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Synthesis, Spectral Characteristics, and Molecular Docking Studies of 2,4-Dichloro-*N*-(2,2,2-trichloro-1-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide.

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molecules MDPI

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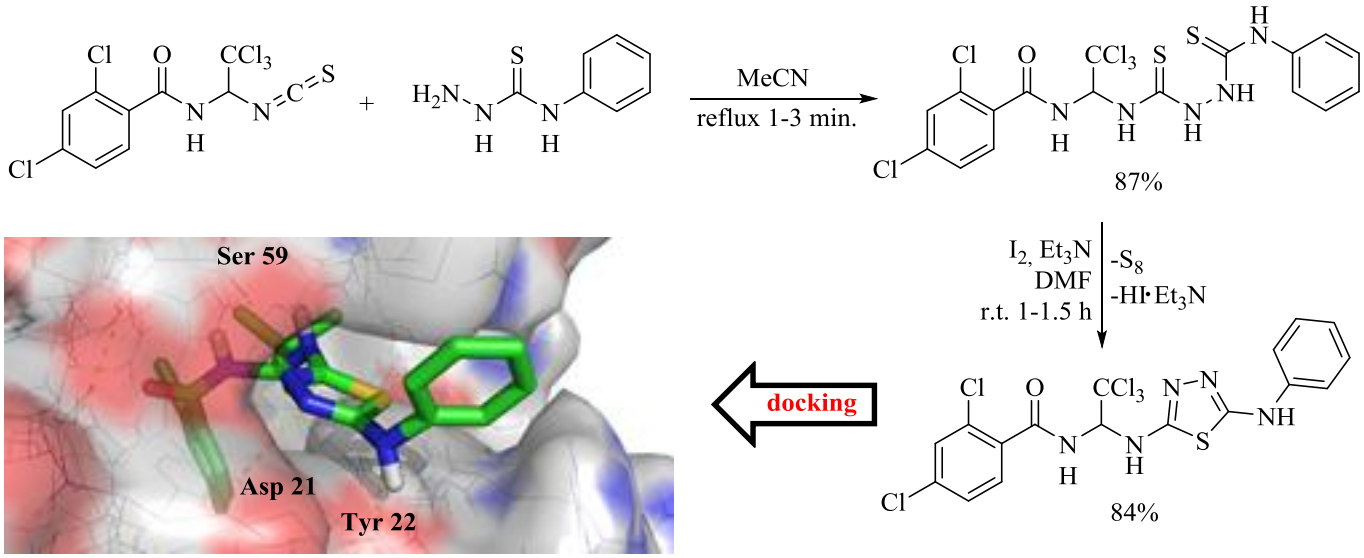
Synthesis, Spectral Characteristics, and Molecular Docking Studies of 2,4-Dichloro-*N*-(2,2,2-trichloro-1-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide.

Graphical Abstract



Abstract: Derivatives of 1,3,4-thiadiazole are of great interest for scientific and practical human activities as biologically active substances, dyes, components for creating semiconductors, energy accumulators, liquid crystals, polymers, nanomaterials, etc. Here we report the synthesis of 2,4-dichloro-*N*-(2,2,2-trichloro-1-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide based on *N*,*N'*-disubstituted hydrazinecarbothioamide - 2,4-dichloro-*N*-(2,2,2-trichloro-1-(2-(phenylcarbamothioyl)-hydrazine-1-carbothioamido)ethyl)benzamide. The method for obtaining the target product is based on the dehydrosulfurization reaction of the starting hydrazinecarbothioamide under the action of a mixture of iodine and triethylamine in a DMF medium. A new derivative of 1,3,4-thiadiazole was obtained in 84% yield, and its structure was confirmed by ^{1}H and ^{13}C NMR spectroscopy data. Molecular docking studies were carried out with the structure of the resulting compound and dihydrofolate reductase (DHFR) in the AutoDock Vina program. The resulting compound is a potential inhibitor of DHFR and surpasses several known analogues in terms of the strength of the complex formed with the active site of this enzyme.

