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Original article

Synthesis, characterization of some benzazoles bearing pyridine moiety: Search for novel anticancer agents

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ABSTRACT

Thirteen novel benzazole derivatives were synthesized as possible anticancer agents. The first intermediate 1,3-benzothiazol-2-ylacetonitrile (**2**) was synthesized via cyclodeamination reaction of o-aminothiophenol (**1**) with malononitrile. Also, the second intermediate 5,6-dimethyl-1*H*-benzimidazol-2-ylacetonitrile (**10**) was afforded via cyclocondensation reaction between 4,5-dimethyl-1,2-phenylenediamine (**9**) and ethylcyanoacetate. Nucleophilic reaction of benzimidazolyl NH of compound (**10**) with ethylcyanoacetate afforded benzimidazolyl-3-oxopropanenitrile (**11**). On the other hand, methylenation of CH_2 function of compound (**10**) with dimethylformamide/dimethylacetal afforded benzimidazolylprop-2-enenitrile **12**. The synthesis of benzothiazoylpyridines **5a**,**b** and **8a**,**b** as well as benzimidazolylpyridines, **14a**,**b** and **17a**–**d** was carried out through Michael addition of compounds **2** or **10** with arylidenemalononitriles **3a**,**b** and **4a**–**d**. The combination of pharmacophoric anticancer moieties, pyridine and benzazoles was the base on which target compounds **5a**,**b**, **8a**,**b**, **14a**,**b** and **17a**–**d** were designed. Among the synthesized compounds, four derivatives **10** and **17b**–**d** were selected by National Cancer Institute (NCI), USA to be screened for their anticancer activity at a single high dose (10^{-5} M) against a panel of 60 cancer cell lines. Compound **17b** 4-[*p*-chlorophenyl]pyridine and **17d** 4-[*p*-methoxyphenyl] pyridine exhibited a broad and moderate antitumor activity against **41** tumor cell lines belonging to the nine subpanels employed and are selected for further evaluation at five dose level screening.

1. Introduction

Benzimidazole derivatives have provided a large number of biologically active compounds that have been intensively used in medicinal chemistry as drugs. They are structural isosteres of naturally occurring nucleotides, which allow them to interact easily with the biopolymers of the living system and different kinds of biological activity have been obtained. Some 2-aminobenzimidazoles displayed an appreciable antimicrobial effect. Their corresponding carbamate derivatives have been synthesized for their significant in vivo antifilarial activity [1].Concerning the high affinity that they display towards a variety of enzymes and protein receptors, they could be considered as pivotal structures in drug design [2]. Optimization of benzimidazole-based structures has resulted in marketed drugs e.g. Omeprazole [3] and Pimobendan [4] that are therapeutically useful in the management of peptic ulcer and congestive heart failure respectively. Many derivatives of benzimidazoles are well known for their antimicrobial [5–9] anthelmintic [10] antiviral [11–14] and antifungal [15–19] activities. The antifungal agent *benomyl* was firstly reported as a fungicide against a wide range of agriculture fungal disease [20]. Many years later, it was proved to be a potent antiproliferative agent against Hela cancer cell line and could be used as adjuvant in cancer chemotherapy [21]. Benzimidazole derivatives containing ester groups on the benzene ring were reported for their antifungal, insecticidal and herbicidal activities [22–24]. Furthermore, many dichlorobenzimidazoles proved high potency against methicillin resistant *Staphylococcus aureus* (MRSA) [25]. Since 1985, benzimidazole containing compounds have been reported as well known anticancer agents [26–31], The role of mammalian DNA topoisomerases as molecular targets for anticancer drugs has been recognized. Some benzimidazoles have been reported as topoisomerase inhibitors e.g. *Hoechst 33258* and *Hoechst 33342* (Fig. 1) [32]. On extension of this work, head to head bis-benzimidazole compounds approved high efficacy as DNA binders [33]. Some widely used anticancer drugs such as *RAF265* (CHIR-265; Novartis Pharmaceuticals, Basel, Switzerland) and *AZD6244* (ARRY-142886;

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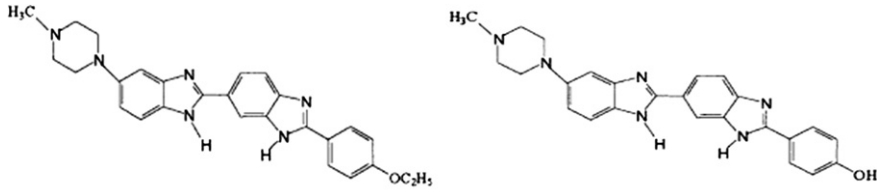


Fig. 1. Examples of topoisomerase inhibitors containing benzimidazole nucleus.

AstraZeneca, London, England) are known to contain benzimidazole moiety. *RAF265* resulted in a reduction in tumor cell growth and in tumor cell apoptosis [34]. Compound *AZD6244* suppresses the growth of melanoma cells through the induction of cytostasis [35]. 2-Arylbenzimidazole moiety has been defined as a pharmacophore for a new class of DNA intercalating agents [36]. The importance of naphthalene benzimidazole compounds as antioxidant on hepatic cytochrome has been explored since 1997 [37–39]. On the other hand, the antiviral activity of 5-chloro and 5,6-dichloro-2-substituted benzimidazole derivatives against several viruses e.g. influenza, human cytomegalovirus, hepatitis B virus.

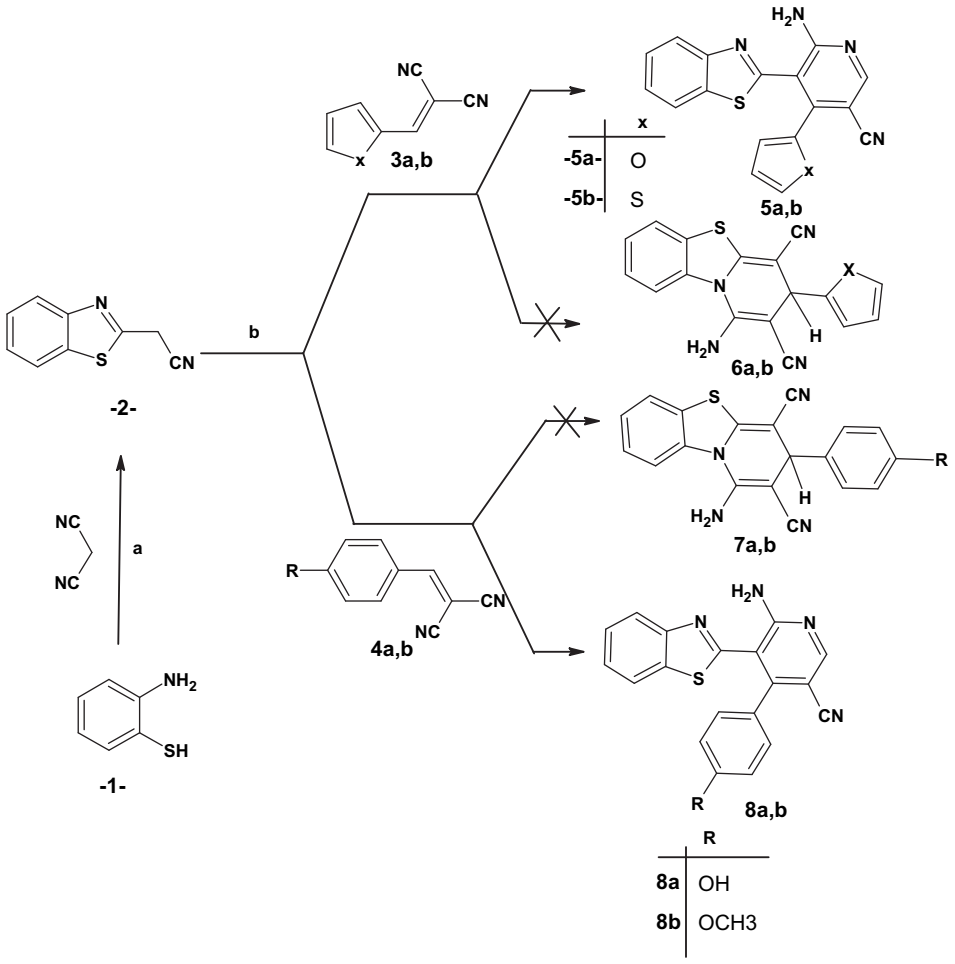
(HBV), hepatitis C virus (HCV) and human immunodeficiency retrovirus (HIV-1) was reported [40–42]. These compounds were also reported as anticancer agents against breast and prostate cancer cell lines [43] or as potential topoisomerase II inhibitors [44]. In 2010 a new series of 2-substituted benzimidazole derivatives having 5-chloro or 5-underivatized carboxylic acid group were reported to exhibit antitumor activity against hepatocellular carcinoma (HEPG2), human breast adenocarcinoma (MCF7) and human colon carcinoma (HCT 116) cell lines [45].

