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Synthesis of the heterocyclic chalconoid derivatives

Chanti Babu Patneedi*, Durga Prasadu K and R. S. K. Sharma

Visakhapatnam, A.P

ABSTRACT

Chalconoids, also known as chalcones, they form the central core for a variety of important biological compounds. They show antibacterial, antifungal, antitumor and anti-inflammatory properties. Some chalconoids demonstrated the ability to block voltage-dependent potassium channels [1]. Chalcones are also natural aromatize inhibitors [2]. Chalcones are starting compounds in synthesis of heterocycles containing di nitrogen atoms which named (di aze) ,an attempt to synthesis of chalcones from acetanilide with aromatic aldehydes such as p-N,N-dimethyl Benzaldehyde and p-hydroxy benzaldehyde by Claisen- Schmidt condensation. The resulting chalcones after purification have been converted into substituted pyrazoline and pyrimidine by reaction with hydrazine hydrate, urea, thiourea and guanidine. All these compounds were characterized by Physical and spectral methods such as melting point, ^{1}H-NMR and C.H.N analysis.

Keywords: Heterocyclic chalcones, Aromatic aldehydes, synthesis of pyrazoline & pyrimidine.

INTRODUCTION

The synthesis of chalcone compounds incorporating with hetero cycles became great importance in medicinal chemistry [3, 4]. The hetero atoms in there structure such as (S, N, O) explain variety applications in the biological engineering and in other field of their specific structures [5]. Chalcones are natural biocides and are well known intermediates in the synthesis of heterocyclic compounds exhibiting various biological activities. Chalcones and their derivatives posses some interesting biological properties such as antibacterial, antifungal, insecticidal, anesthetic, anti-inflammatory, analgesic etc [6-8] .Pyrazole is a class of compounds, which has many applications in different field [9]. In addition, Pyrazolines have played a crucial part in the development of theory in heterocyclic chemistry and also used extensively in organic synthesis. Among the methods employed in synthesis of pyrazolines, condensation of a variety of substituted chalcones with hydrazine and its derivatives is commonly used [10] .pyrimidine derivatives occupy an important place in the present day therapeutics. They were reported to possess abroad spectrum of biological activities such as anticancer, antitubercular antimalarial properties [11].

The resulting chalcones after purification and characterization by physical and spectral methods have been successfully converted into substituted pyrimidines by reaction with guanidine hydrochloride [12-14].

MATERIALS AND METHODS

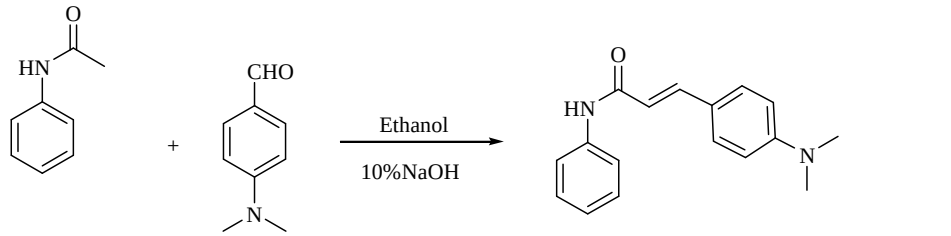
Materials:
All the chemicals were supplied by BDH and Fluka – Chemical Company. The melting points of compounds were determined by Electro thermal melting point apparatus. Elemental analyses were carried out by micro analytical

unit, of 1180 C. H. N Elemental analyzer (Malaysia). The 1H-NMR spectra were obtained in (DMSO) solvent using (Bruker, Ultra. Shield. 3000 MKZ, Switzerland).

Synthesis of chalcones [13]:

1. Preparation of 3-(4-Dimethylamino-phenyl)-N-phenyl-acrylamide:

To Acetanilide (1.35gm, 0.01 mole) added 4-dimethyl amino benzaldehyde (1.49gm, 0.01 mole) in Ethanol (25ml) and catalytic quantity of Sodium hydroxide (10%). The mixture was stirred for 6 hours at room temperature using magnetic stirrer. The reaction was monitored by T.L.C and the solvent was evaporated and the precipitation was recrystallized from absolute Ethanol to give 3-(4-Dimethylamino-phenyl)-N-phenyl-acrylamide :(1.8gm, Yield: 67.6%).



