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SYNTHESIS AND ANTIMICROBIAL ASSESSMENT OF NOVEL ISOXAZOLE, PYRAZOLE, AND BENZODIAZEPINE DERIVATIVES DERIVED FROM CHALCONES

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ABSTRACT
The substituted chalcones were produced through the reaction of quinacetophenone with various substituted aromatic aldehydes. Subsequently, these derivatives underwent treatment with hydrazine hydrate, hydroxylamine hydrochloride, and o-phenylenediamine, leading to the formation of isoxazole, pyrazole, and benzodiazepine derivatives, respectively. The structures of these compounds were verified using spectral techniques, including IR, NMR, and Mass spectrometry. Additionally, they were evaluated for their antimicrobial activity against both gram-negative and gram-positive bacteria, yielding promising results.

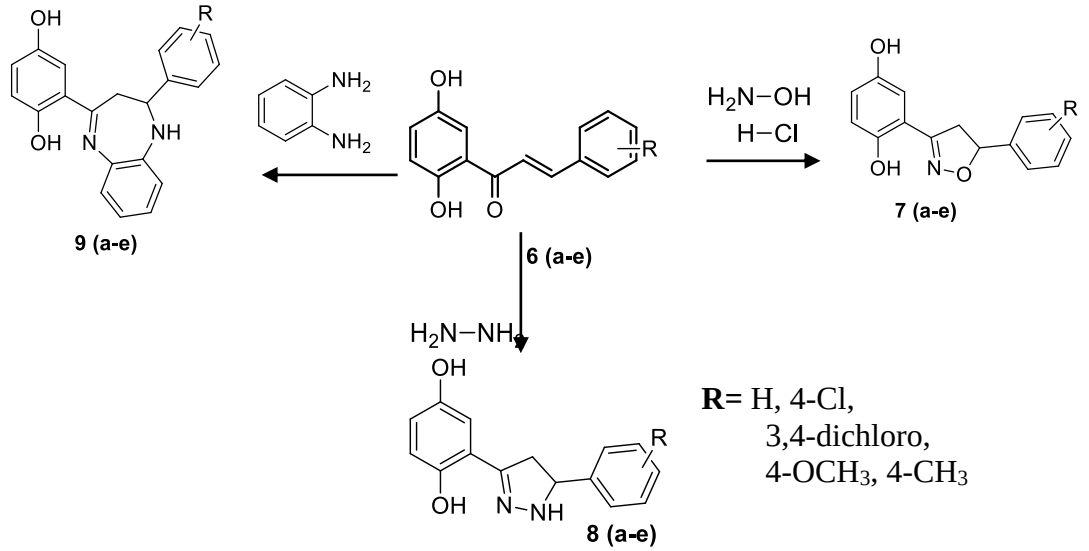
KEY WORDS: Chalcones, pyrazole, isoxazole, benzodiazepine, antibacterial activity.

INTRODUCTION
Heterocyclic compounds are abundant in nature and play a crucial role in sustaining life. Chalcones, characterized as α,β-unsaturated ketones, contain a highly reactive ketoethylenic group (-CO-CH=CH-), which contributes to their biological activity. Substituted chalcones and their derivatives have demonstrated notable biological properties, including antifungal[i], insecticidal[ii], anaesthetic[iii] and ulcerogenic[iv] activities. Furthermore, chalcones act as key intermediates in the synthesis of five-[v, vi], six- [vi, vii] and seven-membered[viii] heterocyclic compounds, which hold significant pharmaceutical importance.
It is consequently not unexpected that numerous synthetic approaches have been established for the synthesis of heterocycles derived from chalcone precursors, which have been evaluated for their antimicrobial properties.

RESULTS AND DISCUSSION
(E)-1-(2, 5-dihydroxyphenyl)-3-(substituted)-prop-2-en-1-one (6a-e) were synthesized by the reaction of quinacetophenone (1) with substituted aromatic aldehydes[ix]. Further, these chalcones derivatives were cyclised to isoxazole **(7)**, pyrazole **(8)** and benzodiazepine **(9)**

derivatives by using hydroxylamine hydrochloride**,** hydrazine hydrate and o-phenylenediamine respectively. The structures of the synthesized compounds have been validated through IR, NMR, and Mass spectrometry. Selected compounds were evaluated for their antimicrobial efficacy against both gram-negative and gram-positive bacteria. The findings indicate that these compounds demonstrate remarkable antibacterial properties.

