Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(15):122-128
(http://derpharmachemica.com/archive.html)

Synthesis, *In Silico* and *In Vitro* evaluation of some novel 5-[2-phenyl vinyl]-pyrazole and pyrazoline derivatives

K. N. V. Chenchu Lakshmi, M. Venkatesh, J. Hareesh, B. Srinivasa Raju and B. Anupama*

Department of Pharmaceutical Chemistry, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada-520010, Andhra Pradesh, India

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ABSTRACT

A series of novel pyrazole and pyrazoline derivatives were prepared from substituted benzaldehydes and acetone as starting materials through dibenzalacetone as intermediate. These intermediates on reaction with hydrazines in acidic media, finally converted into corresponding pyrazoles and pyrazolines. The synthesized compounds were characterized by their physical properties, IR, H^1 NMR, C^{13} NMR spectral studies. The Insilco methods were used to evaluate the drug likeness of compounds, and to assess the inhibition of derivatives against 5 subtypes of cytochrome P450. The compounds 2,5,8 showed inhibition against nuclear , ligand and kinase receptors .The synthesised derivatives were also evaluated for anti bacterial activity against both gram positive and gram negative organisms with standard streptomycin and were found to have inhibition against gram positive organisms.

Keywords: Pyrazoles, pyarazolines , kinase inhibition, anti-bacterial activity.

INTRODUCTION

Pyrazoles are five member ring heterocyclic compounds, have some structural features with two nitrogen atoms in adjacent position and are also called as Azoles [1]. Recently Pyrazole derivatives have been found in nature [1], β-[1-pyrazolyl]alanine was isolated from the seeds of water melons [Citurllus lanatus]. The best described property of almost every group of pyrazoles is in the treatment of inflammation and inflammation associated disorders, such as arthritis [2]. Pyrazole derivatives are the subject of many research studies due to their widespread potential biological activities such as antimicrobial[3], antiviral[4], antitumor[5,6], antihistaminic[7], antidepressant[8], insecticides[9] and fungicides[9]. Several pyrazole derivatives have been found to possess significant activities such as 5-α-red-uctase inhibitor[10], antiproliferative[11], antiparasitic[12], herbicides[13]. A good number of pyrazoles have also been reported to have interesting biological activities like anti-inflammatory[14] and antiprotozoal[15-16] which render them valuable active ingredients of medicine and plant protecting agents.

Further, current literature indicates 1,2-pyrazole derivatives to possess various biological activities [17]. Until now, the binding of heterocyclic compounds with acyclic sugar moiety forming thus the acyclonucleosides have commanded the world-wide attention of many research groups because of their high potential to exhibit chemotherapeutic activity [18,19]. Substituted pyrazole and its analogs have been used as precursors for synthesis of various biologically active molecules. In the recent years, the efficiency of microwave chemistry in dramatically reducing reaction times has recently been proven in several different fields of organic chemistry [20], microwave assisted organic synthesis has shown significant improvement in the generation of combinatorial libraries of small molecules [21]. Taking into consideration the important biological activities of pyrazoles, we have decided to devote some attention for the synthesis and antimicrobial activity of new substituted pyrazoles by following literature [22] methods.

