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FULL-LENGTH PAPER

One pot three component reaction for the rapid synthesis of pyrrolo[1,2-*a*]benzimidazoles

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Abstract An efficient strategy for the synthesis of pyrrolo [1,2-*a*]-benzimidazole (PBI) linked to an ionic liquid (ILs) as a soluble support under microwave irradiation was explored. The key intermediate benzimidazoles were synthesized via N-acylation followed by cyclodehydration of IL-supported methyl-3-amino-4-(isobutylamino) benzoate. The synthesis of the IL-bound PBI was performed by one-pot three-component condensation under microwave dielectric heating, which involved a Knoevenagel condensation and a [4+1]-cycloaddition reaction. The reaction was monitored directly by means of ^{1}H NMR. All final products were obtained in good yield and high purity after precipitation.

Keywords Pyrrolo[1, 2-*a*]benzimidazole · Microwave chemistry · Soluble supported synthesis · Ionic liquid · One-pot three component · Multicomponent reaction (MCR)

Introduction

Benzimidazole heterocycles found in many biologically active natural products and pharmaceutically attractive lead molecules (e.g., albendazole, oxfenbendazole, thiabendazole, mebendazole, pantoprazole, etc.) [1–3]. Benzimidazole analogs were synthesized [4–6] with substitution of different groups or incorporating with a classical heterocyclic moiety, such as pyridine, pyrimidine, pyrazine, and imidazole cyclized compounds [7–11], which have resulted in compounds with significant biological activity of anticancer, antitumor, and topoisomerase inhibitor, e.g., tetrahydroimidazo[4,5,l-j,k] [1,4]-benzodiazepin-2(1H)-one, ciprofloxacin, lansoprazole, and omeprazole [12–14]. Therefore, the search for efficient methods which allows for the facile synthesis of new polyheterocycles containing the benzimidazole scaffold would be attractive to organic as well as medicinal research.

The benzimidazole ring system integrating with pyrrole is an important pharmacophore and significant structure in biologically active compounds (Fig. 1) [1–3,12–14]. Tremendous interest has been received for the development of efficient approaches for the synthesis of PBI due to their wide range of applications in pharmaceutical industry such as useful in treating central nervous system disorder, DNA cleaving agent, and used in synthesis of dyes [15–17]. 6-Aziridinylpyrrolo[1,2-*a*]benzimidazolequinones (PBIs, **III**) which have important medicinal interest such as reductive alkylating agents of the DNA phosphate backbone [17].

Although different methods have been reported for the synthesis of PBI to deliver these heterocycles from various precursors [18–25], these approaches suffer of drawbacks, such as the handling of highly toxic chemicals, prolonged reaction times at elevated temperatures, and transition metal used as a catalyst. Hence, strong interest remains toward the development of new strategies for the construction of these interesting compounds to explore their potential therapeutic applications [26–28]. The ionic-liquid-supported synthesis strategy has many advantages for the synthesis of bioactive molecules, such as straight-forward purification via simple precipitation for IL-bound intermediates and the reaction progress could be easily monitored by proton NMR without cleavage of IL support [29]. Moreover, multicomponent reactions (MCRs) with ILs as a solvent or catalyst are promising methods for eco-compatible heterocyclic synthesis [30,31].

MCRs are useful and powerful methods for the synthesis of bioactive molecules in recent years. The use of IL-supported substrates in MCRs has received a great

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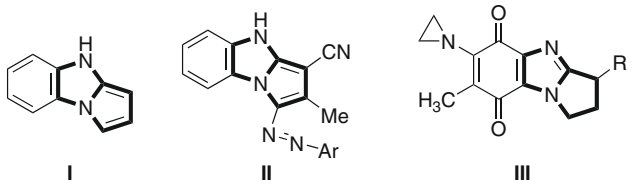


Fig. 1 Biologically active pyrrolo[1,2-*a*]benzimidazole derivatives

demand in heterocyclic chemistry due to advantages such as ecologically benign nature, greater productivity, simple operation process, easy and simple purification, and enhanced reaction efficiency [30–32]. The [4+1] cycloaddition in MCRs of carbenes such as isocyanides with electrophilic heterodienes (*a*-iminonitriles, acylimines, azadienes, diazadienes, α, β-unsaturated carbonyl compounds) is a powerful method for the efficient synthesis of heterocyclic molecular frameworks [33–35]. To the best of our knowledge, there is no solid or ILs support as well as isocyanide-based MCRs for the synthesis of polysubstituted PBI, particularly with regarding to the availability of the starting materials.