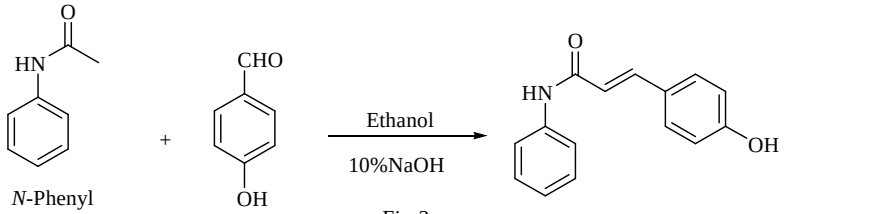
N-Phenyl -acetamide + 4-Dimethylamino -benzaldehyde

Fig-1

3-(4-Dimethylamino-phenyl) -*N*-phenyl-acrylamide $C_{17}H_{18}N_2O$ Mol. Wt.: 266.34

2. Preparation of 3-(4-Hydroxy-phenyl)-N-phenyl-acrylamide:

To Acetanilide (1.35gm, 0.01 mole) added 4-Hydroxy benzaldehyde (1.22gm, 0.01mole)] in Ethanol (25ml) and catalytic quantity of Sodium hydroxide (10%) . The mixture was stirred for 6 hours at room temperature using magnetic stirrer. The reaction was monitored by T.L.C and the solvent was evaporated and the precipitation was recrystallized from absolute Ethanol to give 3-(4-Hydroxy-phenyl)-N-phenyl-acrylamide :(1.6gm, Yield: 66.9%).



N-Phenyl -acetamide + 4-Hydroxy -benzaldehyde

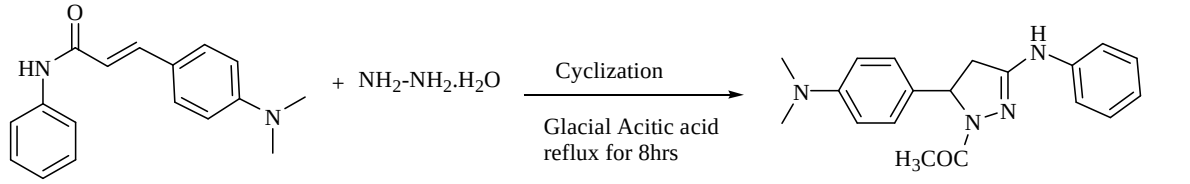
Fig-2

3-(4-Hydroxy-phenyl) -*N*-phenyl-acrylamide $C_{15}H_{13}NO_2$ Mol. Wt.: 239.27

Synthesis of pyrazolines [15]:

3. Preparation of 1-[5-(4-Dimethylamino-phenyl)-3-phenylamino-4, 5-dihydro-pyrazol-1-yl]-ethanone:

To the 3-(4-(dimethylamino)phenyl)-N-phenyl-acrylamide (2.67gm,0.01 moles)in absolute ethanol (25ml) added glacial acetic acid(2 ml) and hydrazine hydrate 99% (0.01mole). Refluxed with stirring at 80° C for 8 hours. The reaction was monitored by T.L.C and the solvent was evaporated and precipitation was recrystallized from absolute Ethanol to give 1-[5-(4-Dimethylamino-phenyl)-3-phenylamino-4, 5-dihydro-pyrazol-1-yl]-ethanone (1.9gm, Yield: 59%).



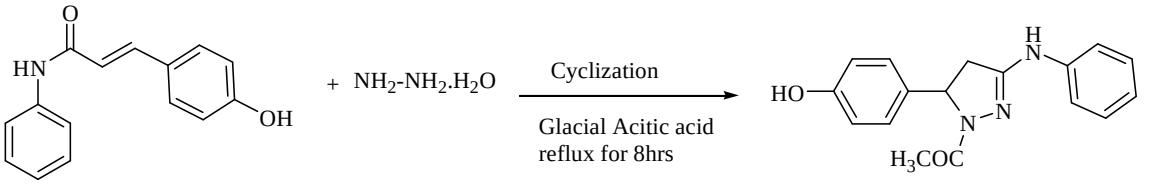
3-(4-Dimethylamino-phenyl) -*N*-phenyl-acrylamide

