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Graphical Abstract

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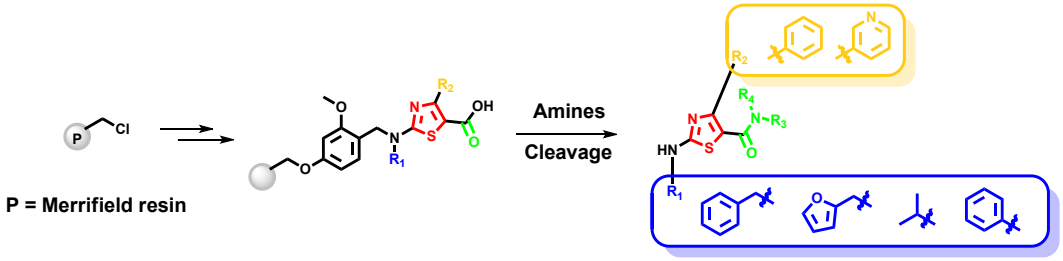

Synthesis of 2-Amino-5-Carboxamide Thiazole derivatives via Dehydrative Cyclization of Thiourea Intermediate Resin on Solid Phase

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Abstract: In this study, we synthesized 2-amino-5-carboxamide thiazole derivatives on solid phase. The synthesis of the library starts with the reductive amination of the 4-formyl-3-methoxy phenoxy resin in order to prevent isomer formation. The dehydrative cyclization of thiourea intermediate resin, which is the key step in the synthetic process, was successfully synthesized using α-bromoketone in the presence of the DMF so as to afford 2-amino-5-carboxylate thiazole resin. The resulting resin is coupled with various amines. Finally, the 2-amino-5-carboxamide thiazole resin was cleaved from the polymer support using a TFA and DCM cocktail. The physicochemical properties of the proposed 2-amino-5-carboxamide thiazole derivatives were calculated and showed potential to be an reasonable oral bioavailability drug properties as determined by Lipinski's Rule.

KEYWORDS: 2-amino-5-carboxamide thiazole, isomer, dehydrative cyclization, solid-phase

Introduction

Solid-phase organic synthesis (SPOS) is a method widely used in drug discovery for its profound effect on making massive numbers of small molecules in short periods of time.[1] These small molelcules usually contain heterocyclic systems, which are considered to be an important class of organic compounds, as they play a vital role in the medicinal field.[2] Among many type of heterocylic compounds, five-membered rings have been used in a number of medicinal research projects due to their activity against diseases.[3]

Thiazole is one of the representative five-membered ring compounds which has attracted research interest in recent years.[4] Thiazole core skeleton has shown various biological activites, such as antibacterial,[5] antioxidant,[6] diuretic,[7] antifungal,[8] antitubercular,[9] anti-inflammatory,[10] anticonvulsant,[11] anti-HIV,[12] antidiabetic,[13] antihypertensive,[14] anti-Alzheimer[15] and anticancer[16] activities. Additionally, most of the antitumor agents contain substituted 1,3-thiazole ring and carboxamide groups (Figure 1).[17] Therefore, thiazole core was a target molecule for synthesis and biological testing with following numerous reported methods so as to afford thiazole core skeleton.[18] Thus, many organic chemists and medicinal chemists have maintained interest in synthesizing thiazole, and there have been several reported methods to afford this core skeleton in the literature.[19]

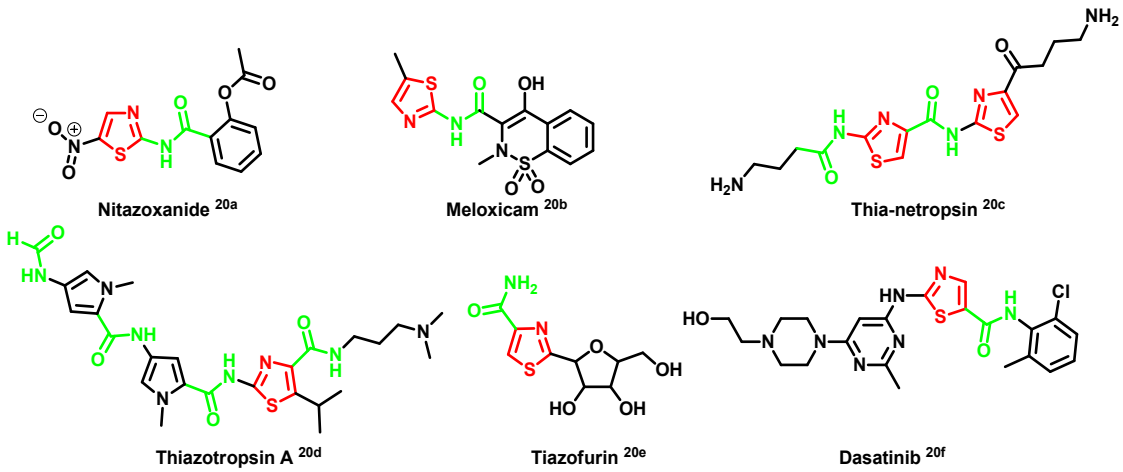
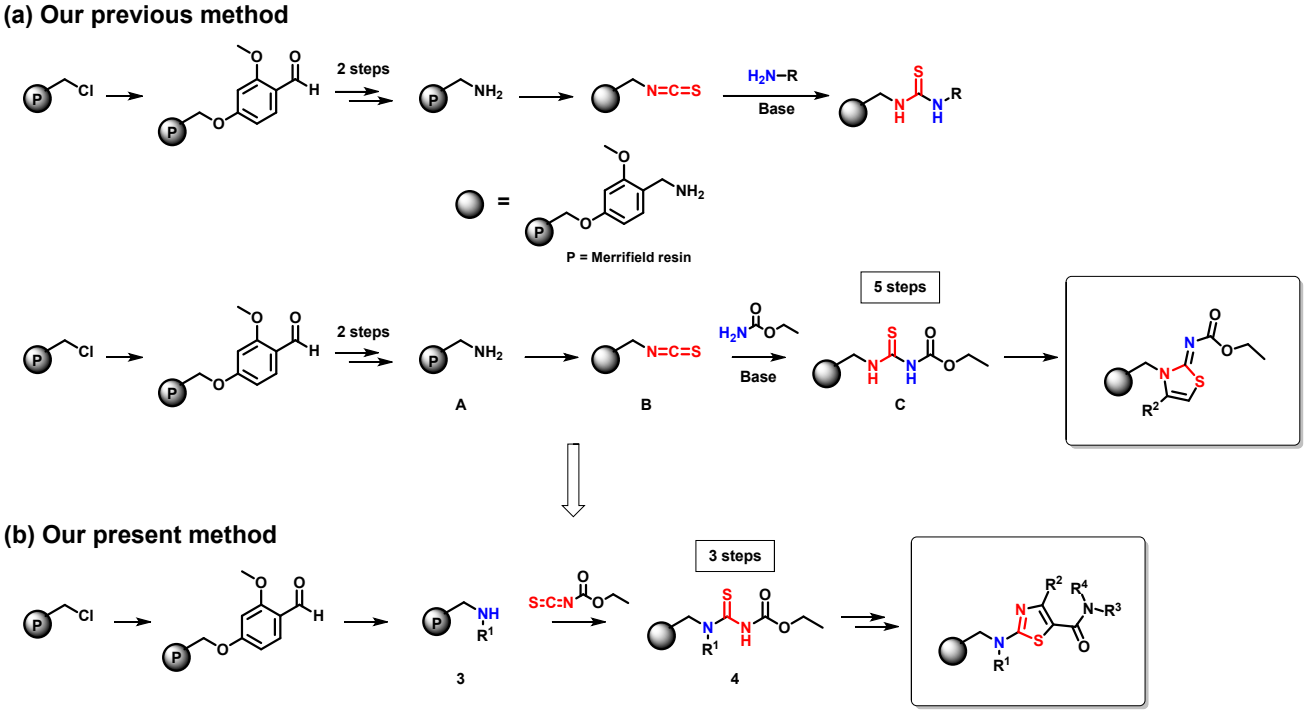


