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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL CHARACTERISTICS OF PYRIMIDINE DERIVATIVES OF SCHIFF BASE AND AZETIDINE

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Abstract

Various substituted acetophenone were reacted with 2,4-dintro phenyl hydrazine subjected to Vilsmeier- Haack reaction yielded pyrazole-4-carbaldehyde derivatives (2a-j). A series of Schiff base and Azetidine were synthesized by reaction of 6-methyl-N-(4-pyridin-3-yl)-pyrimidin-2-yl)-benzene-1,3-diamine with various pyrazole-4- carbaldehyde derivatives (2a-j) in order to determine their in *vitro* antimicrobial and antifungal activities against clinically isolated strains. The chemical structures were confirmed by FTIR, ^{1}H-NMR, ^{13}C and LCMS.

Introduction

Pyrimidine is an aromatic heterocyclic compound analogous to pyridine [1,2], Among pyrimidine and purine the leading compounds investigated by chemists. [3] Their activities include antifungal [4], pesticidal [5], enzyme inhibitory activity [6], rho-associated protein kinase [7] and glycogen synthase.[8]They are active also as inhibitors for N-type Ca-channels [9], endothelin receptors [10], human methionine aminopeptidase [11], and as potential drug candidates for treatment of prion diseases. [12] Furthermore, 4-pyridinylpyrimidines are widely used as ligands for metal complexation [13,14]. In most of the reported literature, the synthesis of N-arylpyrimidin-2-amines was achieved by condensation of substituted guanidine with enones. [15-17]. This approach however is of restricted use for the preparation of diverse derivatives of N-arylpyrimidin-2-amines because of the limited availability of substituted guanidines. Herein we describe a synthesis for a number of N-aryl-4-(substituted) pyrimidin-2-amine.[18] Many compounds containing the 4-(pyridin-3-yl) pyrimidine moiety show good anticancer activity. [19–23] Anti-cancer activity of Schiff bases of pyrazole-4-carbaldehyde derivatives are also reported. [24] The Schiff bases formed from aromatic aldehydes or aromatic ketones and their derivatives are quite stable. Many Schiff bases are known to be medicinally important and are used to design medicinal compounds. [25]

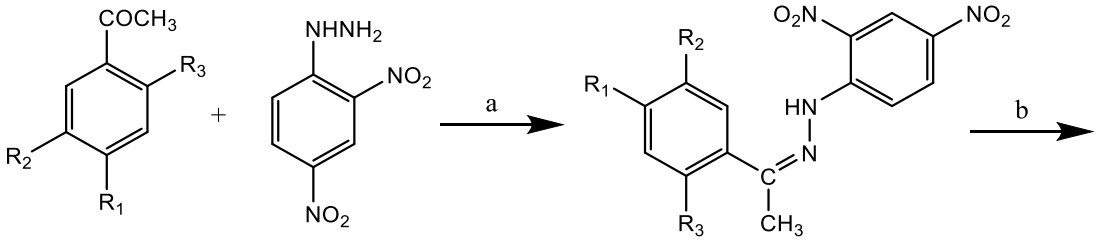
Materials and methods

All the chemicals were purchased from E Merck, S D Fine. All the chemicals used of A R Grade reagent and used without further purification. Melting Points were taken using open capillary and uncorrected. Progress of the reaction was checked by thin-layer chromatography (TLC) using E. Merck silica gel GF254 plates, methanol and toluene used as solvent system, visualization of the developed chromatogram was performed by UV light (254 nm). The FT-IR spectra obtained using KBr pellets on Perkin-Elmer 1600 FTIR. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 500 MHz in DMSO-d_6 as a solvent using tetramethyl silane (TMS) as internal standard respectively. LC-MS were obtained using LCMS.

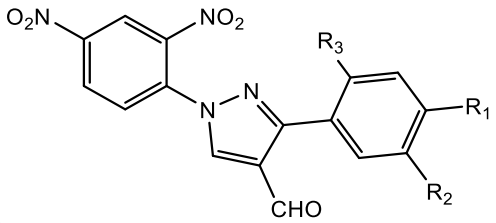
Synthesis of 1-(2,4-dinitrophenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde (2a-j)
1-(2,4-dinitrophenyl)-2-(1-phenylethylidene)-hydrazine (1a-j):
To a methanolic solution of various acetophenone (0.01M) and 2,4-dinitro phenyl hydrazine (0.01M), small amount of concentrated hydrochloric acid was added and solution was stirred at room temperature for about 20 to 25 minutes. The resulting solid was filtered, washed with cold methanol and crystallized.The completion of reaction was confirmed by TLC. After the completion solid was separated and filtered, washed with cold methanol and crystallized using ethanol.

