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Synthesis and Complexation of Monotosylated 4-Aminopyridine with Nickel (II) and Iron (II) Ions

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Abstract

Tosylated 4-aminopyridine and other sulfonylated compounds of amines comprise a substantial class of pharmaceutical drugs used as antibiotics in the field of medicine. This research aimed at the synthesis of tosylated 4-aminopyridine and the complexation of the tosyated 4-aminopyridine with Ni(II) and Fe(II) ions. The sulfonamide was prepared by the action of tosyl chloride on 4-aminopyridine in an aqueous alkaline medium. The complexes were synthesized by the reaction of $Ni(NO_3)_2.6H_2O$ /$Fe(NO_3)_2.6H_2O$ with sulfonamide derivative. These compounds were characterized through Ultraviolet Visible spectroscopy (UV–Vis), Fourier Transform Infer-Red (FTIR) spectroscopy, Proton Nuclear Magnetic Resonance (1HNMR), Carbon-13 Nuclear Magnetic Resonance (^{13}CNMR) and Electron Spray Ionisation-Mass Spectrometer (ESI-MS) and micro-analysis. The IR spectral data suggested that the sulfonamide derivative acts as a neutral ligand towards Ni (II) and Fe (II). In their complexes, the coordination frequency bands of 1665.55 and 1674.21 cm^{-1} were assigned to Ni–N and Fe–N bonds, and 1687.70 cm^{-1} was assigned to free tosylated 4-aminopyridine. This decrease in the frequency band of free imine to coordinated imine complexes indicates that electron transfer occurred from the ligand to the d-orbitals of the metals. The complexation of4-Methyl-*N*-(pyridin-4-yl)benzene sulfonamide can increase the biological and catalytic potential of the ligand in the pharmaceutical and chemical industries.

Keywords: 4-aminopyridines, complexation, syntheses, tosyl chloride

Introduction

The emergence of pathogenic bacteria resistant to several current antibiotics is one of the major public health concerns in clinical settings. The world economic forum recently identified antibiotic resistance as one of the greatest threats to human health [1, 2]. Metal complexes increasingly used in drug discovery are commonly used as therapeutic compounds to treat several human diseases such as infection, diabetes, anti-inflammatory issues and neurological disorders [3–5]. Significant interest in the synthesis of metal complex-based drugs is currently observed in medicinal organic chemistry to address unique research, therapeutic, and diagnostic opportunities.

4-aminopyridine ($C_5H_6N_2$) holds essential functional moieties of an aromatic pyridine nucleus and an amine group. The pyridine moiety contains both carbon and hetero nitrogen atoms that are capable of eliciting both electrophilic and nucleophilic reactions at different conditions. The amine function is capable of undergoing protonation/deprotonation, nucleophilic and elimination reactions. 4-aminopyridine is used as an important intermediate in the chemical industry, as well as in medicine manufacturing companies; it is also utilized in perfume, fragrances, dyes, pharmaceuticals, etc [6–8].

Monotosylation of 4-aminopyridine with tosyl chloride is an essential transformation in pharmaceutical studies, because of the formation of a drug molecule having functional moieties (such as pyridine ring, benzene nucleus and sulphonamide) with various applications in pharmaceutical and organic chemistry [9, 10].

Sulfonamide nuclei containing pyridine based ligands have been reported in numerious biochemical reactions used to design and develop molecular systems of biological and medical importance. Such ligating species on coordination with metal ions may emerge as metal-mediated drugs [11–13]. Metal complexes of sulfonamide derivatives have numerous applications including antibacterial, antifungal and other biological applications. Such complexes are used in clinical, analytical, and industrial sectors, as well as in catalysis [14, 15]. Metals in their free and combined state are corrosive and very reactive. Very few metals (such as

copper, magnesium, molybdenum, calcium, iron, zinc, chromium, nickel, iron and vanadium) are known to play significant roles in biological processes in the human body. This is due to the formation of certain metal-protein complexes and various biological activities [16–18]

Aminopyridine ligands depend on both the presence of heteroatoms in the pyridine ring for coordination with metals and sulfonamide to enhance the biological activity. Chelating ligands containing O and N donor atoms exhibit broad biological activity and are of special interest because of their different bonding patterns with metals [19–21].