Further, benzothiazoles play an important role as biologically active natural products, marketed drugs or drug candidates [46–49]. Various benzothiazoles are known as industrial chemicals, dyes and drugs [50,51]. Many compounds with benzothiazole skeleton are reported to possess different therapeutic effects as anticancer, antibacterial, antifungal and anthelmintic activities [52,53]. Also, no one can ignore the role of pyridine as an appreciable pharmacophore for antimicrobial and anticancer activity [54,55]. These promising findings oriented our study to the synthesis of new compounds containing a substituted pyridine moiety directly attached to benzazole nucleus. Further, the recent study in 2010 that proved the anticancer activity of a variety of 5-chloro and 5,6-dichlorobenizimidazoles [45], prompted the author in this work to design new benzimidazole compounds substituted at 5 and 6 positions with two methyl groups aiming to get a new anticancer agents.

2. Results and discussion

2.1. Chemistry

This work focused on the synthesis of novel benzazole compounds through preparation of two key elements. The first key element, 1,3-benzothiazol-2-ylacetonitrile (**2**) was afforded via a convenient one-step cyclization reaction between o-aminothiophenol (**1**) and malononitrile at room temperature in absolute ethanol and glacial AcOH adopting the reported procedures [56,57]. Compound **2** was subjected to Michael addition with various arylidenemalononitriles **3a**,**b** and **4a**,**b** in ethanol under base catalysis adopting the reported reaction condition [58] (Scheme 1). However the reported literature [58] mentioned that the final product of the reaction was fused pyrido [1,2-b]benzothiazole-2,4-dicarbonitriles (**6a**,**b**) and (**7a**,**b**). Herein, the structure of the fused compounds **6a**,**b** and **7a**,**b** was ruled out and the corresponding isomers benzothiazolylpyridines **5a**,**b** and **8a**,**b** were considered more likely. This finding is based on The ^{1}H NMR spectra of the obtained compounds that showed no signals due to the aliphatic 3*H*-pyridobenzothiazole proton (typically *d* 3.20 ppm) [59] which excluded the possible pyridobenzothiazole structures **6a**,**b** and **7a**,**b**. On the other hand, ^{1}H NMR spectrum revealed an aromatic 2-pyridyl C*H* proton (typically δ 8.14–8.69 ppm) [59]. In continuation of this work, the second part that includes the synthesis of benzimidazolylpyridines **14a**,**b** and **17a**–**d** began with the synthesis of the key intermediate 5,6-dimethyl-1H-benzimidazol-2-ylacetonitrile (**10**). In 2007, 5-Substituted benzimidazol-2-ylacetonitrile was reported to be synthesized via heating the corresponding 1,2-phenylenediamine with ethylcyanoacetate in oil bath for 20 min [60]. Herein, 5,6-dimethyl-1*H*-benzimidazol-2-ylacetonitrile (**10**) was prepared in acceptable yield by a one pot two components solvent free reaction of 4,5-dimethyl-1,2-phenylenediamine (**9**) and ethylcyanoacetate for 2 h, using glycerol bath at 170 °C. IR spectrum of the product clearly showed the C≡N stretching at 2197 cm^{-1}, in addition to the stretching of NH function at 3240 cm^{-1}. The ^{1}H NMR spectrum exhibited D_2O-exchangeable signal of NH proton at δ 12.27 ppm, in addition to the singlet of the 5,6-dimethyl groups at δ 2.29 ppm. Also, a sharp singlet was recorded at δ 4.29 ppm assigned the proton of the methylene group linked to benzimidazole nucleus. Heating compound **10** with 1 mol equivalent of ethylcyanoacetate was carried out on-neat leading to the synthesis of benzimidazolyl-3-oxopropanenitrile **11**. So, a nucleophilic reaction was suggested between benzimidazolyl NH and CO moiety of ethylcyanoacetate with removal of 1 mol of ethanol. Spectral and elemental analyses support the proposed structure of **11**. Proton NMR spectrum exhibited two singlets at 3.82 and 3.87 ppm (two protons of each) assigned the two acetonitriles CH_2 groups (Scheme 2). Refluxing 5,6-dimethyl-1*H*-benzimidazol-2-ylacetonitrile (**10**) with equivalent amount of dimethylformamide/dimethylacetal (DMF/DMA) in dry xylene under base catalysis, afforded the corresponding enaminonitrile derivative **12**, in good yield (Scheme 2). Elemental and spectral analyses was consistent with the proposed structure of **12.** IR spectrum revealed the presence of C≡N group stretching band at 2193 cm^{-1}. Also, ^{1}H NMR showed a singlet at 3.24 ppm for the protons of dimethylamino group, together with a singlet at 7.88 ppm for the proton of ethenyl group. MS spectrum proved that the base peak was the molecular ion peak appeared at 240*m/z*. In 1993 fused pyridobenzimidazole-2,4-dicarbonitriles were reported as the final products of the reaction that was carried out between benzimidazol-2-ylacetonitrile and different arylidenemalononitriles [61]. On the other hand, Kovalenko et al in 1998 [62] reported a condensation reaction of benzimidazol-2-ylacetonitrile with salisaldehyde derivatives under base catalysis condition to yield benzimidazolyl-2-iminocoumarines. Later on, in 2006 Samia Rida et al. [63] unexpectedly synthesized the fused pyrido [1,2-a]benzimidazole-4-carbonitriles rather than the corresponding benzimidazol-2-ylpyridines, when a mixture of appropriate acetophenones, p-chlorobenzaldehyde and ammonium acetate was refluxed with



