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Original Article

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL STUDY OF SOME BENZENESULFONAMIDE BASED BIPYRAZOLES

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ABSTRACT

Objectives: To synthesize, characterize and evaluate antimicrobial properties of some benzenesulfonamide based bipyrazole.

Methods: The benzenesulfonamide based bipyrazole **1a-d & 2a-f** have been synthesized by the reaction between 1-[1-aryl / (benzothiazol-2-yl)-5-hydroxy-3-methylpyrazol-4-yl]butane-1,3-diones **5** and 2-hydrazinobenzothiazoles or Aryl hydrazines **3**. The structures of these compounds have been characterized from the rigorous analysis of their IR, ^{1}H-NMR, HRMS and elemental analysis. These compounds were screened for their anti-microbial activity.

Results: The results revealed that compounds **1a**, **2b** and **2f** exhibited good antibacterial activity and **1b**, **1c**, **2a**, and **2d** showed moderate antibacterial activity as compared with standard drug Ofloxacin.

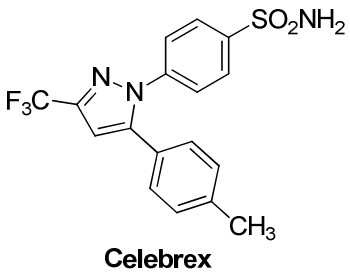
Conclusion: This study provides the simple method for the synthesis of new benzenzenesulfonamide based bipyrazoles which plays important role in numerous bioactive compounds.

Keywords: Bipyrazole, Butane-1,3-diones, 2-Hydrazinobenzothiazoles, Arylhydrazines, Benzenesulfonamide, Anti-microbial.

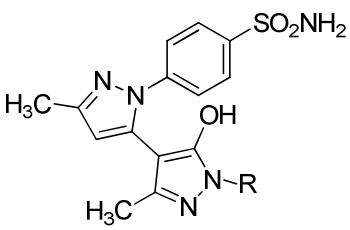
INTRODUCTION

Benzenesulfonamide functional group plays important role in numerous bioactive compounds [1, 2]. The interest in this functional group has widened since the discovery of two Cyclooxygenase (COX) isoforms in the early 1990s [3-5]. Pyrazole derivatives have a long history of application in the agrochemical and the pharmaceutical industry [6, 7] as herbicides, insecticides [8, 9] and as part of biologically active pharmaceuticals [10, 11]. Celebrex [10], a currently marketed selective COX-2 inhibitor, is a pyrazole derivative incorporated with benzenesulfonamide functional group. In place of the central pyrazole ring a large no of heterocycles [1] such as thiophene, furanone, pyridine, thiazole, triazole and oxazole have been reported to possess good COX-2 inhibitory activity. There are only few examples of replacement of the aryl substituents with some heterocycles [10] have been reported to possess excellent potency and selectivity. Several COX-2 inhibitors containing sulfone / sulfonamide moiety have been withdrawn from the market or clinical development. In fact celecoxib is still in the market but being prescribed cautiously. Inhibition of carbonic anhydrase is another problem of sulfonamide class of compounds.

In view of above facts and observations, we have therefore, synthesized two series of compounds, namely, 1-[(4-aminosufonyl)phenyl]-3-methyl-5-[1-aryl/heterocyclyl-5-hydroxy-3-methylpyrazol-4-yl]pyrazoles (1a-d) and 1-aryl/heterocyclyl-3-methyl-5-[1-(4-aminosulfonyl)phenyl-5-hydroxy-3-methylpyrazol-4-yl]pyrazoles (2a-f), in which the 5-aryl substituent of the lead class 1,5-diarylpyrazoles have been replaced by a heterocyclyl pyrazole moiety.

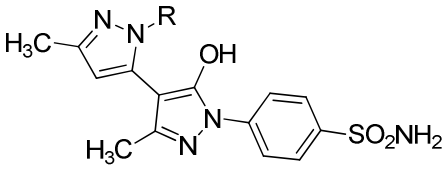


Celebrex



1a-d

R	
1a	C_6H_5
1b	4-ClC_6H_4
1c	6-Chlorobenzothiazol-2-yl
1d	4-$SO_2NH_2C_6H_4$



2a-f

R	
2a	C_6H_5
2b	4-ClC_6H_4
2c	2,4-$Cl_2C_6H_3$
2d	6-Methylbenzothiazol-2-yl
2e	6-Chlorobenzothiazol-2-yl
2f	6-Methoxybenzothiazol-2-yl

Fig. 1

MATERIALS AND METHODS

All the chemicals required were purchased from the local suppliers and were purified by established methods. The melting points were recorded by open capillary method and are uncorrected. The purity and homogeneity of the synthesized compounds were routinely ascertained by the thin layer chromatography, performed on plates coated with silica gel-G. All compounds were isolated and purified by thin layer chromatography and column chromatography respectively. The visualization was done using iodine vapours and U. V. light chamber.

The ^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument using $CDCl_3$ or DMSO-d_6 solvents and TMS (Tetra methyl silane) as internal standard. Chemical shifts (δ) are reported in ppm and coupling constants *J* are given in Hz. IR spectra were recorded using KBr disks with a Buck Scientific IR M-500 infrared spectrometer. High-resolution mass spectra were measured on a Kratos MS-50 mass spectrometer.

