



# Synthesis and Characterization of Some Complexes of Azo-Chalcone Ligand and Assessment of their Biological Activity

HASAN SHAMRAN MOHAMMED\*

University of Al-qadisiyah, Science College, 58002, Al-qadisiyah, Iraq

**Abstract.** The azo-chalcone dye of theophylline namely (E)-1-(4-((E)-(theophyllin-8-yl) diazenyl)phenyl)-3-(4-dimethylaminophenyl)prop-2-en-1-one (TDPP) has been prepared and characterized by H-NMR, infrared, and electronic spectra, elemental analysis. Three solid complexes Mn(II), Ni(II) and Cu(II) of TDPP dye have been prepared and characterized by IR, electronic spectra, magnetic and conductivity measurements. The antibacterial and antifungal activities of the TDPP ligand and metal (II) complexes of Ni, and Cu are notable, with the copper(II) complex being more potent than the others. The TDPP ligand has interesting spectral properties as a pH sensor, solvent polarity sensor, and switches.

**Keyword:** chalcone, biological activity, Azo dye, pH sensor, photochromism

## 1. Introduction

The chalcones are important classes of compounds widely used as antibacterial, anti-inflammatory, antifungal, anti-tubercular, antioxidant, antiviral, antitumor, anti-Alzheimer's disease agents and antimalarial [1–3]. The chalcone compounds synthesized under clean conditions such as under room temperature, small amount of solvent, high yield, and it is possible under ultrasound irradiation which is considered reactions of green chemistry doing fast under neat conditions [4].

All plant kingdom, fruits, vegetables and other plants have flavonoids that have chalcone structure [5–7]. Chalcones show trans (E) and cis (Z) isomers but in general trans isomer is more stable thermodynamic than cis isomer because there is high steric effect in structure of the cis isomer [6,8]. The vanadyl VO(II) complexes of chalcones which derivatives from benzaldehyde and acetophenone show activity against types of bacteria such as *E. coli* and *Staphylococcus aureus* and against fungus such as *P. notatum* [9]. Ruthenium (II) chalcone complexes show binds with DNA through major groove of the DNA [10].

Azo dyes and their complexes show large applications in medical, dying sensor devices and indicators in chemistry. The 2-aminothiazole azo dye complexes exhibited antimicrobial activity in vitro against positive Gram bacteria such as *Bacillus subtilis*, negative Gram bacteria such as *Escherichia coli*, and against the yeast such as *Candida albicans* and fungus such as *Aspergillus favus* [11].

Chalcones and azo dyes are important classes of compounds appearing photochemistry applications which consider good photochromism based on forming a trans-cis isomerization process [12,13]. Azo-chalcone hybrids exhibited wide spectrum biological properties and photochemistry properties [14,15]. Diazenyl having chalcone exhibited activity against different microorganisms [16] and gave excellent fastness properties on fibre and polyester [17].

Therefore, based on the promising biological activity of chalcones and azo compounds in the medicine and Industrial fields, we attempt to synthesize azo chalcone theophylline (E)-1-(4-((E)-(theophyllin-8-yl) diazenyl)phenyl)-3-(4-dimethylaminophenyl)prop-2-en-1-one and its complexes of manganese, nickel and copper ions in divalent state and screening for their biological activities.

## 2. Materials and methods

Electronic spectra of TDPP dye and its complexes were assessed by UV-Vis, T80, PG instruments Ltd. IR spectra were done by (FTIR)-Platinum utilizing KBr disk in the range of (400-4000)  $\text{cm}^{-1}$ . Molar conductivity measurements of TDPP complexes were performed on 720(WTW). Mass spectrum of

\*email: [Hasan.sh.mohammed@qu.edu.iq](mailto:Hasan.sh.mohammed@qu.edu.iq)

TDPP dye was done by AB SCIEX 3200 QTRAP Mass analyzer. The elemental analysis C.H.N of TDPP dye and its complexes were done by Costech ECS Elemental 4010. Magnetic measurements of complexes carried out by Balance Magnetic Susceptibility Model - M.S.B Auto. A Bruker Avance-111 300 MHz NMR Sp. was used to record the  $^1\text{H-NMR}$  spectrum of TDPP dye in DMSO- $d_6$  solvent. The metal chlorides ( $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ ,  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  and  $\text{CuCl}_2$ ) were from Merck, theophylline, 4-dimethylaminobenzaldehyde, and 4-aminoacetophenone were from the B.D.H company.

