WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 15, 556-565. Research Article ISSN 2277– 7105

SYNTHESIS AND ANTIMICROBIAL SCREENING OF SOME NEW PYRAZOLINE AND 1,6-DIHYDROPYRIMIDINE DERIVATIVES.

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Article Received on
22 Sept. 2017,
Revised on 12 Oct. 2017,
Accepted on 02 Nov. 2017
DOI: 10.20959/wjpr201715-9921

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ABSTRACT

A series of novel Pyrazoline 5a-l and 1,6-dihydropyrimidine 6a-l derivatives have been synthesized as potential antimicrobial agents. The Pyrazoline derivatives 5a-l have been synthesized by reaction of various Chalcones 4a-l with hydrazine hydrate in ethanol. The 1,6-dihydropyrimidine 6a-l were prepared by the reaction of Chalcone (4a-l) with thiourea in presence of alkaline medium. The structures of the newly synthesized compounds were established on the basis of ^{1}H-NMR, Mass, IR spectra and elemental analysis data. All the newly synthesized compounds were screened for their antibacterial activity against *E. coli*, *S. thyphi* (Gram-negative bacteria), *S. aureus*, *M. luteus* (Gram-positive bacteria) and antifungal activity against *Candida albicans (Fungi)*.

KEYWORDS: Pyrazoline, 1,6-Dihydropyrimidine, Antimicrobial activity, Antifungal activity.

INTRODUCTION

The rising of multi-drug resistant bacteria provide impetus for the search and discovery of novel antimicrobial agents active against these pathogens. Pyrazoline and 1,6-Dihydropyrimidine moieties are an important class of heterocycles widely used as key pharmaceutical agents. Available data suggest that N-containing heterocyclic compounds such as pyrazoline synthesized from chalcones possesses biological activities like antitumor[1], antibacterial[2], antifungal[3], analgesic[4] and Pyrimidine derivatives were found to be associated with a variety of chemotherapeutic effects including anticancer,[5] antiviral,[6] antibacterial,[7] antifungal,[8] antiprotozoal,[9] antihypertensive,[10] antihistaminic,[11] anti-inflammatory.[12]

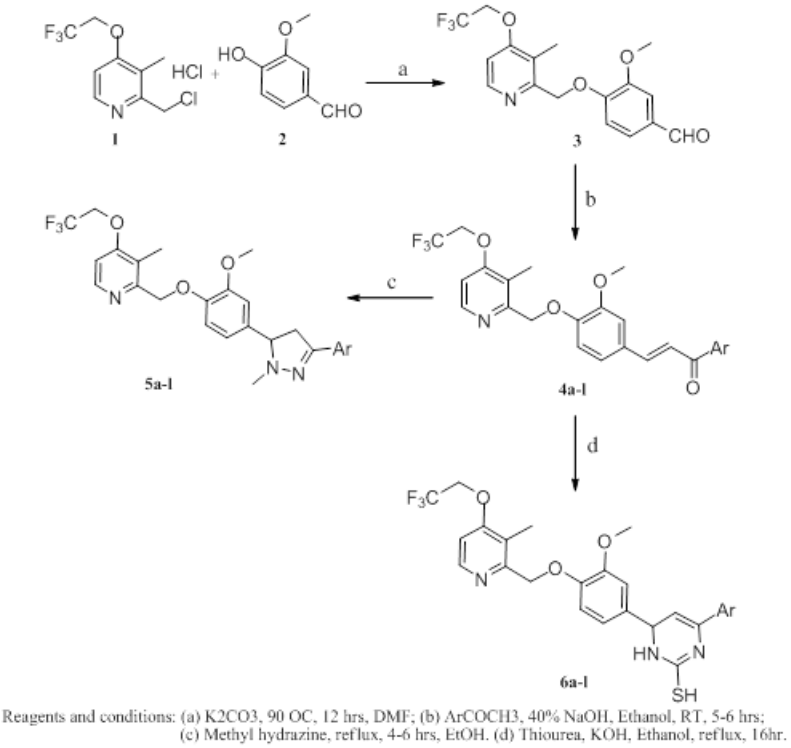
The medicinal use of natural compounds which are derived from natural sources i.e. plants, animals or micro-organisms has been recorded in human history. The structural analysis of natural compounds and the ability to synthesize them allowed chemists to modify them in order to suppress or enhance certain characteristics such as solubility, efficiency or stability in the human body.[13] Moreover, natural products have also been an invaluable source of inspiration for organic chemists to synthesize novel drug candidates.[14] Vanillin is the major constituent of beans of some plants of vanilla genus with a "generally regarded as safe" (GARS) status having acceptable daily intake of 10mg/Kg. Synthetic vanillin is also used as an intermediate in the chemical and pharmaceutical industries for the synthesis of herbicides and drugs.[15] The antimicrobial activity of vanillin was investigated against *E. coli*, *Lact. plantarum* and *L. innocua* in laboratory media. MIC levels of vanillin indicated that the inhibitory action of vanillin was bacteriostatic rather than bactericidal.[16]