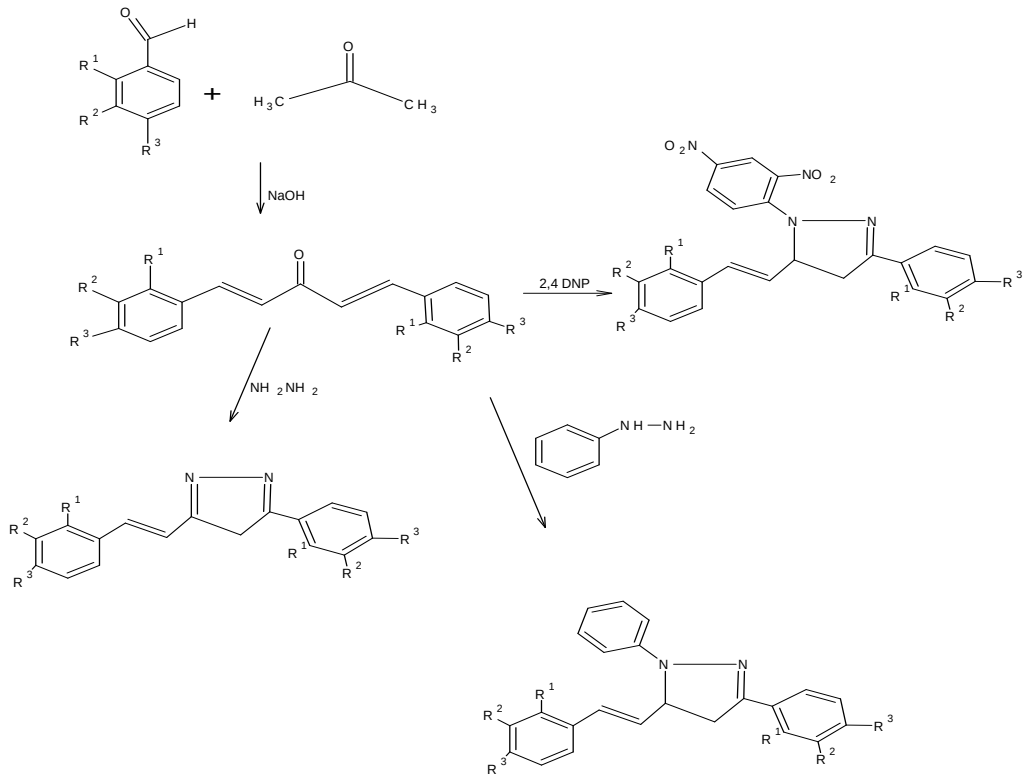
MATERIALS AND METHODS

Melting points were measured by a Stuart Scientific melting point apparatus in open capillaries and are uncorrected. Infrared spectra (KBr discs) were recorded on a Bruker Alpha (FTIR) Spectrometer. 1H-NMR spectra were recorded on a Bruker spectrometer operating at 400 MHz using DMSO-d6 and $CDCl_3$ as a solvent with TMS as an internal standard. Acme silica gel-G and Merck silica gel (100 to 200, 60 to 120 meshes) were used for analytical TLC and Column chromatography respectively. All other analytical grade chemicals and solvents were obtained from commercial sources and used as received standard procedure.

General procedure for the synthesis of 5-[2-phenyl vinyl]-pyrazole and pyrazoline derivatives (compound1-9): The synthesis involves two steps.

Step1: In a roundbottom flask 30 mmol of substituted aldehydes (salicaldehyde, benzaldehyde, vanillin) and 15 mmol of acetone were dissolved in methanol. The round bottomed flask was placed in an ice bath and the mixture was stirred for 30 minutes with addition of 11% NaOH (cold solution) drop by drop. The resultant mixture was left to stand for 30 minutes. The yellow precipitate was crystallized from methanol to afford dibenzalacetone. Yield: 90%, m.p.112 °C

Step-2: 5 mmol of dibenzalacetone and 10 mmol of amine (hydrazine hydrate, phenyl hydrazine, 2, 4-DNP) were taken and dissolved in 5 mL of ethanol. To this sulphuric acid were added in drop wise. The reaction mixture was refluxed for 6 h with constant stirring. The resultant solution was cooled and poured into crushed ice. The crude reaction product was recrystallized from ethyl acetate to afford compound **in** 80% yield. The procedure was illustrated under **Scheme 1** .The physical properties of the molecules tabulated in **table-1**



Scheme-1(compound-1-9)

