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Original Article

Pyrazole, Isoxazoline and Bypyrimidine Derivatives from *Polygonum senegalense* and *Psiadia punctulata* Flavonoids and their Anti-Microbial Activities

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ABSTRACT

Currently, researchers have given special attention to the synthesis of heterocyclic compounds with nitrogen and oxygen five in five- or six-membered ring systems. This is mainly due to their wide range of biological activities. Hence, in this study, isoxazoline, pyrazole and bypyrimidine derivatives were synthesized from flavonoids, previously isolated from *Polygonum senegalense* and *Psiadia panctulata,* and assessed for their anti-fungal activity. A flavone was reacted with hydrazine hydrate to afford a pyrazole analogue 5-methoxy-2-(5-(2,3,4,5-tetramethoxyphenyl)-1*H*-pyrazol-3-yl)benzene-1,3-diol (**1**) Two isoxazoline derivatives namely, 2-(4,5-dihydro-5-phenylisoxazol-3-yl)-5-methoxybenzene-1,3-diol (**2**) and 2-(-4,5-dihydro-5-phenylisoxazol-3-yl)-3,5-dimethoxyphenol (**3**) were successfully synthesized by the reaction of chalcones with hydroxylamine hydrochloride. An oxime derivative (**4**) was also generated from a similar procedure. A reaction between a chalcone and thiourea gave a bypyrimidine derivative, 4,5-dihydro-6-(2,4-dihydroxy-3,6-dimethoxyphenyl)-4-phenylpyrimidine-2-(1H)-thione (**5**). The products were then assessed for their anti-bacterial and anti-fungal activity. All compounds showed no significant activity except compound **2** that demonstrated activity against standard anti-bacterial agent, *Streptococcus aureus* with IC_{50} value of 7.56 and anti-fungal *Candida neoformans, Candida krusei* and *Candida glabrata* strains with IC_{50} values 8.01, 8.11 and 13.74 µg/mL respectively. We, therefore, recommend synthetic optimization of compound **2** as a potential anti-microbial agent.

Key words: Bypyrimidine, Isoxazolines, Oxime, Pyrazole, Chalcones

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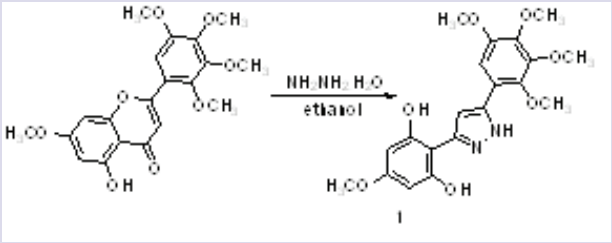
INTRODUCTION

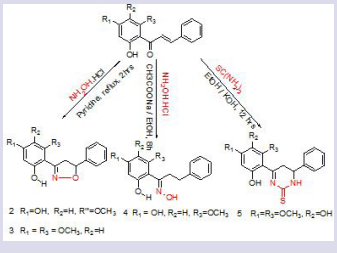
Pyrazoles fused with different heterocycles are known to contribute to various chemotherapeutic effects and have emerged as anti-microbial, anti-fungal and anti-viral agents.1-3 Similarly, a large number of pyrimidine derivatives have been reported to exhibit anti-microbial[4,5] and anti-fungal[4,6] activities.

The isoxazolines possess a variety of significant and diverse pharmacological activities including anti-fungal, anti-bacterial, anti-muscarinic, anti-inflammatory, anticancer and anti-depressant activities.[7] Consequently, there have been extensive studies on these compounds as promising disease-controlling agents.[1] In addition, different pyrimidine derivatives have remarkable pharmaceutical importance because of their biological activity as anti HIV, anti-tubercular and anti-diabetic compounds.[8] In view of the above mentioned facts, it was thought of interest to synthesize some new heterocyclic compounds containing isoxazoline, pyrazole and pyrimidine rings and examine their anti-microbial properties. The substrates were flavonoids of *Polygonum senegalense,*[9,10] and *Psiadia punctulata* flavonoids.[11]

