Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2015, 7(3):163-166
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Lacatums of thiazol-4-ones

Vijay V Dabholkar* Sagar D. Shah and Viral M. Dave

Organic Research Laboratory, Department of Chemistry, KC College, Churchgate, Mumbai

---

ABSTRACT

4H-2-(substituted-benzylidino)-hydrazino-4-phenyl-5-oxo-1,3-thiazole were prepared by reacting Ethyl-2-bromo-2-phenylethanoate and Schiff's base of thiosemicarbazide. The product was obtained in 10 mins in the presence of acohol as a solvent. The obtained product was further converted into β-lactum by reacting with chloroacetylchloride. Structure of thiazoles and β-lactum was confirmed by spectral techniques.

Keywords: Thiazole, thiosemicarbazide, β-lactum, CAC.

INTRODUCTION

In today's time, drugs having several pharmacophores which are responsible for different kinds of pharmacological activities are very effective. The potential solution to the antibiotic resistance is to design and explore innovative heterocyclic agents with novel mode of actions.

Thiazole derivatives have been playing a crucial role in medicinal chemistry[1-3]. They display quite a broad spectrum of biological activities, which have found applications in the treatment of allergies[4], hypertension, inflammation, schizophrenia, cancer[5-6], microbial infections and HIV infections[7]. Thiazoles also have emerged as a new class of potent antimicrobial agents[8], which are reported to inhibit bacteria by blocking the biosynthesis of certain bacterial lipids and/or by additional mechanism.

Many biological important Schiff bases ligands have been reported which possess antibacterial, antifungal[9], antimicrobial[10], anticonvulsant, antioxidant[11], anti-inflammatory[12] and antitumor activity[13].

The most common method for the synthesis of 2-azetidinones is the Staudinger keteneimine cycloaddition, which involves the reaction of imines with acid chloride in the presence of a tertiary base. Which are widely used as antibiotics[14] and have marked their presence as key synthons for an important biological class of compounds in organic chemistry[15-20]. β-lactums effective against inflammation[21] which is a symptom and early phase of lethal diseases like heart vascular diseases[22-23], cancer[24], Alzheimer and various rheumatoid arthritis[25].

MATERIALS AND METHODS

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminium plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

General Procedure:

Synthesis of 2-Bromo-2-phenylacetic acid (1):

In a round bottom flask mixture of Phenyl acetic acid (0.1mole, 13.6g) and N-Bromosuccnimide (0.15mole, 26.7g) were allowed to reflux for 8-10 hrs in CCl_4 (30ml) as a solvent and small quantity of benzoyl peroxide as a catalyst. The progress of the reaction was monitored on TLC. Upon completion, reaction mixture was quenched into the water and CCl_4 (10ml). Organic layer was separated and washed with water. CCl_4 was distilled out completely to yield crystals of compound **1**. Yield 70%, m.p. 81-83^{0}C.

Synthesis of Ethyl-2-bromo-2-phenylethanoate (2):

Compound **1** (0.1mole, 21.5g), $SOCl_2$ (0.15mole, 10.9ml), CCl_4 (10ml) as a solvent were refluxed for 2-3 hrs and ethanol (20ml) was then added. The reaction mixture was stirred further for 5-10 mins and was washed using aqueous solution of Na_2CO_3 to remove traces of compound **1** if present. The organic layer so obtained was distilled off to obtain compound **2**. Yield 83%, b.p. 88-93^{0}C.

Synthesis of 5H-2-(substituted-benzylidin)hydrazino-5-phenyl-4-oxo-1,3-thiazole (3a-g):

A mixture of compound **2** (0.01mole), substituted thiosemicarbazone (0.01mole) and pyridine (0.02mole) in ethanol (10ml) were refluxed for 10 mins. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was poured onto ice. The solid product thus obtained was filtered, washed and recrystallized using ethanol to yield **3**. Thus compounds **3a-g** were synthesized.

