Cent Nerv Syst Agents Med Chem
. 2023;23(1):57-64.
doi: 10.2174/1871524923666230130134501.

Synthesis, Computational and Pharmacological Evaluation of 7-(2-(2- (3- (Substituted Phenyl) Acryloyl) Phenoxy) Ethoxy)-4-Methyl-2H-Chromen- 2-Ones as CNS Agents

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- PMID: 36717998

- DOI: 10.2174/1871524923666230130134501

Title: Synthesis, Computational and Biological Evaluation of 7-(2-(2- (3-(Substituted Phenyl) Acryloyl) Phenoxy) Ethoxy)-4-Methyl-2H-Chromen-2-Ones as CNS Agents

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Abstract:

Background: Provoked by the promising medicinal and therapeutic applications of hybrid molecules for biological potentials. Through chemical hybridization strategy it is expected to explore the coumarin–chalcone hybrids for the skeletal muscle and antianxiety activity.

Objective: Naturally and synthetically originated hybrid molecules are the promising sources for the new drug development approaches due to the multiple advantages like high efficacy, mode of action at receptors, minimum side effects and better pharmacokinetic properties. In view of these applications, we herein designed the some coumarin-chalcone hybrids and explore them for skeletal muscle and antianxiety potential.

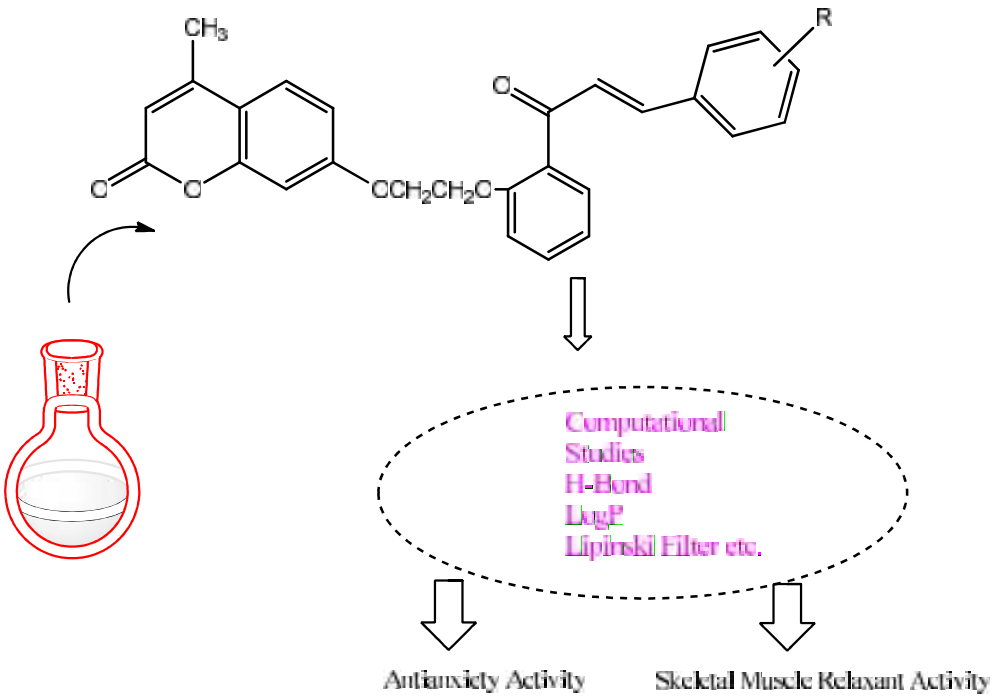
Methods: Using chemical hybridization strategy coumarin-chalcone hybrids has been synthesized and evaluated for skeletal muscle and antianxiety activity. The target compounds were synthesized by reaction of 7-hydroxy-4-methylcoumarion with haloalkane to afford 7-(2-bromoethoxy)-4-methyl-2H-chromen-2-one which further treated with hydroxychalcones**.** The structures of target compounds were confirmed on the basis of their M.P. TLC, IR, 1HNMR and Mass studies. The computational properties of target compounds were also determined through online software. Skeletal muscle and antianxiety potential were performed in Swiss albino mice.