Experimental

Synthesis of 4-[5-(1-substituted-5-hydroxy-3-methylpyrazol-4-yl]-3-methylpyrazol-1-yl]benzenesulfonamides (1) and 4-[5-hydroxy-3-methyl-4-(1-substituted-3-methylpyrazol-5-yl)pyrazol-1-yl]benzenesulfonamides (2)

Phenylhydrazone of DHAA (4a)

Dehydroacetic acid (DHAA) (3.36 g, 0.02 mol) was dissolved in ethanol (50 ml) by warming and phenylhydrazine (2 ml, 0.02 mol) was added in it while shaking. The contents were stirred for 10 min. and allowed to stand at room temperature for 2 hrs. The yellow solid so obtained was filtered, crystallized from acetonitrile, mp 211° (mp 212° [12]) yield 81%.

Other hydrazones of DHAA (**4b-4d**) were prepared similarly by treating DHAA with corresponding hydrazines.

4-Chlorophenylhydrazone of DHAA (4b)

mp 250° (mp 252°[12]), yield 66%.

6-Chlorobenzothiazol-2-ylhydrazone of DHAA (4c)

mp 185-186° (mp 186°[13]), yield 60%.

4-Sulfamoylphenylhydrazone of DHAA (4d)

mp 232-234°, yield 70%, IR (KBr) cm^{-1}: 3309-3081 (br, O-H & N-H stretch), 1716 (s, C=O stretch), 1317 & 1149 (s, SO_2 stretch), ^{1}H NMR ($CDCl_3$, 300MHz): δ 2.28 (s, 3H, pyrone C_6-CH_3), 2.64 (s, 3H, CH_3-C=N-), 6.01 (s, 1H, pyrone C_5-H),7.10-7.13 (d, 2H, J=8.8Hz, $C_{3'}$-H & $C_{5'}$-H), 7.71-7.68 (d, 2H, J=8.8Hz, $C_{2'}$-H & $C_{6'}$-H)

1-[5-Hydroxy-3-methyl-1-phenylpyrazol-4-yl]butane-1,3-dione (5a)

Phenylhydrazone of DHAA (0.01 mol) was dissolved in glacial acetic acid (30 ml) and the solution refluxed for 1.5 hrs. The solvent was distilled off at reduced pressure and the residue was crystallized from acetonitrile, mp 101° (mp 101-102°[12]), yield 66%.

All other compounds were synthesized by following the above procedure.

1-[1-(4-Chlorophenyl)-5-hydroxy-3-methylpyrazol-4-yl]butane-1,3-dione (5b)

mp 150°(mp 151°[12]), yield 67%.

1-[1-(6-Chlorobenzothiazol-2-yl)-5-hydroxy-3-methylpyrazol-4-yl]butane-1,3-dione (5c)

mp 216° (mp 217°[13]), yield 63%.

1-[1-(4-Sulfamoylphenyl)-5-hydroxy-3-methylpyrazol-4-yl]-butane-1,3-dione (5d)

mp 195-197°, yield 55%, IR (KBr) cm^{-1}: 3294 & 3174 (br, O-H & N-H stretch), 1666 (s, C=O stretch), 1324 & 1159 (s, SO_2 stretch). ^{1}H NMR ($CDCl_3$, 300MHz): δ 2.12 (s, 3H, -CO-CH_3), 2.51 (s, 3H, pyrazolone C_3-CH_3), 6.65 (s, 2H, -CO-CH_2-CO-), 7.90-8.01 (m, 4H, $C_{2'}$-H, $C_{3'}$-H, $C_{5'}$-H & $C_{6'}$-H).

4-[5-(5-hydroxy-3-methyl-1-phenylpyrazol-4-yl)-3-methylpyrazol-1-yl]benzenesulfonamide (1a)

To an ethanolic solution of 1-[5-hydroxy-3-methyl-1-phenylpyrazol-4-yl]butane-1,3-dione (5 mmol) was added 4-sulfamoyl phenylhydrazine (5 mmol) and the contents having a few drops of concentrated HCl were refluxed for 3 hrs. The reaction mixture was concentrated and cooled at room temperature. A crystalline solid was obtained, filtered and dried. mp 152-154°, yield 51%, IR (KBr) cm^{-1}: 3570 (m, O-H stretch), 3394 & 3315 (m, N-H stretch), 1624 (s, N-H bend), 1335 & 1162 (s, SO_2 stretch). ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ1.95 (s, 3H, pyrazolone $C_{3''}$-CH_3), 2.36 (s, 3H, pyrazole C_3-CH_3), 6.29 (s, 1H, pyrazole C_4-H), 7.22-7.27 (t, 1H, J=7.6Hz, $C_{4'''}$-H), 7.38-7.43 (t, 2H, J=7.6Hz, $C_{3'''}$-H & $C_{5'''}$-H), 7.53-7.56 (d, 2H, J=8.6Hz, $C_{2''}$-H & $C_{6''}$-H), 7.67-7.70 (d, 2H, J=7.6Hz, $C_{2'''}$-H & $C_{6'''}$-H), 7.85-7.88 (d, 2H, J=8.6Hz, $C_{3''}$-H & $C_{5''}$-H); MS: m/z 409.1212 (M^+, 35.5%); Anal. Found: C, 58.45; H, 4.80; N, 17.51%. Calcd. for $C_{20}H_{19}N_5O_3S$: C, 58.67; H, 4.68; N, 17.10%.

