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Synthesis, Characterization and Biological Screening of Some Novel Fluorinated pyrano Fused Sulfonyl Pyrimidine Derivatives.

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Abstract: ***The synthesis of Fluorinated pyrano fused sulfonyl pyrimidine derivatives [D1-D8] were carried out by the reaction of substituted sulfonyl urea's 3a-b with malonic acid to produce sulfonyl pyrimidines 4a-b which on treatment with various aldehydes 5a-d to produce final products D1-D8 (Scheme 3.II).***
Keywords: ***Sulfonyl Pyrimidine derivatives, malonic acid, substituted sulfonyl urea, meldrum acid***

I. INTRODUCTION

It is no great surprise that around a fifth of all drugs on the market today contain at least one Fluorine substituent. The inclusion of a fluorine atom in a drug molecule can influence not only pharmacokinetic properties, such as absorption, tissue distribution, secretion, and the route and rate of biotransformation but also its pharmacodynamics and toxicology. Introducing fluorine substituent often improves lipophilicity, and suppresses metabolic detoxification processes to increase the *in vivo* lifetime of drugs.
The fused pyrimidines are an important class of compounds as chemotherapeutic agents for their antibacterial[1], antiviral[2] and cytotoxic[3] properties. The pyran of used pyramiding showed a broad range of biological activities such as ant tubercular, antimicrobial[4,5], antiplatelet[6], antifungal[7], antiviral[8], analgesic as well as anticonvulsant activities and also showed effects against amphetamine induced stereotypy and on potentiating of pentobarbitone sodium hypnosis[9]. Moreover, all the compounds which have a uracil moiety in the skeleton of an organic molecule sshowed antitumor, antibacterial, bronchodilator, vasodilator, antihypertensive, cardiotonic, hepato protective, and ant allergic activities; some of them also exhibit antimalarial, analgesic, antifungal, and herbicidal properties[10,11,12]. In a view of the above facts, aim is to synthesize novel fluorinated pyrano fused pyrimidine derivatives.

II. MATERIALS AND METHODS

A. *Synthesis of methyl 2-(3-(4-fluorophenyl)-2,4,6-trioxotetrahyropyrimidin-1(2H)-ylsulfonyl)benzoate [4a].*

In a 250 ml round bottom flask, methyl 2-(N-(4-fluorophenylcarbamoyl) sulfamoyl) benzoate 3a (0.01mol) was heated with Malonic acid (0.01 mol) and acetyl chloride (20 ml) under reflux temperature for 2-3 hrs. Cooled mass was then poured into crushed ice under vigorous stirring & stirred for 1 hr. The formed precipitates was filtered out, washed & crystallized by MeOH to give 4a. Similarly other compound [4b] were prepared and characterized. (Scheme 3.II).

B. *Synthesis of methyl 2-(1-(4-fluorophenyl)-5-(4-methoxyphenyl)-2,4,7-trioxo-6,7-dihydro-1H-pyrano[2,3-d]pyrimidin-3(2H,4H,5H)-ylsulfonyl)benzoate [D1]*

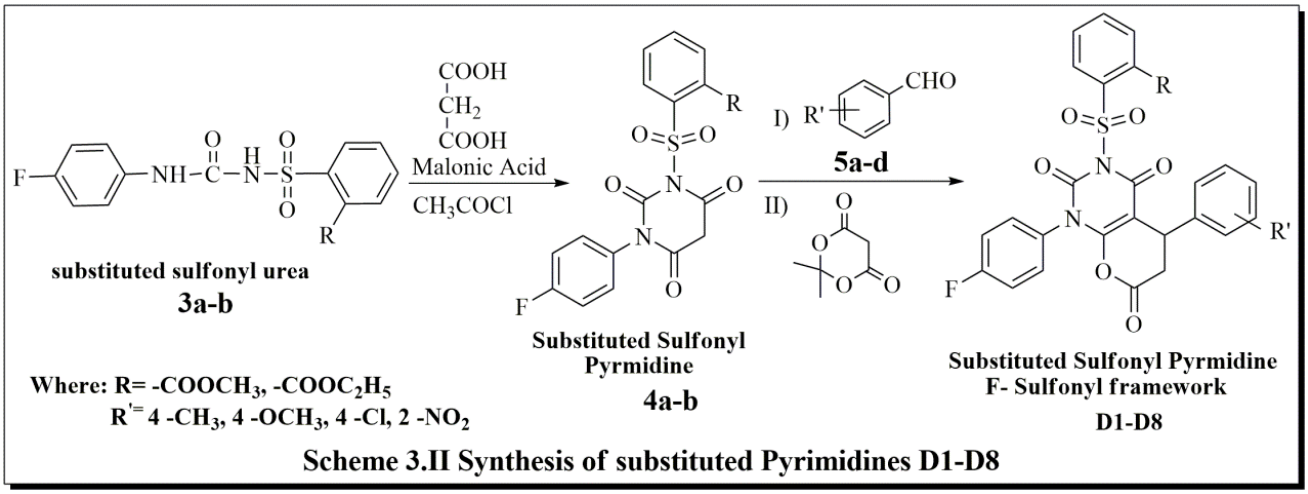
In a 250 ml round bottom flask, A mixture of 4a (0.01 mol), 4-methoxybenzaldehyde 5a (0.01 mol), meldrum acid (0.01mol) and catalytic amount of piperidine in 20 ml ethanol was refluxed for 3-4 hrs. The reaction mass was cooled to room temperature, separated solid was filtered out and recrystallized by ethanol to give D1. Similarly other compounds [D2-D8] were prepared and characterized. (Scheme 3.II).

