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KNOEVENAGEL–HETERO-DIELS–ALDER TANDEM AND DOMINO REACTIONS AS A PLATFORM FOR DESIGNING BIOLOGICALLY RELEVANT MOLECULES IN ORGANIC AND MEDICINAL CHEMISTRY : A REVIEW

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This article presents a critical analysis of the development of Knoevenagel–hetero-Diels–Alder domino and tandem reactions (KHDA) as an integrated synthetic strategy that provides a high level of atom economy and structural complexity in modern organic synthesis and medicinal chemistry. Particular attention is paid to the application of this methodology for the synthesis of thiopyrano[2,3-d]thiazole systems – heterocyclic frameworks with proven or predicted biological activity. The evolution of reaction conditions, the use of new generation catalytic systems, the possibilities of microwave activation, as well as the prospects for integrating the studied reactions into multicomponent, tandem and domino sequences are considered. The possibilities of using KHDA in the design of biologically active molecules are considered in the context of searching for new potential pharmaceutical agents with antiepileptic, antitumor and antimicrobial activity.

Keywords: domino reactions, hetero-Diels–Alder, Knoevenagel condensation, thiopyranothiazoles, heterocyclic compounds, pharmacological activity.

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Introduction

Domino, cascade, or tandem reactions represent a powerful toolkit of organic synthesis, enabling the construction of complex molecular architectures through the sequential formation of multiple chemical bonds within a single synthetic operation. In his seminal review *Domino Reactions in Organic Synthesis*, published in *Chemical Reviews* in 1996, L.F. Tietze defined domino reactions as a key synthetic methodology, offering significant advantages such as high efficiency, atom economy, and reduced by-product formation.

The importance of domino reactions in pharmacy is due to their ability to efficiently form biologically relevant heterocyclic rings, key moieties of active pharmaceutical ingredients (APIs). Such strategies reduce the number of synthesis steps, solvent consumption, and environmental impact. Domino reactions are defined by their ability to undergo two or more sequential transformations, in which each subsequent reaction occurs as a direct consequence of the functionality formed in the previous step. Among the most studied are those that combine polar and pericyclic steps, in particular the Knoevenagel condensation followed by a hetero-Diels-Alder (HDA) cycloaddition, which form the core of the Knoevenagel-HDA domino sequence.

The Knoevenagel condensation, which involves a base-catalyzed reaction between carbonyl compounds and active methylene moieties, leads to the formation

of highly reactive alkenes. These intermediates participate in Diels-Alder or HDA reactions, opening access to polyfunctional, stereochemically complex products. The combination of these two transformations, known as the Domino Knoevenagel *hetero*-Diels-Alder (DKHDA) reaction, has gained recognition for its ability to rapidly, stereoselectively construct a variety of heterocycles under mild and often environmentally benign conditions. Since Tietze's initial work, this method has become a valuable tool in medicinal chemistry, increasingly being used for the generation of libraries of active molecules, green chemistry approaches, and the total synthesis of active pharmaceutical ingredients.

This review traces the evolution of the Knoevenagel–*hetero*-Diels–Alder (KHDA) reaction from its first conceptual formulations to its current status as a versatile, robust, and biologically relevant synthetic methodology. Particular attention is paid to the progress achieved over the past twenty years: improvement of reaction conditions, broadening of the starting substrate spectrum, involvement of new-generation catalysts, and integration with multicomponent and domino processes. Emphasis is placed on its growing role in the design of pharmacologically active compounds, improving atom economy, selectivity, and scalability for industrial synthesis.

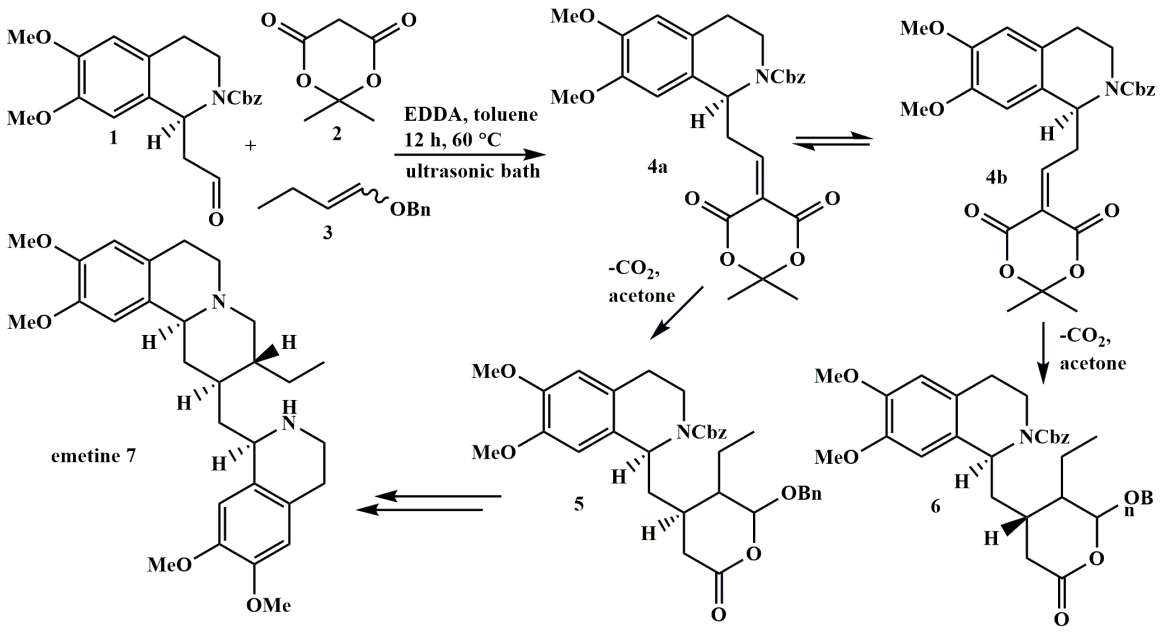
Results and discussion

Tietze and Rackelmann [1] made an important contribution to the development of cascade chemistry by introducing the enantioselective domino Knoevenagel-hetero-Diels-Alder reaction for the synthesis of epimethine analogues (Scheme 1) [1].

The strategy described in their work involved a multicomponent reaction between racemic aldehydes **1**, Meldrum's acid **2** and enol esters **3**, leading to highly functionalized intermediates **4a**, **4b**. Subsequent solvolysis, amine condensation, and asymmetric hydrogenation using a chiral catalyst provided enantiomerically pure tetrahydroisoquinolines **5** and **6**. This approach demonstrated important principles of economy of synthetic steps, diastereocontrol, and flexibility in varying functional groups. The synthesized structures exhibited cytotoxic and antiparasitic activities, making this method promising for medicinal chemistry and the development of antimalarial and anticancer drugs.

Sabitha et al. developed a highly diastereoselective DKHDA reaction for the synthesis of dihydropyrans using 1,3-dicarbonyl compounds **8** and sugar aldehydes with a dienophilic moiety **9** as starting materials (Scheme 2) [2]. The reaction was catalyzed by ethylenediaminediacetate (EDDA) in acetonitrile at moderate temperature.

After Knoevenagel condensation, the resulting intermediates **10** underwent intramolecular heterocyclic addition via a hetero-Diels-Alder mechanism. The resulting scaffolds were characterized by high cis-stereochemistry due to the chirality of the carbohydrate precursors. The synthesized dihydropyrans **11** demonstrate structural similarity to polyhydroxylated

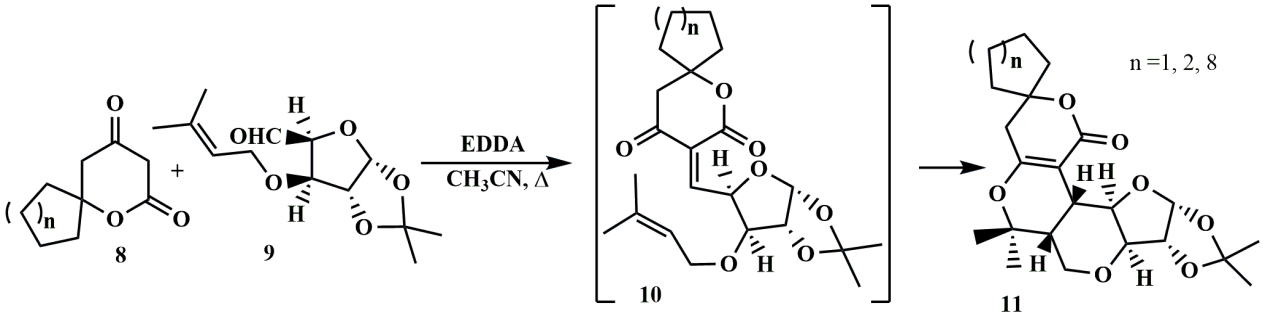


Scheme 1

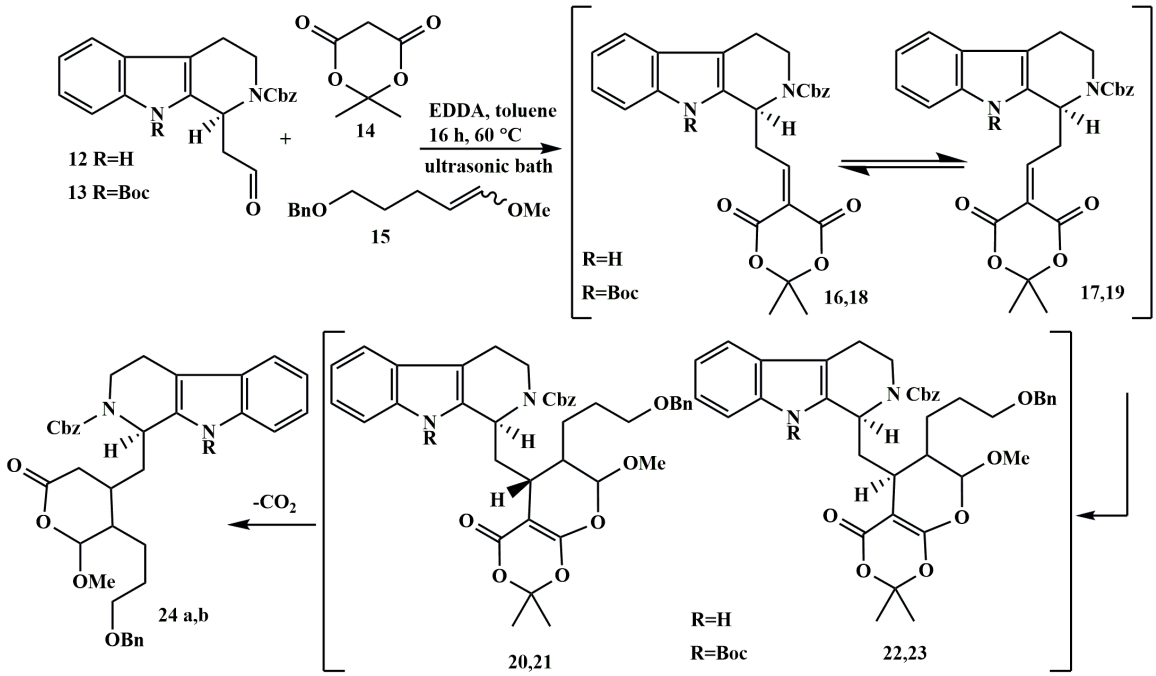
natural products with antimicrobial activity, which allows us to consider this approach as promising for the creation of glycomimetics and nucleoside analogues [2].

Klapa, in his doctoral dissertation [3], demonstrated the utility of the Knoevenagel-hetero-Diels-Alder cascade in the total synthesis of complex natural products, including the alkaloids yohimbine and camptothecin. The core of this approach involved Knoevenagel condensations between formyl-substituted arenes and 1,3-dicarbonyl compounds, generating electron-rich alkenes as precursors for intramolecular heterocyclizations. This method enabled the stereoselective construction of oxygen-containing tricyclic systems **24a,b** (Scheme 3). Notably, the strategy avoided protection/deprotection steps, simplifying the synthetic route and improving overall efficiency. The resulting heterocycles exhibited strong structural similarity to known bioactive agents with antitumor, anticonvulsant, and neurotropic properties, highlighting the versatility of the KHDA reaction for synthesizing pharmacophore-rich polycyclic frameworks in medicinal chemistry.

Majumdar et al. [4] proposed a strategy for conducting the DKHDA reaction in an aqueous medium to construct novel indole-fused pentacyclic heterocycles **28**, **29**. The reaction utilized O-allyl salicylaldehydes (26) and 1-methylindoline-2-thione (25) as starting materials and proceeded via a Knoevenagel–hetero-Diels–Alder sequence in the presence of acetic acid and triethylamine as a catalytic system (Scheme 4) [4].



