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ORIGINAL PAPER

Modular access to heterocycles: methyl 3-aminobenzo[*b*]thiophene-2-carboxylate–thiourea linkage or pyrimidine-4-one-2-thione formation

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Abstract Modular conditions for the formation of thioureas or pyrimidine-4-one-2-thiones connected to the benzo[*b*]thiophene, benzene and indole structures were performed. A benzo[*b*]thiophene isothiocyanate derivative was used as a model to study the condensation with simple aromatic amines and amino-L-sorbose derivative. The construction of pyrimidine-4-one-2-thiones using basic conditions afforded efficiently new heterocyclic aromatics, which were further transformed using the alkylated sulfur as a leaving group in palladium-catalyzed cross-coupling reactions.

Keywords Amino acids · Carbohydrates · Cyclizations · Heterocycles · Homogeneous catalysis

Introduction

Benzo[*b*]thiophenes are an important class of heterocycles in organic chemistry, either as biologically active molecules or as luminescent components used in organic materials [1–3]. Aromatics and heteroaromatics bearing an *ortho*-amino and ester groups, such as anthranilic acid [4, 5], are useful synthons for the preparation of various condensed heterocyclic systems. Methyl 3-aminobenzo[*b*]thiophene-2-carboxylate (**1**) was prepared from *o*-nitrobenzonitrile and methyl thioglycolate under basic conditions following Beck's previously described methodology (Scheme 1) [6, 7]. This easily accessible skeleton could be the starting material of various biologically active molecules: several diarylamines prepared by palladium-catalyzed amination of **1** have antimicrobial and antioxidant properties [3, 8]. The benzo[*b*]thiophenecarboxamide analog of **1** was evaluated as a potential antipsychotic agent [9]. Moreover, a benzothieno[2,3-*d*][1,3]oxazin-4-one derivative was described to be a human leucocyte elastase (HLE) inhibitor [10]. The synthesis of fused 4-hydroxy-3-phenyl[1]benzothieno[3,2-*b*]pyridin-2-one as a potent AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonist has been developed from the ethyl ester analog of **1** [11].

In the field of additionally fused heterocycles, fused pyrimidines as phosphodiesterase 7 (PDE 7) inhibitors, benzothieno[3,2-*a*]thiadiazine dioxides were also described [12]. Compound **1** is also a precursor in the preparation of benzothieno[3,2-*d*]pyrimidine derivatives, which are potent inhibitors of tyrosine kinase [13–15]. Compound **1** was involved into the formation of more complex polycyclic structures, which contain pyrimido[2,1-*a*]phthalazine skeleton that may show biological activities [16].

Very few examples of urea and thiourea intermediates formed from the amino-ester **1** have been described in the literature: 3-[2-[4-[4-(1-methylethyl)phenyl]pyperazin-1-yl]ethyl]-benzothieno[3,2-*d*]pyrimidin-(1H,3H)2,4-dione was developed as an antagonist of α_1-AR (adrenergic receptors) [17], and well (±)-2-[(3-amino-3,4-dihydro-4-oxo-[1]benzothieno[3,2-*d*]pyrimidin-2-yl)thio]-propionic and (±)-α-[(3-amino-3,4-dihydro-4-oxo-[1]benzothieno[3,2-*d*]pyrimidin-2-yl)thio]-phenylacetic acids were designed as inhibitors of COX-1 and COX-2 (cyclooxygenase) [18].

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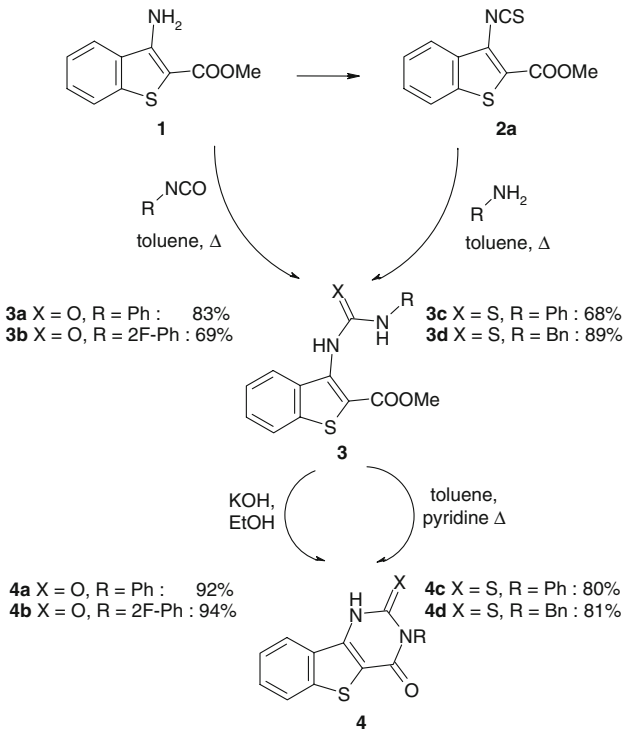


Scheme 1

In light of these broad biological properties of benzo[*b*]thiophene compounds, and the scarce chemical and synthetic transformations found in the literature, we have engaged in a study for controlling the reactivity of the benzo[*b*]thiophene moiety to form ureas and thioureas with subsequent selective cyclization, and explored the potential of the resulting heterocycles in palladium-catalyzed cross-coupling reactions.

Results and discussion

Two approaches were then investigated (Scheme 1) for establishing the urea or thiourea linkage:

- reacting the amino-ester **1** with isocyanates or isothiocyanates;
- condensing amines with the previously formed electrophile **2a** [19].

Condensation of phenyl and 2-fluorophenyl isocyanates with compound **1** proceededs with reasonable to good yields to produce ureas **3a** and **3b**, whereas phenyl isothiocyanate failed to condense with compound **1**, and no thiourea **3c** was formed. The isothiocyanate **2a** was therefore synthesized from **1** (88% yield) according to Fukumi's method [19]. The condensation of simple amines with **2a** was performed under mild and neutral conditions to afford thioureas **3c** and **3d** in good yields. However, when applying slightly basic conditions, a spontaneous cyclization took place to form the thieno[3,2-d]pyrimidyl systems **4c** and **4d** in fair yields.

Two more isothiocyanates were submitted to the same protocol: the commercially available **2b** derived from methyl anthranilate and **2c**—prepared in 86% yield from 6-amino-5-methoxycarbonylindole following the same procedure as for **2a** [20]. In both cases, condensation in a toluene–pyridine mixture (Scheme 2) resulted in smooth cyclization to form **5** and **6** (98 and 72% yield, respectively).

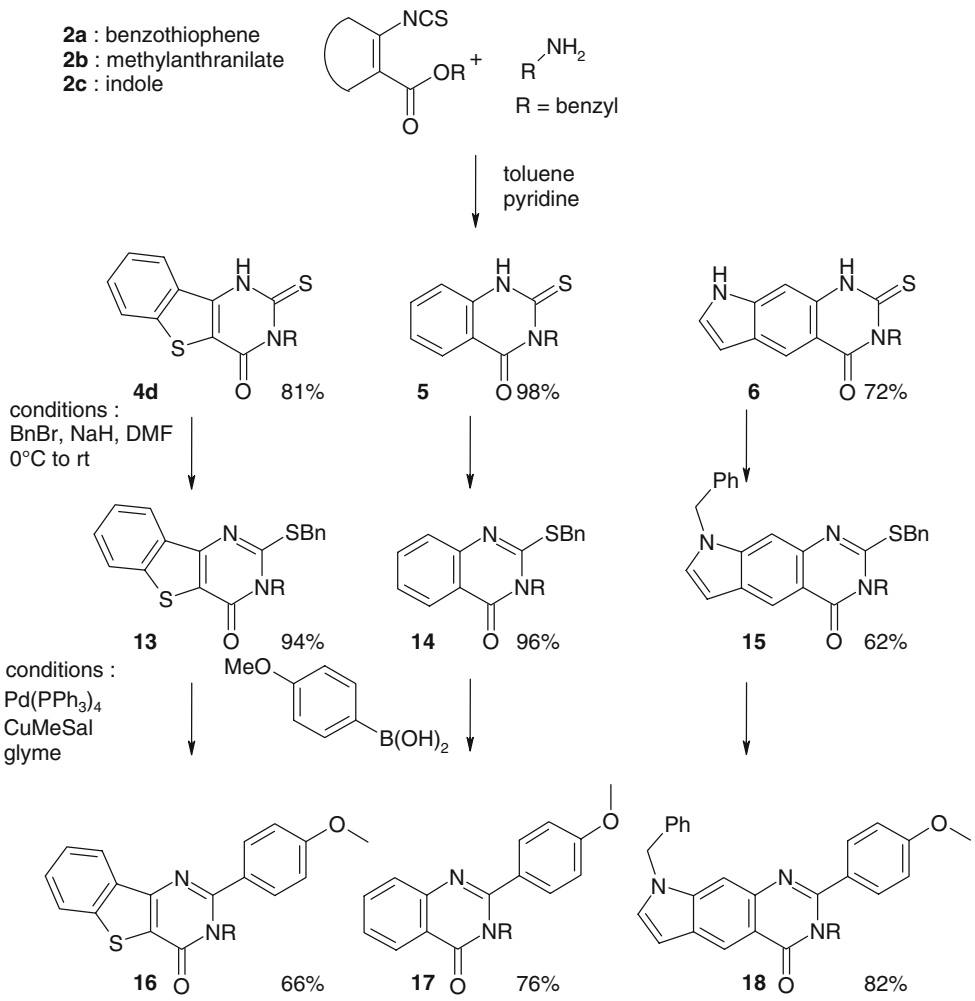
The above-mentioned one-pot condensation–cyclization procedure could not be applied to isocyanates [21], for which a two-step sequence is needed. After formation of ureas **3a** and **3b**, the second step proceeded under strongly basic conditions (KOH) to give excellent yields of **4a** and **4b**.