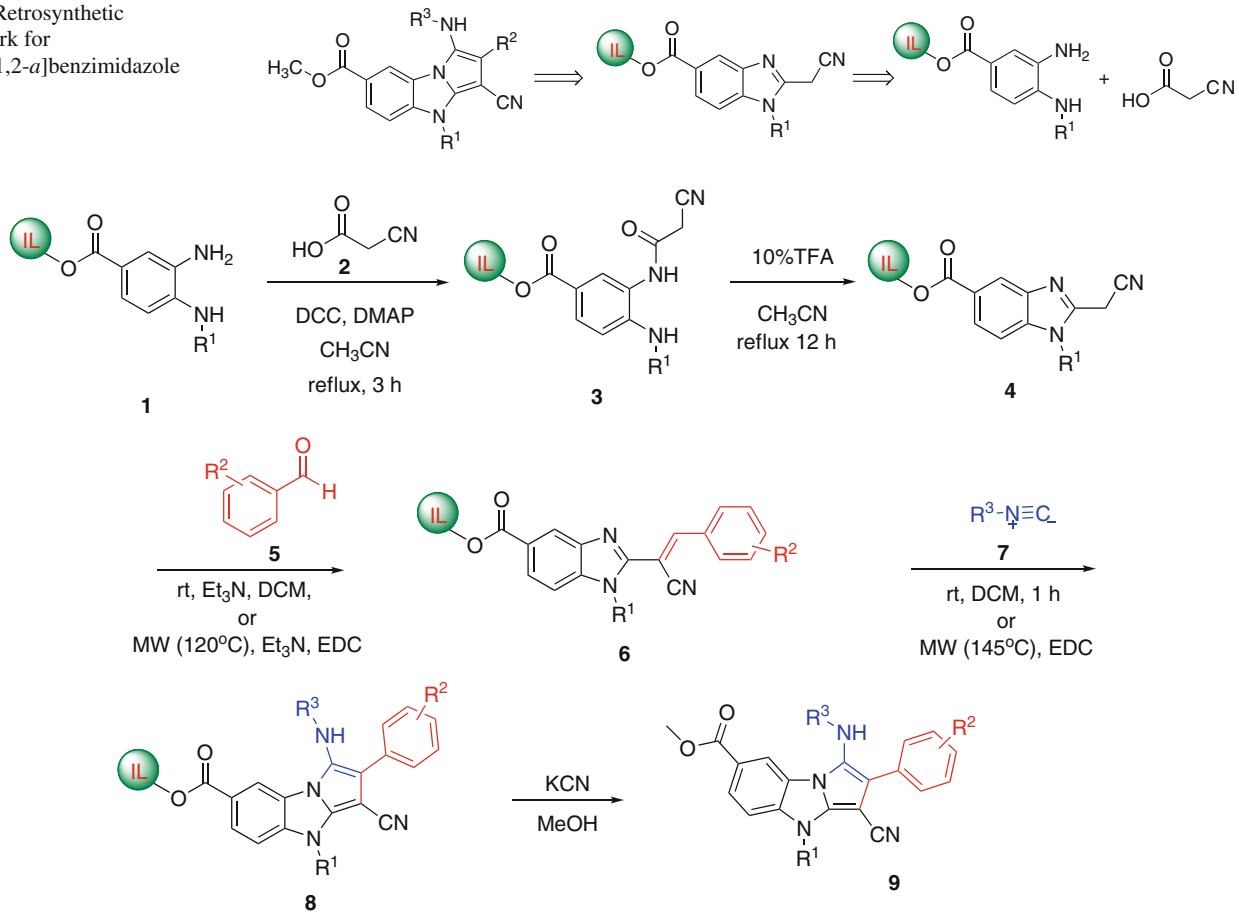
In continuation of our interest in the synthesis of novel polyfunctionalized heterocycles of biological importance [36–39], we report here a novel and efficient synthetic strategy for the one-pot three-component synthesis of pyrrolo [1, 2 − *a*]benzimidazoles on an ionic liquid support under microwave irradiation. The synthetic approach to develop the PBI scaffold is illustrated in Fig. 2.

Results and discussion

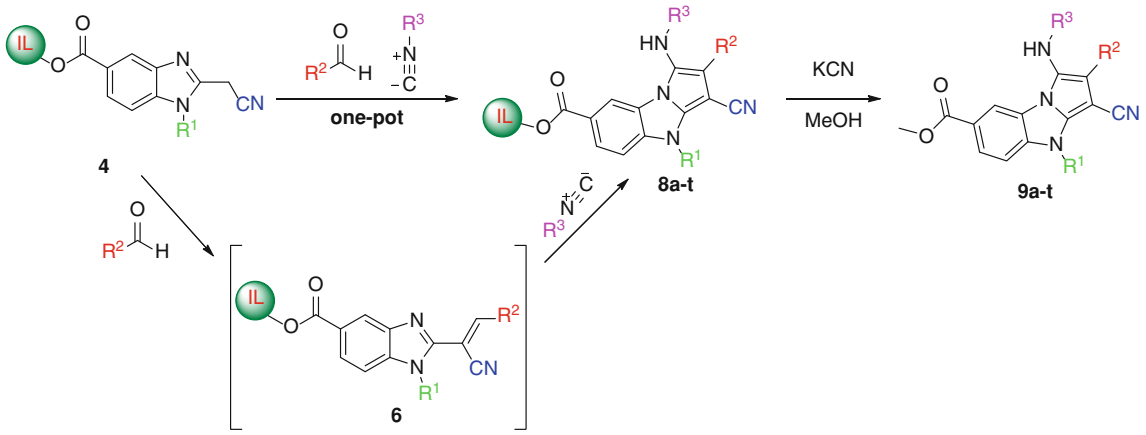
Our synthetic strategy commenced with the synthesis of IL-supported methyl-3-amino-4-(isobutylamino)benzoate **1** by linking commercially available 4-fluoro-3-nitrobenzoic acid to 1-(2-hydroxyethyl)-3 -methylimidazolium tetrafluoroborate ([hydemim][BF_4]) (IL) via an esterification reaction followed by an *ipso*-fluoro displacement of the activated aromatic fluoride with various primary amines followed by aromatic nitro reduction [40].

For the synthesis of PBIs, we started with methyl-3-amino-4-(isobutylamino) benzoate **1** as shown in Scheme 1. The IL-supported **1** was coupled with cyanoacetic acid **2** in

Fig. 2 Retrosynthetic framework for pyrrolo[1,2-*a*]benzimidazole



Scheme 1 Stepwise synthesis route of pyrrolo[1,2-*a*]benzimidazoles



Scheme 2 Synthesis of substituted PBI via the MCR approach

the presence of 4-dimethylaminopyridine (DMAP) and dicyclohexylcabodiimide (DCC) in refluxing acetonitrile for 3 h to obtain amide **3** in good yield. The suspended dicyclohexyl urea (DCU) was then filtered off and ionic liquid conjugated methyl-3-(2-cyanoacetamido)-4-(isobutylamino) benzoate **3** was precipitated out with ether to remove the excess unreacted reagents and side products. Compound **3** was confirmed by ^{1}H NMR where the alpha proton of the cyano group ($-CH_2CN$) was at ~3.35 ppm, and mass spectroscopy (MS). Cyclodehydration of **3** in the presence of TFA afforded the desired PBI **4** confirmed by MS and ^{1}H NMR (disappearance of ($-CH_2$ CN) proton at 3.6 ppm).

In a subsequent step, benzimidazole **4** was condensed with aldehyde **5** in presence of Et_3N at either in dichloromethane room temperature for 60 min or in ethylene dichloride under microwave irradiation (120 °C) for 10 min to obtain Knoevenagel adduct **6** in good yields. Adduct **6** was then reacted with isocyanide **7** at either room temperature in dichloromethane for 60 min or under microwave irradiation in ethylene dichloride (145 °C, 10 min) to afford cyclized IL-PBI **8**. Although these conditions afforded **8**, they both suffered from low overall yields.

