One-Pot Synthesis of Novel Isoxazoline, Pyrazines, Bypyrimidine and Oxime Templates

Evans O. Kenanda

Department of Chemistry, School of Pure and Applied Science, Kisii University, Kenya

**Corresponding author: ekenanda@kisiiuniversity.ac.ke*

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Abstract

Retrieval of low bioactivity phytochemicals and activity optimization through semi-synthetic derivatization is currently the most promising route to drug development. The flavonoids, especially chalcones, from Polygonum senegalense are biologically active. However, they have not been commercialized as drugs because of their low therapeutic value, as guided by the World Health Organization (WHO). In the current study, the flavonoids were derivatised to new isoxazoline, pyrazole, oxime, and bypyrimidine. Two isoxazoline analogues, 4-(4,5-dihydro-5-phenylisoxazol-3-yl)-5-methoxybenzene-1,3-diol (1), and 2-(4,5-dihydro-3-phenylisoxazol-5-yl)-3,6-dimethoxyphenol (2) were successfully afforded by reactions of two chalcones, (E)-1-(2,4-dihydroxy-6-methoxyphenyl)-3-phenyprop-2-en-1-one and (E)-1-(2-hydroxy-4,6-dimethoxyphenyl)-3-en-1-one with hydroxylamine hydrochloride in pyridine respectively. A similar reaction between 1',4'-dihydroxy-6'-methoxychalcone (or (E)-1-(2,4-dihydroxy-6-methoxyphenyl)-3-phenyprop-2-en-1-one) and hydroxylamine hydrochloride in ethanol, adopted for synthesis of oxazole derivative, yielded an oxime instead (3). to introduce heteroatomic Sulphur on a six-membered ring and obtain a bypyrimidine derivative, 4,5-dihydro-6-(2,4- dihydroxy-3,6-dimethoxyphenyl)-4-phenylpyrimidine-2-(1H)-thione (4) □□□-unsaturated chalcone was reacted with thiourea. The structure elucidation was done using ESIHRMS, ^{1}H-NMR, ^{13}C-NMR, and DEPT spectral data analyses. The study revealed that it is possible to generate several semi-synthetic products, most of which are heterocyclic, with improved functionality and bioactivity from natural products by leveraging □□□-unsaturation and other active sites.

Keywords: Pyrazole, Isoxazoline, Oxime, Bypyrimidine

Introduction

Pyrazoles belong to a category of compounds called azoles. These are heterocyclic bases having ring systems composed of two adjacent nitrogen atoms and three carbon atoms (*Figure* 1). Scientists have directed their research on this class of compounds owing to their wide application in medicine and industry. Pyrazolines (dihydropyrazoles) have a wide spectrum of biological activities such as anti-convulsant, muscle relaxant, antidepressant, anti-hypertensive, anti-fungal, anti-bacterial, anti-viral, anti-parasitic, anti-tubercular, insecticidal, anti-inflammatory, anti-diabetic, and anaesthetic and analgesic properties.[1–3]. Most molecules with a pyrazole moiety have exhibited anti-hyperglycemic, analgesic, anti-inflammatory, anti-pyretic, anti-bacterial, and sedative-hypnotic properties. [4,5].

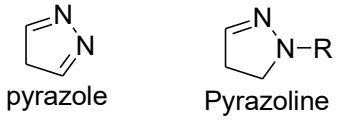


Figure 1: Pyrazole and pyrazoline ring systems

The synthesis of pyrimidines was elicited by recent studies indicating these heterocyclic compounds have wide applications in the pharmaceutical and agrochemical industry. They have been found to possess anti-cancer, anti-viral, anti-HIV, anti-plasmodial, anti-hypertensive, anti-inflammatory, sedative and hypnotic, anti-bacterial, anti-convulsant, and anti-histaminic activities. [1,6,7]. 1,3-dicarbonyls are mainly the starting materials for the synthesis. Chalcones are, therefore, suitable substrates for the provision of reactive intermediates that undergo intermolecular cyclization to pyrimidine derivatives. In the present study, a bypyrimidine was successfully synthesized from a chalcone previously isolated from *Polygonum senegalense* [8]. Similarly, amino methylation of aromatic compounds as starting material by use of the Mannich reaction is considerably important for the synthetic modification of bioactive molecules. The products, Mannich bases biological properties such as antibacterial, anti-inflammatory, anti-histamine, and anti-fungal activities[9,10].

Research surveys have revealed that heterocycles with isoxazole ring systems are widely exploited for the development of biologically active compounds. Studies suggest that isoxazoles have a wide range of bioactivities, such as antianxiety, antidepressant, anti-stress, MAO inhibitory, and anticonvulsant.[11–14].