Results: The coumarin-chalcones hybrids showed skeletal muscle and antianxiety potential in Swiss albino mice and computational properties of the target compounds were also showed similarity as compare with diazepam.

Conclusion: Among the target compounds, the fluoro group containing compound was found to be more potent as compared to standard drug diazepam.

Key Words: Chalcones, Coumarin, Chemical hybridization, Skeletal and Antianxiety Potential.

Graphical Abstract:



1. INTRODUCTION:

Naturally and synthetically derived hybrid molecules are attractive source for therapeutic agent development due to their dual or multiple modes of action and other advantages. Coumarin and chalcone, two important classes of synthetic chemistry affording diverse pharmacological activities, make themselves ideal blocks for building a coumarin– chalcone hybrid scaffold as a bioactive agent [1-3]. Provoked by the promising medicinal applications of such hybrids, the scientific community has reported dozens of coumarin– chalcone hybrids with a wide spectrum of biological properties including anticancer [4], antimalarial [5] antioxidant [6], antimicrobial [7], central nervous system disorders [8] and so on, through molecular hybridization strategy [9]. In view of these observations, we herein report the chemical synthesis and computational studies of some new Coumarin-Chalcone hybrids with the aim of evaluating their skeletal and antianxiety potential as therapeutic agents.

2. Materials and Methods

1-(2-Hydroxyphenyl) ethanone, ethyl acetoacetate, resorcinol and substituted benzaldehyde and dibromoethane were purchased from Himedia and CDH. All other chemicals and solvents were purchased from CDH. All chemicals used were of analytical grades and purified before used. The Glassware's were cleaned and dried before the use. Melting point of the synthesized compounds is determined by the open capillary method and is uncorrected. The IR spectra of synthesized compounds were recorded in the potassium bromide discs on Perkin Elmer RX1. The ^{1}H NMR spectra were recorded on a Bruker Avance neo 500 MHz spectrophotometer in DMSO containing TMS as internal standard. All chemical shift values are reported in ppm (δ).The reactions progress was monitored by thin-layer chromatography (TLC) using silica gel G and spots were visualized in an iodine chamber. All the test compounds were recrystallized, dried and kept under vacuum desiccator. The computational properties (physicochemical properties) of target compounds were computed by online software (Chem Draw 12, Swiss ADME) and target compounds further subjected to biological evaluation for their skeletal muscle relaxant and antianxiety activity.

3. Experimental

3.1 Synthesis of 7-hydoxy-4-methylcoumarin (1)

7-Hydoxy-4-methylcoumarin was synthesized by reported procedure [10] % Yield: 85; m.p.:188-190 °C; R_f: 0.77(n-Hexane: Ethyl acetoacetate: 1; 1)

3.2 Synthesis of 7-(2-bromoethoxy)-4-methyl-2H-chromen-2-one (3)

Place 1.76 g (0.01 mole) of 7-hydoxy-4-methylcoumarin (1) and 1.72 ml (0.02 mole) of 1, 2-dibromoethane (2) was dissolved in 100 ml of acetonitrile in a 250 ml round bottom flask. 2.76 g (0.02 mole) of anhydrous potassium carbonate was added into the above solution. The above mixture was refluxed for 24h. After completion of reaction, the reaction mixture was filtered and solvent was removed under reduced pressure to obtain the crude product. The crude residue was washed with water and recrystallized from ethanol to afford the target compound (3). %Yield: 75**;** m.p.: 140-145 °C;R_f: 0.85 (n-hexane: ethyl acetate: 1:1)

3.3 General procedure for the synthesis of hydroxychalcones (6)

Place 0.01 mole of 1-(2-hydroxyphenyl) ethanone(4) and 0.01 mole substituted benzaldehyde(5) was dissolved in ethanol (50 ml) and aqueous of potassium hydroxide (40%, 15ml) was added to it and stirred for 12 h at room temperature. The reaction mixture was kept overnight and then it

was poured into crushed ice and acidified with dilute hydrochloric acid. The solid separated was filtered and dried to obtain the hydroxychalcones (6).

