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"SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF NOVEL DIHYDROXYBEZALDEHYDE DERIVATIVES OF 4-AMINOPYRROLO [2, 3-*d*] PYRIMIDINE"

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Abstract
The main aims of this work were to prepare new pyrrolopyrimidine compounds, analyse their properties, and assess their effectiveness against bacteria and fungi. The objective of this study was to synthesise dihydroxybenzaldehyde derivatives of the pyrrolopyrimidine. The synthesised compounds were characterised using spectroscopic techniques. The synthesised compounds were evaluated for their antimicrobial efficacy against four bacterial strains and two yeast strains, namely, *S. aureus* MCC 2010, *B. subtilis* MCC 2010, *E. coli* MCC 2412, *P. aeruginosa* MCC 2080, *C. albicans* MCC 1439, and *S. cerevisiae*. Each of the synthesised compounds exhibited prominent peaks in FT(IR), ^{1}H and ^{13}C NMR, and UV spectral studies. The compound **2a** was proven to have greater antibacterial and antifungal activity in vitro compared to the gold standards *streptomycin* and *fluconazole*.

Keywords: 2,6-dihydroxy benzaldehyde, 4-aminopyrrolo[2,3-*d*]pyrimidine, Antibacterial activity

1. Introduction:

The significance of pyrimidines and associated chemicals is generally recognised. Pyrimidines and purines are the predominant heteroaromatic compounds occurring in nature. Pyrrolopyrimidine (PPRD) derivatives are of interest to researchers due to their pharmacological and chemotherapeutic implications. Heterocycles that are fused and share structural similarities with them are of interest due to their potential bioactive characteristics. Some of the recognised biological roles of these substances include inhibiting enzyme activity [1], causing cell death [2], fighting against viruses [3], reducing inflammation [4-6], alleviating allergies [7], combating tumours [8-12], and acting as antibacterial and antifungal agents [13]. This work presents the synthesis and antibacterial properties of a new group of PPRD compounds derived from dihydroxy benzaldehydes, as determined by our research.

Experimental:

Unless explicitly specified, all items were obtained from commercial sources and utilised in their raw, unprocessed states. The TLC testing utilised silica gel plates. Not all melting points have been calibrated for precision. The spectral region between 4000 and 500 cm^{-1} in the KBr pellet FT(IR) spectra was obtained using a BRUKER FT-IR spectrophotometer. The UV spectra were obtained by utilising a JASCO V650 spectrophotometer in a methanol solution at room temperature. Brucker ^{1}H NMR spectra were acquired in DMSO d_6 at a frequency of 400 MHz, using TMS as the internal

standard. The contents of carbon (C), hydrogen (H), and nitrogen (N) were all within a 0.4% margin of their expected values across the whole sample set. **Table 1** presents an overview of the statistical information for the artificially prepared compounds. The spectrum information is displayed in **Tables 2, 3**, and **4**.

Preparation of PPRD derivatives 2(a and **b):**
After refluxing for 3 hours in a solution of 50 ml of ethanol and 0.5 ml of strong hydrochloric acid (HCl), a mixture comprising 10 mmol of PPRD and 10 mmol of dihydroxy benzaldehyde derivatives (**a-b**) was obtained. The end products obtained were **2a-b**, which underwent filtration, methanol washing, and drying.

PPRD-2,6-dihydroxy benzaldehyde (2a):
Colour, Yellow; M.W., 243; Yield (%), 69.35; M.P. (°C), 198; Element content: C, 61.41; H, 3.96; N, 22.04; O, 12.59. FT-IR (cm^{-1}): 3322 (-OH), 3109 (NH), 3029 (C-H), 1586/1480 (>C=C<), 1674 (>C=N-), 1333 (C-N), 724 (trisubstituted benzene ring (TSBR)), 688 (monosubstituted benzene ring (MSBR)). ^{1}H NMR (ppm): 11.1 (Ar-OH), 10.83 (aro-NH), 9.22 (-CH=), 7.43-7.72 (aromatic amine), UV spectrum (λ_{nm}): 295 ($\pi \rightarrow \pi^*$), 360 ($n \rightarrow \pi^*$).

