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MODELING OF NEW POTENTIAL INHIBITORS OF DIHYDROFOLATE REDUCTASE BASED ON 1,3,4-THIADIAZOLE AMIDOALKYL DERIVATIVES

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Derivatives of 1,3,4-thiadiazole are very important for medical chemistry and pharmacy as potential drug substances. In this work, we carried out molecular docking studies of amidoalkyl derivatives of 1,3,4-thiadiazole: *N*-(2,2,2-trichloro-1-((5-aryl-1,3,4-thiadiazol-2-yl)amino)ethyl)carboxamides and *N*-(2,2,2-trichloro-1-((5-(arylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)carboxamides with dihydrofolate reductase (DHFR). The AutoDock Vina program based on the PyRx 0.8 platform was used for docking. Before docking, the enzyme structure (PDB ID: 1DLS) was prepared using the Chimera 1.14 program, and the structures of potential inhibitors and reference preparations were optimized by the PM3 method in the ArgusLab 4.0.1 program. According to the results of molecular docking, the analyzed compounds effectively interact with the active site of DHFR. It is shown that the introduction of an NH group between the 1,3,4-thiadiazole and aromatic rings leads to stronger binding of ligands to DHFR. Based on the results of molecular docking, the following hit compounds were selected: 4-methyl-*N*-(2,2,2-trichloro-1-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide and 4-methyl-*N*-(2,2,2-trichloro-1-((5-(*p*-tolylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide, which are superior to the reference compounds according to the strength of the formed complex.

Keywords: 1,3,4-thiadiazole, amidoalkyl derivatives, dihydrofolate reductase, molecular docking, inhibitor, in silico.

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Introduction

Dihydrofolate reductase (DHFR) is a widespread enzyme that plays a key role in folic acid metabolism by reducing dihydrofolate to tetrahydrofolate in eukaryotic and prokaryotic cells. Inhibition of DHFR leads to a decrease in the intracellular level of tetrahydrofolate, cessation of RNA and DNA synthesis, and, as a result, a slowdown in their proliferation [1]. This makes DHFR an attractive therapeutic target for the treatment of cancer [1], bacterial and protozoal infections [2,3], and several other diseases [4].

DHFR is a relatively small, water-soluble protein with a molecular weight of 18–25 kDa. The mechanism of action of some drugs is associated with the inhibition of this enzyme, such as Methotrexate, Raltitrexed, Pemetrexed, Pralatrexate, and many others [1]. A large number of works were devoted to the development and search for new DHFR inhibitors among derivatives of 1,3,5-triazine, 2-mercapto-quinazolin-4-one, pyrimidine, thiazole, pyrazole, and other acyclic and heterocyclic systems [5].

A promising class of substances with the ability to inhibit DHFR are 1,3,4-thiadiazole derivatives. These compounds include (E)-5-benzylidene-1-(5-(3,5-dinitrophenyl)-1,3,4-thiadiazol-2-yl)-3-phenyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (1), N-(4-((Z)-1-(((Z)-5-(4-methoxyphenyl)-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)hydrazono)ethyl)phenyl)-4-methylbenzenesulfonamide (2), 2-((5-amino-1,3,4-thiadiazol-2-yl)thio)-6-methyl-3-(4-phenoxyphenyl)quinazolin-4(3H)-one (3) and 6-chloro-2-(((5-((4-chlorophenyl)amino)-1,3,4-thiadiazol-2-yl)methyl)thio)-3-(4-methoxyphenyl)quinazolin-4(3H)-one (4) (Fig. 1) [6].

