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A new general three component solution-phase synthesis of 2-amino-1,3-thiazole and 2,4-diamino-1,3-thiazole combinatorial libraries

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Abstract—A general procedure for the solution-phase synthesis of amino-1,3-thiazole libraries **9** and **10** is described. Their preparation is based on the condensation of amidines **1** and thiouronium salts **2** with isothiocyanates **3**, affording amidino–thioureas and thioureido-thioureas of types **4** and **5**. Subsequent treatment with α-bromo ketones **6** led to the *S*-alkylated intermediate, which yielded 1,3-thiazoles of types **9** and **10** via a base-catalysed ring closure process (Scheme 1). In addition, this methodology tolerates a diverse range of functionality without recourse to protection.

The richness of the pharmacopeia in compounds containing heterocyclic systems is the basis of a continuing search for versatile processes towards these key structural elements. The 1,3-thiazole ring has been identified as a central structural element of a number of biological active natural products[1–3] and of pharmacological active substances.[4,5] Preparation of 1,3-thiazoles can be readily accomplished using both classical and nonclassical approaches, for example: (a) the Hantzsch synthesis,[6,7] (b) via thiazolines by condensation of aldehydes with a cysteine derivative followed by oxidation,[8] (c) reaction of 1-amidinothiourea with α-bromo ketones,[9] (d) condensation of α-halomethyl ketimines with thioamides.[10] and (e) reaction of ethyl diazopyruvate with thioamides.[11]

Despite the existing approaches to 1,3-thiazoles, there is still need for new general procedures, especially considering the potential opportunities in parallel and combinatorial chemistry.[12,13] Thus, in the course of our investigations towards the development of potentially valuable strategies for the combinatorial production of versatile heterocycles,[14–18] we report herein a general, rapid, and effective procedure for the solution-phase synthesis of 2-amino- and 2,4-diamino-1,3-thiazole libraries of types **9** and **10**.

This versatile solution-phase procedure to 2-amino- and 2,4-diamino-1,3-thiazole libraries is based on the condensation of amidines **1** and thiouronium salts **2** with isothiocyanates **3** in the presence of a base such as 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) or *N*,*N*-diisopropylethyl amine (DIPEA) to give amidino–thioureas and thioureido-thioureas of type **4** and **5**, followed by treatment with α-bromo ketones **6** leading to the *S*-alkylated intermediates **7** and **8**, which underwent base-catalysed intramolecular Knoevenagel-type condensation to furnish 1,3-thiazoles of type **9** and **10**. Thereby, intermediates of type **7** (R^1=alkyl, aryl) and **8** (R^1=SCH_2Ar) yield, respectively by elimination of ammonia, the 1,3-thiazoles **9**, and by elimination of the corresponding thiols, the 1,3-thiazoles **10** (Scheme 1).

Preliminary studies on the synthesis of the 1,3-thiazoles using amidines **1** in dry DMF with isothiocyanates **3** in the presence of DBU or DIPEA afforded the corresponding amidino–thiourea derivatives **4** in good yields (Table 1; Method A). Subsequent *S*-alkylation with α-bromo ketones **6**, followed by base-catalysed ring closure with elimination of NH_3 gave 2-aminothiazoles **9** in excellent yields (Table 2; Scheme 1; Method B). It is useful to note that this reaction sequence was conveniently performed in one-pot reaction without isolation of the intermediates **4** and **5**.

We extended our process to thiouronium salts of type **2**, which were easily accessible by literature methods from thiourea and a large variety of alkyl halides in excellent yields.[14,15,17]

Pleasingly, these compounds gave on reaction with isothiocyanates **3** in the presence of DBU or DIPEA the corresponding thiourea derivatives **5** in good yield (Method C), which upon subsequent treatment with α-bromo ketones **6**

