Diversity-oriented synthesis of *N*-aryl-*N*-thiazolyl compounds

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ABSTRACT

An efficient approach toward the parallel solid-phase synthesis of highly diversified *N*-aryl-*N*-thiazolyl compounds is presented. The treatment of resin-bound aniline derivatives with Fmoc-isothiocyanate generated aryl thioureas which, following Hantzsch's reaction with a variety of α-haloketones and cleavage of the solid support, led to the desired *N*-aryl-*N*-thiazolyl compounds in good yield and high purity.

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The thiazole ring is an important heterocycle which plays a prominent role in nature and has broad applications in agricultural and medicinal chemistry.[1] Specifically, 2-aminothiazoles present an important class of heterocycles found in numerous biologically active compounds. They have been reported to possess antiviral,[2] antibacterial,[3] antiprion,[4] and psychotropic activities.[5] Compounds containing the aminothiazole moiety are also known to be a ligand of estrogen receptors,[1h] adenosine receptor antagonists,[1i] while other analogs exhibit antitumor properties.[1j] 2-Aminothiazoles were successfully employed as heterocyclic bioisosteres of the phenol moiety on dopamine agonists and the widely used anti-Parkinsonian agent, pramipexole. These resulted in improved pharmacological properties including longer duration of action and improved bioavailability.[6] Conjugated polyaminothiazole films were reported to display electrochemical properties with high thermal stability.[7] A number of biologically important aminothiazole analogs have been disclosed. For example, MTIP inhibits the binding of corticotrophin-releasing factor (CRF) to the CRF1 receptor[8], and MB06322 is an orally bioavailable phosphoramidase sensitive-prodrug for the treatment of type 2 diabetes (Fig. 1).[9]

2-Aminothiazoles are readily obtained by Hantzsch's cyclocondensation of thiourea with α-haloketones,[10] or by the reaction of α-thiocyanate carbonyl compounds with aromatic or aliphatic amine hydrochlorides.[11] They can also be obtained by following the one-pot reaction of ketones with a mixture of *N*-bromosuccinimide, thiourea, and benzoyl peroxide.[12]

Herein, we describe an efficient approach for the parallel solid-phase diversity-oriented synthesis[13] of *N*-aryl-*N*-thiazolyl derivatives. Starting from *p*-methylbenzhydrylamine hydrochloride

Table 1
Synthesized *N*-aryl-*N*-thiazolyl compounds **4**

| Entry	R$_1$	R$_2$	X	MW obtained[a] (MH$^+$)	Purity[b] (%)
4a	–CH$_3$	–H	NH	318 (MH$^+$)	90
4b	–CH$_3$	–CH$_3$	NH	332 (MH$^+$)	95
4c	–(CH$_2$)$_4$–		NH	358 (MH$^+$)	70[c]
4d	OH (phenol)	–H	NH	396 (MH$^+$)	85
4e	adamantyl/methyl	–H	NH	437 (MH$^+$)	93
4f	–CH$_3$	–H	O	319 (MH$^+$)	95
4g	–CH$_3$	–CH$_3$	O	333 (MH$^+$)	95
4h	–(CH$_2$)$_4$–		O	359 (MH$^+$)	92
4i	OH (phenol)	–H	O	397 (MH$^+$)	88
4j	adamantyl	–H	O	438 (MH$^+$)	95
4k	–CH$_3$	–H	CH$_2$	317 (MH$^+$)	89
4l	–CH$_3$	–CH$_3$	CH$_2$	331 (MH$^+$)	91
4m	–(CH$_2$)$_4$–		CH$_2$	357 (MH$^+$)	88
4n	OH (phenol)	–H	CH$_2$	395 (MH$^+$)	90
4o	adamantyl	–H	CH$_2$	436 (MH$^+$)	89

[a] Determined by ESI-MS.
[b] The products were run on a Vydac column, gradients 5–95% (1% formic acid in ACN) in 7 min. The purity was estimated on analytical traces at λ = 214 nm and 254 nm.
[c] Incomplete cyclization was observed.
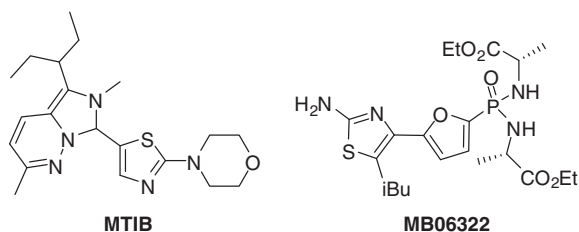
Figure 1.

