SYNTHESIS, ANTIMICROBIAL EVALUATION, DENSITY FUNCTIONAL THEORY, AND DOCKING STUDIES OF SOME NEW 2-MERCAPTO PYRIMIDINE SCHIFF BASES

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ABSTRACT

Objective: Pyrimidine derivatives are reported to possess antibacterial, antifungal, anticancer, and anticonvulsant activities. Encouraged by this remarks, we decided to synthesize novel compounds of new 2-macaptopyrimidine linked to Schiff’s bases.

Methods: The present work involves the synthesis of new 2-mercaptopyrimidine linked to Schiff’s bases. The starting, 2-mercaptopyrimidine, compound (1) reacted with thiourea to afford the corresponding 1-(pyrimidin-2-yl) thiourea (2). Then compound (2) was used as the key intermediate to prepare the -1-(2-hydroxy benzylidene)-3-(pyrimidin-2-yl) thiourea (3), and (1-benzylidene)-3-(pyrimidin-2-yl) thiourea (4), through the reaction with 2-hydroxybenzaldehyde, and benzaldehyde, respectively.

Results: All the synthesized compounds were characterized by Fourier-transform infrared and H-nuclear magnetic resonance spectroscopy. The synthesized derivatives were screened for their in vitro, antibacterial activity against two Gram-positive bacteria: Bacillus subtilis and Staphylococcus aureus and four Gram-negative bacteria: Klebsiella pneumoniae, Escherichia coli, and Salmonella typhi, and the results showed that most of them have good antibacterial activity. While their antifungal activity against four fungi species (Aspergillus fumigatus, Aspergillus niger, Aspergillus terreus and Rhizopus) revealed that compounds (2-4) displayed the most potent antifungal activity. Density functional theory (DFT) calculations for the synthesized 2-mercaptopyrimidine derivatives were conducted, using a molecular structure with optimized geometry. Highest occupied molecular orbital/lowest unoccupied molecular orbital energies and structures are demonstrated.

Conclusion: The antimicrobial activity indicates that compounds (3) and (4) are the most active than the compounds (1) and (2). Molecular docking revealed that compounds (3) and (4), with bulky phenyl groups are essential to blocking the active centers of glucose-6-phosphate synthase in the bacteria and fungi.

Keywords: Antimicrobial, Density functional theory, 2-Mercapto pyrimidine, Schiff bases, Glucose-6-phosphate synthase.

INTRODUCTION

Pyrimidines are essential six-membered heterocyclic compounds containing two nitrogen atoms. Pyrimidines present in the form of nucleic acids and vitamins. It has basic properties. It has been found to be associated with different biological activities. Further work led to the development of antimalarial drugs such as pyrimethamine and trimethoprim. Additional chemical modifications have afforded interesting pyrimidine derivatives like oxothiamine. The variety of compounds having a pyrimidine nucleus exhibit wide range of biological activities such as antiviral [1], antileishmanial [2], antimalarial [3], antihistaminic[4], anti-inflammatory [5], and antitubercular [6] activities. Many essential drugs and agrochemicals containing pyrimidines and their derivatives possess numerous and remarkable biological activities such as antiepileptic, antihypertensive Minocyclid, and potent phosphodiesterase inhibitors [9,10]. Schiff bases are condensation products of primary amines with carbonyl compounds. The main structural feature of these compounds is the azomethine group with a general formula RHC=N-R1, where R and R1 are alkyls, aryl, cycloalkyl or heterocyclic groups which may be variously substituted [11].

The chemical formula of Schiff bases contains N-donor atom has been widely investigated and has acquired great attention due to the azomethine C=N bond essential for biological activity, nowadays, cases of microbial resistance pose a big deal to the scientific community and have become a threat to human life worldwide. Moreover, invasive microbial infections caused by multidrug-resistant Gram-positive bacteria and microbes are difficult to diagnose. Therefore, the development of new, effective, and safe antimicrobial agents is urgently required, to overcome the problems of microbial resistance [12]. The goal of this work is to synthesize of some new Schiff bases, derived from 2-mercapto pyrimidine [1], by reacting it, with thiourea, using acetic acid medium, then, the produced thiourea derivative will be treated with two different aromatic aldehydes to afford Schiff bases. The titled compounds (1-4) would be screened, in vitro, for their antimicrobial activities.

