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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

An efficient synthesis of flavanones and their docking studies with aldose reductase

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Abstract A series of flavanone derivatives have been synthesized from 2-hydroxy acetophenone and benzaldehyde using fused calcium chloride in good to moderate yields, and their in vitro aldose reductase inhibitory activity has been tested on aldose reductase purified enzyme from Bovine lens. Most of the synthesized compounds exhibited potent aldose reductase inhibitory activity, and the obtained results are supported by the docking studies. Among the tested derivatives, 2, 3, 4-methoxy derivative **19** (IC_{50} 5.88 ± 0.03 μM) exhibited the highest inhibitory activity whereas 2-methoxy derivative **12** showed the lowest, and the remaining compounds exhibited moderate activity with IC_{50} in the range of 6.09–7.89 μM. The spatial configuration of the most active derivative **19** was compared with pharmacophore requirements of the aldose reductase inhibitor site using a molecular modeling system.

Keywords Aldose reductase inhibitor · Flavanone · Calcium chloride · Bovine lens · Molecular docking

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Introduction

Hyperglycemia leads to several diabetic complications such as retinopathy, neuropathy, cataracts, nephropathy and cardiovascular complication. In 2010, 285 million people were suffering from diabetes, and this number is estimated to increase to 439 million by 2030. However, the available oral antidiabetic drugs are ineffective in preventing complications associated with diabetics. Aldose reductase (AR; EC: 1.1.1.21) is the key rate limiting enzyme of the polyol pathway involved in the conversion of glucose to sorbitol utilizing NADPH as the cofactor (Chen et al. 2011). The activity of the enzyme is found to be enhanced in diabetic patients (Gabbay et al. 1996). It is a major risk factor leading to cataract, a major cause of blindness over the world. Various pharmacological strategies have been used to prevent the cataract formation, among them AR inhibitors (ARIs) have received much attention because of its involvement in the pathophysiology of diabetic complications including cataract (Ghahary et al. 1991, Wild et al. 2004). Inhibition of this crucial enzyme would therefore constitute a vital strategy in control of secondary complications associated with diabetes. Studies directed towards the development of ARIs to prevent these complications have yielded many structurally diverse ARIs such as tolrestat, sorbinil, zopolrestat, and from other sources (Obrosova et al. 2010; Costantino et al. 2000; Miyamoto 2002; Soni et al. 2008; Jung et al. 2011; Hamada et al. 2000). Flavonoids are credited with a number of biological activities (Aherne and O'Brien 2002; Middleton et al. 2000), and possess significant health-promoting activities, such as inhibition of AR and sorbitol accumulation (Haraguchi et al. 1996a, 1996b; Wirasathien et al. 2007), lipid-lowering effect (Kigarashi et al. 1996), and antioxidant activity (Haraguchi et al. 1996a). Keeping in view of the diverse biological effects displayed

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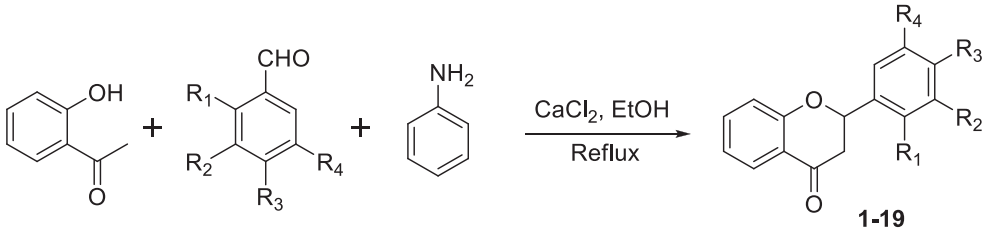

Scheme 1 Synthesis of flavanone derivatives

by flavanones, a simple cost-effective one-pot method has been developed for flavanones from easily available raw materials (Scheme 1), and their in vitro ARI studies have been carried out.

A number of methods exist in literature for synthesis of flavanones from substituted 2-hydroxychalcones using acid catalysts (Monserrat et al. 2010; Kumar et al. 2008; Kagawa et al. 2005), bases (Akcok and Çağır 2010; Chandrasekhar et al. 2005), thermal, photochemical methods and electrochemical transformations (Maki et al. 1988; Pandey et al. 1987; Sanicanin and Tabakovic 1986; Matsushima and Kageyama 1985). Other alternate procedures for flavanones include oxidation of flavan-4-ols (Sing 1993; Izumi et al. 1992) reaction of aldehydes with 1,3-diones in basic medium (Bhatia et al. 1968), transformation of phenyl alkenyl aryl ethers in the presence of $Hg(OCOCF_3)_2$ (Joglekar and Samant 1988), intramolecular Oxa Michael addition of activated α, β-unsaturated ketones (Subramanian and Balasubramanian 1990), Juliae Kocienski olefination of 2-(Benzo[d]thiazol-2-ylsulfonyl)-1-phenylethanones with aldehydes in the presence of base, and intermolecular C–O addition of carboxylic acids to arynes (Kumar et al. 2010; Wang et al. 2008) and from 3-hydroxy-1-(2-hydroxylphenyl)-3-arylpropan-1-ones. (Dubrovskiy and Larock 2010) Herein, we have employed one-pot synthesis of flavanones using anhydrous calcium chloride from O-hydroxyacetophenone and substituted benzaldehyde.

Results and discussion

Chemistry

The three-component Mannich reaction of aldehyde, amine and acetophenone, an enolisable ketone, yields β-amino carbonyl compounds, and this transformation has been effected by calcium chloride (Kulkarni et al. 2012), and we extend this strategy to furnish flavanone under mild conditions. The flavanone analogs **1–20** were synthesized by treating 2-acetyl phenol, appropriate aldehyde and aniline with fused calcium chloride in ethanol under reflux condition (Scheme 1).

As presented in Table 1, the reaction proceeded well with a variety of substrates to yield the corresponding flavanones in moderate yield. Aldehydes bearing substituent at *ortho* position required more time for completion and suffered in terms of yield. Aldehydes bearing electron withdrawing group like nitro underwent smooth reaction in short time as compared to unsubstitued aldehyde (**6**, **10** and **13**). The nature of substituent and its position on the aromatic ring of the aldehyde had effect on the reaction yield and time. Aldehydes bearing substituents at *para* position underwent smooth reaction to afford the corresponding flavanone in good yield, and also naphthaldehyde underwent smooth transformation to afford the corresponding flavanone in high yield.

Table 1 Synthesis of flavanone derivatives

Compounds	R_1	R_2	R_3	R_4	Time in h	% yield
1	H	H	H	H	10	92
2	H	H	Cl	H	8	91
3	H	H	Me	H	11	88
4	H	H	OMe	H	8	89
5	H	H	Br	H	10	90
6	H	H	NO_2	H	7.5	85
7	H	H	F	H	9	86
8	OMe	H	H	H	12	82
9	F	H	H	H	12	76
10	NO_2	H	H	H	7.5	80
11	Cl	H	H	H	10	70
12	H	OMe	H	H	13	74
13	H	NO_2	H	H	7.5	80
14	Cl	H	Cl	H	9	83
15	Me	H	Me	H	11	79
16	H	Me	Me	H	11	78
17	OMe	H	H	OMe	10	75
18	H	OMe	H	OMe	12	80
19	H	OMe	OMe	OMe	11	78
20	Naphthyl flavanone				12	80

As far as mechanism is concerned, we speculate that the reaction proceeds via Schiff's base formed with benzaldehyde in line with literature reports using iodine as catalyst for the same one-pot reaction (Kavala et al. 2012). It seems cyclization involving knocking off amino moiety from the Mannich intermediate may play crucial role in determining the rate and yield. Calcium chloride being very mild and

inexpensive makes this protocol attractive from synthetic point of view, and also the protocol can be extended to acid/base sensitive molecules of biological importance.

