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Recent advances in the chemistry of 3-nitro-2*H*- and 3-nitro-4*H*-chromenes

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The review integrates and systematically describes data on the methods of synthesis, reactivity and biological activity of 3-nitro-2*H*-chromenes published over the last five years and data on 3-nitro-4*H*-chromenes and related 3-nitro-4*H*-pyrans published over the whole investigation period. Nucleophilic addition, including asymmetric synthesis, cycloaddition and redox reactions involving the C=C double bond and the nitro group of 3-nitro-2*H*-chromenes, are considered. The transformations of new and poorly investigated 3-nitro-4*H*-chromenes include reactions of 4-sulfanyl-substituted 3-nitro-4*H*-chromenes with nucleophiles, reactions of the nitroenamine moiety and removal of the alkylsulfanyl group using reductive processes. Reaction mechanisms and stereochemistry of the reaction products are discussed.
The bibliography includes 103 references.

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1. Introduction

3-Nitro-2*H*-chromenes (3-nitro-2*H*-1-benzopyrans) are important oxygen-containing heterocyclic compounds, actively studied in recent years owing to their accessibility and high reactivity. Among other reasons, the enhanced attention to 3-nitrochromenes is due to the fact that many chromene derivatives are frequently found in nature and have proved themselves as pesticides and promising pharmaceutical agents.[1–5] The introduction of a nitro group into position 3 of the chromene system often leads to a considerable increase in the biological activity. Indeed, 2-nitroacronicine and 6-demethoxy-2-nitroacronicine (Fig. 1) showed higher cytotoxicity against L1210 leukemia cells than analogous derivatives without the nitro group; the inhibitory effect of 2-nitroacronicine was 300 times higher than that of acronicine.[6]

A pronounced antitumour activity against some types of cancer was also found for many synthetic nitrochromenes, for example, compounds with commercial designations S14161,[7,8] BENC-511,[9] DHM12[10] and DHM25 (see Fig 1).[10] Recently, it was reported[11] that 3-nitro-2-trifluoromethyl-2*H*-chromene (TIM-38) exhibits anti-inflammatory activity owing to selective inhibition of the $P2Y_6$ receptor. According to the data available from the literature, high biological activity of 3-nitro-2*H*-chromenes is caused by their covalent binding to the target *via* nucleophilic addition of a protein amino group to the C(4) atom of chromene (Michael reaction).[10–12]

Furthermore, 3-nitro-2*H*-chromenes are actively used to prepare more complex natural and synthetic compounds with useful properties. Methods have been developed for the synthesis of the natural insecticide munduserone,[13] a synthetic antagonist of dopamine D_1-like receptors, doxanthrine,[14] and polyfunctional 6*H*-benzo[*c*]chromenes with the cannabinol skeleton based on nitrochromenes (Fig. 2).[15–17]

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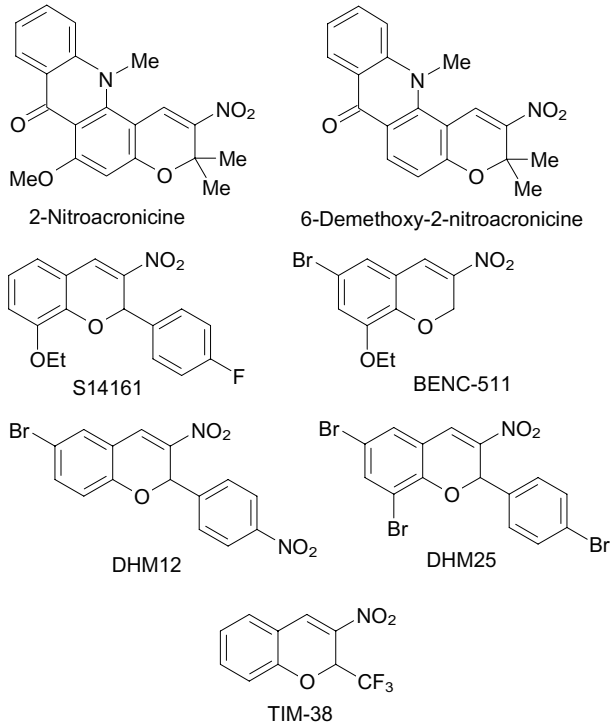


Figure 1. 3-Nitro-2*H*-chromenes with antitumour and anti-inflammatory activities.

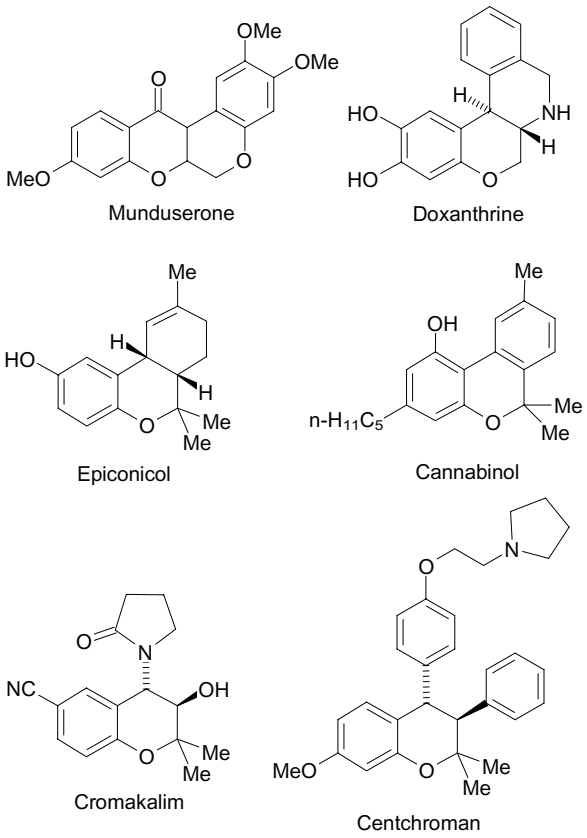
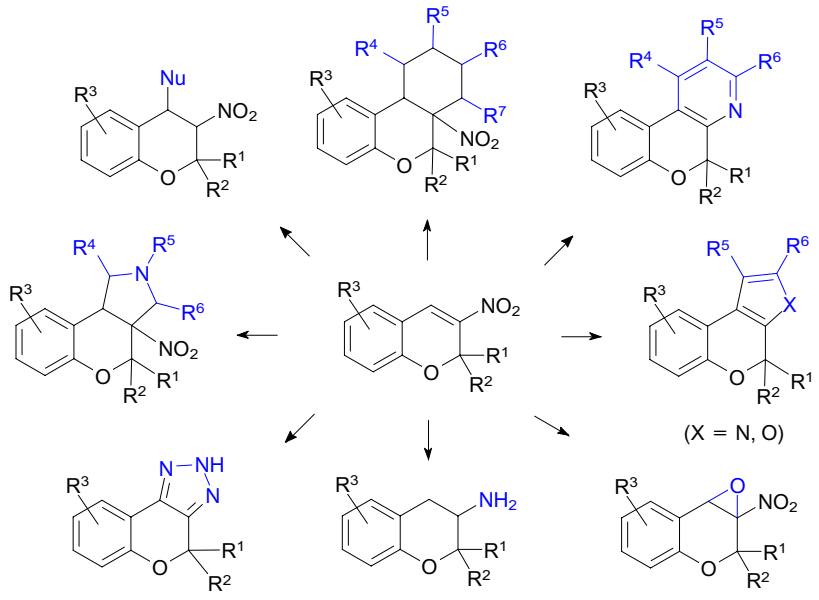


Figure 2. Natural and synthetic bioactive chromenes and chromanes.

The chemical properties of 3-nitro-2*H*-chromenes are determined, first of all, by the presence of the β-nitrostyrene moiety in the molecule; therefore, nucleophilic addition and cycloaddition are the most typical reactions of this heterocyclic system (Scheme 1). These reactions usually give chromane (3,4-dihydro-2*H*-1-benzopyran) derivatives,[1] which, like chromenes, are encountered in nature and exhibit diverse biological activities. For example, epiconicol isolated from ascidians (see Fig. 2) possesses high antibacterial and cytotoxic activities;[18] cromakalim is an efficient potassium channel opener and can be used to treat hypertension[19] and urologic disorders,[20] and centchroman has proved itself as a selective modulator of the estrogen receptors and is used in medicine as a non-steroidal oral contraceptive.[21]

Scheme 1



R^1, R^2, R^3, R^4, R^5, R^6, R^7 = H, Alk, Ar, *etc.*;
Nu is nucleophile

The presence of a nitro group, capable of coordination to various chiral organocatalysts, in position 3 of chromene [22] enables asymmetric nucleophilic addition and cycloaddition to the C=C bond, while the stability of the ambident nitronate anion formed upon nucleophile addition opens up the way to cascade and multicomponent processes giving a broad range of products.[22] The redox reactions involving the double bond and the nitro group successfully supplement the abundant synthetic potential of the 3-nitro-2*H*-chromene system shown in Scheme 1.

Starting from publication of the first review [23] devoted to the chemistry of 3-nitro-2*H*-chromenes in 2013, considerable advances were made in both the synthesis and study of properties of these compounds. Using regio- and stereoselective nucleophilic addition and cycloaddition reactions, new diastereo- and enantioselective methods for Δ^3-annulation of the 3-nitro-2*H*-chromene system by carbo- and heterocycles were developed; as a result, the range of known nitrochromenes was extended and their biological activity was evaluated.

The reviews published over this period, considering various aspects of the chemistry of 2*H*-chromenes [24] and unsaturated compounds as a whole,[22, 25 – 29] contain only fragmentary information on the synthesis and reactivity of 3-nitro-2*H*-chromenes. The present study integrates data on the methods of synthesis, chemical properties and biological activity of 3-nitro-2*H*-chromenes published over the last 5 years.

The first publication dealing with the synthesis of 3-nitro-4*H*-chromenes (3-nitro-4*H*-1-benzopyrans) appeared in 2009;[30] now active research along this line is in progress. This is due to both the ease of preparation of 3-nitro-4*H*-chromenes from available salicylaldehydes and nitroketene N,S-acetals [31] and the discovery of various types of biological activity of these compounds. The present review gives the first systematic account of all published data devoted to this new class of chromenes, including few studies devoted to related 3-nitro-4*H*-pyrans.

The following abbreviations are used:

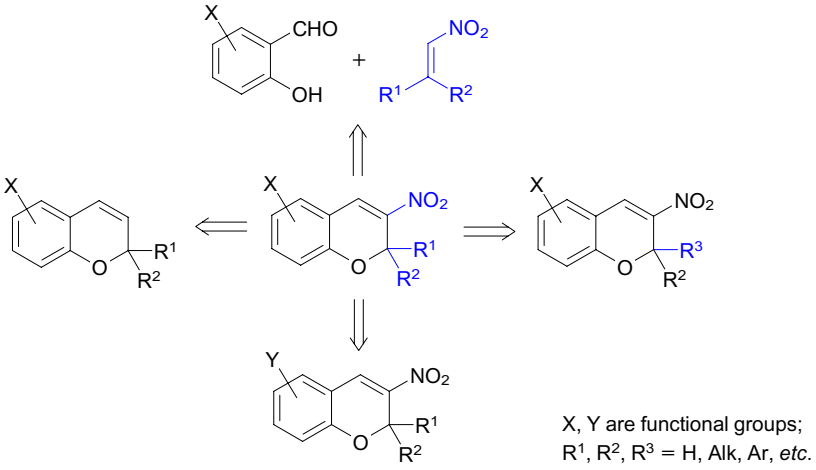
AIBN — 2,2′-azabis(isobutyronitrile);
:B — base;
BM — ball mill;
Boc — *tert*-butoxycarbonyl;
ChOH — choline hydroxide;
DCE — 1,2-dichloroethane;
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene;
DDQ — 2,3-dichloro-5,6-dicyanoquinone;
DIAD — diisopropyl azodicarboxylate;
ee — enantiomeric excess;
Fc — ferrocenyl;
Fu — furyl;
IC_{50} — half-maximal inhibitory concentration;
KC — kinetic control;
MBC — minimum bactericidal concentration;
MIC — minimum inhibitory concentration;
MS — molecular sieves;
MW — microwave radiation;
Naph — naphthyl;
Ni-Ra — Raney nickel;
Py — pyridyl;
rt — room temperature;
Solv — solvent;
TEAB — tetraethylammonium bromide;
TBTH — tri-n-butyltin hydride;
TC — thermodynamic control;
Th — thienyl;
TMG — 1,1,3,3-tetramethylguanidine;
TMS — trimethylsilyl;
Ts — *p*-toluenesulfonyl (tosyl).

2. Methods for the synthesis of 3-nitro-2*H*- and -4*H*-chromenes

The synthetic routes to 3-nitro-2*H*-chromenes can be classified into three major groups (Scheme 2). The first one includes condensation of salicylaldehydes or their imines with unsaturated nitro compounds (nitroalkenes, β-nitroenamines and β-nitroacetaldehyde dialkyl acetals). The second group includes methods based on nitration of the double bond of the 2*H*-chromene pyran ring, which is especially relevant for the synthesis of 3-nitro-2*H*-chromenes from natural compounds (for example, from precocene or acronicine). The third approach is based on modification of the 3-nitro-2*H*-chromene basic structure by introducing a substituent into position 2 (*e.g.*, by transamination) or into the chromene aromatic ring (*e.g.*, by nitration), or on the transformation of side-chain functional groups of nitrochromene. An exhaustive analysis of all synthetic routes towards 3-nitro-2*H*-chromenes is presented in a review.[23]

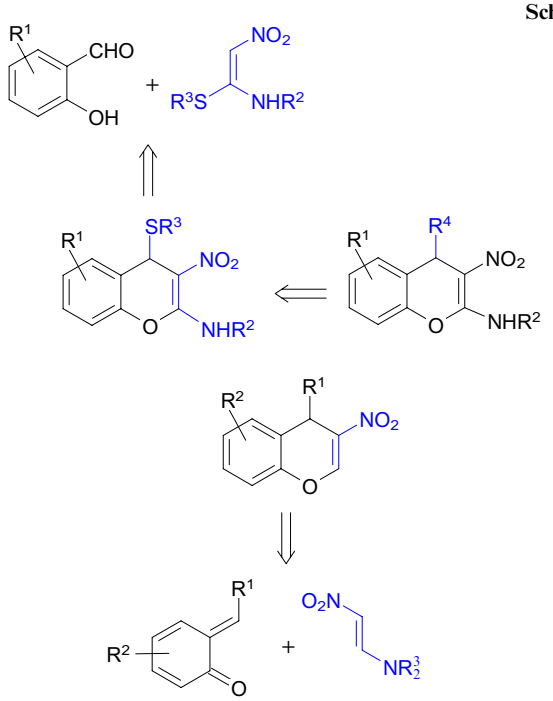
The construction of the 3-nitro-4*H*-chromene skeleton is based on either tandem condensation of salicylaldehydes with nitroketene N,S-acetals (used to prepare 2-amino-3-

Scheme 2



nitro-4-sulfanylamino-4*H*-chromenes) or reaction between highly reactive *o*-quinone methides and β-nitroenamines (used to prepare 2-unsubstituted 3-nitro-4*H*-chromenes). The replacement of the sulfanyl group in position 4 by an aryl group, or removal of the sulfanyl group upon nucleophilic substitution or reduction are also possible (Scheme 3).

Scheme 3

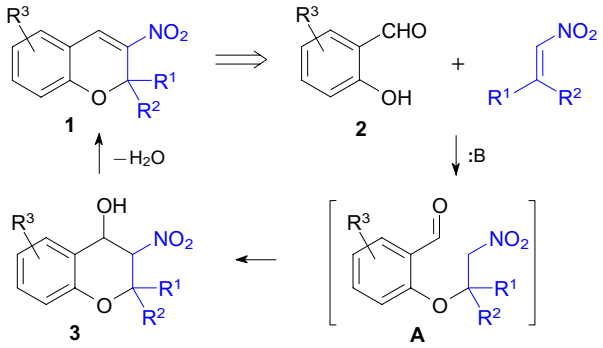


R^1, R^2, R^3, R^4 = H, Alk, Ar, *etc.*

2.1. 3-Nitro-2*H*-chromenes

Among all existing strategies towards 3-nitro-2*H*-chromenes **1**, the strategy based on reaction of salicylaldehydes **2** with conjugated nitroalkenes in the presence of a base is most popular, since the starting reactants (aliphatic and aromatic nitroalkenes) are rather readily accessible. The synthesis includes successive nucleophilic addition of the appropriate phenolate anion to the nitroalkene molecule to give intermediate **A** and the intramolecular Henry condensation yielding 4-hydroxy-3-nitrochromane **3**, which is dehydrated to give the target product **1** (Scheme 4).

Scheme 4



R^1, R^2, R^3 = H, Alk, Ar, *etc.*; **:B** is base

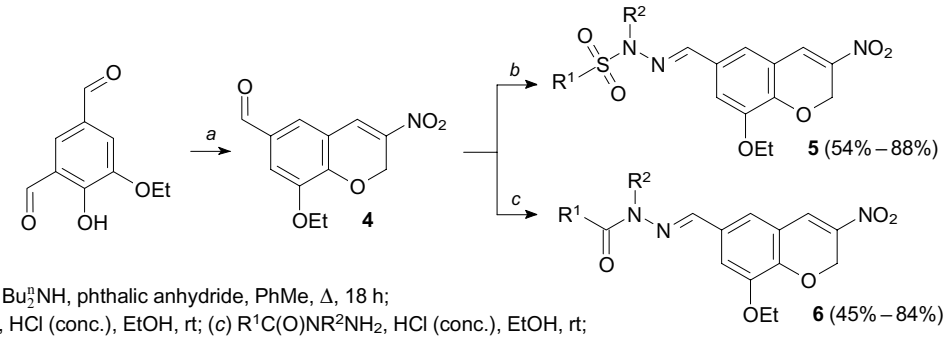
In the synthesis of 2-unsubstituted 3-nitro-2*H*-chromenes, highly reactive nitroethylene, which is prone to polymerization, is normally generated *in situ* by dehydration of 2-nitroethanol on treatment with phthalic anhydride in refluxing toluene. Using this procedure, 8-ethoxy-6-formyl-3-nitro-2*H*-chromene (**4**) was prepared in 40% yield and then converted to sulfonyl hydrazones **5** and acyl hydrazones **6** (Scheme 5).[32–34] Di-n-butylamine was used as a base.

Using a similar procedure, Boc-protected (Boc is *tert*-butoxycarbonyl) 5-amino-3-ethoxysalicylaldehyde was converted to 6-*tert*-butoxycarbonylamino-8-ethoxy-3-nitro-2*H*-chromene (**7**) in 50% yield. This product paved the way to a broad range of derivatives at the amino group such as compounds **8**–**11** (Scheme 6).[35]

2-Unsubstituted chromenes **12a**–**d** and 2-nitro-3*H*-benzo[*f*]chromene (**12e**) were prepared[36] from the corresponding salicylaldehydes and 2-nitroethyl acetate as a source of nitroethylene. The reaction was conducted by refluxing the reactants in toluene in the presence of a catalytic amount of piperidine (Scheme 7).

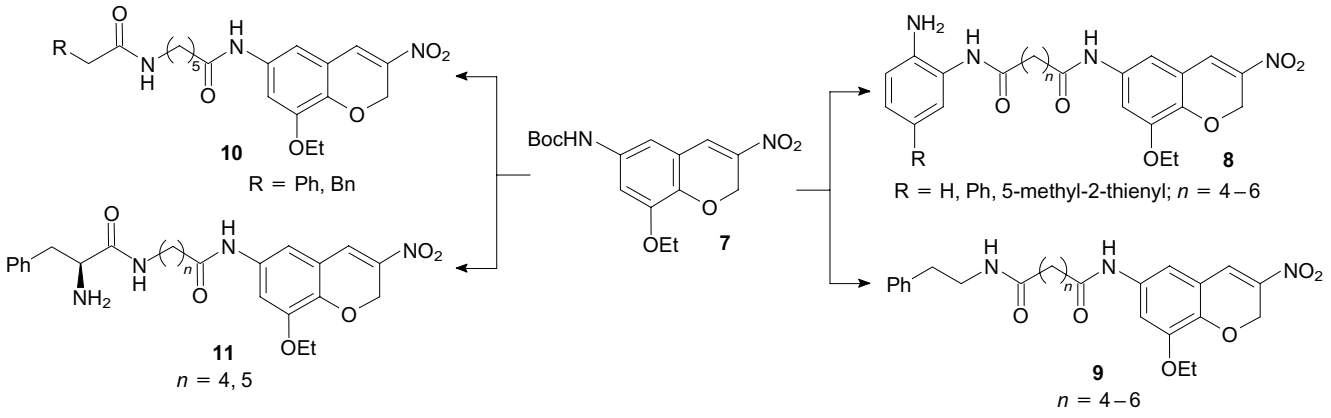
The tandem condensation of salicylaldehydes **2** with conjugated nitroalkenes is extensively used to obtain 3-nitro-2*H*-chromenes with a 2-aryl or 2-alkyl substituent. Recently,[37,38] 2-phenyl-2-trifluoromethyl-substituted chromenes **13**, combining fragments of known 3-nitro-2-trifluoromethyl-2*H*-chromenes and 3-nitro-2-phenyl-2*H*-chromenes, were synthesized from salicylaldehydes and (*E*)-3,3,3-trifluoro-1-nitro-2-phenylprop-1-ene in 64%–96% yields (Scheme 8). The reaction was carried out in

Scheme 5

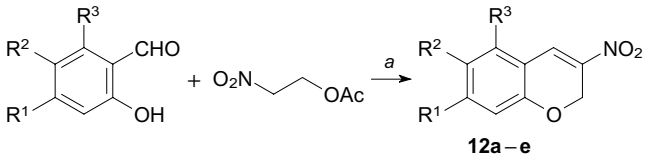


(*a*) $HO(CH_2)_2NO_2$, Bu^n_2NH, phthalic anhydride, PhMe, Δ, 18 h;
(*b*) $R^1SO_2NR^2NH_2$, HCl (conc.), EtOH, rt; (*c*) $R^1C(O)NR^2NH_2$, HCl (conc.), EtOH, rt;
5: R^1 = 4-MeC_6H_4, 3-$O_2NC_6H_4$, 3-Py, 2-Th, 5-methyl-2-pyridyl; R^2 = H, Me;
6: R^1 = 4-$AcHNC_6H_4$, 3-$AcHNC_6H_4$, 3-Py, 2-Py; R^2 = H, Me;
Th is thienyl, Py is pyridyl

Scheme 6

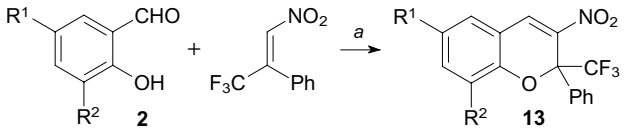


Scheme 7



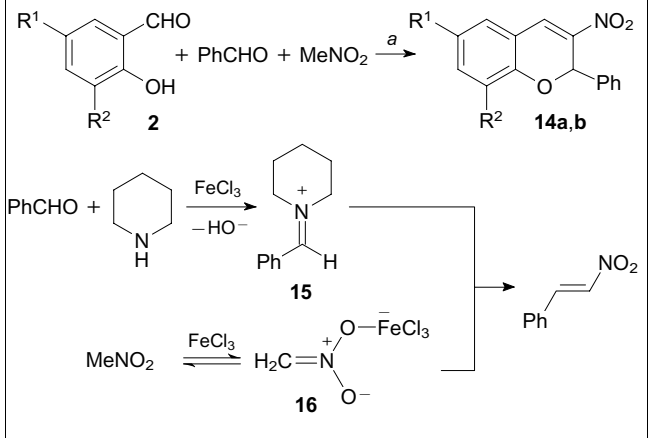
(*a*) piperidine, PhMe, Δ, 24 – 48 h;
$R^1 = R^3 = H$: $R^2 = H$ (**a**, 44% yield), Br (**b**, 41%), Me (**c**, 57%);
$R^2 = R^3 = H$, $R^1 = MeO$ (**d**, 37%); $R^1 = H$, $R^2 – R^3$ is benzo (**e**, 69%)

Scheme 8



(*a*) Et_3N, CH_2Cl_2, rt, 3 h;
R^1 = H, Me, MeO, Cl, Br; R^2 = H, EtO, Cl, Br

Scheme 9



(*a*) piperidine (10 mol.%), $FeCl_3$ (10 mol.%), PhMe, Δ, 4 h;
R^1 = MeO, R^2 = H (**14a**); $R^1 = R^2$ = Cl (**14b**)

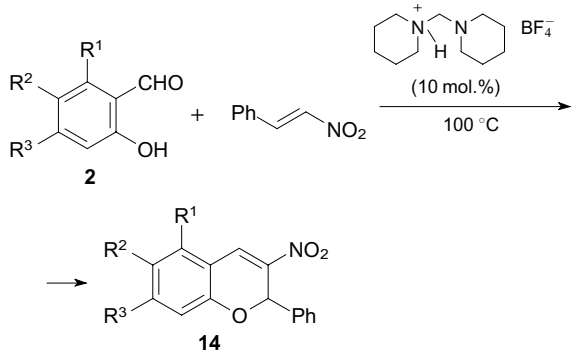
dichloromethane at room temperature for 3 h with triethylamine added as a base. The preparation of chromenes **13** from 5-chloro- and 5-bromosalicylaldehydes required additional refluxing for 3 min and the yields were lowest in this case (64% and 69%, respectively).

