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Cyanoacetamides (IV): Versatile One-Pot Route to 2-Quinoline-3-carboxamides

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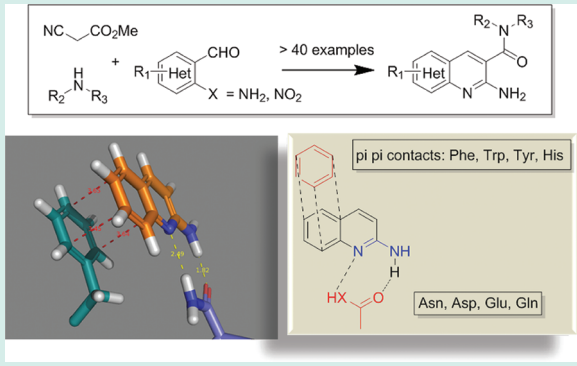
Supporting Information

ABSTRACT: Cyanoacetic acid derivatives are the starting materials for a plethora of multicomponent reaction (MCR) scaffolds. Herein, we describe scope of a valuable general protocol for the synthesis of arrays of 2-aminoquinoline-3-carboxamides from cyanoacetamides and 2-aminobenzaldehydes or heterocyclic derivatives via a Friedländer reaction variation. In many cases, the reactions involve a very convenient work up by simple precipitation and filtration. More than 40 new products are described. We foresee our protocol and the resulting derivatives becoming very valuable to greatly expanding the scaffold space of cyanoacetamide derivatives.



KEYWORDS: *cyanoacetic acid derivatives, multicomponent reaction, Friedländer reaction*

Quinoline is one of the most important heterocycles for drug discovery, with a broad range of biological activities, from treatment from malaria (quinine, chloroquine et al.), arthritis, lupus, asthma to allergies (e.g., singulair). The 2-aminoquinoline fragment exists in the skin cancer medicine Aldara and many other medicines. Recently, many potential biologically important 2-aminoquinoline analogous, such as adenosine A2A receptor antagonists,[1,2] β-secretase (BACE) inhibitor,[3] melanin-concentrating hormone (MCH) antagonist,[4] etc. (Figure 1), have been studied and developed.

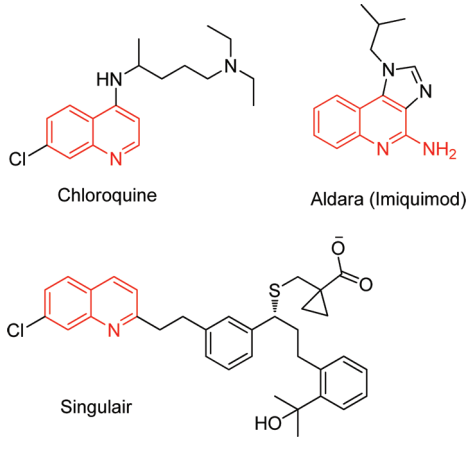


Figure 1. Some marketed (2-amino)quinoline drugs.

Recently the discovery of 2-aminoquinolines as potent and selective anti-Alzheimer BACE1 inhibitors showing good blood-brain barrier permeability, cellular activity, and animal PKPD profile has proven to be a remarkably useful case study to better understand their outstanding binding properties. (Figure 2). The advanced 2-aminoquinoline derivative **3** was evolved from a fragment-based drug discovery approach.[5,6] Herein a fragment library of low molecular weight compounds was screened using surface plasmon resonance (SPR) technology and 2-aminoquinoline **1** was found as a weak hit while also showing excellent ligand efficacy. The initial hit **1** was also characterized by cocrystal structure analysis (Figure 2).[6,7]

Highly optimized compounds like **3**, emerged and intermediate compounds like **2** were structurally characterized along the chemical optimization pathway (Figure 2). In all three cocrystal structure analyses the amidine-like moiety of the 2-aminoquinoline forms a bifurcated electrostatic interaction with the two catalytic Asp residues of the asp-protease BACE1. Additionally, the phenyl ring of the 2-aminoquinoline undergoes a T-shaped pi-pi interaction with the Tyr-71. A substructure search with the 2-aminoquinoline (smiles [H]N-([H])C1=NC2=C(C=CC=C2)C=C1) in the protein databank results in 9 cocrystal structures. Intriguingly, all the structures show the two main interactions of 2-aminoquinoline

