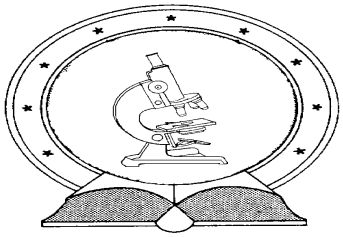
DE TTK



1949

Synthesis and Chemical Transformations of Substituted 2,2-Dimethyl-2*H*-1-benzopyrans; Development of a Novel and Efficient Column Chromatography Method

Ph.D dissertation

Zsolt Zsótér

Supervisor:

Prof. Dr. Tamás Patonay

UNIVERSITY OF DEBRECEN

Doctoral Council of Natural Sciences

Doctoral School of Chemistry

Debrecen, 2014

Ezen értekezést a Debreceni Egyetem Természettudományi Doktori Tanács Kémiai Doktori Iskola K/6 programja keretében készítettem a Debreceni Egyetem természettudományi doktori (Ph.D) fokozatának elnyerése céljából.

Debrecen, 2014. máj. 5. ……..

Tanúsítom, hogy Zsótér Zsolt doktorjelölt 2012 - 2014 között a fent megnevezett Doktori Iskola K/6 programjának keretében irányításommal végezte munkáját. Az értekezésben foglalt eredményekhez a jelölt önálló alkotó tevékenységével meghatározóan hozzájárult. Az értekezés elfogadását javasolom.

Debrecen, 2014. máj.5. ……

SYNTHESIS AND CHEMICAL TRANSFORMATIONS OF SUBSTITUTED 2,2-DIMETHYL-2*H*-1-BENZOPYRANS; DEVELOPMENT OF A NOVEL AND EFFICIENT COLUMN CHROMATOGRAPHY METHOD

Értekezés a doktori (Ph.D) fokozat megszerzése érdekében
a kémia tudományágban

Írta: Zsótér Zsolt, okleveles vegyész

Készült a Debreceni Egyetem kémiai doktori iskolája
(K/6 programja) keretében

Témavezető: Prof. Dr. Patonay Tamás

A doktori szigorlati bizottság:

elnök: Prof. Dr. Farkas Etelka …..……...

tagok: Prof. Dr. Antus Sándor . ……

Dr . Novák Zoltán ……..

A doktori szigorlat időpontja: 2014. jan. 15.

Az értekezés bírálói:

Dr. ....

Dr. ....

Dr. ....

A bírálóbizottság:

elnök: Dr. ....

tagok: Dr. ....

Dr. ....

Dr. ....

Dr. ....

Az értekezés védésének időpontja: 2014. ……

Table of content

In memoriam Dr. pharm. József P. Zsótér (1935-2000); my beloved father whom I got my first inspiration for chemistry.

Thesis Acknowledgements

First and foremost I want to thank my advisor Prof. Dr. Tamás Patonay, it has been an honor to be his Ph.D. student. I appreciate all his contributions of time, ideas to make my Ph.D. experience productive and stimulating.

I would like to express my heartfelt gratitude to my external advisor Dr. Tibor Tímár who is not only my former boss, mentor and a tough 'referee' but dear friend. He inspired me to be synthetic organic chemist.

During this work I have collaborated with many colleagues for whom I have great regard, and I wish to extend my warmest thanks to all those who have helped me with my work especially Dr. Tibor Eszenyi, Dr. Péter Sebők, Dr. József Jekő and all staff of Department of Research, Alkaloida Chemical Company and Department. of Organic Chemistry, University of Debrecen.

My thanks are due to Dr. Zoltán Szabó (Royal Institute of Technology), Dr. Krisztina Kónya (University of Debrecen) and Dr. Attila Balázs (Ubichem) for NMR measurements and for valuable discussions and to Dr. Attila Kiss (University of Debrecen) for taking IR spectra and to Dr. Pál Szabó (Chemical Research Center) for interpreting ESI-MS spectra. The author also acknowledges the technical help of Katalin Palcsu (Chemical Research Center) and Ágnes Gerencsér (Ubichem).

This work was supported by Alkaloida Chemical Company/Sun Pharma Industries Ltd. Tiszavasvári, Hungary and Ubichem Research Ltd., Budapest, Hungary.

Finally, I would like to thank my family for their patience, love and encouragement. Special thanks to Andrea, Ágnes and to my wife, Gina for their technical help.

1. Introduction

Pest insects can damage agricultural crops, consume and/or damage harvested food, or transmit diseases to humans and animals. The past 30 years has witnessed a dramatic reemergence of epidemic vector-borne diseases throughout much of the world.[1]

Twenty years after synthetic insecticides (organochlorines, organophosphates, carbamates and later the pyrethroids and neonicotinoids) were extremely entrenched in 'modern' agricultural production; they induce widespread environmental contamination, toxicity to non-target organisms, development of resistance against insecticides, and negative effects on animal and human health.[2] Consequently, there was an urgent need to explore and utilize naturally occurring products or their synthetic analogues for combating pests.

Insect growth regulators (IGRs) are chemical compounds that alter growth and development in insects. They do not directly kill insects, but interfere with the normal mechanisms of development, resulting in insects dying before they reach adulthood.

As of 2000, nearly one billion people or ~26% of the adult population of the world had hypertension which is a major risk factor for stroke, myocardial infarction, heart failure, aneurysms of the arteries, peripheral arterial disease and is a cause of chronic kidney disease.

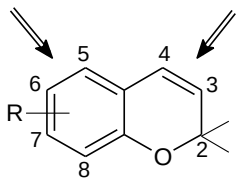
That incidence level drove/drives intense research activities worldwide on new, more effective antihypertensive agents.

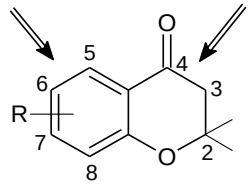
Alkaloida Chemical Company (Tiszavasvári, Hungary) started intense research on development of 'biorational pesticide' with new mode of actions in the field of 2,2-dimethyl-2*H*-1-benzopyrans in 1979. Research on the development of new antihypertensive agents also in the field of 2,2-dimethyl-2*H*-1-benzopyrans began in 1988. Majority of the research work in this dissertation is connected to these two projects.

2. General Research Objectives

1) Synthesis and chemical transformations (on aromatic ring and at C3-C4) of substituted 2,2-dimethyl-2*H*-chromenes with potential insecticide/antihypertensive properties

2) Synthesis and chemical transformations (on aromatic ring and at C3-C4) of substituted 2,2-dimethyl-4-chromanones with potential insecticide/antihypertensive properties





substituted 2,2-dimethyl-2*H*-chromenes substituted 2,2-dimethyl-4-chromanones

Figure 1.

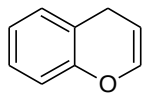
3) Development of a novel and efficient column chromatography method for the fast and effective separation of mixtures of substituted 2,2-dimethyl-*2H*-1-benzopyrans prepared

3. Literature Review

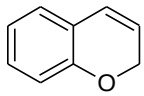
3.1 General overview of benzopyrans

Compounds in which a benzene and pyran ring are fused together with various levels of saturation and oxidation are very common in Nature.[3] Several thousand compounds including natural products and synthetic structures with 2,2-dimethyl-2*H*-1-benzopyran moiety can be found in the literature.[4] The relatively high incidence of this benzopyran unit in natural products is partially attributable to the numerous prenylation and cyclization reactions in many polyketide biosynthesis pathways.[5] Typical examples of those products are the coumarins, chromenes, chromene glycosides, flavonoids, rotenoids, and stilbenoids and; several of them have potential applications in medicine.[6]

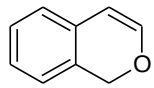
Benzopyran is a bicyclic ring system that results from the fusion of a benzene ring to a heterocyclic pyran ring. According to IUPAC nomenclature it is called chromene. There are two additional isomers of benzopyran that vary by the orientation of the fusion of the two rings compared to the oxygen, resulting in chromene and isochromene.



4*H*-chromene
(4*H*-1-benzopyran)



***2H*-chromene**
(2*H*-1-benzopyran)



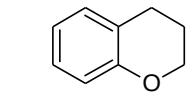
1*H*-isochromene
(1*H*-2-benzopyran)

Figure 2.

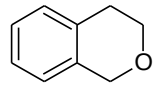
As a class of compounds the 4*H*-chromenes (4*H*-1-benzopyrans) are rather unusual and only a few examples of natural products containing this structure have been isolated.[7] The chromene skeletons have also elicited pharmaceutical interest as structural elements in compounds of future drugs.[8]

2*H*-1-benzopyrans are synthesized by several plant species in the genus *Ageratum*[9] and are therefore called ageratochromenes.[10]

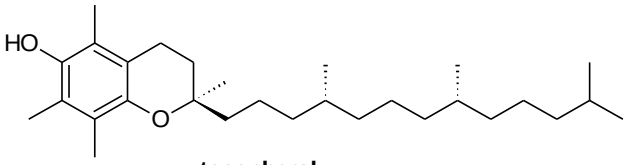
The chromanes are bicyclic heterocycles in which a benzene ring is fused to one of dihydro-pyran; it is the base unit of tocopherols[11].



3,4-dihydro-2*H*-chromene
(chromane)



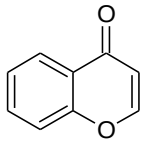
3,4-dihydro-1*H*-isochromene
(isochromane)



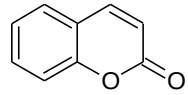
α-tocopherol

Figure 3.

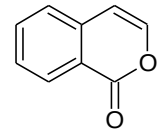
Coumarin can be found naturally in many plants, notably in high concentration in the tonka bean (Dipteryx odorata). The name comes from a French word, 'coumarou', for the tonka bean. It has a sweet odor, readily recognized as the scent of new-mown hay.



4*H*-chromen-4-one
(chromone)



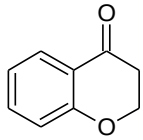
2*H*-chromen-2-one
(coumarin)



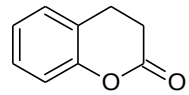
1*H*-isochromen-1-one
(isochromone)

Figure 4.

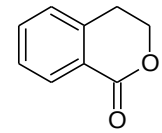
Chromanones are important intermediates; 4-chromanones can be easily converted to the corresponding chromenes (see in part 3.10)



2,3-dihydro-4*H*-chromen-4-one
(4-chromanone)



3,4-dihydro-2*H*-chromen-2-one
(2-chromanone),
(dihydrocoumarin)



3,4-dihydro-1*H*-isochromen-1-one
(dihydroisocoumarin)

Figure 5.

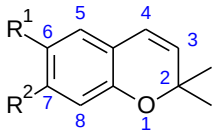
3.2 Precocenes

Ageratum houstonianum has evolved an ingenious method of protecting itself from insects; it produces 2,2-dimethyl-2*H*-1-benzopyran compounds which interfere with the normal function of the *corpus allatum* (plural: *corpora allata*), the organ which secretes juvenile hormone. The effect caused by these chemical triggers on young larvae is precocious changeover resulting in sterile adultiforms, and sterilization of adult females – hence the compounds were named 'precocenes'.[12]

Figure 6. *Ageratum houstonianum* (flossflower)
(in Hungarian: kék bojtocska)

Precocene 1 and 2 (**1a,b**) isolated from that and other natural source are known insect antijuvenile hormones (AJH). They induce precocius metamorphosis and have nematocidal activity[13].

Several analogs of natural precocenes have been synthesized and the 7-ethoxy-6-methoxy-2,2-dimethyl-chromene (Precocene 3, **1c**) was found to be the most active synthetic precocene derivatives[14].



1

Figure 7.

1a: Precocene 1 (P1): R^1 = H R^2 = MeO

1b: Precocene 2 (P2): R^1 = MeO R^2 = MeO

1c: Precocene 3 (P3): R^1 = MeO R^2 = EtO

Owing to their insecticide activities such substances (several hundreds) have mainly been prepared and investigated as potential plant protecting agent[15].

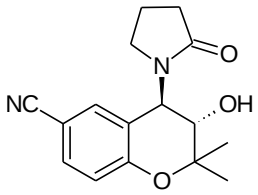
Structure-optimization studies of C-5–C-8-substitued precocene (P) analogues revealed that a) compounds disubstitued asymmetrically at C-6, C-7 had an anti-allatal effect (definition: any effect which blocks the *corpus allatum* selectively) only if the C-6 side-group was shorter than that at C-7; b) in the case of C-5, C-7 disubstitution, activity was enhanced by Me at C-5 whereas MeO caused inactivity.[16]

P1, 2 and 3 as well as 36 additional derivatives of 2,2-dimethylchromene were tested for direct toxicity on newly moulted 3rd and 4th instar larvae of *Pieris brassicae* and 4th instar larvae of *Leptinotarsa decemlineata*. The chemicals were applied to the insects topically or by treated food assay. In topical tests the highest activity was observed in both species when 6,7-dialkoxy analogues, especially those having a 7-(2-propynyloxy) group, had been used. In most cases a further increase of toxicity was found if two chlorine atoms were introduced to the C3 and C4 position.[17] In *P. brassicae* larvae the higher toxicity of some 6,7-dialkoxy derivatives was in accordance with the greater size of the alkoxy group at C7. In the same test series, among disubstituted 7-alkoxy analogues the positive influence of 5-methyl or 8-mehtoxy substituents was also detected. Stricter structural requirements of chromene toxicity were demonstrated in *L. decemlineata* than in the other test insect.[17]

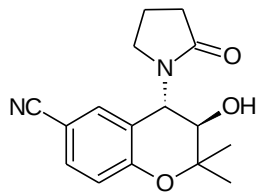
3.3 Cromakalim

The research on modulation of potassium (K^+) channels by drugs was one of the most rapidly growing areas of pharmacology and as a result of these intensive studies a new class of the K^+ channel activators (or potassium channel openers: PCOs) containing benzopyran skeleton was reported in 1986.[18]

Cromakalim [racemate: 3S, 4R (**2a**); 3R, 4S (**2b**)], the leading compound of the benzopyran type PCOs, has been found to exert a marked antihypertensive activity. During several years, cromakalim and levcromakalim (**2a**) the more active (-)-enantiomer (3S,4R) have been regarded as the reference myorelaxant PCOs. Unfortunately, the use of cromakalim in clinical practice was not recommended because many side-effect were reported.[19] Cromakalim had stimulated a widespread synthetic effort for better and more selective agents.[20,21] At Alkaloida Chemical Company an intensive research on new synthetic pathways to cromakalim/levcromakalim and syntheses of new analogues[22,23] with PCO activities had started in 1988.



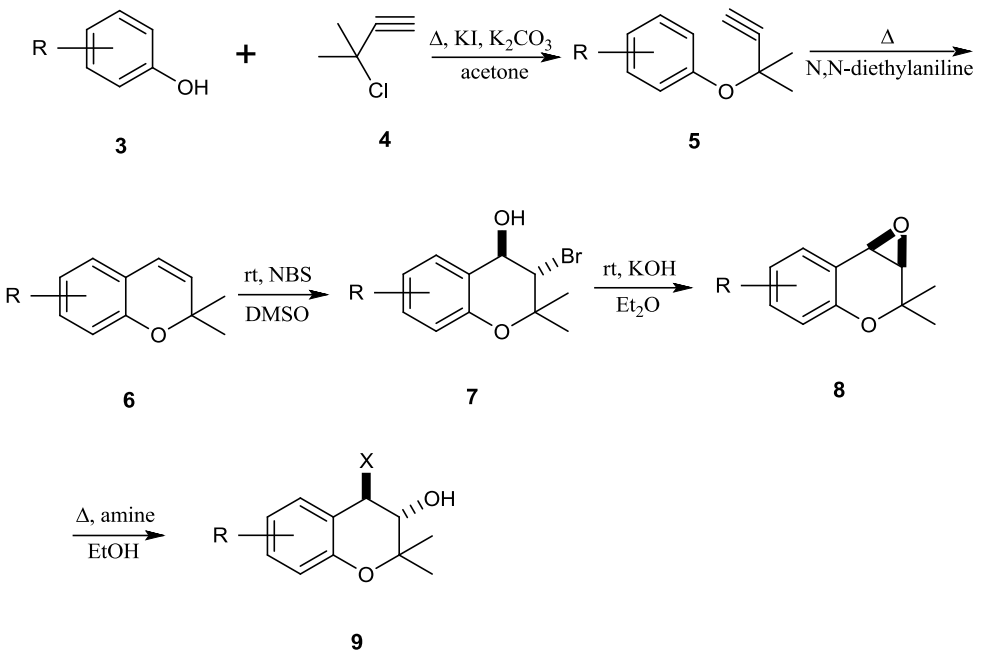
2a



2b

Figure 8.

The synthetic route to these compounds involves cyclization of aryl-propargyl ethers to 2*H*-1-benzopyrans, followed by conversion via bromohydrins to 3,4-epoxides, which were submitted to ring-opening with appropriate amines.[24] (Scheme 1)



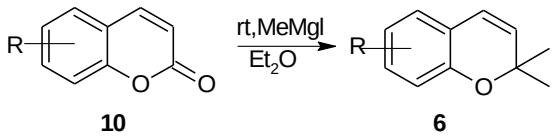
R= NO_2, CN, Cl, F, Me, MeO, COOMe (in positions 5,6 or 7); X= $NHCHMe_2$, NH_2, NHMe, NMe_2, NEt_2, $NHCMe_3$

Scheme 1.

3.4 Synthesis of 2,2-dimethyl-2*H*-chromenes[25]

3.4.1 Grignard reaction of coumarins

2,2-dimethyl-2*H*-chromenes **6** were prepared by Shriner and Sharp by the reaction of coumarin with Grignard reagent in 1939.[26] Later, Precocene 1 (P1)[27] and Precocene 2 (P2)[28] have been prepared by the reaction of the appropriate coumarins with methylmagnesium iodine (Scheme 2.)



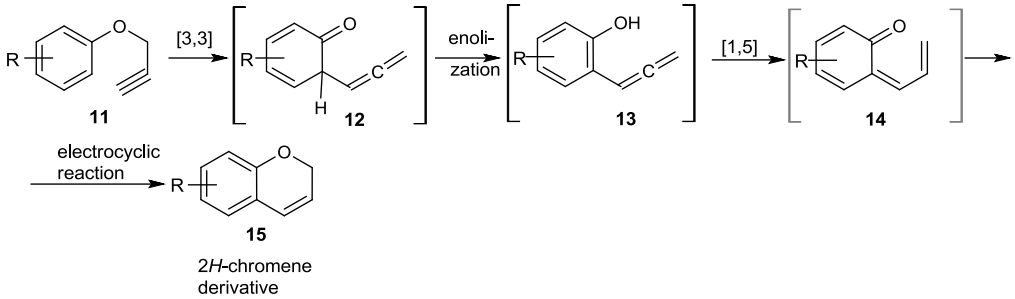
10 **6**

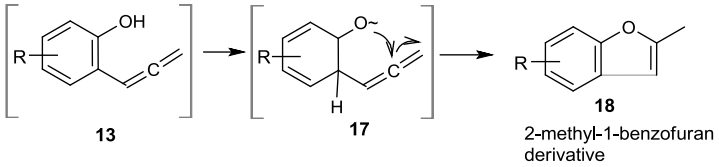
R=H, 7-MeO, 6-EtO

Scheme 2.

3.4.2 Thermal rearrangement of aryl propargyl ethers

Thermal rearrangement of aryl propargyl ethers **11** have been recognized as one of the general methods for the synthesis of 2*H*-1-benzopyrans.[29]





R= H, 7-Me, 7-MeO

Scheme 3.

The mechanism of the thermal cyclization of aryl propargyl ethers had been studied by Zsindely and Schmid.[30] The proposed mechanism (Scheme 3) involves an initial Claisen rearrangement of the aryl propargyl ether **11** to give the allene intermediate **12**. Enolization of **12** followed by a [1,5] sigmatropic hydrogen shift would give **14**, which can undergo an electrocyclic reaction to give 2*H*-chromene.[31]

Iwai and his co-workers found that electron donating group in *meta* position increases the 2*H*-chromene / 2-methyl-1-benzofuran ratio.[32]

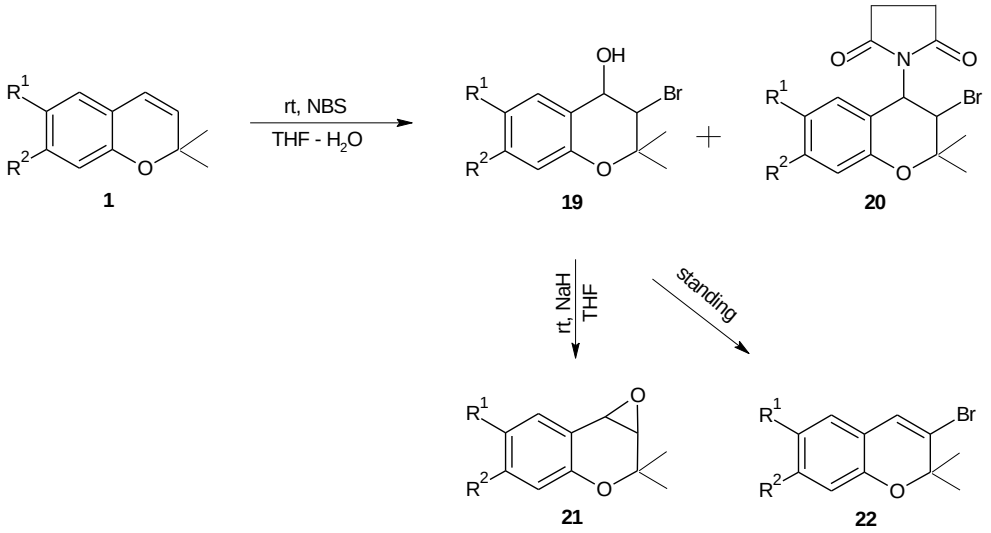
Substituent and solvent effect of this reaction was studied. Aryl propargyl ethers rearranged cleanly on heating in poly(ethylene glycol)-200 (PEG) at 220 ^{o}C. The reaction had been found to be 2 to 2.5 times faster in that solvent when compared with in N,N-diethylanyline.[33]

With meta-substituted aryl propargyl ethers, cyclization was at first reported to occur regioselectively para to the substituent[34]. This observation was debated and discussed by Anderson *et al.*[35] They found that the cyclization of 3-methoxy-phenyl propargyl ether did not lead to the formation of 7-methoxy-2*H*-chromene regioselectively but lead to the formation of 5- and 7-substituted derivatives in a ratio of approximately 46:54.

3.5 Relevance of 3,4-Epoxyprecocenes; Reaction of 2,2-dimethyl-2H-chromenes with *N*-bromosuccinimide (NBS)

Previous studies have suggested that precocenes are converted by the allatal monooxygenases into the corresponding 3,4-epoxy derivatives which are their active metabolites.[36] These highly reactive intermediates are assumed to be the responsible for the cytotoxic reaction on the *corpora allata*.[37]

Several methods are published for preparation of 3,4-epoxy derivatives of Precocene 1 (P1) and Precocene 2 (P2). The reactions[38] in Scheme 4 were found to be applicable to provide a high-yield pathway to the desired epoxide.



(R^1 = H, MeO; R^2 = MeO)

Scheme 4.

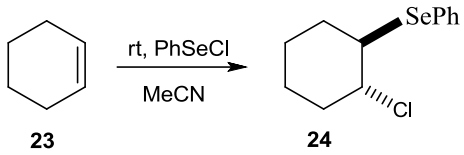
Reaction of **1** with *N*-bromosuccinimide in aqueous tetrahydrofuran yielded the bromohydrin **19**, however as well as the product **20** resulting from the direct addition of *N*-bromosuccinimide to 3,4-double bound. (This compound could be obtained as the sole product from the reaction of **1** with NBS in anhydrous dichloromethane. It is a highly crystalline, stable material which survives chromatography.) The epoxide **21** could be obtained in high yield by treating the bromohydrin with sodium hydride under anhydrous conditions.

