ISSN: 2319-8753

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 3, Issue 1, January 2014

Microwave assisted synthesis of 3-(Tetrahydro-3,4,5-trihydroxy-6-hydroxymethyl-2*H*-pyran-2-yloxy)-2-aryl/heteroaryl-4*H*-chromones and their biological importance

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Abstract: This research communication is toward the investigation of microwave synthesis and biological evaluation of 3-(tetrahydro-3,4,5-trihydroxy-6-hydroxymethyl-2*H*-pyran-2-yloxy)-2-aryl/heteroaryl-4*H*-chromones (3-*O*-β-D-glucopyranosyloxyflavones). These compounds have been obtained by the interaction of α-acetobromoglucose with 3-hydroxy-2-aryl/heteroaryl-4*H*-chromones under microwave condition. The structures of these newly synthesized 3-*O*-β-D-glucopyranosides were established on the basis of chemical, elemental, and spectral analyses. Further, All compounds were evaluated for antimicrobial activity. The inhibition caused by 3-hydroxy flavones was relatively low whereas that of its 3-*O*-β-D-glucopyranosides analogues was substantially more.

Keywords: Flavones, 3-*O*-β-D-glucopyranosides, microwave irradiation, antimicrobial.

I. INTRODUCTION

The clinical relevance of bacterial and fungal diseases has increased over the past 30 years due to an increasing population of immune-compromised patients who have cancer, AIDS or have received transplants. Actually the problems of multi-drug resistant microorganism have reached on alarming level in many countries around the world. A numbers of recent clinical reports describe the increasing occurrence of penicillin-resistant *Staphylococcus aureus* and other antibiotic-resistant human pathogenic microorganisms in United States of America and European countries. Infections caused by those microorganisms pose a serious challenge to the medical community and need for an effective therapy has led to a search for novel more selective and efficient antimicrobial agents. In this work, we report the microwave synthesis and antimicrobial activity of *O*-β-D-glucoside derivatives of 3-hydroxy flavones. Flavones and carbohydrate have broad spectrum of medicinal values.

The chromones are also interesting as structural scaffolds and have been assigned as privileged structures for drug development. Flavones (2-phenyl-4*H*-chromones) are natural components of plants [1,2]. Flavonols (3-hydroxy-2-phenyl-4*H*-chromones) have been demonstrated to have excellent fluorescent properties[3-7], which could be exploited in various applications, e.g. as probes to study lipid membranes and proteins [8-10]. The versatile biological applicability of chromone derivatives and their potential use in drug discovery implicates the importance of access to efficient synthetic routes to well designed substituted chromones. They are known to exhibit activities *e.g.*, antioxidant [11-13], anti-inflammatory, antimicrobial, antihypertensive, antiplatelet, gastroprotective, antitumor [14,15], antiallergic, anticoagulant [16], anticancer [17,18], antidiabetic [19], etc. Consideration has been given to increase the understanding of the mode of action of these natural fungicides and of improving their effectiveness through substitutions. There is evidence that their actions are linked with lipophilicity, suggesting it may be possible to increase fungitoxicity by replacing a hydroxy group on a flavone molecule with an ester group [20].

ISSN: 2319-8753

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

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Correspondingly, Carbohydrats increase the water and lipid solubility of drug and act as a drug carrier as well as it decreases the side effect of drug and also useful as a food supplement. Carbohydrate based therapeutics play an important role in imminomodulation of immune system. The members of aza-sugar glucosidase inhibitors from natural sources are of great interest because of the unique structures and therapeutical values as anticancer and anti HIV agents. The relatively recent recognition of carbohydrates as a medicinally relevant class of biomolecules has led to the investigation of therapeutic agents based on either glycan structure or mimics thereof [21]. For example, cancer cell metastasis [22] and cell-cell adhesion in the inflammatory response [23] are dependent on cell surface presentation of specific glycans. Synthetic carbohydrates-based cancer vaccines [24] and small molecules selective inhibitors [25] are thereof being pursued as potential medicinal agents, respectively. Likewise, the initial stages of bacterial or viral infection often rely on the recognition of host cell glycoconjugates by the invading organism [26].
The great importance of this category of heterocycles and glycoconjugates and in continuation of our research work on chromone-based heterocycles and their O-β-D-glucosides oriented our attention to the synthesis of a series of new heterocyclic derivatives combining chromone and glucose residue in one molecular frame as new possible biological active compounds [27].

II. EXPERIMENTAL

2.1 *Materials, Instruments and Methods*
FT-IR spectra were recorded on Shimadzu spectrophotometer using KBr discs. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker II-400 NMR spectrophotometer, using TMS as an internal standard in $CDCl_3$, chemical shifts (δ) were measured in ppm. Mass spectra were determined on Shimadzu gas chromatograph. Optical rotations were recorded on JASCO digital polarimeter. Elemental analyses were carried out on CHN Elemental Analyzer Perkin Elmer 2400. Purity of the compounds was checked on silica gel plates using iodine vapour as a visualizing agent. Melting points measured in open capillary tubes were uncorrected. The solvents various essential chemicals and reagents were purified and dried according to recommended procedures.
2.2 *General methods of preparation*
3-(Tetrahydro-3,4,5-triacetoxy-6-(acetoxymethyl)-2H-pyran-2-yloxy)flavone 5a: The mixture of 3-hydroxyflavone **4a** (0.238 gm, 0.001 m), K_2CO_3 (2.8979 gm, 0.012 m), and acetonitrile + DMF (9:1; 14 ml) was stirred at room temperature under nitrogen atmosphere. 18-Crown-6 (0.074 gm, 0.0003 m) was added followed by TAGBr (0.7267 gm, 0.003 m). The reaction mixture was stirred magnetically at room temperature for 1 min. The flask was exposed to microwave condition (intermittently at 1 min intervals; 90W, 100 ^{o}C) for 4 min. The purity was checked by TLC in hexane:ethyl acetate (7:3) and $FeCl_3$ test. The mixture was poured in to ice cold water and neutralized with H_2SO_4 (1 mol/L). The product was extracted in ethyl acetate (25 ml ^{x} 4). Removal of the volatiles under reduced pressure afforded yellow residue, purified by silica gel column chromatography (hexane:ethyl acetate 7:3 v/v) to give a colourless β-anomer **5a**. The main advantage of this method is that the overall yield and regioselectivity is in favour of β-anomer.

