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A novel one-pot synthesis of 2-arylpyrazoloquinolinone derivatives

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ABSTRACT

Two regioisomers of 2-arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-ones and 2-arylpyrazolo[4,3-*c*]quinolin-4(5*H*)-ones were synthesized by utilizing 3-arylsydnones, ethyl 3-bromopropynoate, and 2-aminophenylboronic acid pinacol ester in presence of catalytic agent $Pd(PPh_3)_4$. This efficient one-pot synthesis methodology involved 1,3-dipolar cycloaddition, Suzuki coupling reaction, and intramolecular cyclization three sequence steps.

1. Introduction

An endogenous adenosine modulates a wide range of physiological processes in the nervous, cardiovascular, renal, and immune systems, interacts with at least four cell surface receptor subtypes classified as A_1, A_{2A}, A_{2B}, and A_3.[1–4] In 2000 and 2007, Colotta et al.,[3] reported that 2-arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-one compounds **1** can be potent and selective binding activity at bovine A_1, A_{2A} AR, and human cloned A_3 as adenosine receptor antagonists (see Fig. 1).[5,6] Moreover, another structural isomers 2-arylpyrazolo[4,3-*c*]quinolin-4(5*H*)-ones **2** were also synthesized to evaluate as potent and selective A_3 adenosine receptor antagonists by Baraldi et al. (see Fig. 1).[7] As a result, the pyrazoloquinolinone structure have been extensively investigated the biological functions in the central nervous and periphery system.

A few of methods were provided to prepare 2-arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-one and 2-arylpyrazolo[4,3-*c*]quinolin-4(5*H*)-one two core compounds. Currently, Catarzi et al.[8] reported an improved microwave irradiation synthesis of 2-arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-one from 3-thoxalylindole. However, this methodology is usually performed on a small scale and the special analogues owing to 3-ethoxalylindole is an expensive restricted starting material and requires tedious procedures for manufacture. For preparation of 2-arylpyrazolo[4,3-*c*]quinolin-4(5*H*)-ones, the standard procedure was the multiple synthetic pathways involving imination of the corresponding phenylhydrazines,[9] Vilsmeier reaction, oxidation, esterification, and the sequential hydrogenation of nitro group and intramolecular cyclization.[7] Herein, we have successfully developed the efficient one-pot synthesis methodology involved 1,3-dipolar cycloaddition, Suzuki coupling reaction, and intramolecular cyclization three steps to prepare 2-arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-ones **1** and 2-arylpyrazolo[4,3-*c*]quinolin-4(5*H*)-ones **2** two classes products. After the further chromatography purification, the

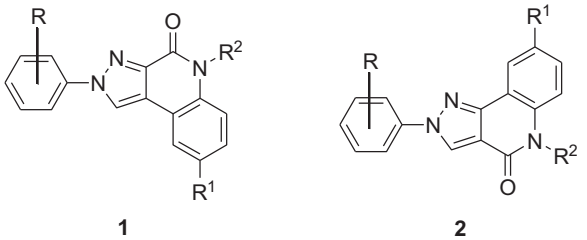

Fig. 1. 2-Arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-one compounds **1** and 2-arylpyrazolo[4,3-*c*]quinolin-4(5*H*)-ones **2**.

