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Synthesis, characterization and biological screening of *N*-heterocyclic carbene Ag(I) catalysts for aldehyde–amine–alkyne coupling reaction

Lamia Boubakri[1], Aziza Mnasri[1], Donia Ben Salah[1], Lamjed Mansour[2], Nevin Gürbüz[3,4] İsmail Özdemir[3,4], Mathieu Sauthier[5], Naceur Hamdi[1*]

[1] *Research Laboratory of Environmental Sciences and Technologies (LR16ES09), Higher Institute of Environmental Sciences and Technology, University of Carthage, Hammam-Lif, Tunisia*
[2] *Zoology Department, College of Science, King Saud University, Saudi Arabia, P.O. Box 2455, Riyadh 11451, Saudi Arabia*
[3] *İnönü University Catalyst Research and Application Center, 44280-Malatya, Türkiye*
[4] *nönü University Drug Application and Research Center, 44280-Malatya, Türkiye*
[5] *Ecole Nationale Superieure de Chimie de Lille, Unite de Catalyse et Chimie du Solide, Villeneuve d'Ascq, France*

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Abstract

N-heterocyclic carbenes (NHCs) are widely recognized for their applications in organometallic chemistry, catalysis, and pharmaceutical research due to their unique steric and electronic properties. In this study, we report the synthesis of six novel unsymmetrical N,N-disubstituted benzimidazolium salts (2a–f) and their corresponding silver-NHC complexes (3a–f). The structures of all compounds were characterized using nuclear magnetic resonance (NMR), Fourier-transform infrared spectroscopy (FT-IR), and elemental analysis. The biological potential of these compounds was evaluated through *in vitro* antimicrobial assays against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Candida glabrata*. Additionally, anticancer activity was tested against A549, HCT116, and BEAS-2B cell lines, revealing promising results for some derivatives. Preliminary catalytic studies demonstrated the effectiveness of the silver-NHC complexes in A3-coupling reactions involving aldehydes, alkynes, and amines. These reactions yielded propargylamines with high conversion rates (up to 90%) using minimal catalyst amounts. This work highlights the dual utility of these compounds as both potent biological agents and efficient catalysts, paving the way for further exploration of their applications in medicinal chemistry and sustainable catalysis.

Keywords: Catalysis, Structure analysis, N-heterocyclic carbene; benzimidazolium salts; silver(I)-NHC complexes; antioxidant; enzyme inhibition

1. Introduction

Benzimidazoles and their derivative compounds are among the most significant nitrogen-containing heterocycles, serving as fundamental building block ligands and being extensively investigated for drug discovery [1]. The structures of numerous natural compounds incorporate benzimidazole rings, which are regarded as biologically active and intriguing for chemical synthesis [2]. Furthermore, the biological characteristics of these compounds represent a vital area of research, having undergone extensive evaluation [3–5]. Recently, metal-NHC complexes have garnered considerable interest due to their diverse catalytic and pharmacological applications [6–7]. NHC precursors and their metal complexes containing the benzimidazole core are widely used in the fields of organometallic chemistry, catalysis, and pharmaceutical chemistry [8-9]. Especially silver compounds attract attention due to their biological properties such as anticancer, antimicrobial, and antibacterial [10-11]. The fact that silver plays a role as an essential micronutrient in human health has led researchers to conduct investigations on silver-containing compounds [12]. Furthermore, the design of a new intravenous pro-drug against leukemia must take into account the antioxidant efficiency and compatibility with the components of human blood; however, it is still unclear how to engage late transition metal complexes with an appropriate ligand architecture for this purpose. However, the field of intravenous antileukemial drug discovery has expanded due to recent studies on the creation of efficient small compounds with suitably functionalized heterocyclic structures [13]. Leukemia cell proliferation can be controlled by using appropriately crafted small compounds with physiologically active heterocyclic systems or systems and functionality [14], as long as the design doesn't interfere with normal cell shape or other components. Thus, it is a benefit in the event of a novel

* Corresponding author.
E-mail address: hamdi.naceur@isste.ucar.tn (N. Hamdi).
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antileukemia agent design with promising antioxidant potential and a high degree of compatibility with blood constituents [15]. Accordingly, in a number of in vitro tests against several human-derived cancer cell lines, the proper design and production of transition metal complexes carrying N-heterocyclic carbene (NHC) ligands is essential [16]. Over the past ten years, a lot of research has been conducted on silver-based bioinorganic chemistry, which has led to the discovery of multiple series of derivatives that are active against a variety of human-derived cancer cell lines [17] and resistant bacterial strains [18]. As safer and less expensive substitutes for platinum-based complexes are created, the usefulness of silver derivatives continues to grow. Among other things, NHC derivative silver complexes were given a lot of attention as possible antibacterial and anticancer agents [19]. There are a number of potential ligand variations that could be the cause of this, as they greatly enhance the activity of the resulting complexes. Additionally, the ability to modify the NHC ligand design to raise the proper steric and electrical requirements surrounding the metal atom aids in customizing ideal candidates for specific applications [20]. Specifically, the incorporation of bioactive heterocyclic systems including pyridine, imidazole, coumarin, and others into the NHC scaffold resulted in the discovery of multiple coinage metal NHC complexes that showed encouraging activity in biological applications [21]. A triazolium salt or silver source was found to be inactive in radical scavenging activity, indicating the potential of NHC silver complexes. Lui et al. recently reported a few series of coumarin-substituted 1,2,4-triazole-based NHC silver complexes that displayed DPPH–based antioxidant potential with an IC50 (a concentration of test sample required to neutralize DPPH radicals by 50%) in the range of 61–224 μM [22]. Ag-NHC compounds attract much attention due to their biocompatible nature with the human body and biological activities such as anticancer and enzyme inhibition. Therefore, in recent years, studies on the synthesis and applications of these compounds have become widespread [10,12]. Compound inhibition of certain enzymes has often been associated with the treatment of various health problems. Till now, the enzyme inhibitory activities of many salts and metal complexes have been investigated [23-24]. Acetylcholinesterase (AChE) is an important enzyme for the breakdown of the neurotransmitter acetylcholine (ACh) at synapses in the nervous system [24]. ACh serves as a vital neurotransmitter involved in numerous cognitive functions, including learning and memory. This rapid hydrolysis of ACh by AChE is critical for the termination of synaptic transmission and proper signal transduction [25]. Although AChE is found in all tissue cells, it is predominantly found in muscles, brain, and cholinergic neurons [23]. In Alzheimer's disease (AD), a neurodegenerative disease characterized by progressive cognitive decline, a remarkable decrease in AChE activity has been seen, especially in the later stages. This decrease in AChE leads to the degradation of ACh, contributing to the cognitive deficits and symptoms associated with AD [26]. The importance of ACh in cognitive processes has led to the development of a therapeutic strategy aimed at inhibiting AChE. By inhibiting this enzyme, AChE inhibitors increase the availability of ACh at synapses, thereby increasing cholinergic transmission and potentially improving cognitive function. Currently, four AChE inhibitors (tacrine, donepezil, galantamine, and rivastigmine) are approved for the symptomatic treatment of AD [27]. These medications have been shown to be effective in improving cognitive function, behavior, and the ability to perform daily activities in Alzheimer's patients. AChE inhibitors may help alleviate some of the cognitive deficits associated with the disease by increasing ACh levels. Even if these treatments do not cure AD or stop its progression, they provide symptomatic relief and improve the quality of life for many patients [26]. Keeping in view, designing and proposing new AChE inhibitors is vital in the quest to better understand and treat AD. Many previous studies revealed that the NHC precursors and their metal complexes are important in several biological activities [28-29]. However, complex compounds can be obtained in a single step using multicomponent reactions (MCRs), which start with more than two simple building ingredients. As a result, they are significant in many areas of organic synthesis. One of the best illustrations of an MCR is the A^3-coupling reaction. Propargylamines are repeating components of physiologically active chemicals and intermediates that produce more complicated N-heterocycles; this method provides a beneficial approach to them. A3-coupling is a promising method since it has great selectivity for the desired product and only produces water as a byproduct. This process has often been catalyzed by transition metal complexes that contain copper, silver, gold, iron, cobalt, and zinc [30–33] In light of the aforementioned information and as a continuation of our previous work on the synthesis of NHC silver complexes, the aim of this study was to report the synthesis of various novel silver complexes and conduct biological screening of the compounds as antioxidant potential and enzyme inhibition activity. All salts and complex structures were characterized by elemental analysis, Fourier transform infrared (FTIR), ^1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopies. We hope that the metal NHC complexes formed by transmetallation by using these silver NHC complexes can be employed as effective catalysts. Besides, findings regarding catalytic tests of the complexes in A^3-coupling reactions are presented.

