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INTRAMOLECULAR AMINATION OF *ORTHO*-NITRO-*TERT*-ANILINES AS A METHOD FOR THE SYNTHESIS OF CONDENSED BENZIMIDAZOLE DERIVATIVES WITH A NODAL NITROGEN ATOM

R. S. Begunov[1,2], L. I. Savina[1,2], D. A. Astafieva[2]

Roman Sergeevich Begunov, Candidate of Chemical Sciences, Associate Professor; **Luisa Ilinichna Savina**, Master's Student**, Daria Aleksandrovna Astafieva**, Student
[1]Yaroslavl State Medical University, Yaroslavl, Russia, begunov@bio.uniyar.ac.ru, luizasavina2000@mail.ru
[2]P.G. Demidov Yaroslavl State University, Yaroslavl, Russia, begunov@bio.uniyar.ac.ru, luizasavina2000@mail.ru, cherry23_00@mail.ru

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***Abstract.** The paper examines the applicability limits of the intramolecular reductive cyclisation reaction of ortho-nitroarenes containing various limiting azagetherocycles for the synthesis of condensed benzimidazole derivatives with a nodal nitrogen atom. The process of intramolecular heterocyclisation occurred during the reduction of 4-(2-nitroaryl)-4-morpholine and 1-(2-nitroaryl)-4-methylpiperidine. At the same time, the presence of the 4-methyl-piperazine cycle in the substrate prevented the formation of a condensed polyazaheterocycle.*

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Introduction

Nowadays, the issue of development of new heterocyclic compounds is a topical issue in organic chemistry and related disciplines – pharmaceutical and medicinal chemistry. These compounds possess various valuable properties due their structure. First of all, it refers to condensed benzimidazole derivatives. They contain the limited azaheterocycles annelated to imidazole demonstrating a wide range of biological activity. These heterocyclic compounds are interesting as anticancer drugs [1-11] (Fig. 1).

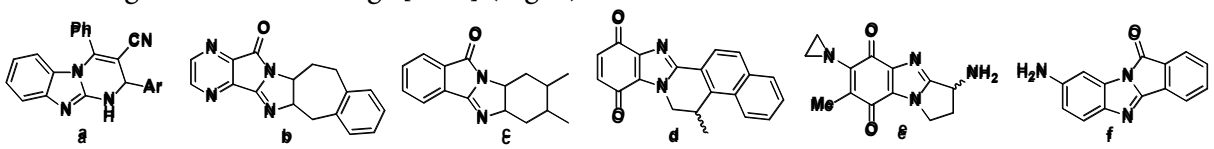


Fig. 1. Condensed benzimidazole derivatives with cytotoxicity against cancer cell lines: **a** - leukaemia, breast and lung; **b**, **c** - human ovarian (IGR-OV-1), breast (MCF-7) and CNS (SF-295); **d** - human cervix (HeLa) and prostate (DU145); **e** - Fanconi anaemia; **f** - murine leukaemia P-388

Furthermore, condensed benzimidazole derivatives are found to have antihelminthic (**a**) [12], antimicrobial (**b**) [13-16], antifungal (**c**) [17, 18], antiviral (**d**) [19, 20], analgesic, and anti-inflammatory (**e**) properties [21-22]. They are also used as anti-ulcer agents (**f**) [23] and in endocrinology for the treatment of congenital adrenal hyperplasia (**g**) [24] (Fig. 2).

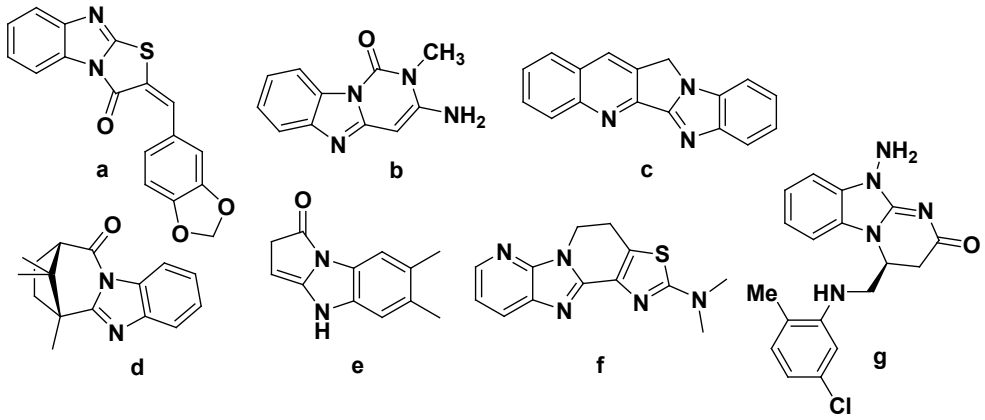
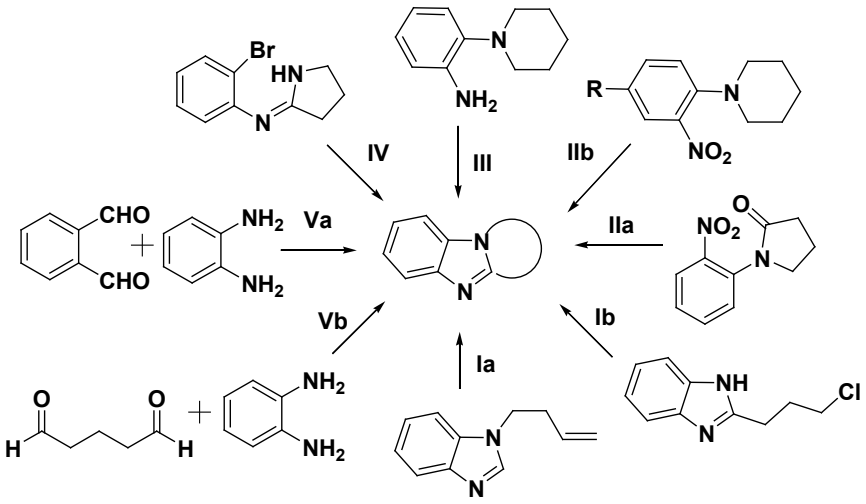


Fig. 2. Condensed benzimidazole derivatives with various biological activities

However, the development of such drugs is challenging procedure. Their synthesis includes various stages of heterocyclic core formation and further functionalisation. It allows ones to obtain molecules with the required periphery.