The drug likeness study

The drug likeness of the designed molecules have been studied using quantitative structure activity relationship module of the VLife MDS 4.3 and the major five properties including molecular weight (MW), hydrogen-bond acceptor atoms (HBA), hydrogen-bond donor atoms (HBD), rotatable bond count (RBC), Clog P were calculated for the synthesized molecules. It is obvious from the Table 2; the designed molecules displayed acceptable Lipinski parameters with good drug likeness.

Inhibition of AR

All compounds were tested for their ability to inhibit AR by measuring the decrease in NADPH absorption at 340 nm over a 4-min period on an Ultrospec_2100pro UV/Visible spectrophotometer with Quercetin (well known ARI) as reference, and the results are summarized in Table 3 and Fig. 1, and comparative dose response curve of all molecules with Quercetin in different concentrations (10, 25, 50 and 100 μM) are depicted in Fig. 2.

The results revealed that almost all flavanones exhibit moderate to good activity in the potency range of 5.88–9.07 μM, as compared to Quercetin (5.01 ± 0.02 μM). In particular, the trisubstituted 2, 3, 4-methoxy derivative 19 (5.88 ± 0.03 μM) showed highest AR inhibition followed by compound **2** (IC_{50} 5.93 ± 0.04 μM) whereas 2-methoxy derivative 12 (9.07 ± 02 μM) showed the lowest inhibitory activity while the remaining flavanone derivatives showed moderate AR inhibitory activity in the IC_{50} range of 6.09–7.89 μM concentration.

Table 2 Physical properties (Lipinski parameters) of compounds **1–20**

Compounds	MW	HBA	HBD	RBC	Clogp
1	224.259	1	0	1	3.19
2	258.704	1	0	1	3.809
3	238.286	1	0	2	3.471
4	254.285	2	0	3	3.153
5	303.155	1	0	1	3.986
6	269.257	4	0	2	3.062
7	242.25	2	0	1	3.292
8	254.285	2	0	3	3.153
9	242.25	2	0	1	3.292
10	269.257	4	0	2	3.062
11	258.704	1	0	1	3.809
12	254.285	2	0	3	3.153
13	269.257	4	0	2	3.062
14	293.149	1	0	1	4.428
15	252.313	1	0	3	3.752
16	252.313	1	0	3	3.752
17	284.312	3	0	5	3.116
18	284.312	3	0	5	3.116
19	314.338	4	0	7	3.079
20	274.319	1	0	1	4.476

MW molecular weight, *Clog P* calculated logarithm of the octanole: water partition coefficient, *HBA* hydrogen-bond acceptor atoms, *HBD* hydrogen-bond donor atoms, *RBC* rotatable bond count

Docking analysis

In order to gain some insight about the binding mode of the designed inhibitors, the docking analysis of newly synthesized analogs in the active site of aldoreductase enzyme were carried out using the enzyme AR (protein data base (PDB): 1AH0). Docking of the flavones derivatives with the active site of the enzyme AR was performed using grip-based docking simulation in biopredicta module of Vlife MDS 4.3, wherein rigid docking is carried out by keeping protein structure rigid with flexible ligand. All the designed molecules were docked into the active site of the enzyme AR, and the results indicated that all the molecules fit well into the active site of the enzyme with multiple interactions as shown in (Table 4). Among the flavanones studied, **19** (2-(3,4,5-trimethoxyphenyl) chroman-4-one), **2** (2-(4-chlorophenyl) chroman-4-one), **4** (2-(4-methoxyphenyl) chroman-4-one) with potent ARI inhibition in the range of 98% under in vitro studies displayed high affinity binding with the enzyme as shown in (Table 4). 2-(3,4,5-trimethoxyphenyl) chroman-4-one (**19**) showed significant interactions with the AR enzymes via the formation of

Table 3 In vitro ARI activity of flavanone derivatives

Compound	IC_{50} (μM)[a]	Compound	IC_{50} (μM)[a]
1	6.67 ± 0.02	**11**	6.24 ± 0.04
2	5.93 ± 0.04	**12**	9.07 ± 0.03
3	6.12 ± 0.02	**13**	7.36 ± 0.01
4	6.09 ± 0.01	**14**	7.86 ± 0.01
5	6.37 ± 0.01	**15**	6.56 ± 0.04
6	8.73 ± 0.05	**16**	6.22 ± 0.02
7	7.89 ± 0.04	**17**	6.76 ± 0.02
8	6.94 ± 0.02	**18**	6.84 ± 0.03
9	7.23 ± 0.03	**19**	5.88 ± 0.03
10	8.23 ± 0.03	**20**	7.12 ± 0.02
Quercetin[b]	5.01 ± 0.02		

[a] IC_{50} values are expressed as mean ± SD for three determinations

[b] Quercetin used as positive control

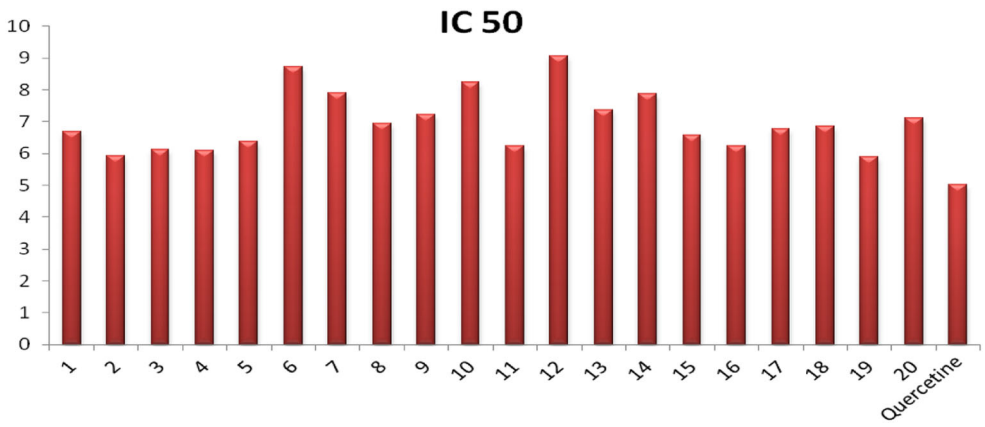

Fig. 1 Inhibition of AR against bovine lens AR by compounds (**1–20**) comparing with those of Quercetin. The results are expressed as mean ± SD values from three independent experiments