2. Materials and methods

2.1. Materials and measurements

Standard Schlenk techniques were used to conduct all of the reactions for the produced compounds in flame-dried glassware under argon. All chemicals and solvents were purchased/acquired from Sigma-Aldrich and Merck. The following solvents were transferred under Ar after being purified by distillation over the designated drying agents: Et_2O (Na/K alloy), CH_2Cl_2 (P_4O_{10}), hexane, and toluene (Na). Elemental analyses were carried out in an Elementar Vario EL III Carlo Erba 1108. The Electrothermal-9200 instrument was used for measuring melting points in glass capillaries, which were ascertained in the presence of air. A Perkin Elmer Spectrum 100 GladiATR FT/IR spectrophotometer was used to record the IR spectra. A Bruker Avance III HD 400 MHz NMR spectrometer was used to record ^1H, ^{13}C NMR spectra in $CDCl_3$ or DMSO-d6 solutions. Chemical shifts were reported for the ^1H, ^{13}C NMR spectra relative to tetramethylsilane as a reference. Signals are expressed as parts per million as measured downfield from an internal standard of tetramethylsilane (0.00). J values for coupling constants are provided in hertz. The abbreviations for NMR multiplicities are as follows: s

for singlet, d for doublet, t for triplet, and m for multiplet signal. In the laboratory of the Department of Medical Genetics at the School of Medicine of İnönü University, experiments on antimicrobial activity have been performed. In this study, Daihan WIS 20 and 20 R Cooled Shaking Incubators, NF 800 Core brand Centrifuge devices, Allsheng AMR-100 Microplate Reader AC120 240 V, 50/60 Hz plate reader, and UV, Blue, Red, and Green) Spectrophotometer/Fluorometer was employed.

2.1.1. Preparation of benzimidazolium salts 2

Reaction of 1-isobutyl-benzimidazole (1 mmol) (1) with various alkyl chloride(1,1mmol) in dimethylformamide (DMF; 5 mL) at 80° C for 24 h afford benzimidazole salts 2a-f. A white crystalline solid was obtained after adding Diethyl ether (15 mL), which was subsequently filtered off. After washing with diethyl ether (3*10 mL) the solid was dried under vacuum, and the crude product was recrystallized from Dichloromethane/diethyl ether (1:3 ratio).

1-(Isobutyl)-3-(2.3.4.5.6-pentamethylbenzyl) benzimidazolium chloride, 2a

Yield 92%, Mp: 198.2 °C, ν(CN) = 1546 cm^{-1} . ^{1} H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.05 (d, 6H, CH_3 (a,b), J = 4 Hz), 2.24 (s, 6H, CH_3(c,g)), 2.28 (s, 6H, CH_3(d,f)), 2.28 (s, 3H, CH_3(e)), 2.38 (Hep, 1H, $H_{2'}$), 4.51 (d, 2H, H_{10}), 5.94 (s, 2H, $H_{10'}$), 7.22–7.70 (m, 4H, $H_{4, 5, 6, 7}$), 11.29 (s, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 16.9 ($C_{c,g}$), 17.1 ($C_{d,f}$), 17.3 (Ce), 19.7 ($C_{a,b}$), 28.8 (C_{20}), 48.5($C_{1''}$) 54.2 ($C_{1'}$), 113.0 (C_4), 113.9 (C_7), 125.1 ($C_{5''}$), 126.8 (C_5), 127.00(C_6), 131.3 ($C_{4''}$), 131.8 ($C_{6''}$), 133.5 ($C_{3'';7''}$), 133.8 ($C_{8;9}$), 137.2 ($C_{2''}$), 143.7 (C_2). Elemental analysis % calcd. (found) for $C_{23}H_{31}ClN_2$: C, 74.468% % (74.5); H, 8.423% (8.5); N, 7.552% (7.4).

