J. Indian Chem. Soc.,
Vol. 93, December 2016, pp. 1413-1416

Synthesis and biological evaluation of 4-aryl-5-hepta-*O*-benzoyl-β-D-lactosylimino-3-hepta-*O*-benzoyl-β-D-lactosylimino-l,2,4-dithiazolidines (hydrochlorides)

Kavita M. Heda*[a] and Shirish P. Deshmukh[b]

[a]Department of Chemistry, Shri R. L. T. College of Science, Akola-444 001, Maharashtra, India

E-mail : kavitaheda25@gmail.com

[b]P.G. Department of Chemistry, Shri Shivaji College, Akola-444 001, Maharashtra, India

Manuscript received 04 November 2015, accepted 26 October 2016

Abstract : A series of 4-aryl-5-hepta-*O*-benzoyl-β-D-lactosylimino-3-hepta-*O*-benzoyl-β-D-lactosylimino-1,2,4-dithiazolidines (hydrochloride) have been synthesized by the interaction of various 1-hepta-*O*-benzoyl-β-D-lactosyl-3-aryl thiocarbamides with *N*-hepta-*O*-benzoyl-β-D-lactosyl-*S*-chloro isothiocarbamoyl chloride. These compounds were screened for their antibacterial and antifungal activities against *E. coli, P. vulgaries, S. aureus, S. typhimurium, K. pneumonie, Ps. aeruginosa, A. niger* and *C. albicance*. The newly synthesized compounds have been characterized by analytical and IR, ^{1}H NMR and Mass spectral studies.

Keywords : Lactosyl thiocarbamides, hepta-*O*-benzoyl-β-D-lactosyl-*S*-chloro isothiocarbamoyl chloride, 1,2,4-dithiazolidines, antimicrobial activity.

Introduction

The drug containing 1,2,4-dithiazolidines show a diverse range of pharmacological activities[1–3], antimicrobial[4,5], anti-inflammatory[6,8], anti-HIV[9], anti-ulcer[10,11], anti-cancer[12] and anti-convulsant[13,14]. *N*-Lactosylated derivatives[15–18] exhibits a wide range of medicinal activites such as antiviral, antidiabatic, analgesic and other significant activites. Here is reported the synthesis of several *N*-lactosylated-1,2,4-dithiazolidines by the interaction of several 1-hepta-*O*-benzoyl-β-D-lactosyl-3-aryl thiocarbamides with *N*-hepta-*O*-benzoyl-β-D-lactosyl-*S*-chloro isothiocarbamoyl chloride. The required 1-hepta-*O*-benzoyl-β-D-lactosyl-3-aryl thiocarbamides were obtained by the interaction of 1-hepta-*O*-benzoyl-β-D-lactosyl isothiocyanates with various amines.

Results and discussion

Several 4-aryl-5-hepta-*O*-benzoyl-β-D-lactosylimino-3-hepta-*O*-benzoyl-β-D-lactosylimino-1,2,4- dithiazolidines (hydrochloride) have been prepared by the interaction of several 1-hepta-*O*-benzoyl-β-D-lactosyl-3-aryl thiocarbamides (**1a-f**) with *N*-hepta-*O*-benzoyl-β-D-lactosyl-*S*-chloro isothiocarbamoyl chloride (**2**) in $CHCl_3$. After condensation, the solvent was distilled off to obtain a sticky residue. This residue was triturated with petroleum ether (60–80 °C) to afford a pale yellow solid (**3a-f**). The product was found to be non-desulphurizable when boiled with alkaline lead acetate solution. The specific rotations were measured in chloroform. The result is summarized in Table 1. In spectrum analysis of product shows bands due to Ar. C-H, ali. C-H, C=O, C=N, C-N, C-O, C-S, stretching and ^{1}H NMR spectrum of product distinctly displayed signals due to aromatic protons and lactose ring protons. The Mass spectrum of product was also observed. The identities of these new *N*-lactosides have been established on the basis of usual chemical transformations and also IR, ^{1}H NMR and Mass spectral studies[19–21].

