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A mild and convenient protocol for the conversion of toxic acid red 37 into pharmacological (antibiotic and anticancer) nominees: Organopalladium architectures

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ABSTRACT

Diverse applications of azo dyes in textiles, paper, leather, cosmetics, pharmaceutical, and food industries along with their deleterious impacts on human beings and aquatic life have raised urgent calls for the treatment of effluent containing azo dyes to remove them or convert them into useful and safe products. This inspires us to modulate acid red 37 to acid red Schiff bases (ARSBs), which were further palladinated to yield monopalladated products (Pd(II)-ARSBs) with an emphasis to obtain new pharmacological (antibiotic and anticancer) candidates. These new cyclopalladated complexes were structurally characterized and pharmacologically evaluated as well for their in vitro antimicrobial, against a common panel of pathogenic G^+ and G^- bacterial and fungal strains, and anticancer activities against human breast carcinoma (MCF-7) cell lines.

1. Introduction

Synthetic dyes, such as acid red 37 (AR-37) and azo dyes, are widely used in the textile, leather, polyamide fiber, cosmetics, and food industries [1]; however, their toxicity, carcinogenic, or genotoxic effects on the environment and humans [2] remain the major drawbacks and limited their wide applications. Moreover, removal of these dyes from the industrial effluents or converting them into useful byproducts before discharge is a great environmental challenge for safe industries [3]. Conventional physico-chemical methods including adsorption, floatation, coagulation, incineration, neutralization, reduction, oxidation, electrolysis, and ion-exchange of these dyes are quite expensive, inapplicable for a wide variety of dyes, and may produce a lot of more toxic sludge and byproducts [4]. Therefore, identification of a novel strategy to detoxify these synthetic dyes is of great interest. Motivated by our interest in the development of new pharmacologically relevant architectures for pharmaceutical applications [5,6], we aimed herein to apply subsequent Schiff-base (SB) condensation and palladination strategies for conversion of AR-37 into pharmacologically useful active products.

Our choice for SBs and their organopalladium complexes as target products is because of their unrivaled features such as simplicity of the preparation, remarkable flexibility of their molecular and electronic structure, and their wide range of pharmacological activities including antibacterial, antifungal, antimalarial, antitubercular, anti-proliferative, anti-inflammatory, and antiviral [7]. Furthermore, many reported azomethine Pd(II) chelates exhibited

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significant promising antiviral, fungicidal, bactericidal, and antitumor activities [8]. Moreover, palladium plays a crucial role in the metallotherapeutic drugs and metal-based diagnostic agents [8]. For example, anticancer screening for organopalladium of acetone SBs that bear *S*-methyldithiocarbazate and *S*-benzyldithiocarbazate compartments against T-lymphoblastic leukemia cell lines demonstrated excellent cytotoxicity in comparison to the standard anticancer drug, tamoxifen [9].

Inspired by the aforementioned literature outputs and in continuation of our endeavor directed toward designing and development of novel biologically potent materials, we planned herein to apply SB condensation and palladination chemistries for conversion of toxic AR-37 into beneficial pharmacologically (antimicrobial and anticancer) active acid red Schiff bases (ARSBs) and *endo*-cyclic five/six-membered cyclopalladated complexes.

2. Experimental section

2.1. Reagents and materials

Chemicals were obtained from the following suppliers and used without further purification: AR-37, 4-chlorobenzaldehyde, 4-methoxybenzaldehyde, anthracen-9(10*H*)-one, 4-nitrobenzaldehyde, and anthracene-9-carbaldehyde (Sigma–Aldrich) and palladium(II) chloride ($PdCl_2$) (Acros).

