0.85 g, 68%); mp>270 ºC (EtOH); ^{1}H NMR (500 MHz, DMSO): δ = 3.76-3.82 (m, 8H, morpholine CH_2), 7.15-7.24 (m, 4H, CH_{arom}), 7.32-7.36 (m, 2H, CH_{arom}), 7.46 (s, 2H, NH_2), 7.79-7.83 (m, 2H,CH_{arom}), 7.99 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO): δ = 170.8 (C=O), 155.3, 143.6, 133.2, 122.6, 120.7, 117.1, 109.4 (7 benzoimidazol C), 134.0, 130.1, 129.67, 129.2, 127.9, 125.7 (6 benzene C), 135.2, 109.7 (C=C), 65.7, 50.1 (4 morpholino C); MS (m/z): M^+ 382 (25%); IR (KBr, cm^{-1}): 3325 (NH_2), 1685 (C=O), 1660 (C=N); Anal. calcd. for $C_{20}H_{19}ClN_4O_2$ (382.85): C, 62.75; H, 5.00; N, 14.63; Found: C, 62.56; H, 4.88; N, 14.50.

General procedure for the synthesis of imidazolyl-phosphonates 12a-e

A solution of imidazole **1** (0.5 g, 3.3 mmol) and the phosphonyl carbanion (3.5 mmol) [methyl diethyl- or triethyl phosphonoacetate, diethyl-cyanomethyl phosphonate, -methyl thio methyl phosphonate, -ethyl thio methyl phosphonate], **11a-e** was placed with a magnetic stirring bar a microwave quartz vessel in the addition of a few drops of TEA in 10 mL of DMF. The reaction mixture was heated in the microwave reactor at 100 ºC for the appropriate time (40–50 min) at 180 Watt. After the completion of the reaction, the produced mixture was cooled, poured into ice-water, and acidified with HCl (1mol L^{-1}) to pH ≈ 5, followed by extraction with ethyl acetate (3×50 mL). The organic phase was dried over anhydrous sodium sulfate and subsequently filtered and concentrated to afford the corresponding products **12a-e** and recrystallized from a suitable solvent.

Methyl 2-(1H-benzo[d]imidazol-2-yl)-2-(diethoxyphosphoryl)acetate (12a) was obtained as a yellow solid (0.86 g, 81%); mp 210-212 °C (EtOH); ^{1}H NMR (500 MHz, DMSO): δ = 1.24 (dt, J_{HH} = 6.7 Hz, J_{PH} = 3.2 Hz, 6H, 2*H*$_3$CCOP), 3.8 (s, 3H, *H*$_3$CO), 4.25 (dq, J_{HH} = 6.7 Hz, J_{PH} = 5.4 Hz, 4H, 2*H*$_2$COP), 5.23 (d, J_{PH} = 23.5 Hz, 1H, *H*C-P), 7.16, 7.74 (2d, 4H, *H*-Ar), 10. 2 (s, 1H, N*H*); ^{13}C NMR (125 MHz, DMSO): δ = 165.8 (C=O), 162.6 (C-NH), 141.4, 122.5, 123.9, 116.2 (*C*-Ar), 62.6 (2*C*H$_2$OP), 53.3 (*C*H$_3$O), 43.7 (d, J_{PC} = 165.7 Hz, *C*-P), 16.2 (2*C*H$_3$COP); IR (KBr, cm^{-1}): 3460 (NH), 1752 (C=O), 1245 (P=O, bonded), 1045 (P-O-C); MS (m/z): M^+ 326 (22%). Anal. calcd. for $C_{14}H_{19}N_2O_5P$ (326.28): C, 51.53; H, 5.87; N, 8.59. Found: C, 51.65; H, 5.74; N, 8.49.

