The Synthesis and Biological Evaluation of *N*-Substituted 1*H*-Benzimidazol-2-yl-1*H*-pyrazole-3,5-diamines

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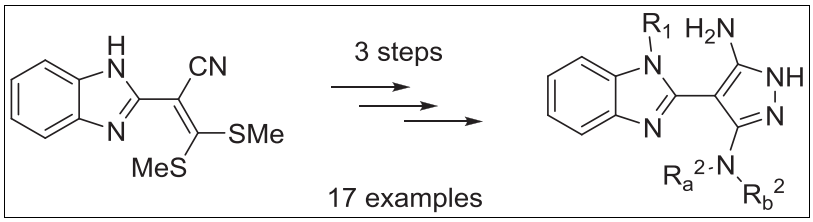

The synthesis of 1*H*-benzimidazol-2-yl-1*H*-pyrazole-3,5-diamines has been developed. Synthesized bisheteroaryls contain two privileged medicinal scaffolds, aminopyrazole and benzimidazole, with two diversity positions at N1 of benzimidazole and C3 of pyrazole, respectively. The three-step synthesis includes the Mitsunobu *N*-alkylation of benzimidazole and subsequent one-pot formation of aminopyrazole involving substitution of methylthio groups with amine and hydrazine followed with final ring closure. Inhibitory activity toward cyclin-dependent kinase 2/cyclin E and cytotoxicity against two cancer cell lines were evaluated for all novel pyrazoles. Two compounds showed modest cyclin-dependent kinase inhibition activity and cytotoxicity against cancer cell lines K562 and MCF7.

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INTRODUCTION

Pyrazole is a five-membered heterocycle, which exhibits a wide range of biological activities [1]. Examples of clinically used pyrazole-containing drugs include nonsteroidal anti-inflammatory and analgesic celecoxib, antidote in alcohol poisoning Fomepizole, and antibacterial Sulfaphenazole. Additionally, metal complexes bearing pyrazole ligands were studied as organic light-emitting diodes, liquid crystals, and catalysts for the carbon–carbon cross-coupling reactions [2].

The standard method for pyrazole preparation involves cyclization of hydrazine or aryl/alkyl hydrazines with 1,3-dicarbonyl compounds such as carboxylic acid esters, ketones, nitriles, enamines, and enolethers [3]. Other approaches toward pyrazoles include palladium-catalyzed four-component coupling of arylhalide, terminal alkyne, hydrazine, and carbon monoxide [4a]; copper-catalyzed domino C-N coupling/hydroamination [4b]; 1,3-dipolar cycloaddition of aryldiazo compounds with terminal alkynes [4c]; base-mediated cycloaddition of hydrazones with nitroolefines [4d]; and rhodium-catalyzed cyclization of hydrazines with alkynes [4e] For recent review on the synthesis of pyrazoles, see Reference [4f].

Benzimidazole is one of the privileged scaffolds in the medicinal chemistry. Compounds containing this motif display a wide range of pharmacological activities such as antiviral, antimicrobial, antiulcer, anticancer, anti-inflammatory, and anticonvulsant [5]. Moreover, benzimidazoles have found applications in the development of chemosensors, lasers, and molecular switches [6].

The common synthesis of benzimidazoles utilizes condensation of *ortho*-aminoanilines with carboxylic acid derivatives [7] or condensation with aldehydes under oxidative conditions [8]. The key intermediate, *ortho*-aminoanilines, are often synthesized in two steps from *ortho*-halonitrobenzenes via nucleophilic substitution of halogen with primary amine and subsequent reduction of the nitro group. Some variations utilize *ortho*-haloanilines instead; the second amino group is introduced by palladium or copper-mediated C-N coupling [9]. In some cases, introducing alkyl substituents at N1 of completed benzimidazole core can be advantageous. Alkylation of N1 using alkyl halides or triflates has been reported, but this method suffers from the unwanted side reaction, quarterization [10]. On the other hand, Mitsunobu alkylation of nitrogen heterocycles such as pyrimidinones, 1,2,3-triazoles, indoles, carbazoles, and imidazoles usually proceeds under mild conditions and usually with high chemoselectivity and regioselectivity [11]. Despite of this, there are only few examples of Mitsunobu *N*-alkylation of benzimidazoles in the literature [12].

During the course of our research program toward inhibitors of cyclin-dependent kinases (CDK), we have found diaminopyrazoles as potent and selective inhibitors of CDK with strong antiproliferative activity *in vitro* [13]. In this article, we disclose the three-step synthesis of bisheteroaryls 1 containing diaminopyrazole and

benzimidazole moieties connected through the C2 of benzimidazole and C4 of pyrazole position, respectively. Synthesized bisheteroaryls 1 were modified at N1 of benzimidazole and C3 of pyrazole position, respectively.

RESULTS AND DISCUSSION

The general synthesis of bisheteroaryls **1** is depicted in Scheme 1. Benzimidazole **2** was prepared according to modified procedure described by Manfred [14]. Nitrile **3** reacted with carbon disulfide in the presence of sodium hydroxide followed with the methylation of the thiol group with methyl iodide. In the next step, various alkyl substituents were introduced at N1 of benzimidazole **2** via Mitsunobu alkylation.

The model reaction of benzimidazole **2** and alcohol **4a** was examined under various conditions (Table 1). The alkylation with two equivalents of diethyl azodicarboxylate (DEAD) and triphenylphosphine in dioxane delivered compound **5a** in 69% yield (entry 1). When the reaction was carried out in tetrahydrofuran (THF), the yield increased to 74% (entry 2). Chlorinated solvents, dichloromoethane and 1,2-dichloroethane, gave lower yields of 56 and 54%, respectively (entries 3 and 4). Diisopropyl azodicarboxylate (DIAD) is considered chemically equivalent but a safer alternative to DEAD. In our case, DIAD gave comparable result with DEAD (80 vs 74% yield, entry 5 vs entry 2). Thus, we continued further experiments using safer DIAD. Reduced amount of triphenylphosphine and DIAD to 1.6 equivalents still

Scheme 1. General synthesis of bisheteroaryls **1a–q**.