Recently, vanillin containing aryl substitution reported as anticancer[17], antimitotic and apoptotic[18] and antimalarial[19] activities. Considering importance of vanillin and pyrazoline/dihydropyrimidine in medicinal chemistry, we prompted to incorporate these moieties in ongoing research program.[20] In this article, we have reported synthesis of 1-Methylpyrazoline **5a-l** and 1,6-Dihydropyrimidine **6a-l** derivatives and study of their biological activities.

RESULTS AND DISCUSSION

Chemistry

The synthetic route adopted to obtain the 1-Methylpyrazoline derivatives **5a-l** and 1,6-Dihydropyrimidine **6a-l** derivatives are shown in Scheme 1. The -Methylpyrazoline derivatives **5a-l** were prepared from Chalcones **4a-l** by refluxing with Methyl hydrazine in ethanol. The isolated product was washed with diethyl ether to get pyrazolines varied 67-86% yield. The 1,6-Dihydropyrimidine derivatives **6a-l** were prepared from Chalcones **4a-l** by reacting with thiourea and alcoholic potassium hydroxide at 50-71^{O}C for 16hrs. The isolated product was washed with diethyl ether to get dihydropyrimidine derivatives varied 71-82% yield. The structures of all newly synthesized compounds were assigned on the basis of spectral data such as IR, ^{1}H-NMR, Mass spectra and elemental analysis.



Scheme 1: The Synthetic scheme for the preparation of compounds 5a-l and 6a-l.

The structural assignment of the title compounds **5a-l** and **6a-l** have been made on the basis of ^{1}H-NMR, Mass, elemental analysis and IR spectral studies which were in full agreement with the proposed structures. IR spectrum of compound **5a** reveals absorption band in the region 3305 cm^{-1} corresponding to carbonyl (N-H) stretching and 1624 cm^{-1} due to C=N of Pyrazoline ring. In ^{1}H-NMR spectra of **5a**, the two CH_3 protons absorbed as a singlet at δ 2.35 and methoxy group at δ 3.81 and the doublet of doublet at δ 3.10, 3.66 and 5.49 due to pyrazoline ring for 1H proton and rest of the aromatic proton appear at their respective position. Mass spectrum of 2-((2-Methoxy-4-(1-methyl-3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)phenoxy)methyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine showed (M^{+}) peak at 472.6 which support the formation of product. The structure of **6a** is interpreted from spectroscopic data. The IR spectrum of **6a** showed a characteristic absorption band at 3250 cm^{-1} due to N-H stretching, 2573 cm^{-1} due to Thiol (S-H) and 1559 cm^{-1} due to vinyl (C=C) stretching. ^{1}H-NMR spectrum of **6a** reveals the presence of methyl group at δ 2.18 and methoxy group at δ 3.72. It also exhibits presence of N-H and S-H as a broad singlet at δ 9.00 and 9.77 respectively. Mass spectrum of 6-(3-Methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-4-pheyl-1,6-dihydropyrimidine-2-thiol showed (M^{+}) peak at 516.3.

Experimental

All the melting points were determined on electro-thermal apparatus using open capillaries and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5mm thickness and spots were located by iodine and UV (254nm). The IR spectra were recorded on a Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GCMS-QP2010 model using Direct Injection Probe technique. ^{1}H-NMR was determined in $CDCl_3$/DMSO-d_6 solution on a Bruker AC 400MHz spectrometer using TMS as internal standard and coupling constants (J) are expressed in Hertz (Hz). Elemental analysis of the all the synthesized compounds were carried out on Elementar Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned. All the reagents were purchased from Rankem (New Delhi, India) and Sigma-Aldrich (New Delhi, India) and are used without further purification.