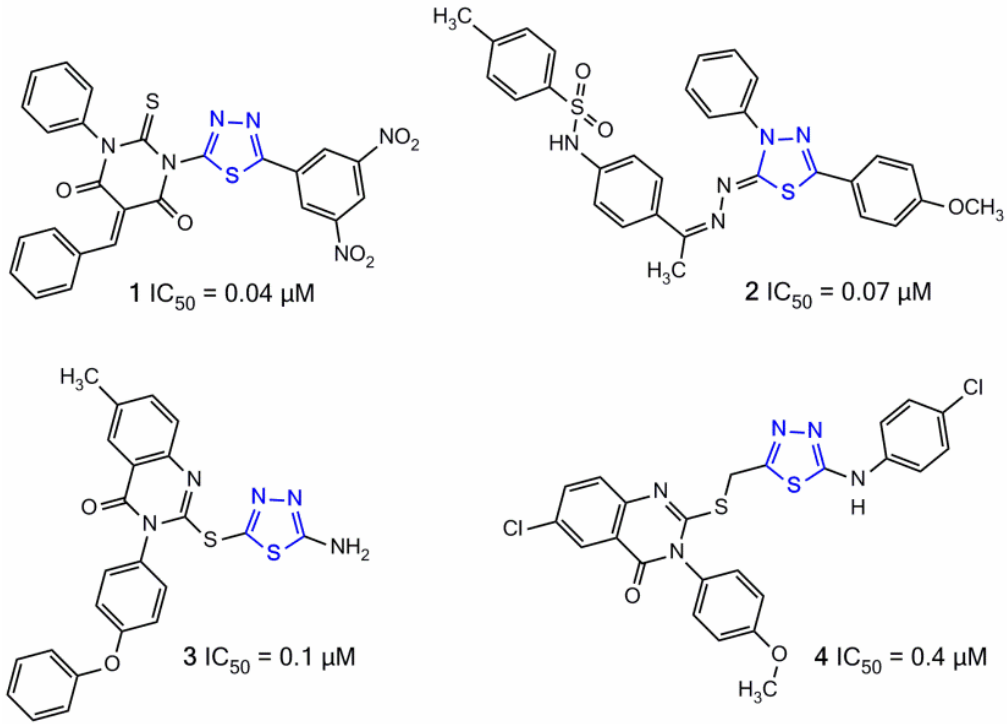
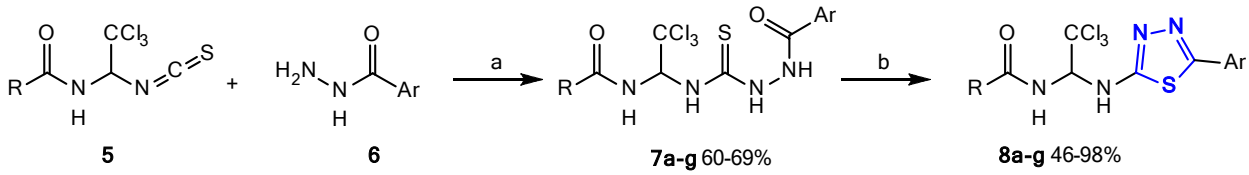


Fig. 1. Structures of some human dihydrofolate reductase inhibitors containing the 1,3,4-thiadiazole ring



R = CH_3, Ar = C_6H_5 (**a**); R = CH_3, Ar = 4-$CH_3C_6H_4$ (**b**); R = C_6H_4, Ar = 4-$CH_3C_6H_4$ (**c**); R = 4-$CH_3C_6H_4$, 4-$CH_3C_6H_4$ (**d**); 4-$CH_3C_6H_4$, C_6H_5 (**e**); 4-$CH_3C_6H_4$, 3-BrC_6H_4 (**f**); 4-$CH_3C_6H_4$, 3-$NO_2C_6H_4$ (**g**).

Scheme 1. Synthesis of 1,3,4-thiadiazole amidoalkyl derivatives (8). Reagents and conditions: a) EtOH, reflux 1-3 min, r.t. 24 h; b) H_2SO_4 conc., r.t. 24 h

In this study, we proposed previously synthesized N-amidoalkylated derivatives of 1,3,4-thiadiazole 8a–g as potential inhibitors of DHFR. These compounds were prepared by the elimination of water from N,N'-disubstituted hydrazinecarbothioamides 7, which, in turn, were obtained by the addition of arylcarboxylic acid hydrazides 6 to isothiocyanates 5 (Scheme 1) [7].

