JadounScience
http://www.jadounscience.com
International Journal of Drug Research and Technology
Scientific Publication of JadounScience
ISSN 2277-1506

Int. J. Drug Res. Tech. 2011, Vol. 1 (1), 26-32

International Journal of Drug Research and Technology

Available online at http://www.ijdrt.com/

Review Article

HETEROCYCLIC CHEMISTRY OF BENZIMIDAZOLES AND POTENTIAL ACTIVITIES OF DERIVATIVES

Ingle R.G.* and Magar D.D.

H. R. Patel Institute of Pharmaceutical Education & Research,
Shirpur, Dhule, Pin-425405, Maharashtra, India

ABSTRACT

The present review article is concerned about the heterocyclic chemistry of benzimidazole synthesis and reactions with nucleophilic reagent, arynes and free radicals, oxidation; reduction in the review article emphasis is given on potential biological activities of benzimidazole derivatives. These exhibit many biological activities like antiulcer, antihelmintic, antipsychotic, antiprotozoal, antifungal.etc. Benzimidazole is important lead owing to its inherent properties and therapeutic action.

Keywords: Heterocyclic chemistry, Benzimidazole synthesis, Nucleophilic Reactions, Antimicrobial activity.

INTRODUCTION

Heterocyclic Chemistry

Heterocyclic compounds are those cyclic compounds whose ring contain besides, carbon, one or more atoms of other elements. The non-carbon atoms such rings are referred to as hetero atoms. The most common hetero atoms are nitrogen, sulphur and oxygen. The heterocyclic compounds having lesser common atoms such phosphorus, tin, boron, silicon, bromine, etc. have been a subject of much investigation in recent years. The heterocyclic compounds having three to six carbons in the ring are numerous, but only those having five or six atoms in the ring are by far the most important. Heterocyclic compounds are very widely distributed in nature and are particularly important because of the wide variety of physiological activities associated with this class of substances. Several of the important compounds contain heterocyclic rings, e.g. most o the members of vitamin B complex, alkaloids, antibiotics, chlorophyll, other plants pigments, amino acids, dyes, drugs, enzymes, the genetic material, DNA etc. Few of the basics rings of the heterocyclic compounds are listed below[1].

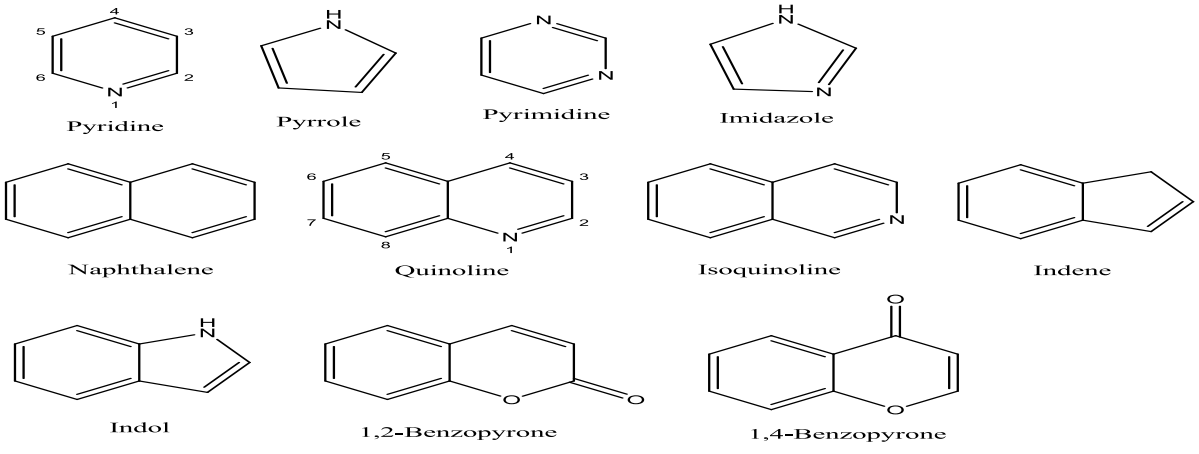
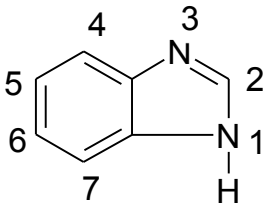


Figure1: Different heterocyclic rings compounds

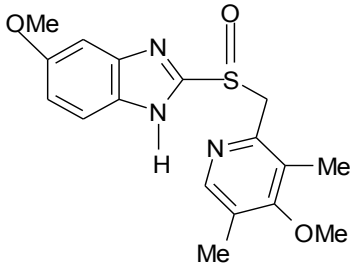
Benzimidazole

Benzimidazole is a fused aromatic imidazole ring system where a benzene ring is fused to the 4 and 5 positions of an imidazole ring. Benzimidazole is also known as 1, 3-benzodiazoles[1].