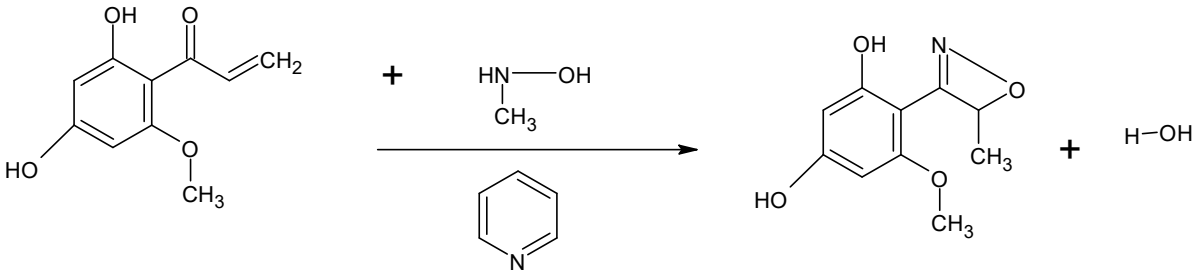
Mannich bases are synthesized from aromatic substrates by the application of the Mannich reaction. The reaction is a condensation reaction involving three components: a hydrogen-containing compound, formaldehyde, and a primary or secondary amine to produce an aldehyde. In addition to the properties mentioned above, Mannich bases also act as bioactive leads, which are further synthetically optimized to various potential agents of high therapeutic value. [15]. They are versatile molecules that are readily modified into other compounds. Research has shown that the conversion of different acrylic conjugated styryl ketones, like chalcones, into these bases leads to increased bioactivity both *in vitro* and *in vivo* [16,17]. The introduction of the amino side chain improves the water solubility of several compounds, thus enhancing their bioavailability. [16,18].

Materials and Methods

The substrates for the synthesis of isoxazoline, pyrazines, bypyrimidine, and Oxime templates were chalcones that were previously isolated from *P. senegalense.*

Synthesis Of 4-(4,5-Dihydro-5-Phenylisoxazol-3-Yl)-5-Methoxybenzene-1,3-Diol (1)

A mixture of 100 mg (write moles) of A(*E*)-1-(2,4-dihydroxy-6-methoxyphenyl)-3-en-one, 10 ml (write moles) of hydroxylamine hydrochloride, and 15 ml (write moles) of pyridine was heated in a reflux for three (3) hours. The reaction was continually monitored by TLC to determine its completion. After cooling, the mixture was poured over crushed ice in a 250 mL beaker. Conc. HCl (3 drops) was added using a plastic dropper. A white precipitate formed was filtered and washed with a lot of water. A TLC analysis gave four spots, indicating the presence of four products. A white solid (compound **1**) crystallized out of the mixture from ethanol. Its R_f was 0.49 in 90 % 1 CH_2Cl_2 in n-hexane, with a yield of 47 %. The spectroscopic data of this compound are recorded in Table 2.



(2*E*)-1-(2,4-dihydroxy-6-methoxyphenyl)but-2-en-1-one

Figure 2: Proposed reaction

Synthesis Of 2-(4,5-Dihydro-3-Phenylisoxazol-5-Yl)-3,6-Dimethoxyphenol (2)

A mixture of 50 mg (molar equivalent) of (*E*)-1-(2-hydroxy-4,6-dimethoxyphenyl)-3-phenylprop-2-en-1-one and 5 mL of hydroxylamine hydrochloride was prepared, followed by the addition of 10 mL of pyridine. The mixture was refluxed in a hot-water bath for 4 h and then poured into an ice-cold beaker. The resulting brown precipitate was filtered and dissolved in 10 mL of ethanol in a 250 mL conical flask. Product 2 crystallized as a grey solid and showed an R_f value of 0.33 in 1% MeOH/CH_2Cl_2[19]. The product was analysed by mass spectrometry and NMR, and the spectral data are summarized in Table 2.

Synthesis of Oxime Derivative (3)

0.02 moles of anhydrous Sodium ethanoate were dissolved in 10ml of ethanoic acid. Hydroxylamine 0.01 moles) was mixed with ethanol (10 ml) and added to (50 mg) of (*E*)-1-(-2,4-dihdroxy-6-methoxyphenyl)-3-phenylprop-2-en-1-one in ethanol. The two solutions were mixed and refluxed for 8 hours and introduced into cold water (ice). The derivative crystallized out as a brown precipitate, which was washed with a lot of water. It registered an R_f 0.53 in 90 % CH_2Cl_2 in n-hexane. The spectral data are given in Table 2.

