Journal of Chemical, Biological and Physical Sciences

An International Peer Review E-3 Journal of Sciences

Available online at www.jcbsc.org

Section A: Chemical Sciences

CODEN (USA): JCBPAT Research Article

The development of sulfonamide drug via N-alkylation of pyrazole, pyridine linked nucleus and their antimicrobial activity

Prabhunath Yogi and Ajit Joshi *

Synthetic Organic Chemistry Laboratory, Department of Chemistry,

Mewar University, Gangrar, Rajasthan, India-312901

Received: 01 November 2015; **Revised:** 20 November 2015; **Accepted:** 28 November 2015

Abstract: The novel sulfonamide drugs 2-chloro -*N*-[(4 -methylphenyl) sulfonyl] -*N*-pyridin -2-ylacetamide compounds **2** and **4** (scheme-**1**) were synthesized by two process. In first process 2amino pyridine reacts with chloro acetyl chloride to give 2-chloro-*N*-pyridin-2-ylacetamide (**1**) and in next step it treated with p-toluene sulfonyl chloride to achieved target molecule (**2**). In another process 2-amino pyridine reacts with p- toluene sulfonyl chloride to give 4-methyl-*N*-pyridin-2-ylbenzenesulfonamide (**3**) and it treated with chloroacetyl chloride and gave final compound (**4**). In scheme-2 ethylacetoacetate cyclized. With hydrazine hydrate to gave 5-methyl-2, 4-dihydro-3*H*-pyrazol-3-one (**5**). In next step compound (**5**) refluxed with substituted aldehyde to achieved 4-[(4-substituted) methylidene]-5-methyl-2, 4-dihydro-3*H*-pyrazol-3-one (**6a-d**). It undergo cyclized with malanonitrile and ammonium acetate to gave 6-amino-4-(4-substituted)-3-methyl-1*H*-pyrazolo [3, 4-*b*] pyridine-5-carbonitrile (**7a-d**). In last step sulphonamide drugs (**4**) treated with compound (**7a-d**) to achieved final nucleus *N*-{2-[6-Amino-4-(4-substitute-phenyl)-5-cyano-3-methyl-pyrazolo[3,4-*b*]pyridin-1-yl]-acetyl}-4-methyl-*N*-pyridin-2-yl-benzenesulfonamide (**8a-d).** All the synthesized compounds confirmed by spectra (IR, NMR, and Mass) and evaluated for their antimicrobial activity.

Keyword: Pyrazole, Sulfonamide drugs, pyridine, malanonitrile and N-alkylation.

INTRODUCTION

Sulphur containing molecules exposed key role in medicinal and agrochemical industries.[1-2] Sulfonamide is most important classes of pharmaceuticals, it exhibit wide range in antibacterial

medicine such as sulfadiazine and hydrochlorothiazide. Both two drugs have been therapeutically used for many years[3-5]. Sulfonamide molecules also play important role in antihypertensive bosentan, have the antiviral HIV protease inhibitor am-prenavir and the phophodiesterase-5 inhibitor sildenafil [6-9]. N-alkylation is an important tool in organic synthesis which provide a rout for transformation of primary and secondary amides into tertiary amides[10-11]. Pyridine derivatives have a broad spectrum of pharmacological evaluation, such as anti-inflammatory[12-15], antiviral[16-19], antihypertensive[20-22], antidiabetic[23-24], anticancer[25-26], osteogenic activities [27-28], antimicrobial[29-30] and treatment of CNS disorders [31-32] .Pyrazole moiety have a broad spectrum of useful medicinal properties such as herbicides, fungicides and analgesics activities.[33-34]

