Syntheses of 7-Phenyl-5*H*-thiazolo[5,4-*e*]pyrrolo[1,2-*a*][1,4]diazepin-10(9*H*)one, 7-Phenyl-5*H*-thiazolo[5,4-*e*][1,2,3,4]tetrazolo[5,1-*c*]-pyrrolo[1,2-*a*][1,4]diazepine and 7-phenyl-5*H*-thiazolo[5,4-*e*]-[1,3,4]triazolo[5,1-*c*]pyrrolo[1,2-*a*][1,4]diazepines [1]

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Fused tricyclic 7-phenyl-5*H*-thizolo[5,4-*e*]pyrrolo[1,2-*a*][1,4]diazepin-10(9*H*)one (**10**) was prepared by thermolysis of 2-phenyl-4-(1-pyrrolylmethyl)thiazole-5-carbonyl azide (**9**) in acetic acid. In addition, starting from **10**, 7-phenyl-5*H*-thiazolo [5,4-*e*][1,3,4]triazolo[5,1-*c*]pyrrolo[1,2-*a*][1,4]diazepines (**13**) and 7-phenyl-5*H*-thiazolo[5,4-*e*][1,2,3,4]tetrazolo[5,1-*c*]pyrrolo[1,2-*a*][1,4]diazepine (**14**) were synthesized.

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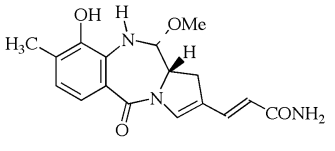
The pyrrolo[2,1-*c*][1,4]benzodiazepine antitumor antibiotics(PBDs), such as anthramycin (**1**) and DC-81 (**2**) are a well-known class of sequence-selective DNA-binding agents derived from *Streptomyces* species [2-4]. The antitumor activity of the PBDs is exterted through sequence-selective covalent binding to a C2-NH_2 group of guanine within the minor groove of double stranded DNA *via* the electrophilic N10-C11 carbinolamineimine functionality.

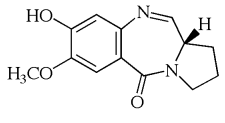
Although the N10-C11 carbinolamine moiety is responsible for the covalent (binding) component of DNA interaction, other features of the molecule, including the overall 3-dimensional shape and the substituents in the A-and C-rings, may also contribute to the non-covalent interaction with duplex DNA. Furthermore, this non-covalent component may constitue part of the DNA-recognition process, leading to the preferred binding site of 5'-Pu-G-Pu.

A recent study showed for the first time that PBD dilactam **3** could bind strongly to DNA as measured by thermal denaturation studies[5].We present in this paper the preparation of title compounds, which are structurally similar to PBDs, as possible effective drugs against cancer.



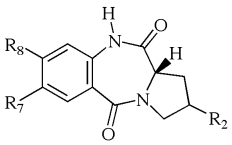
Amtramycin

1



DC-81

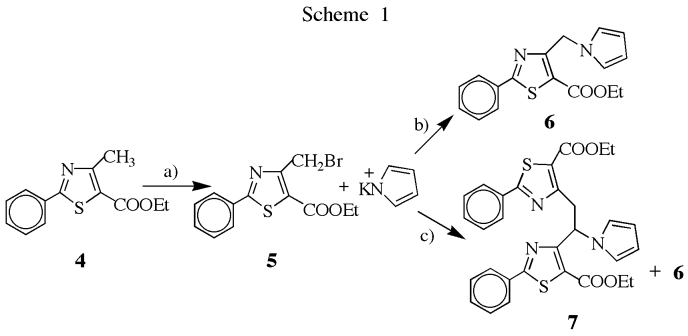
2



3

The starting material, namely ethyl 2-phenyl-4-(1-pyrrolylmethyl)thiazole-5-carboxylate (**6**) was prepared from the reaction of ethyl 4-bromomethyl-2-phenylthiazole-5-carboxylate (**5**) [6] with potassium salt of pyrrole in dry tetrahydrofuran (Scheme 1).

