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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF OXADIAZOLE CLUBBED PYRAZOLE DERIVATIVES

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ABSTRACT
Pyrazole and Oxadiazole in the same molecule are much more interesting due to having vast medicinal applications as antifungal, antibacterial, anti-TB, Hypoglycemia, anticancer, antidepressant, and antipsychotic agents. In the present work, we have prepared pharmaceutical potent derivatives of 2-(5-benzyl-1-oxa,3,4-diazacyclopentadiene-2-ylthio)-1-(4,5-dihydro-3,5-diphenylpyrazol-1-yl)ethanone to resolve the drug resistance issue. Characterization was carried out with ^{1}HNMR,^{13}CarbonNMR, FT-IR, and Mass Spectra. These clubbed scaffolds were investigated against bacterial species to confirm theirpotential as a pharmaceutical agent.
Keywords: Oxadiazole, Pyrazole, Biological Activity, Potential Agents.
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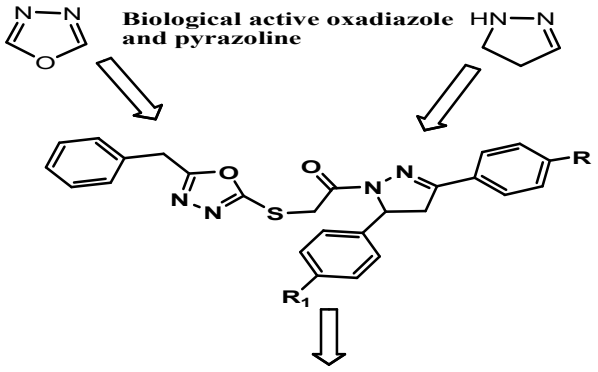
INTRODUCTION

Pyrazole and oxadiazole moiety are individually widely used as a precursor of antidepressant[1-3], antipsychotic[4], anti-inflammatory[5], anticancer[6], and analgesic agent.[7]Zibptantane, Nesapidil, Thiadazosin, Raltegravir drugs contain 1, 3, 4-oxadiazole as a core part[8].Novalgin, Celecoxib, Crizotinib, and purazofuran possessing pyrazole as base moiety are also readily available in the market.[9]Nowadays, many antimicrobial/antibiotic drugs are losing their therapeutic effect on microbes and bacteria due to resistance.[10] Therefore oxadiazole-doped pyrazole scaffolds are getting attention to resolve the resistance issue. In search of novel potent molecules, we tried to put oxadiazole, and pyrazoline in one framework via S-linkage.



In present work,we have synthesized a series of 2-(5-benzyl-1-oxa,3,4-diazacyclopentadiene-2-ylthio)-1-(4,5-dihydro-3,5-substituteddiphenylpyrazol-1-yl)ethanone derivatives6(a-j) from 5-benzyl-1-oxa,3,4-diazacyclopentadiene-2-ylthio (3).Our work also focuses on screening against gram-positive *S.aureus* and gram-negative bacteria *E.coli* to confirm its potential.

EXPERIMENTAL

Material and Methods

All starting materials were acquired from Merck. All reactions were monitored through TLC (Hexane: ethyl acetate; 80: 20). FTIR spectra were carried out through Bruker spectrophotometer. ^{1}H NMR ^{13}C NMR spectra were carried out at 500 MHz through Bruker spectrophotometer.

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Synthesis of 5-benzyl-1-oxa,3,4-diazacycloPentadiene-2-ylthio[11](3)
Phenylacetic acid (0.15mol) in 100 ml CH_3OH with a catalytic amount of H_2SO_4 was refluxed for 7 hours. Then it was poured on ice water and ethyl 2-phenylacetate (1) was collected. Further (1) (0.12 mol) was refluxed for 8 hours with (0.12 mol) hydrazine hydrated. After getting a single spot of the reaction mixture,it was poured intoice water to get 2-phenylacetohydrazide (2).

