MATTER: International Journal of Science and Technology
ISSN 2454-5880

Gümüs & Gümüs, 2017

Volume 3 Issue 2, pp. 165-176

Date of Publication: 18th September 2017

DOI-https://dx.doi.org/10.20319/mijst.2017.32.165176

This paper can be cited as: Gümüş, A., & Gümüş, S. (2017). Synthesis and Computational Calculations of Novel Chiral BIS-1, 2, 3-Triazole Derivatives. MATTER: International Journal of Science and Technology, 3(2), 165-176.

SYNTHESIS AND COMPUTATIONAL CALCULATIONS OF NOVEL CHIRAL BIS-1, 2, 3-TRIAZOLE DERIVATIVES

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Abstract

The one-pot synthesis of novel bis-1, 2, 3-triazole derivatives from homopropargyl alcohol backbones is described. The key intermediates chiral 2-benzothiophenyl (-)-1 and 2-benzofuranyl (-)-2 substituted homopropargyl alcohols are synthesized from their corresponding carboxyaldehyde derivatives by O-propargylation and enzymatic resolution. Enantiomerically enriched homopropargyl alcohol derivatives are reacted with diiodo benzene and sodium azide via one-pot synthesis method and novel chiral bis-benzofuranyltriazole (-)-3 and bis-benzothiophenyltriazole (-)-4 are constructed without isolation of potentially toxic and unstable organic azide intermediates.

Keywords

Enzymatic Resolution, 1, 2, 3-Triazoles, , Benzofuran, Benzothiophene, One-Pot Reaction

