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INVITED ARTICLE

A REVIEW ON SYNTHESIS AND PHARMACOLOGICAL DIVERSITY OF ISOXAZOLES & PYRAZOLINES

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Abstract

Isoxazole is an azole with an oxygen atom next to the nitrogen. It is also the class of compounds containing this ring. Isoxazole rings are found in some natural products, such as ibotenic acid and also found in a number of drugs, including COX-2 inhibitor valdecoxib. Furoxan, a nitric oxide donor is containing isoxazolyl group & found in many beta-lactamase-resistant antibiotics, such as cloxacillin, dicloxacillin and flucloxacillin. The synthetic androgenic steroid danazol also has an isoxazole ring. Pyrazoline is a five-membered heterocyclic having two adjacent nitrogen atoms within the ring. It has only one endocyclic double bond and is basic in nature. Among its various derivatives, 2-pyrazolines seem to be the most frequently studied pyrazoline type compounds. 2-Pyrazolines can be considered as a cyclic hydrazine moiety display a broad spectrum of potential pharmacological activities.

Keywords: *Isoxazole, pyrazoline, synthesis, pharmacological diversity*

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Introduction

Heterocyclic compounds forms a major class of compounds in chemistry. These are cyclic compounds having at-least two different elements as a part of the ring system. On the other hand, a ring system made up of same elements is considered as homocyclic compounds.

Fused saturated 5-membered rings naturally occurring in both carboxylic (Eg. Triquinane) and heterocyclic (Eg. Pyrrolizidin alkaloids) systems have interesting pharmacological importance [1].

Usually 6-membered rings have well defined and readily determined conformations like chair and boat, but 5-membered rings are much flexible and their conformations are difficult to ascertain (Figure 1) [2].

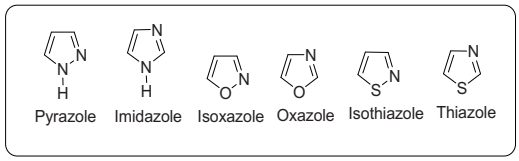

Figure 1: Structures of Various 5-membered Heterocycles

Pyrazolines are well known and important nitrogen containing 5-membered heterocyclic compounds. 2-Pyrazolines show a broad spectrum of pharmacological activities and are present in a number of pharmacologically active molecules such as phenazone, amidopyrine, methampyrone (analgesic and antipyretic), azolid, tandearil (anti-inflammatory), indoxacarb (insecticide) and anturane (uricosuric) [3]. Numerous pyrazoline derivatives have been found to possess considerable biological activities, which stimulated the research activity in this field. They have several prominent effects, such as antimicrobial, antimycobacterial, antifungal, anti-amoebic, antiinflammatory, analgesic, antidepressant and anticancer activities. They also possess some potent, receptor selective biological activity like nitric oxide synthase (NOS) inhibitor and cannabinoid CB1 receptor antagonist activity [4]. The work provides an insight view to pyrazolines synthesis and its biological activities. Isoxazole (C_3H_3NO) is an azole with an oxygen atom next to the nitrogen. Isoxazolyl is the univalent radical derived from isoxazole. Isoxazole ring is found in some natural products, such as ibotenic acid. Isoxazoles also form the basis for a number of drugs, including the COX-2 inhibitor valdecoxib (Bextra) (Figure 2). A derivative, furoxan, is a nitric oxide donor. An isoxazolyl group is found in many beta-lactamase-resistant antibiotics such as cloxacillin, dicloxacillin and flucloxacillin. The synthetic androgenic steroid danazol also has an isoxazole ring [5].

Isoxazoles are unsaturated aromatic heterocyclic compounds containing a ring with three carbon atoms, one oxygen atom and one nitrogen atom. The trivial name for the title five-membered fully unsaturated heterocycles as “isoxazole” was originally proposed by Hantszch as it was the isomer “oxazole” discovered first. The trivial name follows the Hantszch-Widman system of nomenclature: the prefix “iso” represents isomer, “oxa”

represents the oxygen atom "aza" represents the nitrogen atom. The suffix "ole" denotes the ring size as five-membered; altogether the derived name is "isoxazole" [6]. This name has been accepted in IUPAC and has been used in Chemical abstracts. In Chemical Abstracts, the other systematic name 1,2-azole, is also used. Isoxazole being an azole with an oxygen atom next to the nitrogen, exhibits broad spectrum of biological activity and also forms a part of various biodynamic agents [7].