Polygonum senegalense has been found to be rich in flavonoids, especially chalcones.[9,10] This class of compounds has been extensively employed as intermediates in the synthesis of heterocyclic and carbocyclic system.[12] This is due the presence of reactive keto-ethylenic group in their general skeleton. A natural flavone, 5, 9-dihydroxy-2′,3′,4′,5′-tetramethoxy-flavone from *Psiadia panctulata,*[11] was reacted with hydrazine hydrate to produce the semi-synthetic pyrazole product **1** (Equation 1). The protocol followed was a modification of the procedures of Hassan *et al.* (2010).[3] Two chalcones were successively converted to isoxazoline derivatives, **2** and **3** (scheme 1). An effort to convert a chalcone to a substituted oxazole by reacting it with hydroxylamine hypochloride and sodium acetate in ethanol, in accordance with a modified procedures of Ragini *et al.*, 2010,[12] yielded an oxime (**4**) analogue instead (scheme 1). A substituted bypyrimidine derivative (**5**) was also obtained by reacting a chalcone, 3,6-dihydroxy-2,4-dimethoxychalcone, with thiourea (scheme 1).



Equation 1: synthesis of pyrazole derivative



Scheme 1: Synthesis of isoxazoline, oxime and bypyrimidine derivatives

MATERIALS AND METHODS

Procedure for preparation of pyrazole derivative

A sample of 100 mg of flavone 8-hydroxy-6-methoxy-3-(2,3,4,5-tetramethoxyphenyl)naphthalen-1-(4*H*)-one was dissolved in 10 ml of ethanol and excess of hydrazine was added, according to modified procedure of Essam *et al* (2012).[8] The mixture was poured into a quick-fit flask fitted with a thermometer and a refluxing condenser and refluxed for 3 hours on a magnetic stirrer. The mixture was allowed to stand overnight. Shiny pale yellow crystals from ethanol were filtered and washed with excess ethanol.

General procedure for preparation of isoxazoline analogues

A sample of 100 mg of a chalcone was mixed with 10 ml of hydroxylamine hydrochloride in 15 ml pyridine. The mixture, in a quick-fit flask fixed with a thermometer and a refluxing condenser and on a magnetic stirrer, was heated in a reflux for 3 hours (the reaction was monitored by Thin Layer Chromatography, TLC). The reaction mixture was allowed to cool and then poured over crushed ice in a 250 ml beaker. A few drops of concentrated HCl were added. A precipitate formed that was filtered and washed with a lot of water. A TLC analysis was done and product (isoxazoline derivative) was crystallized out of the mixture from ethanol.

Procedure for preparation of oxime derivative

Anhydrous sodium acetate (0.02 mol) was dissolved to 10 ml of acetic acid. Hydroxylamine hydrochloride (0.01 mol) in ethanol (10 ml) was added to the solution of 2',4'-dihydroxy-6'-methoxychalcone (50 mg) in ethanol. The solution of sodium acetate in acetic acid was transferred to this reaction mixture in a quick-fit flask fitted with a thermometer and refluxing condenser on a magnetic stirrer and refluxed for 8 hr at temperature range of 40-60°C. The progress of the reaction was monitored by TLC. The completion of The reaction was poured into ice cold water. A brown precipitate that formed was washed with excess water and spotted on a TLC. The precipitate gave a single spot with R_f0.53 in 90 % CH_2Cl_2 in n-hexane.

