Scientific article
UDC 547.525.5
DOI: 10.52957/27821900_2022_02_92

ONE-POT REDUCTION AND HALOGENATION OF N-(2,4-DINITROPHENYL)PIPERIDINE

R. S. Begunov, A. A. Sokolov

Roman S. Begunov, Candidate of Chemical Sciences, Associate Professor
Demidov Yaroslavl State University, Yaroslavl, Russia, begunov@bio.uniyar.ac.ru
Alexander A. Sokolov, Candidate of Chemical Sciences, Senior Researcher
Yaroslavl State Technical University, Yaroslavl, Russia

Keywords:
N-(2,4-dinitrophenyl)piperidine, tin(II) chloride, reduction, halogenation, regioselectivity

Abstract. *The paper concerns the developing of a one-pot method for the preparation of ortho-chloranilines containing the piperidine cycle by reduction of dinitrosubstrates with tin(II) chloride.*

For citation:
Begunov, R.S. & Sokolov, A.A. (2022) One-pot reduction and halogenation of N-(2,4-dinitrophenyl)piperidine, *From Chemistry Towards Technology Step-By-Step*, 3(2), pp. 92-97 [online]. Available at: http://chemintech.ru/index.php/tor/2022tom3no2

Introduction

The chlorine atom is one of the most common functional groups in medicinal products, forming the composition more than 15% of them [1]. The greatest number of chlorine-containing drugs are used for treatment the deseases of the nervous system (18%), the cardiovascular system (17%) and cancer (14%) [2]. The halogen atom in these remedies is not the necessary pharmacophore part and is often used to adjust other parameters such as lipophilicity. In addition, the presence of halogen improves the permeability of the blood-brain barrier for drugs targeting the central nervous system (2). The most important influence on the biological activity of compounds has the non-reactive chlorine atom as a substituent of the aromatic or heteroaromatic fragment [3]. The introduction of halogen atoms into different positions of the (het)arenes is often used to establish structure-biological activity relationships in the development of new drugs [4].

The development of methods for the chlorination of organic substrates is therefore an urgent task. Although Cl_2 gas is an available and inexpensive reagent, direct halogenation with its excess is limited by the inconvenience of handling it and the formation of toxic HCl [5]. Therefore, research is actively being undertaken to develop new chlorination methods with high regioselectivity control.

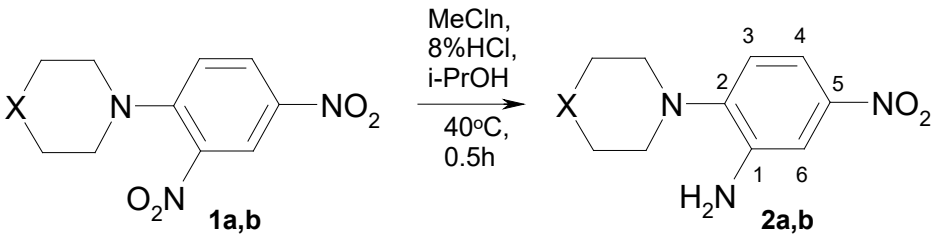
Earlier in [6, 7] the reduction of aromatic dinitrosubstrates with tin(II) chloride discovered amino by-products containing Cl atom. However, the halogenation process has not been studied separately, nor have the conditions been investigated to produce the chloronitroanilines of interest due to their high biological activity [8-12] in the pure form.

The aim of this work is to develop a method for the selective mono-reduction of dinitrobenzene with simultaneous chlorination of the molecule.

Main body

Studies on the development of a cascade method for the synthesis of chloronitroanilines containing an aliphatic azaheterocycle from the corresponding dinitrosubstrates in the presence of a reducing agent consisted of two stages. At the first stage, we investigated the influence of various factors on the orientation of the mono-reduction. The second stage we devoted to the selection of conditions of the proceeding of the chlorination reaction.