The effectiveness of the interaction of compounds 8a–g with the DHFR active site was evaluated using molecular docking methods. In addition, based on compounds 8a–g, structures containing an NH group between the 1,3,4-thiadiazole and aromatic rings [6] were simulated virtually. The model structures were also tested in silico for their ability to inhibit DHFR.

Materials and methods

All calculations were carried out on a Toshiba personal computer, the Satellite L650D model, AMD Phenom(tm) II P820 Triple-Core Processor. A 64-bit operating system was used. The structure of dihydrofolate reductase was downloaded in pdb format from the Protein Data Bank (PDB ID: 1DLS) [8]. To prepare the structure of this enzyme for the docking procedure, the Chimera 1.14 program was used [9]. By using this software, water molecules and Methotrexate were removed from the active site of DHFR. The structures of compounds 8a–g and

model structures of MSa–g [6] were constructed and optimized by the PM3 method [10] using the ArgusLab 4.0.1 program [11–13]. Molecular docking was performed using the AutoDock Vina program [14] based on the PyRx 0.8 platform. The docking site was determined by creating a grid with dimensions X: 25.0 Y: 25.0 Z: 25.0 Å, centered on X: 31.8, Y: 13.8, Z: −0.83 Å. This grid was centered on amino acids Ile 5, Ala 6, Ala 7, Asp 27, Leu 28, Phe 31, Lys 32, Ser 49, Ile 50, Arg 52, Leu 54, Arg 57, Ile 94, Tyr 100 and Thr 113 [6]. Visualization and evaluation of intermolecular ligand-enzyme interactions were performed using the PyMOL 0.99rc6 program [15].

Results and discussion

When docking, we used compounds 1–4 as comparators (Fig. 1,b). According to the results obtained, these compounds effectively interacted with the DHFR active site. In this case, the calculated data on DG correlated well with the experimental values of IC_{50} [6]. As expected, compound 1 was bound most strongly to DHFR with IC_{50}=0.04 μM, while compound 4 formed the least stable complex with IC_{50}=0.4 μM. The molecule of compound 1 formed six hydrogen bonds with amino acids of the active site, two of which were formed with Leu 28 (lengths of 2.7 and 3.2 Å), two more were formed with Ser 59 (lengths of 2.9 and 3.3 Å), and one hydrogen bond each was formed with Asp 31 and Gln 35 (lengths of 3.1 and 2.7Å, respectively) (Fig. 2,a). The energy of the complex was −8.4 kcal/mol. The molecule of inhibitor 2 was efficiently fixed in the active site of DHFR due to four intermolecular hydrogen bonds (Fig. 2,b): one was formed by the methoxy group and Gln 35 (length 3.0Å) and three more were formed by the sulfamide group and the amino acid Glu 30 (lengths of 3.1, 3.2 and 3.6 Å, respectively). The energy of the complex was −8.2 kcal/mol. The molecule of compound 3 in the DHFR active site was fixed due to the formation of only one hydrogen bond 3.1 Å long, which was formed between the amino group and Pro 66 (Fig. 2,c). The ΔG value was −7.0 kcal/mol. The molecule of compound 4 in the DHFR active site was fixed by two intermolecular hydrogen bonds with Lys 68 (Fig. 2,d), the bond lengths being 3.1 and 3.3 Å. The energy of the formed complex was −6.8 kcal/mol.

Among the compounds we analyzed, most surpassed the standards in terms of the strength of the complex formed with DHFR (Table). The only exceptions were compounds 8a and 8b, as well as the model structure of MSa. The introduction of an NH group between the thiadiazole and aromatic rings mainly led to stronger binding to the enzyme, except for MSa and MSc, which formed complexes of the same strength with 8a and 8c.

