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Overview on Nitrogen containing compounds and their assessment based on 'International Regulatory Standards'

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ABSTRACT

Heterocyclic compounds have a role in most fields of sciences such as medicinal chemistry, biochemistry also another area of sciences. More than 90% of new drugscontain heterocycles and the interface between chemistry and biology, at which so much new scientific insight, discovery and application is taking place is crossed by heterocyclic compounds. Compounds derived from heterocyclic rings in pharmacy, medicine, agriculture, plastic, polymer and other fields.Most active heterocycles that have shown considerable biological actions as antifungal, anti-inflammatory, antibacterial, anticonvulsant, antiallergic, herbicidal, anticancer activity. There is always a strong need for new and efficient processes in synthesizing of new Heterocycles.Alum have been used as a novel catalyst in the synthesis of Schiff's bases. Synthesized Schiff's bases are free from use of ICH class 1 and Class 2 solvents and also free from structural alerts genotoxic impurities. This review highlights on various aspects of heterocyclic compounds with its biological activity & regulatory assessment based on the 'International Regulatory Standards'.

Keywords: Heterocycles. Nitrogen containing compounds Biological activity, History, Regulatory assessment, International Regulatory Standards

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INTRODUCTION

Today there are a lot of heterocyclic compounds are known, day by day the number is increasing rapidly due to the enormous synthetic research and also their synthetic utility[1]. Heterocyclic compounds have a role in most fields of sciences such as medicinal chemistry, biochemistry also another area of sciences[2]. Thename heterocyclic comes from the Greek word "heteros" which means "different." Generally, the Heterocyclic compounds are cyclic organic compounds that contain at least one hetero atom, the familiar hetero atoms are Nitrogen, Oxygen and Sulphur and other variety of atoms[3].Heterocyclic compounds constitute the largest and most varied family of organic compounds.

Heterocyclic chemistry is one of the most significant and important fundamental division of organic chemistry dealing with synthesis, properties, and applications of heterocycles[4].

History of Heterocyclic Chemistry:

Two hundred years ago, the chemical science was an undivided field around 1900 a division into inorganic, organic and physical chemistry became necessary. An increase of factual material enforced a progressive segmentation into sub disciplines Heterocyclic compounds constitute the largest and most varied family of organic compounds[5].

The history of heterocyclic chemistry began in the 1800s, in step with the development of organic chemistry. Some noteworthy developments 1818. Brugnatelli isolates Alloxan from uric acid 1832. Dobereiner produces furfural (afuran) by treating starch with sulfuric acid1834: Runge obtains pyrrole ("fiery oil") by dry distillation of bones1906[6,7]. Friedlander synthesizes indigo dye, allowing synthetic chemistry to displace a large agricultural industry1936: Treibsisolates chlorophyll derivatives from crude oil, explaining the biological origin of petroleum1951: Chargaff's rules aredescribed, highlighting the role of heterocyclic compounds (purines and pyrimidines) in the genetic code[8].

several notable development in heterocycles are, In general, the physical and chemical properties of heterocyclic compounds are best understood by comparing them with ordinary organic compounds that do not contain heteroatoms[9].

Heterocyclic compounds have played an important role in medicinal chemistry. It helps into the development of various therapeutic agents. The chemistry of Heterocycles is an interesting branch in organic chemistry. Heterocyclic

compounds are widely distributed in nature. Almost all the compounds we know as drugs, vitamins, and many other natural products areheterocycles[10].

Classification of Heterocyclic Compounds:

We classified heterocyclic compounds according to number of member and type of hetero atoms (N ,S , O, Se,.....) of such a replacement are numerous[11].

Aromaticity of heterocyclic compounds:

Aromaticity is one of the most important concepts in chemistry and is of particular interest in understanding the structure and properties of heterocyclic compounds. Heterocyclic compounds play an important role in biological processes; hence, the scientists are trying to understand the chemistry of heterocyclic compounds in order to improve the quality of human life[12,13]. Aromaticity is of particular importance in understanding the structure and properties of heterocyclic compounds. In recent years, the quantitative assessment of Aromaticity has become possible using which the aromatic properties of heterocyclic compounds andtheir polycyclic fused derivatives can be determined[14,15,16].