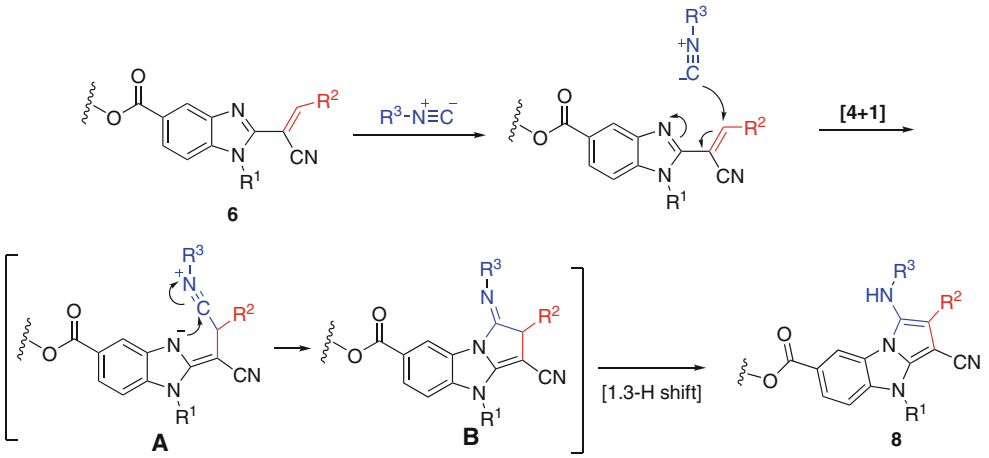
In order to improve yields and reaction efficiency, we decided to modify the strategy into one-pot three-component reaction under microwave irradiation. A model reaction of IL-supported benzimidazole **4** condensed with the aldehyde **5** and isocyanide **7** via one-pot three-component condensation was performed (Scheme 2). The formation of intermediate **6** was confirmed by ^{1}H NMR of the newly formed azomethine proton shown at ~8.33 ppm and disappearance of alpha proton of cyano group.

The one-pot MCR reaction in acetonitrile with Et_3N under microwave irradiation at 150 °C for 15 min offered the best yield for IL-supported PBI **8**. The final removal of the IL support from compound **8** was achieved via transesterification using KCN in MeOH to obtain methyl ester PBI **9**. The IL support was removed by precipitation followed by an ether wash. Final product **9** was confirmed by ^{1}H NMR where the $-OCH_3$ singlet was recorded at 3.9 ppm and broad –NH singlet at ~3.5 ppm.

A plausible mechanistic pathway for the formation of PBI **8** is depicted in Scheme 3. During the initial reaction of benzimidazole moieties **4** and aldehyde **5**, condensation via nucleophilic addition of **4** to a carbonyl group of aldehyde followed by dehydration reaction to afford condensed product **6**. This intermediate was isolated and its structure was confirmed. Then [4 + 1]-cycloaddition between Knoevenagel adduct **6** and isocyanides led to the formation of intermediate **A** which underwent intermolecular cyclization to give intermediate **B**. Ultimately, this adduct could not be isolated due to tautomerization into PBI **8**.

Under these conditions, the scope for this reaction was explored and the results are summarized in Table 1. Use of different substituted aldehydes, various amines, and numerous isocyanides in this one-pot reaction smoothly produced respective PBI with additional set of diversity that highlighted the versatility of this method. The reaction proceeded well with aromatic aldehydes containing both electron-withdrawing and electron-donating substituents as well as cyclic or acyclic isocyanides. Unambiguous structural elucidation was accomplished by single crystal X-ray diffraction of **9h** as shown with an ORTEP diagram in Fig. 3.

In conclusion, we have developed IL-supported one-pot three-component reaction targeted to the synthesis of bi-heterocyclic fused pyrrole[1,2-a]-benzimidazole under microwave condition. This reaction proceeds stepwise via the condensation of aldehyde with active methylene group of benzimidazole moiety followed by [4 + 1]-cycloaddition with isocyanides to obtain polyfunctionalized PBI. The ionic liquid bound intermediates and final products were purified by precipitation in all steps. These results suggest that the



Scheme 3 Plausible mechanism for cycloaddition reaction

use of MCRs and ILs under MW irradiation not only reduced the reaction time but also significantly enhanced the reaction efficiency and outcome.

Experimental

General synthetic procedures for 1-amino-4*H*-pyrrolo-[1,2-*a*]-benzimidazole by ionic solution

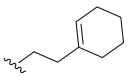
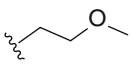
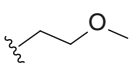
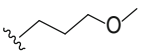
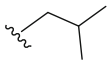
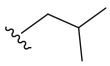
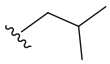
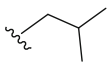
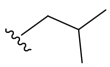
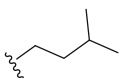
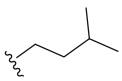
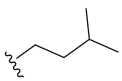
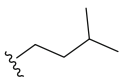
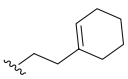
Synthesis of ionic-liquid-supported intermediate **1** was followed the procedure published in [40]. Ionic liquid-bound *o*-phenylediamine **1** (0.50 g, 1.2 mmol, 1 equiv) was dissolved in acetonitrile (100 mL) followed by addition of 2-cyanoacetic acid **2** (0.157 g, 1.85 mmol, 1.5 equiv) and *N*, *N*′-DCC (0.382 g, 1.85 mmol, 1.5 equiv) as well as DMAP (0.226 g, 1.85 mmol, 1.5 equiv) at room temperature. After addition was over, the system was flushed with nitrogen thoroughly, the resultant reaction mixture was refluxed for 3 h. The progress of reaction was monitored by proton NMR. The white powder byproduct *N*, *N*′-DCU was removed and ether was slowly added to precipitate compound **3** to obtain the desired *N*-acylated **3** product. To a solution of **3** (0.471 g, 1 mmol, 1 equiv) in acetonitrile (100 mL) 10 % TFA with acetonitrile was added. The resulting homogenous mixture was refluxed until the reaction completion and diluted with ether (100 mL). The precipitate of **4** was filtered through a sintered funnel and washed with excess ether to give the desired benzimidazole **4**. For the multicomponent reaction, a solution of **4** (0.50 g, 1.13 mmol, 1 equiv) in acetonitrile (15 mL), in a microwave vial, aldehyde (0.25 g, 1.65 mmol, 1.5 equiv), and isocyanides (0.13 g, 1.65 mmol, 1.5 equiv) were added with Et_3N (0.05 g, 0.55 mmol, 0.5 equiv). The reaction mixture was microwave irradiated at 150 °C (250 W) for 20 min. After reaction completion, the solvent was diluted by the addition of ether to precipitate the desired IL-supported PBI **8**. Cleavage of the IL-support from **8** (0.50 g, 0.74 mmol, 1 equiv) was performed with potassium cyanide (0.243 g, 3.73 mmol, 5 equiv) in methanol (20 mL). The mixture was stirred at ambient temperature until the complete release of **8** to support-free compound **9**. The mixture was filtered, washed with excess ether, and the resulting crude residue was subjected to HPLC analysis immediately (80 % purity). The residue was purified by silica column chromatography (eluent: 20 % EA in hexane) to obtain the corresponding 1-amino-4*H*-pyrrolo-[1,2-*a*]-benzimidazole **9a** (85 %), and its structure was confirmed by ^{1}H NMR, ^{13}C-DEPT NMR, 2D NMR, HRMS, and X-ray crystallography analysis.

