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Synthesis of new chromeno-carbamodithioate derivatives and preliminary evaluation of their antioxidant activity and molecular docking studies

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ABSTRACT

New chromeno carbamodithioates (**7a-i**), have been synthesised from 2, 3-dimethyl-7-(oxiran-2-ylmethoxy)-4H-chromen-4-one (**5**), carbondisulphide and commercially available acyclic and cyclic secondary amines in acetonitrile with good to excellent yields. The free radical scavenging activity of novel chromone-carbamodithioate analogues was quantitatively estimated by spectrophotometric method. Whereas, molecular docking studies were performed with the active site of cyclooxygenase-2 to identify hydrogen bonding, hydrophobic and ionic interactions between protein and ligands. The compounds **7g** and **7h** demonstrated potent antioxidant activity with IC_{50} of 1.405 ± 0.019mM and 1.382 ± 0.35mM respectively compared to Ascorbic acid.

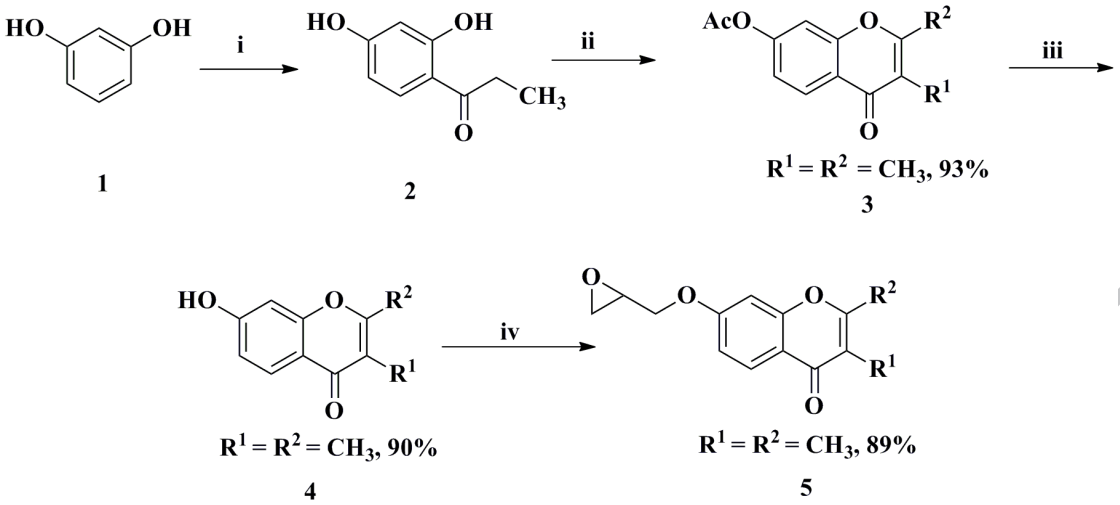
1. Introduction

Reactive Oxygen Species (ROS) and free radicals play an important role in a number of biological processes, some of which are necessary for life such as the intra cellular killing of bacteria by phagocytic cells.[1] However, excessive production of Reactive Oxygen Species and free radicals can cause damage to bio-molecules such as lipids, proteins, enzymes, and DNA in cells and tissues.[2] This triggers to various diseases such as atherosclerosis, heart failure, neuro degenerative disorders, aging, cancer, diabetes mellitus, hypertension. Furthermore, the free radicals can also be generated from environmental pollutants, radiation, chemicals, toxins, deep fried and spicy food, oxidative stress, physical stress, which cause depletion of immune system[3]. Thus, the utility of antioxidants in diet would combat the attacks caused by the free radicals and ROS and reduce the risk of various diseases[4,5]. Apparently, the antioxidants have been currently fabricated as drug candidate to counter these diseases.