Soderlund *et al.* reported that the bromohydrins convert into the more stable 3-bromo-chromenes on standing.[39]

Adam *et al*. prepared 2,2-dimethyl-3,4-epoxychromans **21** in good yields and high enantioselectivities (81-93% e.e.) by employing a novel combination of Mn(III)salen complexes and dimethydioxirane (DMD).[40]

3.6 Reaction of 2,2-dimethyl-2*H*-chromenes with phenylselenyl chloride

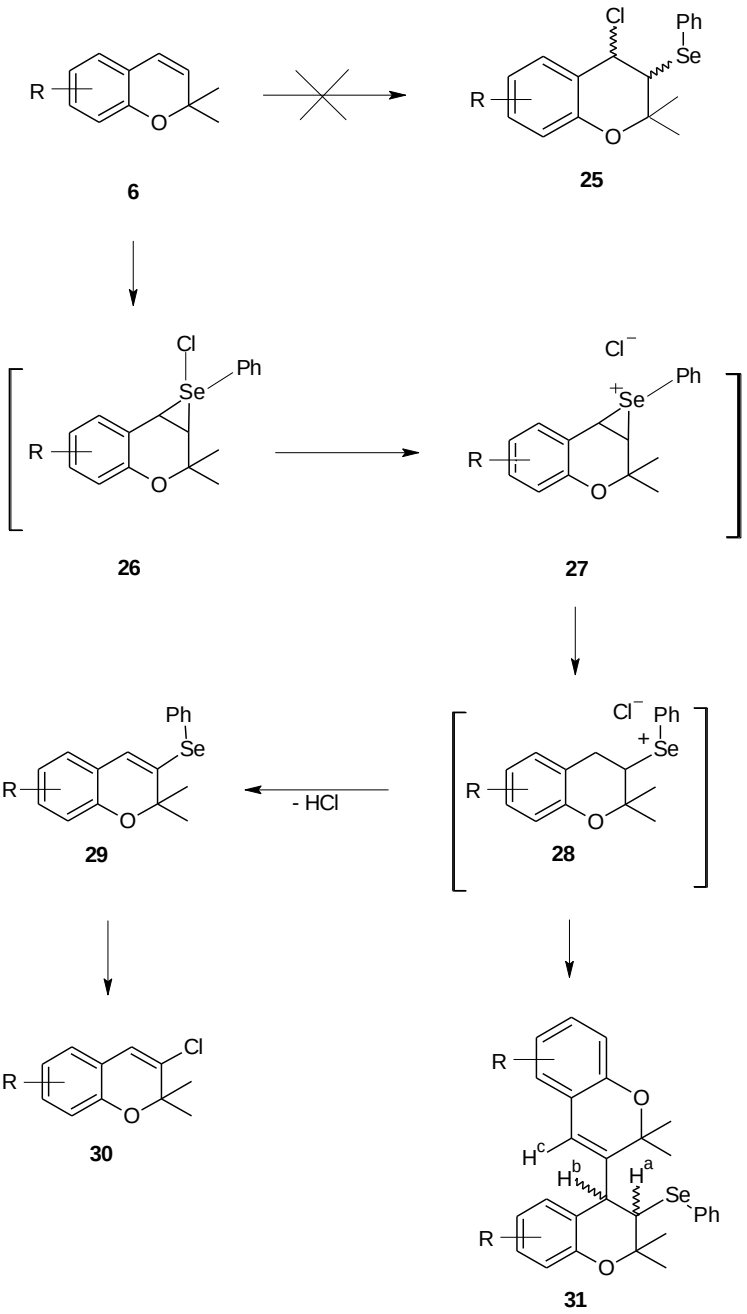
The electrophilic addition of benzeneselenyl compounds to unsaturated system (*e.g.* **23**) is a facile, well-documented reaction.[41,42,43,44] In most cases this reaction is fast and shows *anti* stereospecifity with various olefins, although the regiochemistry control varies by the substituation pattern of the individual olefins[45, 46] (Scheme 5). Duddeck *et al*. studied the phenylselenyl cyclohexane derivatives; ring inversion barriers were determined. Extraordinarily large diamagnetic γ effects of ca 30–40 ppm per CH_2 group were found.[47]



Scheme 5.

Results of preliminary investigations without synthetic details, yields and spectral data were reported[48] on the treatment of 2,2-dimethyl-2*H*-chromene derivatives **6** with

phenylselenyl chloride in methylene dichloride solution which affords a mixture of unusual phenylselenylation products **29**, **30** and **31** instead of the expected addition derivatives **25** which can be seen in Scheme 6. Reaction pathways and the proposed mechanism are shown in Scheme 6. In the case of 6-unsubstitued chromenes C-6 aromatic substitution phenylselenylation) takes place also. The chlorination step **29** →**30** was not completely unexpected.[49]

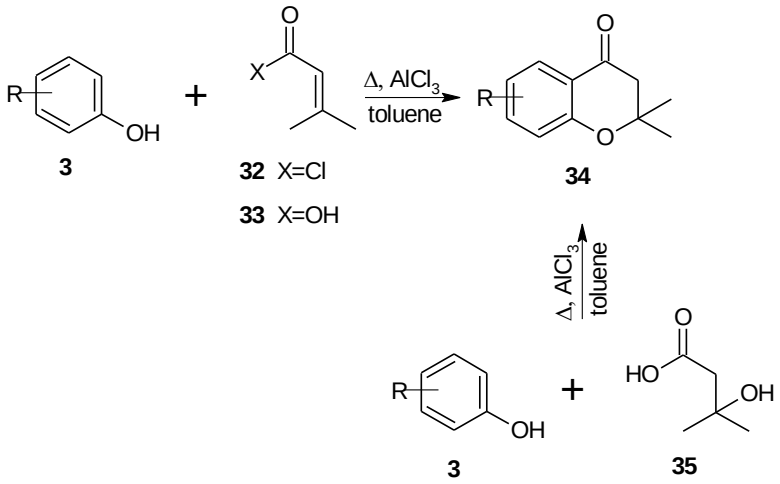


Scheme 6.

3.7 Synthesis of 2,2-dimethyl-4-chromanones[50]

The first synthesis of 2,2-dimethyl-4-chromanones **34** was published in 1920. An appropriately substituted phenol **3** was allowed to react with 3-methylbut-2-enoyl chloride (**32**) in the presence of aluminium chloride to afford the target compound.[51]

Similar Friedel-Crafts - type reaction of substituted phenol **3** with 3-methylbut-2-enoic acid (**33**)[52] or β-hydroxyisovaleric acid (**35**)[53] also yields the corresponding 2,2-dimethyl-4-chromanones derivatives **34** (Scheme 7).



R= H, MeO, EtO (in positions 6 and 7)

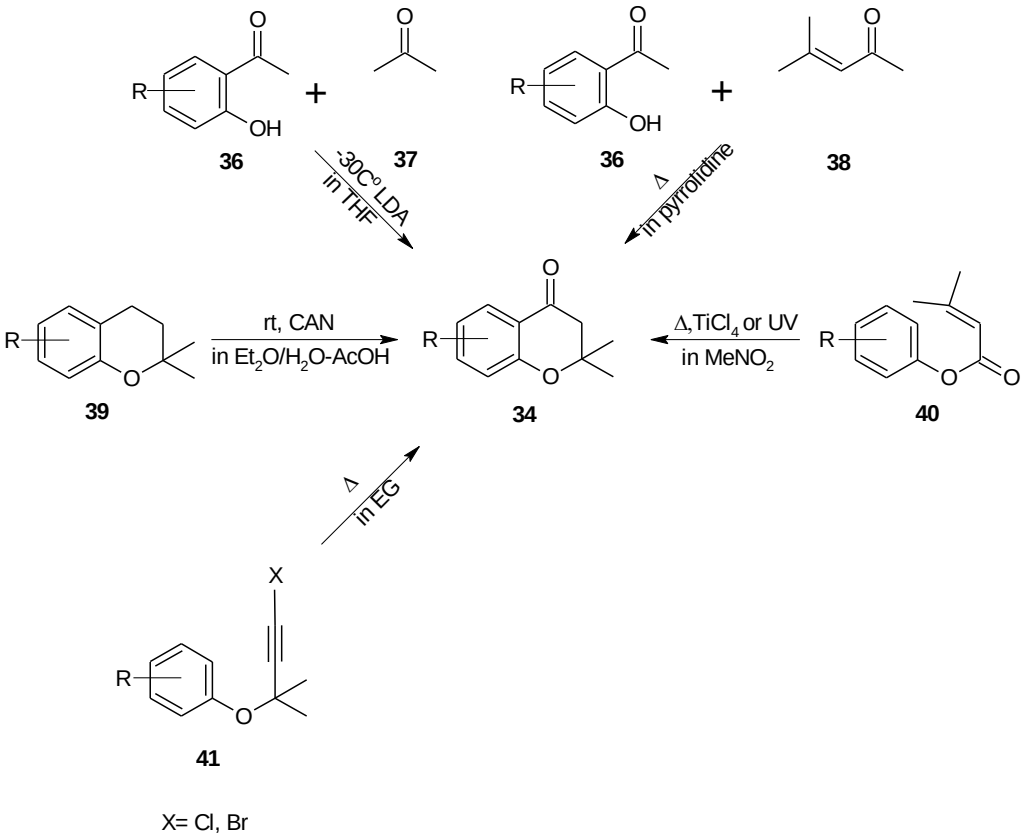
Scheme 7.

Alternative approaches to 2,2-dimethyl-4-chromanones **34** are shown by Scheme 8. Reaction of 2-hydroxy-acetophenones **36** with acetone (**37**) in the presence of lithium diisopropylamide (LDA) at -30 C^{o} or with mesityl oxide (**38**) leads to the formation 2,2-dimethyl-4-chromanones **34**.[54]

Fries rearrangements of 3-methylbut-2-enoates of substituted phenols **40** with Lewis-acids or under photochemical conditions can be also utilized.[55]

Thermal cyclizations of aryl γ-halopropargyl ethers provide a simple route to the target compounds.[56]

Mild and efficient oxidation of 2,2-dimethyl-chromans **39** into 2,2-dimethyl-4-chromanones **34** using CAN (ceric ammoniun nitrate) is also a facile synthetic pathway.[57]

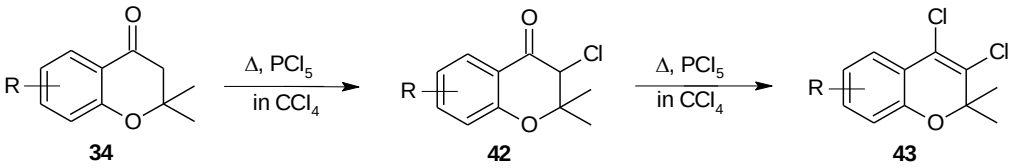


R=7-MeO, 5-OH, 6-Cl, 6-Br

Scheme 8.

3.8 Halogenations of 2,2-dimethyl-4-chromanones

Camps *et al.*[58] reported that the reaction of 2,2-dimethyl-4-chromanones **34** with two equivalents of phosphorus pentachloride affords 3,4-dichloro-2,2-dimethyl-2*H*-chromene **43**. They suggested the participation of PCl_5 in two consecutive processes, in which the intermediates **42** formed in the first reaction step should be more reactive towards the reagent than the starting chromanone (Scheme 9).



34 **42** **43**

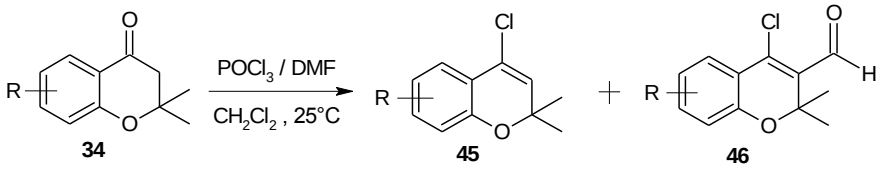
R=H, 6-MeO, 7-MeO, 6,7-diMeO

Scheme 9.

Eszenyi *et al.*[59] studied the formation of 4-halo-2*H*-chromenes **45** from the corresponding 4-chromanones **34** and phosphorus trihalides because it appeared that 4-halo-substitution (Cl, Br) is able to efficiently protect the pyran moiety under basic conditions, where the corresponding 4-chromanone would undergo ring-opening. In the reaction an excess of PX_3 at reflux temperature was used as a halogenating agent. Besides the major products 4-halo-2*H*-chromenes no 3-halo-4-chromanone was formed, except in the reaction of 2,2-dimethyl-7-methoxy-4-chromanone and phospourus trichloride when 3-chloro-2,2-dimethyl-7-methoxy-4-chromanone was obtained in small amounts. Neither 3,4-dichloro-2*H*-chromene nor 3,4-dibromo-2*H*-chromene formation was observed. Their experiments confirmed that the ready halogenation at C-3 position might be avoided by the use of the less reactive phosphorus trihalide.

Brown *et al.* found that the action of Vilsmeier reagent on 2,2-dimethyl-7-methoxy-4-chromanone (**34a**) and its 6-bromo (**34b**) and 6-methoxy (**34c**) analogues gave low yields (2-12%) of 4-chlorochromene-3-carbaldehydes **46**. In addition 4-chloro-

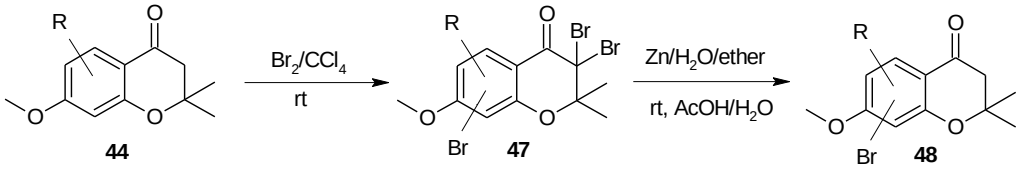
2*H*-chromenes **45** which are not precursors of the carbaldehydes , were obtained in high yields.[60]



	R
a	7-MeO
b	6-Br, 7-MeO
c	6,7-diMeO

Scheme 10.

Bromination of **44** with the excess of bromine in carbon tetrachloride affords the 3,3,6-tribromo derivatives **47**. Their debromination with zinc in aqueous ether gave chromanones **48**.[60]

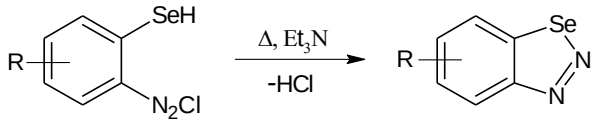


R=H, 6-NO_2, 6-MeO

Scheme 11.

3.9 Synthesis of 1,2,3-selenadiazoles

The first representative of 1,2,3-selenadiazoles were the compounds **50** prepared from o-aminobenzeneselenol (precursor of **49**) in 1935[61] although 1,2,3-thiadiazole ring system had been known for some time.[62,63]

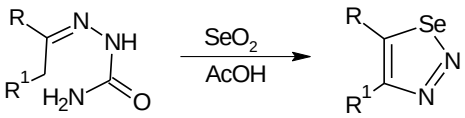


49 **50**

R= Me, MeO, Cl

Scheme 12.

Lalezari *et al.* reported the first general[64] route to this selenium heterocyclic system (1,2,3-selenadiazole) in Scheme 13. Further extensions were published later.[65, 66]



51 **52**

R=H, Me R^1=H, Me

Scheme 13.

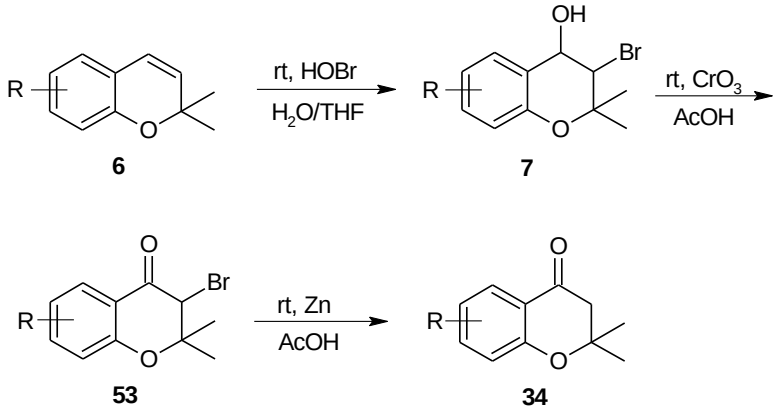
They obtained the unsubstitued 1,2,3-selenadiazole (**50**, R=R^1=H) with 25% yield by the reaction of acetaldehyde semicarbazone (**51**, R=R^1=H) with selenium dioxide in cold glacial acetic acid. It is a colorless pungent-smelling liquid boiling at 55 ^oC (16 mmHg). It is quite stable in the dark at 0 ^oC but decomposes slowly when exposed to sunlight at room temperature. 5-Alkyl and aryl derivatives were also obtained.

The direction of ring closure, when both α positions are available for oxidation, depends on the effect of substituent on the acidity of the α hydrogens. Thus, electron-attracting substituent such as chlorine or phenyl on acetone, which increase the acidity of the adjacent methylene hydrogens relative to the methyl groups, lead to the preferential ring closure on the methylene side.[67]

Most authors use either selenium dioxide suspended in acetic acid or the solution of selenium dioxide in aqueous dioxane.[68]

3.10 Interconversion of 2,2-dimethyl-2*H*-chromanones and 2,2-dimethyl-2*H*-chromenes

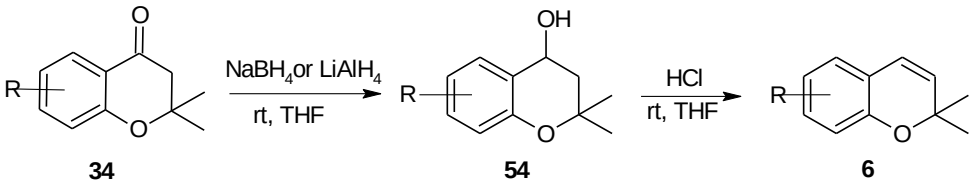
The reaction of 2,2-dimethyl-2*H*-chromenes **6** with hypobromous acid furnished the corresponding 3-bromo-4-hydroxy-2,2-dimethychromans **7**. Then, these compounds were oxidized with chromium trioxide in acetic acid giving 3-bromo-2,2-dimethyl-4-chromanones **53**. Treatment with zinc dust in acetic acid converted the bromoketones **53** into 2,2-dimethyl-4-chromanones **34** with 70-80% overall yield [69] (Scheme 14).



R=H, 7-MeO

Scheme 14.

For the preparation of 2,2-dimethyl-2*H*-chromenes **6** the most convenient and the most popular method[70] is undoubtedly the dehydration of the appropriate 2,2-dimethyl-4-hydroxychromans **54** which can be obtained by the reduction of 2,2-dimethyl-4-chromanone **34** with sodium borohydride or lithium aluminium hydride. Compounds **54** can then be dehydrated on treatment with hydrochloric acid to afford the desired 2,2-dimethyl-2*H*-chromenes **6** in high yields. The utilization of this protocol made available the synthesis of different series of variously substituted 2,2-dimethyl-2*H*-chromenes **6** required for the study of their structure-activity relationship[25] (Scheme 15).



R=H, 7-MeO, 6-MeO

Scheme 15.

3.11 Column chromatography

In a usual laboratory day, the greatest share of working time is devoted to sample isolation and purification. Usually, chromatographic separation plays a central role in this effort. I outline here some column chromatographic methods which were developed for more efficient and faster separations of mixtures.

3.11.1 Low pressure column chromatography

Still *et al.* described a simple absorption chromatography technique for the routine purification of organic compounds[71]. Large scale preparative separations are traditionally carried out by tedious long column chromatography. Although the results are sometimes satisfactory, the technique is always time consuming and frequently gives poor recovery due to band tailing. These problems are especially acute when samples of greater than 1 or 2 g must be separated. In recent years several preparative systems have evolved which reduce separation times to 1-3 h and allow the resolution of components having $\Delta Rf \geq 0.05$ on analytical TLC. Medium pressure chromatography and short column chromatography were found most successful during the laboratory work. Still *et al.* developed a substantially faster technique for the routine purification of reaction products which they call flash chromatography. Although its resolution was only moderate ($\Delta Rf \geq 0.15$), the system was extremely inexpensive to set up and operate and allows separations of samples weighing 0.01-10.0 g in 10-15 min. Flash chromatography is basically an air pressure driven hybrid of medium pressure and short column chromatography which has been optimized for particularly rapid separations.

They found that one of the most popular grades of silica gel 60, 70-230 mesh (63-200 μm**),** gives the poorest resolution of any gel studied under their standard conditions. Particle sizes less than 40 μm offer no improvement in resolution with their method of packing.

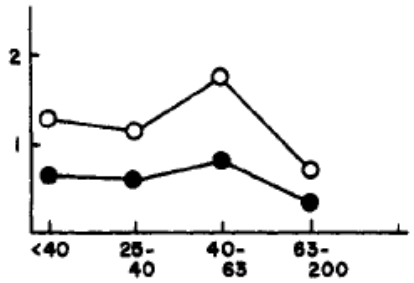


Figure 9. x axis: silica gel particle size (in μm); y axis: Resolution,
'●' relates r/w; 'o' relates r/(w/2); w= peak width; r= retention time

Column performance is quite sensitive to the rate of elution and is best with relatively high eluant flow rates.

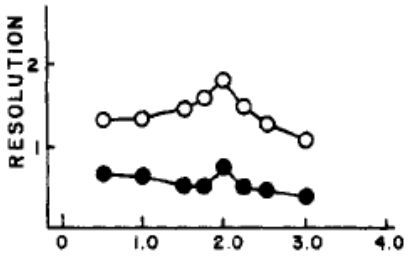


Figure 10. y axis: eluent flow rate (inch/min, 1 inch=2.54 cm)
The peak width shows the expected increase with the sample size. Sample recovery was ≥ 95%.

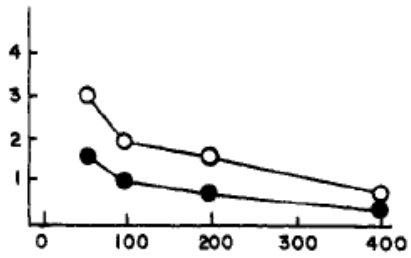


Figure 11. Sample size (mg); resolution, y axis

The apparatus required for this technique consists of a set of chromatography columns and a flow controller valve (Figure 12).

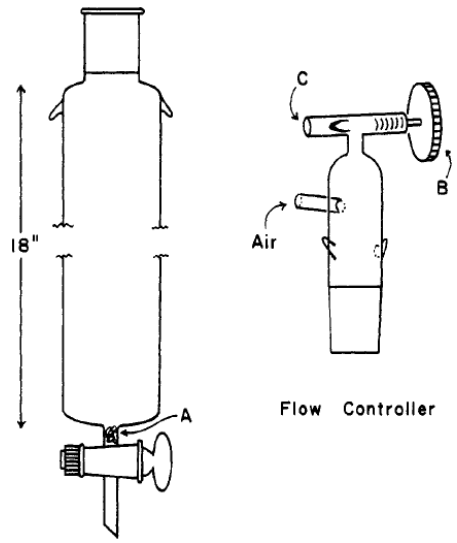


Figure 12. Flow Controller apparatus

Taber *et al.* outlined a procedure for column chromatography[72] that is both efficient (mixtures showing $\Delta Rf = 0.05$ by TLC are routinely separated) and easy to scale up. There are two central concerns in column chromatography: packing of the absorptive bed and sample application. This procedure, a modification of the short-column technique,[73] effectively addresses both of these concerns. The silica gel bed is

first allowed to settle by gravity flow and then further compacted by application of air pressure. This assures a dense, evenly packed bed. Then, rather than application of the

mixture to be chromatographed in liquid form, the solution of the sample is first evaporated onto coarse silica gel. This assures even application of the sample on to the top of the column and avoids concerns about mixtures that are not soluble in the (usually nonpolar) column solvent. For routine separations, the polarity of the eluant is adjusted so that the first component of the mixture appears in about fraction 10. It is usually then sufficient to collect 20 fractions, with fraction collection and TLC monitoring being effected simultaneously. When components of the mixture are widely separated, it is appropriate to switch to a more polar eluant after the less polar components have come off the column. The entire process of column construction, elution, and fraction analysis usually takes a little less than 1 h. The procedure described here is adequate for most routine separations. It clearly does not have the inherent resolving power of medium-pressure liquid chromatography.[74]

3.11.2 Vacuum Liquid Chromatography

Targett *et al.* reported on development of vacuum liquid chromatography (VLC) method.[75] The development of this method arose from the need to have a simple inexpensive chromatographic system at the bench, capable of producing good resolution in a short time. VLC method enables organic chemists to separate both large and small quantities of mixtures efficiently, rapidly, and inexpensively.

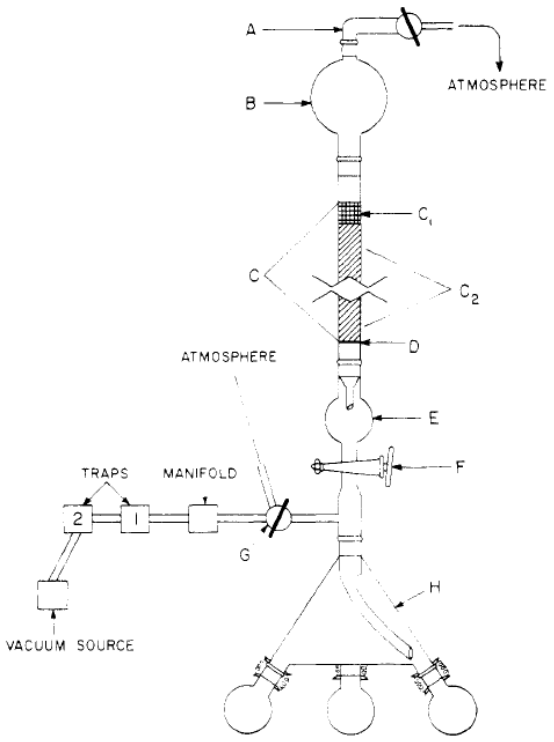


Figure 13. VLC apparatus and some specifications

A, stopcock/stopper; B, solvent reservoir (2 L); C, column; C_1 preabsorbent layer (diatomaceous earth, celite, filter aid or equivalent); C_2, sorbent (TLC grade, 10-40 μm); D, sintered glass frit (10-20 μm pore size); E, eluent reservoir (250 mL); F, column isolation stopcock; G, vacuum/atmosphere stopcock; H, receiver head; trap 1, 250 mL; trap 2, 50 mL; vacuum, mechanical pump.

4. Detailed Research Objectives

1) Investigation of bromination reactions of 2,2-dimethyl-4-chromanones and preparations of various bromo-derivatives of alkoxy-2,2-dimethyl-4-chromanones as intermediates.