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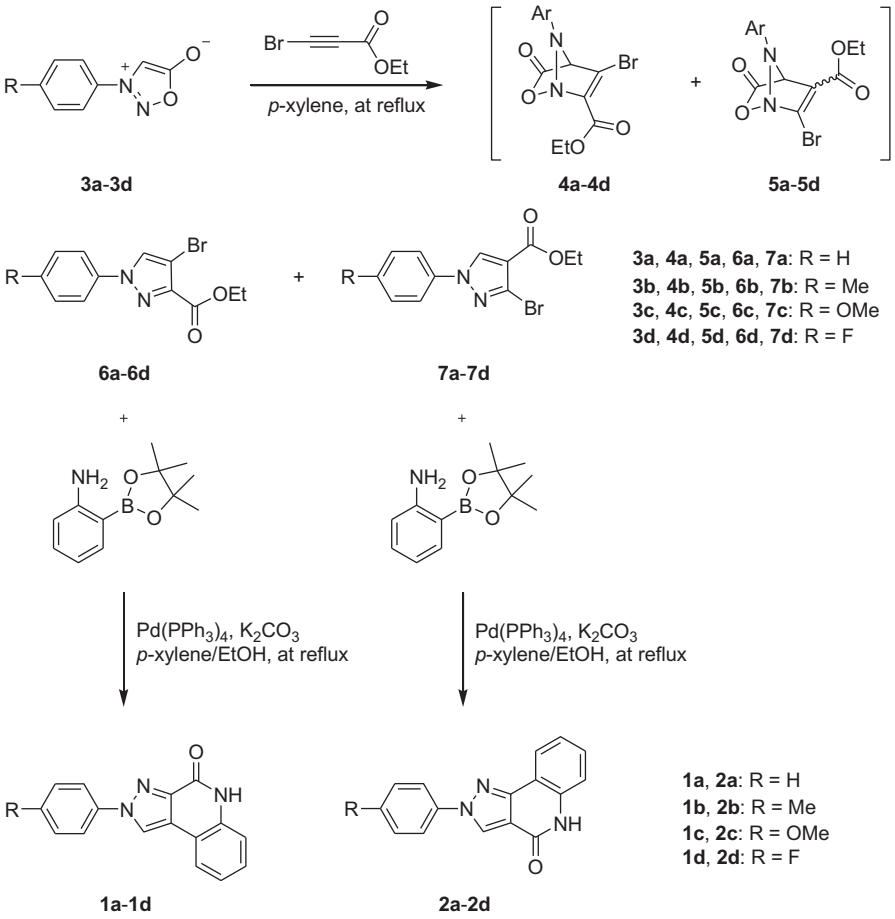
corresponding two 2-arylpyrazoloquinolinone isomers products **1** and **2** were separated and obtained in 27–32% and 39–43% isolated yields, respectively (total yields 68–75%).

2. Results and discussion

To evaluate the one-pot multicomponent processes for preparation of 2-arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-ones **1** and 2-arylpyrazolo[4,3-*c*]quinolin-4(5*H*)-ones **2**, the step-by-step synthesis methodology were preliminarily carried out to research the modeling synthetic study (see Scheme 1). Sydnones **3** bearing with various *para*-substituted aryl group substituents, including Me, OMe, and F, were prepared as the starting materials by the published procedure.[10] They underwent smooth cycloaddition with ethyl 3-bromopropynoate to give two isomer pyrazoles **6** and **7**.[11] The reaction involves a 1,3-diploar cycloaddition of the sydnones, behaving like a *N*-bridged cyclic azomethine imine intermediates (**4** and **5**, see Scheme 1).[12] The initially formed cycloadducts readily extrude carbon dioxide to produce a mixture of five-membered regioisomeric pyrazoles (**6** and **7**, see Scheme 1). After the further chromatography purification, the corresponding two isomers products **6a**–**d** and **7a**–**d** were obtained in 43–49% and 33–41% isolated yields, respectively (see Table 1). Moreover, the ratios of regioisomers (**6**/**7**) were detected from 59/41 to 53/47 (see Table 1, the ratios were identified by ^{1}H NMR spectrometer technique). The structure assignment of the regioisomers (**6**/**7**) was made on the basis of their characteristic ^{1}H NMR spectrum. Particular attention was given to the chemical shift of the special proton at 5-position in pyrazolic ring. The identical ring proton in the 3-carboethoxy-substituted isomers (**6a**–**d**) appeared 0.35–0.37 ppm upfield relative to the 4-carboethoxy-substituted isomers (**7a**–**d**).[12]

The individual isolated regioisomeric pyrazole **6** or **7** was performed the 3- or 4-arylation with 2-aminophenylboronic acid pinacol ester[13] under the optimal Suzuki cross-coupling reaction condition.[14] The efficient cross-coupling could be accomplished by using 10 mol % amount of $Pd(PPh_3)_4$ as palladium source, K_2CO_3 (5 equiv) as base, and *p*-xylene/ethanol solvent under reflux, which afforded the corresponding desired products 2-arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-ones **1a**–**d** in 73–82% or 2-arylpyrazolo[4,3-*c*]quinolin-4-(5*H*)-ones **2a**–**d** in 78–82% isolated yields (see Table 1).

To evaluate the one-pot multicomponent processes for preparation of 2-arylpyrazoloquinolinone derivatives **1a**–**d** and **2a**–**d**, compound 3-phenyl sydnone **3a** was used as modeling case to choose the optimal three sequence steps condition (see Scheme 2). Initial studies involved using $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$ as Pd(0) catalyst source in the presence of K_2CO_3 as base in toluene/EtOH solvent under reflux, which gave compound **1a** and **2a** (from **3a**) in low total yield (<56%). However, the efficient standard condition could be accomplished by switching to $Pd(PPh_3)_4$ (10 mol %), K_2CO_3 (5 equiv) as base, and *p*-xylene/EtOH/H_2O co-solvent under reflux, which afforded the corresponding 2-arylpyrazoloquinolinones **1a** and **2a** in modest total yield (>70%, see Table 2). Furthermore, we employed the same reaction condition to 3-aryl sydnone substrates **3b**–**e** bearing with *meta*-chloro and various *para*-substituted aryl group substituents, including Me, OMe, and F, the one-pot synthesis methodology was also smoothly performed to give the corresponding 2-arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-ones **1b**–**e** and 2-arylpyrazolo[4,3-*c*]quinolin-4(5*H*)-ones **2b**–**e** products in 27–32% and 39–43% yields, respectively (see Scheme 2 and Table 2).



