Medicinal Chemistry & Drug Discovery

# Calcium Channel Blockers: The Effect of Glutathione S-Transferase Enzyme Activity and Molecular Docking Studies

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Recently, as a drug target in cancer treatment, the superfamily of glutathione S-transferase (GSTs, EC 2.5.1.18) have been invited considerable interest by scientists. In particular, as they are overexpressed in many human cancer cell lines, GSTs can catalyze the conjugation of the cellular nucleophile glutathione (GSH) with a wide range of electrophilic carcinogens toxins and drugs, meanwhile producing oxidative stress. For this purpose, the GST was purified by GSH-agarose affinity chromatography, and some calcium channel blockers (CCBs), such as amlodipine, cinnarizine, isradipine, nifedipine, and nilvadipine, were assessed for their inhibitory actions against GST. The CCBs demonstrated micromolar levels inhibitory activity towards GST ($K_i$s spanning within the 98.84 ± 0.53 μM–502.70 ± 2.53 μM range). The best GST inhibitory activity was observed for the isradipine. Additionally, molecular docking study was performed for competitive inhibitor nilvadipine on GST to describe the possible interaction with the active site to confirm the inhibitory activity.

## Introduction

In biological transformation, glutathione S-transferase (GSTs, EC 2.5.1.18) are the most crucial phase II metabolizing enzymes found in most plants and animals, such as cotton, tomato, Arabidopsis, soybean, and maize.[1] In mammals, GSTs play a crucial role in the detoxification system of cells against cancer and damage.[2–4] Many xenobiotics or endogenous compounds are removed from the cells by the conjugation to an anionic group (sulfate, glucuronate, or glutathione), transport, and oxidation into the extracellular space.[5–7] GSTs can catalyze the conjugation of chemicals to glutathione and thus decrease the cytotoxic effect of these chemicals.[8] The crucial roles of GSTs and glutathione (GSH) in the detoxification of xenobiotics predict their significance in drug resistance.[9,10] In the design of new chemotherapeutic drugs, both GSTs and GSH have been manipulated as targets.[11] On the other hand, GSTs have arisen as a therapeutic goal because specific isoenzymes are overexpressed in several tumors and may play a crucial role in the etiology of diseases, such as asthma, multiple sclerosis, and neurodegenerative diseases.

Calcium channel blockers (CCBs) may serve to target dysregulation mentioned above. Dihydropyridines (DHPs) are a class of CCBs and have been commonly employed as antihypertensive effects, with more importance given to their potential to maintain neuronal damage related to various pathological circumstances.[12,13] Especially, DHPs have been displayed to decline memory deterioration in animal models of

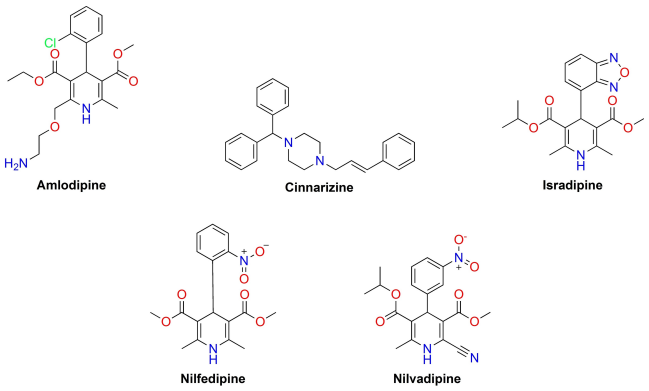


**Figure 1.** Chemicals structures of CCBs, amlodipine (PubChem CID: 2162), cinnarizine (PubChem CID: 1547484), isradipine (PubChem CID: 3784), nifedipine (PubChem CID: 4485), and nilvadipine (PubChem CID: 4494).