Figure 1. Examples of 2-amino-5-carboxamide thiazole derivatives with broad-spectrum antitumor activities [20]

Herein, we were interested in developing new synthetic methodology for thiazole carboxamide moiety. As an extension of our previous work,[21] we envisioned synthesizing thiazole from the isothiocyanate-terminated resin (Scheme 1 (a)). Unfortunately, our previous methodology was limited to the use of ethyl carbamate, as undesired dihydrothiazole was formed. In order to improve the synthetic methodology, we synthesized *N*-alkylated amine resin **3** from the reductive amination of AMEBA resin. Next, we synthesized thiourea resin **4** in the absence of base. We then synthesized isothiourea resin by modifying the functional group on Merrifield resin (Scheme 1 (b)). In contrast to the previous method, this method increases the reactivity of the intermediate and also reduces the number of reaction steps. Herein, we report our recent progress on this project.

Scheme 1. Synthetic Strategy for the Synthesis of Ethyl (*N*-alkyl-benzylcarbamothioyl)carbamate resins

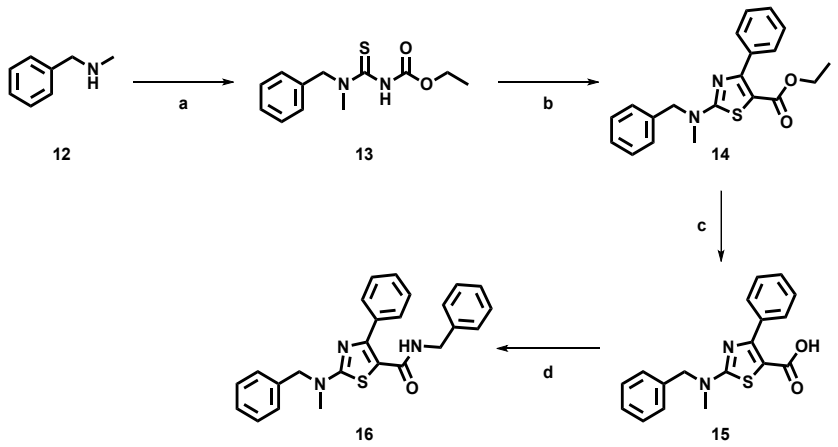


Results and Discussion

Preliminary studies show the reaction conditions for 2-amino-5-carboxamide thiazole derivatives on solution phase (Scheme 2). The synthesis began with the preparation of *N*-acylthiourea. The reaction between ethoxycarbonyl isothocyante with primary amine **17** affored ethoxycarbonyl thiourea **18**.

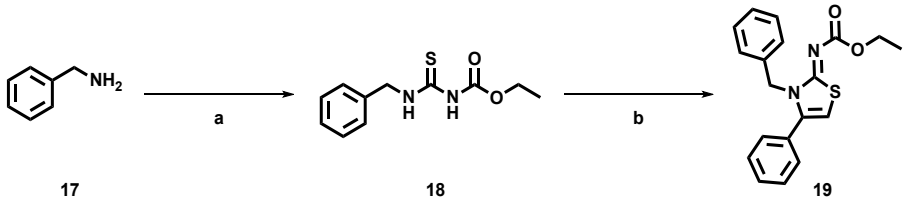
Unfortunately, the cyclization reaction between ethoxycarbonyl thiourea **18** and α-bromoacetophenone resulted in the formation of undesired dihydrothiazole **19** (Scheme 3). A convincing mechanism for this cyclization reaction is depicted in Scheme S1.[22] In order to prevent isomer formation, we used a secondary amine as a starting marterial instead of primary amine. The *N*-benzyl-*N*-methyl-*N*'-(ethoxycarbonyl)thiourea **13** was succesfuly cyclized to form ethyl 2-(benzyl(methyl)amino)-4-phenylthiazole-5-carboxylate **14** under conditions using TEA and α-bromoacetophenone in DMF. A plausible mechanism for the above cyclization reaction is shown in Scheme S2.[23] Hydorylsis of the thiazole-5-carboxylate **14** with 2 M NaOH in EtOH at 70 ℃, results in 2-(benzyl(methyl)amino)-4-phenylthiazole-5-carboxylic acid **15**. Further, *N*-benzyl-2-(benzyl(methyl)amino)-4-phenylthiazole-5-carboxamide **16** was obtained by the amide coupling of benzylamine using EDC·HCl and HOBt in DMF for 6 h.