Furthermore, conducting (density functional theory [DFT]) and docking studies to calculate some important physical parameters, and to observe the binding sites of the functional groups of the synthesized derivatives (2-4) with the enzyme glucose-6-phosphate synthase, respectively.

MATERIALS AND METHODS

Chemicals used during the synthesis, supplied by Sigma-Aldrich. Solvents were dried and distilled before use. Completion of reactions and the purity of compounds were ascertained by thin-layer chromatography (TLC), using Silica gel GF254, (type 60) pre-coated aluminum sheets, Merck (Germany). Melting points were measured using Koehler hot-stage apparatus and are uncorrected. IR (KBr) spectra (υ, cm⁻¹) were recorded using Thermo Scientific™ Nicolet™ iS™10 Fourier-transform infrared spectrophotometer in College of Education Ibn al-Haitham-Iraq. Nuclear magnetic resonance (1H-NMR) spectra were recorded on Bruker FT-NMR spectrometer 300, at Al-Bayt University-Amman/Jordan, using deuterated dimethyl sulfoxide (DMSO-d₆) as a solvent,
and tetramethylsilane as an internal standard. A computational study was performed for the prepared compounds using Chemical Bio Office 2016, version 16, DFT study with 3_21G* basis, while molecular docking study was run using molecular operation environment program, 2105.

**Synthesis of 1-(pyrimidin-2-yl) thiourea (2)**

A mixture of pyrimidine-2-thiol (1) (0.01 mol, 1.2 g) and thiourea (0.01 mol, 1.82 g) was dissolved in absolute ethanol (30 ml). 2 ml of acetic acid was added, and the reaction mixture was refluxed on a water bath for about 6 h. The solid separated after concentration and cooling was recrystallized from methanol to give (2). IR (KBr), (υ, cm⁻¹): 3366, 3287 cm⁻¹ (NH); 3161 (N-H) str; 3053 (C-H) str; 1633 (C=N) str; 1533 (N=CH); 7.39 (1H, s, NH (C=S); 7.93 (2H, d, 2Ar-H); 7.73 (1H, t, Ar-H).

**Synthesis of 1-(2-hydroxybenzylidene)-3-(pyrimidin-2-yl)thiourea (3)**

Compound (2) (0.01 mol, 1.38 g) was added with continuous stirring to a solution of 2-hydroxybenzaldehyde (0.01 mol, 1.22 g), and five drops of glacial acetic acid in (40 ml) absolute ethanol. The mixture was refluxed for 6 h, and the reaction was monitored by TLC, the orange colored precipitate was formed, and collected by filtration, washed with ether, then dried and recrystallized from methanol. IR (KBr), (υ, cm⁻¹): 3399 (OH) str; 3166 (NH) str; 3113 Ar (C-H) str; 1608 (C=N) str; 1568 (N-H) bend; 1217 (C=S) str; 1489 Ar (C=C) str; 1186 (C-N) str; 1049 and 982 in plane and out of plane Ar (C-H) bend; 793 out of plane Ar (C=C) bend; 744 cm⁻¹ (C-S) str.

**Synthesis of 1-(pyrimidin-2-yl) thiourea (2)**

Compound (2) prepared from pyrimidine-2-thiol (l), by its reaction with thiourea, and was used as starting material for the present study. The objective of synthesis of the other new derivatives. Thus, compound (2) was treated with aromatic aldehydes namely, 2-hydroxy benzaldehyde, and benzaldehyde in ethanol, containing glacial acetic acid, to give the corresponding compounds (3) and (4), respectively.

**Scheme 1: Synthesis of some new mercaptopyrimidine Schiff bases**

**Antifungal screening**

The titled compounds 1–4 were screened for their preliminary antifungal activity using agar disk-diffusion method against pathogenic strains of *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus terrus*, and *Rhizopus*. The compounds (1–4) were stored dry at room temperature at concatenation 50 and 100 µg/ml. It is prepared in the quality control on feed department/animals/resources directorate. The Sabouraud’s agar media (15 cm²), kept at 45°C, were poured into petri dishes, then allowed to solidify. Sterile filter paper discs of 10 mm diameter were impregnated with prepared derivative (50 µL) and placed on to the media, seeded with fungus. The plates were then, incubated at 37°C for 1 day. The test compounds were previously dissolved in DMSO, which is used as a control, the zone of inhibition (ZI) was measured in (mm).