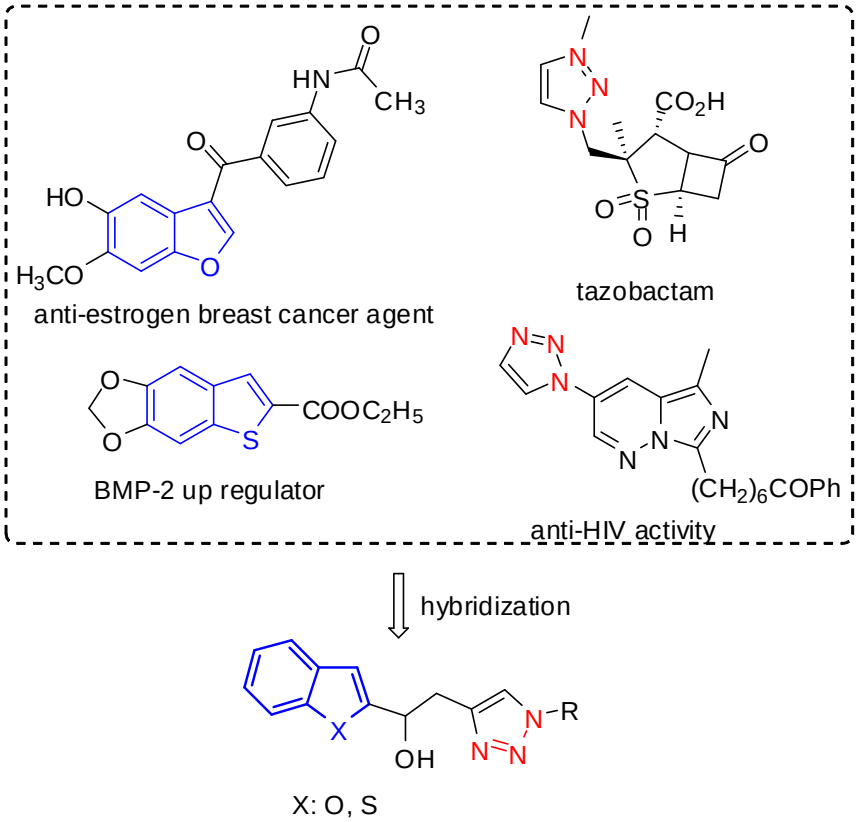
1. Introduction

Triazole ring which can be readily prepared from click chemistry is a potential pharmacophore that has gained interest over the past years. Compounds having triazole ring show various biological activities including antimicrobial (Esvaran, Adhikari, & Shetty, 2009; Bayrak, Demirbaş, Demirbaş, & Karaoğlu, 2009), anti-inflammatory (Kumarc & Kavitha, 2013), antidepressant (Radhika, Venkatesham, & Sarangapani, 2012; Nikitina, et.al. 2012), anticonvulsant (Plech, Luszczki, Wujec, Flieger, & Pizon, 2013; Mahdavi, et.al. 2010), antifungal (Chaudhary, et.al. 2009; Kategaonkar, Shinde, Pasale, Shingate, & Shingare, 2010), enzyme inhibition activities (Zhou, et.al. 2009; Owen, Dhanani, Patel, & Ahmed, 2007). Two examples are shown in Scheme 1. The extraordinary remarkable stability toward metabolic transformations, aromatic nature of the triazole ring, H-bonding capacity and high dipole moment, make it a functional group of great potential utility as a connecting group (Seo, Li, Ruparel, & Lu, 2003; Sivakumar, Xie, Cash, Long, & Barnhill, 2004; Dondoni, & Marra, 2006).

The 'click' chemistry term brings together a universe of reliable, quick and highly selective reactions (Moses, & Moorhouse, 2007). The most recognized one is copper-catalyzed 1,3-dipolar cycloaddition of azide and alkynes to form 1,2,3-triazoles (Sharpless, Rostovtsev, Green, & Fokin, 2002). The regioselective one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles has been reported (Appukkuttan, Dehaen, Fokin & Eycken, 2004; Kacprzak, 2005; Odlo, Hoydahl & Hansen, 2007; Feldman, Colasson & Fokin, 2004). The advantages of this method are not only low time and cost of complex molecule synthesis but also in situ generation of potentially toxic and explosive organic azide without isolation.

Benzothiphene and benzofuran derivatives are important classes of heterocyclic compounds, which have been interested over the past years. Synthetic and natural benzofuran derivatives display potent biological activities, such as antiparasitic, antioxidant, antibacterial, anti-inflammatory, anticancer activities (Ho, et.al. 2001; Marques, Buchet, Popowycz, Lemaire, & Mebarek, 2016; Hoang, et.al. 2009). In addition, 3-benzoylbenzofuran derivatives have been used as anti-estrogen breast cancer agent (Shamsuzzaman, 2015), as exemplified in Scheme 1. Benzothiophene molecules are currently of interest due to their wide range of pharmacological activities, such as antibacterial, antimicrobial, antifungal, antiviral and anticancer activities (Androsov, Solovyev, Petrov, Butcher & Jasinski, 2010; Guruprasad & Mruthyunjayaswamy, 2012; Queiroz, et.al. 2006; Dit Chabert, et.al. 2007). In addition, benzothiophene derivative

containing 5,6-methylenedioxy group was reported to show activity as BMP-2 up regulator (Scheme 1) (Guo, et.al. 2010).