More than 90% of new drugs contain heterocycles and the interface between chemistry and biology, at which so much new scientific insight, discovery and application is taking place is crossed by heterocyclic compounds[17,18,19].

Several new heterocyclic derivatives containing fused pyrazoloxazine moieties were synthesized via cycloaddition reactions of bi-nucleophilic dentates, including hydrazine hydrate and its derivatives as well as active methylene compounds and aniline derivatives, resulting in novel five-, six- and seven-membered heterocyclic compounds[20,21,22].

I. Medicinal significance of Heterocyclic compounds:

There is huge number of pharmacologically active heterocycliccompounds having application in many common diseases. There are huge number of pharmacologically active heterocyclic compounds having application in many common diseases as antimicrobial, herbicides, urinary antiseptics and anti-inflammatory agents. Some heterocycles exhibits antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic activity[23,24].

II. Biological significance of Heterocyclic compounds:

Few heterocyclic compounds containing the five-membered oxadiazole nucleus possessa diversity of useful biological effects.Moieties are important because of their versatilebiological actions. Following are categories of drugs are having heterocyclesnucleus &used for treatment of various diseases. Antihistaminic, Antioxidant, Antitubercular, Antidiabetic, Antiobesity as Antimicrobial, Anti inflammatory, Analgesic, Immunomodulatory agents, Antiepileptic, Antiviral, Antineoplastic, Antihypertensive, Antimalarial, Local Anesthetic, Antianxiety, Antidepressant. Antibiotics such as Penicillin's, Cephalosporin[25,26,27].

III. Other versatile applications of Heterocyclic compounds:

Heterocyclic compounds exhibit significant solvatochromic, photochromic, andbiochemi-luminescence properties. Theenormous applications of major heterocycles arein materials science as dyestuff, fluorescentsensor, brightening agents, information storage, plastics, and analytical reagents, supramolecular and especially in conjugated polymers. Furthermore they act as organic conductors, optical data carriers, organic light-emittingdiodes, semiconductors, molecular wires, photovoltaic cells, light harvestingsystems, liquid crystalline compounds andchemically controllable switches. [28,29,30].

Regulatory affairs:

Regulatory affairs (RA) professionals play critical roles in a pharmaceutical industry because it is concern about the healthcare product lifecycle, it provide strategic, tactical and operational direction and support for working within regulations to expedite the development and delivery of safe and effective healthcare products to individuals around the world.Drug development and commercialization is highly regulated the path to drug registration Marketing approval is paved with good intention but can be complicated Things change constantly[31,32].

Regulatory affairs in R&D:

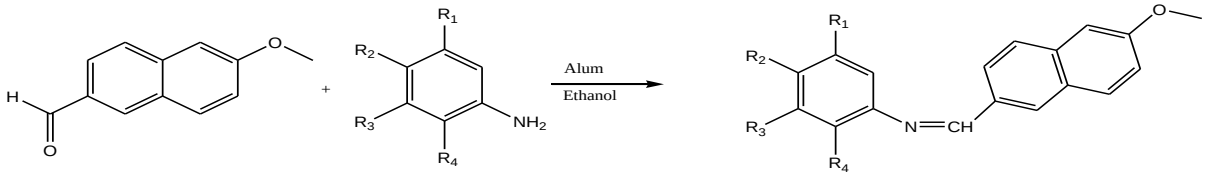
The regulatory affairs personnel work hand in hand with marketing and R&D to develop, innovative products that take advantage of new technological and regulatory developments to accelerate time to market. With new products expected to add significant revenues to the company's bottom lines, small decreases in time to market equate to large material gains in revenue and profit. Employing adaptive clinical trial strategies, obtaining quick approval from regulatory authorities and avoiding pitfalls in processes can accelerate development of new products and help to reduce costly errors and time lags[33,34]

Regulatory bodies in different countries:

- Central Drugs Standard Control Organization
- Therapeutic Goods Administration
- Medicines and Health care products Regulatory Agency.
- European Medicines Evaluation Agencies
- European Directorate for Quality ofMedicines,
- Medicines Control Council.
- USA FDA Food and Drug Administration etc[35,36].