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.202103100

diabetes,[14] hypoxia,[15] Parkinson's disease,[16] and cerebral ischemia.[17] Isradipine is a CCB of the DHP class, has been displayed to protect against stroke in rat models of hypertension.[18] Smooth muscle contraction was inhibited by cinnarizine. It is a calcium channel antagonist and employed the treatment of motion sickness because of its anti-histaminic impact.[19] Nilvadipine exhibits anti-hypertensive properties and blocks L-type calcium channels.[20] Amlodipine and nifedipine are regularly employed to treat hypertension. Nifedipine was found to producing systemic hypotension in patients that suffer pulmonary hypertension.[21] In patients with pulmonary hypertension, amlodipine creates acute pulmonary vasodilatation. Moreover, amlodipine was also found to be an efficient pulmonary vasodilator.[22]

There is no research in the literature about the correlation of GST activity with CCBs. In this study, as mentioned above,

**Table 1.** The inhibition results of the isradipine, nilvadipine, amlodipine, nifedipine, and cinnarizine against GST.

| Inhibitor | $IC_{50}$ (μM)[a] | $R^2$ | $K_I$ (μM)[a] | $R^2$ | Inhibition type |
|---|---|---|---|---|---|
| Isradipine | 169.70 ± 8.90 | 0.9917 | 98.84 ± 0.53 | 0.9999 | Uncompetitive |
| Nilvadipine | 295.90 ± 6.26 | 0.9975 | 127.30 ± 4.23 | 0.9987 | Competitive |
| Amlodipine | 227.30 ± 3.74 | 0.9992 | 239.00 ± 1.01 | 0.9999 | Uncompetitive |
| Nifedipine | 145.10 ± 1.67 | 0.9992 | 255.40 ± 1.14 | 0.9999 | Noncompetitive |
| Cinnarizine | 227.70 ± 9.17 | 0.9935 | 502.70 ± 2.53 | 0.9999 | Noncompetitive |

[a] The test results were expressed as means of triplicate assays ± SEM.