RESULT AND DISCUSSION

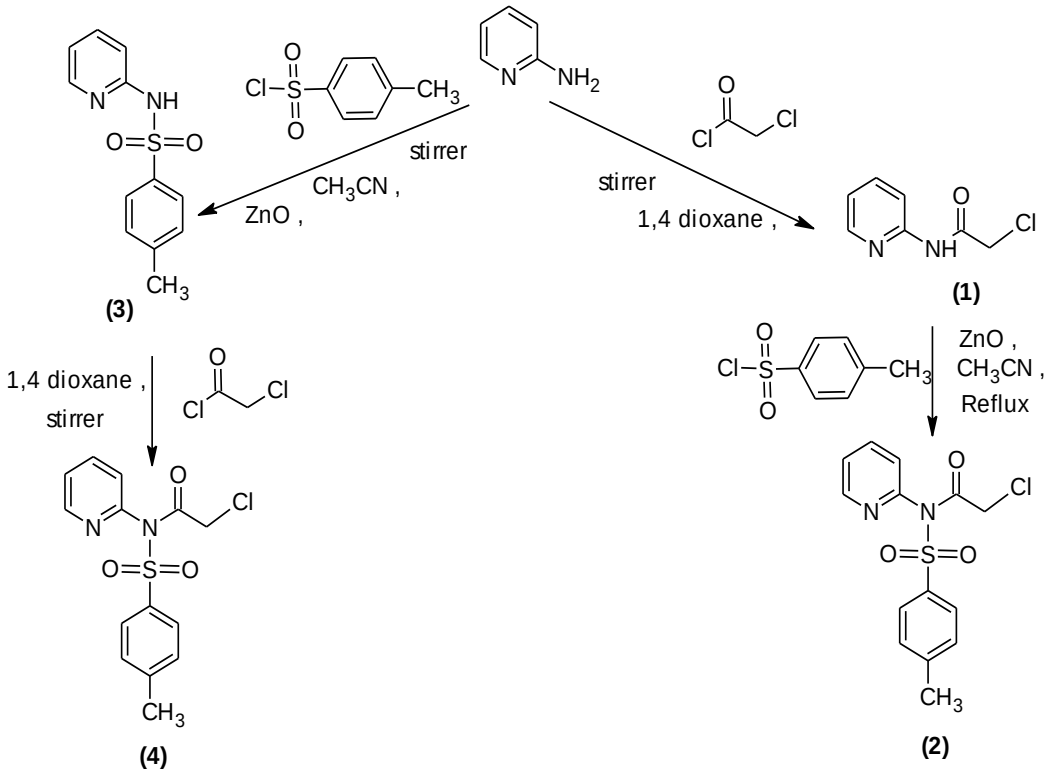
Compound **1** was synthesized by reaction of 2-aminopyridine and chloroacetyl chloride. It confirmed by ^{1}HNMR, in this spectra N-H group give singlet at δ 6.80. In IR spectra C=O, amide give frequency at 1581cm^{-1}. Further it reacts with p-toluene sulfonyl chloride gave to sulphonamide drugs (**2**) and it was identified by ^{1}HNMR. In this compound singlet of N-H δ 6.80 disappeared and formation of new singlet at 2.15 of CH_3 group. Similarly Compound **3** achieved by reaction of 2-aminopyridine and p-toluene sulfonyl chloride. The structure of this compound confirmed by ^{1}HNMR, presence of a singlet at δ 6.75 due to (N-H) group and IR absorptions at 1391 cm^{-1} due to the (N-S) group. In next step comp.**3** treated with chloroacetylchloride to give compound **4**. It was identified by ^{1}HNMR. In this spectra singlet of N-H disappeared and formation of new sharp singlet at 4.73 due to CH_2 group and IR absorptions at 1621cm^{-1} due to the (C=O) group. In scheme-**2** compound **5** achieved by reaction between hydarazine hydrate and ethylacetoacetate. It confirmed by ^{1}HNMR, appearance of singlet at 2.20 (CH2), and 8.11(NH). In IR spectra C=O group give frequency at 1726. In next step compound **5** reacts with substituted aldehyde to give product **6a.** It identified by disappearance of singlet at 2.20 (CH_2) group. Compound **6a** reacts with malanonitrile and ammonium acetate converted into compound **7a**. It confirmed by ^{1}HNMR, singlet at δ 6.78 due to NH_2 , and δ 8.33 of NH group of pyridine ring and IR absorption at 2192 due to CN of pyridine ring. The final targeted nucleus (**8a**) synthesized by reaction of compound **7a** and sulphonamide drugs (**4**) in presence of THF media and TEA as a catalyst. It identified by ^{1}HNMR, formation of new singlet at δ 3.69 due to CH_2 and δ 2.59 singlet of CH_3 (benzene). In IR spectra frequency of N-H at 3260 disappeared and formation of new peak at 1724 of C=O,amide group. All the synthesized compound were evaluated for their antimicrobial activity.

Biological activity: All the synthesized compounds were tested against four bacterial strains *viz. B. subtilis, S. typhi, P. aeruginosa , E. coli,* and and two fungal strains *A. fumigatus* and *C. albicans* by using cup and well method at 200 ppm concentrations in DMF. It is clear that compounds **1** exhibit good activity against *E. Coli.* Compound **2** and **4** show strong activity against *B. subtilis*, similarly show good activity against *C. albicans.* Another compound **7a** to **7d** exhibit poor to moderate against both microbial strains. The final compound **8b** show strong activity against *E. coli* as well as *C. Albicans,* similarly compound **8c** and **8d** exhibit moderate to good activity against both bacterial and fungal strains. Hence, the conclusion can be drawn that synthesized compounds are better antibacterial and antifungal. The screening have been summarized in table **Table II.**

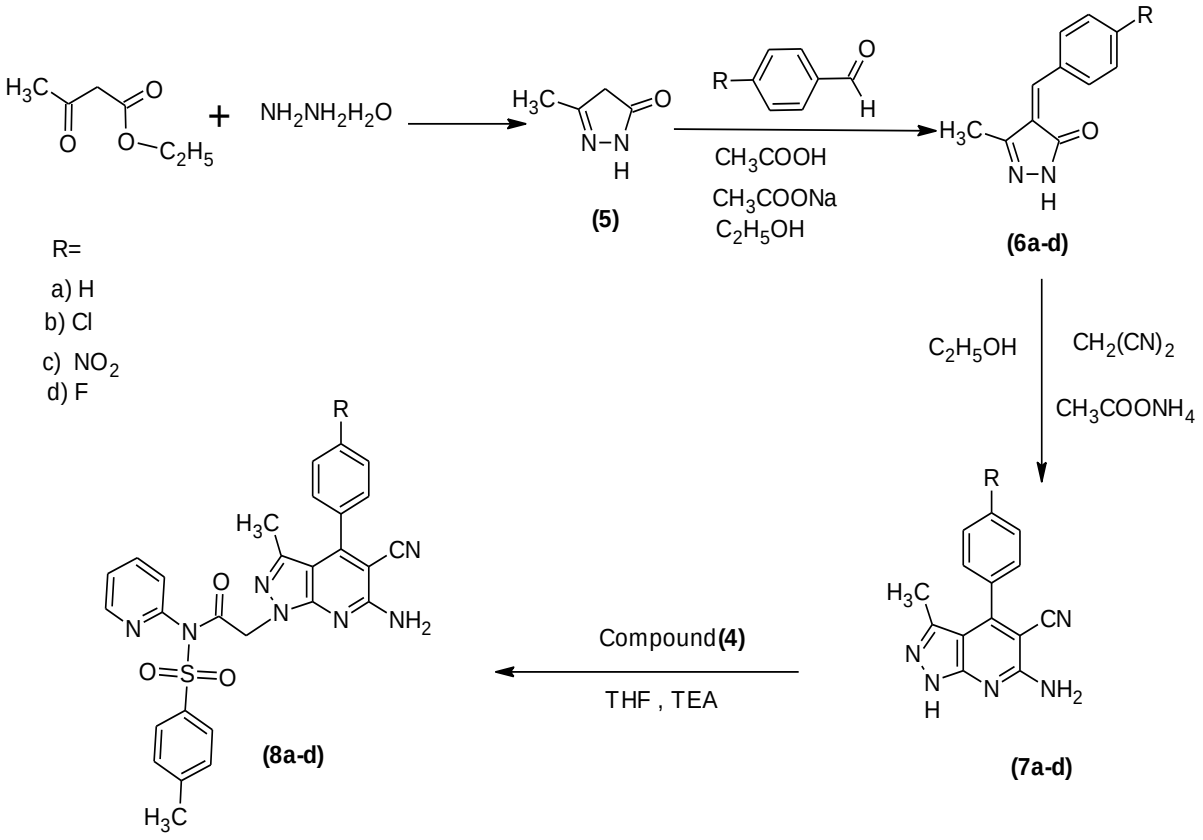
Experimental Section: All melting points were determined in open capillary tube and are uncorrected. The IR spectra were recorded on Perkin-Elmer-1800 spectrometer. The ^{1}H NMR spectra ($CDCl_3$) were scanned on a DRX-300 (300 MHz) spectrometer using TMS as internal standard and chemical shifts are expressed in δ, ppm. The mass spectra were recorded on Jeol SX-102 (FAB)