The chemical processes used to produce a condensed polynuclear heterocyclic system are the most diverse (Scheme 1).



Scheme 1. Methods of condensed benzimidazole derivatives synthesis: **I** - annelation of the limit cycle (**a** - with formation of C-C bond; **b** - with formation of C-N bond); **II** - intramolecular reductive cyclisation (**a** - nitroanilides; **b** - nitro compounds containing the limit azagetheterocycle); **III** - oxidative amination; **IV** - N-arylation of amidines; **V** - condensation of *ortho*-phenylenediamines with dialdehydes (**a** - to form tricycliccompounds; **b** - to form tetracyclic compounds).

They can be classified into three groups. The first group includes methods based on annelation of the limit heterocycle to imidazole (Scheme 1, **I**) [26-30]. In the second group, the formation of the imidazole cycle occurs (Scheme 1, **II-IV**) [31-45]. These reactions are intramolecular reductive [31-39] or oxidative amination [11, 40-42] as well as N-arylation reactions of amidines [43, 44]. Methods of synthesis of condensed heterocyclic nucleus are also

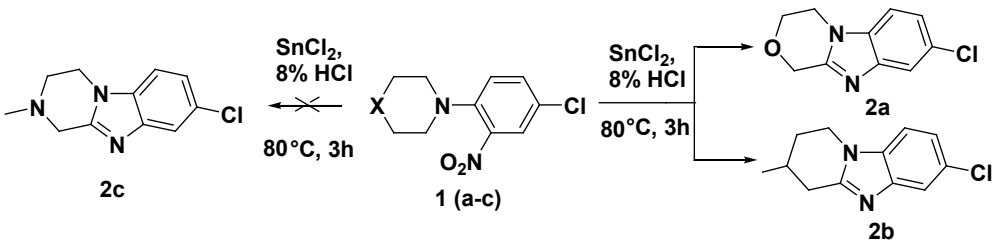
described; it causes the formation of two annelated heterocycles at once – a limit and an unsaturated one (Scheme 1, **V**) [45, 46].

The method based on the reaction of intramolecular reductive amination seems to be more promising among the methods of synthesis of condensed benzimidazole derivatives shown on Scheme 1. The advantages are that several processes (reduction and heterocyclisation) are performed in one reactor at once. As a result, the number of reagent loading, isolation, and purification of target products is reduced. Substrates for this reaction can be readily obtained using cheap and available reagents.

We have previously used this strategy to prepare 1,2,3,4-tetrahydropyrido[1,2-a]benzimidazoles [32]. To determine the limits of applicability of this method for the synthesis of other condensed benzimidazole derivatives, we conducted the intramolecular reductive amination reaction of various *ortho*-nitro-*tert*-anilines: 4-(2-nitro-4-chlorophenyl)-4-morpholine (**1a**), 1-(2-nitro-4-chlorophenyl)-4-methylpiperidine (**1b**) and 1-(2-nitro-4-chlorophenyl)-4-methylpiperazine (**1c**). These substances contained both atoms and groups of atoms increasing (Compound **1b**) and decreasing (Compound **1a, c**) the electron density at the reaction centre.

Main body

The reductive heterocyclisation of *ortho*-nitro derivatives **1 (a-c)** was conducted under previously established conditions [32]: reducing agent was $SnCl_2$; reducing agent application time was 3 h; HCl concentration was 8%; temperature was 80 °C. The reducing agent was taken in the amount necessary to reduce the nitro group to nitroso-, since it was assumed that cyclisation occurs as a result of the attack of this group on the methylene carbon atom of the heterocycle [31].



1 a X = O, **b** X = CH-CH_3, **c** X = N-CH_3

Scheme 2.

Analysis of the composition of the products obtained by ^1H and ^{13}C NMR spectroscopy and mass spectrometry showed the formation of the target heterocyclic systems upon reduction of compounds **1a** and **1b**.

The ^1H NMR spectrum of 8-chloro-3,4-dihydro-1H-*[1,4]oxazino[4,3-*a*]benzimidazole* (**1b**) had a characteristic arrangement of aliphatic and aromatic proton signals typical for similar compounds [32] (Fig. 3). Three signals of doubled intensity from 6 aliphatic protons of the morpholine cycle were recorded in the strong-field region of the spectrum.

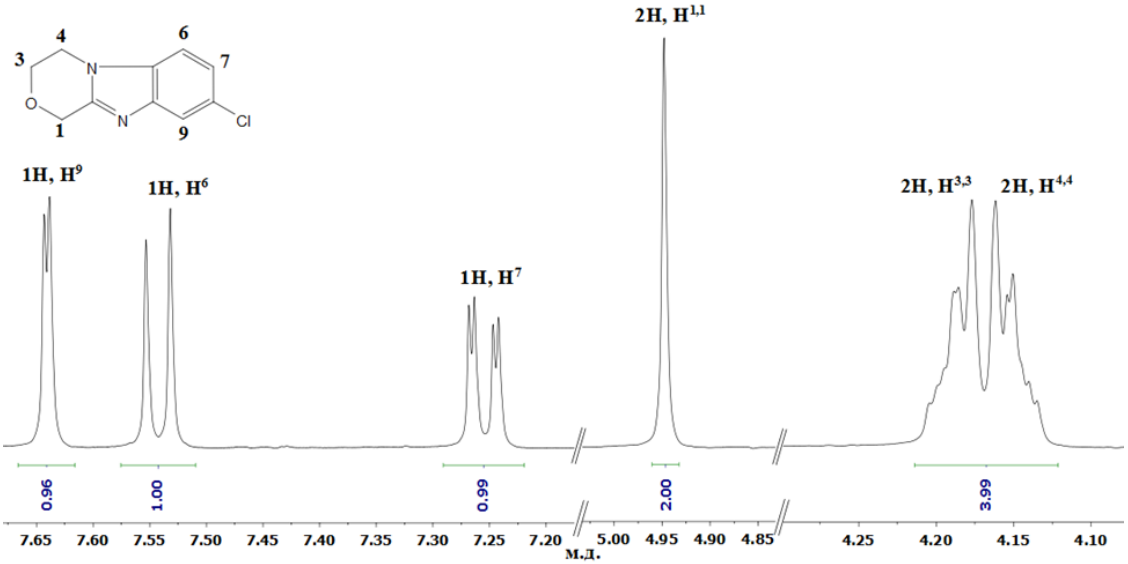


Fig. 3. Fragments of ^{1}H NMR spectrum of 8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**2a**)

The proton signals of methylene groups also had double intensity in the ^{1}H NMR spectrum of the previously obtained 7-chloro-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole (Fig. 4) [31].