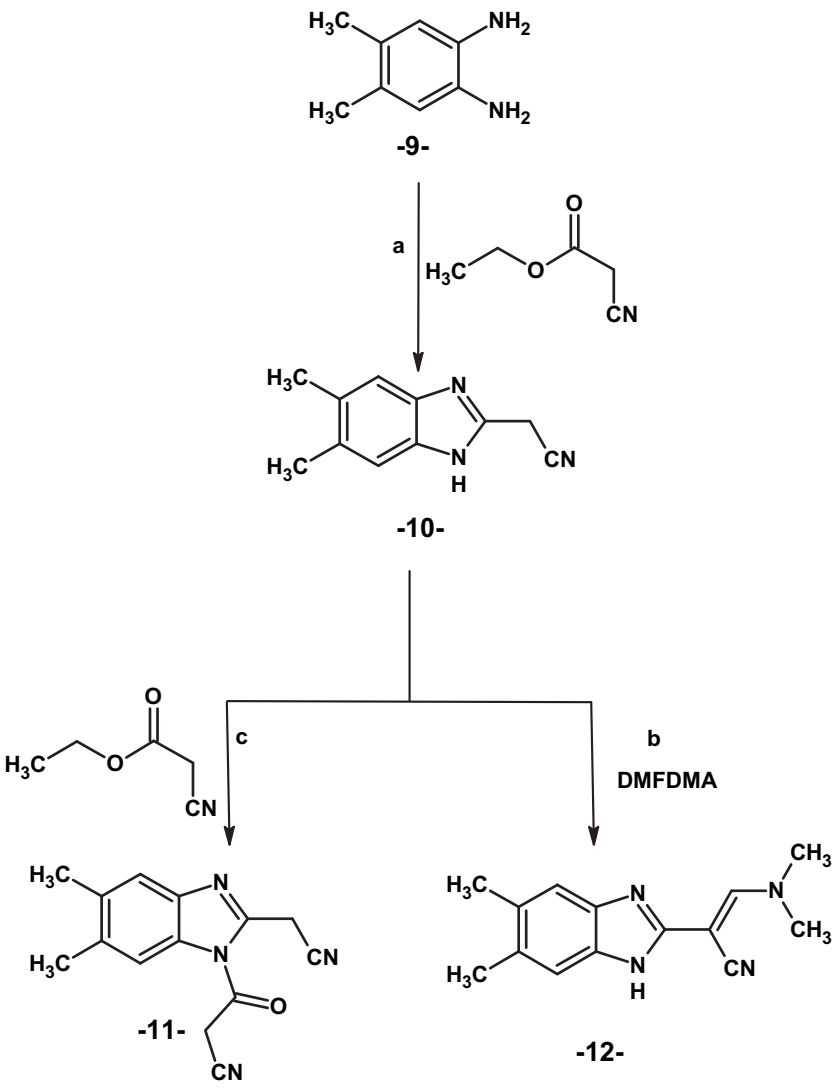
Scheme 1. Reagents and conditions: (a) absolute ethanol, AcOH (b) absolute ethanol, piperidine.

benzimidazol-2-ylacetonitrile in ethanol. In this study, the reaction of 5,6-dimethyl-1H-benzimidazol-2-ylacetonitrile (**10**) with arylidenemalononitriles **3a**,**b** and **4a**–**d** was performed under similar reaction condition, used for the synthesis of compounds **5a**,**b** and **8a**,**b** to afford in each case only one isolable product as examined by TLC. The ethanolic reflux continued until the starting substrate **10** was completely consumed resulting in the formation of the target products benzimidazol-2-ylpyridines **14a**,**b** and **17a**–**d** that separated while hot from the reaction medium (Schemes 3 and 4). Fused benzimidazoles **15a**,**b** and **18a**–**d** could be also considered as final products. Their synthesis was assumed to proceed via nucleophilic attack of benzimidazolyl NH function on C≡N group of the non-isolable intermediates **13a**,**b** and **16a**–**d**. However, The structure of benzimidazolylpyridines **14a**,**b** and **17a**–**d** was preferred based on their spectral analyses. IR spectrum revealed C≡N stretching at range of 2236–2200 cm^{-1}. In addition NH stretching was confirmed in IR spectra at a range of 3407–3467 cm^{-1} with concomitant appearance of bands corresponding to NH_2 function at a range of 3250–3368 cm^{-1}. Also, ^1H NMR of the obtained compounds showed characteristic signals due to aromatic 2-pyridyl *CH* proton (typically at a range of *d* 8.08–8.46 ppm). The elemental analyses and mass spectra also support the assigned structures of benzimidazol-2-ylpyridines **14a**,**b** and **17a**–**d** rather than fused pyridobenzimidazole-2,4-dicarbonitriles **15a**,**b** and **18a**–**d**. For example mass spectrum (*m/z* 339) of the reaction product **17a** was compatible with the molecular formula $C_{21}H_{17}N_5$ of 6-amino-5-(5,6-dimethyl-1*H*-benzimidazol-2-yl)-4-phenylpyridine-3-carbonitrile (**17a**) but not with the corresponding fused pyridobenzimidazole **18a** having the molecular formula $C_{21}H_{15}N_5$. These mass spectral features are also recorded for compounds **14a**,**b** and **17b**–**d**.

As illustrated in Scheme 5, the formation of benzazolylpyridines **5a**,**b**, **8a**,**b**, **14a**,**b** and **17a**–**d** was assumed to occur via Michael addition between the carbanion radical of compounds **2** or **10** (which generated under base catalysis) to the double bond of arylidenemalononitriles **3a**,**b** and **4a**–**d** to give the non-isolable Micheal adduct **I**. Next, intramolecular cyclization of **I** occurred through the nucleophilic attack of the imine group onto C≡N moiety to give intermediate **II**. Finally ring rearrangement of **II** via 1,3-migration of 2 hydrogen atoms should lead to benzazolylpyridines **5a**,**b**, **8a**,**b**, **14a**,**b** and **17a**–**d**.

2.1.1. Mass spectroscopy

The mass spectrum decomposition modes of compound **17a** has been suggested and investigated. The molecule of *m/z* 339 fragmented as illustrated in Scheme 6 via different pathways as representative example. Fragmentation of the molecule afforded different peaks ranged from moderate to high intensity. Compound **17a**, *m/z* 339 could be fragmented into two molecular ion peaks, one possesses *m/z* 145 representing dimehtylbenzimidazole moiety and the second one possesses *m/z* 194 representing phenylpyridine moiety. Both molecular ion peaks afforded further fragmentations that led to ions of *m/z* 115, *m/z* 117 and *m/z* 91 respectively. Other fragmentations could be afforded through loosing hydrogen radical, phenyl cation, ammonia or ethane molecules as outlined in



