

Synthesis, Structural and Biological Studies of 3-(1, 3-benzothiazol-2-yl) - 4H- spiro[indole2,3-[1,3]thiazolidine]-2,4(1H) dion with Cr (III), Mn (II), Co (II), Ni (II), Cu (II), and Zn (II) ions

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Abstract

This paper describes the synthesis of a new derivative 3-(1,3-benzothiazol-2-yl)- 4H- spiro[indole2,3-[1,3]thiazolidine]-2,4(1H) dion [L], which have been obtained from the cyclization of 3-(benzo [d] thiazol-2-ylimino) indolin -2-one[AB] through the addition of α -mercapto acetic acid. The product [L] was characterized by (FT.IR) and (U.Vis) spectroscopy and in addition to element analysis (C.H.N.S.).

A number of metal complexes were synthesized from the reaction of the ligand [L] with ions Cr (III), Mn (II), Co (II), Ni (II), Cu (II), and Zn (II) . The prepared complexes were isolated and characterized by using (FT.IR) and (U.Vis) spectroscopy in addition to element analysis (C.H.N.S.), flame atomic absorption technique, in addition to magnetic susceptibility and conductivity measurement.

The antibacterial activity of the ligand [L] and its complexes were studied against two selected micro-organisms (*Pseudomonas aeruginosa*) as gram negative and (*Bacillus subtilis*) as gram positive.

Keywords: Thiazolid, 3,4(H) dion, Complexes of Thiazolidin derivatives, Biological studies

تحضير ودراسة تركيبية وحيوية لـ 3`-(1, 3-benzothiazol-2-yl)-4`H- spiro[indole2,3-[1, 3]thiazolidine]-2,4` (1H) dion with Cr(III), Mn(II), Co(II). Ni(II), Cu(II) and Zn(II) ions

الخلاصة

يتضمن هذا البحث تحضير المشتق الجديد [L] 3-(1, 3-benzothiazol-2-yl)- 4H- spiro[indole2,3-[1,3]thiazolidine] -2,4(1H) dion من عملية الغلق الحلقي لكل من (مشتق الازوميثين) 3-(benzo[d] thiazol-2-ylimino) indolin-2-one [AB] مع α -mercaptoacetic acid ، جرى تشخيص [L] بطرائق تحليل طيف الأشعة تحت الحمراء المعززة بتحويلات فورير (FT.IR) وطيف الأشعة فوق البنفسجية المرئية والتحليل الدقيق للعناصر (C.H.N.S) ثم استخدام [L] كالكاند في تحضير معقدات الايونات الفلزية :- الكروم (III) ، المنغنيز (II) ، الكوبلت (II) ، النيكل (II) ، النحاس (II) والخراسين (II) . تم تشخيص المعقدات الجديدة بوساطة طيف الأشعة تحت الحمراء (FT.IR) المعززة بتحويلات فورير وطيف الأشعة فوق البنفسجية المرئية والتحليل الدقيق للعناصر (C.H.N.S) وتقنية الامتصاص

الذري للهي للعناصر اضافة الى لقياسات الحساسية المغناطيسية والتوصيلية الكهربائية . ثم تقويم الفعالية المضادة للبكتريا لليكاند [L] ومعقداته واحتير نوعان من البكتريا (*Pseudomonas aeruginosa*) سالبة الصبغة ، (*Bacillus subtilis*) موجبة الصبغة لهذا الغرض.

Introduction

Derivatives of thiazolidine-4-one [1] find a variety of application ranging from antimicrobial [2] , anti-tubercular, carbonic anhydrazes inhibitors, anti-inflammatory [3], local anaesthetics, anthelmintic, anticonvulsant and hypoglycemic agents activity [4]. Due to this, the investigation of chemistry and biology of these compounds continue to appeal the synthetic and medicinal organic chemistry.

Keeping this in mind, it was worth while to develop the synthesis of title compounds 1,2,3,4-tetra hydrocarbazoyl azetidionones and tetra hydrocarbazoyl thiazetidionones [5] Moreover, the microwave assisted reactions using dry media [6] have attracted much interest because of the simplicity in operation greater selectivity and rapid synthesis of a variety of heterocyclic compound. In view of the above observations, the synthesis of thiazolidine-4-one derivatives [7] has been developed starting from various substituted benzylidene-anilines with the aim of investigation their biological activities [8].

The present paper describes the preparation of new Schiff's base [AB], derivative produced from the reaction of izatine [A] and 2-amino phenyl thiazole [B] then

cyclization [AB] by using α -mercapto acetic acid to be using as a ligand (L), which provided four potential doner sites to form complexes with some metal ions.

Experimental

All chemicals were used as received (by either fulka or BDH) of highest purity and were used as received.

