Review Article

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Regio-Selective Reaction, Spectroscopic Characterization and Computational Chemical Study of (Hesperidin) Hesperetin-7-*O*-Rutinoside Analogs as Antimicrobial Agents

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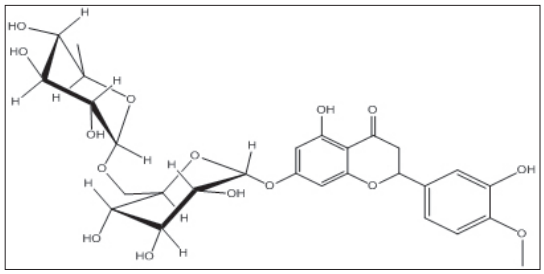
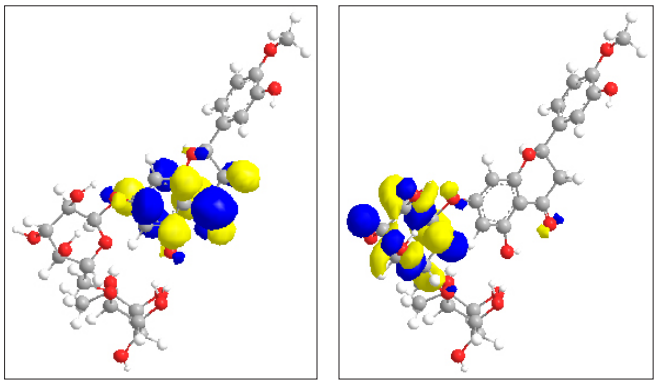




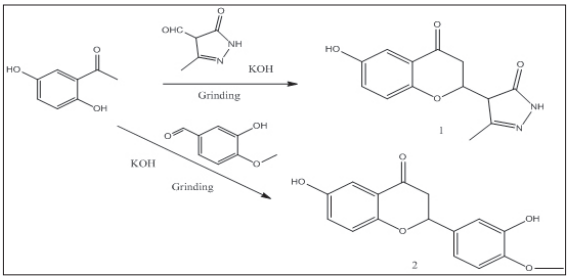
LUMOHOMO

Introduction

Flavonoids display a strong antioxidant and radical scavenging activity and seem to beassociated with reduced danger for certain chronic diseases, the prevention of some cardiovascular sicknesses and certain types of cancerous processes [1-4]. Flavonoids show also antiviral, antimicrobial, and anti-inflammatory activities, helpful on capillary fragility and prevent human platelet aggregation, antiulcer and antiallergenic [5-11]. Though, the actual in vivo mechanism of action is largely unknown. Most studies have attentivein vitro tests at amounts much higher than in humans,however few clinical investigations have been carried out around the diseases [12].Additional clinical trials are required to evaluate a more precise correlation between flavonoids consumption and human health benefits [13]. The possible mechanism of potential experimentalactionhas been studied [14]. Citrus juices attitude among the most significant phenolicrich dietary sources [15]. The most common acid Citrus fruits, e.g.lemons, grapefruits and bergamots.Although more than thousands of flavonoids have been exclusive, only alimited number of characteristic derivatives have been creating and identified.Their significance may outweigh their simple concentration levels. Overall, flavonoidsdonate to fruit and juice, the taste and the nutritional value of the product from the plant [16-18].The classes of flavonoids that characterize Citrus species flavanones hesperidin present intense peaks at 280 nm. The ESI-MS spectrum in negative mode of an O-disaccharide-substituted flavanone, i.e. hesperidin (hesperetin 7-Orutinoside,1) [19]. The fragment m/e 463 was generated by the loss of one sugar unit (rhamnose). Lemon (C. limon) juice is characterized by the presence of significant amounts of the flavanones, hesperidin (1, 20.5 mg/100 mL) [20-24].This amount is very small to study and reaction. We can synthesize the analogs. Computational chemical study and biological evaluation outlined the effect of hesperidin was due to the chromone moiety. To ease the reaction, simplicity and no cost. We synthesize the newly chromones 2,3 and 4 to study their behavior towards some electrophilic and nucleophilic reagents beside the biological evaluation.

