# Synthesis and Characterization of 2-((4R,4aR,5aS,6S)-1,3-dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[f]isoindol-2(1*H*)-yl)-N-(Substituted Phenyl) Acetamides Derivatives Anticipated to Inhibit HIV-1 Activity

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## ABSTRACT

The acquired immune deficiency syndrome(AIDS) has been believed to result from the infection of T cells by a pathogenic human retrovirus, causing HIV infectious diseases. In the current investigation, a class of non-nucleoside reverse transcriptase compounds was synthesized which was anticipated to inhibit HIV-1 activity. In this work, the synthesis of some new 2-((4R,4aR,5aS,6S)-1,3-dioxo-3,3a,4,4a,5,5a6,6a-octahydro-4,6-ethenocyclopropa[f]isoindol-2(1H)-yl)-N-(substituted phenyl) acetamides (3a-i) by reaction of (4R,4aR,5aS,6S)-1,3-dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[f]isoindole-1,3-(2H,3aH)-dione (1) with 2-chloro-N-(substituted phenyl) acetamides (2) was described in the presence of potassium carbonate in refluxing acetonitrile as a solvent. The results reported here suggested that these derivatives can be simply synthesized, purified, and identified by spectroscopic methods including, IR, 1H-NMR, and elemental analysis (CHN).

**Key Words:** Acetamides Derivatives, HIV-1 Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Maleimide, Retrovirus, Reverse Transcriptase.

**eIJPPR 2018; 8(5):7-11**

**HOW TO CITE THIS ARTICLE:** Abdulmajeed S. H. Alsamarrai, Noor H. Abdulla, Malath Khalaf Aldoori (2018). "Synthesis and Characterization of 2-((4R,4aR,5aS,6S)-1,3-dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[f]isoindol-2(1H)-yl)-N-(Substituted Phenyl) Acetamides Derivatives Anticipated to Inhibit HIV-1 Activity", International Journal of Pharmaceutical and Phytopharmacological Research, 8(5), pp.7-11.

## INTRODUCTION

HIV-1 infections have been major leading threats to life death. There have been several types of anti-HIV-1 inhibitors. The earlier treatment of HIV-1 has been using a class of drugs called antiretrovirals nucleoside reverse transcriptase inhibitors (NRTIs). [1] Because the later inhibitors exhibited side effects [2, 3] , a new type of antiretroviral inhibitors have been used to treat HIV-1, which has advanced so quickly in a short time. These new types have been Non-nucleoside reverse transcriptase (NNRT ) which are structurally different from the reverse transcriptase inhibitors (NRTIs) [4, 5]; the members of this class of compounds have been active against the subtype HIV-1 but not HIV-2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been of current research interest which have been biologically active because of pharmacological properties and clinical application. [6] In the past decades, there was an increasing concern over synthetic pyrrolidine-2,5-dione (maleimide) and their N-derivatives. These compounds have been well known to exhibit a broad range of biological activity such as anti-inflammantory [7-9] anticancer, [10, 11]

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**Relevant conflicts of interest/financial disclosures:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest .
**Received:** 12 July 2018; **Revised:** 29 September 2018; **Accepted:** 07 October 2018

antibacterial, [12-14] and and HIV-1 inhibitors. [15] Some of them have been isolated from a wide variety of natural sources. [16-20] Many NNRTIs including tetrahydroimidazo[4,5,1-jkj] benzodiazepin-2(1H)-one and α-anilinophenyl acetamide derivatives have been playing a major role in many physiological processes and their action has been terminated as reverse transcriptase inhibitors in the treatment of HIV-1 infection. [21, 22] Recently, Penta, et al., [23] have reported the synthesis of tetrahydrophthalimide derivatives as the inhibitors of HIV-1 reverse transcriptase. In the present study, the most fundamental objective was to synthesize and characterize new aromatic amines acetamides via reaction of (4R,4aR, 6S, 5aS)-4,4a,5,5a,6,6a-hexahydro-4,6-ethenocyclopropa[*f*]isoindole-1,3(2H,3aH)-dione with 2-chloro-N-(substituted phenyl) acetamides, and to test their future anti-HIV-1 activity.

## MATERIALS AND METHODS

Commercially available compounds were used without further purification unless otherwise noted. Infrared (IR) spectra were recorded on Shimadzu FT-IR 8400S device, and were calibrated using a polystyrene film and m.p's were uncorrected. Solid compounds were recorded in potassium bromide disks (KBr) [1] . Dimethyl sulfoxide (DMSO-d¬6) was utilized as a solvent, and tetramethylsilane (TMS) was used as an internal standard, and H-NMR spectra were recorded on 400 MHz AV III-HD-800 Bio Spin spectrometer. Chemical shifts were quoted in parts per million (ppm) downfield from TMS. The elemental analysis was administered on the CHN elemental (Eur.Vector EA 3000A) Germany.

