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FULL-LENGTH PAPER

The synthesis of low molecular weight pyrrolo[2,3-*c*]pyridine-7-one scaffold

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Abstract A facile method for the synthesis of substituted pyrrolo[2,3-*c*]pyridine-7-ones is developed that applies an acid-promoted intramolecular cyclization of 2-pyrrolecarboxylic acid amidoacetals as key step. The synthesis is easily scaled up to 1.5 mol quantity with no yield decrease. The alkylation/arylation reaction of the pyrrolo[2,3-*c*]pyridine-7-ones proceeds regioselectively giving *N*6-substituted derivatives.

Keywords Pyrrolo[2,3-*c*]pyridine · 2-Pyrrolecarboxylic acid · Aminoacetal · Heterocyclization · Diversification · Marine alkaloids

Introduction

The establishment of the modern lead-likeness criteria [1] resulted in ordering the chemist's strategies toward the design of novel diversity-oriented synthesis for the purposes of drug discovery. These criteria are more strict than the original Lipinski's rules [2] and focused on lower molecular weights and lipophilicity to reserve the possibility for further lead structure optimization. In particular, the molecular weight does not need to exceed 350 Da because the medicinal chemistry optimization can add further 100–200 U [3,4]. On the other hand, the need of chemical diversity requires the possibility of flexible structural variations of the target scaffold that can be provided by means of either a direct synthesis or further diversification. An extensive synthetic organic chemistry background does not guarantee a chemist can create a new scaffold fulfilling all or the majority of the leadlikeness criteria and structural requirements. Nevertheless, there is still a great number of potentially fruitful scaffolds whose syntheses are not properly elaborated and the methods for their diversification need to be fully elucidated. Thus, the current task of diversity-oriented synthesis is not only restricted by the need to discover new cores but also the need to provide synthetic feasible routes for such new scaffold cores.

Among such rare scaffolds the pyrrolo[2,3-*c*]pyridine-7-one moiety is found in the secondary metabolites ugibohlin [5] and dibromoisophakellin [5,6] derived from sponge *Axinellacarteri* and *N*-methyldibromoisophakellin [6] derived from Caribbean sponge *Stylissacaribica* (Fig. 1).

The pyrrolo[2,3-c]pyridine-7-one scaffold nicely fits in the modern criteria of leadlikeness and has several points of diversity that can be used for the generation of large collections of organic compounds for high-throughput screening. Available synthetic pathways to the scaffold of the marine alkaloids (Fig. 1) are summarized in Scheme 1. They include (i) the reduction of Weinreb-type amide **1** with $LiAlH_4$ followed by cyclization giving a mixture of compound **2** and the target tricycle **3** containing the pyrrolo[2,3-*c*]pyridine-7-one moiety [7] or (ii) an intramolecular acid-promoted cyclization of amidoacetals **4a** and **4b** yielding the corresponding pyrrolo[2,3-*c*]pyridine-7-ones **5a** [8,9] and **5b** [10]. Another

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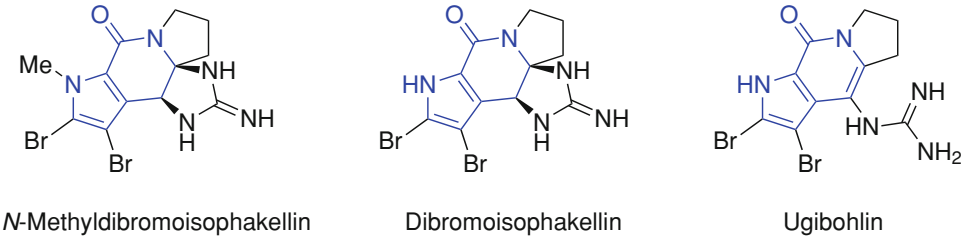
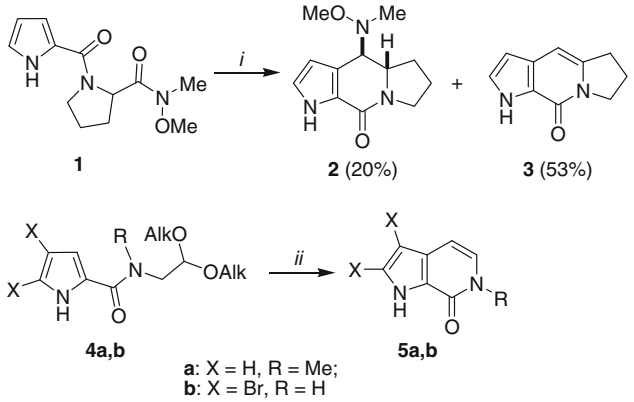


Fig. 1 Structures of the marine metabolites containing pyrrolo[2,3-*c*]pyridine-7-one fragment



Scheme 1 Previously described methods for the synthesis of compounds containing pyrrolo[2,3-*c*]pyridine-7-one. *Reagents and conditions:i* $LiAlH_4$ (5 equiv), THF, 0 °C, 1h then 1N HCl; *ii* $POCl_3$, Et_2O, 0 °C, 1h, **5a** (71 %) [8] or *p*-TSA, toluene, reflux 3h, **5a** (32 %) [9] or $MeSO_2OH$, 45 °C, 4 days, **5b** (80 %) [10]

method includes the multistep synthesis of 3-(1-benzyl-1*H*-pyrrol-3-yl)acryloylazide followed by its heterocyclization [11] (not shown in Scheme 1).

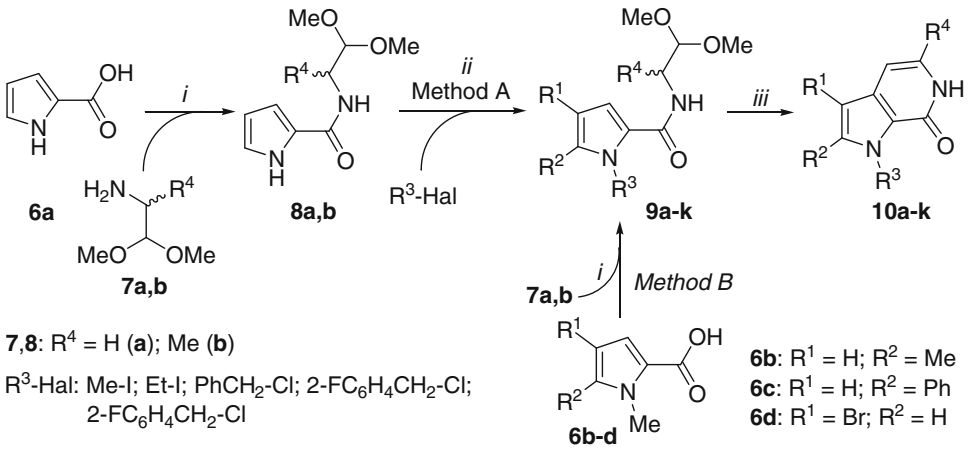
The described synthetic pathways to these heterocycles are, however, of little general use. In this study, a general method for the synthesis of *N*1-substituted pyrrolo[2,3-*c*]pyridine-7-ones and their regioselective functionalization is reported.