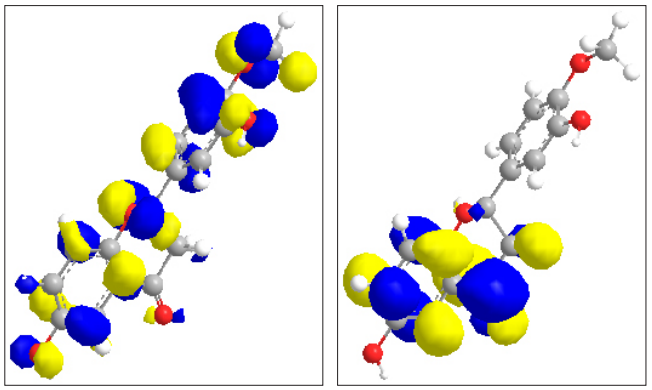
Result and Discussion

One pot reaction of 2.5-dihydroxyacetophenone, aromatic aldehyde namely, 4-chlorobenzaldehyde, 3-hydroxy-4-methoxybenzaldehyde (vanillin) and 5-methyl-4-formyl-3-pyrazolone in the presence of anhydrous potassium hydroxide under grinding method (15-25 min) afforded the corresponding chromone derivatives 2-4 respectively. The heat content in grinding method was sufficient to cyclize the chalcone to give the desired products (Scheme 1). After several hours, autoxidation of the chromone1 afforded the chromone3 (thermodynamic stable product) (Scheme 2).

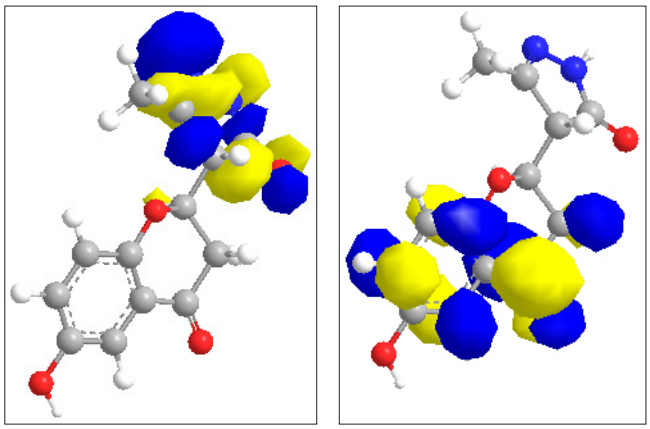


Scheme 1: Outline formation of the chromone products 1 and 2

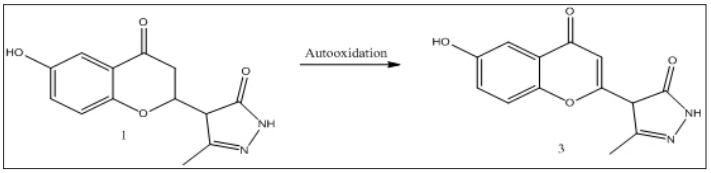
Quantum chemical computation and antimicrobial evaluation can be confirmed that chromone (flavonoid species) were the main structure not the glucoside species when we compared between the synthesize chromone and extracted hesperidin.Grindingof chromone 3, ethyl-acetoacetate and sodium acetate afforded ester 6. Formation of 1,3-dipolar ylide via three pot reaction of chromone 3, sarcosine and maleic acid afforded the Spiro derivative 7. Reaction of chromone 3 with 4-nitrobenzaldehyde in the presence of anhydrous potassium hydroxide afforded the corresponding arylidene 8. Isomerization of the chromone 8 to chromone 9 can be investigated by reaction with thiourea and hydroxyl amine to give the corresponding thiochromone and oxime