5H-2-(benzylidin)hydrazino-5-phenyl-4-oxo-1,3-thiazole (3a)

Anal.Calcd for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23; O, 5.42; S, 10.86%. Found C, 65.08; H, 4.41; N, 14.24; O, 5.24; S, 10.85%. IR(cm^{-1}): 1320 (C-S), 1600(C=N), 1650 (C=N), 1720(C=O), 3100(C-H) ^{1}H NMR(δ ppm): 4.65(s,1H,CH), 5.7(s,1H,CH), 7.2-7.5(m,10H,Ar-H), 8.9(s,1H,NH) ^{13}C NMR(δ ppm): 54(CH), 128-140 (Ar-C), 152(C=N), 163(C=N), 188(C=O).

5H-2-(4'-Hydroxy-3'-methoxy--benzylidin)hydrazino-5-phenyl-4-oxo-1,3-thiazole (3b)

Anal.Calcd for $C_{17}H_{15}N_3O_3S$: C, 59.81; H, 4.43; N, 12.31; O, 14.06; S, 9.39%. Found C, 59.82; H, 4.39; N, 12.31; O, 14.07; S, 9.38%. IR(cm^{-1}): 1320(C-S), 1600(C=N), 1650(C=N), 1720(C=O), 3100(CH), 3500(OH) ^{1}H NMR(δ ppm): 3.75(s,3H,OCH_3), 4.7(s,1H,CH), 5.3(s,1H,OH), 5.8 (s,1H,CH), 7.62-7.75(m,8H,Ar-H), 8.95(s,1H,NH) ^{13}C NMR(δ ppm): 54(CH), 58(OCH_3), 128-140(Ar-C), 152 (C=N), 163(C=N), 188(C=O).

Synthesis of 2-[3-Chloro-2-(substituted)-phenyl-4-oxo-azetidin-1-yl]-5-phenyl-thiazol-4-one (4a-g):

A mixture of compound **3** (0.01mole) and triethylamine (0.1mole) was dissolved in 1,4-dioxane (10ml), kept in an ice bath, and stirred for 30 mins. To this, a cold solution of chloroacetyl chloride (0.1mole) was added slowly, further stirred for 3-4 hours at RT. The progress of the reaction was monitored on TLC. After completion of the reaction 1,4-dioxane was distilled off. Residue was poured on to cold water and the resulting solid was filtered, washed with n-hexane, and recrystallized from alcohol to obtain product **4a-g.**

Table I: Characterization data of compounds 3 and 4

Compounds	R	Melting point ^{0}C	Yield %
3a	H	236-238	78
3b	4-OH, 3-OCH_3	225-227	76
3c	4-OCH_3	251-253	80
3d	4-OH	210-212	72
3e	2-OH	198-200	70
3f	4-Cl	159-161	75
3g	1-CH=CH-CHO	172-174	68
4a	H	281-283	50
4b	4-OH, 3-OCH_3	265-267	75
4c	4-OCH_3	270-272	68
4d	4-OH	250-252	70
4e	2-OH	278-280	54
4f	4-Cl	213-215	62
4g	1-CH=CH-CHO	221-223	58

2-[3-Chloro-2-phenyl-4-oxo-azetidin-1-yl]-5-phenyl-thiazol-4-one (4a)

Anal.Calcd for $C_{18}H_{14}ClN_3O_2S$: C, 58.14; H, 3.79; Cl, 9.53; N, 11.30; O, 8.61; S, 8.62%. Found C, 58.14; H, 3.77; Cl; 9.55; N, 11.30; O, 8.60; S, 8.61%. IR(cm^{-1}): 660 (C-Cl), 1320 (C-S), 1600 (C=N), 1720 (C=O), 1750 (C=O),