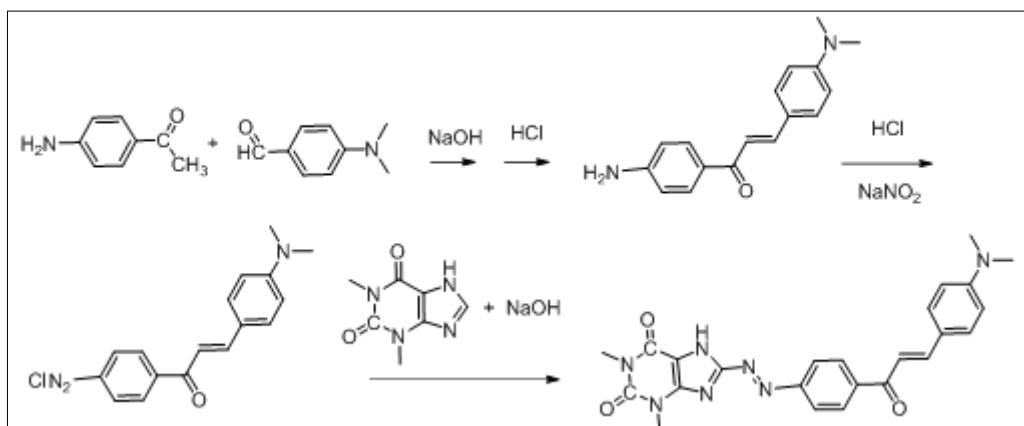
The chalcone dye synthesized under stirring for 3h by mixing 4-aminoacetophenone (1g, 0.0067 mole) with 4-dimethylaminobenzaldehyde (0.9 g, 0.0067 mole) in 30 mL ethanol in an alkaloid medium (KOH 0.5 g). The reaction mixture was neutralized by adding hydrochloric acid under cooling. The solution filtrated off, the yield was 90 %, bright orange powder. Azo-chalcone dye (TDPP) synthesized under cooling at  $0^\circ\text{C}$  by mixing diazoinium salt of chalcone dye (0.5 g, 0.0018 mole of chalcone dye in 10 mL water with 3 mL HCl mixed with 0.13 g, 0.0018 mole of sodium nitrite under cooling) with 10 ml aqueous solution of theophylline (0.32g, 0.0018 mole) in alkaline medium (NaOH 0.5 g). Azo-chalcone dye was dark red powder, 60% yield. We also synthesized Azo-chalcone dye (TDPP) by diazotization of 4-aminoacetophenone then coupling with theophylline to form azo dye then coupling with 4-dimethylaminobenzaldehyde to form chalcone but the yield was low.

Complexes preparation: The dye complexes were made in the same way, by combining 0.2 g, 0.43 mmole dye dissolved in 30 mL ethanol with 0.21 mmole metal chloride (0.04g, 0.05 g and 0.02g corresponding to  $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ ,  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  and  $\text{CuCl}_2$  respectively dissolving in 5 mL distillate water, and then refluxing the mixture solution for 45 min. The solution was then filtered, and the precipitate was dried in a desiccator.

Elemental analyses (C.H.N %) for TDPP dye,  $\text{C}_{25}\text{H}_{26}\text{N}_7\text{O}_3$ : C 63.55 (experimental 62.95), H 5.55 (5.45), N 20.75 (20.45), mp  $123.7^\circ\text{C}$ , IR, red powder. Mn complex  $\text{MnC}_{50}\text{H}_{52}\text{N}_{14}\text{O}_6\text{Cl}_2$ : C 56.08 (55.95), H 4.89 (4.35), N 18.31 (18.24), dark marron powder, m.p. more than  $350^\circ\text{C}$ , Yield 70. Ni complex  $\text{NiC}_{50}\text{H}_{52}\text{N}_{14}\text{O}_6\text{Cl}_2$ : C 55.88 (55.65), H 4.88 (4.67), N 18.25 (18.16), m.p. more than  $350^\circ\text{C}$ , dark brown powder, yield 65%. Cu complex  $\text{CuC}_{50}\text{H}_{52}\text{N}_{14}\text{O}_6\text{Cl}_2$ : C55.63 (55.56), H 4.86 (4.67), N 18.17 (18.04), dark grey, m.p  $152^\circ\text{C}$ , yield 75%.

