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Synthesis, Characterization and Evaluation the Biological Activity of New Payrazolo{3,4 d} Pyrimidine Derivatives

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Abstract: ***Allopurinol derivative were prepared by reacting the allopurinol with chloroacetyl chloride in the presence triethylamine as an catalyst and diethylether as a solvent gave the (1-chloroacetyl)-2-Hydropyrazolo{3,4-d}pyrimidine-4-one which reaction with substituted 2-amino benzothiazole under certain conditions to give new compounds(A-A$_{10}$) and reaction of 5-substituted-2-amino-1,3,4-oxadiazolein in the presence of potassium carbonate anhydrous to give new compounds (A21-A30) respectively. The chemical structure synthesis compound were identified by spectral methods their (FT-IR and^{1}H- NMR) and measurement some of its physical properties. The synthesized compoundS were screened for antibacterial activity.***

Keywords: Allopurinol, 2-aminobenzothiazole, 5-substituted-2-amino-1,3,4-oxadiazole, antimicrobial.

1. Introduction

Allopurinol, 1H-pyrazolo [3,4-d]pyrimidin-4(2H)-one is a drug used primarily to treat hyperuricemia and its complications, including chronic gout. It is administered orally and is an inhibitor of the enzyme xanthine oxidase which is responsible for the successive oxidation of hypoxanthine and xanthine, resulting in the production of uric acid, the product of human purine metabolism [(1)]. It is a very weak acid therefore essentially unionized at all physiological pH values. Allopurinol is a polar compound with strong intermolecular hydrogen bonding and limited solubility in both polar and non polarmedia[(2)] .

2. Material and Methods

Chemicals used in this work are supplied from Merck, BDH, Sigma Aldirch, Fluka, GCC companies and are used without further purification. Melting points were recorded using digital stuart scientific SMP3 Melting points apparatus and are uncorrected. SHIMAZU FT-IR-8400 Fourier transform Infrared spectrophotometer using KBr discs in the (4000 - 6000) cm-1 spectral range. 1H-NMR spectra were recorded on using DMSO-d6 as solvent and TMS as internal reference.

3. Experimental

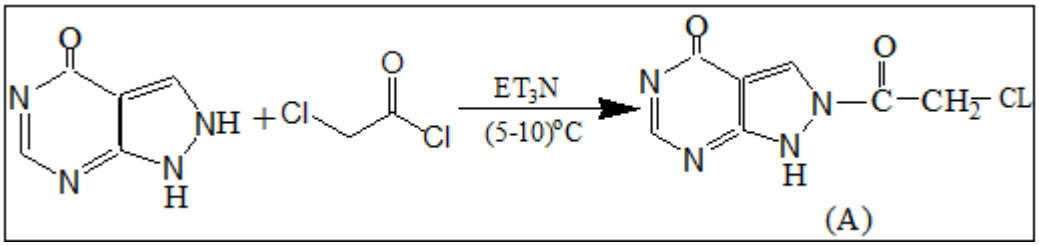
Synthesis of 2-Chloroacetyl Allopurinol[(3)](compound A)
To a mixture of Allopurinol (0.01 mol) in Diethyl ether (15ml), triethylamine (0.025 mol), was added chloroacetylchloride(0.025 mol) drop-wise at (5-10) C°.The reaction mixture was then stirred for (6) hrs. And left at room temperature for 24 hours then poured into crushed ice. The solid separated was dried and recrystallized from ethanol and water. Melting points, yield% data are listed in Table (1).

Synthesis of N-(2-aminoacetyl substituted benzothiazole-2-yl)Allopurinol[(4)] (A-A10)
A mixture of compound (A) (0.008 mol.) in absolute ethanol (25 ml.) and potassium carbonate anhydrous (0.008 mol.) was refluxed and added dropwise to a solution of (0.008 mol.) of substituted-2-aminobenzothiazole dissolved in (30 ml.) of absolute ethanol, the reaction mixture was refluxed for (8-10) hrs. after cooling the separated precipitate was filtered and recrystalized from a suitable solvent. Physical properties are listed in Tables (1).

