Synthesis, Characterization and Antidiabetic Evaluation of 6-acetyl-5-Aryl-7-methyl-1H-pyrano[2,3-d]pyrimidine-2,4(3H,5H)-thione derivatives

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Abstract.

Pyrimidine derivatives are known as essential pharmacophores in the field of medicine. Owing to their remarkable activities, we synthesize a series of compounds having pyrimidine moiety. First of all we prepared two acetyl derivatives of thiopyrimidine (**5 and 6**), then they react with different Aryl aldehydes to form various chalcones .The synthesized compounds were characterized by different analytical techniques and screened for their antidiabetic activity. Almost all synthesized compounds showed good to excellent antidiabetic activity.

Keywords; 5-Arylfuran-2-carbaldehyde, Chalcones, Antidiabetic activity, pyrimidine derivative, Claisen Schmidt condensation etc.

Introduction:

Pyrimidine (**1**) and its derivatives are important heterocyclic compounds which are biologically active and characterize by extreme ubiquitous members of the diazine with Cytosine (**2**) Uracil (**3**) Thymine (**4**) which constituents of ribonucleic acid and deoxyribonucleic acid. They also involves for production of biological compounds like synthesis of lipids and protein. [1] Pyrimidine derivatives display antimalarial, antitumor, antitubercular, antiviral activities. Moreover they also act as cardiovascular agent, anti-HIV, diuretic and cardiovascular agents.[2]

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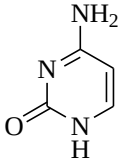

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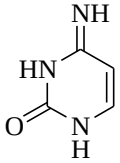

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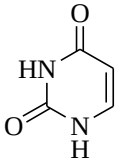

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Thiopyrimidine represent one of the most active classes of compounds possessing a wide spectrum of biological activities, such as significant in vitro activity against unrelated DNA and RNA viruses (including polio and Herpes simplex viruses), diuretic, spermicidal, herbicidal, etc. Thiopyrimidines show

good pharmacological properties[3], including antiviral and antitumor, anti-inflammatory and analgesic, antifilarial, anticancer and herbicidal, antileishmanial, antineoplastic, antimicrobial, antitubercular, etc

Herein, we prepared derivatives of pyranothiopyrimidine through the simple, facile and efficient strategies, by one pot reaction of 6-acetyl-5-aryl-7-methyl-1H-pyrano[2,3d]pyrimidine-2,4(3H,5H)-thione (**5 or 6**) derivatives via Claisen Schmidt condensation with different 5-Arylfuran-2-aldehydes in the presence of basic media. While 6-acetyl-5-aryl-7-methyl-1H-pyrano[2,3d]pyrimidine-2,4(3H,5H)-thione (**5 and 6**) derivatives were prepared by simple condensation of 4-chloro benzaldehyde/3-nitro benzaldehyde, acetyl acetone and thiobarbituric acid.

Experimental:

Materials and Methods

All reagents and solvents were used as obtained from the supplier or recrystallized or redistilled as necessary. Thin layer chromatography was performed using aluminium sheets (Merck) coated with silica gel 60 F_{254}. IR spectra were recorded using an IR Perkin-Elmer Spectrum 1 FTIR spectrophotometer and peaks were reportedmax(neat)/cm^{-1}which refer to the min wave numbers. Proton magnetic resonance spectra were recorded in $CDCl_3$ with Bruker AM 300 spectrometer (Rheinstetten–Forchheim, Germany) operating at 300 MHz, respectively. The ^{13}C NMR spectra were recorded in $CDCl_3$ with Bruker AM 100spectrometer operating at 100 MHz.Tetramethyl-silanewas used as an internal standard. Elemental analysis for C, H and N were recorded with Perkin-Elmer 2400 Series II CHN Analyzer. Melting points were recorded on a GallenKamp apparatus and are uncorrected.

Synthesis of stating material:

Equimolar mixture of 4-chloro benzaldehyde/3-nitro benzaldehyde, acetyl acetone and thiobarbituric acid is stir at 70^0C for 4 hours in round bottom flask in presence of NaOH in ethanol. After cooling at room temperature crystalline product obtain which further recrystallized with ethanol.

6-acetyl-5-(4-chlorophenyl)-7-methyl-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d] pyrimidine-4(5H)-one(5)

Yield: 0.75 g (85%) white powder, **M.P:** 230^{0}C, **FTIR (υ, cm^{-1}):** 2341.12 (Ar-H), 1664.91(C=O), 1593.85(C=C) 1562.44 and 1040-1010 (C=S), 1033.83 (C-Cl) , 1460-1430 (-CH3), 3500 (C-NH), **^{1}HNMR: δ:** 2.0 (s, 3H) 8.0 (s, 1H) 7.17-7.37 (m, 4H) 3.94(s, m), 2.24-2.26(s, 3H),

6-acetyl-5-(3-nitrophenyl)-7-methyl-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d] pyrimidine-4(5H)-one(6)

Yield: 0.75 g (85%) white powder, **M.P:** 220-230^{0}C, **FTIR (υ, cm^{-1}):** 2341.12 (Ar-H), 1664.91(C=O), 1593.85(C=C) 1562.44 and 1040-1010 (C=S), 1460-1430 (-CH3), 3500 (C-NH), 1358.00 (-NO_2), **^{1}HNMR: δ:** 2.0 (s, 3H) 8.0 (s, 1H) 7.17-7.37 (m, 4H) 3.94(s, m), 2.24-2.26(s, 3H),

General procedure for the synthesis of Chalcones:

Equimolar quantities of Aryl furan-2-carbaldehyde and Synthesis of 6-acetyl-5-(4-chlorophenyl)-7-methyl-2-thioxo-2,3dihydro-1H-pyrano[2,3-d] pyrimidine-4(5H)-one was taken in Ethanol and water mixture in the presence of NaOH as a catalyst in ice bath , stirred the mixture for 4 hours. Solid product formed was filtered, dried and recrystallized from Ethanol.

5-(4-chlorophenyl)-7-methyl-6-(3-(5-(2-methyl-5-nitrophenyl)furan-2-yl)acryloyl)-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one (7)

Yield: 0.63 g (71%), **M.P:** 140^{0}C, **FTIR (υ, cm^{-1}):** 2357.18 (Ar-H), 1661.58 (C=O), 1599.41(C=C), 1561.80 and 1331.93 (-NO_2), 1033.32 (C-Cl bond), **Mass Spectra m/z (%):** $C_{28}H_{20}ClN_3O_6S$: 559.06 (M^+), 524.07 (M^+-Cl), 544.02 (M^+-CH_3), 425.07 (M^+-PhMeNO_2), 513.04 (M^+-NO_2), 402.04 (M^+-PhCl) **^{1}HNMR: δ:** 2.24-2.59 (m, 6H) 3.94 (s, 1H) 7.17-8.53 (m, 6H) 13.76 (s, 1H) **^{13}CNMR: δ:** 189.76 (C=O), 133.89, 128.70 (C=C), 155.78, 153.50, 149.76, 144.30, 140.76, 131.64, 127.65, 122.90, 119.40, 110.65 (Ar-C) 21.63 **Anal.Calcd.for** $C_{28}H_{20}ClN_3O_6S$: C 59.83; H 3.58; N 7.47%

5-(4-chlorophenyl)-6-(3-(5-(2,4-dichlorophenyl)furan-2-yl)acryloyl)-7-methyl-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one (8)

Yield: 0.72 g (82%), **M.P:** 130^{0}C, **FTIR (υ, cm^{-1}):** 2362.18(Ar-H), 1663.58 (C=O), 1588.55 (C=C) , 1113.99 (C-Cl), **Mass Spectra m/z (%):** $C_{27}H_{17}Cl_3N_2O_4S$: 570.84 (M^+), 534.04 (M^+-Cl), 553.93 (M^+-

CH_3), 425.07 (M^+-$PhCl_2$), 534.94(M^+-PhCl), **^{1}HNMR: δ:** 2.24 (s, 3H) 3.90 (s, 1H) 7.03 (d, 1H) 7.66 (d, 1H) 7.37-7.67 (m, 6H) 8.0 (s, 1H) 13.76 (s, 1H),**^{13}CNMR: δ:** 187.65, 155.29, 151.36, 137.55, 133.25, 132.19, 131.44, 127.34, 130.78, 129.46, 126.45, 122.74, 118.90, 110.68 (Ar-C), **Anal.Calcd.for** $C_{27}H_{17}Cl_3N_2O_4S$: C 56.70; H 3.01; N 4.90%

6-(3-(5-(2-chloro-5-nitrophenyl)furan-2-yl)acryloyl)-5-(4-chlorophenyl)-7-methyl-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one (9)

Yield: 0.68 g (74%), **M.P:** 160^{0}C, **FTIR (υ, cm^{-1}):** 2360.49(Ar-H), 1671.70 (C=O), 1601.75(C=C), 1553.0 and 1342.12 (-NO_2), 1093.25 (C-Cl), **Mass Spectra m/z (%):** $C_{27}H_{17}Cl_2N_3O_6S$: 580.0 (M^+), 544.03 (M^+-Cl), 563.93 (M^+-CH_3), 468.07 (M^+-PhCl), 425.05(M^+-$PhClNO_2$), 533.02 (M^+-NO_2),**^{1}HNMR: δ:** 1.60 (s, 3H), 4.40 (s, 4H), 6.48-6.98 (q, 4H), 7.00-7.94 (m, 6H), 8.11-8.14 (m, 10H), **^{13}CNMR**:**δ:** 187.63, 155.01, 150.90, 149.74, 142.39, 131.95, 131.15, 129.69, 128.30, 126.35, 123.83, 122.00, 120.88, 118.47, 110.14 (Ar-C), **Anal.Calcd. for** $C_{27}H_{17}Cl_2N_3O_6S$: C 55.67; H 2.92; N 7.20%