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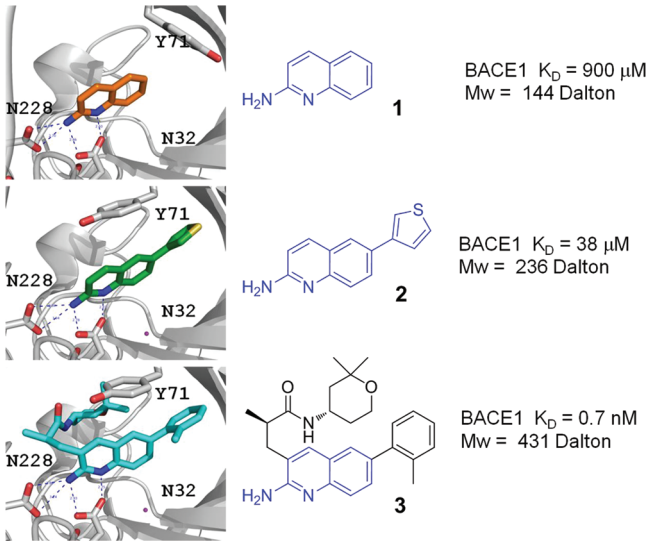
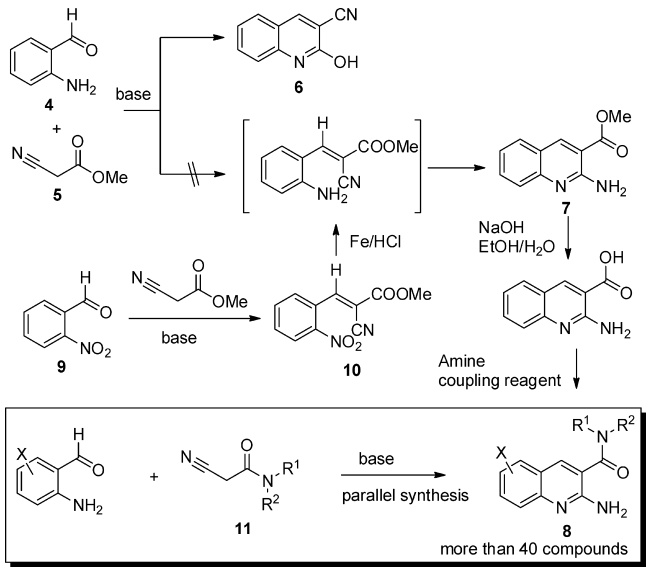


Figure 2. Fragment-based drug discovery of potent anti-Alzheimer BACE1 inhibitors. Left column: The small 2-aminoquinoline containing molecules **1** (PDB 2OHL, orange sticks), **2** (PDB 2RSX, green sticks), and **3** (PDB 3RSV, cyan sticks) cocrystallized in BACE1 (surface and stick representation). Only key amino acids important for the herein discussion are shown in stick representation. Hydrogen bonds are indicated by red dotted lines.

are a) electrostatic interactions of the amidine substructure and b) pi-pi interactions to adjacent hydrophobic or aromatic amino acids. Clearly, these two interactions very well characterize the biological key interactions of the 2-aminoquinoline moiety toward their protein targets. This taken together with their other favorable properties such as cLog P = 1.7, tPSA = 38.4 and M_w = 144 Da, might explain the privileged structure character of the 2-aminoquinoline.

