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CuCl-catalyzed one-pot synthesis of 5,6-dihydropyrazolo[1,5-*c*]quinazolines

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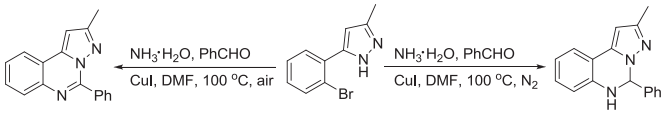
ABSTRACT

A simple and efficient procedure for the preparation of 5,6-dihydropyrazolo[1,5-*c*]quinazolines via CuCl-catalyzed tandem reaction of 5-(2-bromoaryl)-1*H*-pyrazoles with aldehydes and aqueous ammonia under nitrogen atmosphere has been developed. The usefulness of this novel methodology was showcased by its successful application in the preparation of a potential Eg5 inhibitor.

1. Introduction

In recent years, copper-catalyzed tandem reactions have attracted much attention due to their high efficiency in carbon—carbon and carbon—heteroatom bond formation reactions as well as in the construction of various heterocyclic skeletons.[1,2] As part of our research in this regard,[3,4] we have disclosed a copper-catalyzed synthesis of pyrazolo[1,5-*c*]quinazolines through the tandem reaction of 5-(2-bromoaryl)-1*H*-pyrazoles with aldehydes and aqueous ammonia under air atmosphere.[4] In studying the mechanism of this tandem process, we found that when the reaction was carried out under nitrogen atmosphere, 5,6-dihydropyrazolo[1,5-*c*]quinazoline, other than pyrazolo[1,5-*c*]quinazoline, was exclusively obtained (Scheme 1). Literature searching revealed that 5,6-dihydropyrazolo[1,5-*c*]quinazolines appear promising as excitatory amino acid and adenosine receptor and Gly/NMDA receptor antagonists,[5] and potential vaccinia virus and Eg5 ATPase inhibitors.[6] Notwithstanding their importance, protocols for the preparation of 5,6-dihydropyrazolo[1,5-*c*]quinazolines are very limited and usually suffer from multistep sequence, limited substrate scope, and poor overall yield.[5–7] Therefore, it is highly desirable to develop a more efficient and practical synthetic method



Scheme 1.

for the preparation of 5,6-dihydropyrazolo[1,5-*c*]quinazoline derivatives. Based on the above facts, we decided to study the copper-catalyzed tandem reaction of 5-(2-bromoaryl)-1*H*-pyrazoles with aldehydes and aqueous ammonia under nitrogen atmosphere in detail, thereby providing a straightforward and efficient route toward 5,6-dihydropyrazolo[1,5-*c*]quinazolines. In this paper, we wish to disclose our research results in this aspect.

2. Results and discussion

Initially, 5-(2-bromophenyl)-3-methyl-1*H*-pyrazole (**1a**), benzaldehyde (**2a**), and aqueous ammonia were used as model substrates to optimize the reaction conditions including catalysts, solvents, and reaction temperature (Table 1). It turned out that treatment of a mixture of **1a** (0.4 mmol), **2a** (0.8 mmol), and aqueous ammonia (0.4 mL) with CuI (10 mol %) in DMF (1.5 mL) at 100 °C in a sealed tube under nitrogen atmosphere for 12 h could give rise to the desired 2-methyl-5-phenyl-5,6-dihydropyrazolo[1,5-*c*]quinazoline (**3a**) in 82% yield (Table 1, entry 1). Reducing the amount of **2a** from 2.0 to 1.2 equiv (relative to **1a**) resulted in

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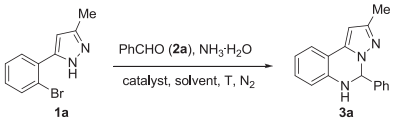
Table 1
Optimization for the synthesis of **3a**[a]



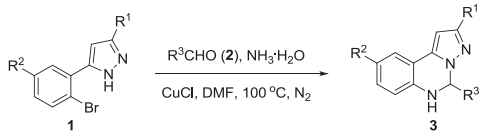
Entry	Catalyst	Solvent	*T* (°C)	Yield (%)[b]
1	CuI	DMF	100	82
2	CuBr	DMF	100	81
3	**CuCl**	**DMF**	**100**	**86**
4	$Cu(OAc)_2$	DMF	100	47
5	$CuCl_2$	DMF	100	53
6	CuCl	DMSO	100	74
7	CuCl	DMF	80	49
8	CuCl	DMF	120	71

