Zagazig J. Pharm. Sci., December. 2006
Vol. 15, No. 2, pp.29 - 37

ISSN 1110-5089

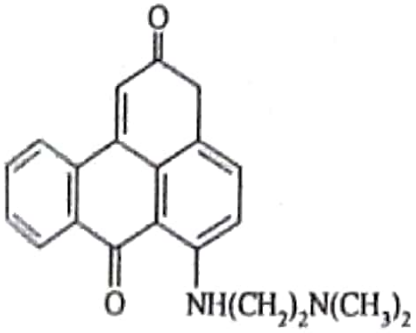
SYNTHESIS OF CERTAIN NOVEL PYRIDOTHIOPYRANOQUINOLINES AS POTENTIAL ANTICANCER AGENTS

Khaled R. El-Shemy, Osama M. El-Badry, Sameha. Roshdy, Mervat M. El-Enany and Mohamed A. H. Ismail*

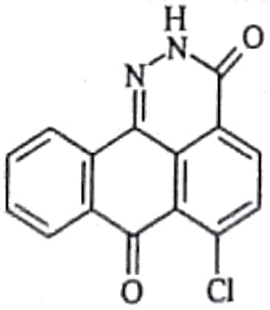
Organic Chemistry Department, Faculty of Pharmacy, Cairo University, Cairo
* Medicinal Chemistry Department, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt

ABSTRACT

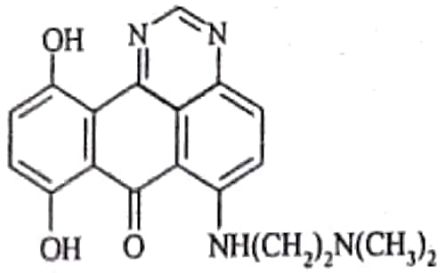
A series of ethyl 2-substituted aminopyrido[3',2': 5,6]thiopyrano [4,3,2-de]quinoline-1-carboxylate (VII_{a})$_{i\text{-}viii}$ was obtained by reacting ethyl2-chloropyrido[3',2':5,6]thiopyrano[4,3,2-de]quinoline-1-carboxylate (VI_{a}) with certain aromatic amines. Another series of ethyl 6-chloro-9,11-dimethyl-2-substituted aminopyrdo [3',2':5,6]thiopyrano [4,3,2-de]quinoline-1-carboxylate (VII_{b})$_{i\text{-}viii}$ was also obtained by reacting ethyl 2,6-dichloro-9,11-dimethylpyrido [3',2':5,6]thiopyrano[4,3,2-de] quinoline-1-carboxylate (VI_{b}) with different amines. Molecular modeling study and *in vitro* cytotoxic effect of some samples of the synthesized compounds were also achieved.



(1)



(2)



(3)

INTRODUCTION

Literature survey illustrates that DNA intercalators represent one of the most important anticancer chemotherapeutic agents.

Several anthracyclines and some of their chromophoric modification analogues are of useful anticancer activity by DNA intercalation.

Anthracyclines analogues are fused linear tricyclic or tetracyclic system having the necessary area needed for efficient intercalation binding, but that is not sufficient for effective antitumor activity. An absolute requirement for antitumor activity appears to be a suitably placed basic side chain. The latter presumably has the function of additionally stabilizing the drug / DNA complex formation and influencing the kinetics of this binding process.[1]

Anthracenedione, anthrapyrazole and anthrapyridazone systems with two basic side arms exhibit comparable or lower activity than their analogues with side chain.[2]

In the anthracene diones, replacement of carbon with nitrogen retained the antitumor activity and abolished cardiotoxicity.[3]

Bearing in mind these structural characteristics, our interest was confined to the synthesis of two groups of pyridothiopyrano quinolines (VIIa)i-viii and (VIIb)i-viii carrying the required pharmacophoric groups with the hope that the new products would show superior antitumor activity and lower cardiotoxicity. The two synthesized series have structural relationship to certain naphthoquinolones [4], naphtophthalezones [5], and naphtoquinazolines [6], which have been reported as potent antitumor agents.

RESULTS AND DISCUSSION

According to reported procedures[7] cyclization of $I_{a,b}$ could be affected by using polyphosphoric acid to give 6-chloro-5H-[1]benzothiopyrano[2,3-b]pyridine-5-one (II_{a}) and 6,9-dichloro-2,4-dimethyl-5H-[1] benzothiopyrano [2,3-b] pyridine-5-one(II_{b})respectivelely. Reacting $II_{a,b}$ with p-toluenesulphonamide followed by hydrolysis yielded the corresponding amino derivatives $III_{a,b}$. Treating the latter with diethyl malonate afforded the respective ethoxycarbonylacetylamino derivatives $IV_{a,b}$ in a good yield. Compounds $IV_{a,b}$ were cyclized via heating under reflux with sodium ethoxide in ethanol to give 2-hydroxy tetracyclic compounds $V_{a,b}$. Treating the latter with PCl_5 afforded the corresponding 2-chloro derivatives $VI_{a,b}$. The target compounds (VII_{a})$_{i\text{-}viii}$ and (VII_{b})$_{i\text{-}viii}$ were produced via condensation of $VI_{a,b}$ with different aromatic amines respectively.

