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SYNTHESIS, SPECTRAL CHARACTERISTICS AND MOLECULAR DOCKING STUDIES OF *N*-(2,2,2-TRICHLORO-1-THIOUREIDOETHYL)CARBOXAMIDES

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Abstract: Thiourea and its derivatives are widely used in various fields of human practice. In this work, we report the development of a new, easy-to-implement and highly productive method for synthesizing *N*-(2,2,2-trichloro-1-thioureidoethyl)carboxamides. These substances were obtained by interacting *N*-(2,2,2-trichloro-1-isothiocyanatoethyl)carboxamides with ammonia in a chloroform medium. The target products were obtained with 81-92% yield and ^{1}H, ^{13}C NMR and IR spectroscopy reliably proved their structure. All the obtained compounds were tested for their ability to bind to the active site of the GADD34:PP1 holoenzyme using molecular docking.

***Keywords*:** Synthesis, Thiourea, Salubrinal, Sal 003, Molecular docking.

Introduction

People widely use thiourea and its derivatives in their practical and scientific activities. Various substituted thioureas are important classes of organic compounds that are used for the synthesis and functionalization of

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many acyclic and (hetero)cyclic systems. For example, substituted thioureas have found use as starting reagents for the synthesis of *N,N′*-disubstituted carbamimidothioates derivatives and isothiuronium salts,[1] carboxylic acid thioesters,[2] carbodiimides,[3-4] guanidines[5] and cyanamides.[6] The presence of several reaction centers in these compounds made them unique reagents for the synthesis of various heterocycles, such as 1,3-thiazetidines,[7-8] 1,3-benzothiazoles,[9-10] 1,3-thiazolidines,[8,11-12] imidazolidines,[13] triazoles,[14-15] tetrazoles,[16] pyrimidines,[17-18] 1,3-thiazines,[19] 1,3,5-oxadiazines[20-23] and many others.[24]

Substituted thioureas, due to the presence of a lone pair of electrons on the S and N atoms, are unique ligands capable of forming complexes of various coordination number with many metals. For example, we know thiourea complexes with Ag(I), Cu(I/II), Au(I), Zn(II), Cd(II), Pd(II), Pt(II), Ru(II), Hg(II), Co(II), Pb(II), In(III) and many other metals.[25-28] Due to these properties, thiourea derivatives have found use as chemosensors for the detection of various metal cations. For example, these compounds are used to detect cations such as Ag^{+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Pb^{2+}, Mn^{2+}, Cu^{2+}, Co^{2+}, Al^{3+}, Cr^{3+}, Ga^{3+}, In^{3+}, Ru^{3+}, Fe^{3+} and many others in various samples.[29] In addition, thioureas are included in catalysts for reactions catalyzed by transition metals. For example, thioureas have found application as catalysts for asymmetric multicomponent reactions,[30-31] polymerization processes accompanied by the opening of heterocycles[32] and many other reactions.[33]

Substituted thioureas are of particular interest in medicine, pharmacy and agriculture as biologically active compounds. The thiourea moiety is a very common pharmacophore group and is found in many drugs used in practical and experimental medicine (Figure 1).[34] For example, thiourea derivatives include the antituberculosis drug Thiocarlide (Isoxyl),[35-36]

histamine H2 receptor antagonists Metiamide[37] and Burimamide,[38] HIV reverse transcriptase inhibitors Trovirdine, LY73497, PETT-1 and PETT-2,[39-40] antimicrobial drug used for abdominal lavage Noxythiolin,[42] human glutaminyl cyclase inhibitor PBD150[43-44] and many others. Recently, thioureas containing an alkylamide moiety have attracted the attention of many researchers as biologically active substances. Among these compounds, effective selective inhibitors of the GADD34:PP1 haloenzyme complex are known, such as Salubrinal, Sal003 and their analogs.[45-48] These substances are used to fight endoplasmic reticulum stress and study its role in pathophysiological processes at the molecular level.[49-50] Among such thioureas, moderate inhibitors of the hERG ion channel[51] and a series of enzymes of the P450 family[52] are known.