2.2a *3-(Tetrahydro-3,4,5-triacetoxy-6-(acetoxymethyl)-2H-pyran-2-yloxy)-2-phenyl-4H-chromone (**5a**)*: Yield 92%; mp 112 ^{0}C; FT-IR (KBr): 2954 (glucosidic -CH), 1761 (-C=O of O-acetyl group of glycone ring), 1660 (-C=O), 1055 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90, 1.99, 2.04, 2.12 (s, 3H, OAc), 3.63 (m, 1H, glucosidic -CH), 3.89 (dd, 1H, J=12.08 and 2.26), 4.01 (dd, 1H, J=12.08 and 4.53), 5.03 (t, 1H, J=9.82), 5.11-5.29 (m, 2H, -CH_2), 5.72 (d, 1H, J=7.55), 7.27-8.23 (m, 9H, Ar protons); MS-EI: m/z = 591 $(M+Na)^{+}$; Anal. Calcd for $C_{29}H_{28}O_{12}$: C, 61.27; H, 4.96; Found: C, 61.35; H, 4.91.

2.2b *3-(Tetrahydro-3,4,5-triacetoxy-6-(acetoxymethyl)-2H-pyran-2-yloxy)-2-(4-chlorophenyl)-4H-chromone (**5b**)*: Yield 94%; mp 103 ^{0}C; FT-IR (KBr): 2950 (glucosidic -CH), 1755 (-C=O of O-acetyl group of glycone ring), 1663 (-C=O), 1065 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92, 1.97, 2.03, 2.11 (s, 3H, OAc), 3.64 (m, 1H, glucosidic -CH), 3.88 (dd, 1H, J=12.07 and 2.27), 4.03 (dd, 1H, J=12.07 and 4.54), 5.04 (t, 1H, J=9.83), 5.12-5.28 (m, 2H, -CH_2), 5.70 (d, 1H, J=7.54), 7.28-8.24 (m, 8H, Ar protons); MS-EI: m/z = 625 $(M+Na)^{+}$; Anal. Calcd for $C_{29}H_{27}ClO_{12}$: C, 57.77; H, 4.51; Found: C, 57.82; H, 4.49.

2.2c *3-(Tetrahydro-3,4,5-triacetoxy-6-(acetoxymethyl)-2H-pyran-2-yloxy)-2-(4-fluorophenyl)-4H-chromone (**5c**)*: Yield 89%; mp 97 ^{0}C; FT-IR (KBr): 2962 (glucosidic -CH), 1748 (-C=O of O-acetyl group of glycone ring), 1658 (-

ISSN: 2319-8753

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

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C=O), 1059 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92, 1.98, 2.05, 2.13 (s, 3H, OAc), 3.65 (m, 1H, glucosidic -CH), 3.91 (dd, 1H, J=12.06 and 2.24), 4.03 (dd, 1H, J=12.06 and 4.54), 5.05 (t, 1H, J=9.80), 5.13-5.24 (m, 2H, $-CH_2$), 5.71 (d, 1H, J=7.55), 7.28-8.27 (m, 8H, Ar protons); MS-EI: m/z = 609 $(M+Na)^+$; Anal. Calcd for $C_{29}H_{27}FO_{12}$: C, 59.39; H, 4.64; Found: C, 59.43; H, 4.66.

2.2d *3-(Tetrahydro-3,4,5-triacetoxy-6-(acetoxymethyl)-2H-pyran-2-yloxy)-2-(3,4-dimethoxyphenyl)-4H-chromone* (**5d**): Yield 90%; mp 124 ^{0}C; FT-IR (KBr): 2957 (glucosidic -CH), 1765 (-C=O of O-acetyl group of glycone ring), 1656 (-C=O), 1060 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90, 1.97, 2.05, 2.11 (s, 3H, OAc), 3.30 (s, 6H, $-OCH_3$) 3.60 (m, 1H, glucosidic -CH), 3.88 (dd, 1H, J=12.07 and 2.25), 4.02 (dd, 1H, J=12.07 and 4.54), 5.04 (t, 1H, J=9.81), 5.11-5.27 (m, 2H, $-CH_2$), 5.70 (d, 1H, J=7.56), 7.20-8.24 (m, 7H, Ar protons); MS-EI: m/z = 651 $(M+Na)^+$; Anal. Calcd for $C_{31}H_{32}O_{14}$: C, 59.23; H, 5.13; Found: C, 59.31; H, 5.18.

2.2e *3-(Tetrahydro-3,4,5-triacetoxy-6-(acetoxymethyl)-2H-pyran-2-yloxy)-2-(4-(dimethylamino)phenyl)-4H-chromone (**5e**)*: Yield 91%; mp 99 ^{0}C; FT-IR (KBr): 2963 (glucosidic -CH), 1759 (-C=O of O-acetyl group of glycone ring), 1664 (-C=O), 1067 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88, 1.98, 2.02, 2.11 (s, 3H, OAc), 3.35 (s, 6H, $N(CH_3)_2$), 3.68 (m, 1H, glucosidic -CH), 3.92 (dd, 1H, J=12.06 and 2.24), 4.04 (dd, 1H, J=12.06 and 4.50), 5.04 (t, 1H, J=9.80), 5.13-5.31 (m, 2H, $-CH_2$), 5.75 (d, 1H, J=7.56), 7.32-8.29 (m, 8H, Ar protons); MS-EI: m/z = 634 $(M+Na)^+$; Anal. Calcd for $C_{31}H_{33}NO_{12}$: C, 60.88; H, 5.44; Found: C, 60.93; H, 5.48.

2.2f *3-(Tetrahydro-3,4,5-triacetoxy-6-(acetoxymethyl)-2H-pyran-2-yloxy)-6-chloro-2-phenyl-4H-chromone* (**5f**): Yield 93%; mp 100 ^{0}C; FT-IR (KBr): 2943 (glucosidic -CH), 1760 (-C=O of O-acetyl group of glycone ring), 1650 (-C=O), 1065 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90, 1.99, 2.04, 2.12 (s, 3H, OAc), 3.63 (m, 1H, glucosidic -CH), 3.89 (dd, 1H, J=12.08 and 2.26), 4.01 (dd, 1H, J=12.08 and 4.53), 5.03 (t, 1H, J=9.82), 5.11-5.29 (m, 2H, $-CH_2$), 5.72 (d, 1H, J=7.55), 7.27-8.23 (m, 8H, Ar protons); MS-EI: m/z = 625 $(M+Na)^+$; Anal. Calcd for $C_{29}H_{27}ClO_{12}$: C, 57.77; H, 4.51; Found: C, 57.74; H, 4.58.