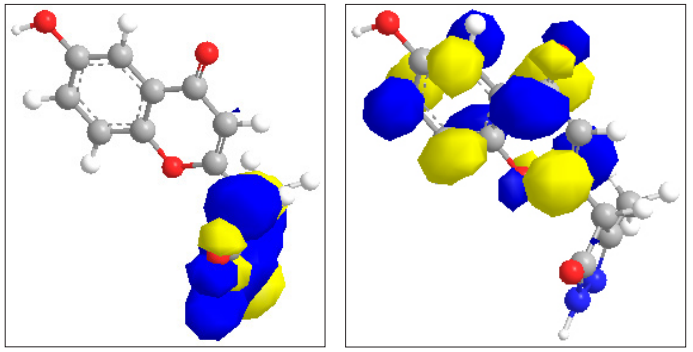
HOMO(2)LUMO



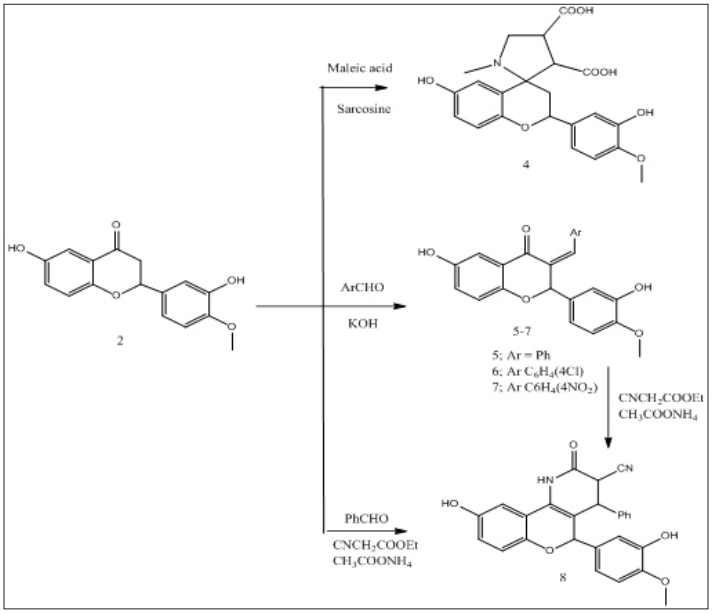
HOMO (1)LUMO

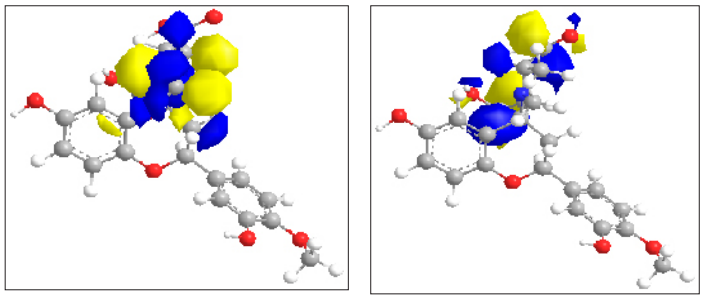


Scheme 2: the autoxidation of the chromone 1 to give the product 3

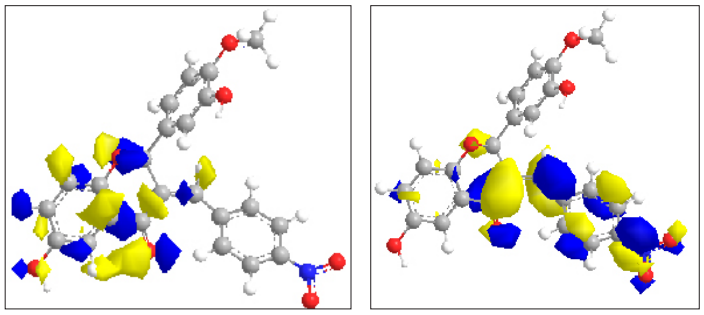


HOMO 3LUMO

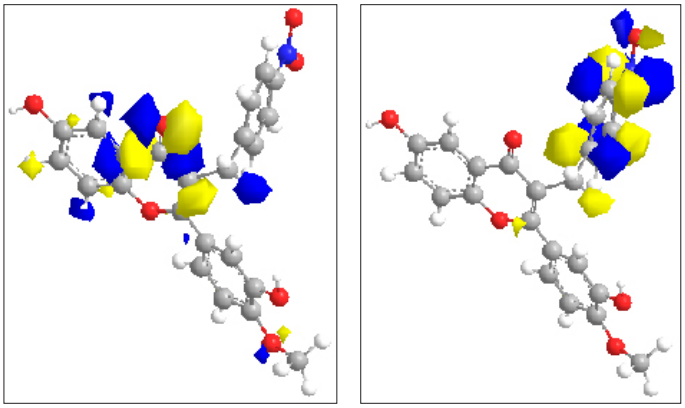




HOMO (7)LUMO



HOMO (8)LUMO



HOMO (Isomerize 8)LUMO

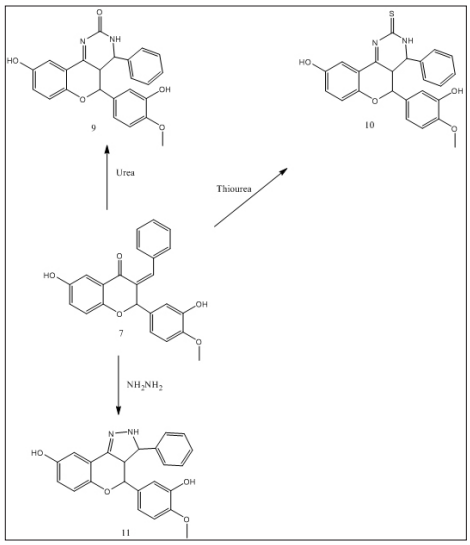
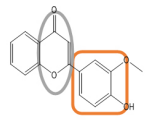
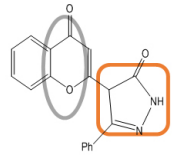


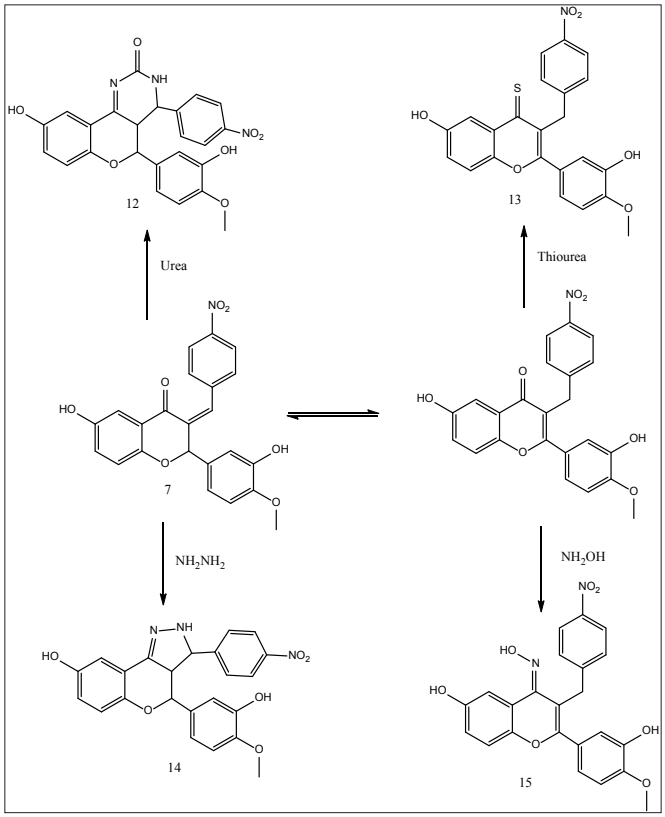
Table 1: Molecular interactions and interacting residues of the AchE with Chromene derivatives

S. No.	Compound structure	Binding energy k.cal/ mol	Docked complex (amino acid –ligand) interactions	Bond Distance (Å)
1	 Chromene3	-7.0	**Hydrogen bonds** TYR456:OH---ligand 1 TYR249:OH---ligand 1 SER250:OH---ligand 1 **Pi–Pi interactions** TRP212---ligand 1 TRP212---ligand 1	2.811 2.699 2.825 3.906 3.744
2	 Chromene2	-8.2	**Hydrogen bonds** TYR249:OH ---ligand 2 TYR258:OH---ligand 2 **Pi–Pi interactions** TRP212---ligand 2 TRP212---ligand 2 **Pi-sigma interactions** ASP200---ligand2	2.786 2.801 4.550 5.137 3.707

The chromene derivatives with the best binding energy are represented with docking interactions in the table showing H-bonding, Pi-Pi, and Pi–sigma interactions. Phenolic moiety is represented in red square while the pyran moiety is in green cycle.