PPRD-3,5-dihydroxy benzaldehyde (2b):
Colour, Yellow; M.W., 246; Yield (%), 72.33; M.P. (°C), 195; Element content: C, 61.41; H, 3.96; N, 22.04; O, 12.59. FT-IR (cm^{-1}): 3383 (-OH), 3118 (NH), 2993 (C-H), 1582/1475 (>C=C<), 1655 (>C=N-), 1330 (C-N), 725 (TSBR), 695 (MSBR). ^{1}H NMR (ppm): 11.17 (Ar-OH), 10.88 (aro-NH), 9.21 (-CH=), 7.48-7.72 (aromatic amine), UV spectrum (λ_{nm}): 233 ($\pi \rightarrow \pi^*$), 327 ($n \rightarrow \pi^*$).

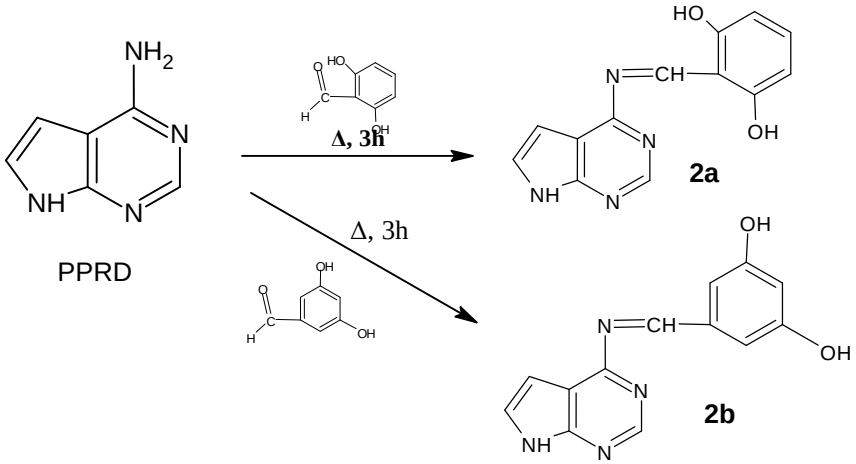

Figure 1: The synthesis of dihydroxybenzaldehyde-PPRD derivatives

Test Microorganisms:
The synthesised compounds were assessed for their antibacterial efficacy against two gram-positive bacteria and two gram-negative bacteria. The Muller Hilton agar medium was sterilised using autoclaving at a pressure of 15 pounds per square inch for a duration of 15 minutes, to prepare it for antimicrobial testing. To ascertain the presence of antibacterial characteristics in the newly synthesised compounds, researchers employed the disc diffusion technique [14]. The initial culture was diluted to a concentration of approximately 108 colony-forming units per millilitre (cfu/mL) by suspending it in sterile distilled water. The culture of each microbial strain was transferred onto a Petri dish containing 20 mL of Muller Hilton agar medium and let to incubate for a duration of 15 minutes. The wells, with a diameter of 6 mm, were created using a sterile borer. Then, 100 L of a solution containing each drug at a concentration of 4.0 mg/mL was added to the infected plates. Following a 24-hour incubation period at a temperature of 37 °C, the contents of all the plates were examined. The

antibacterial activity of all synthesised compounds was evaluated by measuring the diameter of the zone of inhibition surrounding the wells. *Streptomycin* served as the positive control, whereas DMF served as the negative control.

