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Synthesis and Antimicrobial Screening of 2,4-Dithiobiuret Derivatives

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Abstract
A simple and efficient method has been developed for the synthesis of a series of 2,4-dithiobiuret derivatives. In this work, a new series of N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-substituted-2,4-dithiobiurets derivatives have been prepared from 1-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl] thiourea. 1-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl] thiourea in turn was obtained by interaction of 3-chloro-4-(furan-2-yl)-1-(3-nitrophenyl) azetidin-2-one and thiourea. All the synthesized products were characterized by IR and H^1 NMR spectroscopic data and elemental analysis. All the synthesized products were evaluated for their antimicrobial activity. The title compounds have been assayed for their biological activity.

Keywords: *N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-substituted-2,4-dithiobiurets, N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl] thiourea, 3-chloro-4-(furan-2-yl)-1-(3-nitrophenyl) azetidin-2-one, alkyl/aryl isothiocyanate, anti-microbial screening.*

Introduction

Heteroacyclic containing heterocycles drugs show remarkable drug absorption, transmission and other drug effects. Hence they have created their own identity in pharmaceutical, medicinal, agricultural and drug sciences. Dithiobiuret compounds have applications in industrial, pharmaceutical, medicinal and drug chemistry**.** The synthesized heteroacycles are used as intermediates in the synthesis of thiadiazoles, dithiazoles, thiadizines, triazines, Hector's bases etc. Acyclic 2,4-dithiobiurets are excellent and potent biological moieties.[1,2,3] Synthesis and biological evaluation of novel 2,4-dithiobiurets is an interesting field in Organic Chemistry. These 2,4-dithiobiurets are a good class of organic inter-mediated[4-7] for the synthesis of various active heterocycles. More especially, nitrogen and sulphur containing and derived compounds from the chalcones possess a variety of anti-microbial[8], anti-viral[9] and anti-bacterial activities[10].

Materials and Methods

All the required chemicals were purchased from S-D Fine Chemicals. All the chemicals used were of A.R.

grade. Melting points were measured in open capillary tube and are uncorrected. The purity of the compounds was check by TLC on silica gel in petroleum ether and ethyl acetate [80:20] and the spots were located using iodine vapour as visualizing agent. The IR spectra were recorded on Agilent Technology spectrophotometer. H^1 NMR was recorded on Bruker AVANCE 400 MHZ spectrometer using TMS as an internal standard.

Experimental method

Heteroacyclic substituted 2,4-dithiobiurets were prepared by the condensation of 1-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl] thiourea and substituted isothiocyanates in 60% acetone-ethanol medium. 1-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl] thiourea thus obtained from 3-chloro substituted azetidin-2-one and thiourea was refluxed in Isopropanol.

Scheme-I

Synthesis of 1-(2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-3-thiourea (III).

A reaction mixture of 3-chloro-4-(furan-2-yl)-1-(3-nitrophenyl) azetidin-2-one (I) and thiourea (II) taken in equimolar (0.02 mol) proportion in isopropanol was refluxed for 4 hours on a water bath and the resulting yellow crystals were separated out at room temperature, filtered, dried and recrystallized from aqueous ethanol. The completion of the reaction was monitored by TLC, yield 67%, m.p.181°C.

Elemental analysis: The result of elemental analysis are given in Table 1.

Table 1. Elemental Analysis of Compound III

Sr. No.	Elements	Found %	Calculated (%)
1	Carbon	50.39	50.60
2	Hydrogen	03.53	03.64
3	Nitrogen	16.30	16.86
4	Oxygen	18.91	19.26
5	Sulphur	09.41	09.65

From the analytical data the molecular formula was found to be $C_{14}H_{12}N_4O_4S$

IR Spectrum: IR spectrum of the compound was carried out in KBr pellets. The important absorptions are depicted in Table 2.

