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Synthesis of Novel Schiff Base Derivates Containing a Fragment of the HIV Integrase Inhibitor Drug Raltegravir †

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Abstract: An eco-friendly methodology for the synthesis of novel Schiff base analogs of Raltegravir, an Integrase inhibitor drug is described. Pertinence of these imine derivatives is related to Medicinal Chemistry to develop new anti-VIH compounds. To our knowledge, this is the first report of the synthesis of Schiff base using a Raltegravir drug fragment as amino component. In addition, these Imines will be used as a synthetic precursor to prepare other nitrogen heterocycles of biological relevance such as 1,5-disubstituted Tetrazoles.

Keywords: Raltegravir; Schiff base; complex imines

1. Introduction

The key process for drug discovery is the development of efficient methodologies that allow the synthesis of novel chemical entities with a high biological potential and may be drug candidates [1–3]. Part of this process consists of designing molecule analogues from a leading bioactive compound or active pharmaceutical ingredient (API), whose concept was developed by Sir James White Black winner of the Nobel Prize in Medicine, who cited the following: ''The most fruitful basis for the discovery of a new drug is to start with an old drug" [4–7]. On this basis, an efficient synthetic tool that allows derivatizations with a wide variety of simple or complex substituents, such as heterocyclic scaffolds of medicinal interest, is the Schiff condensation. Schiff bases are formed by condensation of a primary amine with an aldehyde or ketone and they are of great importance in medicinal chemistry being considered as "privileged ligands "[8–10].

On the other hand, Raltegravir drug **1** (Figure 1) is an integrase inhibitor, an enzyme catalyzing the integration of viral DNA into the host genomic DNA, thus preventing further virus replication. Raltegravir is sold under the brand name ISENTRESS® developed by Merck & Co., used to treat HIV infection [11,12]. Actually, a big threat to global health is HIV drug resistance which is caused by mutation in the genetic structure of HIV that affects the ability of a specific drug or combination of drugs to block replication of the virus causing thousand of death per year [13]. Therefore, continuous searching for new anti-HIV agents are needed, remaining an important research objective for synthetic chemist.

Herein, we report the synthesis of novel Schiff base analogs of Raltegravir (Imines-Ralt) in moderate to good yields, which to best of our knowledge there is not report in the literature where the key fragment of Raltegravir drug a primary amino compound (blue color Figure 1) is used for the synthesis of Schiff bases.

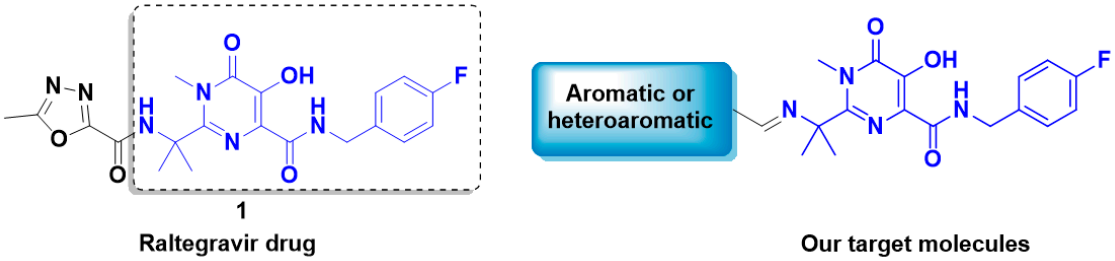


Figure 1. Raltegravir drug **1** and target molecules (Imines-Ralt).

2. Materials and Methods

2.1. Experimental Section

All chemical reagents and solvents were purchased from Sigma-Aldrich (Toluca, México) without further purification. Melting points were determined on a Fischer apparatus and were not corrected. NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C on a Varian Mercury 400 NMR spectrometer, using $CDCl_3$ as the solvent, and TMS as the internal standard. Chemical Shift (δ) are reported in ppm, and *J* values are given in Hertz.

*2.2. General Procedure for Imines-Ralt **4a–g***

Amino-Ralt **2** (1 eq) and aldehyde **3** (1 eq) were suspended on Ethanol (0.5 M) and stirred at room temperature until reaction complete. After, the reaction mixture was filtered and washed with 2 mL of Ethanol and dried under vacuum to afford the imines-Ralt **4a–g**. All chemical reactions were monitored by TLC.

