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SYNTHESIS, CHARACTERIZATION AND PHARMACOLOGICAL EVALUATION OF NOVELLY SUBSTITUTED ALIPHATIC AMIDES CONTAINING PYRIMIDINE NUCLEUS AS ANTIBACTERIAL AND ANTHELMINTIC AGENTS

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ABSTRACT

The paper presents the synthesis of some new amides containing pyrimidine as core moiety 6a-e by the reaction between acid 4 with different substituted amines in the presence of base. The key intermediate 4 was synthesized from compound 1 *via* Suzuki coupling and then hydrolysis reaction. The structures of compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and CHN elemental analysis. The newly synthesized compounds were evaluated for their antibacterial activity. It was found that few amides exhibited significant antibacterial activity.

KEYWORDS: Suzuki coupling, pyrimidine, dikis, cesium carbonate, 3-(3-dimethylaminopropyl) carbodiimide hydrochloride, hydroxybenzotriazole, antibacterial activity.

INTRODUCTION

Substituted amides exhibit different biological activity such as antibacterial[1-3], analgesic[4], anticancer[5], diuretic[6], anticonvulsant[7], insecticidal[8], antifungal, photosynthesis inhibiter[9]

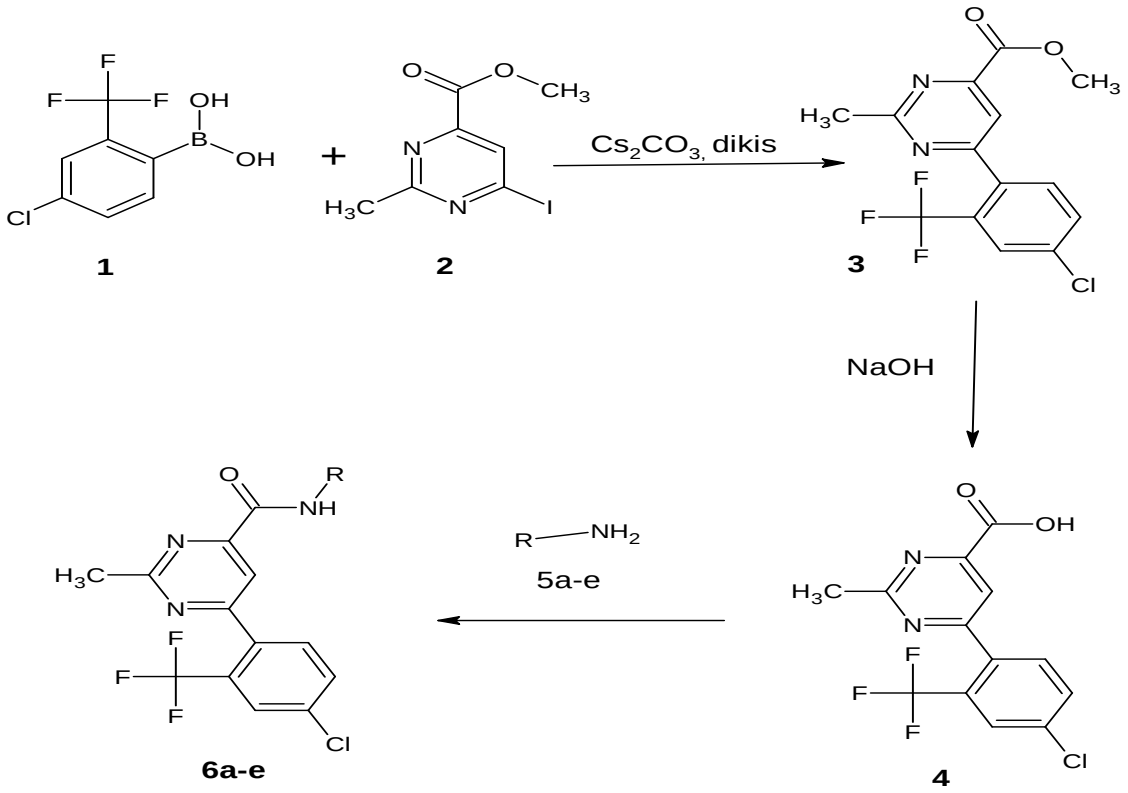
and antiviral activity.[10-12] In addition to that, dihidroquinoline carboxylic amides with a wide spectrum of biological effects including antitubercular and anti-inflammatory activity.[13] Although the preparation of amides using conventional methods is well documented[14], clean and lesser time consumption methods are less common. It has been reported that secondary and tertiary amides were synthesized by adopting microwave irradiation method.[15] Amides of Pyrimidine derivatives promising structural moiety for drug designing and acts as component in a number of useful drugs and are associated with many biological and therapeutical activities. Condensed pyrimidine derivatives and Pyrimidine compounds and have been reported as anticancer[16-19], anti-microbial[20-22] analgesic[23], anti-inflammatory, ulcerogenic[24-25], anti-viral[26], anti-tumour[27], antioxidant[28-29], antifungal[30], anti-HIV-1[31], anthelmintic agents[32] and also used as drugs for COX-2[33] and dynamin inhibitors.[34]