Procedure for preparation of bypyrimidine derivative

An amount of 100 mg of a,b-unsaturated chalcone, (*E*)-1-(2,4-dihydroxy-3,6-dimethoxyphenyl)-3-phenylprop-2-en-1-one, was mixed with 100 mg of thiourea and dissolved in 20 ml of ethanol. A catalytic amount of KOH was added. The mixture, in a quick-fit flask fitted with a thermometer and refluxing condenser and on a magnetic stirrer, was heated on reflux for 12 hours. It was then transferred to a 250 ml beaker into which crushed ice was poured. A few drops of HCl were added. A brown precipitate, which formed almost immediately was filtered out and washed with excess water to afford product **5.** It registered an R_f of 0.46 in 40% EtOAc (ethyl acetate) in n-hexane and a yield of 59%. The spectral data is recorded in table 1.

In vitro anti-microbial activity assay

The anti-microbial susceptibility assays were done using Clinical and Laboratory Standard Laboratory Institute (CLSI) method.[16] The positive controls were ciprofloxacin (≥ 98% purity assessed by HPLC at ICN Biomedicals, Ohio) for bacteria and amphotericin B (≈ 80& purity assessed by HPLC at ICN Biomedicals, Ohio). The test organisms, *C. albicans* (ATCC 90028), *C. glabrata* (ATCC 90030), *C. krusei* (TCC 6258), *A. fumigatus* (ATCC 90906), *C. neoformans* (ATCC 9011), *S. aureus* (ATCC 29213), Methicillin-resistant *S. aureus* (ATCC 33591), *E. coli* (ATCC 35218), *P. aeruginosa* (ATCC 27853) and *M. intracellulare* (ATCC 23068) were obtained from the American Type Culture Collection, ATCC (Manassas, Virginia).

RESULTS AND DISCUSSION

structure elucidation

5-Methoxy-2-(5-(2,3,4,5-tetramethoxyphenyl)-1H-pyrazol-3-yl) benzene-1,3-diol (1)

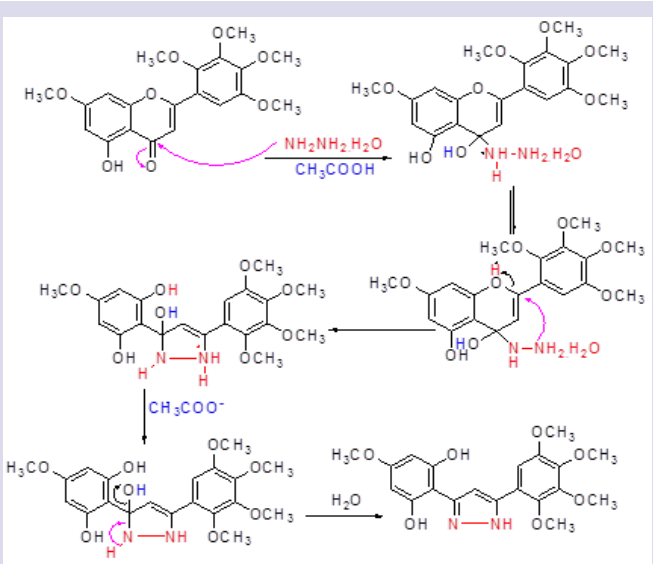
It was isolated as a light yellow solid with R_f value of 0.63 in 2% MeOH in CH_2Cl_2 and a yield of 74% w/w. Electron Spray Ionization High Resolution Mass Spectrometry (ESIHRMS) spectrum of this product gave molecular ion peak at m/z 402 (, which was consistent with its molecular formula, $C_{20}H_{22}N_2O_7$. In ^{13}C-NMR spectrum, characteristic imine and amine C-5 and C-3 peaks appeared at δ_C 147.7 and 149.9 respectively. They appeared downfield due to aromaticity of pyrazole ring and deshielding anisotropic effects in unsaturated systems. The NH proton was also downward shifted to δ_H 11.50 because of the deshielding effects of the heteroatomic nitrogen. A summary of both ^{1}H- and ^{13}C-NMR chemical shift assignments is given in Table 1. Scheme 2 below outlines the proposed mechanism for this conversion.

