

SYNTHESIS OF SUBSTITUTED DITHIAZINE ON AZETIDIN-2-ONE MOIETY AND THEIR ANTIOXIDANT ACTIVITY

FARHANULLAH A. KHAN*¹, RAHIM S. SHEIKH², SHAIKESH G. ATRAM³

Research Scholar, Department of Chemistry,
Govt. Vidarbha Institute of Science and Humanities, Amravati, Maharashtra, 444604-India.

Abstract: It was thought interesting to synthesized derivative of dithiazine. A simple and efficient procedure for the synthesis of substituted dithiazine. In this work new substituted dithiazine have been reported from N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-substituteddicarbanodithioimidic and phenylisocyanodichloride. The newly synthesized compound were fully characterized using IR, ¹H-NMR, and elemental analysis and screened for their in vitro antioxidant activity using 1,1-diphenylpicrylhydrazyl (DPPH) radical scavenging methods by this method. Thus the title compounds are a new class of potent antioxidant agent and worthy of further investigation.

Keywords: 3-chloro-substitutedazetidin-2-one, Thiourea, phenylisothiocyanate, phenyl isocyanodichloride, anti-oxidant activity.

I. INTRODUCTION

Heterocyclic chemistry is fundamental to biology and medicine. It is not implausible to say that we are living in the age of heterocyclic chemistry. It constitutes a large group of organic molecules exhibiting a wide range of biological activities which is basis of life and society. The majority of pharmaceutical products that mimic natural products with biological activity are heterocyclic in nature¹⁻². The dithiazine structure is a heterocyclic ring, analogue to the six membered benzene ring but with three carbons replaced by two sulphur and one nitrogen atom³⁻⁷. Some of the natural compounds like alkaloids such as morphine, reserpine; antibiotics such as penicillin's cephalosporin, etc have heterocyclic moiety as an active part of the system⁸⁻¹². Most of the pharmaceutical products show heterocyclic nature that resembles natural molecules with biological activities¹³⁻¹⁴. Dithiazine derivatives nucleus exhibits antihypertensive and diuretics activities, while exhibits moderate anticancer activity¹⁵⁻¹⁶. We thought it would be worthwhile to explore a synthetic route towards a new series of 4-[(furan-2-yl)-3-[[2-phenylimino-4-phenylimino]-1,3,5-dithiazin-6-yl]amino]-1-(3-nitrophenyl) azetidin-2-one.

Materials and Methods:-

The reagent grade chemicals were obtained from commercial sources and purified by either distillation or recrystallization before use. Purity of synthesized compounds has been checked by thin layer chromatography. Melting points were determined by open capillary method and are uncorrected. IR spectra are recorded on FT-IR Bruker with KBr disc. ¹H-NMR spectra are recorded in DMSO-d₆ on a Bruker AVANCE 400 MHZ spectrometer using TMS as an internal standard.

Synthetic Procedures:

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

3-chloro-substituted azetidin-2-one and thiourea were taken in equimolar (0.02mol) proportion and dissolved in isopropanol. The reaction mixture was refluxed in isopropanol medium for four hour on waterbath, faint yellow crystal were separated out at room conditions, filtered and dried. Recrystallised from ethanol, completion of reaction was monitored by TLC, yield 73%, m.p 184^oC. Molecular formula: C₁₄H₁₂N₄O₄S, % Composition found (calculated): C-50.21 (50.60), H-3.51 (3.64), N-16.78 (16.86), O-19.12 (19.26) and S-09.61 (09.65).

IR spectrum of compound was recorded using KBr-pellets and important absorption are shown below,

IR : 3076.76 cm⁻¹ (Ar, C-H str); 1533.05cm⁻¹ (Ar, C=C str); 1645.19(C=O str); 1210.31cm⁻¹ (C-N str); 1130.40 cm⁻¹(C-O str); 1346-1504.87 cm⁻¹ (O=N asy str); 2150.30 cm⁻¹(C=S).