2) To investigate the chlorination reactions of 2,2-dimethyl-4-chromanones and to prepare different alkoxy derivatives of 4-chloro-2,2-dimethyl-2*H*-chromenes and derivatives of different 3,4-dichloro-2,2-dimethyl-2*H*-chromenes which were needed for the syntheses of target compounds with insecticidal activity.

3) Development a combined TLC mesh column chromatographic system that unifies the advantages of the vacuum-driven and low-pressure methods for the fast and efficient separation of substituted 2,2-dimethyl-1-benzopyrans having small *Rf* differences.

4) - Preparation a set of selenium-containing[76,77] derivatives of 2,2-dimethyl-2*H*-chromenes with sterically and electronically modified $\Delta^{3,4}$ double bonds which may have effect on the formation of their active metabolite (3,4-epoxy derivatives)[78].
- Testing of the non-specific toxic activities of 1,2,3-selenadiazolo derivatives prepared

5) Preparation of 2*H*-chromenes and study of the thermal cyclization of aryl propargyl ethers.

6) Study the reaction of 2,2-dimethyl-2*H*-chromenes with N-bromosuccinimide (NBS)

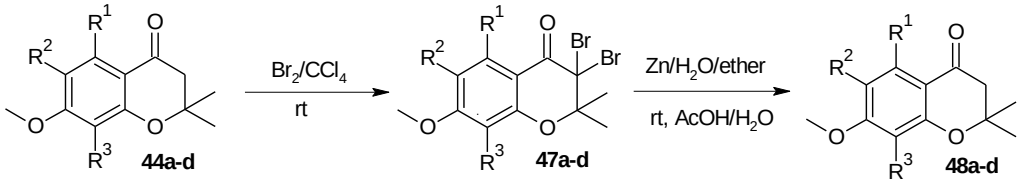
7) Study the reaction of 2,2-dimethyl-2*H*-chromenes with phenylselenyl chloride.

5. Results and Discussion

5.1 Bromination of 2,2-dimethyl-4-chromanones

My aim was to functionalise the aromatic ring of different alkoxy-2,2-dimethyl-4-chromanones **44** with bromine. The electron-donating alkoxy groups on the aromatic ring enhance the bromination. Dibromination at C-3 cannot be avoided under these reaction conditions but bromine in C-3 position can be easily removed by reductive debromination afterwards.

Bromination method of Brown *et al.*[60] was used to prepare different bromo-derivatives of alkoxy-2,2-dimethyl-4-chromanones.



Scheme 16.

Yields are summarized in Tables 1 and 2. Beyond the experimental data of Brown *et al.*[60] we observed the formation of (**47a'**) as a minor product; we did not observe formation of 6,8-dibromo derivatives. The bromination of (**44d**) led to the formation of tetrabromo derivative as sole product in the first reaction step.

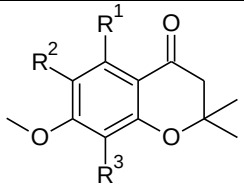
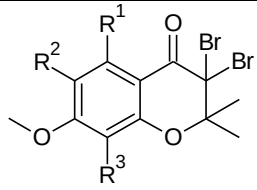
									
	Starting material **44**				Product **47**				
Entry	Code	R^1	R^2	R^3	Code	R^1	R^2	R^3	Yield (%)
1	**44a**	H	H	H	**47a**	H	Br	H	80
					47a'	H	H	Br	10
2	**44b**	H	MeO	H	**47b**	H	MeO	Br	53
3	**44c**	H	H	MeO	**47c**	H	Br	MeO	85
4	**44d**	MeO	H	H	**47d**	MeO	Br	Br	62

Table 1. Bromination of 2,2-dimethyl-4-chromanones

The presence of electron-donating substituens such as methoxy groups at C-5 and C-7 position highly activate C-6 and C-8 positions for electrophilic substitution. New compounds prepared: **47a'-d, 48a'-d.**

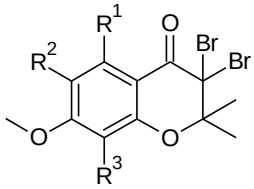
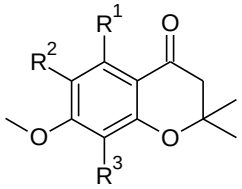
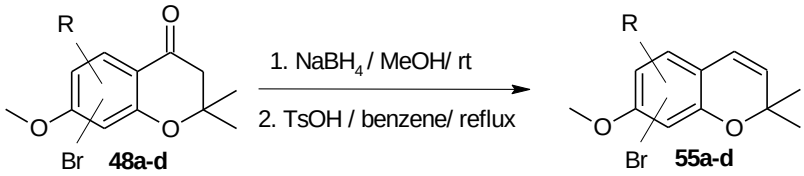
									
	Starting material **47**				Product **48**				
Entry	Code	R^1	R^2	R^3	Code	R^1	R^2	R^3	Yield (%)
1	**47a**	H	Br	H	**48a**	H	Br	H	75
2	**47a'**	H	H	Br	**48a'**	H	H	Br	70
3	**47b**	H	MeO	Br	**48b**	H	MeO	Br	80
4	**47c**	H	Br	MeO	**48c**	H	Br	MeO	64
5	**47d**	MeO	Br	Br	**48d**	MeO	Br	Br	42

Table 2. Debromination of 3,3-dibromo-2,2-dimethyl-4-chromanone derivatives

5.2 Preparation of bromo derivatives of 2,2-dimethyl-2*H*-chromenes

From bromo-derivatives of alkoxy-2,2-dimethyl-4-chromanones **48** we obtained the corresponding target compound bromo-chromene derivatives **55** (precocene analogues with modifications on their aromatic rings) with 70-80% yield using the well-known method.[69] After the reduction step we used TsOH in benzene for the dehydration of 4-hydroxy-chromane. An alternative reagent, *i.e.* 4M HCl in THF solution did not work.

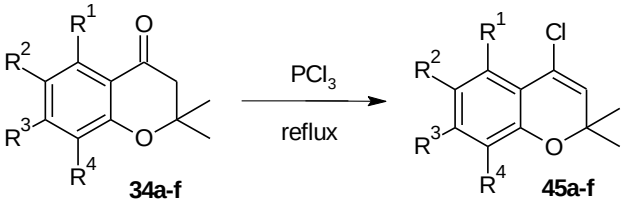


55a: R=H, Br position: 6; **55a'**: R=H, Br position: 8; **55b**: R=6-MeO, Br position: 8; **55c**: R=8-MeO, Br position: 6; **55d**: R=5-MeO, Br position: 6,8

Scheme 17.

5.3 Chlorination 2,2-dimethyl-4-chromanones

We extended the procedure of Eszenyi *et al.*[59] to prepare different alkoxy derivatives of 4-chloro-2,2-dimethyl-2*H*-chromenes **45** because it provides simple reaction conditions in line with the industrial requirements (originally 7-alkyloxy, cyclopentane <spiro-2> and cyclohexane <spiro-2> derivatives were prepared). The target compounds were obtained with moderate to good yields.



Scheme 18.

4-chloro-2,2-dimethyl-2*H*-chromenes having electron-withdrawing groups on their aromatic rings (**45a-c**) are stable against acidic hydrolysis during the work-up procedure (pouring the reaction mixture onto crushed ice).

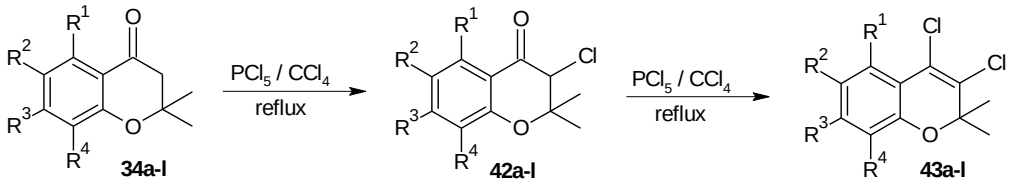
Meanwhile (**45d-f**) with electron-donating group on their aromatic rings undergo fast hydrolysis to the corresponding 4-chromanones which are reflected in their lower yields.

New compounds prepared: **45a-f**

Code	R^1	R^2	R^3	R^4	Reaction time (h)	Yield (%)
45a	H	Cl	MeO	H	12	63
45b	H	Cl	EtO	H	10	72
45c	H	Cl	PropargylO	H	8	75
45d	H	EtO	MeO	H	11	60
45e	H	MeO	EtO	H	10	33
45f	H	MeO	MeO	H	11	27

Table 3. Preparation of alkoxy-4-chloro-2,2-dimethyl-2*H*-chromenes

Alkoxy- 3,4-dichloro-2,2-dimethyl-2*H*-chromenes were prepared by the reaction of 2,2-dimethyl-4-chromanones (**34**) with two mol equivalents of phosphorus pentachloride.[60]



Scheme 19.

Typical reaction time: 8 h at 25°C; **42** as intermedier were not detectable during the procedure. New compounds prepared: **43b-f, h-l**

Code	R^1	R^2	R^3	R^4	Reaction time (h)	Yield (%)
43a	H	H	MeO	H	8	75
43b	H	H	EtO	H	8	69
43c	H	H	*n*-PrO	H	6	74
43d	H	H	*i*-PrO	H	8	70
43e	H	H	*i*-BuO	H	10	65
43f	H	H	PropargylO	H	8	58
43g	H	MeO	MeO	H	12	70
43h	H	H	MeO	MeO	7	60
43i	MeO	Cl[#]	MeO	H	12	30
43j	H	MeO	EtO	H	8	78
43k	H	EtO	MeO	H	8	76
45l	H	H	MeO	Me	7	82

Table 4. Preparation of alkoxy-3,4-dichloro-2,2-dimethyl-2*H*-chromenes

#: 3,4, 6 or 8-dichloro-2,2-dimethyl-2*H*-chromenes was isolated; on the basis of ^{1}H-NMR data the position of Cl on the aromatic ring could not be decided.

In the next phase of our research project another set of 3,4-dichloro-2,2-dimethyl-2*H*-chromenes **43** were needed for the syntheses of target compounds with insecticidal activity.[79] The reaction of 7-methoxy- 2,2-dimethyl-4-chromanones and PCl_5

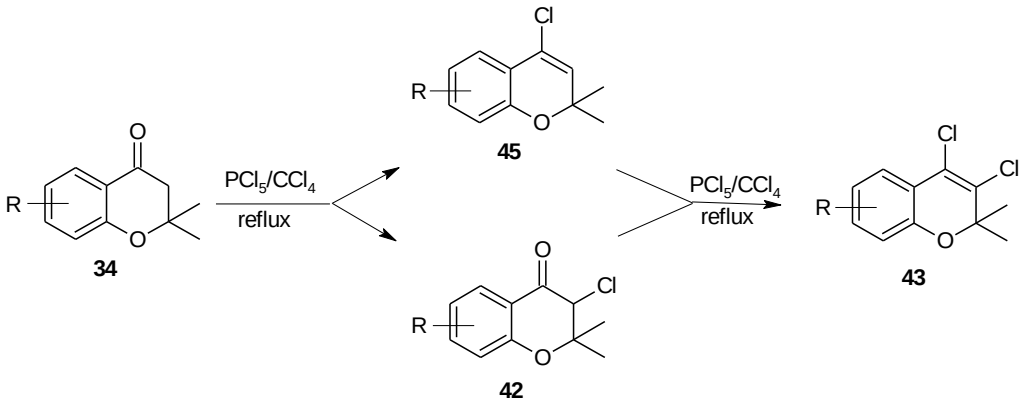
was reinvestigated. The product distributions for the reactions of several acetoxy derivatives of 2,2-dimethyl-4-chromanones and PCl_5 were studied to confirm an extended pathway.[80]

We attempted the preparation of (**43a**) according to the literature procedure[60] (4h reflux in CCl_4 using a *1:1* (**34a**) and PCl_5 molar ratio). We obtained 14% of (**45a**) and 54% of (**43a**) after TLC mesh chromatography[81]. Compound (**43a**) was earlier described as a homogenous oil. We obtained it as pale yellow crystals from n-hexane (m.p. 34-35 ^{o}C).

This result was unexpected because it was reported[60] that under these conditions only (**43a**) had been prepared in excellent (98%) yield and no conditions had been

found which led to the formation of the corresponding 4-chloro-2*H*-chromene (**45a**). When we repeated the experiment using *1:1.5* (**34a**) and PCl_5 molar ratio 7% of (**45a**) and 60% of (**43a**) were obtained after chromatography. Applying *1:3* (**34a**) and PCl_5 molar ratio the reaction mixture did not contain any chlorochromene (**45a)**.

According to the procedure published by Camps and co-workers[58] we repeated the preparation of (**43a**) using *1:2* (**34a**) and PCl_5 molar ratio (4h in CCl_4 at room temperature). We got practically the expected result but a small amount of (**45a**) was detected by TLC from the reaction mixture (compared to an authentic sample[59]). These results suggest that, both the formation of 4-chloro-2*H*-chromenes **45** followed by their futher chlorination at C-3 and the formation of 3-chloro-2,2-dimethyl-4-chromanones **42** are involved as pathways in this reaction.[58]



Scheme 20.

To prove this assumption we made a control experiment. 4-chloro-2*H*-chromene (**45a**) was quantitatively converted into (**43a**) using *1:1* and PCl_5 molar ratio (4h reflux in CCl_4).Thus, we have confirmed both the original pathway (*via* **42**) suggested by Camps *et al.*[58] and the extended one (*via* **45**) outlined in the Scheme 20. are in operation as an extension. The product-distribution for the reactions between different acetoxy derivatives of 2,2-dimethyl-4-chromanones (**34m-q**) and PCl_5 was also investigated. The results are referred in the Table 5.
New compounds prepared: **45m-q, 42m-q, 43m-q**

R	Starting chromanone	Products, yield (%)					
7-MeO	**34a**	**45g**	4	**42a**	3	**43a**	83
7-AcO	**34m**	**45m**	7	**42m**	35	**43m**	50
7,8-di-AcO	**34n**	**45n**	57	**42n**	11	**43n**	19
7-AcO, 6-*t*Bu	**34o**	**45o**	23	**42o**	39	**43o**	29
6-AcO, 7-*i*PrO	**34p**	**45p**	4	**42p**	6	**43p**	80
6-AcO, 7-MeO	**34q**	**45q**	5	**42q**	4	**43q**	75

Table 5. Preparation of different acetoxy derivatives of 2,2-dimethyl-4-chromanones

Table 5. shows that the acetoxy-substituent at different positions on the aromatic ring has remarkable influence on the product-distribution. From this observation one can synthesize such acetoxy derivates of 4-chloro-2*H*-chromenes (**45**) which are difficult to be prepared by the method (using PCl_3) described earlier.[59] It is important to note, that these chloro-benzopyran derivatives (**45, 42** and **43**) are versatile intermediates for a wide variety of further transformations in the field of benzopyranoid chemistry.[82, 83, 84, 85]

5.4 Synthesis of 1,2,3-selenadiazolo-benzopyran derivatives from 2,2-dimethyl-4-chromanones

As a continuation of the previous work on the chromenes with modified $\Delta^{3,4}$ double bond our goal was to prepare a set of selenium-containing derivatives of 2,2-dimethyl-2*H*-chromenes with similarly modified $\Delta^{3,4}$ double bonds. Recently, selenium containing heterocyclic compounds received considerable attention because they exhibit various biological activities such as anti-inflammatory agents, immunomodifiers, cytokine inducers, enzyme inhibitors and virucides.[76,77]

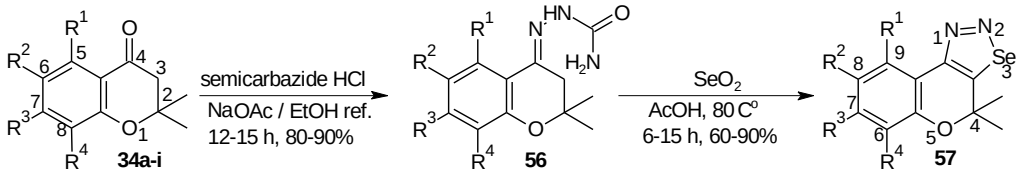
We chose Lalezari's method method[64] to prepare the new 1,2,3-selenadiazolo annellated benzopyran derivatives (Scheme 21). The synthesis and the detailed characterization of 4,4-dimethylchromeno[4,3-d]selenadiazole derivatives **58** representing a new ring system yield are reported.[86,87]

Our synthesis started from various 4-chromanones **34** which were prepared in our laboratory by the reaction of substituted phenol **3** with 3-methylbut-2-enoic acid (**33**).[52]

First, 4-chromanones **34** were converted into their corresponding semicarbazones **56** by a traditional method and then cyclized into 1,2,3-selenadiazole derivatives **57** by oxidative ring closure with equimolar amount of selenium dioxide under acidic conditions and elevated temperature. Due to the high efficiency of the reaction the crude products could be purified by simple crystallization. The characteristics of the two-step synthesis are shown by Scheme 21 and Table 6. Selenadiazoles could be characterized by their spectral data. It is noteworthy their MS spectra in all cases showed two typical fragmentation pathways. In the first pathway loss of a nitrogen molecule followed the splitting of a methyl group took place while loss of a N_2Se unit followed the splitting of a methyl group could also be observed.

We found this pathway very useful for the preparation of new derivatives with biological activity (see in Part 6.1).

New compounds prepared: **56a-i**, **57a-i**



Scheme 21.

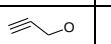
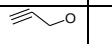
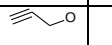
Starting chromanone	R^1	R^2	R^3	R^4	Semicarbazone	Reaction time (h)	Yield (%)	Selenodiazole	Reaction time (h)	Yield (%)
34a	H	H	MeO	H	**56a**	16	87	**57a**	13	68
34b	H	MeO	MeO	H	**56b**	15	89	**57b**	8	57
34c	H	H	MeO	MeO	**56c**	15	84	**57c**	10	60
34d	Me	H	MeO	H	**56d**	18	81	**57d**	11	56
34e	H	H	MeO	Me	**56e**	16	83	**57e**	7	62
34f	H			H	**56f**	18	88	**57f**	6	52
34g	H	H		H	**56g**	17	91	**57g**	15	87
34h	H	MeO	EtO	H	**56h**	16	85	**57h**	10	80
34i	H	EtO	MeO	H	**56i**	18	90	**57i**	11	72

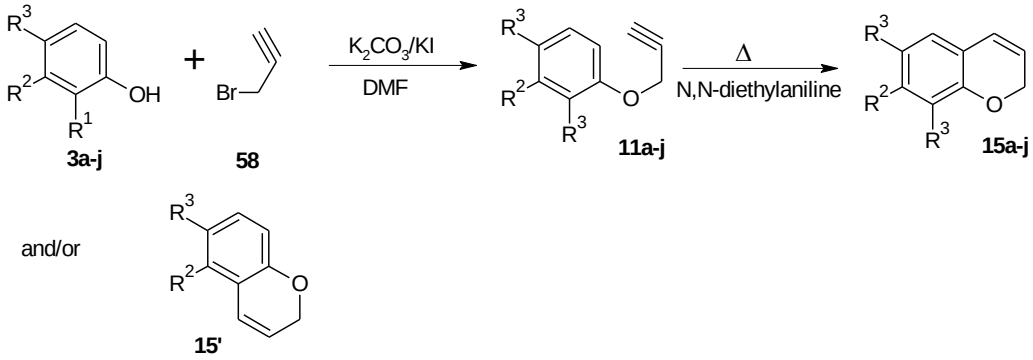
Table 6. Reaction times and yields for the preparation of semicarbazones **56** from the corresponding 4-chromanones **34**
Reaction times and yields for preparation of 4,4-dimethyl-chromeno [4,3-d]selenadiazoles **57** from the corresponding semicarbazones;

5.5 Preparation and thermal cyclization of aryl propargyl ethers

Aryl propargyl ethers were prepared from substituted phenols by Williamson ether synthesis[88,89] (WES) then they were refluxed in a solvent of high boiling point to afford the corresponding 2*H*-chromenes.

In the first part of our work we synthesized such derivatives of 2*H*-chromenes where position C-2 were unsubstituted. The reasons for this were twofold: we intended to study thermal cyclization reactions with wider scope and to obtain control compounds.[90]

The substituted phenols were reacted with propargyl bromide in the presence of K_2CO_3 in DMF at 80 °C to yield aryl propargyl ethers which underwent thermal cyclization in refluxing N,N-diethylaniline.



Scheme 22.

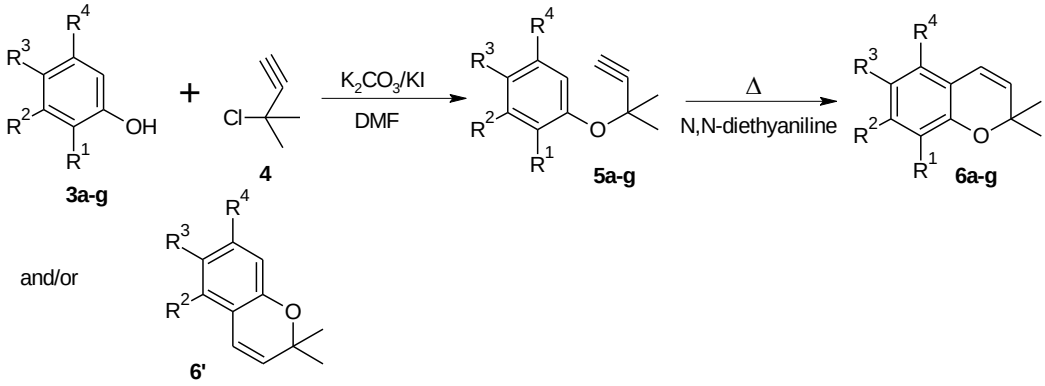
Results are summarized in Table 7. New compound: **15h, 15i-i',15j**

Entry	Starting ether	R^1	R^2	R^3	Product	Reaction time (h)	Yield (%)	Isomeric ratio[a]
1	**11a**	H	H	H	**15a**	13	63	-
2	**11b**	MeO	H	H	**15b**	13	49	-
3	**11c**	H	MeO	H	**15c+15c'**	4	70	58:42
4	**11d**	H	H	MeO	**15d**	12	79	-
5	**11e**	Me	H	H	**15e**	12	69	-
6	**11f**	H	Me	H	**15f+15f'**	5	60	67:33
7	**11g**	H	H	Me	**15g**	13	58	-
8	**11h**	Cl	H	H	**15h**	12	79	-
9	**11i**	H	Cl	H	**15i+15i'**	7	74	70:30
10	**11j**	H	H	Cl	**15j**	9	68	-

Table 7. Preparation of 2*H*-chromene derivatives by thermal cyclization of the corresponding aryl-propargyl ethers ([a]:regioisomer ratios are based on gas chromatographic area %)

As it can be seen in Table 7. the cyclization of the meta-substituted aryl-propargyl ethers **11** yielded a mixture of the corresponding 5- and 7- substituted - 2*H*-chromenes as the ring-closure can take place in two different positions. According to the GC measurement the major isomer was the 5- substituted product, *i.e.* preferred ring-closure position was sterically more hindered (the products were separated and their structure were deternined by NMR spectroscopy). This finding is in agreement with the results of Anderson *et al.* [31] and in contrast with the findings Hlubucek, *et al*. as discussed in the literature review.[34]

Similarly to the conditions used in the preparation of 2*H*-chromene derivatives **15** substituted phenols **3** were reacted with 3-chloro-3-methylbut-1-yne and the products **5** were submitted to thermal cyclization in refluxing N,N-diethylaniline to give the desired 2,2-dimethyl-2*H*-chromenes **6**.



Scheme 23.

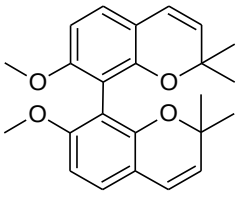
Results are summarized in Table 8. New compound: **6f**

Entry	Starting ether	R^1	R^2	R^3	R^4	Product	Reaction time (h)	Yield (%)	Isomeric ratio[a]
1	**5a**	H	MeO	H	H	**6a+6a'**	0.5	87	69:31
2	**5b**	H	H	MeO	H	**6b**	1.0	65	-
3	**5c**	MeO	H	H	H	**6c**	1.0	65	-
4	**5d**	H	H	Me	H	**6d**	1.0	70	-
5	**5e**	H	H	Cl	H	**6e**	0.5	77	-
6	**5f**	Cl	H	Cl	Cl	**6f**	1.0	71	-
7	**5g**	H	NO_2	H	H	**6g+6g'**	0.5	82	63:27

Table 8. Preparation of 2,2-dimethyl-2*H*-chromene derivatives by thermal cyclization of the corresponding aryl-propargyl ethers ([a]:regioisomer ratios are based on gas chromatographic area %)

As it can be seen in Table 8. the cyclization of the meta- substituted aryl-propargyl ethers (**5a,g**) proceeded to yield 5- substituted 2,2-dimethyl-2*H*-chromenes (**6a,g**) with high isomeric ratios similar to our findings presented earlier (similar regioslectivity occurs at Claisen-rearrangement of allyl ethers). Again,there is a discrepancy between our results and the findings of Hlubucek, *et al*.[34] They reported that the cyclization of meta-substitued aryl-propargyl ether (**5a**) proceeded in a 'regioselective fashion' to yield (**6b**). Anderson *et al*.[35] found that the cyclization of (**5a**) afforded a mixture of (**6a**) and (**6b**) in approximately equal amounts.