Prompted by the above data we planned to synthesize new series of amides bearing pyrimidine nucleus and to evaluate their antibacterial potential.

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 are dichloromethane / methanol (9:1) and petroleum ether / ethyl acetate (6:4) and further purification was done using column chromatography. Melting points were determined in one end open capillary tubes on a liquid paraffin bath and are uncorrected. 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 (100 MHz, ^{13}C NMR) instruments respectively. Chemical shifts were reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard, physical characterization data are given in Table 1.

Experimental: Synthetic route for the preparation of amides **6a-e** is shown in **Scheme 1.**



Procedure for the preparation of methyl-6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidine-4-carboxylate (3)

Compound 4-chloro-2-(trifluoromethyl)phenylboronic acid (1) (20 g, 71.94 mmol) was taken in 200 mL of 1,4-dioxane, ethanol and water solvent system (2;2;1) at room temperature under nitrogen atmosphere. The reaction mixture was degassed with argon for 20 min and Cs_2CO_3 (58.45 g, 179.85 mmol), dikis (2.21 g, 3.16 mmol) were added and degassed for 30 min. Methyl 6-iodo-2-methylpyrimidine-4-carboxylate (20.49 g, 79.13 mmol) (2) was added and the reaction mixture was heated at 65^{o}C for 5 h. Reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate filtered over celite, washed with ethyl acetate. The filtrate was washed with water and brine solution. The ethyl acetate was dried over anhydrous $MgSO_4$ and concentrated to get the crude product which was further purified by column chromatography using pet ether and ethyl acetate as eluent to get the title compound (3) as off white solid. The structure of the compound was confirmed by IR & NMR data as given below. IR: ν_{max} /cm^{-1}: 1673.2 (CO). ^{1}H-NMR ($CDCl_3$) δ ppm: 8.06 (s, 1H, Ar-H), 7.83 (s, 1H, Ar-H), 7.69 (d, 1H, Ar-H), 7.50 (d, 1H, Ar-H), 3.79 (s, 3H, O-CH_3), 2.81(s, 3H, Ar-CH_3) MP: 199-200 ^{o}C. Yield: 64%.

Procedure for the preparation of 6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidine-4-carboxylic acid (4)

Methyl-6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidine-4-carboxylate (5) (20 g, 10.66 mmol) and sodium hydroxide (41.81 g, 181.81 mmol) taken in aqueous THF (200 mL) and heated the reaction mixture at 60 ^{o}C for 1 h. Cool the reaction mixture, adjusted to pH 6 using 1.5 N HCl, precipitate was filtered and dried to get title compound (6). ^{1}H-NMR ($CDCl_3$) δ ppm: 8.00 (s, 1H, Ar-H), 7.83 (s, 1H, Ar-H) 7.69 (d, 1H, Ar-H), 7.50 (d, 1H, Ar-H) 2.89 (s, 3H, Ar-CH_3). LCMS: 415.12 (M+1). MP: 221-222^{o}C. Yield 90%.