Scheme 2



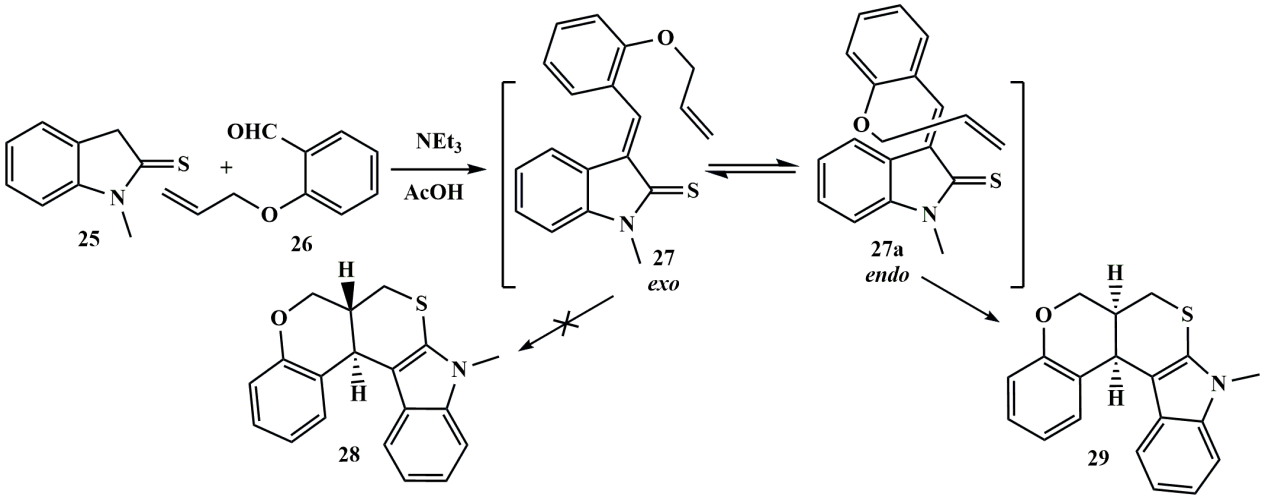
Scheme 3

Kiamer and Moghaddam [5] proposed a new variant of the DKHDA reaction using ZnO nanoparticles as a heterogeneous catalyst for the synthesis of thiopyranochromene derivatives. The reaction between O-propargylsalicylaldehydes **31a–d** and 1-methylindoline-2-thione **30a–c** in the presence of ZnO in acetonitrile provided high yields of polycyclic structures 33a-j (Scheme 5) [5]. The obtained products contain fragments with sulfur and oxygen heteroatoms, inherent in molecules with antioxidant, anti-inflammatory and cytotoxic activity. The ZnO catalyst was found to be stable and reusable, demonstrating its sustainable nature and convenience for scaling up the process. The developed method is characterized by compliance with the principles of green chemistry, which makes it attractive for practical application in medicinal chemistry and pharmaceutical synthesis.

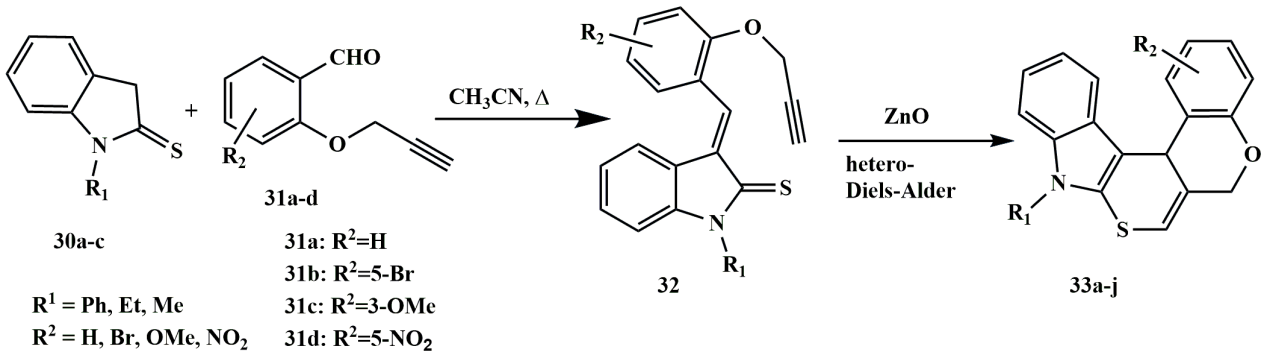
Moghaddam et al. developed a DKHDA reaction for the synthesis of pentacyclic thiopyranocoumarins using 4-hydroxy-dithiocoumarin **35** and acrylic-containing salicylaldehydes **34a-h** (Scheme 6). This approach fully complies with the principles of "green chemistry", due to the fact that it is carried out in an aqueous medium without the use of solvents or catalysts [6]. The resulting heterocyclic derivatives **36a–h** and **37a–h** is characterized by structural features that correlate with potential antibacterial, anticoagulant and antitumor activities, which opens prospects for their further pharmacological study.

The high regioselectivity, mild reaction conditions, functional tolerance, and minimal need for purification demonstrate the practicality and scalability of the method. This variant of the DKGDA reaction is of significant value for the generation of combinatorial libraries of new drugs.

Majumdar et al. [7] improved previous approaches to DKHDA reactions by introducing a variant involving terminal alkynes in an aqueous medium without catalysts. The starting components were O-propargyl-salicylaldehydes **38a–f** and 1-methylindoline-2-thione **25**, which under the reaction conditions provided highly efficient formation



Scheme 4



Scheme 5

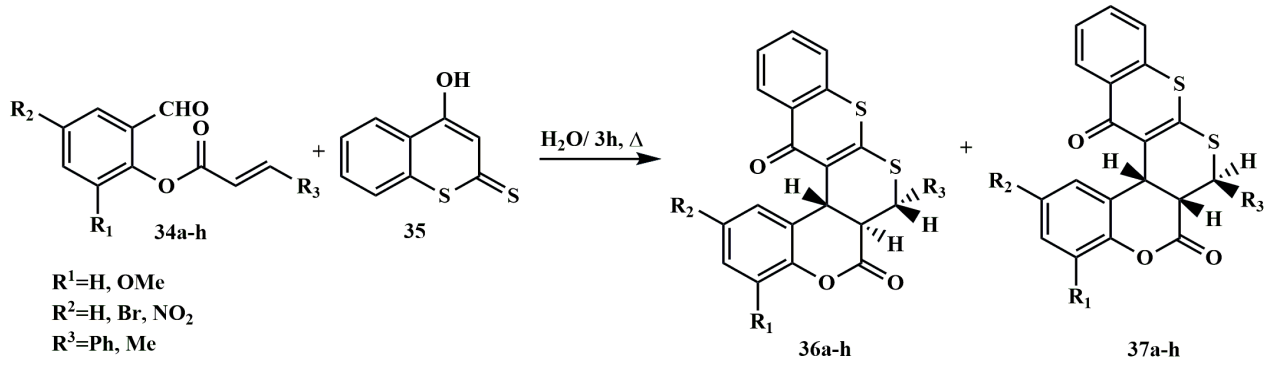
of condensed thiopyrano[2,3-d]indole systems **41c–f** (Scheme 7). The method showed high regioselectivity, good yields, and complete absence of the need for organic solvents or metals.

The integration of alkynes into the logic of domino reactions in water extends the chemistry of DKHDA and demonstrates its potential in creating environmentally sustainable synthetic routes to bioactive polyheterocycles.

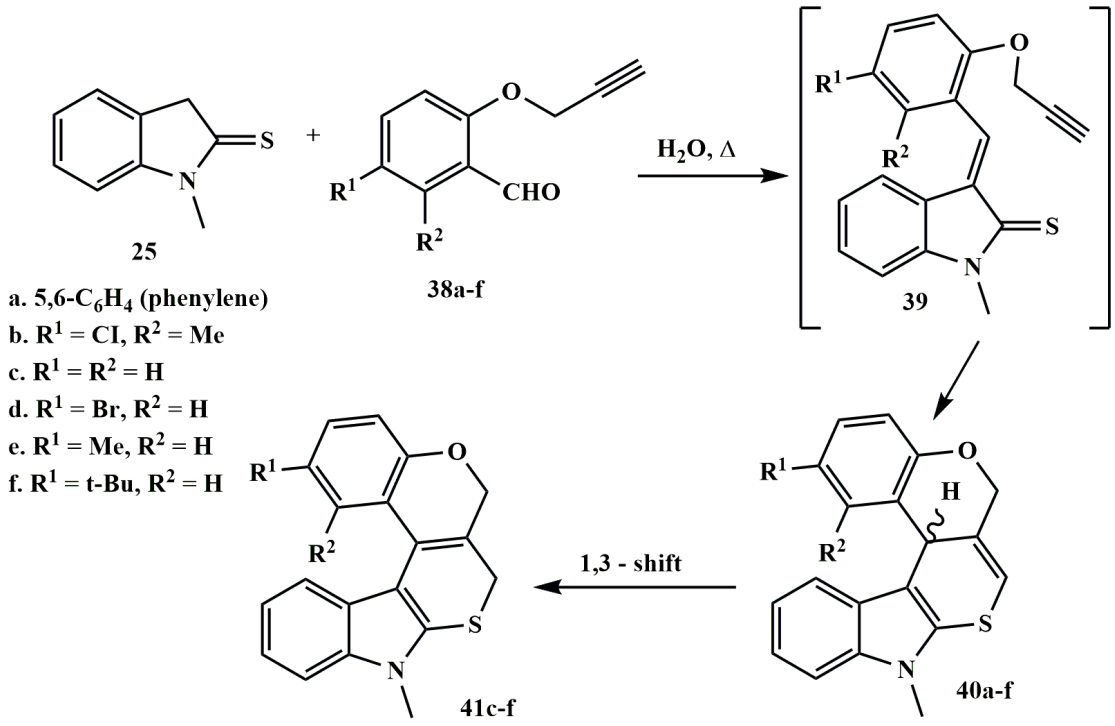
In 2011, Tietze et al. [8] proposed a three-component approach to the DKHDA reaction for the synthesis of aminosugar precursors, important moieties in glycosylated natural products such as macrolides and anthracyclines. They used nitroacetone **42**, formaldehyde **43**, and ethoxyvinyl acetate **44** in a cascade process (Scheme 8). The products formed had the structure of 2-acetoxyaminosugars **45** and **46** in high yield and good diastereoselectivity.

The method features the minimization of synthetic steps and the possibility of incorporating polar functional groups, which provides efficient access to polyoxygenated heterocycles. This approach demonstrates how domino reactions can be adapted to obtain complex biomolecules with potential antibiotic and antitumor activity.

In the following works, the possibility of integrating DKHDA with other chemical processes to achieve even higher yields in the synthesis of heterocycles was discussed. Particular attention was paid to the efficiency of these reactions in reducing



Scheme 6



Scheme 7

the number of synthetic steps and increasing selectivity, which makes them attractive for industrial use.

In the study [9], a new method for the synthesis of octahydrochromeno[4,3-a]xanthen-1(2H)-ones **49** using 10% DL-proline as a catalyst in ethanol via the DKHDA reaction between alkene-containing chromene-3-carbaldehydes **47** and cyclic 1,3-diketones **48** is presented (Scheme 9). This is the first example of a one-step synthesis of pentacyclic chromene derivatives with preliminary evaluation of their cytotoxicity against A549 and B-16 cell lines.

The *hetero*-Diels–Alder reaction is also an effective method for obtaining the tetrahydropyran skeleton of carbohydrates. Several 3-deoxyaminosugars have been synthesized using this method in good yields and with high regioselectivity. In [10], the synthesis of deoxysugars, in particular forosamine **52a–d**, in a three-component reaction using simple and readily available starting materials is described (Scheme 10).

The reaction of nitroacetone **42**, formaldehyde **43**, and alkyl vinyl ethers **50a–d** in dichloromethane (DCM) at 80°C afforded the corresponding racemic dihydropyrans **51a–d** in 23–37% yields. Further transformations of these compounds afforded the racemic deoxysugar forosamine **52a–d** [10].

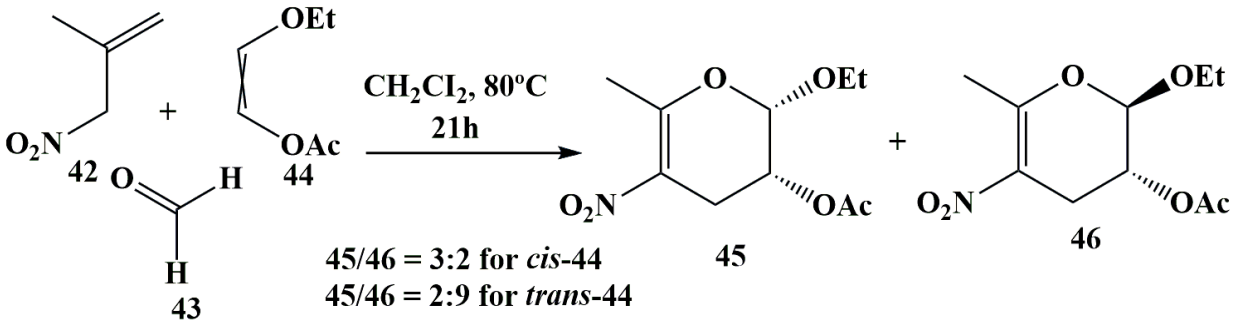
Khoshkholgh et al. [11] synthesized tetracyclic uracil derivatives **55a–d** using terminal alkynes via the Knoevenagel-*hetero*-Diels-Alder domino reaction, using modern trends in «green synthesis» (Scheme 11).

The reactions of N,N-dimethylbarbituric acid **53** with O-propargylated salicylaldehyde derivatives **31a**, **54b–d** were carried out in boiling water in the presence of CuI (40 mol.%) with yields of **55 a–d** [11].

