Synthesis of some new thiazole derivatives as potential anticancer agents

In the search for new cytotoxic agents with improved anticancer profile, some new thiazole derivatives which bearing a free sulfonamide moiety were synthesized. All the newly synthesized target compounds were subjected to *in vitro* anticancer screening against human breast cancer cell line MCF-7.The most potent compounds, as concluded from their *in vitro* anticancer screening, were selected to be evaluated for their *in vitro* inhibitory activity against carbonic anhydrase enzyme. Moreover, a molecular docking study was carried out by docking the newly synthesized compounds in the active site of the carbonic anhydrase enzyme.

The thesis includes the following parts:

1. **Introduction**

This part includes a brief literature review on cancer, chemotherapy and radiotherapy then on the reported anticancer activity of different thiazole derivatives and sulfonamide derivatives and their mechanisms of action. In addition, various methods for the synthesis of thiazole and thiazolodinone derivatives were discussed.

2. **Aim of the present investigation:**

The present investigation deals with the design and the synthesis of novel thiazole derivatives bearing a sulfonamide moiety in their molecules in order to explore the effect of combining the thiazole moiety with the biologically active sulfonamide group on the antitumor activity of the synthesized compounds.

3. Theoretical Discussion:

This part deals with the discussion of the experimental methods adopted for the synthesis of the target compounds, as well as the analytical methods adopted for the identification and verification of the structures of the synthesized compounds by elemental analysis and spectroscopic methods. In addition, this section includes schemes (1-4) which illustrate the synthetic pathways adopted for the preparation of the designed compounds.

4. Experimental:

This part includes the detailed practical methods for the synthesis of twenty new compounds, one new intermediate and fourteen known intermediates that are listed below with their elemental analyses and spectral data (IR, ^{1}H-NMR and mass spectroscopy).

Known intermediates:

- 2-Chloro-*N*-(4-sulfamoylphenyl)acetamide **(II).**
- 4-((4-Oxo-4,5-dihydrothiazol-2-yl)amino)benzenesulfonamide **(III).**
- 4-((4-Chlorothiazol-2-yl)amino)benzenesulfonamide **(V).**
- 2-Benzamidoacetic acid **(IXa).**
- 2-(4-Chlorobenzamido)acetic acid **(IXb).**
- 4-Benzylidene-2-phenyloxazol-5(4*H*)-one **(Xa).**
- 4-(4-Chlorobenzylidene)-2-phenyloxazol-5(4*H*)-one **(Xb).**
- 4-[4-(Dimethylamino)benzylidene]-2-phenyloxazol-5(4*H*)-one **(Xc).**
- 4-Benzylidene-2-(4-chlorophenyl)oxazol-5(4*H*)-one **(Xd).**
- 4-(4-Chlorobenzylidene)-2-(4-chlorophenyl)oxazol-5(4*H*)-one **(Xe).**

- 4-[4-(Dimethylamino)benzylidene]-2-(4-chlorophenyl)oxazol-5(4*H*)-one **(Xf).**
- 4-Oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile **(XIIIa).**
- 6-(4-Chlorophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile **(XIIIb).**
- 6-[4-(Dimethylamino)phenyl]-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile **(XIIIc).**

New intermediate:

- 4-((4-Hydrazinylthiazol-2-yl)amino)benzenesulfonamide **(VII).**

New final compounds:

- 4-(2-(4-Oxo-2-((4-sulfamoylphenyl)amino)thiazol-5(4*H*)-ylidene)hydrazinyl)benzenesulfonamide (**IVa).**
- 4-((5-(2-(4-Chlorophenyl)hydrazono)-4-oxo-4,5-dihydrothiazol-2-yl)amino)benzenesulfonamide (**IVb).**
- 4-(2-(4-Oxo-2-((4-sulfamoylphenyl)amino)thiazol-5(4*H*)-ylidene)hydrazinyl)benzoic acid (**IVc).**
- *N*-Carbamimidoyl-4-(2-(4-oxo-2-((4-sulfamoylphenyl)amino)thiazol-5(4*H*)-ylidene)hydrazinyl)benzenesulfonamide (**IVd).**
- 4, 4′-(Thiazole-2,4-diylbis(azanediyl))dibenzenesulfonamide (**VIa).**
- 4-((2-((4-Sulfamoylphenyl)amino)thiazol-4-yl)amino)benzoic acid (**VIb).**
- 4-((4-((4-Fluorophenyl)amino)thiazol-2-yl)amino)benzenesulfonamide (**VIc).**
- 4-((4-(Piperidin-1-yl)thiazol-2-yl)amino)benzenesulfonamide (**VId).**

- 4-((4-((4-Benzylidene-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)amino)thiazol-2-yl)amino)benzenesulfonamide (**XIa).**
- 4-((4-((4-(4-Chlorobenzylidene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)amino)thiazol-2-yl)amino)benzenesulfonamide (**XIb).**
- 4-((4-((4-(4-(Dimethylamino)benzylidene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)amino)thiazol-2-yl)amino)benzenesulfonamide (**XIc).**
- 4-((4-((4-Benzylidene-2-(4-chlorophenyl)-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)amino)thiazol-2-yl)amino)benzenesulfonamide (**XId).**
- 4-((4-((4-(4-Chlorobenzylidene)-2-(4-chlorophenyl)-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)amino)thiazol-2-yl)amino)benzenesulfonamide (**XIe).**
- 4-((4-((2-(4-Chlorophenyl)-4-(4-(dimethylamino)benzylidene)-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)amino)thiazol-2-yl)amino)benzenesulfonamide (**XIf).**
- 4-((4-(2-(5-Cyano-6-oxo-4-phenyl-1,6-dihydropyrimidin-2-yl)hydrazinyl)thiazol-2-yl)amino)benzenesulfonamide (**XIVa).**
- 4-((4-(2-(4-(4-Chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyrimidin-2-yl)hydrazinyl)thiazol-2-yl)amino)benzenesulfonamide (**XIVb).**
- 4-((4-(2-(5-Cyano-4-(4-(dimethylamino)phenyl)-6-oxo-1,6-dihydropyrimidin-2-yl)hydrazinyl)thiazol-2-yl)amino)benzenesulfonamide (**XIVc).**
- 4-((4-((5-Cyano-6-oxo-4-phenyl-1,6-dihydropyrimidin-2-yl)thio)thiazol-2-yl)amino)benzenesulfonamide (**XVa).**
- 4-((4-((4-(4-Chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyrimidin-2-yl)thio)thiazol-2-yl)amino)benzenesulfonamide (**XVb).**
- 4-((4-((5-Cyano-4-(4-(dimethylamino)phenyl)-6-oxo-1,6-dihydropyrimidin-2-yl)thio)thiazol-2-yl)amino)benzenesulfonamide (**XVc).**

5. Pharmacological screening and molecular modeling:

Twenty new compounds were screened for their *in-vitro* anticancer activity against human breast cancer cell line MCF-7.

The newly synthesized compounds **IVa-d, VIa-d, XIb** and **XIVa** were docked into the active site of carbonic anhydrase II to predict the expected mechanism of action. CA inhibition assay was conducted on human (h) CA isoforms hCA I, II and IX with compounds **IVa-d, VIa-d, XIb, XIVa** and acetazolamide (AZA) as a standard inhibitor by a stopped- flow CO_2 hydrase assay.

6. References:

This part includes 162 references covering the period up to 2015.

7. Arabic summary