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Green synthesis and Biological Evaluation of Pyrimidine Derivatives

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ABSTRACT

A study was carried out on the amination of substituted-4-chloro-pyrimidine under conventional and microwave conditions in presence of bis (dibenzylideneacetone) palladium (0) ($Pd(dba)_2$) as a metal ligand catalyst and xantphos which acts as a bidentate ligand. The reaction of 2-amino-4-chloro-6-methylpyrimidine with aromatic and aliphatic amines in presence of a catalyst gives 2-Amino-6-subsituted-pyrimidine derivatives. The reactions were studied under microwave irradiation showed moderately better results when compared to conventional method. The compounds were screened for their antimicrobial activity against pathogenic strains such as S.aureus, E.coli, K. aerogenes, A. flavus and C. albicans and anthelmintic activity conducted using P. posthuma (Indian Earthworm). Among the synthesized compounds ***6a, 6c*** *&* ***6f*** *have shown significant antibacterial activity.*

Keywords: Aminopyrimidine, bis (dibenzylideneacetone) palladium (0), xantphos, antimicrobial activity, microwave irradiation

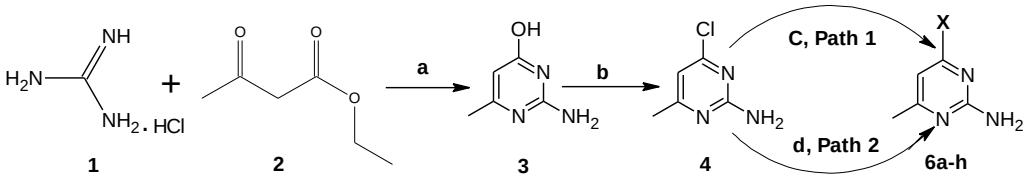
INTRODUCTION

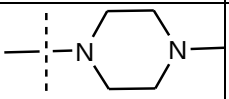
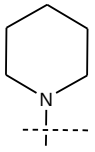
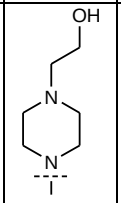
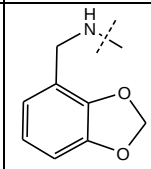
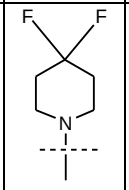
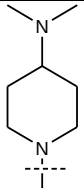
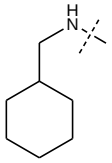
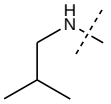
In the microwave irradiation method, direct and rapid heating in sealed tubes in many cases enables reactions to be carried out with in a fraction of time. Microwave reaction greatly reduces reaction times, increases yields and enhances purity of the product by reducing unwanted side-reactions compared to conventional heating methods [1-3]. Many heterocyclic compounds have been synthesized because of their wide range of biological activity [4-6]. Pyrimidine a six-member heterocyclic compound, contains two nitrogen atoms at positions 1 and 3 and its derivatives have shown various biological activities such as antimicrobial, antitumor, antifungal, and antileishmanial (chronic disease) activities and are also useful for the treatment of thyroid and leukemia [7]. In addition to that, aminopyrimidines are important heterocyclic compounds; many such derivatives are biologically active. Particularly, 2–aminopyrimidines have attracted a great deal of interest as analgesic agents, fungicidal, bactericidal agents [8-13]. In previous studies it has been discovered that substituted pyrimidines have antibacterial, anthelmintic, anti-inflammatory and antitumor properties also [14-17].

In view of these observations, it was therefore contemplated to replace the chloro group of pyrimidine by primary/secondary amino groups via Buchwald coupling reaction [18-23] and authors gave emphasis on *in vitro* antimicrobial and anthelmintic properties.

MATERIALS AND METHODS

Chemicals were purchased from Merck India, Spectrochem and Sigma–Aldrich, solvents and chemicals used were of LR grade. The purity of the compounds was confirmed by thin layer chromatography using precoated TLC plates and solvent systems of dichloromethane / methanol (9:1) and petroleum ether / ethyl acetate (6:4) further purification was done by column chromatography using neutral alumina. Melting points were determined in one end open capillary tubes on a liquid paraffin bath. Mass spectra, ^{1}H nuclear magnetic resonance spectra and ^{13}C nuclear magnetic resonance spectra were recorded for the compounds on Agilent mass spectrometer, Bruker model Avance II (400 MHz, ^{1}H NMR) and Bruker model Avance II (400 MHz, ^{13}C NMR) instrument, respectively. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. Elemental (C, H and N) analysis was performed on the Elementar vario MICRO cube. Synthetic procedure is route in scheme 1.