Experimental

All chemicals were research grade. Melting points determined are uncorrected. IR spectra were recorded in KBr on a FT-IR Perkin-Elmer RXI (4000–450 cm^{-1}) spectrophotometer. ^{1}H NMR measurements were performed on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in $CDCl_3$) solution with TMS as internal reference. The Mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap Mass spectro-

Table 1. Physical data for characterization of compounds (**3a-f**)

Reactant : *N*-Hepta-*O*-benzoyl-β-D-lactosyl-*S*-chloro isothiocarbamoyl chloride (**2**) (0.001 *M*, 1.150 g)

1-Hepta-*O*-benzoyl-β-D-lactosyl-3-aryl thiocarbamides (**la-f**)	Product	Yield (%)	m.p. (°C)	R_f value (Petroleum ether : acetone, 6 : 4)	$[\alpha]_D^{31}$ (*c*, $CHCl_3$)	Analysis (%) : Found (Calcd.)	
						N	S
3-Phenyl	**3a**	83.00	142	0.67	–45.5 (*c*, 0.011)	1.80 (1.76)	2.71 (2.68)
3-*o*-Cl-Phenyl	**3b**	80.41	150	0.58	–72.7 (*c*, 0.011)	1.77 (1.73)	2.62 (2.64)
3-*m*-Cl-Phenyl	**3c**	89.00	147	0.76	–107.1 (*c*, 0.015)	1.75 (1.73)	2.68 (2.64)
3-*p*-Cl-Phenyl	**3d**	78.00	135	0.59	+163.6 (*c*, 0.011)	1.76 (1.73)	2.60 (2.64)
3-*o*-Tolyl	**3e**	88.33	130	0.72	+238 (*c*, 0.013)	1.80 (1.75)	2.71 (2.66)
3-*p*-Tolyl	**3f**	65.00	127	0.78	+254.5 (*c*, 0.011)	1.78 (1.75)	2.69 (2.66)

meter. Optical rotation $[\alpha]_D^{31}$ measured on a Equip-Tronics Digital Polarimeter EQ-800 at 31°C in $CHCl_3$. Thin layer chromatography (TLC) was performed on silica gel G and spots were visualized by iodine vapour. The compounds were screened for their antibacterial and anti-fungal activities by the disc diffusion assay method[22]. The compounds describe in this paper were first time synthesized by the multistep reaction protocol.

General procedure :

Synthesis of 1-hepta-O-benzoyl-β-D-lactosyl-3-aryl thiocarbamides[23] (**1a-f**) :

l-Hepta-*O*-benzoyl-β-D-lactosyl-3-aryl thiocarbamides (**1a-f**) were synthesized by interaction of hepta-*O*-benzoyl-β-D-lactosyl isothiocyanate with different amines in benzene medium.

Synthesis of N-hepta-O-benzoyl-β-D-lactosyl-S-chloro isothiocarbamoyl chloride (**2**) :

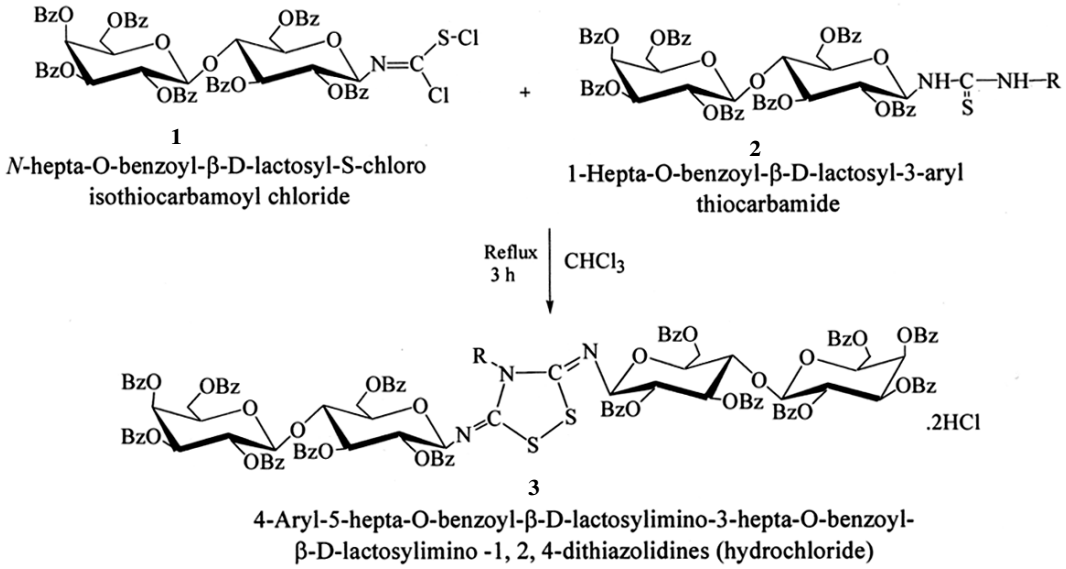
N-Hepta-*O*-benzoyl-β-D-lactosyl-*S*-chloro isothiocarbamoyl chloride (**2**) was prepared by passing a calculated amount of chlorine through a chloroformic solution of hepta-*O*-benzoyl-β-D-lactosyl isothiocyanate maintaining the temperature below 10 °C.