Titanium (III) and tin (II) chlorides were used as reducing agents to investigate the selectivity of the mono-reduction process. We conducted the reaction by simultaneously introducing an alcohol solution of dinitrosubstrate and a solution of the reducing agent in 8% hydrochloric acid into the reactor. N-(2,4-dinitrophenyl)piperidine (**1a**) and N-(2,4-dinitrophenyl)morpholine (**1b**) were used as substrates. In order to avoid the formation of a diamine product which would interfere with the interpretation of the mono-reduction reaction results, we took the reducing agent at a rate of 50% conversion of one nitro group. Using $TiCl_3$ and $SnCl_2$ for both starting substances at 40 °C we observed the formation of nitroamines **2.** The reduction process was not accompanied by halogenation.



where **a** X=CH, **b** X=O, Me = Ti (n=3) or Sn (n=2)

The structure of the nitroanilines **2a,b** was proved by ^{1}H NMR spectroscopy and high-resolution mass spectrometry. The ^{1}H NMR spectrum of 5-nitro-2-piperidine-1-ylaniline (**2a**) is shown in Fig. 1. In contrast to dinitrosubstrate **1a**, an additional peak appeared in the spectrum as a broad singlet with an integral intensity of 2 at 5.10 ppm corresponding to the protons of the amino group. All three proton signals of the benzene ring shifted to the low frequency range due to the conversion of the electron acceptor NO_2 group to the donor NH_2 group. The largest change of the chemical shift was observed for H^6, by 1.03 ppm. The signal shift of the *para*-located to the amino group H^4 decreased by 0.83 ppm and that of the *meta*-located H^5 only by 0.45 ppm.

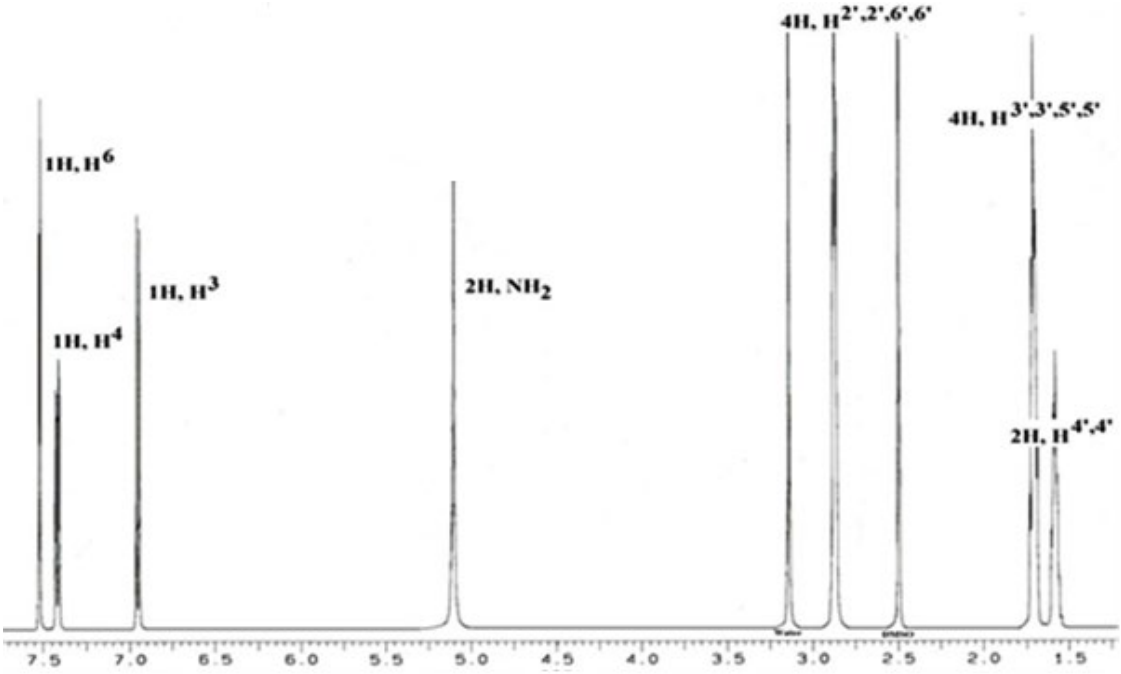


Fig. 1. [1]H NMR spectrum of 5-nitro-2-piperidine-1-ylaniline (**2a**) (Bruker DRX400, SF=400 MHz, solvent and internal standard DMSO-d_6)

Fig. 2 shows the [1]H NMR spectrum of 5-nitro-2-morpholine-4-ylaniline (**2b**). It had five signals from 13 protons, differing from **2a** only in the peaks from the heterocycle. The proton signals of the morpholine fragment were in the form of multiplets at 3.21-3.32 ppm from 4 hydrogen nuclei of $N(CH_2)_2$ and 3.65-3.82 ppm from 4 hydrogen nuclei of $O(CH_2)_2$. The chemical shifts and the shape of the aromatic proton signals were identical **2a**.

