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Charge-transfer chemistry of azithromycin, the antibiotic used worldwide to treat the coronavirus disease (COVID-19). Part III: A green protocol for facile synthesis of complexes with TCNQ, DDQ, and TFQ acceptors

Abdel Majid A. Adam, Hosam A. Saada, Amnah M. Alsuhaibani, Moamen S. Refata, Mohamed S. Hegab

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1. Introduction

Coronaviruses (CoVs) belong to the Coronaviridae family and Coronavirinae subfamily, which is composed of four genera, α-CoVs, γ-CoVs, β-CoVs, and δ-CoVs. The first CoV outbreak in humans occurred in China in 2003 and was termed severe acute respiratory syndrome coronavirus (SARS-CoV). The second outbreak, known as Middle East respiratory syndrome coronavirus (MERS-CoV), was first identified in the Middle East in 2012 [1,2]. The third outbreak, first described in Wuhan, China on December 9, 2019, was caused by a novel CoV named SARS coronavirus 2 (SARS-CoV-2). This most recent outbreak is the first with pandemic potential in non-immune populations in the 21st century [3]. SARS-CoV-2, believed to have originated from a seafood market in Wuhan, spread very quickly throughout China and then around the globe, thereby causing a destabilizing global pandemic [4]. The World Health Organization (WHO) named the disease caused by this novel virus the Coronavirus disease 2019 (COVID-19) and announced it as a global pandemic on March 12, 2020 [5]. One year later, more than 93 million people worldwide have been definitively diagnosed with COVID-19 (23.6 million in the USA), 2 million of which have since died. To date, no gold standard treatment or vaccine exists to effectively combat this contagious, life-threatening condition. Many pharmacologically effective molecules are being investigated for antiviral efficacy against SARS-CoV-2 (e.g., lopinavir/ritonavir, remdesivir, tocilizumab, azithromycin, hydroxychloroquine, chloroquine, etc.). Azithromycin, a member of the macrolide class of antibiotics, has shown promising results when used to treat COVID-19 (Fig. 1a). Azithromycin has a broad spectrum of antibacterial properties that render it highly effective against both G+ and G- bacteria. Moreover, its anti-inflammatory, antiviral, immunomodulatory, and antimalarial properties make it particularly well-suited to not only reign in this novel, highly contagious virus but also to mitigate the life-threatening symptoms (i.e., COVID-19) associated with its infection [6-9]. The use of this antibiotic has been strongly recommended and widely implemented to treat COVID-19 worldwide.
either alone or in combination with chloroquine and its derivative hydroxychloroquine [10-18].

Charge-transfer complexes (CTCs) contribute to many important applications in biology, chemistry, physics, and industry [19-40]. Every year, extensive research efforts are dedicated to producing new CTCs, investigating their properties (e.g., kinetic, photo-physical, thermodynamic, crystallographic, spectral), determining which factors affect the CT interactions (e.g., time, temperature, type of solvent, time, concentration), and exploring and developing novel applications [26,41-64]. Exploring the modifiability of azithromycin and the chemistry underlying the formation of these novel derivatives could provide insight into the mechanisms underlying this antibiotic’s efficacy, which could help to optimize its application to the treatment of COVID-19. As a continuation of our previous works [65,66] that aim to furnish a big-picture perspective on the CT chemistry of azithromycin by examining its interactions with several σ- and π-acceptors and the resultant CTCs, in this work, we describe a highly efficient, straightforward, and environmentally friendly protocol for the facile synthesis of CTCs between azithromycin and three π-acceptors (TCNQ, DDQ, and TFQ; Fig. 1b).

2. Experimental

2.1. Reagents

The starting reagents used for the synthesis of the CTCs were commercially available and analytical grade chemicals obtained from BDH (United Kingdom) and Sigma-Aldrich (USA) chemical companies and used without any additional purification. Azithromycin powder (C38H72N2O12; 748.98 g/mol; purity 98%) and acceptors were prepared at a concentration of 1 × 10⁻³ M in methanol solvent. The free azithromycin solubilized in methanol solvent. The solubilized azithromycin donor molecule and TCNQ, DDQ, and TFQ acceptors were attempted by grinding their solid powders on a dry, clean porcelain mortar using a pestle under the following reaction conditions:

- Starting reagent: solvent-free, solid–solid interaction
- Temperature: ambient
- Time: ~3 min
- Stoichiometry: 1:1 (donor to acceptor)