spectrometer. Purity of synthesized compounds was checked by element analysis and homogeneity was checked by TLC using silica gel-G, as adsorbent and visualization was accomplished by iodine.

Scheme-1



Scheme-2



Synthesis of 2-chloro-*N*-pyridin-2-ylacetamide (1): 2-aminopyridine (0.1 m mole) and 1, 4-dioxane (50 ml) were taken in dry beaker than added CH_3COONa (0.1m mole), mixed well above all component and make a clean solution. Chloroacetyl chloride (0.1 m mole) were added drop by drop in above solution, after complete the addition, reaction mass stay for 30 min. at RT and success of reaction checked by TLC. End of the reaction solid appear, it poured into ice cold water than filtered and recrystalized from Benzene.

Table I: Physical and analytical data of new synthesized compounds 1-5 and 6ad-8ad

Com.	Mol.formula	MW	mp °C	Yield (%)	(%) of C Found/cal.	(%) of H Found/cal.	(%) of N Found/cal.	(%) of S Found/cal.
1	$C_7H_7ClN_2O$	170	203	82	49.25/49.28	4.13/4.14	16.40/16.42	
2	$C_{14}H_{13}ClN_2O_3S$	324	234	75	51.75/51.77	4.01//4.03	8.59/8.63	9.84/9.87
3	$C_{12}H_{12}N_2O_2S$	248	218	80	58.01/58.05	4.85/4.87	11.26/11.28	12.87/12.91
4	$C_{14}H_{13}ClN_2O_3S$	324	234	85	51.75/51.77	4.01//4.03	8.59/8.63	9.84/9.87
5	$C_4H_6N_2O$	98	220	75	48.95/48.97	6.14/6.16	28.55/28.56	-
6a	$C_{11}H_{10}N_2O$	186	163	72	70.93/70.95	5.40/5.41	15.01/15.04	-
6b	$C_{11}H_9ClN_2O$	220	169	75	59.85/59.88	4.09/4.11	12.68/12.70	-
6c	$C_{11}H_9N_3O_3$	231	170	65	57.10/57.14	3.90/3.92	18.14/18.17	
6d	$C_{11}H_9FN_2O$	204	173	60	64.67/64.70	4.42/4.44	13.70/13.72	
7a	$C_{14}H_{11}N_5$	249	273	65	67.43/67.45	4.44/4.45	28.09/28.10	
7b	$C_{14}H_{10}ClN_5$	283	264	69	59.22/59.27	3.52/3.55	24.66/24.68	
7c	$C_{14}H_{10}N_6O_2$	294	269	58	57.10/57.14	3.41/3.43	28.55/28.56	
7d	$C_{14}H_{10}FN_5$	267	271	63	62.90/62.92	3.76/3.77	26.18/26.20	
8a	$C_{28}H_{23}N_7O_3S$	537	284	75	62.52/62.56	4.29/4.31	18.22/18.24	5.94/5.96
8b	$C_{28}H_{22}ClN_7O_3S$	572	286	76	58.75/58.79	3.86/3.88	17.12/17.14	5.59/5.61
8c	$C_{28}H_{22}N_8O_5S$	582	287	64	57.70/57.72	3.80/3.81	19.20/19.23	5.47/5.50
8d	$C_{28}H_{22}FN_7O_3S$	555	289	77	60.50/60.53	3.95/3.99	17.64/17.65	5.76/5.77

IR (KBr)cm^{-1} : 3433 (N-H str) 3251 (Ar-H, str.), 2840 (CH_2, str.), 1680 (C=N str.), 1581 (C=O, str.), ^1H NMR ($CDCl_3$) δ: 7.10-7.50 (m, 4H, Ar-H), 6.80 (s, 1H, N-H), 4.28 (s, 2H, CH_2); MS: *m/z* 170 $[M]^{+\cdot}$,172$[M+2]^+$

Synthesis of 2-chloro-*N*-[(4-methylphenyl) sulfonyl]-*N*-pyridin-2-ylacetamide (2): Comp.1 (0.01 m mol) and acetonitrile (25 ml) were taken in dry beaker than p-toluene sulfonyl chloride (0.01 m mole) added portion wise in above solution. ZnO added as a catalyst in small amount than reaction mass refluxed for 12 hrs, progress of reaction checked by TLC. After complete the reaction solid appear, which was isolated, dried and recrystalized from benzene.