5-(4-chlorophenyl)-6-(3-(5-(2,3-dichlorophenyl)furan-2-yl)acryloyl)-7-methyl-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one(10)

Yield: 0.62 g (70%), **M.P:** 140^{0}C, **FTIR (υ, cm^{-1}):** 2339.89 (Ar-H), 1664.73(C=O), 1590.64(C=C) , 1028.07 (C-Cl bond), **Mass Spectra m/z (%):** $C_{27}H_{17}Cl_3N_2O_4S$: 567.96 (M^+), 533.03 (M^+-Cl), 552.95 (M^+-CH_3), 425.02 (M^+-$PhCl_2$), 533.05 (M^+-PhCl), **^{1}HNMR: δ:** 7.32-7.96 (m, 6H), 9.73 (s, 4H), **^{13}CNMR: δ:** 113.93, 127.57, 127.62, 129.84, 130.99, 151.79, 154.76, 177.56, **Anal.Calcd.for** $C_{27}H_{17}Cl_3N_2O_4S$: C 56.70; H 3.00; N 4.90%

5-(4-chlorophenyl)-6-(3-(5-(3-chlorophenyl)furan-2-yl)acryloyl)-7-methyl-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one (11)

Yield: 0.60 g (68%), **M.P:** 130^{0}C, **FTIR (υ, cm^{-1}):** 2360.08 (Ar-H), 1661.90(C=O), 1586.59(C=C), 1022.88 (C-Cl), **Mass Spectra m/z (%):** $C_{27}H_{18}Cl_2N_2O_4S$: 535.40 (M^+), 499.03 (M^+-Cl), 519.0 (M^+-CH_3), 423.01 (M^+-PhCl), 425.03(M^+-PhCl), **^{1}HNMR: δ:** 7.00-7.96 (m, 5H), **^{13}CNMR: δ:** 110.51, 11.06, 123.31, 123.97, 124.21, 125.06, 128.97, 129.50, 129.87, 130.74, 131.44, 131.67, 131.76, 134.47, **Anal.Calcd.for** $C_{27}H_{18}Cl_2N_2O_4S$: C 60.33; H 3.37; N 5.20%

5-(4-chlorophenyl)-6-(3-(5-(4-chlorophenyl)furan-2-yl)acryloyl)-7-methyl-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one(12)

Yield: 0.55 g (64%), **M.P:** 145^{0}C, **FTIR (υ, cm^{-1}):** 2341.92 (Ar-H), 1656.89 (C=O), 1582.98 (C=C), 1024.07 (C-Cl), **Mass Spectra m/z (%):** $C_{27}H_{18}Cl_2N_2O_4S$: 536.40 (M^+), 536.40 (M^+-Cl), 520.02 (M^+-CH_3), 424.02 (M^+-PhCl), 500.05(M^+-Cl), **^{1}HNMR: δ:** 6.75-6.86 (m, 6H), 7.03-7.80 (m, 10H), 9.68 (s, 2H), **^{13}CNMR: δ:** 127.22, 129.81, 178.36, DMSO peak 39.36-40.61, **Anal.Calcd.for** $C_{27}H_{18}Cl_2N_2O_4S$: C 60.33; H 3.37; N 5.20%

5-(4-chlorophenyl)-6-(3-(5-(4-ethoxyphenyl)furan-2-yl)acryloyl)-7-methyl-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one(13)

Yield: 0.65 g (70%), **M.P:** 130^{0}C, **FTIR (υ, cm^{-1}):** 2338.69 (Ar-H), 1664.19 (C=O), 1589.57 (C=C) , 1715.45 (C=O), **Mass Spectra m/z (%):** $C_{29}H_{23}ClN_2O_5S$: 546.02 (M^+), 510.12 (M^+-Cl), 530.05 (M^+-CH_3), 434.05 (M^+-PhCl), 425.05(M^+-PhOCH_2CH_3), 500.05 (M^+-OCH_2CH_3), **^{1}HNMR: δ:** 1.12-1.47 (m, 4H), 2.08-2.64 (d, 3H), 3.01 (s, 1H), 4.43-4.45 (d, 4H), 7.04-7.87(m, 10H), 8.13-8.15 (d, 4H), **^{13}CNMR: δ:** 187.87, 152.06, 149.80, 149.43, 147.21, 142.28, 134.03, 132.37, 130.40, 130.91, 127.95, 130.29, 129.77, 129.55, 124.00, 122.36, 119.75, 113.54 (Ar-C), **Anal.Calcd.for** $C_{27}H_{23}ClN_2O_4S$: C 63.66; H 4.22; N 5.10%

4-(5-(3-(5-(4-chlorophenyl)-7-methyl-4-oxo-2-thioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidin-6-yl)-3-oxoprop-1-en-1-yl)furan-2-yl)benzoic acid (14)

Yield: 0.66 g (73%), **M.P:** 160^{0}C, **FTIR (υ, cm^{-1}):** 2361.27 (Ar-H), 1664.18 (C=O), 1584.49 (C=C), 3343.44 (-OH),1701.87 (C=O), **Mass Spectra m/z (%):** $C_{28}H_{19}ClN_2O_6S$: 545.95 (M^+), 510.07 (M^+-Cl), 530.05 (M^+-CH_3), 434.05 (M^+-PhCl), 425.05(M^+-PhCO_2H), 500.05 (M^+-COOH), **^{1}HNMR: δ:** 1.12-1.28 (t, 4H), 7.04-7.73(m, 6H), **^{13}CNMR: δ:** 187.97(C=O), 129.86, 127.54 (C=C), 151.25, 150.68, 142.27, 132.68, 132.54, 130.98, 129.76, 129.60, 129.35, 129.03, 128.91, 128.27, 127.73, 124.97, 120.04, 115.16 (Ar-C), **Anal.Calcd.for** $C_{28}H_{19}ClN_2O_6S$: C 61.47; H 3.49; N 5.85%

4-(5-(3-(5-(4-chlorophenyl)-7-methyl-4-oxo-2-thioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidin-6-yl)-3-oxoprop-1-en-1-yl)furan-2-yl)benzenesulfonic acid(15)

Yield: 0.75 g (84%), **M.P:** 155^{0}C, **FTIR (υ, cm^{-1}):** 2368.02 (Ar-H), 1662.07 (C=O), 1587.94(C=C) 1107.92(C-Cl), **Mass Spectra m/z (%):** $C_{27}H_{19}ClN_2O_7S_2$: 582.02 (M^+), 545.05 (M^+-Cl), 565.05 (M^+-CH_3), 470.03 (M^+-PhCl), 425.03(M^+-PhSO_3H), 500.03 (M^+-SO_3H), **^{1}HNMR: δ:** 2.0 (s, 1H) 2.24 (s, 3H) 7.17-7.37 (m, 4H) 7.92-8.07 (m, 6H), **^{13}CNMR: δ:** 178.36 (C=O), 131.01, 124.87 (C=C), 155.47, 152.23,

148.57, 130.93, 130.70, 130.42, 129.75, 123.90, 123.06, 122.35, 120.62, 119.21, 118.66, 111.67, 110.83 (Ar-C), **Anal.Calcd.For** $C_{27}H_{19}ClN_2O_7S_2$: C 55.61; H 3.26; N 4.81%

5-(4-chlorophenyl)-6-(3-(5-(2-hydroxyphenyl)furan-2-yl)acryloyl)-7-methyl-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one(16)

Yield: 0.72 g (80%), **M.P:** 135^0C, **FTIR (υ, cm^{-1}):** 2361.78 (Ar-H), 1651.46 (C=O), 1586.88 (C=C), 1098.52 (C-Cl), 2981.28 (-OH), **Mass Spectra m/z (%):** $C_{27}H_{19}ClN_2O_5S$: 517.94 (M^+), 482.06 (M^+-Cl), 502.02 (M^+-CH_3), 406.05 (M^+-PhCl), 425.03(M^+-PhOH), 500.02 (M^+-OH), **^{1}HNMR: δ:** 1.24-1.55 (d, 4H), 5.41(s, 5H), 6.46-6.98 (d, 6H), 7.0-7.82(m, 8H), **^{13}CNMR: δ:** 178.24(C=O), 130.23, 128.18 (C=C), 154.90, 153.17, 147.14, 133.02, 132.51, 129.73, 129.08, 123.95, 124.42, 123.58, 122.99, 122.32, 119.75, 112.94, 112.30 (Ar-C)**, Anal.Calcd.for** $C_{27}H_{19}ClN_2O_5S$ C 62.48; H 3.68; N 5.41%

6-(3-(5-(4-chloro-2-hydroxyphenyl)furan-2-yl)acryloyl)-5-(4-chlorophenyl)-7-methyl-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one(17)

Yield: 0.69 g (78%), **M.P:** 170^0C, **FTIR (υ, cm^{-1}):** 2362.60(Ar-H), 1655.89 (C=O), 1590.67(C=C), 3262.34 (-OH), 1091.05 (C-Cl)**, Mass Spectra m/z (%):** $C_{27}H_{18}Cl_2N_2O_5S$: 553.42 (M^+), 517.04 (M^+-Cl), 537.02 (M^+-CH_3), 441.02 (M^+-PhCl), 425.05(M^+-PhOHCl), 535.02 (M^+-OH), **^{1}HNMR: δ:** 1.59 (s, 2H), 5.41 (s, 3H), 7.56-7.69 (m, 6H) 9.52 (s, 2H), **^{13}CNMR: δ:** 187.67 (C=O), 131.08, 128.48 (C=C), 154.44, 151.11, 149.74, 142.33, 133.95, 131.10, 130.86, 129.73, 123.89, 123.82, 123.00, 120.71, 118.77, 110.69 (Ar-C), **Anal.Calcd.for** $C_{27}H_{19}ClN_2O_5S$: C 58.61; H 3.26; N 5.05%