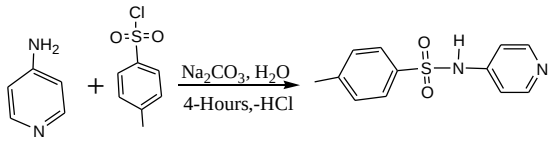
Considering these facts and the biological significance of metals, this research aims to synthesize aminopyridine base sulfonamide through the condensation of 4-aminopyridine and tosyl chloride in an aqueous alkaline medium. We also considered the complexation of monotosylated 4-aminopyridine with nickel (II) ion and iron (II) ion. Melting point analysis, Thin-layer chromatography (TLC) investigation, and the solubility test were used to confrim the purity level of the synthesized ligand and metal complexes. Then, further structural elucidation of the ligand and complexes were achieved throug spectroscopic analysis.

Material and Method

Equipment used in this study. The chemicals 4-aminopyridine, tosyl chloride ethanol, acetic acid, acetone, sodium trioxocarbonate (IV) etc. were of analytical grade and used without further purification. TLC was performed using a Merck pre-coated silica gel plate (10×10 cm); the Rf value was obtained using a solvent mixture of acetic acid and ethanol at a ratio of 1:2. The chromatogram was visualized using an ultraviolet lamp at 256nm. The melting point was recorded using a Digital Melting Point Electrothermal IA9300X1 instrument. The IR spectra were obtained using the FTIR-8400S Fourier Transform Infrared spectrophotometer at NARICT Zaria using an ATR disc to identify the functional groups, Liquid Chromatography/Mass Spectrometer was used for molecular formula/mass identification, Proton Nuclear Magnetic Resonance (^{1}HNMR) and Carbon-13 Nuclear Magnetic Resonance(^{13}CNMR) spectra were recorded using a JEOLA-LA-400 MHz-NMR Spectrophotometer at University of the Strathclyde, United Kingdom.

Experimental Methods

Tosylation of aminopyridine. The method adopted for the tosylation of 4-aminopyridine was developed by Rehman *et al*. [22] and Abdul-Qaduir *et al*. [23]. Aminopyridine (0.053 mol, 5 g) and sodium trioxocarbonate (IV) (1M, 20 ml) were placed in distilled water (25 mL) and stirred vigorously for 15 minutes. Subsequently, tosyl chloride (0.053 mol, 10 g) was gradually added to the mixture and stirred vigorously at room temperature for 4 h. After completion of the reaction monitored by pH change and TLC analysis, the solid product formed was washed several times using distilled water and recrystallized with a mixed solvent system of ethanol and water at a ratio of 1:5. The resulting crystal was collected through filtration, washed with distilled water and dried (the chemical equation in Scheme 1).

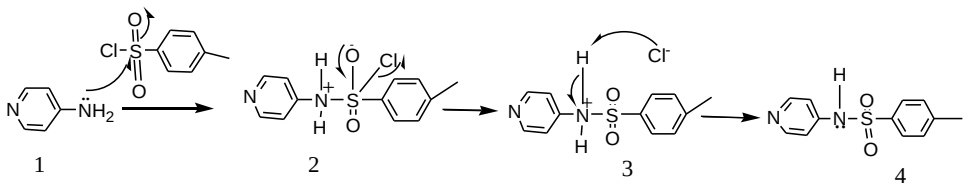


Scheme 1. Monotosylation of 4-Aminopyridine

The complexation of 4-Methyl-*N*-(pyridin-4-yl)benzene sulphonamide. A hot ethanolic solution of $C_{12}H_{12}N_2O_2S$ (4Mmol) was placed in a boiled ethanolic solution of $Ni(NO_3)_2.6H_2O$ /$Fe(NO_3)_2.6H_2O$ (4Mmol.). The mixture was stirred for 2 h allowed to stand for 2 h undisturbed. The precipitate formed was filtered and then washed several times with ethanol. The products were recrystallized with mixed solvent of DMSO and ethanol (1:6) and allowed to dry at ambient temperature (Scheme 2).

$$M^{2+} + L_A \rightarrow [M(L_A)_2] \quad L_A = \text{4-Methyl-}N\text{-(pyridin-4-yl)benzene sulfonamide}$$
$$M^{2+} = Ni^{2+}, Fe^{2+}$$

Scheme 2. Complexation of 4-methyl-N-(pyridin-4-yl)benzene Sulfonamide



Scheme 3. Mechanism of Tosylation of 4-aminopyridine

Results and Discussions

Physiochemical parameters of Methyl-*N*-(pyridin-2-yl)benzene sulphonamide. The mechanistic design of monotosylation of 4-aminopyridine is shown in Scheme 3.