Keywords: synthesis; 1,3,4-thiadiazole; dehydrosulfurization; dihydrofolate reductase; molecular docking

Introduction

Biologically active substances

Components for creating semiconductors

Polymers

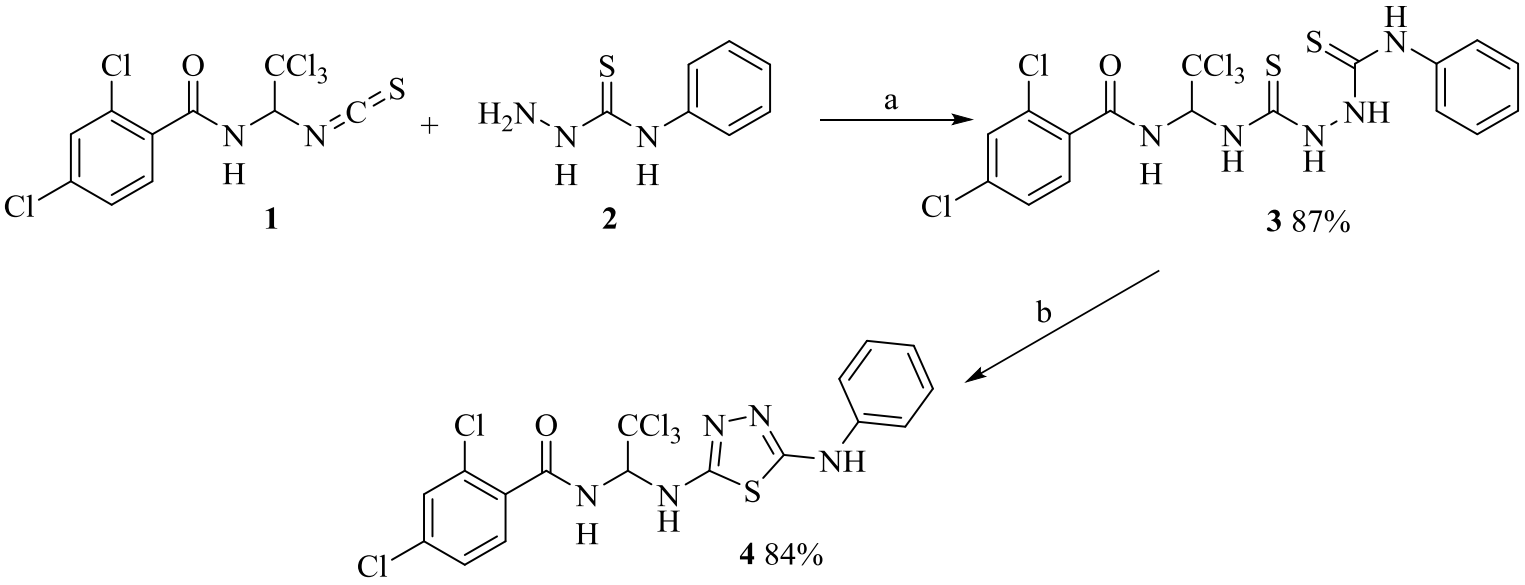
1,3,4-thiadiazole

Dyes

Liquid crystals

Energy accumulators

Results and discussion



Scheme 1. Synthesis of 2,4-dichloro-*N*-(2,2,2-trichloro-1-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide (**4**). Reagents and conditions: a) CH_3CN, reflux 1-3 min, r.t. 24 h; b) I_2, Et_3N, DMF, r.t. 1-1.5 h.