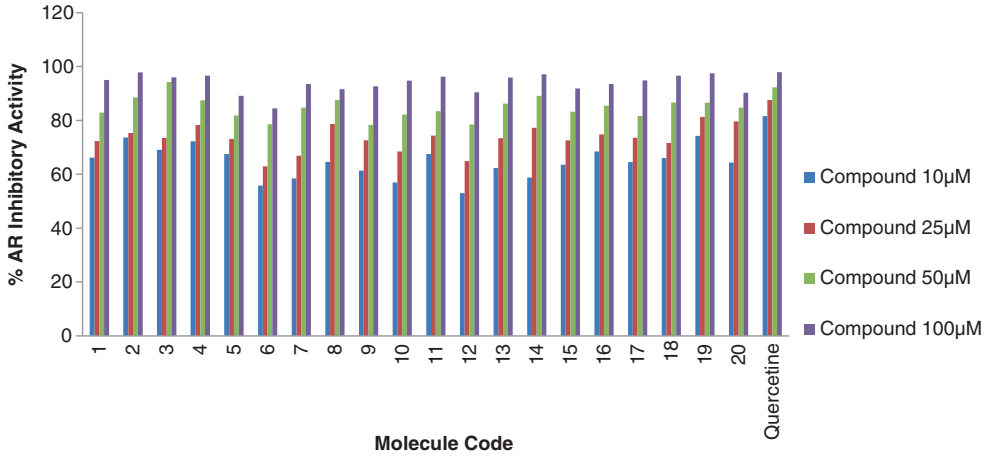

Fig. 2 Concentration-dependent AR inhibitory activity of synthesized derivatives

hydrogen bond interaction between CH_2 and NH of Trp20 with a distance of 2.6 Å, while 3,4,5-trimethoxyphenyl ring showed aromatic interaction with Trp219, Trp20 with distance of 4.4 Å and 4.6 Å, and hydrophobic interaction with Leu 300. 2-(4-chlorophenyl) chroman-4-one showed hydrogen bond interaction between C=O and NH of Trp111 with distance of 1.8 Å and aromatic interaction between phenyl ring of benzpyran with His110 (5.4 Å), Trp 20(5 Å), Trp 79(4.9 Å) and 4-chlorophenyl ring sowed aromatic interaction with Trp219(5.4 Å) and Phe 322 (4.3 Å) and hydrophobic interaction with Leu 300. 2-(4-methoxyphenyl) chroman-4-one showed hydrogen bond interaction between O of chroman-4-one and NH of with Trp20 with distance of 2.2 Å and 4-methoxyphenyl ring showed aromatic interactions with Trp20(4.3 Å), Trp219 (4.6 Å), hydrophobic interaction with Leu 300 (Fig. 3). It is worth mentioning that the binding pocket can accommodate flavones bearing different substituent with ease (Table 4) and hence allow modification of substituent to enhance potency.

Pharmacophore Modeling studies

Pharmacophore modeling of the designed set of the inhibitors were carried out to identify the basic framework of the molecules that regulate their pharmacodynamic potential. Pharmacophore identification studies showed involvement of two aromatic features and one hydrogen bond accepter as three important features. The two aromatic features are separated by the 6.741 Å, while hydrogen bond acceptor is separated from the aromatic features by 3.9 and 5.5 Å, respectively, as shown in Figs. 4 and 5. The two aromatic features play vital role in the observed biological activity of the molecules as the hydrophobic pocket of enzyme comprising of Trp111, Leu300 and Phe122 attribute to significant binding and hence higher activity. The proposed pharmacophore hypothesis would be useful for the design of new ARIs of therapeutic significance. (Figs. 4 and 5).

Table 4 Key interactions of the best docked conformations of the designed derivatives in the active site of aldose reducatse

Mol. No.	Type of interaction	Amino acid	Binding energy
1	Hydrogen bond interaction	TRP111	−47.33
	Aromatic interaction	PHE122, TRP20, TRP 79	
2	Hydrogen bond interaction	TRP111	−47.50
	Aromatic interaction	HIS110,PHE122, TRP20, TRP 79	
	Hydrophobic interaction	LEU300	
3	Hydrogen bond interaction	TRP111	−50.91
	Aromatic interaction	HIS110,PHE122, TRP20, TRP 79	
	Hydrophobic interaction	LEU300	
4	Hydrogen bond interaction	TRP111	−55.57
	Aromatic interaction	HIS110,PHE122, TRP20, TRP 79, TRP219	
	Hydrophobic interaction	LEU300	
5	Hydrogen bond interaction	TRP111	−54.03
	Aromatic interaction	HIS110,PHE122, TRP20, TRP79, TRP219	
	Hydrophobic interaction	LEU300	
6	Hydrogen bond interaction	TRP20	−48.80
	Aromatic interaction	TRP20, TRP219	
7	Hydrogen bond interaction	TRP20	−48.21
	Aromatic interaction	TRP20, TRP219	
	Hydrophobic interaction	LEU300, CYS298	
8	Hydrogen bond interaction	TRP111	−55.13
	Aromatic interaction	HIS110, PHE122, TRP20, TRP79, TRP219	
	Hydrophobic interaction	LEU300, SER302	
9	Hydrogen bond interaction	TRP20	−60.51
	Aromatic interaction	TRP20	
	Hydrophobic interaction	LEU300, VAL47, TRP20	
10	Hydrogen bond interaction	TRP20	−53.59
	Aromatic interaction	TRP20	
	Hydrophobic interaction	LEU300, VAL47, TRP20	
11	Hydrogen bond interaction	TRP20	−55.68
	Aromatic interaction	TRP20	
	Hydrophobic interaction	LEU300, VAL47, TRP20, CYS298	
12	Hydrogen bond interaction	TRP111	−50
	Aromatic interaction	HIS110,PHE122, TRP20, TRP 79, TRP219	
	Hydrophobic interaction	LEU300	
13	Hydrogen bond interaction	TRP111	−55.13
	Aromatic interaction	HIS110,PHE122, TRP20, TRP 79, TRP219	
	Hydrophobic interaction	LEU300	
14	Hydrogen bond interaction	TRP111	−53.51
	Aromatic interaction	PHE122, TRP219	
	Hydrophobic interaction	LEU300, SER302	
15	Hydrogen bond interaction	TRP20	−51.11
	Aromatic interaction	TRP20	
	Hydrophobic interaction	LEU300,CYS298	
16	Aromatic interaction	TRP20	−36.47
17	Hydrogen bond interaction	TRP111, SER302	−50.21
	Aromatic interaction	PHE122, TRP219, TYR48, TRP20	
	Hydrophobic interaction	LEU300, SER302	

Table 4 continued

Mol. No.	Type of interaction	Amino acid	Binding energy
18	Hydrogen bond interaction	TRP111	−53.13
	Aromatic interaction	PHE122, TRP219, TYR48, TRP20	
	Hydrophobic interaction	LEU300	
19	Hydrogen bond interaction	TRP20	−50.46
	Aromatic interaction	TRP219, TRP20	
	Hydrophobic interaction	LEU300	
20	Hydrogen bond interaction	TRP111	−48.68
	Aromatic interaction	TRP219, TRP20, HIS110	
	Hydrophobic interaction	LEU300	