5-benzyl-1-oxa,3,4-diazacyclo Pentadiene-2-ylthio(3) was synthesized by mixing (0.06 mol) of **(2)** in (0.10 mol) KOH and 100 ml methanol in RBF. Then (0.10 mol) CS_2 was added portion and the reaction mixture was refluxed with stirring for 11 hours. The reaction mixture was poured into ice water and treated with dil. HCl to get oxadiazol at 3-4 PH. **5-benzyl-1-oxa,3,4-diazacyclo pentadiene-2-ylthio** was collected through filtration and re-crystallized with ethanol Yield 78 %, M.P. 118^0 C, FTIR (cm^{-1}, KBr) 2948 (C-H str), 1617 (C=N), 1230 (C-O).

Synthesis of Chalcones[12](4a-j)
Acetophenone (0.06 mol) and aldehydes (0.06 mol) were dissolved in 100 ml methanol. Then 40 % aq. NaOH was added dropwiseto the reaction mixture at 10^0 C and stirred for 3 hours. The mixture was left overnight in the refrigerator. The reaction mixture was poured in cold water to get solid chalcones. Solids were filtered off and recrystallization was carried out with ethanol. Yield 75% - 85% FTIR (cm^{-1}, KBr)1656 (C=O), 1323 (C=C).

Synthesis of Chloro Acetyl Pyrazoline Derivatives[13](5a-j)
Chalcone (0.04mol) and hydrazine hydrate (0.04) were dissolved in ethanol in RBF. It was refluxed for 12 hours. After the completion of the reaction,chloroacetyl chloride was added and stirred for 7 to 8 hours. Solid were obtained through vacuum distillation and re-crystallized by ethanol. Yield: 61% -72%, FTIR (cm^{-1}, KBr): 1680(C=O), 1265 (CH_2Cl), 3035 (C-H).

Synthesis ofNovel Title Compound 6a-j
3 (0.002mol)and(5a-l)(0.002mol)were dissolved in 20 ml DMF in a conical flask. Anhydrous K_2CO_3 was added and stirred for 8 hours at 30 -35^0C**.** Then it was poured into ice water. Solids were filtered off and re-crystallized with ethanol.

In Vitro Antibacterial Evaluation
The antibacterial potential of Novel compounds was investigated against gram-positive S. aureus andgram-negative E.coli through the Disc Diffusion method.[14]5mm Discs were saturated with 100 µg/ml solution in DMSO and placed on media inoculated with bacteria. It was incubated at 35^0C for 24 hours.Zone inhibition diameters were measured.

RESULTS AND DISCUSSION

All novel molecules have been synthesized as mentioned in scheme-1 and confirmed with characterization.

2-(5-benzyl-1-oxa,3,4-diazacyclopentadiene-2-ylthio)-1-(4,5-dihydro-5-(4-methoxyphenyl)-3-phenylpyrazol-1-yl)ethanone (6a)
White solid, yield 78%, M.P. 201^0 C;M. Formula:$C_{27}H_{24}N_4O_3S$; MW (Grams /mole):484; FT-IR(cm^{-1}, KBr): 1664 (C=O amide), 2833 (C-H- methoxy), 1514 (C=C str- aromatic ring) 1582 (C=N str – oxadiazole), 691 (str of S-C), ^{1}HNMR(500 MegaHz,δ ppm): 3.64 ppm (s,OCH_3), 4.06 ppm (s, CH_2), 5.42 (t, CH), 6.78 CH (5H,m, Ar-H of benzyl),7.0-7.6(9H, m, Ar-H); ^{13}CarbonNMR (500 MegaHz,δ ppm): 31.82, 38.35, 42.32,55.39, 60.16, 114.38 -130.11, 155.69 -166.23 Mass: M^+485.