2.2g *3-(Tetrahydro-3,4,5-triacetoxy-6-(acetoxymethyl)-2H-pyran-2-yloxy)-6-chloro-2-(4-chlorophenyl)-4H-chromone* (**5g**): Yield 92%; mp 109 ^{0}C; FT-IR (KBr): 2966 (glucosidic -CH), 1766 (-C=O of O-acetyl group of glycone ring), 1664 (-C=O), 1058 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89, 1.98, 2.05, 2.14 (s, 3H, OAc), 3.66 (m, 1H, glucosidic -CH), 3.92 (dd, 1H, J=12.09 and 2.27), 4.03 (dd, 1H, J=12.09 and 4.55), 5.04 (t, 1H, J=9.80), 5.10-5.30 (m, 2H, $-CH_2$), 5.72 (d, 1H, J=7.55), 7.29-8.25 (m, 7H, Ar protons); MS-EI: m/z = 659 $(M+Na)^+$; Anal. Calcd for $C_{29}H_{26}Cl_2O_{12}$: C, 54.64; H, 4.11; Found: C, 54.70; H, 4.15.

2.2h *3-(Tetrahydro-3,4,5-triacetoxy-6-(acetoxymethyl)-2H-pyran-2-yloxy)-6-chloro-2-(4-fluorophenyl)-4H-chromone* (**5h**): Yield 87%; mp 102 ^{0}C; FT-IR (KBr): 2948 (glucosidic -CH), 1772 (-C=O of O-acetyl group of glycone ring), 1674 (-C=O), 1068 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89, 1.98, 2.05, 2.14 (s, 3H, OAc), 3.66 (m, 1H, glucosidic -CH), 3.92 (dd, 1H, J=12.09 and 2.27), 4.03 (dd, 1H, J=12.09 and 4.55), 5.04 (t, 1H, J=9.80), 5.10-5.30 (m, 2H, $-CH_2$), 5.72 (d, 1H, J=7.55), 7.29-8.25 (m, 7H, Ar protons); MS-EI: m/z = 653 $(M+Na)^+$; Anal. Calcd for $C_{29}H_{26}ClFO_{12}$ C, 56.09; H, 4.22; Found: C, 56.02; H, 4.26.

2.2i *3-(Tetrahydro-3,4,5-triacetoxy-6-(acetoxymethyl)-2H-pyran-2-yloxy)-6-chloro-2-(3,4-dimethoxyphenyl)-4H-chromone (**5i**)*: Yield 88%; mp 128 ^{0}C; FT-IR (KBr): 2955 (glucosidic -CH), 1763 (-C=O of O-acetyl group of glycone ring), 1665 (-C=O), 1059 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90, 1.97, 2.05, 2.11 (s, 3H, OAc), 3.30-3.33 (s, 6H, $-OCH_3$) 3.60 (m, 1H, glucosidic -CH), 3.88 (dd, 1H, J=12.07 and 2.25), 4.02 (dd, 1H, J=12.07 and 4.54), 5.04 (t, 1H, J=9.81), 5.11-5.27 (m, 2H, $-CH_2$), 5.70 (d, 1H, J=7.56), 7.18-8.25 (m, 6H, Ar protons); MS-EI: m/z = 685 $(M+Na)^+$; Anal. Calcd for $C_{31}H_{31}ClO_{14}$: C, 56.16; H, 4.71; Found: C, 56.11; H, 4.78.

2.2j *3-(Tetrahydro-3,4,5-triacetoxy-6-acetoxymethyl)-2H-pyran-2-yloxy)-6-chloro-2-(4-(dimethylamino)phenyl)-4H-chromone (**5j**)*: Yield 92%; mp 132 ^{0}C; FT-IR (KBr): 2957 (glucosidic -CH), 1769 (-C=O of O-acetyl group of glycone ring), 1663 (-C=O), 1057 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88, 1.98, 2.02, 2.11 (s, 3H, OAc), 3.35 (s, 6H, $N(CH_3)_2$), 3.68 (m, 1H, glucosidic -CH), 3.92 (dd, 1H, J=12.06 and 2.24), 4.04 (dd, 1H, J=12.06 and 4.50), 5.04 (t,

ISSN: 2319-8753

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

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1H, J=9.80), 5.13-5.31 (m, 2H, -CH_2), 5.75 (d, 1H, J=7.56), 7.30-8.29 (m, 7H, Ar protons); MS-EI: m/z = 678 $(M+Na)^+$; Anal. Calcd for $C_{31}H_{32}ClNO_{12}$: C, 57.63; H, 4.99; Found: C, 57.71; H, 4.90.

2.2k *3-(Tetrahydro-3,4,5-triacetoxy-6-(acetoxymethyl)-2H-pyran-2-yloxy)-2-(furan-2-yl)-4H-chromone* (***5k***): Yield 87%; mp 85 ^{0}C; FT-IR (KBr): 2970 (glucosidic -CH), 1768 (-C=O of O-acetyl group of glycone ring), 1670 (-C=O), 1062 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89, 1.99, 2.02, 2.10 (s, 3H, OAc), 3.60 (m, 1H, glucosidic -CH), 3.90 (dd, 1H, J=12.08 and 2.25), 4.02 (dd, 1H, J=12.08 and 4.52), 5.04 (t, 1H, J=9.83), 5.11-5.22 (m, 2H, -CH_2), 5.74 (d, 1H, J=7.53), 6.41-8.20 (m, 7H, Ar protons); MS-EI: m/z = 581 $(M+Na)^+$; Anal. Calcd for $C_{27}H_{26}O_{13}$: C, 58.07; H, 4.69; Found: C, 58.02; H, 4.75.

2.2l *3-(Tetrahydro-3,4,5-triacetoxy-6-(acetoxymethyl)-2H-pyran-2-yloxy)-6-chloro-2-(furan-2-yl)-4H-chromone* (***5l***): Yield 90%; mp 84 ^{0}C; FT-IR (KBr): 2962 (glucosidic -CH), 1767 (-C=O of O-acetyl group of glycone ring), 1668 (-C=O), 1061 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89, 1.99, 2.02, 2.10 (s, 3H, OAc), 3.60 (m, 1H, glucosidic -CH), 3.90 (dd, 1H, J=12.08 and 2.25), 4.02 (dd, 1H, J=12.08 and 4.52), 5.04 (t, 1H, J=9.83), 5.11-5.22 (m, 2H, -CH_2), 5.74 (d, 1H, J=7.53), 6.32-8.25 (m, 6H, Ar protons); MS-EI: m/z = 615 $(M+Na)^+$; Anal. Calcd for $C_{27}H_{25}ClO_{18}$: C, 54.69; H, 4.25; Found: C, 54.74; H, 4.21.