Results and discussion

As shown in Scheme 2, the amide coupling reaction between 2-pyrrolecarboxylic acid **6a** with 2,2-dimethoxyethanamine and 1,1-dimethoxypropan-2-amine gives amides **7a** (R^4 = *H*) and **7b** (R^4 = Me), respectively. Alkylation of the pyrrole ring of **7a**, **b** in DMF in the presence of NaH occurs regioselectively resulting in *N*1-alkylated amides **8a**–**e** (Method A). These compounds then undergo an acid-promoted heterocyclization to give the desired *N*1-substituted pyrrolo[2,3-*c*]pyridine-7-ones **10a**–**k**. The use of trifluoroacetic acid (TFA) as the reaction medium generally resulted in higher yields requiring shorter reaction times compared to *p*-toluenesulfonic acid (*p*-TSA) (Scheme 1).

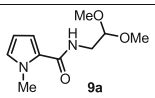
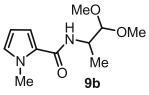
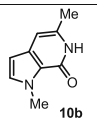
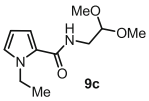
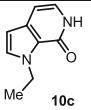
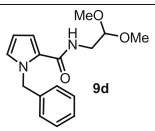
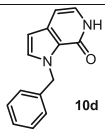
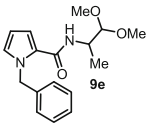
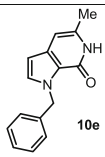
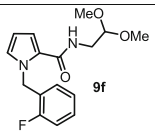
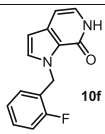
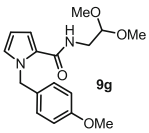
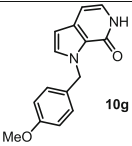
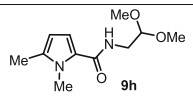
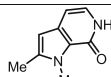
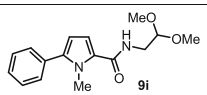
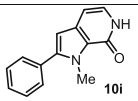
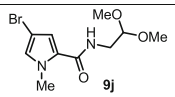
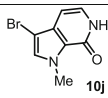
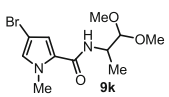
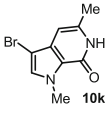
Initially, the synthesis of compounds **10a**–**k** was performed on a 100-mmol scale. The synthesis of compound **10a** was then scaled up to a 1.5-mol scale with no changes in the experimental procedure and yield.

The advantage of Method A (Scheme 2) is that the main diversity point is introduced into the scaffold on the stage of alkylation of amides **8a**, **b** using general reaction conditions for different alkylating agents and a simple workup. An alternative strategy shown in Scheme 1 is Method B that involves available *N*-methyl-2-pyrrolecarboxylic acids **6b**–**d** with different substituents in the pyrrole ring. The amidation of acids **6b**–**d** proceeds under the same conditions as in Method A. These two methods are very efficient providing



Scheme 2 Two ways for synthesis of *N*1-substituted pyrrolo[2,3-*c*]pyridine-7-ones **10**. *Reagents and conditions*: *i* CDI, dioxane, 70 °C, 3 h; *ii* NaH, DMF, 40 °C, 12 h; *iii* TFA, rt, 12 h

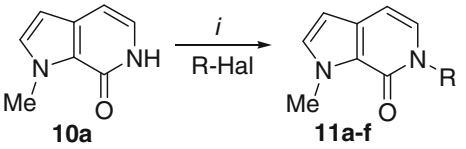
Table 1 Isolated yields for *N*1-substituted pyrrolo[2,3-*c*]pyridine-7-ones **10a–k**

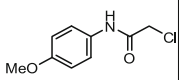
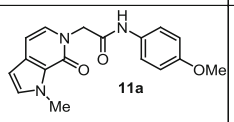
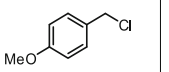
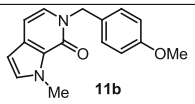
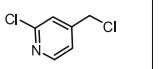
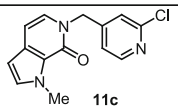
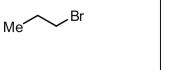
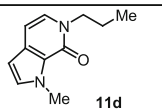
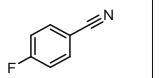
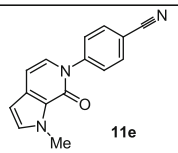
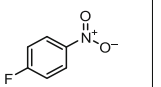
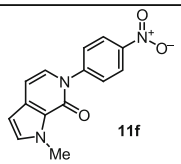
Entry	Intermediate amide	Yield (%) (method)	Product	Yield (%)
1	 **9a**	88 (A)	 **10a**	71
2	 **9b**	72 (A)	 **10b**	65
3	 **9c**	95 (A)	 **10c**	66
4	 **9d**	-[a] (A)	 **10d**	77[a]
5	 **9e**	-[a] (A)	 **10e**	82[a]
6	 **9f**	-[a] (A)	 **10f**	74[a]
7	 **9g**	-[a] (A)	 **10g**	80[a]
8	 **9h**	83 (B)	 **10h**	90
9	 **9i**	84 (B)	 **10i**	99
10	 **9j**	78 (B)	 **10j**	84
11	 **9k**	-[a] (B)	 **10k**	86[a]

Yields are given for the last step

[a] Amides **9d–g**, **k** were obtained as oils and used immediately for the next stage in the same pot, yields for the products are given over two last steps

Table 2 Isolated yields for pyrrolo[2,3-*c*]pyridine-7-ones **11a–f** obtained by the standard alkylation arylation reactions



Entry	Alkylating/arylating agent (R-Hal)	Equiv (R-Hal)	Reaction product	Yield (%)
1		1	 **11a**	51
2		2	 **11b**	68
3		2	 **11c**	58
4		4	 **11d**	71
5		2	 **11e**	50
6		2	 **11f**	85

[a] Reagents and conditions: (i) DMF, K_2CO_3, 100 °C, 24 h

[b] Molar equivalent of alkylating arylating agent

good-to-high yields per step (Table 1). Although Method B is one reaction step shorter, the structural diversity of available *N*-substituted 2-pyrrolecarboxylic acids **6** is quite limited.

