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$Mg(OMe)_2$ as a versatile catalyst for one-pot synthesis of 6-aryl-5-cyano-2-(oxo / thio) uracil derivatives and their antimicrobial evaluations

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Abstract: A series of substituted 6-aryl 5-cyano 2-uracil and 6-aryl 5-cyano 2-thiouracils (1a-1l) were achieved by the reaction of various aldehydes, ureas, thioureas and ethylcyanoacetate using Magnesium methoxide as a versatile catalyst. All compounds were screened for antibacterial and antifungal activities against 6 strains *Bacillus substilis*, *Streptococcus sp*, *Pseudomas aeruginosa*, *Klebsiella pneumoniae*, *Candida albicans*, *Aspergillus niger* microorganisms using Muller-Hinton broth method. Some of the prepared compounds exhibited promising activities when compared to the standard Linezolid & Amphotercine-B.

Keywords: Magnesium methoxide; oxo/thio uracil derivatives; antimicrobial activity; methodology.

1. Introduction

Pyrimidine and its derivatives play an important role in several biological processes and have considerable chemical and pharmacological importance; particularly pyrimidine ring can be found in nucleoside antibiotics, antibacterial cardio-vascular as well agro chemical and veteran products.[1-7] One of the possible reasons for the growing interest in Pyrimidine heterocyclic is that, it comprises the base for thiamine, uracil and cytosine nitrogen bases which are building blocks of the nucleic acids. Among these bases, uracil and its analogues gained much importance in medicinal chemistry. Derivatives of uracil are well known for their enzyme inhibition and antiretroviral properties.[8-13] It is well known fact that the C5 substituted derivatives possesses excellent biological activities for example 5-Fluorouracil is an important anticancer agent widely used in oncology.[14]

Some improved procedures were reported for this transformation of with catalysts, such as sodium ethoxide[15], in addition under microwave irradiations with potassium carbonate[16,17] and acetic acid. 5-Cyano-2-thiouracils are readily available by a number of methods[18-21], synthesis of these 6-substituted analogues (R.aryl, heteroaryl or tert-alkyl) involves condensation of an aldehyde with ethyl cyanoacetate and thioureas in the presence of potassium carbonate.[18,19] The product is isolated by acidification followed by crystallization of the resultant precipitate.The above mentioned methods have certain limitations such as costly catalysts, drastic reaction conditions, need excess of catalyst and also require extended reactions times etc. Hence the development of new reagents with great efficiency, time saving and more convenient and eco friendly approaches is of interest. Catalysts are derived from heavy or rare metals and they have several draw backs for large scale applications. In

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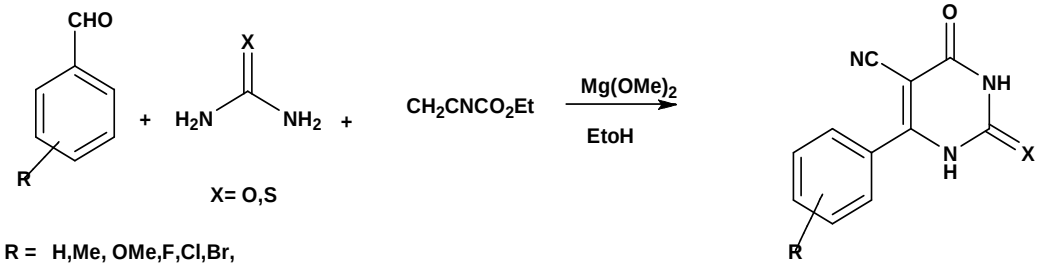
contrast, magnesium is one of the most abundant metals on earth and consequently one of the most inexpensive and environmental friendly. Magnesium methoxide is a cheap and easily prepared by using magnesium hydroxide and methanol under reflux conditions. Hence it is proposed to synthesize the uracil/thiouracil derivatives employing magnesium methoxide as a versatile catalyst. The synthetic scheme is presented in scheme 1.