**Antibacterial screening**

The antimicrobial activities of the synthesized derivatives were measured using well diffusion technique [13], and it was done in the quality control on feed department/animals/resources directorate. The synthesized derivatives had been evaluated *in vitro* against Gram-positive *Bacillus subtilis* and *Staphylococcus aureus*, and Gram-negative *Klebsiella pneumoniae*, *Escherichia coli*, and *Salmonella* typhi. DMSO was used as a solvent and control [13-16].

**RESULTS AND DISCUSSION**

The first compound (2) was used as the key intermediate, to prepare compounds (3) and (4), through its reaction with 2-hydroxy benzaldehyde and benzaldehyde, respectively. The analytical and physical data are listed in Table 1.

**Antimicrobial activity**

The antimicrobial activity was evaluated by a filter paper disk agar diffusion method. For antibacterial studies, HiMedia bacteriological nutrient broth, and bacteriological nutrient agar were used against two Gram-positive *B. subtilis* and *S. aureus*, and three Gram-negative *K. pneumoniae*, *E. coli*, and *S. typhi*. Antifungal studies were carried out, using Sabouraud’s dextrose broth and dextrose agar against *A. fumigatus*, *A. niger*, *A. terrus* and *Rhizopus*. The concentrations of the compounds were taken and 100 µg/ml. The sensitivity of microorganisms to the compounds is identified in Figs. 1 and 2. Electron-rich nitrogen heterocyclic, play an essential role in diverse biological activities. Introducing pyrimidine derivative rings compounds (1, 2, 3, and 4) influence the antibacterial or pharmacokinetic properties. The antimicrobial activity of compounds (1–4) was tested, and the results are shown in Figs. 1 and 2, and Tables 2 and 3, respectively.

The evaluation of the new compounds (3) and (4) at a concentration of 100 µg/ml have shown the highest inhibitory activity against Gram-positive bacteria, *B. subtilis* and *S. aureus* also have displayed the same inhibitory activity against the Gram-negative bacteria. The compounds (1) and (2) at a concentration of 100 µg/ml have shown slight inhibitory activity against Gram-positive bacteria *B. subtilis* and *S. aureus*; while compounds (1) and (2) have shown moderate to potent inhibitory activity against Gram-negative bacteria.

The compound (4) at a concentration of 50 µg/ml have shown slight inhibitory activity against Gram-positive bacteria *B. subtilis* and *S. aureus*; furthermore, compounds (2) and (3), at a concentration of 50 µg/ml have shown the same slight inhibitory activity against Gram-positive bacteria, while compound (1) was not sensitive against Gram-positive at a concentration of 50 µg/ml.
The compounds (1) and (2) revealed moderate inhibitory activity toward all of the fungi, while compounds (3) and (4) displayed more potent activity against the tested fungi, at a concentration of 100 µg/ml [Fig. 1].

Finally, when the concentration equal to 50 µg/ml, the compounds (1) and (2) revealed slight sensitive activity toward all of the fungi, while compounds (3) and (4) were with more moderate activity against the tested fungi (Fig. 1).

**Computational studies**

The quantum chemical calculations were validated on the new pyrimidine derivatives using DFT methodology with 3-21G* basis, while the molecular, atomic charges were approved using the Mulliken population analysis.

The molecular representation sketch of the new pyrimidine compounds was plotted using ChemBioOffice 2010 software [17].

**Structural and electronic properties**

DFT calculations were carried out for 2-mercapto pyrimidine compound. The compounds 1, 2, 3, and 4, respectively, with optimized geometries and 3D geometrical structures, are given in (Fig.3).

The determined bond angle and twist angle, stretch, bend, stretch-bend, torsion, and total energy, and the 3D geometrical structure confirmed that compounds (1) and (2) have no stereochemistry, while compound (3), the stereochemistry is: N (36)-C(38) is (Z), and compound (4) the stereochemistry is: N (9)-C(11) is (Z). The physical parameters are calculated and displayed in Table 4.