2.3 ***3-(Tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2H-pyran-2-yloxy)flavone*** **6a:** The mixture of 3-(tetrahydro-3,4,5-triacetoxy-6-(acetoxymethyl)-2H-pyran-2-yloxy)flavone (0.07 gm), dry methanol (5 ml) and anhydrous potassium carbonate (0.088 gm) was stirred for 1 h. It was filtered through cation-exchange resin. The solvent was removed under vacuum and the residue, purified by silica gel chromatography (Hexane: Ethyl acetate, 7:3) to get the final product **6a.**

2.3a *3-(Tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2H-pyran-2-yloxy)-2-phenyl-4H-chromone* (***6a***): Yield 86%; $[\alpha]_D^{30}$ = -17.4 (c, 0.1, DMSO); mp 151 ^{0}C; FT-IR (KBr): 3400 (glucosidic -OH), 2904 (glucosidic -CH), 1610 (-C=O), 1065 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79-1.99 (m, 4H, glucosidic -OH), 3.13-3.82 (m, 6H, glucosidic -CH and CH_2), 5.50 (d, 1H, J=7.48 anomeric proton), 6.75-8.22 (m, 9H, Ar protons); ^{13}C NMR (400 MHz, DMSO-*d6*): δ 61.25 (-CH_2), 70.22, 73.93, 76.42, 76.92 (glucosidic -CH), 101.52 (anomeric carbon atom), 173.90 (-C=O pyrone ring), 118-156.14 (aromatic carbons); Mass Spectrum (GC/MS): m/z = 423 $(M+Na)^+$; Anal. Calcd for $C_{21}H_{20}O_8$: C, 63.00; H, 5.03; Found: C, 63.08; H, 4.97.

2.3b *3-(Tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2H-pyran-2-yloxy)-2-(4-chlorophenyl)-4H-chromone* (***6b***): Yield 84%; $[\alpha]_D^{30}$ = -15.2 (c, 0.1, DMSO); mp 169 ^{0}C; FT-IR (KBr): 3405 (glucosidic -OH), 2905 (glucosidic -CH), 1612 (-C=O), 1060 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81-1.98 (m, 4H, glucosidic -OH), 3.11-3.85 (m, 6H, glucosidic –CH and CH_2), 5.52 (d, 1H, J=7.51 anomeric proton), 6.73-8.20 (m, 8H, Ar protons); ^{13}C NMR (400 MHz, DMSO-*d6*): δ 61.21 (-CH_2), 70.20, 73.95, 76.40, 76.95 (glucosidic -CH), 101.55 (anomeric carbon atom), 174.01 (-C=O pyrone ring), 117.98-156.15 (aromatic carbons); Mass Spectrum (GC/MS): m/z = 457 $(M+Na)^+$; Anal. Calcd for $C_{21}H_{19}ClO_8$: C, 58.01; H, 4.40; Found: C, 57.98; H, 4.45.

2.3c *3-(Tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2H-pyran-2-yloxy)-2-(4-fluorophenyl)-4H-chromone* (***6c***): Yield 85%; $[\alpha]_D^{30}$ = -15.4 (c, 0.1, DMSO); mp 146 ^{0}C; FT-IR (KBr): 3404 (glucosidic -OH), 2902 (glucosidic -CH), 1613 (-C=O), 1063 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80-2.01 (m, 4H, glucosidic -OH), 3.10-3.85 (m, 6H, glucosidic -CH and CH_2), 5.48 (d, 1H, J=7.49 anomeric proton), 6.70-8.25 (m, 8H, Ar protons); ^{13}C NMR (400 MHz, $CDCl_3$): δ 61.19 (-CH_2), 70.23, 73.94, 76.44, 76.90 (glucosidic –CH), 101.42 (anomeric carbon atom), 173.91 (-C=O pyrone ring), 118.21-156.14 (aromatic carbons). Mass Spectrum (GC/MS): m/z = 441 $(M+Na)^+$; Anal. Calcd for $C_{21}H_{19}FO_8$: C, 60.29; H, 4.58; Found: C, 60.33; H, 4.65.

2.3d *3-(Tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2H-pyran-2-yloxy)-2-(3,4-dimethoxyphenyl)-4H-chromone* (***6d***): Yield 82%; $[\alpha]_D^{30}$ = -16.3 (c, 0.1, DMSO); mp 206 ^{0}C; FT-IR (KBr): 3401 (glucosidic -OH), 2914 (glucosidic -CH), 1614 (-C=O), 1064 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79-1.99 (m, 4H, glucosidic -OH), 3.03-3.87 (m,

ISSN: 2319-8753

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

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12H, glucosidic -CH, CH_2 and Ar-OCH_3), 5.62 (d, 1H, J=7.58 anomeric proton), 6.61-8.02 (m, 7H, Ar protons); ^{13}C NMR (400 MHz, $CDCl_3$): δ 56.28, 56.29 $(OCH_3)_2$, 61.20 (-CH_2), 70.22, 73.94, 76.41, 76.90 (glucosidic -CH), 101.54 (anomeric carbon atom), 173.95 (-C=O pyrone ring), 118.41-156.19 (aromatic carbons); Mass Spectrum (GC/MS): m/z = 483 $(M+Na)^+$; Anal. Calcd for $C_{23}H_{24}O_{10}$: C, 60.00; H, 5.25; Found: C, 60.10; H, 5.19.

2.3e *3-(Tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2H-pyran-2-yloxy)-2-(4-(dimethylamino)phenyl)-4H-chromone (**6e**)*: Yield 83%; $[\alpha]_D^{30}$ = -20.1 (c, 0.1, DMSO); mp 182 ^{0}C; FT-IR (KBr): 3410 (glucosidic -OH), 2906 (glucosidic -CH), 1615 (-C=O), 1075 (C-O-C). ^1H NMR (400 MHz, $CDCl_3$): δ 1.79-1.99 (m, 4H, glucosidic -OH), 2.56 (s, 6H, $N(CH_3)_2$), 3.25-3.98 (m, 6H, glucosidic -CH and CH_2), 5.62 (d, 1H, J=7.50 anomeric proton), 6.70-8.23 (m, 8H, Ar protons). ^{13}C NMR (400 MHz, $CDCl_3$): δ 40.54 $(N(CH_3)_2)$, 61.23 (-CH_2), 70.24, 73.91, 76.45, 76.95 (glucosidic -CH), 101.61 (anomeric carbon atom), 173.95 (-C=O pyrone ring), 118.16 – 156.18 (aromatic carbons); Mass Spectrum (GC/MS): m/z = 466 $(M+Na)^+$; Anal. Calcd for $C_{23}H_{25}NO_8$: C, 62.30; H, 5.68; Found: C, 62.28; H, 5.72.