Determination of MIC:

The MICs of all compounds were determined using the modified disc diffusion method15. Compounds were synthesised with concentrations ranging from 10 g/mL to 1000 g/mL using a stock solution of 4 mg/mL in DMF. The microorganism under examination is plated onto agar at a concentration of 100 µL, using a standard inoculum of 108 cfu/mL. Triplicate wells are then inoculated with each dilution. After 24 hours of incubation at 37 ℃, the plates were examined for the presence of inhibitory zones. *Streptomycin* has been employed as a reference standard.

Antifungal Activity:

The compounds underwent testing against two distinct fungal species (*C. albicans* 1439 and *S. cerevisiae* MCC1033) utilising the cup-and-plate method [16-17]. The test solution was pipetted onto discs with a diameter of 5 mm and a thickness of 1 mm using micropipettes. Subsequently, the plates were incubated at a temperature of 37 °C for a duration of 72 hours. Throughout this duration, the test solution had sufficient time to spread evenly throughout the substance and influence the growth of the fungus that was infected. The size of the inhibitory zone was evaluated after 36 hours of incubation at 37 °C. The minimal inhibitory doses of promising compounds against fungus were investigated. The minimum inhibitory concentration (MIC) of an antifungal drug was defined as the lowest dosage at which observable inhibition of microbiological growth took place after a 24-hour incubation period. Clinical laboratories utilise the minimum inhibitory concentration (MIC) to verify the resistance of microorganisms to antimicrobial agents and assess the effectiveness of new antimicrobials.

***In vitro* cytotoxicity:**

The cytotoxicity of synthesised compounds was assessed through a bioassay employing brine prawns. We placed prawn eggs on one side of the tank, while on the other side, we provided artificial saltwater consisting of 38 grammes of sodium chloride per 1000 millilitres of tap water. Within a span of 48 hours, the prawn eggs underwent hatching and then progressed into nauplii. The recently hatched prawns were removed for examination. Various concentrations (2.5, 5.0, 7.5, 10.0, and 12.0 mg/10 mL) of dehydrated complexes were put in individual test tubes. The cytotoxicity of the complexes was assessed by dissolving them in DMSO. Each test tube contained a total of 10 live prawns that were transferred using a Pasteur pipette. To confirm the dependability of the cytotoxic activity test and its outcomes, a control group was included. Following a 24-hour incubation period, the tubes were scrutinised using a microscope, and detailed observations were recorded regarding the observed phenomena and the number of surviving nauplii. Each experiment consisted of three sets of duplicates, resulting in a total of five. Using the available data, we successfully calculated the LC50, 95% confidence interval, LC_{90}, and chi-square value. Abbott's formula [19] was employed to make adjustments to the figures to take into consideration the deaths of the controls.

Results and Discussion:

When subjected to reflux conditions for a duration of 2-5 hours, PPRD undergoes a reaction with dihydroxybenzaldehydes, leading to the formation of these compounds. The target compounds were obtained with yields ranging from 69.35% to 72.33%. The process for synthesising dihydroxybenzaldehydes-PPRD derivatives is illustrated in **Figure 1**. The synthesised compounds exhibit compatibility with a wide range of organic solvents while being incompatible with water. The elemental analysis data confirms that all derivatives possess the expected compositions. The compounds are pigmented powders that exhibit negligible moisture absorption. The compound's purity was assessed using TLC following its synthesis.

FT(IR) spectra:

The effectiveness of the PPRD bond to dihydroxybenzaldehydes was determined by examining the FT(IR) spectra of the synthesised compounds and free PPRD. We conducted a study on the impact of PPRD vibration on substituted dihydroxybenzaldehydes by carefully selecting relevant bands. The azomethine group (HC=NN-), indicated by a spectral region between 1655-1674 cm^{-1}, appeared as a distinct and significant band. This confirms the formation of all the synthesised compounds and demonstrates that the presence of aldehyde (CHO) and amino (NH_2) groups in the amino derivatives inhibits their stretching vibrations. The identification of a consistent spectral range at 3109–3118 cm^{-1}, which has been determined to be associated with aromatic (NH) molecules, indicates the existence of these compounds in their processed states [21,22]. The spectral range from 2993 to 3029 cm^{-1} exhibits distinctive features of aldehydic compounds. The infrared spectra of **2a–b** compounds exhibit two distinct bands, located at 1582–1586 and 1475–1480 cm^{-1}, respectively. These bands are associated with the >C=C functional group present in the aromatic ring. The FT(IR) spectra of compounds **2a-b** exhibited the presence of the aromatic (C-N) band within the range of 1330-1333 cm^{-1}. Additionally, a di/trisubstituted benzene ring was detected at 724-725 cm^{-1}, whereas a monosubstituted benzene ring was found at 688-695 cm^{-1}.