5-(4-chlorophenyl)-7-methyl-6-(3-(5-(2-nitrophenyl)furan-2-yl)acryloyl)-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one(18)

Yield: 0.68 g (75%), **M.P:** 130^0C, **FTIR (υ, cm^{-1}):** 2362.34 (Ar-H), 1667.89 (C=O), 1570.45(C=C), 1533.08 and 1358.00 (-NO_2), 1091.23 (C-Cl), **Mass Spectra m/z (%):$C_{27}H_{18}ClN_3O_6S$: 546.95** (M^+), 510.06 (M^+-Cl), 530.01 (M^+-CH_3), 434.03 (M^+-PhCl), 425.03(M^+-PhNO_2), 500.03 (M^+-NO_2), , **^{1}HNMR: δ:** 1.59 (s, 2H), 6.33-6.99 (q, 5H), 7.01-7.44 (m, 6H), 8.54 (s, 2H), **^{13}CNMR: δ:** 188.12 (C=O), 130.89, 127.11 (C=C), 152.95, 150.46, 149.07, 142.64, 131.32, 130.99, 129.64, 128.52, 127.12, 123.65, 114.19, 109.45 (Ar-C), **Anal.Calcd. For** $C_{27}H_{18}ClN_3O_6S$: C 59.17; H 3.30; N 7.66%

7-methyl-5-(3-nitrophenyl)-6-(3-(5-(3-nitrophenyl)furan-2-yl)acryloyl)-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one (19)

Yield: 0.60 g (68%) , **M.P:** 145^{0}C, **FTIR (υ, cm^{-1}):** 2359.78 (Ar-H) 1651.42(C=O), 1589.25(C=C), 1526.37 and 1351.70 (-NO_2),**Mass Spectra m/z (%):** $C_{27}H_{18}N_4O_9$: 542.40 (M^+), 496.10 (M^+-NO2), 527.05 (M^+-CH_3), 420. 07(M^+-PhNO_2), 420.07 (M^+-PhNO_2), **^{1}HNMR: δ:** 1.58 (s, 3H), 5.41 (s, 4H), 7.56-7.73 (q, 5H), 8.14-8.38 (m, 6H), 9.70(s. 2H), **^{13}CNMR: δ:** 188.65 (C=O), 131.24, 127.65 (C=C) 155.43, 151.78, 146.89, 141.32, 137.98, 134.26, 133.89, 126.45, 122.62, 121.60, 119.92, 109.65 (Ar-C), **Anal.Calcd.for** $C_{27}H_{18}N_4O_9$**:** C 59.76, H 3.32, N 10.32%

7-methyl-5-(3-nitrophenyl)-6-(3-(5-(4-nitrophenyl)furan-2-yl)acryloyl)-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one (20)

Yield: 0.68 g (76%), **M.P:** 140^{0}C **FTIR (υ, cm^{-1}):** 2360.10 (Ar-H), 1662.46 (C=O), 1593.43 (C=C), 1551.32 and 1351.64 (-NO_2) **Mass Spectra m/z (%):** $C_{27}H_{18}N_4O_9$: 542.44(M^+), 496.10 (M^+-NO2), 527.05 (M^+-CH_3), 420.07 (M^+-PhNO_2), **^{1}HNMR: δ:** 1.54 (s, 3H), 7.60-7.73(t, 6H), 8.13-8.39 (q, 6H), 9.70 (s, 4H), **^{13}CNMR: δ:** 188.00 (C=O), 131.25, 129.74, (C=C) 21.86 (CH_3) 153.26, 151.24, 149.77, 146.29, 142.79, 142.38, 133.04, 124.01, 123.93, 122.78, 120.04, 119.50, 114.31 (Ar-C) , **Anal.Calcd.For** $C_{27}H_{18}N_4O_9$**:** C 59.77; H 3.32; N 10.32%

7-methyl-5-(3-nitrophenyl)-6-(3-(5-(2-nitrophenyl)furan-2-yl)acryloyl)-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one(21)

Yield: 0.27g, **M.P:** 150^{0}C, **FTIR (υ, cm^{-1}):** 2342.93 (Ar-H), 1596.43 (C=C), 1437.64 and 1334.74(-NO_2), **Mass Spectra m/z (%):**$C_{27}H_{18}N_4O_9$: 542.44(M^+), 496.10 (M^+-NO2), 527.05 (M^+-CH_3), 420.05 (M^+-PhNO_2), , **^{1}HNMR: δ:** 13.76 (s, 1H) 7.62-8.13 (m, 4H) 7.67-8.05 (m, 4H) 2.24 (d, 3H) 3.94 (q, 1H), **^{13}CNMR: δ:** 188.67 (C=O), 130.76, 129.85, (C=C) 153.78, 152.84, 129.11, 126.09, 123.93, 122.56, 120.88, 120.07, 117.27 (Ar-C), **Anal.Calcd. for** $C_{27}H_{18}N_4O_9$: C 59.76; H 3.32; N 10.32%

7-methyl-6-(3-(5-(2-methyl-5-nitrophenyl)furan-2-yl)acryloyl)-5-(3-nitrophenyl)-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one (22)

Yield: 0.65 g (70%), **M.P:** 160^{0}C, **FTIR (υ, cm^{-1}):** 2362.31(Ar-H), 1688.76 (C=O), 1586.71(C=C), 1539.10 and 1348.23 (-NO_2), **Mass Spectra m/z (%):** $C_{28}H_{20}N_4O_9$: 556.46(M^+), 510.12 (M^+-NO2), 541.08 (M^+-CH_3), 419.05 (M^+-PhNO_2), 420.07 (M^+-PhMeNO_2), **^{1}HNMR: δ:** 2.24 (s, 3H) 2.59 (m, 3H) 7.03 (s, 3H) 7.66 (q, 1H) 7.55-8.53 (m, 6H) 13.76 (s, 2H), **^{13}CNMR: δ:** 187.80 (C=O), 166.26 (C=O of

ester) 131.24, 127.76 (C=C) 155.39, 152.09, 137.83, 133.65, 132.97, 130.66, 127.18, 126.45, 122.78, 119.68, 110.98 (Ar-C), 16.76 (CH_3), **Anal.Calcd.for** $C_{28}H_{20}N_4O_9$**:** C 60.42; H 3.60; N 10.06%

6-(3-(5-(2,4-dichlorophenyl)furan-2-yl)acryloyl)-7-methyl-5-(3-nitrophenyl)-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one (23)

Yield: 0.71 g (80%), **M.P:** 130^0C, FTIR (υ, cm^{-1}): 2361.76 (Ar-H), 1690.89 (C=O), 1576.33 (C=C), 1553.34 and 1347.01 (-NO_2), 1089.03 (C-Cl**), Mass Spectra m/z (%):** $C_{27}H_{17}Cl_2N_3O_6S$: 582.40(M^+), 535.02 (M^+-NO_2), 566.00 (M^+-CH_3), 436.04 (M^+-$PhCl_2$), 546.04 (M^+-PhCl), **^{1}HNMR: δ:** 2.24 (d, 3H) 3.94 (q, 1H) 7.59-8.07 (m, 4H) 13.7 (d, 1H), **^{13}CNMR: δ:** 188.39 (C=O), 130.72, 128.21 (C=C) 155.45, 151.24, 139.17, 136.55, 134.50, 129.83, 129.16, 128.94, 128.27, 125.71, 119.22, 118.35, 114.98, 108.69 (Ar-C), **Anal.Calcd. for** $C_{27}H_{17}Cl_2N_3O_6S$: C 55.66; H 2.92; N 12.15%

6-(3-(5-(2,3-dichlorophenyl)furan-2-yl)acryloyl)-7-methyl-5-(3-nitrophenyl)-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one (24)

Yield: 0.75 g (83%), **M.P:** 150^0C, **FTIR (υ, cm^{-1}):** 2363.34 (Ar-H), 1679.90 (C=O), 1578.54 (C=C), 1552.32 and 1344.23 (-NO_2), 1094.03 (C-Cl), **Mass Spectra m/z (%):** $C_{27}H_{17}Cl_2N_3O_6S$: 582.40 (M^+), 535.04 (M^+-NO2), 566.00 (M^+-CH_3), 459.01 (M^+-$PhNO_2$), 436.01 (M^+-$PhCl_2$), 546.05(M^+-Cl), **^{1}HNMR: δ**: 2.24 (d, 3H) 3.94 (q, 1H) 7.03-7.66 (q, 2H) 7.33-7.59 (m, 4H), **^{13}CNMR: δ:** 188.15(C=O), 130.06, 128.95, (C=C), 152.44, 150.54, 139.33, 136.33, 131.91, 129.89, 129.61, 129.30, 128.99, 128.15, 127.95, 123.99, 123.13, 119.68, 118.03, 112.32 (Ar-C) , **Anal.Calcd.for** $C_{27}H_{17}Cl_2N_3O_6S$**:** C 55.66; H 2.92; N 12.15%

6-(3-(5-(2-chloro-5-nitrophenyl)furan-2-yl)acryloyl)-7-methyl-5-(3-nitrophenyl)-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one (25)