General Procedure for the preparation for final compounds (6a-e)

6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidine-4-carboxylic acid (4) (1.5 g, 4.74 mmol), different substituted amines (5f-j) (5.69 mmol), 3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC.HCl) (33.01 g, 117.12 mmol), hydroxybenzotriazole (HOBT) (0.317 g, 2.35 mmol) and triethylamine (21.8 Ml, 141.00 mmole) were stirred in dry ethylene dichloride (16 mL) under nitrogen atmosphere at room temperature for 12 h. The reaction mixture was washed with 10% $NaHCO_3$, the organic phase was washed with water and brine, then dried over Na_2SO_4 and evaporated. Residue was purified by neutral alumina column chromatography using MDC / MeOH as a eluent (9:1) to get title compounds (6a-e) in moderate yield. Physical data of all the final compounds and IR, ^{1}H NMR, ^{13}C NMR values are tabulated in Table 1 and Table 3 respectively.

RESULTS AND DISCUSSION

In the present work we reported the synthesis of novel amide of pyrimidines 6f-j according to Scheme 1. The key intermediate scaffold 4 was generated from commercially available compound 1 *via* Suzuki coupling[35-36] and hydrolysis reaction. The scaffold 4 underwent condensation reaction[37-38] with various alkyl, aryl substituted amines in the presence of base, dehydrating agent and coupling agent to yield the desired compounds 6a-e.

Invitro antibacterial activity

Amides containing pyrimidine derivatives 6f-j was studied against Gram positive *Staphylococcus aureus* (NCIM-5022) and Gram negative *Klebsiella aerogenes* (NCIM-2098), *Escherichia coli* (NCIM-5051), *Pseudomonas aeruginosa* (NCIM-2242) bacterial strains. All the bacterial strains were procured form CSIR-National Chemical Laboratory (NCL) Pune. Agar well diffusion method[39] was incorporated for the study broth cultures of bacterial strains were incubated for 24 h and were uniformly smeared on sterile nutrient agar

medium in each petri plates using sterile L-Shaped glass rod. Five uniform wells with 6 mm diameter were bored using cork borer to accommodate 50 µml of solution in each well. Samples were dissolved in dimethylsulfoxide (DMSO) a negative control which showed no zone of inhibition and Ciprofloxacin (5 µg/50 µL) 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 the zone of inhibition of each well was measured in mm, the experiment was performed in triplicates the average values were calculated are given in Table 2.

Table 1: Physical data of final molecules 6a-e.

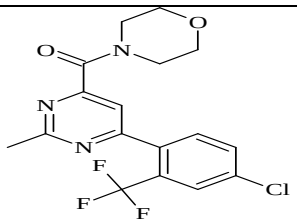
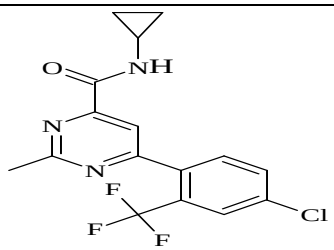
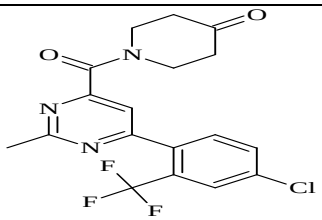
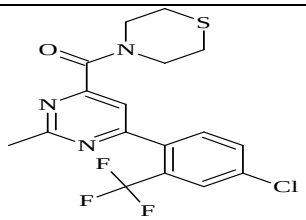
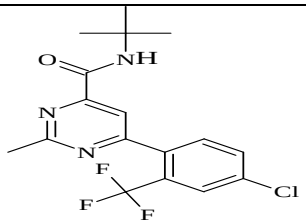
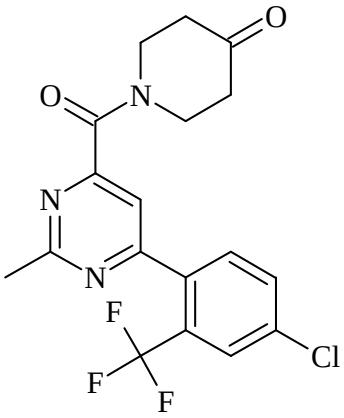
Compound	MP (^{0}C)	Yield (%)	LCMS (M+1)	Structures	Calculated (Found) % C H N
6f	17	65	386.7		52.93 3.92 10.89 (52.90) (3.91)(10.87)
6g	188	72	356.8		54.02 3.68 11.81 (54.03)(3.69)(11.81)
6h	177	68	398.8		54.35 3.80 10.56 (54.34) 3.79) (10.57)
6i	187	78	402.7		50.81 3.76 10.46 (50.79)(3.75)(10.45)
6j	202	58	372.1		54.92 4.61 11.30 (54.91)(4.59)(11.29)