An attempt to convert another flavone, 5,7-dihydroxy-3,4´-dimethoxyflavone, in the same way was not successful. This could be attributed to the bulky methoxy group at C-3 which hinders nucleophilic attack on C-2 (see Scheme 3).

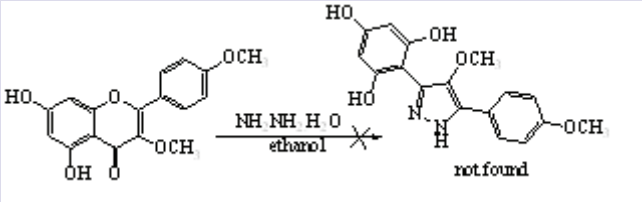
2-(4,5-dihydro-5-phenylisoxazol-3-yl)-5-methoxybenzene-1,3-diol (2)

This is a white compound. It registered an R_f value of 0.49 in 90 % CH_2Cl_2 in n-hexane and a yield of 47 % w/w. its EIS-HRMS spectrum gave molecular ion peak at 284 which was in agreement with its molecular formula, $C_{16}H_{15}NO_4$. The characteristics peaks for C=N and C–O groups of the isoxazoline ring were typical at δ_C 153.1 and 76.4 respectively. A *sp3* carbon bonded to heteroatomic oxygen in a five membered ring system appears in this region due to strong deshielding from the electronegative oxygen and for being close to the benzene ring experiencing deshielding anisotropic effects.

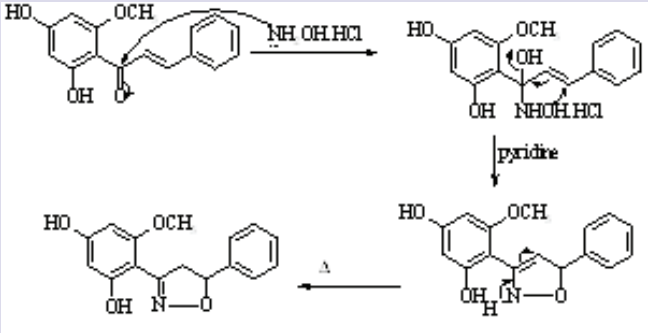
The DEPT spectrum showed a methylene carbon at δ_C 29.6 which was the CH_2 formed during cyclization of the substrate to isoxazoline system. The presence of methylene and methine groups was further revealed by the ABX spin system exhibited by the protons. CH_2 protons experienced geminal coupling, and vicinal coupling with methine proton and as a result formed doublet of doublets in the regions of δ_H 2.77-2.84 (J_{gem}=12.0, J_{vic}=4.0) and 3.32-3.37(J_{gem}=12.0, J_{vic}=4.0). Methine proton also coupled



Scheme 2: Proposed mechanism for the conversion of flavone to pyrazoles



Scheme 3: Conversion of 3-methoxysubstituted flavones to pyrazoles



Scheme 4: Proposed mechanism for conversion of chalcones to isoxazoline analogues

with the axial and geminal CH_2 protons and formed doublet of doublets in the range δ_H 5.18-5.22 (J_{ax}=12.0, J_{eq}=4.0). The methine proton was downfield of CH_2 because the former experiences more deshielding anisotropic and electron withdrawing effect of the benzene ring and the heteroatomic oxygen respectively; otherwise a proton on a *sp3* carbon in a five-membered cyclic compound appears below δ_H 3.00.

Another characteristic peak is that of quaternary aromatic C-6 of the monosubstituted aryl ring typically appearing at δ_C 140.0. The two pairs of chemically equivalent carbons, C–7/11 and 8/10 produced intense signals at δ_C 128.9 and δ_C 126.9 respectively. C-9 at the *para* position resonated at δ_C 128.8. The corresponding protons of these ArCs were observed as multiplets in the region of δ_H 7.33 to 7.49.