Some recent publications report one-pot syntheses of 2-aryl-substituted 3-nitro-2*H*-chromenes using β-nitrostyrenes generated *in situ* from nitroalkanes and aromatic aldehydes. For instance, Indian chemists[39] obtained 6-methoxy-3-nitro-2-phenyl-2*H*-chromene (**14a**) and 6,8-dichloro-3-nitro-2-phenyl-2*H*-chromene (**14b**) in 69% and 55% yields, respectively, by a three-component reaction involving benzaldehyde, nitromethane and salicylaldehydes, with β-nitrostyrene being generated *in situ* from benzaldehyde and nitromethane using $FeCl_3$ as the catalyst. The reaction was carried out in the presence of piperidine on refluxing in toluene for 4 h. The function of the Lewis acid ($FeCl_3$) was to activate the aldehyde group of benzaldehyde (generation of iminium cation **15**) and the methyl group of nitromethane (stabilization of *aci*-form **16**). The subsequent reaction of intermediates **15** and **16** gave rise to β-nitrostyrene, which reacted with salicylaldehydes **2** to give target nitrochromenes **14a**,**b** (Scheme 9).

Climent *et al.*[40] conducted the synthesis of 2-phenylnitrochromenes **14** from β-nitrostyrene and salicylaldehydes **2** at 100 °C without a solvent in an acid-base liquid phase using protonated bis(piperidylmethane) tetrafluoroborate ionic liquid. The yields of chromenes **14** were 56% – 100% (Scheme 10).

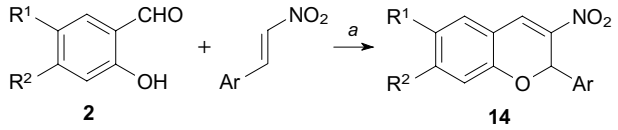
Chinese researchers[41] proposed an original method for the synthesis of 2-aryl-substituted 3-nitro-2*H*-chromenes **14** in which the tandem condensation of aldehydes **2** with nitrostyrenes was carried out in a ball mill at room temperature without a solvent in the presence of K_2CO_3 as a

Scheme 10



R^1 = H, MeO; R^2 = H, MeO, F; R^3 = H, Me, Cl, O_2N

Scheme 11



(*a*) K_2CO_3, BM, rt, 0.5 h;
R^1 = H, Me, Br, F_3C, MeO_2C; R^2 = H, Cl, Br; Ar = Ph, 3-$MeOC_6H_4$, 2-FC_6H_4, 2-BrC_6H_4, 3-BrC_6H_4, 2-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 2,4-$Cl_2C_6H_3$, 2-Cl-5-$O_2NC_6H_3$; BM is ball mill

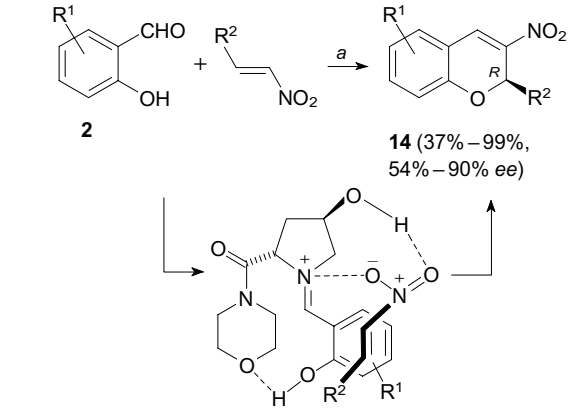
catalyst. The yields of the target products after column chromatography reached 60%–97% (Scheme 11).

2-(4-Bromophenyl)-3-nitro-2*H*-chromenes **14c**–**e** with a biotin probe (**14c**,**d**) or with a xanthine derivative (**14e**) in side chain position 6 were synthesized in order to elucidate the causes behind high antitumour activity of 2-arylnitrochromenes and the mechanism of their action on cancer cells (Scheme 12).[10]

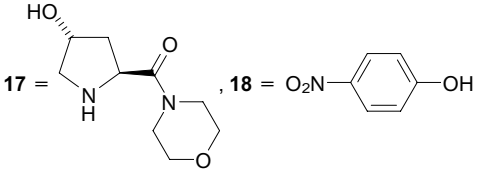
One approach to asymmetric synthesis of 3-nitro-2*H*-chromenes is based on tandem reaction of salicylaldehydes with nitroalkenes in the presence of chiral secondary amines based on commercially available cyclic α-amino acids, such as proline, containing a Lewis base group. Presumably, the role of the catalyst is not only to activate the aldehyde formyl group *via* the formation of the iminium cation (iminium activation), but also to create conditions for the selective approach of a nitroalkene molecule from the sterically unhindered side (asymmetric induction). Efficient asymmetric syntheses of a number of 2-aryl-substituted 3-nitrochromenes **14** based on this strategy were reported by Chen and co-workers,[42] who used optically active amide **17** as a catalyst and 4-nitrophenol (**18**) as a co-catalyst. The latter, being an acid, promotes the generation of the iminium cation *via* protonation of the aldehyde group and increases the nucleophilicity of the hydroxy group of aldehyde **2** owing to the sufficient basicity of the 4-nitrophenoxide anion (Scheme 13).

Moderate enantiomeric excess (*ee*) values for nitrochromenes obtained from 5-methoxy- and 5-bromosalicylaldehydes (54% and 67% *ee*, respectively) are attributable to the proximity of these substituents to the 4-hydroxy group of

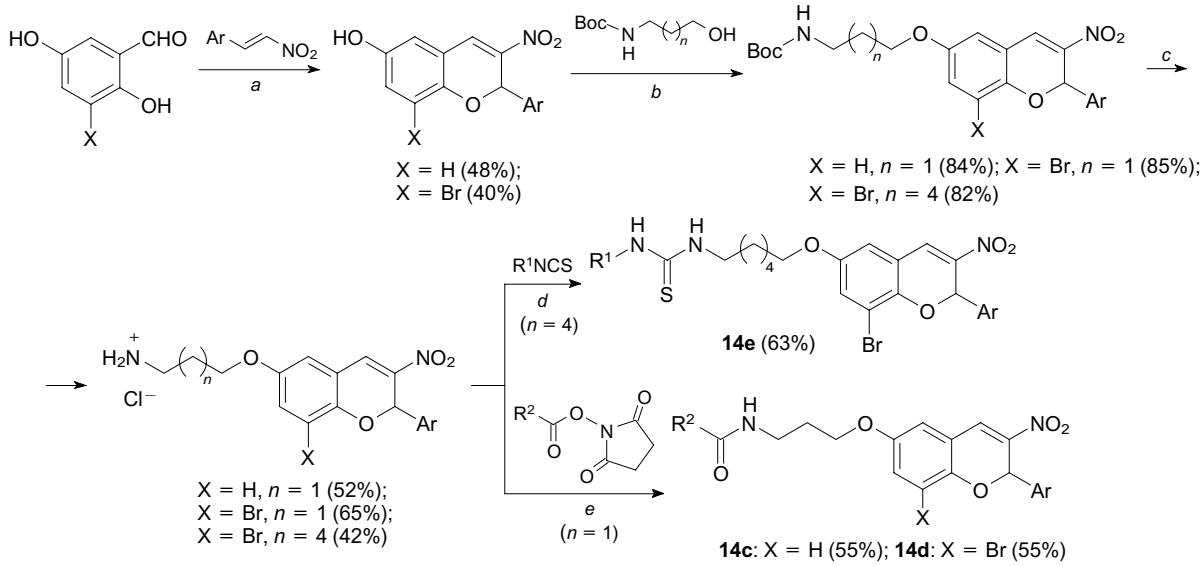
Scheme 13



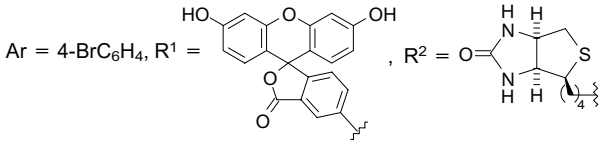
(*a*) **17** (20 mol.%), **18** (20 mol.%), MS 4 Å, $CHCl_3$, rt;
R^1 = H, MeO, Br; R^2 = Ph, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-Fu, Pr^n;



Scheme 12



(*a*) TMG, 4-$O_2NC_6H_4CO_2H$, PhMe, 100 °C, 24 h; (*b*) PPh_3, DIAD, THF, 0 °C→rt, 12 h; (*c*) AcCl, MeOH, 0 °C→rt, 16 h; (*d*) Et_3N, DMF, rt, 20 h; (*e*) TEAB, DMF, rt, 24 h; TMG is 1,1,3,3-tetramethylguanidine, DIAD is diisopropyl azodicarboxylate, TEAB is tetraethylammonium bromide;



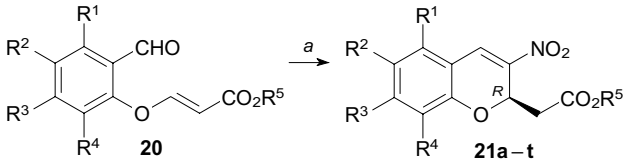
amide **17** in the iminium intermediate, which prevents the formation of a strong hydrogen bond with β-nitroalkene.[42]

A reaction cascade consisting of the Henry and Michael reactions and dehydration with the chiral Takemoto catalyst (**19**) was used to convert salicylaldehydes **20** to the *R*-enantiomers of 3-nitro-2*H*-chromene-2-methylcarboxylates **21a – t** in 10% to 30% yields (Scheme 14, Table 1).[43] Generally, the nature of the substituents $R^1 - R^5$ did not have a considerable effect on the enantioselectivity of this domino reaction; however, the introduction of a chlorine atom into position 3 of the aldehyde decreased the optical purity of product **21n** down to 51% *ee*.

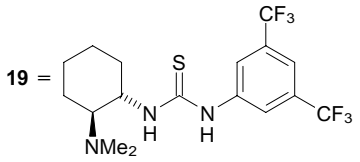
In the same study, in order to carry out comparative assays of antibacterial activity, aldehydes **20** were converted to racemic nitrochromenes **21a – t** (the authors[43] did not report product yields) using a similar procedure with equimolecular amounts of quinine and quinidine as a base (see below, Section 5).

Single diastereomers of 3-bromo-4-hydroxy-3-nitrochromane **22a – c** (74% – 91% yields) containing a glycosyl substituent in position 2 were prepared by reactions of geminal (*Z*)-bromonitroalkenes with salicylaldehydes in the presence of triethylamine. The subsequent treatment of this product with SmI_2 (2 equiv.) in THF afforded enantiopure nitrochromenes **23a – c** in 45% – 85% yields. A probable mechanism of dehydroxybromination includes formal substitution of samarium iodide for bromine followed by β-elimination of the hydroxy group (Scheme 15).[44]

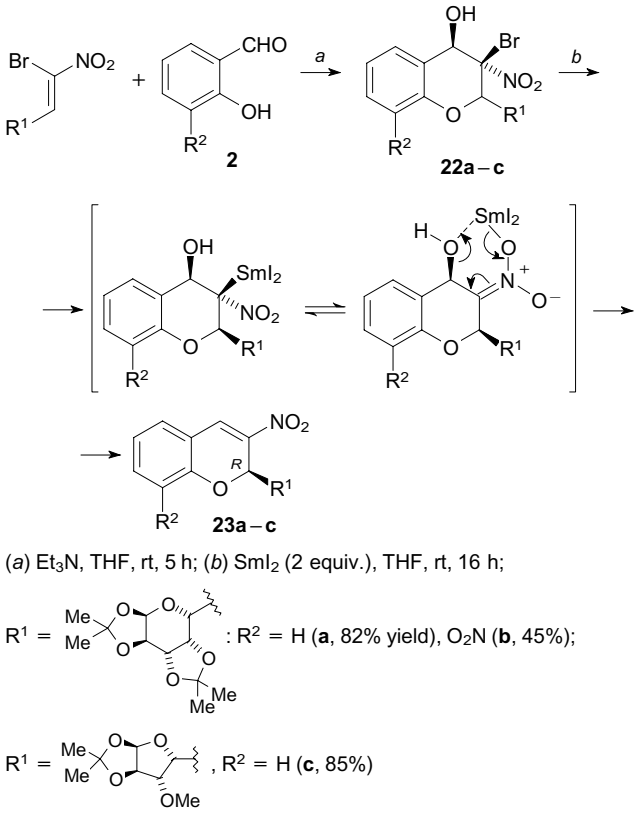
Scheme 14



(*a*) $MeNO_2$, **19** (10 mol.%), $PhCF_3$, rt;



Scheme 15



(*a*) Et_3N, THF, rt, 5 h; (*b*) SmI_2 (2 equiv.), THF, rt, 16 h;

R^1 = : R^2 = H (**a**, 82% yield), O_2N (**b**, 45%);

R^1 = , R^2 = H (**c**, 85%)

Table 1. Synthesis of nitrochromenes **21** (see Scheme 14).[43]

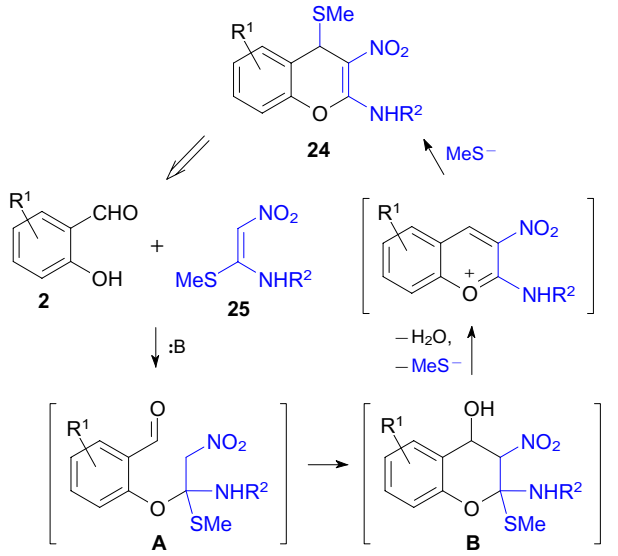
Compound **21**	R^1	R^2	R^3	R^4	R^5	Time /h	Yield (%)	*ee* (%)
a	H	H	H	H	Et	72	27	93
b	H	Me	H	H	Et	72	30	92
c	H	MeO	H	H	Et	72	27	93
d	H	H	MeO	H	Et	72	12	93
e	H	H	H	All	Et	72	29	93
f	H	H	Et_2N	H	Et	72	11	89
g	H	Bu^t	H	Bu^t	Et	70	16	93
h	H	F	H	H	Et	60	19	90
i	H	Cl	H	H	Et	65	17	91
j	H	Br	H	H	Et	72	20	91
k	H	H	H	F	Et	72	17	90
l	H	H	H	Br	Et	72	10	90
m	H	H	Cl	H	Et	72	17	90
n	Cl	H	H	H	Et	36	13	51
o	H	Cl	H	Cl	Et	72	10	84
p	H	Br	H	Br	Et	72	10	84
q	See [a]		H	H	Et	72	10	81
r	H	H	H	H	Me	72	26	90
s	H	Me	H	H	Me	72	25	93
t	H	Br	H	H	Me	72	22	90

[a] $R^1 - R^2$ is benzo.

2.2. 3-Nitro-4*H*-chromenes

Out of 3-nitro-4*H*-chromenes known to date, 2-amino-4-methylsulfanyl derivatives **24** are most readily accessible (Scheme 16). The method for preparation of these compounds developed in 2009 by Rao and Geetha [30] is based on tandem condensation of salicylaldehydes **2** with nitroketene N,S-acetals **25** in the presence of a base. As in the synthesis of 3-nitro-2*H*-chromenes, the first two steps of the process comprise a sequence of oxa-Michael reaction and Henry reaction to give intermediates **A** and **B**, respectively. The latter easily loses an H_2O molecule and a methylsulfanyl group, being converted to benzopyrylium cation **C**, which furnishes the target product **24** upon the addition of the MeS^- anion at position 4 (see Scheme 16).

Scheme 16

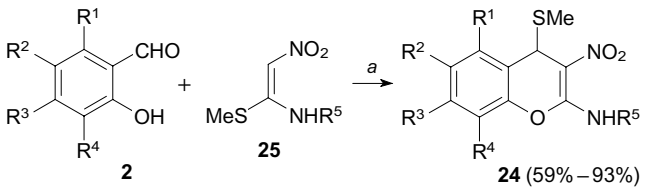


A broad range of 2-alkyl(aryl)amino-4-methylsulfanyl-3-nitro-4*H*-chromenes **24** with various substituents both in the benzene ring and at the nitrogen atom of amino group were prepared in high yields using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base and methanol as the solvent under mild conditions (Scheme 17). The lowest yield of product **24** (59%) was observed in the reaction of salicylaldehydes **2** with nitroketene acetal **25** containing the bulky PhCHMe group at the amino-group nitrogen atom.[30]

However, this procedure proved to be unsuitable for the preparation of nitrochromenes **24** with electron-donating substituents (R^3 = OMe, OBz) in position 7 due to low reactivity of the carbonyl group in the corresponding aldehydes.

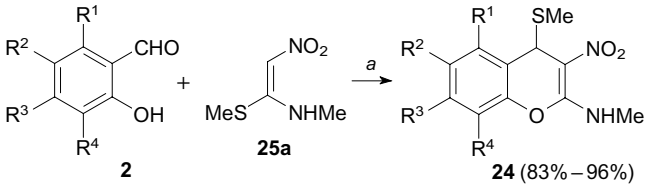
A recent publication [45] describes the synthesis of 3-nitro-4*H*-chromenes **24** from salicylaldehydes **2** and acetal **25a**

Scheme 17

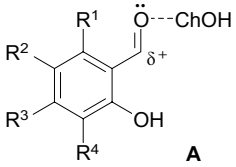


(*a*) DBU (10 mol.%), MeOH, rt, 12 – 31 h;
R^1, R^2, R^3, R^4 = H, Me, Et, Bu^t, MeO, BnO, Cl, Br; R^5 = Me, Bu^n, Bn, $Ph(CH_2)_2$, 4-$MeOC_6H_4(CH_2)_2$, PhCHMe, Ph

Scheme 18



(*a*) ChOH (10 mol.%), H_2O, rt, 5 – 6 h;
R^1 = H: R^2 = H, Me, Et, Bu^t, O_2N, Cl, Br; R^1 – R^2 is benzo; R^3 = H, Et_2N, 4-$FC_6H_4CH_2O$, 4-$O_2NC_6H_4CH_2O$, MeO, EtO, Bu^{n}O, BnO, n-$C_8H_{17}O$, 1-NaphthCH$_2$O; R^4 = H, Bu^t, MeO, EtO, Cl, Br;
Naph is naphthyl



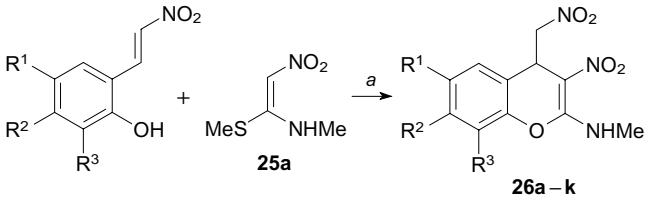
carried out in water in the presence of choline hydroxide (ChOH) (Scheme 18), the catalytic action of which includes activation of the aldehyde group by increasing the partial positive charge on the carbonyl carbon atom (intermediate **A**).

Under the indicated conditions, the outcome of the reaction depends little on the electron-donating or -withdrawing properties of groups R^1 – R^4 and the reaction can be used to prepare chromenes **24** with different substituents in the aromatic ring.

ortho-Hydroxy-β-nitrostyrenes react with acetal **25a** similarly to salicylaldehydes to give *N*-methyl-3-nitro-4-nitromethyl-4*H*-chromen-2-amines **26a** – **k** in 60% – 86% yields. The reaction is carried out at room temperature in methanol in the presence of DBU (Scheme 19, Table 2).[46]

Perumal and co-workers [47] developed a regioselective method for the synthesis of hydrogenated chromen-5-ones

Scheme 19



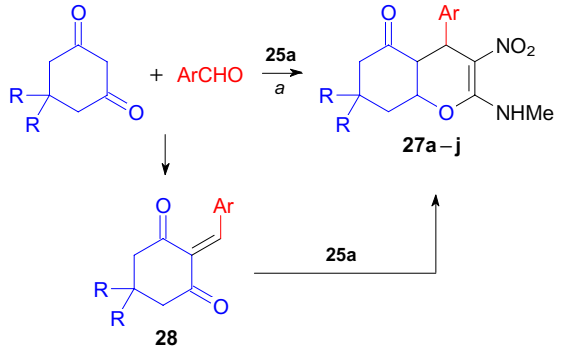
(*a*) DBU (10 mol.%), MeOH, rt, 10 – 15 h

Table 2. Synthesis of nitrochromenes **26** (see Scheme 19).[46]

Compound **26**	R^1	R^2	R^3	Yield (%)
a	H	H	H	86
b	Me	H	H	60
c	Et	H	H	81
d	MeO	H	H	84
e	H	H	MeO	66
f	EtO	H	H	79
g	Cl	H	H	70
h	Cl	Me	H	60
i	Cl	H	Cl	80
j	Br	H	H	70
k	O_2N	H	H	60

27 based on a three-component reaction of acetal **25a** with aromatic aldehydes and cyclohexane-1,3-diones, which occurs on heating in ethanol in the presence of a catalytic amount of piperidine (Scheme 20). Janhav *et al.*[48] carried out the same reaction on silica gel modified by tungstic acid. The yields of products **27a** – **j** were 85% – 94%. Presumably, this is a cascade transformation including successive Knoevenagel, Michael and Henry reactions to give intermediate **28** in the first step.