Beside (**6a,b**) we observed the formation of a minor product below (**60**, new compound) with 4% yield and its structure was elucidated NMR spectroscopic methods.



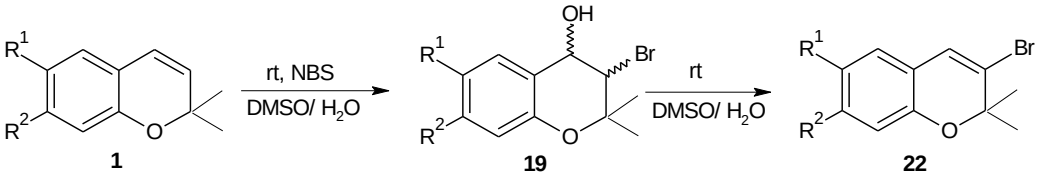
59

Figure 14.

Similar 8,8-bis(6-methoxy-2,2-dimethyl-2H-chromene was isolated from *Lactarius fuliginosus* and *L. picinus*.[91]

5.6 Reaction of 2,2-dimethyl-2H-chromenes with *N*-bromosuccinimide (NBS)

To prepare 3-bromo derivatives **22** we investigated the reactions of various 2*H*-chromenes (P1, P2, P3) with NBS[24] in DMSO-water mixture (5:1 molar ratio). The reactions were conducted at room temperature and the multicomponent reaction mixture was separated using column chromatography.



Scheme 24.

Entry	Starting precocene	R^1	R^2	Product: bromohydrin	Isolated yield (%)	Product: 3-bromo-chromene	Isolated yield (%)	R^1	R^2
1	**1a** (P1)	H	MeO	**19a**	80	**22a**	10	H	MeO
				19a'	52	**22a'**	-	Br	MeO
2	**1b** (P2)	MeO	MeO	**19b**	85	**22b**	-	MeO	MeO
3	**1c** (P3)	Meo	EtO	**19c**	76	**22c**	-	Meo	EtO

Table 9. Reaction of various precocenes with NBS

Findings:

Reaction of P1 (**1a**) with 1 equivalent NBS gave (**19a**) with 80% yield which converted to (**22a**) on standing. Reaction of P1 (**1a**) with 2 equivalent NBS gave a two component reaction mixture (**19a**:**19a'**) = 1:2 (estimated on the basis of ^{1}H-NMR spectrum;

electron-rich aromatic compounds can be also brominated with NBS). The compound (**19a**) could not be separated by column chromatography; we obtained (**22a**, 10%) and (**19a'**, 52%) instead. **19a'** converted to **22a'** on standing.

Reaction of P2 (**1b**) with molequivalent NBS gave (**19b**) with 85% yield (1h, at room temperature) which converted to (**22b**) on standing. Reaction of P2 (**1b**) with 2 equivalent NBS gave ca. 1:1 mixture of (**19b**) and (**22b**) which could not be separated by column chromatography because during the separation (**19b →22b**) conversion occurred.

Reaction of P3 (**1c**) with equivalent NBS gave (**19c**) with 76% yield which did not convert to (**22c**) on standing due to the higher electron-density at C-4.

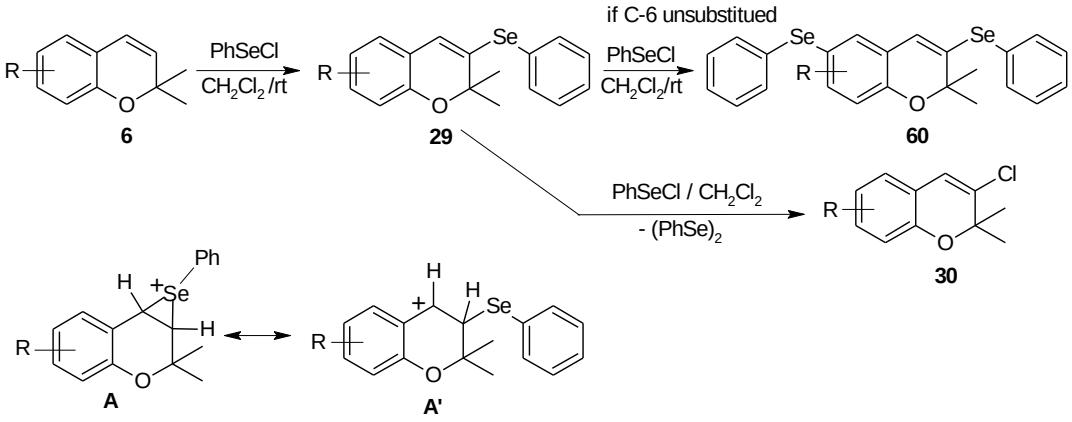
5.7 Reaction of 2,2-dimethyl-2H-chromenes with phenylselenyl chloride

We utilized the reaction of 2,2-dimethyl-2*H*-chromenes with phenylselenyl chloride to prepare phenylselenyl derivatives of 2,2-dimethyl-*2H*-chromenes and derivatives of 3-chloro-2,2-dimethyl-*2H*-chromenes.[87]

Instead of the desired 4-chloro-2,2-dimethyl-3-phenylselenyl-2*H*-benzopyrans, 2,2-dimethyl-3-phenylselenyl-2*H*-benzopyrans **29** were obtained in moderate-to-good yields (Scheme 25, Table 11) in line with our preliminary experiments which have been published earlier[Wagner, 1989] without synthetic details, yields and spectral data.

The formation of derivatives **29** can be rationalized on the basis of a proton-loss from the stable benzyl-type carbocation **A**' instead of the attack of the chloride ion. The carbocation **A**' is formed in the first step of the reaction *via* electrophilic attack of the phenylselenyl group. (The conjugation between the re-formed double bond and the aromatic system could be the driving force of this unusual reaction. However, secondary products could be isolated from the reaction mixture even with short reaction period (Table 10). 3-Chloro-2,2-dimethyl-2*H*-benzopyrans **30** formed in each cases. With higher reaction time this species became the major product (Table 10) which clearly

shows the intermediacy of 3-phenylselenyl-2,2-dimethyl-2*H*-benzopyrans **29**. Probably a second phenylselenyl chloride molecule attacks the primary product **29** leading to the formation of the stable diphenyl diselenide and 3-chloro derivatives **30**. We confirmed this sequence in a control experiment treating **29b** with 1 equivalent of phenylselenyl chloride (4h, room temperature) obtaining **30b** and diphenyl diselenide in almost quantitative yield. To our best knowledge this is the only synthetically useful method of the synthesis of 3-chloro-2,2-dimethyl-2*H*-benzopyrans **11**. These 3-chloro derivatives may be useful building blocks for substitutions or cross-coupling reactions.



6,29,30,60	R
a	7-MeO
b	6,7-di-MeO
c	7,8-di-MeO
d	7-EtO, 6- MeO

Scheme 25.

The starting chromenes (**6**) were prepared in our laboratory using the method of dehydration of 2,2-dimethyl-4-hydroxychromans.[25] P1 'analogues: **29a**, **60a** and **30a**; P2 'analogues: **29b**, **60b** and **30b**; P3 'analogues: **29d**, **60d** and **30d**.

Starting material	Yield[a] (%)					
	29		**60**		**30**	
	1 h	5 h	1 h	5 h	1 h	5 h
6a	50	10	12	6	10	42
6b	68	21	0	0	28	60
6c	62	20	7	4	14	56
6d	65	25	0	0	22	58

Table 10. Time-dependent product ratios in the reaction of 2,2-dimethyl-2*H*-benzopyrans **6** with phenylselenyl chloride; [a] Yields refer to pure isolated products

In addition, a second phenylselenylation was observed in the lack of substituent in position 6 to give bis(phenylselenyl) products **60** being formed in an electrophilic substitution reaction by phenylselenyl chloride. This is a relatively slow reaction and should be reversible since the amount of products **30a**,**c** decreases at longer reaction period.

In conclusion, we synthetized new 2,2-dimethyl-2*H*-benzopyran derivatives having considerable insecticide effect and developed a new and efficient method for the preparation of 3-chloro-2,2-dimethyl-2*H*-benzopyrans.

In that way we completed our chloro derivative series:

- ✓ 3,4-dichloro-2,2-dimethyl-2*H*-chromenes **43**
- ✓ 4-chloro-2,2-dimethyl-2*H*-chromenes **45**
- ✓ 3-chloro-2,2-dimethyl-*2H*-chromenes **30**

5.8 TLC Mesh Column Chromatography: Facile Combination of Vacuum-Driven and

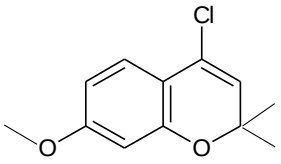
Low-Pressure Methods

Due to the constant need in synthetic organic chemistry to separate mixtures of small or large quantities with the best possible result, common column chromatographic methods have been significantly improved in the last two decades. A column

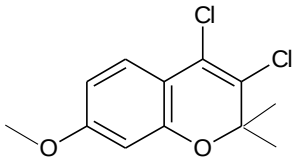
chromatographic method can be characterized from a practical point of view with the following requirements: resolution, time needed for the separation, cost of the system, and convenience. TLC mesh column chromatography[72] (vacuum or low pressure driven) has very good resolution and the time needed for the separation is not long. The system is inexpensive, but in the case of vacuum-driven method manipulation of the eluate is rather difficult and the maximum pressure differential (1 bar) between the top and the bottom of the column limits the variability of the flow rates. In the case of the low-pressure method the packing and compacting of the bed and the application of the sample are inconvenient and in some cases the expulsion of air is not sufficient.[71]

We developed a combined TLC mesh column chromatographic system[81] which unifies the advantages of the vacuum-driven and low-pressure methods and can be considered as an improvement of Taber's method. The first part of the chromatography, from packing until the solvent front has reached the bottom of the bed, is conducted under vacuum. Here we utilize the advantage of the vacuum-driven method where any manipulation at the top of the column can be achieved at will because it is at atmospheric pressure (first part in Figure 17). Then the vacuum is broken and pressure is applied to the top of the column. In that part of the separation eluate manipulation can be easily done because the bottom of the bed is at atmospheric pressure (second part in Figure 17). These modifications make our method efficient and convenient to use. Our procedure was found to be efficient for separations of mixtures showing $\Delta Rf \geq 0.05$ by TLC. In comparison with Taber's low-pressure method[72] we achieved the same or better separation. To test the system on a preparative scale, 1 g of a 1:l mixture of 4-chloro-7-methoxy-2,2-dimethyl-2*H*-chromene (**45a**) and 3,4-dichloro-7-methoxy-2,2-dimethyl-2*H*-chromene (**43a**) (Figure 15) ΔRf = 0.06 by TLC) was quantitatively separated on 50 g of silica gel using 1,2-dichloroethane-hexane (1:8) as eluent.

Parameters: Column diameter = 35 mm, height/ diameter = 4.6, fraction volume = 25 mL, number of fractions = 29. **43a** appeared in fractions nos. 9-14 (495 mg) and **45a** in fractions nos. 17-23 (491 mg). In fraction nos. 15-16 no material was detected by TLC. Time of the separation = 45 min.



45a



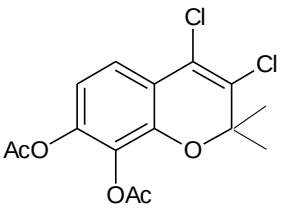
43a

Figure 15.

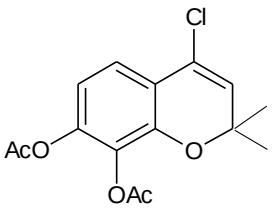
no.	column internal diameter (mm)	mass of silica gel (g)	height of the bed (mm)	sample size (g)	fraction voulme (mL)	
					manual collecting	automatic collecting
1	15	5,1	90	0.10	5	5
2	25	23,6	150	0.47	20	20
3	35	64,6	210	1,30	50	25
4	45	135,0	270	2,70	120	25

Table 12. Typical Parameters Where Height/Diameter Ratio = 6 and the Mass of the Gel/Mass of the Sample = 50; no.= numbering of entries; composition of sample= 1:l mixture of 7,8-diacetoxy-3,4-dichloro-2,2-dimethyl-2*H*–chromene (**43n**) and 7,8-diacetoxy-4-chloro-2,2-dimethyl-2*H*–chromene (**45n**)

To compare our method with Taber's low-pressure method, 1.3 g of a 1:l mixture of 7,8-diacetoxy-3,4-dichloro-2,2-dimethyl-2*H*–chromene (**43n**) and 7,8-diacetoxy-4-chloro-2,2-dimethyl-2*H*–chromene (**45n**) (*Δ Rf* = 0.05 by TLC) was separated by both methods using 1,2-dichloroethane- hexane (1:3) as eluent and silica gel.



43n



45n

Figure 16.

For parameters see Table 12. no. 3. In both cases quantitative separation was achieved. In the course of our work we improved Taber's low-pressure method, making it more practical and convenient to use and possessing the same resolution and recovery factor. Typically we use our combined method for separations of 3-4 component mixtures with little differences in their *Rf* values (analogues). Yields given in the dissertation are isolated yields.

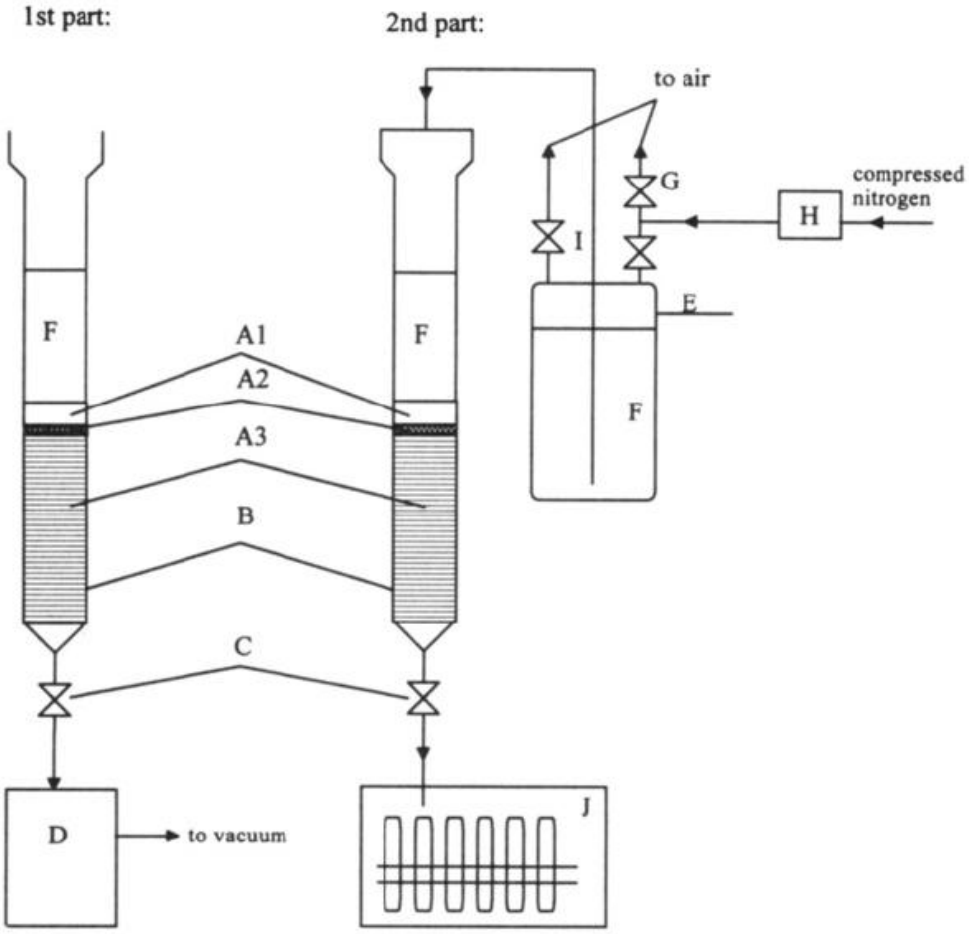


Figure 17. The apparatus and some specifications: A_1, sand layer; A_2, preadsorbent layer; A_3 sorbent; B, column; C, column isolation stopcock; D, collecting vessel (for the eluent); E, eluent reservoir; F, eluent; G, relief valve; H, three-stage regulator; I, relief stopcock; J, automatic fraction collector.

6. Biological results

6.1 Non-specific toxic activities of 1,2,3-selenadiazolo derivatives of P1 and P2

Selected compounds of **57** were tested for non-specific toxic activities on *P. brassicae* and *L. decemlineata* larvae in a comparative study. 1,2,3-selenadiazolo derivatives of P1 and P2 were more effective on insect larvae than P1, P2, respectively.[79] (3,4-Dichloro-2,2-dimethyl-2*H*-chromenes **43** were also tested in this study showing similar superior effects.)

	LD_{90} (nmol/larva)	
Compounds	*P. brassicae*	*L. decemlineata*
1a (P1)	389	525
57a	*37*	*54*
1b (P2)	234	148
57b	*62*	*34*

Table 13. 4,4-Dimethyl-chromeno[4,3-d]selenadiazoles **57** with significantly lower LD_{90} in comparison with the corresponding reference precocenes (P1, P2)

This finding clearly shows the pertinence of our working hypothesis on the role of an annelated ring system in the insecticide effect.

6.2 Challenging 'dogma' in stucture-activity model for Cromakalim analogues

Several hundreds of Cromakalim analogues were sythesized in our laboratories and were tested by our in-house biological screening. It was found that the 6,7 dimethoxy Cromakalim analougue (see Figure 18) had the most effective blood-pressure lowering effect among the analogues synthesized according to our in-house biological screening.

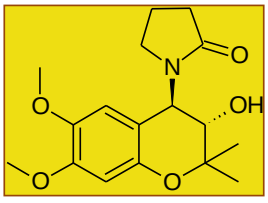
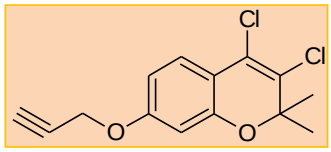


Figure 18. 6,7- dimethoxy analogue of Cromakalim

According the pharmacophoric model for hypotensive activity of Cromakalim series the molecule should contain an electron-withrawing group at C-6.[19] Our finding had challenged that prevailing structure-activity 'dogma'.

6.3 Exploitation of the results

3,4-Dichloro-7-propargyloxy-2,2-dimethyl-2*H* -chromene (**43f**), our lead compound among the derivatives of 3,4,-dichloro-2,2-dimethyl-2*H* -chromene showed synergistic effect when used in conjuction with certain pyrethroid insecticides (Figure 19) .



43f

Figure 19.

Chinoin Inc. bought the patent[92] and manufactured that compound; it had been in commercial use for ten years.

7. Experimental

Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. Thin layer chromatography was carried out on silica gel plates (E.M. Science 5554, Kieselgel $60F_{254}$). For column chromatography MN-Kieselgel (40-63μm) was used. Solvents were used either as purchased or dried and purified by standard methodologies. ^{1}H-NMR and ^{13}C -NMR spectra were recorded with a Bruker AM 360 (360 MHz for 1H; 90 MHz for ^{13}C nuclei) spectrometer (A) in $CDCl_3$ solution or in deuterated dimethyl sulfoxide unless otherwise specified (internal standard TMS, 0.00 ppm or residual peaks $CHCl_3$ (delta = 7.26 ppm) for ^{1}H -NMR and (delta = 77.00) for ^{13}C -NMR) or with Varian Gemini-200 (B) or with Bruker-Avance 500 (C) instruments. MS data were obtained on a VG TRIO-2 mass spectrometer in EI mode at 70 eV. ESI-MS spectrum were taken by a MS-03 Micromass Quattro LC instrument. IR spectra were recorded with Perkin-Elmer 16 PC-FT-IR (D) or Nicolet Nexus 670 FT-IR (E) instruments in KBr disks. Microanalyses were performed by Laboratory of Organic Analysis of University of Debrecen.

7.1 TLC Mesh Column Chromatography: Facile Combination of Vacuum-Driven and

Low-Pressure Methods

First Part: Column packing.

Single portion, vacuum dry-pack method is used.[75] The sorbent is poured into the column and allowed to settle by gravity. MN-Kieselgel N-HR purchased from Macherey Nagel Co. (Germany) was used for the separation of 4-chloro-7-methoxy-2,2-dimethyl-2*H*-chromene (**45a**) and 3,4-dichloro-7-methoxy-2,2-dimethyl-2*H*-chromene (**43a**) and TLC Silica gel 60H (mean particle size 15 μm) purchased from E. Merck, was used for the separation of 7,8-diacetoxy-3,4-dichloro-2,2-dimethyl-2*H*–chromene (**43n**) and 7,8-diacetoxy-4-chloro-2,2-dimethyl-2*H*–chromene (**45n**), respectively. Manual tapping helps to eliminate the major air pockets.

Vacuum was applied (Figure 1) to the column by opening the stopcock (C) to compact the sorbent. Its total compression was approximately 30 % by volume. Then the stopcock (C) is closed.

Sample Application

The solution of the mixture to be separated is slurried with coarse silica gel (Silica gel 60; 60-200μm; purchased E. Merck) and the solvent removed under vacuum. This dry gel is applied to the top of the column to make an even layer. Subsequently the top is covered with a layer of sand to at least 1-in. depth.

Elution

The first part of the elution is performed under vacuum (we use the central vacuum system in our laboratory; 20-80 mmHg) that s applied to the system until the eluent front has passed through the length of the bed and a few mLs of eluent has been collected. Then the stopcock (C) is closed and the vacuum is released. The collecting vessel is removed (D).

Second Part:

The fraction collector (J) is connected to the end of the column and a screw-thread connector is secured to the top. The connection between the connector and the eluent reservoir is a flexible metal tube. The reservoir (E) is then pressurized and the stopcock **(C)** is opened; the elution is continued. (We used compressed nitrogen reduced by three-stage regulator to 1-2.5 bar. Although we have run many separations without any difficulty, glass columns coated with transparent adhesive tape are recommended for safety reasons.) The change over takes no more than 1-2 min.

