SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF FRIEDELIN [2, 3-*d*] SELENADIAZOLE

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ABSTRACT

The new 1, 2, 3, selenadiazole derivative (3) was prepared from friedelin (1) via the corresponding semicarbazone (2) using Lalezari cyclization. The compounds were prepared, separated and characterized on the basis of microanalysis and spectral studies. The isolated friedelin and its selenadiazole were screened in vitro *for their antimicrobial activities against various pathogenic bacterial were found to be highly active against all the selected pathogens. Compound* ***3*** *showed an inhibition zone of 14 mm and 12 mm respectively against highly resistant S. albus and C. albicans. A general mechanistic scheme for these reactions is also suggested based on current and previous results.*

Keywords: *Friedelin, semicarbazone, ketomethylene, cyclization, selenadiazole*

INTRODUCTION

Many triterpenoids structures are known for their anti-inflammatory, antiviral, antibacterial and suppression of tumor promotion activities.[1-2] Incorporating nitrogen and selenium atom individually or in combination to natural system leads in most instances to the appearance of new pharmacological properties in modified compound.[3-8] Research on the chemical modification of friedelin is interesting because of broad spectrum of its biological activities.[9] Screening the current literature reveals that no attention has been paid however to synthesize of system containing 1, 2, 3 and other selenadiazoles in triterpenoid which are good candidates for possessing the therapeutic activities.[10-12] Synthetically, compound (**1**) offers the possibility of easy structural modifications in ring A having proximal functional group in designing novel structures. Such functionality is the α- ketomethylene[13] group which has been used as a building block for selenadiazole system. We now report the preparation of the desired friedelin selenadiazole (**3**). The reaction of friedelin (**1**) with semicarbazide and sodium acetate gave friedelin semicarbazone (2) which with SeO_2 in acetic acid under reflux yielded the desired product (**3**) having fused heterocycle attached at the C-2 and C-3 position of the friedelin skeleton.

EXPERIMENTAL SECTION

General

All melting points were determined on a Kofler block and are uncorrected. IR spectra were recorded on KBr pellets with Pye Unicam sp3-100-spectrophotometer and its values are given in cm^{-1}. ^{1}H-NMR spectra were run in $CDCl_3$ on a Bruker AC-300 (300MHz) with TMS as standard and its values are given in ppm (δ). Thin layer chromatography (TLC) plates were coated silica gel G and exposed to iodine vapors to check purity as well as progress of reaction. Petroleum ether refers to fraction b.p. 40-60°.

Friedelin semicarbazone (2)

To a solution of friedelin (500 mg) in 50 mL ethanol was added a solution of semicarbazide hydrochloride (1 g) and 15% aqueous solution of sodium acetate (32 mL). The resulting mixture was refluxed for 1 h and cool to furnish a solid which was filtered under suction and washed with water. The residue was air-dried and recrystallised from methanol to give semicarbazone (**2**). yield 270 mg, m.p. 252 °C, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.5 (s, 2H, NH_2), 7.8 (s, 1H, NH), 1.25-1.58 (22H, CH_2 protons), 0.72-1.18 (s, 24H, CH_3 protons), ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2 (C-3), 59.8 (C-10), 39.6 (C-4), 53.2 (C-8), 42.8 (C-18), 42.2 (C-5), 26.4 (C-2), 41.4 (C-6), 40.0 (C-13), 39.8 (C-22), 38.6 (C-14), 37.5 (C-9), 36.0 (C-16), 35.8

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(C-11), 35.4 (C-19), 35.2 (C-29), 32.4 (C-21), 32.8 (C-15), 31.9 (C-28), 31.5 (C-30), 30.6 (C-12), 29.2 (C-17), 28.4 (C-20), 22.8 (C-1), 20.8 (C-26), 18.4 (C-27), 18.8 (C-7), 17.2 (C-25), 15.8 (C-24), 16.9 (C-23). IR, (KBr): v (cm^{-1}) 3462, 3325 (s) (N-H), 2360 (CH_2) 1689 (C=O), 1582 (-C=N), 1300 & 1126 (-C-N), $C_{31}H_{53}N_3O$, (M^+ 483), found C, 76.88 H, 11.14 N, 8.74 requires C, 76.96; H 11.04; N, 8.69.

