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SYNTHESIS, CHARACTERIZATION, & ANTIMICROBIAL SCREENING OF NEW PYRIMIDINE DERIVATIVES FROM CHALCONES

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ABSTRACT

The substituted chalcones were synthesized by the reaction of quinacetophenone with substituted aromatic aldehydes. Further these derivatives were treated with substituted urea-thiourea, and guanidine hydrochloride to form a series of new pyrimidine derivatives. The structures have been confirmed by spectral techniques (IR, NMR & Mass) and they were screened for their anti-microbial activity against gram-negative and gram-positive bacteria which shows promising results.

Key words: Chalcones, urea, thiourea, guanidine, pyrimidine, antibacterial activity.

INTRODUCTION

Heterocyclic compounds are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics etc. A practical method for the synthesis of such compounds is of great interest in synthetic organic chemistry. Chalcones and the corresponding heterocyclic analogs are an important group of natural products and possess a wide range of biological activities such as antimicrobial[1-3], anticancer[4], antitubercular[5], anti-viral[6] and anti-inflammatory[7] etc. Pyrimidine and their derivatives have been found to possess a broad spectrum of biological activities such as antimicrobial, anti-inflammatory, analgesic, antiviral, and anticancer activities[8].

The wide range of application encourage us to synthesize a series of pyrimidine derivatives from chalcones which can be act as pharmaceutical active ingredient.

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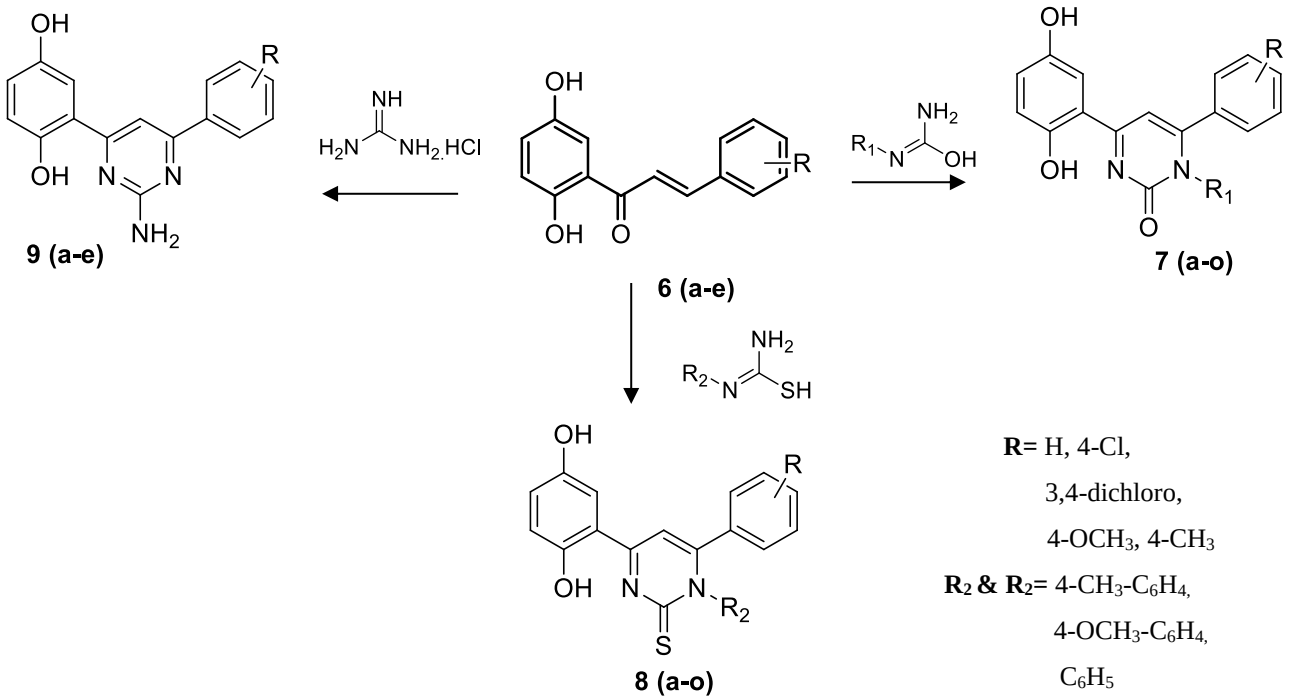
RESULTS AND DISCUSSION

(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[9]. Further, these chalcones derivatives were cyclised to pyrimidine analogs **(7), (8) & (9)** by using substituted urea-thiourea[10, 11] and guanidine hydrochloride. The structures of the synthesized compounds have been confirmed by IR, NMR and Mass. Representative compounds were screened for their anti-microbial activity against gram-negative bacteria, and gram-positive bacteria. The result shows these compounds exhibit excellent antibacterial activity.