Comp Code	5a/6a	5b/6b	5c/6c	5d/6d	5e/6e	5f/6f	5g/6g	5h/6h
X								

Scheme 1

Reagents and conditions: (a) Neat reaction (b) $POCl_3$, Reflux (c) Path 1: Substituted primary and secondary amines **(5a-h)**, Xantphos, $Pd(dba)_2$, Cs_2CO_3, dry AcCN, Δ 80 ^{o}C, 10-17 h; (d) Path 2 : Substituted primary and secondary amines **(5a-h)**, Xantphos, $Pd(dba)_2$, Cs_2CO_3,dry AcCN, MW, 30-50 min.

Procedure for the preparation of 2-amino-6-methylpyrimidin-4-ol (3): A mixture of guanidine hydrochloride **(1)** and ethyl acetoacetate **(2)** was taken in round bottomed flask, contents were refluxed at 170-180 ^{o}C for 4 h [24]. Completion of the reaction was confirmed by TLC, maximum solvent was removed by vacuum, resulting red solution was cooled to 0 ^{o}C and allowed to crystallize overnight. Precipitate was filtered, washed with a mixture of methanol/toluene and dried to get compound (**3**). Yield: 50%. White solid; m.p: 298-300 ^{o}C; R_f = 0.38 (CH_2Cl_2/CH_3OH, 9:1); ^{1}H NMR (400 MHz, DMSO, δ ppm,): 11.62 (s, 1H, -OH), 6.72 (s, 2H, Ar-NH_2), 5.28 (s, 1H, Ar-H), 2.06 (s, 3H, Ar-CH_3). MS (MM – ES + APCI^{+}) (m/z): 126.1 (M+).

Procedure for the preparation of 2-amino-4-chloro-6-methylpyrimidine (4): A mixture of 2-amino-6-methylpyrimidin-4-ol **(3)** and $POCl_3$ was taken in round bottomed flask, reaction mixture was refluxed for 2 h. Reaction was monitored by TLC, contents were cooled and poured slowly on to vigorously stirred ice cold water. The red colored solution became colorless and a precipitate is formed which was filtered. Obtained precipitate was dissolved in 25 ml of sodium hydroxide, solution then cooled with ice and acidified with dilute acetic acid (10% v/v) with constant stirring. The precipitate was separated, washed with water and dried to get brownish product (4). Yield: 60%. Brown solid; m.p.: 183-186 ^{o}C; R_f = 0.48

(CH_2Cl_2/CH_3OH, 9:1); ^1H NMR (400 MHz, DMSO, δ ppm,): 6.75 (d, *J* = 2.9 Hz, 1H, Ar-H), 6.51 (s, 2H, Ar-NH_2), 2.33 (s, 3H, Ar-CH_3). MS (MM – ES + APCI$^+$) (m/z): 144.58 (M+).

General Procedure for the preparation of 2-Amino-6-subsituted-pyrimidine derivatives (6a-h) by conventional method: 2-amino-4-chloro-6-methylpyrimidine (**4)** (1.39 mmol), primary or secondary amines **(5a-h)** (2.08 mmol), Xantphos (0.055 mmol), $Pd(dba)_2$ (0.111 mmol), Cs_2CO_3 (2.78 mmol) and freshly distilled dry Acetonitrile (6 mL) were charged in round bottom flask fitted with condenser and joints sealed with teflon tape and refluxed at 85 ^{o} C for 12 h under nitrogen atmosphere for reaction to complete. Solvent was removed under vacuum; the crude mass was purified by column chromatography using neutral alumina, dichloromethane/methanol as an eluent (9:1) to yield **6a-h,** yield and time taken for the completion of reaction were given in table 1.