Example of Regulatory Assessment of Schiff's bases using alum as a novel catalyst:

To understand Regulatory Assessment of Hetrocyclic compounds here we taken example with our previously published work Synthesis, Characterization and Regulatory Assessment of Schiff's bases using alum as a novel catalyst. Alum [KAI $(SO4)_2 \cdot 12H_2O$] performs as a novel catalyst for the synthesis of Schiff's bases from 6-methoxy naphthalene 2-carbaldehyde with various substituted amines in good to excellent isolated yield (65–89%) using ethanol as a solvent at ambient temperature[38]. The synthetic scheme is provided below:



Heterocyclic compounds have played an important role in medicinal chemistry. It helps into the development of various therapeutic agents. The chemistry of Heterocycles is an interesting branch in organic chemistry. We do not found synthetic research based on the regulatory science, hence to demonstrate safety, quality and efficacy of the synthesized compounds, regulatory science has been introduced as a back-bone of the synthesis. Our research demonstrated the following important aspects of the regulatory science:

- Advancing product manufacturing and quality
- Ensuring the safety and effectiveness of the compounds
- Advancing to promote global health

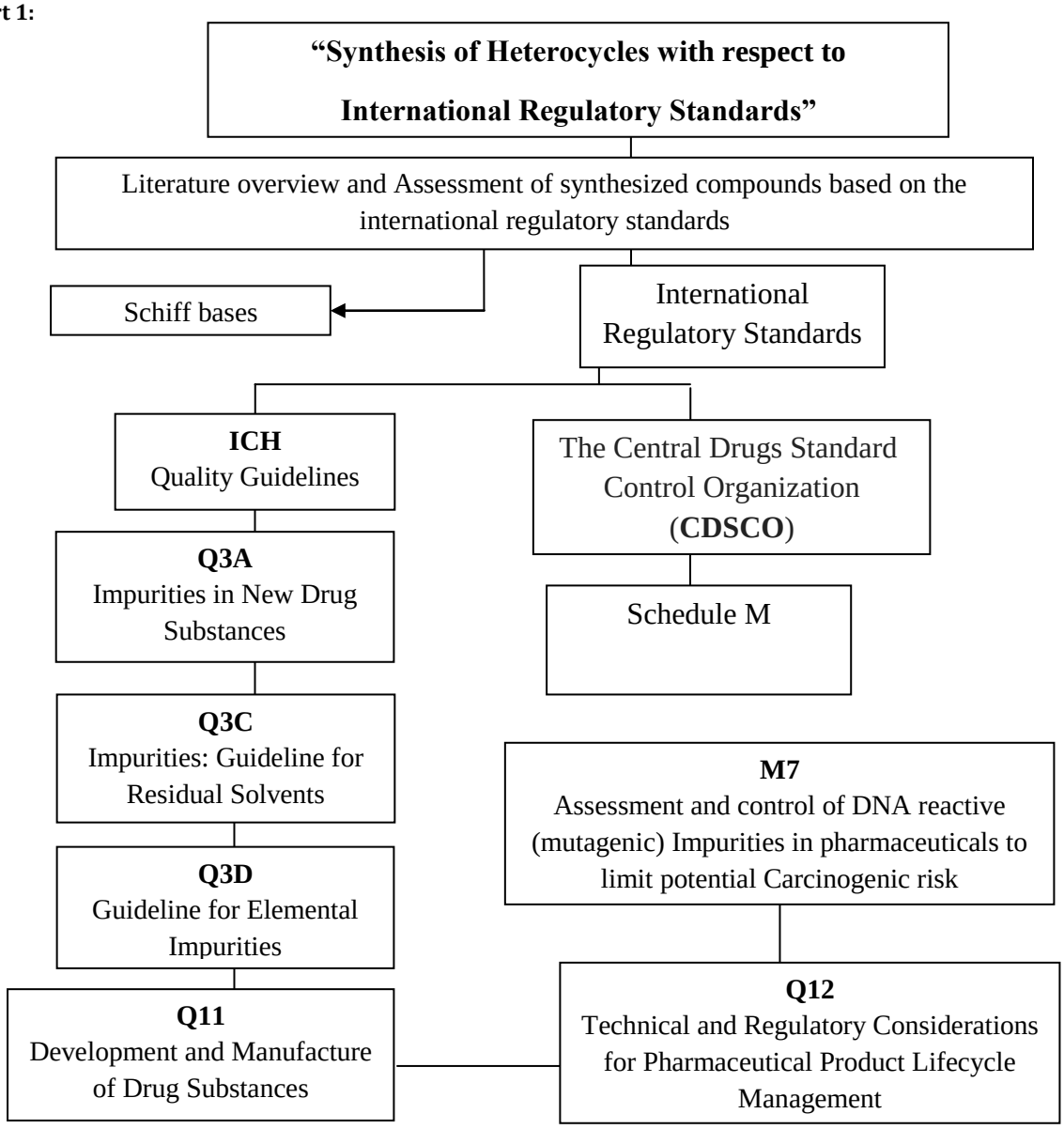
Our synthesized compounds are building blocks of the key starting materials of number of active pharmaceutical ingredients (API). According to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (**ICH**) guidance Q7 an "API Starting Material" is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API.