Scheme 1

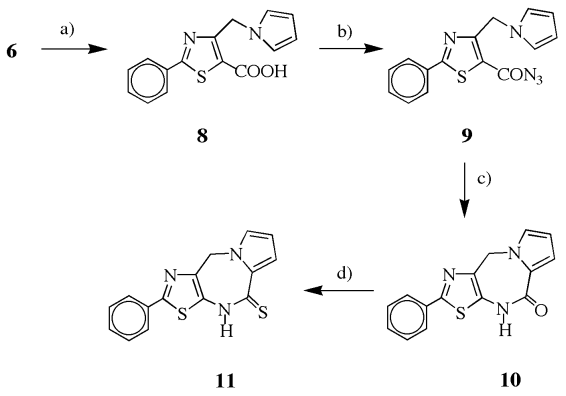


The product of this reaction depended on the reaction condition. When to a suspension of potassium salt of pyrrole in tetrahydrofuran at 0°, a solution of compound **5** was added and stirred for 3 hours compound **7** was obtained as a major product.We could presume that initially the expected product **6** was formed. However, hydrogen of the methylene group in compound **6** under experimental condition gave an anion, which in a nucleophilic substitution reaction with compound **5** gave compound **7**. When the reagents were added at 25º and refluxed for 4 hours, compound **6** could be obtained in a good yield.

Alkaline hydrolysis of compound **6** afforded 2-phenyl-4-(1-pyrrolylmethyl)thiazole-5-carboxylic acid (**8**). This acid was treated successively with triethylamine, ethylchloroformate and sodium azide [7] to give carbonyl azide **9** in 75% yield. Heating the carbonyl azide **9** in a large excess of acetic acid gave 7-phenyl-5*H*-thiazolo-[5,4-*e*]pyrrolo[1,2-*a*][1,4] diazepin-10(9*H*)one (**10**) in 47% yield [8,9]. Reaction of 1 equivalent of compound **10** in the presence of 1.1 equivlent of Lawesson's reagent in dioxane at 75º gave thiolactam **11** (Scheme 2) [10].

Reaction of compound **11** with hydrazine hydrate in ethanol at room temperature for 48 hours gave poor yield of 10-hydrazino-7-phenyl-5*H*-thiazolo[5,4-*e*]pyrrolo[1,2-*a*][1,4] diazepine(**12**). Refluxing compound **11** with hydrazine hydrate in ethanol resulted in decomposition of the starting material. However, compound **12** could be obtained in good yield, when compound **11** was reacted

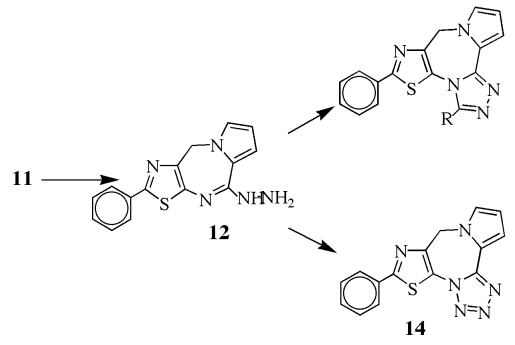
Scheme 2



with hydrazine hydrate in ethanol under ultrasonic irradiation for 12 minutes. Treatment of hydrazine **12** with substituted triethyl orthoformates in the presence of *p*-toluenesulfonic acid gave substituted triazoles **13a-d** [10]. The 7-phenyl-5*H*-thiazolo[5,4-*e*][1,2,3,4]tetrazolo[5,1-*c*]pyrrolo[1,2-*a*][1,4]diazepine (**14**) was obtained from the reaction of hydrazine **12** with sodium nitrite in 10% acetic acid (Scheme 3).

The structures of the designed fused diazepines**10-14** were supported by their ir, nmr and mass spectra as well as by their elemental analyses.The physical constants of triazoles **13a-d** are summarized in table 1.

Scheme 3



EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected.^{1}H nmr spectra were recorded on a Brucker FT-80 spectrometer. Tetramethylsilane was used as an internal standard. The infrared spectra were acquired on a Nicolet 550-FT spectrometer. The mass spectra were run on Finigan TSQ 70 spectrometer at 70 eV. Elemental analyses were carried out with a Perkin-Elmer Model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4% of the calculated amounts. Ethyl 4-methyl-2-phenylthiazole-5-carboxylate (**4**) and ethyl 4-bromomethyl-2-phenylthiazole-5-carboxylate (**5**) were prepared according to reported methods [5].

Ethyl 2-Phenyl-4-(1-pyrrolylmethyl)thiazole-5-carboxylate (**6**).

