

ABSTRACT

In the present work, seventy one target compounds have been designed and synthesized; they are classified into seven main series.

The first comprises derivatives of ethyl-1-cyano-3-phenylcarbamoyl-6,7-dihydro-5H-pyrrolizin-2-yl-carbamate.

The second comprises derivatives of 2,4-dioxo-1H-pyrimido[4,5-b]pyrrolizine-9-carbonitrile.

The third comprises derivatives of 1-cyano-2-(3-substituted ureido)-3N-phenyl-6,7-dihydro-pyrrolizine-3-carboxamide.

The fourth comprises derivatives of 3-(substituted)-4-imino-2-oxo-9N-phenyl-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.

The fifth comprises derivatives of 4-amino-3-(substituted)-2-oxo-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.

The sixth comprises derivatives of 2-amino-3N-phenyl-6,7-dihydro-5H-pyrrolizine-1,3-dicarboxamide.

The seventh comprises derivatives of 4-oxo-9N-phenyl-4,5,6,7-tetrahydro-3H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.

Our aim was the design, synthesis and bioscreening of new antineoplastic compounds depending on the structural correlation with several reported antineoplastic pyrrolizines.

2-Amino-1-cyano-3N-phenyl-6,7-dihydro-5H-pyrrolizine-3-carboxamide and substituted carboxamide **73** were reacted with ethyl chloroformate and alkyl / aryl isocyanates to give 2-ethyl carbamoyl derivatives **57** and 2-(3-alkyl /3-aryl)ureido derivatives **59** which upon refluxing in sodium ethoxide afforded the tricyclic pyrimido[4,5-b]pyrrolizines **58** and pyrimido[5,4-a]pyrrolizines **60** respectively. The tricyclic pyrimido[5,4-a]pyrrolizine was obtained by refluxing compound **73** with formic acid.

4-Imino group of compounds **60** were reduced using sodium borohydride to give the 4-amino analogs.

Hydrolysis of the 1-cyano group of compounds **73** to 1-carboxamide was carried out using alkaline hydrogen peroxide.

In addition 2-amino-1-cyano-6,7-dihydro-5H-pyrrolizine-3-carboxamide **66** was reacted with acid chloride, phenyl isocyanate and benzaldehyde to give 2-acyl amino **69**, 2-(3-aryl ureido) **74** and 2-benzylideneamino **70** derivatives respectively. Hydrolysis of the cyano to carboxamide group was achieved using alkaline hydrogen peroxide. The tricyclic derivatives pyrimido[4,5-b]pyrrolizine **67** and pyrimido[5,4-a]pyrrolizine **68** was obtained by refluxing compound **66** with ethyl chloroformate and formic acid respectively.

Eleven new compounds were selected for screening their antitumor activity against breast cell line in National Cancer Institute. The data were treated with a computerized program (probit analysis) in order to calculate the IC₅₀ and IC₁₀ of these compounds.

Synthesis of the following compounds was found to be essential for our study.

Known intermediate

- 1- 2-Pyrrolidin-2-ylidene-malononitrile
- 2- 2-Chloro-1N-phenylacetamide.
- 3- 2-Chloro-1N-(4-methylphenyl)acetamide.
- 4- 2-Chloro-1N-(4-methoxyphenyl)acetamide.
- 5- 2-Chloro-1N-(4-chlorophenyl)acetamide.
- 6- 2-Chloro-1N-(4-sulfamoylphenyl)acetamide.
- 7- 2-Amino-1-cyano-3N-phenyl-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 8- 2-Amino-1-cyano-6,7-dihydro-5H-pyrrolizine-3-carboxylic acid.