Scheme 2. Study for solution-phase synthesis of 2-amino-5-carboxamide thiazole derivatives[a]



[a] Reagents and conditions: (a) Ethoxycarbonyl isothiocyanate, DCM, rt, 1.5 h. (b) α-bromoacetophenone, TEA, DMF, rt, 4 h.(c) 2 M NaOH, EtOH, 70 ℃, 12 h. (d) Benzylamine, EDC·HCl, HOBt, DMF, rt, 6 h

Scheme 3. Formation of the undesired isomers 2-aminothiazole 8[a]



[a] Reagents and conditions: (a) Ethoxycarbonyl isothiocyanate, DCM, rt, 4 h. (b) α-bromoacetophenone, DMAP 5% AcOH in DMF, 90 ℃, 4 h.

Thus, as the solution-phase reaction conditions were successfully optimized, the solid-phase synthesis of 2-amino-5-carboxamide derivatives introduced various amines. Merrifield resin **1** was used as a starting material, and reacted with 4-hydroxy-2-methoxybenzaldehyde, K_2CO_3, and KI in DMF for 16 h in order to yield the 4-formyl-3-methoxy phenoxy resin **2**.[24] This process was monitored using ATR-FTIR, the results of which showed an ester (C=O) peak at 1675 cm^{-1} (Figure S1(2)). After the reductive amination of resin **2**, with amines and $NaBH(OAc)_3$ in DCM, the representative ester (C=O) peak at 1675 cm^{-1} disappeared (Figure S1(**3**{*1*})). The attachment of ethoxycarbonyl isothiocyanate to *N*-alkylated resin **3** in DCM obtained Ethyl (*N*-alkyl-benzylcarbamothioyl)carbamate resin **4**, whose FTIR spectrum showed the ester (C=O) peak at 1735 cm^{-1} (Figure S1(**4**{*1*})). The dehydrative cyclization of Ethyl (*N*-alkyl-benzylcarbamothioyl)carbamate resin **4** was successfully conducted using *α*-bromoacetophenone or 3-(Bromoacetyl)pyridine hydrobromide in the presence of the DMF so as to afford 2-amino-5-carboxylate thiazole resin **7**, and its FTIR spectrum showed a shift in the ester (C=O) peak from 1735 cm^{-1} to 1667 cm^{-1} (Figure S1(**7**{*1,1*})). Following the hydrolysis of 2-amino-5-carboxylate thiazole resin **7** with 2M NaOH in DMSO at 60 ℃, we could obtain 2-amino-thiazole-5-carboxylic acid resin **8**, and its FTIR spectrum showed carboxylic acid (C=O) peak at 1610 cm^{-1} and an OH peak at 3369 cm^{-1} (Figure S1(**8**{*1,1*})). In order to obtain the 2-amino-thiazole-5-carboxylic acid **9**, resin **8** was cleaved from the polymer support under TFA in DCM (1:2, v/v) at room temperature for 12 h (Table 2).

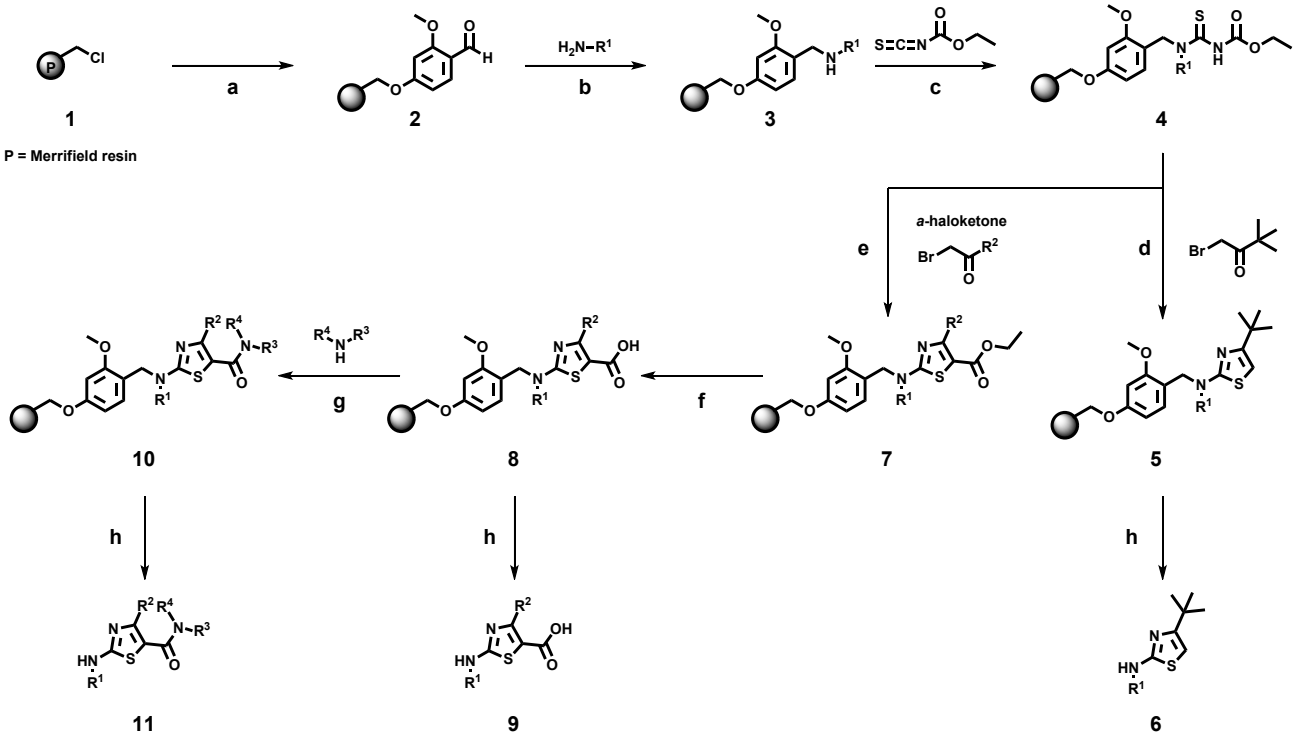
As we can see in Table 2, The yield of compound **9**{*1,2*} was high (57%), while the yield of compound **9**{*2,1*} was low (6%). The plausible mechanistic pathway for cyclization of thiourea intermediate resin **4** is shown in Scheme S3. In the reaction, cyclization using 3-(Bromoacetyl)pyridine has better reactivity than cyclization using 2-bromoacetophenone because of the electron withdrawing effect of the pyridine ring. Also, compounds which the R^1 group is a furfuryl group show a lower yield than compounds with a benzyl group because of the electron-withdrawing effect of the oxygen in furan ring.