COMPOUND-1: R_1-OH; R_2=R_3-H
COMPOUND-2: R_1-OH; R_2=R_3-H
COMPOUND-3: R_1-OH; R_2=R_3-H
COMPOUND-4: R_1=R_2=R_3-H
COMPOUND-5: R_1=R_2=R_3-H
COMPOUND-6: R_1=R_2=R_3-H
COMPOUND-7: R_1-H; R_2-OCH_3; R_3-H
COMPOUND-8: R_1-H; R_2-OCH_3; R_3-H
COMPOUND-9: R_1-H; R_2-OCH_3; R_3-H

Table-1

Compound	MF	MW	Physical state		MP(^{O}C)	% yield
			Colour	State		
1	$C_{17}H_{14}N_2O_2$	278	Yellow	Solid	200	79.29%.
2	$C_{23}H_{19}N_2O_2$	356	Dark yellow	Solid	190	86.20%
3	$C_{23}H_{18}N_4O_6$	446	Orange-red	Solid	220	83.3%
4	$C_{17}H_{14}N_2$	246	Yellow	Solid	130	74.07%
5	$C_{23}H_{20}N_2$	324	Dark yellow	Solid	150	83.3%.
6	$C_{23}H_{18}N_4O_4$	414	Orange-red	Solid	170	76%.
7	$C_{19}H_{19}N_2O_4$	338	Yellow	Solid	200	83%
8	$C_{25}H_{24}N_2O_4$	416	Dark yellow	Solid	190	80%
9	$C_{25}H_{22}N_4O_8$	506	Orange-red	Solid	230	99%

Compound-1:2-{(*E*)-2-[5-(2-hydroxyphenyl)-4*H*-pyrazol-3-yl]vinyl}phenol:Elemental composition- C(48.5%) H (40%) N(5.7%) O(5.7%) FTIR (γ max, cm^{-1}))- 3531.70(OH- stretching) 3146.75(CH- stretching) 1574.77(C=N bonding) 1413.29(C=C bonding)*;* ^{1}H NMR:(400MHZ,$CDCl_3$) *δ*5.35(aromaticOH), *δ*6.92,6.72,7.41,7.52,7.02,7.16, 6.96,6.72(aromaticCH)*δ*6.78,7.06(vinylicprotons)*δ*1.4CH_2.^{13}CNMR:(400MHZ,$CDCl_3$)*δ*132.1,121.4,132.4,118.8,117 .8,117.6,129.3,121.2,128.9,122.6 (aromatic carbons), 157.1,162.5 (aromaticC-OH) *δ* 164 (C-NH2), *δ* 31.3 (CH_2), *δ* 118,122.6 (vinylic carbons).

Compound-2:-2-{(*E*)-2-[3-(2-hydroxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl]vinyl}phenol: Elemental composition- C(50%) H(41.3% N(4.3%) O(4.3%) C; FTIR (γ max, cm^{-1})- 3541.70(OH- stretching)3016.35(CH-stretching)1521.11(C=N bonding 1421.97(C=Cbonding).^{1}HNMR:(400MHZ,$CDCl_3$) *δ*5.25(aromaticCOH),*δ*6.85, 6.72,7.34,7.52,7.02,7.56,6.46,6.92,7.15,7.43,6.87(aromaticCH)*δ*6.78,7.06(vinylicprotons)*δ*1.4 (CH_2) ^{13}CNMR: (400MHZ,$CDCl_3$) *δ*132.1, 121.4, 132.4, 118.8, 117.8, 117.6, 129.3, 121.2, 128.9,122.6, 116.7,129.5, 120.8,129.5, 116.7 (aromatic carbons) 156,162.9 (aromaticC-OH) *δ* 164 (C-NH2), *δ* 31.3 (CH_2), *δ* 129.5,128.8 (vinylic carbons).