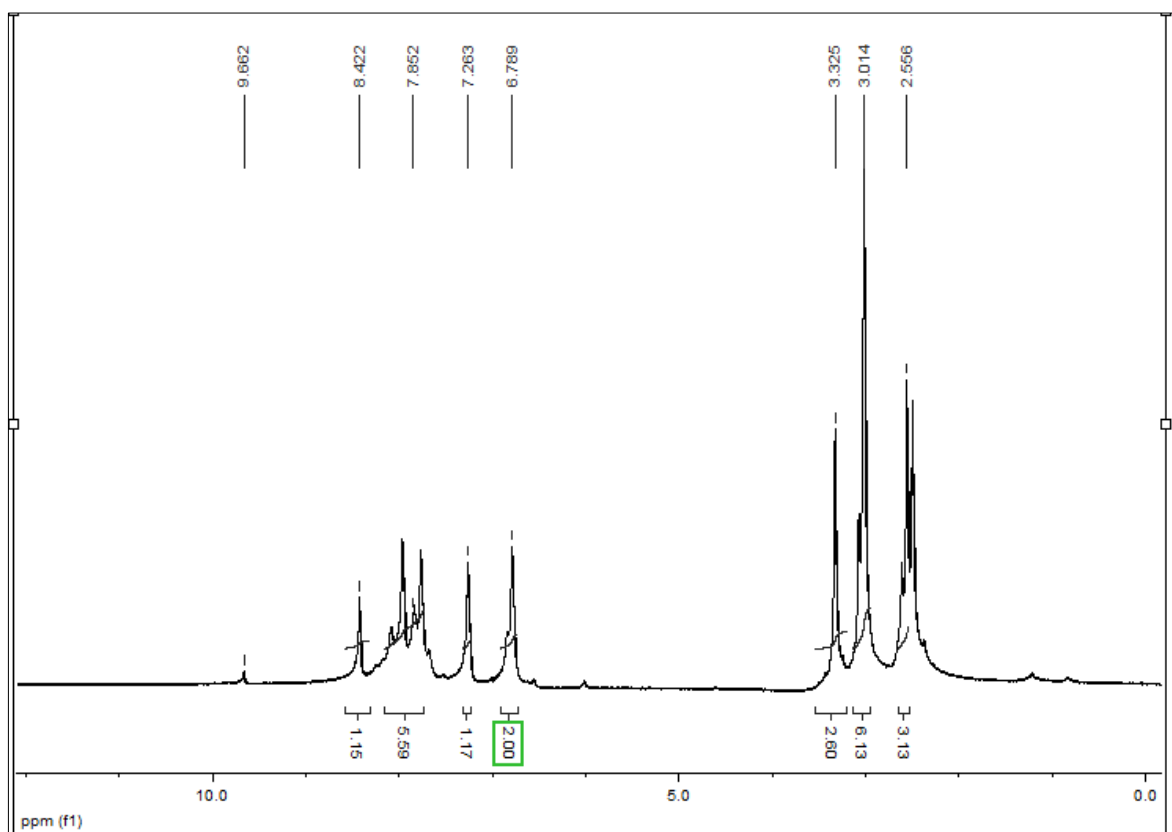
### 3.Results and discussions

Theophylline's azo-chalcone dye (TDPP) was made in two steps (Scheme 1), the first stage involved reacting 4-aminoacetophenone with 4-dimethylaminobenzaldehyde in ethanol with sodium hydroxide to produce orange chalcone with a 90% yield. The second stage included diazotization of chalcone followed by the diazotization salt of chalcone with an aqueous solution of theophylline in basic medium, resulting in a dye yield of 60%.



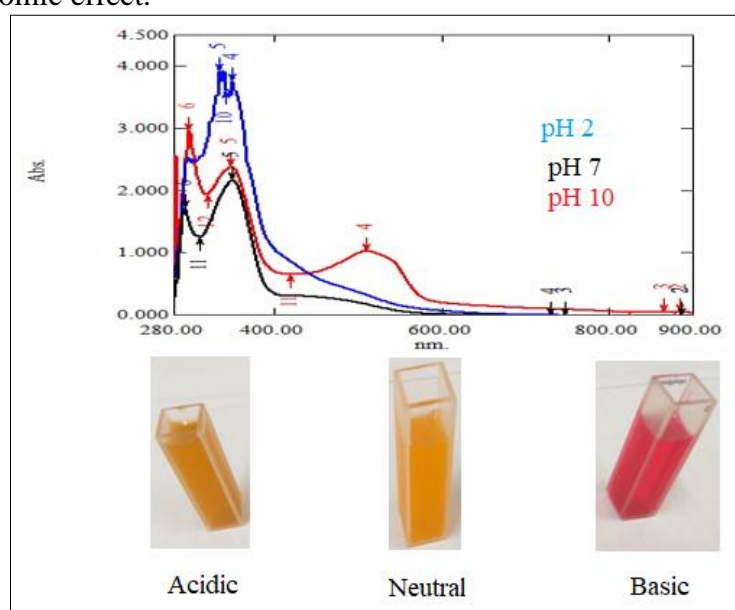
**Scheme 1.** Preparation steps of azo-chalcone dye (TDPP) of theophylline

$^1\text{H-NMR}$  spectrum of (TDPP) as shown in Figure 1, the TDPP dye exhibited the following chemical shift, 9.66 (s, 1H), 8.42 (d, 1H), 7.85 (multi, 6H), 7.26 (d, H), 6.78 (d, 2H), 3.32 (s, 3H), 3.01 (s, 6H), 2.55 (s, 3H), which is in agreement with protons number of the TDPP dye.



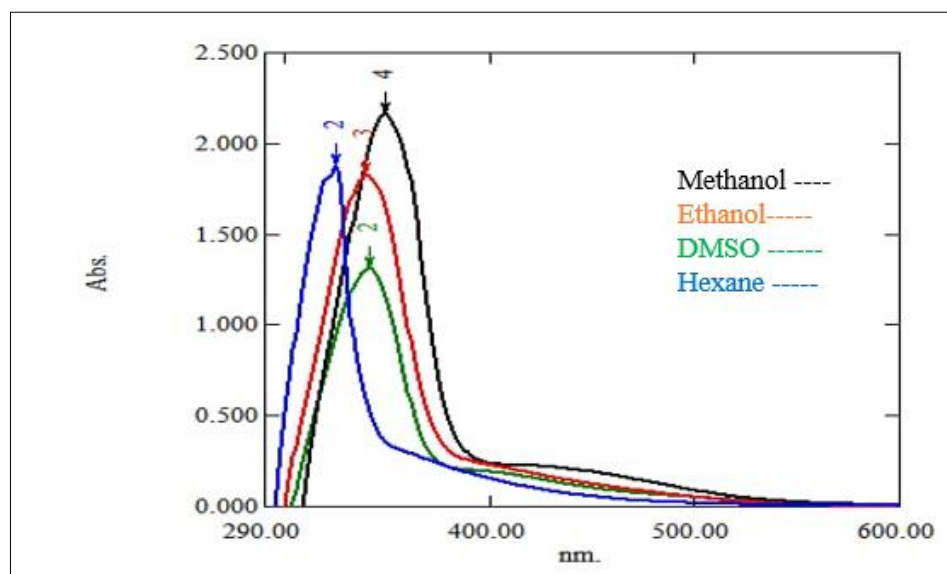
**Figure 1.**  $^1\text{H-NMR}$  spectrum of TDPP dye in DMSO (d6) at room temperature

