



Synthesis of poly-substituted pyrazolo[1,5-*a*]quinolines through one-pot two component cascade reaction



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ABSTRACT

A diversity-oriented method for the synthesis of novel poly-substituted pyrazolo[1,5-*a*]quinolines has been developed on the basis of an S_NAr /Knoevenagel cyclization cascade reaction or an S_NAr /Dieckmann–Thorpe cyclization cascade reaction. The methods provide a variety of poly-substituted pyrazolo[1,5-*a*]quinolines bearing an amino, alkyl or aryl substituent at the 5-position. In addition, a diversity-oriented method for the synthesis of 2-substituted pyrazolo[1,5-*a*]quinolines from a readily available 2-[(trifluoromethyl)sulfonyl]oxy]pyrazolo[1,5-*a*]quinoline has also been disclosed.

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1. Introduction

A facile preparation of a structurally diverse small-molecule library plays a crucial role in drug discovery. Heterocyclic privileged scaffolds have recently emerged as one of the most guiding principles of modern drug discovery.¹ A number of fused aza-heterocycles, such as indoles, quinolines, benzodiazepines and pyrazolo[1,5-*a*]pyridines **1** are known to act as privileged scaffolds. Therefore, many diversity-oriented synthesis of these aza-heterocycles have been developed.² Apart from these fused aza-heterocycles, pyrazolo[1,5-*a*]quinoline, benzo-fused analogues of pyrazolo[1,5-*a*]pyridines **2**, are also expected to act as a potential privileged scaffold of promise.³ This expectation is based upon the previous works, in which 3-substituted pyrazolo[1,5-*a*]quinoline derivatives have been reported to bind to two independent proteins with high affinities exhibiting dopamine D4 antagonistic and GPR109a agonistic activities, respectively, upon fine-tuning substituents at the 3-position of the pyrazolo[1,5-*a*]quinolines **1** (Fig. 1).^{4,5} However, besides these two examples, the pyrazolo[1,5-*a*]quinoline subunit has not been applied to seek further biologically active compounds as a privileged scaffold, which might be due to the lack of diversity-oriented methods for the synthesis of pyrazolo[1,5-*a*]quinoline derivatives.³

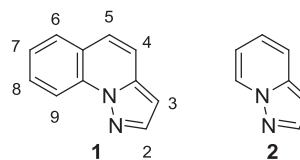
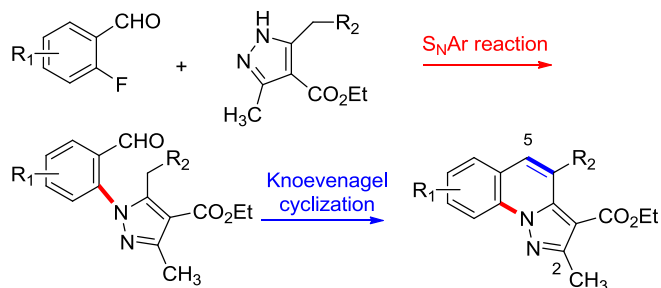


Fig. 1. Structures of pyrazolo[1,5-*a*]quinoline and pyrazolo[1,5-*a*]pyridine.

In our study directed on the development of novel synthetic methods of fused aza-heterocycles with high diversity,⁶ we recently disclosed a one-pot, two-step cascade synthesis of pyrazolo[1,5-*a*]quinolines.^{6a} This cascade reaction involves a sequential intermolecular aromatic nucleophilic substitution (S_NAr) and intramolecular Knoevenagel condensation,⁷ and substituted pyrazolo[1,5-*a*]quinoline derivatives having a variety of substituents at varied positions that could be synthesized, upon selecting two readily available substrates (Scheme 1). However, there is still in the possibility of extending this methodology to applying the facile introduction of substituents to the 5-position. The purpose of this paper is to demonstrate a new cascade process leading to novel pyrazolo[1,5-*a*]quinolines having representative substituents at the 5-position. In addition to this process, we have also developed a versatile intermediate useful for the synthesis of pyrazolo[1,5-*a*]quinolines possessing a variety of substituents at the 2-position.

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Scheme 1. A cascade synthesis of pyrazolo[1,5-a]quinolines.

2. Results and discussion

2.1. Synthesis of 5-methyl and 5-phenyl pyrazolo[1,5-a]quinolines

To verify the validity of our cascade reaction for the synthesis of 5-substituted pyrazolo[1,5-a]quinolines, first, we chose 2-fluoroarylketones **3a–f** as one of the substrates in our cascade reaction from 1*H*-pyrazole **4**. These cascade reactions are expected to introduce a variety of alkyl or aryl substituents at the 5-position upon fine-tuning the 2-fluoroarylketones. In our previous studies on the cascade reaction from 2-fluoroarylaldehydes and 3,5-disubstituted 1*H*-pyrazoles (Scheme 1), K_2CO_3 was found to be the best base promoting this reaction in DMF at 120 °C.^{6a} We also found the reaction was accelerated upon using Cs_2CO_3 instead of K_2CO_3 as a base in our related cascade reaction providing benzimidazo[1,2-*a*]quinolines.^{6b} With these findings in mind, the reaction of **4** with 2-fluoroarylketones was examined under two representative conditions. The results are summarized in Table 1.

As shown in Table 1, almost all of the tested reactions under the conditions using either K_2CO_3 or Cs_2CO_3 successfully produced the desired pyrazolo[1,5-*a*]quinoline derivatives **5a–f** having a methyl or phenyl substituent at the 5-position in modest to excellent isolated yield. It should be noted that K_2CO_3 is a better base than Cs_2CO_3 for the cascade reaction with electron-deficient 2-fluoroarylketones (entries 3 and 4). When the reactions were carried out with K_2CO_3 in DMF, the cascade products **5c** and **5d** were isolated in 80% and 99% yields, respectively (entries 3 and 4). However, **5c** and **5d** were obtained in modest yield upon using Cs_2CO_3 as a base (entries 3 and 4). In these reactions,

fluoroarylketones **3c** and **3d** rapidly decomposed under the conditions⁸ and a large amount of 1*H*-pyrazole **4** remained unreacted. On the contrary, Cs_2CO_3 was determined to be the better base to induce the cascade reaction with electron-sufficient 2-fluoroarylketone **3e** and 2-fluorobenzophenone (**3f**). In these cases, dramatic improvement in yield was observed upon replacement of K_2CO_3 with Cs_2CO_3 (entries 5 and 6).

2.2. Synthesis of 5-aminopyrazolo[1,5-a]quinoline derivatives

The amines possess versatile functions to elaborate a variety of chemical structures through amide formations and reductive alkylation sequences, and have been used as key intermediates in drug discovery.⁹ Therefore, we next focused on introduction of the amino functionality to the 5-position of pyrazolo[1,5-*a*]quinoline skeleton. In this context, we examined the reactions of 1*H*-pyrazole **4** with 2-fluorobenzonitriles **6**, instead of 2-fluorobenzaldehydes and -ketones. The attempted reaction is expected to proceed through the sequential S_NAr reaction and the Dieckmann–Thorpe cyclization¹⁰ (S_NAr /Dieckmann–Thorpe cyclization cascade reaction) to give 5-aminopyrazolo[1,5-*a*]quinolines. The results are shown in Table 2.

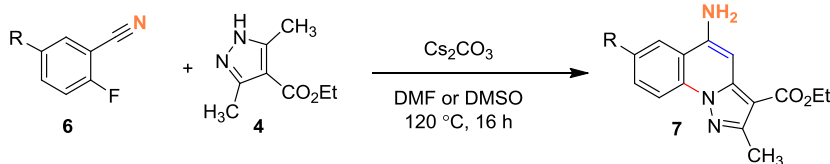
Initially, a mixture of 2-fluorobenzonitrile (**6a**) and 1*H*-pyrazole **4** was heated at 120 °C in DMF in the presence of Cs_2CO_3 for 16 h as a model reaction (entry 1). This reaction gave the expected cascade product **7a** in a 46% yield. The yield significantly increased to 65%, upon switching the solvent to DMSO (entry 1). In an effort to survey the scope of the present cascade reaction, a variety of fluoroarylnitriles were used as a substrate. Although almost all of the tested combinations successfully produced the desired 5-aminopyrazolo[1,5-*a*]quinolines **7a–f**, the yields varied depending on the solvent applied. For example, in the case of 2-fluorobenzonitriles **6e** and **6f** bearing an electron-donating group, these substrates showed poor reactivity in DMF under the conditions to give trace amounts of desired products **7e** and **7f** (entries 5 and 6). In these reactions, the S_NAr adducts **8** and **9** were isolated in 38% and 29% yields, respectively (Scheme 2). These results suggest to us that the Dieckmann–Thorpe cyclization of **8** and **9** is inert to the conditions using Cs_2CO_3 in DMF at 120 °C. Yields of the cascade products **7e** and **7f** dramatically increased to moderate yields, upon switching the solvent to DMSO (entries 5 and 6). The structures of the new compounds **7a–f** were readily confirmed by the conventional spectroscopic analysis. The structure of **7d** was further confirmed by X-ray crystallographic analysis (Fig. 2).

Table 1
The cascade reaction toward 5-alkyl and 5-aryl pyrazolo[1,5-*a*]quinolines

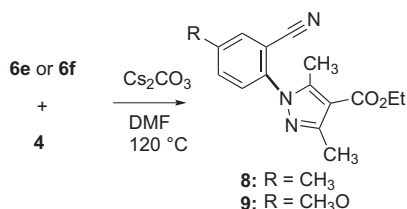
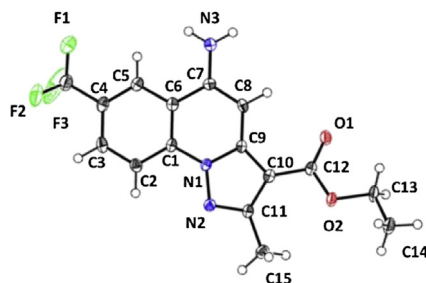
Entry	Arylketone					Product 5	Yield % with K_2CO_3 ^a	Yield % with Cs_2CO_3 ^b
	3	R ₁	R ₂	R ₃	X			
1	3a	H	H	CH ₃	CH	5a	34	78
2	3b	F	H	CH ₃	CH	5b	35	44
3	3c	CF ₃	H	CH ₃	CH	5c	80	45
4	3d	H	H	CH ₃	N	5d	99	31
5	3e	H	CH ₃ O	CH ₃	CH	5e	13	55
6	3f	H	H	C ₆ H ₅	CH	5f	1	45

^a Arylketone (1.0 mmol) and pyrazole (1.0 mmol) were reacted in DMF (5.0 mL) in the presence of K_2CO_3 (3.0 mmol) at 120 °C for 16 h.