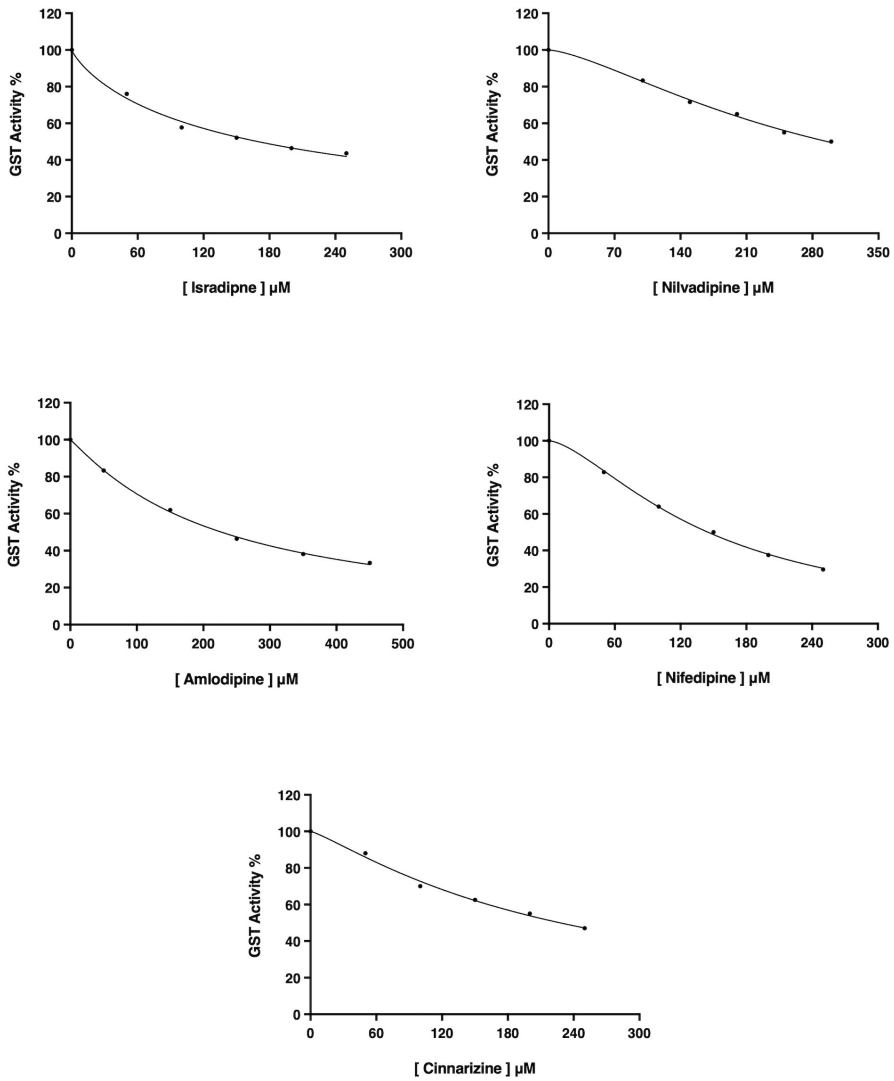


**Figure 2.** In-vitro effect of isradipine, nilvadipine, amlodipine, nifedipine, and cinnarizine at five different concentrations on the GST activity.

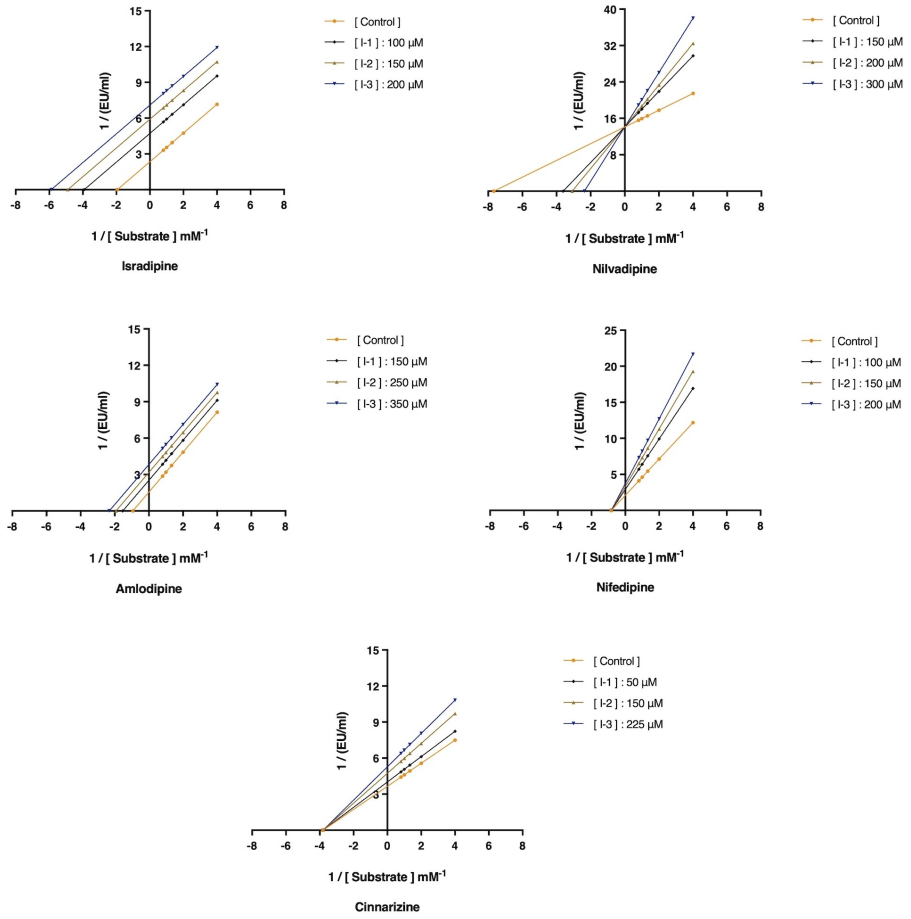


**Figure 3.** Lineweaver-Burk curves used to determine the $K_I$ constants and inhibition types of isradipine, nilvadipine, amlodipine, nifedipine, and cinnarizine.

GST, which has a vital role in metabolism, was purified from human erythrocyte, and some CBBs, such as amlodipine, cinnarizine, isradipine, nifedipine, and nilvadipine (Figure 1), were tested on GST activity both in-vitro and *in silico* effects.

