Synthesis and In-vitro Antifungal Evaluation of 5- Pyrazolones

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Supplementary Material

Experimental: All chemicals and solvents, reagents used in the present study were of analytical grade and solvents were used after distillation. All the melting points of the synthesized compounds were determined by open capillary and are uncorrected. The purity of the compounds was checked using precoated TLC plates (MERCK) using chloroform: ethyl acetate (8:2) solvent system. The developed chromatographic plates were visualized under UV at 254nm. IR spectra were recorded using KBr on Perkin Elmer spectrophotometer. $^1$HNMR and $^{13}$CNMR spectra in CDCl$_3$ on a BRUKER FT-NMR instrument using TMS as internal standard and chemical shift values were expressed in ppm. Elemental analysis (CHN) was performed on Elementarvario MICRO cube CHN analyser.

General Procedure for the Synthesis of Thiosemicarbazide (1a-g)

N-(substituted phenyl) thiosemicarbazide has been synthesized in two steps. N-(substituted phenyl) isothiocyanate has been synthesized by the reaction of substituted aniline dissolved in ethanol (30mL) in presence of aqueous ammonia solution, carbondisulphide and mixture was continuously stirred at 0-5°C after 25 min ammonium (substitutedphenyl) carbamodithioate have been obtained. A solution of lead nitrate (90 gm dissolved in 200 mL water) was added in resulting solution and reaction mixture was continuously stirred till the lead sulphide precipitated out. The reaction mixture was finally distilled by steam distillation process. The white shining crystals has been separated out from the distillate and dried over anhydrous calcium chloride. It was purified by recrystallization with diethyl ether. Now the solution of isothiocyanatobenzene (0.1M) in ethanol was taken in a round bottom flask. The solution of hydrazine hydrate (0.1 M) in ethanol was added to it at once, followed by continuous shaking. An exothermic reaction accompanied by vigorous effervescences was observed. The Contents of the Flask were refluxed on a water bath for 4-5 hours, resulting in the formation of a white precipitate of phenyl thiosemicarbazide, which was filtered and washed repeatedly with ethanol. The product was found to be soluble in dioxane, dimethylsulphoxide and dimethylformamide.

General Procedure for the Synthesis of 4- Chloro -3- Methyl -N-(Substituted Phenyl)-5- Oxo-4, 5-Dihydro-1H-Pyrazole-1-Carbothioamide (3a-g)

Take intimate mixture of phenyl thiosemicarbazide (0.01 mole, 1.67 gm), ethyl-2-chloro acetoacetate (0.01 mole, 1.28 mL) and dimethyl formamide (DMF) 25 mL were taken in a round bottom flask fitted with air condenser and refluxed for 10 hrs. at 80-90°C. Now mixture was melted and obtained transparent colour. The progress of the reaction was checked by TLC. Refluxing was continued till the reaction was completed. After completion of reaction mixture was allowed to stand overnight, next day excess of solvent was distilled off and the resultant residue was poured on crushed ice with few drops of H$_2$SO$_4$. The solid precipitated were filtered and recrystallized with ethanol. Yield= 70%, M.P. = 145°C.
Supplementary Fig. (1).

Supplementary Fig. (2).
Antifungal activity diagram

(A) inoculated agar plate with discs  (B) Uninoculated agar plate:

(C) inoculated agar plate with discs  (D) Agar Plate, Showing zone of inhibition

Supplementary Fig. (3).

Supplementary Fig. (4).