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SYNTHESIS OF SOME PYRIMIDINE DERIVATIVES OF EXPECTED BIOLOGICAL ACTIVITIES

Wafaa A. Zaghary[1], Aida A. El-Azzouny[2], Mohammed A. Motaleb[3] and Mohammed A. Kedr[1]

[1]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Helwan University, Cairo, Egypt*
[2]*Department of Pharmaceutical Sciences, National Research Center, Dokki, Giza*
[3]*Hot Labs. Center, Atomic Energy Authority, Cairo, Egypt*

استهدف هذا البحث تحضير بعض مركبات البيريميدين المستبدلة الجديدة و اختبار فاعليتها البيولوجية كمضادات للأورام و قد تم تحضير مركب 2-ميثيل-4- أمينو-6- هيدروكسى-5-(ايمينوثنائى حمض الخليك) بيريميدين والكشف عن نشاطة البيولوجى باستخدام العناصر المشعة. ولتحقيق هذا الهدف أستخدم مركب 2-ميثيل-4- أمينو-6- هيدروكسى بيريميدين كمادة بادئة.
وقد تأيدت التركيبات الكيميائية لهذة المشتقات بواسطة القياسات التحليلية والطيفية مثل الأشعة تحت الحمراء وطيف الرنين المغناطيسى لنواة ذرة الهيدروجين وكذلك طيف الكتلة.

*A series of 4-substituted pyrimidines and fused pyrimidine ring system e.g. pyrido[2,3-d] pyrimidine were synthesized and the antitumor activity have been carried out for 8 compounds. Compound **4a** also, which carries the pharmacophoric group IDA was tested for the hepatobilliary imaging effect.*

INTRODUCTION

Pyrimidine derivatives are widely distributed in natural materials and living organisms and they are possessing a variety of biological activities such as, antiallergic,[1,2] antiinflammatory,[3,4] anxiolytic,[5] tranquilizers,[6] anticonvulsant,[7,8] antimalarial,[9] antiviral[10-12] and antitumor[13,14] activity.

This encourages the authors to synthesize a new series of this type of compounds for cytotoxic evaluation.

Moreover, it is well known that imminodiacetic acid derivatives (IDA) are well known for their hepatobilliary imaging effect. From this point of view we aimed to synthesize a substituted pyrimidine-IDA derivative **4a** and test its hepatobilliary imaging effect.

Chemistry

Reaction of **1** with methylbromoacetate and ethylbromoacetate yielded the acetic acid methyl and ethyl esters **2a-b** reacted with different hydrazines to afford different substituted hydrazides **3a-c**. On the other hand, the reaction of the hydrazide **3a** with different aldehydes yielded different Schiff's bases **9a-f**. Some of these Schiff's bases were condensed with thioglycolic acid to give thiazolidine derivatives **10a-c**. Condensation of **3a** with acetylacetone and ethylacetoacetate yielded the pyrazole derivatives **11** and **12**, respectively. While, reaction of **3a** with carbondisulfide in potassium hydroxide afforded the intermediate salt **13** which upon reaction with hydrazine hydrate and/or phenyl hydrazine yielded the triazol derivative **14** and **15** respectively.

In addition, Mannich bases **4a-c** were produced by reacting of **1** with different amines in presence of paraformaldehyde. Etherification of 6-chloropyrimidine **5**, obtained from **1** and $POCl_3$ with p-hydroxyacetophenone yielded the ethanone derivative **6**. Also, compound **1** was allowed to react with phosphorousoxychloride in presence of glacial acetic acid to give **7** which upon fusion with 3,4,5-trimethoxy benzaldehyde afforded **8.**