*2-(2-(benzylideneamino)propan-2-yl)-N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide (**4a**):* White solid, mp = 181–183 °C; R_F = 0.42 (DCM-MeOH 9:1 *v*/*v*); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.70 (s, 6H), 3.58 (s, 3H), 4.62 (d, *J* = 6.3 Hz, 2H), 7.04–7.09 (m, 2H), 7.32–7.36 (m, 2H), 7.40–7.47 (m, 3H), 7.71–7.74 (m, 2H), 7.89 (t, *J* = 6.3 Hz, 1H), 8.21 (s, 1H), 11.94 (bs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.7, 34.5, 42.3, 65.1, 115.8 (d, *J* = 21.4 Hz), 123.9, 128.1, 128.8, 129.3 (d, *J* = 8.1 Hz), 131.5, 133.1 (d, *J* = 3.3 Hz), 135.7, 146.9, 153.8, 159.8, 160.0, 163.5, 168.4.

*2-(2-((2,5-difluorobenzylidene)amino)propan-2-yl)-N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide (**4b**)*: White solid, mp = 178–180 °C; R_F = 0.35 (DCM-MeOH 9:1 *v*/*v*); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.71 (s, 6H), 3.56 (s, 3H), 4.62 (d, *J* = 6.3 Hz, 2H), 7.04–7.16 (m, 4H), 7.3–7.37 (m, 2H), 7.6–7.68 (m, 1H), 7.86 (t, *J* = 6.3 Hz, 1H), 8.48 (d, *J* = 2.3 Hz, 1H), 11.97 (bs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.7, 34.4, 42.3, 65.7, 112.9 (dd, *J* = 25.2, 3.0 Hz), 115.8 (d, *J* = 21.5 Hz), 117.3 (dd, *J* = 24.0, 8.1 Hz), 119.8 (dd, *J* = 24.8, 9.0 Hz), 123.9, 124.6 (dd, *J* = 11.7, 7.2 Hz), 129.3 (d, *J* = 8.1 Hz), 133.1 (d, *J* = 3.3 Hz), 147.0, 152.6 (dd, *J* = 4.5, 1.9 Hz), 153.2, 157.1 (d, *J* = 2.3 Hz), 157.7, 159.6 (d, *J* = 2.2 Hz), 159.7, 160.1 (d, *J* = 2.2 Hz), 162.3 (d, *J* = 246.4 Hz), 168.4.

*2-(2-((3,5-difluorobenzylidene)amino)propan-2-yl)-N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide (**4c**)*: White-off solid, mp = 153–156 °C; R_F = 0.30 (DCM-MeOH 9:1 *v*/*v*); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.71 (s, 6H), 3.54 (s, 3H), 4.61 (d, *J* = 6.2 Hz, 2H), 6.88–6.93 (m, 1H), 7.06 (at, *J* = 8.5 Hz, 1H), 7.24–7.29 (m, 2H), 7.34 (dd, *J* = 8.3, 5.2 Hz, 2H), 7.85 (t, *J* = 6.1 Hz, 1H), 8.15 (s, 1H), 11.97 (bs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.7, 34.5, 42.4, 65.4, 106.6 (t, *J* = 25.5 Hz), 110.8 (d, *J* =

26.1 Hz), 110.8 (d, *J* = 11.7 Hz), 115.8 (d, *J* = 21.5 Hz), 123.9, 129.3 (d, *J* = 8.2 Hz), 133.1 (d, *J* = 3.2 Hz), 138.9, 147.0, 153.2, 157.8, 159.7, 162.3 (d, *J* = 246.4 Hz), 161.9 (d, *J* = 12.2 Hz), 164.4 (d, *J* = 12.4 Hz), 168.4.

