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Synthesis of some nucleoside compounds based on saccharinyl hydrazide of expected biological activity

M.M.H. Arief[1], W.I.A. EI-Dougdoug[2] A.Y. Elgazzar[3], Manar.H.Mabrouk[4]

Chemistry department, faculty of science, Benha University

1-mmharief@gmail.com 2-Wagdy.ali@sstbu.adu.eg 3-amaal_elgazzar@yahoo.com

Abstract

3-Hydrazinylidene-2,3-dihydro1H,2-benzothiazole **1** was synthesized as reported before. Compound 1 was allowed to react with different electrophilic reagents (aldehyde-sugars, aldehydes, and anhydride).

Structures of all synthesized compounds were elucidated from (IR, Mass spectrum) and elemental analysis. Some of the resulting compounds were screened against selected microbes to test their antimicrobial activities.

Keywords: Saccharinely hydrazine, aldehyde sugar, urea.

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1. Introduction

Saccharin is commonly used as sugar substitute because it doesn't contain calories or carbohydrates also, the reported pharmaceutical properties [1-6] (anxiolytic agent, enzyme inhibitors and analgesic agent) of saccharin and some of its derivatives promoted our interest for construction of systems involving saccharin and aldehyde – sugar and/or carbonyl compounds searching for potent leads as antimicrobial agents also, in connection [7-13] with our ongoing interest to synthesize new systems involving saccharin or its derivative due to its significant biological and pharmacological activities Schiff bases also, were reported to exhibit abroad range of biological and pharmacological properties.[12].

2. Experimental

All reactions were carried out with the exclusion of moisture. All solvents were dried. The melting points are uncorrected. The IR spectra were recorded as potassium bromide pellets on Aldrich FT-IR spectrometer (central lab at faculty of science, Benha, Ain Shams and Cairo University). Mass spectra were recorded on GCMS (Gas chromatography-Mass Spectrometer) (micro analytical center, Ain shams university).

Elemental analysis was determined on elementary analysis system Ain shams University. TLC were carried out on silica gel plates (Fluka, 706. 43-50EA) using U.V light.

Synthesis of:(3*Z*) - 3- hydrazinylidene- 2,3- dihydro-1*H*-1λ^6,2-benzothiazole- 1,1- dione 1

Saccharin 1.5 was dissolved in 30ml ethanol and few drops glacial acetic acid, then 3 ml hydrazine hydrate added drop wisely, the reaction mixture was heated under refluxed for 12 hr. the solid formed was filtered off, dried recrystallized from methanol.

M.p: (187-190) °C in yield %: 76% and solvent of crystallization: methanol, Color: white and molecular formula: C_7 H_7 N_3 SO_2 (197), analysis (cal): c: 42.63, H: 3.55, N:21.31, found C: 42.60, H: 3,52, N:21.27

General procedure for the preparation of sugar hydrazine:

Hydrazide derivative **1** (2.19 g, 10 m mole) in ethanol (10 ml) was added to a well stirred solution of the respective mono- saccharides (10 mmol) in water (2ml) and drops of glacial acetic acid. the mixture was heated under reflux for 3h and left to cool. The formed precipitated washed with water and cold ethanol, dried and recrystallized from ethanol to afford the corresponding sugar hydrazine in yield (85-88%).

Reaction of hydrazide derivative 1 with glucose:

Synthesis of :(3Z)-3-[(2Z) -(2,2,3,4,5-penta hydroxyl heptylidene)hydrazinylidene]-2,3-dihydro-1H-1λ^6,2-benzothiazole-1,1-dione 2a.

Yellow, m.p: > 300°C, molecular formula: C_{13} H_{17} N_3 O_7 S (359), analysis (cal): C: 43.45, H: 4.73, N:11.70, found C:43. 40, H: 4.68, N: 11.64.

Mass-spectra: mass spectrum showed molecular ion peak at m/z= 359 (1%)

Reaction of hydrazide derivative 1 with mannose:

Synthesis of: (3Z)-3- [(2Z)-(2,3,4,5,6-pentahydroxyhexylidene) hydrazinylidene] -2, 3- dihydro- 1H- 1λ^6,2- benzothiazole-1,1-dione 2b.

Deep yellow and m.p: 280-282°C and molecular formula: C_{13} H_{17} N_3 O_7 S (359), analysis (Cal): C:43.45, H:4.73, N:11.70, found C:43.40, H:4.68, N:11.64

Reaction of hydrazide derivative 1 with galactose

Synthesis of: (3*Z*)-3-[(2*E*)- (2,3,4,5,6-penta hydroxyl hexylidene)hydrazinylidene]-2,3-dihydro-1*H*-1λ^6,2-benzothiazole-1,1dione 2c.

