Int. J. Bio-Inorg. Hybr. Nanomater., 8(4): 135-141, Winter 2019

# Synthesis, characterization and antibacterial activity of some tetrahydro benzo[b]pyran and Pyrano[2,3-d]pyrimidine derivatives

***M. Shahi****

*Department of Organic Chemistry, Faculty of Pharmaceutical Chemistry, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran*

Received: 22 June 2019; Accepted: 25 August 2019

**ABSTRACT:** In this study, a simple and efficient one-pot synthesis of tetrahydrobenzo[b]pyrans from the three-component reaction between dimedone, different aromatic aldehydes and malonitril compounds using $NH_4Al(SO_4)_2 \bullet 12H_2O$ (Alum) as a catalyst at 80 °C is described. As a part of our research works in the synthesis of pyrimidine derivatives containing biological activities, a series of novel pyrano[2,3-d] pyrimidine derivatives 2 were synthesized via reaction of tetrahydrobenzo[*b*]pyrano derivatives 1 with different reagents in suitable yields. The structures of the entire synthesized compound were well analyzed and their structures established by using various spectral techniques ($^1$H NMR, $^{13}$C NMR and IR). Furthermore, all compounds were evaluated for their in vitro antimicrobial activity against different bacterial strains. Antibacterial behavior of product was studied based on reference Gram-positive and Gram- negative bacteria.

**Keywords:** *Antimicrobial activity, Alum, One-pot synthesis, Pyrimidine, Tetrahydrobenzo[b]pyrans.*

## INTRODUCTION

Tetrahydrobenzo[b]pyransbearing oxygen atom has received an increasing interest because of attractive pharmacological and biological properties [1, 2]. They are class of drugs which work as antianaphylactin, anticoagulant, anticancer, diuretic, and spasmolitic agents [3, 4] and can be used as cognitive enhancers for the treatment of neurodegenerative disease, including Alzheimer's disease, Huntington's disease, Parkinson's disease, Down's syndrome and schizophrenia [5, 6]. Furthermore, these compounds occur in a series of natural. On the other hand, heterocyclic compounds containing a pyrimidine or quinoline nucleus are of special interests due to their applications in medicinal chemistry as they are the basic skeleton of a number of several bioactive compounds such as antifungal [7], antibacterial [8, 9], antitumor [10], antitubercular [11, 12], anticonvulsant [13] and ureas inhibitor [14, 15]. A combination of these two ring systems may have a variety of structural and biological activities. Therefore, preparation of heterocyclic compounds containing a pyran and pyrimi-

(*) Corresponding Author - e-mail: maso0omeh_21@yahoo.com

dine moieties is still a significant synthetic challenge. In this article, we report the preparation and characterization of a tetrahydrobenzo[b]pyrano derivatives and novel pyrano[2,3-d]pyrimidine derivatives. In addition, we have evaluated for their in-vitro antibacterial activity against some gram-positive and gram-negative microorganisms.

## EXPERIMENTAL

All melting points were uncorrected and measured using capillary tubes on an Electrothermal digital apparatus. IR spectra were recorded on a Shimadzo FT-IR 300 spectrophotometer in KBr. NMR spectra were recorded on a Brucker 500 and 300 MHz spectrometer in $CDCl_3$ with TMS as an internal standard. The progress of the reaction was monitored by thin-layer chromatography TLC (Thin-Layer Chromatography) using $CH_2Cl_2$/EtOAc (3:1) as an eluent. The starting material tetrahydrobenzo[b]pyrano derivatives 1(a-h) are easily obtained via one pot reaction of malonitrile, dimedone and aromatic aldehyde in presence of Alum [16].

