Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2012, 4(5):2029-2035
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

A facile synthesis, characterization of N-substituted 7-methoxy-3-phenyl-4-(3-piperizin-1-yl-propaxy) chromen-2-one

Devender Mandala[a, b], Sravanthi Chada[a], Umapathi Nalla[a], Jalapathi Pochampalli[a]*

[a]*Department of chemistry, PG College of Science, Osmania University, Hyderabad- 500004, India*
[b]*Allied Fabrichem Pvt. Ltd, Plot No-185, Phase-II, IDA-Mallapur, Hyderabad-500076, India*

ABSTRACT

A series of novel N-substituted 7-methoxy-3-phenyl-4-(3-piperizin-1-yl-propaxy) chromen-2-one compounds have been synthesized by reacting 7-methoxy-3-phenyl-4-(3- piperizin-1-yl-propaxy) chromen-2-one with various substituted halo compounds in the presence of triethylamine/dichloromethane. The newly synthesized compounds were purified and their structures were characterized by IR, ^{1}H-NMR and Mass spectroscopy.

Key Words: Coumarins, 1, 3-Dibromopropane, Halo compounds, Piperizine.

INTRODUCTION

The piperizines are a broad class of chemical compounds with several vital pharmalogical properties. These compounds have been shown to potent analgesics, psychotolytic [1] and antifungal activities [2] [3]. N-substituted piperizines have been reported to possess various activities like, local anesthetic, antihyperlipidemic, anticoagulant [4] and also antihelmenthic, anticancer [5] [6] [7], antihistamic [8], antidepressant [9]. Some aryl piperizine derivatives possess antienteroviral activity [10] [11], anti-HIV properties [12], Certain 1, 4-disubstituted aromatic piperizines with extreme selectivity for the dopamine D_4 receptor interact with a common micro domain [13] 1, 4-disulfoally piperizines are used as buffering agents.

The incorporation of different halo substitutes in piperizine moiety is an significant synthetic strategy in medicinal chemistry due to its wide range of biological applications, proper alkality, solubility nature in water and physicochemical properties [14] [15]. General applications of these substituted piperizines including development of different pharmaceutical intermediates, peptide analogues, antibiotics and other biologically active molecules for different clinical drugs development [16] [17] [18].

Coumarins are wide spread in nature and also biological activities of different coumarins and its derivatives are distinguished, they are anticoagulant, antimicrobial [19], anti-HIV, antioxidant [20], antiallergic, anticancer [21] and antiviral activities [22]. A large number of structurally novel coumarins derivatives have ultimately been reported to show substantial cytotoxicity and anti-HIV in vitro and in vivo [23] [24]. Several biological activities have been reported in natural-occurring coumarins, from photo sensitizers to vasodilatation. Recently, the interest has been given to synthetic derivatives of coumarins, such as fluorinated and 1-azo coumarins, which displayed moderate analgesia properties and excellent anti-inflammatory. In this connection we report synthesis of new molecules which contain piperizine and coumarin moieties within the framework.

MATERIALS AND METHODS

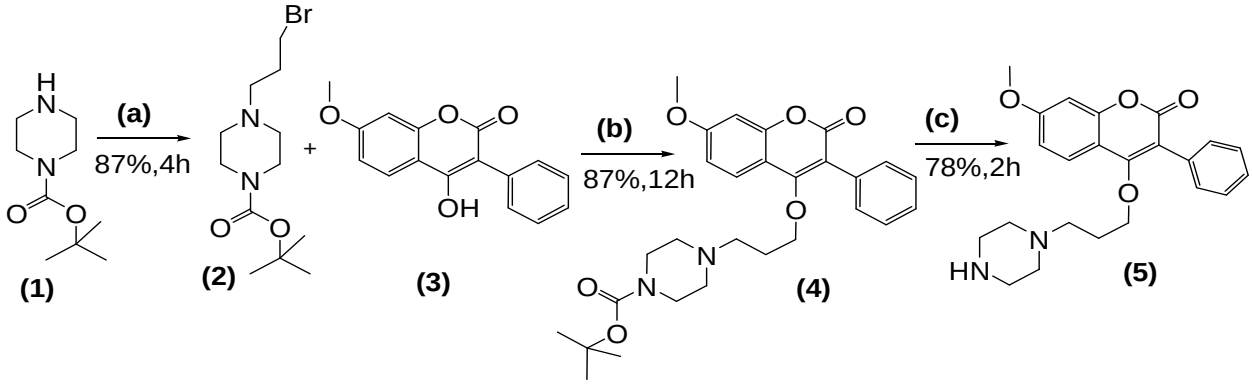
Thin Layer Chromatography (TLC) was performed on E.Merk AL Silica gel 60 F254 plates and visualized under UV light. The infrared (IR) spectra were determined in a perkin-Elmer Fourier transform (FDIR spectrum). ^{1}H-NMR spectra were recorded on Varian EM-360 (400MHz mercury plus) spectrometer in DMSO-d_6 or $CDCl_3$ and calibrated using solvent signals [7.25($CDCl_3$) and 2.50(DMSO-d_6)]. All chemical shifts recorded in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Agilent ion trap MS. Spectrometer at energy of ionizing electron equal to 70ev. Most of the reagents were purchased from Aldrich chemical company, Fluka and Merck Company.

