

Short Communication

Synthesis of three formamidine disulphide derivatives as potential integrase inhibitors of human immunodeficiency virus (HIV)

Afolabi Ezekiel O.* and Jegede Abiodun O.

Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, University of Jos,
P.M.B. 2084, Jos, Plateau State, Nigeria.

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Three analogues of formamidine disulphide (FMD) were synthesized as potential integrase inhibitor of human immunodeficiency virus (HIV). Piperonal, 3-Nitrobenz-aldehyde and 3,4,5-trimethoxybenzaldehyde, were respectively coupled with formamidine disulphide to prepare piperoforamidine disulphide (P-FMD), 3-Nitro-formamidine disulphide (N-FMD) and 3,4,5-trimethoxyformamidine disulphide (T-FMD). The structures of the three products were confirmed with infrared (IR), nuclear magnetic resonance (NMR) and mass spectrometry (MS) spectroscopic techniques, as reported.

Key words: Human immunodeficiency virus (HIV), acquired immune deficiency syndrome (AIDS), formamidine disulphide (FMD).

INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is a set of symptom and infections resulting from damage to the human immune system caused by human immunodeficiency virus (HIV) (Weiss, 1993). After years of hard work, a number of reverse transcriptase and protease inhibitors were discovered and introduced into clinical practice (Roberto et al., 2003). A new therapeutic target however is the integrase enzyme (Angelo and Mouscadet, 2001). Integrase inhibitors have been shown to display synergy when used in combination with reverse transcriptase and protease inhibitors (Matte, 2001) and has helped to reduce incidence of resistance due to monotherapy (Stephenson, 2007). Many classes of compounds have been shown to inhibit the HIV-1 integrase enzyme. These include DNA binders, peptides, oligonucleotides, nucleotides and polyhydroxylated aromatics (Pani, 2000). Studies have shown that disulphiram (An alcohol dehydrogenase inhibitor is some worth beneficial to victims of AIDS).

A similarity between the alcohol dehydrogenase and the HIV viral integrase was proposed by AHFS-Drug Info, 2007. Thus, it is possible to synthesis HIV integrase inhibitors with similar spatial arrangement to disulfram. This line of thought led to the synthesis of formamidine disulphide derivatives as potential integrase inhibitor of HIV.

METHODOLOGY

Typical synthesis of formamidine disulphide derivative (Scheme I)

A solution of 12 g of thiourea in 40 ml of concentrated H_2SO_4 was added to an acidified $KMnO_4$ until the purple colour disappeared. The excess acid was then neutralized to blue litmus paper with $NaHCO_3$. The formamidine disulphide (FMD) precipitated was filtered and air dried. The desired aldehyde (0.025 M) was added to a solution of FMD weighing 2 g (0.0133 M) in 5 ml of CH_3OH . The

*Corresponding author. E-mail: afolabie@unijos.edu.ng. Tel: +234 (0) 803 5889 579.