## Results and Discussion

In this study, the procedures applied in biological and molecular docking studies are provided in the Supporting Information.[23–71]

Calcium signaling has been associated with tumor progression and tumorigenesis with studies on the importance of calcium channels in; invasion and tumor metastasis abnormal proliferation, evasion, apoptosis, and abnormal differentiation.[72] CCBs have commonly employed drugs in several widespread circumstances, such as atrial fibrillation, angina, and hypertension. Many studies have hypothesized that CCBs have a therapeutic potential in cancer. They are displayed to possesses antineoplastic impacts via regulation of calcium influx and cell proliferation in in-vitro studies.[73,74] CCBs possess a favorable side impact profile, and they are inexpensive and well tolerated according to standard anticancer drugs. This could make CCBs ideal candidates for drug reuse make them suitable complements to currently available chemotherapy regimens. Clinical studies indicated that CCBs were related to the advanced survival of patients with gastric cancer.[75]

Metabolic enzymes and drug-enzyme interaction researches are increasing their importance day by day in the science world. GST has multiple biological functions and has been the subject of many kinds of research because of its potential role in several diseases. It is always highly expressed in many kinds of cancer cells, such as human breast, colon, liver, pancreatic, stomach, and uterine cancers, osteosarcoma, melanoma, lymphoma, and others. However, the expression level of GST P1-1 in healthy human cells is relatively low. A drug inhibiting GST can weaken toxicity against healthy cells or perform potent anticancer effects on cancer cells.[76] In this direction, there is no literature about the inhibition activity and mechanism of the CCBs on GST currently. Thus, in this study, we focused on the in-vitro inhibition role of some CCBs, including amlodipine and cinnarizine isradipine, nifedipine, and nilvadipine on GST enzyme activity. We identified from Table 1 that all drugs exhibited potent inhibition profiles against GST. $IC_{50}$ values were ranging between $145.10 \pm 1.67$ µM and $295.90 \pm 6.26$ µM for CCBs and the order of CCBs that affect as inhibitor follows: Isradipine ($K_I = 98.84 \pm 0.53$ µM) > nilvadipine ($K_I = 127.30 \pm 4.23$ µM) > amlodipine ($K_I = 239.00 \pm 1.01$ µM) > nifedipine ($K_I =$