Keywords: amidines and thiouronium salts; isothiocyanates; ring closure process.
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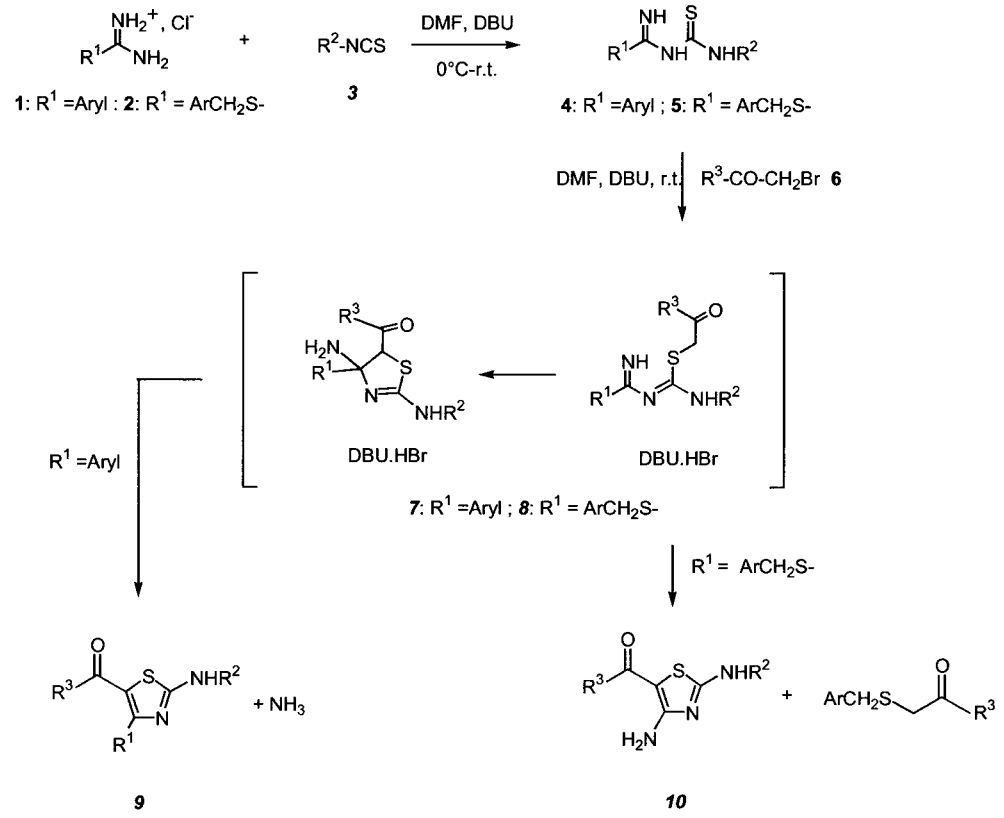

Scheme 1.

Table 1. Amidino- and thioureido-thiourea derivatives of type **4** and **5**

Compounds	R^1	R^2	Products	Yields [%]
1a	C_6H_5	C_6H_5	**4a**	91
1b	2-thienyl	C_6H_5	**4b**	61
2a	3-NC–C_6H_4–CH_2S	2-Cl–C_6H_4	**5a**	70
2a	3-NC–C_6H_4–CH_2S	C_6H_5	**5b**	86
2b	4-Cl–C_6H_4–CH_2S	C_6H_5	**5c**	84

led to the desired 2,4-diamino-1,3-thiazoles **10** in good yields (Table 2; Method D). We assume that this approach involves initial *S*-alkylation of the thiourea moiety, followed by base-catalysed ring closure and elimination of the corresponding thiol group ($ArCH_2SH$) instead of NH_3 (Scheme 1). Isolation of the corresponding disulfides or thiomethylketones (obtained by reaction of thiols with excess of α-bromo ketones) supported this prediction.

This approach constitutes a novel and efficient synthesis towards 2,4-diamino-1,3-thiazoles using a three component reaction between highly versatile thiouronium salts of type **2**, isothiocyanates **3** and α-bromo ketones **6** in combination with elimination of the thiol part after *S*-alkylation and base-catalysed ring closure of the thiouera derivative **5**. Finally, this reaction sequence could conveniently be performed in one-pot without isolation of the intermediates, allowing the development of a straightforward, simple and efficient procedure for the generation of libraries. Applications of this sulfur linkage strategy to new heterocyclic systems are under investigation, as well as an extension of the present process to solid-support, and will be published in due course.