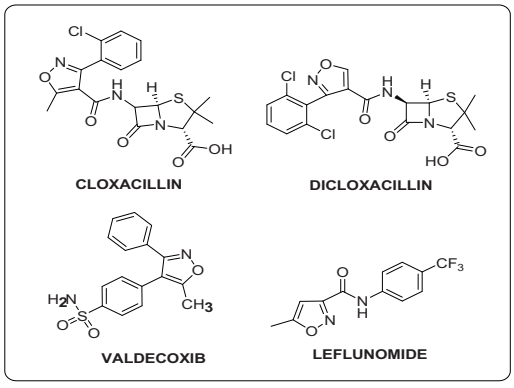

Figure 2: Isoxazole derivative having established pharmacological activity

The substituted isoxazoles are also considered to be important synthons due to their versatility towards chemical transformations to useful synthetic intermediates. Isoxazole derivatives show hypoglycemic, analgesic, antiinflammatory, antifungal, anti-bacterial and HIV-inhibitory activities [8]. Synthesis of hybrid natural products has gained momentum in recent years. It is expected that combining features of more than one biologically active natural segment in a single molecule may result in pronounced pharmacological activity while retaining high diversity and biological relevance [9-11]. The nitrogen hetero atom is more pronounced for electron withdrawing effect, while the oxygen atom is more pronounced for electron donating effect. As neutral molecules, isoxazoles undergo electrophilic substitution rather more readily at the position-4 than benzene. Effects of substituents can modify their behavior.

Substituents at the position-5 apparently have more activating and deactivating effect than substituents at the position-3. In natural product synthesis, isoxazoles are used as latent synthons, such as masked new heterocyclic rings, masked fused rings, masked aromatic rings and masked aldol and related moieties. The capability of isoxazole undergoing reaction is diverse: protonation, quaternization, complexation, oxidation, reduction, carbanionic condensations, thermolysis, photolysis, transformations into other heterocyclic ring systems and reaction with electrophiles, nucleophiles and Grignard reagents [12].

The naturally occurring antibiotic cycloserine [13]; the monoamine oxidase inhibitor isocarboxazide; isoxazole steroids, ibotenic acid; muscimol isolated from *Amanita muscaria* [14] and isoxazoline-5-ones isolated from Legume seed [15] are potential isoxazole derivatives.

Methods of synthesis of isoxazoles

Figure 3 showed regioselective cyclo-condensation of acrylophenone dibromide derivatives with hydroxylamine

hydrochloride giving corresponding isoxazoles [16].

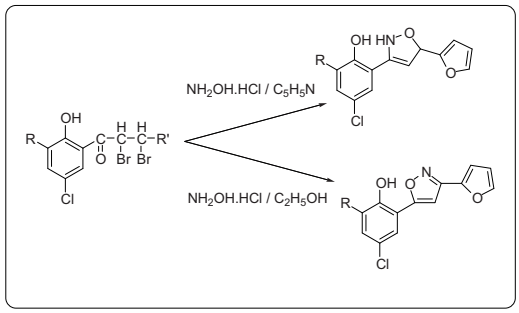

Figure 3: Synthesis of isoxazoles from acrylophenone dibromide

3-Alkyl, 5-aryl isoxazoles can be prepared from aryl cycolpropanes (Figure 4) with $NaNO_2$ in CF_3COOH [17].