Vilsmeier-Haack Formylation

In the first part Vilsmeier-Haack reagent was prepared by adding 3 mL $POCl_3$ into 15 mL DMF at 0° to 5° C and stirred for 10 minutes.1-(2,4-dinitrophenyl)-2-(1-phenylethylidene)-hydrazine was added in slot wise a mixture of Vilsmeier-Haack reagent. This mixture was stirred at 0° to 5° C for 30 minutes and stirred at 60° C for 1 hour and at room temperature for overnight. The completion of reaction was confirmed by TLC. The reaction mixture was poured into crushed ice and. The resulting product was filtered, washed with dist. water and dried.



1a-j



2a-j

Where a = Methanol, CH_3COOH. b = DMF, $POCl_3$
R_1 = -NO_2, -Br, -Cl, -CH_3, -OCH_3, -OH, -NH_2, R_2 = -OH, R_3 = -OH

Synthesis of 2-Methyl-5-nitroaniline-(3)

To sulfuric acid (225 g) cooled at 0-5 ºC, *o*-toluidine (1.15 g, 140 mmol) was added dropwise with vigorous stirring. Mixed acid (14 g of 65% nitric acid and 50 g of sulfuric acid) was then added dropwise at 0-5 ºC during 2 hours. The mixture was then poured onto crushed ice and made alkaline with aqueous sodium hydroxide. The solid obtained was collected by filtration and air-dried. Subsequent recrystallization from 50% ethanol provided 17.28 g (81%), of product as maroon crystals, mp: 105-107 ºC

Synthesis of N-(2-Methyl-5-nitrophenyl) guanidinium nitrate-(4)

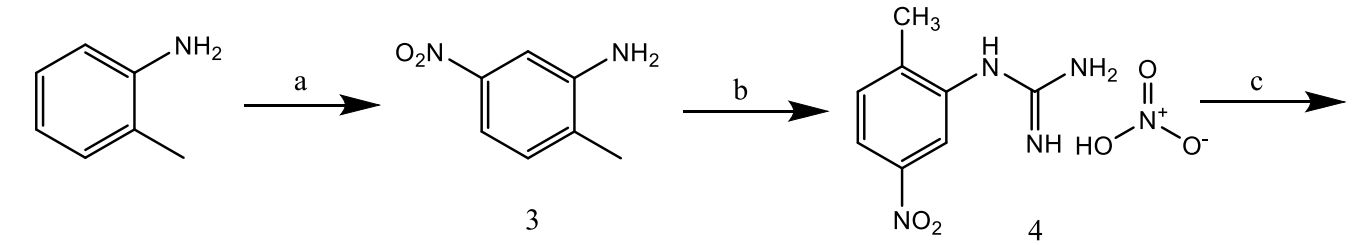
To a solution of 2-methyl-5-nitroaniline (20.46 g, 135 mmol) in n-butanol (120 mL), 65% nitric acid (10.5 mL) was added dropwise followed by a 50% aqueous solution of cyanamide (22.7 mL, 22.81 g, 270 mmol). The reaction mixture was refluxed for 12 h and then cooled to 0 ºC. The solid was collected by filtration and washed with chilled solution of methanol and diethyl ether (1:1, 20 mL) and air-dried to afford 18.48 g (53%) of the title product as a yellow solid, mp: 216-218 ºC.

N-(2-Methyl-5-nitrophenyl)-4-pyridin-3-yl-pyrimidin-2-yl-amine (5)

To a suspension of 3-dimethylamino-1-(pyridin-3-yl)-propenone (26.96 g, 153 mmol) and N-(2-methyl-5-nitrophenyl)-guanidinium nitrate (3, 51.40 g, 200 mmol) in n-butanol (200 mL), solid sodium hydroxide (8.63 g, 216 mmol) was added. The mixture was refluxed for 16 hours and then cooled to 0 ºC. The solidwas collected by filtration and washed with methanol and diethyl ether, and air-dried to afford 43.62 g (92.4 %) of product as a yellow solid, mp: 196-197 ºC.

6-Methyl-N1 -(4-pyridin-3-yl-pyrimidin-2-yl)-benzene-1,3-diamine-(6)

To a solution of stannous chloride dihydrate (11.29 g, 50 mmol) in hydrochloric acid (30 mL) cooled at 0 ºC, N-(2-methyl-5-nitrophenyl)-4-pyridin-3-yl-pyrimidin-2-ylamine (3.69 g, 12 mmol) was added in portions while the mixture was vigorously stirred for 6 h. The mixture was then poured into crushed ice, made alkaline with solid sodium hydroxide, and extracted three times with ethyl acetate (100 mL). The combined organic phase was dried over anhydrous sodium sulphate and the filtrate was evaporated to dryness in vacuo. The residue was recrystallized from methylene chloride to afford 2.52 g (75%) of product as a yellow solid, mp: 142-144 ºC.



