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SYNTHESIS, STRUCTURAL STUDY AND ANTIMICROBIAL SCREENING OF SUBSTITUTED 1,2,4-DITHIAZOLE DERIVATIVES

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Abstract:
A simple and efficient method has been developed for the synthesis ofsubstituted 1,2,4-dithiazole. In this work new 4-[(furan-2-yl)-3-{[5-(substitutedimino)-3*H*-1,2,4-dithiazol-3-yl]amino}-1-(3-nitrophenyl) azetidin-2-one have been reported from N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-substituteddicarbonodithioimidic diamide.The N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-substituted dicarbonodithioimidic diamidein turn were obtained from 1-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-2-one] thiourea and aryl/alkylisothiocyanate in acetone-ethanol medium. 1-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-2-one] thiourea which was obtained 3-chloro-4-(furan-2-yl)-1-(3-nitrophenyl) azetidin-2-one and thiourea.The Justification and identification of the structure of these newly synthesized compounds had been established on the basis of chemical characteristics, elemental analysis and through spectral data. The title compounds have been assayed for their biological activity against gram-positive as well as gram-negative microorganism.

Keywords: 3-Chloro-4-(furan-2-yl)-1-(3-nitrophenyl) azetdin-2-one, Thiourea, N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-substituteddicarbonodithioimidic diamide, 4-[(furan-2-yl)-3-{[5-(substitutedimino)-3H-1,2,4-dithiazol-3-yl]amino}-1-(3-nitrophenyl)azetidin-2-one, bromine in chlorine,anti-microbial screening.

Introduction

Heterocyclic compounds are one of the most significant areas of research in the field of medicinal chemistry[i]. The Azetidin-2-one heterocyclic are considered as an important contribution of science to humanity[ii,iii], since they have been constituents of living organism, natural products, Drugs and many more substances useful to mankind and society in all walks of life. The synthesis of heterocyclic compound has always drawn the attention of chemists over the years mainly because of their important biological properties. It is equally interesting for its theoretical implication for the diversity of its physiological and industrial significances. The continual discovery of novel therapeutics against varying strains of both viruses and bacteria are essential due to their ability to adapt and become resistant to current

treatments. During this decade there has been considerable interest in the synthesis of heterocyclic compounds. In addition to this, heterocyclic compounds is having potent biological properties. 1,2,4-dithiazole have various therapeutic applications and various 1,2,4-dithiazole are in clinical use. In recent years, several 1,2,4-dithiazole and their derivatives were found to be have prominent pharmacological activities such as anticonvulsant, analgesic, anti-inflammatory activity[iv,v]. Dithiazole nucleus useful in industrial, pharmacological, biological, agriculture and medical fields. Drugs of these type showed a various range of anti-fungal, anti-bacterial[vi-xiii].Thus, 1,2,4-dithiazole have incredible applications[xiv-xxi]. The literature survey reveals that heterocyclic compounds containing sulphur and nitrogen have brought massive important in human life.

As a part of research work presently being undertaken the synthesis of new five membered heterocyclic compound, it was thought interesting the cyclisation of N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-substituteddicarbonodithioimidic diamide with liquid bromine in chloroformmedium to obtain a novel series of 4-[(furan-2-yl)-3-{[5-(substitutedimino)-3H-1,2,4-dithiazol-3-yl]amino}-1-(3-nitrophenyl)azetidin-2-one which are either to unknown.

Materials and Method:

The melting points of all synthesized compounds were recorded using hot paraffin-bath and are uncorrected. All chemicals used were AR-grade.IR spectra were recorded on Perkin-Elmer spectrophotometer in the range 4000-400cm^{-1} in nujol mul and as KBr pellet. H^1-NMR spectra were recorded with TMS as internal standard using $CDCl_3$ and DMSO-d_6 as solvents. The Purity of compound was checked on silica Gel-G Plates by TLC.

Scheme-I

1-(2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-3-thiourea (I).

A reaction mixture of 3-chloro substituted azetidin-2-one and thiourea were taken in equimolar (0.03mol) proportion in isopropanol medium was refluxed for 4 hours on water bath, brown crystals were separated out at room condition, filtered and dried. It was recrystallized of aqueous ethanol. Completion of reaction was monitored by TLC, yield 73%, melting point 184.