Brown, m.p :(300-302) °C and molecular formula: C_{13} H_{15} N_3 O_7 S (359), analysis (Cal): C: 43:45 H:4.73, N:11.70, found C:43.50, H:4.68, N:11.74.

Reaction of hydrazide derivative 1 with xylose: Synthesis of: (3*Z*)- 3- [(2*Z*)- (2,3,4,5- tetrahydroxy

pentylidene) hydrazinylidene] -2,3-dihydro-1*H*-1□^{6},2-benzothiazole-1,1-dione 2d.

Deep Yellow, m.P: >300°C and molecular formula: C_{12} H_{15} N_3 O_6 S (329), analysis (Cal): C:43.76, H:4.55, N:12.76, found C:43.70, H:4.50, N:12.72.

Reaction of hydrazide derivative 1 with aldehydes and or anhydrides.

General Procedure:

A mixture of hydrazide derivative **1** (2.19 g, 10 mmole) and appropriate of aldehyde namely glutaric aldehyde, Salicaldehyde or anhydride namely phthalic anhydride, tetra-bromo phthalic anhydride (10 mmole) in (2ml) glacial acetic acid in(15) ml absolute ethanol was left under reflux for (6hr). The solid product was filtered off cooling, dried and crystallized from ethanol to give compounds (3a, 3b and 4a,4b) respectively in 85-92% yield.

Reaction of hydrazide 1 with glutter di aldehyde:

Synthesis of: (5*Z*)-5-[(2*Z*) -(1,1-dioxo-1,2-dihydro-3*H*-1□^{6},2-benzothiazol- 3ylidene)hydrazinylidene]pentanal 3a.

M.p: 240-245 °C, deep brown and molecular formula: C_{12} H_{12} N_3 O_3 S (278), analysis (Cal): C:51.80, H: 4.31, N:15.11, found C:51. 78, H:4.29, N:15.7.

Reaction of hydrazide 1 with salicylaldehyde: Synthesis of:(3*Z*)-3-{(2*Z*)- [(2-hydroxy phenyl) methylidene] hydrazinylidene} -2,3-dihydro-1*H*-1□^{6},2-benzothiazole-1,1-dione 3b.

M.P: 300-302°C, Brown and molecular formula: C_{14} H_{11} N_3 O_3 S (301), analysis (Cal): C:55.81, H:3.65, N:13.95, found C:55.78, H:3.61, N:13.91.

Reaction of hydrazide 1 with phthalic anhydride: Synthesis of: (3*Z*)-3-[(1,3-dioxo-1,3- dihydro-2*H*-isoindol-2-yl)imino]-2,3-dihydro-1*H*- □^{6},2benzothiazole -1,1-dione 4a.

White, m.p: 170-172 °C and molecular formula: c_{15} H_g N_3 O_4 (327) analysis (Cal): C:55.04 H: 2.75, N: 12.80, found C:55.03, H:2.71, N:12. 20.

Reaction of hydrazide with tetra bromo phthalic anhydride

Synthesis of: (3*Z*)-3-[(4,5,6,7-tetrabromo-1,3-dioxo-1,3,4,5,6,7-hexahydro-2*H*-isoindol-2-yl)imino]-2,3-dihydro-1*H*-1□^{6},2-benzothiazole-1,1-dione 4b.

Yellow, m.p: 195-198 °C and mass - spectra: mass spectrum showed molecular ion peak at m/z = 643 (1%), base peak at m/z= 183 (100%).

Molecular formula: C15 H_5 N_3 O_4S Br_4 (643), analysis (Cal): C: 27. 99. H: 0.78, N: 6.53, found C: 27.96, H: 0.74, N: 6.50.

Synthesis of: *N*-(1,1-dioxo-1,2-dihydro-3*H*-1λ^6,2-phenyl -benzothiazol-3-ylidene) urea 5.

Saccharin 1.5 was dissolved in 30ml ethanol and few drops glacial acetic acid, then 0.49 gm. from urea added, the reaction mixture was heated under refluxed for 20 hr. the solid formed was filtered off, dried recrystallized from methanol. , melting point: 160-162 °C, white and molecular formula: C_8 H_7 N_3 O_3 (328), analysis (Cal): C: 51..22, H: 3, 35 N: 12.8, found C: 51.20., H: 3.33, N: 12.5.

Reaction of Urea derivatives with aldehydosugar.