1. Experimental

All reactions which require air- or moisture-sensitive reactants and solvents were carried out in oven- or flame-dried glassware under a positive pressure of dry argon. Reaction solvents and liquid reagents were purified before use or purchased in abs. quality. Anal. TLC: 2.5×10 cm precoated TLC plates, SiO_2 60F-254, layer thickness 0.25 mm (E.

Table 2. 2-Amino- and 2,4-diamino-1,3-thiazoles of type **9** and **10**

Compounds	R^1	R^2	R^3	Products	Yields [%]
4a	C_6H_5	C_6H_5	4-MeO–C_6H_4	**9a**	70
4a	C_6H_5	C_6H_5	4-Br–C_6H_4	**9b**	94
4b	2-thienyl	C_6H_5	C_6H_5	**9c**	73
4b	2-thienyl	C_6H_5	4-Br-C_6H_4	**9d**	74
5b	3-NC–C_6H_4–CH_2S	C_6H_5	C_6H_{11}	**10a**	65
5c	4-Cl–C_6H_4–CH_2S	C_6H_5	4-MeO–C_6H_4	**10b**	90
5c	4-Cl–C_6H_4–CH_2S	C_6H_5	4-Br–C_6H_4	**10c**	84
5c	4-Cl–C_6H_4-CH_2S	C_6H_5	4-F–C_6H_4	**10d**	99

Merck & Co., Darmstadt, Germany). Flash chromatography (FC):[19] E. Merck SiO_2 60 (70–230 Mesh ASTM). ATR/FT-IR: Nicolet-7199 FT-IR spectrometer; solids in KBr pellets, liquids as thin films; characteristic bands in cm^{-1}. ^1H NMR and ^{13}C NMR spectra: Bruker-AC-250 apparatus, at 250 MHz; in d_6-DMSO or $CDCl_3$; TMS as internal standard; chemical shift of signal centres and ranges in ppm (δ), J in Hz. EI-MS: Finnigan MS9-AEI or Mat90; m/z (rel.).

1.1. General procedures

1.1.1. Amidino–thioureas 4. *Method A:* To a mixture of amidine **1** (1.00 mmol) and isothiocyanate **3** (1.05 mmol) in dry dimethylformamide (DMF; 5 ml) under argon at 0°C, is added DBU or DIPEA (1.05 mmol). The reaction mixture is then stirred at rt until total consumption **1**, quenched with a 1N aq. HCl solution and extracted with AcOEt. The combined org. layers were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by FC (SiO_2) as indicated in the corresponding description yielding **4**.

1.1.2. 2-Aminothiazoles 9. *Method B:* To a mixture of **4** (1.00 mmol) and α-bromoketone **6** (1.05 mmol) in DMF; (5 ml) under argon at 0°C, is added DBU (2.1 mmol). The reaction mixture is then stirred at rt until total consumption **4**, quenched with a 1N aq. HCl solution and extracted with AcOEt. The combined org. layers were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by FC (SiO_2) as indicated in the corresponding description yielding **9**.

1.1.3. Thioureido–thioureas 5. *Method C:* To a mixture of thiouronium salts **2** (1.00 mmol) and isothiocyanate **3** (1.05 mmol) in dry dimethylformamide (DMF; 5 ml) under argon at 0°C, is added DBU or DIPEA (1.05 mmol). The reaction mixture is then stirred at rt until total consumption **2**, quenched with a 1N aq. HCl solution and extracted with AcOEt. The combined org. layers were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by FC (SiO_2) as indicated in the corresponding description yielding **5**.

1.1.4. 2,4-Diaminothiazoles 10. *Method D:* To a mixture of **5** (1.00 mmol) and α-bromoketone **6** (1.2 mmol) in dry DMF (5 ml) under argon at 0°C, is added DBU (2.1 mmol). The reaction mixture is then stirred at rt until total consumption **5**, quenched with a 1N aq. HCl solution and extracted with AcOEt. The combined org. layers were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified as indicated by FC (SiO_2) as indicated in the corresponding description yielding **10**.