3.4 General procedure for the synthesis of coumarin-chalcone hybrids (AK1-8)

Place 0.004 mole of 7-(2-bromoethoxy)-4-methyl-2H-chromen-2-one (3) and 0.004 mole hydroxychalcone (6) was dissolved in 100 ml of anhydrous acetonitrile in a 250 ml round bottom flask. 0.008 mole of anhydrous potassium carbonate and catalytic amount of potassium iodide were added into above solution. The above mixture was refluxed for 12 h. After completion of reaction, the reaction mixture was filtered and solvent was removed under reduced pressure to obtain the crude product. The crude residue was washed with water and recrystallized from ethanol to afford the target compounds (AK1-8).

7-(2-(2-(3-(phenyl) acryloyl) phenoxy) ethoxy)-4-methyl-2H-chromen-2-one (AK1)

IR (KBR)cm^{-1}: 3075 (C-H Str Ar), 2920 (C-H Str Ali), 1712 (C=O Str), 1601 (C=O Str), 1463 (C=C Str), 1069 (C-O-C Str), ^{1}H-NMR (500MHz, DMSO) δ: 6.98- 7.81 (13H, Ar-H), 6.21-6.22 (2H, CH=CH), 5.81- 5.84 (2H, OCH_2), 4.43- 4.50 (2H, OCH_2), 3.84 (3H, CH_3). Yield: 72.0 %, M.P: 118-128^{o}C, R_f: 0.78 (n-Hexane: Ethyl acetate; 1:1).

7-(2-(2-(3-(4-chlorophenyl) acryloyl) phenoxy) ethoxy)-4-methyl-2H-chromen-2-one (AK2)

IR (KBR)cm^{-1}: 3038 (C-H StrAr), 2920 (C-H Str Ali),1717 (C=O Str), 1608 (C=O Str),1450 (C=C Str), 1077 (C-O-C Str), ^{1}H-NMR (500MHz, DMSO) δ: 6.88- 7.80 (12H, Ar-H), 6.20-6.22 (2H, CH=CH), 5.81- 5.84 (2H, OCH_2), 4.43- 4.50 (2H, OCH_2), 3.81 (3H, CH_3). Yield: 70.0 %, M.P: 228-230^{o}C, R_f: 0.88 (n-Hexane: Ethyl acetate; 1:1).

7-(2-(2-(3-(4-bromophenyl) acryloyl) phenoxy) ethoxy)-4-methyl-2H-chromen-2-one (AK3)

IR (KBR)cm^{-1}: 3075 (C-H StrAr), 2920 (C-H Str Ali), 1712 (C=O Str), 1601 (C=O Str), 1463 (C=C Str), 1069 (C-O-C Str), ^{1}H-NMR (500MHz, DMSO) δ: 6.90- 7.84 (12H, Ar-H), 6.20-6.21 (2H, CH=CH), 5.80- 5.82 (2H, OCH_2), 4.42- 4.48 (2H, OCH_2), 3.82 (3H, CH_3). Yield: 60.0 %, M.P: 103-105^{o}C, R_f: 0.77 (n-Hexane: Ethyl acetate; 1:1).

7-(2-(2-(3-(4-fluorophenyl) acryloyl) phenoxy) ethoxy)-4-methyl-2H-chromen-2-one (AK4)

IR (KBR)cm^{-1}: 3075 (C-H StrAr), 2920 (C-H Str Ali), 1712 (C=O Str), 1601 (C=O Str),1463 (C=C Str), 1069 (C-O-C Str), ^{1}H-NMR (500MHz, DMSO) δ: 6.89- 8.02 (12H, Ar-H), 6.20-6.21 (2H, CH=CH), 5.67- 5.70 (2H, OCH_2), 4.44- 4.50 (2H, OCH_2), 3.83 (3H, CH_3). Yield: 64.0 %, M.P: 110-112^{o}C, R_f: 0.92 (n-Hexane: Ethyl acetate; 1:1).MS (TOF MS ES^+): ***m/z*** (M+H): 445.29.