Scheme 1: *Design of novel hybrid compounds*

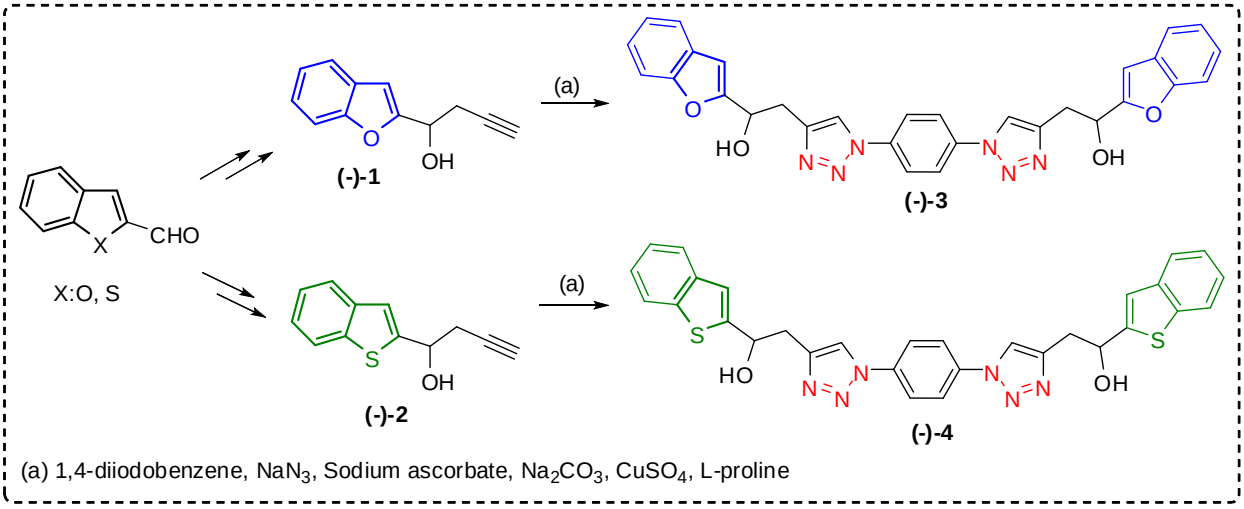
Hybridization is one of the useful strategies for the construction of chemotherapeutic agents and contains the combination of two different bioactive units. Herein we report the synthesis of novel hybrid compounds between benzofuran or benzothiophene and triazole units (Scheme 1). Chiral heteroaryl-substituted homopropargylic alcohols are good skeletons for the preparation of chiral triazole systems which have the potential of showing various biological activities.

2. Results and Discussion

The addition of propargyl group to carbonyl moiety is one of the most useful methods for the synthesis of homopropargylic alcohols which are useful precursors for the construction of triazole scaffolds. The parent benzofuranyl and benzothiophenyl homopropargylic alcohols **1** and

2 were synthesized by O-propargylation and enzymatically resolved in our previos study (Büyükadalı, Seven, Aslan, Yenidede & Gümüş, 2015). The terminal alkyne moiety on homopropargylic alcohols **1-2** make them valuable precursors for the synthesis of 1,4-disubstituted 1,2,3-triazole derivatives by one-pot synthesis.

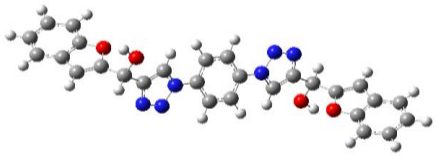
In one-pot synthesis method, aromatic and aliphatic azides can easily be generated from corresponding halides as intermediates and converted to triazole derivatives without isolation. This method is attractive and widely used because of its operational simplicity. In our previous study, novel mono 1,4-Disubstituted 1,2,3-Triazole derivatives were obtained (Büyükadalı, et al., 2015). Here, enantiomerically enriched (-)-1-(benzo[*b*]thiophen-2-yl)but-3-yn-1-ol (-)-**1** and (+)-1-(benzofuran-2-yl)but-3-yn-1-ol (-)-**2** were subjected to one-pot method by reacting with sodium azide and 1,4-diiodobenzene, individually (Scheme 2). Chiral benzofuranyl (-)-**3** and benzothienyl (-)-**4** bis-triazole derivatives were synthesized by one-pot triazole reactions with good yields (54% and 56%, respectively).



Scheme 2: *One-pot synthesis of 1,4-disubstituted 1,2,3-triazole derivatives*

The newly obtained hybrid compounds were subjected conformational analysis at B3LYP/6-31G(d,p) level to obtain the most stable geometry optimized structures (Figure 1). The connection between the central benzene and the triazine moities has free rotation resulting in infinite number of conformations. Therefore, this bond was rotated around itself by 5 degrees in each step to observe the energy change through rotation. In Figure 2, the resulting energy profile

for compound **3** is given. The most unstable structure was observed when one of the triazines is perpendicular to benzene moiety. Although opposite alignment of the two triazines resulted in an energetically favorable structure, the most stable structure was obtained when the aforementioned tortional angle is 180º (Figure 2).