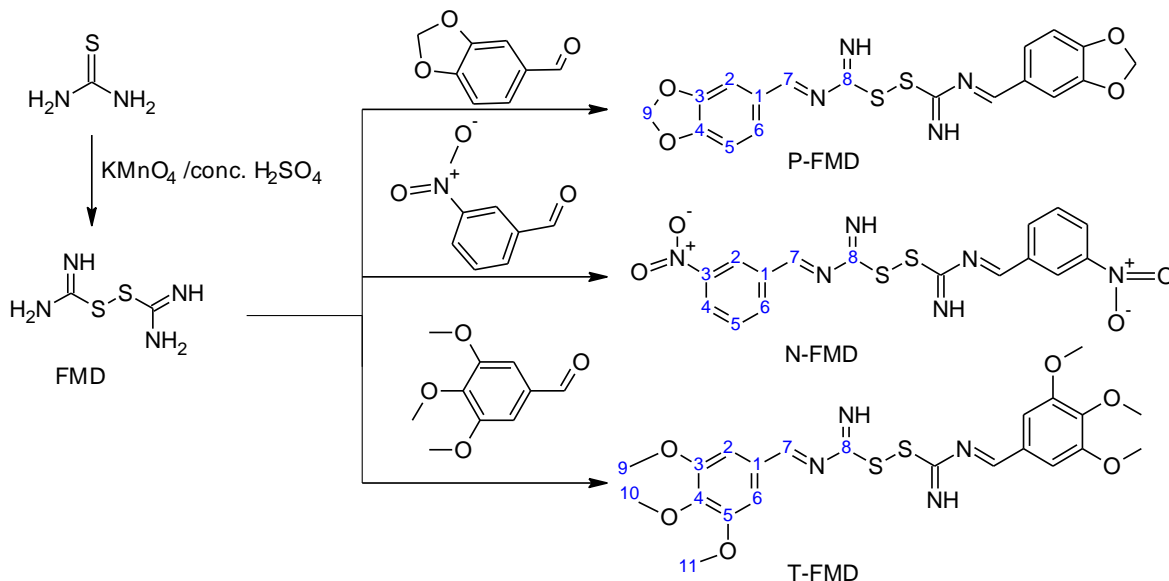


Figure 1. Synthesis of formamidine disulphide derivatives.

mixture was warmed on a water bath for 0.25 h with continuous stirring. On cooling, the crystals formed were filtered and air dried. Piperonal, 3-Nitrobenzaldehyde and 3,4,5-trimethoxybenzaldehyde, were used, respectively to prepare piperoforamidine disulphide (P-FMD), 3-Nitroformamidine disulphide (N-FMD) and 3,4,5-trimethoxyformamidine disulphide (T-FMD).

RESULTS

Spectral analyses of piperoforamidine disulphide

Infrared (IR) (ν_{\max}): 750, 1100, 1250, 1050, 1960, 2350 cm^{-1} ; ^1H nuclear magnetic resonance (NMR) (CDCl_3), δ : 6.9[2H, s], 7.32[1H, d], 7.38[1H, s], 7.41[1H, d] and 9.8[2H, s] correspond with C-9, C-6, C-2, C-5 and C-7; ^{13}C NMR (CDCl_3), δ : 190.2, 153.1, 148.7, 131.9, 128.6, 108.3, 106.9 and 102.1 correspond with C-7,8, C-3, C-4, C-1, C-6, C-5, C-6 and C-9, respectively; mass spectrometry (MS) fragmentation pattern: 414 m/z [M^+], 196, 181, 150, 149 [base peak], 125, 121, 110, 77, 68, 91 and 63 m/z .

Spectral analyses of 3-Nitroformamidine disulphide

IR (ν_{\max}): 610, 720, 800, 1350, 1380, 1550, 1620 and 2350 cm^{-1} ; ^1H NMR (CDCl_3), δ : 7.78[1H, t], 8.2[1H, d], 8.4[1H, d], 8.7[1H, s] and 10.13[1H, s] correspond with C-5, C-6, C-4, C-2 and C-7; ^{13}C NMR (CDCl_3), δ : 189.7, 148.8, 137.4, 134.7, 130.4, 128.5 and 124.3 correspond with C-7,8, C-3, C-2, C-1, C-4, C-6 and C-5, respectively; MS fragmentation pattern [M^+][Metastable]: 150, 121 [base peak], 105, 92, 83 and 77 m/z .

Spectral analyses of 3,4,5-trimethoxyformamidine disulphide

IR (ν_{\max}): 680, 1100, 1300, 1650 and 2350 cm^{-1} ; ^1H NMR (CDCl_3), δ : 3.92[9H, s], 7.12[2H, s] and 9.85[1H, s] correspond with C-9, 10, 11, C-2, 6 and C-7; ^{13}C NMR (CDCl_3), δ : 190.9, 153.6, 143.7, 131.7, 106.8, 60.9 and 56.3 correspond with C-7,8, C-3,5, C-4, C-1, C-2,6, C-10 and C-9,11, respectively; MS fragmentation pattern [M^+][Metastable]: 196[base peak], 181, 153, 132, 125, 110, 93, 77 and 65 m/z .