Synthesis of Bypyrimidine Derivative (4)

A mixture of 100 mg of (*E*)-1-(2,4-dihydroxy-3,6- dimethoxyphenyl)-3-phenylprop-2-en-1-one and 100 mg of thiourea was added to 20 ml of CH_3CH_2OH. A catalytic amount of potassium hydroxide was added to the mixture and refluxed for 12 hours. It was then transferred into a 250 ml beaker, and some ice and three drops of dilute hydrochloric acid were added. Brown crystals were formed, filtered out, and washed with a lot of water.[19]. The product had an R_f of 0.46 in 40% Ethyl acetate in n-hexane and a 59% yield. The product was spectroscopically analyzed by MS and NMR, and the information was summarized in Table 2.

Spectroscopic Analysis

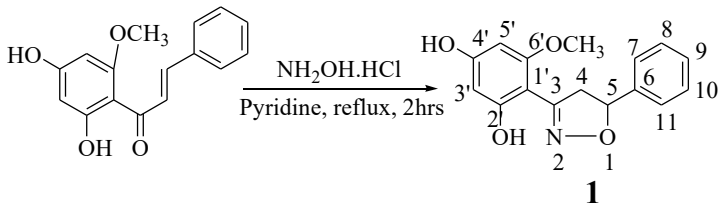
NMR tubes were thoroughly washed with water and acetone, cleaned with cotton wool, and sufficiently dried in the oven. Approximately 5mg of sample was dissolved in 0.6-0.7 mL of a deuterated DMSO, $CDCl_3$, methanol, or acetone, depending on its solubility, and then filtered through a Pasteur pipette, equipped with a glass wool plug that discharges into an NMR tube. It was filled to a depth of approximately 4 cm. The tube was tightly closed and placed in the NMR equipment for sample analysis.

Results and Discussion

Four semisynthetic analogues were derivatised from flavonoids of P. senegalense.

4-(4,5-Dihydro-5-Phenylisoxazol-3-Yl)-5-Methoxybenzene-1,3-Diol (1)

The isoxazoline derivative (**1**) was generated from the reaction of (*E*)-1-(2,4-dihydroxy-6-methoxyphenyl)-3-en-one and hydroxylamine hydrochloride. It was crystallized from ethanol as a white solid with an R_f value of 0.49 in 90 % CH_2Cl_2 / n-C_6H_{14} with a yield of 47 % w/w.



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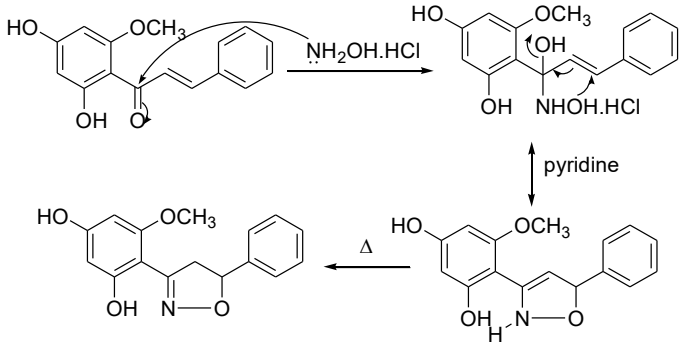
Scheme 1: Reaction of flavone with hydrazine hydrate

The structural proof of the product was provided by both ESIHRMS and NMR analyses. EIS-HRMS gave $M^+ + 1$ Peak at 284 is in line with its molecular formula, $C_{16}H_{15}NO_4$. The characteristic C−O and C=N signals of the isoxazoline ring were typically observed at δ_C 76.4 and 153.1, respectively. The tetrahedral carbon adjacent to the oxygen in the ring system emerged at this point because of the strong deshielding of the oxygen and its proximity to the benzene ring. The DEPT spectrum revealed the existence of a CH_2 carbon at δ_C 29.6 (carbon number 4). The CH_2 and CH groups were further confirmed by the ABX spin system exhibited by their protons. The *dd* in the regions of δ_H 3.32-3.37(*Jgem*=12.0, J_{vic}=4.0) and 2.77-2.84 (J_{gem}=12.0, J_{vic}=4.0) is due to vicinal and germinal coupling among the three protons. The methine proton also magnetically interacted with the axial and germinal CH_2 protons and formed a *dd* at δ_{H} 5.18- 5.22

(J_{ax}=12.0, J_{eq}=4.0). The CH proton is downfield of CH_2 due to the higher deshielding anisotropic and electron-withdrawing effect of the benzene ring and oxygen, respectively.