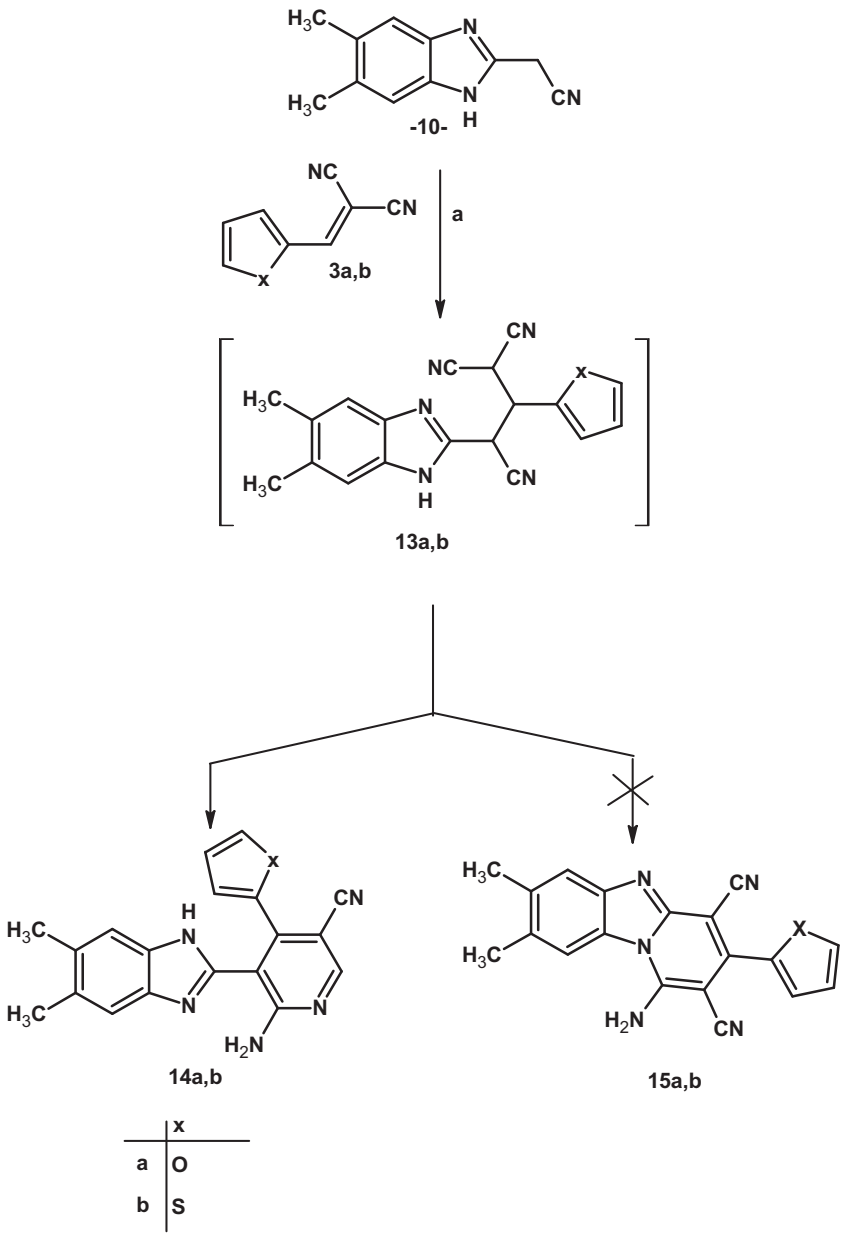
Scheme 2. Reagents and conditions: (a) glycerol bath, 170 °C, 2 h, 36% (for solvent free); (b) dry xylene; (c) glycerol bath, 170 °C, 1h.

Scheme 6. From the foregoing results it can be concluded that benzazol-2-ylpyridines **5a**,**b**, **8a**,**b**, **14a**,**b** and **17a**–**d** are the final products of Micheal addition of the active methylene of benzazole acetonitriles **2** and **10** to arylidenemalononitriles **3a**,**b** and **4a**–**d** as outlined in schemes 1,3 and 4.

2.2. Anticancer activity

Compounds **10**, **17b**–**d** were selected by National Cancer Institute (NCI) to be evaluated for their in-vitro antitumor activity. They are evaluated at a single dose assay (10^{-5} M) on a panel of 60 human cell lines. The cancer cell lines are derived from nine cancer types: Leukemia, Non-Small Cell Lung Cancer, Colon Cancer, CNS Cancer, Melanoma, Ovarian Cancer, Renal Cancer, Prostate Cancer and Breast Cancer. Compounds that satisfy pre-determined threshold inhibition criteria would progress to the five dose screen. Selected compounds are tested again in all 60 cell lines in 5× 10 fold dilutions with the top dose being10^{-4} M ending with 10^{-8} M. The data were reported as a mean graph of the percent growth of treated cells and presented as percentage growth inhibition (GI%) caused by the test compounds. Anticancer assay was performed in accordance with the protocol of the Drug Evaluatiotion Branch, National Cancer Institute, Bethesda [64–66].

Compounds **10** and **17c** produced a little antitumor activity at single dose assay (10^{-5} M). Almost all cell lines showed weak sensitivity towards both of them with the only exception of Renal cancer cell line (UO-31) which exhibited appreciable sensitivity towards compound **17c** (GI 33.40%). On the other hand, most of the tested cancer cell lines exhibited reliable sensitivity towards compounds **17b** and **17d**. They were selected to five dose assay and the response parameters for both were calculated e.g. $\log_{10}GI_{50}$ ($\log_{10}$ of molar sample concentration resulting in 50% growth inhibition), $\log_{10}TGI$ ($\log_{10}$ of molar sample concentration resulting in total growth inhibition, cytostatic activity) and LC50 (median lethal concentration, cytotoxic activity) Table 1. Both compounds **17b** and **17d** displayed limited activity against Leukemia cell lines with GI50 values ranged from 5.55 μM to a value higher than 100 μM. Non-Small Cell Lung Cancer subpanel exhibited variable sensitivity profiles, HOP-92 was the most sensitive line for both **17b** and **17d** with GI50 values of 0.275 and 2.65 μM respectively. Regarding Colon Cancer, Compound **17b** exhibited GI50 value of 3.47 μM against HCT-116 while KM12 was the most sensitive line towards **17d** (GI50 4.79 μM) in this subpanel. SF-539 and SNB-75 belonging to CNS Cancer were the most sensitive lines for **17b** and **17d** respectively (GI50 2.07 and 2.36 μM). Compound **17d** displayed more pronounced activity than **17b** against Melanoma Cancer as MDA-



Scheme 3. Reagents and conditions: (a) absolute ethanol, piperidine.

MB-435 and SK-MEL-2 cell lines were relatively the most sensitive lines for **17d** (GI50 1.95 and 1.08 μM respectively). RXF 393 cell line that belongs to Renal Cancer showed reliable sensitivity against **17b** with GI50 value of 3.18 μM, while the rest of the tested cell lines displayed a weak sensitivity for both compounds.