IR (KBr) cm^{-1} : 3245 (Ar-H str), 2947 (CH_2, str.), 2899 (CH_3, str.), 1632 (C=N str.), 1627 C=O, str), (1398(N-S str) ^{1}H-NMR ($CDCl_3$) δ: 7.06- 7.38 (m, 8H, Ar-H), 4.73 (s, 2H, CH_2); 2.15(s, 3H, CH_3); MS: *m/z* 248 $[M]^+$, 250 $[M+2]^+$

Table II: Antimicrobial activity of synthesized compounds on 200 ppm 1-4 and 7ad-8ad

Zone of inhibition (mm), Antibacterial activity and antifungal activity

Compd	***B.*** *subtilis*	***E.*** *coli*	***S.*** *typhi*	***P.*** *aeruginosa*	***A.*** *fumigatus*	***C.*** ***albicans***
1	+	++	++	++	++	+
2	++++	++	++	+	+	+++
3	+	+++	+	++	++	+
4	++++	++	++	+	+	+++
7a	+	++	+	++	+	+
7b	++	+	+	++	+	++
7c	++	+	+	++	+	++
7d	+	+	++	+	+	+
8a	+	++	+	+	++	++
8b	++	++++	++	+++	+++	++++
8c	+	++	++	+	+	+
8d	++	+++	+	++	++	+++
STD_1	+++	+++	++	+++	--	--
STD_2	--	--	--	--	+++	+++

+ = 10-14 (poor activity), ++ =15-18(moderate activity), +++ = 19-22 (good activity), ++++ = 23-26 (strong activity).

Standard:

STD_1 =Ciprofloxacin, STD_2 = Flucanazole,

Synthesis of 4-methyl-*N*-pyridin-2-ylbenzenesulfonamide (3): 2 amino pyridine (0.01 m mol) and acetonitrile (25 ml) were taken in dry beaker than p-toluene sulfonyl chloride (0.01 m mole) added portion wise in above solution. ZnO added as a catalyst in small amount, than stirrer at RT for 2 hrs, progress of reaction checked by TLC. After complete the reaction solid appear, which was isolated, dried and recrystalized from CH_3CN.

IR (KBr) cm^{-1} : 3431 (N-H str), 3243 (Ar-H str), 2821 (CH_3, str.), 1631 (C=N str.), 1391(N-S str) ^{1}H-NMR ($CDCl_3$) δ: 7.22- 8.33 (m, 8H, Ar-H), 6.75 (s, 1H, N-H), 2.36(s, 3H, CH_3); MS: *m/z* 248 $[M]^+$.

Synthesis of 2-chloro-*N*-[(4-methylphenyl) sulfonyl]-*N*-pyridin-2-ylacetamide (4): Comp.3 (0.1 m mole) and 1, 4-dioxane (50 ml) were taken in dry beaker than added CH_3COONa (0.1m mole), mixed

well above all component and make a clean solution. Chloroacetyl chloride (0.1 m mole) were added drop by drop in above solution with gently shaking, after complete the addition, reaction mass stay for 30 min. at RT and success of reaction checked by TLC. End of the reaction solid appear, it poured into ice cold water than filtered and recrystalized from Benzene.

IR (KBr)cm^{-1} : 3252 (Ar-H, str.), 2924 (CH_2, str.), 2822 (CH_2, str.),1631 (C=N str.), 1621 (C=O, str.), 1391 (N-S, str.), ^{1}H NMR ($CDCl_3$) δ: 7.06-7.38 (m, 8H, Ar-H), 4.73 (s, 2H, CH_2), 2.15 (s, 3H, CH_3); MS: *m/z* 324 $[M]^{+\cdot}$,326 $[M+2]^+$

Synthesis of 4-methyl-*N*-pyridin-2-ylbenzenesulfonamide (5): Ethylacetoacetate (0.01 m mole) taken in dry conical flask than added 25 ml ethanol and well mixed to it. Hydrazine hydrate (0.01 M mole) added drop wise with stirrer, temperature rised during reaction and it was maintained at 60^o C. Reaction mass further stirrer for 3 hrs, progress of reaction was checked by TLC , after complete the reaction solid appear and which was isolated, washed with ice cold methanol and recrystalized from ethanol.

IR (KBr) cm^{-1}: 3416 (N-H, str.), 3055 (Ar-H, str.), 2926 (CH_3, str.), 2962 (CH_2, str.), 1726 (C=O, str.), 1592 (C=N, str.); ^{1}H NMR ($CDCl_3$) δ: 8.11 (s, 1H, N-H,) , 2.20 (s, 2H, CH_2,), ; 1.82 (s, 3H, CH_3,), MS: *m/z* 98 $[M]^{+\cdot}$

Synthesis of 5-methyl-4-(phenylmethylidene)-2,4-dihydro-3*H*-pyrazol-3-one (6a): A mixture of 3-methyl-2, 4-dihydro-3H-pyrazol-3-one (0.01mole), benzaldehyde (0.01mole), and anhydrous sodium acetate (0.01 mole) were suspended in acetic acid (30 ml) and refluxed for 10 hrs. The mixture was filtrate and the filtrate was poured on cursed ice. The solid obtained, was crystallized from ethanol.

Compounds **6b-d** were also synthesized the similar method using appropriate reactants with required change in reflux time.

IR (KBr) cm-1: 3419 (N-H str.), 3050 (C-H str., Ar-H), 2925 (C-H str., CH3), 1725 (C=O str.), 1590 (C=N str.). 1H NMR (CDCl3) δ: 8.12 (s, 1H, NH), 7.22-7.76 (m, 5H, Ar-H), 6.20 (s, 1H, =CH-Ar), 1.93 (s, 3H, CH3), (*m/z*) 186 [M+].

