

Synthesis of Novel Triazole-Linked Schiff Base Derivative

Aysegul GUMUS

Van Yuzuncu Yil University

Selcuk GUMUS

Van Yuzuncu Yil University

Abstract: The nitrogen atom of azomethine C=N double bond in Schiff base exhibits a strong affinity for transition metal ions. Schiff base derivatives incorporating a fluorescent moiety are appealing tools for optical sensing of metal ions. In this work, fluorescent Schiff base derivatives were synthesized by reacting triazole-linked salicylaldehyde derivative with aminopyrene and aminoanthracene, which are very good fluorophores. These compounds have high potential to be used as metal chemosensors. Detection of a specific type of a metal is very important in terms of bio-use of the related compound. In order to determine the sensitivity of the novel compounds, a series of spectroscopic measurements were carried out upon synthesis. Moreover, the metal coordination characteristics of the new compounds were also investigated theoretically at the level of Density Functional theory with the application of B3LYP/6-31++G(d,p), which is a combination of hybrid exchange function and basis set.

Keywords: Schiff base, Anthracene, Pyrene, Triazole

Introduction

The evolution of fluorescence sensing has been known as an essential and fascinating research field of analytical chemistry at present, due to its simplicity in measurements, low detection limit, low cost, real-time analysis and quantified applications in the environment, biological systems and molecular catalysis[1-6].

Molecular probes containing pyrene or anthracene framework were well suited for the development of chemosensors due to their extended π -conjugation property, chemical stability, high quantum yield and effective photoluminescence features [7-10].

Schiff bases are known to be good ligand for metal ions [11] and used to develop chemosensors since the nitrogen atom of azomethine C=N double bond in Schiff base exhibits a strong affinity for transition metal ions. Schiff base metal complexes have numerous applications like antitumor properties [12], antioxidative activities [13], and attractive electronic and photophysical properties [14]. In addition, Schiff base derivatives incorporating a fluorescent moiety are appealing tools for optical sensing of metal ions. Tetradentate ligands such as salen- or pyridine-type symmetrical Schiff bases are capable of forming complexes with certain metal ions which can exhibit unusual coordination, high thermodynamic stability, good fluorescent properties and biological activities [15].

Triazole-containing compounds show various biological activities including antimicrobial [16], anti-inflammatory [17], antidepressant [18], anticonvulsant [19], antifungal [20], enzyme inhibition [21] activities. 1,2,3-Triazoles have also a wide range applications in industry as anticorrosive agents, dyes, photostabilizers, photographic materials, and agrochemicals [22–24]. Remarkable stability toward metabolic transformations, H-bonding capability, and high dipole moment make triazoles attractive building components [25–27].

Motivated by these studies, Schiff base structure was built between benzyl substituted salicylaldehyde and amino anthracene. Triazole bridge connecting benzyl and salicylaldehyde could furnish an extra binding site.

- This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 Unported License, permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

- Selection and peer-review under responsibility of the Organizing Committee of the Conference

Salicylaldehyde was connected with anthracene by C=N structure. Anthracene and pyrene were employed as fluorophore due to their outstanding photophysical properties and easy modification [28]. The C=N structure might provide another binding state, which could improve the selectivity.

Experimental

General

All experiments were carried out in pre-dried glassware an inert atmosphere of argon. All the chemicals used in the biologic assay studies were purchased from Sigma (Sigma-Aldrich GmbH, Sternheim, Germany). ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ on a Agilent NMR spectrometer (400 MHz). ¹H (400 MHz) and ¹³C NMR (100 MHz) were recorded in CDCl₃ and the chemical shifts are expressed in ppm relative to CDCl₃ (δ 7.26 and 77.0 for ¹H and ¹³C NMR, respectively) as the internal standard.

Flash column chromatography was performed by using thick-walled glass columns and silica gel (60-mesh; Merck). The reactions were monitored by thin-layer chromatography (TLC) using Merck 0.2-mm silica gel 60 F254 analytical aluminium plates, visualized by UV light.

Synthesis of 2-(prop-2-ynyloxy)benzaldehyde, 1.