The mechanistic design of the reaction of 4-aminopyridine and tosyl chloride is shown in Scheme 3. Step 1 demonstrates the nucleophilic attack of the amine on the sulfonyl group of tosyl chloride. Step 2 and 3 depict the departure of chlorine one and the deprotonation of tosylated 4-aminopyridine. This mechanistic design is consistent with that of Lakrout *et al*,[21]. Some physical data of the ligands and their metal complexes are presented in Table 1.

All the complexes and the ligand synthesized exhibited a melting point value that depicted high purity (Table 1). The percentage yield of both the ligand and complexes were in the range of 40-50%. These yields were obtained after different considerations of the volume of Na_2CO_3 (1M) during the synthesis. The TLC analyses were performed in mixed solvent at different ratios. The solvents and their ratios are shown in Table 1.

The solubilities of the ligand ($C_{12}H_{12}N_2O_2S$) and the complexes, $[Ni(C_{12}H_{12}N_2O_2S)_2]$ and $[Fe(C_{12}H_{12}N_2O_2S)_2$ were studied in various solvents (Table 2). The ligand was soluble in DMSO, DMF, acetic acid and ethanol, but insoluble in water, hexane, acetone and ethyl acetate. The complexes were insoluble in water, hexane, acetone and ethyl acetate but soluble in DMSO, DMF and acetic acid (Table 2). Their solubility is a result of the interaction between the hydrogen ion in the complexes and the oxygen atom in the solvent that results in the formation of a hydrogen bond [20, 23].

Table 1. Physical Properties of Ligand and Complexes

Compound	Color	Mol. Weight	Melting Point, °C	% Yield	TLC Analysis	
					R_F Value	Solvent Mixture/Ratio
$C_{12}H_{12}N_2O_2S$	Offwhite	249.00	210-212	45	0.80	AA:ETOH:H_2O (2:1:1)
$[Ni(C_{12}H_{12}N_2O_2S)_2]$	White	556.70	190-2192	50	0.86	AA:ACE (2:1)
$[Fe(C_{12}H_{12}N_2O_2S)_2]$	Yellow	553.80	195-197	40	0.92	AA:ACE (2:1)

Table 2. Solubility of Ligand and Complexes in Different Solvents

Serial No	Ligand/Complexes	Hex	EtOH	Ace	EA	AA	DMF	DMSO	H_2O
1	$C_{12}H_{12}N_2O_2S$	x	S	x	x	S	S	S	x
2	$[NiC_{12}H_{12}N_2O_2S)_2]$	x	x	x	x	S	S	S	x
3	$[Fe(C_{12}H_{12}N_2O_2S)_2]$	x	x	x	x	S	S	S	x

Where S; soluble and X; insoluble, Hex: hexane, EtOH: ethanol, Ace: acetone, EA: ethyl acetate, AA: acetic acid, DMF: dimethylformamide, DMSO: dimethyl sulfoxide, H_2O: water

