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A short commentary on substituted Indoles, pyrazolones and imidazolinones

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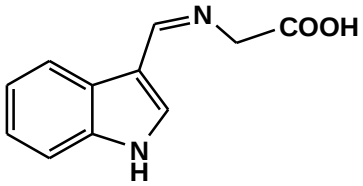
Introduction

German scientist Hugo Schiff discovered compounds which have azomethine group. Various azomethines were prepared for different of amines and aldehydes and used for diverse industrial applications.[1-3] Schif's bases were also used for their industrial applications such as metal chelating ability and analytical purpose for various metal ions testing.[4] They were used as intermediates for the synthesis of various biological active heterocycles compounds like β-lactums and thiazolidinones. The mechanism of action of some antibiotics such as streptomycin, tetracycline, aspergillic acid and usinic acid were exhibited antibacterial effect due to their metal chelating activities.[5,6] Metal chelating abilities of Schif's bases, inspired several chemist to test the antibacterial and other biological activities of Schif's bases. This was a distraction from research on diazo compounds, as diazo compounds were proved to be toxic and azomethines were believed as substitute to diazo compounds in search for novel molecules and resulted in synthesis of various Schif's bases for testing their biological activities. Some amino acid-schiff bases 1, 2 were tested for their antibacterial activity against various gram positive and gram negative bacterial strains and some of the tested Schiff's bases exhibited promising activity.[7] A series of Schif's bases 3 which have isatin nucleus and exhibited moderate pharmacological activities such as analgesic, anti-inflammatory, and anti-pyretic activities. All the tested compounds.[8]



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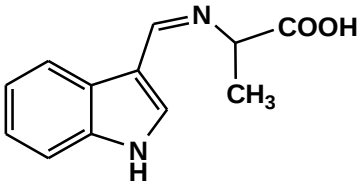

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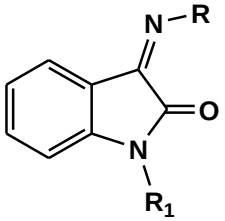
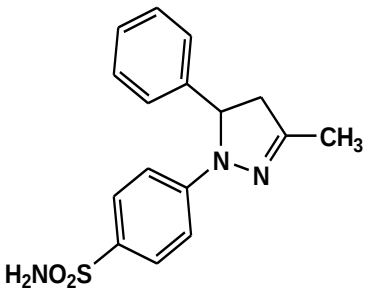
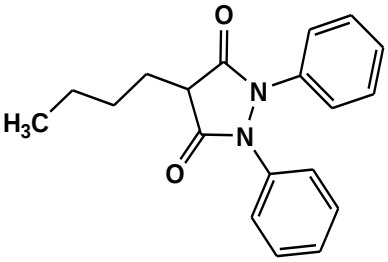


3 R= substituted phenyl R'=alkyl, substituted alkyl

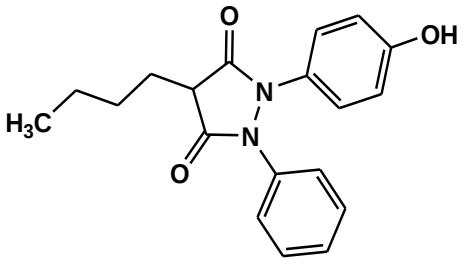
Substituted Pyrazolinones: Some Schiff bases of macrocyclic-2,6-bis (2- and 4-formylaryloxy-methyl) pyridines were exhibited anti-cancer activity against cancer cells of breast, colon, non-small cell lung, ovarian and renal cancers.[9] A number of azomethines were possess significant antibacterial, anti-mycobacterial, antiviral, antifungal, anticancer, analgesic, anti-inflammatory, antioxidant, anthelmintic, and diuretic activities.[10-12] Pyrazole and its derivatives are important nitrogen containing heterocyclic compounds having extensive spectrum of biological activities. Some of the useful drugs like Celecoxib (COX-2 inhibitor), Oxypheynylbutazone, Phenylbutylzone, Phenazone (NSAID) and Sulphinpyrazone (uricosuric agent) contain pyrazole as basic skeleton.