***General procedure for synthesis of tetrahydro benzo[b]pyran derivatives 1(a-h)***

Aluminum potassium disulfide (10 mol%) was added to mixture of dimedone (1 mmol), benzaldehyde derivatives (1 mmol) and malonitrile (1 mmol) in 8 mL water and was heated under reflux. The reaction progress was monitored by TLC in 5 min interval. Upon completion of the reaction, the reaction mixture was cooled and the crystalline product so obtained was filtered, washed with water, and dried in vacuum. The desired compounds, tetrahydrobenzo[b]pyrans 1(*a-h*) were isolated in high yields in essentially pure form.

***2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(phenyl)-5-oxo-4H-benzopyran(1a)***

IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3400 ($NH_2$), 3200-2850 ($CH_{aliphatic \& aromatic}$), 2200 (CN), 1680 (C=O) and1650 (C=C). $^1H$ NMR ($CDCl_3$, 500MHz) δ ppm: (δ): 7.21-7.33 (5H, m, aromatic), 4.55 (2H, s, $NH_2$), 4.39 (1H, s, H pyran), 2.52 (2H, d, $CH_2$, J=16 Hz), 2.26 (2H, d, $CH_2$, J=16 Hz), 1.14 (3H, s, $CH_3$) and 1.07 (3H, s, $CH_3$).

***2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4-methylphenyl)-5-oxo-4H-benzopyran(1b)***

IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3423 ($NH_2$), 3223-2924 ($CH_{aliphatic \& aromatic}$), 3043 ($CH_3$), 2193 (CN), 1676 (C=O), 1602 (C=C) and 1033-1367 (O-C). $^1H$ NMR (DMSO-$d_6$, 500 MHz) δ ppm: (δ): 7.00-7.10 (6H, m, 4CH, aromatic and 2H, $NH_2$), 4.13 (1H, s, H pyran), 2.46 (3H, s, $CH_3$), 2.06-2.24 (4H, d, $2CH_2$), 1.03 (3H, s, $CH_3$) and 0.95 (3H, s, $CH_3$).

***2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-4H-benzopyran(1c)***

IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3400 ($NH_2$), 3050-2880 ($CH_{aliphatic \& aromatic}$), 2180 (CN), 1680 (C=O), 1650 (C=C), 1370 and 1530 ($NO_2$). $^1H$ NMR (DMSO-$d_6$, 500MHz) δ ppm: (δ): 8.12 (1H, d, aromatic, CH), 8.06 (1H, s, aromatic, CH), 7.70 (1H, d, aromatic, 1 CH, J = 4.6 Hz), 7.51 (1H, t, aromatic, 1 CH, J = 4.7 Hz), 4.79 (2H, s, $NH_2$), 4.56 (1H, s, H pyran), 2.55 (2H, d, d $CH_2$, J = 10.7, 14.7 Hz), 2.26 (2H, d, d $CH_2$, J = 9.8, 18.5 Hz), 1.15 (3H, s, $CH_3$) and 1.07 (3H, s, $CH_3$).

***2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(2-cholorophenyl)-5-oxo-4H-benzopyran(1d)***

IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3379 ($NH_2$), 3050-2880 ($CH_{aliphatic \& aromatic}$), 2188 (CN), 1674 (C=O) and 1631 (C=C). $^1H$ NMR (DMSO-$d_6$, 500MHz) δ ppm: (δ): 8.12 (1H, d, aromatic, CH), 8.06 (1H, d, aromatic, CH), 7.70 (1H, d, aromatic, 1 CH), 7.51 and 7.53 (1H, t, aromatic, 1 CH), 4.79 (2H, s, $NH_2$), 4.19 (1H, s, H pyran), 2.22 (2H, d, d $CH_2$, J = 10.7, 14.7 Hz), 2.12 (2H, d, d $CH_2$, J = 9.8, 18.5 Hz), 1.05 (3H, s, $CH_3$) and 0.96 (3H, s, $CH_3$)

***2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-4H-benzopyran(1e)***

IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3408 ($NH_2$), 3075-2943 ($CH_{aliphatic \& aromatic}$), 2183 (CN), 1670 (C=O), 1631 (C=C) and 1595 ($NO_2$). $^1H$ NMR (DMSO-$d_6$, 500MHz) δ ppm: (δ): 8.16 (2H, d, aromatic, CH), 7.45 (2H, d, aromatic, CH), 7.11 (2H, s), 4.36 (1H, s), 2.52 (2H, s, d $CH_2$, J = 10.7, 14.7 Hz), 2.26 (2H, d, d $CH_2$, J = 9.8, 18.5 Hz), 1.05 (3H, s, $CH_3$) and 1.07 (3H, s, $CH_3$).

