ABSTRACT

Everyday scientific researches reveal the increasing significance of discovering newly anti-inflammatory agents with elevated safety margins to control cellular inflammatory response. The present work shows design and synthesis of several trisubstituted pyrazole derivatives **VIIa-h, VIIIa-f, XIIa,b, XIIIa,b** and **XIVa-d**. 4-Methanesulfonylphenylhydrazine hydrochloride **III** reacted with the appropriate acetophenone **IVa,b** to produce phenylhydrazine derivatives **Va,b**. Then, the formed compounds **Va,b** underwent Vilsmeier-Haack reaction to form carbaldehyde derivatives **VIa,b** which were considered as key intermediates for the preparation of compounds **VIIa-h** and **VIIIa-f** via reaction with the appropriate amine or ketone, respectively. Furthermore, oxidation of the carbaldehydes **VIa,b** afforded the corresponding carboxylic acids **IXa,b** which upon esterification followed by reaction with hydrazine hydrate produced compounds **Xa,b** and **XIa,b**, respectively. 4-Carbohydrazide derivatives **XIa,b** were used as second key intermediates for the synthesis of compounds **XIIa,b**, **XIIIa,b** and **XIVa-d** through reactions with CS_2/KOH, ethyl acetoacetate or the appropriate aldehyde, respectively. Chemical structures of the newly synthesized compounds were characterized using spectral and elemental analyses. The prepared compounds were evaluated for their *in vitro* (SI range = 20.67 – 348.71) and *in vivo* (% edema inhibition range after 3 hours = 29.77 – 85.21) activities compared to the reference standard, celecoxib (SI = 308.163 and % edema inhibition after 3 hours = 74.02) with calculation of ED_{50} values. Also, ulcerogenic liability of the most active compounds **VIId,f**, **VIIIb,e,f, XIIb, XIIIb** and **XIVb,d** was evaluated.

Finally, docking studies were performed for the most active compounds to determine their binding mode in the active site of the enzyme.

This thesis consists of the following parts:

1- Introduction:

This section presents a literature review about inflammation, anti-inflammatory targets, various biological activities of pyrazole nucleus and certain synthetic approaches for pyrazole derivatives.

2- Aim of the work:

It includs the research objectives and the major aims that directs the theoretical and practical work.

3- Discussion:

This part discusses several experimental methods and conditions of reactions adopted for the preparation of the designed compounds. Also, it deals with the confirmation of the newly synthesized compounds by different methods including microanalytical data, infrared, mass, ^{1}H NMR and ^{13}C NMR spectra.

4- Expermintal:

This section shows the practical procedures used for the synthesis of the reported and newly synthesized intermediates as well as the new final compounds. In addition, it includes their spectral and microanalytical data.
Synthesis of the following compounds was found to be essential for our study.

Reported intermediates: (3 compounds)

1. 1-(1-(4-methoxyphenyl)ethylidene)-2-(4-(methylsulfonyl)phenyl)hydrazine **(Va).**
2. 1-(1-(4-bromophenyl)ethylidene)-2-(4-(methylsulfonyl)phenyl)hydrazine **(Vb).**
3. 3-(4-bromophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole-4-carbaldehyde **(VIb)**.

Newly synthesized intermediates: (7 compounds)

1. 3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole-4-carbaldehyde **(VIa)**.

2. 3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole-4-carboxylic acid **(IXa)**.

3. 3-(4-bromophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole-4-carboxylic acid **(IXb)**.

4. Methyl 3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole-4-carboxylate **(Xa)**.

5. Methyl 3-(4-bromophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole-4-carboxylate **(Xb)**.

6. 3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole-4-carbohydrazide **(XIa)**.

7. 3-(4-bromophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole-4-carbohydrazide **(XIb)**.

Newly synthesized final compounds: (22 compounds)

1. The first series included:

1. N-((3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)methylene)aniline **(VIIa)**.

2. 4-chloro-N-((3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)methylene)aniline **(VIIb)**.

3. 4-(((3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)methylene)amino)phenol **(VIIc)**.

4. 4-methoxy-N-((3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)methylene)aniline **(VIId)**.

5. N-((3-(4-bromophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)methylene)aniline **(VIIe)**.

6. N-((3-(4-bromophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)methylene)-4-chloroaniline **(VIIf)**.

7. 4-(((3-(4-bromophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)methylene)amino)phenol **(VIIg)**.

8. N-((3-(4-bromophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)methylene)-4-methoxyaniline **(VIIh)**.

2. The second series included:

1. 3-(3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)-1-phenylprop-2-en-1-one **(VIIIa)**.

2. 1-(4-chlorophenyl)-3-(3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)prop-2-en-1-one **(VIIIb)**.

3. 1-(4-methoxyphenyl)-3-(3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)prop-2-en-1-one **(VIIIc)**.

4. 3-(3-(4-bromophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)-1-phenylprop-2-en-1-one **(VIIId)**.

5. 3-(3-(4-bromophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)-1-(4-chlorophenyl)prop-2-en-1-one **(VIIIe)**.

6. 3-(3-(4-bromophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)-1-(4-methoxyphenyl)prop-2-en-1-one **(VIIIf)**.

3. The third series included:

1. 5-(3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)-1,3,4-oxadiazole-2(3H)-thione **(XIIa)**.

2. 5-(3-(4-bromophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-4-yl)-1,3,4-oxadiazole-2(3H)-thione **(XIIb)**.

4. The fourth series included:

1. 1-(3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole-4-carbonyl)-3-methyl-1H-pyrazol-5(4H)-one **(XIIIa)**.

2. 1-(3-(4-bromophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole-4-carbonyl)-3-methyl-1H-pyrazol-5(4H)-one **(XIIIb)**.

5. The fifth series included:

1. N-benzylidene-3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole-4-carbohydrazide **(XIVa)**.

2. N-benzylidene-3-(4-bromophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole-4-carbohydrazide **(XIVb)**.

3. N-(furan-2-ylmethylene)-3-(4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole-4-carbohydrazide **(XIVc)**.

4. N-(furan-2-ylmethylene)-3-(4-bromophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole-4-carbohydrazide **(XIVd)**.

5- Biological screening:

It involves the techniques used for *in vitro* and *in vivo* pharmacological evaluation of the finally synthesized compounds. In addition, all results of biological evaluation of finally synthesized compounds were listed in tables and illustrated with charts in comparison to standard reference, celecoxib.

- ***In vitro* screening:**

The ability of the newly synthesized compounds to inhibit both COX-1 and COX-2 activities was determined using COX colorimetric inhibitor screening kit. The finally synthesized compounds were evaluated for their COX inhibitory activity where they showed better selectivity towards COX-2 than COX-1.

- ***In vivo* screening:**

1. Anti-inflammatory screening:

The anti-inflammatory activity of the finally synthesized compounds was evaluated using "rat paw carrageenan edema" method. The compounds showed moderate to high anti-inflammatory activity compared to the standard celecoxib. Also, ED_{50} value was evaluated for the most active compounds relative to celecoxib.

2. Ulcerogenic liability:

Ulcer index was calculated for the most active compounds compared to celecoxib and indomethacin. All compounds were less ulcerogenic than indomethacin and compounds **VIIIb,e,f**, **XIIIb** and **XIVb** were less ulcerogenic than celecoxib. The results proved the safety gastric profile of the newly synthesized compounds.

5- Molecular Docking

6- References:

This part included 156 references covering the period 1901-2018.

7- Arabic summary