**Molecular modeling studies**

The HOMO and the LUMO studies have been carried out using DFT based quantum chemical descriptors. Fig. 4 shows that charge transfer occurs within the molecules and the calculated HOMO and LUMO in electron volt value. The HOMO energies of 2-mercapto pyrimidine derivatives

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### Table 1: Physical data of synthesized compounds (1–4)

| Compound no. | Chemical formula | Melting point | Physical state       | Rf  | %Yield |
|--------------|------------------|---------------|----------------------|-----|--------|
| 1            | C_4H_4N_2S       | 230°C         | Deep yellow crystals | 0.9 | -      |
| 2            | C_5H_6N_4S       | 89°C          | Pale yellow crystals | 0.66| 80     |
| 3            | C_12H_10N_4OS    | 134°C         | Orange crystals     | 0.58| 70     |
| 4            | C_12H_10N_4S     | 165°C         | Orange crystals     | 0.52| 60     |
Global reactivity descriptors and electronic properties

The energy gap (8.531eV, 2.449eV, 2.918eV, and 1.432eV) of synthesized 2-mercaptopyrimidine derivatives (1–4) (Table 5). The charge density delocalization over the amide group in the compounds (1–4) detects measurable differences for HOMO and LUMO of 2-mercaptopyrimidine derivatives (1–4). For the band gaps, it was clear that highest band gap is for compound (3), which was 2.918eV, and the next value is for compound (2), −0.819eV, (Table 5). The charge density, reactivity index, and bond properties of 2-mercaptopyrimidine derivatives (1–4) were calculated depending on the dipole moment. It can be calculated with the help of dipole moment of bonds. The values of dipole moment for 2-mercaptopyrimidine derivatives (1–4) are shown in Table 5. The ionization potential (IP) and electron affinity (EA) can be expressed as the total of energy released when an electron absorbed by a neutral molecule [18] which is approximated as (IP) = −E\textsubscript{HOMO} and EA= −E\textsubscript{LUMO}, respectively, based on Koopman’s theorem [19]. The electrophilicity index has been used as structural chemical hardness (\( \eta \)), a chemical potential (\( \mu \)), softness descriptor for the analysis of the chemical reactivity of 1/2 \( \eta \), and electrophilicity index (\( \omega \)) of a molecule.

A molecule with a lower value of \( \mu \) and \( \omega \) considered the more reactive nucleophile, while, in the opposite, a molecule with a high value of \( \mu \) and \( \omega \) recognized as a good electrophile [20]. The electro-negativity and hardness are most commonly used to predict the chemical behavior to clarify aromaticity in the organic compounds [21]. The molecule that has large HOMO–LUMO gap is considered a hard molecule, while a molecule that has small HOMO–LUMO gap, considered a soft molecule. The LUMO represents electron(s) accepting ability, and HOMO as electron donating ability of a molecule [22]. The energy band gap, HOMO, LUMO, dipole moment, softness, chemical potential, nucleophilicity N°, power electron-accepting, and electrophilicity index (\( \omega \)), are calculated and displayed in Table 5.

Molecular docking

In this work, molecular docking investigational study was performed for the synthesized compounds, and Glu-hydroxamate (2-amino-

### Table 2: Antifungal activity of the tested compounds

| Compound No. | Zone of inhibition (mm) |
|--------------|------------------------|
| Aspergillus fumigates | Aspergillus niger | Aspergillus terreus | Rhizopus |
| Conc. µg/ml | 100 | 50 | 100 | 50 | 100 | 50 | 100 | 50 |
| 1 | 13 | 7 | 14 | 8 | 15 | 9 | 15 | 10 |
| 2 | 12 | 6 | 13 | 7 | 14 | 9 | 15 | 10 |
| 3 | 25 | 12 | 28 | 13 | 30 | 13 | 36 | 15 |
| 4 | 27 | 11 | 34 | 12 | 37 | 15 | 45 | 15 |
| DMSO | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| SD | +0.8 | +4.3 | +12 | +4.6 | +13 | +5.2 | +16.2 | +5.5 |

Highly sensitive (>15 mm)=+++; moderately sensitive (10–15 mm)=++; slightly sensitive (5–10 mm)=+; and not sensitive (0 mm)=−. SD: Standard deviation, DMSO: Dimethyl sulfoxide