The aromatic C-6 of the mono-substituted aryl ring typically emerges at δ_{C} 140.0. The symmetrically two pairs of carbons, C−7/11 and 8/10 intense showed up at δ_C 128.9 and δ_C 126.9, respectively. Resonance signal at δ_C 128.8 was due to C-9 at the *para* position. Three aryl carbons, C-2 ',- 4 ', and -6', of the 2,4,6-trisubstituted aromatic ring with oxygen substitution were assigned to chemical shifts at δ_C 158.1, 159.4, and 162.3 in ^{13}C-NMR. The protonated aryl carbons, C-3' and C-5', between these oxygenated aryl carbons, commonly appeared at δ_C 95.7 and 94.3, respectively. The protons bonded to these carbons overlapped at δ_H 6.08. The sp^2 quaternary aryl carbon, C-1', which is also between 1,3-*diortho* oxygen-substituted carbons, resonated at δ_C 98.7. The carbon of the methoxy substituent on C-6' formed at δ_C 55.8, and its protons appeared as a singlet at δ_H 3.69. In proton NMR, the signal at δ_{H} 11.42 was due to ArOH of C-2' which undergoes great hydrogen bonding with the imine group.

This synthesis leverages nucleophilic addition of hydroxylamine to the *β*-carbon of the (*E*)-1-(2,4-dihydroxy-6-methoxyphenyl)-3-en-one (*Scheme 2*).



Scheme 2: Synthesis of isoxazoline analogues from chalcones

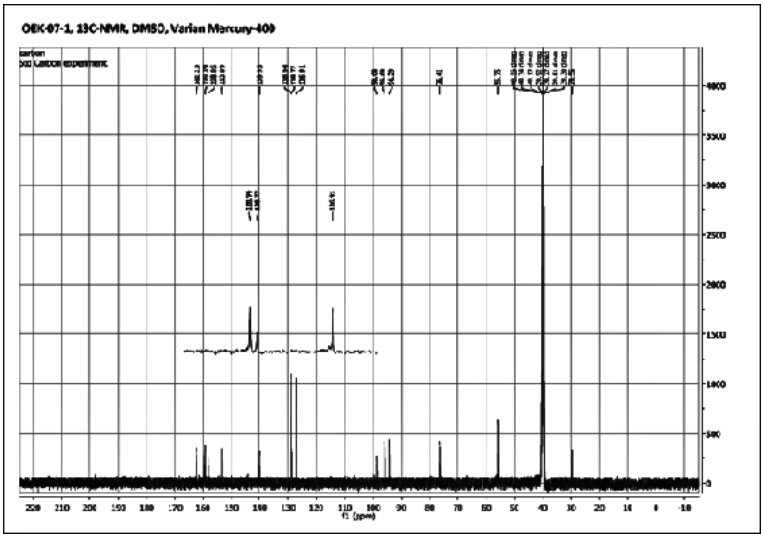
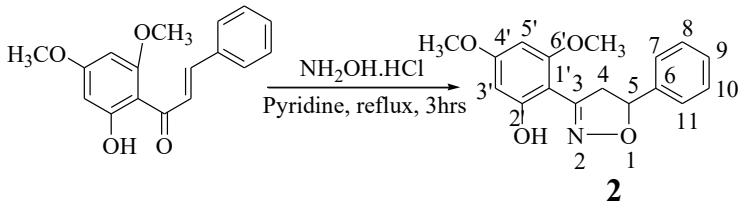


Figure 3: ^{13}C- NMR Spectrum of Compound 1

2-(-4,5-Dihydro-5-Phenylisoxazol-3-Yl)-3,5-Dimethoxyphenol (2)

A reaction between 2'-hydroxy-4',6-dimethoxychalcone and hydroxylamine hypochlorite in pyridine afforded the product (*Scheme 3*). After refluxing for three hours, the mixture obtained was introduced into ice-cold water, from which a brown solid crystallized. The product was put in 15 mL of ethanol in a conical flask for recrystallization and further purification. It is a grey solid with an R_f of 0.33 in 1% MeOH in CH_2Cl_2 with a yield of 86%.



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Scheme 3: Synthesis of 2-(-4,5-dihydro[A1.1]-5-phenylisoxazol-3-yl)-3,5-dimethoxyphenol (2)

The ESIHRMS M^+ peak at m/z 300 was undoubted confirmation of the success of the synthetic reaction. Both ^{1}H- and ^{13}C-NMR spectra gave signals typical of isoxazoline ring systems (*Table 1*). The C=N and C−O carbons appeared at δ_C 147 and 76.7, respectively. The CH_2 carbon was typically observed at δ_C 30.7. ^{1}H-NMR spectrum showed a peak $\delta_{\square}$ at δH 2.67 and 3.75 for methylene protons, whereas the methine proton signal emerged in the downfield region at $\delta_{\delta H\ 5.08}$. ArC-6 of the mono-substituted benzene ring was observed at δ_C 140.5. The other carbons appeared in the δ_C 126.7−128.9 with their appearing as multiplets in the region of δ_H 7.38 to 7.45, respectively. In the other aromatic ring, C−3' and C-5' appeared downfield shifted to δ_C 93.7 and 94.7. The oxygenated aromatic C-6', 4' and 2' emerged at δ_C 159.0, 159.4, and 161.3, respectively. The peaks at δ_C 55.7 and 56.1 were for methoxylated carbons at C−4' and 6'. The ArC-1' was assigned to δ_C 102.3. In summary, both proton and Carbon-NMR spectroscopic information are in Table 1.