It is known that chromone system is present in many compounds widely found in plants and particularly in flavones and isoflavones.[6] In recent years chromone heterocyclic synthesis had attracted tremendous interest among researchers due to their potential applications in medicinal chemistry. Scientific studies on chromones make public hundreds of structures with laxative effect,[7] anti-inflammation,[8] tyrosinase inhibition,[9] skin protection,[10] anti-ulcer[11] and other biological activities. In this context, in continuous of our study on the synthesis of different chromeno analogues and their biological activity,[12,13] here we have synthesized some promising chromone-carbamodithioate analogues with good to excellent yields and inspected their antioxidant activity by Charge Transfer Complex (CTC), a simple spectrophotometric method. Molecular docking studies were also performed on these analogues to suggest the binding site interactions between protein and ligands. To the best of our knowledge, this is the first aspect of study of antioxidant activity on chromeno-carbamodithiates.

2. Results & Discussion

Epoxy chromone **5** is an ideal source for diversity of reactions, as they can be opened with various nucleophiles. The epoxide opening took place in highly regioselective manner preferentially from less hindered site in appropriate reaction times by terminal attack of the nucleophiles[14-17]. In most of the epoxide ring opening reactions nucleophiles were amines (primary or secondary) [15-21] in which, β-amino alcohols were formed by C-N bond linkage with designed core moiety. The scrutiny of the earlier reports on ring opening of 1,2-epoxide with thiol-derived nucleophiles revealed that there are practically seldom reports on only the synthesis of hydroxy dithiocarbamates[22-25] but not on their biological activity studies. Hydroxy dithiocarbamates are very important biologically active compounds and have diverse applications in medicinal chemistry[26], agriculture[27], intermediates in organic synthesis[28] and multifunctional lubricant additives[29].



Scheme 1: Reaction Conditions: (i) CH_3CH_2COOH, Fused $ZnCl_2$, 140-150 °C, 2 h, 82%; (ii) Ac_2O, NaOAc, reflux, 14 h; (iii) $NaHCO_3$/MeOH, (1:1, v:v), rt, 3 h, 90%; (iv) epichlorohydrine (excess), K_2CO_3, 100 -110 ℃, 4-5 h.

Hence, it was thought of considerable interest to undertake the synthesis and activity of novel chromeno-carbamodithiates *via* nucleophilic epoxide ring opening reaction with carbondisulphide (CS_2) and aliphatic cyclic and acyclic secondary amines wherein, alkylcarbamodithioate, the nucleophile was *in situ* generated and C-S bond takes place with interior moiety. The target compounds (**7a, 7b-i**), were synthesized using a straight forward chemistry from epoxy chromone **5**. The epoxy chromone **5** was prepared from resorcinol as shown in **Scheme 1**, Friedel-Crafts reaction of recorcinol **1** with propanoic acid in presence of fused $ZnCl_2$ at 140-150 ^{0}C for 2h afforded the compound **2** a good yield of 82%. The hydroxy chromone derivative **4** was prepared starting from the compound **2** in two simple steps according to previous reports.[20,21] A mixture of compound **2**, acetic anhydride and sodium acetate was heated under reflux condition for 14h yielded the compound **3**, which upon de-acetylation with 1:1 mixture of MeOH and sat. aq $NaHCO_3$ at rt for 6h to afford **4** in 90% yield. The epoxy chromone precursor **5** was prepared by reaction of hydroxy chromone **4** with epichlorohydrine in presence of K_2CO_3 at 100-110 ^{0}C for 4-5 h with excellent yield of 89%. Finally 2,3-dimethyl-7-(oxiran-2-ylmethoxy)-4H-chromen-4-one (**5)** moiety was easily transformed into chromeno-carbamodithioates, by the reaction of **5** with carbondisulphide (CS_2), commercially available diethyl amine (acyclic secondary amine) (Table **2**, Entry 1) and cyclic secondary amines (Table **2**, Entry 2-9) in acetonitrile as a solvent at 0°C to room temperature for the period of 30 min. Later the reaction mixture was refluxed for 5-6 h to afford **7a** and **7b-i** with good to excellent yields (72-96 %).

3. Antioxidant activity

Several methods were reported for the estimation of antioxidant activity of synthetic or natural source. In order to develop simple and sensitive spectrophotometric method, CTC can be used as free radical source. The CTC which was formed between DDQ and tri ethylamine was used to investigate chromeno-carbamodithioate antioxidant activity[30]. The antioxidant activity of the extracts was expressed as IC_{50} and compared with standard. The capacity to scavenging the DDQ radical was calculated using the following equation.

$$\% \text{ Radical Scavenging Activity } (R_s) = \frac{A_b - A_a}{A_b} \text{ X } 100$$

Where, Ab = Initial absorbance of the CTC, Aa = Absorbance of the test/ standard compound.

