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SYNTHESIS OF 2,4,7,9-TETRAPHENYL-4,4A,9,9A-TETRAHYDROTHIOPYRANO[2,3-*G*]THIOCHROMENE-5,10(5A*H*,10A*H*)-DIONE AND ANALYSIS OF ITS BIOLOGICAL ACTIVITY

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2H-thiopyranes, molecular docking, Diels–Alder heterocyclic reaction, $GABA_{B(1)}$ receptor, affinity, toxicity, PASS-Online

Abstract. *2,4,7,9-Tetraphenyl-4,4a,9,9a-tetrahydro-thiopyrano[2,3-g]thiocromene-5,10(5aH,10aH)-dione has been synthesised. Molecular docking with the $GABA_{B(1)}$ receptor was performed, and its affinity and toxicity were calculated. Computational studies were conducted using the PASS-Online programme to identify substance biological activities.*

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Introduction

For many decades, sulphur-containing heterocycles have attracted the interest of researchers in various fields of chemistry due to their unique properties. It facilitates the conversion of functional groups for the synthesis of biologically active compounds. These heterocycles are found in many antimicrobial drugs, including penicillin. Sulphur-containing heterocycles are widely used in the manufacture of disinfectants, antibiotics, antioxidants, dyes, and pigments. Additionally, they play an important role in the pharmaceutical industry [1].

Quinones are promising dienophiles as they possess a variety of biological properties, including antimicrobial and anti-inflammatory activity. Structural modifications of quinones enable the synthesis of new compounds with improved pharmacological properties [2–4].

Derivatives of 2*H*-thiopyran are of particular scientific interest, as they constitute the main structural elements of a number of natural compounds with fungicidal and pharmacological activity. The number of pharmaceutical preparations containing thiopyran derivatives. For instance, tazorotene is the main component of a crema used to treat psoriasis and acne; dorzolamide is used as an antiglaucoma agent [5]. The presence of double bonds and divalent sulphur in the structure of these compounds makes 2*H*-thiopyranes promising

chemicals for the synthesis of skeletal sulphur-containing heterocycles [6]. Therefore, a priority task is to develop methods for synthesising these compounds from readily available starting materials and study their biological activity. A typical representative of these is 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiochromene-5,10(5a*H*,10a*H*)-dione.

Main body

2*H*-thiopyran derivatives are obtained from *α*,*β*-unsaturated ketones and dienophiles via the Diels–Alder heterocyclic reaction. The reaction procedure depends on the number of stages involved: in the one-step variant the reaction is conducted by heating in toluene at atmospheric pressure [7]; in the two-step variant it is conducted by boiling in benzene at atmospheric pressure [8]. Lavesson's reagent is used as the activating agent (Fig. 1).

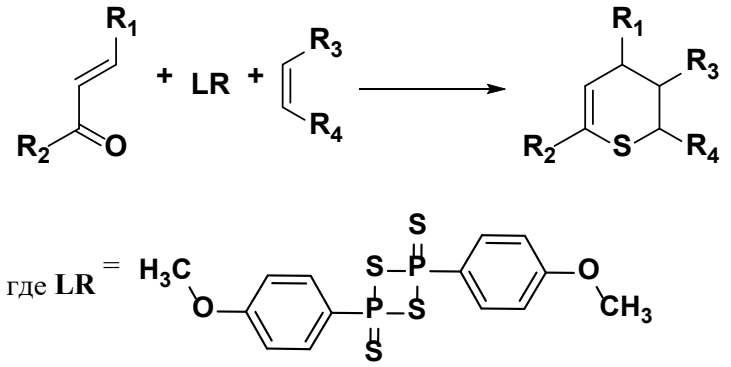


Fig. 1. Schematic diagram of the synthesis of thiopyranes via the Diels-Alder reaction.

1,4-benzoquinone was used as a dienophile in the synthesis of 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiochromene-5,10(5a*H*,10a*H*)-dione. In cycloaddition chemistry, 1,4-benzoquinone is widely used both as a dipolarophile and as a dienophile. In [4+2] cycloaddition reactions, the processes can proceed chemoselectively, interacting with both C=O carbonyl groups and C=C double bonds. However, reactions with various 1,3-dienes and heterodienes proceed via a C=C double bond addition mechanism [9].