1.1.5. 1-(Imino-phenyl-methyl)-3-phenyl-thiourea (4a). According to *Method A* with **1** (0.20 g, 1.66 mmol), **3a** (0.205 ml, 1.75 mmol) and DBU (0.261 ml, 1.75 mmol): 0.386 g (91%) of **4a** after FC purification with AcOEt/hexane [1:3–1:1]. Yellow solid. Mp 150–154°C. ^1H NMR (250 MHz, d_6-DMSO): 10.49 (br.s, 2×NH); 9.28 (br.s, NH); 8.10–8.01 (m, 1H arom.); 7.86–7.82 (m. 1H arom.); 7.70–7.50 (m, 2H arom.); 7.43–7.19 (m, 3H arom.); 7.70–7.50 (m, 2H arom.); 7.10–7.02 (m, 1H arom.). IR (KBr): 3050m, 2925m, 1678s, 1604s, 1593s, 1557s, 1497s, 753m, 703m. MS: 255 [M^+] (40%), 135 (100%).

1.1.6. 1-(Imino-thiophen-2-yl-methyl)-3-phenyl-thiourea (4b). According to *Method A* with **1** (0.2 g, 1.23 mmol), **3b** (0.150 ml, 1.29 mmol) and DBU (0.170 ml, 1.29 mmol): 0.195 g (61%) of **4b** after FC purification with AcOEt/hexane [1:3–1:1]. Pale yellow solid. Mp 122–127°C. ^1H NMR (250 MHz, d_6-DMSO): 10.49 (br.s, 2×NH); 9.28 (br.s, NH); 8.10–8.01 (m, 1H arom.); 7.86–7.82 (m. 1H arom.); 7.70–7.50 (m, 2H arom.); 7.43–7.19 (m, 3H arom.); 7.70–7.50 (m, 2H arom.); 7.10–7.02 (m, 1H arom.). IR (KBr): 3350w, 3197w, 1600s, 1543s, 1176s, 758m, 690m. MS: 261 [M^+] (30%), 135(100%).

1.1.7. 1-[Imino-(3-cyanobenzylsulfinyl)-methyl]-3-(2-chlorophenyl)-thiourea (5a). According to *Method B* with **2** (3 g, 11 mmol), **3a** (1.90 ml, 11.58 mmol) and DBU (1.73 ml, 11.58 mmol): 2.77 g (70%) of **5a** after FC purification with AcOEt/hexane [1:3–1:1].White solid. Mp 114–115°C. ^1H NMR (250 MHz, d_6-DMSO): 10.43 (s, NH); 9.43 (br.s, 2×NH); 7.70–7.05 (m, 8H arom.); 4.07 (s, 2H aliph.).IR (KBr): 3350w, 3197w, 2250w, 1600s, 1543s, 1176s, 758m, 690m. MS: 361 [$M+H]^+$ (20%), 169 (100%).

1.1.8. 1-[Imino-(3-cyanobenzylsulfinyl)-methyl]-3-phenylthiourea (5b). According to *Method B* with **2** (3 g, 11 mmol), **3b** (1.38 ml, 11.58 mmol) and DBU (1.73 ml, 11.58 mmol): 3.09 g (86%) of **5b** after FC purification with AcOEt/hexane [1:3–1:1].White solid. Mp 125–127°C. ^1H NMR (250 MHz, d_6-DMSO): 10.49 (s, NH); 9.43 (br.s, 2×NH); 7.70–7.05 (m, 9H arom.); 4.07 (s, 2H aliph.). IR (KBr): 3350w, 3197w, 2200w, 1595s, 1523s, 745m. MS: 336 [$M+H]^+$ (100%).

1.1.9. 1-[Imino-(4-chlorobenzylsulfinyl)-methyl]-3-phenylthiourea (5c). According to *Method B* with **2** (4 g, 14.6 mmol), **3d** (1.84 ml, 15.4 mmol): 4.13 g (84%) of **5c** after FC purification with AcOEt/hexane [1:3–1:1]. White solid. Mp 143–145°C. ^1H NMR (250 MHz, d_6-DMSO): 10.49 (s, NH); 9.43 (br.s, 2×NH); 7.70–7.05 (m, 9H arom.); 4.07 (s, 2H aliph.). IR (KBr): 3350w, 3197w, 1595s, 1523s, 745m. MS: 336 [$M+H]^+$ (100%).