General Procedure for the preparation of 2-Amino-6-subsituted-pyrimidine derivatives (6a-h) by microwave irradiation method: 2-amino-4-chloro-6-methylpyrimidine **(4)** (1.39 mmol), primary or secondary amines **(5a-h)** (1.66 mmol), Xantphos (0.027 mmol), $Pd(dba)_2$ (0.055 mmol), Cs_2CO_3(2.085 mmol) and freshly distilled dry acetonitrile(4 mL) was charged in the dry microwave vial which was sealed and purged with a three cycles of vacuum / nitrogen and irradiated under microwave condition for 30 - 50 min for reaction to complete. Solvent was removed under vacuum; the crude was purified by neutral alumina column chromatography using dichloromethane / methanol as an eluent to yield **6a-h.**

Spectral interpretation of final target molecules 6a-h

4-methyl-6-(4-methylpiperazine-1-yl) pyrimidine-2-amine (6a): White solid; m.p.: 126 – 128 ^{o}C; R_f = 0.48 (CH_2Cl_2/CH_3OH, 9:1); ^1H NMR (400 MHz, DMSO, δ ppm,): δ 5.98 (s, 2H), 5.93 (s,1H), 3.49 (t, *J* = 4.8 Hz, 4H), 2.32 (t, *J* = 4.8 Hz, 4H), 2.20 (s, 3H), 2.05 (s, 3H).^{13}C NMR (400 MHz, DMSO, δ ppm): 170.2, 168.0, 166.6 ,95.5 ,57.6, 57.5, 57.3, 57.1, 38.7, 20.9 : MS (MM – ES + APCI$^+$) (m/z): 208.0 (M+).

4-methyl-6-(piperidine-1-yl) pyrimidine-2-amine (6b): White solid; m.p.: 148 – 150 ^{o}C. R_f = 0.45 (CH_2Cl_2 / CH_3OH, 9:1); ^1H NMR (400 MHz, DMSO_d_6, δ ppm): 5.87 (s, 1H), 5.83 (s, 2H), 3.49 (t, *J* = 5.6 Hz, 4H), 2.03 (s, 3H), 1.59 - 1.55 (m, 2H), 1.47-1.41 (m, 4H); ^{13}C NMR (400 MHz, DMSO, δ ppm): 165.6, 163.2, 163.1, 91.7, 44.6, 40.5, 25.6, 24.2, 24.0, 22.9 : MS (MM – ES + APCI$^+$) (m/z): 193.0(M+).

2-(4-(2-Amino-6-methylpyrimidine-4-yl) piperazin-1-yl) ethanol (6c): White solid; m.p.: 131-133 ^{o}C; R_f = 0.22 (CH_2Cl_2 / CH_3OH,9:1); ^1H NMR (400 MHz, DMSO, δ ppm): 5.98 (s, 1H), 5.92 (s, 1H), 3.55 (s, 1H), 3.52 (t, *J* = 6.4 Hz, 4H), 2.98 (t, *J* = 4.8 Hz, 2H), 2.57 (t, *J* = 5.2 Hz, 2H), 2.41 (t, *J* = 2.0 Hz, 4H), 2.03 (s, 3H); ^{13}C NMR (400 MHz, DMSO, δ ppm): 170.2, 168.0, 166.6, 95.5, 62.7, 57.9, 57.6, 56.5, 55.4, 55.2, 23.4. MS (MM – ES + APCI$^+$) (m/z): 238.0 (M+).

N4-(1, 3-benzodioxal-5-ylmethyl)-N4, 6-dimethylpyrimidine-2,4-diamine (6d): White solid; m.p.: 136–138 ^{o}C, R_f = 0.51(CH_2Cl_2 / CH_3OH, 9:1); ^1H NMR (400 MHz, DMSO, δ ppm): 6.84 - 6.67 (m, 3H), 6.16 (s, 2H), 5.96 (s, 2H), 5.86 (s, 1H), 4.62 (s,2H), 2.89 (s,3H), 2.079 (s, 3H); ^{13}C NMR (400 MHz, DMSO_d_6, δ ppm):163.5, 162.9, 161.5, 147.3, 146.1, 131.9, 120.3, 108.1, 107.7, 100.8, 91.4, 50.8, 34.8, 22.9. MS (MM – ES + APCI$^+$) (m/z): 273.0 (M+1).

4-(4, 4-difluoropipreidine-1-yl)-6-methylpyrimidine-2-amine (6e): White solid; m.p.: 176 – 178 ^{o}C; R_f = 0.55 (CH_2Cl_2/CH_3OH, 9:1); ^1H NMR (400 MHz, DMSO δ ppm): 6.31 (s, 2H), 6.13 (s, 1H), 3.69 - 3.68 (t *J* = 5.6 4H), 2.10 (s, 3H), 1.99-1.89 (m, 4H); ^{13}C NMR (400 MHz, DMSO, δ ppm) 171.4, 169.1, 166.6, 109.4, 96.5, 43.1, 43.0, 36.6, 36.4, 22.1; MS (MM – ES + APCI$^+$) (m/z): 229.0(M+).