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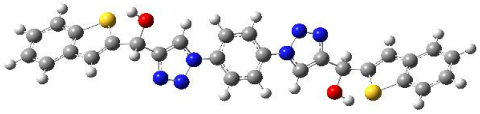

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Figure 1: *Geometry optimized structures of **3** and **4***

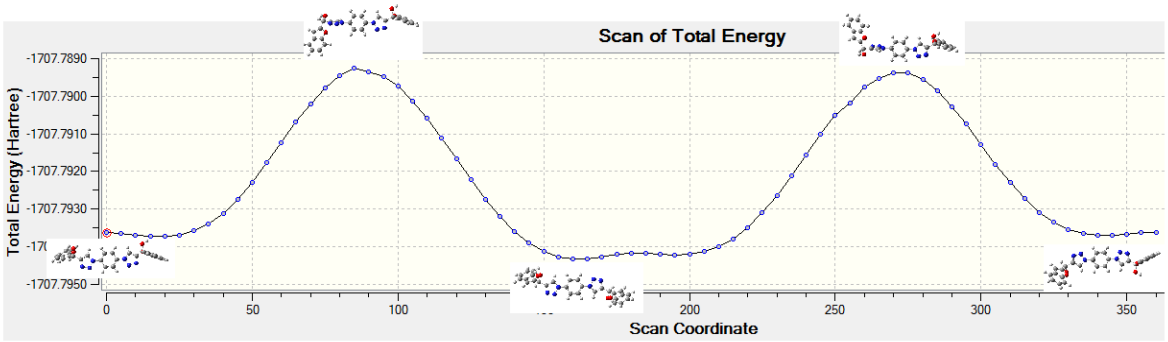
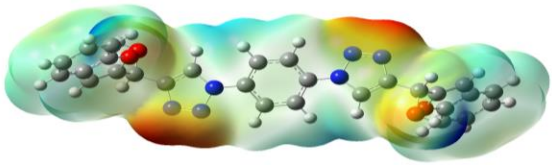


Figure 2: *Scan of total energy through rotation around the single bond connecting central benzene and triazine moiety for compound **3***

In order to investigate the charge distribution throughout the structure, three-dimensional electrostatic maps of **3** and **4** were carefully inspected. Triazine moieties and OH groups locate the negative charge as expected (Figure 2).



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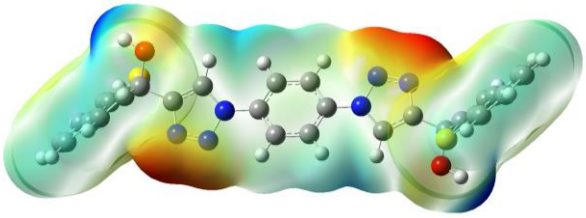

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Figure 3: *3D electrostatic potential maps of **3** and **4***

The Highest Occupied Molecular Orbital (HOMO) is the highest energy filled molecular orbital which acts as an electron donor; on the other hand, Lowest Unoccupied Molecular Orbital (LUMO) being the unfilled orbital with lowest energy and it is the electron acceptor part of the structure. HOMO and LUMO are both named as the frontier molecule orbitals (FMOs). The energy gap between FMOs gives information about the chemical stability of a molecule and is an important parameter in terms of electronic transport properties. The computed HOMO and LUMO energies for are tabulated in Table 1. The FMO energy gaps for the present structures are relatively high which may suggest stability of the structures through acid-base type reactions.

The excitation energies (eV), oscillator strengths (f) and absorption wavelengths (λ_{max} in nm) of UV–VIS electron absorption spectroscopy of the novel compounds were calculated in gas phase by the application of TD-DFT/B3LYP method with 6-31G(d,p) basis set and are presented in Table 1.