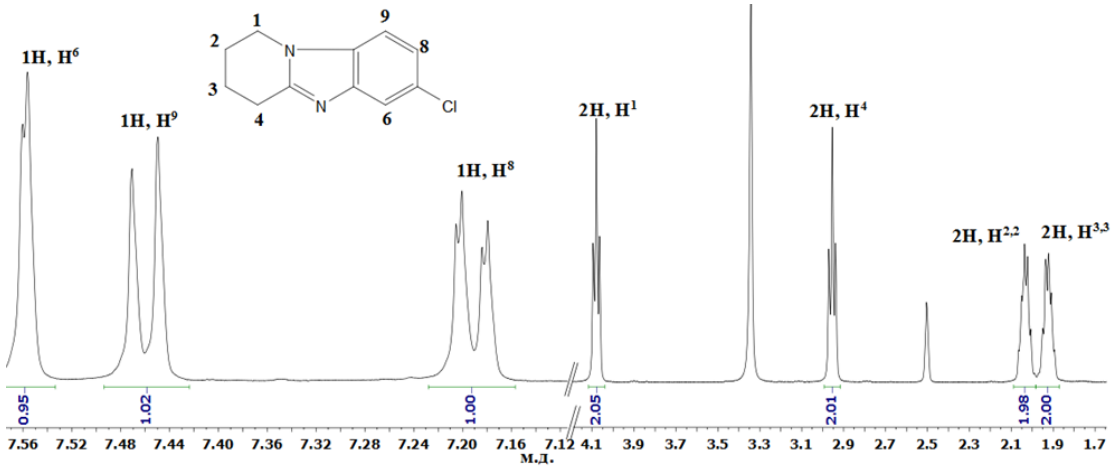


Fig. 4. ^{1}H NMR fragments of the spectrum of 7-chloro-1,2,3,3,4-tetrahydropyrido[1,2-*a*]benzimidazole

In contrast to the ^{1}H NMR spectra of these substances, the 1H NMR spectrum of 3-methyl-7-chloro-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole **2b** contained only one instead of the expected 3 signals of doubled intensity originating from protons of methylene groups (Fig. 5, horizontal part of the spectrum). Other methylene protons gave single signals. The attribution of aliphatic proton signals was made based on 2D ^{1}H-^{1}H NOESY spectrum data (Fig. 5).

Interaction cross-peaks of one of the C**1**H^{2} group protons with the methylene proton H_3, methylene $H^{2',2''}$ and aromatic H^{9} were observed in the 2D spectrum of compound ^{2b}. The other proton of this methylene group $H^{1'}$ had cross peaks only with H^{9} and $H^{2'',2'''}$. The H^{4} and $H^{4'}$ protons also differed in their interactions with aliphatic protons. $H^{4'}$ gave a cross-peak with protons of the methyl and $C^{2}H_2$ groups, while interaction with methyl and methine H^{3} protons was observed for H^{4}.

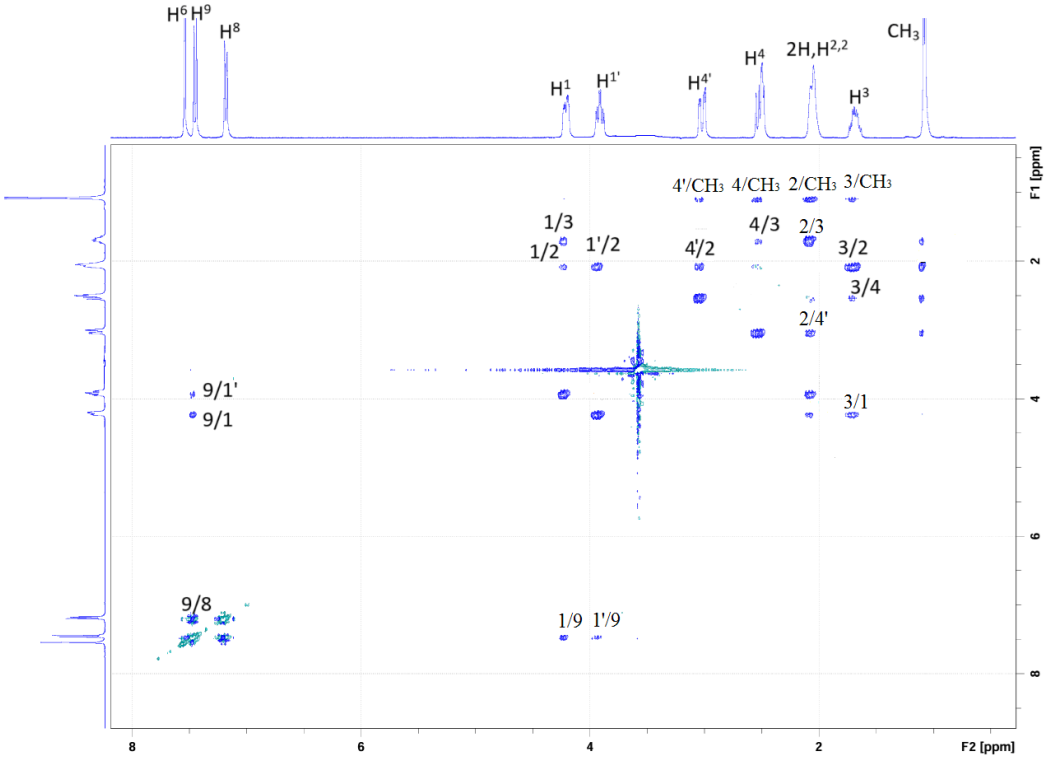


Fig. 5. 2D ^{1}H-^{1}H NOESY spectrum of 3-methyl-7-chloro-1,2,3,3,4-tetrahydropyrido[1,2-*a*]benzimidazole (**2b**)

To explain the ^{1}H NMR spectroscopy data, the geometrical parameters of the molecule 3-methyl-7-chloro-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole **2a** were calculated (Fig. 6). The calculation was performed using density functional theory with hybrid exchange-correlation functional with the DFT method B3LYP/6-31G** using ORCA 5.0.4 software. Geometry optimisation was performed using a discrete SMD solvation model. DMSO was used as a solvate shell.