Table 2: ADMET proprieties of the chromene derivatives

S. No.	Compound	Molecular Weight (g/mol)	Blood-Brain Barrier (BBB+)	Human Intestinal Absorption (HIA+)	Caco-2 Permeability (Caco2+)	AMES toxicity	Carcino-genicity
1	Chromene3	516.68	0.847	0.994	0.613	Nontoxic	Non carcinogenic
2	Chromene 2	560.69	0.509	0.977	0.569	Nontoxic	Non carcinogenic



4-(6-Hydroxy-4-oxochroman-2-yl)-5-methyl-2,4-dihydro-3H-pyrazol-3-one (1)

Yield 77%.m.p. 154-156 ºC. FT-IR (KBr) spectrum shows absorption bands at (in cm^{-1}): 1695, 1655 (CO), 3420 (OH), 3333, 3205 (NH). The ^{1}H-NMR (DMSO) spectrum shows signals in ppm at: 2.02 (s, 3H, CH_3 PY), 2.91 (d, CH PY J = 8.3 Hz), 3.63-3.68 (dd, 2H, CH_2 diastereotopic protons, J = 12.6, 5.4 Hz), 4.43 (m, methineproton CH), 6.78-7.51 (m, 3ArH), 9.32 (s, acidic OH proton of chromone which exchanged in D_2O), 12.34 (bs, acidic NH proton which exchanged in D_2O). EIMS, 260[M^+.], 178, 152, 108,77 Elemental analysis; M.wt260 Calc. $C_{13}H_{12}N_2O4$, Calc. % C 60.00, H 4.65, N 10.76; found % C 59.72, H 4.45, N 10.53.

6-Hydroxy-2-(3-hydroxy-4-methoxyphenyl)chroman-4-one (2)

Yield 82%.m.p. 174-176 ºC. FT-IR (KBr) spectrum shows absorption bands at (in cm^{-1}): 1676 (CO), 3468, 3385 (OH). The 1H-NMR ($CDCl_3$) spectrum shows signals in ppm at: 3.71-3.75 (dd, 2H, CH_2 diastereotopic protons, J = 12.6, 5.4 Hz), 4.03 (s, 3H, OCH_3), 5.20

(dd, methine proton CH, J = 12.6, 5.4 Hz), 6.94-7.73 (m, 6ArH), 9.20 (s, acidic OH proton of chromone which exchanged in D_2O), 9.62 (bs, acidic OH proton which exchanged in D_2O). EIMS, 286[M^+.], 260, 152, 108,77. Elemental analysis; M.wt286 Calc. $C_{16}H_{14}O_5$, Calc. % C 67.13, H 4.93; found % C 66.92, H 4.70.

4-(6-Hydroxy-4-oxo-4H-chromen-2-yl)-5-methyl-2,4-dihydro-3H-pyrazol-3-one (3)

Yield 65%.m.p. 182-184 ºC. FT-IR (KBr) spectrum shows absorption bands at (in cm^{-1}): 1673, 1653 (CO), 3484 (OH), 3310, 3243 (NH). The ^{1}H-NMR (DMSO) spectrum shows signals in ppm at: 1.92 (s, 3H, CH3 PY), 3.53 (d, CH PY J = 8.3 Hz), 6.72-7.26 (m, 4ArH), 9.32 (s, acidic OH proton of chromone which exchanged in D_2O), 12.34 (bs, acidic NH proton which exchanged in D_2O). EIMS, 260[M^+.], 178, 152, 108, 77Elemental analysis; M.wt258 Calc. $C_{13}H_{10}N_2O_4$, Calc. % C 60.47, H 3.90, N 10.85; found % C 60.22, H 3.75, N 10.70.