General procedure:

Urea derivative **5** (2.25g, 10mmole) in absolute ethanol was added to a well stirred solution of the respective mono saccharide (glucose and or galactose) (10mmole) in water (2ml) and few drops of glacial acetic acid. The mixture was heated under reflux (5-6hr) and the resulting solution was concentrated under reduced pressure (water pumps) and left to cool. The formed precipitated was filtered off washed with water and cold ethanol, then dried and recrystallized from ethanol.

Reaction of urea derivative 5 with glucose.

M.p**:** (160-162) °C, White powder, Molecular formula**:** C_{20} H_{21} N_3 O_8 (463) Analysis (cal): C: 51.83, H: 4.53, N :9.07, found C:51.53,
H: 4.23, N :8.77.

Reaction of urea derivative 5 with galcactose.

Synthesis of: N-(1,1-dioxo-1,2-dihydro-3H-1λ^6, 2 pheny benzothiazol- 3-ylidene) N- [(e)- 2,3,4,5,6-pentahydroxyhexli dene] urea 6b.

M.p: 218-220°C, white and molecular formula: C_{20} H_{21} N_3 O_8S (463), analysis (cal): C:51.83, H:4.53, N:9.07 found C: 51.43,H:4.03, N:8.67.

Reaction of urea derivative 5 with aromatic aldehydes.

General procedure:

A mixture of urea derivative **5** (5 mmol) and aromatic aldehyde namely salysaldehyde (2 hydroxyl benzaldehyde) and/or anisalysaldehyde (4. melhoxy benzaldehyde) (2 mmol) and few drops of glacial acetic acid in 15 ml ethanol was left under reflux for 4 hr. the solid product was filtered after cooling, dried and crystallized from ethanol to afford compounds (7a, 7b) respectively.

Reaction of urea derivative 5 with salisaldehyde:

Synthesis of: *N*-(1,1-dioxo-2-phenyl-1,2-dihydro-3*H*-1λ^6,2-benzothiazol-3-ylidene)-*N*'-[(*Z*)-(2-hydroxy phenyl) methylidene] urea7a.

M.p: 248-250°C, white (powder), yield %: 78%

IR (KBr cm^{-1}): displayed bands at 3427 cm^{-1} (broad) for OH, NH, aromatic CH, 1717 cm^{-1} for CO, 1636 cm^{-1}, 1606 cm^{-1} for C=N and 1398 cm^{-1}, 1115 cm^{-1} for SO_2 groups.

Molecular formula: C21 H_{15} N_3 O_4 S (405), mass spectrum: m/z= 329 [m+].

Analysis: (cal) C:62.22 , H:3.703 , N:10.37 , found C:62.12 , H:3.6 , N:10.27.

Reaction of urea derivative 5 with anisalicaldehyde:

Synthesis of: N-(1,1- dioxo- 2 –phenyl -1,2- dihydro-3*H*-1λ ^{6},2- benzothiazol-3-ylidene)-*N*'- [(*E*)-(4-methoxy phenyl) methylidene] urea 7b.

M.p: > 300°C , white and IR (KBr cm^{-1}): displayed bands at 3165 cm^{-1} for NH, 30/6 cm^{-1} for aromatic CH, 2891 cm^{-1}, for aliphatic CH, 1662 cm^{-1} for (CO), 1601 cm^{-1}, 1594 cm^{-1} for (CN), and 1330 cm^{-1}, 1262 cm^{-1} for SO_2 groups, molecular formula**:** C_{17} $H1_5$ N_3 O_4 S (357).

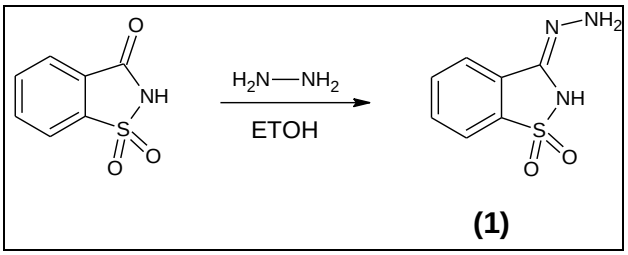
C: 57.14, H:4.20, N:11.76 found C:56.94, H:4.01, N:11.46.

3. Result and discussion

3.1- Synthesis of (3Z) -3 Hydrazinylidene-2,3- dihydro-1H λ^6, 2-benzothiazole-1,1-dione 1

The Hydrazide **(1)** was synthesis as reported before [17]. The structure of compound **(l)** was confirmed from: Correct elemental analysis.

