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New chroman-4-one/thiochroman-4-one derivatives as potential anticancer agents

Seref Demirayak[a], Leyla Yurttas[b,*], Nalan Gundogdu-Karaburun[b], Ahmet Cagri Karaburun[b], Ismail Kayagil[c]

[a]Department of Pharmaceutical Chemistry, School of Pharmacy, Medipol University, 34083 Istanbul, Turkey

[b]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Anadolu University, 26470 Eskisehir, Turkey

[c]Department of Chemistry, Faculty of Arts & Science, Mehmet Akif Ersoy University, 15030 Burdur, Turkey

*Corresponding author. e-mail address: lyurttas@anadolu.edu.tr

Phone no : +90 222 335 05 80 / 3783. Fax +90 222 335 07 50

New chroman-4-one/thiochroman-4-one derivatives as potential anticancer agents

Abstract The synthesis of 3-[3/4-(2-aryl-2-oxoethoxy)arylidene]chroman/thiochroman-4-one derivatives (**1-34**) and evaluation of their anticancer activities were aimed in this work. Final compounds were obtained in multistep synthesis reactions using phenol/thiophenol derivatives as starting materials. For anticancer activity evaluation, all compounds were offered to National Cancer Institute (NCI), USA and selected ones were tested against sixty human tumor cell lines derived from nine neoplastic diseases. The activity results were evaluated according to the drug screening protocol of the institute. Compounds containing thiochromanone skeleton exhibited higher anticancer activity.

Keywords : Chromanone; Thiochromanone; Benzopyranone; Benzothiopyranone; Flavone; α,β-Unsaturated carbonyl; Anticancer activity

1. Introduction

Natural sourced flavones are known with a large scale of biological activities which attribute to subclasses divided according to their molecular structures: These subclasses are flavonols, flavones, flavanones, flavan-3-ols, anthocyanidins, isoflavones, proanthocyanidins, homoisoflavonoids, aurones and chalcones (Mahapatra et al., 2015; Kupcewicz et al. 2013). Among these groups, synthetic derivatives of chalcones, homoisoflavonoids and aurones (Figure 1) constitute our subjects of study which they fall apart possessing a common α,β-unsaturated carbonyl as pharmacophoric group alongwith high anticancer activity reported in many studies (Modranka et al., 2012).

Flavon derivatives are essential compounds, such as their corresponding chalcone derivatives that they act as flavon precursors which are very important scaffolds in terms of anticancer effects (Boumendjel et al., 2008; Kupcewicz et al., 2014; Brien et al., 2012; Cotelle, 2001; Lopez-Lazaro, 2002; Gul et al., 2007). The significant advantage of chalcone derivatives as cytotoxic agents is the low propensity to interact with DNA and to

decrease the risk of mutagenicity as a common side effect of current chemotherapeutic agents (Noushini et al., 2013). Studies on chalcone derivatives are mostly based on the replacement of the phenyl rings with heterocyclic rings and poly-aromatic groups, introduction of different substituents on the phenyl moieties and cyclization of the chalcone to give rigid analogs such as tetralone, benzofuranone (aurone), benzopyranones (chromanone) and 3-benzylidene-4-benzothiopyranones(thiochromanone) were reported to exhibit promising cytotoxic activities (Letafat et al., 2013; Okombi et al., 2006; Pouget et al., 2002; Zheng-yue et al., 2011).

Chromanone and its analogs are also important pharmacophores and privileged structures in medicinal chemistry and have featured in a number of clinically used drugs (Keri et al., 2014; Emami et al., 2015;), especially, as anticancer agents (Seifert et al., 2014; Lampronti et al., 2003; Gamal-Eldeen et al., 2009; Alizadeh et al., 2015). Furthermore, various chromenes (Figure 1) moiety-containing compounds which are structural analogs of chromanones were also reported with high anticancer activity (Kwon et al., 2015; Alizadeh et al., 2008; Venkateswararao et al., 2014). Homoisoflavonoids (3-benzylidene-4-chromanones) are the other molecular framework in similar structure and increasing anticancer activity potency (Nafisi and Namdar, 2012; Yen, 2010; Perjesi et al., 2008; Ivanova et al., 2013; Alipour et al., 2014; Thapa et al., 2011).

3-Arylidenechroman-4-one/thiochromanon-4-one, 2-aryl-1-indanone, 2-aryl-1-tetralone are known as structural analogs and bioisosteres of aurones and possess anticancer activities (Hartmann et al., 1994; Chen et al., 1994; Hartmann et al., 1996; Dimmock et al., 1999; Ohtsu et al., 2002; Dimmock et al., 2002; Boulamwini and Assefa, 2002; Gupta et al., 2004).

In this study, using molecular modification strategy which would provide modifying selectivity profile, activating in different or dual modes and/or reducing undesired side effects (Sandhu et al., 2014) and considering literature findings on α,β-unsaturated carbonyl as pharmacophore group for anticancer activity and arylidene moiety as a synthon (El-Gohary, 2014) some new 3-arylidenechroman-4-one and 3-arylidenethiochroman-4-one derivatives were designed and synthesized as a continuation of our previous and present studies containing 2-arylidene-1-indanon, 2-benzylideneaurone and 2-arylidene-1-tetralone (Gundogdu-Karaburun et al., 2014; Demirayak et al., 2015; Demirayak et al., 2016) molecules. The antiproliferative activity of the compounds were evaluated against various cancer cell lines comparing with standard drugs.

2. Materials and methods

2.1. General

All reagents and solvents were obtained from Sigma-Aldrich Chemical Co (Sigma-Aldrich Corp., St. Louis, MO, USA) and Merck KGaA (Darmstadt, Germany). Melting points were determined using a Electrothermal 9100 digital melting point apparatus (Essex, UK) and are uncorrected. All reactions were monitored by thin layer chromatography (TLC) using Silica Gel 60 F254 TLC plates (Merck KGaA, Darmstadt, Germany). Petroleum ether and ethyl acetate were used as mobile phase prepared in various ratios for TLC. Spectroscopic data were recorded as follows: IR spectra were IR Shimadzu 8400S FT-IR spectrometer (Tokyo, Japan), ^{1}H-NMR spectra on a Bruker 500 MHz spectrometer (Billerica, MA, USA) in DMSO-d_6 with TMS as internal standard ^{13}C-NMR spectra on a Bruker 75 MHz spectrometer (Billerica, MA, USA) and mass spectra using a Agilent 110 MSD spectrometer (Santa Clara, CA, USA) instruments.

2.2. Synthesis of chroman/thiochroman-4-one derivatives ***(IIIa-IIIe)***

Chroman/thiochroman-4-one derivatives (**IIIa-IIIe**) were obtained by gradual synthetic reaction. Firstly, phenol/thiophenol derivative was reacted with acrylonitrile in tetrahydrofuran (THF) using benzyltrimethylammonium hydroxide (Triton-B) as a catalyst to gain 3-aryloxy/arylthioxy-propionitrile derivatives (**Ia-Ie**). Then, the obtained nitrile intermediates were hydrolyzed in acetic acid-hydrochloric acid mixture to acquire corresponding carboxylic acids (**IIa-IIe**). Subsequently, these intermediates were heated to 50-100 ^{o}C with excess polyphosphoric acid (PPA) for 3-4 h to reach chromanone and thiochromanones (**IIIa-IIIe**) with cyclization reaction. Later, this viscous mixture was reacted with ice-water and neutralized with sodium bicarbonate, the collapsed portion was get by filtering and it was crystallised from ethanol.

2.3. Synthesis of 3-(3/4-hydroxyarylidene)chroman/thiochroman-4-one derivatives ***(IVa-IVj)***

Chromanone (**IIIa, IIIb**) and thiochromanone (**IIIc-IIIe**) derivatives (20 mmol) were refluxed with 3- or 4-hydroxybenzaldehyde (22 mmol) in 70 mL *n*-butanol for 30 minutes using hydrochloric acid as a catalyst (1 mL). The precipitate formed upon cooling was filtered and crytallised. The chemical properties of the obtained ten derivatives (**IVa-IVj)** were given in Table 1.

*2.4. General procedure of the synthesis 3-[3/4-(2-aryl-2-oxoethoxy)arylidene]chroman/thiochroman-4-one derivatives **(1-34)***

Equimolar quantities (3 mmol) of 3-(3/4-hydroxyarylidene)chroman/thiochroman-4-one (**IVa-IVj**) derivative and brominated acetophenone derivative were refluxed for 6 hours in acetone in the presence of potassium carbonate. After TLC check, the reaction solvent was evaporated and the obtained residue was washed with water and crystallised from ethanol to achieve final compounds (**1-34)**. The chemical properties of the obtained compounds (**1-34**) were given in Table 2.

*2.4.1. 3-[3-(2-Phenyl-2-oxoethoxy)benzylidene]chroman-4-one **(1)***

IR (KBr) ν_{max} (cm^{-1}): 3071, 3044 (Ar-H and =CH-), 2956, 2921, 2863 (Aliphatic C-H), 1703, 1687 (C=O), 1600-1489 (C=C), 1276, 1220 (C-O). ^{1}H-NMR δ (ppm): 5.44 (2H, d, J: 1.82 Hz, Chromanone C_2-H), 5.71 (2H, s, O-CH_2-), 7.06-7.19 (5H, m, Ar-H), 7.65 (1H, t, J:7.03 Hz, Ar-H), 7.61-7.65 (3H, m, Ar-H), 7.75-7.77 (2H, m, Ar-H), 7.92 (1H, dd, J: 1.66 Hz, J: 7.85 Hz, Ar-H), 8.08 (2H, d, J: 8.20 Hz, Ar-H). ^{13}C-NMR δ (ppm): 67.84, 70.64, 116.59, 116.93, 118.41, 121.92, 122.48, 123.18, 127.74, 128.34, 129.29, 130.30, 131.48, 134.28, 134.84, 135.53, 136.77, 136.95, 158.53, 161.12, 194.86. For $C_{24}H_{18}O_4$ calculated: 77.82 % C, 4.90 % H; found: 77.76 % C, 4.82 % H. MS $[M+1]^+$: *m/z* 371.