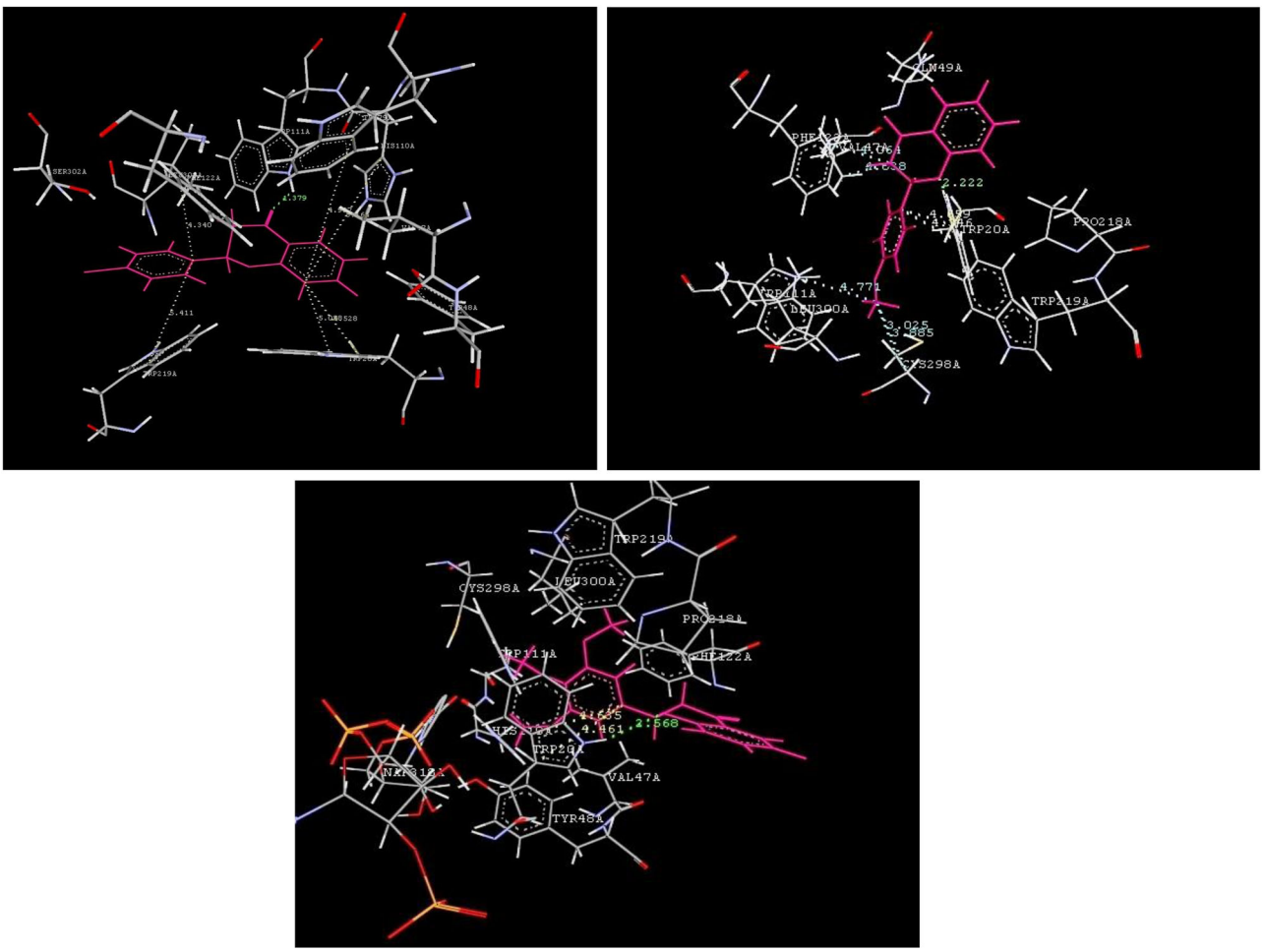

Fig. 3 Docking poses for some most active compounds (inhibitors having interactions with amino acids are colored in *pink*. Hydrogen bond interactions: *green* color, aromatic interaction: *yellow* color). **a** Figure showing binding mode of molecule 2 with AR. **b** Figure showing binding mode of molecule 2 with AR. **c** Figure showing binding mode of molecule 19 with AR

Conclusion

- The present work describes a facile route to flavanones from readily available starting materials and their development as ARIs.
- The IC_{50} values of flavanones **2**, **4** and **19** were found to be comparable to that of standard quercetin.
- Molecular docking and biological activity of developed inhibitors indicated electron withdrawing substitutions on phenyl ring might infusing AR inhibition potential.

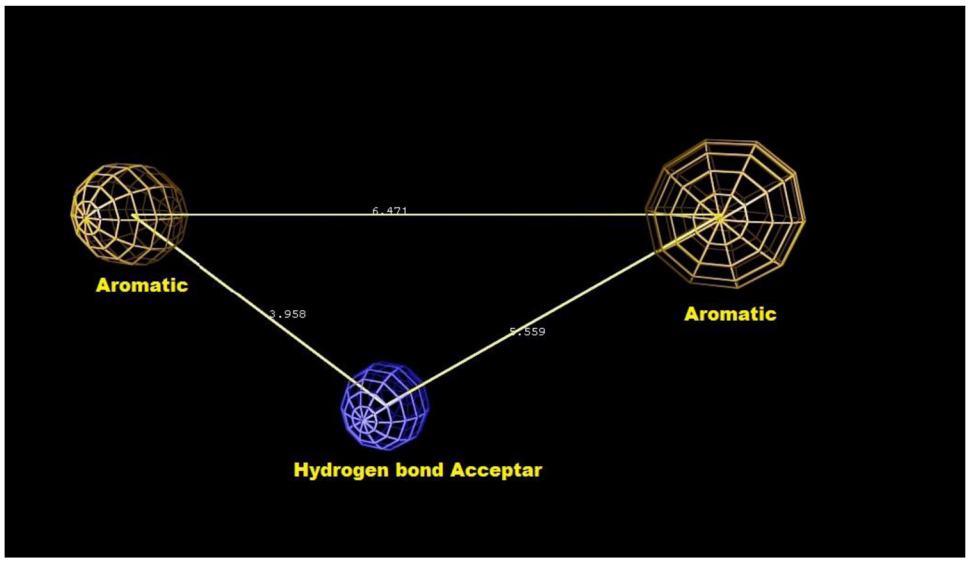

Fig. 4 Selected pharmacophoric hypotheses of flavones for aldoreductase inhibitory activity

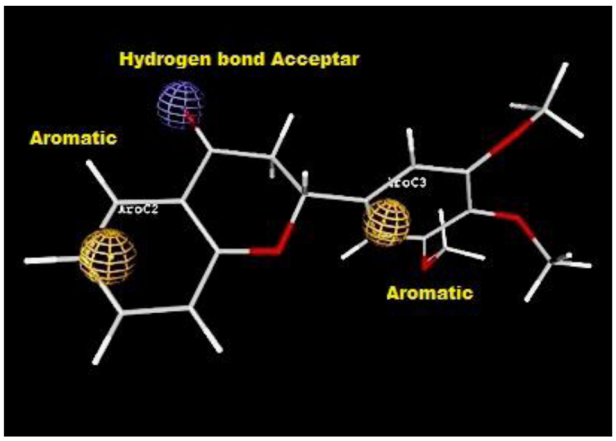

Fig. 5 Pharmacophoric feature of the synthesized inhibitor **19**

- Pharmacophore modeling-indicated derivatives with two aromatic features and one hydrogen bond accepter will act as ARIs.
- Molecular docking studies reveal the mode of interactions as well as binding with the enzyme. The proposed pharmacophore model would facilitate design of new ARIs of therapeutic significance.

Experimental section

Chemistry

Solvents for extraction and chromatography were distilled before use. All chemicals were purchased from Merck and Sigma Aldrich, and used directly without any purification. Analytical thin-layer chromatography was performed using E. Merck silica gel 60F glass plates, and E. Merck silica gel (230–400 mesh) was used in flash chromatography separations. Chemical shifts were reported in parts per million (δ) using trimethyl silane as internal standard, and coupling constants were expressed in hertz. The melting points were determined in open capillaries.

General procedure for the synthesis of compounds 1–20

To a mixture of substituted benzaldehyde (1.0 mmol), aniline (1.5 mmol), 2-hydroxyacetophenone (1.2 mmol) in ethanol (1.0 mL), fused calcium chloride ($CaCl_2$ 2 mmol) was added, and the reaction mixture was subjected to reflux for 7–12 h. The progress of the reaction was monitored by TLC. After completion of the reaction (monitored by TLC), water work-up followed by extraction with methylene chloride and concentration of the extracts dried over sodium sulphate afforded the crude product. The products were purified either by recrystallization from hexane:ethyl acetate or by short flash chromatography on silica gel using petroleum ether: ethyl acetate (9:1) as eluent.