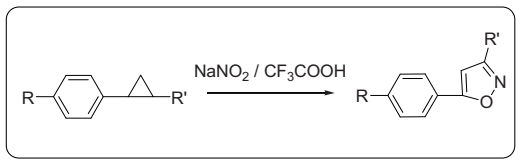

Figure 4: Synthesis of isoxazoles from aryl cyclopropanes

Solid phase synthesis of isoxazole derivative from diaryl 1,3-diketones (Figure 5) can be carried out in presence of hydroxylamine hydrochloride and silica gel [18].

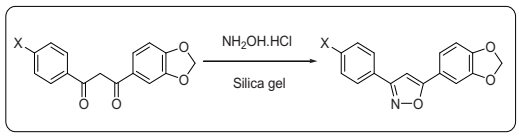

Figure 5: Solid phase synthesis of isoxazoles from diaryl 1,3-diketones

Reaction of various substituted acetophenones with diethyl oxalate in the presence of sodium ethoxide forms resulting 2,4-diketo esters which on treatment with hydroxylamine hydrochloride furnishes substituted 3-isoxazole esters (Figure 6) [19].

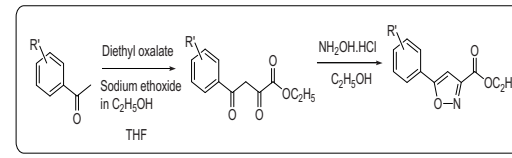

Figure 6: Synthesis of 3-isoxazoles from acetophenones

Pharmacological aspects of isoxazole

Anti-convulsant activity

The search for antiepileptic compounds with more selective activity and lower toxicity continues to be an area of investigation in medicinal chemistry [20]. Many patients with epilepsy fail to experience adequate control of their seizures, despite the optimal use of available antiepileptic drugs. Other patients do so only at the expense of significant toxic side effects. In recent years it has been established that inhibitors of GABA transport and in particular as troglial uptake can act as anticonvulsant agents and several isoxazole derivative (compound-A) (Figure 7) [21]. Compound-B is also a synthesized isoxazole derivative which affects the sodium channel to show its activity [22].

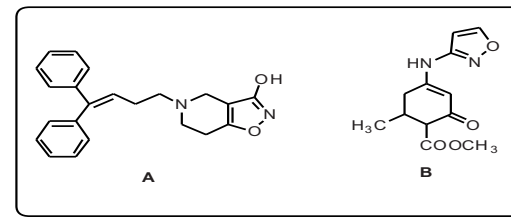

Figure 7: Isoxazoles having anti-convulsant activity

Anti-cancer activity

The effects of curcumin and of its isoxazole analogue in breast cancer cell line and in its multidrug-resistant (MDR) variant were examined. The isoxazole analogue Compound A has shown more potent antitumor and molecular activities both in parental and in MDR tumor cells. Isoxazole derivatives produces significantly higher direct inhibition of the COX-2 catalytic activity than curcumin. The isoxazole derivatives proved better because of minimum metal chelation when compared to curcumin [23]. The compound B has been found highly effective against human tumor cell lines especially on renal cancer, CNS cancer cell and ovarian cancer cell lines [24]. Recently NO-NSAID has been established as potent anti-cancer agents rather than their anti-inflammatory property [25]. Compound C is a NO donating compound used as anti-cancer agent.

Anti-microbial activity

Drazoxolon is a commonly used fungicidal agent. Acetyl Sulfisoxazole is another important anti-microbial agent from the isoxazole family which is widely used in pediatric suspensions (Figure 8). Cycloserine is a well-established molecule widely known for its potency against Mycobacterium tuberculosis [26-28].

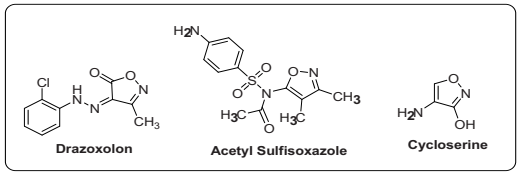

Figure 8: Isoxazoles having antimicrobial activity

Pyrazoline

Pyrazole is a π-excessive aromatic monocyclic heterocycle containing two nitrogen atoms in a five membered 1,2-diazole ring. Pyrazoles exhibit aromatic character with properties resembling those of both pyrrole and pyridine. 1-pyrazoline, 2-pyrazoline and 3-pyrazoline are the three partially reduced forms of the pyrazole structure with different positions of the double bonds and exists in equilibrium one with the other [29]. 2-pyrazoline exhibits the monoimino character and hence more stable than the rest. Pyrazole is freely basic and forms salts with inorganic acids. The imino hydrogen may be replaced by an acyl group. Pyrazole is very resistant to oxidation and reduction, but may be hydrogenated catalytically, first to pyrazoline and then to pyrazolidine [30].