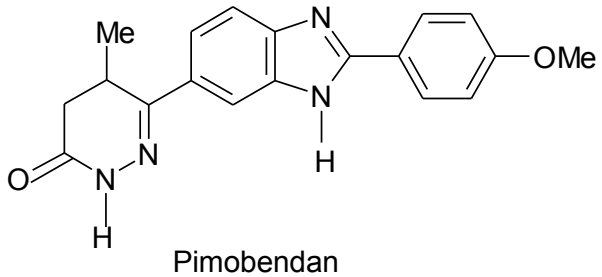


They possess both acidic and basic characteristics. The NH group present in benzimidazole is relatively strongly acidic and also weakly basic. Another characteristic of benzimidazole is that they have the capacity to form salts. Benzimidazole with unsubstituted NH groups, exhibit fast prototropic tautomerism which leads to equilibrium mixtures of asymmetrically substituted compounds. The benzimidazole scaffold is a useful structural modification for the development of molecules of pharmaceutical or biological interest. Appropriately substituted benzimidazole derivatives have found diverse therapeutic applications such as in antiulcer, antihypertensive, antiviral, antifungal, anticancer, and antihistaminics[1]. The optimization of benzimidazole-based structures has resulted in various drugs that are currently on the market, such as omeprazole (Proton pump inhibitor), pimobendan (Ionodilator), and mebendazole (Anthelmintic) figure2.

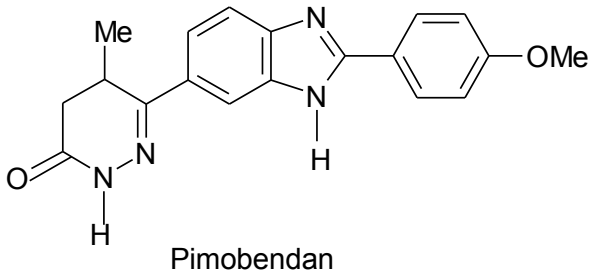
The spectrum of pharmacological activity exhibited by benzimidazoles has been reviewed by several authors[1-4]. Since the publications of these reviews, a number of new methods for the synthesis of benzimidazoles have been discovered and reported; such work continues due to their wide range of pharmacological activities and their industrial and synthetic applications. The present review focuses on the synthetic methodologies and biological activities of the benzimidazoles reported from 2000 to early 2007.



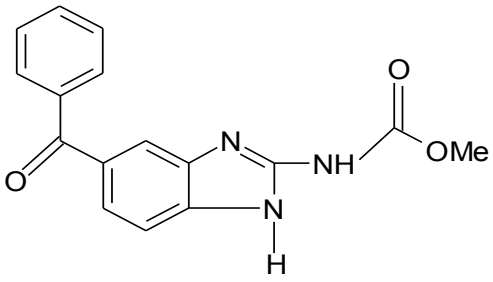
Omeprazole



Pimobendan



Pimobendan



Mebendazole

Figure2: Pharmacologically active benzimidazole drugs

Synthesis of benzimidazole

Benzimidazoles have most commonly been prepared from the reaction of 1, 2-diaminobenzenes with carbonyl-containing compounds (Carboxylic acids, Aldehyde, etc.) under harsh dehydrating reaction conditions, utilizing strong acids such as polyphosphoric acid, hydrochloric acid, boric acid, or p-toluenesulfonic acid. The use of milder reagents, particularly Lewis acids, inorganic clays[6], or mineral acids, has improved both the yield and purity of this reaction[2].

