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3-Hydroxyquinolin-2(1*H*)-ones As Inhibitors of Influenza A Endonuclease

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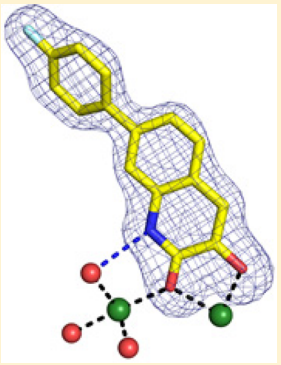
Supporting Information

ABSTRACT: Several 3-hydroxyquinolin-2(1*H*)-ones derivatives were synthesized and evaluated as inhibitors of 2009 pandemic H1N1 influenza A endonuclease. All five of the monobrominated 3-hydroxyquinolin(1*H*)-2-ones derivatives were synthesized. Suzuki-coupling of *p*-fluorophenylboronic acid with each of these brominated derivatives provided the respective *p*-fluorophenyl 3-hydroxyquinolin(1*H*)-2-ones. In addition to 3-hydroxyquinolin-2(1*H*)-one, its 4-methyl, 4-phenyl, 4-methyl-7-(*p*-fluorophenyl), and 4-phenyl-7-(*p*-fluorophenyl) derivatives were also synthesized. Comparative studies on their relative activity revealed that both 6- and 7-(*p*-fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one are among the more potent inhibitors of H1N1 influenza A endonuclease. An X-ray crystal structure of 7-(*p*-fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one complexed to the influenza endonuclease revealed that this molecule chelates to two metal ions at the active site of the enzyme.



KEYWORDS: *antiviral, influenza A, quinolinones, 3-hydroxyquinolin-2-ones, endonuclease*

Antiviral agents are used for both prophylactic and therapeutic treatments of influenza infection. The antiviral agents in clinical use against influenza infection target the M2 ion-channel protein (adamantanes) and neuraminidase (zanamivir and oseltamivir). The adamantane drugs, amantadine and rimantadine, are ineffective due to emergence of resistance (predominantly through a M2 mutation, S31N) that limit their clinical use. The neuraminidase (NA)-inhibiting oral drug, oseltamivir (Tamiflu) is widely used for treating flu. Oseltamivir-resistant seasonal influenza A strains have been circulating for several years.[1] The mutant viruses predominantly contain the NA H274Y mutation. When accompanied by compensatory mutations, the mutant viruses exhibit fitness comparable to wild-type influenza A and remain resistant to oseltamivir.[2] These mutations can emerge in almost all influenza A subtypes/strains, including the pandemic 2009 H1N1 virus, resulting in a major concern for an effective treatment of flu.[3] Therefore, new drugs are essential for treating drug-resistant and future pandemic flu strains.

Influenza A contains eight negative-stranded RNA genomic segments. The three largest genomic RNA segments encode the viral RNA-dependent RNA polymerase (RdRP) proteins consisting of the polymerase acidic protein (PA) and polymerase basic protein 1 (PB1) and 2 (PB2) subunits. The PA subunit (i) has endonuclease activity, (ii) is involved in viral RNA (vRNA)/complementary RNA (cRNA) promoter binding, and (iii) interacts with the PB1 subunit.[4] PA has two domains, PA_N (~25 kDa N-terminal domain; residues 1−197) and PA_C (~55 kDa C-terminal domain; residues 239−716). Crystal structures of PA_C have been determined in complexes with N-terminal fragments of PB1.[5] The structure of PA_N has been solved in several crystal forms both unliganded and with various ligands.[6−8]

The RdRP of influenza A is responsible for the replication and transcription of the viral RNA genes. Viral mRNA transcription involves a cap-snatching mechanism in which the polymerase binds to cellular mRNA via the 5′-cap and cleaves the mRNA 12−13 nucleotides downstream. The cleaved RNA fragment containing the 5′ cap acts as a primer for viral mRNA synthesis.[9] Cap-snatching is an important event in the life cycle of all members of the Orthomyxoviridae family including influenza A, B, and C viruses, and the host cell has no analogous activity. Inhibitors of cap-snatching have the potential to selectively act against all influenza subtypes and strains, including oseltamivir-resistant influenza A viruses without interfering with host cell activities.