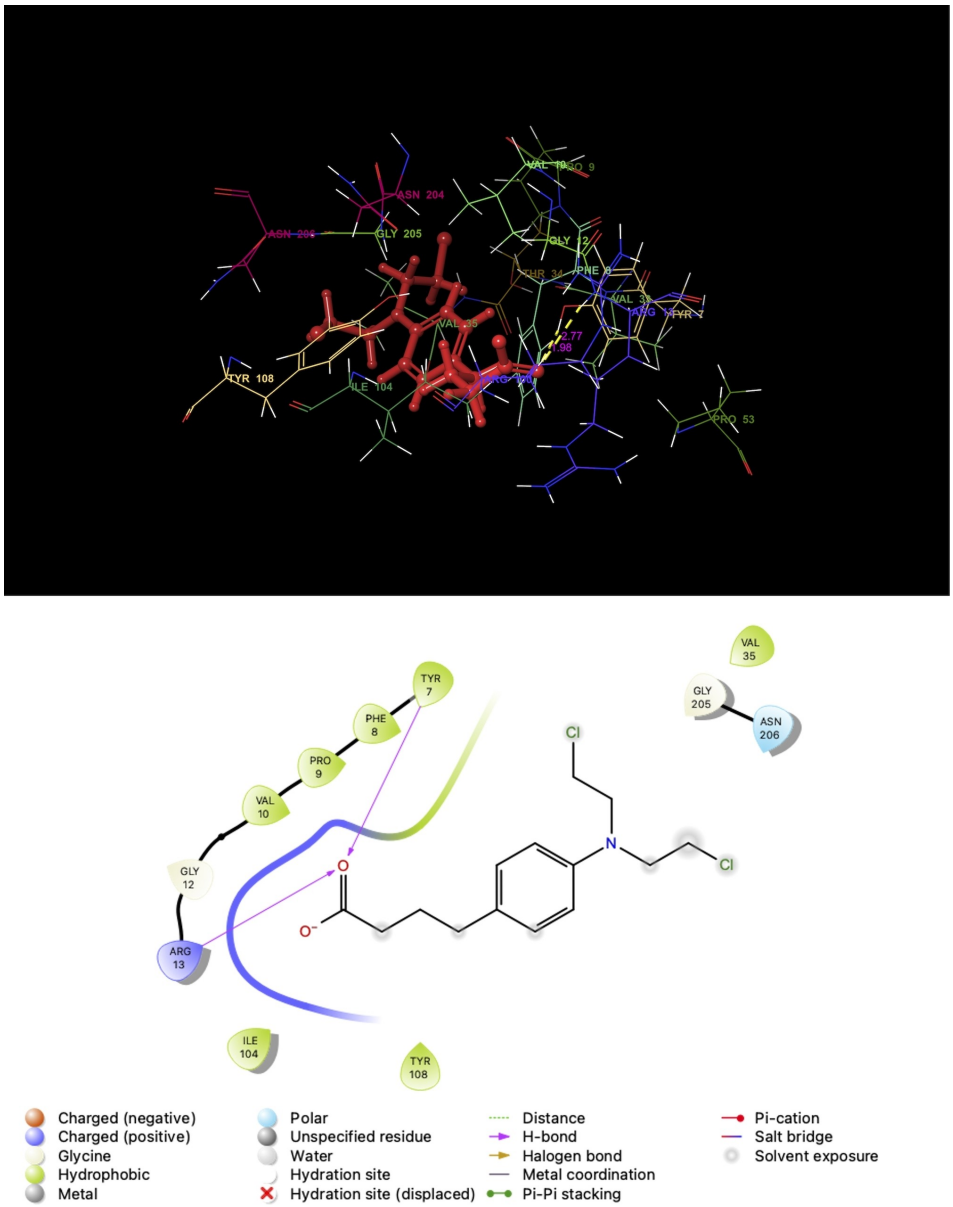


**Figure 4.** The 3D and 2D binding modes of native ligand CBL (Chlorambucil, PubChem CID: 2708, 4-(4-[bis(2-chloroethyl)amino]phenyl)butanoic acid) in the binding sites of GST.

255.40 ± 1.14 μM) > cinnarizine ($K_I$ = 502.70 ± 2.53 μM). These results show that nilvadipine exhibited competitive inhibition, whereas isradipine and amlodipine displayed uncompetitive inhibition, and other drugs had non-competitive inhibition (Figures 2 and 3).

Moreover, in order to detail the molecular basis of the binding affinities of these CCBs, molecular docking studies were carried out, and it was compared with a co-crystallized ligand ($C_{14}H_{19}Cl_2NO_2$, CBL) in the binding site of the GST. As reported in our previous studies,[77,78] in the redocking study performed, the root means square deviation (RMSD) value between the docking pose and 3D crystallographic structure (PDB code 3CSJ) was computed, and the RMSD value was 0.75 Å. This displayed that the Glide XP docking protocol was reproduced the very near-native conformation of the native ligand (CBL) in the GST complex. According to this, because RMSD ≤ 2.0 Å was considered successful docking (Figure 4).

As shown in Figures 1 and 3 and Table 1, the five active CCBs we used in our study have diverse structures and scaffolds. Isradipine showed the most potent inhibitory activity ($K_I$ = 98.84 ± 0.53 μM), whereas cinnarizine exhibited the weakest inhibitory activity ($K_I$ = 502.70 ± 2.53 μM). Although isradipine had the lowest inhibition constant for GST, its inhibition type was uncompetitive. For this reason, the binding structure of the competitive inhibitor, nilvadipine with the $IC_{50}$ value and $K_I$ constant 295.90 ± 6.26 μM and 127.30 ± 4.23 μM, respectively, were predicted by molecular docking simulation, and it was predicted to be located in the hydrophobic pocket formed