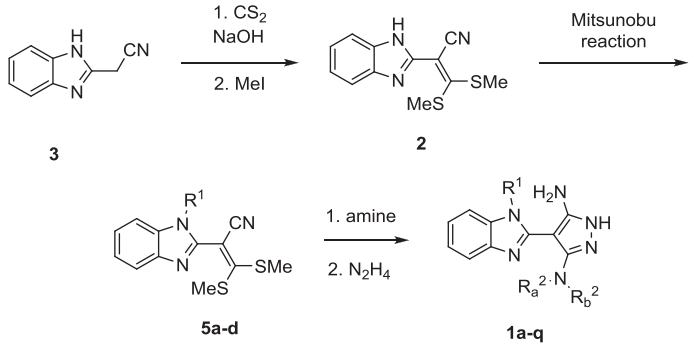
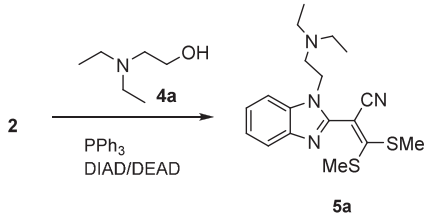


Table 1

Optimization of the Mitsunobu reaction[a].



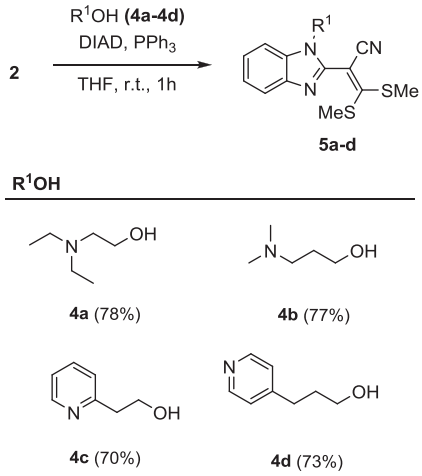
Entry	Reagent (equivalent)	Solvent	Time (h)	Yield[b] (%)
1	DEAD/PPh_3 (2.0)	Dioxane	2	69
2	DEAD/PPh_3 (2.0)	THF	1	74
3	DEAD/PPh_3 (2.0)	DCM	5	56
4	DEAD/PPh_3 (2.0)	DCE	5	54
5	DIAD/PPh_3 (2.0)	THF	1	80
6	DIAD/PPh_3 (1.6)	THF	1	78
7	DIAD/PPh_3 (1.2)	THF	4	53[c]

THF, tetrahydrofuran; DCM, dichloromethane; DCE, dichloroethane.
[a]Reactions were carried out with one equivalent of 2-(diethylamino)ethanol **4a** and monitored by thin-layer chromatography and liquid chromatography–mass spectrometry.
[b]Isolated yield after extraction to dichloromethane and chromatography.
[c]Unreacted starting material 2 was recovered (16%).

provided full conversion of starting material 2 resulting in product **5a** in 78% yield (entry 6). On the other hand, further decrease of reagents to 1.2 equivalents led to incomplete conversion. The title compound **5a** was isolated only in 53% yield together with 16% of unreacted starting material 2 (entry 7). Thus, we used 1.6 equivalents of DIAD/PPh_3 in THF (entry 6, Table 1) as standard conditions for the synthesis of *N*-alkylated benzimidazoles **5a–d** with aminoalcohols **4a–d** (Scheme 2).

Next, we examined the transformation of benzimidazole **5a** into the final bisheteroaryl **1a** derivative. The one-pot reaction started with the substitution of methylthio group with benzylamine leading to intermediate **6a**, which subsequently underwent cyclization with hydrazine to yield the desired bisheteroaryl **1a** (Table 2). The substitution of methylthio group with benzylamine, carried out at room temperature, gave only low conversion in ethanol, acetonitrile, and THF (entries 1, 2, and 3). The reaction proceeded smoothly at higher temperatures. More than 95% conversion was achieved (entries 4, 5, and 6). Then, hydrazine monohydrate was added, and the reaction mixture was heated under reflux until the intermediate **6** was completely transformed into bisheteroaryl **1** [monitored by liquid chromatography–mass spectrometry (LC-MS)]. Good yields of bisheteroaryl **1a** were achieved in THF and ethanol (entries 4 and 6); however, the highest isolated yield was observed in acetonitrile (entry 5).

Scheme 2. Mitsunobu *N*-alkylation with alcohols **4a–d**.

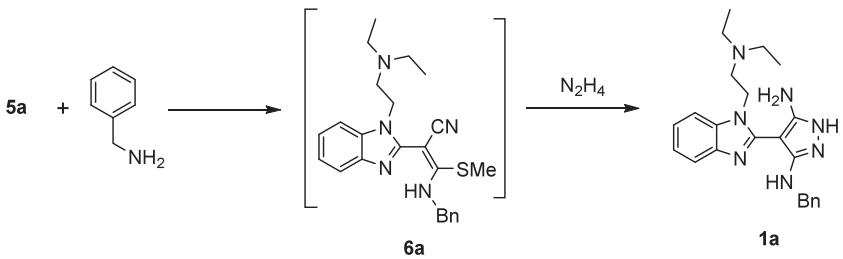


Subsequently, optimized conditions were applied in the synthesis of 17 bisheteroaryls **1a–q** from intermediates **5a–d** (Scheme 3). All compounds were prepared in good to excellent isolated yields, 67–91%. The substitution of methylthio group with aniline required longer reaction time, 24 h, presumably because of lower nucleophilicity of the amino group conjugated with aromatic system (entry **1h** and **1n**, Scheme 3).

Because of the similarity of 1*H*-benzimidazol-2-yl-1*H*-pyrazole-3,5-diamines to previously discovered diaminopyrazoles [13], the biological activity of prepared compounds was evaluated. The compounds have been tested in kinase inhibition assays for their inhibitory potency toward

Table 2

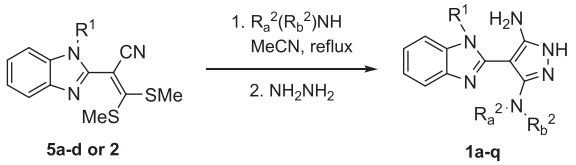
Optimization of the one-pot aminopyrazole formation.