Several small molecules have been identified that have the ability to inhibit viral endonuclease. These include 2,4-dioxobutanoic acid derivatives,[8−11] 5-hydroxy-1,6-dihydropyrimidine-4-carboxylic acid derivatives,[9] flutimide and its

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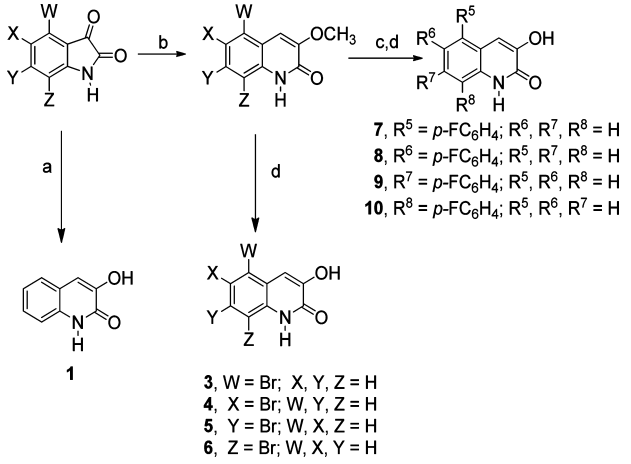
derivatives,[8,11−13] and tetramic acid derivatives.[14] As correctly hypothesized, the endonuclease activity of influenza polymerase belongs to the two metal ion group of phosphate-processing enzymes.[14] Fragment screening of influenza A endonuclease enzyme using X-ray crystallography, performed using similar methods as we previously reported,[15] identified the compound 5-chloro-3-hydroxypyridin-2(1*H*)-one as a bimetal chelating ligand at the active site of the enzyme. Using this information, we developed a 3-hydroxyquinolin-2(1*H*)-ones series. Here we describe the synthesis and structure−activity relationships associated with various 3-hydroxyquinolin-2(1*H*)-ones with regard to their ability to inhibit the endonuclease activity as measured by a high-throughput fluorescence assay.

3-Hydroxyquinolin(1*H*)-2-one, **1**, was prepared as outlined in Scheme 1 by ring expansion of isatin with (TMS)-

Scheme 1. Synthesis of 3-Hydroxyquinolin-2(1*H*)-one, 5-, 6-, 7-, and 8-Bromo 3-Hydroxyquinolin-2(1*H*)-ones, and 5-, 6-, 7-, and 8-(*p*-Fluorophenyl) 3-Hydroxyquinolin-2(1*H*)-ones[a]

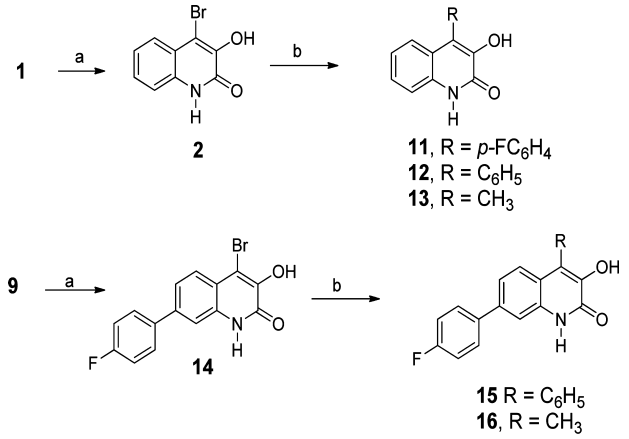


[a]Reagents and conditions: (a) $TMSCHN_2$ (1.0 mol equiv), EtOH, TEA under Ar; (b) $TMSCHN_2$ (2.0 mol equiv), EtOH, TEA under Ar; (c) *p*-fluorophenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, dioxane/H_2O (2:1); (d) BBr_3 in CH_2Cl_2, 0° to r.t.

