ABSTRACT

The work carried out during my research tenure has been compiled in the form of a thesis entitled ‘synthesis of novel heterocyclic compounds and evaluation of their activity for different biological profiles.’ The present investigation aimed to synthesize novel Nitrogen containing biologically active compounds of following heterocyclic moieties has been synthesized.

1) Pyrimidine analogues
2) Triazino benzimidazole
3) Benzopyrans

The whole thesis is divided into six chapters. The chapter 1 deals with general introduction of anticancer agents, antimicrobial agents and antiinflammatory agents. This chapter also contains some general considerations of statins for their biological activity.

The chapter 2 consists of general aim and objectives of present work of this thesis.

The chapter 3 deals with design, synthesis and biological evaluation of pyrimidine analogues. The chapter 3 further consists of three sub chapters, which are as follows


b) Design, synthesis and evaluation of antimicrobial and antiinflammatory activity of some new 5-substituted isoxazolyl and pyrazolyl pyrimidines.

c) Design, synthesis and evaluation of antimicrobial and antiinflammatory activity of some new substituted 1,3,4-oxadiazolyl pyrimidines.
The chapter 4 deals with synthesis, characterisation and evaluation of anticancer activity of some pyrimidinyl-3,4-dihydro [1,3,5] triazino benzimidazole analogues.

The chapter 5 comprise of synthesis of some novel substituted isoxazolyl benzopyran derivatives and evaluation of their antimicrobial activity.


The Scheme-1 is the synthesis of substituted pyrimidinyl benzothiazoles and phenoxy compounds. The targeted compounds were synthesized as per the scheme-1. The required intermediate (S-3) was synthesized starting from p-fluorobenzaldehyde which was converted in to methyl 2-(4-fluoro benzylidene)-4-methyl-3-oxopentanoate (S-1) by treating with methyl-4-methyl-3-oxo pentanoate in the presence of piperidine as catalyst. The methyl 2-(4-fluoro benzylidene)- 4-methyl-3-oxopentanoate (S-1) was further converted into methyl 4-(4-fluoro phenyl)-6-isopropyl-2-(methyl thio) pyrimidine-5-carboxylate (S-2) upon treatment with S-methyl thiourea hydrogen sulphate and Hexa methyl phosphoramide (HMPA) followed by aromatization with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone(DDQ). The compound (S-2) was further oxidized by using m-chloro perbenzoic acid to furnish the required intermediate (S-3). The substituted pyrimidine compounds (S 4a-o) and (S 5a-j) were prepared from the compound (S-3) by treating with different or appropriate substituted phenols and 2-amino benzothiazoles respectively.

The anticancer activity of the synthesized substituted pyrimidine phenoxy and 2-amino benzothiazole compounds was carried out against different human cell lines namely HT-29 (Colon cancer) HEK-293 (Kidney cancer) and MDA-231 (Breast cancer)
The overall observation on the anticancer activity of these series of compounds revealed that they are active compounds against different cell lines used for the study and hence further detailed study of these compounds is quite essential and may be quite rewarding.

Chapter 3 Part-B: Design, synthesis and evaluation of antimicrobial and antiinflammatory activity of some new substituted isoxazolyl and pyrazolyl pyrimidines.

The Scheme-2 is the synthesis of Isoxazolidinyl and pyrazolidinyl substituted pyrimidines. The targeted compounds were synthesized as per the scheme-2. The required intermediate (S-3) was synthesized starting from P-fluorobenzaldehyde which converted in to methyl 2-(4-fluoro benzylidene)- 4-methyl-3-oxopentanoate (S-1) by treating with Methyl-4-methyl-3-oxo pentanoate in the presence of piperidine as catalyst. The methyl 2-(4-fluoro benzylidene)- 4-methyl-3-oxopentanoate (S-1) was further converted into methyl 4-(4-fluoro phenyl)-6-isopropyl-2-(methyl thio) pyrimidine-5-carboxylate (S-2) upon treatment with S-methyl thiourea hydrogen sulphate and Hexa methyl phosphoramide (HMPA) followed by aromatization with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone(DDQ). The compound (S-2) was further oxidized by using m-chloro perbenzoic acid to furnish the required intermediate (S-3). Whereas the compound (S-6) was synthesized by treating the compound (S-3) with 25% methylamine in methanolic medium upon stirring at 0-5 ºC for 1h and refluxing for 2h. The compound (S-6) was converted in to the compound (S-7) by treating with CH$_3$SO$_2$Cl by using sodium hydride (NaH) in DMF medium. The compound (S-7) was reduced to a compound containing primary alcohol group(S-8) by using DIBAL-H in toluene medium. The key intermediate aldehyde compound (S-9) was synthesized from compound (S-8) by oxidation with active MnO$_2$. The required titled
compounds isoxazolyl and pyrazolyl pyrimidines were prepared via formation of respective oxime (S-10) or hydrazones (S-12) upon treatment of compound (S-9) with hydroxylamine hydrochloride or hydrazine hydrate. The oxime (S-10) was cyclized in to respective Isoxazoles (S-11a-j) and hydrazones are converted corresponding pyrazoles (S-12a-j).

Both pyrimidines isoxazole and pyrazoles were synthesized as per the scheme 2 evaluated for their antibacterial and antifungal activity following the literature method. The compounds were also screened for their antiinflammatory activity using carrageenan induced paw oedema model in albino rats of either sex.

Chapter-3 Part-C: Design, synthesis and evaluation of anti-microbial and anti-inflammatotory activity of some new substituted 1,3,4-oxadiazolyl pyrimidines.