The most of the chromeno-carbamodithioates analogue's have shown higher percentage of radical scavenging activity than the reference compound, ascorbic acid. The compounds **7g** and **7h** demonstrated comparatively the more potent activity with IC_{50} values of 1.405 ± 0.019mM, 1.382 ± 0.35mM respectively (Table-1).

Table-1: Antioxidant activity of tested compounds

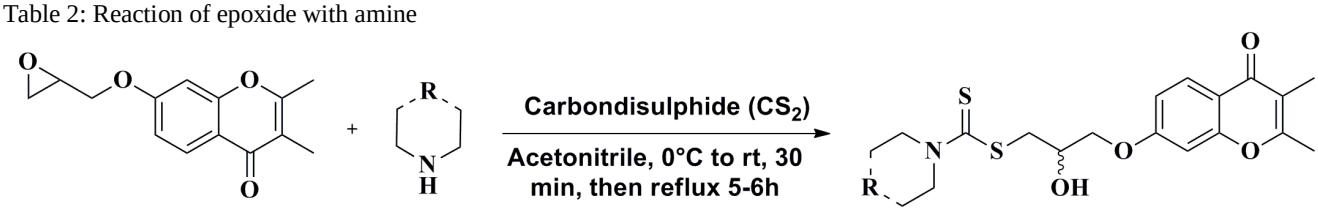
Entry	Compound	%RS	IC_{50} mM ± SD	Activity
1	7a	29.475	1.709±0.15	0.7673
2	7b	29.455	1.721±0.206	0.7643
3	7c	24.760	2.241±0.70	0.6496
4	7d	24.755	2.042±0.21	0.6568
5	7e	31.603	1.588±0.095	0.7992
6	7f	31.835	1.573±0.058	0.8033
7	7g	35.605	1.405±0.019	0.8516
8	7h	36.785	1.382±0.35	0.8595
9	7i	30.895	1.618±0.012	0.7911
10	Ascorbic acid	30.40	1.644±0.01	0.7840