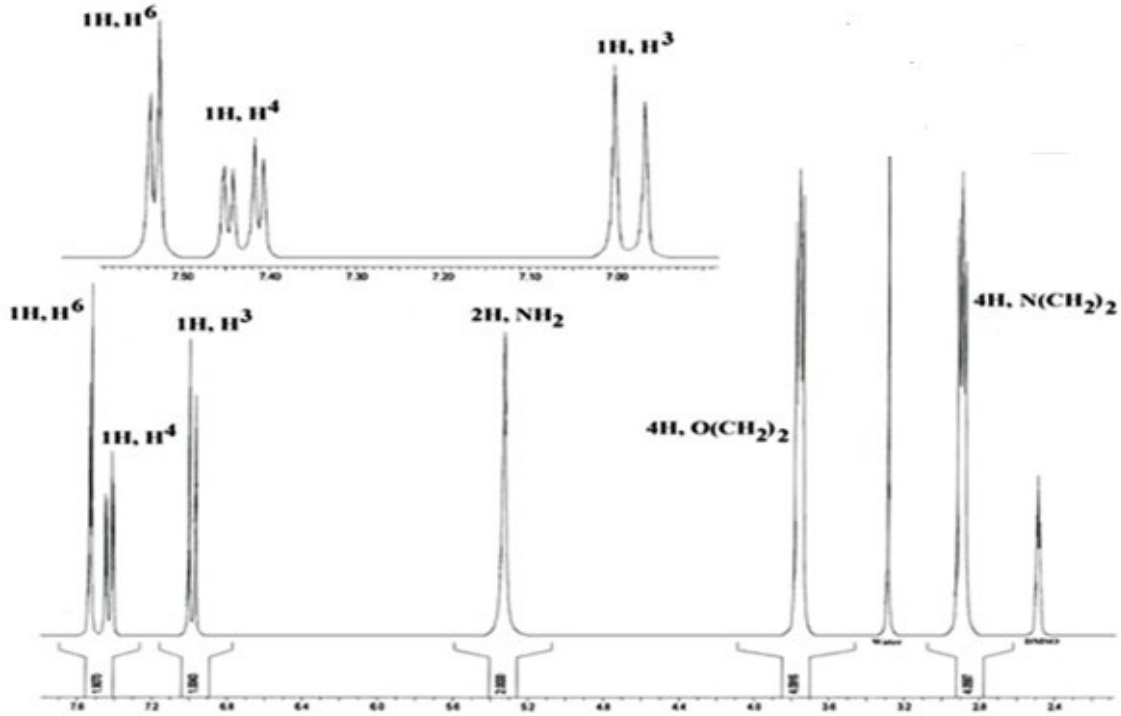


Fig. 2. [1]H NMR spectrum of 5-nitro-2-morpholine-4-ilaniline (**2b**) (Bruker DRX 400, SF=400 MHz, solvent and internal standard DMSO-d_6)

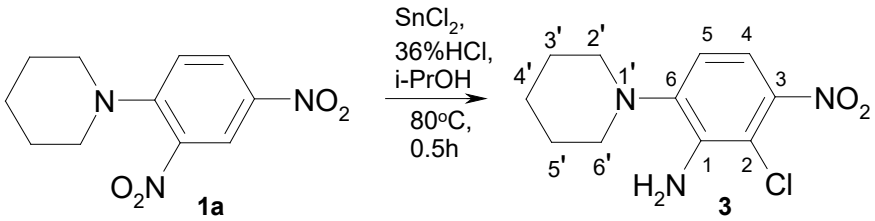
Thus, it was shown that both dinitroarenes with different heterocyclic fragments were highly selectively reduced to form *ortho*-nitro group reduction products. No chlorination was observed. Therefore we studied the effect of temperature and hydrochloric acid concentration on the reduction of model compound **1a**. The use of $TiCl_3$ as reducing agent did not allow to obtain a halogenated product during the experiments, the results for $SnCl_2$ are presented in Table 1. We took the reducing agent at the rate of 100% conversion per nitro group.