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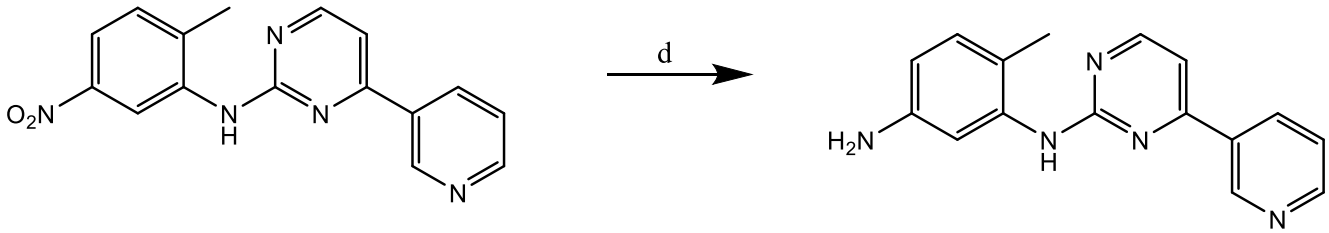

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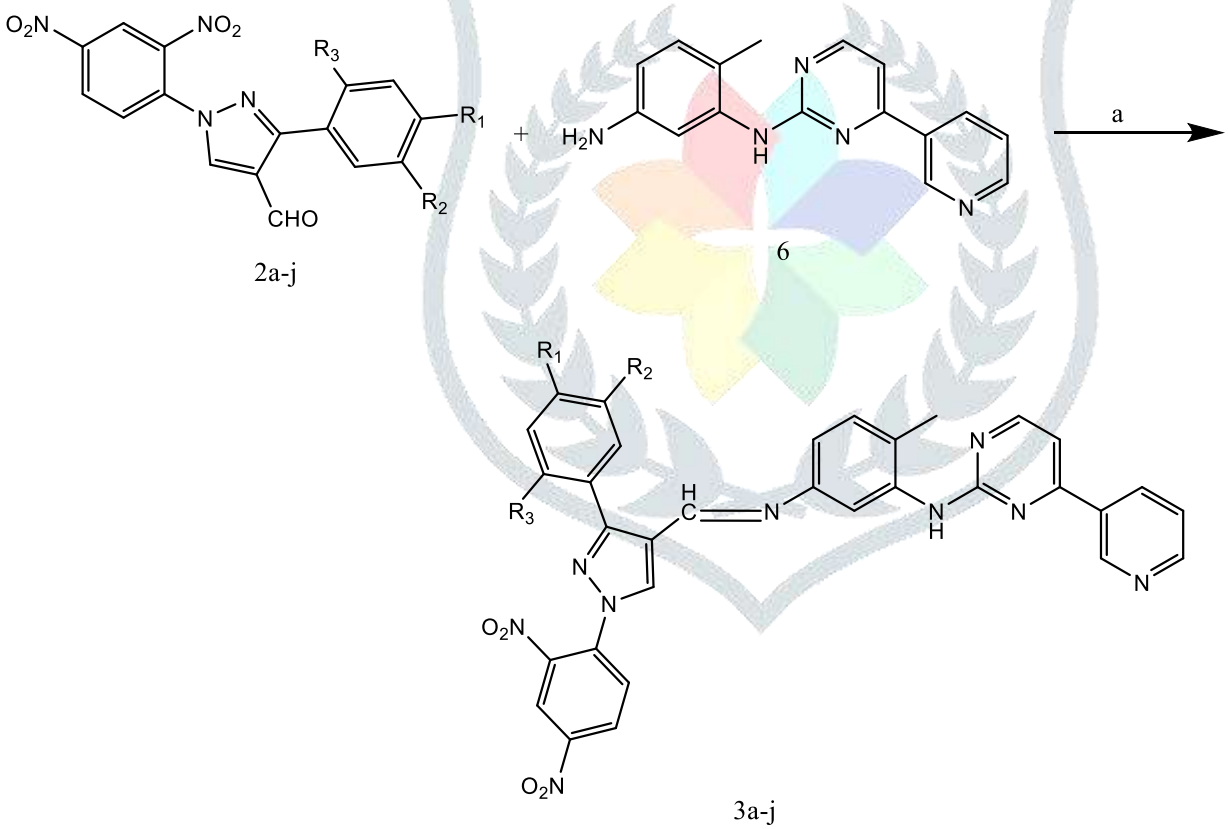
a = Nitric acid and sulphuric acid, b = cyanamide, n-butanol, nitric acid c =d = Sn/ HCl

Synthesis of (E)-N-(5-(((1-(2,4-dinitrophenyl)-3-phenyl-1H-pyrazol-4-yl)-methylene)-amino)-2- meth-ylphenyl)-4-(pyridine-3-yl)-pyrimidin-2-amine(3a-j)

0.01 mole of various 1-(2,4-dinitrophenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde derivatives(2a-j) was dissolved in 30 mL methanol and dissolved solution of 0.01 mole of (E)-N-(5-(((1-(2,4-dinitrophenyl)-3-phenyl-1H-pyrazol-4-yl)-methylene)-amino)-2-methylphenyl)-4-(pyridine-3-yl)-pyrimidin-2-amine in 30 ml methanol was added. Few drops of glacial acetic acid also added to this mixture and was refluxedfor about 4 hours. The completion of reaction was confirmed by TLC. The reaction mixture was poured into crushed ice and. The resulting product was filtered, washed and dried.