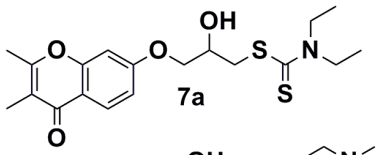
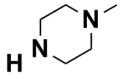
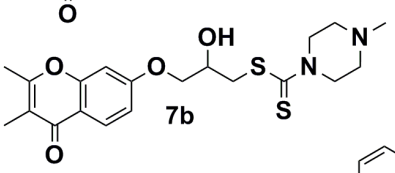
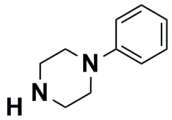
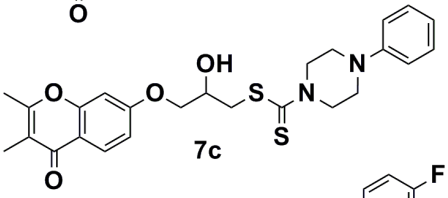
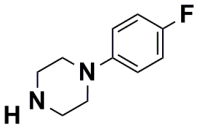
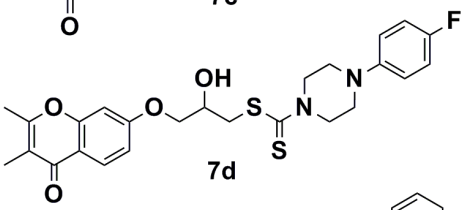
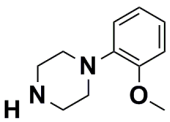
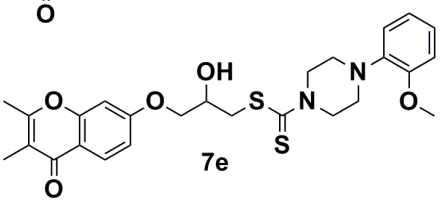
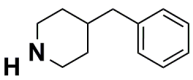
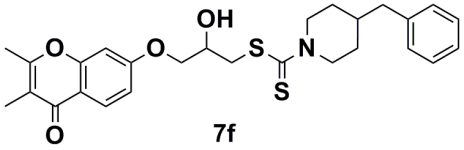
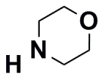
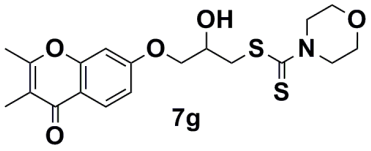
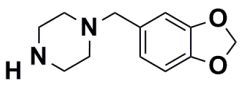
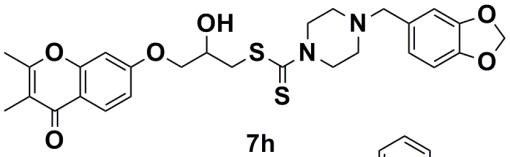
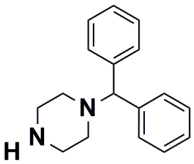
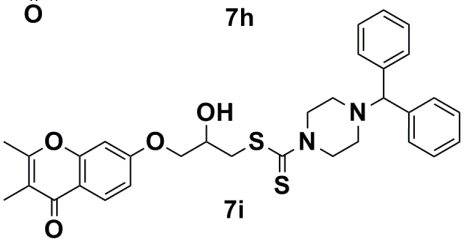
It was interesting to note that the compounds-**7e**, **7f** and **7i** also showed appreciable free radical scavenging activity with IC_{50} values of 1.588 ± 0.095mM, 1.573 ± 0.058mM and 1.618 ± 0.012mM respectively. The other compounds such as **7a**, **7b**, **7c**, and **7d** exhibited comparatively less activity with IC_{50} values 1.709 ± 0.15mM, 1.721 ± 0.206mM, 2.241 ± 0.70mM and 2.042 ± 0.21mM in comparison with reference compound, ascorbic acid (1.644 ± 0.01mM). By observing the structural activity relationships (SAR) of these compounds revealed that the antioxidant activity was associated with basic skeleton of chromeno-carbamodithioate and N-substituted moieties. A reduction in the activity was observed when the substituted N-methyl group was replaced by a N-phenyl ring, which was observed in compounds **7b** and **7c** with respective IC_{50} values (1.721±0.206mM and 2.241±0.70mM). The radical scavenging activity seems to increase with presence of the electron donating groups on the N-substituted moieties compared to electron withdrawing substituents.

4. Genetic optimization for ligand docking

In the present study, version 2.0 of the GOLD (Genetic optimization for ligand docking) docking program was evaluated. The GOLD program used a genetic algorithm (GA) to explore

Table 2: Reaction of epoxide with amine



Entry	Epoxide 5	Amine 6a-i	Product[a] 7a-i	Yield[b] %
1	5		 7a	73
2	5		 7b	78
3	5		 7c	83
4	5		 7d	77
5	5		 7e	96
6	5		 7f	75
7	5		 7g	72
8	5		 7h	87
9	5		 7i	77

[a]All products were characterised by 1H NMR, IR, and mass spectroscopy.
[b]Isolated yields.

the full range of ligand flexibility and the rotational flexibility of selected receptor hydrogens[31]. There were two different built in scoring functions in the GOLD program-Gold Score and Chem Score. The interaction of the ligands with the receptor in the modeled complexes was investigated and observed the fitness function ability of oxidoreductase protein by different inhibitors. The 3D structure of selected protein cyclooxygenase-2 (4COX) was selected from PDB Bank RCSB[32] with an X-ray resolution in the range of 2.90A°. The protein active site can be viewed through Swiss Protein Data Base Viewer (spdbv) 3.7[33]. Docking has been performed and their corresponding Gold score and Chem score have been produced in the Table-3**.**