This procedure was used for the synthesis of all **9** derivatives.

*Methyl 1-(tert-butylamino)-3-cyano-4-cyclopentyl-2-(4-nitrophenyl)-4H-benzo[d]-pyrrolo[1,2-a]imidazole-7-carboxylate (**9a**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.81 (d, J = 1.5 Hz, 1H), 8.35 (d, J = 8.9 Hz, 2H), 8.08 (dd, J = 8.7, 1.6 Hz, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.7 Hz, 1H), 5.08 (quin, J = 9.0 Hz, 1H), 4.00 (s, 3H), 2.33–2.86 (m, 4H), 2.10–2.65 (m, 2H), 1.88–1.1.84 (m, 3H), 0.99 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ 167.1, 147.0, 141.3, 139.8, 138.9, 130.2, 126.5, 126.0, 124.4, 123.2, 122.7, 122.5, 117.8, 115.2, 110.1, 64.3, 57.7, 57.4, 52.8, 30.3, 30.1, 24.7; IR (cm^{-1}, neat) 2954, 2200, 1718, 1668, 1525; MS (ESI) m/z: 499.3 (M^+); HRMS: Calculated for $C_{28}H_{29}N_5O_4$: 499.2220; Found: 499.2222 m/z; HPLC purity: 80 %.

Table 1 Scope of the one-pot three-component synthetic approach for the synthesis of substituted PBIs

Entry	R^1	R^2	R^3	Yield[a] (%)	Purity[b] (%)	LRMS[c]
9a		4-NO_2–Ph	*t*-Bu	86	80	500
9b		4-NO_2–Ph	Benzyl	80	79	534
9c		4-NO_2–Ph	C_6H_{11}	90	80	526
9d		C_2H_5	*t*-Bu	77	75	447
9e		*iso*-C_3H_7	*t*-Bu	80	95	411
9f		4-OMe–Ph	*t*-Bu	85	95	475
9g		$Ph(CH_2)_2$	*t*-Bu	73	75	473
9h		4-NO_2–Ph	*t*-Bu	85	87	487
9i		5-NO_2-furan	*t*-Bu	89	95	477
9j		4-Br–Ph	*t*-Bu	83	89	520
9k		5-Benzo[1,3]dioxole	Benzyl	71	67	521
9l		4-NO_2–Ph	C_6H_{11}	85	73	514
9m		2-F–Ph	*t*-Bu	81	87	474
9n		C_2H_5	*t*-Bu	79	89	408
9o		3-NO_2–Ph	*t*-Bu	77	81	501
9p		3-Furaldehyde	*t*-Bu	82	85	446
9q		*iso*-C_3H_7	*t*-Bu	79	91	460
9r		C_2H_5	*t*-Bu	76	92	380
9s		*n*-C_3H_7	*t*-Bu	72	95	394
9t		*iso*-C_3H_7	*t*-Bu	78	98	394

Reaction performed under MW irradiation (150 °C, 15 min)

[a] Isolated yield after column purification

[b] HPLC recorded after the cleavage followed by precipitation and washing

[c] Mass is ESI(M+1)

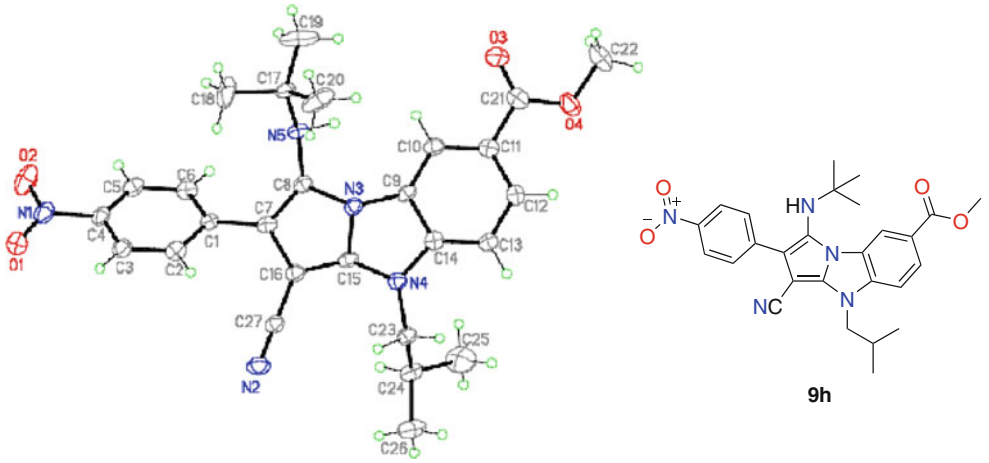


Fig 3 ORTEP diagram of methyl 1-(*tert*-butylamino)-3-cyano-4-isobutyl-2 -(4-nitrophenyl)-4H-benzo[d]pyrrolo[1,2-a]imidazole-7-carboxylate (**9h**)