Next, Resin **8** undergoes amide coupling under conditions using EDC·HCl, HOBt, and various

amines and the reaction was monitored using FTIR, which shows the disappearance of the OH peak (Figure S1(10{*1,1,1*})). In order to afford the 2-amino-5-carboxamide thiazole derivatives **11**, resin **10** was cleaved from the polymer support under TFA in DCM (1:2, v/v) at RT for 12 h (Table 3).

In the case of a cyclization reaction using a 1-bromopinacolone, the decarboxylative cyclization of Ethyl (*N*-alkyl-benzylcarbamothioyl)carbamate resin **4** was carried out using DMF at 80 ℃. As a result, we could obtain 4-*tert*-butyl thiazole resin **5**, not in the dehydrative cyclization form. The IR spectra of the compounds that can support this were shown in Figure S2. In order to obtain the 4-*tert*-butyl thiazole **6**, resin **5** was cleaved from the polymer support under TFA in DCM (1:2, v/v) at room temperature for 12 h (Table 1).

Scheme 4. Synthesis of 2-Amino-5-Carboxamide Thiazole Derivatives on Solid Phase[a]



[a] Reagents and conditions: (a) 4-hydroxy-2-methoxybenzaldehyde, K_2CO_3, KI, 60 °C, 16 h. (b) $NaBH(OAc)_3$, 1,2-dichloroethane, rt, 1.5 h. (c) DCM, rt, 19 h. (d) DMF, 80 ℃, 12 h. (e) TEA, DMF, rt, 2~12 h. (f) 2 M NaOH, DMSO, 60 °C, 72 h (g) EDC·HCl, HOBt, DMF, rt, 24 h. (h) TFA/DCM (1:2, v/v), rt, 12 h.

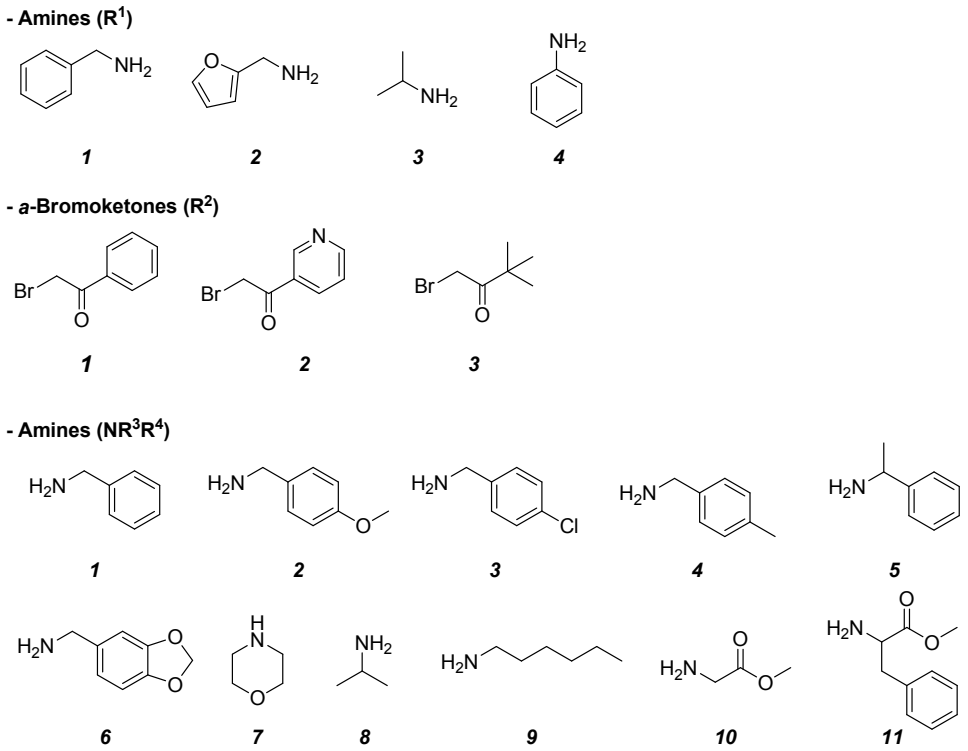


Figure 2. Building Block for 2-Amino-5-carboxamide Thiazole Derivatives

Table 1. Yields and Purities of 4-*tert*-butyl Thiazole **6**

Compound	R^1	R^2	Yield (%)[a]	Purity (%)[b]
6{*1,3*}			35	100
6{*2,3*}			17	100

[a]For five -step overall yields (loading capacity of resin 1 is 2.28 mmol/g). [b]All of the purified products were checked by LC/MS at 254 nm.