Phenylbutazone is a pyrazoline derivative known for its analgesic and anti-inflammatory and anti-pyretic properties (Figure 9). Muzolimine is a pyrazoline derivative used as a diuretic which differs from the structures of other conventional diuretic compounds.

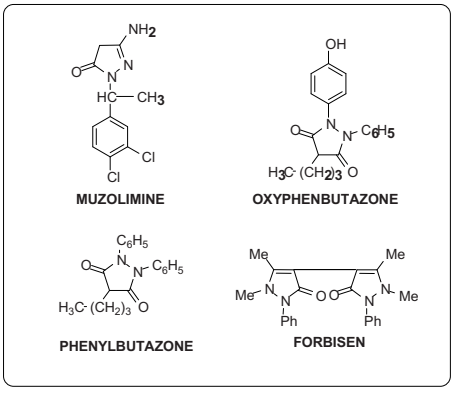

Figure 9: Pyrazoline derivative having established pharmacological activity

Forbisen is a byproduct separated during synthesis of antipyrine. This pyrazoline is used in bovine analplasomosis. Oxyphenbutazone is a pyrazoline derivative similar to phenylbutazone. It is an active metabolite of phenyl butazone. The difference with phenyl butazone is the presence of *p*-hydroxyphenyl group instead of phenyl at position 1 of phenylbutazone [31].

Methods of synthesis of pyrazolines

α, β-unsaturated carboxylic acid esters reacts with diazomethane to give 2-pyrazolines (Figure 10). The primary product of this reaction is a 1-pyrazoline, formed by 1, 3-dipolar cyclo addition, which spontaneously isomerizes into its thermodynamically more stable 2-pyrazoline isomer by a 1, 3-H shift [32].

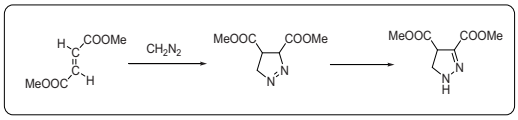

Figure 10: Synthesis of pyrazolines from α, β-unsaturated carboxylic acid esters

Figure 11 showed an example of synthesis of a pyrazoline from the reaction of an α,β-unsaturated ketone and diazomethane. Benzylidene-acetone on reaction with diazomethane by 1,3- dipolar cycloaddition yield 2-pyrazolines [33-35].

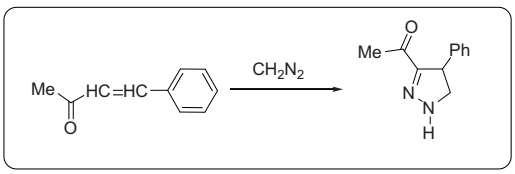

Figure 11: Synthesis of pyrazolines from α, β-unsaturated ketone

Cycloaddition reaction (Figure 12) of substituted styrenes with *p*-anisyl diazomethane at low temperature yield *trans*-3, 5-bis-(*p*-anisyl)-1-pyrazoline [36].

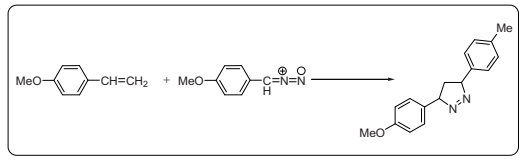

Figure 12: Synthesis of pyrazolines by cycloaddition reaction

Chalcone derivatives on reacting with hydrazine hydrate and glacial acetic acid, form corresponding N-phenyl-3,5-diphenyl pyrazoline & 3,5-diphenyl pyrazoline derivatives respectively (Figure 13) [37].