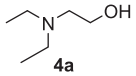
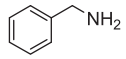
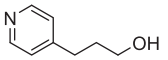
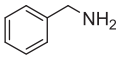
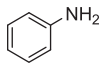
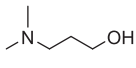
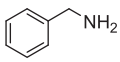
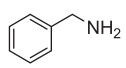
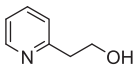
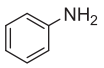
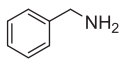
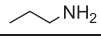


Entry	Solvent	T (°C)	Time (h)[c]	Conversion to **6a** (%)[a]	Yield of **1a** (%)[b]
1	EtOH	r.t.	22/—	44	NI
2	MeCN	r.t.	22/—	56	NI
3	THF	r.t.	22/—	49	NI
4	EtOH	Reflux	8/14	>95	72
5	MeCN	Reflux	8/14	>95	80
6	THF	Reflux	8/14	>95	71

NI, not isolated.
[a]Estimated by high-performance liquid chromatography.
[b]Isolated yield after column chromatography on silica gel.
[c]Time for the SMe substitution/cyclization.

Scheme 3. The synthesis of bisheteroaryls **1a–q**.



Product	R^1OH	$R_a^2(R_b^2)NH$	Yield (%)	Product	R^1OH	$R_a^2(R_b^2)NH$	Yield (%)
1a	 **4a**		80	**1k**	 **4d**		87
1b			83	**1l**			77
1c			79	**1m**			86
1d			67	**1n**	**R^1 = H**		73[b]
1e	 **4b**		89	**1o**			78
1f			81	**1p**			91
1g			76	**1q**			84
1h	 **4c**		81[b]				
1i			90				
1j			84				

[a] General conditions: benzimidazole (**2, 5a-5d**, 0.5 mmol), amine (0.6 mmol), and MeCN reflux for 8h (or 24h for entry **1h** and **1n**), then hydrazine (1.0 mmol) and reflux for additional 14h. [b] The first step (substitution of SMe) was prolonged to 24 h.

recombinant CDK2/cyclin E and for their cytotoxicity against two cancer cell lines. None of the tested compounds was active, with the exception of **1n** and **1o** (Table 3). These two compounds displayed inhibitory activity toward CDK2 (IC_{50} values 24 and 62 μ*M*, respectively) and also cytotoxicity in MCF7 and K562 cell lines. Both **1n** and **1o** bear aromatic substituents, while all inactive compounds have aliphatic side chains. However, aromatic substitution of the diaminopyrazole must be combined with unsubstituted benzimidazole; any substitution at nitrogen of the benzimidazole moiety is not compatible with

Table 3

Biological evaluation of bisheteroaryls **1**.

Compound	CDK2/E (IC_{50})	MCF7 (GI_{50})	K-562 (GI_{50})	Compound	CDK2/E (IC_{50})	MCF7 (GI_{50})	K-562 (GI_{50})
1a	>100	>100	>100	**1k**	>100	>100	>100
1b	>100	>100	>100	**1l**	>100	>100	>100
1c	>100	>100	>100	**1m**	>100	>100	>100
1e	>100	>100	>100	**1n**	24.9	33.32	21.17
1h	>100	>100	>100	**1o**	62.3	63.35	41.09
1i	>100	>100	>100	**1p**	>100	>100	>100
1j	>100	>100	>100	**1q**	>100	>100	>100

CDK2 inhibition, as seen for **1a**, **1e**, **1h**, **1i**, or **1k**. These data correlate with our previous findings, showing that small aromatic substitution of 3,5-diaminopyrazole in position 4 is important for CDK inhibition [13].

CONCLUSION

In conclusion, a three-step protocol leading to 1*H*-benzimidazol-2-yl-1*H*-pyrazole-3,5-diamines **1a–q** from readily available benzimidazole **2** was developed. The Mitsunobu alkylation of benzimidazole **2** gave *N*-substituted benzimidazoles **5a–d** in high yields, 70–78%. Next, the one-pot substitution of methylthio group and cyclization with hydrazine afforded bisheteroaryls **1a–q** in good to high yields, 67–91%. As expected, the substitution of methylthio group with aniline required longer reaction time comparing with aliphatic amines, 24 versus 8 h, because of lower nucleophilicity of aromatic amino group. Bisheteroaryls **1** were assayed toward CDK2/cyclin E, but only compounds **1n** and **1o** showed modest inhibition activity.

EXPERIMENTAL SECTION

All starting materials, solvents, and reagents were purchased from commercial suppliers and were used as received without further purification. Melting points were determined on a Boetius stage. The high-performance LC-MS (HPLC-MS) analyses were carried out on an ultra-HPLC-MS system consisting of an Accela ultra-HPLC chromatograph with a photodiode array detector and a TSQ Quantum Access triple quadrupole mass spectrometer (both Thermo Scientific, CA, USA), using a Nucleodur Gravity C18 column (Macherey-Nagel, 1.8 µm, 2.1 × 50 mm, Germany) at 30°C and a flow rate of 800 µL/min. The atmospheric-pressure chemical ionization source operated at a discharge current of 5 µA, vaporizer temperature of 400°C, and capillary temperature of 200°C. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO-d_6 at 20 °C on a Bruker 400 and 300 Fourier transform NMR spectrometer, respectively. Elemental analyses were performed on a Flash 2000 CHNS Elemental Analyzer (Thermo Scientific).

2-(1*H*-Benzimidazol-2-yl)-3,3-bis(methylthio)prop-2-enenitrile (2). Compound **2** was prepared according modified procedure described by Manfred *et al*.[14]

To a solution of benzimidazole **3** (15.7 g, 100 mmol) in THF (300 mL) was added aqueous solution of sodium hydroxide (3.0 g, 120 mmol in 50 mL) and carbon disulfide (7.25 mL, 120 mmol). The mixture was stirred for 0.5 h; then, methyl iodide (15.0 mL, 240 mmol) was added and stirring continued for additional 2 h. Then, the mixture was extracted with ethyl acetate (3 × 40 mL), and the solvent was removed under vacuum. The crude material was crystallized from MeOH-CH_2Cl_2 to yield 2-(1*H*-benzimidazol-2-yl)-3,3-bis(methylsulphanyl)prop-2-enenitrile as yellow crystalline solid 10.38 g (39%); mp 196–200°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 2.46 (s, 3*H*), 2.66 (s, 3*H*), 7.22 (dd, *J* = 5.7, 2.9 Hz, 2*H*), 7.59 (br. s., 2*H*), 12.73 (br. s., 1*H*); calcd for $C_{12}H_{11}N_3S_2$ (261.37); C, 55.14; H, 4.24; N, 16.08; found: C, 55.36; H, 4.11; N, 15.78.