[2, 3 d] friedelin-3-selenadiazole (3)

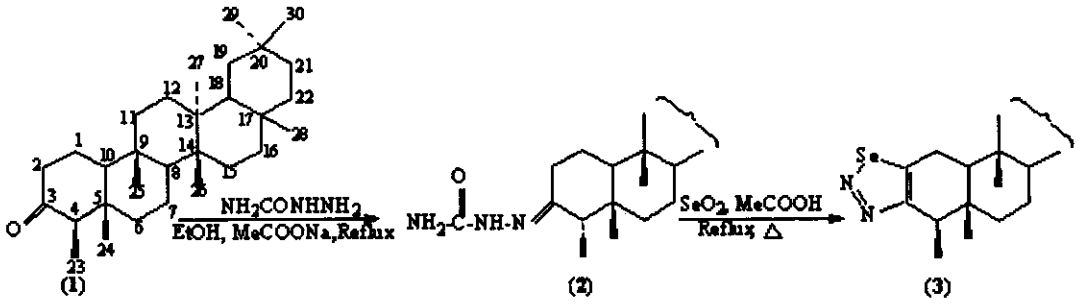
Friedelin semicarbazone (2) (200 mg) in acetic acid (50 mL) was treated with selenium dioxide (I g) and heated on a water bath for 18 h. Then it was poured into ice cold water and extracted with ether. The ethereal layer was washed with water, $NaHCO_3$ solution (5%) and dried over Na_2CO_3 (anhydrous). Evaporation of the solvent gave semi solid which on crystallization in chloroform-ethanol gives [2, 3 d] friedelin-3-selenadiazole (**3**). Yield 120 mg, m.p. 98 °C, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.06 (m, 2H, $C1H_2$), 1.22-1.62 (20H, CH_2 protons), 0.70-1.22 (s, 24 H, CH_3 protons), ^{13}C NMR (100 MHz, $CDCl_3$): 170.5 (C-2), 136.8 (C-3), 45.4 (C-4), (values of other carbons almost remain the same as in compound **2**), IR, (KBr): v (cm^{-1}) = 1612 (C=C), 1550 (N=N), 1350 (C-N), 590 (C-Se), $C_{30}H_{50}N_2Se$ (M^+ 517), found C, 69.54; H, 9.76; N, 5.37 requires C, 69.60; H, 9.73; N, 5.41).

Antimicrobial Activity

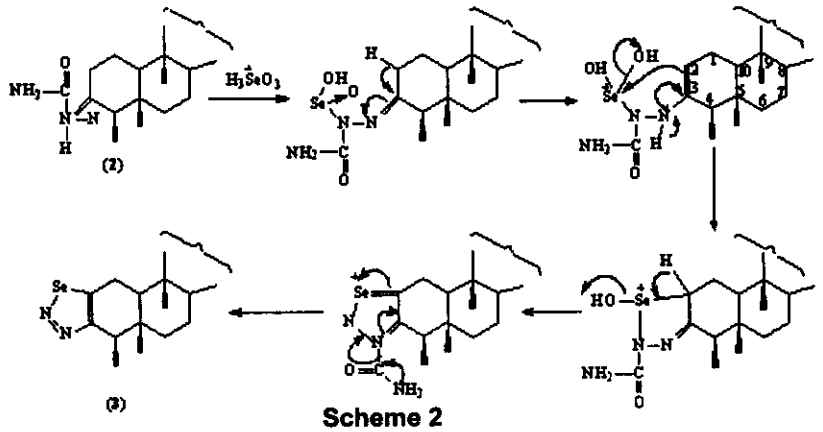
The *in vitro* antibacterial activity was carried out against *E. coli, S. typhi, S. albus* and *B. subtilis* and *in vitro* antifungal activity was carried out against *P. notatum, F. oxysporum, T. viridae, Candida albicans, A. flavus* and *A. niger* by Disc Diffusion method.[20-21] 0.1 mL of diluted inoculum (10^5 cfu/mL) was spread on Mueller Hinton Agar plates (Hi-Media Pvt. Ltd., Mumbai, India). The wells of 8 mm diameter were punched into the agar medium and filled with 100 µl of test compounds (**1-3**). Negative controls were prepared using the same solvent (DMSO). The plates were incubated at 37 °C overnight. The antibiotic Ofloxacin (5 µg $Disc^{-1}$) and antifungal disc Clotrimazole (10 µg $Disc^{-1}$) were used in the test system as positive controls. Zone of inhibition of bacterial and fungal growth around each well was measured in mm.