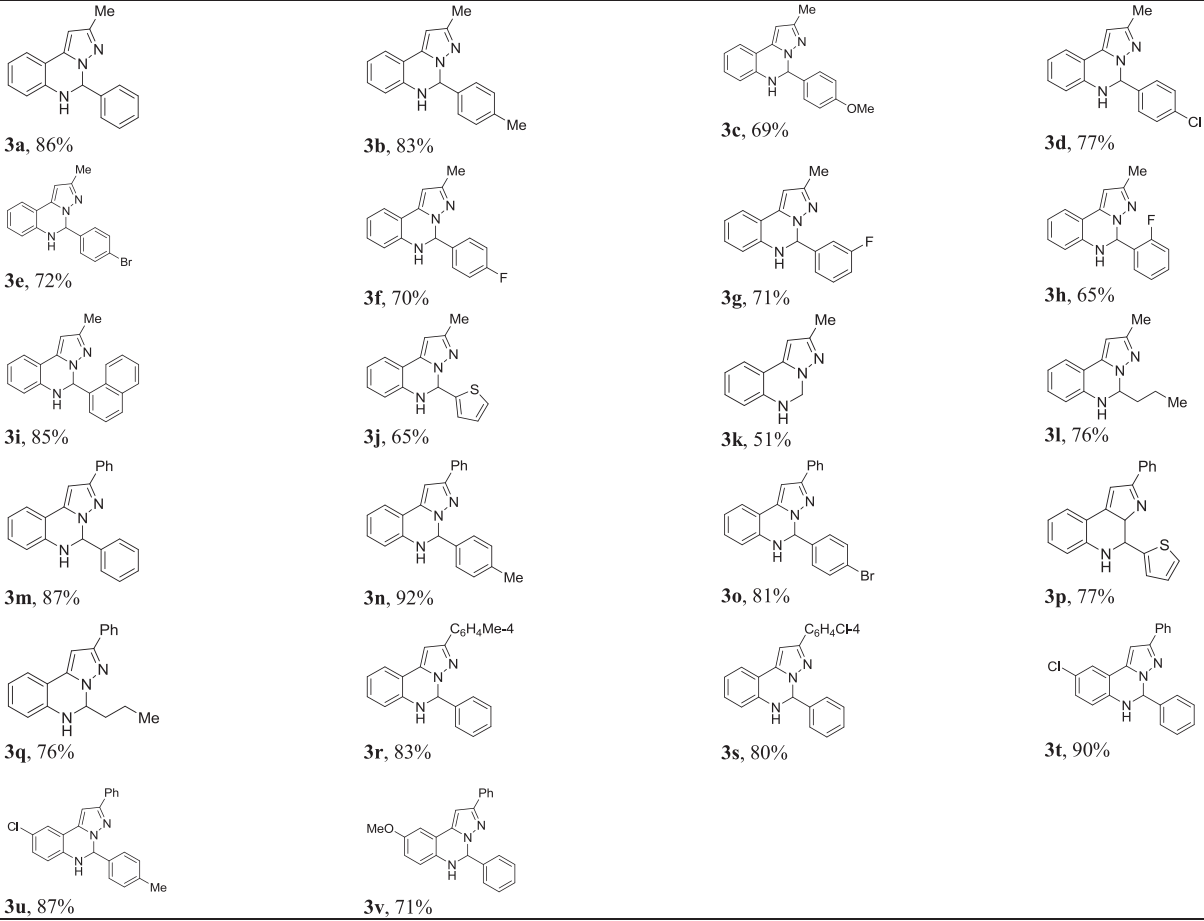
The bold in the entry signifies the best reaction conditions.
[a] All the reactions were performed with **1a** (0.4 mmol), **2a** (0.8 mmol), catalyst (0.04 mmol), 26% aqueous ammonia (0.4 mL), and solvent (1.5 mL) in a sealed tube (15 mL) under nitrogen atmosphere for 12 h.
[b] Isolated yield.

a lower yield of 75%.[4] Next, other copper catalysts were investigated, and the highest yield of 86% was obtained with CuCl as the catalyst (Table 1, entry 3). When DMSO was used to replace DMF as the reaction medium, the yield of **3a** decreased (Table 1, entry 3 vs 6). Moreover, the reaction temperature was also screened by using CuCl as catalyst and DMF as solvent, and 100 °C proved to be optimal (Table 1, entry 3 vs 7–8).

With the optimized reaction conditions (Table 1, entry 3) in hand, we were then interested in exploring the scope of aldehydes and 5-(2-bromoaryl)-1*H*-pyrazoles in the 5,6-dihydropyrazolo[1,5-*c*]quinazoline formation reaction. As shown in Table 2, aromatic aldehydes with a variety of substituents on the aryl ring (including: Me, MeO, Cl, Br, and F) reacted very well with **1a** and aqueous ammonia to afford the desired products **3a**–**h** in 65–86% yields (Table 2, entries 1–8). 1-Naphthaldehyde and thiophene-2-carbaldehyde also underwent the tandem reactions smoothly, thus generating the corresponding products **3i** and **3j** in 85% and 65% yields, respectively (Table 2, entries 9 and 10). In addition, alkyl-substituted aldehydes were found to be compatible with the reaction conditions to provide **3k** and **3l** in yields of 51% and 76% (Table 2, entries 11 and 12). Next, pyrazoles **1** with different

Table 2
Synthesis of 5,6-dihydropyrazolo[1,5-*c*]quinazolines **3**[a,b]

