International Journal of Theoretical & Applied Sciences, Special Issue-NCRTAST 8(1): 41-44(2016)

ISSN No. (Print): 0975-1718
ISSN No. (Online): 2249-3247

Antifungal and Anti Bacterial Activity of Neoteric Subtituted Thiocarbamide

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(Received 11 April, 2016 Accepted 20 May, 2016)
(Published by Research Trend, Website: www.researchtrend.net)

ABSTRACT: A series of substituted thiocarbamide derivatives were synthesized by condensation of substituted phenol and benzaldeyde with compound containing active hydrogen atom like thiocarbamide. The synthesized compounds were confirmed by melting point and TLC. The structure of synthesized compounds was established by elemental analysis and various analytical techniques such as IR, 1HNMR and MASS spectral studies. All the newly synthesized compounds were evaluated for their antibacterial and anti fungal activities.

Keywords: Resorcinol, Thiourea, Betti Base, Antimicrobial.

I. INTRODUCTION

UREA is the first organic compound that was synthesized in lab in 1928, which became the important synthesis step in the history of synthetically organic chemistry and played important physiological and biological roles in animal kingdom [1]. Thiourea is the analogue compound to urea with Replacement of oxygen atom in urea by sulphur atom, also thiourea have a considerably wide range of applications. The properties of urea and thiourea differ significantly because of the difference in electronegativity between sulfur and oxygen [2].

Urea and thiourea are important functional groups in numerous natural products and drug intermediates, and are used as neutral receptor for various anions (anion complexation) [3-4], and building blocks for various heterocycles. Urea and thiourea derivatives possess many promising biological activities, such as antimicrobial [5], antioxidant [6], anti tubercular [7], anti-HIV [8-9] and antitumor [1] activity, while urea derivatives exhibit anti-inflammatory [10], antimalarial, antidiabetic and anticonvulsant activities [10,12,13-14].

Thiourea and its derivatives are used as corrosion inhibitors in industrial equipment such as boilers [15]. It has various agricultural [16] and analytical applications which include applications in rubber industries as accelerators [17], in photography as fixing agents and to remove stains from negatives [18-19]. Thiourea, which is the simplest and one of the most reactive sulfur compounds, can be oxidized by a wide variety of oxidizing agents. The reaction pathways and the final products of the oxidation reaction depend on the reagents used and condition of the reaction mixtures. The oxidation products may be urea, disulfide, and, in some cases, it may undergo either oxidative cyclization or degradation [20]. Preparation of wet strength paper from filter paper with NaOH-Urea-Thiourea aqueous solution is also done these days [21].

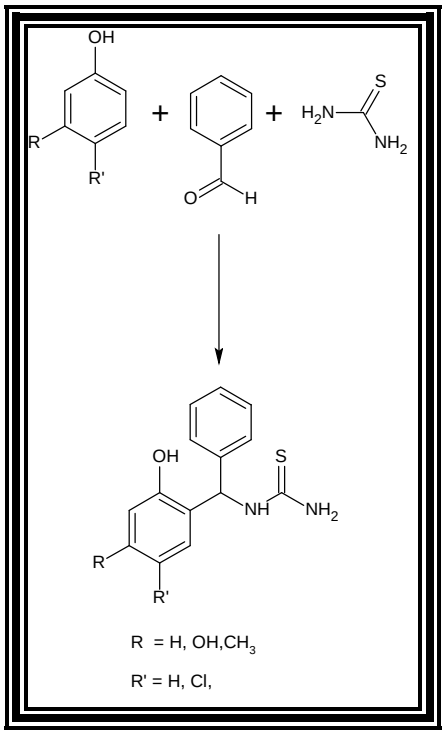
In the present paper, we report the synthesis, characterization, and antimicrobial studies of some neoteric substituted thiocarbamide compounds. The structure of synthesized compounds were assigned based on Elemental analysis, I.R. 1H-NMR and Mass spectral data. The antimicrobial activity was assayed by using the disc diffusion method by measuring the zone of inhibition in mm. All the compounds were screened in vitro for their antimicrobial activities against gram negative bacterial strains such as *E. coli* and fungi *Aspergillus flavus* at three different concentrations. Standard drugs like Ciprofloxacin, Ketoconazole were used for comparison purpose.

II. EXPERIMENTAL SECTION

Sigma-Aldrich and Merck chemicals were used as such without further purification. Solvents used for spectroscopic and other physical studies were reagent grade and were further purified by literature methods. Melting points were taken in open capillary tubes are uncorrected.

IR spectra were obtained in on a Bruker spectrophotometer and expressed in wave numbers (cm^{-1}). 1H- NMR spectra were recorded on a Bruker Avance III 500 MHz spectrometer operating at 500 MHz for $1H^{-}$. The 1H-chemical shifts were expressed in ppm with reference to tetramethylsilane. Elemental analyses were performed at IISER Bhopal.

