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Biological Activities of NHC–Pd(II) Complexes Based on Benzimidazolylidene N-heterocyclic Carbene (NHC) Ligands Bearing Aryl Substituents

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Abstract: N-heterocyclic carbene (NHC) precursors (**2a–i**), their pyridine-enhanced precatalyst preparation stabilization and initiation (PEPPSI)-themed palladium N-heterocyclic carbene complexes (**3a–i**) and palladium N-heterocyclic triphenylphosphines complexes (**4a–i**) were synthesized and characterized by elemental analysis and ^{1}H NMR, ^{13}C NMR, IR, and LC–MS spectroscopic techniques. The (NHC)Pd(II) complexes **3–4** were tested against *MCF7* and *MDA-MB-231* cancer cells, *Escherichia coli*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Candida albicans* microorganisms, *Leishmania major* promastigotes and amastigotes, *Toxoplasma gondii* parasites, and Vero cells in vitro. The biological assays indicated that all compounds are highly active against cancer cells, with an $IC_{50} < 1.5$ µg mL^{-1}. Eight compounds proved antibacterial and antileishmanial activities, while only three compounds had strong antifungal activities against *C. albicans*. In our conclusion, compounds **3** (**b**, **f**, **g**, and **h**) and **4b** are the most suitable drug candidates for anticancer, antimicrobial, and antiparasitical.

Keywords: Pd(II)–N-heterocyclic carbene (NHC) complexes; benzimidazolium salts; biological activities; cytotoxicity

1. Introduction

Since the discovery of N-heterocyclic carbenes (NHCs) [1], NHCs have emerged as efficient ligands, and their transition metal complexes have been widely applied as organometallic catalysts [2–8]. In particular, NHC–Pd complexes have been utilized in coupling reactions [2–4]. In many cases, NHC–Pd complexes are formed in situ, which sometimes gives different results compared to those obtained with preformed compounds [9–12]. As a result, a series of well-defined NHC–Pd complexes were developed, and their catalytic activities were fully evaluated in organic transformations [13–26]. The Pd(II)–NHC complexes are the foremost agents and are applied as catalytic agents in many organic reactions [27–29]. They are also promising candidates with diverse bioassays properties [19,30].

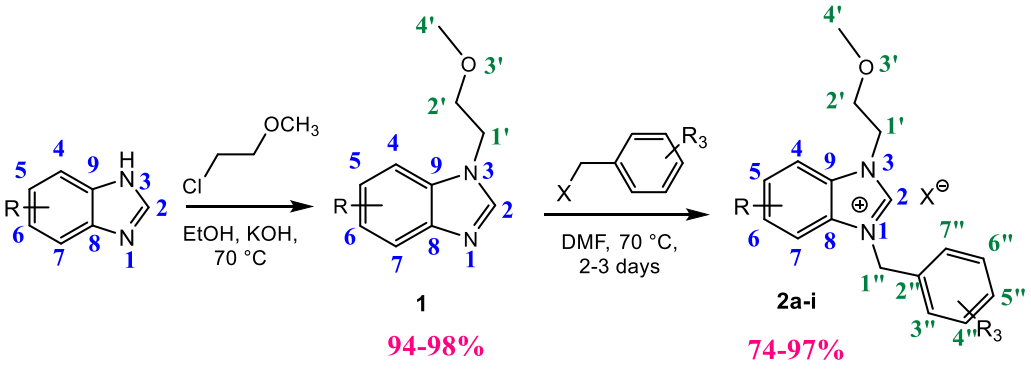
Based on the structural correlations between palladium and platinum complexes, Pd(II)-based complexes have become a group of antitumor compounds of interest with the same activities as Pt(II)-based compounds for metallotherapeutical uses [31]. However, despite their potential activity as antitumor agents, only a few numbers of Pd(II)–NHC compounds have been mentioned previously, but their antitumor activities were found to be more efficient [32–34]. There is similarity in the mode of action for both Pd(II) and Pt(II)–NHC by affecting directly the organelles of cancer cells [35]. In our recent results, we found the structure of Ag(I)–NHC compounds and respective benzimidazolium salt to be of potent antitumor property [36,37].