1-(Isobutyl)-3-(2.3.4.5.6-pentamethylbenzyl)-5.6-dimethylbenzimidazolium chloride, 2b Yield 93%, Mp: 219.9 °C, ν(CN) = 1550 cm-1 . ^{1} H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.98 (d, 6H, CH_3(a,b), J = 8 Hz), 2.14 (Hep, 1H, H20, J = 8 Hz), 2.25 (s, 6H, CH_3(c,d)), 2.30 (t, 12H, $CH_{3(e,f,h,i)}$), 2.41 (s, 3H, CH_3(g)), 2.37 (Hep, 1H, H_{20}), 4.46 (d, 2H, H_{10}), 5.80 (s, 2H, $H_{10'}$), 7.05 (s, 1H, H_7), 7.38 (s, 1H, H_4), 10.48 (s, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 16.9 ($C_{f,h}$), 17.1 ($C_{e,i}$), 17.3 (Cg), 19.7 ($C_{a,b}$), 20.6 ($C_{c,d}$), 28.7 ($C_{2'}$), 47.9 ($C_{1''}$), 54.1 ($C_{1'}$), 112.7 (C_4), 113.4 (C_7), 125.2 ($C_{5'}$), 129.9 (C_8), 130.4 (C_9), 133.8 ($C_{3'';7''}$), 133.5 ($C_{4'';6''}$), 136.8 (C_5), 136.9 (C_6), 137.1 ($C_{2''}$), 142.3 (C_2). Elemental analysis % calcd. (found) for $C_{25}H_{35}ClN_2$: C, 75.253% (75.3); H, 8.841% (8.9); N, 7.021% (7.1).

1-(Isobutyl)-3-(4- methylbenzyl) benzimidazolium chloride 2c

Yield 87%, Mp: 176.1 °C, ν(CN) = 1550 cm^{-1} . ^{1} H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.05 (d, 6H, $CH_{3(a,b)}$), 2.31 (s, 3H, CH_3(c)), 2.43 (Hep, 1H, $H_{2'}$), 4.44 (d, 2H, $H_{1'}$), 5.88 (s, 2H, $H_{10'}$), 7.15–7.71 (m, 8H, $H_{4, 5, 6, 7, 3'', 4'', 6'',7''}$), 12.05 (s, 1H, H_2).). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.8 ($C_{a,b}$), 21.1 (Cc), 28.9 (C_{20}), 51.2 ($C_{1''}$), 54.3 ($C_{1'}$), 113.1 (C_4), 113.9 (C_7), 127.0 ($C_{5;6}$), 128.3 ($C_{3;7}$), 129.9 (C_5), 129.9 ($C_{4;6}$), 131.0 (C_8), 131.7 (C_9), 139.1 (C_{20}), 143.9 (C_2). Elemental analysis % calcd. (found) for $C_{19}H_{23}ClN_2$: C, 72.480% (72.5); H, 7.363% (7.4); N, 8.897% (8.9).

1-(Isobutyl)-3-(2.4.6-trimethylbenzyl) 5.6- dimethylbenzimidazolium chloride 2d

Yield 89%, Mp: 249.7 °C, ν(CN) = 1550 cm^{-1} . ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.01 (d, 6H, $CH_{3(a,b)}$), 2.29 (d, 6H, $CH_{3(c,d)}$), 2.32 (s, 6H, $CH_{3(e,g)}$), 2.40 (s, 3H, $CH_{3(f)}$), 2.44 (Hep, 1H, H_{20}), 4.40 (d, 2H, H_{10}), 5.84 (s, 2H, $H_{10'}$), 6.9–7.38 (m, 4H, $H_{4, 7, 4, 6}$), 11.34 (s, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.7 ($C_{a,b}$), 20.2 ($C_{c,d}$), 20.6 (C_e), 20.8 (C_g), 21.0 (C_f), 28.7 ($C_{2'}$), 47.1 ($C_{1''}$), 54.1 ($C_{1'}$), 112.6 (C_4), 113.5 (C_7), 125.4 ($C_{4;6}$), 130.0 ($C_{3; 5'';7''}$), 137.02 ($C_{8;9}$), 137.89 ($C_{5;6}$), 139.52 (C_2), 142.91 (C_2). Elemental analysis % calcd. (found) for $C_{23}H_{31}ClN_2$: C, 74.468% (74.5); H, 8.423% (8.5); N, 7.552% (7.6).

1-(Isobutyl)-3-(naphthyl)-5.6-dimethylbenzimidazolium chloride 2e

Yield 98%, Mp: 178.3 C, ν(CN) = 1550 cm-1 . ^{1} H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.04 (d, 6H, $CH_{3(a,b)}$), 2.33 (s, 3H, $CH_{3(d)}$), 2.39(s, 3H, CH_3(c)), 2.44 (Hep, 1H, $H_{2'}$), 4.38 (d, 2H, $H_{1'}$), 6.04 (s, 2H, $H_{1'}$), 7.28–7.96 (m, 9H, $H_{4, 7, 3, 5, 6, 7, 8, 1, 11}$), 11.52 (s, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) (ppm)19.8 ($C_{a,b}$), 20.6 ($C_{c,d}$), 28.8 (C_2), 51.2(C_1), 54.3 ($C_{1'}$), 112.8 (C_4), 113.4 (C_7), 125.0 (C_7), 126.7 (C_3), 126.8 (C_1), 127.6 (C_5), 127.7 (C_8), 128.1 (C_6), 129.4 ($C_{11''}$), 130.4 ($C_{8;9}$), 133.2 ($C_{5;6}$), 137.4 ($C_{2''}$), 141.9 (C_2). Elemental analysis % calcd. (found) for $C_{24}H_{27}BrN_2$: C, 68.083% (68.1); H, 6.428% (6.5); N, 6.616% (6.7).

1-(Isobutyl)-3-(anthracen-9-ylmethyl)-5.6- dimethylbenzimidazolium chloride 2f

Yield 97%, Mp: 269,7 C, ν(CN) = 1666 cm^{-1} . ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.00 (d, 6H, $CH_{3\ (a,b)}$), 1.91 (s, 3H, CH_3(d)), 2.23 (s, 3H, CH_3(c)), 2.34 (Hep, 1H, $H_{2'}$), 4.32 (d, 2H, $H_{1'}$), 6.90 (s, 2H, $H_{1'}$), 6.65 (s, 1H, H_9), 7.23–8.58 (m, 10H, $H_{4, 7, 4'', 5'', 6'', 7'', 11'', 12'', 13'', 14''}$), 11.95 (s, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.7 ($C_{a,b}$), 20.4 (Cc), 20.4 (Cd), 28.6 ($C_{2'}$), 45.2 ($C_{1''}$), 54.2 ($C_{1'}$), 112.3 (C_4), 114.2 (C_7), 122.1 ($C_{9''}$), 123.1 ($C_{5'', 6'', 12'', 13''}$), 125.4 ($C_{4'', 14''}$), 128.0 ($C_{7'', 11''}$), 129.7 ($C_{4'', 15''}$), 129.8 (C_8), 130.1 (C_9), 130.4 (C_8), 130.9 (C_1), 131.2 (C_2), 136.65 (C_5), 136.72 (C_6), 143.04 (C_2). Elemental analysis % calcd. (found) for $C_{28}H_{29}ClN_2$: C, 78.392% (78.4); H, 6.814% (6.9); N, 6.530% (6.6).