EXPERIMENTAL

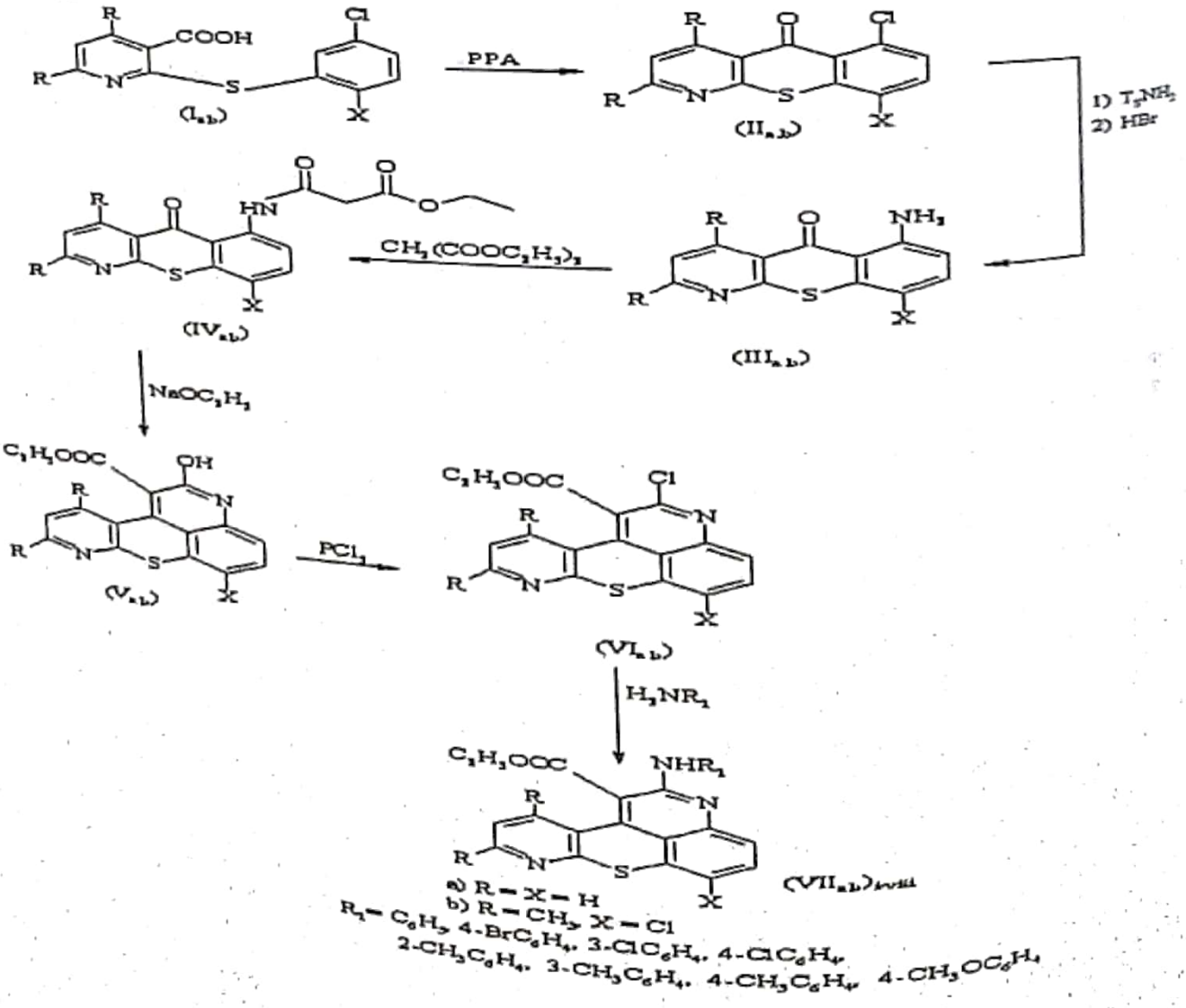
All melting points were determined on a Graffin apparatus and are uncorrected. Microanalyses were

carried out at the Microanalytical center, Cairo University. IR spectra were recorded on a Shimadzu 435 Spectrometer using KBr discs. ^{1}H-NMR spectra were performed on a Jeol NMR FXQ-200MHZ Spectrometer using TMS as an internal standard. Mass spectra were recorded on a GCMS-QP 1000 EX Mass Spectrometer. Progress of the reactions was monitered by TLC using percolated aluminium sheets silica gel MERCK 60 F 254 and were visualized by UV lamp. Molecular modeling studies were carried out at the department of medicinal chemistry, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt. Antitumer screening was done at National Cancer Institute, Cairo University, Cairo, Egypt. Compounds $I_{a,b}$ and $II_{a,b}$ were prepared in our recent publications[7]. Compounds III_a, IV_a and V_a were prepared according to reported procedures[8].