Salicylaldehyde (1.2 g, 10 mmol) was dissolved in 30 mL THF. K₂CO₃ (4.14 g, 30 mmol) was added and the mixture was refluxed for 30 min. Then propargyl bromide (1.7 mL, 12 mmol) was added slowly. The mixture was refluxed overnight and cooled. After filtration solvent was evaporated. Crude product was purified by column chromatography (EtOAc: Hexane 1:5).

White solid. (1.52 g, 95% yield); ¹H NMR (CDCl₃, 400 MHz): δ 10.49 (s, 1H), 7.86 (dd, *J*=1.8 and 7.7 Hz, 1H), 7.59-7.55 (m, 1H), 7.13-7.07 (m, 2H), 4.83 (d, *J*=2.4 Hz, 2H), 2.57 (t, *J*=2.4 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 189.5, 159.7, 135.7, 128.6, 125.5, 121.7, 113.2, 56.4.

Synthesis of 2-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde, 2.

A mixture of benzyl bromide (1 mmol), 2-(prop-2-ynyloxy), salicylaldehyde (1 mmol), L-proline (24 mg, 0.2 mmol), Na₂CO₃ (24 mg, 0.2 mmol), NaN₃ (65 mg, 1 mmol), sodium ascorbate (20 mg, 0.1 mmol), DMSO/H₂O (18:2, 2.0 mL), and CuSO₄·5H₂O solution (1 M, 0.05 mL) in a 20 mL scintillation vial was stirred overnight at 65°C. The crude mixture was poured into cold dilute NH₄OH solution (30 mL) and extracted with ethyl acetate (3×20 mL). The collected organic layer was washed with brine, dried over MgSO₄, and concentrated in *vacuo*. The crude product was purified by flash column chromatography.

White solid. (264 mg, 90% yield); ¹H NMR (CDCl₃, 400 MHz): δ 10.40 (s, 1H), 7.80 (dd, *J*=1.8 and 7.7 Hz, 1H), 7.58 (s, 1H), 7.56-7.51 (m, 1H), 7.40-7.35 (m, 3H), 7.28-7.26 (m, 2H), 7.14 (d, *J*=8.4 Hz, 1H), 7.04 (t, *J*=7.7 Hz, 1H), 5.54 (s, 3H), 5.30 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 189.5, 160.4, 143.7, 136.0, 134.3, 129.2, 128.9, 128.6, 128.1, 122.8, 121.3, 113.0, 62.6, 54.3.

General procedure for the synthesis of Schiff Bases, SB-1 and SB-2.

2-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde 2 (147 mg, 0.5 mmol) and aryl amine (0.5 mmol) were dissolved in 5 mL ethanol. Reaction mixture was mixed at room temperature overnight. Solid was filtered and dried.

(E)-N-(2-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)benzylidene)anthracen-1-amine, SB-1.

Yellow solid. (190 mg, 81% yield); ¹H NMR (CDCl₃, 400 MHz): δ 8.99 (s, 1H), 8.86 (s, 1H), 8.42 (s, 2H), 8.00 (s, 2H), 7.87-7.82 (m, 1H), 7.48-7.40 (m, 5H), 7.28 (s, 3H), 7.16 (s, 4H), 6.93 (s, 1H), 5.43 (s, 2H), 5.28 (s, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 158.2, 156.1, 150.3, 143.9, 136.0, 132.9, 132.1, 131.9, 131.5, 129.2, 129.1,

128.7, 128.3, 128.1, 128.0, 127.9, 127.8, 125.9, 125.8, 125.6, 125.5, 125.3, 122.9, 122.8, 121.6, 112.8, 111.4, 62.6, 54.2.

(E)-N-(2-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)benzylidene)pyren-1-amine, SB-2.