Results and discussion

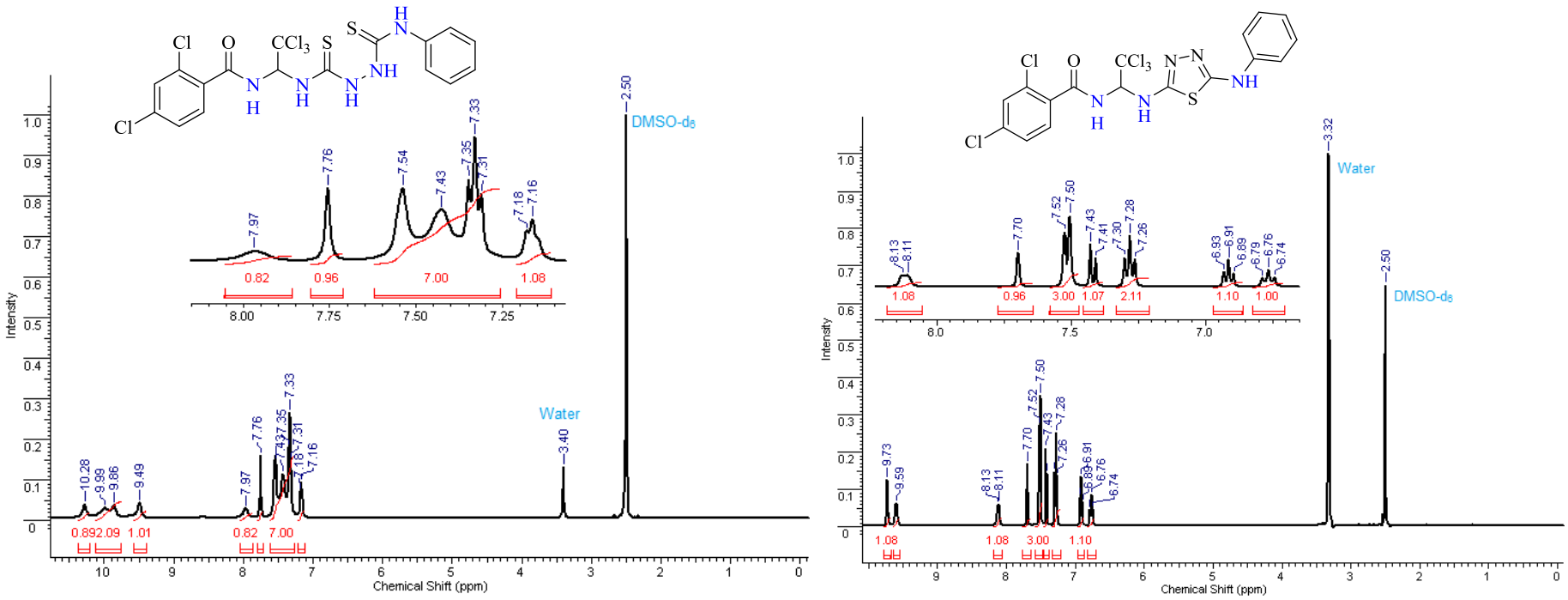


Figure 1. ^{1}H NMR spectra of 2,4-dichloro-*N*-(2,2,2-trichloro-1-(2-(phenylcarbamothioyl)hydrazine-1-carbothioamido)ethyl)benzamide (left) and 2,4-dichloro-*N*-(2,2,2-trichloro-1-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide (right).