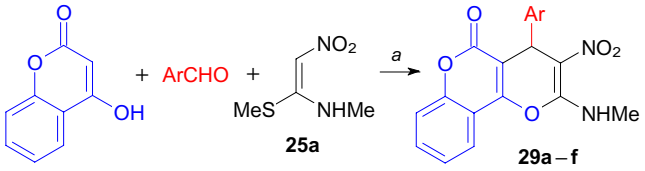
Scheme 20



(*a*) piperidine (20 mol.%), EtOH, rt, 2 – 5 h;
27: R = H: Ar = 4-ClC$_6$H$_4$ (**a**, 84% yield), 4-BrC$_6$H$_4$ (**b**, 85%);
R = Me: Ar = 4-MeC$_6$H$_4$ (**c**, 79%), 4-MeOC$_6$H$_4$ (**d**, 78%), 2-FC$_6$H$_4$ (**e**, 78%), 4-BrC$_6$H$_4$ (**f**, 80%), 2,4-Cl$_2$C$_6$H$_3$ (**g**, 80%), 2-O$_2$NC$_6$H$_4$ (**h**, 76%), 3-O$_2$NC$_6$H$_4$ (**i**, 76%), 4-O$_2$NC$_6$H$_4$ (**j**, 86%)

A similar three-component reaction involving 4-hydroxycoumarin resulted in the formation of pyrano[3,2-*c*]-chromen-5-ones **29a** – **f** in 76% – 86% yields (Scheme 21).[47]

Scheme 21



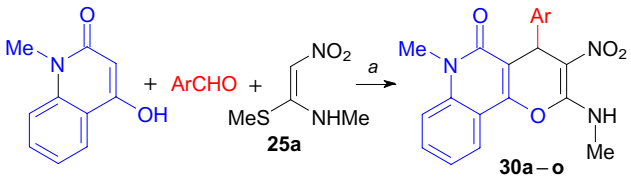
(*a*) piperidine (20 mol.%), EtOH, rt, 2 – 5 h;
29: Ar = 4-MeC$_6$H$_4$ (**a**, 86% yield), 4-MeOC$_6$H$_4$ (**b**, 79%), 2-FC$_6$H$_4$ (**c**, 80%), 4-ClC$_6$H$_4$ (**d**, 81%), 4-BrC$_6$H$_4$ (**e**, 83%), 3-O$_2$NC$_6$H$_4$ (**f**, 76%)

4-Hydroxy-1-methylquinolin-2-one was introduced into a similar domino reaction as the methylene component; in the presence of the $ZnCl_2$ catalyst, the reaction gave pyrano[3,2-*c*]quinolin-5-ones **30a** – **o** in high yields (Scheme 22).[49]

Recently, a three-component reaction of N,S-acetal **25a**, benzaldehydes and nitrile **31** furnished 2-*tert*-butyl-4*H*-pyran-3-carbonitriles **32a** – **m** in good yields. The reaction was carried out on heating the reactants in ethanol under microwave radiation in the presence of ammonium acetate (4 equiv.) (Scheme 23).[50]

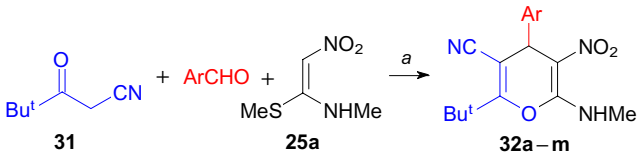
Kamalraja and Perumal[51] carried out a similar process involving indole-containing nitriles **33**; in order to increase the yield of 2-(indol-3-yl)-4*H*-pyran-3-carbonitriles **34a** – **o** and decrease the reaction time, they additionally activated

Scheme 22



(*a*) $ZnCl_2$ (30 mol.%), EtOH, Δ, 4 – 8 h;
30: Ar = Ph (**a**, 90% yield), 2-MeC$_6$H$_4$ (**b**, 89%), 4-MeC$_6$H$_4$ (**c**, 91%), 4-Pr^{i}C$_6$H$_4$ (**d**, 90%), 4-MeOC$_6$H$_4$ (**e**, 85%), 2,5-(MeO)$_2$C$_6$H$_3$ (**f**, 88%), 3-FC$_6$H$_4$ (**g**, 87%), 4-FC$_6$H$_4$ (**h**, 93%), 2-ClC$_6$H$_4$ (**i**, 89%), 4-ClC$_6$H$_4$ (**j**, 92%), 2,3-Cl$_2$C$_6$H$_3$ (**k**, 89%), 2,4-Cl$_2$C$_6$H$_3$ (**l**, 91%), 3-BrC$_6$H$_4$ (**m**, 88%), 4-O$_2$NC$_6$H$_4$ (**n**, 92%), 1-Naph (**o**, 92%)

Scheme 23



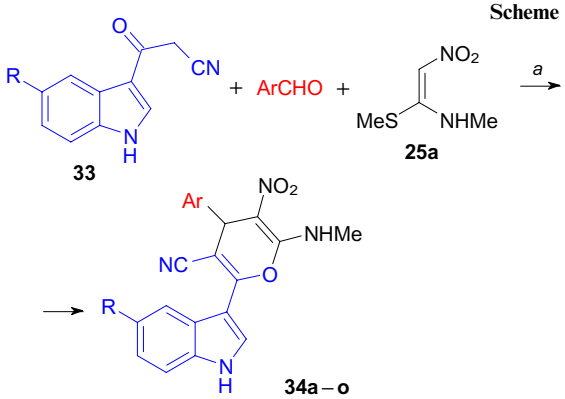
(*a*) NH$_4$OAc, EtOH, MW, 80 °C, 5 min;
32: Ar = Ph (**a**, 80% yield), 3-MeC$_6$H$_4$ (**b**, 81%), 4-MeC$_6$H$_4$ (**c**, 81%), 4-MeOC$_6$H$_4$ (**d**, 82%), 2-FC$_6$H$_4$ (**e**, 78%), 3-FC$_6$H$_4$ (**f**, 77%), 4-FC$_6$H$_4$ (**g**, 79%), 3-ClC$_6$H$_4$ (**h**, 78%), 3,4-F$_2$C$_6$H$_3$ (**i**, 75%), 3-O$_2$NC$_6$H$_4$ (**j**, 65%), 2-Fu (**k**, 80%), 2-Th (**l**, 78%), 1-Naph (**m**, 78%);
MW is microwave radiation, Fu is furyl

the nitrile methylene group and the benzaldehyde formyl group by adding $InCl_3$ (Scheme 24).

Using the same catalyst, pyrazolones **35** and isatins **36** were introduced into the reaction.[52] As in the previous cases, a Michael and Henry reaction cascade takes place, involving the Knoevanagel condensation intermediate **37**. These transformations give high yields of dihydrospiro(indoline-3,4′-pyrano[2,3-*c*]pyrazol)-2-ones **38** (Scheme 25).

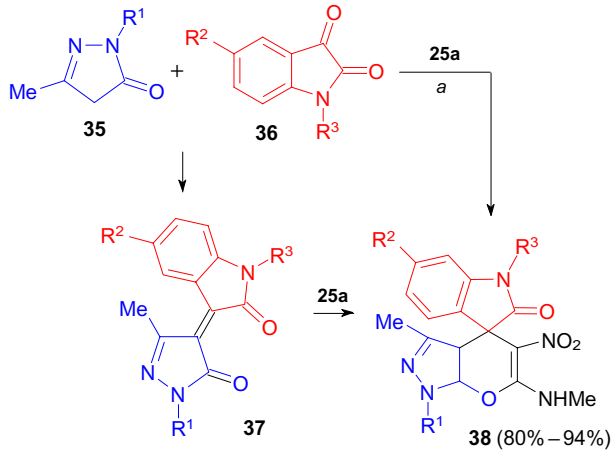
2-Unsubstituted 3-nitro-4*H*-chromenes are currently unknown, but their benzannulated analogues have been

Scheme 24



(*a*) $InCl_3$ (20 mol.%), solvent free, MW, 3 – 7 min;
34: R = H: Ar = 4-MeC$_6$H$_4$ (**a**, 90% yield), 4-MeOC$_6$H$_4$ (**c**, 85%), 2-FC$_6$H$_4$ (**d**, 92%), 4-BrC$_6$H$_4$ (**f**, 93%), 4-ClC$_6$H$_4$ (**h**, 86%), 2,4-Cl$_2$C$_6$H$_3$ (**i**, 89%), 3-O$_2$NC$_6$H$_4$ (**j**, 90%), 4-O$_2$NC$_6$H$_4$ (**k**, 91%), 2-N$_3$C$_6$H$_4$ (**o**, 87%); R = Br: Ar = 4-MeC$_6$H$_4$ (**b**, 88%), 4-FC$_6$H$_4$ (**e**, 84%), 4-BrC$_6$H$_4$ (**g**, 90%), 4-O$_2$NC$_6$H$_4$ (**l**, 93%);
R = MeO: Ar = 4-MeC$_6$H$_4$ (**m**, 86%), 4-BrC$_6$H$_4$ (**n**, 87%)

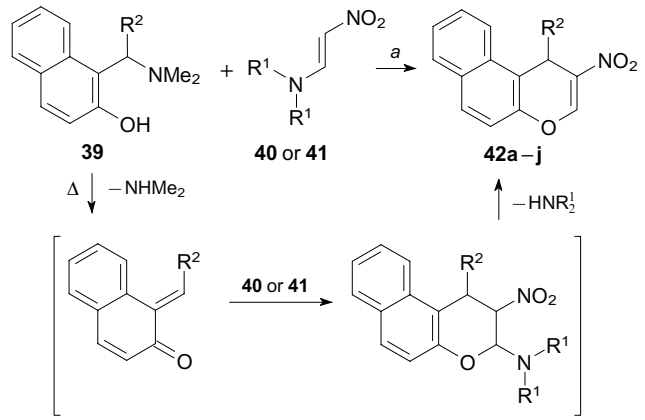
Scheme 25



(*a*) $InCl_3$ (20 mol.%), EtOH, Δ, 5–7 h;
R^1 = H, Ph; R^2 = H, Me, F, Cl, Br, O_2N;
R^3 = H, Me, Et, Bn, All, $CH_2C{\equiv}CH$

prepared.[53] The reaction of *o*-quinone methides, generated from Mannich base **39**, with 4-(2-nitrovinyl)morpholine (**40**) (method A) or with *N*,*N*-dimethyl(2-nitrovinyl)amine (**41**) (method B) on heating in acetic anhydride for 6 h resulted in the formation of compounds **42a**–**j** in 32% to 85% yields (Scheme 26). In the latter case, with the reaction time being reduced to 0.5–1.5 h, products **42a**,**b**,**f** (R = H, Ph, 2-ClC_6H_4) were isolated in 26%–76% yield. The lowest yield of product **42h** containing an electron-withdrawing nitro group in the aryl substituent is apparently due to the difficulty of generation of the corresponding quinone methide.

Scheme 26



(*a*) Ac_2O, Δ, 0.5–6 h;
R^1 – R^1 = $(CH_2)_2O(CH_2)_2$ (**40**); R^1 = Me (**41**)

Compound **42**	R^2	Yield (%)	
		Method A	Method B
a	H	60	76
b	Ph	75	71
c	4-$MeOC_6H_4$	80	–
d	3,4-$(MeO)_2C_6H_3$	60	–
e	3,4,5-$(MeO)_3C_6H_2$	45	–
f	2-ClC_6H_4	–	26
g	4-ClC_6H_4	61	–
h	3-$O_2NC_6H_4$	32	–
i	1,3-Benzodioxol-5-yl	46	–
j	2-Th	85	–

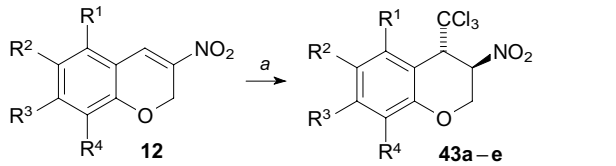
3. Reactions of 3-nitro-2*H*-chromenes

This Section consists of three parts covering reactions of 2-unsubstituted 3-nitro-2*H*-chromenes, 2-alkyl- and 2-aryl-3-nitro-2*H*-chromenes and our recent results dealing with 2-trifluoromethyl- and 2-trichloromethyl-3-nitro-2*H*-chromenes.

3.1. Nucleophilic substitution

2-Unsubstituted 3-nitrochromenes **12** stereoselectively add trimethyl(trichloromethyl)silane (a chlorinated analogue of the Ruppert reagent) giving rise to chromanes **43a**–**e**, which are formed as only *trans*-isomers in 61%–95% yields (Scheme 27).[54] The reaction proceeds in toluene or THF with tetra-n-butylammonium triphenyldifluorosilicate as a promoter.

Scheme 27



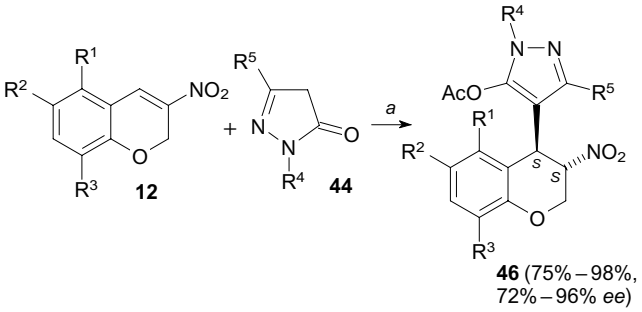
(*a*) $TMSCCl_3$ (1.25 equiv.), $Bu^n_4NPh_3SiF_2$ (5 mol.%), THF or PhMe, 20 °C, 0.5 h; R^1 = R^2 = R^3 = R^4 = H (**a**, 95% yield); R^1 = MeO, R^2 = R^3 = R^4 = H (**b**, 72%); R^2 = OMe, R^1 = R^3 = R^4 = H (**c**, 61%); R^3 = MeO, R^1 = R^2 = R^4 = H (**d**, 68%); R^1 = R^3 = H, R^2 = R^4 = Bu^t (**e**, 94%); TMS is trimethylsilyl

Li and Du [55] conducted the reaction of nitrochromenes **12** and pyrazolones **44** in the presence of chiral squaramide **45** and thus prepared the (3*S*,4*S*)-enantiomers of *trans*-3-nitro-4-pyrazolylchromanes **46** (Scheme 28). Bifunctional catalyst **45** forms a complex with nitrochromene **12** and pyrazolone **44**, in which position 4 of chromene is attacked from the *re*-side.

The use of chiral catalyst **47** and benzoic acid as the co-catalyst in the reaction of nitrochromenes **12** with arylmethylideneacetones induced an asymmetric cascade of two Michael reactions (inter- and intramolecular ones) producing hexahydro-6*H*-benzo[*c*]chromenes **48** in 45%–90% yields with satisfactory optical purity (Scheme 29).[56] The lowest yields of products **48** (45%–59%) were observed in the reactions of 4-chlorobenzylideneacetone (R^3 = 4-ClC_6H_4) with chromenes **12** containing one or two halogen atoms in positions 6 and 8 (R^1, R^2 = Cl, Br).

Enders' research team [57] accomplished a triple asymmetric reaction cascade consisting of successive inter- and intramolecular Michael reactions and aldol condensation involving nitrochromenes **12**, aliphatic aldehydes and α,β-unsaturated aldehydes in the presence of a chiral catalyst based on diphenylprolinol **49**; this gave tetrahydro-6*H*-benzo[*c*]chromenes **50** in 25%–66% yields with >99% optical purity (Scheme 30). In the reactions with participation of propionaldehyde (R^4 = Me), products **50** were formed in the highest yields, whereas introduction of more

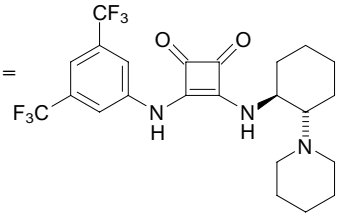
Scheme 28



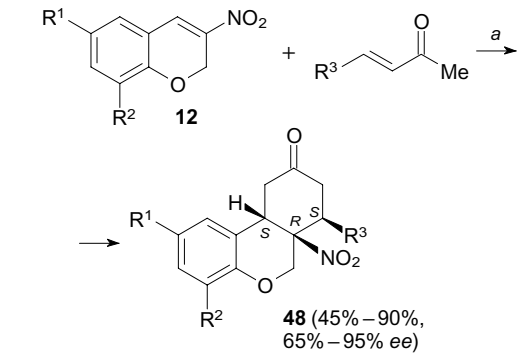
46 (75% – 98%, 72% – 96% *ee*)

(*a*) 1) **45** (0.2 mol.%), CH_2Cl_2, −15 °C, 96 h; 2) Et_3N (30 mol.%), Ac_2O (1 equiv.), rt, 0.5 h;
R^1 = H: R^2 = H, Cl, Br, O_2N; R^1 – R^2 is benzo; R^3 = H, EtO; R^4 = Ph, 4-MeC_6H_4, 4-ClC_6H_4; R^5 = Me, Et, F_3C, Ph;

45 =



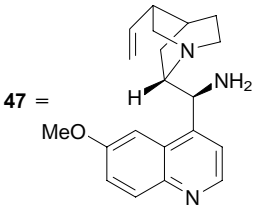
Scheme 29



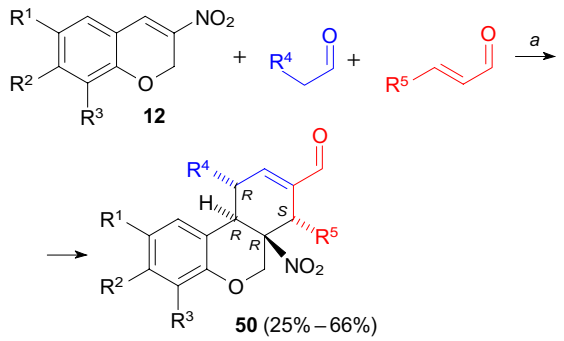
48 (45% – 90%, 65% – 95% *ee*)

(*a*) **47** (20 mol.%), BzOH (30 mol.%), $CHCl_3$, rt, 96 h;
R^1 = H, Cl, Br; R^2 = H, Cl, Br, MeO, EtO; R^3 = Ph, 4-MeC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 4-$Me_2NC_6H_4$, 4-ClC_6H_4, 2-BrC_6H_4, 4-BrC_6H_4, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 1-Naph;

47 =



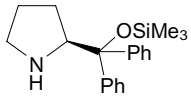
Scheme 30



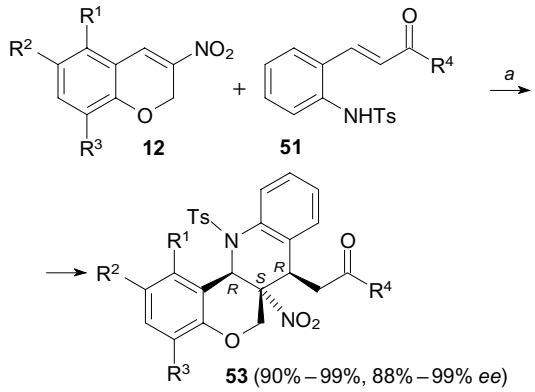
50 (25% – 66%)

(*a*) **49** (20 mol.%), PhMe, 0 → 20 °C, 48 h;
R^1 = H, Me, Bu^t, MeO, F, Cl, Br, I, O_2N; R^2 = H, MeO, Et_2N;
R^3 = H, Bu^t, Cl, I; R^4 = Me, Et, Pr^n, Bn; R^5 = Me, Ph, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4;

49 =



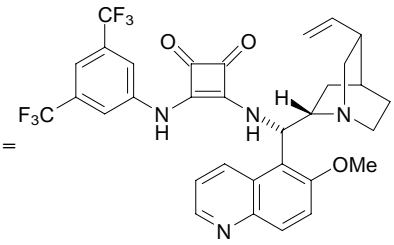
Scheme 31



53 (90% – 99%, 88% – 99% *ee*)

(*a*) **52** (1 mol.%), DCE, PhMe, rt, 2 – 6 h;
R^1 = H: R^2 = H, Cl, Br; R^1 – R^2 is benzo; R^3 = MeO, EtO; R^4 = Me, Bu^t, EtO, 4-MeC_6H_4, 2-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4;
Ts is *p*-toluenesulfonyl (tosyl), DCE is 1,2-dichloroethane;

52 =



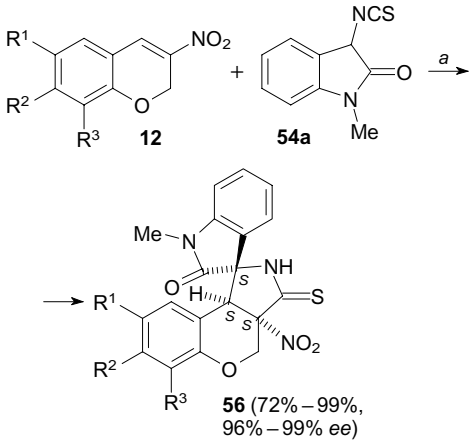
bulky substituents (R^4 = Et, Pr^n, Bn) into position 2 of aliphatic aldehyde decreased the yields of benzochromenes to 25% – 37%.

Yang *et al.*[58] investigated asymmetric Δ^3-annulation of 3-nitrochromenes **12** with *o*-tosylaminophenyl-enones **51** catalyzed by chiral squaramide **52**. The process is a sequence of two stereoselective Michael reactions, resulting in the formation of tetrahydro-6*H*-chromene[3,4-*b*]quinolines **53** in high yields and with high optical purity (Scheme 31).

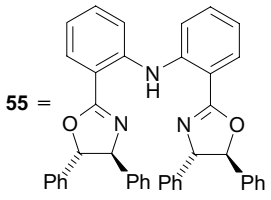
The reaction of nitrochromenes **12** with 3-isothiocyanato-1-methylindolin-2-one (**54a**) was efficiently catalyzed by compound **55**.[59] The process was induced by zinc triflate and occurred in toluene over a period of 16 h. Spirooxindoles **56** were formed in 72% – 99% yields with optical purity > 99% (Scheme 32).

A similar reaction of 1-alkyl-3-isothiocyanatoindolin-2-ones **54** with 2-aryl-3-nitrochromenes **14** in the presence of chiral catalyst **57** afforded a mixture of approximately equal amounts of diastereomeric products **58** and **59**, differing in the configuration of the spirocyclic carbon atom.[60] Despite low diastereoselectivity of the reaction, both products were

Scheme 32



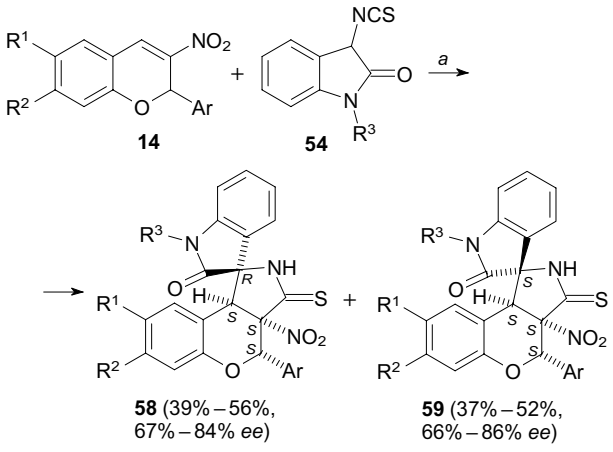
(*a*) $Zn(OTf)_2$ (10 mol.%), **55** (11 mol.%), PhMe, rt, 12 – 17 h;
R^1 = H, Me, MeO, F, Cl, Br, O_2N; R^2 = H, MeO; R^3 = H, MeO, Br;



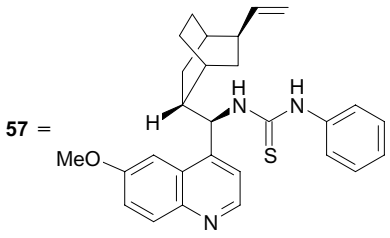
isolated with high optical purity and had *S*-configuration of the asymmetric carbon atoms in the pyran ring (Scheme 33).