A single-reactor method [7] was tested for the synthesis of 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiocromene-5, 10(5a*H*,10a*H*)-dione via a Diels-Alder heterocyclic reaction of chalcone, Laveson's reagent, and 1,4-benzoquinone as the dienophile. The reaction was conducted at a temperature of 65–70 °C in a water bath, with continuous stirring, at atmospheric pressure, in toluene as the solvent for 4–6 hours at the following molar ratios: chalcone: Laveson's reagent: 1,4-benzoquinone = 1:0.5:0.5; 1:0.5:1; 1:0.5:2. (Fig. 2).

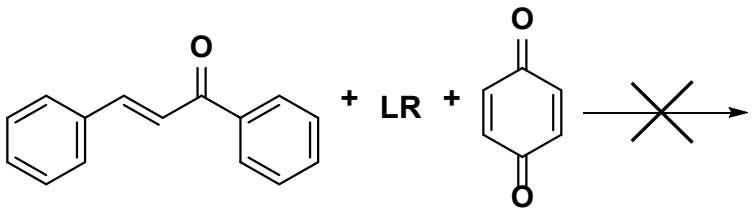


Fig. 2. Schematic diagram of a single-reactor synthesis of 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiochromene-5,10(5a*H*,10a*H*)-dione.

Analysis of the reaction mixture by thin-layer chromatography revealed the absence of the product. The likely reason for this is competitive interaction between the sulphurising agent – Laveson's reagent – and 1,4-benzoquinone.

To prevent interaction between the Laveson reagent and 1,4-benzoquinone, a two-step synthesis of 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiocromene-5, 10(5a*H*,10a*H*)-dione was attempted using a two-stage method [8]. In the first stage, a mixture of chalcone and the Laveson reagent was boiled in benzene for 1–1.5 hours until a dark blue solution of the thiochalcon dimer formed as a result of the thionation of the *α*,*β*-unsaturated ketone. In the second stage, 1,4-benzoquinone was added to the solution of the thiochalcone dimer and boiled for an hour (reaction monitored by TSC). The reaction was performed at the following molar ratios: chalcone: Laveson's reagent: 1,4-benzoquinone = 1:0.5:0.5; 1:0.5:1; 1:0.5:2. (Fig. 3)

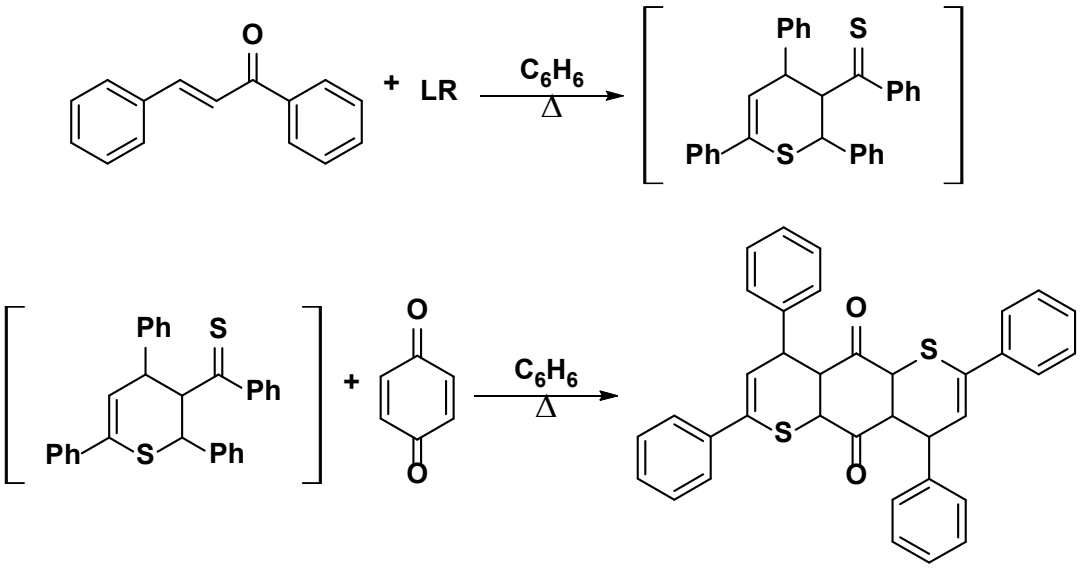


Fig. 3. Schematic diagram of a two-stage synthesis of 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiochromene-5,10(5a*H*,10a*H*)-dione.