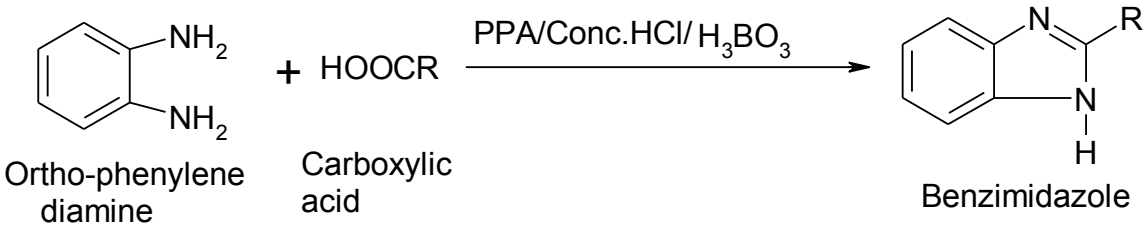


Figure3: Scheme for the synthesis of benzimidazole from o-arylenediamines

From O-nitro aryl amines and O-Dinitroarenes

The synthesis of benzimidazole from O-nitro aryl amines and O-dinitroarenes is an acid catalyzed cyclization reaction. In this N-(O-nitroanilino)- substituted amines are cyclized to N-aminobenimidazoles under reflux in aqueous hydrochloric acid.

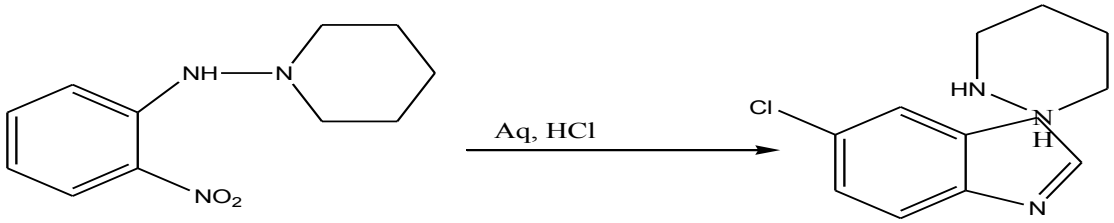


Figure4: Scheme for the synthesis of benzimidazole from o-nitro anilines

From Amidines and Related Compounds

The formation of benzimidazoles from N-aryl amidines is obtained by reacting it with benzenesulfonyl chloride in triethylamine under anhydrous condition.

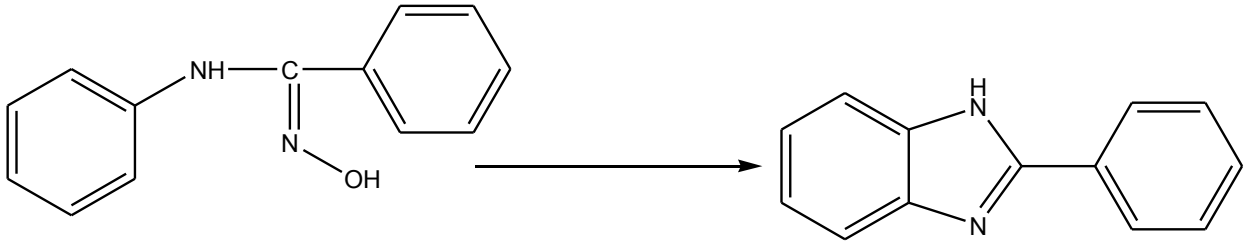


Figure5: Scheme for the synthesis of benzimidazole from amidines

From Five-Membered Ring Heterocycles

Benzimidazole is formed in good yield by photolysis of indazoles.

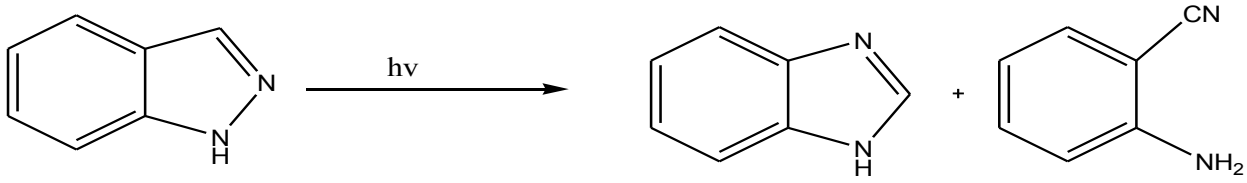


Figure6: Scheme for the synthesis of benzimidazole from five- membered ring Heterocycles

From Six-Membered Ring Heterocycles

Benzimidazole and its 1-methyl derivative are obtained in 100 and 50% yields, respectively. By allowing O-phenylene diamine or N-methyl-O-phenylene diamine to react with S-triazine at temperature just over the melting point of diamine.