2-(5-benzyl-1-oxa,3,4-diazacyclopentadiene-2-ylthio)-1-(4,5-dihydro-3-(4-methoxyphenyl)-5-(3-nitrophenyl) pyrazol-1-yl)ethanone (6b)
White solid, yield 75%, M.P. 230^0 C; M. Formula:$C_{27}H_{23}N_5O_5S$; MW(Grams /mole):529; FT-IR(cm^{-1}, KBr): 1657 (C=O amide), 2839 (C-H- methoxy), 1526 (C=C str- aromatic ring) 1608 (C=N str – oxadiazole), 689 (str of S-C), 1344 str of NO_2^{1}HNMR(500 MegaHz,δ ppm): 3.72 ppm (s,OCH_3), 4.44 ppm (s, CH_2), 5.58 (t,CH), 6.90 (5H,m, Ar-H of benzyl), 7.44-8.05(8H, m, Ar-H); ^{13}CarbonNMR(500 MegaHz,δ ppm): 31.78, 35.36, 42.35,55.49, 59.8, 114.33 -133.48, 142.52-166.32; Mass: M^+530.

2-(5-benzyl-1-oxa,3,4-diazacyclopentadiene-2-ylthio)-1-(4,5-dihydro-5-phenyl-3-p-tolylpyrazol-1-yl)ethanone (6c)

White solid, yield 77%, M.P. 218^0 C;M. Formula:$C_{27}H_{24}N_4O_2S$;MW (Grams /mole):468; FT-IR(cm^{-1}, KBr): 1658 (C=O amide), 1530 (C=C str- aromatic ring) 1590 (C=N str – oxadiazole), 687 (str of S-C), ^{1}HNMR(500 MegaHz,δ ppm): 4.45 ppm (s,CH_2), 5.53 (t,CH), 7.12 (5H,m, Ar-H of benzyl),7.49 -7.92 (9H, m, Ar-H); ^{13}CarbonNMR(500 MegaHz,δ ppm): 32.10, 35.38,42.35,59.82,114.43-131.78,149.98 -167.22; Mass: M^+467.

2-(5-benzyl-1-oxa,3,4-diazacyclopentadiene-2-ylthio)-1-(5-(4-chlorophenyl)-4,5-dihydro-3-p-tolylpyrazol-1-yl)ethanone (6d)

White solid, yield 73%, M.P. 180^0 C;M. Formula:$C_{27}H_{23}ClN_4O_2S$;MW (Grams /mole):503 FT-IR(cm^{-1}, KBr): 1661 (C=O amide), 1527 (C=C str- aromatic ring) 1581 (C=N str – oxadiazole), 854 (str of C-Cl), 690 (str of S-C), ^{1}HNMR (500 MegaHz,δ ppm): 4.61 ppm (s,CH_2), 5.48(t,CH), 6.74 (5H,m, Ar-H),7.35-7.87 (8H, m, Ar-H of phenyl); ^{13}CarbonNMR: 31.52, 36.29, 42.46,59.90, 115.24 -135.66, 145.72 -166.46; Mass: M^{+2} 505.

2-(5-benzyl-1-oxa,3,4-diazacyclopentadiene-2-ylthio)-1-(5-(4-(dimethylamino)phenyl)-4,5-dihydro-3-p-tolylpyrazol-1-yl)ethanone(6e)

yellow solid, yield 78%, M.P. 150^0 C;M. Formula:$C_{29}H_{29}N_5O_2S$;MW (Grams /mole):511; FT-IR(cm^{-1}, KBr): 1665 (C=O amide), 1525 (C=C str- aromatic ring) 1588 (C=N str – oxadiazole), 685 (str of S-C), ^{1}HNMR(500 MegaHz,δ ppm): 4.51ppm (2H,s,CH_2), 5.66 (H,t,CH), 6.84 (5H,m, Ar-H of benzyl),7.36-7.75 (8H, m, Ar-H); ^{13}CarbonNMR(500 MegaHz,δ ppm): 31.56, 39.23, 41.40,61.09, 114.58-133.42, 145.36-166.50; Mass: M^+ 512.