*Methy 1-(benzylamino)-3-cyano-4-cyclopentyl-2-(4-nitrophenyl)-4 H-pyrrolo [1,2-a]benzimidazole-7-carboxylate (**9b**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.59 (d, J= 1.5 Hz, 1H), 8.27 (d, J = 8.7 Hz, 2H), 8.12 (dd, J = 8.7, 1.5 Hz, 1H), 7.59 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 1H), 7.33–7.22 (m, 5H), 5.09 (m, 1H), 4.22 (d, J = 4.4 Hz, 2H), 3.97 (s, 3H), 3.67 (br, 1H), 2.50–1.77 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$, δ166.9, 146.8, 140.0, 139.9, 138.9, 138.1, 129.5, 129.2, 128.6, 128.3, 126.4, 126.0, 125.0, 124.5, 123.1, 118.4, 117.8, 114.4, 110.1, 63.4, 57.8, 53.7, 52.7, 30.1, 24.6; IR (cm^{-1}, neat) 2960, 2931, 2198, 1716, 1585; MS (EI) m/z: 534 (M+1); HPLC purity: 79 %.

*Methyl 3-cyano-1-(cyclohexylamino)-4-cyclopentyl-2-(4-nitrophenyl)-4H-pyrrolo[1,2-a]benzimidazole-7-carboxylate (**9c**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.50 (s, 1H), 8.35 (d, J = 6.9 Hz, 2H), 8.09 (dd, J = 8.7, 1.5 Hz, 1H), 7.77 (d, J = 6.9 Hz, 2H), 7.37 (d, J = 8.7 Hz, 1H), 5.07 (quin, J = 9.0 Hz, 1H), 3.99 (s, 3H), 3.42 (m, 1H), 2.88 (br, 1H), 2.38–2.11(m, 7H), 1.90–1.53 (m, 9H), 1.57–1.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ167.0, 146.7, 140.6, 139.8, 138.9, 129.6, 126.2, 126.1, 124.6, 124.5, 122.9, 118.8, 118.0, 114.6, 109.9, 63.3, 57.8, 57.4, 52.7, 34.1, 30.0, 25.9, 25.1, 24.6; IR (cm^{-1}, neat) 2931, 2856, 2198, 1718, 1624; MS (EI) m/z: 525.3 (M$^+$); HRMS: Calculated for $C_{30}H_{31}N_5O_4$: 525.2376; found: 525.2377 m/z; HPLC purity: 80 %.

*Methyl 1-(tert-butylamino)-3-cyano-4-[2-(cyclohex-1-en-1-yl)ethyl]-2-ethyl-4H-pyrrolo[1,2-a]benzimidazole-7-carboxylate (**9d**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.61 (d, J = 1.2 Hz, 1H), 7.97 (dd, J = 8.6, 1.5 Hz, 1H), 7.16 (d, J = 8.7 Hz, 1H), 5.24 (s, 1H), 4.26 (t, J = 7.2 Hz, 2H), 3.95 (s, 3H), 2.66 (q,J = 7.5 Hz, 2H), 2.47 (t, J = 6.9 Hz, 2H), 1.98 (brs, 2H), 1.76 (s, 2H), 1.54–1.51 (m, 2H), 1.43–1.40 (m, 3H), 1.33 (t, J = 7.5 Hz, 3H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ167.4, 140.1, 139.6, 133.6, 126.4, 126.0, 125.5, 125.1, 121.8, 121.0, 118.0, 114.5, 108.6, 63.0, 55.6, 52.6, 43.5, 37.1, 30.6, 30.5, 28.7, 25.6, 23.1, 22.3, 19.5, 15.5; IR (cm^{-1}, neat) 3325, 2966, 2931, 2197, 1716; MS (EI) m/z: 446.3 (M$^+$); HRMS: Calculated for $C_{27}H_{34}N_4O_2$: 446.2682, found: 446.2678 m/z; HPLC purity: 75 %.

*Methyl 1-(tert-butylamino)-3-cyano-4-(2-methoxyethyl)-2-(propan-2-yl)-4H-pyrrolo[1,2-a]benzimidazole-7-carboxylate (**9e**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.66 (d, J = 1.5 Hz, 1H), 8.00 (dd, J = 8.6, 1.6 Hz, 1H), 7.33 (d, J = 8.7 Hz, 1H), 4.42 (t, J = 5.25 Hz, 2H), 3.96 (s, 3H), 3.88 (t, J = 5.1 Hz, 2H), 3.35 (s, 3H), 3.15–3.06 (m, 1H), 2.60 (brs, 1H), 1.43 (d, J = 6.9 Hz, 6H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ167.4, 140.9, 140.6, 130.4, 126.5, 125.4, 122.1, 120.1, 118.5, 114.5, 109.3, 71.3, 60.7, 59.6, 55.4, 52.6, 44.8, 30.5, 26.3, 23.3; IR (cm^{-1}, neat): 3325, 2964, 2929, 2197, 1716; MS (EI) m/z: 410.3 (M$^+$); HRMS: Calculated for $C_{23}H_{30}N_4O_3$: 410.2318; found: 410.2323 m/z; HPLC purity: 95 %.

*Methyl 1-(tert-butylamino)-3-cyano-4-(2-methoxyethyl)-2-(4-methoxyphenyl)-4H-pyrrolo [1,2-]benzimidazole-7-carboxylate (**9f**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.73 (d, J = 1.2 Hz, 1H), 8.03 (dd, J = 8.6, 1.5 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.7 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 4.45 (t, J = 5.1 Hz, 2H), 3.97 (s, 3H), 3.90–3.88 (m, 3H), 3.86 (s, 3H), 3.35 (s, 3H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ167.3, 159.2, 140.5, 140.0, 130.6, 126.6, 125.7, 124.5, 122.4, 122.0, 117.8, 114.8, 114.6, 109.5, 71.2, 63.7, 59.6, 56.7, 55.7, 52.7, 44.9, 30.3; IR (cm^{-1}, neat) 3348, 2960, 2362, 2198, 1714; MS (EI) m/z: 474.3 (M^+); HRMS: Calculated for $C_{27}H_{30}N_4O_4$: 474.2267, found: 474.2265 m/z; HPLC purity: 95 %.

