Bioorganic & Medicinal Chemistry Letters 27 (2017) 4601–4605

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of potent antiviral (HSV-1) quinazolinones and initial structure-activity relationship studies

Carla E. Brown [a], Tiffany Kong [a], James McNulty [a,*], Leonardo D'Aiuto [b], Kelly Williamson [b], Lora McClain [b], Paolo Piazza [b], Vishwajit L. Nimgaonkar [b,*]

[a] Department of Chemistry & Chemical Biology, McMaster University, Hamilton, Ontario L8S 4M1, Canada
[b] Department of Psychiatry, WPIC, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA

ARTICLE INFO

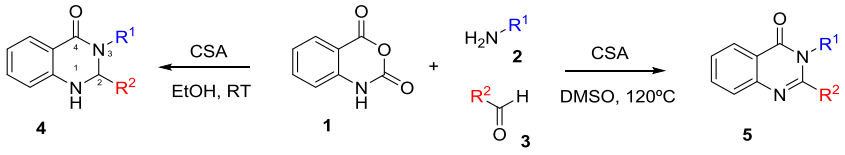
Article history:
Received 4 August 2017
Revised 11 September 2017
Accepted 12 September 2017
Available online 14 September 2017

Keywords:
Quinazolinone
Multi component coupling
Antiviral
HSV-1
Herpesvirus

ABSTRACT

The discovery of antiviral activity of 2,3-disubstituted quinazolinones, prepared by a one-pot, three-component condensation of isatoic anhydride with amines and aldehydes, against Herpes Simplex Virus (HSV)-1 is reported. Sequential iterative synthesis/antiviral assessment allowed structure-activity relationship (SAR) generation revealing synergistic structural features required for potent anti-HSV-1 activity. The most potent derivatives show greater efficacy than acyclovir against acute HSV-1 infections in neurons and minimal toxicity to the host.

Herpes Simplex Virus 1 (HSV-1), a virus belonging to the family herpesviridae and a common human pathogen,[1] affects approximately 67% of the global population and is causing increasing concern for neonatal and immunocompromised patients.[2] HSV-1 displays both lytic and latent forms of infection in humans.[3] Recently, HSV-1 infection has been associated with cognitive impairment among persons with schizophrenia[4,5] and even persons without psychiatric illnesses.[6,7] Lytic HSV-1 infections are characterized by active viral replication causing substantial morbidity through recurrent cold sores, gingivostomatitis, and corneal infections that can culminate in blindness through stromal keratitis. While HSV-1 encephalitis is rare, the incidence of neonatal encephalitis is rising and survivors suffer from severe cognitive deficits. In the latency phase, the viral genome persists in neurons, only a handful of loci are transcribed. Latent infections can be reactivated by systemic or localized stress and is uncontrollable and unpredictable.[8] During latency, viral gene repression is controlled by host-cell epigenetic regulation, specifically by binding of deacetylated histones to viral DNA, and reactivation of latent infections involves histone acetylation.[9,10] Reactivation of latent infections can be induced by treatment of histone deacetylase inhibitors.[11,12] HSV-1 is currently treated with nucleoside analogs such as acyclovir (ACV), but these drugs do not affect latent infection.[1] Additionally, resistance to ACV is increasing, particularly in



Scheme 1. The dichotomous solvent and temperature-dependent Bronsted acid catalyzed three component coupling of isatoic anhydride **1**, amines **2** and aldehydes **3** to yield dihydroquinazolinones **4** and quinazolinones **5**.

* Corresponding authors.
E-mail addresses: jmcnult@mcmaster.ca (J. McNulty), vishwajitNL@upmc.edu (V. L. Nimgaonkar).

http://dx.doi.org/10.1016/j.bmcl.2017.09.026
0960-894X/

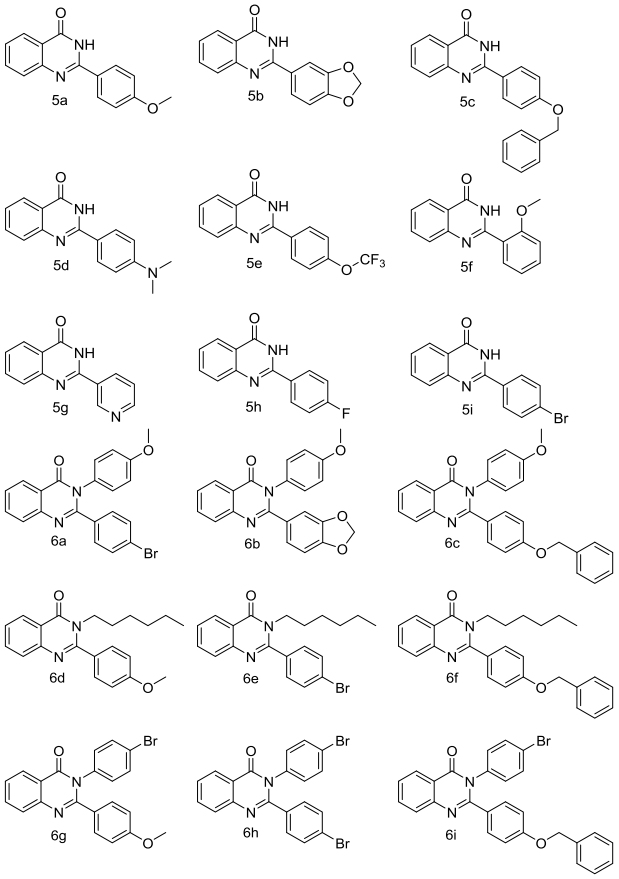
immunocompromised patients who receive treatment for extended periods. There is a need to discover structurally novel compounds (i.e. non-nucleoside based) and/or mechanisms for treating lytic HSV-1 and reactivation.[13]

