Synthesis of Pyrazole-containing Derivatives as New Potential anti-tubercular

Preeti Sharma[1#], Jinendra Singh Chauhan[2], Birjesh Singh[3]
[1#]AISECT University, Bhopal, M.P., India
[2]Govt. BLP PG College, MHOW, Indore, M.P., India
[3]AISECT University, Bhopal, M.P., India

Abstract: - The synthesized all the compounds are found in good yield and highly sensitive compounds, 1-{3-[5H-pyrazol- sulphonyl] -2 methyl amino benzyloxy-4,5 dihydro-3H pyrazol 4yl} ethanone (I) occurs 12.6 gm. Similarly 1-{5-[4-Dimethylamino-3-(4H-pyrazole-3-sulfinyl)-benzyloxy]-3H-pyrazol-3-yl}-ethanone and 1-(3-{2-Dimethylamino-5-[dimethylene-(4H-pyrazol-3-yl)-sulfanyl]-benzyloxy}-4H-pyrazol-4-yl)-ethanone occurs as 1.2 gm and 14.1 gm respectively. The synthesized compounds **(I), (II), (III),** 1-{3-[5H pyrazole sulphonyl-2 methyl amino benzyloxy-4,5 dihydro-3H pyrazole-4yl}ethenone**,** have been shows remarkable progress without and with streptomycin 94.80% of resistance against the straining MTB bacteria.Compounds 1-{5-[4-Dimethylamino-3-(4H-pyrazole-3-sulfinyl)-benzyloxy]-3H-pyrazol-3-yl}-ethanone**,**1-(3-{2-Dimethylamino-5-[dimethylene-(4H-pyrazole-3-yl)-sulfinyl]-benzyloxy}-4H-pyrazol-4-yl)-ethanoneand1-{3-[1-(4-Chloro-4H-pyrazol-3-ylmethyl)-piperidin-4-ylamino]-6-fluoro-3H-indazol-5-yl}-ethanone is more reliable than streptomycine and shows 94.9% resistance power with MTB bacteria.

Keywords: - Pyrazole Derivative, Mycobacterium tuberculosis, MTB Bacteria

I. INTRODUCTION

Tuberculosis (TB) is considered to be the most infectious disease with a sizable portion of the total world population infected with this disease. The above- mentioned proportion includes both latent and active patients. When the infected person does not produce any evident symptoms, the disease is said to be in latent form. While when the disease is with symptoms it is said to be the active form of disease. TB is a communicable and airborne bacterial disease caused by mycobacterium, which once inside the body can invade any system such as kidney, brain, spines etc. Bacteria causing TB, is a slow-growing bacteria and it grows best in an area where lot of blood and oxygen is available. Therefore, it generally attacks the lungs. TB is one of the disease which causes mass death worldwide. As per global TB report published in 2016, an estimated 10.4 million people were said to be affected with TB in which 90% were adult, 65% male and 10% people with HIV. Around 74% of the infected person worldwide are from Africa and 56% are from developing countries like India, Indonesia, Pakistan, and Bangladesh (Figure 1). Number of death due to TB is unacceptably higher than one can think [1].

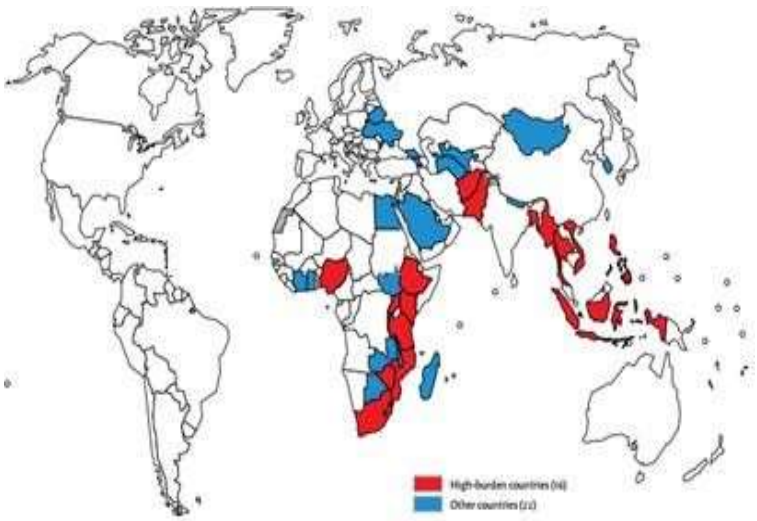


Figure 1: Countries with High Burden of TB

TB is one of the infectious diseases which can communicate from diseased person to another healthy person. The disease is airborne and major source of infection is a person suffering from pulmonary or laryngeal TB which expectorates bacilli. The most common way to get exposed to this disease is when one healthy person is near an infected person and the infected person either sneezes, coughs or through the transmission of respiratory secretions without taking precaution or preventive measures.

Table 1: Estimated Burden of TB in 2016

Estimate of TB burden (2016)	**Global**	**India**
Incidence of HIV/TB	11.7 lakh (1.17 million)	1.1 lakh (110,000)
Incidence of TB cases	104 lakh (10.4 million)	28 lakh (2.79 million)
MDR-TB	4.8 lakh (480,000)	0.84 lakh (84,000)
Mortality of HIV/TB	3.9 lakh (390,000)	12,000
TB Mortality	14 lakh (1.4 million)	4.35 lakh (435,000)