There are many classic named synthetic protocols for the preparation of the quinoline heterocycle, such as the Combes quinoline synthesis, the Conrad-Limpach synthesis, the Doebner–Miller reaction, the Friedländer synthesis, the Skraup reaction, the Povarov reaction, Camps quinoline synthesis, the Knorr quinoline synthesis, the Gould-Jacobs reaction, the Niementowski quinoline synthesis and the Pfitzinger reaction. Including among these classic name reactions, the Friedländer annulation is a general protocol to prepare quinoline derivatives.[8] However the condensation of 2-aminobenzaldehyde with other 1,3-dicarbonyl starting materials, such as ethyl acetoacetate or dimethyl malonate, the condensation of 2-aminobenzaldehyde with nitrile derivatives, which will generate 2-aminoquinoline, (e.g., 2-phenylacetonitril,[9] 2-(benzo[d]-thiazol-2-yl)acetonitrile[10] malonodinitrile[11]) is limited due to the poor reactivity of nitrile group. For example, the condensation of 2-aminobenzaldehyde (4) with cyanoacetic acid ester (5) affords 2-hydroxy-3-cyanoquinoline (6), not the desired 2-aminoquinoline-3-carboxylic acid ester (7). As a useful starting material, ester 7 is hoped to be hydrolyzed under basic conditions followed by amine coupling to afford diversity of 2-aminoquinoline-3-carboxamides (8).[12] As a result, an alternative route uses Knoevenagel condensation of 2-nitrobenzaldeydes (9) with cyanoacetic acid methyl esters to produce acrylonitrile intermediates (10) following reduction/cyclization under different conditions, such as Pd/C/H_2, Fe/HOAc, Zn/NH_4Cl, etc., to generate 2-aminoquinoline-3-carboxylic acid ester (7) (Scheme 1).

Scheme 1. Different Synthetic Pathways to 2-Quinoline Derivatives



The direct condensation of 2-aminobenzaldehyde (4) with cyanoacetamide (11) is rarely reported,[13] and the scope and limitations are not described. On the basis of the recently described facile and convenient access to multiple cyanoacetamides as starting materials for an interesting group of multicomponent and other reactions we herein would like to report a more convenient method to prepare 2-aminoquinoline-3-carboxamides (8) from aminobenzaldehydes and cyanoacetamides.[14−18]

RESULT AND DISCUSSION

2-Aminobenzaldehydes are of limited commercial availability or they are quite expensive. In this report, starting material 2-aminoaldehydes (**4**{*1*−*8*}, Scheme 2), which are available or are conveniently in situ prepared by Fe/HCl reduction of the corresponding cheap and commercial 2-nitrobenzaldehyde (**9**{*1*−*8*}),[19] were examined.

Twenty-eight different cyanoacetamides (**11**{*1*−*28*}) starting materials are prepared from methyl cyanoacetate (**5**) and corresponding amines under neat conditions are recently reported by us (Scheme 2).[14] The structures and yields of the obtained products (**8**{*1*−*8*,*1*−*28*}) are summarized in Table 1.

All compounds precipitated while the reaction cooled down. As a result, the purification was as easy as simply collecting the solid after filtration. All products indicate excellent purity by NMR and LC-MS (Supporting Information). We were able to grow several single crystals suitable for X-ray structure determination. Figure 3 shows the identity and orientation of **8**{*7*,*24*} and **19a** in the crystalline state. It is noteworthy that the 2-aminoquinoline substructure makes extensive hydrogen bonding contacts via the amidine substructure. The phenyl substructure of the 2-aminoquinoline on the other hand makes multiple intra- and intermolecular hydrophobic contacts (Figure 4). The carbonyl oxygen of the 3-carboxamide forms a 6-membered ring involving an intramolecular hydrogen bridge in both structures.

The intramolecular hydrogen bridge in 2-aminoquinoline-3-carboxamides is an important observation as it can reduce the hydrophilic character of the compounds in a biological setting