The aim of this work was to study the activities against cancer cells, *Escherichia coli*, *methicillin-resistant Staphylococcus aureus* (MRSA), *Candida albicans*, *Leishmania major*, *Toxoplasma gondii* of novel benzimidazolium salts **2a-i**, PEPPSI-type N-functionalized N-heterocyclic carbene complexes **3** and palladium N-heterocyclic triphenylphosphine complexes **4**. In addition, their cytotoxicity was tested using Vero cells.

2. Results and Discussion

2.1. Synthesis and Characterization

N-heterocyclic carbene ligands have proven to be very useful for designing new metal complexes for catalysis. [38]. All of the benzimidazolium salts used as NHC precursors were prepared similarly by using the published procedures [39,40]. As shown in Scheme 1, benzimidazole salts **2a–2i** were synthesized in good yields by quaternization of compound **1** in DMF at 70 °C for 3 days with the corresponding arylchlorides or bromides. The benzimidazolium salts **2a–2i** are stable in air and moisture, both in the solid-state and in solution. They were characterized by ^{1}H-NMR, ^{13}C{1H} NMR, IR, and elemental analysis techniques.

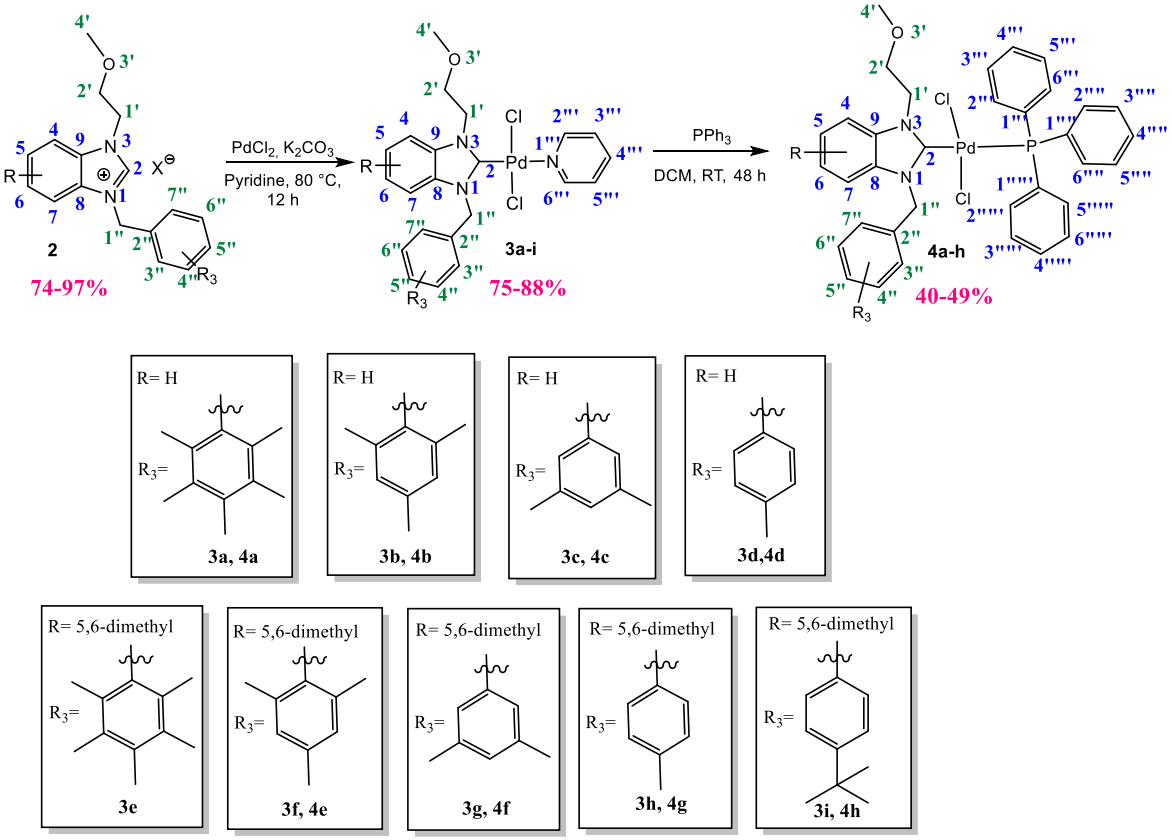


2a: R= H, R_3= 2,3,4,5,6-pentamethyl, X= Cl
2b: R= H, R_3= 2,4,6-trimethyl, X= Cl
2c: R= H, R_3= 3,5-dimethyl, X= Br
2d: R= H, R_3= 4-methyl, X= Br
2e: R= 5,6-dimethyl, R_3= 2,3,4,5,6-pentamethyl, X= Cl
2f: R= 5,6-dimethyl, R_3= 2,4,6-trimethyl, X= Cl
2g: R= 5,6-dimethyl, R_2= 3,5-dimethyl, X= Br
2h: R= 5,6-dimethyl, R_3= 4-methyl, X= Br
2i: R= 5,6-dimethyl, R_3= 4-tertbutyl, X= Br

Scheme 1. Protocol synthesis of benzimidazolium salts **2a–2i**.