4-[5-{1-(4-chlorophenyl)-5-hydroxy-3-methylpyrazol-4-yl}-3-methylpyrazol-1-yl]benzenesulfonamide (1b)

mp 187-189°, yield 53%, IR (KBr) cm^{-1}:3360 (m, O-H stretch), 3230 & 3105 (m, N-H stretch), 1642 (s, N-H bend), 1336 & 1163 (s, SO_2 stretch); ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ2.01 (s, 3H, pyrazolone $C_{3'}$-CH_3), 2.43 (s, 3H, pyrazole C_3-CH_3), 6.36 (s, 1H, pyrazole C_4-H), 7.38-7.41 (d, 2H, J=8.5Hz, $C_{3'''}$-H & $C_{5'''}$-H), 7.56-7.59 (d, 2H, J=8.2Hz, $C_{2''}$-H & $C_{6''}$-H), 7.67-7.70 (d, 2H, J=8.5Hz, $C_{2'''}$-H & $C_{6'''}$-H), 7.91-7.94 (d, 2H, J=8.2Hz, $C_{3''}$-H & $C_{5''}$-H); MS: m/z 445.0834 / 443.0826 (M^++2 / M^+, 13.4%); Anal. Found: C, 58.37; H, 4.48; N, 15.51%. Calcd. for $C_{20}H_{18}ClN_5O_3S$: C, 54.11; H, 4.09; N, 15.78%.

4-[5-{1-(6-chlorobenzothiazol-2-yl)-5-hydroxy-3-methyl pyrazol-4-yl}-3-methylpyrazol-1-yl]benzenesulfonamide (1c)

mp 276-277°, yield 52%, IR (KBr) cm^{-1}: 3355-3058 (br, O-H & N-H stretch), 1648 (s, N-H bend), 1338 & 1161 (s, SO_2 stretch); ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ2.00 (s, 3H, pyrazolone $C_{3''}$-CH_3), 2.37 (s, 3H, pyrazole C_3-CH_3), 6.33 (s, 1H, pyrazole C_4-H), 7.40-7.44 (dd, 1H, J=8.5 & 1.9Hz, $C_{5'''}$-H), 7.60-7.63 (d, 2H, J=8.6Hz, $C_{2''}$-H & $C_{6''}$-H), 7.72-7.75 (d, 1H, J=8.5Hz, $C_{4'''}$-H), 7.85-7.86 (d, 1H, J=1.9Hz, $C_{7'''}$-H), 7.89-7.92 (d, 2H, J=8.6Hz, $C_{3''}$-H & $C_{5''}$-H); MS: m/z 502.0460 / 500.0491 (M^++2 / M^+, 100%); Anal. Found: C, 50.67; H, 3.68; N, 16.93%. Calcd. for $C_{20}H_{17}ClN_6O_3S_2$: C, 50.35; H, 3.42; N, 16.78%.

4-[5-hydroxy-3-methyl-4-{3-methyl-1-(4-sulfamoylphenyl)pyrazol-5-yl}pyrazol-1-yl]benzenesulfonamide (1d)

mp 284°(decomp), yield 54%, IR (KBr) cm^{-1}: 3596 (m, O-H stretch), 3374 & 3272 (m, N-H stretch), 1625 (s, N-H bend), 1330 & 1160 (s, SO_2 stretch); ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ1.95 (s, 3H, pyrazolone $C_{3''}$-CH_3), 2.38 (s, 3H, pyrazole C_3-CH_3), 6.30 (s, 1H, pyrazole C_4-H), 7.57-7.60 (d, 2H, J=8.1Hz, $C_{2''}$-H & $C_{6''}$-H), 7.86-7.93 (m 6H, $C_{3''}$-H, $C_{5''}$-H, $C_{2'''}$-H, $C_{3'''}$-H, $C_{5'''}$-H & $C_{6'''}$-H); MS: m/z 488.0941 (M^+, 47.9%); Anal. Found: C, 49.52; H, 4.38; N, 16.93%. Calcd. for $C_{20}H_{20}N_6O_5S_2$: C, 49.17; H, 4.13; N, 17.20%.

4-[5-hydroxy-3-methyl-4-(3-methyl-1-phenylpyrazol-5-yl)pyrazol-1-yl]benzenesulfonamide (2a)

mp 199-200°, yield 42%, IR (KBr) cm^{-1}: 3431 (m, O-H stretch), 3294 & 3216 (m, N-H stretch), 1650 (s, N-H bend), 1332 & 1170 (s, SO_2 stretch); ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 1.91 (s, 3H, pyrazolone $C_{3'}$-CH_3), 2.48 (s, 3H, pyrazole C_3-CH_3), 6.46 (s, 1H, pyrazole C_4-H), 6.96-7.49 (m, 8H, $C_{2''}$-H, $C_{3''}$-H, $C_{4''}$-H, $C_{5''}$-H, $C_{6''}$-H, pyrazole C_5-OH & $C_{4'''}$-SO_2NH_2), 7.94 (bs, 4H, $C_{2'''}$-H, $C_{3'''}$-H, $C_{5'''}$-H & $C_{6'''}$-H); MS: m/z 409.1204 (M^+, 37.1%); Anal. Found: C, 58.40; H, 4.78; N, 17.51%. Calcd. for $C_{20}H_{19}N_5O_3S$: C, 58.67; H, 4.68; N, 17.10%.