4-[(4-chlorophenyl) methylidene]-5-methyl-2, 4-dihydro-3*H*-pyrazol-3-one (6b): IR (KBr) cm-1: 3434 (N-H str.), 3055 (C-H str., Ar-H), 2930 (C-H str., CH3), 1732 (C=O str.), 1601 (C=N str.), 736 (C-Cl str.). 1H NMR (CDCl3) δ : 8.15 (s, 1H, NH),7.30-7.90 (m, 4H, Ar-H), 6.32 (s, 1H, =CH-Ar), 2.10 (s, 3H, CH3), MS : (*m/z*) [M]+. 220, [M+2] 222.

5-methyl-4-[(3-nitrophenyl)methylidene]-2,4-dihydro-3*H*-pyrazol-3-one (6c): IR (KBr) cm-1: 3436 (N-H str.), 3060 (C-H str., Ar-H), 2936 (C-H str., CH3), 1740 (C=O str.), 1611 (C=N str.), 1H NMR (CDCl3) δ : 8.19 (s, 1H, NH),7.36-7.94 (m, 4H, Ar-H), 6.37 (s, 1H, = CH-Ar), 2.14 (s, 3H, CH3). MS: (*m/z*) [M]+. 231, [M+2] 233.

4-[(4-fluorophenyl)methylidene]-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (6d): IR (KBr) cm-1: 3442 (N-H str.), 3065 (C-H str., Ar-H), 2942 (C-H str., CH3), 1746 (C=O str.), 1618 (C=N str.), 1H NMR(CDCl3) δ : 8.18 (s, 1H, NH),7.35-7.96 (m, 4H, Ar-H), 6.35 (s, 1H, =CH-Ar), 2.12 (s, 3H, CH3). MS: (*m/z*) [M] +. 204, [M+2] 206.

Synthesis of 6-amino-3-methyl-4-phenyl-1*H*-pyrazolo [3, 4-*b*] pyridine-5-carbonitrile (7a): Compound **6a** (0.01 mole), malononitrile (0.01mole) and ammonium acetate (0.08 mole) were dissolved in ethanol (30 ml) and refluxed for 12 hrs. The mixture was cooled and poured over crushed ice. Solid was filtered, dried and from ethanol.

IR (KBr) cm^{-1}: 3372,3310 (N-H, str., NH_2), 3170 (Ar-H, str.), 3261 (N-H, str, ring.), 2850(CH_3, str), 2192(CN, str), 1648 (C=N, P ,str),1596 (C=N,B, str.), 1489(C=C,P,str), 1452(C=C,B,str)1172 (N-N, str.); ^1H NMR ($CDCl_3$) δ: 8.33 (s, 1H, N-H), 7.22-7.79 (m, 5H, Ar-H), 6.78 (s, 2H, NH_2) , 2.37 (s, 3H, CH_3) ; MS: *m/z* $[M]^{+\cdot}$249

Similarly comp. **5b-d** was prepared with some change in refluxed time and work up process.

6-amino-4-(4-chlorophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (7b): IR (KBr) cm^{-1}: 3374,3315 (N-H, str., NH_2), 3172 (Ar-H, str.), 3264 (N-H, str, ring.), 2852(CH_3, str), 2194(CN, str), 1649 (C=N, P ,str),1598 (C=N,B, str.), 1490(C=C,P,str), 1454(C=C,B,str)1175 (N-N, str.); ^1H NMR ($CDCl_3$) δ: 8.33 (s, 1H, N-H), 7.23-7.80 (m, 4H, Ar-H), 6.79 (s, 2H, NH_2) , 2.38 (s, 3H, CH_3) ; MS: *m/z* $[M]^{+\cdot}$283, $[M]^{+2\cdot}$285

6-amino-3-methyl-4-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (7C): IR (KBr) cm^{-1}: 3375,3318 (N-H, str., NH_2), 3174 (Ar-H, str.), 3266 (N-H, str, ring.), 2854(CH_3, str), 2195(CN, str), 1650(C=N, P ,str),1599 (C=N,B, str.), 1494(C=C,P,str), 1456(C=C,B,str)1180 (N-N, str.); ^1H NMR ($CDCl_3$) δ: 8.34 (s, 1H, N-H), 7.25-7.83 (m, 4H, Ar-H), 6.80 (s, 2H, NH_2) , 2.39 (s, 3H, CH_3) ; MS: *m/z* $[M]^{+\cdot}$294

6-amino-4-(4-fluorophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (7d): IR (KBr) cm^{-1}: 3378,3320 (N-H, str., NH_2), 3176 (Ar-H, str.), 3266 (N-H, str, ring.), 2860(CH_3, str), 2196(CN, str), 1652 (C=N, P ,str),1598 (C=N,B, str.), 1496(C=C,P,str), 1458(C=C,B,str)1184 (N-N, str.); ^1H NMR ($CDCl_3$) δ: 8.36 (s, 1H, N-H), 7.27-7.87 (m, 4H, Ar-H), 6.79 (s, 2H, NH_2) , 2.40 (s, 3H, CH_3) ; MS: *m/z* $[M]^{+\cdot}$267, $[M]^{+2\cdot}$269

Synthesis of *N*-[2-(6-Amino-5-cyano-3-methyl-4-phenyl-pyrazolo[3,4-*b*]pyridin-1-yl)-acetyl]-4-methyl-*N*-pyridin-2-yl-benzenesulfonamide (8a): Comp. **7a** (0.01 m mole), sulfonamide drug, comp.**4** (0.01 M mole), and tetrahydrofurane (THF, 20 ml) were taken in dry round bottom flask, triethyl amine used as a catalysis and refluxed it to 24 hrs. Reaction progress checked by TLC, end of the reaction, resultant product poured into crushed ice, solid appear, which was isolated, dried and recrystalized from ethanol.

