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Hybrid molecules comprising 1,2,4-triazole or diaminothiadiazole Schiff-bases and ionic liquid moieties as potent antibacterial and marine antibiofouling nominees

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ABSTRACT

The buildup of marine biofouling is a serious problem due to its harmful impacts upon maritime activities and mariculture. So there is urgent call to explore novel strategy to battle this phenomenon. In pursuit of this, we have successfully prepared and characterized new thiadiazole-based bis-Schiff-bases and triazole derivatives by a combination of quaternization, heterocyclization, Schiff-base strategies. These new architectures exhibited moderate to excellent and broad-spectrum antibacterial efficacy in comparison to standard antifoulant, Diuron®, against common panel of biofilm-inducing marine bacteria. The new compounds were blended in the matrix of inert commercial paint to formulate anticipated antibiofouling coatings. Our antibiofouling field study reveals that such materials can effectively inhibit the formation of slime films, the adhesion and colonization of diverse marine biofouling organisms such as macroalgae, tube worms, bryozoan, asidian and zooids. Further study is needed on blending these compounds which may offer promising antifouling hybrid composite and novel strategy to fight marine biofouling.

1. Introduction

Marine biofouling, the undesirable growth and colonization of marine micro- and macro-organisms on submerged natural or artificial marine structures, leading to serious environmental and economic negative impacts [1]. More than 4000 marine species are responsible for biofouling [2]. Among these microorganisms, bacteria are considered to be the major microfoulants. Where bacterial adhesion to immersed surface is a crucial step in biofilm formation, the initial step in a complex marine biofouling process [3]. For examples, *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) are responsible for biofouling of fabric and medical devices [4] and their pronounced effect on marine biofouling was reported [5]. Moreover, the marine bacterial strains (*Aeromonas* sp. and *Vibrio* sp.) were found to be essential volunteers in construction bacterial biofilm as a precursor for marine biofouling [6]. To remedy surface biofouling while preserving the bulk properties of the marine structures, metal-based antibiofouling coatings (such as copper(I) compounds and organotin) have been developed [7] and used for a long time to solve the fouling problem. However, due to their severe harmful effects to the marine ecosystem, International Maritime Organization (IMO) put an end to the regime of these antifoulants [8]. Thus, the development of effective and safe antifoulants with synergistic antibacterial efficacy, to prevent the initial settlement of marine bacteria and other macroorganisms over marine-submerged surfaces, remains one of the most important challenging tasks since the primary settlement facilitates secondary colonization by marine creatures [9]. These new antifouling agents may be further incorporated into the matrix of commercial coatings to obtain safe marine eco-friendly antibacterial and antibiofouling coatings for vast applications.

Diversity of the pharmacological properties of 1,3,4-thiadiazoles and triazole including antibacterial [10], antifungal [11],

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antioxidant [12], antidepressant [13], antidiabetic [14], and anti-inflammatory effects [15], makes them two of the most attractive classes of heterocyclic compounds for designing new chemotherapeutic agents. Particularly, thiadiazole-based Schiff bases are of considerable interest due to their widespread antimicrobial, antiviral, analgesic, and anti inflammatory activities [16].

Interestingly, antimicrobial susceptibility assessments of imidazolium, pyridinium and quaternary ammonium ionic liquid (IL)-based architectures revealed significant broad-spectrum biocidal activities [17]. This may be ascribed to strong electrostatic interaction between organic cation and anionic microbial cell wall [18] followed by diffusion and disruption of the cytoplasmic membrane causing leakage of microorganism constituents and finally death [19]. Notably, many ionic liquids display biocidal activity against Gram-positive/-negative bacteria, fungi and algae [20].

Inspired by above literature outputs and in continuation of our endeavor directed toward designing and development of novel biologically potent materials [17a–c,21], we aimed herein to explore the antibacterial and antibiofouling profiles of novel IL-based 1,3,4-thiadiazoles Schiff bases and triazole derivative for exploration a new generation of safe eco-marine friendly antibiofoulants.