2.2. Analytical instrumentation

The elemental composition of the synthesized CTCs were analyzed using a Perkin-Elmer 2400CHN Elemental Analyzer to determine their hydrogen, carbon, and nitrogen content (%). The NMR (¹H and 13C), FTIR, and UV–visible spectra of the synthesized CTCs were registered with Bruker DRX-250 Digital FT-NMR, Shimadzu FTIR, and Perkin – Elmer Lambda 25 UV/Vis spectrophotometers, respectively, at room temperature. The electronic spectra were collected from the CTCs solubilized in methanol from 200 to 800 nm, while solid-state CTCs were used to collect FTIR spectra in the 400 to 4000 cm⁻¹ range. At 400 MHz, the Bruker DRX-250 instrument generated the ¹H and 13C NMR spectra of the solid-state CTCs in DMSO-d₆ solution, where the chemical shift values are presented in δ scale relative to the internal reference tetramethylsilane (TMS).

2.3. Synthetic protocol

Complexation of the azithromycin donor with the TCNQ, DDQ, and TFQ acceptors was attempted by grinding their solid powders on a dry, clean porcelain mortar using a pestle under the following reaction conditions:

- Starting reagent: solvent-free, solid–solid interaction
- Temperature: ambient
- Time: ~3 min
- Stoichiometry: 1:1 (donor to acceptor)

3. Results and discussion

3.1. Preliminary steps

Three preliminary steps should be conducted prior to preparing the CTCs of azithromycin by the solid–solid interaction. These steps are: i) observe whether a color change occurs upon mixing azithromycin with each acceptor in solution, ii) analyze the λₜₐ of the CTCs in solution by UV–visible spectroscopy, and iii) verify the composition of azithromycin and each acceptor in solution for use in the preparation of the CTCs through solid–solid interactions.

3.1.1. Color change

Before preparing the azithromycin-based CTCs using solid–solid interactions, it’s necessary to observe the CT interaction between the solubilized azithromycin donor molecule and TCNQ, DDQ, and TFQ acceptors. The physical property most indicative of a CT interaction is color, which changes upon combining the donor and acceptor. To observe the changing color after mixing azithromycin with each of the acceptors, solutions of azithromycin and the acceptors were prepared at a concentration of 1 × 10⁻³ M in methanol solvent. The free azithromycin solubilized in methanol was coreless. In methanol solvent, the TCNQ acceptor had a light green color, the DDQ acceptor had a brown color, and the TFQ acceptor had a pale brown color. Striking color changes visible to the naked eye occurred when azithromycin was mixed with each acceptor at ambient temperature at a 1:1 ratio. The color changed from light green to pale brown in the resultant CTC with TCNQ (Fig. 2), from brown to intense red in the resultant CTC with DDQ (Fig. 3), and from pale brown to canary yellow in the resultant CTC with TFQ (Fig. 4). These types of color changes areindicative of strong CT interactions between azithromycin and all of the acceptors, reflecting the strong donating property of azithromycin and the strong accepting properties of TCNQ, DDQ, and TFQ. Indeed, the azithromycin molecule bears several electron-donating groups such as methoxy, hydroxy, ether, and carboxyl groups, as well as two nitrogen atoms [-N(CH₃)₂, -N(CH₃)]; the TCNQ, DDQ, and TFQ acceptor molecules contain different types of electron-withdrawing groups. The TCNQ molecule has one type of electron-withdrawing group (four cyano groups). The TFQ mole-

![Fig. 1a. Structure of the azithromycin molecule.](image)

![Fig. 1b. Structures of the investigated π-acceptors.](image)
cule has two types of electron-withdrawing groups (two carbonyl groups and four fluorine groups), while the DDQ molecule has three types of electron-withdrawing groups (two cyano groups, two carbonyl groups, and two chloro groups). The presence of three different types of electron-withdrawing groups in the DDQ molecule greatly decreases the electron density of its aromatic ring, thereby rendering the DDQ molecule a robust, very strong electron-accepting system that resulted in the formation of the distinctive intense red color with azithromycin, compared with the pale brown color formed with the TCNQ acceptor and canary yellow color formed with the TFQ acceptor. The intensity of the color of the resultant CTC increased with the types of electron-accepting groups in the acceptor molecule. This increase was as follows: pale brown (TCNQ; one type) < canary yellow (TFQ; two types) < intense red (DDQ; three types).

