Synthesis of Two Novel Classes of Tetracycles Bearing Tetrahydro Ring System From Benzothiazole: 7,8,9,10-Tetrahydrothiazolo[5,4-*a*]acridine and 1,2,3,4-Tetrahydro-12*H*-benzothiazolo[2,3-*b*]quinazolin-12-one

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Novel 7,8,9,10-tetrahydrothiazolo[5,4-*a*]acridine and 1,2,3,4-tetrahydro-12*H*-benzothiazolo[2,3-*b*]-quinazolin-12-one derivatives were synthesized in one step from the corresponding benzothiazoles. These two new tetracyclic skeletons were unambiguously characterized and are presently in pharmacological tests.

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Neurodegenerative diseases have been the subject of extensive studies in recent years. Oxidative stress has been linked to a variety of neurodegenerative conditions such as Parkinson's diseases and Alzheimer's disease [1]. Many drugs have been considered for the treatment of these conditions. Among these are aryl-substituted 2-benzothiazolamines (*e.g.* Riluzole) [2], which were reported to be potent anticonvulsant agents that functioned *via* a glutamatergic mechanism [3] and indeed reduced different oxidative stress [4]. On the other hand, Huperzine A (Figure 1) [5] has been shown to exhibit significant neuroprotection against H_2O_2 insult [6] and was used therapeutically as an acetylcholinesterase (AChE) inhibitor, such as tacrine (THA, Cognex) [7] and donepezil (Aricept) [8]. Recently, a series of new tacrine analogues has been described to potently and selectively inhibit AchE [9], Huperzine A derivatives [10] were the most recently reported.

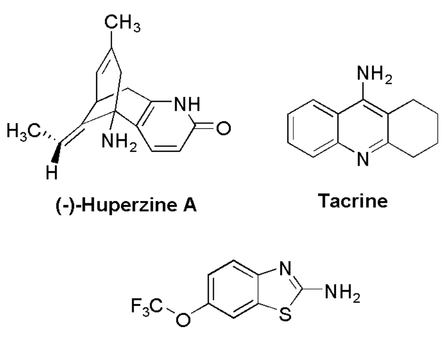
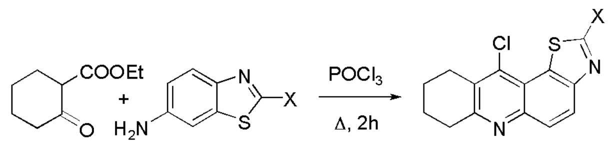


Figure 1

As a part of our program aimed at developing new tetracycle bearing thiazole ring, we have developed the synthesis of 9-chlorotetrahydroacridine, with benzothiazole derivatives as starting materials. By heating the cyclohexanone and anthranilic acid in $POCl_3$, the corresponding 9-chlorotetrahydroacridine could be obtained [11]. We have adapted this method to synthesize new tetrahydrothiazoloacridine. This synthesis was carried out by the Friedländer reaction of ethyl cyclohexanone-2-carboxylate (**1**) and 6-amino-2-chlorobenzothiazole (**2a**) [12], in $POCl_3$ under reflux for 2 hours (Scheme 1). The 2,11-dichloro-7,8,9,10-tetrahydrothiazolo[5,4-*a*]acridine **3** was obtained in 21% yield. Following the same procedure we have used 2,6-diaminobenzothiazole (**2b**). This compound under Ullmann condensation conditions provided the corresponding acridine derivative in good yield [13].

Scheme 1



1 **2a** X=Cl **2c** X=$NHCOCH_3$ **3, 4**

Surprisingly, with our conditions we obtained the 8-amino-1,2,3,4-tetrahydro-12*H*-benzothiazolo[2,3-*b*]–quinazolin-12-one (**5**) in 12% yield (Figure 2). The cyclohexanone has reacted with the amino group in position 2, and the cyclization was done with the intra-cyclic nitrogen of the thiazole ring [14].

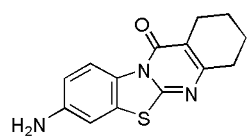


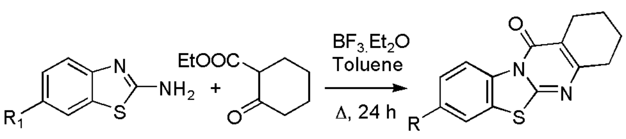
Figure 2. 8-Amino-1,2,3,4-tetrahydro-12*H*-benzothiazolo[2,3-*b*]quinazolin-12-one (**5**).