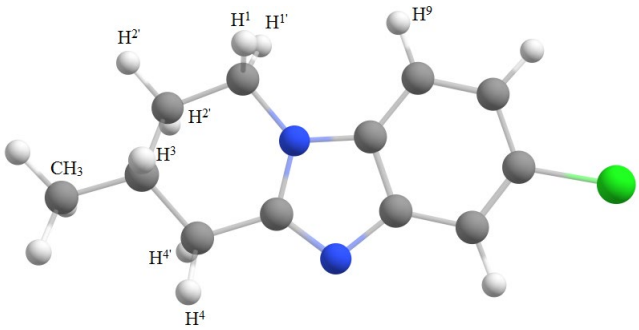


Fig. 6. Optimised molecule of 3-methyl-7-chloro-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole (**2b**) by DFT B3LYP/6-31G** using ORCA 5.0.4 software.

The distances between hydrogen atoms were determined in the optimised molecule of 3-methyl-7-chloro-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole. The protons H^{1} и H^{3}, $H^{2'}$ и $H^{4'}$ were spatially close. The distance between them was 2.62 Å and 2.58 Å, respectively. The distances between $H^{1'}$ и H^{3}, $H^{2'}$-H^{4}, atoms, for which no cross-peaks were present in 2D ^{1}H-^{1}H NOESY, were much larger: 3.78 Å and 3.75 Å, respectively.

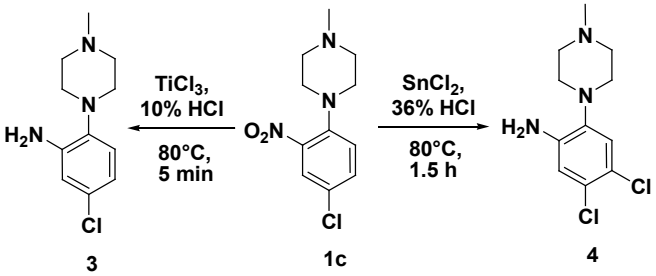
No formation of the intramolecular cyclisation product **2c** occurred upon reduction of compound **1c** containing the piperazine cycle. Analysis of the composition of the reaction mass

showed the presence of starting substance **1c,** 5-chloro-2-(4-methylpiperazin-1-yl)aniline (**3**) and 4,5-dichloro-2-(4-methylpiperazin-1-yl)aniline (**4**) in the ratio 1:0.21:0.33. The ^{1}H NMR spectrum of the mixture also contained trace amounts of the undetermined product. The presence of chlorination products was noted earlier in the reduction of similar dinitroarenes [47].

Varying the synthesis conditions and using different protogenic media did not cause the formation of 2-methyl-8-chloro-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole (**2c**). Nitro compound **1c** and amino products **3** and **4** were always present in the reaction mass. Only their ratio varied depending on the conditions.

The absence of the condensed heterocyclic product in the reaction mass was apparently explained by protonation of the nitrogen atom of the heterocycle bound to three alkyl substituents. Therefore, the nucleophilic properties of the reaction centre decreased and the intramolecular cyclisation process did not occur.

Individually, amino compound **3** was obtained by reduction of **1c** $TiCl_3$ in 10% HCl (Scheme 3).



Scheme 3.

Two signals from 8 protons of 4-methylene groups were observed in the ^{1}H NMR spectrum of amine **3** (Fig. 7) in the strong-field region. The signal of the doubled intensity of the amino group protons in the form of a broad singlet was released at 4.99 ppm. The spectrum also contained 3 signals from 3 aromatic protons. The more shielded of the two was H^4, which was in the *para*-position to the NH_2 group. The H^3 proton with J = 8.3 Hz was fixed in the weakest field at 6.85 ppm.

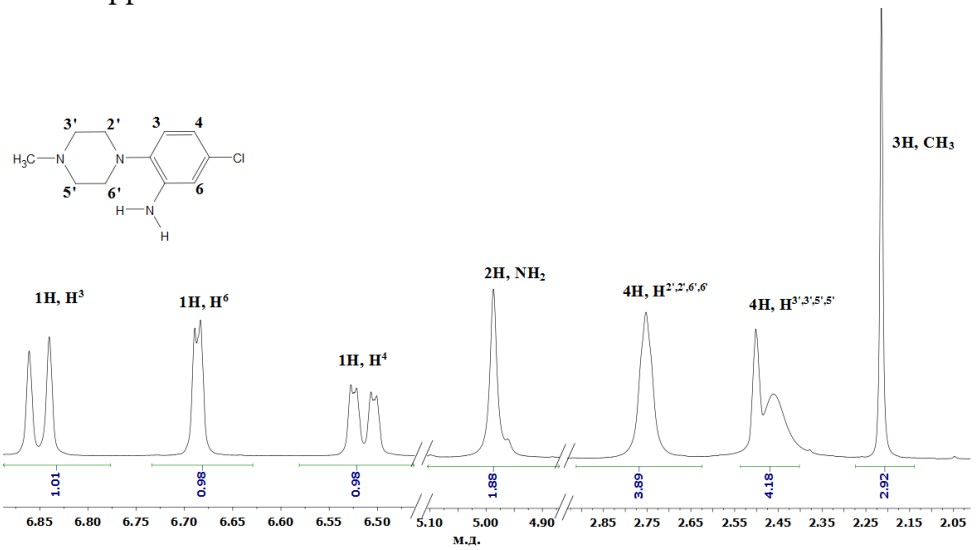


Fig. 7. ^{1}H NMR fragments of the spectrum of 5-chloro-2-(4-methylpiperazin-1-yl)aniline (**3**)

Dichloroaniline **4** was synthesised in 36% HCl using $SnCl_2$ as a reducing agent. As compared to amine[3], only two signals of aromatic protons at 6.84 ppm and 6.97 ppm were observed in the **1**H NMR spectrum (Fig. 8) of this compound. Their appearance indicated the introduction of a substituent in the 4th position. The proton signal of the amino group shifted slightly to the weak-field region of the spectrum at 5.09 ppm.