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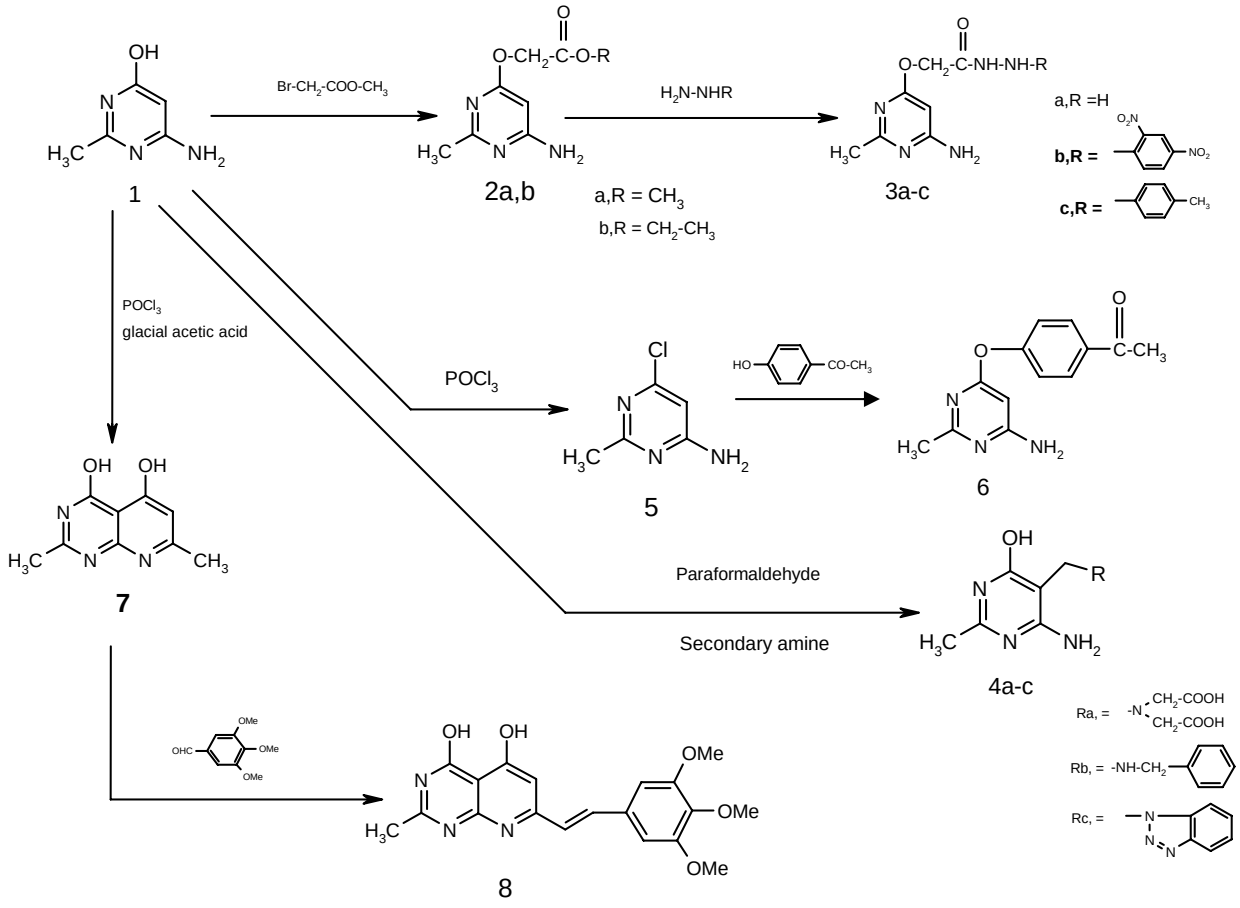
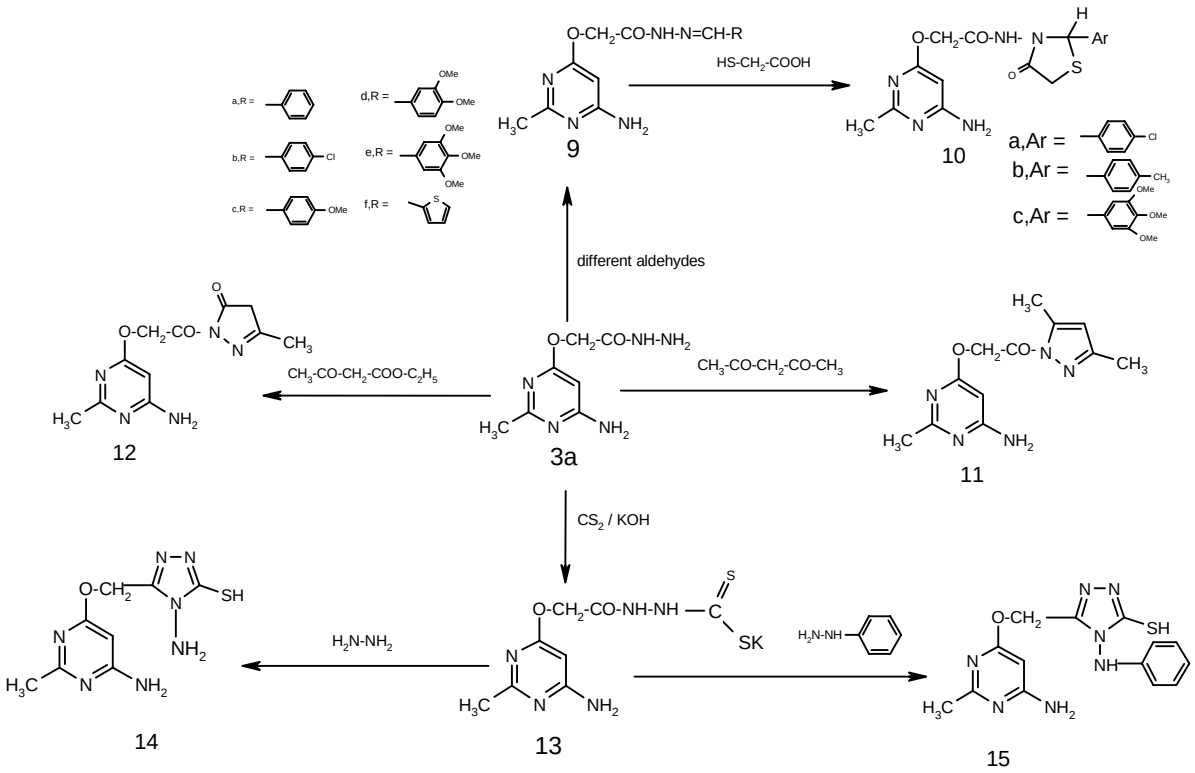
MATERIALS AND METHODS