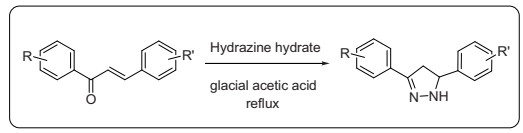

Figure 13: Synthesis of pyrazolines from Chalcone derivatives

Pharmacological aspects of pyrazolines:

2-pyrazoline is insoluble in water but soluble in propylene glycol because of its lipophilic character [38]. 2-pyrazolines display a broad spectrum of potential pharmacological activities and are present in a number of pharmacologically active molecules such as phenazone, amidopyrene, methampyrone (analgesic and antipyretic), azolid/ tandearil (anti-inflammatory), indoxacarb (insecticidal), anturane (uricosuric), etc. Considerable interest has been focused on the pyrazoline structure. The discovery of this class of drugs provides an outstanding case history of modern drug development and also

points out the unpredictability of pharmacological activity from structural modification of a prototype drug molecule. It is having a variety of medicinal applications. Pyrazoline derivatives were found to have potential antipyretic-analgesic, tranquilizing, muscle relaxant, psycho analeptic, antiepileptic, antidepressant, anti-inflammatory, insecticidal, antimicrobial and anti-hypotensive activities. Their derivatives were also found to exhibit cytotoxic activity, inhibitory activity of platelet aggregation, herbicidal activity and cannabinoid CB1-receptor modulators. Pyrazoline interest is also extended to dyes and dye couplers [39]. Given below is a brief account of various modifications reported on chalcones, which resulted in a variety of biological and pharmacological activities.

Anti-cancer agents

Cancer is a leading cause of death worldwide, accounting for 8.7 million deaths (around 14% of all deaths) in 2012. Although many chemotherapeutic agents, such as cisplatin, 5 fluorouracil and taxol, have been developed to treat different kinds of cancer effectively, some side effects could happen simultaneously. Therefore, it is important and urgent to develop novel compounds as anticancer agents with higher bioactivities and lower side effects [40, 41]. It is well known that a number of multi-cyclic compounds containing heterocycle fragments exhibit a wide variety of biological activities. Pyrazoline and pyrazole are important structural fragments of many bioactive compounds.

As the diverse pharmacological importance of pyrazoline have already been explained in the earlier sections, some of the pyrazoline derivatives showed potent anti-cancer activity (Figure 14).

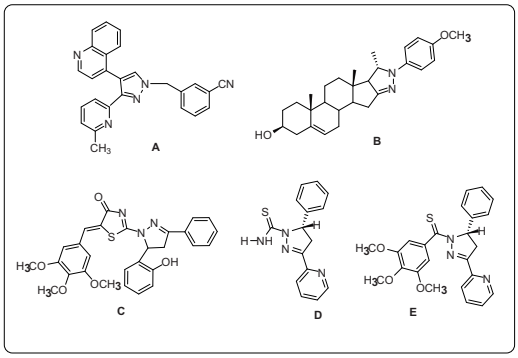

Figure 14: Pyrazolines having Anti-cancer activity

Compound A showed potential ALK5 inhibitory activity as transforming growth factor-β type 1 receptor kinase inhibitors [42]. But this compound showed some extent of cytotoxicity. This problem is eradicated when *p*-methoxy phenyl pyrazoline fragment is introduced to the ring-D of steroid in Compound B [43]. Compound C is proven to be active with selective influence on colon cancer cell lines [44]. The above mentioned compounds A and B have been examined for anti-proliferative activity against human colon carcinoma and highly metastatic human breast carcinoma [45].

Anti-microbial agents

The pyrazoline nucleus is a ubiquitous feature of various compounds possessing many pharmacological and physiological activities and therefore they are useful materials in drug research. It was reported

in the literature that different substituted 2-pyrazolines possess antimicrobial activities (Figure 15).

