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Synthesis, Characterization and Antibacterial Activity of Some New 1, 2, 3-Selenadiazole derived from 4-amino acetophenone

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Abstract. Several derivatives of azo compounds have been synthesized by a reaction of 4-amino acetophenon with several phenols derivatives that react with simicarbazide to give semicarbazone derivatives. Then these have been converted into the corresponding1,2,3 derivative selenadiazoles in cold glacial acetic acid reaction with selenium dioxide. The synthesized compounds were assays against two gram-positive and two gram-negative bacteria for antibacterial activity at different concentrations that showed remarkable biological activity. Elemental analysis, IR, 1H-NMR,13C NMR and mass spectral data confirmed the structures of the new compounds.

1 Introduction

Berzelius discovered the Selenium element in 1817. The new element was named in relation to Selene, the Greek goddess of the moon, by the world Berzelius (selenium).[1]. Detailed study of the properties of this element and its inorganic compounds. The first compound of organoselenium was prepared by Wöhler and Siemens in 1847 called ethyl selenol[2]. . Selenium was first used in organic chemistry in 1929 for the use of selenium dioxide as an oxidant in synthetic organic chemistry [3]. Selenium, an essential trace element, is a key component of several major human metabolic pathways, including the metabolism of thyroid hormones, the antioxidant protection system [4]. Because of their potential pharmaceutical properties, selenium containing heterocyclic systems is of interest [5]. first general synthesis route was introduced in 1970 for the heterocyclic system containing the selenium atom (1,2,3-selenadiazoles) [6]. To yield high antibacterial activity, 1,2,3-selenadiazole derivatives were evaluated [7]. Some of them have also been identified as antifungal activities [8], but a number of Selenadiazol derivatives such as4-Methyl-1,2,3-selenadia-zole-5-carboxylic acid amides have also been synthesized and found to be more important in pharmaceutical chemistry for antitumor agents [9]. In this study some of new 1,2,3-selenadiazole derivatives for azo compounds were synthesized and their biological activities were investigated.

2 Experimental

2.1. Solvent materials and methods were purified in accordance with standard procedures. A Shimadzu 8400S – Japan, FT-IR spectrophotometer recorded IR spectra. 1H-NMR spectra were obtained from inova DMSO-d6 FT-NMR (500 MHz) devices using TMS as internal standard. The spectrum of mass (electron impact, 70 eV). The elemental analysis for the EA1112 analyzer was determined on Eager 300. With an electro-thermal device, melting points were recorded

2.2. Synthesis compounds

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2.2.1. Synthesis of the azo dyes

2.2.1.1 synthesis (E)-1-(4-((4-hydroxyphenyl) diazenyl) phenyl) ethanone (A1)

Solution A was prepared by mixing pure 4-amino acetophenone (A, 0,670 g, 0,005 mol) with concentrated HCl (3 mL) and water (3 mL) and ice bath cooling at 5 ° C. In order to obtain solution B, $NaNO_2$(0.35 g, 0.005 mol) was dissolved in water (10 mL) at 5 ° C. Solution A was then added dropwise with stirring to solution B at 5 ° C. The mixture was then slowly added to the phenol solution (0.470 g, 0.005 mol) dissolved at 5 ° C in ethanol. The mixture in the ice bath was kept chilled and continuously stirred for 30 minutes. TLC monitored the reaction using eluent (n-hexan4: 6ethanol) filtering and recrystallizing the precipitate formed from ethanol gave yellow solid (0.86g, yield=72%) R_f =0.59, m.p 188- 190 ^{0}C[10]

2.2.1.2 synthesis (E)-1-(4-((4-hydroxy-3-methylphenyl) diazenyl) phenyl) ethanone (A2)