GENERAL PROCEDURE FOR MITSUNOBU ALKYLATION

A mixture of 2-(1*H*-benzimidazol-2-yl)-3,3-bis(methylthio)-prop-2-enenitrile **2** (0.26 g, 1.0 mmol), triphenylphosphine (0.42 g, 1.6 mmol), DIAD (0.32 mL, 1.6 mmol), and appropriate alcohol (1.0 mmol) in dry THF (8 mL) was stirred for 1 h under nitrogen atmosphere. The resulting solution was extracted to dichloromethane and washed with diluted hydrochloric acid. The aqueous layer of hydrochloride salt was neutralized with 10% aqueous sodium hydroxide, and the formed yellow oil was extracted to dichloromethane. The crude material was purified with column chromatography on silica gel, eluting with 0–10% methanol in dichloromethane

2-(1-(2-(Diethylamino)ethyl)-1H-benzo[d]imidazol-2-yl)-3,3-bis(methylthio)prop-2-enenitrile (5a). Prepared according to general procedure for Mitsunobu alkylation using 2-(diethylamino)ethanol **4a** as pale yellow oil (0.28 g, 78%), which solidified upon standing to low melting almost white solid; ^{1}H-NMR (400 MHz, DMSO-d_6) 0.73 (t, *J* = 7.0 Hz, 6*H*), 2.30 (s, 3*H*), 2.40 (q, *J* = 7.0 Hz, 4*H*), 2.64 (t, *J* = 6.1 Hz, 2*H*), 2.69 (s, 3*H*), 4.21 (t, *J* = 6.1 Hz, 2*H*), 7.25 (td, *J* = 7.4, 1.2 Hz, 1*H*), 7.32 (td, *J* = 7.4, 1.2 Hz, 1*H*), 7.62–7.69 (m, 2*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 11.4, 17.4, 18.1, 43.3, 46.9, 51.1, 99.1, 111.1, 116.4, 119.5, 122.3, 123.2, 134.4, 142.3, 145.5, 167.1.

2-{1-[3-(Dimethylamino)propyl]-1H-benzimidazol-2-yl}-3,3-bis(methylsulthio)prop-2-enenitrile (5b). Prepared according to general procedure for Mitsunobu alkylation using 3-(dimethylamino)propanol **4b** as pale yellow oil (0.27 g, 77%), which solidified upon standing to low melting almost white solid; ^{1}H-NMR (400 MHz, DMSO-d_6) 1.87 (tt, *J* = 7.0, 6.7 Hz, 2*H*), 2.10 (s, 6*H*), 2.17 (t, *J* = 6.7 Hz, 2*H*), 2.30 (s, 3*H*), 2.72 (s, 3*H*), 4.25 (t, *J* = 7.0 Hz, 2*H*), 7.23–7.30 (m, 1*H*), 7.34 (td, *J* = 7.6, 1.2 Hz, 1*H*), 7.64–7.72 (m, 2*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 17.5, 18.4, 26.9, 42.0, 45.0, 55.7, 97.6, 111.1, 116.2, 119.6, 122.4, 123.4, 134.5, 142.3, 144.8, 169.2.

3,3-Bis(methylthio)-2-(1-2-(pyridin-2-yl)ethyl)-1H-(benzo[d]imidazol-2-yl)prop-2-enenitrile (5c). Prepared according to general procedure for Mitsunobu alkylation using 2-(pyridin-2-yl)ethanol **4c** as pale yellow oil (0.26 g, 70%), which solidified upon standing to low melting almost white solid; ^{1}H-NMR (400 MHz, DMSO-d_6) 2.26 (s, 3*H*), 2.70 (s, 3*H*), 3.23 (t, *J* = 6.8 Hz, 2*H*), 4.66 (t, *J* = 6.8 Hz, 2*H*), 7.05 (d, *J* = 7.8 Hz, 1*H*), 7.20 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1*H*), 7.25 (td, *J* = 7.6, 1.2 Hz, 1*H*), 7.32 (td, *J* = 7.6, 1.2 Hz, 1*H*), 7.59 (td, *J* = 7.6, 1.9 Hz, 1*H*), 7.62–7.68 (m, 2*H*), 8.49–8.52 (m, 1*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 17.5, 18.5, 36.9, 43.6, 97.7, 111.2, 116.1, 119.5, 121.9, 122.4, 123.3, 123.4, 134.2, 136.2, 142.3, 144.9, 149.3, 157.2, 168.9.

3,3-Bis(methylthio)-2-(1-3-(pyridin-4-yl)propyl)-1H-(benzo[d]imidazol-2-yl)prop-2-enenitrile (5d). Prepared according to general procedure for Mitsunobu alkylation using 3-(pyridon-4-yl)propan-1-ol **4d** as pale yellow oil (0.28 g, 73%), which solidified upon standing to low melting

almost white solid; ^{1}H-NMR (400 MHz, DMSO-d_6) 2.08 (tt, J = 7.8, 7.4 Hz, 2*H*), 2.27 (s, 3*H*), 2.64 (t, J = 7.8 Hz, 2*H*), 2.67 (s, 3*H*), 4.25 (t, J = 7.4 Hz, 2*H*), 7.21 (dd, J = 4.3, 1.6 Hz, 2*H*), 7.28 (td, J = 7.0, 1.2 Hz, 1*H*), 7.34 (td, J = 7.0, 1.2 Hz, 1*H*), 7.65–7.71 (m, 2*H*), 8.45 (dd, J = 4.3, 1.6 Hz, 2*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 17.5, 18.4, 29.6, 31.3, 43.5, 97.2, 111.1, 116.2, 119.7, 122.5, 123.5, 123.7, 134.4, 142.3, 144.7, 149.4, 149.6, 169.7.

GENERAL PROCEDURE FOR THE PREPARATION OF BIARYLS (1A–Q)

A mixture of benzimidazole **5** (0.5 mmol) and appropriate amine (0.6 mmol) were stirred in dry boiling acetonitrile (4 mL) for 8 h. Then, hydrazine monohydrate (0.05 mL, 1.0 mmol) was added, and the mixture was stirred at ~80°C for an additional 14 h. Solvent was removed under vacuum, and the residue was purified by column chromatography on silica gel, eluting with 0–10% methanol in dichloromethane. After column chromatography, title product was crystallized from dichloromethane–hexane or acetonitrile.