*2.4.2. 3-[3-(2-(4-Methylphenyl)-2-oxoethoxy)benzylidene]chroman-4-one **(2)***

IR (KBr) ν_{max} (cm^{-1}): 3082, 3033 (Ar-H and =CH-), 2964, 2920, 2860 (Aliphatic C-H), 1697, 1668 (C=O), 1606-1479 (C=C), 1286, 1230 (C-O). ^{1}H-NMR δ (ppm): 2.40 (3H, s, Ar-CH_3), 5.42 (2H, d, J: 1.71 Hz, Chromanone C_2-H), 5.62 (2H, s, O-CH_2-), 7.04-7.18 (5H, m, Ar-H), 7.40-7.46 (3H, m, Ar-H), 7.63 (1H, d, J: 8.65 Hz, Ar-H), 7.75 (1H, s, =CH-), 7.91 (1H, dd, J: 1.66 Hz, J: 7.85 Hz, Ar-H), 7.95 (2H, d, J: 8.16 Hz, Ar-H). For $C_{25}H_{20}O_4$ calculated: 78.11 % C, 5.24 % H; found: 78.08 % C, 5.32 % H. MS $[M+1]^+$: *m/z* 385.

*2.4.3. 3-[3-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]chroman-4-one **(3)***

IR (KBr) ν_{max} (cm^{-1}): 3080, 3032 (Ar-H and =CH-), 2961, 2920, 2871 (Aliphatic C-H), 1698, 1669 (C=O), 1608-1475 (C=C), 1282, 1234 (C-O). ^{1}H-NMR δ (ppm): 3.88 (3H, s, Ar-OCH_3), 5.43 (2H, d, J: 1.73 Hz, Chromanone C_2-H), 5.63 (2H, s, O-CH_2-), 7.11-7.15 (2H, d, J: 7.80 Hz Ar-H), 7.38-7.44 (3H, m, Ar-H), 7.65 (2H, d, J: 8.55 Hz, Ar-H), 7.76 (1H, s, =CH-), 7.88-7.91 (3H, m, Ar-H), 7.97 (2H, d, J: 8.24 Hz, Ar-H). For $C_{25}H_{20}O_5$ calculated: 74.99 % C, 5.03 % H; found: 75.04 % C, 5.10 % H. MS $[M+1]^+$: *m/z* 401.

*2.4.4. 3-[3-(2-(4-Chlorophenyl)-2-oxoethoxy)benzylidene]chroman-4-one **(4)***

IR (KBr) ν_{max} (cm^{-1}): 3074, 3026 (Ar-H and =CH-), 2960, 2917, 2876 (Aliphatic C-H), 1697, 1668 (C=O), 1611-1470 (C=C), 1287, 1231 (C-O). ^{1}H-NMR δ (ppm): 5.44 (2H, d, J: 1.75 Hz, Chromanone C_2-H), 5.65 (2H, s, O-CH_2-), 7.13-7.16 (2H, d, J: 7.84 Hz Ar-H), 7.42-7.48 (3H, m, Ar-H), 7.69 (2H, d, J: 8.64 Hz, Ar-H), 7.78 (1H, s, =CH-), 7.89-7.93 (3H, m, Ar-H), 7.99 (2H, d, J: 8.20 Hz, Ar-H). For $C_{24}H_{17}ClO_4$ calculated: 71.20 % C, 4.23 % H; found: 71.27 % C, 4.25 % H. MS $[M+1]^+$: *m/z* 404.5.

*2.4.5. 3-[4-(2-Phenyl-2-oxoethoxy)benzylidene]chroman-4-one **(5)***

IR (KBr) ν_{max} (cm^{-1}): 3077, 3054 (Ar-H and =CH-), 2987, 2863 (Aliphatic C-H), 1711, 1687 (C=O), 1603-1479 (C=C), 1276, 1228 (C-O). ^{1}H-NMR δ (ppm): 5.45 (2H, d, J: 1.70 Hz, Chromanone C_2-H), 5.74 (2H, s, O-CH_2-), 7.09 (1H, d, J: 8.29 Hz, Ar-H), 7.13-7.18 (3H, m, Ar-H), 7.48 (2H, d, J: 8.75 Hz, Ar-H), 7.63 (3H, t, J: 7.01 Hz, Ar-H), 7.73-7.76 (2H, m, =CH- and Ar-H), 7.91 (1H, dd, J: 1.61 Hz, J: 7.83 Hz, Ar-H), 8.08 (2H, d, J: 7.20 Hz, Ar-H). ^{13}C-NMR δ (ppm): 67.96, 70.66, 115.54, 118.32, 122.04, 122.38, 127.12, 127.68, 128.36, 129.15, 129.32, 132.86, 134.36, 136.53, 159.74, 160.96, 181.51, 194.66. For $C_{24}H_{18}O_4$ calculated: 77.82 % C, 4.90 % H; found: 77.72 % C, 4.86 % H. MS $[M+1]^+$: *m/z* 371.

*2.4.6. 3-[4-(2-(4-Methylphenyl)-2-oxoethoxy)benzylidene]chroman-4-one **(6)***

IR (KBr) ν_{max} (cm^{-1}): 3059, 3030 (Ar-H and =CH-), 2904, 2950 (Aliphatic C-H), 1711, 1649 (C=O), 1589-1508 (C=C), 1294, 1269, 1249 (C-O). ^{1}H-NMR δ (ppm): 2.43 (3H, s, Ar-CH_3), 5.46 (2H, d, J: 1.70 Hz, Chromanone C_2-H), 5.67 (2H, s, O-CH_2-), 7.09 (1H, d, J: 8.39 Hz, Ar-H), 7.11-7.18 (3H, m, Ar-H), 7.43 (2H, d, J: 8.05 Hz, Ar-H), 7.48 (2H, t, J: 8.76 Hz, Ar-H), 7.62 (1H, d, J: 8.15 Hz, Ar-H), 7.76 (1H, s, =CH-), 7.91 (1H, dd, J: 1.64, 1.66 Hz, J: 7.84 Hz, Ar-H), 7.98 (2H, d, J: 7.2 Hz, Ar-H). ^{13}C-NMR δ (ppm): 21.72, 67.96, 70.56, 115.52, 118.32, 122.03, 122.38, 127.08, 127.68, 128.46, 129.13, 129.85, 132.26, 132.86, 136.53, 136.85, 144.87, 159.77, 181.51, 194.14. For $C_{25}H_{20}O_4$ calculated: 78.11 % C, 5.24 % H; found: 78.14 % C, 5.34 % H. MS $[M+1]^+$: *m/z* 385.

*2.4.7. 3-[4-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]chroman-4-one **(7)***

IR (KBr) ν_{max} (cm^{-1}): 3076, 3031 (Ar-H and =CH-), 2972, 2924, 2873 (Aliphatic C-H), 1696, 1665 (C=O), 1611-1474 (C=C), 1275, 1229 (C-O). ^{1}H-NMR δ (ppm): 3.88 (3H, s, Ar-OCH_3), 5.42 (2H, d, J: 1.70 Hz, Chromanone C_2-H), 5.62 (2H, s, O-CH_2-), 7.12-7.16 (2H, d, J: 7.78 Hz Ar-H), 7.44-7.46 (3H, m, Ar-H), 7.67 (2H, d, J: 8.52 Hz, Ar-H), 7.74 (1H, s, =CH-), 7.85-7.90 (3H, m, Ar-H), 7.98 (2H, d, J: 8.20 Hz, Ar-H). ^{13}C-NMR δ (ppm): 56.13, 67.96, 70.38,

114.56, 115.52, 118.32, 122.38, 127.05, 129.11, 130.74, 132.86, 136.54, 136.85, 159.82, 181.51, 192.96. For $C_{25}H_{20}O_5$ calculated: 74.99 % C, 5.03 % H; found: 75.08 % C, 5.07 % H. MS $[M+1]^+$: *m/z* 401.

2.4.8. 3-[4-(2-(4-Chlorophenyl)-2-oxoethoxy)benzylidene]chroman-4-one ***(8)***

IR (KBr) ν_{max} (cm^{-1}): 3067, 3034 (Ar-H and =CH-), 2978, 2814 (Aliphatic C-H), 1704, 1682 (C=O), 1615-1479 (C=C), 1275, 1224 (C-O). ^{1}H-NMR δ (ppm): 5.48 (2H, d, J: 1.71 Hz, Chromanone C_2-H), 5.73 (2H, s, O-CH_2-), 7.09 (1H, d, J: 8.26 Hz, Ar-H), 7.13-7.18 (3H, m, Ar-H), 7.48 (2H, d, J: 8.77 Hz, Ar-H), 7.62 (1H, d, J: 8.05 Hz, Ar-H), 7.71 (2H, d, J: 8.84 Hz, Ar-H), 7.76 (1H, s, =CH-), 7.91 (1H, dd, J: 1.70 Hz, J: 7.82 Hz, Ar-H), 8.09 (2H, d, J: 8.56 Hz, Ar-H). For $C_{24}H_{17}ClO_4$ calculated: 71.20 % C, 4.23 % H; found: 71.25 % C, 4.29 % H. MS $[M+1]^+$: *m/z* 404.5.