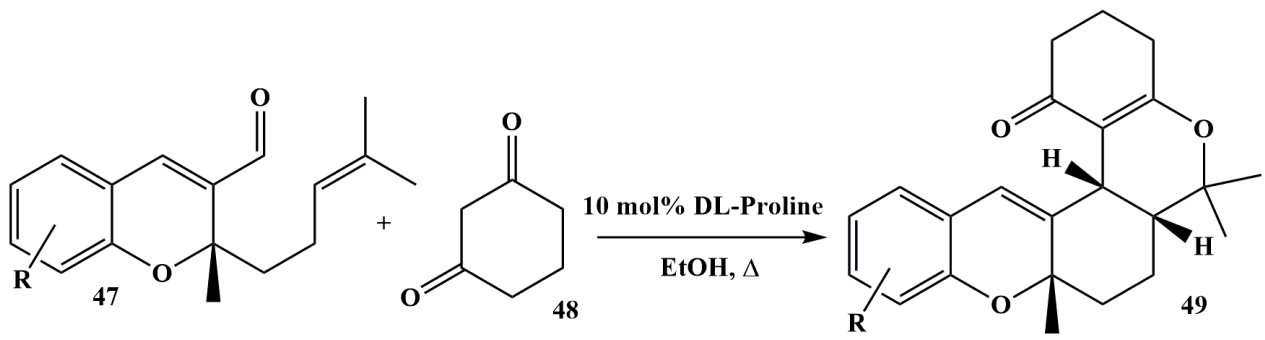
Another example of [1,4]-cycloaddition catalyzed by CuI is the reaction of O-propargylated salicylaldehyde derivatives **31a, 54b,c** with 1,3-indanedione **56** (Scheme 12). In this reaction, diammonium hydrogen phosphate was used as a base and acetonitrile as a solvent to obtain pentacyclic pyran derivatives **57a–c** [12].

In [13], the reaction of aldehyde **58** with 4-thioxo-1,3-thiazolidin-2-one **59** in the presence of EDDA in acetonitrile or acetic acid at room temperature was described to give the trans-condensed product **60** in 79% yield. Similarly, compound **59** reacted with 2-allyloxy-benzaldehyde **26** to give product **61b** in 80% yield at room temperature. In boiling acetic acid, the cycloaddition was not diastereoselective, so both products, **61a** and **61b**, were formed in 13% and 65% yields, respectively (Scheme 13).

By a similar mechanism, aldehydes **62, 63a,b** and **64a,b**, containing an allylic group acting as a dienophile, in the reaction with **59** gave only trans-



Scheme 8



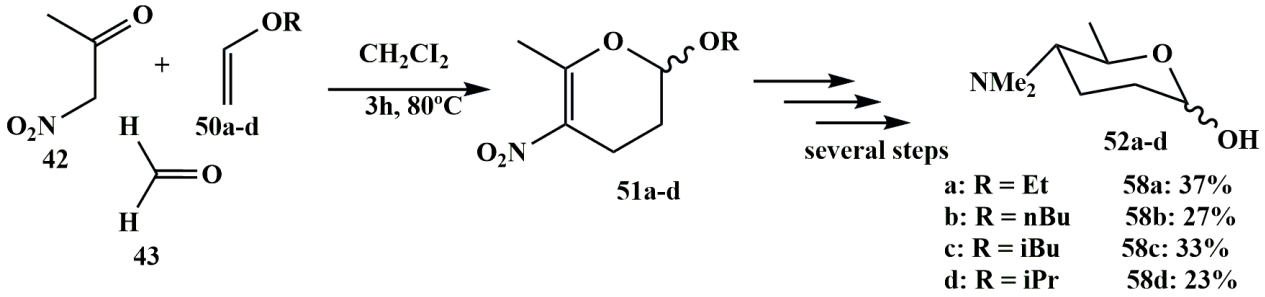
Scheme 9

diastereomers **66**, **67a,b** and **68a,b,** respectively, but aldehydes **65a,b** formed only cis-diastereomers **69a,b**.

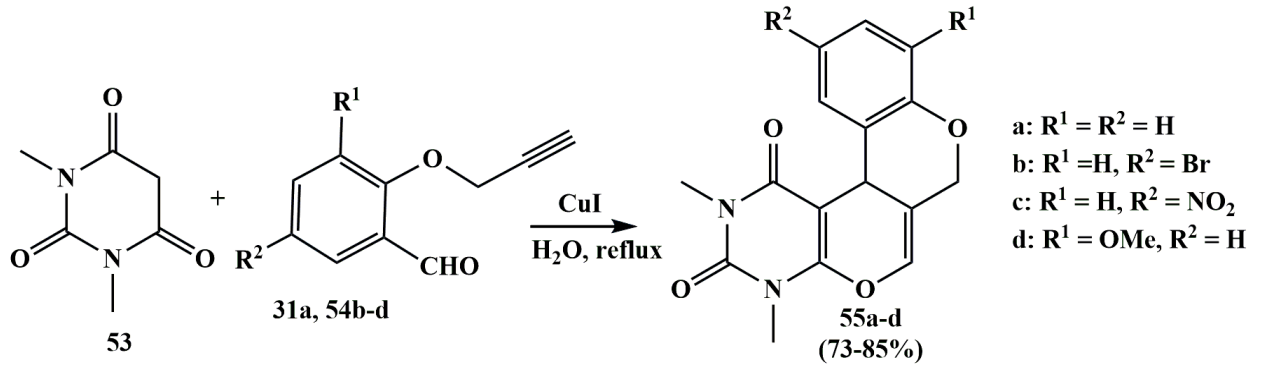
The authors explain this by the possible endo- or exo-orientation of the dienophile in the transition state [13]. In the case of compounds with an allylic group, the exo-transition state prevails. In derivatives **65a,b,** the endo-transition state participates through secondary orbital interactions, leading to the formation of cis-diastereomers **69a,b** (Scheme 14).

The domino Knoevenagel–hetero-Diels–Alder (DKHDA) reaction of O-allylsalicylic aldehyde **26** with 4-hydroxydithiocoumarin **35a** in boiling acetic acid in the presence of triethylamine proceeded smoothly within 4 h to give the thiochromone-fused benzopyranthiopyran derivative **71a** in 85% yield. To compare the solvent effect, the same reaction was performed under identical conditions in boiling water, affording **71a** in 84% yield (Scheme 15). Notably, the DKHDA reaction of 4-hydroxydithiocoumarins **35a,b** with a series of O-allylsalicylic aldehydes **26**, **70b–e,g** could also be carried out in the absence of any catalysts, leading to the corresponding products **71a–g** [14].

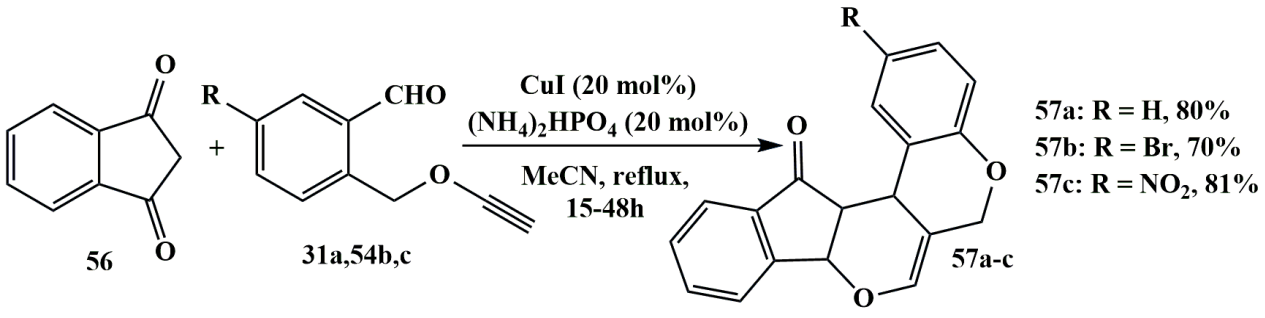
Kiamehr et al. [15] reported the efficient synthesis



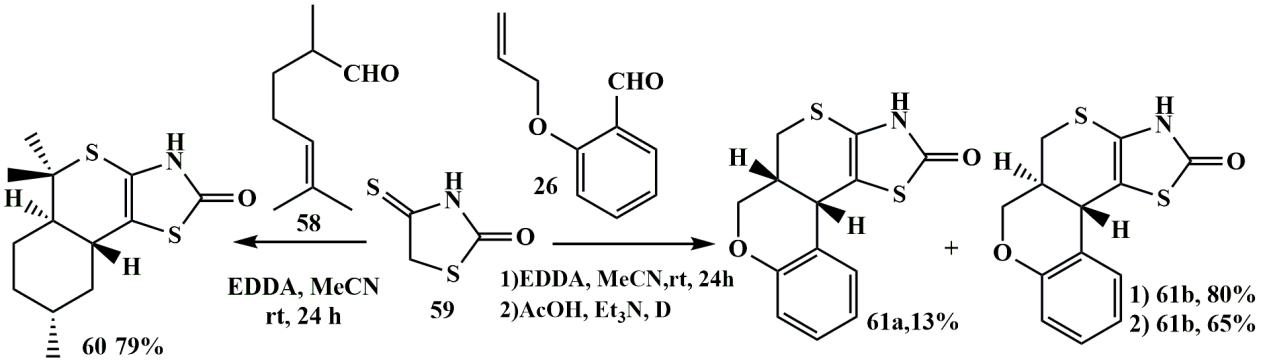
Scheme 10



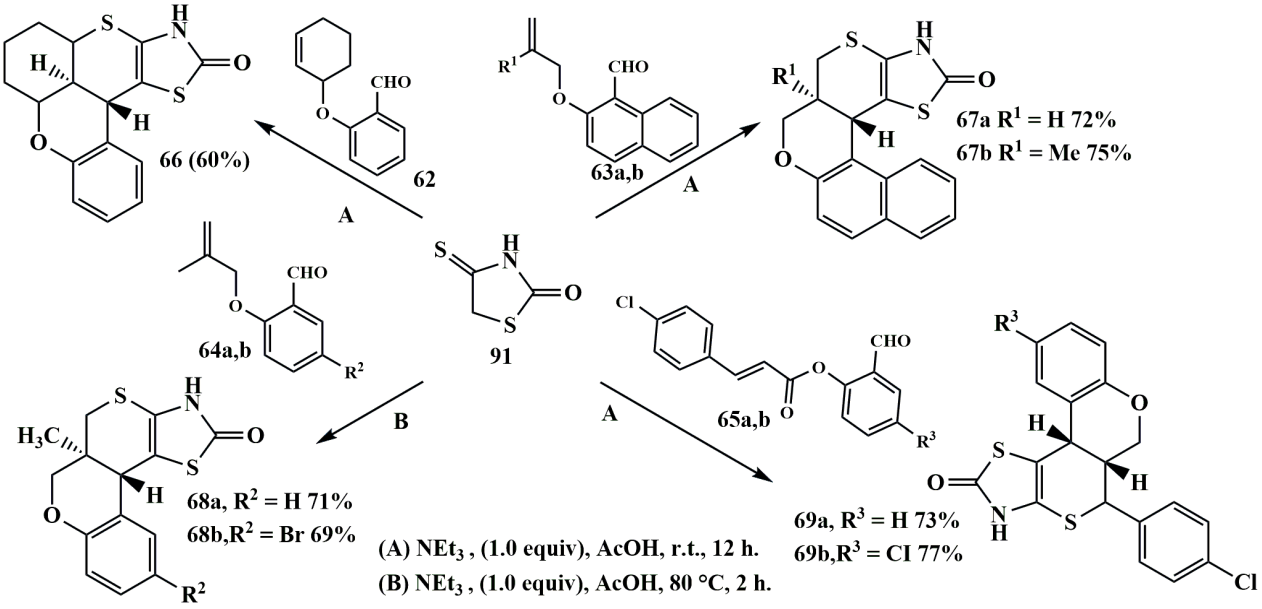
Scheme 11



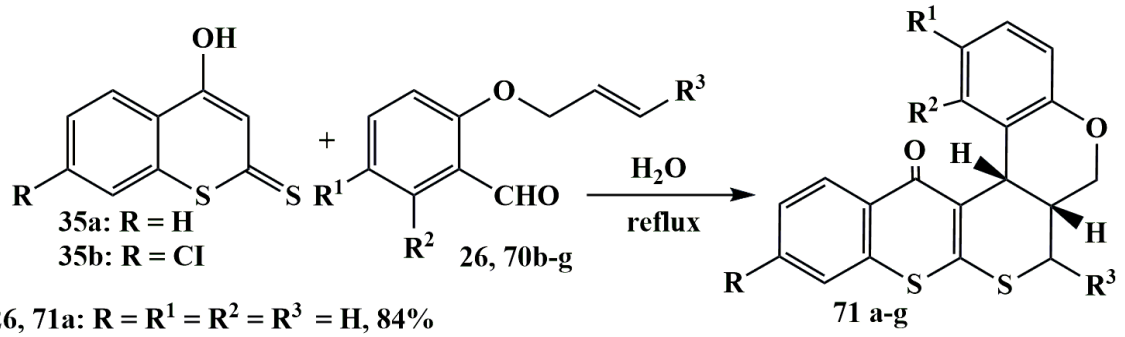
Scheme 12



Scheme 13



Scheme 14



26, 71a: R = R¹ = R² = R³ = H, 84%
70, 71b: R = R² = R³ = H, R¹ = Br, 82%
70, 71c: R = R² = R³ = H, R¹ = Me, 74%
70, 71d: R = R² = R³ = H, R¹ = t-Bu, 73%
70, 71e: R = R³ = H, R¹ = CI, R² = Me, 65%
70, 71f: R = R¹=R² = H, R³ = Me, 70%
70, 71g: R = CI, R¹ = t-Bu, R² = R³ = H, 72%

Scheme 15

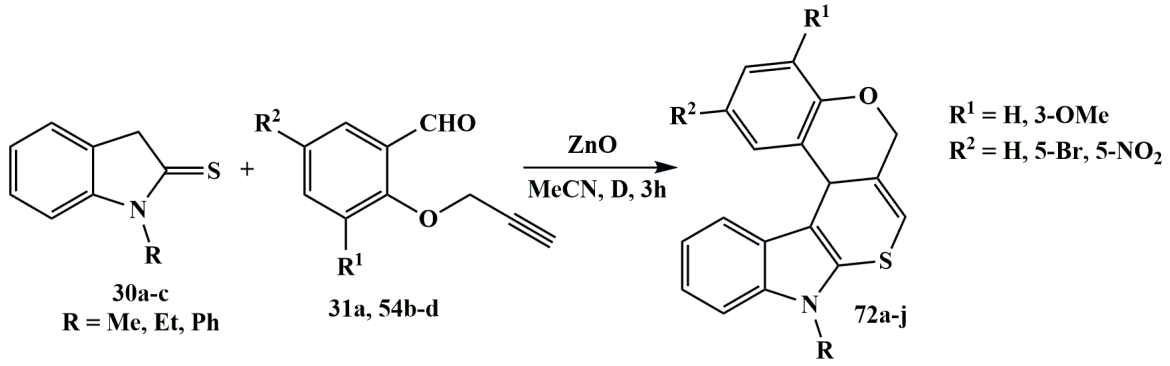
of indole-fused thiopyranobenzopyran derivatives in 85–95% yields via domino-Knovenagel–*hetero*-Diels–Alder reactions of unactivated alkynes **31a, 54b–d** with thioindoles **30a–c** (Scheme 16). They used ZnO as a catalyst to activate the unactivated alkynes and acetonitrile as the reaction medium to afford products **72a–j**.