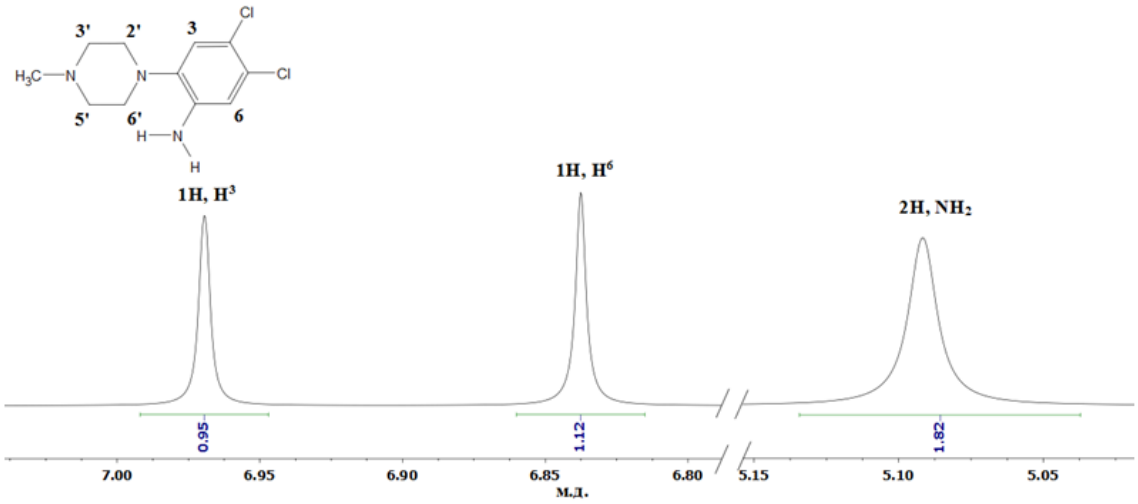


Fig. 8. [1]H NMR fragments of the spectrum of 4,5-dichloro-2-(4-methylpiperazin-1-yl)aniline (**4**)

Thus, the reductive heterocyclisation of *ortho*-nitro-*tert*-anilines can be used to prepare condensed benzimidazole derivatives containing various limiting azagetheterocycles. A limitation of the process is the presence of a heteroatom in the heterocyclic fragment of the substrate protonating during the reduction reaction.

Experimental part

We determined the melting points on a PolyTherm A device at a heating rate of 3 °C/min and did not adjust. We recorded NMR spectra on a Bruker DRX-400 for DMSO-d_6 solutions. We used the signals of residual solvent protons in [1]H NMR (δ 2.5 ppm) or in [13]C NMR (δ = 39.5 ppm) as a reference for counting chemical shifts. Mass spectra were recorded on a FINNIGAN MAT instrument. INCOS 50, electron flux energy 70 eV.

General procedure for the synthesis of 8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (2a) 3-methyl-7-chloro-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole (2b)

We added a solution of 0.98 g (0.0043 mol) of SnCl2-**2H**2O in 45 mL of 8% HCl to a solution of 0.0041 mol of $_{nitro}$ compound $_{1a}$ or 1b in 45 mL of 8% HCl at 80 °C for 2 h. The reaction mixture was then stirred for 0.5 h. After cooling, the reaction mixture was treated with NH_4OH to pH 8 and extracted with chloroform. After distillation of chloroform, the resulting dry residue was recrystallised in chloroform.

8-Chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**2a**) Yield is 91%. $T_{melt.}$ 193-196 °C. [1]H NMR spectrum (400 MHz, DMSO-d_6) δ 7.64 (d, 1H, H-9, J=1.9), 7.54 (d, 1H, H-6, *J*=8.5), 7.26 (dd, 1H, H-7, *J*=8.5, 1.9), 4.95 (s, 2H, H-1,1), 4.18 (dtt, 4H, H-3,3,4,4, *J*=8.4, 5.8, 2.9). [13]C NMR spectrum (101 MHz, DMSO-d_6) δ 150.44, 143.86, 133.61,

127.02, 122.44, 118.77, 111.82, 65.01, 63.91, 42.62. HRMS: *m/z* calculated $C_{10}H_{10}ClN_2O$ 209.6516 $[M+H]^+$, found 209.6511.

3-Methyl-7-chloro-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole (**2b**). Yield is 92%. $T_{melt.}$ 127-129 °C. ^{1}H NMR Spectrum (400 MHz, DMSO-d_6) δ 7.54 (d, 1H, H-6, J=1.3), 7.45 (d, 1H, H-9, J=8.4), 7.18 (dd, 1H, H-8, J=8.5, 1.8), 4.16 – 4.26 (m, 1H, H-1), 3.87 – 3.97 (m, 1H, H-1'), 2.95 – 3.07 (m, 1H, H-4'), 2.57 – 2.46 (m, 2H, H-4), 2.12 – 2.01 (m, 2H, H-2,2), 1.61-1.75 (m, 1H, H-3), 1.08 (d, 3H, CH_3, J=6.4). Spectrum ^{13}C NMR (101 MHz, DMSO -d_6) δ 154.13, 144.07, 133.87, 126.64, 121.87, 118.09, 111.59, 42.11, 33.31, 30.14, 27.34, 21.38. HRMS: *m/z* calculated $C_{12}H_{14}ClN_2$ 221.7054 $[M+H]^+$, found 221.7056.

Methods for the synthesis of 5-chloro-2-(4-methylpiperazin-1-yl)aniline (**3**).