Melting points were determined on STUART scientific melting point apparatus and uncorrected. The infrared spectra (IR) were recorded on Bruker FT-IR spectrophotometer using potassium bromide discs. Mass spectra (MS) were performed at 70 eV with Shimadzu GCMS, QP1000 EX using the Electron Ionization Technique (EI). ^{1}HNMR spectra were recorded in (DMSO-d_6 and $CDCl_3$) on Varian Gemini spectrophotometer at 200 MHz and Varian Mercury spectrophotometer at 300 MHz, using tetramethylsilane (TMS) as internal reference and the chemical shift values (δ) are given in parts per million (ppm). Elemental microanalyses were carried out in the Microanalytical Center, Faculty of Science, Cairo University.

4–Amino-6–hydroxy-2-methyl pyrimidine **1**,[15] 4-Amino-2-methyl-6-chloropyrimidine **5**[16] were prepared according to the literature procedures.



Scheme I



Scheme II

6-Amino-2-methyl-pyrimidin-4-yloxy-acetic acid methyl ester (2a)

A mixture of **1** (1.25 g, 0.01 mol), ethylbromoacetate (4.56 g, 0.03 mol) and potassium carbonate (4.14 g, 0.03 mol) in 200 ml dry acetone, was refluxed under continuous stirring for 6 hrs. The reaction mixture was cooled, filtered, neutralized with acetic acid, followed by extraction with chloroform. Upon evaporation of the chloroformic extract a brownish precipitate was obtained, washed with petroleum ether (40-60°) then recrystallized from ethanol to give compound **2** (Table I).