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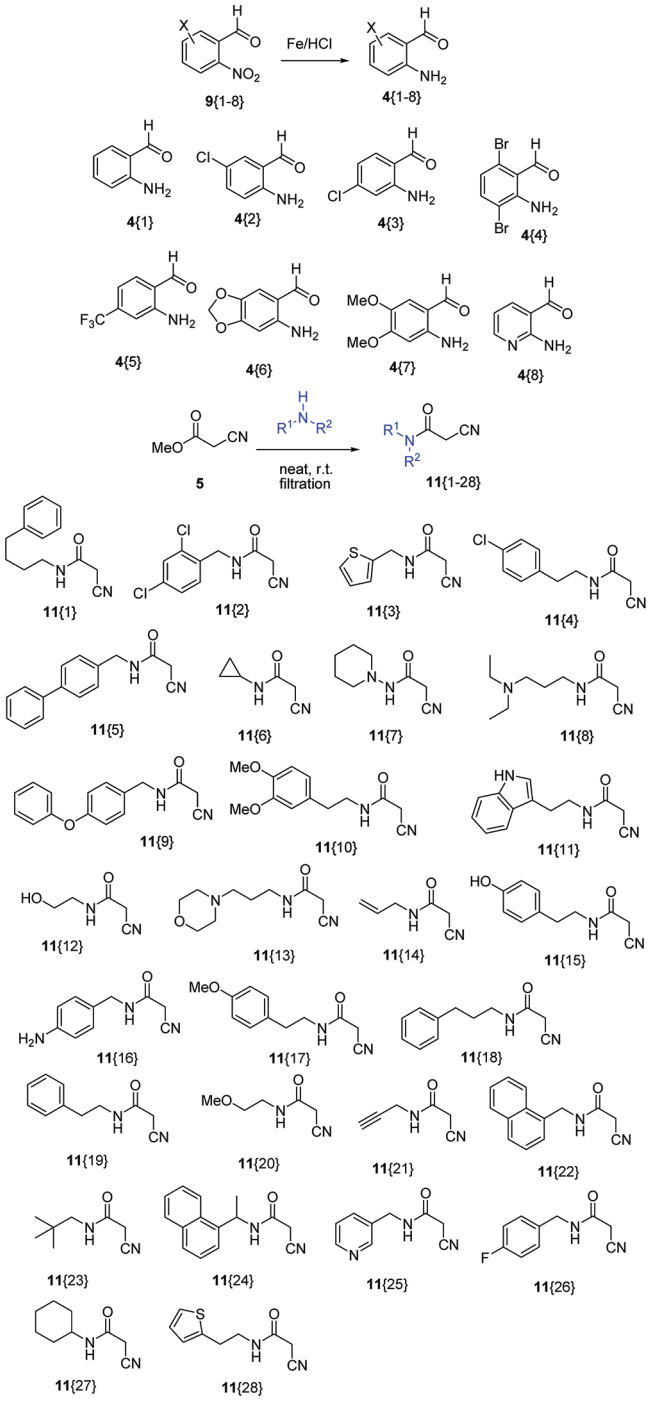
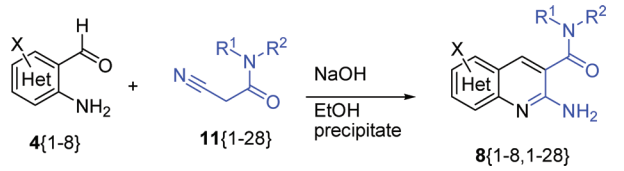
Scheme 2. Starting Materials of Reactions



and can potentially facilitate transmembrane transport. Adjacent hydrogen bond donor and acceptor moieties in a molecule can lead to the temporary formation of ring systems and open conformations with differential exposure of the polar groups to the solvent. The formation of an intramolecular hydrogen bond mediated ring should effectively remove one donor and one acceptor function from the surface of a molecule and thus result in increased lipophilicity leading to an increase of membrane permeability and a reduction of aqueous solubility. In fact multiple measurements of the passive permeability, the octanol/water partition coefficient and kinetic solubility in related systems support this hypothesis.[20] Recently

Table 1



compound	yield	compound	yield	compound	yield
8{*1,1*}	65	**8**{*1,2*}	78	**8**{*1,3*}	67
8{*1,4*}	64	**8**{*1,5*}	96	**8**{*2,6*}	88
8{*2,7*}	94	**8**{*2,8*}	76	**8**{*2,9*}	87
8{*2,10*}	86	**8**{*2,11*}	78	**8**{*2,12*}	66
8{*2,13*}	79	**8**{*2,2*}	77	**8**{*2,14*}	63
8{*2,15*}	77	**8**{*2,16*}	87	**8**{*3,17*}	75
8{*3,18*}	84	**8**{*4,19*}	98	**8**{*4,20*}	95
8{*4,22*}	97	**8**{*4,23*}	90	**8**{*5,11*}	66
8{*5,24*}	88	**8**{*6,25*}	67	**8**{*6,11*}	77
8{*6,26*}	78	**8**{*6,19*}	76	**8**{*7,11*}	87
8{*7,24*}	76	**8**{*7,13*}	67	**8**{*7,27*}	59
8{*8,11*}	76	**8**{*8,6*}	78	**8**{*8,27*}	76
8{*8,28*}	87				

we observed similar intramolecular hydrogen bridges during our synthesis of 2-aminothiophene-3-carboxamides.[16,21]

A one-pot strategy to synthesize target product from scratch from the amine using cyanoacetic acid methyl ester (**5**) and 2-aminobenzaldehyde (**4**) was also investigated (Scheme 3). For example, 2-bromobenzylamine and methyl cyanoacetate are neatly mixed together. After 1 h, 2-amino-4-chloro-benzaldehyde, NaOH and ethanol are added and heated in an oil bath. The target product (**12**) was collected with high yield (90%). The one-pot reaction was also performed with a diversity of amines and 2-aminobenzaldehydes resulting in compound library synthesis.