The structure of the compounds BH_3 was confirmed by ^{1}H NMR, ^{13}C NMR and LCMS analysis; (yield: 64.32%, m.p. 293º C), IR (KBr, cm^{-1}): ν = -C=N 1610, -NH 3480, C-N 1340, C-H aromatic 3059, C-Cl 715, N-O 1650 of nitro group. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.44 (s, 3H of methyl group), 8.84 and 7.36 (s, CH of pyrimidine ring), 8.41, 7.58, 8.71,9.23 (s, CH of pyridine ring), 8.88 (s, NH), 9.26 (s, CH of aldimine) 8.41 (s, CH of pyrazol ring), 8.00, 8.88, 8.98 (s, CH of benzene ring), 7.96,7.52, 7.51, 7.94 (s, CH of benzene ring) ; ^{13}C NMR (500 MHz, DMSO-d_6) δ: 17.68, 106.94, 107.60, 110.97, 116.40, 123.65, 125.99, 127.25, 127.95, 128.82, 128.88, 129.82, 129.95, 130.02, 131.98, 132.17, 133.49, 134.12, 134.55, 197.37, 142.67, 144.23, 145.83, 146.60, 147.92, 147.99, 150.77, 159.20, 159.31, 160.91, 161.17, 161.42; EIS-MS: *m/z* 631.15 (M$^+$), 632.15 (M + 1), Anal. Calcd for $C_{32}H_{22}ClN_9O_4$ (631.15): C, 60.81; H, 3.50; Cl, 5.62; N, 19.96; O, 10.11; found: C, 60.78; H, 3.50; Cl, 5.58; N, 19.93; O, 10.12%.

The structure of the compounds BH_5 was confirmed by ^{1}H NMR, ^{13}C NMR and LCMS analysis; (yield: 56.13%, m.p. 271º C), IR (KBr, cm^{-1}): ν = -C=N 1608, -NH 3359, C-N 1341, C-H aromatic 3120, C-H 2915 of aliphatic, N-O 1620 of nitro group. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.28 (s, 3H of methyl group), 2.40 (s, 3H of methyl group), 8.87, 7.52 (s, CH of pyrimidine ring), 8.87, 7.52, 8.90, 9.20 (s, CH of pyridine ring), 8.98 (s, NH), 9.25 (s, CH of aldimine) 8.69 (s, CH of pyrazol ring), 8.33, 8.91, 8.98 (s, CH of benzene ring), 7.59,7.15, 7.15, 7.59 (s, CH of benzene ring) ; ^{13}C NMR (500 MHz, DMSO-d_6) δ: 17.62, 21.25 106.98, 107.62, 110.94, 116.41, 123.64, 125.95, 127.25, 127.98, 128.80, 128.80, 129.85, 129.99, 130.12, 131.98, 132.27, 133.50, 134.22, 134.45, 197.32, 142.60, 144.22, 145.83, 146.60, 147.92, 147.99, 150.57, 159.22, 159.35, 160.98, 161.17, 161.45; EIS-MS: *m/z* 611.20 (M$^+$), 612.20 (M + 1), Anal. Calcd for $C_{33}H_{25}N_9O_4$ (611.20): C, 64.81; H, 4.12; N, 20.61; O, 10.46; found: C, 64.79; H, 4.11; N, 20.58; O, 10.45%.



where a = Methanol, CH_3COOH. b = DMF, $POCl_3$
R_1 = -NO_2, -Br, -Cl, -CH_3, -OCH_3, -OH, -NH_2, R_2 = -OH, R_3 = -OH

