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Synthesis and Characterization of Fluorinated 4-Thiazolidinones, 4-Imidazolidinones and 2-Azetidinones bearing Pyrimidine Nucleus

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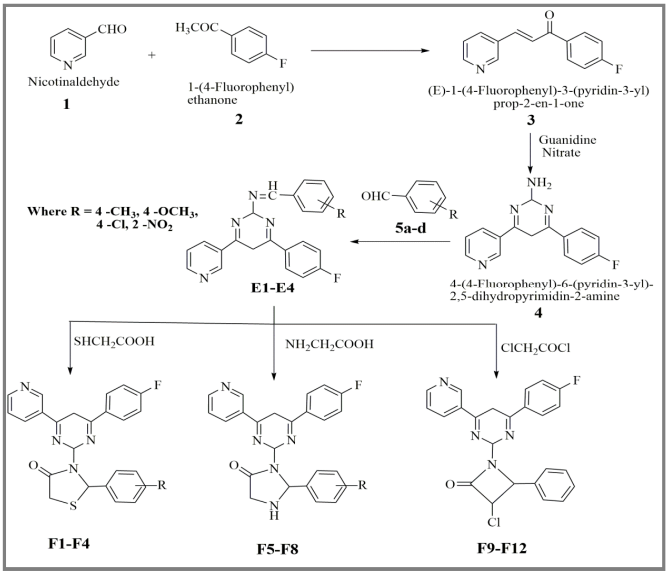
ABSTRACT

Nicotinaldehyde 1 and 1-(4-Fluorophenyl) ethanone 2 were treated to produce α, β-unsaturated ketone 3 which on treatment with Guanidine nitrate to give amine 4. Prepared amine 4 on treatment with various aldehydes 5a-d to produced products E1-E4. Prepared compounds E1-E4 were treated with Thioglycolicacid, Amino acetic acid and Chloroacetylchloride respectively to produce final products 4-thiazolidinones (F1-F4), 4-imidazilidinones (F5-F8) and 2-azetidinones (F9-F12) respectively.

Graphical Abstract



Synthesis of fluorinated pyrimidines compounds [F1-F12].

Keywords: Nicotinaldehyde, Guanidine nitrate, 4-thiazolidinones, 4-imidazilidinones, 2-azetidinones.

INTRODUCTION

Literature reveals that most of the compounds having pyrimidine or thiazolidinone, imidazolidinone and azetidinone nucleus possess pharmacological action [**1-3**]. A wide spectrum of biological activities like anti-inflammatory [**4**], antibacterial [**5**], antifungal [**6**], antitubercular [**7**], analgesic and hypothermic [**8**] are found to be associated with compounds having pyrimidine moiety. **4-thiazolidinones** and its derivatives are known to possess a variety of physiological properties viz analgesics, local [**9**], spiral [**10**] anesthetic, CNS stimulant [**11**], hypnotics [**12**], antibacterial [**13**], antifungal [**14**], antitubercular [**15**], anticancer and anti- HIV [**16**]. **Azetidinones** are also very good anti-bacterial [**17**], antitubercular [**18**] and antifungal [**19**] agents as well as possess pharmacological properties [**20, 21**]. **Imidazolidines** have been reported to have important biological activities such as potential α-adrenergic agonist [**22**], antimicrobial [**23**] antiparasitic [24], oral hypoglycaemic[25], antiarrhythmic and anticonvulsant [**26, 27**], anti-inflammatory [**28**] analgesic [**29**].

One of the most important factors in drug design is that **fluorine** is much more lipophilic than hydrogen; so incorporating fluorine atom in a molecule will make it more fat soluble. This means it percolates into membranes much more readily, and hence the fluorinated molecule has a higher bioavailability. In a view of the above facts, aim is to synthesize novel fluorinated 4-Thiazolidinones, 4-Imidazolidinones and 2-Azetidinones containing pyrimidine nucleus.