Scheme I: Synthesis of new Pyrimidine derivatives.



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).

Representative procedure for synthesis of 4-(2,5-dihydroxyphenyl)-1,6-(substituted)-pyrimidin-2(1H)-one by using substituted urea (7a-o).

A mixture of (E)-1-(2, 5-dihydroxyphenyl)-3-(substituted)-prop-2-en-1-one (0.01mole) and substituted urea (0.01mole) in absolute ethanol (25ml) with 40% sodium hydroxide solution (10ml) were refluxed with stirring for 8h. The progress of reaction was monitored by TLC. Upon completion of the reaction, solvent was evaporated to dryness and the residue was poured on to cold water, filtered, washed with cold water. The crude compound was

recrystallized from absolute Ethanol to yield 4-(2,5-dihydroxyphenyl)-1,6-(substituted)-pyrimidin-2(1H)-one **(7a-o)**.

4-(2,5-dihydroxyphenyl)-6-phenyl-1-(p-tolyl)pyrimidin-2(1H)-one (**7a)**:

brown solid, yield 71%; **m.p.** (°C): 236-240; **IR** (KBr, cm-1): 3510-3550 (OH), 2925-3142 (C-H), 1265-1355 (C=N), 1710 (C=O), 738-925 (C-H) **^{1}H NMR** (500 MHz, DMSO, δ ppm): 2.43 (s, 3H, CH_3), 5.67 (s, 2H, OH), 6.78-7.86 (m, 13H, Ar-H) ppm, **^{13}C NMR** (500 MHz, DMSO, δ ppm): 22.6 (CH_3), 102.6-151.4 (C=C, Ar-C), 150.3 & 163.6 (C-N, C=N), 152.3 (C=O),

Mass: EI MS m/z: 371.15 $[M+1]^+$

4-(2,5-dihydroxyphenyl)-6-(4-methoxyphenyl)-1-(p-tolyl)pyrimidin-2(1H)-one **(7d):**

Beige colour solid, yield 77%; **m.p.** (°C): 275-280; **IR** (KBr, cm-1): 3520-3570 (OH), 2945-3162 (C-H), 1255-1365 (C=N), 1730 (C=O), 728-915 (C-H) **^{1}H NMR** (500 MHz, DMSO, δ ppm): 2.33 (s, 3H, CH_3), 3.97(s, 3H, OCH_3), 5.56 (s, 2H, OH), 6.85-7.79 (m, 12H, Ar-H) ppm, **^{13}C NMR** (500 MHz, DMSO, δ ppm): 22.6 (CH_3), 52.6 (OCH_3), 101.6-150.4 (C=C, Ar-C), 151.3 & 164.1 (C-N, C=N), 153.4 (C=O), **Mass :** EI MS m/z: 401.15 $[M+1]^+$

4-(2,5-dihydroxyphenyl)-1-(4-methoxyphenyl)-6-phenylpyrimidin-2(1H)-one **(7f):**

Light brown solid, yield 69%; **m.p.** (°C): 262-264; **IR** (KBr, cm-1): 3440-3510 (OH), 2915-3154 (C-H), 1245-1375 (C=N), 1690 (C=O), 755-932 (C-H) **^{1}H NMR** (500 MHz, DMSO, δ ppm): 3.89 (s, 3H, OCH_3), 5.63 (s, 2H, OH), 6.75-7.89 (m, 13H, Ar-H) ppm, **^{13}C NMR** (500 MHz, DMSO, δ ppm): 53.6 (OCH_3), 105.6-150.6 (C=C, Ar-C), 151.3 & 164.1 (C-N, C=N), 152.1 (C=O), **Mass :** EI MS m/z: 387.13 $[M+1]^+$