General procedure for synthesis of compounds: To a mixture of substituted phenol, benzaldehyde and ehanolic solution of thiocarbamide were added slowly on hot water bath maintained at 90°C with constant stirring for 1 hr. the solid separated on cooling of reaction mixture was recrystallise by ethanol [22].



Scheme

Analytical and Spectral data of synthesized compounds

1-[(5-chloro-2-hydroxyphenyl) (phenyl) methyl] thiourea (compound- I):

Color: white, Yield: 53.53%, M.P: 164^{0}C, Elemental Analysis: C: 57.43%, H: 4.47%, N: 9.56%, O: 5.47%, S: 10.95%, Cl: 12.11%, Molecular Formula: $C_{14}H_{13}ClN_2OS$

IR ($\nu_{max,}$ cm^{-1}): 3757.22 (Phenol, O-H streching), 3445.87 (primary amine, N-H streching), 3346.66 (Secondary amine, N-H sterching), 1135.89 (primary amine, C-N streching), 1210.05 (Secondary amine, C-N sterching), 1082.20 (Phenol, C-O), 680.27 (Thiourea, C=S). ^{1}HNMR ($CDCl_3$) δ: 9.02 (s, H, OH), 3.21 (s, 2H, NH_2), 1.82 (d, H, NH), 6.52 (H, CH). MS:m/z: 290.78.

1-[(2-hydroxy-4-methylphenyl) (phenyl) methyl] thiourea (compound- II):

Color: Reddish brown, Yield: 62.25%, M.P: 170^{0}C, Elemental Analysis: C: 66.15%, H: 5.92%, N: 10.29%, O: 5.87%, S: 11.77%, Molecular Formula: $C_{15}H_{16}N_2OS$

IR ($\nu_{max,}$ cm^{-1}): 3746.81 (Phenol, O-H streching), 3370.19 (primary amine, N-H streching), 3250.53 (Secondary amine, N-H sterching), 1158.88 (primary amine, C-N streching), 1201.05 (Secondary amine, C-N sterching), 1076.08 (Phenol, C-O), 624.96 (Thiourea, C=S). ^{1}HNMR ($CDCl_3$) δ: 8.63 (s, H, OH), 2.34 (s, 2H, NH_2), 1.32 (d, H, NH), 7.01 (H, CH). MS:m/z: 272.02.

1-[(2, 5-dihydroxyphenyl) (phenyl) methyl] thiourea (compound- III):

Color: white, Yield: 53.53%, M.P: 144^{0}C, Elemental Analysis: C: 61.29%, H: 5.14%, N: 10.21 %, O: 11.66%, S: 11.69%, Molecular Formula: $C_{14}H_{14}N_2O_2S$

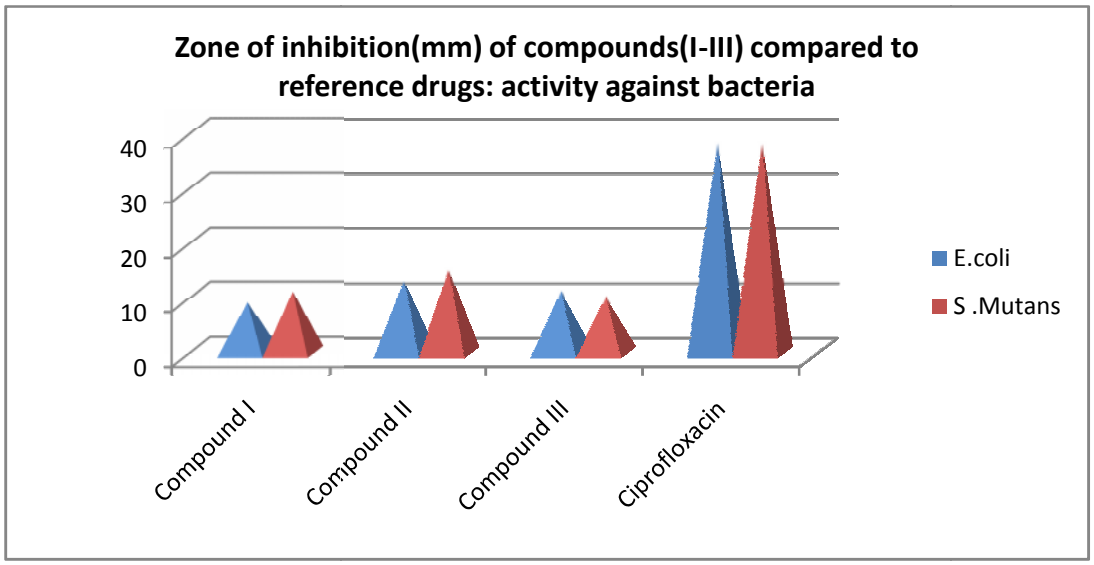
IR ($\nu_{max,}$ cm^{-1}): 3732.72 (Phenol, O-H streching), 3326.59 (primary amine, N-H streching), 3154.82 (Secondary amine, N-H sterching), 1167.26 (primary amine, C-N streching), 1192.36 (Secondary amine, C-N sterching), 1084.29 (Phenol, C-O), 689.70 (Thiourea, C=S). ^{1}HNMR ($CDCl_3$) δ: 9.42 (s, H, OH), 2.57 (s, 2H, NH_2), 1.67 (d, H, NH), 6.32 (H, CH). MS:m/z: 274.22.

