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Original Article

# Synthesis of Some Novel (Z)-3-ethylidene-5,7-dimethylthiochroman-4-one Derivatives and Study of its Monoamine Oxidases Inhibitory Activity

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## ABSTRACT

**Background:** Chroman-4-one, also known as 2,3-dihydro-1-benzopyran-4-one, is a heterocyclic compound with a benzene nucleus fused to a 2,3-dihydro-g-pyranone ring. The synthesis of chroman-4-one derivatives is a very appealing aspect in the field of natural and medicinal chemistry. **Materials and Methods:** The *(Z)-3-ethylidene-5,7-dimethylthiochroman-4-one* derivatives were, synthesized and evaluated intended for their Monoamine oxidases (MAO)-A and MAO-B inhibitory activity using *in vitro* fluorometric technique. The majority of synthetic process to acquire*(Z)-3-ethylidene-5,7-dimethylthiochroman-4-one* derivatives engage condensation catalyzed by acid or base of a range of derivatives of 5,7-dimethylchroman-4-one and 4,6-dimethylbenzofuran-3(2H)-one with the benzaldehyde. The Z-isomers that resulted were usually obtained by photoisomerization of the synthesized E-isomers. Synthesized molecules structures (S-1 to S-18) were established by IR, NMR, mass and elemental analysis. **Results:** The *in vitro* activity of *synthesized (Z)-3-ethylidene-5,7-dimethylthiochroman-4-one* derivatives against MAO isoform displayed selectivity in the direction of MAO B isoform. The synthesized derivatives S11 of *(Z)-3-ethylidene-5,7-dimethylthiochroman-4-one* displayed 7.32 µM ($IC_{50}$) against MAO-B. **Conclusion:** Weak to moderate electron pumping and withdrawing groups favor selectivity for hMAO-B, whereas strong deactivators render them non-selective for isoforms. Mono-substitution of methoxy groups at the o- and m-positions improves potency while bi-substitution improves potency and selectivity. The active compounds' ADME predictions revealed that these synthesized compounds may possess drug likeliness confirmed by excellent pharmacokinetic profiles.

**Keywords:** Chromanone, Chalcones, Schiff base, hMAO inhibitory activity, dimethylthiochroman-4-one.

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## INTRODUCTION

Chroman-4-one scaffolds are important building blocks in drug discovery as well as critical intermediates in organic synthesis. Based on structural diversity, the chroman-4-one family is divided into many classes, including benzylidene-four-chromanones, flavanones (2-phenyl-4-chromanones), isoflavanones (3-phenyl-4-chromanones), spirochromanones, and C-four modified chroman-four-ones, which include hydrazones and oxime derivatives. Chroman-4-one, also known as 2,3-dihydro-1-benzopyran-4-one, is a heterocyclic compound with a benzene nucleus fused to a 2,3-dihydro-g-pyranone ring. The synthesis of chroman-4-one derivatives is a very appealing aspect in the field of natural and medicinal chemistry.[1,2]

Flavanones (2-phenyl chroman-4-one derivatives) are chroman-4-one compounds with diverse biological activities, such as sakuranetin (flavanone) acting as a phytoalexin and naringin (flavanone glycoside) having protective effects on cognition and oxidative damage via inhibitory activity of vascular endothelial growth factor in rats.[3,4] Flavanones with flavor-modifying properties (Eriodictyol and sterubin).[5-9] Many more chromanone analogues have been shown to have anticancer, angioprotective, antiallergic, antihistaminic, antimicrobial, antioxidant, and anti-HIV properties. Monoamine oxidases, also known as Monoamine oxidases A (MAO-A) and Monoamine oxidases B (MAO-B), are neuronal enzymes that regulate the formation and functions of neurobiological activity. There are two types of monoamine oxidase inhibitors. MAO-A inhibitors are used to treat depression and anxiety, while MAO-B inhibitors are used to treat neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Currently used MAO inhibitors have lost interest due to some side effects or disadvantages such as food and drug interactions, prompting scientists to search for a new series of drugs. The therapeutic potential of selective and reversible MAOIs is reviving interest in their synthesis.[10-12]