Table 2. IR absorption frequencies of Compound III

Sr. No.	Absoption Observed (cm^{-1})	Assignment	Absorption expected (cm^{-1})
1	3320.23	N-H Stretching	3500-3300
2	1110.01	C=S Stretching	1200-1050
3	3010.08	C-H(Ar) Stretching	3100-3000
4	1520 & 1367.32	NO2 Stretching	1560-1515 & 1385-1345
5	1280.52	C-N Stretching	1360-1080
6	1640.45	C=O Stretching	1650

H^1-NMR spectrum: H^1-NMR spectrum of the compound was carried out in DMSO-d6 and CDCl3. This spectrum distinctly displayed the signals at δ 8.12 (s, 1H, Ar-H); δ 7.72 (dd, 2H, Ar-H); δ 2.9 (s, 1H, NH) and δ 3.9 (d, 1H, NH).

Scheme-II

Synthesis of N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-N-phenyl 2,4-dithio Biurets (Va).

1-(2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-3-thiourea and phenylisothiocyanate were taken in equimolar proportion (0.01 mol) in 60% acetone-ethanol. The reaction mixture was refluxed for four hours on a water bath and the resulting brown crystals were separated out at room temperature, filtered and dried. The product was purified by column chromatography over silica-gel coated plates by using ethyl acetate and recrystallised from ethanol. Yield 67%, m.p.181°C.

Elemental analysis: The result of elemental analysis are given in Table 3.

Table 3. Elemental Analysis of Compound Va

Sr. No.	Elements	Found (%)	Calculated (%)
1	Carbon	51.69	53.95
2	Hydrogen	03.43	03.67
3	Nitrogen	14.78	14.98
4	Oxygen	13.51	13.69
5	Sulphur	13.41	13.71

From the analytical data the molecular formula was found to be $C_{21}H_{17}N_5O_4S_2$

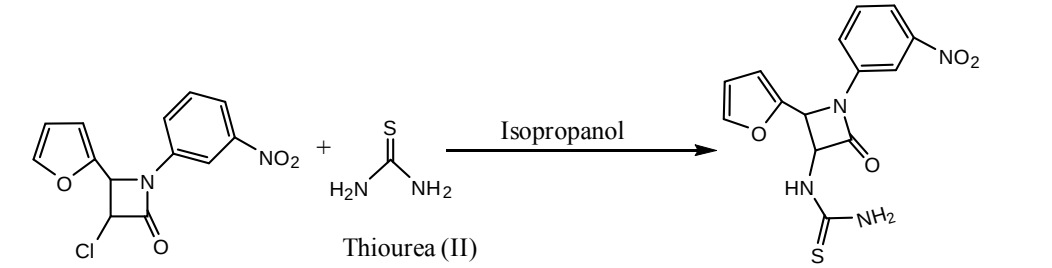
IR Spectrum: IR spectrum of the compound was carried out in KBr-pellets. The importance absorptions are in Table 4.

Table 4. IR absorption frequencies of Compound Va

Sr.No.	Absoption Observed (cm^{-1})	Assignment	Absorption expected (cm^{-1})
1	3410.20	N-H Stretching	3500-3300
2	1101.01,1141.03	C=S Stretching	1200-1050
3	3042.12	C-H(Ar) Stretching	3100-3000
4	1517.21 & 1366	NO2 Stretching	1560-1515 & 1385-1345
5	1266.13	C-N Stretching	1360-1080
6	1660.15	C=O Stretching	1650

H^1-NMR Spectrum: H^1-NMR spectrum of the compound was carried out in DMSO-d6 and CDCl3. This spectrum distinctly displayed the signals at δ 8.09 (s, 1H, Ar-H); δ 7.87 (dd, 2H, Ar-H); δ 2.6 (s, 1H, NH) and δ 3.4 (s, 1H, NH).

Scheme I: Synthesis of 1-(2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-3-thiourea (III).