***2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4-bromophenyl)-5-oxo-4H-benzopyran(1f)***

IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3398 ($NH_2$), 3211-2893 ($CH_{aliphatic\ \&\ aromatic}$), 2191 (CN), 1683 (C=O) and 1656 (C=C). $^1H$ NMR (DMSO-$d_6$, 500MHz) δ ppm: (δ): 7.49-7.53 (2H, m, aromatic, 2CH, C3,5), 7.13-7.15( 4 H, m, aromatic, 2CH, $NH_2$) , 4.41 (1H, s, H pyrani), 3.45-3.51 (2H, m, $CH_2$), 2.10-2.31 (2H, d, $CH_2$, J=15,18 Hz), 1.08 (3H, s, $CH_3$) and 0.97 (3H, s, $CH_3$).

***2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4-methoxyphenyl)-5-oxo-4H-benzopyran(1g)***

IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3390 ($NH_2$), 3200-2810 ($CH_{aliphatic\ \&\ aromatic}$), 2180 (CN), 1690 (C=O), 1650 (C=C) and 1100-1300 (C-O). $^1H$ NMR (DMSO-$d_6$, 500MHz) δ ppm: (δ): 6.81-7.05 (4H, m, aromatic, 4CH), 6.96 (2H, s, $NH_2$), 4.10 (1H, s, H pyran), 3.69 (3H, s, $OCH_3$), 2.10-2.49 (4H, d, $2CH_2$) and 0.93-1.01 (6H, t, $2CH_3$).

***2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(3-hydroxyphenyl)-5-oxo-4H-benzopyran(1h)***

IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3464 ($NH_2$), 3336-3363 (OH), 3022-2929 ($CH_{aliphatic\ \&\ aromatic}$), 2196 (CN), 1690 (C=O) and 1660 (C=C). $^1H$ NMR ($CDCl_3$, 500MHz) δ ppm: (δ): 6.99 (2H, aromatic, 2CH), 6.63 (2H, aromatic, 2CH), 5.7 (2H, s, $NH_2$), 4.57 (1H, s, H pyran), 2.37 (1H, s, OH), 2.05-2.15 (4H, d, $2CH_2$, J=16 Hz), 1.15 (3H, s, $CH_3$) and 1.01 (3H, s, $CH_3$).

***General procedure for synthesis of pyrano[2,3-d]pyrimidine derivatives 2(a-h)***

A solution of compound 1 (1 mmol) in Ac2O (1.5 mL) with catalytic amount of concentrated sulfuric acid (3-4 drops) was heated under reflux for 1 h. The reaction mixture was cooled at room temperature and kept for one day. The mixture was poured into water and the formed solid was filtrated, washed with water, and recrystallized from 2-propanol.

***2,8,8-Trimethyl-5-phenyl-5,7,8,9-tetrahydro-4H-chromno-[2,3-d]pyrimidine-4,6(3H)-dione (2a)***

White solid; m.p. 256-258 °C; Yield 60%; IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3400 (NH), 2962 (CH), 1674, 1610 (C=O) and1452 (C=N). $^1H$ NMR ($CDCl_3$) δ ppm: 1.05, 1.12 (both s, 3H each, C(8) $(CH_3)_2$); 2.35 (s , 3H, C(2)-$CH_3$); 2.26 (m, 2H, $CH_2$); 2.58 (m. 2H, $CH_2$); 4.92 (s, 1H, H-5)); 7.12-7.32 (m, 5H, $C_6H_5$) and 13.10 (s, 1H, NH). $^{13}C$ NMR ($CDCl_3$) δ ppm: 21.30, 27.74, 29.29, 32.51, 33.28, 41.12, 50.89, 103.02, 114.50, 127.02, 128.29, 128.66, 128.29, 143.32, 148.31, 158.56, 161.15, 165.44 and 196.62.