¹H-NMR Spectrums of compound was recorded using in a mixture of DMSO-d₆ and this spectrum distinctly displayed signals and is shown below,

¹H-NMR (DMSO): δ 8.10. (s, 1H, Ar-H); δ 7.61(dd, 1H, Ar-H); δ 7.69(d, 1H, Ar-H); δ 5.02(d, 1H, CH); δ 6.46(d, 1H, CH); δ 4.49(d, 1H, CH); δ 9.01(d, 1H, NH); δ 9.30 (s, 1H, NH).

Synthesis of N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-phenyl 2,4-dithiobiurets.

1-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl] thiourea and phenyl isothiocyanate were taken in equimolar (0.01mol) proportion and dissolved in 60% acetone ethanol. The reaction mixture was refluxed in 60% acetone ethanol medium for four hour on waterbath, brown crystal were separated out at room conditions, filtered and dried. Recrystallised from ethanol, completion of reaction was monitored by TLC, yield 68%, m.p 179^oC.

Molecular formula: C₂₁H₁₇N₅O₄S₂, % Composition found (calculated): C-53.81 (53.95), H-3.55 (3.67), N-14.84 (14.98), O-13.52 (13.69) and S-13.61 (13.71).

IR spectrum of compound was recorded using KBr-pellets and important absorption are shown below,

IR : 3102.01 cm⁻¹ (Ar, C-H str); 1503.04cm⁻¹ (Ar, C=C str); 1630.01(C=O str); 1230.03cm⁻¹ (C-N str); 1150.06 cm⁻¹(C-O str); 1355-1516.31 cm⁻¹ (O=N asy str); 2185.05 cm⁻¹(C=S).

¹H-NMR Spectrums of compound was recorded using in a mixture of DMSO-d₆ and this spectrum distinctly displayed signals and is shown below,

¹H-NMR (DMSO): δ 8.11. (s, 1H, Ar-H); δ 8.13 (d, 1H, Ar-H); δ 7.70(d, 1H, Ar-H); δ 6.42(d, 1H, CH); δ 6.46 (d, 1H, CH); δ 5.09 (d, 1H, CH); δ 9.01(d, 1H, NH); δ 12.30 (s, 1H, NH), δ 7.63 (d, 1H, Ar-H); δ 7.07 (d, 1H, Ar-H).

Synthesis of 4-[(furan-2-yl)-3-{[2-phenylimino-4-phenylimino]-1,3,5-dithiazin-6-yl}amino]-1-(3-nitrophenyl) azetidin-2-one.

A reaction mixture of N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-phenyl 2,4-dithiobiuret and phenyl isocyanodichloride were taken in equimolar (0.01mol) proportion was refluxed in 60% acetone ethanol medium for 4 hours on water bath. During refluxing evolution of hydrochloride gas was clearly noticed. Dark brown crystals were separated out at room condition, filtered and dried. It was recrystallised from ethanol. Completion of reaction was monitored by TLC, yield 61%, m.p.187°C.

Molecular formula: $C_{28}H_{20}N_6O_4S_2$, % Composition found (calculated): C-58.99 (59.14), H-3.52 (3.55), N-14.74 (14.78), O-11.12 (11.25) and S-11.21 (11.28).

IR spectrum of compound was recorded using KBr-pellets and important absorption are shown below,

IR : 3015.17 cm^{-1} (Ar, C-H str); 1598.19 cm^{-1} (Ar, C=C str); 1635.26(C=O str); 1230.05 cm^{-1} (C-N str); 1165.40 cm^{-1} (C-O str); 1343-1510 cm^{-1} (O=N asy str); 2182.09 cm^{-1} (C=S).

