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REVIEW ARTICLE

Direct spectrophotometric determination of 5-nitroimidazoles - A review

G V S R Pavan Kumar*, B Sreerama Murty, K T V S Sai Kumar

Department of Chemical Engineering, Maharaj Vijayaram Gajapathiraj College of Engineering, Chintalavalasa, Vizianagaram 535005 (AP)

ABSTRACT

Nitroimidazoles, classified as anti parasitic drugs, have wide spread applications in their action against various microbial infections in humans. For the quantitative determination of these drugs, various methods are found in literature, which include UV-VIS, HPLC etc. Recently a direct spectrophotometric method was developed and reported in literature for the detection and determination of 5-nitroimidazoles in pure form as well in pharmaceutical formulations in the form of tablets. The method reported was based on the formation of a reddish-purple colour dye, due to the diazotization reaction between the nitro group of drug sample solution with sulphanilamide and NEDA. The drug sample was dissolved in hot water followed by the addition of 2ml each of 0.5% sulphanilamide and 0.3% NEDA solutios. It exhibited a stable instantaneous reddish purple, colour which showed maximum absorbance at 540nm. It was found that all the drug samples under study have shown the same colour with the specified reagents. It was reported to be convenient over earlier methods involving a two step reaction namely reduction followed by diazotization, which can be detrimental to LOD and accuracy.

Keywords: Nitroimidazole, 5-nitroimidazole, metronidazole, ornidazole, tinidazole, secnidazole, stranidazole and spectrophotometry

***Coresponding Author:**
G V S R Pavan Kumar* (F/7472/LM)
Department of Engineering Chemistry,
Maharaj Vijayrama Gajapathiraj College of Engineering
Chintalavalasa, Vizianagaram 535005 (AP)
Mobile No: +919989206996
Email: prs_ganti@yahoo.co.in

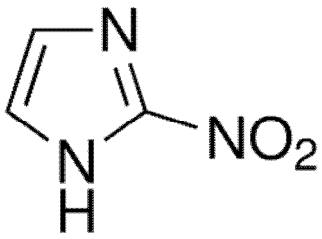
INTRODUCTION

Imidazole, with formula $(CH)_2N(NH)CH$ is a colourless solid that dissolves in water to give a weak basic solution. It is an aromatic heterocyclic compound classified as a diazole and is an alkaloid.

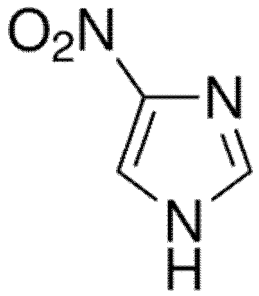
Derivatives of imidazole, called imidazoles are a common family of heterocyclic alkaloids with common 1,3-C_3N_2 ring, but with different substituents. This ring system is present in important biological building-blocks, such as histidine, and the related histamine. Many antifungal drugs like nitroimidazole, and the sedative midazolam contain an imidazole ring,.[1][2][3][4][5]

Nitroimidazoles are synthetic antibacterial preparations with a high sensitivity against anaerobic microorganisms and protozoal infections in humans. The first medication of metronidazole was approved for medical use in 1960. Another set of nitroimidazoles include: tinidazole, ornidazole, secnidazole and ternidazole. Nitroimidazoles are found to have selective bactericidal action against the microorganisms in which enzymatic systems can reduce nitro group. Active reductive forms of medications inhibit DNA replication and protein synthesis in microbial cell and inhibit their respiratory chains (cellular respiration). Nitroimidazoles are active against the majority of gram-negative and gram-positive anaerobes: bactericides (including B.fragilis), clostridium (including C.difficile), Fusobacterium spp., Eubacterium spp., Peptostreptococcus spp., P.niger, G.vaginalis. P.acnes are resistant to imidazoles. T.vaginalis, E.histolytica, G.lamblia, L.intestinalis, E.coli, Leishmania spp. are also found to be resistant to nitroimidazoles. These drugs are used in the treatment of Vaginitis, Bacterial vaginosis, Acne, Seborrheic eczema, Acne rosacea.