Yield: 0.70 g (78%), **M.P:** 140^0C, **FTIR (υ, cm^{-1}):** 2360.52 (Ar-H), 1665.12 (C=O), 1589.39 (C=C), 1568.59 and 1348.50 (-NO_2), 1088.29 (C-Cl) , **Mass Spectra m/z (%):** $C_{27}H_{17}ClN_4O_8S$: 592.94 (M^+), 546.04 (M^+-NO2), 577.01 (M^+-CH_3), 470.01 (M^+-$PhNO_2$), 436.05(M^+-PhClNO2), 557.07(M^+-Cl), **^{1}HNMR: δ:** 1.11-1.58 (t, 3H), 2.10-2.64(d, 4H), 6.83 (s, 5H), **^{13}CNMR: δ:** 188.17(C=O), 132.09, 129.89, (C=C), 156.93, 152.72 149.40, 146.86, 140.39, 139.43, 136.29, 135.00, 134.74, 133.91, 129.72, 129.55 124.22, 120.09, 117.90, 112.74 (Ar-C) , **Anal.Calcd.for** $C_{27}H_{17}ClN_4O_8S$: C 54.68; H 2.88; N 9.44%

6-(3-(furan-2-yl)acryloyl)-7-methyl-5-(3-nitrophenyl)-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one (26)

Yield: 0.66 g (70%), **M.P:** 130^{0}C, **FTIR (υ, cm^{-1}):** 2355.78 (Ar-H), 1645.34 (C=O), 1612.31 (C=C), 1578.10 and 1368.75 (-NO_2),**Mass Spectra m/z (%):** $C_{21}H_{15}N_3O_6S$: 437.43(M^+), 391.07(M^+-NO2), 577.01 (M^+-CH_3), 315.03 (M^+-PhNO_2), **^{1}HNMR: δ:** 1.60 (s, 3H), 2.52 (s, 4H), 4.64(s, 4H), 5.44 (s, 3H), 6.34-6.68 (q, 4H), 7.45-7.93 (m, 5H), 8.52 (s, 4H), 10.29 (s, 3H), **^{13}CNMR: δ:** 189.15(C=O), 130.70, 129.82, (C=C), 153.70, 151.28 139.17, 135.45, 133.67, 132.09, 128.94, 125.93, 122.69, 119.20, 118.40, 108.78 (Ar-C), **Anal.Calcd.for** $C_{21}H_{15}N_3O_6S$: C 57.65; H 3.45; N 9.60%

Ethyl-4-(5-(3-(7-methyl-5-(3-nitrophenyl)-4-oxo-2-thioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidin-6-yl)-3-oxoprop-1-en-1-yl)furan-2-yl)benzoate (27)

Yield: 0.65 g (72%), **M.P:** 140^{0}C, **FTIR (υ, cm^{-1}):** 2363.12 (Ar-H), 1690.04 (C=O), 1589.90 (C=C), 1534.56 and 1390.63 (-NO_2), 1712.90 (C=O ester) , **Mass Spectra m/z (%):** $C_{30}H_{23}N_3O_8S$: 585.57 (M^+), 539.12 (M^+-NO2), 570.09 (M^+-CH_3), 314.03 (M^+-PhCO_2Et), 4512.08(M^+-CO_2Et), **^{1}HNMR: δ:** 1.29 (q, 3H) 2.24 (m, 3H) 3.94 (m, 1H) 7.59-7.94 (m, 6H), **^{13}CNMR: δ:** 188.41(C=O), 130.46, 129.90, (C=C), 151.31, 151.25, 139.32, 136.43, 133.13, 132.13, 129.55, 129.05, 127.92, 127.51, 119.57, 118.60, 114.71, 112.79, 110.18, 108.20 (Ar-C), **Anal. Calcd. For** $C_{30}H_{23}N_3O_8S$: C 61.52; H 3.95; N 7.17%

Methyl-4-(5-(3-(7-methyl-5-(3-nitrophenyl)-4-oxo-2-thioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidin-6-yl)-3-oxoprop-1-en-1-yl)furan-2-yl)benzoate (28)

Yield: 0.8 g (85%), **M.P:** 150^{0}C, **FTIR (υ, cm^{-1}):** 2362.31(Ar-H), 1688.76 (C=O), 1586.71(C=C), 1539.10 and 1348.23 (-NO_2),**Mass Spectra m/z (%):** $C_{29}H_{21}N_3O_8S$: 571.55 (M^+), 525.10 (M^+-NO2), 556.09 (M^+-CH_3), 449.07 (M^+-PhNO_2), 436.08 (M^+-PhCO2CH3), 512.08(M^+-CO_2CH_3), **^{1}HNMR: δ:** 1.33-1.37 (q, 5H), 2.55 (s, 3H), 4.33-4.38(q, 5H), 5.38-5.41 (d, 5H), 7.33-7.86 (q,5H)), 8.02-8.09 (m,6H), **^{13}CNMR: δ:** 187.46(C=O), 130.04, 126.44 (C=C), 151.02, 150.77, 138.08, 136.08, 133.45, 130.39, 130.31, 130.13, 129.90, 129.76, 129.30, 128.91, 128.79, 128.74, 119.39, 113.59 (Ar-C), **Anal.Calcd.for** $C_{29}H_{21}N_3O_8S$: C 60.93; H 3.70; N 7.34%

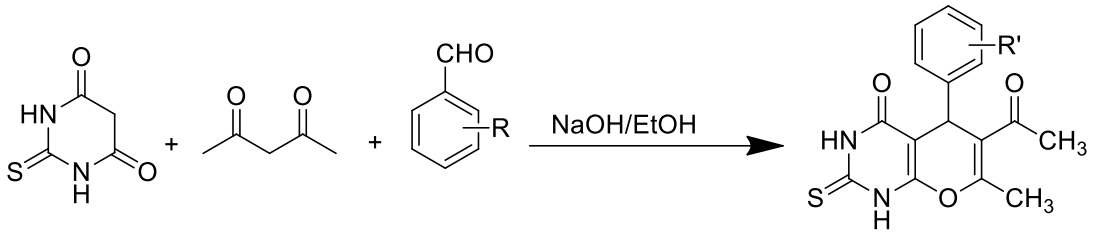
7-methyl-5-(3-nitrophenyl)-6-(3-(5-(2-nitrophenyl)furan-2-yl)acryloyl)-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d]pyrimidin-4(5H)-one (29)

Yield: 0.75 g (85%), **M.P:** 120^{0}C, **FTIR (υ, cm^{-1}):** 2363.21(Ar-H), 1691.24 (C=O), 1582.54(C=C), 1545.30 and 1346.34 (-NO_2),, **Mass Spectra m/z (%):** $C_{27}H_{18}N_4O_8S$: 558.51(M^+), 512.09 (M^+-NO_2), 543.05 (M^+-CH_3), 436.05 (M^+-PhNO_2), , **^{1}HNMR: δ:** 1.24-1.57 (s, 4H), 4.40 (d, 5H), 5.41 (d, 3H), 6.45-

6.98 (m, 6H), 7.0-7.95(m, 8H), **^{13}CNMR: δ:** 188.29(C=O), 130.39, 129.89, (C=C), 153.73, 153.70 148.91, 139.39, 136.41, 131.38, 129.72, 129.45, 129.03, 128.83, 122.88, 119.47, 118.74, 118.08, 110.44, 108.36 (Ar-C), **Anal.Calcd.for** $C_{27}H_{18}N_4O_8S$**:** C 58.05; H 3.24; N 10.02%

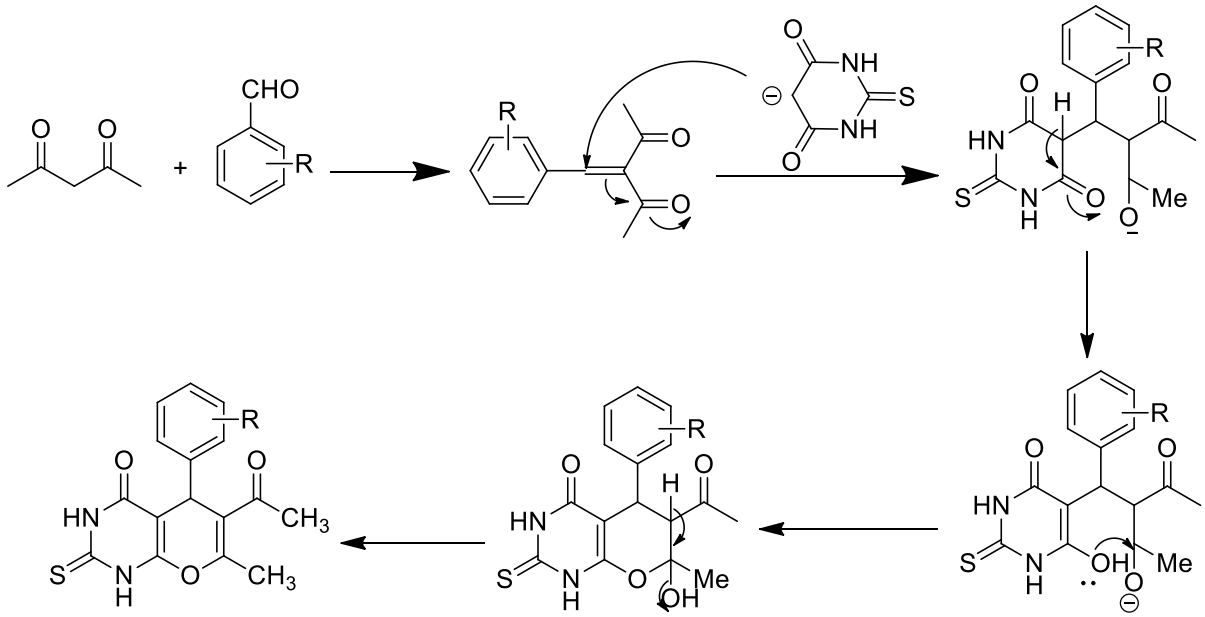
Results and Discussion:

Herein, we prepared thioxopyrano[2,3-d]pyrimidines (**5 and 6**) from the reaction of substituted benzaldehydes with thiobarbituric acid and acetylacetone in the presence of basic catatlyst in refluxing Ethanol **Scheme 1.** A reasonable mechanism for the formation of targeted products via three component reaction is outlined in (**Scheme 2**). Then these pyrano[2,3-d]pyrimidines reacted with 5-Arylfuran-2-carbaldehydes in the presence of basic media to synthesized a series of chalchones **7-29** by Claisen-Schmidt condensation **Scheme 3.**

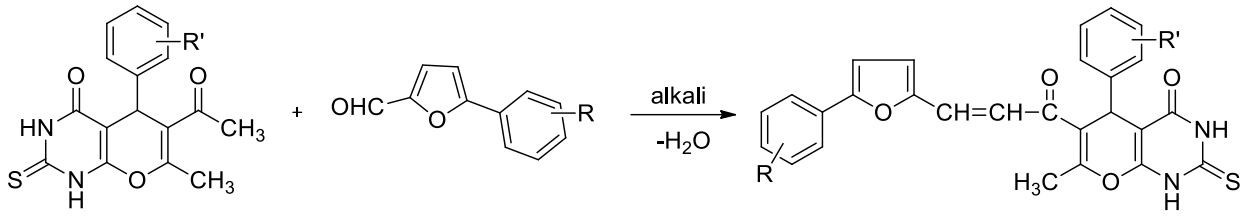


Scheme 1

Mechanism:



Scheme 2



Scheme 3

The structure of prepared compound (**7-29**) were confirmed by FTIR, Mass spectra, ^{1}H-NMR, ^{13}C-NMR and CHN analysis and data is presented in experimental section.