Yellow solid. (214 mg, 87% yield); ¹H NMR (CDCl₃, 400 MHz): δ 9.08 (s, 1H), 8.63 (d, *J*=9.1 Hz, 1H), 8.44 (dd, *J*=1.8 and 7.7 Hz, 1H), 8.17-8.13 (m, 3H), 8.08-7.98 (m, 4H), 7.65 (d, *J*=8.1 Hz, 1H), 7.50-7.47 (m, 2H), 7.28-7.25 (m, 3H), 7.19-7.15 (m, 4H), 5.47 (s, 2H), 5.32 (s, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 158.3, 156.7, 146.5, 144.1, 134.3, 132.8, 131.5, 129.4, 129.1, 128.8, 128.1, 128.0, 127.3, 126.9, 126.5, 126.0, 125.5, 125.2, 124.9, 124.8, 123.4, 122.7, 121.6, 115.7, 112.9, 62.7, 54.2.

Computational Method

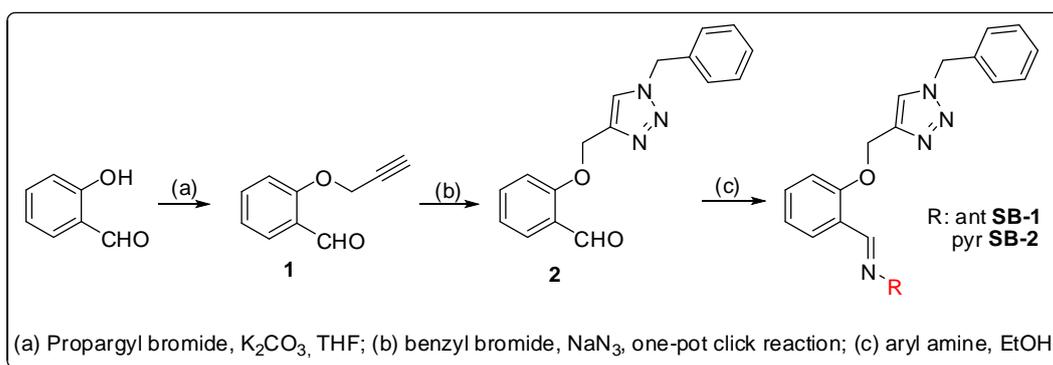
The three-dimensional ground state (*S*₀) geometry of the compound was geometry optimized using Density Functional Theory (DFT) by using the Gaussian 09W package program and the hybrid functional B3LYP. The B3LYP is composed of Becke's three parameter exchange functional (B3) and the nonlocal correlation functional by Lee, Yang, and Parr (LYP). The basis set used for all atoms was 6-31++G(d,p) in both DFT and time-dependent density functional theory (TD-DFT) method. We have applied default G09 grid for computations.

For the nonel compound, vibrational analyses were carried out using the same basis set employed in the corresponding geometry optimizations. The frequency analysis of none of the compounds yielded any imaginary frequencies, indicating that the structure of each molecule corresponds to at least a local minimum on the potential energy surface. The normal mode analysis was performed for 3N-6 vibrational degrees of freedom, N being the number of atoms in the molecule.

The low-lying triplet (*T*) and singlet excited states (*S*) of the compounds were relaxed to obtain their minimum energy geometries using the TD-DFT as implemented in G09 package program. The vertical excitation energies and oscillator strengths were obtained for the lowest triplet and singlet transitions at the optimized ground state equilibrium geometries by using TD-DFT at the same hybrid functional and basis set [22]. Optimized ground state structures were utilized to obtain the electronic absorption spectra, including maximum absorption wavelengths, oscillator strengths, and main configuration assignment by using TD-DFT.

Results and Discussion

The key substrate 2-(prop-2-ynyloxy)benzaldehyde was synthesized by the addition of propargyl bromide to commercially available salicylaldehyde by O-propargylation method (Scheme 1). Terminal acetylene unit on 2-(prop-2-ynyloxy)benzaldehyde **1** make it a valuable candidate for one-pot synthesis of the target triazole structure **2**. Aliphatic and aromatic azides from corresponding halides can easily be generated as intermediates in one-pot synthesis method and converted to desired triazole derivatives without isolation. The operational simplicity of this method makes it attractive for wide variety of applications. Initially, 2-(prop-2-ynyloxy)benzaldehyde was employed in one-pot, two-step procedure by reacting with sodium azide and benzyl bromide (Scheme 1).