In order to study the structural diversification alkylation of the pyrrolo[2,3-*c*]pyridine-7-one scaffold, analog **10a** was investigated [12]. The alkylating agents used in reactions with **10a** are given in Table 2 (Entries 1–4) [13]. In all cases, the alkylation resulted in *N*6-alkylated derivatives **11a–d** in good yields. Similarly, the arylation of **10a** with activated fluoroarenes led to the corresponding *N*6-aryl derivatives **11e**, **f** (Table 2, Entries 5, 6). An excess of alkylating/arylating agent was generally used to ensure the full conversion of starting material.

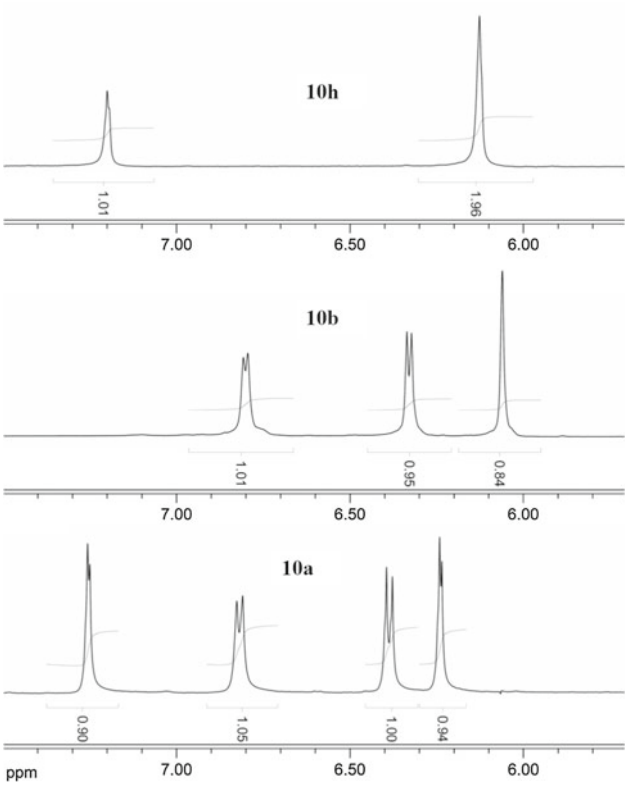


Fig. 2 AX Proton coupling systems of pyrrolo[2,3-*c*]pyridine-7-one moiety

The ^{1}H NMR spectrum of *N*1-methyl-pyrrolo[2,3-*c*]pyridine-7-one **10a** contains four doublets of two AX spin systems found between 5.5 and 7.5 ppm with different coupling constants $J = 2.49$ Hz for the first AX system and $J = 6.64$ Hz for the second one. Comparing this spectrum with those for the derivatives containing methyl group in the pyridone (**10b**) and pyrrole (**10h**) fragment one can easily assign the AX systems in the spectrum of **10a**. (Fig. 2)

Thus, in the ^{1}H NMR spectrum of **10h** which bears methyl group at position 2, the AX system doublets have coupling constants $J = 6.75$ Hz at 6.33 ppm and $J = 6.23$ Hz at 6.80 ppm, respectively. The latter coupling is absent in the ^{1}H NMR spectrum of **10b** with methyl-substituted pyridone ring. Notably, the signals of the pyrrole protons are often observed as singlets. Therefore, the AX system doublets with large coupling constant (6.23–6.75 Hz) correspond to the pyridone protons and those with the smaller constant (0–2.59 Hz) to the pyrrole protons. This statement was also proved by the analysis of HMBC spectra for these compounds (see Supplementary material for details).

Two-dimensional (2D) NOESY and HMBC experiments were performed with compound **11a**. As illustrated in Fig. 3, the NOESY spectrum of compound **11a** has a cross-signal between the doublet of pyridone proton at position 5 of the pyrrolo[2,3-*c*]pyridine-7-one moiety (7.14 ppm) and the CH_2-protons singlet (4.74 ppm) as well as the HMBC cross-signal between the same proton doublet (7.14 ppm) and carbon signal of CH_2-group (1.2 ppm). Both correlations can only be expected for *N*-alkylated derivative **11a**. Similarly, the presence of the NOE cross-signal between doublet at 7.11 ppm, and CH_2 protons triplet at 3.87 ppm for compound **11d** confirms the *N*-alkylation.

The close disposition of the proton in position 5 giving doublet at 7.15 ppm with *ortho*-protons of cyanophenyl fragment (7.66 ppm) in compound **11e** was also confirmed by NOE.

Conclusion

In conclusion, a facile method for the synthesis of substituted pyrrolo[2,3-*c*]pyridine-7-ones has been developed. Besides high purity of the target compounds and good isolated yields, this work presents a simple, high-yielding, and scalable synthetic route. Low molecular weights and the possibility of 3D structural variations of this scaffold as well as its similarity to structure of the natural products make it an attractive target for further modifications and biological screening. As the simplest option of such modifications, the alkylation/arylation reaction was performed under uniform conditions and proved to proceed regioselectively giving *N*6-substituted derivatives.