RESULTS AND DISCUSSION

Several N-substituted piperizine derivatives were synthesized by the reaction between 7-Methoxy-3-phenyl-4-(3-piperzin-1-yl-propoxy)-chromen-2-one **(5)** and various substituted halo/other aromatic substituted compounds in presence of a mild base (triethylamine) in dichloromethane as a solvent. The compound 4-(3-Bromo-propyl)-piperazine-1-carbaxylic acid *tert*-butyl ester **(2)** was prepared by the reaction of Piperazine-1-carbaxylic acid *tert*-butyl ester **(1)** with 1,3-dibromo propane using K_2CO_3-acetone to yielded 4-(3-Bromo-propyl)-piperazine-1-carbaxylic acid *tert*-butyl ester **(2)** as white solid, the compound **(2)** alkylated with 4-Hydroxy-7-methoxy-3-phenyl-chromen-2-one **(3)** [25] in presence of K_2CO_3 in acetonitrile to afford 4-[3-(7-Methoxy-2-oxo-3-phenyl-2H-chromen-4-yloxy)-propyl]-piperazine-1-carboxylic acid *tert*-butyl ester **(4)**. The compound **(4)** was deprotected with TFA/DCM to afforded **7**-Methoxy-3-phenyl-4-(3-piperzin-1-yl-propoxy)-chromen-2-one **(5)** a brown color solid.

Preparation of 4-(3-Bromo-propyl)-piperazine-1-carbaxylic acid tert-butyl ester (2):
Anhydrous potassium carbonate (5.55g, 40.32mmol) was added to a solution of Piperazine-1-carbaxylic acid *tert*-butyl ester **(1)** (5.0g, 26.88mmol) in dry acetone followed by 1, 3-dibromo propane (3.27mL, 32.25mmol) at room temperature. The reaction mixture stirred for 4h at same temperature and then the volatiles were evaporated under reduced pressure, diluted with water and extracted with ethyl acetate (3x50mL). The combined organic layers dried over Na_2SO_4 and evaporated by rotary to afford 7.20g (87.2%) of 4-(3-Bromo-propyl) - Piperazine-1-carbaxylic acid *tert*-butyl ester (2) as off white color solid.

^{1}H-NMR-(400MHz) in $CDCl_3$: *δ* 1.49 (s, 9H, -boc); 1.78 (m, 2H, -NCH_2**CH_2**CH_2Br); 2.02 (t, 2H, -NCH_2CH_2**CH_2**Br); 2.38 (t, 4H, **Piperazine**); 3.46 (t, 4H, **Piperazine**); 3.82 (t, 2H, -N**CH_2**); MS-*m/z:* 307 $(M+H)^+$; ESI-HRMS: *m/z* calcd. For $C_{12}H_{23}BrN_2O_2$ $[M+H]^+$ 307.1390; Found: 307.1381.



Reagents & Conditions:(a)1,3-dibromo propane,K_2CO_3-Acetone(b) Compound-(3), K_2CO_3, ACN (c) TFA-CH_2Cl_2

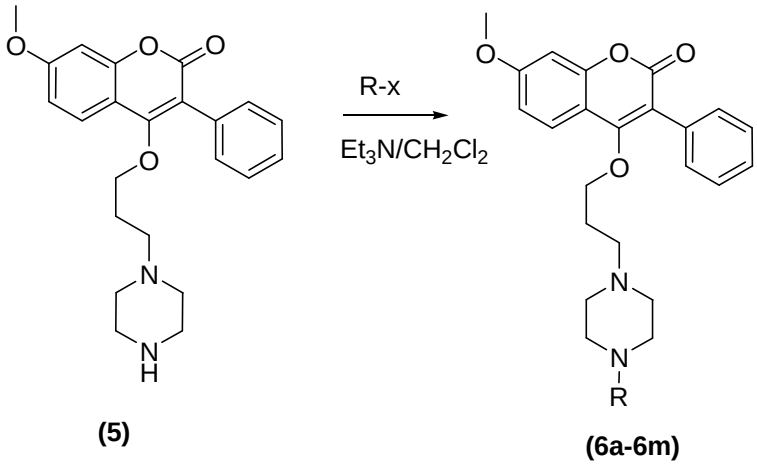
Scheme-1

Preparation of 4-[3-(7-Methoxy-2-oxo-3-phenyl-2H-chromen-4-yloxy)-propyl]-piperazine-1-carboxylic acid tert-butyl ester (4):
Potassium carbonate (3.3g, 24.42mmol) was added to a solution of 4-Hydroxy-7-methoxy-3-phenyl-chromen-2-one **(3)** (4.3g, 16.28mmol) in acetonitrile (40mL) at room temperature. The mixture stirred for 30min, then added a solution of 4-(3-Bromo-propyl)-piperazine-1-carbaxylic acid *tert*-butyl ester **(2)** (5.0g, 16.28mmol) in acetonitrile (10mL). This mixture heated at 80°C for 12h, cool to room temperature evaporated the solvent and dilute with water, extracted with ethyl acetate (3x100mL) to get crude compound. The crude compound was purified by column chromatography using neutral alumina. The pure compound elute at 1% methanol in chloroform as a mobile phase to afford 11.2g (86.6%) of 4-[3-(7-Methoxy-2-oxo-3-phenyl-2H-chromen-4-yloxy)-propyl]-piperazine-1-carboxylic acid *tert*-butyl ester **(4)** as a brown color solid.