Solution A has been prepared by mixing pure 4-amino acetophenone (A, 0,670 g, 0,005 mol) with concentrated HCl (3 mL) and water (3 mL) and ice bath cooling at 5 ° C. In order to obtain solution B, $NaNO_2$(0.35 g, 0.005 mol) was dissolved in water (10 mL) at 5 ° C. Solution A was then added dropwise with stirring to solution B at 5 ° C. The mixture was then slowly added to the 4-hydroxy-3-methylphenyl solution (0.540 g, 0.005 mol) dissolved at 5 ° C in ethanol. The mixture was kept chilled in the ice bath and continuously stirred for 30 min. TLC monitored the reaction using eluent (n-hexan4: 6ethanol) filtering and recrystallizing the precipitate formed from ethanol gave red solid. (0.88g, yield=69%) R_f =0.69, m.p 162- 164 ^{0}C[10]

2.2.1.3 synthesis (E)-1-(4-((4-hydroxy-2-methylphenyl) diazenyl) phenyl) ethanone (A3)

Solution A was prepared by mixing pure 4-amino acetophenone (A,0,670 g, 0,005 mol) with concentrated HCl (3 mL) and water (3 mL) and ice bath cooling at 5 ° C. In order to obtain solution B, $NaNO_2$(0.35 g, 0.005 mol) was dissolved in water (10 mL) at 5 ° C. Solution A was then added dropwise with stirring to solution B at 5 ° C. The mixture was then slowly added to the 4-hydroxy-2-methylphenyl solution (0.540 g, 0.005 mol) dissolved at 5 ° C in ethanol. The mixture in the ice bath was kept chilled and continuously stirred for 30 minutes. TLC monitored the reaction using eluent (n-hexan4: 6ethanol) filtering and recrystallizing the precipitate formed from ethanol gave red solid (0.52g, yield=50%) R_f =0.64, m.p 152- 153^{0}C[10]

2.2.1.4 synthesis (E)-2-(1-(4-((E)-(4-hydroxyphenyl) diazenyl) phenyl) ethylidene) hydrazinecarboxamide (CZ1)

Dissolved in absolute ethanol (30 mL) a mixture of simicarbazide hydrochloride (0.356 g, 0.0015mol) and sodium acetate (0.26g,0.003mol). The mixture was heated under reflux for 15 min, then filtered to remove precipitated sodium chloride while it was hot. The filtrate was then mixed with (E)1-(4-(4-hydroxy-phenyl) phenyl) ethanon (0.77g,0.003mole) and the resulting mixtures heated to reflux, added a few drops of concentrated hydrochloric acid and continued overnight heating under reflux with continuous removal of the produced water. TLC monitored the reaction. Using eluent (n - hexan6:4ethyl acetate). The solvent was removed under vacuum precipitate formed and recrystallized from chloroform gave orange solid (0.38g, yield=40%) R_f =0.73, m.p 204-206^{0}C[11]

2.2.1.5 synthesis(E)-2-(1-(4-((E)-(4-hydroxy-3-methylphenyl) diazenyl) phenyl) ethylidene) hydrazinecarboxamide (CZ2)

A mixture of simicarbazide hydrochloride (0.378 g, 0.0015mol) and sodium acetate (0.26g,0.003mol) was dissolved in absolute ethanol (30 mL). The mixture was heated under reflux for 15 minutes, then filtered while it was hot to remove precipitated sodium chloride. The filtrate was then mixed with (E)1-(4-(4-hydroxy-3-methylphenyl) phenyl) ethanon (0.77g,0.003mole) and the resulting mixtures were heated under reflux, added some drops of concentrated hydrochloric acid and continued overnight heating under reflux with continuous removal of the produced water. The reaction was monitored by TLC using eluent (n-hexane 6: 4 ethyl acetate). The solvent was filtered under vacuum precipitate formed and recrystallized from chloroform gave orange solid (1.039g, yield=77%) R_f =0.92 , m.p 194-196^{0}C[11].