## MATERIALS AND METHODS

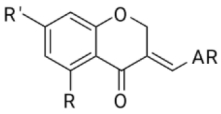
### Experimental

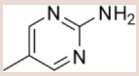
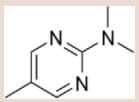
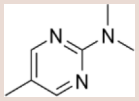
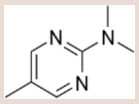
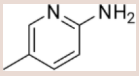
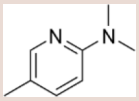
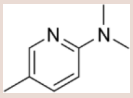
The subsequent approaches have been utilized to uncover effective MAO-B inhibitors. Synthesis and *in vitro* activity study of synthesized*(Z)-3-ethylidene-5,7-dimethylthiochroman-4-one* derivatives have been performed via monoamine oxidase inhibitory activity with ADME studies of active synthesized molecules to predict drug likeliness.

**Synthesis and biological evaluation of newer *(Z)-3-ethylidene-5,7-dimethylthiochroman-4-one* derivatives:** All reagents were analytical grade along with utilized without any additional purification. Completion of reactions were observed via TLC plates of silica gel (Merck, Germany) using suitable solvent system. TLC plates were developed in mobile phase and observed under ultraviolet light. Digital melting point apparatus were used to determine melting points of compounds. General scheme 1 represents few designed unsubstituted compounds which were synthesized. Substitutions details of synthesized compounds are presented in Table 1.


**Scheme 1:** Reagents and conditions (i) Pyrrolidine, dry MeOH, rt, l-24h or 120C, 1h

**Table 1: Newly designed *(Z)-3-ethylidene-5,7-dimethylthiochroman-4-one* derivatives.**



| Compound Name | R | R¹ | Ar | IUPAC name |
|---|---|---|---|---|
| S-1 | H | H |  | (Z)-3-((2-aminopyrimidin-5-yl)methylene)thiochroman-4-one |
| S-2 | H | H |  | (Z)-3-((2-(dimethylamino) pyrimidin-5-yl)methylene) thiochroman-4-one |
| S-3 | Cl | Cl |  | (Z)-5,7-dichloro-3-((2-(dimethylamino) pyrimidin-5-yl)methylene) thiochroman-4-one |
| S-4 | H | OCH3 |  | (Z)-5-chloro-3-((2-(dimethylamino) pyrimidin-5-yl)methylene)-7 methoxythiochroman-4-one |
| S-5 | H | H |  | (Z)-3-(pyridin-2-ylmethylene)thiochroman-4-one |
| S-6 | H | H |  | (Z)-3-(pyridin-4-ylmethylene)thiochroman-4-one |
| S-7 | H | H |  | (Z)-3-(pyridin-3-ylmethylene)thiochroman-4-one |
| S-8 | H | H |  | (Z)-3-((6-aminopyridin-3-yl) methylene)thiochroman-4-one |
| S-9 | H | H |  | (Z)-3-((6-(dimethylamino) pyridin-3-yl)methylene) thiochroman-4-one |
| S-10 | Cl | Cl |  | (Z)-5,7-dichloro-3-((6-(dimethylamino) pyridin-3-yl)methylene) thiochroman-4-one |
| S-11 | H | H |  | (Z)-3-((1H-indol-3-yl) methylene)thiochroman-4-one |
| S-12 | H | H |  | (Z)-3-((1H-pyrrol-2-yl) methylene)thiochroman-4-one |
| S-13 | H | H |  | (Z)-3-((1H-imidazol-2-yl) methylene)thiochroman-4-one |
| S-14 | Cl | Cl |  | (Z)-3-((1H-imidazol-2-yl)methylene)-5,7-dichlorothiochroman-4-one |
| S-15 | H | OCH3 |  | (Z)-3-((1H-imidazol-2-yl) methylene)-5-chloro-7-methoxythiochroman-4-one |
| S-16 | H | H |  | (Z)-3-(furan-2-ylmethylene) thiochroman-4-one |
| S-17 | H | H |  | (Z)-3-(thiophen-2-ylmethylene)thiochroman-4-one |
| S-18 | H | H |  | (Z)-3-(thiophen-3-ylmethylene)thiochroman-4-one |