Results and discussion

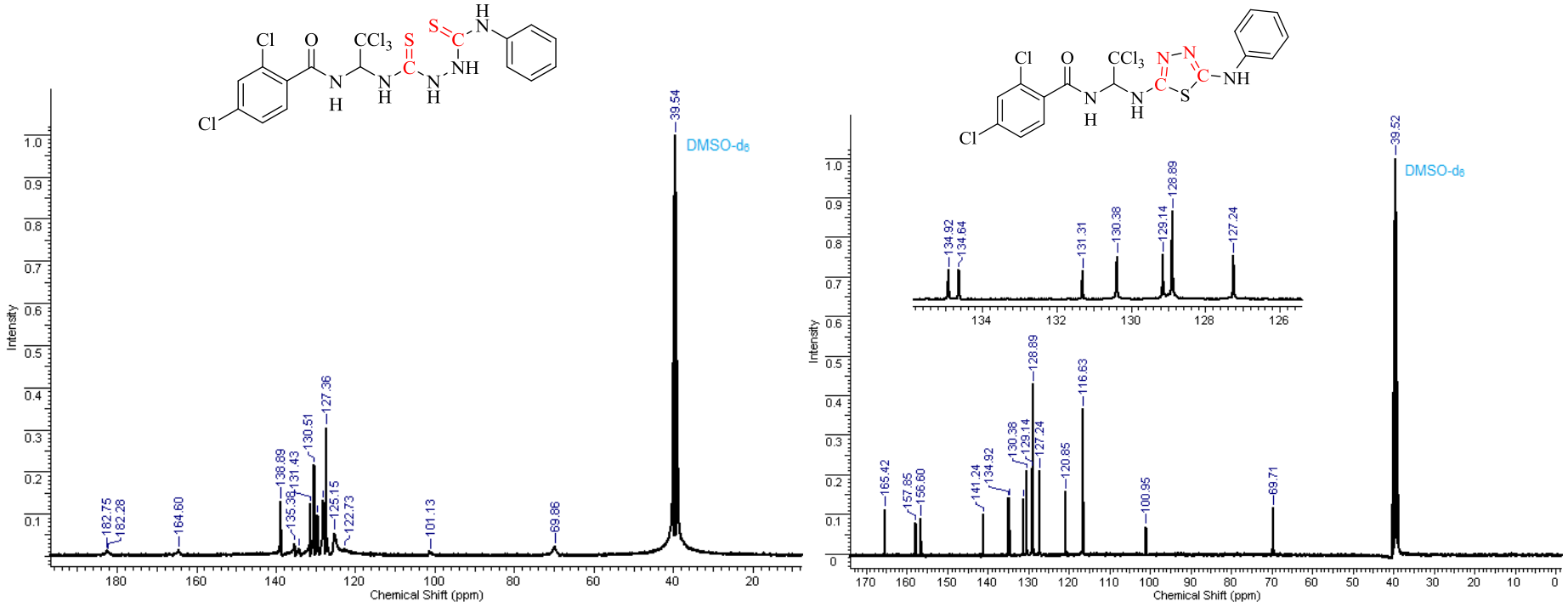
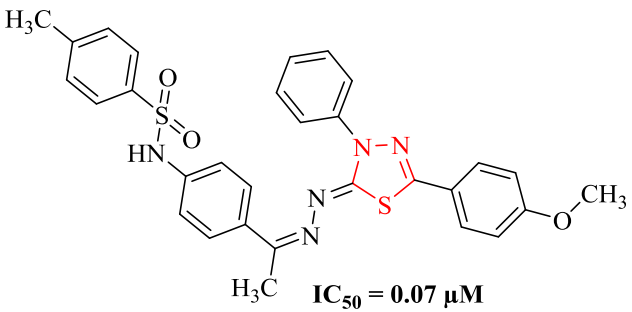


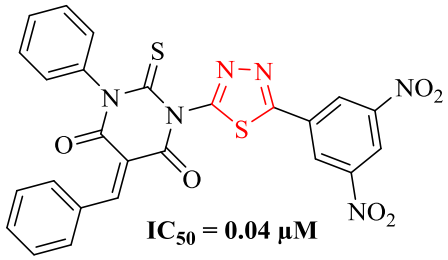
Figure 2. ^{13}C NMR spectra of 2,4-dichloro-*N*-(2,2,2-trichloro-1-(2-(phenylcarbamothioyl)hydrazine-1-carbothioamido)ethyl)benzamide (left) and 2,4-dichloro-*N*-(2,2,2-trichloro-1-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide (right).

