In search for new antitumor agents and encourage by marked cytotoxic activity of acridines, it is of interest to synthesize and screen the potential antitumor activity of some new acridine derivatives.

The thesis consists of the following parts:

1- Introduction

This section contains a brief literature review on different classes of antitumor agents relative to their mechanism of action as well as antitumor activity of acridine derivatives.

2- Aim of the work

This part presents the aim, rationale and molecular modeling study upon which the newly synthesized compounds are designed and synthesized.

3- Discussion

It deals with the discussion of the experimental methods adopted for synthesis of designed compounds. Schemes 1, 2, 3 and 4 illustrate the synthetic pathway followed for preparation of designed compounds.

4- Experimental

This part includes practical procedures for synthesis of designed and known compounds. Physical, spectral and microanalytical data are included in this part.

In the present investigation, 13 known starting compounds, 8 novel intermediates and 40 novel final compounds belonging to 4 series of new acridine derivatives of anticipated antitumor activity have been synthesized.

The first series comprises derivatives of 2-oxo-2-[2-(4-substituted phenylhydrazino)]ethyl 9-oxo-9,10-dihydroacridine-4-carboxylate.The second series consists of phenylhydrazinocarbonylmethyl 9-(4-substituted phenyl)aminoacridine-4-carboxylate derivatives, while the third series is 4-substituted phenylcarbamoylmethyl 9-(4-substituted phenyl)aminoacridine-4-carboxylate derivatives. The fourth one belongs to phenylcarbamoyl methyl 9-(4-substituted phenyl)aminoacridine-4- carboxylate derivatives.

The rational behind the synthesis of these compounds, their methods of synthesis, molecular modeling study as well as their antitumor screening are discussed.

In this thesis the following compounds were prepared:

I- Known starting and intermediate compounds

1) 4-Methylphenylhydrazine **(105a)**.
2) 4-Methoxyphenylhydrazine **(105b)**.
3) 4-Chlorophenylhydrazine **(105c)**.
4) 4-Bromophenylhydrazine **(105d)**.
5) 4-Hydrazinobenzoic acid **(105e)**.
6) 4-Nitrophenylhydrazine **(105f)**.
7) 4-Hydrazinobenzenesulfonamide **(105g)**.
8) 2-Chloro-N-phenylacetohydrazide **(106a)**.
9) 2-Chloro-N-(4-methyl phenyl)acetohydrazide **(106b)**.
10) 2-Chloro-N-(4-bromophenyl)acetohydrazide **(106e)**.
11) N-(2-Carboxyphenyl)anthranilic acid **(109)**.
12) 9-Oxo-9,10-dihydroacridine-4-carboxylic acid **(110)**.
13) Sodium 9- oxo-9,10-dihydroacridine-4-carboxylate**(111)**.

II- Novel intermediate compounds

1) 2-Chloro-N-(4-methoxy phenyl)acetohydrazide **(106c)**.
2) 2-Chloro-N-(4-chlorophenyl)acetohydrazide **(106d)**.
3) 4-[2-(2-Chloroacetyl)]hydrazinobenzoic acid **(106f)**.
4) 2-Chloro-N-(4-nitrophenyl)acetohydrazide **(106g)**.
5) 4-[2-(2-Chloroacetyl)]hydrazinobenzenesulfonamide **(106h)**.
6) 2-Oxo-2-(2-phenylhydrazino)ethyl 9-chloroacridine-4-carboxylate **(112)**.
7) (9-Oxo-9,10-dihydroacridin-4-yl)carbonyloxyacetic acid **(113)**.
8) 2-Chloro-2-oxoethyl 9-chloroacridine-4-carboxylate **(114)**.

III- Novel final compounds

1) 2-Oxo-2-(2-phenylhydrazino)ethyl 9-oxo-9,10-dihydroacridine-4-carboxylate **(99a)**.

2) 2-[2-(4-Methylphenyl)hydrazino]-2-oxoethyl 9-oxo-9,10-dihydro acridine-4-carboxylate **(99b)**.

3) 2-[2-(4-Methoxyphenyl)hydrazino]-2-oxoethyl 9-oxo-9,10-dihydro acridine-4-carboxylate **(99c)**.

4) 2-[2-(4-Chlorophenyl)hydrazino]-2-oxoethyl 9-oxo-9,10-dihydro acridine-4-carboxylate **(99d)**.

5) 2-[2-(4-Bromophenyl)hydrazino]-2-oxoethyl 9-oxo-9,10-dihydro acridine-4-carboxylate **(99e)**.

6) 4-[2-(9-Oxo-9,10-dihydroacridin-4-yl) carbonyloxyacetyl]hydrazino benzoic acid **(99f)**.

7) 2-[2-(4-Nitrophenyl) hydrazino]-2-oxoethyl 9-oxo-9,10-dihydro acridine-4-carboxylate **(99g)**.

8) 2-[2-(4-Sulfamoylphenyl) hydrazino]-2-oxoethyl 9-oxo-9,10-dihydro acridine-4-carboxylate **(99h)**.

9) Phenylhydrazinocarbonylmethyl 9-anilinoacridine-4-carboxylate **(100a)**.

10) Phenylhydrazinocarbonylmethyl 9-(4-methylphenyl)aminoacridine-4-carboxylate **(100b)**.

