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First synthesis of pyrrolo[1,2:1′,2′]azepino[5,6-*b*]indole derivatives

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Abstract—A new family of pyrrolo[1,2:1′,2′]azepino[5,6-*b*]indole derivatives **8**,**15** related to anthramycin skeleton was prepared in good yield from indole-2-carboxylic acid and β-aminoesters **4** through intramolecular cyclisation.

The pyrrolo[2,1-*c*][1,4]benzodiazepine (PDB) antitumor antibiotics are a well-known class of sequence-selective DNA-binding agents.[1] Among the PDB family, anthramycin (Fig. 1) have shown significant in vitro cytotoxicity but have not progressed in clinical trials due to side effects (cardiotoxicity,…). Improvements to enhance antitumor potency and to surmount this drawback have been done.[2] Nevertheless the need for analogous structures was still of interest.[3,4] Recently Erba et al. have reported the preparation of the pyrrolo[1,2-*c*]1,4-diazepine ring **A** from 2-amidinylindole-3-carbaldehyde.[5] This prompts us to report our own preliminary results.

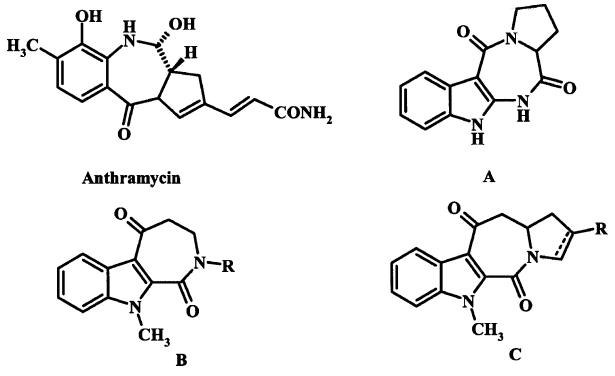
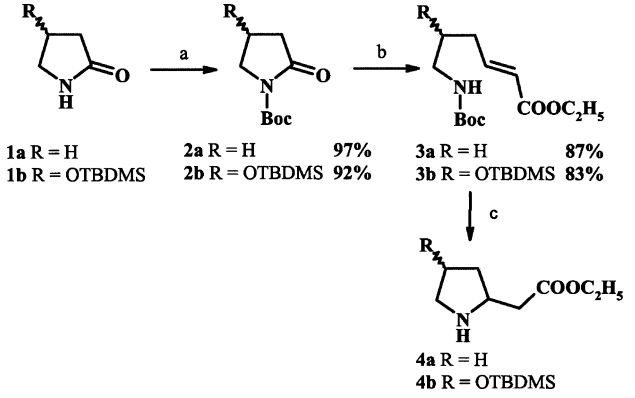


Figure 1.

In continuation of our work in the synthesis of azepino[3,4-*b*]indole-1,5-dione framework **B**[6] as a potential scaffold for PKC inhibitors, we became interested in the design of tetracyclic compounds **C**.

In our synthetic approach of derivatives **C**, β-aminoesters **4** with a pyrrolidino structure was first prepared in a different way described by Benn et al.[7] The latter were obtained in three steps from 2-pyrrolidinones **1** (Scheme 1). Compound **1a** is commercially available. Pyrrolidinone **1b** was prepared in 99% yield by selective silylation of commercially available (*R*)-4-hydroxy-2-pyrrolidinone (or (*S*)-4-hydroxy-2-pyrrolidinone).[8] Boc protection[8] on 2-pyrrolidinones **1** was



Scheme 1. *Reagents and conditions*: (a) Boc_2O (1 equiv.), DMAP (10% mol), MeCN, rt, 18 h; (a) i. $LiBEt_3H$ (1 equiv.), THF, −78°C, 30 min; ii. $(EtO)_2P(O)CH_2CO_2Et$ (1 equiv.), NaH (1 equiv.), THF, 2 h; (c) i. TFA/CH_2Cl_2 1/1, 0°C, 2 h; ii. Et_3N, CH_2Cl_2, rt, 2 h.

Keywords: anthramycin; indole; pyrrolidine; intramolecular cyclisation.