The addition of 4-hydroxycoumarin to 3-nitro-2-phenylchromenes **14** under the action of triethylamine on refluxing in ethanol for 3 h yielded unstable adducts **60**, which were readily oxidized with atmospheric oxygen under the reaction conditions to give chromene and coumarin conjugates **61a – j** in good yields (Scheme 34, Table 3).[61]

Scheme 33



(*a*) **57** (10 mol.%), CH_2Cl_2, −50 °C, 1 min;
R^1 = H, Me, MeO, Cl, Br, O_2N; R^2 = H, MeO; R^3 = Me, Et;
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 2-BrC_6H_4, 3-BrC_6H_4;



Scheme 34

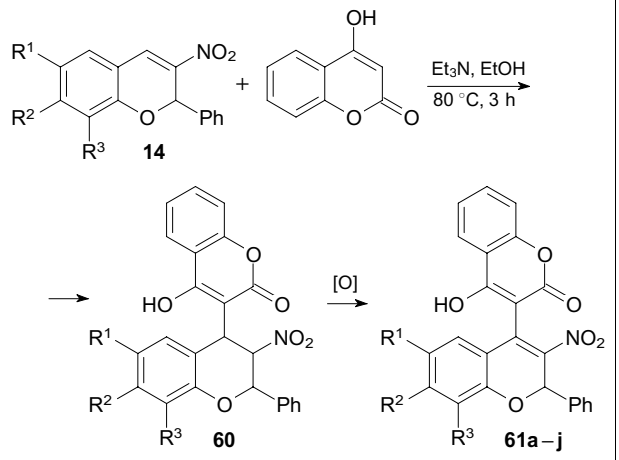


Table 3. Synthesis of nitrochromenes **61** (see Scheme 34).[61]

Compound **61**	R^1	R^2	R^3	Yield (%)
a	H	H	HO	72
b	H	H	MeO	72
c	H	MeO	H	68
d	H	H	EtO	77
e	Cl	H	H	75
f	Br	H	H	81
g	Cl	H	Cl	83
h	Br	H	Br	83
i	Cl	H	MeO	88
j	Cl	H	Br	78

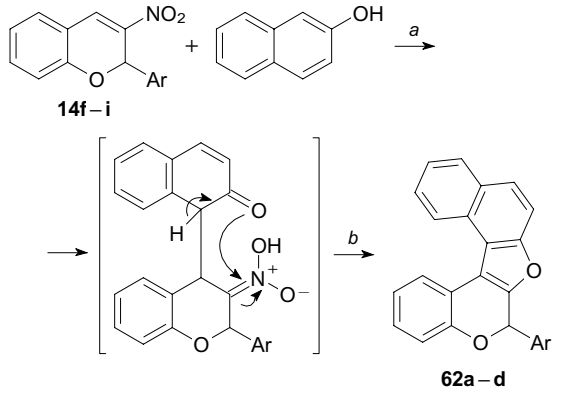
The Michael reaction involving nitrochromenes **14f – i** and β-naphthol, which takes place on refluxing in dry ethanol in the presence of 0.5 equiv. of K_2CO_3, is accompanied by intramolecular cyclization with elimination of a water molecule and nitroxide (Nef reaction) and gives fused furans **62a – d** (Scheme 35).[62]

Furo[2,3-*c*]chromenes **63a – h** were synthesized in moderate yields from nitrochromenes **14** and benzoylacetonitrile under similar conditions (Scheme 36, Table 4).[63]

In the reaction of nitrochromenes **14** with pivaloylacetonitrile conducted in THF at 40 °C, addition of a second nitrile molecule to tricyclic intermediate **A** takes place instead of nitroxide elimination, and thus the reaction gives dihydrofuro[2,3-*c*]chromenes **64** (Scheme 37).[63]

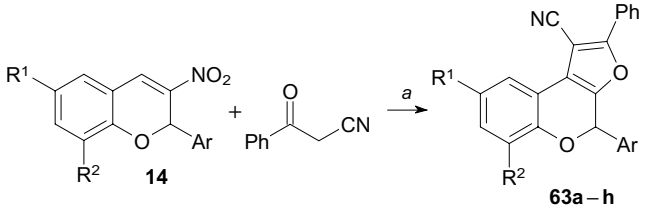
If the reaction of chromenes **14** with pivaloylacetonitrile is carried out in refluxing ethanol (methanol) or in a sealed tube in methanol at 100 °C, chromeno[3,4-*b*]pyridines **65a – p** are formed in high yields (Scheme 38, Table 5).[63] These products are apparently formed *via* a reaction sequence including the addition of an alcohol molecule to dihydrofuran **64**, furan ring opening and intramolecular cyclization accompanied by elimination of, first, hydrogen cyanide and then pivalic acid. The proposed mechanism is convincingly proved by the synthesis of chromenopyridines **65c** (90% yield) and **65h** (85%) from dihydrofurans **64** on refluxing in ethanol in the presence of Et_3N within 8 h.

Scheme 35



(*a*) K_2CO_3, EtOH, Δ; (*b*) elimination of H_2O, HNO;
Ar = Ph (**14f**; **62a**; 41% yield), 4-MeC_6H_4 (**14g**; **62b**; 43%),
4-$MeOC_6H_4$(**14h**; **62c**; 48%), 4-ClC_6H_4 (**14i**; **62d**; 45%)

Scheme 36



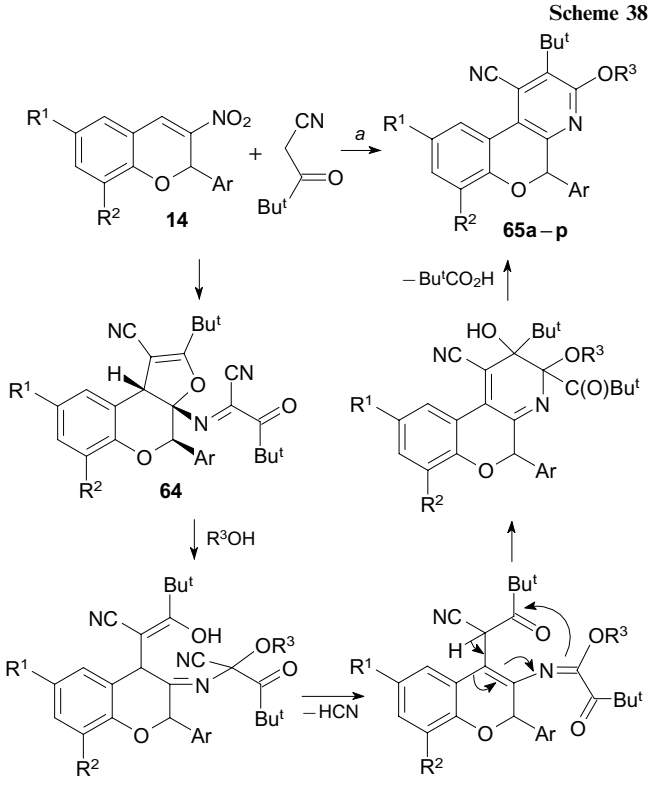
(*a*) Et_3N, EtOH, 60 °C, 8 h

Table 4. Synthesis of furo[2,3-*c*]chromenes **63** (see Scheme 36).[63]

Compound **63**	R^1	R^2	Ar	Yield (%)
a	H	H	3-FC_6H_4	74
b	H	H	4-ClC_6H_4	60
c	H	H	2-MeC_6H_4	80
d	Me	H	4-BrC_6H_4	77
e	Cl	H	4-MeC_6H_4	63
f	Br	H	4-MeC_6H_4	67
g	Br	Br	4-MeC_6H_4	49
h	Br	Br	4-$MeOC_6H_4$	52

The addition of nitromethane and aniline to 3-nitro-2-phenyl-2-(trifluoromethyl)-2*H*-chromene (**13a**) was nonselective and gave a mixture of three [*cis*,*trans* (*ct*), *cis*,*cis* (*cc*) and *trans*,*cis* (*tc*)] out of four possible diastereomers of chromanes **66a** – **c** (44 : 33 : 18 ratio) and **67a** – **c** (9 : 36 : 55

Scheme 38



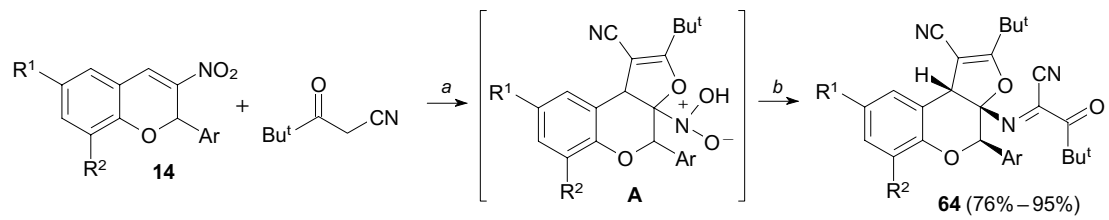
(*a*) Et_3N, R^3OH, Δ, 8 h

Table 5. Synthesis of chromenopyridines **65** (see Scheme 38).[63]

Compound **65**	R^1	R^2	R^3	Ar	Yield (%)
a	Br	H	Et	2-BrC_6H_4	81
b	Br	H	Et	2-$O_2NC_6H_4$	85
c	Cl	H	Et	2-ClC_6H_4	82
d	Me	H	Et	2-MeC_6H_4	65
e	Cl	Cl	Et	2-BrC_6H_4	90
f	Br	H	Me	2-$O_2NC_6H_4$	91
g	Br	Br	Me	2-$O_2NC_6H_4$	89
h	Cl	H	Me	2-ClC_6H_4	81
i	Cl	H	Me	2-BrC_6H_4	85
j	H	H	Me	2-$O_2NC_6H_4$	91
k	H	H	Me	2-MeC_6H_4	72
l	H	MeO	Me	2-ClC_6H_4	83
m	Br	H	Me	4-MeC_6H_4	81 [a]
n	H	H	Me	4-$Bu^tC_6H_4$	72 [a]
o	H	H	Me	3-FC_6H_4	69 [a]
p	Me	H	Me	4-$MeOC_6H_4$	75 [a]

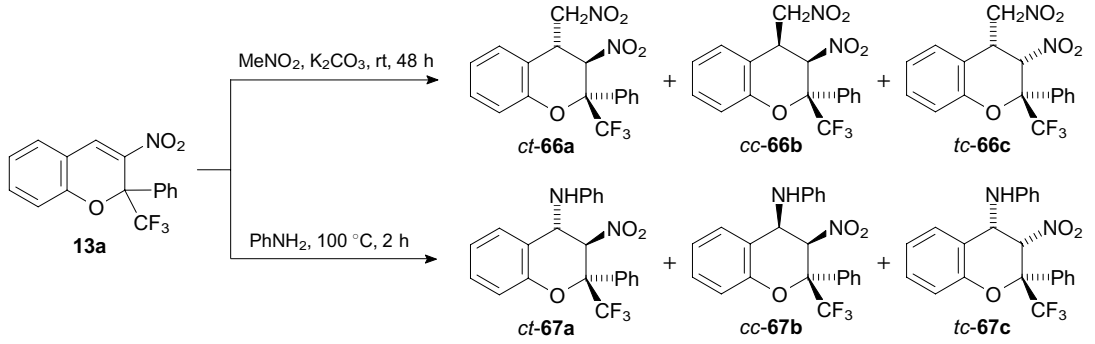
[a] Prepared in methanol in a sealed tube at 100 °C.

Scheme 37

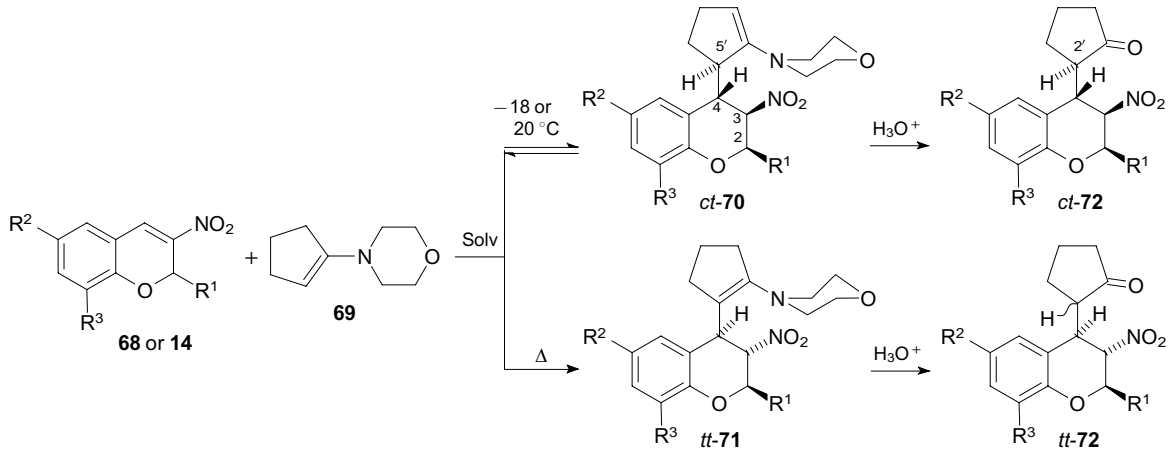


(*a*) Et_3N, THF, 40 °C, 8 h; (*b*) $Bu^tC(O)CH_2CN$ ($-H_2O$); R^1 = H, Me, Br; R^2 = H, MeO, EtO, Br; Ar = Ph, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4

Scheme 39



Scheme 40



R^1 = F_3C, Cl_3C, Ph; R^2 = H, MeO, Cl, Br; R^3 = H, MeO, Cl, Br; Solv is solvent

ratio) in 77% and 37% overall yields, respectively (Scheme 39).[37]

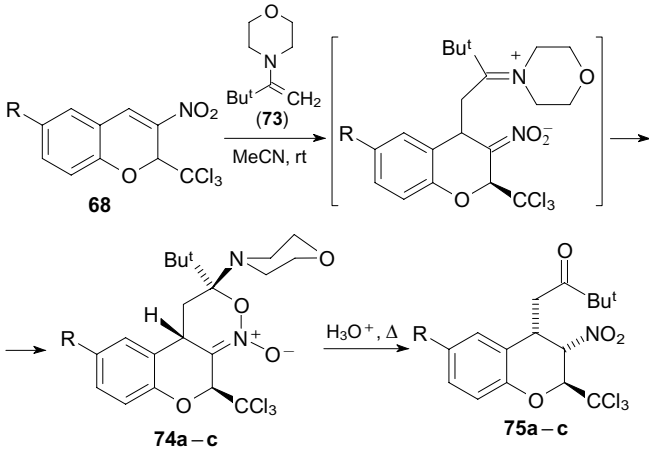
Recently, a study was undertaken with our participation [37, 64 – 70] dealing with the reaction of 2-chloro(trifluoromethyl)-substituted nitrochromenes **68** or 3-nitro-2-phenyl-2*H*-chromenes **14** with enamines derived from carbonyl and β-dicarbonyl compounds.

Under kinetically controlled conditions (– 18 or 20 °C, 0.5 – 48 h), 2-$CHal_3$-nitrochromenes **68** (R^1 = F_3C, Cl_3C) and chromenes **14** (R^1 = Ph) react with 1-morpholinocyclopentene **69** in acetonitrile and *tert*-butyl methyl ether, respectively (Scheme 40).[64] Adducts *ct*-**70** (49% – 83% yields) are formed as single *ct*-isomers with a trisubstituted double bond in the enamine moiety and gradually crystallize from the reaction mixture as colourless prisms. The yields of chromane enamines *ct*-**70** were the lowest in the reactions of enamine **69** with chromenes **68** and **14** containing electron-donating substituents in positions 6 and 8 (R^2 = MeO, R^3 = EtO). The lower yields of 2-CF_3-chromanes *ct*-**70** (49% – 62%) compared with 2-CCl_3-analogues (52% – 83%) are caused by their higher solubility in acetonitrile. When 2-CF_3-nitrochromenes **68** react with enamine **69** in methanol at 35 °C for 3 – 8 h, thermodynamically more stable chromane enamines *tt*-**71** with the *trans*,*trans*-configuration of substituents in the pyran ring and with a tetrasubstituted double bond in the enamine moiety are formed in 39% – 78% yields. In this case, too, the introduction of electron-donating substituents into the chromene molecule decreases the target product yield. 3-Nitro-2-trichloromethyl- and 3-nitro-2-phenyl-2*H*-chromenes were converted to the corresponding *trans*,*trans*-chromane enamines *tt*-**71** at 40 – 100 °C in lower yields (34% – 69%). Hydrolysis of chromane enamines *ct*-**70** conducted in aqueous methanol under mild conditions furnishes chromanoketones *ct*-**72** (70% – 99% yields) with retention of the configuration both at the C(2), C(3), C(4) atoms and at the C(2′) atom. The acid hydrolysis of chromanes *tt*-**71** under non-epimerizing conditions affords high yields (71% – 96%) of epimeric chromanoketones *tt*-**72** differing only in the configuration at C(2′), with the more stable epimer with *anti*-positions of the 4-CH and 2′-CH hydrogen atoms predominating (see Scheme 40).[64]

The reaction of 2-CCl_3-nitrochromenes **68** with enamine **73** obtained from morpholine and pinacoline is accompanied by intramolecular cyclization of the intramolecular betaine to give 1,2-oxazine *N*-oxides **74** in moderate yields. They are subjected to acid hydrolysis to give ketones **75** as only *trans*,*cis*-isomers (Scheme 41).[65]

The kinetically controlled reaction of chromenes **68** with α-morpholinostyrene (**76**) leads to the preferred formation of chromane enamines *tc*-**77** (54% – 85% yields), while on heating thermodynamically more stable isomers *tt*-**77** (32% – 84% yields) with *E* double bond configuration in the enamine moiety are formed.[66] Low yields of 6-chloro- and 6-bromo-substituted 2-CF_3-chromanes *tt*-**77** (32% and 47%, respectively) and 6-methoxy-substituted 2-CCl_3-chromanes *tc*-**77** (54%) and *tt*-**77** (38%) can be attributed to partial loss of the product during isolation because of high solubility of these chromane enamines in acetonitrile. Acid hydrolysis of chromane stereoisomers *tc*-**77** and *tt*-**77** on

Scheme 41



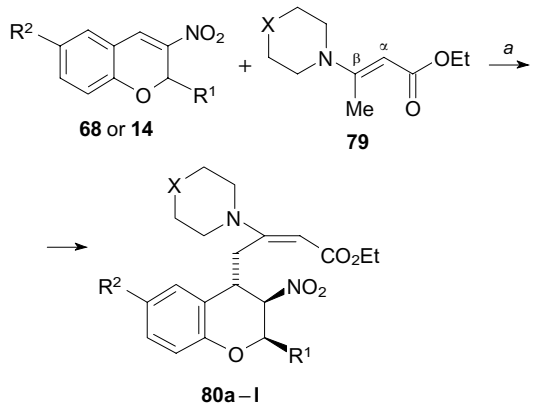
Compounds **74**, **75**	R	Yield (%)	
		74	**75**
a	Br	64	63
b	MeO	43	77
c	O_2N	67	52

treatment with dilute HCl at room temperature does not change the pyran ring configuration and results in the formation of 4-phenacylchromanes *tc*-**78** and *tt*-**78** in 68% – 100% yields (Scheme 42). An analogous reaction of 3-nitro-2-phenyl-2*H*-chromene affords a mixture of diastereomeric products in good yields, but with low stereoselectivity.

Morpholine- and piperidine-based enamines of ethyl acetoacetate **79** add to chromenes **68** ($R^1 = F_3C$, Cl_3C) and **14** (R^1 = Ph) through the vinylogous β-methyl group to give *cis*,*trans*-2,3,4-trisubstituted chromanes **80a** – **l**. The lowest yields of adducts **80** (14% – 41%) were obtained for chromenes containing the electron-donating MeO group in position 6 (Scheme 43, Table 6).[67]

Acid hydrolysis of compounds **80** is accompanied by decarboxylation and gives 4-acetylmethyl-3-nitrochromanes **81** (16% – 91% yields) with retention of the pyran ring configuration.[67] Products **81** were formed in the lowest yields (16% – 19%) in the case of hydrolysis of chromanes

Scheme 43



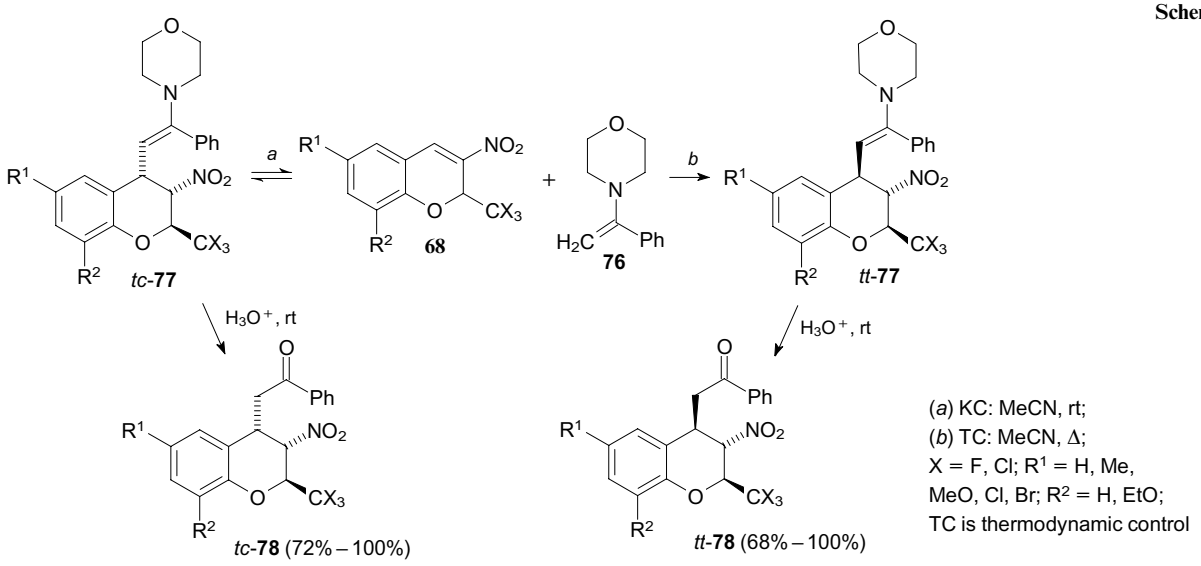
(*a*) 1) MeCN, 50 °C, 1 – 2 min; 2) rt, 24 – 48 h

Table 6. Synthesis of *cis*,*trans*-2,3,4-trisubstituted chromanes **80** (see Scheme 43).[67]

Compound **80**	R^1	R^2	X	Yield (%)
a	F_3C	H	O	79
b	F_3C	Br	CH_2	76
c	F_3C	Br	O	67
d	F_3C	O_2N	O	49
e	F_3C	MeO	CH_2	37
f	F_3C	MeO	O	41
g	Cl_3C	H	CH_2	54
h	Cl_3C	H	O	41
i	Cl_3C	Br	O	56
j	Cl_3C	MeO	CH_2	26
k	Cl_3C	MeO	O	14
l	Ph	H	O	63

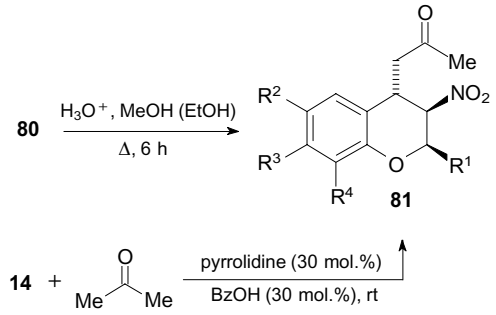
80 with the electron-donating methoxy group in position 6. Wang's research team[71] synthesized 2-aryl 4-substituted acetonylchromanes **81** in 75% – 86% yields by the addition of acetone to 2-aryl-3-nitro-2*H*-chromenes **14** in the presence of pyrrolidine and benzoic acid (Scheme 44).

Scheme 42



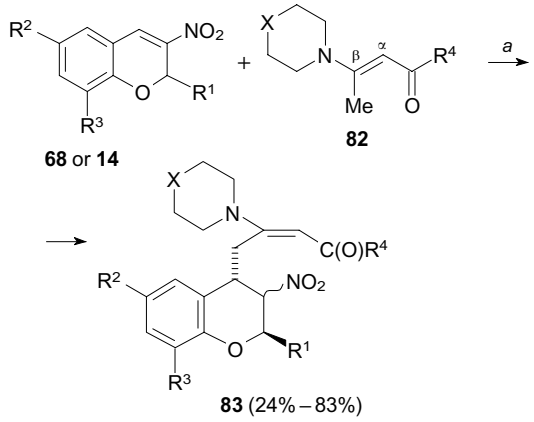
(*a*) KC: MeCN, rt;
(*b*) TC: MeCN, Δ;
X = F, Cl; R^1 = H, Me, MeO, Cl, Br; R^2 = H, EtO;
TC is thermodynamic control

Scheme 44



R^1 = F_3C, Cl_3C, Ph, 4-MeC_6H_4, 4-ClC_6H_4; R^2 = H, MeO, Cl, Br, O_2N; R^3, R^4 = H, MeO

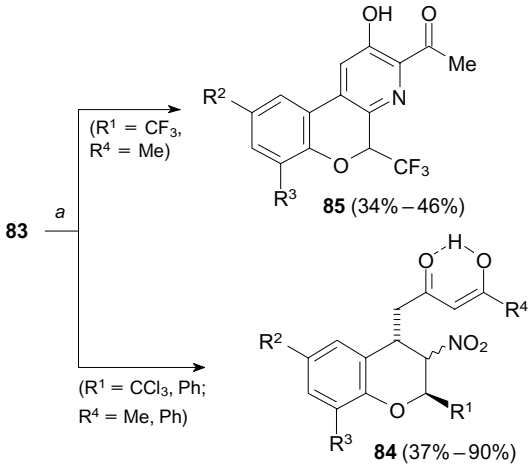
Scheme 45



(*a*) 1) MeCN, 50 °C, 1 – 2 min; 2) rt, 0.25 – 48 h;
R^1 = F_3C, Cl_3C, Ph; R^2 = H, Me, MeO, Cl, Br, O_2N; R^3 = H, EtO, Br; R^4 = Me, Ph; X = CH_2, O

Korotaev *et al.*[68] showed that morpholine- and piperidine-based enamines of acetylacetone and benzoylacetone **82** react, like enamines **79**, with chromenes **68** (R^1 = F_3C, Cl_3C) and **14** (R^1 = Ph) at the β-methyl group being converted to chromanes **83** with *cis*,*trans*- or *trans*,*cis*-configuration of the pyran ring and *E*-configuration of the enamine double bond (Scheme 45). The lowest yields of adducts **83** (24% – 34%) were observed for reactions involving 2-trichloromethyl-substituted nitrochromenes **68** with electron-donating MeO and EtO groups in positions 6 and 8.