IR (KBr) cm^{-1}: 3372,3314 (N-H, str., NH_2), 3165 (Ar-H, str.),2860 (CH_2 ,str,), 2923 (CH_3, str), 2192(CN, str), 1724 (C=O, str) , 1637,1611 (S=O, str)1498 (C=N, P ,str),1488 (C=N,B, str.), 1393 (C=C,P,str), 1383 (C=C,B,str), 1281(N-S str)1142 (N-N, str.); ^1H NMR ($CDCl_3$) δ: 7.22-7.89 (m, 13H, Ar-H), 6.77 (s, 2H, NH_2) , 3.69 (s, 2H, CH_2), 2.59 (s, 3H, CH_3, B) 2.37 (s, 3H, CH_3, P) ; MS: *m/z* $[M]^{+\cdot}$537

Similarly comp. **8b-d** was prepared with some change in stirrer time and work up process.

***N*-{2-[6-Amino-4-(4-chloro-phenyl)-5-cyano-3-methyl-pyrazolo[3,4-*b*]pyridin-1-yl]-acetyl}-4-methyl-*N*-pyridin-2-yl-benzenesulfonamide (8b):** IR (KBr) cm^{-1}: 3374,3315 (N-H, str., NH_2), 3167 (Ar-H, str.),2862 (CH_2 ,str,), 2925 (CH_3, str), 2195(CN, str), 1726 (C=O, str) , 1637,1611 (S=O, str)1499 (C=N, P ,str),1490 (C=N,B, str.), 1395 (C=C,P,str), 1385 (C=C,B,str), 1284(N-S str)1144 (N-N, str.); ^1H NMR ($CDCl_3$) δ: 7.24-7.80 (m, 12H, Ar-H), 6.78 (s, 2H, NH_2) , 3.70 (s, 2H, CH_2), 2.62 (s, 3H, CH_3, B) 2.38 (s, 3H, CH_3, P) ; MS: *m/z* $[M]^{+\cdot}$573, $[M]^{+2\cdot}$575

***N*-{2-[6-Amino-5-cyano-3-methyl-4-(3-nitro-phenyl)-pyrazolo[3,4-*b*]pyridin-1-yl]-acetyl}-4-methyl-*N*-pyridin-2-yl-benzenesulfonamide (8c):** IR (KBr) cm^{-1}: 3376,3320 (N-H, str., NH_2), 3169 (Ar-H, str.),2864 (CH_2 ,str,), 2930 (CH_3, str), 2197(CN, str), 1728 (C=O, str) , 1639,1614 (S=O, str)1502 (C=N, P ,str),1493 (C=N,B, str.), 1396 (C=C,P,str), 1387 (C=C,B,str), 1286(N-S str) 1146 (N-

N, str.); ^{1}H NMR ($CDCl_3$) δ: 7.26-7.85 (m, 12H, Ar-H), 6.79 (s, 2H, NH_2) , 3.71 (s, 2H, CH_2), 2.64 (s, 3H, CH_3, B) 2.39 (s, 3H, CH_3, P) ; MS: *m/z* $[M]^{+\cdot}$573, $[M]^{+2\cdot}$582

***N*-{2-[6-Amino-5-cyano-4-(4-fluoro-phenyl)-3-methyl-pyrazolo[3,4-*b*]pyridin-1-yl]-acetyl}-4-methyl-*N*-pyridin-2-yl-benzenesulfonamide (8d):** IR (KBr) cm^{-1}: 3377,3322 (N-H, str., NH_2), 3170 (Ar-H, str.),2865 (CH_2 ,str,), 2932 (CH_3, str), 2198 (CN, str), 1730 (C=O, str) , 1644,1616 (S=O, str)1504 (C=N, P ,str),1495 (C=N,B, str.), 1398 (C=C,P,str), 1388 (C=C,B,str), 1290(N-S str) 1150 (N-N, str.); ^{1}H NMR ($CDCl_3$) δ: 7.29-7.88 (m, 12H, Ar-H), 6.80 (s, 2H, NH_2) , 3.72 (s, 2H, CH_2), 2.66 (s, 3H, CH_3, B) 2.40 (s, 3H, CH_3, P) ; MS: *m/z* $[M]^{+\cdot}$555.

CONCLUSION

In this research paper, pyrazole, pyridine and their derivative were synthesized using N-alkylation approach and novel sulfonamide drugs. Synthesized nucleous are tested for anti bacterial and antifungal activity. Compound **2** and **4** exhibit strong activity against *B.Substilis*, similarly show good activity against *C. Albicanc.* Another comp. **7a** to **7d** exhibit poor to moderate activity against both microbial. All over result is that compound **8b** shows strong activity against *C. albicanc* fungal strains and *E. coli* bacterial strains as compared to the standard drugs (STD).

AKNOWLEDGEMENT

Authors are thankful to the Head, Department of Chemistry, MEWAR University, Chittorgarh, for providing laboratory facilities. Authors are also thankful to the MNIT Jaipur, India, for providing us analytical facilities.