ICH is a joint initiative involving both regulators and research-based industry representatives of the European Union (EU), Japan and the United States (US) in scientific and technical discussions. The mission of ICH is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed.

'The Central Drugs Standard Control Organization (**CDSCO**)' is the national regulatory body for Indian pharmaceuticals and medical devices, and serves parallel function to the 'European Medicines Agency (**EMA**)' of the European Union, 'the Pharmaceutical and Medical Devices Agency (**PMDA**)' of Japan, 'the Food and Drug Administration of the United States (**USFDA**)' and 'the Medicines and Healthcare Products Regulatory Agency (**MHRA**)' of the United Kingdom[37].

Taking consideration of regulatory requirement (as provided in below **flow chart 1**) we have synthesized novel series of compounds containing biologically important pharma-cophores and investigate their pharmacological activities.

Flow chart 1:



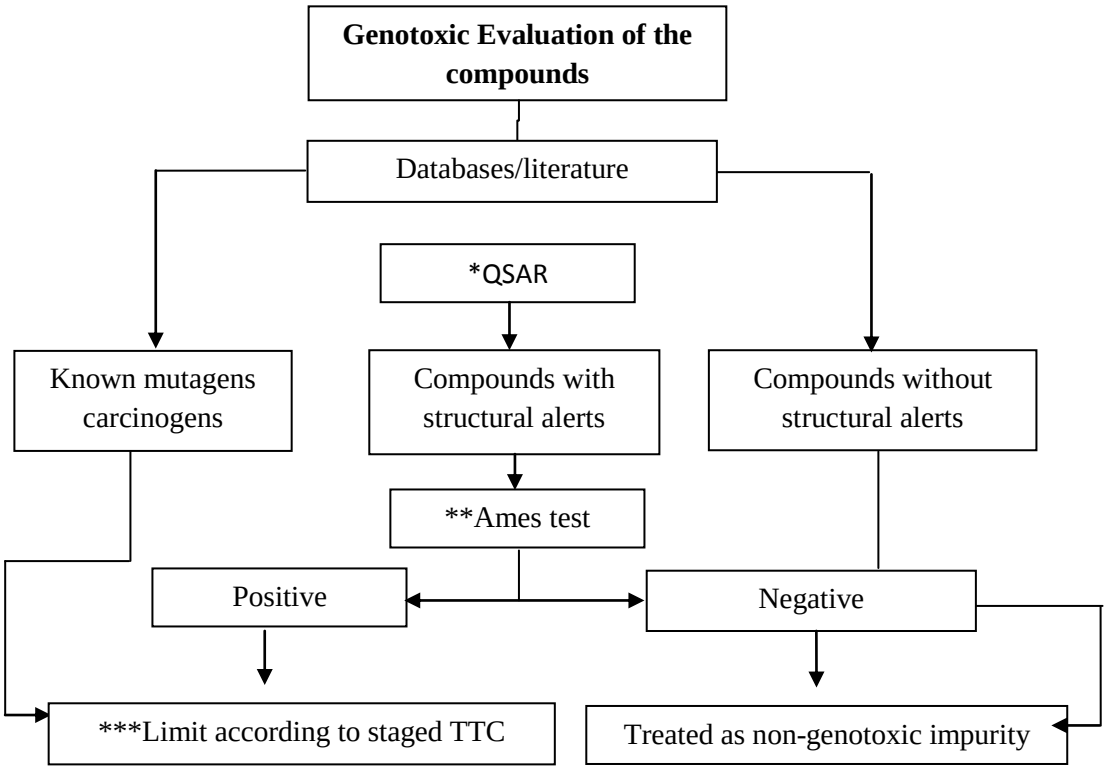
- **Regulatory assessment on genotoxiciy of synthesized Schiff's bases:**