2. Experimental section

2.1. Materials

Chemicals were obtained from the following suppliers and used without further purification: salicylaldehyde (Sal), 4-*tert*-butylphenol, 1,2-dimethylimidazole (1,2-Me_2-Im), 2-Methylpyridine (2-picoline, Pic), 4-methoxyphenyl isothiocyanate and hydrazine monohydrate (Sigma–Aldrich), paraformaldehyde ($(CH_2O)_n$) (Roth), anhydrous zinc chloride ($ZnCl_2$) (Grüssing GmbH), thiosemicarbazide hydrochloride (3) (TCI), potassium thiocyanate (KSCN), anhydrous potassium carbonate (K_2CO_3), sodium bicarbonate ($NaHCO_3$) sodium sulphate anhydrous (Na_2SO_4), sodium hydroxide (NaOH) and 3% hydrogen peroxide (H_2O_2) (ADWIC) and ethyl chloroacetate (Acros).

2.2. Instrumentation

Elemental analyses for C, H, N and S were performed with a Perkin–Elmer 263 elemental analyzer. FT-IR spectra were recorded on a BRUKER Tensor-37 FT-IR spectrophotometer in the range 400–4000 cm^{-1} as KBr discs or in the 4000–550 cm^{-1} region 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). NMR-spectra were obtained with a Bruker Avance DRX200 (200 MHz for ^1H) or Bruker Avance DRX500 (500 MHz for ^{13}C) spectrometer with calibration to the residual proton solvent signal in DMSO-d_6 (^1H NMR: 2.52 ppm, ^{13}C NMR: 39.5 ppm), $CDCl_3$ (^1H NMR: 7.26 ppm, ^{13}C NMR: 77.16 ppm) against TMS with $\delta = 0.00$ ppm. Multiplicities of the signals were specified s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). The mass spectra of the synthesized compounds were acquired in the linear mode for positive ions on UHR-QTOF maXis 4G (Bruker Daltonics) and BRUKER Ultraflex MALDI-TOF instrument equipped with a 337 nm nitrogen laser pulsing at a repetition rate of 10 Hz. The 2+ charge assignment of ions in HR-ESI–MS was confirmed by the $m/z - 0.5$ difference between the isotope peaks (x, x + 1, x + 2). The MALDI matrix material (1,8-dihydroxy-9(10H)-anthracenone (dithranol, DIT, $C_{14}H_{10}O_3$, M = 226.077 g/mol)) was dissolved in chloroform at a concentration of 10 mg/mL. MALDI probes were prepared by mixing compound solution (1 mg/mL in CH_2Cl_2) with the matrix solution (1:10, v/v) in a 0.5 mL Eppendorf® micro tube. Finally 0.5 mL of this mixture was deposited on the sample plate, dried at room temperature and then analyzed. Peaks with chlorine showed the isotope ratio $^{35/37}Cl = 75.8:24.2$. For the mass spectral assignment: Peaks are based on ^{12}C with 12.0000 Da and ^{35}Cl with 34.968 Da.

2.3. Synthesis of 5-chloromethyl-salicylaldehyde (**1**)

It was synthesized as described in the literature [17]. Obtained as white needles (65.0% Yield). ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 11.12 (s, 1H, Ar—O**H**) 9.93 (s, 1H, Ar—**H**C=O), 7.57 (m, 2H, 2 × Ar—**H**), 7.00 (d, 1H, $J_{HH} = 8.34$ Hz, Ar—**H**), 4.58 (s, 2H, C**H**$_2$—Ar).

2.4. Preparation of salicylaldehyde ionic liquids (Sal-ILs, **2***a,b*)

They were prepared according to procedure described in the literature [17]. To a vigorously stirred solution of *N*-heterocyclic derivatives (21.39 mmol) in dry toluene (25 mL) at room temperature was added the solution of chloromethyl-salicylaldehyde **1** (4.15 g, 19.50 mmol) in dry toluene (25 mL), drop-wise over 30 min, under nitrogen atmosphere. The resulting solution was stirred under nitrogen atmosphere at 60 °C for 24 h. After cooling, the isolated products were washed intensively with 2 × 5 mL dry toluene, several with ether (5 × 10 mL), to remove the unreacted materials, and dried under vacuum to give the desired products which used for the following preparations without further purification.

