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MIXED ISATIN WITH 3-(2-(ARYL)HYDRAZONO)ACETYLACETONE Mn(II), Co(II) AND Ni(II) COMPLEXES: ANTIBACTERIAL EVALUATION AND MOLECULAR PROPERTIES PREDICTION

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ABSTRACT. The metal complexes {Ni (II), Co (II) and Mn (II)} of 3-(2-(aryl)hydrazono)acetylacetone with isatin were synthesized and screened for their *in vitro* antibacterial activity against four pathogenic microorganisms {two Gram-positive and two Gram negative}. The results of antibacterial activities revealed that all the metal complexes **1-9** exhibited moderate activities. Also, Lipinski's rule of five (RO5) of the mixed ligand metal complexes were calculated by SwissADME website.

KEY WORDS: Isatin, 3-(2-(Aryl)hydrazono)acetylacetone, Metal complexes, Antibacterial activities, Lipinski rules

INTRODUCTION

There is recently a growing interest in the field of synthesizing mixed ligand metal complexes due to various biological applications. In 2018, Sakr *et al.* have prepared Zn(II), Sn(II) and Ce(III) of gemifloxacin with glycine **(A)** as antibacterial agents [1]. Also, in 2017, Omar *et al*., have prepared the complexes of Mn(II), Co(II), Ni(II) and Zn(II) of Schiff base and 2,2′-bipyridine **(B)** for evaluation their antimicrobial and anticancer activities [2]. Literature survey revealed that isatin and its derivatives show a wide range of biological applications [3-5] such as 1-(1-(3-methylbenzyl)-2-oxoindolin-3-ylidene)-thiosemicarbazide (**C**) showed highly active against *Mycobacterium bovis bacillus* Calmette-Guerin [6] and 3-(benzylimino)-7-chloroindolin-2-one (**D**) display significant cytotoxic activity against HeLa, SK-BR-3 and MCF-7 cells [7]. Also, there are some isatin-based drugs, e.g. Sunitinib (Sutent®) (E) acts as tyrosine kinase inhibitor [8]. Nintedanib **(F)** acts as triple angiokinase inhibitor [9] (Figure 1). In addition, arylhydrazono-1,3-diketone derivatives are useful synthons in the synthesis of a large number of biologically compounds [10-12].

In view of these facts and in continuation of our target [13-25], the metal complexes {Ni(II), Co(II) and Mn(II)} of 3-(2-(aryl)hydrazono)acetylacetone with isatin have been synthesized to evaluate their antibacterial activity against four pathogenic microorganisms {two Gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and two Gram negative (*Escherichia coli* and *Pseudomonas aeruginosa*)}. Also, the study has been extended to calculate the physicochemical properties and drug-likeness (Lipinski's rule) of the mixed ligand metal complexes (Figure 2).

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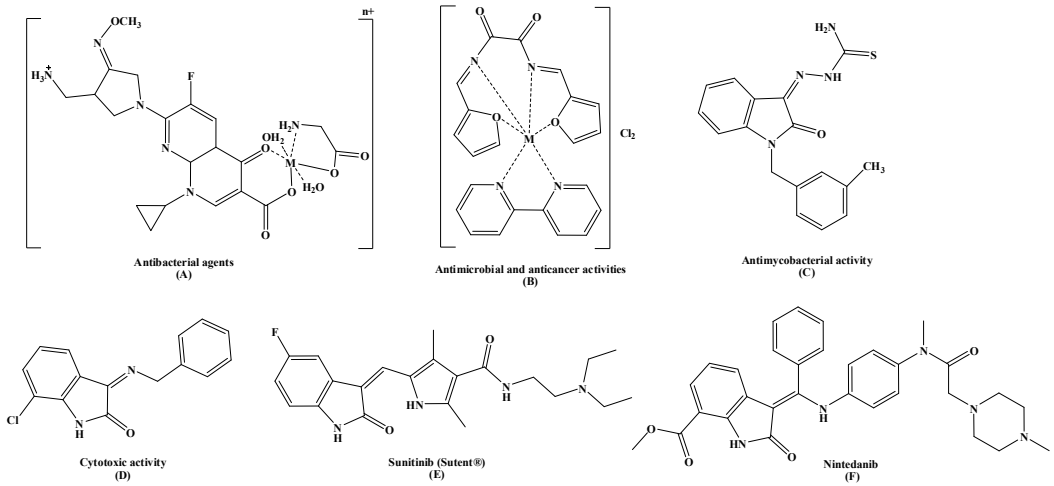


Figure 1. Structures of mixed complexes **(A** and **B)** and isatin derivatives **C-F**.

