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Synthesis of novel 2-cyanothiazolocarbazoles analogues of ellipticine

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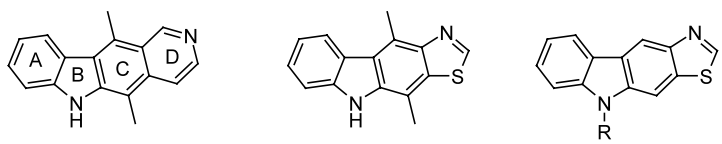
Abstract—Novel linear thiazolocarbazoles, which are structurally very close to the natural alkaloid ellipticine, have been rapidly synthesised via imino-1,2,3-dithiazoles, themselves readily obtained by treatment of the appropriate 3-aminocarbazoles with 4,5-dichloro-1,2,3-dithiazolium chloride **1** (Appel salt). © 2002 Elsevier Science Ltd. All rights reserved.

Ellipticine (**I**) (5,11-methyl-6*H*-pyrido[4,3-*b*]carbazole) is a naturally occurring alkaloid which is known for its promising antitumour properties and has been attracting considerable interest.[1] A number of structure–activity studies have already been made to determine the essential structural requirements associated with its biological activity.[2] In order to overcome some limitations, such as low water solubility or cardiovascular side effects, in the therapeutic use of ellipticine and early pyridocarbazole congeners, a number of analogues have been synthesised and evaluated so far. In particular, one of the strategies developed consisted in replacement of the pyridine in these pyridocarbazoles by other heterocycles like pyrroles, pyrimidines or thiophenes.[3] Because we are interested in original heterocyclic systems with potential pharmacological value and in association with our work on the chemistry of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt),[4] we decided to prepare original tetracyclic thiazolo analogues of ellipticine (**II**) by fusing the dimethylcarbazole and the thiazole rings. Simultaneously, demethylated congeners (**III**) were also produced from *N*-substituted carbazoles. In this paper we describe the synthetic route to these new polyheterocyclic compounds (Fig. 1).

The thiazolocarbazole ring (9*H*-1-thia-3,9-diazacyclopenta[*b*]fluorene) was very rarely described in literature, and one of the most recent syntheses of such a ring was performed via the Fischer-indole synthesis,[5] a method which allowed synthesis of demethylated 4-ethoxycarbonyl thiazolocarbazole analogues of ellipticine for which no cytotoxic evaluation was described.

Studying the chemistry of 4,5-dichloro-1,2,3-dithiazolium chloride **1** (Appel salt) and its derivatives, we showed that 5-(*N*-arylimino)-4-chloro-5*H*-1,2,3-dithiazoles **2**, which are stable crystalline solids readily prepared in high yield from anilines and the salt **1**, cyclised by vigorous heating to give sulfur, hydrogen chloride and 2-cyanobenzothiazoles (Fig. 2).[6]



Ellipticine (**I**) (**II**) (**III**)

Figure 1.

Keywords: ellipticine analogues; 4,5-dichloro-1,2,3-dithiazolium chloride; thiazolocarbazoles.

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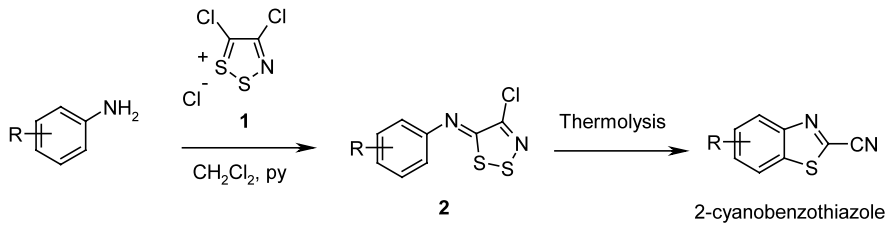


Figure 2.