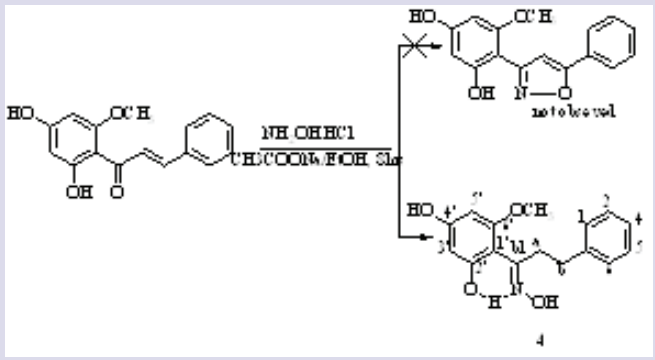
In ^{1}H-NMR, the signal at 11.42 was due to phenolic proton of C-2' which undergoes strong chelation by the imine group. A summary of spectral and ^{13}C- and ^{1}H- NMR assignments are recorded in Table 1.

This is Michael addition reaction with the hydroxylamine adding to the β-carbon of the chalcone (see Scheme 4).

2-(-4,5-dihydro-5-phenylisoxazol-3-yl)-3,5-dimethoxyphenol (3)

Compound **3** was isolated as an amorphous grey solid having R_f of 0.33 in 1% MeOH in CH_2Cl_2 and a yield of 86%. The ESIHRMS molecular ion peak appeared at m/z 300 which was concrete proof of the success of this conversion. Both ^{1}H- and ^{13}C-NMR spectra showed peaks characteristic of isoxazoline ring systems. The carbons of C–O and C=N groups were observed at δ_C 76.7 and 147 respectively. The methylene carbon was also typically noted at δ_C 30.7. Its protons resonated at δ_H 2.67 and 3.75 whereas methine proton appeared downfield at δ_H 5.08.

The non-substituted aromatic carbons of the monosubstituted aryl ring were observed in the region of δ_C 126.7–128.9, with their corresponding protons forming multiplets in the range of δ_H 7.38–7.45 in 1H-NMR spectrum respectively. The quaternary aromatic C-6 of the ring generated ^{13}C-NMR signal at δ_C 140.5. A summary of both ^{1}H- and ^{13}C-NMR chemical shift assignments of product 3 are given in Table 1.



Scheme 5: Reaction of 2',4'-dihdroxy-6'-methoxychalcone with ammonium hydrochloride

Oxime derivative (4)

A reaction between 1',4'-dihydroxy-6'-methoxychalcone and hydroxylamine hydrochloride, adopted for synthesis of an oxazole,[4] gave an oxime derivative as revealed by NMR analyses.

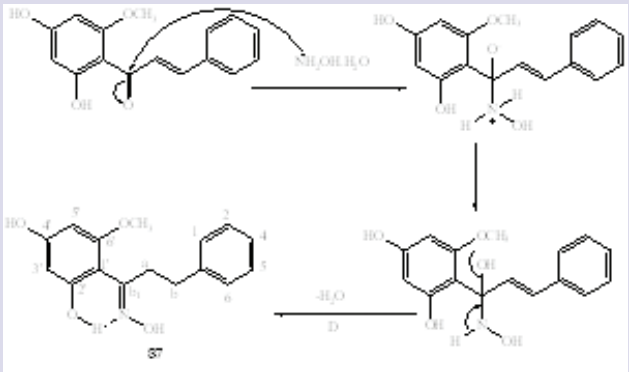
It was obtained as an amorphous brown solid with R_f 0.53 in 90 % CH_2Cl_2 in n-hexane and a yield of 78%. Both ^{13}C-NMR and DEPT spectra of the compound showed the chemical shifts of the two methylene carbons at δ_C 28.2 and 33.7 in the upfield region of ^{13}C-NMR spectrum. The triplets at δ_H 3.04($^3J_{HH}$=8.0) and δ_H 3.15 ($^3J_{HH}$=8.0) were due to protons bonded to these carbons. The imine carbon was typical at δ_C 153.5.