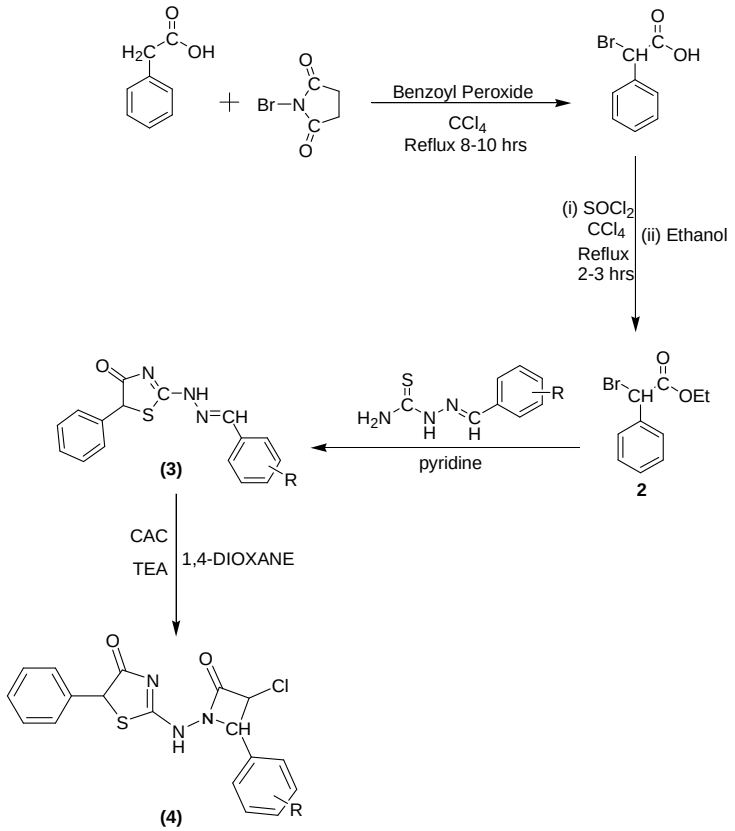
3100 (C-H), 3350 (NH) ^{1}H NMR(δ ppm): 4.7(s,1H,CH), 5.25(d,1H, CH), 5.4(d,1H,CH), 7.2-7.4(m,10H,Ar-H), 9.2(s,1H,NH) ^{13}C NMR(δ ppm): 54(CH), 58.2(CH), 64.0(C), 124-138(Ar-C), 162.2(C=N), 164.2(C=O), 188(C=O)

2-[3-Chloro-2-(4-hydroxy-3-methoxy-phenyl)-4-oxo-azetidin-1-yl]-5-phenyl-thiazol-4-one (4b)
Anal.Calcd for $C_{19}H_{16}ClN_3O_4S$: C, 54.61; H, 3.86; Cl, 8.48; N, 10.06; O, 15.32; S, 7.67%. Found C, 54.61; H, 3.83; Cl; 8.50; N, 10.05; O, 15.32; S, 7.66%. IR(cm^{-1}): 660(C-Cl), 1100(OCH_3), 1320(C-S), 1600(C=N), 1720(C=O), 1750(C=O), 3100(C-H), 3350(NH), 3580(OH) ^{1}H NMR(δ ppm): 3.8(s,3H,OCH_3), 4.65(s,1H,CH), 5.00(s,1H,OH), 5.28(d,1H,CH), 5.4(d,1H,CH), 7.0-7.5(m,8H,Ar-H), 9.2(s,1H,NH) ^{13}C NMR(δ ppm): 54 (CH), 56.4(OCH_3), 58.2(CH), 64(C), 124-138(Ar-C),162.2(C=N), 164.2(C=O), 188(C=O).

Antibacterial Evaluation
The newly synthesized representative compounds were tested for their antimicrobial activity against the following microorganisms: (a) Gram-negative: Escherichia coli, P.aeruginosa;

(b) Gram-positive: S.aureus, C.diphtheria. The preliminary screening of the investigated compounds was performed using the filter paper disc-diffusion method. The compounds were tested at a concentration of 100 Kg/ml. The zone of inhibition was measured in mm and compared with reference standard ampicillin trihydrate (100 Kg/ml). The compounds tested displayed promising antimicrobial activity. The results of antibacterial screening studies are reported in **Table II**.

General Scheme



RESULTS AND DISCUSSION

In the present study, a series of 1,3-thiazoles and azitidiones derivatives were designed and synthesized , it involves four steps , the compounds **3a-g** were synthesized in high yields by reacting substituted thiosemicarbazons with compound **2** in the presence of pyridine as a catalyst and ethanol as a solvent. Further, the various derivatives **(3a-g)** were treated with chloroacetyl chloride in the presence of triethylamine to yield desired azitidone derivatives **(4a-g)** The representative compounds were evaluated for their antifungal and antibacterial activity, which showed promising activity. The structures of all the synthesized compounds were characterized on the basis of the chemical and spectral techniques such as IR, ^{1}H NMR, ^{13}C NMR and elemental analysis techniques.