To a well stirred suspention of potassium salt of pyrrole [prepared from pyrrole (1.79 g, 26 mmoles) and potassium metal (1.04 g, 26 mg-atom)] in dry tetrahydrofuran, a solution of compound **5** (7.85 g, 24 mmoles) in 32 ml THF was added dropwise under argon atmosphere at 25°. The mixture was heated under reflux for 4 hours. After cooling to room temperature, the solvent was evaporated. The residue was treated with 50 ml of water and the mixture was extracted with *n*-hexane (3×25 ml). The combined organic layers were washed with brine, dried (anhydrous sodium sulfate) and evaporated under reduced pressure to give the crude product. The crude product was crystallized from methanol/diethyl ether (7:3) to yield 4.5 g (60%) of compound **6** as white solid, mp 78- 79°; ir (potassium bromide): ν 3414, 2927, 1710, 1525, 1269, 1092, 755, 717 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.4 (t, J=7 Hz, 3H, OCH_2CH_3), 4.39 (q, J=7 Hz, 2H, OCH_2), 5.5 (s, 2H, CH_2-N), 6.1 (t, J=2 Hz, 2H, H_3 and H_4 pyrrole),6.92 (t, J=1 Hz, 2H, H_2 and H_5 pyrrole), 7.39-7.47 (m, 3H, aromatic), 7.88-7.97 (m, 2H, aromatic); ms: m/z (%) 312 (M^+, 100), 283 (48), 239 (84).

Anal. Calcd. for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.28; H, 5.21; N, 8.99.

Ethyl 2-Phenyl-4-[1-(pyrrolyl)-2-(2'-phenyl-5'-ethoxycarbonyl-4'-thiazolyl)ethyl]thiazole-5-carboxylate (**7**).

This compound was prepared as explained for compound **6**, but reagents were added at 0° and stirred for 3 hours. The solvent was removed under reduced pressure and the residue was treated with 50 ml of water. The mixture was extracted with hexane (3×25 ml). The combined organic layers were washed with brine, dried (anhydrous sodium sulfate) and evaporated under reduced pressure to give the crude product. The crude product was crystallized from diethyl ether to yield 7 g (49%) of compound **7** as yellow solid, mp 158-160°; ir (potassium bromide): ν 3429, 2925, 1706, 1527, 1420, 1275, 1082, 724 cm^{-1};

Table 1

Physical data for **13a-d**

Comp.	R	Mp [a]	Yield	Formula	Calc	Found	Calc	Found	Calc	Found
					C%		H%		N%	
13a	H	215-217	72	$C_{16}H_{11}N_5S$	62.93	62.65	3.63	3.83	22.93	22.78
13b	Me	272-274	65	$C_{17}H_{13}N_5S$	63.93	63.85	4.10	4.22	21.93	21.85
13c	Et	238-239	71	$C_{18}H_{15}N_5S$	64.84	64.72	4.53	4.44	21.00	21.14
13d	Ph	295-296	68	$C_{22}H_{15}N_5S$	69.27	69.32	3.96	3.81	18.36	18.42

[a] All compounds were crystallized from chloroform/ether.

^{1}H nmr (deuteriochloroform):δ 1.36 (t, J=7.1 Hz, 6H, 2 OCH_2CH_3), 4.13-4.45 (m, 6H, CH-CH_2 and 2 OCH_2CH_3), 6.05 (t, J=2 Hz, 2H, H_3 and H_4 pyrrole), 6.8-7.01 (m, 3H, C*H*-CH_2, H_2 and H_5 pyrrole), 7.41-7.50 (m, 6H, aromatic), 7.81-8.17 (m, 4H, aromatic); ms: m/z (%) 557 (M^+, 30), 511 (14), 417 (18), 311(100), 265 (64).

Anal. Calcd. for $C_{30}H_{27}N_3O_4S$: C, 64.61; H, 4.88; N, 7.53. Found: C, 64.56; H, 4.76; N, 7.61.

The remaining ether solution was concentrated under reduced pressure and crystallized from methanol/diethyl ether (7:3) to yield 1.5 g (20%) of compound **6**, mp 78-79°.

2-Phenyl-4-(1-pyrrolylmethyl)thiazole-5-carboxylic Acid (**8**).