2.2.1.6 synthesis(E)-2-(1-(4-((E)-(4-hydroxy-2-methylphenyl) diazenyl) phenyl) ethylidene) hydrazinecarboxamide (CZ3)

Dissolved in absolute ethanol (30 mL) a mixture of simicarbazide hydrochloride (0.378 g, 0.0015mol) and sodium acetate (0.26g,0.003mol). The mixture was heated for 15 minutes under reflux, then filtered to remove precipitated sodium chloride while it was hot. The filtrate was then mixed with (E)1-(4-(4-hydroxy-2-methylphenyl) phenyl) ethanon (0.77g,0.003mole) and the resulting mixtures heated under reflux, added a few

drops of concentrated hydrochloric acid and continued overnight heating under reflux with continuous removal of the produced water. The reaction was monitored by TLC using eluent (n-hexane 6: 4 ethyl acetate). The solvent was removed by vacuum and recrystallized from the chloroform, gave orange solid (0.40, yield=35%) R_f =0.66, m. p152- 155^{0}C[11].

2.2.1.7 synthesis(E)-4-((4-(1,2,3-selenadiazol-4-yl) phenyl) diazenyl) phenol (AS1)
Semicarbazones (0.35g,0.001mol) were dissolved in glacial acetic acid (40 mL) with strong stirring and gentle heating of up to 60 ^{0}C The solution was treated with selenium dioxide powder (0.129,0.001 mmol.) and the mixture was subsequently kept under vigorous stirring 2 Min. the mixture's color turns red. The reaction was monitored by TLC using eluent (n-hexane 4:6 ethanol). The mixture was filtered after 4 h and the filtrates poured into ice water and removed with a CH_3Cl of (3x50 mL). A saturated solution of sodium hydrogen carbonate washed the combined organic layers. Dried on magnesium sulfate, filtered off and remove the solvent by vacuum, recrystallization the crude product from methanol gave red solid (0.116, yield=31%) R_f =0.76, m.p 154-156^{0}C[11, 12]

2.2.1.8 synthesis(E)-4-((4-(1,2,3-selenadiazol-4-yl) phenyl) diazenyl)-2-methylphenol (AS2)
Semicarbazones (0.35g,0.001mol) were dissolved in glacial acetic acid (40 mL) with vigorous stirring and gentle heating up to 60 0C The solution was treated with selenium dioxide powder (0.129,0.001 mmol) and the mixture was kept under vigorous stirring afterwards. 2 Min the mixture's color becomes red. TLC reaction monitoring using eluent (n-hexane 4:6 ethanol). The mixture was filtered after the 4 h and the filtrates poured into ice water and extracted with CH_3Cl (3x50 mL). The organic layers combined have been washed with a solution of saturated sodium hydrogen carbonate. Dried on magnesium sulfate, filtered off and removed the solvent by vacuum recrystallization the crude product from methanol gave red solid (0.04, yield=30%) R_f =0.71, m.p 120-122^0 C[11, 12]

2.2.1.9 synthesis(E)-4-((4-(1,2,3-selenadiazol-4-yl) phenyl) diazenyl)-3-methylphenol (AS3)
Semicarbazones (0.35g,0.001mol) were dissolved in glacial acetic acid (40 mL) with vigorous stirring and gentle heating up to 60 ^{0}C The solution was treated with selenium dioxide powder (0.129,0.001 mmol) and the mixture was kept under vigorous stirring afterwards. 2 Min the mixture's color becomes red. TLC reaction monitoring using eluent (n-hexane 4:6 ethanol). The mixture was filtered after the 4 h and the filtrates poured into ice water and removed with CH_3Cl (3x50 mL). The organic layers combined have been washed with a solution of saturated sodium hydrogen carbonate. Dried on magnesium sulfate, filtered off and removed the solvent by vacuum, recrystallized crude product from methanol gave red solid (0.04, yield=27%) R_f =0.83, m.p 128-130^{0}C[11, 12].