Under various  $p\text{H}$  values, the color and electronic properties of TDPP dye changed drastically as shown in Figure 2. The TDPP dye showed orange color in neutral aqueous, red color in basic aqueous with red shift and hyperchromic effect, and dark orange in acidic aqueous accompanied with little bit red shift and hyperchromic effect.



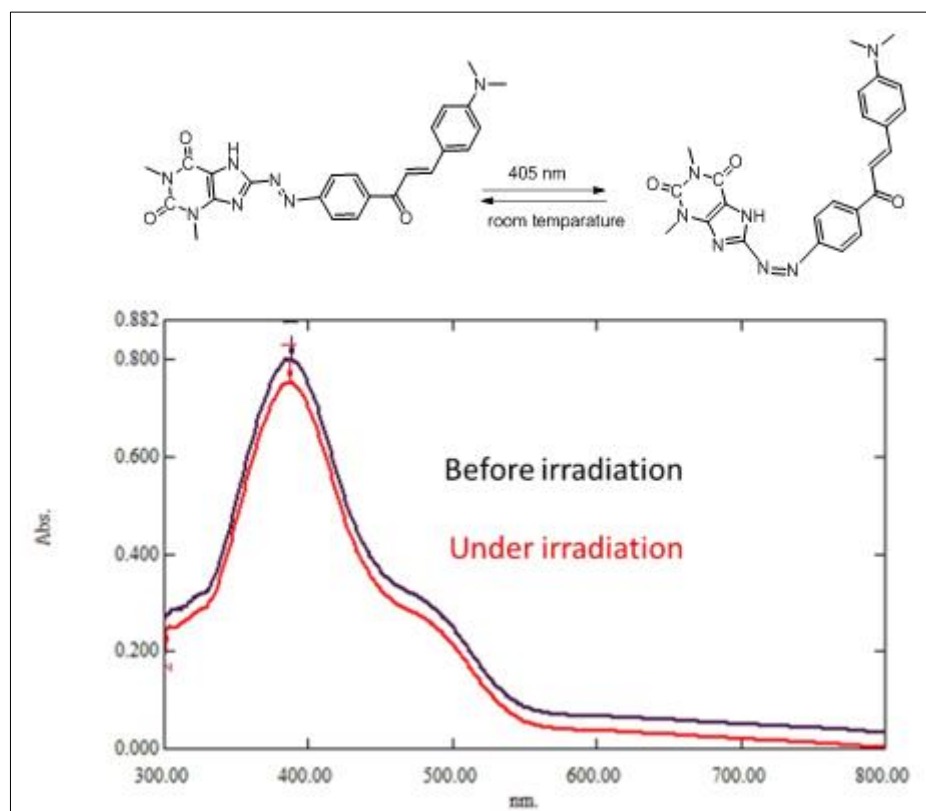
**Figure 2.** The colors and electronic spectra of TDPP under different values of  $p\text{H}$

The TDPP dye exhibited red shift under increasing the polarity from hexane, DMSO, and ethanol to methanol as shown in (Figure 3).



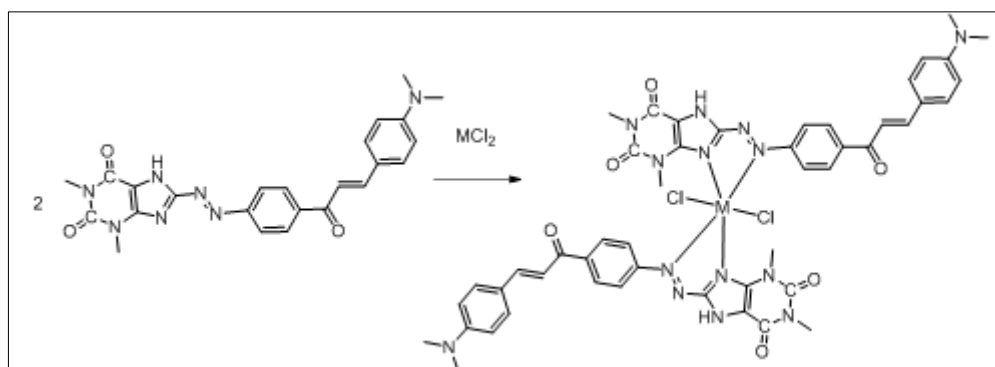
**Figure 3.** Polarity Effect of solvents on TDPP dye

Theophylline's azo-chalcone dye (TDPP) showed actual photochromic behaviour (Figure 4) when exposed to 395 nm light, with trans azo converting to cis isomer with contribution from the converted trans chalcone isomer to cis under irradiation [18–20]. The new spectra of dye returned to the original spectra over time when the light was removed, which is consistent with real photochromic behaviour [21].