REFERENCES

1. J.M. Chezal, synthesis and antiviral activity of an imidazo[1,2-a]pyrrolo[2,3-c]pyridine series against the bovine viral diarrhea virus, European Journal of Medicinal Chemistry, 2010, 45, 2044–2047.
2. J.K. Son, E.S. Lee, Synthesis of 2,6-diaryl-substituted pyridines and their antitumor activities, European Journal of Medicinal Chemistry, 2008, **43**, 675-682.
3. C. Richards, P.S. Thomas, Sulfonylation of aromatic compounds with sulfonic acids using silica gel-supported AlCl3 as a heterogeneous Lewis acid catalyst. Pestic. Sci., 1990, **30**, 275
4. C.J. Dinsmore, T.M. Williams, T.J. O Neill, D. Liu, E. Rands, J.C. Culberson, R.B. Lobell, K.S. Koblan, N.E. Kohl, J.B. Gibbs, A.I. Oliff, S.L. Graham, C.D. Hartman, Imida-zole-containing diarylether and diarylsulfone inhibitors of farnesyl-protein transferase. Bioorg. Med. Chem. Lett., 1999, 9, 3301.
5. D.J. Abraham (Ed.), Burger's medicinal chemistry & drug discovery, John Wiley and Sons, 2003.
6. C.T. Supuran, A. Casini, A. Scozzafava, Protease inhibitors of the sulfonamide type: Anticancer, antiinflam-matory, and antiviral agents. Med. Res. Rev. 2003, **5**, 535.
7. A. Scozzafava, T. Owa, A. Mastrolorenzo, C.T. Supuran, Anticancer and antiviral Sulfonamides. Curr. Med. Chem., 2003, 10, 925.
8. J.B. McMohan, R.J. Gulakowsky, O.S. Weislow, R.J. Schultz, V.L. Narayanan, D.J. Clanton, R. Pedemonte, F.W. Wass-mundt, R.W. Buckheit Jr., W.D. Decker, E.L. White, J.P. Bader, M.R. Boyd, Diarylsulfones, a new chemical class of nonnucleoside antiviral

inhibitors of human immu-nodeficiency virus type 1 reverse transcriptase. Antimicrob. Agents. Chemother. 1993, **37** ,754

9. K. Ohta, S. Itoh, J. Yamada, K. Masumoto, H. Yoshikawa, Y. Ishida, An eco-friendly N-sulfonylation of amines us-ing stable and reusable Zn–Al–hydrotalcite solid base catalyst under ultrasound irradiation. J. Pest. Sci. 1993, 18, 183
10. J.L. Moore, S.M. Taylor and V.A. Soloshonok, An efficient and operationally convenient general synthesis of tertiary amines by direct alkylation of secondary amines with alkyl halides in the presence of Huenig's base, *ARKIVOC*, 2005, (**vi),** 287-292.
11. C.M. Clay, H.M. Abdallah, C. Jordan, K. Knisley, and D.M. Ketcha, N-Alkylation of isatins utilizing KF/alumina, *ARKIVOC*, 2012, (**vi**), 317-325.
12. D.H. Boschelli, B. Wu, A.C. Barrios Sosa, J. Chen, M. Asselin, D.C. Cole, J. Lee, X. Yang and D. Chaudhary, Synthesis and PKCtheta inhibitory activity of a series of 4-(indol-5-ylamino)thieno[2,3-b]pyridine-5-carbonitriles, *Bioorg Med Chem Lett.*, 2008, **18**, 2850-53.
13. K. Madhusudana, B. Shireesha, V.G. Naidu, S. Ramakrishna, B. Narsaiah, A.R. Rao and P.V. Diwan, Anti-inflammatory potential of thienopyridines as possible alternative to NSAIDs. *Eur J Pharmacol.* 2012, 678, 48-54.
14. L. Nathan Tumey, D.H. Boschelli, J. Lee and D. Chaudhary, 2-Alkenylthieno[2,3-b]pyridine-5-carbonitriles: Potent and selective inhibitors of PKCtheta., *Bioorg Med Chem Lett.* 2008, **18**,4420,3.
15. H. Liu, Y. Li, X.Y. Wang, B. Wang, H.Y. He, J.Y. Liu, M.L. Xiang, J. He, X.H. Wu and L. Yang, Synthesis, preliminary structure-activity relationships, and in vitro biological evaluation of 6-aryl-3-amino-thieno [2,3-b]pyridine derivatives as potential anti-inflammatory agents., *Bioorg Med Chem Lett.* 2013, **23**, 2349-52.
16. M.E. Schnute, D.J. Anderson, R.J. Brideau, F.L. Ciske and S.A. Collier, 2-Aryl-2-hydroxyethylamine substituted 4-oxo-4,7-dihydrothieno[2,3-b]pyridines as broad-spectrum inhibitors of human herpesvirus polymerases, *Bioorg Med Chem Lett*, 2007, 17, 3349-53.
17. D. Shuck-Lee, F. Chen, R. Willard, S. Raman and R. Ptak, Heterocyclic Compounds That Inhibit Rev-RRE Function and Human Immunodeficiency Virus Type 1 Replication**.** *Antimicrob. Agents Chemother.* 2008, 52, 3169-3179.
18. L.C.S Pinheiro, J.C. Borges, C.D. Oliveira, V.F. Ferreira and G.A. Romeiro. Synthesis of new (phenylamino)thieno [2,3-b]pyridines and derivatives of the novel benzo[b]thieno[3,2-h]-1,6-naphthyridinetetracyclic system, *Arkivoc.* 2008, 17, 77-87.
19. A. Chaubey and S.N. Pandeya, Pyridine: a versatile nucleuse in pharmaceutical field, *Asian J. Pharm. Clin. Res.*, 2011, **4**, 5-8.
20. I. Adachi, Y. Hiramatsu, M. Ueda and M. Kawakami, 4,7-dihydrothieno[2,3-b] pyridine derivatives useful in the treatment of cardiovascular diseases, *US Patent.* 1987; 4,703-051.
21. M. Ueda, S. Matsumura, M. Masui, E. Matsuura, M. Kawakami, H. Fujitomo, T. Umeda, H. Kagawa, S. Hirohata and K. Shima, Pharmacological studies on a new dihydrothienopyridine calcium antagonist : antihypertensive effects of S-(+) -methyl-4,7 -dihydro -3-isobutyl -6-methyl -4 -(3-nitrophenyl)thieno [2,3-b] pyridine -5- carboxylate in hypertensive rats and dogs, *Arzneimittelforschung,* 1993,43,1282-90.
22. I. Adachi, T. Yamamori, Y. Hiramatsu, K. Sakai, S. Mihara, M. Kawakami, M. Masui, O. Uno and M. Ueda, Studies on dihydropyridines. III. Synthesis of 4,7-dihydrothieno [2,3-

b]-pyridines with vasodilator and antihypertensive activities, *Chem Pharm Bull (Tokyo)*, 1988, 36,4389- 402.