1.1.10. 2-Phenylamino-4-phenyl-5-[(4-methoxyphenyl)carbonyl]carbonylthiazole (9a). According to *Method C* with **4a** (0.20 g, 0.784 mmol), **6a** (0.190 g, 0.822 mmol) and DBU (0.245 ml, 1.64 mmol): 0.210 g (70%) of **9a**. Yellow solid. Mp 148–152°C. ^1H NMR (250 MHz, d_6-DMSO): 10.84 (s, NH); 7.70–7.67 (d, J=7.70 Hz, 2H arom.); 7.52–7.49 (d, J=8.78 Hz, 2H arom.); 7.24–7.19 (m, 3H arom.); 7.08–7.02 (t, J=7.32 Hz, 1H arom.); 6.76–6.72 (d, J=7.70 Hz, 2H arom.); 3.72 (s, 3H aliph.). IR (KBr): 3162w, 2920w, 1594m, 1517s, 1254s, 1026m, 756m, 710m. MS: 386 [M^+] (100%).

1.1.11. 2-Phenylamino-4-phenyl-5-[(4-bromophenyl)-carbonyl]thiazole (9b). According to *Method C* with **4a** (0.2 g, 0.784 mmol), **6b** (0.228 g, 0.822 mmol) and DBU (0.245 ml, 1.64 mmol): 0.320 g (94%) of **9b**. Yellow solid. Mp 18–182°C. ^1H NMR (250 MHz, d_6-DMSO): 10.95 (s, NH); 7.70–7.67 (d, J=7.70 Hz, 2H arom.); 7.41–7.32 (m, 8H arom.); 7.25–7.04 (m, 4H arom.). ^{13}C

NMR (400 MHz, d_6-DMSO): δ 187.3 (s); 166.07 (s); 158.42 (s); 140.29 (s); 137.50 (s); 134.75 (s); 131.14 (2×d); 131.06 (2×d); 130.12 (2×d); 129.61 (2×d); 129.08 (d); 128.05 (2×d); 125.63 (s); 123.34 (d); 121.55 (s); 118.61 (2×d). IR (KBr): 3285w, 2924w, 1611m, 1507s, 1254s, 1119m, 747m. MS: 434 [M^+] (100%).

1.1.12. 2-Phenylamino-4-(thiophen-2-yl)-5-phenylcarbonylthiazole (9c). According to *Method C* with **4b** (0.20 g, 0.765 mmol), **6c** (0.160 g, 0.803 mmol) and DBU (0.239 ml, 1.606 mmol): 0.205 g (73%) of **9c**. Yellow solid. Mp 135–138°C. ^{1}H NMR (250 MHz, d_6-DMSO): 10.89 (s, NH); 7.71–7.60 (m, 6H arom.); 7.59–7.36 (m, 5H arom.); 7.11–7.04 (t, J=7.35 Hz, 1H arom.); 6.97–6.94 (t, J=4.45 Hz, 1H arom.). IR (KBr): 3162w, 2924w, 1609m, 1495s, 1292s, 1119m, 858m, 767m, 693. MS: 362 [M^+] (100%).

1.1.13. 2-Phenylamino-4-(thiophen-2-yl)-5-[(4-bromophenyl)carbonyl]thiazole (9d). According to *Method C* with **4b** (0.20 g, 0.765 mmol), **6b** (0.223 g, 0.803 mmol) and DBU (0.239 ml, 1.606 mmol): 0.23 g (74%) of **9d**. Yellow solid. Mp 132–134°C. ^{1}H NMR (250 MHz, d_6-DMSO): 10.95 (s, NH); 7.68–7.58 (m, 8H arom.); 7.43–7.36 (m, 2H arom.); 7.11–7.04 (t, J=7.35 Hz, 1H arom.); 6.98–6.94 (m, 1H arom.). IR (KBr): 3276w, 2924w, 1614m, 1525s, 1290s, 1011m, 791m, 767m, 714. MS: 442 [M+H]$^+$ (100%).