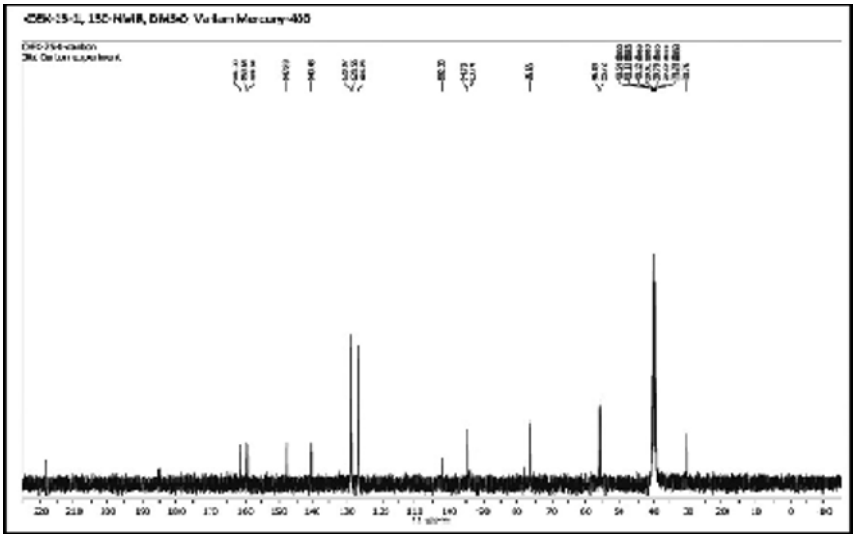


Figure 4: 13C- NMR Spectrum of Compound 2

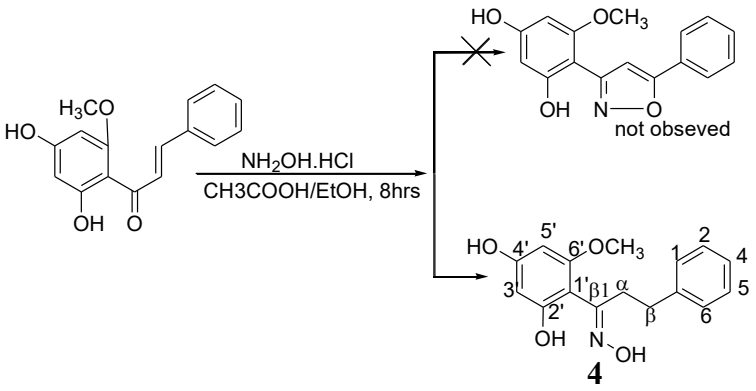
Table 1: Spectral Data of Compounds 1 And 2

Compound 1			Compound 2		
X	^{13}C-NMR and DEPT (DMSO-D6, 400 MHz)	^{1}H-NMR ($CDCl_3$, 400 MHz)	X	^{13}C-NMR and DEPT (ppm) (DMSO-d_6)	^{1}H-NMR (ppm) (DMSO- d_6)
4	29.5 (1C, CH_2)	2.77-2.84 (*dd,* 1H, CH_2, J_{gem}=12.0, J_{vic}=4.0) 3.32-3.37 (*dd,* 1H, CH_2, J_{gem}=12.0, J_{vic}=4.0)	4	30.7 (1C, CH_2)	2.64-2.71, 3.75 (*dd*, 2H, J_{gem}=16.0, J_{vic}=4.0
4'-OCH_3	55.7 (1C, OCH_3)	3.69 (*s*, 3H, OCH_3)	4', 6'-OCH_3	55.7, 56.1 (2C, CH_3)	3.34 (s, 6H, CH_3)
5	76.4 (1C, C-O)	5.18-5.22 (J_{ax}=12.0, J_{eq}=4.0) ppm	5	76.7 (1C, CH)	5.08 (*d*, 1H, CH, J = *16.0*)
5'	94.3 (1C, ArC)	6.06 (*d*, 1H, ArH, $^{4}J_{HH}$=2.45)	3', 5'	93.7 (1C, CH, ArC) □□□□□□1C, CH, ArC)	6.18, 6.22 (*s*, 2H, ArHs)
3'	95.7 (1C, ArC)	6.08 (*d*, 1H, ArH, $^{4}J_{HH}$=2.45)	1'	102.3 (1C, *q*, ArC)	
1'	98.7 (1C, *q*, ArC)		7/11	126.7 (2C, CH, ArC)	7.38-7.45 (*s*, 5H, ArHs)
7/11	126.9 (2C, ArHs)	7.2-7.25 (*m*, 5H, ArH,)	9	128.6 (1C, CH, ArC)	
9	128.8 (1C, ArH)		8/10	128.9 (1C, CH, ArC)	
8/10	128.9 (2C, ArHs)		6	140.5 (1C, *q*, ArC)	
6	134.9 (1C, *q*, ArC)		3	147.9 (1C, *q*, C=N)	
3	153.1 (1C, *q*, C=N)		6'	159.0 (1C, *q*, ArC-OCH_3)	
4'	158.1 (1C, ArC-OH)	3.51 (*s*, 1H, ArOH)	2'	159.4 (1C, *q*, ArC-OH)	11.08 (*s*, 1H, ArOH)
6'	159.4 (1C, ArC-OCH_3)		4'	161.3 (1C, *q*, ArC-OCH_3)	
2'	162.3 (1C, ArC-OH)	11.31 (*s*, 1H, ArOH)			