Scheme 46

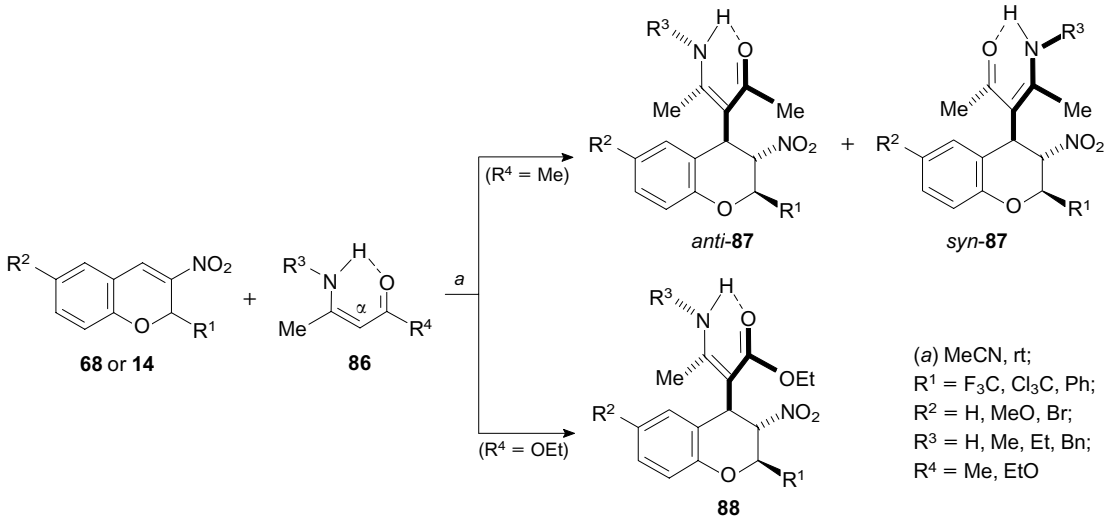


(*a*) H_3O^+, EtOH, Δ;
R^2 = H, Me, OMe, Cl, Br, NO_2; R^3 = H, OEt, Br; X = CH_2, O

On heating in ethanol in the presence of HCl, adducts **83** are either hydrolyzed to the corresponding chromane β-diketones **84** (R^1 = Cl_3C, Ph; R^4 = Me, Ph) or undergo ring closure to give chromenopyridines **85** (R^1 = F_3C, R^4 = Me) (Scheme 46).[68] In both cases, the yields virtually do not depend on the electron-donating or -withdrawing properties of substituents in the benzene ring. The lowest yields of chromane diketones **84** (37% and 43%) were obtained in the case of hydrolysis of 2-CCl_3-chromanes **83** with methyl (R^2 = R^4 = Me, R^3 = H) and nitro groups (R^2 = O_2N, R^3 = H, R^4 = Ph) in position 6, respectively.

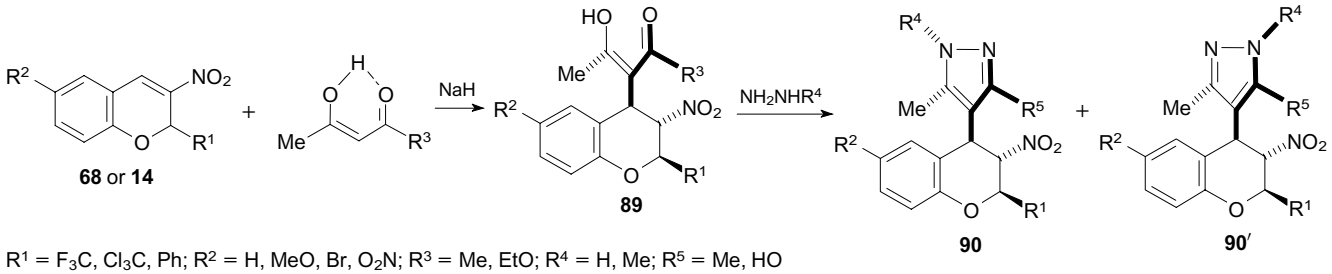
Unlike tertiary enamines **79** and **82**, primary and secondary enamines of acetylacetone and ethyl acetoacetate **86** add to the activated double bond of chromenes **68** (R^1 = F_3C, Cl_3C) and **14** (R^1 = Ph) by their central α-C atom, thus affording *trans*,*trans*-2,3,4-trisubstituted chromanes **87** and **88**. The yields of products **87** (25% – 84%) and **88** (28% – 85%) vary over a broad range and depend little on the nature of substituents in both chromene and enamine.[69] Adducts **87** formed from acetylacetone enamines

Scheme 47



(*a*) MeCN, rt;
R^1 = F_3C, Cl_3C, Ph;
R^2 = H, MeO, Br;
R^3 = H, Me, Et, Bn;
R^4 = Me, EtO

Scheme 48



R^1 = F_3C, Cl_3C, Ph; R^2 = H, MeO, Br, O_2N; R^3 = Me, EtO; R^4 = H, Me; R^5 = Me, HO

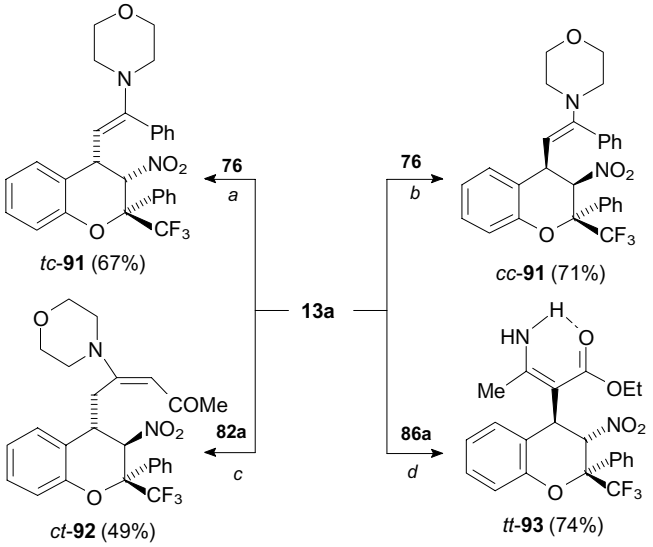
are mixtures of comparable amounts of configurationally stable atropoisomers, which appear as a result of hindered rotation about the $C(sp^3)-C(sp^2)$ bond. The reaction of chromenes **14** and **68** with ethyl acetoacetate enamines gives virtually a single atropoisomer of chromane **88** with *anti*-positions of the 4-CH hydrogen atom and the ester group (Scheme 47).

The *trans*,*trans*-2,3,4-trisubstituted chromanes **89**, resulting from nucleophilic addition of 1,3-dicarbonyl compounds to 2-R^1-3-nitro-2*H*-chromenes **68** (R^1 = F_3C, Cl_3C) and **14** (R^1 = Ph), as well as 4-(4-pyrazolyl)chromanes obtained from them exist as single (**90**) or as pairs (**90**, **90′**) of diastereomeric atropoisomers (Scheme 48).[70] The structures of these compounds were studied by NMR spectroscopy techniques.

2,2-Disubstituted 3-nitro-2*H*-chromene **13a** reacts stereoselectively with enamines **76**, **82a** (R^4 = Me, X = O) and **86a** (R^3 = H, R^4 = EtO) giving addition products **91** – **93** (Scheme 49).[37]

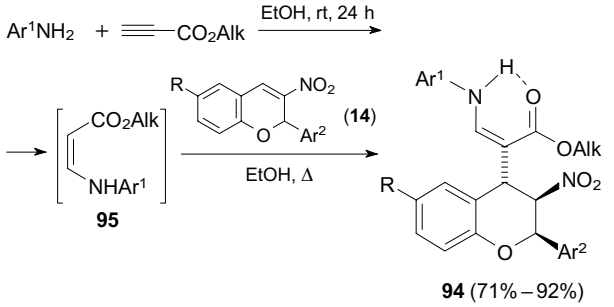
Zhang *et al.*[72] proposed a stereoselective one-pot synthesis of *cis*,*trans*-chromane enamines **94** from arylamines, propiolic acid esters and 2-aryl-3-nitrochromenes **14**. The essence of the method is in the addition of nitrochromene **14** to an ethanol solution of enamine **95**, which is presynthesized in the first reaction step from arylamine and alkyl propiolate in the same solvent. The reaction proceeds without a catalyst, with the yields of target products being 71% – 92% (Scheme 50).

Scheme 49



(*a*) MeCN, rt, 24 h; (*b*) MeCN, 60 °C, 4 h; (*c*) MeCN, 60 °C, 5 h; (*d*) MeCN, rt, 72 h

Scheme 50

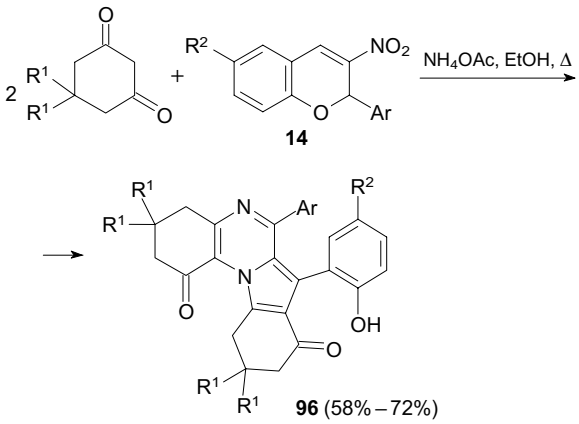


Alk = Me, Et; R = H, Cl, Br; Ar^1 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4; Ar^2 = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4

Fang and Yan [73] carried out a three-component reaction involving nitrochromenes **14**, dimedone or cyclohexane-1,3-dione and ammonium acetate, which gave 3,4,10,11-tetrahydroindolo[1,2-*a*]quinoxaline-1,8-diones **96** (Scheme 51).

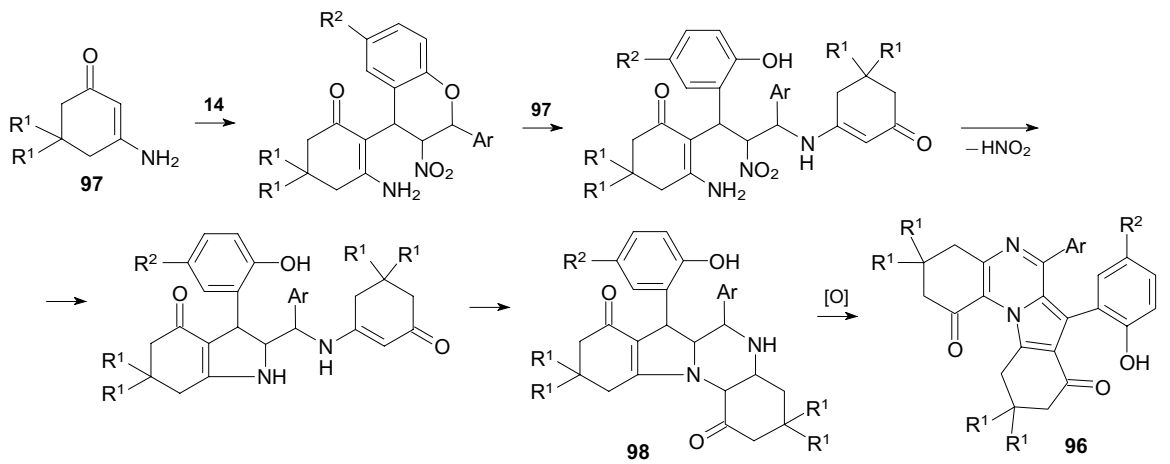
The presumptive mechanism of the reaction includes the following steps: formation of enamine **97**; successive addition of two enamine molecules **97** to nitrochromene **14** first through the carbon atom and then through the amino group; intramolecular displacement of the nitro group and nucleophilic addition of the secondary amino group to the enamine double bond; and oxidation of partially hydrogenated indolo[1,2-*a*]quinoxaline **98** with air oxygen (Scheme 52).

Scheme 51



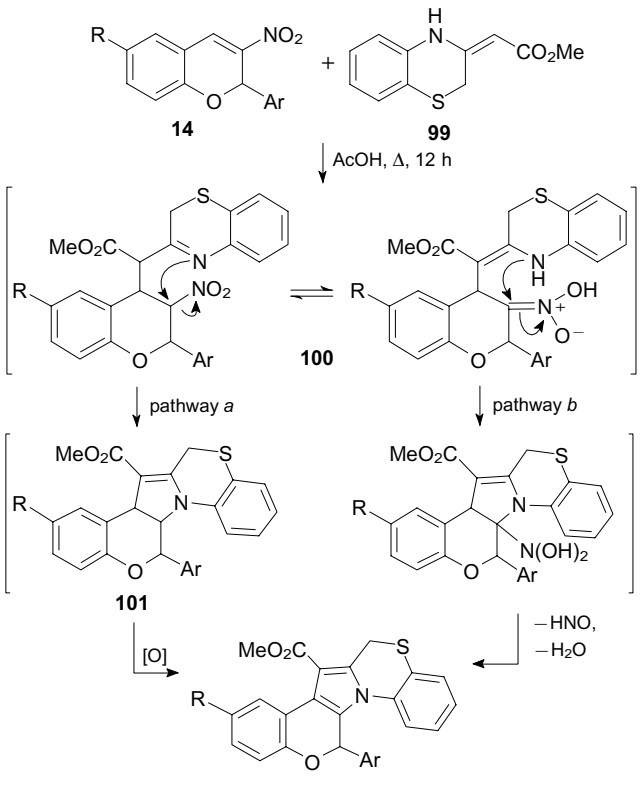
R^1 = H, Me; R^2 = H, Cl, Br; Ar = Ph, 4-MeC_6H_4, 4-BrC_6H_4

Scheme 52



The acetic acid-catalyzed reaction of nitrochromenes **14** with methyl (*E*)-(2*H*-benzo[*b*][1,4]thiazin-3-ylidene)acetate (**99**) afforded pyrrolothiazines (Scheme 53).[74] In the authors' opinion, first, intramolecular substitution of imine for the nitro group in Michael adducts **100** takes place and then dihydropyrroles **101** are oxidized with air oxygen (pathway *a*). As a result, dihydrobenzo[*b*]chromeno[4′,3′:4,5]pyrrolo[1,2-*d*][1,4]thiazines **102** are formed in 52% – 67% yields. In our opinion, the cyclization of Michael adducts **100** to products **102** follows pathway *b* and represents yet another example of the known Grob reaction.[23]

Scheme 53



R = H, Cl, Br; Ar = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 3-$O_2NC_6H_4$

3.2. Cycloaddition reactions

The cycloaddition reactions underlie the one-step method for Δ^3-annulation of the 3-nitro-2*H*-chromene system by a carbo- or heterocycle. Most reactions proceed under mild conditions without a catalyst and are distinguished by high regio- and stereoselectivity and by easy isolation of the target product, which makes them rather valuable for organic synthesis. During the last five years, especially intensive studies were made on 1,3-dipolar cycloaddition of 1,3-dipoles such as sodium azide and stabilized azomethine ylides to the nitro group-activated double bond of 2*H*-chromenes.

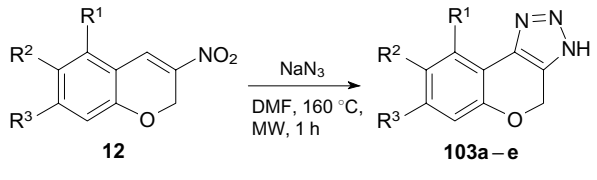
The 1,3-dipolar cycloaddition of sodium azide to 3-nitro-2*H*-chromenes accompanied by elimination of the nitro group is an efficient route to chromeno[1,2,3]triazoles. For instance, chromeno[3,4-*d*][1,2,3]triazoles **103a** – **e** were prepared from 2-unsubstituted nitrochromenes **12** in 63% – 89% yields under microwave radiation (Scheme 54) (Ref. 36).

The use of sulfonic acids for double bond activation in 2-aryl-3-nitro-2*H*-chromenes **14f**,**g** in the synthesis of chromenotriazoles **104a**,**b** has been reported [75, 76] (Scheme 55).

Our research team developed [38] a synthetic route to 4-(trihalomethyl)chromeno[3,4-*d*][1,2,3]triazoles **105** and **106** based on the reaction of 2-$CHal_3$-substituted nitrochromenes **13** (R^1 = Ph) and **68** (R^1 = H) with sodium azide in the presence of *p*-toluenesulfonic acid (Scheme 56).

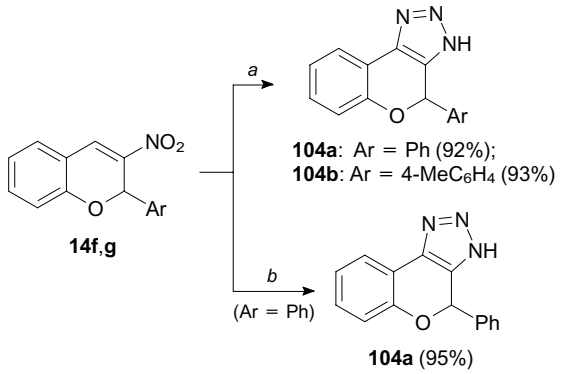
Lower yields of 4-CCl_3-chromenotriazoles **105** (37% – 64%) in comparison with 4-CF_3-analogues (84% – 96%) are due to the formation of 4-(dichloromethylidene)chromeno[3,4-*d*]triazoles **107** as side products upon elimination of HCl from triazoles **105** under the reaction conditions. Compounds **107** can also be formed *via* elimination of HCl

Scheme 54



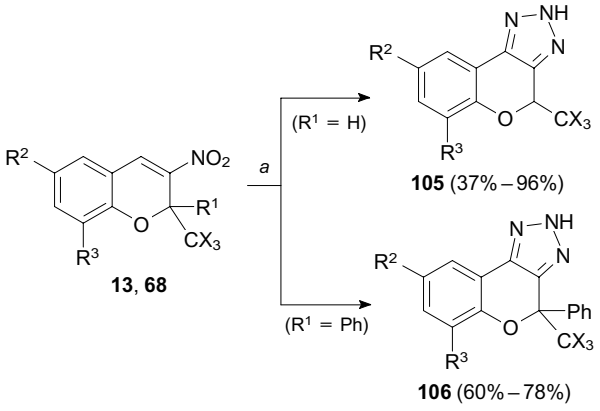
R^1 = R^2 = H: R^3 = H (**a**, 63% yield), MeO (**b**, 64%);
R^1 = R^3 = H: R^2 = Me (**c**, 80%), Br (**d**, 63%); R^1 – R^2 is benzo, R^3 = H (**e**, 89%)

Scheme 55



(*a*) NaN_3 (2 equiv.), H_2NSO_3H (0.4 equiv.), DMF, 60 °C, 10 – 45 min;[75]
(*b*) NaN_3 (1.5 equiv.), TsOH (0.5 equiv.), DMF, 60 °C, 3 h;[76]
Ar = Ph (**14f**), 4-MeC_6H_4 (**14g**)

Scheme 56

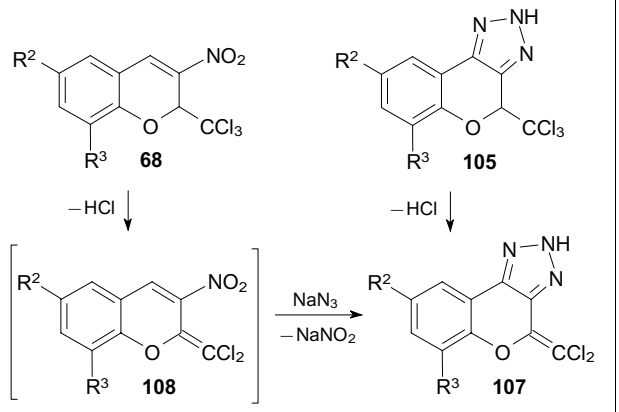


(*a*) NaN_3 (2 equiv.), TsOH (0.25 equiv.), DMF or DMSO, 60 – 70 °C, 5 – 90 min;
R^1 = H, Ph; R^2 = H, Me, MeO, Cl, Br; R^3 = H, EtO, Cl, Br; X = F, Cl

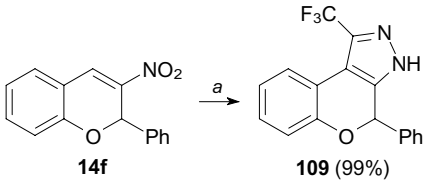
from 2-CCl_3-nitrochromenes **68** and subsequent addition of sodium azide to intermediate 2-(dichloromethylidene)chromenes **108**. In addition, partial resinification of unstable nitrochromenes **108** is possible (Scheme 57).[38]

A method was developed for the preparation of 1-(trifluoromethyl)-4-phenyl-chromeno[3,4-*c*]pyrazole (**109**) from 3-nitro-2-phenyl-2*H*-chromene (**14f**) and 2,2,2-trifluorodiazoethane in the presence of Ag_2O and Cs_2CO_3 (Scheme 58).[77] The synthesis can also be carried out as a one-pot reaction without isolation of the diazo compound

Scheme 57



Scheme 58



(*a*) CF_3CHN_2, Ag_2O, Cs_2CO_3, THF, 40 °C, 10 h

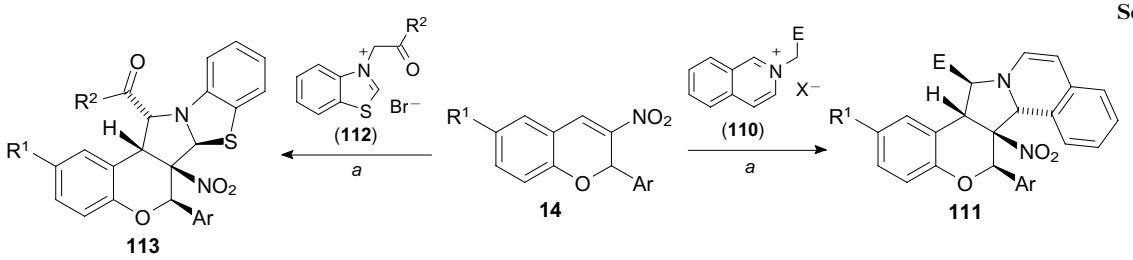
in a pure state. In this case, the overall yield of chromenopyrazole **109** over two steps is 72%.