6-Hydroxy-2-(3-hydroxy-4-methoxyphenyl)-1'-methylspiro[chromane-4,2'-pyrrolidine]-3',4'-dicarboxylic acid (4)

Yield 75%.m.p. 108-110 ºC. FT-IR (KBr) spectrum shows absorption bands at (in cm^{-1}): 1705 (CO), 3420, 3373 (OH). The 1H-NMR (DMSO) spectrum shows signals in ppm at: 2.43 (s, 3H, NCH3), 2.71-3.25 (m, 4H, CH_2-CH-CH, pyrrolid), 3.53 (s, 3H, OCH_3), 3.71-3.75 (dd, 2H, CH_2 diastereotopic protons, J = 12.6, 5.4 Hz), 4.23 (m, methine proton CH),7.44-7.73 (m, 6ArH), 9.12-9.20 (bs, acidic 2OH protons which exchanged in D_2O), 12.01-12.09 (bs, acidic 2COOH protons which exchanged in D_2O). EIMS, 429[M^+.], 260, 252, 208, 165, 146, 121. Elemental analysis; M.wt429 Calc. C22H23NO8, Calc. % C 61.53, H 5.40, N 3.26; found % C 61.31, H 5.16, N3.00.

3-Benzylidene-6-hydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one (5)

Yield 75%.m.p. 178-180 ºC. FT-IR (KBr) spectrum shows absorption bands at (in cm-1): 1685 (CO), 3500, 3433 (OH). The 1H-NMR (DMSO) spectrum shows signals in ppm at: 3.62 (s, 3H, CH_3), 5.53 (s, CH, chrom), 6.72-7.66 (m, 11ArH), 9.32 (s, acidic OH proton of chromone which exchanged in D_2O), 10.34 (s, acidic OH proton which exchanged in D_2O). EIMS, 374[M^+.], 260, 252, 208, 165, 146, 121. Elemental analysis; M.wt374 Calc. $C_{23}H_{18}O_5$, Calc. % C 73.59, H 4.85; found % C 73.41, H 4.62.

3-(4-Chlorobenzylidene)-6-hydroxy-2-(3-hydroxy-4-methoxyphenyl)chroman-4-one (6)

Yield 77%.m.p. 192-194 ºC. FT-IR (KBr) spectrum shows absorption bands at (in cm^{-1}): 1685 (CO), 3500, 3433 (OH). The 1H-NMR (DMSO) spectrum shows signals in ppm at: 3.62 (s, 3H, CH_3), 5.53 (s, CH, chrom), 6.72-7.80 (m, 10ArH), 9.32 (s, acidic OH proton of chromone which exchanged in D_2O), 10.34 (s, acidic OH proton which exchanged in D_2O). EIMS, 410[M^+.+2], 408[M^+.], 260, 252, 208, 165, 146, 121. Elemental analysis; M.wt408 Calc. $C_{23}H_{17}ClO_5$, Calc. % C 67.57, H 4.19; found % C 67.34, H 3.92.

3-(4-Nitrobenzylidene)-6-hydroxy-2-(3-hydroxy-4-methoxyphenyl)chroman-4-one(7)

Yield 75%.m.p.212-214 ºC. FT-IR (KBr) spectrum shows absorption bands at (in cm^{-1}): 1685 (CO), 3500, 3433 (OH). The ^{1}H-NMR (DMSO) spectrum shows signals in ppm at: 3.62 (s, 3H, CH_3), 5.57 (s, CH, chrom), 6.84-7.96 (m, 10ArH), 9.32 (s, acidic OH proton of chromone which exchanged in D_2O), 10.34 (s, acidic OH proton which exchanged in D_2O). EIMS, 419[M_+.], 260, 252, 208, 165, 146, 121. Elemental analysis; M.wt419 Calc. $C_{23}H_{17}NO_7$, Calc. % C 65.87, H 4.09, N 3.34; found % C 65.66, H 3.89, N 3.03.

9-Hydroxy-5-(3-hydroxy-4-methoxyphenyl)-2-oxo-4-phenyl-1,3,4,5-tetrahydro-2H-chromeno[4,3-b]pyridine-3-carbonitrile (8)

Yield 75%.m.p.236-238 ºC. FT-IR (KBr) spectrum shows absorption bands at (in cm^{-1}): 1665 (CO), 3500, 3433 (OH), 3247 (NH). The ^{1}H-NMR (DMSO) spectrum shows signals in ppm at: 3.62 (s, 3H, CH_3), 3.82 (d, CH, Pyrid), 3.95 (d, CHCN), 5.57 (s, CH, chrom), 6.64-7.68 (m, 11ArH), 9.32 (s, acidic OH proton of chromone which exchanged in D_2O), 10.34 (s, acidic OH proton which exchanged in D_2O), 11.20 (s, acidic NH proton which exchanged in D_2O). EIMS, 440[M^+.], 260, 252, 208, 165, 146, 121. Elemental analysis; M.wt440 Calc. $C_{26}H_{20}N_2O_5$, Calc. % C 70.90, H 4.58, N 6.36; found % C 70.66, H 4.29, N 6.13.