MATERIALS AND METHODS

Synthesis of (z)-4-(4-fluorophenyl)-N-(4-methoxybenzylidiene)-6-(pyrimidin-3-yl) pyrimidin-2-amine [E1]: A mixture of Nicotinaldehyde **1** (0.01mol), 4-fluoroacetophenone **2** (0.01mole) and Sodium hydroxide (97% purity) (0.02 mol) was ground together in mortar with pestle till the fine powder was obtained. TLC was checked and solid was taken in cold water followed by acidification using dilute hydrochloric acid till the pH observed 5-6. Stir the mixture for 30 min and solid was filtered, dried and recrystallized from ethanol to give yellow colored product **3**. A mixture of **3** (0.01 mol), Guanidine Nitrate (0.01 mol) and 50% aq. NaOH solution (0.02 mol) was refluxed in 20 mLl ethanol for 8-10 h. Mass was cooled to room temperature and separated solid was filtered out, washed with ethanol, dried to give yellowish white product **4**. A mixture of **4** (0.01 mol), 4-methoxy benzaldehyde **5a** (0.0105 mol) and catalytic amount of glacial acetic acid was refluxed in 20 mL methanol for 6-8 h. Mass was then cooled to room temperature and poured into chilled water. Separated solid was filtered out, dried and crystallized by ethanol to get E1. Similarly, other compounds **[E2-E4]** were prepared and characterized.

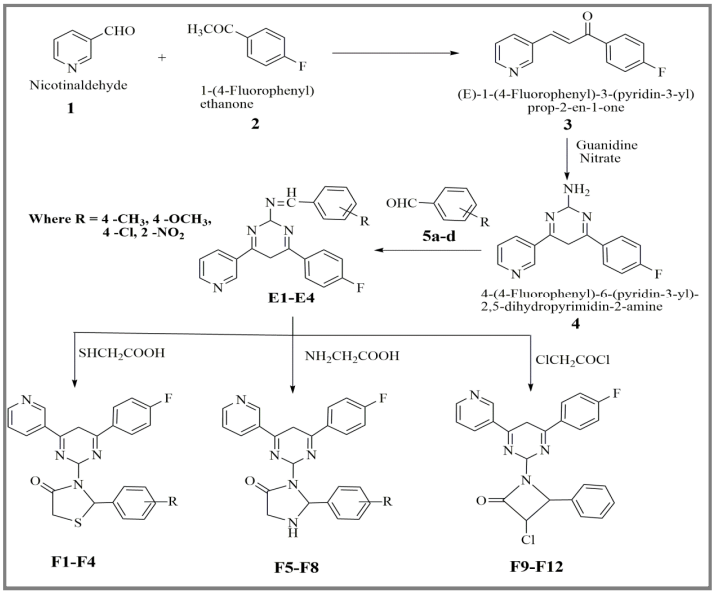
Synthesis of 3-(4-(4-fluorophenyl)-6-(pyrimidin-3-yl)-2,5-dihydropyrimidin-2-yl)-2-(4-methoxy phenyl)thiazolidin-4-one. [F1]: A mixture of compound **E1** (0.01 mole), thioglycolic acid (0.02 mole) and pinch of anhydrous zinc chloride was refluxed for 7-9 h in 20 mL 1,4-dioxane. The progress of reaction was monitored by TLC (toluene:ethyl acetate, 7.5:2.5). After completion, reaction mass was dumped in ice cold water. The product formed was isolated, washed with water and recrystallized from ethanol to give product **F1.** Similarly other compounds **[F2-F4]** were prepared and characterized (Scheme 1).

Synthesis of 3-(4-(4-fluorophenyl)-6-(pyridine-3-yl)-2,5-dihydropyrimidin-2-yl)-2-(4-methoxy phenyl) imidazolidin-4-one [F5]: A mixture of compound **E1** (0.01 mole), glycine (0.01 mole) was refluxed in 20 ml toluene for 8-10 h and formed water was removed using Dean-stark apparatus azeotropically. Mass was cooled and Separated solid was filtered out, dried and crystallized by ethanol to give product **F5.** Similarly other compounds **[F6-F8]** were prepared and characterized (Scheme 1).

