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DITHIAZOLIDINES: SYNTHESIS AND ANTI-MICROBIAL ACTIVITY OF SOME NOVEL *N*-MALTOSIDES

Atul V. Yadgire*, Dipali L. Barate and Shirish P. Deshmukh
P. G. Department of Chemistry, Shri Shivaji College, Akola-444 001(M.S.), India.
*E-mail: atulyadgire@gmail.com

ABSTRACT

A series of 3-hepta-*O*-acetyl-β-D-maltosylimino-4-phenyl-5-arylimino-1,2,4-dithiazolidines (hydrochloride) have been synthesized by the interaction of *N*-hepta-*O*-acetyl-β-D-maltosyl-*S*-chloro isothiocarbamoyl chloride with 1-phenyl-3-aryl thiocarbamides. The identities of these newly synthesized *N*-maltosides have been established on the basis of usual chemical transformations and IR, ^{1}H NMR and Mass spectral studies. These compounds were screened in vitro for their antibacterial and antifungal activities.

Key words: Isothiocarbamoyl chloride, Thiocarbamides, Dithiazolidines, Antimicrobial activity.

INTRODUCTION

A family of structurally distinct compounds having dithiazolidine heterocycle core possess potent biological and physiological activities and having good pharmacological properties like antimicrobial[1], antitumor and anti-inflammatory[2]. Literature survey revealed that 1,2,4-dithiazolidines attached to various carbohydrate templates have been reported earlier[3-6]. Acetylated *N*-maltosides having 1,2,4-dithiazolidine heterocyclic core yet not to be synthesized. With this approach, herein several 3-hepta-*O*-acetyl-β-D-maltosylimino-4-phenyl-5-arylimino-1,2,4-dithiazolidines(hydrochloride) have been synthesized by the interaction of *N*-hepta-*O*-acetyl-β-D-maltosyl-*S*-chloro isothiocarbamoyl chloride with 1-phenyl-3-aryl thiocarbamides. *N*-hepta-*O*-acetyl-β-D-maltosyl-*S*-chloro isothiocarbamoyl chloride was prepared for the first time by the interaction of hepta-*O*-acetyl-β-D-maltosyl isothiocyanate with chlorine gas. Required 1-phenyl-3-aryl thiocarbamides have been prepared by the interaction of phenyl isothiocyanate with aryl amines. The identities of these newly synthesized *N*-maltosides have been established on the basis of usual chemical transformations and IR, ^{1}H NMR and Mass spectral studies. All new identities to be tested for their in vitro antimicrobial properties against Gram positive and Gram negative bacteria and fungi.

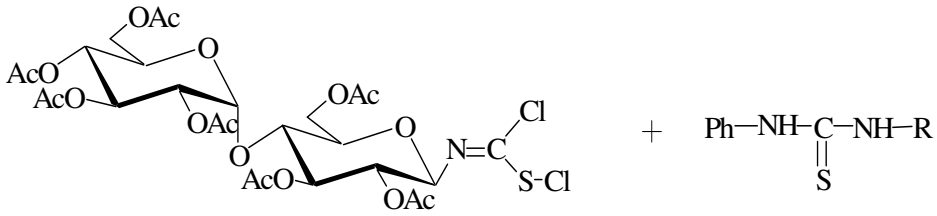
EXPERIMENTAL

Melting points were taken in open capillary tube on Mac digital melting point apparatus and were uncorrected. IR spectra were recorded in solid phase KBr on a Perkin-Elmer Spectrum RXI FTIR Spectrometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 MHz on a Bruker DRX- 300 NMR Spectrometer. The Mass spectra were recorded on a JEOL-AccuTOF JMS-T100LC Mass Spectrometer having DART (Direct Analysis in Real Time) source. The given samples were subjected as such in front of DART source. Dry Helium was used with 4 LPM flow rate for ionization at 350^{o}C. Optical rotations $[\alpha]_D^{30}$ were measured on Equip-Tronics EQ-800 Digital Polarimeter at 30^{0}C in Chloroform. Thin Layer Chromatography [TLC] was performed on E. Merck silica gel plates.

N-hepta-*O*-acetyl-β-D-maltosyl-*S*-chloro isothiocarbamoyl chloride (I)

N-hepta-*O*-acetyl-β-D-maltosyl-*S*-chloro isothiocarbamoyl chloride (1) was prepared for the first time by the extension of earlier method[7] by passing calculated quantity of gaseous chlorine (0.71g, 0.01M) into the chloroformic solution of hepta-*O*-acetyl-β-D-maltosyl isothiocyanate (6.77g, 0.01M). During chlorination the temperature of reaction mixture was maintained at 4-5^{o}C by keeping it in freezing mixture. After chlorination yellow solution was mixed with petroleum ether when a *N*-hepta-*O*-acetyl-β-

D-maltosyl-*S*-chloro isothiocarbamoyl chloride was obtained as a pale yellow oil (7.48g). (Anal. Calcd for $C_{27}H_{35}O_{17}NSCl_2$: N, 1.87; S, 4.27%. Found: N, 1.85; S, 4.26%).

