RESEARCH ARTICLE Am. J. PharmTech Res. 2015; 5(1) ISSN: 2249-3387

AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Synthesis and Antimicrobial Evaluation of Some Novel Perbenzoylated N-Lactosyl-1,2,4-Thiadiazolidines (Hydrochloride)

Kedar P. Pande[1]*

1. Mauli College of Engineering and Technology, Shegaon-444203 (Maharashtra) INDIA.

ABSTRACT

Heterocyclic compounds have been employed in the synthesis of number of pharmaceutical compounds because of the significant activities possessed by them. One of the most interesting reactions in synthetic carbohydrate chemistry is the control chlorination of sugars. A series of some novel perbenzoylated *N*-Lactosyl-1, 2, 4- thiadiazolidines (hydrochloride) were synthesized by the interaction of hepta-*O*-benzoyl-β-D-lactosyl-3-aryl carbamides and *N*-phenyl-*S*-chloro isothiocarbamoyl chloride in chloroform medium. The purity of newly synthesized compounds were judge by their C, H, N and S analysis and the structure was analyzed on the basis of IR, ^{1}H NMR and Mass spectral studies. The antimicrobial activities of the title compounds were determined against bacteria *Escherichiacoli*, *Staphylococcusaureus*, *Proteusvulgaris*, *Salmonellatyphi*, *Klebsiella Pneumoniae*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and fungi *Candida albicancs* and *Aspergillus niger*.

Keywords: *N*-Lactosyl carbamides, *N*-Phenyl-*S*-chloroisothiocarbamoylchloride, Thiadiazolidines, Antimicrobial activity.

---

*Corresponding Author Email: kedarpande@yahoo.co.in

Received 16 January 2015, Accepted 21 January 2015

Please cite this article as: Pande KP, Synthesis and Antimicrobial Evaluation of Some Novel Perbenzoylated N-Lactosyl-1,2,4-Thiadiazolidines (Hydrochloride). American Journal of PharmTech Research 2015.

INTRODUCTION

The 1, 2, 4 thiadiazoles exhibit broad spectrum of biological activity, possibly due the presence of toxophoric N-C-S moiety. It is class of heterocycles, which are potent inhibitors of Human Immunodeficiency Virus type I (HIV I) replication. One of the most interesting reactions in synthetic carbohydrate chemistry is the oxidative cyclization of sugar carbamides. Depending on the substitution pattern of the thioures, the oxidizing agent and the polarity of the medium, variety of the products are formed. Compounds containing thiazole moieties have been reported to possess biological activity, especially antibacterial[1], antifungal[2], and anticonvulsant[3]properties. Heterocyclic compounds like 3-oxo-thiazolidines are known for their wide range of activities such as, antidiabetic[4,5], anthelmintic[6], anti-leishmanial[7], antiinflammatory[8] and neuroprotective[9]etc. In view of our interest in the synthesis if newer types of *N*-lactosylated compound, it appears sufficiently interesting to interact 1-hepta-*O*-benzoyl-β-D-lactosyl-3-aryl carbamides with *N*-phenyl-*S*-chloro isothiocarbamoyl chloride.

MATERIALS AND METHOD

Experimental

All the chemicals and solvents were obtained from commercial and purified using standard procedure wherever required. Melting points were taken by the open capillary method and were uncorrected. The reactions were monitored by thin layer chromatography on silica gel G plates (Merck silica- 60 F_{258}). Optical rotations $[\alpha]_D^{31}$ were measured on the Equip-Tronics EQ-800 Digital Polarimeter at 31^0C in $CHCl_3$. The structures of all the newly synthesized compounds were confirmed by IR Spectra which recorded on Perkin-Elmer spectrum RXI FTIR Spectrometer (Range: 4000-450 cm^{-1}). ^{1}H NMRwas obtained on Bruker DRX-300NMR spectrometer operating at 300 MHz Samples were prepared in $CDCl_3$ with TMS as an internal reference. Mass spectrawere obtained on Thermo Finnegan LCQ Advantage max ion trap mass spectrometer.

