Chapter 5

SUMMARY

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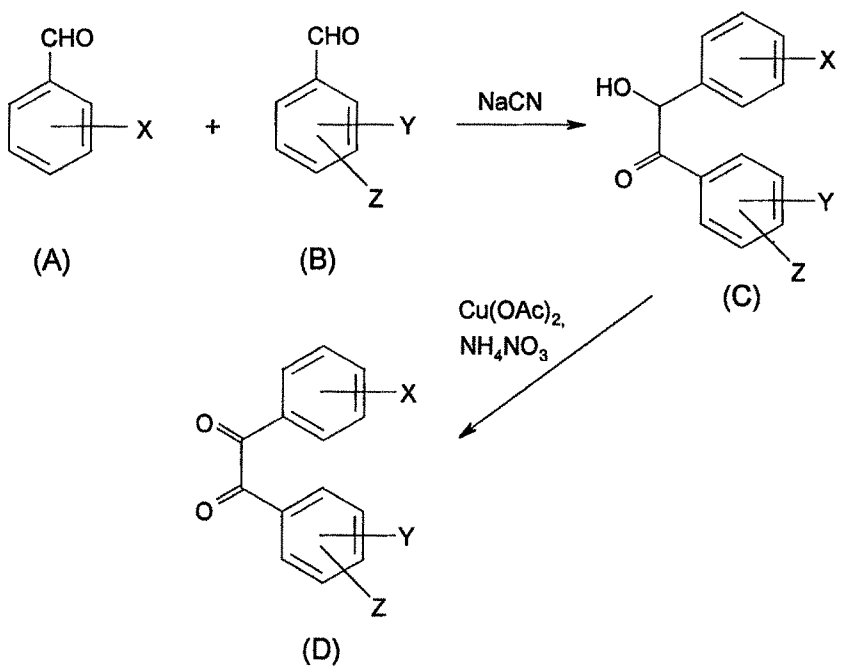
In the past hundred years aspirin has proven its value as an analgesic, anti-inflammatory and anti-thrombotic agent. Although the gastro-intestinal liabilities associated with regular aspirin usage were well documented by the late thirties, little could be done to remedy the situation. Most of the NSAIDs developed since the sixties failed to achieve the title of safer drugs due to their most common side effects of gastric or intestinal ulceration due to the presence of free acidic carboxyl group in their structures. Cyclooxygenase enzyme has now been proved to be not one enzyme but exists in two isoforms. i.e. COX-I and COX-II. COX-I was considered to be performing a house-keeping function in certain tissues while COX-II was expressed in response to external stimuli and produced inflammation in those tissues. Selectivity in binding to the COX-II isoenzyme could avoid certain undesirable side effects shown by majority of NSAIDs. COX-II, the true molecular target for the anti-inflammatory action of NSAIDs has provided the rationale behind development of selective COX-II inhibitors. Selective inhibition of COX-II promises to provide NSAIDs with increased safety profile.

Although selective COX-II inhibitors show structural diversity, there are certain common structural features present in them. All of them possess a central carbocyclic/heterocyclic ring to which two aryl rings are attached on vicinal positions. In a majority of them the carbocyclic/heterocyclic ring is a five-membered ring system like pyrazole, imidazole, oxazole, isoxazole, furanone, thiophene and pyrrole. Amongst hundreds of such compounds celecoxib, rofecoxib and valdecoxib are currently in clinical use.

The present study details the synthesis of 3,4-diaryl-1,2,5-oxadiazoles **(I)** and 3,4-diaryl-1,2,5-oxadiazole N-oxides **(J),** and biological evaluation of their COX-II inhibition potential.

For synthesizing of 3,4-diaryl-1,2,5-oxadiazole **(I)** and 3,4-diaryl-1,2,5-oxadiazole N-oxides **(J),** 1,2-diarylethane-1,2-dione system was prepared which was converted into 1,2-dioximino derivatives. The 1,2-dioximino derivatives were then cyclized to the desired 1,2,5-oxadiazole system. Some of the disubstituted 1,2-ethanedione derivatives were synthesized through the preparation of benzoins **(C)** followed by mild oxidation of benzoins **(C)** to benzils **(D)** as depicted in **Scheme-1.**