Compound-3:2,4-dinitro-{(*E*)-2-[3-(2-hydroxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl]vinyl}phenol: Elemental composition- C(45.09%) H(35.29%) N(7.84%) O(11.76%); FTIR (γ max, cm^{-1})- 3545.04(OH-stretching) 3062.85(CH- stretching) 1510.11 (C=Nbonding) 1461.51(C=Cbonding) 822.91(NO_2) ^{1}HNMR: (400MHZ,$CDCl_3$)*δ*5.25(aromaticCOH),6.25,6.42,7.31,7.52,7.62,7.16,6.76,6.72,8.58,8.43,7.92(aromaticCH)*δ*6.78,7. 06(vinylicprotons)*δ*3.13,2.88CH_2,*δ*3.3aliphaticCH.^{13}CNMR:(400MHZ,$CDCl_3$)*δ*132.1,121.4,132.4,118.8,117.8,117.6 ,129.3,121.2,128.9,122.6(aromatic carbons), *δ* 157.5,161 (aromaticC-OH) *δ* 164 (C-NH2), *δ* 31.3 (CH_2), *δ* 118,122.6 (vinylic carbons).

Compound4:3-phenyl-5-[(*E*)-2-phenylvinyl]-4*H*-pyrazole : Elemental composition- C(51.51%) H(42.42%) N(6.06%) .FTIR (γ max, cm^{-1}) 3010.25(CH- stretching) 1509.78(C=Nbonding) 1417.37(C=Cbonding) ^{1}HNMR:(400MHZ,$CDCl_3$)*δ* CH_2 1.4 methylene, *δ*7.62,7.26,7.62, 7.26, 7.29,7.26,7.29 (aromaticprotonsH). ^{13}CNMR:(400MHZ,$CDCl_3$)*δ*132.1,121.4,132.4,118.8,117.8,117.6,129.3,121.2,128.9,122.6(aromatic carbons), *δ* 157.5, *δ* 162.8(1-emine), *δ* 162.8(1-enine) , *δ* 31.3 (CH_2), *δ* 118,122.6 (vinylic carbons).

Compound 5: 3-phenyl-5-[(*E*)-2-phenylvinyl]-4*H*-pyrazole: Elemental composition- C(51.51%) H(42.42%) N(6.06%) .FTIR (γ max, cm^{-1}) 3015.690(CH- stretching) 1510.55 (C=N bonding) 1459.66(C=C bonding) ^{1}HNMR:(400MHZ,$CDCl_3$)*δ*1.5(methyne), *δ* 1.37(methylene),*δ*7.26benez-1-ene (CH), *δ*7.62, 7.26, 7.62, 7.26. 7.29, 7.26, 7.29 (aromaticprotons H). *δ* 7.62benzylidinimine, *δ* 7.26 1-benzene, ^{13}CNMR :(400MHZ, $CDCl_3$) *δ*132.1,121.4, 132.4, 118.8, 117.8, 117.6,129.3,121.2,128.9,122.6(aromatic carbons), *δ* 162.8(1-emine), *δ* 162.8(1-enine) , *δ* 31.3 (CH_2), *δ* 128.5(1-benzene), *δ* 123.3(1-ethylene)

Compound6:1-(2,4-dinitrophenyl)-3-phenyl-5-[(*E*)-2-phenylvinyl]-4,5-dihydro-1*H*-pyrazole:Elemental composition- C(51.51%) H(42.42%) N(6.06%) FTIR (γ max, cm^{-1}) 3539.72(OH- stretching) 3085.39(CH-stretching) 1520.98(C=N bonding) 1417.78(C=C bonding) ^{1}HNMR:(400MHZ,$CDCl_3$)*δ*1.5(CH_4), *δ* 1.37(CH_2), *δ* 7.26 benez-1-ene(CH), *δ*7.62,7.26,7.62,7.26.7.29,7.26,7.29(aromaticprotonsH). *δ* 7.62benzylidinimine, *δ* 7.26 1-benzene,^{13}CNMR:(400MHZ,$CDCl_3$)*δ*132.1,121.4,132.4,118.8,117.8,117.6,129.3,121.2,128.9,122.6(aromatic carbons), *δ* 162.8(1-emine), *δ* 162.8(1-enine) , *δ* 31.3 (CH_2), *δ* 128.5(1-benzene), *δ* 123.3(1-ethylene)