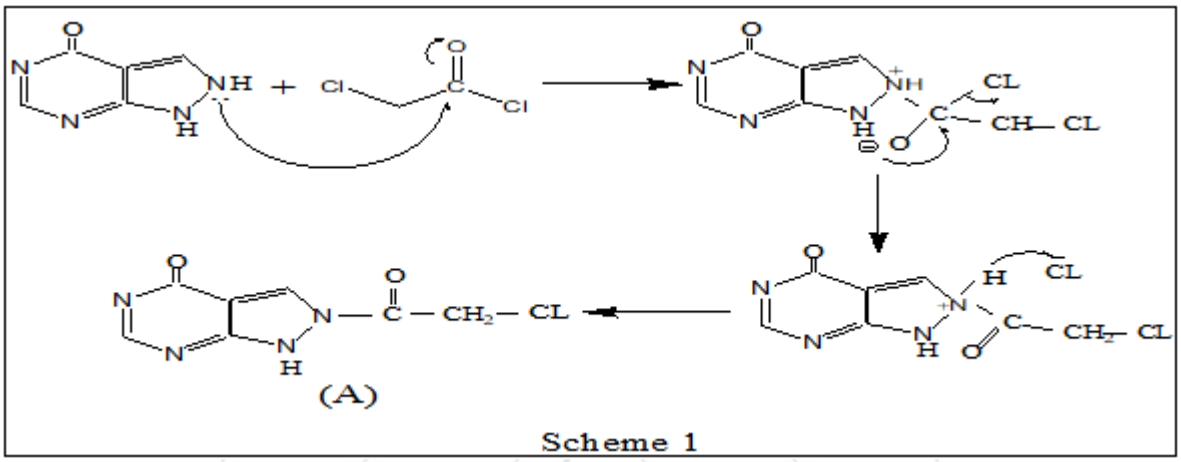
Synthesis of N-(2-aminoacetyl-5-substituted-1,3,4-oxadiazoles-2- yl) Allopurinol[(4)] (A$_{21}$-A$_{30}$)
A mixture of compound (A) (0.004 mol.) in absolute ethanol (10 ml.) and potassium carbonate anhydrous (0.004 mol.) was refluxed and added dropwise to a solution of (0.004 mol.) of 2-amino-5-substituted-1,3,4-oxadiazole dissolved in (10 ml.) abs. ethanol, the mixture was refluxed for (6-8) hrs. The resulted mixture was cooled to room temperature before pouring into crushed ice. The obtained precipitate was filtered, washed thorough by with water and dried then was purified by recrystallization from a suitable solvent. Melting points, yield% data are listed in Table (1).

4. Result and Discussion

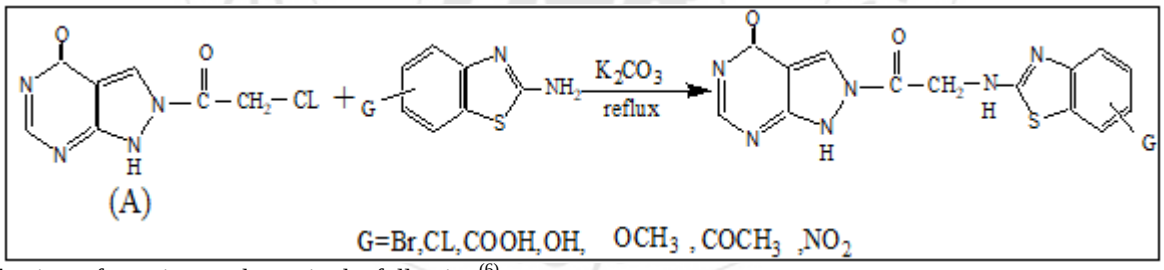
Allopurinol was converted to 2-Chloroacetyl Allopurinol by the reaction with Chloroacetyl chloride at (5-10) ℃ in the presence of triethylamine and Diethylether as asolvent,as shown in the following equation:



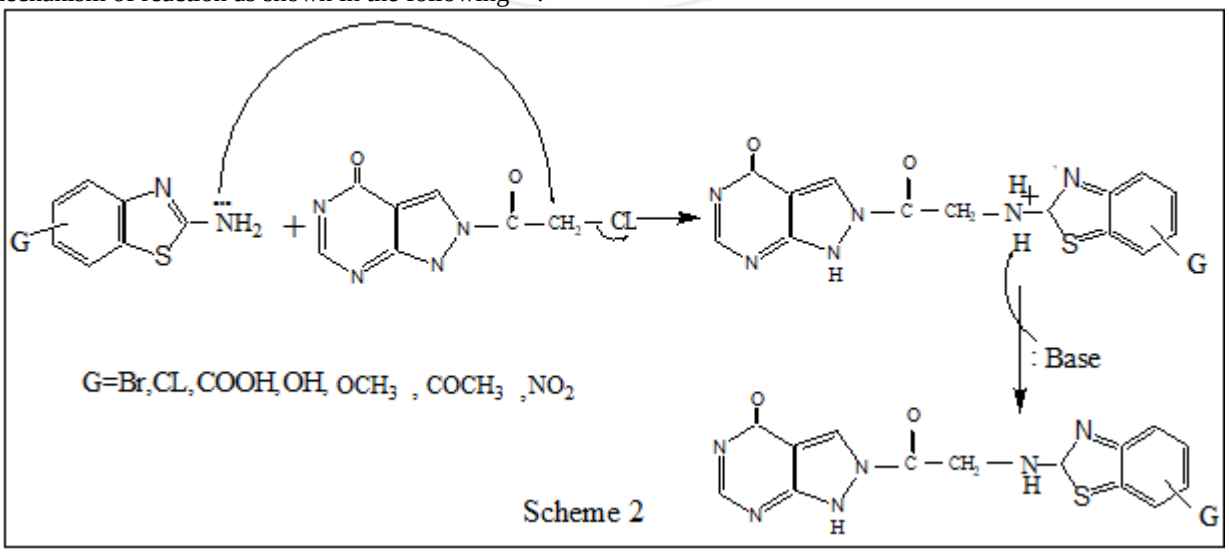
The mechanism for these reaction involves nucleophilic attack of amino group in Allopurinol on reaction with carbonyl group in chloroacetylchloride give the final product(A), as shown in the following[5] :