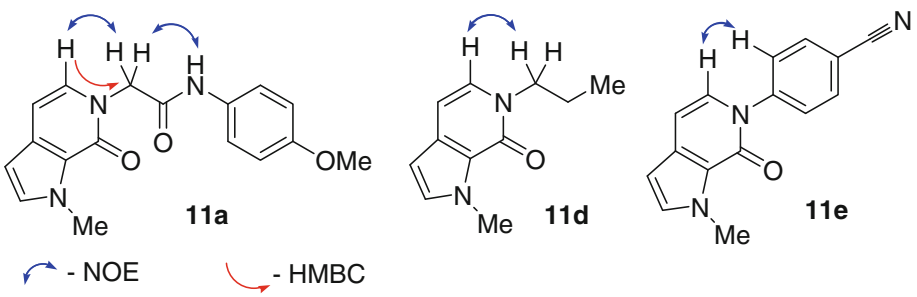


Fig. 3 The key NOE and HMBC correlation supporting *N*6- alkylation/arylation of the model derivative **10a**

Experimental section

General comments

All starting materials were commercially available and used without additional purification. The commercial pyrrol-2-carboxylic acid **6a** was purified by dissolving it in 1N aqueous solution of NaOH, filtrating the solution, and precipitating the acid by adding conc. aqueous HCl. Acids **6b–d** available from Enamine Ltd. were used without additional purification. Melting points are uncorrected. Micro-analyses were obtained using a EuroVector EA-3000. IR spectra were recorded on a Specord M80 spectrometer in KBr. ^{1}H NMR spectra were recorded on a Bruker Avance drx 500 (500 MHz) and Varian Unity plus 400 (400 MHz) spectrometers using TMS as an internal standard. ^{13}C NMR (126 MHz) and 2D NMR experiments were performed on the 500-MHz spectrometer. Copies of NMR spectra were prepared using ACD/NMR Processor software (academic edition) and can be found in Supplementary material. LC/MS spectra were recorded using a chromatography/mass spectrometrer system that consists of high-performance liquid chromatograph equipped with a diode-matrix and mass-selective detector. Ionization method, chemical ionization under atmospheric pressure (APCI). Ionization mode, simultaneous scanning of positive ions in the mass range of 80–1,000 *m*/*z*. According to HPLC MS and ^{1}H NMR spectral data, all synthesized compounds have purity >95 %.

General amide-coupling procedure (synthesis of **8a**, **b** and **9h–k**)

Pyrrole-2-carboxylic acid **6a–d** (100 mmol) was dissolved in 200 mL of dry dioxane and heated to 60 °C, and then CDI (100 mmol) was added portionwise. The reaction mixture was stirred at this temperature until no more liberation of CO_2 is observed, then 2,2-dimethoxyethanamine **7a** or 1,1-dimethoxypropan-2-amine **7b** (120 mmol) was added in one portion. The mixture was heated at 70 °C for 3 h. The solvent was removed on a rotary evaporator, the residue dissolved in 100 mL of ethyl acetate and extracted three times with 100 mL portions of water followed by flash-column chromatography (ethyl acetate as eluent) yielding compounds **8a**, **b** and **9h–j**. Compound **9k** was obtained as an oily substance and used for the next stage immediately.

*N-(2,2-Dimethoxyethyl)-1H-pyrrole-2-carboxamide (**8a**)*

White crystalline powder, yield 64 %, m.p. = 67–69 °C; IR (KBr), ν_{max} (cm^{-1}): 3357, 3252, 1635, 1563, 1526; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.41 (br. s, 1H), 8.02 (br. s, 1H), 6.86 (br. s, 1H), 6.79 (br. s, 1H), 6.08 (br. s, 1H), 4.42–4.50 (m, 1H), 3.34 (br. s, 2H), 3.30 (s, 6H); LCMS: 167.1 (M + H − OMe)$^+$; Anal. Calcd for $C_9H_{14}N_2O_3$: C 54.53 %, H 7.12 %, N 14.13 %, Found: C 54.62, H 7.21, N 13.99.

*N-(1,1-Dimethoxypropan-2-yl)-1H-pyrrole-2-carboxamide (**8b**)*

White crystalline powder, yield 72 %, m.p. = 92–94 °C; IR (KBr), ν_{max} (cm^{-1}): 3371, 3251, 2929, 1630, 1557, 1519; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.40 (br. s, 1H), 7.71 (d, J = 8.56 Hz, 1H), 6.85 (d, J = 1.04 Hz, 1H), 6.81 (br. s, 1H), 6.04–6.11 (m, 1H), 4.30 (d, J = 5.71 Hz, 1H), 4.09–4.19 (m, 1H), 3.34 (s, 3H), 3.29 (s, 3H), 1.10 (d, J = 7.01 Hz, 3H); LCMS: 181.2 (M + H − OMe)$^+$; Anal. Calcd for $C_{10}H_{16}N_2O_3$: C 56.59 %, H 7.60 %, N 13.20 %, Found: C 56.63, H 7.58, N 13.21.

*N-(2,2-Dimethoxyethyl)-1,5-dimethyl-1H-pyrrole-2-carboxamide (**9h**)*

White crystalline powder, yield 83 %; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (t, J = 5.45 Hz, 1H, NH), 6.70 (d, J = 3.89 Hz, 1H, 3-CH), 5.82 (d, J = 3.37 Hz, 1H, 4-CH), 4.46 (t, J = 5.45 Hz, 1H, CH^{Alk}), 3.75 (s, 3H, N–CH$_3$), 3.28 (s, 6H, 2O–CH$_3$), 3.24–3.26 (m, 2H, CH$_2$), 2.18 (s, 3H, C–CH$_3$); ^{13}C NMR, APT, HMBC (126 MHz, DMSO-d_6) δ 162.1 (CO), 134.7 (5-C), 125.2 (2-C), 112.2 (3-CH), 106.6 (4-CH), 102.7 (CH^{Alk}), 53.7 (2O–CH$_3$), 40.9 (CH$_2$), 32.3 (N–CH$_3$), 12.5 (C–CH$_3$); δ 162.1, 134.7, 125.2, 112.2, 106.5, 102.7, 53.7, 40.9, 32.3, 12.5; LCMS: 195.1 (M+H−OMe)$^+$; Anal. Calcd for $C_{11}H_{18}N_2O_3$: C 58.39 %, H 8.02 %, N 12.38 %, Found: C 58.30, H 8.11, N 12.36.

*N-(2,2-Dimethoxyethyl)-1-methyl-5-phenyl-1H-pyrrole-2-carboxamide (**9i**)*

White crystalline powder, yield 84 %; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (br. s, 1H), 7.45 (br. s, 4H), 7.40 (d, J = 2.91 Hz, 1H), 6.90 (d, J = 3.32 Hz, 1H), 6.18 (d, J = 3.32 Hz, 1H), 4.51 (br. s, 1H), 3.81 (s, 3H), 3.31 (br. s, 6H), 3.28–3.35 (br. s, 8H)); LCMS: 257.1 (100 %) (M + H − OMe)$^+$, 289.2 (30 %) (M + H)$^+$; Anal. Calcd for $C_{16}H_{20}N_2O_3$: C 66.65 %, H 6.99 %, N 9.72 %, Found: C 66.73, H 7.08, N 9.73.