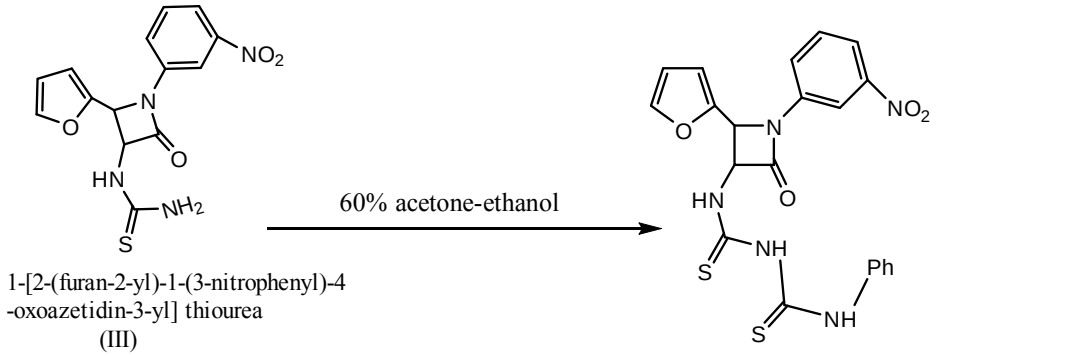


3-Chloro-4-(furan-2-yl)-1-(3-nitrophenyl)azetidin-2-one(I)

Thiourea (II)

1-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-3-thiourea(III)

Scheme II: Synthesis of N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-N-phenyl 2,4-dithiobiurets (Va).



1-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl] thiourea (III)

Ethyl Isothiocyanate (VIa)

N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-phenyldicarbonodithioimidic diamide

(Va)

Similarly, N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-N-ethyl 2,4-dithiobiuret(Vb) and N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-N-o-tolyl 2,4-dithiobiuret (Vc) were synthesized by the interaction of ethyl isothiocyanate (IVb) and o-tolyl isothiocyanate (IVb) in acetone-ethanol medium respectively by the above mentioned method. (Table V).

Table 5. Yield and mp of Compounds Vb Vc

Sr.No.	N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-N-substituted 2,4-dithiobiurets (Vb-c)	Yield %	m.p ºC
1	N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-N-ethyl 2,4-dithiobiurets(Vb)	78	178
2	N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-N-o-tolyl 2,4-dithiobiurets (Vc)	61	189

Antimicrobial Screening

The synthesized products (Va-c) were screened for their antimicrobial activity by using cup plate diffusion method. The bacterial organisms used included both gram-positive as well as gram negative strain like *E. coli, S. aureus, S. typhi, B. subtilis* and *A. aerogenes*. Sensitivity plates were seeded with a bacterial innoculum of $1x10^6$ CIU mL^{-1} and each well (diameter 10 mm) was loaded with 0.1 mL of test compound solution (1000 µg mL^{-1}) in DMF, so that concentration of each test compound was 100 µg mL^{-1}. The zones of inhibition were recorded after incubation for 24 hr at 37^0C, using vernier caliper. Inhibition zone record of the compound clearly indicated that Va and Vc were highly active against *E. coli, S. aureus, S. typhi* and moderately active against *A. aerogenes*. Va and Vb compounds were found to be inactive against *B. subtilis* (Table 3).

Table 3: Antibacterial activity of compounds (Va-c)

Compounds	Antibacterial activity				
	E. coli	*S. aureus*	*S. typhi*	*B. subtili*	*A. aerogene*
Va	+++	+++	+++	–	++
Vb	–	+	++	–	–
Vc	+++	+++	++	+	++

(+++): Highly active (21 mm and above), (++): Moderately active (17-20mm), (+): Weakly active (13-16mm), (-): Inactive (12mm and less).

Conclusions

The objective of the present study was to synthesize and evaluate the antimicrobial activities of a new series of 2,4-dithiobiuret compounds that could be used as potent antimicrobial drugs. Three new compounds were synthesized. All compounds showed a broad antimicrobial spectrum with activity against pathogenic microorganisms associated with various human diseases. Our results clearly revealed that compounds Va and Vc exhibited good antimicrobial activity. New antimicrobial drug development has global emphasis and there is a need to investigate further antibiotic activity.

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