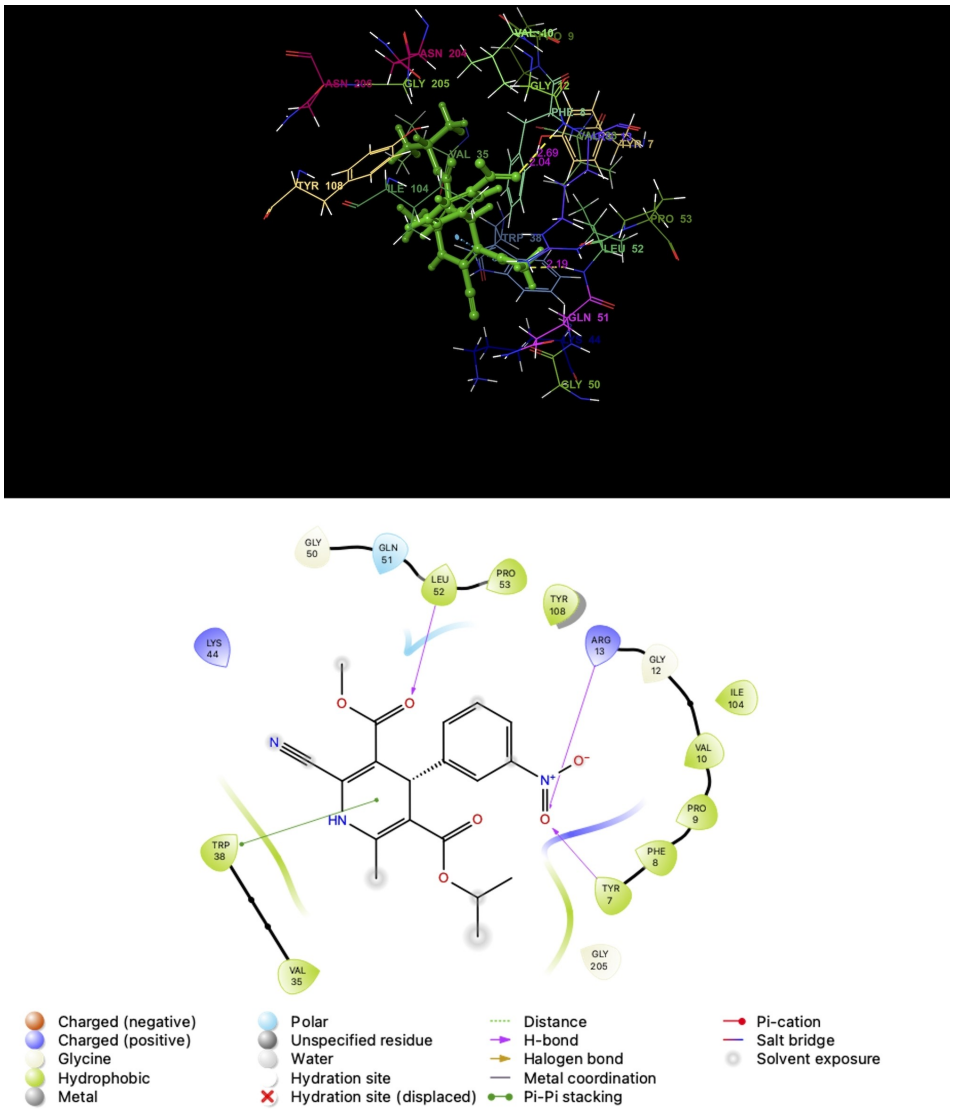


**Figure 5.** The 3D and 2D binding modes of nilvadipine in the binding sites of GST.

by the side chains of residues Tyr7, Phe8, Pro9, Val10, Val35, Trp38, Leu52, Pro53, Ile104, and Tyr108. Figures 4 and 5 show that the green lines display hydrophobic interactions, while the pink arrow exhibits the hydrogen bond interaction. The nilvadipine (docking score of −4.69 kcal/mol and MM-GBSA value of −44.12 kcal/mol) form three H-bond interactions with residues Tyr7 (distance of 2.04 Å), Arg13 (distance of 2.69 Å), and Leu58 (distance of 2.19 Å), which is consistent with the native ligand CBL. Pyridine ring also forms π-π stacking interaction with residue Trp38 (Figure 5).