Table 2. Yields and Purities of 2-Amino-Thiazole-5-Carboxylic Acid **9**

Compound	R^1	R^2	Yield (%)[a]	Purity (%)[b]
9{*1,1*}			30	100
9{*2,1*}			6	92.53
9{*3,1*}			19	100
9{*4,1*}			18	97.75

9{*1,2*}			57	100
9{*2,2*}			9	100
9{*3,2*}			21	99.6
9{*4,2*}			23	98.4

[a]For six-step overall yields (loading capacity of resin 1 is 2.28 mmol/g). [b]All of the purified products were checked by LC/MS at 254 nm.

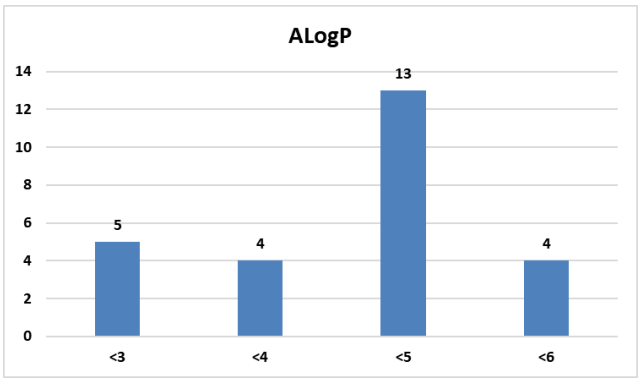
Table 3. Yields and Purities of 2-Amino-5-Carboxamide Thiazole **11**

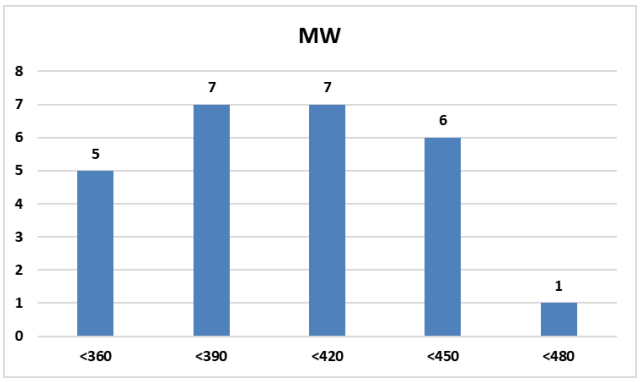
No.	R^1	R^2	NR^3R^4	Yield (%)[a]	Purity (%)[b]	No.	R^1	R^2	NR^3R^4	Yield (%)[a]	Purity (%)[b]
11 {*1,1,1*}				15	100	**11** {*1,2,10*}				24	97
11 {*1,1,2*}				19	100	**11** {*1,2,11*}				13	97.2
11 {*1,1,3*}				19	85.9	**11** {*3,1,1*}				13	99
11 {*1,1,10*}				12	85.9	**11** {*3,1,2*}				15	100
11 {*1,2,1*}				21	98	**11** {*3,1,3*}				15	95
11 {*1,2,2*}				25	96	**11** {*3,1,7*}				11	99
11 {*1,2,3*}				29	97	**11** {*3,1,10*}				13	100
11 {*1,2,4*}				16	100	**11** {*3,2,1*}				19	100
11 {*1,2,5*}				23	93.8	**11** {*4,2,1*}				19	100
11 {*1,2,6*}				21	95.3	**11** {*4,2,4*}				15	100
11 {*1,2,7*}				28	99	**11** {4,*2,5*}				14	100

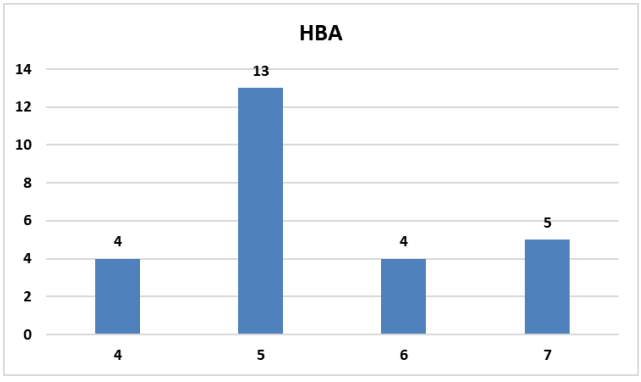
11 {1,2,8}				12	100	**11** {4,2,6}				12	100
11 {1,2,9}				20	95.6	**11** {4,2,10}				18	90.6

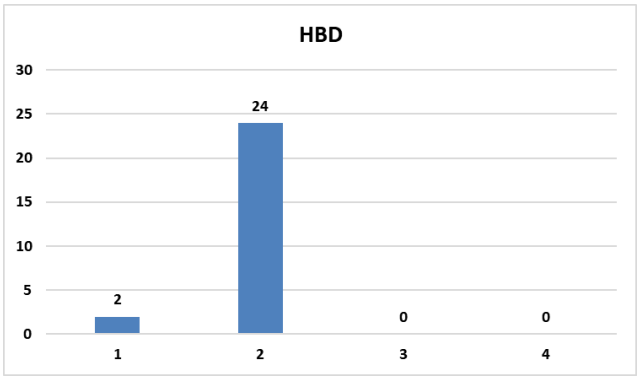
[a]For seven-step overall yields (loading capacity of resin 1 is 2.28 mmol/g). [b]All of the purified products were checked by LC/MS at 254 nm.