6-Amino-9-chloro-2,4-dimethyl- 5H - [1] benzothio-pyrano [2,3-b] pyridine -5-one (IIIb)

A mixture of 6,9-dichloro-2,4-dimethyl-5H-[1]benzothiopyrano [2,3-b] pyridine-5-one (II_b) (15.45g, 0.05 mol.), p-toluenesulphonamide (17.1g, 0.1 mol.) anhydrous sodium acetate (8.2g, 0.1 mol.), copper (II) acetate monohydrate (1.0g, ~ 0.05 mol.) and n-amyl alcohol (160 ml.) was stirred under reflux for 8 hrs in an oil bath at 160-170°C. After cooling, the resulting solid was filtered, dried to give 6-p-toluenesulphonamido derivative, which was mixed with phenol (14.1 g, 0.15 mol.) and 47% HBr (150 ml). The mixture was stirred and heated under reflux for 8 hrs. After cooling, the acidic solution was extracted with chloroform. The aqueous layer was poured into 30% sodium hydroxide (25 ml). The formed precipitate was filtered, dried and recystallized from methanol to give III_b. m.p., 212-214°. Yield, 9.3g, 32%. Anal. Calcd. for $C_{14}H_{11}ClN_2OS$: C, 57.83, H, 3.78, N 9.63. Found: C, 57.67, H, 3.82, N, 9.52. IR (KBr, ν Cm^{-1}): 3405, 3381 (NH_2), 1665 (C=O). ^{1}HNMR (DMSO, δppm): 1.7 (br. S, 2H, NH_2, D_2O exchangeable), 2.45 (s, 3H, CH_3), 2.8 (s, 3H, CH_3), 6.45 (d, 1H, H7), 7 (s, 1H, H3), 7.3 (d, 1H, H8). MS, m/z : 290 (M^+., 100.0%), (M^+ +2) 292 (42.7%).

Scheme (1) :



9-chloro-6-Ethoxycarbonylacetamido-2,4-dimethyl-5H-[1] benzothiopyrano [2,3-b] pyrisin-5-one (IV_b):

Asolution of 6-amino, 9-chloro-2,4dimethyl-5H-[1] benzothiopyrano[2,3-b] pyridin-5-one (III_b) (8.72g, 0.03 mol.) in diethyl malonate (60 ml, 0.37 mol.) was boiled for 20 minutes then an exess of diethyl malonate was removed by evaporation. The residue was purified by column chromatography on silica gel ($CHCl_3$) to give IV_b as pale yellow needles. m.p., 128-130°. Yield, 9.3g, 72%. Anal. Calcd. for $C_{19}H_{17}ClN_2O_4S$: C, 56.37, H, 4.23, N 6.92. Found: C, 56.13, H, 4.63, N, 7.52. IR (KBr, ν Cm^{-1}): 3395-3345 (NH), 1738 (C=O, ester), 1660 (C=O, ketone), 1618 (C=O, amide). ^{1}HNMR (DMSO, δppm): 1.25 (t, 3H, CH_3), 1.65 (s, 1H, NH, D_2O exchangeable), 2.6 (s, 3H, CH_3), 2.8 (s, 3H, CH_3), 3.6 (s, 2H, $COCH_2$), 4.25 (quartet, 2H, CH_2), 7.1 (s, 1H, H-3), 7.6 (d, 1H, H-7). 8.65 (d, 1H, H-8). MS, m/z : 404 (M^+., 46.2%), (M^+. +2) 406 (18.2%).

Ethyl6-chloro-9,11-dimethyl-2-hydroxyprido [3',2': 5,6] thiopyrano [4,3, 2-de] quinoline-1-carboxylate (V_b):

A solution of sodium ethoxide in ethanol, prepared from sodium (0.92g, 0.043 mol.) and ethanol (30 ml) was added to a boiling suspension of 9-chloro-6-ethoxycarbonylacetamido-2,4-dimethyl-5H-[1] benzothiopyrano [2,3-b] pyridin-5-one (IV_b) (4.04g, 0.01 mol.) in ethanol (90 ml). The mixture was boiled for 15 minutes, cooled and poured into cold water. The solid product was stirred 20 minutes with diluted HCl, washed with water, dried and crystallized from acetic acid as yellow Crystals m.p., 174-176°. Yield, 9.3g, 70%. Anal. Calcd. for $C_{19}H_{157}ClN_2O_3S$: C, 58.99, H, 3.91, N 7.24. Found: C, 58.79, H, 3.98, N, 7.12. IR (KBr, ν Cm^{-1}): 3412-3402 (OH), 1725 (C=O, ester). ^{1}HNMR (DMSO, δppm): 1.1 (t, 3H, CH_3), 2.2 (s, 3H CH_3) 2.4 (s, 3H, CH_3), 2.45 (s, 1H, OH, D_2O exchangeable), 3.45 (q, 2H, CH_2), 6.65 (d, 1H, H_4), 7.0 (d, 1H, H_{10}). 7.25 (d, 1H, H5) MS, m/z : 386 (M^+., 0.8%).

Ethyl 2-chloropyrido [3',2':5,6] thiopyrano [4,3,2-de] quinoline-1-carboxylate (VI_a) and ethyl 2,6-dichloro - 9,11- dimethylpyrido- [3',2': 5,6] thiopyrano [4, 3, 2-de] quinoline-1-carboxylate (VI_b):

A mixture of the appropriate hydroxyl compound $V_{a\ or\ b}$ (0.005 mol.) and phosphorus pentachloride (1.04g, 0.005 mol.) was heated under gentle reflux for 1hr., then cooled and poured onto ice. The resulting product was filtered, washed with 5% sodium hydrogen carbonate and crystallized from aqueous ethanol to give $VI_{a\ or\ b}$ as yellow crystals. Table (1).