The IR spectrum of **2b** showed bands at 3433, 3335 cm^{-1} (NH_2), 1740 cm^{-1} (C=O, ester). The mass spectra of **2b** has been found compatible with the assigned structure. MS (m/z, %): M^+ 211 (4.2%), (M+1) 212, (M+2) 213, 166 (6.47%), 138 (69.25%), 67 (100%).

6-Amino-2-methyl-pyrimidin-4-yloxy-acetic acid substituted hydrazides (3a-c)

A mixture of **2** (0.39 g, 0.002 mol) and the appropriate hydrazine derivative (0.002 mol) namely hydrazine hydrate, phenylhydrazine and p-tolylhydrazine in absolute ethanol (50 ml) was refluxed for 8 hrs. After cooling, the precipitate was filtered off and recrystallized from ethanol to give compounds **3a-c** (Table I).

The IR spectrum of **3a** showed bands at 3325, 3163 cm^{-1} (NH_2), 1658 cm^{-1} (C=O, amide). The mass spectrum of **3a** has been found compatible with the assigned structure. MS (m/z, %): M^+ 198 (3.6%), 166 (100%), 165 (1.4%),138 (35.4%).

5-(Substituted-methyl)-2-methyl-6-amino-4-hydroxy-pyrimidines (4a-c)

A solution of compound **1** (1.25 g, 0.01 mol) in 5 ml of absolute ethanol was added with stirring to a hot mixture of paraformaldehyde (0.32 g, 0.0034 mol) and the requisite secondary amine namely, imminodiacetic acid, benzylamine, and/or benzotriazol (0.01 mol) in 70 ml of absolute ethanol. The reaction mixture was refluxed for 4-6 hrs. After cooling, the resulted white crystals were filtered off, washed with water and recrystallized from the proper solvent to give compounds **4a-c** (Table I).

Table I: Physical and analytical data for the newly synthesized compounds.

Comp No	M.P.° (Solvent)	Yield %	Formula (M.wt)	Analysis (Calcd / Found)		
				C%	H%	N%
2a	160-162 (ethanol)	70	$C_8H_{11}N_3O_3$ 197.22	48.72 48.66	5.63 5.95	21.31 21.12
2b	173-175 (ethanol)	69	$C_9H_{13}N_3O_3$ 211.25	51.17 51.11	6.22 6.18	19.90 19.73
3a	260-262 (ethanol)	65	$C_7H_{11}N_5O_2$ 197.23	42.63 42.42	5.63 5.71	35.52 35.55
3b	275-277 (ethanol)	75	$C_{13}H_{13}N_7O_6$ 363.33	42.97 43.23	3.61 4.22	26.99 26.68
3c	268-270 (ethanol)	60	$C_{14}H_{17}N_5O_2$ 287.36	58.51 59.41	5.98 5.92	24.38 25.01
4a	210-212 (ethanol)	79	$C_{10}H_{14}N_4O_5$ 270.28	44.43 44.45	5.23 5.33	20.73 20.63
4b	255-257 (ethanol)	85	$C_{13}H_{16}N_4O$ 244.33	63.90 63.65	6.62 6.37	22.94 22.15
4c	280-282 (ethanol)	70	$C_{12}H_{11}N_6O$ 256.3	56.23 56.33	4.73 4.82	32.79 32.34
6	90-93 (ethanol)	75	$C_{13}H_{13}N_3O_2$ 243.29	64.17 64.23	5.39 5.41	17.28 17.38
7	220-222 (ethanol)	80	$C_9H_9N_3O_2$ 191.21	56.53 56.94	4.75 4.55	21.98 22.38
8	85-87 (ethanol)	90	$C_{19}H_{19}N_3O_5$ 369.41	61.77 61.97	5.19 5.34	11.38 11.52
9a	92-94 (methanol)	60	$C_{14}H_{15}N_5O_2$ 285.34	58.93 58.85	5.31 5.54	24.55 24.75
9b	240-242 (ethanol)	55	$C_{14}H_{14}N_5O_2Cl$ 319.73	52.59 52.77	4.42 4.68	21.91 21.71
9c	210-212 (ethanol)	71	$C_{15}H_{18}N_5O_3$ 315.37	57.12 57.34	5.43 5.65	22.21 22.75
9d	125-127 (ethanol)	62	$C_{16}H_{21}N_5O_4$ 345.4	55.63 55.69	5.56 5.93	20.28 20.67
9e	63-65 (ethanol)	58	$C_{17}H_{24}N_5O_5$ 375.43	54.38 55.12	5.65 5.45	18.66 18.65
9f	180-182 (ethanol)	61	$C_{12}H_{13}N_5O_5S$ 293.39	49.12 49.33	5.16 5.56	23.88 23.63
10a	150-152 (ethyl acetate)	71	$C_{16}H_{16}N_5O_3SCl$ 393.84	48.79 48.99	4.10 4.84	17.78 18.21
10b	100-102 (ethyl acetate)	65	$C_{17}H_{19}N_5O_4S$ 389.48	52.42 52.56	4.92 5.22	17.98 17.91
10c	200-202 (ethyl acetate)	73	$C_{19}H_{25}N_5O_6S$ 451.56	50.53 50.59	5.59 5.66	15.51 15.89
11	155-157 (ethanol)	69	$C_{12}H_{15}N_5O_2$ 261.32	55.15 55.75	5.79 5.35	26.81 26.86
12	70-72 (ethanol)	71	$C_{11}H_{13}N_5O_3$ 263.29	50.18 50.39	4.99 4.59	26.59 26.67
14	>300 (ethanol)	60	$C_8H_{11}N_7OS$ 253.33	37.93 38.11	4.39 4.42	38.71 39.11
15	>300 (gl.acetic acid)	68	$C_{14}H_{15}N_7OS$ 329.43	51.04 51.43	4.60 4.86	29.77 29.93