***N*^{3}*-Benzyl-4-(1-(2-(diethylamino)ethyl)-1H-benzo[d]imidazol-2-yl)-1H*-pyrazol-3,5-diamine (1a).** Prepared according to general procedure using benzimidazole **5a** and benzylamine, white needles 0.16 g (80%), mp 76–78°C (dichloromethane–hexane); ^{1}H-NMR (400 MHz, DMSO-d_6) 0.74 (t, J = 7.0 Hz, 6*H*), 2.31 (q, J = 7.0 Hz, 4*H*), 2.57 (t, J = 6.7 Hz, 2*H*), 4.31 (d, J = 5.9 Hz, 2*H*), 4.39 (t, J = 6.7 Hz, 2*H*), 5.40 (br. s., 2*H*), 5.92 (br. s., 1*H*), 7.09–7.16 (m, 2*H*), 7.19 (t, J = 7.2 Hz, 1*H*), 7.27 (t, J = 7.2 Hz, 2*H*), 7.33 (d, J = 7.2 Hz, 2*H*), 7.47–7.55 (m, 2*H*), 10.68 (br. s., 1*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) ppm 11.6, 42.6, 46.5, 46.8, 50.9, 80.6, 110.0, 117.7, 120.8, 121.0, 126.4, 127.3, 128.0, 135.1, 141.0, 143.6, 148.7, 149.8, 152.7; calcd for $C_{23}H_{29}N_7$ (403.52); C, 68.46; H, 7.24; N, 24.30; found: C, 68.13; H, 7.29; N, 24.58.

4-(1-(2-(Diethylamino)ethyl)-1H-benzo[d]imidazol-2-yl)-3-morpholino-1H-pyrazol-5-amine (1b). Prepared according to general procedure using benzimidazole **5a** and morpholine, white needles (0.16 g, 83%); mp 74–76°C (dichloromethane–hexane); ^{1}H-NMR (400 MHz, DMSO-d_6) 0.75 (t, J = 7.0 Hz, 6*H*), 2.35 (q, J = 7.0 Hz, 4*H*), 2.44 (t, J = 7.2 Hz, 2*H*), 2.85 (dd, J = 4.7, 4.3 Hz, 4*H*), 3.63 (dd, J = 4.7, 4.3 Hz, 4*H*), 4.58 (t, J = 7.0 Hz, 2*H*), 5.44 (br. s., 2*H*), 7.11–7.20 (m, 2*H*), 7.50 (dd, J = 6.8, 1.8 Hz, 1*H*), 7.55 (dd, J = 6.8, 1.6 Hz, 1*H*), 11.15 (br. s, 1*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 11.8, 41.3, 46.8, 49.5, 50.9, 65.9, 82.4, 110.0, 118.1, 121.1, 121.2, 135.0, 143.4, 149.4, 150.0, 154.3; calcd for $C_{20}H_{29}N_7O$ (383.49); C, 62.64; H, 7.62; N, 25.57; found: C, 62.29; H, 7.74; N, 25.80.

4-(1-(2-(Diethylamino)ethyl)-1H-benzo[d]imidazol-2-yl)-3-(4-methylpiperazin-1-yl)-1H-pyrazol-5-amine (1c). Prepared according to general procedure using benzimidazole **5a** and 1-methylpiperazine, white needles 0.16 g (79%); mp 69–71°C (dichloromethane–hexane); ^{1}H-NMR (400 MHz, DMSO-d_6) 0.75 (t, J = 7.0 Hz, 6*H*), 2.16 (s, 3*H*), 2.33–2.38 (m, 4*H*), 2.34 (q, J = 7.0 Hz, 4*H*), 2.40 (t, J = 7.0 Hz, 2*H*), 2.82–2.90 (m, 4*H*), 4.58 (t, J = 7.0 Hz, 2*H*), 5.41 (br. s., 2*H*), 7.11–7.19 (m, 2*H*), 7.48–7.57 (m, 2*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 11.9, 41.3, 45.8, 46.7, 48.9, 50.9, 54.4, 82.6, 109.9, 118.0, 121.1, 121.2, 135.0, 143.4, 149.6, 150.2, 154.1; calcd for $C_{21}H_{32}N_8$ (396.53); C, 63.61; H, 8.13; N, 28.26; found: C, 63.22; H, 8.26; N, 28.52.

N*^{3}*-Propyl-4-(1-(2-(diethylamino)ethyl)-1H-benzo[d]imidazol-2-yl)-1H-pyrazol-3,5-diamin (1d). Prepared according to general procedure using benzimidazole **5a** and propylamine, white needles 0.12 g (67%); mp 70–73°C (dichloromethane–hexane); ^{1}H-NMR (400 MHz, DMSO-d_6) 0.75 (t, J = 7.2 Hz, 6*H*), 0.88 (t, J = 7.4 Hz, 3*H*), 1.52 (qt, J = 7.4, 7.0 Hz, 2*H*), 2.32 (q, J = 7.2 Hz, 4*H*), 2.56 (t, J = 6.8 Hz, 2*H*), 3.04 (br. t, J = 7.0 Hz, 2*H*), 4.39 (t, J = 6.8 Hz, 2*H*), 5.27 (br. s, 2*H*), 5.49 (br. s, 1*H*), 7.10–7.16 (m, 2*H*), 7.47–7.55 (m, 2*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 11.5, 11.6, 22.6, 42.5, 44.8, 46.8, 50.9, 85.0, 109.9, 117.7, 120.7, 121.0, 135.1, 143.6, 149.3, 145.0, 152.2; calcd for $C_{19}H_{29}N_7$ (355.48); C, 64.20; H, 8.22; N, 27.58; found: C, 63.94; H, 8.57; N, 27.37.