2.4.9. 3-[3-(2-Phenyl-2-oxoethoxy)benzylidene]-6-chlorochroman-4-one ***(9)***

IR (KBr) ν_{max} (cm^{-1}): 3067, 3058 (Ar-H and =CH-), 2982, 2860 (Aliphatic C-H), 1713, 1685 (C=O), 1604-1481 (C=C), 1274, 1231 (C-O). ^{1}H-NMR δ (ppm): 5.43 (2H, d, J: 1.75 Hz, Chromanone C_2-H), 5.73 (2H, s, O-CH_2-), 7.12 (1H, d, J: 8.24 Hz, Ar-H), 7.15-7.22 (3H, m, Ar-H), 7.52 (2H, d, J: 8.20 Hz, Ar-H), 7.69 (2H, t, J: 7.26 Hz, Ar-H), 7.79-7.84 (2H, m, =CH- and Ar-H), 7.96 (1H, dd, J: 1.73 Hz, J: 7.86 Hz, Ar-H), 8.14 (2H, d, J: 7.32 Hz, Ar-H). For $C_{24}H_{17}ClO_4$ calculated: 71.20 % C, 4.23 % H; found: 71.15 % C, 4.31 % H. MS $[M+Na]^+$: *m/z* 427.1.

2.4.10. 3-[3-(2-(4-Methoxyphenyl-2-oxoethoxy)benzylidene]-6-chlorochroman-4-one ***(10)***

IR (KBr) ν_{max} (cm^{-1}): 3082, 3035 (Ar-H and =CH-), 2976, 2925, 2872 (Aliphatic C-H), 1695, 1667 (C=O), 1613-1475 (C=C), 1276, 1232 (C-O). ^{1}H-NMR δ (ppm): 3.89 (3H, s, Ar-OCH_3), 5.43 (2H, d, J: 1.65 Hz, Chromanone C_2-H), 5.63 (2H, s, O-CH_2-), 7.16-7.19 (2H, d, J: 7.74 Hz Ar-H), 7.52-7.59 (2H, m, Ar-H), 7.71 (2H, d, J: 8.12 Hz, Ar-H), 7.75 (1H, s, =CH-), 7.82-7.88 (3H, m, Ar-H), 7.91 (2H, d, J: 8.10 Hz, Ar-H). ^{13}C-NMR δ (ppm): 56.12, 68.19, 70.37, 114.55, 115.55, 117.30, 120.73, 123.00, 126.41, 126.52, 126.90, 127.62, 128.19, 130.74, 133.04, 136.05, 137.73, 159.61, 160.00, 164.11, 180.51, 192.91. For $C_{25}H_{19}ClO_5$ calculated: 69.05 % C, 4.40 % H; found: 69.09 % C, 4.32 % H. MS $[M+1]^+$: *m/z* 435.1.

2.4.11. 3-[3-(2-(4-Chlorophenyl-2-oxoethoxy)benzylidene]-6-chlorochroman-4-one ***(11)***

IR (KBr) ν_{max} (cm^{-1}): 3072, 3036 (Ar-H and =CH-), 2979, 2815 (Aliphatic C-H), 1705, 1680 (C=O), 1618-1477 (C=C), 1273, 1227 (C-O). ^{1}H-NMR δ (ppm): 5.47 (2H, d, J: 1.70 Hz,

Chromanone C_2-H), 5.73 (2H, s, O-CH_2-), 7.10 (1H, d, J: 8.12 Hz, Ar-H), 7.16-7.18 (2H, m, Ar-H), 7.54 (2H, d, J: 8.70 Hz, Ar-H), 7.65 (1H, d, J: 8.23 Hz, Ar-H), 7.75 (2H, d, J: 8.84 Hz, Ar-H), 7.76 (1H, s, =CH-), 7.91 (1H, dd, J: 1.74 Hz, J: 7.62 Hz, Ar-H), 8.11 (2H, d, J: 8.54 Hz, Ar-H). For $C_{24}H_{16}Cl_2O_4$ calculated: 65.62 % C, 3.67 % H; found: 65.65 % C, 3.61 % H. MS $[M+Na]^+$: *m/z* 461.0.

2.4.12. 3-[4-(2-Phenyl-2-oxoethoxy)benzylidene]-6-chlorochroman-4-one ***(12)***

IR (KBr) ν_{max} (cm^{-1}): 3055, 3015 (Ar-H and =CH-), 2968, 2905 (Aliphatic C-H), 1717, 1666 (C=O), 1602-1473 (C=C), 1284, 1271, 1228 (C-O). ^{1}H-NMR δ (ppm): 5.48 (2H, d, J: 1.80 Hz, Chromanone C_2-H), 5.72 (2H, s, O-CH_2-), 7.12 (3H, t, J: 8.73 Hz, Ar-H), 7.46 (2H, d, J: 8.60 Hz, Ar-H), 7.58-7.65 (3H, m, Ar-H), 7.62 (1H, t, J: 7.54 Hz, Ar-H), 7.75 (1H, bs, =CH-), 7.88 (1H, d, J: 7.82 Hz, Ar-H), 8.05 (2H, d, J: 8.64 Hz, Ar-H). ^{13}C-NMR δ (ppm): 29.00, 70.64, 115.51, 126.31, 127.62, 128.36, 129.32, 130.17, 131.22, 132.21, 132.43, 133.72, 134.34, 134.75, 137.09, 137.38, 140.94, 159.29, 185.46, 194.71. For $C_{24}H_{17}ClO_4$ calculated: 71.20 % C, 4.23 % H; found: 71.16 % C, 4.34 % H. MS $[M+1]^+$: *m/z* 404.5.

2.4.13. 3-[4-(2-(4-Methoxyphenyl-2-oxoethoxy)benzylidene]-6-chlorochroman-4-one ***(13)***

IR (KBr) ν_{max} (cm^{-1}): 3076, 3045 (Ar-H and =CH-), 2988, 2864 (Aliphatic C-H), 1705, 1689 (C=O), 1606-1474 (C=C), 1278, 1226 (C-O). ^{1}H-NMR δ (ppm): 3.88 (3H, s, Ar-OCH_3), 5.48 (2H, s, Chromanone C_2-H), 5.72 (2H, s, O-CH_2-), 7.15 (3H, d, J: 8.74 Hz, Ar-H), 7.46 (2H, d, J: 8.32 Hz, Ar-H), 7.63 (1H, dd, J: 2.75 Hz, J: 8.84 Hz, Ar-H), 7.67 (2H, d, J: 8.53 Hz, Ar-H), 7.75 (1H, s, =CH-), 7.80 (1H, d, J: 2.69 Hz, Ar-H), 8.06 (2H, d, J: 8.53 Hz, Ar-H). For $C_{25}H_{19}ClO_5$ calculated: 69.05 % C, 4.40 % H; found: 69.11 % C, 4.33 % H. MS $[M+1]^+$: *m/z* 435.1.

2.4.14. 3-[4-(2-(4-Chlorophenyl-2-oxoethoxy)benzylidene]-6-chlorochroman-4-one ***(14)***

IR (KBr) ν_{max} (cm^{-1}): 3078, 3044 (Ar-H and =CH-), 2987, 2865 (Aliphatic C-H), 1712, 1684 (C=O), 1602-1477 (C=C), 1275, 1222 (C-O). ^{1}H-NMR δ (ppm): 5.47 (2H, s, Chromanone C_2-H), 5.70 (2H, s, O-CH_2-), 7.13 (3H, d, J: 8.74 Hz, Ar-H), 7.46 (2H, d, J: 8.32 Hz, Ar-H), 7.63 (1H, dd, J: 2.73 Hz, J: 8.80 Hz, Ar-H), 7.68 (2H, d, J: 8.50 Hz, Ar-H), 7.74 (1H, s, =CH-), 7.84 (1H, d, J: 2.72 Hz, Ar-H), 8.12 (2H, d, J: 8.50 Hz, Ar-H). For $C_{24}H_{16}Cl_2O_4$ calculated: 65.62 % C, 3.67 % H; found: 65.55 % C, 3.58 % H. MS $[M+1]^+$: *m/z* 439.

2.4.15. 3-[3-(2-Phenyl-2-oxoethoxy)benzylidene]thiochroman-4-one ***(15)***

IR (KBr) ν_{max} (cm^{-1}): 3065, 3039 (Ar-H and =CH-), 2969, 2950 (Aliphatic C-H), 1706, 1658 (C=O), 1603-1490 (C=C), 1285, 1221 (C-O). ^{1}H-NMR δ (ppm): 4.27 (2H, s, Thiochromanone

C_2-H), 5.69 (2H, s, O-CH_2-), 7.08 (2H, d, J: 8.79 Hz, Ar-H), 7.32 (1H, d, J: 7.98 Hz, Ar-H), 7.40-7.422 (1H, m, Ar-H), 7.49-7.53 (3H, m, Ar-H), 7.57-7.63 (3H, m, Ar-H and =CH-), 7.70-7.73 (1H, m, Ar-H), 8.03-8.05 (3H, m, Ar-H). For $C_{24}H_{18}O_3S$ calculated: 74.59 % C, 4.69 % H; found: 74.55 % C, 4.59 % H. MS $[M+1]^+$: *m/z* 387.