Scheme 1. The step-by-step synthesis of 2-arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-ones **1a**–**d** and 2-arylpyrazolo[4,3-*c*]quinolin-4-(5*H*)-ones **2a**–**d**.

Table 1
The result of step-by-step synthesis of 2-arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-ones **1a**–**d** and 2-arylpyrazolo[4,3-*c*]quinolin-4-(5*H*)-ones **2a**–**d**

Sydnones	R	Pyrazoles			Final products **1** and **2**			
		No.	Yields (**6**/**7**, %/%)[a]	The ratios of regioisomers **6**/**7**[b]	No.	Yields[c] (%)	No.	Yields[d] (%)
3a	H	**6a**/**7a**	48/41	54/46	**1a**	82	**2a**	80
3b	Me	**6a**/**7a**	49/41	56/44	**1b**	78	**2b**	82
3c	OMe	**6a**/**7a**	49/33	59/41	**1c**	73	**2c**	79
3d	F	**6a**/**7a**	43/38	53/47	**1d**	80	**2d**	78

[a] The yields of regioisomers **6**/**7** were detected by the individual isolated yields from the chromatography separation method.
[b] The ratios of regioisomers **6**/**7** were detected by ^{1}H NMR spectrometer technique.
[c] The yields of products **1a**–**d** were based on the weight of individual isolated compounds **6a**–**d**.
[d] The yields of products **2a**–**d** were based on the weight of individual isolated compounds **7a**–**d**.

Although this newly developed method can provide the convenient and effective one-pot synthesis to give tricyclic pyrazoloquinolinone products, the low regioselectivity was observed in multicomponent reaction.

Furthermore, we tried to perform the sequential three-component study. 3-Aryl sydnone **3** was simultaneously treated with ethyl 3-bromopropynoate and 2-aminophenylboronic acid pinacol ester in presence of catalytic agent $Pd(PPh_3)_4$ and *p*-xylene/EtOH/H_2O co-solvent under reflux. The reaction was continuously stirred and monitored for more than 72 h. However, the starting material sydnone was not totally consumed. When the reaction was terminated and worked-up, only the low yield of the desired pyrazoloquinolinone product was obtained (<15% yield).

In conclusion, we have successfully developed the one-pot method to prepare two arylpyrazoloquinolinone regioisomers by treating 3-aryl sydnones, ethyl 3-bromopropynoate, and 2-aminophenylboronic acid pinacol ester in presence of catalytic agent $Pd(PPh_3)_4$. Through the convenient column chromatography purification, the corresponding two arylpyrazolo[3,4-*c*]quinolinone **1** and arylpyrazolo[4,3-*c*]quinolinone **2** products were obtained in 27–32% and 39–43% isolated yields, respectively.

3. Experimental section

3.1. General procedure

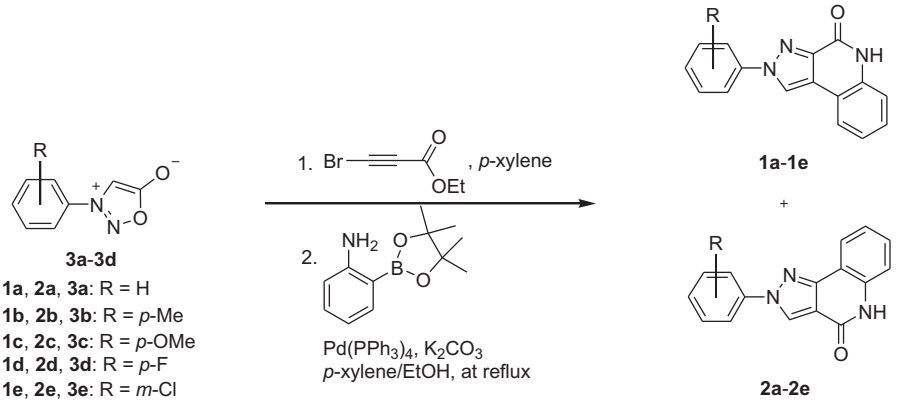
All chemicals were reagent grade and used as purchased. All reactions were carried out under nitrogen atmosphere and monitored by TLC analysis. Flash column chromatography was carried out on silica gel (230–400 mesh). Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wavenumbers reported are referenced to the polystyrene 1601 cm^{-1} absorption. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker (300 MHz) spectrometer by use of $CDCl_3$ and DMSO-d_6 as solvent. Carbon-13 NMR spectra were obtained on a Bruker (75 MHz) spectrometer by used of $CDCl_3$ as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (hertz). Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer. ESI-MS spectra were obtained from an Applied Biosystems API 300 mass spectrometer. High-resolution mass spectra were obtained by means of a JEOL JMS-HX110 mass spectrometer.