9-Hydroxy-5-(3-hydroxy-4-methoxyphenyl)-4-phenyl-1,3,4,5-tetrahydro-2H-chromeno[4,3-d]pyrimidin-2-one (9)

Yield 75%.m.p.260-262 ºC. FT-IR (KBr) spectrum shows absorption bands at (in cm^{-1}): 1665 (CO), 3500, 3433 (OH), 3312, 3247 (NH). The ^{1}H-NMR (DMSO) spectrum shows signals in ppm at: 3.72 (s, 3H, CH_3), 4.87 (s, CH, Pyrid), 5.49 (s, CH, chrom), 6.57-7.48 (m, 11ArH), 9.32 (s, acidic OH proton of chromone which exchanged in D_2O), 9.54 (s, acidic OH proton which exchanged in D_2O), 10.03-10.12 (bs, acidic 2NH proton which exchanged in D_2O). EIMS, 416[M^+.], 260, 252, 208, 165, 146, 121. Elemental analysis; M.wt416 Calc. $C_{24}H_{20}N_2O_5$, Calc. % C 69.22, H 4.84, N 6.73; found % C 69.00, H 4.60, N 6.47.

9-Hydroxy-5-(3-hydroxy-4-methoxyphenyl)-4-phenyl-1,3,4,5-tetrahydro-2H-chromeno[4,3-d]pyrimidin-2-thione (10)

Yield 75%.m.p.224-226 ºC. FT-IR (KBr) spectrum shows absorption bands at (in cm-1): 3500, 3433 (OH), 3312, 3247 (NH). The 1H-NMR (DMSO) spectrum shows signals in ppm at: 3.72 (s, 3H, CH3), 4.87 (s, CH, Pyrid), 5.49 (s, CH, chrom), 6.57-7.48 (m, 11ArH), 9.32 (s, acidic OH proton of chromone which exchanged in D_2O), 9.54 (s, acidic OH proton which exchanged in D_2O), 10.03-10.12 (bs, acidic 2NH proton which exchanged in D_2O). EIMS, 435, 432[M+.], 260, 252, 208, 165, 146, 121. Elemental analysis; M.wt432 Calc. C24H20N2O4S, Calc. % C 66.65, H 4.66, N 6.48, S 7.41; found % C 66.35, H 4.40, N 6.27, S 7.20..

4-(3-hydroxy-4-methoxyphenyl)-3-phenyl-2,3,3a,4-tetrahydrochromeno[4,3-c]pyrazol-8-ol (11)

Yield 75%.m.p.292-294 ºC. FT-IR (KBr) spectrum shows absorption bands at (in cm^{-1}): 3500, 3433 (OH), 3312, 3247 (NH). The ^{1}H-NMR (DMSO) spectrum shows signals in ppm at: 3.88 (s, 3H, CH_3), 4.54 (dd, C3H, chrom), 5.17 (d, C2H, Pyrid),5.57 (d, CH, chrom), 6.83-7.62 (m, 11ArH), 9.13 (s, acidic OH proton of chromone which exchanged in D2O), 9.37 (s, acidic OH proton which exchanged in D_2O), 12.25 (s, acidic 1NH proton which exchanged in D_2O). EIMS, 388[M^+.], 260, 252, 208, 165, 146, 121. Elemental analysis; M.wt388 Calc. $C_{23}H_{20}N_2O4$, Calc. % C 71.12, H 5.19, N 7.21; found % C 70.90, H 4.93, N 6.97.