^{1}H NMR spectra:

Every substance can be identified by its ^{1}H NMR spectra. In this case, the presence of a -NH- group in the pyrrolyl ring is indicated by the occurrence of significant singlet signals ranging from 10.83 to 10.88 ppm. The singlet peaks for all of the generated compounds can be observed within the intervals of 11.15-11.17 ppm (aromatic -OH) and 9.21-9.22 ppm (aldehydic -CH=). To verify the successful substitution of the amino group by Schiff base [23], we examine the ^{1}H NMR spectra of all synthesised derivatives. We observe a broad singlet signal at 9.84ppm (2H), which corresponds to the -NH_2 group of 4-chloro-7H-pyrrolo[2, 3-d] pyrimidine. The ^{1}H NMR spectra are consistent with the previous data [23,24].

UV-Visible spectra:

The synthesised compounds **2a-b** were dissolved in DMF and their UV spectra were recorded at ambient temperature. The **2a-b** aromatic band, with a wavelength range of 233-295 nm, is a result of the $\pi \rightarrow \pi^*$ transition occurring in the benzene ring. The non-bonding electrons on the nitrogen of the azomethine groups in compounds **2a-b** undergo an $n \rightarrow \pi^*$ transition, resulting in a band that extends to a wavelength range of 327-360 nm.

Antibacterial studies:

The synthesised compounds were evaluated for their antibacterial activity using in vitro testing against a range of bacterial and fungal species. All the compounds tested in the antibacterial screening exhibited minimum inhibitory concentration (MIC) values ranging from 12.5 to 22.5 millimetres against *S. aureus, B. subtilis, E. coli*, and *P. aeruginosa*. The synthesised compounds exhibited higher inhibitory values (ranging from 18.5 to 20.5 mm) against *Staphylococcus aureus* compared to streptomycin.

Compound	Antibacterial Activity (zone of inhibition)			
	S. aureus	***B. subtilis***	***E. coli***	***P. aeruginosa***
2a	20.5	12.5	22.5	17.5
2b	18.5	19.0	16.5	21.5
Streptomycin	15.5	14.5	12.0	14.0

Antifungal studies:

The synthesised compounds exhibited approximately 2 times greater efficacy than the reference drug *fluconazole* (22.5-24.0 mm) in antifungal studies conducted on two fungi, namely C. *albicans* MCC1439 and *S. cerevisiae* MCC1033.

Compound	*Candida albicans*	*Saccharomyces cerevisiae*
2a	24.0	22.5
2b	23.5	23.0
Fluconazole	10.5	14.0

***In vitro cytotoxicity*:**
All of the synthesised compounds exhibited cytotoxic activity against Artemia salina, with LD50 values ranging from 8.50 to 9.50 x10^{-4} M/mL [25-28].