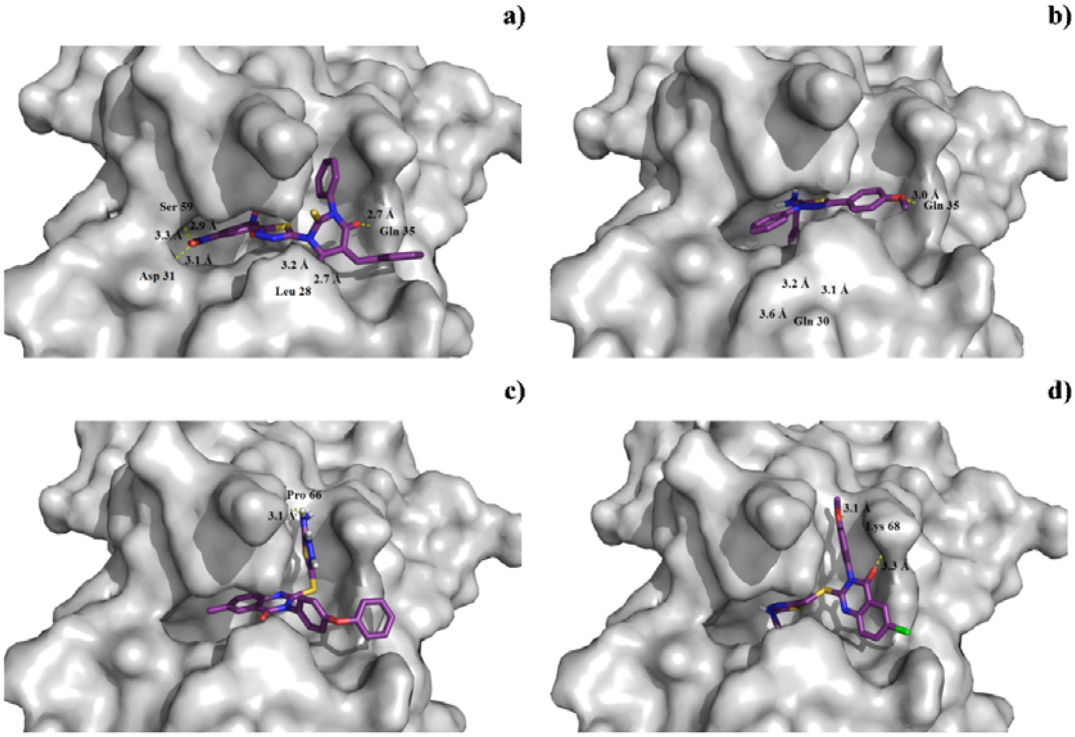
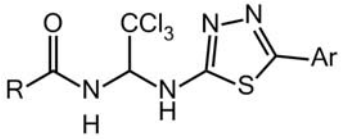
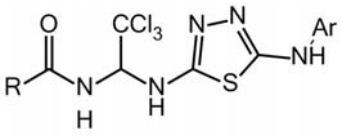


Fig. 2. Position of molecules of compounds 1–4 in the DHFR active site according to molecular docking data

Molecular docking results of compounds 8a–g and MSa–g with DHFR





Compounds	R	Ar	ΔG, kcal/mol	Compounds	R	Ar	ΔG, kcal/mol
8a	CH_3	Ph	–8.1	MSa	CH_3	Ph	–8.1
8b	CH_3	*p*-Tol	–7.9	MSb	CH_3	*p*-Tol	–8.7
8c	Ph	*p*-Tol	–9.2	MSc	Ph	*p*-Tol	–9.2
8d	*p*-Tol	*p*-Tol	–9.8	MSd	*p*-Tol	*p*-Tol	–10.0
8e	*p*-Tol	Ph	–9.7	MSe	*p*-Tol	Ph	–9.8
8f	*p*-Tol	*m*-BrC_6H_4	–9.4	MSf	*p*-Tol	*m*-BrC_6H_4	–9.6
8g	*p*-Tol	*m*-$NO_2C_6H_4$	–9.6	MSg	*p*-Tol	*m*-$NO_2C_6H_4$	–9.7

Among the tested compounds 8a–g, 4-methyl-N-(2,2,2-trichloro-1-((5-(p-tolyl)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide (8d) and 4-methyl-N-(2,2,2-trichloro-1-((5-phenyl-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide (8e) interacted the most effectively with DHFR. Model structures created on their basis, 4-methyl-N-(2,2,2-trichloro-1-((5-(p-tolylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide (MSd) and 4-methyl-N-(2,2,2-trichloro-1-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide (MSe), were also leaders in their series. In addition, MSd and MSe outperformed the original compounds 8d and 8e in terms of the strength of the complex formed with the enzyme and were hit compounds. It is noteworthy that both molecules of compounds 8d and 8e, as well as molecules of MSd and MSe, were fixed in the DHFR active site exclusively due to lipophilic interactions and π–π contacts, without forming intermolecular hydrogen bonds (Fig. 3).