The microorganism causing this infection is a tiny bacterium which is hard to see through naked eye and is known as *Mycobacterium tuberculosis*. Chances to get infected with TB generally depend on the duration of exposure to this bacterium, so people at high risk are especially those who live or work with the infected person [2]. *Mycobacterium tuberculosis* is a group of species that include *Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium africanam, Mycobacterium microti and Mycobacterium canetti,* all these species are capable of causing TB in humans but it is generally caused due to *Mycobacterium tuberculosis*. Beside the above mentioned species several other species like *Mycobacterium laprae* cause leprosy and there are some non TB mycobacteria which can also cause some clinical manifestations similar to those like that of TB [3,4]. There are number of signs and symptoms which reveal the exposure to tubercular bacterium and a lot of them are self-reported which includes a cough, shortness of breath or difficulty of breathing (dyspnoea), night sweats, coughing up of blood (haemopysis), chest pain and other symptomatic characters which can be observed are: e.g. anemia, tachycardia, an axillary temperature higher than that of 37^0C, body mass index comparatively lower etc**.** [5, 6]. Exposure to *Mycobacterium tuberculosis* does not necessarily show positive sign and symptoms of TB and in most of the cases they do not transmit the infection, but pulmonary TB is a origin of *Mycobacterium tuberculosis* bacilli which can infect other part of the body like kidney, bone, skin etc. [7]. TB can be detected by locating *Mycobacterium tuberculosis* through laboratory diagnosis either by traditional methods like that of smear microscopic identification, culture and phenotypic identification [8].

Anti-TB drugs are classified into five groups based on evidence of efficacy, potency, drug class and experience of use [1]. All first line anti TB drug names has a standard three letter and/or a single letter abbreviation. The first line anti-TB drugs are ethambutol (EMB/E) [2, 3], isoniazid (INH/H) [4, 5], pyranamide (PZ/Z) [6-9], rifampicin (RIF/R) [10-13], and streptomycin (STM/S) [14-15] given for 6 months second line drugs (SLDs) are those that are less effective than the first line or have some side effect. The unavailability of a drug in many developing countries also makes it SLD. If the treatment fails as a result of bacterial drug resistance, or intolerance to one or more drug, SLDs are used. The SLDs are only used to treat disease that is resistant to first line therapy (i.e. extensively drug-resistant tuberculosis (XDR-TB) or multidrug resistant tuberculosis (MDR-TB) [16]. Further, the SLDs are divided into six classes; these are (i) aminoglycosides (amikacin/AMK, kanamycin/KM), (ii) polypeptides (capreomy-cin, viomycin, enviomycin) (iii) fluoroquinolones (ciprofloxacin/CIP, moxifloxacin/MXF, levofloxacin), (iv) thioamides (prothionamide, ethionamide), (v) cycloserine, and (vi) ter-izidone and p-ainosalicylic acid/PAS/P.

The third line drugs are either not very efficient or their effectiveness is not yet established. This includes rifabutin, macrolides: e.g., clarithromycin (CLR); linezolid (LZD); thin-acetazone (T); thioridazine; arginine; vitamin D; bedaquiline. Rifabutin is effective, but is not included on the WHO list because for most developing counties. It is impractically expensive [17]. WHO recommended directly observed treatment short Couse (DOTS) anti-TB therapy involves the administration of four drugs: INH, RIF, PZA and EMB or SM. Treatment with these so called first line drugs is carried out initially over 2 months, leading to the destruction of bacteria in all growth stages, after which treatment continues with RIF and INH alone 4 months, where any residual dormant bacilli are eliminated by RIF and any remaining RtF-resistant mutants are killed by INH [18].

Namrata and co-workers [19] identified benzyloxy phenyl butenyl azoles as anti-TB agents. Trivedi et al. carried out synthesis of pyrazolo (3,4-d) pyrimidine derivatives and assessed antimycobacterial active-ities against Mtb using MABA. Compounds exhibited best results (1.2 mg/mL) when compared with first line drugs such as INH and RIP. SAR study reveals, the presence of 2-chloro-, 3-chloro-, 4-methyl- and 2-chloro-5-sulfonyl substitu-ents markedly enhances anti-TB activity [20].

An efficient domino approach for the synthesis of novel pyrrolo (2, 3, 4-kl) acridin-1-one derivatives has been established by Huiyuan et al. [21]. This reaction represents the first facile conversion of an isatin to a pyrrolo (2, 3,4-kl)

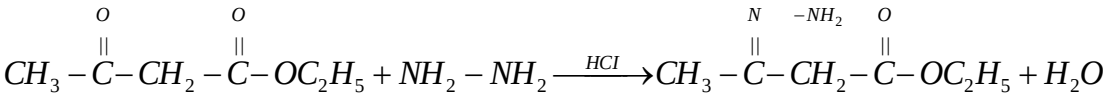
acridin-1-one via a C-N bond cleavage reaction without the need for a multistep reaction process anti-tuberculosis drug induced Hespatotoxicity was studied by Jaime R. and others. [22].
Cerebrospinal fluid drug concentrations and the treatment of tuberculous meningitis were studied by Gordon et al. [23].
In the substituted cinnolinepyrazole series, the compounds which are halogen mainly choro, Bromo and Fluoro substituted were showed potent antibacterial, anti-inflammatory and antifungal activity then other compounds, especially chloro substituted compounds showed more potent anti-inflammatory activity among all the substituted cinnolinepyrazole compounds.

II. RESEARCH METHODOLOGY

First we synthesized the pyrazole from knorr synthesis method [14, 15] and obtained 76% yield of compound .For this synthesis we are using AR grade chemicals acetoacetic ester and hydrazine hydrogen chloride.20ml ester and 10ml Hydrazine hydrogen chloride mix together then exothermic reaction is going on which given white powder of compound A(87%) and added 15ml dimethyl aniline and 5ml formic acid and heated. Reaction mixtures settle down round bottom flask for 3 hr. The yellow crystal are produced which washed by alcohol and re-crystalized by an ether and alcohol to get 76% product.

1-{3-[5H-pyrazol- sulphonyl] -2 methyl amino benzyloxy-4,5 dihydro-3H pyrazol 4yl} ethanone.