*Methyl 1-(tert-butylamino)-3-cyano-4-(3-methoxypropyl)-2-(2-phenylethyl)-4H-pyrrolo[1,2-a]benzimidazole-7-carboxylate (**9g**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.62 (d, J = 1.2 Hz, 1H), 8.01 (dd, J = 8.6, 1.4 Hz, 1H), 7.28 (t, J = 8.0 Hz, 3H), 7.25–7.17 (m, 3H), 4.36 (t, J = 6.5 Hz, 2H), 3.94 (s, 3H), 3.38 (t, J = 5.6 Hz, 2H), 3.30 (s, 3H), 2.99–2.93 (m, 4H), 2.25–2.18 (m, 3H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ167.3, 142.1, 140.1, 140.0, 129.0, 128.8, 126.5, 126.4, 125.4, 123.1, 122.4, 122.0, 117.9, 114.7, 108.6, 69.1, 63.1, 59.0, 55.5, 52.6, 41.3, 37.1, 30.5, 29.6, 28.8; IR (cm^{-1}, neat) 3329, 2958, 2870, 2197, 1716; MS (EI) m/z: 486.3 (M^+); HRMS: Calculated for $C_{29}H_{34}N_4O_3$: 486.2631; found: 486.2621 m/z; HPLC purity: 75 %.

*Methyl 1-(tert-butylamino)-3-cyano-4-(2-methylpropyl)-2-(4-nitrophenyl)-4H-pyrrolo[1,2-a]benzimidazole-7-carboxylate (**9h**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.75 (d, J = 1.2 Hz, 1H), 8.33 (d, J = 6.9 Hz, 2H), 8.09 (dd, J = 8.6, 1.5 Hz, 1H), 7.78 (d, J = 7.05 Hz, 2H), 7.30 (d, J = 8.8 Hz, 1H), 4.10 (d, J = 7.5 Hz, 2H), 3.99 (s, 3H), 3.23 (br, 1H), 2.48–2.39 (m, 1H), 1.09 (d, J = 6.9 Hz, 6H), 0.99 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ167.1, 146.9, 141.3, 141.0, 140.2, 130.1, 126.3, 126.2, 124.4, 122.8, 122.7, 122.6, 117.1, 115.1, 109.2, 63.4, 57.4, 52.8, 52.0, 30.3, 29.3, 20.4; IR (cm^{-1}, neat) 3623, 2964, 2198, 1711, 1593, 1516; MS (EI) m/z: 487.3 (M^+); HRMS: Calculated for $C_{27}H_{29}N_5O_4$: 487.2220; found: 487.2223 m/z; HPLC purity: 87 %.

*Methyl 1-(tert-butylamino)-3-cyano-4-isobutyl-2-(5-nitrofuran-2-yl)-4H-benzo-[d]pyrrolo [1,2-a]imidazole-7-carboxylate (**9i**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.75 (s, 1H), 8.08 (d, J = 8.7, 1H), 7.43 (d, J = 3.6, 1H), 7.26 (d, J = 8.4, 1H), 6.97 (d, J = 3.6, 1H), 4.04 (d, J = 7.5, 2H), 3.99 (s, 3H), 3.77 (br, 1H), 2.43–2.30 (m, 1H), 1.19 (s, 9H), 1.06 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 152.1, 150.8, 141.4, 140.4, 126.8, 126.0, 125.9, 122.9, 116.4, 115.9, 114.7, 110.8, 109.3, 61.0, 58.1, 52.8, 51.9, 29.9, 29.2, 20.4; IR (cm^{-1}, neat) 3122, 2962, 2197, 1709, 1626; MS (EI) m/z: 477.2 (M^+); HRMS: Calculated for $C_{25}H_{27}N_5O_5$: 477.2012; found: 477.2007 m/z; HPLC purity: 95 %.

*Methyl 2-(4-bromophenyl)-1-(tert-butylamino)-3-cyano-4-isobutyl-4H-benzo[d]-pyrrolo[1,2-a]imidazole-7-carboxylate (**9j**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.73 (d, J = 1.5 Hz, 1H), 8.04 (dd, J = 8.6, 1.6 Hz, 1H), 7.57 (d, J = 6.6 Hz, 2H), 7.43 (d, J = 7.2 Hz, 2H), 7.24 (d, J = 8.4 Hz, 1H), 4.04 (d, J = 7.5 Hz, 2H), 3.97 (s, 3H), 3.21 (br, 1H), 2.45–2.36 (m, 1H), 1.05 (d, J = 6.6 Hz, 6H), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ167.2, 140.6, 140.1, 133.2, 132.2, 131.1, 126.4, 125.9, 123.7, 122.3, 122.0, 121.6, 117.4, 115.0, 109.0, 63.5, 57.0, 52.7, 51.9, 30.3, 29.3, 20.4; IR (cm^{-1}, neat) 3369, 2966, 2873, 2200, 1711; MS (EI) m/z: 520.2 (M^+); HRMS: Calculated for $C_{27}H_{29}BrN_4O_2$: 520.1474; found 520.1475 m/z; HPLC purity: 89 %.

*Methyl 2-(benzo[d][1,3]dioxol-5-yl)-1-(benzylamino)-3-cyano-4-isobutyl-4H-benzo[d]pyrrolo[1,2-a]imidazole-7-carboxylate (**9k**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.54 (d, J = 1.2 Hz, 1H), 8.27 (dd, J = 8.7, 1.5 Hz, 1H), 7.33–7.26 (m, 6H), 6.94–6.87 (m, 3H), 6.02 (s, 2H), 4.20(s, 2), 4.09 (d, J = 7.5 Hz, 2H), 3.93 (s, 3H), 3.65 (brs, 1H), 2.50–2.40 (m, 1H), 1.09 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ167.1, 148.4, 147.3, 140.3, 140.0, 138.7, 129.0, 128.6, 128.0, 126.7, 126.1, 125.9, 124.0, 122.8, 122.6, 199.8, 117.6, 114.2, 109.6, 109.1, 108.9, 101.5, 63.2, 53.9, 52.6, 52.0, 29.4, 20.4; IR (cm^{-1}, neat) 3569, 2958, 2927, 2200, 1714, 1618; MS (ESI) m/z: 521 (M+1); HPLC purity: 67 %.