2-(5-benzyl-1-oxa,3,4-diazacyclopentadiene-2-ylthio)-1-(4,5-dihydro-5-(3,4-dimethoxyphenyl)-3-p-tolylpyrazol-1-yl)ethanone(6f)

white solid, yield 67%, M.P. 243^0 C; M. Formula:$C_{29}H_{28}N_4O_4S$;MW (Grams /mole):528 FT-IR(cm^{-1}, KBr): 1670.5 (C=O amide), 1513 (C=C str- Ar ring) 2830 (Carbon –H; methoxy)1590 (C=N str – oxadiazole), 688 (str of S-C), ^{1}HNMR(500 MegaHz,δ ppm): 4.43 ppm (2H,s,CH_2), 5.64 (H,t,CH), 7.0(5H,m, Ar-H of benzyl),7.3.(8H, m, Ar-H); ^{13}CarbonNMR(500 MegaHz,δ ppm): 31.49, 39.82,41.82,61.34, 114.86-134.47, 148.11-162.83; Mass: M^+ 529.

2-(5-benzyl-1-oxa,3,4-diazacyclopentadiene-2-ylthio)-1-(5-(4-(dimethylamino)phenyl)-4,5-dihydro-3-phenylpyrazol-1-yl)ethanone (6g)

yellow solid, yield 77%, M.P. 228^0 C;M. Formula:$C_{28}H_{27}N_5O_2S$;MW (Grams /mole):497 FT-IR(cm^{-1}, KBr): 1659 (C=O amide), 1508 (C=C str- aromatic ring) 1587 (C=N str – oxadiazole), 693 (streching of S-C), ^{1}HNMR(500 MegaHz,δ ppm): 4.45 ppm (2H,s,CH_2), 5.62 (H,t,CH) 6.98 (5H,m,Ar-H of benzyl),7.3-7.7(9H, m, Ar-H); ^{13}CarbonNMR(500 MegaHz,δ ppm): 30.92, 38.75, 40.66,59.54, 115.62-138.37, 145.24-166.28; Mass: M^+ 498.

2-(5-benzyl-1-oxa,3,4-diazacyclopentadiene-2-ylthio)-1-(4,5-dihydro-5-(3-nitrophenyl)-3-phenylpyrazol-1-yl) ethanone (6h)