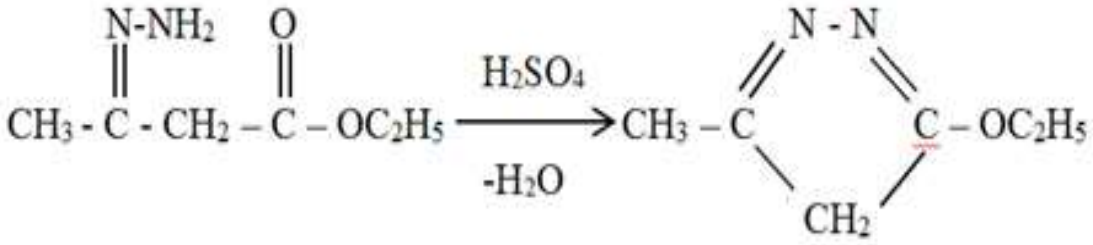
Scheme-I



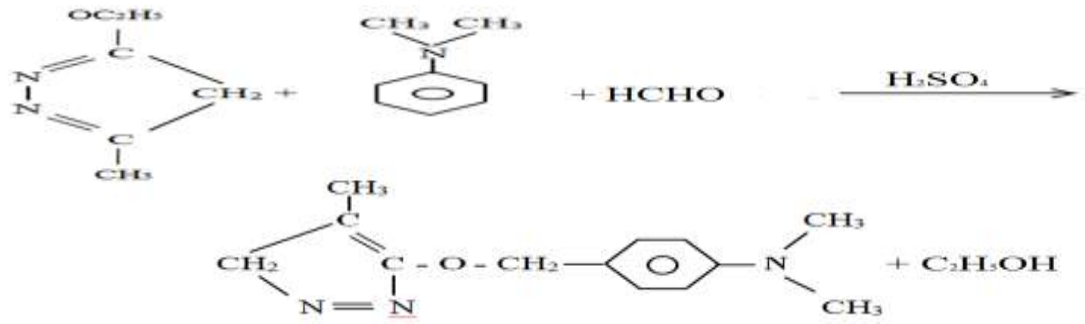
Acetoester Hydrazine Pyrazole Derivative

In this scheme of reaction aceto ester reacted with hydrazine in presence of acid (HCl) to produce pyrazole derivative after the dehydration of A with H_2SO_4 catalysis, Dehydration of A is given B as follows.

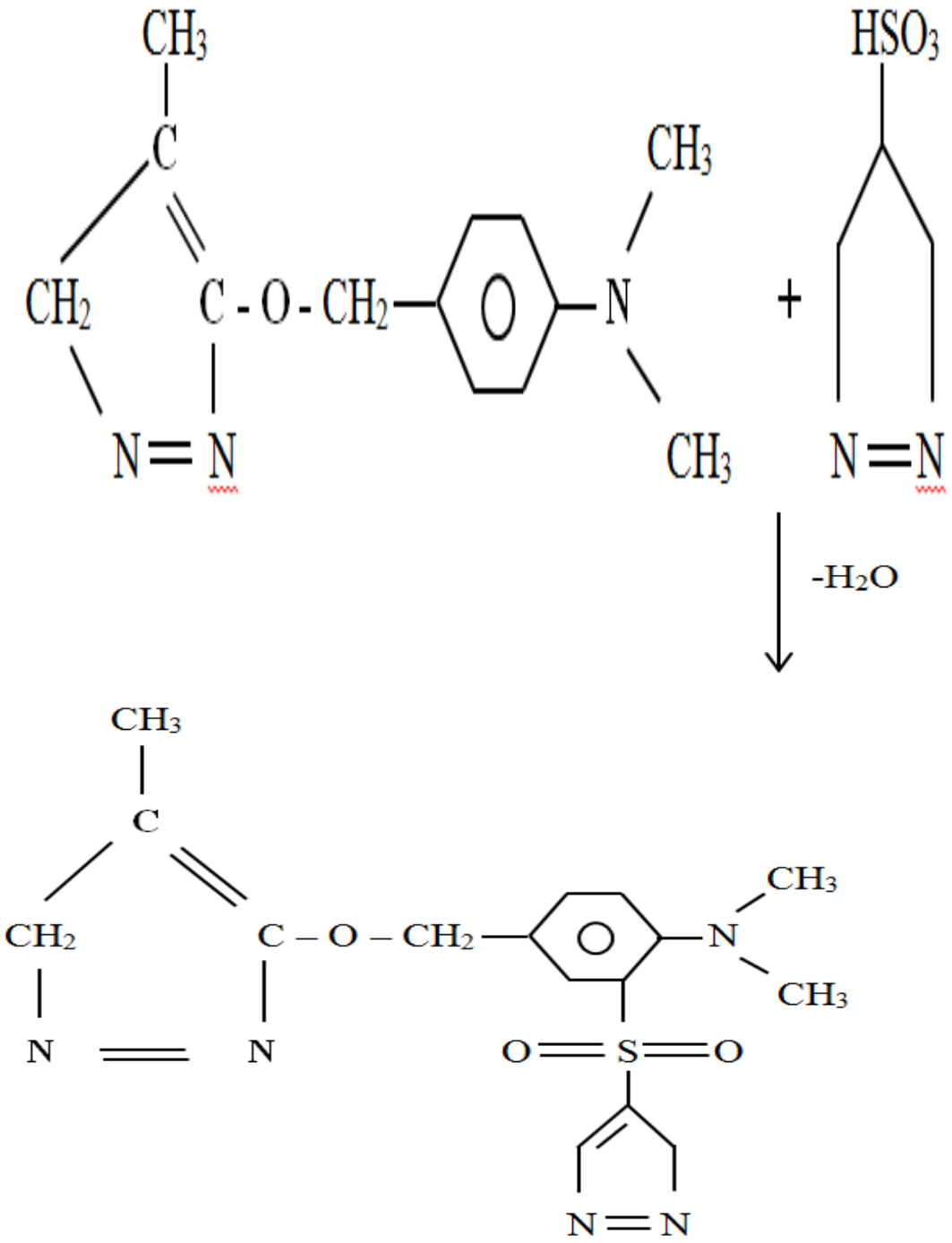
Scheme-II



Scheme-III



Scheme-IV: -C product of Mannich base reaction reacted with H_2SO_4 and pyrazole to give D