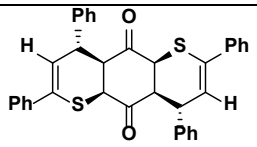
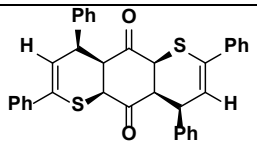
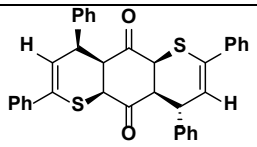
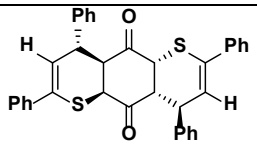
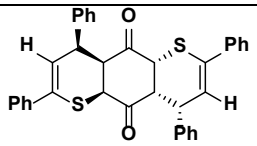
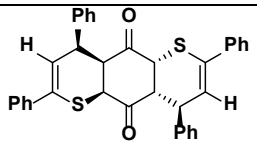
Performing the synthesis using this method at the following molar ratios: chalcone: Laveson's reagent: 1,4-benzoquinone = 1:0.5:1; 1:0.5:2 resulted in significant osmolisation of the product. By altering the molar ratio of chalcone: Laveson's reagent: 1,4-benzoquinone to 1:0.5:0.5, a selective reaction was achieved and the target product was formed.

The structure of the obtained 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiocromene-5,10(5a*H*,10a*H*)-dione was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. These methods are highly informative in determining the composition and main structural fragments of the molecule. However, they do not allow its spatial configuration to be defined.

To determine the most probable molecular configuration, quantum- chemical modelling was performed using the ORCA software, version 6.1.0 [10–12], using the DFT method, the REVPBE0 (an updated version of the PBE0 method) [13, 14] with the Grimme D4 dispersion correction [15, 16] in a valence-split triexponential 3ζ basis set with def2-TZVPD polarisation functions [17–19]. The calculations used approximations of Coulomb interactions and exchanged HF integrals by the RIJCOSX method [20] in the Def2/J basis set [21].

Six configurations of the synthesised 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiocromene-5, 10(5a*H*,10a*H*)-dione, and their thermodynamic parameters were calculated for a temperature of 298.15 K. Table 1 presents the results.

Table 1. Calculation of thermodynamic parameters for 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiocromene-5,10(5a*H*,10a*H*)-dione at a temperature of 298.15 K.

Item n/a	Molecule configuration	Total energy, Eh	H, Eh	S, Eh	G, Eh	ΔG, kJ/mol
1		–2335.515405	–2334.940103	0.089324	–2335.0294280	19.10
2		–2335.501754	–2334.925784	0.089518	–2335.015302	60.05
3		–2335.515671	–2334.938928	0.091183	–2335.030112	21.17
4		–2335.520967	–2334.944525	0.093650	–2335.038176	0
5		–2335.517607	–2334.940573	0.092304	–2335.032877	13.91
6		–2335.519495	–2334.943094	0.092192	–2335.035286	7.58

The thermodynamic stability of the particles was compared based on the Gibbs free energy of formation at 298.15 K. A zero value was assigned to isomer 4 (Table 1), which has the lowest Gibbs free energy. This isomer also corresponds to the lowest total energy value.

According to Gibbs's principle of energy minimisation, this structure will predominantly be formed during the reaction, as it possesses the highest thermodynamic stability compared with alternative structures. Figure 4 presents the configuration.

Molecular docking and the PASS-Online programme are used to assess the biological activity.

Molecular docking is a tool in structural biology and medicinal chemistry that enables the prediction of interactions between small molecules and macromolecules, such as proteins [22, 23]. The result of molecular docking is the determination of the binding affinity of the ligand for the receptor. The binding affinity of a compound for a protein is a critically important parameter that determines its potential biological activity. High affinity may indicate more effective binding and, consequently, a more pronounced therapeutic effect [24–27].

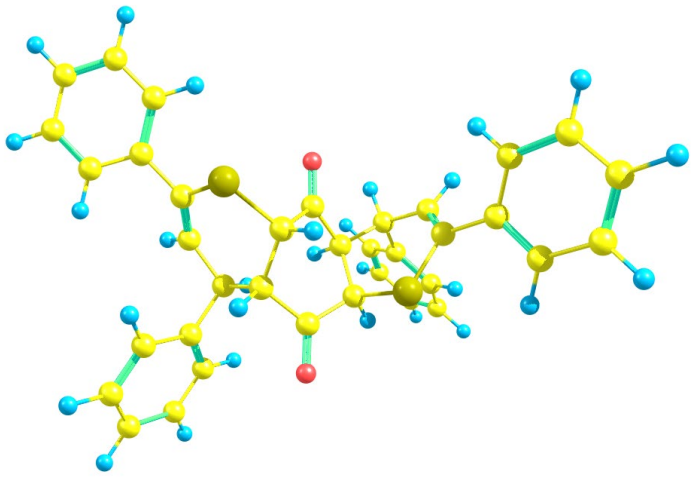


Fig. 4. The most stable configuration of 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiochromene-5,10(5a*H*,10a*H*)-dione.