The ^{1}H–NMR signal at δ_H 10.80 was due to proton of the phenolic hydroxyl group on C-2'. This proton experiences great deshielding caused by chelation by the imine moiety. However, the imine group proton was highfield shifted and appeared as a broad signal at δ_H 3.25 because of the immense shielding from oxygen to which it is directly bonded. A summary of spectral data is given in Table 1.

The formation of the oxime derivative followed 1, 2-addition reaction where there was nucleophilic attack on the chalcone carbonyl carbon (see Scheme 6).

4,5-dihydro-6-(2,4-dihydroxy-3,6-dimethoxyphenyl)-4-phenylpyrimidine-2-(1H)-thione (5)

This a brown solid with R_f of 0.48 in 40 % EtOAc in n-hexane and a yield of 57 %. HRMS showed its molecular ion at *m/z* 346.1921 which was in agreement with the formula $C_{17}H_{18}O_2N_4S$. Both ^{1}H- and ^{13}C-NMR signals characteristic were observed. The thiocarbonyl carbon (C=S) of



Scheme 6: Stepwise synthesis of oxime analogues from a,b-unsaturated chalcones

Table 1: ^{1}H- and ^{13}C-NMR spectral data of compounds 1-5

1 (DMSO			2 (Acetone-d_6)			3 (DMSO)			4 (DMSO)			5 (DMSO)		
Position	δ_C	δ_H	Position	δ_C	δ_H	Position	δ_C	δ_H	Position	δ_C	δ_H	Position	δ_C	δ_H
10	55.1		4	29.5	2.81 (*dd,*) 3.34 (*dd*)	4	30.7	2.69 (*dd*)	β	28.2	3.04 (*t*)	5	45.0	2.67, 3.75 (*m*)
9	56.5		4'-OCH_3	55.7	3.69 (*s*)	4', 6'-OCH_3	55.7, 56.1	3.34 (s)	α	33.7	3.15 (*t*)	2'-, 4'-OCH_3	56.0, 60.9	3.63, 3.69 (*s*)
8	61.0	3.67 -3.86 (*s*)	5	76.4	5.20 (d)	5	76.7	5.08 (*d*)	4'-OCH_3	56.1	3.75 (s)	6	78.8	5.50 (*m*)
7	61.1		5'	94.3	6.06 (*d*)	3', 5'	93.7, 94.7	6.18, 6.22 (*s*)	3', 5'	84.9, 97.8	6.25, 6.62 (*s*)	5'	93.7	
4'	61.5		3'	95.7	6.08 (*d*)	1'	102.3		1'	105.5		1'	105.2	
3'/5'	93.5	6.03 (*s*)	1'	98.7		7/11	126.7	7.42(*m*)	4	126.5	7.22(*m*)	8/12	125.7	6.14 (*s*)
1'	99.2		7/11	126.9		9	128.6		2/6	128.7		10	128.9	7.43 (*m*)
3'	105.4	7.32 (*s*)	9	128.8	7.22 (*m*)	8/10	128.9		3/5	128.8		9/11	128.3	
11	106.0	7.12 (*s*))	8/10	128.9		6	140.5		1	141.4		3'	129.6	
6	119.0		6	134.9		3	147.9		b '	153.5		7	139.5	
9	138.9		3	153.1		6'	159.0		4'	157.4		2'	155.6	
8	140.0		4'	158.1	3.51 (*s*)	2'	159.4	11.08 (*s*)	6'	163.8		6'	157.7	10.50 (*s*)
7	143.0		6'	159.4		4'	161.3		2'	166.8	10.80(*s* (broad)	4'	157.6	
10	144.9		2'	162.3	11.31 (*s*)						3.25 (*s*) (broad)	4	164.6	
4	147.7											2	188.7	
3	149.9													
2'/6'	158.4	10.80 (*s*)												
4'	160.0													
4-NH		11.50 (*s*)												