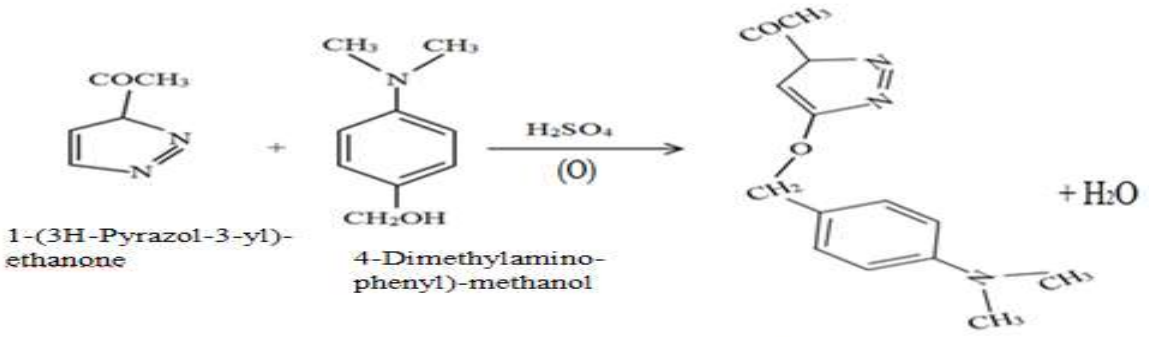
Compound (I)

1-{3-[5H-pyrazol- sulphonyl] -2 methyl amino benzyloxy-4,5 dihydro-3H pyrazol 4yl} ethanone (I).

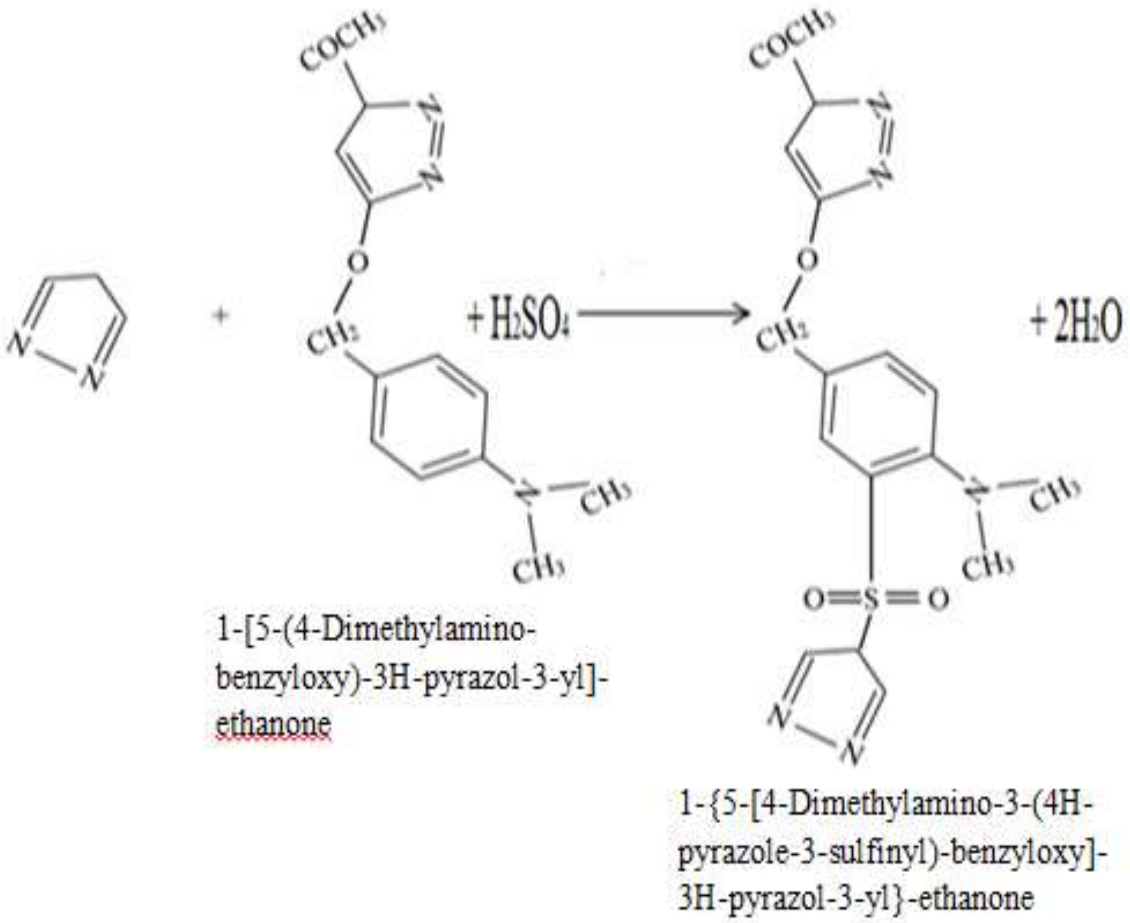
From above method we get 76% yield of 1-{3-[5H-pyrazole-sulphonyl]-2methyl amino benzyloxy-4,5 dihydro-3H pyrazole-4yl} ethanol in scheme IV of reaction of dehydration which occure at ortho position in dimethyl aniline ring which attached with S=O group andpyrazole ring.