***2,8,8-Trimethyl-5-(4-methylphenyl)-5,7,8,9-tetrahydro-4H-chromno-[2,3-d]pyrimidine-4,6(3H)-dione (2b)***

White solid; m.p. 238-239 °C; Yield 50%; IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3430 (NH), 2961 (CH), 1670, 1610 (C=O) and 1512 (C=N). $^1H$ NMR ($CDCl_3$) δ ppm: 1.05, 1.11 (both s, 3H each, C(8) $(CH_3)_2$); 2.24, 2.37 (both s, 3H each, C(5)-p-$CH_3$-Phenyl, C(2)-$CH_3$);; 2.28 (m, 2H, $CH_2$); 2.57 (m, 2H, $CH_2$); 4.88 (s, 1H, H(5)); 7.00-7.11 (m, 4H, Ar-H) and 13.10 (br, 1H, NH). $^{13}C$ NMR ($CDCl_3$) δ ppm: 21.40, 27.77, 29.30, 32.51, 32.83, 41.12, 50.92, 103.17, 114.98, 128.49, 129.021, 136.57 140.45, 158.45, 161.05, 163.40, 165.29 and 196.66.

***2,8,8-Trimethyl-5-(3-nitrophenyl)-5,7,8,9-tetrahydro-4H-chromno-[2,3-d]pyrimidine-4,6(3H)-dione (2c)***

Pale Yellow solid; m.p>285 °C; Yield 81%; IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3439(NH), 2961 (CH), 1674, 1632 (C=O) and 1526 (C=N). $^1H$ NMR ($CDCl_3$) δ ppm: 1.10, 1.16 (both s, 3H each, C(8) $(CH_3)_2$); 2.26 (s, 3H, C(2)-$CH_3$); 2.40 (m, 2H, $CH_2$); 2.65 (m, 2H, $CH_2$); 5.04 (s, 1H, H(5)); 7.40-8.21 (m, 4H, Ar-H) and 13.35 (br, 1H, NH).$^{13}C$ NMR ($CDCl_3$) δ ppm: 21.46, 27.76, 29.23, 32.56, 33.52, 41.10, 50.77, 101.74, 113.72, 122.16, 123.81, 129.07, 134.80, 145.33, 148.29, 159.36, 161.27 165.27 and 195.53.

***2,8,8-Trimethyl-5-(2-chlorophenyl)-5,7,8,9-tetrahydro-4H-chromno-[2,3-d]pyrimidine-4,6(3H)-dione (2d)***

White solid; m.p. 224-225 °C; Yield 50%; IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3430 (NH), 2961 (CH), 1663, 1620 (C=O) and 1512 (C=N). $^1H$ NMR ($CDCl_3$) δ ppm: 1.07, 1.15 (both s, 3H each, C(8) $(CH_3)_2$); 2.21(m, 2H, $CH_2$); 2.50(s, 3H, C(2)-$CH_3$); 2.57 (m, 2H, $CH_2$); 5.05 (s, 1H, H(5)); 7.01-7.50 (m, 4H, Ar-H) and 13.10 (br, 1H, NH). $^{13}C$ NMR ($CDCl_3$) δ ppm: 27.40, 29.52, 32.05, 32.25, 41.70, 40.09, 50.87, 113.87, 115.43, 126.56, 126.90, 127.91, 130.00, 130.37, 131.83, 133.12, 133.63, 140.06, 161.27 163.27 and 196.84.