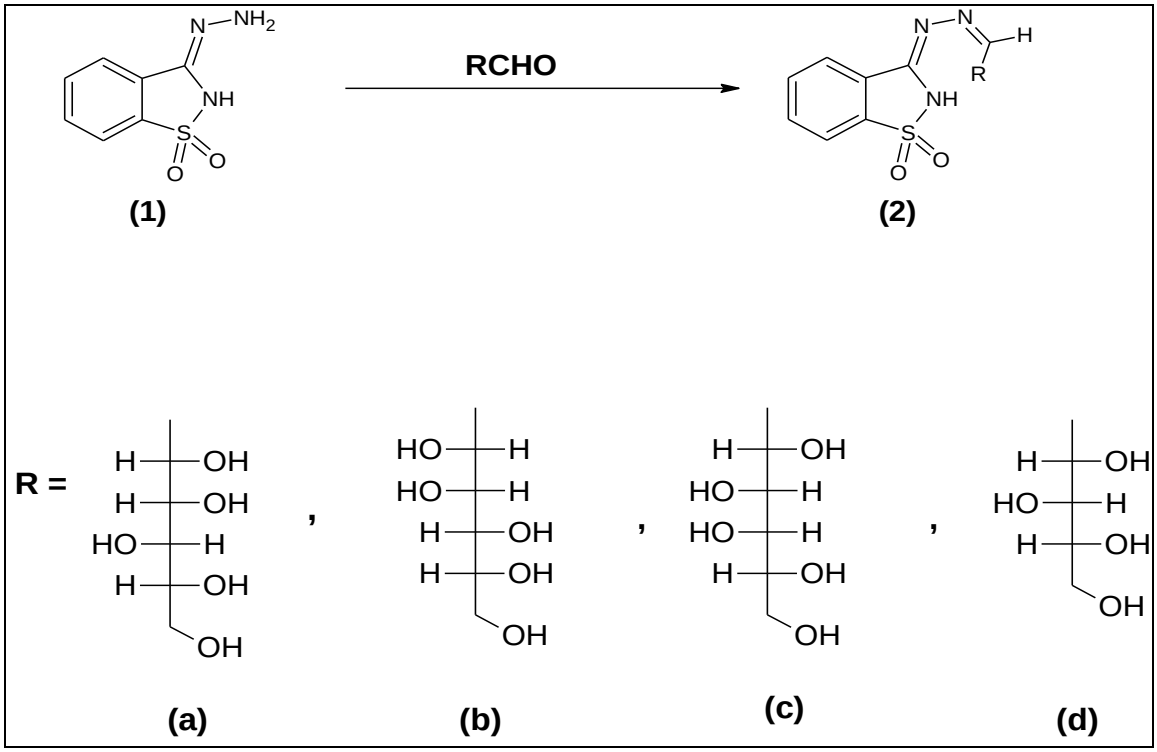
IR-spectrum displayed absorption broad band at 3341 cm^{-1} 3068 cm^{-1} for NH, NH_2, aromatic CH, 1662 cm^{-1} for C=N and 1335 cm^{-1}; 1168 cm^{-1} for SO_2. groups.



In the present investigation saccharinyl hydrazine **1** was used as a building block to study its reaction with aldehydosugar and or certain carbonyl compound to furnish Schiff Bases with the aim of synthesizing compounds of expected biological activities.

3.2- Reaction of Hydrazide derivative 1 with aldehydosugar.

Treatment of hydrazide derivative **1** with mono-Saccharide named glucose, mannose, galactose and xylose in aqueous ethanolic solution and catalytic amount of glacial acetic acid to give the corresponding hydrazinosugar derivatives **2a-d** in good yield .



The structure of compounds 2a was confirmed from: Correct elemental analysis., IR spectrum showed bands at 3419 cm^{-1} (broad) for (OH groups, NH, aromatic CH), 2937 cm^{-1} for aliphatic CH, 1634 cm^{-1}, 1583 cm^{-1} for (C=N) groups and 1338 cm^{-1}, 1151 $cm^{-1}$for SO_2,mass spectrum of compounds **2a** showed molecular ion peak at m/z = 359 (1%). While the structure of compounds **2b** was elucidated from: Correct elemental analysis, IR spectrum displayed bands at 3442 cm^{-1} (broad) for (OH groups, NH, aromatic CH), 2982 $cm^{-1}$for CH. aliphatic, 1632 cm^{-1}, 1582 cm^{-1} for (C=N) groups and 1336 cm^{-1}, 1119 cm^{-1} for SO_2.