Synthesis of 4-aryl-5-hepta-O-benzoyl-β-D-lactosylimino-3-hepta-O-benzoyl-β-D-lactosylimino-1,2,4-dithiazolidines (hydrochloride) :

A mixture of l-hepta-*O*-benzoyl-β-D-lactosyl-3-phenyl thiocarbamide (**la**, 0.001 *M*, 1.204 g in 20 ml $CHCl_3$) and *N*-hepta-*O*-benzoyl-β-D-lactosyl-*S*-chloro isothiocarbamoyl chloride (**2**) (0.001 *M*, 1.150 g, in 5 ml $CHCl_3$) was gently refluxed for 3 h. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was brought to room temperature and the solvent removed under reduced pressure to obtain residue. This residue was triturated several times with petroleum ether (60–80 °C) to afford a pale yellow solid (**3a**).

(3a) IR (KBr) : υ 3062 (Ar. C-H), 2958 (Ali. C-H), 1730 (C=O), 1539 (C=N), 1315 (C-O), 1026, 908 (lactosyl ring deformation), 709 (C-S), 474 (S-S) cm^{-1}; ^1H NMR (δ in ppm, $CDCl_3$) : 88.13–7.16 (75H, m, 14-COC_6H_5, C_6H_5), 6.74–3.75 (28H, m, lactose ring protons); Mass (*mlz*) : 2386 (M^+) (not located), 1333 (M^+-$C_{61}H_{49}O_{17}$), 1053 (HBL^+), 948 (HBL^+-C_7H_5O), 932 (HBL^+-$C_7H_5O_2$), 918 (HBL^+-$C_8H_7O_2$), 579 (TBG^+), 458 (TBG^+-$C_7H_5O_2$), 335 (TBG^+-$C_{14}H_{12}O_4$), 105 (C_6H_5CO) (Found : C, 65.44; H, 4.35; N, 1.80; S, 2.71. Calcd. for $C_{130}H_{103}O_{34}N_3S_2.2HCl$. Required : C, 65.38; H, 4.31; N, 1.76; S, 2.68%).

(3b) IR (KBr); υ 3062 (Ar. C-H), 2958 (Ali. C-H), 1730 (C=O), 1583 (C=N), 1269 (C-O), 1026, 910 (lactosyl ring deformation), 709 (C-S), 418 (S-S) cm^{-1}; ^1H NMR (δ in ppm, $CDCl_3$) : 8.08–7.18 (74H, m, 14-COC_6H_5, C_6H_4), 6.75–3.72 (28H, m, lactose ring pro-



1
N-hepta-O-benzoyl-β-D-lactosyl-S-chloro isothiocarbamoyl chloride

2
1-Hepta-O-benzoyl-β-D-lactosyl-3-aryl thiocarbamide

3
4-Aryl-5-hepta-O-benzoyl-β-D-lactosylimino-3-hepta-O-benzoyl-β-D-lactosylimino -1, 2, 4-dithiazolidines (hydrochloride)

where OBz = COC_6H_5 (benzoyl) : R = (a) Phenyl, (b) *o*-Cl-Phenyl, (c) *m*-Cl-Phenyl, (d) *p*-Cl-Phenyl, (e) *o*-tolyl, (f) *p*-tolyl.

tons); Mass (*m/z*) : 2420.5 (M^+) (not located), 1367.5 (M^+-$C_{61}H_{49}O_{17}$), 1126 (M^+-$C_{69}H_{53}O_{17}N_3S_2Cl$), 1053 ($HBL^+$), 948 ($HBL^+$-$C_7H_5O$), 932 ($HBL^+$-$C_7H_5O_2$), 579 ($TBG^+$), 475 ($TBG^+$-$C_7H_5O$), 335 ($TBG^+$-$C_{14}H_{12}O_4$), 105 ($C_6H_5CO$) (Found : C, 64.48; H, 4.25; N, 1.77; S, 2.70. Calcd. for $C_{130}H_{102}O_{34}N_3S_2Cl.2HCl$. Required : C, 64.44; H, 4.21; N, 1.73; S, 2.64%).