2.2. Instrumentation

Melting points were measured using a Gallenkamp melting point apparatus; all melting points were measured in open glass capillaries and are uncorrected. Thin layer chromatography was performed with fluorescent silica gel plates HF254 (Merck), and plates were viewed under ultraviolet light at 254 and 265 nm. The elemental analyses for C, H, and N were determined by a Perkin–Elmer Analyzer 2440. Fourier transform infrared (FTIR) spectra were recorded on a Bruker Vector Germany and on a Mattson FTIR spectrophotometer in the range of 400–4000 cm^{-1} as KBr disc with 2 cm^{-1} resolution. For signal intensities the following abbreviations were used: br (broad), sh (sharp), w (weak), m (medium), s (strong), vs (very strong). ^1H NMR spectra were recorded on a Gemini 200 MHz spectrometer, in dimethyl sulfoxide (DMSO)-d_6 solution with calibration to the residual proton solvent signal in DMSO-d_6 (^1H NMR: 2.52 ppm) against tetramethylsilane (TMS) ($\delta = 0.00$ ppm). Multiplicities of the signals were specified as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). The mass spectra of the synthesized compounds were measured on GCQ Finnigan MAT. For the mass spectral assignment, peaks are based on ^{12}C with 12.0000 Da.

2.3. Solvent-free microwave-assisted synthesis of ligands (ARSB**1**–**6**)

AR-37 SB ligands were synthesized according to the literature procedure [10] assisted with microwave irradiation. Generally, in a microwave flask, the AR-37 (0.25 mmol) and appropriate aromatic aldehydes (0.50 mmol) were introduced and homogenized. The mixture was submitted to microwave irradiation at ambient pressure for 15 min at 200 W (150 °C) without the solvent. The crude product was cooled, washed with CH_2Cl_2 (5 mL), and crystallized from the suitable solvent. The pure product was filtered off under reduced pressure. The details for the physical, elemental analysis, and spectral data of all ligands (ARSB**1**–**6**) are provided in our previous work [10].

2.4. Synthesis of organopalladium complexes (Pd(II)-ARSBs)

Generally, 1 mmol of the parent ligand (ARSB**1**–**6**) was added to an ethanolic solution (60 mL) of palladium(II) chloride (1 mmol) containing few drops of concentrated HCl. Then, the mixture was stirred for 4 h under reflux and nitrogen atmosphere, the isolated product was filtered off, washed with cold ethanol (5 mL ×3), ether (5 mL ×3), and finally dried under vacuum. Further crystallization from the methanol affords pure complexes (Pd(II)-ARSBs). Samples of isolated organopalladium complexes were characterized as follow.

[Pd(ARSB**1**)Cl] (Pd-ARSB**1**): Obtained as orange crystals in 80.5% yield; mp = 330 °C. FTIR (KBr, cm^{-1}): 3405 (s, br, $\nu_{(O-H)}$), 3065 (m, sh, $\nu_{asym(C-H)}$, Ar), 3040 (m, sh, $\nu_{sym(C-H)}$, Ar), 2940 (s, br, $\nu_{(C-H)}$), 1644 (s, sh, $\nu_{(C=O)}$), 1599 (s, sh, $\nu_{(C=N)}$, azomethine), 1497, 1421 (s, sh, $\nu_{(C=C_{Ar}+C-H_{bend})}$), 575 (m, sh, $\nu_{(C-Pd)}$). ^1H NMR (200 MHz, DMSO-d_6) δ (ppm): 12.28 (s, 1H), 10.20 (s, 1H), 8.10 (S, 1H), 7.83 (d, $J = 6.8$ Hz, 1H), 7.78–7.65 (m, 5H), 7.59 (s, 1H), 7.45–7.33 (m, 3H), 7.30–7.19 (m, 2H), 7.11–6.98 (m, 3H), 2.50 (s, br, 2H), 2.02 (s, 2H). EI-MS: *m*/*z* (intensity) 883.50 (31.05%) ($C_{32}H_{21}Cl_3N_4O_8PdS_2$ $[M]^{+\bullet}$). Anal. Calcd (%) for $C_{33}H_{21}Cl_3N_4O_8PdS_2$ (M = 866.44 g/mol): C, 44.36; H, 2.44; N, 6.47; S, 7.40. Found (%): C, 44.28; H, 2.56; N, 6.32; S, 7.11.