7.2 Bromination and debromination of alkoxy- 2,2-dimethyl-4-chromanone derivatives

a) 10 mmol alkoxy-2,2-dimethyl-4-chromanones **44** were dissolved in 100 mL carbon tetrachloride and treated dropwise with 5.6 g bromine (1.8 mL, 35 mmol) in 100 mL carbon tetrachloride at room temperature. The resultant solution was allowed to stand overnight. The solution was then filtered through a short column of alumina and the solvent was removed *in vacuo*. Column chromatography of the resultant red gummy residue on silica gel using benzene as eluent afforded the corresponding tribromo-4-chromanones **47** (see yields in Table 1).

b) 2.5 mmol tribromo-4-chromanones **47** were dissolved in 30 mL tetrahydrofuran then an excess of zinc powder (0.7 g, 10.7 mmol), 0.2 mL glacial acetic acid and 0.2 mL water were added. The reaction mixture was stirred at room temperature until its completion. The solvents were removed and residue was purified by column chromatography using benzene as eluent to give chromanones with bromo substituent(s) in the aromatic ring **48** (see yields in Table 2)

3,3,6-Tribromo-7-methoxy-2,2-dimethyl-4-chromanone (47a)

mp: 160-161 ^{o}C (benzene); lit. mp: 161-162 ^{o}C (chloroform-light-petroleum) [60]

Anal. calcd. for $C_{12}H_{11}Br_3O_3$ (M=442.96): C 32.53, H 2.65, Br 54.12 found: C 32.50, H 2.63, Br 54.33

^{1}H-NMR ($CDCl_3$) (B): δ 1.30-2.20 (6H, b), 3.92 (3H, s), 6.45 (1H, s), 8.15 (1H, s) [60] (in line with the literature data)

3,3,8- Tribromo-7-methoxy-2,2-dimethyl-4-chromanone (47a')

mp: 146-147 ^{o}C (benzene)

Anal. calcd. for $C_{12}H_{11}Br_3O_3$ (M=442.96): C 32.53, H 2.650, Br 54.12 found: C 32.61, H 2.43, Br 54.28

^{1}H-NMR ($CDCl_3$) (B): δ 1.40-2.10 (6H, b), 4.00 (3H, s), 6.75 (1H, d, J=8), 8.00 (1H, d, J=8)

3,3,8-Tribromo-6,7-dimethoxy-2,2-dimethyl-4-chromanone (**47b**)

mp: 94-96 ^{o}C (benzene)

Anal. calcd. for $C_{13}H_{13}Br_3O_4$ (M=472.97): C 33.01, H 2.76, Br 50.69 found: C 33.13, H 2.86, Br 51.20

^{1}H-NMR ($CDCl_3$) (B): δ 1.50-2.10 (6H, b), 3.90 (3H, s), 4.00 (3H, s), 7.45 (1H, s)

3,3,6-Tribromo-6,8-dimethoxy-2,2-dimethyl-4-chromanone (**47c**)

mp: 110-112 ^{o}C (benzene)

Anal. calcd. for $C_{13}H_{13}Br_3O_4$ (M=472.97): C 33.01, H 2.76, Br 50.69 found: C 33.12, H 2.88, Br 51.10

^{1}H-NMR ($CDCl_3$) (B): δ 1.50-2.20 (6H, b), 3.90 (3H, s), 4.05 (3H, s), 7.95 (1H, s)

3,3,6,8-Tetrabromo-5,7-dimethoxy-2,2-dimethyl-4-chromanone (**47d**)

mp: 135-137 ^{o}C (benzene)

Anal. calcd. for $C_{13}H_{12}Br_4O_4$ (M=551.88): C 28.29, H 2.19, Br 57.92 found: C 28.35, H 2.30, Br 58.27

^{1}H-NMR ($CDCl_3$) (B): δ 1.60-1.80 (6H, b), 3.80 (3H, s), 3.90 (3H, s)

6-Bromo-7-methoxy-2,2-dimethyl-4-chromanone (**48a**)

mp: 96-98 ^{o}C (benzene); lit. mp: 98 ^{o}C[60]

Anal. calcd. for $C_{12}H_{13}BrO_3$ (M=285.13): C 50.54, H 4.59, Br 28.02 found: C 50.77, H 4.63, Br 28.20

^{1}H-NMR (DMSO-d_6) (B): δ 1.42 (6H, s), 2.70 (2H, s), 3.70 (3H, s), 6.70 (1H, s), 7.90 (1H,s)

8- Bromo-7-methoxy-2,2-dimethyl-4-chromanone (**48a'**)

mp: 92-94 ^{o}C (benzene)

Anal. calcd. for $C_{12}H_{13}BrO_3$ (M=285.13): C 50.54, H 4.59, Br 28.02 found: C 50.66, H 4.71, Br 28.23

^{1}H-NMR ($CDCl_3$) (B): δ 1.50 (6H, s), 2.71 (2H, s), 3.95 (3H, s), 6.60 (1H, d, J=8), 7.8 (1H,d, J=8)

8-Bromo-6,7-dimethoxy-2,2-dimethyl-4-chromanone (**48b**)

mp: 86-89 ^{o}C (benzene)

Anal. calcd. for $C_{13}H_{15}BrO_4$ (M=315.16): C 49.53, H 4.79, Br 25.35 found: C 49.44, H 4.85, Br 25.70

^{1}H-NMR ($CDCl_3$) (B): δ 1.50 (6H, s), 2.70 (2H, s), 3.88 (3H, s), 3.94 (3H, s), 7.35 (1H,s)

6- Bromo-7,8-dimethoxy-2,2-dimethyl-4-chromanone (**48c**)

mp: 52-53 ^{o}C (benzene)

Anal. calcd. for $C_{13}H_{15}BrO_4$ (M=315.16): C 49.53, H 4.79, Br 25.35, found: C 49.59, H 4.68, Br 25.70

^{1}H-NMR ($CDCl_3$) (B): δ 1.50 (6H, s), 2.70 (2H, s), 3.90 (3H, s), 4.01 (3H, s), 7.88 (1H,s)

6,8-Dibromo-5,7-dimethoxy-2,2-dimethyl-4-chromanone (**48d**)

mp: 126-128 ^{o}C (benzene)

Anal. calcd. for $C_{13}H_{14}Br_2O_4$ (M=394.07): C 39.62, H 3.58, Br 40.56 found: C 39.71, H 3.60, Br 41.00

^{1}H-NMR ($CDCl_3$) (B): δ 1.50 (6H, s), 2.70 (2H, s), 3.90 (3H, s), 3.95 (3H,s)

7.3 Preparation of bromo derivatives of 2,2-dimethyl-2*H*-chromenes

The corresponding bromo-derivatives of alkoxy-2,2-dimethyl-4-chromanones **48** (15 mmol) was dissolved in methanol (50mL). To the stirred solution $NaBH_4$ (2.83 g; 75 mmol) was added in portions. The solvent was removed in vacuum, 50 mL of water was added and extraction was performed with dichloromethane (3x25 mL). The combined dichloromethane solution was washed with cold water (3x25 mL), dried over anhydrous sodium sulfate, filtered and evaporated in vacuum. The residue was dissolved in a solution of TsOH (75 mg in 30 mL absolute benzene) and refluxed. The reaction mixture was evaporated in vacuum onto coarse silica gel and it was subjected to TLC mesh column chromatography[81] to obtain the bromo-chromene derivatives **55** (hexane:diethyl ether = 9:1 was used as eluent).

6-Bromo-7-methoxy-2,2-dimethyl-2*H*-chromene (**55a**)

oil,

Anal. calcd. for $C_{12}H_{13}BrO_2$ (M=269.13): C 53.55, H 4.86, Br 29.69, found: C 53.50, H 4.73, Br 30.00

^{1}H-NMR ($CDCl_3$) (B): δ 1.40 (6H,s), 3.85 (3H,s), 5.50 (1H,d,J=10), 6.20 (1H,d,J=10), 6.40 (1H,s), 7.12 (1H,s)

8-Bromo-7-methoxy-2,2-dimethyl-2*H*-chromene (**55a'**)

oil,

Anal. calcd. for $C_{12}H_{13}BrO_2$ (M=269.13): C 53.55, H 4.86, Br 29.69, found: C 53.44, H 4.75, Br 30.01

8-Bromo-6,7-dimethoxy-2,2-dimethyl-2*H*-chromene (**55b**)

oil,

Anal. calcd. for $C_{12}H_{15}BrO_3$ (M=299.16): C 52.19, H 5.05, Br 26.71, found: C 52.10, H 4.94, Br 27.02

^{1}H-NMR ($CDCl_3$) (B): δ 1.46 (6H,s), 3.80 (3H,s), 5.60 (1H, d, J=10), 6.22 (1H, d, J=10), 6.55 (1H,s)

6-Bromo-7,8-dimethoxy-2,2-dimethyl-2*H*-chromene (**55c**)

oil,

Anal. calcd. for $C_{12}H_{15}BrO_3$ (M=299.16): C 52.19, H 5.05, Br 26.71, found: C 52.10, H 4.94, Br 27.02

^{1}H-NMR ($CDCl_3$) (B): δ 1.47 (6H,s), 3.90 (6H,s), 5.60 (1H, d, J=10), 6.20 (1H, d, J=10), 6.90 (1H,s)

6,8-Dibromo-5,7-dimethoxy-2,2-dimethyl-2*H*-chromene (**55d**)

oil,

Anal. calcd. for $C_{12}H_{14}Br_2O_3$ (M=378.07): C 41.29, H 3.73, Br 42.27, found: C 41.33, H 3.85, Br 42.50

^{1}H-NMR ($CDCl_3$) (B): δ 1.48 (6H,s), 3.80 (3H,s), 3.87 (3H,s), 5.65 (1H, d, J=10), 6.54 (1H, d, J=10)

7.4 Chlorination 2,2-dimethyl-4-chromanones

Reaction with PCl_3 – typical procedure:

4 mmol of the corresponding 4-chromanones **34** was refluxed in 5 mL PCl_3 until the starting material disappeared, the reaction time was 8-12 hours. The mixture was poured onto 50 grams of crushed ice; this was extracted with 3x50 mL $CHCl_3$ and the organic layer was dried over sodium sulfate. Evaporation gave colourless oil, which was purified by column chromatography giving the 4-halo-2,2-dimethyl-2*H*-chromenes **45**. These compounds must be stored cool due to their instability. (see yields in Table 3)

Reaction with PCl_5 – typical procedure:

2 mmol of chromanone **34** was refluxed in 10 mL of CCl_4 with 4 mmol PCl_5 until the starting material was consumed (1- 5h based on TLC monitoring). The mixture was poured into 50 mL cold, $KHCO_3$ solution, extracted with $CHCl_3$ and the organic layer was washed with water, dried on Na_2SO_4 and evaporated. The residue was subjected to TLC mesh column chromatography.[81] All new compounds gave statisfactory elemental microanalyses and their structures had been proved by ^{1}H-NMR and MS. (see yields in Table 4,5)

4,6-Dichloro-7-methoxy-2,2-dimethyl-2*H*-chromene (**45a**)

mp: 109-111 ^{o}C (dichloromethane)

Anal. calcd. for $C_{12}H_{12}Cl_2O_2$ (M=259.13): C 55.61, H 4.66, Cl 27.36, found: C 55.70, H 4.60, Cl 27.30

^{1}H-NMR ($CDCl_3$) (B): δ 1.45 (6H,s), 3.85 (3H, s), 5.65 (1H, s), 6.42 (1H, s), 7.40 (1H, s)

MS (m/z, %): 252 (M^+, 10), 243 (100), 228 (10), 193 (8)

4,6-Dichloro-7-ethoxy-2,2-dimethyl-2*H*-chromene (**45b**)

mp: ^{o}C 73.5-75 (dichloromethane)

Anal. calcd. for $C_{13}H_{14}Cl_2O_2$ (M=273.15): C 57.15, H 5.16, Cl 25.96 found: C 57.05 H 5.20, Cl 26.07

^{1}H-NMR ($CDCl_3$) (B): δ 1.45 (6H, s + 3H, t, J=6), 4.10 (2H, q J=6), 5.65 (1H, s), 6.40 (1H, s) 7.40 (1H, s)

MS (m/z, %): 272 (M^+, 15), 257 (75), 229 (100), 194 (10), 115 (25)

4,6-Dichloro-7-propargyloxy-2,2-dimethyl-2*H*-chromene (**45c**)

oil,

Anal. calcd. for $C_{14}H_{12}Cl_2O_2$ (M=273.15): C 59.38, H 4.27, Cl 25.04 found: C 59.29, H 4.35, Cl 25.28

^{1}H-NMR ($CDCl_3$) (B): δ 1.46 (6H, s), 2.58 (1H, t, J=2), 4.72 (2H, d J=2), 5,68 (1H, s), 7.45 (1H, s)

MS (m/z, %): 282 (M^+, 18), 267 (100), 228 (22), 200 (18), 115 (27)

4-Chloro-6-ethoxy-7-methoxy-2,2-dimethyl-2*H*-chromene (**45d**)

oil,

Anal. calcd. for $C_{14}H_{17}ClO_3$ (M=268.74): C 62.56, H: 6.37, Cl 13.19,

found: C 62.66, H 6.45, Cl 13.26

^{1}H-NMR ($CDCl_3$) (B): δ 1.45 (6H, s + 3H, t, J=6), 3.81 (3H, s), 4.08 (2H, q, J=6), 5.60 (1H, s), 6.40 (1H, s), 6.98 (1H, s)

MS (m/z, %): 268 (M+, 88), 253 (100), 225 (42), 195 (10)

4-Chloro-7-ethoxy-6-methoxy -2,2-dimethyl-2*H* -chromene (**45e**)

mp: 67-68 ^{o}C (dichloromethane)

Anal. calcd. for $C_{14}H_{17}ClO_3$ (M=268.74): C 62.56, H 6.37, Cl 13.19 found: C 62.70, H 6.31, Cl 12.93

^{1}H-NMR ($CDCl_3$) (B): δ 1.43 (6H, s), 1.49 (3H, t, J=6), 3.85 (3H, s), 4.08 (2H, q, J=6), 5.60 (1H, s), 6.40 (1H, s), 6.98 (1H, s)

MS (m/z, %):268 (M+, 24), 253 (100), 225 (60), 210 (18)

4-Chloro-6,7-dimethoxy -2,2-dimethyl-2*H*-chromene (**45f**)

mp: 55-56 ^{o}C (dichloromethane)

Anal. calcd. for $C_{13}H_{15}ClO_3$ (M=254.71): C 61.29, H 5.93, Cl 13.92, found: C 6.47, H 6.01, Cl 14.01

^{1}H-NMR ($CDCl_3$) (B): δ 1.43 (6H, s), 3.80 (3H, s), 3.83 (3H, s), 5.60 (1H, s), 6.42 (1H, s), 6.95 (1H, s)

MS (m/z, %): 254 (M+, 17), 239 (100), 223 (8), 195 (10)

4-Chloro-7-methoxy-2,2-dimethyl-2*H*-chromene (**45g**)

colorless oil,

Anal. calcd. for $C_{12}H_{13}ClO_2$ (M=224.67): C 64.15, H 5.83, Cl 15.78 found: C 64.10, H 5.90, Cl 15.86

^{1}H-NMR ($CDCl_3$) (B): δ 1.42 (6H, s), 3.76 (3H,s), 5.60 (1H, s), 6.40 (1H, d, J=2), 6.49 (1H, dd, J_1=2, J_2=9) (in line with the literature data) [60]

MS (m/z, %): 224 (M^+, 20), 209 (100), 194 (10), 166 (15)

3,4-Dichloro-7-methoxy-2,2-dimethyl-2*H*-chromene (**43a**)

pale yellow crystals (n-hexane), m.p. 34-35 °C

Anal. calcd. for $C_{12}H_{12}Cl_2O_2$ (M=259.13): C 55.61, H 4.66, Cl 27.36, found: C 55.72, H 4.52, Cl 27.40

IR (KBr): ν_{max} cm^{-1} 2980, 2920, 1610, 1500, 1440, 1360, 1280, 1200, 1150, 1115, 1030, 980, 830

^{1}H-NMR ($CDCl_3$) (B): δ 1.55 (6H, s), 3.76 (3H, s), 6.40 (1H, d, J=2), 6.50 (1H, dd, J_1=2, J_2=9), 7.31 (1H, d, J=9)

MS (m/z, %): 258 (M^+, 25), 243 (100), 223 (38)

3,4-Dichloro-7-ethoxy-2,2-dimethyl-2*H*-chromene (**43b**)

oil,

Anal. calcd. for $C_{13}H_{14}Cl_2O_2$ (M=273.15): C 57.17, H 5.16, Cl 25.96, found: C 57.33,

H 5.22, Cl 26.01

^{1}H-NMR ($CDCl_3$) (B): δ 1.41 (3H, t, J=6), 1.56 (6H, s), 4.00 (2H, q, J=6), 6.40 (1H, d, J=2), 6.50 (1H, dd, J_1=2, J_2=9), 7.32 (1H, d, J=9)

MS (m/z, %): 272 (M^+, 29), 257 (100), 229 (58), 209 (20)

3,4-Dichloro-7-*n*-propyloxy-2,2-dimethyl-2*H*-chromene (**43c**)

oil,

Anal. calcd. for $C_{14}H_{16}Cl_2O_2$ (M=287.18): C 58.54, H 5.61, Cl 24.69, found: C 58.65, H 5.72, Cl 25.00

^{1}H-NMR ($CDCl_3$) (B): δ 1.02 (3H, t, J=6), 1.55 (6H, s), 1.77 (2H, m), 3.90 (2H, t, J=6), 6.45 (1H, d, J=2), 6.55 (1H, dd, J_1=2, J_2=9), 7.35 (1H, d, J=9)

MS (m/z, %): 286 (M^+, 33), 271 (100), 251 (20), 229 (78), 209 (30)

3,4-Dichloro-7-*i*-propyloxy-2,2-dimethyl-2*H*-chromene (43d)

mp: 50-53 °C (hexane-diethyl ether)

Anal. calcd. for $C_{14}H_{16}Cl_2O_2$ (M=287.18): C 58.54, H 5.61, Cl 24.69, found C 58.46, H 5.58, Cl 24.70

^{1}H-NMR ($CDCl_3$) (B): δ 1.35 (6H, d, J=7), 1.57 (6H, s), 4.52 (1H, m), 6.40 (1H, d, J=2), 6.50 (1H, dd, J_1=2, J_2=9), 7.31 (1H, h, J=9)

3,4-Dichloro-7-*i*-butyloxy-2,2-dimethyl-2*H*-chromene (43e)

oil,

Anal. calcd. for $C_{15}H_{18}Cl_2O_2$ (M=301.21): C 59.81, H 6.02, Cl 23.54,

found: C 59.96, H 5.89, Cl 23.40

^{1}H-NMR ($CDCl_3$) (B): δ 1 1.02 (6H, m), 1.57 (6H, s), 2.10 (1H, m), 3.76, (2H, m), 6.40 (1H, d, J=2), 6.53 (1H, dd, J_1=2, J_2=9), 7.33 (1H, d, J=9)

3,4-Dichloro-7-propargyloxy-2,2-dimethyl-2*H*-chromene (43f)

oil,

Anal. calcd. for $C_{14}H_{12}Cl_2O_2$ (M=283.15): C 59.38, H 4.27, Cl 25.04,

found: C 59.18, H 4.33, Cl 24.77

^{1}H-NMR ($CDCl_3$) (B): δ 1.56 (6H, s), 2.52 (1H, t, J=2), 4.63 (2H, d, J=2), 6.47 (1H, d, J=2), 6.57 (1H, dd, J1=2, J2=9), 7.33 (1H, d, J=9)

3,4-Dichloro-6,7-dimethoxy-2,2-dimethyl-2*H*-chromene (43g)

mp: 68-69.5 °C (hexane-diethylether); lit. mp: 69.5-70 °C[58]

Anal. calcd. for $C_{13}H_{14}Cl_2O_3$ (M=289.15): C 53.99, H 4.87, Cl 12.26

found: C 54.07 H 4.90 Cl 12.11

IR (KBr): ν_{max} cm^{-1} 2980, 1610, 1505, 1460, 1445, 1400, 1360, 1285, 1245, 1200, 1150, 1030, 1020, 1000, 950, 940, 850, 810, 710

^{1}H-NMR ($CDCl_3$) (B): δ 1.43 (6H, s), 3.73 (6H, s), 6.33 (1H, s), 6.83 (1H, s)

MS (m/z, %): 288 (M^+, 28), 273 (100), 253 (54), 229 (10)

3,4-Dichloro-7,8-dimethoxy-2,2-dimethyl-2*H*-chromene (43h)

mp: 52-53 °C (hexane-diethylether)

Anal. calcd. for $C_{13}H_{14}Cl_2O_3$ (M=289.15): C 53.99, H 4.87, Cl 12.26
found: C 54.01, H 5.10, Cl 12.30
^{1}H-NMR ($CDCl_3$) (B): δ 1.60 (6H, s), 3.82 (6H, s), 6.50 (1H, d, J=9), 7.10 (1H, d, J=9)
MS (m/z, %): 288 (M^+, 67), 273 (100), 253 (75), 223 (10)

3,4,6 or 3,4,8-Trichloro-5,7-dimethoxy-2,2-dimethyl-2*H*-chromene (**43i**)
oil,
Anal. calcd. for $C_{13}H_{14}Cl_3O_3$ (M=323.61): C 48.24, H 4.04, Cl 32.87 found: C 48.41, H 4.15, Cl 33.00
^{1}H-NMR ($CDCl_3$) (B): δ 1.51 (6H, s), 3.85 (3H, s), 3.88 (3H, s), 6.37 (1H, s)

3,4-Dichloro-7-ethoxy-6-methoxy-2,2-dimethyl-2*H*-chromene (**43j**)
oil,
Anal. calcd. for $C_{14}H_{16}Cl_2O_3$ (M=303.18): C 55.45, H 5.32, Cl 23.38
found: C 55.40, H 5.43, Cl 23.40
^{1}H-NMR ($CDCl_3$) (B): δ 1.45 (3H, t, J=6), 1.55 (6H, s), 3.85 (3H, s), 4.07 (2H, q, J=6), 6.47 (1H, s), 6.92 (1H, s)

3,4,-Dichloro-6-ethoxy-7-methoxy -2,2-dimethyl-2*H*-chromene (**43k**)
oil,
Anal. calcd. for $C_{14}H_{16}Cl_2O_3$ (M=303.18): C 55.45, H 5.32, Cl 23.38,
found: C 55.56, H 5.40, Cl 23.50
^{1}H-NMR ($CDCl_3$) (B): δ 1.47 (3H, t, J=6), 1.55 (6H, s), 3.85 (3H, s9), 4.08 (2H, q, J=6), 6.45 (1H, s), 6.95 (1H, s)

3,4,-Dichloro-7-methoxy-2,2,8-trimethyl-2*H*-chromene (**43l**)
oil,
Anal. calcd. for $C_{13}H_{14}Cl_2O_2$ (M=273.15): C 57.15, H 5.16, Cl 25.96,
found: C 57.26, H 5.07, Cl 25.10
^{1}H-NMR ($CDCl_3$) (B): δ 1.55 (6H, s), 2.07 (3H, s), 3.82 (3H, s), 6.48 (1H, d, J=8), 7.22 (1H, d, J=8)

7.5 Synthesis of 1,2,3-selenadiazolo-benzopyran derivatives

General procedure for the preparation of selenadiazolo-benzopyrans **57**:

a) 40 mmol 4-chromanone derivative (**34a-i**), semicarbazide-hydrocloride (4.8 g, 43 mmol) and sodium acetate (4.9 g, 60 mmol) were dissolved in ethanol (100 mL). The solution was refluxed until the reaction was completed (monitored by tlc, eluent:
1:4 /EtOAc - toluene). The mixture was cooled and the separated solid was washed with water and dried to give the corresponding 4-chromanon-semicarbazone derivative (**56a-i)**; analytical samples were crystallized from ethanol.

b) 20 mmol semicarbazones **56** was dissolved in glacial acetic acid (50mL) then selenium dioxide (2.22 g, 20 mmol) was added. The reaction mixture was stirred at 80 ^{o}C till the evolution of gas (CO_2) ceased. The solvent was removed under reduced pressure, and $CHCl_3$ (100 mL) was added to the residue for dissolving. It was washed thoroughly with aqueous sodium carbonate solution (5%, 2 x 50 mL), and water (2 x 50 mL) and dried. The chloroform was removed in vacuum and the residue was crystallized from hexane to give products **57a-i**. (see yields in Table 6)

2,2-Dimethyl-7-methoxy-2,3-dihydro-4*H*-1-benzopyran-4-one semicarbazone (56a)

yellowish crystalline powder (ethanol), mp: 229-231 ^{o}C

Anal. calcd. for $C_{13}H_{17}N_3O_3$ (M=287.29): C 59.30, H 6.50, N 15.96 found: C 59.45, H 6.55, N 16.00

IR (D): 3475 (NH), 3192 (NH_2), 2976, 1682 (C=O), 1622 (C=N), 1573, 1326, 1268, 1202 (C-O-C), 1164, 1128, 982 cm^{-1};

^{1}H-NMR (DMSO-d_6) (A): δ 1.29 (s, 6H, 2-Me_2), 2.70 (s, 2H, 3-H), 3.73 (s, 3H, 7-MeO), 6.36 (d, J = 8.7, 1H, 8-H), 6.45-6.55 (m, 3H, 6-H, NH_2), 8.00 (d, J = 8.7, 1H, 5-H), 9.23 (s, 1H, NH);

^{13}C-NMR (DMSO-d_6) (A): δ 26.9 (2-Me_2), 35.6 (C-3), 55.7 (7-MeO), 76.0 (C-2), 101.8 (C-8), 108.7 (C-6), 113.1 (C-4a), 126.1 (C-5), 139.5 (C-4), 156.1, 157.9 (C-8a, C=O), 161.9 (C-7);

6,7-Dimethoxy-2,2-dimethyl-2,3-dihydro-4*H*-1-benzopyran-4-one semicarbazone (56b) yellowish crystalline powder (ethanol), mp 232-235 ^{o}C.

Anal. calcd. for $C_{14}H_{19}N_3O_4$ (M= 293.32): C 57.30; H 6.53; N 14.30. found: C 57.20; H 6.61; N, 14.70.

IR (D): 3449 (NH), 3194 (NH_2), 2934, 1679 (C=O), 1578, 1505, 1465, 1451, 1441, 1418, 1369, 1275, 1254, 1213, 1200 (C-O-C), 1127, 897 cm^{-1};

^{1}H-NMR (DMSO-d_6) (A): δ 1.28 (s, 6H, 2-Me_2), 2.67 (s, 2H, 3-H), 3.73, 3.76 (2xs, 2x3H, 6-MeO, 7-MeO), 6.41 (s, 1H, 8-H), 6.56 (s, 2H, NH_2), 7.51 (s, 1H, 5-H), 9.18 (s, 1H, NH);

^{13}C-NMR (DMSO-d_6) (A): δ 27.3 (2-Me_2), 36.1 (C-3), 56.4, 57.1 (6-MeO, 7-MeO), 76.1 (C-2), 102.1 (C-8), 107.1 (C-4a), 114.8 (C-5), 140.3 (C-6), 144.3 (C-4), 150.1 (C-8a), 152.4 (C-7), 158.3 (C=O);

7,8-Dimethoxy-2,2-dimethyl-2,3-dihydro-4*H*-1-benzopyran-4-one semicarbazone (56c).

off-white crystalline powder (ethanol), mp 197-198 ^{o}C.

Anal. calcd. for $C_{14}H_{19}N_3O_4$ (M=293.32): C 57.30, H 6.53, N 14.30, found: C 57.43, H 6.63, N 14.70

IR (D): 3473 (NH), 3327, 3207 (NH_2), 2972, 1684 (C=O), 1620 (C=N), 1568, 1419, 1335, 1291, 1203 (C-O-C), 1105, 1092 cm^{-1};

^{1}H-NMR (DMSO-d_6) (A): δ 1.32 (s, 6H, 2-Me_2), 2.71 (s, 2H, 3-H), 3.66, 3.79 (2xs, 2x3H, 7-MeO, 8-MeO), 6.52 (br s, 2H, NH_2), 6.62 (d, J = 8.9, 1H, 6-H), 7.83 (d, J = 8.9, 1H, 5-H), 9.27 (s, 1H, NH);

^{13}C-NMR (DMSO-d_6) (A): δ 27.4 (2-Me_2), 36.1 (C-3), 56.7, 60.9 (7-MeO, 8-MeO), 76.6 (C-2), 106.1 (C-6), 115.3 (C-4a), 120.3 (C-5), 138.0, 139.1 (C-4, C-8), 149.3 (C-8a), 154.8 (C-7), 158.3 (C=O).