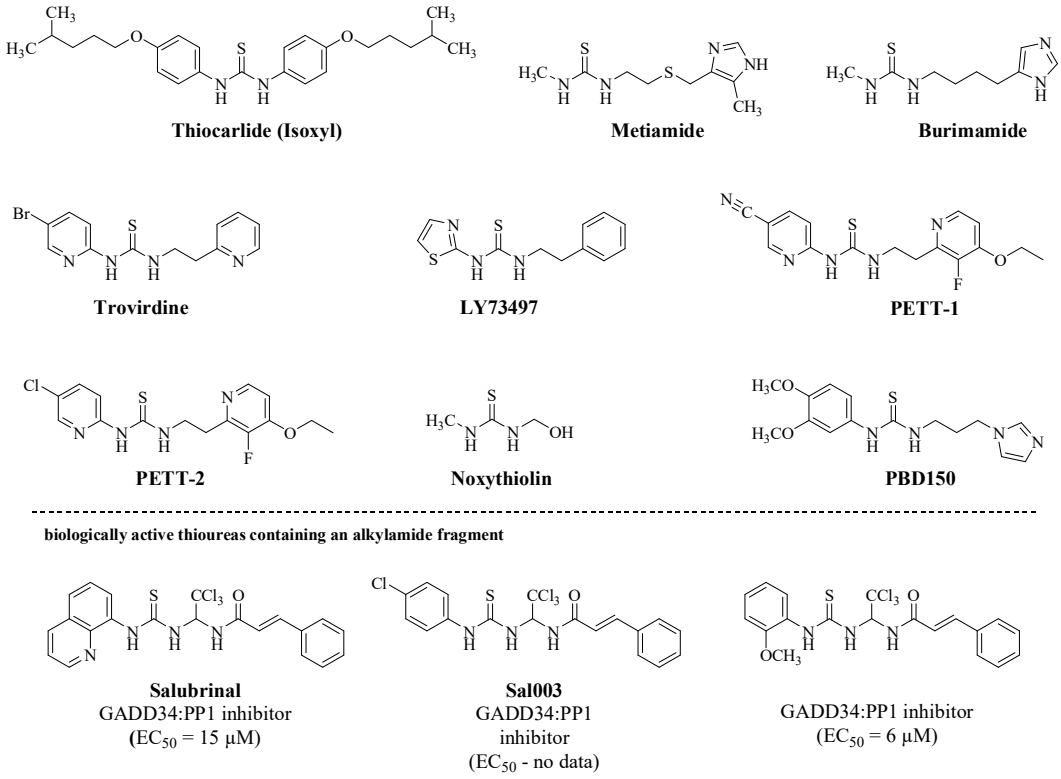
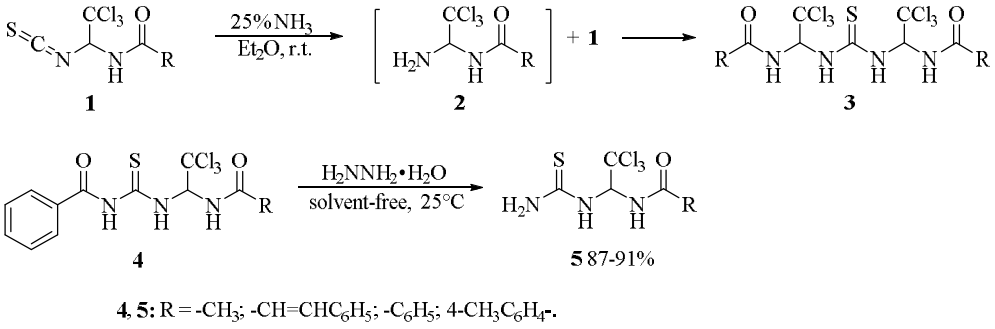


Figure 1. Structures of some biologically active substances containing a thiourea fragment.