Table 3: Brine shrimp bioassay of **2a-h** compounds

Compound	LD_{50} (M)
2a	$>9.50 \times 10^{-4}$
2b	$>8.50 \times 10^{-4}$

Conclusion

We have successfully synthesised a variety of novel derivatives of substituted dihydroxybenzaldehydes (**1a-b**) using PPRD as the basis for our work. The synthesis of the proposed compounds is supported by analytical data, spectral studies, and electrochemical data. The benzaldehyde-based compounds that were generated were examined using spectrum analysis and elemental analysis, namely for carbon (C), hydrogen (H), nitrogen (N), and oxygen (O). Based on the results, it is recommended to mix PPRD with dihydroxybenzaldehydes in a 1:1 ratio. Each compound that was synthesised had strong antibacterial activity. Upon examination using sensitive cell lines, it was shown that all of the synthesised compounds exhibited significant cytotoxicity.

References:

[1] C.T. Supuran, A. Scozzafava, B.C. Jurca, M.A. Iiies, Synthesis of substituted ureido and thioureido derivatives of aromatic/heterocyclic sulfonamides with increased affinities for isozyme I. European Journal of medicinal chemistry, Synthesis of substituted ureido and thiourea derivatives of aromatic/heterocyclic sulfonamides with increased affinities for isozyme I, Euro J of Med Chem. 33:2, (1998) 83-93. https://doi.org/10.1016/S0223-5234(98)80033-0

[2] G. Mangalagiu, M. Ungureanu, G. Grousu, I. Nangalagiu, M. Petrovanu, New pyrrolo-pyrimidine derivatives with antifungal or antibacterial properties in vitro Pharm. Fr. 59 (2001) 139-140.

[3] C.V. Varaprasad, K.S. Ramasamy, J.L. Girardet, E. Gunic, V. Lai, W. Zhong, H. An, Z. Hong, Synthesis of new pyrrolo[2,3-d]pyrimidine derivatives as antibacterial and antifungal agents, Chem. Pharm. Bull. 56 (2008) 1617. https://doi.org/10.1016/j.ejmech.2010.08.043.

[4] C.V. Varaprasad, K.S. Ramasamy, J.L. Girardet, E. Gunic, V. Lai, W. Zhong, H. An, Z. Hong, Synthesis of pyrrolo[2,3-d]pyrimidine nucleoside derivatives as potential anti-HCV agents, Bioorg. Chem. 35 (2007) 25-34. https://doi.org/10.1016/j.bioorg.2006.07.003.

[5] M.A. Ivanov, A.V. Ivanov, I.A. Krasnitskaya, O.A. Smirnova, I.L. Karpenko, E.F. Belanov, V.S. Prasolov, V.L. Tunitskaya, L.A. Alexandrova, New furano- and pyrrolo[2,3-d]pyrimidine nucleosides and their 5′-O-triphosphates: Synthesis and biological properties, Russ. J. Bioorg. Chem. 34 (2008) 593–601. https://doi.org/10.1134/S1068162008050099.

[6] M.S. Mohamed, A.E. Rashad, M. Adbel-Monem, S.S. Fatahalla, Z. Naturforsch C; New Anti-Inflammatory Agents, Zeitschrift für Naturforschung C. 62 (2007) 27-31. https://doi.org/10.1515/znc-2007-1-205.

[7] S. Nagashima, T. Hondo, H. Nagata, T. Ogiyama, J. Maeda, H. Hoshii, T. Kontani, S. Kuromitsu, K. Ohga, M. Orita, K. Ohno, A. Moritomo, K. Shiozuka, M. Furutani, M. Takeuchi, M. Ohta, S. Tsukamoto, Novel 7H-pyrrolo [2, 3-d] pyrimidine derivatives as potent and orally active STAT6 inhibitors, Bioorg. Med. Chem. 17(2009) 6926-6936. https://doi.org/10.1016/j.bmc.2009.08.021.

[8] B.A. Harrison, N.A. Whitlock, M.V. Voronkov, Z.Y. Almstead, K.J. Gu, R. Mabon, M. Gardyan, B.D. Hamman, J. Allen, S. Gopinathan, B. McKnight, M. Crist, Y. Zhang, Y. Liu, L.F. Courtney,

B. Key, J. Zhou, N. Patel, P.W. Yates, Q. Liu, A.G. Wilson, S.D. Kimball, C.E. Crosson, D.S. Rice, D.B. Rawlins, iscovery of bis-aryl urea derivatives as potent and selective Limk inhibitors, J. Med. Chem. 52(2009) 7464-7477. https://doi.org/10.1016/j.bmc.2015.10.041.