Compound (II)
1-{5-[4-Dimethylamino-3-(4H-pyrazole-3-sulfinyl)-benzyloxy]-3H-pyrazol-3-yl}-ethanone

Scheme-I



Scheme-II

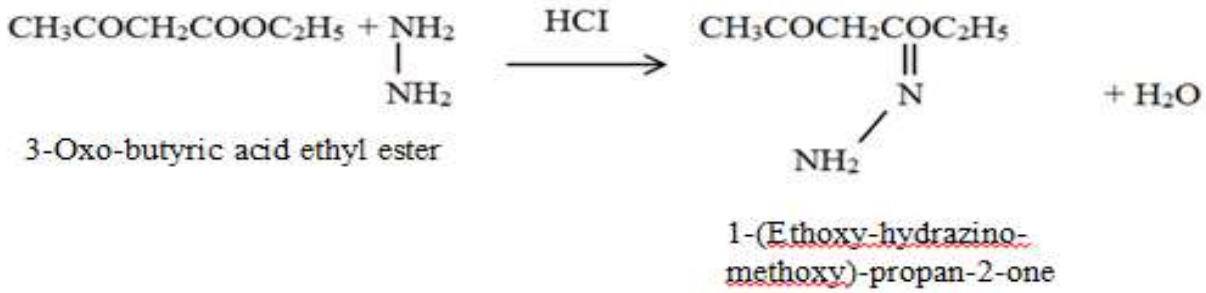


Compound (II)

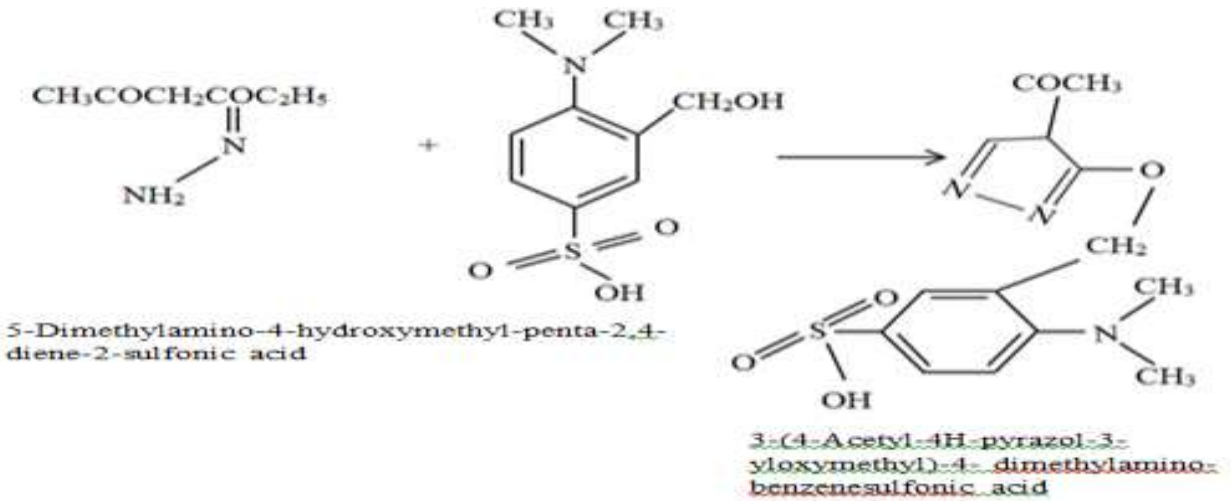
Compound (III)

1-(3-{2-Dimethylamino-5-[dimethylene-(4H-pyrazole-3-yl)-sulfinyl]-benzyloxy}-4H-pyrazol-4-yl)-ethanone

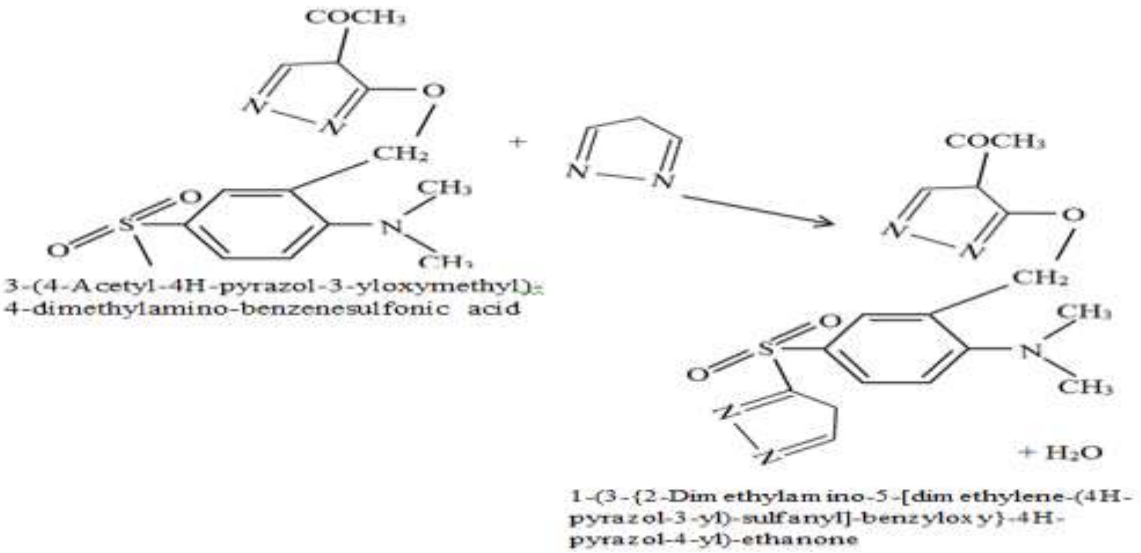
Scheme-I



Scheme-II



Scheme-III



Compound (III)