^{1}H-NMR-(400MHz) in $CDCl_3$: δ 1.45 (s, 9H, -boc); 1.76-1.69 (m, 2H, **-CH_2-** propyl); 2.25 (t, 4H, **Piperazine**); 2.38 (d, 2H, N**CH_2** propyl); 3.35 (t, 4H, **Piperazine**); 3.69 (t, 2H, O**CH_2** propyl); 3.94 (s, 3H, O**CH_3**); 6.85 (s, 1H, **Ar-H**); 6.88 (d, 1H, **Ar-H**); 7.47-7.34 (m, 5H, **Ar-H**); 7.75 (d, 1H, **Ar-H**); **^{13}C-NMR in $CDCl_3$ (75 MHz):** δ 166.32, 163.76, 161.12, 156.76, 152.80, 133.65, 132.10, 130.43, 128.94, 114.87, 111.54, 108.98, 98.42, 80.43, 66.32, 58.64, 52.08, 51.19, 49.21, 29.34, 28.80; MS-m/z: 495 $(M+H)^+$; ESI-HRMS: *m/z* calcd. For $C_{28}H_{34}N_2O_6$ $[M+H]^+$495.2322; Found: 495.2301.

Preparation of 7-Methoxy-3-phenyl-4-(3-piperzin-1-yl-propoxy)-chromen-2-one (5):
To a solution of 4-[3-(7-Methoxy-2-oxo-3-phenyl-2H-chromen-4-yloxy)-propyl]-piperazine-1-carboxylic acid tert-butyl ester **(4)** (10g, 20.24mmol) in DCM (5vol, 50mL) was added TFA (1vol, 10mL) at 0 °C. The reaction mixture was allowed to come to room temperature and stirred for 2 h. The solvent was evaporated under reduced pressure and basified with saturated $NaHCO_3$ solution, extracted with chloroform (3x100mL). the combined organic layers dried over Na2SO4 evaporated by rotary to get 6.2g (78.4%) of 7-Methoxy-3-phenyl-4-(3-piperzin-1-yl-propoxy)-chromen-2-one **(5)** as a brown color solid.

^{1}H-NMR-(400MHz) in $CDCl_3$: δ 1.73-1.64 (m, 2H, **-CH_2-** propyl); 2.28 (t, 2H, -N**CH_2** propyl); 2.42 (t, 4H, **Piperazine**); 2.98 (t, 4H, **Piperazine**); 3.66 (t, 2H, -O**CH_2** propyl); 3.89 (s, 3H, -O**CH_3**); 6.85 (s, 1H, **Ar-H**); 6.88 (d, 1H, **Ar-H**); 7.48-7.30 (m, 5H, **Ar-H**); 7.77 (d, 1H, **Ar-H**); **^{13}C-NMR in $CDCl_3$(75 MHz):** δ 164.32, 154.86, 133.65, 132.10, 129.18, 124.94, 117.78, 77.50, 111.24, 72.43, 68.12, 56.75, 55.92, 54.26, 52.08, 50.12, 39.21, 28.86; MS-m/z: 395 $(M+H)^+$; ESI-HRMS: *m/z* calcd. For $C_{23}H_{26}N_2O_4$ $[M+H]^+$: 395.1832; Found: 395.1821.

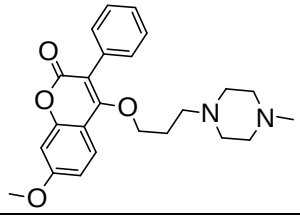
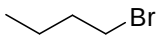
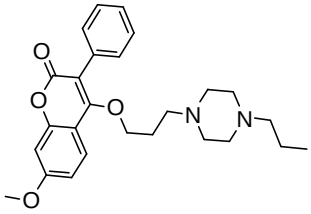
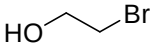
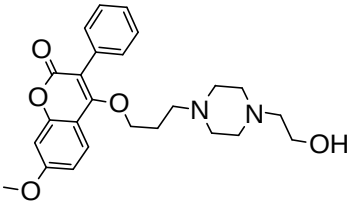
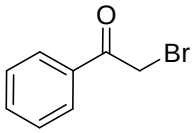
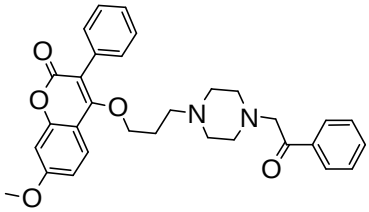
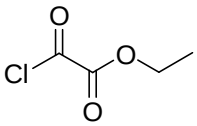
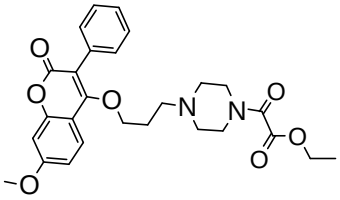
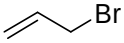
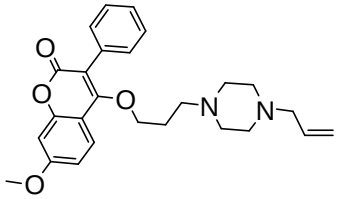
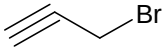
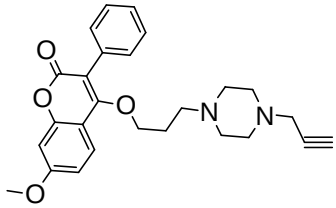
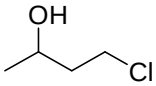
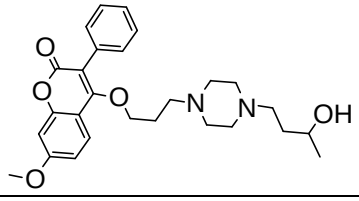