Fig-3

1-[5-(4-Dimethylamino-phenyl)-3-phenylamino -4,5-dihydro-pyrazol-1-yl]-ethanone

$C_{19}H_{22}N_4O$
Mol. Wt.: 322.40

4. Preparation of 1-[5-(4-Hydroxy-phenyl)-3-phenylamino-4, 5-dihydro-pyrazol-1-yl]-ethanone:
To the 3-(4-Hydroxy-phenyl)-N-phenyl-acrylamide (2.41gm, 0.01 moles) in absolute ethanol (25ml) added glacial acetic acid (2 ml) and hydrazine hydrate 99% (0.01mole). Refluxed with stirring at 80° C for 8 hours. The reaction was monitored by T.L.C and the solvent was evaporated and precipitation was recrystallized from absolute Ethanol to give 1-[5-(4-Hydroxy-phenyl)-3-phenylamino-4, 5-dihydro-pyrazol-1-yl]-ethanone (1.6gm, Yield: 54%).



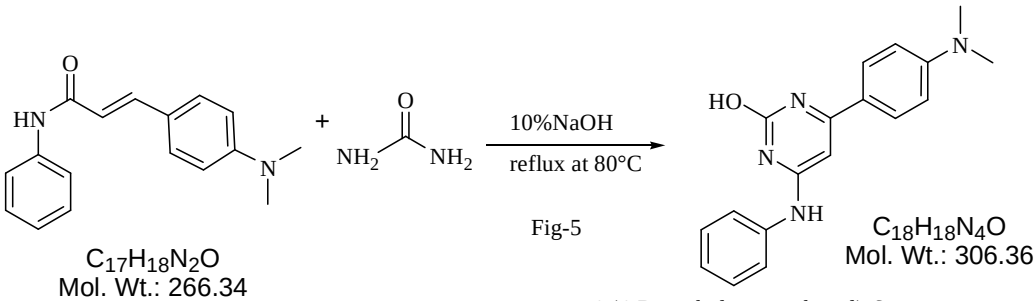
3-(4-Hydroxy-phenyl)
-*N*-phenyl-acrylamide

Fig-4

1-[5-(4-Hydroxy-phenyl)-3-phenylamino
-4,5-dihydro-pyrazol-1-yl]-ethanone
$C_{17}H_{17}N_3O_2$
Mol. Wt.: 295.34

Synthesis of pyrimidines [16] from Chalcones:

5. Preparation of 4-(4-Dimethylamino-phenyl)-6-phenylamino-pyrimidin-2-ol with urea:
To 3-(4-(dimethylamino) phenyl)-N-phenyl-acrylamide (2.67 g,0.01mole) added urea (0.01mole) in absolute ethanol (25ml) and catalytic quantity of 10%Sodium hydroxide (2ml) were refluxed with stirring for 8h. The reaction was monitored by T.L.C and the solvent was evaporated and the precipitation was recrystallized from absolute Ethanol to give 4-(4-Dimethylamino-phenyl)-6-phenylamino-pyrimidin-2-ol (1.7 g, Yield: 55.5%).



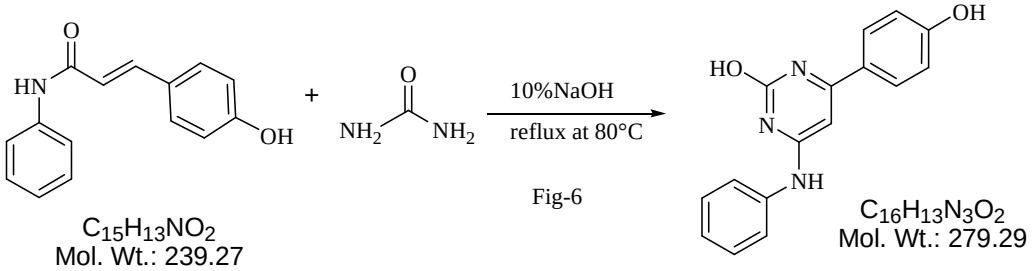
$C_{17}H_{18}N_2O$
Mol. Wt.: 266.34

Fig-5

$C_{18}H_{18}N_4O$
Mol. Wt.: 306.36

4-(4-Dimethylamino-phenyl)-6
-phenylamino-pyrimidin-2-ol

6. Preparation of 4-(4-Hydroxy-phenyl)-6-phenylamino-pyrimidin-2-ol with urea:
To 3-(4-Hydroxy-phenyl)-N-phenyl-acrylamide (2.4 g, 0.01mole) added urea (0.01mole) in absolute ethanol (25ml) and catalytic quantity of 10%Sodium hydroxide (2ml) were refluxed with stirring for 8h. The reaction was monitored by T.L.C and the solvent was evaporated and the precipitation was recrystallized from absolute Ethanol to give 4-(4-Hydroxy-phenyl)-6-phenylamino-pyrimidin-2-ol. (1.6 g, Yield: 57.3%).