In this paper, we report a new, simple and highly efficient method for the synthesis of monosubstituted thioureas containing the *N*-(2,2,2-trichloroethyl)carboxamide fragment - *N*-(2,2,2-trichloro-1-thioureidoethyl) carboxamides. The first attempt to synthesize these compounds was made about thirty years ago.[53] The reaction of *N*-(2,2,2-trichloro-1-isothiocyanatoethyl)carboxamides (**1**) with an aqueous solution of ammonia in diethyl ether was carried out for this purpose (Scheme 1). However, it was not successful. Instead of the expected *N*-(2,2,2-trichloro-1-thioureidoethyl)carboxamides (**2**), the corresponding *N,N′*-diamidoalkylated thioureas **4** were obtained. This reaction presumably proceeded via forming *N*-(1-amino-2,2,2-trichloroethyl)carboxamides (**3**). Recently was proposed an alternative route for obtaining these compounds based on the hydrazinolysis of *N*-((1-carboxamido-2,2,2-trichloroethyl)carbamothioyl) carboxamides.[54] This method allows obtaining the target products in high yields but is significantly complicated by the presence of additional stages. In this regard, we have selected the conditions for the reaction of *N*-(2,2,2-trichloro-1-isothiocyanatoethyl)carboxamides (**1**) with an aqueous solution of ammonia leading to monosubstituted thioureas **5**.

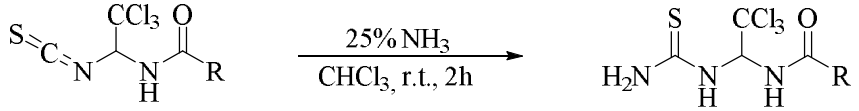
previous works



Scheme 1. Strategic approaches to synthesize *N*-(2,2,2-trichloro-1-thioureidoethyl)carboxamides (**5**).

Results and Discussion

We used a previously developed method described in reference[55] to obtain the starting *N*-(2,2,2-trichloro-1-isothiocyanatoethyl)carboxamides **(1a-j)**. Compounds **1a** and **1c-i** were known before. Compounds **1b** and **1j** were described in this work for the first time. The interaction of the obtained isothiocyanates **1** with ammonia in a chloroform medium led to the formation of *N*-(2,2,2-trichloro-1-thioureidoethyl)carboxamides (**5**). This reaction was carried out at room temperature with vigorous stirring for two hours (Scheme 2). The target thioureas were obtained in good yields, ranging from 81 to 92%. Thioureas **5a**, **5e**, **5f** and **5h** were known previously,[54] the rest were obtained ones for the first time.



1 **5a-j** 81-92%

R = -CH_3 (**a**); -$CH_2CH(CH_3)_2$ (**b**); -CH_2Cl (**c**); -$CH{=}CH_2$ (**d**); -$CH{=}CHC_6H_5$ (**e**); -C_6H_5 (**f**); 2-$CH_3C_6H_4$- (**g**); 4-$CH_3C_6H_4$- (**h**); 2-ClC_6H_4- (**i**); 2-BrC_6H_4- (**j**).

Scheme 2. Synthesis of *N*-(2,2,2-trichloro-1-thioureidoethyl)carboxamides (**5a-j**).

^1H, ^{13}C NMR and IR spectroscopy confirmed the structure of the obtained compounds. In the ^1H NMR spectra of compounds **5a-j**, doublet signals of two NH protons were observed, which appeared in the 9.46 - 8.02 ppm region. At the same time, the protons of the NH_2 group appeared as broadened singlets in the region of 8.02 - 7.56 ppm. The signal of the CH proton also appeared as a broadened singlet, less often as a doublet of doublets, at 7.29 - 7.09 ppm. In the ^{13}C NMR spectrum, the signals of C=S and C=O carbons were indicative, which appeared at 183.7 - 183.5 ppm and 170.9 - 163.8 ppm, respectively. In turn, the signals of the CCl_3 group and CH carbon appeared at 101.9 - 101.3 and 70.7 - 70.1 ppm, respectively. In the IR spectra, the bands of NH group stretching vibrations were located at 3390 - 3110 cm^{-1}. The band corresponding to the vibrations of the C=O group appeared at 1677 - 1650 cm^{-1}.