***2,8,8-Trimethyl-5-(4-nitrophenyl)-5,7,8,9-tetrahydro-4H-chromno-[2,3-d]pyrimidine-4,6(3H)-dione (2e)***

White solid; m.p. 250-251 °C; Yield 70%; IR (KBr)

$\nu_{max}$ ($cm^{-1}$): 3438 (NH), 2926 (CH), 1655, 1610 (C=O) and 1510 (C=N). $^1$H NMR ($CDCl_3$) δ ppm: 1.05, 1.14 (both s, 3H each, C(8) $(CH_3)_2$); 2.31(m, 2H, $CH_2$); 2.40 (s, 3H, C(2)-$CH_3$); 2.61 (m, 2H, $CH_2$); 5.02 (s, 1H, H(5)); 8.11-7.51 (m, 4H, Ar-H) and 13.10 (br, 1H, NH).

***2,8,8-Trimethyl-5-(4-bromophenyl)-5,7,8,9-tetrahydro-4H-chromno-[2,3-d]pyrimidine-4,6(3H)-dione (2f)***
Pale yellow solid; m.p. >310 °C; Yield 51%; IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3431 (NH), 2959 (CH), 1667, 1611 (C=O) and 1485 (C=N). $^1$H NMR ($CDCl_3$) δ ppm: 1.05, 1.13 (both s, 3H each, C(8) $(CH_3)_2$); 2.23 (m, 2H, $CH_2$); 2.36 (s, 3H, C(2)-$CH_3$); 2.58 (m, 2H, $CH_2$); 4.88 (s, 1H, H(5)); 7.18-7.33 (m, 4H, Ar-H) and 13.10 (br, 1H, NH).

***2,8,8-Trimethyl-5-(4-methoxyphenyl)-5,7,8,9-tetrahydro-4H-chromno-[2,3-d]pyrimidine-4,6(3H)-dione (2g)***
Cream solid; m.p. 220-221 °C; Yield 60%; IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3457 (NH), 2930 (CH), 1659, 1640 (C=O) and 1504 (C=N). $^1$H NMR ($CDCl_3$) δ ppm: 1.11, 1.18 (both s, 3H each, C(8) $(CH_3)_2$); 2.25 (m, 2H, $CH_2$); 2.33 (s, 3H, C(2)-$CH_3$); 2.59 (m, 2H, $CH_2$); 3.68 (s, 3H, O-$CH_3$); 4.68 (s, 1H, H(5)); 7.07-7.11 (m, 4H, Ar-H) and 13.03 (br, 1H, NH).

***2,8,8-Trimethyl-5-(3-hydroxyphenyl)-5,7,8,9-tetrahydro-4H-chromno-[2,3-d]pyrimidine-4,6(3H)-dione (2h)***
White solid; m.p. 201-203 °C; Yield 67%; IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3450 (NH), 2961 (CH), 1678, 1636 (C=O) and 1488 (C=N). $^1$H NMR ($CDCl_3$) δ ppm: 1.06, 1.12 (both s, 3H each, C(8) $(CH_3)_2$); 2.24 (m, 2H, $CH_2$); 2.36 (s, 3H, C(2)-$CH_3$); 2.59 (m, 2H, $CH_2$); 4.94 (s, 1H, H(5)); 6.68-7.27 (m, 4H, Ar-H); 7.02 (s, 1H, OH) and 13.30 (br, 1H, NH).

***Antibacterial activity***
Antibacterial activity of synthesized compounds was assessed by the disc diffusion method [17] using Mueller-Hinton Agar against Escherichia Coli (ATTC-25922) as a gram negative bacteria as well as Bacillus anthracic (ATTC-25924) and Staphylococcus aureus (ATTC-25923) as gram positive bacteria. Cefazolin was used as a standard. Normal saline was used for preparation of inoculants having turbidity equal to 0.5

Table 1. Antibacterial activity of newly synthesized compounds (inhibition zones, mm).