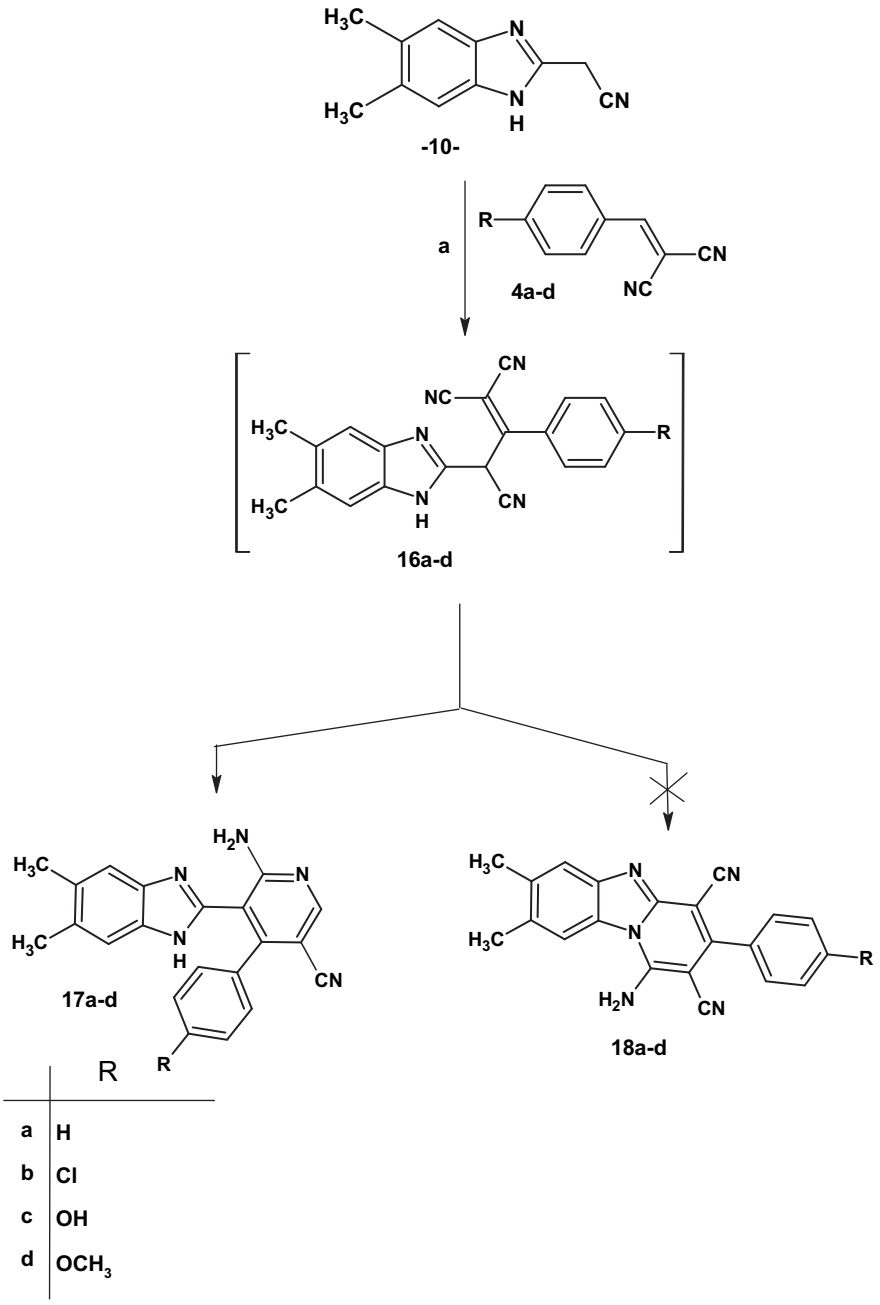
2.3. Structural activity relationship

Four benzimidazole derivatives **10** and **17b–d** were selected to be evaluated for their antitumor activity against 60 human cancer cell lines. Compounds **17b** (p-chlorophenyl at pyridine-C4) and **17d** (p-methoxyphenyl at pyridine- C4) were significantly more effective than the parent benzimidazolylacetonitrile **10** and the compound **17c** (p-hydroxyphenyl at pyridine- C4). The synergistic action was not achieved via introduction of p-hydroxyphenylpyridine moiety to the parent compound **10** as both compounds **10** and **17c** did not show a pronounced activity against most of cancer cell lines. On the other hand, replacement of p-hydroxy group in **17c** with p-chloro and p-methoxy groups as in compounds **17b** and **17d** respectively, significantly improve the antitumor activity. Both compounds **17b** and **17d** displayed a broad spectrum activity against 23 different human cancer cell lines belonging to the nine subpanels employed.

3. Experimental

3.1. General

Melting points were measured with a Gallenkamp apparatus (Weiss-Gallenkamp, London, UK) and are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer (Shimadzu, Tokyo, Japan). NMR spectra were determined in DMSO-d6 at 300 MHz (^{1}H NMR) and at 75 MHz (^{13}C NMR) on a Varian Mercury VX-300 NMR spectrometer (Varian Inc., Palo Alto, CA, USA). Chemical shifts are quoted in *d* and were related to that of the solvents. Mass spectra were measured on a GCMS-QP1000 EX



Scheme 4. Reagents and conditions: (a) absolute ethanol, piperidine.

spectrometer (Shimadzu) at 70 eV. Elemental analyses were carried out at the Microanalytical center of Cairo University.

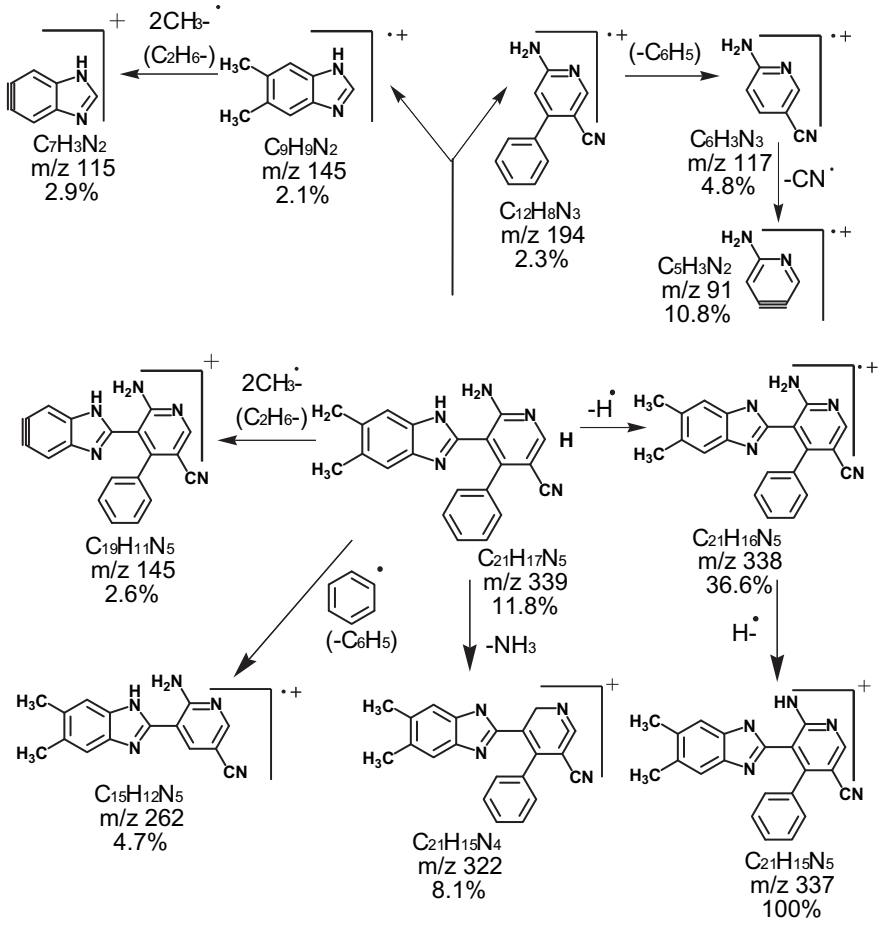
4,5–Dimethyl-1,2-phenylenediamine and dimethylformamide/dimethylacetal (DMFDMA) were obtained from Aldrich and used without further purification. Ethylcyanoacetate was obtained from Merck.

3.2. Synthesis of 1,3-benzothiazol-2-ylacetonitrile (*2*)

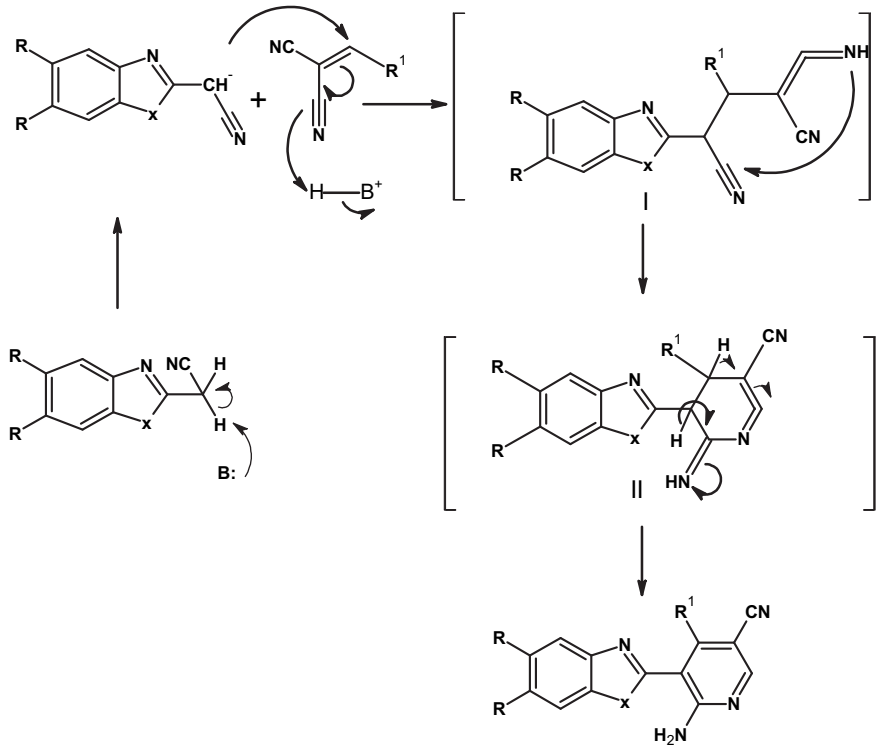
A mixture of o-aminothiophenol (**1**) (0.01 mol) and malononitrile (0.01 mol) was stirred in absolute ethanol (10 ml) and glacial AcOH (1 ml) at RT for 10 h, the precipitate was filtered and crystallized from the proper solvent. **2**: yellow powder (85%); mp 100–102 °C (EtOH) [56,57].