diazomethane, followed by treatment of the resulting 3-methoxyquinolin-2(1*H*)-one with BBr_3 as previously described.[16] Employing this methodology, several bromo 3-hydroxyquinolin(1*H*)-2-one derivatives, **3**−**6**, were prepared using the appropriately substituted bromo isatin and with (TMS)diazomethane. As illustrated in Scheme 1, treatment of the 5-, 6-, 7-, and 8-bromo-3-methoxyquinolin-2(1*H*)-one intermediates with excess BBr_3 in dichloromethane provided **3**−**6** (Scheme 1). Suzuki-coupling of each of the brominated 3-methoxyquinolin-2-(1*H*)-ones with *p*-fluorophenylboronic acid as outlined in Scheme 1 provided the *p*-fluorophenyl derivatives **7**−**10**. 4-Phenyl-3-hydroxyquinolin-2(1*H*)-one, **12**, and 4-methyl-3-hydroxyquinolin-2(1*H*)-one, **13**, have been previously synthesized.[16,17] In this study, we synthesized 4-bromo-3-hydroxyquinolin-2(1*H*)-one, **2**, from **1** as previously described.[18] and used this as an intermediated for the preparation of the 4-substituted 3-hydroxyquinolin-2(1*H*)-ones, **11**−**13**.

Treatment of **2** with *p*-fluorophenylboronic acid as illustrated in Scheme 2 provided 4-(*p*-fluorophenyl)-3-hydroxy-quinolin-2(1*H*)-one, **11**. Under similar reaction conditions, treatment of **2** with either phenylboronic acid or trimethylboroxine provided

Scheme 2. Formation of Compounds 2 and 14 and Use in Suzuki-Coupling Reactions[a]



[a]Reagents and conditions: (a) NBS, DMF, under Ar; (b) phenylboronic acid (for **12** and **15**), $Pd(PPh_3)_4$, Na_2CO_3, dioxane/H_2O (2:1), trimethylboroxine (for **13** and **16**), TMSCl, NEt_3; $Pd(PPh_3)_4$, Na_2CO_3, dioxane/H_2O (2:1).

4-phenyl-3-hydroxyquinolin-2(1*H*)-one, **12**, and 4-methyl-3-hydroxyquinolin-2(1*H*)-one, **13**, respectively.

Treatment of **9** with *N*-bromosuccinimide in DMF gave exclusively the 4-bromo derivative, **14** (Scheme 2), which underwent Suzuki-coupling with either phenylboronic acid or trimethylboroxine to yield 4-phenyl-7-(*p*-fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one, **15**, or 4-methyl-7-(*p*-fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one, **16**, respectively.

Each of these 3-hydroxyquinolin-2-(1*H*)ones were evaluated as inhibitors of influenza A endonuclease. A high-throughput 96-well plate based assay, similar to those developed by Kowalinski et al.[19] as well as Noble et al.,[20] was used to demonstrate the inhibition of endonuclease cleavage by PA_N. A TaqMan-like oligonucleotide contains a 6-carboxy-fluorescein (FAM) fluorophore at the 5′-end followed by 19 nucleotides and a minor groove binding nonfluorescent quencher (MGBNFQ, Applied Biosystems) at the 3′-end (Figure 1).

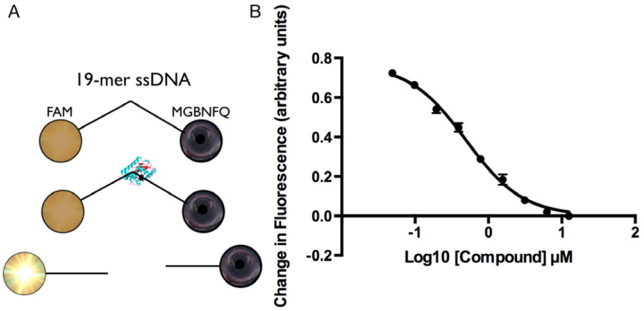


Figure 1. (A) Diagram showing the cleavage of nucleic acid probe by PAN. After cleavage the FAM fluorophore fluoresces when excited by light with a wavelength of 488 nm. (B) Change in fluorescence after 1 h measured for compound **9** during a titration, IC_{50} of 0.5 μM.