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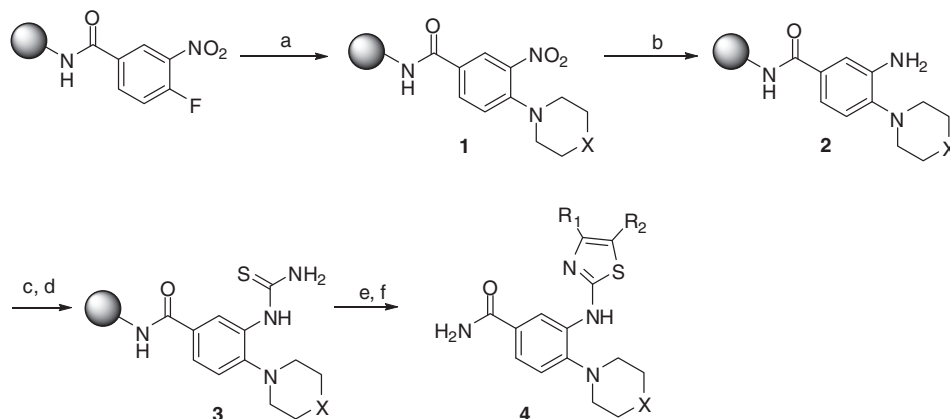
Scheme 1. Reagents and conditions: (a) 20 equiv of amine in DMF (0.3 M), 20 equiv DIEA in DMF, rt, 20 h; (b) 10 equiv $SnCl_2 \cdot 2H_2O$ in DMF (2 M), rt, overnight; (c) 6 equiv Fmoc-NCS in DMF (0.3 M), rt, overnight; (d) 20% piperidine/DMF; (e) 20 equiv α-halogenoketones in DMF (0.3 M), 70 °C, overnight; (f) HF/anisole (95:5), 0 °C, 90 min.

Table 2
Synthesized N-aryl-N-thiazolyl compounds **6**

Entry	R_1	R_2	R_3	MW obtained[a] (MH⁺)	Purity[b] (%)
6a		–CH₃	–H	466	91
6b		–CH₃	–CH₃	480	85
6c		–(CH₂)₄–		506	78
6d			–H	544	83
6e			–H	586	93
6f		–CH₃	–H	494	86
6g		–CH₃	–CH₃	508	81
6h		–(CH₂)₄–		534	75
6i			–H	572	82
6j			–H	614	81
6k		–CH₃	–H	437	68
6l		–CH₃	–CH₃	451	72
6m		–(CH₂)₄–		477	68
6n			–H	515	70
6o			–H	557	65