### Table 3: Antibacterial activity of the tested compounds (1-4)

| Compound. No. | Zone of inhibition (mm) |
|---------------|------------------------|
| Gram-positive | Staphylococcus aureus | Bacillus subtilis |
| Conc. µg/ml | 100 | 50 | 100 | 50 |
| 1 | 10 | 0 | 9 | 0 | 13 | 8 | 14 | 9 |
| 2 | 13 | 8 | 14 | 9 | 15 | 10 | 25 | 10 |
| 3 | 10 | 9 | 12 | 10 | 24 | 11 | 27 | 13 |
| 4 | 20 | 13 | 23 | 14 | 28 | 14 | 36 | 15 |
| DMSO | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| SD | ±6.4 | ±5.2 | ±7.4 | ±5.6 | ±9.7 | ±4.7 | ±12.4 | ±5.2 |

SD: Standard deviation, DMSO: Dimethyl sulfoxide

| Gram-negative | Klebsiella pneumoniae | Escherichia coli | Salmonella typhi |
|---------------|----------------------|-----------------|-----------------|
| Conc. µg/ml | 100 | 50 | 100 | 50 | 100 | 50 |
| 1 | 10 | 0 | 9 | 0 | 13 | 8 | 14 | 9 | 15 | 10 |
| 2 | 13 | 8 | 14 | 9 | 15 | 10 | 25 | 10 | 35 | 10 |
| 3 | 10 | 9 | 12 | 10 | 24 | 11 | 27 | 13 | 33 | 14 |
| 4 | 20 | 13 | 23 | 14 | 28 | 14 | 36 | 15 | 45 | 15 |
| DMSO | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| SD | ±6.4 | ±5.2 | ±7.4 | ±5.6 | ±9.7 | ±4.7 | ±12.4 | ±5.2 | ±16 | ±5.3 |

(1–4) are calculated as: −0.999eV, 1.634eV, 0.612eV, and 0.411eV, respectively (Table 5).
5-(hydroxyamino)-5-oxopentanoic acid) used as a competitive reference inhibitor (Figs. 15 and 16) [23]. This study was carried out to gain further insight into the binding modes of the synthesized compounds, into the amino acids in the binding site of glutaminase domain of glucosamine 6-phosphate synthase (ID: 1XFF). The binding free energies (DG) were reported in (Table 6). The free energies, with their negative values, indicate the spontaneity of bindings. The reported key binding site of glutaminase domain of glucosamine 6-phosphate synthase consists of amino acid residues of Asp123, Arg73, Gly99, Trp74, Cys1, His86, His77, and Thr76, (Fig. 5). The proposed binding mode of Glu-hydroxamate showed affinity value equals - 5.78 kcal/mol, with root mean square deviation value of 1.25 [Figs. 15 and 16]. The essential pharmacophoric features atoms formed interactions with the different key residues of Arg73, Gly99, Trp74, Cys1, Thr124, His77, and Thr76. The acidic NH group of amid moiety formed a hydrogen bonding interaction with Thr124. The C=O group of amid moiety formed a hydrogen bonding interaction with Asp123. The study provided the following conclusions: 1. The synthesized compounds showed inhibition against the enzyme, with compound 2 being the most active. 2. The proposed binding mode of Glu-hydroxamate showed affinity value equals - 5.78 kcal/mol, with root mean square deviation value of 1.25 [Figs. 15 and 16].

### Table 4: Physical parameters for compounds 1, 2, 3, and 4 using DFT with 3-21G* basis

| Parameter | Compound 1 | Compound 2 | Compound 3 | Compound 4 |
|-----------|------------|------------|------------|------------|
| Stretch   | 0.1774     | 0.395      | 1.0776     | 0.7193     |
| Bend      | 0.955      | 2.5456     | 14.6172    | 3.5875     |
| Stretch-Bend | 0.0211   | -0.01      | 0.074      | 0.0259     |
| Torsion   | 2.0002     | 3.1066     | -3.8034    | -5.7453    |
| Log P     | 0.8        | 0.05       | 2.55       | 2.65       |
| Total energy: kcal/mol | 8.9552     | 8.1715     | 22.1441    | 9.7626     |