Ethyl 2-(1H-benzo[d]imidazol-2-yl)-2-(diethoxyphosphoryl)acetate (12b) was obtained as a yellow solid (0.92 g, 83%); mp 221-223 °C (EtOH); ^{1}H NMR (500 MHz, DMSO): δ = 1.21 (dt, J_{HH} = 6.3 Hz, J_{PH} = 2.8 Hz, 6H, 2*H*$_3$CCOP), 1.37 (t, J_{HH} = 7.5 Hz, 3H, *H*$_3$CCH$_2$), 4.18 (dq, J_{HH} = 6.3 Hz, J_{PH} = 4.9 Hz, 4H, 2*H*$_2$COP), 4.25 (q, J_{HH} = 7.5 Hz, 2H, *H*$_2$CO), 5.21 (d, J_{PH} = 25.1 Hz, 1H, *H*C-P), 7.15, 7.74 (2d, 4H, *H*-Ar), 10.6 (s, 1H, N*H*); ^{13}C NMR (125.7 MHz, DMSO): δ = 166.9 (C=O), 160.3 (C-NH), 140.7, 121.9, 117.6, 115.6 (*C*-Ar), 63.8 (2*C*H$_2$OP), 61.3 (*C*H$_2$O), 48.4 (d, $^1J_{PC}$ = 171.5 Hz, *C*-P), 16.8 (2*C*H$_3$COP), 13.5 (*C*H$_3$CO); IR (KBr, cm^{-1}): 3449 (NH), 1246 (P=O, bonded), 1750 (C=O), 1052 (P-O-C); MS (m/z): M^+ 340 (27%). Anal. calcd. for $C_{15}H_{21}N_2O_5P$ (340.31): C, 52.94; H, 6.22; N, 8.23. Found: C, 52.82; H, 6.09; N, 8.08.

***Diethyl (1H-benzo[d]imidazol-2-yl)(cyano) methyl-phosphonate* (12c)** was obtained as a yellow solid (0.72 g, 75%); mp 215-217 °C (EtOH); ^{1}H NMR (500 MHz, DMSO): δ = 1.22 (dt, J_{HH} = 6.5 Hz, J_{PH} = 4.3 Hz, 6H, 2*H*$_3$CCOP), 4.24 (dq, J_{HH} = 6.5 Hz, J_{PH} = 5.9 Hz, 4H, 2*H*$_2$COP), 5.26 (d, J_{PH} = 22.3 Hz, 1H, *H*C-P), 7.22, 7.84 (2d, 4H, *H*-Ar), 10.4 (s, 1H, N*H*); ^{13}C NMR (125.7 MHz, DMSO): δ = 162.3 (C-NH), 140.4, 139.5, 123.9, 117.8 (*C*-Ar), 118.9 (*C*N), 62.1 (2*C*H$_2$OP), 44.5 (d, J_{PC} = 163.6 Hz, *C*-P), 16.5 (2*C*H$_3$COP); IR (KBr, cm^{-1}): 3450 (NH), 2250 (CN), 1245 (P=O, bonded), 1050 (P-O-C); MS (m/z): M^+ 293 (19%). Anal. calcd. for $C_{13}H_{16}N_3O_3P$ (293.26): C, 53.24; H, 5.50; N, 14.33. Found: C, 53.41; H, 5.37; N, 14.24.

Diethyl (1H-benzo[d]imidazol-2-yl)(methylthio) methylphosphonate (12d) was obtained as a pale yellow solid (0.80 g, 78%); mp 243-245 °C (EtOH); ^{1}H NMR (500 MHz, DMSO): δ = 1.21 (dt, J_{HH} = 6.9 Hz, J_{PH} = 2.9 Hz, 6H, 2*H*$_3$CCOP), 2.17 (d, J_{PH} = 4.4, 3H, *H*$_3$C-S), 4.13 (dq, J_{HH} = 6.9 Hz, J_{PH} = 5.4 Hz, 4H, 2*H*$_2$COP), 5.12 (d, J_{PH} = 27.3 Hz, 1H, *H*C-P), 7.26, 7.44 (2d, 4H, *H*-Ar), 10.54 (s, 1H, N*H*); ^{13}C NMR (125.7 MHz, DMSO): δ = 156.6 (C-NH), 140.4, 136.5, 122.5, 123.9, 119.2 (*C*-Ar), 63.6 (2*C*H$_2$OP), 34.9 (d, $^1J_{PC}$ = 156.3 Hz, *C*-P), 17.7 (*C*H$_3$-S), 16.1 (2*C*H$_3$COP); IR (KBr, cm^{-1}): 3465 (NH), 1245 (P=O, bonded), 1053 (P-O-C); MS (m/z): M^+ 314 (23%). Anal. calcd. for $C_{13}H_{19}N_2O_3PS$ (314.34): C, 49.67; H, 6.09; N, 8.91. Found: C, 49.83; H, 5.92; N, 8.75.