**Synthesis of the precursors (1) and (2).**

The precursors (1) [24] and (2a-i) [23] were synthesized according to the previous literature.

**General products for the synthesis of the compounds 2-((4R,4aR,5aS,6S)-1,3-dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-2(1H)-yl)(-N- substituted phenyl) (3a-i) acetamides.**

To a solution of (4R,4aR, 6S, 5aS)-4,4a,5,5a,6,6a-hexahydro-4,6- ethenocyclopropa[*f*] isoindole-1,3(2H,3aH)-dione. (1) (2mmol) in acetonitrile containing, 2-chloro-N-(substituted phenyl) acetamides (2a-i, Ar = $C_6H_5$, 4-$BrC_6H_4$, 2-$COOHC_6H_4$, 4- $NO_2C_6H_4$, 4-$COOHC_6H_4$, 4-$CH_3COC_6H_4$, 4-$EtO_2CC_6H_4$, 3,5-$Cl_2C_6H_3$ ) (2mmol) and a finely powdered potassium carbonate (6mmol) was added and refluxed for 8h. On completion of the reaction as observed by TLC, the contents were poured on crushed ice, and the resulted precipitate was filtered off, dried and recrystallized from benzene to obtain pure products (3a-i).

**2-((4R,4aR,5aS,6S)-1,3-dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-2(1*H*)-yl)-N-phenylacetamide (3a, Ar = $C_6H_5$):** White solid (yield: 82%; m. p , 194-196 °C). $C_{19}H_{18}N_2O_3$ (%) Calculated C, 70.70; H, 5.50; N, 8.68). Found C, 70.9; H, 5.39; N, 8.60. IR [KBr] 3350 $cm^{-1}$ (NH); 1755, 1705 (C=O imide); 1699 (C=O amide); and 1660 $cm^{-1}$ (C=C aromatic). $^1$H-NMR (DMSO-d6) δ 0.11, 0.25[2H, 2xm, $CH_{2(3)}$] ; 1.10 (2H, 2xm, $H_{2,4}$) ; 2.5 (2H , 2xm, $H_{1,5}$) ; 3.40 (2H, s, $H_{8,9}$); 4.2 (2H, s, $>NCH_2$); 5.75 (2H, dxd, $H_{7,6}$); 7.0 (5H, m, aromatic); and 10.3 ppm (s, NH).

**N-(4-bromophenyl)-2-((3aS,4R,4aR,5aS,6S)-1,3-dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-2(1*H*)-yl)acetamide (3b,Ar=4-$BrC_6H_4$):**

White solid (yield: 71%; m. p, 191-194 °C). $C_{19}H_{17}N_2BrO_3$ (%) Calculated C, 50.7; H, 4.23; N, 6.9. Found C, 50.62; H,4.35; N, 6.71. IR [KBr] 3332 (NH); 1712 (C=O imide);1699 (C=O amide); and 1600 $cm^{-1}$ (C=C aromatic).

**N-(3,5-dichlorophenyl)-2-((3aS,4R,4aR,5aS,6S)-1,3-dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-2(1*H*)-yl)acetamide (3c; Ar = 3,5-$Cl_2C_6H_3$).**

White solid (yield: 79%; m. p, 200-202 °C). .$C_{19}H_{16}N_2O_3Cl_2$ (%) Calculated C, 58.28; H, 4.08; N, 7.15). Found C, 58.43, H, 4.14; N, 7.32. IR [KBr] 3365 (NH); 1720 (C=O imide);1695 (C=O amide); and 1577 $cm^{-1}$ (C=C aromatic). $^1$H-NMR (DMSO-$d^6$) δ 0.15,0.30 [2H, 2xm, $CH_{2(3)}$] ; 1.10 (2H, 2xm, $H_{2,4}$) ; 2.50 (2H , 2xm, $H_{1,5}$) ; 3.40 (2H, s, $H_{8,9}$); 4.20 (2H, s, $>NCH_2$); 5.75 (2H, dxd, $H_{7,6}$); 7.30-7.60 (3H, 3s, aromatic); and 9.9 ppm (1H, s, NH).

**2-(1,3-dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-2(1H)-yl)-N-(4-nitrophenyl)acetamide (3d, Ar = 4-$NO_2C_6H_4$):**

Yellow solid (yield: 70%; m. p, 203-204 °C). $C_{19}H_{16}N_2O_3Cl_2$ (%) Calculated C, 58.28; H, 4.08; N,7.15. Found C, 57.7; H, 4.24; N, 7.42.