New compounds that were synthesized

- 1- Ethyl-1-cyano-3-phenylcarbamoyl-6,7-dihydro-5H-pyrrolizin-2-yl-carbamate.
- 2- Ethyl-1-cyano-3-(4-methylphenylcarbamoyl)-6,7-dihydro-5H-pyrrolizin-2-yl-carbamate.
- 3- Ethyl-1-cyano-3-(4-methoxyphenylcarbamoyl)-6,7-dihydro-5H-pyrrolizin-2-yl-carbamate.
- 4- Ethyl-1-cyano-3-(4-chlorophenylcarbamoyl)-6,7-dihydro-5H-pyrrolizin-2-yl-carbamate.
- 5- Ethyl-1-cyano-3-(sulphamoylphenylcarbamoyl)-6,7-dihydro-5H-pyrrolizin-2-yl-carbamate.
- 6- 2,4-Dioxo-3-phenyl-2,3,4,6,7,8-hexahydro-1H-pyrimido[4,5-b]pyrrolizine-9-carbonitrile.
- 7- 2,4-Dioxo-3-(4-tolylphenyl)-2,3,4,6,7,8-hexahydro-1H-pyrimido[4,5-b]pyrrolizine-9-carbonitrile.
- 8- 3-(4-Methoxyphenyl)-2,4-dioxo-2,3,4,6,7,8-hexahydro-1H-pyrimido[4,5-b]pyrrolizine-9-carbonitrile.
- 9- 3-(4-Chlorophenyl)-2,4-dioxo-2,3,4,6,7,8-hexahydro-1H-pyrimido[4,5-b]pyrrolizine-9-carbonitrile.
- 10- 2,4-Dioxo-3-(4-sulfamoylphenyl)-2,3,4,6,7,8-hexahydro-1H-pyrimido[4,5-b]pyrrolizine-9-carbonitrile.
- 11- 1-Cyano-2-(3-ethylureido)-3N-phenyl-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 12- 1-Cyano-2-(3-ethylureido)-3N-(4-tolyl)-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 13- 1-Cyano-2-(3-ethylureido)-3N-(4-methoxyphenyl)-6,7-dihydro-5H-pyrrolizine-3-carboxamide.

- 14- 3N-(4-Chlorophenyl)-1-cyano-2-(3-ethylureido)-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 15- 1-Cyano-2-(3-ethylureido)-3N-(4-sulfamoylphenyl)-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 16- 1-Cyano-3N-phenyl-2-(3-phenylureido)-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 17- 1-Cyano-3N-(4-methylphenyl)-2-(3-phenylureido)-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 18- 1-Cyano-3N-(4-methoxyphenyl)-2-(3-phenylureido)-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 19- 1-Cyano-3N-(4-chlorophenyl)-2-(3-phenylureido)-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 20- 1-Cyano-2-(3-phenylureido)-3N-(4-sulfamoylphenyl)-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 21- 1-Cyano-2-[3-(4-chlorophenyl)ureido]-3N-phenyl-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 22- 1-Cyano-2-[3-(4-chlorophenyl)ureido]-3N-(4-methylphenyl)-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 23- 1-Cyano-2-[3-(4-chlorophenyl)ureido]-3N-(4-methoxyphenyl)-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 24- 1-Cyano-2-[3-(4-chlorophenyl)ureido]-3N-(4-chlorophenyl)-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 25- 1-Cyano-2-[3-(4-chlorophenyl)ureido]-3N-(4-sulfamoylphenyl)-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 26- 3-Ethyl-4-imino-2-oxo-9N-phenyl-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a] pyrrolizine-9-carboxamide.

- 27- 3-Ethyl-4-imino-2-oxo-9N-(4-methylphenyl)-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a] pyrrolizine-9-carboxamide.
- 28- 3-Ethyl-4-imino-2-oxo-9N-(4-methoxyphenyl)-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a] pyrrolizine-9-carboxamide.
- 29- 9N-(4-Chlorophenyl)-3-ethyl-4-imino-2-oxo-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a] pyrrolizine-9-carboxamide.
- 30- 3-Ethyl-4-imino-2-oxo-9N-(4-sulfamoylphenyl)-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a] pyrrolizine-9-carboxamide.
- 31- 4-Imino-2-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a] pyrrolizine-9-(N-phenylcarboxamide).
- 32- 4-Imino-2-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a] pyrrolizine-9-(N-(4-methylphenyl)carboxamide).
- 33- 4-Imino-2-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a] pyrrolizine-9-(N-(4-methoxyphenyl)carboxamide).
- 34- 4-Imino-2-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a] pyrrolizine-9-(N-(4-chlorophenyl)carboxamide).
- 35- 4-Imino-2-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a] pyrrolizine-9-(N-(4-sulfamoylphenyl)carboxamide).
- 36- 3-(4-Chlorophenyl)-4-Imino-2-oxo-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-(N-phenylcarboxamide).
- 37- 3-(4-Chlorophenyl)-4-imino-9N-(4-methylphenyl)-2-oxo-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 38- 3-(4-Chlorophenyl)-4-imino-9N-(4-methoxyphenyl)-2-oxo-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 39- 3-(4-Chlorophenyl)-4-imino-2-oxo-9N-(4-chlorophenyl)-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.