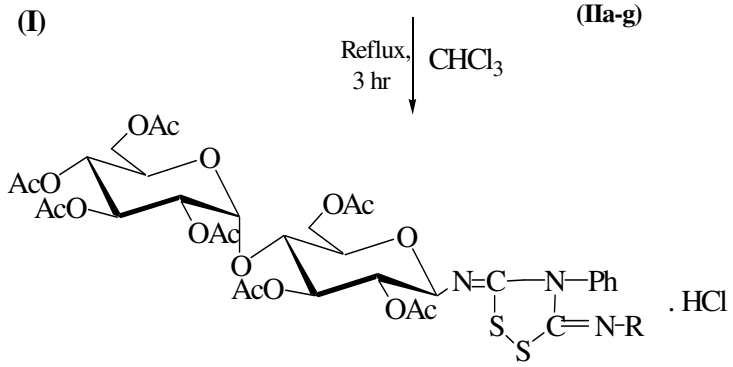


N-hepta-*O*-acetyl-*β*-D-maltosyl-*S*-chloro isothiocarbamoyl chloride

(I)

1-phenyl-3-aryl thiocarbamides

(IIa-g)



3-hepta-*O*-acetyl-*β*-D-maltosylimino-4-phenyl-5-arylimino-1,2,4-dithiazolidines (hydrochloride)

(IIIa-g)

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

SCHEME I

Synthesis of 3-hepta-*O*-acetyl-β-D-maltosylimino-4-phenyl-5-arylimino-1,2,4-dithiazolidines (hydrochloride) (IIIa-g)

A chloroformic mixture of *N*-hepta-*O*-acetyl-β-D-maltosyl-*S*-chloro isothiocarbamoyl chloride (7.48g, 0.01M) and appropriate amount of 1-phenyl-3-aryl thiocarbamides **(IIa-g)** were taken in round bottom flask and refluxed over boiling water bath for 3 hours. After refluxing, the solvent was distilled off and the sticky residue obtained was triturated with petroleum ether (60-80^{0}C) to afford solid products **(IIIa-g)**. The products were purified by recrystalization from ethanol-water. The products were found non-desulphurisable when boiled with lead acetate solution. The specific rotation was measured in chloroform. The purity of products was checked by TLC and recorded the R_f values.

All the newly synthesized compounds **IIIa-g** were characterized by m.p., elemental analysis and spectroscopic data[8-10] (IR, ^{1}H NMR and Mass). On the basis of these facts, the new compounds reported in this correlate with the proposed structure.

3-hepta-*O*-acetyl-β-D-maltosylimino-4-phenyl-5-phenylimino-1,2,4-dithiazolidine (hydrochloride) (IIIa)

IR (KBr, cm^{-1}): 2961 (Ali C-H), 1752 (C=O), 1637 (C=N), 1594 (S-C=N), 1543 (Ar-C=C), 1372 (C-N), 1232 (C-O), 1038, 940 and 901 (maltose unit). ^{1}H NMR ($CDCl_3$, ppm) δ: 6.78-7.88 (m, 10H, Ar-H), δ: 3.82-5.94 (m, 14H, maltose unit), 2.00-2.22 (m, 21H, 7$COCH_3$). Mass *m/z*: 939(M^+), 903, 619, 559, 331. Anal. Calcd for $C_{40}H_{45}O_{17}N_3S_2$ .HCl: C, 51.11; H, 4.79; N, 4.47; S, 6.81%. Found: C, 51.08; H, 4.75; N, 4.42; S, 6.78%.

3-hepta-*O*-acetyl-β-D-maltosylimino-4-phenyl-5-*o*-tolylimino-1,2,4-dithiazolidine (hydrochloride) (IIIb)

IR (KBr, cm^{-1}): 2963 (Ali C-H), 1752 (C=O), 1637 (C=N), 1598 (S-C=N), 1544 (Ar-C=C), 1374 (C-N), 1232 (C-O), 1038, 942 and 900 (maltose unit). ^{1}H NMR ($CDCl_3$) δ: 6.78-7.67 (m, 9H, Ar-H), δ: 3.75-5.83 (m, 14H, maltose unit), 2.31 (s, 3H, CH_3), 2.00-2.44 (m, 21H, $7COCH_3$). Mass *m/z*: 953(M^+), 918, 619, 559, 331. Anal. Calcd for $C_{41}H_{47}O_{17}N_3S_2$ .HCl: C, 51.62; H, 4.93; N, 4.40; S, 6.71%. Found: C, 51.58; H, 4.90; N, 4.37; S, 6.68%.