Table1: some physical properties data of azo, Cabazon and Selenadizol compounds

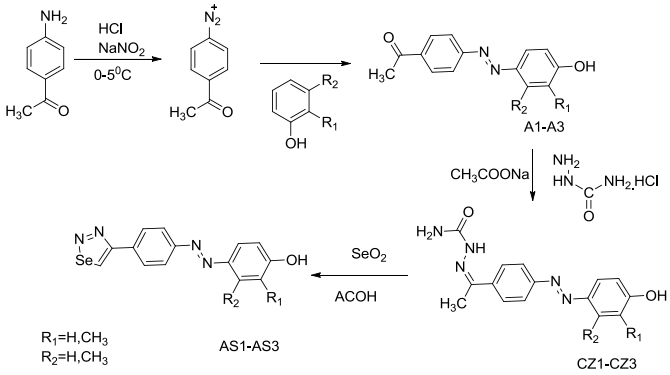
Sym	colure	Melting point (^{0}C)	Yield %	R_f	CHN analysis		
					CHN analysis	Sym	colure
A1	Yellow	188-190	72	0.59	---	---	---
A2	red	162-164	69	0.64	---	---	---
A3	red	153-152	50	0.67	---	---	---
CZ1	orang	204-206	40	0.73	---	---	---
CZ2	orang	194-196	77	0.92	---	---	---
CZ3	orang	155-152	35	0.66	---	---	---
AS1	red	154-156	31	0.76	51.08 51.18	3.23 3.33	17.02 16.98
AS2	red	120-122	30	0.71	52.49 52.31	3.52 3.33	16.32 16.45
AS3	red	128-130	27	0.83	52.49 52.36	3.52 3.38	16.32 16.25

2.3 Preparation and Doping of the polymer blends

A mixture of polyvinyl alcohol (PVA) and Pluronic F-127 (1:1) were dissolved in distilled water and stirred with high-speed mixer at constant temperature for 30 minutes. Doping polymer blends with Flavonoid was carried out by adding the weighed of extraction Flavonoid to the solution of PVA- Pluronic F-127 after the prepared directly to give a polymer blend / Flavonoid system containing (0.03, 0.05, 0.07, 0.09 and 0.12) g wt.% of doping . The mixture was stirred well for 15 minutes to guarantee that the homogenous distribution of Flavonoid in the polymer matrix.

3. Results and Discussion

1,2,3 Selenadiazol was a three-step synthesis shown in Scheme 1, all of which were obtained as red solids and were characterized by their melting points, IR ,1H-NMR,13C-NMR, Mass Spectroscopic and CHN elemental analysis, which is in line with previously reported data. The first step was to prepare azo compounds by reacting the 4-amino acetophenon with phenol derivatives with sodium nitrite and drops of hydrochloric acid, the second step was to react the simicarbazide with ethanol azo compounds to give the semicarbazone compounds and finely react with selenium dioxide SeO2 in glacial acetic acid.



Scheme 1 syntheses Selenadiazol compounds

The IR spectra of all azo compounds (A1-A3) show an absorption band between 1400-1431 for υ (N=N),band between 1658-1670 for υ (C=O) and band between the 3255-3397 for υ (OH)[13, 14],

The IR spectra of all semicarbazones compounds (CZ1-CZ3) show an absorption band between 1431-1465 for υ (N=N),band between 1660-1597 for υ (C=N)[15]

1H NMR spectra of compounds CZ1-CZ3 were recorded in (DMSO-d6) and gave a further support for the formation of these compounds,1H NMR appeared strong signal at (2.22-2.36) ppm attributed to methyl group (CH3), signal between 6.55 -6.71ppm to (NH2), signal at 9.44-9.45ppm to (NH) and singlet signal at 10.26 -10.31ppm to (OH).

The IR spectra of all 1,2,3 Selenadiazol compounds (AS1-AS3) show an absorption band between 1589-1597 for υ (N=N), band between 513-∼520 for υ (Se-C)[16, 17].