7-(2-(2-(3-(3-nitrophenyl) acryloyl) phenoxy) ethoxy)-4-methyl-2H-chromen-2-one (AK5)

IR (KBR)cm^{-1}: 3075 (C-H StrAr), 2920 (C-H Str Ali), 1712 (C=O Str), 1601 (C=O Str),1463 (C=C Str),1069 (C-O-C Str), ^{1}H-NMR (500MHz, DMSO) δ: 6.89- 8.02 (12H, Ar-H), 6.20-6.21 (2H, CH=CH), 5.67- 5.70 (2H, OCH_2), 4.44- 4.50 (2H, OCH_2), 3.83 (3H, CH_3). Yield: 66.0 %, M.P: 183-185^{o}C, R_f: 0.83 (n-Hexane: Ethyl acetate; 1:1).

7-(2-(2-(3-(2-methylphenyl) acryloyl) phenoxy) ethoxy)-4-methyl-2H-chromen-2-one (AK6)

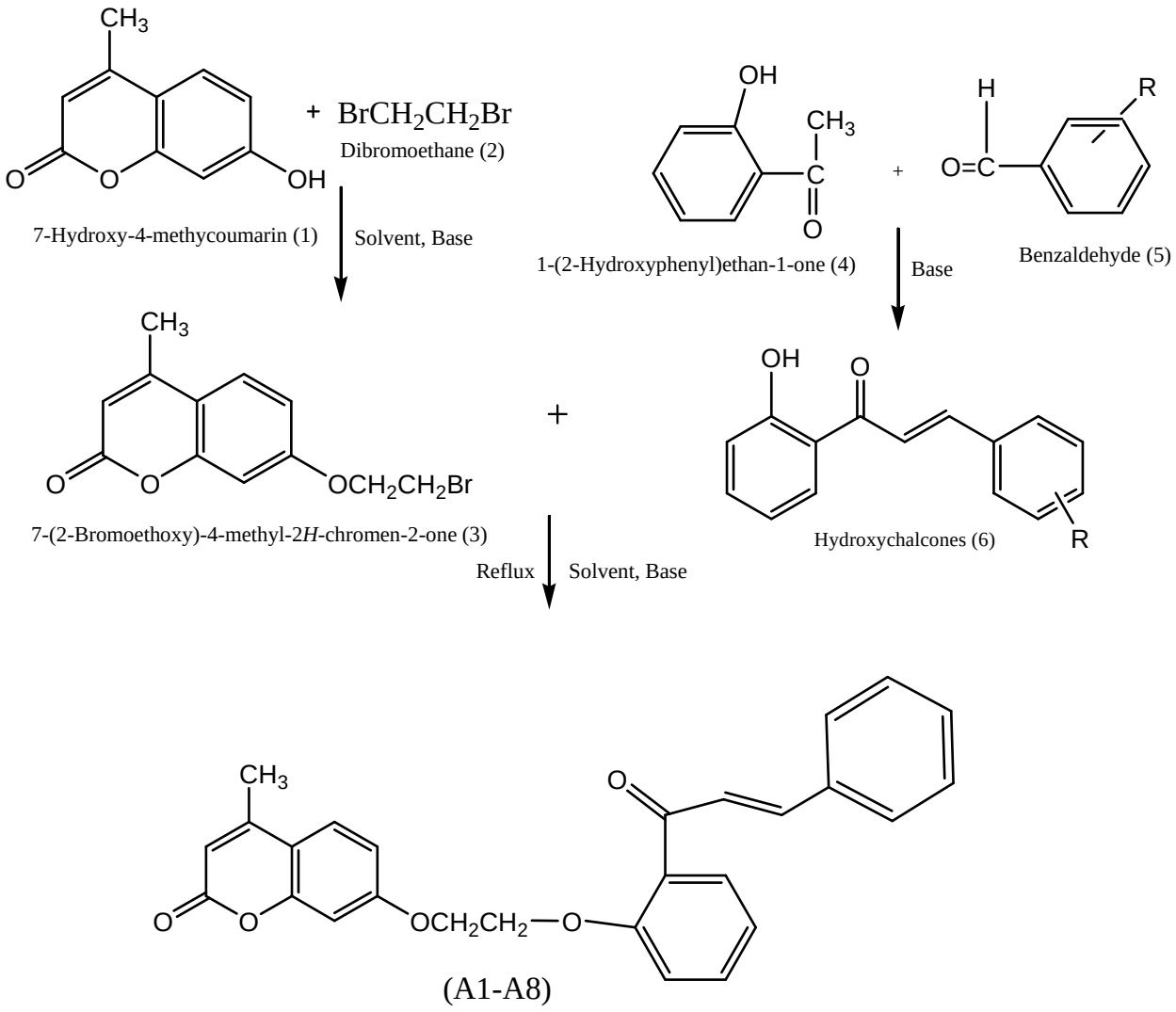
IR (KBR)cm^{-1}: 3075 (C-H StrAr), 2920 (C-H Str Ali), 1712 (C=O Str), 1601 (C=O Str),1463 (C=C Str),1069 (C-O-C Str), ^{1}H-NMR (500MHz, DMSO) δ: 6.88- 8.04 (12H, Ar-H), 6.21-6.22 (2H, CH=CH), 5.65- 5.68 (2H, OCH_2), 4.42- 4.50 (2H, OCH_2), 3.82 (3H, CH_3). Yield: 65.0 %, M.P: 123-125^{o}C, R_f: 0.83 (n-Hexane: Ethyl acetate; 1:1).