Diethyl (1H-benzo[d]imidazol-2-yl)(ethylthio) methyl-phosphonate (12e) was obtained as a pale yellow solid (0.81 g, 76%); mp 249-251 °C (EtOH); ^{1}H NMR (500 MHz, DMSO): δ = 1.17 (t, J_{HH} = 6.4 Hz, 3H, *H*$_3$CCS), 1.23 (dt, J_{HH} = 7.3 Hz, J_{PH} = 3.1 Hz, 6H, 2*H*$_3$CCOP), 2.46 (q, J_{HH} = 6.4 Hz, 2H, *H*$_2$CS), 4.18 (dq, J_{HH} = 7.3 Hz, J_{PH} = 5.2 Hz, 4H, 2*H*$_2$COP), 5.16 (d, J_{PH} = 23.1 Hz, 1H, *H*C-P), 7.28, 7.34 (2d, 4H, *H*-Ar), 10.51 (s, 1H, N*H*); ^{13}C NMR (125.7 MHz, DMSO): δ = 155.9 (C-NH), 140.1, 136.9, 123.5, 118.9 (*C*-Ar), 62.9 (2*C*H$_2$OP), 61.9 (d, J_{PC} = 149.5 Hz, *C*-P), 25.5 (*C*H$_2$S), 16.5 (2*C*H$_3$COP), 14.6 (*C*H$_3$CH$_2$S); IR (KBr, cm^{-1}): 3462 (NH), 1243 (P=O,

bonded), 1053 (P-O-C); MS (m/z): M^+ 328 (25%). Anal. calcd. for $C_{14}H_{21}N_2O_3PS$ (328.37): C, 51.21; H, 6.45; N, 8.53. Found: C, 51.39; H, 6.28; N, 8.34.

4.3. General procedure for the synthesis of imidazolylphosphonates 14a-c:

A stirred mixture of imidazole **1** (0.5 g, 3.3 mmol), and trimethyl (**13a**), triethyl (**13b**) or triisopropyl phosphite (**13c**) (3.8 mmol) in 10 mL dimethyl sulfoxide (DMSO) containing 10% $FeCl_3$ was placed in a microwave quartz vessel, with a magnetic stirring bar. The reaction mixture was heated in the microwave reactor at 100 ºC for the appropriate time (55–60 min) at 180 Watt. After completion of the reaction (TLC), 10 mL AcOEt was added to the mixture. The organic phase was separated, washed with 20 mL distilled water, and dried over anhydrous sodium sulfate. Solvents were evaporated under vacuum, and the residue was crystallized from a proper solvent to give the known compounds **14a–c**. Products **14a-c** were equally obtained, in almost the same yields, when dimethyl (**15a**), diethyl (**15b**) or diisopropyl phosphite (**15c**) replaced the trialkyl phosphite counterpart in the above reactions.

Dimethyl 1H-benzo[d]imidazol-2-ylphosphonate **(15a)** was obtained as a pale yellow solid (0.75 g, 64%); mp 202-204 °C (lit 200 °C) (EtOH) [24].

Diethyl 1H-benzo[d]imidazol-2-ylphosphonate (**15b**) was obtained as a yellow solid (0.81 g, 76%); mp 275-277 °C (lit 283 °C) (EtOH) [25].

Diisopropyl 1H-benzo[d]imidazol-2-ylphosphonate **(15c)** was obtained as a yellow solid (0.78 g, 72%); mp 139-141 °C (lit 134-136 °C) (EtOH) [26].

Synthesis of 17a,b by reaction of *benzimidazole* 1 with hexaalkyltriamidophosphites:

Hexalkylphosphorustriamide (4.2 mmol) in 5 mL EtOH was added dropwise to 0.5 g of imidazole **1** (3.3 mmol) in 10 mL EtOH. The reaction mixture was refluxed for 2h (TLC). The precipitate was collected and washed several times with light petroleum (40–60 °C) and crystallized from a proper solvent to give compounds **17a,b**.

p-1H-benzimidazol-2-yl-N,N,N',N'-tetramethy lphosphonic diamide (17a) was obtained as a greenish solid (0.64 g, 78%); mp 224-226 °C (EtOH); ^{1}H NMR (500 MHz, DMSO): δ = 2.42 (d, 6H, J_{PH} = 10.4 Hz, 2H_3CNP), 2.73 (d, 6H, J_{PH} = 10.7 Hz, 2H_3CNP), 7.34-7.51 (m, 4H, *H*-Ar), 11.40 (s, 1H, N*H*); ^{13}C NMR (125.7 MHz, DMSO): δ = 161.5 (d, J_{PC} = 178.8 Hz, *C*-P), 143.6, 139.2, 123.8, 116.5, 114.8 (*C*-Ar), 38.8, 37.1 (4CH_3N); IR (KBr, cm^{-1}): 3440 (NH), 1241 (P=O); MS (m/z): M^+ 252 (20%). Anal. calcd. for $C_{11}H_{17}N_4OP$ (252.25): C, 52.38; H, 6.79; N, 22.21. Found: C, 52.47; H, 6.68; N, 22.11.