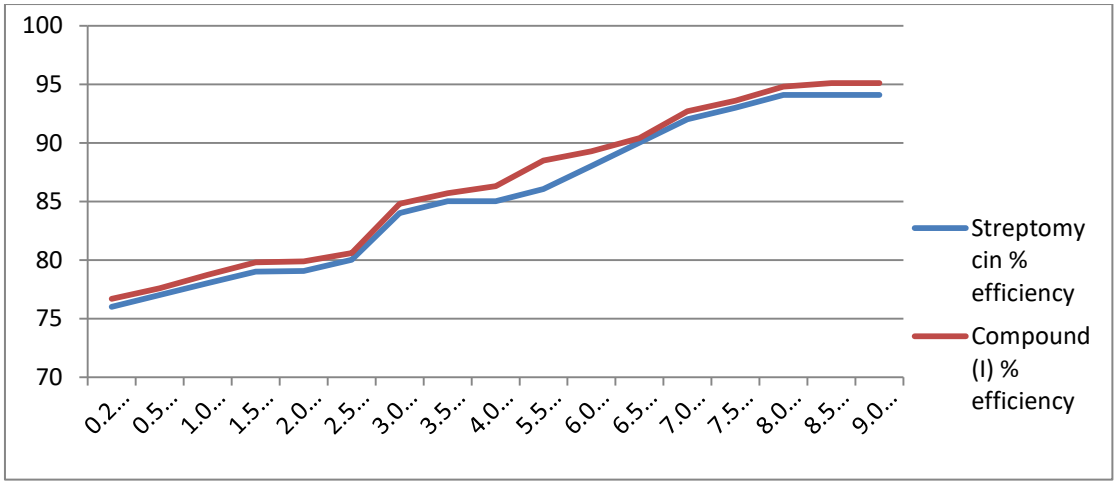
III. RESULT AND DISCUSSION

All the four compounds1-{3-[5H pyrazole sulphonyl-2 methyl amino benzyloxy-4,5 dihydro-3H pyrazole-4yl}ethenone**(I),**1-{5-[4-Dimethylamino-3-(4H-pyrazole-3-sulfinyl)-benzyloxy]-3H-pyrazol-3-yl}-ethanone**(II) and** 1-(3-{2-Dimethylamino-5-[dimethylene-(4H-pyrazole-3-yl)-sulfinyl]-benzyloxy}-4H-pyrazol-4-yl)-ethanone**(III)** is compared with dose of streptomycin and calculated efficiency of the compounds. Compound **(I)** is compared with dose of streptomycin is represent in table II. The graphical represent in graph 1.

All the four pyrazole compounds 1-{3-[5H pyrazole sulphonyl-2 methyl amino benzyloxy-4,5 dihydro-3H pyrazole-4yl}ethenone**(I),**1-{5-[4-Dimethylamino-3-(4H-pyrazole-3-sulfinyl)-benzyloxy]-3H-pyrazol-3-yl}-ethanone**(II)** and 1-(3-{2-Dimethylamino-5-[dimethylene-(4H-pyrazole-3-yl)-sulfinyl]-benzyloxy}-4H-pyrazol-4-yl)-ethanone**(III)** compared with each other.

Table II: Efficiency of Compound **(I)** with Dose of Streptomycin

S. No.	Dose of streptomycin	Streptomycin % efficiency	Compound **(I)**% efficiency
1	0.2 µg/ml	76	76.7
2	0.5 µg/ml	77.02	77.6
3	1.0 µg/ml	78.04	78.73
4	1.5 µg/ml	79.01	79.8
5	2.0 µg/ml	79.06	79.9
6	2.5 µg/ml	80.03	80.6
7	3.0 µg/ml	84.01	84.8
8	3.5 µg/ml	85.02	85.7
9	4.0 µg/ml	85.03	86.3
10	5.5 µg/ml	86.07	88.5
11	6.0 µg/ml	88.03	89.3
12	6.5 µg/ml	90.02	90.4
13	7.0 µg/ml	92.03	92.7
14	7.5 µg/ml	93.02	93.6
15	8.0 µg/ml	94.1	94.8
16	8.5 µg/ml	94.1	95.1
17	9.0 µg/ml	94.1	95.1

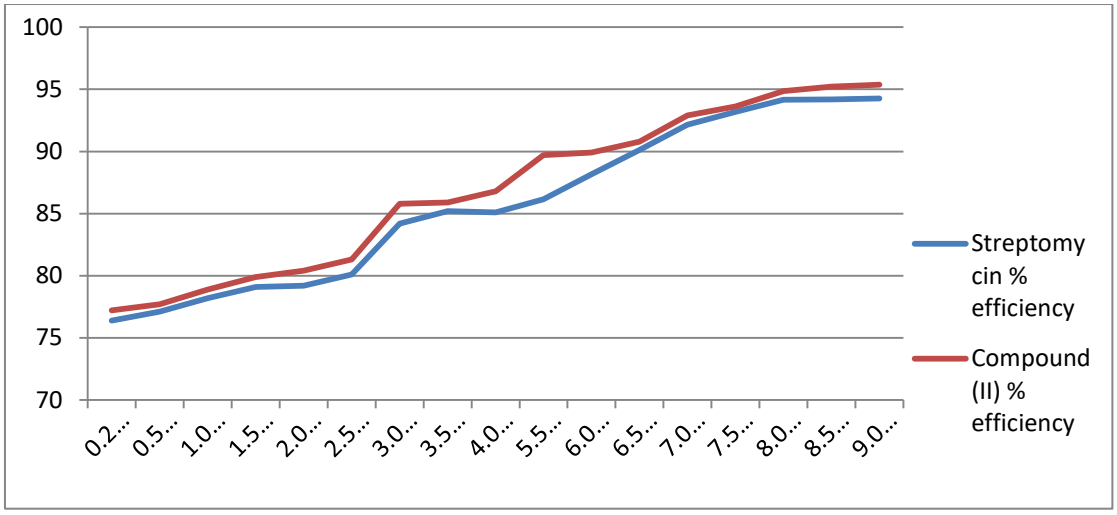


Graph 1: Graphical represent of Compound **(I)** with Dose of Streptomycin Efficiency

Compound **(II)** is compared with dose of streptomycin is represent in table III. The graphical represent in graph 2.