The IR spectrum of **4b** showed bands at 3400 cm^{-1} (OH), 1550, 1620 cm^{-1} (C=C, of aromatic ring). The ^{1}HNMR (DMSO-d_6) δ ppm showed the following peaks: 2.2 (s, 3H, CH_3),

3.57 (s, 2H, CH_2), 3.64 (s, 2H, CH_2), exchangeable protons of NH_2, OH, NH at δ 4, 6.5, 7.8 respectively and 7.3 (m, 5H, aromatic protons). The mass spectra of 4b has been found compatible with the assigned structure. MS (m/z, %): 91 (100%) (tropylium ion), 138 (21.29%),165 (53%).

1-[4- (6-Amino-2-methyl-pyrimidin-4-oxy)] -phenyl-ethanone (6)

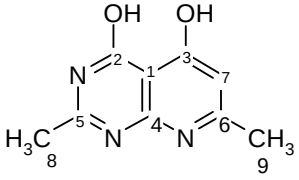
A mixture of compound **5** (1.43 g, 0.01 mol), p-hydroxyacetophenone (2.72 g, 0.02 mol) and K_2CO_3 (5 g) in 25 ml dry acetone was refluxed for 8 hrs. The reaction mixture was cooled and poured onto ice water. The formed precipitate was filtered, washed several times with water and recrystallized from ethanol to give compound **6** (Table I).

2,7-Dimethyl-pyrido[2,3-d]pyrimidin-4,5-diol (7)

Compound **1** (2.37 g, 0.019 mol) was dissolved in 15ml of glacial acetic acid and then treated with phosphorousoxychloride 5 ml. The reaction mixture was refluxed for 20 minutes. The formed product was filtered off and washed several times with water. The pricipetate was extracted with chloroform and the chloroformic layer was evaporated, to give compound **7** (Table I).