*Methyl 3-cyano-1-(cyclohexylamino)-4-(2-methylpropyl)-2-(4-nitrophenyl)-4H-pyrrolo[1,2-a]benzimidazole-7-carboxylate (**9l**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.46 (d, J = 1.2 Hz, 1H), 8.32 (d, J = 7.8 Hz, 2H), 8.09 (dd,

J = 8.6, 1.4 Hz, 1H), 7.79 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 9 Hz, 1H), 4.09 (d, J = 7.5 Hz, 2H), 3.98 (s, 3H), 3.43 (br, 1H), 2.90 (s, 1H), 2.48–2.39 (m, 1H), 1.86–1.83 (m, 2H), 1.63–1.54 (m, 2H), 1.31–1.24 (m, 4H), 1.09 (d, J = 6.6 Hz, 6H), 0.90–0.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ167.0, 146.6, 141.1, 140.6, 140.2, 129.4, 126.5, 125.8, 124.6, 124.5, 123.0, 118.4, 117.2, 114.5, 109.1, 62.5, 57.5, 52.8, 52.0, 34.1, 29.4, 25.9, 25.1, 20.4; IR (cm^{-1}, neat) 2931, 2856, 2198, 1716, 1597; MS (EI) m/z: 513.3 (M^+); HRMS: Calculated for $C_{29}H_{31}N_5O_4$:513.2376; found: 513.2371 m/z; HPLC purity: 73 %.

*Methyl 1-(tert-butylamino)-3-cyano-2-(2-fluorophenyl)-4-(3-methylbutyl)-4H-pyrrolo[1,2-a]benzimidazole-7-carboxylate (**9m**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.81 (d, J = 1.5 Hz, 1H), 8.07 (dd, J = 8.6, 1.6 Hz, 1H), 7.62 (td, J = 7.5, 1.9 Hz, 1H), 7.36–7.15 (m, 4H), 4.32 (t, J = 7.65 Hz, 2H), 3.97 (s, 3H), 3.15 (br, 1H), 1.91–1.84 (m, 2H), 1.81–1.72(m, 1), 1.05 (d, J = 6.3 Hz, 6H), 0.99 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ167.2, 161.6, 158.4, 140.6, 139.6, 132.1, 132.0, 129.7, 129.5, 126.5, 126.0, 125.1, 125.1, 123.8, 122.3, 122.0, 121.8, 117.9, 117.2, 116.4, 116.1, 115.3, 108.4, 63.8, 56.5, 52.7, 43.1, 38.0, 30.1, 26.5, 22.9; IR (cm^{-1}, neat) 3367, 2960, 2873, 2202, 1718; MS (EI) m/z: 474.4 (M^+); HRMS: Calculated for $C_{28}H_{31}FN_4O_2$: 474.2431; found: 474.2433 m/z; HPLC purity: 87 %.

*Methyl 1-(tert-butylamino)-3-cyano-2-ethyl-4-(3-methylbutyl)-4H-pyrrolo[1,2-a] benzimidazole-7-carboxylate (**9n**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.62 (d, J = 1.5 Hz, 1H), 7.97 (dd, J = 8.7, 1.5 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 4.20 (t, J = 7.6 Hz, 2H), 3.95 (s, 3H), 2.66 (q, J = 7.5 Hz, 2H), 1.86–1.67 (m, 3H), 1.33 (t, J = 7.5 Hz, 3H), 1.23 (s, 9H), 1.02 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 167.3, 140.1, 139.5, 126.5, 126.1, 125.2, 121.9, 121.1, 117.9, 114.5, 108.2, 62.9, 55.6, 52.6, 43.0, 37.9, 30.5, 26.4, 22.9, 19.5, 15.4; IR (cm^{-1}, neat) 3311, 2962, 2873, 2189, 1714, 1590; MS (EI) m/z: 408.4 (M^+); HRMS: Calculated for $C_{24}H_{32}N_4O_2$: 408.2525; found: 408.2516 m/z; HPLC purity: 89 %.

*Methyl 1-(tert-butylamino)-3-cyano-4-(3-methylbutyl)-2-(3-nitrophenyl)-4H-pyrrolo [1,2-a]benzimidazole-7-carboxylate (**9o**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.72 (d, J = 1.2 Hz, 1H), 8.48 (s, 1H), 8.17 (d, J = 8.7 Hz, 1H), 8.08 (dd, J = 8.4, 1.2 Hz, 1H), 7.96 (d, J = 7.5 Hz, 1H), 7.63 (t, J = 8.1 Hz, 1H), 7.27 (d, J = 8.7 Hz, 1H), 4.27 (t, J = 7.65 Hz, 2H), 3.98 (s, 3H), 3.25 (br, 1H), 1.88–1.72 (m, 3H), 1.04 (d, J = 6.3 Hz, 6H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 148.7, 140.4, 139.6, 136.0, 135.5, 130.1, 126.4, 126.2, 124.3, 122.6, 122.5, 122.3, 117.0, 115.0, 108.8, 63.2, 57.0, 52.8, 43.2, 38.0, 30.4, 26.5, 22.9; IR (cm^{-1}, neat) 3357, 3084, 2958, 2871, 2198, 1711; MS (EI) m/z: 501.4 (M^+); HRMS: Calculated for $C_{28}H_{31}N_5O_4$: 501.2376; found: 501.2372 m/z; HPLC purity: 81 %.