2. Results and discussion



Scheme 1. The synthesis of 6-aryl 5-cyano 2-uracil and 6-aryl 5-cyano 2-thiouracil derivatives **1a-1l**

The synthesis of 6-aryl 5-cyano 2-uracil and 6-aryl 5-cyano 2-thiouracil derivatives **1a-1l** (Scheme 1) were accomplished by condensing various substituted aromatic aldehydes, urea, thiourea and ethylcyanoacetate in presence of magnesium methoxide. Initially it was proposed to optimise the suitable solvent system to proceed the reaction. The reaction was monitored in different solvents like acetonitrile, dichloromethane, methanol, ethanol and isopropyl alcohol. The results were tabulated in Table 1. From the table, it was clearly evident that ethanol was the best solvent to proceed this reaction. After attaining the suitable solvent system, we focused our interest towards the percentage of catalyst required for the reaction. We checked the reaction in 5 mmol, 10 mmol, 15 mmol & 20 mmol respectively. These results were listed in Table 2. From Table 2, mole ratio of the catalyst had significant effect on the reaction. The best ratio was 15 mmol. When we used less than 15 mmol of the catalyst, the reaction requires large reaction times and the yields were poor. Whereas in the case of 20 mmol of the catalyst, the reaction requires the same reaction time as in the case of 15 mmol but some by-products were observed. Hence we continued the reaction using 15 mmol of Mg $(OMe)_2$.

Table 1. Effect of different solvents on the reaction

S.No	Solvent	Yield (%)*
1	CH_3CN	40
2	CH_2Cl_2	32
3	CH_3OH	54
4	C_2H_5OH	80
5	IPA	60

*yields are compared to isolated products

Table 2. Optimization of catalyst percentage

S.No	% of $Mg(OMe)_2$	Reaction time (hr)	Yield (%)
1	5 mmol	18	20
2	10 mmol	12	38
3	15 mmol	5	80
4	20 mmol	5	48[a]

[a]The product formed along with by-product

After completion of reaction all the products were isolated and duly characterized by advance spectroscopy methods viz) IR, NMR & MASS. The substrate scope of the reaction was reevaluated by using a variety of structurally diverse aldehydes and the results are tabulated in **Table-3**. The presence of electron donating groups on the phenyl ring requires high reaction times and the yields are moderate. When the presence of electron withdrawing groups on the phenyl ring, less reaction times noted and yields are good. Short reaction times were observed, which is more economy in terms of enhanced reaction rates, improved yields and high selectivity are observed than the earlier reported methods. The results are presented in Table 3.

Microbial studies

The results of antimicrobial activity revealed that most of the synthesized compounds showed good activities when compared to standard linezolid against *Bacillus subtilis*-MTCC 2274, *Streptococus* SP-MTCC 1929, *Pseudomas aeruginosa*-MTCC 1688, *Klebsiella pneumoniae*-MTCC109, *Candida albicans*-MTCC3017, *Aspergillus niger*-MTCC281.In addition, it was found that **1j** showed maximum activity against *Pseudomas aeruginosa* and this may be due to presence of fluoro group at 4th position on aromatic ring. But **1c** did not show any activity against *Bacillus substilis.* Surprisingly, this compound showed very good activity against *Pseudomas aeruginosa*-MTCC 1688, *Klebsiella pneumonia*-MTCC109, *Candida albicans*-MTCC3017,*Aspergillus niger*-MTCC281. Moreover, it was also observed that the compounds with halogens also showed remarkable activity. However, the uracil derivatives were found to be more potent on all the bacterial strains. Compounds **(1a-1l)** also showed significant antifungal activity at minimum concentration levels when compared with standard. Compounds **1d, 1g, 1h** and **1l** showed maximal anti bacterial activity. The results clearly revealed the contribution of electron withdrawing groups and electron releasing groups on the aromatic ring in enhancing the antibacterial and antifungal activity. The results are presented **in the Graphs**. The main advantage of using Muller -Hinton broth method is the time saving, media saving advanced method.

Experimental

General Procedure: A mixture of 10 mmol of ethyl cyanoacetate, 10 mmol of substituted aromatic aldehydes, 10mmol of urea or thiourea and catalytic amount (15 mmol) of magnesium methoxide in 50 ml dry ethanol were refluxed. The completion of the reaction was monitored by thin layer chromatography using hexane: ethyl acetate as eluent.After completion of the reaction, the reaction mixture was cooled and solvent was removed under reduced pressure. The solid residue was washed with water and dried in vacuum. Then the solid compound was subjected to filter column to remove methoxide impurities and recrystallised in ethanol to afford the pure compounds.