Key: X - position of carbon atom

Synthesis of Oxime Derivative, Compound 3

An oxime was generated through a reaction between (E)-1-(2,4-dihydroxy-6-methoxphenyl)-3-phenylprop-2-en-1-one and hydroxylamine hydrochloride that was adopted for the synthesis of an oxazole. The semi-synthetic compound precipitated as a brown solid registered an R_f of 0.53 in 90 % DCM in n-C_6H_{12} and 78% yield.



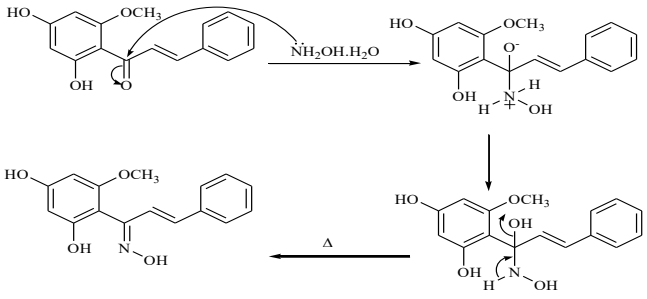
Scheme 4: : A Reaction Scheme for the Synthesis of Oximes

The structure of the oxime-derived product was elucidated from its NMR data. The ^{13}C-NMR and DEPT spectra showed peaks of the two methylene groups at δ_C 28.2 and 33.7 in the shielded region. The protons of these carbons gave signals at δ_H 3.04 ($^3J_{HH}$=8.0) and δ_H 3.15 ($^3J_{HH}$=8.0). The characteristic imine carbon was typically observed at δ_C 153.5.

As usual, oxygen-substituted aromatic carbons of 2,4,6-trisubstituted aryl ring emerged at δ_C 157.5, 173.7, and 166.3, and the 1,3-*diortho* protonated carbons were downfield shifted to δ_C 84.8 and 97.8. The protons attached to these carbons appeared as singlets at δ_H 6.25 and 6.62 in the proton NMR spectrum. The quaternary C-1' attached to the imine carbon had its signal at δ_C 105.5. The ^{1}H–NMR peak at δ_H 10.80 was due to OH in the aromatic ring A. The immense deshielding effect on the proton due to chelation by the imine moiety brings its resonance to the downfield region. However, the imine OH proton appeared upfield as a broad peak at δ_H 3.25 due to great shielding from oxygen directly attached to it.

A quaternary carbon resonating at δ_C 141.4 in ^{13}C-NMR was assuredly C-6 of the mono-substituted aryl ring. The rest of the carbons were observed at δ_C 128.7 (two symmetric carbons), 128.8 (two symmetric carbons), and 126.5 (carbon at the *para* position). The multiplets of peaks appearing between δ_H 7.14 and 7.27 in the ^{1}H-NMR spectrum were assigned to protons bonded to these carbons.

This reaction mechanism starts with the nucleophile hydroxylamine attacking the carbonyl carbon of the chalcone, as shown below.