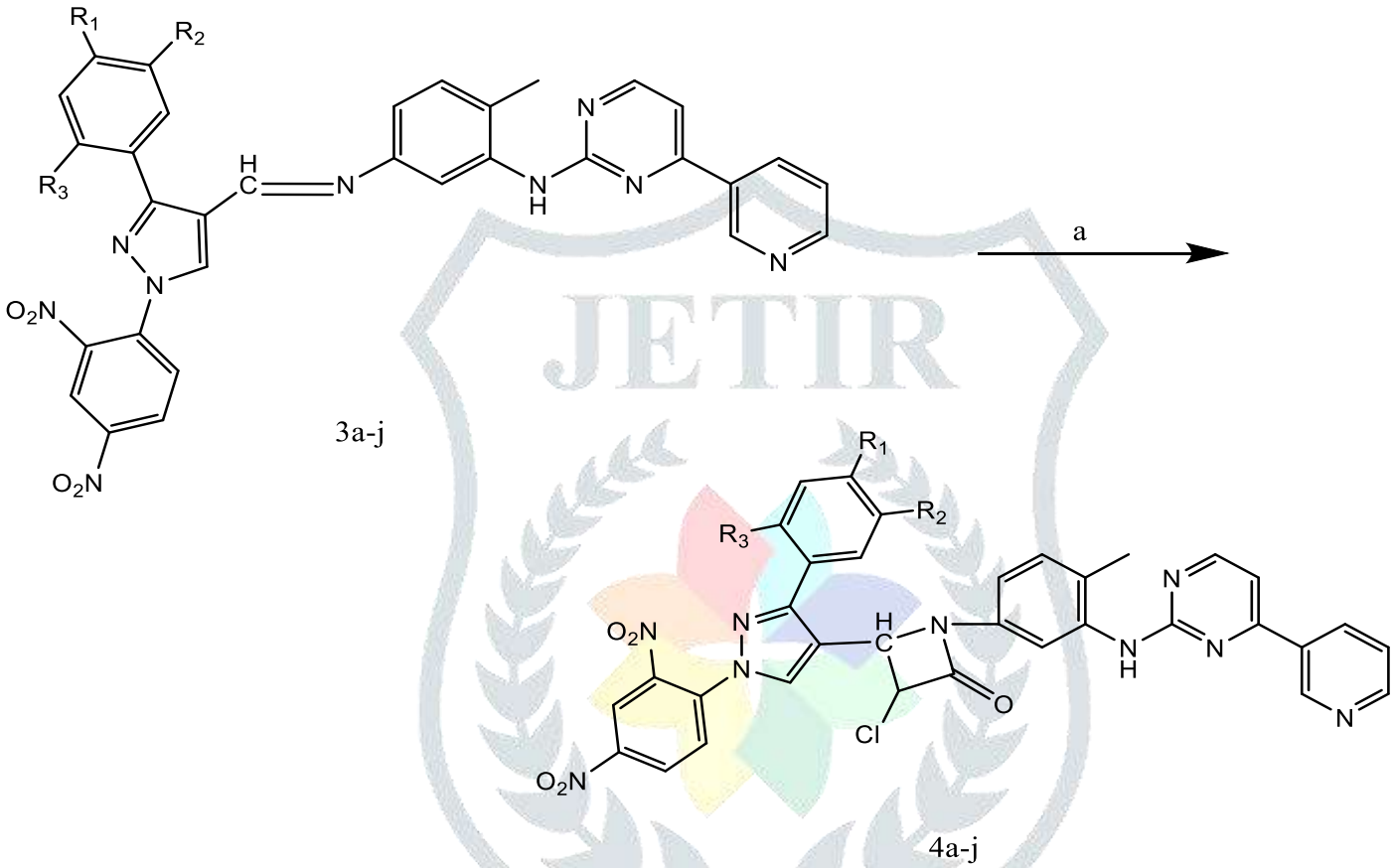
Synthesis ofN-(5-(((1-(2,4-dinitrophenyl)-3-phenyl-1H-pyrazol-4-yl)-methylene)-amino)-2-methylphenyl)-4-(pyridine-3-yl)-pyrimidin-2-amine

Chloroacetyl chloride (0.01 mol) was added drop wise to a mixture of Schiff`s base (0.01 mol) and tri-ethyl amine (0.02 mol) in 25 mL at room temperature. The mixture was stirred for 8 hours and allowed to stand at room temperature for 24 hours. The content was poured on crushed ice and the solid obtained was filtered, washed with 10% w/v sodium bicarbonate solution, dried and recrystallized using absolute ethanol.

The structure of the compounds SR_5 was confirmed by ^{1}H NMR, ^{13}C NMR and LCMS analysis; (yield: 55.57%, m.p. 236º C), IR (KBr, cm^{-1}): ν = -C=O 1655 of Azetidinone, N-H 3410, C-N 1298, C-H 3059 aromatic, C-Cl 699 of four member ring. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.37 (s, 3H of methyl group), 2.51 (s, 3H of methyl group), 8.91, 7.36 (s, CH of pyrimidine ring), 8.35, 7.70, 8.71,9.36 (s, CH of pyridine ring), 8.93 (s, NH), 4.27 (d, CH of propiolactam), 4.90 (d, CH of propiolactam), 7.65 (s, CH of pyrazol ring), 8.18, 8.86, 8.89 (s,

CH of benzene ring), 7.57,7.16, 7.17, 7.55 (s, CH of benzene ring) ; ^{13}C NMR (500 MHz, DMSO-d_6) δ: 17.5, 21.4, 58.9, 62.8, 103.39,108.8 112.9, 120.5, 123.4, 124, 124.1, 124.7, 127.6, 128.3, 128.39, 129.49, 129.45, 130, 130.1, 130.3, 131.6, 133.1, 136, 139.4, 142.1, 142.2, 146.3, 147.5, 147.6, 150.4, 157.8, 157.9, 162.1, 168.6; EIS-MS: *m/z* 687.17 (M^+), 688.17 (M + 1), Anal. Calcd for $C_{35}H_{26}ClN_9O_5$ (687.17): C, 61.09; H, 3.81; Cl, 5.15; N, 18.32; O, 11.63; found: C, 60.99; H, 3.80; Cl, 5.13; N, 18.33; O, 10.99 %.