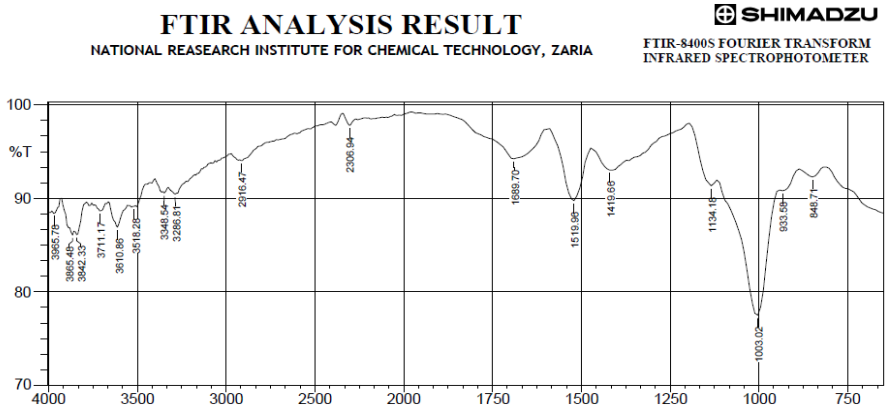


Figure 1. FTIR Spectrum of 4-Methyl-N-(pyridin-4-yl)benzene Sulfonamide

Spectroscopic analysis of 4-Methyl-*N*-(pyridin-4-yl)benzene sulphonamide. From the FTIR spectrum shown in Figure 1 (obtained from ATR cell), the absorption band 1003.02 cm^{-1} was assigned to the stretching vibration of the $-N-SO_2$ (sulfonamide). This frequency band confirms the condensation of 4-aminopyridine and tosyl chloride. The frequency band at1681.70 cm^{-1} was assigned to the imine of the pyridine ring. Other frequency bands are shown in Figure 1 and Table 5, the results confirm the presence the anticipated product and agree well with the result of Tsapkov *et al.* [16] and Abdul-Qadir *et al*.,[23].

The proton chemical shift of 14.37 ppm (1H, s) was assigned to the proton of the sulfonamide (O_2S-N-H). This observation confirms the condensation reaction of 4-aminopyridine with tosyl chloride. Other chemical shifts indicated were 7.47(m, 2H CH), 7.40(m, 2H CH), 7.04 (m, 2H, CH), 6.95 (m, H, CH) and 2.11 (s, H, CH_3). The chemical shift range of 6.95–7.47 pmm is within the aromatic zone of the ^{1}H NMR spectrum, thus, confirming the presence of benzene and the pyridine ring of 4-methyl-*N*-(pyridin-4-yl)benzene sulfonamide. The peak with the chemical shift value 2.11pmm was assigned to the methyl group of toluene. The chemical shift within the range of 114.32-152.89 ppm confirms the presence of an aromatic ring and 21.33 ppm indicates the presence of the methyl group attached to the aromatic ring [19, 22]

The molecular formula of the ligand, 4-methyl-*N*-(pyridin-4-yl)benzene sulfonamide was found to be $C_{12}H_{12}N_2O_2$ based on *m/z* 249.0 of ESI-MS of the ligand. The complexes have the molecular weight of 553.8 and 556.7 for iron (II) and nickel (II) complexes respectively. The molecular mass obtained through ESI-MS analysis agreed with that of the anticipated proposed product and was confirmed through NMR analysis structural elucidation.

The elemental analysis of the ligand and its complexes are listed in Table 4. The analytical data were found to be in good agreement with the ESI-MS estimation and the proposed empirical formula of the complexes [5, 20, 23].

Electronic analysis of ligand and complexes. The electronic spectra of the pure sulfonamide, and the Ni(II) and Fe(II) complexes were measured in DMSO solution between 200 and 1100 nm at room temperature (Table 4). The absorption below 250 nm was obscured in the DMSO spectra due to solvent absorption. The absorption band at 225–203 nm corresponds to the $\pi \rightarrow \pi^*$ transition of the benzene rings, and the absorptions at 299–256 nm and 345–301 nm were assigned to the $\pi \rightarrow \pi^*$ of the double-bonded carbons and $n \rightarrow \pi^*$ transitions and the azomethine group (HC=N) of 2-aminopyridine respectively (Table 5). The spectrum of the nickel (II) complex exhibits a prominent band at 340 nm associated with ligand to Ni(II) charge transfer transition (LMCT), and the broadband at 620 nm region corresponds to the d−d transition of the Ni(II) complexes [23, 24]. The spectrum of the iron (II) complex exhibits a prominent band at 339–3311 nm associated with ligand to the Fe(II) charge transfer transition (LMCT) and the broad electronic band at 652 nm region corresponds to the d-d transition of the Iron (II) complex [10, 25].