Raghunathan et al. [16] first used N-alkenylaldehydes in an intramolecular *hetero*-Diels–Alder reaction for the stereoselective synthesis of pyranopyrrole derivatives (Scheme 17).

The reaction between aliphatic aldehydes **73a** and barbituric acid **53** in the presence of EDDA in toluene at reflux gave *trans*- and *cis*-pyranopyrrole products **74a** and **75a** (in a ratio of 65:35) with an overall yield of 62%. Microwave irradiation was also used to improve the yields. When the same reaction was carried out in toluene under microwave irradiation conditions, better results were observed: 74% yield in 2 min at a ratio of 70:30 products (**74a:75a**), respectively. Similar results (**74b–d** and **75b–d**) were also obtained in the reactions of **73b–d** with **81** [16].

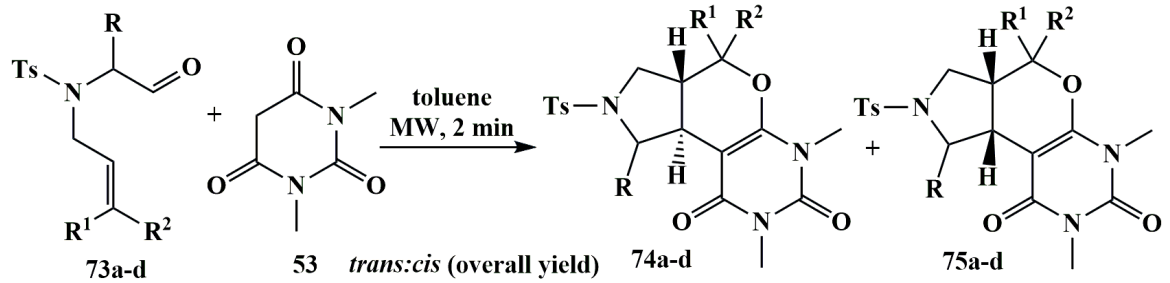
Yadav et al. [17] also reported the single-reactor synthesis of tetrahydroquinoline-fused pyranones **78a–c** via the domino-Knoevenagel-*hetero*-Diels–Alder reaction of N-prenylated aldehydes **77a–c** with Meldrum's acid **76** using L- or D,L-proline as a catalyst. This is a unique example of simultaneous acetone release and decarboxylation in a single reaction cycle in a domino-Knoevenagel-hetero-Diels–Alder reaction (Scheme 18).

In 2019, Kiamer et al. [18] reported a Lewis acid-catalyzed DKHDA reaction to construct tetrahydropyrazolo[4',3':5,6]pyrano[3,4-c]quinolone scaffolds, combining N-acrylated anthranilic aldehydes **80** with pyrazolones **81** (Scheme 19). The reaction proceeded via Knevenagel condensation followed by intramolecular Diels-Alder heterocyclization, which



72a: R = Ph, $R^1 = R^2 = H$, 90%
72b: R = Et, $R^1 = R^2 = H$, 85%
72c: R = Me, $R^1 = R^2 = H$, 88%
72d: R = Ph, $R^1 = H$, $R^2 = Br$, 95%
72e: R = Et, $R^1 = H$, $R^2 = Br$, 90%
72f: R = Me, $R_1 = H$, $R_2 = Br$, 88%
72g: R = Ph, $R^1 = OMe$, $R^2 = H$, 85%
72h: R = Et, $R_1 = OMe$, $R_2 = H$, 85%
72i: R = Ph, $R^1 = H$, $R^2 = NO_2$, 95%
72j: R = Me, $R^1 = H$, $R^2 = NO_2$, 95%

Scheme 16



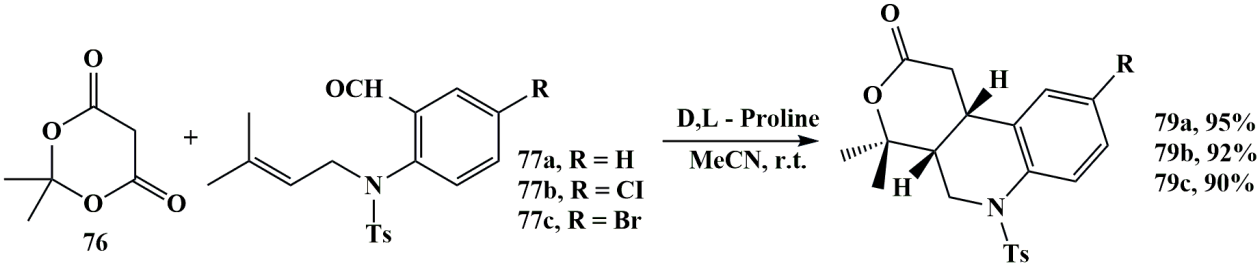
	trans:cis (overall yield)	
74a, R = H, $R^1 = R^2 = Me$	70:30 (74%)	75a, R = H, $R^1 = R^2 = Me$
74b, R = Et, $R^1 = R^2 = Me$	85:15 (80%)	75b, R = Et, $R^1 = R^2 = Me$
74c, R = H, $R^1 = H$, $R^2 = Ph$	70:30 (72%)	75c, R = H, $R^1 = H$, $R^2 = Ph$
74d, R = Et , $R^1 = H$, $R^2 = Ph$	75:25 (75%)	75d, R = Et , $R^1 = H$, $R^2 = Ph$

Scheme 17

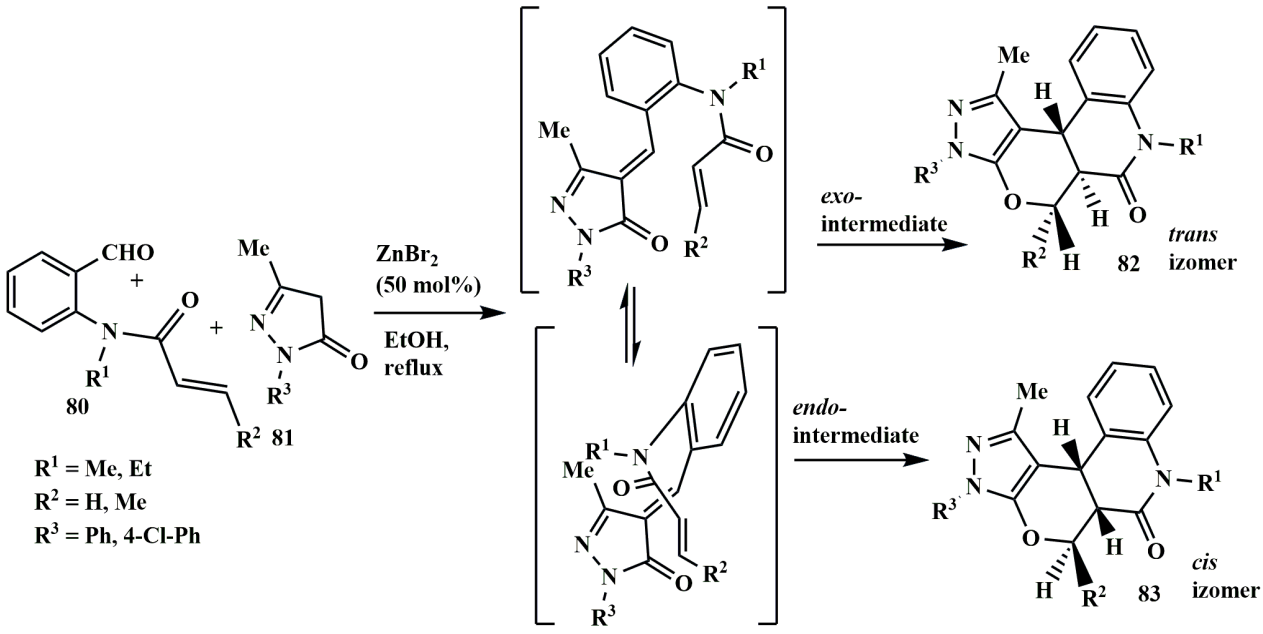
afforded tetracyclic systems with notable cis-diastereoselectivity. The resulting scaffolds **82, 83** have nitrogen- and oxygen-containing rings and resemble pharmacophores found in kinase inhibitors and antiproliferative drugs. The authors demonstrated high regioselectivity and product yields under mild reaction conditions and highlighted the compatibility of their method with various pyrazolone derivatives. Biological evaluations were not performed, but structural parallels with known active substances indicate potential applications in anticancer or anti-inflammatory therapeutics. This work illustrates how DKHDA chemistry provides efficient access to highly functionalized and complex heterocycles.

Wu et al. [19] developed a domino catalyzed Knevenagel-*hetero*-Diels–Alder reaction for the synthesis of chromone derivatives and oxabicyclo[3.3.1]nonene **85**, **86**. Using salicylaldehydes **26, 84** and cyclohexane-1,3-dione **48** as substrates, they employed $FeCl_3 \cdot 6H$, O under mild conditions in ethanol, demonstrating a cost-effective, environmentally friendly catalytic system (Scheme 20). The cascade of transformations provided access to fused oxygen-containing heterocycles in excellent yields, with good functional group compatibility and ease of operation.

The authors in the work [20] proposed a one-step approach to the synthesis of polycyclic quinones via a cascade Knevenagel–*hetero*-Diels–Alder reaction. Compound **90** was obtained as a result of a multicomponent reaction of the benzoquinone embelin **87**, 4-chlorobenzaldehyde **88** and malononitrile **89** (Scheme 21). Starting from hydroxyaryl aldehydes and active methylene compounds, the author achieved the construction of highly conjugated aromatic systems with quinonoid nuclei. The resulting structures of compound series **90** are close analogues of anthracyclines and mitoxantrone, known for DNA



Scheme 18



Scheme 19

intercalation and reactive oxygen species generation. Preliminary studies revealed cytotoxicity against certain cancer cell lines, highlighting their potential as chemotherapeutics.

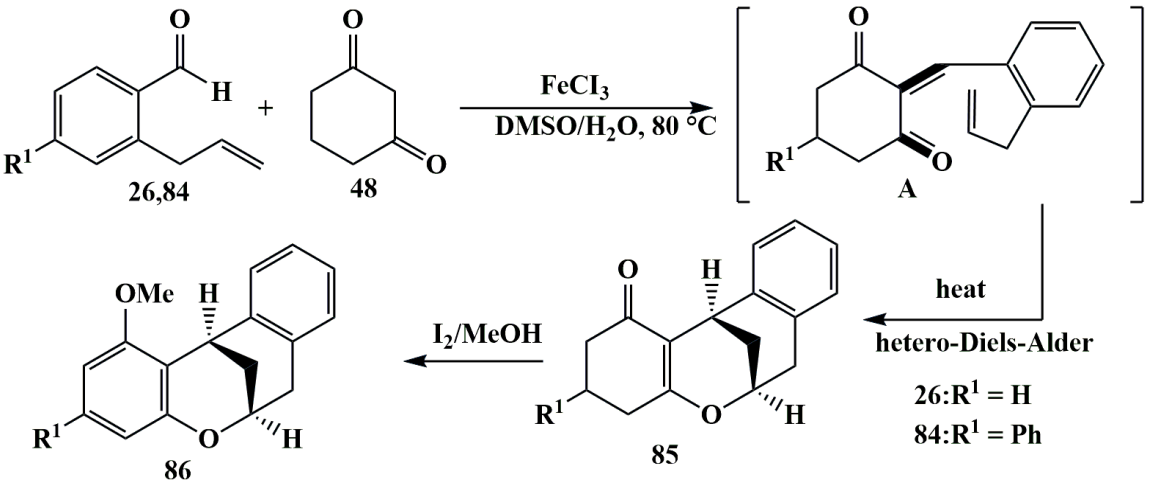
The reaction's simplicity, functional group tolerance, and medical relevance make it valuable for rapid development of DNA-intercalating drug candidates.