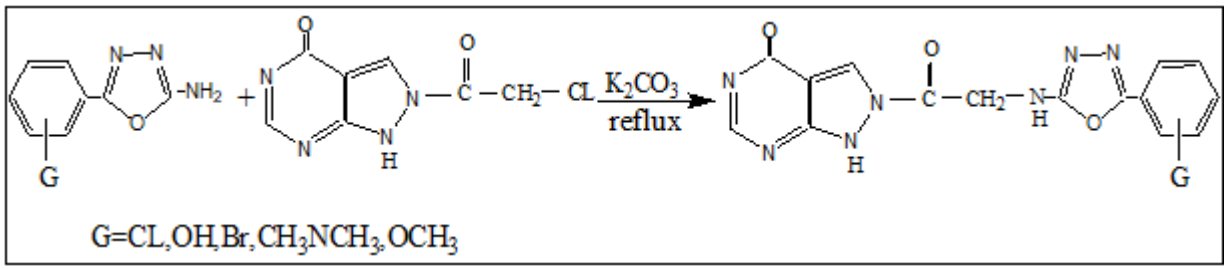
FT-IR spectra show the absence at (3167) cm^{-1} for imide (NH) in the starting material and appearance of the (C=O) group band at (1716) cm^{-1} and(C-CL) at (1037) cm^{-1} which is agood indication of successful condensation listed in table (3). In the ^{1}H-NMR spectrum of compound (A) showed the signal at (1.0-1.4)(s,1H,CH-N), (3.0)(s,1H,CH-N), (4.2)(s,1H,CH2C=O), (8.0-8.1)(d,2H,NH) these spectrum and other are shown in table (5). The reaction compound (A) with 2-amino benzothiazole derivatives in the presence of potassium carbonate anhydrous and Diethylether as asolvent, as shown in the following equation:



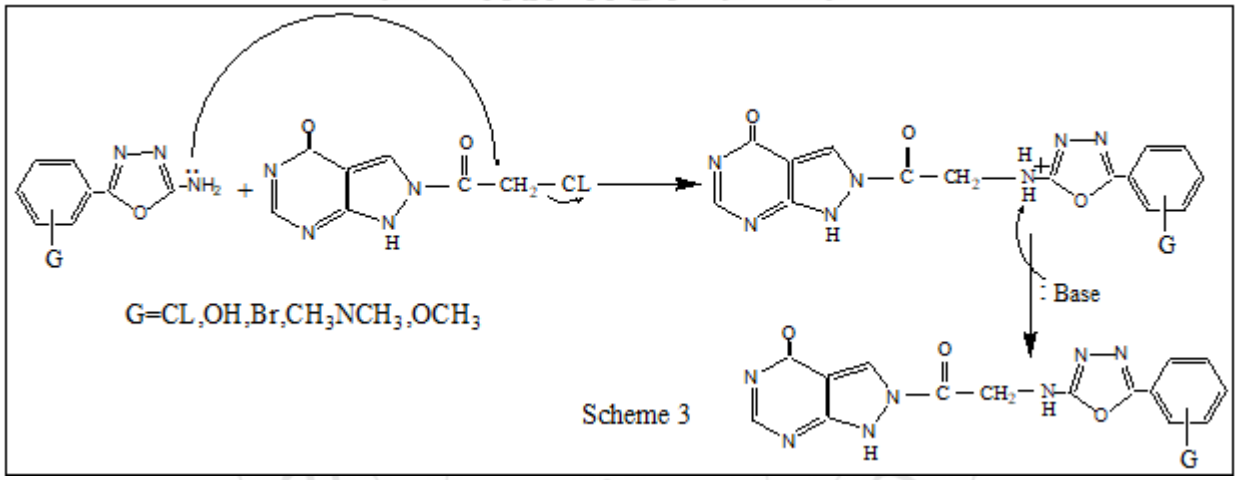
The mechanism of reaction as shown in the following[6] :



The FTIR of Compounds (A_1-A_{10}) have absorption bands at (3263-3468) cm^{-1} for (N-H), (3074-3099) cm^{-1} (C-H) aromatic, (1631-1716) cm^{-1} (C=O) and (1415-1597) cm^{-1} (C=N) listed at table (3). In the ^{1}H-NMR spectrum of compound (A_3) showed the signal (1.5),(s,1H,CH-N), (1.5-1.6)(t,2H,CH2-C=O), (7.1)(s,2H, aromatic), (8.1)(s,1H, NH), (8.1-8.8)(s,1H,NH) these spectrum and other are shown in table (5). The reaction compound(A) with 5-substituted-2-amino-1,3,4-oxadiazole in the presence of potassium carbonate anhydrous and Diethylether as asolvent,as shown in the following equation:



The mechanism of reaction involves The amine N functions as the nucleophile and attacks the electrophilic C of the alkyl halide displacing the chloride and creating the new C-N bond. The base deprotonates the positive N (ammonium) center creating the alkylation product, here a secondary amine[6].



The FTIR of compounds (A_{21}-A_{30}) have absorption band at (3205-3475) cm^{-1} for (N-H), (1666-1724) cm^{-1} (C=O), (1419-1481) cm^{-1} (C=N) and (1134-1172) cm^{-1} (C-O-C) listed at table (4).