Mass spectrum of compounds **2b** showed molecular ion peak at M/Z= 359 (1%)

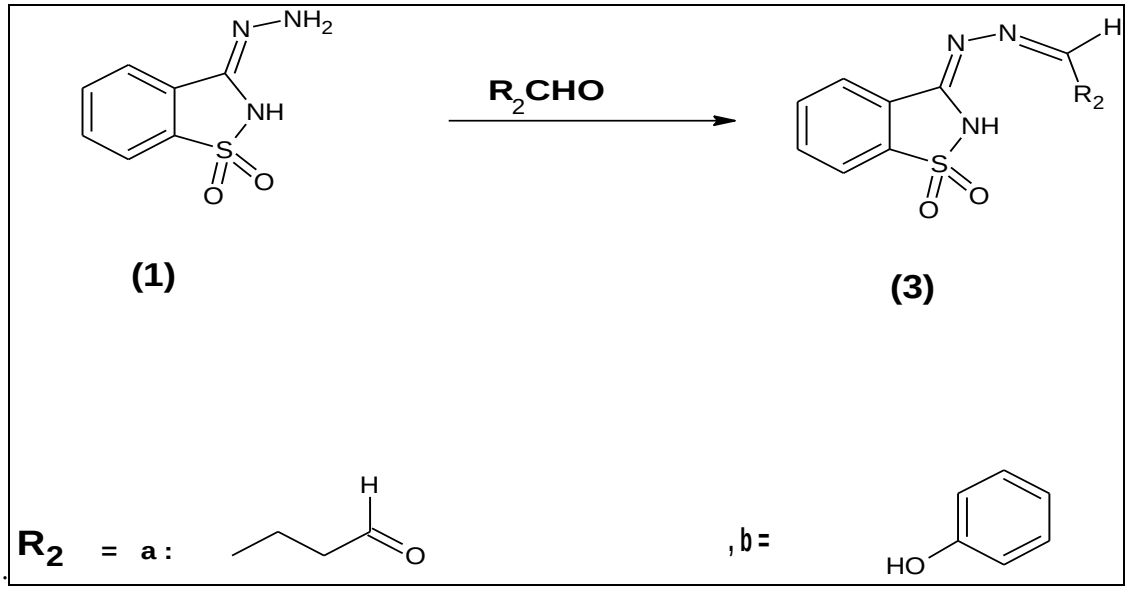
Also the structure of compounds **2c** was confirmed from: correct elemental analysis., IR spectrum which showed bands at 3406 m^{-1} (broad) for (OH, NH) aromatic CH. groups, 2937 cm^{-1} for aliphatic CH, 1632 cm^{-1}, 1581 cm^{-1} for (C=N) groups and 1335 cm^{-1}, 1120 cm^{-1} for SO_2 .

The structure of compounds **2d** was also confirmed from: Correct elemental analysis, IR spectrum which showed bands at 3443 cm^{-1}(broad) for (OH, NH, aromatic CH groups), 2927 cm^{-1} for aliphatic CH, 1634 cm^{-1}, 1583 cm^{-1} for (C=N) groups and 1335 cm^{-1} 1165 cm^{-1} for SO_2 .

3.3- Reaction of hydrazide derivative 1 with aldehydes.

Refluxing a mixture of aldehydes namely: Glutaric-dialdehyde and /or salicylaldehyde in absolute ethanol and few drops of glacial acetic acid furnished the corresponding Schiff base **3a** and **3b**.

Mass spectrum of compounds 3a showed molecular ion peak at m/z= 278 (8%).