The condensation of 2-aminobenaldehyde with 2-cyano-*N*-(prop-2-ynyl)acetamide in the presence of sodium hydroxide generated 2-amino-*N*-(prop-1-ynyl)quinoline-3-carboxamide (**14**). However, when the similar reaction have been performed under weak basic conditions over longer time, for example, 1-methylpiperidine, the desired compounds (**8**{*4,21*} and **8**{*8,21*}) without isomerization were collected in high yield. It is interesting that the formed proparyl amide was isomized to more thermodynamic stable propynyl amide under strong basic conditions (Scheme 4).

Some other Friedländer annulations have been examined, too. Generally, the condensation of 2-aminobenzaldehyde with 2-cyanoacetone derivatives, such as 3-oxo-3-phenylpropanenitrile (**15**) under mild or strong basic conditions, resulted in the formation of 2-arylquinoline-3-carbonitrile (**16**); the ketone products (**17**) were not found (Scheme 5). However, when 2-aminonicotinaldehyde and 3-oxo-3-(2-phenyl-1*H*-indol-3-yl)-propanenitrile (**18**) have been heated in ethanol under the presence of sodium hydroxide only (2-amino-1,8-naphthyridin-3-yl)(2-phenyl-1*H*-indol-3-yl)methanone (**19a** and **19b**) was isolated in high yield (89%), [structure was confirmed by single crystal structure analysis of (Figure 3b)]. LC-MS curve did not indicate the existence of nitrile product (**20**, Scheme 5). Mechanism for the different products from similar starting materials is not clear. Further investigation of this interesting reaction is in progress.

Furthermore, we developed a convenient transformation to 3-alkylpyrimido[4,5-b]quinolin-4(3*H*)-ones (**21**) from 2-ami-

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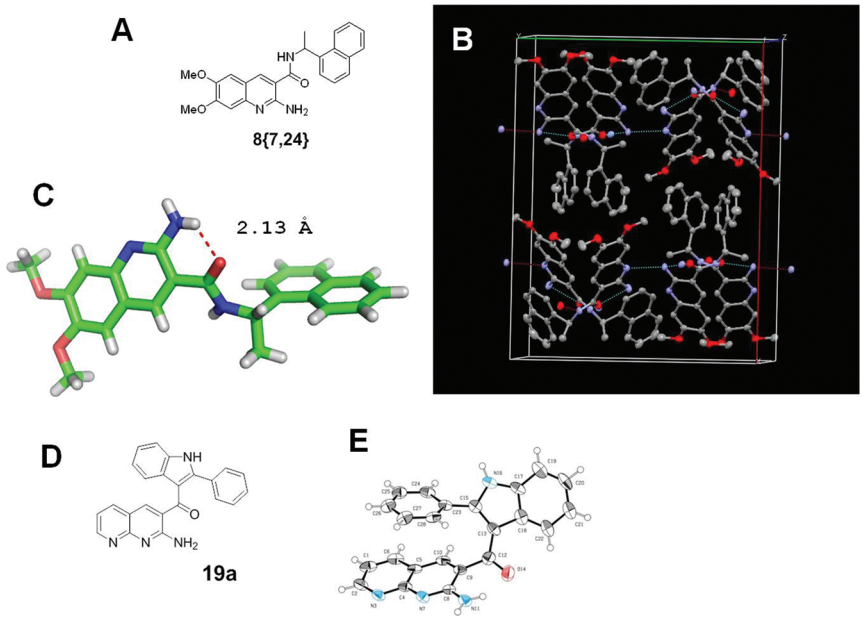

Figure 3. Crystal structures. A: Structure of **8**{*7,24*}. B: Unit cell of **8**{*7,24*} showing the inter- and intermolecular hydrogen contacts (Mercury software). The amidine moiety is forming a bifurcated hydrogen bridge to a neighbor amidine (red dotted lines). The amide carbonyl is forming an intermolecular hydrogen bridge to the adjacent amidine-NH_2 thus forming a 6-membered ring (green dotted lines). Additionally the phenyl groups form multiple staggered and T-shaped contacts with distances around 3.7 Å. C: Stick model of **8**{*7,24*} showing the 6-membered ring featuring an intermolecular hydrogen bridge of 2.13 Å. D: Structure of **19a**. E: ORTEP drawing of **19a** (ORTEP drawing with 50% ellipsoids).