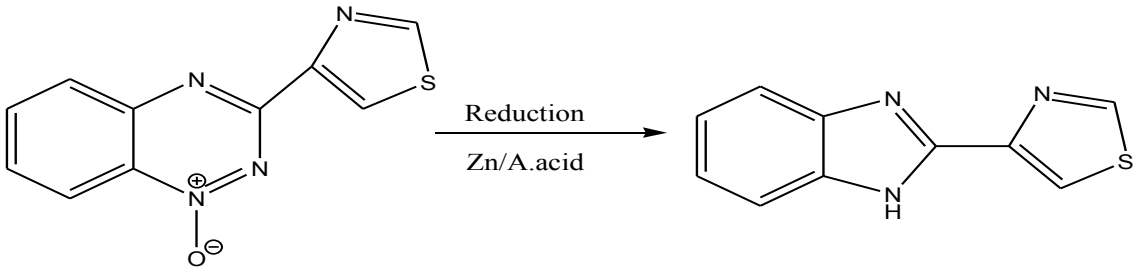


Figure7: Scheme for the synthesis of benzimidazole from six- membered Heterocycles

Reactions of benzimidazole

Nucleophilic substitution in the imidazole ring

The chichibabin reaction is used for the synthesis of a number of 2-aminobenzimidazole derivatives. For unsubstituted 2-halobenzimidazole a competition exist between proton abstraction by the nucleophile at the 1 position with concomitant retardation of 2-substitution. Accordingly chloride ion is not displaced from 2-Chlorobenzimidazole by powerful nucleophiles. Whereas, 2-Chloro-1-mehtyl benzimidazole reacts readily with sodium methoxide or ethoxide.

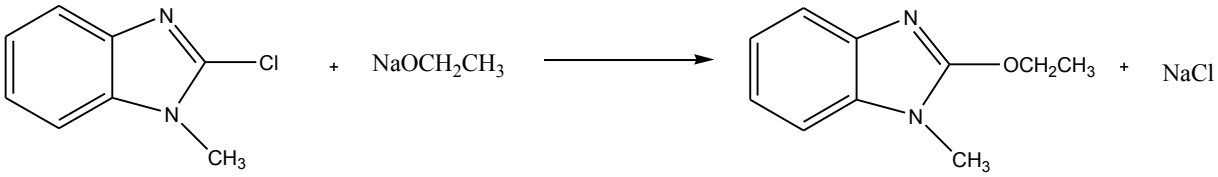


Figure8: Scheme for the nucleophilic substitution in the imidazole ring

Reaction involving Aryens and Free radicals

Benzimidazole reacts as a nucleophile with benzyne to give 2-phenyl benzimidazole.

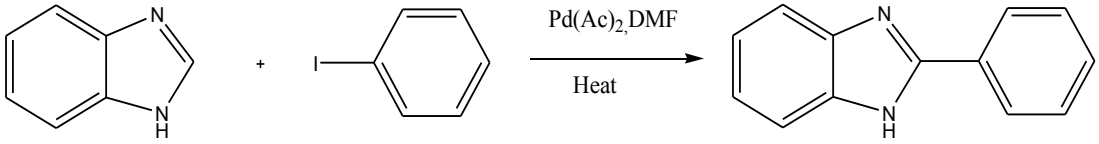


Figure9: Scheme for reaction with aryne

Benzimidazole reacts with free radicals by thermal or photochemical methods.

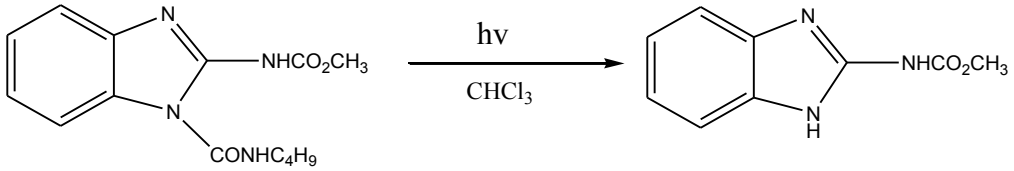


Figure10: Scheme for reaction with free radical

Reduction

The standard method for reduction of benzimidazole involves hydrogenation in the presence of a platinum catalyst in acetic acid, palladium used.