We added 28 mL of a 15% solution of TiCl**3** in 10% HCl to a solution of 1 g (0.0039 mol) of nitro compound $_{1c}$ in 35 mL of 10% HCl at 80 °C. The reaction mixture was stirred for 5 min and cooled. After cooling, the reaction mixture was treated with NH_4OH to pH 8 and extracted with chloroform. After distillation of chloroform, the resulting dry residue was recrystallised in a mixture of hexane and chloroform. Yield is 91%. T_{melt}. 150-152 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 6.85 (d, 1H, H-3, J=8.3), 6.69 (d, 1H, H-6, J=2.5), 6.51 (dd, 1H, H-4, J=8.3, 2.5), 4.99 (s, 2H, NH_2), 2.75 (t, 4H, H-2',2',6',6', J=4.8), 2.53 – 2.37 (t, 4H, H-3',3',5',5', J=4.8), 2.21 (s, 3H, CH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6) δ 144.65, 137.67, 128.65, 121.16, 116.27, 113.97, 55.76, 50.88, 46.53. HRMS: *m/z* calculated $C_{11}H_{17}ClN_3$ 226.7252 $[M+H]^+$, found 226.7250

Methods for the synthesis of 4,5-dichloro-2-(4-methylpiperazin-1-yl)aniline (**4**).

We added 2.7 g (0.0119 mol) of $SnCl2_{\cdot 2H}2_O$ in 45 mL of 36% HCl to a solution of 1 g (0.0039 mol) of nitro compound 1s in 35 mL of 36% HCl at 80 °C for 1.5 h. After cooling, the reaction mixture was treated with NH_4OH to pH 8 and extracted with chloroform. After distillation of chloroform, the resulting dry residue was recrystallised in methanol. Yield is 64%. T_{melt}. 128-131 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) δ 6.97 (s, 1H, H-3), 6.84 (s, 1H, H-6), 5.09 (s, 2H, NH_2), 2.79 (t, 4H, H-2',2',6',6', J=4.8), 2.54 (t, 4H, H-3',3',5',5', J=4.8), 2.22 (s, 3H, CH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6) δ 144.69, 137.68, 128.68, 121.19, 116.32, 113.99, 55.77, 50.88, 46.53. HRMS: *m/z* calculated $C_{11}H_{16}Cl_2N_3$ 261.1703 $[M+H]^+$, found 261.1707

We performed quantum chemical calculations of the electronic structure using the ORCA 5.0.4 software within the density functional theory with hybrid exchange-correlation functional (DFT B3LYP/6-31G** method) for open electron shells. The effect of the medium was considered using an electron density solvation model (SMD). DMSO was used as a solvate shell. We used software and ChemCraft [48] for data processing, visualisation, and estimation of the interatomic distances of the optimised molecules.

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References

1. **Demirayak S., Mohsen U.A., Karaburun A.C.** Synthesis and anticancer and anti-HIV testing of some pyrazino[1,2-a]benzimidazole derivatives. *Eur. J. Med. Chem.,* 2002, 37(**3**), 255–260. DOI: 10.1016/S0223-5234(01)01313-7.
2. **Nowicka A., Liszkiewicz H., Nawrocka W.P., Wietrzyk J., Kempińska K., Dryś A.** Synthesis and antiproliferative activity *in vitro* of new 2-aminobenzimidazole derivatives. Reaction of 2-arylideneaminobenzimidazole with selected nitriles containing active methylene group. *Cent. Eur. J. Chem*., 2014, 12, 1047-1055. DOI: 10.2478/s11532-014-0533-3.
3. **Sondhi S.M., Rani R., Singh J., Roy P., Agrawal S.K., Saxena A.K.** Solvent free synthesis, anti-inflammatory and anticancer activity evaluation of tricyclic and tetracyclic benzimidazole derivatives. *Bioorg. Med. Chem. Lett.,* 2010, 20(**7**), 2306-2310. DOI: 10.1016/j.bmcl.2010.01.147.
4. **Moriarty E., Carr M., Bonham S., Carty M. P., Aldabbagh F.** Synthesis and toxicity towards normal and cancer cell lines of benzimidazolequinones containing fused aromatic rings and 2-aromatic ring substituents. *Eur. J. Med. Chem*., 2010, 45(**9**), 3762-3769. DOI: 10.1016/j.ejmech.2010.05.025.
5. **O'Donovan L., Carty M. P., Aldabbagh F.** First synthesis of N-[(aziridin-2-yl)methyl]benzimidazolequinone and analysis of toxicity towards normal and Fanconi anemia cells. *Chem. Commun.,* 2008, (**43**), 5592–5594. DOI: 10.1039/B814706J.
6. **Fahey K., O'Donovan L., Carr M., Carty M. P., Aldabbagh F.** The influence of the aziridinyl substituent of benzimidazoles and benzimidazolequinones on toxicity towards normal and Fanconi anaemia cells. *Eur. J. Med. Chem*., 2010, 45(**5**), 1873–1879. DOI: 10.1016/j.ejmech.2010.01.026.
7. **Thummanagoti S., Yellol G. S., Sun C.** Microwave-Assisted Tandem Transformation on an Ionic-Liquid Support: Efficient Synthesis of Pyrrolo/Pyridobenzimidazolones and IsoindolinoneFused Benzimidazoles. *Chem. Asian J*., 2011, 6(**9**), 2471 – 2480. DOI: 10.1002/asia.201100277.
8. **Enumula S., Pangal A., Gazge M., Shaikh J. A.** Diverse Pharmacological aspects of Benzimidazole Derivatives: A Review. *Res. J. Chem. Sci.*, 2014, 4, 78-88. Available at: https://isca.me/rjcs/Archives/v4/i4/12.ISCA-RJCS-2014-032.pdf
9. **Lynch M., Hehir S., Kavanagh P., O`Shaughnessy J., Carty M.P., Aldabbagh F.** Synthesis by radical cyclization and cytotoxicity of highly potent bioreductive alicyclic ring fused [1,2-a]benzimidazolequinones. *Chemistry*, 2007, 13(**11**), 3218-3226. DOI: 10.1002/chem.200601450.
10. **Fagan V., Bonham S., Carty M.P., Aldabbagh F.** One-pot double intramolecular homolytic aromatic substitution routes to dialicyclic ring fused imidazobenzimidazolequinones and preliminary analysis of anticancer activity. *Org. Biomol. Chem*., 2010, 8(**14**), 3149-3156. DOI: 10.1039/c003511d.
11. **Suleman A., Skibo E.B.** A comprehensive study of the active site residues of DT-Diaphorase: rational design of benzimidazolediones as DT-Diaphorase substrates. *J. Med. Chem*., 2002, 45 (**6**), 1211-1220. DOI: 10.1021/jm0104365.
12. **A. Ts. Mavrova.** Synthesis and antitrichinellosis activity of some 2-substituted-[1,3]thiazolo[3,2-a]benzimidazol-3(2H)-ones. *Org. Biomol. Chem*., 2005, 13, 5550–5559. DOI: 10.1016/j.bmc.2005.06.046.
13. **Pridvorov G.V., Mukha O.Yu., Lipatov V.A.** Protivosudorozhnye svoistva kondensirovannykh proizvodnykh imidazobenzimidazola: tezisy dokladov Rossiiskoi konferentsiya po meditsinskoi khimii s mezhdunarodnym uchastiem «MedKhim-Rossiya 2021», 2021, 439. DOI: 10.19163/medchemrussia2021-2021-439 (in Russian).
14. **Dolzhenko A.V., Chui W.K., Dolzhenko A.V., Chan L.W.** Synthesis and biological activity of fluorinated 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-a]benzimidazoles. *J. Fluorine Chem*., 2005, 126(**5**), 759–763. DOI: 10.1016/j.jfluchem.2005.02.009.
15. **Kaur P., Wakode S. R.** Antimicrobial properties of benzimidazole and Mannich bases of benzimidazole: A review. *Int. J. Sci. Res.*, 2016, 5(**3**), 762-772. Available at: https://www.ijsr.net/archive/v5i3/NOV161972.pdf (accessed 11.11.2024).
16. **Badawey E.S.A., Rida S.M., Soliman F.S., Kappe T.** Benzimidazole condensed ring systems, VI: Organic azides in heterocyclic synthesis, X: Synthesis of some substituted pyrimido[1,6-a]-benzimidazoles as potential antimicrobial agents. *Monatsh Chem.*, 1989, 120, 1159–1164.