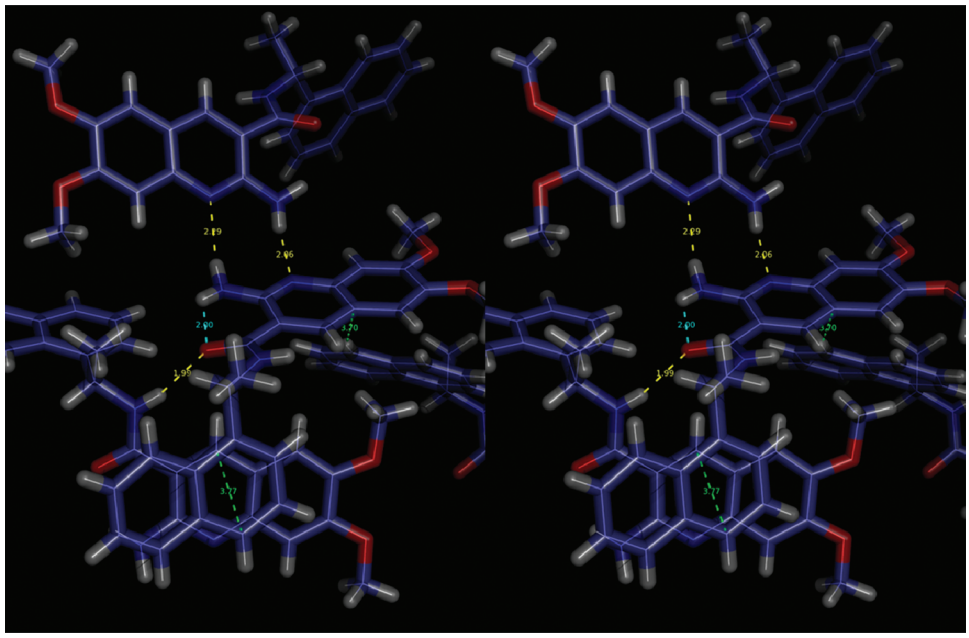

Figure 4. Key short contacts of **8**{*7,24*} in the crystal rendered with Pymol in a stereo picture. Intermolecular contacts between two amidine moieties are 2.1 and 2.3 Å (yellow dotted lines). The intramolecular hydrogen bridge between the amide carbonyl and the amidine-NH_2 is 2 Å (cyan dotted lines). A intermolecular hydrogen bridge between the amide NH and the amide carbonyl is 1.95 Å short (yellow dotted line). Several short phenyl phenyl contacts (~3.7 Å) are shown as green dotted lines.

noquinoline-3-carboxamides (**8**). 1,1-Dimethoxy-*N*,*N*-dimethylmethanamine (DMFDMA) was added to **8** under neat conditions and the reaction was allowed to stir for 10 min in 110 °C. The reaction was cooled down to room temperature and some EtOH was added. The formed precipitate was filtered and washed with EtOH to directly offer purified **21**. However, this reaction is sensitive to the amide side chain. In some cases, when the side chain is large, for example, 2,2-dimethylpropyl (**22**{*4,23*}), 1-(naphthalen-1-yl)ethyl (**22**{*5,24*}), or cyclohexyl (**22**{*7,27*}), no desired compound **21**, but dimethylamino intermediate **22** was collected with high yields as a precipitate. The structures and yields of the obtained products (**21**{*1*−*8,1*−*28*} or **22**{*1*−*8,1*−*28*}) are summarized in Table 2.

It is not surprisingly that free amino in **8**{*2,16*} will condensed with DMFDMA to afford compound **23** (eq 1).