According to the results obtained, MSd and MSe bind most effectively to the DHFR active site. These compounds are superior to the reference compounds in terms of the strength of the complex formed, and they can be recommended for *in vitro* testing.

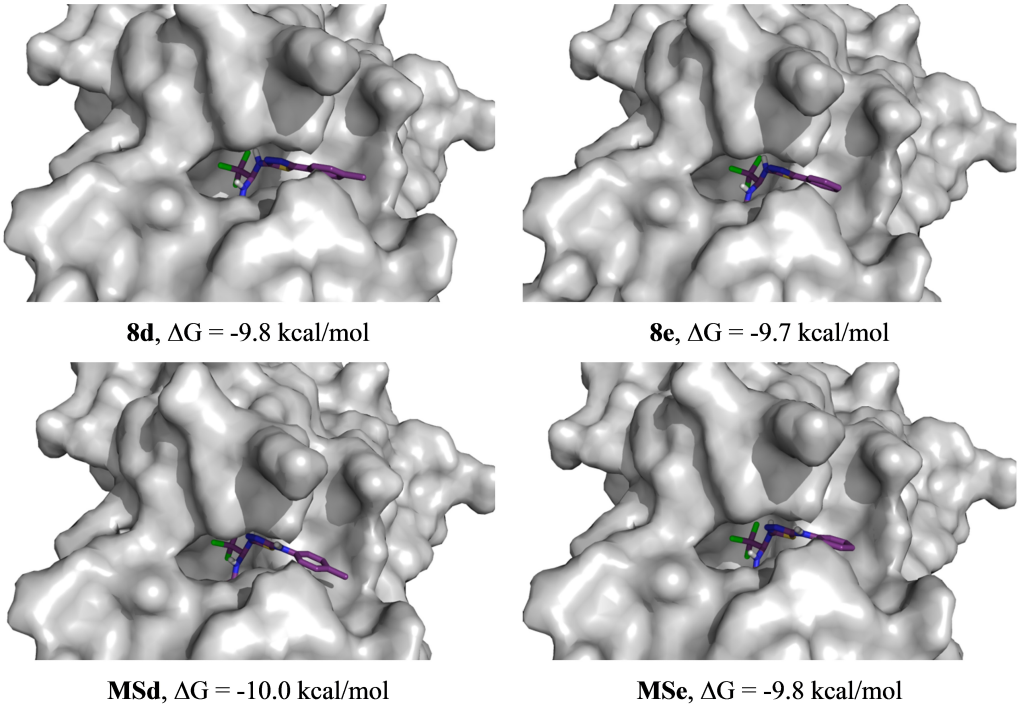


Fig. 3. Position of molecules of compounds 8d, 8e, and MSd, MSe in the DHFR active site

It should be noted that the 1,3,4-thiadiazole derivatives under consideration are also of interest as potential stabilizers and size regulators of silver nanoparticles [16], which are known for their high biological activity and a number of other useful properties [17,18].

Conclusions

In this work, using molecular docking methods, we have searched for potential DHFR inhibitors among N-amidoalkylated derivatives of 2-amino-1,3,4-thiadiazole and 2,5-diamino-1,3,4-thiadiazole. It has been shown that the studied compounds are effectively fixed in the active site of this enzyme due to lipophilic interactions. According to the results of molecular docking, the model structures of 4-methyl-N-(2,2,2-trichloro-1-((5-(p-tolylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide (MSd) and 4-methyl-N-(2,2,2-trichloro-1-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide (MSe) form the most stable complexes with DHFR, which are recommended for further *in vitro* testing.