FTIR analysis:

Assignment of selected characteristics IR absorption bands provides significant indication for the formation of acetyl thioxo pyrano[2,3-d]pyrimidine **6, 7** and their chalcones derivatives **7-29**. The carbonylic group (C=O) of starting material and chalcones absorbed in the expected regions; (C=O) in the 1610-1681cm^{-1}, while NO_2 group present in some compounds shows stretching of N-O shifts to low wave numbers of 1530-1460cm^{-1} and 1350-1300cm^{-1}. Asymmetrical vibrations occur 1540cm^{-1} and symmetrical vibrations present near 1540cm^{-1} While CONHCO- g peaks have been observed in all compounds in region of 4000-400cm^{-1}. In synthesis of chalcone NH shows stretching vibrations in region of 3000-2840cm^{-1} in strong region with broad band. Chloro group attached to carbon in compound shows medium absorption in region of 800-490cm^{-1}. Methyl -CH_3 group also shows strong band in region of 1360cm^{-1}. C-O give rise intense peak and observed in region of 1300-980cm^{-1} due to high polarity of bond. In benzene ring C-H stretching vibrations occurs between 3100-3000cm^{-1} and benzene is substituted with other group so shows intense band of 800cm^{-1}. However C=S bond shows IR peak at 1030cm^{-1} while S-O stretching vibrations appear in region of 1200cm^{-1} . Amines –NH shows medium stretching vibration in region of 3400cm^{-1} when primary amines are present in compound. While ester group present in compound **27,28** shows intense peak around 1650cm^{-1}, O-H bond also appear shows sharp peak near 3600cm-1 in compound **11**. While compound 9 having SO3H group shows IR spectra peak near 1200-1000cm^{-1} .

^{1}H-NMR analysis:

The ^{1}H-NMR spectra (300 MHz, $CDCl_3$) of chalcones CH=CH shows characteristic signals between 7.32-7.53 ppm (d, 1.59). While acetyl group gives value of chemical shift 2.1 ppm in the spectrum. Aromatic benzene shows chemical shift of 7.0ppm in ^{1}HNMR. Sometimes signals appear at 8.20 ppm if nitro group is directly attached to benzene ring. Ortho protons are more deshielded as compare to para and then meta.

The ^{1}H NMR spectrum of the compounds (**7-29**) showed the H–peak at δH 9.35-10.99 due to the N protons in the compound which were strongly de-shielded and appeared as singlet in the ^{1}H NMR spectrum. The aromatic protons of all compounds showed chemical shift at δH 6.72-7.91 in their nmr spectrum. NH protons shows chemical shift value between 2-4 ppm in all synthesized compounds while NH_2 shows 6.5-7.1 ppm chemical shift value in ^{1}HNMR. O-H paak in compound 11 shows value of chemical shift near 1-6ppm. In compound 8 carboxylic acid –COOH appears 11-12ppm chemical shift in spectra. Aromatic aldehydes show 10ppm and Alkenes shows 3.7-6.4 value of chemical shift.

^{13}C-NMR analysis

Finally, ^{13}C-NMR (75 MHz $CDCl_3$) spectra of all compounds were recorded, and spectral signals are in good agreement with the structures. The carbon of C=O displayed signals at 170-220 ppm in the starting material due to sp^2 hybridization. The ^{13}C NMR spectrum of the benzene shows spectrum of 128ppm which shows one chemical environment of all carbons. Nitrobenzene shows chemical shift of 129.4 ppm and Carbonyl group in aldehyde shows 190-200ppm chemical shift value in all synthesized compounds due to smaller magnetic field require for higher chemical shift. In alkenes –C=C- peak value appear around 110-135ppm and 35-45ppm for amines RCH_2NH_2 in ^{13}C-NMR analysis of compounds. When methyl group attaches to alkyl group RCHE it shows peak around 10-15ppm in ^{13}C analysis.

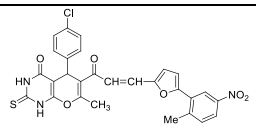
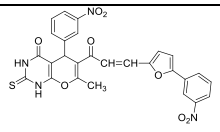
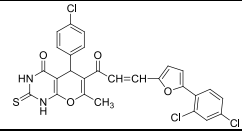
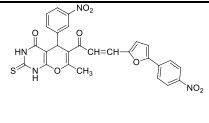
Mass spectra

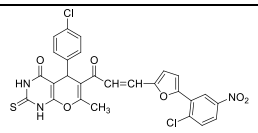
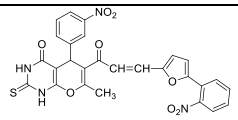
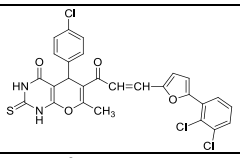
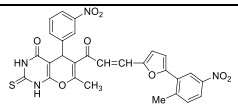
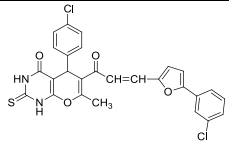
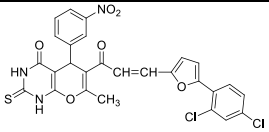
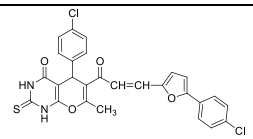
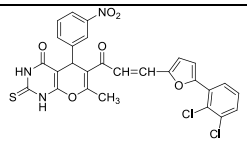
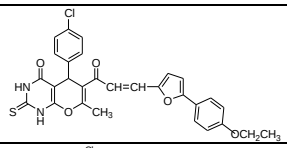
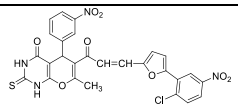
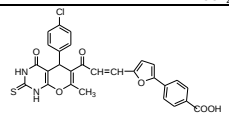
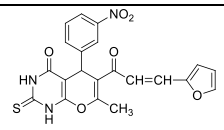
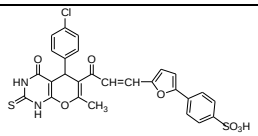
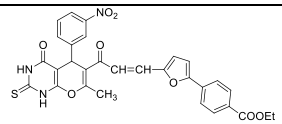
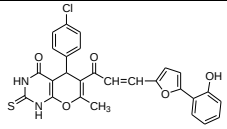
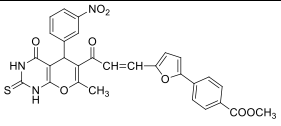
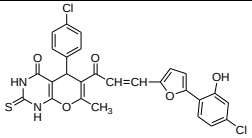
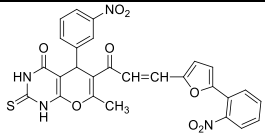
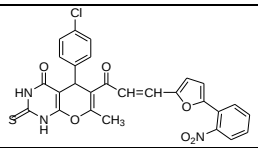
Mass spectra of all the compounds were recorded, and their values are given in the experimental section. These also help characterize the formation of acetyl pyrano[2,3-d]pyrimidine **5,6** as starting materials and their chalcones derivatives **7-29**. The molecular ion peaks in all of the new compounds were as predicted.

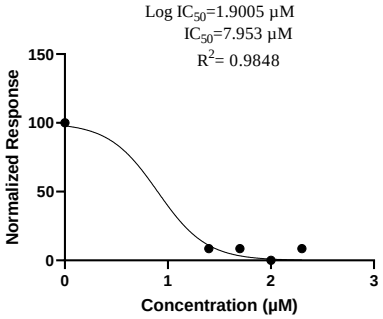
Antidiabetic Activity

The disease of high blood glucose levels is characterized as diabetes, which becomes a serious problem nowadays. So, the main goal of the scientist is to develop treatment or medication that can effectively treat diabetes by controlling the levels of blood sugar. Despite these developments, all the treatment modes and medications are still related to some side effects which open up the ways for further investigation. In this study, we have checked the antidiabetic activity of newly synthesized pyrano[2,3-d]pyrimidines (**7-29**) by in vitro alpha-amylase analysis. In vitro antidiabetic activity of all the synthesized compounds shown the results summarized in Table 1 and 2. Acarbose was used as a standard. The inhibitory effects of each synthesized compound were evaluated with the calculation of IC50 which interprets the concentration of the inhibitor that is required to inhibit 50% of its targeted enzyme. The lower IC50 values indicate the greater antidiabetic activity of compounds. In comparison to the overall result, almost all the compounds showed a strong inhibitory activity which may be attributed to the presence of pyrimidine ring in the synthesized compounds.