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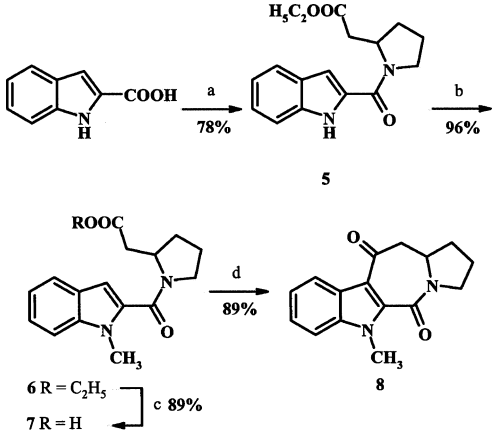
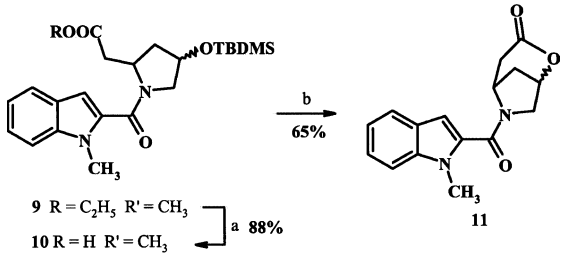
performed to give **2** in 92–97% yield. Reduction of the lactam function was carried out with super Hydride® in THF at −78°C,[9] the resulting aminal was then treated with the sodium salt of ethyl phosphonoacetate (1 equiv.) at room temperature. The two-step procedure afforded **3** from **2** in 83–87% overall yield. Deprotection of **3** in acidic medium afforded the trifluoroacetate salt which upon basic treatment gave the cyclic ethyl aminoesters **4**. Compounds **4** were directly used in next step without purification.

Crude compound **4a** was coupled with indole-2-carboxylic acid to provide, under classical conditions, amide **5** in 78% yield. Methylation of the nitrogen indolic atom was achieved with iodomethane in refluxing acetonitrile to afford **6** in 96% yield. Acid **7** was obtained by basic hydrolysis (lithium hydroxide) of the ester **6** in 89% yield. Final cyclisation of **7** in the presence of PPA was performed at 110°C for 30 min to give the desired framework **8** in 89% yield (Scheme 2).

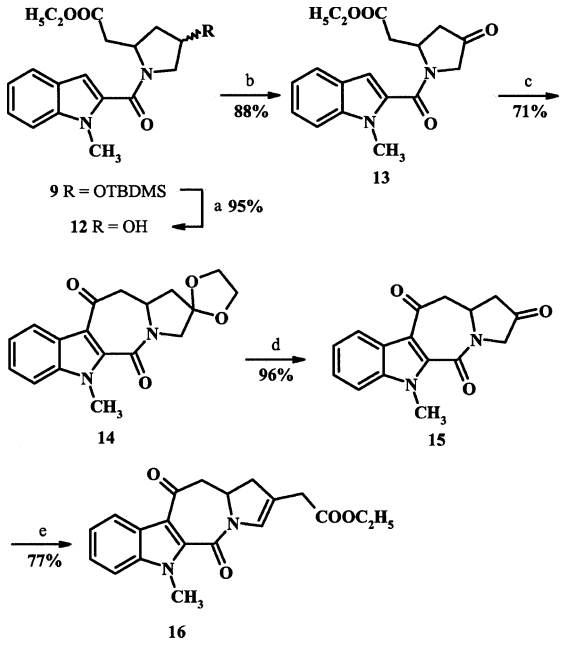
The synthesis of the analogous compound **15** with a ketonic group on the pyrrolidino moiety was more problematic. Treatment of 1-methyl-indole-2-carboxylic acid with **4b** afforded amide **9** in 71% yield as a mixture of diastereomers (7/3) which were separated by column chromatography. Hydrolysis of **9** (mixture of diastereomers or each one separately) with LiOH afforded the acid **10** in excellent yield. A first attempt of cyclisation on one diastereomer (presumably the *cis* one) with PPSE in nitromethane provided exclusively the lactone **11** in 65% yield. The other diastereomer gave in the same conditions a mixture of compounds from which lactone **11** is isolated in 30% yield (Scheme 3).



Scheme 2. *Reagents and conditions*: (a) **3a** (1 equiv.), EDCI (1.5 equiv.), DMAP (0.2 equiv.), CH_2Cl_2, rt, 18 h; (b) K_2CO_3 (5 equiv.), MeI (5 equiv.), MeCN reflux; (c) LiOH (1.5 equiv.), EtOH, 15 h, rt; (d) PPA, 110°C, 30 min.

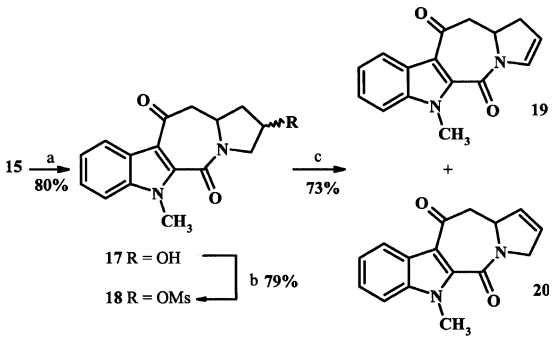


Scheme 3. *Reagents and conditions*: (a) LiOH (1.5 equiv.), EtOH, rt, 15 h; (b) PPSE, 110°C, 30 min.