4-[4(dimethylamino) pyperidine-1-yl]-6-methylpyrimidine-2-amine (6f): White solid; m.p.: 241 – 243^{o}C; R_f = 0.58 (CH_2Cl_2 /CH_3OH, 9:1); ^1H NMR (400 MHz, DMSO δ ppm): 6.02 (s, 2H) 5.98 (s, 1H), 3.68 (t *J* = 4.1 Hz, 4H) 2.19 (s, 3H), 2.06 (s, 3H), 1.36 (t, j=8.4 Hz, 4H); ^{13}C NMR (400 MHz, DMSO, δ

ppm): 171.8, 169.1, 167.6, 97.5, 58.4, 52.2, 39.9, 39.7, 30.9, 30.7, 21.2; MS (MM - ES + APCI$^+$) (m/z): 236.0 (M+).

N4-(cyclohexylmethyl)-6-methylpyrimidine-2,4-diamine (6g): White solid; m.p.: 168 – 170 ^{o}C; R_f = 0.38 (CH_2Cl_2 / CH_3OH, 9:1); ^{1}H NMR (400 MHz, DMSO_d_6 δ ppm): 6.01 (s, 2H) 5.99 (s, 1H), 3.15 (d, *J* = 4.8 2H) 2.49 (m, 1H), 1.20 (m, 6H), 0.93 (m, 4H); ^{13}C NMR(400 MHz, DMSO, δ ppm): 169.0, 168.4, 167.0, 95.5, 56.0, 33.8, 29.4, 29.1, 29.0, 27.4, 24.6, 24.2, 20.9.MS (MM – ES + APCI$^+$) (m/z): 221.0 (M+).

N4-isobutyl-6-methylpyrimidine-2,4-diamine (6h): White solid; m.p.: 155 – 157 ^{o}C; Rf = 0.59 (CH_2Cl_2 / CH_3OH, 9:1); ^{1}H NMR (400 MHz, DMSO δ ppm): 6.01 (s, 2H) 5.96 (s, 1H), 5.94 (t, *J* = 8.1 Hz, 1H) 3.10 (s, 2H), 1.81-1.72 (m, 1H), 0.89 (s, 6H); ^{13}C NMR (400 MHz, DMSO, δ ppm): 170.4, 167.0, 166.6, 94.9, 59,7, 29.9, 20.2, 19.6, 19.4; MS (MM – ES + APCI$^+$) (m/z): 181.0(M+).

RESULTS AND DISCUSSION

In conventional method, Xantphos in presence of Pd $(dba)_2$ act as a good coupling agent in acetonitrile at 85 ^{o} C along with primary and secondary amines employed as substrates, moderate yields were obtained. We have carried out reaction under micro wave irradiation using Xantphos with Pd $(dba)_2$ in lower molar ratios better yield, less time, eco friendly, to minimize the impurity and same was achieved. The comparison of yield and reaction time were given in table 1. Among the tested compounds **6a, 6c** and **6f** possess significant antimicrobial and anthelmintic activity. It can be concluded that this class of compounds certainly hold great promise for discovering safer antimicrobial and anthelmintic agents.

Table 1: Comparison of % yield and time taken for conventional and microwave synthesis

Comp Code	Conventional Method% Yield (Time)	Microwave Method% Yield (Time)
6a	51.03 (12 h)	71.91 (35 min)
6b	30.32 (13 h)	57.86 (42 min)
6c	42.52 (15 h)	78.89 (48 min)
6d	42.42 (10h)	66.56 (30 min)
6e	41.15 (15 h)	68.37 (50 min)
6f	47.12 (16 h)	71.51 (50 min)
6g	46.25 (12 h)	78.67 (32 min)
6h	37.41 (17h)	50.69 (48 min)