All the compounds were characterised by principle IR absorption bands at 2201-2226 cm^{-1} (CN) and 1629-1642 cm^{-1} (CO). The structures of the compounds were confirmed by spectral analysis (IR, ^{1}H and ^{13}C NMR). Melting points were determined by open capillary tubes and are uncorrected. FTIR spectra of the powdered compounds were recorded using KBr pellets on a Shimadzu FTIR spectrometer using "Diffuse Reflectance Attachment" and are reported in cm^{-1}.The ^{1}H NMR and the ^{13}C NMR spectra were obtained at 400 MHz and 100 MHz, respectively, by using DMSO(d_6) and TMS as an internal reference..^{1}H NMR spectras were recorded on a Bruker (400 MHz FT NMR) spectrophotometer (chemical shift represented in δ ppm).In ^{1}H NMR the proton present on 2nd nitrogen atom observed at δ 10-12, proton on 1st nitrogen atom is not visible in some of the compounds due to D_2O Dutereable exchange. Mass spectra were recorded on LC–MS.

(1a) 4-Oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile: mp: 240 ^{0}C; IR (KBr): 3366,3144,3031,2204,1633,1514,1399 cm^{-1}; ^{1}H NMR (DMSO-d_6 400 MHz)δ 7.40-8.00 (m, 5H, Ar-H),11.50 (bs, exchangeable with D_2O, 2NH);^{13} C NMR (DMSO-d_6 100-MHz) δ 85.0, 118.9, 127.9, 128.1, 129.1, 137.7, 162.8, 167.1, 183.1; LC Mass *m/z:* 229(M^+, 100) .

(1b) 2, 4-Dioxo-6-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carbonitrile: mp: 299 ^{0}C; IR(KBr): 3350, 3132, 3030, 2220, 1630, 1590, 1320 cm^{-1}; ^{1}H NMR (DMSO-d_6 400 MHz)δ 7.20-8.00 (m, 5H, Ar-H), 11.40 (s, 1H, NH); ^{13}C NMR (DMSO-d_6 100-MHZ)δ 82.0, 119.1, 127.8, 128.1, 129.3, 135.1, 163.3, 167.5, 171.1.; LC Mass *m/z:*213 (M^+, 100) .

(1c) 6-(4-chlorophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile: mp:285 ^{0}C; IR (KBr):3357,3024,2939,2208,1637,1510,1410,897 cm^{-1}; ^{1}H NMR (DMSO-d_6 400 MHz) δ7.50 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 11.60 (s,1H,NH);^{13}C NMR (DMSO- d_6 100 MHz) δ 84.9, 118.0, 128.0, 130.0, 134.7, 136.5, 162.3, 165.9,1 83.1.; LC Mass *m/z:* 263(M^+, 100).

(1d) 6-(4-Chlorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile: mp: 238 ^{0}C; IR (KBr):3441, 3124, 2215, 1647, 1632, 1405, 830 cm^{-1}; ^{1}H NMR (DMSO-d_6 400 MHz)δ 7.60-8.10 (m, 4H, Ar-H),11.60 (s, 1H, NH),^{13}CNMR (DMSO-$d_6$100-MHz)δ 85.1, 117.3, 128.0, 130.0, 136.2, 136.4, 162, 162.8,165.4; LC Mass *m/z:* 247.

(1e) 6-(4-methylphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile: mp:260 ^{0}C; IR (KBr): 3416, 3329, 3154, 3060, 2214, 1644, 1511, 1124 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.00 (s, 3H,CH_3),7.20-7.50 (m, 4H, Ar-H),11.60 (s,1H,NH), ^{13} C NMR (DMSO-d_6 100-MHz) δ 20.9, 85.0,118.0, 127.0, 128.0, 130.0, 137, 162.8, 167.4, 183.0; LC Mass *m/z:*243.

(*1f) 6-(4-methylphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile:* m.p: 218 ^{0}C; IR (KBr): 3340, 3129, 2214, 1637, 1629, 1255 cm^{-1}; ^{1}H NMR (DMSO-d_6 400 MHz)δ 3.5(s, 3H,OCH_3), 3.89 (s,1H,NH), 7.2-7.4 (m, 4H, Ar-H), 10.50 (s, 1H, NH), ^{13} C NMR (DMSO-d_6, 100 MHz) δ 20.9, 80.2, 118.7, 125.1, 127.8, 128.5, 130, 136.6, 156.3, 164.7, 169.6.; LC Mass *m/z:*227.