Scheme 4. *Reagents and conditions*: (a) $Bu_4N^+F^-$ (1 equiv.), THF, rt, 5 min; (b) PDC (3 equiv.), molecular sieves 4 Å, CH_2Cl_2, rt, 24 h; (c) ethyleneglycol (5 equiv.), PTSA (2 equiv.), toluene reflux, 8 h; (d) 20% aq. HCl, MeOH reflux, 30 min; (e) NaH (2 equiv.), $(C_2H_5O)_2P(O)CH_2COOC_2H_5$ (2 equiv.), THF, rt, 5 min.

This result indicated the need for a more resistant hydroxyl protective group. Fluoride deprotection in THF of the silyl ether **9** afforded after 5 min the alcohol **12** with a 95% yield. Unfortunately the benzyl protection of **12** was not possible and gave only a mixture of degradation products. So the alcoholic function was further oxidised into the ketonic derivative **13** (88% yield) using PDC. Saponification of **13** immediately afforded again a degradation. Compared to **7**, the low stability of acid was due to the presence of the keto group, so an acetal protection was performed on **13** in the presence of ethyleneglycol and a catalytic amount of PTSA. We observed to our delight the concomitant formation of the acetal derivative and traces of cyclised compound **14**. The cyclisation conditions were optimised and finally the treatment of **13** with 5 equiv. of ethyleneglycol and 2 equiv. of PTSA in refluxing toluene for 8 h in a Dean Stark afforded the cyclised derivative **14** in 71% yield (Scheme 4). A TLC monitoring indicates first the formation of acetal derivative then cyclisation. This data was confirmed by the inertness of the keto ester in absence of ethylene glycol.



Scheme 5. *Reagents and conditions*: (a) $NaBH_4$ (1 equiv.), MeOH, rt, 5 min; (b) MsCl (5 equiv.), pyridine, rt, 30 min; (c) DBU (3 equiv.), DMF, reflux, 8 h.

Deprotection of the ketone occurred by refluxing **14** in methanol with 20% aq. HCl for 30 min and furnished **15** in 96% yield. The keto group of the pyrrolidino moiety was expected to be more reactive towards nucleophilic reagents and this was illustrated by treatment of **15** with the ethyl phosphonate anion (2 equiv.) in THF at room temperature. After 5 min, compound **16** was obtained as the major product and the sole product after basic isomerisation, in the mixture, of the exocyclic double bond into the pyrrolidino moiety of the minor isomer.

The keto group of compound **15** was also reduced into the alcohol **17** (80% yield) by $NaBH_4$ in MeOH. Compound **17** was treated with methanesulfonyl chloride as described by Rault et al.[10] to lead to the mesylate **18** (79% yield) which was heated in the presence of DBU to give both compounds **19** and **20**[11] which were purified by column chromatography (73% overall yield 3/1 ratio) (Scheme 5).

In summary, a new pyrrolo[1,2:1′,2′]azepino[5,6-*b*]-indole family was developed in fair yield. We are now investigating the reactivity of the system and more particularly the position 4 of the azepino ring which is involved in biological properties.