3.1.2. Observing the CT bands

After observing the color change that resulted from the interaction of azithromycin with TCNQ, DDQ, and TFQ, it was necessary to observe the CT bands (shape, position, $\lambda_{CT}$) that characterized the resultant CTCs in solution using UV–visible spectroscopy. To observe the characteristics of the CT bands, solutions of azithromycin and the acceptors were prepared at concentrations of $5 \times 10^{-4}$ M in methanol and these were scanned with a UV–visible spectrophotometer from 200 to 800 nm at ambient temperature. The electronic absorption of free azithromycin, free acceptor (TCNQ, DDQ, or TFQ), and the CTC derived by mixing the two solutions (1:1) are presented in Figs. 5a-c. Free azithromycin in methanol had no measurable absorption bands in the UV–visible region. The free TCNQ acceptor solubilized in methanol had a very strong, broad absorption band that ranged from 300 to 450 nm with a $\lambda_{max}$ of 393 nm. Upon complexation between TCNQ and the donor, this band disappeared and a new, very strong, broad band appeared from 285 to 375 nm, centered at $\lambda_{CT}$ 336 nm. The free DDQ acceptor had a strong, sharp absorption band at 295 nm with a long tail.

Fig. 2. Pronounced color change upon mixing TCNQ acceptor (far left; light green) with azithromycin (middle; colorless) to produce the CT complex (far right; pale brown) in the methanol solvent.

Fig. 3. Pronounced color change upon mixing DDQ acceptor (far left; brown) with azithromycin (middle; colorless) to produce the CT complex (far right; intense red) in the methanol solvent.

Fig. 4. Pronounced color change upon mixing TFQ acceptor (far left; pale brown) with azithromycin (middle; colorless) to produce the CT complex (far right; canary yellow) in the methanol solvent.

Fig. 5a. The UV–visible spectra of the donor (azithromycin), the TCNQ acceptor, and resultant CT complex in methanol solvent.
ranging from 340 to 600 nm, gradually decreasing in intensity. After DDQ interacted with the donor, the intensity of this band decreased greatly with a slight shift in its maximum to 290 nm. The decreased intensity of the characteristic band of DDQ was coupled with the formation of a new, strong, broad absorption band that ranged from 360 to 600 nm, centered at $\lambda_{CT} 460$ nm. The free TFQ acceptor had two weak absorption bands: a narrow band at 290 nm and a wide band that ranged from 330 to 460 nm, centered at $\lambda_{CT} 385$ nm. Upon complexing TFQ with the donor, the intensity of the narrow band located at 290 nm greatly increased, about 10-fold, and slightly shifted its maximum to 296 nm. The intensity of the wide band centered at 385 nm also increased, becoming broader with a maximum shifted to $\lambda_{CT} 400$ nm. These spectral results indicate that the complexation of the donor with the TCNQ and DDQ acceptors was characterized by the formation of a new band where neither the free donor nor acceptor previously had any measurable absorption (hypsochromic shifts), while the complexation with the TFQ acceptor was characterized by the increased intensity and size of the absorption band that characterized the free TFQ (bathochromic shift).

3.1.3. Composition of the interaction

The third preliminary step is to verify the composition of the interaction between the donor and TCNQ, DDQ, and TFQ acceptors in solution using the spectrophotometric titration method [67] and Job’s continuous variation method [68]. The molar ratio (donor to acceptor) derived using these two methods will be used to prepare the CTCs with azithromycin by solid–solid interaction. Fig. 6a presents the curves obtained from the spectrophotometric titration method. These curves were derived by plotting the absorbances ($k_{CT}$) of a series of 10 solutions containing molar ratios ranging from 4:1 to 1:4 donor to acceptor against the corresponding acceptor volume. The curves in Fig. 6a show the intersection of the resultant two straight lines corresponded to an acceptor volume of 1.0 mL, indicating that the interaction between the donor and all of the acceptors occurred at a 1:1 M ratio. Fig. 6b presents the curves obtained using Job’s continuous variation method. These curves were derived by plotting the absorbances ($k_{CT}$) of a series of 10 solutions containing varied molar fractions ($C_D + C_A$) of the donor and acceptor against the corresponding molar fraction of the acceptor [$\chi_A = C_A/(C_D + C_A)$]. The curves in Fig. 6b show that the maximum absorbance corresponded to a molar fraction of 0.50, reflecting that the donor formed a 1:1 CTC with each of the

Fig. 5b. The UV–visible spectra of the donor (azithromycin), the DDQ acceptor, and resultant CT complex in methanol solvent.