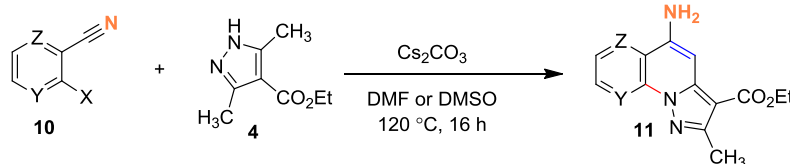
^b Arylketone (1.0 mmol) and pyrazole (1.0 mmol) were reacted in DMF (5.0 mL) in the presence of Cs_2CO_3 (3.0 mmol) at 120 °C for 16 h.

Table 2The cascade reaction of 1*H*-pyrazole **4** with fluoroarylnitriles

Entry	Arylnitrile		Product 7	Yield % in DMF ^a	Yield % in DMSO ^b
	6	R			
1	6a	H	7a	46	65
2	6b	Cl	7b	51	30
3	6c	Br	7c	NE ^c	70
4	6d	CF ₃	7d	38	31
5	6e	CH ₃	7e	1	39
6	6f	CH ₃ O	7f	1	55

^a Arylnitrile (1.00 mmol) and pyrazole (1.00 mmol) were reacted in DMF (5.0 mL) in the presence of Cs₂CO₃ (3.00 mmol) at 120 °C for 16 h.^b Arylnitrile (1.00 mmol) and pyrazole (1.00 mmol) were reacted in DMSO (5.0 mL) in the presence of Cs₂CO₃ (3.00 mmol) at 120 °C for 16 h.^c Not examined.**Scheme 2.** Isolation of S_NAr adducts from the reaction between **6e** (or **6f**) and **4**.**Fig. 2.** ORTEP drawing of **7d**.

Halogenated heteroaromatic nitriles were also available to the S_NAr/Dieckmann–Thorpe cyclization cascade reaction (Table 3). In these reactions, DMF was found to be a better solvent than DMSO to induce the reaction with 3-fluoropicolinonitrile (**10a**) (entry 1). The

Table 3The cascade reaction of 1*H*-pyrazole **4** with halogenated heteroaromatic nitriles

Entry	Arylnitrile				Product 11	Yield % in DMF ^a	Yield % in DMSO ^b
	10	X	Y	Z			
1	10a	F	CH ₂	N	11a	78	36
2	10b	F	N	CH ₂	11b	35	NE ^c
3	10c	Cl	N	CH ₂	11b	38	NE ^c

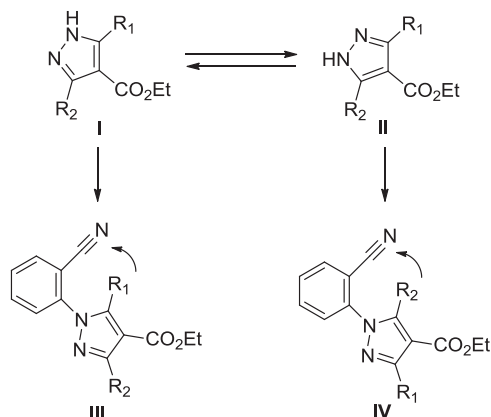
^a Heteroaromatic nitrile (1.00 mmol) and pyrazole (1.00 mmol) were reacted in DMF (5.0 mL) in the presence of Cs₂CO₃ (3.00 mmol) at 120 °C for 16 h.^b Heteroaromatic nitrile (1.00 mmol) and pyrazole (1.00 mmol) were reacted in DMSO (5.0 mL) in the presence of Cs₂CO₃ (3.00 mmol) at 120 °C for 16 h.^c Not examined.

desired 5-aminopyrazolo[1,5-*a*]quinoline **11a** was obtained in a 78% yield upon using DMF as a solvent. It may be of worth noting that 2-chloronicotinonitrile (**10c**) reacted with **4** to give **11b** in a comparable yield to that with the reaction from 2-fluoronicotinonitrile (**10b**) (entry 2 vs 3).

2.3. Reaction of 2-fluorobenzonitrile **6a** with various unsymmetrical 1*H*-pyrazoles

Unsymmetrical 1*H*-pyrazoles, such as **I** exist as an equilibrium mixture of their tautomers **I** and **II** (Scheme 3). Therefore, the S_NAr sequence of our cascade reaction with unsymmetrical 1*H*-pyrazoles theoretically provides a regioisomeric mixture of the corresponding adducts **III** and **IV**. The regiochemical outcome of the S_NAr adducts are highly affected by the steric and electronic nature of the substituents. In the case that both substituents (R₁ and R₂) of S_NAr adducts **III** and **IV** can participate in the Dieckmann–Thorpe cyclization, two types of the corresponding cascade products would be produced. With these hypotheses in mind, we next examined the reaction of 2-fluorobenzonitrile (**6a**) with unsymmetrical pyrazoles **12a–g** having substituents at the varied positions to extend the scope and diversity for the present cascade reaction. These results are listed in Table 4.

Initially, the reaction of **6a** with unsymmetrical 1*H*-pyrazoles **12a–c** was examined (entries 1–3). In these 1*H*-pyrazoles, one substituent can participate in the Dieckmann–Thorpe cyclization but the other substituents are inert to these cyclization. From these



Scheme 3. Tautomerism of 3,5-disubstituted unsymmetrical 1H-pyrazoles.

Table 4

Scope of 1H-pyrazoles in the S_NAr /Dieckmann–Thorpe cyclization sequences

Entry ^a	Pyrazole	R ₁	R ₂	X	Product	R ₃	Yield %
1 ^b	12a	CH ₃	C ₆ H ₅	CO ₂ Et	13aa	H	41
2	12b	CH ₃	CH ₃ S	CO ₂ Et	13ab	H	41
3	12c	CH ₃ CH ₂	CH ₃ S	CO ₂ Et	13ac	CH ₃	31
4 ^c	12d	CH ₃	CH ₃ CH ₂	CO ₂ Et	13ad	H	23
5	12e	CH ₃	CH ₃	Br	13ae	H	46
6	12f	CH ₃	CF ₃	H	13af	H	49
7	12g	CH ₃ CH ₂	CF ₃	H	13ag	CH ₃	28

^a All reaction were carried out in the presence of 2-fluorobenzonitrile (**6a**) (1.00 mmol), pyrazole **11** (1.00 mmol) and Cs₂CO₃ (3.00 mmol) in DMSO (5 mL) at 120 °C for 16 h unless otherwise noted.

^b An excess (1.20 mmol) of pyrazole **12a** was used.

^c A large excess (2.00 mmol) of pyrazole **12d** was used.

reactions with **12a** and **12b**, the desired cascade products **13aa** and **13ab** were obtained with virtually the same yields (41%) (entries 1 and 2). In these reactions, the S_NAr adducts for either type III or type IV shown in Scheme 3 were not detected. The yields of **13aa** and **13ab** were slightly poorer than that of **8a** from the symmetrical 1H-pyrazole **4** under the same conditions (cf. Table 2, entry 1). The modest yields of **13aa** and **13ab** may have arisen from the modest distribution ratio of the S_NAr adducts leading to the desired cascade product.¹¹ The reaction of **6a** with **12c**, ethyl analogue of **12b**, gave 4-methyl-5-aminopyrazolo[1,5-*a*]quinoline (**13ac**) in a 31% yield (entry 3). Although both substituents of unsymmetrical 1H-pyrazole **12d** having methyl and ethyl substituents at 3- and 5-position can be participate in the Dieckmann–Thorpe cyclization, the

cascade product **13ad** was determined to be a separable product in a low yield (23%) (entry 4). In this reaction, the isomer **13** (R₂=R₃=Me, X=CO₂Et) was not detected. The results suggest to us that the S_NAr reaction preferably occurs at the sterically less congested nitrogen of 1H-pyrazole **12d**. It should be noted that our cascade reaction does not require the carboethoxy group at the 4-position (entries 5–7). Thus, symmetrical pyrazole **12e** bearing a bromo group instead of the carboethoxy group reacted with **6a** to give the desired cascade product **13ae** in a 46% yield (entry 5). In cases where 1H-pyrazoles possess a CF₃ group at the 3-position, electron-withdrawing substituents, such as carboethoxy and bromo groups at the 4-position can be replaced with a hydrogen atom to give the desired cascade products **13af** and **13ag** in moderate yields (entries 6 and 7).¹²

2.4. Synthesis of versatile intermediates for diverse-oriented synthesis of 2-substituted pyrazolo[1,5-*a*]quinolines

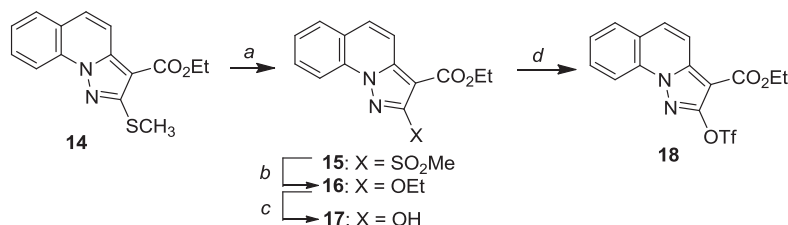
In our previous paper,^{6a} we reported on the facile and high yield synthesis of ethyl 2-(methylthio)pyrazolo[1,5-*a*]quinoline-3-carboxylate (**14**) through our S_NAr /Knoevenagel cyclization cascade reaction. In this section, we describe the transformation of **14** to the versatile triflate **18** and its applications to the diversity-oriented synthesis of 2-substituted pyrazolo[1,5-*a*]quinolines. The required triflate **18** was readily synthesized by the sequences shown in Scheme 4. Thus, compound **14** was first transformed to sulfone **15** in a 94% yield though oxidation with Oxone[®] under standard conditions. The sulfone **15** was briefly treated with NaOEt in refluxing THF to give **16** in a 64% yield.¹³ The selective deethylation of **16** with BBr₃ in CH₂Cl₂, followed by trifluoromethanesulfonylation of the resulting alcohol **17**, gave triflate **18** in a 71% yield for two steps.