Table 1: *Calculated absorption wavelength (λ_{max} in nm), excitation energies (eV), oscillator strengths (f), HOMO and LUMO energies (eV) and FMO energy gap for the final products*

Compound	Transition	Probability	λ_{max}	Excitation Energy	Oscillator Strength	HOMO	LUMO	Δε
3	H→L	0.70029	305.59	4.06	0.4300	-6.08	-1.62	4.46
4	H→L	0.70003	309.13	4.01	0.2258	-6.03	-1.63	4.40

3. Experimental Studies

3.1 Synthesis of bis-triazole derivatives

Homopropargyl alcohol (50 mg, 0.25 mmol), 1,4-diiodobenzene (0.125 mmol), L-proline (6 mg, 0.05 mmol), NaN_3 (16 mg, 0.25 mmol), Na_2CO_3 (6 mg, 0.05 mmol), $CuSO_4 \cdot 5H_2O$ solution (1 M, 0.02 mL), sodium ascorbate (5 mg, 0.025 mmol) and DMSO/H_2O (1.8:0.2, 2.0 mL) were mixed in a scintillation vial and stirred overnight at 65°C. After the reaction completed, cold dilute NH_4OH solution (10 mL) was added to the reaction mixture and extracted with ethyl acetate (4 × 10 mL). The collected organic layer was washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The crude product was purified by flash column chromatography using ethylacetate and hexane mixtures.

2,2'-(1,1'-(1,4-phenylene)bis(1H-1,2,3-triazole-4,1-diyl))bis(1-(benzofuran-2-yl)ethanol), (-)-**3**

White solid (298 mg, 56% yield); mp 248-250 °C; $[\alpha]_D^{25}$= -35.8 (c 0.5, acetone); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (s, 2H), 7.33-7.31 (m, 2H), 7.20-7.18 (m, 2H), 7.06-6.97 (m, 4H), 6.57-6.55 (m, 2H), 6.46 (s, 2H), 4.97-4.94 (m, 2H), 3.26-3.11 (m, 4H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 159.3, 154.5, 144.3, 128.1, 123.7, 122.5, 121.8, 120.8, 120.6, 115.1, 110.9, 102.6, 66.8, 32.8.

(-)-2,2'-(1,1'-(1,4-phenylene)bis(1H-1,2,3-triazole-4,1-diyl))bis(1-(benzo[b]thiophen-2-yl)ethanol), (-)-**4**

White solid (304 mg, 54% yield); mp 215-220 °C; $[\alpha]_D^{25}$= -45.5 (c 0.5, acetone); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (s, 2H), 7.55 (s, 2H), 7.44-7.42 (m, 2H), 7.36-7.34 (m, 2H), 7.29-7.26 (m, 4H), 7.17-7.08 (m, 4H), 5.05-5.01 (m, 2H), 4.50 (s, 2H), 3.34-3.19 (m, 4H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 159.8, 148.2, 144.3, 128.2, 123.8, 122.7, 121.9, 120.9, 120.7, 114.8, 111.1, 102.6, 66.8, 31.4.

3.2 Computational Method

The ground state structures of the compounds were computed by geometry optimization followed by conformatonal analysis using Density Functional Theory with the B3LYP/6-31G(d,p) basis set without symmetry restrictions. Full optimization of the structural parameters such as; bond lengths, bond angles and torsional angles was achieved by using the aforementioned method sucessfully. The application of all the computational calculations was performed with Gaussian 09 package program (Frisch, et al., 2009). For each hybrid compound, vibrational analyses were done using the same basis set employed in the corresponding geometry

optimizations. The frequency analysis of the compounds did not yield any imaginary frequencies, which implies that the structures of molecules are located on a local minimum on the potential energy surface. The vibrational mode analysis was applied for 3N-6 degrees of freedom, where N shows the number of atoms in the molecule.