Procedure for synthesis of 3-Methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy) benzaldehyde (3). A mixture of 2-(chloromethyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine hydrochloride (10.87g, 39.4 mmol), potassium carbonate (13.61g, 98.6 mmol) and vanillin (5.0g, 32.8 mmol) in 50 mL DMF was stirred for 12 hrs at 90 ^{O}C. After completion of the reaction, the reaction mixture was poured in to ice cold water (500 mL). The precipitates obtained were filtered to get required product. Yield 87% (off white solid); m.p 143-145^{O}C, IR (KBr, cm^{-1}): 3017, 2975, 1723, 1021, 980, 845; ^{1}H-NMR (DMSO-d_6, □ ppm): 9.83 (s, 1H, -CHO), 8.33-8.34 (d, 1H, *J* = 5.6 Hz, aromatic), 7.50-7.52 (d, 1H, *J* = 8.4 Hz, aromatic), 7.39 (s, 1H, aromatic), 7.29-7.31 (d, 1H, *J* = 8.4 Hz, aromatic), 7.13-7.15 (d, 1H, *J* = 5.6 Hz, aromatic), 5.28 (s, 2H, -O-CH_2-), 4.86-4.93 (q, 2H, -O-CH_2-CF_3), 3.80 (s, 3H, -OCH_3), 2.19 (s, 3H, -CH_3); MS : (m/z) 356.3 (M^+); Anal. Calcd. for $C_{17}H_{16}F_3NO_4$: C: 57.47, H: 4.54, N: 3.94 Found: C: 57.23%, H: 4.71%, N: 3.87%.

General procedure for synthesis of 3-(3-Methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-1-arylprop-2-en-1-one (4a-l). To a solution of 3-Methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)benzaldehyde **3** (2.81 mmol) in ethanol was added appropriate Acetophenone (3.09 mmol) followed by catalytic amount of 40% aqueous NaOH solution and the reaction mixture was stirred for 5-6 hrs at room temperature. After completion of reaction on TLC, the reaction mixture was filtered.

(E)-3-(3-Methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-1-phenylprop-2-en-1-one(4a): Yield 90% (light yellow solid); m.p 148-150^{O}C; IR (KBr, cm^{-1}): 1651 (C=O), 1582 (C=C); ^{1}H-NMR ($CDCl_3$, □ ppm): 8.37-8.39 (d, 1H, *J* = 5.6 Hz, aromatic), 7.98-8.01 (m, 2H, aromatic), 7.72-7.76 (d, 1H, *J* = 16 Hz, ethylenic), 7.56-7.58 (m, 1H, aromatic), 7.48-7.52 (m, 2H, aromatic), 7.35-7.39 (d, 1H, *J* = 16 Hz, ethylenic), 7.08-7.19 (m, 3H, aromatic), 6.69-6.70 (d, 1H, *J* = 5.6 Hz, aromatic), 5.32 (s, 2H, -O-CH_2-), 4.37-4.43 (q, 2H, -O-CH_2-CF_3), 3.91 (s, 3H, -OCH_3), 2.35 (s, 3H, -CH_3); MS : (m/z) 458.4 (M^+); Anal. Calcd. for $C_{25}H_{22}F_3NO_4$: C: 65.64%, H: 4.85%, N: 3.06%; Found: C: 65.45%, H: 4.90%, N: 3.24%.

General procedure for synthesis of 2-((2-Methoxy-4-(1-methyl-3-aryl-4,5-dihydro-1H-pyrazol-5-yl)phenoxy)methyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine (5a-l). To a solution of Chalcone 4a-i (1.62 mmol) in ethanol (10 ml) was added Methyl hydrazine hydrate (0.5 ml, 8.12mmol) and heated to reflux for 4-6 hrs. After completion of the reaction, the reaction mixture was poured in ice water and basified to pH 7.5 using sodium bicarbonate and extracted with ethyl acetate (2 x 20 ml). The organic layer was washed with brine, dry over sodium sulphate and evaporated under reduced pressure. The crude residue was washed with diethyl ether to give pure product as solid. The physical and spectral data of compound are as following.