6-(3,4-dichlorophenyl)-4-(2,5-dihydroxyphenyl)-1-(4-methoxyphenyl)pyrimidin-2(1H)-one **(7h):** Brown solid, yield 65%; **m.p.** (°C): 220-224; **IR** (KBr, cm-1): 3530-3590 (OH), 2945-3172 (C-H), 1195-1285 (C=N), 1720 (C=O), 738-957 (C-H) **^{1}H NMR** (500 MHz, DMSO, δ ppm): 3.77 (s, 3H, OCH_3), 5.43 (s, 2H, OH), 6.81-7.44 (m, 11H, Ar-H) ppm **^{13}C NMR** (500 MHz, DMSO, δ ppm): 54.3 (OCH_3), 102.9-153.2 (C=C, Ar-C), 150.3 & 162.1 (C-N, C=N), 152.1 (C=O), **Mass :** EI MS m/z: 456.05 $[M+1]^+$

4-(2,5-dihydroxyphenyl)-6-(4-methoxyphenyl)-1-phenylpyrimidin-2(1H)-one **(7n) :**

Dark brown solid, yield 73%; **m.p.** (°C): 232-235; **IR** (KBr, cm-1): 3460-3525 (OH), 2942-3190 (C-H), 1265-1315 (C=N), 1680 (C=O), 728-915 (C-H) **^{1}H NMR** (500 MHz, DMSO, δ ppm): 3.69 (s, 3H, OCH_3), 5.33 (s, 2H, OH), 6.69-7.59 (m, 13H, Ar-H) ppm **^{13}C NMR** (500 MHz, DMSO, δ ppm): 52.3 (OCH_3), 101.9-153.2 (C=C, Ar-C), 151.3 & 163.1 (C-N, C=N), 152.4 (C=O), **Mass :** EI MS m/z: 387.13 $[M+1]^+$

4-(2,5-dihydroxyphenyl)-1-phenyl-6-(p-tolyl)pyrimidin-2(1H)-one **(7o) :**

Light brown solid, yield 76%; **m.p.** (°C): 229-233; **IR** (KBr, cm-1): 3510-3540 (OH), 2965-3175 (C-H), 1285-1375 (C=N), 1710 (C=O), 728-955 (C-H) **^{1}H NMR** (500 MHz, DMSO, δ ppm): 2.69 (s, 3H, CH_3), 5.43 (s, 2H, OH), 6.69-7.59 (m, 13H, Ar-H) ppm **^{13}C NMR** (500 MHz, DMSO, δ ppm): 23.6 (CH_3), 104.6-150.4 (C=C, Ar-C), 151.3 & 162.1 (C-N, C=N), 152.4 (C=O) **Mass :** EI MS m/z: 371.31 $[M+1]^+$

Representative procedure for synthesis of 4-(2,5-dihydroxyphenyl)-1,6-(Substituted)-2(1H)-thione (8a-o).

A mixture of (E)-1-(2, 5-dihydroxyphenyl)-3-(substituted)-prop-2-en-1-one (0.01mole) and substituted thiourea (0.01mole) in absolute ethanol (25ml) with 40% sodium hydroxide solution (10ml) were refluxed with stirring for 12h. The progress of reaction was monitored by TLC. Upon completion of the reaction, solvent was evaporated to dryness and the residue was poured on to cold water, filtered, washed with cold water. The crude compound was recrystallized from absolute Ethanol to yield 4-(2,5-dihydroxyphenyl)-1,6-(Substituted)-2(1H)-thione **(8a-o)**.

4-(2,5-dihydroxyphenyl)-6-phenyl-1-(p-tolyl)pyrimidine-2(1H)-thione **(8a) :**

Brown solid, yield 75%; **m.p.** (°C): 216-220; **IR** (KBr, cm-1): 3510-3540 (OH), 2965-3175 (C-H), 1285-1375 (C=N), 1410 (C=S), 728-955 (C-H), **^{1}H NMR** (500 MHz, DMSO, δ ppm): 2.63 (s, 3H, CH_3), 5.77 (s, 2H, OH), 6.87-7.81 (m, 13H, Ar-H) ppm, **^{13}C NMR** (500 MHz, DMSO, δ ppm): 23.6 (CH_3), 103.6-151.4 (C=C, Ar-C), 153.3 & 165.3 (C-N, C=N), 172.1 (C=S), **Mass :** EI MS m/z: 387.11 $[M+1]^+$