Scheme 5: Proposed reaction scheme for semi-synthesis of oxime analogues

Sodium ethanoate

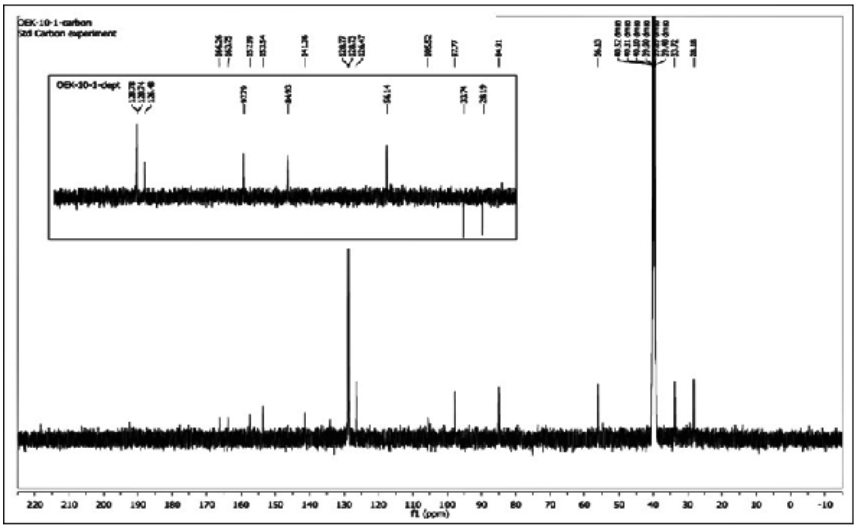
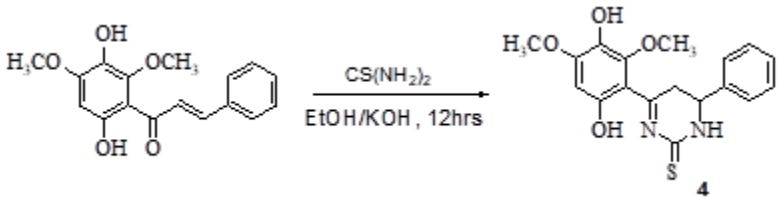


Figure 5: 13C- NMR Spectrum of Compound 4

4,5-Dihydro-6-(2,4-Dihydroxy-3,6-Dimethoxyphenyl)-4- Phenylpyrimidine-2-(1*H*)-Thione (4)

The reaction between (*E*)-1-(2,4-dihydroxy-3,6-dimethoxyphenyl)-3-phenylprop-2-en-1-one and thiourea afforded a pyrimidine derivative, compound 4. It is a brown compound which posed R_f of 0.48 in 40% EtOAC in n-hexane and a 57% yield w/w.



Scheme 6: Synthesis of compound 4

Structural proof of this analogue (4) was attained by the use of spectroscopic methods. Characteristic signals were observed for confirmation purposes. ^{13}C-NMR of the carbon attached to Sulphur (C=S) was typically observed at δ_C 188.7 (*Figure 6*). The carbon attached to the imine group emerged at δ_C 164.6. The CH_2 carbon, which is highly deshielded because of its closeness to the benzene ring, appeared in the deshielded region at δ_C 78.8. In DEPT and ^{13}C-NMR analyses, the CH_2 carbon of the pyrimidine ring appeared at δ_C 45.0. The broad peak in ^{1}H-NMR at δ_H 7.36 was for the NH proton. Also typical of this compound are the CH_2 and CH protons appearing as a doublet of doublets at δ_H 2.73 (J=13.2) and 2.98 (J=10.4, 2.4, and a singlet at δ_H 5.50 (J=8.8), respectively.

In the 2',4',5',6'-tetrasubstituted aromatic ring, the ^{13}C NMR peak for the non-substituted aromatic carbon between the oxygenated C-4' and C-6' typically appeared at δ_C 93.7. The singlet at δ_H 6.14 was due to the proton bonded to the carbon. Other carbons in the ring appeared in the low-field region of the ^{13}C-NMR spectrum. The hydroxy substituted C-2' and C-6' were assigned to δ_C 129.6 and 157.7, respectively. C-2'

was upfield since it experiences great shielding from the methoxy groups in the *ortho* position. Methoxylated ArCs of the same ring were commonly observed at δ_C 155.6 and 157.6, and the more shielded quaternary C-1' at δ_C 104.2.

The signal at δ_C 139.1 was for C-7 of the mono-substituted aryl ring. The two pairs of symmetrical carbons, C−8/12 and 9/11, produced intense peaks at δ_C 125.7 and 128.3, respectively. The *para*- carbon, C-10, appeared at δ_C 128.9. The corresponding protons appeared in the region of δ_H 7.34-7.53 as multiplets. A summary of ^{1}H- and ^{13}C-NMR spectroscopic data is given in Table 2.

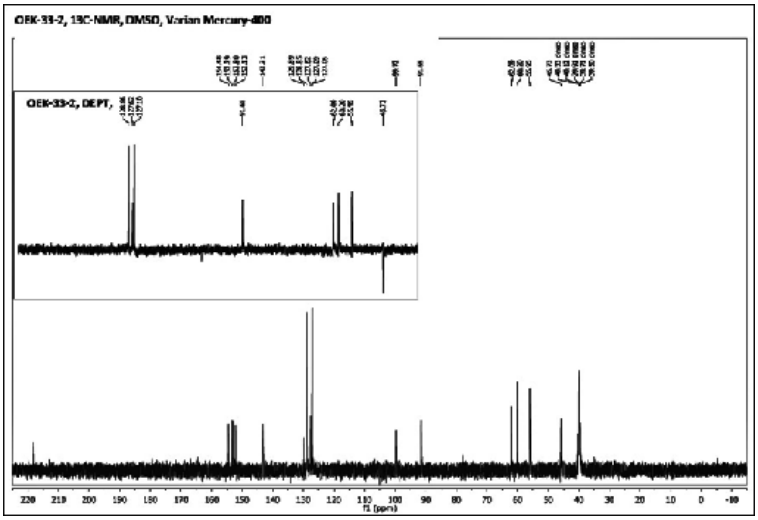


Figure 6: 13C- NMR Spectrum of Compound 4 (bypyrimidine)