The structures of the benzimidazole salts **2** can be easily confirmed by the spectroscopic data of ^{1}HNMR. The characteristic carbonic protons (NCHN) are located at 10.56, 11.06, 11.40, 11.24, 10.01, 10.81, 11.05, 11.23, and 11.27 ppm, respectively. The corresponding methylene protons appear at 4.94, 5.76; 4.91, 5.83; 4.89, 5.73; 4.87, 5.83; 4.83, 5.59; 4.81, 5.74; 4.73, 5.59; 4.78, 5.72; 4.79, and 5.73 ppm,

respectively, which are comparable to the literature reported values [41–44]. As expected, the absence of pro-carbenic protons can be observed upon coordination of the benzimidazole salts with the palladium (II), confirming the formation of the NHC–Pd(II) complexes **3–4**. In the ^{13}C NMR spectra, the signals for the carbene carbon atoms of salts **2a–2i** appear at 142.98, 143.67, 142.62, 142.79, 141.38, 142.32, 141.81, 141.78, and 141.81 ppm, respectively, which are consistent with signals for other NHC–Pd(II) complexes [45]. The Pd(II)–N-heterocyclic carbene (NHC) complexes **3** were synthesized by treatment of the benzimidazolium salts **2** with the precursor $PdCl_2$ in pyridine in the presence of an excess of potassium carbonate. These metal(II) complexes were obtained as colored solids in 75%–88% yield. Complexes **4** were obtained by substitution of the pyridine by the triphenylphosphine, with moderate yields (40%–49%) (Scheme 2).



Scheme 2. Protocol synthesis of Pd(II)–N-heterocyclic carbene (NHC) complexes **3–4.**

The elemental analysis data of the Pd(II)–N-heterocyclic carbene (NHC) complex **3c** is in agreement with the theoretical values for the synthesized complexes. The benzylic -CH_2- proton signals $H_{1'}$ and $H_{1''}$ for complex **3c** as representatives were observed at 5.03 and 5.99 ppm, respectively, and the aromatic protons appeared at δ between 6.86 and 7.48 ppm whilst the pyridine protons were detected as three signals at 7.28, 7.70 and 8.95 ppm.

The carbene carbon signals of Pd(II)–N-heterocyclic carbene (NHC) complex **3c** were observed at δ 163.37 ppm in the ^{13}C NMR spectrum, while the $C_{1'}$ and $C_{1''}$ carbon signals were at δ 48.76 and 53.31 ppm, respectively. The mass spectrum of the same complex gave the most prominent peak at m/z = 295.2.

The ^{1}H NMR spectra of the Pd(II)–N-heterocyclic carbene (NHC) complexes **3–4** showed less intense and downfield shifted signals of benzimidazoles compared to the free ligands. In the ^{13}C NMR spectra of the complexes, a downfield shift in C=N resonance of the ligands upon complexation indicates the binding of benzimidazoles to palladium through the NHC carbene atom. The aromatic carbons of the benzene ring resonate between 112 and 152 ppm. The methyl peak in the Pd(II)–N-heterocyclic

carbene (NHC) complexes **3–4** is observed approximately between 16 and 34 ppm. These results are in agreement with the data of other such complexes [46–49].

2.2. Biological Evaluation

2.2.1. Anticancer Evaluation

Table 1 indicates that all of the compounds were highly efficient and active against the two types of cancer cells investigated in this study. Their IC_{50} were in the range of 1.4 to 0.3 μg mL^{-1}. Regarding *MCF7*, **3g** and **3f** were the most active with IC_{50} = 0.518 and 0.675 μM, respectively.

Table 1. Anticancer activity of Pd(II)–N-heterocyclic carbene (NHC) complexes **3–4**.