*N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-2-(2-((pyridin-2-ylmethylene)amino)propan-2-yl)-1,6-dihydropyrimidine-4-carboxamide (**4d**)*: White-off solid, mp = 182–184 °C; R_F = 0.41 (DCM-MeOH 9:1 *v*/*v*) ; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.73 (s, 6H), 3.57 (s, 3H), 4.62 (d, *J* = 6.3 Hz, 2H), 7.07 (t, *J* = 8.7 Hz, 2H), 7.31–7.39 (m, 3H), 7.79 (td, *J* = 7.7, 1.7 Hz, 1H), 7.85–7.88 (m, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 8.36 (s, 1H), 8.65–8.67 (m, 1H), 11.96 (bs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.6, 34.4, 42.3, 65.5, 115.7 (d, *J* = 21.5 Hz), 120.9, 123.9, 125.4, 129.3 (d, *J* = 8.1 Hz), 133.1 (d, *J* = 3.2 Hz), 136.8, 147.0, 149.6, 153.3, 154.0, 159.8, 161.4, 168.4.

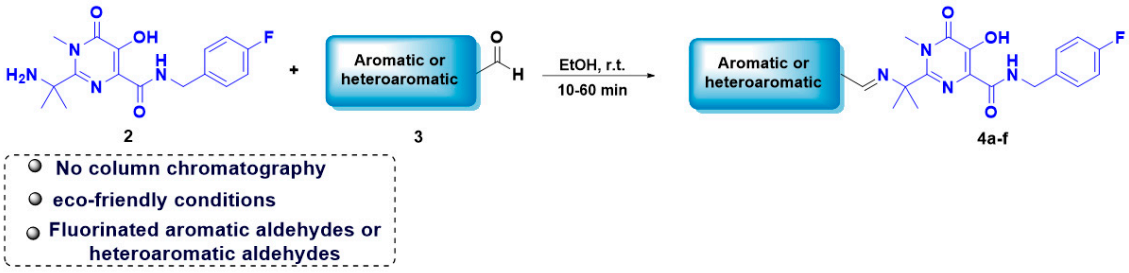
*N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-2-(2-((pyridin-3-ylmethylene)amino)propan-2-yl)-1,6-dihydropyrimidine-4-carboxamide (**4e**)*: White solid, mp = 185–188 °C; R_F = 0.33 (DCM-MeOH 9:1 *v*/*v*); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 6H), 3.57 (s, 3H), 4.62 (d, *J* = 6.3 Hz, 2H), 7.04-7.09 (m, 2H), 7.32–7.40 (m, 3H), 7.87 (t, *J* = 6.3 Hz, 1H), 8.11 (dt, *J* = 7.9, 2.0 Hz, 1H), 8.28 (s, 1H), 8.69 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.87 (d, *J* = 1.4 Hz, 1H), 11.98 (bs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.6, 34.4, 42.3, 65.5, 115.7 (d, *J* = 21.7 Hz), 123.8, 123.9, 129.3 (d, *J* = 8.3 Hz), 131.3, 133.1 (d, *J* = 3.4 Hz), 134.3, 147.0, 150.3, 152.2, 153.3, 157.4, 159.7, 162.3 (d, *J* = 246.4 Hz), 168.4.

*N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-2-(2-((4-(pyridin-4-yl)benzylidene)amino)propan-2-yl)-1,6-dihydropyrimidine-4-carboxamide (**4f**)*: White solid, mp = 222–225 °C; R_F = 0.28 (DCM-MeOH 9:1 *v*/*v*); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.73 (s, 6H), 3.59 (s, 3H), 4.62 (d, *J* = 6.3 Hz, 2H), 7.05–7.09 (m, 2H), 7.33–7.36 (m, 2H), 7.5–7.54 (m, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.84–7.90 (m, 3H), 8.27 (s, 1H), 8.69 (d, *J* = 6.1 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.7, 34.5, 42.4, 65.4, (d, *J* = 21.6 Hz), 121.5, 123.9, 127.4, 128.9, 129.4 (d, *J* = 8.0 Hz), 133.1 (d, *J* = 3.1 Hz), 136.3, 141.0, 147.0, 147.2, 150.4, 153.6, 159.3, 159.8, 162.3 (d, *J* = 246.4 Hz), 168.4.