With triflate **18** in hand, several cross-coupling reactions were examined to show their efficacy with introduction of a variety of functionalized substituents to the 2-position (Scheme 5).

The Heck reaction of triflate **18** with *tert*-butyl acrylate in the presence of PdCl₂(PPh₃)₂ in DMF containing TEA gave cross-coupling product **19** in a 26% yield.¹⁴ The Suzuki coupling reaction of **18** with phenylboronic acid was catalyzed by Pd(PPh₃)₄ in refluxing dioxane in the presence of K₃PO₄ and KBr to give **20** in a 46% yield.¹⁴ The Negishi coupling reaction with (4-ethoxy-4-oxobutyl)zinc(II) bromide was carried out in THF in the presence of Pd(OAc)₂ and Xphos for 16 h to give **21** in a 68% yield.¹⁵ Although, the Buchwald amination of **18** with morpholine using a palladium catalyst under the representative conditions failed,¹⁶ it was found that the amination proceed rapidly to give **22** in a 58% yield through an aromatic nucleophilic substitution upon heating a mixture of **18** and a large excess of morpholine.

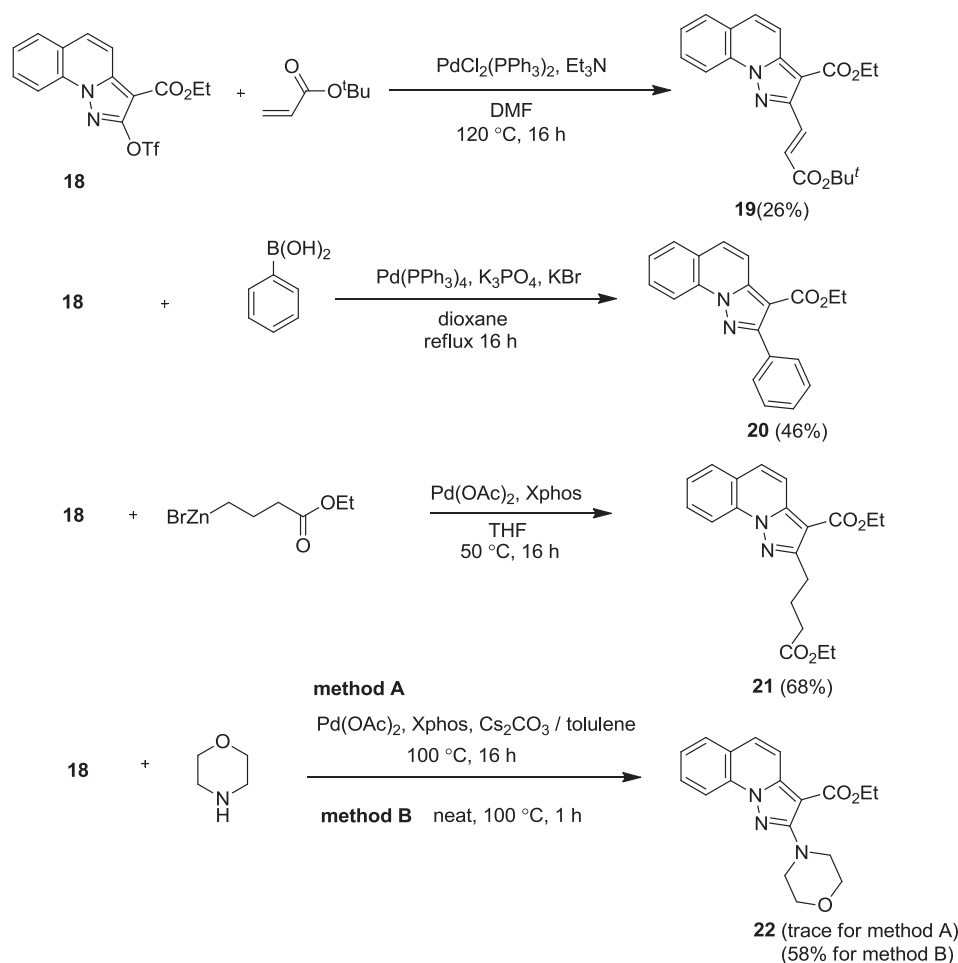
3. Conclusions

In conclusion, we have demonstrated diversity-oriented approaches for the effective preparation of poly-substituted pyrazolo



Reagents and conditions: a) Oxone[®], THF–MeOH–H₂O, rt, 16 h (94%); b) NaOEt, THF, 20 min (64%); c) BBr₃, CH₂Cl₂, rt, 16 h, (85%); d) Tf₂O, Et₃N, CH₂Cl₂, 16 h, (83%).

Scheme 4. Synthesis of versatile intermediate **18**.



Scheme 5. Cross-coupling reactions of **18** with various reagents.

[1,5-*a*]quinolines through novel $\text{S}_{\text{N}}\text{Ar}$ /Knoevenagel cyclization cascade reactions or $\text{S}_{\text{N}}\text{Ar}$ /Dieckmann–Thorpe cyclization cascade reactions. A characteristic feature of these syntheses is that a variety of substituents including an alkyl, aryl or amino functional group can be readily introduced to the 5-position upon fine-tuning 2-fluoroarylketones or 2-fluoroarylnitriles. In addition to these results, a versatile intermediate applicable to the diversity-oriented synthesis of 2-substituted pyrazolo[1,5-*a*]quinolines has been developed. The present methods are complementary to our $\text{S}_{\text{N}}\text{Ar}$ /Knoevenagel cyclization cascade reaction using 2-fluoroarylaldehydes^{6a} to synthesize a variety of poly-substituted pyrazolo[1,5-*a*]quinolines, and should be useful to prove that pyrazolo[1,5-*a*]quinoline skeleton acts as a potential privileged scaffold for the discovery of potential biological active compounds. The study about this issue is now in progress and will be reported in due course.

4. Experimental

4.1. General

All reagents and solvents were pure analytical-grade materials purchased from commercial sources and were used without further purification except for the 1*H*-pyrazoles **12b–c** and **12d**. Compounds **12b–c**¹⁷ and **12d**¹⁸ were synthesized by a known method. All melting points were taken on a Yanagimoto micromelting point apparatus and were uncorrected. IR spectra were recorded on a JASCO FTIR-620. Mass spectra were measured on JEOL GCmate by electron ionization and Micromass Autospec by electrospray

ionization. NMR spectra were obtained on a JEOL JNM-ECP400 NMR Spectrometer (^1H NMR: 400 MHz), a Bruker DPX400 NMR Spectrometer (^1H NMR: 400 MHz and ^{13}C NMR: 100 MHz) or a Bruker AVANCE III NMR spectrometer (^1H NMR: 400 MHz and ^{13}C NMR: 100 MHz). The chemical shift data for each signal on ^1H NMR were given in units of δ relative to CHCl_3 ($\delta=7.26$ ppm) for CDCl_3 solution and to DMSO ($\delta=2.50$ ppm) for DMSO- d_6 solution. For ^{13}C NMR spectra, the chemical shifts in CDCl_3 were relative to CDCl_3 ($\delta=77.0$ ppm) resonances and the chemical shifts in DMSO- d_6 were relative to DMSO- d_6 ($\delta=39.5$ ppm) resonances. Column chromatography was carried out using 63–210 μm silica gel 60N (Kanto Chemical Co., Inc.). Analytical TLC was carried out with Merck plates precoated with silica gel 60F₂₅₄ plates (0.25 mm). Crystallographic data (excluding structure factors) for the X-ray crystal structure analysis reported in this paper have been deposited with the Cambridge Crystallographic Data Center (CCDC) as supplementary publication No. CCDC 982642, copies of these data can be obtained, free of charge, upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.2. General procedures for the preparation of pyrazolo[1,5-*a*]quinolines **5**

4.2.1. Ethyl 2,5-dimethylpyrazolo[1,5-*a*]quinoline-3-carboxylate (5a**). Condition A:** A mixture of 2-fluoroacetophenone **3a** (138 mg, 1.00 mmol), 1*H*-pyrazole **2a** (202 mg, 1.20 mmol) and K_2CO_3 (420 mg, 3.00 mmol) in DMF (5.0 mL) was stirred at 120°C

for 16 h. After monitoring the end of the reaction on TLC, the mixture was cooled to room temperature and diluted with water. The resulting mixture was extracted with ethyl acetate twice. The combined organic layers were washed with water twice, dried over MgSO_4 and the solvent was removed in vacuo to afford a residue. The residue was purified by flash column chromatography (hexane:EtOAc=5:1) on silica gel to afford **5a** (92.0 mg, 34% yield). *Condition B*: The reaction was carried out with Cs_2CO_3 instead of K_2CO_3 under the same conditions as that of *Condition A* to afford **5a** (210 mg, 78% yield).