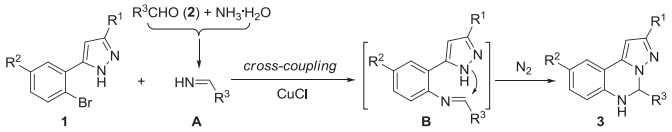




[a] Reaction conditions: **1** (0.4 mmol), **2** (0.8 mmol), CuCl (0.04 mmol), 26% aqueous ammonia (0.4 mL), DMF (1.5 mL), 100 °C, under nitrogen, 12 h for R^1 = Me; 18 h for R^1 = Aryl.
[b] Isolated yields are shown.

substitution patterns were examined, and it was found that the electronic effect and steric hindrance of R^1 and R^2 groups on pyrazoles **1** did not influence the formation of products **3m**–**v** obviously (Table 2, entries 13–22).

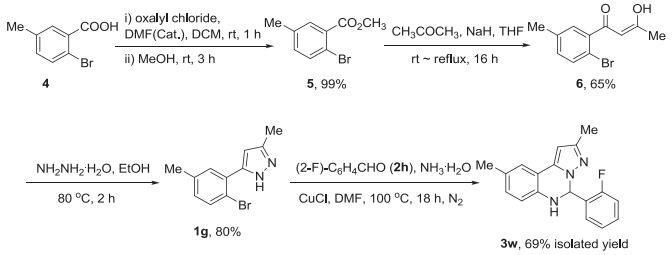
On the basis of the above results and our previous observations,[4] a possible mechanism for the formation of **3** is illustrated in Scheme 2. Initially, CuCl-catalyzed cross-coupling of pyrazole **1** with the in situ generated imine **A** affords intermediate **B**. Subsequent intramolecular nucleophilic cyclization of **B** gives rise to the final product **3** under nitrogen atmosphere.



Scheme 2. Possible mechanism for the formation of **3**.

As mentioned above, compounds containing the 5,6-dihydropyrazolo[1,5-*c*]quinazoline scaffold often exhibit significant biological activities.[5,6] In particular, 5-(2-fluorophenyl)-2,9-dimethyl-5,6-dihydropyrazolo[1,5-*c*]quinazoline (**3w**) was recently identified as a potential Eg5/Kinesin spindle protein inhibitor by Pae et al. through virtual screening.[6b] To the best of our knowledge, synthetic method for the preparation of **3w** has not been reported yet.

In our following studies, we were gratified to find that by employing the synthetic strategy developed in this paper, **3w** could be conveniently synthesized in 69% yield through the tandem reaction of 5-(2-bromo-5-methylphenyl)-3-methyl-1*H*-pyrazole (**1g**), which could be prepared from 2-bromo-5-methylbenzoic acid (**4**), with 2-fluorobenzaldehyde (**2h**), and aqueous ammonia under nitrogen atmosphere (Scheme 3).



Scheme 3. The synthesis of potential Eg5 inhibitor (**3w**).

3. Conclusion

In summary, we have developed an efficient synthetic approach toward 5,6-dihydropyrazolo[1,5-*c*]quinazolines via the copper-catalyzed tandem reaction of 5-(2-bromoaryl)-1*H*-pyrazoles with aldehydes and aqueous ammonia under nitrogen atmosphere without using any additional ligand and base. As an application, this methodology offers a straightforward route toward a potential Eg5 inhibitor (**3w**). The present protocol displays broad substrate scope, good yields, and mild reaction conditions.

4. Experimental section

4.1. General

Unless noted, all commercial reagents and solvents were used without further purification. THF was distilled from sodium/benzophenone. Melting points were recorded with a micro melting point apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. High-resolution mass spectra (HRMS) were obtained by using a MicrOTOF mass spectrometer. All reactions were monitored by thin-layer chromatography (TLC) using silica gel plates (silica gel 60 F254 0.25 mm) and components were visualized by observation under UV light (254 and 365 nm).

4.2. General procedure for the preparation of products 3a–v

To a mixture of 5-(2-bromoaryl)-1*H*-pyrazole **1** (0.4 mmol), aldehyde **2** (0.8 mmol), CuCl (0.04 mmol), and DMF (1.5 mL) in a sealed tube (15 mL) was added 26% aqueous ammonia (0.4 mL) under nitrogen atmosphere. Then, the tube was sealed and the resulting solution was stirred at 100 °C until the reaction was completed as monitored by TLC (ca. 12 h for R^1=Me; 18 h for R^1=Aryl). After being cooled to room temperature, the reaction was quenched with NH_4Cl solution and extracted with ethyl acetate two times. The combined organic layer was washed with H_2O and brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate (3:1), to afford the corresponding product **3**.