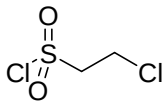
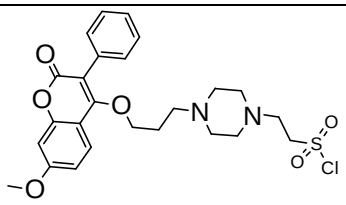
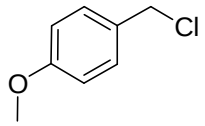
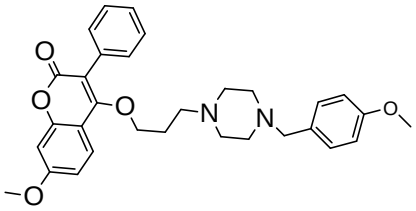
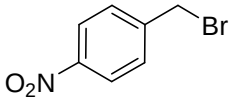
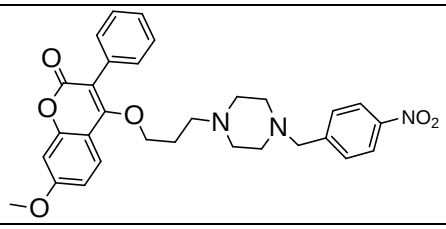
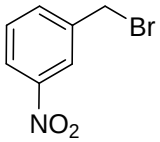
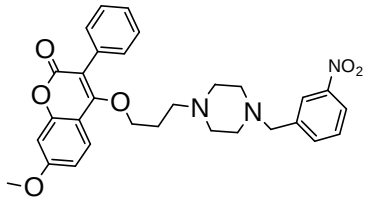
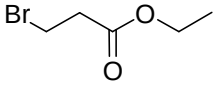
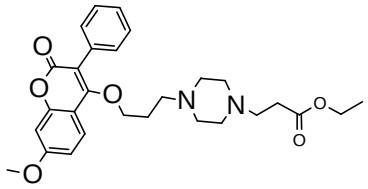
Scheme-2

General procedure: Preparation of 7-Methoxy-3-phenyl-4-(3-piperzin-1-yl-propoxy)-chromen-2-one derivatives (6a-6m):
Triethylamine (1.5eq) and corresponding halo compounds (1.1eq) was added to a solution of 7-Methoxy-3-phenyl-4-(3-piperzin-1-yl-propoxy)-chromen-2-one **(5)** (1.0eq) in dichloromethane at 0°C. Then the reaction mixture allow to room temperature for 1-12h. After completion of the reaction, as indicated by TLC, The mixture was washed with water and brine solution and extracted with dichloromethane. The organic layers dried over Na_2SO_4, evaporated by rotary to afford corresponding products **(6a-6m)**. All the products were confirmed by ^{1}H-NMR, ^{13}C-NMR, FT-IR, HRMS and Mass spectral analysis.

Spectral data for compounds-(6a-6m):
7-Methoxy-4-[3-(4-methyl-piperzin-1-yl)-propoxy]-3-phenyl-chromen-2-one (6a), off white solid**: ^{1}H-NMR-(400MHz) in $CDCl_3$:** δ 1.73-1.64 (m, 2H, **-CH_2-** propyl); 2.16 (s, 3H, -N**CH_3**); 2.28 (t, 2H, -N**CH_2** propyl); 2.42 (t, 4H, **Piperazine**); 2.98 (t, 4H, **Piperazine**); 3.76 (t, 2H, -O**CH_2-** propyl); 3.92 (s, 3H, -O**CH_3**); 6.95 (s, 1H, **Ar-H**); 6.98 (d, 1H, **Ar-H**); 7.42-7.32 (m, 5H, **Ar-H**);7.76 (d, 1H, **Ar-H**); ^{13}C-NMR in $CDCl_3$ (75 MHz): δ 166.43; 162.08, 159.86, 148.42, 132.10, 129.28, 127.18, 125.94, 117.78, 111.24, 109.18, 98.60, 77.50, 65.12, 57.57, 54.91, 50.12, 42.98, 29.26; MS-*m/z:* 407 $(M-1)^-$ -Ve Scan.

Table 1: synthesis of N-alkyl derivatives of - 7-Methoxy-3-phenyl-4-(3-piperzin-1-yl-propoxy)-chromen-2-one (6a-6m)

Entries	Reagents R=	Product code	Products	Reaction Time	% of yields
1.	CH_3I	6a		2h.	90%
2.		6b		4h.	78%
3.		6c		3h.	96%
4.		6d		4h.	88%
5.		6e		12h.	87%
6.		6f		1h.	98%
7.		6g		1h	97%
8.		6h		12h	56%