7-(2-(2-(3-(2, 3, 4-trimethylphenyl) acryloyl) phenoxy) ethoxy)-4-methyl-2H-chromen-2-one (AK7)

IR (KBR)cm^{-1}: 3078 (C-H StrAr), 2922 (C-H Str Ali), 1716 (C=O Str), 1615 (C=O Str),1486 (C=C Str),1085 (C-O-C Str), ^{1}H-NMR (500MHz, DMSO)δ: 6.77- 7.77 (10H, Ar-H), 6.22 (2H, CH=CH), 5.81- 5.84 (2H, OCH_2), 4.43- 4.48(2H, OCH_2), 3.84 (3H, CH_3), 3.33 (3H, CH_3), 3.03 (3H, CH_3), 2.91 (3H, CH_3).Yield: 70.0 %, M.P: 210-212^{o}C, R_f: 0.82 (n-Hexane: Ethyl acetate; 1:1).

7-(2-(2-(3-(2, 3, 4-trimethoxyphenyl) acryloyl) phenoxy) ethoxy)-4-methyl-2H-chromen-2-one (AK8)

IR (KBR)cm^{-1}: 3078 (C-H StrAr), 2922 (C-H Str Ali), 1716 (C=O Str), 1615 (C=O Str), 1486 (C=C Str), 1085 (C-O-C Str), ^{1}H-NMR (500MHz, DMSO) δ: 6.64- 7.89 (10H, Ar-H), 6.20 (2H, CH=CH), 5.83- 5.84 (2H, OCH_2), 4.40- 4.42(2H, OCH_2), 3.83 (3H, CH_3), 3.32 (3H, CH_3), 3.01 (3H, CH_3), 2.90 (3H, CH_3). Yield: 65.0 %, M.P: 145-150^{o}C, R_f: 0.86 (n-Hexane: Ethyl acetate; 1:1).



Scheme 1: Synthesis of target compounds (A1-A8)

3.5 Computational studies

The set of physicochemical properties was computed for the target compounds as well as standard drugs diazepam by the using Chem 3D Ultra version 12.0 and Swiss ADME free software programs. These observations are depicted in the Tables1 and Table 2. The log P values, and other physicochemical descriptors include topological polar surface area, Connolly solvent accessible surface area (SAS, A^2), Connolly molecular surface area (MSA, A^2), Connolly solvent excluded volume (SEV, A^3), molecular weight (MW), molar refractivity (MR), and Ovality were computed for test the compounds along with standard drug[11].

Table 1: Physicochemical properties of target compounds (AK1-8)

Cpd. Code	MW[a]	MR[b]	tPSA[c]	CAA[d]	CMA[e]	CSEV[f]	Ov[g]	Log P
AK1	426.46	126.37	61.83	657.65	349.78	301.15	1.6098	5.09
AK2	460.91	130.97	61.83	755.50	405.60	346.34	1.7006	5.65
AK3	505.36	134.06	61.83	764.15	410.96	352.09	1.7042	5.92
AK4	444.45	126.77	61.83	734.56	392.96	334.55	1.6861	5.25
AK5	471.46	133.39	113.64	625.03	337.96	306.48	1.5373	4.74
AK6	440.49	132.27	61.83	682.19	365.63	317.38	1.6249	5.58
AK7	468.54	144.06	61.83	809.62	443.09	392.43	1.7093	6.55
AK8	516.54	148.12	89.52	815.25	446.03	394.14	1.7157	4.71
Diazepam	284.74	80.88	32.67	475.26	246.16	214.22	1.4217	2.84

MW[a]: Molecular Weight.