3.2. Standard procedure for synthesis of pyrazoles (6 and 7)

A solution of 3-aryl sydnone (**3**, 0.20 g, 1.0 equiv) in 4 mL *p*-xylene was added ethyl 3-bromopropynoate (0.23 g, 1.05 equiv) and heated to reflux for 5 h. When the reaction was completed, the reaction mixture was concentrated under reduced pressure to remove *p*-xylene. The residue solution was purified by column chromatography on silica gel to give the corresponding pyrazoles (**6** and **7**) in 43–49% and 33–41% isolated yields, respectively.

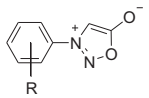
*3.2.1. Ethyl 4-bromo-1-phenyl-1H-pyrazole-3-carboxylate (**6a**).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (t, *J*=7.5 Hz, 3H, ArH), 4.46 (q, *J*=7.0 Hz, 2H, CH), 7.38 (t, *J*=3.1 Hz, 1H, ArH), 7.47 (t, *J*=7.5 Hz, 2H, ArH), 7.68–7.70 (d, *J*=5.9 Hz, 2H, ArH), 7.99 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 61.4, 98.2, 119.9, 128.1, 129.6, 129.8, 139.0, 141.8, 161.0; Anal. Calcd for $C_{12}H_{11}BrN_2O_2$; C: 48.84; H: 3.76; N: 9.49; found: C: 48.87; H: 3.73; N: 9.45.

*3.2.2. Ethyl 3-bromo-1-phenyl-1H-pyrazole-4-carboxylate (**7a**).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38 (t, *J*=7.5 Hz, 3H, CH), 4.35 (q, *J*=8.1 Hz, 2H, CH), 7.37 (t, *J*=3.1 Hz, 1H, ArH), 7.47 (t, *J*=7.5 Hz, 2H, ArH), 7.66–7.68 (d, *J*=5.9 Hz, 2H, ArH), 8.35 (s, 1H, CH); ^{13}C NMR



Scheme 2.

Table 2
The result of one-pot synthesis of 2-arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-ones **1a**–**e** and 2-arylpyrazolo[4,3-*c*]quinolin-4(5*H*)-ones **2a**–**e**



		The ratios of regioisomers (**1** and **2**)[a]		The isolated yields (%) of **1** and **2**	
				Yields of **1**/**2**[b]	Total yields (%)
3a	R=*p*-H	**1a**/**2a**	45/55	32/40	72
3b	R=*p*-Me	**1b**/**2b**	42/58	32/43	75
3c	R=*p*-OMe	**1c**/**2c**	43/57	29/39	68
3d	R=*p*-F	**1d**/**2d**	38/62	27/43	70
3e	R=*m*-Cl	**1e**/**2e**	41/59	30/42	72

[a] The ratios of regioisomers **1**/**2** were detected by ^{1}H NMR spectrometer technique.
[b] The yields of regioisomers **1**/**2** were detected by the individual isolated yields from the chromatography separation method.

(75 MHz, $CDCl_3$) δ 14.3, 60.7, 115.6, 119.3, 128.0, 129.4, 129.6, 132.0, 138.7, 161.3; Anal. Calcd for $C_{12}H_{11}BrN_2O_2$; C: 48.84; H: 3.76; N: 9.49; found: C: 48.83; H: 3.75; N: 9.50.

*3.2.3. Ethyl 4-bromo-1-(4-methylphenyl)-1H-pyrazole-3-carboxylate (**6b**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.32 (t, J=6.1 Hz, 3H, CH), 2.34 (s, 3H, ArCH), 4.33 (q, J=6 Hz, 2H, CH), 7.32–7.34 (d, J=6.1 Hz, 2H, ArH), 7.72–7.74 (d, J=6.1 Hz, 2H, ArH), 8.86 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.1, 20.5, 60.8, 97.0, 119.0, 130.1, 131.0, 136.4, 137.6, 140.6, 160.3; Anal. Calcd for $C_{13}H_{13}BrN_2O_2$; C: 50.50; H: 4.24; N: 9.06; found: C: 50.51; H: 4.20; N: 9.03.