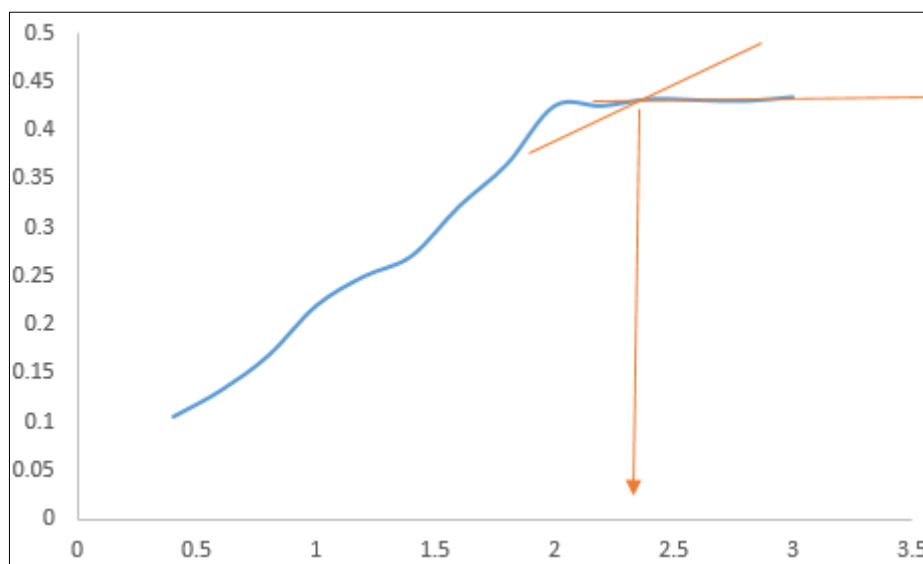


**Figure 4.** Electronic spectra of TDPP dye under irradiation at 395 nm

The complexes of Mn, Ni and Cu divalent ions of TDPP dye were prepared as shown in (Scheme 2) by reacting a hot solution of TDPP dye and hot solution of metal chloride of Mn, Ni and Cu divalent under mole ratio equal to 1:2 (M:Dye) which was suggested depending on mole ratio results as shown in Figure 5 for Mn (II) complex.