2.4.16. 3-[3-(2-(4-Methylphenyl)-2-oxoethoxy)benzylidene]thiochroman-4-one ***(16)***

IR (KBr) ν_{max} (cm^{-1}): 3076, 3024 (Ar-H and =CH-), 2965, 2850 (Aliphatic C-H), 1698, 1650 (C=O), 1599-1474 (C=C), 1274, 1222 (C-O). ^{1}H-NMR δ (ppm): 2.09 (3H, s, Ar-CH_3), 4.28 (2H, s, Thiochromanone C_2-H), 5.69 (2H, s, O-CH_2-), 7.06 (2H, d, J: 8.73 Hz, Ar-H), 7.32-7.35 (1H, m, Ar-H), 7.41-7.43 (1H, m, Ar-H), 7.49-7.53 (3H, m, Ar-H), 7.57-7.61 (2H, m, Ar-H and =CH-), 7.69-7.73 (1H, m, Ar-H), 8.03-8.05 (3H, m, Ar-H). ^{13}C-NMR δ (ppm): 28.67, 123.99, 124.73, 126.43, 128.43, 130.25, 130.79, 132.01, 134.59, 135.52, 136.39, 136.50, 141.19, 185.32. For $C_{25}H_{20}O_3S$ calculated: 74.98 % C, 5.03 % H; found: 74.93 % C, 5.08 % H. MS $[M+1]^+$: *m/z* 401.

2.4.17. 3-[3-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]thiochroman-4-one ***(17)***

IR (KBr) ν_{max} (cm^{-1}): 3075, 3020 (Ar-H and =CH-), 2969, 2857 (Aliphatic C-H), 1695, 1655 (C=O), 1594-1471 (C=C), 1272, 1221 (C-O). ^{1}H-NMR δ (ppm): 3.89 (3H, s, Ar-OCH_3), 4.29 (2H, s, Thiochromanone C_2-H), 5.66 (2H, s, O-CH_2-), 7.10 (2H, d, J: 8.70 Hz, Ar-H), 7.30-7.32 (1H, m, Ar-H), 7.43-7.45 (1H, m, Ar-H), 7.51-7.54 (3H, m, Ar-H), 7.59-7.63 (2H, m, Ar-H and =CH-), 7.75-7.78 (1H, m, Ar-H), 8.10-8.13 (3H, m, Ar-H). ^{13}C-NMR δ (ppm): 28.67, 123.98, 124.72, 126.42, 128.42, 130.25, 132.00, 134.09, 135.51, 136.37, 141.19, 148.50, 185.31. For $C_{25}H_{20}O_4S$ calculated: 72.09 % C, 4.84 % H; found: 72.03 % C, 4.88 % H. MS $[M+1]^+$: *m/z* 417.

2.4.18. 3-[3-(2-(4-Chlorophenyl)-2-oxoethoxy)benzylidene]thiochroman-4-one ***(18)***

IR (KBr) ν_{max} (cm^{-1}): 3056, 3027 (Ar-H and =CH-), 2976, 2860 (Aliphatic C-H), 1692, 1659 (C=O), 1592-1470 (C=C), 1274, 1225 (C-O). ^{1}H-NMR δ (ppm): 4.29 (2H, s, Thiochromanone C_2-H), 5.68 (2H, s, O-CH_2-), 7.12 (2H, d, J: 8.60 Hz, Ar-H), 7.35-7.37 (1H, m, Ar-H), 7.41-7.44 (1H, m, Ar-H), 7.50-7.52 (3H, m, Ar-H), 7.61-7.63 (2H, m, Ar-H and =CH-), 7.74-7.76 (1H, m, Ar-H), 8.11-8.14 (3H, m, Ar-H). ^{13}C-NMR δ (ppm): 28.99, 70.63, 116.56, 116.96, 117.18, 117.36, 118.41, 121.59, 121.90, 122.49, 123.23, 127.74, 129.41, 130.31, 131.49, 133.52, 135.54, 136.77, 136.93, 137.23, 139.15, 158.45, 161.12, 181.61, 193.99. For $C_{24}H_{17}ClO_3S$ calculated: 68.48 % C, 4.07 % H; found: 68.53 % C, 4.12 % H. MS $[M+1]^+$: *m/z* 420.5.

2.4.19. 3-[4-(2-Phenyl-2-oxoethoxy)benzylidene]thiochroman-4-one ***(19)***

IR (KBr) ν_{max} (cm^{-1}): 3075, 3039 (Ar-H and =CH-), 2951, 2867 (Aliphatic C-H), 1696, 1650 (C=O), 1599-1474 (C=C), 1272, 1224 (C-O). ^{1}H-NMR δ (ppm): 4.25 (2H, s, Thiochromanone C_2-H), 5.69 (2H, s, O-CH_2-), 7.06 (2H, d, J: 8.73 Hz, Ar-H), 7.32-7.35 (1H, m, Ar-H), 7.40-7.42 (1H, m, Ar-H), 7.49-7.53 (3H, d, J: 8.73 Hz, Ar-H), 7.57-7.61 (3H, m, Ar-H and =CH-), 7.69-7.73 (1H, m, Ar-H), 8.03-8.05 (3H, m, Ar-H). For $C_{24}H_{18}O_3S$ calculated: 74.59 % C, 4.69 % H; found: 74.53 % C, 4.58 % H. MS $[M+1]^+$: *m/z* 387.

2.4.20. 3-[4-(2-(4-Methylphenyl)-2-oxoethoxy)benzylidene]thiochroman-4-one ***(20)***

IR (KBr) ν_{max} (cm^{-1}): 3063, 3039 (Ar-H and =CH-), 2963, 2950 (Aliphatic C-H), 1709, 1658 (C=O), 1608-1490 (C=C), 1286, 1252, 1221 (C-O). ^{1}H-NMR δ (ppm): 2.40 (3H, s, Ar-CH_3), 4.27 (2H, s, Thiochromanone C_2-H), 5.63 (2H, s, O-CH_2-), 7.07 (2H, d, J: 8.80 Hz, Ar-H), 7.32 (1H, d, J: 1.20 Hz, J: 7.50 Hz, Ar-H), 7.37-7.41 (3H, m, Ar-H), 7.48-7.52 (3H, m, Ar-H), 7.61 (1H, s, =CH-), 7.93 (2H, d, J: 8.18 Hz, Ar-H), 8.15 (1H, dd, J: 1.30 Hz and 8.73 Hz, Ar-H). For $C_{25}H_{20}O_3S$ calculated: 74.98 % C, 5.03 % H; found: 74.94 % C, 5.11 % H. MS $[M+1]^+$: *m/z* 401.

2.4.21. 3-[4-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]thiochroman-4-one ***(21)***

IR (KBr) ν_{max} (cm^{-1}): 3075, 3039 (Ar-H and =CH-), 2950, 2867 (Aliphatic C-H), 1696, 1650 (C=O), 1599-1474 (C=C), 1275, 1224 (C-O). ^{1}H-NMR δ (ppm): 3.87 (2H, s, Ar-OCH_3), 4.27 (2H, s, Thiochromanone C_2-H), 5.61 (2H, s, O-CH_2-), 7.06 (2H, d, J: 8.93 Hz, Ar-H), 7.12 (2H, d, J: 8.81 Hz, Ar-H), 7.31 (1H, dd, J: 7.96, 8.63 Hz, J: 15.92 Hz, Ar-H), 7.41 (1H, d, J: 7.62 Hz, Ar-H), 7.49-7.53 (3H, m, Ar-H), 7.61 (1H, s, =CH-), 8.01-8.08 (3H, m, Ar-H), 8.24 (1H, d, J: 2.06 Hz Ar-H). For $C_{25}H_{20}O_4S$ calculated: 72.09 % C, 4.84 % H; found: 72.01 % C, 4.89 % H. MS $[M+1]^+$: *m/z* 417.

2.4.22. 3-[4-(2-(4-Chlorophenyl)-2-oxoethoxy)benzylidene]thiochroman-4-one ***(22)***

IR (KBr) ν_{max} (cm^{-1}): 3062, 3030 (Ar-H and =CH-), 2957, 2880 (Aliphatic C-H), 1704, 1675 (C=O), 1599-1474 (C=C), 1272, 1224 (C-O). ^{1}H-NMR δ (ppm): 4.27 (2H, s, Thiochromanone C_2-H), 5.67 (2H, s, O-CH_2-), 7.09 (2H, d, J: 8.93 Hz, Ar-H), 7.32 (1H, d, J: 7.45 Hz, Ar-H), 7.40-7.42 (1H, m, Ar-H), 7.49-7.53 (3H, m, Ar-H), 7.61 (1H, s, =CH-), 7.42 (2H, d, J: 8.0 Hz, Ar-H), 8.03-8.06 (3H, m, Ar-H). For $C_{24}H_{17}ClO_3S$ calculated: 68.48 % C, 4.07 % H; found: 68.54 % C, 4.13 % H. MS $[M+1]^+$: *m/z* 420.5.

2.4.23. 3-[3-(2-Phenyl-2-oxoethoxy)benzylidene]-6-methylthiochroman-4-one ***(23)***

IR (KBr) ν_{max} (cm^{-1}): 3074, 3042 (Ar-H and =CH-), 2964, 2869 (Aliphatic C-H), 1699, 1660 (C=O), 1598-1476 (C=C), 1273, 1226 (C-O). ^{1}H-NMR δ (ppm): 2.42 (3H, s, Ar-CH_3), 4.26 (2H, s, Thiochromanone C_2-H), 5.70 (2H, s, O-CH_2-), 7.09 (2H, d, J: 8.56 Hz, Ar-H), 7.30-7.33 (1H, m, Ar-H), 7.48-7.52 (1H, m, Ar-H), 7.58-7.60 (3H, d, J: 8.56 Hz, Ar-H), 7.61-7.63 (2H, m, Ar-H and =CH-), 7.65-7.72 (1H, m, Ar-H), 8.04-8.06 (3H, m, Ar-H). For $C_{25}H_{20}O_3S$ calculated: 74.98 % C, 5.03 % H; found: 75.04 % C, 5.10 % H. MS $[M+1]^+$: *m/z* 415.