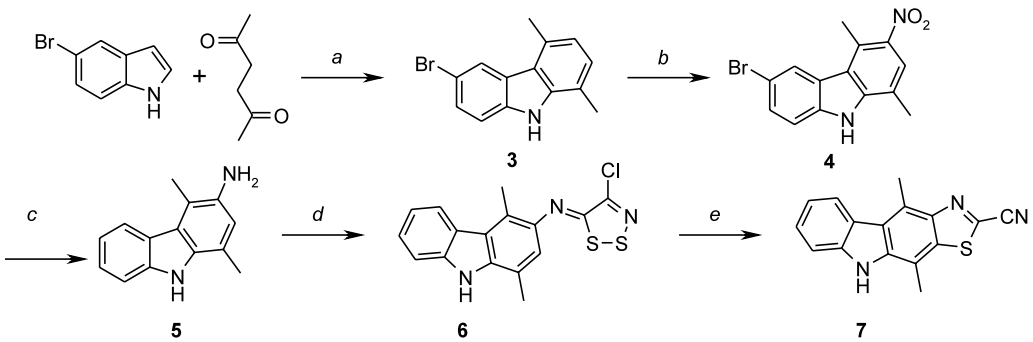
Synthesis of the rare thiazolocarbazole ring was performed in five steps via the intermediate 3-amino-1,4-dimethyl-9*H*-carbazole, which was prepared from the starting 5-bromoindole. As previously described,[7] in such a sequence, starting from indole may lead to a polynitrated compound in positions 3 and 6 of the carbazole skeleton. A strategy which consists in forming the benzothiazole moiety before creating the carbazole ring was also studied with no success.

The 6-bromo-1,4-dimethyl-9*H*-carbazole **3** was prepared, in a yield of 46% by treatment of the 5-bromoindole with hexane-2,4-dione in the presence of *p*-toluenesulphonic acid. Regioselective nitration in position 3 of the carbazole ring was performed in good yield (70%) by treatment of **3** with nitric acid in the presence of acetic anhydride. Reduction of the nitrocarbazole **4** was accompanied by dehalogenation of the aromatic skeleton and led to the desired 3-amino-1,4-dimethylcarbazole **5**.

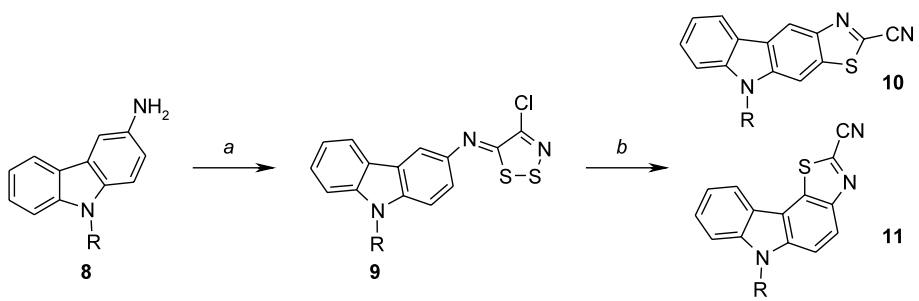
Using a standard method applied for the preparation of *N*-arylimino-1,2,3-dithiazoles,[6a–d] the aminocarbazole **5** was condensed with 4,5-dichloro-1,2,3,-dithiazolium chloride **1** in dichloromethane at room temperature, followed by addition of pyridine, to give the desired imino-1,2,3-dithiazolocarbazole **6** in good yield (73%) (Scheme 1).