**Scheme 2.** Preparation steps of complexes of TDPP dye where M = Mn(II), Ni(II) and Cu(II)

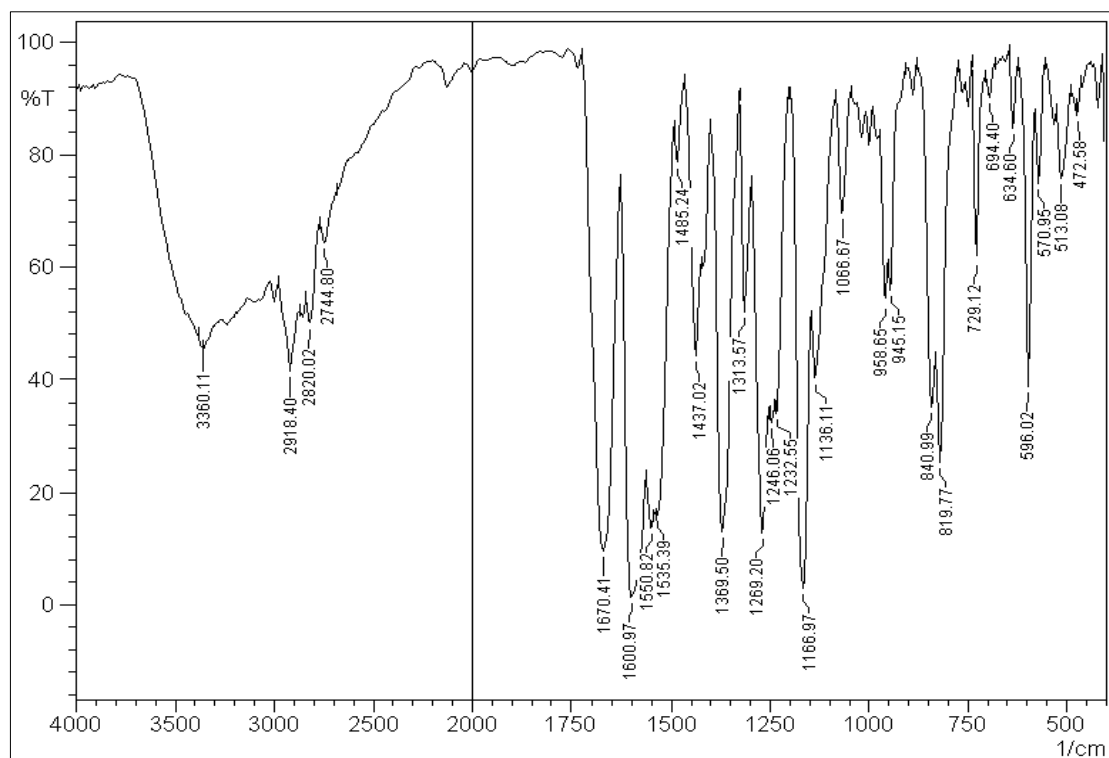


**Figure 5.** Mole ratio results for Mn (II) complex with TDPP dye

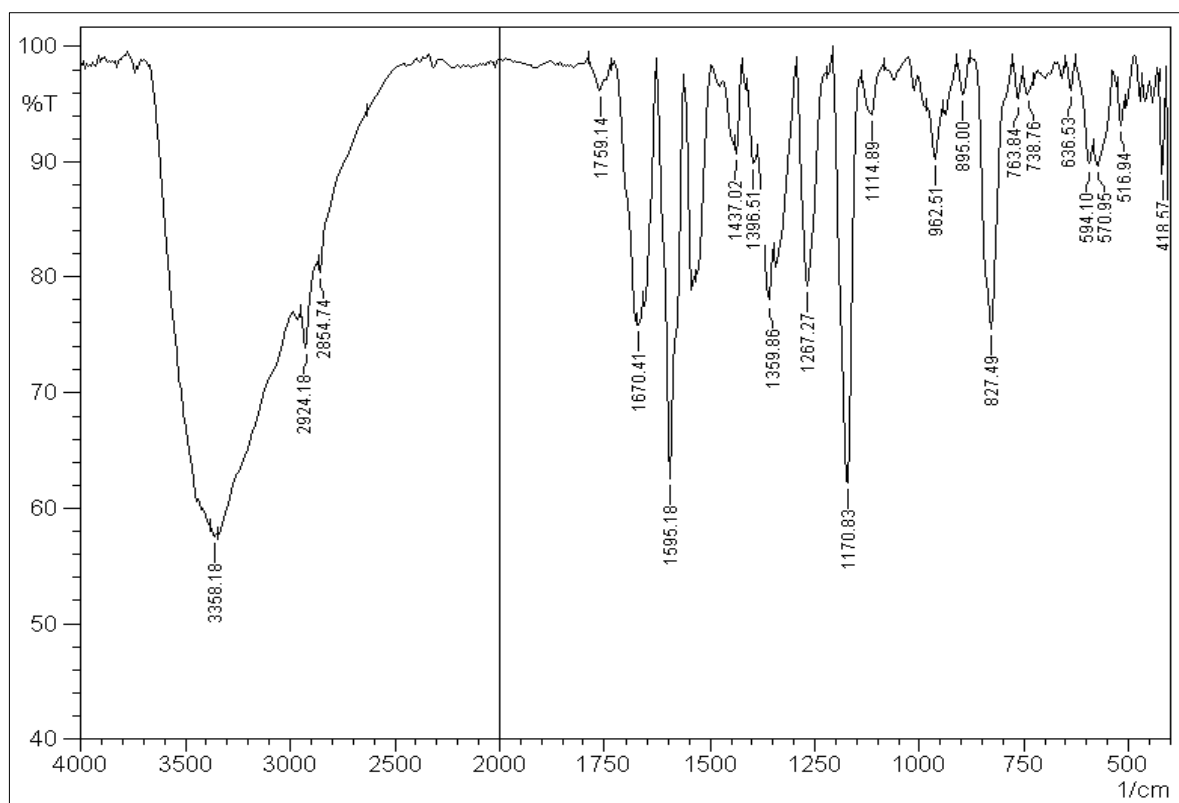
Infrared spectra of TDPP dye and its complexes exhibited important functional groups which are depicted in Table 1 such as N-H, CH aromatic and aliphatic, C=O, C=N, C=C, azo group. The basic differences between the spectra of dye (Figure 6) and the spectra of complexes like the spectrum of Mn complex (Figure 7) are that the peaks of imine (C=N) and azo groups suffered down (red shift) around 5-19  $\text{cm}^{-1}$ , indicating that these groups associated with metal ions.

**Table 1.** The infrared frequencies of TDPP dye and its complexes in KBr billet

Compound	N-H	CH aromatic	CH aliphatic	C=O	C=N	C=C	N=N	CH scissoring	CH bending
TDPP dye	3360	3060	2918, 2820	1670	1600	1550	1535	1369	1166, 819, 729,
Mn complex	3358	3060	2924, 2854	1670	1595	1550	1521	1359	1117, 962, 827
Ni complex	3352	3065	2920, 2830	1672	1591	1553	1516	1365	1160, 819, 730
Cu complex	3358	3060	2926, 2830	1670	1589	1550	1519	1360	1172, 821, 720