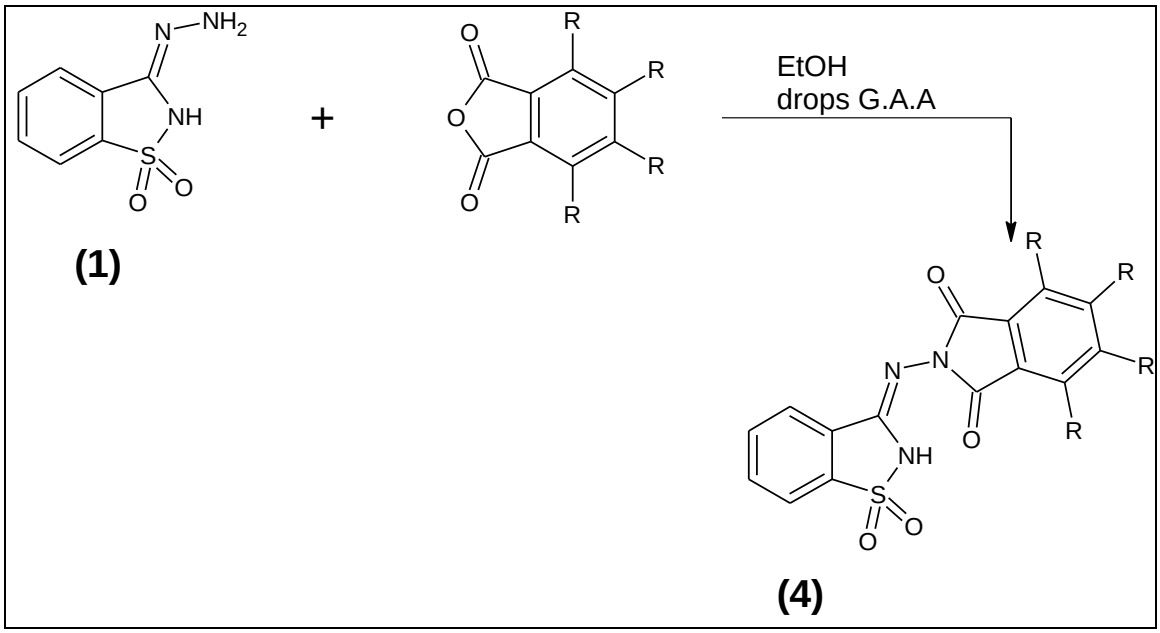
The **structure of compounds 3a was confirmed from:** Correct elemental analysis, IR- spectrum showed bands at 3431 cm^{-1} (broad) for (OH, NH, aromatic CH groups), 2928 cm^{-1}, 2961 cm^{-1} for aliphatic CH, 1717 cm^{-1} for CO (aldehyde), 1630 cm^{-1}, 1579 cm^{-1} for (C=N) groups and 1335 cm^{-1}, 1118 cm^{-1} for SO_2 .Mass spectrum of compound **3a** showed molecular ion peak at m/z= 278 (8%)

While the structure of compounds **3b** was confirmed from: Correct elemental analysis. IR- spectrum showed bands at 3384 cm^{-1} – 3253 cm^{-1} (broad) for (OH, NH, aromatic CH groups) 2933 cm^{-1} for aliphatic CH, 1630 cm^{-1} 11581 cm^{-1} for (C=N groups), and 1335 cm^{-1}, 1119 cm^{-1} for SO_2 .

Mass spectrum showed molecular ion peak at m/z 301 (1%) base peaks at m/z 240

3.4- Reaction of hydrazide derivative 1 with anhydrides.

Also, the reaction of hydrazide derivative **1** with anhydride namely phthalic anhydride and/or tetra Bromo-phthalic anhydride was investigated, Thus refluxing a mixture of phthalic anhydride and or/tetrabromophthalic anhydride in absolute ethanol and few drops of glacial acetic acid furnished (32)-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl) imino]-2,3-dihydro-1H-1λ^6,2- benzothiazole - 1,1- dione **4a** and its tetrabromo-derivative **4b** respectively.



R, a = H, b = Br

The structure of compound 4a was confirmed from: Correct elemental analysis.IR. Spectrum showed bands at 3218 cm^{-1} for NH, 3092 cm^{-1} from aromatic CH, 2971 cm^{-1} for aliphatic CH, 1796 cm^{-1}, 1780 cm^{-1} for coupling carbonyl anhydride. 1680 cm^{-1}, 1663 cm^{-1} for (CN) groups, and 1337 cm^{-1}, 1138 cm^{-1} for SO_2 .

Also, the structure of **4b** was confirmed from: Correct elemental analysis. IR spectrum which showed bands at 3291 cm^{-1} for NH, 3093 cm^{-1} for aromatic CH, 2979 cm^{-1}

for aliphatic CH, 1786 cm^{-1}, 1741 cm^{-1} for (coupling carbonyl anhydride), 1638 cm^{-1}, 1592 cm^{-1} for (CN) groups and 1339 cm^{-1}, 1136 cm^{-1} for SO_2 .

Mass spectrum of compounds **4b** showed molecular ion peak at m/z= and base peak at m/z= 183 (100%)

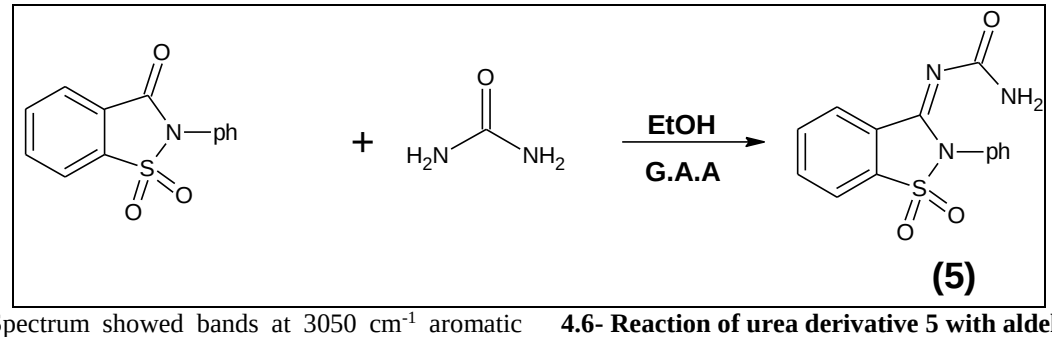
Synthesis of N-phenyl saccharin were synthesized as reported before [18].