The obtained compounds were tested for their ability to bind to the active site of the GADD34:PP1 holoenzyme using molecular docking. We used a known inhibitor of this enzyme, Salubrinal as a standard in this work.[45] Before molecular docking, the structures of thioureas **5a-j** were optimized using the PM3 method. According to the obtained results, for most of them, the energetically most favorable conformation was stabilized by an intramolecular hydrogen bond between the oxygen atom of the amide fragment and NH of the thiourea fragment. The presence of an intramolecular hydrogen bond in the Salubrinal molecule and its analogs was previously postulated in semi-empirical[48] and *ab initio*[56] calculations.

According to the molecular docking results, all tested compounds interacted with the active site of the target (Figure 2a). The best results were shown by *N*-(2,2,2-trichloro-1-thioureidoethyl)cinnamamide (**5e**) (Figure 2b-c). However, compound **5e** was inferior to Salubrinal in the strength of the complex formed. For Salubrinal ΔG = -12.0 kcal/mol, while for **5e** this value was -9.8 kcal/mol. This indicates the importance of the substituent at the thiourea moiety for the efficiency of GADD34:PP1 inhibition.

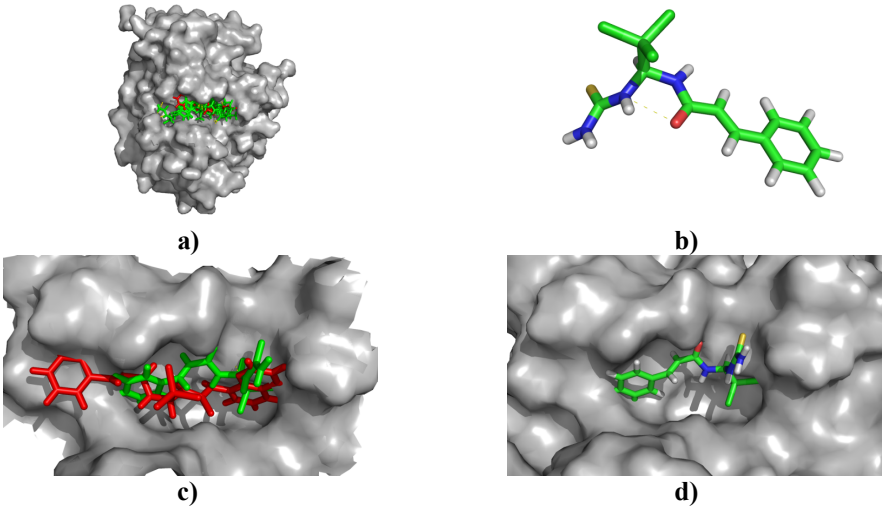


Figure 2. Results of *in silico* experiment: a) position of molecules of compounds **5a-j** (green) and Salubrinal (red) in the active site of GADD34:PP1; b) structure of **5e** optimized by PM3 method; c) alignment of positions of **5e** (green) and Salubrinal (red) in the active site of GADD34:PP1; d) position of the molecule of compound **5e** in the active site of GADD34:PP1.

Experimental

Chemistry

IR spectra were recorded on a Spectrum BX II spectrometer in KBr pellets. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were measured for solutions in DMSO-d_6 on a Varian VXR-400 spectrometer. Elemental analysis was performed on a LECO CHNS-932 instrument. The reaction and purity of the compounds were monitored by TLC on Silufol UV-254 plates using a chloroform/acetone mixture (3:1) as an eluent. Melting points were carried out using an Electrothermal 9100 Digital Melting Point apparatus and were uncorrected.