Synthesis of 3-chloro-1-(4-(4-fluorophenyl)-6-(pyridine-3-yl)-2,5-dihydropyrimidin-2-yl)-4-(4-methoxy phenyl) azetidin-2-one [F9]: To a stirred solution of compound **E1** (0.01 mol) in 1,4-

dioxane (20 mL), chloro acetyl chloride (0.01 mol) was added drop by drop at 0-5°C in the presence of triethyl amine (0.01 mol) as catalyst. The reaction mixture was heated at 90°C for 2-4 h. The mass was then cooled and poured on to crushed ice with constant stirring. The solid thus obtained was recrystallized from DMF to give product **F9.** Similarly other compounds **[F10-F12]** were prepared and characterized (Scheme 1).

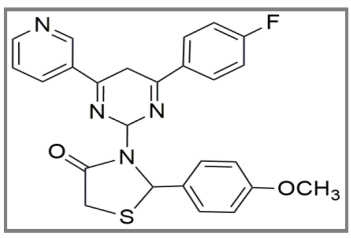
Characterization of compounds F1-F12: Melting points (M P.) were measured using µ-Thermo Cal_{10} (Analab scientific Pvt. Ltd.) melting point apparatus & are uncorrected. TLC was carried out using silica gel 60 F_{254} precoated with aluminum sheets. ^{13}C NMR and ^{1}H NMR spectra were recorded on a Bruker Avance 400 spectrophotometer operating at 100 MHz for NMR and 400 MHz for ^{1}H ^{13}C NMR under solutions in DMSO-d_6. Chemical shifts (δ) are designated in ppm and referenced to the residual protic solvent. FT-IR spectra were measured using Shimadzu FT-IR 8401 spectrophotometer with KBr disc, and are written in wave numbers (cm^{-1}). The mass spectra (LCMS) were measured using Shimadzu LCMS-2010 spectrometer.



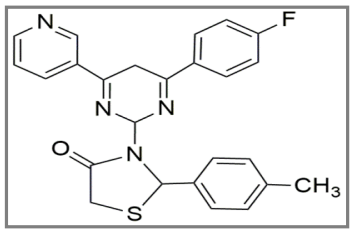
Scheme 1. Synthesis of fluorinated pyrimidines compounds [F1-F12].

Spectral Data analysis of some selected compounds

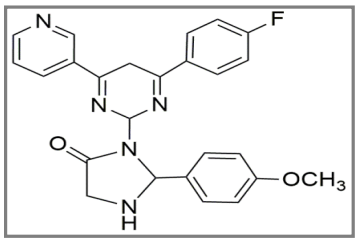
Compound F1: Molecular formula $C_{25}H_{21}FN_4O_2S$, **M. P. (°C):** >250, **^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:** 3.0 (2H, CH_2, s), 3.3 (2H, CH_2, s), 3.6 (3H, OCH_3, s), 4.7 (1H, CH, s), 5.2 (1H, CH, s), 6.86-7.40 (12H, Ar-H, m). **^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:** 33.4, 35.2, 39.6, 60.2, 90.0, 128.1, 129.3, 130.1, 131.4, 131.9, 142.2, 143.6, 145.1, 149.2, 151.8, 153.6, 154.1, 155.1, 155.8, 170, **IR cm^{-1} (KBr):** 3005 (Aromatic stretch), 1701 (C=O Stretch.), 1644 (C=N Strech.), 1635 (C-S Strech)., 1614, 1592 (Aromatic C=C bend.), 1560 (Aromatic C=C Stretch.), 752, 700 (bending of substituted Ar ring). **Mass (M+1):** 460.0, **Elemental analysis: Calculated (%):** C: 60.20; H: 4.60; N:12.17, **Found (%):** C:60.32; H: 4.76; N:12.36.