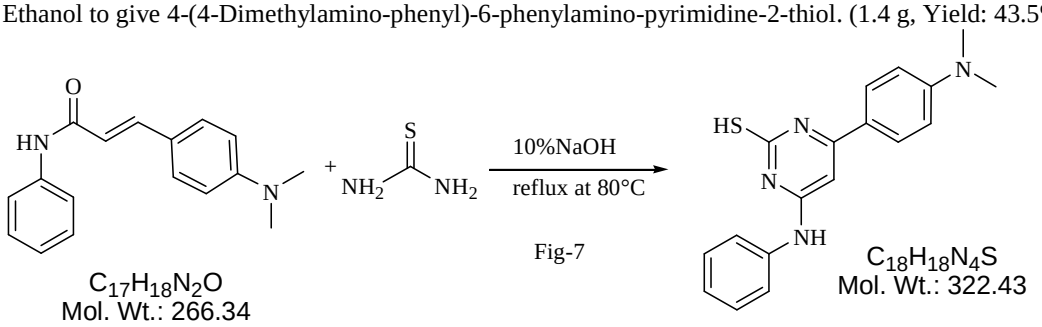
$C_{15}H_{13}NO_2$
Mol. Wt.: 239.27

Fig-6

$C_{16}H_{13}N_3O_2$
Mol. Wt.: 279.29

4-(4-Hydroxy-phenyl)-6
-phenylamino-pyrimidin-2-ol

7. Preparation of 4-(4-Dimethylamino-phenyl)-6-phenylamino-pyrimidine-2-thiol with thiourea:
To 3-(4-(dimethylamino) phenyl)-N-phenyl-acrylamide (2.66 g, 0.01mole) added thiourea (0.01mole) in absolute ethanol (25ml) and catalytic quantity of 10%Sodium hydroxide (2ml) were refluxed with stirring for 8h. The reaction was monitored by T.L.C and the solvent was evaporated and the precipitation was recrystallized from absolute Ethanol to give 4-(4-Dimethylamino-phenyl)-6-phenylamino-pyrimidine-2-thiol. (1.4 g, Yield: 43.5%).



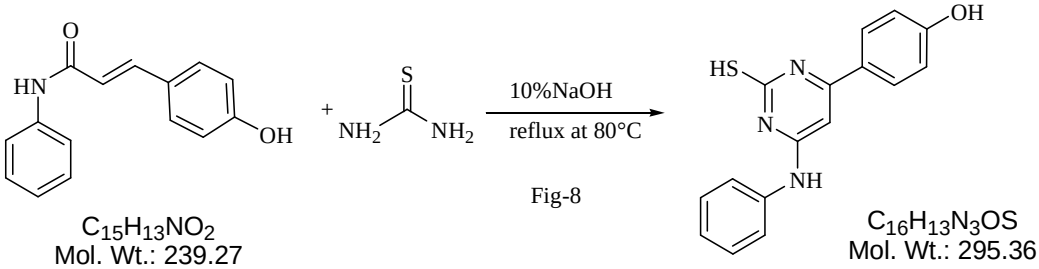
$C_{17}H_{18}N_2O$
Mol. Wt.: 266.34

Fig-7

$C_{18}H_{18}N_4S$
Mol. Wt.: 322.43

4-(4-Dimethylamino-phenyl)-6
-phenylamino-pyrimidine-2-thiol

8. Preparation of 4-(2-Mercapto-6-phenylamino-pyrimidin-4-yl)-phenol with thiourea:
To 3-(4-Hydroxy-phenyl)-N-phenyl-acrylamide (2.39 g, 0.01mole) added thiourea (0.01mole) in absolute ethanol (25ml) and catalytic quantity of 10%Sodium hydroxide (2ml) were refluxed with stirring for 8h. The reaction was monitored by T.L.C and the solvent was evaporated and the precipitation was recrystallized from absolute Ethanol to give 4-(2-Mercapto-6-phenylamino-pyrimidin-4-yl)-phenol. (1.5 g, Yield: 51%).