*3.2.4. Ethyl 3-bromo-1-(4-methylphenyl)-1H-pyrazole-4-carboxylate (**7b**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.30 (t, J=5.8 Hz, 3H, CH), 2.33 (s, 3H, CH), 4.27 (q, J=5.8 Hz, 2H, CH), 7.30–7.32 (d, J=5.8 Hz, 2H, ArH), 7.74–7.77 (d, J=9.1 Hz, 2H, ArH), 9.02 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.2, 20.4, 60.2, 114.5, 118.9, 128.4, 130.0, 133.4, 136.1, 137.3, 160.7; Anal. Calcd for $C_{13}H_{13}BrN_2O_2$; C: 50.50; H: 4.24; N: 9.06; found: C: 50.48; H: 4.20; N: 9.09.

*3.2.5. Ethyl 4-bromo-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (**6c**).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (t, J=6.1 Hz, 3H, CH), 3.74 (s, 3H, OCH), 4.37 (q, J=6.9 Hz, 2H, CH), 6.84–6.87 (d, J=9.1 Hz, 2H, ArH), 7.48–7.51 (d, J=9.1 Hz, 2H, ArH), 7.84 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 55.3, 61.0, 97.5, 114.3, 121.1, 129.6, 132.3, 141.0, 159.1, 160.8; Anal. Calcd for $C_{13}H_{13}BrN_2O_3$; C: 48.02; H: 4.03; N: 8.62; found: C: 47.98; H: 3.99; N: 8.67.

*3.2.6. Ethyl 3-bromo-1-(4-methoxyphenyl)-1H-pyrazole-4-carboxylate (**7c**).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34 (t, J=7.5 Hz, 3H, CH), 3.79 (s, 3H, OCH), 4.30 (q, J=7.5 Hz, 2H, CH), 6.90–6.93 (d, J=8.8 Hz, 2H, ArH), 7.50–7.53 (d, J=8.8 Hz, 2H, ArH), 8.21 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 55.4, 60.5, 114.5, 115.0, 120.9, 128.8, 131.8, 132.2, 159.1, 161.3; Anal. Calcd for $C_{13}H_{13}BrN_2O_3$; C: 48.02; H: 4.03; N: 8.62; found: C: 47.99; H: 4.04; N: 8.54.

*3.2.7. Ethyl 4-bromo-1-(4-fluorophenyl)-1H-pyrazole-3-carboxylate (**6d**).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (t, J=7.5 Hz, 3H, CH), 4.46 (q, J=7.1 Hz, 2H, CH), 7.17 (t, J=8.9 Hz, 2H, ArH), 7.64–7.69 (m, 2H, ArH), 7.94 (s, 1H, ArH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.2, 61.5, 98.3, 116.3, 116.7, 121.8, 121.9, 132.1, 141.9, 160.4, 160.9, 163.7; Anal. Calcd for $C_{12}H_{10}BrFN_2O_2$; C: 46.03; H: 3.22; N: 8.95; found: C: 45.97; H: 3.26; N: 8.91.

*3.2.8. Ethyl 3-bromo-1-(4-fluorophenyl)-1H-pyrazole-4-carboxylate (**7d**).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38 (t, J=7.5 Hz, 3H, CH), 4.36 (q, J=6.9 Hz, 2H, CH), 7.17 (t, J=9.0 Hz, 2H, ArH), 7.63–7.67 (m, 2H, ArH), 8.29 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 60.8, 115.8, 116.4, 116.7, 121.3, 121.4, 129.5, 132.1, 160.3, 161.3, 163.6; Anal. Calcd for $C_{12}H_{10}BrFN_2O_2$; C: 46.03; H: 3.22; N: 8.95; found: C: 46.06; H: 3.19; N: 8.98.

3.3. Standard procedure for synthesis of 2-arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-ones 1a–d and 2-arylpyrazolo[4,3-*c*]quinolin-4-(5*H*)-ones 2a–d from pyrazoles (6 or 7) via of step-by-step method

A solution of (**6** or **7**, 100 mg, 1.0 equiv) in 8.0 mL *p*-xylene/EtOH (1/1) was added 2-aminophenylboronic acid pinacol ester (820 mg, 1.1 equiv), $Pd(PPh_3)_4$ (39 m g, 0.1 equiv), and K_2CO_3 (2 mL, 2 M aqueous solution). The solution was heated to reflux for 24 h. After the reaction was completed, the reaction mixture was concentrated under reduced pressure to remove *p*-xylene and EtOH. The residue was added with 20 mL water, and extract with EtOAc (40 mL). The organic layer was filtered to remove the insoluble substances, then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel to give the corresponding 2-arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-one products **1a**–**d** in 73–82% or 2-arylpyrazolo[4,3-*c*]quinolin-4-(5*H*)-one products **2a**–**d** in 78–82% isolated yields.