Table 3. Elemental Analysis of the Ligand and Complexes

Compounds	Mol. Weight	Analysis Found (calculated)%					
		M	C	H	N	O	S
$C_{12}H_{12}N_2O_2S$	249.00	-	57.56(57.83)	5.09(4.82)	11.80(11.24)	13.46(12.85)	11.89(12.85)
$[Ni(C_{12}H_{12}N_2O_2S)_2]$	556.70	11.48(10.54)	50.79(51.70)	4.64(4.31)	9.85(9.98)	11.66(10.06)	11.58(10.06)
$[Fe(C_{12}H_{12}N_2O_2S)_2]$	553.80	11.55(10.09)	52.37(52.00)	4.62(4.33)	10.27(10.11)	10.55(11.56)	10.64(11.56)

Table 4. UV-VIS Electronic Transition for Ligand and Complexes

Compound	Adsorption nm	Band Assignment
$C_{12}H_{12}N_2O_2S$ N_2O_2S	225–203,299–256, 345–301	$\pi \rightarrow \pi^*$,$n \rightarrow \pi^*$
$[Ni(C_{12}H_{12}N_2O_2S)_2]$	340-307, 652	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$
$[[Fe(C_{12}H_{12}N_2O_2S)_2]$	339–311, 652	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$, d→ d

$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$: Electronic transition from highest occupy molecular orbital(HOMO) to lowest unoccupied molecular orbital(LUMO)

Table 5. FTIR Analysis for Ligand and Complexes

S/no	Ligand/complex	V_{N-H}	$V_{C=N}$	$V_{C=C}$	V_{CH}	$V_{-N-S=O}$
1	$(C_{12}H_{12}N_2O_2S)$	3610.88,	1687.70	1515.90	2916.47	1003.02-1134.10
2	$[Fe(C_{12}H_{12}N_2O_2S)_2]$	3610.86	1674.21	1519.96	2931.90	1010.73-1134.118
3	$[Ni(C_{12}H_{12}N_2O_2S)_2]$	3618.58	1665.55	1527.67	2901.04	1003.02

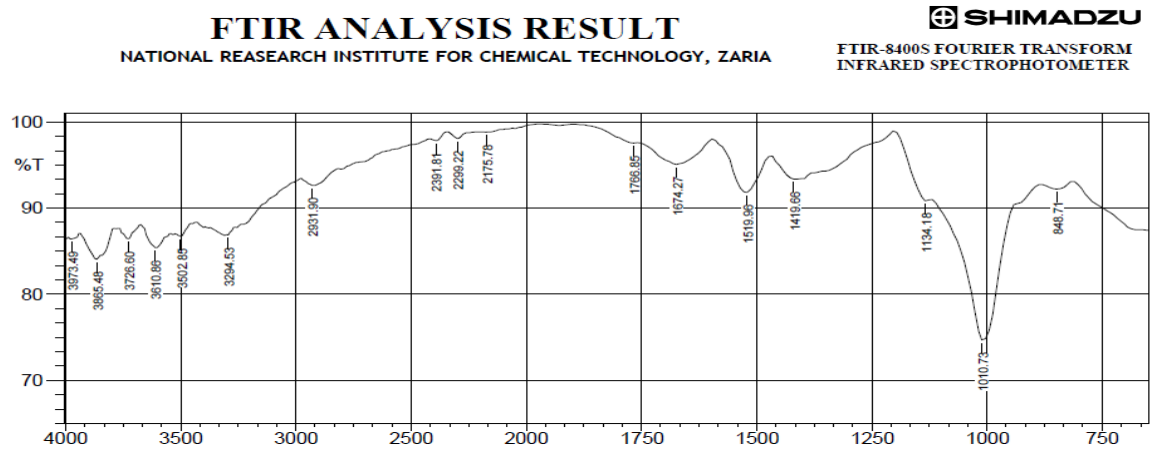


Figure 2. FTIR Spectrum of Iron Complexed with Methyl-N-(pyridin-2-yl)benzene Sulfonamide