The final goal of the drug discovery process is to develop orally active drugs. Lipinski's rule and some related parameters are used as guidelines to determine the potentials of orally available drugs. In this context, in order to evaluate the potential orally available drug properties, we calculated the physicochemical properties of 2-amino-5-carboxamide thiazole derivatives via Discovery Studio 2018. According to Lipinski's rule of five, orally absorbed drugs must obey following rules : a molecular weight should be less than 500. It must have less than 5 hydrogen bond donor groups and less than 10 hydrogen bond acceptor groups. The calculated logP value should be less than 5.[25] It is also demonstrated that more flexible molecules are less likely to be orally active, few rotational bonds, with polar surface area less than 140 $Å^2$ are preferable drugs.[26] As can be seen in Figure 3, most of the physicochemical parameters of 2-amino-5-carboxamide thiazole derivatives are within the ranges of those predicted for orally bioavailable drugs.









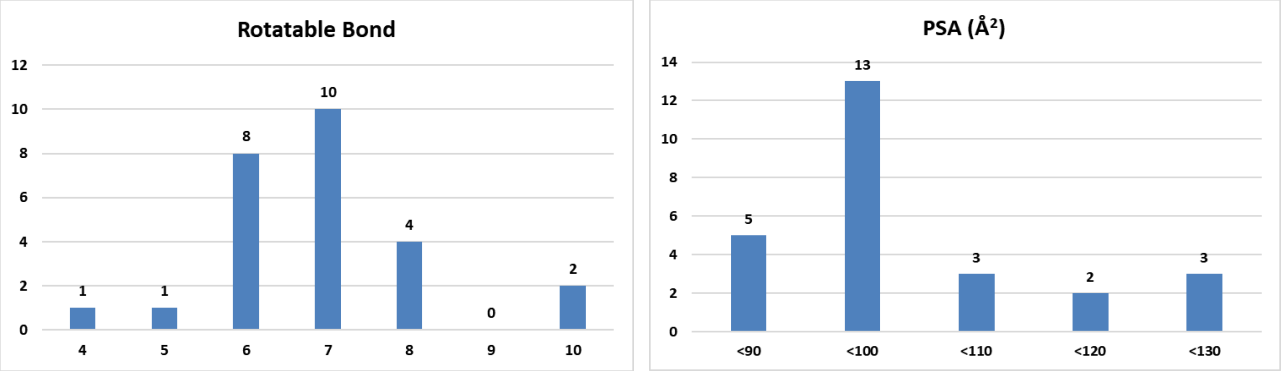


Figure 3. Calculated physicochemical properties of 2-amino-5-carboxamide thiazole derivatives

(MW : Molecular Weight, HBA : Hydrogen Bonding Acceptor, HBD : Hydrogen Bonding Donor, PSA : Polar Surface Area)

In conclusion, we have established a solid-phase synthetic method for constructing 2-amino-5-carboxamide thiazole derivatives which avoids the formation of undesired isomers. Analogously to our solution-phase synthesis, solid-phase synthesis was carried and contained three diversity sites that were introduced, including amines (R^1), α-haloketone (R^2), and amines (NR^3R^4). The thiazole core was prepared from the Ethyl (*N*-alkyl-benzylcarbamothioyl)carbamate resin **4** via the dehydrative cyclization approach. Additionally, following the hydrolysis of the ester group, amide coupling was carried out with various amines such as benzylamine, aliphatic amine, and amino acid. Following the functionalization of 2-amino-5-carboxaminde thiazole, the supporting resin was treated with a cocktail of TFA and DCM, affording the desired final compounds. Finally, in order to determine whether the synthesized library has the potential to be used as an orally bioavailable drug, we calculated physicochemical parameters such as Alog P, molecular weight, the number of hydrogen bond acceptors and donors, the number of rotatable bonds, and polar surface area. As a result, most of the key parameters of constructed 2-amino-5-carboxamide thazole derivatives fall within the ranges for orally active drugs.

Experimental section

General procedure for synthesis: All chemicals were reagent grade and used as purchased. Reactions were monitored by TLC analysis using Merk silica gel 60 F-254 thin layer plates (for solution-phase synthesis) and an ATR-FTIR spectrometer (for solid-phase synthesis). Flash column chromatography was carried out on Merk silic gel 60 (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded in δ units relative to deuterated solvent as an internal reference using a 500 MHz NMR instrument (Bruker). Liquid chromatography tandem mass spectrometry (Agilent 6460 Triple Quad LC/MS) analysis was performed using an electro spray ionization (ESI) mass spectrometer with photodiode-array detector (PDA) detection. High-resolution mass spectrometry spectra were obtained using aTOF LC/MS system (Agilent 6550 iFunnel Q-TOF LC/MS).

Preparation of AMEBA resin 2

To a suspension of Merrifield resin **1** (2.28 mmol/g, 5.00 g, 11.4 mmol) in DMF (25 mL), potassium carbonate (4.73 g, 34.2 mmol) and potassium iodide (0.02 g, 0.11 mmol) were added, followed by 3-methoxy-4-formylphenol (5.20 g, 34.2 mmol). The resulting mixture was stirred at 60 ℃ for 16 h, after the resin was filtered and washed successively with DMF, MeOH, H_2O, MeOH, DCM, and MeOH. The resin was then dried under high vacuum. Resin **2** was obtained as a white solid. Single-Bead ATR-FTIR: 3023, 2920, 1675 (C=O), 1595, 1491, 1451, 1395, 1291, 1258, 1197, 1162, 1113, 1102, 1026, 1017, 815, 757, 697 cm^{-1}.