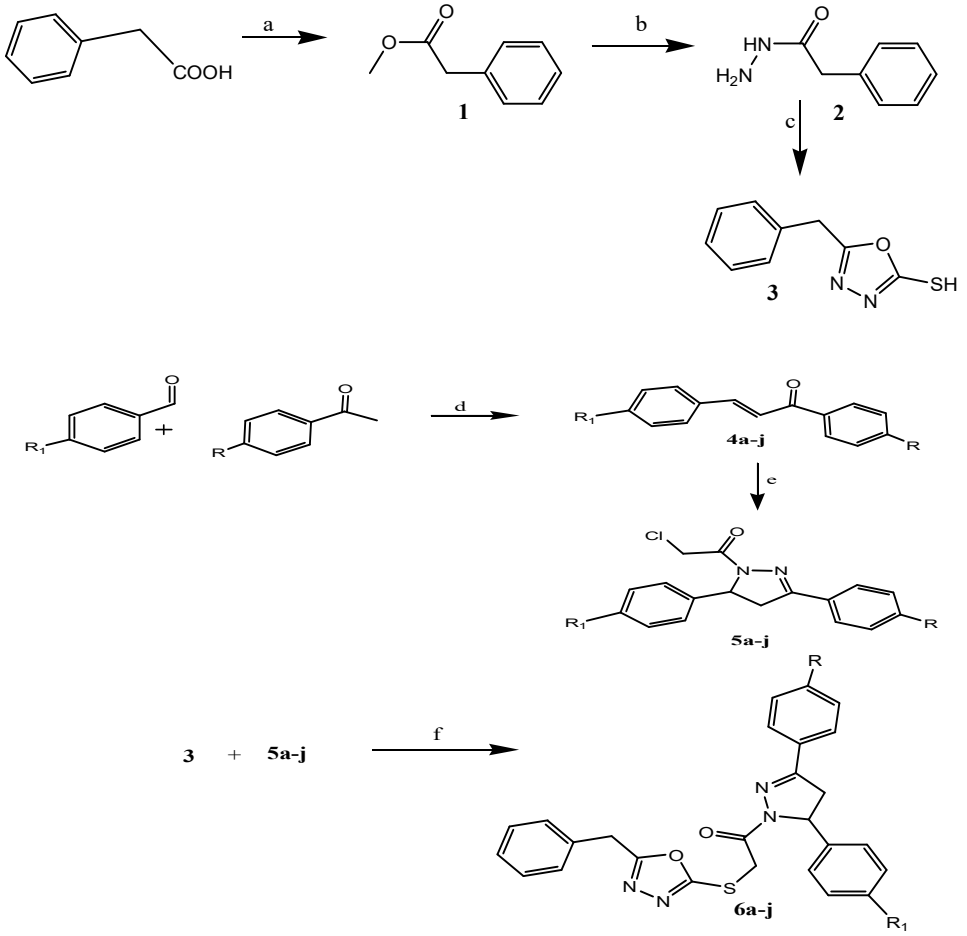
yellow solid, yield 71%, M.P. 251^0 C;M. Formula:$C_{26}H_{21}N_5O_4S$;MW (Grams /mole):499 FTIR(cm^{-1}, KBr): 1665 (C=O amide), 1510 (C=C str- aromatic ring) 1592 (C=N str – oxadiazole), 691 (str of S-C), ^{1}HNMR(500 MegaHz,δ ppm): 4.51 ppm (s,CH_2), 5.64 (t,CH), 6.84 (5H,m, Ar-H of benzyl),7.29-7.75(9H, m, Ar-H); ^{13}CarbonNMR(500 MegaHz,δ ppm): 30.62, 38.78, 41.61,61.43, 114.85-136.61, 149.07-168.95; Mass: M^+ 500

2-(5-benzyl-1-oxa,3,4-diazacyclopentadiene-2-ylthio)-1-(3-(4-chlorophenyl)-4,5-dihydro-5phenylpyrazol-1-yl)ethanone (6i)

White solid, yield 69%,M.P. 165^0C;M. Formula:$C_{26}H_{21}ClN_4O_2S$;MW (Grams /mole):488 FTIR(cm^{-1}, KBr): 1665(C=O amide),1522(C=Cstr- aromatic ring), 1590(C=N str – oxadiazole),859 (str of C-Cl), 694(str of S-C), ^{1}HNMR(500 MegaHz,δ ppm): 4.51 ppm (s,CH_2), 5.53 (t, CH), 6.69 (5H,m, Ar-H of benzyl), 7.15-7.58 (9H, m, Ar-H); ^{13}CarbonNMR (500 MegaHz,δ ppm): 32.05, 39.6, 41.15,62.5, 114.35 -134.78, 142.37-164.34; Mass: M^{+2} 490.

2-(5-benzyl-1-oxa,3,4-diazacyclopentadiene-2-ylthio)-1-(3-(4-chlorophenyl)-4,5-dihydro-5-(3,4dimethoxyphenyl) pyrazol-1-yl)ethanone(6j)

Pale yellow solid, yield 63%, M.P. 205^0 C;M. Formula:$C_{28}H_{25}ClN_4O_4S$;MW (Grams /mole):548 FTIR(cm^{-1}, KBr): 1662 (C=O amide), 1528 (C=C str- aromatic ring), 1593 (C=N str – oxadiazole), 862 (str of C-Cl), 687 (str of S-C), ^{1}HNMR(500 MegaHz, δ ppm): 4.43 ppm (2H,s,CH_2), 5.51 (H, t, CH), 6.95 (5H,m, Ar-H of benzyl),7.28-7.7(8H, m, Ar-H of phenyl); ^{13}CarbonNMR (500 MegaHz,δ ppm): 31.82, 39.47, 40.59,61.12, 113.83 -132.64, 149.69-166.38; Mass: M^{+2} 550