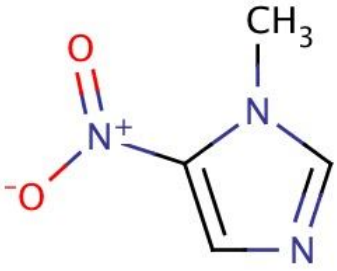
These nitroimidazoles fall into different categories such as 2-nitroimidazoles, 4-nitroimidazoles[6] and 5-nitroimidazoles. **5-Nitroimidazole** contains a nitro group. Several derivatives of nitroimidazole constitute the class of nitroimidazole antibiotics that have been used to combat anaerobic bacterial and parasitic infections.[7] Perhaps the most common example is metronidazole under trade name **Flagyl**. Other heterocycles such as nitrothiazoles (thiazole) are also used for this purpose. Nitro heterocycles are supposed to be reductively activated in hypoxic cells, and then undergo redox recycling or decompose to toxic products.[8]



2-nitroimidazole

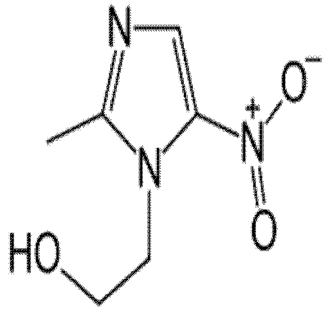


4-nitroimidazole

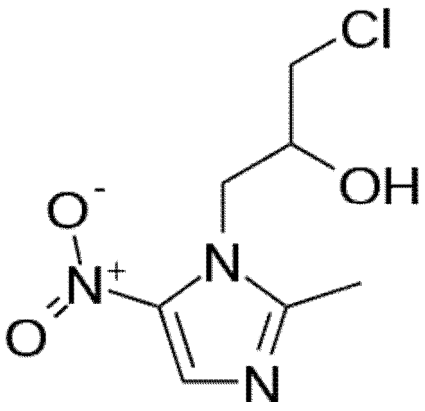


5-nitroimidazole

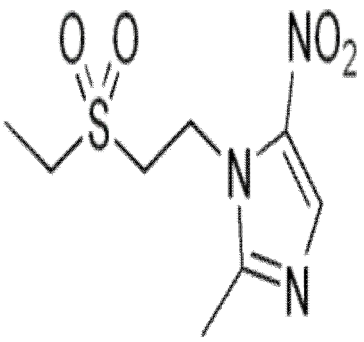
The structures of various 5-nitroimidazoles are as given below.



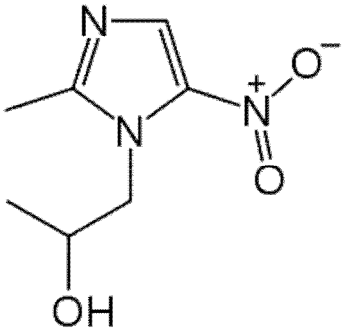
Metronidazole



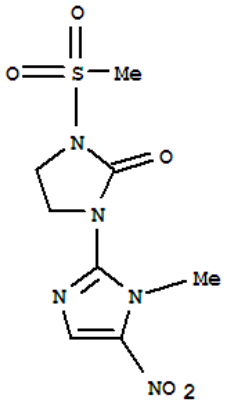
ornidazole



Tinidazole



secnidazole



Satranidazole

Metronidazole, developed in 1960, is a nitroimidazole used particularly against anaerobic bacteria and protozoal infections in humans. It is an antibiotic, amoebicide, and antiprotozoal.[9] It is a drug of first choice for mild-to-moderate *Clostridium difficile* infection.[10] Metronidazole is also used as a gel preparation in the treatment of the dermatological infections such as rosacea and tumours associated with fungal infections.