3.3. Synthesis of (5,6-dimethyl-1H-benzimidazol-2-yl)acetonitrile (*10*)

A mixture of 4,5-dimethyl-1,2-phenylenediamine (**9**) (0.01 mol) and ethylcyanoacetate (0.01 mol) was heated on-neat in a glycerol bath at 170 °C for 2 h, after cooling the residue was broken up and washed several times with ether. The product was then washed several times with hot ethanol and crystallized from the proper solvent. **10**: brown powder (36%); mp 208–210 °C (DMF); IR (KBr) cm^{-1} 3277 (NH), 2227 (C≡N), 1629 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 6H, 2CH_3), 4.29 (s, 2H, CH_2–CN), 7.30 (s, 2H, 4,7 benzimidazole *H*), 12.27 (1H, D_2O-exchangeable NH); MS *m/z* (%) 186 (M^{+1}, 18.8), 185 (M^+, 100), 170 (99.2), 145 (4.0). Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.98; N, 22.69. Found: C, 70.83; H, 6.09; N, 22.49.



Scheme 5. Mass fragmentation pattern of compound **17a**.



Scheme 6. Proposed mechanism of the reaction leading to compounds **5a,b, 8a,b, 14a,b, 17a-d; R=H, CH_3; X=S, NH; R^1=Aryl**.

Table 1
NCI DTP in-vitro testing results of compounds**17b** and **17d** at five dose assay.

Panel	Cell Line	**17b** values (*u*M)			**17d** values (*u*M)		
		GI50	TGI	LC50	GI50	TGI	LC50
Leukemia	CCRF-CEM	24.6	>100	>100	25.6	>100	>100
	K-562	31.5	>100	>100	6.03	>100	>100
	MOLT-4	100	>100	>100	>100	>100	>100
	RPMI-8226	5.55	>100	>100	32.5	>100	>100
	SR	28.7	>100	>100	5.64	>100	>100
Non-Small Cell Lung Cancer	A549/ATCC	4.17	24.9	>100	6.54	72.5	>100
	EKVX	14.4	76.7	>100	15.8	>100	>100
	HOP-92	0.275	5.23	44.2	2.65	16.3	>100
	HOP-62	6.36	21.7	55.9	3.65	14.4	45.2
	NCI-H522	4.07	27.9	96.5	474	54.7	>100
	NCI-H23	8.10	30.7	99.7	5.37	33.3	>100
	NCI-H322M	27.7	>100	>100	15.5	>100	>100
	NCI-H460	3.04	>100	>100	18.1	>100	>100
	NCI-H226	15.0	46.3	100	16.4	>100	>100
Colon Cancer	COLO 205	6.24	83.4	>100	7.78	63.7	>100
	HCC-2998	20.9	>100	>100	11.0	>100	>100
	HCT-15	30.6	>100	>100	5.81	>100	>100
	HCT-116	3.47	19.7	66.3	4.63	>100	>100
	HT29	6.06	>100	>100	4.79	>100	>100
	KM12	14.8	>100	>100	3.47	>100	>100
	SW-620	32.4	>100	>100	6.76	>100	>100
CNS Cancer	SF-265	19.8	84.2	>100	9.80	65.7	>100
	SF-295	10.0	27.5	75.6	6.41	23.4	68.2
	SF-539	2.07	5.78	27.0	11.5	41.9	>100
	SNB-19	19.5	75.6	>100	7.06	57.1	>100
	SNB-75	12.9	32.4	81.3	2.36	8.19	32.4
	U251	5.48	21.4	66.2	3.65	12.7	53.9
Ovarian Cancer	OVCAR-4	4.40	25.4	>100	22.5	>100	>100
	OVCAR-3	13.9	76.0	>100	14.8	30.4	62.2
	OVCAR-8	4.53	29.6	>100	5.20	26.8	>100
	OVCAR-5	14.7	>100	>100	52.4	>100	>100
	IGROV1	18.7	>100	>100	16.0	>100	>100
	NCI/ADR-RES	15.7	>100	>100	6.84	>100	>100
	SK-OV-3	11.9	27.9	65.1	4.84	18.4	59.6
Melanoma	LOX IMVI	5.83	26.0	80.7	5.74	>100	>100
	MALME-3M	14.5	78.8	>100	6.0	48.3	>100
	MDA-MB435	2.62	>100	>100	1.95	5.39	100
	SK-MEL-2	20.4	>100	>100	10.8	98.0	>100
	SK-MEL-5	10.0	33.4	>100	8.78	>100	>100
	SK-MEL-28	5.8	40.2	>100	17.2	>100	>100
	UACC-257	11.4	82.6	>100	52.0	>100	>100
	UACC-62	11.0	53.2	>100	72.2	>100	>100
Renal Cancer	A498	11.8	59.2	>100	10.7	63.6	>100
	ACHN	11.1	>100	>100	3.98	>100	>100
	CAKI-1	12.1	>100	>100	14.6	>100	>100
	RXF 393	3.18	13.7	42.6	6.68	20.4	54.1
	SN12C	31.0	>100	>100	25.4	>100	>100
	TK-10	4.67	21.3	69.5	5.94	26.4	99.6
Prostate Cancer	PC-3	65.9	39.3	>1.00	8.86	>1.00	>1.00
	DU-145	5.68	27.1	93.1	6.92	23.8	61.8
Breast Cancer	MCF7	9.34	>100	>100	6.34	>100	>100
	MDA-MB-231	10.5	44.2	>100	8.28	>100	>100
	HS 578T	12.0	>100	>100	5.87	>100	>100
	BT-549	37.6	>100	>100	30.6	>100	>100
	T-47D	4.63	>100	>100	15.4	>100	>100
	MDA-MB-468	12.4	51.5	>100	6.22	23.1	68.0

*3.4. Synthesis of 3-[2-(cyanomethyl)-5,6-dimethyl-1H-benzimidazol-1-yl]-3-oxopropanenitrile (**11**)*

A mixture of **10** (0.01 mol) and ethylcyanoacetate (0.01 mol) was heated on-neat for 1 h, after cooling the residue was broken up and washed several times with ether. The product was then washed several times with hot ethanol and crystallized from the proper solvent. **11**: brown powder (73%); mp 249–251 °C (DMF); IR (KBr) cm^{-1} 2204 (C≡N), 1661, 1623 (C═O), (C═N); ^{1}H NMR (DMSO-d_6) δ 2.33 (*d*, 6H, 2CH_3), 3.8**2** (s, 2H, CH_2-CN), 3.8**7** (s, 2H, N–CH2–CN), 7.20 (s, 1H, 4-benzimidazole *H*), 7.82 (1H, 7-benzimidazole *H*); MS *m/z* (%) 253 (M^{+1}, 23.9), 252 (M^+, 100), 212 (M^+ – CH_2CN, 97.0), 186

(10.4), 184 (212 - CO, 40.3), 186 (10.4), 171 (6.00), 169 (184 − CH_3, 26.9), 159 (22.4), 77 (22.4). Anal. Calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.33; H, 4.52; N, 22.47.