The structure of the compounds SR_7 was confirmed by ^{1}H NMR, ^{13}C NMR and LCMS analysis; (yield: 60.14%, m.p. 225º C), IR (KBr, cm^{-1}): ν = -C=O 1635 of Azetidinone, N-H 3440, C-N 1270, C-H 3075 aromatic, C-Cl 665 of four member ring, -OH 3314 phenolic. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.37 (s, 3H of methyl group), 9.21 (s, OH of phenolic group), 8.93, 7.38 (s, CH of pyrimidine ring), 8.36, 7.71, 8.71,9.36 (s, CH of pyridine ring), 8.92 (s, NH), 4.28 (d, CH of propiolactam), 4.92 (d, CH of propiolactam), 7.65 (s, CH of pyrazol ring), 8.18, 8.86, 8.89 (s, CH of benzene ring), 7.58,7.16, 7.17, 7.55 (s, CH of benzene ring) ; ^{13}C NMR (500 MHz, DMSO-d_6) δ: 17.5, 58.9, 62.8, 103.39,108.8 112.9, 120.5, 123.4, 124, 124.1, 124.7, 127.6, 128.3, 128.39, 129.49, 129.45, 130, 130.1, 130.3, 131.6, 133.1, 136, 139.4, 142.1, 142.2, 146.3, 147.5, 147.6, 150.4, 157.8, 157.9, 162.1, 168.6; EIS-MS: *m/z* 690.07 (M^+), 691.07 (M + 1), Anal. Calcd for $C_{34}H_{24}ClN_9O_6$ (690.07): C, 59.18; H, 3.51; Cl, 5.14; N, 18.27; O, 13.91; found: C, 59.10; H, 3.50; Cl, 5.15; N, 18.26; O, 13.89 %.



where a = Chloroacetyl chloride, Triethyl amine, Dioxane
R_1 = -NO_2, -Br, -Cl, -CH_3, -OCH_3, -OH, -NH_2, R_2 = -OH, R_3 = -OH

Table:1 Schiff base of pyrimidine derivatives

No	Sample	Name	M. F.	Substituted			M.P.(°C)	Yield (%)
				R_1	**R_2**	**R_3**		
1	3a	BH_1	$C_{32}H_{22}N_{10}O_6$	-NO_2	-H	-H	295º C	65.48%
2	3b	BH_2	$C_{32}H_{22}BrN_9O_4$	-Br	-H	-H	289º C	63.53%
3	3c	BH_3	$C_{32}H_{22}ClN_9O_4$	-Cl	-H	-H	293º C	64.32%
4	3d	BH_4	$C_{32}H_{23}N_9O_5$	-OH	-H	-H	280º C	52.22%
5	3e	BH_5	$C_{32}H_{25}N_9O_4$	-CH_3	-H	-H	271º C	56.13%
6	3f	BH_6	$C_{33}H_{25}N_9O_5$	-OCH_3	-H	-H	274º C	58.25%
7	3g	BH_7	$C_{32}H_{23}N_9O_5$	-H	-OH	-H	260º C	53.24%
8	3h	BH_8	$C_{32}H_{24}N_{10}O_4$	-NH_2	-H	-H	245º C	60.22%
9	3i	BH_9	$C_{32}H_{23}N_9O_6$	-H	-OH	-H	266º C	52.33%
10	3j	BH_{10}	$C_{32}H_{23}N_9O_6$	-OH	-H	-OH	278º C	48.23%

Table:2 Azetidine of pyrimidine derivatives

No	Sample	Name	M. F.	Substituted			M.P.(°C)	Yield (%)
				R_1	**R_2**	**R_3**		
1	4a	SR_1	$C_{34}H_{23}ClN_{10}O_7$	$-NO_2$	-H	-H	255º C	66.18%
2	4b	SR_2	$C_{34}H_{23}BrClN_9O_5$	-Br	-H	-H	246º C	62.43%
3	4c	SR_3	$C_{34}H_{23}Cl_2N_9O_5$	-Cl	-H	-H	251º C	66.15%
4	4d	SR_4	$C_{34}H_{24}ClN_9O_6$	-OH	-H	-H	247º C	53.70%
5	4e	SR_5	$C_{35}H_{26}ClN_9O_5$	$-CH_3$	-H	-H	236º C	55.57%
6	4f	SR_6	$C_{35}H_{26}ClN_9O_6$	$-OCH_3$	-H	-H	238º C	57.80%
7	4g	SR_7	$C_{34}H_{24}ClN_9O_6$	-H	-OH	-H	225º C	60.14%
8	4h	SR_8	$C_{34}H_{25}ClN_{10}O_5$	$-NH_2$	-H	-H	232º C	65.37%
9	4i	SR_9	$C_{34}H_{24}ClN_9O_7$	-H	-OH	-H	236º C	59.58%
10	4j	SR_{10}	$C_{34}H_{24}ClN_9O_7$	-OH	-H	-H	240º C	55.57%