**Synthesis of chromone 4-one derivatives:** Condensation catalyzed by acid or base of diverse chroman-4-one and benzofuran-3(2H)-one derivatives correspondingly with the suitable benzaldehyde produced (Z)-3-ethylidene-5,7-dimethylthiochroman-4-one and (Z)-2-ethylidene-4,6-dimethylbenzofuran-3(2H)-one derivatives.

## Synthesis of S-1

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of chroman-4-one and 10 mmol of 2-aminopyrimidine-5-carbaldehyde were mixed in dry MeOH stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n- hexane.

## Synthesis of S-2

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of chroman-4-one and 10 mmol of 2-(dimethylamino)pyrimidine-5-carbaldehyde were mixed in dry MeOH stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n-hexane.

## Synthesis of S-3

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of 5,7-dichlorochroman-4-one and 10 mmol of 2-(dimethylamino) pyrimidine-5-carbaldehyde were mixed in dry Methanol stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n-hexane.

## Synthesis of S-4

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of 7-methoxychroman-4-one and 10 mmol of 2-(dimethylamino) pyrimidine-5-carbaldehyde were mixed in dry Methanol stirred at room temperature up to 24h on end of reactions. The progression

was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n-hexane.

## Synthesis of S-5

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of chroman-4-one and 10 mmol of picolinaldehyde were mixed in dry Methanol stirred at room temperature up to 24hr on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n- hexane.

## Synthesis of S-6

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of chroman-4-one and 10 mmol of isonicotinaldehyde were mixed in dry Methanol stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n- hexane.

## Synthesis of S-7

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of chroman-4-one and 10 mmol of nicotinaldehydewere mixed in dry Methanol stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n- hexane.

## Synthesis of S-8

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of chroman-4-one and 10 mmol of 6-aminonicotinaldehyde were mixed in dry Methanol stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n- hexane.

## Synthesis of S-9

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of chroman-4-one and 10 mmol of 6-(dimethylamino)nicotinaldehyde were mixed in dry Methanol stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n- hexane.

## Synthesis of S-10

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of 5,7-dichlorochroman-4-one and 10 mmol of 6-(dimethylamino) nicotinaldehyde were mixed in dry Methanol stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n- hexane.

## Synthesis of S-11

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of chroman-4-one and 10 mmol of 1H-indole-3-carbaldehyde were mixed in dry Methanol stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n- hexane.

## Synthesis of S-12

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of chroman-4-one and 10 mmol of 1H-pyrrole-2-carbaldehyde were mixed in dry Methanol stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n- hexane.

## Synthesis of S-13

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of chroman-4-one and 10 mmol of 1H-imidazole-2-carbaldehyde were mixed in dry Methanol stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n- hexane.

## Synthesis of S-14

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of 5,7-dichlorochroman-4-one and 10 mmol of 1H-imidazole-2-carbaldehyde were mixed in dry Methanol stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n- hexane.

## Synthesis of S-15

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of 1H-imidazole-2-carbaldehyde and 10 mmol of 1H-imidazole-2-carbaldehyde were mixed in dry Methanol stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was

filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n- hexane.

### Synthesis of S-16

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of chroman-4-one and 10 mmol of furan-2-carbaldehyde were mixed in dry Methanol stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n- hexane.

### Synthesis of S-17

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of chroman-4-one and 10 mmol of thiophene-2-carbaldehyde were mixed in dry Methanol stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n- hexane.