C. *Characterization Of Compounds D1-D8*

Melting points (M P.) were measured using µ-ThermoCal$_{10}$ (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.

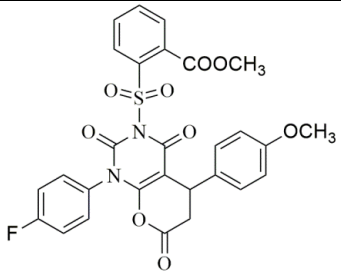
Chemical shifts (δ) are designated in ppm and referenced to the residual protic solvent. FT-IR spectra were measured using Shimadzu FT-IR 8401 spectrophotometer with KBr disc, and are written in wave numbers (cm^{-1}). The mass spectra (LCMS) were measured using Shimadzu LCMS-2010 spectrometer.

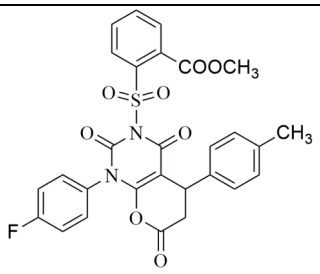
D. Reaction Scheme for The Synthesis Of Compounds [D1-D8]

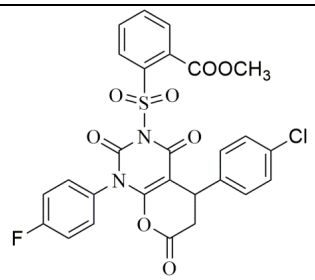


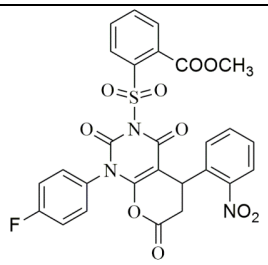
Scheme 3.II Synthesis of substituted Pyrimidines D1-D8

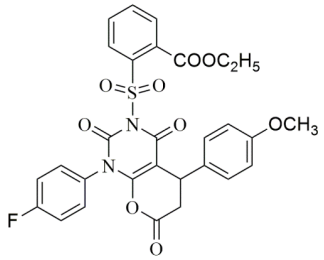
E. Spectral data analysis of compounds

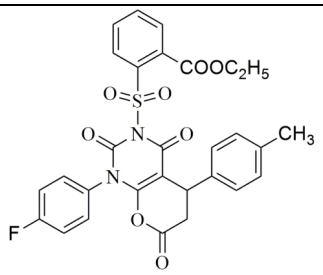
Compound code: D1	
Molecular formula: $C_{28}H_{21}FN_2O_9S$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.0 (2H, CH_2, d), 3.4 (3H, OCH_3, s), 3.8 (1H, CH, t), 4.2 (3H, OCH_3, s), 6.86-7.40 (12H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.4, 35.2, 39.6, 40.2, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168, 170, 173
IR cm^{-1} (KBr):	3032 (C-H Aromatic stretch.), 1770 (C=O Aliphatic Ester), 1750 (C=O Cyclic Ester), 1644 (C=O amide Stretch.), 1635 (S=O Stretch.), 1600 (C=C Aliphatic stretch.), 1515 (C-F bend)., 1560 (C=C Ar. Stretch.), 753 (Ar C-H bend).
Mass (M+1):	580.0
Elemental analysis:	Calculated (%): C: 57.93; H: 3.65; N:4.83 Found (%) : C:58.12; H: 3.76; N:4.89