Scheme 1: Synthetic route of the Heterocyclic compounds from chalcones.



EXPERIMENTAL

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminium plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyser.

Experimental procedure

Representative procedure for synthesis of 2-(5-(substituted)-4,5-dihydroisoxazol-3-yl)benzene-1,4-diol by using hydroxylamine hydrochloride.

A mixture of (E)-1-(2, 5-dihydroxyphenyl)-3-(substituted)-prop-2-en-1-one (0.01mole) and hydroxylamine hydrochloride (0.01 mol) and sodium acetate in ethanol 25 ml was refluxed for 6hr. The mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice water. The precipitate obtained was filtered, washed and recrystallized from absolute ethanol to give 2-(5-(substituted)-4,5-dihydroisoxazol-3-yl)benzene-1,4-diol.

2-(5-phenyl-4,5-dihydroisoxazol-3-yl)benzene-1,4-diol (**7a)**:

Off white cream solid, yield 79%; **m.p.** (°C): 169-173; **IR** (KBr, cm-1): 3511-3520 (OH), 1632 (C=N), 1412-1484 (Ar-H), 1240 (C-O), **^{1}H NMR** (500 MHz, DMSO, δ ppm): 3.70 &3.95 (2dd, 2H, CH_2), 5.39 (s, 2H, OH), 5.93 (dd, 1H, CH), 6.84-7.87 (m, 8H, Ar-H) ppm, **^{13}C NMR** (500 MHz, DMSO, δ ppm): 45.3 (CH_2), 86.1(CH), 114.3-150.2 (C=C, Ar-C), **Mass:** EI MS m/z: 258.3 $[M+1]^+$

2-(5-(4-methoxyphenyl)-4,5-dihydroisoxazol-3-yl)benzene-1,4-diol (**7d)**:
Light brown solid, yield 72%; **m.p.** (°C): 172-175; **IR** (KBr, cm-1): 3491-3510 (OH), 1672 (C=N), 1432-1486 (Ar-H), 1225 (C-O), **^{1}H NMR** (500 MHz, DMSO, δ ppm): 3.72 (s, 3H, OCH_3), 3.65 &3.95 (2dd, 2H, CH_2), 5.34 (s, 2H, OH), 5.83 (dd, 1H, CH), 6.74-7.92 (m, 7H, Ar-H) ppm, **^{13}C NMR** (500 MHz, DMSO, δ ppm): 45.3 (CH_2), 54.2 (CH_3), 87.1(CH), 113.3-149.2 (C=C, Ar-C),
Mass: EI MS m/z: 286.3 $[M+1]^+$

Representative procedure for synthesis of 2-(5-(substituted)-4,5-dihydro-1H-pyrazol-3-yl)benzene-1,4-diol by using hydrazine hydrate.

A mixture of (E)-1-(2, 5-dihydroxyphenyl)-3-(substituted)-prop-2-en-1-one (0.01mole), and hydrazine hydrate (0.02 mol) in ethanol (25 ml) containing 2-3 drops of glacial acetic acid was refluxed for 12h. The mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice water. The precipitate obtained was filtered, washed and recrystallized from absolute ethanol to give 2-(5-(substituted)-4,5-dihydro-1H-pyrazol-3-yl)benzene-1,4-diol.

2-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)benzene-1,4-diol **(8a)**
Brownish solid, yield 62%; **m.p.** (°C): 133-137; **IR** (KBr, cm-1): 3440-3510 (OH), 3270 (NH), 2875 (CH), 1595 (C=N), 1610,1522 (Ar-H), **^{1}H NMR** (500 MHz, DMSO, δ ppm): 3.75 &3.91 (2dd, 2H, CH_2), 5.45 (s, 2H, OH), 5.91 (dd, 1H, CH), 6.35 (s, 1H, NH), 6.83-7.83 (m, 8H, Ar-H) ppm, **^{13}C NMR** (500 MHz, DMSO, δ ppm): 47.5 (CH_2), 58.1(CH), 116.3-155.2 (C=C, Ar-C), **Mass:** EI MS m/z: 255.11 $[M+1]^+$
2-(5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)benzene-1,4-diol **(8d)**
Light brownish solid, yield 66%; **m.p.** (°C): 163-166; **IR** (KBr, cm-1): 3480-3530 (OH), 3170 (NH), 2778 (CH), 1495 (C=N), 1632,1572 (Ar-H),**^{1}H NMR** (500 MHz, DMSO, δ ppm): 3.79 (s, 3H, OCH_3), 3.65 & 3.91 (2dd, 2H, CH_2), 5.39 (s, 2H, OH), 5.85 (dd, 1H, CH), 6.45 (s, 1H, NH), 6.89-7.91 (m, 7H, Ar-H) ppm, **^{13}C NMR** (500 MHz, DMSO, δ ppm): 44.3 (CH_2), 53.2 (CH), 58.1(CH_3), 116.3-155.2 (C=C, Ar-C), **Mass:** EI MS m/z: 285.11 $[M+1]^+$