Isothiocyanate condensation with amines proved somewhat troublesome in our case as overheating could induce direct cyclization to the pyrimidino derivative even under neutral conditions, as observed during crystallization from toluene of the thiourea **3c**.

Literature data on condensations between aryl isothiocyanate-esters and amines showed some important variations on the product formation [22–27], but, in most cases, the thioureas were formed under neutral conditions at room temperature while cyclization occurred through heating under basic conditions. A Staudinger process involving benzyl azide and the thianaphthen isothiocyanate **2a** was then tested. It was anticipated that the iminophosphorane intermediate could favor the thiourea formation. The putative betaine intermediate might hamper the cyclization process and produce the desired thiourea after hydrolysis. The main drawback under such conditions rested in the purification problems caused by triphenyl phosphine oxide. The best results were obtained with tricyclohexyl phosphine, with a 72% yield of thiourea **3d**. Depending on the starting material, such a methodology could be used as an alternative in particular cases.

The amine-isothiocyanate condensation involving a carbohydrate scaffold was tested on an appropriately prepared L-sorbo derivative. In carbohydrate chemistry, sugar-derived isothiocyanates rank among the most versatile synthetic intermediates in the preparation of a variety of functional groups [28, 29]. Their reactivity has been intensively exploited in the case of glycosyl isothiocyanates, for which several syntheses have been developed [30–35]. In contrast, non-anomeric sugar-derived isothiocyanates have received less attention [36–38]. The previously mentioned versatile methodology involving a Staudinger reaction, which—through iminophosphorane formation—can either reduce the azide into an amine or convert it directly into an isothiocyanate [39], looked

Scheme 2

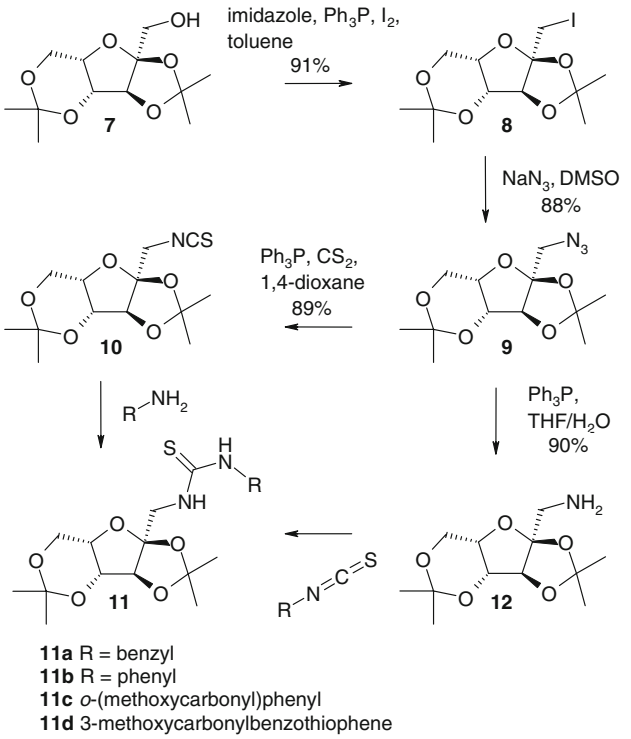


promising. We have thus prepared the 1-deoxy-1-isothiocyanato-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (**10**) via a three-step sequence from 2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (**7**) (Scheme 3) [40].

The reactivity of the sugar-derived isothiocyanate was first tested with different amines: using the previous conditions (toluene–pyridine, 50 °C), the isothiocyanate **10** condensed with benzylamine and arylamines to give the expected thioureas **11**, and no further cyclization into pyrimidine-4-one-2-thiones was observed. Reaction with benzylamine furnished **11a** in 91% yield, while aromatic amines were less suitable nucleophiles: from 83% yield with aniline and 73% with methyl anthranilate to a poor 14% yield when the benzothiophene ring was involved. This could clearly be attributed to the aromatic influence, but also to the steric effect of the heterocycle. We thus switched to the "inverted" pathway through condensing the amino sugar **12** with the benzothiophene-derived isothiocyanate **2a**: this approach proved far more efficient and afforded **11d** in 81% yield. Unfortunately, all attempts to induce cyclization of **11d** to the corresponding pyrimidine-4-one-2-thione failed whatever the conditions used: steric hindrance was suspected to block the process.

Finally, the pyrimidine-4-one-2-thiones **4d**, **5**, and **6** were tested as substrates for palladium-catalyzed coupling reactions (Scheme 2) according to protocols previously developed for structural modulation of pyrimidine structures [41–49]. Compounds **4d**, **5**, and **6** were first *S*-benzylated in standard conditions to afford the corresponding 2-benzylsulfanylpyrimidin-4-ones **13**, **14**, and **15** in 94, 96, and 62% yields, respectively. In our hands the benzylsulfanyl segment did not show efficient leaving group ability in reactions with stannanes, whereas cross-couplings involving *p*-methoxyphenylboronic acid gave efficient results in furnishing coupling products **16**, **17**, and **18** in 66–82% yields.

In summary, we have devised modular conditions for the formation of thioureas or pyrimidine-4-one-2-thiones connected to the benzothiophene structure **1** as a model to the construction of more complex heteroaromatic molecules. Further developments of combined methods for palladium-catalyzed coupling on carbohydrate templates are under



Scheme 3

current study in our laboratory and will be disclosed in due time.

Experimental

Melting points were determined on a Büchi 510 and a Büchi Melting Point B-540 and Electrothermal Mel-Temp apparatus. IR spectra (KBr disk or film on NaCl disk) were measured on a Perkin-Elmer Paragon 1000 PC, Bio–Rad Digilab FTS-40, or Perkin-Elmer Spectrum BX II FT-IR System spectrophotometers. ^{1}H and ^{13}C NMR spectra were recorded in *CDCl$_3$* or *DMSO-d$_6$* solutions on a Bruker Avance DPX-250 instrument (250 MHz ^{1}H frequency/62.5 MHz ^{13}C frequency) and on a Varian Unity Inova instrument (300 MHz ^{1}H frequency/75 MHz ^{13}C frequency). Chemical shifts δ are reported in ppm from the internal *TMS* standard. Whenever appropriate, signal assignments were deduced from DEPT, COSY, and CH CORRELATION NMR experiments. Mass spectra (MS) were recorded on a Perkin-Elmer SCIEX API 300 (Ion Spray®, IS) and on an Aligent 110 (serie MS with VL) apparatus. Optical rotations were measured at 20 °C on a Perkin–Elmer 141 polarimeter using a sodium lamp. Elemental analysis was performed with an Exeter Analytical CE-440 Elemental Analyzer; their results were found to be in good agreement (±0.2%). Analytical TLC was carried out on precoated Silica Gel 60F-254 plates (E. Merck); spots were visualized by UV light (254 nm) and—for carbohydrate compounds—developed by charring after spraying a 5% H_2SO_4 ethanolic solution. Column chromatography was carried out on Silica Gel SI 60 (43–60 μm) (E. Merck) using mixtures of petroleum ether (PE) and ethyl acetate (EA).