Compound7:-4-{(*E*)-2-[5-(4-hydroxy-3-methoxyphenyl)-4*H*-pyrazol-3-yl]vinyl}-2-methoxyphenol: Elemental composition- C(43.90%) H(41.46%) N(4.87%) O (8.16%) FTIR (γ max, cm^{-1}) 3539.72(OH- stretching) 3085.39(CH- stretching) 1520.98(C=N bonding) 1417.78(C=C bonding) ^{1}HNMR:(400MHZ,$CDCl_3$)*δ*5.25(aromatic C-OH), *δ* 1.4(CH_2), *δ* 7.26benez-1-ene(CH),*δ*7.33,7.16,6.91,6.99,7.41,6.79(aromaticprotonsH).*δ*3.83 (CH_3) , *δ*

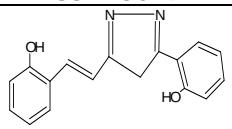
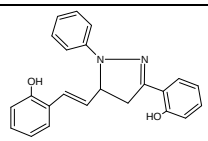
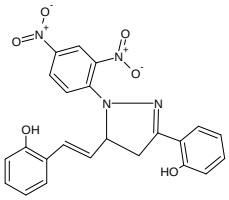
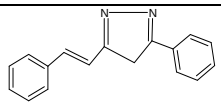
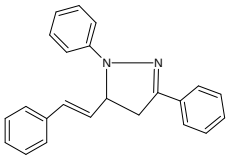
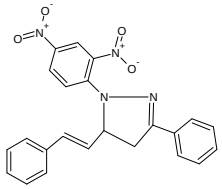
6.95,7.64(CH_2=CH_2)(C,^{13}CNMR:(400MHZ,$CDCl_3$)δ149.3,149.1,151,147.9,127.6,114.7,111.9,117,116.8,121.4,122.9 (aromatic carbons), δ 164.6(1-emine), δ 31 (CH_2) , δ 56.3 (CH_3) δ 129.5,120(1-ethylene)

Compound 8: N-phenyl-4-{(*E*)-2-[5-(4-hydroxy-3-methoxyphenyl)-4*H*-pyrazol-3-yl]vinyl}-2-methoxyphenol: Elemental composition- C(45.45%) H(43.63%) N(3.63%) O(7.27%) FTIR (γ max, cm^{-1}) 3560.20(OH-stretching)3194.28(CH- stretching) 1514.91(C=N bonding) 1417.78 (C=Cbonding) ^{1}HNMR:(400MHZ,$CDCl_3$) δ5.35(aromaticCOH),δ3.13,2.87(CH_2),δ3.3(CHmethyne),δ7.25,7.33,7.16,6.91,6.99,7.25,7.41,7.12,7.23,6.77(aromaticprotonsH).δ3.83(CH_3),δ6.19,6.56(ethylene)^{13}CNMR:(400MHZ,$CDCl_3$)δ149.3,149.1,151,147.9,143.8,127.6,132.3,116.7,114.7,111.9,117,116.8,116.7,121.4,120.4,129.5,120.8 (aromatic carbons), δ 125.7(1-emine), δ 39.3 (CH_2) , δ 56 (CH_3) δ 128.8,134.4(1-ethylene) δ 60 (CH aliphatic)

Compound9: N-phenyl(2,4-dinitro)-4-{(*E*)-2-[5-(4-hydroxy-3-methoxyphenyl)-4*H*-pyrazol-3-yl]vinyl}-2-methoxyphenol : Elemental composition- C(42.37%) H(37.28%) N(6.77%) O(13.55%) FTIR (γ max, cm^{-1}) 3530(OH- stretching) 3158(CH- stretching)1507.20(C=N bonding) 1417.78(C=C bonding) 827.95(NO_2) ^{1}HNMR:(400MHZ,$CDCl_3$) δ5.35(aromatic C-OH),δ3.13,2.87(CH_2), δ7.50(CHhydrazide), δ8.88,7.16,6.99,6.82,6.84,7.12,8.43,7.12,6.90,6.84(aromaticprotonsH).δ3.83(CH_3)3.3(CHaliphatic),δ6.19,6.56(ethylene)^{13}CNMR:(400MHZ,$CDCl_3$)δ149.3,149.1,151,147.9,141.2,137.4,137.2127.6,132.3,116.7,114.7,111.9,117,116.8,130.8,121.4,120.4,129.5,120.8 (aromatic carbons), δ 151.7(1-emine), δ 39.3 (CH_2), δ 56.1 (CH_3)δ 128.8,134.4(1-ethylene) δ 59 (CH aliphatic).