When excited, MGBNFQ quenches the fluorescence of FAM via fluorescence resonance energy transfer. Upon cleavage of the oligonucleotide, the quencher is no longer coupled to the fluorophore, and therefore, FAM fluoresces. The *Z*′ score for this assay as described in the Supporting Information was a very

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acceptable 0.87. This assay was used to determine the inhibitory activity of the compounds.

The results of these assays are summarized in Table 1. These data indicate that the presence of a *p*-fluorophenyl substitutent

Table 1. Inhibition Assay of Influenza A Endonuclease

	compound	IC_{50} (μM)
1	3-OH-quinolin-2-one (3HQ)	24
2	4-Br-(3HQ)	53
3	5-Br-(3HQ)	12
4	6-Br-(3HQ)	7.4
5	7-Br-(3HQ)	7.6
6	8-Br-(3HQ)	11
7	5-(*p*-FC_6H_4)-(3HQ)	3.3
8	6-(*p*-FC_6H_4)-(3HQ)	0.5
9	7-(*p*-FC_6H_4)-(3HQ)	0.5
10	8-(*p*-FC_6H_4)-(3HQ)	4.7
11	4-(*p*-FC_6H_4)-(3HQ)	11
12	4-C_6H_5-(3HQ)	>20
13	4-CH_3-(3HQ)	>100
14	4-Br-7-(*p*-FC_6H_4)-(3HQ)	1.1
15	4-Phenyl-7-(*p*-FC_6H_4)-(3HQ)	2.0
16	4-CH_3-7-(*p*-FC_6H_4)-(3HQ)	13

at either the 6- or 7-position of 3-hydroxyquinolin-2(1*H*)-one is associated with a significant enhancement in enzyme inhibition relative to other positional isomers, as well as the unsubstituted parent compound, **1**.

Substitution at the 4- and 8-positions was frequently associated with reduced activity. Among the bromo-substituted 3-hydroxyquinolin-2(1*H*)-ones, the 6- and 7-positional isomers were the more active. A similar trend was observed for the *p*-fluorophenyl substituted 3-hydroxyquinolin-2(1*H*)-ones. The presence of either a 4-methyl or a 4-phenyl substituent attached to 3-hydroxyquinolin-2(1*H*)-one did not enhance enzyme inhibition relative to the unsubstituted derivative. In the case of 7-(*p*-fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one, the presence of either a 4-methyl or 4-phenyl substituent was detrimental to its ability to inhibit endonuclease activity.

The X-ray crystal structure of influenza A endonuclease with **9** was obtained by soaking unliganded endonuclease crystals with 10 mM **9** (Figure 2). The crystal structure clearly shows **9** chelating to the two active site metals. Additionally, the core scaffold is coordinated by a hydrogen bond between the hydroxyl at the 3-position and the ε nitrogen of Lys134. The protonated nitrogen of the core scaffold also coordinates to a water molecule chelating to Mn2. Importantly, unlike what has been determined for known endonuclease inhibitors, the ring system binds at 50° tilt toward His41.[9,19] The binding angle increases $\pi-\pi$ stacking interactions with His41 and allows for development of additional interactions as the molecule is extended into the surrounding pockets. The 7-*p*-fluorophenyl extends the molecule into a pocket formed by Ala20, Met21, Tyr24, Asp26, Lys34, and Ile38. A hydrophobic network is formed between the fluorophenyl and Ala20, Tyr24, and Ile38.

These data are consistent with the structure−activity data associated with the inhibition of influenza A endonuclease. The data indicate that these compounds bind through bimetal chelation at the active site. The presence of substituents at either the 4- or 8-position could interfere with the establishment of a favorable interaction with these two metals. Several 3-hydroquinolin-2(1*H*)ones were reported as inhibitors of D-