Table (1): Ethyl 2-chloropyrido [3',2' : 5,6] thiopyrano[4,3,2-de] quinoline-1-carboxylate (VI_a) and ethyl 2,6-dichloro-9,11-dimethylpyrido [3',2':5,6] thiopyrano [4,3,2-de] quinoline-1-carobxylate (VI_b):

VI	R	X	m.p.°	Yield %	Molecular formula	Analysis %	
						Calcd.	Found
a	H	H	220-222	60	$C_{17}H_{11}ClN_2O_2S$ (342.81)	C 59.56 H 3.23 N 8.17	59.21 3.14 8.34
B	CH_3	Cl	205-207	65	$C_{19}H_{14}Cl_2N_2O_2S$ (405.31)	C 56.31 H 3.48 N 6.91	56.13 3.61 6.91

Spectral data for VI_b:

IR (KBr, ν Cm^{-1}): 1723 (C=O, ester). ^{1}HNMR (DMSO, δppm): 1.1 (t, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.45 (q, 2H, CH_2), 7.1 (s, 1H, H_{10}), 7.45 (d, 1H, H4), 7.65 (d, 1H, H_5). MS, m/z : 404 (M^+., 1.53%), 406 (M^+. +2, 0.9%).

Ethyl 2-substituted aminopyrido [3',2'' :5,6] thiopyrano [4,3,2-de]quinoline-1-carboxylate (VIIa) i-viii and ethyl 6-chloro-9,11-dimethyl-2-substituted aminopyrido [3',2':5,6] thiopyrano [4,3,2-de] quinoline-1-carboxylate (VII_b)$_{i-viii}$

General procedure:

A mixture of the appropriate chloro compound $VI_{a\ or\ b}$ (0.005 mol.), the selected primary aromatic amine (0.005 mol.) and triethylamine (2 drops) in ethanol (20 ml) was heated under gentle reflux for 45-90 minutes depending on the used amine. The mixture was cooled and the formed solid was filtered, dried and crystallized from the suitable solvent, tables (2,3).

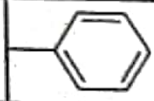
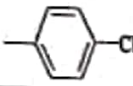
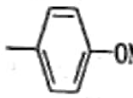
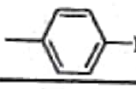
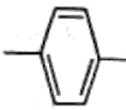
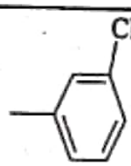
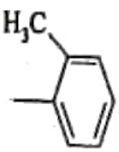
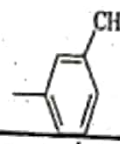
Molecular modeling studies

General methodology

All molecular modeling studies were performed on a Silicon Graphics workstation, running under IRIX 64 operating system, using HipHop procedure of Catalyst software (version 7.7)[9]. The molecular model produced by Catalyst is called a hypothesis (Hypothetical model). A Catalyst hypothesis can contain an arbitrary set of 3D data, 2D (topology) data, 1D (scaler) parameters, and constraint descriptions.

The basic modeling methodologies leading to the pharmacophore-based alignments (e.g., conformational analysis, molecule fitting, etc.), were performed with Catalyst using the implemented chemical features[10-12] and the energy minimization procedure[13]. Conformational analysis was performed as implemented in the program using the above-described minmizer coupled to "poling" function to assess conformational variation[14] and the BEST algorithm. The latter intends to optimize the conformational coverage versus the size of the assembly[15,16].

Table (2): Ethyl 2-substituted aminopyrido [3',2':5,6]thiopyrano [4,3,2-de] quinoline-1-carboxylate $(VII_a)_{i\text{-}viii}$:

VII_a	R_1	Reflux time in minutes	Yield %	m.p.°	Solvent of cryst.	Mol. Form (Mol.Wt.)	Analysis %	
							Calc.	Found
I		60	40	210-212	acetone	$C_{23}H_{17}N_3O_2S$ 399.47	C 69.16 H 4.29 N 10.52	69.13 4.10 10.50
I_i		45	45	227-229	acetone	$C_{24}H_{19}N_3O_2S$ 413.49	C 69.71 H 4.63 N 10.16	69.49 4.90 10.20
I_{ii}		45	50	> 300	benzene	$C_{24}H_{19}N_3O_3S$ 429.49	C 67.12 H 4.46 N 9.78	67.32 4.53 9.75
I_v		90	30	187-189	methanol	$C_{23}H_{16}BrN_3O_2S$ 478.36	C 57.75 H 3.37 N 8.78	57.83 3.41 8.79
V		90	30	195-197	methanol	$C_{23}H_{16}ClN_3O_2S$ 433.91	C 63.67 H 3.72 N 9.68	63.84 3.82 9.40
Vi		90	30	200-202	methanol	$C_{23}H_{16}ClN_3O_2S$ 433.91	C 63.67 H 3.72 N 9.68	63.31 3.62 9.39
Vii		45	45	243-245	acetone	$C_{24}H_{19}N_3O_2S$ 413.49	C 69.71 H 4.63 N 10.16	69.97 4.38 10.23
Viii		45	40	261-263	acetone	$C_{24}H_{19}N_3O_2S$ 413.49	C 69.71 H 4.63 N 10.16	69.44 4.92 10.33