General Procedure

Preparation of 1-hepta-*O*-benzoyl-β-D-lactosyl-3-aryl carbamides (1a-g)

A 0.005M of aryl amines in a 5ml of benzene was added to a 0.005M solution of hepta-*O*-benzoyl-β-D-lactosyl isocyanate in 15ml benzene.The reaction of mixture was refluxed over boiling water bath for 3 hr. After refluxing, the solvent was distilled off and the sticky residue obtained was triturated with petroleum ether (60-80^0C) to afford a solid (**1a-g**). The product was purified by chloroform-petroleum ether.

Preparation of *N*-phenyl-*S*-chloro isothiocarbamoyl chloride (2)

The *N*-*o*-tolyl-*S*-chloro isothioocarbamoyl chloride was prepared by the interaction of *o*-tolyl isothiocyanate and by passing calculated quantity of Cl_2 gas.

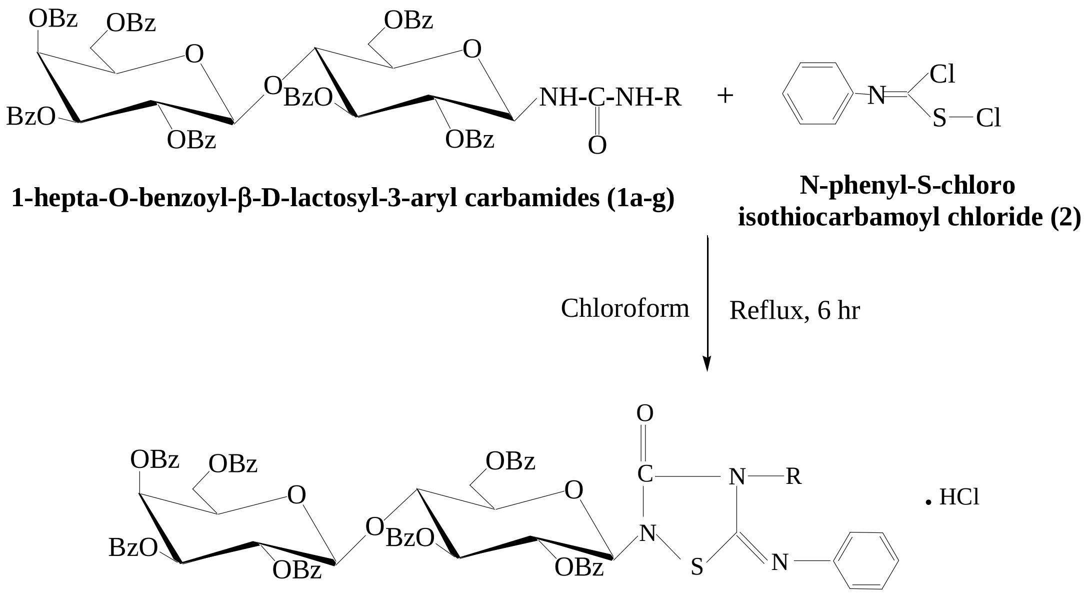
Synthesis of 3-oxo-2-hepta-*O*-benzoyl-β-D-lactosyl-4-aryl-5-phenylimino-1,2,4-thiadiazolidines (hydrochloride) (3a-g)

A 0.005 M of *N*-phenyl-*S*-chloro isothiocarbamoylchloride **(2)** in a 5ml of chloroform was added to a 0.005 M solution of 1-hepta-*O*-benzoyl-β-D-lactosyl-3-aryl carbamides (**1a-g**) in 15ml of chloroform, reaction mixture was refluxed over boiling water bath for 6 hr. The evolution of hydrogen chloride was noticed. Afterward, the solvent chloroform was distilled off and resultant syrupy mass was triturated several times with petroleum ether (60-80^{o}C) to afford a solid, crystallized from ethanol-water.

