ABSTRACT

In the present work, forty two target compounds had been designed and synthesized (schemes 1-3). The new compounds were screened for either antiinflammatory or anticonvulsant activity.

- We aimed for the design, synthesis and bioscreening of new antiinflammatory and anticonvulsant compounds depending on the structural correlation and similarity with several actively reported compounds.

- Variations on the para position of the phenyl ring of the key compounds **Va-c** were performed using nitro, hydroxy and carboxy groups.

- Two series of substituted benzylidene amino derivatives were obtained by condensation of the key compounds **Va-c** with vanillin and anisaldehyde.

- Hypridization of the key compounds **Va-c** with some antiinflammatory drugs (ibuprofen and ketoprofen) was carried out as synergistic combination that may affect activity.

- Reactions of the key compounds **Va-c** with three cyclic anhydrides were done, which brought about acylation with or without intramolecular rearrangement of the nitrile group into pyrimidine ring. The resulting tricyclic derivatives may or may not bear a free carboxylic group.

- Acylation of the parent compounds **Va-c** with chloroacetyl chloride and chlorobutyryl chloride was done in different organic solvents.

- Cyclization of the haloacyl side chain in compounds **XIIa-c** into diazepine derivatives **XIIIa-c** was achieved through intramolecular dehydrohalogenation reaction.

- Alkylation of the amidic nitrogen in **XIIIa-c** was done using methyl iodide in presence of suitable acid removing agent affording **XIVa-c**.

- Cyclization of the 4-chlorobutyryl side chain in compounds **XVa-c** was performed to afford 2-oxo-pyrrolidin-1-yl derivatives **XVIa-c**.

- Oxalyl chloride was reacted with the starting compounds **Va-c** in three solvent systems where dimmer derivatives **XVIIIa-c** were obtained.

- The rationale for these compounds syntheses has been discussed

 The new compounds (schemes 1 and 2) were evaluated for their antiinflammatory activities where the amide derivatives **VIIa-f** and the pyrimidopyrrolizine derivatives **IXa-c**, **Xa-c** and **XIa-c** showed good activity compared to the reference standard (ketorolac **13**), while the new compounds (scheme 3) were tested for their anticonvulsant activity where compounds **XVIa-c** exhibited moderate anticonvulsant activity compared to the reference standard (phenobarbitone).

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

Known intermediates:

1- 2-Chloro-*N*-phenylacetamide (**IIa**).

2- 2-Chloro-*N*-(4-methylphenyl)-acetamide (**IIb**).

3- 2-Chloro-*N*-(4-chlorophenyl)-acetamide (**IIc**).

4- 2-Chloro-*N*-(4-nitrophenyl)-acetamide (**IId**).

5- 2-Chloro-*N*-(4-hydroxy-phenyl)-acetamide (**IIe**).

6- 4-(2-Chloroacetylamino)-benzoic acid (**IIf**).

7- 2-Pyrrolidin-2-ylidene-malononitrile (**IV**).

8- 6-Amino-7-cyano-*N*-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**Va**).

9- 6-Amino-7-cyano-*N*-(4-methylphenyl)-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**Vb**).

10- 6-Amino-*N*-(4-chlorophenyl)-7-cyano-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**Vc**).

11- 6-(2-Chloroacetylamino)-7-cyano-*N*-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**XIIa**).

12- 6-(2-Chloroacetylamino)-7-cyano-*N*-(4-methylphenyl)-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**XIIb**).

13- 6-(2-Chloroacetylamino)-*N*-(4-chlorophenyl)-7-cyano-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**XIIc**).

Newly synthesized compounds:

Include 42 new compounds classified into twelve series.

1. The first series includes:

- 6-Amino-7-cyano-*N*-(4-nitrophenyl)-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**Vd**).
- 6-Amino-7-cyano-*N*-(4-hydroxyphenyl)-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**Ve**).
- 4-[(6-Amino-7-cyano-2,3-dihydro-1*H*-pyrrolizine-5-carbonyl)-amino]-benzoic acid **(Vf)**.

2. The second series includes:

- 7-Cyano-6-[(4-methoxy-benzylidene)amino]-*N*-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**VIa**).
- 7-Cyano-6-[(4-methoxy-benzylidene)amino]-*N*-(4-methylphenyl)-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**VIb**).
- *N*-(4-Chlorophenyl)-7-cyano-6-[(4-methoxy-benzylidene)amino]-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**VIc**).
- 7-Cyano-6-[(4-hydroxy-3-methoxy-benzylidene)-amino]-*N*-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**VId**).
- 7-Cyano-6-[(4-hydroxy-3-methoxy-benzylidene)-amino]-*N*-(4-methylphenyl)-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**VIe**).
- *N*-(4-Chlorophenyl)-7-cyano-6-[(4-hydroxy-3-methoxy-benzylidene)-amino]-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**VIf**).

3. The third series includes:

- (RS)-7-Cyano-6-[2-(4-isobutyl-phenyl)-propionylamino]-*N*-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**VIIa**).
- (RS)-7-Cyano-6-[2-(4-isobutyl-phenyl)-propionylamino]-*N*-(4-methylphenyl)-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**VIIb**).
- (RS)-*N*-(4-Chlorophenyl)-7-cyano-6-[2-(4-isobutyl-phenyl)-propionylamino]-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**VIIc**).
- (RS)-6-[2-(3-Benzoyl-phenyl)-propionylamino]-7-cyano-*N*-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**VIId**).
- (RS)-6-[2-(3-Benzoyl-phenyl)-propionylamino]-7-cyano-*N*-(4-methylphenyl)-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**VIIe**).
- (RS)-6-[2-(3-Benzoyl-phenyl)-propionylamino]-*N*-(4-chlorophenyl)-7-cyano-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**VIIf**).