Table 1. The effect of temperature and hydrochloric acid concentration on the ratio of* 5-nitro-2-piperidine-1yl aniline (**2a**) and 6-chloro-5-nitro-2-piperidine-1-ilaniline (**3**) during the reduction of **1a** $SnCl_2$

T,°C	HCl concentration, %				
	8	12	18	24	36
40	1	1/0.1	1/0.28	1/0.64	1/2.85
80	1/0.35	1/0.43	1/0.57	1/1.08	1/15.67

*- According to ^{1}H NMR spectroscopy

The data in the table show that with increasing of the hydrochloric acid concentration and the reaction temperature the amount of the chlorination product **3** increased. Therefore for the synthesis of 6-chloro-5-nitro-2-piperidin-1-ylaniline (**3**) we used the reduction process in a mixture of isopropyl alcohol and 36% hydrochloric acid at 80 °C.



In the ^{1}H NMR spectrum of the nitroaniline obtained (Fig. 3) as opposed to compound **2a**, only two peaks were observed in the aromatic area: two doublets at 7.00 and 7.27 ppm with J = 8.6 Hz. In the process, we observed a "roof effect", which indicated the *ortho*-location of the hydrogen nuclei giving the signals. Thus, there was a proton missing between the NH_2 and NO_2 groups in the molecule, which is possible when it is replaced by a halogen atom.

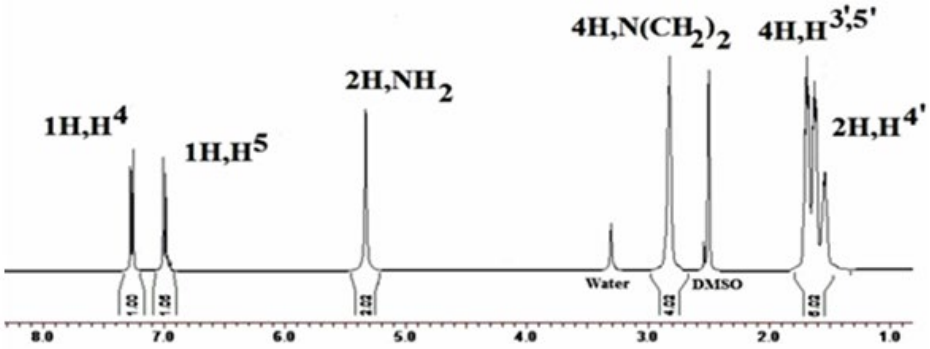


Fig. 3. ^{1}H NMR spectrum of 2-chloro-3-nitro-6-(piperidine-1-yl)aniline (**3**) (Bruker DRX 400, SF=400 MHz, solvent and internal standard DMSO-d_6)

As a result of our study we have developed the method of selective mono-reduction of dinitrobenzene containing saturated heterocyclic fragments into nitroamines and the method of preparation of derivatives of anilines having chlorine atom in *ortho*-position to NH_2-group.

Experimental part

We determined the melting points on a PolyTherm A device at a heating rate of 3 °C/min without the correction. We recorded the NMR spectra on a "Bruker DRX-400" instrument for DMSO-d_6 solutions at 30 °C. As reference for the chemical shifts we used the signals of the residual solvent protons in ^{1}H NMR (δ 2.50 ppm) and ^{13}C NMR (δ 39.5 ppm). We recorded high resolution mass spectra on a "Bruker micrOTOF II" (Bruker Daltonics), electrospray ionisation (ESI), mass scanning range (*m/z* 50) 3000 Da, syringe injection. We used MeCN or MeOH as solvent and the solution flow rate was 3 μl/min. The interface temperature was 180°C, the spraying gas was nitrogen (4.0 l/min).

Methodology for the synthesis of compounds 2a, b

In a three-necked flask while stirring simultaneously we added a solution (0.004 mole) of **1a** or **1b** preheated to 40 °C in 20 ml isopropyl alcohol and a solution of 2.708 g (0.012 mole) of $SnCl_2 \cdot 2H_2O$ in 20 ml of 8% hydrochloric acid. The reaction mixture was stirred at 40 °C for 0.5 h. The reaction mixture was then cooled down, alkalized to pH = 7-8 and extracted with hot chloroform. Chloroform was distilled off. The resulting dry residue was recrystallized in petroleum ether.

5-Nitro-2-piperidine-1-ylaniline (**2a**). Yield 87%. Tm = 78-80 °C. Spectrum ^{1}H NMR (DMSO-d_6, δ, ppm, *J* /Hz): 1.55 (m, 2H, CH_2), 1.70 (m, 4H, $(CH_2)_2$), 2.85 (m, 4H, $N(CH_2)_2$), 5.10 (s, 2H, NH_2), 6.95 (d, 1H, H^3, *J* 8.0 Hz), 7.40 (dd, 1H, H^4, *J* 8.0 Hz, *J* 1.5 Hz), 7.55 (d, 1H, H^6, *J* 1.5 Hz). HRMS: *m/z* calculated $C_{11}H_{16}N_3O_2$ 222.1243 $[M+H]^+$, found: 222.1231.