4-[4-{1-(4-chlorophenyl)-3-methylpyrazol-5-yl}-5-hydroxy-3-methylpyrazol-1-yl]benzenesulfonamide (2b)

mp 290°, yield 53%, IR (KBr) cm^{-1}: 3410 (m, O-H stretch), 3345 & 3270 (m, N-H stretch), 1553 (s, N-H bend), 1336 & 1163 (s, SO_2

stretch); ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 1.99 (s, 3H, pyrazolone $C_{3'}$-CH_3), 2.37 (s, 3H, pyrazole C_3-CH_3), 6.89 (bs, 2H, pyrazole C_4-H & pyrazolone $C_{5'}$-OH), 7.39-7.42 (d, 2H, J=8.8Hz, $C_{3''}$-H & $C_{5''}$-H), 7.48-7.51 (d, 2H, J=8.8Hz, $C_{2''}$-H & $C_{6''}$-H), 7.93-7.96 (d, 2H, J=8.7Hz, $C_{2'''}$-H & $C_{6'''}$-H), 8.11-8.14 (d, 2H, J=8.7Hz, $C_{3'''}$-H & $C_{5'''}$-H); MS: m/z 445.0781 / 443.0827 (M^++2 / M^+, 32.0%); Anal. Found: C, 58.29; H, 4.28; N, 16.93%. Calcd. for $C_{20}H_{19}N_5O_3S$: C, 58.67; H, 4.68; N, 17.11%.

4-[4-{1-(2,4-dichlorophenyl)-3-methylpyrazol-5-yl}-5-hydroxy-3-methylpyrazol-1-yl]benzenesulfonamide (2c)

mp 158-160°, yield 59%, IR (KBr) cm^{-1}: 3510 (m, O-H stretch), 3214 & 3136 (m, N-H stretch), 1587 (s, N-H bend), 1337 & 1185 (s, SO_2 stretch); ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 2.04 (s, 3H, pyrazolone $C_{3'}$-CH_3), 2.37 (s, 3H, pyrazole C_3-CH_3), 6.26 (s, 1H, pyrazole C_4-H), 7.28-7.32 (dd, 1H, J=8.6 & 2.3Hz, $C_{5''}$-H), 7.43-7.44 (d, 1H, J=2.3Hz, $C_{3''}$-H), 7.52-7.55 (d, 1H, J=8.6Hz, $C_{6''}$-H), 7.83-7.86 (d, 2H, J=8.8Hz, $C_{2'''}$-H & $C_{6'''}$-H), 7.89-7.92 (d, 2H, J=8.8Hz, $C_{3'''}$-H & $C_{5'''}$-H); MS: m/z 481.0631 / 479.0542 / 477.0431 (M^++4 / M^++2 / M^+, 52.3%); Anal. Found: C, 50.11; H, 4.01; N, 14.51%. Calcd. for $C_{20}H_{17}Cl_2N_5O_3S$: C, 50.22; H, 3.58; N, 14.64%.

4-[5-hydroxy-3-methyl-4-{3-methyl-1-(6-methylbenzothiazol-2-yl)pyrazol-5-yl}pyrazol-1-yl]benzenesulfonamide (2d)

mp 298°, yield 54%, IR (KBr) cm^{-1}: 3499 (m, O-H stretch), 3110 & 3059 (m, N-H stretch), 1633 (s, N-H bend), 1331 & 1163 (s, SO_2 stretch); ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 2.27 (s, 3H, pyrazolone $C_{3'}$-CH_3), 2.41 (s, 3H, pyrazole C_3-CH_3), 2.48 (s, 3H, $C_{6''}$-CH_3), 6.34 (s, 1H, pyrazole C_4-H), 6.82 (bs, 2H, $C_{4'''}$-SO_2NH_2), 7.27-7.30 (dd, 1H, J=8.3 & 1.1Hz, $C_{5''}$-H), 7.64 (d, 1H, J=1.1Hz, $C_{7''}$-H), 7.66-7.68 (d, 1H, J=8.3Hz, $C_{4''}$-H), 7.99-8.02 (d, 2H, J=8.8Hz, $C_{2'''}$-H & $C_{6'''}$-H), 8.07-8.10 (d, 2H, J=8.8Hz, $C_{3'''}$-H & $C_{5'''}$-H); MS: m/z 480.1041 (M^+, 100%); Anal. Found: C, 54.58; H, 4.03; N, 17.51%. Calcd. for $C_{22}H_{20}N_6O_3S$: C, 54.98; H, 4.19; N, 17.49%.

4-[4-{1-(6-chlorobenzothiazol-2-yl)-3-methylpyrazol-5-yl}-5-hydroxy-3-methylpyrazol-1-yl]benzenesulfonamide (2e)

mp 300°(decomp), yield 65%, IR (KBr) cm^{-1}: 3511-3077 (br, O-H & N-H stretch), 1630 (s, N-H bend), 1332 & 1162 (s, SO_2 stretch); ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 2.23 (s, 3H, pyrazolone $C_{3'}$-CH_3), 2.41 (s, 3H, pyrazole C_3-CH_3), 6.35 (s, 1H, pyrazole C_4-H), 6.82 (bs, 2H, $C_{4'''}$-SO_2NH_2), 7.38-7.41 (dd, 1H, J=8.7 & 1.8Hz, $C_{5''}$-H), 7.69-7.72 (d, 1H, J=8.7Hz, $C_{4''}$-H), 7.82-7.83 (d, 1H, J=1.8Hz, $C_{7''}$-H), 7.97-8.00 (d, 2H, J=8.9Hz, $C_{2'''}$-H & $C_{6'''}$-H), 8.04-8.07 (d, 2H, J=8.9Hz, $C_{3'''}$-H & $C_{5'''}$-H); MS: m/z 502.0460 / 500.0500 (M^++2 / M^+, 100%); Anal. Found: C, 50.05; H, 3.61; N, 16.48%. Calcd. for $C_{22}H_{17}ClN_6O_3S_2$: C, 50.35; H, 3.42; N, 16.78%.