*Methyl 3-isothiocyanatobenzo[b]thiophene-2-carboxylate (**2a**, $C_{11}H_7NO_2S_2$)*

To a solution of 0.081 g $NaHCO_3$ (0.96 mmol) in 0.5 cm^3 water, a solution of 0.096 cm^3 $CSCl_2$ (1.25 mmol) in 0.9 cm^3 of chloroform and a solution of the amino-ester **1** (0.2 g, 0.96 mmol) in 2.3 cm^3 chloroform were added dropwise. The mixture was stirred at room temperature for 24 h. The organic layer was separated, and the aqueous layer was extracted with chloroform. The combined organic layer was dried over $MgSO_4$, filtered, the solvent removed by evaporation in vacuo, and the obtained residue was purified by flash chromatography (eluent: PE/EA:95/5, *v*/*v*; $R_f = 0.55$) to give **2a** (0.212 g, 88%) as pale yellow needles; mp 118–119 °C (chloroform) [18] 117–120 °C); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.98$ (s, 3H, CH_3), 7.44–7.56 (m, 2H, H-5, H-6), 7.79 (d, 1H, $J_{7,6} = 7.7$ Hz, H-7), 7.91 (d, 1H, $J_{4,5} = 7.7$ Hz, H-4) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 52.9$ (CH_3), 123.0, 123.2, 125.6, 125.8, 126.0, 126.5, 128.5, 134.8, 138.3 (C=S), 161.8 (C=O) ppm; IR (KBr): $\bar{\nu} = 2140$, 2107 (NCS), 1716 (C=O) cm^{-1}; MS (IS): $m/z = 250$ $[M + 1]^+$.

*Ethyl 6-isothiocyanato-1H-indole-5-carboxylate (**2c**, $C_{12}H_{10}N_2O_2S$)*

To a solution of 0.041 g $NaHCO_3$ (0.49 mmol) in 0.25 cm^3 water, a solution of 0.048 cm^3 $CSCl_2$ (0.64 mmol) in 0.45 cm^3 chloroform and a solution of ethyl 6-amino-1H-indole-5-carboxylate (0.10 g, 0.49 mmol) in 1.15 cm^3 chloroform were added dropwise. The mixture was stirred at room temperature for 5 h. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was dried over $MgSO_4$, filtered, and the solvent removed by evaporation in vacuo. The obtained residue was purified by flash chromatography (eluent: PE/EA:7/3, *v*/*v*; $R_f = 0.57$) to give **2c** (0.103 g, 86%) as a pale yellow solid; mp 152–153 °C (chloroform); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.46$ (t, 3H, $J_{vic} = 7.2$ Hz, CH_3), 4.44 (q, 2H, $J_{vic} = 7.2$ Hz, CH_2), 6.64 (s, 1H, H-3), 7.32-7.36 (m, 2H, H-2, H-7), 8.34 (s, 1H, H-4), 8.61 (bs, 1H, NH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 15.1$ (CH_3), 61.6 (CH_2), 104.0, 112.1, 118.1, 122.5, 125.2, 127.3, 130.5, 131.6, 137.9 (C=S), 165.7 (C=O) ppm; IR (KBr): $\bar{\nu} = 3297$ (NH), 2990 (CH_{aliph}), 2147 (NCS), 1683 (C=O) cm^{-1}; MS (IS): $m/z = 247$ $[M + 1]^+$.

*Methyl 3-(3-phenylureido)benzo[b]thiophene-2-carboxylate (**3a**, $C_{17}H_{14}N_2O_3S$)*

To a solution of **1** (0.1 g, 0.48 mmol) in 1.5 cm^3 dry toluene, 0.063 cm^3 phenyl isocyanate (0.58 mmol) was added dropwise and the mixture stirred under reflux for 24 h. After cooling, the white precipitate formed was collected by filtration, washed with toluene, and recrystallized to afford **3a** (0.130 g, 83%) as a white solid; mp 220–221 °C (ethanol); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 3.88$ (s, 3H, CH_3), 7.01 (t, 1H, $J_{6,5} = J_{6,7} = 8$ Hz, H-6), 7.28–7.34 (m, 2H, CH_{Ar}), 7.42–7.57 (m, 4H, H-5, CH_{Ar}), 7.94 (d, 1H, $J_{6,7} = 8$ Hz, H-7), 7.98 (d, 1H, $J_{4,5} = 8$ Hz, H-4), 9.13 (s, 1H, NH), 9.63 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 52.4$ (CH_3), 115.0, 118.3 (2×CH), 122.2, 122.9, 124.3, 126.0, 127.8, 128.9 (2×CH), 134.1, 138.0, 138.9, 139.5, 152.0 (C=O), 163.3 (COOR) ppm; IR (KBr): $\bar{\nu} = 3280$ (NH), 3060, 3038 (CH_{Ar}), 1713 (C=O), 1646 (C=O) cm^{-1}; MS (IS): $m/z = 327$ $[M + 1]^+$.

*Methyl 3-(2-fluorophenylureido)-benzo[b]thiophene-2-carboxylate (**3b**, $C_{17}H_{13}FN_2O_3S$)*

To a solution of **1** (0.5 g, 2.41 mmol) in 10 cm^3 dry toluene, 0.41 cm^3 2-fluorophenyl isocyanate (3.65 mmol) was added dropwise and the mixture stirred under reflux for 20 h. After cooling, the white precipitate formed was collected by filtration, washed with toluene and dichloromethane, then recrystallized to afford **3b** (0.57 g, 69%) as a white solid; mp 227–228 °C (ethanol); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 3.82$ (s, 3H, CH_3), 6.97–7.24 (m, 3H, CH_{Ar}), 7.39 (t, 1H, $J_{6,5} = J_{6,7} = 8$ Hz, H-6), 7.48 (t, 1H, $J_{5,4} = J_{5,6} = 8$ Hz, H-5), 7.84 (d, 1H, $J_{7,8} = 8$ Hz, H-7), 7.92 (d, 1H, $J_{4,5} = 8$ Hz, H-4), 8.06 (t, 1H, $J = 8$ Hz, CH_{Ar}), 9.35 (s, 1H, NH), 9.38 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 52.3$ (CH_3), 115.0, 116.4, 121.1, 122.9, 123.0, 124.4, 124.5, 125.4, 127.3, 127.7, 134.3, 137.8, 150.6, 151.9, 153.8 (C=O), 162.8 (COOR) ppm; IR (KBr): $\bar{\nu} = 3304$ (NH), 3064, 3038 (CH_{Ar}), 1710 (COOR), 1663 (C=O) cm^{-1}; MS (IS): $m/z = 345$ $[M + 1]^+$.

*Methyl 3-(3-phenylthioureido)benzo[b]thiophene-2-carboxylate (**3c**, $C_{17}H_{14}N_2O_2S_2$)*

To a solution of **2a** (0.1 g, 0.4 mmol) in 2 cm^3 dry toluene, 0.073 cm^3 aniline (0.8 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 12 h. The formed precipitate was collected by filtration, washed with diethyl ether to afford **3c** (0.093 g, 68%) as a white solid; mp 198–199 °C (ethanol); ^{1}H NMR (250 MHz, *DMSO*-d_6): $\delta = 3.86$ (s, 3H, CH_3), 7.16–7.58 (m, 7H, CH_{Ar}), 7.84 (d, 1H, $J_{4,5} = 6.7$ Hz, H-4), 8.01 (d, 1H, $J_{6,7} = 6.7$ Hz, H-7), 9.67 (s, 1H, NH), 10.18 (s, 1H, NH) ppm; ^{13}C NMR (62.5 MHz, *DMSO*-d_6): $\delta = 53.4$ (CH_3), 114.7, 123.5, 124.0, 124.5 (2×CH), 124.8, 127.6, 128.2, 128.5 (2×CH), 129.0, 135.8, 139.1, 140.5, 176.7 (C=O), 180.6 (C=S) ppm; IR (KBr): $\bar{\nu} = 3382$ (NH), 3082 (CH_{Ar}), 1695 (C=O) cm^{-1}; MS (IS): $m/z = 343$ $[M + 1]^+$.