Fig. 5c. The UV–visible spectra of the donor (azithromycin), the TFQ acceptor, and resultant CT complex in methanol solvent.

Fig. 6a. Composition of the interaction between azithromycin with acceptors determined by spectrophotometric titration method.
acceptors. In conclusion, the results from both methods agreed and confirmed that azithromycin reacted with the TCNQ, DDQ, and TFQ acceptors via a 1:1 M ratio.

3.2. Methodology

CTCs of azithromycin with TCNQ, DDQ, and TFQ acceptors were produced using a fast, clean, and straight-forward two-step method based on mortar-grinding their solids under four conditions: i) solvent-free solid–solid reaction type, ii) ambient reaction temperature, iii) ~3 min reaction time, and iv) 1:1 (donor to acceptor) reaction stoichiometry. A pronounced color change was observed after grinding the pair of compounds (donor and

![Fig. 6b](image)

**Fig. 6b.** Composition of the interaction between azithromycin with acceptors determined by Job’s continuous variation method.

![Fig. 7a](image)

**Fig. 7a.** TCNQ complex generated by grinding azithromycin (white powder) and TCNQ (brown powder) for 3 min.

![Fig. 7b](image)

**Fig. 7b.** DDQ complex generated by grinding azithromycin (white powder) and DDQ (light brown powder) for 3 min.
acceptor) for ~1 min, as shown in Figs. 7a-c. The grinding was continued for 2 min to ensure the completeness of the reaction and the homogeneity of the solid product. Next, the crude solid homogenates were rinsed with 5 mL of diethyl ether to remove any unreacted compounds and then dried with a water pump. The complex obtained with TCNQ had a light-brown color, with DDQ had a dark-brown color, while the TFQ CTC had a light-violet color, as depicted in Fig. 8.

3.3. Characterization data of the CTCs

The generated CTCs were characterized by UV–visible, FTIR, ¹H NMR, ¹³C NMR spectral data as well as elementary data. Figs. 9a-c contains UV–visible spectra of the synthesized CTCs. The FTIR of the free donor and acceptor molecules are presented in Figs. 10a-c.
Fig. 10a. FTIR spectrum of the free azithromycin molecule.

Fig. 10b. FTIR spectrum of the free TCNQ molecule.

Fig. 10c. FTIR spectrum of the free DDQ molecule.

Fig. 10d. FTIR spectrum of the free TFQ molecule.

Fig. 11a. FTIR spectrum of the TCNQ complex.

Fig. 11b. FTIR spectrum of the DDQ complex.

d. Figs. 11a-c contains the FTIR spectra of the synthesized CTCs. Fig. S1 presents the structure of free azithromycin along with its atom numbers to facilitate interpreting the $^1$H and $^{13}$C NMR
spectra for the synthesized CTCs given in Fig. S2-S5. The elemental and spectral data collected for the CTCs were:

3.3.1. Free azithromycin

White powder; CHN elemental data: C_{38}H_{72}Cl_{2}N_{4}O_{14} (975.98 g mol^{-1}); Calculated (%): C 63.14; H 7.80; N 9.05. Calculated (ppm): C 62.95; H 7.97; N 8.81. UV-visible data (nm): 336. FTIR data (cm^{-1}): 461, 570, 726, 796, 893, 998, 1040, 1172, 1267, 1380, 1460, 1555, 1677, 2224, 2284, 2826, 2885, 2933, 2972, 3236, 3487. 1H NMR data (400 MHz, DMSO d_{6}) (ppm): δ = 7.55 (s, 4H, TCNQ ring H), 5.74 (t, 1H, (C_{2}-CH)), 5.69 (t, 1H, (C_{2}-CH)), 5.37 (dd, 1H, (C_{2}-CH)), 5.11 (m, 1H, (C_{2}-CH)), 4.95 (dd, 1H, (C_{2}-CH)), 4.81 (dd, 1H, J = 5.6, (C_{2}-CH)), 4.83 (dd, 1H, J = 5.4, (C_{2}-CH)), 4.72 (m, 1H, (C_{2}-CH)), 4.50 (s, 3H, (C_{2}-CH)), 4.23 (dd, 1H, (C_{2}-CH)), 3.68 (s, 5H, 50H), 3.57 (d, 1H, J = 3.2, (C_{2}-CH)), 3.51 (m, 1H, J = 3.2, (C_{2}-CH)), 3.29 (m, 1H, (C_{2}-CH)), 3.26 (m, 1H, (C_{2}-CH)), 2.46 (m, 1H, (C_{2}-CH)), 2.41 (s, 3H, (N_{3}-CH), 2.22 (s, 6H, (C_{2}-N(CH_{2})_{2})), 2.04 (m, 1H, (C_{2}-CH)), 2.01 (d, 2H, J = 5.4, (C_{2}-CH)), 1.87 (dd, 2H, (C_{2}-CH)), 1.79 (m, 1H, (C_{2}-CH)), 1.77 (d, 2H, (C_{2}-CH)), 1.54 (m, 2H, (C_{2}-CH)), 1.40 (d, 3H, J = 3.2, (C_{2}-CH)), 1.38 (s, 3H, (C_{2}-CH)), 1.22 (s, 3H, (C_{2}-CH)), 1.11 (d, 3H, J = 4.8, (C_{2}-CH)), 1.09 (d, 3H, (C_{2}-CH)), 1.08 (d, 3H, J = 5.3, (C_{2}-CH)), 1.00 (s, 3H, (C_{2}-CH)), 0.95 (d, 3H, (C_{2}-CH)), 0.88 (d, 3H, J = 3.4, (C_{2}-CH)), 0.83 (t, 3H, (C_{2}-CH)). 13C NMR data (100 MHz, DMSO d_{6}) (ppm): δ = 169.9 (C_{2}-CH), 169.9 (TCNQ 2 ring C = C-CN), 134.7 (TCNQ 4 ring C), 114.2 (4CN), 102.8 (C_{2}-CH), 94.71 (C_{2}-CH), 83.60 (C_{1}-C), 80.66 (TCNQ = C-CN), 77.36, 77.21 (C_{1}-C), 75.34 (C_{2}-CH), 74.50 (C_{2}-CH), 74.26 (C_{2}-CH), 73.65 (C_{2}-CH), 72.85 (C_{2}-CH), 69.99 (C_{2}-CH), 66.66 (C_{2}-CH), 65.16 (C_{2}-CH), 62.61 (C_{2}-CH), 61.01 (C_{2}-CH), 49.90 (C_{2}-O), 49.58 (C_{2}-CH), 49.13 (N=CH_{2}), 45.65 (C_{2}-N(CH_{2})_{2}), 42.79 (C_{2}-CH), 36.50 (C_{2}-CH), 36.33 (C_{2}-CH), 34.90 (C_{2}-CH), 31.38 (C_{2}-CH), 25.91 (C_{2}-CH), 25.39 (C_{2}-CH), 22.80 (C_{2}-CH), 21.45 (C_{2}-CH), 21.18 (C_{2}-CH), 21.06 (C_{2}-CH), 18.81 (C_{2}-CH), 17.04 (C_{15}-CH), 11.50 (C_{2}-CH), 9.11 (C_{2}-CH), 8.33 (C_{2}-CH).
N 5.95. Calculated (%): C 56.56; H 7.38; N 5.74. UV–visible data (nm): 293, 346, 460. FTIR data (cm−1): 472, 570, 734, 803, 853, 901, 995, 1040, 1170, 1266, 1374, 1452, 1535, 1656, 1719, 2219, 2277, 2840, 2879, 2935, 2965, 3238, 3483. 1H NMR data (100 MHz, DMSO d6) (ppm): δ = 5.69 (t, 1H, (C–CH3)), 5.64 (t, 1H, (C–CH3)), 5.38 (d, 1H, (C–CH3)), 5.14 (m, 1H, (C–CH3)), 5.01 (dd, 1H, (C–CH3)), 4.71 (d, 1H, J = 4.8, (C–CH3)), 4.60 (d, 1H, J = 5.2, (C–CH3)), 4.56 (m, 1H, (C–CH3)), 4.30 (s, 3H, (CH3)), 4.27 (dd, 1H, (C–CH3)), 3.67 (s, 5H, 5OH), 3.45 (d, 1H, J = 3.6, (C–CH3)), 3.31 (d, 2H, J = 3.1, (C–CH3)), 3.26 (m, 1H, (C–CH3)), 3.01 (m, 1H, (C–CH3)), 2.97 (m, 1H, (C–CH3)), 2.81 (s, 1H, (N6–CH3)), 2.78 (6H, (C6–N(CH3)2)), 2.25 (m, 1H, (C12–CH3)), 2.22 (d, 2H, J = 4.4, (C–CH3)), 2.20 (dd, 2H, (C–CH3)), 1.84 (m, 1H, (C–CH3)), 1.70 (d, 2H, (C–CH3)), 1.55 (m, 2H, (C–CH3-CH3)), 1.53 (d, 3H, J = 3.6, (C–CH3)), 1.22 (s, 3H, (CH3)), 1.20 (s, 3H, (CH3)), 1.17 (d, 3H, J = 4.8, (C–CH3)), 1.10 (d, 3H, (C–CH3)), 1.04 (d, 3H, J = 5.4, (C–CH3)), 0.99 (s, 3H, (CH3)), 0.95 (d, 3H, (C–CH3)), 0.85 (d, 3H, J = 3.6, (C–CH3)), 0.81 (t, 3H, (CH3)), 13C NMR data (100 MHz, DMSO d6) (ppm): δ = 177.9 (C4), O=C–H), 141.7 (DDQ 2), 65.37 (N6), 51.95 (C14), 49.91 (C4–CH3), 49.58 (C4–CH3), 49.13 (N6–CH3), 45.65 (C4–N(2CH3)), 42.79 (C4–CH3), 36.76 (C6–CH3), 36.33 (C6–CH3), 34.90 (C5–CH3), 31.38 (C5–CH3), 25.50 (C6–CH3), 25.26 (C12–CH3), 22.84 (C12–CH3), 21.74 (C6–CH3), 21.35 (C6–CH3), 21.32 (C6–CH3), 18.17 (C6–CH3), 17.09 (C5–CH3), 11.71 (C6–CH3), 9.85 (C5–CH3), 9.01 (C12–CH3).