[9] S.I. Alqasoumi, M.M. Ghorab, Z.H. Ismail, S.M. Abdel-Gawad, M.S. El-Gaby, H.M. Aly, Novel antitumor acetamide, pyrrole, pyrrolopyrimidine, thiocyanate, hydrazone, pyrazole, isothiocyanate and thiophene derivatives containing a biologically active pyrazole moiety, Arzneimittel-Forschung. 59 (2009) 666-671. DOI: 10.1055/s-0031-1296457.

[10] M.H. Jung, H. Kim, W.K. Choi, M.I. El-Gamal, J.H. Park, K.H. Yoo, T.B. Sim, S.H. Lee, D. Baek, J.M. Hah, J.H. Cho, C.H. Oh, Synthesis of pyrrolo [2, 3-d] pyrimidine derivatives and their antiproliferative activity against melanoma cell line, Bioorg. Med. Chem. Lett. 19 (2009) 6538-6543. https://doi.org/10.1016/j.bmcl.2009.10.051.

[11] Y. Asukai, A. Valladares, C. Camps, E. Wood, K. Taipale, J. Arellano, A. Cassinello, J.A. Sacristán, T. Dilla, Synthesis of pyrrolo [2, 3-d] pyrimidine derivatives and their antiproliferative activity against melanoma cell line, BMC Cancer. 10 (2010) 6538-6543. https://doi.org/10.1016/j.bmcl.2009.10.051.

[12] T. McHardy, J.J. Caldwell, K.-M. Cheung, L.J. Hunter, K. Taylor, M. Rowlands, R. Ruddle, A. Henley, A. de-Haven Brandon, M. Valenti, T.G. Davies, L. Fazal, L. Seavers, F.I. Raynaud, S.A. Eccles, G.W. Aherne, M.D. Garrett, I. Collins, Discovery of 4-amino-1-(7 H-pyrrolo [2, 3-d] pyrimidin-4-yl) piperidine-4-carboxamides as selective, orally active inhibitors of protein kinase B (Akt), J. Med. Chem. 53 (2010) 2239-2249. https://doi.org/10.1021/jm901788j.

[13] M.S. Mohamed, R.A. El-Domany, R.H. Abd El-Hameed, Synthesis of certain pyrrole derivatives as antimicrobial agents, Acta Pharm. 59 (2009) 145-158. https://doi.org/10.2478/v10007-009-0016-9.

[14] Magaldi S., Mata-Essayag S., Hartung de Capriles C., Perez C., Colella M., Olaizola C. and Ontiveros Y., Well diffusion for antifungal susceptibility testing, Int J of Infectious Diseases. 1 (2004) 39-45. doi:10.1016/j.ijid.2003.03.002.

[15] Adeyemi A. I., Vincent I. I., and Olujenyo O. M., Phytochemical screening and antifungal activity of Chromolaena odorata extracts against isolate of Phytophthora megakarya using agar-well diffusion method, Asian J of Med and Bio Res. 4:1 (2018), 7-13. doi:10.3329/ajmbr.v4i1.36815.

[16] Kumar A. and Mishra A., Synthesis and antimicrobial activity of some new diphenylamine derivatives, J of Pharma and Bioallied Sci. 7:1 (2015):81. doi:10.4103/0975-7406.148774.

[17] Nath A. R. and Reddy M. S., Design, Synthesis, Antibacterial and Antifungal Activity of Novel 2-[(E)-2-aryl-1-ethenyl]-3-(2-sulfanyl-1H-benzo[d]imidazole-5-yl)-3,4- dihydro-4-quinolinones, E-J. of Chem. 9:3 (2012) 1481-1489. doi:10.1155/2012/795698.