To overcome this undesired side-reaction we have protected this amino group as an acetyl derivative **2c**. In this case, we obtained the corresponding tetrahydroacridine skeleton **4** in 51% yield. In these two reactions, we have only obtained thiazolo[5,4-*a*]acridines, the "bent" structure. This structure was unambiguously determined by ^{1}H- and ^{13}C-NMR, and was in agreement with our previous study on acridine derivative [15].

The new quinazoline derivatives formed with **2b** have afforded an entry into a new tetracyclic skeletal system. Otherwise, it was known that 2-chlorobenzothiazole and anthranilic acid [16] (or ethyl anthranilate) [17] formed in an exothermic reaction benzothiazolo[2,1-*b*]quinazolin-12(6*H*)-one. This reaction has been extended to benzimidazole compounds [18].

The condensation of 2-aminobenzothiazole and **1** by thermal cyclization gave poor yield (12%). To increase the yield we have used the cyclodehydratation mediated by Lewis acid, which usually gave tacrine [19]. We obtained an increase to 51% yield of **6**. We have found that boron trifluoride diethyl etherate (BF_3:Et_2O) was the most convenient Lewis acid to obtain our compounds **5-10** (Scheme 2).

Scheme 2



We have synthesized a series of new tetrahydrobenzothiazolo[2,3-*b*]quinazolinones with the commercially available 2-aminobenzothiazole derivatives (Table 1).

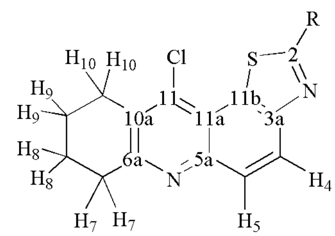
Table 1
Preparation of 1,2,3,4-Tetrahydro-12*H*-benzothiazolo[2,3-*b*]quinazolin-12-one

Reagent	R	Product	Time (H)	Yield %
2b	NH_2	5	24	32
2d	H	6	24	51
2e	Cl	7	24	53
2f	OC_2H_5	8	24	28
2g	CH_3	9	24	21
2h	F	10	24	49
2i	NO_2	No Product	24	0

In brief, we have synthesized two new classes of tetracyclic compounds: 7,8,9,10-tetrahydrothiazolo[5,4-*a*]acridine using 6-amino-benzothiazole, and 1,2,3,4-tetrahydro-12*H*-benzothiazolo[2,3-*b*]quinazolin-12-one with 2-aminobenzothiazole. This work is the first step in the development of a new tetracycle bearing tetrahydro ring in our laboratory. This method allows synthesis of new original heterocyclic compounds.

EXPERIMENTAL

Reagents and solvents were purchased from common commercial suppliers. Compounds (**2a**, **2c**) were previously described [20]. Melting points were determined with an Electrothermal 9300 apparatus and are uncorrected. The NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 200 MHz for ^{1}H and ^{13}C. 2D NMR spectra, both of homonuclear (COSY) and heteronuclear (HMBC, HMQC) correlations, were obtained with a Bruker AMX 400. In all cases TMS was used as an internal standard. High resolution mass measurements were obtained by the Service Central d'Analyse CNRS (69390 Vernaison, France).



Structures of the compounds 7,8,9,10-tetrahydrothiazolo-[5,4-*a*]acridine **3, 4** (the numbering of the carbons is arbitrary).

2,11-Dichloro-7,8,9,10-tetrahydrothiazolo[5,4-*a*]acridine (**3**).