Table:3 Antibacterial activity of Schiff base and Azetidine pyrimidine derivatives

Antibacterial Activity					
Minimal Inhibition Concentration					
Sr.No.	Code No.	*E. Coli*	*P. Aeruginosa*	*S. Aureus*	*S. Pyogenus*
		MTCC 443	MTCC 1688	MTCC 96	MTCC 442
1	BH-1	25	50	100	125
2	BH-2	62.5	100	125	50
3	BH-3	62.5	100	125	250
4	BH-4	125	100	50	12.5
5	BH-5	100	125	50	100
6	BH-6	125	250	250	62.5
7	BH-7	50	100	250	100
8	BH-8	100	12.5	100	62.5
9	BH-9	125	250	125	100
10	BH-10	250	250	100	250
11	SR-1	100	100	250	500
12	SR-2	62.5	62.5	125	125
13	SR-3	12.5	25	50	100
14	SR-4	100	125	250	125
15	SR-5	125	250	250	250
16	SR-6	125	250	100	125
17	SR-7	62.5	100	125	250
18	SR-8	125	62.5	100	125
19	SR-9	250	100	125	100
20	SR-10	125	250	100	500

Table:4 Antifungal activity of Schiff base and Azetidine pyrimidine derivatives

Antifungal Activity				
Minimal Inhibition Concentration				
Sr. No.	Code	*C.Albicans*	*A.Niger*	*A.Clavatus*
		MTCC 227	MTCC 282	MTCC 1323
1	BH-1	250	1000	500
2	BH2	500	500	1000
3	BH-3	250	1000	1000
4	BH-4	1000	1000	1000
5	BH-5	250	1000	500
6	BH-6	1000	1000	1000
7	BH-7	500	500	500
8	BH-8	500	500	500
9	BH-9	500	1000	>1000
10	BH-10	500	1000	>1000
11	SR-1	500	500	1000
12	SR-2	250	1000	1000
13	SR-3	250	1000	1000
14	SR-4	250	500	1000
15	SR-5	200	>1000	1000
16	SR-6	500	>1000	1000
17	SR-7	250	500	500
18	SR-8	500	1000	1000
19	SR-9	250	1000	1000
20	SR-10	250	500	500

Table:5 Antimalarial activity of Schiff base and Azetidine pyrimidine derivatives

MINIMAL INHIBITION CONCENTRATION		
Sr. No.	Compound Code	MEAN IC50 Valuesa
1	BH-1	1.32µg/mL
2	BH2	0.68µg/mL
3	BH-3	0.95µg/mL
4	BH-4	1.02µg/mL
5	BH-5	1.71µg/mL
6	BH-6	1.50µg/mL
7	BH-7	0.60µg/mL
8	BH-8	1.24µg/mL
9	BH-9	0.88µg/mL
10	BH-10	1.41µg/mL
11	SR-1	0.23µg/mL
12	SR-2	0.50µg/mL
13	SR-3	0.98µg/mL
14	SR-4	1.08µg/mL
15	SR-5	1.30µg/mL
16	SR-6	0.57µg/mL
17	SR-7	0.87µg/mL
18	SR-8	0.25µg/mL
19	SR-9	0.56µg/mL
20	SR-10	1.64µg/mL

Table:6 Antituberculosis activity of Schiff base and Azetidine pyrimidine derivatives

Sr. No.	Code No	MIC µg/mL
1	BH-1	250
2	BH2	100
3	BH-3	62.5
4	BH-4	250
5	BH-5	100
6	BH-6	250
7	BH-7	500
8	BH-8	250
9	BH-9	100
10	BH-10	250
11	SR-1	50
12	SR-2	125
13	SR-3	100
14	SR-4	250
15	SR-5	62.5
16	SR-6	500
17	$SR\text{-}7_1$	250
18	SR-8	25
19	SR-9	250
20	SR-10	100

Remarks: Isoniazid=0.20µg/mL(99%Inhibition)

Result and discussion:

1-(2,4-dinitrophenyl)-2-(1-phenylethylidene)-hydrazine was prepared by condensation of various acetophenone and 2,4-dinitro phenyl hydrazine in equal proportion, small amount of concentrated hydrochloric acid was added and solution was stirred at room temperature for about 20 to 25 minutes in methanol solvent and followed by Vilsmeier hack reaction gave 1-(2,4-dinitrophenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde. Reaction between carbaldehyde and 6-Methyl-N1 -(4-pyridin-3-yl-pyrimidin-2-yl)-benzene-1,3-diamine gave final product Schiff base of pyrimidine derivatives. Further reaction with chloro acetyl chloride in DMF at 0º to 5º C gave Azetidine of pyrimidine derivatives.