The best thermolysis procedure consisted of heating the imine **6** at 200°C in the presence of diphenyl ether for 30 minutes. A short exploration of various alternatives has shown that heating **6** at 200°C (neat) for 2 min, or at 140°C for 2 or 3 days in sealed tube in the presence of toluene, gave worse results. Exposing the same imine to microwave irradiation,[6b] neat in a glass vial with a screw cap lid, was also unsuccessful. The expected compound **7** was then obtained in a reasonable yield (39%).[8]

Following a similar strategy, demethylated analogues of ellipticine were prepared from various 3-aminocarbazoles **8** via the corresponding imino-1,2,3-dithiazoles **9**. Whatever thermolysis conditions were used, the wanted linear thiazolocarbazoles **10** were the minor products, whilst their angular counterparts (**11**) were the major ones (Scheme 2). Unfortunately, when the reactions were performed from carbazole, no trace of the linear



Scheme 1. *Reaction conditions and yields*: (a) APTS, EtOH, reflux, 2 h, 46%; (b) HNO_3, Ac_2O, rt, 3 h, 70%; (c) H_2, Pd/C, EtOH, 50°C, 3 h, 60%; (d) **1**, pyridine, rt, 45 min, 73%; (e) diphenyl ether, 200°C, 30 min, 39%.



Scheme 2. Reaction conditions (for yields see Table 1): (a) **1**, pyridine, rt, 1 h; (b) neat, 200°C, 2 min.

Table 1. Synthesis of the imines **9** and thermolysis results

Starting material	R	Yield of **9** (%)	Yield of **10** (%)	Yield of **11** (%)
8a[a]	H	50	n.d.[b]	5
8b[c]	Et	70	12	38
8c[d]	$(CH_2)_2CO_2Et$	70	15	45

[a] The synthesis of **8a** involves nitration (HNO_3/CH_3COOH) of the carbazole (yield: 85%) and reduction of the nitro group (H_2, Pd/C in ethyl acetate) to give the corresponding amine (yield: 60%, see Refs 7b and 7c).
[b] n.d.: not detected.
[c] Commercially available.
[d] Prepared as described in Ref. 9.

derivative **10a** was detected and a very low yield of the angular product **11a** was obtained. Yields of compounds **9**, **10** and **11** are listed in Table 1.

In conclusion, we have described the synthesis of novel polyheterocyclic systems, which are structurally very close to the natural alkaloid ellipticine or pyridocarbazole congeners. In connection with our recently published results,[10] this work is a further example of the utility of 4,5-dichloro-1,2,3-dithiazolium chloride in the preparation of novel thiazolo heterocyclic systems. Preparation of various substituted derivatives is underway and their biological evaluation[11] will be described later.