*4-Bromo-N-(2,2-dimethoxyethyl)-1-methyl-1H-pyrrole-2-carboxamide (**9j**)*

White crystalline powder, yield 78 %; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (br. s, 1H), 7.09 (s, 1H), 6.88 (s, 1H), 4.46 (t, J = 4.54 Hz, 1H), 3.82 (s, 3H), 3.33 (s, 2H), 3.29 (d, J = 1.30 Hz, 6H); LCMS: 260.1 (M+H−OMe)$^+$; Anal. Calcd for $C_{10}H_{15}BrN_2O_3$: C 41.25 %, H 5.19 %, N 9.62 %, Found: C 41.29, H 5.13, N 9.64.

General procedure for alkylation of amidoacetals **8a**, **b** (synthesis of **9a–g**)

Amidoacetal **8a**, **b** (50 mmol) was dissolved in 40 mL of dry DMF and the mixture was cooled to 0 °C. Sodium hydride (60 % in mineral oil, 55 mmol) was added portionwise under stirring to the cooled solution. The mixture was stirred for 20 min and then heated to 50 °C and stirred at this temperature for additional 30 min, then cooled to rt. Alkylhalide (55 mmol) was added portionwise in such a rate to keep the temperature below 40 °C and then the mixture was stirred at 50 °C for 5 h. The resulting reaction mixture was extracted two times with hexane (30 mL) to remove mineral oil, DMF was evaporated under reduced pressure, the residue was dissolved in 50 mL of ethyl acetate and extracted three times with 50 mL portions of water followed by flash-column chromatography (using ethyl acetate as eluent) yielding the compounds **9a–g**. Benzyl derivatives **9d–g** were obtained as oily substances and used for the next stage immediately.

*N-(2,2-Dimethoxyethyl)-1-methyl-1H-pyrrole-2-carboxamide (***9a***)*

White crystalline powder, yeild 88 %; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.02 (t, J = 5.26 Hz, 1H), 6.89 (s, 1H), 6.81 (d, J = 2.45 Hz, 1H), 5.95–6.06 (m, 1H), 4.48 (t, J = 5.50 Hz, 1H), 3.84 (s, 3H), 3.30 (s, 6H), 3.28 (br. s, 2H); LCMS: 181.1 $(M + H - OMe)^+$; Anal. Calcd for $C_{10}H_{16}N_2O_3$: C 56.59 %, H 7.60 %, N 13.20 %, Found: C 56.51, H 7.55, N 13.30.

*N-(1,1-Dimethoxypropan-2-yl)-1-methyl-1H-pyrrole-2-carboxamide (***9b***)*

White crystalline powder, yield 72 %; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.69 (d, J = 8.56 Hz, 1H), 6.89 (s, 1H), 6.80 (dd, J = 1.69, 3.76 Hz, 1H), 6.00 (dd, J = 2.60, 3.89 Hz, 1H), 4.30 (d, J = 5.97 Hz, 1H), 4.07–4.14 (m, 1H), 3.83 (s, 3H), 3.33 (s, 3H), 3.28 (s, 3H), 1.09 (d, J = 6.75 Hz, 3H); LCMS: 195.2 $(M + H - OMe)^+$; Anal. Calcd for $C_{11}H_{18}N_2O_3$: C 58.39 %, H 8.02 %, N 12.38 %, Found: C 58.38, H 8.09, N 12.41.

*N-(2,2-Dimethoxyethyl)-1-ethyl-1H-pyrrole-2-carboxamide (***9c***)*

White crystalline powder, yield 95 %; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.01 (t, J = 5.50 Hz, 1H), 6.95 (s, 1H), 6.78 (dd, J = 1.47, 3.67 Hz, 1H), 5.96–6.05 (m, 1H), 4.48 (t, J = 5.50 Hz, 1H), 4.31 (q, J = 7.09 Hz, 2H), 3.36 (s, 2H), 3.29 (s, 6H), 1.25 (t, J = 7.09 Hz, 3H); LCMS: 195.1 $(M + H - OMe)^+$; Anal. Calcd for $C_{11}H_{18}N_2O_3$: C 58.39 %, H 8.02 %, N 12.38 %, Found: C 58.31, H 8.01, N 12.42.

General procedure for heterocyclisation of amidoacetals **9a–k** (synthesis of **10a–k**)

Amidoacetal **9a–k** (50 mmol) was added in one portion at rt to vigorously stirred trifluoroacetic acid (50 mL). The mixture was stirred for 12 h and then poured into 300 mL of water. The precipitate was filtered off, washed with water, and suspended in water (150 mL). Potassium carbonate was added to this suspension to pH ~10, the product was filtered, and washed with water to give compounds **10a–k**.

*1-Methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (***10a***)*

Pale-brown crystalline powder, yield 71 %; m.p. = 190–191 °C; IR (KBr), ν_{max} (cm^{-1}): 3126, 2982, 2844, 1641, 1461, 1325; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (br. s, 1H, NH), 7.25 (d, J = 2.49 Hz, 1H, 2-CH), 6.82 (d, J = 6.64 Hz, 1H, 5-CH), 6.39 (d, J = 6.64 Hz, 1H, 4-CH), 6.24 (d, J = 2.49 Hz, 1H, 3-CH), 4.05 (s, 3H, N–CH_3); ^{13}C NMR, DEPT, APT, HMBC (DMSO-d_6) δ 35.7 (N–CH_3), 101.3 (4-CH), 102.0 (3-CH), 123.2 (7a-C), 125.2 (5-CH), 131.8 (3a-C), 132.0 (2-CH), 156.3 (CO); LCMS: 149.0 $(M+H)^+$; Purity >99 %; Anal. Calcd for $C_8H_8N_2O$: C 64.85 %, H 5.44 %, N 18.91 %Found: C 64.94, H 5.40, N 18.90.