The IR spectrum of **7** showed bands at 1260.21 cm^{-1}, 3274.17 cm^{-1}, 3377.29 cm^{-1} (2 OH groups), 1177.71 cm^{-1} (C-O). The ^{1}HNMR (DMSO-d_6) δ ppm showed the following peaks: 2.2 (S, 6H, $2CH_3$), 6.2 (S, 1H, aromatic), 8.2 (s, 1H, OH exchangeable), 8.7 (s, 1H, OH exchangeable). The mass spectrum of 7 has been compatible with the assigned structure. MS (m/z, %): M^+ 191 (100%), 138 (4%), 85 (6.3%).

^{13}CNMR compound **7**: δ ppm 20.15 (C9), 26.47 (C8), 96.88 (C1), 112.26 (C7), 164.04 (C4), 165.73 (C3), 167.88 (C2), 170.96 (C5), 179.15 (C6).



2-Methyl-7-[2-(3,4,5-trimethoxyphenyl) ethenyl]-pyrido[2,3-d] pyrimidin-4,5-diol (8)

Compound **7** (3.82 g, 0.02 mol) was added to 3,4,5-trimethoxy benzaldehyde (1.96 g, 0.01 mol) and heated at 140° in the presence of 5 drops acetic anhydride for one hour. The reaction mixture was cooled and left over night, then treated with petroleum ether to give compound **8** (Table I).

6-Amino-2-methyl-pyrimidin-4-yloxy-acetic acid yiledene hydrazides (9a-f)

A mixture of compound **3a** (0.197 g, 0.001 mol) and the appropriate aromatic or heterocyclic aldehyde namely benzaldehyde, p-chloro-benzaldehyde, p-anisaldehyde, 3,4-dimethoxybenzaldehyde, 3,4,5-trimethoxy benzaldehyde or thiophen-2-carbaldehyde (0.0016 mol) in 15 ml absolute ethanol was refluxed for 5 hrs. The reaction mixture was concentrated, cooled and the formed precipitate was filtered off, dried and recrystallized from ethanol to give the title compounds **9a-f** (Table I).

2-(6-Amino-2-methyl-pyrimidin-4-yloxy)-N-[2-(substituted-phenyl)-4-oxo-thiazolidin-3-yl]acetamide (10a-c)

A mixture of compounds **9b-e** (0.001 mol) and thioglycolic acid (0.001 mol) was refluxed in 8ml of glacial acetic acid for 10 hrs. The reaction mixture was cooled and neutralized with sodium bicarbonate solution. The formed product was filtered off and recrystallized from dilute acetic acid to give compounds **10a-c** (Table I).

2-[2-(6-Amino-2-methyl-pyrimidin-4-yloxy)]-1-(3,5-dimethyl-pyrazol-1-yl)ethanone (11)

A mixture of compound **3a** (3.12 g, 0.016 mol) and acetylacetone (0.68 ml, 0.065 mol) was heated over steam bath for 10 hrs and then cooled. Upon treating with petroleum ether (40-60º), a precipitate of compound **11** was formed (Table I).

The IR spectrum of **11** showed bands at 3342 cm^{-1} (NH_2), 1645 cm^{-1} (C=O). The mass spectrum of **11** has been compatible with the assigned structure. MS (m/z, %): M^+ 261 (0.1%), 183 (1.55%), 95 (88%), 96 (100%), 124 (1.3%).

2-[(6-Amino-2-methyl-pyrimidin-4-yloxy)-acetyl]-5-methyl-3, 4- dihydro-pyrazol-3-one (12)

A mixture of compound **3a** (3.15 g, 0.016 mol) and 0.68 ml of ethylacetoacetate in 20 ml absolute ethanol was heated over steam bath for 10 hrs, cooled and treated with petroleum ether to yield compound **12** (Table I).

Potassium-1-[2-(6-amino-2-methyl-pyrimidin-4-yl)oxy-methyl]dithiocarbazate (13)

Carbon disulphide (0.14 ml, 0.002 mol) was added dropwise to an ice cold solution of KOH (0.03 g, 0.001 mol) in absolute ethanol (20 ml) containing compound **3a** (0.19 g, 0.001 mol). The mixture was stirred at room temperature for 8 hrs, the separated solid was filtered off and washed several times with ether. The yellow solid product obtained in nearly quantitative yield was employed in the next reaction without further purification.