7-Methoxy-2,2,5-trimethyl-2,3-dihydro-4*H*-1-benzopyran-4-one semicarbazone (56d) off-white crystalline powder (ethanol), mp 242-244 ^{o}C.

Anal. calcd. for $C_{14}H_{19}N_3O_3$ (M=277.32): C 60.60, H 6.85, N 15.10 found: C 60.71, H 6.93, N 15.31

IR (D): 3477 (NH), 3277, 3176 (NH_2), 2870, 1681 (C=O), 1613, 1572, 1468, 1443, 1419, 1340, 1310, 1287, 1129, 843 cm^{-1};

^{1}H-NMR (DMSO-d_6) (A): δ 1.28 (s, 6H, 2-Me_2), 2.53 (s, 3H, 5-Me), 2.73 (s, 2H, 3-H), 3.71 (s, 3H, 7-MeO), 6.16 (d, J = 2.6, 1H, 8-H), 6.39 (d, J = 2.6. 1H, 6-H), 9.32 (s, 1H, NH), NH_2 appears as an extremely broad signal at ca. 6.2 ppm;

^{13}C-NMR (DMSO-d_6) (A): δ 25.6 (5-Me), 27.3 (2-Me_2), 36.7 (C-3), 56.0 (7-MeO), 75.8 (C-2), 100.8 (C-8), 112.2 (C-6), 112.4 (C-4a), 139.4 (C-5), 142.6 (C-4), 157.8, 158.4 (C-8a, C=O), 160.6 (C-7).

7-Methoxy-2,2,8-trimethyl-2,3-dihydro-4*H*-1-benzopyran-4-one semicarbazone (56e) brownish crystalline powder (ethanol), mp 182-185 ^{o}C.

Anal. calcd. for $C_{14}H_{19}N_3O_3$ (M= 277.32): C 60.60, H 6.85, N 15.10, found: C 60.44, H 7.01, N 14.90

IR (D): 3467 (NH), 3209 (NH_2), 2975, (1687 (C=O), 1578, 1466, 1414, 1281, 1115 cm^{-1};

^{1}H-NMR (DMSO-d_6) (A): δ 1.29 (s, 6H, 2-Me_2), 1.96 (s, 3H, 8-Me), 2.69 (s, 2H, 3-H), 3.79 (s, 3H, 7-MeO), 6.50 (br s, 2H, NH_2), 6.58 (d, J = 8.6, 1H, 6-H), 7.94 (d, J = 8.6, 1H, 5-H), 9.22 (s, 1H, NH);

^{13}C-NMR (DMSO-d_6) (A): δ 9.1 (8-Me), 27.6 (2-Me_2), 36.1 (C-3), 56.5 (7-MeO), 76.1 (C-2), 104.6 (C-6), 113.5, 114.0 (C-4a, C-8), 123.3 (C-5), 140.5 (C-4), 154.9 (C=O), 158.4, 159.7 (C-7, C-8a).

2,2-Dimethyl-6,7-dipropargyloxy-2,3-dihydro-4*H*-1-benzopyran-4-one semicarbazone (56f)

off-white crystalline powder (ethanol), mp 190-193 ^{o}C

Anal. calcd. for $C_{18}H_{19}N_3O_4$ (M=341.36): C 63.33, H 5.61, N 12.30, found: C 63.21, H 5.77, N 12.45

IR (D): 3470 (NH), 3291 (NH_2), 2976, 1688 (C=O), 1573, 1501, 1433, 1270, 1123 cm^{-1};

^{1}H-NMR (DMSO-d_6) (A): δ 1.28 (s, 6H, 2-Me_2), 2.68 (s, 2H, 3-H), 3.53, 3.60 (2xt, J = 2.3, 2x1H, 2x ≡CH), 4.79 (overlapping s's, 2x2H, 2xOCH_2), 6.52 (s, 1H, 8-H), 6.6 (br s, 2H, NH_2), 7.63 (s, 1H, 5-H), 9.25 (s, 1H, NH);

^{13}C-NMR (DMSO-d_6) (A): δ 26.9 (2-Me_2), 35.5 (C-3), 56.4, 57.2 (2xO**C**H_2), 75.9 (C-2), 78.5, 79.1, 79.4, 80.0 (alkyne carbons), 103.4 (C-8), 109.8 (C-5), 112.3 (C-4a), 139.3 (C-4), 141.7 (C-6), 149.9 (C-8a), 157.8 (C-7).

2,2-Dimethyl-7-propargyloxy-2,3-dihydro-4*H*-1-benzopyran-4-one semicarbazone (56g) yellowish crystalline powder (ethanol), mp 172-175 ^{o}C.

Anal. calcd. for $C_{15}H_{17}N_3O_3$ (M=287,31): C 62.70, H 5.96, N 14.62, found: C 62.90, H 6.03, N 15.01

IR (KBr) (D): 3458 (NH), 3285 (NH_2), 2976, 1691 (C=O), 1622, 1574, 1430, 1328, 1262, 1168, 1128, 1027 cm^{-1};

^{1}H-NMR (DMSO-d_6) (A): δ 1.30 (s, 6H, 2-Me_2), 2.50 (s, 1H, ≡CH), 2.71 (s, 2H, 3-H), 4.78 (s, 2H, CH_2-C≡), 6.43 (d, J = 2.6, 1H, 8-H), 6.49 (s, 2H, NH_2), 6.54 (dd, J = 8.7, 2.6, 1H, 6-H), 8.02 (d, J = 8.7, 1H, 5-H), 9.25 (s, 1H, NH);

^{13}C-NMR (DMSO-d_6) (A): δ 26.9 (2-Me_2), 35.5 (C-3), 56.0 (***C***H_2-C≡), 76.1 (C-2), 78.8, 79.6 (-***C***≡***C***H), 102.9 (C-8), 109.2 (C-6), 113.8 (C-4a), 126.2 (C-5), 139.3 (C-4), 155.9, 157.9, 159.7 (C-7, C-8a, C=O).

2,2-Dimethyl-7-ethoxy-6-methoxy-2,3-dihydro-4*H*-1-benzopyran-4-one semicarbazone (56h)

yellow crystalline powder (ethanol), mp. 205-207 ^{o}C

Anal. calcd. for $C_{15}H_{21}N_3O_4$ (M=307.35): C 58.61, H 6.88, N 13.67, found: C, 58.37; H 7.01, N 14.00

IR (KBr) (D): 3446 (NH), 3186 (NH_2), 2977, 2934, 1677 (C=O), 1577, 1504, 1423, 1252, 1174, 1112 cm^{-1};

^{1}H-NMR (DMSO-d_6) (A): δ 1.27, 1.31 (overlapping s and t, 9H, 2-Me_2 + 7-OCH_2C***H***$_3$), 2.66 (s, 2H, 3-H), 3.76 (s, 3H, 6-OMe), 3.97 (br q, 2H, 7-OC***H***$_2CH_3$), 6.38 (s, 1H, 8-H), 6.53 (br s, 2H, NH_2), 7.50 (s, 1H, 5-H), 9.15 (s, 1H, NH);

^{13}C-NMR (DMSO-d_6) (A): δ 15.5 (7-OCH_2***C***H_3), 27.3 (2-Me_2), 36.2 (C-3), 57.0 (6-MeO), 64.5 (7-O***C***H_2CH_3), 76.1 (C-2), 102.7 (C-8), 107.6 (C-5), 111.7 (C-4a), 140.3 (C-4), 144.4 (C-6), 150.1, 151.6, 158.3 (C-7, C-8a, C=O).

2,2-Dimethyl-6-ethoxy-7-methoxy-2,3-dihydro-4*H*-1-benzopyran-4-one semicarbazone (56i)

brownish crystalline powder (ethanol) mp. 185-188 ^{o}C

Anal. calcd. for $C_{15}H_{21}N_3O_4$ (M=307.35): C 58.61, H 6.88, N 13.67, found: C 58.45,

H 7.10, N 13.43

IR (KBr) (D): 3406 (NH), 3237 (NH_2), 2977, 1681 (C=O), 1506, 1447, 1276, 1252, 1123 cm^{-1};

^{1}H-NMR (DMSO-d_6) (A): δ 1.30 (overlapping s and t, 9H, 2-Me_2 + 6-$OCH_2C\boldsymbol{H}_3$), 2.67 (s, 2H, 3-H), 3.73 (s, 3H, 7-OMe), 4.03 (br q, 2H, 6-$OC\boldsymbol{H}_2CH_3$), 5.87 (br s, 2H, NH_2), 6.41 (s, 1H, 8-H), 7.61 (s, 1H, 5-H), 9.53 (s, 1H, NH);

^{13}C-NMR (DMSO-d_6) (A): δ 15.8 (6-$OCH_2\boldsymbol{C}H_3$), 27.3 (2-Me_2), 39.8 (C-3), 56.4 (7-MeO), 65.5 (6-$O\boldsymbol{C}H_2CH_3$), 76.1 (C-2), 102.0 (C-8), 109.6 (C-5), 111.7 (C-4a), 141.6, 143.5 (C-4, C-6), 150.4, 153.0, 157.2 (C-7, C-8a, C=O)

7-Methoxy-4,4-dimethylchromeno[4,3-*d*]selenadiazole (**57a**)

brownish crystalline powder (hexane), mp 81-82 °C

Anal. calcd. for $C_{12}H_{12}N_2O_2Se$ (M= 295.20): C 48.82, H 4.10, N 9.49, found: C 48.97, H 4.30, N 9.71

IR (KBr) (D): 2973, 1624, 1582, 1496, 1469, 1313, 1285 (C-O-C), 1191, 1149 (C-O-C), 1082, 794 cm^{-1};

^{1}H-NMR (DMSO-d_6) (A): δ 1.77 (s, 6H, 4-Me_2), 3.83 (s, 3H, 7-MeO), 6.68 (d, J = 2.0, 1H, 6-H), 6.76 (dd, J = 2.0, 9.0, 1H, 8-H), 8.00 (d, J = 9.0, 1H, 9-H);

^{13}C-NMR (DMSO-d_6) (A): δ 30.7 (4-Me_2), 56.3 (7-MeO), 81.8 (C-4), 103.7 (C-6), 109.5 (C-8), 111.4 (C-9a), 126.2 (C-9), 154.0, 157.2 (C-3a, C-9a), 162.1 (C-7);

MS (m/z, %,^{80}Se): 296 ($M^{+\bullet}$, 30), 268 ($M^{+\bullet}$ - N_2, 54), 253 ($M^{+\bullet}$ - N_2 - $Me^{\bullet}$, 32), 188 ($M^{+\bullet}$ - N_2Se, 100), 173 ($M^{+\bullet}$ - N_2Se - $Me^{\bullet}$, 97

7,8-Dimethoxy-4,4-dimethylchromeno[4,3-*d*]selenadiazole (**57b)**

off-white crystalline powder (hexane), mp. 101-102 °C

Anal. calcd. for $C_{13}H_{14}N_2O_3Se$ (M=325.22): C 48.01, H 4.34, N 8.61, found: C 48.17,

H 4.43, N 8.43

IR (KBr) (D): 3435, 3002, 2971, 1619, 1506, 1463, 1309, 1276 (C-O-C), 1241 (C-O-C), 1197, 1157 (C-O-C), 1003, 856, 804 cm^{-1};

^{1}H-NMR (DMSO-d_6) (A): δ 1.70 (s, 6H, 4-Me_2), 3.77, 3.80 (2xs, 2x3H, 7- MeO, 8-MeO), 6.75 (s, 1H, 6-H), 7.55 (s, 1H, 9-H);

^{13}C-NMR (DMSO-d_6) (A): δ 30.5 (4-Me_2), 56.7, 57.0 (7-MeO, 8-MeO), 81.4 (C-4), 102.9 (C-6), 108.3 (C-9), 109.8 (C-9a), 145.7, 147.1, 151.7, 153.4, 157.5 (C-3a, C-5a, C-7, C-8, C-9b); MS (m/z, %, ^{80}Se): 326 ($M^{+\bullet}$, 42), 298 ($M^{+\bullet}$ - N_2, 59), 283 ($M^{+\bullet}$ - N_2 - $Me^{\bullet}$, 34), 218 ($M^{+\bullet}$ - N_2Se, 100), 203 ($M^{+\bullet}$ - N_2Se - $Me^{\bullet}$, 44), 174 (32).

6,7-Dimethoxy-4,4-dimethylchromeno[4,3-*d*]selenadiazole (**57c**)

brownish crystalline powder (hexane), mp. 125-127 ^oC.

Anal. calcd. for $C_{13}H_{14}N_2O_3Se$ (M=325.22): C 48.01, H 4.34, N 8.61, found: C 48.19, H 4.30, N 8.55

^{1}H-NMR (DMSO-d_6) (A): 1.69 (s, 6H, 4-Me_2), 3.75, 3.78 (s, 3H, 7-MeO), 6.21 (d, J = 8.8, 1H, 6-H), 6.75 (d, J = 8.8, 1H, 9-H);

7-Methoxy-4,4,9-trimethylchromeno[4,3-*d*]selenadiazole (**57d**)

brownish-white crystalline powder (hexane), mp. 100-101 ^oC

Anal. calcd. for $C_{13}H_{14}N_2O_2Se$ (M=309.22): C 50.49, H 4.56, N 9.06, found: C 50.44,

H 4.61, N 9.00

^{1}H-NMR (DMSO-d_6) (B): δ 1.72 (s, 6H, 4-Me_2), 2.80 (s, 3H, 9-Me), 3.80 (s, 3H, 7-MeO), 6.45, 6.55 (2xm, 2x1H, 6-H, 8-H);

MS (m/z, %,^{80}Se): 310 ($M^{+\bullet}$, 18), 282 ($M^{+\bullet}$ - N_2, 30), 267 ($M^{+\bullet}$ - N_2 - $Me^{\bullet}$, 28), 202 ($M^{+\bullet}$ - N_2Se, 100), 187 ($M^{+\bullet}$ - N_2Se - $Me^{\bullet}$, 85).

7-Methoxy-4,4,6-trimethylchromeno[4,3-*d*]selenadiazole (**57e**)

off-white crystalline powder (hexane), mp 75-77 ^{o}C

Anal. calcd. for $C_{13}H_{14}N_2O_2Se$ (M= 309.22): C 50.49, H 4.56, N 9.06 found: C 50.74, H 4.29, N 9.14

^{1}H-NMR (DMSO-d_6) (B): δ 1.73 (s, 6H, 4-Me_2), 2.15 (s, 3H, 6-Me), 3.85 (s, 3H, 7-MeO), 6.61 (d, J = 8.0, 1H, 8-H), 7.95 (d, J = 8, 1H, 9-H);

MS (m/z, %, ^{80}Se): 310 ($M^{+\bullet}$, 20), 282 ($M^{+\bullet}$ - N_2, 32), 267 ($M^{+\bullet}$ - N_2 - $Me^{\bullet}$, 22), 202 ($M^{+\bullet}$ - N_2Se, 100), 187 ($M^{+\bullet}$ - N_2Se - $Me^{\bullet}$, 88).

4,4-Dimethyl-7,8-dipropargyloxychromeno[4,3-*d*]selenadiazole (**57f**)

yellowish crystalline powder (hexane), mp 78-81 ^{o}C

Anal. calcd. for $C_{17}H_{14}N_2O_3Se$ (M=373.27): C 54.70, H 3.78, N 7.50, found: C 54.91, H 3.60, N 7.66

^{1}H-NMR (DMSO-d_6) (B): δ 1.74 (s, 6H, 4-Me_2), 2.50, 2.53 (2xt, J = 2.0, 2x1H, ≡CH), 4.67, 4.70 (2xd, J = 2.0, 2x2H, CH_2-C≡), 6.65 (br s, 1H, 6-H), 7.82 (br s, 1H, 9-H).

4,4-Dimethyl-7-propargyloxychromeno[4,3-*d*]selenadiazole (**57g**)

brownish-white crystalline powder (hexane), mp 86-87 ^{o}C

Anal. calcd. for $C_{14}H_{12}N_2O_2Se$ (M= 319.22): C 52.68, H 3.79, N 8.78 found: C 52.77,

H 3.85, N 8.91

IR (KBr) (D): 3281, 2984, 1620, 1489, 1369, 1285, 1270 (C-O-C), 1167, 1147 (C-O-C), 1081, 1027, 837 cm^{-1};

^{1}H-NMR (DMSO-d_6) (A): δ 1.78 (s, 6H, 4-Me_2), 2.50 (br s, 1H, ≡CH), 4.89 (d, J = 2.9, 2H, C***H***$_2$-C≡), 6.74 (d, J = 2.0, 1H, 6-H), 6.81 (dd, J = 2.0, 8.5, 1H, 8-H), 8.01 (d, J = 8.5, 1H, 9-H);

^{13}C-NMR (DMSO-d_6) (A): δ 30.8 (4-Me_2), 56.6 (***C***H_2-C≡), 79.5, 79.9 (-***C***≡***C***H), 81.9 (C-4), 104.6 (C-6), 110.2 (C-8), 112.1 (C-9a), 126.2 (C-9), 153.9, 157.5 (C-5a, C-9b), 160.0 (C-7).

7-Ethoxy-8-methoxy-4,4-dimethylchromeno[4,3-*d*]selenadiazole (**57h**)

off-white crystalline powder (hexane), mp. 85-88 ^{o}C

Anal. calcd. for $C_{14}H_{16}N_2O_3Se$ (M=339.25): C 49.57, H 4.75, N 8.26, found: C 49.45, H 4.90, N 8.03

^{1}H-NMR (DMSO-d_6) (B): δ 1.41 (t, J = 6.0, 3H, 7-OCH_2C***H***$_3$), 1.70 (s, 6H, 4-Me_2), 3.81 (s, 3H, 8-MeO), 4.11 (q, J = 6.0, 2H, 7-OC***H***$_2CH_3$), 6.48 (br s, 1H, 6-H), 7.55 (br s, 1H, 9-H).

8-Ethoxy-7-methoxy-4,4-dimethylchromeno[4,3-*d*]selenadiazole (**57i**)

off-white crystalline powder (hexane), mp. 70-72 ^{o}C

Anal. calcd. for $C_{14}H_{16}N_2O_3Se$ (M=339.25): C 49.57, H 4.75, N 8.26, found: C 49.70,

H 4.63, N 8.11

^{1}H-NMR (DMSO-d_6) (B): δ 1.45 (t, J = 6.0, 3H, 8-OCH_2C***H***$_3$), 1.70 (s, 6H, 2-Me_2), 3.85 (s, 3H, 7-MeO), 4.15 (q, J = 6.0, 2H, 8-OC***H***$_2CH_3$), 6.55 (br s, 1H, 6-H), 7.60 (br s, 1H, 9-H).

7.6 Thermal cyclization of aryl propargyl ethers

General procedure for preparation of aromatic propargyl ethers *via* direct Williamson etherification:

Mixture of the appropriate phenol **3** (1.0 mol), the acetylenic bromide (**59**) (0.9 mol), anhydrous K_2CO_3 (~1.2 mol) and KI (~1 g) in 400 ml of reagent grade acetone was heated under reflux with vigorous stirring. The cooled mixture was filtered, and the inorganic residue was dissolved in H_2O (500 ml) and extracted with ether *(*2 x 50 ml). The filtrate was concentrated *in vacuo* and the residue was dissolved in ether (350 ml). The combined ethereal solution was washed with *5%* NaOH solution (until pH of the ethereal layer gave a neutral reaction to moist pH paper), then with H_20 (200 ml). The ether solution was dried (anhydrous Na_2SO_4) and concentrated in *vacuo.* The residue was distilled under vacuum.

Thermal cyclization of aryl propargyl ethers **11**:

Solution of 20 mmol appropriate aryl propargyl ether **11** in N,N-diethylamine (distilled; 5 ml/g of aryl propargyl ether) was refluxed (217-220 ^oC) under a nitrogen atmosphere without stirring until the starting material disappeared. The mixture was poured onto 200 g of crushed ice; this was extracted with 3 x 70 mL diethyl ether. The organic phase was washed with 4 x 100 mL 4 M HCl solution, 2 x 50 mL water and 2 x 50 mL brine then was dried over sodium sulfate. Evaporation gave colourless oils, which was purified by column chromatography using CCl_4 as eluent giving the corresponding derivatives of 2*H*-chromenes. (see yields in Table 7, 8)

1-(Ethynyloxy)-benzene (**11a**)
oil,
^{1}H-NMR ($CDCl_3$) (B): δ 2.5 (1H, m), 4.34 (1H, m), 6.97 (3H, m), 7.15 (2H,m)

1-(Ethynyloxy)-2-methoxybenzene (**11b**)

oil,

^{1}H-NMR ($CDCl_3$) (B): δ 2.5 (1H, t), 3.85 (3H. m), 4.74 (2H.m), 6.75-7.13 (4H, m)

MS (m/z, %,): 162 (M^+, 45), 147 (3), 137 (10), 131 (3), 123 (100)

1-(Ethynyloxy)-3-methoxybenzene (**11c**)

oil,

^{1}H-NMR ($CDCl_3$) (B): δ 2.53 (1H, m), 3.78 (3H, s), 4.66 (2H, d), 6.55 (3H, m), 7.2 (1H, m)

MS (m/z, %,): 162 (M^+, 32), 161 (100), 147 (34), 131 (32)

1-(Ethynyloxy)-4-methoxybenzene (**11d**)

oil,

^{1}H-NMR ($CDCl_3$) (B): δ 2.5 (1H, t), 3.76 (3H, s), 4.62 (2H, d), 6.75-6.95 (4H, m)

MS (m/z, %,): 162 (M^+, 20), 147 (1), 131 (1), 123 (100), 108 (2)

1-(Ethynyloxy)-2-methylbenzene (**11e**)

oil,

^{1}H-NMR ($CDCl_3$) (B): δ 2.25 (3H,s), 2.48 (1H,t), 4.68 (2H, d), 6.9 (2H,m), 7.15 (2H,m)

MS (m/z, %,): 146 (M^+, 6), 131 (15), 121 (18), 107 (26), 39 (100)

1-(Ethynyloxy)-3-methylbenzene (**11f**)

oil,

^{1}H-NMR ($CDCl_3$) (B): δ 2.33 (2H,s), 2.5 (1H,t), 4.65 (2H, d), 6.78 (3H, t), 7.16 (1H, m)

1-(Ethynyloxy)-4-methylbenzene (**11g**)

oil,

^{1}H-NMR ($CDCl_3$) (B): δ 2.28 (3H, s), 2.48 (1H, t), 4.63 (2H, d), 6.85 (2H, m), 7.08 (2H, m)

1-Chloro-2- (ethynyloxy)benzene (**11h**)

oil,

^{1}H-NMR ($CDCl_3$) (B): δ 2.55 (1H, t), 4.76 (2H, d), 6.95 (1H, m), 7.08 (1H, m), 7.23

(1H, m), 7.38 (1H,m)

MS (m/z, %,): 166 (M^+, 28), 137 (25), 131 (100), 127 (8)

1-Chloro-3-(ethynyloxy)benzene (**11i**)

oil,

^{1}H-NMR ($CDCl_3$) (B): δ 2.55 (1H, t), 4.68 (2H,d), 6.8-7.05 (3H, m), 7.2 (1H, m)

1-Chloro-4-(ethynyloxy)benzene (**11j**)

oil,

^{1}H-NMR ($CDCl_3$) (B): δ 2.53 (1H, m), 4.63 (2H,m), 6.88 (2H, m), 7.23 (2H, m)

2*H*–chromene (**15a**)

oil,

^{1}H-NMR ($CDCl_3$) (B) : δ 4.81 (2H,m), 5.76 (1H,m), 6.4 (1H,m), 6.68-7.11 (4H, m)

(in line with the literature data) [93]

MS (m/z, %,): 132 (M^+, 32), 131 (100), 106 (44)

8-Methoxy-2*H*–chromene (**15b**)

oil,

^{1}H-NMR ($CDCl_3$) (B): δ 3.88 (3H,s), 4.89 (2H, dd), 5.79 (1H, dt), 6.42 (1H, dt), 6.58-6.95 (3H, m)

MS (m/z, %,): 162 (M^+, 100), 161 (94.9), 147 (22.3), 131 (19.7)

(in line with the literature data] [31]

5-methoxy-2*H*–chromene (**15c**)

oil,

^{1}H-NMR ($CDCl_3$) (B) : δ 3.83 (3H, s), 4.76 (2H, m), 5.73 (1H, dt), 6.45 (2H. m), 6.75 (1H, m), 7.05 (1H, t)

MS (m/z, %,): 162 (M^+, 71), 161 (100), 147 (35), 131 (15), 118 (14), 91 (32)
(in line with the literature data) [31]

7-Methoxy-2*H*–chromene (15c')

oil,

^{1}H-NMR ($CDCl_3$) (B): δ 3.77 (3H,s), 4.79 (2H, m), 5.61 (1H, dt), 6.33-6.46 (3H, m), 6.88 (1H,m)