9.		6i		6h	73%
10.		6j		4h.	78%
11.		6k		1h	98%
12.		6l		2h	86%
13.		6m		4h.	96%

7-Methaoxy-3-phenyl-4-[3-(4-propyl-piperazin-1-yl)-propoxy]-chromen-2-one (6b), off white solid: ^{1}H-NMR-(400MHz) in $CDCl_3$: δ 0.90 (t, 3H, **-CH$_3$**); 1.36-1.30 (m, 2H, **-CH$_2$**CH$_3$); 1.58-1.50 (m, 2H, **-CH$_2$** propyl); 1.98 (t, 2H, -N**CH$_2$**); 2.38 (t, 4H, **Piperazine**); 2.67 (t, 4H, **Piperazine**); 2.88 (t, 2H, -N**CH$_2$**); 3.83 (t, 2H, -O**CH$_2$** propyl); 3.93(s, 3H, -O**CH$_3$**); 6.79 (s, 1H, **Ar-H**); 6.98 (d, 1H, **Ar-H**); 7.47-7.32 (m, 5H, **Ar-H**); 7.75 (d, 1H, **Ar-H**); ^{13}C-NMR in $CDCl_3$ (75 MHz): δ 165.42; 163.56, 156.86, 146.12, 132.10, 131.08, 128.98, 126.24, 116.98, 110.43, 107.28, 101.10, 77.50, 65.12, 58.57, 52.61, 49.42, 38.92, 27.16, 22.65, 12.80; MS-*m/z:* 437 $(M+H)^+$; ESI-HRMS: *m/z* calcd. For $C_{26}H_{32}N_2O_4$ $[M+H]^+$437.3226; Found: 437.3221.

4-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl)-propoxy]-7-methaxy-3-phenyl-chromen-2-one(6c), thick liquid: ^{1}H-NMR-(400MHz) in $CDCl_3$: δ 1.58-1.50 (m, 2H, **-CH$_2$** propyl); 1.98 (t, 2H, -N**CH$_2$** propyl); 2.38 (t, 4H, **Piperazine**); 2.68 (t, 4H, **Piperazine**); 2.90 (t, 2H, N**CH$_2$**); 3.86 (t, 2H, -O**CH$_2$** propyl); 3.94 (q, 2H, -O**CH$_2$**); 3.98 (s, 3H, -O**CH$_3$**); 6.79 (s, 1H, **Ar-H**); 6.98 (d, 1H, **Ar-H**); 7.37-7.28 (m, 5H, **Ar-H**); 7.72 (d, 1H, **Ar-H**); FT-IR in cm^{-1}: 1054, 1171, 1456, 1742, 2925, 3435; MS-*m/z:* 439 $(M+H)^+$; ESI-HRMS: *m/z* calcd. For $C_{25}H_{30}N_2O_5$ $[M+H]^+$439.2433; Found: 439.2421.

7-Methoxy-3-phenyl-4-[3-(4-phenyl acetyl-piperzin-1-yl)-propoxy]-chromen-2-one (6d), black solid: ^{1}H-NMR-(400MHz) in $CDCl_3$: δ 1.73-1.64 (m, 2H, **-CH$_2$** propyl); 2.28 (t, 2H, -N**CH$_2$**); 2.42 (t, 4H, **Piperazine**); 2.98 (t, 4H, **Piperazine**); 3.52 (s, 2H, -CO**CH$_2$**); 3.76 (t, 2H, -O**CH$_2$** propyl); 3.92 (s, 3H, -O**CH$_3$**); 6.95 (s, 1H, **Ar-H**); 6.98 (d, 1H, **Ar-H**); 7.22-7.15 (m, 5H, **Ar-H**); 7.42-7.36 (m, 5H, **Ar-H**); 7.78 (d, 1H, **Ar-H**); ^{13}C-NMR in $CDCl_3$ (75 MHz): δ 168.34, 166.32, 162.89, 160.43, 152.26, 137.16, 132.98, 129.78, 127.50, 124.02, 112.78, 110.24, 106.56, 98.12, 68.90, 64.12, 56.26, 52.65, 49.76, 26.98; MS-*m/z:* 513 $(M+H)^+$ +Ve Scan.

{4-[3-(7-Methoxy-2-oxo-3-phenyl-2H-chromen-4-yloxy)-propyl}-piperzin-1-yl}-oxo-acetic acid ethyl ester (6e), colorless liquid: ^{1}H-NMR-(400MHz) in $CDCl_3$: δ 1.23 (t, 3H, -OCH$_2$**CH$_3$**); 1.72-1.66(m, 2H, **-CH$_2$** propyl); 2.32(m, 4H, **Piperazine**); 2.48 (t, 4H, **Piperazine**); 2.68 (t, 2H, -N**CH$_2$** propyl); 3.82 (t, 2H, -OC**H2**); 3.88 (s, 3H, -

O**CH$_3$**); 4.02 (q, 2H, -O**CH$_2$**); 6.84 (s, 1H, **Ar-H**); 6.88 (d, 1H, **Ar-H**); 7.44-7.33 (m, 5H, **Ar-H**); 7.75 (d, 1H, **Ar-H**); ^{13}C-NMR in $CDCl_3$ (75 MHz): δ 168.90, 163.22, 161.26, 159.56, 158.16, 152.78, 135.58, 129.08, 128.64, 126.58, 112.34, 109.44, 106.83, 98.10, 66.12, 60.02, 59.17, 56.78, 51.11, 49.42, 46.92, 28.65, 14.60; FT-IR in cm^{-1}: 1055, 1450, 1665, 1728, 1742, 2925, 3035; MS-*m/z:* 495 $(M+H)^+$; ESI-HRMS: *m/z* calcd. For $C_{27}H_{30}N_2O_7$ $[M+H]^+$495.2033; Found: 495.2101.