4.1. Autodock

Autodock4.0[34] was used to estimate binding free energy and inhibition constant (K_i). Molecular docking studies were performed on a series of title compounds against cyclooxygenase-2 target (4COX) to predict and compare the ligand conformations and orientations of binding properties of compounds with that of the experimental bioassay. The binding mode analysis of the compounds with the active site residues provided important information about catalytic activity. **Figure 1** shows the lowest energy confirmation of compound **7g**. It was noted that the hydroxyl group formed one hydrogen bond from residue of TYR385 oxygen atom on morpholine ring received two hydrogen bonds from backbone residues of GLY527 and ALA527 at the bottom of the active site. The morpholine ring in compound **7g** seems to be an effective moiety to enhance the antioxidant activity of the compound (Table-1). It was also noted that the sulphur atom of carbamodithioate group also forms hydrogen bond with TRP387 (NH). The sulphur containing hydrogen bond was suggested to play an important role in the process of protein ligand interactions. The binding mode of compound **7h** in the active of cyclooxygenase (4COX) was shown in **Figure 2**. The best docked lowest energy mode of compound **7h** formed three interactions with amino acids of active site. The two hydrogen bonds formed between OH group and two residues of LEU531, SER530. The third hydrogen bond formed between chromone ring oxygen and TYR385.

The binding energy, inhibition constant, fitness score and chem score values were in the range of -0.97 to -6.14 Kcal/mol, 0.037mM to 197.37mM, 80.73 to 60.51 and 58.67 to 39.31 respectively. The title compounds showed good antioxidant activity compared to standard compound and also they have shown significant binding scores. The compounds **7g** and **7h** were found to have high activity. In the morpholine ring of compound **7g**, S and OH groups seemed to be effective groups to enhance the antioxidant activity due to formation of multiple hydrogen bonds in the active site of cyclooxygenase-2. The two hydrogen bonds formed between OH group and two residues, LEU531, SER530 and third hydrogen bond formed between chromone ring oxygen and TYR385 seems to be responsible for high efficacy of compound **7h**.

Table-3 Gold score values of chromone molecules

Compound	Fitness	S(hb)	Chem score	S(lipo)	B.E(Kcal/mol)	K_i (mM)
7a	60.51	6.03	42.20	305.58	-2.48	15.09
7b	60.91	0.00	41.71	303.86	-6.14	0.031
7c	63.58	8.34	45.21	402.82	-5.71	0.064
7d	69.60	1.98	45.70	398.21	-0.97	193.97
7e	68.84	1.60	45.76	399.07	-1.54	73.79
7f	71.60	6.09	58.67	468.90	-4.75	0.327
7g	60.99	0.34	41.47	318.05	-5.50	0.093
7h	80.73	2.90	44.86	422.45	-5.99	0.044
7i	75.75	6.02	39.31	412.73	-3.18	4.66

S(hb)=Hydrogen bonding score, S(lipo)=Lipophilicity, K_i=Inhibition constant.

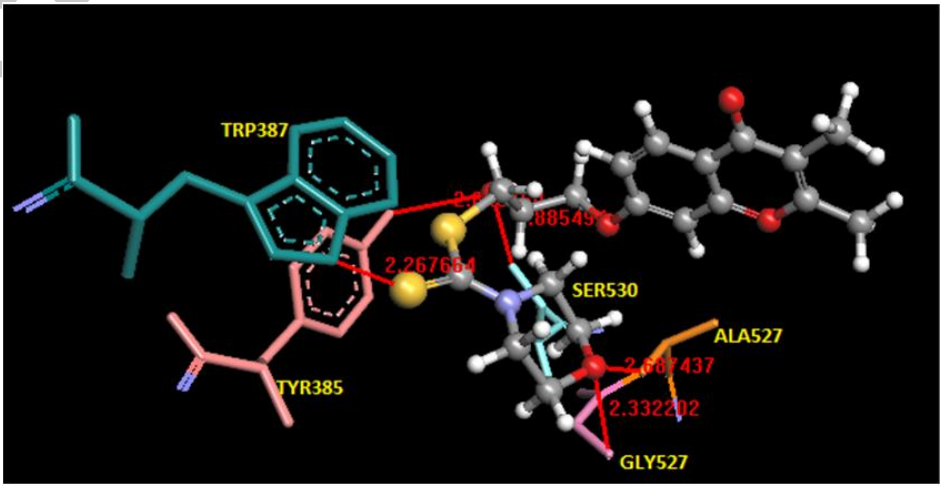


Figure 1. Binding mode of compound **7g** in the active site of cyclooxygenase (4COX). Ligand indicated in ball and cylinder low model residues were indicated in cylinder high model. Red colour dotted lines indicated the hydrogen bonds.