Pd(II)–NHC Complexes 3–4	Anticancer Activity IC_{50} in μM	
	MCF7	*MDA-MB-231*
3a	1.180	1.011
3b	1.416	0.885
3c	1.270	1.452
3d	1.677	1.304
3e	1.288	1.127
3f	0.675	1.012
3g	0.518	1.036
3h	1.062	0.708
3i	1.812	1.318
4a	1.160	1.546
4b	1.871	0.936
4c	1.499	1.226
4d	1.111	1.25
4e	1.417	1.031
4f	1.181	1.05
4g	0.802	0.936
4h	1.139	0.886
4i	0.6 ± 0.04	0.4 ± 0.03

2.2.2. Antimicrobial Activities

Table 2 indicates that 8 compounds had antibacterial activity against *E. coli* better than the reference drug, but **3g** and **4f** were the most potent with an inhibition zone (IZ) of 26.3 mm. The compounds **3f**, **4f**, and **4c** were more active compounds than the reference drug against MRSA with IZ of 28.5, 28.0, and 27.0 mm, respectively. Compounds **3b**, **3g**, and **4e** had the best antifungal activity against *C. albicans* with IZ of 32.0, 29.5, and 29.0 mm, respectively. Table 2 NHC metals, particularly silver synthesized compounds as well as copper derivatives, have been previously found to have potent antibacterial activities [50,51]. Our findings support the previous results.

Table 2. Antimicrobial profile of synthesized derivative Pd(II)–N-heterocyclic carbene (NHC) complexes **3–4.**

Pd(II)–NHC Complexes 3–4 [a]	Antimicrobial Activity (50 μg/disc)		
	E.coli	*MRSA*	*C.albicans*
3a	20.3 ± 1.1	17.4 ± 0.3	18.0 ± 0.2
3b	18.3 ± 1.6	17.5 ± 0.4	32.0 ± 0.3
3c	19.3 ± 0.6	19.0 ± 0.1	12.0 ± 0.3
3d	18.3 ± 0.6	15.0 ± 1.0	19.0 ± 0.6
3e	12.0 ± 0.6	18.0 ± 0.8	20.0 ± 0.7
3f	25.0 ± 0.4	28.5 ± 2.5	26.0 ± 0.0
3g	26.3 ± 1.8	26.5 ± 1.4	29.5 ± 1.4
3h	22.4 ± 0.6	23.0 ± 0.1	28.0 ± 0.0
3i	19.0 ± 1.2	18.5 ± 0.6	20.0 ± 0.8
4a	25.0 ± 0.5	22.0 ± 0.4	26.0 ± 0.9
4b	23.0 ± 0.5	26.0 ± 0.5	27.0 ± 0.5
4c	25.0 ± 0.6	27.0 ± 0.5	28.0 ± 0.3
4d	18.5 ± 2.2	19.5 ± 0.6	19.0 ± 0.4
4e	19.3 ± 1.5	18.5 ± 0.6	29.0 ± 0.7
4f	26.3 ± 0.6	28.0 ± 0.0	15.0 ± 0.9
4g	18.3 ± 0.6	15.0 ± 1.5	22.0 ± 0.8
4h	24.0 ± 0.6	20.0 ± 0.3	23.0 ± 0.9
4i	22.0 ± 1.0	24.5 ± 2.5	26.0 ± 0.0
Tetracycline	22.3 ± 1.5	26.5 ± 1.5	-
Fluconazole	-	-	28.0 ± 0.8

Values are mean, value ± standard deviation of three different replicates. [a] The concentration was 50 μg.

2.2.3. Antileishmanial Activities

Table 3 shows that all of the compounds except **3e**, **4g**, and **4h** possess antileishmanial activity against both *L. major* amastigotes and promastigotes in vitro with an IC_{50} less than 7 μg mL^{-1}. Eight compounds had an IC_{50} less than 1.0 μg mL^{-1} against the two stages. Nine compounds had an IC_{50} less than 1.0 μg mL^{-1} against *L. major* amastigotes, namely, **3** (**a**–**d**, **f**, and **h**) and **4** (**a**, **b**, and **i**). In addition, 11 compounds showed an IC_{50} less than 1.0 μg mL^{-1} against *L. major* promastigotes, namely, **3** (**a**–**d**, **f**) and **4** (**a–d**, **f**, and **i**). The SI values of all active compounds were in the range of 6–46.6, which indicates the safety threshold of these compounds. Compound **4b** was the most active and strongest among all of them with an IC_{50} less than 0.2 and 0.4 μg mL^{-1} against *L. major* amastigotes and promastigotes, respectively, with SI values greater than 24 and 12, respectively, better than the results of the amphotericin B (AmB) reference drug. In recent conducted investigations, NHC gold complexes showed promising antileishmanial activities against *L. infantum* promastigotes and amastigotes in vitro [52]. These results support our finding here for Pd(II)–NHC complexes **3–4** against *L. major* promastigotes and amastigotes in vitro.