APPLICATIONS

Antimicrobial studies: *In vitro* antibacterial activity of newly synthesized compounds were screened against pathogenic strains Gram positive *Staphylococcus aureus* (NCIM-5022) and Gram negative *Klebsiella aerogenes* (NCIM-2098), *Escherichia coli* (NCIM-5051) by agar well diffusion method (25). All the bacterial strains were purchased form National Chemical Laboratory (NCL) Pune, these strains were maintained on nutrient agar slant at 4 ^{o}C. Nutrient agar plates are prepared and swabbed using sterile L-Shaped glass rod with 100 µL of 24 h matured broth culture of individual bacterial strains. The well is made by using sterile cork borer, 6 mm wells are created in each petriplates. Various concentrations of compounds (200 and 400 µg µL^{-1}) are used to assess the activity of the compounds. Compound were dissolved in dimethylsulfoxide (DMSO) a negative control which showed no zone of inhibition and Ciprofloxacin (10 µg 50 µL^{-1}) was taken as standard drug a positive control, purchased from Himedia,

Mumbai. Concentrations of 200 and 400 µg/ well were used to assess the dose dependent activity. Sterile micropipette tips were used to load the wells with appropriate amount of sample, control and standard. Then the plates were incubated at 37 °C for 36 h. After the incubation period, the diameter of zone of inhibition of each well was measured in mm, the experiment was performed in triplicates the average values were calculated and are shown in fig.1.

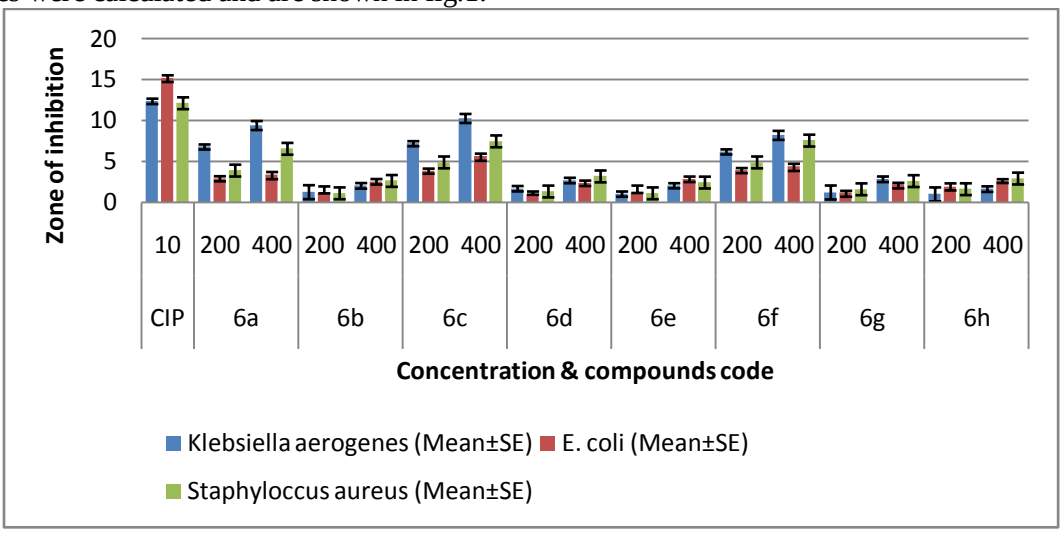


Fig 1: Antibacterial activities of 6a-h

Antifungal activity: Antifungal activity by agar well diffusion method (26). Antifungal activity of the culture strains of fungi such as *A. flavus* and *C. albicans* were carried out on potato dextrose agar (PDA) slant at 27±0.2 °C for 24-48 h, till sporulation. Spore of strains were transferred into 5 mL of sterile 1% saline solution. 100 µL of each fungal spore suspension was spread on each sterile PDA plate. Using the sterile cork borer, wells (6 mm) were made into the each petriplate. Various concentrations of compounds (200 and 400µg μL^{-1}) were used to assess the dose dependent activity of the compound. Fluconazole (100µg50 μL^{-1}) was used as standard drug. Then these plates were incubated at 27 ^{o}C for 48-72 h. After incubation period the results were observed and the diameter of inhibitor zone in mm around the each well was measured. Triplicates were maintained in each compound and the average values were calculated for the ultimate antifungal activity data are given in the fig. 2

