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SYNTHESIS, CHARACTERIZATION AND MICROBIAL ASSAY OF 4-ARYL-5-PHENYLIMINO-3-*S*-HEPTA-*O*-BENZOYL MALTOSYL-1, 2, 4-THIADIAZOLINES

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ABSTRACT

*A series of some novel maltosyl-substituted thiadiazolines **3** have been synthesized by the interaction of S-hepta-O-benzoyl maltosyl-1-arylisothiocarbamides **1** with the N-phenyl-S-chloro isothiocarbamoyl chloride **2**. The identities of these new compounds have been established on the basis of chemical transformation and IR, ^{1}H NMR and Mass spectral studies. In the present investigation the In-vitro microbial assay of compounds has been evaluated by using several bacteria such as Escherichia coli, Staphylococcus aureus, Proteus vulgaris and Pseudomonas aeruginosa and fungi such as Candida albicance and Aspergillus niger. All compounds studied shows satisfactory microbial assay.*

Keywords: *1,2,4-thiadiazolines, isothiocarbamides, N-phenyl-S-chloro isothiocarbamoyl chloride, Microbial assay.*

Introduction

Thiadiazolines shows many applications such as antioxidant, radio protective, and anti-leishmanial activities[1-4]. Various substituted thiadiazolines also exhibit biological behavior[5-6]. Therefore, interest in the syntheses of thiadiazoline derivatives is significant. Thus, synthesis of maltosides with a thiadiazolinyl group substituted at a suitable position by a convenient method is an important part of developing new and potentially biological active compounds.

In view of the continued interest in the development of simpler and more convenient synthetic routes for preparing heterocyclic systems, an efficient and useful method is reported herein to synthesize some novel maltosyl-substituted thiadiazolines **3** by the interaction of *S*-hepta-*O*-benzoyl maltosyl-1-arylisothiocarbamides **1** with the *N*-phenyl-*S*-chloro isothiocarbamoyl chloride **2**.

Result and discussion

N-phenyl–*S*–chloro isothiocarbamoyl chloride **2** (0.001 M. 0.215 g) in 10 ml chloroform was added gradually to cold solution of *S*-hepta-*O*-benzoyl maltosyl-1-phenyl isothiocarbamide **1a** (0.001M, 1.2 g) in 20 ml chloroform. The reaction was quite brisk and exothermic with the evolution of hydrogen chloride. The mixture was refluxed for 3 h. The chloroform was distilled off. The resultant solution was allowed to stand for several hours but no solid was separated out. The sticky mass thus obtained was triturated several times with petroleum ether (60-80°C). It furnished a granular solid. It was purified by ethanol-water. The spectral analysis of compounds was carried out. The IR spectrum of the product indicated the presence of absorption bands due to Aromatic C-H, Aliphatic C-H, C=O, C=N, C-N, C-S and bands due to maltosyl ring deformation. The NMR spectrum of the product displayed signals due to aromatic protons and maltosyl ring protons. The mass spectrum shows peaks for molecular ion and related fragments.

Similarly, when several hepta-*O*-benzoyl maltosyl-1-aryl isothiocarbamides **1b-f** interacts with *N*-phenyl–*S*–chloro isothiocarbamoyl chloride **2** the related 4-aryl-5-phenylimino-3-*S*-hepta-*O*-benzoyl maltosyl-1, 2, 4-thiadiazolines **3b-f** were obtained. The characteristics of the synthesized compounds are mentioned Table1.

In microbial assay some of these compounds show interesting results. 3c and 3d exihibited more significant activities against *Escherichia coli,* 3d and 3e *exihibited* more significant activities against *Staphylococcus aureus,* 3b, 3e and 3f exihibited more significant activities against *Proteus vulgaris* and 3a and 3e exihibited more significant activities against

Pseudomonas aeruginosa. 3b and 3d exihibited more significant activities against *Candida albicance* and 3c and 3e exihibited more significant activities against *Aspergillus niger*. All the other compounds exihibited low to moderate activities. The results of bacterial and fungal assay are tabulated inTable2.

Experimental

Melting points of all synthesized compounds were determined using open capillary tube on Mac digital melting point apparatus and were uncorrected. The IR spectrum was recorded in KBr Disks on SHIMADZU IR affinity – 1 – FTIR spectrometer. The NMR spectrum was recorded in Brucker DRX – 300 instruments operating at 300 mHz using $CDCl_3$ solution with TMS as internal standard. The mass spectrum was recorded on a THERMO Finnigan LCO Advantage max ion trop Mass Spectrometer. Specific rotations were measured on Equip-Tronics EQ-801 Digital Polarimeter. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spot were visualized by iodine vapours.