Scheme 1. Synthesis of Schiff-base derivatives

The Schiff bases **SB-1** and **SB-2** were prepared by the condensation reaction of triazole-substituted salicylaldehyde with the corresponding amino anthracene and amino pyrene as illustrated in Figure 1 below.

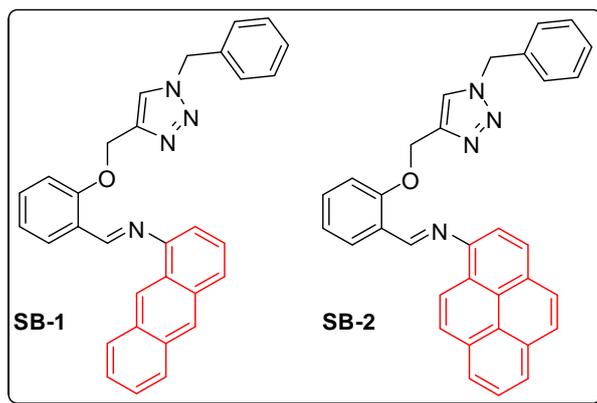


Figure 1. Synthesized Schiff bases

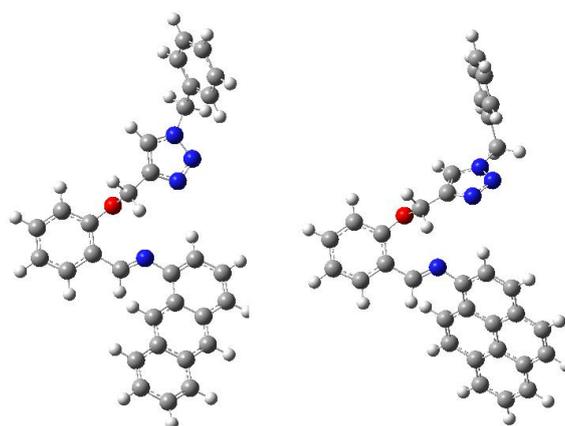


Figure 2. Geometry optimized structures of Schiff bases

The geometry optimizations of the compounds have been performed at B3LYP/6-31++G(d,p) level of theory. After obtaining the ground state geometries of the Schiff bases we have went through the metal coordination process with Zn^{2+} ion. The metal coordination is proven upon TDDFT investigation of the UV-Vis spectra of the compounds. In Figure 3, the structures of the compounds and corresponding spectra are given. As can be observed there exist a visible band at around 420 nm on both structure without metals. We observe a red-shift at these band upon metal addition to the system, which proves the metal coordination at triazole and imine nitrogens.

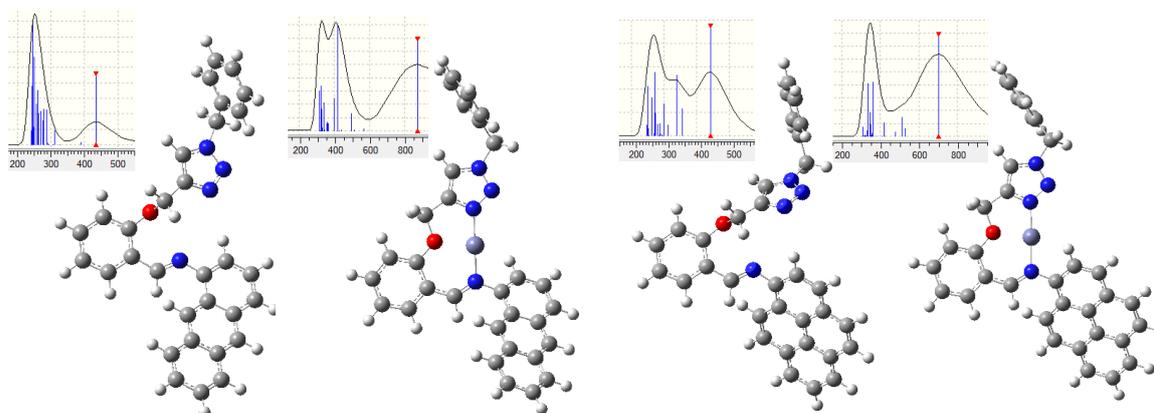


Figure 3. Geometry optimized structures and corresponding UV-Vis spectra of the Schiff bases.