4-(2,5-dihydroxyphenyl)-6-(4-methoxyphenyl)-1-(p-tolyl)pyrimidine-2(1H)-thione **(8d):**

Brownish yellow solid, yield 67%; **m.p.** (°C): 215-219; **IR** (KBr, cm-1): 3410-3540 (OH), 2915-3175 (C-H), 1215-1345 (C=N), 1390 (C=S), 738-925 (C-H), **^{1}H NMR** (500 MHz, DMSO, δ ppm): 2.33 (s, 3H, CH_3), 3.97(s, 3H, OCH_3), 5.56 (s, 2H, OH), 6.85-7.79 (m, 12H, Ar-H) ppm, **^{13}C NMR** (500 MHz, DMSO, δ ppm): 23.1 (CH_3), 54.1 (OCH_3), 102.1-153.1 (C=C, Ar-C), 155.2 & 163.2 (C-N, C=N), 171.4 (C=S), **Mass :** EI MS m/z: 417.11 $[M+1]^+$

4-(2,5-dihydroxyphenyl)-1-(4-methoxyphenyl)-6-phenylpyrimidine-2(1H)-thione **(8f) :**

Beige solid, yield 63%; **m.p.** (°C): 191-194; **IR** (KBr, cm-1): 3440-3510 (OH), 2935-3125 (C-H), 1235-1365 (C=N), 1420 (C=S), 728-935 (C-H), **^{1}H NMR** (500 MHz, DMSO, δ ppm): 3.96 (s, 3H, OCH_3), 5.27 (s, 2H, OH), 6.67-7.87 (m, 13H, Ar-H) ppm, **^{13}C NMR** (500 MHz, DMSO, δ ppm): 53.3 (OCH3), 104.2-151.1 (C=C, Ar-C), 153.2 & 164.2 (C-N, C=N), 170.3 (C=S), **Mass :** EI MS m/z: 403.11 $[M+1]^+$

6-(3,4-dichlorophenyl)-4-(2,5-dihydroxyphenyl)-1-(4-methoxyphenyl)pyrimidine-2(1H)-thione **(8h):** Light Brown solid, yield 71%; **m.p.** (°C): 210-214; **IR** (KBr, cm-1): 3480-3550 (OH), 2955-3145 (C-H), 1255-1345 (C=N), 1390 (C=S), 725-951 (C-H), **^{1}H NMR** (500 MHz, DMSO, δ ppm): 3.87 (s, 3H, OCH_3), 5.33 (s, 2H, OH), 6.71-7.59 (m, 11H, Ar-H) ppm **^{13}C NMR** (500 MHz, DMSO, δ ppm): 55.3 (OCH3), 102.2-152.1 (C=C, Ar-C), 150.2 & 163.2 (C-N, C=N), 172.1 (C=S), **Mass :** EI MS m/z: 472.11 $[M+1]^+$

4-(2,5-dihydroxyphenyl)-6-(4-methoxyphenyl)-1-phenylpyrimidine-2(1H)-thione **(8n) :**

Dark brown solid, yield 63%; **m.p.** (°C): 222-225; **IR** (KBr, cm-1): 3490-3540 (OH), 2925-3135 (C-H), 1245-1335 (C=N), 1410 (C=S), 729-935 (C-H), **^{1}H NMR** (500 MHz, DMSO, δ ppm): 3.79 (s, 3H, OCH_3), 5.28 (s, 2H, OH), 6.79-7.89 (m, 13H, Ar-H) ppm **^{13}C NMR** (500 MHz, DMSO, δ ppm): 53.1 (OCH3), 107.1-153.3 (C=C, Ar-C), 150.2 & 162.2 (C-N, C=N), 171.2 (C=S),