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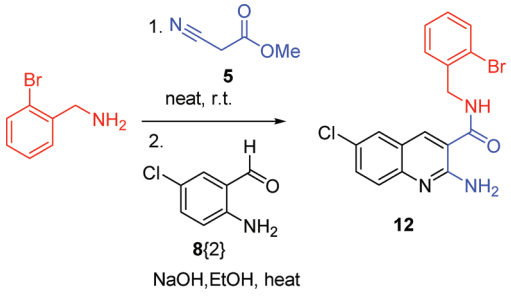
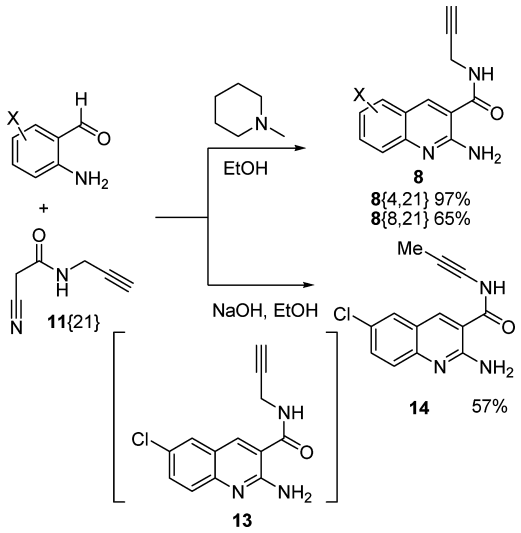
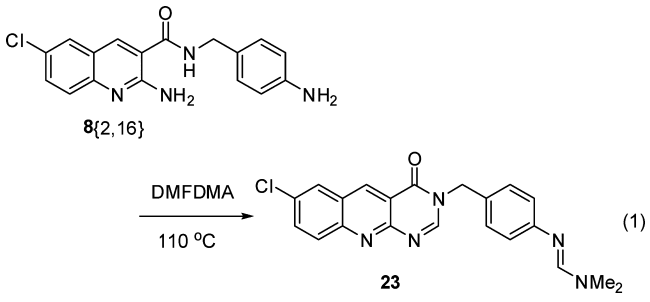
Scheme 3. One-Pot Three-Component 2-Aminoquinoline-3-carboxamide Synthesis



Scheme 4. Isomerization of Proparyl Amide under Strong Basic Conditions



In summary, we have developed a highly versatile, high yielding and easy to perform one-pot synthesis of highly substituted 2-aminoquinolines and heterocyclic derivatives. Key features include broadly available stating materials, convenient product separation and purification by precipitation and diverse product structures. Our procedure will be of general use due to the privileged structure character of the 2-aminoquinoline.



EXPERIMENTAL SECTION

General Procedure for Preparing 2-Amino-6-chloro-*N*-cyclopropylquinoline-3-carboxamide (8{*2,6*}). 2-Amino-5-chlorobenzaldehyde (155 mg, 1 mmol), 2-cyano-*N*-cyclopropylacetamide (124 mg, 1 mmol), NaOH (17.2 mg, 0.2 mmol), and ethanol (2 mL) were added into a 20 mL vial. Then, it was heated in the 70 °C oil bath with stirring for 10 min. Then, it was cooled it down to 0 °C. The precipitate was filtered and washed with cold ethanol. The title product (230 mg, 88%) was obtained as a yellow solid. HRMS ESL-TOF for $C_{13}H_{12}ClN_3O$ (M^+) Found: m/z 261.0663; Calcd Mass 261.0669. ^{1}H NMR (d_6-DMSO, 600 MHz): 8.77 (s, 1H), 8.27 (s, 1H), 7.75 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.12 (s, 2H), 2.85−2.87 (m, 1H), 0.71−0.73 (m, 2H), 0.59−0.61 (m, 2H) ppm. ^{13}C NMR (d_6-DMSO, 150 MHz): 168.8, 156.8, 147.5, 137.1, 131.6, 127.4, 127.3, 126.0, 122.9, 116.6, 23.5, 19.0 ppm.