The ^1H ((500 MHz) NMR of compound BH_3 in DMSO-d_6 suggest that value of δ 2.44 of three protons of CH_3 group, 8.84 and 7.36 of CH of pyrimidine ring, 8.41, 7.58, 8.71,9.23 of CH of pyridine ring, 8.88 of proton of secondary amine, 9.26 of CH of aldimine, 8.41 of CH of pyrazol ring. The ^1H ((500 MHz) NMR of compound BH_5 in DMSO-d_6 suggest that value of δ 2.48 of three protons of CH_3 group, 8.87 and 7.52 of CH of pyrimidine ring, 8.87, 7.52, 8.90,9.20 of CH of pyridine ring, 8.98 of proton of secondary amine, 9.25 of CH of aldimine, 8.69 of CH of pyrazol ring. The ^1H ((500 MHz) NMR of compound SR_5 in DMSO-d_6 suggest that value of δ 2.37 of three protons of CH_3 group, 8.91 and 7.36 of CH of pyrimidine ring, 8.35, 7.70, 8.71, 9.36 of CH of pyridine ring, 8.93 of proton of secondary amine,

4.27 and 4.90 of CH of propiolactam , 8.41 of CH of pyrazol ring. The ^1H ((500 MHz) NMR of compound SR_7 in DMSO-d_6 suggest that value of δ 2.37 of three protons of CH_3 group, 9.21 of phenolic OH group, 8.93 and 7.38 of CH of pyrimidine ring, 8.36, 7.71, 8.71, 9.36 of CH of pyridine ring, 8.92 of proton of secondary amine, 4.28 and 4.92 of CH of propiolactam , 7.65 of CH of pyrazol ring.

Antimicrobial activity

According to antimicrobial activity it is clear that the Schiff base compounds of pyrimidine derivatives viz. BH_1, BH_4 and BH_8 show good antimicrobial activity. Particularly BH_1 shows good antibacterial activity against *E. coli.*, BH_4 shows good antibacterial activity against *S. Pyogenus,* while BH_8 shows good activity against *P.Aeruginosa*. Azetidine derivatives of pyrimidine derivatives like SR_2, SR_3 and SR_7 also show good antibacterial activity. The relative data suggest that Azetidine derivatives of pyrimidine show good activity as compared to Schiff base of pyrimidine. SR_2 exhibits good activity against *E. Coli* and *P. Aeruginosa*.

Antifungal activity

According to the results of antifungal activity the data of Schiff base of pyrimidine derivatives like BH_1 and BH_3 show average to good activity and Azetidine of pyrimidine derivatives like SR_4, SR_5, SR_9 and SR_{10} show good antifungal activities.

Antitubercular activity

The encouraging results from the antibacterial studies prompted us to go for preliminary screening against *M. tuberculosis;* Antituberculosis activity performed by using conventional method such as L. J. Medium. Here $H_{37}Rv$ bacteria was used and the standard drug was Isoniazid which show 99% inhibition. The MIC value is 0.20 µg/mL. Schiff base of pyrimidine derivatives like BH_3 shows good antituberculosis activity and Azetidine of pyrimidine derivatives like SR_1, SR_5 and SR_8 show good antituberculosis activity.

The data of MIC of antimalarial activity shown in the table-4. According to data it is clear that Schiff base of pyrimidine derivatives such as BH_1 to BH_{10} show good activity. Among them MIC value for BH_7 is 0.60 µg/mL, MIC value for BH_2 is 0.68 µg/mL, MIC value for BH_9 is 0.88 µg/mL. While Azetidine of pyrimidine derivatives such as SR_1 to SR_{10} show the best MIC values as compared to Schiff base of pyrimidine derivatives. Among the Azetidine of pyrimidine derivatives MIC value for SR_1 is 0.23 µg/mL, MIC value for SR_8 is 0.25 µg/mL, MIC value for SR_2 is 0.50 µg/mL and MIC value for SR_6 is 0.57 µg/mL.

The MIC data suggest that the best MIC value of SR_1 as compared to all the Schiff base pyrimidine derivatives and Azetidine of pyrimidine derivatives. All experiments were performed in duplicate. Standard like Chloroquine and Quinine were used. The mean values of MIC of chloroquine is 0.020 µg/mL. and quinine are 0.268 µg/mL.

Conclusion

According to antimicrobial activity data it is clear that Schiff base of pyrimidine derivatives show good antibacterial activity but Azetidine of pyrimidine derivatives show best antibacterial activity than Schiff base. Same the Azetidine of pyrimidine derivatives show good antifungal activity as well as antituberculosis activity than Schiff base.

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