3.5-Reaction of saccharin derivative with urea formation of N-(1,1-dioxo-1,2-dihydro-3H-1λ^6 2-phenyl benzothiazol-3-ylidene) urea 5.

Urea derivatives are an important class of carbonyl compound.

They found to have a significant biological importance and wide spread applications as plant protecting agents, also as stabilizers in dye chemistry [16,17].

Thus, when saccharin derivative was subjected to react with urea in boiling ethanol containing few drops of glacial acetic acid; it afforded the desire compound **5.**



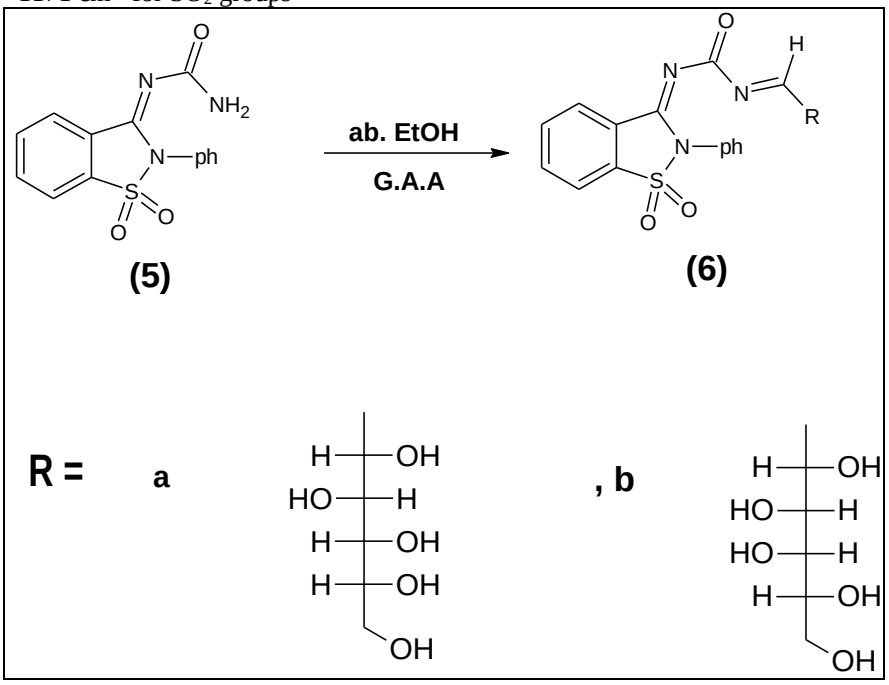
* IR. Spectrum showed bands at 3050 cm^{-1} aromatic CH; 1650 cm^{-1} of co, 1330 cm^{-1}, 1150 cm^{-1} of SO_2.

The structure of urea derivative **5** was confirmed from: Correct elemental analysis.

IR. Spectrum showed bands at 3317 cm^{-1} for NH, 3057 cm^{-1} for aromatic CH, 1666 cm^{-1} for **(1),** 1622 cm^{-1} for C=N, and 1351 cm^{-1} 1171 cm^{-1} for SO_2 groups

4.6- Reaction of urea derivative 5 with aldehydo-sugar.

When urea derivative **5** was subjected to react with different mono-saccharide namely: glucose and/or galactose in absolute ethanol containing catalytic amount of glacial acetic acid, it furnished the corresponding also, Glycoside derivative **6a, 6b.**