RESULT AND DISCUSSION

The compound friedelin was isolated from petroleum ether extract from the leaves of Garcinia mangostana.[14] Its identity was confirmed by comparison of the m.p., m.m.p., co. TLC and spectral data with that of authentic samples.[15-17] Friedelin semicarbazone (**2**) was prepared, isolated, characterized and subjected to Lalezari *et al.* method to furnish friedelin selanadiazole (**3**) (Scheme 1).



Scheme 1



Scheme 2

Table 1. *In vitro* antimicrobial activity of the compounds **1-3** by Disc Diffusion method (Zone of inhibition in mm)

Compound	*E. coli*	*S. typhi*	*S. albus*	*B. subtilis*	*P. notatum*	*F. oxysporum*	*T. virdae*	*C. albicans,*	*A. flavus*	*A. niger*
1	6	10	4	-	-	-	-	-	6	4
2	11	14	8	12	18	12	14	20	7	17
3	8	-	14	6	-	-	8	12	8	10
Ofloxacin	21	18	18	22		-	-	--	-	-
Clotrimazole					12	20	14	12	14	18

The structure of the compounds (**2**) and (**3**) were established by the spectral and elemental analysis. The IR spectrum of (2) reveals characteristic N-H vibration in the higher energy region at 3462. cm^{-1} and 3325 cm^{-1} as very intense peak. They are assigned to N-H stretch of the -N-C=O group and to the $-NH_2$ group. The symmetric and asymmetric stretching mode of CH_2 group gave bands at 2932 cm^{-1} and 2860 cm^{-1}. The bands at 2360 and 2067 cm^{-1} are due to CH_2 overtone. The C=O stretching vibration displayed sharp band at 1689 cm^{-1}. The peaks at 1582, 1126 and 1300 cm^{-1} are assigned to –C=N and –C-N stretching vibrations. The ^1H NMR spectrum of the compound (**2**) showed characteristic resonance below 2.5 ppm for ring and methyl groups of various positions. The $-NH_2$ and –NH give characteristic signals at δ 5.5 and 7.8 ppm.

The IR spectrum of friedelin selanadiazole (**3**) displayed bands at 1612 cm^{-1} (C=C), 1550 cm^{-1} (N=N), 1350 cm^{-1} (C-N) and 590 cm^{-1} (C-Se)[18] indicating the presence of selanadiazole ring.[18] The ^1H NMR spectrum of (**3**) showed a multiplet at δ 2.06 and a doublet at δ 2.75 assigned to C1-H_2 and C10-H respectively. Methyls, methylene and methenes protons were observed at δ 0.70-1.16, 1.26-1.52 and 2.20-2.34 respectively. Besides the ^1H NMR resonance, ^{13}C NMR data (see Experimental), IR bands and elemental analysis, the appearance of the molecular ion peak at m/z (M^+ 517) is in good agreement with the molecular formula $C_{30}H_{50}N_2Se$ (**3**) which further establishes its formation. Therefore the product is characterized as friedelin-2-eno [2, 3-*d*] 1, 2, 3-selanadiazole, satisfying all observed spectral properties.

In the light of available mechanism[19] formations of (**3**) from (**2**) under the conditions can be shown according to scheme 2. Although the detailed mechanism of this reaction has not been determined, some inferences can be drawn on the basis of previous work. This may be taken as tentative in the absence of studies to establish the mechanism of reaction.

The *in vitro* antibacterial activity of the compound **1**, **2**, and **3** was carried out against *E. coli, S. typhi, S. albus* and *B. subtilis* and *In vitro* antifungal activity was carried out against *P. notatum, F. oxysporum, T. viridae, Candida albicans, A. flavus* and *A. niger* by agar well diffusion method.[20-21]

The parent compound **1** was found active only against the bacteria *S. typhi* (10 mm) (**Table 1**).

The compound **2** showed high activity against the bacteria *E. coli* (11 mm), *S. typhi* (14 mm) and *B. subtilis* (12 mm) and very high activity against fungus *P. notatum* (18 mm). This compound was also found highly active against fungus *F. oxysporum* (12 mm), *T. viridae* (14 mm) and very highly active against *A. niger* (17 mm) and *C. albicans* (20 mm). (**Table 1**)

The compound **3** showed high activity against *S. albus* (14) and *C. albicans* (12 mm) but moderately active against fungus *A. niger* (10 mm). (**Table 1**)

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