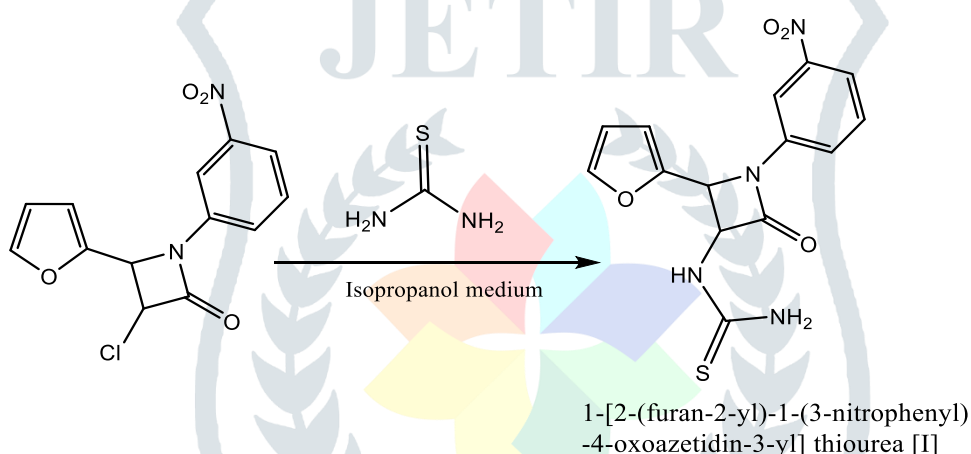
¹H-NMR Spectrums of compound was recorded using in a mixture of DMSO-d₆ and this spectrum distinctly displayed signals and is shown below,

¹H-NMR (DMSO): δ 8.12. (s, 1H, Ar-H); δ 7.63(dd, 1H, Ar-H); δ 7.70(d, 1H, Ar-H); δ 6.43 (d, 1H, CH); δ 7.45 (d, 1H, CH); δ 5.02(d, 1H, CH); δ 4.51(dd, 1H, CH); δ 6.83 (d, 1H, Ar-H); δ 7.32(d, 1H, Ar-H); δ 13.03 (d, 1H, NH).

REACTION:

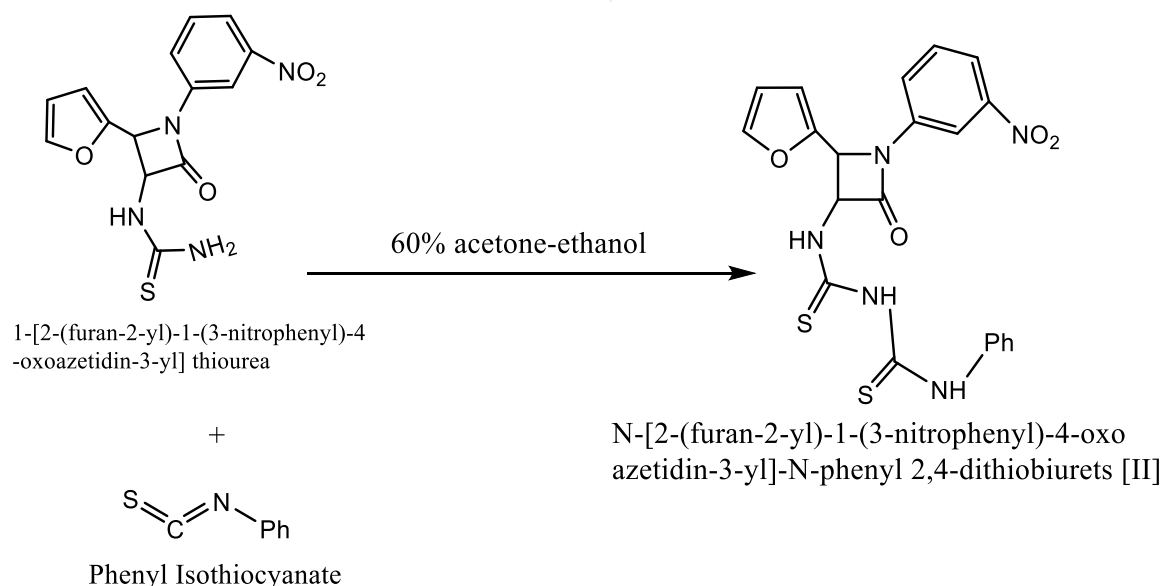
SCHEME-1

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



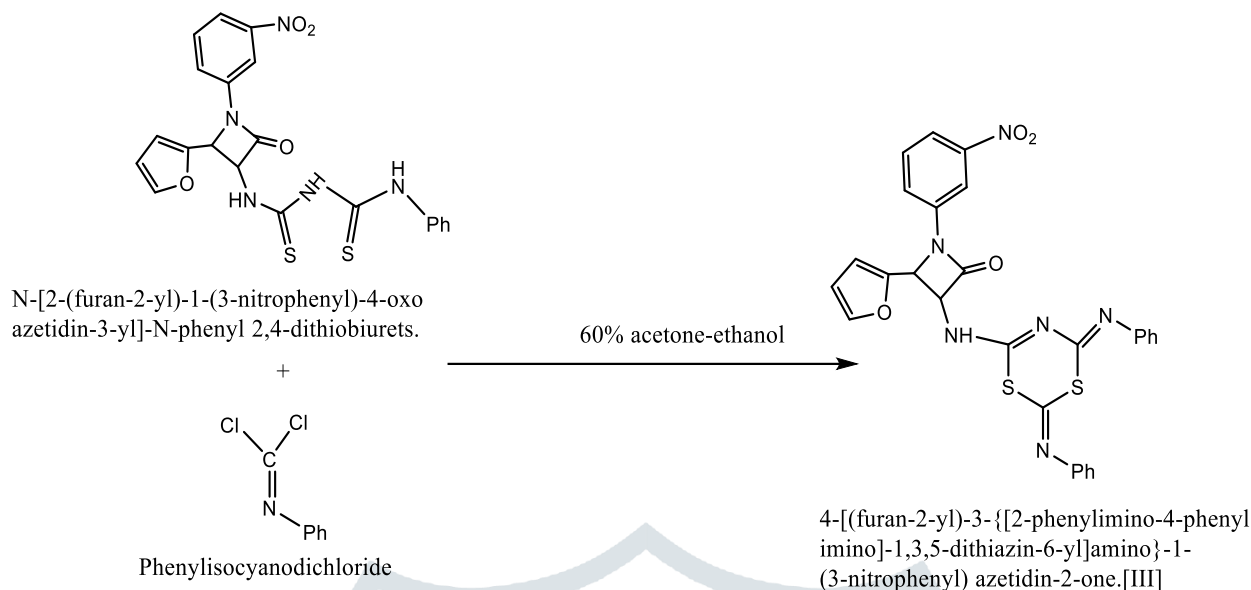
SCHEME -II

Synthesis of N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-phenyl 2,4-dithiobiurets.



Scheme-III

Synthesis of 4-[(furan-2-yl)-3-[[2-phenylimino-4-phenylimino]-1,3,5-dithiazin-6-yl]amino]-1-(3-nitrophenyl) azetidin-2-one.

**Anti-Oxidant Activity:-****In vitro methods****DPPH Radical Scavenging Activity**

Procedure: To 1ml of DPPH solution, equal amount of test compound at various concentrations (20-100 ug/ml) were added in a final volume of 2.0 ml. After incubation for 20 minutes at room temperature, absorbance due to changes in color from deep violet to light yellow were recorded at 517 nm. The control solution was prepared by mixing ethanol (3.5 mL) and DPPH radical solution (0.3 mL). Lower absorbance of the reaction mixture indicated higher free radical activity. The experiment was performed in triplicate.

