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

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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 the greatly expanding the scaffold space of cyanoacetamide derivatives.

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} beta-secretase (BACE) inhibitor,³ melanin-concentrating hormone (MCH) antagonist⁴ et. al. (Figure 1) have been studied and developed.

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. (Fig. 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 co-crystal 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 co-crystal 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 co-crystal

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Supporting information **available**: Proton and carbon NMR, HR MS characterization and experimental procedures.

structures. Intriguingly, all the structures show the two main interactions of 2-aminoquinoline 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 towards their protein targets. This taken together with their other favorable properties such as cLog P = 1.7, tPSA = 38.4 and Mw = 144 Dalton, might explain the privileged structure character of the 2-aminoquinoline.

There are many classic name synthetic protocols for the preparation of the quinoline heterocycle, such as the Combes quinoline synthesis, the Conrad-Limpach synthesis, the Doebner-Miller reaction, the Friedlander 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 amongst 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-phenylacetone nitrile,⁹ 2-(benzo[d]thiazol-2-yl)acetone nitrile¹⁰ malonodinitrile¹¹) 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-nitrobenzaldehydes (**9**) with cyanoacetic acid methyl esters to produce acrylonitrile intermediates (**10**) following reduction/cyclization under different conditions, such as Pd/C/H₂, Fe/HOAc, Zn/NH₄Cl et. al. to generate 2-aminoquinoline-3-carboxylic acid ester (**7**) (Scheme 1).

The direct condensation of 2-aminobenzaldehyde (**4**) with cyanoacetamide (**11**) is rarely reported¹³ and the scope and limitations are not described. Based on 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 very 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 (supplementary material). 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 (Fig. 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 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 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 will also be performed with diversity of amines and 2-aminobenzaldehydes resulting in compound library synthesis.

The condensation of 2-aminobenzaldehyde 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, e.g. 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 propargyl amide was isomerized 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 6). However, when 2-aminonicotinaldehyde and 3-oxo-3-(2-phenyl-1H-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-1H-indol-3-yl)methanone (**19a** and **19b**) was isolated in high yield (89%), [structure was confirmed by ORTEP of single crystals (Fig. 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(3H)-ones (**21**) from 2-aminoquinoline-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, e.g. 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).

(1)

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 starting 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})

Into a 20 ml vial added 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. Heat it in the 70 °C oil bath with stirring 10 min. Cool it down to 0 °C. Filter the precipitate following 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; Calc. Mass 261.0669; 1H 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(3H)-one (**21**{2,6})

Added 0.5 ml 1,1-dimethoxy-N,N-dimethylmethanamine (DMFDMA) into 2-amino-3-carboxamide (0.2 mmol) and the reaction was allowed to stir 10 min in 110°C. The reaction was cooled down to room temperature and 1 ml EtOH was added. Filter the precipitate and washed with another 1 ml EtOH. HRMS ESL-TOF for $C_{14}H_{10}ClN_3O$ (M^+) found: m/z : 270.0516; Calc. Mass: 271.0512; 1H 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

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) co-crystallized in BACE1 (surface and stick representation). Only key amino acids important for the hereindiscussion are shown in stick representation. Hydrogen bonds are indicated by red dotted lines.

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-NH2 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-NH₂ 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.

Scheme 1. Different synthetic pathways to 2-quinoline derivatives

Scheme 2.
Starting materials of reactions.

Scheme 3. One-pot three-component 2-aminoquinoline-3-carboxamide synthesis

Scheme 4. Isomerization of propargyl amide under strong basic conditions

Scheme 5.
Difference products from similar starting materials.

Table 1

Compound	yield	Compound	yield
8{1,1}	65	8{1,2}	78
8{1,4}	64	8{1,5}	96
8{2,7}	94	8{2,8}	76
8{2,10}	86	8{2,11}	78
8{2,13}	79	8{2,2}	77
8{2,15}	77	8{2,16}	87
8{3,18}	84	8{4,19}	98
8{4,22}	97	8{4,23}	90
8{5,24}	88	8{6,25}	67
8{6,26}	78	8{6,19}	76
8{7,24}	76	8{7,13}	67
8{8,11}	76	8{8,6}	78
8{8,28}	87		

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