Table 2: Spectra of compounds 3 and 4

Compound 3			Compound 4		
X	^{13}C-NMR and DEPT (DMSO-D_6, MHz 400)	^{1}H-NMR DMSO-d_6, 400MHz)	X	13C-NMR and DEPT DMSO-D_6, MHz 400)	1H-NMR DMSO-D_6, MHz 400)
	28.2 (1C, CH_2)	3.04 (*t*, CH_2, $^3J_{HH}$=8.0	5	45.0 (1C, CH_2)	2.67 and 3.75 (*m*, 2H, CH_2)
	33.7 (1C, CH_2)	3.15 (*t*, CH_2, $^3J_{HH}$=8.0)	2'-, 4'-OCH_3	56.0, 60.9 (2C, CH_3)	3.63, 3.69 (*s*, 6H, CH_3)
4'-OCH_3	56.1 (1C, OCH_3)	3.75 (s, 3H, CH_3)	6	78.8 (1C, CH)	5.50 (*m*, 1H, CH)
3', 5'	84.9, 97.8 (2C, CH, ArC)	6.25, 6.62 (*s*, 2H, ArH)	5'	93.7 (1C, CH, ArC)	
1'	105.5 (1C, *q*, ArC)		1'	105.2 (1C, *q*)	
4	126.5 (1C, ArC)	7.16-7.27 (*m*, ArHs)	8/12	125.7 (2C, CH, ArC)	6.14 (*s*, 1H, ArH)
2/6	128.7 (2C, ArC)		10	128.9 (1C, CH, ArC)	

3/5	128.8 (2C, ArC)		9/11	128.3 (2C, CH, ArCs)	7.37- 7.50 (*m*, 5H, ArH)
1	141.4 (1C, *q*, ArC)		3'	129.6 (1C, *q*, ArC-OH	
□ '	153.5 (1C, *q*, C=N)		7	139.5 (1C, *q*, ArC)	
4'	157.4 (1C, *q*, ArC)		2'	155.6 (1C, *q*, ArC-OCH_3)	
6'	163.8 (1C, *q*, ArC)		6'	157.7 (1C, *q*, ArC-OH)	10.50 (*s, broad*), 1H, OH, ArOH)
2'	166.8 (1C, *q*, ArC)	10.80(*s* (broad), 1H, ArH)	4'	157.6 (1C, *q*, ArC-OCH_3)	
		3.25 (*s* (broad), 1H, N-OH	4	164.6 (1C, *q*, C=N)	
			2	188.7 (1C, *q*, C=S)	

Key: X – position of carbon atom

Conclusion

In general, five compounds were synthesized using chalcones isolated from *P. senegalense* as starting materials. The derivatives are 4-(4,5-dihydro-5-phenylisoxazol-3-yl)-5-methoxybenzene-1,3-diol (1), 2-(-4,5-dihydro-5-phenylisoxazol-3-yl)-3,5-dimethoxyphenol (2), 5-methoxy-2-(5-(2,3,4,5-tetramethoxyphenyl)-1*H*-pyrazol-3- yl) benzene-1,3-diol (3), and oxime and 4,5-dihydro-6-(2,4-dihydroxy-3,6-dimethoxyphenyl)-4- phenylpyrimidine-2-(1*H*)-thione (4).

List of Abbreviations

ArC	–	Aromatic carbon
ArC—O	–	Aromatic carbon bonded to hetero-atomic oxygen
ArC-OCH_3	–	Methoxylated Aromatic carbon
ArC-OH	–	Hydroxylated ArC
ArH	–	Aromatic proton
ArOH	–	Phenolic proton
ASA	–	Acetylsalicylic Acid
CC	-	Column chromatography
CFU	-	Colony-Forming Unit
EIS-HRMS	-	Electrospray Ionization High-Resolution Mass Spectroscopy
J	-	Coupling constant
*J*ax	-	Coupling with axial proton
*J*eq	-	Coupling with the equatorial proton
*J*gem	-	Germinal coupling
*J*vic	-	Vicinal coupling

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Conflict of Interest

The author declares that he has no competing interests

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