IR [KBr] 3299 (NH); 1725 (C=O imide);1689 (C=O amide); and 1612 (C=C aromatic). $^1$H-NMR (DMSO-$d^6$) δ 0.15,0.30 [2H, q, $CH_{2(3)}$] ; 1.15 (2H, q, $H_{2,4}$) ; 3.10 (2H ,2xm, $H_{1,5}$) ; 3.40 (2H, s, $H_{8,9}$); 4.15 (2H, s, $>NCH_2$); 5.80 (2H, dxd, $H_{7,6}$); 7.11, 8.11 (4H, m, aromatic); and 10.6 ppm (1H, s, NH).

**4-(2-(1,3-dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-2(1H)-yl)acetamido)benzoic acid (3e, Ar = 4-$COOHC_6H_4$):**

White solid (yield: 89%; m. p, 260-263 °C). $C_{19}H_{17}N_2O_5$ (%) Calculated C, 60.5; H, 4.90; N, 7.9. Found C 60.32; H, 4.7; N, 7.41. IR [KBr] 3330 (NH); 2800 ( br, OH); 1750 (C=O imide);1699 (C=O acid); and 1606 $cm^{-1}$ (C=O amide).

**N-(4-acetylphenyl)-2-((3aS,4R,4aR,5aS,6S)-1,3-dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-2(1H)-yl)acetamide (3f, Ar = 4-$CH_3COC_6H_4$):**

White solid (yield: 76%; m. p, 210-212 °C). $C_{21}H_{22}N_2O_4$ (%) Calculated C, 69.1; H, 5.4; N, 7.68. Found C, 68.96, H, 5.4; N, 7.85. IR [KBr] 3352 (NH); 1725 (C=O imide);1699 (C=O ketone); and 1598 $cm^{-1}$ (C=O amide). $^1$H-NMR (DMSO-d6) δ 0.15,30 [2H, 2xm, $CH_{2\,(3)}$] ; 1.15 (2H, 2xm, $H_{2\,,4}$) ; 3.10 (2H , 2xm, $H_{1,\,5}$) ; 3.40 (2H, s, $H_{8,\,9}$); 3.50 (3H, s, $CH_3$) 4.10 (2H, s, >$NCH_2$); 5.80 (2H, dxd, $H_{7,\,6}$); 7.50, 7.75 (4H,dxd, aromatic); and 10.5 ppm (1H, s, NH).

**Ethyl 4-(2-((3as,4R,4aR,5aS,6S)-1,3-dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-2(1H)-yl)acetamido)benzoate (3g, Ar = 4-$EtO_2CC_6H_4$):**

Brown solid (yield: 72%; m. p, 115-116 °C). $C_{21}H_{22}N_2O_4$ (%) Calculated C, 69.1; H, 5.4; N, 7.68. Found C,68.96; H, 5.4, N, 7.85). IR [KBr] 3332 (NH) 1768 (C=O imide);1712 (C=O ester); and 1693 $cm^{-1}$ (C=O amide).

**2-(2-(1,3-dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-2(1H)-yl)acetamido)benzoic acid (3h, Ar = 2-$COOHC_6H_4$):**

Yellow solid (yield: 79%; m. p, 222-221 °C). $C_{20}H_{18}N_2O_5$ (%) Calculated C, 69.1; H, 5.4, N, 7.68. Found C,68.96; H, 5.4; N, 7.85. IR [KBr] 3410 (NH) 3100-2850 (OH); 1750 (C=O imide); 1710 $cm^{-1}$ (C=O carbonyl);1695 $cm^{-1}$ (C=O amide);. $^1$H-NMR (DMSO-$d^6$) δ 0.14,0.33 [2H, 2xm, $CH_{2\,(3)}$] ; 1.15 (2H, 2xm, $H_{2\,,4}$) ; 3.10 (2H , 2xm, $H_{1,5}$) ; 3.49 (2H, s, $H_{8,9}$); 4.10 (2H, s, >$NCH_2$); 5.80 (2H, dxd, $H_{7,6}$); 7.00-8.10 (4H,4xm, aromatic); 9.80 (1H, s, NH) and 15.30 ppm (1H, s, OH).

**N-benzyl-2-((3aS,4R,4AR,5aS,6S)-1,3-dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-2(1H)-yl)acetamide. (3i, Ar = $CH_2C_6H_5$ ):**

White solid (yield: 75%; m. p,115-116 °C). $C_{20}H_{20}N_2O_3$ (%) Calculated C, 58.28; H, 4.08; N, 7.15. Found C, 57.80; H, 4.24; N, 7.42). IR [KBr] 3350 (NH); 1725 (C=O imide);1699 (C=O amide); and 1652 $cm^{-1}$ (C=C aromatic). $^1$H-NMR (DMSO-$d^6$) δ 0.15,0.30 [2H, 2xm, $CH_{2\,(3)}$]; 1.18 (2H, 2xm, $H_{2\,,4}$) ; 3.15 (2H , 2xm, $H_{1,5}$) ;3.40 (2H, s, $H_{8,9}$); 3.50 (2H, s, benzylic CH) 4.25 (2H, s, >$NCH_2$); 5.8 (2H, dxd, $H_{7,6}$); 7.4 (5H aromatic); and 9.55 ppm (1H, s, NH).