C-General procedure for the preparation of silver(I)-NHC complexes 3a-f

A solution of benzimidazolium salt (1.0 mmol) and Ag_2O (1.0 mmol) in dichloromethane (15 mL) was stirred at room temperature for 24 h. The reaction mixture was filtered through celite and the solvent was removed under reduced pressure. The crude product was recrystallized from dichloromethane/diethyl ether (1:3).

Chloro[1-isobutyl-3-(2.3.4.5.6-pentamethylbenzyl) benzimidazole-2-ylidene]silver 3a

Yield 86%, Mp: 275.3 °C, ν(CN) = 1458 cm-1 . ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.93 (d, 6H, CH_3(a,b), J = 4 Hz), 2.19 (s, 6H, CH_3 (d,f)), 2.28 (s, 6H, CH_3(c,g)), 2.30 (Hep, 1H, H_{20}, J = 8 Hz), 2.33 (s, 3H, CH_3(e)), 4.15 (d, 2H, H_{10} , J = 8 Hz), 5.48 (s, 2H, $H_{10'}$), 7.27–7.48 (m, 4H, H_4, 5, 6, 7). ^{13}C NMR ($CDCl_3$, 100 MHz) d (ppm)17.1 ($C_{c,d,f,g}$), 17.3 (Ce), 20.2 ($C_{a,b}$), 29.3 (C_{20}), 47.8 ($C_{1''}$), 57.3 (C_{10}), 111.4 (C_4), 111.6 (C_7), 123.9 (C_5), 124.1 (C_6), 126.5 ($C_{5''}$), 132.9 ($C_{4;6}$), 133.2 ($C_{8;9;3;7}$), 137.2(C_2), 189.0 (C_2).

Elemental analysis % calcd. (found) for $C_{23}H_{30}AgClN_2$: C, 57.814% (57.9); H, 6.328% (6.4); N, 5.863% (5.9).

Chloro[1-isobutyl-3-(2.3.5.6-tetramethylbenzyl)-5.6- dimethylbenzimidazole-2-ylidene]silver 3b

Yield 89%, Mp: 208.3 °C, ν(CN) = 1591 cm^{-1} . ^{1} H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.91 (d, 6H, CH_3(a,b), J = 8 Hz), 2.18 (s, 6H, CH_3(f,h)), 2.24 (Hep, 1H, H_{20} , J = 8 Hz), 2.28 (s, 6H, CH_3(e,i)), 2.33 (s, 3H, CH_3(g)), 2.41(s, 6H, CH_3(c,d)), 4.08 (d, 2H, H_{10}, J = 8 Hz), 5.39 (s, 2H, H_{10}'), 7.20 (s, 1H, H_4), 7.27 (s, 1H, H_7). ^{13}C NMR ($CDCl_3$, 100 MHz) d (ppm) 17.0 ($C_{f,h}$), 17.1 ($C_{e,i}$), 17.3 (C_g), 20.4 ($C_{a,b}$), 20.4 (Cc), 20.5 (Cd), 29.1 (C_{20}), 47.3 ($C_{1"}$), 57.3 (C_{10}), 111.5 (C_4), 111.8 (C_7), 126.7 ($C_{5"}$), 132.9 ($C_{8;9}$), 133.2($C_{3"}$), 133.5 (C_7), 134.2 ($C_{5;6;4";6}$), 137.1 (C_2), 185.2 (C_2). Elemental analysis % calcd. (found) for $C_{25}H_{34}AgClN_2$: C, 59.356% (59.4); H, 6.774% (6.8); N, 5.538% (5.6).

Chloro[1-isobutyl-3-(4–methylbenzyl) benzimidazole-2-ylidene] silver 3c

Yield 79%, Mp: 202.3 °C, ν(CN) = 1468 cm^{-1} . ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.01 (d, 6H, CH_3(a,b), J = 8 Hz), 2.31 (s, 3H, CH_3(c)), 2.83 (Hep, 1H, $H_{2'}$, J = 8 Hz), 4.24 (d, 2H, H_{10} , J = 8 Hz), 5.57 (s, 2H, $H_{10'}$), 7.11–7.48 (m, 8H, $H_{4, 5, 6, 7, 3", 4", 6", 7"}$). ^{13}C NMR ($CDCl_3$, 100 MHz) d (ppm) 20.3 ($C_{a,b}$), 21.1 (Cc), 29.3 (C_{20}), 53.3 (C_1), 56.8 (C_{10}), 112.2 (C_4), 111.6 (C_7), 124.1 (C_5), 124.2 (C_6), 127.1 ($C_{3",7"}$), 129.7 ($C_{4;6}$), 131.8 (C_5), 133.6 (C_8), 134.2 (C_9), 138.4 (C_2).

Ag-Ccarbene: not observed. Elemental analysis % calcd. (found) for $C_{19}H_{22}AgClN_2$: C, 54.114% (54.2); H, 5.258% (5.3); N, 6.643% (6.7).

Chloro[1-isobutyl-3-(2.4.6-trimethylbenzyl)-5.6-dimethylbenzimidazole-2-ylidene]silver 3d Yield 86%, Mp: 273.4 °C, ν(CN) = 1459 cm^{-1} . ^{1} H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.94 (d, 6H, CH_3(a,b), J = 4 Hz), 2.23 (s, 6H, CH_3(c,d)), 2.28 (Hep, 1H, H_{20}, J = 8 Hz), 2.34 (s, 3H, CH_3(e)), 2.35 (s, 3H, CH_3(f)), 2.38 (s, 3H, CH_3(g)), 4.11 (d, 2H, H_{10}, J = 8 Hz), 5.40 (s, 2H, $H_{1',}$), 6.97 (s, 2H, $H_{4, 6}$), 7.18 (s, 2H, $H_{4, 7}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 20.2 ($C_{(c,d)}$), 20.3 ($C_{(a,b)}$), 20.4 (Ce), 20.5 (Cg), 21.1 (C_f), 29.2 ($C_{2'}$), 47.4 ($C_{1"}$), 57.1 (C_{10}), 111.7 (C_4), 111.8 (C_7), 126.8 ($C_{4;6}$), 130.2 ($C_{3;5;7}$), 133.3 ($C_{8;9}$), 137.4 ($C_{5;6}$), 139.4 (C_2), 187.9 (C_2).Elemental analysis % calcd. (found) for $C_{23}H_{30}AgClN_2$: C, 57.814% (57.9); H, 6.328% (6.4); N, 5.863% (5.9).