On the basis of above facts the product was assigned a structure as 4-aryl-5-phenylimino–3-*S*–hepta–*O*–benzoyl maltosyl-1, 2, 4–thiadiazolines.

General Method

The reagents used for the synthesis were prepared as follows-

i) Synthesis of *S*-Hepta-*O*-benzoyl maltosyl-1-arylisothiocarbamides

S-Hepta-*O*-benzoyl maltosyl-1-arylisothiocarbamides **1a-f** was synthesized by the interaction of Hepta-*O*-benzoyl maltosyl bromide with arylthiocarbamides[7] in propane-2-ol.

ii) Preparation of Phenyl isothiocyanate[8]

The phenyl isothiocyanate was prepared by already known method i.e. by oxidative decomposition of ammonium phenyl dithiocarbamate with lead nitrate.

iii)Preparation of *S*-Chloro-*N*-phenyl isothiocarbamoyl chloride[9] 2

It was prepared by the extension of earlier method i.e. by passing calculated quantity of gaseous chlorine into the chloroform solution of phenyl isothiocyanate. *S*-chloro-*N*-phenyl isothicarbamoyl chloride was obtained as pale yellow oil (Chemically it is phenyl-imino chloromethane sulphanyl chloride).

iv)4-aryl-5-phenylimino-3-*S*-hepta-*O* benzoyl maltosyl-1, 2, 4-thiadiazolines

v) 3a-f

N-Phenyl-*S*-Chloro isothiocarbomoyl chloride **2** in chloroform was added gradually to cold solution of *S*-Hepta-*O*-benzoyl maltosyl-1-aryl isothiocarbamides **1a-f** in chloroform.

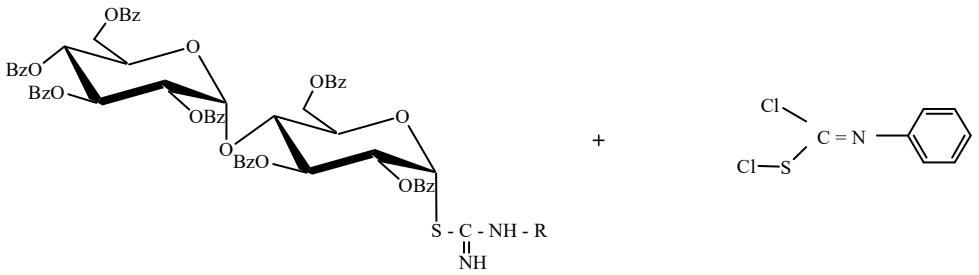
Spectral analysis[10-17]

3a: IR(KBr cm^{-1}): 3062 (Aromatic C-H), 2962 (Aliphatic C-H), 1730 (C=O), 1600 (C=N), 1452 (C-N), 1271 (C-O), 1039, 1026, 1001 and 937 (Characteristics of maltose), 709 (C-S); **^{1}H NMR ($CDCl_3$, ppm):** δ 8.097 – 7.147 (45H, m, aromatic protons), δ – 3.824 (14H, m, maltosyl protons); **Mass (m/z):** 1338 (M^+ protonated), 1234 (M^+-C_7H_5N), 1026 (HBM^+-CO), 931 (HBM^+-$C_7H_5O_2$), 579 (TBG^+).

3b: IR(KBr cm^{-1}): 3062 (Aromatic C-H), 2962 (Aliphatic C-H), 1730 (C=O), 1600 (C=N), 1450 (C-N), 1269 (C-O), 1070, 1026, 1001 and 937 (Characteristics of maltose), 709 (C-S); **NMR ($CDCl_3$, ppm):** δ 8.096 – 7.148 (44H, m, aromatic protons), δ – 3.809 (14H, m, maltosyl protons); **Mass (m/z):** 1371 (M^+ not located), 1343 (M^+-CO), 1136 (M^+-C_7H_5N), 1026 (HBM^+-CO), 931 (HBM^+-$C_7H_5O_2$), 579 (TBG^+).