In silico drug-likeness and toxicity predictions [22-23]
The Cheminformatics programmes were used to evaluate the drug likeness (**table-2**) and bioactive scores (**table-3**) of compounds by MOLINSPIRATION and to assess the inhibition of the derivatives against 5 subtypes of cytochrome P450 by OCHEM Property Explorer (**table-4**).

Table-2

COMPOUND	Mi log p	TPSA	N atoms	MW	n ON	Nohnh	N violation	n rot b	volume
	3.94	65.18	21	278.31	4	2	0	3	251.38
	5.72	56.06	27	356.43	4	2	1	4	329.14
	5.56	147.71	33	446.42	10	2	1	6	375.81
	4.24	24.73	19	246.31	2	0	0	3	235.5
	6.02	15.60	25	324.43	2	0	1	4	313.11
	5.86	107.25	31	414.42	8	0	1	6	359.78

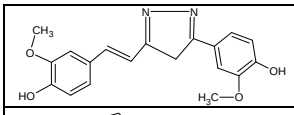
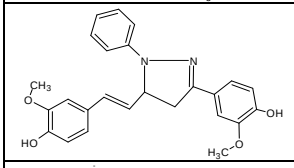
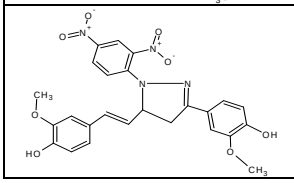
	2.92	83.65	25	338.36	6	2	0	5	302.48
	4.69	74.53	31	416.48	6	2	0	6	380.24
	4.54	166.17	37	506.47	12	2	2	8	426.90S

Table-3

Compound	Gpcr Ligand	Ion Channel Inhibitor	Kinase Inhibitor	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
1	-0.57	-0.55	-0.80	-0.46	-0.70	-0.39
2	-0.21	-0.38	-0.65	0.26	-0.34	-0.21
3	-0.34	-0.34	-0.64	-0.05	-0.45	-0.27
4	-0.71	-0.63	-0.88	-0.66	-0.81	-0.45
5	-0.22	-0.42	-0.63	0.24	-0.31	-0.22
6	-0.36	-0.38	-0.62	-0.09	-0.43	-0.29
7	-0.46	-0.53	-0.57	-0.35	-0.54	-0.33
8	-0.20	-0.39	-0.52	0.21	-0.32	-0.18
9	-0.32	-0.42	-0.52	-0.05	-0.43	-0.25

Table-4

COMPOUND	AQ.SOLUBILITY	LOG IGC 50	AMES	CYP3 A4	CYP2 D6	CYP2 C19	CYP2 C9	CYP1 A2
1	3.8	2.4	inactive	+	+	+	+	+
2	4.4	2.1	inactive	+	+	+	+	+
3	5.5	2.5	active	+	+	+	+	+
4	4.5	1.5	inactive	-	+	+	-	+
5	5.1	1.4	inactive	-	+	+	+	+
6	6.1	2.4	active	+	-	+	+	-
7	4.4	2.5	inactive	+	+	+	+	+
8	4.8	2.2	inactive	+	+	+	+	+
9	5.1	2.6	active	+	+	+	+	+

Antibacterial activity:

The cup plate method [23-24] using Mueller agar medium was employed to study the preliminary antibacterial activity against Bacillus subtilis, Staphylococcus aureus, Eischerria coli and Pseudomonas aeroginosa. The agar medium was purchased from HI-media laboratories limited, Mumbai, INDIA. Preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water was done as per the standard procedure. Each test compound (5mg) was dissolved in 5ml of dimethyl sulfoxide, benzyl pencillin was employed s reference standard to compare the results..