| Comp. No | E. Coli | Ba. anthracic | St. aureus |
|---|---|---|---|
| 1a | 8 | 7 | 7 |
| 1b | 28 | 6 | 7 |
| 1c | 10 | 10 | 3 |
| 1d | 16 | 6 | 14 |
| 1e | 25 | 5 | 4 |
| 1f | 12 | 10 | 2 |
| 1g | 10 | 9 | 4 |
| 1h | 14 | 8 | 20 |
| 2a | - | 15 | 10 |
| 2b | 11 | 15 | 17 |
| 2c | - | 14 | 20 |
| 2d | 13 | 10 | 3 |
| 2e | 18 | 14 | 5 |
| 2f | 15 | 18 | 4 |
| 2g | 16 | 15 | 10 |
| 2h | 12 | 10 | 10 |
| Cefazolin | 13 | 8 | 6 |

Table 2. MIC values of compounds 1(a-h) and 2(a-h).

| Comp. No | MIC (μg.mL$^{-1}$) | | |
|---|---|---|---|
| | E. Coli | Ba. anthracic | St. aureus |
| 1a | 1800 | 1800 | 900 |
| 1b | 1800 | - | 900 |
| 1c | 900 | 900 | 225 |
| 1d | - | - | 1800 |
| 1e | 450 | 900 | 450 |
| 1f | - | 1800 | 1800 |
| 1g | 1800 | 900 | 450 |
| 1h | - | 1800 | 900 |
| 2a | 225 | 450 | 112 |
| 2b | NP | 1800 | 1800 |
| 2c | 900 | 900 | 112 |
| 2d | 225 | 450 | 112 |
| 2e | 450 | 1800 | 900 |
| 2f | 450 | 1800 | 900 |
| 2g | 225 | 900 | 112 |
| 2h | 1800 | NP | 1800 |
| Cefazolin | 450 | 900 | NP |

NP: not performed

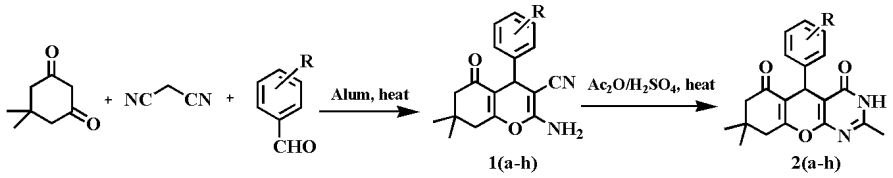
McFarland standards. The compounds were dissolved in dimethyl formamide (DMF) for bioassay. The solvent control was included, although no inhibition zone was found. The plates were incubated at 37 °C for 24 h. All samples were tested in triplicate and the average results of inhibitory effects are illustrated in Table 1.

Determination of the minimum inhibitory concentration (MIC) values for synthesized compounds against three microorganisms was carried out using disc diffusion method [18]. In this method, concentrations of 1800, 900, 450, 225, 112.5, 56.2, 28.1, 14, 7, 3.5, 1.7 and 0.87 μg.mL$^{-1}$ were used per disc and incubated at 37 ºC for 24 h. Values of minimum inhibitor concentration (MIC) were recorded as the lowest concentration of substance, which gives no growth of inoculated bacteria. The Results are presented in Table 2.

## RESULTS AND DISCUSION

Initially, The benzaldehyde derivatives with substitution in aromatic ring with 2-chloro, 4-methoxy, 4-methyl, 3-nitro, 4-nitro,3-hydroxy and 4-bromo groups were reacted with malonitrile, and dimedone in the presence of aluminum potassium disulfide as a catalyst under reflux condition to prepare a series of tetrahydrobenzo[b]pyran derivatives 1(a-h). Compounds 1(a-h) were used as precursors for the synthesizes of pyrano[2,3-d]pyrimidine derivatives 2(a-h) (Scheme 1). The reaction of compounds 1(a-h) with a mixture of acetic anhydride in the presence of sulfuric acid under reflux, produced pyrano[2,3-d]pyrimidine derivatives 2(a-h).