5-nitro-2-morpholine-4-ylaniline (**2b**). Yield 93%. Tm = 153-155 °C. Spectrum ^{1}H NMR (DMSO-d_6, δ, ppm, *J* /Hz): 2.95 (m, 4H, $N(CH_2)_2$), 3.80 (m, 4H, $O(CH_2)_2$), 5.20 (s, 2H, NH_2), 7.00 (d, 1H, H^3, *J* 9.0 Hz), 7.45 (dd, 1H, H^4, *J* 8.5 Hz, *J* 2.0 Hz), 7.55 (d, 1H, H^6, *J* 2.0 Hz). HRMS: *m/z* calculated $C_{10}H_{14}N_3O_3$ 224.1036 $[M+H]^+$, found: 224.1036.

Methods for the synthesis of 2-chloro-3-nitro-6-(piperidin-1-yl)aniline (3)

To a solution of 1.000 g (0.004 mole) N-(2,4-dinitrophenyl)piperidine in 20 ml isopropyl alcohol at 80 °C a solution of 2.708 g (0.012 mole) $SnCl_2 \cdot 2H_2O$ in 20 ml of 36% hydrochloric acid was added. The reaction mixture was stirred at 40 °C for 0.5 h. The reaction mixture was then cooled down, alkalized to pH = 7-8 and extracted with hot chloroform. Chloroform was distilled off. The resulting dry residue was recrystallized in petroleum ether.

2-chloro-3-nitro-6-(piperidin-1-yl)aniline (**3**) Yield 81%, Tm = 103–107°C. ^{1}H NMR spectrum (DMSO-d_6, δ, ppm, *J* /Hz): 1.55 (m, 2H, CH_2), 1.70 (m, 4H, $(CH_2)_2$), 2.82 (m, 4H, $N(CH_2)_2$), 5.36 (s, 2H, NH_2), 7.00 (d, 1H, H^5, *J* 8.6 Hz), 7.27 (d, 1H, H^4, *J* 8.6 Hz). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): 24.4, 26.4, 52.0, 109.0, 114.0, 118.0, 141.2, 144.3, 145.0. HRMS: *m/z* calculated $C_{11}H_{15}ClN_3O_2$ 256.0854 $[M+H]^+$, found: 256.0854.

This work was carried out with the financial support of grant No MK-3459.2022.1.3 from the President of the Russian Federation for state support of young Russian scientists - candidates of science.