2.4.24. 3-[3-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]-6-methylthiochroman-4-one ***(24)***

IR (KBr) ν_{max} (cm^{-1}): 3078, 3054 (Ar-H and =CH-), 2971, 2854 (Aliphatic C-H), 1698, 1662 (C=O), 1592-1470 (C=C), 1275, 1220 (C-O). ^{1}H-NMR δ (ppm): 2.42 (3H, s, Ar-CH_3), 3.87 (3H, s, Ar-OCH_3), 4.26 (2H, s, Thiochromanone C_2-H), 5.72 (2H, s, O-CH_2-), 7.15 (2H, d, J: 8.34 Hz, Ar-H), 7.32-7.34 (1H, m, Ar-H), 7.49-7.51 (1H, m, Ar-H), 7.58-7.60 (3H, d, J: 8.56 Hz, Ar-H), 7.60-7.62 (2H, m, Ar-H and =CH-), 7.68-7.70 (1H, m, Ar-H), 8.04-8.06 (2H, m, Ar-H). For $C_{26}H_{22}O_4S$ calculated: 72.54 % C, 5.15 % H; found: 72.51 % C, 5.21 % H. MS $[M+1]^+$: *m/z* 431.

2.4.25. 3-[3-(2-(4-Chlorophenyl)-2-oxoethoxy)benzylidene]-6-methylthiochroman-4-one ***(25)***

IR (KBr) ν_{max} (cm^{-1}): 3065, 3039 (Ar-H and =CH-), 2969, 2950 (Aliphatic C-H), 1706, 1658 (C=O), 1603-1490 (C=C), 1285, 1221 (C-O). ^{1}H-NMR δ (ppm): 2.33 (3H, s, Ar-CH_3), 4.19 (2H, s, Thiochromanone C_2-H), 5.65 (2H, s, O-CH_2-), 7.06 (1H, dd, J: 2.36 Hz, J: 8.25 Hz, Ar-H), 7.12-7.13 (2H, m, Ar-H), 7.30 (1H, d, J: 7.99 Hz, Ar-H), 7.35 (1H, dd, J:1.68 Hz, J: 8.05 Hz, Ar-H), 7.40 (1H, t, J: 7.35 Hz, Ar-H), 7.60 (1H, s, =CH-), 7.66 (2H, d, J: 8.61 Hz, Ar-H), 7.86 (1H, bs, Ar-H), 8.05 (2H, d, J: 8.59 Hz, Ar-H). For $C_{25}H_{19}ClO_3S$ calculated: 69.04 % C, 4.40 % H; found: 69.13 % C, 4.50 % H. MS $[M+1]^+$: *m/z* 435.1.

2.4.26. 3-[4-(2-Phenyl-2-oxoethoxy)benzylidene]-6-methylthiochroman-4-one ***(26)***

IR (KBr) ν_{max} (cm^{-1}): 3065, 3039 (Ar-H and =CH-), 2951, 2867 (Aliphatic C-H), 1696, 1650 (C=O), 1599-1474 (C=C), 1272, 1224 (C-O). ^{1}H-NMR δ (ppm): 2.34 (3H, s, Ar-CH_3), 4.24 (2H, s, Thiochromanone C_2-H), 5.69 (2H, s, O-CH_2-), 7.08 (2H, d, J: 8.81 Hz, Ar-H), 7.29-7.38 (2H, m, Ar-H), 7.52 (2H, d, J: 8.77 Hz, Ar-H), 7.57-7-58 (2H, m, Ar-H), 7.60 (1H, s, =CH-), 7.68-7.76 (1H, m, Ar-H), 7.89 (1H, bs, Ar-H), 8.05 (2H, d, J: 8.60 Hz, Ar-H). For $C_{25}H_{20}O_3S$ calculated: 74.98 % C, 5.03 % H; found: 74.88 % C, 5.08 % H. MS $[M+1]^+$: *m/z* 401.

2.4.27. 3-[4-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]-6-methylthiochroman-4-one ***(27)***

IR (KBr) ν_{max} (cm^{-1}): 3067, 3045 (Ar-H and =CH-), 2952, 2921, 2860 (Aliphatic C-H), 1711, 1691 (C=O), 1610-1472 (C=C), 1273, 1211 (C-O). ^{1}H-NMR δ (ppm): 2.34 (3H, s, Ar-CH_3), 3.87 (3H, s, Ar-OCH_3), 4.23 (2H, s, Thiochromanone C_2-H), 5.61 (2H, s, O-CH_2-), 7.06 (2H, d, J: 8.73 Hz, Ar-H), 7.11 (2H, d, J: 8.80 Hz, Ar-H), 7.27-7.35 (2H, m, Ar-H), 7.51 (2H, d, J: 8.61 Hz, Ar-H), 7.60 (1H, s, =CH-), 7.85 (1H, bs, Ar-H), 8.02 (2H, d, J: 8.95 Hz, Ar-H). For $C_{26}H_{22}O_4S$ calculated: 72.54 % C, 5.15 % H; found: 72.62 % C, 5.08 % H. MS $[M+1]^+$: *m/z* 431.

2.4.28. 3-[4-(2-(4-Chlorophenyl)-2-oxoethoxy)benzylidene]-6-methylthiochroman-4-one ***(28)***

IR (KBr) ν_{max} (cm^{-1}): 3105, 3035 (Ar-H and =CH-), 2975, 2866 (Aliphatic C-H), 1704, 1680 (C=O), 1601-1475 (C=C), 1275, 1230 (C-O). ^{1}H-NMR δ (ppm): 2.34 (3H, s, Ar-CH_3), 4.23 (2H, s, Thiochromanone C_2-H), 5.67 (2H, s, O-CH_2-), 7.09 (2H, d, J: 8.73 Hz, Ar-H), 7.28-7.35 (2H, m, Ar-H), 7.52 (2H, d, J: 8.61 Hz, Ar-H), 7.60 (1H, s, =CH-), 7.67 (2H, d, J: 8.21 Hz, Ar-H), 7.86 (1H, bs, Ar-H), 8.06 (2H, d, J: 8.95 Hz, Ar-H). For $C_{25}H_{19}ClO_3S$ calculated: 69.04 % C, 4.40 % H; found: 69.09 % C, 4.52 % H. MS $[M+1]^+$: *m/z* 435.

2.4.29. 3-[3-(2-Phenyl-2-oxoethoxy)benzylidene]-6-chlorothiochroman-4-one ***(29)***

IR (KBr) ν_{max} (cm^{-1}): 3105, 3040 (Ar-H and =CH-), 2958, 2922, 2870 (Aliphatic C-H), 1688, 1649 (C=O), 1601-1490 (C=C), 1275, 1260, 1221 (C-O). ^{1}H-NMR δ (ppm): 4.26 (2H, s, Thiochromanone C_2-H), 5.67 (2H, s, O-CH_2-), 7.07 (1H, dd, J: 2.19 Hz, J: 8.26 Hz, Ar-H), 7.12-7.15 (2H, m, Ar-H), 7.41 (1H, t, J: 7.92 Hz, Ar-H), 7.47 (1H, d, J: 8.47 Hz, Ar-H), 7.58-7.60 (3H, m, Ar-H), 7.64 (1H, s, =CH-), 7.71 (1H, t, J: 7.41, 7.42 Hz, Ar-H), 7.97 (1H, d, J: 2.46 Hz, Ar-H), 8.05 (2H, d, J: 7.13 Hz, Ar-H). ^{13}C-NMR δ (ppm): 28.99, 70.64, 115.52, 126.31, 127.68, 128.35, 129.43, 130.17, 131.25, 132.21, 132.43, 133.71, 137.07, 139.23, 140.94, 159.21, 185.45, 193.86. For $C_{24}H_{17}ClO_3S$ calculated: 68.48 % C, 4.07 % H; found: 68.57 % C, 4.14 % H. MS $[M+1]^+$: *m/z* 420.5.

2.4.30. 3-[3-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]-6-chlorothiochroman-4-one ***(30)***

IR (KBr) ν_{max} (cm^{-1}): 3077, 3045 (Ar-H and =CH-), 2950, 2921, 2860 (Aliphatic C-H), 1702, 1689 (C=O), 1587-1470 (C=C), 1273, 1231 (C-O). ^{1}H-NMR δ (ppm): 3.86 (3H, s, Ar-OCH_3), 4.27 (2H, s, Thiochromanone C_2-H), 5.58 (2H, s, O-CH_2-), 7.05 (1H, dd, J: 1.84 Hz, J: 8.44 Hz, Ar-H), 7.09 (2H, d, J: 9.0 Hz, Ar-H), 7.12 (2H, d, J: 8.57 Hz, Ar-H), 7.40 (1H, t, J: 8.18

Hz, Ar-H), 7.46 (1H, d, J: 8.41 Hz, Ar-H), 7.58 (1H, dd, J: 2.36 Hz, J: 8.71 Hz, Ar-H), 7.64 (1H, s, =CH-), 7.97 (1H, d, J: 2.47 Hz, Ar-H), 8.02 (2H, d, J: 8.77 Hz, Ar-H). For $C_{25}H_{19}ClO_4S$ calculated: 66.59 % C, 4.25 % H; found: 66.63 % C, 4.17 % H. MS $[M+1]^+$: *m/z* 450.5.