[18] Marimuthu alias Antonysamy J., Janarthanan G., Arumugam S., Narayanan J. and Mani N., Antioxidant, Larvicidal, and Cytotoxic Studies on Asplenium aethiopicum (Burm. f.) Becherer, Int Scholarly Res Notices. 2014(2014). doi:10.1155/2014/876170.

[19] Abbott W. S., A Method of Computing the Effectiveness of an Insecticide, J. of Eco Entomology. **18:2** (1925) 265. doi:10.1093/jee/18.2.265a.

[20] A. R. Moosavi-Zare, H. Goudarziafshar, K. Saki, Synthesis of pyranopyrazoles using nano-Fe-[phenylsalicylaldiminemethylpyranopyrazole]Cl2 as a new Schiff base complex and catalyst, Applied Organometallic Chemistry. 32.1 (2017) e3968. https://doi.org/10.1002/aoc.3968.

[21] M. Singh, A. K. Paul, V. Singh, Isatin as a 2-aminobenzaldehyde surrogate: transition metal-free efficient synthesis of 2-(2′-aminophenyl) benzothiazole derivatives, Org & Biomolecular Chem. 18:23 (2020) 4459-4469. doi:10.1039/d0ob00888e.

[22] S. M. Abd El-Hamid, S. A. Sadeek, W. A. Zordok, W. H. El-Shwiniy, W. H., Synthesis, spectroscopic studies, DFT calculations, cytotoxicity and antimicrobial activity of some metal complexes with ofloxacin and 2,2′-bipyridine, J. of Mol Str. (2018). doi:10.1016/j.molstruc.2018.08.08.

[23] Singh M., Paul A. K. and Singh V., Isatin as a 2-aminobenzaldehyde surrogate: transition metal-free efficient synthesis of 2-(2′-aminophenyl) benzothiazole derivatives, Org & Biomol. Chem., **18:23** (2020) 4459. doi:10.1039/d0ob00888e.

[24] Abd El-Hamid S. M., Sadeek S. A., Zordok W. A. and El-Shwiniy W. H., Synthesis, spectroscopic studies, DFT calculations, cytotoxicity and antimicrobial activity of some metal complexes with ofloxacin and 2,2′-bipyridine, J. of Mole Str. 1176 (2019) 422-433. doi:10.1016/j.molstruc.2018.08.08.

[25] El Sayed Aly M. R., Abd El Razek Fodah H. H. and Saleh S. Y., Antiobesity, antioxidant and cytotoxicity activities of newly synthesized chalcone derivatives and their metal complexes, Eur. J. of Med. Chem. 76 (2014): 517-530. doi:10.1016/j.ejmech.2014.02.021.

[26] Milbeo P., Quintin F., Moulat L., Didierjean C., Martinez J., Bantreil X. and Lamaty F., Synthesis, characterisation and cytotoxic activity evaluation of new metal-salen complexes based on the 1,2-bicyclo[2.2.2]octane bridge, Tetrahedron Letters. 63 (2021): 152706. doi:10.1016/j.tetlet.2020.152706.

[27] Guney E., Yilmaz V. T., Ari F., Buyukgungor O. and Ulukaya E.,Synthesis, characterization, structures and cytotoxic activity of palladium(II) and platinum(II) complexes containing bis(2-pyridylmethyl)amine and saccharinate, Polyhedron. 30, no. 1 (2011) 114-122. doi:10.1016/j.poly.2010.09.037.

[28] Atta E. M., Hegab K. H., Abdelgawad A. A. M. and Youssef A. A., Synthesis, characterization and cytotoxic activity of naturally isolated naringin-metal complexes, Saudi Pharmaceutical J. 27:4 (2019): 584-592. doi:10.1016/j.jsps.2019.02.006.