2.2.4. Antitoxoplasmal Activities

Table 4 indicates that only 7 compounds possess good antitoxoplasmal activity against *T. gondii* in vitro with an IC_{50} less than 5 μg mL^{-1}. These compounds are **3a**, **3b**, **3c**, **3h**, **4a**, **4b**, and **4c** with IC_{50} of 4.2, 3.9, 4.6, 1.2, 4.8, 3.6, and 3.9 μg mL^{-1}, respectively. However, their SI values were found to be less than 2. Although NHC carbene metal complexes with silver and gold derivatives were found in previous studies to show good antiparasitical activities against apicomplexan protozoa such as *Plasmodium* spp. [53], these findings are not in agreement with our results for (NHC) palladium metallic complexes against *T. gondii*.

Table 3. Antileishmanial activity of Pd(II)–N-heterocyclic carbene (NHC) complexes **3–4** against *L. major* promastigotes and amastigotes.

Pd(II)–(NHC) Complexes 3–4	CC_{50} of Vero Cells at μg mL^{-1}	Amastigote IC_{50} at μg mL^{-1}	Promastigotes IC_{50} at μg mL^{-1}	Amastigote SI	Promastigote SI
3a	6.1 ± 1.8	0.5 ± 0.07	0.5 ± 0.09	12.2	12.2
3b	3.6 ± 1.2	0.3 ± 0.04	0.6 ± 0.07	12.0	6.0
3c	6.6 ± 1.7	0.4 ± 0.05	0.6 ± 0.11	16.4	11.0
3d	28.0 ± 3.6	0.6 ± 0.09	0.7 ± 0.13	46.6	39.9
3e	22.8 ± 3.3	17.4 ± 3.8	7.6 ± 1.9	1.3	3.0
3f	16.4 ± 2.8	0.7 ± 0.12	0.6 ± 0.09	23.4	27.3
3g	29.8 ± 6.4	2.7 ± 0.6	3.2 ± 0.7	11.1	9.3
3h	1.8 ± 0.7	0.7 ± 0.09	1.6 ± 0.3	2.6	1.1
3i	15.9 ± 3.0	2.9 ± 0.8	6.3 ± 2.0	5.5	2.5
4a	8.9 ± 2.9	0.3 ± 0.07	0.4 ± 0.07	29.	22.4
4b	4.8 ± 1.5	<0.2	0.4 ± 0.08	>24	12.0
4c	4.9 ± 1.1	1.1 ± 0.6	0.8 ± 0.06	4.5	6.2
4d	6.1 ± 1.6	1.6 ± 0.7	0.4 ± 0.03	3.8	15.2
4e	13.1 ± 2.7	2.4 ± 0.9	1.6 ± 0.5	5.5	8.2
4f	19.9 ± 3.2	1.7 ± 0.7	0.5 ± 0.07	11.7	39.8
4g	34.4 ± 6.6	2.9 ± 0.9	15.4 ± 2.8	11.9	2.2
4h	35.4 ± 5.9	14.3 ± 2.6	32.8 ± 6.1	2.5	1.1
4i	9.9 ± 2.8	0.5 ± 0.03	0.9 ± 0.1	19.8	11.0
AmB	7.4 ± 2.64	0.46 ± 0.07	0.78 ± 0.09	16.09	9.49

Table 4. Antitoxoplasmal activity of Pd(II)–N-heterocyclic carbene (NHC) complexes **3–4** against *T. gondii*.