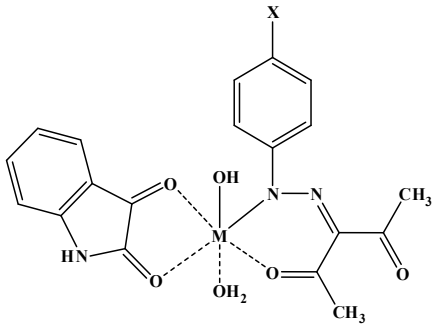


Figure 2. Mixed ligand metal complexes and their studies.

EXPERIMENTAL

*Preparation of 3-(arylhydrazono)acetylacetone (**HL**)*

The 3-(arylhydrazono)acetylacetone derivatives (**HL**) were prepared by coupling acetylactone with different diazonium salts, where acetylactone (0.01 mol) was placed in a beaker containing ethanol (50 mL) and sodium acetate (5 g) then the diazonium salt (0.01 mol) was added with stirring. The reaction proceeded at 0-5 °C for 30 min. The 3-(arylhydrazono)acetylacetone derivatives were precipitated and collected by filtration, washed with cold deionized water and recrystallized from ethanol [26-28].

*3-(2-Phenylhydrazono)acetylacetone (**HL^1**).* Yellow needles; yield: 86%; m.p. 86-87 ºC; anal. calcd. (%) for $C_{11}H_{12}N_2O_2$ (204.23): C, 64.69; H, 5.92; N, 13.72. Found: C, 64.50; H, 6.10; N, 13.65%; IR (KBr) ν_{max}/cm^{-1} 3430-3092 (N-H…O=C, hydrogen bonded), 1673 (C=O, free), 1623 (C=O, hydrogen bonded), 1593 (C=N), 1518 (N-H); ^{1}H NMR (DMSO-d_6, δ ppm) 2.36 (s, 3H, CH_3CO free), 2.43 (s, 3H, CH_3CO hydrogen bonded), 7.16 (t, 1H, aromatic), 7.27 (t, 2H, aromatic), 7.52 (d, 2H, *J*=8.5 Hz, aromatic), 14.02 (s, 1H, NH, D_2O exchangeable).

*3-(2-(4-Chlorophenyl)hydrazono)acetylacetone (**HL^2**).* Yellow needles; yield: 86%; m.p. 147-148 ºC; anal. calcd. (%) for $C_{11}H_{11}ClN_2O_2$ (238.67): C, 55.36; H, 4.65; N, 11.74. Found: C, 55.50; H, 4.52; N, 11.80%; IR (KBr) ν_{max}/cm^{-1} 3432-3094 (N-H…O=C, hydrogen bonded), 1667 (C=O, free), 1625 (C=O, hydrogen bonded), 1589 (C=N), 1519 (N-H); ^{1}H NMR (DMSO-d_6, δ ppm) 2.37 (s, 3H, CH_3CO free), 2.42 (s, 3H, CH_3CO hydrogen bonded), 7.43 (d, 2H, *J* = 8.4 Hz, aromatic), 7.57 (d, 2H, *J* = 8.4 Hz, aromatic), 13.81 (s, 1H, NH, D_2O exchangeable).