In the 1H-NMR spectrum of compound (A_{27}) showed the signal δ(1.2 1.6) (d,1H,NH) , (4.5) (s,1H,NH), δ(4.54) (s,2H,CH_2-C=O), (6.6-7.6) (d,4H, aromatic), (7.8-8.2) (d,1H, NH), these spectrum and other are shown in table (5).

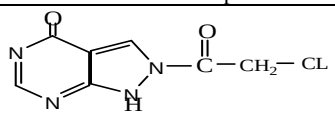
Biological study[7]

The cup plate method using nutrient agar medium was employed in studying the antibacterial activity of some of the prepared compounds (A,A_6,A_{26}) against two types of bacteria, staphylococcus aureous (Gram positive) and Escherichia Coli (Gram negative) respectively and DMSO was used as sample solution .Using asterilizedcork borer cups were scooped out of agar medium contained in a Petri dish which was previously inoculated with the microorganisms. The test compound solution (0.1 mL) was added in the cups and the Petri dishes were subsequently incubated at (37 0C) for 48 hrs. Zones of inhibition produced by each compound was measured in mm and the results are listed in Table (6).

5. Conclusions

The biological activity of compounds were determined by measuring the diameter of the empty region around the well (In hibition zone) . From the data obtained, it is found clearly that compounds (A,A_6,A_{26}) have the highest activity against staphylococcus aurens and Escherichia coli in concentration (100g/ml).The compound (A) have agood biological activity whenecomparation with Allopurinol drug

Table 1: Physical properties of compounds (A-A_{10}) .

Compd.No.	Structure product	Yield %	Color	M.P.°C
A		95	Brown	120-122

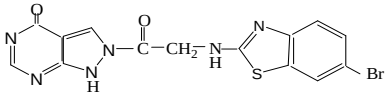
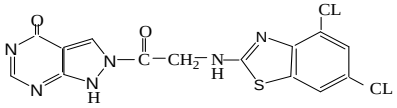
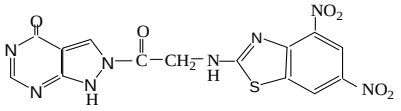
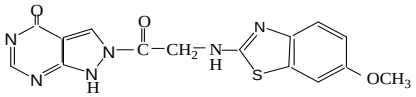
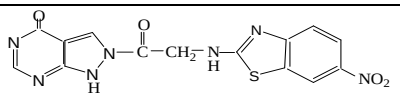
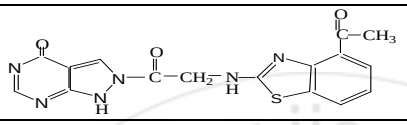
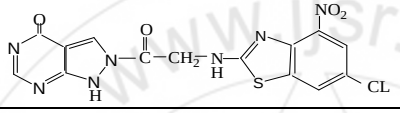
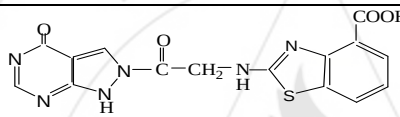
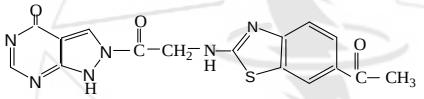
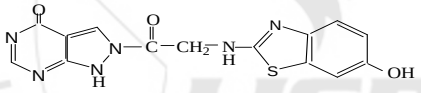
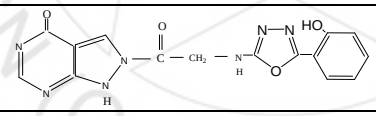
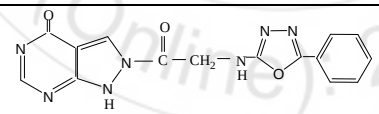
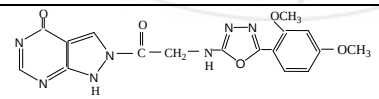
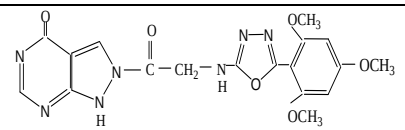
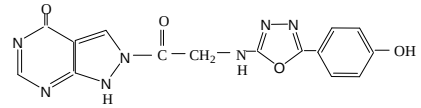
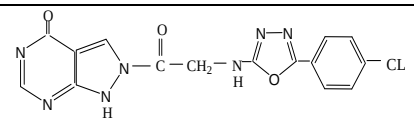
A_1		80	Brown	>300
A_2		95	Brown	210-212
A_3		85	Brown	106-108
A_4		98	Brown	>300
A_5		80	Brown	>300
A_6		98	Dark brown	Oily
A_7		85	Orange	102-104
A_8		80	Grey	266-268
A_9		85	Brown	184-186
A_{10}		90	Brown	>300

Table 2: Physical properties of compound(A_{21}-A_{30}) :

Compd. No.	Structure Product	Yield %	Color	M.P.°C
A_{21}		80	Brown	>300
A_{22}		85	Brown	>300
A_{23}		70	Brown	>300
A_{24}		85	Brown	216-218
A_{25}		90	Brown	190-192
A_{26}		95	Brown	>300