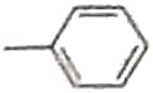
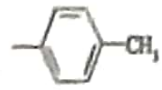
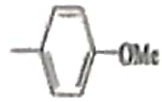
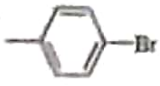
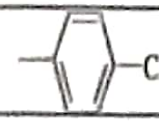
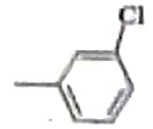
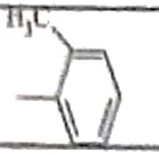
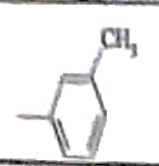
IR (KBr, ν Cm^{-1}) for $(VII_a)_{i\text{-}viii}$: 3435-3415 (NH), 1710-1703 (C=O, ester). MS, m/z for $(VII_a)_{ii}$: 413 (M^+, 1.0%).

Catalyst pharmacophore construction (hypothesis generation):

Generally, the hypothesis generation within Catalyst was based on the analysis of the training (lead) compounds in their most stable conformation. Consequently, the common chemical features of the training set compounds as well as the valid geometric arrangement of these chemical features were used to generate the pharmacophore model.

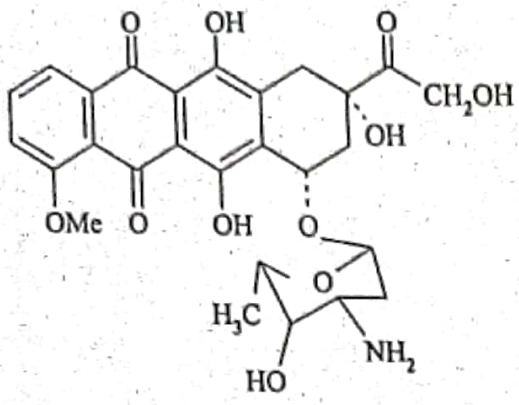
In the present study, best conformational analysis, using Catalyst program, was performed to 9 lead compounds [7, 8, 9, 10, 11, 12, 13, 14, 15] in order to approximate all energetically accessible shapes the molecule may adopt. Best conformational analysis was performed for each compound using a threshold of 250 conformers per molecule and a maximum value of 20 Kcal / mol for conformer energy.

Table (3): Ethyl 6-chloro-9,11-dimethyl-2-substitutd aminopyrido[3',2':5,6] thiopyrano[4,3,2-de] quinoline-1-carboxylate $(VII_b)_{i-viii}$:

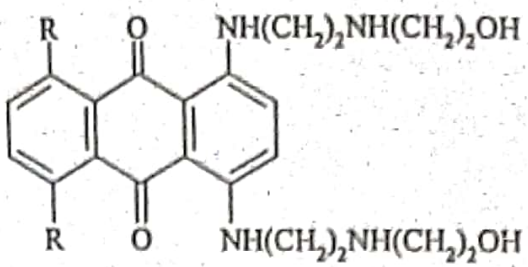
VII_b	R_1	Reflux time in minutes	Yield %	m.p.°	Solvent of cryst.	Mol. Form (Mol.Wt.)	Analysis % Calc.	Found
i		60	40	210-212	acetone	$C_{25}H_{20}ClN_3O_2S$ 461.97	C 65.00 H 4.36 N 9.10	64.82 4.23 9.11
ii		45	45	> 300	acetone	$C_{26}H_{22}ClN_3O_2S$ 475.99	C 65.61 H 4.66 N 8.83	65.51 4.82 8.81
iii		45	50	> 300	benzene	$C_{26}H_{22}ClN_3O_3S$ 491.99	C 63.47 H 4.51 N 8.54	63.12 4.23 8.56
iv		90	35	217-219	methanol	$C_{23}H_{19}BrN_3O_2S$ 540.86	C 55.52 H 3.54 N 7.77	55.32 3.50 7.71
v		90	35	205-207	acetone	$C_{25}H_{19}Cl_2N_3O_2S$ 496.41	C 60.49 H 3.86 N 8.46	60.47 3.75 8.45
vi		90	30	194-196	methanol	$C_{25}H_{19}Cl_2N_3O_2S$ 496.41	C 60.49 H 3.86 N 8.46	60.71 3.98 8.77
vii		45	40	215-217	acetone	$C_{26}H_{22}ClN_3O_2S$ 475.99	C 65.61 H 4.66 N 8.83	65.0 4.81 8.53
viii		45	40	203-205	acetone	$C_{26}H_{22}ClN_3O_2S$ 475.99	C 65.61 H 4.66 N 8.83	65.33 4.81 8.92

IR (KBr, ν Cm^{-1}) for $(VII_b)_{i-viii}$: 3435-3415 (NH), 1710-1703 (C=O, ester). ^{1}H-NMR (DMSO, δppm) for $(VII_b)_{iii}$: 1.10 (t, 3H, CH_3), 1.70 (br. S, 1H, NH, D_2O exchangeable), 2.2 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 3.45 (q, 2H CH_2), 3.85 (s, 3H, OCH_3), 6.85-7.45 (m, 6H, aromatic), 7.8 (d, 1H, H_8). MS, m/z for $(VII_b)_{iii}$: M^+ 491 (14.90%), (M^++ 2) 493 (4.8%).