3-hepta-*O*-acetyl-β-D-maltosylimino-4-phenyl-5-*p*-tolylimino-1,2,4-dithiazolidine (hydrochloride) (IIId)

IR (KBr, cm^{-1}): 2963 (Ali C-H), 1752 (C=O), 1637 (C=N), 1593 (S-C=N), 1543 (Ar-C=C), 1374 (C-N), 1232 (C-O), 1039, 940 and 900 (maltose unit). ^{1}H NMR ($CDCl_3$) δ: 6.83-7.54 (m, 9H, Ar-H), 3.75-5.82 (m, 14H, maltose unit), 2.31 (s, 3H, CH_3), 2.00-2.35 (m, 21H, $7COCH_3$). Mass *m/z*: 953(M^+), 619, 559, 331. Anal. Calcd for $C_{41}H_{47}O_{17}N_3S_2$ .HCl: C, 51.62; H, 4.93; N, 4.40; S, 6.71%. Found: C, 51.59; H, 4.89; N, 4.36; S, 6.66%.

3-hepta-*O*-acetyl-β-D-maltosylimino-4-phenyl-5-*p*-Cl-phenylimino-1,2,4-dithiazolidine (hydrochloride) (IIIg)

IR (KBr, cm^{-1}): 2961 (Ali C-H), 1750 (C=O), 1636 (C=N), 1594 (S-C=N), 1544 (Ar-C=C), 1373 (C-N), 1230 (C-O), 1038, 940 and 900 (maltose unit). ^{1}H NMR ($CDCl_3$) δ: 6.80-7.30 (m, 9H, Ar-H), 3.72-5.61 (m, 14H, maltose unit), 2.00-2.35 (m, 21H, $7COCH_3$). Mass *m/z*: 973(M^+), 619, 559, 331. Anal. Calcd for $C_{40}H_{44}O_{17}N_3S_2Cl$.HCl: C, 49.33; H, 4.52; N, 4.31; S, 6.57%. Found: C, 49.30; H, 4.48; N, 4.29; S, 6.51%.

Table-1: Physical characterization data of the newly synthesized compounds.

Compound	m.p. ^{0}C	Yield %	$[\alpha]_D^{30}$ (*c*, $CHCl_3$)	R_f (EtOAc:n-Hexane, 1:1)
IIIa	125-127	75.18	+58.71° (c,0.968)	0.62
IIIb	112-113	60.07	+49.86° (c, 1.008)	0.71
IIIc	156-158	53.00	+66.75° (c, 1.002)	0.85
IIId	110-112	67.13	+74.46° (c, 0.988)	0.71
IIIe	127-129	64.84	+85.72° (c, 1.060)	0.68
IIIf	132-133	61.43	+79.51° (c, 1.021)	0.82
IIIg	102-104	59.72	+67.27° (c, 1.000)	0.75

Table-2: Anti-microbial activities of the synthesized compounds.
(Invitro activity - zone of inhibition measured in mm[a])

Compound	Bacteria							Fungi	
	E. coli	*P. aeruginosa*	*B. subtilis*	*S. aureus*	*P. vulgaris*	*K. pnemoniae*	*S. typhi*	*A. niger*	*C. albicans*
IIIa	13	15	12	16	14	11	---	15	---
IIIb	12	19	15	18	13	12	---	16	---
IIIc	12	20	17	17	---	---	---	14	---
IIId	13	16	14	18	13	11	16	17	---
IIIe	16	21	13	17	---	---	---	18	--
IIIf	15	15	20	21	---	14	---	20	---
IIIg	15	19	25	20	---	13	14	18	16
Co-trimazine	18	20	21	20	18	19	18	---	---
Fluconazole	---	---	---	---	---	---	---	22	22

--- No activity was observed.
[a] Values are the average of three readings.

Antimicrobial activity

The antimicrobial activity of newly synthesized compounds were tested in vitro against a panel of selected Gram positive and Gram negative bacteria and also fungi are presented in Table-2 in comparison with those of the references drugs Co-trimazine and Fluconazole respectively. The antimicrobial activity was evaluated against different bacterial strains such as *E. coli*, *P. aeruginosa*, *B. subtilis*, *S. aureus, P. vulgaris*, *K. pneumoniae, S. typhi* and fungal strains such as *A. niger* and *C. albicans* by using cup plate agar diffusion method. The compounds investigated were dissolved in DMSO (1mg/mL) and filled in 6mm wells in agar media. Inhibition zones read after incubation at 30^0C for 24 hr for bacterial strains and for fungal strains inhibition zones read after incubation at 35^0C for 48 hr.

RESULTS AND DISCUSSION

Antimicrobial activity

Most of the synthesized compounds exhibited mild to moderate anti-microbial activity against the tested microorganisms. Compounds IIIe, IIIf and IIIg were found to possess significant antibacterial and antifungal activity when compared to standard drug (Co-trimazine and Fluconazol for antibacterial and antifungal respectively). The entire synthesized compounds exhibited mild to moderate activity are shown in Table -2.

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