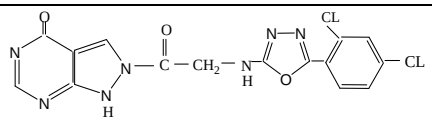
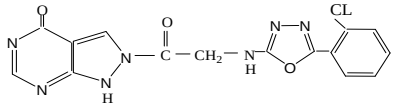
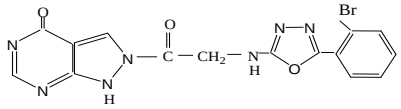
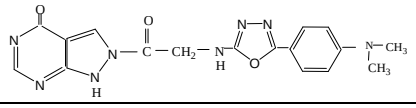
A_{27}		90	Brown	>300
A_{28}		70	Brown	>300
A_{29}		75	Brown	116-118
A_{30}		98	Brown	>300

Table 3: The FT-IR spectra data $cm^{-1}$of the prepared compounds (A-A10)

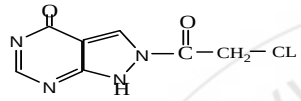
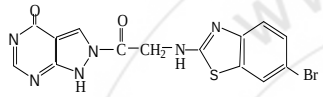
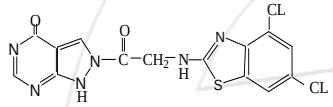
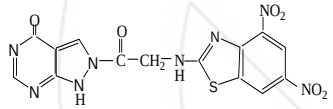
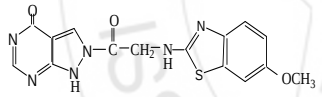
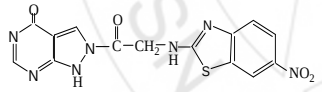
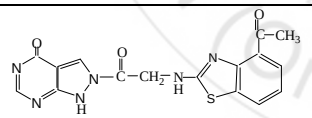
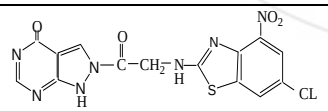
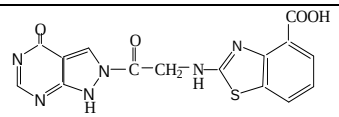
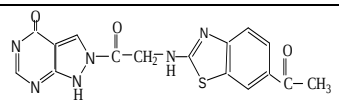
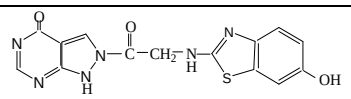
Compd. No.	Compd. Structure	υ(N-H)	υ(C-H) aromatic	υ(C=O)	υ(C=N)	Others
A		3163	-	1716	1477	υ(C-CL) 806
A_1		3163	3082	1701	1597	υ(C-Br) 1083
A_2		3167	3074	1697	1462	υ(C-CL) 1072
A_3		3236	3070	1631	1415	υ(NO_2) 1496
A_4		3163	3082	1712	1477	υ(OCH_3) 1172
A_5		3167	3078	1701	1481	υ(NO2) 1481
A_6		3170	3078	1701	1477	-
A_7		3178	3099	1631	1450	υ(NO2) 1450 , υ(C-CL) 1080
A_8		3263	3078	1712	1435	υ(OH) 3390
A_9		3178	3082	1666	1481	-
A_{10}		3167	3078	1701	1477	υ(OH) 3480

Table 4: The FT-IR spectra data $cm^{-1}$of the prepared compounds(A_{21}-A_{30})

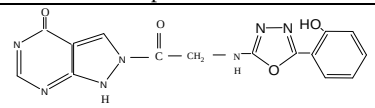
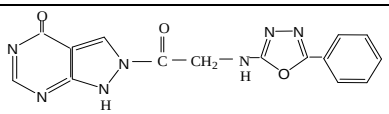
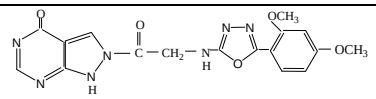
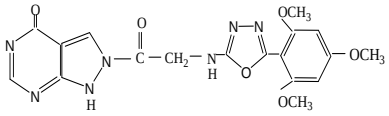
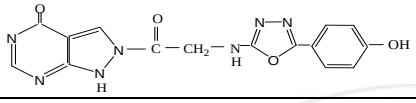
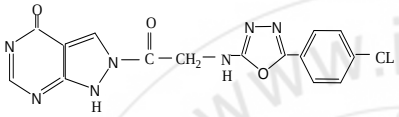
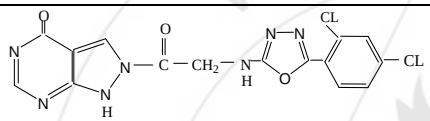
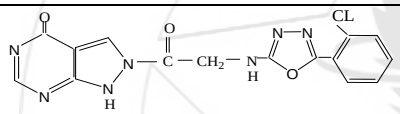
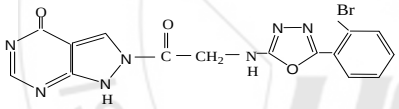
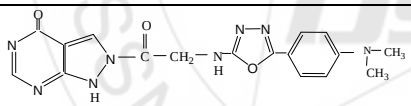
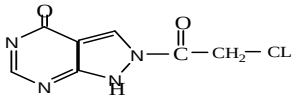
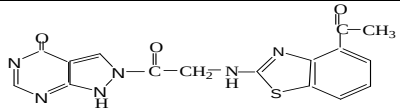
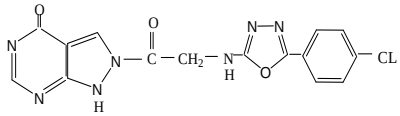
Compd. No.	Compd. Structure	υ(N-H)	υ(C=O)	υ(C=N)	υ(C-O-C)	Others
A_{21}		3205	1666	1473	1172	υ(OH) 3414
A_{22}		3170	1697	1481	1157	-
A_{23}		3167	1697	1477	1157	υ(OCH_3) 1161
A_{24}		3232	1697	1419	1134	υ(OCH_3) 1134
A_{25}		3182	1697	1481	1161	υ(OH) 3437
A_{26}		3167	1705	1481	1141	υ(C-CL) 1083
A_{27}		3163	1724	1469	1161	υ(C-CL) 1095
A_{28}		3163	1697	1423	1157	υ(C-CL) 1090
A_{29}		3178	1701	1477	1157	υ(C-Br) 1083
A_{30}		3156	1678	1473	1168	-