A solution of 1.85 g (10 mmol) of 6-amino-2-chloro-benzothiazole (**2a**) and 1.71 g (10 mmol) of ethyl 2-oxocyclohexane carboxylate (**1**) in 10 mL of $POCl_3$ was heated under reflux for 2 hours. The solution was then allowed to cool to room temperature and poured into 100 mL of petroleum ether (60/80). Excess of solvent was removed under vacuum, and the mixture was poured onto 100 g of ice. The solution was neutralized with NH_4OH 16%, the precipitate formed was isolated by filtration, washed with water, air dried to yield 0.65 g (21%) of **3**, mp: 222 °C. ^{1}H NMR ($CDCl_3$): δ 1.96 (bs, 4H, (2-CH_2)$_{8,9}$), 3.01 (bs, 2H, (CH_2)$_{10}$), 3.14 (bs, 2H, (CH_2)$_7$), 8.02 (d, 1H, *J*=8.9 Hz, C-H_5), 8.15 (d, 1H, *J*=8.9 Hz, C-H_4). ^{13}C NMR ($CDCl_3$): δ 22.6 (C-8, C-9), 27.7 (C-10), 34.0 (C-7), 121.1 (C-11a), 124.8 (C-4), 128.9 (C-5), 129.3 (C-11b), 130.1 (C-10a), 135.3 (C-11), 145.4 (C-5a), 150.0 (C-3a), 154.8 (C-2), 159.2 (C-6a).

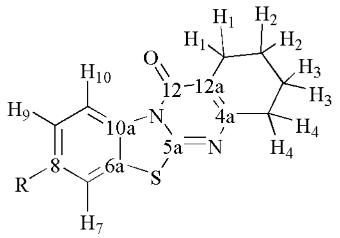
Anal. Cald. for $C_{14}H_{10}Cl_2N_2S$: C, 54.38; H, 3.26; N, 9.06. Found: C, 54.42; H, 3.24; N, 9.11.

N-(11-Chloro-7,8,9,10-tetrahydrothiazolo[5,4-*a*]acridin-2-yl) Acetamide (**4**).

Following the same procedure as for (**3**), 2-acetamido-6-aminobenzothiazole (**2c**) (2.07 g, 10 mmol), ethyl 2-oxocyclohexane carboxylate (**1**) (1.71 g, 10 mmol) and $POCl_3$ (10 mL) we obtain a palish powder of **4** (1.69 g), yield 51%, mp: 260 °C. ^{1}H NMR (TFA+D_2O): δ 2.48 (bs, 3H, (CH_3)$_{14}$), 2.94 (bs, 4H, 2(CH_2)$_{8,9}$), 3.59 (bs, 2H, (CH_2)$_{10}$), 3.79 (bs, 2H, (CH_2)$_7$), 8.78 (d, 1H, *J*=8.9 Hz, C-H_5), 8.91 (d, 1H, *J*=8.9 Hz, C-H_4). ^{13}C NMR (TFA+D_2O): δ 19.9* (C-9), 20.7* (C-8), 21.9 (CO*C*H_3), 27.1 (C-10), 29.5 (C-7), 122.3 (C-4), 124.4 (C-5), 135.7 (C-11), 136.1 (C-11b), 138.9 (C-11a), 151.3 (C-3a), 158.7 (C-6a), 164.8 (*C*OCH_3), 173.2 (C-2). * May be reversed.

Anal. Calcd. for $C_{16}H_{14}ClN_3OS$: C, 57.91; H, 4.25; N, 12.66. Found: C, 57.89; H, 4.24; N, 12.71.

Typical Procedure for the Preparation of 1,2,3,4-Tetrahydro-12*H*-benzothiazolo[2,3-*b*]quinazolin-12-one derivatives **5-10**.



A mixture of ethyl cyclohexanone **1** (1.71 g, 10 mmol) and the corresponding 2-aminobenzothiazole derivatives (10 mmol), in sodium dried toluene (50 mL), boron trifluoride diethyl etherate (1.74 g, 11 mmol) was added slowly *via* syringe, and the reaction mixture was heated at reflux for 22 hours. Then, 10 mL of concentrated HCl was added and heated under reflux for 2 hours. On cooling, the toluene was decanted and, to liberate the product, the remaining solid was treated with sodium hydroxide (2 *M*, 70 mL). The precipitate formed was filtered and washed with water to give compounds **5** to **10**.

8-Amino-1,2,3,4-tetrahydro-12*H*-benzothiazolo[2,3-*b*]quinazolin-12-one (**5**).