The Scheme-3 is the synthesis of oxadiazolyl substituted pyrimidines. The targeted compounds were synthesized as per the scheme-3. The required intermediate (S-3) was synthesized starting from p-fluorobenzaldehyde which converted in to methyl 2-(4-fluoro benzyldene)-4-methyl-3-oxopentanoate (S-1) by treating with methyl-4-methyl-3-oxo pentanoate in the presence of piperidine as catalyst. The methyl 2-(4-fluoro benzyldene)- 4-methyl-3-oxopentanoate (S-1) was further converted into methyl 4-(4-fluoro phenyl)-6-isopropyl-2-(methyl thio) pyrimidine-5-carboxylate (S-2) upon treatment with S-methyl thiourea hydrogen sulphate and Hexa methyl phosphoramide (HMPA) followed by aromatization with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone(DDQ). The compound (S-2) was further oxidized by using m-chloro perbenzoic acid to furnish the required intermediate (S-3). Whereas the compound (S-6) was synthesized by treating the compound (S-3) with 25% methylamine in methanolic medium upon stirring at 0-5 °C for 1h and refluxing for
2h. The compound (S-6) was converted into the compound (S-7) by treating with CH$_3$SO$_2$Cl by using sodium hydride (NaH) in DMF medium. The key intermediate carboxyl hydrazide compound (S-13) was synthesized from compound (S-8) by reacting with hydrazine hydrate solution. The required titled compounds oxadiazolyl pyrimidines were prepared from hydrazide (S-13) by reacting with appropriate substituted carboxylic acids in the presence of POCl$_3$ cyclized in to respective oxadiazoles (S-14a-k).

The pyrimidine oxadiazole derivatives were evaluated for their antibacterial, antifungal and antiinflammatory properties.

Some of the compounds screened for these activities appear to be potent against each type of the activity screened. However the antiinflammatory screening results indicate that the compounds may serve better antiinflammatory agents as almost all compounds of this group exhibited activity in varied ranges.

The 4$^{th}$ Chapter deals with synthesis and evaluation of anti-cancer activity of some pyrimidinyl-3,4-dihydro [1,3,5] triazino benzimidazole analogues. The compounds were synthesized as per the scheme-4. The targeted compounds were synthesised starting from o-phenylene diamine, which could be converted into 2-benzimidazolyl guanidine (BG) by treating with cyanoguanidine in the presence of acidic catalyst. The 2-benzimidazolyl guanidine (BG) was further converted into 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-a] benzimidazoles (SNG 1-16) and spiro [cyclopentyl\ cyclohexyl\ piperidyl -1,4' (1'H)-[1,3,5] triazino[1,2-a]-benzimidazol-2-amine (SNG 17-24) by reacting the 2-benzimidazolyl guanidine (BG) with different aldehydes and ketones. Whereas the 4,4-disubstituted-3-(2-substituted pyrimidino)-3,4-dihydro benzo [4,5] imidazo[1,2-a] [1,3,5] triazin-2-amines (SNGP 1-24) were prepared from the respective triazino compounds (SNG 1-
by treating with 2-(methyl sulfonyl) 4,6-dimethoxy pyrimidine expecting the reaction between the primary amino group of triazine system and –SO₂CH₃ group of 2-(methyl sulfonyl) 4,6-dimethoxy pyrimidine and structures of the compounds were characterized by using IR, ¹H NMR, ¹³C NMR and Mass spectra techniques.

All the synthesized compounds evaluated for their in vitro anticancer activity against the cell lines HT-29 (Colon cancer), HEK-293 (Kidney cancer) and MDA-231 (Breast cancer) and their IC₅₀ values were determined. Among the tested 24 compounds, some of them showed good activity.

The 5th chapter presents synthesis, characterization of 20 isoxazolyl benzopyrans and in vitro evaluation of their antimicrobial activity.

The design and synthetic scheme for the preparation of this class of compounds is as per the description given in the scheme-5. The intermediates benzimidazolyl-2-acetonitrile (1a) and benzoxazolyl-2-acetonitrile (1b) required for the synthesis of isoxazolyl benzopyrans were synthesized by reacting O-phenyl diamine or 2-amino-5-methyl phenol with ethyl cyano acetate under reflux. The required nitrile compounds (SBP 1-20) were synthesized by Knoevenagel reaction conditions by treating the compound 1a or 1b or malononitrile (1c) with different substituted aromatic aldehydes. The compounds SBP 1-20 were further cyclized to the benzopyran derivatives (SBP 21-40) by reacting with resorcinol in the presence of Aliquate-336. The titled compounds isoxazolyl benzopyrans were synthesized by treating the compounds SBP 21-40 with 3-(2,6-dichlorophenyl)-5-methyl isoxazole carboxylic acid chloride in the presence of triethyl amine in MDC medium. The characterization of the synthesized compounds is carried out with the help of IR, ¹H NMR, ¹³C NMR and Mass spectral studies. These data of compounds are in full agreement with assigned structures for the synthesized compounds.
The screening of antibacterial and antifungal activity revealed that the compounds possess moderate to good activity.

The 6th chapter consists of overall summary and conclusions of the thesis. In conclusion the biological activity of the present study revealed that in each type of compounds containing different series, majority of the compounds possess the particular activity in varied ranges. However the potent in vitro anticancer activity of the compounds is worth mentioning and needs special attention. The results encourage that it is better if the compounds are screened for their in vivo studies to establish high potency of the compounds synthesized in the current study.