Table 5: 1H-NMR spectral data ($^{\delta}$ppm) for selected compounds

Compd.No.	1H-NMR spectral data ($^{\delta}$ppm)
A	δ(1.0-1.4)(s,1H,CH-N),δ(3.0)(s,1H,CH-N),δ(4.2)(s,1H,CH_2C=O),δ(8.0-8.1)(d,2H,NH)
A_3	δ(1.5),(s,1H,CH-N),δ(1.5-1.6)(t,2H,CH2-C=O), δ(7.1)(s,2H, aromatic), δ(8.1)(s,1H, NH), δ(8.1-8.8)(s,1H,NH)
A_{27}	δ(1.2-1.6)(d,1H,NH),δ(4.5)(s,1H,NH),δ(4.54)(s,2H,CH_2-C=O), δ(6.6-7.6)(d,4H, aromatic), δ(7.8-8.2)(d,1H, NH),

Table 6: Antibacterial activity data of Allopurinol derivatives

Compd. No.	Compd.Structure	Gram Positive *Staphylococcus aureus* Conc. Of extract g/ml			Gram negative *Escherichia coli* Conc. Of extract g/ml		
		25	50	100	25	50	100
A		20	25	30	17	23	28
A_6		10	14	18	8	12	15
A_{26}		8	8	11	-	9	12

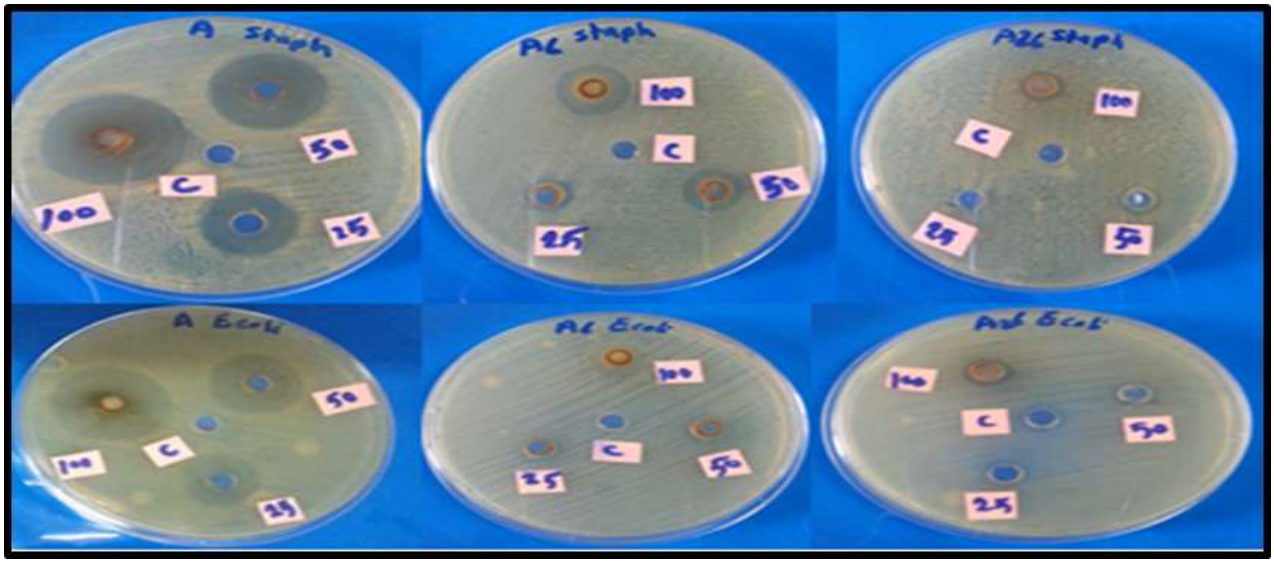


Figure 1: The effect on staphylococcus and E.coli.