The quinazolinone core is found within both natural products and in pharmaceuticals, representing a privileged scaffold given the range of activity (antimicrobial,[14] antitubercular,[15] and anticancer activity[16]) noted for certain constituents. A number of quinazolinones have been identified as antiviral agents with activity against influenza,[17] HIV,[18] and TMV.[19] Quinazolinone analogs are also known to affect epigenetic regulation through inhibition of bromodomains (BET).[20] On the basis of these data, we hypothesized that quinazolinones may exhibit novel activity against HSV-1 and recently reported a comparative HSV-1 drug screening assay that demonstrated preliminary antiviral activity of quinazolinones.[21] In this Letter, we describe the synthesis of dihydroquinazolinones **4** and quinazolinones **5** via a three-component coupling of isatoic anhydride **1**, amines **2** and aldehydes **3** (Scheme 1), optimizing this new potent antiviral HSV-1 pharmacophore through successive rounds of SAR.[21]

While the synthesis of quinazolinones has been reported through various methods, we were attracted to reports describing the condensation of *o*-aminobenzamides and carbonyl compounds.[22–30] These have been conducted under a variety of conditions including the use of Bronstead acid,[22,23] Lewis acid,[24] and other catalysts.[25,26] Aldehydes and ketones are common substrates, however diketones,[27] ß-ketoesters,[22] and alcohols[28] have also been incorporated. These reactions often require the prior preparation of the substituted *o*-aminobenzamide, thus involving at least two synthetic steps. In addition, to generate quinazolinones **5** from dihydroquinazolinones **4**, additional oxidants are sometimes employed.[28,29] Multicomponent approaches to quinazolinone synthesis have also been reported in the literature.[30] We initiated the present work directed toward development of a one-pot, three-component-coupling to quinazolinones (Scheme 1) following a recent report of such a process from isatoic anhydride, primary amines and aldehydes using catalytic iodine.[24] In our hands, following this procedure, the direct condensation of isatoic anhydride **1** with an amine **2** and aldehyde **3** was found to proceed readily in alcoholic solvents such as EtOH, however we found that incomplete oxidation yielded intractable mixtures of dihydroquinazolinone **4** and quinazolinone **5** products. A catalyst-free method employing urea and thiourea as ammonia equivalents has also been reported,[31] however under these conditions, no cyclization products were obtained.

Further experimentation with various catalysts, solvents and temperatures resulted in the discovery of distinct reaction conditions leading exclusively to either dihydroquinazolinone **4** or quinazolinone product **5**, separately through one-pot processes. The reaction of isatoic anhydride, NH_4OAc or an amine, and aldehydes or ketones using a catalytic amount of the mild Bronsted acid camphor sulfonic acid (CSA) (Scheme 1) conducted in ethanol at room temperature led to dihydroquinazolinone **4** products in 39–88% isolated yield. In all cases, the product precipitated from the reaction mixture and could be purified simply by washing with ethanol. The dihydroquinazolinones proved to be devoid of antiviral activity in all cases and were not further pursued in the present investigation.

In contrast, when the same reaction was performed in dimethyl sulfoxide (DMSO) at 110 °C in air with a catalytic amount of CSA, aromatic quinazolinone products **5** were isolated exclusively. The 2-substituted quinazolinones so prepared precipitated as described for the dihydroquinazolinones leading to a first generation of derivatives **5a**–**5i**, Fig. 1 (top). A second generation of 2,3-disubstituted quinazolinones **6a**–**6i**, Fig. 1 (centre) was similarly accessed from anilines or amines in isolated yields of 27–83%.



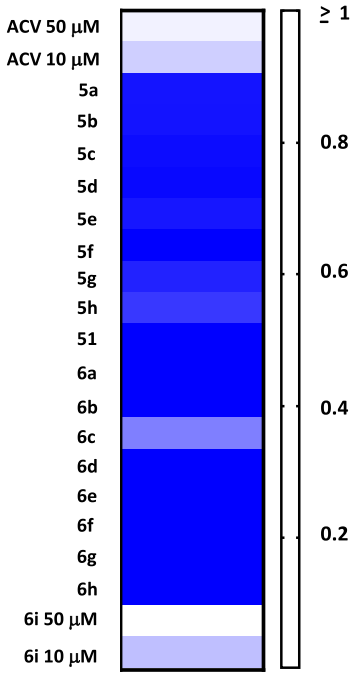


Fig. 1. Analysis of 2- and 2,3-disubstituted quinazolinones and their antiviral activity. *Top panel:* Structures of 2- and 2,3-disubstituted quinazolinones. *Bottom panel.* Heat map of quinazolinones antiviral activity. The drug effect was calculated as the proportion of $EGFP^+$ cells exposed to a specific drug by the proportion of $EGFP^+$ cells in untreated infected cultures. At 50 μM, **6c** and **6i** show significant reduction in fluorescence, indicating inhibition of viral replication. **6i** shows significant inhibition of HSV-1 at 10 μM.