(**3e**) IR (KBr) : υ 3062 (Ar. C-H), 2976 (Ali. C-H), 1730 (C=O), 1583 (C=N), 1390 (C-O), 1026, 910 (lactosyl ring deformation), 707 (C-S), 509 (S-S) cm^{-1}; ^1H NMR (δ in ppm, $CDCl_3$) : 8.08–7.18 (74H, m, 14-COC_6H_5, C_6H_4), 6.74–3.72 (28H, m, lactose ring protons), 2.45–2.16 (3H, s, Ali. CH_3); Mass (*mlz*) : 2400 (M^+) (not located), 1347 (M^+-$C_{61}H_{49}O_{17}$), 1053 (HBL^+), 948 (HBL^+-C_7H_5O), 932 (HBL^+-$C_7H_5O_2$), 579 (TBG^+), 475 (TBG^+-C_7H_5O), 335 (TBG^+-$C_{14}H_{12}O_4$), 105 (C_6H_5CO) (Found : C, 66.1; H, 4.40; N, 1.80; S, 2.71. Calcd. for $C_{131}H_{105}O_{34}N_3S_2.2HCl$. Required : C, 66.5; H, 4.37; N, 1.75; S, 2.66%).

Antimicrobial activity :

All the compounds have been screened for both antibacterial and antifungal activity by using disc diffusion

Table 2. Antimicrobial activity of 4-aryl-5-hepta-*O*-benzoyl-β-D-lactosylimino-3-hepta-*O*-benzoyl-β-D-lactosylimino-1,2,4-dithiazolidines (hydrochloride)

Compd.	*E. coli*	*S. aureus*	*P. vulgaris*	*Ps. aeruginosa*	*S. typhi*	*K. pneumonie*	*A. niger*	*C. albicance*
A	12	16	10	14	16	16	19	18
B	10	17	9	11	14	–	20	16
C	11	12	11	15	12	11	–	21
D	15	13	18	11	18	12	11	9
E	12	–	13	13	12	13	17	16
F	16	10	15	–	19	15	19	20
DMSO	–	–	–	–	–	–	–	–
Amikacin	18	21	23	19	20	21	–	–
Fluconazole	–	–	–	–	–	–	24	24

Zone size was interpreted by

Sample	Disc content	Resistant	Intermediate	Sensitive
Amikacin	100 ug/ml	≤ 15 mm	16–20 mm	≥ 21 mm
Fluconazole	100 ug/ml	≤ 15 mm	16–20 mm	≥ 21 mm

assay. For this sterile filter paper disc (6 mm) impregnated with fixed doses of compounds was placed on pre-inoculated surface. The disc bearing plates were incubated at 37 °C for 24 h. Inhibition zones read after incubation at 37 °C for 24 h. for bacterial strains and for fungal strains inhibition zones read after incubation at 35 °C for 48 h. The compounds were taken at a concentration or 1 mg/ml using dimethyl sulphoxide as a solvent. Amikacin (100 ug/ml) was used as standard for antibacterial and Fluconazole (100 ug/ml) as a standard for antifungal activity. The compound were screened for antibacterial activity against *Escherichia coli, Proteus vulgaris, Staphylococcus aureus, Salmonella typhi, Klebsiella pneumonie, Psudomonas aeruginosa* in nutrient agar medium and for *Aspergillus niger* and *Candida albicance* in potato dextrose agar medium. It has been observed that all the compounds showed nearly same activity against both bacteria and fungi. **3d** and **3f** exhibites most significant activity against *Salmonella typhi*. **3b** exhibits good activity against *S. aureus*. The compounds **3a**, **3b** and **3f** showed good activity against *A. niger* while compounds **3c** and **3f** showed good activity against *C. albicance*. All other compounds exhibited low to moderate activity.