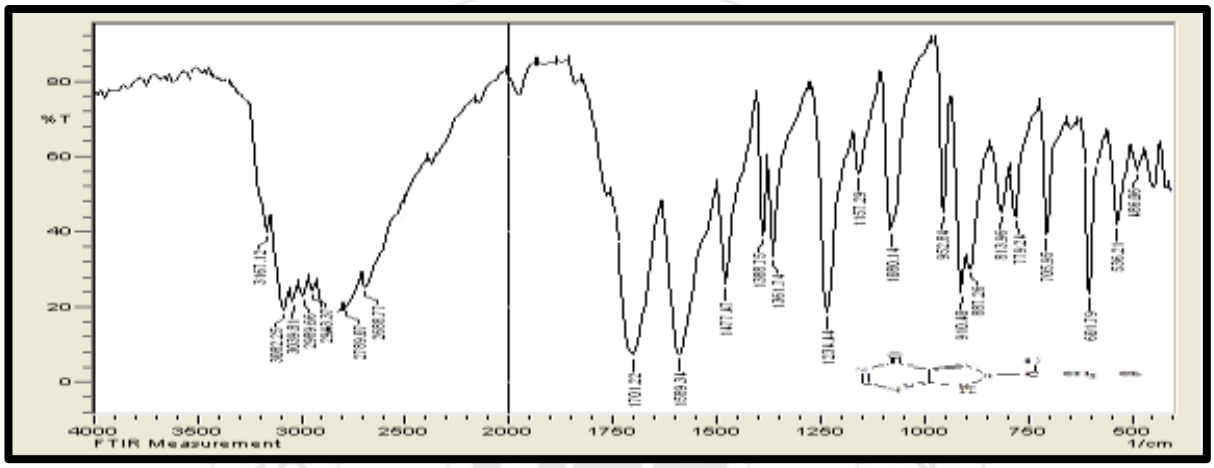


Figure 2: FT-IR Spectral of compound (A)

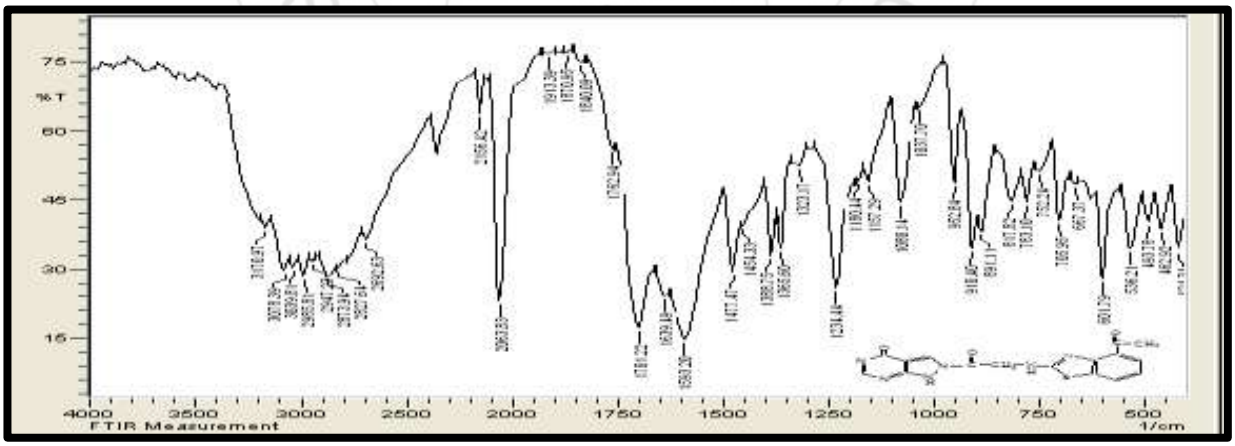


Figure 3: FT-IR Spectral of compound (A_6)

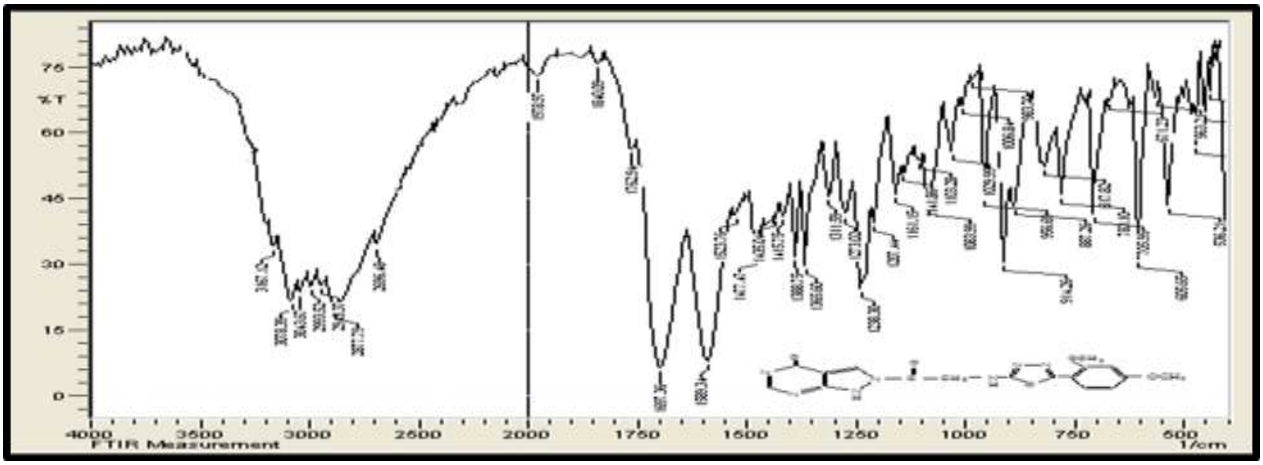


Figure 4: FT-IR Spectral of compound (A_{23})