4-[5-hydroxy-4-{1-(6-methoxybenzothiazol-2-yl)-3-methyl pyrazol-5-yl}-3-methylpyrazol-1-yl]benzenesulfonamide (2f)

mp 304°, yield 73%, IR (KBr) cm^{-1}: 3500-3083 (br, O-H & N-H stretch), 1627 (s, N-H bend), 1334 & 1165 (s, SO_2 stretch). ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 2.19 (s, 3H, pyrazolone $C_{3'}$-CH_3), 2.39 (s, 3H, pyrazole C_3-CH_3), 3.86 (s, 3H, $C_{6''}$-OCH_3), 6.36 (s, 1H, pyrazole C_4-H), 6.99-7.03 (dd, 1H, J=8.9 & 2.5Hz, $C_{5''}$-H), 7.18 (bs, 1H, pyrazolone $C_{5'}$-OH), 7.38-7.39 (d, 1H, J=2.5Hz, $C_{7''}$-H), 7.62-7.65 (d, 1H, J=8.9Hz, $C_{4''}$-H), 7.94-7.97 (d, 2H, J=8.8Hz, $C_{2'''}$-H & $C_{6'''}$-H), 8.01-8.04 (d, 2H, J=8.8Hz, $C_{3'''}$-H & $C_{5'''}$-H); MS: m/z 496.0979 (M^+, 100%); Anal. Found: C, 53.35; H, 3.92; N, 16.78%. Calcd. for $C_{22}H_{20}N_6O_4S_2$ requires: C, 53.21; H, 4.06; N, 16.92%.

Evaluation of antibacterial activity

A Disc Diffusion Method (Kirby Bauer Method) was employed for the *in vitro* study of antibacterial activity against two gram positive bacteria namely *Staphylococcus aureus* and *Bacillus subtilis* and two gram negative bacteria namely *Salmonella species* and *Pseudomonas species*. Ofloxacin was used as standard drug.

Approximately 4 to 5 well isolated colonies of the bacterial strain are inoculated into 5 ml of nutrient broth and incubated at 37°C. After standardization of bacterial suspension, sterile cotton swap was immerged in it and the swap was rotated several times, with firm pressure on the inside wall of the tube to remove excess fluid. Nutrient agar media plate was prepared with a depth of 4 mm (millimetre).

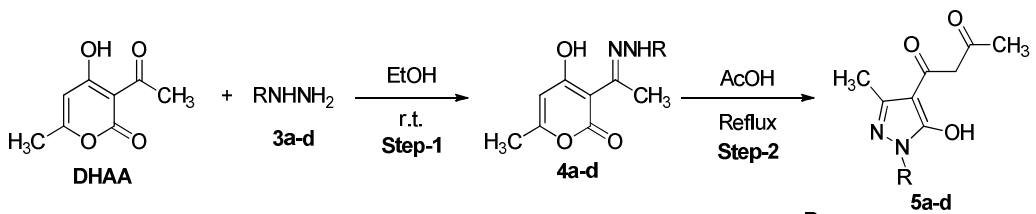
Dried surface of nutrient agar plate was inoculated by streaking the swab 3 times over the entire agar surface. Antibacterial impregnated disc was placed on the surface of the agar using sterile forceps and disc was pressed gently to provide uniform contact. Compounds (1a-1d and 2a-2f) were evaluated for antibacterial activity.

RESULTS AND DISCUSSION

Condensation of appropriate hydrazine and 1,3-diketone is one of the most widely used methods for the synthesis of pyrazoles. Mechanism of this apparently simple reaction still evolves a lot of interest in the scientific community as complications are encountered in the delineation of reaction pathways when a substituted hydrazine and an unsymmetrical 1,3-diketone react.

The present study concerns the preparation of bipyrazoles incorporated with benzenesulfonamide functional group. The reaction of dehydroacetic acid (DHAA) with aryl / benzothiazol-2-yl hydrazines (**3a-d**) in ethanol resulted in the formation of hydrazones (**4a-d**) which on refluxing in acetic acid underwent a rearrangement involving a nitrogen nucleophilic attack at the C_2-lactone carbonyl with ring opening to yield 1-[1-aryl / (benzothiazol-2yl)-5-hydroxy-3-methylpyrazol-4-yl]-butane-1,3-diones (**5a-d**) (Scheme 1).

Various arylhydrazines [15] and 2-hydrazinobenzothiazoles [16] needed for the present study, were prepared according to the literature procedures. The bipyrazoles (**1a-d**) were prepared by the reaction between 1-[1-aryl / (benzothiazol-2yl)-5-hydroxy-3-methylpyrazol-4-yl]-butane-1,3-diones (**5a-d**) and (4-aminosulfonyl)phenyl hydrazine as shown in scheme-3.