Pd(II)–NHC Complexes 3–4	CC_{50} of Vero Cells at μg mL^{-1}	Antitoxoplasma IC_{50} at μg mL^{-1}	SI
3a	6.1 ± 1.8	4.2 ± 0.9	1.5
3b	3.6 ± 1.2	3.9 ± 0.9	0.9
3c	6.6 ± 1.7	4.6 ± 1.1	1.4
3d	28.0 ± 3.6	18 ± 3.6	1.6
3e	22.8 ± 3.3	8.1 ± 1.9	2.8
3f	16.4 ± 2.8	13.8 ± 2.7	1.2
3g	29.8 ± 6.4	18.1 ± 2.8	1.6
3h	1.8 ± 0.7	1.2 ± 0.2	1.5
3i	15.9 ± 3.0	8.5 ± 1.7	1.9
4a	8.9 ± 2.9	4.8 ± 1.1	1.9
4b	4.8 ± 1.5	3.6 ± 0.9	1.3
4c	4.9 ± 1.1	3.9 ± 0.8	1.3
4d	6.1 ± 1.6	11.9 ± 2.0	0.5
4e	13.1 ± 2.7	6.3 ± 1.8	2.1
4f	19.9 ± 3.2	38.4 ± 6.5	0.5
4g	34.4 ± 6.6	25.3 ± 4.1	1.4
4h	35.4 ± 5.9	21.7 ± 4.3	1.6
4i	9.9 ± 2.8	7.8 ± 1.7	1.3
ATO Atovaquone is an antitoxoplasma reference drug	9.3 ± 2.08	0.09 ± 0.02	103.33

3. Experimental Section

General Methods

All manipulations were carried out under argon using standard Schlenk line techniques. Chemicals and solvents were purchased from Sigma-Aldrich Co. (Poole, Dorset, UK). The solvents used were purified by distillation and were transferred under argon. DMAc analytical grade (99%) was not distilled before use. KOAc (99%) was employed. Benzimidazoles salts **1–2**, palladium PEPPSI complexes **3**, palladium triphenylphosphine **4**, and biological assays were done according to our

previous work [40,52] and they are given in supplementary materials. Elemental analyses were performed by ElementarVario EL III Carlo Erba 1108 (Malatya, Turkey). The melting points of the complexes and NHC precursors were determined using Stuart automatic melting point apparatus (SMP-40) (Malatya, Turkey). IR spectra were recorded on ATR unit in the range of 400–4000 cm^{-1} with Perkin Elmer Spectrum 100 Gladi ATR FT/IR Spectrophotometer (Malatya, Turkey). ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance III HD spectrometer operating at 400 MHz (^{1}H NMR) and at 100 MHz (^{13}C NMR) in $CDCl_3$ or DMSO-d_6 (Malatya, Turkey). NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, hept = heptet, and m = multiplet signal. The NMR studies were carried out in high-quality 5-mm NMR tubes. The chemical shifts (d) are reported in ppm relative to tetramethylsilane for ^{1}H, ^{13}C NMR spectra as standard. Coupling constants (J values) are given in hertz. The HRMS (ESI) electrospray ionization mass spectra were recorded on a Shimadzu LCMS-IT-Toff spectrometer in $CH_3CN/CHCl_3$. (Malatya, Turkey) Column chromatography was performed using silica gel 60 (70–230 mesh).