*3-(2-(4-Bromophenyl)hydrazono)acetylacetone (**HL^3**).* Yellow needles; yield 86%; m.p. 141-142 ºC; anal. calcd. (%) for $C_{11}H_{11}BrN_2O_2$ (283.12): C, 46.66; H, 3.92; N, 9.89. Found: C, 46.50; H, 4.10; N, 10.00%; IR (KBr) ν_{max}/cm^{-1} 3422-3073 (N-H…O=C, hydrogen bonded), 1667 (C=O, free), 1623 (C=O, hydrogen bonded), 1585 (C=N), 1513 (N-H); ^{1}H NMR (DMSO-d_6, δ ppm) 2.37 (s, 3H, CH_3CO free), 2.42 (s, 3H, CH_3CO hydrogen bonded), 7.50 (d, 2H, *J* = 9.15 Hz, aromatic), 7.56 (d, 2H, *J* = 9.15 Hz, aromatic), 13.75 (s, 1H, NH, D_2O exchangeable).

*Isatin (**L'**).* IR (KBr) ν_{max}/cm^{-1} 3191 (N-H), 1745 (C=O), 1731 (C=O); ^{1}H NMR (DMSO-d_6, δ ppm) 6.88 (d, 1H, *J* = 7.7 Hz, aromatic), 7.03 (t, 1H, aromatic), 7.46 (d, 1H, *J* = 7.7 Hz, aromatic), 7.54 (t, 1H, aromatic), 10.98 (s, 1H, NH, D_2O exchangeable).

*Preparation of the complexes **1-9***

A solution of the metal chloride (3.4 mmol) in a minimum amount of water was added to a hot solution of the mixed ligand in methanol (3.4 mmol each). A clear solution was obtained. The pH was raised from 6.0 to 8.0 with dilute NaOH solution. The mixture was refluxed with stirring for 6 hours. The formed complex was filtered off, washed several times with hot methanol and dried under reduced pressure [29].

*[NiL'L^1(OH)(H_2O)] (**1**).* Greenish yellow; yield 50%; m.p. 215-218 ºC; anal. calcd. (%) for $C_{19}H_{19}N_3NiO_6$ (444.06): C, 51.39; H, 4.31; N, 9.46. Found: C, 51.50; H, 4.25; N, 9.55%; IR (KBr) ν_{max}/cm^{-1} 3522 (O-H), 3181 (N-H, L'), 1717 (C=O, L'), 1709 (C=O, L'), 1667 (C=O free, L^1), 1600 (C=O coordinated, L^1), 1590 (C=N, L^1), 583 (Ni-N), 493 (Ni-O); ^{1}H NMR (DMSO-d_6, δ ppm) 2.34 (s, 3H, CH_3CO free, L^1), 2.64 (s, 3H, CH_3CO coordinated, L^1), 6.76-7.58 (m, 9H, aromatic, L' and L^1), 10.20 (s, 1H, NH, D_2O exchangeable, L'); UV-Vis. λ = 963, 576, 420 nm; magnetic moment (μ_{eff}/B.M.): 3.17; molar conductivity (Ω^{-1} cm^2 mol^{-1}): 11.6.

*[CoL'L^1(OH)(H_2O)] (**2**).* Dark green; yield 53%; m.p. 209-211 ºC; anal. calcd. (%) for $C_{19}H_{19}CoN_3O_6$ (444.30): C, 51.36; H, 4.31; N, 9.46. Found: C, 51.55; H, 4.25; N, 9.55%; IR (KBr) ν_{max}/cm^{-1} 3580 (O-H), 3183 (N-H, L'), 1715 (C=O, L'), 1707 (C=O, L'), 1669 (C=O free, L^1), 1602 (C=O coordinated, L^1), 1591 (C=N, L^1), 584 (Co-N), 491 (Co-O); UV-Vis. λ = 654, 540 nm; magnetic moment (μ_{eff}/B.M.): 4.92; molar conductivity (Ω^{-1} cm^2 mol^{-1}): 12.8.

*[MnL'L^1(OH)(H_2O)] (**3**).* Green; yield 45%; m.p. 210-212 ºC; anal. calcd. (%) for $C_{19}H_{19}MnN_3O_6$ (440.31): C, 51.83; H, 4.35; N, 9.54. Found: C, 51.70; H, 4.40; N, 9.47%; IR (KBr) ν_{max}/cm^{-1} 3544 (O-H), 3182 (N-H, L'), 1719 (C=O, L'), 1711 (C=O, L'), 1661 (C=O free,

L^1), 1605 (C=O coordinated, L^1), 1590 (C=N, L^1), 540 (Mn-N), 487 (Mn-O); UV-Vis. λ = 752, 618, 520 nm; magnetic moment (μ_{eff}/B.M.): 5.82; molar conductivity (Ω^{-1} cm^2 mol^{-1}): 15.4.