In 2020, Kiamehr et al. [21] contributed to the development of the chemistry of domino reactions of the Knovenagel-hetero-Diels–Alder type by proposing a new option for the synthesis of thiopyrano[2,3-b]indole derivatives in aqueous conditions without catalyst. This approach not only provided high yields of the target products with good regio- and stereoselectivity, but also complied with the principles of «green» chemistry. They used the reaction of 1-methylindoline-2-thione **30a,c** with acrylated salicylaldehydes **91a–c** to obtain pentacyclic heterocycles containing sulfur and nitrogen atoms **92a–f, 93a–f** (Scheme 22). The methodology confirms the feasibility of using the DKHDA reaction for the synthesis of complex heterocycles within the framework of the concept of sustainable and environmentally friendly organic synthesis.

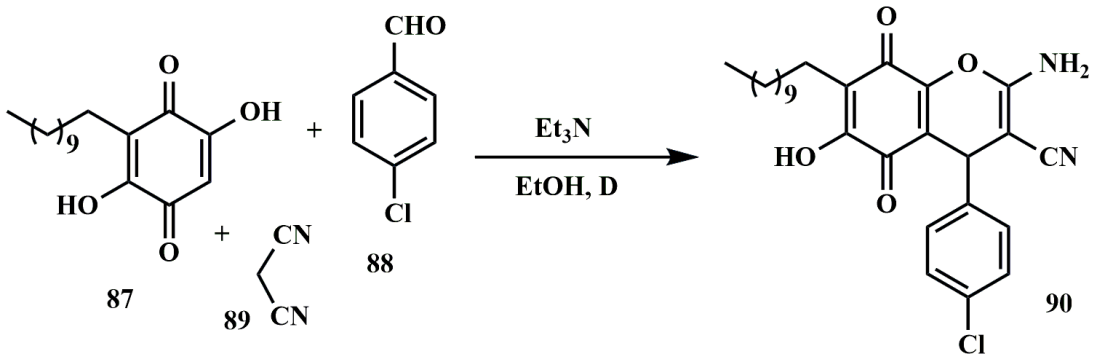
In 2020, Suri et al. [22] reported a $Fe_3O_4{\cdot}SiO_2$ nanocatalyst for the directed three-component synthesis of chromenes under solvent-free conditions. The catalyst was used to react 1,3-cyclohexanedione **48**, salicylaldehyde **94**, and dimedone or active alkenes **95** to afford cyclic scaffolds **96** in preparative yields (Scheme 23). A feature of this approach is that the catalyst could be easily separated using an external magnet and reused for several cycles without significant loss of activity. The high atom economy, the absence of solvents, and the multiple use of the catalyst make the method suitable for sustainable synthesis. Furthermore, the multicomponent design allowed access to structurally diverse compounds, supporting its use in high-throughput medicinal chemistry workflows.

Bakthadoss and Vinayagam developed a solid-state melt reaction (SSMR) for the synthesis of hybrid polycyclic quinone scaffolds based on the DKHDA sequence (Scheme 24) [23].

Using quinone derivatives **97**, aldehydes **98**, **99**,



Scheme 20

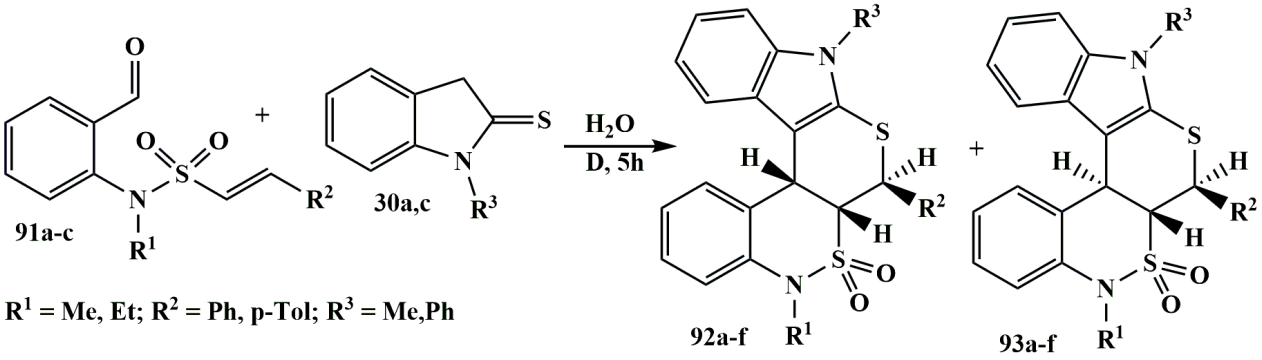


Scheme 21

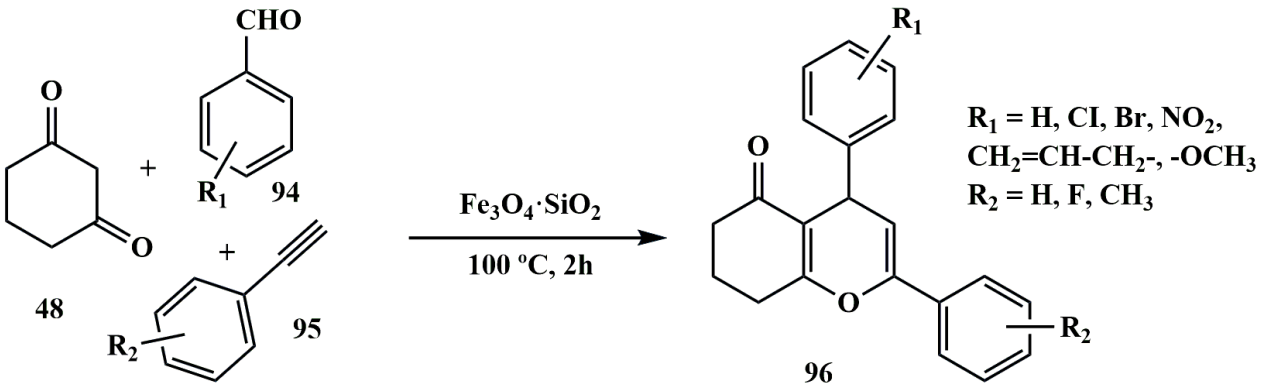
the authors carried out the reaction under thermal conditions without solvents, which ensured the formation of condensed aromatic systems with three adjacent stereocenters **100** and **101** [23]. The method allows avoiding the use of organic solvents, reduce energy consumption and eliminate post-synthetic purifications. The use of a solid-state approach ensures the production of highly crystalline products with good or excellent yields, which makes it promising for large-scale synthesis of medicinal compounds.

Kiraly et al. [24] investigated a polycascade transformation based on the Knevenagel reaction, which initiates successive cyclizations, including *hetero*-Diels–Alder and [2+2] cycloadditions. The methodology allowed the synthesized chromenes and chromanes with a variety of functional groups **104, 105** (Scheme 25).

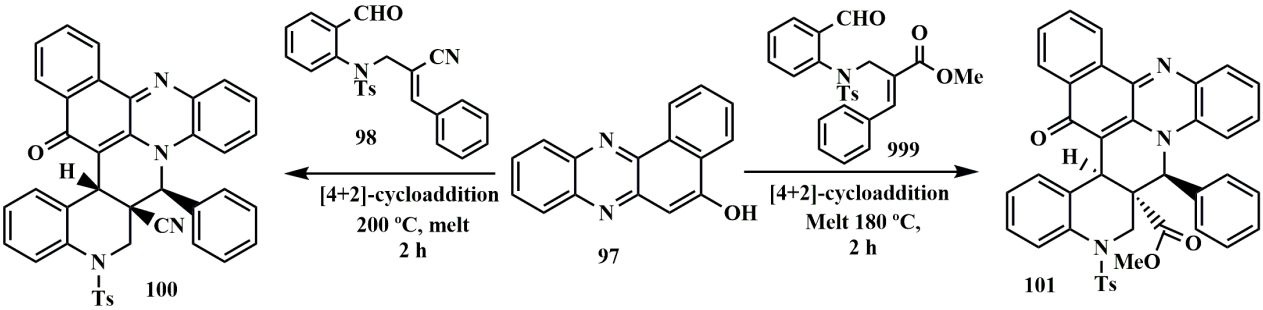
The synthesized compounds showed notable in vitro antiproliferative activity, indicating their promise for oncology research. Variation of substituents and



Scheme 22



Scheme 23



Scheme 24

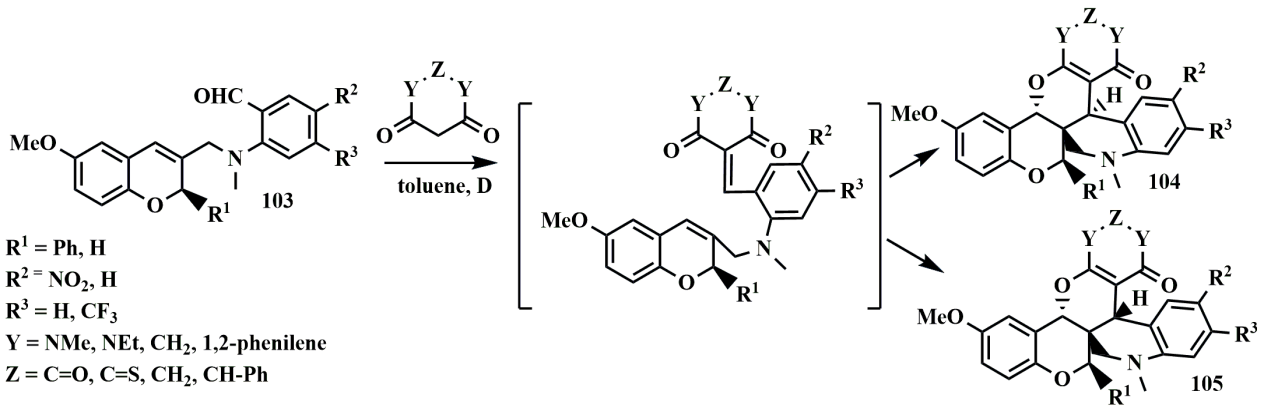
reaction conditions enabled control over cascade transformations, offering new opportunities for designing drug-like compounds.

Kajtar et al. [25] presented Knovenagel domino reactions followed by cyclization of N-arylcinnamylamines with active methylene reagents, which were accompanied by the implementation of several competing cyclization mechanisms: intramolecular hetero-Diels–Alder, stepwise polar [2+2] cycloaddition, styryl or aza-Diels–Alder with subsequent re-aromatization, and [1,3]-hydride shift with 6-endo-cyclization (Scheme 26).

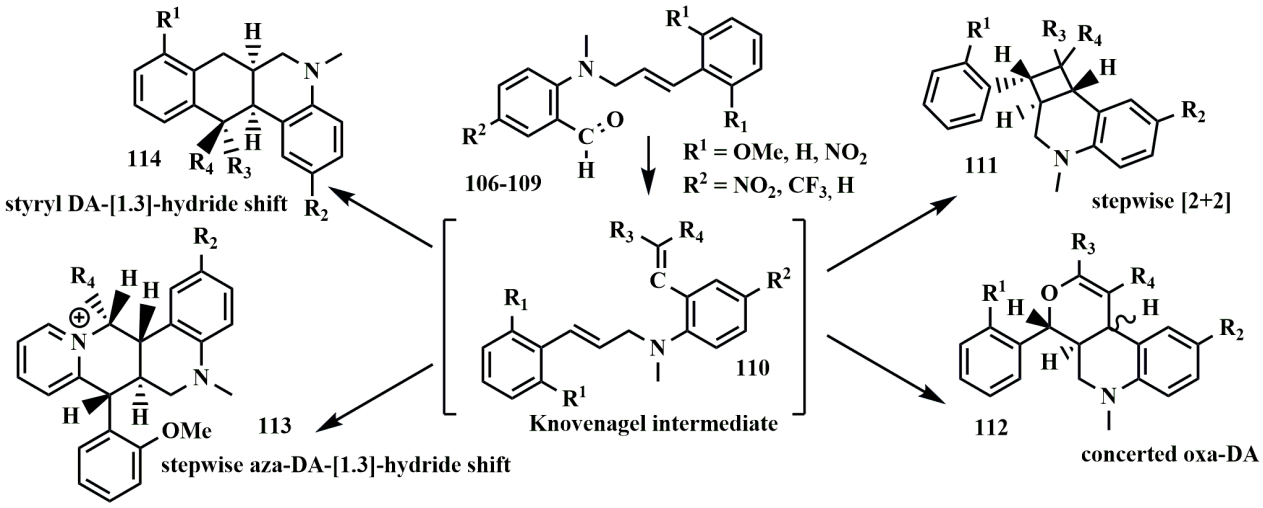
This approach provided access to a wide range of polyheterocyclic scaffolds from single precursors under controlled conditions. Some of the synthesized compounds demonstrated pronounced cytotoxic activity in the low micromolar range against cancer cell lines. This strategy is a powerful tool for generating the molecular diversity needed to identify bioactive lead structures in pharmaceutical screening.