Afterwards, the emerged conformers for each lead compound were used to build up the hypothetical model using HipHop[17,18] method of catalyst program. HipHop tool identifies the common chemical features within the lead compounds starting from the conformers of the principle compound in the lead compounds. Compound 12 took a value of 2 in the principle column and considered to be the principle one. In addition, the following parameters were loaded into the Catalyst program in order to specify the hypothesis where, Max Omit Feat sited to be one for all compounds. Moreover, Hydrogen Bond Acceptor (HBA), Hydrogen Bond Donor (HBD) and hydrophobic (H) function were specified to be the chemical features that would be considered in the generate of the hypothetical model. At the end of these procedures, Catalyst program generate 10 hypotheses, ranked according to their scores, which most likely express the common chemical features of the lead compounds. Among the generated 10 hypotheses, the highest ranking one is that most likely expressed the common chemical features composition of the lead compounds. The highest ranking hypothesis composed of six features (two hydrophobic, two hydrogen acceptors and two hydrogen doners).

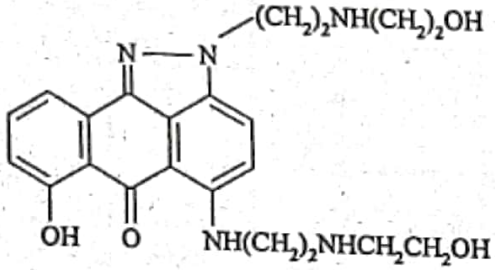


doxorubicin (4)

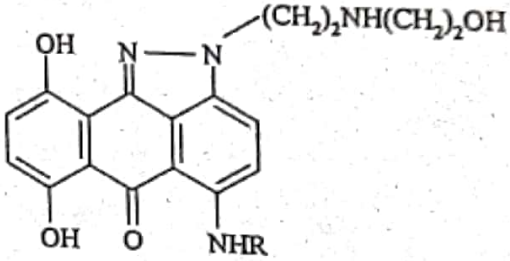


ametantrone (5) R = H

mitoxantrone (6) R = OH

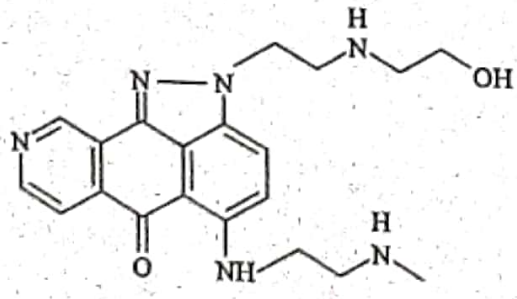


losoxantrone (7)

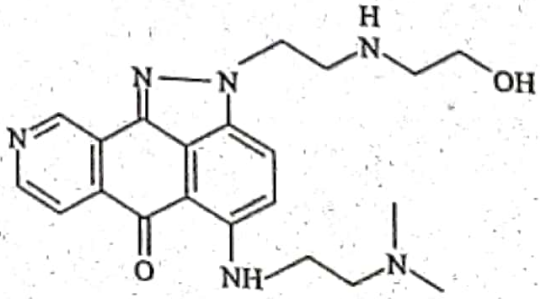


teloxantrone (8) $R = (CH_2)_2NHCH_3$

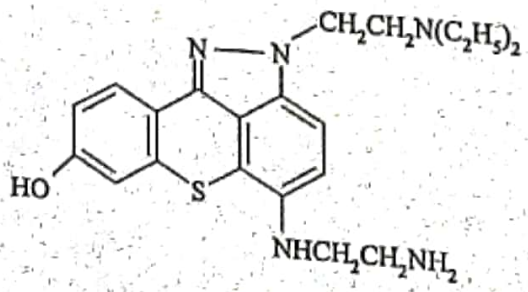
piroxantrone (9) $R = (CH_2)_2NH_2$



(10)



(11)

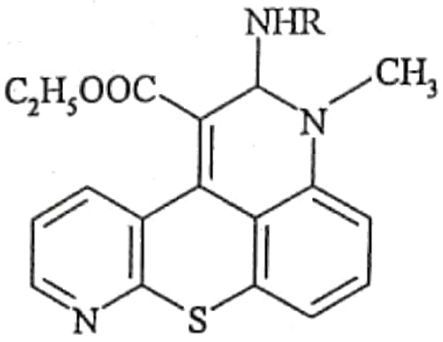


(12)

Zagazig J. Pharm. Sci., December. 2006
Vol. 15, No. 2, pp.29 - 37

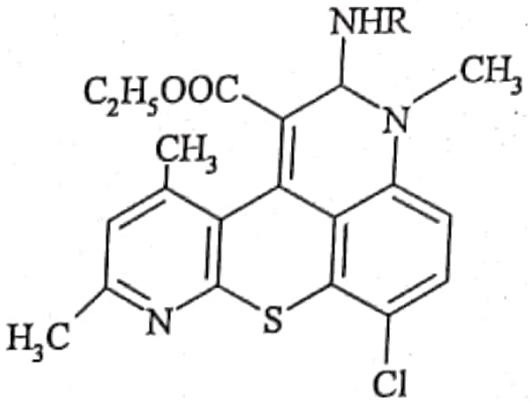
Validation of the hypothetical model[19,20]:

The performance of the modified hypothetical model was evaluated by fitting the test compounds **$(VII_a)_{ii}$, $(VII_a)_{iii}$, $(VII_b)_{ii}$ and $(VII_b)_{iii}$.**



$(VII_a)_{ii}$ R = 4-$C_6H_4CH_3$

$(VII_a)_{iii}$ R = 4-$C_6H_4OCH_3$



$(VII_b)_{ii}$ R = 4-$C_6H_4CH_3$

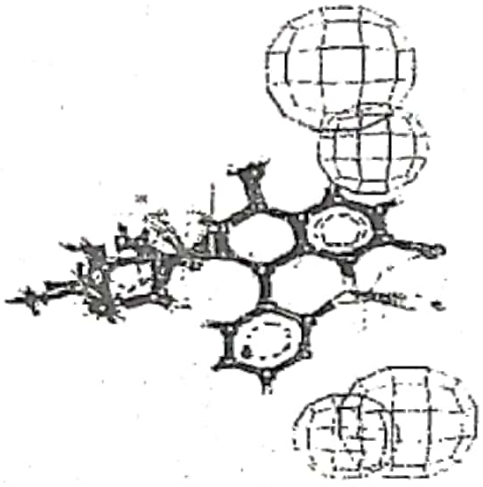
$(VII_b)_{iii}$ R = 4-$C_6H_4OCH_3$

Fitting operations to the modified hypothetical model were accomplished through; firstly. Best conformational analysis was done utilizing a threshold of 250 conformers per molecule and a maximum value of 20 Kcal / mol for conformer energy. Secondly, the conformers of each compound in the test set were allowed to fit to the modified hypothesis using best fit option and the fit values of the test set compounds were obtained. Table (4), figure (1). The obtained fit value for each compound is a measure of how many and how well its functional features fit to the features of the pharmacophore.

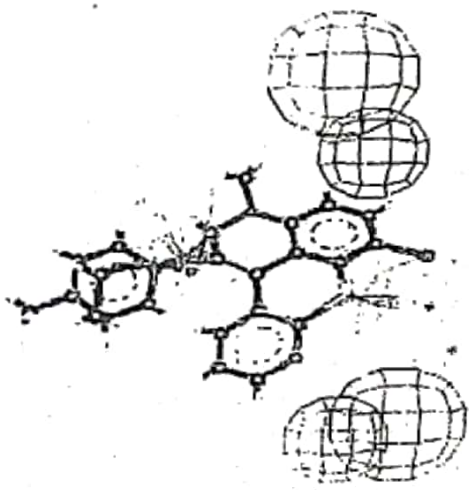
Table (4): Validation results of the hypothetical model:

Compound	Number of conformers	Fit value
$(VII_a)_{ii}$	75	3.46
$(VII_a)_{iii}$	104	3.53
$(VII_b)_{ii}$	41	3.42
$(VII_b)_{iii}$	52	3.72

Figure (1) :



Compound $(VII_b)_{ii}$ mapped to hypothesis



Compound $(VII_b)_{iii}$ mapped to hypothesis

Compound $(VII_a)_{ii}$ mapped to hypothesis

In vitro test for cytotoxic effect:

Experiment

A set of sterile test tubes was used, where 2.5 x 10^5 tumour cells per ml were suspended in phosphate buffer saline. Then 25, 50, 100 µg/ml from test compound were added to the suspension, kept at 37°C for 2 hours. Trypan blue dye exclusion test was then carried out to calculate the percentage of nonviable cells[21].

Table (5): Results of in vitro test for cytotoxic effect

Test compounds	% Inhibition of cell viability µg/ml		
	100	50	25
$(VII_a)_{ii}$	-	-	-
$(VII_a)_{iii}$	-	-	-
$(VII_b)_{ii}$	50	20	10
$(VII_b)_{iii}$	-	-	-

Conclusion: Compound $(VII_b)_{ii}$ showed inhibition of viability of EAC (Ehrlich Ascites Carcinoma) cells at different doses while DMSO free liquid (control) showed no activity.

REFERENCES

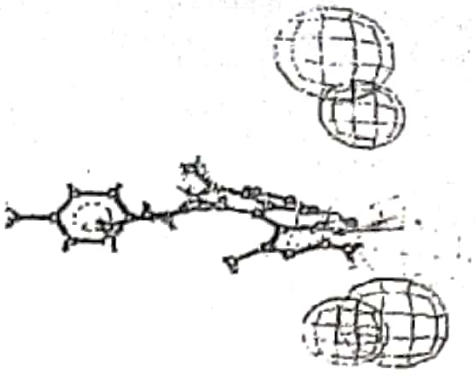
1- Atwell, G.J, Cain, B.F., Baguley, B.C., Finaly, G.J. and Danny, W.A.; **J. Med. Chem** 27, 1481 (1984).

2- Stefanska, B., Araiemuik, M., Botontem Gracz, M.M., Dzieduszyka, M., Kupiec, A. Martelli, S. and Borowsku, E, **Biorganic and Medical Chemistry**. 11,561 (2003).