Results and discussion



N-(4-((*Z*)-1-(((*Z*)-5-(4-methoxyphenyl)-3-phenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)hydrazono)ethyl)phenyl)-4-methylbenzenesulfonamide

Compound A



(*E*)-5-benzylidene-1-(5-(3,5-dinitrophenyl)-1,3,4-thiadiazol-2-yl)-3-phenyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione

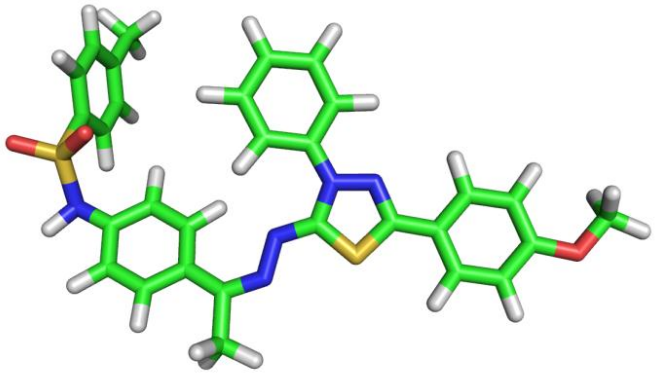
Compound B

Riyadh, S.M.; El-Motairi, S.A.; Ahmed, H.E.A.; Khalil, K.D.; Habib, E.E. Synthesis, Biological Evaluation, and Molecular Docking of Novel Thiazoles and [1,3,4]Thiadiazoles Incorporating Sulfonamide Group as DHFR Inhibitors. *Chem. Biodivers.* **2018**, *15*, e1800231. https://doi.org/10.1002/cbdv.201800231

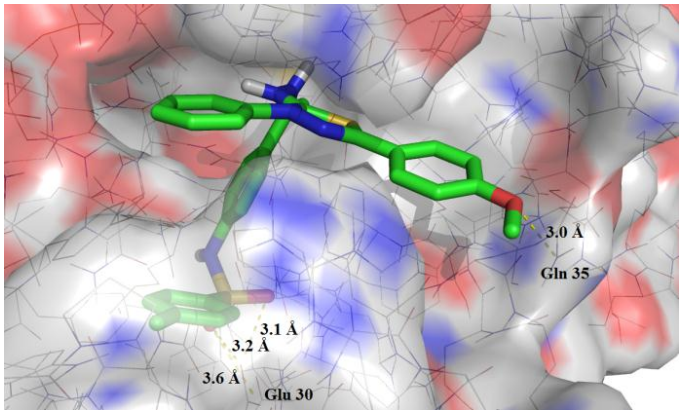
El-Naggar, M.; Sallam, H.A.; Shaban, S.S.; Abdel-Wahab, S.S.; Amr, A.E.E.; Azab, M.E.; Nossier, E.S.; Al-Omar, M.A. Design, Synthesis, and Molecular Docking Study of Novel Heterocycles Incorporating 1,3,4-Thiadiazole Moiety as Potential Antimicrobial and Anticancer Agents. *Molecules* **2019**, *24*, 1066. https://doi.org/10.3390/molecules24061066

Figure 4. Structures of reference compounds **A** and **B**.