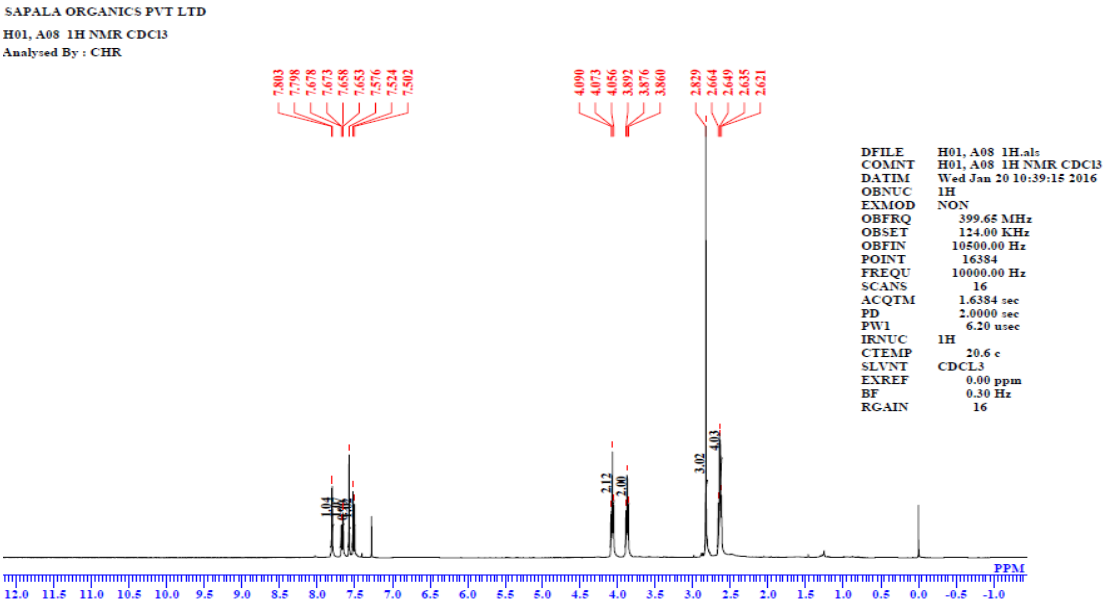
Table 2: Antibacterial activity of 6f-j.

Samples	Treatment (µg/50µL)	*Klebsiella aerogenes* (Mean±SE)	*E.coli* (Mean±SE)	*Staphyloccus aureus*(Mean±SE)
Standard	10	12.33±0.33	15.12±0.43	12.10±0.39
6f	200	_	7.68±0.21**	1.01±0.07**
	400	_	9.28±0.35**	3.12±0.30**
6g	200	_	4.25±0.85**	1.12±0.33**
	400	_	5.02±0.34**	2.95±0.33**
6h	200	6.18±0.24**	5.25±0.48**	2.45±0.21**
	400	9.12±0.17**	7.08±0.62**	2.92±0.15**
6i	200	_	3.98±0.34**	3.95±0.10**
	400	_	5.82±0.27**	5.90±0.41**
6j	200	4.58±0.59**	4.15±0.60**	3.38±0.27**
	400	6.95±0.53**	7.28±0.24**	6.08±0.42**