9-Hydroxy-5-(3-hydroxy-4-methoxyphenyl)-4-(4-nitrophenyl)-1,3,4,5-tetrahydro-2H-chromeno[4,3-d] pyrimidin-2-one (12)

Yield 75%.m.p.260-262 ºC. FT-IR (KBr) spectrum shows absorption bands at (in cm^{-1}): 1665 (CO), 3500, 3433 (OH), 3312, 3247 (NH). The 1H-NMR (DMSO) spectrum shows signals in ppm at: 3.72 (s,

3H, CH_3), 4.87 (s, CH, Pyrid), 5.49 (s, CH, chrom), 6.57-7.48 (m, 10ArH), 9.32 (s, acidic OH proton of chromone which exchanged in D_2O), 9.54 (s, acidic OH proton which exchanged in D_2O), 10.03-10.12 (bs, acidic 2NH proton which exchanged in D_2O). EIMS, 461[M_+.], 260, 252, 208, 165, 146, 121. Elemental analysis; M.wt461 Calc. $C_{24}H_{20}N_3O_7$, Calc. % C 62.47, H 4.15, N 9.11; found % C 62.23, H 3.91, N 8.87.

6-Hydroxy-2-(3-hydroxy-4-methoxyphenyl)-3-(4-nitrobenzyl)-4H-chromene-4-thione (13)

Yield 75%.m.p.154-156 ºC. FT-IR (KBr) spectrum shows absorption bands at (in cm^{-1}): 3500 (OH). The 1H-NMR (DMSO) spectrum shows signals in ppm at: 3.53 (s, CH_2 benz), 3.62 (s, 3H, CH_3), 6.84-8.16 (m, 10ArH), 9.32 (s, acidic OH proton of chromone which exchanged in D_2O), 10.34 (s, acidic OH proton which exchanged in D_2O). EIMS, 435[M+.], 260, 252, 208, 165, 146, 121. Elemental analysis; M.wt435 Calc. $C_{23}H_{17}NO_6S$, Calc. % C 63.44, H 3.94, N 3.22, S 7.36; found % C 63.26, H 3.79, N 3.00, S 7.11.

4-(3-hydroxy-4-methoxyphenyl)-3-(4-nitrophenyl)-2,3,3a,4-tetrahydro-chromeno[4,3-c]pyrazol-8-ol (14)

Yield 75%.m.p.308-310 ºC. FT-IR (KBr) spectrum shows absorption bands at (in cm^{-1}): 3500, 3433 (OH), 3312, 3247 (NH). The ^{1}H-NMR (DMSO) spectrum shows signals in ppm at: 3.88 (s, 3H, CH_3), 4.54 (dd, C3H, chrom), 5.17 (d, C2H, Pyrid), 5.57 (d, CH, chrom), 6.83-7.62 (m, 10ArH), 9.13 (s, acidic OH proton of chromone which exchanged in D_2O), 9.37 (s, acidic OH proton which exchanged in D_2O), 12.25 (s, acidic 1NH proton which exchanged in D_2O). EIMS, 433[M^+.], 260, 252, 208, 165, 146, 121. Elemental analysis; M.wt433 Calc. $C_{23}H_{20}N_3O_6$, Calc. % C 63.74, H 4.42, N 9.70; found % C 63.50, H 4.23, N 9.47.

6-Hydroxy-2-(3-hydroxy-4-methoxyphenyl)-3-(4-nitrobenzyl)-4H-chromen-4-one oxime (15)

Yield 75%.m.p.128-130 ºC. FT-IR (KBr) spectrum shows absorption bands at (in cm^{-1}): 3515, 3465 (OH). The 1H-NMR (DMSO) spectrum shows signals in ppm at: 3.59 (s, CH_2, benz), 3.68 (s, 3H, CH_3), 6.84-8.16 (m, 10ArH), 9.32 (s, acidic OH proton of chromone which exchanged in D_2O), 10.34 (s, acidic OH proton which exchanged in D_2O), 11.14 (s, acidic OH proton of oxime which exchanged in D_2O). EIMS, 434[M^+.], 260, 252, 208, 165, 146, 121. Elemental analysis; M.wt434 Calc. $C_{23}H_{18}N_2O_7$, Calc. % C 63.59, H 4.18, N 6.45; found % C 63.31, H 3.93, N 6.22.

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