Table III: Efficiency of Compound **(II)** with Dose of Streptomycin

S. No.	Dose of streptomycin	Streptomycin % efficiency	Compound **(II)** % efficiency
1	0.2 µg/ml	76.4	77.2
2	0.5 µg/ml	77.1	77.7
3	1.0 µg/ml	78.2	78.9
4	1.5 µg/ml	79.1	79.9
5	2.0 µg/ml	79.2	80.4
6	2.5 µg/ml	80.1	81.3
7	3.0 µg/ml	84.2	85.8
8	3.5 µg/ml	85.2	85.9
9	4.0 µg/ml	85.1	86.8
10	5.5 µg/ml	86.15	89.7
11	6.0 µg/ml	88.17	89.9
12	6.5 µg/ml	90.12	90.8
13	7.0 µg/ml	92.14	92.9
14	7.5 µg/ml	93.19	93.62
15	8.0 µg/ml	94.17	94.86
16	8.5 µg/ml	94.19	95.22
17	9.0 µg/ml	94.26	95.36

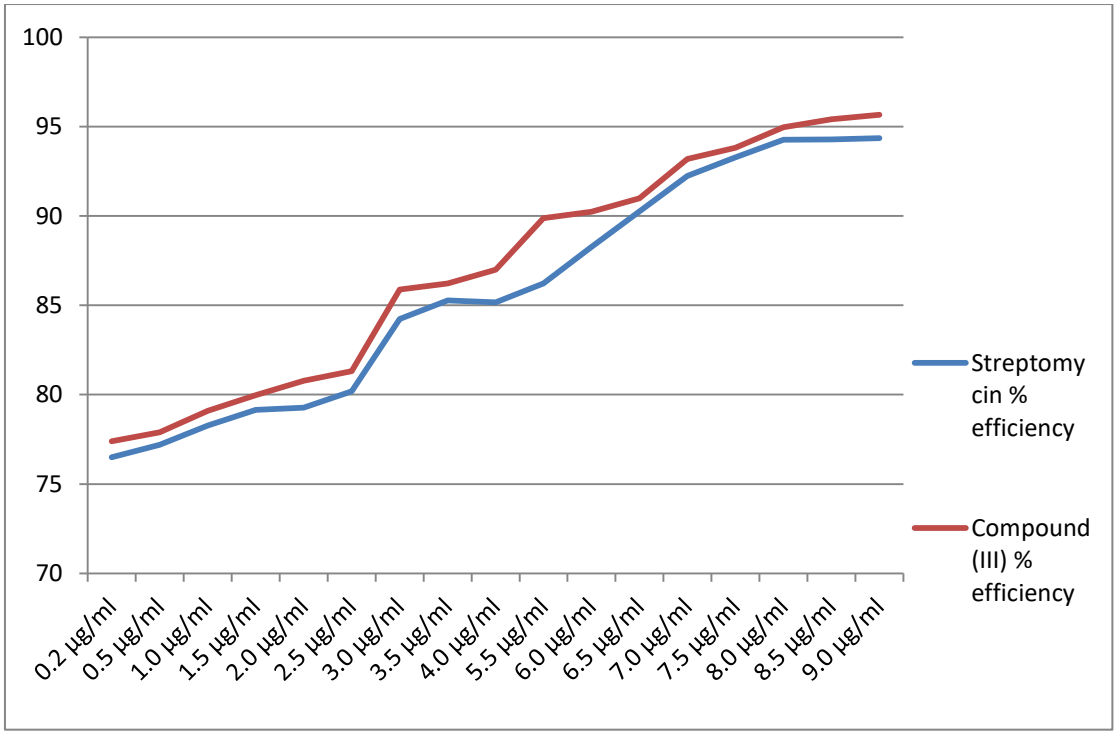


Graph 2: Graphical represent of Compound **(II)** with Dose of Streptomycin Efficiency

Compound **(III)** is compared with dose of streptomycin is represent in table IV. The graphical represent in graph 3.

Table 5.7: Efficiency of Compound **(III)** with Dose of Streptomycin

S. No.	Dose of streptomycin	Streptomycin % efficiency	Compound **(III)** % efficiency
1	0.2 µg/ml	76.5	77.4
2	0.5 µg/ml	77.2	77.9
3	1.0 µg/ml	78.27	79.1
4	1.5 µg/ml	79.14	79.97
5	2.0 µg/ml	79.27	80.77
6	2.5 µg/ml	80.19	81.32
7	3.0 µg/ml	84.24	85.89
8	3.5 µg/ml	85.28	86.22
9	4.0 µg/ml	85.17	86.99
10	5.5 µg/ml	86.22	89.88
11	6.0 µg/ml	88.26	90.23
12	6.5 µg/ml	90.26	90.99
13	7.0 µg/ml	92.24	93.19
14	7.5 µg/ml	93.29	93.82
15	8.0 µg/ml	94.27	94.96
16	8.5 µg/ml	94.29	95.42
17	9.0 µg/ml	94.36	95.66



Graph 3: Graphical represent of Compound **(III)** with Dose of Streptomycin Efficiency

IV. CONCLUSION

All pyrazole compounds is very effective and capable to reduce problem and side effects of gestro, severe neurotoxicity, peripheral nevlopath, central nervous system, ototoxosity, Hepnotoxicity etc. Therefore these compounds are more effective than other because of its basic compounds pyrazole.

