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ABSTRACT

Three novel compounds i.e. 1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)methyl]-1,10-phenanthrolin-1-ium bromide (**Phen-PHTH**), {2-[2-methoxy-4-(3-methoxy-4-{2-[tris(propan-2-yl)silyl]ethynyl}phenyl)phenyl]ethynyl}tris(propan-2-yl)silane (**4SGN-1**) and 1-(3-chloropropyl)-1,10-phenanthrolin-1-ium chloride (**SND-Cl2B**) were synthesized and characterized using NMR, MS, UV, FTIR and CNH analysis. Few reported compounds were also synthesized either with new procedures or modified procedures including 1-methyl-1,10-phenanthrolin-1-ium iodide (**SN1-OLD**),[25] diethyl [(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)methyl]phosphonate (**SN2-B**),[26] 5*H*-6,7-dihydro-[1,4]diazepino[1,2,3,4-*lmn*][1,10]phenanthrolinediium dibromide (**SN1**),[27] 2,9-dichloro-1,10-phenanthroline (**SN3**),[27,28] 4,4'-diiodo-3,3'-dimethoxy-1,1'-Biphenyl (**DI**),[29] [2,2'-Bipyridine]-5,5'-diamine (**4,4-amin-2,2**),[30] (1E)-1-phenyl-N-[4-(3-{4-[(E)-(phenylmethylidene)amino]phenoxy}phenoxy)phenyl]methanimine (**S11**),[31] 4-(1*H*-phenanthro[9,10-*d*]imidazol-2-yl)-phenol (**PPHOH**)[32] and octahydroimidazo[4,5-d]imidazolidine-2,5-dione (**glycoluril**).

Keywords: phenanthrolines, N-alylation, organic synthesis, Sonogashira coupling.

INTRODUCTION

Free radicals are beneficial – unless their amount is in limit – members of human body that takes part in biological processes. Their excess is can damage all major components of cells, including cell membranes, DNA and proteins, that can lead to cancer[1][2]. Antioxidants (AOs)[3][4] are very important moieties to stop oxidation within living bodies. Scientists are always in search of new natural[5][6] or synthesized[7][8] AOs. AOs have been reported to treat myasthenia gravis[9] and glaucoma[10].

Anticholinesterase inhibitors are well known medically important to treat myasthenia gravis[11], glaucoma[12], postural tachycardia syndrome,[13] antidote to anticholinergic poisoning[14], muscle relaxants[15], neuropsychiatric symptoms of diseases such as Alzheimer's disease,[16] particularly apathy [17], Lewy Body Dementia[18], Parkinson's disease[19], schizophrenia [20][21], autism[22] and to increase the percentage of rapid eye movement sleep in autistic children[23][24].

Nature-derived AOs are versatile, multifunctional and in most cases they don't have side effects. But it is very tedious to isolate a pure compound from a natural source. Most of the time, they are obtained in very less amount. There are also very less chances for a molecule to be AO and at the same time harmless. Synthesized compounds are good alternatives to be used at commercial scale. It is easy to incorporate any specific functional group into certain molecule that will result our desired properties.

RESULT & DISCUSSION

Molecules synthesized are given in Figure 1. Among the synthesized molecules, **phen-PHTH** and **4SGN-1** are novel and were synthesized during this study for the first time. Nitrogen in the phenanthroline is very good ligand as well as good nucleophile. On the other hand, N-bromomethylphthlamide possess a good leaving group i.e. bromine and can be used as an electrophile. They were mixed and reacted to obtain **phen-PHTH**, an organic salt. This molecule is useful to be used in the biological systems as it is water soluble.

The synthesis of 4SGN-1 is consists of Sonogashira coupling. This cross coupling reaction is used to make C-C bond between sp and sp^2 carbons. $Pd(PPh_3)_2Cl_2$ was used as a catalyst while CuI was

used as a co-catalyst during the reaction. K_2CO_3 was used as a base while trimethylamine and dichloromethane were used as solvents. Previously, we have tried diethylamine as a solvent but it performed Buchwald-Hartwig reaction i.e. secondary nitrogen of diethylamine made a C-N bond with the aromatic ring instead of Sonogashira product C-Ar bond.

Other molecules given in Figure 1 were synthesized by various procedures that are given in the experimental part in detail. These molecules will be used in various products and in the synthesis of their higher oligomers.