MS (m/z, %,): 162 (M^+, 71), 161 (100), 147 (35), 131 (15), 118 (14), 91 (32)
(in line with the literature data] [31]

6-Methoxy-2*H*–chromene (15d)

oil,

^{1}H-NMR ($CDCl_3$) (B): δ 3.75 (3H,s), 4.75 (2H, m), 5,8 (1H, dt), 6.4 (1H, m), 6.53-6.75
(3H,m)

MS (m/z, %,): 162 (M^+, 88), 161 (100), 147 (26), 131 (5), 118 (15), 91 (40)
(in line with the literature data) [31]

8-Methyl-2*H*–chromene (15e)

oil,

^{1}H-NMR ($CDCl_3$) (B): δ 2.18 (3H,s), 4.85 (2H, m), 5.75 (1H, dt), 6.4 (1H, dt), 6.55-6.95 (3H, m)

MS (m/z, %,): 146 (M^+, 80), 145 (100), 131 (27), 106 (47), 91 (63)

5-Methyl-2*H*–chromene (15f)

oil,

^{1}H-NMR ($CDCl_3$) (B) : δ 2.28 (3H, s), 4.74 (2H, q), 5.83 (1H, dt), 6.58-6.88 (3H, m), 7.0 (1H, dt)

(in line with the literature data) [32]

7-Methyl-2*H*–chromene (15f')

oil,

^{1}H-NMR ($CDCl_3$) (B): : δ 2.28 (3H,s), 4.78 (2H, q), 5.7 (1H, dt), 6.4 (1H, dt), 6.58-6.88 (3H, m)
(in line with the literature data) [32]

6-Methyl-2*H*–chromene (15g)
oil,
^{1}H-NMR ($CDCl_3$) (B): δ 2.25 (3H,s), 4.77 (2H, m), 5.75 (1H, dt), 6.38 (1H, m), 6.78 (1H, m), 6.8 (1H, m), 6.9 (1H, m)
MS (m/z, %,): 146 (M^+, 79), 145 (100), 131 (19)
(in line with the literature data) [32]

8-Chloro-2*H*–chromene (15h)
oil,
^{1}H-NMR ($CDCl_3$) (B): δ 4.94 (2H,m), 5.83 (1H, dt), 6.4 (1H, dt), 6.68-7.18 (3H, m)
MS (m/z, %,): 166 (M^+, 71), 165 (100), 131 (31)

5-Chloro-2*H*–chromene (15i)
oil,
^{1}H-NMR ($CDCl_3$) (B): δ 4.79 (2H, m), 5.88 (1H, dt), 6.64-7.05 (4H, m)
MS (m/z, %,): 166 (M^+, 47), 165 (100), 131 (25)

7-Chloro-2*H*–chromene (15i')
oil,
^{1}H-NMR ($CDCl_3$) (B): δ 4.79 (2H, m), 5.88 (1H, dt), 6.38 (1H, m), 6.64-7.05 (3H, m)
MS (m/z, %,): 166 (M^+, 48), 165 (100), 131 (25)

6-Chloro-2*H*–chromene (15j)
oil,
^{1}H-NMR ($CDCl_3$) (B): δ 4.80 (2H, m), 5.80 (1H, dt), 6.35 (1H, m), 6.68 (1H, m), 6.9 (1H, d), 7.03 (1H, dd)
MS (m/z, %,): 166 (M^+, 52,9), 165 (100), 131 (23)

(in line with the literature data) [93]

5-Methoxy-2,2-dimethyl-2*H*-chromene (**6a**)

oil,

Anal. calcd. for $C_{12}H_{14}O_2$ (M=190.23): C 75.76, H 7.42, found: C 75.90, H 7.30

^{1}H-NMR ($CDCl_3$) (B): δ 1.43 (6H, s), 3.81 (3H,s), 5.54 (1H, d, J=10), 6.40 (2H, m), 6.65 (1H, d,J=10), 7.02 (1H, m)

7-Methoxy-2,2-dimethyl-2*H*-chromene (**6a'**)

oil,

Anal. calcd. for $C_{12}H_{14}O_2$ (M=190.23): C 75.76, H 7.42, found: C 75.71, H 7.18

^{1}H-NMR ($CDCl_3$) (B): δ 1.40 (6H, s), 3.75 (3H,s), 5.47 (1H, d, J=10), 6.25 (1H, d, J=10), 6.40 (2H, m), 6.85 (1H, d, J=8)

6-Methoxy-2,2-dimethyl-2*H*-chromene (**6b**)

oil,

Anal. calcd. for $C_{12}H_{14}O_2$ (M=190.23): C 75.76, H 7.42; found: C 75.80, H 7.38

^{1}H-NMR ($CDCl_3$) (B): δ 1.43 (6H, s), 3.81 (3H, s), 5.61 (1H, d, J=10), 6.25 (1H, d, J=10), 6.50-6..80 (3H, m)

8-Methoxy-2,2-dimethyl-2*H*-chromene (**6c**)

oil,

Anal. calcd. for $C_{12}H_{14}O_2$ (M=190.23): C 75.76, H 7.42, found: C 75.70, H 7.50

^{1}H-NMR ($CDCl_3$) (B): δ 1.47 (6H, s), 3.78 (3H, s), 5.61 (1H,d,J=10), 6.30 (1H, d, J=10), 6.61 (1H, m), 6.80 (2H, m)

2,2,6-Trimethyl-2*H*-chromene (**6d**)

oil,

Anal. calcd. for $C_{12}H_{14}O$ (M=174.23): C 82.72, H 8.10, found: C 82.90, H 8.23

^{1}H-NMR ($CDCl_3$) (B): δ 1.42 (6H, s), 2.25 (3H, s), 5.60 (1H,d, J=10), 6.27 (1H, d, J=10), 6.70-6.98 (3H, m)

6-Chloro-2,2-dimethyl-2*H*-chromene (**6e**)

oil,

Anal. calcd. for $C_{11}H_{11}ClO$ (M=194.56): C 67.35, H 5.70, Cl 18.21, found: C 67.40, H 5.81, Cl 18.32

^{1}H-NMR ($CDCl_3$) (B): δ 1.42 (6H, s), 5.65 (1H, d, J=10), 6.25 (1H, d, J=10), 6.70-7.15 (3H, m)

5,6,8-Trichloro-2,2-dimethyl-2*H*-chromene (**6f**)

oil.

Anal. calcd. for $C_{11}H_9Cl_3O$ (M=263.55): C 50.13, H 3.44, Cl 40.36, found: C 50.05, H 3.35, Br 40.73

^{1}H-NMR ($CDCl_3$) (B): δ 1.47 (6H, s), 5.80 (1H, d, J=10), 6.72 (1H, d, J=10), 7.3 (1H, s)

2,2-Dimethyl-5-nitro-2*H*-chromene (**6g**)

oil,

Anal. calcd. for $C_{11}H_{11}NO_3$ (M=205.21): C 64.38, H 5.40, N 6.83, found: C 64.30, H 5.53, N 6.89

^{1}H-NMR ($CDCl_3$) (B): δ 1.45 (6H, s), 5.85 (1H,d, J=10), 6.95 (1H, d, J=10), 7.00-7.30 (2H, m), 7.50 (1H, dd, J_1=1.5, J_2=8)

2,2-Dimethyl-7-nitro-2*H*-chromene (**6g'**)

oil,

Anal. calcd. for $C_{11}H_{11}NO_3$ (M=205.21): C 64.38, H 5.40, N 6.83, found: C 64.19, H 5.33, N 6.92

^{1}H-NMR ($CDCl_3$) (B): δ 1.48 (6H, s), 5.85 (1H,d, J=10), 6.40 (1H, d, J=10), 7.10 (1H, d, J=8), 7.59 (1H, d, J=2), 7.69 (1H, dd, J_1=2, J_2=8)

8,8-bis(7-methoxy-2,2-dimethyl-2*H*-chromene (**59**)

^{1}H-NMR ($CDCl_3$) (B): 1.45 (12H, s), 3,81 (6H, s), 5.58 (2H, d, J= 10), 6.25 (2H, d, J= 8), 6.58 (2H, d, J= 10), 7.45 (2H, d, J= 8).

7.7 Reaction of alkoxy-2,2-dimethyl-2H-chromenes with *N*-bromosuccinimide (NBS)

General procedure:

3.6 g (20.2 mmol) freshly recrystallized NBS was added in one portion to a vigourosly stirred solution of 10 mmol chromenes **1** in 30 mL DMSO and 0.4 mL distilled water. After the exotermic reaction, the stirring was continued until the starting material disappeared (monitoring by TLC). The reaction mixture was poured into 100 g crushed ice then extracted with 100 mL benzene. The organic phase was washed with 2 x 100 mL water and 2 x 100 mL brine then it was dried on Na_2SO_4 and evaporated. The reaction products were separated using column chromatography using benzene as eluent. (see yields in Table 9)

3-Bromo-3,4-dihydro-7-methoxy-2,2-dimethyl-2*H*-1-benzopyran-4-ol (**19a**)

mp. 69-72 ^oC (benzene)

Anal. calcd. for $C_{12}H_{15}BrO_3$ (M=287.16) C 50.19, H 5.26, Br 27.83,

found: C 50.30, H 5.39, Br 28.00

^{1}H-NMR ($CDCl_3$) (B): δ 1.42 (3H, s), 1.59 (3H, s), 2.44 (1H, d, J=5), 3.78 (3H, s), 4.10 (1H,d, J=9), 4.91 (1H, dd, J_1=5, J_2=9), 6.34 (1H, d, J=2), 6.58 (1H, dd, J_1=2, J_2=8), 7.36 (1H, d, J=8)

3,6-Dibromo-3,4-dihydro-7-methoxy-2,2-dimethyl-2*H*-1-benzopyran-4-ol (**19b**)

oil,

Anal. calcd. for $C_{12}H_{14}BrO_3$ (M=366.06) C 39.37, H 3.85, Br 43.66,

found: C 39.40, H 3.72, Br 43.90

^{1}H-NMR ($CDCl_3$) (B): δ 1.41 (1H,s), 1.60 (3H,s), 2.1 (1H, b), 3.85 (3H, s), 4.10 (1H,d, J=9), 4.88 (1H, m), 6.38 (1H, s), 7.62 (1H,s)

3-Bromo-3,4-dihydro-6,7-dimethoxy-2,2-dimethyl-2*H*-1-benzopyran-4-ol (**19c**)

mp: 84-86 ^oC (benzene); lit. mp: 94-95 ^oC[39]

Anal. calcd. for $C_{13}H_{17}BrO_4$ (M=317.18) C 49.22, H 5.40, Br 25.19,

found: C 49.20, H 5.50, Br 25.20

^{1}H-NMR (CDCl$_3$) (B): δ 1.40 (3H, s), 1.59 (3H, s), 2.60 (1H, b), 3.80 (3H, s), 3.85 (3H,s), 4.10 (1H, d, J=9), 4.85 (1H, d, J=9), 6.30 (1H, s), 6.94 (1H, s)

3-Bromo-3,4-dihydro-7-ethoxy-6-methoxy-2,2-dimethyl-2*H*-1-benzopyran-4-ol (19d)

mp: 114-116 °C (benzene)

Anal. calcd. for $C_{14}H_{13}BrO_4$ (M=331.20) C 50.76, H 5.78, Br 24.13,

found: C 50.88, H 5.83, Br 24.00

^{1}H-NMR (CDCl$_3$) (B): δ 1.40 (3H, s), 1.45 (3H, t, J=6), 1.61 (3H, s), 2.50 (1H, b), 3.79 (3H, s), 4.05 (3H, m), 4.85 (1H, d, J=9), 6.39 (1H, s), 6.92 (1H, s)

3-Bromo-7-methoxy-2,2-dimethyl-2*H*-chromene (22a)

oil,

Anal. calcd. for $C_{12}H_{13}BrO_2$ (M=269.14) C 53.55, H 4.87, Br 29.69

found: C 53.70, H 4.80, Br 29.90

^{1}H-NMR (CDCl$_3$) (B): δ 1.54 (6H, s), 3.76 (3H, s), 6.42 (2H, m), 6.55 (1H, s), 6.79 (1H, d, J=8),

3,6-Dibromo-7-methoxy-2,2-dimethyl-2*H*-chromene (22b)

oil,

Anal. calcd. for $C_{12}H_{12}Br_2O_2$ (M=348.05) C 41.41 , H 3.48, Br 45.92,

found: C 41.20, H 3.56, Br 46.07

^{1}H-NMR (CDCl$_3$) (B): δ 1.54 (6H, s), 3.86 (3H, s), 6.40 (1H, s), 6.58 (1H, s), 7.10 (1H, s)

3-Bromo-6,7-dimethoxy-2,2-dimethyl-2*H*-chromene (22c)

oil,

Anal. calcd. for $C_{13}H_{15}BrO_3$ (M=299.17) C 52.19, H 5.05, Br 26.71,

found: C 52.00, H 5.00, Br 27.03

^{1}H-NMR (CDCl$_3$) (B): δ 1.52 (6H, s), 3.78 (3H, s), 3.81 (3H, s), 6.40 (1H, s), 6.45 (1H, s), 6.60 (1H, s)

7.8 Reaction of 2,2-dimethyl-2*H*-chromenes with phenylselenyl chloride

General procedure for reaction of alkoxy-2,2-dimethyl-chromenes with phenylselenyl chloride:

10 mmol chromenes **6** were dissolved 50 mL dichloromethane then 1.92 g (10 mmol)
phenylselenyl chloride was added at 25 ^{o}C while stirring. The reactions were monitored by tlc (eluent: 1:9/ EtOAc - hexane). When the starting chromenes were disappeared the solvent was removed in vacuum and the residue was roughly separated using automated flash-chromatography equipment (CombiFlash® Rf).[94] Our combined column chromatography method[81] was used to afford compounds (**29a-d**, **60a,c** and **30a-d**) as oils.
(see yields in Table 10)

7-Methoxy-2,2-dimethyl-3-(phenylselenyl)-chromene (**29a**)
^{1}H -NMR (DMSO-d_6) (B): δ 1.50 (s, 6H), 3.75 (s, 3H), 6.40 (m, 3H), 6.80 (d, J=8, 1H), 7.30 (m, 3H), 7.60 (m, 2H)

6,7-Dimethoxy-2,2-dimethyl-3-(phenylselenyl)-chromene (**29b**)
^{1}H-NMR (DMSO-d_6) (B): δ 1.50 (s, 6H), 3.78 (s,3H), 3.85 (s, 3H), 6.33 (s, 1H), 6.41 (s, 1H), 6.42 (s, 1H), 7.30 (m, 3H), 7.60 (m, 3H)
MS (m/z, %, ^{80}Se): 376 (M^{+},18), 361(24), 281(10), 219 (100), 175(15); high-resolution (^{78}Se): 374.0585 (calcd.), 374.0586 (measured)

7,8-Dimethoxy-2,2-dimethyl-3-(phenylselenyl)-chromene (29c)
^{1}H-NMR (DMSO-d_6) (B): δ 1.55 (s, 6H), 3.82 (s, 3H), 3.85 (s, 3H), 6.35 (s, 1H), 6.40 (d, J=8, 1H), 6.57 (d, J=8, 1H), 7.30 (m, 3H), 7.62 (m, 2H)
MS (m/z, %, ^{80}Se): 376 (M^{+}, 18), 361 (40), 219 (100), 189 (35)

6-Methoxy-7-ethoxy-2,2-dimethyl-3-(phenylselenyl)-chromene (**29d**)

IR (KBr) (E): ν_{max} cm^{-1} 451, 487, 551, 583, 648, 692, 769, 816, 828, 846, 867, 890, 926, 957, 1000, 1044, 1063, 1301, 1315, 1348, 1358, 1379, 1392, 1413, 1435, 1575, 2834, 2869, 2907, 2978, 3058, 3424 cm^{-1}

^{1}H -NMR (DMSO-d_6) (C): δ 1.45 (t, J=7, 3H, CH_3/EtO), 1.50 (s, 6H, diMe), 3.79 (s, 3H, MeO), 4.06 (q, J=7, 2H, -CH_2-), 6.36 (s, 1H), 6.43 (s, 2H), 7.32 (m, 3H), 7.61 (m, 2H)

^{13}C -NMR [95] (DMSO-d_6) (C): δ ppm 14.67 (CH_3 -Et) 26.55 (diMe), 56.33 (MeO), 64.28 (OCH_2), 80.43, 101.99 (C4), 109.30, 114.41, 127.79, 127.85, 129.36 (C3, C5-SePh) 129.74, 131.06, 133.75 (C1, C6-SePh), 143.62, 146.62, 149.29

ESI-MS (ES^+, m/z, %) 454.1 (49), 452.1 (27), 413 ($M+Na^+$, 11), 390.6 ($M+H^+$, 11), 234.8 (20), 233.8 (100), 204.7 (10)

7-Methoxy-2,2-dimethyl-3,6-bis(phenylselenyl)-chromene (**60a**)

^{1}H -NMR (DMSO-d_6) (C): δ 1.42 (6H,s, diMe), 3.75 (3H,s, MeO), 6.50 (1H, s), 6.59 (1H,s), 6.99 (1H,s), 7.24-7.35 (8H,m), 7.55 (2H, t, 4-H-phenyl-Se)

MS (m/z, %, ^{80}Se): 502 (M^+,7), 487 (8), 433 (8), 365(38), 331 (100), 189 (40)

7,8-Dimethoxy-2,2-dimethyl-3,6-bis(phenylselenyl)-chromene (**60c**)

^{1}H -NMR (DMSO-d_6) (B) : δ 1.55 (s, 6H, diMe), 3.82 (s, 3H, MeO), 3.90 (s, 3H, MeO), 6.18 (s, 1H), 6.52 (s, 1H), 7.15-7.65 (m, 10H)

MS (m/z, %, ^{80}Se): 532 (M^+, 37), 517 (20), 375 (100), 345(12), 218 (50), 77(55)

3-Chloro-6,7-dimethoxy-2,2-dimethyl-2*H*-chromene (**30b**)

^{1}H -NMR (DMSO-d_6) (B): δ 1.50 (s, 6H, diMe), 3.80 (s, 3H, MeO), 3.85 (s, 3H, MeO), 6.40 (s, 1H), 6.45 (s, 1H), 6.50 (s, 1H)

MS (m/z, %): 254 (M^+, 55), 239 (100), 219 (80), 195 (20), 175 (10)

3-Chloro-7,8-dimethoxy-2,2-dimethyl-2*H*-chromene (30c)

^{1}H -NMR (DMSO-d_6) (B): δ 1.58 (s, 6H, diMe), 3.81 (s, 3H, MeO), 3.84 (s, 3H, MeO), 6.40 (s, 1H + d, 1H, J=8), 6.48 (s, 1H)

MS (m/z, %): 254 (M^+, 27), 239 (100), 219 (38), 175 (5)

3-Chloro-6-methoxy-7-ethoxy-2,2-dimethyl-2,2-dimethyl-2*H*-chromene (**30d**)

^{1}H -NMR (DMSO-d_6) (B): δ 1.44 (t, 3H, J=7, Me in EtO), 1.50 (s, 6H, diMe), 3.80 (s, 3H, MeO), 4.07 (q, 2H, J=7, CH_2), 6.41 (s, 1H), 6.45 (s, 1H), 6.49 (s, 1H)

8. Summary

My dissertation mainly deals with the syntheses and chemical transformations of 2,2-dimethyl-2*H*-1-benzopyrans. These research works aim at the development of 'biorational pesticide' with new mode of actions and the development of new antihypertensive agents (Cromakalim analogues).
Development of column chromatography was also a part of my reasearch activities.

Major new scientific results of the dissertation:

1. We prepared many new compounds with potential insecticidal and antihypertensive activity by chlorination and bromination reactions of 2,2-dimethyl-4-chromanones.
We proved that the formation of 4-chloro-2*H*-chromenes and their further chlorination at C-3 as the formation of 3-chloro-2,2-dimethyl-4-chromanones are involved in the pathway of this reaction.
2. We prepared new, selenium-containing derivatives of 2,2-dimethyl-2H-chromenes with sterically and electronically modified $\Delta^{3,4}$ double bonds: we synthesized 1,2,3-selenadiazolo-benzopyran derivatives as new ring systems.
3. We synthesized 3-chloro-2,2-dimethyl-*2H*- chromene derivatives by reaction of 2,2-dimethyl-2*H*-chromenes with phenylselenyl chloride. To our best knowledge this is the only synthetically useful pathway to the derivatives of 3-chloro-2,2-dimethyl-*2H*-chromene.
4. We developed a combined TLC mesh column chromatographic system that unifies the advantages of the vacuum-driven and low-pressure methods. Our procedure was found to be efficient for separations of mixtures showing $\Delta Rf \geq 0.05$ by TLC. In comparison with Taber's low-pressure method we achieved the same or better separation.
5. Selected compounds obtained by *via* oxidative ring-closure of the corresponding semicarbazone derivatives by treatment with selenium dioxide. showed superior non-specific toxic activities on *P. brassicae* and *L. decemlineata* larvae in a comparative study vs. P1 and P2, respectively

9. Összefoglalás

Disszertációmban 2,2-dimetil-2*H*-1-benzopiránok körében végzett szintéziseket és kémiai átalakításokat mutatom be. Ezek a kutatási munkák új hatásmechanizmusú, 'bioracionális inszekticidek' előállítására valamint új hatásmechanizmusú vérnyomáscsökkentő hatóanyagok (Cromakalim analógok) szintézisére irányultak elsődlegesen. Munkám részét képezte továbbá oszlopkromatográfiás módszerfejlesztés is.

A dolgozat fontosabb új tudományos eredményei:

1. 4-kromanon származékok brómozási és klórozási reakciójával nagyszámú , potenciálisan inszekticid és vérnyomáscsökkentő hatású, új vegyületet állítottunk elő. Bizonyítottuk, hogy 4-klór-2,2-dimetil-2*H*-kromének képződése és azok további klórozódása C-3 pozícióban hasonlóan 3-klór-2,2-dimetil-2-kromanonok képződéséhez a reakcióút részét képezi.
2. 2,2-dimetil-2*H*-kromén olyan szelén- tartalmú új származékait állítottam elő, ahol a $\Delta^{3,4}$ kettős kötés sztérikusan és elektronikusan módosulva van; megvalósítottuk 1,2,3-szelenodiazolo-benzopirán származékok szintézisét új gyűrűrendszerként.
3. 2,2-dimetil-2*H*-kromén származékok és fenilszelenil-klorid reakciójával 2,2-dimetil-3-klór-2*H*-kromén származékokat allítottunk elő, amely a legjobb tudásunk szerint az egyetlen szintetikusan hasznosítható módszer.

4. Az előállított analógok hatékony és gyors szétválasztására egy kombinált oszlopkromatográfiás módszer fejlesztettünk ki. Módszerünk effektívnek bizonyult olyan keverékek szétválasztására, ahol a Δ Rf $\geq$ 0.05 vékonyréteg-kromatográfiánál. A Taber-féle alacsony nyomású módszerrel összehasonlítva ugyanolyan vagy jobb elválasztásokat értünk el.
5. Kiválasztott vegyületek, amelyeket oxidatív gyűrűzárással alakítottunk ki a megfelelő szemikarbazon származékokból szelén-dioxiddal, egy nagyságrenddel jobb nem-specifikus toxikus aktivitást mutattak *P. brassicae* and *L. decemlineata* lárváin, mint a megfelelő P1 és P2 egy összehasonlító vizsgálatban.

10.Publications

10.1 List of publications included in the dissertation

1) Zsótér, Zs.; Eszenyi, T.; Tímár, T.: TLC Mesh Column Chromatography: Facile Combination of Vacuum-Driven and Low-Pressure Methods, *J. Org. Chem*. 59, 672 (**1994**)
Impact factor= 3.193

2) Eszenyi, T.; Zsótér, Zs.; Tímár, T.; Sebők, P: On the Formation of 3,4-Dichloro-2,2-dimethyl-2*H*-chromenes from 2,2-Dimethyl-4-chromanones, *Heterocycl. Commun. 4,* 155 (**1998**)
Impact factor= 0.469

3) Zsótér, Zs.; Tímár, T.; Kónya, K; Patonay, T.; Jekő, J.: Facile synthesis of novel selenium-containing benzopyran derivatives, *J. Heterocycl. Chem.* (**2014**) (in press)
Impact factor= 1.224

Aggregate IF of the papers published/in press: 4.886

10.2 Publications not included in the dissertation

1) Tóth, Z.; Zsótér, Zs.; Beck, M.T.: Testing the Photocatalytic Activity of Cyanogen- and Thiocyanogen-based Inorganic Polimers., *React. Kinet. Catal. Lett*. *47*, 29 (**1992**)
Impact factor= 0.334

2) Pados, Gy.; Kiss, Z.; Zsótér, Zs.; Karádi, I.; Paragh, Gy.: LDL-koleszterin, LDL-koleszterin kalkulátor, *Háziorvos Továbbképző Szemle, 13,* 569 (**2008**)
[title: LDL-cholesterol, LDL-cholesterol calculator; published in Hungarian in the postgraduate medical journal]

10.3 Permisson for publication

See the correspondence below:

From: Harin.Mehta@alkaloida.com [mailto:Harin.Mehta@alkaloida.com]

Sent: Thursday, January 19, 2012 11:46 AM

To: Tímár Tibor

Subject: Re: FW: Benzopyran chemistry and request for your permission

Dear Tibor,

Sorry, I forgot to reply.