1H NMR spectra of compounds AS1-AS3 appeared ,singlet signal at (2.22-2.69)ppm attributed to methyl group CH3 (AS2,AS3),signals in low field of H-aromatic at the range 6.93-8.34 ppm ,all spectra showed singlet signal downfield between 8.73 and 7.95 ppm due to the H-Selenadiazol ring, which agrees well with the literature values[17].

13C NMR are support the formulation of 1,2,3 Selenadiazol compounds, for all Selenadiazol compounds the methyl group CH3 appear at δ=15,17 ppm the C=Se appear at =162-161 ppm, C=N appear at 143-145 ppm and the aromatic carbon atom appear at 161-114ppm.[18, 19].

The mass spectra of compounds (AS1-AS3) showed the molecular ion peaks with (m/z) (M+) values corresponding to their molecular weights. Further fragmentation pattern was also consistent with the assumed structure. included elimination of nitrogen molecule (M-28),and then loss of selenium atom[20-23].

4-Antibacterial activity

In many literatures, 1,2,3 Selenadiazol compounds gave a biological activity. The prepared compounds in this study had antibacterial activity against four types of bacteria such as Staphylococcus aureus, Bacillus cereus (Gram positive bacteria), Escherichia coli, and Salmonella spp (Gram-negative bacteria).

The compounds AS1and AS2 had high antibacterial activity against Staph aureus, but AS3 compound had high activity against both of E. coli and B. Cereus Table 2,3,4.
The prepared compounds were compared with several types of standard antimicrobial discs (Bio analyses) listed in table 5. The CIP standard antimicrobial discs had biological activity of the four types of bacteria. TE standard disc had biological activity on B. cereus, Staph aureus and E. Coli Table 5.

Table2: Inhibition zone for AS1 compound

Type of bacteria	Concentration of AS1 (mg/ml) Inhibition zone (mm)						
	250	200	150	100	25	10	5
E. coli	10	9	8	8	0	0	0
Staph aureus	14	13	12	11	8	8	7
Bacillus cereus	12	10	9	8	0	0	0
Salmonella spp.	0	0	0	0	0	0	0

Table3: Inhibition zone for AS2 compound

Type of bacteria	Concentration of AS2 (mg/ml) Inhibition zone (mm)						
	250	200	150	100	25	10	5
E. coli	23	21	21	16	4	0	0
Staph aureus	33	31	28	25	23	20	16
Bacillus cereus	27	25	23	21	18	9	6
Salmonella spp.	23	22	21	19	4	0	0

Table 4 Inhibition zone for AS3 compound

Type of bacteria	Concentration of AS3 (mg/ml) Inhibition zone (mm)						
	250	200	150	100	25	10	5
E. coli	18	16	16	15	0	0	0
Staph aureus	16	14	12	12	0	0	0
Bacillus cereus	18	18	17	17	17	15	13
Salmonella spp.	0	0	0	0	0	0	0

Table5. Inhibition zone for standard disc

Type of bacteria	Type the disc/ conc mcg (S,R)						
	CIP 10 mcg	AMC 30 mcg	S 10 mcg	TE 30 mcg	C 30 mcg	P (10U)	OX 1 mcg
E. coli	28(S)	0(R)	0(R)	18(S)	0(R)	0(R)	0(R)
Staph aureus	29(S)	0(R)	0(R)	10(S)	0(R)	0(R)	0(R)
Bacillus cereus	29(S)	0(R)	0(R)	18(S)	0(R)	0(R)	0(R)
Salmonella spp.	20(S)	0(R)	0(R)	0(R)	0(R)	0(R)	0(R)

S= sensitive, R= resistance
Whereas: CIP= Ciprofloxacin; AMC= Amoxicillin with clavulanic acid; S= Streptomycin; TE= Tetracycline; C= Chloramphenicol; P= penicillin; OX= Oxacillin

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