*N-(4-fluorobenzyl)-2-(2-((2-fluorobenzylidene)amino)propan-2-yl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide (**4g**)*: White solid, mp = 187–190 °C; R_F = 0.41 (DCM-MeOH 9:1 *v*/*v*); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.71 (s, 6H), 3.58 (s, 3H), 4.62 (d, *J* = 6.3 Hz, 2H), 7.03–7.13 (m, 3H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.34 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.42–7.48 (m, 1H), 7.89 (t, *J* = 6.3 Hz, 1H), 7.97 (td, *J* = 7.5, 1.8 Hz, 1H), 8.56 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.62, 34.4, 42.3, 65.6, (d, *J* = 21.6 Hz), 115.7 (d, *J* = 21.4 Hz), 116.0, 123.4 (d, *J* = 9.1 Hz), 123.9, 124.5 (d, *J* = 3.5 Hz), 127.0 (d, *J* = 2.5 Hz), 129.3 (d, *J* = 8.2 Hz), 133.1 (d, *J* = 8.6 Hz), 133.1, 146.9, 153.4 (d, *J* = 4.9 Hz), 153.5, 160.4 (d, *J* = 125.9 Hz), 163.5 (d, *J* = 7.0 Hz), 168.4.

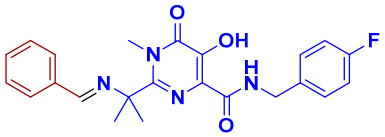
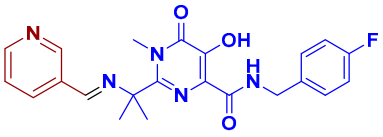
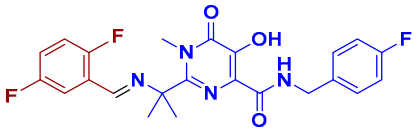
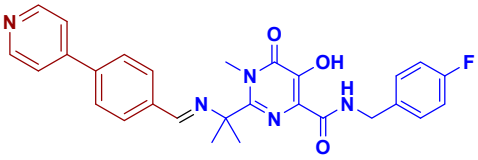
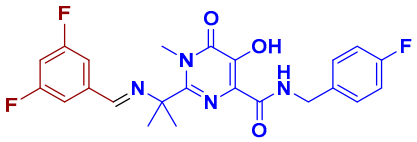
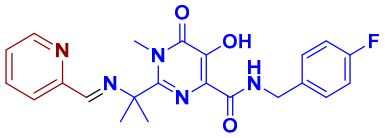
3. Results and Discussion

The amino-Ralt **2** containing the fragment hydroxypyrimidinone was firstly synthesized according the literature report which eight reaction steps were involved starting from acetone cyanohydrin [14]. Thus, once obtained the amino compound **2** (amino-Ralt), seven imines-Ralt **4a–g** were synthesized in moderate to good yields by classic Schiff condensation of amino-Ralt **2** and heterocyclic or aromatic aldehydes **3** according the general synthetic scheme (Scheme 1) but using ethanol as the solvent, and avoiding chromatographic purifications, deriving in an eco-friendly methodology. Aldehydes with different structural and electronic nature were used to study the reaction scope and reaction products are shown in Table 1. NMR analysis of all compounds provided significative chemical shift changes, suggesting the derivatives formation, mainly at the iminic portion, since typical resonances in the range of δ 8.15–8.87 in ^{1}H, and those in 147 ppm ^{13}C were clearly observed.



Scheme 1. General synthetic scheme for the synthesis of imines-Ralt **4a–f**.

Table 1. Imines-Ralt **4a–f** synthesized by Schiff condensation reaction.

Imines-Ralt	Yield	Imines-Ralt	Yield
 **4a**	77%	 **4e**	63%
 **4b**	70%	 **4f**	50%
 **4c**	54%	 **4g**	80%
 **4d**	60%		

The synthesized imines-Ralt **4a–g** besides they are structural analogs of Raltegravir drug, will be of great interest in medicinal chemistry due the imines **4d–f** are considered pharmacophoric hybrids molecules because both the fragments hydroxypyrimidinone and pyridine are known as privileged scaffolds. In addition, fluorinated aromatic aldehydes were used due the biological and pharmacological relevance of fluorine in medicinal chemistry.

4. Conclusions

The imines-Ralt **4a–g** considered Raltegravir drug analogs were synthesized in moderate to good yields and aldehydes with different stereoelectronic nature were used to study the reaction scope. These analogs are considered of biological relevance because pharmacophoric fragments such as hydroxypyrimidinone and pyridine are present. Finally, in-vitro studies against HIV integrase will be realized.

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Conflicts of Interest: The authors declare no conflicts of interest or state.

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