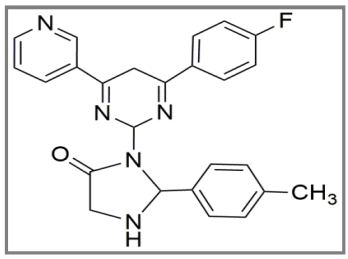
Compound F2: Molecular formula $C_{25}H_{21}FN_4OS$, **M. P. (°C):** >250, **^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:** 2.3 (3H, CH_3, s), 3.0 (2H, CH_2, s), 3.3 (2H, CH_2, s), 4.7 (1H, CH, s), 5.2 (1H, CH, s), 6.86-7.40 (12H, Ar-H, m). **^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:** 33.4, 35.2, 39.6, 40.2, 90.0, 128.1, 129.3, 130.1, 131.4, 131.9, 142.2, 143.6, 145.1, 149.2, 151.8, 153.6, 154.1, 155.1, 155.8, 170. **IR cm^{-1} (KBr):** 3002 (Aromatic Stretch), 1705 (C=O Stretch.), 1650 (C=N Strech.), 1635 (C-S Strech), 1614, 1592, 1570 (Aromatic C=C bend.), 752, 701 (bending of substituted Ar ring). **Mass (M+1):** 444.0, **Elemental analysis: Calculated (%):** C: 67.55; H: 4.76; N:12.60, **Found (%):** C: 67.60; H: 4.86; N:12.70,



Compound F5: Molecular formula $C_{25}H_{22}FN_5O_2$, **M. P. (°C):** >250, **^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:** 2.1(NH, s), 3.2 (2H, CH_2, s), 3.3 (2H, CH_2, s), 3.6 (3H, OCH_3, s), 4.7 (1H, CH, s), 5.2 (1H, CH, s), 6.86-7.40 (12H, Ar-H, m). **^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:** 33.4, 35.2, 39.6, 60.2, 90.0, 128.1, 129.3, 130.1, 131.4, 131.9, 142.2, 143.6, 145.1, 149.2, 151.8, 153.6, 154.1, 155.1, 155.8, 170, **IR cm^{-1} (KBr):** 3400 (N-H Stretch)., 3005 (Aromatic Stretch.), 1701 (C=O Stretch.), 1644 (C=N Strech.), 1635 (C-S Strech.), 1614, 1592, 1560 (Aromatic C=C bend.), 752, 700 (bending of substituted Ar ring). **Mass (M+1):** 443.0. **Elemental analysis: Calculated (%):** C: 67.71; H: 5.00; N:15.79, **Found (%):** C: 67.85; H: 5.12; N:15.85.

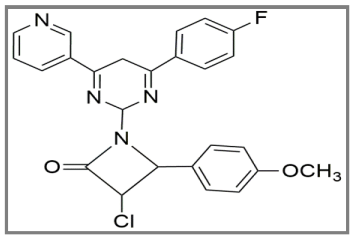


Compound F6: Molecular formula $C_{25}H_{22}FN_5O$, **M. P. (°C):** >250, **^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:** 2.1 (1H, NH), 2.3 (3H, OCH_3, s), 3.2 (2H, CH_2, s), 3.3 (2H, CH_2, s), 4.7 (1H, CH, s), 5.2 (1H, CH, s), 6.86-7.40 (12H, Ar-H, m). **^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:** 33.4, 35.2, 39.6, 40.2, 90.0, 128.1, 129.3, 130.1, 131.4, 131.9, 142.2, 143.6, 145.1, 149.2, 151.8, 153.6, 154.1, 155.1, 155.8, 170. **IR cm^{-1} (KBr):** 3350 (N-H Stretch.), 3002 (Aromatic Stretch.), 1705 (C=O Stretch.), 1650 (C=N Stretch.), 1640 (C-S Stretch.), 1614, 1592, 1570 (Aromatic C=C bend.), 752, 701 (bending of substituted Ar ring). **Mass (M+1):** 427.0, **Elemental analysis: Calculated (%):** C: 70.24; H: 5.19; N: 16.38, **Found (%):** C: 70.60; H: 5.86; N: 16.70

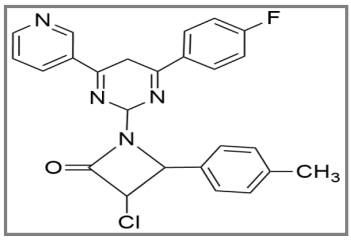


Compound F9: Molecular formula $C_{25}H_{20}FClN_4O_2$, **M. P. (°C):** >250, **^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:** 3.3 (2H, CH_2, s), 3.6 (3H, OCH_3, s), 3.8 (1H, CH, t), 4.7 (1H, CH, d), 5.2 (1H, s), 6.86-7.40