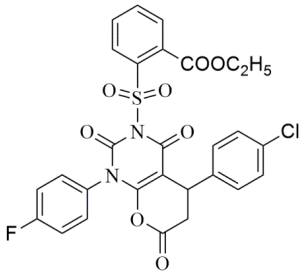
Compound code: D2	
Molecular formula: $C_{28}H_{21}FN_2O_8S$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	2.3 (3H, CH_3, s), 3.0 (2H, CH_2, d), 3.8 (1H, CH, t), 4.2 (3H, OCH_3, s), 6.86-7.40 (12H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.4, 35.2, 36.1, 40.2, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168, 170, 173
IR cm^{-1} (KBr):	3100 (C-H Aromatic stretch)., 1760 (C=O Aliphatic Ester), 1745 (C=O Cyclic Ester), , 1644 (C=O amide Stretch.), 1640 (S=O Stretch.)., 1600 (C=C Aliphatic stretch.), 1592 (C-F bend)., 1550 (C=C Ar. Stretch.), 752 (Ar C-H bend).
Mass (M+1):	564.0
Elemental analysis:	Calculated (%): C: 59.57; H: 3.75; N:4.96 Found (%) : C:59.70; H: 3.81; N:4.98

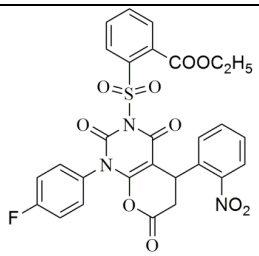
Compound code: D3	
Molecular formula: $C_{28}H_{18}FClN_2O_8S$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, CH_2, d), 3.7 (3H, OCH_3, s), 3.8 (1H, CH, t), 6.86-7.40 (12H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.4, 35.2, 40.2, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168, 170, 173
IR cm^{-1} (KBr):	2900 (C-H Aromatic stretch.), 1770 (C=O Aliphatic Ester), 1750 (C=O Cyclic Ester), 1645 (C=O amide Stretch.), 1635 (S=O Stretch), 1600 (C=C Aliphatic stretch.), 1591 (C-F bend)., 1560 (C=C Ar. Stretch.), 650 (Ar C-H bend).
Mass (M+1):	584.0
Elemental analysis:	Calculated (%): C: 55.44; H: 3.10; N:4.79 Found (%) : C:55.54; H: 3.12; N:4.89

Compound code: D4	
Molecular formula: $C_{27}H_{18}FN_3O_{10}S$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, CH_2, d), 3.8 (1H, CH, t), 4.2 (3H, OCH_3, s), 6.86-7.40 (12H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.4, 35.2, 40.2, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168, 170, 173
IR cm^{-1} (KBr):	3020 (C-H Aromatic stretch.), 1766 (C=O Aliphatic Ester), 1750 (C=O Cyclic Ester), 1644 (C=O amide Stretch.) 1635 (S=O Stretch), 1614 (NO_2 Bend)., 1600 (C=C Aliphatic stretch.), 1592 (C-F bend). 1560 (C=C Ar. Stretch.), 752 (Ar C-H bend).
Mass (M+1):	595.0
Elemental analysis:	Calculated (%): C: 54.46; H: 3.05; N:7.06 Found (%) : C:54.56; H: 3.15; N:7.12

Compound code: D5	
Molecular formula: $C_{29}H_{23}FN_2O_9S$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, CH_2, d), 3.4 (3H, OCH_3, s), 3.6 (3H, OCH_3, s), 3.8 (1H, CH, t), 4.5 (2H, CH_2, q), 6.86-7.40 (12H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.4, 35.2, 38.1, 39.6, 40.2, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168, 170, 173
IR cm^{-1} (KBr):	2950 (C-H Aromatic stretch.), 1770 (C=O Aliphatic Ester), 1750 (C=O Cyclic Ester), 1644 (C=O amide Stretch.) 1635 (S=O Stretch), 1600 (C=C Aliphatic stretch.), 1592 (C-F bend)., 1560 (C=C Ar. Stretch.), 752 (Ar C-H bend).
Mass (M+1):	594.0
Elemental analysis:	Calculated (%): C: 58.58; H: 3.90; N:4.71 Found (%) : C:58.60; H: 3.95; N:4.89