Chloro[1-isobutyl-3-(3-(naphthyl)-5.6-dimethylbenzimidazole2-ylidene] silver 3e

Yield 85%, Mp: 284.6 °C, ν(CN) = 1400 cm^{-1} . ^{1} H NMR ($CDCl_3$, 400 MHz) d (ppm) 0.98 (d, 6H, CH_3(a,b)), J = 8 Hz), 2,26 (s, 3H, CH_3(d)), 2.35 (s, 3H, CH_3(c)), 2.36 (Hep, 1H, $H_{2'}$, J = 8 Hz), 4.19 (d, 2H, H_{10}), J = 8 Hz), 5.71 (s, 2H, $H_{10'}$), 7.10–7.76 (m, 9H, $H_{4, 7, 3", 5", 6", 7", 8", 1"', 11"}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 20.3 (C (a,b)), 20.3 (C (c,d)), 29.2 (C_{20}), 53.2 ($C_{1"}$), 56.6 (C_{10}), 111.8 (C_4), 112.2 (C_7), 124.4 ($C_{7"}$), 125.9(C_3), 126.3 (C_1), 126.5(C_5), 127.7 (C_8), 127.9 (C_6), 129.0 (C_{11}), 132.3 (C_8), 132.8 (C_9), 133.0 (C_5), 133.1 (C_6), 133.6 (C_2), 168.6 (C_2). Elemental analysis % calcd. (found) for $C_{24}H_{26}AgClN_2$: C, 59.337% (59.4); H, 5.395% (5.4); N, 5.766% (5.8). 2.22.

Chloro[1-isobutyl-3-(anthracen-9-ylmethyl) dimethylbenzimidazole-2-ylidene]silver 3f Yield 86%, Mp: 214.2°C, m(CN) = 1469 cm^{-1} . ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.90 (d, 6H, CH_3(a,b), J = 4 Hz), 2.12 (s, 3H, CH_3 (d)), 2.22 (Hep, 1H, H_{20}, J = 8 Hz), 2.31 (s, 3H, CH_3(c)), 4.08 (d, 2H, H_{10}, J = 4 Hz), 6.38 (s, 2H, $H_{10'}$), 7.87–8.22 (m, 11H, $H_{4, 7, 4, 5, 6, 7, 9, 11, 12, 13, 14}$). ^{13}C NMR ($CDCl_3$, 100 MHz) d (ppm) 20.2(C (a,b)), 20.3 (C (c)), 20.4 (C (d)), 29.1 (C_2), 46.2 (C_1), 57.0 (C_{10}), 111.7 (C_4), 112.3 (C_7), 122.9 (C_9), 125.2 ($C_{5; 6; 12; 13}$), 127.5 ($C_{4; 7; 11; 14}$), 129.9 ($C_{3, 8, 10, 15}$), 131.1 ($C_{8;9}$), 131.4 ($C_{5;6}$), 132.7 ($C_{2"}$), C_2: Ag-Ccarbene: not observed. Elemental analysis % calcd. (found) for $C_{28}H_{28}AgClN_2$: C, 62.759% (62.8); H, 5.267% (5.3); N, 5.228% (5.3)

2.2 Antimicrobial study

Pathogenic yeast species Candida albicans (ATCC MYA-2876) and Candida glabrata (ATCC 2001) were used in antifungal tests, whereas Escherichia coli (ATCC 25922), Staphylococcus aureus (ATCC 29213), and Pseudomonas aeruginosa (ATCC 27853) bacteria species were utilized in antibacterial tests. The School of Medicine at Inonu University's Laboratory of the Department of Genetics provided all varieties of bacteria and fungi used in the study (Battalgazi, Malatya, Turkey). The BMD (Broth Microdilution) test, as described in EUCAST EDef 7.3.2 [31] for yeasts and CLSI M07 [32] for bacteria inside various media mentioned in these papers, was used to conduct antifungal and antibacterial MIC analyses. In summary, the stock solution of chemically synthesized powdered compounds (NHCs) used in antifungal and antimicrobial tests was made in 100% DMSO, and serial dilutions were made in flat-bottom 96-well plates, in YPD (Yeast Peptone Dextrose) medium (2% peptone, 2% glucose, 1% yeast extract) at pH 6,5 for yeasts, and LB (Luria-Bertani). To achieve the requisite cell density and quantities of chemical compounds to be evaluated, yeast (1-5x105 CFU/mL) and bacteria (1x106 CFU/mL) cell solutions (inoculums) were produced in sterile water and introduced in equal volumes to 96-well plates containing various concentrations of the chemicals. The final concentrations of the chemicals were between 0.8 and 800 mg/L after the cell solutions had been added, and the cell concentrations needed for the test were 0.5–2.5x105 CFU/mL for yeasts and 5x105 CFU/mL for bacteria in the last phase. After incubation in yeasts for 24 h at 37 ºC and bacteria for 16 to 18 h at 37 ºC, plates were examined visually for bacteria and spectrophotometrically for the MIC. The lowest drug concentration that results in a growth reduction of at least 50% or more in yeasts when compared to the control (no drug) cell group, as well as the lowest drug concentration that results in no discernible growth in bacteria, is known as the MIC value.

2.3. Anticancer study

In this work, anticancer properties of samples were evaluated against A549, HCT116 and BEAS-2B cell lines. All cells were allowed to grow in DMEM medium supplemented with 10% fetal bovine serum and 1% penicillin & streptomycin at 37 °C in 5% CO_2 atmosphere. Cells that have reached a confluence of 70–80% were chosen for plating purposes. Old medium was discarded, and cells were washed several times with sterile PBS (pH 7.4). Afterward, trypsin was added and distributed evenly onto cell surfaces. After the incubation with trypsin for 5 min

at 37 °C, trypsin activity was inhibited by adding 2-fold volume fresh media. The solution was gently triturated to obtain cell segregation. Obtained solution was centrifuged at 1000 rpm for 7 min, and then, old medium was changed with 5 mL fresh medium. Cells were counted and diluted to get final concentration of $1*10^5$ cells/mL followed by seeding of the solution into wells ($1*10^4$ cells/well). Finally, plates containing the cells were incubated at 37 °C in 5% CO_2 atmosphere for 24 h in order to allow cell attachment. Anticancer activity measurements were carried out according to CellTiter-Blue® Cell Viability Assay.