The *exo*-cycloaddition to nitrochromenes **14** of the ylides generated from isoquinolinium salts **110** on treatment with Et_3N in ethanol at room temperature affords hydrogenated chromenopyrrolo[2,1-*a*]isoquinolines **111** (83% – 96% yields).[78] Under similar conditions, *endo*-cycloadducts **113** were formed in 72% – 95% yields from chromenes **14** and benzothiazolium bromides **112** (Scheme 59).[79]

In relation to 2-(4-methoxyphenyl)-3-nitro-2*H*-chromenes **14** (Ar = 4-$MeOC_6H_4$), it was shown that successive treatment of a mixture of the starting chromene and salt **112** first with triethylamine and then with 2,3-dichloro-5,6-dicyanoquinone (DDQ) leads to the synthesis of benzo[*d*]-chromeno[3′,4′:3,4]pyrrolo[2,1-*b*]thiazoles **114** without isolation of cycloaddition products **113** (Scheme 60).[79]

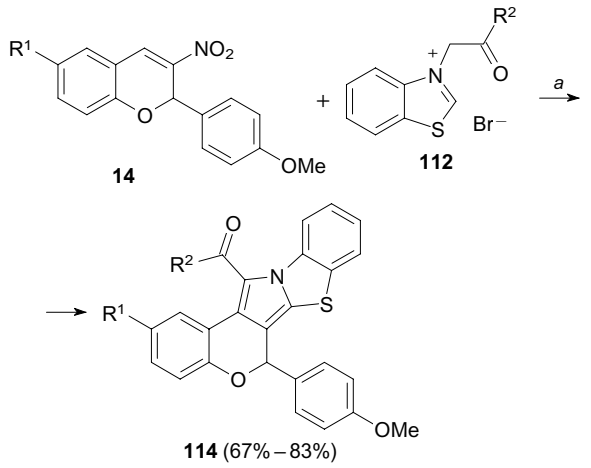
In recent years, considerable attention has been given to the development of synthetic routes to new derivatives of spirooxindoles, the structural moiety of which is present in synthetic pharmaceutical agents and natural products. One approach to the synthesis of spirooxindoles comprises regio- and stereoselective 1,3-dipolar cycloaddition of sta-

Scheme 59



(*a*) Et_3N (1.2 equiv.), EtOH, rt, 3 – 12 h; R^1 = H, Cl, Br; Ar = 3-MeC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$; R^2 = Ar, MeO, EtO; E = EtO_2C, Bz, CN; X = Cl, Br

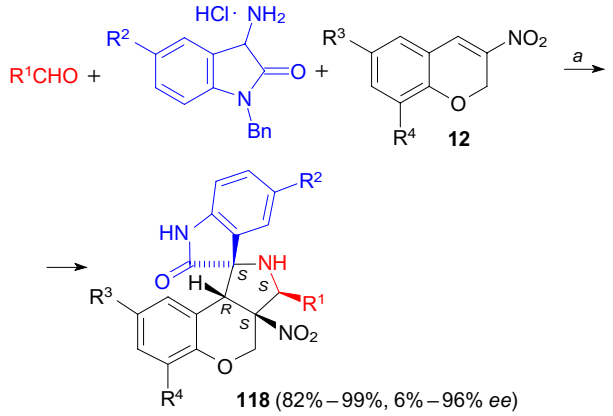
Scheme 60



114 (67% – 83%)

(*a*) 1) Et_3N, EtOH, rt; 2) DDQ, Δ;
R^1 = H, Cl, Br; R^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4

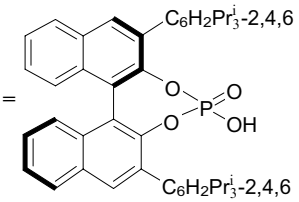
Scheme 62



118 (82% – 99%, 6% – 96% *ee*)

(*a*) **117** (20 mol.%), $NaHCO_3$, MS 3 Å, PhMe, rt, 6 – 7 days;
R^1 = Ar, 1-Naph, 2-Th, cyclo-C_6H_{11}; R^2 = H, Me, F;
R^3 = H, Me, Cl, Br; R^4 = H, Cl; MS means molecular sieves

117 =



bilized ylides based on isatin and α-amino acids to conjugated nitroalkenes. For example, refluxing of nitrochromenes **14** and **23** with ylides generated *in situ* from sarcosine, proline or pipecolic acid and isatin in toluene or in acetonitrile for 17 – 24 h results in the formation of *endo*-spiroadducts **115** and **116** (Scheme 61).[80, 81] Proline adducts **116** (n = 1) were obtained in 78% – 89% yields by refluxing chromenes **14** in ethanol for 2 h.[82]

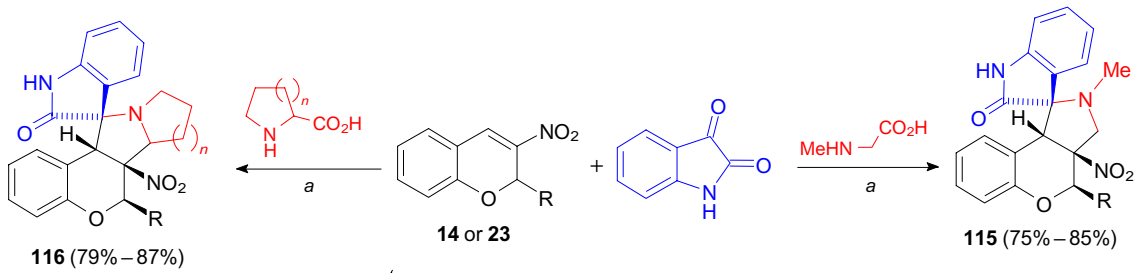
Qu and Wang[83] used chiral catalyst **117** to carry out asymmetric synthesis of spirooxindole derivative **118** (Scheme 62). The three-component reaction involved 2-unsubstituted chromenes **12**, aromatic aldehydes and 3-amino-1-benzylindolin-2-one hydrochlorides. In this case, azomethine ylides were generated by treatment of Schiff bases (formed in the first step from aminoindolinones and aldehydes) with $NaHCO_3$.

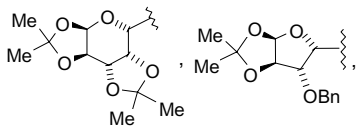
Rao and Raghunathan[81] reported the *endo*-cycloaddition of acenaphthenequinone- or 11*H*-indeno[1,2-*b*]quinoxalin-11-one-based ylides and α-amino acids (sarcosine, proline or pipecolic acid) to chromenes **23a**,**d** to give spirocycloadducts **119** – **122**. The reaction is carried out in refluxing acetonitrile for 17 – 20 h (Scheme 63).

Our research team[84] ascertained that 1,3-dipolar cycloaddition of stabilized ylides generated *in situ* from ninhydrin and proline to the nitro group-activated double bond of 2-(trifluoromethyl)- and 2-phenyl-substituted 3-nitro-2*H*-chromenes **68** (R^3 = F_3C) and **14** (R^3 = Ph) on heating in ethanol proceeds regio- and stereoselectively and results in the formation of spiro(indene-2,11′-chromeno[3,4-*a*]pyrrolizidine)-1,3-diones **123** containing three pharmacophoric moieties in the molecule (Scheme 64). The yields of spirocycloadducts **123** are 80% – 90% and depend little on the electron-donating or -withdrawing properties of substituents R^1 and R^2. When other solvents are used (benzene, methanol, 2-propanol), the yields decrease by 10% – 30%.

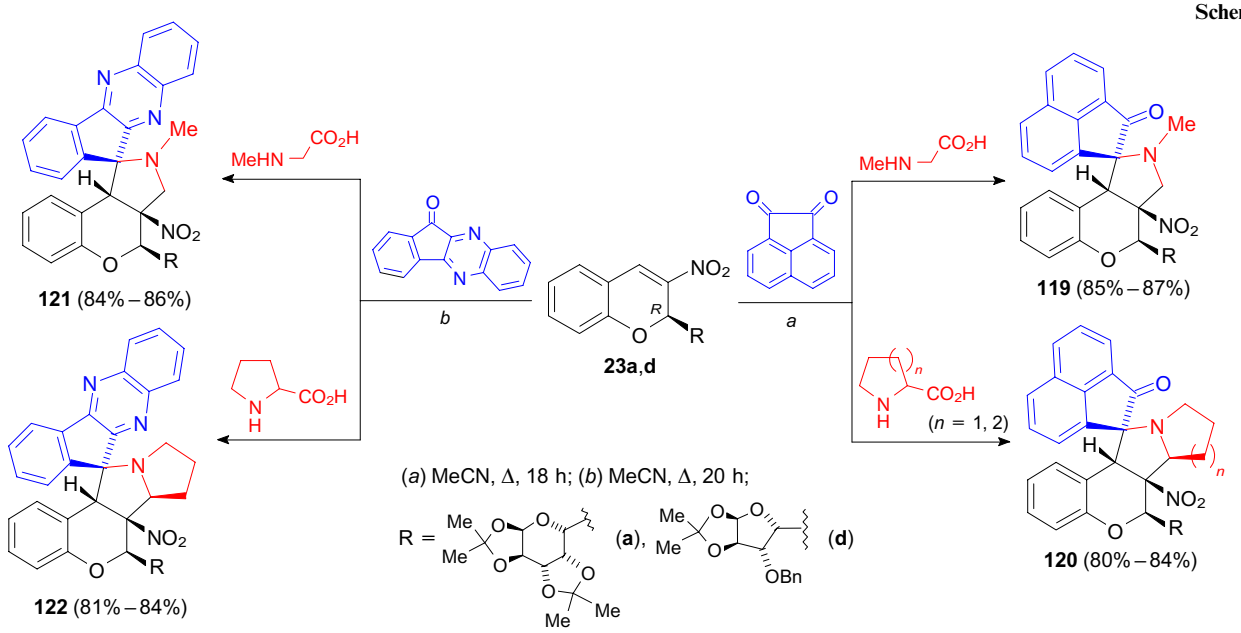
3-Nitro-2-phenyl-2*H*-chromenes **14** react with *N*,*N*′-cyclic azomethine imines **124** based on pyrazolidin-3-one and benzaldehydes to give tetrahydrochromeno[4,3-*c*]pyrazolo[1,2-*a*]pyrazol-11-ones **125** (42% – 81% yields) as single stereoisomers with *cis*-positions of substituents at the C(6), C(6a) and C(7) atoms and the hydrogen atom in position 12a.[85] The lowest yields of products **125** (42% – 54%) were observed in the case of azomethine imines **124** with one or two chlorine atoms in the aryl moiety (Ar = 4-ClC_6H_4 and 2,4-$Cl_2C_6H_3$). This transformation is the first and still the

Scheme 61

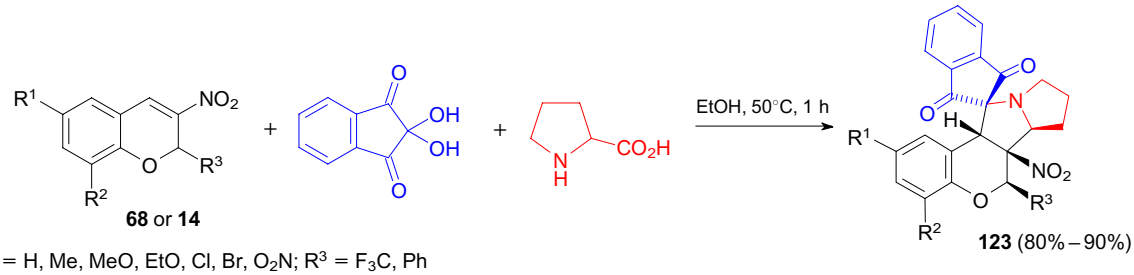


(*a*) PhMe or MeCN, Δ; R = , Ph, 4-$MeOC_6H_4$, 1-Naph, Fc, 1-methylindol-3-yl; n = 1, 2;
Fc is ferrocenyl

Scheme 63

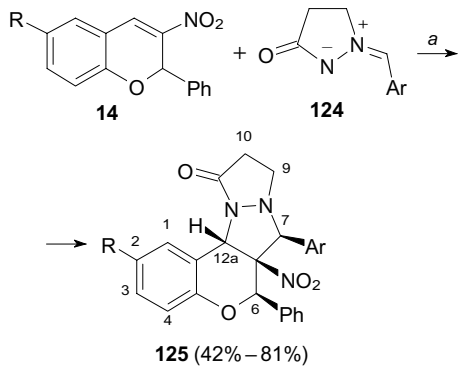


Scheme 64



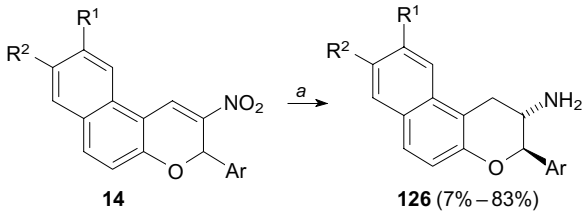
R^1, R^2 = H, Me, MeO, EtO, Cl, Br, O_2N; R^3 = F_3C, Ph

Scheme 65



(*a*) Pr^iOH, 50 °C, 2 days;
R = H, MeO, Br; Ar = Ph, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$

Scheme 66



(*a*) 1) $NaBH_4$, MeOH, THF, rt, 20 min; 2) Zn, HCl, EtOH, rt, 3 h;
R^1 = H, MeO, Br, NC, 3-$MeSO_2C_6H_4$; R^2 = H, MeO, Br, CN, morpholino; Ar = 2-FC_6H_4, 3-FC_6H_4, 2-ClC_6H_4, 2,4-$F_2C_6H_3$, 2,5-$F_2C_6H_3$, 2,4,5-$F_3C_6H_2$

only one case of azomethine imine cycloaddition to the double bond of 3-nitro-2*H*-chromenes (Scheme 65).

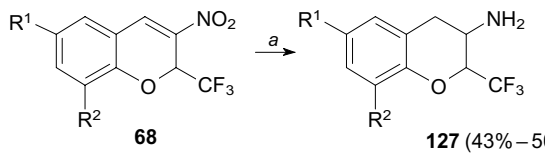
3.3. Redox reactions

The reduction of the double bond and the nitro group in the 3-nitro-2*H*-chromene molecule affords 3-aminochromanes.[86,87] The successive reduction of benzo[*f*]chromenes **14** with sodium tetrahydroborate and zinc resulted in the synthesis of *trans*-3-amino-2-arylchromanes **126** (Scheme 66).[86] No clear correlation is observed between the yields of reduction products and the size or electron-donating or -withdrawing properties of substituents.

Treatment of 2-CF_3-chromenes **68** with a more reactive diborane and then with sodium tetrahydroborate was also accompanied by complete reduction of the nitrostyrene moiety to give 2-trifluoromethyl-substituted 3-aminochromanes **127** (Scheme 67).[87]

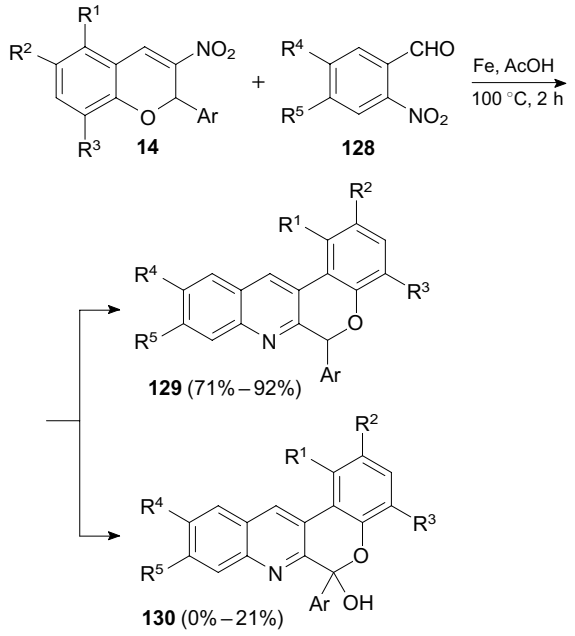
Quing *et al.*[88] investigated the reductive cyclization of chromenes **14** with 2-nitrobenzaldehydes **128**, giving rise to 6-aryl-6*H*-chromeno[3,4-*b*]quinolines **129** or their mixture with 6-aryl-6*H*-chromeno[3,4-*b*]quinolin-6-ols **130** (Scheme 68).

Scheme 67



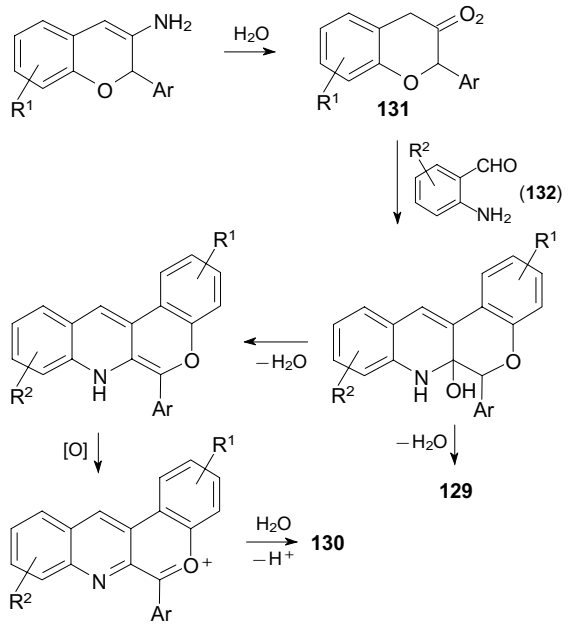
(*a*) 1) B_2H_6 (4 equiv.), THF, 5 °C, 1 h; 2) $NaBH_4$ (0.4 equiv.), THF, Δ, 8 h; R^1 = H, Me, MeO, Cl, Br; R^2 = H, Me, MeO, Br

Scheme 68



R^1 = H: R^2 = H, Cl, Br; R^1 – R^2 is benzo; R^3 = H, EtO; R^4 = H, Cl; R^5 = H, Br; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-Th

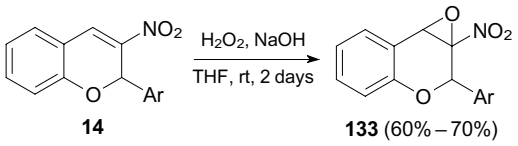
Scheme 69



The key step is the Povarov reaction between chromanones **131** and aminoaldehydes **132**, which are formed upon the reduction of chromenes **14** and nitroaldehydes **128** (Scheme 69).

Epoxynitrochromanes **133** were obtained by oxidation of 2-arylnitrochromenes **14** with 30% aqueous H_2O_2 in an alkaline medium;[89] these products are of interest as the starting reactants for the synthesis of Δ^3-annulated chromenopyrroles,[90] chromenothiazoles[91] and chromenoquinoxalines[92] (Scheme 70).

Scheme 70



Ar = Ph, 4-MeC_6H_4, 4-HOC_6H_4, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 2-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4

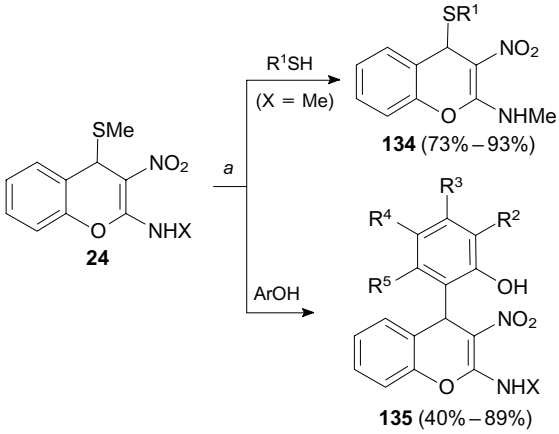
4. Reactions of 3-nitro-4*H*-chromenes

Owing to the presence of an electron-donating oxygen atom in position 1, a good leaving group in position 4, and a common chain of conjugation in the molecule, 4-sulfanyl 3-nitro-4*H*-chromene derivatives **24** show a high reactivity towards S_N1 reactions with nucleophiles, which may be accompanied by pyran ring opening or ring transformation. One more group of reactions described in the literature includes transformation of the nitroenamine moiety and removal of the alkylsulfanyl substituent in nitrochromenes **24** using reductive methods.

4.1. Nucleophilic substitution

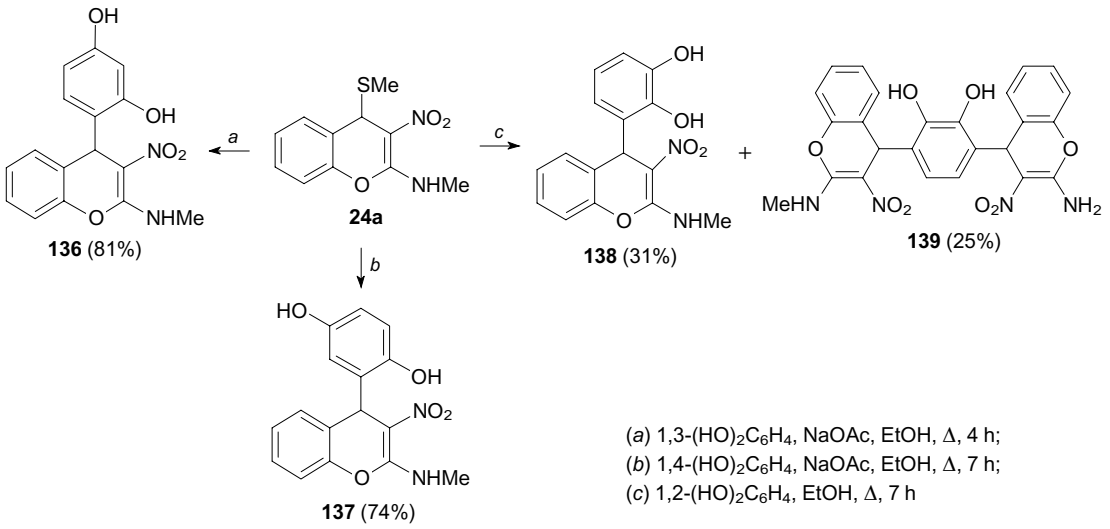
Chromenes **134** with various sulfanyl substituents in position 4 were prepared by the reaction of 2-methylamino-4-methylsulfanyl-3-nitro-4*H*-chromene (**24a**) with thiols in refluxing ethanol (Scheme 71).[30] Under the same conditions, phenols and naphthols behave as C-nucleophiles and

Scheme 71



(*a*) EtOH, Δ, 8 – 29 h;
R^1 = Bu^n, n-C_8H_{17}, Ph, 4-MeC_6H_4, 4-ClC_6H_4; R^5 = H:
R^2, R^3 = H, Me; R^4 = H, Me, Cl; R^2 – R^3, R^4 – R^5 is benzo;
X = Me, Bu^n, Bn, Ph; Ar = $R^2R^3R^4R^5C_6H$

Scheme 72



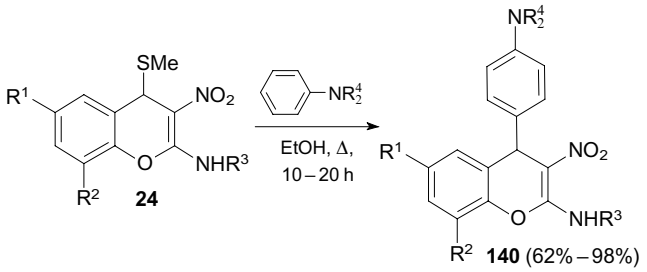
(*a*) 1,3-$(HO)_2C_6H_4$, NaOAc, EtOH, Δ, 4 h;
(*b*) 1,4-$(HO)_2C_6H_4$, NaOAc, EtOH, Δ, 7 h;
(*c*) 1,2-$(HO)_2C_6H_4$, EtOH, Δ, 7 h

react with chromenes **24** by their *ortho*-carbon atom to give 4-aryl-3-nitrochromenes **135** (see Scheme 71).[93]

A similar reaction of nitrochromene **24a** with resorcinol and hydroquinone affords 4-aryl-substituted chromenes **136** and **137** in 81% and 74% yields, respectively, while the reaction with pyrocatechol gives a mixture of products **138** and **139** in a total yield of 56% (Scheme 72).[93] A sterically hindered phloroglucinol (1,3,5-trihydroxybenzene) does not react with chromene **24a**.

The reactions of chromenes **24** with aromatic amines proceed with the participation of the amine C(4) atom and give 4-arylchromenes **140** in high yields (Scheme 73).[94]

Scheme 73



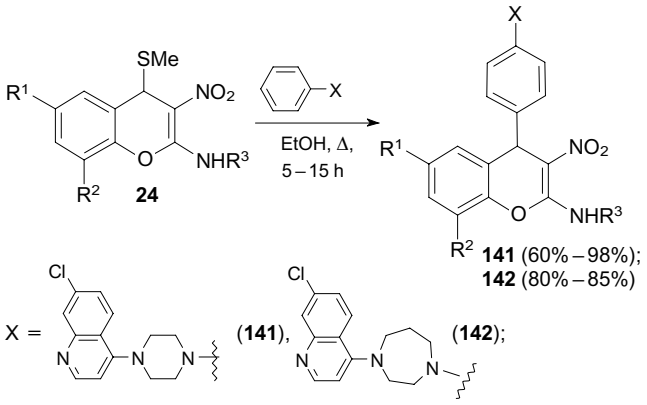
R^1 = H, Me, Et, MeO, EtO, Br; R^2 = H, MeO; R^3 = Me, Bn, Ph, 4-$MeOC_6H_4(CH_2)_2$; R^4 = Et, cyclo-C_6H_{11}; $R^4 – R^4$ = $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_6$, $(CH_2)_2O(CH_2)_2$, $(CH_2)_2NPh(CH_2)_2$; R^4_2N is 1,2,3,4-tetrahydroquinolino

In order to assess the antimalarial activity, Parthiban *et al.*[95] synthesized an extensive series of chromenes **141** and **142** containing the 7-chloroquinoline pharmacophoric moiety (Scheme 74).