2.4.31. 3-[3-(2-(4-Chlorophenyl)-2-oxoethoxy)benzylidene]-6-chlorothiochroman-4-one ***(31)***

IR (KBr) ν_{max} (cm^{-1}): 3075, 3020 (Ar-H and =CH-), 2965, 2850 (Aliphatic C-H), 1698, 1650 (C=O), 1599-1474 (C=C), 1274, 1222 (C-O). ^{1}H-NMR δ (ppm): 4.62 (2H, s, Thiochromanone C_2-H), 5.65 (2H, s, O-CH_2-), 7.07 (1H, dd, J: 2.22 Hz, J: 8.12 Hz, Ar-H), 7.13 (2H, d, J: 8.67 Hz, Ar-H), 7.41 (1H, t, J: 8.0 Hz, Ar-H), 7.47 (1H, d, J: 8.77 Hz, Ar-H), 7.59 (1H, dd, J: 1.77 Hz, J: 8.43 Hz, Ar-H), 7.64 (1H, s, =CH-), 7.67 (2H, d, J: 8.52 Hz, Ar-H), 7.97 (2H, d, J: 2.28 Hz, Ar-H), 8.06 (1H, d, J: 8.57 Hz, Ar-H). For $C_{24}H_{16}Cl_2O_3S$ calculated: 63.30 % C, 3.54 % H; found: 63.33 % C, 3.47 % H. MS $[M+1]^+$: *m/z* 455.

2.4.32. 3-[4-(2-Phenyl-2-oxoethoxy)benzylidene]-6-chlorothiochroman-4-one ***(32)***

IR (KBr) ν_{max} (cm^{-1}): 3108, 3044 (Ar-H and =CH-), 2952, 2931, 2872 (Aliphatic C-H), 1687, 1654 (C=O), 1608-1485 (C=C), 1273, 1262, 1220 (C-O). ^{1}H-NMR δ (ppm): 4.25 (2H, s, Thiochromanone C_2-H), 5.66 (2H, s, O-CH_2-), 7.10 (1H, dd, J: 2.19 Hz, J: 8.26 Hz, Ar-H), 7.18-7.20 (2H, m, Ar-H), 7.47 (1H, t, J: 7.92 Hz, Ar-H), 7.52 (1H, d, J: 8.47 Hz, Ar-H), 7.59-7.61 (3H, m, Ar-H), 7.65 (1H, s, =CH-), 7.74 (1H, t, J: 7.42 Hz, Ar-H), 7.98 (1H, d, J: 2.47 Hz, Ar-H), 8.07 (2H, d, J: 7.23 Hz, Ar-H). For $C_{24}H_{17}ClO_3S$ calculated: 68.49 % C, 4.07 % H; found: 68.54 % C, 4.15 % H. MS $[M+1]^+$: *m/z* 420.1.

2.4.33. 3-[4-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzylidene]-6-chlorothiochroman-4-one ***(33)***

IR (KBr) ν_{max} (cm^{-1}): 3074, 3046 (Ar-H and =CH-), 2956, 2924, 2866 (Aliphatic C-H), 1705, 1684 (C=O), 1583-1474 (C=C), 1276, 1238 (C-O). ^{1}H-NMR δ (ppm): 3.85 (3H, s, Ar-OCH_3), 4.26 (2H, s, Thiochromanone C_2-H), 5.57 (2H, s, O-CH_2-), 7.05 (1H, dd, J: 1.80 Hz, J: 8.42 Hz, Ar-H), 7.11 (2H, d, J: 8.90 Hz, Ar-H), 7.15 (2H, d, J: 8.54 Hz, Ar-H), 7.44 (1H, t, J: 8.28 Hz, Ar-H), 7.47 (1H, d, J: 8.42 Hz, Ar-H), 7.59 (1H, dd, J: 2.32 Hz, J: 8.70 Hz, Ar-H), 7.66 (1H, s, =CH-), 7.98 (1H, d, J: 2.49 Hz, Ar-H), 8.05 (2H, d, J: 8.70 Hz, Ar-H). For $C_{25}H_{19}ClO_4S$ calculated: 66.59 % C, 4.25 % H; found: 66.65 % C, 4.14 % H. MS $[M+Na]^+$: *m/z* 473.1.

2.4.34. 3-[4-(2-(4-Chlorophenyl)-2-oxoethoxy)benzylidene]-6-chlorothiochroman-4-one ***(34)***

IR (KBr) ν_{max} (cm^{-1}): 3076, 3027 (Ar-H and =CH-), 2968, 2856 (Aliphatic C-H), 1695, 1656 (C=O), 1587-1472 (C=C), 1270, 1221 (C-O). ^{1}H-NMR δ (ppm): 4.63 (2H, s, Thiochromanone C_2-H), 5.65 (2H, s, O-CH_2-), 7.09 (1H, dd, J: 2.20 Hz, J: 8.10 Hz, Ar-H), 7.15 (2H, d, J: 8.63 Hz, Ar-H), 7.40 (1H, t, J: 8.12 Hz, Ar-H), 7.48 (1H, d, J: 8.70 Hz, Ar-H), 7.64 (1H, dd, J: 1.75 Hz, J: 8.40 Hz, Ar-H), 7.65 (1H, s, =CH-), 7.64 (2H, d, J: 8.50 Hz, Ar-H), 7.99 (2H, d, J: 2.24 Hz, Ar-H), 8.07 (1H, d, J: 8.56 Hz, Ar-H). ^{13}C-NMR δ (ppm): 28.87, 70.63, 115.53, 127.45, 128.36, 129.20, 129.32, 130.30, 130.39, 130.95, 132.01, 132.37, 133.30, 134.36, 134.74, 138.04, 139.99, 159.46, 184.44, 194.68. For $C_{24}H_{16}Cl_2O_3S$ calculated: 63.30 % C, 3.54 % H; found: 63.38 % C, 3.46 % H. MS $[M+Na]^+$: *m/z* 477.0.

2.5. Anticancer Activity

The evaluation of anticancer activity was performed at the National Cancer Institute (NCI) of Bethesda, USA. To determine anticancer activity of the selected compounds were tested against sixty human tumour cell lines derived from nine neoplastic diseases namely; leukemia (L, 4 or 6 cell lines), non-small cell lung cancer (NSCLC, 9 cell lines), colon cancer (CC, 7 cell lines), central nervous system cancer (CNSC, 6 cell lines), melanoma (M, 8 or 9 cell lines), ovarian cancer (OC, 6 or 7 cell lines), renal cancer (RC, 8 cell lines), prostate cancer (PC, 2 cell lines), breast cancer (BC, 6 or 8 cell lines). The cytotoxic and/or growth inhibitory effects of the compounds were evaluated at one concentration as a first stage. According to the *in vitro* screening program of the institute promising compounds were tested at lower five concentrations ranging from 10^{-4} to 10^{-8} M. The percentage growth was evaluated spectrophotometrically versus controls not treated with test agents. Three dose response parameters (GI_{50}, TGI and LC_{50}) were calculated for each experimental agent (Boyd, 1989; Boyd, 1995).

3. Results and discussion

New thirty four 3-[3/4-(2-aryl-2-oxoethoxy)arylidene]chroman/thiochroman-4-one derivatives (**1-34**) were synthesized, in this study. The synthesis of the compounds was carried out in a multi-step reaction. In the first step, appropriate phenol or thiophenol derivative was reacted with acrylonitrile in THF using Triton-B as a catalyst. The resulting 3-aryloxy/arylthioxy propionitrile compounds (**Ia-Ie**) were hydrolyzed by acetic acid/hydrochloric acid mixture to get corresponding carboxylic acid derivatives (**IIa-IIe**) which were heated with polyphosphoric acid (PPA) to acquire ring closure products, chromanon-4-one or thiochroman-4-one derivatives (**IIIa-IIIe**). The obtained cyclic ketone compounds were reacted with 3-/4-hydroxybenzaldehyde derivatives catalyzed by

hydrochloric acid in *n*-butanol to get hydroxyarylidene intermediates **(IVa-IVj)** which were then reacted with appropriate 2-bromoacetophenone derivatives in acetone and in a basic medium provided by K_2CO_3. The structures of the final compounds (**1-34**) were proved by IR, ^{1}H NMR, MS spectral data and elemental analysis data. In the IR spectra of the compounds, characteristic stretching bands were observed at about 1700-1680 cm^{-1} and 1680-1650 cm^{-1} belong to two ketone C=O bonds. In finger print region, the stretching bands for C-O bonds were seen at about 1270-1225 cm^{-1}. In the NMR spectra of the compounds, all protons were seen at estimated fields of the spectrum. The signals at about 4.19-5.48, 5.57-5.74 and 7.60-7.78 ppm were assigned to -CH_2C-, $COCH_2$- and -C=CH- groups, respectively and they were observed as common peaks in all spectrums. The protons of 1,4-disubstituted phenyl moiety were seen as doublet peaks and they were determined in accordance with splitting pattern of AB system. In the ^{13}C-NMR spectra of the compounds, as common to all compounds carbon atom of the acetyl group was seen at about 70.37-71.66 ppm. C-2 carbon atom of the chroman-4-one ring was given signal at about 67.84-68.19 ppm, whereas C-2 carbon atom of the thiochroman-4-one was given 28.67-29.00 ppm field. The carbonyl carbons were resonated at ppm. Besides, all other aromatic carbons were observed at estimated regions. In the MS spectra of the compounds, M+1 peaks or M+Na peaks were observed consistent with calculated molecular weights. Also, elemental analysis results gave confirmative molecular formulas.