4. The fourth series includes:

- 7-Cyano-6-(1,3-dioxoisoindolin-2-yl)-*N*-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**VIIIa**).
- 7-Cyano-6-(1,3-dioxoisoindolin-2-yl)-*N*-(4-methylphenyl)-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**VIIIb**).
- 7-Cyano-6-(1,3-dioxoisoindolin-2-yl)-*N*-(4-chlorophenyl)-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**VIIIc**).

5. The fifth series includes:

- 7,13-Dioxo-5*N*-phenyl-2,3,7,13-tetrahydro-1*H*-pyrrolizino[1′,2′**:**5,6]pyrimido[2,1-a] isoindole-5-carboxamide (**IXa**).
- 5*N*-(4-Methylphenyl)-7,13-dioxo-2,3,7,13-tetrahydro-1*H*-pyrrolizino[1′,2′**:**5,6]pyrimido [2,1-a]isoindole-5-carboxamide (**IXb**).
- 5*N*-(Chlorophenyl)-7,13-dioxo-2,3,7,13-tetrahydro-1*H*-pyrrolizino[1′,2′**:**5,6]pyrimido [2,1-a]isoindole-5-carboxamide (**IXc**).

6. The sixth series includes:

- (EZ)-3-(4-Oxo-9-(phenylcarbamoyl)-4,5,6,7-tetrahydro-3*H*-pyrimido[5,4-a]pyrrolizin-2-yl)acrylic acid (**Xa**).
- (EZ)-3-(9-(4-Methylphenylcarbamoyl)-4-oxo-4,5,6,7-tetrahydro-3*H*-pyrimido[5,4-a] pyrrolizin-2-yl)acrylic acid (**Xb**).
- (EZ)-3-(9-(4-Chlorophenylcarbamoyl)-4-oxo-4,5,6,7-tetrahydro-3*H*-pyrimido[5,4-a] pyrrolizin-2-yl)acrylic acid (**Xc**).

7. The seventh series includes:

- 3-(4-Oxo-9-(phenylcarbamoyl)-4,5,6,7-tetrahydro-3*H*-pyrimido[5,4-a]pyrrolizin-2-yl) propanoic acid (**XIa**).
- 3-(9-(4-Methylphenylcarbamoyl)-4-oxo-4,5,6,7-tetrahydro-3*H*-pyrimido[5,4-a]pyrrolizin-2-yl)propanoic acid (**XIb**).
- 3-(9-(4-Chloro-phenylcarbamoyl)-4-oxo-4,5,6,7-tetrahydro-3*H*-pyrimido[5,4-a]pyrrolizin-2-yl)propanoic acid (**XIc**).

8. The eighth series includes:

- 2,5-Dioxo-4-phenyl-1,2,3,4,5,7,8,9-octahydro-[1,4]diazepino[5,6-b]pyrrolizine-10-carbonitrile (**XIIIa**).
- 2,5-Dioxo-4-(4-methylphenyl)-1,2,3,4,5,7,8,9-octahydro-[1,4]diazepino[5,6-b]pyrrolizine-10-carbonitrile (**XIIIb**).
- 4-(4-Chlorophenyl)-2,5-dioxo-1,2,3,4,5,7,8,9-octahydro-[1,4]diazepino[5,6-b]pyrrolizine-10-carbonitrile (**XIIIc**).

9. The ninth series includes:

- 1-Methyl-2,5-dioxo-4-phenyl-1,2,3,4,5,7,8,9-octahydro-[1,4]diazepino[5,6-b]pyrrolizine-10-carbonitrile (**XIVa**).
- 1-Methyl-4-(4-methylphenyl)-2,5-dioxo-1,2,3,4,5,7,8,9-octahydro-[1,4]diazepino[5,6-b] pyrrolizine-10-carbonitrile (**XIVb**).
- 4-(4-Chlorophenyl)-1-methyl-2,5-dioxo-1,2,3,4,5,7,8,9-octahydro-[1,4]diazepino[5,6-b] pyrrolizine-10-carbonitrile (**XIVc**).

10. The tenth series includes:

- 6-(4-Chlorobutyrylamino)-7-cyano-*N*-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**XVa**).
- 6-(4-Chlorobutyrylamino)-*N*-(4-methylphenyl)-7-cyano-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**XVb**).
- 6-(4-Chlorobutyrylamino)-*N*-(4-chlorophenyl)-7-cyano-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**XVc**).

11. The eleventh series includes:

- 7-Cyano-*N*-phenyl-6-(2-oxopyrrolidin-1-yl)-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**XVIa**).

- 7-Cyano-*N*-(4-methylphenyl)-6-(2-oxopyrrolidin-1-yl)-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**XVIb**).

- *N*-(4-Chlorophenyl)-7-cyano-6-(2-oxopyrrolidin-1-yl)-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**XVIc**).

12. The twelfth series includes:

- *N*,*N*′-Bis-(7-cyano-5-(phenylcarbamoyl)-2,3-dihydro-1*H*-pyrrolizin-6-yl)-oxalamide (**XVIIIa**).

- *N*,*N*′-Bis-(7-cyano-5-(4-methylphenylcarbamoyl)-2,3-dihydro-1*H*-pyrrolizin-6-yl)-oxalamide (**XVIIIb**).

N,*N*′-Bis-(5-[4-chlorophenylcarbamoyl]-7-cyano-2,3-dihydro-1*H*-pyrrolizin-6-yl)-oxalamide (**XVIIIc**).