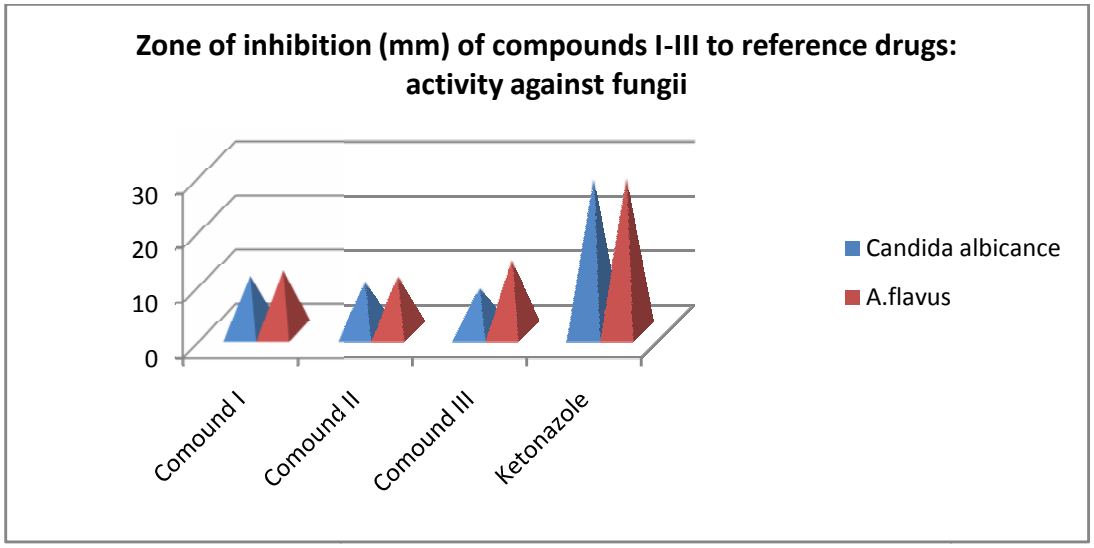
Antimicrobial activity: The synthesized compounds (I-III) were screened for antibacterial and antifungal activities against certain pathogenic bacteria by disc diffusion method[23-24] at different concentrations such as 25µg/ml, 50µg/ml, 100 µg/ml using E.coli, S mutans and antifungal activity against Candida albicance and A.flavus. The zone of inhibition was measured in mm and the activity was compared with the standard drug ciprofloxacin for bacteria and ketonazole for fungi.

III. RESULT AND DISCUSSION

The synthesis of 1-[(5-chloro-2-hydroxyphenyl) (phenyl) methyl] thiourea, 1-[(2-hydroxy-4-methylphenyl) (phenyl) methyl] thiourea and 1-[(2, 5-dihydroxyphenyl) (phenyl) methyl] thiourea was carried out in one step, by the condensation of substituted phenol, aromatic aldehyde with thiocarbamide (scheme).

The formulas of the selected compounds were confirmed by the elemental analysis and their structures were determined by IR, 1 H-NMR, and mass spectral data.





A. Antibacterial Activity

It has been observed from the microbiological data that all compounds (I-III) were found to be mild to moderately active against bacterial strains. However the maximum activity was observed in compound III against *S.mutans*. The mild activity was observed in compounds I and III against *S.mutans.* However, the compounds I- III were shown mild activity against *E. coli*.

B. Antifungal Activity

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by all the compounds against *Candida albicance* and exhibit mild to moderate antifungal activity against *A. flavus*. The antibacterial activity was compared with standard drug viz. Ciprofloxacin and antifungal activity was compared with standard drug viz. Ketonazole.

IV. CONCLUSION

The present study leads to a convenient synthetic method for the synthesis of neoteric derivatives of thiocarbamide. These were characterized by IR, NMR, Mass spectrometry study and elemental analyses. The substrates were obtained in good yield in basic conditions which show mild antibacterial and antifungal activity. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products.

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