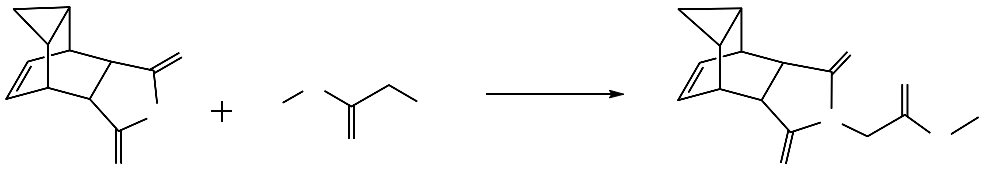
## RESULTS AND DİSCUSSİON

The acetamides (3a-i) (scheme 1) containing tricyclic imide (1) unit were designed and synthesized in the present study, and prepared by the reaction of unit (2) with moiety (1) unit. It was previously reported that the starting adduct (1) could be synthesized from cycloheptatriene and maleimide using ethanol, acetonitrile, and or dichloromethane as solvents to give the corresponding adduct (1) in no more than 75% yield. Herein, in this examination, the modified procedure smoothly produced tricyclic compound of the structure (1) in 95% yield by reacting commercially available cycloheptatriene and maleimide using water as a solvent accompanied by vigorous stirring. The reaction of substituted anilines with 2-chloroacetly chloride in $CH_2Cl_2$ and $Et_3N$ as a base under dry nitrogen afforded the intermediate compounds (2a-i). As expected, the conversion of the acetamides (2a-i) and the tricyclic nucleus (1) into the acetamides (3a-i) proceeded completely within almost 8 h in refluxing acetonitrile and in the existence of anhydrous potassium carbonate as demonstrated in scheme (1). All the reactions were conducted on mmol scale, 2:2:6 (1)/(2a-i)/$K_2CO_3$. The conversion could be monitored by TLC analysis of the reaction mixture. After the completion of the reaction, the target products were easily purified upon the removal of potassium carbonate by diluting the mixture on ice bath and the filtration of crude products, dried with the following purification by the recrystallized from benzene to obtain pure products (3a-i). The yields of (3a-i) were based on the weight of isolated products by crystallization. In all cases, the yields were high at around 70% to 89%, and no formation of byproducts could be observed.

The assignment of the all 9 structures (3a-i) was based on their IR, 1H-NMR, and the elemental analysis data. In general the compounds (3a-i) showed bands for N-H stretching at around 3410 to 3299 $Cm^{-1}$. Also, the IR spectra showed the absorption bands for C=O stretching (imide) around 1755-1725 $Cm^{-1}$, while C=O stretching (amide) showed bands at around 1705 to 1995 $cm^{-1}$ .

The $^1$H-NMR spectra of synthesized products were consistent with the structures (3a-i), in particular in the appearance of signals expected for nine protons $H_1$ to $H_9$ of the tricyclic nucleus. It was also possible to observe broad signals for NH at around δ 10.5 to 9.8 ppm.

The results obtained illustrated the efficiency of the present method. As shown in scheme (1), the reaction were mild enough to be applied to the compounds possessing similar functional groups. The general strategy for the synthesis of acetamide derivatives (3a-i) involved covalently linking of the moiety (1) with the moiety (2a-i) using potassium carbonate as catalyst in refluxing dry acetonitrile, as it has been mentioned above. The introduction of a chloro functional group in the acetamide moiety dramatically improved and facilitated coupling between precursor moieties (1) and (2a-i).



**Scheme 1: Synthesis of the acetamide derivatives (3a-i)**

## CONCLUSIONS

From the results reported here, it could be concluded that the synthesis of new acetamide derivatives having a (4R,4aR,6S,5aS)-4,4a,5,5a,6,6a-hexahydro-4,6-ethenocyclopropa[*f*] isoindole-1,3(2H,3aH)-dione nucleus seemed to be of general application, since a wide range of derivatives of these acetamides could be prepared. The method has been successfully administered to get a variety of tricyclic acetamide derivatives such as (3a-i). In the present examination, an experimentally mild, and clean synthetic method has been established for the synthesis of these tricyclic acetamides based on the coupling of the nucleus (1) with (2) using potassium carbonate as a catalyst.

## ACKNOWLEDGMENTS

The authors would like to thank the department of chemistry, university of Samarra, Iraq, for providing the needed facilities and financial support.

### Abbreviation

HIV= human immunodeficiency virus, NRTIs= nucleoside reverse transcriptase inhibitors, NNRTs= Non-nucleoside reverse transcriptase inhibitors

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