Table II. Antimicrobial activities of some newly synthesized compounds

Compounds	Inhibition Zone (mm)			
	Gram-negative		Gram-positive	
	E.coli	P.aeruginosa	S.aureus	C.diphtheria
4a	11	15	16	14
4b	19	21	21	23
4c	12	16	20	18
4d	11	10	25	23
4e	15	14	21	16
4f	18	20	17	19
4g	17	18	24	22
Amphicilin trihydrate	21	24	26	28
DMSO	0	0	0	0

Acknowledgement

The Authors are thankful to the principal Ms. Manju J Nichani and Management of K.C. College, Churchgate, Mumbai for constant encouragement and providing necessary facilities. Authors are also thankful to TIFR, Mumbai for providing spectral data.

REFERENCES

[1] Narendra Singh, *J. Chem. Pharm. Res.* **2010,** 2(3), 691-698.
[2] Bharti SK and Nath G. *Eur. J. Med. Chem.* **2010**, 45, 651-660.
[3] Nuray Ulusay and Guzelde mirci, J. Med. Chem. **2010**, 45, 63-68.
[4] Hargrave KD, Hess FK and Oliver JT, *J. Med. Chem.*, **1983**, 26, 1158-1163.
[5] Zeng-Chen Liu and Bao-Dui Wang, *Eur. J. Med. Chem.* **2010**, 45, 5353-5361.
[6] Nadeem Siddiqui and Satish Kumar Arya, *Int. J. Drug Dev. & Res.*, **2011**, 3(4), 55-67.
[7] Lakshmana Doss M and Lalitha KG, *J. Curr. Chem. Pharm. Sci.* **2011**, 1(1), 52-58.
[8] Prakash Karegoudar and Mari Sithambaram, *Eur. J. Med. Chem.* **2008**, 43, 261-267.
[9] Sridhar SK, Saravan M, Ramesh A, *Eur. J. Med. Chem.* **2001**, 36, 615-623.
[10] Raman N, Kulandaisamy A, Thangaraja C, *Trans Met Chem*, **2003**, 28, 29-36.
[11] Al-Amiery AA, Al-Majedy YK, Ibrahim HH, AlTamimi AA. *Organic and Medicinal Chemistry Letters* **2012**, 2(4), 1-7.
[12] Janos G, Tamas L, *Curr Med Chem*, **2009**, 16, 1091-1114.
[13] Billman JH, Schmidgall RL, *J Pharm Sci*, **2006**, 59, 1191-1194.
[14] R. Southgate, *Contemporary Organic Synthesis*, **1994**, 1(6), 417-431.
[15] Zhou, Z.; Alper, H. *J. Org. Chem.* **1996**, 61, 1256.
[16] Alcaide, B.; Almendros, P. *Curr.Med. Chem.* **2004**, 11, 1921.
[17] Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.Jayanthi, A. *Curr. Med. Chem.* **2004**, 11, 1889.
[18] Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, 107, 4437.
[19] Todorov, A. R.; Kureteva, V. B.; Bontchev, R. P.; Vassilev, N. G. *Tetrahedron* **2009**, 65,10339.
[20] Arumugam, N.; Raghunathan, R. *Tetrahedron* **2010**, 66, 969.
[21] Dundar Y., Cakir B., Kupeli E., Sahin M. F. and Noyanalpan N.; Turk. J. Chem., **2007**, 31, 301.
[22] Anderson S. E., Edvinsson M. L. and Edvinsson L., *Clin. Sci.*, **2003**, 105, 699.
[23] Omoigui S., *Med. Hypotheses*, **2005**, 65, 559.
[24] Blasko I. and Grubeck-Loebenstein B., *Drugs Aging*, **2003**, 20(2), 101.
[25] Charles P., Elliott M. J., Davis D., Potter A., Kalden J. R., Antoni C., Ebrel G.,Feldmann M. and Maini R. N., *J. Immunol.*, **1999**, 163(3), 1521.