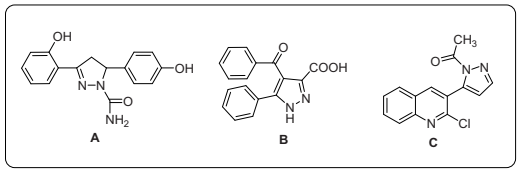

Figure 15: Pyrazolines having Anti-microbial activity

Compound A have structural similarities to siderophores and evaluated as novel antimicrobials against *Mycobacterium tuberculosis* and *Yersinia pestis* [46]. Compound B and C possess antibacterial activities against *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas putida* [47].

Hypotensive agent

Clonidine and Clonidine like thiazolo-imidazoline derivatives (Figure 16) encouraged the development of pyrazoline derivatives of this class which are proven to have hypotensive activity. These derivatives also bear structural and isosteric relationship to Clonidine [48].

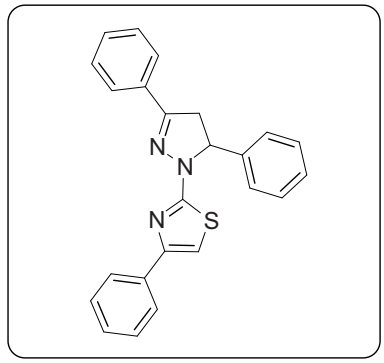

Figure 16: Pyrazoline having hypotensive activity

Analgesic agent

Pain is one of the most prevalent conditions that limits productivity and diminishes quality of life. Although there is an arsenal of effective and widely used analgesics, there is some concern regarding their safety and side-effects, making their clinical use problematic. In the recent years pyrazoline has emerged as Class of analgesics having very high pharmacological activity [49]. Dipyrone (metamizol) is a drug that belongs to the pyrazole derived family. Reports in the literature have shown that dipyrone, although generally considered as belonging to the nonsteroidal anti-inflammatory drug family, seems not to present the typical side effects of this drug class. Antipyrine (phenazone) is also a widely used analgesic belonging to pyrazoline family.

Anti-depressant activity

Depression is a serious disorder with estimates of lifetime prevalence as high as 21% of the general population in some developed countries [50]. Treatment for this disease is possible with antidepressant medications and psychotherapy for some patients [51].

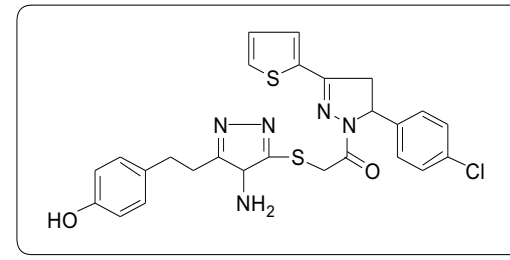

Figure 17: Pyrazoline having anti-depressant activity

Although antidepressants have been used in the clinic for several decades, most of them are inadequate in efficiency and have many serious adverse side effects. Pyrazolines were also reported as potential antidepressant agents (Figure 17) which act by MAO inhibition. The compound shown above has been proven as a potent anti-depressant activity involving serotonergic system for its activity [52].

Conclusion

Review emphasizes on detailed information of Isoxazole and Pyrazoline. Isoxazole, an azole with an oxygen atom next to the nitrogen, is found in many natural products and also found in number of drugs, including COX-2 inhibitor valdecoxib. Furoxan, is a nitric oxide donor is containing isoxazolyl group is found in many beta-lactamase-resistant antibiotics, such as cloxacillin, dicloxacillin and flucloxacillin. The synthetic androgenic steroid danazol also has an isoxazole ring. Pyrazoline, a five-membered heterocycle having two adjacent nitrogen atoms within the ring, has only one endocyclic double bond and is basic in nature. Among its various derivatives, 2-pyrazolines seem to be the most frequently studied pyrazoline type compounds. 2-Pyrazolines can be considered as a cyclic hydrazine moiety display a broad spectrum of potential pharmacological activities. Both ring systems are having many pharmacological activity including but not limited to anti-cancer, anticonvulsant, antimicrobial, etc. These ring systems can further exploit in future to design novel pharmacologically active molecules.

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