General Procedure of Preparing 7-Chloro-3-cyclopropylpyrimido[4,5-b]quinolin-4(3*H*)-one (21{*2,6*}). 1,1-Dimethoxy-*N*,*N*-dimethylmethanamine (DMFDMA, 0.5 mL) was added into 2-amino-3-carboxamide (0.2 mmol), and the reaction mixture was stirred for 10 min in 110 °C. The reaction mixture was cooled down to room temperature and 1 mL EtOH was added. The precipitate was filtered and washed

Scheme 5. Difference Products from Similar Starting Materials

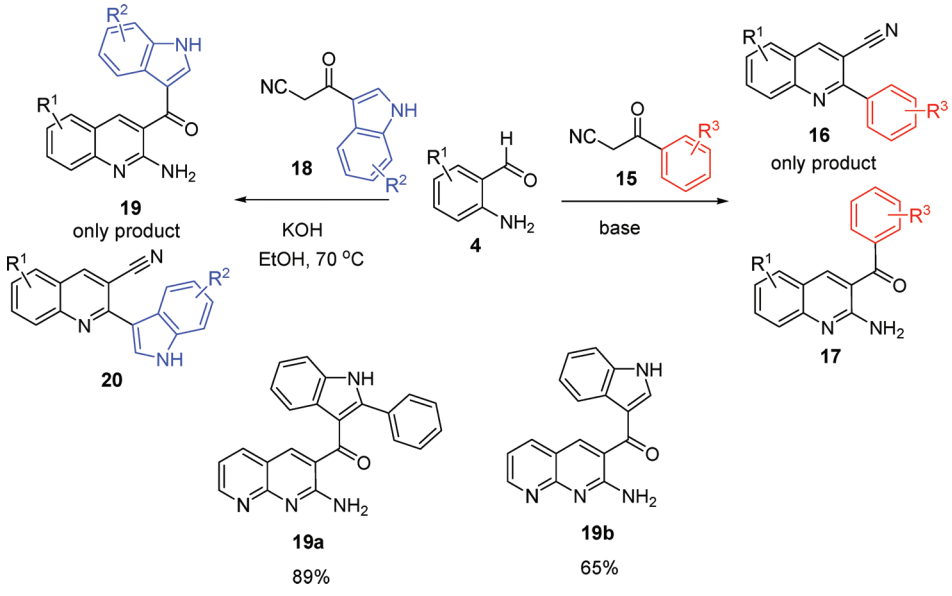


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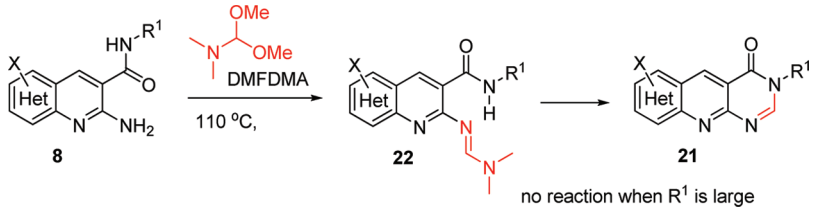
Table 2



compound	yield	compound	yield	compound	yield
21{*1,2*}	76	**21**{*1,4*}	65	**21**{*1,5*}	86
21{*2,2*}	67	**21**{*2,6*}	57	**21**{*2,7*}	82
21{*2,9*}	76	**21**{*2,10*}	53	**21**{*2,11*}	58
21{*2,13*}	48	**21**{*2,14*}	56	**21**{*2,5*}	56
21{*3,17*}	78	**21**{*6,19*}	65	**21**{*6,25*}	49
21{*6,26*}	58	**21**{*8,11*}	64	**21**{*8,28*}	46
22{*4,23*}	65	**22**{*5,24*}	72	**22**{*7,27*}	77

with another 1 mL of EtOH. HRMS ESL-TOF for $C_{14}H_{10}ClN_3O$ (M^+) found: *m/z* 270.0516; Calcd Mass 271.0512; ^{1}H NMR (d_6-DMSO, 600 MHz): 9.24 (s, 1H), 8.48 (s, 1H), 8.26 (s, 1H), 8.07 (d, *J* = 9.0 Hz, 1H), 7.81 (d, *J* = 9.0 Hz, 1H), 2.51 (s, 1H), 1.13 (s, 2H), 1.00 (s, 2H) ppm. ^{13}C NMR (d_6-DMSO, 150 MHz): 162.3, 155.8, 152.1, 149.4, 138.3, 133.7, 131.9, 130.9, 128.0, 127.3, 116.9, 29.5, 6.5 ppm.

■ ASSOCIATED CONTENT

Supporting Information

Proton and carbon NMR, HR MS characterization, and experimental procedures.This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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