Compound code: D6	
Molecular formula: $C_{29}H_{23}FN_2O_8S$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (3H, OCH_3, s), 3.2 (2H, CH_2, d), 3.6 (3H, OCH_3, s), 3.8 (1H, CH, t), 4.5 (2H, CH_2, q), 6.86-7.40 (12H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.4, 35.2, 36.2, 38.1, 40.2, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168.0, 170.0, 173.0.
IR cm^{-1} (KBr):	3000 (C-H Aromatic stretch.), 1770 (C=O Aliphatic Ester), 1750 (C=O Cyclic Ester), 1644 (C=O amide Stretch.), 1640 (S=O Stretch), 1600 (C=C Aliphatic stretch.),1589 (C-F bend)., 1560 (C=C Ar. Stretch.), 750 (Ar C-H bend)..
Mass (M+1):	578.0
Elemental analysis:	Calculated (%): C: 60.20; H: 4.01; N:4.84 Found (%) : C:60.60; H: 3.95; N:4.89

Compound code: D7	
Molecular formula: $C_{28}H_{20}FClN_2O_8S$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, CH_2, d), 3.7 (3H, OCH_3, s), 3.8 (1H, CH, t), 4.5 (2H, CH_2, q), 6.86-7.40 (12H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.4, 35.2, 36.2, 38.1, 40.2, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168, 170, 173
IR cm^{-1} (KBr):	3251 (C-H Aromatic stretch.), 1770 (C=O Aliphatic Ester), 1750 (C=O Cyclic Ester), 1644 (C=O amide Stretch.), 1635 (S=O Stretch), 1600 (C=C Aliphatic stretch.), 1588 (C-F bend)., 1560 (C=C Ar. Stretch.), 752 (Ar C-H bend).
Mass (M+1):	598.0
Elemental analysis:	Calculated (%): C: 56.15; H: 3.37; N:4.68 Found (%) : C:56.60; H: 3.45; N:4.89

Compound code: D8	
Molecular formula: $C_{28}H_{20}FN_3O_{10}S$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, CH_2, d), 3.6 (3H, OCH_3, s), 3.8 (1H, CH, t), 4.5 (2H, CH_2, q), 6.86-7.40 (12H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.4, 35.2, 36.2, 38.1, 40.2, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168, 170, 173
IR cm^{-1} (KBr):	3000 (C-H Aromatic stretch.), 1770 (C=O Aliphatic Ester), 1750 (C=O Cyclic Ester), 1644 (C=O amide Stretch.), 1630 (S=O Stretch), 1614 (NO_2 Bend.), 1600 (C=C Aliphatic stretch.), 1591 (C-F bend)., 1560 (C=C Ar. Stretch.), 752 (Ar C-H bend).
Mass (M+1):	609.0
Elemental analysis:	Calculated (%): C: 55.17; H: 3.31; N: 6.89 Found (%) : C:55.60; H: 3.45; N:6.91

III. RESULTS AND DISCUSSIONS

Table 3.2 show the various condensation products D1-D8 derived from substituted sulfonyl urea (3a-b). It clearly indicates that the compounds bearing electron withdrawing group are synthesized in shorter reaction time as compared to compounds bearing electron donating group. Compounds D4 & D8 bearing electron withdrawing group were synthesized in 4.5 hr. as shorter time as compared to compound D1 & D5 bearing electron donating group in 6.5 hr.

Table 3.2 Characteristic data of synthesized compounds D1-D8 from substituted sulfonyl urea 3a-b.

Sr.No.	Compounds Code	R'	R	Reaction Time[a] (hr.)	% Yield[b]
1	D1	4-OCH_3	-$COOCH_3$	6.5	65
2	D2	4-CH_3	-$COOCH_3$	6	67
3	D3	4-Cl	-$COOCH_3$	5	70
4	D4	2-NO_2	-$COOCH_3$	4.5	76
5	D5	4-OCH_3	-$COOC_2H_5$	6.5	64
6	D6	4-CH_3	-$COOC_2H_5$	6	68
7	D7	4-Cl	-$COOC_2H_5$	5	72
8	D8	2-NO_2	-$COOC_2H_5$	4.5	76