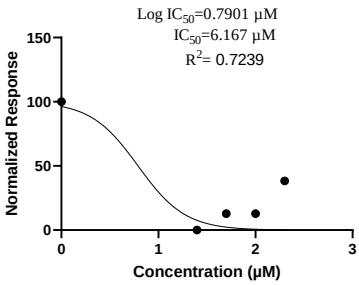
Table1. Antidiabetic activity of 6-acetyl-5-aryl-7-methyl-2-thioxo-2,3dihydro-1H-pyrano[2,3-d] pyrimidine-4(5H)-one 24

Sr. No	Structure	IC_{50}(µM)	Log IC_{50} (µM)	Sr No	Structure	IC_{50} (µM)	Log IC_{50} (µM)
7		7.953	1.9005	**19**		-	-
8		6.167	0.7901	**20**		45.46	1.658

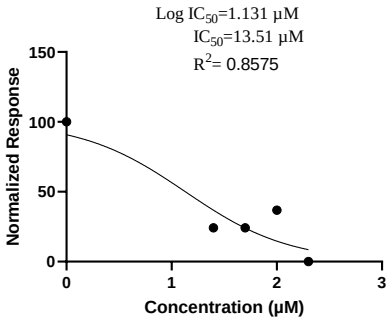
9		13.51	1.131	**21**		-	-
10		0.00	140069	**22**		7.468	0.8732
11		35.30	1.548	**23**		19.07	1.280
12		11.79	1.071	**24**		-	-
13		9.152	0.9615	**25**		5.120	0.7093
14		24.40	1.387	**26**		-	-
15		6.272	0.7974	**27**		-	-
16		5.070	1.7050	**28**		-	-
17		5.147	0.7115	**29**		-	-
18		-	-				


Log IC50=1.9005 µM
IC50=7.953 µM
R2= 0.9848
Normalized Response
Concentration (µM)

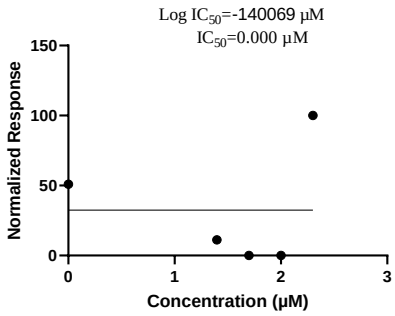
7


Log IC50=0.7901 µM
IC50=6.167 µM
R2= 0.7239
Normalized Response
Concentration (µM)

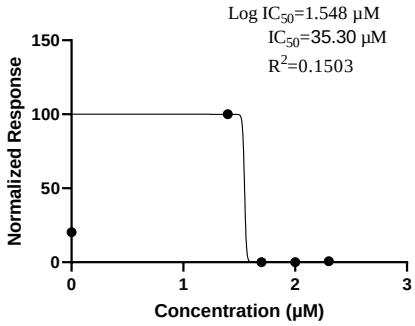
8


Log IC50=1.131 µM
IC50=13.51 µM
R2= 0.8575
Normalized Response
Concentration (µM)

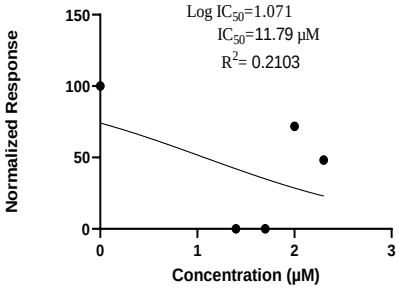
9


Log IC50=-140069 µM
IC50=0.000 µM
Normalized Response
Concentration (µM)

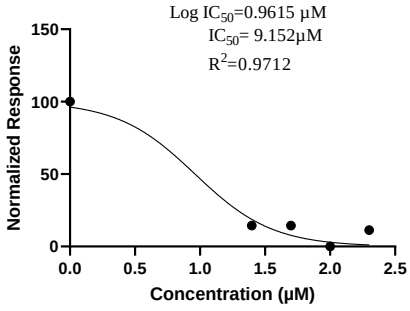
10


Log IC50=1.548 µM
IC50=35.30 µM
R2=0.1503
Normalized Response
Concentration (µM)

11


Log IC50=1.071
IC50=11.79 µM
R2= 0.2103
Normalized Response
Concentration (µM)

12



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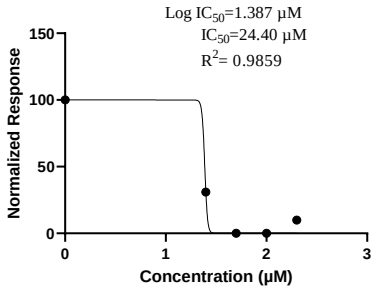

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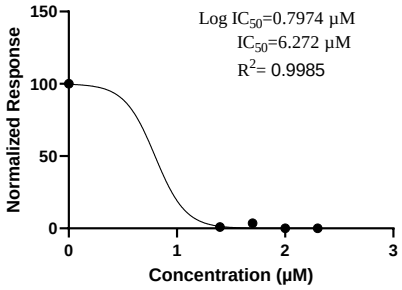

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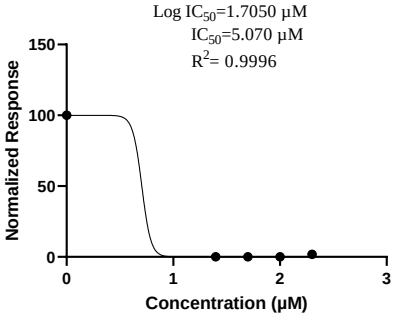

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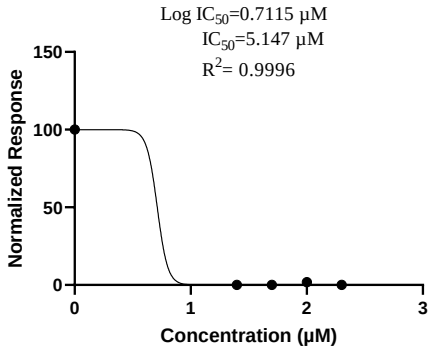

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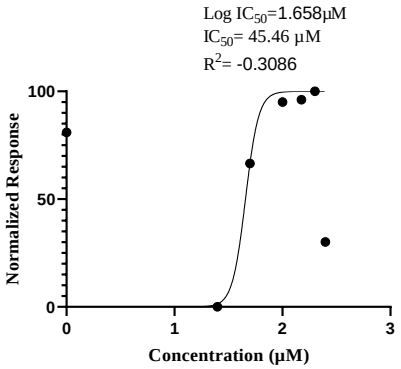

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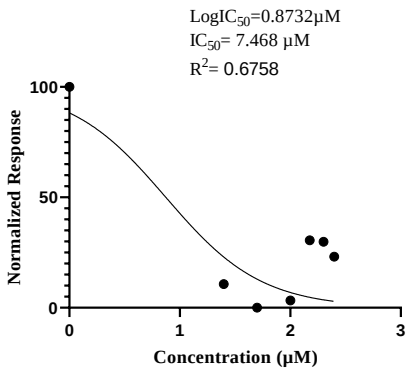

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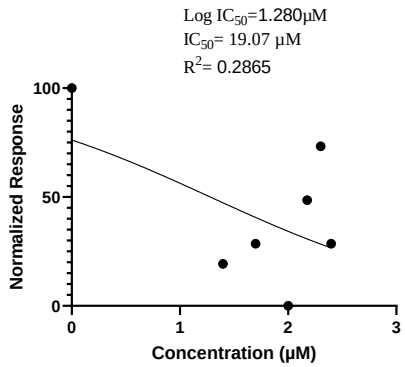

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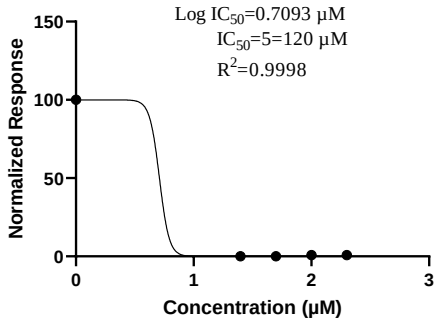

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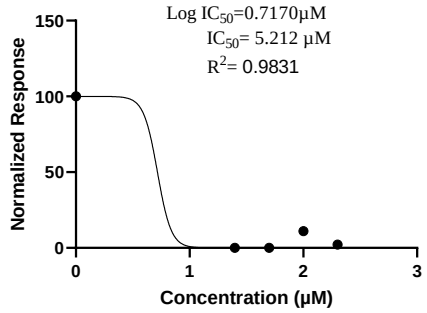
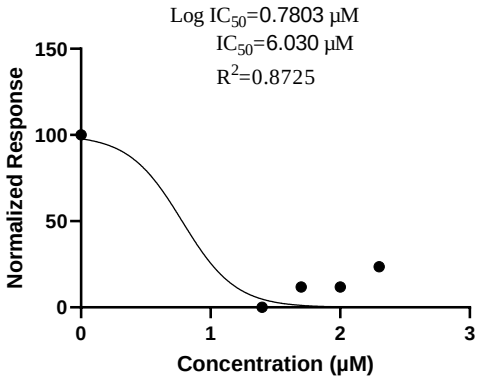
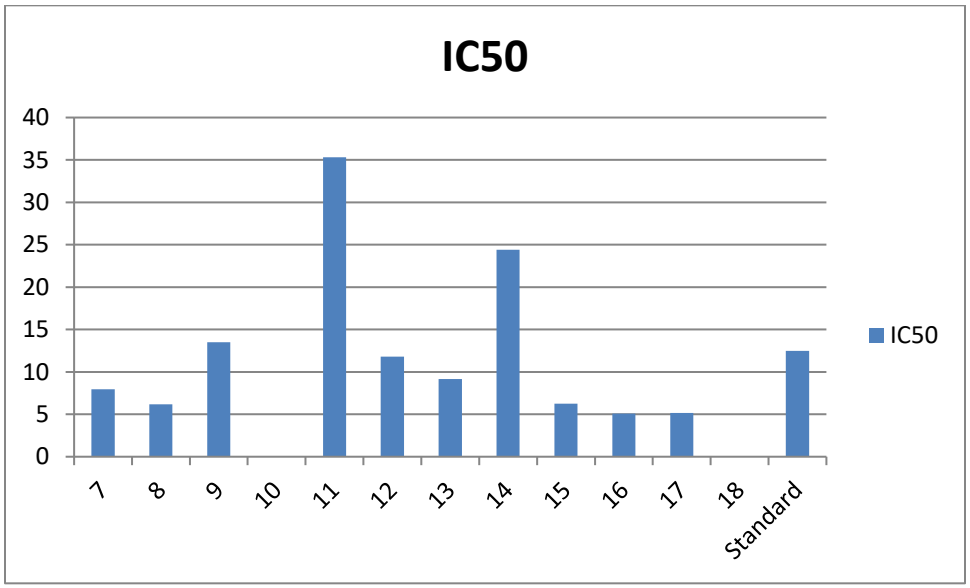


26



29

Fig 1: Graphical representation of anti-diabetic activity (7-29) and estimation of IC50 value by non-linear regression analysis in GraphPad Prism.