Pale yellow solid, mp 121–123 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 1697, 1624, 1126, 1090; ^1H NMR (CDCl_3 , 400 MHz) δ 8.59 (d, $J=8.5$ Hz, 1H), 7.91–7.89 (m, 2H), 7.70 (td, $J=8.1$ Hz, 1.2 Hz, 1H), 7.51 (td, $J=8.1$ Hz, 1.2 Hz, 1H), 4.40 (q, $J=7.0$ Hz, 2H), 2.71 (s, 3H), 2.66 (d, $J=0.8$ Hz, 3H), 1.44 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 164.41, 153.96, 140.08, 135.36, 133.57, 129.60, 125.03, 124.91, 123.62, 116.20, 116.042, 103.11, 59.72, 19.37, 14.59, 14.51; HR-MS (ESI) calcd for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ requires 269.1290, found 269.1294.

4.2.2. Ethyl 7-fluoro-2,5-dimethylpyrazolo[1,5-a]quinoline-3-carboxylate (5b). Prepared from **3b** and **4** in an analogous manner for preparation of **5a**. Yield: 35% for *Condition A*, 44% for *Condition B*; Pale yellow solid, mp 143–144 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 1698, 1566, 1235, 1147; ^1H NMR (CDCl_3 , 400 MHz) δ 8.59 (dd, $J=9.2$ Hz, 5.0 Hz, 1H), 7.94 (s, 1H), 7.55 (dd, $J=9.6$ Hz, 2.7 Hz, 1H), 7.46–7.41 (m, 1H), 4.40 (q, $J=7.3$ Hz, 2H), 2.70 (s, 3H), 2.62 (d, $J=0.8$ Hz, 3H), 1.44 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 164.30, 159.78 (d, $^1J_{\text{CF}}=243.4$ Hz), 153.97, 139.60, 134.54 (d, $^4J_{\text{CF}}=3.6$ Hz), 130.24, 125.0 (d, $^3J_{\text{CF}}=8.4$ Hz), 118.14 (d, $^3J_{\text{CF}}=8.9$ Hz), 117.84, 117.38, 110.13 (d, $^2J_{\text{CF}}=23.0$ Hz), 103.34, 59.82, 19.33, 14.51 (2C); HR-MS (ESI) calcd for $\text{C}_{16}\text{H}_{16}\text{FN}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ requires 287.1196, found 287.1191.

4.2.3. Ethyl 7-trifluoromethyl-2,5-dimethylpyrazolo[1,5-a]quinoline-3-carboxylate (5c). Prepared from **3c** and **4** in an analogous manner for preparation of **5a**. Yield: 80% for *condition A*, 45% for *condition B*; Pale yellow solid, mp 130–131 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 1696, 1624, 1541, 1313, 1159, 1119; ^1H NMR (CDCl_3 , 400 MHz) δ 8.68 (d, $J=8.8$ Hz, 1H), 8.15 (s, 1H), 7.96 (s, 1H), 7.90 (dd, $J=8.8$ Hz, 1.5 Hz, 1H), 4.41 (q, $J=7.3$ Hz, 2H), 2.71 (s, 3H), 2.69 (d, $J=0.8$ Hz, 3H), 1.45 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 164.07, 154.72, 140.52, 135.10, 134.92, 126.97 (q, $^2J_{\text{CF}}=32.0$ Hz), 125.82 (q, $^3J_{\text{CF}}=3.0$ Hz), 124.00 (q, $^1J_{\text{CF}}=270.0$ Hz), 123.21, 122.66 (q, $^3J_{\text{CF}}=4.0$ Hz), 117.59, 116.94, 103.99, 59.97, 19.25, 14.57, 14.48; HR-MS (ESI) calcd for $\text{C}_{17}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ requires 337.1164, found 337.1165.

4.2.4. Ethyl 2,5-dimethylpyrazolo[1,5-a][1,8]naphthyridine-3-carboxylate (5d). Prepared from **3d** and **4** in an analogous manner for preparation of **5a**. Yield: 99% for *condition A*, 31% for *condition B*; Pale yellow solid, mp 172–174 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 1693, 1626; ^1H NMR (CDCl_3 , 400 MHz) δ 8.87 (dd, $J=4.6$ Hz, 1.9 Hz, 1H), 8.27 (dd, $J=8.1$ Hz, 1.6 Hz, 1H), 7.98 (d, $J=0.8$ Hz, 1H), 7.52 (dd, $J=8.1$ Hz, 4.6 Hz, 1H), 4.41 (q, $J=7.3$ Hz, 2H), 2.76 (s, 3H), 2.66 (d, $J=1.2$ Hz, 3H), 1.44 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 164.24, 155.24, 150.28, 143.63, 141.92, 134.63, 134.19, 121.14, 118.97, 117.30, 104.56, 60.02, 18.71, 14.76, 14.51; HR-MS (ESI) calcd for $\text{C}_{15}\text{H}_{16}\text{N}_3\text{O}_2$ ($\text{M}+\text{H}$) $^+$ requires 270.1243, found 270.1237.

4.2.5. Ethyl 8-methoxy-2,5-dimethylpyrazolo[1,5-a]quinoline-3-carboxylate (5e). Prepared from **3e** and **4** in an analogous manner for preparation of **5a**. Yield: 13% for *condition A*, 55% for *condition B*; Pale yellow solid, mp 150–152 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 1697, 1617, 1541, 1223, 1127; ^1H NMR (CDCl_3 , 400 MHz) δ 7.98 (d, $J=2.7$ Hz, 1H), 7.79 (d, $J=8.9$ Hz, 1H), 7.75 (d, $J=1.2$ Hz, 1H), 7.10 (dd, $J=8.8$ Hz,

2.7 Hz, 1H), 4.40 (q, $J=7.3$ Hz, 2H), 4.01 (s, 3H), 2.71 (s, 3H), 2.63 (d, $J=1.2$ Hz, 3H), 1.44 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 164.48, 161.01, 154.09, 140.72, 135.47, 134.94, 126.47, 117.68, 115.48, 113.66, 102.70, 97.35, 59.67, 55.83, 19.36, 14.64, 14.53; HR-MS (ESI) calcd for $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$ requires 299.1396, found 299.1390.

4.2.6. Ethyl 2-methy-5-phenylpyrazolo[1,5-a]quinoline-3-carboxylate (5f). Prepared from **3f** and **4** in an analogous manner for preparation of **5a**. Yield: trace for *condition A*, 45% for *condition B*; Pale yellow solid, mp 147–148 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 1698, 1611, 1113; ^1H NMR (CDCl_3 , 400 MHz) δ 8.68 (dd, $J=8.5$ Hz, 0.7 Hz, 1H), 8.01 (s, 1H), 7.81 (dd, $J=8.3$ Hz, 0.92 Hz, 1H), 7.73 (td, $J=7.2$ Hz, 1.3 Hz, 1H), 7.54–7.50 (m, 5H), 7.43 (td, $J=8.3$ Hz, 1.2 Hz), 4.40 (q, $J=7.1$ Hz, 2H), 2.77 (s, 3H), 1.41 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 164.32, 154.38, 140.45, 139.73, 138.27, 133.98, 129.87, 129.63 (2C), 128.53 (2C), 128.26, 127.31, 124.96, 122.74, 116.83, 116.07, 104.09, 59.82, 14.63, 14.52; HR-MS (ESI) calcd for $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_2$ ($\text{M}+\text{H}$) $^+$ requires 331.1447, found 331.1449.

4.3. General procedure for the preparation of 5-aminopyrazolo[1,5-a]quinolone derivatives 7 and the related compounds 10

4.3.1. Ethyl 5-amino-2-methylpyrazolo[1,5-a]quinoline-3-carboxylate (7a). *Condition C*: A mixture of 2-fluorobenzonitrile **6a** (121 mg, 1.00 mmol), 1H-pyrazole **4** (202 mg, 1.20 mmol) and Cs_2CO_3 (980 mg, 3.00 mmol) in DMF (5.0 mL) was stirred at 120 °C for 16 h. After monitoring the end of the reaction on TLC, the mixture was cooled to room temperature and diluted with water. The resulting mixture was extracted with ethyl acetate twice. The combined organic layers were washed with water twice, dried over MgSO_4 and the solvent was removed in vacuo to afford a residue. The residue was purified by flash column chromatography (hexane:EtOAc=1:1) on silica gel to afford **7a** (124 mg, 46% yield). *Condition D*: The reaction was carried out in DMSO instead of DMF under the same conditions as that of *condition C* to afford **7a** (175 mg, 65% yield).

Yellow solid, mp 166–168 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3207, 1649, 1604, 1097; ^1H NMR (CDCl_3 , 400 MHz) δ 8.56 (d, $J=8.2$ Hz, 1H), 7.75–7.69 (m, 2H), 7.46 (td, $J=8.2$ Hz, 1.1 Hz, 1H), 7.25 (d, $J=4.1$ Hz, 1H), 4.37 (q, $J=7.2$ Hz, 2H), 2.66 (s, 3H), 1.42 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 164.76, 154.22, 142.38, 142.14, 134.09, 130.15, 124.44, 121.69, 116.75, 116.53, 101.10, 95.75, 59.46, 14.72, 14.59; HR-MS (ESI) calcd for $\text{C}_{15}\text{H}_{16}\text{N}_3\text{O}_2$ ($\text{M}+\text{H}$) $^+$ requires 270.1243, found 270.1242.

4.3.2. Ethyl 5-amino-7-chloro-2-methyl-2-methylpyrazolo[1,5-a]quinoline-3-carboxylate (7b). Prepared from **6b** and **4** in an analogous manner for preparation of **7a**. Yield: 51% for *condition C*, 30% for *condition D*; Yellow solid, mp 251–253 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3438, 3196, 1650, 1603, 1552, 1344, 1123; ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 8.35–8.33 (m, 2H), 7.76 (dd, $J=9.0$ Hz, 1.6 Hz, 1H), 7.03 (s, 1H), 4.24 (q, $J=7.0$ Hz, 2H), 2.49 (s, 3H), 1.34 (t, $J=7.0$ Hz, 3H); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz) δ 163.45, 153.23, 144.41, 142.30, 132.06, 130.25, 128.85, 123.07, 117.63 (2C), 99.09, 92.44, 58.82, 14.40 (2C); HR-MS (ESI) calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2\text{Cl}$ ($\text{M}+\text{H}$) $^+$ requires 304.0853, found 304.0854.