5-(6-Amino-2-methyl-pyrimidin-4-yloxy-methyl)-4-amino-4H-[1,2,4] triazole-3-thiol (14)

Compound **13** (0.3 g, 0.001 mol) and 2ml of hydrazine hydrate was refluxed for 7 hrs and then cooled. 10 ml of water was added and the mixture was neutralized with acetic acid, the solid product obtained was filtered off, washed several times with ether and then recrystallized from ethanol to afford compound **14** (Table I).

The IR spectrum of **14** showed bands at 3100-3346 cm^{-1} (NH-NH_2), 1620 cm^{-1} (C=N), 1608 cm^{-1} (C=C). The mass spectrum of **14** has been compatible with the assigned structure. MS (m/z, %): M^+ 256 (7.9%), 69 (100%), 84 (31.22%), 127 (7.76%).

5-(6-Amino-2-methyl-pyrimidin-4-yloxy-methyl)-4-phenylamino-4H-[1,2,4] triazole-3-thiol (15)

Compound **13** (0.3 g, 0.001 mol) and phenyl hydrazine (0.47 g, 0.004 mol) in 10 ml of 65% ethanol was refluxed for 8 hrs, cooled and recrystallized from glacial acetic acid to produce compound **15** (Table I).

Biology

Evaluation of antitumor activity

A line of Ehrlich ascites carcinoma (E.A.C) was used in this study for evaluation of **3b**, **4a**, **4c**, **6**, **7**, **8**, **9e**, **9f** for their antitumor activity.

Materials and Methods

- **Animals:** Female Swiss Albino mice from the animal house of Cairo Cancer Institute, weighing 18-22 gm were used. Animals were maintained on standard pellet diet and water.
- **Tumor:** Ehrlich ascites (E.A.C), mained in the laboratory since 1982 by weakly interperitoneal transplantation in female Swiss Albino mice.

In vitro test for cytotoxic effect

The biological evaluation of these compounds was carried out at the National Cancer Institute

A set of sterile test tubes were used, where $2.5x10^5$ tumor cells per ml were suspended in phosphate buffer saline, then 25, 50, 100 µg/ml of the tested compounds were added to the suspension kept at 37° for 2 hours. Trypan blue dye exclusion test was then carried out to calculate the percentage of nonviable cells.[17]

Results

The data of selected pyrimidines derivatives **3b**, **4a**, **4c**, **6**, **7**, **8**, **9e**, **9f** showed that the compound bearing 2, 4-dinitrophenyl substituent **3b** showed higher activity than the compound with imminodiacetic acid substituent **4a** or with the bulky substituent (3, 4, 5-trimethoxyphenyl) compound **9e**.

The other tested compounds showed no antitumor activity on E.A.C cells.

Table II: Effect of some pyrimidine derivatives on the viability of tumor cells in vitro.

Sample No	% Inhibition of cell viability µg/ml		
	100	50	25
3b	70	20	10
4a	20	50	Zero
4c	zero	zero	Zero
6	zero	zero	Zero
7	zero	zero	Zero
8	zero	zero	Zero
9e	30	10	Zero
9f	zero	zero	Zero

Testing The Hepatobilliary Effect of Compound 4a After Labelling With radioactive ^{99m}Tc

The localization of ^{99m}Tc-complexes in particular target organs like liver, kidney, brain, bone, ect, is the bases for use of these complexes as a diagnostic agent in nuclear medicine. All IDA derivatives are bound to hepatocytes in the liver. The mechanism of their binding varies depending mainly on the strength and the amount of the binding to

interhepatocyte proteins. An increase of the percentage of binding to proteins leads to a decrease of the glomerular filtration rate, but it also can slow down the complex binding to hepatocytes.[18-23]

Experimental parameters affecting the labelling process were studied as follows:

a) **Effect of ligand amount**: the labelling yield is dependant on the amount of the ligand used in the range of 5 mg up to 10 mg. Increasing the ligand amount to 15 mg, the radiochemical yields reached the optimum value 94.2% (Table III).