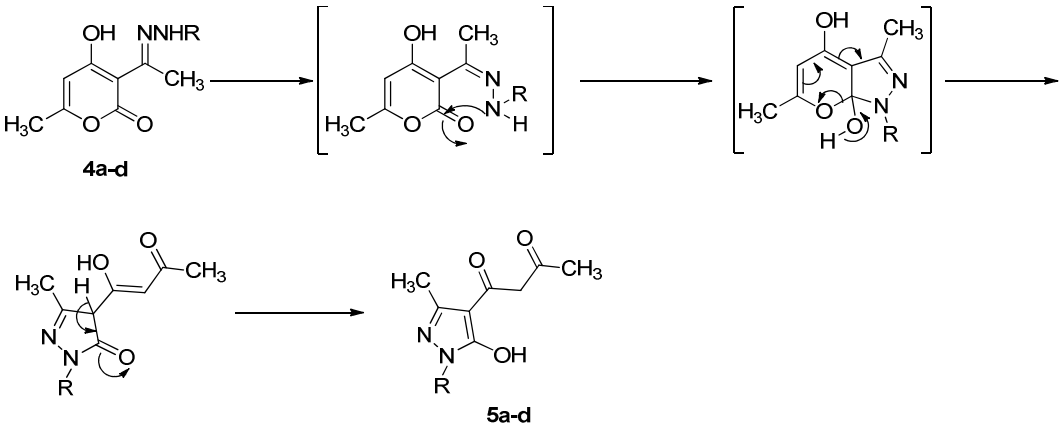


R

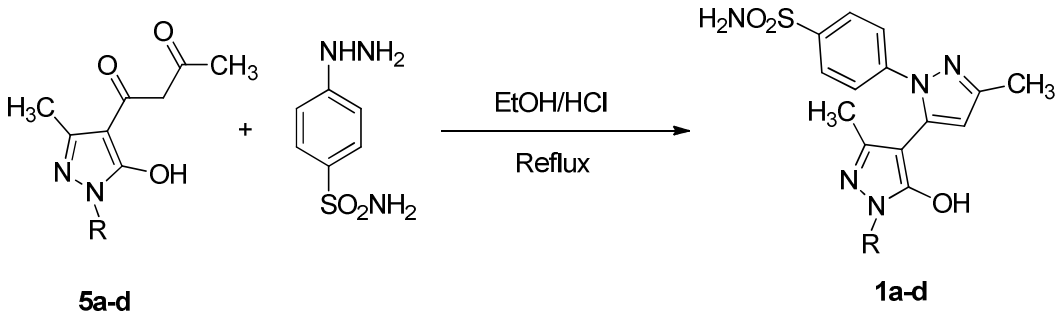
3a; 4a; 5a;	C_6H_5
3b; 4b; 5b;	4-ClC_6H_4
3c; 4c; 5c;	6-Chlorobenzothiazol-2-yl
3d; 4d; 5d;	4-$SO_2NH_2C_6H_4$

Scheme 1

A plausible mechanism [14] for the formation of 1-[1-aryl / (benzothiazol-2yl)-5-hydroxy-3-methylpyrazol-4-yl]-butane-1,3-diones (**5a-d**) is outlined in Scheme 2.

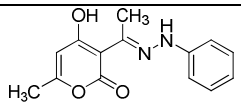
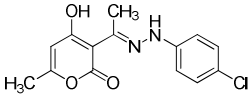
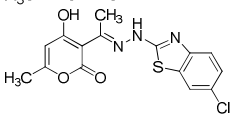
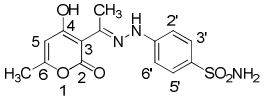
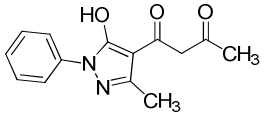
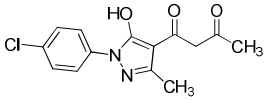
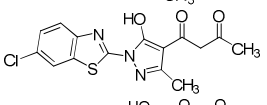
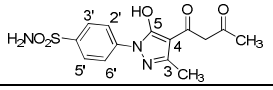


Scheme 2



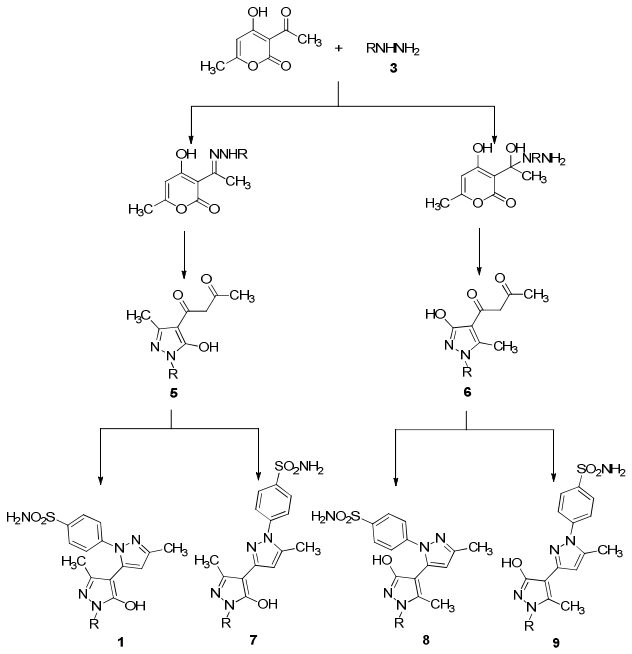
Scheme 3

Table 1: The physical data of substituted hydrazones (4a-d) and diketones (5a-d)