DISCUSSION

The fragmentation pattern, Figure 2 shows that the base peaks for both P-FMD and T-FMD are due to fragment (b), while that of N-FMD is due to fragment (c), because the substituent(s) on P-FMD and T-FMD are electron donating while that of N-FMD is electron withdrawing, as such the fragments of N-FMD is less stable than those of T-FMD and P-FMD. The D_{2h} -Point group symmetry in all the compounds is shown by the presence of fragment (a) corresponding, respectively to 207, 208 and 253 m/z for P-FMD, N-FMD and T-FMD. All the compounds show the presence of C-N (1280 to 1350 cm^{-1}) and C=N (1620 to 1650 cm^{-1}) functional groups on their IR charts. The peaks around 1100 and 1300 cm^{-1} confirmed the presence of ether linkage in T-FMD and P-FMD, while these peaks are absent in N-FMD but rather the peaks at 1350 and 1550 cm^{-1} are characteristics for symmetric and anti symmetric NO_2 stretches. The NMR spectra of T-FMD (^1H and ^{13}C) are simpler than those of P-FMD and N-FMD (it has fewer peaks). The 4-Methoxy group on T-

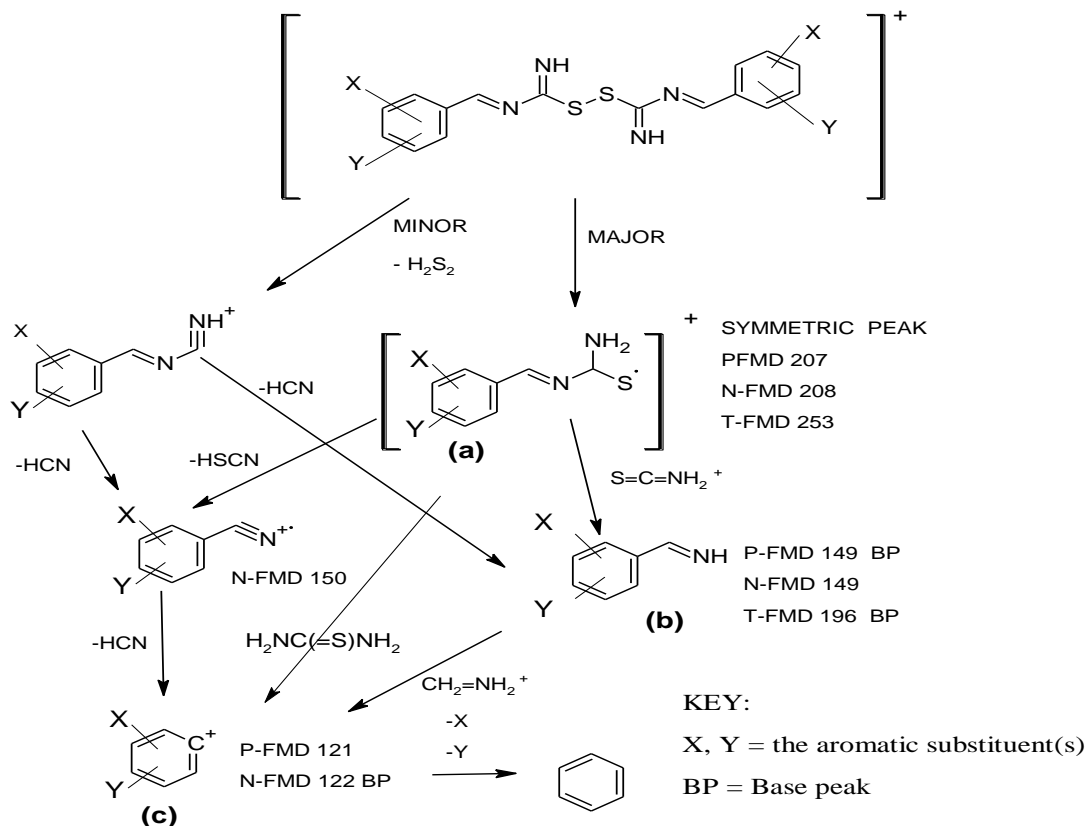


Figure 2. Fragmentation pattern of formamidine derivatives.

FMD provides another point of symmetry other than the disulphide bond which is common to the three compounds. The ^{13}C nmr spectra of all the compounds have a constant overlapping peaks at 190 ppm. These two peaks are attributed to the two imine carbons. The substituent(s) on the aromatic nucleus however helped at differentiating the various carbons as shown in Figure 1.

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