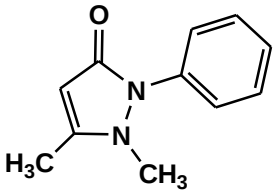
Celecoxib (COX-2 Inhibitor)



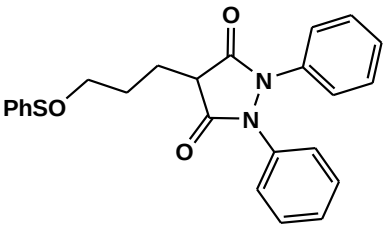
Phenylbutazone (NSAID)



Oxyphenylbutazone (NSAID)

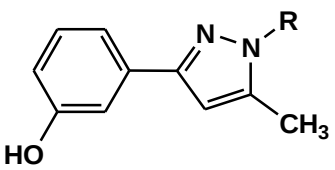


Phenazone (NSAID)

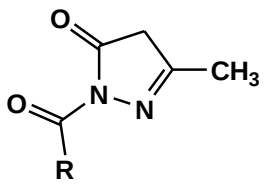


Sulphinpyrazone (Uricosuric agent)

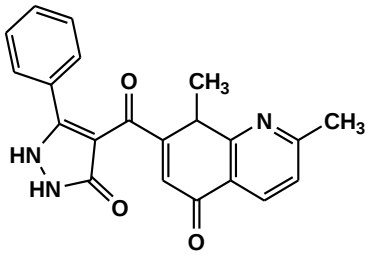
Various substituted pyrazoline 4 were exhibited analgesic activity[13] and pyrazolone 5 were exhibited analgesic, ulcerogenic and antioxidant activities. Few compounds were exhibited analgesic activity equal to Diclofenac sodium.[14] Some pyrazolone derivatives were exhibited the antifungal activity 6.[15]



4 R=phenyl, substituted phenyl



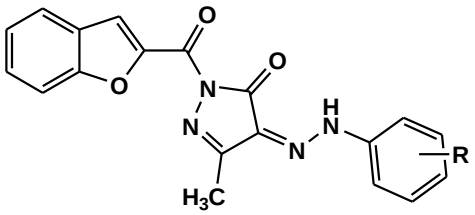
5 R=pyridy [phenyl, substituted phenyl



6

Pyrazolone derivatives are also possess antitubercular, anti-cancer, anti-HIV, anthelmintic and CNS activities.[16-19] The azo functionality, pyrazolone derivatives are important pharmacophoric functionalities which are present in various compounds which possess wide range of biological activities. Significance of benzofuran as a biopotent moiety, hence, an attempt to synthesize compounds which contain benzofuran moiety, azo functionality and pyrazolone ring system.

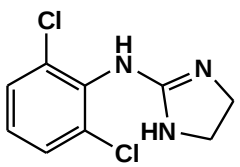
Compounds which contain all the three pharmacophoric groups, i.e. azo functionality, pyrazolone moiety and benzofuran nucleus.[20] Aromatic primary amine group having compounds like various anilines were first diazotized, and then treated with compounds which contain active methylene group like ethyl acetoacetate, which form the hydrazono compounds. The hydrazono compounds were refluxed with $NH\text{-}NH_2$ group containing compounds resulting in formation of compounds which contain azo group, pyrazolone moiety and the substituent which is attached to $NH\text{-}NH_2$ group. Some of the (4)-1-(1-benzofuran-2-ylcarbonyl)-3-methyl-1-N-pyrazole-4,5-dione-4-[(aryl) hydrazones 7a-g exhibited antibacterial and antifungal activities.



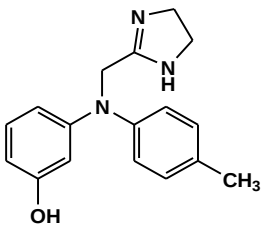
7a-g

7a R = H
7b R = 2-C1
7c R = 4-C1
7d R = 4-CH_3
7e R = 3-C1-4-F
7f R = 4-NO_2
7g R = 4-OCH_3

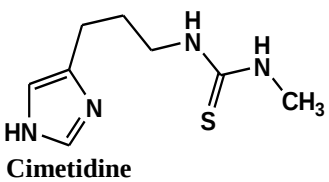
Substituted Imidazolinones: Various compounds containing imidazole ring were used for various disorders such as hypertension, hypersecrtion of gastric acid (anti-ulcer agents), fungal infections and cancer.