Acknowledgements

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11. Physical data of **8**: white solid; mp 156–158°C (ethyl acetate); IR (KBr) ν 1640 (CO), 1622 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.81–2.10 (m, 3H, CH_2), 2.30–2.37 (m, 1H, CH_2), 2.76–3.03 (m, 2H, CH_2), 3.73–3.93 (m, 2H, CH_2), 4.08 (s, 3H, CH_3), 4.24–4.33 (m, 1H, CH), 7.30–7.41 (m, 3H, H_{ar}), 8.49 (d, 1H, $J=8.0$ Hz, H_{ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 23.2 (CH_2), 32.9 (CH_3), 33.2 (CH_2), 47.2 (CH_2), 50.4 (CH_2), 54.0 (CH), 110.2 (CH), 116.0 (C), 123.7 (CH), 123.8 (CH), 125.3 (C), 125.5 (CH), 135.3 (C), 138.2 (C), 159.5 (CO), 194.3 (CO); LRMS (CI) m/z 269 (MH^+); HRMS (CI) m/z calcd for $C_{16}H_{17}N_2O_2$ (MH^+): 269.1290. Found: 269.1287. Compound **15**: white solid; mp 216–218°C (ethyl acetate); IR (KBr) ν 1735 (CO), 1641 (CO), 1607 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.54 (dd, 1H, $J=3.2$, 19.2 Hz, CH_2), 2.87 (dd, 1H, $J=1.2$, 19.2 Hz, CH_2), 3.08–3.23 (m, 2H, CH_2), 4.08 (s, 3H, CH_3), 4.16 (d, 1H, $J=20.1$ Hz, CH_2), 4.34 (d, 1H, $J=20.1$ Hz, CH_2), 4.81–4.91 (m, 1H, CH), 7.33–7.45 (m, 3H, H_{Ar}), 8.48 (d, 1H, $J=8.4$ Hz, $1H_{Ar}$); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.9 (CH_3), 43.5 (CH_2), 51.1 (CH_2), 51.5 (CH), 53.0 (CH_2) 110.4 (CH), 116.6 (C), 123.9 (CH), 124.1 (CH), 125.2 (C), 126.1 (CH), 133.4 (C), 138.6 (C), 160.4 (CO), 193.0 (CO), 207.0 (CO); LRMS (CI) m/z 283 (MH^+); HRMS (CI) m/z calcd for $C_{16}H_{15}N_2O_3$ (MH^+): 283.1082. Found: 283.1081. Compound **16**: white solid; mp 138–140°C (ethyl acetate); IR (KBr) ν 1735 (CO), 1637 (CO), 1612 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.30 (t, 3H, $J=7.3$ Hz, CH_3), 2.53 (dd, 1H, $J=3.2$, 18.1 Hz, CH_2), 2.81 (d, 1H, $J=18.1$ Hz, CH_2), 3.22 (s, 2H, CH_2), 3.23–3.34 (m, 2H, CH_2), 4.09 (s, 3H, CH_3), 4.19 (q, 2H, $J=7.3$ Hz, CH_2), 4.70–4.80 (m, 1H, CH), 7.03 (s, 1H, CH=), 7.34–7.44 (m, 3H, H_{Ar}), 8.57 (d, 1H, $J=8.4$ Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 14.4 (CH_3), 32.9 (CH_3), 34.2 (CH_2), 40.2 (CH_2), 51.1 (CH_2), 54.4 (CH), 61.3 (CH_2), 110.3 (CH), 116.1 (C), 118.9 (C), 124.0 (CH), 124.0 (CH), 125.3 (CH), 125.5 (C), 125.9 (CH), 134.2 (C), 138.7 (C), 156.2 (CO), 170.2 (CO), 193.3 (CO); LRMS (CI) m/z 353 (MH^+); HRMS (CI) m/z calcd for $C_{20}H_{21}N_2O_4$ (MH^+): 353.1501. Found: 353.1504. Compound **19**: white solid; mp 160–

162°C (ethyl acetate); IR (KBr) ν 1644 (CO), 1615 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.48–2.58 (m, 1H, CH_2), 2.80 (d, 1H, $J=18.0$ Hz, CH_2), 3.17–3.32 (m, 2H, CH_2), 4.11 (s, 3H, CH_3), 4.67–4.78 (m, 1H, CH), 5.42–5.46 (m, 1H, CH=), 7.08–7.12 (m, 1H, CH=), 7.33–7.42 (m, 3H, H_{Ar}), 8.50 (d, 1H, $J=8.5$ Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.9 (CH_3), 37.8 (CH_2), 51.1 (CH_2), 53.8 (CH), 110.3 (CH), 111.7 (CH), 116.2 (C), 124.0 (2CH), 125.5 (C), 125.9 (CH), 127.7 (CH), 134.4 (C), 138.7 (C), 156.4 (CO), 193.3 (CO); LRMS (CI) m/z 267 (MH^+); HRMS (CI) m/z calcd for $C_{16}H_{15}N_2O_2$ (MH^+): 267.1133. Found: 267.1135. Compound **20**: white solid; mp 140–142°C (ethyl acetate); IR (KBr) ν 1643 (CO), 1615 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.90–2.95 (m, 2H, CH_2), 4.12 (s, 3H, CH_3), 4.55–4.59 (m, 2H, CH_2), 5.00–5.08 (m, 1H, CH), 5.76–5.80 (m, 1H, CH=), 5.99–6.04 (m, 1H, CH=), 7.33–7.45 (m, 3H, H_{Ar}), 8.50 (d, 1H, $J=8.3$ Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 33.0 (CH_3), 49.5 (CH_2), 53.8 (CH_2), 60.8 (CH), 110.3 (CH), 116.2 (C), 123.9 (CH), 124.0 (CH), 125.5 (C), 125.7 (CH), 125.8 (CH), 128.8 (CH), 134.8 (C), 138.4 (C), 159.4 (CO), 193.3 (CO); MS m/z 267 (MH^+); LRMS (CI) m/z 267 (MH^+); HRMS (CI) m/z calcd for $C_{16}H_{14}N_2O_2$ (MH^+): 267.1133. Found: 267.1136.