2.3f *3-(Tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2H-pyran-2-yloxy)-6-chloro-2-phenyl-4H-chromone (**6f**)*: Yield 85%; $[\alpha]_D^{30}$ = -17.8 (c, 0.1, DMSO); mp 164 ^{0}C; FT-IR (KBr): 3406 (glucosidic -OH), 2909 (glucosidic -CH), 1614 (-C=O), 1069 (C-O-C); ^1H NMR (400 MHz, $CDCl_3$): δ 1.81-1.98 (m, 4H, glucosidic -OH), 3.11-3.85 (m, 6H, glucosidic -CH and -CH_2), 5.52 (d, 1H, J=7.51 anomeric proton), 6.73-8.20 (m, 8H, Ar protons); ^{13}C NMR (400 MHz, $CDCl_3$): δ 61.23 (-CH_2), 70.21, 73.95, 76.40, 76.95 (glucosidic -CH), 101.55 (anomeric carbon atom), 174.01 (-C=O pyrone ring), 117.98-156.15 (aromatic carbons); Mass Spectrum (GC/MS): m/z = 457 $(M+Na)^+$; Anal. Calcd for $C_{21}H_{19}ClO_8$: C, 58.01; H, 4.40; Found: C, 58.08; H, 4.44.

2.3g *3-(Tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2H-pyran-2-yloxy)-6-chloro-2-(4-chlorophenyl)-4H-chromone (**6g**)*: Yield 85%; $[\alpha]_D^{30}$ = -19.5 (c, 0.1, DMSO); mp 172 ^{0}C; FT-IR (KBr): 3412 (glucosidic -OH), 2911 (glucosidic -CH), 1614 (-C=O), 1068 (C-O-C); ^1H NMR (400 MHz, $CDCl_3$): δ 1.77-1.98 (m, 4H, glucosidic -OH), 3.11-3.84 (m, 6H, glucosidic -CH and -CH_2), 5.55 (d, 1H, J=7.49 anomeric proton), 6.77-8.22 (m, 7H, Ar protons); ^{13}C NMR (400 MHz, $CDCl_3$): δ 61.21 (-CH_2), 70.20, 73.95, 76.43, 76.91 (glucosidic -CH), 101.51 (anomeric carbon atom), 174.04 (-C=O pyrone ring), 117.98-156.15 (aromatic carbons); Mass Spectrum (GC/MS): m/z = 491 $(M+Na)^+$; Anal. Calcd for $C_{21}H_{18}Cl_2O_8$: C, 53.75; H, 3.87; Found: C, 53.79; H, 3.90.

2.3h *3-(Tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2H-pyran-2-yloxy)-6-chloro-2-(4-fluorophenyl)-4H-chromone (**6h**)*: Yield 84%; $[\alpha]_D^{30}$ = -18.9 (c, 0.1, DMSO); mp 150 ^{0}C; FT-IR (KBr): 3412 (glucosidic -OH), 2911 (glucosidic -CH), 1609 (-C=O), 1062 (C-O-C); ^1H NMR (400 MHz, $CDCl_3$): δ 1.79-1.98 (m, 4H, glucosidic -OH), 3.10-3.84 (m, 6H, glucosidic -CH and -CH_2), 5.55 (d, 1H, J=7.49 anomeric proton), 6.77-8.22 (m, 7H, Ar protons); ^{13}C NMR (400 MHz, $CDCl_3$): δ 61.22 (-CH_2), 70.21, 73.95, 76.44, 76.91 (glucosidic -CH), 101.50 (anomeric carbon atom), 174.06 (-C=O pyrone ring), 117.98-156.15 (aromatic carbons); Mass Spectrum (GC/MS): m/z = 475 $(M+Na)^+$; Anal. Calcd for $C_{21}H_{18}ClFO_8$: C, 55.70; H, 4.01; Found: C, 55.66; H, 4.09.

2.3i *3-(Tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2H-pyran-2-yloxy)-6-chloro-2-(3,4-dimethoxyphenyl)-4H-chromone (**6i**)*: Yield 80%; $[\alpha]_D^{30}$ = -21.2 (c, 0.1, DMSO); mp 215 ^{0}C; FT-IR (KBr): 3408 (glucosidic -OH), 2901 (glucosidic -CH), 1613 (-C=O), 1070 (C-O-C); ^1H NMR (400 MHz, $CDCl_3$): δ 1.80 – 1.99 (m, 4H, glucosidic -OH), 3.03-3.87 (m, 12H, glucosidic -CH, CH_2 and Ar-OCH_3), 5.62 (d, 1H, J=7.58 anomeric proton), 6.61-8.02 (m, 7H, Ar protons); ^{13}C NMR (400 MHz, $CDCl_3$): δ 40.55 $(N(CH_3)_2)$, 61.22 (-CH_2), 70.24, 73.91, 76.45, 76.97 (glucosidic -CH), 101.62 (anomeric carbon atom), 173.95 (-C=O pyrone ring), 118.16 – 156.19 (aromatic carbons); Mass Spectrum (GC/MS): m/z = 517 $(M+Na)^+$. Anal. Calcd for $C_{23}H_{23}ClO_{10}$: C, 55.82; H, 4.68; Found: C, 55.87; H, 4.73.

2.3j *3-(Tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2H-pyran-2-yloxy)-6-chloro-2-(4-(dimethylamino)phenyl)-4H-chromone (**6j**)*: Yield 81%; $[\alpha]_D^{30}$ = -20.8 (c, 0.1, DMSO); mp 226 ^{0}C; FT-IR (KBr): 3420 (glucosidic -OH), 2914 (glucosidic -CH), 1616 (-C=O), 1065 (C-O-C); ^1H NMR (400 MHz, $CDCl_3$): δ 1.79-1.99 (m, 4H, glucosidic -OH), 2.56 (s, 6H, $N(CH_3)_2$), 3.25-3.98 (m, 6H, glucosidic -CH and -CH_2), 5.62 (d, 1H, J=7.50 anomeric proton), 6.70-8.23 (m, 7H,

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Ar protons); ^{13}C NMR (400 MHz, $CDCl_3$): δ 61.25 (-CH_2), 70.22, 73.93, 76.42, 76.92 (glucosidic -CH), 101.52 (anomeric carbon atom), 173.90 (-C=O pyrone ring), 118-156.14 (aromatic carbons); Mass Spectrum (GC/MS): m/z = 500 $(M+Na)^+$; Anal. Calcd for $C_{23}H_{24}ClNO_8$: C, 57.18; H, 5.06; Found: C, 57.85; H, 5.02.