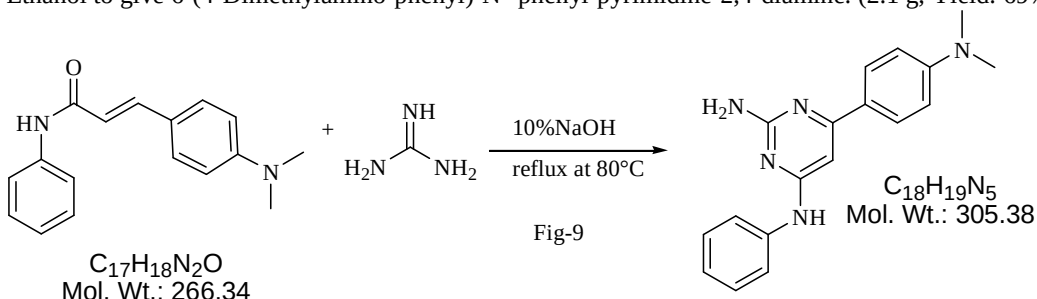
$C_{15}H_{13}NO_2$
Mol. Wt.: 239.27

Fig-8

$C_{16}H_{13}N_3OS$
Mol. Wt.: 295.36

4-(2-Mercapto-6-phenylamino
-pyrimidin-4-yl)-phenol

9. Preparation of 6-(4-Dimethylamino-phenyl)-N^4-phenyl-pyrimidine-2, 4-diamine with guanidine:
To 3-(4-(dimethylamino) phenyl)-N-phenyl-acrylamide (2.66 g, 0.01mole) added guanidine (0.01mole) in absolute ethanol (25ml) and catalytic quantity of 10%Sodium hydroxide (2ml) were refluxed with stirring for 8h. The reaction was monitored by T.L.C and the solvent was evaporated and the precipitation was recrystallized from absolute Ethanol to give 6-(4-Dimethylamino-phenyl)-N^4-phenyl-pyrimidine-2,4-diamine. (2.1 g, Yield: 69%).



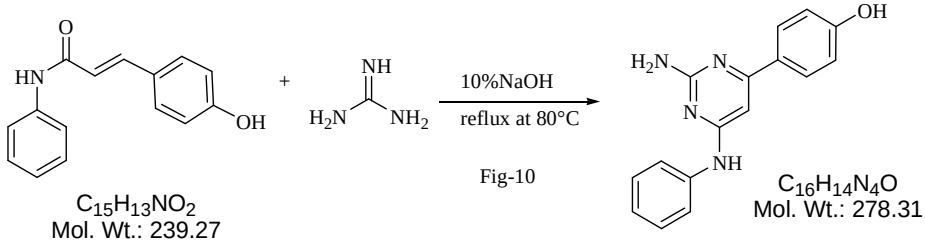
$C_{17}H_{18}N_2O$
Mol. Wt.: 266.34

Fig-9

$C_{18}H_{19}N_5$
Mol. Wt.: 305.38

6-(4-Dimethylamino-phenyl)-N^4
-phenyl-pyrimidine-2,4-diamine

10. Preparation of 4-(2-Amino-6-phenylamino-pyrimidin-4-yl)-phenol with guanidine:
To 3-(4-Hydroxy-phenyl)-N-phenyl-acrylamide (0.01mole) added guanidine (0.01mole) in absolute ethanol (25ml) and catalytic quantity of 10%Sodium hydroxide (2ml) were refluxed with stirring for 8h. The reaction was monitored by T.L.C and the solvent was evaporated and the precipitation was recrystallized from absolute Ethanol to give 4-(2-Amino-6-phenylamino-pyrimidin-4-yl)-phenol. (1.9 g, Yield: 62.3%).



$C_{15}H_{13}NO_2$
Mol. Wt.: 239.27

Fig-10

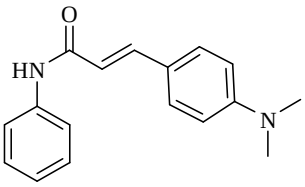
$C_{16}H_{14}N_4O$
Mol. Wt.: 278.31

4-(2-Amino-6-phenylamino
-pyrimidin-4-yl)-phenol

RESULTS AND DISCUSSION

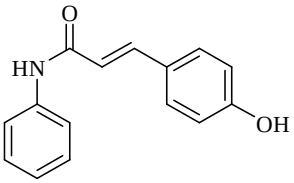
All synthesized derivatives [1-10] have been characterized by their melting points and spectroscopic methods such as ^{1}HNMR spectra and C.H.N analysis.