2.4. CellTiter-Blue® Cell Viability Assay

While the cells were incubating, test substance was diluted with fresh media to obtain the desired concentration from the stock. Old medium was aspirated out of the wells containing the cells, and 100 µl of test substance was added to the wells. Afterward, plates were allowed to incubate for 24 h at 37 °C in 5% CO_2 for the treatment. After this period, 10 µL of CellTiter-Blue® reagent (Promega, Madison, Wisconsin, United States) and 90 µL of fresh media were added to each well to give a final concentration of 10% CellTiter-Blue® followed by incubating at 37 °C for 4 h. The optical density was read on an ELISA reader at 570 nm and 600 nm. Cell viability percentages are determined by using the formula [((O2 x A1) - (O1 x A2))/((O2 x P1) - (O1 x P2))] x 100. In this formula; O1 = molar extinction coefficient (E) of oxidized CellTiter-Blue® at 570 nm, O2 = E of oxidized CellTiter-Blue® at 600 nm, A1 = absorbance of test wells at 570 nm, A2 = absorbance of test wells at 600 nm, P1 = absorbance of positive growth control well (cells plus CellTiter-Blue® but no test agent) at 570 nm, P2 = absorbance of positive growth control well (cells plus CellTiter-Blue® but no test agent) at 600 nm. IC_{50} was calculated on the basis of linear cell viability percentages.

3. Results

Benzimidazolium salts (2a-2f) were synthesized via the two-step *N*-alkylation process. By N-alkylating alkylbenzimidazole with isobutyl bromide (1-bromo-2-methylpropane) in DMSO with KOH present for eight hours at 80°C, Compound 1 was produced. N-(isobutyl)-benzimidazole (1) was reacted with different aryl chlorides in DMF for 24 hours at 80 °C to produce the benzimidazolium salts (2a-2f) (Figure 1). The generation of salts (2a-2f) for each target compound has been detected after the reaction has been monitored after thin layer chromatography. Both in the solid state and in solution, the benzimidazolium salts (2a–2f) were stable in the presence of oxygen and moisture.

Silver compounds 3a–3f based on benzoimidazole were synthesized using the in situ deprotonation method. The appropriate benzimidazole salts 2a–2f were reacted with silver(I) oxide (Ag_2O) in DCM at room temperature at 50°C (Figure 1) in order to conduct the reactions under dark conditions [38–40]. Following the completion of the reaction, the crude products underwent recrystallization, ether dilution, and Celite filtering. Silver complexes 3a-3f are air and moisture-stable but sensitive to light and were therefore stored behind the aluminum foil. Analytical and spectroscopic techniques were used to characterize the complexes, which are stable both in the solid state and in solution. When these complexes were dissolved in CDCl3 and subjected to overnight (~16h) heating at 80oC, no changes were observed in the ^{1}H NMR spectra.

3.1. Synthesis and Characterization of Silver(I)-NHC Complexes

The structures of the salts and their silver-NHC complexes were characterized by spectroscopic and analytical techniques. Their ^{1}H and ^{13} C NMR spectra are consistent with the proposed formula.

The ^{1}H NMR spectra of the prepared salts 2 showed the expected signals for the common signals The signal of proton H_2 (NC*H*N) appeared in the range δ 9.78-12.02 as a singlet peak for all salts 2. The benzylic protons appeared in the range δ 4.40-5.81 as sharp singlet peaks in the case of salts 2. While the peaks of the aromatic ring were observed as multiplets in the range of 7.32-7.81 ppm. The peak belonging to the -CH_2 proton was seen as a singlet at 5.81 ppm. When the **^{13}C** NMR spectrum was examined, the carbon belonging to the NCHN group was observed at 143 ppm

We have reported similar spectroscopic properties for related NHC silver(I) complexes [41–42] to those seen for silver(I) complexes **3a–3f**. A typical ν(NCN) band may be seen at 1458, 1591, 1468, 1459, 1469, and 1487 cm−1 in the Fourier transform infrared spectra for **3a–3f**, respectively. After complexing with silver, the ligand precursors' NCHN protons vanish from the 1 H NMR spectra. The Ag-carbene signal for complexes **3e** and **3f** resonated at 165.2 and 165.7 ppm, respectively, in the ^{13}C NMR spectra; the remaining complexes **3a-d** did not exhibit this peak.

The fluxional nature of NHC complexes has been explained by this characteristic in the literature [43–44]. One of the crucial techniques for determining a compound structure is elemental analysis. Examining the elemental analysis results (C, H, and N) of every compound revealed that the calculated and discovered results agreed with one another. Furthermore, every piece of information gathered is consistent with previous research [45]. The signals of the aromatic protons in the arene ring appeared in various shapes in the range of δ 7.0–7.9. IR peaks pertaining to the salts' -C=N-group stretching vibrations may be found between 1554 and 1562 cm–1. However, for the metal complexes, their values drop to 1400 cm–1. The literature

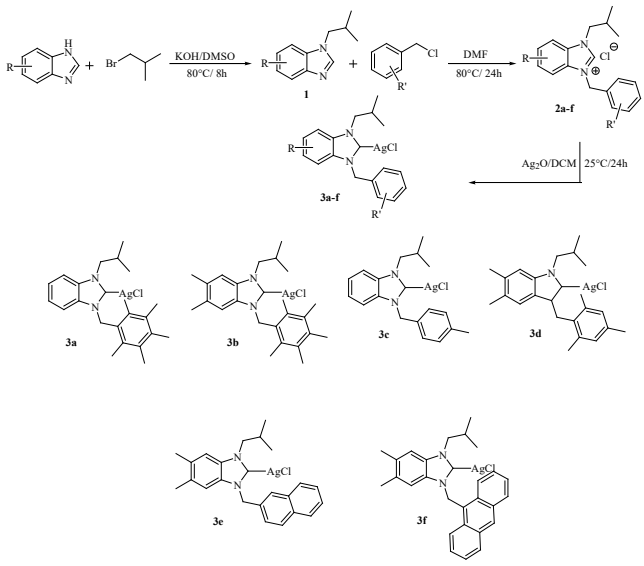


Fig. 1. Protocol synthesis and structures of complexes (**3a-3f**).

is consistent with these observations [46].

For ten days, ^{1}H NMR spectroscopy was used to examine the stability of the silver complexes in solution. On the day their DMSO-d_6 solutions were made, as well as one, four, seven, and ten days later, 1H NMR spectra were captured. It is clear from the results that even after 10 days, the complexes remain stable in solution. Although numerous transition metal ions have been used to catalyze A3-coupling reactions, there isn't much research that uses NHC silver complexes. This study examined the catalytic properties of Ag(I) compounds for a three-component coupling reaction including a few amines, aldehydes, and phenylacetylene. Several solvents were used to conduct the reaction between p-formaldehyde, diethylamine, and phenylacetylene.To assess complex 3a's catalytic capability and improve the reaction conditions, we have chosen the reaction of benzaldehyde, piperidine, and phenylacetylene as our model. We started our optimization method by employing 0.5 mol% of silver-(N-heterocyclic carbene) complex 3a as a catalyst to screen a range of solvents. The reactions were always loaded outside, and technical-grade (nondegassed, nonanhydrous) solvents were utilized. The maximum conversion of the required propargylamine was achieved with DMC in our NHC–Ag(I) system (Figure 2 and Table 1).