N*^{3}*-Benzyl-4-(1-(3-(dimethylamino)propyl)-1H-benzo[d]imidazol-2-yl)-1H-pyrazol-3,5-diamine (1e). Prepared according to general procedure using benzimidazole **5b** and benzylamine, white needles 0.18 g (89%), mp 116–118°C (dichloromethane–hexane); ^{1}H-NMR (400 MHz, DMSO-d_6) 1.66 (quin, J = 7.0 Hz, 2*H*), 2.00 (s, 6*H*), 2.02 (t, J = 7.0 Hz, 2*H*), 4.30 (d, J = 6.3 Hz, 2*H*), 4.35 (t, J = 7.0 Hz, 2*H*), 5.34 (br. s, 2*H*), 5.56 (br. s, 1*H*), 7.10–7.17 (m, 2*H*), 7.19 (t, J = 7.4 Hz, 1*H*), 7.27 (dd, J = 7.4, 7.0 Hz, 2*H*), 7.34 (d, J = 7.0 Hz, 2*H*), 7.47–7.51 (m, 1*H*), 7.53–7.56 (m, 1*H*), 10.58 (br. s, 1*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 26.9, 41.9, 45.0, 46.4, 56.0, 80.6, 110.0, 117.9, 120.8, 121.0, 126.4, 127.3, 128.0, 135.0, 141.3, 143.6, 149.4, 150.0, 154.1; calcd for $C_{22}H_{27}N_7$ (389.50); C, 67.84; H, 6.99; N, 25.17. found: C, 67.57; H, 7.08; N, 25.35.

4-(1-(3-(Dimethylamino)propyl)-1H-benzo[d]imidazol-2-yl)-3-morpholino-1H-pyrazol-5-amine (1f). Prepared according to general procedure using benzimidazole **5b** and morpholine, white needles 0.15 g (81%), mp 90–92°C (dichloromethane–hexane); ^{1}H-NMR (400 MHz, DMSO-d_6) 1.63 (tt, J = 7.4, 7.0 Hz, 2*H*), 1.99 (s, 6*H*), 2.04 (t, J = 7.0 Hz, 2*H*), 2.84 (dd, J = 4.7, 4.3 Hz, 4*H*), 3.61 (dd, J = 4.7, 4.3 Hz, 4*H*), 4.47 (t, J = 7.4, 7.0 Hz, 2*H*), 5.37 (br. s, 2*H*), 7.11–7.20 (m, 2*H*), 7.49–7.59 (m, 2*H*), 11.12 (br. s, 1*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 27.0, 41.5, 44.9, 49.4, 56.0, 65.8, 82.2, 110.2, 118.2, 121.2, 135.0, 143.4, 149.0, 149.7, 154.7, 162.3; calcd for $C_{19}H_{27}N_7O$ (369.46); C, 61.77; H, 7.37; N, 26.54; found: 61.42; H, 7.45; N, 26.83.

4-(1-(3-(Dimethylamino)propyl)-1H-benzo[d]imidazol-2-yl)-3-(4-methylpiperazin-1-yl)-1H-pyrazol-5-amine (1g). Prepared according to general procedure using benzimidazole **5b** and 1-methylpiperazine, white needles 0.14 g (76%), mp 89–91°C (dichloromethane–hexane); ^{1}H-NMR (400 MHz, DMSO-d_6) 1.61 (ddd, J = 7.4, 7.0, 6.7 Hz, 2*H*), 1.98 (s,

6*H*), 2.02 (dd, *J* = 7.0, 6.7 Hz, 2*H*), 2.12 (s, 3*H*), 2.27–2.37 (m, 4*H*), 2.79–2.91 (m, 4*H*), 4.47 (dd, *J* = 7.9, 7.4 Hz, 2*H*), 5.34 (br. s., 2*H*), 7.06–7.24 (m, 2*H*), 7.45–7.61 (m, 2*H*), 11.09 (br. s, 1*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 27.0, 41.5, 45.0, 45.9, 48.8, 54.3, 56.0, 82.4, 110.1, 118.2, 121.2, 135.0, 143.4, 149.2, 149.8, 154.8, 162.4; calcd for $C_{20}H_{30}N_8$ (382.51); C, 62.80; H, 7.91; N, 29.29; found: C, 62.47; H, 8.05; N, 29.48.

***N*^{3}-Fenyl-4-(1-(2-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)-1H-pyrazol-3,5-diamine (1h).** Prepared according to general procedure using benzimidazole **5c** and aniline. The mixture was heated for 24 h instead of 8 h, white needles 0.16 g (81%), mp 68–71°C (dichloromethane–hexane); ^{1}H-NMR (400 MHz, DMSO-d_6) 3.02 (t, *J* = 7.4 Hz, 2*H*), 4.63 (t, *J* = 7.4 Hz, 2*H*), 5.49 (br. s., 2*H*), 6.70 (td, *J* = 7.4, 1.2 Hz, 1*H*), 6.87 (d, *J* = 7.8 Hz, 1*H*), 7.03 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1*H*), 7.11–7.20 (m, 4*H*), 7.33 (d, *J* = 7.8 Hz, 2*H*), 7.46 (td, *J* = 7.6, 2.0 Hz, 1*H*), 7.49–7.53 (m, 1*H*), 7.60–7.65 (m, 1*H*), 8.12 (br. s., 1*H*), 8.35 (ddd, *J* = 4.7, 1.6, 0.8 Hz, 1*H*), 11.16 (br. s., 1*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 36.9, 43.8, 82.8, 110.2, 115.4, 118.1, 118.3, 121.1, 121.2, 121.5, 122.9, 128.6, 134.9, 136.2, 143.2, 143.5, 147.3, 148.4, 148.6, 148.7, 157.8; calcd for $C_{23}H_{21}N_7$ (395.46); C, 69.85; H, 5.35; N, 24.79; found: C, 69.52; H, 5.43; N, 25.05.

***N*^{3}-Benzyl-4-(1-(2-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)-1H-pyrazol-3,5-diamine (1i).** Prepared according to general procedure using benzimidazole **5c** and benzylamine, white needles 0.18 g (90%), mp 68–70°C (dichloromethane–hexane); ^{1}H-NMR (400 MHz, DMSO-d_6) 3.02 (t, *J* = 7.6 Hz, 2*H*), 4.29 (d, *J* = 5.9 Hz, 2*H*), 4.71 (t, *J* = 7.6 Hz, 2*H*), 5.25 (br. s., 2*H*), 5.77 (br. s., 1*H*), 7.01 (d, *J* = 7.4 Hz, 1*H*), 7.11–7.14 (m, 2*H*), 7.15–7.21 (m, 2*H*), 7.25 (td, *J* = 7.2, 1.6 Hz, 2*H*), 7.33 (dd, *J* = 7.2, 1.6 Hz, 2*H*), 7.45–7.50 (m, 1*H*), 7.52–7.56 (m, 1*H*), 7.57–7.60 (m, 1*H*), 8.43–8.48 (m, 1*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 37.0, 43.6, 46.5, 80.6, 110.1, 117.8, 120.9, 121.1, 121.6, 123.1, 126.4, 127.3, 128.0, 134.9, 136.4, 141.0, 143.6, 148.9, 149.0, 149.4, 152.6, 158.0; calcd for $C_{24}H_{23}N_7$ (409.49); C, 70.39; H, 5.66; N, 23.94; found: C, 70.14; H, 5.58; N, 24.27.