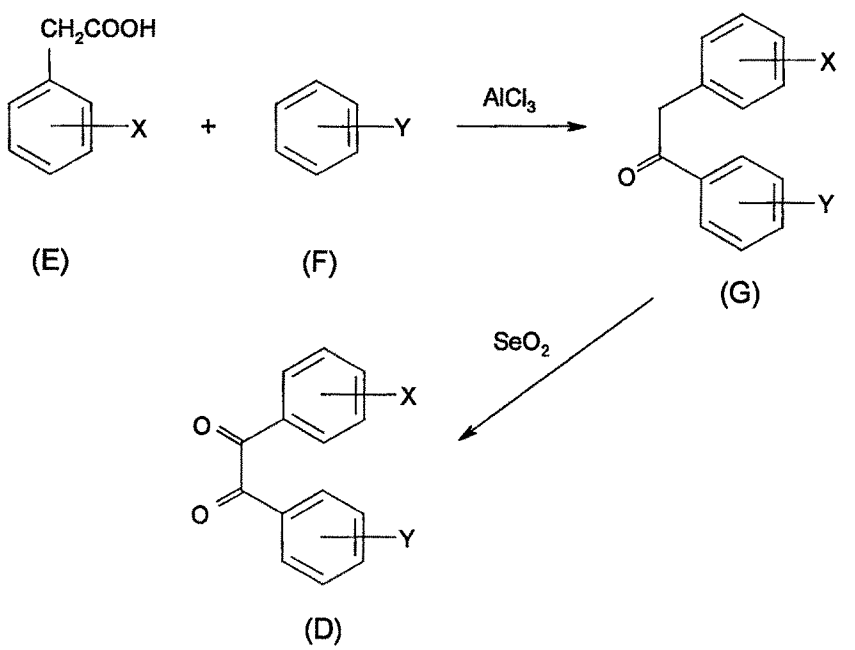


SCHEME-1

Condensation of substituted aromatic aldehydes **(A)** and **(B)** in aqueous ethanol using sodium cyanide as a catalyst was carried out to obtain substituted benzoins **(C).** Both symmetrical and mixed benzoins were synthesized by this well established route of benzoin condensation. The

substituted benzoins (**C**) were then oxidized using a mild oxidizing system like copper acetate/ammonium nitrate to get the desired substituted benzils (**D**).

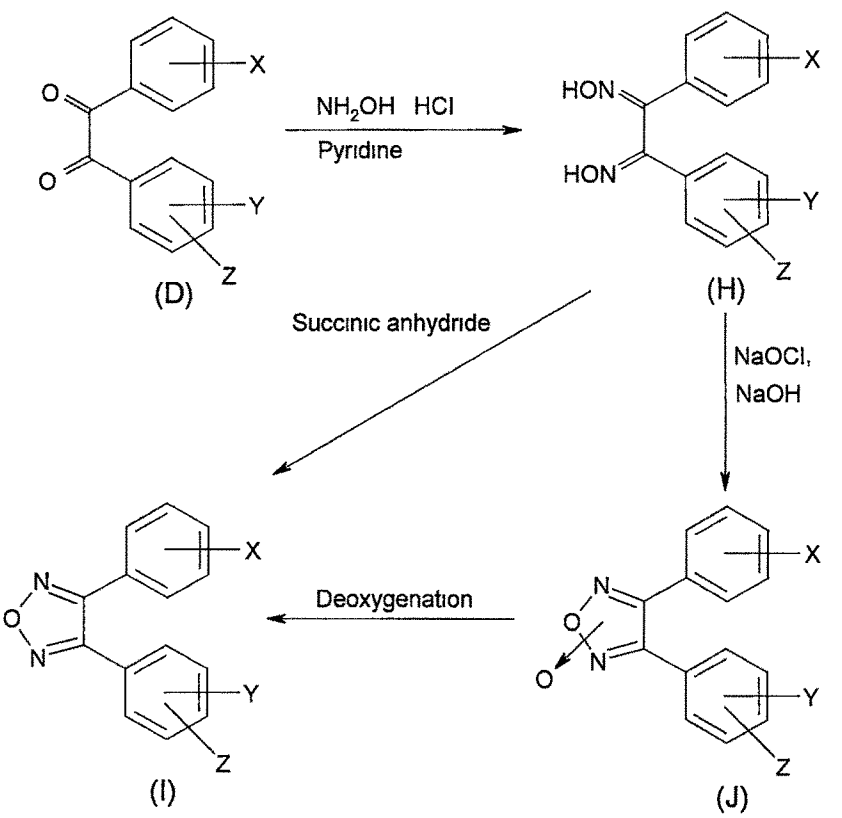
The diaryl substituted 1,2-ethanedione derivatives (**D**) were also prepared as shown in **Scheme-2**. Friedel–Crafts acylation reaction of substituted phenylacetic acids (**E**) with substituted benzenes (**F**) in presence of anhydrous aluminium chloride as a catalyst afforded the substituted desoxybenzoins (**G**), which were oxidized to the corresponding benzils (**D**) using selenium dioxide as an oxidizing agent.



SCHEME-2

Synthesis of the desired 1,2,5-oxadiazole systems (**I**) involved oximation of the suitably substituted benzils (**D**) using different reagents like hydroxylamine hydrochloride/pyridine or hydroxylamine hydrochloride/sodium acetate to afford the substituted benzil dioximes (**H**) (**Scheme-3**). The dioximes (**H**) were cyclized to the 1,2,5-oxadiazole derivatives (**I**) using succinic anhydride as a dehydrating agent. The 1,2,5-