3.5. Synthesis of ((2E)-3-(dimethylamino)-2-(5,6-dimethyl-1H-benzimidazol-2-yl)prop-2-enenitrile (**12**)

A mixture of compound **10** (0.01 mol), dimethylformamide/dimethylacetal (DMFDMA) (0.01 mol) and piperidine (0.2 ml) in dry xylene (30 ml) was refluxed for 7 h, then left to cool. The solid product was filtered off and crystallized from the proper solvent. **12**: brown powder (54%); mp 275–278 °C (DMF); IR (KBr) cm^{-1} 3264 (NH), 2193 (C≡N), 1628 (C═N); ^1H NMR (DMSO-d_6) δ 2.25 (s, 6H, 5, 6 benzimidazole 2C*H*$_3$), 3.24 (s, 6H, N(C*H*$_3$)$_2$), 7.12 (s, 1H, ═C*H*), 7.88 (s, 2H, 4,7 benzimidazole *H*), 11.64 (s, 1H, D_2O-exchangeable N*H*); MS *m/z* (%) 241 (M^{+1} 12.4), 240 (M^+, 100), 239 (18.8), 145 (4.1). Anal. Calcd for $C_{14}H_{16}N_4$: C, 69.98; H, 6.71; N, 23.32. Found: C, 69.54; H, 6.73; N, 23.00.

3.6. General procedures for synthesis of 6-amino-4-aryl-5-(1,3-benzothiazol-2-yl)pyridine-3-carbonitrile (**5a**,**b**) and (**8a**,**b**) 6-amino-4-aryl-5-(5,6-dimethyl-1H-benzimidazol-2-yl)pyridine-3-carbonitrile (**14a**,**b**) and (**17a**–**d**)

A mixture of compounds **2** or **10** (0.01 mol), appropriate arylidenemalononitriles **3a**,**b**, **4a**–**d** (0.01mol), and piperidine (0.2 ml) in absolute ethanol (30 ml) was refluxed for 4 h, then left to cool, the separated product was filtered of and crystallized from proper solvents.

3.6.1. 6-Amino-5-(1,3-benzothiazol-2-yl)-4-(furan-2-yl)pyridine-3-carbonitrile (**5a**)

Black powder (92%) mp 280–282 °C. IR (KBr) cm^{-1} 3311 (NH_2), 2213 (C≡N), 1648, 1611 (C═N, C═C); ^1H NMR (DMSO-d_6) δ 6.71–6.76 (m, 1H, 4-furfuryl C*H*), 7.14–7.18 (m, 1H, 4-furfuryl C*H*), 7.29–7.34 (m, 1H, 5-furfuryl C*H*), 7.42–7.56 (m, 2H, 5, 6 benzothiazole *H*), 7.98 (*d*, 1H, 4-benzothiazole *H*, *J* = 6 Hz), 8.09–8.14 (m,2H, 7-benzothiazole *H* + 2-pyridyl C*H*), 8.52 (s, 2H, D_2O-exchangeable NH_2); MS *m/z* (%) 319 (M^{+1} 12.92), 318 (M^+, 79.63), 301 (10.85), 292 (4.07), 276 (7.64), 235 (13.41), 184 (6.39), 108 (35.42). Anal. Calcd for $C_{17}H_{10}N_4OS$: C, 64.14; H, 3.17; N, 17.60. Found: C, 64.00; H, 2.99; N, 17.91.

3.6.2. 6-Amino-5-(1,3-benzothiazol-2-yl)-4-(thiophen-2-yl)pyri-dine-3-carbonitrile (**5b**)

Brown powder (40%) mp 158–160 °C. IR (KBr) cm^{-1} 3300 (NH_2), 2212 (C≡N), 1608 (C═N, C═C); ^1H NMR (DMSO-d_6) δ 7.30 (*d*, 1H, 5-thiohenyl C*H*, *J* = 9 Hz), 7.41–7.47 (m, 1H, 4-thiohenyl C*H*), 7.50–7.55 (m, 1H, 3-thiohenyl C*H*), 7.98–8.02 (m, 2H, 5, 6-benzothiazole *H*), 8.08–8.10 (m, 4H, 4, 7-benzothiazole *H* + D_2O-exchangeable NH_2); 8.58 (s, 1H, 2-pyridyl C*H*); ^{13}C NMR (DMSO-d_6) δ 101.06, 116.17, 122.23, 122.79, 125.91, 126.92, 128.53, 134.20, 135.04, 136.30, 138.07, 140.67, 152.90, 162.71; MS *m/z* (%) 334 (M^+ 1.59), 202 (6.36), 184 (8.25), 173 (3.66), 134 (63.13), 117 (23.07), 108 (72.00), 102 (5.92), 101 (5.92), 90 (15.76). Anal. Calcd for $C_{17}H_{10}N_4S_2$: C, 61.06; H, 3.01; N, 16.75. Found: C, 61.22; H, 3.33; N, 16.62.

3.6.3. 6-Amino-5-(1,3-benzothiazol-2-yl)-4-(4-hydroxyphenyl)-pyridine-3-carbonitrile (**8a**)

Brown powder (84%) mp > 333–335 °C. IR (KBr) cm^{-1} 3432 (OH), 3377 (NH), 3347 (NH_2), 2203 (C≡N), 1609, 1547, (C═N, C═C); ^1H NMR (DMSO-d_6) δ 5.82 (s, D_2O-exchangeable O*H*), 7.14–7.18 (m, 2H, 2, 6 Ar*H*), 7.31–7.36 (m, 2H, 3, 5 Ar*H*), 7.39–7.58 (m, 2H, 5, 6-benzothiazole *H*), 7.77 (*d*, 1H, 7-benzothiazole *H*, *J* = 6 Hz), 7.96 (*d*, 1H, 4-benzothiazole *H*, *J* = 6 Hz), 8.69 (s, 1H, (s,1H, 2-pyridyl C*H*); 8.92 (s, 2H, D_2O-exchangeable NH_2); MS *m/z* (%) 344 (M^+, 24.95), 302 (M^+ − C═N, NH_2, 24.07), 168 (21.85), 134 (35.40), 91 (26.21), 75 (25.38). Anal. Calcd for $C_{19}H_{12}N_4OS$: C, 66.26; H, 3.51; N, 16.27. Found: C, 66.01; H, 3.22; N, 16.30.

3.6.4. 6-Amino-5-(1,3-benzothiazol-2-yl)-4-(4-methoxyphenyl)-pyridine-3-carbonitrile (**8b**)

Yellow powder (98%) mp > 141–142 °C. IR (KBr) cm^{-1} 3429 (NH_2), 2218 (C≡N), 1620, 1589 (C═N, C═C); ^1H NMR (DMSO-d_6) δ 3.88 (s, 3H, OCH_3), 7,17 (*d*, 2H, 2, 6 Ar*H*, *J* = 9 Hz), 7.47–7.58 (m, 4H, 3, 5 Ar*H* + 5, 6 benzothiazole *H*), 8.07–8.18 (m, 4H, 4,7 benzothiazole *H* + D_2O-exchangeable NH_2), 8.34 (s,1H, 2-pyridyl C*H*), MS *m/z* (%) 359 (M^{+1} 0.02), 251 (M^+ − C_7H_7O, 18.62), 224 (2.05), 222 (32.44), 197 (2.06), 198 (1.32), 134 (24.13), 108 (78.98), Anal. Calcd for $C_{20}H_{14}N_4OS$: C, 67.02; H, 3.94; N, 15.63. Found: C, 67.23; H, 4.21; N, 15.50.