2-((2-Methoxy-4-(1-methyl-3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)phenoxy)methyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine (5a): Yield 76% (off white solid); m.p 140^{O}C; IR (KBr, cm^{-1}): 1238 (C-N), 1643 (C=N); ^{1}H-NMR ($CDCl_3$, □ ppm): 8.35-8.36 (d, 1H, *J* = 5.6 Hz, aromatic), 7.63-7.64 (m, 2H, aromatic), 7.30-7.46 (m, 3H, aromatic), 6.89-7.08 (m, 3H, aromatic), 6.67-6.71 (m, 1H, aromatic), 5.28-5.32 (dd, 1H, Pyrazoline), 5.26 (s, 2H,-O-CH_2-), 4.37-4.43 (q, 2H, -O-CH_2-CF_3), 3.93 (s, 3H, -OCH_3), 3.39-3.46 (dd, 1H, Pyrazoline), 3.10-3.16 (dd, 1H, Pyrazoline), 2.92 (s, 3H, -NCH_3), 2.36 (s, 3H, -CH_3); MS : (m/z) 486.3.64 (M^+); Anal. Calcd. for $C_{26}H_{26}F_3N_3O_3$: C: 64.32%; H: 5.40%; N: 8.66%; Found: C: 64.48%, H: 5.27%, N: 8.71%.

General procedure for synthesis of 6-(3-Methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-4-aryl-1,6-dihydropyrimidine-2-thiol (6a-l). A mixture of (E)-3-{(3′-Methoxy)-4′-[(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-1-phenylprop-2-en-1-one (0.5gm, 1.09 mol) and thiourea (0.166gm, 2.18 mol) in ethanol (15 ml) was refluxed in presence of alcoholic KOH for 16 hrs. The

excess solvent was distilled out and the product was poured in to crushed ice, the separated solid was filtered out and crystallized from ethanol.

6-(3-Methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-4-phenyl-1,6-dihydropyrimidine-2-thiol (6a): Yield 61% (off white solid); m.p 160^{O}C; IR (KBr, cm^{-1}): 2573 (S-H), 3249 (N-H), 1559 (C=C), 1624 (C=N); ^{1}H-NMR (DMSO, □ ppm): 9.77 (bs, 1H, SH), 9.00 (bs, 1H, NH), 8.31-8.32 (d, 1H, *J* = 8 Hz, aromatic), 7.49 (m, 2H) 7.35-7.36 (m, 3H, aromatic), 7.08-7.12 (m, 3H, aromatic), 6.94 (s, 1H, aromatic), 6.79-6.81 (d, 1H, *J* = 8 Hz, aromatic), 5.36 (s, 1H), 5.04 (s, 2H, -O-CH_2-), 4.86-4.92 (q, 2H, -O-CH_2-CF_3), 3.72 (s, 3H, -OCH_3), 2.18 (s, 3H, -CH_3); MS : (m/z) 516.3 (M^+); Anal. Calcd. for $C_{26}H_{24}F_3N_3O_3S$: C: 60.57%, H: 4.69%, N: 8.15%; Found: C: 60.64%, H: 4.73%, N: 8.26%.

Similarly all other Pyrazoline and 1,6-dihydropyrimidine compounds were and physical data were given in **Table 1.**