The vertical excitation energies, oscillator strengths (f) and excited state energies were obtained via application of Time-Dependent Density Functional Theory (TD-DFT) calculations in terms of excitations between the occupied and virtual orbitals for benzofuran and bicyclic cyclopentenone and also benzothiophene and bicyclic cyclopentenone hybrid structures (Casida, Jamorski, Casida & Salahub, 1998). During TD-DFT computations, the same basis set that is applied for geometry optimizations was used to calculate the wavelengths of absorption and the oscillation strength (f) within visible to near-UV region.

4. Conclusion

The parent benzofuranyl and benzothiophenyl homopropargylic alcohols **1** and **2** were synthesized and resolved by lipases to obtain enantiomerically enriched (-)-1-(benzo[*b*]thiophen-2-yl)but-3-yn-1-ol (-)-**1** and (+)-1-(benzofuran-2-yl)but-3-yn-1-ol (-)-**2**. They were subjected to one-pot, two-step reaction with sodium azide and 1,4-diiodobenzene, individually. One-pot triazole reactions afforded chiral benzofuranyl (-)-**3** and benzothienyl (-)-**4** bis-triazole derivatives with good yields.

References

Androsov, D. A., Solovyev, A. Y., Petrov, M. L., Butcher, R. J. & Jasinski, J. P. (2010). A convenient approach towards 2- and 3-aminobenzo[*b*]thiophenes. Tetrahedron, 66, 2474–2485. https://doi.org/10.1016/j.tet.2010.01.069

Appukkuttan, P., Dehaen, W., Fokin, V. V. & der Eycken, E. V. (2004). A microwave-assisted click chemistry synthesis of 1,4-disubstituted 1,2,3-triazoles via a copper(I)-catalyzed three-component reaction. Org. Lett. 6, 4223–4225. https://doi.org/10.1021/ol048341v

Bayrak, H., Demirbaş, A., Demirbaş, N. & Karaoğlu, S. A. (2009). Synthesis of some new 1,2,4-triazoles starting from isonicotinic acid hydrazide and evaluation of their antimicrobial activities. Eur. J. Med. Chem. 44, 4362–4366.

https://doi.org/10.1016/j.ejmech.2009.05.022 https://doi.org/10.1016/j.ejmech.2008.06.019

Büyükadalı, N. N., Seven, S., Aslan, N., Yenidede, D. & Gümüş, A. (2015). Chemoenzymatic synthesis of novel 1,4-disubstituted 1,2,3-triazole derivatives from 2-heteroaryl substituted homopropargyl alcohols. Tetrahedron-Asymm. 26, 1285-1291. https://doi.org/10.1016/j.tetasy.2015.10.001

Casida, M.E., Jamorski, C., Casida, K.C. & Salahub, D.R. (1998). Molecular excitation energies to high-lying bound states from time-dependent density-functional response theory: Characterization and correction of the time-dependent local density approximation ionization threshold. J. Chem. Phys. 109, 4439-4448. https://doi.org/10.1063/1.475855

Chaudhary, P. M., Chavan, S. R., Shirazi, F., Razdan, M., Nimkar, P., Maybhate, S. P., Likhite, A. P., Gonnade, R., Hazara, B. G. & Deshpande, S. R. (2009). Exploration of click reaction for the synthesis of modified nucleosides as chitin synthase inhibitors. Bioorg. Med. Chem. Lett. 17, 2433–2440. https://doi.org/10.1016/j.bmc.2009.02.019

Dit Chabert, J. F., Marquez, B., Neville, L., Joucla, L., Broussous, S. & Bouhours, P. (2007). Synthesis and evaluation of new arylbenzo[*b*]thiophene and diarylthiophene derivatives as inhibitors of the NorA multidrug transporter of *Staphylococcus aureus*. Bioorg. Med. Chem. 15, 4482–4497. https://doi.org/10.1016/j.bmc.2007.04.023

Dondoni, A. & Marra, A. (2006). "Click chemistry" inspired synthesis of pseudo-oligosaccharides and amino acid glycoconjugates. J. Org. Chem. 71, 364–367. https://doi.org/10.1021/jo051731q