17. **Villa P., Arumugam N., Almansour A.I., Kumar R.S., Mahalingam S.M., Maruoka K., Thangamani S.** Benzimidazole tethered pyrrolo[3,4-b]quinoline with broad-spectrum activity against fungal pathogens. *Bioorg. Med. Chem. Lett*., 2019, 29(**5**), 729-733. DOI: 10.1016/j.bmcl.2019.01.006.
18. **Mohamed B.G., Abdel-Alim A.M., Hussein M.A.** Synthesis of 1-acyl-2-alkylthio-1,2,4-triazolobenzimidazoles with antifungal, anti-inflammatory and analgesic effects. *Acta Pharm.*56(**1** 31. Available at: https://core.ac.uk/download/pdf/14378832.pdf (accessed 11.11.2024).
19. **Chernyshov V.V., Yarovaya O.I., Fadeev D.S., Gatilov Y.V., Esaulkova Y.L., Muryleva A.S., Sinegubova K.O., Zarubaev V.V., Salakhutdinov N.F.** Single-stage synthesis of heterocyclic alkaloid-like compounds from (+)-camphoric acid and their antiviral activity. *Mol Divers*, 2020, 24, 61–67. DOI: 10.1007/s11030-019-09932-9.
20. **De Palma, A.M., Heggermont, W., Leyssen, P., Pürstinger, G., Wimmer, E., De Clercq, E., Rao A., Monforte A.M., Chimirri A., Neyts J.** Antienterovirus activity and structure–activity relationship of a series of 2,6-dihalophenyl-substituted 1H,3H-thiazolo[3,4-a]benzimidazoles. *Biochem. Biophys. Res. Commun.*, 2007, 353 (**3**), 628-632. DOI: 10.1016/j.bbrc.2006.12.063.
21. **Gaba M., Sing S., Mohan C.** Benzimidazole: An emerging scaffold for analgesic and anti-inflammatory agents. *Eur. J. Med. Chem*., 2014, 76, 494-505. DOI: 10.1016/j.ejmech.2014.01.030.
22. **Srikanth L., Raj V.V., Raghunandan N., Venkateshwerlu L.** Recent advances and potential pharmacological activities of benzimidazole derivatives. *Der Pharma Chem*., 2011, 3(**2**), 172-193. DOI: 10.5555/20113163843.
23. **Jain K.S., Shah A.K., Bariwal J., Shelke S.M., Kale A.P., Jagtap J.R., Bhosale A.V.** Recent advances in proton pump inhibitors and management of acid-peptic disorders. *Bioorg. Med. Chem*., 2007, 15(**3**), 1181-1205. DOI: 10.1016/j.bmc.2006.07.068.
24. **Vandyshev D.Yu., Kovygin Y.A., Khmelevskaya T.N., Shcherbakov K.A.,** Shikhalieva K.D., Smoliannikova M.Yu., Shikhaliev H.S. Synthesis of 3,4-dihydropyrimido[1,2-a]benzimidvzols, promising CRF1 receptor antagonists. *Russian Chemical Buelletin*, 2024, 73(**4**), 994-1004.
25. **Aso K., Kobayashi K., Takai T., Kojima T., Tokumaru K., Mochizuki M.** U.S. Patent No. 8901141, 2009.
26. **Tan K.L., Bergman R.G., Ellman J.A.** Annulation of alkenyl-substituted heterocycles via rhodium-catalyzed intramolecular C-H activated coupling reactions. *J. Am. Chem. Soc*., 2001, 123(**11**), 2685-2686. DOI: 10.1021/ja0058738.
27. **Tan K.L., Park S., Ellman J.A., Bergman R.G.** Intermolecular coupling of alkenes to heterocycles via C-H bond activation. *J. Org. Chem*., 2004. 69(**21**), 7329-7335. DOI: 10.1021/jo048666p.
28. **Haque M.R., Rasmussen M.** Ambident heterocyclic reactivity: Intramolecular alkylations of 2,4-disubstituted benzimidazoles. *Tetrahedron*, 1997, 53(**20**), 6937-6958. DOI: 10.1016/S0040-4020(97)00394-3.
29. **Bastug G., Eviolitte C., Marko I.E.** Functionalized orthoesters as powerful building blocks for the efficient preparation of heteroaromatic bicycles. *Org. Lett*., 2012, 14(**13**), 3502-3505. DOI: 10.1021/ol301472a.
30. **Allin S.M., Bowman W.R., Karim R., Rahman S.S.** Aromatic homolytic substitution using solid phase synthesis. *Tetrahedron*, 2006, 62(**18**), 4306-4316. DOI: 10.1016/j.tet.2006.02.071.
31. **Begunov R.S., Sakulina V.O., Syroeshkin M.A., Saverina E.A., Sokolov A.A., Minyaev M.E.** Electroreductive heterocyclization of *ortho*-piperidino substituted nitro(het)arenas. *Mendeleev Commun*., 2020, 30(**5**), C. 633-635. DOI: 10.1016/j.mencom.2020.09.027.
32. **Begunov R.S., Sokolov A.A., Filimonov S.I.** Synthesis of Quinone's Derivatives of Benzannelated Heterocycles with a Bridgehead Nitrogen. *ZhOrKh*., 2020, 56(**8**), 1222-1232. DOI: 10.31857/S051474922008008X (in Russian).
33. **Hubbard J.W., Piegols A.M., Söderberg B.C.G.** Palladium-catalyzed N-heteroannulation of N-allyl- or N-benzyl-2-nitrobenzenamines: synthesis of 2-substituted benzimidazoles. *Tetrahedron*, 2007, 63(**30**), 7077-7085. DOI: 10.1016/j.tet.2007.05.010.
34. **Meth-Cohn O., Suschitzky H.** Heterocycles by ring closure of *ortho*-substituted *t*-anilines (The *t*-amino effect). *Adv. Heterocycl. Chem.,* 1972, 14, 211-278. DOI: 10.1016/S0065-2725(08)60954-X.
35. **Tong S., Xu Z., Mamboury M., Wang Q., Zhu J.** Aqueous Titanium Trichloride Promoted Reductive Cyclization of *o*-Nitrostyrenes to Indoles: Development and Application to the Synthesis of Rizatriptan and Aspidospermidine. *Angew. Chem.*, Int. Ed., 2015, 54(**40**), 11809-11812. DOI: 10.1002/anie.201505713.