***N*^{3}-Propyl-4-(1-(2-(pyridin-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)-1H-pyrazol-3,5-diamine (1j).** Prepared according to general procedure using benzimidazole **5c** and propylamine, white needles 0.15 g (84%), mp 70–72°C (dichloromethane–hexane); ^{1}H-NMR (400 MHz, DMSO-d_6) 0.85 (t, *J* = 7.4 Hz, 3*H*), 1.50 (qt, *J* = 7.4, 7.0 Hz, 2*H*), 2.97–3.07 (m, 4*H*), 4.68 (t, *J* = 7.8 Hz, 2*H*), 5.12 (br. s, 2*H*), 5.34 (br. s, 1*H*), 7.03 (d, *J* = 7.8 Hz, 1*H*), 7.09–7.18 (m, 3*H*), 7.43–7.49 (m, 1*H*), 7.51–7.55 (m, 1*H*), 7.58 (td, *J* = 7.6, 2.0 Hz, 1*H*), 8.44 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 11.6, 22.6, 37.0, 43.6, 44.8, 80.5, 110.1, 117.8, 120.9, 121.1, 121.6, 123.1, 134.9, 136.4, 143.6, 149.0, 149.5, 149.6, 152.3, 158.0; calcd for $C_{20}H_{23}N_7$ (361.44); C, 66.46; H, 6.41; N, 27.13; found: C, 66.15; H, 6.36; N, 27.49.

***N*^{3}-Benzyl-4-(1-(3-(pyridin-4-yl)propyl)-1H-benzo[d]imidazol-2-yl)-1H-pyrazol-5-amine (1k).** Prepared according to general procedure using benzimidazole **5d** and benzylamine, white needles 0.18 g (87%), mp 83–85°C (dichloromethane–hexane); ^{1}H-NMR (400 MHz, DMSO-d_6) 1.91 (tt, *J* = 7.4 Hz, 2*H*), 2.37 (t, *J* = 7.4 Hz, 2*H*), 4.29 (d, *J* = 6.7 Hz, 2*H*), 4.34 (t, *J* = 7.0 Hz, 2*H*), 5.20 (br. s, 2*H*), 7.02 (dd, *J* = 4.7, 1.6 Hz, 2*H*), 7.12–7.16 (m, 2*H*), 7.17 (td, *J* = 7.0, 1.6 Hz, 1*H*), 7.22 (ddd, *J* = 7.0, 6.8, 1.9 Hz, 2*H*), 7.31 (dd, *J* = 6.8, 1.6 Hz, 2*H*), 7.47–7.51 (m, 1*H*), 7.54–7.58 (m, 1*H*), 8.37 (dd, *J* = 4.7, 1.6 Hz, 2*H*), 10.69 (br. s, 1*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 29.1, 31.2, 43.2, 46.4, 80.7, 110.2, 118.0, 120.9, 121.1, 123.6, 126.4, 127.3, 128.0, 134.9, 140.1, 143.7, 149.3, 149.4, 149.9, 150.6, 154.4; calcd for $C_{25}H_{25}N_7$ (423.51); C, 70.90; H, 5.95; N, 23.15; found: C, 0.77; H, 6.31; N, 22.92.

***3*-Morpholino-4-(1-(3-(pyridin-4-yl)propyl)-1H-benzo[d]imidazol-2-yl)-1H-pyrazol-5-amine (1l).** Prepared according to general procedure using benzimidazole **5d** and morpholine, white needles 0.16 g (77%), mp 97–99°C (dichloromethane–hexane); ^{1}H-NMR (400 MHz, DMSO-d_6) 1.88 (tt, *J* = 7.4, 7.0 Hz, 2*H*), 2.43 (t, *J* = 7.4 Hz, 2*H*), 2.75 (t, *J* = 4.3 Hz, 4*H*), 3.52 (t, *J* = 4.3 Hz, 4*H*), 4.45 (t, *J* = 7.0 Hz, 2*H*), 5.39 (br. s, 2*H*), 7.04 (d, *J* = 5.1 Hz, 2*H*), 7.12–7.21 (m, 2*H*), 7.52 (d, *J* = 7.8 Hz, 1*H*), 7.58 (d, *J* = 7.0 Hz, 1*H*), 8.37 (d, *J* = 5.1 Hz, 2*H*), 11.15 (br. s, 1*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 28.8, 31.1, 42.6, 49.3, 65.8, 82.2, 110.2, 118.3, 121.2, 121.3, 123.6, 134.8, 143.5, 149.1, 149.4, 149.8, 150.3, 154.7; calcd for $C_{22}H_{25}N_7O$ (403.48); C, 65.49; H, 6.25; N, 24.30; found: C, 65.61; H, 6.46; N, 23.97.

***N*^{3}-Propyl-4-(1-(3-(pyridin-4-yl)propyl)-1H-benzo[d]imidazol-2-yl)-1H-pyrazol-5-amine (1m).** Prepared according to general procedure using benzimidazole **5d** and propylamine, white needles 0.16 g (86%), mp 92–94°C (dichloromethane–hexane); ^{1}H-NMR (400 MHz, DMSO-d_6) 0.83 (t, *J* = 7.4 Hz, 2*H*), 1.48 (qt, *J* = 7.4, 7.0 Hz, 2*H*), 1.92 (tt, *J* = 7.4, 7.0 Hz, 2*H*), 2.39 (t, *J* = 7.4 Hz, 2*H*), 3.01 (td, *J* = 7.0, 5.2 Hz, 2*H*), 4.33 (t, *J* = 7.2 Hz, 2*H*), 5.09 (br. s, 2*H*), 5.30 (br. s, 1*H*), 7.04 (dd, *J* = 4.3, 1.6 Hz, 2*H*), 7.12–7.18 (m, 2*H*), 7.47–7.51 (m, 1*H*), 7.54–7.58 (m, 1*H*), 8.37 (dd, *J* = 4.3, 1.6 Hz, 2*H*), 10.72 (br. s, 1*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 11.5, 22.5, 29.0, 31.2, 43.1, 44.8, 80.5, 110.1, 117.9, 120.9, 121.1, 123.6, 134.9, 143.7, 149.4, 149.6, 149.9, 150.3, 154.3; calcd for $C_{21}H_{25}N_7$ (375.47); C, 67.18; H, 6.71; N, 26.11; found: C, 66.91; H, 6.75; N, 28.34.