Conclusion

In conclusion, propargyl unit was attached to salicylaldehyde by O-propargylation and alkyne derivative was obtained. Then, triazole-substituted salicylaldehyde **2** was synthesized with high yield by one-pot method.

Target fluorescent Schiff-bases were isolated from the reaction of aldehyde group on salicylaldehyde ring with amino anthracene and amino pyrene successfully.

Theoretical calculation on the coordination ability of the compounds showed that the UV-Vis spectra of the compounds are highly sensitive to metal coordination. TDDFT computations of the metal coordinated Schiff bases yielded red-shifted bands.

Acknowledgements or Notes

We are grateful to Presidency of Scientific Research Projects of Van Yuzuncu Yil University for financial support (FDP-2019-7847).

References

- A.P. de Silva, H.Q. Gunaratne, T. Gunnlaugsson, A.J.M. Huxley, C.P. McCoy, J.T. Rademacher, T.E. Rice, Signaling Recognition Events with Fluorescent Sensors and Switches, *Chem. Rev.* 97 (1997) 1515-1566.
- R. Hu, J. Feng, D.H. Hu, S.Q. Wang, S. Li, Y. Li, G.Q. Yang, A Rapid Aqueous Fluoride Ion Sensor with Dual Output Modes, *Angew. Chem., Int. Ed.* 49 (2010) 4915-4918.
- J. Fan, M. Hu, P. Zhan, X. Peng, Energy transfer cassettes based on organic fluorophores: construction and applications in ratiometric sensing, *Chem. Soc. Rev.* 42 (2013) 29-43.
- Y. Yang, Q. Zhao, W. Feng, F. Li, Luminescent Chemodosimeters for Bioimaging, *Chem. Rev.* 113 (2013) 192-270.
- X. Lim, The Nanoscale Rainbow, *Nature.* 531 (2016) 26.
- M. Gao, B.Z. Tang, Fluorescent Sensors Based on Aggregation-Induced Emission: Recent advances and perspectives, *ACS Sens.* 2 (2017) 1382-1399.
- G.B. Demirel, B. Daglar, M. Bayindir, Extremely fast and highly selective detection of nitroaromatic explosive vapours using fluorescent polymer thin films, *Chem Commun.* 55 (2013) 6140-6142.
- (a) L. Ding, Y. Fang, Chemically assembled monolayers of fluorophores as chemical sensing materials, *Chem Soc Rev.* 11 (2010) 4258-4273. (b) G. Sivaraman, A.Gulyani, Chemically diverse small molecule fluorescent chemosensors for copper ion. *Coord. Chem rev.*, 357 (2018) 50-104
- S. Shanmugaraju, H. Jadhav, R. Karthik, P. S. Mukherjee, Electron rich supramolecular polymers as fluorescent sensors for nitroaromatics, *RSC Adv.* 15 (2013) 4940-4950.
- R. Pandey, L. Reddy, S. Ishihara, A. Dhir, V. Krishnan, Conformation induced discrimination between picric acid and nitro derivatives/anions with a Cu-pyrene array: the first decision making photonic device , *RSC Adv.* 3 (2013) 21365-21368.
- D.M. Epstein, S. Choudhary, M.R. Churchill, K.M. Keil, A.V. Eliseev, J.R. Morrow, Chloroform-Soluble Schiff-Base Zn(II) or Cd(II) Complexes from a Dynamic Combinatorial Library, *Inorg. Chem.* 40 (2001) 1591-1596.
- V.C. Da Silveira, J.S. Luz, C.C. Oliveira, I. Graziani, M.R. Ciriolo, A.M. Ferreira, Double-strand DNA cleavage induced by oxindole-Schiff base copper(II) complexes with potential antitumor activity, *J. Inorg. Biochem.* 102 (2008) 1090-1103.
- Y. Li, Z.Y. Yang, DNA binding affinity and antioxidative activity of copper(II) and zinc(II) complexes with a novel hesperetin Schiff base ligand, *Inorg. Chim. Acta* 362 (2009) 4823-4831.
- S. Kasselouri, A. Garoufis, A. Katehanakis, G. Kalkanis, S.P. Perlepes, N. Hadjiliadis, 1:1 Metal complexes of 2-(2'-pyridyl)quinoxaline, a ligand unexpectedly formed by the reaction between 2-acetylpyridine and 1,2-phenylenediamine, *Inorg. Chim. Acta* 207 (1993) 255-258.
- G. A. Morris, H. Zhou, C.L. Stern, S.T. Nguyen, A General High-Yield Route to Bis(salicylaldehyde) Zinc(II) Complexes: Application to the Synthesis of Pyridine-Modified Salen-Type Zinc(II) Complexes, *Inorg. Chem.* 40 (2001) 3222-3227.
- S. Esvaran, A. V., Adhikari, N. S. Shetty, Synthesis and antimicrobial activities of novel quinoline derivatives carrying 1,2,4-triazole moiety, *Eur. J. Med. Chem.* 44 (2009) 4637-4647.