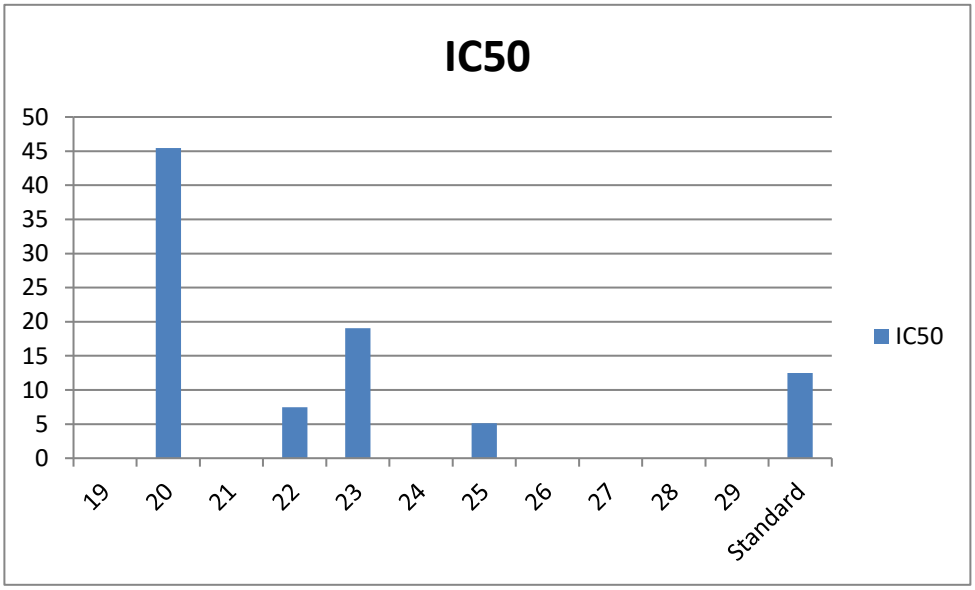


Fig 2: Graphical representation of IC50 value of chalcones derivatives of 6-acetyl-5-(4-chlorophenyl)-7-methyl-2-thioxo-2,3-dihydro-1H-pyrano[2,3-d] pyrimidine-4(5H)-one 1 (7-29)

Molecular Docking Studies:

Molecular Docking

Ligands with good inhibitory concentration (IC_{50}) further undergoes molecular docking to check the binding affinity of these ligands with the protein of alpha-amylase enzyme. Protein of alpha amylase enzyme researched from the literature and then their parameters check on the RCSB.PDB. Proteins with the organism *Homo sapiens* and resolution less than 2.0Å such as:

Pdb id	Protein name	Resolution	Organism
4W93	Human pancreatic alpha-amylase in complex with montbretin A	1.35 Å	*Homo sapiens*
1HNY	The structure of human pancreatic alpha-amylase at 1.8 angstroms resolution and comparisons with related enzymes	1.80 Å	*Homo sapiens*

Molegro virtual docker **(MVD)** used to check the binding affinity of ligands with these proteins on the bases of MolDock score. The range of MolDock score is in between -60 to -180. So, ligands will be screened out on the bases of this MolDock score.

4w93

All the selected ligands such as (**8, 16 and 22**) docked with protein 4W93. After the docking it has been shown that the ligand **8** has the best MolDock score -167.277 that is greater than all the above ligands. Ligand **8** shows 5 hydrogen bond amino acid interactions such as *ARG195, HIS299, HIS305, HIS301, TRP59 and 17 hydrophobic interactions. So with 4W93, **8** is the lead ligand due to its great binding affinity with protein.*

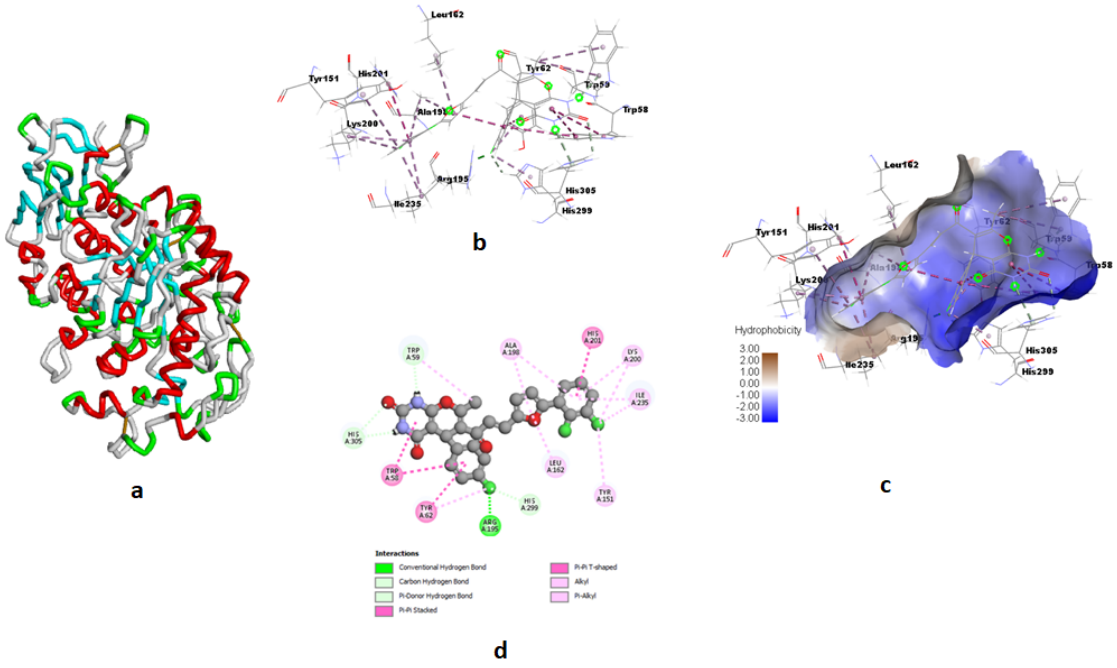


*Figure 1: a) Represents the protein structure b) interaction of 4W93 with ligand **8** along amino acid residue, c) Hydrophobic interaction of protein and ligand d) 2D structure of protein and ligand.*

1HNY

All the selected ligands such as (**8,16 and 22**) docked with protein 1HNY. After the visualization of docking results it has been seen that the ligand **8** has the best MolDock score -165.689 that is more than all the other ligands. 1HNY has the 3 hydrogen bond interaction with amino acid residue *ASP300, THR163, GLU233. . So with 1HNY, **8** is the lead ligand due to its great binding affinity with protein.*

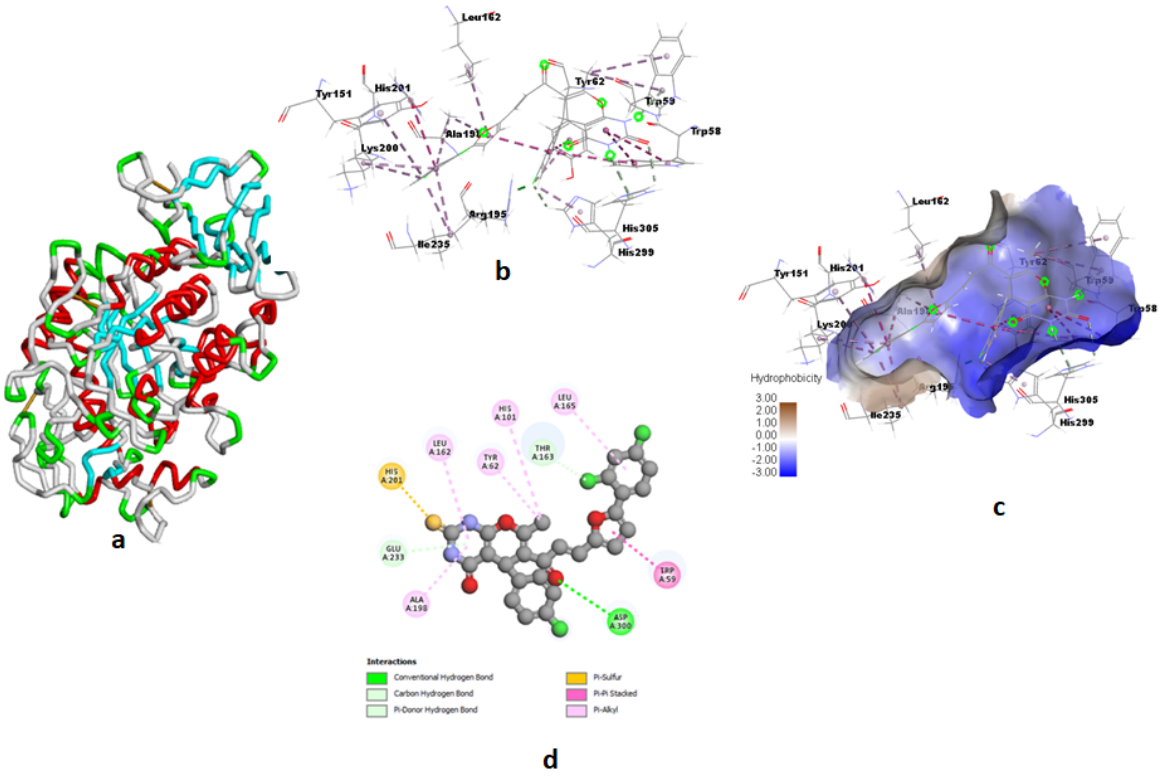


*Figure 2:a) Represents the protein structure b) interaction of 1HNY with **ligand 8** along amino acid residue, c) Hydrophobic interaction of protein and ligand d) 2D structure of protein and ligand.*