Compound No.	Structure	Formula	MW	[a]mp ([o]C)	[b]Yield %
4a		$C_{14}H_{14}N_2O_3$	258.27	211-212 (212)	81
4b		$C_{14}H_{13}ClN_2O_3$	292.72	250-252 (252)	66
4c		$C_{15}H_{12}ClN_3O_3S$	349.79	185-186 (186)	60
4d		$C_{14}H_{15}N_3O_5S$	337.35	232-234	70
5a		$C_{14}H_{14}N_2O_3$	258.27	100-101 (102)	66
5b		$C_{14}H_{13}ClN_2O_3$	292.72	150 (151)	67
5c		$C_{15}H_{12}ClN_3O_3S$	349.79	216 (217)	63
5d		$C_{14}H_{15}N_3O_5S$	337.35	195-197	55

[a]uncorrected melting points, [b]synthesized yields

Formally, Dehydroacetic acid (DHAA) possesses four sites for nucleophilic attack [17]. In principle, the condensation of either of the two nitrogen atoms of the hydrazine can occur on the side chain carbonyl group of DHAA followed by acidic arrangement involving a nitrogen nucleophilic attack at the C2-lactone carbonyl with ring opening leads to the formation of two isomeric β-diketones which on reaction with (4-aminosulfonyl)phenylhydrazine can yield four isomeric (bipyrazolyl)benzenesulfonamides (Scheme 4).



Scheme 4

However, the determination of β-diketone structure will simplify the problem of assigning one of the four isomeric (bipyrazolyl) benzenesulfonamides. Literature results [18] showed that the secondary nitrogen atom is less nucleophilic than primary nitrogen atom; the most probable route for this reaction seems to be that leading to the formation of β-diketone **5**. The formation of β-diketone **5** is also supported by the similar results obtained in the literature [12, 14]. Further NOE experiment study provided convincing evidence that the β-diketone in our case is **5** not isomer **6**. Therefore, possibility of formation of (bipyrazolyl)benzene sulfonamides **8** and **9** stand discarded.

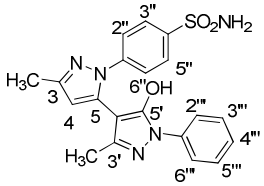
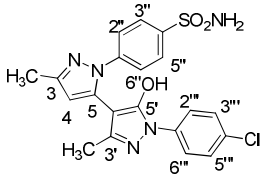
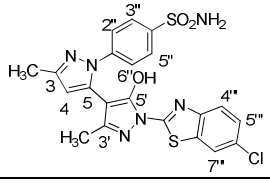
In the event, condensation of β-diketone **5a** with (4-aminosulfonyl) phenylhydrazine in absolute ethanol containing few drops of conc. HCl resulted in the formation of hydrazone followed by cyclization through an intramolecular Friedel-Crafts reaction yielded only a single product as confirmed by thin layer chromatography (TLC) and the ^{1}H NMR spectra. The structure of this product was assigned as 4-[5-(5-hydroxy-3-methyl-1-phenylpyrazol-4-yl)-3-methylpyrazol-1-yl]benzenesulfonamide (**1a**), based on a rigorous analysis of its 300 MHz ^{1}H NMR spectrum. The 300 MHz ^{1}H NMR spectrum of compound **1a** showed two three-proton singlets due to two methyl groups appearing at δ1.95 and δ2.36 in the aliphatic region. It has earlier been observed through the NOE experimental study that upfield signal is due to methyl group located on the pyrazolone moiety ($C_{3'}$-CH_3) while the downfield signal is due to methyl group located on the pyrazole moiety (C_3-CH_3) [19].

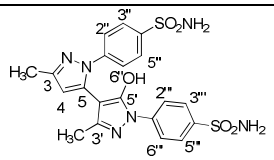
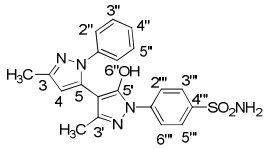
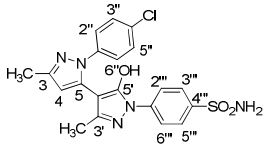
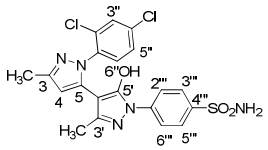
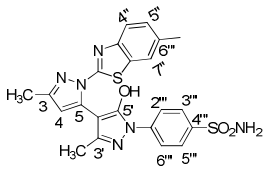
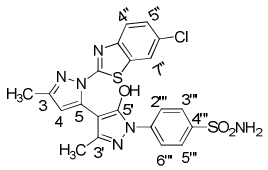
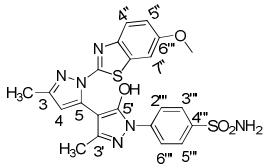
The unexpected shielding of the 3-methyl protons of the pyrazolone moiety can be explained on the basis that the $C_{3'}$-CH_3 protons fall in the shielding zone of the phenyl ring. The signal of the C_3-CH_3 group at δ2.36 in DMSO-d_6 is singlet which showed that there is no coupling between this methyl group and C_4-H. This is the characteristics of a methyl group in position 3 of the pyrazole ring [20]. Had it been the isomeric **7a**, the signal for the methyl group would show allylic coupling of 0.5-0.7 Hz with C_4-H. These observations all support the structure **1a** for the isolated product.