4-[3-(4-allyl-piperazin-1-yl)-propoxy]-7-methoxy-3-phenyl-chromen-2-one (6f), thick liquid: ^{1}H-NMR-(400MHz) in $CDCl_3$: δ 1.63-1.56 (m, 2H, -**CH$_2$** propyl); 1.78 (t, 4H, **Piperazine**); 2.37-2.31 (m, 4H, **Piperazine**); 3.06 (d, 2H, -**CH$_2$** allylic); 3.12 (t, 2H, -N**CH$_2$**); 3.68 (t, 2H, -O**CH$_2$**); 3.88 (s, 3H, -O**CH$_3$**); 5.32 (dd, 2H, CH_2 allylic); 5.96 (q, 1H, -**CH** allylic); 6.84 (d, 2H, **Ar-H**); 7.47-7.33 (m, 5H, **Ar-H**); 7.78 (d, 1H, **Ar-H**); ^{13}C-NMR in $CDCl_3$ (75 MHz): δ 166.20, 158.76, 153.48, 146.65, 135.58, 132.85, 129.98, 128.64, 124.28, 118.78, 112.34, 111.94, 107.43, 96.80, 62.92, 57.28, 52.90, 47.42, 42.62, 26.87; MS-m/z: 435 $(M+H)^+$; ESI-HRMS: *m/z* calcd. For $C_{26}H_{32}N_2O_4$ $[M+H]^+$435.5474; Found: 435.5461.

7-Methaoxy-3-phenyl-4-[3-(4-prop-2-ynyl-piperazin-1-yl)-propoxy]-chromen-2-one (6g), brown color solid: ^{1}H-NMR-(400MHz) in $CDCl_3$: δ 1.52-1.45 (m, 2H, -**CH$_2$** propyl); 1.82 (t, 4H, **Piperazine**); 2.37-2.31 (m, 4H, **Piperazine**); 2.54 (t, 2H, -N**CH$_2$** propyl); 3.36 (d, 2H, -N**CH$_2$** propargyl); 3.42 (s, 1H, -**CH** propargyl); 3.65 (t, 2H, -O**CH$_2$** propyl); 3.88 (s, 3H, -O**CH3**); 6.84 (d, 2H, **Ar-H**); 7.47-7.33 (m, 5H, **Ar-H**); 7.78 (d, 1H, **Ar-H**); ^{13}C-NMR in $CDCl_3$ (75 MHz): δ 165.60l, 161.90, 160.43, 151.26, 132.68, 128.87, 122.92, 114.15, 111.24, 107.56, 98.12, 78.78, 72.12, 64.67, 58.10, 54.16, 52.25, 45.86, 28.68; MS-*m/z*: 433 $(M+H)^+$ +Ve Scan.

4-{3-[4-(3-Hydroxy-butyl)-piperazin-1-yl]-propoxy}-7-methoxy-3-phenyl-chromen-2-one(6h), color less liquid: ^{1}H-NMR-(400MHz) in $CDCl_3$: δ 1.02 (d, 3H, -**CH$_3$** butanol); 1.52-1.45 (m, 2H, -**CH$_2$** propyl) 1.66 (q, 2H, -**CH$_2$** butanol); 2.44 (t, 4H, **Piperazine**); 2.54 (t, 4H, **Piperazine**); 2.66 (m, 4H, 2x –N**CH$_2$** propyl and butanol); 3.68-3.62 (m, 1H, -**CH** butanol); 3.72 (t, 2H, -O**CH$_2$** propyl); 3.98 (s, 3H, -O**CH$_3$**); 6.84 (d, 2H, **Ar-H**); 7.37-7.28 (m, 5H, **Ar-H**); 7.72 (d, 1H, **Ar-H**); ^{13}C-NMR in $CDCl_3$(75 MHz): δ 25.60, 29.15, 38.88, 46.92, 48.22, 55.01, *58*.48, 62.92, 66.12, 102.90, 107.86, 111.34, 113.38, 125.58, 127.74, 129.08, 136.38, 152.78, 160.66, 162.52, 166.80; FT-IR in cm^{-1}: 3415, 2910, 1725, 1463, 1150, 1055; MS-m/z: 465 $(M-1)^-$ -Ve Scan.

2-{4-[3-(7-Methoxy-2-oxo-3-phenyl-2H-chromen-4-yloxy)-propyl]-piperazin-1-yl}-ethanesulfonyl chloride(6i), brown color solid: ^{1}H-NMR-(400MHz) in DMSO-d$_6$: δ 1.72-1.67 (m, 2H, -**CH$_2$** propyl), 2.34-2.27 (m, 4H, **Piperazine**); 2.49-2.43 (m, 4H, **Piperazine**); 2.68 (t, 2H, -N**CH$_2$** propyl); 2.96 (t, 2H, -N**CH$_2$** Chloroethyl sulfonyl); 3.68 (t, 2H, -**CH$_2$** Chloroethyl sulfonyl); 3.76 (t, 2H, -OCH_2 propyl); 3.88 (s, 3H, -O**CH$_3$**); 6.84 (s, 1H, **Ar-H**); 6.88 (d, 1H, **Ar-H**); 7.44-7.33 (m, 5H, **Ar-H**); 7.75 (d, 1H, **Ar-H**); MS-*m/z:* 522 $(M+H)^+$+Ve Scan.