*[NiL'L^2(OH)(H$_2$O)] (**4**).* Greenish yellow; yield 60%; m.p. 217-220 ºC; anal. calcd. (%) for $C_{19}H_{18}ClN_3NiO_6$ (478.51): C, 47.69; H, 3.79; N, 8.78. Found: C, 47.50; H, 3.70; N, 8.70%; IR (KBr) ν_{max}/cm^{-1} 3565 (O-H), 3180 (N-H, L'), 1715 (C=O, L'), 1707 (C=O, L'), 1661 (C=O free, L^2), 1605 (C=O coordinated, L^2), 1585 (C=N, L^2), 579 (Ni-N), 448 (Ni-O); ^{1}H NMR (DMSO-d_6, δ ppm) 2.30 (s, 3H, CH_3CO free, L^2), 2.60 (s, 3H, CH_3CO coordinated, L^2), 6.74-7.60 (m, 8H, aromatic, L' and L^2), 10.20 (s, 1H, NH, D_2O exchangeable, L'); UV-Vis. λ = 988, 581, 422 nm; magnetic moment (μ_{eff}/B.M.): 3.20; molar conductivity (Ω^{-1} cm^2 mol^{-1}): 20.5.

*[CoL'L^2(OH)(H$_2$O)] (**5**).* Dark green; yield 58%; m.p. 207-209 ºC; anal. calcd. (%) for $C_{19}H_{18}ClCoN_3O_6$ (478.75): C, 47.67; H, 3.79; N, 8.78. Found: C, 47.50; H, 3.85; N, 8.70%; IR (KBr) ν_{max}/cm^{-1} 3553 (O-H), 3186 (N-H, L'), 1716 (C=O, L'), 1708 (C=O, L'), 1662 (C=O free, L^2), 1602 (C=O coordinated, L^2), 1584 (C=N, L^2), 572 (Co-N), 438 (Co-O); UV-Vis. λ = 661, 548 nm; magnetic moment (μ_{eff}/B.M.): 4.94; molar conductivity (Ω^{-1} cm^2 mol^{-1}): 22.1.

*[MnL'L^2(OH)(H$_2$O)] (**6**).* Greenish yellow; yield 55%; m.p. 216-219 ºC; anal. calcd. (%) for $C_{19}H_{18}ClMnN_3O_6$ (474.75): C, 48.07; H, 3.82; N, 8.85. Found: C, 48.20; H, 3.75; N, 8.80%; IR (KBr) ν_{max}/cm^{-1} 3550 (O-H), 3183 (N-H, L'), 1718 (C=O, L'), 1710 (C=O, L'), 1661 (C=O free, L^2), 1605 (C=O coordinated, L^2), 1580 (C=N, L^2), 569 (Mn-N), 444 (Mn-O); ^{1}H NMR (DMSO-d_6, δ ppm) 2.33 (s, 3H, CH_3CO free, L^2), 2.61 (s, 3H, CH_3CO coordinated, L^2), 6.74-7.58 (m, 8H, aromatic, L' and L^2), 10.21 (s, 1H, NH, D_2O exchangeable, L'); UV-Vis. λ = 758, 622, 526 nm; magnetic moment (μ_{eff}/B.M.): 5.90; molar conductivity (Ω^{-1} cm^2 mol^{-1}): 19.8.