Elemental Analysis: C [(found 50.49%) calculated 50.60%], H [(found 3.50%) calculated 3.64%], N [(found 16.73%) calculated 16.86%], O [(found 19.23%) calculated 19.26%], S [(found 9.59%) calculated 9.65%].

IR Spectrum: The IR spectrum was carried out in KBr plates: 3176.76 cm^{-1}(Ar, C-H str); 1523cm^{-1} (Ar, C=C str); 1693(C=O str); 1230.09cm^{-1} (C-N str); 1170.79 cm^{-1}(C-O str) ; 1346-1487 cm^{-1} (NO_2asy str); 2126 cm^{-1}(C=S).

H^1-NMR Spectrum: The H^1-NMR spectrum of compound was carried out in $CDCl_3$ and DMSO d_6. This spectrum distinctly displayed the signals due to, 8.10 (s, 1H, Ar-H); 7.42(dd, 1H, Ar-H); 8.14(d, 1H, Ar-H); 5.44(d, 1H, CH); 7.56(d, 1H, CH); 6.39(dd, 1H, CH) ; 6.43(d, 1H, CH); 5.39(d, 1H, CH); 7.3(q, 1H, NH); 2.8 (d, 3H, CH); 9.4 (d, 1H, NH).

Scheme-II

Synthesis of N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-ethyldicarbonodithio imidic diamide (IIIa).

A reaction mixture of 1-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl] thiourea(I) and ethylisothiocyanate (IIa) in 1:1 molar proportion was refluxed in 60% acetone-ethanol medium for 4 hours on water bath, brown crystal separated out, filtered and dried at room conditions. Recrystallised from aqueous ethanol, completion of reaction was monitored by TLC, yield 62%, m.p.195°C.

Elemental Analysis: C [(found 49.70%) calculated 50.42%], H [(found 3.65%) calculated 3.99%], N [(found 13.73%) calculated 13.85%], O [(found 15.04%) calculated 15.82%], S [(found 15.69%) calculated 15.85%].

IR Spectrum: The IR spectrum was carried out in KBr plates: 3111 cm^{-1}(Ar, C-H str); 1583cm^{-1} (Ar, C=C str); 1712 (C=O str); 1043 cm^{-1}(C-O str); 1348-1523cm^{-1}(-NO_2 str); 1205 cm^{-1}(C=S).

H^1-NMR Spectrum: The H^1-NMR spectrum of compound was carried out in $CDCl_3$ and DMSO d_6. This spectrum distinctly displayed the signals due to, 8.10 (s, 1H, Ar-H); 7.42(dd, 1H, Ar-H); 8.14(d, 1H, Ar-H); 5.44(d, 1H, CH); 6.39(dd, 1H, CH); 6.43(d, 1H, CH); 5.39(d, 1H, CH); 7.3(q, 1H, NH); 9.4 (d, 1H, NH).

Scheme-III

Synthesis of 4-[(furan-2-yl)-3-{[5-(ethylamino)-3H-1,2,4-dithiazol-3-yl]imino}-1-(3-nitrophenyl)azetidin-2-one (IVa).

4-[(furan-2-yl)-3-{[5-(ethylimino)-3H-1,2,4-dithiazol-3-yl]amino}-1-(3-nitrophenyl)azetidin-2-one (IVa) was synthesized by the oxidative cyclization of N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-ethyldicarbonodithioimidic diamide (IIIa) with liquid bromine in chloroform.A paste of N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-ethylcarbonodithioimidic diamide (IVa) was prepared in chloroform. 10% liquid bromine in chloroform was added toN-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-ethyldicarbonodithioimidic diamide (IVa) with constant stirring.Colour of bromine initially disappear in the reaction mixture. The reaction mixture was allowed to stand for 6 hours, it afforded dark brown colored product. It was recrystallized from ethanol, yield 76%, m.p.205^0C.