(1g) 6-(4-methoxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile: mp : 230 ^{0}C; IR (KBr):3357, 3124, 3015, 2206, 1632, 1511, 1252 cm^{-1}; ^{1}H NMR (DMSO-d_6 400 MHz) δ 3.50 (s, 3H,OCH_3), 7.10-7.90 (m, 4H, Ar-H), 11.50(s, 1H, NH), ^{13} C NMR (DMSO-d_6 100-MHz) δ 55.9, 84.7, 119, 128.2, 128.5, 134.8, 139.8, 162.6, 167.1, 182.7.;. LC Mass *m/z:*259.

(1h) 6-(4-Methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile: mp: 223 ^{0}C; IR (KBr):3348, 3240, 2220, 1640, 1620, 1400, 800 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.6 (s, 3H,OCH_3), 4.41(s, 1H, NH),7.2-7.9(m,4H, Ar-H),11.2(s, 1H, NH); ^{13} C NMR (DMSO-d6 100-MHz)δ55.8, 83.5, 116.8, 118.7, 128.9, 133.1, 148.0, 152.9, 162.7, 165.7.; LC Mass *m/z:*243 (M^+, 100).

(1i)6-(4-fluorophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile: m.p.:255 ^{0}C; IR (KBr):3345, 3131, 2218, 1640, 1519, 1120 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.30 (d, *J*=8 Hz, 2H), 7.80 (d , *J*=8 Hz, 2H) 11.60 (s, 1H, NH); ^{13} C NMR (DMSO- d_6 100 -MHz) δ 84.8, 114.7, 118.8, 130.5, 134.0, 161.8, 162.0, 164.0, 166.0, 183.0; LC Mass *m/z:*247.

(1j) 6-(4-fluorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile: mp : 225 ^{0}C; IR cm^{-1}(KBr): 3359, 3210, 2221, 1648,1634, 1127; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.40 (s,1H, NH), 7.20-7.90 (m, 4H, Ar-H), 10.10(s, 1H, NH), ^{13} C NMR (DMSO-d_6 100-MHz)δ 78.2, 114.5, 119.9, 124.5,130.3, 135.1, 158.4, 165.7, 170.8.; LC Mass *m/z:* 231.

(1k) 6-(4-bromophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile: mp : 240 ^{0}C; IR (KBr):3347, 3218, 2201, 1642, 1529, 1120 cm^{-1}; ^{1}H NMR (DMSO-d_6 400 MHz)δ 7.70 (m,4H, Ar-H),11.60 (s, 1H, NH), ^{13} C NMR (DMSO-d_6 100-MHz) δ 84.9, 118.9, 123.4, 130.0, 131.0, 136.9, 163.2, 166.0, 183.6; LC Mass *m/z:*308.

(1l) 6-(4-bromophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile: m.p. : 230 ^{0}C; IR (KBr): 3338, 3124, 2214, 1630, 1629, 1128 cm^{-1} ; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.5(s,1H, NH), 7.20 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 10.20 (s, 1H, NH), ^{13} C NMR (DMSO-d_6,100-MHz)δ 78.7, 119.7, 123.1, 131.1, 137.9, 162.8, 165.8, 166.1, 171.0; LC Mass *m/z:*292.