*[NiL'L^3(OH)(H$_2$O)](**7**).* Greenish yellow; yield 53%; m.p. 223-226 ºC; anal. calcd. (%) for $C_{19}H_{18}BrN_3NiO_6$ (522.96): C, 43.64; H, 3.47; N, 8.04. Found: C, 43.50; H, 3.55; N, 8.00%; IR (KBr) ν_{max}/cm^{-1} 3575 (O-H), 3184 (N-H, L'), 1722 (C=O, L'), 1711 (C=O, L'), 1660 (C=O free, L^3), 1600 (C=O coordinated, L^3), 1580 (C=N, L^3), 578 (Ni-N), 447 (Ni-O); ^{1}H NMR (DMSO-d_6, δ ppm) 2.33 (s, 3H, CH_3CO free, L^3), 2.62 (s, 3H, CH_3CO coordinated, L^3), 6.75-7.57 (m, 8H, aromatic, L' and L^3), 10.20 (s, 1H, NH, D_2O exchangeable, L'); UV-Vis. λ = 979, 572, 420 nm; magnetic moment (μ_{eff}/B.M.): 3.19; molar conductivity (Ω^{-1} cm^2 mol^{-1}): 18.7.

*[CoL'L^3(OH)(H$_2$O)] (**8**).* Greenish yellow; yield 51%; m.p. 212-215 ºC; anal. calcd. (%) for $C_{19}H_{18}BrCoN_3O_6$ (523.20): C, 43.62; H, 3.47; N, 8.03. Found: C, 43.80; H, 3.40; N, 8.10%; IR (KBr) ν_{max}/cm^{-1} 3535 (O-H), 3184 (N-H, L'), 1719 (C=O, L'), 1707 (C=O, L'), 1662 (C=O free, L^3), 1601 (C=O coordinated, L^3), 1582 (C=N, L^3), 584 (Co-N), 481 (Co-O); UV-Vis. λ = 659, 544 nm; magnetic moment (μ_{eff}/B.M.): 4.87; molar conductivity (Ω^{-1} cm^2 mol^{-1}): 16.9.

*[MnL'L^3(OH)(H$_2$O)] (**9**).* Green; yield 45%; m.p. 215-218 ºC; anal. calcd. (%) for $C_{19}H_{18}BrMnN_3O_6$, (519.20): C, 43.95; H, 3.49; N, 8.09. Found: C, 44.10; H, 3.40; N, 8.15%; IR (KBr) ν_{max}/cm^{-1} 3545 (O-H), 3182 (N-H, L'), 1721 (C=O, L'), 1712 (C=O, L'), 1661 (C=O free, L^3), 1602 (C=O coordinated, L^3), 1582 (C=N, L^3), 571 (Mn-N), 472 (Mn-O); ^{1}H NMR (DMSO-d_6, δ ppm) 2.32 (s, 3H, CH_3CO free, L^3), 2.60 (s, 3H, CH_3CO coordinated, L^3), 6.74-7.58 (m, 8H, aromatic, L' and L^3), 10.21 (s, 1H, NH, D_2O exchangeable, L'); UV-Vis. λ = 755, 621, 524 nm; magnetic moment (μ_{eff}/B.M.): 5.87; molar conductivity (Ω^{-1} cm^2 mol^{-1}): 17.3.

Antibacterial activities

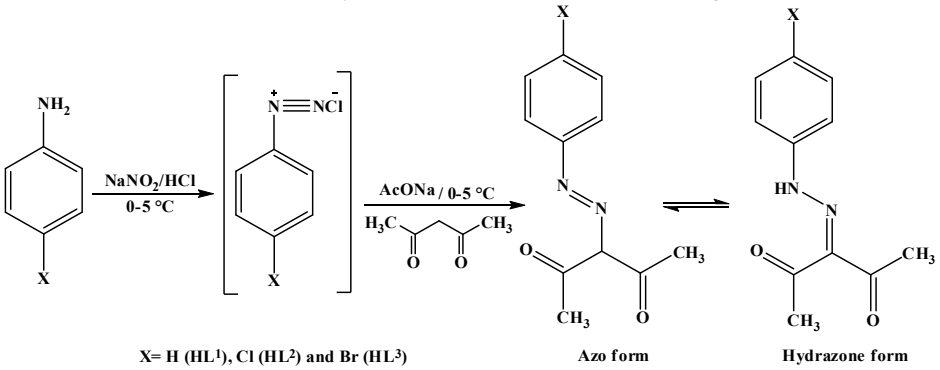
Mn(II), Co(II) and Ni(II) complexes of mixed isatin with 3-(2-(aryl)hydrazono)acetylacetone **1-9** were screened *in vitro* for their antibacterial activities against two Gram-positive bacteria