REFERENCES

1. World Health Organization, treatment of tuberculosis Guidelines, 4th edition, World Health Organization, (2010).
2. Ethambutol, Chemical Entities of Biological Interest European Bioinfomatics Institute, UK (2010), 18 August Main, Retrieved April 26, (2012).
3. Yendapally R, and Lee R. E., Bioorg Med. Chem. Lett., 18, 1607-1611 (2008).
4. Bernstein J., Lott W. A, Steinberg B. A. and Yale H. L., Am. Rev. Tuberc, 65, 357, Pharmacotherapy, 21, 1037-1045 (2001).
5. Sycheva T. P., Pavlova T. N. and Shchukina M. N, Pharm. Chem. J., 6, 696-698 (1972).
6. Fox, H. H. Science 116(1952), 129-134. (b) Spaia S., Magoula I, Tsapas G. Vayonas G, Perit. Dial. Int, 20, 47-52 (2000).
7. Yeager R.L., Munroe W. G. C. and Dessau F.I, Am. Rev. Tuberc., 65, 523-546 (1952).
8. Kushner S, Dalalian H., Sanjurjo J. L., Bach F. L., Safir S. R., Smith V. K, William Jr J. H., Jr. J. Am. Chem. Soc. 74, 3617-3621, (1952).
9. Steele, M. A. and Des Prez, R. M. Chest, 94, 845-850, (1988).
10. Hofmann AF. Gut, 51(5), 756-757 (2002).
11. Sensi P., Rev. Infect. Dis., 5, S402-S406, (1983)
12. Hammam E., Beltagi A. M., Ghoneim M. M. and J. Microchem 77, 53-62 (2004).
13. Singh B., Mitchison D. A., Br. Med. J., 1, 130-132 (1954).
14. Zhu M., Burman W. J., Jaresko G. S., Berning S. E., Jelliffe R. W., Peloquin C. A, Pharmacotheraphy, 21, 1037-1045(2001).
15. M. D. Iseman, N. Engl. J. Med., 329, 784-790 (1993).
16. Veronique Dartois, Clifton E Barry, Curr. Clinical Pharmacology, 5, 96-114 (2010).
17. Onyebujoh P., Zumla A., Ribeiro I., Rustomjee R., Mwaba P., Gomes M., Grange J. M, Bull. World Health Organization, 83, 857-865 (2005).
18. World Health Organization, the Five Elements of DOTS, WHO, (2007).
19. Anand N., Ramakrishna K. K., Gupt G., Chaturvedi M. P., Singh V., Srivastava S., Sharma K. K. Rai P., Ramachandran N., Dwivedi R., Gupta A.. K. Kumar, V., Pandey B., Shukla S., Pandey P. K., Lal S. K. and Tripathi R. P. J., ACS Med. Chem. Lett., 4, 958-963 (2013).
20. Trivedi A., Dodiya D., Surani J., Jarasania S., Mathukiya H., Ravat N. and Shah V., Arch. Pharm. Chem. Life Sci., 341, 4335-439, (2008).
21. Wang H., Li L., Lin W., Xu P., Huang Z. and Shi D., "An Efficient Synthesis of Pyrrolo [2, 3, 4-kl] acridin-1-one Derivatives Catalyzed by L-proline", 14(17), 4598-4601, (2012).
22. Jaime R. U., Jones D., Ashkin D., Elena S. H., Bernstein D., Anthony P. A. and Arthur E. P., "Anti-tuberculosis Drug-Induced Hepatotoxicity", J. Am. of Resp. and Critical Care Medicine, 157(6), 1871-1876, (1988).
23. Ellard G. A., Humphies M. J. and Allen B. W., "Cerebrospinal Fluid Drug Concentrations and the Treatment of Tuberculous Meningitis", American Review of Respiratory Disease, 148(3), 650-655, (1993).
24. Koul A, Arnoult E, Lounis N., Guillemont J. and Andries K., "The challenge of new drug discovery for tuberculosis", 469, 4823-4890 (2011).
25. Sahu S. K., Banerjee M., Samantray A., Behera C. and Azam M. A., "Tropical", Journal of Pharmaceutical Res., 7(2), 961-968, (2008).
26. Mishra P., Saxena A., Keshri M., and Saxena V., "Derivatives, IOSR Synthesis, Characterization and anti-inflammatory activity of crinolines (pyrazole)", Journal of pharmacy and biological sciences 2, 77-82, (2015).
27. Sahu S. K., Banerjee M, Samantray A, Behera C, Azam M. A., "Tropical", Journal of Pharmaceutical Res., 7, 961-968 (2008).
28. Shoman M. E., Mohamed A. A., Omar A. M, Hassan F. H., Morsy M. and A. Eur. J. Med Chem, 44, 3068–3076, (2009).
29. Chimenti F, Bizzarri B, Manna F, Bolasco A, Secci D, Chimenti P. Bioorg Med Chem.Lett., 15,603–607, (2005).
30. Moged A., Berghot E., Moawad B., Eur J Pharm Sci, 20, 173–179, (2003).
31. Sherif A. F. and Rostom, "Poly substituted pyrazoles", Bioorg. Med. Chem. 2767–2776, (2010).
32. Kalluraya. B, Lingappa B, Rai N.S., "Synthesis & antimicrobial activity studies of some novel pyrazolones carrying pyrimidine moiety", Indian J. Hetero. Chem. 17, 67-70, (2008).
33. Gaiker R.B, Gadhave A.G, Karale B.K., "Synthesis of some biologically active pyrazolones", Indian J. Heter. Chem., 19, 325-328(2010).