3e: IR(KBr cm^{-1}): 3062 (Aromatic C-H), 2972 (Aliphatic C-H), 1730 (C=O), 1600 (C=N), 1452 (C-N), 1271 (C-O), 1070, 1039, 1026, 1001 and 937 (Characteristics of maltose), 709 (C-S); **NMR ($CDCl_3$, ppm):** δ 8.094 – 7.329 (44H, m, aromatic protons), δ – 3.085 (14H, m, maltosyl protons), 1.257 (3H, S, CH_3); **Mass (m/z):** 1352 (M^+ protonated), 1248(M^+-C_7H_5N), 1026 (HBM^+-CO), 931 (HBM^+-$C_7H_5O_2$), 579 (TBG^+).

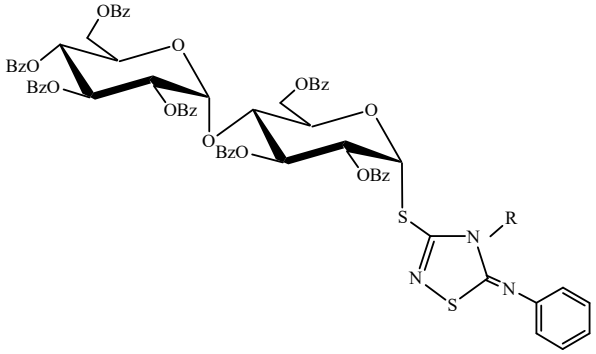
Scheme



S-hepta-*O*-benzoyl maltosyl-1-aryl Isothiocarbamides **1a-f**

N-phenyl-*S*-chloro isothiocarbamoyl chloride **2**

Chloroform,
Reflux, 3 h



4-aryl-5-phenylimino-3-*S*-hepta-*O*-benzoyl maltosyl-1, 2, 4-thiadiazolines **3a-f**

Where, R - a) Phenyl, b) *o*-Cl-phenyl, c) *m*-Cl-phenyl,
d) *p*-Cl-phenyl, e) *o*-tolyl, f) *p*-tolyl.
Bz - $-COC_6H_5$

Table1:- Characterization of 4-Aryl-5-phenylimino-3-*S*-hepta–*O*-benzoyl maltosyl-1, 2, 4-thiadiazoline 3a-f.

Compds	Mol. Formula	Yield (%)	m.p. (^oC)	R_f Value	Elemental Analysis % Found (Required)		$[\alpha]_D^{31}$ (c, in $CHCl_3$)
					N	S	
3a	$C_{75}H_{59}O_{17}N_3S_2$	72	132	0.55	2.99 (3.06)	4.42 (4.66)	+90.90° (0.055 in $CHCl_3$)
3b	$C_{75}H_{58}O_{17}N_3S_2Cl$	66	134	0.25	2.88 (2.98)	4.32 (4.54)	+188.88 (0.255 in $CHCl_3$)
3c	$C_{75}H_{58}O_{17}N_3S_2Cl$	58	125	0.45	2.90 (2.98)	4.45 (4.54)	+42.86° (0.035 in $CHCl_3$)
3d	$C_{75}H_{58}O_{17}N_3S_2Cl$	61	130	0.67	2.79 (2.98)	4.38 (4.54)	+25° (0.055 in $CHCl_3$)
3e	$C_{76}H_{61}O_{17}N_3S_2$	62	140	0.42	2.94 (3.028)	4.48 (4.614)	+109.09° (0.04 in $CHCl_3$)
3f	$C_{76}H_{61}O_{17}N_3S_2$	67	143	0.57	2.82 (3.028)	4.55 (4.614)	+227.27° (0.055 in $CHCl_3$)

Microbial Assay

The microbial assay of all the compounds have been observed using cup plate agar diffusion method[18-19] by measuring the zone of inhibition in mm. The compounds were taken at a concentration of 1 mg/ml using dimethyl sulphoxide (DMSO) as solvent. The results are presented in Table2.

Bacterial assay

The bacterial assay of compounds was observed against *Escherichia coli, Staphylococcus aureus, Proteus vulgaris and Pseudomonas aeruginosa* in nutrient agar medium. Amikacin (100 µg/ml) was used as standard for bacterial aassay.