*4.2.1. 2-Methyl-5-phenyl-5,6-dihydropyrazolo[1,5-c]quinazoline (**3a**).* White solid; yield: 89.9 mg (86%); ^{1}H and ^{13}C NMR of compound **3a** are the same as the previously reported ones.[4]

*4.2.2. 2-Methyl-5-p-tolyl-5,6-dihydropyrazolo[1,5-c]quinazoline (**3b**).* White solid; yield: 91.4 mg (83%); mp 146–148 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3H), 2.31 (s, 3H), 4.63 (br s, 1H), 6.36 (s, 1H), 6.44 (s, 1H), 6.65 (d, J=8.0 Hz, 1H), 6.86 (t, J=8.0 Hz, 1H), 7.09–7.13 (m, 3H), 7.19 (d, J=8.0 Hz, 2H), 7.46 (dd, J=1.2, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 21.2, 72.2, 99.4, 114.2, 114.9, 119.6, 124.0, 126.6, 129.2, 129.5, 137.0, 138.2, 139.0, 139.4, 149.5. HRMS (ESI) calcd for $C_{18}H_{18}N_3$ $[M+H]^+$: 276.1495, found: 276.1504.

*4.2.3. 5-(4-Methoxyphenyl)-2-methyl-5,6-dihydropyrazolo[1,5-c]quinazoline (**3c**).* White solid; yield: 80.4 mg (69%); mp 101–103 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.27 (s, 3H), 3.74 (s, 3H), 4.67 (br s, 1H), 6.35 (s, 1H), 6.39 (s, 1H), 6.64 (d, J=8.0 Hz, 1H), 6.82–6.88 (m, 3H), 7.11 (dt, J=1.6, 7.6 Hz, 1H), 7.22–7.24 (m, 2H), 7.45 (dd, J=1.6, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 55.3, 72.0, 99.4, 114.2, 114.8, 119.6, 124.0, 128.2, 129.2, 132.0, 138.2, 139.5, 149.5, 160.2 (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{18}H_{18}N_3O$ $[M+H]^+$: 292.1444, found: 292.1462.

*4.2.4. 5-(4-Chlorophenyl)-2-methyl-5,6-dihydropyrazolo[1,5-c]-quinazoline (**3d**).* Light yellow solid; yield: 91.0 mg (77%); mp 107–109 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.27 (s, 3H), 4.69 (br s, 1H), 6.36 (s, 1H), 6.46 (s, 1H), 6.68 (d, J=8.0 Hz, 1H), 6.88 (t, J=7.2 Hz, 1H), 7.13 (t, J=8.0 Hz, 1H), 7.20 (d, J=8.4 Hz, 2H), 7.27 (d, J=8.0 Hz, 2H), 7.45 (d, J=7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 71.5, 99.7, 114.2, 115.1, 120.0, 124.1, 128.1, 129.0, 129.4, 135.0, 138.2, 138.4, 138.9, 149.8. HRMS (ESI) calcd for $C_{17}H_{15}ClN_3$ $[M+H]^+$: 296.0949, found: 296.0969.

*4.2.5. 5-(4-Bromophenyl)-2-methyl-5,6-dihydropyrazolo[1,5-c]-quinazoline (**3e**).* Yellow oil; yield: 98.0 mg (72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.27 (s, 3H), 4.76 (br s, 1H), 6.36 (s, 1H), 6.41 (s, 1H), 6.66 (d, J=8.0 Hz, 1H), 6.88 (t, J=7.6 Hz, 1H), 7.10–7.13 (m, 3H), 7.41 (d, J=8.4 Hz, 2H), 7.45 (d, J=7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 71.6, 99.7, 114.2, 115.1, 120.0, 123.2, 124.1, 128.4, 129.4, 132.0, 138.2, 138.9, 139.0, 149.9. HRMS (ESI) calcd for $C_{17}H_{15}BrN_3$ $[M+H]^+$: 340.0444, found: 340.0423.

*4.2.6. 5-(4-Fluorophenyl)-2-methyl-5,6-dihydropyrazolo[1,5-c]-quinazoline (**3f**).* Light yellow solid; yield: 78.2 mg (70%); mp

158–160 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.27 (s, 3H), 4.64 (br s, 1H), 6.36 (s, 1H), 6.47 (s, 1H), 6.69 (d, J=8.4 Hz, 1H), 6.86–6.90 (m, 1H), 6.98–7.02 (m, 2H), 7.11–7.15 (m, 1H), 7.26–7.30 (m, 2H), 7.45–7.47 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 71.6, 99.6, 114.2, 115.0, 115.8 (d, J=21.9 Hz, 2C), 120.0, 124.1, 128.6 (d, J=8.0 Hz, 2C), 129.3, 135.8 (d, J=2.2 Hz, 1C), 138.2, 139.1, 149.7, 163.1 (d, J=245.8 Hz, 1C). HRMS (ESI) calcd for $C_{17}H_{15}FN_3$ $[M+H]^+$: 280.1245, found: 280.1258.