7-Methoxy-4-{3-[4-(4-methoxy-benzyl)-piperzin-1-yl]-propoxy}-3-phenyl-chromen-2-one (6j), white color solid: ^{1}H-NMR-(400MHz) in $CDCl_3$: δ 1.73-1.64 (m, 2H, -**CH$_2$** propyl); 2.42 (t, 4H, **Piperazine**); 2.98 (t, 4H, **Piperazine**); 3.02 (t, 2H, -N**CH$_2$** propyl); 3.70 (s, 2H, -N**CH$_2$**Ar); 3.76 (t, 2H, -O**CH$_2$**); 3.92 (s, 6H, 2x-O**CH$_3$**); 6.95 (s, 1H, **Ar-H**); 6.96 (d, 3H, **Ar-H**); 7.12 (d, 2H, **Ar-H**); 7.42-7.36 (m, 5H, **Ar-H**); 7.78 (d, 1H, **Ar-H**); ^{13}C-NMR in $CDCl_3$ (75 MHz): δ 167.20, 166.22, 161.76, 159.46, 152.78, 137.89, 132.58, 129.68, 127.64, 126.58, 117.89, 114.34, 110.34, 107.73, 97.90, 66.12, 59.17, 55.58, 52.31, 49.12, 26.55; MS-*m/z*: 515 $(M+H)^+$; ESI-HRMS: *m/z* calcd. For $C_{38}H_{34}N_2O_5$ $[M+H]^+$ 515.1421; Found: 515.1429.

7-Methoxy-4-{3-[4-(4-nitro-benzyl)-piperzin-1-yl]-propoxy}-3-phenyl-chromen-2-one (6k), pale yellow solid: ^{1}H-NMR-(400MHz) in $CDCl_3$: δ 1.73-1.64 (m, 2H, -**CH$_2$** propyl); 2.42 (t, 4H, **Piperazine**); 2.98 (t, 4H, **Piperazine**); 3.44 (t, 2H, -N**CH$_2$** propyl); 3.70 (s, 2H, -N**CH$_2$**Ar); 3.76 (t, 2H, -O**CH$_2$** propyl); 3.92 (s, 3H, -O**CH$_3$**); 6.95 (s, 1H, **Ar-H**); 6.98 (d, 1H, **Ar-H**); 7.12 (d, 2H, **Ar-H**); 7.42-7.36 (m, 5H, **Ar-H**); 7.78 (d, 1H, **Ar-H**); 8.22 (d, 2H, **Ar-H**); ^{13}C-NMR in $CDCl_3$ (75 MHz): δ 167.02, 163.76, 159.86, 152.78, 147.87, 142.24, 137.77, 135.58, 134.65, 129.08, 126.34, 124.28, 114.44, 110.44, 107.13, 96.80, 64.72, 58.17, 49.42, 40.92, 29.05; MS-*m/z*: 530 $(M+H)^+$ +Ve Scan.

7-Methoxy-4-{3-[4-(3-nitro-benzyl)-piperzin-1-yl]-propoxy}-3-phenyl-chromen-2-one (6l), pale yellow solid: ^{1}H-NMR-(400MHz) in $CDCl_3$:δ 1.72-1.66 (m, 2H, -**CH$_2$**); 2.46 (t, 4H, **Piperazine**); 2.95 (t, 4H, **Piperazine**); 3.60 (t, 2H, -N**CH$_2$** propyl); 3.72 (s, 2H, -N**CH$_2$**Ar); 3.76 (t, 2H, -O**CH$_2$** propyl); 3.92 (s, 3H, -**CH$_3$**); 6.95 (s, 1H, **Ar-H**); 6.98 (d, 1H, **Ar-H**); 7.42-7.36 (m, 5H, **Ar-H**); 7.62 (d, 2H, **Ar-H**); 7.78 (d, 1H, **Ar-H**); 8.12 (d, 2H, **Ar-H**). MS-*m/z*: 530 $(M+H)^+$+Ve Scan.

3-{4-[3-(7-Methoxy-2-oxo-3-phenyl-2H-chromen-4-yloxy)-propyl]-piperazin-1-yl}-propionic acid ethyl ester (6m), brown color solid: ^{1}H-NMR-(400MHz) in $CDCl_3$: δ 1.23 (t, 3H, -OCH2**CH$_3$**); 1.27 (t, 2H, -CH_2 propyl); 1.72 (t, 2H, -CO**CH$_2$**); 2.34-2.27 (m, 5H, **Piperazine,** - N**CH$_2$**); 2.49-2.43 (m, 5H, **Piperazine,** -N**CH$_2$**); 2.68 (t, 2H, -

N**CH$_2$**CH$_2$CO); 3.67 (t, 2H, -O**CH$_2$**); 3.88 (s, 3H, -O**CH$_3$**); 4.14 (q, 2H, -O**CH$_2$**CH$_3$); 6.84 (s, 1H, **Ar-H**); 6.88 (d, 1H, **Ar-H**); 7.12 (d, 5H, **Ar-H**); 7.75 (d, 1H, **Ar-H**); ^{13}C-NMR in $CDCl_3$ (75 MHz): δ 173.86, 168.87, 164.32, 158.86, 134.65, 132.10, 128.78, 125.34, 112.62, 110.64, 108.78, 100.90, 77.43, 61.01, 56.80, 55.08, 54.12, 32.50, 30.61, 27.20, 14.82; MS-*m/z*: 495 $(M+H)^+$ +Ve Scan.