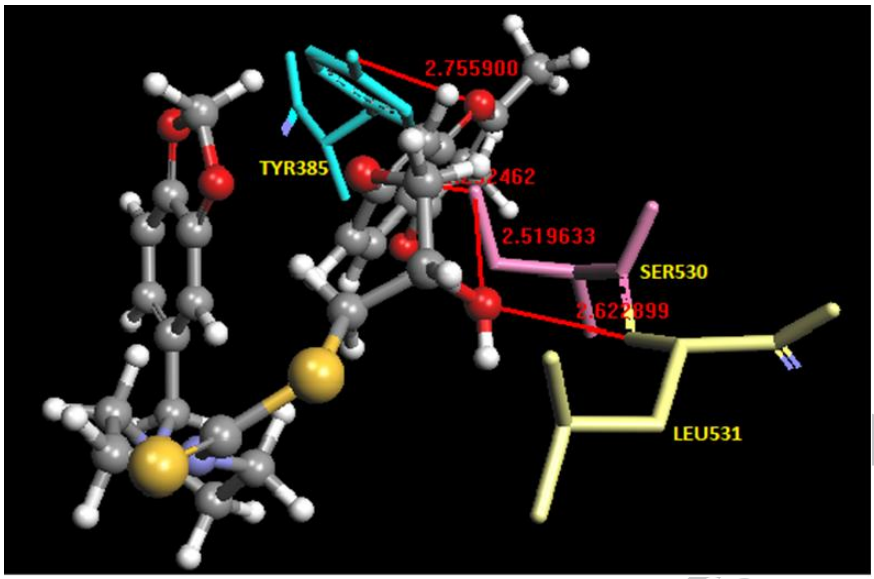


Figure 2. Binding mode of compound **7h** in the active site of cyclooxygenase (4COX). Ligand indicated in ball and cylinder low model residues were indicated in cylinder high model. Red colour dotted lines indicated the hydrogen bonds