11) Phenylhydrazinocarbonylmethyl 9-(4-methoxyphenyl)aminoacridine-4-carboxylate **(100c)**.

12) Phenylhydrazinocarbonylmethyl 9-(4-chlorophenyl)aminoacridine-4-carboxylate **(100d)**.

13) Phenylhydrazinocarbonylmethyl 9-(4-carboxyphenyl)aminoacridine-4-carboxylate **(100e)**.

14) Phenylhydrazinocarbonylmethyl 9-(4-nitrophenyl)aminoacridine-4-carboxylate **(100f)**.

15) Phenylhydrazinocarbonylmethyl 9-(4-sulfamoylphenyl)amino-acridine-4-carboxylate **(100g)**.

16) Phenylhydrazinocarbonylmethyl 9-[4-(N-amidino)sulfamoylphenyl] aminoacridine-4-carboxylate **(100h)**.

17) Phenylhydrazinocarbonylmethyl 9-{4-[N-(4,6 dimethylpyrimidin-2-yl)] sulfamoyl phenyl}aminoacridine-4-carboxylate **(100i)**.

18) Phenylhydrazinocarbonylmethyl 9-{4-[N-(pyrimidin-2-yl)] sulfamoyl phenyl}aminoacridine-4-carboxylate **(100j)**.

19) Phenylhydrazinocarbonylmethyl 9-{4-[N-(5-methylisoxazol-3-yl)] sulfamoyl phenyl}aminoacridine-4-carboxylate **(100k)**.

20) Phenylcarbamoylmethyl 9-anilinoacridine-4-carboxylate **(101a)**.

21) 4-Methylphenylcarbamoylmethyl 9-(4-methylphenyl)aminoacridine-4-carboxylate **(101b)**.

22) 4-Methoxyphenylcarbamoylmethyl 9-(4-methoxyphenyl)amino-acridine-4-carboxylate **(101c)**.

23) 4-Chlorophenylcarbamoylmethyl 9-(4-chlorophenyl)aminoacridine-4-carboxylate **(101d)**.

24) 4-Carboxyphenylcarbamoylmethyl 9-(4-carboxyphenyl)amino-acridine-4-carboxylate **(101e)**.

25) 4-Nitrophenylcarbamoylmethyl 9-(4-nitrophenyl)aminoacridine-4-carboxylate **(101f)**.

26) 4-Sulfamoylphenylcarbamoylmethyl 9-(4-sulfamoylphenyl)amino-acridine-4-carboxylate **(101g)**.

27) 4-(N-Amidino)sulfamoylphenylcarbamoylmethyl 9-[4-(N-amidino) sulfamoylphenyl]aminoacridine-4-carboxylate **(101h)**.

28) 4-[N-(4, 6-Dimethylpyrimidin-2yl)]sulfamoylphenylcarbamoylmethyl 9-{4-[N-(4, 6 dimethylpyrimidin-2-yl)]sulfamoylphenyl}aminoacridine-4-carboxylate **(101i)**.

29) 4-[N-(Pyrimidin-2-yl)]sulfamoylphenylcarbamoylmethyl 9-{4-[N-(pyrimidin-2-yl)]sulfamoylphenyl}aminoacridine-4-carboxylate **(101j)**.

30) 4-[N-(5-Methylisoxazol-3-yl)]sulfamoylphenylcarbamoylmethyl 9-{4-[N-(5-methylisoxazol-3-yl)]sulfamoylphenyl}aminoacridine-4-carboxylate **(101k)**.

31) Phenylcarbamoylmethyl 9-(4-methylphenyl)aminoacridine-4-carboxylate **(102a)**.

32) Phenylcarbamoylmethyl 9-(4-methoxyphenyl)aminoacridine-4-carboxylate **(102b)**.

33) Phenylcarbamoylmethyl 9-(4-chlorophenyl)aminoacridine-4-carboxylate **(102c)**.

34) Phenylcarbamoylmethyl 9-(4-carboxyphenyl)aminoacridine-4-carboxylate **(102d)**.

35) Phenylcarbamoylmethyl 9-(4-nitroyphenyl)aminoacridine-4-carboxylate **(102e)**.

36) Phenylcarbamoylmethyl 9-(4-sulfamoylphenyl)aminoacridine-4-carboxylate **(102f)**.

37) Phenylcarbamoylmethyl 9-[4-(N-amidino)sulfamoylphenyl]amino-acridine-4-carboxylate **(102g)**.

38) Phenylcarbamoylmethyl 9-{4-[N-(4, 6 dimethylpyrimidin-2-yl)] sulfamoylphenyl}aminoacridine-4-carboxylate **(102h)**.

39) Phenylcarbamoylmethyl 9-{4-[N-(pyrimidin-2-yl)]sulfamoylphenyl} aminoacridine-4-carboxylate **(102i)**.

40) Phenylcarbamoylmethyl 9-{4-[N-(5-methylisoxazol-3-yl)] sulfamoyl-phenyl}aminoacridine-4-carboxylate **(102j)**.

5- Antitumor screening

Seventeen compounds were tested for their antitumor activity against breast carcinoma cell line MCF7. Survival curves and IC_{50} are illustrated. This part also includes statistics of the results. Data obtained indicated that compounds (**100g**, **100h**, **100k**, **101g**, **101h**, **102f**, **102g**, **102j**) exhibited good level of antitumor activity.

6- References

This part includes **131** references.

7- Arabic summary