An organocatalytic approach to the DKHDA sequence was reported by Karthik et al. [26] for the synthesis of chromenopyrans **116a–r** (Scheme 27). This methodology, employing an amine-based organocatalyst, enabled the efficient construction of polyoxygenated scaffolds structurally related to flavonoids and coumarins. This work demonstrates the synthetic flexibility of metal-free catalysis in the creation of biologically active chiral molecules and opens up prospects for environmentally-oriented drug design.

Kajtar et al. [27] employed intramolecular hetero-Diels–Alder (IMHDA) and sulfur-Diels–Alder (IMSDA) variants, in combination with the Knoevenagel reaction, to synthesize fused O-, N-, and S-heterocycles **118–119** containing four contiguous stereocenters (Scheme 28). Excellent stereoselectivity and high yields were obtained under carefully optimized reaction conditions. The resulting compounds feature structural motifs resembling the pharmacophore cores of clinically relevant drugs, particularly those with antiviral and cytotoxic activities.



Scheme 25



Scheme 26

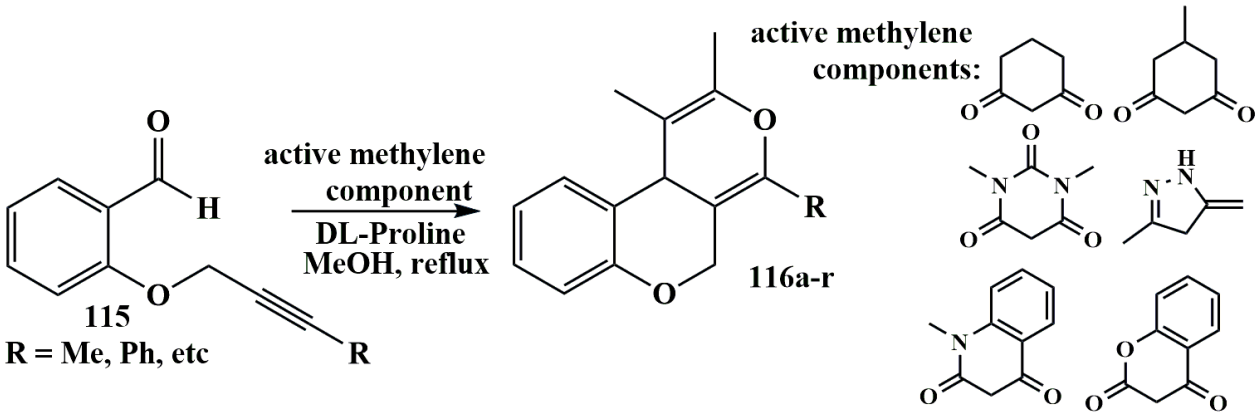
Kryshchyshyn et al. [28] investigated the antitumor potential of a series of 3-substituted thiopyrano[2,3-d]thiazole derivatives obtained via the DKHDA reaction, complementing the synthetic studies presented (Scheme 29) with a systematic analysis of their structure–activity relationships. It was found that compounds **122–132**, and **133** exhibited a pronounced cytostatic effect against multiple tumor cell lines, indicating a broad spectrum of antitumor activity. A clear correlation was observed between biological activity and both the nature and position of substituents in the aromatic ring. Electron-withdrawing and electron-donating groups exerted different effects on bioactivity, with the highest potency observed for derivatives bearing the following substituents: 3-CF_3>3,4-Cl_2>2-OMe>4-COOEt>4-Cl>4-Me, 3-OMe, 4-OMe, 2-Me [28].

Zelisko et al. [29] synthesized a series of thiopyrano[2,3-d]thiazoles by two methods. Method A involved the preparation of condensed derivatives from 5-arylideneisorodananes **134e–f** and *trans*-aconic acid. In method B, itaconic acid was used as the dienophile. The reactions were carried out in acetic acid to give the corresponding thiopyrano [2,3-d]thiazoles **135a,b** (Scheme 30) [29].

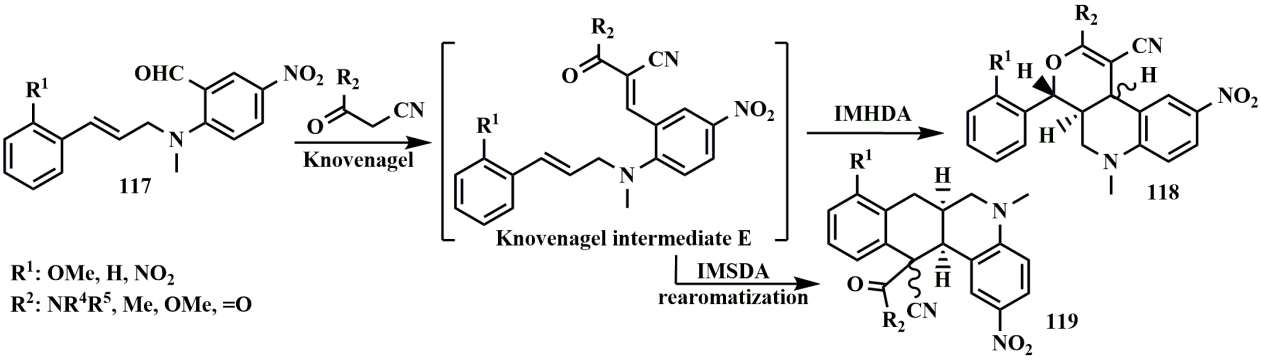
Method C was based on a three-component reaction using 5-arylideneisorodananes **134a–g** as heterodiene systems with trans-aconic acid (Scheme 31).

Subsequently, aromatic amines were introduced into the reaction, resulting in aminolysis of the ester group, which led to the formation of spiro-derivatives of thiopyrano[2,3d]thiazoles **137a–i**. The synthesized derivatives possess antitrypanosomal activity. Compound **137e** was found to be the most active against *T. brucei* (IC50 6.74 μM).

Zhang et al. [30] synthesized a series of spiro-thiazolidinediones, spiro-rhodainines, and fused thiopyrans using a sequential approach based on the DKHDA reaction, and investigated their antitumor and antifungal activities (Scheme 32). Derivatives **138, 139,** and **140a** exhibited inhibitory activity against the ZR-75-30 breast cancer cell line, with the spiro derivative **140a** being the most potent (IC_{50}=14.7 mM). Compounds **140b** and **140c**, obtained from 4-methoxy-2-aminobenzoic acid and morpholine,



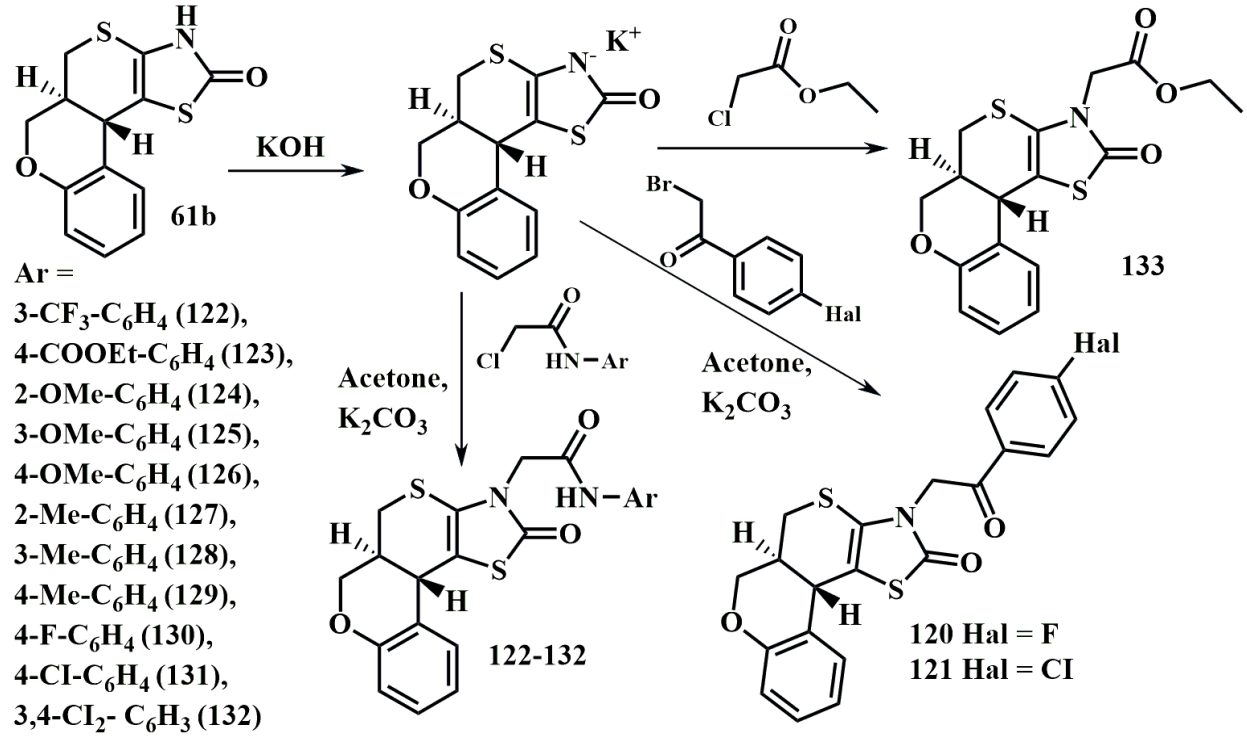
Scheme 27



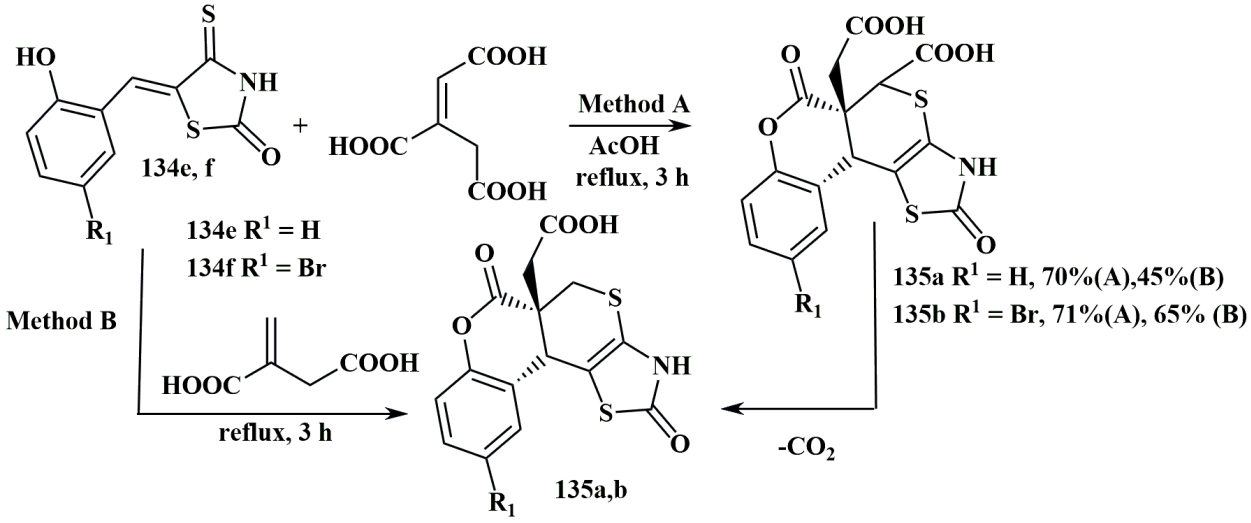
Scheme 28

were less active, and modification of the hydroxyl group in thiopyran **139** did not improve activity. In vitro antifungal assays revealed that **141a, 141b,** and **139** were active against *Candida albicans* and *Cryptococcus neoformans*, with compound **142a** showing the highest potency (MIC=16 μg/ml and 8 μg/ml, respectively) due to the methyl group and double bond in the pyran ring [30].