Antimicrobial activity

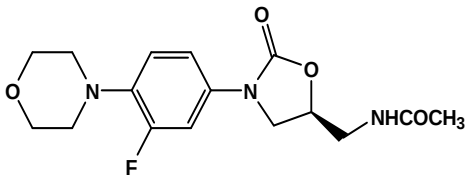


Figure 1. Linezolid

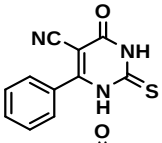
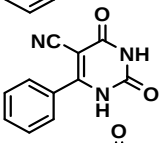
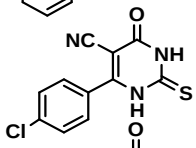
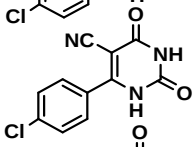
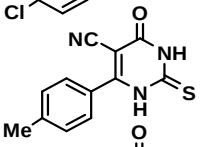
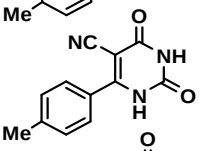
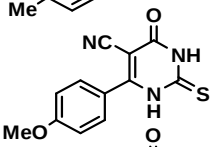
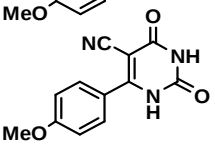
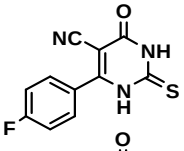
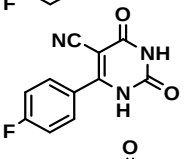
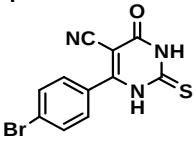
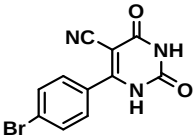
Mueller-Hinton broth medium was employed to study the preliminary antibacterial activity of **(1a-1l)** against *Bacillus subtilis*-MTCC 2274, *Streptococus* SP-MTCC 1929, *Pseudomas aeruginosa*-MTCC1688,*Klebsiella pneumonia*-MTCC109,*Candida albicans*- MTCC 3017,*Aspergillus niger*-MTCC 281. The bacterial /fungal strains on nutrient agar at 37 ^{0}C for 24 hr were grown and after 24hr incubation, bacterial cells are suspended in normal saline containing Tween 20 at 0.05% at a concentration approximately 1.0-2.0 to 10-7 cells/ml. Each test compound (5 mg) was dissolved in 1 ml of dimethyl sulfoxide, Linezolid & Amphotercine-B were employed as reference standard to compare the results.

In 96 well cell culture plates (maximum volume of well is 300µL), added 180µL of Muller-Hinton broth to each Well.100µL of Serially diluted culture was added in to each well and Incubate at 37 ^{0}C for 24 hr. After 24 hrs incubation, readings at 620 nm by using Elisa reader .The pH of all the test solutions and control was maintained at 6-7 by using buffer .All the compounds were tested at a concentration of 0.05 ml (50 µg) and 0.1 ml (100 µg) level and DMSO as control did not show any inhibition. 96 well cellulose coated plate Muller Hinton broth microbial medium was employed to study the preliminary antifungal activity of **(1a-1l)** against *Aspergillus niger* and *Candida albicans* MTCC. The MTCC medium was purchased from MTCC Chandigarh, India. Preparation of nutrient broth, subculture, base layer medium and MTCC medium was done as per the standard procedure.[22] The pH of the all the test solutions and control was maintained at 6-7 by using Buffer.

Conclusion

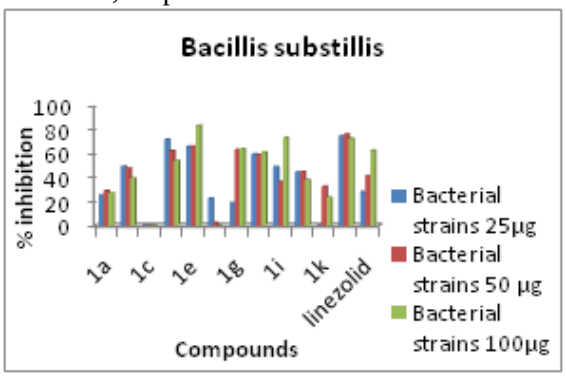
In summary, we have demonstrated an efficient and one pot method towards the expeditious synthesis of uracil and thiouracil derivatives under reflux conditions. They showed potentially anti-bacterial and anti fungal agents. Present methodology offers very attractive features such as reduced reaction times, higher yields and environmentally benign condition. The simple procedure combined with ease of work-up and entirely reflux conditions make this method economic, environmentally benign and a waste-free chemical process for the synthesis of uracil and thiouracil derivatives of biological importance.