We expanded our research to include various aldehyde, piperidine, and alkyne combinations in order to investigate the range of this three-component coupling reaction. Under the reaction conditions, cyclic or acyclic aliphatic aldehydes showed high reactivity. (Entries 1–5 in Table 2. In good to outstanding conversion, aromatic aldehydes with both electron-donating and electron-withdrawing properties provided the matching propargylamines (Table 2, Entries 4-8).

Subsequently, a variety of alkynes were also examined for the A^3-coupling by using paraformaldehyde/piperidine/alkynes (Table 2, Entries 6–8). As can be seen from Table 2, results indicated reactions of aldehydes with electron-withdrawing or electron-donating groups as well as proceeded well and corresponding propargylamines were obtained in excellent conversions. Aromatic alkynes, including phenylacetylene and (p-methylphenyl) acetylene, produced the respective products in great conversion and underwent the three-component coupling smoothly (Table

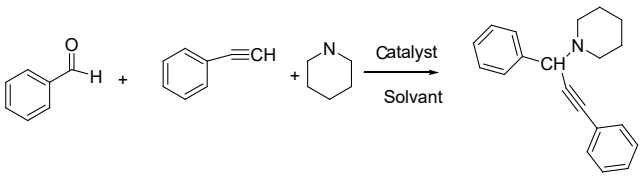


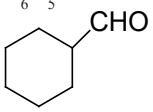
Fig. 1. Catalytic potential of complex **3a** to optimize the reaction conditions.

Table 1. Effect of solvent on the conversion in the A3-coupling reaction catalyzed by complex 3a.

Entry	Solvent	Conversion (%)[a,b,c]
1	acetone	20
2	CH_2Cl_2	46
3	CH_3CN	32
4	DMF	28
5	Toluene	10
6	DMC	92
7	MeOH	85
8	EtOH	80

[a]Reaction conditions: aldehyde (1.0 mmol), piperidine (1.1 mmol), phenylacetylene (1.1 mmol), complex **3a** (0.5 mol%), solvent (0.5 mL), 25°C, 2 h. [b]Conversion into product determined by GC (average of 2 runs). [c]Conditions: complex **3a** (1 mol%), 2 h.

Table 2. A^3 (aldehyde/piperidine/alkyne) coupling reaction catalyzed by silver-(N-heterocyclic carbene) complex **3a**.

Entry	Alkyne	Aldehyde	Conversion (%)[a,b,c]
1	C_6H_5—	CH_2O	55
2	C_6H_5—	C_6H_5CHO	15
3	C_6H_5—		35
4	C_6H_5—	$pCH_3C_6H_5CHO$	32
5	C_6H_5—	$pClC_6H_5CHO$	26
6	C_6H_5—	CH_2O	10
7	$pCH_3C_6H_5$—	CH_2O	90
8	$pBrC_6H_5$—	CH_2O	85

[a]Reaction conditions: aldehyde (1.0 mmol), piperidine (1.1 mmol), phenylacetylene (1.1 mmol), complex **3a** (0.5 mol%), solvent (0.5 mL), 25°C, 3 h. [b]Conversion into product determined by GC (average of 2 runs). [c]Conditions: complex **3a** (1 mol%), 2 h.

2, Entries 7–8).

A comparable process using a similar compound with a 3-methoxybenzyl group on the NHC ligand yielded a 59% yield in a prior study [47]. The complex **3a** catalytic activity may be reduced by the presence of more alkyl groups on the benzyl substituent in this instance. The produced compound exhibits lower activity than monomeric NHC silver complexes when the results are compared, which may be due to steric hindrance. This outcome is in line with previous research [48].

3.2. Antimicrobial activities

The antimicrobial and antifungal properties of the synthesized functionalized precursor salts (2a-f) and Ag-NHC complexes (3a-f) were evaluated. The antimicrobial activity of the synthesized compounds is summarized in Table 3. Amphotericin B and Voriconazole were used as controls for the yeast species, while Ampicillin and Tetracycline served as controls for the bacterial strains. The Minimum Inhibitory Concentration (MIC) values for both the new compounds and the reference antimicrobial agents are provided in Table 3. These MIC values were determined by assessing the activity of the synthesized complexes against antifungal yeasts such as C. albicans and C. glabrata, as well as bacterial strains including E. coli, P. aeruginosa, and S. aureus. The MIC values were analyzed individually for both yeast and bacterial targets.

The synthesized N-Alkyl Benzimidazole salts (2e) exhibited no antimicrobial activity against P. aeruginosa and S. aureus bacteria. The other salts demonstrated varying levels of activity, with MIC values ranging from 100 µg/mL to 800 µg/mL. When tested for antifungal activity against C. albicans, the most effective MIC values were 7.25 µg/mL for 2d, 11.5 µg/mL for 2c, and 13.5 µg/mL for 2f. Against C. glabrata, the lowest MIC values were 50 µg/mL for compounds 2c, 2d, and 2f. The remaining salts showed antifungal effects against yeasts with MIC values ranging from 50 µg/mL to 400 µg/mL.

The antibacterial activities of the synthesized N-Alkyl Benzimidazole–Silver complexes were evaluated against E. coli and S. aureus. For S. aureus, the MIC values were 50 µg/mL for 3d and 25 µg/mL for the other silver complexes. Against P. aeruginosa, the MIC values were 100 µg/mL for 3d and 50 µg/mL for the other silver complexes. The antifungal activities of these complexes against C. albicans were also tested, with MIC values of 12.5 µg/mL for 3c and 3d, and 25 µg/mL for 3a, 3b, 3e, and 3f. For C. glabrata, the MIC values were 25 µg/mL for 3c, 3e, and 3f, and 50 µg/mL for 3a, 3b, and 3d. The strongest antifungal activity was observed in compound 2d against C. albicans, and in compounds 3c, 3e, and 3f against C. glabrata. When evaluating the antibacterial properties of the synthesized complexes, it was found that the precursor salts, as well as the 3d compound, exhibited higher MIC values compared to the other silver complexes. The remaining silver complexes demonstrated consistent MIC values across all bacterial species.

3.3. Anticancer activities

The IC50 values of the synthesized compounds were determined and compared with the anticancer drug Cisplatin. All compounds tested exhibited cytotoxic activity against the cell lines (IC50 < 800 µM), with the IC50 values listed in Table 4.

When comparing the IC50 values of the compounds to those of Cisplatin, all synthesized compounds demonstrated greater cytotoxic activity. Among these, compound 2f showed the lowest cytotoxic activity against all cell lines, while compound 3d exhibited the highest cytotoxic activity.