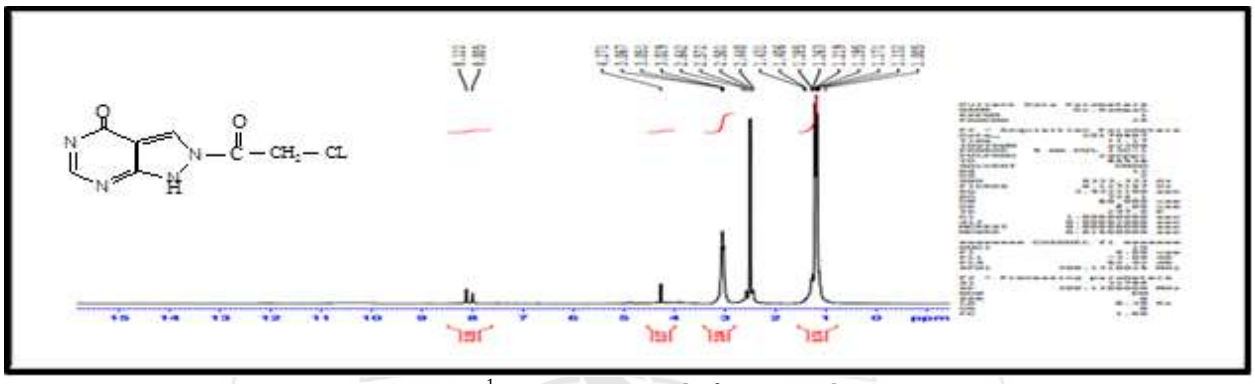


Figure 4: ^{1}H-NMR Spectral of compound (A)

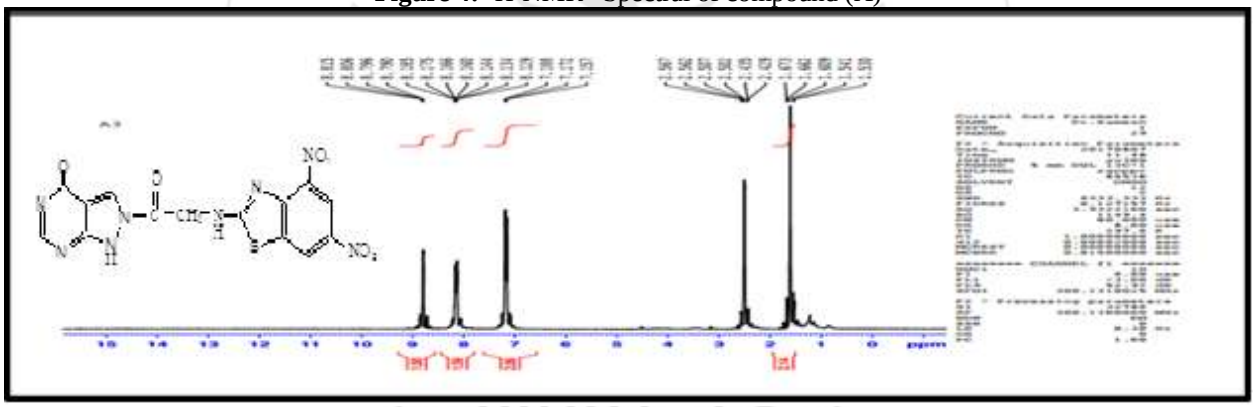


Figure 5: ^{1}H-NMR Spectral of compound (A_3)

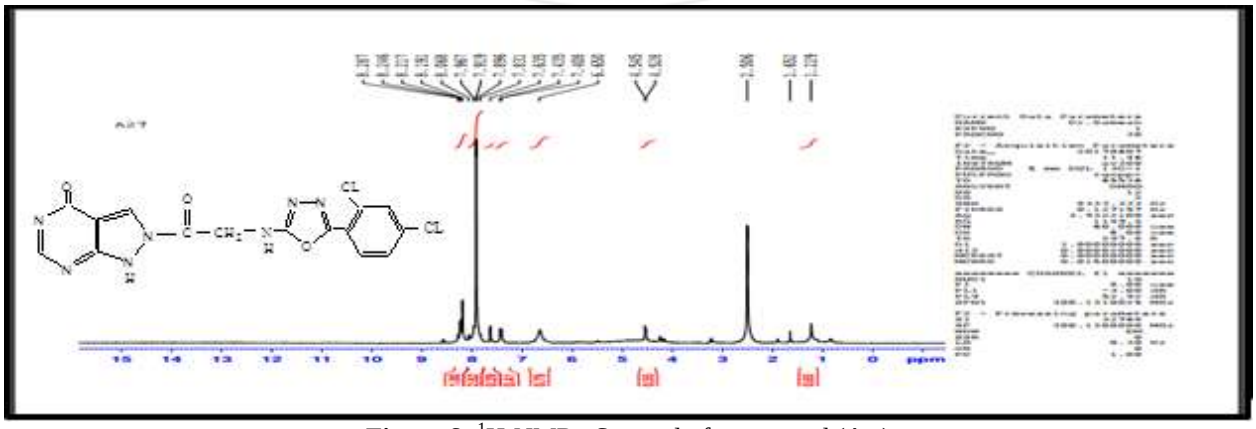


Figure 6: ^{1}H-NMR Spectral of compound (A_{27})

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