Synthesis of *N*-(2,2,2-trichloro-1-isothiocyanatoethyl) carboxamides (1a-j). *N*-2,2,2-Trichloro-1-isothiocyanatoethyl) carboxamides (**1a-j**) were prepared according to the procedure described previously.[55] Compounds **1b** and **1j** were obtained for the first time. The remaining isothiocyanates were known previously.[55,57]

3-Methyl-*N*-(2,2,2-trichloro-1-isothiocyanatoethyl)butanamide (1b). Light yellow crystals; yield 89%; mp 112-114°C (MeCN); R_f = 0.73. IR: ν_{max} 3421, 3220, 3175 (NH), 3021, 2956, 2935, 2870, 2827, 2771, 2736, 2649, 2592 (CH), 2017 (N=C=S), 1663 (C=O), 1525, 1464, 1432, 1389, 1310, 1249, 1207, 1137, 1110, 1093, 1028, 982, 884, 857, 806, 762, 714, 613, 547, 488 cm^{-1}. ^{1}H NMR: δ 9.52 (d, *J* = 9.3 Hz, 1H, NH), 6.44 (d, *J* = 9.3 Hz, 1H, CH), 2.19-2.17 (m, 2H, *i*-Bu), 2.07-1.96 (m, 1H, *i*-Bu), 0.91-0.89 (m, 6H, *i*-Bu). ^{13}C NMR: δ 172.1 (C=O), 140.2 (N=C=S), 99.0 (CCl_3), 72.3 (CH), 43.8, 25.6, 22.12 (*i*-Bu). Anal. Calcd (%) for $C_8H_{11}Cl_3N_2OS$ (289.60): C, 33.18; H, 3.83; N, 9.67; S, 11.07. Found: C, 33.22; H, 3.81; N, 9.71; S, 11.10.

2-Chloro-*N*-(2,2,2-trichloro-1-isothiocyanatoethyl)benzamide (1j). Light yellow crystals; yield 87%; mp 116-118°C (MeCN); R_f = 0.70. IR: ν_{max} 3420, 3224, 3187 (NH), 3027, 2996, 2936, 2783, 2634, 2624, 2857, 2516 (CH), 2013 (N=C=S), 1665 (C=O), 1591, 1528, 1434, 1322, 1304, 1258, 1168, 1160, 1120, 1052, 1008, 952, 902, 808, 764, 755, 710, 686, 615, 574, 483 cm^{-1}. ^1H NMR: δ 10.37 (d, *J* = 8.8 Hz, 1H, NH), 7.57-7.44 (m, 4H, $4H_{arom}$), 6.67 (d, *J* = 8.8 Hz, 1H, CH). ^{13}C NMR: δ 166.5 (C=O), 140.8 (N=C=S), 134.8, 131.6, 130.1, 129.7, 129.0, 127.1 ($C_{arom.}$), 98.9 (CCl_3), 72.5 (CH). Anal. Calcd (%) for $C_{10}H_6Cl_4N_2OS$ (344.03): C, 34.91; H, 1.76; N, 8.14; S, 9.32. Found: C, 34.88; H, 1.74; N, 8.17; S, 9.34.

Synthesis of *N*-(2,2,2-trichloro-1-thioureidoethyl)carboxamides (5a-j). 1 mL of a 25% aqueous ammonia solution was added to a solution of 10 mmol of one of the isothiocyanates **1a-j** in 20 mL of chloroform. The mixture was stirred at room temperature for 2 hours. Then the formed precipitate was filtered and washed with 50 mL of water. The obtained product was dried and purified by recrystallization from ethanol.

***N*-(2,2,2-Trichloro-1-thioureidoethyl)acetamide (5a).**[54]
White solid; yield 81% (2.14 g); mp 231-233°C (EtOH); R_f = 0.22. Anal. Calcd (%) for $C_5H_8Cl_3N_3OS$ (264.55): C, 22.70; H, 3.05; N, 15.88; S, 12.12. Found: C, 22.76; H, 3.01; N, 15.93; S, 12.16.