2.3k *3-(Tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2H-pyran-2-yloxy)-2-(furan-2-yl)-4H-chromone* (***6k***): Yield 80%; $[\alpha]_D^{30}$ = -17.1 (c, 0.1, DMSO); mp 138 ^{0}C; FT-IR (KBr): 3404 (glucosidic -OH), 2910 (glucosidic -CH), 1615 (-C=O), 1060 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79-1.99 (m, 4H, glucosidic -OH), 3.13-3.82 (m, 6H, glucosidic -CH and -CH_2), 5.50 (d, 1H, J=7.48 anomeric proton), 6.75-8.22 (m, 7H, Ar protons); ^{13}C NMR (400 MHz, $CDCl_3$): δ 61.10 (-CH_2), 71.54, 74.12, 76.35, 76.43 (glucosidic -CH), 101.65 (anomeric carbon atom), 172.80 (-C=O pyrone ring), 112.75-154.16 (aromatic carbons); Mass Spectrum (GC/MS): m/z = 413 $(M+Na)^+$; Anal. Calcd for $C_{19}H_{18}O_9$: C, 58.46; H, 4.65; Found: C, 58.41; H, 4.71.

2.3l *3-(tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2H-pyran-2-yloxy)-6-chloro-2-(furan-2-yl)-4H-chromone* (***6l***): Yield 82%; $[\alpha]_D^{30}$ = -17.5 (c, 0.1, DMSO); mp 142 ^{0}C; FT-IR (KBr): 3410 (glucosidic -OH), 2904 (glucosidic -CH), 1608 (-C=O), 1071 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79-1.99 (m, 4H, glucosidic -OH), 3.13-3.82 (m, 6H, glucosidic -CH and -CH_2), 5.51 (d, 1H, J=7.50 anomeric proton), 6.75-8.22 (m, 6H, Ar protons); ^{13}C NMR (400 MHz, $CDCl_3$): δ 61.08 (-CH_2), 71.56, 74.10, 76.33, 76.40 (glucosidic -CH), 101.61 (anomeric carbon atom), 172.78 (-C=O pyrone ring), 112.78-154.06 (aromatic carbons); Mass Spectrum (GC/MS): m/z = 447 $(M+Na)^+$; Anal. Calcd for $C_{19}H_{17}ClO_9$: C, 53.72; H, 4.03; Found: C, 53.78; H, 4.13.

2.4 Biological screening

Antimicrobial activity of all synthesized compounds was determined by agar diffusion method. All human pathogenic bacteria *viz. Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas Aeruginosa* and fungi such as *Candida albicans, Aspergia niger* were obtained from the department of Pharmacy RTM Nagpur University, Nagpur, India. Stock solutions of compounds were diluted in dimethyl formamide (DMF) to give a final concentration for determining the Minimum inhibitory concentration (MIC) value. MIC was defined as the lowest concentration of compound required for a complete inhibition of the bacterial growth after incubation time. The test compounds were dissolved in dimethyl sulphoxide at a concentration of 100 µg/mL.

Table1. Antimcrobial activity of 3-hydroxyflavones **4a-l**

Compd.[a]	Zone of Inhibition[b] (mm)					
	Antibacterial Activity				Antifungal Activity	
	Gram-positive		Gram-negative			
	S. aureus	*B. subtillis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
4a	14	13	15	12	13	12
4b	15	16	16	15	14	15
4c	16	15	17	17	16	18
4d	16	17	15	15	14	16
4e	15	14	12	13	12	13
4f	12	14	12	11	-	-
4g	13	12	12	11	14	12
4h	16	17	17	15	14	14
4i	15	16	16	14	14	15
4j	16	18	18	17	15	17
4k	17	18	18	17	16	17
4l	18	17	18	18	18	16
Std	**33**	**31**	**34**	**29**	**32**	**30**

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International Journal of Innovative Research in Science, Engineering and Technology

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Table 2. Antimcrobial activity of 3-*O*-β-D-glucopyranosyloxyflavones **6a-l**

Compd.[a]	Zone of Inhibition[b] (mm)					
	Antibacterial Activity				Antifungal Activity	
	Gram-positive		Gram-negative			
	S. aureus	*B. subtillis*	*E. coli*	*P. aeruoginosa*	*C. albicans*	*A. niger*
8a	16	17	18	15	14	15
8b	17	18	17	16	15	16
8c	18	17	18	17	16	16
8d	15	16	15	14	12	14
8e	12	13	14	12	12	13
8f	17	18	19	18	17	17
8g	18	19	19	20	18	17
8h	18	20	20	19	19	20
8i	16	17	17	16	15	15
8j	15	15	16	15	14	14
8k	24	23	26	27	25	24
8l	26	25	27	28	27	26
Std	**33**	**31**	**34**	**29**	**32**	**30**

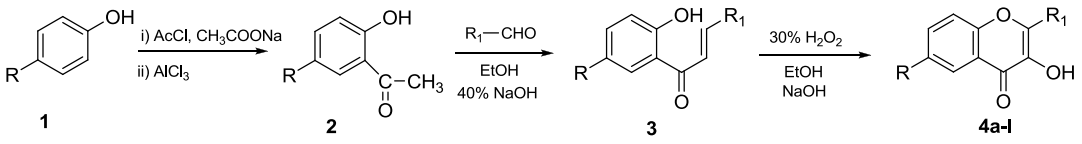
[b]= Average zone of inhibition in mm,

For antibacterial activity: Std. = Ciprofloxacin and for antifungal activity: Std. = Gentamycin

III. RESULTS AND DISCUSSION

3.1 *Synthesis*

Acetylation (esterification) of phenols followed by Fries migration gave 2-hydroxy acetophenones, reaction of 2-hydroxy acetophenones with different aromatic aldehydes produced 1-(2-hydroxyphenyl)-3-arylprop-2-en-1-one (chalcones) **3(a-l)**, which on cyclization in alkaline H_2O_2 yielded 3-hydroxy-2-aryl/heteroaryl-4*H*-chromones (flavones) [28] **4(a-l)** (**Scheme 1**). The IR spectrum of **4a** shows a broad peak at 3222 (Ar-OH), due to presence of phenolic –OH group, 3033, 3075 (aromatic str.), 1611 (C=O pyrone ring). ^{1}H NMR δ 7.02 (s, 1H, OH), 7.26-8.27 (m, 9H, Ar-H) [29].