$GABA_B$ receptors, being the metabotropic receptors, play a key role in modulating neurotransmission. The $GABA_{B(1)}$ protein is one of the subunits of this receptor. The interaction of $GABA_{B(1)}$ with various ligands may affect the neuropathological conditions such as epilepsy, anxiety disorders, and schizophrenia. Therefore, the investigation of potential inhibitors or modulators of this receptor using molecular docking is of high scientific interest [28].

We performed molecular docking of the synthesised 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiocromene-5,10(5a*H*,10a*H*)-dione with the $GABA_{B(1)}$ receptor. The affinity of this compound was assessed using the AutoDock Vina programme [29, 30]. The result showed an affinity of –8.7 kcal/mol, indicating a strong binding to the protein.

Fig. 5 shows the position of 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiocromene-5, 10(5a*H*,10a*H*)-dione within the protein molecule relative to the position of the previously studied baclofen molecule.

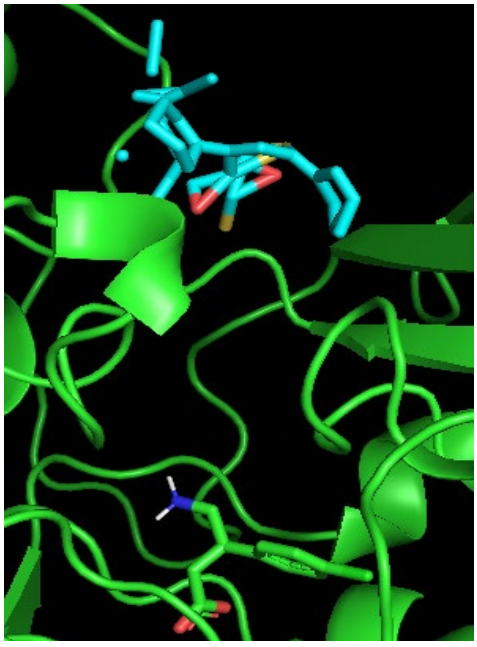


Fig. 5. The position of 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiocromene-5,10(5a*H*,10a*H*)-dione within the $GABA_{B(1)}$ protein molecule.

In addition to affinity, assessing the toxicity of compounds is very important. Many quinone derivatives possess significant biological activity. However, they may also exhibit toxic effects. Approaches based on molecular docking can be used to predict potential toxicity, which is critically important for the early stages of drug development. For example, analysing the interaction of quinones with enzymes associated with toxic metabolic pathways can help identify the risks of use of these compounds in clinical practice [31].

A toxicity assessment was performed using the ProTox-3.0 software (Prediction of Toxicity of Chemicals) [32]. The analysis revealed that the substance belongs to toxicity class 4 and is relatively safe.

Furthermore, to identify the potential biological activities of the compound synthesised, computational analyses were conducted using the PASS-Online software. The PASS software package employs Bayesian probability methods to determine the biological activity of the selected compound [33]. The results of the calculations showed a high probability of the compound's activity in various biological systems. In particular, the Pa value was 0.865 for the inhibition of complement factor D, indicating the substance's significant potential in modulating immune responses. A Pa value of 0.828 was also obtained for the inhibition of aspulvinon-dimethylallyltransferase, suggesting its potential for use in the treatment of diseases associated with metabolic disorders. Finally, a Pa value of 0.817 indicates activity as an inhibitor of testosterone-17β-dehydrogenase. It provides the prospects for the use of this compound in endocrine therapy.

Potential protein targets for the synthesised compound were identified using the new Galaxy Sagittarius protein-ligand docking protocol, available on the Galaxy Web server [34-36]. Molecular mechanics methods in the MM2 force field were applied for the preliminary optimisation of the compounds' 3D structures. It improves the geometry and the minimisation of energy. Docking was performed in two modes: prediction of binding affinity and re-evaluation using docking.