3-Methyl-*N*-(2,2,2-trichloro-1-thioureidoethyl)butanamide (5b).
Pale yellow crystals; yield 87% (2.67 g); mp 219-221°C (MeCN); R_f = 0.22. IR: ν_{max} 3279, 3169, 3114 (NH), 3031, 2957, 2930, 2870 (CH), 1666 (C=O), 1633, 1567, 1521, 1467, 1404, 1366, 1318, 1261, 1210, 1163, 1130, 1024, 982, 938, 896, 832, 806, 750, 711, 661, 592, 531 cm^{-1}. ^1H NMR: δ 8.63 (d, *J* = 8.3 Hz, 1H, NH), 7.92 (br. s, 1H, NH), 7.90 (d, *J* = 8.3 Hz, 1H, NH), 7.56 (br. s, 1H, NH), 7.09 (br. s, 1H, CH), 2.10-1.95 (m, 3H, *i*-Bu), 0.90-0.88

(dd, *J* = 2.0 Hz, 6H, *i*-Bu). ^{13}C NMR: δ 183.5 (C=S), 170.9 (C=O), 101.9 (CCl_3), 70.1 (CH), 44.3, 25.6, 22.2 (*i*-Bu). Anal. Calcd (%) for $C_8H_{14}Cl_3N_3OS$ (306.63): C, 31.34; H, 4.60; N, 13.70; S, 10.46. Found: C, 31.28; H, 4.56; N, 13.76; S, 10.50.

2-Chloro-*N*-(2,2,2-trichloro-1-thioureidoethyl)acetamide (5c).

Pale yellow crystals; yield 84% (2.51 g); mp 218-220°C (MeCN); R_f = 0.23. IR: ν_{max} 3391, 3274, 3201, 3122 (NH), 3081, 2953, 2928, 2854 (CH), 1676 (C=O), 1618, 1573, 1520, 1503, 1402, 1359, 1329, 1267, 1208, 1175, 1083, 1028, 829, 819, 772, 730, 705, 660, 616, 586, 550, 518, 482, 455 cm^{-1}. ^{1}H NMR: δ 9.31 (d, *J* = 8.3 Hz, 1H, NH), 8.17 (d, *J* = 9.3 Hz, 1H, NH), 8.00 (br. s, 1H, NH), 7.65 (br. s, 1H, NH), 7.13 (br. s, 1H, CH), 4.20 (s, 2H, CH_2Cl). ^{13}C NMR: δ 183.6 (C=S), 165.4 (C=O), 101.3 (CCl_3), 70.5 (CH), 42.3 (CH_2Cl). Anal. Calcd (%) for $C_5H_7Cl_4N_3OS$ (298.99): C, 20.09; H, 2.36; N, 14.05; S, 10.72. Found: C, 20.01; H, 2.29; N, 14.11; S, 10.79.

***N*-(2,2,2-Trichloro-1-thioureidoethyl)acrylamide (5d).**

Pale yellow crystals; yield 89% (4.51 g); mp 235-237°C (MeCN); R_f = 0.23. IR: ν_{max} 3385, 3282, 3262, 3190 (NH), 3103, 3066, 2949, 2853 (CH), 1677 (C=O), 1622, 1575, 1497, 1404, 1363, 1321, 1219, 1172, 1092, 1020, 974, 890, 808, 730, 662, 637, 539 cm^{-1}. ^{1}H NMR: δ 8.96 (d, *J* = 8.3 Hz, 1H, NH), 8.10 (d, *J* = 8.8 Hz, 1H, NH), 7.96 (br. s, 1H, NH), 7.65 (br. s, 1H, NH), 7.20 (dd, *J* = 8.3, 8.8 Hz, 1H, CH), 6.40 (dd, *J* = 11.7, 15.7 Hz, 1H, C<u>H</u>=CH_2), 6.20 (dd, *J* = 15.7, 1.5 Hz, 1H, CH=C<u>H</u>$_2$), 5.72 (dd, *J* = 11.7, 1.5 Hz, 1H, CH=C<u>H</u>$_2$). ^{13}C NMR: δ 183.6 (C=S), 163.8 (C=O), 130.6 ($CH=CH_2$), 127.5 ($CH=CH_2$), 101.6 (CCl_3), 70.3 (CH). Anal. Calcd (%) for $C_6H_8Cl_3N_3OS$ (276.56): C, 26.06; H, 2.92; N, 15.19; S, 11.59. Found: C, 26.11; H, 2.87; N, 15.26; S, 11.64.