(12H, Ar-H, m). **^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:** 32.4, 35.2, 39.6, 60.2, 92.0, 128.1, 130.3, 130.1, 131.4, 131.9, 142.2, 143.6, 145.1, 149.2, 151.8, 153.6, 154.1, 155.1, 155.8, 170. **IR cm^{-1} (KBr):** 2980 (Aromatic Stretch.), 1705 (C=O Stretch.), 1644, 1635 (C=N Stretch.), 1614 (C-S Stretch.), 1592, 1560 (Aromatic C=C bend.), 752, 700 (bending of substituted Ar ring). **Mass (M+1):** 462.0, **Elemental analysis: Calculated (%):** C: 64.87; H: 4.35; N:12.10 , **Found (%):** C: 64.92; H: 4.76; N:12.36.



Compound F10: Molecular formula $C_{25}H_{20}FClN_4O$, **M. P. (°C):** >250, **^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:** 2.3 (3H, CH_3, s), 3.3 (2H, CH_2, s), 3.8 (1H, CH, t), 4.7 (1H, CH, d), 5.2 (1H, CH, s), 6.86-7.40 (12H, Ar-H, m). **^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:** 32.4, 35.2, 39.6, 49.2, 92.0, 128.1, 130.3, 130.1, 131.4, 131.9, 142.2, 143.6, 145.1, 149.2, 151.8, 153.6, 154.1, 155.1, 155.8, 170. **IR cm^{-1} (KBr):** 2980 (Aromatic Stretch.), 1705 (C=O Stretch.), 1644 (C=N Stretch.), 1635 (C-S Strech.), 1614, 1592, 1560 (Aromatic C=C bend.), 752, 700 (bending of substituted Ar ring). **Mass (M+1):** 446.0, **Elemental analysis: Calculated (%):** C: 67.19; H: 4.51; N:12.54, **Found (%):** C: 67.50; H: 4.76; N:12.66.



RESULTS AND DISCUSSION

Table 1 shows the various condensation products **F1-F12** from the condensation reaction between **E1-E4** with thioglycolic acid, amino acetic acid and Chloroacetylchloride respectively. It clearly indicates that the compounds bearing electron withdrawing group are synthesized in shorter reaction time as compared to compounds bearing electron donating group.

Table 1. Characteristic data of synthesized compounds F1-F12 from E1-E4

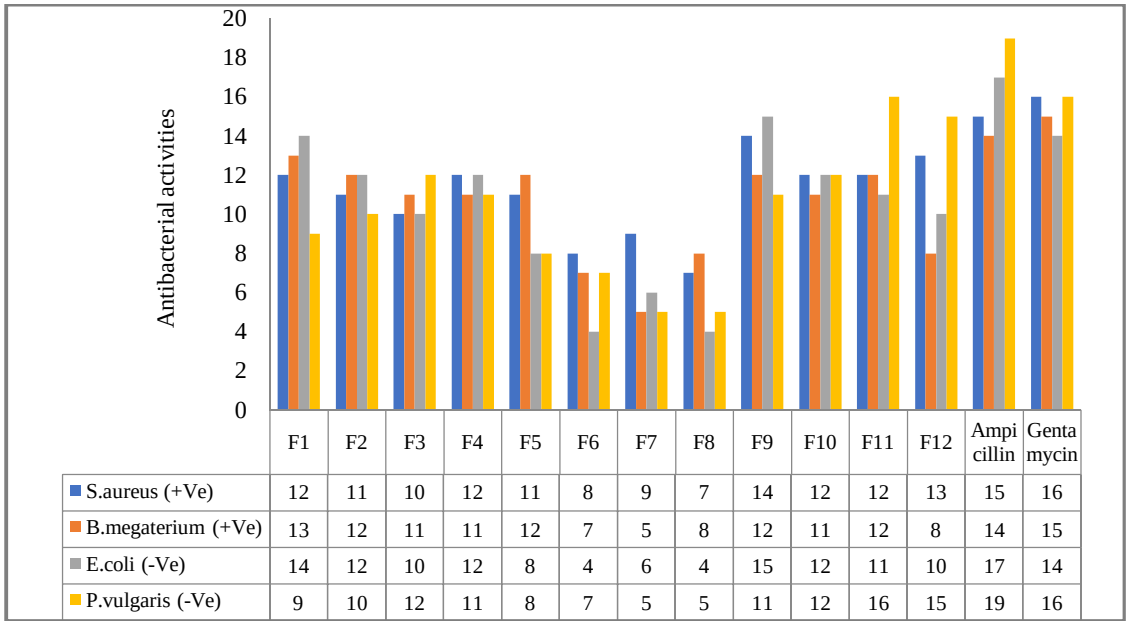
S. No.	Compounds Code	R'	Condensation with	Reaction Time[a] (h)	% Yield[b]
1	**F1**	4-OCH_3	$SHCH_2COOH$	9	60
2	**F2**	4-CH_3	$SHCH_2COOH$	8.5	65
3	**F3**	4-Cl	$SHCH_2COOH$	7	70
4	**F4**	2-NO_2	$SHCH_2COOH$	7	77
5	**F5**	4-OCH_3	NH_2CH_2COOH	10	58
6	**F6**	4-CH_3	NH_2CH_2COOH	9.5	63
7	**F7**	4-Cl	NH_2CH_2COOH	8	71
8	**F8**	2-NO_2	NH_2CH_2COOH	8	78
9	**F9**	4-OCH_3	$ClCH_2COCl$	3	60
10	**F10**	4-CH_3	$ClCH_2COCl$	3	67
11	**F11**	4-Cl	$ClCH_2COCl$	2	70
12	**F12**	2-NO_2	$ClCH_2COCl$	2	77