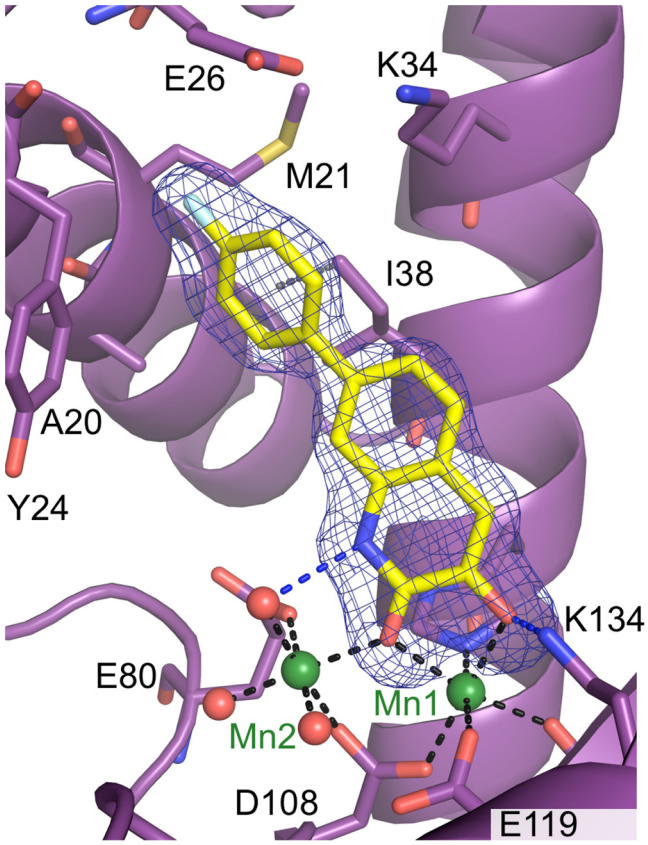

Figure 2. Binding of **9** at the endonuclease active site. Ligand is shown in yellow, while the receptor is purple. Chelation is depicted as black dashes, hydrogen bonds are depicted as blue dashes, and strong hydrophobic interactions are gray dashes. The blue mesh around the ligand is calculated from a 4.5σ omit map. The figure was generated using PyMol (www.pymol.org). PDB code: 4KIL.

amino acid oxidase (DAAO).[16] As the binding modes for DAAO inhibitors do not involve metal chelation, it is not surprising that the structure−activity relationships for DAAO inhibition is unique.

A series of 3-hydroxyquinolin-2-(1*H*)-ones was also recently reported as selective inhibitors of HIV-1 reverse transcriptase associated RNase H activity.[21] This series of compounds consisted of 4-carboxylic acids, 4-ethylcarboxylates, and 4-carboxamides. The formation of magnesium chelation was examined in this study. The authors noted that the ability of their three oxygen pharmacophore to chelate both metal cofactors within the active site of the enzyme was consistent with their results. The *N*-hexylamide and various *N*-benzylamides were among the more active compounds. The authors reported that, with these 4-substituted 3-hydroxyquinolin-2(1*H*)-ones, significant cytotoxicity was observed in cell culture. In light of these results, we did evaluate the relative cytotoxic activity of **3**−**6** toward Madin−Darby canine kidney (MDCK) cells and human embryonic kidney 293 (HEK 293) cells using the MTT-microtiter plate tetrazolium cytotoxicity assay. The assays were performed as previously described.[22] The IC_{50} values for all of these compounds were >10 μM, which was the highest concentration tested.

The results suggest that 6- and 7-substituted 3-hydroxyquinolin-2(1*H*)-ones could provide a useful scaffold for the development of endonuclease inhibitors that could block the cap snatching associated with influenza A replication. Studies

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are in progress to design and discover more potent endonuclease inhibitors using soakable endonuclease crystals with varied 6- and 7- substituted 3-hydroxyquinolin-(1*H*)-ones.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic methods and spectral characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors J.D.B., K.D., E.A., and E.J.L. are cofounders of Prodaptics Pharmaceuticals, Inc., which has licensed the technology associated with these compounds from Rutgers University

The authors declare the following competing financial interest(s): Dr. Joseph Bauman, Dr. Kalayan Das, Dr. Eddy Arnold, and Dr. Edmond LaVoie are co-founders of Prodaptics Pharmaceuticals, Inc. Using a soakable crystal developed at CABM, we are working on developing small molecule inhibitors of influenza endonuclease A. Successful development of a clinically useful agent would be of financial benefit to the founders.

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