**Figure 6.** Infrared spectrum of azo-chalcone dye (TDPP) of theophylline

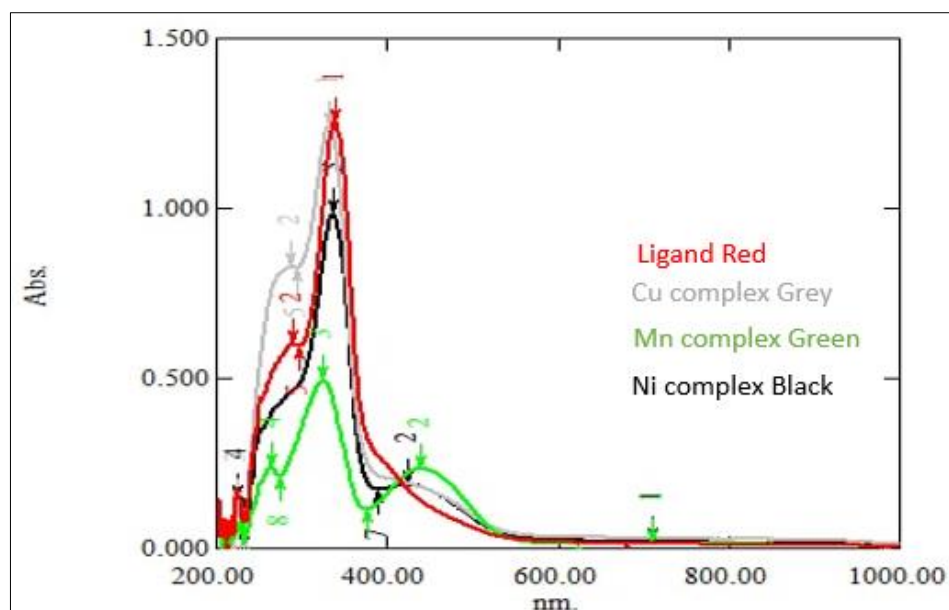


**Figure 7.** Infrared spectrum of Mn complex of azo-chalcone dye (TDPP)

The electronic spectra of the complexes of TDPP dye as shown in (Figure 8) were done in ethanol at room temperature. The electronic spectrum of TDPP dye exhibited band at 339 nm due to  $\pi \rightarrow \pi^*$  and another band is a shoulder at 405 nm due to  $n \rightarrow \pi^*$ . The electronic spectrum of manganese (II) of TDPP dye exhibited band at 324 nm due to  $\pi \rightarrow \pi^*$  of ligand and the second band was at 460 nm due to

and another band was at 723 nm. The magnetic susceptibility was 5.65 B.M. in agreement with the environment of the octahedral complex of manganese (II). The electronic spectrum of nickel complex of TDPP dye exhibited bands at 250 nm and 339 nm due to  $\pi \rightarrow \pi^*$  of TDPP dye in complex, and a band at 451 nm due to  ${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(P)$  and a band at 728 due to  ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$  of d-d transition of octahedral complex of nickel (II). The magnetic susceptibility was 3.35 B.M. in agreement with the environment of the octahedral complex of nickel (II).

The electronic spectrum of copper complex of TDPP dye exhibited three bands at 332 nm due to  $\pi \rightarrow \pi^*$  of TDPP dye in complex, and a band at 469 nm due to  ${}^2B_{1g} \rightarrow {}^2E_g$  and another band at 724 nm due to  ${}^2B_{1g} \rightarrow {}^2A_{1g}$  of d-d transition of octahedral complex of copper (II). The magnetic susceptibility was 1.87 B.M. in agreement with the environment of the octahedral complex of copper (II).



**Figure 8.** Electronic spectrum of TDPP dye of theophylline in DMF at room temperature

### Biological activity

The antimicrobial activity of the synthesized ligand (TDPP dye) and its metal complexes were tested against two local bacterial organisms, Gram positive bacteria (*Staphylococcus aureus*) and Gram negative bacteria (*Escherichia coli*) (Table 2). The antibacterial efficacy of synthesized compounds of TDPP dye was investigated (*Staphylococcus aureus* and *Escherichia coli*). The copper compound seemed to be selective against the bacteria. The copper complex had the highest inhibition zone and antibacterial efficacy against the bacteria. Nickel complex also exhibited high inhibition zone and antibacterial efficacy against *Staphylococcus aureus*. The ligand and other complexes did not show activity against all of gram +ve bacteria and gram -ve bacteria.

**Table 2.** Inhibition zone (cm) of TDPP dye and its complexes against types of bacteria

Compound	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>
TDPP dye	-	-
Mn complex	-	-
Ni complex	5.25	-
Cu complex	6	7.5



## 4. Conclusions

A new azo-chalcone dye of theophylline namely (E)-1-(4-((E)-(theophyllin-8-yl) diazenyl)phenyl)-3-(4-dimethylaminophenyl)prop-2-en-1-one (TDPP) and its complexes of Mn(II), Ni(II) and Cu(II) were synthesized and characterized. The TDPP dye exhibited a bathochromic shift under increasing the polarity of solvents. The UV-Vis spectral changes of TDPP dye indicated that light-induced trans to cis isomerization and reverse isomerism from cis to trans around the -N=N- bond with contribution from cis chalcone to trans chalcone isomer at room temperature. Antimicrobial experiments on a number of bacteria show that the complexes TDPP are more effective bactericides than the TDPP ligand and have high efficiency.