*4.2.7. 5-(3-Fluorophenyl)-2-methyl-5,6-dihydropyrazolo[1,5-c]-quinazoline (**3g**).* Light yellow solid; yield: 79.3 mg (71%); mp 76–77 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.29 (s, 3H), 4.69 (br s, 1H), 6.37 (s, 1H), 6.51 (s, 1H), 6.69 (d, J=8.0 Hz, 1H), 6.86–7.01 (m, 3H), 7.04–7.06 (m, 1H), 7.13 (dt, J=1.2, 7.6 Hz, 1H), 7.24–7.30 (m, 1H), 7.46 (dd, J=1.6, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 71.5, 99.7, 113.6 (d, J=22.5 Hz, 1C), 114.2, 115.2, 116.1 (d, J=21.1 Hz, 1C), 120.1, 122.2 (d, J=2.9 Hz, 1C), 124.1, 129.4, 130.5 (d, J=8.0 Hz, 1C), 138.1, 138.7, 142.5 (d, J=6.6 Hz, 1C), 149.9, 162.9 (d, J=245.8 Hz, 1C). HRMS (ESI) calcd for $C_{17}H_{15}FN_3$ $[M+H]^+$: 280.1245, found: 280.1251.

*4.2.8. 5-(2-Fluorophenyl)-2-methyl-5,6-dihydropyrazolo[1,5-c]-quinazoline (**3h**).* Light yellow solid; yield: 72.6 mg (65%); mp 118–120 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.33 (s, 3H), 4.78 (br s, 1H), 6.41–6.45 (m, 2H), 6.64 (d, J=8.0 Hz, 1H), 6.85 (dt, J=0.8, 7.2 Hz, 1H), 6.91–6.95 (m, 2H), 7.03–7.10 (m, 2H), 7.20–7.25 (m, 1H), 7.46–7.48 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 66.3 (d, J=4.3 Hz, 1C), 99.4, 114.0, 115.2, 115.6 (d, J=21.1 Hz, 1C), 119.8, 124.0, 124.5 (d, J=3.6 Hz, 1C), 127.0 (d, J=2.9 Hz, 1C), 127.6 (d, J=12.4 Hz, 1C), 129.3, 130.4 (d, J=8.7 Hz, 1C), 138.6, 138.9, 149.8, 159.6 (d, J=244.4 Hz, 1C). HRMS (ESI) calcd for $C_{17}H_{15}FN_3$ $[M+H]^+$: 280.1245, found: 280.1237.

*4.2.9. 2-Methyl-5-(naphthalen-1-yl)-5,6-dihydropyrazolo[1,5-c]-quinazoline (**3i**).* White solid; yield: 105.9 mg (85%); mp 88–90 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 4.76 (br s, 1H), 6.44 (s, 1H), 6.49 (d, J=7.6 Hz, 1H), 6.86 (t, J=8.0 Hz, 1H), 6.93 (d, J=6.8 Hz, 1H), 7.04 (t, J=8.0 Hz, 1H), 7.14 (s, 1H), 7.30 (t, J=8.4 Hz, 1H), 7.47–7.53 (m, 3H), 7.80 (d, J=8.4 Hz, 1H), 7.86–7.89 (m, 1H), 8.10–8.12 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 70.6, 99.4, 114.0, 115.1, 119.6, 123.1, 124.0, 125.31, 125.35, 125.8, 126.7, 129.1, 129.2, 129.8, 130.3, 134.1, 134.3, 138.9, 139.4, 149.8. HRMS (ESI) calcd for $C_{21}H_{18}N_3$ $[M+H]^+$: 312.1495, found: 312.1480.

*4.2.10. 2-Methyl-5-(thiophen-2-yl)-5,6-dihydropyrazolo[1,5-c]-quinazoline (**3j**).* Light yellow solid; yield: 69.5 mg (65%); mp 114–116 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.29 (s, 3H), 4.85 (br s, 1H), 6.34 (s, 1H), 6.74 (d, J=8.4 Hz, 1H), 6.78 (s, 1H), 6.87–6.92 (m, 2H), 7.01 (d, J=2.4 Hz, 1H), 7.13–7.20 (m, 2H), 7.45 (dd, J=0.8, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 68.1, 99.8, 114.5, 115.6, 120.3, 124.1, 125.8, 126.4, 126.6, 129.3, 137.6, 138.6, 143.4, 149.8. HRMS (ESI) calcd for $C_{15}H_{14}N_3S$ $[M+H]^+$: 268.0903, found: 268.0912.

*4.2.11. 2-Methyl-5,6-dihydropyrazolo[1,5-c]quinazoline (**3k**).* White solid; yield: 37.8 mg (51%); mp 94–96 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32 (s, 3H), 4.45 (br s, 1H), 5.35 (s, 2H), 6.28 (s, 1H), 6.75 (d, J=8.4 Hz, 1H), 6.88 (t, J=8.0 Hz, 1H), 7.13 (t, J=8.0 Hz, 1H), 7.41 (d, J=8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 59.6, 99.4, 115.4, 115.7, 120.3, 124.2, 129.0, 138.1, 140.4, 149.2. HRMS (ESI) calcd for $C_{11}H_{12}N_3$ $[M+H]^+$: 186.1026, found: 186.1040.