[a] Determined by ESI-MS.
[b] The products were run on a Vydac column, gradients 5–95% (1% formic acid in ACN) in 7 min. The purity was estimated on analytical traces at $\lambda = 214$ nm and 254 nm.
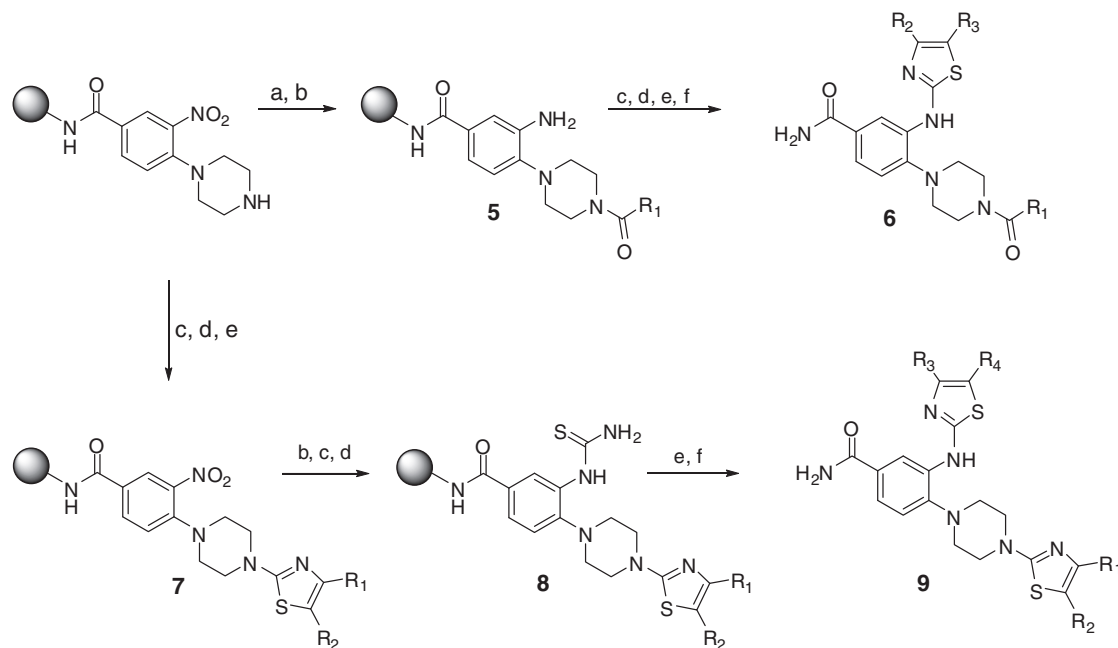
Scheme 2. Reagents and conditions: (a) 10 equiv carboxylic acids or isocyanate in DMF (0.3 M), 10 equiv DIC, rt, 3 h; (b) 10 equiv SnCl$_2$·2H$_2$O in DMF (2 M), rt, overnight; (c) 6 equiv Fmoc-NCS in DMF (0.3 M), rt, overnight; (d) 20% piperidine/DMF; (e) 20 equiv α-haloketone in DMF (0.3 M), 70 °C, overnight; (f) HF/anisole (95:5), 0 °C, 90 min.

Table 3
Synthesized piperazino aryl bis-thiazole compounds **9**

Entry	R_1	R_2	R_3	R_4	MW obtained[a] (MH$^+$)	Purity[b] (%)
9a	Methyl	–H	Methyl	–H	415	76
9b	Methyl	Methyl	Methyl	–H	429	71
9c	–(CH$_2$)$_4$–		Methyl	–H	455	50
9d	3-Hydroxyphenyl	–H	Methyl	–H	493	70
9e	1-Adamantyl	–H	Methyl	–H	535	75
9f	Methyl	–H	Methyl	Methyl	429	77
9g	Methyl	Methyl	Methyl	Methyl	443	80
9h	–(CH$_2$)$_4$–		Methyl	Methyl	469	56
9i	3-Hydroxyphenyl	–H	Methyl	Methyl	507	85
9j	1-Adamantyl	–H	Methyl	Methyl	549	89
9k	Methyl	–H	–(CH$_2$)$_4$–		455	74
9l	Methyl	Methyl	–(CH$_2$)$_4$–		469	65
9m	–(CH$_2$)$_4$–		–(CH$_2$)$_4$–		495	58
9n	3-Hydroxyphenyl	–H	–(CH$_2$)$_4$–		533	65
9o	1-Adamantyl	–H	–(CH$_2$)$_4$–		575	83
9p	Methyl	–H	3-Hydroxyphenyl	–H	493	79
9q	Methyl	Methyl	3-Hydroxyphenyl	–H	507	59
9r	–(CH$_2$)$_4$–		3-Hydroxyphenyl	–H	533	56
9s	3-Hydroxyphenyl	–H	3-Hydroxyphenyl	–H	571	75
9t	1-Adamantyl	–H	3-Hydroxyphenyl	–H	613	56
9u	Methyl	–H	1-Adamantyl	–H	535	76
9v	Methyl	Methyl	1-Adamantyl	–H	549	76
9w	–(CH$_2$)$_4$–		1-Adamantyl	–H	575	53
9x	3-Hydroxyphenyl	–H	1-Adamantyl	–H	613	51

[a] Determined by ESI-MS.
[b] The products were run on a Vydac column, gradients 5–95% (1% formic acid in ACN) in 7 min. The purity was estimated on analytical traces at λ = 214 nm and 254 nm.