1. 3-(4-Dimethylamino-phenyl)-N-phenyl-acrylamide:



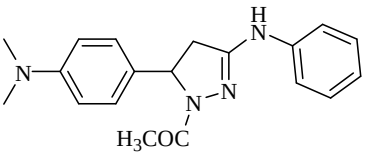
M.F: $C_{17}H_{18}N_2O$,M.Wt: 266.34,Colour:Yellow, m.p:300°C, Elemental Analysis:C-76.5%,H-6.7%,N-10.5% & O-6.0%,^{1}HNMR(3000 MKZ, DMSO) ppm: 10.0, (s, 1H, -NH-C=O) , 6.85-7.60(m, 9H, aromatic) , 3.4(s,6H, N(CH3)2) , 6.81-7.21 (d, 2H, CH=CH=C=O).

2. 3-(4-Hydroxy-phenyl)-N-phenyl-acrylamide:



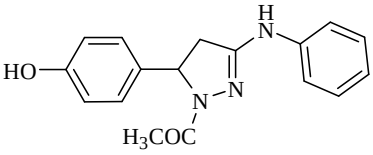
M.F: $C_{15}H_{13}NO_2$,M.Wt: 239.27,Colour: Light gray, m.p: 108-110°C, Elemental Analysis:C-75.2%,H-5.4%,N-5.8% & O-13.4%,^{1}HNMR(3000 MKZ, DMSO) ppm: 9.7, (s, 1H, -NH-C=O) , 6.84-7.64(m, 9H, aromatic) , 3.9(s,1H,-OH) ,6.81-7.21 (d, 2H, CH=CH=C=O).

3. 1-[5-(4-Dimethylamino-phenyl)-3-phenylamino-4, 5-dihydro-pyrazol-1-yl]-ethanone:



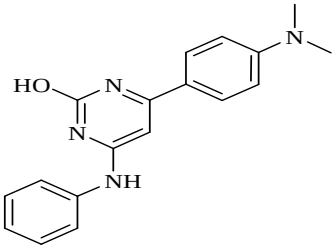
M.F: $C_{19}H_{22}N_4O$,M.Wt: 322.40,Colour: Brown, m.p: 300°C, Elemental Analysis:C-70.7%,H-6.8%,N-17.4% & O-5.0%,^{1}HNMR(3000 MKZ, DMSO) ppm: 9.5 (s ,1H, -NH-) , 2.1(s , 3H,CH3-C=O), 6.7- 7.5(m , 9H , aromatic) ,3.4,3.5 , (d , 2H , t ,1H) pyrazoline cycle ,3.6 (s ,6H, $N(CH3)_2$.

4. 1-[5-(4-Hydroxy-phenyl)-3-phenylamino-4, 5-dihydro-pyrazol-1-yl]-ethanone:



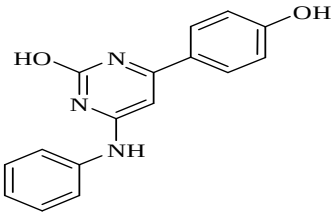
M.F: $C_{17}H_{17}N_3O_2$,M.Wt: 295.34,Colour: Earthy color, m.p: 159-161°C, Elemental Analysis:C-70.7%,H-6.8%,N-17.4% & O-5.0%,^{1}HNMR(3000 MKZ, DMSO) ppm: 9.5 (s ,1H, -NH-) , 2.1(s , 3H,CH3-C=O), 6.7- 7.5(m , 9H , aromatic) ,3.4,3.5 , (d , 2H , t ,1H) pyrazoline cycle ,4.2 (s ,1H, -OH).

