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Application of the Morita-Baylis-Hillman reaction in the synthesis of 3-[(*N*-cycloalkylbenzamido)methyl]-2-quinolones as potential HIV-1 integrase inhibitors

Khethobole C. Sekgota [a], Swarup Majumder [a], Michelle Isaacs [c], Dumisani Mnkandhla [c], Heinrich C. Hoppe [b,c], Setshaba D. Khanye [a,c], Frederik H. Kriel [d], Judy Coates [d], Perry T. Kaye [a,c,*]

[a] Department of Chemistry, Rhodes University, Grahamstown 6140, South Africa
[b] Department of Biochemistry and Microbiology, Rhodes University, Grahamstown 6140, South Africa
[c] Centre for Chemico- and Biomedicinal Research, Rhodes University, Grahamstown 6140, South Africa
[d] Centre for Metal-based Drug Discovery, Advanced Materials Division, Mintek, Randburg 2125, South Africa

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ABSTRACT

A practicable six-step synthetic pathway has been developed to access a library of novel 3-[(*N*-cycloalkylbenzamido)methyl]-2-quinolones using Morita-Baylis-Hillman methodology. These compounds and their 3-[(*N*-cycloalkylamino)methyl]-2-quinolone precursors have been screened as potential HIV-1 integrase (IN) inhibitors. A concomitant survey of their activity against HIV-1 protease and reverse-transcriptase reveals selective inhibition of HIV-1 IN.

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1. Introduction

2-Quinolones [quinoline-2(1*H*)-ones], while less prominent than the isomeric 4-quinolones, nevertheless enjoy significant attention as scaffolds in compounds exhibiting a variety of biological activities. These include: 4-aryl-6-chloroquinolin-2-ones **1** (Fig. 1) prepared by Cheng et al. [1] as *in vitro* anti-hepatitis B viral agents; 3-indolylquinolin-2(1*H*)-ones prepared by Kuethe et al. [2] as KDR kinase inhibitors; 3-anilinoquinolin-2(1*H*)-ones **2** reported by O'Brien et al. [3] as PDK1 enzyme inhibitors; and, more recently,4-hydroxy-2-quinolone-3-carboxamides developed by Mugnaini et al. [4] as cannabinoid receptor 2 (CB2R) ligands. Of particular relevance to our own research on novel HIV-1 enzyme inhibitors are the results reported by Freeman et al. [5] and by Cheng et al. [6] on the synthesis of 2-quinolone derivatives as HIV-1 reverse transcriptase (RT) inhibitors, and a virtual screening approach by Debnath and co-workers [7] to the identification and anti-HIV activity of benzo-fused benzamidazoles and 3-(amidomethyl)-2-quinolones, such as compound **3**, which were specifically designed to bind to the C-terminal domain of the HIV-1 capsid.

Thus far only three HIV-1 integrase (IN) inhibitors have been approved for clinical use, *viz.*, Raltegravir (2007) [8], the 4-quinolone derivative, Elvitegravir (2012) [9], and Dolutegravir (2013).[10] Drug resistance issues have arisen with the use of Raltegravir and Elvitegravir [11], and recent studies [12] have indicated that use of Dolutegravir as a monotherapy should be halted. An ongoing search for new lead compounds with HIV-1 IN inhibition potential is clearly warranted and, in this paper, we report: (i) the development of a novel synthetic pathway to a series of 3-[(*N*-cycloalkylbenzamido)methyl]-2-quinolones which contain the privileged 2-quinolone scaffold and which were identified as potential HIV-1 integrase (IN) inhibitors, using *in silico* modelling methods; [13] and (ii) their biological evaluation as HIV-1 IN inhibitors.

2. Results and discussion

2.1. Synthesis

We have previously reported the application of the atom-economical Morita-Baylis-Hillman methodology in the preparation

* Corresponding author at: Department of Chemistry, Rhodes University, Grahamstown 6140, South Africa.
E-mail address: P.Kaye@ru.ac.za (P.T. Kaye).

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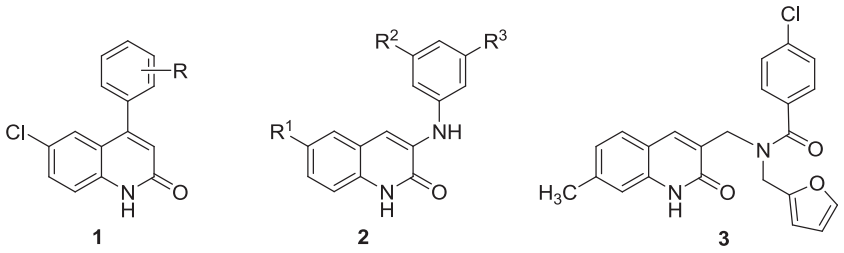
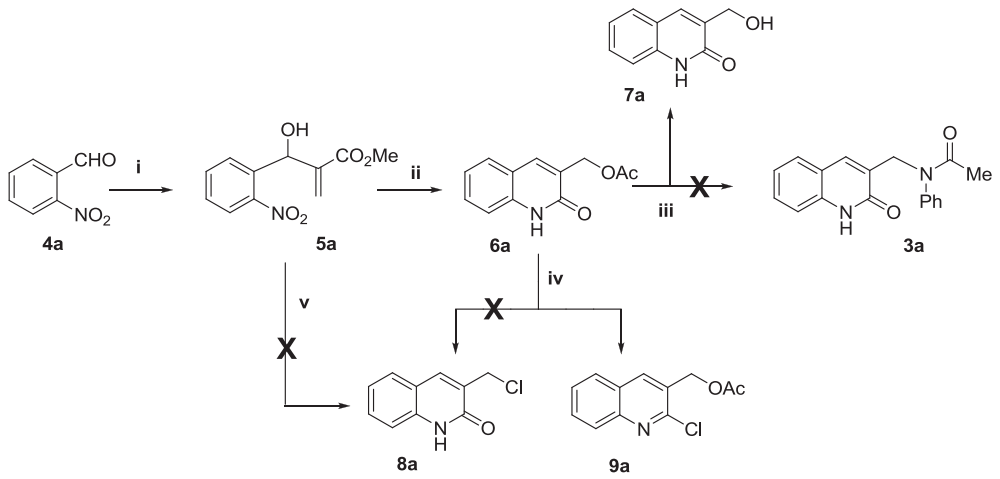