***4*-(1H-Benzimidazol-2-yl)-*N*^{3}-phenyl-1H-pyrazol-3,5-diamine (1n).** Prepared according to general procedure using benzimidazole **2** and aniline. The mixture was heated for 24 h instead of 8 h, white solid 0.11 g (73%), mp 272–274°C (acetonitrile); ^{1}H-NMR (400 MHz, DMSO-d_6) 6.03 (br. s., 2*H*), 6.79 (t, *J* = 7.2 Hz, 1*H*), 7.08–7.17 (m, 2*H*), 7.24 (t, *J* = 7.8 Hz, 2*H*), 7.46 (d, *J* = 7.0 Hz, 1*H*), 7.55 (d, *J* = 7.0 Hz, 2*H*), 7.59 (d, *J* = 7.4 Hz, 1*H*), 9.79 (br. s., 1*H*), 11.15 (br. s., 1*H*), 11.76 (s, 1*H*); ^{13}C-NMR (75 MHz, DMSO-d_6) 82.0, 110.4, 115.9, 116.9, 118.7, 120.9, 121.2, 128.8, 133.6,

142.5, 142.8, 146.2, 148.6, 150.0; calcd for $C_{16}H_{14}N_6$ (290.32); C, 66.19; H, 4.86; N, 28.95; found: C, 65.93; H, 5.03; N, 29.04.

4-(1H-Benzimidazol-2-yl)-N³-benzyl-1H-pyrazol-3,5-diamine (1o). Prepared according to general procedure using benzimidazole **2** and benzylamine, white solid 0.12 g (78%), mp 258–260°C (acetonitrile); ^{1}H-NMR (400 MHz, DMSO-d_6) 4.46 (d, J = 5.9 Hz, 2*H*), 5.88 (br. s., 2*H*), 6.73 (br. s., 1*H*), 7.03–7.11 (m, 2*H*), 7.23 (d, J = 7.4 Hz, 1*H*), 7.32 (dd, J = 7.4, 7.0 Hz, 2*H*), 7.40 (d, J = 7.0 Hz, 2*H*), 7.43–7.48 (m, 2*H*), 10.76 (br. s., 1*H*), 11.57 (br. s., 1*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 46.3, 81.1, 110.1, 116.6, 120.4, 120.9, 126.6, 127.3, 128.2, 133.6, 140.7, 143.0, 148.6, 149.2, 153.2; calcd for $C_{17}H_{16}N_6$ (304.35); C, 67.09; H, 5.30; N, 27.61; found: C, 66.85; H, 5.43; N, 27.72.

4-(1H-Benzo[d]imidazol-2-yl)-3-(4-methylpiperazin-1-yl)-1H-pyrazol-5-amine (1p). Prepared according to general procedure using benzimidazole **2** and 1-methylpiperazine, white solid 0.14 g (91%), mp 214–216°C (acetonitrile); ^{1}H-NMR (400 MHz, DMSO-d_6) 2.26 (s, 3*H*), 2.55–2.61 (m, 4*H*), 2.97–3.05 (m, 4*H*), 6.11 (br. s, 2*H*), 7.04–7.10 (m, 2*H*), 7.46–7.54 (m, 2*H*), 10.99 (br. s, 1*H*), 11.24 (br. s, 1*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 45.9, 50.6, 53.9, 83.9, 111.1, 116.9, 120.6, 120.9, 133.7, 143.1, 148.6, 149.6, 156.0; calcd for $C_{15}H_{19}N_7$ (297.34); C, 60.59; H 6.44; N, 32.97; found: C, 60.21; H, 6.56; N, 33.15.

4-(1H-Benzimidazol-2-yl)-N³-propyl-1H-pyrazol-3,5-diamine (1q). Prepared according to general procedure using benzimidazole **2** and propylamine, white solid 0.11 g (84%), mp 244–246°C (acetonitrile); ^{1}H-NMR (400 MHz, DMSO-d_6) 0.95 (t, J = 7.4 Hz, 3*H*), 1.61 (qt, J = 7.4, 7.0 Hz, 2*H*), 3.17 (t, J = 7.0 Hz, 2*H*), 5.60 (br. s., 2*H*), 6.51 (br. s, 1*H*), 7.02–7.10 (m, 2*H*), 7.40–7.45 (m, 2*H*), 10.80 (br. s., 1*H*), 11.47 (br. s., 1*H*); ^{13}C-NMR (101 MHz, DMSO-d_6) 11.6, 22.7, 44.6, 80.9, 110.1, 116.4, 120.54, 120.63, 133.6, 142.9, 148.9, 149.4, 152.1; calcd for $C_{13}H_{16}N_6$ (256.31); C, 60.92; H, 6.29; N, 32.79; found: C, 60.61; H, 6.36; N, 33.03.

BIOLOGICAL ASSAYS

Biological activity of prepared compounds was assayed as described previously 13a. The compounds have been tested in kinase inhibition assays for their inhibitory potency toward human CDK2/cyclin E produced through a baculoviral expression system and using histone H1 as a substrate. The concentration of the test compounds required to decrease the CDK2 activity by 50% was determined from dose–response curves and designated as IC_{50}. The compounds were also assayed for cytotoxicity against MCF7 and K562 cancer cell lines. Briefly, cells were incubated for 72 h with compounds using threefold dilutions in triplicate. After this period, live cells were labeled by Calcein AM and quantified by measurement of their fluorescence with a Fluoroskan Ascent microplate reader (Labsystems). IC_{50} (the drug concentration that reduced the number of viable cells to 50%) values were determined from the dose–response curves.

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