MR[b]: Molar Refractivity.

tPSA[c]: Topological Polar Surface Area.

CAA[d]: Connolly Accessible Area.

CMA[e]: Connolly Molecular Area.

CSEV[f]: Connolly Solvent Excluded Volume.

Ov[g]: Ovality.

The lipophilicity of a molecule is a well-recognized as a crucial physicochemical feature involved to penetrate the blood brain barrier and exhibit CNS activity [12]. Knowledge of lipophilicity helps us understanding pharmacokinetic properties including absorption, distribution, metabolism, and excretion (ADME) processes, as well as toxicity [13]. The lipophilicity of the test compounds was for target compounds (AK1-AK8) within the range as compare with standard drugs which clearly shown penetrability of lipophilic cell membrane by the test compounds. The topological polar surface area (TPSA) is a chemical descriptor for the passive molecular transport through the membranes. TPSA is the allows for the prediction of a transport properties of the drugs and it has been linked to the drug bioavailability [14]. The topological polar surface area (tPSA) is a measure of the molecules is hydrogen bonding capacity and its value should not exceed certain limit. Generally, it has been seen the passively absorbed molecules with a TPSA > 140 $Å^2$ are thought to have low oral bioavailability. The results are showed TPSA of the test compounds were within the range as compare with standard drugs and

showed good oral bioavailability of test drugs. Molecular size is the important descriptor of most physicochemical properties and many biological properties are strongly size-related. Molecular size is generally important for the permeability of a compound. The great majority of the drugs on the market have molecular weights between the 200 and 600 Daltons. Molecular weight of test compounds was also within the range. Another size descriptor is the molar refractivity; it is directly related to the molar volume (molecular weight divided by the liquid density) and a function of the refractive index of the liquid, thus containing information about polarizability of the molecules. Molar refractivity (*MR*) descriptor is related to the specific interactions of the target molecule and the electronic effects in the biological–chemical interaction, mainly for the allosteric effects of interactions between the ligand-receptor. Results showed the molar refractivity of target compounds were within the range. Ovality is the ratio of between the surface of the molecule and the surface of a sphere with the same volume. Results showed the ovality of test compounds were within the range. The other descriptors values is like Connolly solvent accessible surface area (SAS, A^2), Connolly molecular surface area (MSA, A^2) and Connolly solvent excluded, number of rotable bonds, number of hydrogen bond acceptors, number of hydrogen bond donors, GI absorption, Abbott the bioavailability were within the range as compare with the standard drug. Lipinski rule of five was given by Pfizer stating that there should be less than 500 dalton molecular weight, the hydrogen bond acceptor should be not more than 10, the hydrogen bond donor should be more than 5, log P value should be not more than 5 and the biological transporters should not be a part of the drug [15]. Synthetic Accessibility (SA) Score is based on the primarily of the assumption that the frequency of a molecular fragments in the 'really' obtainable molecules correlates with the ease of synthesis. Synthetic accessibility score ranges from 1 (very easy) to 10 (very difficult).

Table 2: Physicochemical properties of target compounds (AK1-8)

Cpd. Code	No. of ratable bonds	No. of H-bond acceptors	No. of H-bond donors	GI absorption	Synthetic accessibility	Abbott Bioavailability score	Lipinski Filter

AK1	8	5	0	High	3.94	0.55	Yes: 0 violation
AK2	8	5	0	High	3.90	0.55	Yes: 0 violation
AK3	8	5	0	High	3.92	0.55	Yes:1 violation :mw>500
AK4	8	6	0	High	3.89	0.55	Yes: 0 violation
AK5	9	7	0	Low	4.00	0.55	Yes: 0 violation
AK6	8	5	0	High	4.10	0.55	Yes: 0 violation
AK7	8	5	0	High	4.34	0.55	Yes: 0 violation
AK8	11	8	0	High	4.51	0.55	Yes: 1 violation :mw>500
Diazepam	1	2	0	High	3.00	0.55	Yes: 0 violation