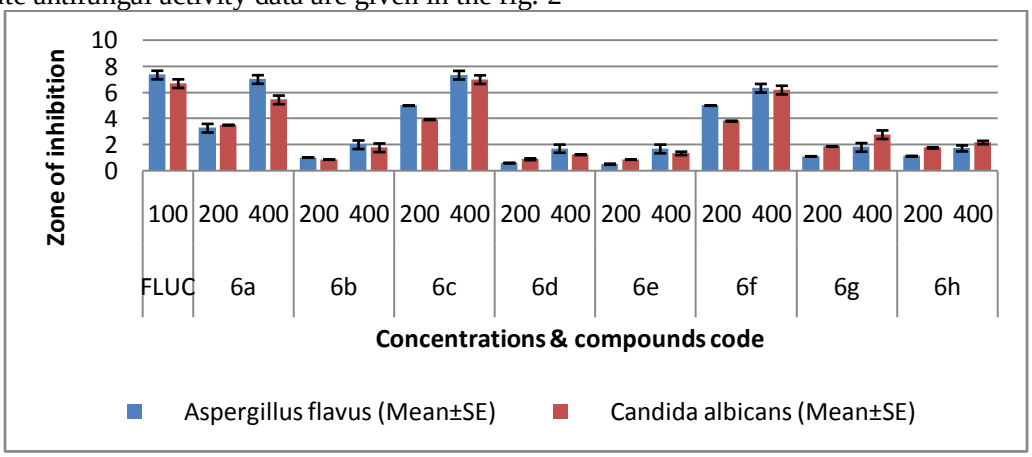


Fig 2: Antifungal activity of 6a-h

Anthelmintic Activity: Anthelmintic activity of **6a-h** compounds were done using P. posthuma (Indian Earthworm), worms were maintained under normal vermicomposting medium with adequate supply of

nourishment and water for about three weeks. Adult earthworms of approximately 4 cm in length and 0.2 - 0.3 cm in width were chosen for experiment. Different concentrations 50 and 100 mg of samples were evaluated as per the standard method reported (27). Eighteen groups each with six earth worms were taken. Each P. posthuma was washed separately with normal saline before the initiation of experimental procedure and were placed into a 20 mL of normal saline. Group I earthworms were placed in 20 mL saline in a clean petri plate and Group II earthworms were placed in 20 mL saline containing standard drug piperazine citrate (50 mg mL^{-1}). Similarly, Group III to XVIII earthworms was placed in a 20 mL saline containing 50 and 100 mg mL^{-1} of test samples (6a-h) respectively. Observation was done keeping time taken for paralysis and the time taken for death as objective and was documented in minutes. Paralysis time was analyzed based on behavior of the worms with no revival body state in normal saline medium. Death was concluded based on total loss of motility with faded body color and the results are illustrated in fig.3.

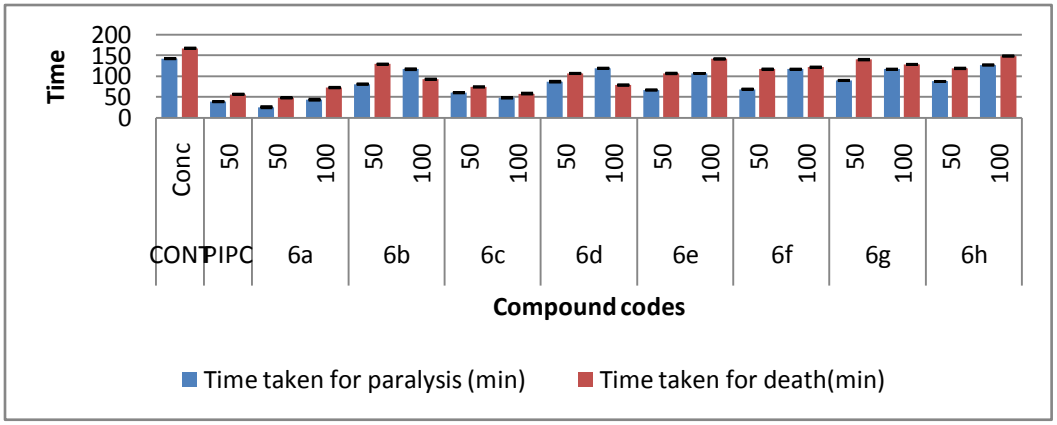


Fig 3: Anthelmintic activity

CONCLUSIONS

A new series of 2-Amino-6-subsituted-pyrimidine derivatives were synthesized conveniently by both conventional and microwave method. Microwave method proved to be an environmentally benign, involving less reaction time and gives better yield compared to conventional method. Synthesized compounds **6a, 6c** and **6f** were found to be potent antimicrobial and anthelmintic agents in comparing with the standard drugs.

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