1.1.14. 2-Phenylamino-4-amino-5-cyclohexylcarbonylthiazole (10a). According to *Method D* with **5b** (0.3 g, 0.919 mmol), **6d** (0.188 ml, 1.10 mmol) and DBU (0.288 ml, 1.93 mmol): 0.180 g (65%) of **10a** after FC purification with AcOEt/CH_2Cl_2 [1:4]. Yellow solid. Mp 211–213°C. ^{1}H NMR (250 MHz, d_6-DMSO): 10.68 (s, NH); 7.95 (br.s, NH_2); 7.62–7.59 (d, J=7.65 Hz, 2H arom.); 7.39–7.32 (t, J=7.48 Hz, 2H arom.); 7.10–7.04 (t, J=7.32 Hz, 1H arom.); 2.29–2.24 (t, J=10.81 Hz, 1H aliph.); 1.75–1.62 (m, 5H aliph.); 1.41–1.13 (m, 5H aliph.). ^{13}C NMR (400 MHz, d_6-DMSO): δ 191.9 (s); 165.66 (s); 164.16 (s); 140.22 (s); 129.56 (2×d); 123.61 (d); 119.31 (2×d); 50.71 (s); 29.31 (2×t); 26.01 (t); 25.80 (2×t). IR (KBr): 3418w, 2930w, 1611m, 1553s, 1451s, 783m, 700m. MS: 301 [M^+] (100%).

1.1.15. 2-Phenylamino-4-amino-5-[(4-methoxyphenyl)carbonyl]thiazole (10b). According to *Method D* with **5c** (0.4 g, 1.19 mmol), **6a** (0.327 g, 1.43 mmol) and DBU (0.372 ml, 2.50 mmol): 0.315 g (90%) of **10b** after FC purification with AcOEt/hexane [1:1]. Yellow solid. Mp 231–233°C. ^{1}H NMR (250 MHz, d_6-DMSO): 10.76 (s, NH); 8.16 (br.s, NH_2); 7.69–7.65 (d, J=8.75 Hz, 2H arom.); 7.63–7.60 (d, J=7.77 Hz, 2H arom.); 7.39–7.33 (t, J=7.52 Hz, 2H arom.); 7.09–7.04 (t, J=7.52 Hz, 1H arom.); 7.03–6.99 (d, J=8.75 Hz, 2H arom.); 3.81 (s, 3H aliph.). IR (KBr): 3413w, 3201w, 1587s, 1522s, 1251m, 761m, 694m. MS: 326 [M+H]$^+$ (100%).

1.1.16. 2-Phenylamino-4-amino-5-[(4-bromophenyl)carbonyl]thiazole (10c). According to *Method D* with **5c** (0.4 g, 1.19 mmol), **6b** (0.397 g, 1.43 mmol) and DBU (0.372 ml, 2.50 mmol): 0.373 g (84%) of **10c** after FC purification with AcOEt/Hexane [1:1]. Orange solid. Mp 205–207°C. ^{1}H NMR (250 MHz, d_6-DMSO): 10.87 (s, NH); 8.25 (br.s, NH_2); 7.70–7.67 (d, J=8.75 Hz, 2H arom.); 7.67–7.63 (d, J=8.75 Hz, 2H arom.); 7.63–7.60 (d, J=7.77 Hz, 2H arom.); 7.39–7.33 (t, J=7.52 Hz, 2H arom.); 7.09–7.04 (t, J=7.52 Hz, 1H arom.). IR (KBr): 3414w, 3271w, 1592s, 1546s, 1431s, 755m, 695m. MS: 374 [M+H]$^+$ (100%).

1.1.17. 2-Phenylamino-4-amino-5-[(4-fluorophenyl)carbonyl]thiazole (10d). According to *Method D* with **5c** (0.4 g, 1.19 mmol), **6e** (0.284 g, 1.43 mmol) and DBU (0.372 ml, 2.50 mmol): 0.367 g (99%) of **10d**. Yellow solid. Mp 190–192°C. ^{1}H NMR (250 MHz, d_6-DMSO): 10.82 (s, NH); 8.25 (br.s, NH_2); 7.77–7.71 (dd, J=14.32, 8.77 Hz, 2H arom.); 7.63–7.60 (d, J=7.77 Hz, 2H arom.); 7.39–7.27 (m, 4H arom.); 7.09–7.04 (t, J=7.52 Hz, 1H arom.). IR (KBr): 3418w, 3197w, 1599s, 1550s, 1431m, 849m, 760m, 694m. MS: 314 [M+H]$^+$ (100%).

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