(a) CH_3OH, H_2SO_4 **(b)** $NH_2NH_2.2H_2O$ **(c)** CH_3OH, KOH **(d)** Ethanol, aq. NaOH
(e) (1)$NH_2NH_2.2H_2O$,(2) chloro acetyl chloride **(f)** DMF , K_2CO_3

Scheme 1

Table-1: In-vitro Antibacterial Evalution

Compound	R	R_1
6a	4-OCH_3	H
6b	4-OCH_3	3-NO_2
6c	4-CH_3	H
6d	4-CH_3	4-Cl
6e	4-CH_3	4-$N(CH_3)_2$
6f	4-CH_3	3,4-di OCH_3
6g	H	4-$N(CH_3)_2$
6h	H	4-NO_2
6i	4Cl	H
6j	4-Cl	3,4 diOCH_3

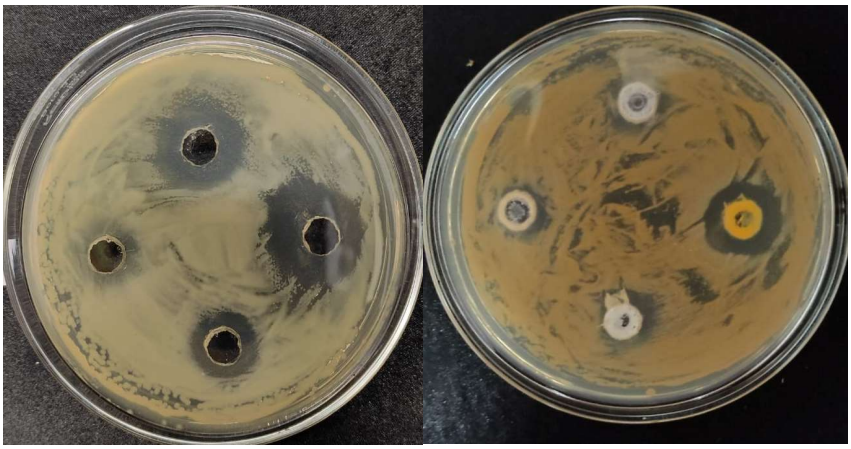


Fig.-1:(a) *E. coli* (b) *S. aureus*

All screened compounds show good antibacterial activitythrough the DD methodas mentioned in Fig.-1(a) E. coli, (b) S.aureus, and Table-2.

Table-2: Inhibition Zone: 1-9 (mild), 10-15 (moderate), 15-20 (high)

Compound	*S aureus*	*E. coli*
6a	11	12
6b	09	10
6c	13	11
6d	14	14
6e	11	12
6f	09	08
6g	13	13
6h	12	11
6i	15	13
6j	13	13
Amoxicillin	14	13

Zone of Inhibition (mm)

Compound 6d and 6i shows the highest activity among all compounds.

Chlorine-substituted compound (6i) is a highly potent molecule against *S. aureus* and *E.coli*.Methyl, di methoxy, and dimethyl amine substituted compounds are moderately active in *S. auresus* and *E.coli*. Molecules bearing methoxy and nitro groups (comp. 6b and 6f) are mild/less active against both bacteria.

These Molecules bear with amide group, oxadiazole, pyrazole, s-linkage as well as electron-withdrawing substitutions, which are responsible for their excellent activity. There are also possibilities of having other therapeutic activities.

CONCLUSION

We have synthesizeda novel series of 2-(5-benzyl-1-oxa,3,4-diazacyclopentadiene-2-ylthio)-1-(4,5-dihydro-3,5-diphenylpyrazol-1-yl)ethanone.Furtherin-vitro antibacterial investigation indicates that oxadiazole clubbed pyrazole derivatives bearing anS-linkage having a higher potential as a pharmaceutical agent.

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CONFLICT OF INTERESTS

Authors express declaration of no conflicted interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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