Other compounds in this series **1b-1d** were prepared following the procedure similar to that adopted for **1a** by the reaction between β-diketones **5** and (4-aminosulfonyl)phenyl hydrazine. Their elemental analyses as well as spectral data were consistent with the assigned structures of all the new compounds.

After successful synthesis of compounds **1a-d**, we focused our attention on the synthesis of regioisomeric compounds **2a-f** in which the (4-aminosulfonyl)phenyl substituent is shifted to N-1 of pyrazolone moiety from the N-1 of the pyrazole ring. In a way it will amount to the shifting of the (4-aminosulfonyl)phenyl grouping from N-1 to the substituent at the 5-position of the pyrazole ring in the lead class 1,5-diarylpyrazoles. 1-Aryl/heterocyclyl-3-methyl-5-[1-(4-aminosulfonyl) phenyl-5-hydroxy-3-methyl pyrazol-4-yl] pyrazoles (**2a-f**) were synthesized by the reaction of 1-[1-(4-aminosulfonyl) phenyl-5-hydroxy-3-methylpyrazol-4-yl]-1,3-butandione (**5d**) with various aryl/heterocyclyl hydrazines following a reaction sequence similar to as shown earlier in Scheme **3**.

Table 2: The physical data of bipyrazoles (1a-d) and (2a-f)

Compound No.	Structure	Formula	MW	[a]mp ([o]C)	[b]Yield %
1a		$C_{20}H_{19}N_5O_3S$	409.46	152-154	51
1b		$C_{20}H_{18}ClN_5O_3S$	443.91	187-189	53
1c		$C_{21}H_{17}ClN_6O_3S_2$	500.98	276-277	52

1d		$C_{20}H_{20}N_6O_5S_2$	488.54	284 (decomp)	54
2a		$C_{20}H_{19}N_5O_3S$	409.46	199-200	42
2b		$C_{20}H_{18}ClN_5O_3S$	443.91	290	53
2c		$C_{20}H_{17}Cl_2N_5O_3S$	478.35	158-160	59
2d		$C_{22}H_{20}N_6O_3S_2$	480.56	298	54
2e		$C_{21}H_{17}ClN_6O_3S_2$	500.98	300(decomp)	65
2f		$C_{22}H_{20}N_6O_4S_2$	496.56	304	73

[a]uncorrected melting points, [b]synthesized yields

Table 3: Antibacterial activity of synthesized compounds

	Zone of Inhibition in mm (millimetre)							
Compounds	**Salmonella sp**	**% Inhibition**	**Pseudomonas sp.**	**% Inhibition**	**S. aureus**	**% Inhibition**	**B. subtilis**	**% Inhibition**
1a	17.4±1.000	60.83	17.2±0.866	60.35	19.2±0.860	67.36	16.8±2.160	54.01
1b	15.2±1.000	53.14	14.9±0.866	52.28	16.9±0.860	59.30	14.8±2.160	47.59
1c	14.4±1.000	50.34	13.6±0.866	47.72	15.5±0.860	54.38	13.8±2.160	44.37
1d	13.3±1.000	46.50	13.1±0.866	45.96	15.1±0.860	52.98	15.8±2.160	50.80
2a	16.2±1.000	56.64	16.5±0.866	57.89	19.5±0.860	68.42	14.6±2.160	46.94
2b	17.8±1.000	62.23	17.2±0.866	60.35	19.2±0.860	67.36	17.3±2.160	55.63
2c	12.6±1.000	44.05	12.2±0.866	42.80	15.2±0.860	53.33	12.8±2.160	41.15
2d	14.9±1.000	52.09	14.2±0.866	49.82	17.2±0.860	60.35	14.6±2.160	46.94
2e	12.3±1.000	43.00	12.2±0.866	42.80	14.2±0.860	49.82	12.9±2.160	41.48
2f	18.2±1.000	63.63	17.7±0.866	62.10	16.7±0.860	58.59	18.1±2.160	58.20
Ofloxacin	28.6±1.890	100	28.5±1.800	100	28.5±1.510	100	31.1±1.500	100

Data presented in Mean ± SD (N=3), Concentration of derivatives = 25µg/dish, Concentration of Ofloxacin = 25µg/ml

Evaluation of antibacterial Activity

The compounds were evaluated for antibacterial activity using disc diffusion method. A few of the compounds showed moderate activity comparing to standard drug. The data is given in the Table-3.

The results revealed that compounds **1a**, **2b** and **2f** exhibited good antibacterial activity and **1b**, **1c**, **2a**, and **2d** showed moderate antibacterial activity as compared with standard drug Ofloxacin.

CONCLUSION

This study provides the simple method for the synthesis of new benzenzenesulfonamide based bipyrazoles which plays important role in numerous bioactive compounds. The compounds were evaluated for antibacterial activity using disc diffusion method. The results revealed that compounds **1a**, **2b** and **2f** exhibited good antibacterial activity and **1b**, **1c**, **2a**, and **2d** showed moderate antibacterial activity as compared with standard drug Ofloxacin.

CONFLICT OF INTERESTS

Declared None

ACKNOWLEDGEMENT

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