The reactions of chromene **24a** with pyrrole and indole, like reactions with phenols and aromatic amines, proceed regioselectively, giving rise to 4-hetarylchromenes **143** and **144** (Scheme 75).[96]

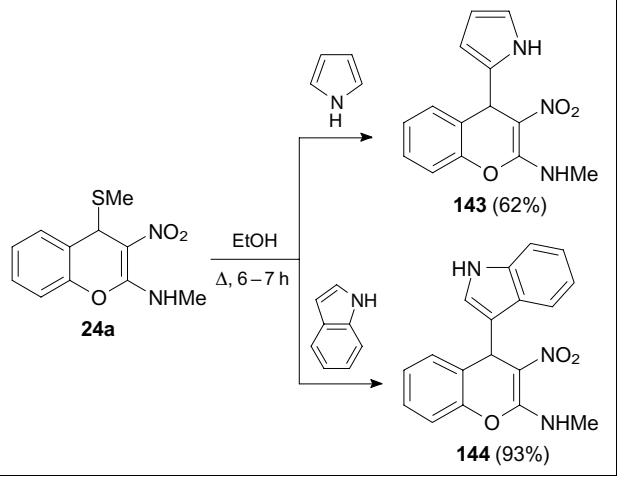
Cyclic ketones containing a enolyzed 1,3-dicarbonyl moiety can also serve as nucleophiles. Thus, the reaction of nitrochromenes **24** with lawsone (2-hydroxynaphthalene-1,4-dione, **145**) in refluxing ethanol is completed as soon as in 15 min giving conjugates **146** in good yields (Scheme 76).[97]

Scheme 74



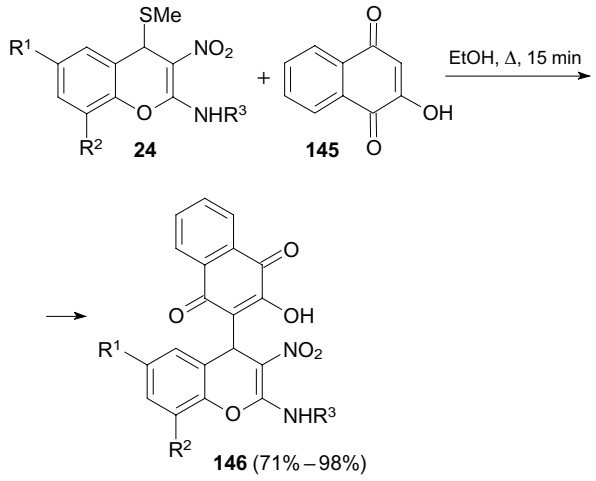
R^1 = H, MeO, Cl, Br, O_2N; R^2 = H, EtO, Cl, Br; R^3 = Me, Et, Bn, $Ph(CH_2)_2$

Scheme 75



Short-term refluxing of chromenes **24** with pyrone **147** in ethanol furnishes unstable nucleophilic substitution products **148**. On longer refluxing, compounds **148** undergo pyran ring opening accompanied by elimination of nitro-

Scheme 76



R^1 = H, MeO, Cl, Br, O_2N; R^2 = H, EtO, Cl, Br; R^3 = Me, Bu^n, 4-$MeOC_6H_4CH_2$

ynamine **149**, which is followed by intramolecular cyclization of intermediates **150** to coumarins **151** (Scheme 77).[98]

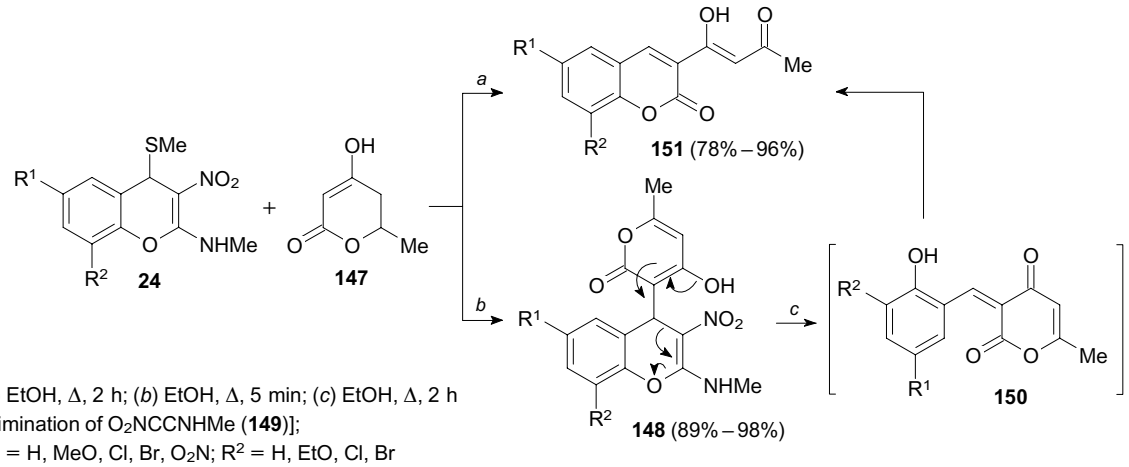
By refluxing nitrochromenes **24** and 4-hydroxycoumarin **152** in ethanol for a short period of time, substitution products **153** were synthesized. If refluxing in ethanol or propanol is carried out for 0.5 – 3 h, *trans*-dihydrofuro[3,2-*c*]chromenes **154** are formed in 51% – 77% yields upon the addition of the alcohol molecule to the C(2′) atom of the *aci*-form of the chromene moiety of compound **153** followed by intramolecular Nef reaction involving the coumarin 4-hydroxy group, accompanied by pyran ring opening (Scheme 78).[98]

Recently, Rao *et al.*[99] reported a three-component condensation of 4*H*-chromenes **24** with aroylacetic acid nitriles and hydrazine (Scheme 79). On moderate heating in ethanol, chromenes **24** and pyrazoles **155** give, first, 4*H*-chromenopyrazoles **156**, which are then converted to 4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridines **157**.

In a previous study,[100] a four-component reaction of salicylaldehydes **2**, hydrazines, ethyl acetoacetate and N,S-acetal **25a** was found to give, despite more drastic conditions, high yields of chromenopyrazoles **158**, structurally similar to **156**, rather than dihydropyrano[2,3-*c*]pyrazoles **159** (Scheme 80).

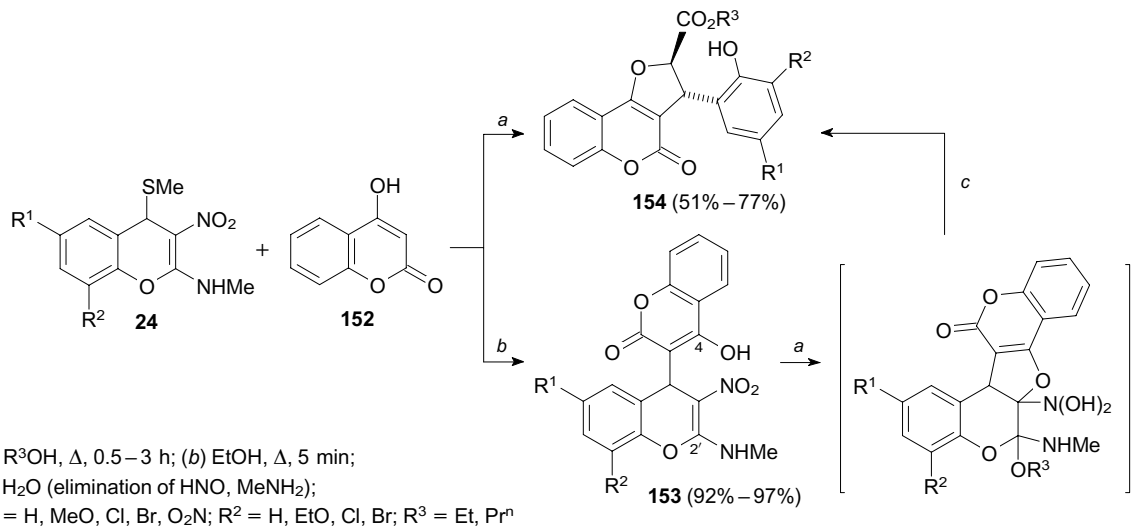
In the authors' opinion, intermediate pyrazole **160** and the specified salicyladehyde **2** give initially the Knoevenagel condensation product **A**; the key step of this complex

Scheme 77



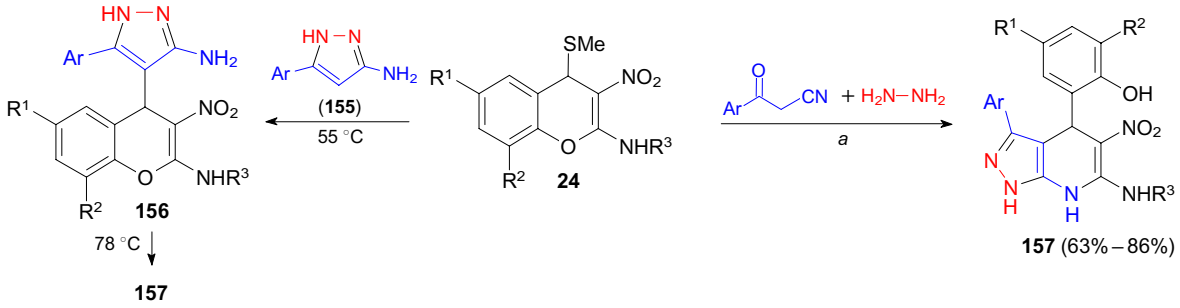
(*a*) EtOH, Δ, 2 h; (*b*) EtOH, Δ, 5 min; (*c*) EtOH, Δ, 2 h [elimination of $O_2NCCNHMe$ (**149**)];
R^1 = H, MeO, Cl, Br, O_2N; R^2 = H, EtO, Cl, Br

Scheme 78



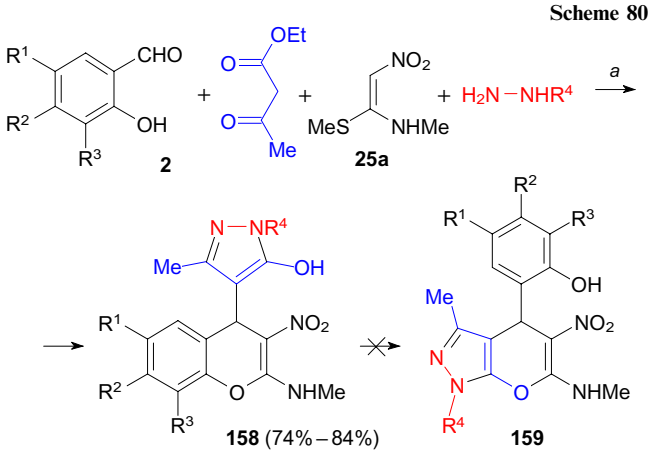
(*a*) R^3OH, Δ, 0.5 – 3 h; (*b*) EtOH, Δ, 5 min;
(*c*) H_2O (elimination of HNO, $MeNH_2$);
R^1 = H, MeO, Cl, Br, O_2N; R^2 = H, EtO, Cl, Br; R^3 = Et, Pr^n

Scheme 79



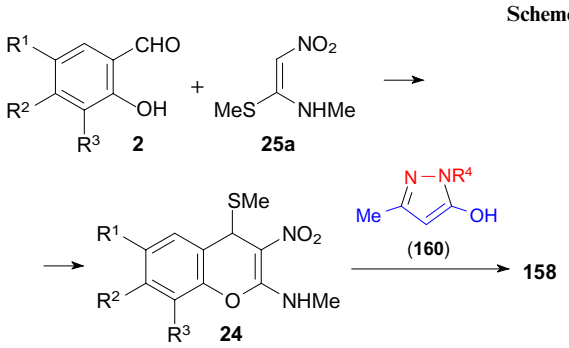
(*a*) 1) AcOH (10 mol.%), EtOH, 55 °C, 2 h; 2) EtOH, Δ, 4–12 h; R^1 = H, Cl, Br; R^2 = H, MeO; R^3 = Me, Bu^n; Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4

Scheme 80



(*a*) piperidine (25 mol.%), 120 °C, 0.75–3 h;
R^1 = H, Cl, Br, O_2N; R^2 = H, MeO; R^3 = H, EtO, Br; R^4 = H, Ph

Scheme 82



domino process is the addition of acetal **25a** to intermediate **A**, affording Michael adduct **161**. However, the intramolecular cyclization of compound **161** can occur with the hydroxy group of either phenol or the pyrazole moiety; this fails to explain the regiospecificity of the reaction (Scheme 81).

Relying on the most recent data obtained by Rao's research team,[99] it is reasonable to assume that products **158** result from nucleophilic displacement of the methylsulfanyl group in nitrochromenes **24**, which are easily formed from salicylaldehydes **2** and acetal **25a** under the reaction conditions (Scheme 82).

Pyrano[2,3-*c*]pyrazoles **159**, devoid of the hydroxy group in the aryl substituent, were synthesized in high yields when benzaldehydes were used instead of salicylaldehydes in a similar four-component reaction; in this case, pyrazolidone **162** is formed intermediately (Scheme 83).[100]

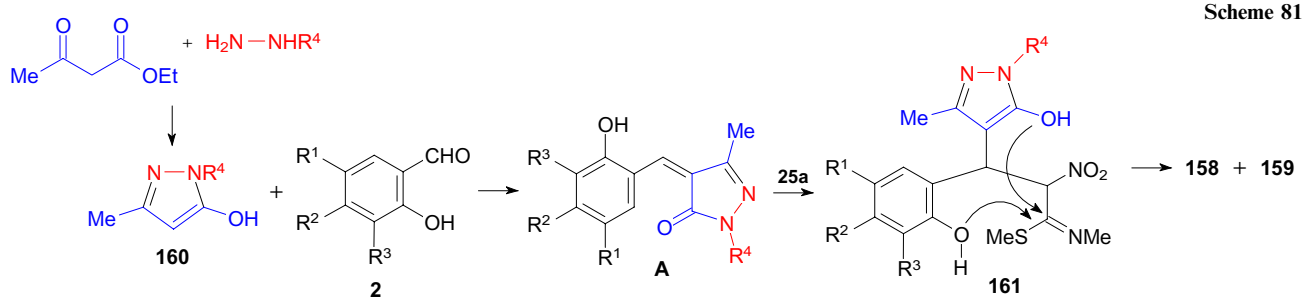
Treatment of 4*H*-nitrochromene **24a** (R^1 = H, R^2 = Me) with phenylmagnesium bromide in THF affords product **163a** in a moderate yield. Various 4-aryl-substituted chromenes **163** were prepared in high yields by cross-coupling of chromenes **24** with arylboronic acids in DMF in the presence of copper(II) acetate (Scheme 84).[101]

4.2. Reductive reactions

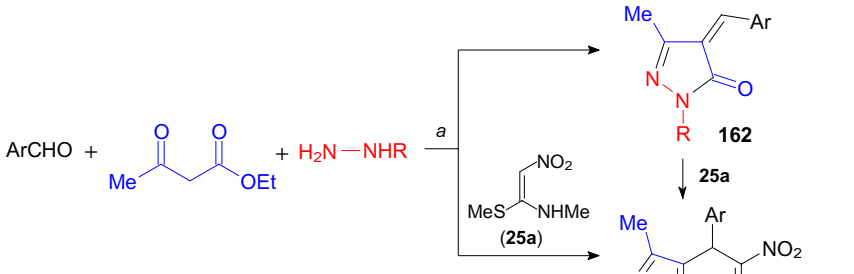
The reaction of nitrochromenes **24** with various reducing agents was studied in detail by Rao *et al.*[96] The reductive desulfurization of chromene **24a** catalyzed by Raney nickel (Ni-Ra) in ethanol at room temperature generated 4-unsubstituted nitrochromene **164a** in a low yield, while the same reaction under reflux gave its dimer **165** (Scheme 85).

The yield of desulfurization products **164a–e** increases to 72%–86% when the reaction is carried out in refluxing methanol and when 1,4-dihydropyridine derivative **166**, which is an available hydride ion donor, is used as the reducing agent (Scheme 86).[96]

Scheme 81

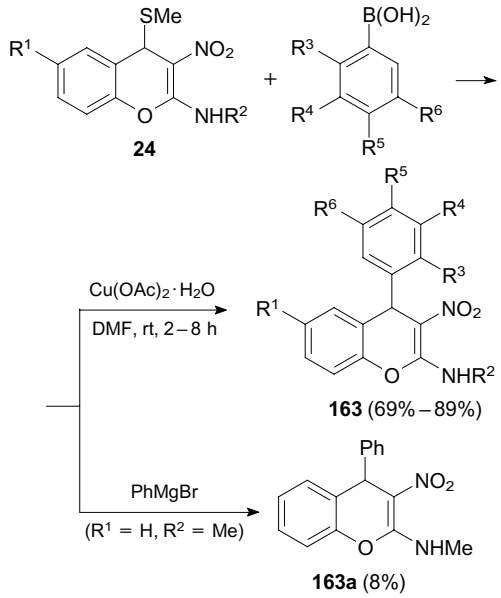


Scheme 83



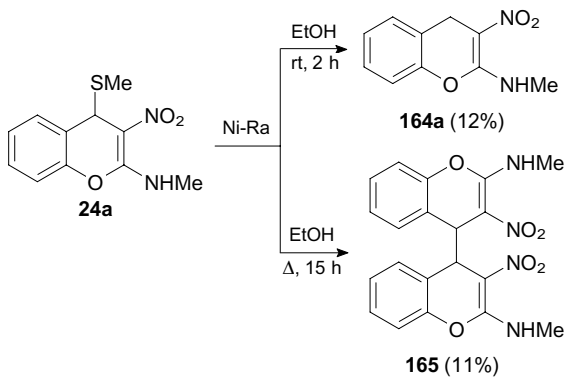
(*a*) piperidine (25 mol.%), 120 °C, 0.5 – 3 h;
R = H, Ph; Ar = 2-MeC_6H_4, 4-MeC_6H_4, 2-FC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 1-Naph

Scheme 84



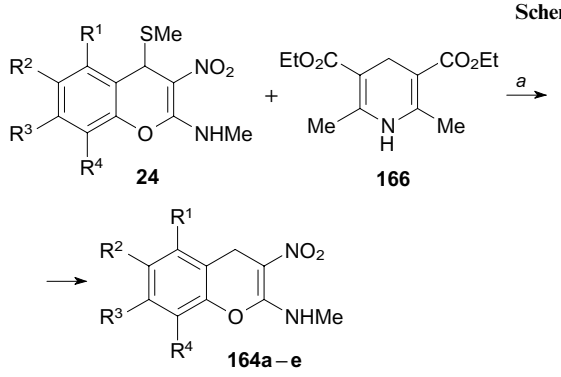
R^1 = H, Cl, Br, Et; R^2 = H, Bu^n; R^3 = H, MeO; R^4 = H, MeO, F, Cl, F_3C; R^5 = H, Et, EtO, BnO, F, Cl, Br, F_3C; R^6 = H, MeO, F, F_3C

Scheme 85



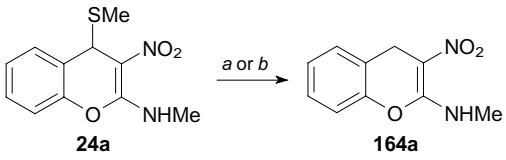
In the same study, chromene **164a** was prepared by treatment of chromene **24a** with tri-n-butyltin hydride (TBTH) in the presence of 2,2′-azobis(isobutyronitrile) (AIBN) in refluxing benzene (82% yield) or by heating chromene **24a** with benzenethiol at 163 °C (88% yield) (Scheme 87).

Scheme 86



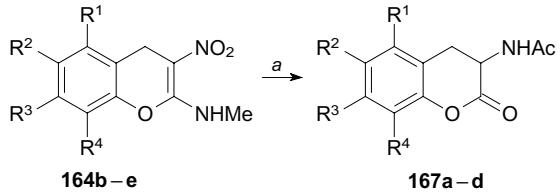
(*a*) MeOH, Δ, 4 – 9 h;
R^1 = R^2 = R^3 = R^4 = H (**a**, 78% yield); R^1 = MeO, R^2 = R^3 = R^4 = H (**b**, 74%); R^1 = R^3 = R^4 = H, R^2 = MeO (**c**, 86%); R^1 = R^2 = R^3 = H, R^4 = MeO (**d**, 72%); R^1 = R^2 = R^4 = H, R^3 = BnO (**e**, 82%)

Scheme 87



(*a*) TBTH, AIBN, PhH, Δ, 0.5 h; (*b*) PhSH, 163 °C, 2.5 h

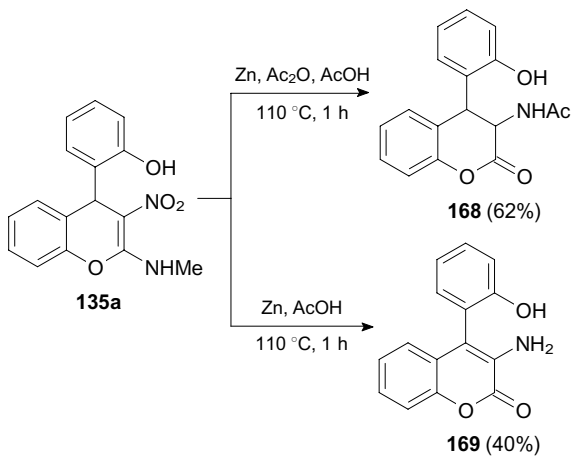
Scheme 88



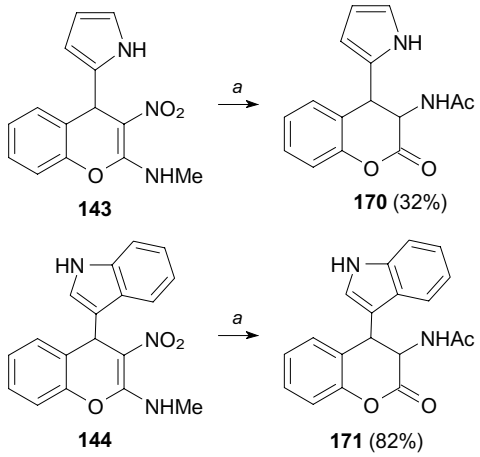
(*a*) Zn, Ac_2O, AcOH, 113 °C, 0.5 – 1 h;
167: R^1 = OMe, R^2 = R^3 = R^4 = H (**a**, 68% yield); R^1 = R^3 = R^4 = H, R^2 = OMe (**b**, 82%); R^1 = R^2 = R^3 = H, R^4 = OMe (**c**, 68%); R^1 = R^2 = R^4 = H, R^3 = OBn (**d**, 61%)

The reduction of the nitro group in chromenes **164b – e** with zinc in a mixture of AcOH and Ac_2O on heating is accompanied by hydrolysis of the enamine moiety giving rise to aminolactones **167a – d** in good yields (Scheme 88).[96]

Scheme 89



Scheme 90



(*a*) Zn, Ac_2O, AcOH, 110 °C, 0.5 – 1 h

Under similar conditions, aminolactone **168** was synthesized in 62% yield from 4-arylnitrochromene **135a**; meanwhile, in the absence of acetic anhydride, zinc reduction afforded enamine **169** (Scheme 89).[93]

4-Hetaryl-substituted aminolactones **170** and **171** were prepared from chromenes **143** and **144** under the same conditions (Scheme 90).[96]

No data on the action of oxidants on the 3-nitro-4*H*-chromene system were reported in the literature.

5. Biological activity of 3-nitro-2*H*- and 3-nitro-4*H*-chromenes

5.1. 3-Nitro-2*H*-chromenes

Many 3-nitro-2*H*-chromenes possess antitumour activity.[23] The highest cytotoxic effect against a broad range of tumour cells was revealed for 6-bromo-8-ethoxy-3-nitro-2*H*-chromene (BENC-511) and 8-ethoxy-2-(4-fluorophenyl)-3-nitro-2*H*-chromene (S14161). Zhang *et al.*[32] investigated the antiproliferative action of sulfonylhydrazones **5a** – **h** and acylhydrazones **6a** – **e** (structural analogues of BENC-511) in cell lines of lung carcinoma (A549), leukaemia (KG-1), ovarian cancer (A2780) and human chronic myeloid leukaemia (K562).