3.4. Standard procedure for one-pot synthesis of 2-arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-ones 1a–e and 2-arylpyrazolo[4,3-*c*]quinolin-4-(5*H*)-ones 2a–e

A solution of 3-phenyl sydnone (**3**, 100 mg, 1.0 equiv) in 4.0 mL *p*-xylene was added ethyl 3-bromopropynoate (120 mg, 1.05 equiv) and heated to reflux for 5 h. The residue was cooled down and added 2-aminophenylboronic acid pinacol ester (820 mg, 1.1 equiv), $Pd(PPh_3)_4$ (39 mg, 0.1 equiv), K_2CO_3 (2 mL, 2 M aqueous solution), and EtOH (4.0 mL). The reaction mixture was stirred at reflux for 24 h. When the reaction was completed, the reaction mixture was concentrated under reduced pressure to remove *p*-xylene and EtOH. The residue was added with 20 mL water, and extract with EtOAc (40 mL). The organic layer was filtered to remove the insoluble substances, then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel to give the corresponding 2-arylpyrazolo[3,4-*c*]quinolin-4(5*H*)-one **1b**–**e** and 2-arylpyrazolo[4,3-*c*]quinolin-4(5*H*)-one **2b**–**e** products in 27–32% and 39–43% yields, respectively.

*3.4.1. 2-Phenylpyrazolo[3,4-c]quinolin-4(5H)-ones (**1a**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.24 (t, J=7.5 Hz, 1H, ArH), 7.35–7.51 (m, 3H, ArH), 7.64 (t, J=7.5 Hz, 2H, ArH), 7.96–8.05 (m, 3H, ArH), 9.49 (s, 1H, CH), 11.49 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 114.9, 116.1, 119.8, 122.3, 122.6, 123.5, 123.8, 127.8, 128.1, 129.8, 136.1, 139.4, 141.6,

156.9; Anal. Calcd for $C_{16}H_{11}N_3O$; C: 73.55; H: 4.24; N: 16.08; found: C: 73.58; H: 4.23; N: 16.09.

*3.4.2. 2-Phenylpyrazolo[4,3-c]quinolin-4(5H)-ones (**2a**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.26 (t, J=7.5 Hz, 1H, ArH), 7.37–7.63 (m, 5H, ArH), 8.13 (t, J=7.5 Hz, 3H, ArH), 9.38 (s, 1H, CH), 11.26 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 113.7, 114.4, 116.3, 119.8, 122.2, 122.3, 127.8, 128.5, 129.7, 138.2, 139.2, 149.1, 158.7; Anal. Calcd for $C_{16}H_{11}N_3O$; C: 73.55; H: 4.24; N: 16.08; found: C: 73.57; H: 4.26; N: 16.05.

*3.4.3. 2-(4-Methylphenyl)pyrazolo[3,4-c]quinolin-4(5H)-ones (**1b**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.40 (s, 3H, CH), 7.23–7.26 (m, 1H, ArH), 7.37–7.44 (m, 4H, ArH), 7.90–7.98 (m, 3H, ArH), 9.43 (s, 1H, CH), 11.48 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.5, 114.9, 116.1, 119.7, 122.2, 122.5, 123.3, 123.8, 127.7, 130.2, 136.1, 137.2, 137.6, 141.3, 156.9; Anal. Calcd for $C_{17}H_{13}N_3O$; C: 74.17; H: 4.76; N: 15.26; found: C: 74.21; H: 4.74; N: 15.29.

*3.4.4. 2-(4-Methylphenyl)pyrazolo[4,3-c]quinolin-4(5H)-ones (**2b**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.39 (s, 3H, CH), 7.25 (t, J=7.5 Hz, 1H, ArH), 7.38–7.51 (m, 4H, ArH), 7.97–8.00 (d, J=8.9 Hz, 2H, ArH), 8.11–8.14 (d, J=8.9 Hz, 1H, ArH), 9.31 (s, 1H, CH), 11.24 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.5, 113.7, 114.2, 116.3, 119.7, 122.2, 122.3, 128.1, 129.6, 130.1, 137.0, 137.3, 138.2, 148.9, 158.7; Anal. Calcd for $C_{17}H_{13}N_3O$; C: 74.17; H: 4.76; N: 15.26; found: C: 74.14; H: 4.743; N: 15.29.