*Methyl 1-(tert-butylamino)-3-cyano-2-(furan-3-yl)-4-(3-methylbutyl)-4H-pyrrolo[1,2-a]benzimidazole-7-carboxylate (**9p**)*

^{1}H NMR (300 MHz, $CDCl_3$ δ = 7.24 ppm as standard) δ 8.63 (d, J = 1.2 Hz, 1H), 8.02 (dd, J = 8.6, 1.3 Hz, 1H), 7.82 (dd, J = 1.5, 0.9 Hz, 1H), 7.51 (t, J = 1.7 Hz, 1H), 7.20 (d, J = 8.7 Hz, 1H), 6.81 (dd, J = 1.8, 0.8 Hz, 1H), 4.21 (t, J = 7.6 Hz, 2H), 3.97 (s, 3H), 3.13 (br, 1H), 1.84–1.70 (m, 3H), 1.09 (s, 9H), 1.03 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 143.3, 140.3, 139.5, 126.5, 125.7, 125.2, 122.2, 121.9, 118.5, 117.7, 116.0, 114.8, 110.9, 108.4, 63.0, 57.0, 52.7, 43.0, 37.9, 30.5, 26.4, 22.9; IR (cm^{-1}, neat) 3346, 2960, 2873, 2200, 1716; MS (EI) m/z: 446.4 (M^+); HRMS: Calculated for $C_{26}H_{30}N_4O_3$: 446.2318; found: 446.2313 m/z; HPLC purity: 85 %.

*Methyl 1-(tert-butylamino)-3-cyano-4-[2-(cyclohex-1-en-1-yl)ethyl]-2-(propan-2-yl-4H-pyrrolo[1,2-a]benzimidazole-7-carboxylate (**9q**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.70 (d, J = 1.5 Hz, 1H), 7.95 (dd, J = 8.4, 1.5 Hz, 1H), 7.30 (d, J = 8.7 Hz, 1H), 5.23 (s, 1H), 4.30 (t, J = 7.05 Hz, 2H), 3.95 (s, 3H), 3.10 (sept, 1H), 2.75 (br, 1H), 2.48 (t, J = 7.05 Hz, 2H), 1.99 (m, 2H), 1.76 (m, 2H), 1.57–1.54 (m, 2H), 1.43–1.41 (m, 8H), 1.23 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$ δ) 167.4, 140.9, 139.7, 133.6, 130.4, 126.5, 125.5, 125.1, 121.9, 119.8, 118.5, 114.5, 108.5, 60.9, 55.4, 52.6, 43.4, 37.1, 30.5, 28.7, 26.3, 25.6, 23.3, 23.1, 22.3; IR (cm^{-1}, neat) 3315, 2962, 2929, 2862, 2185, 1708; MS (EI) m/z: 460.5 (M^+); HRMS: Calculated for $C_{28}H_{36}N_4O_2$: 460.2838; found: 460.2827 m/z; HPLC purity: 91 %.

*Methyl 1-(tert-butylamino)-3-cyano-2-ethyl-4-(propan-2-yl)-4H-pyrrolo[1,2-a]-benzimidazole-7-carboxylate (**9r**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.69 (d, J = 1.5 Hz, 1H), 7.95 (dd, J = 8.7, 1.5 Hz, 1H), 7.30 (d, J = 8.7 Hz, 1H), 4.86 (sept, J = 7.0 Hz, 1H), 3.94 (s, 3H), 2.74 (brs, 1H), 2.67 (q, J = 7.5 Hz, 2H), 1.70 (d, J = 7.2 Hz, 6H), 1.32 (t, J = 7.5 Hz, 3H), 1.23 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 138.8, 138.7, 126.6, 126.3, 125.1, 121.7, 121.1, 119.1, 114.7, 109.5, 64.0, 55.6, 52.6,

48.7, 30.5, 21.4, 19.5, 15.4; IR (cm^{-1}, neat) 3348, 2976, 2939, 2879, 2193, 1706; MS (EI) m/z: 380.4 (M^+); HRMS: Calculated for $C_{22}H_{28}N_4O_2$: 380.2212; found: 380.2215 m/z; HPLC purity: 92 %.

*Methyl 1-tert-butylamino)-3-cyano-4-(propan-2-yl)-2-propyl-4H-pyrrolo[1,2-a]-benzimidazole-7-carboxylate (**9s**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.71 (d, J = 1.5 Hz, 1H), 7.95 (dd, J = 8.5, 1.6 Hz, 1H), 7.30 (d, J = 9.9 Hz, 1H), 4.88 (sept, J = 7.0 Hz, 1H), 3.93 (s, 3H), 2.74 (br, 1H), 2.60 (t, J = 7.9 Hz, 2H), 1.70–1.68 (m, 8H), 1.23 (s, 9H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 138.8, 138.7, 126.6, 125.1, 124.8, 121.7, 121.6, 119.1, 114.7, 109.5, 64.2, 55.7, 52.6, 48.7, 30.5, 28.4, 24.1, 21.4, 14.6; IR (cm^{-1}, neat) 3327, 2962, 2873, 2197, 1714, 1575; MS (EI) m/z: 394.4 (M^+); HRMS: Calculated for $C_{23}H_{30}N_4O_2$: 394.2369; found 394.2374 m/z; HPLC purity: 95 %.

*Methyl 1-(tert-butylamino)-3-cyano-2,4-di(propan-2-yl)-4H-pyrrolo[1,2-a]-benzimidazole-7-carboxylate (**9t**)*

^{1}H NMR (300 MHz, $CDCl_3$, δ = 7.24 ppm as standard) δ 8.72 (d, J = 1.5 Hz, 1H), 7.97 (dd, J = 8.7, 1.5 Hz, 1H), 7.32 (d, J = 8.7 Hz, 1H), 4.94 (sept, J = 6.9 Hz, 1H), 3.96 (s, 3H), 3.12 (sept, J = 6.9 Hz, 1H), 2.70 (brs, 1H), 1.72 (d, J = 6.9 Hz, 6H), 1.44 (d, J = 6.9 Hz, 6H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$ δ) 167.4, 139.8, 138.6, 130.6, 126.7, 125.0, 121.7, 119.9, 119.6, 114.7, 109.7, 61.6, 55.4, 52.6, 48.7, 30.5, 26.2, 23.1, 21.4; IR (cm^{-1}, neat) 3332, 2968, 2873, 2195, 1707; MS (EI) m/z: 394.4 (M^+); HRMS: Calculated for $C_{23}H_{30}N_4O_2$: 394.2369; found: 394.2361 m/z; HPLC purity: 98 %.

Supporting information available

Typical experimental procedure with the spectral data of all compounds is available free of charge via the internet.

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