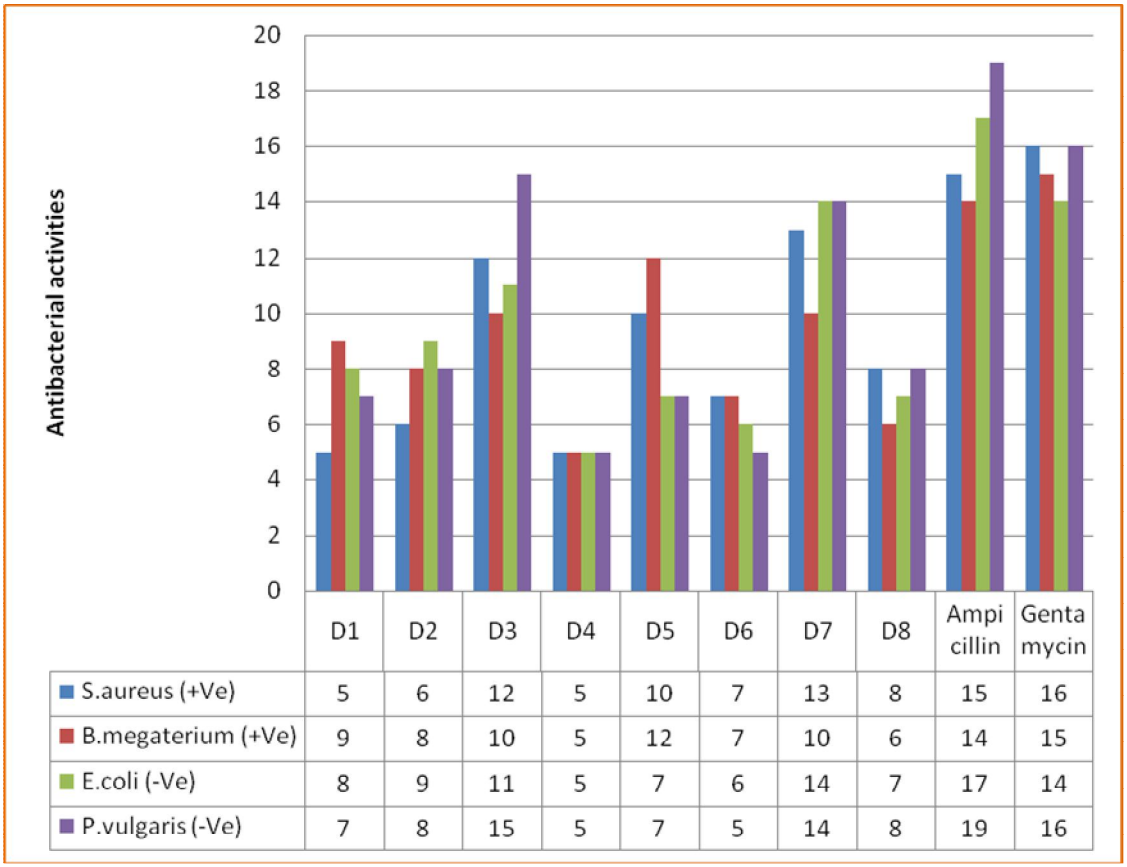
A. Reaction is monitored by TLC.
B. Isolated yield

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.

IV. APPLICATIONS

A. *Biological Evaluations*

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



	D1	D2	D3	D4	D5	D6	D7	D8	Ampicillin	Gentamycin
S.aureus (+Ve)	5	6	12	5	10	7	13	8	15	16
B.megaterium (+Ve)	9	8	10	5	12	7	10	6	14	15
E.coli (-Ve)	8	9	11	5	7	6	14	7	17	14
P.vulgaris (-Ve)	7	8	15	5	7	5	14	8	19	16

B. *Against Staphylococcus aureus*

Maximum activity were found in compounds (D3, D5 & D7) zone of inhibition-13.0 m.m. and minimum activity were found in compounds (D1 & D2) zone of inhibition -6.0 m.m

C. *Against Bacillus megaterium*

Maximum activity were found in compounds (D3, D5 & D7)) zone of inhibition -12.0 m.m where as minimum activity were found in compound (D8) zone of inhibition -6.0 m.m.