Table-5

COMPOUND	B.SUBTILIS	E.COLI	P.AEROGINOSA	S.AUREUS
1	1.5	0.9	1.2	1.1
2	0.3	0.1	0.3	0.4
3	0.3	0.5	0.2	0.1
4	0.5	0.2	0.7	0.5
5	0.2	0.4	0.4	0.6
6	0.3	0.7	0.5	0.4
7	0.5	0.4	0.2	0.1
8	0.3	0.6	0.1	0.3
9	0.2	0.2	0.2	0.7
STD	2	1.8	1.5	1.7

The medium was inoculated at one percent level using 18 hours old cultures of the test organism mentioned above aseptically into sterile petri dishes and allowed to set at room temperature for about 30min.The test and standard

solutions were added into cups left for 90min in a refrigerator for diffusion. After incubation for 24 hours at 37°C, the plates were examined for inhibition zones in mm. The results were represented in the below table-5and figure-1.

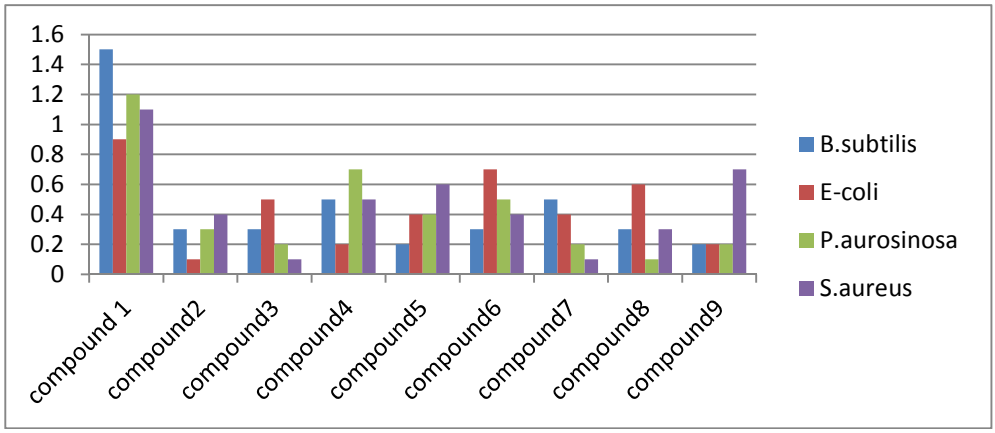


Figure -1

DISCUSSION

All the compounds were checked for their bioactive scores using online software that is molinspiration.com. This highlights the molecules that follow Lipinski rule of five and their bioactivity against the targets in the body. By this software we found that compounds are having better bioactive score against nuclear receptor ligand and kinase inhibition. As per the bioactive score scale values between 0-0.5 are active, 0.5-1 are very active. So as per the score compound-2(0.26), compound-5(0.24), compound-8(0.21) and have bioactive score between 0-0.5 and are active towards nuclear receptor ligand.. Among all the three compound-2 has highest activity against nuclear receptor ligand. The remaining compounds has shown good scores against kinase inhibition. Based on this score further in vitro and *in vivo* studies are to be carried out.

From the above results it is inferred the molecules are active inhibitors of CYP 450 enzymes (CYP3A4, CYP2D6, CYP2C19, CYP2C9, and CYP1A2) which were tested on online CYP 450 predictive model. It was noted that the pyrazoles with hydroxyl (-OH) and methoxy (OCH_3) groups shown a greater activity against nuclear receptor ligand and kinase inhibition.

The compound has shown good antibacterial activity towards gram positive organisms than gram negative. Among all the compounds the compound-1 has shown highest activity. Pyrazoles with hydroxyl substituents exhibited better bacterial effect than the other pyrazoles against gram positive organism.

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