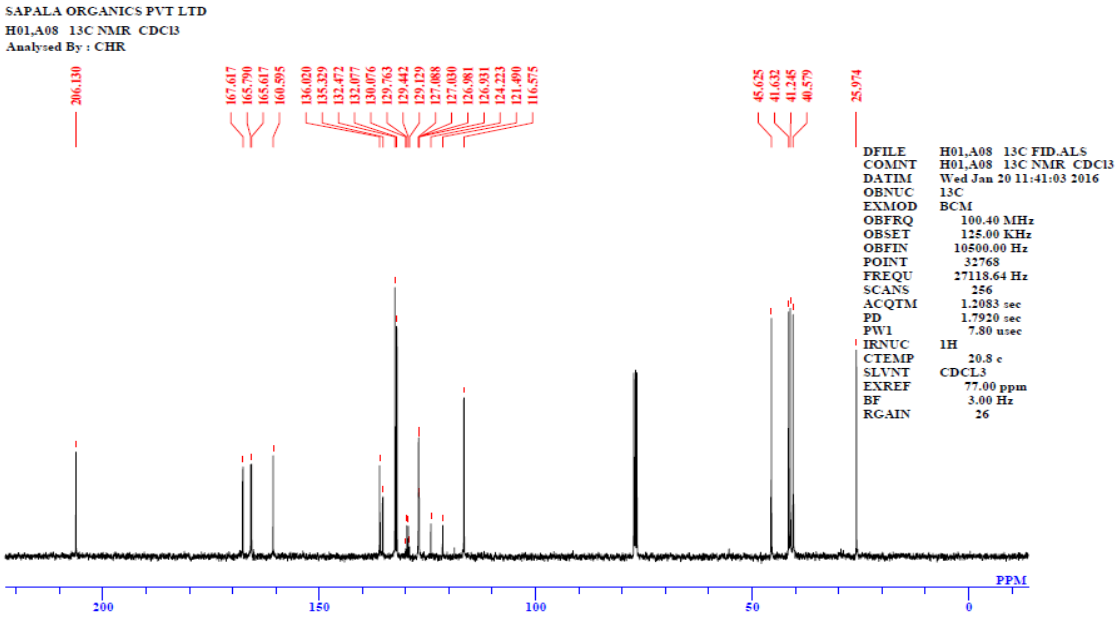
Values are the mean ± SEM of clear zone. Symbols represent statistical significance, *P < 0.05, **P < 0.01 as compared with the control group.

^{1}H NMR Spectra of compound 6h





13C NMR Spectra of compound 6h



6.2. Anthelmintic Activity

Among the most widespread infections in humans, causing distress in huge population of the world are helminthic infections. Majority of infections due to helminthics are generally confined to tropical regions of the world, it cause enormous hazard to health contributing to the prevalence of malnutrition, anemia, eosinophilia and pneumonia.[7] Helminthes becoming resistant to presently available anthelmintic drugs has resulted in the prime difficulty in treatment of helminthes diseases.[8] Hence, there is an cumulative request towards the development of new specifically effective anthelmintics. In this section, in view of identifying new effective anthelmintics, anthelmintic evaluation has been done successfully for all the synthesized compounds (6f-j).

6.2.1 MATERIAL AND METHODS

Anthelmintic activity of all the series of compounds was done using *Pheretima posthuma* (Indian Earthworm), maintained under normal vermicomposting medium with adequate supply of nourishment and water for about three weeks. Standard drug Piperazine citrate was purchased from SD Fine Chemical Ltd., Mumbai. Normal saline (*NS*) 0.90% w/v of sodium chloride in distilled water was prepared for the analysis in lab.