Physical measurement and analysis:

Melting point were recorded on Gatten kamp melting point apparatus and were un corrected FT.IR spectra were recorded using FT.IR .

8300 shimadzu in the range of (4000-200) cm^{-1} (samples were measured as CsI disc).

The percents of metals in the complexes were estimated by flame atomic absorption-Shimadzu AA, 670 with standard addition method.

Electronic spectra were obtained using UV-1650pc. Shimadzu spectro photo meter at room temperature. The measurements were recorded by using a concentration of 10^{-3} M of the complex in absolute ethanol as a solvent.

Micro analytical data for C.H.N.S were obtained using EA-034, mth.

Conductivity measurements were obtained using corning conductivity meter 220-these measurements were obtained using concentration of 10^{-3} M at 25°C and (DMF) as a solvent. Magnetic susceptibility measurement were obtained at 25°C on the solid state applying Faradays method using Bruker BM6 instrument.

Preparation of ligand

(A) Preparation of 3-(benzo[d]thiazol-2-yl)indolin-2-one [AB].

A mixture of isatine [A], (0.15)g and 2-amino benzo thiazol [B] with absolute ethanol as a solvent was refluxed for 6hrs, the solid product [AB] was collected and crystallized from absolute ethanol.

(B) synthesis of 3-(1,3-benzothiazol-2-yl)-4H-spiro[indole-2,3-[1,3]thiazolidine]-2,4(1H)-dione (L).

To a solution of compound [AB] (0.01mole) in absolute ethanol (10ml), α -mercapto acetic acid (0.01M) was added. The mixture was refluxed for (7hrs). the solid product was formed by using 10% sodium bicarbonate then collected and crystallization from absolute ethanol.

Scheme (1).

Preparation of complexes

(C₁ → C₆)

Ethanol solution of each of the following metal ions 1mmole of each (0.238g) of COCl₂.6H₂O and (0.136g) of ZnCl₂ was added to an ethanolic solution of (1mmole, 0.353g) of [L] and 2mmole of each (0.394g) MnCl₂.4H₂O, (0.474g), NiCl₂.6H₂O and (0.34g) of CuCl₂.2H₂O was added to (1mmole, 0.353g) of [L] and (1mmole, 0.266g) of CrCl₃.6H₂O was added to (2mmole, 0.706g) of the ligand with stirring.

The mixture was heated under reflux for two hour during this time a precipitate was formed, the product was isolated by filtration, washed several time with hot absolute ethanol then dried under vacuum. The physical data of the

prepared complexes are show in table (1).

Study of complex formation in solution

Complexes of (L) with metal ions were studied in solution using absolute ethanol as a solvent in order to determined [M: L] ratio in the complex following molar ratio method [9].

A series of solution were prepared having a constant concentration [10⁻³m] of the metal ion and (L). The [M: L] ratio was determined from the relation ship between the absorption of the absorb light and the mole ratio of [M: L]. the result of complexes formation in solution were listed in table (1).

Study of biological activity for ligand [L] and their metal complexes:

The biological screening effects of the investigated compounds were tested against two selected types of bacteria which include (*Pseudomonas aeruginosa*) and (*Bacillus subtilis*) by using the well diffusion method⁽¹⁰⁾ using nutrient agar as method. Stock solutions (10⁻³m) were prepared by dissolving the compounds in DMSO solution. In atypical procedure, a well was made on the agar medium inoculated with microorganisms.

The well was filled with the test solution using a micropipette and the plate was incubated at 30C⁰ for 72hours. During this period, the test solution diffused and the growth of the inoculated microorganisms was affected.

Result and discussion

(A) Elemental analysis

The physical analytical data of (L) and its metal complexes are given in table (1), in a satisfactory agreement with the calculated values the suggest molecular which are formulas also supported by subsequent spectral and molar ratio, as well as magnetic moment.

Infrared Spectroscopic Study

All the recorded spectra were in the solid state using CsI. As expected, FT.IR gave a good information about the complexation behavior of the ligand [L] with various metal ions. The characteristic frequencies of free ligand [L] and its metal complexes were readily assigned based on comparison with literature values [11].

The FT.IR of free ligand [L] was confirmed from the disappearance of the azomethian group (C=N) of compound [AB] and appearance of a new band at 1363cm^{-1} due to ($\overline{\text{N}}-\text{N}$) stretching [12] as well as the ligand [L] has absorption band at 1697cm^{-1} which indicates that free carbonyl group is presence and so the ketimine structure is not ruled out [13, 14], table (2).

(C) Electronic spectra, Magnetic Moment and Conductance Studies

The UV spectrum of ligand [L] mostly showed two intense maxima band at 206nm and 260nm which belong to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ respectively [15, 16], table (3).