Representative procedure for the preparation of *N*-substituted resin **3**{*1*} (R^1 = Bn)

To a mixture of AMEBA resin **2** (1 g, theoretically 1.80 mmol), and $NaBH(OAc)_3$ (1.45 g, 6.84 mmol) in 1,2-DCE (20 mL), benzylamine (0.747 mL, 6.84 mmol) was added and the resulting mixture was shaken at room temperature for 1.5 h. The resin was then filtered and washed several times with DCM, H_2O, and MeOH, then dried under high vacuum. Resin **3**{*1*} was obtained as a light-yellow solid. Single-Bead ATR-FTIR: 3023, 2920, 1610 (C=O), 1586, 1503, 1492, 1450, 1419, 1374, 1284, 1258,

1195, 1157, 1128, 1028, 821, 734, 696 cm^{-1}

Representative procedure for preparation of Ethoxycarbonylthiourea resin 4{*1*} (R^1 = Bn)

To a mixture of *N*-substituted resin **3a** (1.16 g, theoretically 1.80 mmol) in 1,2-DCE (20 mL), ethoxycarbonylisothiocyante (0.94 mL, 7.96 mmol) was added and the resulting mixture was shaken at room temperature for 19 h. The resin was then filtered and washed several times with DCM and MeOH, then dried under high vacuum. Resin **4**{*1*} was obtained as a light-yellow solid. Single-Bead ATR-FTIR: 3023, 2923, 1735 (C=O), 1611, 1586, 1506, 1450, 1414, 1288,1228, 1187, 1160, 1112, 1027, 1012, 820, 759, 734, 697 cm^{-1}

Representative procedure for preparation of Ethyl thiazole-5-carboxylate resin 5{*1,3*} (R^1 = Bn, R^2 = *tert*-butyl)

To a mixture of Ethoxycarbonylthiourea resin **4**{*1*} (0.5 g, theoretically 0.644 mmol) in DMF (10 mL), 1-Bromopinacolone (0.61 g, 3.42 mmol) was added and the resulting mixture was shaken at 80 ^oC for 12 h. The resin was then filtered and washed several times with DMF, MeOH, H_2O, and DCM, then dried under high vacuum. Resin **5**{*1,3*} was obtained as a pink solid. Single-Bead ATR-FTIR: 3023, 2926, 1610, 1583, 1505, 1450, 1286, 1195, 1159, 1128, 1113, 1025, 1015, 817, 697 cm^{-1}

Representative procedure for preparation of Ethyl thiazole-5-carboxylate resin 7{*1,1*} (R^1 = Bn, R^2 = Aryl)

To a mixture of Ethoxycarbonylthiourea resin **4**{*1*} (1 g, theoretically 1.29 mmol) in DMF (10 mL), 2-Bromoacetophenone (1.36 g, 6.84 mmol) was added and the resulting mixture was shaken at room temperature for 2 h. The resin was then filtered and washed several times with DMF, MeOH, H_2O, and DCM, then dried under high vacuum. Resin **7**{*1,1*} was obtained as a light-yellow solid. Single-Bead ATR-FTIR: 3023, 2921, 1667 (C=O), 1610, 1586, 1532, 1504, 1493, 1450, 1419, 1385, 1330, 1285, 1256, 1196, 1158, 1128, 1072, 1027, 822, 752, 697, 623 cm^{-1}

Representative procedure for preparation of Ethyl thiazole-5-carboxylate resin 7{*1,2*} (R^1 = Bn, R^2 = 4-Pyridine)

To a mixture of Ethoxycarbonylthiourea resin **4**{*1*} (0.5 g, theoretically 0.644 mmol) and Et_3N (0.35 g, 9.54 mmol) in DMF (10 mL), 3-(Bromoacetyl)pyridine Hydrobromide (0.961 g, 3.42 mmol) was added and the resulting mixture was shaken at room temperature for 2 h. The resin was then filtered and washed several times with DMF, MeOH, H_2O, and DCM, then dried under high vacuum. Resin **7**{*1,2*} was obtained as a dark-brown solid. Single-Bead ATR-FTIR: 3021, 2923, 1698 (C=O), 1605, 1585, 1530, 1505, 1492, 1450, 1419, 1337, 1284, 1249, 1195, 1159, 1111, 1077, 1023, 817, 756, 697 cm^{-1}

Representative procedure for preparation of thiazole-5-carboxylic acid resin 8{*1,1*} (R^1 = Bn, R^2 = Aryl)

To a mixture of Ethyl thiazole-5-carboxylate Resin **7**{*1,1*} (0.358 g, theoretically 0.408 mmol) in DMSO (40 mL), 2M NaOH (4.1 mL, 8.16mmol) was added and the resulting mixture was shaken at 60 ^oC for 72 h. The resin was then filtered and washed several times with MeOH, H_2O, and DCM, then dried under high vacuum. Resin **8**{*1,1*} was obtained as a light-yellow brown solid. Single-Bead ATR-FTIR: 3359(br), 3024, 2924, 1610 (C=O), 1586, 1505, 1493, 1451, 1420, 1372, 1323, 1286, 1259, 1196, 1159, 1129, 1116, 1027, 822, 754, 697 cm^{-1}

Representative procedure thiazole-5-carboxamide resin 10{*1,1,1*} (R^1 = Bn, R^2 = Aryl, NR^3R^4 = Benzylamino)

A mixture of thiazole-5-carboxylic acid resin **8**{*1,1*} (0.5 g, theoretically 0.589 mmol), EDC·HCl (0.66 g, 3.42 mmol), and HOBt (0.52 g, 3.42 mmol) in DMSO (20 mL) was shaken at room temperature for 24 h. The resin was then filtered and washed several times with DMF, MeOH, H_2O, and DCM, then dried under high vacuum. Resin **10**{*1,1,1*} was obtained as a light-yellow solid. Single-Bead ATR-FTIR: 3023, 2918, 1609 (C=O), 1586, 1505, 1492, 1450, 1419, 1380, 1328, 1286, 1260, 1195, 1159, 1028, 820, 744, 697 cm^{-1}

