Abstract

This thesis comprises four chapters. The first one is an introduction that consists of a brief survey on the different methods to synthesize pyrazolo[3,4-*d*]pyrimidine derivatives and their anti-inflammatory activity.

The second chapter deals with the aim of the work and schemes that have been carried out to get the target new pyrazolo[3,4-*d*]pyrimidine derivatives.

The third chapter illustrate the theoretical discussion of the experimental work for the preparation of the precursor 5-Amino-pyrazole-4-carbonitrile **IIa&b** through the reaction of ketene dithioacetal **I** with either un-substituted or *p*-methylsulphonyl phenylhydrazine, respectively. Cyclization of pyrazole to Pyrazolo[3,4-*d*]pyrimidine occurred through different pathways. The first, fusion of **IIa&b** with formic acid yielded Pyrazolo[3,4-*d*]pyrimidin-4-one **IIIa&b**. the second, 4-amino Pyrazolo[3,4-*d*]pyrimidine **IVa&b** was obtained by reaction of **IIa&b** with excess formamide. Chlorination of **IIIa&b** with phosphorus oxychloride yielded the chloro derivative **Va&b**. The ester derivatives **VIa&b** were accomplished either from chloro compound**s Va&b** and glycine ethyl ester hydrochloride or from amino compounds **IVa&b** and ethylchloroacetate. Hydrazinolysis of the ester moiety in compounds **VIa&b** using hydrazine hydrate yielded the acetohydrazide **VIIa&b**. (**Scheme1**).

Four pyrazolopyrimidine series were prepared with a substitution at position 4 from reaction of the acetohydrazide intermediates **VIIa&b** with a series of various aldehydes to yield the hydrazones **VIIIa-f**. Condensation of **VIIa&b** with ethyl isothiocyanate or 4-substituted phenyl isothiocyanate derivatives furnished triazole-3-thiol derivatives **IXa&b** and **Xa-f**, respectively. Cyclization of the acid hydrazide **VIIa&b** with ethylacetoacetate afforded the ethoxy pyrazole derivatives **XIa&b**. Heating of the acid hydrazide **VIIa&b** with equivalent amount of CS_2 and KOH gave **XIIa&b** bearing oxadiazole scaffold. (**Scheme 2**)

Another new pyrazolopyrimidine series with a substitution at position 5 were prepared from the precursor **IIb** through direct cyclization with ethyl isothiocyanate or 4-substituted phenyl isothiocyanate derivatives gave **XIIIa-d** derivatives. Condensation of compound **IIb** with triethlorthoformate or triethylorthoacetate furnished **XVa&b** that further cyclized with hydroxyl

amine hydrochloride, hydrazine hydrate or 4-substituted phenyl hydrazine hydrochloride derivatives to obtain **XVIa&b**, **XVIIa&b**, **XVIIIa&b** and **XIX**, sequentially. (**Scheme 3**)

New tricyclic pyrazolopyrimidine derivatives were prepared starting by 4-imino-5-aminopyrazolopyrimidine derivative **XVIIa**. Triazepine derivatives **XXa-d** were obtained from reaction of **XVIIa** with ethoxyethylene derivatives. Reaction of **XVIIa** with various aldehydes yielded Schiff base compounds **XXIa-c**. Thiourea derivative **XXII** was prepared from reaction of **XVIIa** with ethylisothiocyanate. Triazolo pyrazolopyrimidine derivative **XXIII** was obtained either from reaction of **XVIIa** with CS_2 or 4-substituted phenylisothiocyanate derivatives.

The structure elucidation of the new compounds was supported by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, [NOESY] NMR in addition to mass spectral data.

Also, a brief account on the docking study was explained through the binding conformations. Additionally, a theoretical discussion of biological anti-inflammatory activity *in vitro* and *in vivo* beside histopathological study for ulcerogenic liability and determination margin of safety of the most active compounds was given.

The fourth chapter consists of the experimental part of this work which contains the detailed procedures used for the synthesis of the new stating materials **IIb**, **IIIb**, **IVb**, **Vb**, **VIa&b**, **VIIa&b** and **XVa&b** and the target pyrazolopyrimidine compounds **VIIIa-f**, **IXa&b**, **Xa-f**, **XIa&b**, **XIIa&b**, **XIIIa-d**, **XIV**, **XVIa&b**, **XVIIa&b**, **XVIIIa&b**, **XIX**, **XXa-d**, **XXIa-c**, **XXII** and **XXIII**. In addition to the data obtained from the elemental and spectral analyses as well as their physical properties are given in this chapter. It also compromise docking procedure followed to know the proposed binding mode inside COX-2 active site, results obtained from carrageenan induced rat paw edema method and enzyme immunoassay (EIA) kit that utilized for evaluation of anti-inflammatory activity for the tested compounds compared with celecoxib, indomethacin and diclofenac sodium as standard drugs. Histopathological results, scoring of different pathological lesions caused by the tested compounds and compared with standard drugs was given in this chapter. Compound **VIIIc** showed the highest anti-inflammatory activity 96% compared to celecoxib 89% and (S.I. = 94.45) with similar gastro protective profile of celecoxib.