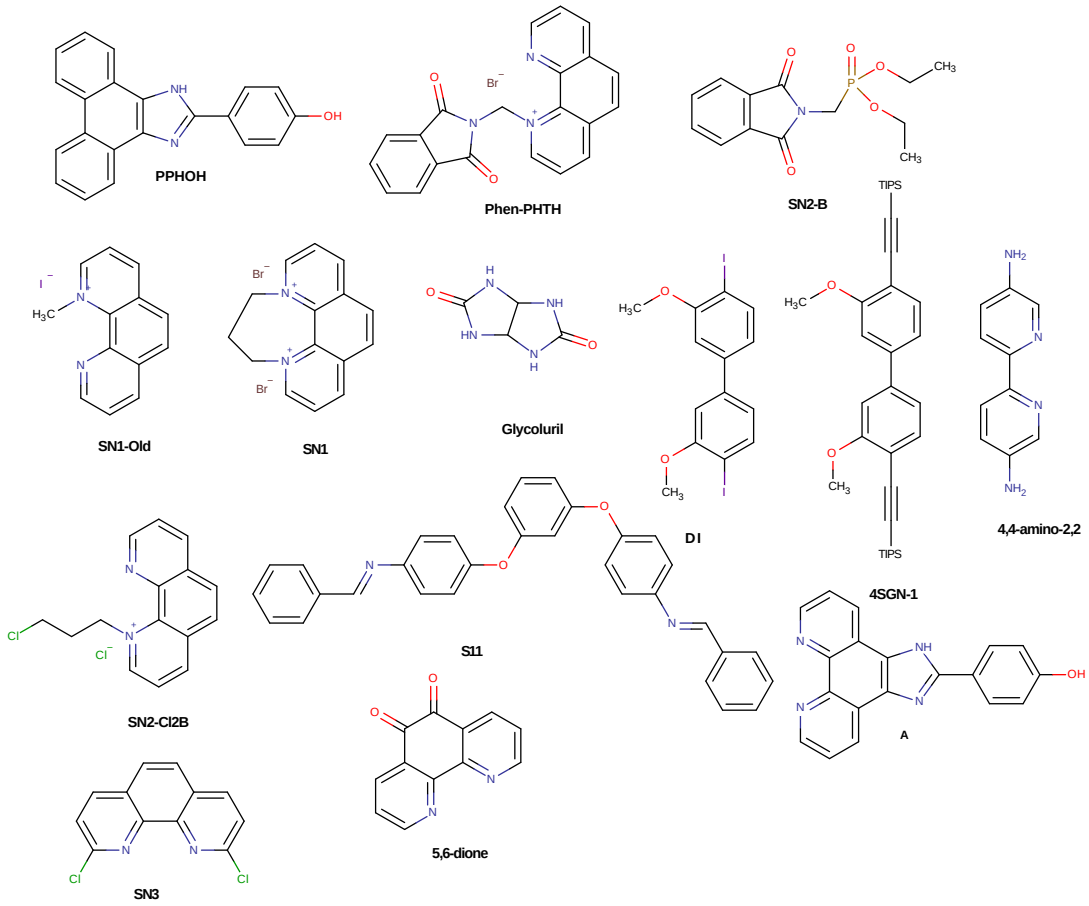

Figure 1: Structures of the synthesized compounds subjected for biological activities

EXPERIMENTAL

Synthesis

[(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)methyl]-1,10-phenanthrolin-1-ium bromide (**Phen-PHTH**):

198 mg (1 mmol) of 1,10-phen monohydrate and 312 mg (1.3 mmol) of *N*-bromomethylphthalimide were added in 5 mL of nitrobenzene. The mixture was heated at 120 ^{o}C with well stirring for 3 hours. White precipitates were formed which were filtered and were washed with hexane, dried under vaccum to ensure the removal of hexane and nitrobenzene. Crystallized out from ethanol:water 5:1 mixture. 1H NMR (300 MHz, DMSO d6): 9.74 (dd, 1H, 4J = 1.1 Hz, 3J = 6.2 Hz), 9.48 (d, 1H, 3J = 8.10 Hz), 9.31 (dd, 1H, 4J = 1.7 Hz, 3J = 4.3 Hz), 8.87 (dd, 2H, 4J = 1.3 Hz, 3J = 8.2 Hz), 8.51 (m, 3H), 8.12 (dd, 1H, 4J = 4.29 Hz, 3J = 8.23 Hz), 7.95 (m, 6H).