In support of regulatory requirements and based on available various international regulatory standards/ guidelines derivatives of Schiff's bases have been synthesized.

These synthesized derivatives as described are meeting to the "international regulatory standards" as provided below:

1. Use of Alum as a novel catalyst which is cheap, effective and non-hazardous.
2. Use of class 3 solvent such as ethanol (aqueous ethanol), which is ecofriendly and very less toxic for human body.
3. No use of toxic metals/catalyst such as Pb, As, Hg, Cd (Class 1 metals), Ni and Co (Class 2A metals) etc.
4. Alkyl esters of P or S Acid, Aromatic Nitro groups, Aromatic Azo groups, Aromatic ring N-Oxide, Aromatic mono or dialkyalamino, Alkyl hydrazines, Alkyl aldehydes, N-methyl alcohol derivatives, Monohaloalkanes, large family of N and S mustards, N-chloramines, Propiolactones and Propiosultones, Aromatic or Aliphatic Aziridinyls, Alkyl halides (both Ar and Aliph), Urethenes (Carbamates), Alkyl N Nitrosamines, Aromatic amines, N-Hydroxy derivatives and derived esters, Epoxides and Alkene derivatives are structural alert for genotoxicity and carcinogenicity. The whole synthesized derivatives having no structural alerts for these genotoxic impurities. Genotoxicity of the compounds can be evaluated using **flow chart 2** as provided below:

Flow Chart 2:



***QSAR**: Quantitative structure–activity relationship model ****Ames test [7]:** an impurity that has been demonstrated to be genotoxic in an appropriate genotoxicity test model, e.g. bacterial gene mutation. ******TTC [7]**: Threshold of toxicological concern

- **Regulatory assessment of Residual Solvents used during the optimization of process of Schiff's bases:**

Table 1:

Entry	Solvent	ICH Class of solvent	Acceptance criteria (ppm)	Defined by ICH guidance
1	$CHCl_3$	2	60	These solvents associated with less severe toxicity (Class 2) should be limited in order to protect patients from potential adverse effects.
2	CH_2Cl_2	2	600	
3	THF	2	720	
4	DMF	2	880	
5	MeOH	2	3000	
6	ACN	2	410	
7	Dioxane	2	380	
8	DMSO	3	5000	Less toxic solvents (Class 3) should be used where practical. Solvents with low toxic potential to man; no health-based exposure limit is needed. Good yield in ethanol as compare to DMSO; hence ethanol is selected for the reaction.
9	EtOH	3	5000	

CONCLUSION

Heterocyclic compounds play an important role in biological processes. Hence, the scientists are trying to understand the chemistry of heterocyclic in order to improve the quality of human life. Structural study of many of these compounds due to limited synthetic methods is difficult; however, using chemical calculations, assessments of sustainability and magnetic properties of many known or unknown heterocyclic compounds would be possible.

There is always a strong need for new and efficient processes in synthesizing of new Heterocycles. Developing environmental friendly and effective technologies coupled with green chemistry is a major challenge facing the chemical community.

Based on the information provided in this overview, we demonstrated that how industrial research to be connected to academic research so that academic research meets the more requirements of "international regulatory standards".

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