species (*Bacillus subtilis*, *Staphylococcus aureus*) and two-Gram negative bacteria species (*Escherichia coli*, *Pseudomonas aeruginosa*) using a modified Kirby-Bauer disc diffusion method [30]. The bacteria were maintained on Meuller-Hinton agar. DMSO showed no inhibition zone. The agar media were incubated at 35-37 ^{o}C for 24-48 hours for bacteria. The diameter of inhibition zone in millimeter (mm) was measured. Tetracycline is used as a reference for antibacterial activities.

RESULTS AND DISCUSSION

Chemistry

3-(Arylhydrazono)acetylacetone (**HL**) [26-28] is prepared *via* coupling between diazotized aromatic amine derivatives and acetylacetone in a 1:1 molar ratio according to Scheme 1.



Scheme 1

3-(Arylhydrazono)acetylacetone (**HL**) and isatin (**L'**) were reacted with hydrated metal(II) chloride in equimolar ratios (1:1:1) for formation the complexes **1-9** having the general structural formula [ML′L(OH)(H_2O)] (Scheme 2) [29].

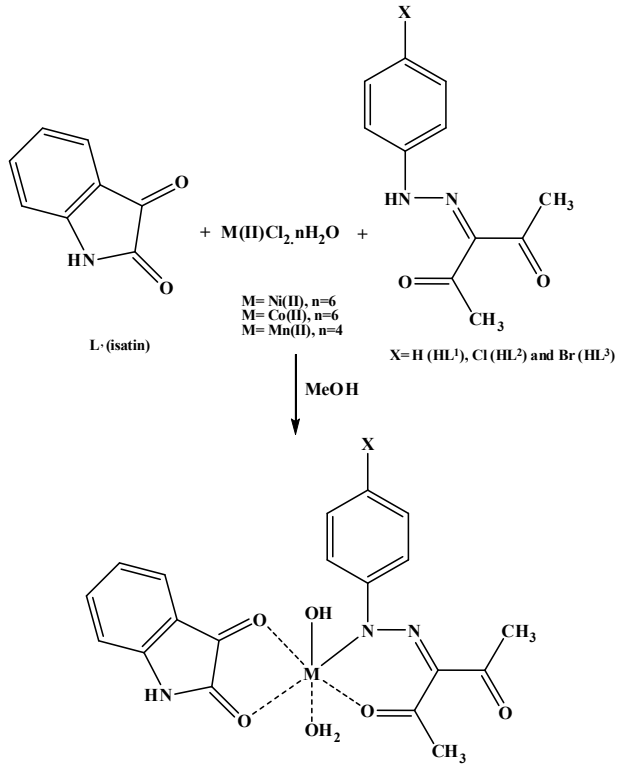
In vitro antibacterial activities

The antibacterial activities of the mixed ligand metal complexes **1-9** against two-Gram negative bacteria species (*Escherichia coli* and *Pseudomonas aeruginosa*) and two Gram-positive bacteria species (*Bacillus subtilis* and *Staphylococcus aureus*) using a modified Kirby-Bauer disc diffusion method [30] are represented in Table 1. The results revealed that the metal complexes exhibited moderate activities.

In case of *E. coli* (G-), all the mixed metal complexes exhibited moderate activities in the range of inhibition zone diameter from 9 to 13 mm. The two complexes **3** and **4** (IZ = 13 mm) were more active than all the other tested complexes. In case of *P. aeruginosa* (G-), the three mixed metal complexes **3**, **5** and **8** (IZ = 13 mm) were more active than all the other tested complexes. By testing the mixed metal complexes against two Gram-positive bacteria species (*Bacillus subtilis* and *Staphylococcus aureus*), complex **6** was more potent (IZ = 13 mm) than the other tested complexes.