Fungal assay

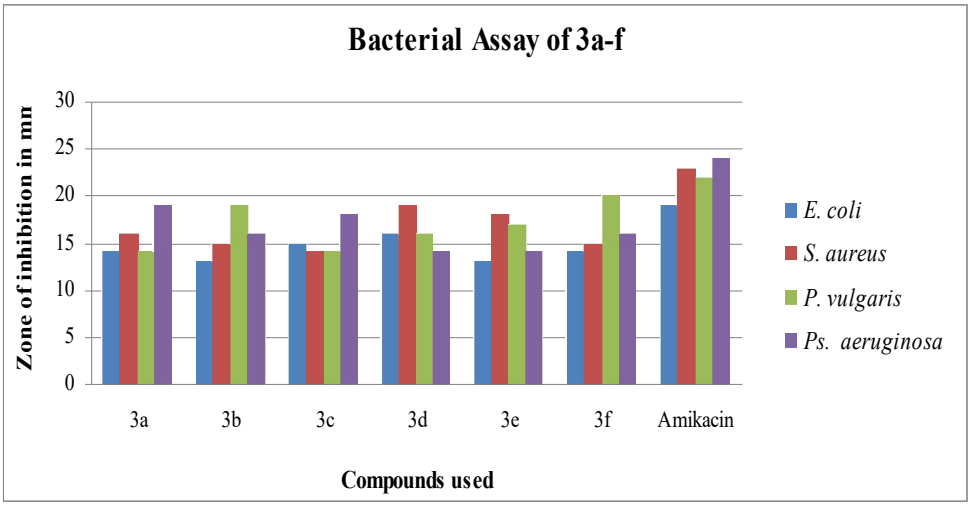
The Fungal assay of compounds was observed against *Aspergillus niger* and *Candida albicance* in potato dextrose agar medium. Fluconazole (100 µg/ml) was used as standard for antifungal activity.

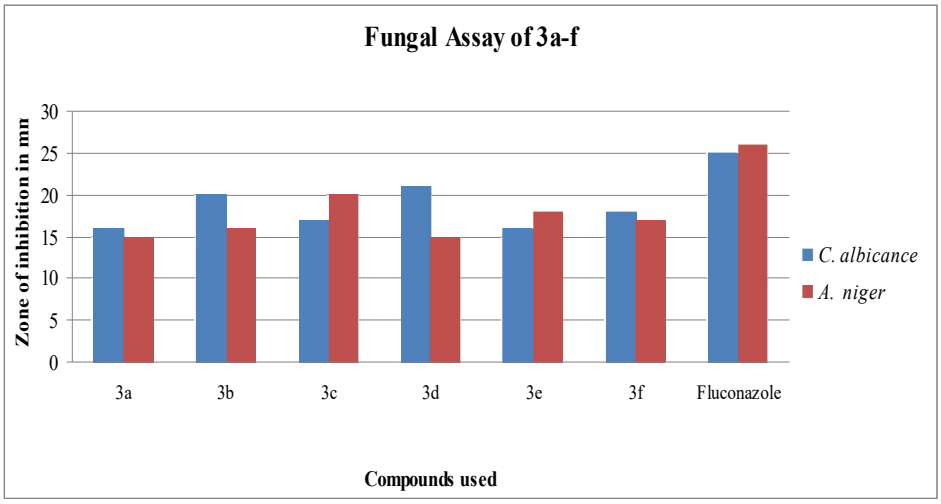
Table2: Microbial assay of 4-aryl-5-phenylimino-3-*S*-hepta-*O*-benzoyl maltosyl-1, 2, 4-thiadiazolines 3b-f.

Compounds	Antibacterial**				Antifungal**	
	E. coli	*S. aureus*	*P. vulgaris*	*Ps. Aeruginosa*	*C. albicance*	*A. niger*
3a	14	16	14	19	16	15
3b	13	15	19	16	20	16
3c	15	14	14	18	17	20
3d	16	19	16	14	21	15
3e	13	18	17	14	16	18
3f	14	15	20	16	18	17
Amikacin	19	23	22	24	-	-
Fluconazole	-	-	-	-	25	26

**zone of inhibition in mm (15 or less) resistance, (16-20mm) moderate and (more than 20mm) sensitive. *Escherichia coli* (*E.* coli), *Staphalococcus aureus* (*S.* aureus), *Proteus vulgaris* (*P.* vulgaris), *Psudomonas auriginosa* (*Ps. auriginosa*), *Candida albicancs* (*C. albicancs*) and *Aspergillus niger* (*A. niger*).

Graphical representation of Microbial Assay of 3a-f





Conclusion

All the chemical transformation and spectral data supports the structure of the synthesized compounds. Thus, the newly synthesized thiomaltosides, exihibits comparable Microbial assay against the organisms tested. The method adopted in this investigation is simple, efficient, inexpensive and is useful in synthesizing pharmacologically important molecules.

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