The electronic spectra of the ligand complexes were recorded for their solution in absolute ethanol in the range (200-1100)nm, while the molar conductance were measurement in dimethyl formamide (DMF) as a solvent.

[C₁]:- the light green chromium complex gave three absorption

bands appeared at (16666, 17094, 25575) cm^{-1} , following octahedral filed with (d^3) configuration [17]. The effective magnetic moment at room temperature was found to be (3.79BM) revealing inner-orbital high-spin octahedral stereo chemistry of the ligand around Cr (III) metal ion [18] Conductivity in (DMF) showed that the complex was to be ionic, table (3).

[C₂]:- The prepared light brown Mn(II) complex showed two band at (14390 , 27027) cm^{-1} due to the transition

${}^6A_{1g} \xrightarrow{\gamma_1} {}^4T_{1g}$ and

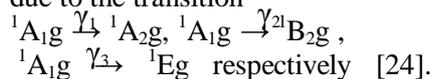
${}^6A_{1g} \xrightarrow{\gamma_2} {}^4E_g, {}^4A_{1g}$ (G), these

assignment when compared to those published for octahedral geometry [19]. In addition the measured magnetic for this complex was found to be (5.08BM), this value refers to high-spin, (d^5) complex [20], table (3). Conductivity measurement in (DMF) showed a non-conductive behavior of the complex.

[C₃]:- the solution spectrum of the deep green Co (II) complex showed three band at (15267, 27173) cm^{-1} due to $A_2 \xrightarrow{\gamma_1} T_1$ (F) and ${}^4A_2 \rightarrow {}^4T_1$ (p) with charge transfer band at 27173 cm^{-1} these bands correspond to those of tetrahedral geometry [21] magnetic moment of the solid complex (4.48BM) showed a high spin Co(II) complex [22] Conductivity in (DMF) showed that the complex was non-conductive behavior Table (3).

[C₄]:- the Ni (II) complex gave a yellow orange colour , which refer to the presence of vacant coordination sites on the metal ion.

The solid was found diamagnetic, indicating square planer geometry [22,23] The new weak bands in the visible region of Ni (II) complex at (21739, 23809, and 27855) cm⁻¹ are assigned as ligand field bands due to the transition



Moreover the magnetic of the solid complex (0.00BM) showed a low spin Ni (II) complex and the conductivity in DMF shows the complex to be non-conducting, table (3).

[C5]:- the electronic spectrum of this complex shown one band 115075cm⁻¹ attributable to 2B_{1g} → 2E_g transition in the square planer geometry [25]. The magnetic moment value (1.76 BM) corresponds to one unpaired electron, table (3). The conductivity measurement in DMF showed a non-conductive behavior.

[C6]:- Zn (II) complex show no absorption peak at rang (380-1000) nm that indicates no (d-d) electronic transition happened (d₁₀- system) invisible region that is a good result for Zn (II) tetrahedral complex [26].

(D) Antibacterial activity

The tested compounds solutions were prepared in dimethyl sulphoxide and evaluated them for their *in vitro* antibacterial against (*Pseudomonas aeruginosa*), (*Bacillus subtilis*).

The complexes [C1 → C6] were found to be more toxic than the corresponding parent ligand [L] against two types of the bacterial, table (4).

Suggested stereo chemistry structure for (L) and their metal complexes.

According to the result obtained from elemental and spectral analysis as well as magnetic moment and conductivity measurements the suggested structure of the above mentioned compounds can be illustrated as follow:

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Table (1) Physical data of (L) and its complexes (C₁→C₆)

Com p. no	coloure	M.p C ^o	% element analysis (Found) (calca)				Metal % Found Calc.	M:L In EtOH	Suggested formula
			C	H	N	S			
L	Off white	(260-262)	56.88 (57.79)	2.24 (3.12)	12.64 (11.89)	17.86 (18.13)	-	-	C ₁₇ H ₁₁ N ₃ S ₂ O ₂
C ₁	Light green	290 d*	47.63 (48.07)	4.60 (4.4)	7.59 (8.0)	13.08 (12.22)	4.09 4.9	1:2	[CrL ₂ CL ₂]Cl (C ₂ H ₅ OH) ₄
C ₂	Light brown	310 d*	31.02 (30.14)	3.23 (2.81)	5.93 (6.21)	9.19 (9.94)	18.75 16.22	2:1	[Mn ₂ LCl ₄ (H ₂ O) ₄]
C ₃	Green	320 d*	44.36 (43.83)	3.86 (4.00)	8.04 (7.31)	10.76 (11.13)	10 10.25	1:1	[CoLCL ₂](C ₂ H ₅ OH) ₂
C ₄	Yellow	300 d*	34.86 (33.32)	2.03 (1.79)	7.53 (6.86)	9.89 (10.45)	19.17 19.5	2:1	[NiLCL ₄]
C ₅	Light green	302 d*	33.79 (34.13)	3.36 (2.54)	7.11 (6.29)	8.83 (9.51)	18.06 19.01	2:1	[Cu ₂ LCl ₄](C ₂ H ₅ OH)
C ₆	Off white	315 d*	43.26 (42.59)	2.69 (3.18)	8.26 (7.84)	12.79 (11.9)	12.2 11.9	1:1	[ZnLCl ₂](C ₂ H ₅ OH)

Table (2) Characteristic stretching vibrational frequencies cm⁻¹ located in the FT.IR of [L] and their metal complexes.