4.3.3. Ethyl 5-amino-7-bromo-2-methylpyrazolo[1,5-a]quinoline-3-carboxylate (7c). Prepared from **6c** and **4** in an analogous manner for preparation of **7a**. Yield: 70% for *condition D*; Yellow solid, mp 244–246 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3453, 3340, 3202, 1649, 1617, 1546, 1148, 1124, 1104, 1103; ^1H NMR (CDCl_3 , 400 MHz) δ 8.48 (d, $J=2.0$ Hz, 1H), 8.28 (d, $J=9.0$ Hz, 1H), 7.88 (dd, $J=9.0$ Hz, 2.0 Hz, 1H), 7.03 (s, 1H), 6.72 (s, 1H), 4.24 (q, $J=7.1$ Hz, 2H), 2.50 (d, $J=2.7$ Hz, 3H),

1.34 (t, $J=7.1$ Hz, 3H), ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 163.46, 153.28, 144.36, 142.34, 133.02, 132.38, 126.10, 118.04, 117.84, 116.97, 99.12, 92.42, 58.84, 14.42 (2C); HR-MS (ESI) calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2\text{Br}$ ($\text{M}+\text{H}$) $^+$ requires 348.0348, found 348.0346.

4.3.4. Ethyl 5-amino-7-trifluoromethyl-2-methyl-2-methylpyrazolo[1,5-*a*]quinoline-3-carboxylate (7d). Prepared from **6d** and **4** in an analogous manner for preparation of **7a**. Yield: 38% for condition C, 31% for condition D; Yellow solid, mp 249–251 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3335, 3228, 1655, 1630, 1611, 1129; ^1H NMR (CDCl_3 , 400 MHz) δ 8.66 (d, $J=8.8$ Hz, 1H), 8.02 (s, 1H), 7.91 (dd, $J=8.8$ Hz, 1.9 Hz, 1H), 7.39 (s, 1H), 4.49 (br s, 2H), 4.38 (q, $J=7.3$ Hz, 2H), 2.66 (s, 3H), 1.42 (t, $J=7.3$ Hz, 3H), ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 163.41, 153.90, 145.12, 143.12, 135.18, 126.31 (q, $^3J_{\text{CF}}=3.0$ Hz), 124.85 (q, $^2J_{\text{CF}}=32.0$ Hz), 124.26 (q, $^1J_{\text{CF}}=271.0$ Hz), 121.86 (q, $^3J_{\text{CF}}=4.0$ Hz), 116.83, 116.15, 99.32, 92.55, 58.92, 14.44, 14.48; HR-MS (ESI) calcd for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_2\text{F}_3$ ($\text{M}+\text{H}$) $^+$ requires 338.1116, found 338.1118.

4.3.5. Ethyl 5-amino-2,7-dimethyl-2-methylpyrazolo[1,5-*a*]quinoline-3-carboxylate (7e). Prepared from **6e** and **4** in an analogous manner for preparation of **7a**. Yield: trace for condition C, 39% for condition D; Yellow solid, mp 221–223 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3477, 3339, 3230, 1668, 1639, 1609, 1126, 1103; ^1H NMR (DMSO- d_6 , 400 MHz) δ 8.27 (d, $J=8.5$ Hz, 1H), 8.04 (s, 1H), 7.59 (d, $J=7.8$ Hz, 1H), 7.01 (s, 1H), 6.60 (br s, 2H), 4.26 (q, $J=7.1$ Hz, 2H), 2.51 (s, 3H), 1.35 (t, $J=7.1$ Hz, 3H), ^{13}C NMR (CDCl_3 , 100 MHz) δ 164.67, 153.87, 142.33, 141.68, 134.39, 132.12, 131.72, 121.36, 116.68, 116.42, 100.97, 95.75, 59.49, 21.43, 14.59 (2C); HR-MS (ESI) calcd for $\text{C}_{16}\text{H}_{18}\text{N}_3\text{O}_2$ ($\text{M}+\text{H}$) $^+$ requires 284.1399, found 284.1391. In the experiment through condition C, the $\text{S}_{\text{N}}\text{Ar}$ adduct **8** was isolated in 38% yield.

4.3.6. Ethyl 1-(cyano-4-methylphenyl)-3,5-dimethyl-1H-pyrazole-4-carboxylate (8). White solid, mp 92–93 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 2980, 2930, 2232, 1702, 1556, 1518, 1479, 1427, 1256, 1120; ^1H NMR (CDCl_3 , 400 MHz) δ 7.59 (s, 1H), 7.52 (dd, $J=8.5$ Hz, 1.9 Hz, 1H), 7.35 (d, $J=8.5$ Hz, 1H), 4.32 (q, $J=7.3$ Hz, 2H), 2.49 (s, 3H), 2.47 (s, 3H), 2.44 (s, 3H), 1.37 (t, $J=7.3$ Hz, 3H), ^{13}C NMR (CDCl_3 , 100 MHz) δ 164.16, 152.34, 145.80, 140.21, 138.39, 134.42, 133.81, 128.34, 115.53, 111.37, 111.17, 59.82, 20.90, 14.34, 14.26, 12.15; MS (EI^+) m/z 283 [M] $^+$, HR-MS (ESI) calcd for $\text{C}_{16}\text{H}_{18}\text{N}_3\text{O}_2$ ($\text{M}+\text{H}$) $^+$ requires 284.1399, found 284.1397.

4.3.7. Ethyl 5-amino-7-methoxy-2-methylpyrazolo[1,5-*a*]quinoline-3-carboxylate (7f). Prepared from **6e** and **4** in an analogous manner for preparation of **7a**. Yield: trace for condition C, 55% for condition D; Pale yellow solid, mp 257–259 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3213, 1653, 1607, 1348, 1239, 839; ^1H NMR (DMSO- d_6 , 400 MHz) δ 8.29 (d, $J=8.9$ Hz, 1H), 7.66 (d, $J=2.5$ Hz, 1H), 7.37 (dd, $J=9.2$ Hz, 2.5 Hz, 1H), 7.00 (s, 1H), 6.61 (br s, 2H), 4.24 (q, $J=7.1$ Hz, 2H), 3.89 (s, 3H), 2.49 (s, 3H), 1.34 (t, $J=7.1$ Hz, 3H), ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 163.63, 156.16, 152.42, 144.93, 141.25, 128.30, 119.60, 117.37, 117.09, 105.16, 98.51, 91.82, 58.67, 55.80, 14.45, 14.40; HR-MS (ESI) calcd for $\text{C}_{16}\text{H}_{18}\text{N}_3\text{O}_3$ ($\text{M}+\text{H}$) $^+$ requires 300.1348, found 300.1338. In the experiment through condition C, the $\text{S}_{\text{N}}\text{Ar}$ adduct **9** was isolated in 29% yield.

4.3.8. Ethyl 1-(cyano-4-methoxyphenyl)-3,5-dimethyl-1H-pyrazole-4-carboxylate (9). Pale yellow solid, mp 81–83 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 2979, 2937, 2233, 1702, 1518, 1310, 1284, 1097; ^1H NMR (CDCl_3 , 400 MHz) δ 7.37 (d, $J=8.5$ Hz, 1H), 7.24 (d, $J=2.7$ Hz, 1H), 7.21 (dd, $J=8.5$ Hz, 2.7 Hz, 1H), 4.32 (q, $J=7.4$ Hz, 2H), 3.89 (s, 3H), 2.48 (s, 3H), 2.43 (s, 3H), 1.37 (t, $J=7.3$ Hz, 3H), ^{13}C NMR (CDCl_3 , 100 MHz) δ 164.18, 159.77, 152.23, 145.97, 133.70, 129.88, 119.63, 117.87, 115.24, 112.58, 111.01, 59.81, 56.02, 14.35, 14.27, 12.10; MS (EI^+) m/z 299

[M] $^+$, 254 [base] $^+$, HR-MS (ESI) calcd for $\text{C}_{16}\text{H}_{18}\text{N}_3\text{O}_2$ ($\text{M}+\text{H}$) $^+$ requires 300.1348, found 300.1343.

4.3.9. Ethyl 2-amino-5-methylpyrazolo[1,5-*a*][1,5]naphthyridine-3-carboxylate (11a). Prepared from **10a** and **4** in an analogous manner for preparation of **7a**. Yield: 78% for condition C, 36% for condition D; Yellow solid, mp 186–188 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3473, 3351, 1678, 1643, 1625, 1557, 1422, 1363, 1336, 1298, 1138; ^1H NMR (CDCl_3 , 400 MHz) δ 8.79 (d, $J=8.4$ Hz, 1.2 Hz, 1H), 8.74 (d, $J=4.4$ Hz, 1.6 Hz, 1H), 7.64 (dd, $J=8.4$ Hz, 4.4 Hz, 1H), 7.32 (s, 1H), 4.38 (q, $J=7.2$ Hz, 2H), 2.65 (s, 3H), 1.43 (t, $J=7.2$ Hz, 3H), ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 163.45, 153.73, 146.19, 145.04, 142.34, 132.58, 129.66, 125.23, 123.60, 99.26, 92.21, 58.88, 14.44, 14.39; HR-MS (ESI) calcd for $\text{C}_{14}\text{H}_{15}\text{N}_4\text{O}_2$ ($\text{M}+\text{H}$) $^+$ requires 271.1195, found 271.1197.