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Selected data for the new linear thiazolocarbazoles analogues of ellipticine:
*4,10-Dimethyl-9*H*-1-thia-3,9-diaza-cyclopenta[*b*]fluorene-2-carbonitrile* ***7***: A solution of the imino-1,2,3-dithiazole **6** (0.3 mmol) in diphenyl ether (2 mL) was heated under argon at 200°C for 30 min. Purification by column chromatography (light petroleum/dichloromethane) afforded the attempted product **7**. Yellow needles, mp>260°C (Found M^+, 277.0677. $C_{16}H_{11}N_3S$ requires 277.0673); ν_{max} (KBr)/cm^{-1} 3394, 3347, 2222 (CN), 1605, 1578, 1458, 1329, 1251, 1120; δ_H (400 MHz, DMSO-d_6), 2.74 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 7.28 (td, 1H, $J=8.3$ and 1.9 Hz, H_{ar}), 7.52 (td, 1H, $J=8.3$ and 1.9 Hz, H_{ar}), 7.59 (d, 1H, $J=8.3$ Hz, H_{ar}), 8.29 (d, 1H, $J=8.3$ Hz, H_{ar}), 11.67 (s, 1H, NH); δ_C (100 MHz, DMSO-d_6) 15.5, 16.5, 108.9, 111.2, 114.1, 119.6, 122.9, 123.0, 123.1, 126.6, 126.8, 129.7, 133.6, 139.7, 141.4, 144.6; m/z 277 (M^+, 100%), 262 (M^+–CH_3, 13). Anal. calcd for $C_{16}H_{11}N_3S$: C, 69.29; H, 3.99; N, 15.15. Found: C, 69.26; H 4.04; N 15.12.
Thiazolocarbazoles ***10b*** *and* ***10c****; thermolysis general procedure.*
N-(4-Chloro-5*H*-1,2,3-dithiazol-5-yliden)anilines **9** were heated under argon at 200°C for 2 min. Separation and isolation of the isomers was performed by column chromatography (light petroleum/ethyl acetate) to afford the expected products **10b** (or **11b**) and **10c** (or **11c**).
*9-Ethyl-9*H*-1-thia-3,9-diaza-cyclopenta[*b*]fluorene-2-carbonitrile* ***10b***.
Pale yellow needles, mp=183–185°C (hexane) (Found M^+, 277.0675. $C_{16}H_{11}N_3S$ requires 277.0673); ν_{max} (KBr)/cm^{-1} 3080, 2924, 2219 (CN), 1598, 1476, 1350, 1287, 1237, 1120, 1071, 745; δ_H (400 MHz, DMSO-d_6), 1.36 (t, 3H, $J=7.2$ Hz, CH_3), 4.45 (q, 2H, $J=7.2$ Hz, CH_2), 7.28 (t, 1H, $J=7.7$ Hz, H_{ar}), 7.56 (t, 1H, $J=7.7$ Hz, H_{ar}), 7.63 (d, 1H, $J=7.7$ Hz, H_{ar}), 8.33 (d, 1H, $J=7.7$ Hz, H_{ar}), 8.35 (s, 1H, H_{ar}), 8.99 (s, 1H, H_{ar}); δ_C (100 MHz, DMSO-d_6), 13.1, 37.4, 110.7, 109.4, 113.8, 115.9, 119.6, 121.3, 121.7, 125.1, 127.6, 132.1, 133.8, 140.7, 141.3, 147.5; m/z 277 (M^+, 71%), 262 (M^+–CH_3, 100). Anal.

calcd for $C_{16}H_{11}N_3S$: C, 69.29; H, 3.99; N, 15.15. Found: C, 69.15; H 4.24; N 15.14.

Ethyl 3-(2-Cyano-1-thia-3,9-diaza-cyclopenta[b]fluoren-9-yl)propionate ***10c***.

Pale yellow needles, mp = 128–130°C (ethanol) (Found M^+, 349.0877. $C_{19}H_{15}N_3O_2S$ requires 349.0885); ν_{max} (KBr)/cm^{-1}, 2985, 2225 (CN), 1729 (CO), 1600, 1537, 1480, 1185; δ_H (400 MHz, $CDCl_3$), 1.15 (t, 3H, J = 7.3 Hz, CH_3), 2.91 (t, 2H, J = 7.0 Hz, CH_2COOEt), 4.08 (q, 2H, J = 7.3 Hz, $COOCH_2$), 4.69 (t, 2H, J = 7.0 Hz, NCH_2), 7.35 (t, 1H, J = 7.7 Hz, H_{ar}), 7.49 (d, 1H, J = 7.7 Hz, H_{ar}), 7.60 (td, 1H, J = 7.7 Hz, J = 1.2 and J = 1.3 Hz, H_{ar}), 7.93 (s, 1H, H_{ar}), 8.22 (d, 1H, J = 7.7 Hz, H_{ar}), 8.85 (s, 1H, H_{ar}); δ_C (100 MHz, $CDCl_3$) 13.7, 32.6, 38.7, 60.1, 101.0, 109.6, 113.7, 115.6, 119.7, 121.2, 121.6, 124.9, 127.4, 132.2, 133.6, 140.5, 141.2, 145.3, 170.8; m/z 277 (M^+, 71%), 262 (M^+–CH_3, 100). Anal. calcd for $C_{19}H_{15}N_3O_2S$: C, 65.31; H, 4.32; N, 12.02. Found: C, 65.21; H, 4.05; N, 11.88.

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