Compound **5** was obtained in a yield of 32 %, mp 202 °C; ^{1}H NMR ($CDCl_3$): δ 1.69 (m, 2H, $(CH_2)_3$), 1.69 (m, 2H, $(CH_2)_2$), 2.42 (t, 2H, $(CH_2)_4$), 2.55 (t, 2H, $(CH_2)_1$), 5.60 (s, 2H, NH_2), 6.68 (dd, 1H, *J*=9; 1.6 Hz, $(CH)_9$), 6.97 (d, 1H, *J*=1.6 Hz, $(CH)_7$), 8.53 (d, 1H, *J*=8.9 Hz, $(CH)_{10}$). ^{13}C NMR ($CDCl_3$): δ 21.6* (C-2), 21.8* (C-3), 22.0 (C-4), 31.1 (C-1), 105.5 (C-9), 112.6 (C-7), 114.7 (C-12a), 119.5 (C-10), 125.1 (C-6a), 125.7 (C-10a), 148.2 (C-8), 156.6 (C-5a), 157.9 (C-12), 159.9 (C-4a). FABMS, *m/z* $[M+H]^+$ 272.1. * May be reversed.

Anal. Calcd. for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49. Found: C, 61.89; H, 4.84; N, 15.52.

1,2,3,4-Tetrahydro-12*H*-benzothiazolo[2,3-*b*]quinazolin-12-one (**6**).

Compound **6** was obtained in a yield of 51 %, mp 129 °C; ^{1}H NMR ($CDCl_3$): δ 1.82 (m, 2H, $(CH_2)_3$), 1.82 (m, 2H, $(CH_2)_2$), 2.63 (t, 2H, $(CH_2)_4$), 2.70 (t, 2H, $(CH_2)_1$), 7.40 (m, 1H, $(CH)_8$), 7.45 (m, 1H, $(CH)_9$), 7.62 (d, 1H, $(CH)_7$), 9.05 (dd, 1H, $(CH)_{10}$). ^{13}C NMR ($CDCl_3$): δ 21.9* (C-2), 22.3* (C-3), 22.3 (C-4), 31.8 (C-1), 116.3 (C-12a), 119.8 (C-10), 121.8 (C-7), 124.2 (C-6a), 126.8** (C-9), 126.8** (C-8), 136.2 (C-10a), 157.8 (C-12), 159.4 (C-4a), 161.6 (C-5a). FABMS, *m/z* $[M+H]^+$ 257.1. *,** May be reversed.

Anal. Calcd. for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.71; N, 10.93. Found: C, 65.57; H, 4.68; N, 10.91.

8-Chloro-1,2,3,4-tetrahydro-12*H*-benzothiazolo[2,3-*b*]quinazolin-12-one (**7**).

Compound **7** was obtained in a yield of 53 %, mp 191 °C; ^{1}H NMR ($CDCl_3$): δ 1.79 (m, 2H, $(CH_2)_3$), 1.79 (m, 2H, $(CH_2)_2$), 2.58 (t, 2H, *J*=5.5 Hz, $(CH_2)_4$), 2.66 (t, 2H, *J*=5.8 Hz, $(CH_2)_1$), 7.37 (dd, 1H, *J*=8.9;1.9 Hz, $(CH)_9$), 7.54 (d, 1H, *J*=1.8 Hz, $(CH)_7$), 8.90 (d, 1H, *J*=9 Hz, $(CH)_{10}$). ^{13}C NMR ($CDCl_3$, δ): 21.8* (C-2), 22.2* (C-3), 22.2 (C-4), 31.8 (C-1), 116.6 (C-12a), 120.5 (C-10), 121.5 (C-7), 125.8 (C-6a), 127.1 (C-9), 132.5 (C-8), 134.6 (C-10a), 157.1 (C-12), 159.6 (C-4a), 161.2 (C-5a). FABMS, *m/z* $[M+H]^+$ 291.0.

Anal. Calcd. for $C_{14}H_{11}ClN_2OS$: C, 57.83; H, 3.81; N, 9.63. Found: C, 57.86; H, 3.85; N, 9.62.

8-Ethoxy-1,2,3,4-tetrahydro-12*H*-benzothiazolo[2,3-*b*] quinazolin-12-one (**8**).