Scheme 1. Synthesis of 3-hydroxyflavones

Glucosylation of 3-hydroxyflavone **4a** in $CH_3CN/DMF/K_2CO_3$ with 2,3,4,6-tetra-o-acetyl-D-glucopyranosyl bromide (TAGBr) in the presence of 18-crown-6 (PTC) at 100 °C in microwave for a few minutes produce 3-(tetrahydro-3,4,5-triacetoxy-6-(acetoxymethyl)-2*H*-pyran-2-yloxy)flavone **5a** in good yield. In the IR spectra of **5a**, the phenolic –OH group stretch at 3222 cm^{-1} is absent, thus indicates the reaction at 3-hydroxyl group, the sharp peaks at 2854 cm^{-1} was assigned to the glucosidic –CH stretch. The -C=O stretch peak was found to be 1660 cm^{-1}. A strong absorption at 1761 cm^{-1} was assigned to -C=O stretch of acetyl groups of glucose moiety. The peak at 1055 was attributed to the C-O-C stretch. The ^{1}H NMR spectrum of the said compound showed the absence of singlet at δ 7.02 indicates that the phenolic –OH is glucosylated and appearance of new peaks at δ 1.90, 1.99, 2.04, 2.12 (s, 3H, OAc), 3.63 (m, 1H, glucosidic -CH), 3.89 (dd, 1H, J=12.08 and 2.26), 4.01 (dd, 1H, J=12.08 and 4.53), 5.03 (t, 1H, J=9.82), 5.11-5.29 (m, 2H, -CH_2), 5.72 (d, 1H, J=7.55), 7.27-8.23 (m, 9H, Ar protons) was recorded in $CDCl_3$. The β-anomer of acetylated **5a** was confirmed by ^{1}H NMR spectrum, the anomeric proton 1-H appeared as a doublet at δ 5.72, with the coupling constant ($J_{1,2}$ = 7.55 Hz). This relatively large coupling constant is characteristic for the β-stereochemistry of the glucosidic bond. The 3-(tetrahydro-3,4,5-triacetoxy-6-(acetoxymethyl)-2*H*-pyran-2-yloxy)flavone **5a** on deacetylation affords 3-(tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2*H*-pyran-2-yloxy)flavone **6a** (β-anomer, 86% yield) (**Scheme 2**). In

ISSN: 2319-8753

International Journal of Innovative Research in Science, Engineering and Technology

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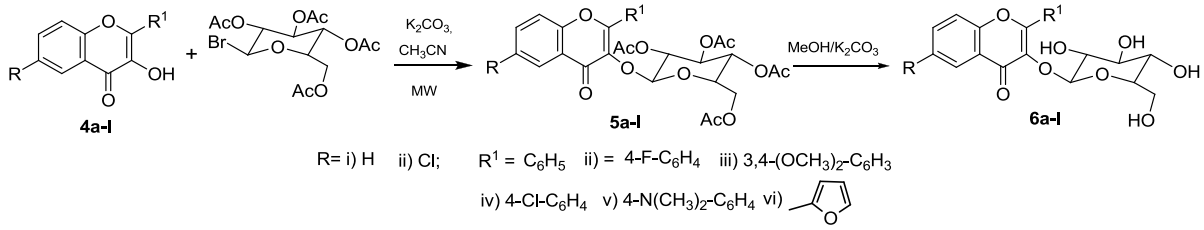
FT-IR the peak at 1761 cm^{-1} -C=O stretch of acetyl groups of glucose moiety and the presence of characteristic absorption peaks at 3400 (broad OH peak of carbohydrate residue), 2865 (glucosidic –CH), 1611 (-C=O, γ-pyrone), 1078 (C-O-C), indicate the formation of deacetylated chromone **6a.** ^{1}H NMR spectra displayed the peaks at δ 1.79-1.99 (m, 4H, glucosidic -OH), 3.13-3.82 (m, 6H, glucosidic -CH and CH_2), 5.50 (d, 1H, J=7.48 anomeric proton), 6.75-8.22 (m, 9H, Ar protons). The anomeric proton H-1 appeared as a doublet at δ 5.50 with a coupling constant $J_{1,2}$ = 7.48 Hz confirming the β-stereochemistry of the glycosidic bond. Thus, confirming the trans-diaxial relation between H-1 and H-2 of the sugar. ^{13}C NMR spectrum showed peaks at δ 61.25 (-CH_2), 70.22, 73.93, 76.42, 76.92 (glucosidic -CH), 101.52 (anomeric carbon atom), 173.90 (-C=O pyrone ring), 118-156.14 (aromatic carbons). The C-1' (anomeric carbon atom) resonated downfield at δ 101.52 comparing to the other glycosyl carbon indicating the formation of *O*-β-D-glucosides. All compounds **6(a-l)** gave satisfactory FT-IR, NMR, Mass spectra and Elemental analysis data correlation with the assigned structure.



Scheme 2. Synthesis of 3-*O*-β-D-glucopyranosyloxyflavones

3.2 *Antimicrobial evaluation*

The compounds (**4** and **6 (a-l)**) were screened for their antibacterial and antifungal activity against some selected bacteria and fungi respectively. The investigation of antimicrobial data (**Tables 1** and **2**) revealed that the compounds **4k**, **4l**, **6k** and **6l** have shown more activity in the series, whereas the compounds **4** (**h**, **i**, **j**) and **6** (**c**, **f**, **g**, **h**, **k**, **i**) showed moderate activity and rest of the compounds showed less activity. All the strains were compared with standard drugs. The presence of electron-withdrawing group on the aromatic ring in general increases the antimicrobial activities of the tested compounds compared to compounds having electron-donating groups. Based upon the results it will also be necessary to optimize the lead compound by substitution in both the phenyl ring by halogen and polar group seems to be very important for antibacterial effect, as well as the presence of glucosidic moiety in the aromatic ring seems to be very important for antibacterial effect and cell-cell recognition. These results suggested that *O*-β-D-glucosides had effective improvement of bioavailability and the electro-acceptor or electro-donor nature of substituent (R) had effective and direct impact on selective antimicrobial activities against both bacteria and fungi. According to these results, the newly synthesized *O*-β-D-glucosides had more promising antimicrobial activity; this functionalized system may be responsible for the enhancement of hydrophobic character and liposolubility of the molecule.