The experimental procedure was realized at National Cancer Institute of USA (NCI) for determining anticancer activity of the compounds. All final compounds (**1-34**) were offered to the institute, fourteen of them was selected to be tested. According to the drug screening protocol of the institute, compounds **1, 7, 8, 11, 17, 18, 21, 22, 24, 25, 27, 28, 30** and **31** were screened against 60 tumor cell lines derived from nine cancer disease at one dose (10^{-5} M) as a first stage study and the results were given as percent cell growth promotion (Table 3). Among them, compounds **1, 11, 17, 18, 24, 25, 30** and **31** which exhibited growth percentage lower than 80 % on tumor cells as a mean value were passed through to second stage and tested at five concentrations (0.01, 0.1, 1, 10 and 100 μM). The results were given as log10 GI50 which is the log value of growth inhibitory activity that corresponds to the concentration of the compounds causing 50 % decrease in net cell growth and they were shown in Table 4. The growth inhibition of half percentage of tumor cells (GI50) calculated from the equation [(Ti - Tz)/(C - Tz)] x 100 = 50 where abbreviations Tz, C, and Ti state absorbance measurements at time zero, (Tz), control

growth (C) and test growth in the presence of sample at the five concentration levels (Ti) (Husain, 2013). Besides, dose-response graphics plotted according to the results were identified for all compounds against all cancer types. (some of them were shown as supplementary data).

As can be shown in Table 3, compounds caused growth percentages of tumor cells ranging from -11.63 to 103.44 %. Compounds **17** and **18** exhibited the highest antiproliferative activity with values of -0.10 and -11.63 % and these two compounds differ from other compounds which have growth percentages even more than 50 %. Furthermore, compounds **1, 37, 30, 25, 24** and **11** have also showed remarkable values of 54.70, 56.67, 69.47, 77.49, 79.08 and 79.53 % which are lower than 80 % thus they are acceptable to be test in the second stage. These eight compounds have attracted attention with carrying 1,3-benzylidene moiety considering 1,4-benzylidene bearing derivatives could not exhibit higher activities. Besides, it appears six of these eight compounds (**17, 18, 24, 25, 30** and **31**) have thiochromanone skeleton. In previous studies, thiochromanone containing compounds were determined to have many potential biological activities; in particular, the ring was introduced some unprecedented benefits to anticancer drug discovery in low doses (Gao et al., 2010). Also, several compounds, based primarily on the benzophenone or thiochromanone thiosemicarbazone molecular structure, were identified as lead compound inhibitors of cathepsin L which increases during cancer progression and aids in cancer metastasis (Song et al., 2012). Additionally, the studies in synthetic flavonoid derivatives showed that the presence of heterocyclic thioether feature will profit the antitumor activities of flavonoids (Huang, 2007). Other remarkable situation was determined that two of these compounds possessed two chlorine atoms and three others possessed one chlorine atom. Also, six thiochromanone compounds were attracted attention with bearing 4-methoxy and 4-chloro phenyl acetyloxy moieties bonded to third position of main structure (3-(hydroxyarylidene) thiochroman-4-one derivatives). A similar finding was determined in our previous study that methoxy and chloro substituents on various molecules have provided increase of anticancer activity (Yurttas, 2013; Yurttas, 2015).

Among the cancer types, leukaemia, melanoma and colon cancer cells were found as the most sensitive cells against the tested compounds. The lowest growth value (-100.00 %) was obtained against the type of cell lines S (leukaemia), LOX IMVI (melanoma) and SW-620 (colon cancer) for compounds **17** and **18**.

Compounds with growth values under 80 % were subjected to further testing and log10 GI50 and MG-MID values were determined as a result of this test. MG-MID value was calculated as mean graph midpoint for each subpanels of cancer types for the tested compounds and standard drugs cisplatin and melphalan which are two of the commonly used chemotherapeutic agents by giving log10 GI50 (Table 4). The test method states that the compounds having log10 GI50 values greater than -4 were considered as inactive. It can be seen that both of the compounds log10 GI50 values are smaller than -4. Accordingly, when we considered MG-MID values of standard drugs and selected compounds; all compounds except **11** and **24** exhibited higher activity than melphalan (-5.09), however all compounds showed lower activity than cisplatin (-6.20).

The lowest concentrations (MG_MID) were reached for compounds **17** (-5.73) and **18** (-5.83) These values which are obtained according to concentration, were found proportional with previously described growth percentage values. The lowest growth percentage values were determined consistent with the MG_MID of these compounds. The lowest log10 GI50 value was obtained against leukaemia cells as -6.39 which was also equals to the value found for the standard used cisplatin and this value was the lowest value obtained for the standard. The obtained average log10 GI50 and MG_MID values against nine types of cancer were represented, collectively in Table 4.

According to the reported literature, compounds possessing chromanone and/or thiochromanone as a main structure and an aryl group/arylidene group with one or more free hydroxyl groups are known to have very high anticancer effects as specified. Considering the results obtained in our study, thiochromanone compounds containing 1,3-disubstituted benzylidene residue were observed to have extremely high anticancer activity. In light of this information, arylidene thiochromanone compounds carrying phenolic groups will be studied in the next part of our work. Furthermore, it will also aimed to examine the change of anticancer effects when the phenacyloxy residue brought into *ortho* position on benzylidene moiety.

4. Conclusion

In this study, 3-[3/4-(2-aryl-2-oxoethoxy)arylidene]chroman/thiochroman-4-one derivatives (**1-34**) and anticancer activity of the selected compounds were investigated by NCI. According to the drug screening protocol of the institute, mostly final compounds (**15-34**) containing thiochromanone skeletone caused lower growth percentages in various cancer cell lines. Additionally, compound **18** namely 3-[3-(2-(4-chlorophenyl)-2-

oxoethoxy)benzylidene]thiochroman-4-one was determined as the most potent molecule which showed higher anticancer activity than standard drug melphalan.

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Conflict of interest

The authors confirm that this article content has no conflict of interest.

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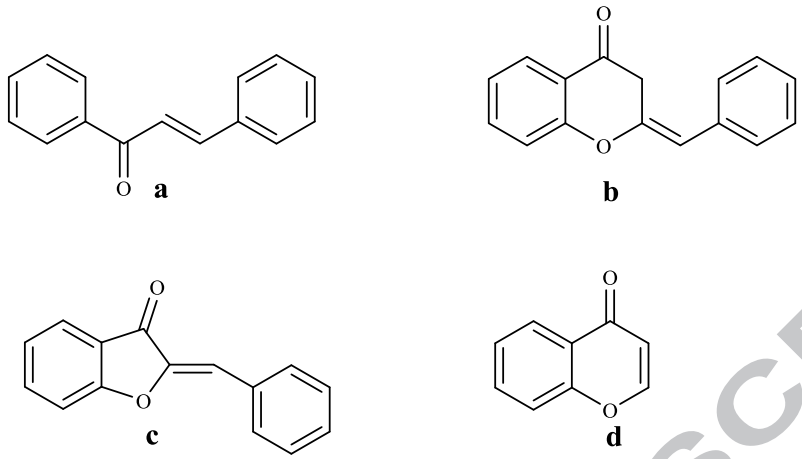
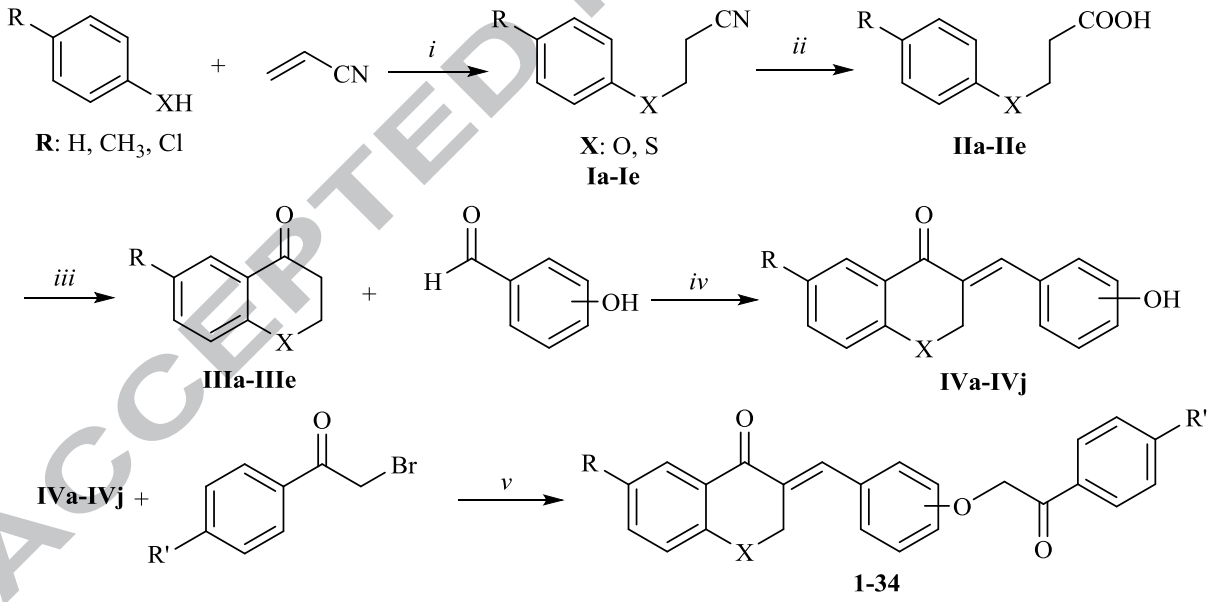
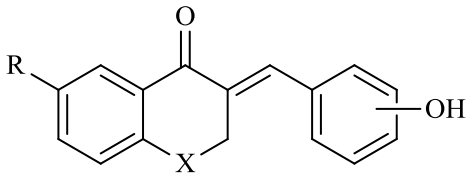


Figure 1. The chemical structures of **a**) chalcone, **b**) homoisoflavonoid, **c**) aurone, **d**) chromenone



Scheme 1. The synthesis of the 3-[3/4-(2-aryl-2-oxoethoxy)arylidene]chroman/thiochroman-4-one derivatives (**1-34**). Reactants/reagents and reaction conditions. ***i*** : THF, Triton-B, reflux, 30 min; ***ii*** : AcOH/HCl, 160-170 ^{o} C; ***iii*** : PPA, 50-100 ^{o} C, 3-4 h; ***iv*** : *n*-butanol, catalytic HCl, reflux, 1 h; ***v*** : K_2CO_3, acetone, reflux, 6 h.