(MBHA·HCl) resin, 3-nitro-4-fluoro benzoic acid was coupled in the presence of diisopropylcarbodiimide (DIC). The fluoro group was displaced with a variety of secondary cyclic amines such as piperidine, morpholine, and piperazine. The nitro group was reduced in the presence of tin chloride and the generated amine was treated with Fmoc-isothiocyanate to provide the corresponding thiourea **3**. Following Fmoc deprotection, the resin-bound aryl thiourea was treated with a variety of α-haloketones to generate the corresponding resin-bound *N*-aryl-*N*-thiazolyl compounds (Scheme 1). The final compounds were obtained following the cleavage of the

solid support with HF/anisole (95:5). All the expected *N*-aryl-*N*-thiazolyl compounds **4** were obtained in high purity and good yields (Table 1), and the selected compounds were characterized by ^{1}H NMR.[14]

In order to generate more diversity around the *N*-aryl-thiazole, the piperazine was acylated with a variety of carboxylic acids and isocyanates (Scheme 2). Thus, following the displacement of the fluoro group with Boc piperazine, the Boc group was deprotected with trifluoroacetic acid and the generated resin-bound aryl-piperazine was treated with various acylating reagents. The nitro group

was reduced and the resin-bound piperazine aniline **5** was treated with Fmoc-NCS. Following Fmoc deprotection, the thiazole was formed using the same procedure described above. The desired *N*-aryl-*N*-thiazolyl compounds **6** were generated following the cleavage of the solid support. We selected adamantyl acetic acid, 4-methoxyphenyl acetic acid, and phenylisocyanate for the diversity R$_1$, and five different commercially available α-haloketones for the position of diversity R$_2$. Fifteen compounds were extracted, lyophilized, and analyzed by LC–MS (Table 2). Starting materials were consumed to completion leading to good yields and good to high purities of the target compound.

Similarly, the same approach was applied for the parallel synthesis[11] of a variety of piperazino aryl bis-thiazole derivatives **9** (Scheme 2). Following deprotection of the Boc group from the piperazine, the generated amine was treated with Fmoc-isothiocyanate and the resin-bound piperazine thiazole **7** was formed using the same Hantzsch's cyclocondensation reaction as described above. Following nitro reduction, the second thiazole was generated and the final aryl-dithiazolyl compounds **9** were obtained following the cleavage of the solid support. Five different commercially available α-haloketones were selected for both the cyclocondensation reactions. We performed the parallel synthesis of 25 piperazino aryl bis-thiazole compounds **9**. All the desired compounds were obtained in good yields and purities (Table 3).

We presented a high yielding approach for the parallel diversity-oriented synthesis of a variety of *N*-aryl-*N*-thiazolyl compounds. Taking advantage of the wide variety of commercially available secondary amines, α-halogenoketones, and different acylating reagents such as carboxylic acids, sulfonyl chlorides, isocyanates, and isothiocyanates, large libraries of highly diversified aminoarylthiazoles can be prepared and screened for the identification of new therapeutics.

Acknowledgments

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14. Compound **4k**: ^{1}H NMR (500 MHz, DMSO-d_6): 8.19 (s, 1H), 7.83 (dd, *J* = 1.8 Hz, *J* = 8.2 Hz), 6.50 (s, 1H), 2.84 (t, *J* = 5.0 Hz, 4H), 2.19 (s, 3H), 1.62 (m, 4H), 1.52 (m, 2H). [13]C (125 MHz, DMSO-d_6): 167.5, 164.4, 146.8, 133.3, 129.2, 123.1, 120.2, 119.3, 102.9, 52.0, 25.5, 23.6, 16.5. Compound **4h**: ^{1}H NMR (500 MHz, DMSO-d_6): 8.17 (s, 1H), 7.84 (s, 1H), 7.60 (dd, *J* = 1.8 Hz, *J* = 8.3 Hz, 1H), 7.24 (s, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.04 (9s, 1H), 4.2 (m, 2H), 3.72 (t, *J* = 4.2 Hz, 4H), 2.88 (t, *J* = 3.4 Hz, 4H), 2.56 (br s, 2H), 1.75 (br s, 4H). [13]C (125 MHz, DMSO-d_6): 167.4, 162.3, 145.8, 133.2, 129.5, 123.3, 120.8, 119.1, 117.7, 116.9, 66.0, 50.9, 25.4, 22.8, 22.4, 22.2.