4.3.10. Ethyl 2-amino-5-methylpyrazolo[1,5-*a*][1,8]naphthyridine-3-carboxylate (11b). Prepared by condition C from **10b** (or **10c**) and **4** in an analogous manner for preparation of **7a**. Yield: 30% from **10b**, 38% from **10c**; Yellow solid, mp 245–247 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3473, 3351, 1678, 1643, 1625, 1557, 1422, 1363, 1336, 1298, 1138; ^1H NMR (CDCl_3 , 400 MHz) δ 8.88 (d, $J=3.9$ Hz, 1H), 8.16 (d, $J=8.1$ Hz, 1H), 7.50 (dd, $J=8.1$ Hz, 4.5 Hz, 1H), 7.33 (s, 1H), 4.39 (q, $J=7.1$ Hz, 2H), 2.72 (d, $J=3.3$ Hz, 3H), 1.43 (t, $J=7.1$ Hz, 3H), ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 163.55, 153.53, 150.55, 144.95, 144.28, 143.30, 133.07, 120.49, 112.05, 99.46, 91.88, 58.91, 14.61, 14.42; HR-MS (ESI) calcd for $\text{C}_{14}\text{H}_{15}\text{N}_4\text{O}_2$ ($\text{M}+\text{H}$) $^+$ requires 271.1195, found 271.1191.

4.4. General procedure for one-pot reaction of 2-fluorobenzonitrile (6a) with substituted 1H-pyrazoles 12

4.4.1. Ethyl 5-amino-2-phenylpyrazolo[1,5-*a*]quinoline-3-carboxylate (13aa). A mixture of 2-fluorobenzonitrile **6a** (121 mg, 1.00 mmol), **12a** (280 mg, 1.20 mmol) and Cs_2CO_3 (980 mg, 3.00 mmol) in DMSO (5.0 mL) was stirred at 120 °C for 16 h. After monitoring the end of the reaction on TLC, the mixture was cooled to room temperature and diluted with water. The resulting mixture was extracted with ethyl acetate twice. The combined organic layers were washed with water twice, dried over MgSO_4 and the solvent was removed in vacuo to afford a residue. The residue was purified by flash column chromatography (hexane:EtOAc=1:1) on silica gel to afford pyrazolo[1,5-*a*]quinoline **13aa** (137 mg, 41% yield).

Pale yellow solid, mp 212–214 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3365, 1680, 1618, 1556, 1438, 1167, 1066; ^1H NMR (CDCl_3 , 400 MHz) δ 8.69 (d, $J=8.3$ Hz, 1H), 7.81–7.77 (m, 3H), 7.74 (td, $J=7.3$ Hz, 1.1 Hz, 1H), 7.53 (dt, $J=8.2$ Hz, 1.0 Hz, 1H), 7.45–7.42 (m, 3H), 7.36 (s, 1H), 4.50 (br s, 2H), 4.29 (q, $J=7.1$ Hz, 2H), 1.27 (t, $J=7.1$ Hz, 3H), ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 163.09, 154.75, 145.55, 143.09, 133.52, 133.30, 130.49 (2C), 129.70, 128.29, 127.42 (2C), 124.71, 123.71, 116.74, 115.74, 98.14, 91.57, 58.92, 14.14; HR-MS (ESI) calcd for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_2$ ($\text{M}+\text{H}$) $^+$ requires 332.1399, found 332.1406.

4.4.2. Ethyl 5-amino-2-(methylthio)pyrazolo[1,5-*a*]quinoline-3-carboxylate (13ab). Prepared from **6a** (1.00 mmol) and **12b** (1.00 mmol) in an analogous manner for preparation of **13aa**. Yield: 41%; Yellow solid, mp 174–176 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3365, 1672, 1618, 1557, 1450, 1312, 1072; ^1H NMR (CDCl_3 , 400 MHz) δ 8.56 (d, $J=8.4$ Hz, 1H), 7.75–7.70 (m, 2H), 7.48 (t, $J=7.4$ Hz, 1H), 7.18 (s, 1H), 4.48 (br s, 2H), 4.39 (q, $J=7.1$ Hz, 2H), 2.30 (s, 3H), 1.44 (t, $J=7.1$ Hz, 3H), ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 162.81, 153.63, 145.88, 143.01, 133.25, 130.56, 124.21, 123.68, 115.90, 115.44, 97.94, 90.84, 58.99, 14.46, 12.90; HR-MS (ESI) calcd for $\text{C}_{15}\text{H}_{16}\text{N}_3\text{O}_2\text{S}$ ($\text{M}+\text{H}$) $^+$ requires 302.0963, found 302.0953.

4.4.3. Ethyl 5-amino 4-methyl-2-(methylthio)pyrazolo[1,5-*a*]quinoline-3-carboxylate (13ac). Prepared from **6a** (1.00 mmol) and **12c**

(1.0 mmol) in an analogous manner for preparation of **13aa**. Yield: 31%; Yellow solid, mp 152–154 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3388, 1683, 1629, 1525, 1308, 1065; ^1H NMR (CDCl_3 , 400 MHz) δ 8.57 (d, $J=8.4$ Hz, 1H), 7.72 (d, $J=8.4$ Hz, 1H), 7.66 (t, $J=7.6$ Hz, 1H), 7.46 (t, $J=7.6$ Hz, 1H), 4.38 (q, $J=7.2$ Hz, 2H), 2.68 (s, 3H), 2.56 (s, 3H), 1.45 (t, $J=7.2$ Hz, 3H), ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 162.98, 153.90, 142.39, 142.23, 132.16, 129.51, 124.32, 123.12, 115.74, 115.57, 100.47, 98.72, 59.55, 14.33, 14.21, 13.45; HR-MS (ESI) calcd for $\text{C}_{16}\text{H}_{18}\text{N}_3\text{O}_2\text{S}$ ($\text{M}+\text{H}$) $^+$ requires 316.1120, found 316.1125.

4.4.4. Ethyl 5-amino-2-ethylpyrazolo[1,5-*a*]quinoline-3-carboxylate (13ad). Prepared from **6a** (1.00 mmol) and **12d** (2.00 mmol) in an analogous manner for preparation of **13aa**. Yield: 23%; White solid, mp 178–180 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3336, 3203, 1655, 1607, 1558, 1121; ^1H NMR (CDCl_3 , 400 MHz) δ 8.62 (d, $J=8.4$ Hz, 1H), 7.77–7.70 (m, 2H), 7.50 (t, $J=8.0$ Hz, 1H), 7.26 (s, 1H), 4.41–4.45 (m, 2H), 3.11 (q, $J=7.6$ Hz, 2H), 1.45–1.36 (m, 6H), ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 163.45, 158.11, 145.32, 142.55, 133.54, 130.32, 124.20, 123.64, 116.42, 115.60, 97.94, 91.59, 58.74, 21.55, 14.41, 13.26; HR-MS (ESI) calcd for $\text{C}_{16}\text{H}_{18}\text{N}_3\text{O}_2$ ($\text{M}+\text{H}$) $^+$ requires 284.1399, found 284.1389.

4.4.5. 3-Bromo-2-methylpyrazolo[1,5-*a*]quinolin-5-amine (13ae). Prepared from **6a** (1.00 mmol) and **12e** (1.00 mmol) in an analogous manner for preparation of **13aa**. Yield: 46%; Yellow solid, mp 168–170 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3303, 3189, 1640, 1619, 1561, 1480, 1244, 1062; ^1H NMR (CDCl_3 , 400 MHz) δ 8.50 (d, $J=8.4$ Hz, 1H), 7.72 (d, $J=8.2$ Hz, 1H), 7.67 (t, $J=8.2$ Hz, 1H), 7.44 (td, $J=8.1$ Hz, 0.9 Hz, 1H), 6.49 (s, 1H), 4.26 (br s, 2H), 2.46 (s, 3H), ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 148.19, 142.79, 138.13, 134.01, 129.93, 123.86, 123.80, 116.86, 114.52, 88.64, 80.94, 12.32; HR-MS (ESI) calcd for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{Br}$ ($\text{M}+\text{H}$) $^+$ requires 276.0136, found 276.0134.

4.4.6. 2-(Trifluoromethyl)pyrazolo[1,5-*a*]quinolin-5-amine (13af). Prepared from **6a** (1.00 mmol) and **12f** (1.00 mmol) in an analogous manner for preparation of **13aa**. Yield: 49%; Yellow solid, mp 159–161 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3333, 3220, 1642, 1443, 1252, 1160, 1114, 970; ^1H NMR (CDCl_3 , 400 MHz) δ 8.64 (d, $J=8.0$ Hz, 1H), 7.77–7.70 (m, 2H), 7.54 (t, $J=7.6$ Hz, 1H), 6.61 (s, 1H), 6.52 (s, 1H), 4.26 (br s, 2H), ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 142.81, 142.24 (q, $^2J_{\text{CF}}=36.5$ Hz), 141.05, 133.68, 130.03, 125.20, 123.87, 121.92 (q, $^1J_{\text{CF}}=267.2$ Hz), 117.81, 115.56, 93.18, 90.74; HR-MS (ESI) calcd for $\text{C}_{12}\text{H}_9\text{N}_3\text{F}_3$ ($\text{M}+\text{H}$) $^+$ requires 252.0749, found 252.0742.

4.4.7. 4-Methyl-2-(trifluoromethyl)pyrazolo[1,5-*a*]quinolin-5-amine (13ag). Prepared from **6a** (1.00 mmol) and **12g** (1.00 mmol) in an analogous manner for preparation of **13aa**. Yield: 28%; Brown solid, mp 113–115 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3397, 1634, 1506, 1455, 1248, 1125, 970; ^1H NMR (CDCl_3 , 400 MHz) δ 8.63 (dd, $J=8.4$ Hz, 0.4 Hz, 1H), 7.77 (d, $J=8.0$ Hz, 1H), 7.68 (td, $J=8.4$ Hz, 1.2 Hz, 1H), 7.53 (td, $J=8.4$ Hz, 1.2 Hz, 1H), 6.60 (s, 1H), 4.43 (br s, 2H), ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 142.46, 142.28 (q, $^2J_{\text{CF}}=36.6$ Hz), 138.33, 132.51, 128.93, 125.24, 123.51, 121.95 (q, $^1J_{\text{CF}}=267.2$ Hz), 117.95, 115.37, 98.27, 93.04 (q, $^3J_{\text{CF}}=1.8$ Hz), 12.53; HR-MS (ESI) calcd for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{F}_3$ ($\text{M}+\text{H}$) $^+$ requires 266.0905, found 266.0898.