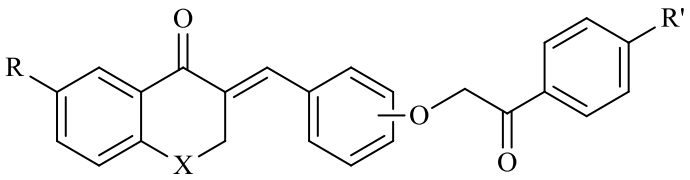
Table 1. 3-(3/4-Hydroxyarylidene)chroman/thiochroman-4-one Derivatives



IVa-j

C.	Chemical name	X	OH	R	M.P. (^{o}C)
IVa	3-(3-Hydroxyarylidene)chroman-4-one	O	3	H	203-204(Mulvagh et al., 1979)
IVb	3-(4-Hydroxyarylidene)chroman-4-one	O	4	H	230-232(Kirkiacharian et al., 1989)
IVc	6-Chloro-3-(3-hydroxyarylidene)chroman-4-one	O	3	Cl	192-194(Siddiah et al., 2006)
IVd	6-Chloro-3-(4-hydroxyarylidene)chroman-4-one	O	4	Cl	238-240(Kirkiacharian et al., 1989)
IVe	3-(3-Hydroxyarylidene)thiochroman-4-one	S	3	H	147-148
IVf	3-(4-Hydroxyarylidene)thiochroman-4-one	S	4	H	192-194(Levai and Schag, 1979)
IVg	6-Methyl-3-(3-hydroxyarylidene)thiochroman-4-one	S	3	CH_3	147-148
IVh	6-Methyl-3-(4-hydroxyarylidene)thiochroman-4-one	S	4	CH_3	222-223
IVi	6-Chloro-3-(3-hydroxyarylidene)thiochroman-4-one	S	3	Cl	156-158
IVj	6-Chloro-3-(4-hydroxyarylidene)thiochroman-4-one	S	4	Cl	202-204

Table 2. 3-[3/4-(2-Aryl-2-oxoethoxy)arylidene]chroman/thiochroman-4-one Derivatives



1-34

Comp.	X	-R	-R'	Position	M.P.(°C)	M.F.
1	O	-H	-H	3	119	$C_{24}H_{18}O_4$
2	O	-H	$-CH_3$	3	146	$C_{25}H_{20}O_4$
3	O	-H	$-OCH_3$	3	161	$C_{25}H_{20}O_5$
4	O	-H	-Cl	3	140	$C_{24}H_{17}ClO_4$
5	O	-H	-H	4	176	$C_{24}H_{18}O_4$
6	O	-H	$-CH_3$	4	179	$C_{25}H_{20}O_4$
7	O	-H	$-OCH_3$	4	200	$C_{25}H_{20}O_5$
8	O	-H	-Cl	4	193	$C_{24}H_{17}ClO_4$
9	O	-Cl	-H	3	130	$C_{24}H_{17}ClO_4$
10	O	-Cl	$-OCH_3$	3	157	$C_{25}H_{19}ClO_5$
11	O	-Cl	-Cl	3	133	$C_{24}H_{16}Cl_2O_4$
12	O	-Cl	-H	4	185	$C_{24}H_{17}ClO_4$
13	O	-Cl	$-OCH_3$	4	160	$C_{25}H_{19}ClO_5$
14	O	-Cl	-Cl	4	188	$C_{24}H_{16}Cl_2O_4$
15	S	-H	-H	3	148	$C_{24}H_{18}O_3S$
16	S	-H	$-CH_3$	3	136	$C_{25}H_{20}O_3S$
17	S	-H	$-OCH_3$	3	137	$C_{25}H_{20}O_4S$
18	S	-H	-Cl	3	137	$C_{24}H_{17}ClO_3S$
19	S	-H	-H	4	146	$C_{24}H_{18}O_3S$
20	S	-H	$-CH_3$	4	140	$C_{25}H_{20}O_3S$
21	S	-H	$-OCH_3$	4	130	$C_{25}H_{20}O_4S$
22	S	-H	-Cl	4	176	$C_{24}H_{17}ClO_3S$
23	S	$-CH_3$	-H	3	110	$C_{25}H_{20}O_3S$
24	S	$-CH_3$	$-OCH_3$	3	165	$C_{26}H_{22}O_4S$
25	S	$-CH_3$	-Cl	3	153	$C_{25}H_{19}ClO_3S$
26	S	$-CH_3$	-H	4	151	$C_{25}H_{20}O_3S$
27	S	$-CH_3$	$-OCH_3$	4	158	$C_{26}H_{22}O_4S$
28	S	$-CH_3$	-Cl	4	200	$C_{25}H_{19}ClO_3S$
29	S	-Cl	-H	3	134	$C_{24}H_{17}ClO_3S$

30	S	-Cl	$-OCH_3$	3	155	$C_{25}H_{19}ClO_4S$
31	S	-Cl	-Cl	3	148	$C_{24}H_{16}Cl_2O_3S$
32	S	-Cl	-H	4	173	$C_{24}H_{17}ClO_3S$
33	S	-Cl	$-OCH_3$	4	177	$C_{25}H_{19}ClO_4S$
34	S	-Cl	-Cl	4	212	$C_{24}H_{16}Cl_2O_3S$

Table 3. 60 human tumor cell lines' anticancer screening data at single dose assay as percent cell growth promotion of selected compounds.

Com	NSCLC	CC	BC	OC	L	RC	M	PC	CNSC	Mean
1	73.59	21.64	37.84	69.31	-18.47	79.67	65.3	101.03	87.66	54.70
7	93.34	94.38	82.99	93.86	66.72	94.15	88.47	105.63	97.01	89.11
8	99.17	101.43	91.74	98.33	90.97	100.15	99.22	108.54	89.01	96.37
11	89.09	83.49	67.44	81.33	19.71	92.74	86.03	124.48	91.17	79.53
17	52.23	-49.79	-36.15	59.22	-64.04	11.74	-58.79	101.83	36.77	-0.10
18	38.66	-46.31	-10.45	51.54	-61.46	-12.38	-82.43	27.66	18.30	-11.63
21	99.93	104.05	96.42	103.53	88.65	101.41	95.23	120.25	95.24	98.34
22	107.89	107.6	103.38	105.13	90.68	100.19	104.18	113.32	106.74	103.44
24	92.05	68.76	79.47	90.17	4.50	93.42	90.58	108.79	99.49	79.08
25	83.42	69.59	73.49	98.21	11.81	78.70	92.49	108.30	102.65	77.49
27	97.49	80.77	96.64	105.17	64.31	99.53	94.86	104.51	106.06	95.19
28	100.28	100.93	106.49	109.23	89.76	102.74	102.74	113.20	102.95	101.83
30	82.47	57.61	63.97	83.82	16.03	81.84	74.95	61.92	92.11	69.47
31	65.29	30.40	45.10	81.01	5.01	75.46	73.05	43.72	78.90	56.67

NSCLC Non-small cell lung cancer, CC Colon cancer, BC breast cancer, OC ovarian cancer, L leukemia, RC renal cancer, M melanoma, PC prostate cancer, CNSC central nervous system cancer.

Table 4. Log10 GI50 Values

Comp	L	NSLC	CC	CNS	M	OC	RC	PC	BC	MG_MID
1	-5.59	-5.15	-5.69	-5.28	-5.44	-5.43	-5.64	-5.45	-5.49	-5.45
11	-5.41	-5.01	-5.25	-4.88	-4.95	-5.11	-4.91	-4.87	-5.20	-5.08
17	-6.26	-5.46	-6.00	-5.68	-5.72	-5.66	-5.55	-5.74	-6.00	-5.78
18	-6.39	-5.48	-6.05	-5.75	-5.77	-5.66	-5.80	-5.76	-5.82	-5.83
24	-5.57	-4.48	-5.25	-4.83	-4.79	-4.75	-4.52	-4.71	-5.03	-4.84
25	-5.63	-4.89	-5.53	-5.11	-5.22	-5.11	-4.99	-5.09	-5.42	-5.22
30	-5.79	-4.92	-5.43	-5.15	-5.03	-4.98	-4.88	-5.36	-5.18	-5.17
31	-6.13	-5.18	-5.14	-5.33	-5.23	-5.48	-5.50	-6.18	-5.27	-5.42
A	-5.48	-5.17	-5.11	-5.12	-5.08	-5.18	-4.99	-4.49	-4.79	-5.09
B	-6.39	-6.20	-6.14	-6.18	-6.08	-6.45	-6.17	-6.41	-6.05	-6.20

A: Melphalan, **B**: Cisplatin