3.4. Elemental and UV–visible spectral results

The elemental results for the synthesized CTCs indicated that the solid–solid interaction between azithromycin and the TCNQ, DDQ, and TFQ acceptors proceeded at a molar ratio of 1:1. This molar ratio agreed with that obtained in solution using both the spectrophotometric titration and Job’s continuous variation methods. The UV–visible spectra of the CTCs dissolved in methanol solvent at a concentration of 5.0 × 10−4 mol L−1 in the 200 to 800 nm region are presented in Figs. 5a–c. The UV–visible absorption spectrum of azithromycin complexed with the TCNQ acceptor was characterized by a sole, very strong, broad band ranging from 286 to 380 nm with a λmax of 336 nm. The UV–visible spectrum of the DDQ complex was characterized by three absorption bands: a very strong, sharp band at 293 nm, a small band detected at 346 nm, and a wide, medium-intensity band ranging from 370 to 600 nm with a λmax of 460 nm. The spectrum of the complex with the TFQ acceptor contained a narrow, high-intensity band at 296 nm and a wide, low-intensity band centered at 400 nm. The shapes of the UV–visible absorption spectra of the synthesized CTCs were similar to those of the CTCs produced by mixing methanol solutions of azithromycin and the acceptors at 1:1 (Fig. 5), with the same λmax positions. The elemental and UV–visible spectral results confirmed that the solvent-free, solid–solid interactions between azithromycin and all of the acceptors produced the same CTCs generated by mixing methanolic solutions of azithromycin with each acceptor.