[Pd(ARSB**2**)Cl] (Pd-ARSB**2**): Obtained as red crystals in 85.5% yield; mp = 327 °C. FTIR (KBr, cm^{-1}): 3435 (s, br, $\nu_{(O-H)}$), 3195 (s, br, $\nu_{(N-H)}$), 3065 (m, sh, $\nu_{asym(C-H)}$, Ar), 3040 (m, sh, $\nu_{sym(C-H)}$, Ar), 2608 (s, br, $\nu_{(C-H)}$), 1644 (s, sh, $\nu_{(C=O)}$), 1598 (s, sh, $\nu_{(C=N)}$, azomethine), 1497, 1393 (s, sh, $\nu_{(C=C_{Ar}+C-H_{bend})}$), 575 (m, sh, $\nu_{(C-Pd)}$). ^1H NMR (200 MHz, DMSO-d_6) δ (ppm): 12.33 (s, 1H), 10.28 (s, 1H), 8.56 (s, 1H), 8.21 (d, $J = 7.1$ Hz, 1H), 7.92 (d, $J = 6.9$ Hz, 2H), 7.79–7.68 (m, 3H), 7.51 (d, $J = 7.2$ Hz, 1H), 7.44 (d, $J = 1.8$ Hz, 1H), 7.38–7.21 (m, 2H), 7.15–7.03 (m, 3H), 3.97 (s, 3H), 3.90 (s, 3H), 2.53 (s, br, 2H). EI-MS: *m*/*z* (intensity) 857.50 (5.06%) ($C_{34}H_{27}ClN_4O_{10}PdS_2$ $[M]^{+\bullet}$). Anal. Calcd (%) for $C_{34}H_{27}ClN_4O_{10}PdS_2$ (M = 857.50 g/mol): C, 47.62; H, 3.17; N, 6.53; S, 7.48. Found (%): C, 47.58; H, 3.25; N, 6.43; S, 7.31.

[Pd(ARSB**3**)Cl] (Pd-ARSB**3**): Obtained as brown crystals in 85.3% yield; mp = 319 °C. FTIR (KBr, cm^{-1}): 3397 (s, br, $\nu_{(O-H)}$), 3299 (s, sh, NH), 3062 (m, sh, $\nu_{asym(C-H)}$, Ar), 3025 (m, sh, $\nu_{sym(C-H)}$, Ar), 2927 (s, br, $\nu_{(C-H)}$), 1658 (s, sh, $\nu_{(C=O)}$), 1595 (s, sh, $\nu_{(C=N)}$, azomethine), 1458, 1403 (s, sh, $\nu_{(C=C_{Ar}+C-H_{bend})}$), 572 (m, sh, $\nu_{(C-Pd)}$). ^1H NMR (200 MHz, DMSO-d_6) δ (ppm): 11.98 (s, 1H), 10.28 (s, 1H), 8.45 (s, 1H), 8.13 (d, $J = 7.3$ Hz, 1H), 7.96–7.78 (m, 5H), 7.63–7.49 (m, 4H), 7.37–7.25 (m, 4H), 7.21–7.07 (m, 4H), 6.96 (d, $J = 1.8$ Hz, 1H), 2.61 (s, br, 2H). EI-MS: *m*/*z* (intensity) 956 (0.56%) ($C_{46}H_{30}ClN_4O_7PdS_2$ $[M-OH]^{+\bullet}$). Anal. Calcd (%) for $C_{46}H_{31}ClN_4O_8PdS_2$ (M = 973.76 g/mol): C, 56.74; H, 3.21; N, 5.75; S, 6.59. Found (%): C, 56.50; H, 3.25; N, 5.54; S, 6.50.