*2, 3-Dihydro-2-phenyl-4H-1-benzopyran-4-one (**1**)*

White solid; yield: 92%; mp: 75–76 °C (Kigarashi et al. 1996); IR (KBr, cm^{-1}): 3358, 3041, 1689 (C=O), 1453, 1294, 1167; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.90 (dd, J = 16.8, 2.8 Hz, 1H, Ha-3), 3.10 (dd, J = 16.8, 13.2 Hz, 1H, Hb-3), 5.49 (dd, J = 13.2, 2.8 Hz, 1H, H-2), 7.06 (m, 2H, ArH), 7.47 (m, 5H, ArH), 7.94 (dd, J = 8.4, 2.0 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 44.7 (C-3), 79.6 (C-2), 118.1, 120.9, 121.6, 126.1, 127.0, 128.8, 128.9, 136.2, 138.7, 161.5 (Ar–C), 192.0 (C=O); EIMS (70 eV) *m/z* (rel

intensity, %): 224 (M^+, 56), 223 (100), 147 (62), 120 (47), 104 (26), 92 (78), 78 (29), 63 (22); anal. calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.02; H, 5.47.

*2, 3-Dihydro-2-(4-chlorophenyl)-4H-1-benzopyran-4-one (**2**)*

White solid; yield: 91%; mp: 85–86 °C (Chimenti et al. 2010); IR (KBr, cm^{-1}): 3366, 3068, 2958, 2899, 1945, 1694(C=O), 1599, 1462, 1300, 1221; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.87 (dd, J = 17.2, 3.2 Hz, 1H, Ha-3), 3.03 (dd, J = 17.2, 13.2 Hz, 1H, Hb-3), 5.45 (dd, J = 13.2, 3.2 Hz, 1H, H-2), 7.05 (m, 2H, ArH), 7.45 (m, 4H, ArH), 7.55 (td, J = 8.4, 1.6 Hz, 1H, ArH), 7.95 (dd, J = 8.0, 2.0 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 44.5 (C-3), 78.7 (C-2), 118.3, 121.0, 121.6, 127.3, 127.6, 129.3, 134.4, 136.5, 137.3, 161.2 (Ar–C), 191.4 (C=O); EIMS (70 eV) *m/z* (rel intensity, %): 258 (M^+, 71), 257 (100), 223 (29), 147 (66), 138 (37), 120 (67), 103 (37), 92 (75); anal. calcd for $C_{15}H_{11}ClO_2$: C, 69.64; H, 4.29. Found: C, 69.55; H, 4.32.

*2, 3-Dihydro-2-(4-methylphenyl)-4H-1-benzopyran-4-one (**3**)*

White solid; yield: 88%; mp: 81–83 °C (Lee et al. 2007); IR (KBr, cm^{-1}): 3362, 3034, 2974, 2892, 1955, 1691(C=O), 1603, 1514, 1460, 1301, 1232, 1147, 1067; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H, CH_3), 2.85 (dd, J = 16.84, 2.80 Hz, 1H, Ha-3), 3.07 (dd, J = 16.84, 13.32 Hz, 1H, Hb-3), 5.45 (dd, J = 13.32, 2.80 Hz, 1H, H-2), 7.00–7.06 (m, 2H, ArH), 7.25 (d, 2H, J = 7.81 Hz, ArH), 7.37 (d, 2H, J = 7.81 Hz, ArH), 7.50 (m, 1H, ArH), 7.92 (dd, 1H, J = 8.08, 1.76 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.13 (CH_3), 44.50 (C-3), 79.47 (C-2), 118.10, 120.90, 121.45, 126.15, 127.02, 129.45, 135.72, 136.10, 138.65, 161.60 (Ar–C), 192.04 (C=O); EIMS *m/z* (relative intensity): 238 (M^+, 29), 181 (19), 141 (33), 139 (100), 118 (27); Anal. calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92 found: C, 80.67; H, 5.95.

*2, 3-Dihydro-2-(4-methoxyphenyl)-4H-1-benzopyran-4-one (**4**)*

Pale yellow solid; yield: 89%; mp: 87–88 °C, (Akcok and Çağır 2010); IR (KBr, cm^{-1}): 3007, 2930, 2836, 1939, 1692(C=O), 1605, 1507, 1474, 1304, 1251, 1166; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.85 (dd, J = 16.84, 2.80 Hz, 1H, Ha-3), 3.10 (dd, J = 16.84, 13.32 Hz, 1H, Hb-3), 3.83 (s, 3H, OCH_3), 5.43 (dd, J = 13.32, 2.80 Hz, 1H, H-2), 6.96 (d, J = 6.88 Hz, 2H, ArH), 7.03–7.07 (m, 2H, ArH), 7.41 (d, J = 6.88 Hz, 2H, ArH), 7.48–7.50 (m, 1H, ArH), 7.92 (dd, J = 8.44, 1.64 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.36 (C-3), 55.29 (OCH_3), 79.28 (C-2), 114.15, 118.05, 120.85, 121.43, 126.95, 127.66, 130.74, 136.06, 159.92, 161.56 (Ar–C), 192.15 (C=O); MS *m/z* (relative intensity): 254 (M^+, 63), 139 (13), 134 (100), 121 (28), 119 (23), 91 (16), 77 (5), 57 (8); anal. calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55 found: C, 75.60; H, 5.58.

*2, 3-Dihydro-2-(4-bromophenyl)-4H-1-benzopyran-4-one (**5**)*

Pale yellow solid; yield: 90%; mp: 116–117 °C, (Choudary et al. 2005); IR (KBr, cm^{-1}): 3358, 3065, 2898, 1917, 1687 (C=O), 1597, 1462, 1410, 1367, 1300, 1222, 1151, 1066, 1013; ^{1}HNMR (400 MHz, $CDCl_3$): δ 2.84(dd, J = 16.8, 3.2 Hz, 1H, Ha-3), 3.03 (dd, J = 16.8, 13.2 Hz, 1H, Hb-3), 5.45 (dd, J = 13.2, 2.8 Hz, 1H, H-2), 7.05 (m, 2H, ArH), 7.35 (dd, J = 8.4, 1.6 Hz, 2H, ArH), 7.55 (td, J = 8.4, 1.6 Hz, 1H, ArH), 7.56 (dd, J = 8.4, 2.0 Hz, 2H, ArH), 7.95 (dd, J = 8.0, 2.0 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.6 (C-3), 78.5 (C-2), 118.2, 120.8, 121.7, 122.6, 127.3, 127.6, 132.2, 136.1, 137.4, 161.2 (Ar–C), 191.3 (C=O); EIMS (70 eV) *m/z* (rel intensity, %): 303 (M^+, 45), 302 (26), 301 (39), 223 (49), 147 (88), 120 (62), 103 (72), 93 (100); anal.calcd for $C_{15}H_{11}BrO_2$: C, 59.43; H, 3.66. Found: C, 59.39; H, 3.69.