3.5. Infra-red spectral results

The free azithromycin molecule displayed the following characteristic IR bands: 570, 737, 797, 836, 895, 992, 1040, 1083, 1181, 1269, 1377, 1465, 1660, 1719, 2834, 2883, 2932, 2971, 3245, and 3490 cm−1. The bands observed at 1181, 1083, 1040, and 992 cm−1 were caused by the v(C = N), v(C = N), v(C ≡ O), and v(C ≡ C) stretching vibrations, respectively [74]. Among these modes, that resulting from the v(C ≡ O) appeared as a very strong band. The bands resonating at 1719 and 1660 cm−1 were caused by the v(C ≡ C) and v(C ≡ O) vibrations, respectively. The former appeared as a sharp, medium-strong band, while the latter appeared as a broad, weak band. The bands located at 570, 797, 1269, 1377, 2834, and 3245–3490 cm−1 were assigned to the vibrational modes of the five methylene (CH2) groups in the azithromycin molecule: δ(NH2-NH2), δ(NH-NH), δ(C=O), δ(C=C), and δ(C≡C), respectively [67-73]. Those located at 2971, 2883, 1465, and 836 cm−1 resulted from the vibrational modes of the 14 methyl (CH3) groups: v(CH3), v(CH3), δ(C–O), and v(C=O), respectively. The bands resonating at 737, 895, and 3245–3490 cm−1 were characteristic of the vibrational modes of the five O–H bonds in the molecule: out-of-plane bending, in-plane bending, and stretching vibrations, respectively [74]. The IR spectrum of the free TCNQ acceptor had absorption bands with wavenumbers (3050 and 2964), (2216 and 2964), 1533, 1350, (1118 and 1052), and 855 cm−1 attributed to the vibrational motions of v(C–H) and v(C ≡ H), v(C ≡ C), v(N ≡ N), v(C = C), δ(C ≡ C), and δ(NH2) deformations, respectively. The IR spectrum of the free DDQ acceptor had absorption bands with wavenumbers 2238, 1675, 1557, 1263 and 1171, 798, 720, and 893 cm−1, attributed to the vibrational motions of v(N ≡ N), v(C = O), v(C = C), δ(NC≡C), and v(C ≡ C), respectively. The free TFQ acceptor displayed three very
strong, intense bands located at 1680, 1320, and 988 cm⁻¹ assigned to the vibrational motions of ν(C = O), ν(C = C), and ν(C-F), respectively.

The IR spectra of the synthesized CTCs contained all of the principal bands of azithromycin and the corresponding acceptor molecule. The ν(C = C) vibration resonated as a medium-strong band at 1533 cm⁻¹ in free TCNQ, a strong band at 1557 cm⁻¹ in free DDQ, and a very strong band at 1320 cm⁻¹ in free TFQ. After complexation with azithromycin, the intensity of this band decreased and shifted to 1555 cm⁻¹ in the TCNQ complex, 1535 cm⁻¹ in the DDQ complex, and 1333 cm⁻¹ in the TFQ complex. The TCNQ, DDQ, and TFQ acceptor molecules bear different types of electron-withdrawing groups. The TCNQ molecule has four cyano groups, the TFQ molecule has two carbonyl groups and four fluorene groups, while the DDQ molecule has two cyano groups, two carbonyl groups, and two chloro groups. These groups pull the electron density from the aromatic ring of the acceptor causing the molecule to be a strong, robust electron-accepting system. These electron-withdrawing groups were affected by the complexation with azithromycin. The ν(C≡N) vibration of free TCNQ appeared as a medium-strong band at 2216 cm⁻¹ with a broad, weak shoulder band at 2964 cm⁻¹. In free DDQ, it appeared as a weak band at 2238 cm⁻¹. After TCNQ and DDQ interacted with azithromycin, this band shifted to 2224–2284 cm⁻¹ in the TCNQ complex and 2277 cm⁻¹ in the DDQ complex. In the free DDQ molecule, the ν(C = O) vibration was recorded at 1675 cm⁻¹, while in its complex with azithromycin, it registered at 1656 cm⁻¹. In the free TFQ molecule, the ν(C = O) vibration was recorded at 1680 cm⁻¹, while in the corresponding complex, this band overlapped. In the free DDQ molecule, the ν(C – Cl) vibrations were recorded at 893, 798, and 720 cm⁻¹, while in the corresponding complex, these were shifted to 901, 853, and 803 cm⁻¹. In the free TFQ molecule, the ν(C – F) vibration registered at 988 cm⁻¹, after complexation with azithromycin, it shifted to 999 cm⁻¹ with decreased intensity. The shifting of the vibrations of withdrawing groups (–CN, –C = O, –Cl, or –F) induced by the increased electron density around the acceptor moiety (TCNQ, DDQ, or TFQ) resulted from the complexation between azithromycin and the acceptors. The asymmetric and symmetric vibrations of C – N registered at 1181 and 1083 cm⁻¹ in the free azithromycin molecule; after complexation, these bands shifted to 1171 and 1090 cm⁻¹ in the TFQ complex. The asymmetric mode of C – N was recorded at 1172 and 1170 cm⁻¹ in the complexes with TCNQ and DDQ, respectively, while the symmetric mode of this band overlapped in both complexes. These observations suggested that the charge transferred from the N – atoms in the azithromycin molecule to the C = C moiety of the TCNQ, DDQ, and TFQ complexes, which represents a direct n → π⁺ transition, as proposed in Fig. 12 [75–83].