Table 2: Anti-microbial activity

Sample Code	*C. albicans* IC_{50}	*C. glabrata* IC_{50}	*C. krusei* IC_{50}	*A. fumigatus* IC_{50}	*C. neoformans* IC_{50}	*S. aureus* IC_{50}
Amphotericin B	1.3	1.31	1.38	0.7	0.37	ND
Ciprofloxacin	ND	ND	ND	ND	ND	0.09
1	NA	NA	NA	NA	NA	NA
2	NA	13.74	8.11	NA	8.01	7.56
3	NA	NA	NA	NA	NA	NA
4	NA	NA	NA	NA	<0.8	NA
5	NA	NA	NA	NA	NA	NA

KEY: NA – not active; ND - not determined

bypyrimidine ring was typical at δ_C 188.7 in ^{13}C-NMR. The imine carbon appeared at δ_C 164.6. The deshielded methine carbon, due to its close proximity to phenyl ring was downfield shifted to δ_C 78.8. The methine peak is characteristic of methine carbons attached to amino group in six-membered heterocyclic ring that normally appear in the region of δ_C 77-110.

From DEPT and ^{13}C-NMR analyses, the methylene carbon of the pyrimidine ring appeared at δ_C 45.0. Both methylene and methine protons appeared at δ_H 2.73 (*dd*, *J*=13.2) and 2.98 (*dd*, *J*=10.4, 2.4) and the latter at δ_H 5.50 (*J*=8.8). The broad ^{1}H-NMR signal at δ_H 7.36 was due to the NH proton. A complete spectral assignment is given in Table 1.

Anti-microbial activity

The compounds were tested for anti-microbial activities. All derivatives showed no significant activity (≥ 40 µg/mL) against standard strains of the diseases. However, compound **2**, an isoxazoline, was reported for moderate anti-microbial activity against *Streptococcus aureus, Candida neoformans, Candida krusei* and *Candida glabrata* strains with inhibitory concentration to 50% microorganism (IC_{50}) values of 7.56, 8.01, 8.11 and 13.74µg/ml respectively (see table 2).

CONCLUSION

The main focus of this study was to synthesize semi-synthetic pyrazole, isoxazoline and bypyrimidine derivatives and evaluate them for their bioactive effects. Five new compounds were synthesized. A reaction of chalcones with hydroxylamine hydrochloride in pyridine yielded isoxazoline heterocyclic systems. Earlier literature[4] indicated that when chalcones are reacted with hydroxylamine hydrochloride in acetic acid, oxazole analogues are found. However, the NMR spectral analysis showed the formation of an oxime. The study also revealed that it is possible to convert α,β-unsaturated ketones to bypyrimidine ring systems (scheme 1).

Besides, flavones and other related compounds can be modified to pyrazole derivatives (equation 1).

All compounds were tested for anti-fungal activity against *Streptococcus aureus, Candida neoformans, Candida krusei* and *Candida glabrata* strains of fungal diseases. Only compound 2 showed moderate activity with inhibitory concentration to 50% microorganism (IC_{50}) values ranging from7.56 to 13.74 µg/ml. Hence, we recommend further synthetic optimization of this compound and other isoxazoline analogues for the better-expected anti-fungal activity.

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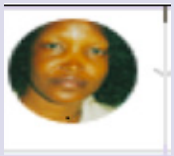

Dr. Leonidah Kerubo Omosa is a Senior Lecturer in Organic Chemistry, in the Department of Chemistry, University of Nairobi, Kenya. Her research interest includes: Drug discovery from Kenyan ethnomedicinal flora with anti-plasmodial, anti-microbial anti-oxidant and anti-cancer potencies. Her interest also includes modifications of compounds with modest bioactivities in order to improve on their activities. Recently, she has ventured into exploring the possibility of discovering bioactive compounds from microbes inhabiting Kenyan soda lakes. To date her research work has resulted in 22 publications in different peer reviewed journals