*4.2.12. 2-Methyl-5-propyl-5,6-dihydropyrazolo[1,5-c]quinazoline (**3l**).* Colorless oil; yield: 69.1 mg (76%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, J=8.0 Hz, 3H), 1.38–1.48 (m, 2H), 1.86–2.06 (m, 2H), 2.32 (s, 3H), 4.42 (br s, 1H), 5.47–5.50 (m, 1H), 6.26 (s, 1H), 6.71 (d, J=8.4 Hz, 1H), 6.81–6.85 (m, 1H), 7.09–7.13 (m, 1H), 7.37–7.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 13.8, 17.7, 37.3, 69.6, 99.2, 114.7, 115.2, 119.6, 123.9, 129.1, 137.5, 139.5, 148.8. HRMS (ESI) calcd for $C_{14}H_{18}N_3$ $[M+H]^+$: 228.1495, found: 228.1500.

*4.2.13. 2,5-Diphenyl-5,6-dihydropyrazolo[1,5-c]quinazoline (**3m**).* White solid; yield: 112.5 mg (87%); mp 83–85 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.75 (br s, 1H), 6.62 (s, 1H), 6.69 (d, J=8.4 Hz, 1H), 6.90–6.94 (m, 2H), 7.15 (dt, J=1.2, 7.6 Hz, 1H), 7.31–7.34 (m, 6H), 7.38–7.42 (m, 2H), 7.57 (dd, J=1.2, 7.6 Hz, 1H), 7.84–7.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 72.2, 96.9, 114.3, 115.3, 120.0, 124.1, 125.8, 126.6, 127.9, 128.6, 128.8, 129.0, 129.5, 133.4, 138.7, 139.2, 139.9, 152.1. HRMS (ESI) calcd for $C_{22}H_{18}N_3$ $[M+H]^+$: 324.1495, found: 324.1517.

*4.2.14. 2-Phenyl-5-p-tolyl-5,6-dihydropyrazolo[1,5-c]quinazoline (**3n**).* White solid; yield: 124.1 mg (92%); mp 106–108 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.31 (s, 3H), 4.69 (br s, 1H), 6.58 (s, 1H), 6.69 (d, J=8.0 Hz, 1H), 6.89 (s, 1H), 6.91 (t, J=8.0 Hz, 1H), 7.10–7.21 (m, 5H), 7.29–7.33 (m, 1H), 7.39 (t, J=8.0 Hz, 2H), 7.56 (dd, J=1.2, 8.0 Hz, 1H), 7.83–7.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 72.1, 96.8, 114.3, 115.3, 119.9, 124.1, 125.8, 126.5, 127.8, 128.6, 129.4, 133.4, 137.0, 138.6, 138.9, 139.3, 152.0 (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{23}H_{20}N_3$ $[M+H]^+$: 338.1652, found: 338.1659.

*4.2.15. 5-(4-Bromophenyl)-2-phenyl-5,6-dihydropyrazolo[1,5-c]-quinazoline (**3o**).* Yellow oil; yield: 130.3 mg (81%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.79 (br s, 1H), 6.52 (s, 1H), 6.69 (d, J=7.6 Hz, 1H), 6.88 (s, 1H), 6.93 (t, J=8.0 Hz, 1H), 7.12–7.18 (m, 3H), 7.30–7.34 (m, 1H), 7.38–7.42 (m, 4H), 7.55 (dd, J=1.2, 7.6 Hz, 1H), 7.82–7.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 71.6, 97.0, 114.3, 115.5, 120.3, 123.1, 124.2, 125.8, 128.0, 128.4, 128.7, 129.6, 131.9, 133.2, 138.6, 138.8, 138.9, 152.3. HRMS (ESI) calcd for $C_{22}H_{17}BrN_3$ $[M+H]^+$: 402.0600, found: 402.0589.

*4.2.16. 2-Phenyl-5-(thiophen-2-yl)-5,6-dihydropyrazolo[1,5-c]-quinazoline (**3p**).* Yellow oil; yield: 101.4 mg (77%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.87 (br s, 1H), 6.78 (d, J=7.6 Hz, 1H), 6.86 (s, 1H), 6.87–6.89 (m, 1H), 6.92 (s, 1H), 6.94–6.98 (m, 1H), 7.02 (d, J=3.2 Hz, 1H), 7.17–7.21 (m, 2H), 7.30–7.35 (m, 1H), 7.39–7.43 (m, 2H), 7.55 (dd, J=1.2, 7.6 Hz, 1H), 7.86–7.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 68.3, 97.2, 114.6, 115.9, 120.6, 124.2, 125.8, 125.9, 126.3, 126.7, 127.9, 128.7, 129.6, 133.3, 138.0, 138.6, 143.3, 152.3. HRMS (ESI) calcd for $C_{20}H_{16}N_3S$ $[M+H]^+$: 330.1059, found: 330.1080.