Many researches were performed about the effects of many agents and chemicals on the GST in literature. Liu et al.[76] designed and synthesized a series of 6-(7-nitro-2,1,3-benzoxadiazol-4-ylthio)hexanol derivatives as GST inhibitors and their evaluated for their biological activity. They found that among the synthesized compounds, **4n** displayed more selective inhibition toward GST P1-1 and GST M2-2, more potent anticancer activities, and better water solubility, against all the tested cancer cells than its parent molecule. In another study, Cetin et al.[79] designed to investigate newly 1-phenyl-3-(thiophen-2-yl)-1H-pyrazole-5-carboxamide derivatives for their in-vitro enzyme inhibitory activities against GST. They also determined that (morpholin-4-yl)[1-phenyl-3-(thiophen-2-yl)-1H-pyrazole-5-yl]methanone (**7**) was the best inhibitor for GST ($K_I = 16.44 \pm 1.58$ μM), and molecular docking simulations revealed important interactions at the GST binding site, and derivative **7** displayed good binding affinities for GST (−9.7 kcal/mol).

Di Paolo, et al.[80] synthesized a novel series 7-nitrobenzo [c][1,2,5]oxadiazole derivative **NBDHEX** and its analogue **MC3181**. Derivatives **3**–**5** showed high inhibitory activity against the GST and showed reactivity towards GSH comparable to that of the respective parent compound. They also determined that agents **4** and **5** were safe and effective when administered intravenously or orally as an aqueous solution to mice xenografted with A375 human melanoma tumors. In

another study, Premetis, et al.[81] examined the interaction of colchicine, is a classical antimitotic, and its derivative 2,3-didemethylcolchicine with human GST. Also, it was investigated by inhibition analysis and *in silico* simulations. They found that both compounds bind reversibly to human GSTs and behave as potent inhibitors and moreover, *in silico* study determined that colchicine overlaps with both H-site and G-site.

Balcı et al.[82] investigated in-vitro inhibition effects of coumarin, ascorbic acid, sodium sulfide, sodium azide, citric acid compounds, and $Cd^{2+}$, $Cu^{2+}$, $Ni^{2+}$, $Mg^{2+}$ metal ions towards the purified GST from Vaccinium arctostapylous L. by the GSH-agarose affinity chromatography and Sephadex G-100 gel filtration steps. Furthermore, they evaluated the molecular docking interactions between these compounds and the GST and found $K_I$ constants of these agents ranged from $0.002 \pm 0.0003$ mM to $15.05 \pm 7.05$ mM. In another work, Ayna et al.[83] purified GST from rat erythrocyte with a specific activity of 6.3 $EUmg^{-1}$ protein, 44% yield, and 115-fold using the GSH-agarose affinity chromatography. They also investigated the effects of gentamicin, clindamycin, cefazolin, ampicillin, and scopolamine butylbromide on the activity of human erythrocyte GST and determined that gentamicin and clindamycin inhibited the enzymatic activity with $IC_{50}$ values of 1.69 mM and 6.9 mM and $K_I$ constants of 1.70 and 2.36 mM, respectively. Moreover, they found that scopolamine butylbromide and ampicillin were activators of the GST, whilst the activity of the GST was insensitive to cefazolin.

## Conclusion

Glutathione transferase has been the subject of research because of its potential role in several diseases, especially as a potential target for anticancer drugs. In this work, some drugs as CCBs, amlodipine, cinnarizine, isradipine, nifedipine, and nilvadipine, were evaluated for their biological activity. Among the target drugs, isradipine ($K_I = 98.84 \pm 0.53$ μM), showed had a higher inhibition effect on GST than other drugs. Molecular docking simulation has supported the obtained GST in-vitro inhibitory activity and described the binding mode for target CCBs within the GST active site, explaining the interaction between the competitive inhibitor nilvadipine and GST. Generally, these CCBs could be considered a promising scaffold for developing efficient anticancer candidates with potent GST inhibitory activities.

## Supporting Information Summary

Experimental Section of the current article, in-vitro analyses and molecular docking studies are provided in the Supporting Information.

## Acknowledgements

*This work was supported by the Research Fund of Anadolu University (grant number 2102 S003).*

## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** Biological Activity · Calcium Channel Blockers · Enzymes · Glutathione S-Transferase · Inhibition

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Submitted: August 31, 2021
Accepted: October 18, 2021