RESULTS AND DISCUSSION

Herein, we report the synthesis of various 3-oxo-2-hepta-*O*-benzoyl-β-D-lactosyl-4-aryl-5-phenylimino-1,2,4-thiadiazolidines (hydrochloride) **(3a-g)** by inteaction of 1-hepta-*O*-benzoyl-β-D-lactosyl-3-aryl carbamides (**1a-g**) and *N*-phenyl-*S*-chloro isothiocarbamoyl chloride **(2)** in chloroform medium. All products were crystalised from ethanol before recording the physical data (Table-1). The purity of compounds were checked by TLC. The spectral analysis[10-12] IR, ^{1}HNMR and Mass spectra of the product were observed. Optical rotation of the product was also recorded.

Scheme for synthesis shown as follows



1-hepta-O-benzoyl-β-D-lactosyl-3-aryl carbamides (1a-g)

N-phenyl-S-chloro isothiocarbamoyl chloride (2)

Oxo-2-hepta-O-benzoyl-β-D-lactosyl-4-aryl-5-phenylimino-1, 2, 4-thiodiazolidines (hydrochloride) (3a-g)

Where, OBz = $OCOC_6H_5$

R = a) phenyl, b) *o*-tolyl, c) *m*-tolyl, d) *p*-tolyl, e) *o*-Cl-phenyl, f) *m*-Cl-phenyl, g) *p*-Cl-phenyl

SPECTRAL DATA

3a]IR (KBr,cm^{-1}) : υ, 1729 (C=O), 1601(C=N), 1269(C-N), 1175 (C-O), 751 (C-S), 1069 & 1026 cm^{-1}(Characteristic of Lactose), 709 (Monosubstituted benzene);

^{1}H NMR (CDCl$_3$, ppm):δ 8.01-7.19(m, 46H, Ar-H), 6.16-3.72(m. 14H, lactosyl protons);

Mass (m/z): 1356(M$^+$), 1052,975, 931, 579, 135, 105, 77.(Anal. Calcd. for $C_{75}H_{60}O_{18}N_3SCl$; Requires: C, 66.27, H, 4.49, N, 3.09, S, 2.35; Found: C, 66.21, H, 4.40, N, 3.06, S, 2.32%.)

3c]IR (KBr,cm^{-1}) : υ, 1728 (C=O), 1601(C=N), 1268(C-N), 1175 (C-O), 757 (C-S), 1069 & 1026 cm^{-1}(Characteristic of Lactose);

^{1}H NMR (CDCl$_3$, ppm):δ 8.02-7.18(m, 44H, Ar-H), δ 1.25 (s, 3H, CH_3), δ 6.16-3.82(m,14H, lactosyl protons);

Mass (m/z):1360(M$^+$), 1053, 975, 931, 135, 105, 77, 579.(Anal. Calcd. for $C_{76}H_{62}O_{18}N_3SCl$, Requires: C, 66.47, H, 4.59, N, 3.06, S, 2.33, Found: C, 66.39, H, 4.52, N, 3.01, S, 2.29%.)

3g]IR (KBr,cm^{-1}) : υ, 1728 (C=O), 1601(C=N), 1270(C-N), 1175 (C-O), 709 (C-S), 1069 & 1026 cm^{-1}(Characteristic of Lactose);

^{1}H NMR (CDCl$_3$, ppm):δ 8.05-7.21(m, 47H, Ar-H), δ 5.97-3.84 (m,14H, lactosyl protons);

Mass (m/z):1367(M$^+$), 1052, 975, 931, 579, 135, 105, 77.(Anal. Calcd. for $C_{75}H_{61}O_{18}N_3SCl_2$, Requires: C, 64.60, H, 4.37, N, 3.01, S, 2.29, Found: C, 64.56, H, 4.33, N, 2.94, S, 2.23%.)