*4.2.17. 2-Phenyl-5-propyl-5,6-dihydropyrazolo[1,5-c]quinazoline (**3q**).* Colorless oil; yield: 88.0 mg (76%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, J=7.6 Hz, 3H), 1.44–1.54 (m, 2H), 1.93–2.03 (m, 1H), 2.06–2.14 (m, 1H), 4.44 (br s, 1H), 5.59–5.62 (m, 1H), 6.75 (d, J=8.0 Hz, 1H), 6.79 (s, 1H), 6.89 (dt, J=0.8, 7.6 Hz, 1H), 7.16 (dt, J=1.2, 8.0 Hz, 1H), 7.31–7.35 (m, 1H), 7.41–7.45 (m, 2H), 7.50 (dd, J=1.6, 8.0 Hz, 1H), 7.87–7.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 17.8, 37.4, 70.0, 96.6, 114.7, 115.4, 119.8, 124.0, 125.7, 127.7, 128.7, 129.3, 133.7, 138.0, 139.5, 151.5. HRMS (ESI) calcd for $C_{19}H_{20}N_3$ $[M+H]^+$: 290.1652, found: 290.1649.

*4.2.18. 5-Phenyl-2-p-tolyl-5,6-dihydropyrazolo[1,5-c]quinazoline (**3r**).* White solid; yield: 112.0 mg (83%); mp 102–104 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.38 (s, 3H), 4.75 (br s, 1H), 6.61 (s, 1H), 6.69 (d, J=7.6 Hz, 1H), 6.87 (s, 1H), 6.91 (t, J=7.2 Hz, 1H), 7.12–7.17 (m, 1H), 7.20 (d, J=8.4 Hz, 2H), 7.28–7.31 (m, 5H), 7.56 (d, J=7.2 Hz, 1H), 7.74 (d, J=7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 72.2, 96.7, 114.4, 115.3, 119.9, 124.1, 125.7, 126.5, 128.8, 129.0, 129.3, 129.4, 130.6, 137.6, 138.6, 139.1, 140.0, 152.2. HRMS (ESI) calcd for $C_{23}H_{20}N_3$ $[M+H]^+$: 338.1652, found: 338.1674.

*4.2.19. 2-(4-Chlorophenyl)-5-phenyl-5,6-dihydropyrazolo[1,5-c]-quinazoline (**3s**).* White solid; yield: 114.5 mg (80%); mp 119–120 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.67 (br s, 1H), 6.62 (s, 1H), 6.72 (d, J=8.0 Hz, 1H), 6.84 (s, 1H), 6.92 (t, J=8.0 Hz, 1H), 7.16 (t, J=8.0 Hz, 1H), 7.32–7.35 (m, 7H), 7.54 (d, J=7.6 Hz, 1H), 7.74 (d, J=8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 72.3, 96.8, 114.2, 115.3, 120.1, 124.1, 126.6, 127.1, 128.7, 128.8, 129.1, 129.6, 131.9, 133.5, 138.8, 139.2, 139.7, 151.0. HRMS (ESI) calcd for $C_{22}H_{17}ClN_3$ $[M+H]^+$: 358.1106, found: 358.1116.

*4.2.20. 9-Chloro-2,5-diphenyl-5,6-dihydropyrazolo[1,5-c]quinazoline (**3t**).* White solid; yield: 128.8 mg (90%); mp 143–145 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.72 (br s, 1H), 6.62 (s, 1H), 6.64 (d, J=8.0 Hz, 1H), 6.87 (s, 1H), 7.09 (dd, J=2.4, 8.0 Hz, 1H), 7.25–7.32 (m, 6H), 7.38 (t, J=7.6 Hz, 2H), 7.52 (d, J=2.4 Hz, 1H), 7.80–7.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 72.1, 97.3, 115.7, 116.6, 123.7, 124.9, 125.8, 126.4, 128.0, 128.6, 128.9, 129.15, 129.17, 133.1, 137.47, 137.53, 139.5, 152.3. HRMS (ESI) calcd for $C_{22}H_{16}ClN_3Na$ $[M+Na]^+$: 380.0925, found: 380.0954.

*4.2.21. 9-Chloro-2-phenyl-5-p-tolyl-5,6-dihydropyrazolo[1,5-c]-quinazoline (**3u**).* Colorless oil; yield: 129.4 mg (87%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3H), 4.75 (br s, 1H), 6.53 (s, 1H), 6.59 (d, J=8.4 Hz, 1H), 6.85 (s, 1H), 7.06–7.16 (m, 5H), 7.28–7.32 (m, 1H), 7.36–7.40 (m, 2H), 7.51 (d, J=2.0 Hz, 1H), 7.80–7.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 72.0, 97.3, 115.6, 116.5, 123.7, 124.7, 125.8, 126.4, 128.0, 128.6, 129.1, 129.5, 133.1, 136.6, 137.5, 137.7, 139.1, 152.2. HRMS (ESI) calcd for $C_{23}H_{19}ClN_3$ $[M+H]^+$: 372.1262, found: 372.1249.