In general, all the mixed metal complexes **1-9** exhibit moderate activities against the four bacteria species used in this study.In particular, the two complexes [MnL'L^1(OH)(H_2O)] **(3)** and [MnL'L^2(OH)(H_2O)] **(6)** which having Mn(II) metal in their structures. May be the introduction

the Mn(II) metal in the structure increasing the activities. Therefore, in the future, we will modify the mixed metal complexes to obtain more active antibacterial agents.



Complexes **1-9**

Complexes	M(II)	X	Complexes	M(II)	X
1	Ni	H	**6**	Mn	Cl
2	Co	H	**7**	Ni	Br
3	Mn	H	**8**	Co	Br
4	Ni	Cl	**9**	Mn	Br
5	Co	Cl			

Scheme 2

Lipinski's rule of five (RO5) of the mixed ligand metal complexes

Lipinski's rule of five (RO5), is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has chemical properties and physical properties that would make it a likely orally active drug in humans. The rule was formulated by Christopher A. Lipinski in 1997, based on the observation that most orally administered drugs are relatively small and moderately lipophilic molecules [31-32].

The molecular weight (MW ≤ 500), lipophilicity (*M*Log*P* ≤ 4.15), the number of hydrogen bond acceptors (nHBA ≤ 10) and donors (nHBD ≤ 5) of Lipinski's rule of five were calculated

using SwissADME web (http://swissadme.ch/index.php#undefined). The computed molecular properties are shown in Table 2.

Table 1. Antibacterial activities of the mixed ligand metal complexes **1-9**.

Complexes No.	Inhibition zone diameter (IZ) in millimeters			
	Gram-negative		Gram-positive	
	E. coli	*P. aeruginosa*	*B. subtilis*	*S. aureus*
Complex **1**	9	10	10	9
Complex **2**	11	11	10	11
Complex **3**	13	13	12	12
Complex **4**	13	12	11	12
Complex **5**	12	13	12	11
Complex **6**	11	12	13	13
Complex **7**	10	9	11	10
Complex **8**	9	13	12	12
Complex **9**	10	10	11	9
Tetracycline	32	34	32	30

Compound: >14 mm, significant activity; 7-13 mm, moderate activity; < 7 mm, weak activity.

Table 2. Lipinski's rule of five for the mixed ligand metal complexes **1-9**.

The mixed ligand metal complexes	MW[a]	*M*LogP[b]	*n*HBA[c]	*n*HBD[d]	$n_{violations}$[e]
Rule	<500	≤4.15	≤10	≤5	0
Complex **1**	444.06	-0.86	7	3	0
Complex **2**	444.30	-0.86	7	3	0
Complex **3**	440.31	-0.86	7	3	0
Complex **4**	478.51	-0.36	7	3	0
Complex **5**	478.75	-0.36	7	3	0
Complex **6**	474.75	-0.36	7	3	0
Complex **7**	522.96	-0.25	7	3	1, MW>500
Complex **8**	523.20	-0.25	7	3	1, MW>500
Complex **9**	519.20	-0.25	7	3	1, MW>500

[a]Molecular weight; [b]Calculated lipophillicity (*M*Log $P_{o/w}$); [c]Number of hydrogen bond acceptor; [d]Number of hydrogen bond donor; [e]Violations from Lipinski's Rule.

From Table 2, all the mixed ligand metal complexes agreement with Lipinski's rule of five,where the metal complexes **1-6** in the range of the Lipinski's rule (MW ≤ 500, MLogP ≤ 4.15, nHBA ≤ 10 and nHBD ≤ 5) expected the three metal complexes **7-9**, where the molecular weight of the complexes **7-9** more than 500.

CONCLUSION

In conclusion, we have synthesized the Mn(II), Co(II) and Ni(II) complexes of mixed isatin with 3-(2-(aryl)hydrazono)acetylacetone **1-9**. All the mixed ligand complexes were screened for their *in vitro* antibacterial activity. The evaluation showed that, among the tested complexes, the five complexes **3**, **4**, **5**, **6** and **8** were the most active complexes against a panel of pathogenic tested organisms. Also, the mixed ligand metal complexes **1-6** agreement with Lipinski's rule of five.

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