*1,5-Dimethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (***10b***)*

Pale-brown crystalline powder, yield 65 %; m.p. = 189–190 °C; IR (KBr), ν_{max} (cm^{-1}): 3122, 2993, 1671, 1626, 1308; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (br. s, 1H, NH), 7.20 (br. s, 1H, 2-CH), 6.13 (br. s, 2H, 4-CH), 4.02 (s, 3H, N-CH_3), 2.13 (s, 3H, C-CH_3); ^{13}C NMR, DEPT, APT, HMBC (126 MHz, DMSO-d_6) δ 156.5 (CO), 134.5 (5-C), 132.5 (3a-C), 132.1 (2-CH), 121.5 (7a-C), 101.4 (3-CH), 99.5 (4-CH), 35.5 (N–CH_3), 18.9 (C–CH_3); LCMS: 163.0 $(M+H)^+$; Purity >99 %; Anal. Calcd for $C_9H_{10}N_2O$: C 66.65 %, H 6.21 %, N 17.27 %, Found: C 66.67, H 6.18, N 17.25.

*1-Ethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (***10c***)*

Brown crystalline powder, yield 66 %; m.p. = 144–146 °C; IR (KBr), ν_{max} (cm^{-1}): 2979, 2837, 1649, 1619, 1460, 1319; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (br. s, 1H), 7.34 (s, 1H), 6.84 (d, J = 4.98 Hz, 1H), 6.40 (d, J = 6.64 Hz, 1H), 6.25 (s, 1H), 4.48 (q, J = 6.78 Hz, 2H), 1.33 (t, J = 7.06 Hz, 3H); ^{13}C NMR, DEPT (126 MHz, DMSO-d_6) δ 155.9, 132.1, 130.6 (CH), 125.2 (CH), 122.4, 102.2 (CH), 101.3 (CH), 43.1 (CH_2), 18.2 (CH_3); LCMS: 163.2 $(M + H)^+$; Purity >99 %; Anal. Calcd for $C_9H_{10}N_2O$: C 66.65 %, H 6.21 %, N 17.27 %, Found: C 66.58, H 6.26, N 17.28.

*1-Benzyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (**10d**)*

Pale-brown crystalline powder, yield 77 %; m.p. = 177–179 °C; IR (KBr), ν_{max} (cm^{-1}): 3161, 3030, 1650, 1603, 1321; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (br. s, 1H), 7.43 (s, 1H), 7.16–7.34 (m, 5H), 6.87 (s, 1H), 6.43 (d, J = 6.64 Hz, 1H), 6.32 (s, 1H), 5.74 (s, 2H); ^{13}C NMR, DEPT (126 MHz, DMSO-d_6) δ 156.1, 139.9, 132.1, 131.3 (CH), 128.9 (CH), 127.7 (CH), 127.7 (CH), 125.5 (CH), 122.6, 103.1 (CH), 101.4 (CH), 50.8 (CH_2); LCMS: 163.2 $(M + H)^+$; Purity >99 %; Anal. Calcd for $C_{14}H_{12}N_2O$: C 74.98 %, H 5.39 %, N 12.49 %, Found: C 75.05, H 5.47, N 12.51.

*1-Benzyl-5-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (**10e**)*

Pale-brown crystalline powder, yeild 82 %; m.p. = 188–189 °C; IR (KBr), ν_{max} (cm^{-1}): 2984, 2636, 1658, 1452, 1246; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.78 (br. s, 1H), 7.35 (d, J = 2.59 Hz, 1H), 7.29 (d, J = 7.01 Hz, 2H), 7.23 (d, J = 7.53 Hz, 3H), 6.20 (d, J = 2.60 Hz, 1H), 6.17 (s, 1H), 5.71 (s, 2H), 2.16 (s, 3H); ^{13}C NMR, DEPT (126 MHz, DMSO-d_6) δ 156.3, 140.0, 134.8, 132.9, 131.3 (CH), 128.9 (CH), 127.7 (CH), 127.6, 120.9, 102.4 (CH), 99.6 (CH), 50.7 (CH_2), 18.9 (CH_3); LCMS: 239.0 $(M+H)^+$; Purity 95 %; Anal. Calcd for $C_{15}H_{14}N_2O$: C 75.61 %, H 5.92 %, N 11.76 %, Found: C 75.60, H 5.96, N 11.73.

*1-(2-Fluorobenzyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (**10f**)*

Brown crystalline powder, yield 74 %; m.p. = 121–123 °C; IR (KBr), ν_{max} (cm^{-1}): 3135, 2992, 2840, 1649, 1619, 1456, 1324; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (br. s, 1H), 7.26–7.42 (m, 2H), 7.20 (t, J = 9.14 Hz, 1H), 7.10 (t, J = 7.27 Hz, 1H), 6.80–6.99 (m, 2H), 6.44 (d, J = 6.64 Hz, 1H), 6.35 (d, J = 2.49 Hz, 1H), 5.72–5.92 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.9 (d, $^1J_{CF}$ = 244.3 Hz), 156.0, 132.2, 131.5 (CH), 129.8 (d, $^3J_{CF}$ = 8.3 Hz, CH), 129.4 (d, $^3J_{CF}$ = 4.2 Hz, CH), 126.8 (d, $^2J_{CF}$ = 14.5 Hz), 125.6 (CH), 125.0 (d, $^4J_{CF}$ = 3.2 Hz, CH), 122,79, 115.6 (d, $^2J_{CF}$ = 21.3 Hz, 1H, CH), 103.2 (CH), 101.4 (CH), 49.9 (d, $^3J_{CF}$ = 4.5 Hz, 1H, CH_2); LCMS: 243.0 $(M+H)^+$; Purity 97 %; Anal. Calcd for $C_{14}H_{11}FN_2O$: C 69.41 %, H 4.58 %, N 11.56 %, Found: C 69.47, H 4.53, N 11.60.

*1-(4-Methoxybenzyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (**10g**)*

White crystalline powder, yield 80 %; m.p. = 149–151 °C; IR (KBr), ν_{max} (cm^{-1}): 3135, 2997, 2850, 1654, 1625, 1513, 1247; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.86 (br. s, 1H), 7.40 (d, J = 2.60 Hz, 1H), 7.26 (d, J = 8.56 Hz, 2H), 6.86 (d, J = 8.56 Hz, 3H), 6.42 (d, J = 6.75 Hz, 1H), 6.29 (d, J = 2.85 Hz, 1H), 5.65 (s, 2H), 3.71 (s, 3H); ^{13}C NMR, DEPT (126 MHz, DMSO-d_6) δ 159.0, 156.1, 132.1, 131.8, 131.0 (CH), 129.4 (CH), 125.4 (CH), 122.4, 114.3(CH), 102.9 (CH), 101.4 (CH), 55.5 (CH_3), 50.2 (CH_2); LCMS: 255.3 $(M+H)^+$; Purity 98 %; Anal. Calcd for $C_{15}H_{14}N_2O_2$: C 70.85 %, H 5.55 %, N 11.02 %, Found: C 70.90, H 5.51, N 11.05.