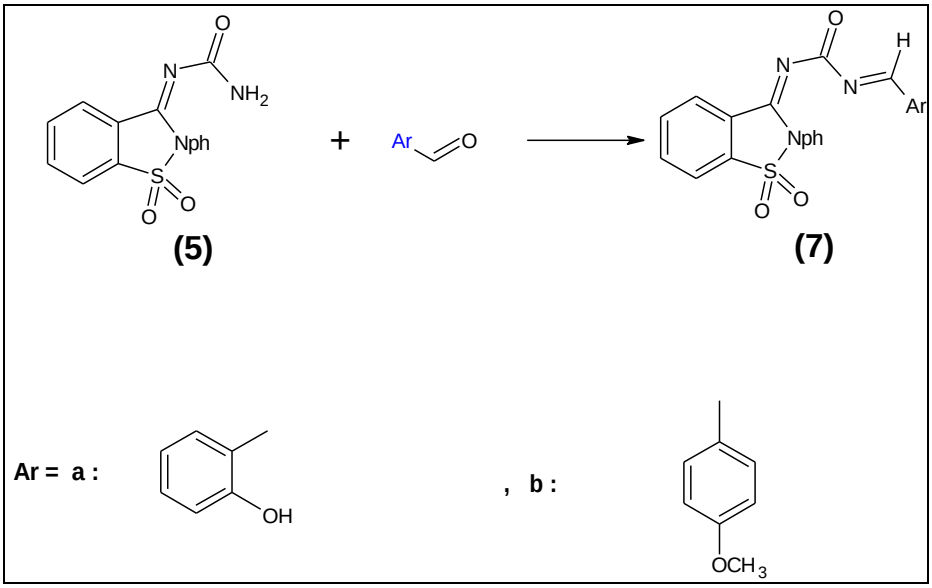
The structure of 6a was confirmed from: Correct e elemental analysis, IR. Spectrum showed bands at 3473 cm^{-1} and 3428 cm-1 broad for OH, aromatic CH, 2952 cm^{-1}, 2992 cm^{-1} for aliphatic CH, 1714 cm^{-1}, 1613 cm^{-1}, 1560 $cm^{-1}$for (C=N), and 1337 cm^{-1}, 1151 cm^{-1} for SO_2 groups.

Also, the structure of **6b** was confirmed from**:** Correct elemental analysis, IR. Spectrum showed bands at 3420 cm^{-1} (broad) for OH, aromatic CH, aliphatic CH, 1717 cm^{-1} for (CO), 1636 cm^{-1} , 1605 cm^{-1} for (C=N) and 1384 cm^{-1}, 1126 cm^{-1} for (SO_2) groups.

3.7- Reaction of urea derivative 5 with aromatic aldehydes.

In this investigation, urea derivative **5** was allowed to react with aromatic aldehydes namely salisaldehyde and/or anisalisaldehyde in refluxing ethanol and few drops of

glacial acetic acid; it gave the corresponding Schiff base **7a, 7b.**



The structure of compound 7a was confirmed from: Correct elemental analysis.IR. Spectrum showed bands at 3427 cm^{-1} (broad) for OH, aromatic CH, 1717 cm^{-1} for CO, 1636 cm^{-1}, 1606 cm^{-1} for (C=N) and 1398 cm^{-1}, 1115 cm-1 for SO_2 groups ,Mass spectrum: showed molecular ion peak at m/z=329 (0.8%)

Also, the structure of compound **7b** was confirmed from**:** Correct elemental analysis, IR-spectrum showed bands at 3016 cm^{-1} for aromatic CH, 2891 cm^{-1} for aliphatic CH, 1662 cm^{-1} for CO, 1601 cm^{-1}, 1594cm^{-1} for (C=N), and 1330cm^{-1} , 1262cm^{-1} for SO_2 groups

Biological study

Antimicrobial activity

The agar diffusion method reported by Cruickshank [19] at al was used for the screening process. The bacteria and fungi were maintained on nutrient agar and (zapek's dox agar media respectively. The assay medium flask containing 50 ml of nutrient agar for bacteria were allowed to reach 40-50 °c to be incubated with 0.5 ml of the tested organism cell suspension. The flasks were mixed well and poured each into a petri dish (15x2 cm) and allowed to solidify.

The synthesized compounds were dissolved each in 2ml/DMSO. In these holes, 100 MI of each compound was placed using an automatic micropipette. The petri dishes were left at 5 °c for 1h to allow diffusion of the samples through the agar medium and retard the growth of the teat organism. The plates were incubated at 30 °c for 24h for bacteria. The diameters of zone of inhibition were measured and compared with that of the standard, the values were tabulated.

Sample ID	Inhibition zone diameter (cm)	
	Gm. (+ve) bacteria staphylococcus	Gm. (-ve) bacteria Escherichia coli
(2a)	0.7	1
(2c)	1.5	0.5
(2b)	1.5	0.8
(2d)	2.5	1.7
(4b)	1.7	1.5
(6a)	2.5	2.7
(3a)	2	1.8
control	1.5	4

+ve control: Cefoxitin for Gram (+ve) bacteria chloramphenicol for G ram (-ve) bacteria.

4. **Conclusion**

Compounds 6a, 2d showed interesting values of biological activities.

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