3-(3-formyl-4-hydroxybenzyl)-1,2-dimethylimidazolium chloride (**2**a): Obtained as of white solid, Yield (4.63 g, 89%). FTIR (KBr, cm^{-1}): 3373 (m, br, $\nu_{(O—H)}$), 2989 (m, sh, $\nu_{(C—H)asym}$, CH_3), 1669 (vs, sh, $\nu_{(C=O)}$), 1547, 1455, 1399 (s, sh, $\nu_{(C=CAr+C—Hbend)}$), 1274 (s, sh, $\nu_{(Ar—O)}$), 1153 (s, sh, $\nu_{(H—C=C+H—C=N)bend}$, Im). ^1H NMR (200 MHz, DMSO-d_6) δ (ppm): 10.80 (s, 1 H, Ar—O**H**), 10.33 (s, 1 H, Ar—**H**C=O), 7.84 (d, $J = 1.76$ Hz, 1 H, N (1)C**H**CHN(3)), 7.67 (d, $J = 2.01$ Hz, 2H, 2 × Ar—**H**), 7.55 (d, $J = 1.69$ Hz, 1 H, N (1)CHC**H**N(3)), 7.41 (m, 3H, 3 × Ar—**H**), 5.38 (s, 2H, N(3)—C**H**$_2$—Ar), 3.86 (s, 3H, N (1)—C**H**$_3$), 2.60 (s, 3H, C(2)—C**H**$_3$). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 197.23, 160.18, 144.71, 137.45, 136.23, 131.03, 127.72, 122.80, 121.91, 120.13, 51.34, 35.39 and 22.16. MALDI-TOF MS, *m/z*: 231.21 ($[C_{13}H_{15}N_2O_2]^+$, M − Cl^-).

3-(3-Formyl-4-hydroxybenzyl)-2-methylpyridinium chloride (**2**b): Obtained as pale yellow solid (4.68 g, 91%). FTIR (KBr, cm^{-1}): 3385 (m, br, $\nu_{(O—H)}$), 2959 (m, sh, $\nu_{(C—H)asym}$, CH_3), 1661 (vs, sh, $\nu_{(C=O)}$), 1573, 1485, 1455 (s, sh, $\nu_{(C=CAr+C—Hbend)}$), 1273 (s, sh, $\nu_{(Ar—O)}$), 1149 (s, sh, $\nu_{(H—C=C+H—C=N)bend}$, Py). ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 10.83 (s, 1H, Ar—O**H**) 10.30 (s, 1H, Ar—**H**C=O), 9.15 (d, $J = 2.10$ Hz, 1H, Py—**H**), 8.68 (m, 2H, Py—**H**), 7.84 (d, 1H, $J = 1.39$ Hz, Py—**H**), 7.75 (d, $J_{HH} = 1.41$ Hz, 1H, Ar—**H**), 7.38 (m, 2H, 2 × Ar—**H**), 5.45 (s, 2H, —C**H**$_2$—Ar), 2.73 (s, 3H, C**H**$_3$). ESI MS: In positive mode peaks at *m/z*: 228.10 ($[C_{14}H_{14}NO_2]^+$, M − Cl^-).

2.5. Synthesis of bithiourea (**4**)

It was synthesized from thiosemicarbazide hydrochloride (**3**) according to the method described by Adediji et al. [22] . Obtained as white crystals, m. p. 203 °C (Lit 201 °C), Yield (52.65%). FTIR (KBr, cm^{-1}): 3356 (s, sh, $\nu_{(N—H)asym}$), 3273 (s, sh, $\nu_{(N—H)sym}$), 3169 (s, sh, $\nu_{(S—H)}$), 1610 (s, sh, $\nu_{(C=N)}$), 1511 (s, sh, $\nu_{(N—H)\ bend}$), 1466 (s, sh, $\nu_{(C=S)}$), 1284 (m, sh, $\nu_{(C—N)}$), 1044 (m, sh, $\nu_{(C—S—C)}$), 826 (m, sh, $\nu_{(C—S—C)bend}$).

2.6. Synthesis of 1,3,4-thiadiazole-2,5-diamine (**5**)

It was synthesized according to reference [22] with slight modification, in brief, bithiourea (3.01 g, 18.2 mmol) was added dropwise with stirring to aqueous hydrogen peroxide solution