Calculation:

Percentage Scavenging activity = Absorbance of Control – Absorbance of sample/ Absorbance of Control × 100

CONTROL:-

Concentration	Absorbance
Ethanol (3.5 mL) and DPPH radical solution (0.3 mL)	1.07

STANDARD: (Ascorbic acid)-

Concentration	Absorbance	Percentage scavenging activity
20 ug /ml	0.931	8.73
40 ug /ml	0.658	35.41
60 ug /ml	0.581	43.03
80 ug /ml	0.414	59.41
100 ug /ml	0.381	62.64

SAMPLE:-

Concentration	Absorbance	Percentage scavenging activity
20 ug /ml	0.710	21.39
40 ug /ml	0.401	29.68
60 ug /ml	0.361	39.60
80 ug /ml	0.325	66.13
100 ug /ml	0.196	76.78

RESULTS AND DISCUSSION

We synthesized here unreported 4-[(furan-2-yl)-3-[[2-phenylimino-4-phenylimino]-1,3,5-dithiazin-6-yl]amino]-1-(3-nitrophenyl) azetidin-2-one by the interaction of N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-phenyl 2,4-dithiobiuret and phenyl isocyanodichloride. N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl]-N-phenyl 2,4-dithiobiuret was obtained by

condensation of 1-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl] thiourea and phenyl isothiocyanate. 1-[2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl] thiourea was obtained by the condensation of 3-chloro-substituted azetidin-2-one and thiourea in isopropanol medium.

CONCLUSION

Thus it was possible for us to reduce reflux time and increase percent yield of new synthesized products. At the higher concentration, synthesized compound showed high activity were tested for higher concentration and low concentration showed moderate activity. The newly synthesized compound showed moderate to good antioxidant activity. These newly synthesized compounds contain bioactive heterocyclic moiety and therefore should be screened for their antioxidant activity.

ACKNOWLEDGEMENT

The authors are thankful to the authority of G.V.I.S.H., Amravati for providing laboratory facilities and VIT for spectral data, Govt Pharmacy collage, Amravati for antioxidant activity.

REFERENCE

1. E. Pomarnacka, Z. Brzozowski, M. Filczewski, K. Szymanska, K. Malgorzata, K. Oledzka; **1985**, *Acta Pol.Pharm.* 42, 501–510.
2. Z. Brzozowski, J. Slawinski, F. Gajewski, S. Angielski, A. Hoppe; **1985**, *Acta Pol. Pharm.*, 42, 413-420.
3. Z. Brzozowski, J. Slawinski; **1984**, *Acta Pol. Pharm.*, 41, 5-13.
4. E. Pomarnacka, P.J. Bednarski, R. Grunert, Z. Brzozowski; **2006**, *Pol. J. Chem.*, 80: 429–438.
5. Z. Brzozowski, F. Saczewski, M. Gdaniec; **2003**, *Bioorg. Med. Chem.*, 11; 3673-3681.
6. Z. Brzozowski, F. Saczewski, M. Gdaniec; **2003**, *Eur. J. Med. Chem.*, 38; 991-999.
7. Z. Brzozowski, F. Saczewski, J. Slawinski, P. Bednarski, R. Gruenert, M. Gdaniec; **2003**, *Bioorg. Med. Chem.*, 15; 2560-2572.
8. C. Alkan, Y. Tek, D. Kahraman; **2011**, *Turk J Chem.*, 35: 769-777.
9. Sriram D, Yogeewari P, Madhu K; **2006**, *Bioorg Med Chem Lett.*, 16: 876-878.
10. Saeed A, Shaheen U, Hameed A, Haider Naqvi SZ **2009**; *J of Fluor Chem.*, 130(11):1028-1034.
11. Siddiqui N and Alam MS., *Der Pharma Chemica.*, **2010**; 44(2):115-137.
12. Monika R. Thakur and Shirish P. Deshmukh; **2015**, *Rasayan J. Chem.*, 8(9):471-476.
13. H.S. PATEL and H.D. DESAI; **2004**; *E-journal of chemistry.*, 1:194.
14. Karakus S, Kucukguzel SG, Kucukguzel I, DeClercq E, Panneccouque C, Andrei G; **2009**; *Eur J Med Chem.*, 44(9):3591-3595.
15. Bell FW, Cantrell AS, Hogberg M, Jaskunas SR; **1995**, *J Med Chem.*, 38(25), 4929-4936.
16. Liu J, Song B, Fan H, Bhadury PS, Wan W, Yang S; **2010**, *Eur J Med Chem.*, 45(11), 5108-5112.