Fig. 1. Biologically active 2-qinolone derivatives: 4-aryl-6-chloroquinolin-2-ones 1 [1]; 3-anilino-quinolin-2(1*H*)-ones 2 [3]; and 3-[(4-chloro-*N*-furfurylbenzamido)methyl]-2-quinolone 3 [7].

of 2-quinolones [14], and several approaches to the targeted 3-amidomethyl-2-quinolones were explored using this methodology. In the first approach, cyclisation of the Morita-Baylis-Hillman adduct **5a** was followed by an attempted direct displacement of acetate from the 2-quinolone intermediate **6a**, using the secondary amide, acetanilide, in the presence of NaH (Scheme 1). However, this failed to afford the corresponding amide **3a**; work-up simply gave the 3-hydroxymethyl derivative **7a**. In the second approach, it was expected that replacement of the acetate leaving group by chloride (to give the chloromethyl derivative **8a**) would facilitate introduction of the amide group. However, treatment of the acetate **6a** with the Vilsmeier-Haack reagent afforded the 2-chloropyridine derivative **9a** instead, while an attempt to access 3-chloromethyl-2-quinolone **8a** by cyclisation of the Morita-Baylis-Hillman adduct **5a** in the presence of NH_4Cl and iron powder in refluxing ethanol afforded an intractable mixture.

Attention was finally turned to the six-step sequence outlined in Scheme 2, which involved: hydrolysis of the 3-(acetoxymethyl)-2-quinolones **6a-f**; conversion of the resulting alcohols **7a-f** to the 3-chloromethyl analogues **8a-f**; and construction of the secondary amide moiety *via* sequential amination and acylation steps. The acetates **6a-f** were readily obtained, in good to excellent yield (62–99%), by reductive cyclisation [15] of the corresponding Morita-Baylis-Hillman adducts **5a-f** using iron powder in refluxing acetic acid. In a slight modification of Basaviah's method [15], hydrolysis of the acetate esters **6a-f** was effected using K_2CO_3 in methanol-water (1:1) to afford the alcohols **7a-f** in yields of up to 87%. The 3-(chloromethyl)-2-quinolones **8a-f** were formed in yields of up to 91% by treating each of the corresponding alcohols **7a-f** with excess thionyl chloride (*CAUTION!*) in a sealed flask at room temperature for 30 min – a significant improvement, in terms of yield and convenience, on an initial method of conducting the reaction in refluxing benzene for 12 h.

Amination was conveniently achieved by stirring each of the selected 3-(chloromethyl)-2-quinolones **8a**,**e**,**f** with an excess of the primary cycloalkylamine (cyclopropylamine, cyclopentylamine or cyclohexylamine) in a stoppered flask at room temperature. The progress of the reactions was monitored by TLC and the corresponding 3-[(cycloalkylamino)methyl]-2-quinolones (**10**, **11** and **12**) were obtained in yields of up to 93%. The final acylation step involved reaction of the 3-[(cycloalkylamino)methyl]-2-quino lones with excess benzoyl chloride to afford the targeted 3-[(*N*-c ycloalkylbenzamido)methyl]-2-quinolones (**13**, **14** and **15**). Analysis of the NMR spectra of many of the these compounds was complicated due to signal broadening and, in some cases, a multiplicity of signals – phenomena attributed to: (i) tautomeric effects in the 3-(chloromethyl)-(1*H*)-2-quinolones (**8**), as illustrated for compound **8c** in Fig. 2a, and in corresponding structures for the 3-aminomethyl (**10**–**12**) and 3-amidomethyl (**13**–**15**) derivatives; (ii) the rotameric equilibria regularly encountered with carboxamide derivatives (Fig. 2b); and (iii) the evident temperature dependence of the foregoing equilibria. Interpretation of the NMR spectra and the assignment of signals was facilitated by running NMR spectra of the 3-[(*N*-cycloalkylbenzamido)methyl]-2-quino lones (**13**, **14** and**15**) in DMSO-d_6 at different temperatures between 298 and 373 K. (^{1}H NMR spectra for compound **13e** at different temperatures is provided in the Supporting Information.) The apparent absence of expected ^{1}H- and/or ^{13}C NMR *N*-methylene and/or *N*-methine signals in certain spectra is attributed to site-exchange line-broadening effects. The presence of these nuclei in such cases is, however, supported by the HRMS data and, in the case of compound **13a**, by an HSQC experiment which



Scheme 1. *Reagents and conditions*: (i) CH_2=$CHCO_2Me$, DABCO, $CHCl_3$; (ii) Fe powder, AcOH, reflux; (iii) PhNHCOMe, NaH, dry THF or MeOH; (iv) $POCl_3$, DMF, CH_2Cl_2; (v) HCl, AcOH, reflux.

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