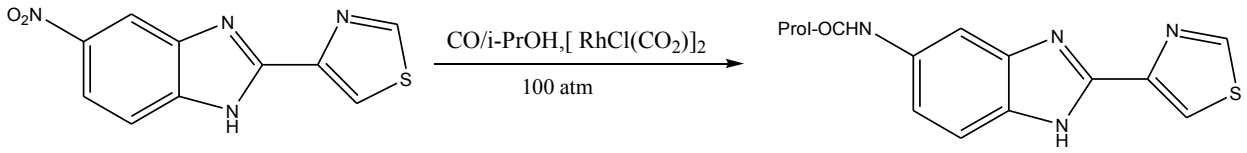


Figure11: Scheme for reduction of benzimidazole

Oxidation

Oxidation is carried out in hydrogen peroxide, lead oxide, lead tetra acetate and chromic acid.

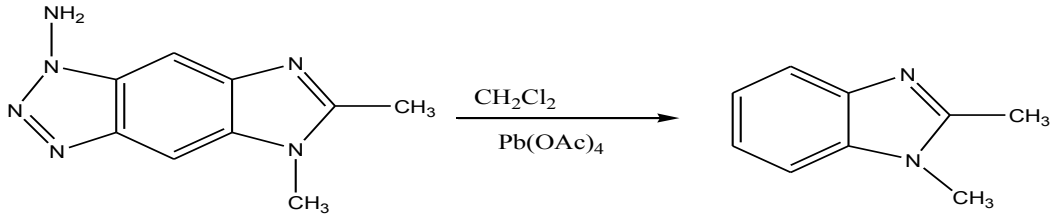


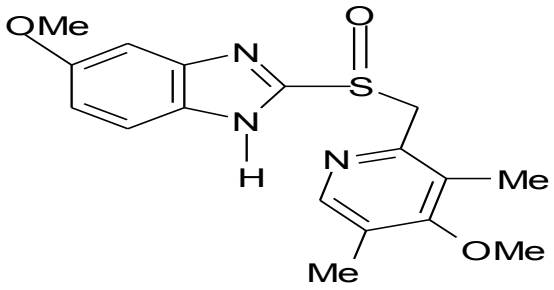
Figure12: Scheme for the oxidation of substituted benzimidazole

Pharmacological Activities of Benzimidazole Derivatives

Drugs in this class differ from all other in that they are designed to inhibit/kill the infecting microorganism and to have no/minimal effect on the recipient. This type of therapy generally called as chemotherapy which has come to mean treatment of systemic infections with specific drugs that selectively suppress the infecting micro-organism without significantly affecting the host. From this they are referred as bacteriostatic and bactericidal respectively.[6]

Anti-ulcer drugs

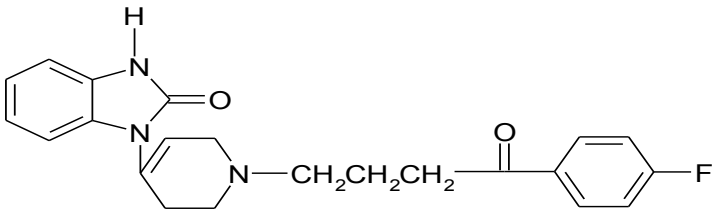
These are the drugs which inhibits both basal and stimulated gastric acid secretion. Some drugs containing benzimidazole nucleus are Pantoprazole, Rabeprazole, Lansoprazole, Omeprazole etc.



Omeprazole

Anti-psychotic agents

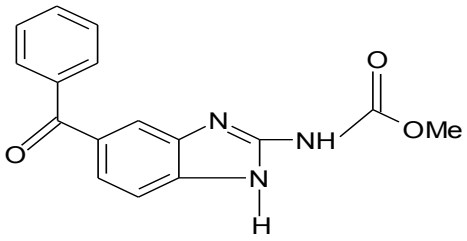
In psychosis thinking of patient becomes illogical, bizarre and loosely organized. Patient has difficulty in understanding reality and their own conditions. Some drugs containing benzimidazole nucleus are droperidol, pimozide, and benperidol.