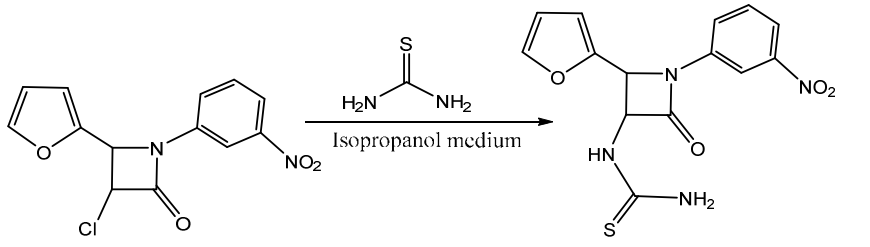
Elemental Analysis: C [(found 48.34%) calculated 48.91%], H[(found 3.50%) calculated 3.62%], N[(found 16.33%) calculated 16.78%], O [(found 14.93%) calculated 15.33%], S[(found 15.30 %) calculated 15.36%].

IR Spectrum: The IR spectrum was carried out in KBr plates: 1620.24cm^{-1}(N-C=O, str), 739.05cm^{-1}(C-S, str), 1514.08cm^{-1}(C=N, str), 1097.06cm^{-1}(C-N, str), 3397.02cm^{-1}(N-H, str), 1315-1503.09cm^{-1}(NO_2, str), 628.06cm^{-1}(S-S,str), 1650cm-1 (Ar C=C, str).

H^1-NMR Spectrum: The H^1-NMRspectrum of compound was carried out in $CDCl_3$ and DMSO d_6. This spectrum distinctly displayed the signals due to Ar-H proton at 7.2-7.4ppm, N-C_2H_5 proton 1.3 ppm, -NH proton at 4.2 ppm, C=C-H proton at ppm.

Reaction

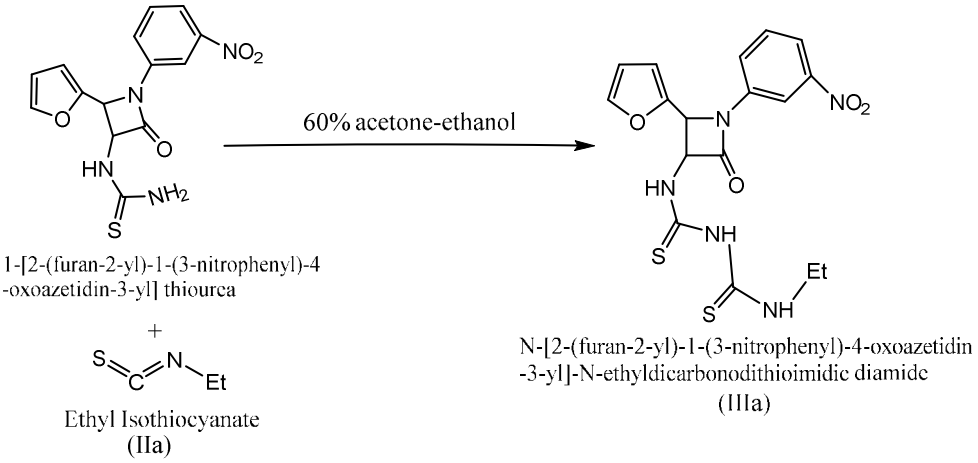
Scheme-I:1-(2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-3-thiourea (I).



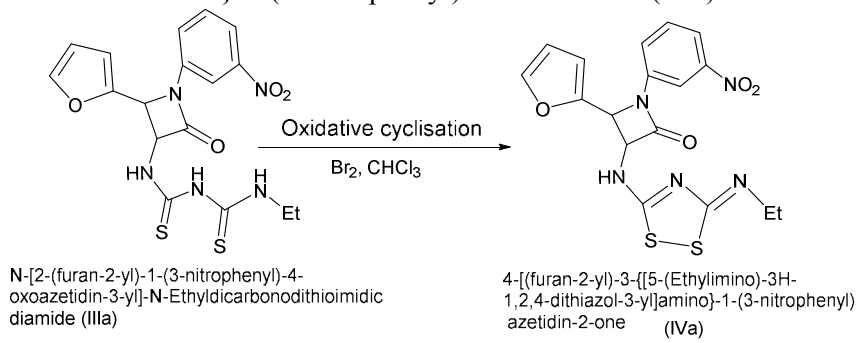
3-Chloro-4-(furan-2-yl)-1-(3-nitrophenyl) azetidin-2-one

1-(2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-3-thiourea (I)

Scheme-II:Synthesis of N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-ethyldicarbonodithio imidic diamide (IIIa).