REFERENCES

[1] Penjisevic, J.; Sukalovic, V.; Andric, D.; Kostic-Rajacic, S.; Soskic, V.; Roglic, G.; *Arch. Pharm. Chem. Life. Sci*., **2007**, 340, 456-465.
[2] Watkins, W.J.; Chong, L.; Cho, A.; Hilgenkamp, R.; Ludwikow, M.; Garizi, N.; Barnard, J.; Singh, R.; Madsen, D.; Lolans, K.; Lomovskaya, O.; Oza, U.; Kumaraswamy, P.; Blecken, A.; Bai, S.; Loury, D.J.; Griffitha, D.C.; Dudley, M. N.; *Bioorg. Med. Chem. Lett.* **2007**, 17, 2802-2806.
[3] Upadhayaya, R. S.; Sinha, N.; Jain, S.; Kishore, N.; Chandra, R.; Arora, S. K.; *Bioorg. Med. Chem*. **2004**, 12, 2225-2238.
[4] Ranise, A.; Spallarossa, A.; Bruno, O.; Schenone, S.; Fossa, P.; Menozzi, G.; *Farmaco*, **2003**, 58(9*)*, 765-780.
[5] Rokosz, L. L.; Huang, C. Y.; Reader, J. C.; Stauffer, T. M.; Chelsky, D.; Sigal, N. H.; Ganguly, A. K.; Baldwin, J. J.; *Bioorg. Med. Chem. Lett.*, **2005**, 15, 5537-5543.
[6] Chen, J. J.; Lu, M.; Jing, Y. K.; Dong, J. H.; *Bioorg. Med. Chem.*, **2006**, 14, 6539-6547.
[7] Shami, P. J., E.Saavedra, J.; Bonofant, C. L.; Chu, J. X.; Udupi, V.; Malaviya, S.; Carr, B. I.; Kar, S.; Wang M. F.; Jia, L.; Ji, X. H. L.; Keefer, K.; *J. Med. Chem.*, **2006**, 49, 4356-4366.
[8] Smits, R. A.; Lim, H. D.; Hanzer, A.; Zuiderveld, O. P.; Guaita, E.; adami, M.; Coruzzi, G.; Leurs, R.; Esch, I. J. P.; *J. Med. Chem.*, **2008**, 51, 2457-2467.
[9] Beaker, O. M.; Dhanoa, D. S.; Marantz, Y.; Chen, D.; shacham, S.; Cheruku, S.; Heifetz, A.; Mohanthy, P.; Fichman, M.; Sharadendu, A.; Nudelman, R.; Kauffman, M.; Noiman, S.; *J. Med. Chem.* **2006**, 49, 3116-3135.
[10] Chern, I. H.; Shia, K. S.; Shih, S. R.; Hsu, T. A.; Tai, C. L.; U. S. Patent 6, 815,444, 2004.
[11] Chern, J. H.; Shia, K. S.; Hsu, T. A.; Tai, C. L.; Chung-chi, L.; Lee, C. C.; Lee, Y. C.; Chang, C. S.; Tseng, S. N.; Shih, S. R.; *Bioorg. Med. Chem. Lett*., **2004**, 14, 2519-2525.
[12] Romero, D.L.; Morge, R.A.; Genin, M.J.; Biles, C.; Busso, M.; Resnick, L.; Althaus, I.W.; Reusser, F.; Thomas, R. C.; Tarpley, W.G.; *J. Med. Chem.*, **1993**, 36, 1505–1508.
[13] Kortagene, Gemeiner, P.; Weinstein, J. H.; schetx, A.; *Mol.Pharmacol*, **2004**, 66(6), 1491-1499.
[14] Foye, W. O.; Lemke, T. L.; William, D. A.; *Principles of Medicinal Chemistry*, 4th Edn., Williams and Wilkins, London, **1995**.
[15] Gan, L. L.; Lu, Y. H.; Zhou, C. H.; *Chin. J. Biochem. Pharma*, **2009**, 30, 127-131.
[16] Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levine, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. J.C.; Blahy, O. M.; Sardana, B. B.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gotlib, LHolloway. M. K.; Lin, Chen, I. W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R.; *Proc. Natl. Acad. Sci. U.S.A.* **1994**, 91, 4096.
[17] Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levine, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. C.; Blahy, O. M.; Sardana, B. B.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gotlib, L.; Holloway, M. K.; Lin, J.; Chen, I. W.; Vastag, K.; Ostovic, D.; Anderson, P. S. E. A.; Emini, J. R.; Huff, *J. Med. Chem*., **1994**, 37, 3443.
[18] Askin, D.; Eng, K. K.; Rossen, K.; Purick, R. M.; Wells, K. M.; Volante, R. P.; Reider, P. J.; *Tetrahedron Lett*., **1994,** 35, 673-676.
[19] Mulwad, V. V.; Shirodkhar, J. M.; *Indian Journal of Heterocyclic Chemistry*, **2002**, 11, 192-202.
[20] Manohar, K.; Manjunath, G.; Raviraj, K.; *Indian Journal of Heterocyclic Chemistry*, **2004**, 13, 201-204.
[21] RajeshwarRao, V.; Srimanth, K.; VijayaKumar, P.; *Indian Journal of Heterocyclic chemistry*, **2004**, 14, 141-144.
[22] Nofal, Z. M.; El-Zahar, M. I.; Abd El-Karim, S. S.; *Journal of Antimicrobial Chemotherapy*, **2005**, 5, 483-488.
[23] Spino, C.; Dodier, M.; Sotheeswaran, S.; *Bioorg. Med. Chem. Lett*., **1998**, *8*, 3475-3478.
[24] Thaisrivongs, S.; Watenpaugh, K.; Howe, W.; Tomich, P.; *J. Med. Chem.*, **1995**, 38, 3624-3637.
[25]. Jalapathi, P., Devender, M., Balanarsimha, D., Umapathi, N., *Journal of Pharmacy Research*, **2012**, 5(4), 1957-1962.