*1,2-Dimethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (**10h**)*

Pale-brown crystalline powder, yeild 90 %; m.p. = 224–226 °C; IR (KBr), ν_{max} (cm^{-1}): 3134, 2983, 2845, 1638, 1543, 1335; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.74 (br. s, 1H, NH), 6.80 (d, J = 6.23 Hz, 1H, 5-CH), 6.33 (d, J = 6.75 Hz, 1H, 4–CH), 6.06 (s, 1H, 3-CH), 4.00 (s, 3H, N–CH_3), 2.29 (s, 3H, C–CH_3); ^{13}C NMR, DEPT, APT, HMBC (126 MHz, DMSO-d_6) δ 155.8 (CO), 139.5 (2-C), 131.2 (3a-C), 124.9 (5-CH), 122.8 (7a-C), 101.4 (3-CH), 100.9 (4-CH), 31.8 (N–CH_3), 12.3 (C–CH_3); LCMS: 163.2 $(M+H)^+$; Purity 96 %; Anal. Calcd for $C_9H_{10}N_2O$: C 66.65 %, H 6.21 %, N 17.27 %, Found: C 66.58, H 6.30, N 17.29.

*1-Methyl-2-phenyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (**10i**)*

Pale-brown crystalline powder, yield 99 %; m.p. = 202–204 °C; IR (KBr), ν_{max} (cm^{-1}): 3136, 2983, 2840, 1648, 1620, 1543, 1336; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (br. s, 1H), 7.37–7.67 (m, 5H), 6.89 (d, J = 6.23 Hz, 1H), 6.43 (d, J = 6.64 Hz, 1H), 6.40 (s, 1H), 3.94–4.17 (m, 3H); ^{13}C NMR, DEPT (126 MHz, DMSO-d_6) δ 156.4, 143.0, 131.8, 131.3, 129.6 (CH), 129.1 (CH), 128.8 (CH), 125.7 (CH), 124.3, 103.1 (CH), 101.0 (CH), 33.9(CH_3); LCMS: 225.0 $(M+H)^+$; Purity 96 %; Anal. Calcd for $C_{14}H_{12}N_2O$: C 74.98 %, H 5.39 %, N 12.49 %, Found: C 74.90, H 5.30, N 12.50.

*3-Bromo-1-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (**10j**)*

Pale-brown crystalline powder, yield 84 %; m.p. = 198–200 °C; IR (KBr), ν_{max} (cm^{-1}): 3141, 2989, 2840, 1664, 1622, 1531, 1338; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (br. s, 1H), 7.51 (s, 1H), 6.95 (d, J = 6.64 Hz, 1H), 6.25 (d, J = 6.64 Hz, 1H), 4.05 (s, 3H); ^{13}C NMR, DEPT (126 MHz, DMSO-d_6) δ 155.7, 131.3 (CH), 130.6, 126.6 (CH), 123.0, 98.6 (CH), 88.7, 35.9 (CH_3); LCMS: 227.0 $(M+H)^+$; Purity >99 %; Anal. Calcd for $C_8H_7BrN_2O$: C 42.32 %, H 3.11 %, N 12.34 %, Found: C 42.30, H 3.16, N 12.31.

*3-Bromo-1,5-dimethyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (**10k**)*

Pale-brown crystalline powder, yeild 86 %; m.p. = 231–233 °C; IR (KBr), ν_{max} (cm^{-1}): 3124, 2996, 2831, 1665, 1619, 1537, 1337; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (br. s, 1H), 7.42 (s, 1H), 6.01 (s, 1H), 4.02 (s, 3H), 2.17 (s, 3H); ^{13}C NMR, DEPT (126 MHz, DMSO-d_6) δ 156.0, 136.1, 131.2 (CH), 122.8, 121.4, 96.8 (CH), 88.0, 35.7 (CH_3), 18.9; LCMS: 241.0 $(M + H)^+$; Purity 95 %; Anal. Calcd for $C_9H_9BrN_2O$: C 44.84 %, H 3.76 %, N 11.62 %, Found: C 44.77, H 3.81, N 11.66.

General procedure for alkylation/arylation of 1-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-7(6*H*)-one **10a** (synthesis of **11a–f**)

1-Methyl-1*H*-pyrrolo[2,3-*c*]pyridin-7(6*H*)-one **10a** (0.01 mol) was dissolved in 2 mL of dry DMF. Potassium carbonate (0.03 mol) was added to this solution followed by alkylating/arylating agent (see Table 2 for the amounts). The mixture was heated at 110 °C for 24 h. Water (10 mL) was added to the cooled solution under stirring. Precipitated product (**11a**, **e**, **f**) was filtered, and washed with water. If no precipitate is formed (**11b–d**), the mixture was extracted two times with 5-mL portions of ethyl acetate and chromatographed on silica gel (ethyl acetate/hexane 1:1 as eluent) to give the target compounds.

*N-(4-Methoxyphenyl)-2-(1-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridin-6(7H)-yl)acetamide (**11a**)*

Pale-brown crystalline powder, yeild 51 %; m.p. = 188–190 °C; IR (KBr), ν_{max} (cm^{-1}): 3271, 2908, 1659, 1594, 1241; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.15 (s, 1H), 7.53 (d, J = 8.82 Hz, 2H), 7.30 (d, J = 2.34 Hz, 1H), 7.14 (d, J = 7.27 Hz, 1H), 6.90 (d, J = 8.82 Hz, 2H), 6.45 (d, J = 7.01 Hz, 1H), 6.27 (d, J = 2.59 Hz, 1H), 4.74 (s, 2H), 4.05 (s, 3H), 3.73 (s, 3H); ^{13}C NMR, DEPT, HMBC (126 MHz, DMSO-d_6) δ 166.4, 155.7, 155.6, 132.6, 132.5(CH), 131.5, 131.1(CH), 122.7, 120.9(CH), 114.4(CH), 102.0(CH), 101.0(CH), 55.6(CH_3), 51.2(CH_2), 35.8(CH_3); LCMS: 312.3 $(M + H)^+$; Purity 95 %; Anal. Calcd for $C_{17}H_{17}N_3O_3$: C 65.58 %, H 5.50 %, N 13.50 %, Found: C 65.64, H 5.59, N 13.47.