## References

1. ILLICACHI, L.A., MONTALVO-ACOSTA, J.J., INSUASTY, A., QUIROGA, J., ABONIA, R., SORTINO, M., ZACCHINO, S., INSUASTY, B., Synthesis and DFT Calculations of Novel Vanillin-Chalcones and Their 3-Aryl-5-(4-(2-(dimethylamino)-ethoxy)-3-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde Derivatives as Antifungal Agents. *Molecules* **2017**, *22*.
2. YADAV, N., DIXIT, S.K., BHATTACHARYA, A., MISHRA, L.C., SHARMA, M., AWASTHI, S.K., BHASIN, V.K., Antimalarial activity of newly synthesized chalcone derivatives in vitro. *Chemical biology & drug design* **2012**, *80*, 340–347.
3. BAI, P., WANG, K., ZHANG, P., SHI, J., CHENG, X., ZHANG, Q., ZHENG, C., CHENG, Y., YANG, J., LU, X., Development of chalcone-O-alkylamine derivatives as multifunctional agents against Alzheimer's disease. *European Journal of Medicinal Chemistry* **2019**, *183*, 111737.
4. ADOLE, V.A., JAGDALE, B.S., PAWAR, T.B., SAGANE, A.A., Ultrasound promoted stereoselective synthesis of 2, 3-dihydrobenzofuran appended chalcones at ambient temperature. *South African Journal of Chemistry* **2020**, *73*, 35–43.
5. GOMES, M.N., MURATOV, E.N., PEREIRA, M., PEIXOTO, J.C., ROSSETO, L.P., CRAVO, P.V., ANDRADE, C.H., NEVES, B.J., Chalcone derivatives: promising starting points for drug design. *Molecules* **2017**, *22*, 1210.
6. K SAHU, N., S BALBHADRA, S., CHOUDHARY, J., V KOHLI, D., Exploring pharmacological significance of chalcone scaffold: a review. *Current medicinal chemistry* **2012**, *19*, 209–225.
7. ZHUANG, C., ZHANG, W., SHENG, C., ZHANG, W., XING, C., MIAO, Z., Chalcone: a privileged structure in medicinal chemistry. *Chemical reviews* **2017**, *117*, 7762–7810.
8. AKSÖZ, B.E., ERTAN, R., Chemical and structural properties of chalcones I. *FABAD J Pharm Sci* **2011**, *36*, 223–242.
9. BORGE, V.V., PATIL, R.M., Stability of Vanadium Chalcone Complexes. In *Stability of Coordination Compounds*; IntechOpen, 2020.
10. GAUR, R., KHAN, R.A., TABASSUM, S., SHAH, P., SIDDIQI, M.I., MISHRA, L., Interaction of a ruthenium(II)-chalcone complex with double stranded DNA: Spectroscopic, molecular docking and nuclease properties. *Journal of Photochemistry and Photobiology A: Chemistry* **2011**, *220*, 145–152.
11. VENUGOPAL, N., KRISHNAMURTHY, G., NAIK, H.B., MANOHARA, J.D., DNA Binding, Molecular Docking and Antimicrobial Evaluation of Novel Azo Dye Ligand and Their Metal Complexes. *Journal of Inorganic and Organometallic Polymers and Materials* **2020**, *30*, 2608–2625.
12. LEYDET, Y., BATAT, P., JONUSAUSKAS, G., DENISOV, S., LIMA, J.C., PAROLA, A.J., MCCLENAGHAN, N.D., PINA, F., Impact of water on the cis-trans photoisomerization of hydroxychalcones. *The Journal of Physical Chemistry A* **2013**, *117*, 4167–4173.
13. LIU, Q., JIN, L.-X., LU, J.-F., The electric memory properties of azo-chalcone derivatives based on different film forming processes. *Journal of Molecular Structure* **2020**, 129480.
14. WEI, H., RUAN, J., ZHANG, X., Coumarin-chalcone hybrids: promising agents with diverse pharmacological properties. *RSC Adv.* **2016**, *6*, 10846–10860.





15. KAUR, H., SINGH, J., NARASIMHAN, B., Antimicrobial, antioxidant and cytotoxic evaluation of diazenyl chalcones along with insights to mechanism of interaction by molecular docking studies. *BMC Chemistry* **2019**, *13*, 87.
16. SIVASANKERREDDY, L., NAGAMANI, B., RAJKUMAR, T., BABU, M.S., SUBBAIAH, N.Y., HARIKA, M.S., NAGESWARAO, R., Novel Diazenyl Containing Phenyl Styryl Ketone Derivatives as Antimicrobial Agents. *Anti-Infective Agents* **2019**, *17*, 28–38.
17. OMAR, A.Z., MAHMOUD, M.N., EL-SADANY, S.K., HAMED, E.A., EL-ATAWY, M.A., A combined experimental and DFT investigation of mono azo thiobarbituric acid based chalcone disperse dyes. *Dyes and Pigments* **2021**, *185*, 108887.
18. CRESPI, S., SIMETH, N.A., KÖNIG, B., Heteroaryl azo dyes as molecular photoswitches. *Nature Reviews Chemistry* **2019**, *3*, 133–146.
19. SIDHARTH, S.N., YUVARAJ, A.R., HUI, T.J., SAROJINI, B.K., MASHITAH, M.Y., HEGDE, G., Light induced properties of chalcones correlated with molecular structure and photophysical properties for permanent optical storage device. In Proceedings of the Advanced Materials Research; Trans Tech Publ, 2014; Vol. 1033, pp. 1149–1153.
20. LIN, L.-R., TANG, H.-H., WANG, Y.-G., WANG, X., FANG, X.-M., MA, L.-H., Functionalized lanthanide (III) complexes constructed from azobenzene derivative and  $\beta$ -diketone ligands: Luminescent, magnetic, and reversible trans-to-cis photoisomerization properties. *Inorganic chemistry* **2017**, *56*, 3889–3900.
21. COELHO, P.J., CARVALHO, L.M., FONSECA, A.M.C., RAPOSO, M.M.M., Photochromic properties of thienylpyrrole azo dyes in solution. *Tetrahedron Letters* **2006**, *47*, 3711–3714.

---

Manuscript received: 5.05.2021