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References

1. Pacher, P.; Beckman, J. S.; Liaudet, L. *Physiol. Rev*. **2007**, *87*, 315.
2. Karalı, N.; Guzel, O.; Ozsoy, N.; Ozbey, S.; Salman, A. *Eur. J. Med. Chem*. **2010**, *45*, 1068.
3. Kumpulainen JT, Salonen JT. Natural Antioxidants and Anticarcinogens in Nutrition, Health and Disease, *Royal Soc. of Chem*, UK **1999**, 178.
4. Nagasawa, T.; Yonekura, T.; Nishizawa, N.; Kitts, D D. *Mol Cell Biochem*.**2001**, *225*, 29.
5. Scartezzini, P.; Speroni, E. *J. Ethnopharmacol*. **2000**, *71*, 23.
6. Anuja chopra, Manpreetkaur, Navpreet, Divneet, Lalit, *Journal of Hormonized Research in Pharmacy*, **2015**, *4*, 162.
7. Hottori, M.; Akao, T.; Kobashi, K.; Namba, T. *Pharmacology* **1993**, *47*, S125.
8. Hutter, J.A.; Salman, M.; Stavinoha, W.B.; Satangi, N.; Williams, R.F.; Streeper, R.T.; Weintraub, S.T. *J. Nat. Prod*. **1996**, *59*, 541.
9. Okamura, N.; Hine, N.; Harada, S.; Fujioka, T.; Mihashi, K.; Yagi, A. *Phytochem* **1996**, *43*, 495.
10. Grollier, J.F.; Lang, G.; Gratien, S.; Forestier, S.; Rosenbaum, G. US **1987**, *29*, 656.
11. Hirata,T.; Suga,T. *Bull.Chem.Soc.Jap*. **1978,** *51*, 842.
12. Naveen Kumar, B.; Venkatesham, A.; Jyothi, M.; Nagaiah, K.; Sujitha, P.; Ganesh Kumar, C.; Rajendra Prasad, K.; Jagadeesh Babu, N. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4061.
13. Jyothi, M.; Venkatesham, A.; Naveen Kumar B.; Nagaiah, K.; Sujitha, P.; Ganesh Kumar, C.; Prabhakar Rao, T.; Jagadeesh Babu N. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4428.
14. Parker, R. E.; Isaacs,N. S. *Chem. Rev*. **1959**, *59*, 737.
15. Bonini, C.; Righi, G. *Synthesis* **1994**, 225.
16. Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323.
17. Smith, J. G. *Synthesis* **1984**, 629.
18. B. Cvek, Z.T. Dvorak, Curr. Pharm. Des. **2007**, *30*, 3155.
19. Wei, H.; Yu, D.; Yan, M.; Liu, M. Z.; Yan, L.; Guang, F. Y. *Eur. J. Med. Chem*. **2009**, *44*, 3687.
20. Kirkiacharian, S.; Lormier, A. T.; Chidiack, H.; Bouchoux, F.; Cérède, E. *IL Farmaco*. **2004**, *59*, 981.
21. Yu, D.; Chen, C.H.; Brossi, A.;Lee, K.H. *J. Med. Chem*. **2004**, *47*, 4072.
22. Azizi, N.; Pourhasan, B.; Aryanasab, F.; Saidi, M. R. *Synlett* **2007**, 8, 1239.
23. Azizi, N. Elham, G. *RSC Adv*., **2012**, 2, 7413.
24. Azizi, N.; Gholibeglo, E.; Maryami, M.; Nayeri, S. D.; Bolourtchian, S. M.; *C. R. Chimie*, **2013**, 16, 412.
25. Barahman, M.; Bahareh, S. *Inter. J. Org. Chem*, **2012**, 2, 248-253
26. Ronconi, L.; Marzano, C.; Zanello, P.; Corsini, M.; Miolo, G.; Macca, C.; Trevisan, A.; Fregona, D. *J. Med. Chem*. **2006**, 49, 1648
27. Rafin, C.; Veignie, E.; Sancholle, M.; Postel, D.; Len, C.; Villa, P.; Ronco, G. *J. Agric. Food Chem*. **2000**, 48, 5283
28. Morf, P.; Raimondi, F.; Nothofer, H.G.; Schnyder, B.; Yasuda, A.; Wessels, J. M.; Jung, T. A. *Langmuir* **2006**, 22, 658
29. Cui, J. L.; Ge, Z. M.; Cheng, T. M.; Li, R. *Synth. Commun*. **2003**, 33, 1969.
30. *H. Salem,; J. Pharm. Biomed. Anal.* **2002**, 29, 527–538
31. Jones, G.; Willett, P.; Glen, R.C. *J. Mol. Biol.* **1995**, *43*, 245.
32. http://www.rcsb.org.
33. Guex N, Peitsch MC Deep View/Swiss Pdb Viewer 3.7 (SP5).Electrophoresis **2006**, *18*, 2714.
34. Morris, G. M.; Goodsell, D. S.; Huey, R.; Olson, A. *J. J. Comput-Aided Mole Des*. **1996**, *10*, 293.

Highlights

- Our approach is straight forward and involved standard reactions with good yields.
- Synthesis proceeds with economical and available starting material resorcinol.
- Friedel-craft acylation, Chromone formation and epoxide opening as the key steps.
- Chromone analogues with potent anti-oxidant activity.
- Chromones may be synthetic targets due to their broad biological activity.

Graphical Abstract

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Synthesis of new chromeno carbamodithioate derivatives and preliminary evaluation of their antioxidant activity and molecular docking studies

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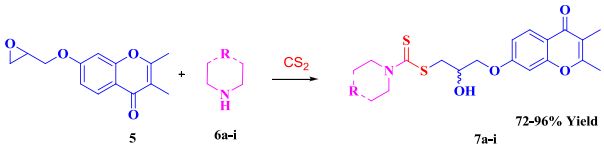

Compound 7g and 7h show highest Antioxidant activity

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