Esvaran, S., Adhikari, A. V. & Shetty, N. S. (2009). Synthesis and antimicrobial activities of novel quinoline derivatives carrying 1,2,4-triazole moiety. Eur. J. Med. Chem. 44, 4637–4647. https://doi.org/10.1016/j.ejmech.2009.06.031

Feldman, A. K., Colasson, B. & Fokin, V. V. (2004). One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from in situ generated azides. Org. Lett. 6, 3897–3899. https://doi.org/10.1021/ol048859z

Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., et al. Gaussian 09. Wallingford, CT, Gaussian Inc., 2009.

Guo, H.F., Shao, H.Y., Yang, Z.Y., Xue, S:T., Li, X., Liu, Z.Y., He, X.B., Jiang, J.D., Zhang, Y.Q., Si, S.Y. & Li, Z.R. (2010). Substituted Benzothiophene or Benzofuran Derivatives

as a Novel Class of Bone Morphogenetic Protein-2 Up-Regulators: Synthesis, Structure−Activity Relationships, and Preventive Bone Loss Efficacies in Senescence Accelerated Mice (SAMP6) and Ovariectomized Rats. J. Med. Chem. 53, 1819–1829. https://doi.org/10.1021/jm901685n

Guruprasad, B. V. & Mruthyunjayaswamy, B. H. M. (2012). Synthesis and antimicrobial activity of some new 3-chloro-6-substituted-*N*-(substituted 2*H*-[1,3]oxazino[6,5-*b*]quinolin-3-(4*H*,5*aH*,9*aH*)-yl) benzo[*b*]thiophene-2-carboxamides**.** Ind. J. Chem. 51B, 514– 520. https://doi.org/10.1002/chin.201229187

Ho, Y. S., Duh, J. S., Jeng, J. H., Wang, Y. J., Liang, Y., Lin, C. H., Tseng, C. J., Yu, C. F., Chen, R. J. & Lin, J. K. (2001). Griseofulvin potentiates antitumorigenesis effects of nocodazole through induction of apoptosis and G2/M cell cycle arrest in human colorectal cancer cellsInt. J. Cancer, 91, 393–401. https://doi.org/10.1002/1097-0215(200002)9999:9999<::AID-IJC1070>3.0.CO;2-#

Hoang, D. M., Ngoc, T. M. Dat, N. T., Ha, D. T., Kim, Y. H., Luong, H. V., Ahn, J. S. & Bae, K. (2009). Protein Tyrosine Phosphatase 1B Inhibitors Isolated From Morus Bombycis. Bioorg. Med. Chem. Lett. 19, 6759–6761. https://doi.org/10.1016/j.bmcl.2009.09.102

Kacprzak, K. (2005). Efficient one-pot synthesis of 1,2,3-triazoles from benzyl and alkyl halides. Synlett, 6, 943–946. https://doi.org/10.1055/s-2005-864809

Kategaonkar, A. H., Shinde, P. V., Pasale, S. K., Shingate, B. B. & Shingare, M. S. (2010). Synthesis and biological evaluation of new 2-chloro-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)quinoline derivatives via click chemistry approach. Eur. J. Med. Chem. 45, 3142–3146. https://doi.org/10.1016/j.ejmech.2010.04.002

Kumar, S. S. & Kavitha, H. P. (2013). Synthesis and biological applications of triazole derivatives. Mini-Rev. Org. Chem. 10, 40–65. https://doi.org/10.2174/1570193X11310010004

Mahdavi, M., Akbarzadeh, T., Sheibani, V., Abbasi, M., Firoozpour, L., Tabatabai, S. A., Shafiee, A. & Foroumadi, A. (2010). Synthesis of two novel 3-amino-5-[4-chloro-2-phenoxyphenyl]-4H-1,2,4-triazoles with anticonvulsant activity. Iran J. Pharm. Res. 9, 265–269.