[a]Reaction is monitored by TLC, [b]Isolated yield

All the compounds were crystallized from hot ethanol and percentage yield was calculated after crystallization step. All the synthesized compounds have been characterized by melting point, ^{1}H NMR, ^{13}C NMR, IR and Mass spectroscopy. All the data were in agreement with the cited literature.

APPLICATION

Biological Evaluations: The antibacterial potency of the drugs was screened by disc plate process [13].The test discs were having 50 µg per disc of the examination drugs. The potency was revealed next to gram +ve bacteria are *Bacillus megaterium* [MTCC (121)], *Staphylococcus aureus* [MTCC (96)] and gram –ve bacteria *Proteus vulgaris* [MTCC (1771)], *Escherichia coli* [MTCC (443)].



	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	Ampicillin	Gentamycin
S.aureus (+Ve)	12	11	10	12	11	8	9	7	14	12	12	13	15	16
B.megaterium (+Ve)	13	12	11	11	12	7	5	8	12	11	12	8	14	15
E.coli (-Ve)	14	12	10	12	8	4	6	4	15	12	11	10	17	14
P.vulgaris (-Ve)	9	10	12	11	8	7	5	5	11	12	16	15	19	16

Figure 1. Antibacterial activities of potency of synthesized drugs.

Against *Staphylococcus aureus*: Maximum activities were found in compounds (**F9** and **F12**) zone of inhibition-14.0 mm where as minimum activities were found in compound (**F7** and **F8**) zone of inhibition-7.0 mm.

Against *Bacillus megaterium*: Maximum activity were found in compounds (**F1, F2, F5, F9** and **F11**) zone of inhibition-13.0 mm and minimum activity were found in compounds (**F7**) zone of inhibition-5.0 mm.

Against *Escherichia coli*: Maximum activity were found in compound (**F1, F2, F4, F9** and **F12**) zone of inhibition -15.0 mm (near to standard drug) and minimum activity were found in compounds (**F6** and **F8**) zone of inhibition-4.0 mm.

Against *Proteus vulgaris*: Maximum activity were found in compounds (**F3, F10, F11** and **F12**) zone of inhibition -16.0 mm and minimum activity were found in compounds (**F7** and **F8**) zone of inhibition-5.0 mm.

CONCLUSION

Synthesized novel fluorinated 4-Thiazolidinones, 4-Imidazolidinones and 2-Azetidinones bearing pyridine-pyrimidine clubbed moiety as potential antimicrobial agents.

ACKNOWLEDGEMENTS

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