3.6. Similarity calculation

The physicochemical similarity of the target compounds with the respect to standard drugs was calculated from a set of 7 physicochemical properties computed using software programs [16] and is shown in Table 3. Firstly, the distance d_i of a particular target compound j to drug molecules e.g., diazepam was calculated by the formula;

$$di^2 = \sum_{j=1}^{n} \frac{\left(\frac{1 - X_{i,j}}{X_{i,std}}\right)^2}{n}$$

Where, Xi, j is the value of molecular parameter 'i' for compound 'j', Xi, std is the value of the same molecular parameter for the standard drug, e.g., Diazepam. Then, the similarity of compound 'j' to the standard drug was calculated as: Similarity (%) = (1 - R) X 100. Where R= $\sqrt{d^2}$ is the quadratic mean (root mean square), a measure of central tendency. The target compounds showed similarity with respect to standard drug.

Table 3: Similarity of target compounds (AK1-8) with respect to diazepam

Cpd. Code	Similarity[a, b](in%) to Diazepam
AK1	46.37
AK2	33.18
AK3	45.03
AK4	23.3
AK5	24.04
AK6	44.24
AK7	27.34
AK8	17.7

[a](1 - R) X 100 where R = quadratic mean (root mean square mean).

[b]Calcd. from physicochemical properties: Molecular weight; Molar refractivity; Connolly solvent accessible surface area; Connolly molecular surface area; Connolly solvent excluded volume; Topological polar surface area; Ovality.

3.7 Biological Evaluation for skeletal muscle and antianxiety activity

Antianxiety activity

The anxiolytic activity was performed by Elevated plus maze method and skeletal muscle relaxant activity was carried out by Rotarod method in Swiss albino mice [17-19]. Prior permission of the Animal Ethics Committee was obtained and all experiments were conducted according to the approved protocol (CPCSEA). Diazepam was employed as a standard (positive control). Statistical analysis of the results in the test group was done by comparison with the results in the control group employing one way ANOVA. Level of significance was fixed at $p<0.05$.

Anxiolytic activity (elevated plus maze method)

Swiss albino mice, weighing 20–24 g each, were selected from the stock colony maintained in the central animal facility with free access to food and water. Animals were maintained in an air-conditioned room. The room was maintained at 25 ± 2 ^{0}C with natural daytime. Concentration of each compound (10 mg/kg) was used in the form of freshly prepared suspensions in 1% tween 80. All solutions were prepared freshly on test days and given intraperitoneally (I.P.) in a volume of 0.5 ml/20-24g body weight of mice. The experimental animals were treated with diazepam (2 mg/ kg, n =6), or the test compounds (10 mg/kg) 60 min before evaluation in the maze. The control group was given saline with 1% tween 80. Elevated plus maze apparatus consisted of two open (16 x 5 cm^2) and two closed arms (16 x 5 x 12 cm^3) facing each other with an open roof). The entire maze is elevated to a height of 25 cm. In the test group, mice were individually examined in 5 min sessions in this apparatus. Each mouse was placed in the central platform facing one open arm. The numbers of entries into open and closed arms and the time spent in open arms were recorded during a 5 min period. The percentage of number of entries into open arms [(open/open +closed) x 100] was calculated for each mouse. The results of EPM have been summarized in Table 4.

Table 4: Antianxiety activity of the target compounds (AK1-8) in elevated plus maze method

Cpd.Code	Spent time (open arm)	Number of entries (open arms)	% Number of entries (open arms)
AK1	64.58±1.72	7.14±0.42	50.92
AK2	58.27±1.81	6.71±0.55	46.14
AK3	57.27±3.45	7.05±0.71	43.36
AK4	84.76±1.96	8.81±0.22	55.73
AK5	47.13±1.66	5.87±0.63	38.32
AK6	52.23±1.73	5.29±0.75	40.52
AK7	51.51±1.91	5.14±0.76	38.48
AK8	52.58±1.21	5.24±0.72	37.43
Diazepam	90.83±2.33	10.09±0.76	62.46

Vehicle	42.12±3.22	2.91±0.90	24.22

Skeletal muscle relaxant activity (Rotarod method)