b) **Effect of Tin (II) content**: Technetium-99m is eluted from the $^{99}Mo/^{99m}Tc$ generator as pertechnetate ion, which has to be reduced before labelling of our synthesized IDA compound. The results show that an amount of stannous chloride exceeding values of 0.2 mg/15 mg of **4a**-IDA does not affect the radiochemical purity of the labelled complex. At pH equals 6, efficient labelling yield was achieved using the optimum amount of stannous chloride which equals to 0.2 mg. (Table IV).

c) **Effect of pH on the reaction mixture**: At pH value equals 6 the optimum radiochemical yield was obtained 94.2%. (Table V).

Results

The biodistribution properties of the formulated **4a**-^{99m}Tc-complex after labelling with technetium-99m was evaluated in mice. The test was carried out by injection the reconstituted IDA derivative kit in the tail vein of albino-Swiss mice.[24-26] The urine was collected in vessels containing filter paper at the bottom. The animals were killed by decapitation and their organs were collected and radioactivity assayed.[27-30]

The data presented in Table (VI), clearly show high extraction index of the **4a**-^{99m}Tc-complex. The high liver uptake (22.1%) was noticed after 5 minutes post injection. A fast biliary excretion for **4a**-^{99m}Tc-complex was observed as the intestine activity was increased markedly from 36.7% at 5 min post injection up to 69.2% after 60 min which indicates very short hepatobiliary transport time for the **4a**-^{99m}Tc-complex. Also, the accumulation of the activity in both kidneys is negligible as time pass after injection reaches to 1.2% at 60 min post injection.

It was observed that there is no significant uptake of the chelate in non-target organs. The accumulation of very small amounts of radioactivity in the stomach indicates that there was no appreciable decomposition of this chelate.

Table III: Effect of ligand amount on the % labelling yield of ^{99m}Tc-complex.

Radiochemical species			
Substrat amount (mg)	$^{99m}TcO_4^-$	Reduced-hydrolysed $^{99m}TcO_4^-$	^{99m}Tc-complex
5	2.8	31.1	66.1
10	5.1	20.3	74.6
15	2.4	2.4	94.2
20	2.1	2.1	73.4
30	2.5	2.5	93.1

Table IV: Effect of Tin (II) content on the % labelling yield of ^{99m}Tc-complex.

Radiochemical species			
Tin (II) content (µg)	$^{99m}TcO_4^-$	Reduced-hydrolysed $^{99m}TcO_4^-$	^{99m}Tc-complex
50	27.1	7.6	65.3
100	16.4	5.7	77.9
150	12.3	5.3	82.4
200	3.4	2.4	94.2
250	4.4	4.7	90.9

Table V: Effect of pH of the reaction mixture on the % labelling yield of ^{99m}Tc-complex.

Radiochemical species,%			
pH	$^{99m}TcO_4^-$	Reduced-hydrolyzed ^{99m}Tc	^{99m}Tc-complex
3	----	----	----
4	45.8	7.9	46.3
5	8.5	8.3	83.2
6	3.4	2.4	94.2
7	7.2	3.7	89.1
10	8.6	16.8	74.6

Table VI: Biological distribution of ^{99m}Tc-**4a**-complex in mice organs.

% injected dose / organ and body fluid at different time post injection				
Organs and body fluids	5 min	15 min	30 min	60 min
Gall bladder	7.4	24.8	10.7	4.34
Liver	22.1	9.6	5.2	4.9
Intestine	36.7	45.7	61.7	69.2
Urine	7.2	8.1	13.3	14.3
Kidneys	2.2	2.1	2.7	1.2
Stomach	0.31	0.2	0.13	0.7
Lung	0.2	0.18	0.2	0.3
Heart	0.21	0.1	0.23	0.16
Spleen	0.77	0.5	0.6	0.09
Bone	1.6	1.3	0.1	0.1
Muscles	11.6	7.3	4.8	4.6
Blood	2.3	0.12	0.16	0.11

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