D. *Against Escherichia coli*

Maximum activity were found in compounds (D3 & D7) zone of inhibition -14.0 m.m and minimum activity were found in compounds (D4) zone of inhibition -5.0 m.m

E. *Against Proteus vulgaris*

Maximum activity were found in compound (D3 & D7) zone of inhibition -15.0 m.m (near to standard drug) and minimum activity were found in compounds (D4 & D6) zone of inhibition -5.0 m.m

V. CONCLUSION

In conclusion, we have synthesized of novel fluorinated pyrano fused sulfonyl pyrimidine derivatives as potential antimicrobial agents.

VI. ACKNOWLEDGMENTS

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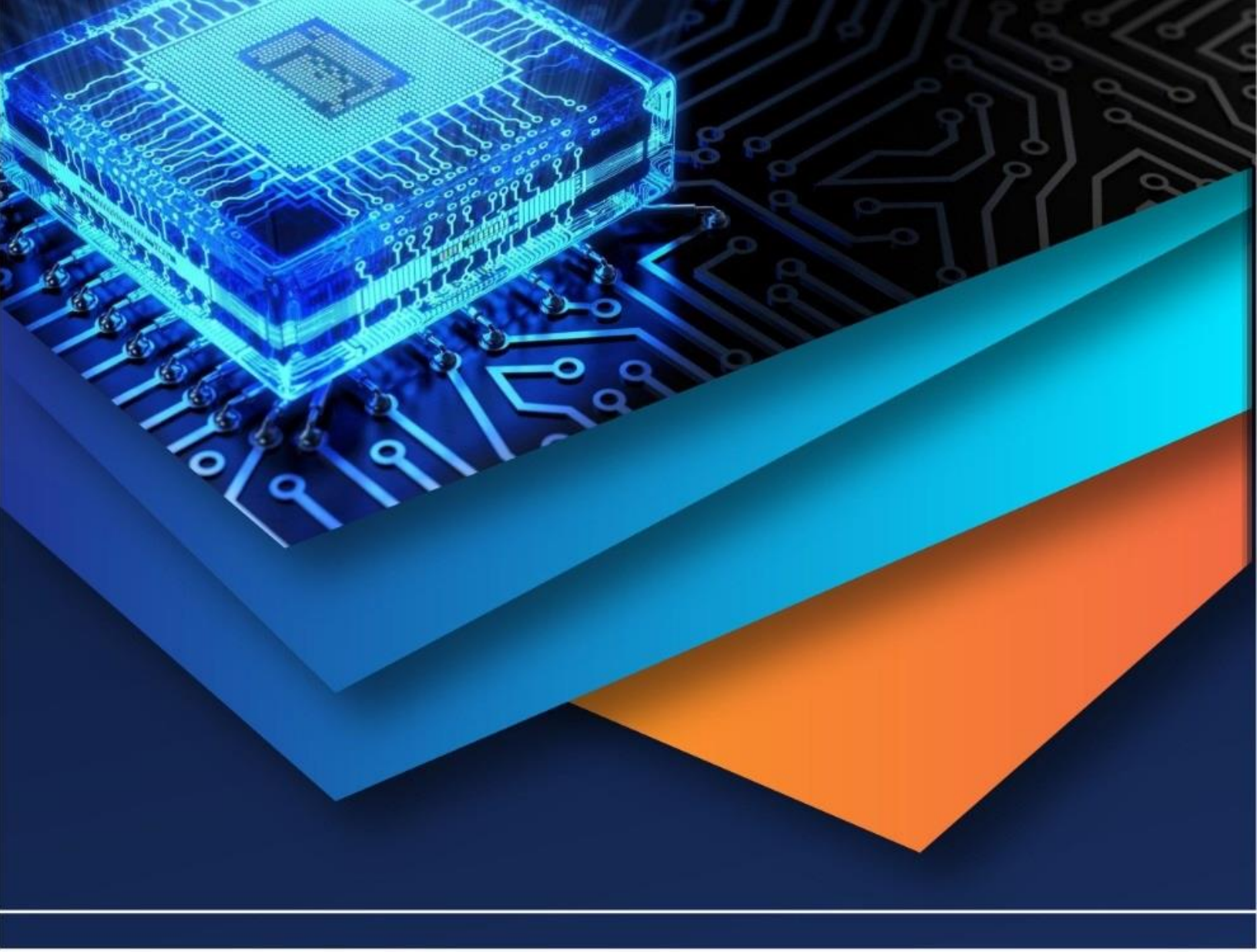

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