Compounds **5** and **6** exhibited marked cytotoxicity against all of the above listed cancer cells in the micromolar concentration range (Table 7); the antiproliferative effect

Structures 5, 6

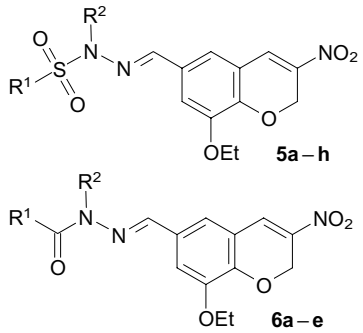


Table 7. *In vitro* antitumour activity of compounds **5a** – **h** and **6a** – **e**.[32]

Compound	R^1	R^2	IC_{50} /μmol litre^{-1}			
			A549	KG-1	A2780	K562
5a	4-MeC_6H_4	H	10.14 ± 0.35	2.99 ± 0.32	0.62 ± 0.08	0.47 ± 0.04
5b	4-MeC_6H_4	Me	7.47 ± 0.05	0.96 ± 0.05	0.57 ± 0.04	1.69 ± 0.21
5c	3-$O_2NC_6H_4$	H	53.32 ± 5.9	2.04 ± 0.11	0.92 ± 0.06	0.75 ± 0.04
5d	3-$O_2NC_6H_4$	Me	13.83 ± 1.6	0.78 ± 0.02	0.24 ± 0.02	2.68 ± 0.26
5e	2-Fu	H	17.79 ± 0.57	2.32 ± 0.23	0.34 ± 0.03	1.11 ± 0.02
5f	2-Fu	Me	4.97 ± 0.53	0.74 ± 0.02	0.14 ± 0.01	1.89 ± 0.01
5g	3-Py	H	30.37 ± 0.44	2.97 ± 0.2	0.15 ± 0.04	0.78 ± 0.02
5h	5-Methyl-2-pyridyl	H	22.67 ± 0.46	2.87 ± 0.25	0.61 ± 0.09	4.26 ± 0.18
6a	2-Py	H	8.07 ± 0.87	0.76 ± 0.01	0.18 ± 0.05	2.62 ± 0.2
6b	3-Py	H	13.38 ± 0.37	0.45 ± 0.03	0.22 ± 0.02	15.96 ± 1.06
6c	3-Py	Me	9.79 ± 0.82	1.21 ± 0.08	0.20 ± 0.03	18.86 ± 1.21
6d	3-$AcNHC_6H_4$	H	12.67 ± 0.69	2.88 ± 0.08	0.20 ± 0.06	0.11 ± 0.009
6e	4-$AcNHC_6H_4$	H	See [a]	See [a]	See [a]	1.90 ± 0.01
BENC-511			12.67 ± 1.33	3.04 ± 0.52	0.10 ± 0.0012	0.076 ± 0.0044
Doxorubicin			0.51 ± 0.04	0.052 ± 0.0012	0.057 ± 0.0026	0.013 ± 0.0015

Note. IC_{50} is the half-maximal inhibitory concentration. [a] IC_{50} value was not determined due to low activity.

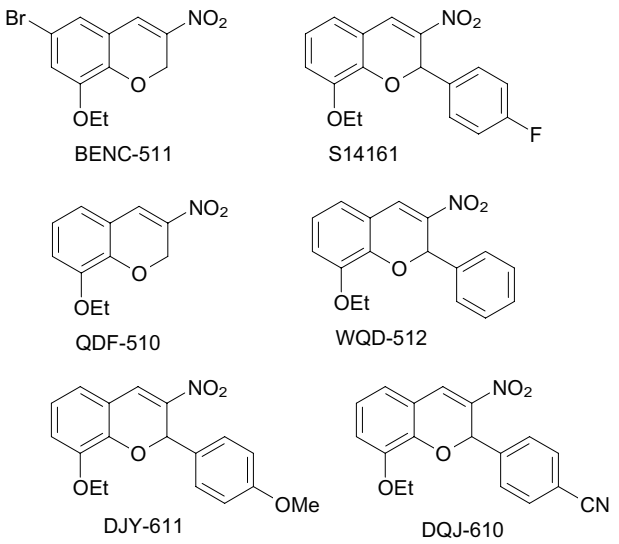


Figure 3. Phosphatidylinositol 3-kinase (PI3K) inhibitors.

towards KG-1 cells was higher for chromenes **5** and **6** than for BENC-511. After 48 h, nitrochromene **6d** taken in concentrations of 1.0 and 5.0 μmol litre^{-1} induced apoptosis of 80.74% and 93.21% of K562 cells, respectively. However, the cytotoxic activity of chromenes **5** and **6** is markedly lower than that of doxorubicin, a known anticancer drug.

o-Aminoanilides **8**, *N*-phenethylamides **9** and α-aminoamides **11** based on 6-amino-8-ethoxy-3-nitro-2*H*-chromene are potent histone deacetylase HADC1 and HADC2 inhibitors when used in the nanomolar concentration range

Table 8. *In vitro* antitumour activity of compound DHM25.[10]

Cell line	IC_{50} /μM
MCF7	6.817
ZR75-1	10.64
T47D	3.904
MDA-MB-231	6.298
BT549	5.463
MDA-MB-468	6.8
Hs578T	2.904
MDA-MB-453	1.141
BT474	4.65

(IC_{50} = 128 – 2915 nmol litre^{-1}); furthermore, compounds **11** were selective to HADC1.[35]

The evaluation of the antitumour activity of S14161 and BENC-511 and their structural analogues (see Fig. 3) showed that they all have cytotoxic action in the RPMI-8226, OPM2 and KMS11 myeloma cells and K562 leukaemia cells.[7–9] The marked antiproliferative effect of these compounds is associated with inhibition of phosphatidyl inositol 3-kinase (PI3K) and initiation of cancer cell apoptosis.[8,9]

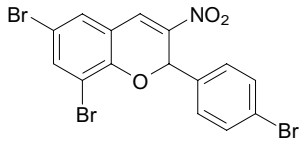
Fouqué *et al.*[10] ascertained that 6,8-dibromo-2-(4-bromophenyl)-3-nitro-2*H*-chromene (DHM25) has high antitumour activity towards various breast cancer cell lines (Table 8), which is caused by selective inhibition of serine – threonine protein kinase mTOR *via* covalent binding of the lysine amino group in position 2187 of the target to the C(4) atom of chromene.

It should be noted that structurally similar 6-bromo-2-(4-bromophenyl)-3-nitro-2*H*-chromene (DHM9) and 6-bromo-2-(4-nitrophenyl)-3-nitro-2*H*-chromene (DHM12) containing no bromine in position 8 also exhibit marked

Table 9. *In vitro* antitumour activities of compounds **14g** – **aa**.[102]

Compound	R^1	R^2	R^3	Ar	IC_{50} /μM		
					MCF-7	T-47D	MDA-MB-231
14h	H	H	H	4-$MeOC_6H_4$	3.3 ± 0.9	3.9 ± 2.4	4.1 ± 0.1
14j	H	H	H	3,4-$(MeO)_2C_6H_3$	3.7 ± 0.2	3.2 ± 2.3	0.4 ± 0.2
14k	H	H	H	3,4,5-$(MeO)_3C_6H_2$	4.3 ± 0.6	2.1 ± 0.9	4.9 ± 1.0
14g	H	H	H	4-MeC_6H_4	3.7 ± 0.5	3.3 ± 2.5	4.6 ± 0.5
14i	H	H	H	4-ClC_6H_4	3.7 ± 0.2	4.5 ± 1.2	4.1 ± 0.1
14l	H	H	H	4-$O_2NC_6H_4$	3.4 ± 0.3	4.5 ± 1.6	4.2 ± 0.1
14m	H	H	H	3,4-$(OCH_2O)C_6H_3$	3.8 ± 0.4	5.6 ± 0.4	4.5 ± 0.4
14n	H	H	MeO	4-$MeOC_6H_4$	1.6 ± 0.2	3.9 ± 1.2	4.7 ± 0.6
14o	H	H	MeO	3,4-$(MeO)_2C_6H_3$	3.1 ± 0.6	9.1 ± 1.06	12.8 ± 2.3
14p	H	H	MeO	3,4,5-$(MeO)_3C_6H_2$	4.6 ± 0.5	6.2 ± 0.5	4.9 ± 0.1
14q	H	H	MeO	4-MeC_6H_4	3.9 ± 0.1	4.6 ± 0.3	3.3 ± 0.8
14r	H	H	MeO	4-ClC_6H_4	0.2 ± 0	3.6 ± 2.1	2.0 ± 0.2
14s	H	H	MeO	4-$O_2NC_6H_4$	2.3 ± 0.5	7.5 ± 0.3	0.5 ± 0.2
14t	H	H	MeO	3,4-$(OCH_2O)C_6H_3$	3.5 ± 0.07	6.3 ± 0.4	4.7 ± 0.4
14u	MeO	MeO	MeO	4-$MeOC_6H_4$	3.8 ± 0.2	4.7 ± 0.7	4.8 ± 0.6
14v	MeO	MeO	MeO	3,4-$(MeO)_2C_6H_3$	4.2 ± 0.1	3.0 ± 0.2	4.6 ± 0.1
14w	MeO	MeO	MeO	3,4,5-$(MeO)_3C_6H_2$	3.9 ± 0.3	12.7 ± 1.2	6.8 ± 0.1
14x	MeO	MeO	MeO	4-MeC_6H_4	3.1 ± 0.7	5.4 ± 1.3	3.6 ± 0.3
14y	MeO	MeO	MeO	4-ClC_6H_4	3.5 ± 0.1	4.5 ± 0.4	5.2 ± 0.1
14z	MeO	MeO	MeO	4-$O_2NC_6H_4$	3.0 ± 1.4	10.3 ± 0.2	6.2 ± 0.7
14aa	MeO	MeO	MeO	3,4-$(OCH_2O)C_6H_3$	4.7 ± 0.8	9.5 ± 1.3	6.1 ± 0.4
Etoposide					7.2 ± 0.8	7.7 ± 0.7	12.8 ± 1.0

Structure of DHM25



DHM25

anticancer activity; however, they do not inhibit mTOR. Their activity is attributable to the inhibition of tyrosine kinase c-Yes and serine–threonine protein kinases p70S6K, LOK, BrSK1, TSSK1 and NLK.

The cytotoxic activity of 2-aryl-substituted nitrochromenes **14g–aa** (Table 9) was evaluated in MCF-7, T-47D and MDA-MB-231 breast cancer cells.[102]

Most of the assayed compounds demonstrated a higher antiproliferative effect (IC_{50} = 1.6–12.7 μmol litre^{-1}) than the reference drug etoposide (7.2–12.8 μmol litre^{-1}). The highest cytotoxic effect in MCF-7 cells (IC_{50} = 0.2 μmol litre^{-1}) was found for 2-(4-chlorophenyl)-8-methoxy-3-nitro-2*H*-chromene (**14r**), which was 36 times more active than the reference. It was shown that nitrochromenes **14g–aa** induce caspase-3-dependent apoptosis of breast cancer cells.

Halogenated chromenes **14** [R^1 = Cl, R^2 = H: R^3 = H, Cl; Ar = 4-YC_6H_4 (Y = F, Cl, I)] at concentrations of 1.2–2.4 μmol litre^{-1} inhibit flavodoxin produced by the bacterium *Helicobacter pylori* and can be used to treat gastric ulcer.[103]

Table 10. *In vitro* antibacterial activity of racemates and *R*-enantiomers of chromenes **21a–t**.[43]

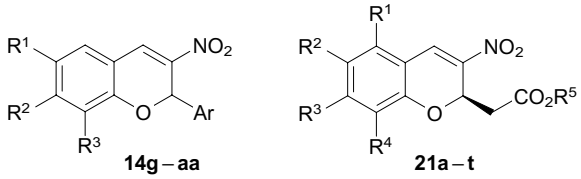
Compound	R^1	R^2	R^3	R^4	R^5	MBC /μg ml^{-1}				
						S. aureus	*B. cereus*	*B. subtilis*	*S. epidermidis*	*Salmonella*
rac-**21a**	H	H	H	H	Et	128	128	128	128	128
(*R*)-**21a**	H	H	H	H	Et	32	32	64	32	64
rac -**21b**	H	Me	H	H	Et	32	16	32	32	64
(*R*)-**21b**	H	Me	H	H	Et	> 128	64	128	> 128	128
rac -**21c**	H	MeO	H	H	Et	128	64	64	64	128
(*R*)-**21c**	H	MeO	H	H	Et	64	4	16	32	16
rac -**21d**	H	H	MeO	H	Et	> 128	128	> 128	> 128	128
(*R*)-**21d**	H	H	MeO	H	Et	128	16	16	128	32
rac -**21e**	H	H	H	All	Et	64	16	32	32	128
(*R*)-**21e**	H	H	H	All	Et	128	64	128	128	128
rac -**21f**	H	H	Et_2N	H	Et	> 128	128	> 128	> 128	128
(*R*)-**21f**	H	H	Et_2N	H	Et	16	8	8	8	64
rac -**21g**	H	Bu^t	H	Bu^t	Et	> 128	> 128	> 128	> 128	128
(*R*)-**21g**	H	Bu^t	H	Bu^t	Et	128	128	> 128	> 128	128
rac -**21h**	H	F	H	H	Et	64	32 [a]	32	16 [a]	128
(*R*)-**21h**	H	F	H	H	Et	128	64	128	128	128
rac -**21i**	H	Cl	H	H	Et	16 [a]	4	16 [a]	16 [a]	16
(*R*)-**21i**	H	Cl	H	H	Et	32	16 [a]	32 [a]	16 [a]	32
rac -**21j**	H	Br	H	H	Et	32	16 [a]	16 [a]	16 [a]	64
(*R*)-**21j**	H	Br	H	H	Et	64	32	32	> 128	128
rac -**21k**	H	H	H	F	Et	128	64 [a]	64	32 [a]	128
(*R*)-**21k**	H	H	H	F	Et	64 [a]	8	16	32	64
rac -**21l**	H	H	H	Br	Et	64	16	32	16 [a]	128
(*R*)-**21l**	H	H	H	Br	Et	32	8 [a]	32 [a]	16 [a]	64
rac -**21m**	H	Cl	H	H	Et	64	16 [a]	32	16 [a]	128
(*R*)-**21m**	H	Cl	H	H	Et	64	64 [a]	64 [a]	32 [a]	128
rac -**21n**	Cl	H	H	H	Et	64	32 [a]	64	32	128
(*R*)-**21n**	Cl	H	H	H	Et	64	8 [a]	64	32 [a]	64
rac -**21o**	H	Cl	H	Cl	Et	32 [a]	8 [a]	8	16 [a]	16
(*R*)-**21o**	H	Cl	H	Cl	Et	16[a]	8 [a]	8 [a]	16	16
rac -**21p**	H	Br	H	Br	Et	8	8 [a]	8 [a]	16 [a]	32
(*R*)-**21p**	H	Br	H	Br	Et	4 [a]	4 [a]	4 [a]	8 [a]	32
rac-**21q**	See [b]		H	H	Et	128	8	32	128	128
(*R*)-**21q**	See [b]		H	H	Et	32	8	32	16	32
rac-**21r**	H	H	H	H	Me	64	32	64	64	128
(*R*)-**21r**	H	H	H	H	Me	32	16	32	64	64
rac-**21s**	H	Me	H	H	Me	64	32	64	64	128
(*R*)-**21s**	H	Me	H	H	Me	32	32	64	32	64
rac-**21t**	H	Br	H	H	Me	32	16	32	32 [a]	128
(*R*)-**21t**	H	Br	H	H	Me	32	16 [a]	16 [a]	16	64

Note. For all compounds, the minimum bactericidal concentration (MBC) towards *E. coli* exceeds 128 μg ml^{-1}. [a] The minimal inhibitory concentration (MIC) /μg ml^{-1} is given; [b] $R^1–R^2$ is benzo.

3-Nitro-2-trifluoromethyl-2*H*-chromene (TIM-38) and 6-bromo-3-nitro-2-trifluoromethyl-2*H*-chromene (**68a**) proved themselves as selective structural human $P2Y_6$ receptor antagonist ($IC_{50} = 4.3$ and 0.9 μmol litre^{-1}, respectively) and are promising anti-inflammatory agents.[11]

Li *et al.*[43] performed a comparative study of the antibacterial activity of *R*-enantiomers of 2-carboxymethyl-3-nitrochromene esters **21a**–**t** and their racemates towards four Gram-positive bacterial strains (*Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus epidermidis*) and two Gram-negative strains (*Salmonella* and *Escherichia coli*) (Table 10).

Structures 14, 21



The results of bioassays demonstrated that all 3-nitrochromene derivatives **21a**–**t** have higher activity towards Gram-positive than towards Gram-negative bacteria. Chromene isomer (*R*)-**21g** containing bulky *tert*-butyl groups in positions 6 and 8, as well as its racemate, virtually do not inhibit any sort of bacteria due to unfavourable steric repulsion, which arises between the target and the chromene molecule. Generally, except for several monosubstituted chromenes **21b**,**e**,**h**–**j**,**m**, the antibacterial activity was higher for *R*-enantiomers than for the corresponding racemates. The highest activity was found for *R*-enantiomers with two electron-withdrawing substituents in the benzene ring. Most of the chromenes proved to be inefficient against Gram-positive bacteria. Only four chromenes [(*R*)-**21c**, *rac*-**21i**, (*R*)-**21o** and *rac*-**21o**] exhibited a noticeable inhibitory activity against the *Salmonella* strain when used at 16 μg ml^{-1} concentration.

5.2. 3-Nitro-4*H*-chromenes

4*H*-Chromenes **26d**,**f** are cytotoxic to HeLa cells (IC_{50} = 115.04 and 18.96 mmol litre^{-1}, respectively) and Hep2 larynx epidermoid carcinoma cells (IC_{50} = 86.94 and 25.08 μmol litre^{-1}, respectively). By means of molecular docking, it was found that the cytotoxic effect of nitrochromenes **26d**,**f** is caused by strong binding to anti-apoptotic proteins Bcl-2, Bcl-w and Bcl-xL.[46]

Antitumour activity against HeLa ($IC_{50} = 9 \pm 0.73$ μmol litre^{-1}), Hep2 (0.75 ± 0.06 μmol litre^{-1}) and A549 ($IC_{50} = 4 \pm 0.35$ μmol litre^{-1}) cells was also found for *N*,6-dimethyl-3-nitro-4-(4-piperidinophenyl)-4*H*-chromen-2-amine (**140a**). In this case, the protein tubulin, which is hydrogen-bonded to ligand **140a**, serves as the target for **140**.[94] An additional tubulin coordination to chromene **140a** is provided by the dispersion interactions between hydrophobic moieties of both molecules.

Compounds **141** and **142**, which are conjugates of 4-aryl-substituted 3-nitro-4*H*-chromenes with chloroquinoline, showed a noticeable antimalarial activity towards chloroquine-sensitive (3D7) and chloroquine-resistant (K1) *Plasmodium falciparum* (Table 11).[95]

Chromenes **146** used at concentration of 200 μg ml^{-1} possess bactericidal action on the Gram-negative bacteria

Structures 26, 140

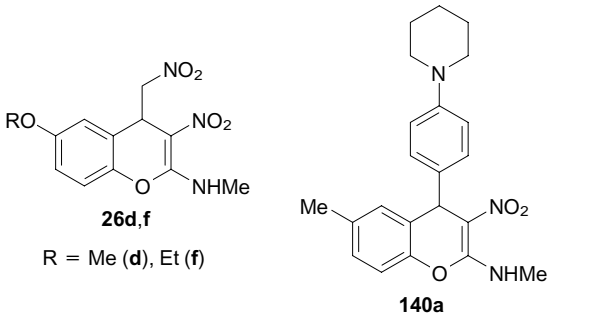
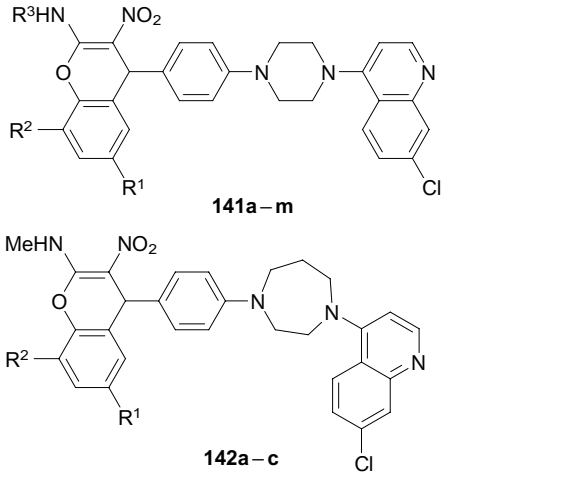


Table 11. *In vitro* antimalarial activity of compounds **141a**–**m** and **142a**–**c**.[95]

Compound	R^1	R^2	R^3	IC_{50} /μmol litre^{-1}	
				3D7	K1
141a	H	H	Me	1.11	3.38
141b	Cl	H	Me	1.37	2.99
141c	Br	H	Me	1.88	1.75
141d	O_2N	H	Me	0.62	1.78
141e	MeO	H	Me	2.48	4.25
141f	H	EtO	Me	2.93	2.95
141g	H	MeO	Me	2.47	2.40
141h	Cl	Cl	Me	3.92	1.45
141i	Br	Br	Me	> 5.0	2.93
141j	Me	Cl	Me	2.34	0.87
141k	H	H	Bn	> 5.0	> 5.0
141l	H	H	$Ph(CH_2)_2$	3.31	1.74
141m	H	H	Bu^n	3.09	3.57
142a	H	H		> 5.0	> 5.0
142b	Cl	H		0.29	0.496
142c	Br	H		2.24	1.27
Chloroquine				0.005	0.254

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E. coli, Gram-positive bacteria *B. subtilis*, methicillin-resistant and methicillin-sensitive *S. aureus*, as well as fungicidal action on the mold fungi *Aspergillus niger* and the yeast fungi *Candida albicans*.[97] As the concentration of compounds was decreased to 6.25 μg ml^{-1}, high antibacterial

and antifungal activities were retained for nitrochromenes **146** containing two halogen atoms in positions 6 and 8.

6. Conclusion

Analysis of the published data shows that the chemistry of 3-nitro-2*H*-chromenes is being actively developed in all directions. In particular, new synthetic routes to these compounds appear, based on one-pot and environmentally benign technologies using catalytic reactions not requiring solvents. Some of numerous currently known 3-nitro-2*H*-chromenes are not only not inferior, but are even superior to the known medicinal drugs in their antitumour activity. The search is in progress for new biologically active molecules by targeted modification of the basic skeleton of nitrochromene. A considerable progress has also been attained in the studies of reactivity of this heterocyclic system towards nucleophilic reagents and 1,3-dipoles; this resulted in the synthesis of a broad range of Δ^3-annulated chromenes structurally similar to known natural and synthetic physiologically active compounds. The reactions of 2-substituted 3-nitro-2*H*-chromenes with enamines were studied in detail; factors controlling the structure and stereochemistry of the reaction products were established; and diastereoselective methods for the synthesis of 2,3,4-trisubstituted chromanes containing one or two carbonyl groups in the side chain in position 4 were developed. In the series of *trans*,*trans*- and *cis*,*cis*-2,3,4-trisubstituted chromanes with an equatorial position of the substituent at the C(4) atom, atropoisomerism caused by hindered rotation about the $C(sp^3)-C(sp^2)$ bond was detected and investigated.

The studies concerning the new 3-nitro-4*H*-chromene system mainly addressed the synthesis and properties of 2-amino-4-sulfanyl derivatives, which is largely caused by ready accessibility of the initial nitroketene N,S-acetals. Meanwhile, other representatives of this class, for example, 2-unsubstituted and 2-alkyl(aryl)-3-nitro-4*H*-chromenes are still unknown. The facile and convenient method for the synthesis of 4*H*-chromenes from easily accessible β-nitroenamines developed by chemists from Samara [53] gives hope that the range of 3-nitro-4*H*-chromenes will be extended and new publications dealing with their properties will appear. The broad synthetic potential of the most studied 3-nitro-4-sulfanyl-4*H*-chromenes is far from being exhausted. Indeed, nucleophilic substitution of the 4-alkylsulfanyl group has yet been performed for a narrow range of C-nucleophiles (phenols, aromatic amines, enols, heterocycles). No data on reactions of these compounds with N- and O-nucleophiles or with enamines as C-nucleophiles are available from the literature. In our opinion, the search for reagents and methods to induce the ring transformation of the 2-aminopyran system involving C(4) and C(2) atoms is also a promising trend. The discovery of biological activity in many derivatives of 3-nitro-4*H*-chromenes attests to good prospects of further studies of this class of heterocyclic compounds.

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