- 40- 3-(4-Chlorophenyl)-4-imino-2-oxo-9N-(4-sulfamoylphenyl)-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 41- 4-Amino-3-ethyl-2-oxo-9N-phenyl-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 42- 4-Amino-3-ethyl-9N-(4-methylphenyl)-2-oxo-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 43- 4-Amino-3-ethyl-9N-(4-methoxyphenyl)-2-oxo-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 44- 4-Amino-9N-(4-chlorophenyl)-3-ethyl-2-oxo-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 45- 4-Amino-3-ethyl-2-oxo-9N-(4-sulfamoylphenyl)-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 46- 4-Amino-2-oxo-3-phenyl-9N-phenyl-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 47- 4-Amino-9N-(4-methylphenyl)-2-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 48- 4-Amino-9N-(4-methoxyphenyl)-2-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 49- 4-Amino-9N-(4-chlorophenyl)-2-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 50- 4-Amino-2-oxo-3-phenyl-9N-(4-sulfamoylphenyl)-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 51- 4-Amino-3-(4-chlorophenyl)-2-oxo-9N-phenyl-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 52- 4-Amino-3-(4-chlorophenyl)-9N-(4-methylphenyl)-2-oxo-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.

- 53- 4-Amino-3-(4-chlorophenyl)-9N-(4-methoxyphenyl)-2-oxo-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 54- 4-Amino-2-oxo-3-(4-chlorophenyl)-9N-(4-chlorophenyl)-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 55- 4-Amino-2-oxo-3-(4-chlorophenyl)-9N-(4-sulfamoylphenyl)-2,3,4,5,6,7-hexahydro-1H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 56- 2-Amino-3N-phenyl-6,7-dihydro-5H-pyrrolizine-1,3-dicarboxamide.
- 57- 2-Amino-3N-(4-methylphenyl)-6,7-dihydro-5H-pyrrolizine-1,3-dicarboxamide.
- 58- 2-Amino-3N-(4-methoxyphenyl)-6,7-dihydro-5H-pyrrolizine-1,3-dicarboxamide.
- 59- 2-Amino-3N-(4-chlorophenyl)-6,7-dihydro-5H-pyrrolizine-1,3-dicarboxamide.
- 60- 4-Oxo-9N-phenyl-4,5,6,7-tetrahydro-3H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 61- 3N-(4-Methylphenyl)-4-oxo-4,5,6,7-tetrahydro-3H-pyrimido[4,5-a]pyrrolizine-9-carboxamide.
- 62- 3N-(4-Methoxyphenyl)-4-oxo-3H-4,5,6,7-tetrahydro-pyrimido[4,5-a]pyrrolizine-9-carboxamide.
- 63- 2-Amino-1-cyano-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 64- 2-Acetamido-1-cyano-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 65- 2-Benzoylamido-1-cyano-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 66- 9-Cyano-2,3,4,5,6,8-hexahydro-1H-pyrimido[4,5-b]pyrrolizine-2,4-dione.
- 67- 1-Cyano-2(3-phenylureido)-6,7-dihydro-5H-pyrrolizine-3-carboxamide.

- 68- 1-Cyano-2(3-(4-chlorophenyl)ureido)-6,7-dihydro-5-pyrrolizine-3-carboxamide.
- 69- 2-(Benzylideneamino)-1-cyano-6,7-dihydro-5H-pyrrolizine-3-carboxamide.
- 70- 4-Oxo-4,5,6,7-tetrahydro-3H-pyrimido[5,4-a]pyrrolizine-9-carboxamide.
- 71- 2-Amino-6,7-dihydro-5H-pyrrolizine-1,3-dicarboxamide.