A mixture of ester **6** (3.12 g, 10 mmoles) and potassium hydroxide pellets (1.5 g, 30 mmoles) in a mixture of methanol (20 ml) and water (5 ml) was refluxed for 3 hours. After cooling, the reaction mixture was concentrated in reduced pressure, diluted with 40 ml of water and extracted with ether (2x30 ml). The aqueous layer was cooled and acidified with hydrochloric solution (1:1). The precipitate was filtered, washed with diethyl ether and finally crystallized from methanol to yield 2.84 g (70%) of compound **8** as white solid, mp 168-169°; ir (potassium bromide):ν 3439, 2925, 1666, 1527, 1414, 1295, 1085, 724cm^{-1}; ^{1}H nmr (deuteriochloroform):δ 5.56 (s, 2 H, CH_2-N), 6.15 (t, J=2 Hz, 2 H, H_3 and H_4 pyrrole), 6.93 (t, J=1 Hz, 2H, H_2 and H_5 pyrrole), 7.12-7.52 (m, 3H, aromatic), 7.9 -8.2 (m, 2H, aromatic); ms: m/z (%) 284 (M^+,100), 266 (16), 239 (42), 219 (40) ,135 (28),104 (50).

Anal. Calcd. For $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.41; H, 4.32; N, 9.79.

2-Phenyl-4-(1-pyrrolylmethyl)thiazole-5-cabonyl Azide (**9**).

To a well stirred and cooled solution of carboxylic acid **8** (9.8 g, 33 mmoles), dry acetone (98 ml) and dry triethylamine (3.55 g, 35 mmoles) was added under an atmosphere of argon, a solution of ethyl chloroformate (4.94 g, 45 mmoles) in dry acetone (13 ml) over a period of 10 minutes. The stirring was continued at 0-5° for 30 minutes and a solution of sodium azide (3.8 g, 59 mmoles) in 13 ml of cool water was added dropwise. After the addition was completed the reaction mixture was stirred at 0° for 1 hour. The mixture was poured on crushed ice and extracted with carbon tetrachloride (3×50 ml). The combined organic layers were washed with water, dried (anhydrous sodium sulfate) and evaporated under reduced pressure to give 7.46 g (70%) of compound **9** as yellow oil. This oil was used for the next reaction without further purification; ir (chloroform): ν 1700, 1275 cm^{-1}; ^{1}H nmr (deuteriochloroform):δ 5.61 (s, 2 H, CH_2-N), 7.31(t, J=2 Hz, 2H, H_3 and H_4 pyrrole), 7.31 (t, J=1 Hz, 2H, H_2 and H_5 pyrrole), 7.42-7.68 (m, 3H, aromatic), 8.1-8.31 (m, 2H, aromatic).

7-Phenyl-5*H*-thiazolo[5,4-*e*]pyrrolo[1,2-*a*][1,4]diazepin-10(9*H*)one (**10**).

A solution of carbonyl azide **9** (1 g, 3.24 mmoles) in 50 ml glacial acetic acid was refluxed vigorously for 2 hours. The solvent was removed under reduced pressure. The residue after trituration with diethyl ether was filtered and crystallized from ethyl acetate/diethyl ether (8:2) to yield 550 mg (47%) of compound **10** as white solid, mp 235-237°; ir (potassium bromide):ν 3423, 2925, 1639, 1281, 1089, 724 cm^1 ; ^{1}H nmr (dimethyl sulfoxide-d_6):δ 5.39 (s, 2H, CH_2-N), 6.12-6.17 (m, 1H, H_2), 6.71-6.82 (m, 1H, H_3), 7.18-7.23 (m, 1H, H_1), 7.41-7.48 (m, 3H, aromatic), 7.77-7.91 (m, 2H, aromatic); ms: m/z (%): 281 (M^+, 100), 252 (15), 219 (57), 121 (59).

Anal. Calcd. for $C_{15}H_{11}N_3OS$: C, 64.04; H, 3.94; N, 14.94. Found: C, 64.14; H, 3.86; N, 14.87.

7-Phenyl-5*H*-thiazolo[5,4-*e*]pyrrolo[1,2-*a*][1,4]diazepine-10(9*H*)thione (**11**).

A solution of compound **10** (8.99 g, 32 mmoles) and Lawesson's reagent (14.25 g, 35 mmoles) in dioxane (80 ml) was heated at 75° for 3 hours. The solvent was removed under reduced pressure. The residue was suspended in 200 ml of 40% aqueous sodium hydroxide and stirred for 1 hour.The mixture was extracted with ethyl acetate (3×20 ml) and the aqueous layer was acidified with acetic acid. The precipitate was collected, dried and crystallized from methanol to yield 6 g (63%) of compound **11** as yellow solid, mp 228- 230°; ir (potassium bromide): ν 3438, 2929, 1701, 1639, 1402, 751 cm^1 ; ^{1}H nmr (deuteriochloroform):δ 5.31 (s, 2H, CH_2-N), 6.23-6.36 (m, 1H, H_2), 6.91-7.15 (m,1H, H_3), 7.35-7.55 (m, 4H, H_1 and aromatic), 7.62-8.13 (m, 2H, aromatic); ms: m/z (%): 297 (M^+, 25), 238(10), 193 (17), 109 (48), 68 (50), 42 (100).