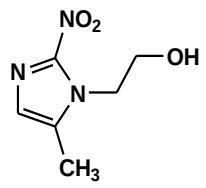
Clonidine
(anti-hypertensive)



Plientolamine
(anti-hypertensive)

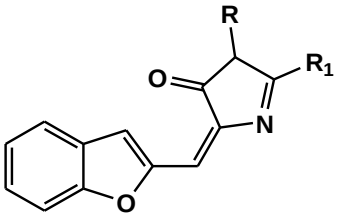


Cimetidine
(anti-hypersecretory)

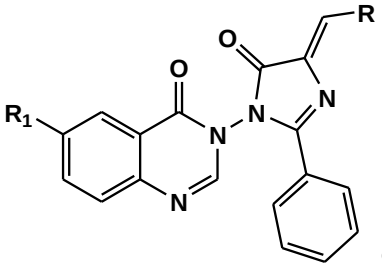


Metronidazole (anti-protozoal)

Imidazolones have also been found to be linked with various biological activities such as potassium channel opener, phosphodiesterase III/IV inhibition and crop protection[21-24] activities. Hence, this class of compounds has become a synthetic target for organic and medicinal chemists. Novel imidazolines 8 which are coupled with benzoxazole ring and tested them for anti-histaminic activity.[25] Compounds 9 which contain imidazolines ring coupled with quinazolone ring system and tested their antimicrobial activity. Some of the tested compounds exhibited activity comparable to that of standard drugs used, Ciproflaxacin.[26] Imidazolines moiety and compounds 10 was tested for their anti-tubercular and anticancer activities. Some of the tested compounds were found to active against lung, breast and brain cancer cell lines.[27]

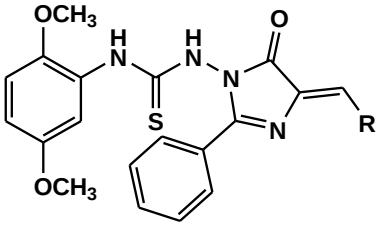


8 R=R =pyridyl, pheny, substituted phenyl



9

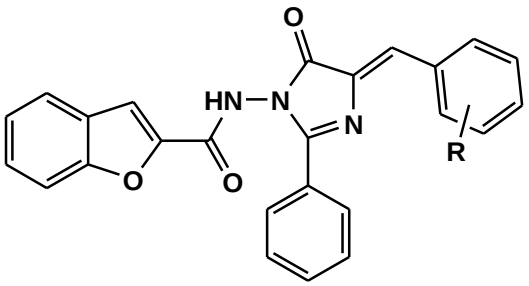
R= phenyl, substituted phenyl R_1= CI, NO_2



10 R=phenyl, substituted phenyl

Imidazolone ring system have wide range of therapeutic activities like anticonvulsant, sedative, hypnotic, fungicidal, anti-inflammatory, mono amino oxidase (MAO) inhibitory, anti-aarkinson's and antihypertensive[28] activities. Inspite of therapeutic impact of imidazolinone ring system, there are hardly only some reports on biological evaluation of compounds which contain both benzofuran and imidazolinone moiety. This inspired to take up the synthesis of novel compounds which contain both benzofuran and imidazolinone ring system and evaluate their biological profile.

Many synthetic strategies have used for synthesis of compounds in which imidazole ring is formed or imidazolinone ring is coupled with other heterocycles, like alteration of esters using aluminum reagents, the reaction between N-ethoxy carbonylthiamides with 1,2-diamines and the reaction of aldehydes with 1,2-diamines followed by N-halosuccinimides.[29-31] Numerous methods have developed where 2-aryl-l,1-dibromoethanes, azalactones, nitriles were used as initial materials. However, various synthetic methods reported so far suffer from difficulties like need anhydrous conditions, harsh reaction situation, prolonged reaction time etc. Hence, attempts are made to find a simple reaction process for forming imidazolinones. In this method amino acid is acetylated or benzoylated using suitable acetylating or benzoylating agent, followed by reaction with aldehydes in acetic anhydride which form 4-arylalkylidene-2-phenyl-5-oxazolinones.[32] These phenyl-5-oxazoIinones can be easily converted to imidazolinones by reaction with compounds which contain free NH_2 group like amines, hydrazines or carbohydrazides.[33] The method relating the use of amino acids for the preparation of imidazolinones is a simple and gives good yields. Hence, similar approach is used for synthesis of benzofuran substituted imidazolinones. Some of the N-[(4)-substituted benzylidene-5-oxo-2-phenyl-4,5-dihydrolN-imidazol-l-yl]-l-benzofuran-2-carboxamides 11a-g have antibacterial and antifungal activities.



11a-g

11a R = H
11b R = 2-Cl
11cR = 4-C1
11d R = 4-OCH_3
11e R = 2-OH
11f R = 4-CH_3
11g R = 4-$N(CH_3)_2$

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