*4.2.22. 9-Methoxy-2,5-diphenyl-5,6-dihydropyrazolo[1,5-c]quinazoline (**3v**).* Light yellow solid; yield: 100.4 mg (71%); mp 105–107 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.82 (s, 3H), 4.52 (br s, 1H), 6.57 (s, 1H), 6.71–6.78 (m, 2H), 6.89 (s, 1H), 7.10 (d, J=2.4 Hz, 1H), 7.29–7.34 (m, 6H), 7.38–7.42 (m, 2H), 7.85–7.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.8, 72.2, 97.1, 108.7, 115.9, 116.6, 118.0, 125.8, 126.6, 127.8, 128.6, 128.7, 128.8, 132.7, 133.4, 138.5, 139.7, 151.9, 154.2. HRMS (ESI) calcd for $C_{23}H_{20}N_3O$ $[M+H]^+$: 354.1601, found: 354.1611.

4.3. Typical procedure for the preparation of potential Eg5 inhibitor 3w

*4.3.1. Methyl 2-bromo-5-methylbenzoate (**5**).*[8] To a suspension of compound **4** (2.15 g, 10 mmol) in dry DCM (40 mL) and DMF (0.2 mL) at 0 °C was slowly added oxalyl chloride (1.3 mL, 15 mmol). After being stirred for 1 h at room temperature, the reaction mixture was treated with MeOH (20 mL) and then stirred for 3 h. The resulting solution was neutralized with saturated aqueous Na_2CO_3 (100 mL) and extracted with DCM (70 mL×2). The combined organic layer was washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate (30:1), to afford compound **5** (2.27 g) as colorless oil in 99% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3H), 3.90 (s, 3H), 7.10 (dd, J=2.4, 8.4 Hz, 1H), 7.49 (d, J=8.0 Hz, 1H), 7.57 (d, J=2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 52.4, 118.2, 131.7, 131.9, 133.5, 134.1, 137.3, 166.8.

*4.3.2. (Z)-1-(2-Bromo-5-methylphenyl)-3-hydroxybut-2-en-1-one (**6**).*[9] To a mixture of compound **5** (2.06 g, 9 mmol) and sodium hydride (18 mmol) in dry THF (30 mL) was slowly added acetone (10 mmol) under nitrogen atmosphere. After being stirred for 2 h at room temperature, the reaction mixture was heated to reflux for 16 h. The reaction was quenched with 1 N HCl (20 mL) and extracted with ethyl acetate (30 mL×2). The combined organic layer was washed with water (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (10 mL), and then dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate (10:1), to afford compound **6** (1.49 g) as yellow oil in 65% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.16 (s, 3H), 2.31 (s, 3H), 5.94 (s, 1H), 7.07 (dd, J=2.0, 8.4 Hz, 1H), 7.29 (d, J=2.0 Hz, 1H), 7.47 (d, J=8.4 Hz, 1H), 15.63 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8, 25.3, 101.7, 116.6, 130.5, 132.5, 133.6, 137.49, 137.52, 186.6, 192.1. HRMS (ESI) calcd for $C_{11}H_{12}BrO_2$ $[M+H]^+$: 255.0015, found: 255.0031.

*4.3.3. 5-(2-Bromo-5-methylphenyl)-3-methyl-1H-pyrazole (**1g**).* To a solution of compound **6** (1.02 g, 4 mmol) in EtOH (5 mL) was added hydrazine hydrate (6 mmol) and the reaction mixture was stirred at 80 °C for 2 h. The solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate (3:1), to afford compound **1g** (0.8 g) as yellow oil in 80% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.17 (s, 3H), 2.25 (s, 3H), 6.45 (s, 1H), 6.96 (dd, J=2.0, 8.4 Hz, 1H), 7.40 (d, J=1.6 Hz, 1H), 7.49 (d, J=8.0 Hz, 1H), 11.30 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.3, 20.8, 105.7, 118.8, 130.1, 131.8, 133.2, 133.6, 137.2, 141.9, 148.6. HRMS (ESI) calcd for $C_{11}H_{12}BrN_2$ $[M+H]^+$: 251.0178, found: 251.0185.

*4.3.4. Potential Eg5 inhibitor (**3w**).* Colorless oil; yield: 81.0 mg (69%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3H), 2.33 (s, 3H), 4.71 (br s, 1H), 6.39 (s, 1H), 6.42–6.46 (m, 1H), 6.55 (d, J=7.6 Hz, 1H), 6.88–6.94 (m, 3H), 7.02–7.07 (m, 1H), 7.18–7.22 (m, 1H), 7.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 20.6, 66.4 (d, J=4.3 Hz, 1C), 99.3, 114.1, 115.3, 115.5 (d, J=21.1 Hz, 1C), 124.2, 124.4 (d, J=2.9 Hz, 1C), 127.1 (d, J=3.0 Hz, 1C), 127.6 (d, J=12.3 Hz, 1C), 129.2, 130.0, 130.3 (d, J=8.0 Hz, 1C), 136.3, 139.0, 149.7, 159.7 (d, J=244.4 Hz, 1C). HRMS (ESI) calcd for $C_{18}H_{17}FN_3$ $[M+H]^+$: 294.1401, found: 294.1413.

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Supplementary data

Copies of ^{1}H NMR and ^{13}C NMR spectra of **3a**–**v**, **5**, **6**, **1g**, and **3w**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.02.027.

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