### Synthesis of S-18

The reaction mixture contains 10 mmol of Pyrrolidine, 6.7 mmol of chroman-4-one and 10 mmol of thiophene-3-carbaldehyde were mixed in dry Methanol stirred at room temperature up to 24h on end of reactions. The progression was examined via TLC then added ice cooled water to get precipitate. Obtained precipitate was filtered then washed with water. Obtained product was further subjected to column chromatography using silica gel (#60), using isocratic elution with ethyl acetate and chloroform mixture (75:25), fractions were collected, dried and crystallized from n- hexane.

### Mono Amine Oxidase (MAO-A and MAO-B) Inhibition Assay

The inhibitory activity of a series of synthesized compounds against monoamine oxidase (h) was determined using a fluorometric method and the MAO-A/B Inhibitor Screening Kit (BioVision USA). Based on the fluorescence generated, fluorescence was observed for 20 min at 535 nm for excitation and 587 nm for emission using a BioTek Synergy H1 microplate reader (USA).

Clorgiline and selegiline were used as standard specific inhibitors of hMAO-A and hMAO-B, respectively. Sample solutions were prepared in DMSO (2%) at concentrations ranging from 10 3 to 10 9 M. The reaction buffer was combined with the recombinant enzymes and the developer. The substrate was mixed with distilled water, while the assay buffer (37 L) was used. In each well, developer solution (1 L), substrate solution (1 L), and OxiRed probe (1 L) were mixed together. In each well of a 96-well microplate, a sample or standard (10 L) and 50 L of recombinant enzyme solution were added and incubated for 10 min at 25°C for MAO-A and 37°C for MAO-B assays. After 10 min, the reaction was started by adding 40 L of working solution to each well and incubated at room temperature for 30 min. Fluorescence was measured in 5-min intervals at 535 nm for excitation and 587 nm for emission. For the blank or control solution, 10 L of DMSO is substituted (2 percent). In a parallel experiment, the apparent inhibitory effect of the inhibitors on the developer was determined by replacing enzyme solutions with 50 L of $H_2O_2$ solution (10 mM) in each well.

However, the ability of inhibitors to change the fluorescence generated in the reaction mixture due to nonenzymatic inhibition was determined by mixing the inhibitor and working solutions. Exact fluorescence readings were calculated by subtracting background activity from wells containing all mixtures except hMAO isoforms, which were substituted in a well with 50 L phosphate buffer. All samples were examined, and the percentage inhibition was calculated using the equation:

$$\text{Inhibition}\ (\%) = \frac{(FCt_{Time2} - FCt_{Time1}) - (FInb_{Time2} - FInb_{Time1})}{FCt_{Time2} - FCt_{Time1}}$$

$FCt_{Time2}$ = Control well Fluorescence at time Time 2

$FCt_{Time1}$ = Control well Fluorescence at time Time 1

$FInb_{Time2}$= inhibitor well fluorescence d at time Time 2

$FInb_{Time1}$ = inhibitor well fluorescence d at time Time 1

$IC_{50}$ of tested compounds were calculated via dose–response plot attained by plotting the inhibition (%) Vs log concentration. All experiments were performed in triplicate and values are represented as mean ± standard deviation.[13,14]

**ADME Profile:** Virtual screening combined with docking protocol and predictions of ADME parameters have forever important to predict acceptation or rejection of molecules due to pharmacokinetic as well as their physiochemical properties such as compound solubility, gastric emptying time and intestinal absorption time. Prediction of ADME properties by *in silico* methods is intended to be an important step in drug discovery pipeline to ensure the drug like properties of novel chemical entities. QikProp module of Schrodinger suite predicts physically significant descriptors which linked to a physiochemical properties of lead molecules. It also plays an important role for the support of find hits via Lipinski's rule which governs the druggablity of compounds and aimed for solubility along with membrane permeability. It includes Molecular weight (Mol_MW), H bond acceptors, H bond donors and the octanol/water partition coefficient (QPlogPo/w). Brief information for ADME analysis is given in table below.