Table 3: Molecular Docking results of 6-acetyl-5-Aryl-7-methyl-1H-pyrano[2,3-d] pyrimidine-2,4(3H,5H)-dione derivatives (7-29)

Compound	*Protein*	*No.of interactions*	*Amino acid*	*Distance*	*Category*	*Type*	*MolDock score*
8	*4w93*	*1*	*GLU233*	*2.80725*	*Hydrogen Bond*	*Conventional Hydrogen*	*-167.277*
		2	*HIS299*	*2.96651*	*Hydrogen Bond*	*Carbon Hydrogen Bond*	
		3	*ASP300*	*3.79187*	*Hydrogen Bond*	*Pi-Donor Hydrogen Bond*	
		4	*ILE235*	*2.62134*	*Hydrophobic*	*Pi-Sigma*	
		5	*TRP58*	*4.79198*	*Hydrophobic*	*Pi-Pi Stacked*	
		6	*HIS305*	*5.18456*	*Hydrophobic*	*Pi-Pi Stacked*	
		7	*HIS201*	*4.85663*	*Hydrophobic*	*Pi-Pi T-shaped*	
		8	*HIS201*	*4.83799*	*Hydrophobic*	*Pi-Pi T-shaped*	
		9	*LYS200*	*5.00668*	*Hydrophobic*	*Alkyl*	
		10	*ILE235*	*4.59222*	*Hydrophobic*	*Alkyl*	
		11	*TYR62*	*4.52045*	*Hydrophobic*	*Pi-Alkyl*	
		12	*TYR151*	*4.74133*	*Hydrophobic*	*Pi-Alkyl*	
		13	*HIS299*	*3.95504*	*Hydrophobic*	*Pi-Alkyl*	
		14	*LEU162*	*4.95361*	*Hydrophobic*	*Pi-Alkyl*	
		15	*ALA198*	*3.99938*	*Hydrophobic*	*Pi-Alkyl*	
		16	*LYS200*	*4.80933*	*Hydrophobic*	*Pi-Alkyl*	
16		*1*	*GLN63*	*2.13439*	*Hydrogen Bond*	*Conventional Hydrogen Bond*	*149.509*
		2	*GLU233*	*1.98645*	*Hydrogen Bond*	*Conventional Hydrogen Bond*	
		3	*TRP59*	*2.79462*	*Hydrogen Bond*	*Carbon Hydrogen Bond*	
		4	*HIS101*	*2.97549*	*Hydrogen Bond*	*Carbon Hydrogen Bond*	
		5	*HIS101*	*3.13487*	*Halogen*	*Halogen (Cl, Br, I)*	
		6	*GLU233*	*4.01795*	*Hydrogen Bond*	*Pi-Donor Hydrogen Bond*	
		7	*TYR62*	*4.83035*	*Hydrophobic*	*Pi-Pi Stacked*	
		8	*LEU165*	*5.16261*	*Hydrophobic*	*Pi-Alkyl*	
		9	*LEU162*	*5.34819*	*Hydrophobic*	*Pi-Alkyl*	
		10	*ALA198*	*3.99332*	*Hydrophobic*	*Pi-Alkyl*	
22		*1*	*ASP300*	*2.75824*	*Hydrogen Bond*	*Conventional Hydrogen Bond*	*-157.952*
		2	*ASP300*	*3.78423*	*Hydrogen Bond*	*Pi-Donor Hydrogen Bond*	
		3	*ILE235*	*2.71698*	*Hydrophobic*	*Pi-Sigma*	
		4	*TRP58*	*4.71622*	*Hydrophobic*	*Pi-Pi Stacked*	
		5	*HIS305*	*5.48083*	*Hydrophobic*	*Pi-Pi Stacked*	
		6	*TYR62*	*4.94574*	*Hydrophobic*	*Pi-Pi T-shaped*	
		7	*HIS201*	*4.89207*	*Hydrophobic*	*Pi-Pi T-shaped*	
		8	*HIS201*	*4.69217*	*Hydrophobic*	*Pi-Pi T-shaped*	
		9	*LYS200*	*3.88294*	*Hydrophobic*	*Alkyl*	
		10	*ILE235*	*4.65671*	*Hydrophobic*	*Alkyl*	
		11	*TYR62*	*5.19683*	*Hydrophobic*	*Pi-Alkyl*	
		12	*HIS201*	*4.89774*	*Hydrophobic*	*Pi-Alkyl*	

		13	LEU162	4.99546	Hydrophobic	Pi-Alkyl	
		14	ALA198	3.99339	Hydrophobic	Pi-Alkyl	
		15	LYS200	4.62845	Hydrophobic	Pi-Alkyl	
8	1HNY	1	ASP300	3.30074	Hydrogen Bond	Conventional Hydrogen Bond	-165.689
		2	THR163	2.60756	Hydrogen Bond	Carbon Hydrogen Bond	
		3	GLU233	3.52271	Hydrogen Bond	Pi-Donor Hydrogen Bond	
		4	HIS201	4.21922	Other	Pi-Sulfur	
		5	TRP59	4.15547	Hydrophobic	Pi-Pi Stacked	
		6	TRP59	4.94641	Hydrophobic	Pi-Pi Stacked	
		7	TYR62	4.6124	Hydrophobic	Pi-Alkyl	
		8	HIS101	4.45735	Hydrophobic	Pi-Alkyl	
		9	LEU162	5.44069	Hydrophobic	Pi-Alkyl	
		10	ALA198	4.34048	Hydrophobic	Pi-Alkyl	
		11	LEU165	5.33481	Hydrophobic	Pi-Alkyl	
16		1	GLN63	1.8558	Hydrogen Bond	Conventional Hydrogen Bond	-150.151
		2	ASP197	1.93771	Hydrogen Bond	Conventional Hydrogen Bond	
		3	GLU233	3.02675	Hydrogen Bond	Conventional Hydrogen Bond	
		4	TRP59	2.44136	Hydrogen Bond	Carbon Hydrogen Bond	
		5	HIS101	2.85708	Hydrogen Bond	Carbon Hydrogen Bond	
		6	HIS305	2.2557	Hydrogen Bond	Carbon Hydrogen Bond	
		7	GLU233	3.62283	Hydrogen Bond	Pi-Donor Hydrogen Bond	
		8	ASP300	3.33059	Hydrogen Bond	Pi-Donor Hydrogen Bond	
		9	TRP59	5.42932	Hydrophobic	Pi-Pi Stacked	
		10	TRP59	4.64512	Hydrophobic	Pi-Pi Stacked	
		11	TYR62	4.53569	Hydrophobic	Pi-Pi T-shaped	
		12	HIS305	4.43508	Hydrophobic	Pi-Alkyl	
		13	LEU165	4.93553	Hydrophobic	Pi-Alkyl	
		14	ALA198	4.63478	Hydrophobic	Pi-Alkyl	
22		1	ASP300	3.29664	Hydrogen Bond	Conventional Hydrogen Bond	-154.592
		2	GLU233	3.43429	Hydrogen Bond	Pi-Donor Hydrogen Bond	
		3	HIS201	4.33457	Other	Pi-Sulfur	
		4	TRP59	4.98635	Hydrophobic	Pi-Pi Stacked	
		5	TRP59	4.12424	Hydrophobic	Pi-Pi Stacked	
		6	LEU165	4.19677	Hydrophobic	Alkyl	
		7	TYR62	4.88479	Hydrophobic	Pi-Alkyl	
		8	HIS101	4.28668	Hydrophobic	Pi-Alkyl	
		9	ALA198	4.44693	Hydrophobic	Pi-Alkyl	
		10	LEU162	5.45957	Hydrophobic	Pi-Alkyl	
		11	LEU165	5.16586	Hydrophobic	Pi-Alkyl	

Conclusion:

This work describes a simple and effective method for the synthesis of thioxo pyrano[2,3-d]pyrimidine derivatives **(7-29)** by reacting different Aryl aldehydes with starting material **5**

and 6 via Claisen-Schmidt condensation. These chalcone derivatives were characterized by various analytical techniques. These prepared derivatives were tested for their antidiabetic activity and showed excellent activity so may act as potential lead molecules in the drug discovery program.

Acknowledgments

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Conflict of Interest

There is no conflict of interest.

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1. Abdelghani, E., Said, S. A., Assy, M. G., & Abdel Hamid, A. M. (2017). Synthesis and antimicrobial evaluation of some new pyrimidines and condensed pyrimidines. *Arabian Journal of Chemistry*, *10*, S2926–S2933. https://doi.org/10.1016/j.arabjc.2013.11.025
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