6.2.2 Experimental Procedure

In vitro anthelmintic activity of all four series of synthesized compounds was studied using Piperazine citrate as standard against *P. posthuma* (Indian Earthworm), due to its anatomical

similarity with the intestinal roundworm parasites in human beings.[9] Different concentrations (50 and 100 mg mL^{-1}/dimethyl sulfoxide, DMSO) of samples (6a-j) were selected according to the mimimum concentration values from Table 3 and were evaluated as per the standard method,[10] using adult earthworms of approximately 4 cm in length and 0.2 - 0.3 cm in width. Twenty four groups, each with six worms were taken, washed with normal saline (*NS*) before the initiation of experimental procedure and were placed in 20 mL of *NS*. Group I earthworms were placed in a petri plate containg 20 mL *NS* and equivalent amount of solvent dimethyl sulfoxide (DMSO), as control. Group II earthworms were placed in 20 mL saline containing standard drug Piperazine citrate (50 mg mL^{-1}). Similarly, Group III to XXIV earthworms was placed in a 20 mL saline containing 50 and 100 mg mL^{-1} of test samples 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 analysed based on behaviour of the worms with no revival body state in normal saline medium. Death was concluded based on total loss of motility with faded body colour.[11] Similarly different groups of earth worms are used for the evaluation of anthelmintic acitivity and the resulting are reported in Table 3 Minimum concentration of compounds for all the four series were selected on the basis of detailed study of anthelmintic activity aginst *Pheretima posthuma* at different concentration 15, 25, 35 and 50 mg mL^{-1}. A set of clean petri plates were taken with different concentrations of test samples in 20 mL of *NS*. One blank petri plate with only *NS* and DMSO with out any compound was taken as control and another positive control petri plate with standart drug Piperazine citrate was taken as reference. All the test systems were observed for 4 hours for paralysis and death, which was concluded, based on total loss of motility and faded body colour of the worm. Minimum concentration at which worms got paralysed and died was taken as the minimum concentration for the anthelmintic acitivity evaluation. Observed minimum comcentrations (MCs) are presented in Table 3.

Statistical Analysis

The data of anthelmintic was expressed as Mean±S.E of triplicates and six *Pheretima posthuma* in each group respectively. The difference in values at **$p \leq 0.01$ was considered as statistically significant. The analysis of variance (ANOVA) was performed using ezANOVA (version 0.98) software to determine the mean and standard error of the standard error of paralysis and death time of earthworms.

Table 3: Anthelmintic activity of pyrimidine derivatives (7a-j)

(Scheme 4 Compounds)

Code	Conc. (mg mL^{-1})	Time taken for paralysis (min)	Time taken for death (min)
Control	-	142.33±0.49	165.33±1.58
PC	50	39.17±0.48**	57.67±0.88**
6a	50	85.33±0.42**	112.67±0.56**
	100	47.50±0.62*	66.83±0.79**
6b	50	55.67±0.71**	89.00±1.12**
	100	38.83±0.48**	50.00±0.58**
6c	50	60.00±0.73**	90.33±1.12**
	100	39.17±0.70**	52.00±1.29**
6d	50	60.83±0.60**	88.67±0.76**
	100	48.67±0.56**	64.17±0.75**
6e	50	70.33±0.71**	100.33±0.71**
	100	42.33±0.49**	56.50±1.09
6f	50	65.17±0.48**	101.83±1.19**
	100	40.67±0.71**	58.00±0.86
6g	50	60.17±0.48**	120.50±0.67**
	100	30.17±0.48**	55.67±0.42*
6h	50	70.00±0.97**	99.00±0.89**
	100	42.50±0.43**	56.67±0.49**
6i	50	69.17±0.60**	105.33±0.61**
	100	43.50±0.43**	56.67±0.49**
6j	50	75.83±0.65**	108.23±0.51**
	100	34.67±0.56**	49.83±0.79**

Values are the mean ± standard error of mean (SEM) of clear zone. Symbols represent statistical significance, **p≤0.01 as compared with the control group.

Control: Dimethyl sulfoxide, PC: Standard drug Piperazine Citrate.

Table 4: IR, ^{1}H NMR, ^{13}C NMR of the final compounds 6a-e.