DFT: Density functional theory

### Table 5: Electronic properties of synthesized 2-mercaptopyrimidine derivatives using DFT with 3-21G* basis

| Parameter                          | Compound 1 | Compound 2 | Compound 3 | Compound 4 |
|------------------------------------|------------|------------|------------|------------|
| Dipole moment (Debye)              | 0.2449     | -3.671     | -2.4073    | -3.9809    |
| IP eV                              | 9.53       | 0.815      | -3.53      | 0.991      |
| EA eV                              | 0.999      | -1.634     | -0.612     | -0.411     |
| Hardness (ρ)                       | 4.27       | 1.225      | -1.5775    | 0.716      |
| Softness (S)                       | 0.117      | -0.408     | -0.317     | 0.698      |
| Electronegativity (μ)              | -10.529    | -3.025     | -0.1215    | 0.58       |
| Electrophilic index (μ0)           | 12.98      | 3.73       | -0.0046    | -0.235     |
| \( E_{\text{HOMO}} \) eV           | -9.53      | -0.815     | 3.53       | -0.991     |
| \( E_{\text{LUMO}} \) eV           | -0.999     | 1.634      | 0.612      | 0.411      |
| Band gap=\( E_{\text{HOMO}} \) - \( E_{\text{LUMO}} \) eV | -8.531     | -0.819     | 2.918      | -1.402     |
| Energy gap=\( E_{\text{HOMO}} \) - \( E_{\text{LUMO}} \) eV | 8.531      | 2.449      | -2.918     | 1.432      |
| Nucleophilicity N°                 | -9.53      | -0.815     | 3.53       | -0.991     |
| Power electron accepting            | 12.98      | 3.73       | -0.0046    | -0.235     |

IP: Ionization potential, EA: Electron affinity
The basic NH₂ group was involved in hydrogen bonding interaction with Gly99. The (C=O) group of carboxylic moiety formed a hydrogen bond with Cys1 Compounds 3 and 4, Fig. 9 and 12 and Trp74 (Fig. 15). The proposed binding mode of compounds (2, 3, and 4) showed affinity values, respectively, equal −5.93, −5.77, and −6.11 kcal/mol with seven hydrogen bonds Gly99, Trp74, Thr76, Cys1, and two pi-pi interactions with Arg73, Compounds 3 and 4, (Fig. 9 and 12). Mapping surface showing compound 3 occupying the active pocket of glutaminase, hydrophobic moiety, shows good block for free active size in pocket.

CONCLUSION

In the present work, a series of new pyrimidine derivatives have been synthesized from 2-mercaptopyrimidine by refluxing of thiourea and 2-mercaptopyrimidine, in an acidic medium, the formation of different Schiff bases by the reaction of a compound (2) with different aromatic aldehydes. The titled pyrimidine derivatives were screened in vitro, for their preliminary antibacterial and antifungal activities using 100 and 50 µg/ml concentrations. Schiff bases of 2-mercaptopyrimidine, compounds (3) and (4) showed good antibacterial activity against Gram-positive, Gram-negative bacteria, and against fungi used in the evaluation.

Docking results revealed that to design optimal compounds that act as glutaminase domain inhibitor, we must consider the following:

Table 6: The table showing (DG), number of bonds and amino acid that bind with pharmacophoric features

| Compound No. | Binding free energies (DG) kcal/mol | Number of bonds | Amino acids |
|--------------|------------------------------------|----------------|-------------|
| 2            | −5.93                              | 7              | Gly99, Trp74, Thr76, Cys1 |
| 3            | −5.77                              | 6              | Gly99, Trp74, Thr76, Cys1, Arg73 |
| 4            | −6.11                              | 6              | Gly99, Trp74, Thr76, Cys1, Asn98, Arg73 |
| Glu-hydroxamate | −5.78                         | 7              | Gly99, Trp74, Thr76, Cys1, Arg73, His77, Thr124 |

Fig. 9: Binding mode of compound 3 as glutaminase domain active site blocker that is showing good blocking effect by hydrophobic bulky groups

Fig. 10: Compound 3 docked into the active site of glutaminase formed seven hydrogen bonds (green) with Gly99, Trp74, Thr76, and Cys1 residues and pi-pi interactions with Cys1 and Arg73

Fig. 11: Mapping surface showing compound 3 occupying the active pocket of glutaminase, hydrophobic moiety, shows good block for free active size in pocket

Fig. 12: Binding mode of compound 4 as glutaminase domain active site blocker that is showing good blocking effect by hydrophobic bulky groups

Fig. 13: Compound 4 docked into the active site of glutaminase formed six hydrogen bonds (green) with Gly99, Trp74, Thr76, Cys1, Asn98 residues, and pi-pi interactions with Cys1, and Arg73

Fig. 14: Mapping surface showing compound 4 occupying the active pocket of glutaminase
CONFLICTS OF INTEREST
All authors have none to declare.

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