References

1. **Serafini, M., Cargnin, S., Massarotti, A., Pirali, T. & Genazzani, A.A**. (2020) Essential Medicinal Chemistry of Essential Medicines, *J. Med. Chem*., 63 (18), pp. 10170-10187. DOI: 10.1021/acs.jmedchem.0c00415 [online]. Available at: https://pubs.acs.org/doi/10.1021/acs.jmedchem.0c00415
2. **Smith, B.R., Eastman, C.M. & Njardarson, J.T.** (2014) Beyond C, H, O, and N! Analysis of the Elemental Composition of U.S. FDA Approved Drug Architectures, *J. Med. Chem.,* 57(23), pp. 9764-9773. DOI: 10.1021/jm501105n [online]. Available at: https://pubs.acs.org/doi/10.1021/jm501105n
3. **Fang, W.-Y., Ravindar, L., Rakesh, K.P., Manukumar, H.M., Shantharam, C.S., Alharbi, N.S. & Qin, H.-L.** (2019) Synthetic approaches and pharmaceutical applications of chloro-containing molecules for drug discovery: A critical review, *Eur. J. Med. Chem.* 173, pp. 117-153. DOI: 10.1016/j.ejmech.2019.03.063 [online]. Available at: https://www.sciencedirect.com/science/article/pii/S0223523419302971?via%3Dihub
4. **Filimonov, S.I., Makarova, E.S., Chirkova, J.V. & Kabanova, M.V.** (2022) Diastereomeric composition of the reaction of the formation of hexahydro-5h-chromeno[4,3-*d*]pyrimidin-5-ones, *From Chemistry Towards Technology Step-By-Step,* 3(1), pp. 131-138. DOI: 10.52957/27821900_2022_01_131 [online]. Available at: http://chemintech.ru/index.php/tor/2022tom3no1
5. **Liu, F., Wu, N. & Cheng, X.** (2021) Chlorination Reaction of Aromatic Compounds and Unsaturated Carbon–Carbon Bonds with Chlorine on Demand, *Org. Lett*., 88(8), pp. 3015-3020. DOI: 10.1021/acs.orglett.1c00704 [online]. Available at: https://pubs.acs.org/doi/abs/10.1021/acs.orglett.1c00704
6. **Begunov, R.S., Nozdracheva, O.I., Kosareva, T.N. & Orlov, V.Yu.** (2006) Minor products at reduction 1-substituted 2,4-dinitrobenzenes, *Izvestiya vuzov. Khimiya i khimicheskaya tekhnologiya*. [ChemChemTech]. 49(10), pp. 33-34 [online]. Available at: www.elibrary.ru/item.asp?id=9301463 (in Russian)
7. **Kosareva, T.N., Begunov, R.S., Valyaeva, A.N. & Jakovleva, Yu.S.** (2010) Basic and collateral processes at the reducing of 2,4-dinitroanizole by tin (II) chloride, *Bashkirskii khimicheskii zhurnal,* 4, pp. 11-15 [online]. Available at: www.elibrary.ru/item.asp?id=15608400 (in Russian).
8. **Li Q.-S., Lv, P.-C., Li, H.-Q., Lu, X., Li, Z.-L., Ruan, B.-F. & Zhu, H.-L.** (2012) Synthesis and biological evaluation of novel N, N′-disubstituted urea and thiourea derivatives as potential anti-melanoma agents, *Journal of Enzyme Inhibition and Medicinal Chemistry,* 27(5), pp. 708-714. DOI: 10.3109/14756366.2011.608665 [online]. Available at: https://www.tandfonline.com/doi/full/10.3109/14756366.2011.608665
9. **Zhao, W., Yang, Y., Zhang, Y.-X., Zhou, C., Li, H.-M., Tang, Y.-L., Liang, X.-H., Chen, T. & Tang, Y.-J.** (2015) Fluoride-containing podophyllum derivatives exhibit antitumor activities through enhancing mitochondrial apoptosis pathway by increasing the expression of caspase-9 in HeLa cell, *Scientific Reports,* 5(17175), pp. 1-15. DOI: 10.1038/srep17175 [online]. Available at: https://www.nature.com/articles/srep17175
10. **Windsor, M.A., Valk, P.L., Xu, S., Banerjee, S. & Marnett, L.J.** (2013) Exploring the molecular determinants of substrate-selective inhibition of cyclooxygenase-2 by lumiracoxib, *Bioorg. Med. Chem. Lett.,* 23(21), pp. 5860-5864. DOI: 10.1016/j.bmcl.2013.08.097 [online]. Available at: https://www.sciencedirect.com/science/article/pii/S0960894X13010469
11. **Gómez-Santacana, X., de Munnik, S.M., Mocking, T.A.M., Hauwert, N.J., Sun, S., Vijayachandran, P., de Esch, I.J.P., Vischer, H.F., Wijtmans, M. & Leurs, R.** (2019) A toolbox of molecular photoswitches to modulate the CXCR3 chemokine receptor with light, *Beilstein J. Org. Chem.,* 15, pp. 2509-2523. DOI: 10.3762/bjoc.15.244 [online]. Available at: https://www.beilstein-journals.org/bjoc/articles/15/244
12. **De La Rosa, M., Kim, H.W., Gunic, E., Jenket, C., Boyle, U., Koh, Y.-h., Korboukh, I., Allan, M., Zhang, W., Chen, H., Xu, W., Nilar, S., Yao ,N., Hamatake, R., Lang, S.A., Hong, Z., Zhang, Z. & Girardet, J.-L.** (2006) Tri-substituted triazoles as potent non-nucleoside inhibitors of the HIV-1 reverse transcriptase, *Bioorg. Med. Chem. Lett.,* 16(17), pp. 4444-4449. DOI: 10.1016/j.bmcl.2006.06.048 [online]. Available at: https://www.sciencedirect.com/science/article/pii/S0960894X06007128?via%3Dihub

Received 10.06.2022
Approved after reviewing 17.06.2022
Accepted 17.06.2022