3- Sissi, C., Morro, S., Richer, S., Gatto, B., Menta E., Spinelli S, Krapcho, A. P., Zunino, F., Palumbo, M., **Molecular Pharmacology** 59 (1), 96(2001).

4- Tarasiuk J., Stefanska B., Plodzich I., Tkaczyk – Gobis K., Skesek O., Martelli S., Garnier – Suillerot A., and Borowski E., **British Journal Of Pharmacology**. 135, 1513 (2002).

5- Stefanska B., Arciemiuk M., Botontemps – Gracz M. M., Dzieduszyka M., Kupiec A., Martelli S., and Borowski E., **Biorganic and Medical Chemistry**. 11,561 (2003).



Compound $(VII_a)_{iii}$ mapped to hypothesis

6- Stefanska B., Dzieduszycka M., Bantemps – Gracz M., and Borowski E. **J. Med. Chem.** 42,3494 (1999).

7- El-Shemy K., El-Badry O. and El-Enany M, **Bull. Fac. Cairo Univ.** (under publication).

8- Hidetoshi Fujiwara and Ichizo Okabayashi, **Heterocycles**, 36, 1105 (1993).

9- Daveu, C., R. Bureau, I. Baglin, H. Prunier, J.C. Lancelot and S. Rault, J. **J. Chem. Inf. Comput. Sci.**, 39, 362-69 (1999).

10- Sprague, P. W., Ed. Muller, K., Escom and Leiden, the Netherlands, 1 (1995).

11- Kaminski, J. J., Rane, D. F., Snow, M. F., Weber, L., Rothofsky, M. L., Anderson, S. D. and Lin, S. L.; **J. Med. Chem.** 40, 4102 (1997).

12- Keller, P., Bowman, M., Dang, K. H., Carner, J., Leach, S. P., Smith, R., McCluskey, A.; **J. Med. Chem.**, 42, 2351 (1999).

13- Brooks, B. R., Bruccoleri, R. E., Olafson, B. D., States, D. J., Swaminathan, S. and Karplus, M.; **J. Comput. Chem.**, 4, 187 (1983).

14- Smellie, A., Teig, S. and Towbin, P.; **J. Comput. Chem.**, 16, 171 (1995).

15- Smellie, A., Kahn, S. and Teig, S.; **J. Chem. Inf. Comput. Sci.**, 35, 285 (1995).

16- Smellie, A., Kahn, S. and Teig, S.; **J. Chem. Inf. Comput. Sci.**, 35, 295 (1995).

17- Greene, J., Kahn, S., Savoj, H., Sprague, P. and Teig, S.; **J. Chem. Inf. Comput Sci.**, 34, 1297 (1994).

18- Barnum, D., Greene, J., Smellie, A. and Sprague, P.; **J. Chem. Inf. Comput Sci.**, 36, 563 (1996).

19- Kurogi, Y. and Guner, O. F.; **Curr. Med. Chem.**, 8, 1035 (2001).

20- Hirashima, A., Pan, C., Kuwano, E., Taniguchi, E. and Eto, M.; **Bioorg. Med. Chem.**, 7, 1437 (1999).

21- Mclimans, W. F., Davis, E. V., Glover, F. L. and Rake, G. W.; **J. Immunol.**, 79, 428 (1957)

Zagazig J. Pharm. Sci., December. 2006
Vol. 15, No. 2, pp.29 - 37

Received: Sept. 23, 2006
Accepted: Dec. 09, 2006

تشييد بعض مشتقات جديدة من البيريدو ثيوبيرانو كينولين كمضادات للسرطان

خالد رشاد الشيمى – أسامه متولى البدرى – سميحه رشدى – مرفت العنانى – محمد عبد الحميد إسماعيل*
قسم الكيمياء العضوية – كلية الصيدلة – جامعة القاهرة – القاهرة
* قسم الكيمياء الطبية – كلية الصيدلة – جامعة عين شمس – القاهرة – مصر

فى هذا البحث تم تحضير سلسلة من الايثيل 2 – مستبدل أمينو بيريدو (3 ، 2 : 5 ، 6)ثيو بيرانـــو (4 ، 3 ، 2 – de) كينولين – 1 – كاربوكسيلات– viii – i (VII a) وذلك بتفاعل إيثيل 2 – كلورو بيريـــدو (3 ، 2 : 5, 6) ثيو بيرانو (4 ، 3 ، 2 – de) كينولين 1– كاربوكسيلات (VI a) مع بعض الأمينات العطرية .

كما تم تحضير سلسلة أخرى من الايثيل 6 – كلورو– 9 ، 11 داى ميثيل – 2 – مستبدل أمينو بيريدو (3 ، 2 : 5 , 6) ثيو بيرانو (4 ، 3 ، 2 – de) كينولين 1– كاربوكسيلات viii – i (VII b) وذلك بتفاعـــل الايثيـــل 2 ، 6 – داى كلورو – 9 ، 11 داى ميثيل بيريدو (3 ، 2 : 5 ، 6) ثيو بيرانو (4 ، 3 ، 2 – de) كينولين 1 – كاربوكسيلات (VI b) مع مختلف الامينات .

هذا وقد تمت دراسة جزئية وتأثير لبعض المركبات المشيدة على الخلايا السرطانية خارج جسم الانسان .