Comp.	γ- NH	γ- C=O	γ- C=N	γ- N-	γ- M-O	γ- M-N	γ- M-Cl
L	3444	1697	1626	1363	-	-	-
C ₁	3416 (b)	1658	1489	1365	400	450	-

C ₂	3437 (b)	1622	1446	1404	410	460	300
C ₃	3408 (b)	1662	1624	1462	420	460	320
C ₄	3493 (b)	1753	1427 (b)	1427 (b)	400	480	310
C ₅	3452 (b)	1668	1624	1400	410	490	280
C ₆	3493	1664	1624	1462 (b)	420	460	300

Table (3) Electronic spectra, conductance (in DMF) , and magnetic moment (B.M) for [L] and their metal complexes.

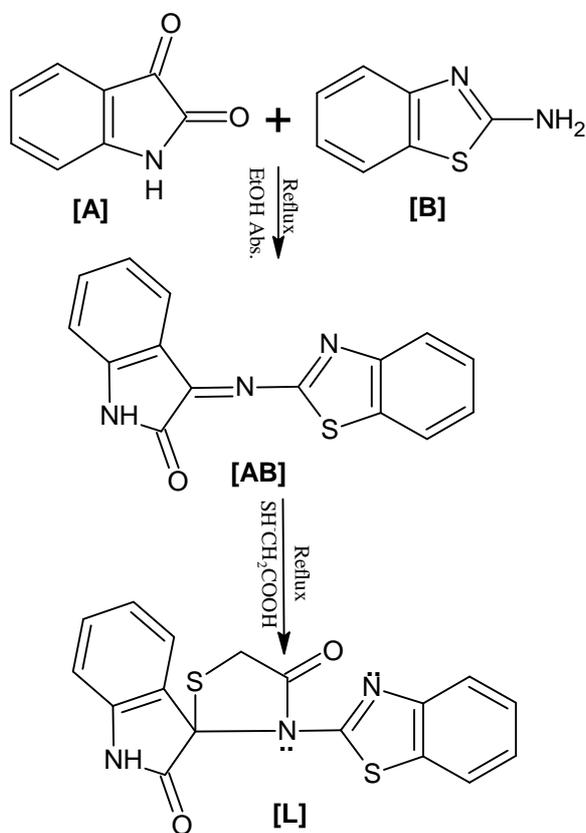
Comp.	Bands cm ⁻¹	Assignment	Molar Cond. μs. Cm ⁻¹	μ eff B.M	Suggested structure
L	48543 38461	π → π* n → π*	-	-	-
C ₁	16666 17094 25575	⁴ A _{2g} ^γ ₁ → ⁴ T _{2g} ⁴ A _{2g} ^γ ₂ → ⁴ T _{1g} (F) ⁴ A _{2g} ^γ ₃ → ⁴ T _{1g} (P)	85	3.79	o.h
C ₂	14390 27027	⁶ A _{1g} ^γ ₁ → ⁴ T _{2g} ⁶ A _{1g} ^γ ₂ → ⁴ Eg ⁴ A _{1g} (G)	18	5.08	o.h
C ₃	15267 16393 27173	⁴ A ₁ → ⁴ T ₁ (F) ⁴ A ₁ ^γ ₂ → ⁴ T ₁ (P) C.T	13	4.48	T.h
C ₄	21739 23809 27855	¹ A _{1g} ^γ ₁ → ¹ A _{2g} ¹ A _{1g} ^γ ₂ → ¹ B _{1g} ¹ A _{1g} ^γ ₃ → ¹ Eg	16	0.00	Sq
C ₅	115075	² Eg → ² T _{2g}	10	1.76	Sq

Table (4)

In vitro antibacterial activity for [L] and their metal complexes.

Comp.	<i>Pse.</i>	<i>Bac.</i>
L	2	4
C ₁	8	14
C ₂	6	10
C ₃	8	10
C ₄	6	12
C ₅	10	16
C ₆	12	16

Where: - 6-8 (+)
8-10 (++)
> 10 (+++)



Scheme (1)