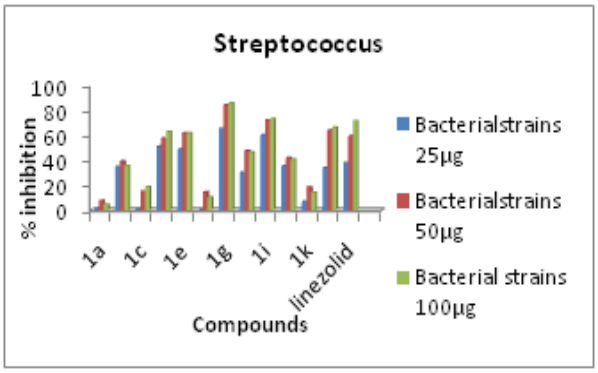
Table 3. Substrates, reaction time and product with yield of the target molecules

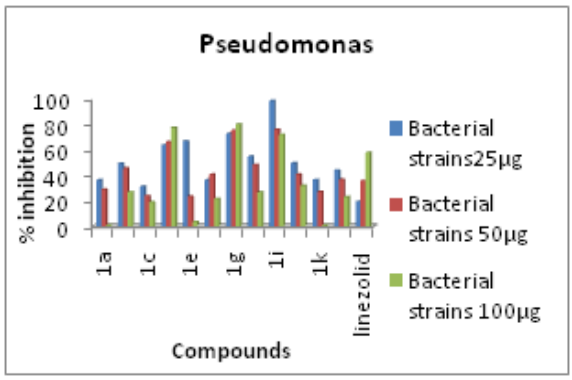
SN	R	X	PRODUCT	YIELD(%)	TIME(hrs)
1a	H	S		85	5
1b		O		84	6
1c	Cl	S		83	4.5
1d		O		83	5
1e	Me	S		75	7
1f		O		77	7.5
1g	OMe	S		76	8
1h		O		75	8.5
1i	F	S		80	6
1j		O		81	7
1k	Br	S		85	6
1l		O		86	6

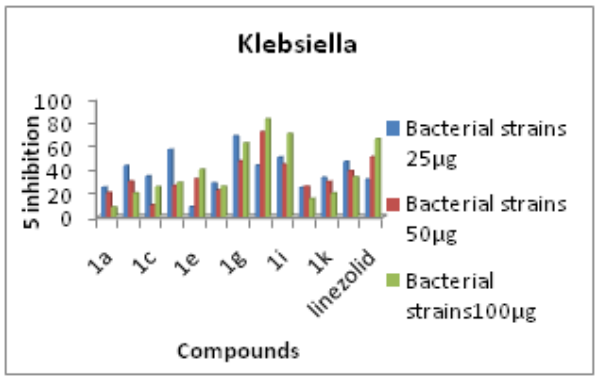
[a] Yields are compared with the isolated products after purification

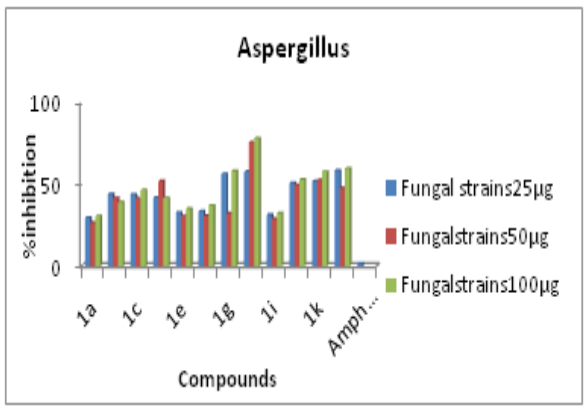
Graphs. The preliminary antimicrobial screening test for the synthesised compounds using linezolid,Amphotersin-B and DMSO as control.

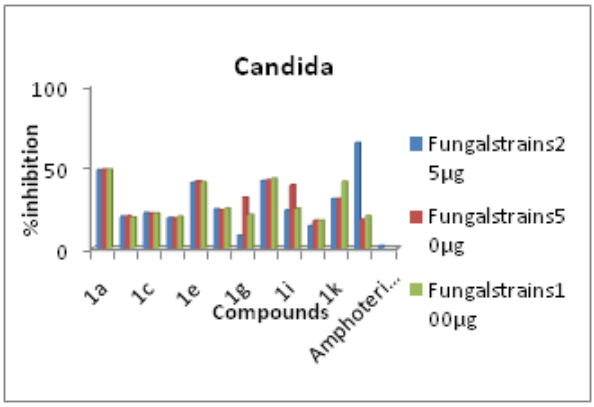












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