36. **Joardar S., Bhattacharyya A., Das S.** A palladium on carbon catalyzed one-pot synthesis of substituted benzimidazoles. *Synthesis*, 2014, 46(**22**), 3121-3132. DOI: 10.1055/s-0034-1378454.
37. **Duchek J., Vasella A.** Synthesis of Benzimidazoles by Phosphine-Mediated Reductive Cyclisation of *ortho*-Nitro-anilides. *Helv. Chim. Acta.*, 2011, 94(**6**), 977-986. DOI: 10.1002/hlca.201100123.
38. **Alonso J., Halland N., Nazaré M., R'kyek O., Urmann M., Lindenschmidt A.** A Direct, Regioselective Palladium-Catalyzed Synthesis of N-Substituted Benzimidazoles and Imidazopyridines. *Eur. J. Org. Chem.* 2011, 2011(**2**), 234–237. DOI: 10.1002/ejoc.201001423.
39. **Nguyen T.B., Ermolenko L., Al-Mourabit A.** Formic acid as a sustainable and complementary reductant: an approach to fused benzimidazoles by molecular iodine-catalyzed reductive redox cyclization of *o*-nitro-*t*-anilines. *Green Chemistry*, 2016, 18(**10**), 2966-2970. DOI: 10.1039/C6GC00902F.
40. **Sun X., Lv X. H., Ye L. M., Hu Y., Chen Y. Y., Zhang X. J., Yan M.** Synthesis of benzimidazoles via iridium-catalyzed acceptorless dehydrogenative coupling. *Org. Biomol. Chem*., 2015, 13(**27**), 7381-7383. DOI: 10.1039/C5OB00904A.
41. **Xue D., Long Y.Q.** Metal-free TEMPO-promoted C (sp^3)–H amination to afford multisubstituted benzimidazoles. *J. Org. Chem*., 2014, 79(**10**), 4727-4734. DOI: 10.1021/jo5005179.
42. **Fagan V., Bonham S., McArdle P., Carty M. P., Aldabbagh F.** Synthesis and Toxicity of New Ring-Fused Imidazo[5,4-f]benzimidazolequinones and Mechanism Using Amine N-Oxide Cyclizations. *Eur. J. Org. Chem.*, 2012., 2012(**10**), 1967-1975. DOI: 10.1002/ejoc.201101687.
43. **Baars H., Beyer A., Kohlhepp S. V., Bolm C.** Transition-metal-free synthesis of benzimidazoles mediated by KOH/DMSO. *Org. Lett*, 2014, 16(**2**), 536-539. DOI: 10.1021/ol403414v.
44. **Liubchak K., Nazarenko K., Tolmachev A.** Synthesis of annulated benzimidazoles via amidine cyclization. *Tetrahedron*, 2012, 68(**14**), 2993-3000. DOI: 10.1016/j.tet.2012.02.027.
45. **Chen J., Qu J., Zhang Y., Chen Y., Liu N., Chen B.** Metal-free construction of tricyclic or tetracyclic compounds-acid-promoted synthesis of benzo[4,5]imidazo[2,1-a]isoindole and 1,2-dialkyl-2,3-dihydrobenzimidazoles. *Tetrahedron*, 2013, 69(**1**), 316-319. DOI: 10.1016/j.tet.2012.10.030.
46. **Elder M. S., Melson G. A., Busch D. I.** Reactions of coordinated ligands. XII. The synthesis of *o*-benzylene-2,1-benzimidazole in the presence of nickel (II) ions, and a study of some of its metal complexes. *Inorg. Chem*., 1966, 5(**1**), 74-77. DOI: 10.1021/ic50035a018.
47. **Begunov R.S., Sokolov A.A.** One-reactor reduction and halogenation of N-(2,4-dinitrophenyl)piperidine. *From Chemistry Towards Technology Step-by-Step*, 2022, 3(**2**), 30-36. DOI: 10.52957/27821900_2022_02_30 (in Russian).
48. **Zhurko G.A.** Chemcraft. Version 1.6. Available at: http://www.chemcraftprog.com (accessed at 12.02.2024).

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