4. Conclusions

In this work, Pd(II)–N-heterocyclic carbene (NHC) complexes **3–4** have been already synthesized and characterized starting from benzimidazolium salts (**2a-i**). The molecular structures of the benzimidazolium salts (**2a-i**) and the Pd(II)–N-heterocyclic carbene (NHC) complexes **3–4** have been characterized by elemental analysis and ^{1}H- and ^{13}C-NMR spectra. The present results indicate that all of the synthesized Pd(II)–N-heterocyclic carbene (NHC) complexes **3–4** had potent anticancer activity, particularly **3g**, **3f**, **3h**, and **4i**. The compounds **3f**, **3g**, and **4c** are the most active antibacterial drugs, while **3b**, **3g**, and **4e** proved to be very strong antifungals. In this investigation, 8 compounds were found to be most active against both *L. major* promastigotes and amastigotes with high SI values. Compound **4b** had the most potent activity against *L. major*. These candidates need more investigations of their mode of action and drug standardization.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/10/10/1190/s1. Figure S1. ^{1}H NMR spectrum of complex **3a** in $CDCl_3$, Figure S2. ^{13}C NMR spectrum of complex **3a** in $CDCl_3$, Figure S3. HRMS spectra of complex **3a**, Figure S4. ^{1}H NMR spectrum of complex **3b** in $CDCl_3$, Figure S5. ^{13}C NMR spectrum of complex **3b** in $CDCl_3$, Figure S6. HRMS spectra of complex **3b**, Figure S7. ^{1}H NMR spectrum of complex **3c** in $CDCl_3$, Figure S8. ^{13}C NMR spectrum of complex **3c** in $CDCl_3$, Figure S9. HRMS spectrum of complex **3c**, Figure S10. ^{1}H NMR spectrum of complex **3d** in $CDCl_3$, Figure S11. ^{13}C NMR spectrum of complex **3d** in $CDCl_3$, Figure S12. HRMS spectra of complex **3d**, Figure S13. ^{1}H NMR spectrum of complex **3e** in $CDCl_3$, Figure S14. ^{13}C NMR spectrum of complex **3e** in $CDCl_3$, Figure S15. ^{1}H NMR spectrum of complex **3f** in $CDCl_3$, Figure S16. ^{13}C NMR spectrum of complex **3f** in $CDCl_3$, Figure S17. HRMS spectra of complex **3f**, Figure S18. ^{1}H NMR spectrum of complex **3g** in $CDCl_3$, Figure S19. ^{13}C NMR spectrum of complex **3g** in $CDCl_3$, Figure S20. HRMS spectra of complex **3g**, Figure S21. ^{1}H NMR spectrum of complex **3h** in $CDCl_3$, Figure S22. ^{13}C NMR spectrum of complex **3h** in $CDCl_3$, Figure S23. HRMS spectra of complex **3h**, Figure S24. ^{1}H NMR spectrum of complex **3i** in $CDCl_3$, Figure S25. ^{13}C NMR spectrum of complex **3i** in $CDCl_3$, Figure S26. HRMS spectra of complex **3h**, Figure S27. ^{1}H NMR spectrum of complex **4a** in $CDCl_3$, Figure S28. ^{13}C NMR spectrum of complex **4e** in $CDCl_3$, Figure S29. ^{31}P NMR spectrum of complex **4a** in $CDCl_3$, Figure S30. HRMS spectra of complex **4a**, Figure S31. ^{1}H NMR spectrum of complex **4b** in $CDCl_3$, Figure S32. ^{13}C NMR spectrum of complex **4b** in $CDCl_3$, Figure S33. ^{31}P NMR spectrum of complex **4b** in $CDCl_3$, Figure S34. HRMS spectra of complex **4b**, Figure S35. ^{1}H NMR spectrum of complex **4c** in $CDCl_3$, Figure S36. ^{13}C NMR spectrum of complex **4c** in $CDCl_3$, Figure S37. ^{31}P NMR spectrum of complex **4c** in $CDCl_3$, Figure S38. HRMS spectra of complex **4c**, Figure S39. ^{1}H NMR spectrum of complex **4d** in $CDCl_3$, Figure S40. ^{13}C NMR spectrum of complex **4d** in $CDCl_3$, Figure S41. ^{31}P NMR spectrum of complex **4d** in $CDCl_3$, Figure S42. ^{1}H NMR spectrum of complex **4e** in $CDCl_3$, Figure S43. ^{13}C NMR spectrum of complex **4e** in $CDCl_3$, Figure S44. ^{31}P NMR spectrum of complex **4e** in $CDCl_3$, Figure S45. HRMS spectra of complex **4b**, Figure S46. ^{1}H NMR spectrum of complex **4f** in $CDCl_3$, Figure S47. ^{13}C NMR spectrum of complex **4f** in $CDCl_3$, Figure S48. ^{31}P NMR spectrum of complex **4f** in $CDCl_3$, Figure S49. ^{1}H NMR spectrum of complex **4g** in $CDCl_3$, Figure S50. ^{13}C NMR spectrum of complex **4g** in $CDCl_3$, Figure S51. ^{31}P NMR spectrum of complex **4g** in $CDCl_3$, Figure S 52. ^{1}H NMR spectrum of complex **4h** in $CDCl_3$, Figure S53. ^{13}C NMR spectrum of complex **4h** in $CDCl_3$, Figure S54. ^{31}P NMR spectrum of complex **4h** in $CDCl_3$, Figure S55. HRMS spectra of complex **4h**.

Author Contributions: I.A.N. and N.T. contributed equally. T.K. contributed on achieving biological assays; N.H. and. W.K. writing—original draft preparation; I.Ö., S.Y. and N.H. writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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