During the docking process, a large number of potential ligand configurations are generated. Some of them are immediately discarded due to collisions with the protein molecule. The remaining options are assessed using an evaluation function. It takes the current position of the ligands as input and returns a numerical value reflecting the probability that this position corresponds to a favourable binding. Modern docking algorithms use three main types of evaluation functions: force field-based, empirical, and statistical ones. Most of these are based on the principles of molecular mechanics force fields and estimate the interaction energy within the binding site. The various components of the docking solution's energy can be represented by the equation:

$$\Delta G_{bind} = \Delta G_{solvent} + \Delta G_{conf} + \Delta G_{int} + \Delta G_{rot} + \Delta G_{t/t} + \Delta G_{vib}.$$

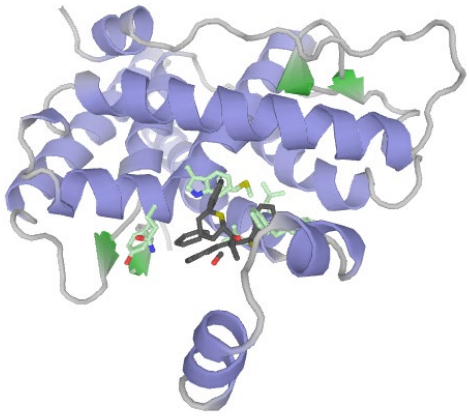


Fig. 6. The position of 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiocromene-5,10(5a*H*,10a*H*)-dione in protein targets.

Table 2 presents the docking results for ten target-ligand complexes, including the minimum binding free energy values (ΔG_{bind}) and the highest estimates of protein-ligand interactions.

Table 2. Results of protein-ligand docking using Galaxy Sagittarius, based on Galaxy Web, for the compound 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiocromene-5,10(5a*H*,10a*H*)-dione.

Protein identifier PDB ID	Protein identifier UniProt ID	Pre-docking assessment of protein-ligand interactions (Predockscore)	Free binding energy, kcal/mol (Dockingscore)	Overall assessment of protein-ligand interactions
6bmm	Q5W0Z9	0.060	–4.709	476.894
6bw5	Q9H3H5, Q9H3H5	0.075	–4.709	476.763
6btq	P13497, P13497	0.047	–4.709	476.185
1os2	P39900, P39900	0.059	–4.709	475.644
1hna	P28161	0.053	–4.708	476.185
2hi4	P05177	0.048	–4.708	475.644
3a73	P02768, P02768	0.051	–4.708	475.934
1soj	Q13370, Q13370	0.056	–4.708	476.359
2n27	P0DP23	0.066	–4.708	477.416
3rpn	Q9Y2Q3, Q9Y2Q3	0.062	–4.707	476.946

The predicted protein targets are identified by their Protein Data Bank (PDB) and UniProt IDs. Thus, this compound can be considered a promising candidate for screening in the search for new therapeutic agents for the treatment of cancer.

Experimental part

In this study, we used commercially available reagents: 1,4-benzenediol, analytical grade (GOST 19627-74), potassium dichromate, analytical grade (GOST 4220-75), sulphuric acid, analytical grade (GOST 4204-77), chloroform, analytical grade (TU 2631-066-44493179-01), anhydrous calcium chloride (TU 6-09-4711-81), anisole, high purity, (TU 6-09-11-1430-80),

phosphorus pentasulphide, (GOST 7200-78), acetophenone, (GOST 16307-79), benzaldehyde, (GOST 157-78), sodium hydroxide, high purity, (GOST 4328-77), benzene, high purity, (GOST 5955-75), dichloromethane, high purity, (TU 20.14-295-44493179-2022), diethyl ether, technical grade, (TU 2600-001-43852015).

Thin-layer chromatography was performed on 'Sorbfil TLC-P-V-UV' plates, using a mobile phase of petroleum ether : ethyl acetate = 3:1. The IR spectrum was recorded using a Perkin Elmer 'Spectrum Two' Fourier transform infrared spectrometer fitted with a total internal reflection (TIR) accessory. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 NMR spectrometer. DMSO-d_6 was used as the solvent. High-resolution mass spectra were recorded using a SCIEX TripleTOF 5600+ instrument with electron spray ionisation, a capillary voltage of 4.5 kV in positive ion mode, and a mass scan range of m/z 100–1000 Da.