Droperidol

Anthelmintic

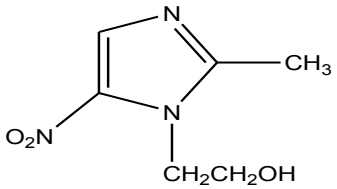
These are the drugs that either kill or expel infesting helminthes. Some drugs containing benzimidazole nucleus are Thibendazole, Mebendazole, and Albendazole etc.



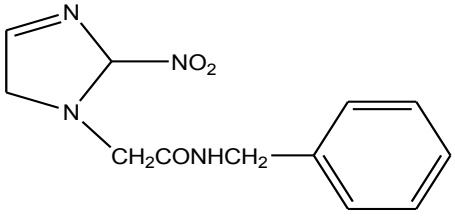
Mebendazole

Anti-protozoal agents

These are the drugs which are used to treat the amoebiasis caused by *E.histolytica*. They exert cytotoxicity by damaging DNA and result in DNA helix destabilization strand breakage. The antiprotozoal drugs containing imidazole nucleus are metronidazole, benznidazole.



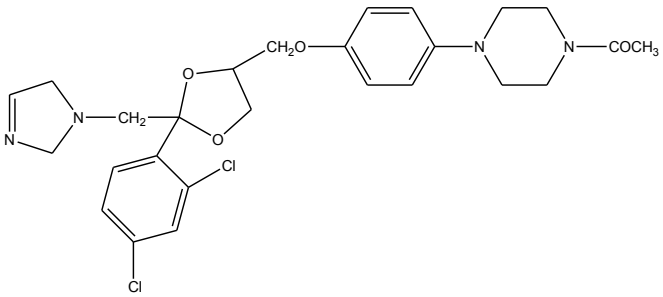
Metronidazole

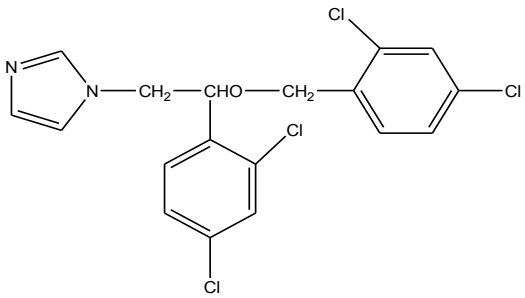


Benznidazole

Antifungal

These are the drugs used for superficial and deep fungal infections. Fungal infections are termed mycoses and in divided in to superficial infections (skin, nails, and scalp) and systemic infections (deeper tissues and organs) some conditions are blastomycosis, histoplasmosis, candidiasis, coccibiomycosis etc. superficial fungal infections can be classified in to the *dermatomycoses* and *candidiasis*. Dermatomycosis are infections of the skin, nails, hair and superficial candidiasis, the yeast-like organism infects the mucous membranes of mouth, skin), vagina or skin[8-10]. Most common antifungal agents containing imidazole nucleus are Clotriamazole, Miconazole, Ketoconazole.





REFERENCES

1. Agrawal, O P, "***Organic Chemistry Reactions and Reagents***", Goel publishing house, New Delhi, 627-628, 686-715.
2. Eldereld, RC (1957), ***Heterocyclic Compounds***,(5), Wiley, New York.

3. Katritzky, AR and Rees, CW (1984), "***Comprehensive Heterocyclic Chemistry***", 5, Pergamon, Oxford.
4. Wilson, Gisvolds (1998), "***Textbook of Organic Medicinal and Pharmaceutical Chemistry***", Lippincott-Williams and Wilkins, A Walter kluwer company, Philadelphia, PA 19106-3621,(10), 217, 672-674, 680-682.
5. Kadam, SS; Mahadik, KR and Bothara, K G (2005), "***Principles of Medicinal Chemistry***", 13th Ed., (1), 233-129.
6. Tiwari, Ashish Kumar and Mishra, Anil (2006), "***Indian Journal of Chemistry***",(45), 489-493.
7. Sundari, V; Kandaswami, P and Valliappan, R (2006), "***Indian Journal of Heterocyclic Chemistry***", (16), 77-78.
8. Jing X, *et al.* (2006), "***Synth Commun***", 36, 259.
9. Tripathi, KD "***Essentials of Medical Pharmacology***", 5th Ed., Jaypee Brother's Medical Publisher, 562-566.
10. Kier, L B and Roche, EB (1967), "***Journal of Pharmaceutical Science"***, 56, 149.