*3.4.5. 2-(4-Methoxyphenyl)pyrazolo[3,4-c]quinolin-4(5H)-ones (**1c**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.85 (s, 3H, OCH), 7.16–7.26 (m, 3H, ArH), 7.37–7.39 (m, 2H, ArH), 7.93–7.97 (m, 3H, ArH), 9.36 (s, 1H, CH), 11.47 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.6, 114.9, 115.0, 116.1, 121.4, 122.3, 122.5, 123.3, 123.8, 127.7, 133.0, 136.1, 141.2, 157.0, 159.0; Anal. Calcd for $C_{17}H_{13}N_3O_2$; C: 70.09; H: 4.50; N: 14.42; found: C: 70.12; H: 4.48; N: 14.39.

*3.4.6. 2-(4-Methoxyphenyl)pyrazolo[4,3-c]quinolin-4(5H)-ones (**2c**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.83 (s, 3H, OCH), 7.10–7.13 (d, J=8.9 Hz, 2H, ArH), 7.23 (t, J=7.4 Hz, 1H, ArH), 7.36–7.50 (m, 2H, ArH), 7.98–8.01 (d, J=8.9 Hz, 2H, ArH), 8.10–8.12 (d, J=6.0 Hz, 1H, ArH), 9.24 (s, 1H, CH), 11.23 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.5, 113.8, 114.1, 114.7, 116.3, 121.4, 122.2, 122.3, 128.0, 129.5, 132.8, 138.1, 148.9, 158.7; Anal. Calcd for $C_{17}H_{13}N_3O_2$; C: 70.09; H: 4.50; N: 14.42; found: C: 70.12; H: 4.48; N: 14.48.

*3.4.7. 2-(4-Fluorophenyl)pyrazolo[3,4-c]quinolin-4(5H)-ones (**1d**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.22–7.26 (m, 1H, ArH), 7.35–7.52 (m, 4H, ArH), 7.94–7.96 (d, J=6.2 Hz, 1H, ArH), 8.05–8.10 (m, 2H, ArH), 9.45 (s, 1H, CH), 11.50 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 114.8, 116.1, 116.5, 116.8, 121.9, 122.1, 122.3, 122.7, 123.8, 127.9, 136.0, 136.1, 141.6, 156.8; Anal. Calcd for $C_{16}H_{10}FN_3O$; C: 68.81; H: 3.61; N: 15.05; found: C: 68.78; H: 3.57; N: 15.01.

*3.4.8. 2-(4-Fluorophenyl)pyrazolo[4,3-c]quinolin-4(5H)-ones (**2d**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.25 (t, J=7.5 Hz, 1H, ArH), 7.37–7.52 (m, 4H, ArH), 8.12–8.16 (m, 3H, ArH), 9.35 (s, 1H, CH), 11.26 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 113.6, 114.4, 116.3, 116.7, 122.0, 122.1, 122.3, 122.4, 128.7, 129.8, 135.8, 138.2, 149.2, 158.7; Anal. Calcd for $C_{16}H_{10}FN_3O$; C: 68.81; H: 3.61; N: 15.05; found: C: 68.85; H: 3.58; N: 15.08.

*3.4.9. 2-(3-Chlorophenyl)pyrazolo[3,4-c]quinolin-4(5H)-ones (**1e**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.24 (t, J=7.5 Hz, 1H, ArH), 7.47–7.56 (m, 3H, ArH), 7.92–7.94 (d, J=6.0 Hz, 1H, ArH), 8.02–8.04 (d, J=6.0 Hz, 1H, ArH), 8.09–8.14 (m, 2H, ArH), 9.55 (s, 1H, CH), 11.51 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 114.8, 116.4, 116.7, 118.5, 119.8, 122.3, 122.9, 123.7, 126.6, 130.1, 131.2, 134.2, 138.2, 139.6, 141.1, 156.6; Anal. Calcd for $C_{16}H_{10}ClN_3O$; C: 64.98; H: 3.41; N: 14.21; found: C: 65.02; H: 3.45; N: 14.25.