In the IR spectra of compound 1 the nitrile and amine groups were observed in the region of 2190 and 3400 cm$^{-1}$, whereas these bands are absent in the IR spectra of compounds 2. The broad absorption band for stretching vibration of NH group was detected in the region of 3200-3450 cm$^{-1}$, which corresponds to the pyrimidine fragment with strong hydrogen bonds. The appearance of absorption bands at 1663-1710 cm$^{-1}$ and 1610-1645 cm$^{-1}$ are the characteristics of the




R=H, 4-Cl, 2-Cl, 3-$NO_2$, 4-$CH_3$, 4-$NO_2$, 4-Br, 4-OMe, 3-OH

Scheme 1. The synthetic pathway for preparation of tetrahydro benzo[b]pyran 1(a-h) and pyrano[2,3-d]pyrimidine derivatives 2(a-h).

ketone and amide carbonyl groups, respectively. In $^1$H NMR spectra of these compounds the resonance of NH proton with integration for pyrimidine ring (compounds 2) was observed in the region of 13.0 and 8.3 ppm, which is in support of these transformations. The resonance of all other protons appeared in the expected region of spectra. Next, all synthesized compounds were tested for their antimicrobial activity by minimum inhibitory concentration (MIC) in-vitro by agar micro dilution method. The results were summarized in Tables 1 and 2. As depicted in Table 1, the most of the synthesized compounds proved to be effective antibacterial against three tested microorganisms, except for 1a, 1b and 2b, which were inactive against E. Coli. Compound 2a and 2d, showed the highest antimicrobial activity against all bacteria in general, while compounds 2b, 2e, 2f, 1f, 1a and 1b showed the lowest activity against St. aureus. The other compounds exerted moderate to good activity against all stains in comparison with Cefazolin.

## CONCLUSION

In conclusion, we have demonstrated one-pot method for synthesis of tetrahydrobenzo[b]pyrans from the three-component reaction between dimedone, different aromatic aldehydes and malonitril compounds using Alum as a catalyst at 80 °C. Then the tetrahydrobenzo[b]pyrans was used as a precursor for synthesis of novel pyrano[2,3-d]pyrimidine derivatives. Screenings of the all synthesized compounds for their antibacterial activity compared with cefazolin were performed at different concentrations: 1800, 900, 450, 225, 112.5, 56.2, 28.1, 14, 7, 3.5, 1.7 and 0.87 $\mu g.ml^{-1}$ by using the Broth Microdilution MIC method. All compounds showed antibacterial activity against both gram-positive and gram-negative standard strains, showing that the antibacterial activity compounds 2a and 2d are greater than Cefazolin.

## REFERENCES

[1] Green, G. R., Evans, J. M., Vong, A. K., Katritzky, A. R., Rees, C. W. & Scriven, E. F. (1995). Comprehensive heterocyclic chemistry II. Pergamon Press, Oxford, (5), 469.

[2] Bonsignore, L., Loy, G., Secci, D. & Calignano, A. (1993). Synthesis and pharmacological activity of 2-oxo-(2H) 1-benzopyran-3-carboxamide derivatives. European Journal of Medicinal Chemistry, 28(6), 517-520.

[3] Foye, W. O. (1991). Principi di Chimica Farmaceutica, II. Piccin, ed, Padua, 416-420.

[4] Andreani, L., Lepi, E. (1960). Aspects and orientations of modern pharmacognosy. Boll. Chim. Farm, (99), 583-586.

[5] Konkoy, C.S., Fick, D.B., Cai, S.X., Lan, N.C., Keana, J.F.W. (2000). PCT Int. Appl. WO 0075123

[6] Konkoy, C.S., Fick, D.B., Cai, S.X., Lan, N.C., Keana, J.F.W. (2001). Chem. Abstr. 134, 29313a.

[7] Chen, Q., Zhu, X. L., Jiang, L. L., Liu, Z. M. & Yang, G. F. (2008). Synthesis, antifungal activity and CoMFA analysis of novel 1, 2,4-triazolo [1,5-a] pyrimidine derivatives. European Journal of Medicinal Chemistry, 43(3), 595-603.