Acknowledgement

Authors are thankful to Sophisticated Analytical Instrumentation Facility, Panjab University, Chandigarh for providing spectra and Principal, Dr. V. D. Nanoty for providing necessary facilities.

References

1. J. R. Webb, H. Mitsuya and S. Broder, *J. Med. Chem.,* 1988, **31**, 1475.
2. A. B. Reitz, R. W. Tuman, C. S. Marchione, A. D. Jordan, C. R. Bowden and B. E. Maryanoff, *J. Med. Chem.,* 1989, **32**, 2110.
3. H. Parrot-Lopez, H. Galons, A. W. Coleman, J. Mahuteau and M. Miocque, *Tetrahedron Lett.,* 1992, **33**, 209.
4. Z. A. Kaplancikli, G. Turan-Zitouni, A. Ozdemir and G. Revial, *Eur. J. Med. Chem.,* 2008, **43**, 155.
5. N. A. Al-Masoudi, Y. A. Al-Soud and M. Irene. Lagoja, *Carbohy. Res.*, 1999, **318**, 67.
6. A. M. Abdel-Megeed, H. M. Abdel-Rahman and S. Gamal-Eldien, *Eur. J. Med. Chem.,* 2009, **44**, 117.
7. P. X. Franklin, A. D. Pillia, P. D. Rathod, S. Yerande, M. Nivsarkar, H. Padh, K. K. Vasu and V. Sudarsanam, *Eur. J. Med. Chem.,* 2008, **43**, 129.
8. V. B. Jadhav, M. V. Kulkarni, V. P. Rasal, S. S. Biradar and M. D. Vinay, *Eur. J. Med. Chem.,* 2008, **43**, 1721.
9. R. K. Rawal, R. Tripathi, S. B. Katti, C. Pannecouque and Erik De Clercq, *Eur. J Med. Chem.*, 2008, **43**, 2800.
10. K. Ishihara, T. Ichikawa, Y. Komuro, S. Ohara and K. Hotta, *Arzneim Forsch, Drug Res.,* 1994, **44**, 827.
11. D. Y. Graham, A. Mccullough, M. Sklar, R. C. Stone and R. H. Bibhop, *Digestive Disease and Sciences,* 1990, **35**, 66.
12. D. Havrytyuk, L. Mosula, B. Zimenkovsky, O. Vasylenko, A. Gzella and R. Lesyk, *Eur. J. Med. Chem.,* 2010, **45**, 5012.
13. A. Geronikaki, P. Eleftheriou, P. Vicini, I. Alam, A. Dixit and A. K. Saxena, *Eur. J. Med. Chem.,* 2008, **51**, 5221.
14. V. Mathew, J. Keshavayya and V. P. Vaidya, *Eur. J. Med. Chem.,* 2006, **41**, 1048.
15. K. M. Heda and S. P. Deshmukh, *Int. J. Chem. Sci.,* 2011, **9**, 1750.
16. D. V. Mangte and S. P. Deshmukh, *Heteroatom Chemistry,* 2007, **18**, 390.
17. P. V. Tale and S. P. Deshmukh, *Indian J. Chem.,* 2006, **45B**, 558.
18. K. M. Heda and S. P. Deshmukh, *Rasayan J. Chem.,* 2012, **5**, 24.
19. R. M. Silverstein and F. X. Webster, "Spectrometric Identification of Organic Compounds", 6th ed., John Wiley and Sons, Inc, New York, 2004.
20. N. B. Colthup, L. H. Daly and S. E. Wibereley, "Introduction to Infrared and Raman spectroscopy", Academic Press, New York, 1964.
21. D. H. Williams and L. Fleming, "Spectroscopic Methods in Organic Chemistry", 4th ed., Tata-McGraw-Hill, 1988.
22. J. G. Collee and W. Marr, "Laboratory control of anti-microbial therapy", in : J. G. College, J. P. Duguid, A. G. Fraser and B. P. Marmion (eds.), Mackie and Me Cartney, 'Practical Medical Microbiology', 14th ed., Edinburgh Churchill Livingeston, 1996, pp. 114-115.
23. P. T. Agrawal and S. P. Deshmukh, *J. Curr. Chem. Pharma. Sci.*, 2012, **2**, 157.