Representative Procedure for the Preparation of 6{*1,3*} (R^1 = Bn, R^2 = *tert*-butyl)

A resin **5**{*1,3*} (0.2 g, theoretically 0.2466 mmol) was treated with a mixture of TFA and DCM (1:3, v/v, 9 mL), then shaken for 12 h at room temperature. The resin was filtered and washed several times with DCM, EA, and MeOH, and organic filtrate was collected and evaporated. The residue was dissolved in EA, washed with H_2O, and neutralized to pH 7 with saturated aqueous $NaHCO_3$ solution. The organic layer was dried with anhydrous Na_2SO_4 and evaporated. The crude mixture was purified by column chromatography on silica gel (hexane/ethyl acetate) and triturated with hexane and diethyl ether (1:1, v/v), affording **6**{*1,3*} (35%, five-step overall yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 4H), 7.29 (d, *J* = 6.0 Hz, 1H), 6.06 (s, 1H), 4.40 (s, 2H), 1.27 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.56, 162.13, 137.63, 128.78, 127.84, 127.81, 98.05, 50.20, 34.64, 29.75. LC-MS (ESI): m/z = 247.2 $[M + H]^+$: HRMS (ESI) calcd for $C_{14}H_{14}N_2S$ $[M + H]^+$: 247.1263, found : 247.1266.

Representative Procedure for the Preparation of 9{*1,1*} (R^1 = Bn, R^2 = Aryl)

A resin **8**{*1,1*} (0.5 g, theoretically 0.589 mmol) was treated with a mixture of TFA and DCM (1:3, v/v, 9 mL), then shaken for 12 h at room temperature. The resin was filtered and washed several times with DCM, EA, and MeOH, and organic filtrate was collected and evaporated. The residue was dissolved in EA, washed with H_2O, and adjusted to pH 4 with saturated aqueous NH_4Cl solution. The organic layer was dried with anhydrous Na_2SO_4 and evaporated. The crude mixture was purified by column chromatography on silica gel (hexane/ethyl acetate) and triturated with hexane and diethyl ether (1:1, v/v), affording **9**{*1,1*} (30%, six-step overall yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.51 (s, 1H), 7.64 (d, *J* = 6.5 Hz, 2H), 7.42 (d, *J* = 6.9 Hz, 2H), 7.37 (s, 4H), 7.34 (s, 2H), 6.48 (s, 1H), 4.49 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.47, 142.33, 134.18, 130.11, 129.44, 129.13, 128.78, 128.61, 128.31, 127.89, 126.01, 98.72, 50.70. LC-MS (ESI): m/z = 267.2 $[M – CO_2 + H]^+$:[27]

Representative Procedure for the Preparation of 11{*1,1,1*} (R^1 = Bn, R^2 = Aryl, NR^3R^4 = Benzylamino)

A resin **10**{*1,1,1*} (0.552 g, theoretically 0.589 mmol) was treated with a mixture of TFA and DCM (1:3, v/v, 9 mL), then shaken for 12 h at room temperature. The resin was filtered and washed several times with DCM, EA, and MeOH, and organic filtrate was collected and evaporated. The residue was dissolved in ethyl acetate, washed with H_2O, and neutralized to pH 7 with saturated aqueous $NaHCO_3$ solution. The organic layer was dried with anhydrous Na_2SO_4 and evaporated. The crude mixture was purified by column chromatography on silica gel (hexane/ethyl acetate) and triturated with hexane and diethyl ether (1:1, v/v), affording **11**{*1,1,1*} (15%, seven-step overall yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.44 (d, J = 5.7 Hz, 2H), 7.36 – 7.14 (m, 11H), 7.01 (s, 2H), 5.68 (s, 1H), 4.32 (d, J = 3.4 Hz, 2H), 4.09 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.93, 161.53, 152.03, 137.79, 136.76, 134.61, 129.51, 129.16, 129.04, 128.73, 128.62, 127.77, 127.62, 127.49, 127.42, 117.77, 49.55, 43.85. LC-MS (ESI): m/z = 400.3 $[M + H]^+$: HRMS (ESI) calcd for $C_{24}H_{21}N_3OS$ $[M + H]^+$: 400.1478, found : 400.1476.

Supporting Information

Full analytical data of compounds, along with the copies of ^{1}H NMR, ^{13}C NMR, LC-MS, and HRMS spectra of all the synthesized compounds, and complete descriptions of the studies for the reactions.

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Graphical Abstract

Synthesis of 2-Amino-5-Carboxamide Thiazole derivatives via Dehydrative Cyclization of Thiourea Intermediate Resin on Solid Phase

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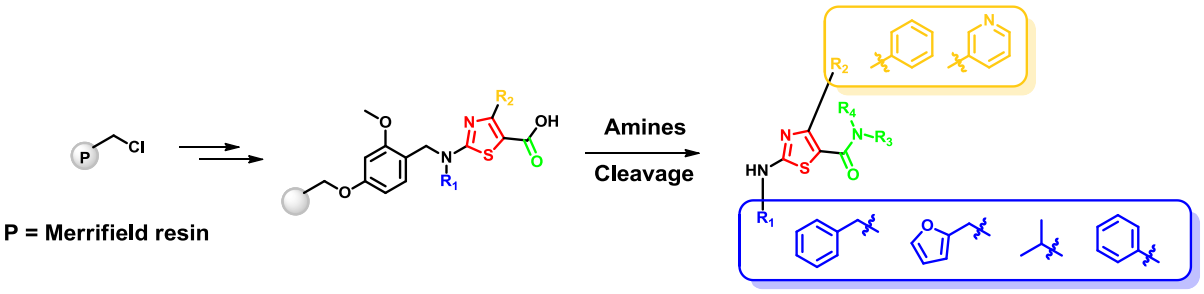

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