*2, 3-Dihydro-2-(4-nitrophenyl)-4H-1-benzopyran-4-one (**6**)*

White solid; yield: 85%; mp: 120–121 °C, (Bhatia et al. 1968); IR (KBr, cm^{-1}): 3433, 2894, 1694 (C=O), 1603, 1530, 1462, 1333, 1223, 1118, 1067; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.98 (dd, J = 16.8, 3.6 Hz, 1H, Ha-3), 3.06 (dd, J = 16.8, 12.4Hz, 1H, Hb-3), 5.65 (dd, J = 12.4, 3.6 Hz, 1H, H-2), 7.12 (m, 2H, ArH), 7.55 (td, J = 8.4, 1.6 Hz, 1H, ArH), 7.68 (dd, J = 8.4, 2.0 Hz, 2H, ArH), 7.94 (dd, J = 8.0, 2.0 Hz, 1H, ArH), 8.33 (dd, J = 8.8, 2.0 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.5 (C-3), 78.4 (C-2), 118.1, 120.8, 122.3, 124.2, 126.7, 127.3, 136.4, 136.2, 148.6, 160.7 (Ar–C), 190.6 (C=O); EIMS (70 eV) *m/z* (rel intensity, %): 269 (M^+, 33), 268 (49), 252 (18), 147 (91), 121 (20), 120 (53), 93 (100), 64 (13); anal. calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.83; H, 4.15; N, 5.13.

*2, 3-Dihydro-2-(4-flurophenyl)-4H-1-benzopyran-4-one (**7**)*

White solid; yield: 86%; mp: 79–80 °C, (Kigarashi et al. 1996); IR (KBr, cm^{-1}): 3348, 3062, 2889, 1915, 1694 (C=O), 1579, 1448, 1428, 1360, 1308, 1227, 1155, 1067, 1012, 904, 865, 749, 639; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.87 (dd, J = 16.8, 2.8 Hz, 1H, Ha-3), 3.09 (dd, J = 16.8, 13.2 Hz, 1H, Hb-3), 5.46 (dd, J = 13.2, 2.8 Hz, 1H, H-2), 7.13 (m, 4H, ArH), 7.46 (m, 2H, ArH), 7.53 (td, J = 8.4, 1.6 Hz, 1H, ArH), 7.95 (dd, J = 8.0, 2.0 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.8 (C-3), 78.6 (C-2), 115.9, 118.3, 120.5, 121.3, 127.4, 128.6, 134.4, 136.2, 161.3, 162.1 (Ar–C), 192.8(C=O); EIMS (70 eV) *m/z* (rel intensity, %): 242 (M^+, 56), 241 (87), 147 (43), 122

(41), 121 (36), 120 (67), 2 (100), 63 (23); anal. calcd for $C_{15}H_{11}FO_2$: C, 74.37; H, 4.58. Found: C, 74.35; H, 4.60.

*2, 3-Dihydro-2-(2-methoxyphenyl)-4H-1-benzopyran-4-one (**8**)*

White solid; yield: 82%; mp: 113–114 °C, (Haraguchi et al. 1996a); IR (KBr, cm^{-1}): 3025, 2928, 2846, 1958, 1692 (C=O), 1615, 1524, 1470, 1315, 1250, 1165; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92–3.00 (m, 2H, Ha-b), 3.84 (s, 3H, OCH_3), 5.87 (dd, $J = 13.40$, 3.96 Hz, 1H, H-2), 6.94 (d, $J = 8.3$ Hz, 1H), 7.08–7.03 (m, 3H, ArH), 7.37–7.32 (m, 1H, ArH), 7.52–7.48 (m, 1H, ArH), 7.63 (dd, $J = 0.8$, 7.5 Hz, 1H, ArH), 7.94 (dd, $J = 1.36$, 7.8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.6 (C-3), 55.7 (OCH_3), 74.3 (C-2), 111.3, 118.2, 121.4, 121.5, 121.7, 126.4, 127.8, 129.5, 136.3, 156.2, 162.4 (Ar–C), 192.1(C=O); MS *m/z* (relative intensity, %): 254 (M^+, 39), 223 (100), 134 (25), 119 (66), 91 (52), 77 (16), 59 (49); anal. calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.60; H, 5.58.

*2, 3-Dihydro-2-(2-fluorophenyl)-4H-1-benzopyran-4-one (**9**)*

Yellow solid; yield: 76%; mp: 147–148 °C, (Bhatia et al. 1968); IR (KBr, cm^{-1}): 3301, 2989, 2872, 1948, 1692 (C=O), 1584, 1432, 1408, 1378, 1348, 1220, 1187, 1057, 1002; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.90 (dd, 1H, $J =$ 16.88, 3.08 Hz, Ha-3), 3.06 (dd, 1H, $J = 16.88$, 13.24 Hz, Hb-3), 5.78 (dd, 1H, $J = 13.24$, 2.96 Hz, H-2), 7.13–7.02 (m, 3H, ArH), 7.25–7.22 (m, 1H, ArH), 7.39–7.34 (m, 1H, ArH), 7.53–7.49 (m, 1H, ArH), 7.72–7.64 (m, 1H, ArH), 7.96 (dd, 1H, $J = 8.56$, 1.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.71 (C-3), 77.3 (C-2), 115.8, 118.4, 122.3, 122.7, 126.4, 126.3, 127.5, 130.6, 136.3, 159.7, 161.6 (Ar–C), 191.75 (C=O); EIMS (70 eV) *m/z* (rel intensity, %): 242 (M^+, 56), 241 (87), 147 (43), 122 (41), 121 (36), 120 (67), 92 (100), 63 (23); anal.calcd for $C_{15}H_{11}FO_2$: C, 74.37; H, 4.58. Found: C, 74.39; H, 4.63.

*2, 3-Dihydro-2-(2-nitrophenyl)-4H-1-benzopyran-4-one (**10**)*

White solid; yield: 80%; mp: 121–122 °C, (Cabrera et al. 2007); IR (KBr, cm^{-1}): 3428, 2889, 1691 (C=O), 1615, 1542, 1460, 1343, 1232, 1181, 1062, 932, 872, 736, 642; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (dd, 1H, $J = 16.88$, 13.12 Hz, Ha-3), 3.23 (dd, 1H, $J = 16.92$, 2.56 Hz, Hb-3), 6.06 (dd, 1H, $J = 13.12$, 2.66 Hz, H-2), 7.03 (d, 1H, $J = 8.0$ Hz), 7.12–7.09 (m, 1H, ArH), 7.60–7.51 (m, 1H, ArH), 7.75 (m, 1H, ArH), 7.95 (dd, 1H, $J = 7.8$, 1.64 Hz, ArH), 8.03 (d, 1H, $J = 8.20$ Hz, ArH), 8.08 (dd, 1H, $J = 8.20$ Hz, 1.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.8 (C-3), 75.6 (C-2), 118.3, 121.5, 122.4, 125.2, 127.6, 128.3, 129.7, 134.1, 134.7, 136.7, 147.8, 161.4 (Ar–C), 190.7(C=O); EIMS (70 eV) *m/z* (rel intensity, %): 269 (M^+, 33), 268 (49), 252(18), 147 (91), 121 (20), 120 (53), 93 (100), 64 (13); anal. calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.87; H, 4.15; N, 5.16.

*2, 3-Dihydro-2-(2,-chlorophenyl)-4H-1-benzopyran-4-one (**11**)*

Pale yellow solid; yield: 70%; mp: 97–98 °C; IR (KBr, cm^{-1}): 3265, 3068, 2958, 2899, 1945, 1693 (C=O), 1599, 1462, 1320, 1300, 1221, 1112, 1066; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.89 (dd, 1H, $J = 16.88$, 13.12 Hz, Ha-3), 3.22 (dd, 1H, $J = 16.92$, 2.56 Hz, Hb-3), 6.05 (dd, 1H, $J =$ 13.12, 2.66 Hz, H-2), 7.03 (d, 1H, $J = 8.0$ Hz, ArH), 7.12–7.09 (m, 1H, ArH), 7.60–7.51 (m, 1H, ArH), 7.75 (m, 1H, ArH), 7.95 (dd, 1H, $J = 7.80$, 1.64 Hz, ArH), 8.03 (d, 1H , $J = 8.20$ Hz, ArH), 8.08 (dd, 1H, $J = 8.20$ Hz, 1.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.1 (C-3), 76.3 (C-2), 117.4, 121.4, 121.7, 127.2, 127.6, 128.8, 130.5, 133.1, 133.8, 134.7, 135.7, 160.4 (Ar–C), 191.2 (C=O); MS *m/z* (relative intensity): 258.04 (100.0%), 260.04 (32.0%), 259.05 (16.4%), 261.05 (5.4%), 260.05 (1.7%); anal. calcd for $C_{15}H_{11}ClO_2$: C, 69.64; H, 4.29. Found: C, 69.60; H, 4.32.