5. 4-(4-Dimethylamino-phenyl)-6-phenylamino-pyrimidin-2-ol:



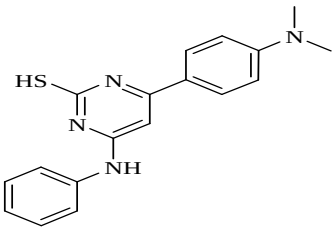
M.F: C $_{18}$H $_{18}$N$_4$ O,M.Wt: 306.36,Colour: Yellow, m.p: 105-107°C, Elemental Analysis:C-70.5%,H-5.9%,N-18.3% & O-5.2%,^{1}HNMR(3000 MKZ, DMSO) ppm: 11.2(s , 1H , OH) , 8.95(s , 1H ,-NH-) , 6.8- 7.6(m , 9H, Phenyl , 1H,pyrimidine), 3.6(s , 6H , N(CH$_3$)$_2$).

6. 4-(4-Hydroxy-phenyl)-6-phenylamino-pyrimidin-2-ol:



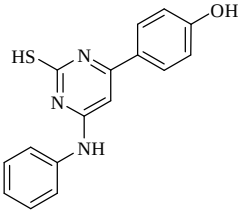
M.F: C $_{16}$H $_{13}$N$_3$ O$_2$,M.Wt: 279.29,Colour: Earthy color, m.p: 300°C, Elemental Analysis:C-68.8%,H-4.7%,N-15.0% & O-11.5%,^{1}HNMR(3000 MKZ, DMSO) ppm: 11.2(s , 1H , OH) , 8.95(s , 1H ,-NH-) , 6.8- 7.6(m , 9H, Phenyl , 1H,pyrimidine), 4.2 (s ,1H, -OH).

7. 4-(4-Dimethylamino-phenyl)-6-phenylamino-pyrimidine-2-thiol:



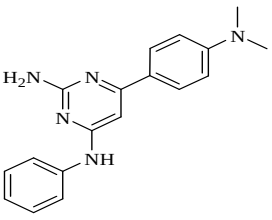
M.F: C $_{18}$H$_{18}$N$_4$S,M.Wt: 322.43,Colour: Orange, m.p: 150-152°C, Elemental Analysis:C-67.0%,H-5.6%,N-17.4% & O-9.9%,^{1}HNMR(3000 MKZ, DMSO) ppm: 3.2(s , 1H , SH) , 8.95(s , 1H ,-NH-) , 6.8- 7.6(m , 9H, Phenyl , 1H,pyrimidine), 3.6(s , 6H , N(CH$_3$)$_2$).

8. 4-(2-Mercapto-6-phenylamino-pyrimidin-4-yl)-phenol:



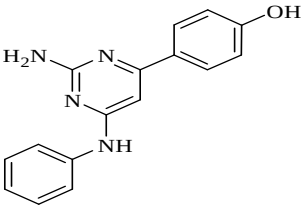
M.F: C$_{16}$H$_{13}$N$_3$OS,M.Wt: 295.36,Colour: Orange, m.p: 103-105°C, Elemental Analysis:C-65.0%,H-4.4%,N-14.2%, O-5.5% & S-10.8%,^{1}HNMR(3000 MKZ, DMSO) ppm: 3.2(s , 1H , SH) , 8.95(s , 1H ,-NH-) , 6.8- 7.6(m , 9H, Phenyl , 1H,pyrimidine), 4.2 (s ,1H, -OH).

9. 6-(4-Dimethylamino-phenyl)-N^4-phenyl-pyrimidine-2, 4-diamine:



M.F: C$_{18}$H$_{19}$N$_5$,M.Wt: 305.38,Colour: Yellow, m.p: 110-112°C, Elemental Analysis:C-70.8%,H-6.2% & N-22.9%,^{1}HNMR(3000 MKZ, DMSO) ppm: 9.10(s , 2H , - NH2) , 8.85 (s ,1H, -NH-), 6.9- 7.8(m , 9H , Phenyl , 1H,pyrimidine) , 3.5(s , 6H, N(CH$_3$)$_2$).

10. 4-(2-Amino-6-phenylamino-pyrimidin-4-yl)-phenol:



M.F: $C_{16}H_{14}N_4O$, M.Wt: 278.31, Colour: Brown, m.p: 120-122°C, Elemental Analysis: C-69.0%, H-5.0%, N-20.1 & O-5.8%,^{1}HNMR(3000 MKZ, DMSO) ppm: : 9.10(s , 2H , - NH2) , 8.85 (s ,1H, -NH-), 6.9- 7.8(m , 9H , Phenyl , 1H,pyrimidine) , 4.2 (s ,1H, -OH).

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