*Methyl 3-(3-benzylthioureido)benzo[b]thiophene-2-carboxylate (**3d**, $C_{18}H_{16}N_2O_2S_2$)*

To a solution of **2a** (0.08 g, 0.32 mmol) in 2 cm^3 dry toluene, 0.035 cm^3 benzylamine (0.321 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 8 h. The formed precipitate was collected by filtration, washed with diethyl ether to afford **3d** (0.102 g, 89%) as a white solid; mp 195–196 °C (ethanol); ^{1}H NMR (250 MHz, *DMSO*-d_6): $\delta = 3.85$ (s, 3H, CH_3), 4.35 (d, 2H, $J = 5.7$ Hz, CH_2), 7.27–7.70 (m, 8H, CH_{Ar} and NH), 7.89 (d, 1H, $J_{7,6} = 8$ Hz, H-7), 7.89 (d, 1H, $J_{4,5} = 8$ Hz, H-4), 8.95 (s, 1H, NH) ppm; ^{13}C NMR (62.5 MHz, *DMSO*-d_6): $\delta = 43.0$ (CH_2), 52.2 (CH_3), 114.0, 122.8, 124.1, 126.0, 126.8, 127.1, 127.7, 128.3, 134.2, 138.0, 139.6, 139.8, 154.6 (C=O), 163.3 (C=S) ppm; IR (KBr): $\bar{\nu} = 3303$ (NH), 3024 (CH_{Ar}), 1677 (C=O) cm^{-1}; MS (IS): $m/z = 357$ $[M + 1]^+$.

*3-Phenyl-1H-benzo[4, 5]thieno[3,2-d]pyrimidin-2,4-dione (**4a**, $C_{16}H_{10}N_2O_2S$)*

A solution of 0.232 g potassium hydroxide (4.13 mmol) in 2.5 cm^3 ethanol was added dropwise to a solution of **3a** (0.45 g, 1.379 mmol) in 5 cm^3 ethanol, and the mixture was stirred at room temperature for 68 h. After removal of the solvent by evaporation in vacuo, the obtained residue was dissolved in water then acidified with 0.46 cm^3 35% HCl (5.19 mmol). The formed precipitate was collected by filtration, recrystallized from ethanol to afford **4a** (0.404 g, 94%) as a white solid; mp >295 °C (decomp.); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 7.35$–7.70 (m, 7H, CH_{Ar}), 8.12 (d, 1H, $J_{6,7} = 8.0$ Hz, H-7), 8.45 (d, 1H, $J_{4,5} = 8.0$ Hz, H-4), 12.68 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 109.9$, 123.3, 124.1, 125.5, 128.3 (3×CH), 128.5 (2×CH), 128.9, 129.2, 135.7, 140.3, 140.5, 151.7, 159.2 (C=O) ppm; IR (KBr): $\bar{\nu} = 3197$ (NH), 1716 (C=O), 1647 (C=O) cm^{-1}; MS (IS): $m/z = 295$ $[M + 1]^+$.

*3-(2-Fluorophenyl)-1H-benzo[4,5]thieno[3,2-d]pyrimidin-2,4-dione (**4b**, $C_{16}H_9FN_2O_2S$)*

A solution of 0.196 g potassium hydroxide (3.49 mmol) in 2 cm^3 ethanol was added dropwise to a solution of **3b** (0.4 g, 1.162 mmol) in 4 cm^3 ethanol, and the mixture was stirred at room temperature for 49 h. After removal of the solvent by evaporation in vacuo, the obtained residue was dissolved in water, then acidified with 0.3 cm^3 35% HCl (3.49 mmol). The formed precipitate was collected by filtration, recrystallized from ethanol to afford **4b** (0.353 g, 92%) as a white solid; mp >305 °C (decomp.); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 7.33$–7.70 (m, 6H, CH_{Ar}), 8.14 (d, 1H, $J_{6,7} = 8.0$ Hz, H-7), 8.46 (d, 1H, $J_{4,5} = 8.0$ Hz,

H-4), 12.88 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 109.5$, 116.0, 116.2, 123.7, 124.2, 124.9, 125.6, 128.4, 129.4, 130.9, 131.5 (2×CH), 140.5, 140.9, 151.0, 158.5 (C=O) ppm; IR (KBr): $\bar{\nu} = 3299$ (NH), 3062 (CH_{Ar}), 1710 (C=O), 1663 (C=O) cm^{-1}; MS (IS): $m/z = 313$ $[M + 1]^+$.

*3-Phenyl-2-thioxo-1H-benzo[4,5]thieno[3,2-d]pyrimidin-4-one (**4c**, $C_{16}H_{10}N_2OS_2$)*

To a solution of **2a** (0.06 g, 0.24 mmol) in 1 cm^3 dry toluene and 0.039 cm^3 pyridine (0.48 mmol) was added 0.044 cm^3 aniline (0.482 mmol), and the mixture was stirred at room temperature for 36 h. The precipitate formed during the reaction was collected by filtration, washed with toluene, and recrystallized from a methanol/acetone mixture to afford **4c** (0.06 g, 80%) as a pale pink solid; mp >145 °C (decomp.); ^{1}H NMR (250 MHz, *DMSO*-d_6): $\delta = 7.09$–7.15 (m, 1H, CH_{Ar}), 7.29–7.36 (m, 4H, CH_{Ar}), 7.47–7.50 (m, 4H, CH_{Ar}), 9.82 (s, 1H, NH) ppm; ^{13}C NMR (62.5 MHz, *DMSO*-d_6): $\delta = 112.3$, 122.7, 122.8, 124.2, 125.6, 126.2, 127.1, 127.7, 128.1 (2×CH), 130.0, 132.8, 136.5, 139.5, 157.3 (C=O), 176.1 (C=S) ppm; IR (KBr): $\bar{\nu} = 3216$ (NH), 3042 (CH_{Ar}), 1699 (C=O) cm^{-1}; MS (IS): $m/z = 311$ $[M + 1]^+$.

*3-Benzyl-2-thioxo-1H-benzo[4,5]thieno[3,2-d]pyrimidin-4-one (**4d**, $C_{17}H_{12}N_2OS_2$)*

To a solution of **2a** (0.080 g, 0.32 mmol) in 1.3 cm^3 dry toluene and 0.050 cm^3 pyridine (0.62 mmol) was added 0.068 cm^3 benzylamine (0.618 mmol), and the mixture was stirred at room temperature for 20 h. After cooling to room temperature, the precipitate formed during the reaction was collected by filtration, washed with toluene, and recrystallized from a methanol/acetone mixture to afford **4d** (0.084 g, 81%) as white needles; mp >265 °C (decomp.); ^{1}H NMR (250 MHz, *DMSO*-d_6): $\delta = 5.79$ (s, 1H, CH_2), 7.17–7.44 (m, 6H, CH_{Ar}, NH), 7.52 (ft, 1H, $J_{7,8} = J_{7,6} = 7.6$ Hz, H-7), 7.60 (ft, 1H, $J_{8,7} = J_{8,9} = 7.6$ Hz, H-8), 8.04 (d, 1H, $J_{6,7} = 7.6$ Hz, H-6), 8.41 (d, 1H, $J_{9,8} = 7.6$ Hz, H-9) ppm; ^{13}C NMR (62.5 MHz, *DMSO*-d_6): $\delta = 49.3$ (CH_2), 113.4, 123.9, 125.3 (2×CH), 126.8 (2×CH), 127.4, 128.2, 128.7, 129.0, 131.1, 134.0, 137.7, 140.7, 158.4 (C=O), 177.3 (C=S) ppm; IR (KBr): $\bar{\nu} = 3205$ (NH), 3042 (CH_{Ar}), 1698 (C=O), 1287 (C=S) cm^{-1}; MS (IS): $m/z = 325.5$ $[M + 1]^+$.