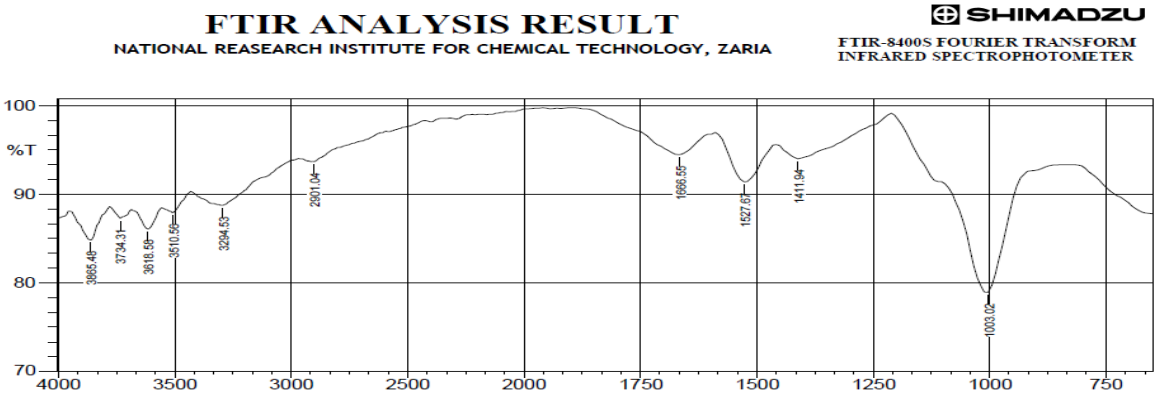


Figure 3. FTIR Spectrum of Nickel Complexed with Methyl-N-(pyridin-2-yl)benzene Sulfonamide

FTIR spectra of synthesized ligand and metal complexes. The vibration frequency of the ligand and its complexes are shown in Figure 1−3. The ligand contains three potential donor sites: the azomethine nitrogen, sulfonamide oxygen and sulfonamide nitrogen. The vibration frequencies 1687.70, 1003.02 and 1134.18 cm^{-1} were assigned assigned to the azomethine nitrogen, sulfonamide oxygen, and sulfonamide nitrogen, respectively (Table 5).

The imine group of 4-aminopyridine in 4-methyl-*N*-(pyridin-4-yl)benzene sulfonamide underwent a shift from high to lower vibration frequency after complexation, indicating the coordination of imine nitrogen to a metal atom; this can be explained by the donation of electrons from nitrogen to the empty d-orbitals of the metal atom[26, 27]. Evidence of the nitrogen bonding of the azomethine (C = N) group to the central metal atom stems from the shift of the ν(C = N) frequency within the range of 15–25 cm^{-1} in all of its metal complexes [28, 29]. The coordination of the N-Ni complex has the vibration frequency of 1665.55 cm^{-1}, and the coordination of the N−Fe complex has the vibration frequency of 1674.21 cm^{-1}. Other frequency bands are given in Table 5. These frequencies of absorption were different from the absorption frequency of the free imine group of the ligand (1687.70 cm^{-1}). These observations are consistent with the findings of Chohan *et al.* [30], Sani and Iliyasu,

[31] and Etaiw *et al.* [32]. The characteristics of the FTIR spectra of all complexes agreed with the suggested structural formulae (Figure 1−3).

Conclusion

Several scientific investigations have revealed the essential attribute of hetero-aromatic sulfonamides and their complexes in the chemical and pharmaceutical industries. In the field of medicinal chemistry, complexation in most cases has been confirmed to enhance the bioactivity of some organic ligands. In this paper, we reported the synthesis of 4-methyl-N-(pyridin-4-yl) benzene sulfonamide, *via* the coupling of 4-aminopyridine and tosyl chloride in an aqueous alkaline medium. This ligand was complexed with Ni(II) and Fe(II) ions. The products were characterized through UV-VIS, FTIR, ^{1}HNMR and ^{13}CNMR, ESI-MS and Mico-analysis. The ligand and its complexes were tested and confirmed to be pure through TLC analysis, melting point analysis and micro-analysis. The structural elucidation of the ligand was achieved using ^{1}HNMR and ^{13}CNMR. Both ESI-MS and Mico-analysis were used to confirm the molecular mass of the ligand and the complexes. The electronic transition and FTIR investigation depicted metal coordination through the azomethine hetero-nitrogen. The method employed in this synthesis and the compound synthesized is a viable potential source of knowledge for chemists because of the lack of evidence of the existence of the method and the compound synthesized in the literature. We recommend using ESR and X-ray diffraction to confirm the structure of the complexes.

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Conflict of Interest

The authors have no potential conflicts of interest to disclose.

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