## RESULTS

The derivatives of (Z)-3-ethylidene-5,7-dimethylthiochroman-4-one were designed and synthesized (Table 1). Condensation of various derivatives of 5,7-dimethylchroman-4-one and 4,6-dimethylbenzofuran-3(2H)-one with the appropriate benzaldehyde catalyzed by acid or base is the standard procedure for obtaining (Z)-3-ethylidene-5,7-dimethylthiochroman-4-one derivatives. Photoisomerization of synthesized E-isomers was commonly used to obtain Z-isomers. Because of the effect of the carbonyl group, the E isomers olefinic proton signal appears at 7.7 ppm. Because of the proximity of the phenyl ring, the signal of C-2 protons was observed at around 5.3 ppm. Whereas Z-isomers with both signals shifted significantly to the up field at about 6.8 ppm and 4.9 ppm, respectively.

## DISCUSSION

Biological evaluation of synthesized compounds (Z)-3-ethylidene-5,7-dimethylthiochroman-4-one and (Z)-2-ethylidene-4,6-dimethylbenzofuran-3(2H)-one derivatives against MAO isoform exhibit selectivity towards MAO B isoform. Against hMAO-B, the most active compound of (Z)-3-ethylidene-5,7-dimethylthiochroman-4-one derivatives S11 displayed an $IC_{50}$ of 7.32 µM whereas (Z)-2-ethylidene-4,6-dimethylbenzofuran-3(2H)-one derivatives AU4 showed $IC_{50}$ of 7.85 µM (Table 2).

**Table 2: $IC_{50}$ (μM) and selectivity of Newly designed *(Z)-3-ethylidene-5,7-dimethylthiochroman-4-one* derivatives S1-S18 against hMAO isoforms**

| Comp. Name | hMAO-A ($IC_{50}$) (μM) | hMAO-B ($IC_{50}$) (μM) | Selectivity |
|---|---|---|---|
| S-1 | 39.63 | 14.56 | MAO-B |
| S-2 | 38.23 | 12.56 | MAO-B |
| S-3 | 40.21 | 17.86 | MAO-B |
| S-4 | 33.35 | 9.65 | MAO-B |
| S-5 | 55.85 | 19.25 | MAO-B |
| S-6 | 41.96 | 19.89 | MAO-B |
| S-7 | 53.96 | 20.21 | MAO-B |
| S-8 | 45.69 | 18.63 | MAO-B |
| S-9 | 39.96 | 17.98 | MAO-B |
| S-10 | 35.54 | 11.12 | MAO-B |
| S-11 | 30.21 | 7.32 | MAO-B |
| S-12 | 61.21 | 19.56 | MAO-B |
| S-13 | 46.28 | 23.14 | MAO-B |
| S-14 | 63.32 | 21.32 | MAO-B |
| S-15 | 48.63 | 20.69 | MAO-B |
| S-16 | 58.36 | 18.96 | MAO-B |
| S-17 | 49.36 | 22.14 | MAO-A |
| S-18 | 59.36 | 19.65 | MAO-B |

Prediction of ADME properties by *in silico* methods is intended to be an important step in new molecule (drug) discovery pipeline to ensure drug like properties of novel chemical entities. The acceptable range value of DonorHB is 0.0 – 6.0 which estimates the amount of hydrogen bonds donated by molecule to water in an aqueous media. In this study all the compounds showing value in the acceptable range whereas the amount of hydrogen bonds that may be accepted by the solutes in an aqueous media is predicted by using descriptor accptHB which value should be ranging between 2.0 to 20.0 and it is also observed good for all the compounds. QPlogPo/w envisaged partition coefficient (octanol/water) is ranging from 0.162 to 3.285 for all compounds. QPPCaco and QPPMDCK Predicted a Caco-2 cell permeability and MDCK permeability respectively in nm/sec for non-active transport which said to be poor if it is below 25 and great if it will be higher than 500. All the compounds showing good permeability except S-10 which showing value of 14.161 for apparent Caco-2 cell and 10.638 for apparent MDCK cell respectively. Percent Oral Absorption envisages oral absorption in human on scale (0 to 100%) based on a quantitative multiple linear regression model. All hits provided fine qualitative model for oral absorption in human. The log BB for brain/blood (95% drugs having -3.0 to 1.2) was -1.169 for most active compound S-11 of the selected series (Table 3). Other physicochemical parameters are also calculated to predict the druggablity of hits which explain capability of compound's polarizability, aqueous solubility, binding, absorption and distribution and toxicity respectively inside the body. The ADME parameters of the entire ligands are found in the allowable range which denotes that the newly identified ligands have drug like properties.