*3.4.10. 2-(3-Chlorophenylphenyl)pyrazolo[4,3-c]quinolin-4(5H)-ones (**2e**).* ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.22–7.24 (m, 1H, ArH), 7.38–7.61 (m, 4H, ArH), 8.12–8.22 (m, 3H, ArH), 9.44 (s, 1H, CH), 11.26 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 113.5, 114.6, 116.3, 118.3, 119.5, 122.3, 122.5, 127.5, 129.0, 130.0, 131.4, 134.1, 138.3, 140.3, 149.3, 158.6; Anal. Calcd for $C_{16}H_{10}ClN_3O$; C: 64.98; H: 3.41; N: 14.21; found: C: 65.01; H: 3.39; N: 14.19.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.04.093.

References and notes

1. Fredhol, B. B.; IJzerman, A. P.; Jacobson, K. A.; Klotz, K. N.; Linden, J. *Pharmacol. Rev.* **2001**, *53*, 527–552.
2. Acobson, K. A.; Knutsen, L. J. S. P1 and P2 Purine and Pyrimidine Receptor Ligands In *Purinergic and Pyrimidinergic Signaling*; Abbracchio, M. P., Williams, M., Eds.; Handbook of Experimental Pharmacology; Springer: Berlin, 2001; Vol. 151/1, pp 129–175.
3. Poulsen, S. A.; Quinn, R. J. *Bioorg. Med. Chem.* **1998**, *6*, 619–641.
4. Salvatore, C. A.; Jacobson, M. A.; Taylor, H. E.; Linden, J.; Johnson, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 10365–10369.
5. Colotta, V.; Catarzi, D.; Varano, F.; Cecchi, L.; Filacchioni, G.; Martini, C.; Trincavelli, L.; Lucacchini, A. *J. Med. Chem.* **2000**, *43*, 1158–1164.
6. Colotta, V.; Catarzi, D.; Varano, F.; Capelli, F.; Lenzi, O.; Filacchioni, G.; Martini, C.; Trincavelli, L.; Ciampi, O.; Pugliese, A. M.; Pedata, F.; Schiesaro, A.; Morizzo, E.; Moro, S. *J. Med. Chem.* **2007**, *50*, 4061–4074.
7. Baraldi, P. G.; Tabrizi, M. A.; Preti, D.; Bovero, A.; Fruttarolo, F.; Romeo Romagnoli, R.; Zaid, N. A.; Moorman, A. R.; Varani, K.; Andrea Borea, P. A. *J. Med. Chem.* **2005**, *48*, 5001–5008.
8. Catarzi, D.; Colotta, V.; Varano, F.; Cecchi, L.; Filacchioni, G.; Galli, A.; Costagli, C. *Arch. Pharm. (Weinheim, Ger.)* **1997**, *330*, 383–386.
9. Werbel, L. M.; Kesten, S. J.; Turner, W. R. *Eur. J. Med. Chem.* **1993**, *28*, 837–852.
10. For the preparation of sydnones: (a) Yeh, M.-Y.; Tien, H.-J.; Huang, L.-Y.; Chen, M.-H. J. *Chin. Chem. Soc.* **1983**, *30*, 29–37; (b) Thoman, C. J.; Voaden, D. J.; Hunsberger, I. M. *J. Org. Chem.* **1964**, *29*, 2044–2045; (c) Dallacker, F.; Kern. *J. Chem. Ber.* **1966**, *99*, 3830–3835; (d) Kuo, W.-F.; Lin, I.-T.; Sun, S.-W.; Yeh, M.-Y. *J. Chin. Chem. Soc.* **2001**, *48*, 769–782; (e) Hans, G.; Friedemann, R. *Liebigs Ann. Chem.* **1979**, *1*, 63–73; (*Chem. Abstr.* 90:203976).
11. (a) Delaunay, T.; Genix, P.; Es-Sayed, M.; Vors, J.-P.; Monteiro, N.; Balme, G. *Org. Lett.* **2010**, *12*, 3328–3331; (b) Chang, E.-M.; Wong, F. F.; Chen, T.-H.; Chiang, K.-C.; Yeh, M.-Y. *Heterocycles* **2006**, *68*, 1007–1015.
12. Chang, E.-M.; Chen, T.-H.; Wong, F. F.; Chang, E.-C.; Yeh, M.-Y. *Synlett* **2006**, 901–904.
13. Horn, J.; Li, H. Y.; Marsden, S. P.; Nelson, A.; Shearer, R. J.; Campbell, A. J.; House, D.; Weingarten, G. G. *Tetrahedron* **2009**, *62*, 9002–9007.
14. (a) Khan, T. A.; Kumar, S.; Venkatesh, C.; Iia, H. *Tetrahedron* **2011**, *67*, 2961–2968; (b) Eskildsen, J.; éstergaard, N.; VedΦ, P.; Begtrup, M. *Tetrahedron* **2002**, *58*, 7635–7644; (c) Susuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.