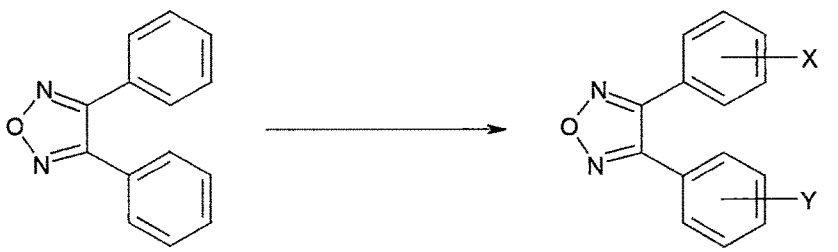
oxadiazole N-oxides **(J)** were obtained by oxidizing the dioxime **(H)** using freshly prepared sodium hypochlorite in alkaline medium **(Scheme-3).**



SCHEME-3

Since cyclization of the dioximes **(H)** to 1,2,5-oxadiazoles **(I)** using succinic anhydride as dehydrating agent, has not provided very good yields, it was tried to deoxygenate the N-oxides **(J)** to respective oxadiazoles **(I)** using different reagents like phosphorus trichloride and triphenyl phosphite **(Scheme-3).** However, all these experiments failed to yield the desired products **(I)** and resulted in isolation of the started material **(J)** only. This route was abandoned after successive failures in isolating the desired products **(I).**

Some of the 1,2,5-oxadiazole derivatives **(K)** were also synthesized by performing electrophilic aromatic substitution reactions on benzene rings of the 3,4-diphenyl-1,2,5-oxadiazole **(I) (Scheme-4).**



(I) (K)

SCHEME-4

All the synthesized compounds were characterized by their spectral and elemental analysis. The data are presented under the respective compounds and are in accordance with the assigned structures.

Since the aim of the current study was to prepare selective COX-II inhibitors, all synthesized compounds were evaluated for their potential to act as selective COX-II inhibitors by performing the *in vitro* receptor binding studies on COX-II enzymes using the Cayman COX-I and COX-II colorimetric screening kit (Cayman chemical company, MI, USA).

The results of *in vitro* study indicated that 3-(2-chlorophenyl)-4-(4-dimethylaminophenyl)-1,2,5-oxadiazole **(152)** was as equipotent as valdecoxib (control) in enzyme inhibition in similar dose. It showed significant COX-II inhibition even at low concentration. 3,4-Di(4-methoxyphenyl)-1,2,5-oxadiazole N-oxide **(181)** also showed significant COX-II inhibition while 3,4-di(4-methoxyphenyl)-1,2,5-oxadiazole **(149),** 3-(4-methoxyphenyl)-4-phenyl-1,2,5-oxadiazole **(154),** 3-(4-methoxyphenyl)-4-phenyl-1,2,5-oxadiazole N-oxide **(185)** and 3-(4-chlorophenyl)-4-(4-methoxyphenyl)-1,2,5-oxadiazole N-oxide **(189)** exhibited reasonable COX-II inhibition suggesting that *para* substitution

of one or both phenyl rings with methoxy group increases the COX-II selectivity.

It was reported that a $-SO_2Me$ or $-SO_2NH_2$ substituent substituted at the *para* position of one of the phenyl rings is essential for COX-II inhibition. Keeping in view the importance of these groups, 3-(4-methanesulphonylphenyl)-4-phenyl-1,2,5-oxadiazole **(168),** 3-(4-methanesulphonylphenyl)-4-(4-tolyl)-1,2,5-oxadiazole **(169),** 3-(4-methanesulphonylphenyl)-4-(4-fluorophenyl)-1,2,5-oxadiazole **(170),** 3-(4-methanesulphonylphenyl)-4-phenyl-1,2,5-oxadiazole N-oxide **(192),** and 3-phenyl-4-(4-sulphamoylphenyl)-1,2,5-oxadiazole **(178)** were synthesized. None of these derivatives however, showed significant activity against COX-II.

4-Biphenylacetic acid **(76)** is an active metabolite of fenbufen **(165)** and showed three times more activity than the parent drug. Taking the structure of 4-biphenylacetic acid **(76)** into consideration, 3-(1-biphenyl)-4-phenyl-1,2,5-oxadiazole **(166)** and 3-(1-biphenyl)-4-(4-tolyl)-1,2,5-oxadiazole **(167)** were synthesized, but these compounds failed to show significant COX-II selectivity.

During the past few years, selective COX-II inhibitors have emerged as important pharmacological tools for the treatment of pain and inflammation. But recent findings of the involvement of COX-II enzyme in some key physiological functions have complicated the scene regarding the use of selective COX-II inhibitors as anti-inflammatory agents. The major side effects observed due to COX-II inhibition are blood clots, myocardial infarction, heart attack, strokes and congestive cardiac failure. It was observed that these side effects differ among structurally distinct COX-II inhibitors with different levels of COX-I and COX-II selectivity. As an example, different studies revealed that rofecoxib and not celecoxib showed cardiovascular toxicities. Keeping this in mind, in the present

study, the N-oxides were prepared with a view to act as precursors of nitric oxide (vasodilatory effect), which would have a favorable cardiovascular profile.

The finding that COX-II enzyme is constitutively expressed in certain tissues has opened new doors for the treatment of certain other ailments as well. Involvement of COX-II expression in various forms of cancer and Alzheimer's disease suggests the role of COX-II inhibitors in these disease states.

A detailed study in this direction for expanding the scope or application of the present work may be planned in future.