Table 1: Physical characterization of 3-Oxo-2-hepta-*O*-benzoyl-β-D-lactosyl-4-aryl-5-phenylimino-1, 2, 4-thiodiazolidines (hydrochloride)

Sr. No.	Compd.	Yield (%)	m. p. (°C)	$[\alpha]_D^{31}$ (c, $CHCl_3$)	Elemental Analysis Found (Required)		R_f (4:6, EtOAc : Pet.ether)
					N	S	
1	3a	70.62	128	94.38° (1.00)	3.06(3.09)	2.32 (2.35)	0.80
2	3b	65.28	120	117.61° (1.00)	3.02 (3.06)	2.28 (2.33)	0.71
3	3c	62.52	142	-87.03° (1.00)	3.01 (3.06)	2.29 (2.33)	0.77
4	3d	72.81	132	55.85° (1.00)	3.02 (3.06)	2.31 (2.33)	0.89
5	3e	52.38	146	108.24° (1.00)	2.91 (3.01)	2.25 (2.29)	0.85
6	3f	68.10	127	77.19° (0.99)	2.96 (3.01)	2.21 (2.29)	0.73
7	3g	67.21	133	-82.22° (0.99)	2.94 (3.01)	2.23 (2.29)	0.56

Antimicrobial Studies

All the compounds have been screened for both antibacterial and antifungal activities using cup plate agar diffusion method[13-15] by measuring the inhibition zone in mm. The compounds were taken at a concentration of 1mg/ml using dimethyl sulphoxide as solvent. Amikacin (100µg/ml) was used as a standard for antibacterial and antifungal activity and Fluconazole (100µg/ml) as a standard for antifungal activity. The compounds were screened for antibacterial activity against *Escherichiacoli*, *Staphylococcusaureus*, *Proteusvulgaris*, *Salmonellatyphi*, *Klebsiella Pneumoniae*, *Pseudomonas aeruginosa*, *Bacillus subtilis* in nutrient agar medium and for antifungal activity against *Candida albicancs* and *Aspergillus niger* in potato dextrose agar medium. These sterilized agar media were poured into Petri dishes and allowed to solidify on the surface of the media, microbial suspensions were spread with the help of sterilized triangular loop. A stainless steel cylinder of 8mm diameter (pre-sterilized) was used to bore the cavities. 0.1 ml portions of the test compounds in solvent were added into these wells. The drug solution was allowed to diffuse for about an hour into the medium. The plates were incubated at 37^{o}C for 24h and 30^{o}C for 48h for antibacterial and antifungal activities respectively. The zone of inhibition observed around the cups after respective incubation was measured. The results are presented in Table 2. It has been observed that some of these compounds exhibit interesting microbial activities. 3a, 3b and 3c exhibit most significant activity against *E.coli* and *P. vulgaris* respectively. All other compounds exhibited low to moderate activity (Table 2).

Table 2: Results of antimicrobial activity tests of the synthesized compounds

Compd.	**Antibacterial****							**Antifungal****	
	E.Coli	*S. aureus*	*P. vulgaris*	*S. typhi*	*K. Pneumoniae*	*P. aeruginosa*	*B.Subtilis*	*C. albicance*	*A.niger*
3a	21	11	22	16	18	15	10	07	09
3b	20	14	14	10	15	-	-	09	08
3c	20	-	22	-	17	17	14	15	10
3d	13	15	-	10	12	13	18	06	09
3e	-	20	-	-	-	14	11	14	-
3f	16	12	14	12	19	-	12	07	-
3g	10	18	19	12	14	-	-	10	08
Amikacin	25	22	25	28	22	25	22	-	
Fluconazole	-	-	-	-	-	-	-	18	27

**zone of inhibition in mm (15 or less) resistance, (16-20mm) moderate and (more than 20mm) sensitive. Escherichia coli (E. coli), Staphylococcus aureus (S. aureus), Proteus vulgaris (P. vulgaris), Salmonella typhi (S. typhi), Klebsialla Pneumoniae (K. Pneumoniae), Pseudomonas auriginosa (P. auriginosa), Bacillus subtilis (B. subtlis), Candida albicancs (C.albicancs) and Aspergillus niger (A. niger).

CONCLUSION

The novel thiadiazolidines exhibits comparable antibacterial and antifungal activities against the organism tested. The method adopted in this investigation is simple efficient inexpensive and is useful in synthesizing pharmacologically important molecules.

ACKNOWLEDGEMENT

Authors are thankful to SAIF, CDRI, Lucknow for providing spectral data and Dr. C. M. Jadhao, Mauli College of Engineering and Technology, Shegaonfor providing necessary facilities.