*3-Benzyl-2-thioxo-2,3-dihydro-1H-quinazolin-4-one (**5**, $C_{15}H_{12}N_2OS$)*

To a solution of **2b** (2.3 g, 11.90 mmol) in 30 cm^3 dry toluene and 1.86 cm^3 pyridine (22.97 mmol) was added 2.51 cm^3 benzylamine (22.97 mmol), and the mixture was stirred at room temperature for 20 h. After partial removal of the solvent by evaporation in vacuo, the precipitate was collected by filtration, washed with ethanol to afford **5** (3.122 g, 98%) as a white solid; mp 244–245 °C (*DMF*); ^{1}H NMR (250 MHz, *DMSO*-d_6): $\delta = 5.67$ (s, 2H, CH_2), 7.19–7.37 (m, 6H, CH_{Ar}), 7.42 (d, 1H, $J_{8,7} = 8$ Hz, H-8), 7.76 (t, 1H, $J_{7,6} = J_{7,8} = 8$ Hz, H-7), 7.95 (d, 1H, $J_{5,4} = 8$ Hz, H-5), 13.04 (br.s, 1H, NH) ppm; ^{13}C NMR (62.5 MHz, *DMSO*-d_6): $\delta = 48.6$ (CH_2), 115.3, 115.6, 124.5, 126.8, 127.0 (2×CH), 127.2, 128.1 (2×CH), 135.5, 136.5, 139.0, 159.3 (C=O), 175.4 (C=S) ppm; IR (KBr): $\bar{\nu} = 3206$ (NH), 3042 (CH_{Ar}), 1688 (C=O), 1291 (C=S) cm^{-1}; MS (IS): $m/z = 269$ $[M + 1]^+$.

*6-Benzyl-7-thioxo-1,6,7,8-tetrahydro-1,6,8-triaza-cyclopenta[b]naphthalen-5-one (**6**, $C_{17}H_{13}N_3OS$)*

To a solution of **2c** (0.08 g, 0.325 mmol) in 1.3 cm^3 dry toluene and 0.05 cm^3 pyridine (0.63 mmol) was added 0.068 cm^3 benzylamine (0.627 mmol), and the mixture was stirred at room temperature for 8 h. After solvent removal by evaporation in vacuo, the obtained residue was purified by flash chromatography (eluent: PE/EA:4/6, *v*/*v*; $R_f = 0.41$) to afford **6** (0.073 g, 72%) as a yellow solid; mp >253 °C (decomp.) (diethyl ether); ^{1}H NMR (250 MHz, *DMSO*-d_6): $\delta = 5.71$ (s, 2H, CH_2), 6.63 (s, 1H, H-6), 7.22–7.35 (m, 5H, CH_{Ar}), 7.45 (s, 1H, H-7), 7.55 (s, 1H, H-9), 8.26 (s, 1H, H-5), 11.56 (s, 1H, NH), 12.91 (s, 1H, NH) ppm; ^{13}C NMR (62.5 MHz, *DMSO*-d_6): $\delta = 48.4$ (CH_2), 95.9, 102.5, 108.9, 119.8, 126.2, 126.7, 127.0 (2×CH), 128.1 (2×CH), 129.0, 133.7, 137.1, 140.1, 160.1 (C=O), 174.1 (C=S) ppm; IR (KBr): $\bar{\nu} = 3056$ (CH_{Ar}) cm^{-1}; MS (IS): $m/z = 308$ $[M + 1]^+$.

*1-Deoxy-1-iodo-2,3:4,6-di-O-isopropylidene-α-L-sorbofuranose (**8**, $C_{12}H_{19}IO_5$)*

2,3:4,6-Di-*O*-isopropylidene-α-L-sorbofuranose **7** (2 g, 7.7 mmol) was dissolved in 52 cm^3 dry toluene. Imidazole (1.57 g, 23.1 mmol), triphenylphosphine (6.25 g, 23.87 mmol), and iodine (2 g, 7.87 mmol) were then added, and the mixture was stirred under reflux for 18 h. After cooling to room temperature, the mixture was diluted with EA, the organic layer was washed with water, dried over $MgSO_4$, and after filtration, the solvent was removed by evaporation in vacuo. The obtained residue was purified by flash chromatography (eluent: PE/EA:9/1, *v*/*v*; $R_f = 0.24$) to afford **8** (1.16 g, 88%) as a yellowish syrup [50]; $[\alpha]_D^{20} = -109°$ g^{-1} cm^3 dm^{-1} ($c = 1$, methanol); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.35$, 1.39, 1.43, 1.46 (4 s, 12H, CH_3), 3.51 (d, 1H, $J_{1a,1b} = 10.6$ Hz, H-1a), 3,62 (d, 1H, $J_{1b,1a} = 10.8$ Hz, H-1b), 3.96 (dd, 1H, $J_{6a,5} = 1.2$ Hz, $J_{6a,6b} = 13.4$ Hz, H-6$_a$,), 3.99 (dd, 1H, $J_{6b,5} = 2.4$ Hz, $J_{6a,6b} = 13.4$ Hz, H-6$_b$,), 4.13 (d, 1H, $J_{5,4} = 2$ Hz, H-5), 4.30 (d, 1H, $J_{4,5} = 2$ Hz, H-4), 4.45 (s, 1H, H-3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 6.8$ (C-1), 18.6, 26.7, 27.6, 28.7 (CH_3), 60.4 (C-6), 73.0 (C-4), 73.4 (C-5), 85.5 (C-3), 97.3 (C-2), 112.5, 112.6 ($C(CH_3)_2$) ppm; MS (IS): $m/z = 371$ $[M + 1]^+$.

*1-Deoxy-1-azido-2,3:4,6-di-O-isopropylidene-α-L-sorbofuranose (**9**, $C_{12}H_{19}N_3O_5$)*

Sodium azide (1.51 g, 23.23 mmol) was added to a solution of **8** (1.72 g, 4.65 mmol) in 8 cm^3 *DMSO*, and the mixture was stirred at 100 °C for 24 h. After cooling to room temperature, the mixture was diluted with EA, and the organic layer was washed with water, then dried over $MgSO_4$. After filtration the solvent was removed by evaporation in vacuo. The obtained residue was purified by flash chromatography (eluent: PE/EA:9/1, *v*/*v*; $R_f = 0.24$) to afford **9** (1.16 g, 88%) as a colorless syrup, which crystallized on standing [40]; mp 55–56 °C; $[\alpha]_D^{20} = -56°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, methanol); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.36$, 1.42, 1.46, 1.52 (4 s, 12H, CH_3), 3.40 (d, 1H, $J_{1a,1b} = 13.1$ Hz, H-1a), 3.71 (d, 1H, $J_{1b,1a} = 13.1$ Hz, H-1b), 3.97-4.04 (m, 2H, H-6a, H-6b), 4.12–4.16 (m, 1H, H-5), 4.33 (d, 1H, $J_{4,5} = 2.1$ Hz, H-4), 4.41 (s, 1H, H-3) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 18.7$, 26.2, 27.6, 28.9 (CH_3), 53.4 (C-1), 60.4 (C-6), 72.8 (C-4), 73.1 (C-5), 84.6 (C-3), 97.4 (C-2), 112.9, 114.1 ($C(CH_3)_2$) ppm; IR (KBr): $\bar{\nu} = 2098$ (N_3) cm^{-1}; MS (IS): $m/z = 286\ [M + 1]^+$.

*1-Deoxy-1-isothiocyanato-2,3:4,6-di-O-isopropylidene-α-L-sorbofuranose (**10**, $C_{13}H_{19}NO_5S$)*

To a solution of **9** (0.2 g, 0.7 mmol) in 12 cm^3 dry 1,4-dioxane was added carbon disulfide (0.81 cm^3, 13.32 mmol), then triphenylphosphine (0.194 g, 0.74 mmol). The mixture was stirred for 5 h at room temperature, then 27 h at 50 °C. After removal of the solvent by evaporation in vacuo, the obtained residue was purified by flash chromatography (eluent: PE/EA:9/1, *v*/*v*; $R_f = 0.24$) to afford **10** (0.188 g, 89%) as a colorless oil; $[\alpha]_D^{20} = -6°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, methanol); ^{1}H NMR (250 MHz, *DMSO*-d_6): $\delta = 1.28$, 1.35, 1.39, 1.44 (4 s, 12H, CH_3), 3.81 (d, 1H, $J_{6b,6a} = 13.1$ Hz, H-6b), 3.96 (d, 1H, $J_{1b,1a} = 14.9$ Hz, H-1b), 4.01-4.07 (m, 1H, H-6a), 4.07 (s, 1H, H-5), 4.16 (d, 1H, $J_{1a,1b} = 14.9$ Hz, H-1a), 4.38 (s, 2H, H-4, H-3) ppm; ^{13}C NMR (62.5 MHz, *DMSO*-d_6): $\delta = 18.6$, 26.5, 27.2, 28.9 (CH_3), 48.5 (C-1), 59.3 (C-6), 72.3 (C-4), 72.7 (C-5), 84.4 (C-3), 96.9 (C-2), 111.6, 112.4 ($C(CH_3)_2$), 128.9 (C=S) ppm; IR (NaCl): $\bar{\nu} = 2178$ (NCS) cm^{-1}; MS (IS): $m/z = 302\ [M + 1]^+$.