Sr No	Ar	Molecular Formula	M.W	M.P ^{O}C	Yield %	% of Nitrogen	
						Calcd.	Found.
5a	C_6H_5-	$C_{26}H_{26}F_3N_3O_3$	485.4	140	76	8.66	8.71
5b	4-CH_3-C_6H_4-	$C_{27}H_{28}F_3N_3O_3$	499.4	121	79	8.41	8.49
5c	4-OCH_3-C_6H_4-	$C_{27}H_{28}F_3N_3O_4$	515.3	137	74	8.15	8.24
5d	4-OH-C_6H_4-	$C_{26}H_{26}F_3N_3O_4$	501.5	227	67	8.38	8.47
5h	3-Br-C_6H_4-	$C_{26}H_{25}BrF_3N_3O_3$	564.4	170	81	7.45	7.58
5e	4-Br-C_6H_4-	$C_{26}H_{25}BrF_3N_3O_3$	564.4	133	85	7.45	7.53
5g	3-Cl-C_6H_4-	$C_{26}H_{25}ClF_3N_3O_3$	520.2	134	79	8.08	8.01
5f	4-Cl-C_6H_4-	$C_{26}H_{25}ClF_3N_3O_3$	520.2	158	78	8.08	8.16
5i	3-NO_2-C_6H_4-	$C_{26}H_{25}F_3N_4O_5$	530.4	158	76	10.56	10.62
5j	2-Thiophenyl-	$C_{24}H_{24}F_3N_3O_3S$	491.5	114	82	8.55	8.69
5k	2-Furanyl-	$C_{24}H_{24}F_3N_3O_4$	475.4	130	86	8.84	8.93
5l	2-Pyridinyl	$C_{25}H_{25}F_3N_4O_3$	486.4	139	80	11.52	11.67
6a	C_6H_5-	$C_{26}H_{24}F_3N_3O_3S$	515.3	160	61	8.15	8.26
6b	4-CH_3-C_6H_4-	$C_{27}H_{26}F_3N_3O_3S$	529.3	149	68	7.93	8.02
6c	4-OCH_3-C_6H_4-	$C_{27}H_{26}F_3N_3O_4S$	545.2	153	65	7.70	7.79
6d	4-OH-C_6H_4-	$C_{26}H_{24}F_3N_3O_4S$	531.4	235	47	7.91	7.95
6e	3-Br-C_6H_4-	$C_{26}H_{23}BrF_3N_3O_3S$	594.3	183	65	7.07	7.11
6f	4-Br-C_6H_4-	$C_{26}H_{23}BrF_3N_3O_3S$	594.3	175	63	7.07	7.12
6g	3-Cl-C_6H_4-	$C_{26}H_{23}ClF_3N_3O_3S$	550.1	172	71	7.64	7.69
6h	4-Cl-C_6H_4-	$C_{26}H_{23}ClF_3N_3O_3S$	550.1	163	59	7.64	7.71
6i	3-NO_2-C_6H_4-	$C_{26}H_{23}F_3N_4O_5S$	560.3	190	70	10.00	10.14
6j	2-Thiophenyl-	$C_{24}H_{22}F_3N_3O_3S_2$	521.5	153	55	8.06	8.19
6k	2-Furanyl-	$C_{24}H_{22}F_3N_3O_4S$	505.4	148	63	8.31	8.36
6l	2-Pyridinyl	$C_{25}H_{23}F_3N_4O_3$	516.3	175	52	10.85	10.91

Antibacterial and antifungal activity

The newly synthesized compounds were screened for their antibacterial activity against Gram-positive (*S. aureus* ATCC 6538, *M. luteus* ATCC 9345), Gram negative (*E. coli* ATCC 4230, *S.thyphi* ATCC 14028) bacteria, as described by the guidelines in NCCLS-approved standard document M7-A4, using the micro dilution broth procedure.[21] Ampicillin trihydrate was used as the reference antibacterial agent. The antifungal activities of the newly synthesized chemical compounds were tested against yeast strain (*C. albicans* ATCC 14053) according to the guidelines in NCCLS-approved standard document M27-A2, using the micro dilution broth procedure.[22] Fluconazole was used as the reference antifungal agent. The solutions of test compounds and reference drug were prepared by dissolving in DMSO at a concentration of 2560 µg/mL. The 2-fold dilutions of the compounds and the reference drug were prepared (1280, 640, 320, 160, 80, 40, 20, 10 µg/mL). Antibacterial activities of the newly synthesized chemical compounds were performed in Mueller-Hinton broth medium at a pH of 7.2 with an inoculum of (1-2) × 10^3 cells/mL by the spectrophotometric method, and an aliquot of 100µL solution was added to each tube of serial dilution. The chemical compounds-broth medium serial tube dilutions inoculated with each bacterium were incubated on a rotary shaker at 37°C for 18 hr at 150 rpm. The minimum inhibitory concentration (MIC) of each chemical compound was recorded as the lowest concentration of each chemical compound in the tubes with no growth (i.e., no turbidity) of inoculated bacteria. Minimum inhibitory concentration (MIC, µg/mL) was measured and compared with control; the MIC values of the compound screened are given in **Table 2.**