3.6.5. 6-Amino-5-(5,6-dimethyl-1H-benzimidazol-2-yl)-4-(furan-2-yl)pyridine-3-carbonitrile(**14a**)

Brown powder (50%), mp 289–291 °C. IR (KBr) cm^{-1} 3307 (NH), 3250 (NH_2), 2218 (C≡N), 1651, 1610 (C═N, C═C); ^1H NMR (DMSO-d_6) δ 2.30 (s, 6H, 2C*H*$_3$), 6.67–6.76 (m, 2H, 4- furfuryl C*H* + 1 D_2O-exchangeable N*H*), 6.87 (d,1H, 3-furfuryl C*H*), 7.41(s, 1H, 5-furfuryl C*H*), 7.94 (d, 2H, 4,7 benzimidazole *H*, *J* = 12 Hz), 8.08 (s,1H, 2-pyridyl C*H*), 8.33 (s, 2H, D_2O-exchangeable NH_2); MS *m/z* (%) 330 (M^{+1} 38.9), 329 (M^+, 63.9), 328 (48.6), 313 (12.5), 303 (12.5), 285 (40.3), 284 (41.7), 222 (58.3), 209 (100), 185 (37.5), 145 (9.7), 91 (36.1). Anal. Calcd for $C_{19}H_{15}N_5O$: C, 69.29; H, 4.59; N, 21.26. Found: C, 68.89; H, 4.55; N, 21.20.

3.6.6. 6-Amino-5-(5,6-dimethyl-1H-benzimidazol-2-yl)-4-(thiophen-2-yl)pyridine-3-carbonitrile (**14b**)

Brown powder (27%); mp >350 °C IR (KBr) cm^{-1} 3430 (NH), 3310 (NH_2), 2214 (C≡N), 1639, 1615, 1580 (C═N, C═C); MS *m/z* (%) 345 (M^+, 10.3), 344 (26.9), 343 (100), 145 (5.8), 90 (12.2). Anal. Calcd for $C_{19}H_{15}N_5S$: C, 66.07; H, 4.37; N, 20.27. Found: C, 66.54; H,4.00; N, 20.29.

3.6.7. 6-Amino-5-(5,6-dimethyl-1H-benzimidazol-2-yl)-4-phenyl-pyridine-3-carbonitrile (**17a**)

Yellow powder (44%) mp > 350 °C. IR (KBr) cm^{-1} 3467 (NH), 3368 (NH_2), 2227 (C≡N), 1639, 1586, (C═N, C═C); ^1H NMR (DMSO-d_6) δ 2.42 (*d*, 6H, 2C*H*$_3$, *J* = 9 Hz), 7.21–7.35 (m, 6H, 5 Ar*H* + 1H, D_2O-exchangeable N*H*), 7.60 (*d*, 2H, 4,7 benzimidazole *H*, *J* = 9 Hz), 8.43 (s,1H, 2-pyridyl C*H*), 8.57 (s, 2H, D_2O-exchangeable NH_2); ^{13}C NMR (DMSO-d_6) δ 19.84, 114.43, 115.76, 118.69, 126.33, 128.60, 129.92, 131.08, 134.80, 135.38, 143.00, 146.39, 151.59, 152.02; MS *m/z* (%) 340 (M^{+1} 3.8), 339 (M^+, 11.8), 337 (100), 323 (2.6), 313 (0.7), 145 (2.1). Anal. Calcd for $C_{21}H_{17}N_5$: C, 74.32; H, 5.04; N, 20.63. Found: C, 74.00; H, 5.38; N, 20.60.

3.6.8. 6-Amino-4-(4-chlorophenyl)-5-(5,6-dimethyl-1H-benzimidazol-2-yl)pyridine-3-carbonitrile (**17b**)

Yellow powder (34%); mp >350 °C. IR (KBr) cm^{-1} 3426 (NH), 3270 (NH_2), 2214 (C≡N), 1646,1584 (C═N, C═C); ^1H NMR (DMSO-d_6) δ 2.42 (*d*, 6H, 2C*H*$_3$, *J* = 12 Hz), 7.64–7.66 (m, 7H, 4 Ar *H* + 2H, 4,7 benzimidazole *H* + 1H, D_2O- exchangeable N*H*), 8.46 (s,1H, 2-pyridyl C*H*), 8.57 (s, 2 D_2O- exchangeable NH_2); MS *m/z* (%) 373 (M^+, 8.0), 372 (25.3), 371 (19.5), 290 (100), 289 (60.9), 256 (32.2), 147 (54), 145 (39.1), 91 (40.2), 77 (42.5). Anal. Calcd for $C_{21}H_{16}ClN_5$: C, 67.47; H, 4.31; N, 18.73. Found: C, 67.30; H, 4.28; N, 19.10.

3.6.9. 6-Amino-5-(5,6-dimethyl-1H-benzimidazol-2-yl)-4-(4-hydroxy- phenyl)pyridine-3-carbonitrile (**17c**)

Brown powder (88%); mp >350 °C. IR (KBr) cm^{-1} 3437 (NH), 3346 (NH_2), 2196 (C≡N), 1646,1585 (C═N, C═C); ^1H NMR (DMSO-

d_6) δ 2.35 (s, 6H, 2CH_3), 7.52–7.62 (m, 3H, 2, 6 ArH + 1 D_2O-exchangeable NH), 7.77–7.82 (m, 4H, 3, 5 ArH + 4,7 benzimidazole H), 8.30 (s,1H, 2-pyridyl CH), 8.55 (s, 2 D_2O- exchangeable NH_2); 10.76 (s, 1 D_2O-exchangeable OH); MS *m/z* (%) 355 (M^+, 3.3), 354 (21.6), 353 (100), 352 (33.3), 327 (14.9), 177 (15), 145 (3.3), 91 (9.2), 77 (9). Anal. Calcd for $C_{21}H_{17}N_5O$: C, 70.98; H, 4.82; N, 19.71. Found: C, 70.52; H, 4.89; N, 19.31.

*3.6.10. 6-Amino-5-(5,6-dimethyl-1H-benzimidazol-2-yl)-4-(4-methoxy-phenyl)pyridine-3-carbonitrile (**17d**)*

Buff powder (50%); mp 319–322 °C. IR (KBr) cm^{-1} 3435 (NH), 3296 (NH_2), 2213 (C≡N), 1641, 1613, 1581 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.40 (s, 6H, 2CH_3), 3.82 (s, 3H, OCH_3), 7.-7.14 (d, 2H, 3", 5" ArH, J = 8.7 Hz), 7.55 (d, 2H, 2", 6" ArH, J = 8.4 Hz), 7.61(s, 2H, 4,7 benzimidazole H), 8.4 (s,1H, 2-pyridyl CH), 8.53 (brs, 3 D_2O-exchangeable NH + NH_2); MS *m/z* (%) 370 (M^{+1} 0.4), 369 (M^+, 3.4), 367 (100), 353 (6.1), 338 (0.4), 145 (1.2). Anal. Calcd for $C_{22}H_{19}N_5O$: C, 71.53; H, 5.18; N, 18.96. Found: C, 71.40; H, 5.38; N, 18.72.

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