*N-(1-deoxy-2,3:4,6-di-O-isopropylidene-α-L-sorbofuranosyl)-N′-benzylthiourea (**11a**, $C_{20}H_{28}N_2O_5S$)*

To a solution of **10** (0.08 g, 0.26 mmol) in 1 cm^3 dry toluene containing pyridine (0.045 cm^3, 0.53 mmol) was added 0.058 cm^3 benzylamine (0.53 mmol). After stirring the mixture at 50 °C for 18 h, the solvent was removed by evaporation in vacuo. The obtained residue was purified by flash chromatography (eluent: PE/EA:7/3, *v*/*v*; $R_f = 0.26$) to afford **11a** (0.078 g, 90%) as a white solid; mp 76–78 °C (diethyl ether); $[\alpha]_D^{20} = -36°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, methanol); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.20$, 1.26, 1.32, 1.38 (4 s, 12H, CH_3), 3.57–3.65 (m, 1H, H-1b), 3.78 (d, 1H, $J_{6a,6b} = 13.3$ Hz, H-6a), 3.94 (d, 1H, $J_{6b,6a} = 13.3$ Hz, H-6b), 3.97 (s, 1H, H-5), 4.21 (s, 1H, H-4), 4.29 (dd, 1H, $J_{1a,1b} = 14.4$ Hz, $J_{1a,NH} = 7.2$ Hz, H-1a), 4.35 (s, 1H, H-3), 4.60–4.80 (m 2H, CH_2-Ph), 6.54 (bs, 1H, NH), 6.77 (bs, 1H, NH), 7.16–7.26 (m, 5H, CH_{Ar}) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 18.6$, 26.3, 27.2, 29.0 (CH_3), 48.9 (C-1), 49.3 (CH_2), 60.2 (C-6), 72.5 (C-4), 73.3 (C-5), 84.9 (C-3), 97.7 (C-2), 113.6 (2×C), 127.6, 128.1 (2×CH), 128.6 (2×CH), 137.6, 183.4 (C=S) ppm; IR (KBr): $\bar{\nu} = 3334$ (NH), 2990, 2933 (CH_{Ar}) $cm^{-1;}$ MS (IS): $m/z = 409.5\ [M + 1]^+$.

*N-(1-deoxy-2,3:4,6-di-O-isopropylidene-α-L-sorbofuranosyl)-N′-phenylthiourea (**11b**, $C_{19}H_{26}N_2O_5S$)*

To a solution of **10** (0.058 g, 0.2 mmol) in 0.8 cm^3 dry toluene containing pyridine (0.033 cm^3, 0.4 mmol) was added 0.036 cm^3 aniline (0.4 mmol). After stirring the mixture at 50 °C for 24 h, the solvent was removed by evaporation in vacuo. The obtained residue was purified by flash chromatography (eluent: PE/AE:7/3, *v*/*v*; $R_f = 0.2$) to afford **11b** (0.054 g, 81%) as white solid; mp 78–80 °C (diethyl ether); $[\alpha]_D^{20} = -58°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, methanol); ^{1}H NMR (250 MHz, *DMSO*-d_6): $\delta = 1.24$, 1.35, 1.38, 1.42 (4 s, 12H, CH_3), 3.82–3.91 (m, 2H, H-1), 3.99 (s, 1H, H-5), 4.04–4.20 (m, 2H, H-6), 4.26 (s, 1H, H-4), 4.59 (s, 1H, H-3), 7.09 (t, 1H, $J = 7.7$ Hz, CH_{Ar}), 7.30 (t, 2H, $J = 7.7$ Hz, CH_{Ar}), 7.49 (d, 2H, $J = 7.7$ Hz, CH_{Ar}), 7.53 (bs, 1H, NH), 9.69 (bs, 1H, N'H) ppm; ^{13}C NMR (62.5 MHz, *DMSO*-d_6): $\delta = 18.8$, 26.5, 27.0, 28.8 (CH_3), 47.8 (C-1), 59.3 (C-6), 71.5 (C-4), 73.0 (C-5), 84.6 (C-3), 96.9 (C-2), 110.8, 113.3 (2×C), 122.9, 124.1, 128.4 (2×CH), 139.5, 181.0 (C=S) ppm; IR (KBr): $\bar{\nu} = 3302$ (NH), 2990, 2934 (CH_{Ar}) cm^{-1}; MS (IS): $m/z = 395.5\ [M + 1]^+$.

*N-(1-deoxy-2,3:4,6-di-O-isopropylidene-α-L-sorbofuranosyl)-N′-(2-methoxycarbonylphenyl)thiourea (**11c**, $C_{21}H_{28}N_2O_7S$)*

To a solution of **10** (0.060 g, 0.2 mmol) in 0.8 cm^3 dry toluene containing pyridine (0.033 cm^3, 0.4 mmol) was added methyl anthranilate (0.052 cm^3, 0.4 mmol). After stirring the mixture at 50 °C for 24 h, the solvent was removed by evaporation in vacuo. The obtained residue was purified by flash chromatography (eluent: PE/EA:7/3, *v*/*v*; $R_f = 0.26$) to afford **11c** (0.066 g, 73%) as a white solid; mp 77–79 °C (diethyl ether); ^{1}H NMR (250 MHz, *DMSO*-d_6): $\delta = 1.28$, 1.35, 1.38, 1.42 (4 s, 12H, CH_3), 3.75 (s, 3H, OCH_3), 3.82–3.91 (m, 2H, H-1a, H-1b), 3.99 (s, 1H, H-5), 4.04–4.20 (m, 2H, H-6a, H-6b), 4.29 (s, 1H, H-4), 4.64 (s, 1H, H-3), 7.19 (t, 1H, $J = 7.6$ Hz, CH_{Ar}), 7.30 (t, 1H, $J = 7.6$ Hz, CH_{Ar}), 7.82 (t, 1H, $J = 7.6$ Hz, CH_{Ar}), 7.98 (d, 1H, $J = 7.6$ Hz, CH_{Ar}), 8.61 (bs, 1H, NH),

9.94 (s, 1H, N′H) ppm; ^{13}C NMR (62.5 MHz, *DMSO*-d_6): δ = 18.8, 26.5, 27.0, 28.8 (CH_3), 47.9 (C-1), 52.3 (OCH_3), 59.4 (C-6), 71.6 (C-5), 72.9 (C-4), 84.6 (C-3), 96.8 (C-2), 111.0, 113.4 (2×C), 123.8, 126.5, 130.0, 132.2, 140.3, 166.7 (C=S), 180.7 (C=O) ppm; IR (KBr): $\bar{\nu}$ = 3312 (NH), 2990, 2935 (CH_{Ar}) cm^{-1}; MS (IS): *m/z* = 453.5 $[M + 1]^+$.

*N-(1-deoxy-2,3,4,6-di-O-isopropylidene-α-L-sorbofuranosyl)-N′-(3-(2-methoxycarbonyl)benzo[b]thiophenyl) thiourea (**11d**, $C_{23}H_{28}N_2O_7S_2$)*

Method A: Compound **1** (0.096 g, 0.46 mmol) was added to a solution of **10** (0.07 g, 0.23 mmol) in 0.9 cm^3 dry toluene containing pyridine (0.038 cm^3, 0.46 mmol). After stirring the mixture at 50 °C for 72 h, the solvent was removed by evaporation in vacuo. The obtained residue was purified by flash chromatography (eluent: PE/EA:6/4, *v/v*; R_f = 0.33) to afford **11d** (0.011 g, 14%) as a white solid.