*2, 3-Dihydro-2-(3-methoxyphenyl)-4H-1-benzopyran-4-one (**12**)*

White solid; yield: 74%; mp: 110–112 °C, (Akcok and Çağır 2010); IR (KBr, cm^{-1}): 3012, 2928, 2815, 1930, 1691 (C=O), 1568, 1470, 1346, 1267, 1156, 978, 852, 738, 647; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.85 (dd, 1H, $J =$ 16.88, 2.96 Hz, Ha-3), 3.07 (dd, 1H, $J = 16.88$, 13.28 Hz, Hb-3), 3.85 (s, 3H, OCH_3), 5.46 (dd, 1H, $J = 13.28$, 2.40 Hz, H-2), 6.95–6.92 (m, 1H, ArH), 7.09–7.06 (m, 4H, ArH), 7.37 (t, 1H, $J = 8.4$ Hz, ArH), 7.55–7.51 (m, 1H, ArH), 7.96 (dd, 1H, $J = 8.24$, 1.64 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.36 (C-3), 55.30 (OCH_3), 79.29 (C-2), 114.18, 118.10, 120.84, 121.47, 126.93, 127.64, 130.75, 136.04, 159.94, 161.53 (Ar–C), 192.14 (C=O); MS *m/z* (relative intensity): 254 (M^+, 63), 147 (35), 134 (100), 91 (16), 77 (5), 57 (8); anal. calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.59; H, 5.62.

*2, 3-Dihydro-2-(3-nitrophenyl)-4H-1-benzopyran-4-one (**13**)*

White solid; yield: 80%; mp: 145–146 °C, (Po-Yuan et al. 2011); IR (KBr, cm^{-1}): 3426, 2892, 1693 (C=O), 1626, 1548, 1476, 1348, 1235, 1183, 1071; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.95 (dd, 1H, $J = 16.8$, 3.2 Hz, Ha-3), 3.06 (dd, 1H, $J = 16.8$, 12.8 Hz, Hb-3), 5.63 (dd, 1H, $J = 12.8$, 3.2 Hz, H-2), 7.13 (m, 2H, ArH), 7.55 (td, 1H, $J = 8.4$, 1.6 Hz, ArH), 7.66 (t, 1H, $J = 8.0$ Hz, ArH), 7.84 (m, 1H, ArH), 7.92 (dd, 1H, $J = 8.0$, 1.6 Hz, ArH), 8.22 (m, 1H, ArH),

8.45 (t, 1H, $J = 2.0$ Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.4 (C-3), 78.4 (C-2), 118.3, 120.8, 121.4, 122.7, 123.3, 127.7, 129.4, 131.5, 136.2, 140.3, 148.7, 160.3 (Ar–C), 190.2 (C=O); EIMS (70 eV) *m/z* (rel intensity, %): 269 (M^+, 35), 268 (39), 147 (100), 121 (33), 120 (66), 92 (99), 64 (19), 63 (23); anal. calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.81; H, 4.22; N, 5.18.

*2, 3-Dihydro-2-(2,4-chlorophenyl)-4H-1-benzopyran-4-one (**14**)*

White solid; yield: 83%; mp: 98–99 °C; IR (KBr, cm^{-1}): 3328, 3128, 2970, 2865, 1940, 1692(C=O), 1585, 1460, 1300, 1205, 1110, 1048; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.90 (dd, 1H, $J = 16.8$, 3.0 Hz, H-3a), 3.10 (dd, 1H, $J =$ 16.8, 13.2 Hz, H-3b), 5.41 (dd, 1H, $J = 13.2$, 3.0 Hz, H-2), 7.11–7.07 (2H, m, ArH), 7.21 (s, 1H, ArH), 7.42 (d, 1H, ArH), 7.55 (dd 1H, $J = 7.8$, 2.4 Hz, ArH), 7.61 (d, 1H, ArH), 7.96 (d, 1H, $J = 8.1$, 2.4 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.1 (C-3), 76.3 (C-2), 117.4, 121.4, 121.7, 127.2, 127.6, 128.8, 130.5, 133.1, 133.8, 134.7, 135.7, 160.4 (Ar–C), 191.2 (C=O); MS *m/z* (relative intensity, %): 292.01 (100.0), 294.00 (63.9), 293.01 (16.4), 295.01 (10.6), 296.00 (10.2), 297.00 (1.7), 294.01 (1.7), 296.01 (1.1); anal. calcd for $C_{15}H_{10}Cl_2O_2$: C, 61.46; H, 3.44. Found: C, 61.43; H, 3.47.

*2, 3-Dihydro-2-(2,4-dimethylphenyl)-4H-1-benzopyran-4-one (**15**)*

Pale yellow solid; yield: 79%; mp: 137–138 °C; IR (KBr, cm^{-1}): 3345, 3028, 2895, 2863, 1922, 1691 (C=O), 1601, 1563, 1508, 1479, 1323, 1256, 1145; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 6H, $2CH_3$), 2.84 (dd, 1H, $J = 16.84$, 2.80 Hz, Ha-3), 3.05 (dd, 1H, $J = 16.84$, 13.32 Hz, Hb-3), 5.43 (dd, 1H, $J = 13.32$, 2.80 Hz, H-2), 7.02–7.05 (m, 2H, ArH), 7.25 (d, 1H, $J = 7.81$ Hz, ArH), 7.50 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8 (CH_3), 21.4 (CH_3), 43.2 (C-3), 80.7 (C-2), 118.7, 120.2, 121.6, 126.8, 127.8, 131.3, 133.1, 134.6, 136.7, 137.3, 160.3 (Ar–C), 189.2 (C=O); MS *m/z* (relative intensity, %): 252.12 (100.0), 253.12 (18.6), 254.12 (2.0); anal. calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found C, 80.95; H, 6.42.

*2, 3-Dihydro-2-(3, 4-dimethylphenyl)-4H-1-benzopyran-4-one (**16**)*

Pale yellow solid; yield: 78%; mp: 112–113 °C; IR (KBr, cm^{-1}): 3256, 3178, 2945, 2872, 1950, 1690 (C=O), 1612, 1568, 1463, 1319, 1236, 1148, 1058; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 6H, $2CH_3$), 3.25 (dd, 1H, $J = 16.65$, 2.80 Hz, Ha-3), 3.38 (dd, 1H, $J = 16.84$, 13.32 Hz, Hb-3), 5.58 (dd, 1H, $J = 13.32$ Hz, 2.80 Hz, H-2), 7.05–7.15 (m, 2H, ArH), 7.04–7.08 (d, 2H, ArH), 7.23 (s, 1H, ArH), 7.43 (m, 1H, ArH), 7.88 (dd, 1H, $J = 8.05$, 1.76 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6 (CH_3), 19.3 (CH_3), 41.7 (C-3), 81.3 (C-2), 117.8, 120.2, 121.3, 122.8, 127.6, 128.9, 131.2, 133.7, 135.4, 135.8, 136.9, 158.7 (Ar–C), 189.2 (C=O); MS *m/z* (relative intensity, %): 252.12 (100.0), 253.12 (18.6), 254.12 (2.0%). anal. calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found C, 80.90; H, 6.47.