Skeletal muscle relaxant activity of target compounds was carried out by Rotarod method. Mice were placed on a horizontal wooden rod rotating at a speed of 25 rpm. The mice capable of remaining on the top for 1 min or more, in three successive trials were selected for the study. The selected animals were divided into 12 groups (n= 6). The stock solutions of all the test samples and standard were prepared by suspending in 1% tween 80. Tween 80 (1%) and diazepam (2 mg/kg, i.p.) were given to group control and standard. Test sample 10 mg/ kg (i.p.) was injected into test groups. Each group of animals was then placed on the rod at an interval of 30 min. The animals that failed more than once on the Rotarod for 1 min were considered as passed the test. The results of skeletal muscle relaxant activity have been summarized in Table 5.

Table 5: Skeletal muscle relaxant activity of target compounds (AK1-8) by Rotarod method

Cpd.Code	Dose	Rotarod test
AK1	10 mg/kg	61.14± 1.21
AK2	10 mg/kg	62.34± 2.13
AK3	10 mg/kg	64.24± 2.12
AK4	10 mg/kg	46.33± 1.18
AK5	10 mg/kg	65.89± 2.44
AK6	10 mg/kg	68.55± 1.34
AK7	10 mg/kg	67.35± 3.48
AK8	10 mg/kg	70.21± 2.11
Diazepam	2 mg/kg	37. 50± 1.33
Vehicle	1% Tween 80	84.08± 1.68

4. DISCUSSION AND CONCLUSION

The target compounds (AK1-8) were prepared as outlined in Scheme 1. The purity of the compounds was monitored by TLC and the structure of the compounds was deduced on the basis of melting point, TLC, IR, NMR and mass analysis. The target compounds obtained in good percentage yield (60-72) and having 3038-3078 (C-H StrAr), 2920-2922 (C-H Str Ali), 1712-

1717 (C=O Str), 1601-1615 (C=O Str), 1450-1486 (C=C Str),1069-1085 (C-O-C Str) characteristic peaks in IR spectra. ^{1}H-NMR (500 MHz, DMSO) δ: 6.77- 8.02 Ar-H), 6.20-6.22 (2H, CH=CH), 5.67- 5.84 (2H, OCH_2), 4.40- 4.50 (2H, OCH_2), characteristic values in proton NMR. The mass spectrum of AK4 was also taken and *m/z* (M+H) was observed at 445.29 confirmed the formation of target compound. The computational study was performed for the target compounds by free online software. All target compounds have molecular weight in the range of 426.46- 516.54 and molar refractivity 126.37-148.12. Topological polar surface area (tPSA) for the target compounds were well within the limits (61.83-113.64). The log P values of target compounds were within the range (4.71-6.55) and shown that these compounds have a potential to effectively cross the cell membrane and other molecular descriptors viz: Connolly solvent accessible surface area (SAS, A^2), Connolly molecular surface area (MSA, A^2), Connolly solvent excluded volume (SEV, A^3) and Ovality of target compounds were within the range as compare with standard drug. Similarity of target compounds was also shown with respect to standard drug. Number of rotable bonds, number of hydrogen bond acceptors, number of hydrogen bond donors, GI absorption, synthetic accessibility (SA) score and Abbott bioavailability score were within the range as compare with standard drug. Lipinski filter are also assessed the properties of target compounds. The target compounds were tested for muscle relaxant activity and antianxiety activity and in Swiss albino mice. Among the compound, AK4 showed better skeletal muscle relaxant and antianxiety and activity.

5. Conclusion

Eight Coumarin-Chalcone hybrids (AK1-8) were synthesized and characterized by their melting point, TLC, and spectroscopic methods. The computational studies were also done for the target compounds by free online software to assess the various physicochemical properties. Similarity of the target compounds is also calculated with respect to standard drug. Among the target compounds, compound (AK4) was most potent as skeletal muscle relaxant and anxiolytic. These analogs are also further required for the refinement of skeletal muscle relaxant and antianxiety activity.

6. ACKNOWLEDGEMENTS

The authors are thankful to Prof. M.P. Pandey, Vice Chancellor, IFTM University, Moradabad (U.P) India for their unbound support during the research work.

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