Anal. Calcd. for $C_{15}H_{11}N_3S_2$: C, 60.58; H, 3.73; N, 14.13. Found: C, 60.43; H, 3.82; N, 14.25.

10-Hydrazino-7-phenyl-5*H*-thiazolo[5,4-*e*]pyrrolo[1,2-*a*][1,4]diazepine (**12**).

A solution of thiolactam **11** (1.1 g, 4 mmoles) and hydrazine monohydrate (1.55 ml, 32 mmoles) in ethanol (30 ml) was stirred under ultrasonic irradiation at room temperature for 12 minutes. The solvent was removed under reduced pressure and the residue was taken up in 50 ml of 20% aqueous hydrochloric acid and stirred for 1 hour. The mixture was extracted with chloroform (3×25 ml). The aqueous layer was neutralized with sodium hydroxide. The precipitate was collected, washed with water and crystallized from water to yield 540 mg (50%) of compound **12** as white solid, mp 144-145°; ir (potassium bromide):ν 3417, 3312, 2918, 1575, 1523, 1453, 1244, 725 cm^1; ms: m/z (%): 295 (M^+, 100), 277 (21), 235 (15), 200 (17), 187 (16), 92 (29).

Anal. Calcd. for $C_{15}H_{13}N_5S$: C, 61.00; H, 4.44; N, 23.71. Found: C, 60.84; H, 4.29; N, 23.66.

7-Phenyl-5*H*-thiazolo[5,4-*e*][1,3,4]triazolo[5,1-*c*]pyrrolo[1,2-*a*]-[1,4] diazepine (**13a**).

A solution of compound **12** (400 mg, 1.35 mmoles), triethyl orthoformate (13 mmoles) and *p*-toluenesulfonic acid (0.5 g) in ethyl acetate was refluxed for 30 minutes.The precipitate was isolated by filtration and purified by flash chromatography on silica gel using diethyl ether/methanol (9:1) as eluent; ir (potassium bromide): ν 3427, 2929, 1738, 1648, 1570, 1454, 1376, 1076, 720 cm^1; ^{1}H nmr (deuteriochloroform): δ 5.34 (s, 2 H, CH_2-N), 6.21 - 6.35 (m, 1H, H_2), 6.85-6.92 (m, 1H, H_3), 7.08-7.23 (m, 1H, H_1), 7.35-7.52 (m, 3H, aromatic), 7.62-7.89 (m, 2H, aromatic), 8.39 (s, 1H, triazole); ms: m/z (%) 305 (M^+, 100), 277 (10), 251 (11), 202 (13),174 (18),147 (20), 121 (25), 103 (62), 70 (75).

Anal. Calcd. for $C_{16}H_{11}N_5S$: C, 62.93; H, 3.63; N, 22.93. Found: C, 62.65; H, 3.83; N, 22.78.

Compounds **13b** to **13d** were prepared similarly (see Table 1).

7-Phenyl-5*H*-thiazolo[5,4-*e*][1,2,3,4]tetrazolo[5,1-*c*]pyrrolo-[1,2-*a*][1,4]diazepine (**14**).

To a solution of compound **12** (1.18 g, 4 mmoles) in 10% acetic acid (40 ml) was added sodium nitrite (0.4 g, 6 mmoles) and stirred at room temperature for 1 hour .The precipitate was isolated by filtration, washed with water and purified by flash chromatography on silica gel using *n*-hexane to yield 310 mg (74%) of compound **14** as pink crystals, mp 263-265°; ^{1}H nmr(deuteriochloroform): δ 5.45 (s, 2 H, CH_2-N), 6.31-6.42 (m, 1H, H_2), 6.93-7.13 (m, 1H, H_3), 7.18-7.26 (m, 1H, H_1), 7.46-7.53 (m, 3H, aromatic), 7.91-8.01 (m, 2H, aromatic); ms: m/z (%) 306 (M^+, 10), 278 (31), 252 (10), 187(17), 148(9), 121 (25), 103 (78), 70 (100).

Anal. Calcd. for $C_{15}H_{10}N_6S$: C, 58.81; H, 3.29; N, 27.43. Found: C, 58.73; H, 3.17; N, 27.32.

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