### 3.6. NMR spectral results

The ¹H NMR spectrum of the free azithromycin molecule showed that it produced 33 protons. These protons were observed with the region of δ = 6.61–0.58 ppm. This region was crowded with triplets, doublets, and singlets from the –CH₃, –CH₂, and –CH protons. The ¹³C NMR spectrum of the free azithromycin molecule showed that it produced 37 carbon resonances, which appeared in the δ = 177.66–9.36 ppm range. In the ¹H and ¹³C NMR spectra of the synthesized CTCs, all of the carbon and proton resonances that characterized the free azithromycin molecule were detected. The complexation between azithromycin and all of the acceptors affected the protons of the tertiary amino group [−N(CH₃)₂] attached to carbon number Cₓ, the tertiary amino group [−N – CH₃] and (OH) groups of the free azithromycin molecule. The protons of the [−N(CH₃)₂] group up-field shifted from 2.99 ppm in the free azithromycin molecule to 2.22, 2.78, and 2.65 ppm in its complexes with TCNQ, DDQ, and TFQ, respectively. The protons of the [−N – CH₃] group up-field shifted from 3.20 ppm in the free azithromycin molecule to 2.41, 2.81, and 2.75 ppm in its complexes with TCNQ, DDQ, and TFQ, respectively. The five protons from the (OH) groups exhibited a singlet at 4.33 ppm in free azithromycin; this signal shifted to 3.68, 3.67, and 3.79 ppm in its complexes with TCNQ, DDQ, and TFQ, respectively. The up-field chemical shifts of these protons were due to the presence of the n → π⁺ transition between azithromycin and the acceptors. This transition affected the electronic environments of the azithromycin protons. The four protons of the TCNQ ring showed a singlet signal at 7.55 ppm in the TCNQ complex. The 37 carbon resonances of the free azithromycin molecule underwent several changes after its complexation with the acceptors. The TCNQ, DDQ, and TFQ complexes displayed 41, 41, and 39 resolved carbon signals in their ¹³C NMR spectra, respectively. In agreement with the proposed structures illustrated in Fig. 12. The chemical shifts for the carbons in the withdrawing groups: –CN in the TCNQ complex was observed at δ 114.2 ppm. The chemical shift for carbons of withdrawing groups, C = O and – C – F, in the TFQ complex, were observed at δ 177.8 and 148.7 ppm, respectively. The carbons of the withdrawing groups – CN, C = O, and – C – Cl in the DDQ complex resonated at δ 116.6, 154.2, and 141.7 ppm, respectively. Carbon number Cₓ that carried the [−N(CH₃)₂] group resonated at δ 65.40 ppm in the free azithromycin molecule; after complexation, this signal shifted to δ 66.66, 66.80, and 66.39 ppm in the azithromycin–TCNQ, DDQ, and TFQ complexes, respectively.

### 4. Conclusions

Human coronavirus SARS-CoV-2, since December 2019, has led to a global pandemic with high morbidity and mortality. In response, numerous treatment options have been studied worldwide. One of these options is based on the broad-spectrum antibiotic azithromycin alone and in conjunction with other compounds. In this work, three CTCs of azithromycin with TCNQ, DDQ, and TFQ acceptors were produced by mortar-grinding at room temperature under solvent-free conditions. Color changes visible to the naked eye were seen when azithromycin formed soluble and solid CTCs with the investigated acceptors. Elemental and spectral analyses suggested that the interaction between azithromycin and all of the investigated acceptors involved a n → π⁺ transition that proceeded at a 1:1 azithromycin to acceptor stoichiometry. The proposed protocol was rapid (5 min), effective, eco-friendly, reproducible, easily performed on a micro- or macroscale, required no specialized equipment, and generated the desired complexes with excellent yields (92–95%).

### CRediT authorship contribution statement

Abdel Majid A. Adam: Data curation, Funding acquisition, Project administration, Writing - original draft, Writing - review & editing. Hosam A. Saad: Supervision, Conceptualization, Software, Validation, Visualization. Amnah M. Alsuhaibani: Investigation, Formal analysis, Methodology, Resources. Moamen S. Refat: Supervision, Conceptualization, Software, Validation, Visualization. Mohamed S. Hegab: Investigation, Formal analysis, Methodology, Resources.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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Appendix A. Supplementary data

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