23. R.H. Bahekar, M.R. Jain, A. Goel, D.N. Patel, V.M. Prajapati, A.A. Gupta, P.A. Jadav and P.R. Patel, Design, synthesis, and biological evaluation of substituted- N-(thieno[2,3-b]pyridin-3-yl)-guanidines,N-(1H-pyrrolo[2,3-b]pyridin-3-yl)-guanidines, and N-(1H-indol-3-yl)-guanidines, *Bioorg Med Chem.*, 2007, 15, 3248-65.
24. R.H. Bahekar, M.R. Jain, P.A. Jadav, V.M. Prajapati, D.N. Patel, A.A. Gupta, A. Sharma, R.Tom, D.Bandyopadhya, H. Modi and PR Patel, Synthesis and antidiabetic activity of 2,5-disubstituted-3-imidazol-2-yl-pyrrolo[2,3-b] pyridines and thieno[2,3-b]pyridines. *Bioorg Med Chem.*, 2007, 15, 6782- 95.
25. L. Feng, I. Reynisdóttir and J. Reynisson, The effect of PLC-g2 inhibitors on the growth of human tumour cells, *Eur. J. Med.Chem.*, 2012, 54, 463-469.
26. R.M. Mohareb, W. Wardakhan, G.A. Elmegeed and R.M. Ashour. Heterocyclizations of pregnenolone: novel synthesis of thiosemicarbazone, thiophene, thiazole, thieno[2,3-b]pyridine derivatives and their cytotoxicity evaluations. *Steroids.* 2012, 77, 1560-9.
27. K. Saito, A .Nakao, T. Shinozuka, K. Shimada, S. Matsui, K. Oizumi, K. Yano, K. Ohata, D. Nakai, Y. Nagai and S. Naito, Discovery and structure-activity relationship of thienopyridine derivatives as bone anabolic agents, *Bioorg Med Chem.*, 2013, 21, 1628-42.
28. S. Ohba, K. Nakajima, Y. Komiyama, F. Kugimiya, K. Igawa, K. Itaka, T. Moro, K. Nakamura, H. Kawaguchi, T. Takato and U.I. Chung, A novel osteogenic helioxanthin-derivative acts in a BMP-dependent manner, *Biochem Biophys Res Commun.*, 2007, 357,854-60.
29. A.M. Bernardino, L.C. da Silva Pinheiro, C.R. Rodrigues, N.I. Loureiro, H.C. Castro, A. Lanfredi-Rangel, J. Sabatini-Lopes, J.C. Borges, J.M. Carvalho, G.A. Romeiro, V.F. Ferreira, I.C. Frugulhetti and M.A. Vannier-Santos, Design, synthesis, SAR, and biological evaluation of new 4-(phenylamino)thieno[2,3-b] pyridine derivatives, *Bioorg Med Chem.* 2006, 14, 5765-70.
30. S.A. Al-Trawneh, M.M. El-Abadelah, J.A. Zahra, S.A. Al-Taweel, F. Zani, M. Incerti, A. Cavazzoni and P. Vicini, Synthesis and biological evaluation of tetracyclic thienopyridones as antibacterial and antitumor agents, *Bioorg Med Chem.*, 2011, 19, 2541-8.
31. E.G. Mohler, S. Shacham, S. Noiman, F. Lezoualc'h, S. Robert, M. Gastineau, J. Rutkowski, Y. Marantz, A. Dumuis, J. Bockaert, P.E. Gold and M.E. Ragozzino, VRX-03011, a novel 5-HT4 agonist, enhances memory and hippocampal acetylcholine efflux. *Neuropharmacology*, 2007, 53, 563-73.
32. H.P. Buchstaller, C.D. Siebert, R. Steinmetz, I. Frank, M.L. Berger, R. Gottschlich, J. Leibrock, M. Krug, D. Steinhilber and C.R. Noe, Synthesis of thieno[2,3-b] pyridinones acting as cytoprotectants and as inhibitors of [3H]glycine binding to the N-methyl-D-aspartate (NMDA) receptor, *J Med Chem.*, 2006, 49, 864-71.
33. M. Propsavin, L. Torovic, S. Spaic, S. Stankov, A. Kapor, Z. Tomic, V. Popsavin, Synthesis and biological evaluation of new pyrazole- and tetrazole-related C-nucleosides with modified sugar moieties, Tetrahedron., 2002, 58, 569-580.
34. P. D. Sauzem, P. Machado, M. A. Rubin, DaS. G. Sant.Anna, H. B. Faber, A. H. De Souza, C. F. Mello, P. Beck, R. A. Burrow, H. G. Bonacorso, N. Zanatta, M. A. Martins, Design and microwaveassisted synthesis of 5-trifluoromethyl-4,5-dihydro-1H-pyrazoles:

Novel agents with analgesic and anti-inflammatory properties, Eur. J. Med. Chem. 2008, 43, 1237-1247.

Corresponding Author: Prabhunath Yogi
Synthetic Organic Chemistry Laboratory, Department of Chemistry,
Mewar University, Gangrar, Rajasthan