- S. S. Kumar, H. P. Kavitha, Synthesis and biological applications of triazole derivatives, *Mini-Rev. Org. Chem.* 10 (2013) 40–65.
- C. Radhika, A. Venkatesham, M. Sarangapani, Synthesis and antidepressant activity of disubstituted-5-aryl-1,2,4-triazoles, *Med. Chem. Res.* 31 (2012) 3509–3513.
- T. Plech, J. J. Luszczki, M. Wujec, J. Flieger, M. Pizon, Synthesis, characterization and preliminary anticonvulsant evaluation of some 4-alkyl-1,2,4-triazoles, *Eur. J. Med. Chem.* 60 (2013) 208–215.
- P. M. Chaudhary, S. R. Chavan, F. Shirazi, M. Razdan, P. Nimkar, S. P. Maybhate, A. P. Likhite, R. Gonnade, B. G. Hazara, S. R. Deshpande, Exploration of click reaction for the synthesis of modified nucleosides as chitin synthase inhibitors, *Bioorg. Med. Chem. Lett.* 17 (2009) 2433–2440.
- J. P. Zhou, H. B. Zhang, H. Qian, L. Lin, W. L. Huang, S. J. Ni, Synthesis and biological evaluation of aromatase inhibitors, *Lett. Drug Design Discov.* 6 (2009) 181–185.
- B. S. Holla, N. S. Mahalinga, Synthesis, characterization and antimicrobial activity of some substituted 1,2,3-triazoles, *Eur. J. Med. Chem.* 40 (2005) 1173–1178.
- M. A. Elmorsi, A. M. Hassanein, Corrosion inhibition of copper by heterocyclic compounds, *Corros. Sci.* 41 (1999) 2337–2352.
- D. K. Kim, J. Kim, H. J. Park, Synthesis and biological evaluation of novel 2-pyridinyl-[1,2,3]triazoles as inhibitors of transforming growth factor beta 1 type 1 receptor, *J. Bioorg. Med. Chem. Lett.* 14 (2004) 2401–2405.
- T. S. Seo, Z. Li, H. Ruparel, J. Lu, Click chemistry to construct fluorescent oligonucleotides for DNA sequencing, *J. Org. Chem.* 68 (2003) 609–612.
- K. Sivakumar, F. Xie, B. M. Cash, S. Long, H. N. Barnhill, A Fluorogenic 1,3-dipolar cycloaddition reaction of 3-azidocoumarins and acetylenes, *Org. Lett.* 6 (2004) 4603–4606.
- A. Dondoni, A. Marra, “Click chemistry” inspired synthesis of *pseudo*-oligosaccharides and amino acid glycoconjugates, *J. Org. Chem.* 71 (2006) 364–367.
- J. Chan, S. C. Dodani and C. J. Chang, Reaction-based small-molecule fluorescent probes for chemoselective bioimaging, *Nature Chemistry* 4 (2012) 973–984.

Author Information

Aysegul Gumus

Van Yuzuncu Yil University

Department of Chemistry

Contact E-mail: gumusa@gmail.com**Selcuk Gumus**

Van Yuzuncu Yil University

Department of Chemistry