Ornidazole is a drug used for some selective protozoan infections, Crohn's disease after bowel resection.[11]. It is also used in the poultry industry against infections to birds.

Tinidazole is an anti-parasitic drug used against protozoan infections in humans under the brand names **Tindamax**, **Fasigyn, Simplotan**, and as **Sporinex**.

Secnidazole (under trade names **Flagentyl**, **Sindose**, **Secnil**) is a nitroimidazole found to be effective in the treatment of dientamoebiasis as has been reported.[12] It has also been tested against *Atopobium vaginae*.[13] It is structurally related to the commonly used 5-nitroimidazoles, metronidazole and tinidazole. These drugs share a common activity against anaerobic micro-organisms and they appear particularly effective in the treatment of amoebiasis.

Satranidazole is also a5-nitroimidazole derivative used widely as antiparasitic

The over dosage of each of the above drugs are found to have adverse effects on human health. Hence quantitative determination of these drugs and drug residues is necessary for proper administration and fixing of dosage. In literature [14-26] it was found that various methods such as chromatography, non aqueous titrimetry, electro-analytical methods, ultra violet and visible spectrophotometry were used for the quantitative determination of nitroimidazoles. Out of all the said techniques, spectrophotometry is found to be simple, accurate and precise. Earlier reports in literature indicated that the spectrophotometric determination of these drugs was performed by initial reduction with Zn and HCl followed by the diazotisation and coupling of the resulting amine. All these methods reported earlier are time consuming and involve tedious procedures such as heating and extraction and an additional diazotisation step detrimental to LOD as well as accuracy. The process of diazotization is performed by various reagents such as p-dimethylcinnamaldehyde, 4-dimethylaminobenzene, β-naphthol, metol-potassium dichromate, N,N-dimethylphenylenediamine, vanillin, chloramines-T, salicylaldehyde, bromocresol green, bromocresol purple, MTBH etc.

In recent years a new method [27-30] was developed and reported in literature for the spectrophotometric determination of metronidazole, ornidazole, tinidazole, secnidazole and satranidazole by a direct spectrophotometric method in separate communications. The method involved the treatment of each one of the above drug sample solutions separately with 0.5% sulphanilamide and 0.3% NEDA. Each one of the drug sample solutions exhibited a stable instantaneous reddish purple colour, which showed maximum absorbance at 540nm. For all of the aforesaid drug samples the maximum absorbance was found at 540nm only, though these drugs vary in their physical, chemical and structural properties. All the drugs responded to the reagents in the same manner. The reddish purple colour produced by the reaction between each

one of the drug sample solution, sulphanilamide and NEDA was found to be stable for more than 24 hours. Each of the drug samples was prepared by dissolving an adequate amount of the powdered sample of the drug in hot water and boiled at 60^{o}C for 90minutes. Then the resulting filtered solution was treated with the reagents. These methods proposed recently in literature were found to be simple, less time consuming, accurate and precise with least possible LOD. The authors proposed that the nitro group in 5-position of the hetero cyclic ring is undergoing diazotization with sulphaniliamide and giving a reddish purple colour dye with NEDA. The reaction is found to be instantaneous and the colour was stable for 24hours and more and thus the method is comparatively easier, quicker and sensitive with least LOD than the earlier methods. The main convenience of this method is that the drug compounds with basic common structure and slight modifications of substituents respond similarily to a chromogen with identical wave length of maximum absorbance for the coloured product formed there on.

CONCLUSION

A simple, direct, accurate and precise spectrophotometric method was developed and reported recently for the determination of metronidazole, ornidazole, tinidazole, secnidazole and satranidazole in pharmaceutical formulations. The reaction between each of the drug samples, sulphanilamide and NEDA produced an instantaneous, stable reddish purple coloured product, showed a maximum absorbance at 540nm, the method was found to be accurate for the qualitative and quantitative determination and with least possible LOD and convenience over earlier reported methods.

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