## CONCLUSION

A total of eighteen (Z)-3-ethylidene-5,7-dimethylthiochroman-4-one derivatives were synthesized and tested for their ability to inhibit specifically hMAO isoforms. The biological evaluation of synthesized compounds (Z)-3-ethylidene-5,7-dimethylthiochroman-4-one derivatives against MAO isoform reveals selectivity for the hMAO B isoform. The benzylidene portion of the activity profile was recorded with limited variations at a single site. To summarize, weak to moderate electron pumping and withdrawing groups favor selectivity for hMAO-B, whereas strong deactivators render them non-selective for isoforms. Mono-substitution of methoxy groups at the o- and m-positions improves potency while bi-substitution improves potency and selectivity. The most active (Z)-3-ethylidene-5,7-dimethylthiochroman-4-one derivative. S11 had an $IC_{50}$ of 7.32 M. In comparison to hMAO-B, the active compounds' ADME prediction revealed that they may have good pharmacokinetic profiles, which is necessary for drug candidates.

**Table 3: Predicted ADME properties for active compounds and their range in 95% of drugs.**

| S. No | Principal descriptors | S-11 | S-4 | S-10 | Range in 95% of drugs |
|---|---|---|---|---|---|
| 1 | mol_MW | 370.385 | 327.4 | 278.27 | 130 to 725 |
| 2 | SASA | 617.516 | 620.64 | 531.748 | 300 to 1000 |
| 3 | FOSA | 134.15 | 171.32 | 155.066 | 0 to 750 |
| 4 | FISA | 231.76 | 149.06 | 267.7 | 7 to 330 |
| 5 | PISA | 227.588 | 266.96 | 108.981 | 0 to 450 |
| 6 | WPSA | 24.018 | 33.3 | 0 | 0.0 to 175.0 |
| 7 | volume | 1071.744 | 1060.75 | 884.821 | 500 to 2000 |
| 8 | donorHB | 3 | 2 | 4 | 0 to 6 |
| 9 | accptHB | 9.25 | 6 | 8 | 2 to 20 |
| 10 | glob | 0.8201835 | 0.8104644 | 0.8382299 | .75 to.95 |
| 11 | QPpolrz | 35.7 | 35.636 | 25.803 | 13 to 70 |
| 12 | QPlogPo/w | 0.162 | 2.083 | -1.044 | 2 to 6.5 |
| 13 | QPlogS | -2.661 | -3.65 | -1.094 | –6.5 to 0.5 |
| 14 | CIQPlogS | -3.525 | -3.655 | -1.877 | –6.5 to 0.5 |
| 15 | QPlogHERG | -4.153 | -4.498 | -3.295 | <-5 |
| 16 | QPPCaco | 34.272 | 210.051 | 14.161 | <25 poor, >500 great |
| 17 | QPlogBB | -1.976 | -1.169 | -2.398 | –3.0 to 1.2 |
| 18 | QPPMDCK | 33.638 | 266.285 | 10.638 | <25 poor, >500 great |
| 19 | QPlogKp | -4.509 | -2.846 | -5.397 | –8.0 to -1.0 |
| 20 | #metab | 4 | 4 | 5 | 1 to 8 |
| 21 | QPlogKhsa | -0.708 | -0.218 | -1.006 | –1.5 to 1.5 |
| 22 | Percent Human Oral Absorption | 55.367 | 80.704 | 41.435 | >80% is high, <25% is poor |
| 23 | PSA | 141.256 | 92.195 | 145.311 | 7 to 200 |
| 24 | RuleOfThree | 0 | 0 | 1 | maximum is 3 |

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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