Mass: EI MS m/z: 403.11 $[M+1]^+$

4-(2,5-dihydroxyphenyl)-1-phenyl-6-(p-tolyl)pyrimidine-2(1H)-thione **(8o) :**

Brown solid, yield 70%; **m.p.** (°C): 219-223; **IR** (KBr, cm-1): 3500-3550 (OH), 2915-3155 (C-H), 1255-1335 (C=N), 1420 (C=S), 735-915 (C-H), **^{1}H NMR** (500 MHz, DMSO, δ ppm): 2.48 (s, 3H, CH_3), 5.33 (s, 2H, OH), 6.59-7.81 (m, 13H, Ar-H) ppm **^{13}C NMR** (500 MHz, DMSO, δ ppm): 22.1 (CH3), 104.1-154.3 (C=C, Ar-C), 151.2 & 163.2 (C-N, C=N), 170.1 (C=S), **Mass:** EI MS m/z: 387.12 $[M+1]^+$

Representative procedure for synthesis of 2-(2-amino-6-(substituted)-pyrimidin-4-yl)-benzene-1,4-diol (9a-e).

A mixture of (E)-1-(2, 5-dihydroxyphenyl)-3-(substituted)-prop-2-en-1-one (0.01mole) and guanidine hydrochloride (0.01mole) in absolute ethanol (25ml) with 40% sodium hydroxide solution (10ml) were refluxed with stirring for 8-10h. The progress of reaction was monitored by TLC. Upon completion of the reaction, solvent was evaporated to dryness and the residue was poured on to cold water, filtered, washed with cold water. The crude compound was recrystallized from absolute Ethanol to yield 2-(2-amino-6-(substituted)-pyrimidin-4-yl)-benzene-1,4-diol **(9a-e)**.

2-(2-amino-6-(4-methoxyphenyl)pyrimidin-4-yl)benzene-1,4-diol **(9d) :**

Buff colour solid, yield 62%; **m.p.** (°C): 178-181; **IR** (KBr, cm-1): 3500-3550 (OH), 3428 (NH_2), 2925-3155 (C-H), 1235-1345 (C=N), 715-945 (C-H), **^{1}H NMR** (500 MHz, DMSO, δ ppm): 3.73 (s, 3H, OCH_3), 4.96 (s, 2H, NH_2), 5.39 (s, 2H, OH), 6.87-7.89 (m, 8H, Ar-H) ppm, **^{13}C NMR** (500 MHz, DMSO, δ ppm): 55.46 (OCH_3), 101.3-150.2 (C=C, Ar-C), 162 & 165.3 (2x C=N), **Mass:** EI MS m/z: 310.11 $[M+1]^+$

2-(2-amino-6-(p-tolyl)pyrimidin-4-yl)benzene-1,4-diol **(9e) :**

Light brown solid, yield 65%; **m.p.** (°C): 186-189; **IR** (KBr, cm-1): 3510-3550 (OH), 3491 (NH_2), 2945-3165 (C-H), 1255-1335 (C=N), 725-957 (C-H),**^{1}H NMR** (500 MHz, DMSO, δ ppm): 2.43 (s, 3H, CH_3), 4.92 (s, 2H, NH_2), 5.47 (s, 2H, OH), 6.77-7.93 (m, 8H, Ar-H) ppm, **^{13}C NMR** (500 MHz, DMSO, δ ppm): 23.2 (CH_3), 105.3-154.2 (C=C, Ar-C), 161 & 166.3 (2x C=N), **Mass:** EI MS m/z: 294.12 $[M+1]^+$

ANTIMICROBIAL ACTIVITIES

Representative compounds were evaluated for their antibacterial activity against gram-negative bacteria, E coli and P aeruginosa and gram-positive bacteria, S aureus, and C diphtheriae using disc diffusion method[12, 13]. The zone of inhibition was measured in mm and the activity was compared with standard drug. The antimicrobial data was 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**
7b	21	22	20	23
7d	23	24	21	26
7f	18	20	19	20
7h	22	23	23	19
7j	20	19	26	21
7k	14	17	22	17
7m	12	14	21	24
8a	23	24	20	22
8d	21	23	19	20
8e	18	17	21	19
8f	16	19	18	20
8i	23	21	19	17
8k	21	22	20	18
8l	22	20	19	17
9a	23	19	17	21
9d	20	18	18	19
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 pyrimidine derivatives synthesized by the reaction of chalcone with substituted urea-thiourea and guanidine hydrochloride. The structures were confirmed by spectral technique. The representative compounds were screened for their antimicrobial activity which shows promising activity against gram positive and gram negative bacteria.

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