*2, 3-Dihydro-2-(2, 5-dimethoxyphenyl)-4H-1-benzopyran-4-one (**17**)*

White solid; yield: 75%; mp: 127–128 °C; IR (KBr, cm^{-1}): 3020, 2930, 2862, 1960, 1692 (C=O), 1600, 1558, 1465, 1378, 1260, 1189, 1038; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.18 (dd, 1H, $J = 16.65$, 2.85 Hz, Ha-3), 3.35 (dd, 1H, $J =$ 16.85, 13.33 Hz, Hb-3), 3.78 (s, 6H, 2OMe), 5.48 (dd, 1H, $J = 13.33$, 2.85 Hz, H-2), 6.62–6.64 (d, 2H, ArH), 7.02–7.08 (m, 2H, ArH), 7.12 (s, 1H, ArH), 7.38 (m, 1H, ArH), 7.57 (dd, 1H, $J = 8.05$, 1.75 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.7 (C-3), 54.7 (OCH_3), 55.2 (OCH_3), 79.8 (C-2), 109.7, 111.5, 113.6, 118.7, 122.3, 123.8, 127.6, 128.7, 133.4, 148.3, 152.7, 161.3 (Ar–C), 191.2 (C=O); MS *m/z* (relative intensity, %): 284.10 (100.0), 285.11 (18.7), 286.11 (2.5); anal. calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found C, 71.85; H, 5. 70.

*2, 3-Dihydro-2-(3, 5-dimethoxyphenyl)-4H-1-benzopyran-4-one (**18**)*

White solid; yield: 80%; mp: 87–88 °C; IR (KBr, cm^{-1}): 3326, 3078, 2868, 1975, 1691 (C=O), 1598, 1525, 1469, 1335, 1268, 1192, 1046; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.20 (dd, 1H, $J = 16.85$, 2.85 Hz, Ha-3), 3.32 (dd, 1H, $J = 16.85$, 13.33 Hz, Hb-3), 3.70 (s, 6H, 2OMe), 5.47 (dd, 1H, $J = 13.33$, 2.85 Hz, H-2), 6.43 (s, 1H, ArH), 6.69 (s, 2H, ArH), 7.01–7.05 (m, 2H, ArH), 7.32 (m, 1H, ArH), 7.55 (dd, 1H, $J = 8.05$, 1.75 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.7 (C-3), 54.9 (OCH_3), 84.3 (C-2), 98.5, 101.6, 117.8, 120.2, 122.3, 127.8, 132.9, 141.6, 159.2, 162.1 (Ar–C), 190.1 (C=O); MS *m/z* (relative intensity, %): 284.10 (100.0), 285.11 (18.7), 286.11 (2.5); anal. calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found C, 71.87; H, 5. 63.

*2, 3-Dihydro-2-(3, 4, 5-trimethoxynitrophenyl)-4H-1-benzopyran-4-one (**19**)*

White solid; yield: 78%; mp: 132–134 °C; IR (KBr, cm^{-1}): 3006, 2936, 2832, 1940, 1689 (C=O), 1605, 1538, 1442, 1373, 1268, 1154, 1025; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.90 (dd, 1H, $J = 16.8$, 3.0 Hz, Ha-3), 3.10 (dd, 1H, $J =$

16.8, 13.2 Hz, Hb-3), 3.85 (s, 3H, 4'-OMe), 3.90 (s, 6H, 3', 5'-2OMe), 5.43 (dd, 1H, $J = 13.2$, 3.0 Hz, H-2), 6.73 (s, 2H, ArH), 7.07–7.11 (m, 2H, ArH), 7.54 (dd, 1H, $J = 7.8$, 2.4 Hz, ArH), 7.95 (d, 1H, $J = 8.1$, 2.4 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.9 (C-3), 56.3 (OCH_3), 56.8 (OCH_3), 79.8 (C-2), 102.7, 119.7, 121.4, 125.1, 126.1, 130.7, 135.1, 140.2, 152.2, 161.4 (Ar–C), 190.1 (C=O); MS *m/z* (relative intensity, %): 274 (M^+, 90), 154 (100), 153 (45), 128 (24), 92 (18), 77 (5); anal. calcd for C_{19} H_{14} O_2: C, 83.19; H, 5.14. Found: C, 83.23; H, 5.20.

*2-(Naphthalen-2-yl) chroman-4-one (**20**)*

White solid; yield: 80%; mp: 122–124 °C; IR (KBr, cm^{-1}): 3375, 3058, 2962, 2884, 1689 (C=O), 1487, 1405, 1375, 1289; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.93 (m, 1H, Ha-3), 3.06 (m, 1H, Hb-3), 5.69 (d, 1H, $J = 12.8$ Hz, H-2), 7.07 (m, 2H, ArH), 7.09–7.11 (m, 2H, ArH), 7.53–7.58 (m, 4H, ArH), 7.89–7.96 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.7 (C-3), 79.3 (C-2), 112.3, 114.5, 118.7, 118.7, 121.5, 121.6, 127.5, 130.3, 136.6, 140.7, 161.9 (Ar–C), 192.3 (C=O); MS *m/z* (relative intensity, %): 274 (M^+, 90), 154 (100), 153 (45), 128 (24), 92 (18), 77 (5); anal. calcd for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found c, 83.23, H, 5.20.

AR inhibitory activity

The preparation of AR was conducted according to the method in a previous publication (Sun et al. 2001). The enzyme activity was assayed spectrophotometrically monitoring the NADPH oxidation that accompanies the reduction of DL-glyceraldehyde used as substrate. The inhibition study was performed by using different concentrations of each flavanone derivatives. The AR activity was determined by measuring the decrease in NADPH absorption at 340 nm over a 4-min period on an Ultrospec_2100pro UV/Visible spectrophotometer. Quercetin, a well known ARI, was used as a reference. The inhibition percentage (%) was calculated as $[1-(\Delta A \text{ sample/min} - \Delta A \text{ blank/min})/(\Delta A \text{ control/min} - \Delta A \text{ blank/min})] - 100$, where ΔA sample/min represents the reduction of absorbance for 4 min with the test sample and substrate, respectively, and ΔA control/min represents the same, but with 100% DMSO instead of the sample. The 50% inhibition concentration (IC_{50}) is expressed as the mean ± SEM. The concentration of inhibitors (μg/0.1 mL reaction mixture) giving 50% inhibition of enzyme activity was estimated from the least-squares regression line of the logarithmic concentrations plot against the remaining activities.

Docking analysis

In order to investigate the binding mode of the flavanone derivatives, grip-based molecular docking analysis of the synthesized derivatives was carried out using biopredicta module of the Vlife MDS 4.3. Docking simulation was carried out using wild type of AR (PDB: 1AH0) downloaded from the www.rcsb.org, which is a free PDB. The protein structure downloaded was optimized for the structure and energy refinement using biopredicta module. The water molecules were removed and hydrogen atoms were added to the protein structure, and then energy of the resulting protein was minimized using MMFF gradient of 0.001 kcal mol^{-1} $Å^{-1}$ was reached.

Pharmacophore Modeling

Pharmacophore modeling was also carried out in Vlife MDS 4.3 using Mol sign module. The minimum number of pharmacophore features generated for an alignment is 4 and tolerance is kept to 10 Å.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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