Representative procedure for synthesis of 2-(2-(substituted)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-benzene-1,4-diol by using o-phenylenediamine.

A mixture of (E)-1-(2, 5-dihydroxyphenyl)-3-(substituted)-prop-2-en-1-one (0.01mole) and o-phenylenediamine (0.01 mol) was dissolved in absolute ethanol (30 ml) in the presence of 20% sodium hydroxide, and the reaction mixture was refluxed for about 10 hrs. After completion of the reaction, the reaction mixture was poured into crushed ice. The product obtained was filtered, washed with cold water and recrystallized from absolute ethanol to give 2-(2-(substituted)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-benzene-1,4-diol.

2-(2-phenyl-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)benzene-1,4-diol **(9a)**
Light brownish solid, yield 69%; **m.p.** (°C): 183-187; **IR** (KBr, cm-1): 3490-3530 (OH), 3370 (NH), 1695 (C=N), 1410-1482 (Ar-H), **^{1}H NMR** (500 MHz, DMSO, δ ppm): 2.91 &3.11 (2dd, 2H, CH_2), 4.11 (t, 1H,CH), 4.91(s,1H,NH), 5.38 (s, 2H, OH), 6.86-7.93 (m, 12H, Ar-H) ppm, **^{13}C NMR** (500 MHz, DMSO, δ ppm): 46.3 (CH_2), 56.1(CH), 112.3-159.2 (C=C, Ar-C), **Mass:** EI MS m/z: 331.41 $[M+1]^+$
2-(2-(4-methoxyphenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)benzene-1,4-diol **(9d)**
Brownish solid, yield 61%; **m.p.** (°C): 191-195; **IR** (KBr, cm-1): 3450-3510 (OH), 3285 (NH), 1655 (C=N), 1415-1475 (Ar-H), **^{1}H NMR** (500 MHz, DMSO, δ ppm): 2.91 &3.11 (2dd, 2H, CH_2), 3.72 (s, 3H, OCH_3), 4.25 (t, 1H,CH), 4.81(s,1H,NH), 5.48 (s, 2H, OH), 6.89-7.97 (m, 11H, Ar-H) ppm, **^{13}C NMR** (500 MHz, DMSO, δ ppm): 46.6 (CH_2), 56.1(CH), 112.3-159.2 (C=C, Ar-C), **Mass:** EI MS m/z: 361.31 $[M+1]^+$

ANTIMICROBIAL ACTIVITIES

The selected compounds were tested for antibacterial activity against gram-negative bacteria (E. coli and P. aeruginosa) and gram-positive bacteria (S. aureus and C. diphtheriae) using the diffusion method[x, xi]. The inhibition zones were measured in millimetres and compared with the standard drug for reference. The antimicrobial results are given in **Table I**.

TABLE I: Antibacterial Activity of compound 7, 8 & 9

Antibacterial Activity of compound 7, 8 & 9				
Comp.	**Zone of inhibition (in mm)**			
	Gram Positive		**Gram negative**	
	S.aureus	**C.diphtheria**	**P.aeruginosa**	**E.coli**
7a	19	21	21	20
7d	21	22	22	17
7e	19	21	18	21
8a	21	19	18	21
8d	22	20	21	19
8e	19	20	18	17
9a	22	20	19	18
9c	23	18	19	17
9d	21	23	22	16
Ampicillin trihydrate	26	28	24	21
DMSO	0	0	0	0

* Diameter of the disc was 6mm;
Concentration of the compounds taken was about 100 µg/mL.

CONCLUSIONS

A series of new isoxazole, pyrazole and benzodiazepine derivatives synthesized by the reaction of chalcone with hydroxylamine hydrochloride**,** hydrazine hydrate and o-phenylenediamine respectively. The structures were validated using spectral techniques. The selected compounds were evaluated for their antimicrobial properties, demonstrating encouraging activity against both gram-positive and gram-negative bacteria.

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