{2-[2-methoxy-4-(3-methoxy-4-{2-[tris(propan-2-yl)silyl]ethynyl}phenyl)phenyl]ethynyl}tris(propan-2-yl)silane (**4SGN-1**) :

100 mg of 4,4'-diiodo-3,3'-dimethoxybiphenyl was added in 3 mL of Et_3N and 2 mL dichloromethane/THF in a clean dried 100 mL round bottom flask. 12 mg $Pd(PPh_3)_2Cl_2$, 6 mg CuI, and 30 mg K_2CO_3 was also added at 0 ^{o}C and stirred. 80 µL TIPS-acetylene was added dropwise by syringe. The reaction was then allowed to reach to room temperature. After one hour stirring at room temperature, the solvent was evaporated from the reaction mixture in vacuum and the residue was extracted three times with dichloromethane from slightly acidic (added a few drops of HCl) distilled water. The combined organic layers were evaporated by rotary evaporator, and purified by column chromatography on flash silica by using n-hexane as eluent. White powdered compound was obtained in pure form. EIMS m/z: 574; ^{1}HNMR, 400 MHz $CDCl_3$ δ (ppm): 7.47 (d, 2H, J = 7.8 Hz), 7.10 (dd, 2H, 4J = 1.5 Hz, 3J = 7.8 Hz), 7.02 (d, 2H, 4J = 1.2 Hz), 3.91 (s, 6H), 1.13 (s, 36H); UV $CHCl_3$ λ_{max} nm (abs): 240 (0.5), 293 (0.73), 329 (1.06); IR KBr υ cm-1: 3433, 2943, 2864, 2148, 1602, 1249, 1024, 667.

1-(3-chloropropyl)-1,10-phenanthrolin-1-ium chloride (**SND-Cl2B**)

A mixture of 4 (1.7 g) and phosphorus pentachloride PCl5 (3 g) was refluxed in thionyl chloride $SOCl_2$ (20 mL) for 16 h. After removing thionyl chloride by evaporation, ice water was added and basified with aqueous ammonia. A pale-brown precipitate was dried, extracted with hot toluene, and subjected to column chromatography using DCM as eluent. The target molecule was 2,9-dichlorophenanthroline. SN'-Cl2B was obtained as a side product. 1H NMR spectrum of 6 displayed three characteris- tic peaks i.e., a broad triplet at 5.17, a well resolved triplet at 3.89 with coupling constant of 7.2 Hz and a multiplet of the central –CH2-protons at 2.59—each peak of 2 protons integral; related to 3 $–CH_2$-protons of N -chloropropyl group. Compound 6 showed six doublets in aromatic region i.e., 8.144, 7.77, 7.64, 7.56, 7.49 and 6.9 that reflects the asymmetry of the mono-N -alkylated phenanthroline.

1-methyl-1,10-phenanthrolin-1-ium iodide (**SN1-OLD**),[25] diethyl [(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)methyl]phosphonate (**SN2-B**),[26] 5*H*-6,7-dihydro-[1,4]diazepino[1,2,3,4-*lmn*][1,10]phenanthrolinediium dibromide (**SN1**),[27] 2,9-dichloro-1,10-phenanthroline (**SN3**),[27,28] 4,4'-diiodo-3,3'-dimethoxy-1,1'-Biphenyl (**DI**),[29] [2,2'-Bipyridine]-5,5'-diamine (**4,4-amin-2,2**),[30] (1E)-1-phenyl-N-[4-(3-{4-[(E)-(phenylmethylidene)amino]phenoxy}phenoxy)phenyl]methanimine (**S11**),[31] 4-(1*H*-phenanthro[9,10-*d*]imidazol-2-yl)-phenol (**PPHOH**)[32] and octahydroimidazo[4,5-d]imidazolidine-2,5-dione (**glycoluril**)[33] were synthesized according to their reported procedures.

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REFERENCES

[1] A.T. Diplock, J.L. Charleux, G. Crozier-Willi, F.J. Kok, C. Rice-Evans, M. Roberfroid, W. Stahl, J. Viña-Ribes, Br. J. Nutr. 80 Suppl 1 (1998) S77.

[2] M. Valko, D. Leibfritz, J. Moncol, M.T.D. Cronin, M. Mazur, J. Telser, Int. J. Biochem. Cell Biol. 39 (2007) 44.

[3] D. Huang, O.U. Boxin, R.L. Prior, J. Agric. Food Chem. 53 (2005) 1841.

[4] G. Tirzitis, G. Bartosz, Acta Biochim. Pol. 57 (2010) 139.

[5] L. Packer, G. Rimbach, F. Virgili, Free Radic. Biol. Med. 27 (1999) 704.