Scheme-III: Synthesis of 4-[(furan-2-yl)-3-{[5-(ethyl amino)-3H-1,2,4-dithiazol-3-yl] imino}-1-(3-nitro phenyl) azetidin-2-one (IVa).



Similarly4-[(furan-2-yl)-3-{[5-phynylimino)-3H-1,2,4-dithiazol-3-yl] amino}-1-(3-nitrophenyl) azetidin-2-one (IVb),4-[(furan-2-yl)-3-{[5-methylimino)-3H-1,2,4-dithiazol-3-yl] amino}-1-(3-nitrophenyl) azetidin-2-one (IVc) were synthesized by oxidative cyclization ofN-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-phenyldicarbonodithioimidicdiamide (IIIb), N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-methyldicarbonodithioimidic diamide(IIIc)respectively by the above mentioned method.

Table No.1

Sr. No.	**4-[(furan-2-yl)-3-{[5-substitutedimino)-3H-1,2,4-dithiazol-3-yl] amino}-1-(3-nitrophenyl) azetidin-2-one (IVb-c)**	**Yield (%)**	**m.p ^{0}C**
2	4-[(furan-2-yl)-3-{[5-phynylimino)-3H-1,2,4-dithiazol-3-yl] amino}-1-(3-nitrophenyl) azetidin-2-one (IVb),	63	214
3	4-[(furan-2-yl)-3-{[5-methylimino)-3H-1,2,4-dithiazol-3-yl] amino}-1-(3-nitrophenyl) azetidin-2-one (IVc)	72	204

Antimicrobial Screening:

The synthesized products (IVa-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 100µg 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 IVa and IVc were highly active against E.coli, S. aureus, S.typhi and moderately active against A. aerogenes. Synthesized compound (IVb) was found inactive against B. subtilis and A.aerogene [Table No.2].

To determine minimum inhibitory concentration (MIC), the serial dilution techniquewas followed using nutrient broth medium. The MIC values of compound IVa,IVb and IVc were determined against E. coli, S. aureus and s. typhi, which were found to be 70,76 and 80 µg mL^{-1}respectively.

Table No.2: Antibacterial activity of compounds (I**Va-c**)

compounds	Antibacterial activity				
	E. coli	*S. aureus*	*S. typhi*	*B. subtili*	*A. aerogene*
IVa	+++	+++	+++	++	++
IVb	-	+	++	--	
IVc	+++	+++	+++	+++	

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

Result and Discussion:

By considering all these things, we have developed new research scheme. During designing this scheme it was also planned to developed a new route to for the synthesis of 4-[(furan-2-yl)-3-{[5-(substitutedimino)-3H-1,2,4-dithiazol-3-yl]amino}-1-(3-nitrophenyl)azetidin-2-one by the oxidative cyclisation of N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-substituted dicarbonodithioimidic diamide. The main objective of this is to synthesize a novel 4-[(furan-2-yl)-3-{[5-(substitutedimino)-3H-1,2,4-dithiazol-3-yl]amino}-1-(3-nitrophenyl) azetidin-2-one and also to set up new reaction condition to reduce the time span of such type of reactions and at the same time it was also thought to increase the yield of the product. This work is useful to incoming researcher in organic chemistry for the synthesis of dithiazole. In the synthesized compound the dithiazole substituent may enhance the potency of the compounds.

Conclusion:

In conclusion, the objective of the presence study was to synthesize and evaluate the antimicrobial activities of some new 1,2,4-dithiazole compounds that could be used as potent antimicrobial Drugs. Three Different compounds were synthesized newly. All compound were shown broad antimicrobial spectrum which have efficiency against pathogenic microorganisms associated with various human diseases. However, our results clearly

revealed that especially compounds IVa and IVcexhibited good antimicrobial activity. New antimicrobial drug development has global emphasis and needs to investigate antibiotic. Because of this reason, we have performed the synthesis and biological evaluation in this study.

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