We performed molecular docking of the synthesised 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiocromene-5,10(5a*H*,10a*H*)-dione with the $GABA_{B(1)}$ receptor on the following stages. In the first stage, the ligand was imported as a three-dimensional structure via an SDF file from PubChem and optimised using the Ligands Input tool in AutoDock (AD) 4. The second stage involved the preparation of the protein molecule. The structure of the $GABA_{B(1)}$ protein was obtained from the Protein Data Bank (PDB) [37]. The *.pdb file was converted to *.pdbqt format using MGL tools. Prior to docking, polar hydrogen atoms were added to the receptor molecule. A three-dimensional affinity grid was then designed, centred on the geometric centre of the target protein (coordinates x = 54, y = 54, z = 84). In the final stage, the protein and ligand interacted. The PyMol visualiser was used to analyse the interaction. It allows us to examine the docking of the protein and ligand molecules. Upon completion of the docking process, the best conformation was selected from the set of obtained variants, corresponding to the densest cluster with the lowest binding energy. The number of conformation variants for the search was set to 500.

The synthesis method for 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiochromene-5,10(5a*H*,10a*H*)-dione has been developed A 10-ml conical flask, fitted with a stirrer, a reflux condenser, and a calcium hypochlorite tube was charged with 0.25 g of chalcone (1.2 mmol), prepared according to the method described in [38], 0.243 g of Lavesson's reagent (0.6 mmol), prepared according to method [39], and 5 ml of benzene, and the mixture was boiled for 1.5 hours until a dark blue solution of thiochalcon dimer was formed. Next, 0.0648 g of 1,4-benzoquinone, prepared according to the method described in [40], was added to the reaction mixture and the mixture was boiled for a further hour. The completion of the reaction was monitored by thin-layer chromatography. To isolate the target product, the solvent was removed under vacuum, and the residue was purified by column chromatography on silica gel using dichloromethane as the eluent. The resulting resinous residue was triturated with a minimal amount of diethyl ether until crystallisation; the precipitate was filtered off. The product was a pale pink powder. The purity of the target product was confirmed by thin-layer chromatography, R_f = 0.62. Yield is 22.8 mg (7%). T_{melt} = 193-195 ℃. IR-spectrum, ν/cm^{-1}: 3081 – 3026 (C–H); 1617.5 (C=C); 1593.97, 1490.22 (Ar); 1685.17 (C=O); 1231.23 (C–CO–C); 693.09 (C_{Ar}=C). NMR spectrum ^{1}H (400 MHz, DMSO-d_6, δ, ppm, *J*, Hz): 8.02

(d, 2H, Ar, *J* = 8.8); 7.70 (t, 1H, Ar, *J* = 7.3); 7.63 – 7.48 (m, 5H, Ar); 7.49 – 7.33 (m, 6H, Ar); 7.26 (t, 3H, Ar, *J* = 7.2); 7.23 – 7.09 (m, 3H, Ar); 6.93 – 6.86 (m, 2H, Ar); 6.42 (d, 2H, CH–C–Ph, *J* = 6.5); 4.97 (dd, 2H, CH–C=O, *J* = 11.3, 4.5); 4.74 (d, 2H, CH–Ph, *J* = 11.3); 4.26 (dd, 2H, CH–C=O, *J* = 6.6, 4.4). NMR spectrum ^{13}C (100 MHz, DMSO-d_6, δ, ppm): 198.50 (2C), 139.86, 139.60, 138.27, 136.69, 134.10, 133.57, 129.19, 129.16, 128.75 (2C), 128.53 (2C), 128.47 (2C), 128.35 (2C), 128.22 (2C), 128.11 (2C), 127.54 (2C), 127.22 (2C), 125.92 (2C), 120.61 (2C), 49.08 (2C), 44.13 (2C), 42.27 (2C). Mass-spectrum (ESI), *m/z*: found for $C_{36}H_{29}O_2S_2$ $[M+H]^+$: 557.1603, calculated for $C_{36}H_{29}O_2S_2$ $[M+H]^+$: 557.1609.

Conclusions

A synthesis method for 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiochromene-5,10(5a*H*,10a*H*)-dione has been developed. The most stable stereoisomer has been identified. Molecular docking with the $GABA_{B(1)}$ receptor was performed, resulting in an affinity of –8.7 kcal/mol. It indicates a strong binding to the protein. A toxicity rating of Class 4 was determined, indicating its relative safety. Computer calculations were performed using the PASS-Online programme, which revealed a fairly large number of variants with a Pa value above 0.8. Thus, 2,4,7,9-tetraphenyl-4,4a,9,9a-tetrahydrothiopyrano[2,3-*g*]thiocromene-5,10(5a*H*,10a*H*)-dione can be considered a promising candidate for further *in vitro* biological testing.

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