***N*-(2,2,2-Trichloro-1-thioureidoethyl)cinnamamide (5e).**[54]

White solid; yield 83% (2.93 g); mp 229-231°C (EtOH); R_f = 0.20. Anal. Calcd (%) for $C_6H_8Cl_3N_3OS$ (352.66): C, 40.87; H, 3.43; N, 11.92; S, 9.09. Found: C, 40.81; H, 3.37; N, 11.95; S, 9.16.

***N*-(2,2,2-Trichloro-1-thioureidoethyl)benzamide (5f).**[54]

White solid; yield 92% (3.00 g); mp 216-218°C (EtOH); R_f = 0.21. Anal. Calcd (%) for $C_{10}H_{10}Cl_3N_3OS$ (326.62): C, 36.77; H, 3.09; N, 12.87; S, 9.82. Found: C, 36.85; H, 3.02; N, 12.98; S, 9.89.

2-Methyl-*N*-(2,2,2-trichloro-1-thioureidoethyl)benzamide (5g).

Pale yellow crystals; yield 88% (4.51 g); mp 230-232°C (MeCN); R_f = 0.32. IR: ν_{max} 3390, 3280, 3181, 3112 (NH), 2955, 2927, 2855 (CH), 1650 (C=O), 1612, 1579, 1513, 1502, 1482, 1399, 1357, 1321, 1289, 1174, 1157, 1117, 1021, 884, 827, 812, 792, 744, 673, 649, 591, 556, 532 cm^{-1}. ^1H NMR: δ 9.22 (d, *J* = 7.8 Hz, 1H, NH), 7.93 (d, *J* = 8.8 Hz, 1H, NH), 7.99 (br. s, 1H, NH), 7.72 (br. s, 1H, NH), 7.38-7.24 (m, 5H, $4H_{arom.}$+CH), 2.36 (s, 3H, CH_3). ^{13}C NMR: δ 183.6 (C=S), 168.3 (C=O), 136.1, 135.3, 130.5, 129.7, 127.1, 125.5 ($C_{arom.}$), 101.8 (CCl_3), 70.6 (CH), 19.4 (CH_3). Anal. Calcd (%) for $C_{11}H_{12}Cl_3N_3OS$ (340.65): C, 38.79; H, 3.55; N, 12.34; S, 9.41. Found: C, 38.72; H, 3.58; N, 12.41; S, 9.47.

4-Methyl-*N*-(2,2,2-trichloro-1-thioureidoethyl)benzamide (5h).[54]

White solid; yield 89% (3.03 g); mp 210-212°C (EtOH); R_f = 0.29. Anal. Calcd (%) for $C_{11}H_{12}Cl_3N_3OS$ (340.65): C, 38.79; H, 3.55; N, 12.34; S, 9.41. Found: C, 38.82; H, 3.48; N, 12.39; S, 9.45.

2-Chloro-*N*-(2,2,2-trichloro-1-thioureidoethyl)benzamide (5i).