Comp	IR	^{1}H NMR	^{13}C NMR
6f	IR (KBr,cm-1) : 1680 (C=O), 1371-1135 (CF_3 stretching).	^{1}H NMR; $CDCl_3$ (ppm): 8.36 (s, 1H, NH); 8.04 (s, 1H, Ar-H); 7.80 (d, 1H, Ar-H); 7.66 (dd, 1H, Ar-H); 7.46 (d, 1H, Ar-H); 3.73 (q, 4H, NCH_2); 3.62 (q, 4H, NCH_3).	^{13}C NMR; $CDCl_3$ (ppm): 173.4, 170.1, 167.7, 161.5, 155.4, 149.4, 138.5, 130.7, 126.1, 125.0, 120.3 (CF_3), 106.0, 64.4, 55.8, 41.5, 42.20.
6g	IR (KBr,cm-1) : 1680 (C=O), 1283-1254 (CF_3 streching).	^{1}H NMR ; $CDCl_3$ (ppm): 8.56 (s, 1H, N-H); 7.79 (s, 1H, Ar-H); 7.66 (d, 2H, Ar-H); 7.56 (dd, 1H, Ar-H); 7.41-7.39 (m, 5H, Ar-H); 3.37 (m, 1H, junction H); 2.1 (t, 4H, -CH_2).	^{13}C NMR; CDCl3 (ppm): 165.4, 163.2, 160.6, 157.3, 140.5, 132.6, 132.5, 130.9, 128.5 (2C), 126.5 (2C), 125.4, 123.6, 123.4, 123.2 (CF_3), 115.1, 40.2, 25.1.
6h	IR (KBr,cm-1) : 1634 (C=O), 1242-1156 (CF_3 streching).	^{1}H NMR ; $CDCl_3$ (ppm): 8.76 (s, 1H, N-H); 8.56 (d, 2H, Ar-H); 7.79 (s, 1H, Ar-H); 7.66 (d, 2H, Ar-H); 7.56 (dd, 1H, A r-H), 7.35 (d, 2H, Ar-H), 4.11 (q, 4H, -CH_2), 3.90 (q, 4H, -CH_2).	^{13}C NMR; $CDCl_3$ (ppm): 206.13, 167.9, 162.3, 161.0, 157.9, 149.8 (2C), 147.6, 134.6, 132.6, 130.9, 129.2, 125.4, 123.4, 123.9, 123.4 (CF_3), 122.4 (2C), 116.0, 43.7, 42.1.
6i	IR (KBr,cm-1): 1635 (C=O), 1210-1160 (CF_3 streching).	^{1}H NMR ; $CDCl_3$ (ppm): 8.87 (s, 1H, N-H); 7.79 (s, 1H, Ar-H); 7.66 (d, 2H, Ar-H); 7.56 (dd, 1H, Ar-H); 7.40-7.31 (m, 5H, Ar-H); 4.97-4.91 (m, 4H, -CH_2), 3.98 (q, 4H, -CH_2).	^{13}C NMR; $CDCl_3$ (ppm): 165.9, 163.4, 160.7, 157.3, 141.5, 134.6, 132.6, 130.9, 128.5 (2C), 126.5 (2C), 126.1, 126.0, 125.4, 123.9, 123.4 (CF_3), 116.0, 49.5, 24.4, 21.5.
6j	IR (KBr,cm-1) : 1648 (C=O), 1270-1160 (CF_3 streching).	^{1}H NMR ; $CDCl_3$ (ppm): 8.55 (s, 1H, N-H); 7.79 (s, 1H, Ar-H); 7.66 (d, 2H, Ar-H); 7.56 (dd, 1H, Ar-H); 1.70 (s, 9H, -CH_3).	^{13}C NMR; $CDCl_3$ (ppm): 165.9, 163.4, 160.7, 157.3, 134.6, 130.9, 129.2, 129.1, 123.9, 123.8, 122.4 (CF_3), 116.0, 81.0, 38.0, 24.0.

CONCLUSION

Some of the new series of compounds were synthesized according to Suzuki and condensation reactions, then screened for their antibacterial activity. Among the tested compounds 6f, and 6h possess significant antibacterial activity, rest of the amide derivatives showed moderate antibacterial activity as compared to standard. It can be concluded that this class of compounds certainly hold great promise for discovering safer antibacterial, anthelmintic and anti-inflammatory agents.

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