Method B: **12** (0.1 g, 0.35 mmol; see preparation below) was dissolved in 4 cm^3 dry *THF*, and triphenylphosphine (0.101 g, 0.39 mmol) was added. The mixture was stirred at room temperature for 45 min, then **2a** (0.102 g, 0.407 mmol) was added. After stirring the mixture at 40 °C for 24 h, the solvent was removed by evaporation in vacuo. The obtained residue was purified by silica gel column chromatography (eluent: PE/EA:8/2 → 7/3, *v/v*) to afford **11d** (0.145 g, 82%) as a colorless syrup, which crystallized on standing; mp 108–110 °C (ethanol); $[\alpha]_D^{20}$ = −63° g^{-1} cm^3 dm^{-1} (*c* = 1, MeOH); ^{1}H NMR (250 MHz, *DMSO*-d_6): δ = 1.24, 1.38, 1.40, 1.44 (4 s, 12H, CH_3), 3.90−4.12 (m, 5H, H-1a, H-1b, H-5, H-6a, H-6b), 4.32 (s, 1H, H-4), 4.69 (s, 1H, H-3), 7.39-7.54 (m, 2H, CH_{Ar}), 7.84 (d, 1H, *J* = 7.8 Hz, CH_{Ar}), 7.98 (d, 1H, *J* = 7.8 Hz, CH_{Ar}), 8.28 (bs, 1H, NH), 9.63 (s, 1H, NH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 18.7, 26.3, 27.1, 29.2 (CH_3), 45.1 (C-1), 52.2 (OCH_3), 60.3 (C-6), 72.0 (C-5), 74.0 (C-4), 85.6 (C-3), 97.8 (C-2), 111.6, 112.5, 113.7, 122.4, 124.1, 127.1, 127.7, 133.5, 139.3, 141.5, 155.0 (C=S), 165.0 (C=O) ppm; IR (KBr): $\bar{\nu}$ = 3331 (NH), 1700 (C=O) cm^{-1}; MS (IS): *m/z* = 509.6 $[M + 1]^+$.

*1-Deoxy-1-amino-2,3:4,6-di-O-isopropylidene-α-L-sorbofuranose (**12**, $C_{12}H_{21}NO_5$)*

To a solution of **9** (0.202 g, 0.71 mmol) in 4 cm^3 *THF* containing 0.44 cm^3 water, triphenylphosphine (0.186 g, 0.71 mmol) was added, and the reaction mixture was stirred at 50 °C for 28 h. The crude material obtained after evaporation was purified by flash chromatography (PE/EA:3/7, *v/v*; R_f = 0.13) to afford **12** (0.16 g, 90%) in the form of needles [51]; mp 78–79 °C (diethyl ether); $[\alpha]_D^{20}$ = −41° g^{-1} cm^3 dm^{-1} (*c* = 1, methanol); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.36, 1.37, 1.44, 1.50 (4 s, 12H, CH_3), 3.07 (br s, 2H, NH_2), 3.40 (d, 1H, $J_{1a,1b}$ = 13.1 Hz, H-1a), 3.71 (d, 1H, H-1b), 3.97–4.04 (m, 2H, H-6a, H-6b), 4.12–4.16 (m, 1H, H-5), 4.33 (d, 1H, $J_{4,3}$ = 2.1 Hz, H-4), 4.41 (s, 1H, H-3) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 18.6, 26.6, 27.4, 28.9 (CH_3), 47.1 (C-1), 60.3 (C-6), 72.0 (C-4), 73.4 (C-5), 85.2 (C-3), 97.3 (C-2), 111.2, 115.4 ($C(CH_3)_2$) ppm; IR (KBr): $\bar{\nu}$ = 3368 (NH_2) cm^{-1}; MS (IS): *m/z* = 260 $[M + 1]^+$.

*3-Benzyl-2-benzylsulfanyl-3H-benzo[4,5]thieno[3,2-d]pyrimidin-4-one (**13**, $C_{24}H_{18}N_2OS_2$)*

To a solution of **4d** (0.212 g, 0.65 mmol) in 6.4 cm^3 DMF were added sodium hydride (0.039 g, 0.98 mmol) and 0.079 cm^3 benzyl bromide (0.666 mmol). The reaction mixture was stirred at 0 °C for 3 h, then diluted with dichloromethane and water. The organic layer was collected, washed with water, brine, then dried over $MgSO_4$, and after filtration the solvent was removed by evaporation in vacuo. The resulting residue was purified by flash chromatography (eluent: PE/EA:9/1, *v/v*; R_f = 0.32) to afford **13** (0.253 g, 94%) as a white solid; mp 175–176 °C (ethanol); ^{1}H NMR (250 MHz, *DMSO*-d_6): δ = 4.65 (s, 2H, SCH_2), 5.38 (s, 2H, NCH_2), 7.23–7.33 (m, 8H, CH_{Ar}), 7.49–7.52 (m, 2H, CH_{Ar}), 7.60–7.72 (m, 2H, CH_{Ar}), 8.16 (d, 1H, $J_{6,7}$ = 7.5 Hz, H-6), 8.37 (d, 1H, $J_{9,8}$ = 7.5 Hz, H-9) ppm; ^{13}C NMR (62.5 MHz, *DMSO*-d_6): δ = 34.7 (SCH_2), 45.5 (NCH_2), 122.0, 122.6, 124.3, 125.3 (2×CH), 126.0 (2×CH), 126.1, 127.0 (2×CH), 127.8 (2×CH), 128.0 (2×CH), 132.0, 133.7, 135.2, 139.3, 149.5 (C=O), 156.5 (C–S), 158.2 (N–C=N) ppm; IR (KBr): $\bar{\nu}$ = 3024 (CH_{Ar}), 1677 (C=O) cm^{-1}; MS (IS): *m/z* = 415.5 $[M + 1]^+$.

*3-Benzyl-2-benzylsulfanyl-3H-quinazolin-4-one (**14**, $C_{22}H_{18}N_2OS$)*

To a solution of **5** (0.5 g, 1.86 mmol) in 15 cm^3 DMF were added sodium hydride (0.116 g, 2.88 mmol) and 0.27 cm^3 benzyl bromide (2.23 mmol). The reaction mixture was stirred at 0 °C for 3 h, then diluted with EA and water. The organic layer was separated, washed with water, then brine, then dried over $MgSO_4$. After filtration the solvent was removed by evaporation in vacuo. The obtained residue was purified by flash chromatography (eluent: PE/AE:9/1, *v/v*; R_f = 0.38) to afford **14** (0.639 g, 96%) as a white solid; mp 105–106 °C (ethanol); ^{1}H NMR (250 MHz, *DMSO*-d_6): δ = 4.52 (s, 2H, SCH_2), 5.30 (s, 2H, NCH_2), 7.19–7.34 (m, 8H, CH_{Ar}), 7.44–7.51 (m, 3H, CH_{Ar}), 7.65 (d, 1H, $J_{8,9}$ = 8 Hz, H-8), 7.83 (t, 1H, $J_{7,6}$ = $J_{7,8}$ = 8 Hz, H-7), 8.11 (dd, 1H, $J_{5,6}$ = 8 Hz, $J_{5,7}$ = 1.3 Hz, H-5) ppm; ^{13}C NMR (62.5 MHz, *DMSO*-d_6): δ = 35.6 (SCH_2), 46.7 (NCH_2), 118.7, 125.9, 126.0, 126.5 (2×CH), 126.6 (2×CH), 127.3 (2×CH), 128.3 (2×CH), 128.5 (2×CH), 129.2, 134.9, 135.5, 136.5, 146.7, 156.4 (C=O), 160.8

(N–C=N) ppm; IR (KBr): $\bar{\nu} = 3056$ (CH_{Ar}) cm^{-1}; MS (IS): $m/z = 359.5$ $[M + 1]^+$.