Id	Ar	Antibacterial Activity				Antifungal Activity
		S.aureus	***M.luteus***	***E.coli***	***S.typhi***	***C.albicans***
5a	C_6H_5-	160	160	80	160	320
5b	4-CH_3-C_6H_4-	80	160	160	80	80
5c	4-OCH_3-C_6H_4-	80	80	80	20	160
5d	4-OH-C_6H_4-	40	40	80	160	80
5e	4-Br-C_6H_4-	80	80	40	80	160
5f	4-Cl-C_6H_4-	20	20	80	40	160
5g	3-Cl-C_6H_4-	20	40	40	20	80
5h	3-Br-C_6H_4-	40	80	40	40	160
5i	3-NO_2-C_6H_4-	40	40	80	40	160
5j	2-Thiophenyl	40	20	160	80	80
5k	2-Furanyl	40	40	80	80	80
5l	2-Pyridinyl	80	40	80	40	80
6a	C_6H_5-	160	80	80	160	160
6b	4-CH_3-C_6H_4-	80	160	80	80	160
6c	4-OCH_3-C_6H_4-	80	80	40	40	80

6d	4-OH-C_6H_4-	40	40	40	20	160
6e	4-Br-C_6H_4-	20	20	80	40	80
6f	4-Cl-C_6H_4-	40	80	80	40	160
6g	3-Cl-C_6H_4-	80	80	40	80	160
6h	3-Br-C_6H_4-	80	40	80	40	80
6i	3-NO_2-C_6H_4-	80	80	80	80	160
6j	2-Thiophenyl	40	40	80	40	80
6k	2-Furanyl	40	40	40	20	80
6l	2-Pyridinyl	20	20	40	40	80
	Ampiciline	20	20	40	20	-
	Fluconazole	-	-	-	-	10

From the result of biological evaluation, it has been observed that the compounds exhibited interesting biological activity, however with a degree of variation. Most of the compounds tested were found to have comparable antibacterial and exhibit low antifungal activity. From the Table 1, it can be observed that compounds 5f, 6f, 6l shows comparable activity against *S. aureus* A, *M. luteus and* compounds 5g, 5i, 6d, 6k shows comparable activity against *E. coli*, *S. thyphi*. The compounds 5d, 5k, 6d, 6j shows moderate activity against *S. aureus* A, *M. luteus*. The compounds 5c, 5e, 6c, 6e, 6f, 6i, 6l were moderate active against *E. coli*, *S. thyphi* and compounds 5h, 5g, 5i, 6h, 6k shows moderate activity against *S. aureus* A, *M. luteus*, *E. coli* and *S. thyphi*., while all the synthesized compounds shows low antifungal activity against *C. albicans*. So result of all preliminary study indicated that the substituted 2-((2-Methoxy-4-(1-methyl-3-aryl-4,5-dihydro-1H-pyrazol-5-yl)phenoxy)methyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine and 6-(3-Methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-4-aryl-1,6-dihydropyrimidine-2-thiol moiety represent a new class of pharmacophore for broad spectrum antibacterial activity.

CONCLUSION

In summary, we have synthesized a series of vanillin incorporated novel Pyrazoline and 1,6-dihydropyrimidine derivatives. All the newly synthesized compounds were confirmed with spectroscopic data like ^{1}H-NMR, Mass, IR Spectra, elemental analysis and evaluated antibacterial and antifungal activity. The antibacterial study shows that Pyrazoline and 1,6-dihydropyrimidine derivatives showed moderate activity with MICs between 20 and 80 µg/mL. The Pyrazolines and 1,6-dihydropyrimidine showed low antifungal activity. The importance of such work lies in the possibility that the new compounds might be more efficacious drugs against bacteria, which could be helpful in designing more potent antibacterial agent for therapeutic use.

ACKNOWLEDGMENTS

The authors are grateful to the Principal, Shree M. & N. Virani Science College, Saurashtra University, Rajkot for providing the research laboratory facility.

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