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МОДЕЛЮВАННЯ НОВИХ ПОТЕНЦІЙНИХ ІНГІБІТОРІВ ДИГІДРОФОЛАТРЕДУКТАЗИ НА ОСНОВІ АМІДОАЛКІЛОВАНИХ ПОХІДНИХ 1,3,4-ТІАДІАЗОЛУ

В.В. Павлова, П.В. Задорожній, В.В. Кисельов, О.В. Харченко, О.В. Охтіна

Похідні 1,3,4-тіадіазолу мають велике значення для медичної хімії та фармації як потенційні лікарські речовини. У цій роботі ми здійснили дослідження молекулярного докінгу амідоалкілованих похідних 1,3,4-тіадіазолу: *N*-(2,2,2-трихлор-1-((5-арил-1,3,4-тіадіазол-2-іл)аміно)етил)-карбоксамідів та *N*-(2,2,2-трихлор-1-((5-(ариламіно)-1,3,4-тіадіазол-2-іл)аміно)етил)карбоксамідів з дигідрофолатредуктазою (ДГФР). Для докінгу використовувалася програма AutoDock Vina на базі платформи PyRx 0.8. Перед проведенням процедури докінгу структуру ферменту (PDB ID: 1DLS) підготували за допомогою програми Chimera 1.14, а структури потенційних інгібіторів і еталонних препаратів оптимізували методом PM3 у програмі ArgusLab 4.0.1. За результатами молекулярного докінгу досліджувані сполуки ефективно взаємодіють з активним центром ДГФР. Показано, що введення групи NH між 1,3,4-тіадіазольним і ароматичним циклами приводить до більш міцного зв'язування лігандів з ДГФР. За результатами молекулярного докінгу відібрано сполуки лідери: 4-метил-*N*-(2,2,2-трихлор-1-((5-(феніламіно)-1,3,4-тіадіазол-2-іл)аміно)етил-)бензамід і 4-метил-*N*-(2,2,2-трихлор-1-((5-(*n*-толіламіно)-1,3,4-тіадіазол-2-іл)аміно)етил)бензамід, які за міцністю утвореного комплексу перевершують еталонні.

Ключові слова: 1,3,4-тіадіазол, амідоалкіловані похідні, дигідрофолатредуктаза, молекулярний докінг, інгібітор, in silico.

MODELING OF NEW POTENTIAL INHIBITORS OF DIHYDROFOLATE REDUCTASE BASED ON 1,3,4-THIADIAZOLE AMIDOALKYL DERIVATIVES

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Derivatives of 1,3,4-thiadiazole are very important for medical chemistry and pharmacy as potential drug substances. In this work, we carried out molecular docking studies of amidoalkyl derivatives of 1,3,4-thiadiazole: *N*-(2,2,2-trichloro-1-((5-aryl-1,3,4-thiadiazol-2-yl)amino)ethyl)carboxamides and *N*-(2,2,2-trichloro-1-((5-(arylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)carboxamides with dihydrofolate reductase (DHFR). The AutoDock Vina program based on the PyRx 0.8 platform was used for docking. Before docking, the enzyme structure (PDB ID: 1DLS) was prepared using the Chimera 1.14 program, and the structures of potential inhibitors and reference preparations were optimized by the PM3 method in the ArgusLab 4.0.1 program. According to the results of molecular docking, the analyzed compounds effectively interact with the active site of DHFR. It is shown that the introduction of an NH group between the 1,3,4-thiadiazole and aromatic rings leads to stronger binding of ligands to DHFR. Based on the results of molecular docking, the following hit compounds were selected: 4-methyl-*N*-(2,2,2-trichloro-1-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide and 4-methyl-*N*-(2,2,2-trichloro-1-((5-(*p*-tolylamino)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide, which are superior to the reference compounds according to the strength of the formed complex.

Keywords: 1,3,4-thiadiazole; amidoalkyl derivatives; dihydrofolate reductase; molecular docking; inhibitor; in silico.

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