In a comparison of the IC50 values between healthy and cancerous cells, all compounds displayed higher cytotoxic activity against the A549 cancer cell line compared to the healthy cell line. However, compounds 2b, 2d, 3b, 3f, 3c, and 3d showed lower cytotoxic activity against the HCT116 cancer cell line compared to the healthy cell line.

Table 3. Antifungal and antibacterial MIC (µg /mL) values.

Comp.	*C. albicans*[a]	*C. glabrata*[a]	*E. coli*[a]	*P. aeruginosa*[a]	*S. aureus*[a]
1a	150	220	220	850	830
1b	55	110	220	850	450
1c	11,5	55	110	250	250
1d	7,25	55	110	250	100
1e	200	450	850	Ineffective	Ineffective
1f	13,5	60	95	220	250
2a	26	60	26	70	27
2b	26	60	26	70	7
2c	13,5	28	26	70	257
2d	13,5	55	55	100	55
2e	28	28	26	70	27
2f	28	28	26	70	27
Ampicillin[b]			14,5	450	4,11
Tetracycline[b]			0.75	11,5	0.3
Amphotericin B[b]	0,05	0,1			
Voriconazole[b]	0,4	0,4			

IC50 values were presented as mean ± SD of two independent experiments. [a]: Tested microorganism. ineffective: MIC>800 µg /mL [b]: Reference Drug.

Table 4. Anticancer IC_{50} (μM) values.

	IC_{50} (μM)		
Comp.	**BEAS-2B[a]**	**A549[a]**	**HCT116[a]**
2a	35,42±0,32	16,70±0,23	32,14±0,45
2b	21,77±0,39	13,19±0,42	22,65±0,65
2c	24,02±0,85	14,31±0,66	22,42±0,41
2d	11,31±0,32	5,36±0,14	42,74±0,82
2e	12,13±0,33	5,77±0,22	11,30±0,35
2f	75,85±2,22	32,95±0,55	45,75±0,45
3a	37,31±0,167	18,54±0,91	32,51±1,42
3b	21,812±0,96	12,82±0,09	22,71±0,75
3c	5,38±0,21	3,34±0,13	5,85±0,12
3d	5,32±0,05	1,77±0,04	4,67±0,15
3e	11,75±0,44	6,09±0,08	8,43±0,25
3f	16,4845±0,67	17,40±0,49	33,01±0,23
Cisplatin[b]	1125,41 ± 4,90	205,01 ± 3,34	311,13 ± 2,08

IC_{50} values were presented as mean ± SD of two independent experiments. [a]: Cell lines, [b]: Reference Drug.

Other synthesized compounds showed lower cytotoxic activity against the BEAS-2B cell line than the activity against the HCT116 cancer cell line.

4. Discussion

In conclusion, a novel series of benzimidazolium based NHC ligands and silver complexes was synthesized and characterized by various analytical techniques. It was observed that all the NHC ligands **2** have much fewer activities compared to respective silver complexes 3 due to coordination of silver to carbene carbon of ligands resulting in enhanced antiproliferative effect of Ag(I)-NHC complexes due to participation of silver ions in the cell death mechanism. It is also evident that increase in chain length decreases the activity of ligands while increases that of silver complexes which is attributed to increased lipophilicity that supports the passage of silver cations through cell membrane into the cell where it penetrates into the cell organelles resulting in inhibition of metabolic and respiratory mechanisms. Hence, increased chain length and presence of methyl substituent on benzimidazole ring enhance the biopotency of Ag(I)-NHC complexes.

The activity of silver coordination compounds against bacteria and fungi is strictly connected with their solubility, stability, lipophilicity and rate of release of the Ag + ions. These properties are rigidly ruled by the choice of suitable ligands and by slight modulations in their steric and electronic effects. Structural modifications are normally achieved through changes in the side chains appended to the nitrogen atoms. A simple substitution on a ligand backbone can change the electronic and steric properties of silver complexes. This accounts for a series of slight variations in both steric and electronic properties of the silver complex, which in turn influence the lipophilicity, solubility and stability of the relative complexes [49]. In our previous studies, we reported that the antimicrobial activities increased due to the increase in the lipophilic properties and rate of release of the Ag + ions of the silver-NHC complexes [50]. For this reason, here, we tried to compare the effect of the N-substituents on the stability and lipophilicity by using different N-substituents on the NHC backbone. Also, we think that etherfunctional substituents such as 3-methoxypropyl can increase the solubility in water and therefore silver-NHCs could be more effective in antimicrobial tests. In this way, we aim to better understand the mechanism of action of silver-NHC compounds on bacteria and fungi, to increase our knowledge about the effectiveness of the antimicrobial agents we use and to better adjust this effect.

5. Conclusion

In conclusion, the novel NHC precursor with a benzimidazole core and its Ag(I) complex was successfully synthesized and characterized using 1H, 13C NMR, FTIR, UV-visible spectroscopy, and elemental analysis techniques. Their biological activities, particularly in vitro AChE inhibitory and antioxidant properties, were also evaluated. Structural analyses confirmed the successful synthesis of the predicted compounds (2-3). All synthesized compounds demonstrated good radical scavenging abilities against DPPH and ABTS radicals, with compound 3 showing the highest potency as an inhibitor of these radicals (43.6% and 84.0%, respectively).

Regarding AChE inhibition, compounds 2 and 3 moderately inhibited the enzyme, with compound 2 displaying the lowest IC50 value (7.53 ± 0.60 μM), comparable to the standard drug donepezil. These findings suggest that compound 2 could serve as a promising synthetic model for developing new anticholinesterase drugs and warrants further exploration through in vitro and in vivo anti-ChE assays in future studies. The ability of Ag compounds to catalyze the aldehyde-amine-alkyne coupling reaction was investigated. Among the catalysts, the most effective NHC-supported Ag catalyst was found to be the methoxy-substituted catalyst 3a, which exhibited high activity at 70°C with a 1 mol% loading. The results indicated that catalysts 3a–3f displayed comparable catalytic activity, and the substituents on the NHC ligand had no significant impact on the reaction yields. Additionally, various transition metal complexes derived from these compounds were synthesized, and their catalytic performances were further evaluated.

Interest conflict
Authors reported no conflict of interest.

Author contributions
Aziza Mnasri, Donia Bensalah and Lamia Boubakri: investigation, formal analysis, data curation. Lamjed Mansour: investigation. Mathieu Sauthier: conceptualisation, methodology, Nevin Gürbüz, İsmail Özdemir and Naceur Hamdi writing – review and editing, and supervision.

Consent for publications
The author read and proved the final manuscript for publication**.**

Availability of data and material
All data generated during this study are included in this published article.

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