IV. CONCLUSION

The present study reports the synthesis of 3-*O*-β-D-glucopyranosyloxyflavones with good yield and purity. 3-*O*-β-D-glucopyranosyloxyflavones were more biologically active than the corresponding 3-hydroxyflavones.

ACKNOWLEDGEMENT

Authors are thankful to the Head, Department of Chemistry, RTM Nagpur University, for the laboratory facilities, the Head, Department of Pharmacy, RTM Nagpur University for FT-IR and antimicrobial activities and the Director, SAIF, Punjab University, Chandigarh for NMR and Mass spectra.

ISSN: 2319-8753

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

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REFERENCES

[1]. T.Yaakov, B. Joseph, Y. Ilan, F. Ari, E. L. Smadar, P. Vitaly, M. Ayala, T. Galil, S. Uzi, R. Ilana, A. Asaph, A. Hagai, A.S. Arthur, L. Efraim, K. Nurit, J. Agric. Food Chem. pp. 10722-10728, 58, 2010.
[2]. A. Noura, M. William, C. Alan, Phytochemistry. pp. 255-264, 72, 2011.
[3]. P.K. Sengupta, M. Kasha, M. Chem. Phys. Lett. pp. 382-385, 68, 1979.
[4]. T.C. Swinney, D.F Kelley, J. Chem. Phys. pp. 211-221, 99, 1993.
[5]. D. Mcmorrow, M. Kasha, J. Phys. Chem. pp. 2235-2243, 88, 1984.
[6]. A.S. Klymchenko, A.P. Demchenko, J. Am. Chem. Soc. pp. 12372-12379, 124, 2002.
[7]. A.S. Klymchenko, Y. Mely, Tetrahedron Lett. pp. 8391- 8394, 45, 2004.
[8]. A.S. Klymchenko, S.V. Avilov, A.P. Demchenko, Anal. Biochem. pp. 43-57, 329, 2004.
[9]. O.P. Bondar, V.G. Pivovarenko, E.S. Rowe, Biochim. Biophys. Acta Biomembr. pp. 119-130, 1369, 1998.
[10]. A.S. Klymchenko, G. Duportail, T. Ozturk, V. G. Pivovarenko, Y. Mely, A.P. Demchenko, Chem. Biol. pp. 1199-1208, 9, 2002.
[11]. M. Montana, N. Pappano, S. Giordano, P. Molina, N. Debattista, N. Garcıa, Pharmazie. pp. 72-76, 62, 1, 2007.
[12]. S. Veronica, G. Gonzalo, N. M. Matias, M. Martin, T. Leonor, R. Natalia, R. Rafael, C. F. Denise, R. M. Francisco, H. H.X. Laurindo, F. Walter, D. Ana, J. Agric. Food Chem. pp. 6430-6437, 59, 2011.
[13]. V.H. Laura, K. Izet, V.C. Serge, D. Dieter, H. Arne, J. Nat. Prod. pp. 1573-1577, 73, 2010.
[14]. T. Fotsis, M. Pepper, E. Aktas, S. Breit, S. Rasku, H. Adlercreutz, K. Wahala, R. Montesano, L. Schweigerer, Cancer Res. pp. 2916-2921, 57, 14, 1997.
[15]. Y. Hsu, L. Kuo, W. Tzeng, C. Lin, Food Chem Toxicol. pp. 704-713, 44, 5, 2006.
[16]. C. Marta, S. Emılia, D. Barbara, M. Franklim, C, Felix, M. C. Luıs , M.M. Madalena, J. Med. Chem. pp. 95-106, 54, 2011.
[17]. C. Srivari, N. C. Sreerangam, V. L. Pushpavalli, C. Srinivas, M. Debasmita, G. Bogonda, V. Kandi, S. Pabbaraja, R. Chada, R. Janaki, B. Utpal, Bioorganic & Medicinal Chemistry Letters. pp. 645-648, 22, 2012.
[18]. L. Xia, C. Chi-Bun, J. Sung-Wuk, P. Sompol, H. Junjian, H. Kunyan, H.P. Lien, F. Stefan, X. Ge, J. Yonghui, R. L. Hongbo, Y. Keqiang, J. Med. Chem. pp. 8274-8286, 53, 2010.
[19]. M. Azadeh, G. Navnath, S. K. Moon, X.Y. Nancy, K.S. Noeris, R.H. Jane, H.R. Rebecca, E. H. David, J. Med. Chem. pp. 6835-6850, 52, 2009.
[20]. M. Heike, W. Martin, A. Rner Susanne, K. Benno, Mycol. Res. pp. 920-922, 101, 8, 1997.
[21]. P. Sears, C.H. Wong, "Carbohydrate mimetics: a new strategy for tackling the problem of carbohydrate mediated biological recognition" Angew. Chem. Intd. Ed. 38; pp 2300-2324, 1999.
[22]. S.I. Hakomori, Y. Zhang, "Glycosphingolipid antigens and cancer therapy" Chem. Biol. pp. 97-104, 4, 1997.
[23]. G.S. Kanas, "Selectins and their ligands: current concepts and controversies" Blood 88, pp. 3259-3287, 1996.
[24]. S.J. Danishefsky, J.R. Allen, "From the laboratory to the clinic: a retrospective on fully synthetic carbohydrate-based anticancer vaccines" Angew. Chem. Intd. Ed. 39; pp. 836-863, 2000.
[25]. E.E. Simanek, G.J. McGarvey, J.A. Jablonowski, C. H. Wong, "Selectins Carbohydrate interactions: from natural ligands to designed mimics" Chem. Rev. pp. 833-862, 98, 1998.
[26]. K.A. Karlsson, "Microbial recognition of target-cell glycoconjugates" Curr. Opin. Struct. Biol. pp. 622-635, 5, 1995.
[27]. V.N. Ingle, K.M. Hatzade, V.S. Taile, P.K. Gaidhane, S.T. Kharche, Journal of Carbohydrate Chemistry pp. 107-123, 26, 2007.
[28]. (a) A. Fougerousse, E. Gonzalez, R. Brouillard, J. Org. Chem. pp. 583-586, 65, 2000. (b) D. M. X. Donnelly, J.F.K. Eades, E. M. Philibin, T.S. Wheeler, Chemistry & Industry, 1453, 1961.
[29]. M. Gharpure, R. Choudhary, V. Ingle, H. Juneja, J. Chem. Sci. pp. 575-582, 125, 3, 2013.