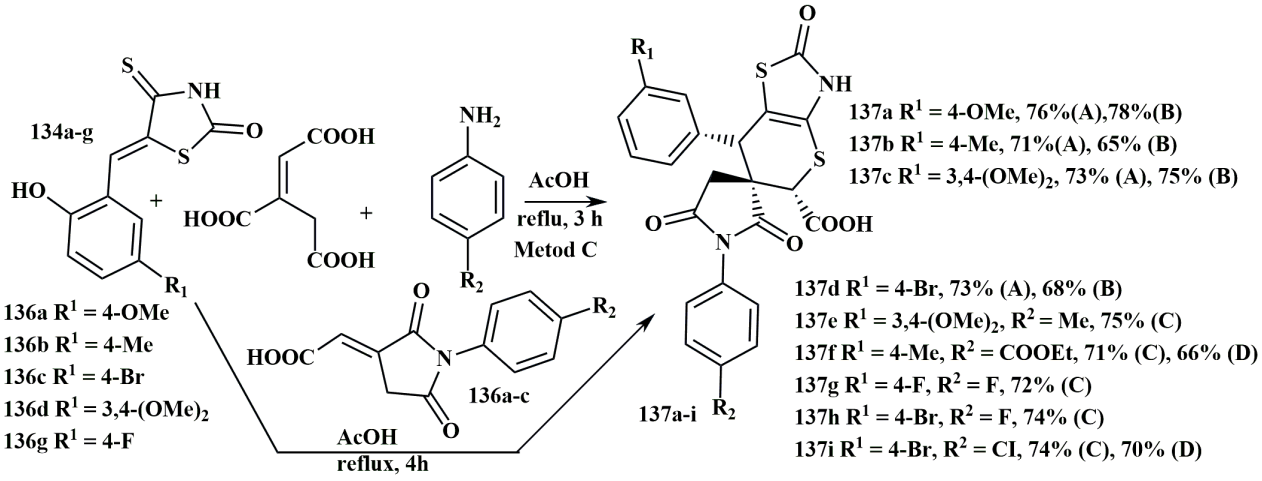
Finiuk et al. [31] investigated a series of thiopyrano[2,3-d]thiazole derivatives synthesized via a tandem hetero-Diels–Alder (HDA) reaction, which served as the key step in constructing the polycyclic heterocyclic framework (Scheme 33). This synthetic strategy enabled the efficient formation of pharmacophore-rich scaffolds containing both sulfur- and nitrogen-heterocycles commonly found in



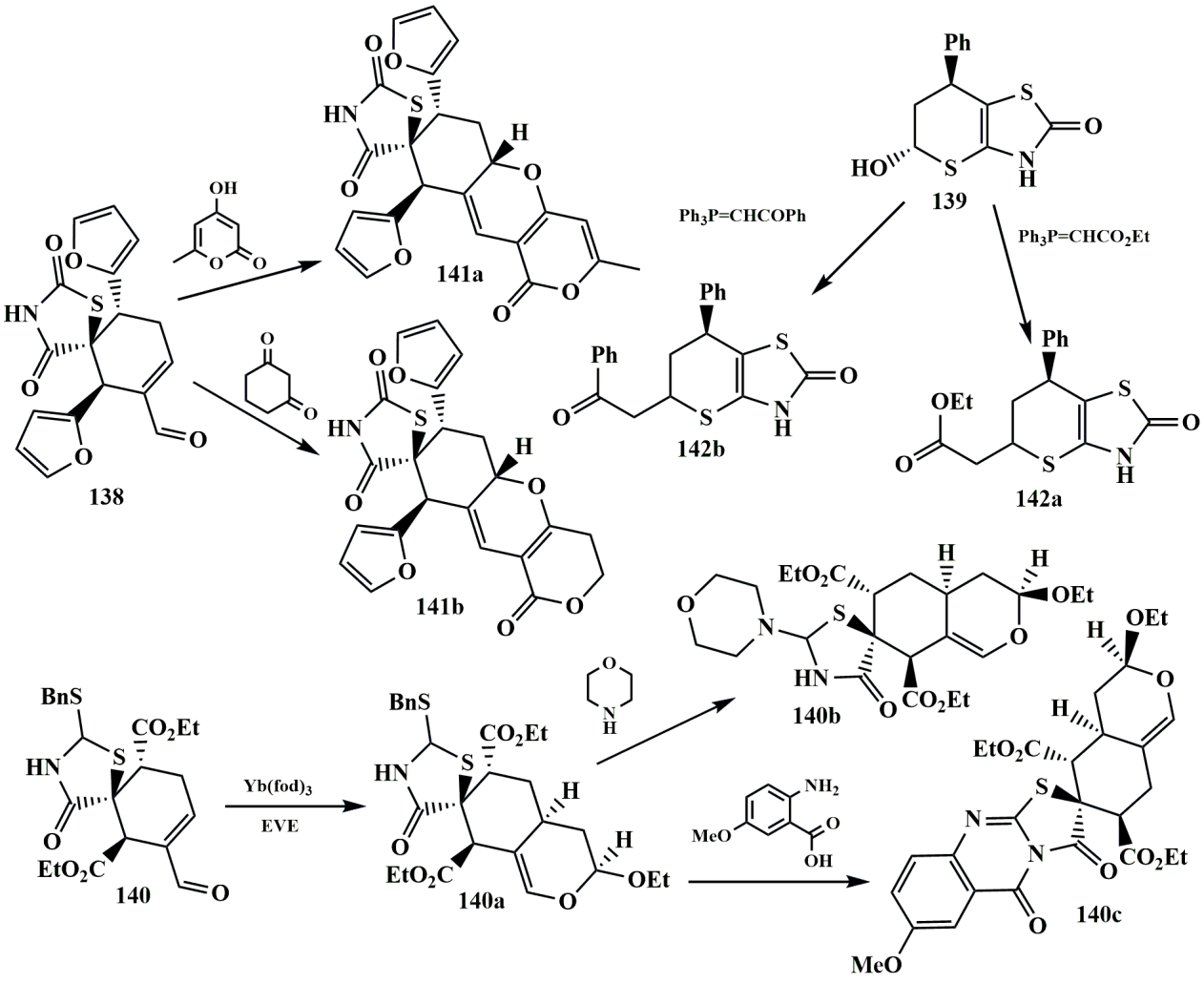
Scheme 29



Scheme 30



Scheme 31



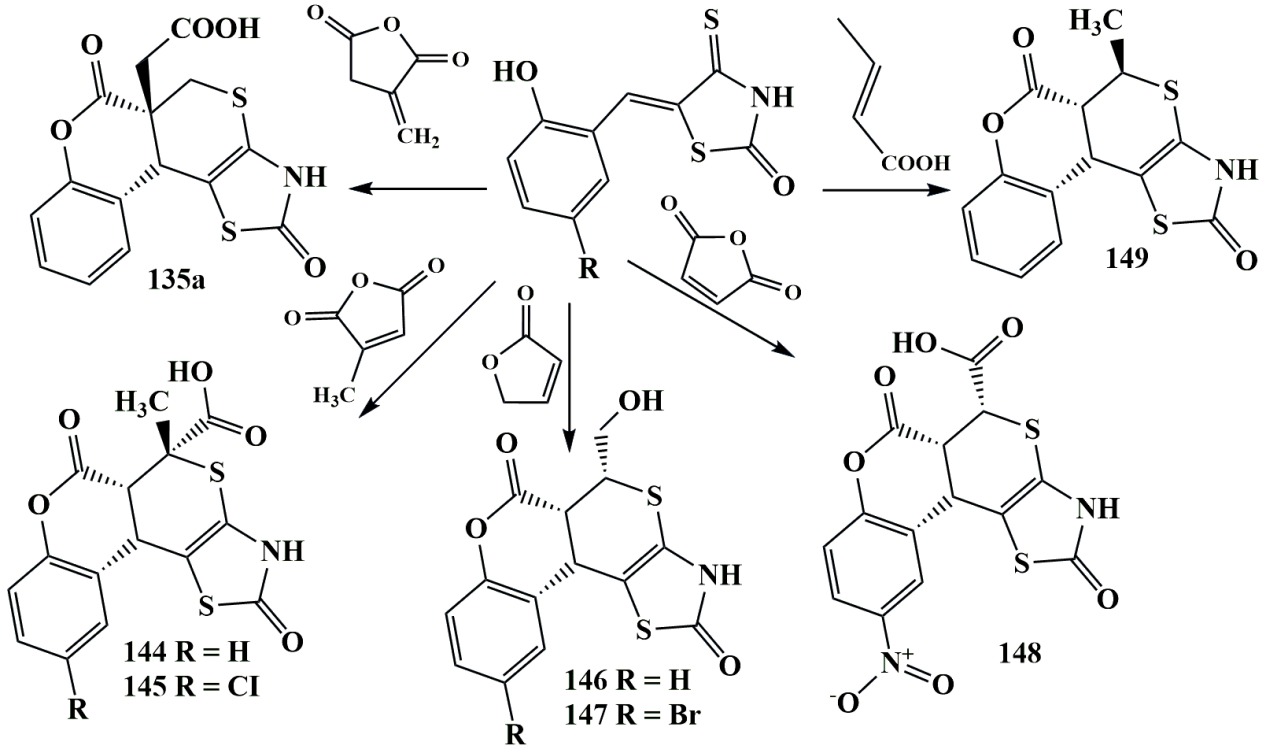
Scheme 32

bioactive compounds. The synthesized derivatives were subjected to comprehensive biological evaluation to assess their antitumor potential, revealing that several compounds exhibited selective cytotoxicity toward specific human cancer cell lines. Notably, derivative **145** demonstrated the highest selectivity index (SI) against human leukemia Jurkat (SI=25.64) and chronic myeloid leukemia K562 (SI=12.35) cells, while showing a negative SI (−3.58) for human glioblastoma U251 cells. Compound **143** displayed selectivity for Jurkat (SI=12.99) and K562 (SI=19.61) cells, compounds **144** and **146** were selective for Jurkat cells (SI=5.15 and 10.87, respectively), and compound **147** was selective for MCF-7 breast cancer cells (SI=4.76).

Metwally et al. [32] synthesized a series of 3-substituted thiazolo-thiopyran derivatives via Knoevenagel, *hetero*-Diels–Alder reactions using environmentally friendly solvents, which is in line with the current trends in green synthesis (Scheme 34). In vitro screening of antibacterial activity was performed for compounds **150a–c, 152a–d, 152f–i** and **152k–n**. The studies showed that compound **150a** showed the highest activity against *E. Coli* with MIC of 15.6 μg/ml, compounds **152b** and **152c** showed slightly lower activity with MIC of 62.5 μg/ml and compounds **152m** and **152n** with MIC values of 200 and 500 μg/ml, respectively. **150a, 150c**, **152f** and **152n** showed the same activity against *K. pneumonia* with MIC 125 μg/ml, compounds **152b, 152c** and **152m** with MIC 250 μg/ml were less active. It is worth noting that **150a, 150c**, **152b, 152c, 152d** and **152l** showed selective activity against *S. mutans*, specifically compound **177a** showed the highest activity with MIC 31.25 μg/ml, then compounds **152b, 152c** and **152l** MIC 62.5 μg/ml.

The ongoing exploration of Knoevenagel and hetero-Diels–Alder reactions was further advanced in the subsequent study [33], in which Metwally et al. demonstrated the synthetic feasibility of obtaining novel 3-substituted thiazolo-thiopyran derivatives (Schemes 35 and 36). For the synthesis of **186e**, ethyl acrylate was used as the dienophile, which did not lead to the expected increase in activity. The synthesized compounds showed significant antitumor activity against breast cancer and liver cancer cell lines. Compound **155a** demonstrated the best activity against both cell lines: IC_{50}=19.3 μg/ml for MCF7 and 10.6 μg/ml for HEPG2.

The least pronounced antitumor activity against both lines was revealed by compound **156d**. The order of increasing activity against MCF7 cells according to IC_{50}: **156c**>**155a**>**156a**>**158e**>**156d**. For HEPG2 cells: **155a**>**156a**>**158e**>**156c**>**156d**. The presence of electron-donating groups in the phenyl substituent increased the activity (compound **156c**), while electron-

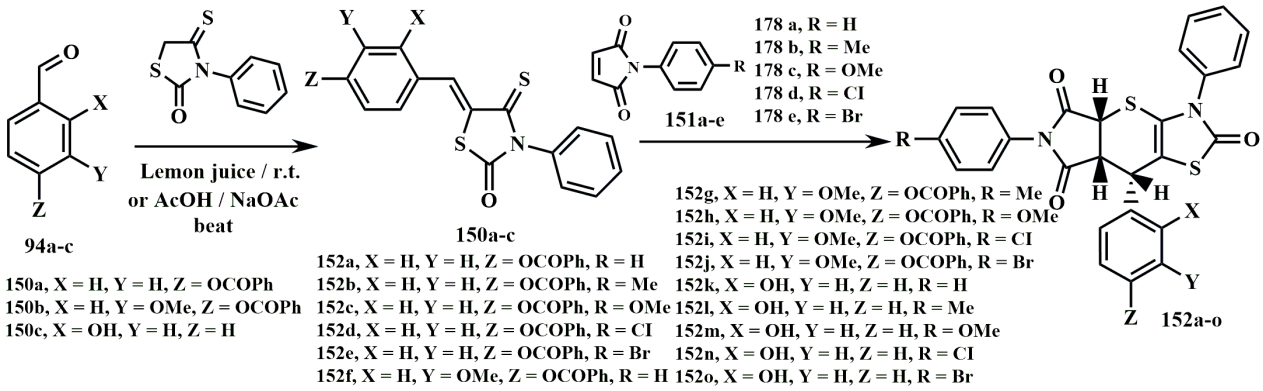


Scheme 33

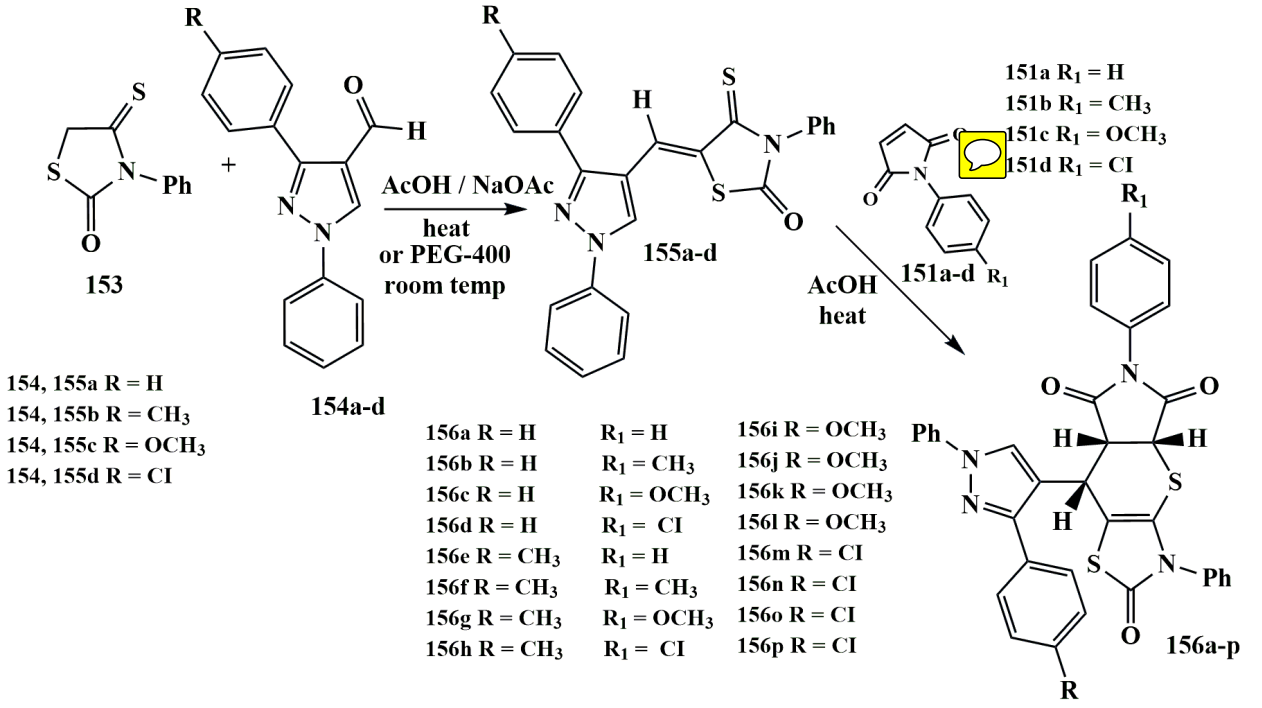
withdrawing substituents led to a decrease in activity (compound **156d**).