Marquès, S., Buchet, R., Popowycz, F., Lemaire, M. & Mebarek, S. (2016). Synthesis of benzofuran derivatives as selective inhibitors of tissue-nonspecific alkaline phosphatase:

effects on cell toxicity and osteoblast-induced mineralization. Bioorg. Med. Chem. Lett. 26, 1457–1459. https://doi.org/10.1016/j.bmcl.2016.01.061

Moses, J. E. & Moorhouse, A. D. (2007). Chem. Soc. Rev. The growing applications of click chemistry. 36, 1249-3015.

Nikitina, I. L., Gabidullin, R. A., Klen, E. E., Tyurina, L. A., Alekhin, E. K. & Khaliullin, F. A. (2012). Computer analysis of the structure-antidepressant activity relationship in series of 1,2,4-triazole and thietane-1,1-dioxide derivatives. Pharm. Chem. J. 46, 213–218. https://doi.org/10.1007/s11094-012-0764-6

Odlo, K., Hoydahl, E. A. & Hansen, T. V. (2007). One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from terminal acetylenes and in situ generated azides. Tetrahedron Lett. 48, 2097–2099. https://doi.org/10.1016/j.tetlet.2007.01.130

Owen, C. P., Dhanani, S., Patel, C. H. & Ahmed, S. Synthesis, biochemical evaluation and rationalisation of the inhibitory activity of a series of 4-substituted phenyl alkyl triazole-based compounds as potential inhibitors of 17a-hydroxylase/17,20- Lyase (P45017a). Lett. Drug Design Discov. 42, 479–483. https://doi.org/10.2174/157018007781788471

Plech, T., Luszczki, J. J., Wujec, M., Flieger, J. & Pizon, M. (2013). Synthesis, characterization and preliminary anticonvulsant evaluation of some 4-alkyl-1,2,4-triazoles. Eur. J. Med. Chem. 60, 208–215. https://doi.org/10.1016/j.ejmech.2012.11.026

Queiroz, M. J., Ferreira, I. C., De Gaetano, Y., Kirsch, G., Calhelha, R. C. & Estevinho, L. M. (2006). Synthesis and antimicrobial activity studies of *ortho*-chlorodiarylamines and heteroaromatic tetracyclic systems in the benzo[*b*]thiophene series. Bioorg. Med. Chem. 14, 6827–6831. https://doi.org/10.1016/j.bmc.2006.06.035

Radhika, C., Venkatesham, A. & Sarangapani, M. (2012). Synthesis and antidepressant activity of disubstituted-5-aryl-1,2,4-triazoles. Med. Chem. Res. 21, 3509–3513. https://doi.org/10.1007/s00044-011-9902-z

Seo, T. S., Li, Z., Ruparel, H. & Lu, J. (2003). Click chemistry to construct fluorescent oligonucleotides for DNA sequencing. J. Org. Chem. 68, 609–612. https://doi.org/10.1021/jo026615r

Shamsuzzaman, H.K. (2015). Bioactive Benzofuran derivatives: A review. Eur. J. Med. Chem. 97, 483-504. https://doi.org/10.1016/j.ejmech.2014.11.039

Sharpless, K. B., Rostovtsev, V. V., Green, L. G. & Fokin, V. V. (2002). A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes. Angew.Chem. Int. Ed. 2596-2599.

Sivakumar, K., Xie, F., Cash, B. M., Long, S. & Barnhill, H. N. A (2004). Fluorogenic 1,3-dipolar cycloaddition reaction of 3- azidocoumarins and acetylenes. Org. Lett. 6, 4603–4606. https://doi.org/10.1021/ol047955x

Zhou, J. P., Zhang, H. B., Qian, H., Lin, L., Huang, W. L. & Ni, S. J. (2009). Synthesis and biological evaluation of aromatase inhibitors. Lett. Drug Design Discov. 6, 181–185. https://doi.org/10.2174/157018009787847846