Pale yellow crystals; yield 85% (3.07 g); mp 228-230°C (MeCN); R_f = 0.21. IR: ν_{max} 3379, 3274, 3179 (NH), 3114, 2953, 2855 (CH), 1662 (C=O), 1613, 1589, 1515, 1502, 1469, 1435, 1399, 1359, 1327, 1300, 1266, 1176, 1158,

1093, 1050, 1028, 885, 827, 808, 782, 749, 735, 661, 645, 589, 539, 471 cm^{-1}. ^1H NMR: δ 9.45 (d, *J* = 7.8 Hz, 1H, NH), 8.00 (br. s, 1H, NH), 7.98 (d, *J* = 9.3 Hz, 1H, NH), 7.67 (br. s, 1H, NH), 7.53-7.41 (m, 4H, $H_{arom.}$), 7.29 (br. s, 1H, CH). ^{13}C NMR: δ 183.7 (C=S), 165.5 (C=O), 135.9, 131.2, 130.0, 129.7, 129.0, 127.1 ($C_{arom.}$), 101.5 (CCl_3), 70.6 (CH). Anal. Calcd (%) for $C_{10}H_9Cl_4N_3OS$ (361.06): C, 33.27; H, 2.51; N, 11.64; S, 8.88. Found: C, 33.21; H, 2.46; N, 11.72; S, 8.93.

2-Bromo-*N*-(2,2,2-trichloro-1-thioureidoethyl)benzamide (5j).

Pale yellow crystals; yield 83% (3.37 g); mp 230-232°C (MeCN); R_f = 0.26. IR: ν_{max} 3375, 3278, 3180 (NH), 3116, 2953, 2927, 2854 (CH), 1660 (C=O), 1614, 1590, 1581, 1521, 1501, 1467, 1401, 1360, 1329, 1264, 1175, 1155, 1093, 1026, 884, 826, 808, 783, 748, 662, 637, 592, 539 cm^{-1}. ^1H NMR: δ 9.46 (d, *J* = 7.8 Hz, 1H, NH), 8.02 (d, *J* = 6.7 Hz, 2H, NH_2), 7.70-7.67 (m, 2H, NH+ $H_{arom.}$), 7.49-7.36 (m, 3H, $H_{arom.}$), 7.28 (dd, *J* = 6.9, 7.8 Hz, 1H, CH). ^{13}C NMR: δ 183.7 (C=S), 166.4 (C=O), 137.9, 132.8, 131.3, 129.0, 127.5, 118.8 ($C_{arom.}$), 101.5 (CCl_3), 70.7 (CH). Anal. Calcd (%) for $C_{10}H_9BrCl_3N_3OS$ (405.52): C, 29.62; H, 2.24; N, 10.36; S, 7.91. Found: C, 29.54; H, 2.18; N, 10.45; S, 8.01.

Molecular modeling studies

Before molecular docking, the structures of compounds **5a-j** were optimized using the semi-empirical PM3 method[58] implemented in the ArgusLab 4.0.1 software package.[59] The three-dimensional crystal structure of the GADD34:PP1 holoenzyme (PDB ID: 4XPN)[60] was downloaded in .pdb format from the Protein Molecule Data Bank (http://www.rcsb.org). All non-amino acid components were removed from the protein structure before docking, except for the phosphoric acid residue 403 PO4. Based on this phosphoric acid residue, a ligand group called Ligand_X-ray was

created. Based on this group, a three-dimensional model of the binding site was created, its dimensions being set manually and were 40 Å along the X-axis, 40 Å along the Y-axis and 40 Å along the Z-axis. The flexible ligand parameter was set during docking. The semi-empirical AScore function, based on the XScore function,[61] was used to evaluate the results. The cell resolution was set at 0.250 Å. Calculation type – Dock; Docking Engin - ArgusLab. The results' visualization was carried out using the PyMOL 0.99rc6 program.[62]

Conclusions

We have developed a simple and high-throughput method for synthesizing *N*-(2,2,2-trichloro-1-thioureidoethyl)carboxamides. It does not require heating; it is carried out on simple and standard laboratory equipment, without catalysts, or expensive and toxic reagents. The method for obtaining target thioureas is based on the reaction of *N*-(2,2,2-trichloro-1-isothiocyanatoethyl)carboxamides with an aqueous ammonia solution in a chloroform medium. The resulting compounds have been tested *in silico* for their ability to inhibit GADD34:PP1. The resulting thioureas are likely to be moderate or weak GADD34:PP1 inhibitors.

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