Compound **8** was obtained in a yield of 28 %, mp 208 °C; ^{1}H NMR ($CDCl_3$): δ 1.42 (t, 2H, (CH_3)), 1.80 (m, 2H, $(CH_2)_2$), 1.80 (m, 2H, $(CH_2)_3$), 2.62 (bs, 2H, $(CH_2)_4$), 2.65 (bs, 2H, $(CH_2)_1$), 4.05 (q, 2H, (OCH_2)), 6.99 (dd, 1H, *J*=1.5;9 Hz, $(CH)_9$), 7.10 (d, 1H, *J*=1.5 Hz, $(CH)_7$), 8.91 (d, 1H, *J*=8.9 Hz, $(CH)_{10}$). ^{13}C NMR ($CDCl_3$): δ 14.7 ($0CH_2CH_3$), 21.8* (C-2), 22.1* (C-3), 22.2* (C-4), 31.4 (C-1), 64.1 (OCH_2CH_3), 106.7 (C-7), 113.9 (C-9), 116.2 (C-12a), 120.6 (C-10), 125.5 (C-6a), 137.4 (C-10a), 157.7** (C-4a), 157.7** (C-12), 158.5 (C-6), 160.9 (C-5a). FABMS, *m/z* $[M+H]^+$ 301.2.

Anal. Calcd. for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 64.01; H, 5.34; N, 9.30.

8-Methyl-1,2,3,4-tetrahydro-12*H*-benzothiazolo[2,3-*b*] quinazolin-12-one (**9**).

Compound **9** was obtained in a yield of 21 %, mp 138 °C; ^{1}H NMR ($CDCl_3$): δ 1.80 (m, 2H, $(CH_2)_3$), 1.80 (m, 2H, $(CH_2)_2$), 2.42 (s, 3H, (CH_3)), 2.61 (t, 2H, *J*=5.7 Hz, $(CH_2)_9$), 2.68 (t, 2H, *J*=5.7 Hz, $(CH_2)_1$), 7.24 (d, 1H, *J*=8.6 Hz, $(CH)_9$), 7.39 (d, 1H, $(CH)_7$), 8.88 (d, 1H, *J*=8.6 HZ, $(CH)_{10}$). ^{13}C NMR ($CDCl_3$): δ 21.4 (CH_3), 21.9* (C-2), 22.3* (C-3), 22.3* (C-4), 31.8 (C-1), 116.2 (C-12a), 119.4 (C-10), 121.8 (C-7), 124.2 (C-6a), 127.7 (C-9), 134.1 (C-10a), 137.1 (C-8), 157.8 (C-12), 159.3 (C-4a), 161.5 (C-5a).

Anal. Calcd. for $C_{15}H_{14}N_3OS$: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.59; H, 5.18; N, 10.39.

8-Fluoro-1,2,3,4-tetrahydro-12*H*-benzothiazolo[2,3-*b*]quinazolin-12-one (**10**).

Compound **10** was obtained in a yield of 49 %, mp 184 °C; ^{1}H NMR ($CDCl_3$): δ 1.79 (m, 2H, $(CH_2)_2$), 1.79 (m, 2H, $(CH_2)_3$), 2.61 (t, 2H, *J*=5.5 Hz, $(CH_2)_4$), 2.69 (t, 2H, *J*=5.5 Hz, $(CH_2)_1$), 7.16 (dt, 1H, *J*=2.3; 9 Hz, $(CH)_9$), 7.32 (dd, 1H, *J*=7.6; 2.3 Hz, $(CH)_7$), 9.03 (dd, *J*=9.2; 4.8 Hz, $(CH)_{10}$). ^{13}C NMR ($CDCl_3$): δ 21.7* (C-2), 22.1* (C-3), 22.1 (C-4), 31.6 (C-1), 108.7 (d, *J*=27 Hz) (C-7), 114.1 (d, *J*=23 Hz) (C-9), 116.4 (C-12a), 120.9 (d, *J*=9 Hz) (C-10), 125.8 (d, *J*=10 Hz) (C-6a), 132.4 (d, *J*=3 Hz) (C-10a), 157.2 (C-12), 159.4 (C-4a), 160.6 (d, *J*=248 Hz) (C-8), 161.1 (C-5a).

Anal. Calcd. for $C_{14}H_{11}FN_2OS$: C, 61.30; H, 4.04; N, 10.21. Found: C, 61.25; H, 4.10; N, 10.22.

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