*6-(4-Methoxybenzyl)-1-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (**11b**)*

White crystalline powder, yield 68 %; m.p. = 75–77 °C; IR (KBr), ν_{max} (cm^{-1}): 3003, 2836, 1655, 1591, 1510, 1245; ^{1}HNMR (500 MHz, DMSO-d_6) δ 7.27 (dd, J = 2.60, 5.71 Hz, 3H), 7.21 (d, J = 7.27 Hz, 1H), 6.89 (d, J = 8.56 Hz, 2H), 6.45 (d, J = 7.01 Hz, 1H), 6.24 (d, J = 2.60 Hz, 1H), 5.07 (s, 2H), 4.07 (s, 3H), 3.72 (s, 3H); ^{13}CNMR, DEPT (126 MHz, DMSO-d_6) δ 159.0, 155.4, 132.6 (CH), 131.0, 130.9, 129.6 (CH), 129.5 (CH), 122.9, 114.3 (CH), 101.9 (CH), 101.8 (CH), 55.5 (CH_3), 49.7 (CH_2), 35.9 (CH_3); LCMS: 269.0 $(M+H)^+$; Purity 95 %; Anal. Calcd for $C_{16}H_{16}N_2O_2$: C 71.62 %, H 6.01 %, N 10.44 %, Found: C 71.55, H 6.09, N 10.45.

*6-((2-Chloropyridin-4-yl)methyl)-1-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (**11c**)*

White crystalline powder, yield 58 %; m.p. = 107–109 °C; IR (KBr), ν_{max} (cm^{-1}): 3063, 1650, 1590, 1439, 1320; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.81 (t, J = 7.79 Hz, 1H), 7.40 (d, J = 8.04 Hz, 1H), 7.31 (d, J = 2.59 Hz, 1H), 7.25 (d, J = 7.27 Hz, 1H), 7.09 (d, J = 7.78 Hz, 1H), 6.52 (d, J = 7.01 Hz, 1H), 6.23–6.32 (m, 1H), 5.21 (s, 2H), 4.04 (s, 3H); ^{13}C NMR, DEPT (126 MHz, DMSO-d_6) δ 159.2, 155.4, 150.2, 141.0(CH), 132.8(CH), 131.4, 130.3(CH), 123.3(CH), 122.8, 120.8(CH), 102.1(CH), 101.9(CH), 52.2(CH_2), 35.9(CH_3); LCMS: 274 $(M+H)^+$; Purity 95 %; Anal. Calcd for $C_{14}H_{12}ClN_3O$: C 61.43 %, H 4.42 %, N 15.35 %, Found: C 61.51, H 4.45, N 15.37.

*1-Methyl-6-propyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (**11d**)*

Yellow oil, yield 71 %; IR (KBr), ν_{max} (cm^{-1}): 2964, 1650, 1590, 1503, 1321; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.26 (d, J = 2.34 Hz, 1H), 7.11 (d, J = 7.01 Hz, 1H), 6.42 (d, J = 7.01 Hz, 1H), 6.22 (d, J = 2.34 Hz, 1H), 4.07 (s, 3H), 3.87 (t, J = 7.27 Hz, 2H), 1.57–1.73 (m, 2H), 0.87 (t, J = 7.40 Hz, 3H); ^{13}C NMR, DEPT, HMBC (126 MHz, DMSO-d_6) δ 155.4, 132.4(CH), 130.9, 129.6(CH), 123.0, 101.7(CH), 101.3(CH), 49.1(CH_2), 35.8(CH_3), 23.0(CH_2), 11.4(CH_3); LCMS: 191.2 $(M+H)^+$; Purity 95 %; Anal. Calcd for $C_{11}H_{14}N_2O$: C 69.45 %, H 7.42 %, N 14.72 %, Found: C 69.42, H 7.48, N 14.73.

*4-(1-Methyl-7-oxo-1H-pyrrolo[2,3-c]pyridin-6(7H)-yl)benzonitrile (**11e**)*

White crystalline powder, yeild 50 %; m.p. = 182–184 °C; IR (KBr), ν_{max} (cm^{-1}): 3053, 1652, 1584, 1430, 1315; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, J = 8.30 Hz, 2H), 7.66 (d, J = 7.89 Hz, 2H), 7.37 (d, J = 2.08 Hz, 1H), 7.15 (d, J = 7.06 Hz, 1H), 6.59 (d, J = 7.06 Hz, 1H), 6.33 (d, J = 2.49 Hz, 1H), 4.05 (s, 3H). ^{13}C NMR, DEPT, HMBC (126 MHz, DMSO-d_6) δ 154.9, 145.5, 133.5(CH), 133.4(CH), 131.3, 129.2(CH), 128.9(CH), 122.4, 118.9, 110.6, 102.8(CH), 102.5(CH), 36.1(CH_3); LCMS: 250.2 $(M + H)^+$; Purity 95 %; Anal. Calcd for $C_{15}H_{11}N_3O$: C

72.28 %, H 4.45 %, N 16.86 %, Found: C 72.23, H 4.52, N 16.90.

*1-Methyl-6-(4-nitrophenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (***11f***)*

Yellow crystalline powder, yeild 85 %; m.p. = 194–196 °C; IR (KBr), ν_{max} (cm^{-1}): 3435, 1665, 1510, 1351; ^1H NMR (500 MHz, DMSO-d_6) δ 8.35 (d, J = 8.56 Hz, 2H), 7.77 (d, J = 8.56 Hz, 2H), 7.40 (br. s, 1H), 7.20 (d, J = 7.01 Hz, 1H), 6.64 (d, J = 7.01 Hz, 1H), 6.35 (br. s, 1H), 4.07 (s, 3H); ^{13}C NMR, DEPT (126 MHz, DMSO-d_6) δ 154.9, 147.1, 146.6, 133.6 (CH), 131.4, 129.12 (CH), 129.08 (CH), 124.6 (CH), 122.3, 103.0 (CH), 102.6 (CH), 36.1 (CH_3); LCMS: 270.2 $(M + H)^+$; Purity 95 %; Anal. Calcd for $C_{14}H_{11}N_3O_3$: C 62.45 %, H 4.12 %, N 15.61 %, Found: C 62.35, H 4.18, N 15.64.

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