On behalf of Alkaloida, I give you subject permission.

I will send a separate email marking copy to Dr. Simon, for his records.

KR

Harin

Tímár Tibor <ttimar@ubichempharma.com> 19/01/2012 11:18

To<harin.mehta@alkaloida.com>

cc

SubjectFW: Benzopyran chemistry and request for your permission

Dear Sir,

You are kindly asked to reply to the message below and give your permission to the publications.

Thanks and Best regards,

Tibor

From: Tímár Tibor

Sent: Wednesday, January 11, 2012 10:14 AM

To: harin.mehta@alkaloida.com
Subject: Benzopyran chemistry and request for your permission
Importance: High

Dear Sir,
Many thanks for the call and as we agreed I provide the information that we just discussed.
In early 80's at the former Alkaloida Chem. Co. there was a research program on precocenes (substituted 2,2-dimethyl-2H-chromenes) that were considered at that time as forth generation selective insecticides.
To the best of my knowledge these derivatives were not able to reach the commercialization, they remained within the walls of chemical and biological research labs.
At that time we have performed several sort of chemical transformation in the field of benzopyrans , synthesized few hundreds of precocene analogs and published some papers on this subject, however some of those results are still waiting to be published.

My request is to ask for your kind permission for these publictions.
Many thanks in advance,
With the best personal regards,
Tibor
TIBOR TIMAR PhD.
Senior Project Manager

UBICHEM Research Ltd.
Hungary

Illatos út 33, Budapest, H-1097
Tel: +36 (1) 347 5060 / ext. 114
Fax: +36 (1) 347 5061
Mobile: +36 (30) 569 6546
---

11. Abbreviations

CAN: ceric ammonium nitrate

DMF: dimethylformamide

DMSO: dimethyl-sulfoxide

EG: ethylene glycol

IGR: insect growth regulator

LDA: lithium diisopropylamide

NBS: *N*-bromosuccinimide

P1, P2, P3: precocene 1, 2 and 3, respectively

PCO: potassium channel opener

PEG: polyethylene glycol

WES: Williamson ether synthesis

IR: infrared spectroscopy

NMR: nuclear magnetic resonance spectroscopy

s: singlet

d: doublet; dd: double doublet

t: triplet; tt: double triplet

q: quartet

b: broad

MS: mass spectroscopy; ESI-MS: electrospray ionization mass spectrometry

rt: room temperature; Δ: heat/reflux

TLC: thin layer chromatography

VLC: vacuum liquid chromatography

12. References

[1] Atkinson, P.W.: *Vector Biology, Ecology and Control*, Springer, London, (**2010**)

[2] Pretty, J. : *The Pesticide Detox, Towards a More Sustainable Agriculture*. Earthscan, London, (**2009**)

[3] Schweizer, E. E.; Meeder-Nycz, D. In Heterocyclic Compounds: Chromenes; Ellis, G. P., Ed., Wiley, New York, 11–139 (**1977**)

[4] Based on a search for substances/substructures on SciFinder (19 August, **2013**)

[5] Nicolaou, K.C.; Pfefferkorn, J.A.; Roecker, A.J.; Cao, G.-Q. ; Barluenga, S.; Mitchell, H. J. : Natural Product-like Combinatorial Libraries Based on Privileged Structures. 1. General Principles and Solid-Phase Synthesis of Benzopyrans, *J. Am. Chem. Soc.* *122*, 9939 (**2000**)

[6] Nicolaou, K.C.; Pfefferkorn, J.A.; Guo-Giang Cao: Selenium-Based Solid-Phase Synthesis of Benzopyrans I: Applications to Combinatorial Synthesis of Natural Products *Angew. Chem., Int. Ed.* *39*, No. 4., **(2000)** and the references cited therein

[7] Joulain, D.; Tabacchi, R.: Two volatile β-chromenes from *Wisteria sinensis* flowers, *Phytochemistry* *37*, 1769 (**1994**)

[8] van Otterlo, W. A. L.; Ngidi, E.L.; Kuzvidza, S.; Morgans, G. L.; Moleele, S.S.; C. B. de Koning: Ring-closing metathesis for the synthesis of 2*H*- and 4*H*-chromenes, *Tetrahedron* *61*, 9996 (**2005**)

[9] Vyas, A.V.; Mulchandani, N.B. : Biosynthesis of precocenes-I and -II, anti-juvenile hormones, *Phytochemistry* *19*, 2597 (**1980**)

[10] Alertsen, A.R.: Ageratochromenes, a heterocyclic compound from the essential oil of Ageratum houstonianum Mill. *Acta Polytech. Scand. Ser. Ch.* *10*, 1 (**1961**)

[11] Meyer, A.: Vitaminic properties of alpha-tocopherols (vitamin E), *Int. Z. Vitaminforsch. Beih.* *29*(1-2), 77 (**1958**)

[12] Bowers, W.S.; Ohta, T.; Cleere, J.S.; Marsella, P.A.: Discovery of Insect Anti-juvenile Hormones in Plants, *Science*, *193*, 542 (**1976**)

[13] Fodor, A; Tímár, T.; Kiss, I; Hosztafi, S.; Varga, E.; Soós, J.; Sebők, P.: Effects of precocene analogs on the nematode Caenorhabditis remanei (var. Bangaloreiensis). I. Structure/activity relations, *Gen. Comp. Endocrinol.* *74*, 18 (**1989**)

[14]Sebők, P.; Tímár, T.; Eszenyi, T.: Patonay, T.: The first synthesis of 7-alkylthio-2,2-dimethyl-2H-chromenes, the sulfur analogs of natural and synthetic precocenes *Synthesis*, *8*, 837 (**1994**) and the references cited therein

[15] Lévai, A.; Tímár, T.: Preparation of 2,2-Dimethyl-2*H*-chromenes with Carboxamide Containing Side Chain *Pharmazie*, *45*, H.9, 660 (**1990**) and the references cited therein

[16] Kiss, I; Fodor, A.; Tímár, T.; Hosztafi, S.; Sebők, P.; Török, T.; Virágh, E.: Biological activity of precocene analogues on *Locusta migratoria*, *Experientia*, *44*, 790 (**1988**)

[17] Darvas, B.; Tímár, T.; Varjas, L.; Kulcsár, P.; Hosztafi, S.; Bordás, B.: Synthesis of Novel 2,2-Dimethylchromene Derivatives and their Toxic Activity on Larvae of *Pieris brassicae (Lep., Pieridae)* and *Leptinotarsa decemlineata (Col., Chrysomelidae)*, *Acta Phytopathologica et Etomologica Hungarica*, *24*, 455 (**1989**)

[18] Ashwood, V.A.; Buckingham, R.E.; Cassidy, F.; Evans, J. M.; Faruk, E.A.; Hamilton, T.C.; Nash, D.J.; Stemp, G.; Willcocks, K.: Synthesis and antihypertensive activity of 4-(cyclic amido)-2*H*-1-benzopyrans**,** *J. Med. Chem*. *29*, 2194 (**1986**)

[19] Sebille, S.; Tullio, P. de; Boverie, S.; Antoine, M.H; Lebrun, P.; Pirotte, B.: Recent Developments in the Chemistry of Potassium Channel Activators: The Cromakalim Analogs, *Curr. Med. Chem. 11*, 1213 **(2004)**

[20] Tímár, T.; Lévai, A.; Eszenyi, T.; Sebők, P.: Synthesis of 2,2-dimethyl-4-chromanones,
J. Heterocycl. Chem. *37*(6), 1389 **(2000)**

[21] Burrell, G.; Cassidy, F.; Evans, J. M.; Lightowler, D.; Stemp, G.: Variation in the Aromatic Ring of Cromakalim: Antihypertensive Activity of Pyranopyridines and 6-Alkyl-*2H*- 1- benzopyrans, *J. Med. Chem*. *33*, 3023 (**1990**)

[22] Tímár, T.; Eszenyi, T.; Sebők, P.; Galamb, V..; Fazekasné, L.; Istvánné, Z.; Kováchné, Á.; Nagyné, Cs. E.: Process for the preparation of anti-hypertensive benzopyran derivative, US Patent 5 145 985, (**1992)**

[23] Adam, W.; Jekő, J.; Lévai, A.; Nemes, Cs.; Patonay, T.; Sebők, P.: Epoxidation of 2,2-Dimethyl-2H-chromenes by Dimethyldioxirane and Jacobsen's Mn(III) Catalysts, *Tetrahedron Lett*. *36*, 3669 (**1995**)

[24] Evans, J. M.; Fake, C.S.; Hamilton, T. C.; Poyser, R. H.; Watts, E. A.: Synthesis and Antihypertensive Activity of substituted trans-4-Amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ols, *J. Med. Chem. 26* (11), 1582 (**1983**)

[25] Lévai, A.; Tímár, T.; Sebők, P.; Eszenyi, T.: Synthesis of 2,2-dimethyl-2*H*-chromenes, *Heterocycles*, *53* (5), 1193 (**2000**)

[26] Shriner, R.L.; Sharp, A.G.: The Action of Alkylmagnesium Halides on Coumarin and Related Compounds. Synthesis of 2,2-Dialkyl-1,2-Benzopyrans, *J. Org. Chem*. *4*, 575 (**1939**)

[27] Mann, J.; Kane, P.D.: The synthesis of cyclopropyl analogues of precocene I *Tetrahedron Lett*. *26*, 4677 (**1985**)

[28] Ohta, T.; Kuhr, R.J.; Bowers, W.S.: Radiosynthesis and metabolism of the insect antijuvenile hormone, precocene II., *J. Agric. Food Chem.* *25*, 478 (**1977**)

[29] Chemistry of Heterocyclic Compounds: Chromenes, Chromanones, and Chromones, Vol. 31, G.P. Ellis, Ed., John Wiley & Sons, (**1977**)

[30] Zsindely, J.; Schmid, H.: Sigmatropische Umlagerungen von Aryl-propargyläthern; Synthese von 1, 5-Dimethyl-6-methylen-tricyclo[3, 2, 1, $0^{2,7}$]-oct-3-en-8-on-Derivaten. Vorläufige Mitteilung , *Helv. Chim. Acta, 51*, 1510 **(1968)**

[31] Anderson, W. K.; La Voie, E. J.: Thermal Cyclization of Substituted Aryl Propargyl Ethers. The Scope and Regioselectivity of the Reaction in the Synthesis of Substituted 3-Chromenes, *J. Org. Chem*. *38*, 3832 (**1973**)

[32] Iwai, I.; Ide, J.: Studies on Acetylenic Compounds. XXXII. Ring Closure Studies on *Chem. Pharm. Bull.* *11*, 1042 **(1963)**

[33] Rao, U.; Balasubramanian, K.K.: Claisen rearrangement of aryl propargyl ethers in poly(ethylene glycol)- a remarkable substituent and solvent effect, *Tetrahedron Lett.* *24*, 5023 **(1983)**

[34] Hlubucek, J.; Ritchie, E.; Taylor, W. C. : Synthesis of 2,2-dimethylchromens, *Aust. J . Chem.* *24*, 2347 **(1971)**

[35]Anderson, W. K.; La Voie, E. J.; Whitkop,P. G.: Steric and Electronic Factors Which Effect the Thermal Cyclization of Meta-Substituted Aryl Propargyl Ethers. Synthesis of 5- and 7-Substituted 3-Chromenes, *J. Org. Chem*. *39*, 881 (**1974**)

[36] Bowers, W.S.: Insecticide Mode of Action, Academic Press, New York, 403-427 (**1982**)

[37] Camps, F.; Conchillo, A.; Messeguer, A: 3,4-Epoxyprecocene as a model of cytotoxic epoxides: synthesis of trans adducts occurring in the glutathione metabolic pathway, *Tetrahedron*, *43*, 3067 (**1987**) and the references cited therein

[38] Jennings, R. C.; Ottridge, A. P.: The synthesis of the Epoxide and some other possible Metabolites of Precocene I, *J. Chem. Soc., Perkin Trans. 1*, 1733 (**1984**)

[39] Soderlund, D.M; Messeguer, A.; Bowers, W. S.: Precocene II Metabolism in Insects: Synthesis of Potential Metabolites and Identification of Initial in Vitro Biotransformation Products, *J. Agric. Food Chem*. *28*, 724 (**1980**)

[40] Adam, W.; Jekő, J.; Lévai, A.; Nemes, Cs.; Patonay, T.; Sebők, P.: Enantioselective Epoxidation of 2,2-Dimethyl-2*H*-chromenes by Dimethyldioxirane and Jacobsen's Mn(III)salen Catalysts, *Tetrahedron Lett*. *36*, 3669 (**1995**)

[41] 'The Chemistry of Organic Selenium and Tellurium Compounds', eds. Saul Patai and Zvi Rappoport, John Wiley and Sons, Chichester, New York, vol. 1 (**1986**)

[42] 'The Chemistry of Organic Selenium and Tellurium Compounds', eds. Saul Patai and Zvi Rappoport, John Wiley and Sons, Chichester, New York, vol. 2 (**1987**)

[43] 'Organoselenium Chemistry,' ed. D. Liotta, John Wiley and Sons, New York, (**1987**)

[44] C. Paulmier, 'Selenium Reagents and Intermediates in Organic Synthesis', ed. J. E. Baldwin, Organic Chemistry Series, vol. 4., Pergamon Press, Oxford, (**1986**)

[45] Liotta, D.; Zima, G.; Saindane, M.: Origins of regio- and stereoselectivity in additions of phenylselenenyl chloride to allylic alcohols and the applicability of these additions to a simple 1,3-enone transposition sequence, *J. Org. Chem.* *47*, 1258 (**1982**)

[46] Liotta, D.; Zima, G.: An examination of the synthetic utility of phenylselenenyl chloride additions to olefins, *Tetrahedron Lett.* *19*, 4977 **(1978)**

[47] Duddeck, H.; Wagner, P.; Gegner, S., Dynamic ^{77}Se nmr of phenylselenyl cyclohexane derivatives**,** *Tetrahedron Lett.* *26* , 1205 **(1985)**

[48] Wagner, P.; Duddeck, H.; Tímár, T.; Csuhai, É.; Jászberényi, J. Cs.: Unusual behaviour of 2,2-dimethyl-2*H*-chromene derivatives (precocenes) in phenylselenenylation
J. Chem. Soc. Perkin Trans 1, 2128 (**1989**)

[49] Garrat, D. G.: The nonstereospecific addition of benzeneselenenyl chloride to 3,4-dihydro-2*H*-pyran, *J. Can. Chem.* *56*, 2184 (**1978**)

[50] Tímár, T.; Lévai, A.; Eszenyi, T.; Sebők, P.: Synthesis of 2,2-Dimethyl-4-chromanones, *J. Heterocycl. Chem.* 37(6), 1389 (**2000**)

[51] Auwers, K. v.; Lämmerhirt, E.: Ring formation I. Unsaturated ketones and chromanones from p-cresol, *Liebigs Ann. Chem.* *421*, 1 (**1920**)

[52] Sebők, P.; Jekő, J.; Tímár, T.; Jászberényi, J. Cs.: On the synthesis of substituted 2,2-dimethyl-4-chromanones and related compounds, *Tetrahedron Lett.* *33*, 2791 **(1992)**

[53] Bhat, H. B.; Venkataraman, K: Synthetical experiments in the chromone group—XXXV: Synthesis of dihydrojacareubin and a new general method for the synthesis of 2,2-dimethylchromanones, *Tetrahedron*, *19*, 77 (**1963**)

[54] Kabbe, H-J; Widdig, A.: Synthesis and Reactions of 4-Chromanones, *Angew. Chem.Int. Ed.* *21*, 247 (**1982**)

[55] Camps, F.; Coll, J.; Colomina, O.; Messeguer, A: Fries Rearrangement of Methoxyphenyl 3-Methylbut-2-enoates, *J. Heterocycl. Chem.* *22*, 363 (**1985**)

[56] Arimala,G.; Balasubramanian, K. K., A simple route for the synthesis of 4-chlorochromenes and chroman-4-ones, *Tetrahedron Lett.* *29*, 3487 (**1988**)

[57] Kanvinde, M. N.; Kulkarni, S. A.; M. A. Paradkar, M. A.: Mild and Efficient Conversion of 2,2-Dimethylchromans into Chromanones Using CAN: Synthesis of Graveolones, *Synth. Commun*. *20*, 3259 (**1990**)

[58] Camps, F.; Coll, J.; Messeguer, A.; Pericás, M.A.: Direct preparation of 3,4-dichloro-2,-dimethyl-3-chromenes from 2,2-dimethyl-4-chromanones, *Tetrahedron Lett*. *40*, 3901 (**1979)**

[59] Eszenyi, T.; Tímár, T ; Sebők, P.: A novel synthesis of 4-halo-2*H*-chromenes, *Tetrahedron Lett.* *32*, 827 (**1991)**

[60] Brown, P. E.; Marcus, W. Y.; Anastasis, A.: Studies of chromenes. Part 5. Reaction of the Vilsmeier reagent with 7-methoxy-2,2-dimethylchroman-4-ones. 4-Chloro-7-methoxy-2,2-dimethyl-2*H*-chromenes and their nitration products.
J. Chem. Soc., Perkin Trans. 1, 1127 (**1985**)

[61] Keimatsu, S.; Satoda, I.: [On the preparation of 1,2,3-selenadiazoles from o-aminobenzeneselenol] *Yakugaku Zhasshi (J. Pharm. Soc. Japan),* *55*, 233 (**1935**)

[62] Wolff, L.: Über 1,2,3-Thiodiazole, *Justus Liebigs Ann. Chem.* *1* 333 (**1904**)

[63] Staudinger, H.; Siegwart, J.: Einwirkung von Schwefelwasserstoff auf Diazoverbindungen, *Ber.* *49*, 1918 (**1916**)

[64] Lalezari, I.; Shafiee, A. : A Novel Synthesis of Selenium Heterocycles: Substituted 1,2,3-Selenodiazoles, *Tetrahedron Lett*. *28*, 5105 (**1969**)

[65] Lalezari, I; Shafiee, A.; Yalpani, M.: Selenium heterocycles. VI. Mechanism of the stereoselective formation of 1,4-diselenafulvenes from 1,2,3-selenadiazoles and base, *J. Org. Chem.* *38*, 338 (**1973**)

[66] Maiti, S.B. ; Chatterjee, A.; S.R. Rayehaudhuri, S.R.: Tricyclic and tetracyclic 1,2,3- selenadiazoles: synthesis of a new class of selenodiazole derivatives, *Ind. J. Chem.* *24B*, 618 (**1985**)

[67] Lalezari, I; Shafiee, A; Yalpani, M.: 1,2,3- Selenadiazole and Its Derivatives, *J. Org. Chem.* *36*, No. 19, 2836 (**1971)**

[68] Meier, H.; Voigt, E. : Bildung und fragmentierung von cycloalkeno-1,2,3-selenadiazolen,
Tetrahedron *28*, 187 (**1972**)

[69] Livingstone, R.: Reaction of some chromens and naphthopyrans with bromine. Part II, *J. Chem. Soc*. *72* (**1962**)

[70] Wolfrom, M. L.; Koos, E.W; Bhat, H.B.: Osage orange pigments. XVIII. Synthesis of osajaxanthone, *J. Org. Chem.* *32*, 1058 (**1967**)

[71] Still, W.C.; Kahn, M.; Mitra, A.: Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution, *J. Org. Chem*. *43*, 2923 (**1978**)

[72] Taber, D. F.: TLC Mesh Column Chromatography, *J. Org. Chem.* *47*, 1351 (**1982**)

[73] Hunt,B. J.; Rigby, W.: Methods, apparatus: new product research, process development and design: short column chromatography, *Chem. Ind. (London)*, 1868 (**1967**)

[74] Meyers, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D.: Separation of Diastereomers Using a Low Cost Preparative Medium-Pressure Liquid Chromatograph *J. Org. Chem.* *44*, 2247 (**1979**)

[75] Targett, N. M.; Kilcoyne, J. P.; Green, B.: Vacuum Liquid Chromatography: An Alternative
to Common Chromatographic Methods, *J. Org. Chem.* *44*, 4962 (**1979**)

[76] Karnik, A.V.; Kulkarni, A.M.; Malviya, N.J.; Mourya, B.R.; Jadhav, B.R.: Synthesis and in vitro anti-bacterial evaluation of tetracyclic-ortho-fused 4*H*-naphtho[1′,2′–5,6]pyrano[3,4-*d*](1,2,3)selenadiazole and its derivatives, *Eur. J. Med. Chem.* *43*, 2615 (**2008**)

[77] Joshi, N. S.; B. K. Karale, B. K.; Gill, C. H.: Synthesis of some thiadiazoles, selenadiazoles and spiroheterocyclic compounds from their 2,2-dimethyl-benzopyran precursors, *Chemistry of Heterocyclic Compounds*, Vol. *42*, No. 5, 681 (**2006**)

[78] Bowers, W.S. Insecticide Mode of Action, Academic Press, New York, 403-427 (**1982**)

[79] Darvas, B.; Jászberényi, J. Cs.; Tímár, T.; Fónagy, A.: Toxic Activity of 2,2-Dimethyl-3,4-dichloro- and 2,2-Dimethyl-[1,2,3]-selenadiazolo-chromenes on *Pieris brassicae* and *Leptinotarsa decemlineata* Larvae, *J. Pesticide Sci*. *18*, 277 **(1993)**

[80] Eszenyi, T.; Zsótér, Zs.; Tímár, T.; Sebők, P: On the Formation of 3,4-Dichloro-2,2-dimethyl-2*H*-chromenes from 2,2-Dimethyl-4-chromanones, *Heterocycl. Commun.* *4*, 155 (**1998**)

[81] Zsótér, Zs.; Eszenyi, T.; Tímár, T.: TLC Mesh Column Chromatography: Facile Combination of Vacuum-Driven and Low-Pressure Methods, *J. Org. Chem*. *59*, 672 (**1994**)

[82] Brown, P.E.; Islam, Q.: A novel silver ion assisted cleavage of a trichlorocyclopropane, *Tetrahedron Lett*. *28*, 3047 (**1987**)

[83] Brown, P.E.; Clegg, W.; Islam, Q.; Steele, J. E.: Studies of chromenes. Part 8. Addition *versus* rearrangement in silver ion-assisted solvolyses of trihalogenocyclopropa[*c*]chromenes, *J. Chem. Soc., Perkin Trans. 1*, 139 (**1990**)

[84] Eszenyi, T.; Tímár, T.: A Novel and Efficient Synthesis of 6-Alkyl-7-alkyloxy-2,2-dimethyl-Chromans, *Synth. Commun*. *20*, 3219 (**1990**)

[85] Alberola, A.; Calvo, B.; Gonzalez-Ortega, A.; Lopez, C.; Villafane, F.: Halogenated 2*H*-1-Benzopyrans: Syntheses and Reactivity toward Aluminium, Magnesium, and Lithium Organometallics, *Heterocycles*, *38*, 819 (**1994**)

[86] Bognár, R.; Jászberényi, J. Cs.; Makleit, S.; Fodor, A.; Deák, P.; Tímár, T.: Benzopyran and benzothiopyran derivatives and compositions containing them, *PTC Int. Appl*. 197, W08800(1988); *Chem. Abstr*. *109*, 73451b (**1988**)

[87] Zsótér, Zs.; Tímár, T.; Kónya, K; Patonay, T.; Jekő, J.: Facile synthesis of novel selenium-containing benzopyran derivatives, *J. Heterocycl. Chem.* (**2014**) (in press)

[88] Williamson, A.: Theory of Aetherification, *Philosophical Magazine, 37*, 350 (**1850**)

[89] *Organic Syntheses*, Coumarone, Coll. *Vol. 5*, 251 (**1973**); Vol. *46*, 28 (**1966**)

[90] Csákai, Z.; Tímár,T. : Unpublished results, Tiszavasvári, Hungary, (**1990**)

[91]Conca, E.; De Bernardi, M.; Fronza, G.; Girometta, M.A.; Mellerio, G.; Vidari, G.; Vita-Finzi, P.: New chromenes from Lactarius fuliginosus fries and Lactarius picinus fries, *Tetrahedron Lett. 22*, 4327 (**1981**)

[92] Darvas, B.; Regecz, M.; Sebők, P.; Timár, T.; Cziáky, Z.; Kóródi, F.; Szabó, Z.; Hatóanyagként új aromás propargil-éter származékokat tartalmazó zoocidek, e vegyületeket tartalmazó szinergista készítmények, valamint eljárás a hatóanyagok előállítására, 210 557 sz. magyar szabadalom. [Hungarian patent]

[93] Schweizer, E.; Lichr, J.; Monaco, D. J.: Reactions of phosphorus compounds. XV. General synthesis of 2H,1-benzopyrans, *J. Org. Chem. 33*, 2416 (**1968**)

[94] Effective Organic Compound Purification: Guidelines and Tactics for Flash Chromatography, 4th edition, Teledyne Isco, Inc., Lincoln, USA (**2010**)

[95] Tímár, T.; Sebők, P.; Kövér, K. E.; Jászberényi, J. Cs.; Batta, Gy.: ^{13}C-NMR Chemical Shifts of Substituted 2,2-Dimethyl-2*H*-chromene, *Magn. Reson. Chem*. *27*, 303 (**1989**)