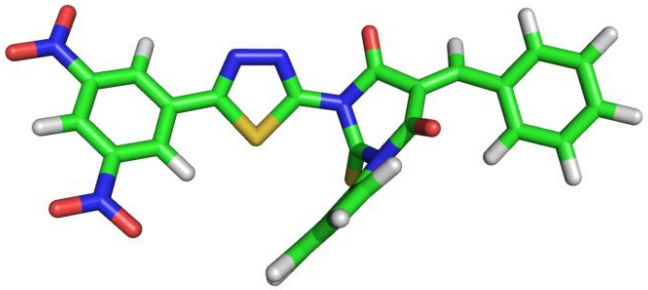
Results and discussion



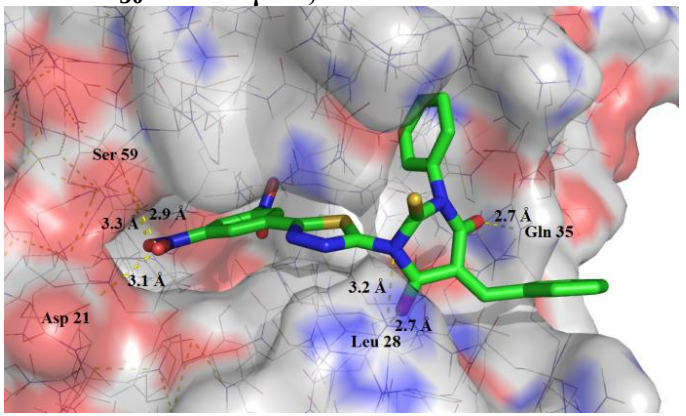
Compound A



IC_{50} = 0.07 µM, ΔG = -8.2 kcal/mol



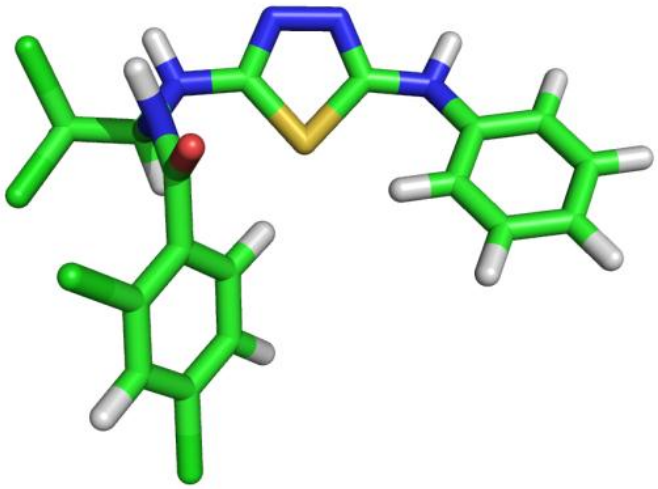
Compound B

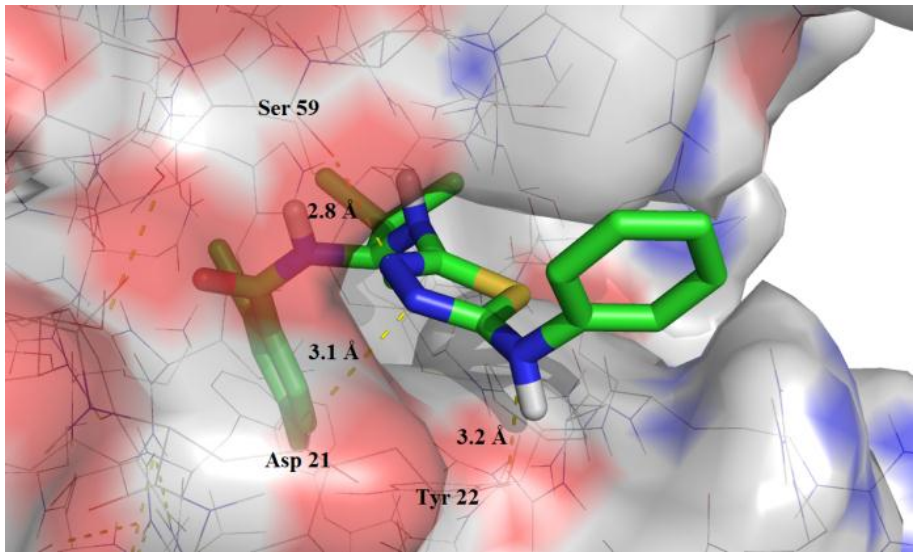


IC_{50} = 0.04 µM, ΔG = -8.4 kcal/mol

Figure 5. Results of molecular modeling studies of reference compounds **A** and **B**.

Results and discussion





ΔG = -9.0 kcal/mol

Figure 6. Results of molecular modeling studies of 2,4-dichloro-*N*-(2,2,2-trichloro-1-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide (**4**).

Conclusions

In this work, we have obtained a new representative of the series of 1,3,4-thiadiazoles - 2,4-dichloro-*N*-(2,2,2-trichloro-1-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide based on 2,4-dichloro-*N*-(2,2,2-trichloro-1-(2-(phenylcarbamothioyl)hydrazine-1-carbothioamido)ethyl)benzamide. The structure of the target and starting compounds has reliably been confirmed by ^{1}H and ^{13}C NMR spectroscopy data. The obtained 1,3,4-thiadiazole derivative is promising as a potential inhibitor of dihydrofolate reductase.

Thank you for your attention!