[6] C.A. Rice-Evans, N.J. Miller, G. Paganga, Free Radic. Biol. Med. 20 (1996) 933.

[7] J. Wang, Q. Zhang, Z. Zhang, J. Zhang, P. Li, Int. J. Biol. Macromol. 44 (2009) 170.

[8] N.J. Reddy, D. Nagoor Vali, M. Rani, S.S. Rani, Mater. Sci. Eng. C 34 (2014) 115.

[9] P. Fuhua, D. Xuhui, Z. Zhiyang, J. Ying, Y. Yu, T. Feng, L. Jia, G. Lijia, H. Xueqiang, Neuroimmunomodulation 19 (2012) 43.

[10] M. Erdurmuş, R. Yağcı, Ö. Atış, R. Karadağ, A. Akbaş, I.F. Hepşen, Curr. Eye Res. 36 (2011) 713.

[11] M.M. Mehndiratta, S. Pandey, T. Kuntzer, Cochrane Database Syst. Rev. 10 (2014) CD006986.

[12] V.P. Nair, Contin. Educ. Anaesthesia, Crit. Care Pain 4 (2004) 164.

[13] S.R. Raj, B.K. Black, I. Biaggioni, P.A. Harris, D. Robertson, Circulation 111 (2005) 2734.

[14] L. Raveh, J. Grunwald, D. Marcus, Y. Papier, E. Cohen, Y. Ashani, Biochem. Pharmacol. 45 (1993) 2465.

[15] A.F. Danilov, Eksp. Klin. Farmakol. 60 83.

[16] L. Gandía, R.M. Alvarez, J.M. Hernández-Guijo, J.M. González-Rubio, R. de Pascual, J. Rojo, L. Tapia, Rev. Neurol. 42 471.

[17] T. Yuschak, Advanced Lucid Dreaming - The Power of Supplements, Lulu.com, 2006.

[18] R. Wild, T. Pettit, A. Burns, Cochrane Database Syst. Rev. (2003) CD003672.

[19] D. Taylor, C. Paton, S. Kapur, The Maudsley Prescribing Guidelines in Psychiatry, Wiley, 2012.

[20] J. Singh, K. Kour, M.B. Jayaram, Cochrane Database Syst. Rev. 1 (2012) CD007967.

[21] K.-H. Choi, T. Wykes, M.M. Kurtz, Br. J. Psychiatry 203 (2013) 172.

[22] M.G. Chez, M. Aimonovitch, T. Buchanan, S. Mrazek, R.J. Tremb, J. Child Neurol. 19 (2004) 165.

[23] A.W. Buckley, K. Sassower, A.J. Rodriguez, K. Jennison, K. Wingert, J. Buckley, A. Thurm, S. Sato, S. Swedo, J. Child Adolesc. Psychopharmacol. 21 (2011) 353.

[24] B.L. Handen, C.R. Johnson, S. McAuliffe-Bellin, P.J. Murray, A.Y. Hardan, J. Child Adolesc. Psychopharmacol. 21 (2011) 43.

[25] M. Böttger, B. Wiegmann, S. Schaumburg, P.G. Jones, W. Kowalsky, H.-H. Johannes, Beilstein J. Org. Chem. 8 (2012) 1037.

[26] J. Gao, Y.H. Guo, Y.P. Wang, X.J. Wang, W.S. Xiang, Chinese Chem. Lett. 22 (2011) 1159.

[27] M. Yamada, Y. Nakamura, S. Kuroda, I. Shimao, Bull. Chem. Soc. Jpn. 63 (1990) 2710.

[28] S. Nadeem, M.R. Shah, S.W. Ng, Acta Crystallogr. Sect. E. Struct. Rep. Online 65 (2009) o922.

[29] Q. Ali, Z. Hussain, M.R. Shah, D. Vanderveer, Acta Crystallogr. Sect. E. Struct. Rep. Online 64 (2008) o1377.

[30] C.M. Asselin, G.C. Fraser, H.K. Hall Jr., W.E. Lindsell, A.B. Padias, P.N. Preston, J. Chem. Soc. Dalt. Trans. (1997) 3765.

[31] S. Nadeem, M.R. Shah, K. Shah, A. Mohammad, B. Khan, Org. Chem. Int. 2012 (2012) Article ID 279097.

[32] E.A. Steck, A.R. Day, J. Am. Chem. Soc. 65 (1943) 452.

[33] E. Vessally, M.D. Esrafili, Z. Alimadadi, M. Rouhani, Green Chem. Lett. Rev. 7 (2014) 119.