*1,6-Dibenzyl-7-benzylsulfanyl-1,6-dihydro-1,6,8-triaza-cyclopenta[b]naphthalen-5-one (**15**, $C_{31}H_{25}N_3OS$)*

To a solution of **6** (0.197 g, 0.64 mmol) in 6 cm^3 DMF were added sodium hydride (0.051 g, 1.28 mmol) and 0.153 cm^3 benzyl bromide (1.28 mmol). The reaction mixture was stirred at 0 °C for 3 h, then diluted with EA and water. The organic layer was separated, washed with water, brine, then dried over $MgSO_4$. After filtration, the solvent was removed by evaporation in vacuo. The obtained residue was purified by flash chromatography (eluent: PE/EA:8/2, *v*/*v*; $R_f = 0.41$) to afford **15** (0.193 g, 62%) as a white solid; mp 136–137 °C (ethanol); ^{1}H NMR (250 MHz, *DMSO*-d_6): $\delta = 4.50$ (s, 2H, SCH_2), 5.30 (s, 2H, NCH_2), 5.57 (s, 2H, NCH_2), 6.75 (d, 1H, $J_{3,2} = 3.2$ Hz, H-3), 7.17–7.36 (m, 13H, CH_{Ar}), 7.45 (d, 2H, $J = 7.5$ Hz, CH_{Ar}), 7.69 (s, 1H, H-9), 7.77 (d, 1H, $J_{2,3} = 3.2$ Hz, H-2), 8.41 (s, 1H, H-4) ppm; ^{13}C NMR (62.5 MHz, *DMSO*-d_6): $\delta = 35.5$ (SCH_2), 46.2 (NCH_2), 49.2 (NCH_2), 102.4, 105.0, 112.3, 119.1, 126.5 (2×CH), 126.9 (2×CH), 127.1, 127.2, 127.4, 127.9, 128.3 (2×CH), 128.4 (2×CH), 128.5 (2×CH), 129.3 (2×CH), 133.1, 136.2, 136.6, 137.7, 140.1, 141.4, 152.7 (C=O), 161.6 (N–C=N) ppm; IR (KBr): $\bar{\nu} = 3056$ (CH_{Ar}), 1655 (C=O) cm^{-1}; MS (IS): $m/z = 488.5$ $[M + 1]^+$.

*3-Benzyl-2-(4-methoxyphenyl)-3H-benzo[4,5]thieno [3,2-d]pyrimidin-4-one (**16**, $C_{24}H_{18}N_2O_2S$)*

To a solution of **13** (0.1 g, 0.24 mmol) in 10 cm^3 dry THF, copper methylsalicylate (0.114 g, 0.53 mmol) and *p*-methoxyphenylboronic acid (0.081 g, 0.53 mmol) were added. After stirring at room temperature for 10 min, tetrakis(triphenylphosphine) palladium (0.014 g, 0.012 mmol) was added, then the suspension was stirred under reflux for 42 h. The reaction mixture was diluted with dichloromethane, washed with a saturated aqueous solution of Na_2CO_3 then brine and finally dried over $MgSO_4$. After filtration, the solvent was removed by evaporation in vacuo. The obtained residue was purified by flash chromatography (eluent: PE/EA:8/2, *v*/*v*; $R_f = 0.35$) to afford **16** (0.063 g, 66%) as a white solid; mp 173–174 °C (ethanol); ^{1}H NMR (250 MHz, *DMSO*-d_6): $\delta = 3.81$ (s, 3H, OCH_3), 5.30 (s, 2H, CH_2), 6.96–7.03 (m, 4H, CH_{Ar}), 7.20–7.28 (m, 3H, CH_{Ar}), 7.47–7.50 (m, 2H, C_{Ar}), 7.56–7.72 (m, 2H, CH_{Ar}), 8.19 (d, 1H, $J_{6,7} = 8$ Hz, H-6), 8.24 (d, 1H, $J_{9,8} = 8$ Hz, H-9) ppm; ^{13}C NMR (62.5 MHz, *DMSO*-d_6): $\delta = 48.6$ (CH_2), 55.3 (CH_3), 113.6 (2×CH), 120.9, 123.3, 123.9, 125.5, 126.1 (2×CH), 127.1 (2×CH), 128.4 (2×CH), 129.2, 129.8 (2xCH), 134.0, 136.5, 140.6, 151.2, 158.1, 158.5 (C=O), 160.3 (N–C=N) ppm; IR (KBr): $\bar{\nu} = 3056$ (CH_{Ar}), 1682 (C=O) cm^{-1}; MS (IS): $m/z = 399.5$ $[M + 1]^+$.

*3-Benzyl-2-(4-methoxyphenyl)-3H-quinazolin-4-one (**17**, $C_{22}H_{18}N_2O_2$)*

To a solution of **14** (0.25 g, 0.7 mmol) in 10 cm^3 dry THF, copper methylsalicylate (0.33 g, 1.53 mmol) and *p*-methoxyphenylboronic acid (0.233 g, 1.53 mmol) were added. After stirring at room temperature for 10 min, tetrakis(triphenylphosphine) palladium (0.040 g, 0.035 mmol) was added, then the suspension was stirred under reflux for 18 h. The reaction mixture was diluted with dichloromethane and washed with a saturated aqueous solution of Na_2CO_3, then brine, and finally dried over $MgSO_4$. After filtration, the solvent was removed by evaporation in vacuo. The obtained residue was purified by flash chromatography (eluent: PE/EA:6/4, *v*/*v*; $R_f = 0.58$) to afford **17** (0.181 g, 76%) as a yellow solid; mp 100–101 °C (ethanol); ^{1}H NMR (250 MHz, *DMSO*-d_6): $\delta = 3.79$ (s, 3H, OCH_3), 5.22 (s, 2H, CH_2), 6.93–7.00 (m, 4H, CH_{Ar}), 7.19–7.31 (m, 3H, CH_{Ar}), 7.40–7.44 (m, 2H, CH_{Ar}), 7.57 (t, 1H, $J_{6,5} = J_{6,7} = 8$ Hz, H-6), 7.70 (d, 1H, $J_{8,7} = 8$ Hz, H-8), 7.86 (t, 1H, $J_{7,6} = J_{7,8} = 8$ Hz, H-7), 8.19 (d, 1H, $J_{5,6} = 8$ Hz, H-5) ppm; ^{13}C NMR (62.5 MHz, *DMSO*-d_6), $\delta = 48.3$ (CH_2), 55.2 (OCH_3), 113.5 (2×CH), 120.1, 126.1 (2×CH), 126.3, 127.0 (2×CH), 127.2, 127.4, 128.4 (2×CH), 129.6 (2×CH), 134.6, 136.8, 146.9, 156.0, 160.1 (C=O), 161.4 (N–C=N) ppm; IR (KBr): $\bar{\nu} = 3056$ (CH_{Ar}), 1683 (C=O) cm^{-1}; MS (IS): $m/z = 343$ $[M + 1]^+$.

*1,6-Dibenzyl-7-(4-methoxyphenyl)-1,6-dihydro-1,6,8-triaza-cyclopenta[b]naphthalen-5-one (**18**, $C_{31}H_{25}N_3O_2$)*

To a solution of **15** (0.107 g, 0.22 mmol) in 10 cm^3 dry THF, copper methylsalicylate (0.104 g, 0.48 mmol) and *p*-methoxyphenylboronic acid (0.074 g, 0.48 mmol) were added. After stirring at room temperature for 15 min, tetrakis(triphenylphosphine) palladium (0.013 g, 0.011 mmol) was added, then the suspension was stirred under reflux for 24 h. The reaction mixture was diluted with dichloromethane and washed with a saturated aqueous solution of Na_2CO_3, then brine, and finally dried over $MgSO_4$. After filtration, the solvent was removed in vacuo. The obtained residue was purified by flash chromatography (eluent: PE/EA:7/3, *v*/*v*; $R_f = 0.29$) to afford **18** (0.085 g, 82%) of as a pale yellow solid; mp 196–197 °C (ethanol); ^{1}H NMR (250 MHz, *DMSO*-d_6): $\delta = 3.78$ (s, 3H, OCH_3), 5.22 (s, 2H, CH_2), 5.53 (s, 2H, CH_2), 6.78 (d, 1H, $J_{3,2} = 3$ Hz, H-3), 6.90-6.96 (m, 4H, CH_{Ar}), 7.17–7.31 (m, 8H, CH_{Ar}), 7.39 (d, 2H, $J = 8.5$ Hz, CH_{Ar}), 7.74 (s, 1H, H-9), 7.81 (d, 1H, $J_{2,3} = 3$ Hz, H-2), 8.48 (s, 1H, H-4) ppm; ^{13}C NMR (62.5 MHz, *DMSO*-d_6): $\delta = 47.8$ (CH_2), 49.3 (CH_2), 55.2 (OCH_3), 102.3, 106.4, 113.4, 113.5, 118.7, 126.0 (2×CH), 126.8, 127.0 (2×CH), 127.4, 127.9, 128.3 (2×CH), 128.5 (2×CH), 128.6 (2×CH), 129.6 (2×CH), 133.4, 137.3, 137.6, 139.9, 141.4, 153.2, 159.8 (C=O), 162.3 (N–C=N) ppm; IR

(KBr): $\bar{\nu} = 3056$ (CH_{Ar}), 1677 (C=O) cm^{-1}; MS (IS): $m/z = 472.5$ $[M + 1]^+$.

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