4.5. Diverse-oriented synthesis of 2-substituted pyrazolo[1,5-*a*]quinolines

4.5.1. Ethyl 2-(methylsulfonyl)pyrazolo[1,5-*a*]quinoline-3-carboxylate (15). To a stirred solution of **14^{6a}** (1.50 g, 5.24 mmol) in a mixture of THF (100 mL), MeOH (100 mL) and H_2O (100 mL), was added Oxone[®] (14 g, 22.0 mmol) in one portion. After being stirred at an ambient temperature for 16 h, the mixture was diluted with water. The resulting mixture was extracted with ethyl acetate twice. The combined organic layers were washed with water twice,

dried over MgSO_4 and the solvent was removed in vacuo to afford to afford analytically pure **15** (1.60 g, 94% yield).

White solid, mp 173–175 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 1707, 1615, 1321, 1245, 1148, 1109; ^1H NMR (DMSO- d_6 , 400 MHz) δ 8.58 (d, $J=8.5$ Hz, 1H), 8.17–8.15 (m, 2H), 8.09 (d, $J=9.6$ Hz, 1H), 7.76 (td, $J=8.1$ Hz, 1.2 Hz, 1H), 4.42 (q, $J=7.3$ Hz, 2H), 3.59 (s, 3H), 1.41 (t, $J=7.4$ Hz, 3H), ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 160.66, 152.72, 140.28, 132.87, 131.19, 130.51, 129.19, 127.18, 123.73, 116.19, 115.45, 103.58, 60.90, 42.62, 13.95; HR-MS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_4\text{NaS}$ ($\text{M}+\text{Na}$) $^+$ requires 341.0572, found 341.0567.

4.5.2. Ethyl 2-ethoxypyrazolo[1,5-*a*]quinoline-3-carboxylate (16). A solution of **15** (2.78 g, 8.74 mmol) and sodium ethoxide (9.00 g of a 20 wt % solution in ethanol, 26.3 mmol) in THF (75 mL) was stirred at reflux for 20 min. The mixture was diluted with water. The resulting mixture was extracted with ethyl acetate twice. The combined organic layers were washed with water twice, dried over MgSO_4 and the solvent was removed in vacuo to afford a residue. The residue was purified by flash column chromatography (hexane:EtOAc=3:1) on silica gel to afford **16** (1.58 g, 64% yield).

Pale yellow solid, mp 83–85 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 2979, 1709, 1618, 1563, 1550, 1510, 1442, 1290, 1106, 814; ^1H NMR (CDCl_3 , 400 MHz) δ 8.44 (d, $J=8.5$ Hz, 1H), 7.98 (d, $J=9.3$ Hz, 1H), 7.78 (d, $J=8.1$ Hz, 1H), 7.72–7.64 (m, 2H), 7.45 (td, $J=8.1$ Hz, 1.2 Hz, 1H), 4.59 (q, $J=7.3$ Hz, 2H), 4.39 (q, $J=6.9$ Hz, 2H), 1.55 (t, $J=6.9$ Hz, 3H), 1.43 (t, $J=7.3$ Hz, 3H), ^{13}C NMR (CDCl_3 , 100 MHz) δ 164.30, 163.32, 140.48, 133.94, 129.99, 128.39, 128.11, 124.51, 122.99, 116.51, 115.57, 91.34, 65.48, 59.75, 14.69, 14.49; HR-MS (ESI) calcd for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$ requires 285.1239, found 285.1247.

4.5.3. Ethyl 2-hydroxypyrazolo[1,5-*a*]quinoline-3-carboxylate (17). To a stirred solution of **16** (400 mg, 1.41 mmol) in CH_2Cl_2 (20 mL) was dropwise added boron tribromide (7.0 mL of a 1.0 M solution in CH_2Cl_2 , 7.00 mmol) under ice-cooling. The ice bath was removed and the mixture was stirred at ambient temperature for 16 h. After monitoring the end of the reaction on TLC, the reaction was quenched with saturated aqueous NaHCO_3 , and diluted with water. The resulting mixture was extracted with CHCl_3 twice. The combined organic layers were washed with water twice, dried over MgSO_4 and the solvent was removed in vacuo to afford a residue. The residue was purified by flash column chromatography (hexane:EtOAc=1:1) on silica gel to afford **17** (305 mg, 85% yield).

Pale pink solid, mp 157–159 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3338, 1665, 1418, 1137, 815; ^1H NMR (CDCl_3 , 400 MHz) δ 8.90 (br s, 1H), 8.50 (d, $J=8.5$ Hz, 1H), 7.80 (dd, $J=8.1$ Hz, 1.2 Hz, 1H), 7.76–7.00 (m, 3H), 7.48 (td, $J=8.1$ Hz, 1.2 Hz, 1H), 4.47 (q, $J=7.3$ Hz, 2H), 1.47 (t, $J=7.3$ Hz, 3H), ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.15, 165.61, 137.97, 133.91, 130.42, 128.81, 128.44, 124.92, 123.19, 115.97, 115.38, 89.29, 60.63, 14.44; HR-MS (ESI) calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ requires 279.0746, found 279.0741.

4.5.4. Ethyl 2-[(trifluoromethyl)sulfonyl]oxy]pyrazolo[1,5-*a*]quinoline-3-carboxylate (18). Compound **17** (550 mg, 2.15 mmol), trifluoromethanesulfonic anhydride (2.42 g, 8.58 mmol) and triethylamine (1.5 mL, 10.8 mmol) were dissolved in CH_2Cl_2 (20 mL), and the mixture was stirred at ambient temperature for 16 h. After monitoring the end of the reaction on TLC, the mixture was diluted with water. The resulting mixture was extracted with ethyl acetate twice. The combined organic layers were washed with water twice, dried over MgSO_4 and the solvent was removed in vacuo to afford a residue. The residue was purified by flash column chromatography (hexane:EtOAc=6:1) on silica gel to afford **18** (693 mg, 83% yield).

White solid, mp 129–131 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 1704, 1426, 1240, 1221, 1204, 1138; ^1H NMR (CDCl_3 , 400 MHz) δ 8.51 (d, $J=8.5$ Hz, 1H), 8.10 (d, $J=9.2$ Hz, 1H), 7.87 (d, $J=7.7$ Hz, 1H), 7.83–7.76

(m, 2H), 7.59 (td, $J=8.1$ Hz, 1.2 Hz, 1H), 4.46 (q, $J=7.3$ Hz, 2H), 1.45 (t, $J=7.4$ Hz, 3H), ^{13}C NMR (CDCl_3 , 100 MHz) δ 161.24, 153.37, 140.57, 133.64, 130.79, 129.68, 128.75, 126.42, 123.76, 118.74 (q, $J_{\text{CF}}=319.2$ Hz), 116.28, 116.01, 96.78, 60.94, 14.23; HR-MS (ESI) calcd for $\text{C}_{15}\text{H}_{11}\text{N}_2\text{O}_5\text{F}_3\text{NaS}$ ($\text{M}+\text{Na}$) $^+$ requires 341.0572, found 341.0567.

4.5.5. (E)-Ethyl 2-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)pyrazolo[1,5-a]quinoline-3-carboxylate (19). The triflate **18** (100 mg, 0.26 mmol), triethylamine (0.4 mL, 2.60 mmol), *tert*-butyl acrylate (0.4 mL, 2.60 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (30 mg, 0.03 mmol) were sequentially added to a sealed tube. The resulting mixture was stirred at 120 °C for 16 h and diluted with water. The resulting mixture was extracted with ethyl acetate twice. The combined organic layers were washed with water twice, dried over MgSO_4 and the solvent was removed in vacuo to afford a residue. The residue was purified by flash column chromatography (hexane:EtOAc=4:1) on silica gel to afford **19** (24.5 mg, 26% yield).

White solid, mp 96–98 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 1703, 1616, 1559, 1151, 1112, 1075; ^1H NMR (CDCl_3 , 400 MHz) δ 8.67 (d, $J=8.5$ Hz, 1H), 8.30 (d, $J=16.2$ Hz, 1H), 8.12 (d, $J=9.2$ Hz, 1H), 7.83 (d, $J=8.1$ Hz, 1H), 7.75 (td, $J=8.5$ Hz, 1.2 Hz, 1H), 7.68 (d, $J=9.6$ Hz, 1H), 7.55 (td, $J=8.1$ Hz, 1.2 Hz, 1H), 7.03 (d, $J=15.8$ Hz, 1H), 4.45 (q, $J=7.3$ Hz, 2H), 1.56 (s, 9H), 1.48 (t, $J=7.3$ Hz, 3H), ^{13}C NMR (CDCl_3 , 100 MHz) δ 165.94, 163.51, 149.46, 140.70, 133.91, 133.49, 130.16, 128.44, 128.05, 126.00, 125.16, 123.99, 117.04, 116.31, 105.06, 80.55, 60.40, 28.20 (3C), 14.44; HR-MS (ESI) calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$ requires 285.1239, found 285.1247.

4.5.6. Ethyl 2-phenylpyrazolo[1,5-a]quinoline-3-carboxylate (20). To a solution of the triflate **18** (100 mg, 0.26 mmol) in 1,4-dioxane (5 mL) were added anhydrous K_3PO_4 (170 mg, 0.78 mmol), phenylboronic acid (95 mg, 0.78 mmol), $\text{Pd}(\text{PPh}_3)_4$ (40 mg, 0.03 mmol) and KBr (35 mg, 0.29 mmol) under an argon atmosphere. The mixture was stirred at reflux for 16 h and diluted with water. The resulting mixture was extracted with ethyl acetate twice. The combined organic layers were washed with water twice, dried over MgSO_4 and the solvent was removed in vacuo to afford a residue. The residue was purified by flash column chromatography (hexane:EtOAc=6:1) on silica gel to afford **20** (38.0 mg, 46% yield).