p-1H-benzimidazol-2-yl-N,N,N',N'-tetraethyl phosphonic diamide (**17b**) was obtained as a greenish solid (0.75 g, 75%); mp 240-242 °C (EtOH); ^{1}H NMR (500 MHz, DMSO): δ = 1.05 (dt, 6H, J_{PH} = 7.5 Hz, 2H_3CCNP), 1.14 (dt, 6H, J_{PH} = 7.5 Hz, 2H_3CNP), 2.85-2.91 (m, 8H, 4H_2CNP), 7.37-7.54 (m, 4H, *H*-Ar), 11.1 (s, 1H, N*H*); ^{13}C NMR (125.7 MHz, DMSO): δ = 167.4 (d, $^1J_{PC}$ = 176.6 Hz, *C*-P), 143.1, 139.5, 123.5, 116.1, 113.9 (*C*-Ar), 39.1, 38.4 (4CH_2N), 14.1, 13.8 (4CH_3CH_2N); IR (KBr, cm^{-1}): 3445 (NH), 1243 (P=O); MS (m/z): M^+ 308 (23%). Anal. calcd. for $C_{15}H_{25}N_4OP$ (308.36): C, 58.43; H, 8.17; N, 18.17. Found: C, 58.54; H, 8.06; N, 18.02.

Biology

Materials and Methods

Roswell Park Memorial Institute (RPMI) 1640 medium was purchased from Sigma Chem. Co. (St. Louis, MO, USA). Fetal bovine serum (FBS) and fetal calf serum (FCS) were purchased from Gibco, UK. Dimethyl sulfoxide (DMSO) and methanol were of HPLC grade and all other reagents and chemicals were of analytical reagent grade.

In vitro anticancer activity:

Cell culture

HepG-2 (Human liver carcinoma), HCT116 (human colorectal carcinoma), MCF-7 (human breast adenocarcinoma), and the normal human skin fibroblast (BJ-1) cell lines were purchased from the American Type Culture Collection (Rockville, MD, USA) and maintained in RPMI-1640 medium which was supplemented with 10% heat-inactivated FBS, 100U/ml penicillin and 100U/ml streptomycin. The cells were grown at 37°C in a humidified atmosphere of 5% CO_2. All experiments were conducted thrice in triplicate (n = 3). All the values were represented as means ± SD.

Lactate dehydrogenase (LDH) assay

To determine the effect of each synthesized compound on membrane permeability in HepG2, MCF-7 and HCT-116 cancer cell lines as well as BJ-1 normal cell line, a lactate dehydrogenase (LDH) release assay was used [29-33]. The cells were seeded in 24-well culture plates at a density of 1×10^5 cells/well in 500 µL volume and allowed to grow for 18h before treatment. After treatment with a series of different concentrations of each compound or Doxorubicin® (positive control), the plates were incubated for 48h. Then, the supernatant (40 µL) was transferred to a new 96 well to determine LDH release and 6% triton X-100 (40 µL) was added to the original plate for determination of total LDH. An aliquot of 0.1 M potassium phosphate buffer (100 µL, pH 7.5) containing 4.6 mM pyruvic acid was mixed to the supernatant using repeated pipetting. Then, 0.1 M potassium phosphate buffer (100 µL, pH 7.5)

containing 0.4 mg/mL reduced β-NADH was added to the wells. The kinetic changes were read for 1 min using ELISA microplate reader in absorbance at wavelength 340 nm. This procedure was repeated with 40 µL of the total cell lysate to determine total LDH. The percentage of LDH release was determined by dividing the LDH released into the media by the total LDH following cell lysis in the same well.

Statistical analysis

All experiments were conducted in triplicate (n = 3). All the values were represented as mean ± SD. Significant differences between the means of parameters as well as IC_{50} were determined by probit analysis using SPSS software program (SPSS Inc., Chicago, IL).

Conclusion

It was an appealing challenge in this work to synthesize novel molecules carrying Benzimidazole moiety with different side chains to obtain potent biological drugs. In addition, a series of heterocyclic phosphorus compounds were synthesized *via* the reactions with Wittig-Horner reagents, alkyl phosphites and tris(dialkylamino) phosphines. All new compounds have potential synthetic and pharmaceutical interest.

Conflicts of interest

"There are no conflicts to declare".

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