[8] Shamsa, F., Foroumadi, A., Shamsa, H., Samadi, N., Faramarzi, M. A. & Shafiee, A. (2011). Synthesis and in-vitro antibacterial activities of acetyl anthracene and acetyl phenanthrene derivatives of some fluoroquinolones. Iranian journal of pharmaceutical research: IJPR, 10(2), 225-231.

[9] Magesh, C. J., Makesh, S. V. & Perumal, P. T.

(2004). Highly diastereoselective inverse electron demand (IED) Diels–Alder reaction mediated by chiral salen–AlCl complex: the first, target-oriented synthesis of pyranoquinolines as potential antibacterial agents. Bioorganic & medicinal chemistry letters, 14(9), 2035-2040.

[10] Lin, R., Johnson, S. G., Connolly, P. J., Wetter, S. K., Binnun, E., Hughes, T. V. & Fuentes-Pesquera, A. R. (2009). Synthesis and evaluation of 2, 7-diamino-thiazolo [4, 5-d] pyrimidine analogues as anti-tumor epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors. Bioorganic & medicinal chemistry letters, 19(8), 2333-2337.

[11] Deshmukh, M. B., Salunkhe, S. M., Patil, D. R. & Anbhule, P. V. (2009). A novel and efficient one step synthesis of 2-amino-5-cyano-6-hydroxy-4-aryl pyrimidines and their anti-bacterial activity. European journal of medicinal chemistry, 44(6), 2651-2654.

[12] Balamurugan, K., Jeyachandran, V., Perumal, S., Manjashetty, T. H., Yogeeswari, P. & Sriram, D. (2010). A microwave-assisted, facile, regioselective Friedländer synthesis and antitubercular evaluation of 2, 9-diaryl-2, 3-dihydrothieno-[3, 2-b] quinolines. European journal of medicinal chemistry, 45(2), 682-688.

[13] Jiang, N., Deng, X. Q., Li, F. N. & Quan, Z. S. (2012). Synthesis of novel 7-substituted-5-phenyl-[1, 2, 4] triazolo [1, 5-a] pyrimidines with anticonvulsant activity. Iranian journal of pharmaceutical research: IJPR, 11(3), 799-806.

[14] Ziarani, G. M., Faramarzi, S., Asadi, S., Badiei, A., Bazl, R. & Amanlou, M. (2013). Three-component synthesis of pyrano [2,3-d]-pyrimidine dione derivatives facilitated by sulfonic acid nanoporous silica (SBA-Pr-SO3H) and their docking and urease inhibitory activity. DARU J. Pharmaceutical Sciences, 21(1), 3.

[15] Foroughifar, N., Mobinikhaledi, A. & Fathine-jadJirandehi, H. (2003). Microwave assisted synthesis of some pyrimidine derivatives using polyphosphate ester (PPE) in ceramic bath. Phosphorus, Sulfur, and Silicon and the Related Elements, 178(6), 1241-1246.

[16] Balalaie, S., Bararjanian, M., Sheikh-Ahmadi, M., Hekmat, S. & Salehi, P. (2007). Diammonium hydrogen phosphate: An efficient and versatile catalyst for the one-pot synthesis of tetrahydrobenzo [b] pyran derivatives in aqueous media. Synthetic Communications, 37(7), 1097-1108.

[17] Cruickshank, R., Duguid, J., Marmion, B. and Swain, R. (1975). 12th ed. London. Medicinal Microbiology, (2), 196-199.

[18] Barry, A. (1976). Philadelphia .The Antimicrobial Susceptibility Test: Principle and Practices, Illus Lea & Febiger (eds), 180.

## AUTHOR (S) BIOSKETCHES

**Masoumeh Shahi**, Assistant Professor, Department of Organic Chemistry, Faculty of Pharmaceutical Chemistry, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran, *Email: maso0omeh_21@yahoo.com*