White solid, mp 121–123 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 1704, 1615, 1456, 1179, 1097, 1066, 815; ^1H NMR (CDCl_3 , 400 MHz) δ 8.70 (d, $J=8.5$ Hz, 1H), 8.16 (d, $J=9.2$ Hz, 1H), 7.86–7.82 (m, 3H), 7.75–7.70 (m, 2H), 7.53 (td, $J=8.1$ Hz, 0.8 Hz, 1H), 7.49–7.44 (m, 3H), 4.34 (q, $J=7.3$ Hz, 2H), 1.32 (t, $J=7.3$ Hz, 3H), ^{13}C NMR (CDCl_3 , 100 MHz) δ 163.74, 155.67, 140.77, 134.11, 132.95, 130.07 (2C), 130.05, 128.71, 128.36, 128.04, 127.73 (2C), 125.56, 123.66, 117.33, 116.20, 103.58, 60.04, 14.22; HR-MS (ESI) calcd for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ requires 317.1290, found 317.1290.

4.5.7. Ethyl 2-(4-ethoxy-4-oxobutyl)pyrazolo[1,5-a]quinoline-3-carboxylate (21). Under an inert and anhydrous condition, $\text{Pd}(\text{OAc})_2$ (7.00 mg, 0.03 mmol) and Xphos (29.0 mg, 0.06 mmol) were dissolved in THF (0.5 mL), and the mixture was stirred at ambient temperature for 15 min. To this mixture were sequentially added a solution of the triflate **18** (100 mg, 0.26 mmol) in THF (0.4 mL) and (4-ethoxy-4-oxobutyl)zinc(II) bromide (0.5 M in THF, 1.6 mL, 0.78 mmol). After being stirred at 50 °C for 16 h, the mixture was cooled to an ambient temperature. The resulting mixture was filtered through Celite®. The Celite® was washed with EtOAc and combined washings and filtrate were dried over MgSO_4 and the solvent was removed in vacuo to afford a residue. The residue was purified by flash column chromatography (hexane:EtOAc=6:1) on silica gel to afford pyrazolo[1,5-a]quinoline **21** (63.0 mg, 68% yield).

Pale yellow solid, mp 43–44 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 2978, 1731, 1698, 1616, 1560, 1440, 1267, 1167, 1106, 815; ^1H NMR (CDCl_3 ,

400 MHz) δ 8.60 (d, $J=8.5$ Hz, 1H), 8.06 (d, $J=9.2$ Hz, 1H), 7.81 (d, $J=8.1$ Hz, 1H), 7.71 (td, $J=8.5$ Hz, 1.6 Hz, 1H), 7.65 (d, $J=9.6$ Hz, 1H), 7.49 (td, $J=8.1$ Hz, 0.8 Hz, 1H), 4.40 (q, $J=7.3$ Hz, 2H), 4.12 (q, $J=7.3$ Hz, 2H), 3.2 (t, $J=7.3$ Hz, 2H), 2.46 (t, $J=7.3$ Hz, 2H), 2.18 (quin, $J=7.4$ Hz, 2H), 1.45 (t, $J=7.3$ Hz, 3H), 1.24 (t, $J=7.3$ Hz, 3H), ^{13}C NMR (CDCl_3 , 100 MHz) δ 173.55, 164.07, 157.04, 140.30, 134.06, 129.98, 128.34, 127.84, 125.23, 123.44, 117.04, 116.02, 103.57, 60.19, 59.89, 34.03, 27.75, 24.23, 14.48, 14.23; HR-MS (ESI) calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$ requires 355.1658, found 355.1659.

4.5.8. Ethyl 2-molpholinopyrazolo[1,5-a]quinoline-3-carboxylate (22). The triflate **18** (82.0 mg, 0.12 mmol) was dissolved in morpholine (1.0 mL) and the mixture was stirred at 100 °C for 1 h. After cooling to ambient temperature, the reaction mixture was directly purified by flash column chromatography (hexane:EtOAc=4:1) on silica gel to afford **22** (40.0 mg, 58% yield).

Pale yellow solid, mp 102–104 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 2960, 2854, 1695, 1615, 1561, 1497, 1115, 1068, 935, 813; ^1H NMR (CDCl_3 , 400 MHz) δ 8.50 (d, $J=8.1$ Hz, 1H), 8.02 (d, $J=9.2$ Hz, 1H), 7.79 (d, $J=7.7$ Hz, 1H), 7.69 (td, $J=8.5$ Hz, 1.2 Hz, 1H), 7.65 (d, $J=9.6$ Hz, 1H), 7.46 (td, $J=8.1$ Hz, 0.8 Hz, 1H), 4.40 (q, $J=7.3$ Hz, 2H), 3.94 (t, $J=4.6$ Hz, 4H), 3.54 (t, $J=4.6$ Hz, 4H), 1.45 (t, $J=7.3$ Hz, 3H), ^{13}C NMR (CDCl_3 , 100 MHz) δ 163.46, 161.17, 141.20, 133.87, 130.03, 128.31, 128.02, 124.78, 123.14, 116.94, 115.87, 94.87, 66.81 (2C), 59.97, 50.58 (2C), 14.53; HR-MS (ESI) calcd for $\text{C}_{18}\text{H}_{20}\text{N}_3\text{O}_3$ ($\text{M}+\text{H}$) $^+$ requires 326.1505, found 326.1497.

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Supplementary data

These data include X-ray data for compound **7d** and $^1\text{H}/^{13}\text{C}$ NMR spectra of all new compounds described in this article. Supplementary data associated with this article can be found in the online version, at <http://dx.doi.org/10.1016/j.tet.2014.02.081>. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

- a) O'Connell, K. M. G.; Galloway, W. R. J. D.; Spring, D. R. In *Diversity-oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology*; Trabocchi, A., Ed.; Wiley & Sons: New Jersey, NJ, 2013; pp 1–26; b) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347; c) Costantino, L.; Barlocco, D. *Curr. Med. Chem.* **2006**, *13*, 65; d) DeSimone, R. W.; Currie, K. S.; Darow, J. W.; Pippin, D. A. *Comb. Chem. High Throughput Screening* **2004**, *7*, 473; e) Muller, G. *Drug Discovery Today* **2003**, *8*, 681.
- (a) LaPorte, M. G.; Goodell, J. R.; Tsegay, S.; Wip, P. In *Diversity-oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology*; Trabocchi, A., Ed.; Wiley & Sons: New Jersey, NJ, 2013; pp 135–176; (b) Horton, D. A.; Bourene, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
- Barrett, D. *Heterocycles* **1997**, *45*, 1839.
- Lober, S.; Hubner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 97.
- Shen, H. C.; Ding, F.-X.; Deng, Q.; Wilsie, L. C.; Krsmanovic, M. L.; Taggart, A. K.; Carballo-Jane, E.; Ren, N.; Cai, T.-Q.; Wu, T.-J.; Wu, K. K.; Cheng, K.; Chen, Q.; Wolff, M. S.; Tong, X.; Holt, T. G.; Waters, M. G.; Hammond, M. L.; Tata, J. R.; Colletti, S. L. *J. Med. Chem.* **2009**, *52*, 2587.
- (a) Kato, J.; Aoyama, H.; Yokomatsu, T. *Org. Biomol. Chem.* **2013**, *11*, 1171; (b) Kato, J.; Ito, Y.; Ijuin, R.; Aoyama, H.; Yokomatsu, T. *Org. Lett.* **2013**, *15*, 3794.
- For a review of domino reactions based on Knoevenagel condensation in the synthesis of heterocyclic compounds: Voskressensky, L. G.; Festa, A. A.; Varlamov, A. V. *Tetrahedron* **2014**, *70*, 551.
- Although decomposition products could not be identified clearly, it may be conceivable that self-aldol condensation of electron-deficient fluoroarylketones **3c** and **3d** occurs prior to the $\text{S}_{\text{N}}\text{Ar}$ reaction.

9. (a) Lawrence, S. A. *Amine: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, UK, 2004; (b) *Amino Group Chemistry: From Synthesis to the Life Sciences*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2008.
10. Rochais, C.; Yougnia, R.; Cailly, T.; Santos, J. S. O.; Rault, S.; Dallemagne, P. *Tetrahedron* **2011**, *67*, 5806.
11. From the reaction with **12b**, the S_NAr adduct derived from **6a** and **13ab** was isolated in an 14% yield. This side reaction also reduced the yield of **13ab**.
12. A reaction between 2-fluorobenzonitrile (**6a**) and 1*H*-pyrazole **12** ($X=H$, $R_1=R_2=CH_3$) without having an electron-withdrawing groups at the pyrazole ring was examined under the conditions using Cs_2CO_3 in DMSO at 120 °C. Although this reaction gave the corresponding S_NAr product in 38% yield, no desired cascade products were detected. These results suggest to us that electron-withdrawing substituents at the pyrazole ring are necessary to induce the Dieckmann–Thorpe cyclization in our cascade sequence. The similar results are observed in our S_NAr /Knoevenagel cyclization cascade reaction from 2-fluorobenzaldehyde (**6a**) and 1*H*-pyrazoles **12** ($X=H$ or CH_3 , $R_1=R_2=CH_3$) without having an electron-withdrawing group.^{6a}
13. Prolonged heating over 20 min resulted in significant loss of the product **16** due to hydrolysis of the carboethoxy functionality.
14. Arbaciauskiene, E.; Vilkauskaitė, G.; Eller, G. E.; Holzer, W.; Sackus, A. *Tetrahedron* **2009**, *65*, 7817.
15. Zang, T.; Gao, X.; Wood, H. B. *Tetrahedron Lett.* **2011**, *52*, 311.
16. Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 4720.
17. Taylor, E. C.; Purdum, W. R. *Heterocycles* **1977**, *6*, 1865.
18. Betard, A.; Wannapaiboon, S.; Fischer, R. A. *Chem. Commun.* **2012**, 10495.