REFERENCES

1. Bhawsar SB, Mane DV, Sinde DB, Shingare MS, Deokate AS and Congwane LV. Synthesis of some 8-[6’-substituted-1’, 3’-benzothiazol-2’-yl) amino methyl] substituted hydroxyl coumarins and Evaluation of their antibacterial activity. Indian J Het Chem 1996; 8: 23.
2. Latrofa A, Franco M, Lopedota A, Rosato A, Carone D and Vitali C. Structural modification and antimicrobial activity of *N*-cycloalkylidene-2, 3-dihydro-1, 3-benzothiazoles, *N*-cycloalkyl-2-acylalkylidene-2, 3-dihydro-1, 3-benzothiazoles. IL Farmaco 2005; 60: 291-297.
3. Siddiqui N, Rana A, Khan SA, Haque SE, Alam MS and Ahsana W. Anticonvulsant and Toxicity Evaluation of Newly Synthesized 1-[2-(3,4-disubstituted phenyl)-3-chloro-4-oxoazetidin-1-yl]-3-(6-substituted-1,3-benzothiazol-2-yl)ureas. Acta Chim Slov 2009; 56: 462-469.
4. Pattan SR, Suresh C, Pujar VD, Reddy VVK, Rasal VP and Koti BC. Synthesis and antidiabetic activity of 2-amino [5’ (4-sulfonylbenzylidine)-2, 4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole. Indian J Chem 2005; 44B: 2404-2408.
5. Moreno DH, Villalobos MR, Ortiz AR, Diaz CD, Medina J.L, Webster S.P, Estrado SS, Ibarra BM, Leon RI, Navarrete VG. Antidiabetic activity on N-(6-substituted-1, 3-benzothiazol-2-yl) benzenesulfonamides. Bioorg Med Chem Lett 2008; 18: 2871-2877.
6. Barde AR, Barsu HK and Bobade AS. Synthesis of 5, 6-Disubstituted-2-(Substituted Phenyl Carboxamido) Benzothiazoles as Potential Anthelmintic and Anti-Microbial agents. Indian Drugs 1998; 35(9): 554-557.
7. Tapia RA, Prieto Y, Pautet F, Domard M, Sarciron ME, Walchshofer N, and Fillion H. Synthesis and Antileishmanial Activity of Indoloquinones Containing a Fused Benzothiazole Ring. Eur J Org Chem 2002; 17: 4005-4010.
8. Dogruer DS, Unlu S, Sahin MF and Yesilada E. Synthesis of (2-benzothiazolone-3-yl and 2-benzothiazolone-3-yl) acetic acid derivatives and Evaluation of their Antinociceptive and Anti-inflammatory Activity. IL Farmaco 1998; 53: 80.
9. Danzeisen R, Schwalenstoecker B and Gillardon F, Targeted antioxidative and neuroprotective properties of the dopamine agonist pramipexole and its nondopaminergic enantiomer

SND919CL2x [(+) 2-amino-4, 5, 6, 7-tetrahydro-6-Lpropylamino-benzathiazole dihydrochloride]. J Pharmacol Exp Ther 2006; 316(1): 189–199.

10. Silverstein RM and Webster FX, “Spectrometric Identification of Organic Compounds”, 6th ed., John Wiley and Sons, Inc, New York; 2011.
11. Williams DH and Fleming I, “Spectroscopic Methods in Organic Chemistry”, 5th ed., Tata McGraw-Hill; 2004.
12. Dyer JR, “Applications of Absorption Spectroscopy of Organic Compounds”, PHI Learning Private Limited, New Delhi; 2010.
13. Kawangh F, Analytical Microbiology, Academic press, New York; 1963.
14. British pharmacopoeia-II, Biological assay and Tests, The Stationary Office Ltd., London; 1998: A-205.
15. Kumar VMMJ, Jayadevaiah KV, Nagaraj TS, Jayachandran E, Bharathi DR Sreenivasa GM et al., Synthesis, characterization and antimicrobial activity of new *N*-substituted-3-chloro-2-azetidinones. Arch Pharm Sci Res 2009; 1(1): 31-29.