In the study [34], the synthesis and structural characterization of a series of thiopyrano[2,3-d]thiazole derivatives **93, 145–149, 159–167** were successfully accomplished using a rationally designed, simple, and highly efficient synthetic strategy, as illustrated in Scheme 37. Construction of the core thiopyrano [2,3-d]thiazole scaffold was achieved through an economically advantageous and diastereoselective tandem approach combining the Knoevenagel condensation with the hetero-Diels–Alder reaction. Within the scope of the study, seven structurally distinct chemotypes of thiopyrano[2,3-d]thiazole derivatives were characterized, differing in the structural variations of the thiazolidine, thiopyrane, and chromene moieties. The synthesized heterocyclic compounds exhibited favorable pharmacokinetic profiles and compliance with drug-likeness criteria, as determined by *in silico* analysis using the SwissADME platform. The anticonvulsant activity was evaluated *in vivo* using the pentylenetetrazole model, which identified three active compounds, **147, 146**, and **148.** These derivatives prolonged the latent period of seizure onset, reduced seizure frequency, mortality, and seizure duration.

The most active compound, **146**, exhibited an



Scheme 34

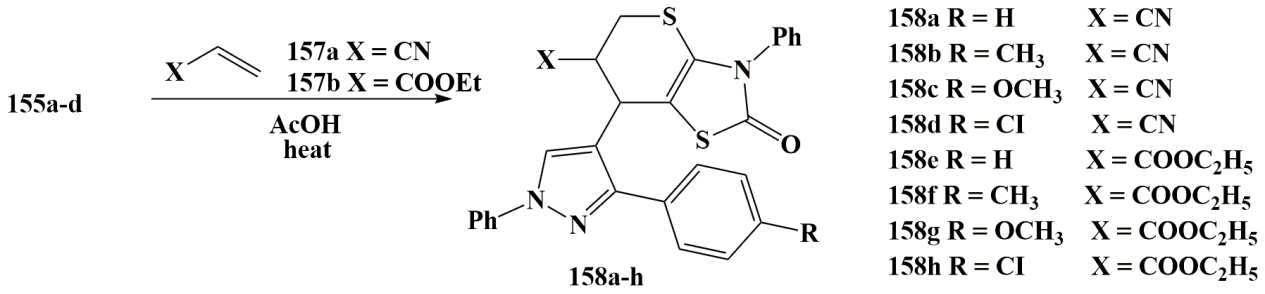


Scheme 35

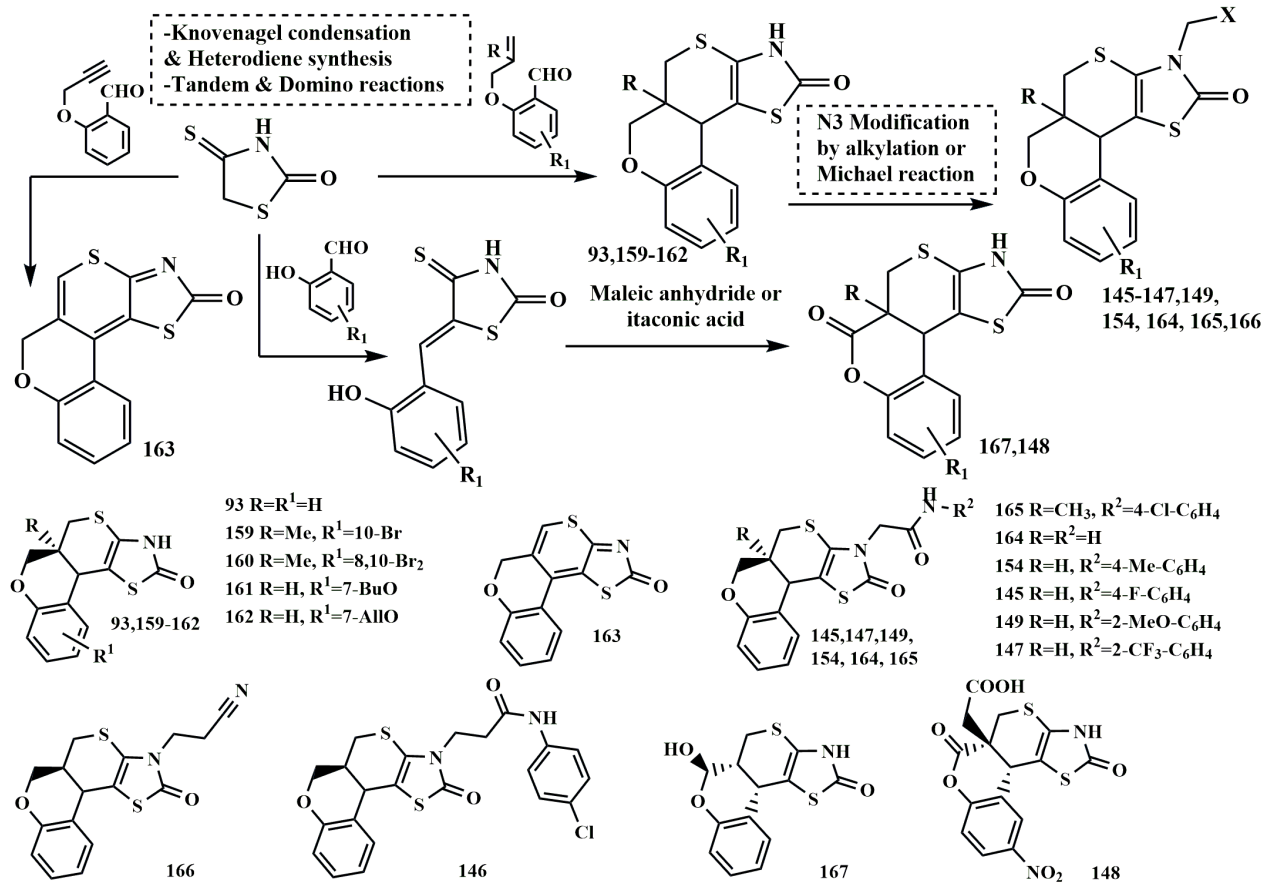
effect comparable to sodium valproate, demonstrated low toxicity, and showed affinity for the $GABA_A$ receptor in molecular docking studies, forming a stable ligand–receptor complex during molecular dynamics simulations, comparable to that of diazepam.

The results of the anticonvulsant activity screening provided preliminary insights into the structure–activity relationships of the thiopyrano[2,3-d]thiazole derivatives (Figure).

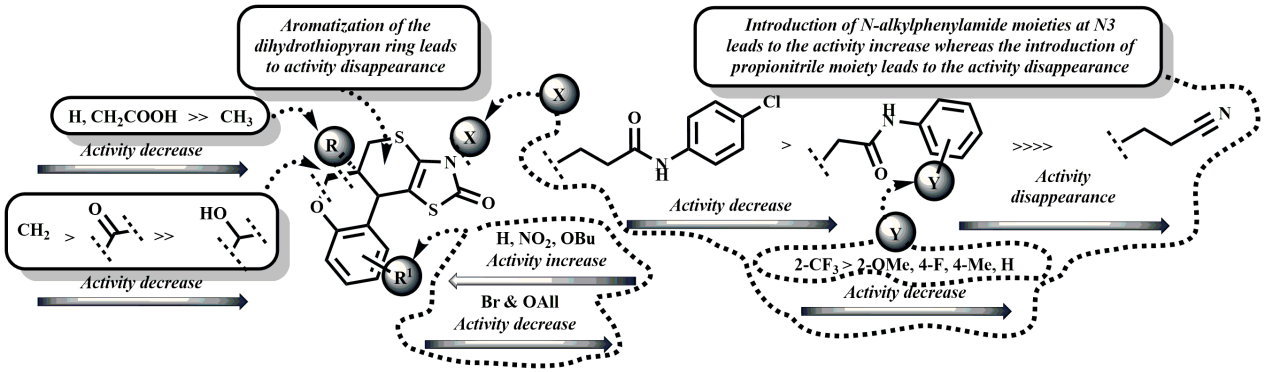
A decisive factor influencing the activity of the compounds is the substituent at the N3 position. The highest efficacy was observed for compound **146** bearing a phenylpropionamide fragment, whereas the introduction of a propionitrile moiety (compound **166**) or aromatization of the thiopyran ring resulted in a complete loss of activity. Substituents in the phenyl core and the chromene ring also modulate the biological effect, underscoring the potential of further SAR studies for the rational design of novel anticonvulsant agents.



Scheme 36



Scheme 37



Some preliminary structure–anticonvulsant activity relationships for the thiopyrano[2,3-d]thiazoles

Conclusions

Knoevenagel–hetero-Diels–Alder (KHDA) reactions have proven to be one of the most efficient synthetic platforms for the construction of functionalized heterocyclic systems, particularly thiopyrano[2,3-d]thiazoles, which are characterized by a high density of pharmacophore elements and considerable potential for applications in medicinal chemistry.

The methodological significance of the KHDA approach lies in its ability to rapidly and stereocontrollably generate polyfunctional heterocycles with high atom economy, integrating KHDA sequences into multicomponent, domino, and cascade processes. Such integration enhances synthetic efficiency, reduces the number of operational steps, lowers solvent consumption and by-product formation, aligns with the principles of green chemistry, and increases the industrial attractiveness of the methodology. The use of mild conditions (aqueous or alcoholic media, catalyst-free or low-cost catalytic systems, solid-phase and solvent-free techniques) reduces the environmental footprint and simplifies downstream processing. Notably, the gradual shift from classical Lewis acid catalysis to organocatalysis has enabled higher regio- and diastereoselectivity, while the application of nanocatalysts and magnetic supports has improved process efficiency and facilitated catalyst recycling.

A major achievement in the development of this methodology is the expansion of structural diversity. Variation of donor–acceptor dienes and dienophiles, including alkynes, nitriles, barbiturates, indole, and coumarin derivatives, has provided access to a wide range of condensed O-, N-, and S-heterocycles. These frameworks reproduce key pharmacophore motifs of natural and synthetic bioactive molecules and demonstrate antiproliferative, antitumor, antimicrobial, antitrypanosomal, and neurotropic activities, confirming their biological relevance.

Over the past two decades, significant progress has been achieved in refining KHDA reactions – from the introduction of solvent-free protocols and microwave-assisted activation to integration with CO_2 reduction processes – which has greatly expanded cascade controllability and opened new opportunities for the creation of complex molecular architectures. Nevertheless, challenges remain, particularly in predicting selectivity for structurally complex substrates, controlling enantiomeric excess without costly catalysts, and ensuring reproducibility for highly condensed systems.

From an applied perspective, KHDA sequences can be regarded as a promising «first-line» approach for the rapid generation and optimization of heterocyclic libraries aimed at the discovery of novel biologically active hits. Future research in this area will likely focus on rationalizing the design of starting materials, developing stereoselective variants of the reaction, and carrying out comprehensive bio-oriented evaluation of the resulting products using advanced in silico screening, molecular docking, and ADME profiling techniques.

Acknowledgements

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ТАНДЕМНІ ТА ДОМІНО-РЕАКЦІЇ КНОВЕНАГЕЛЯ–ГЕТЕРО-ДІЛЬСА–АЛЬДЕРА ЯК ПЛАТФОРМА ДЛЯ ДИЗАЙНУ БІОЛОГІЧНО АКТИВНИХ МОЛЕКУЛ В ОРГАНІЧНІЙ І МЕДИЧНІЙ ХІМІЇ: ОГЛЯД ЛІТЕРАТУРИ

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У статті надано критичний аналіз розвитку тандемних та доміно-реакцій Кновенагеля–гетеро-Дільса–Альдера як інтегрованої синтетичної стратегії, що забезпечує високий рівень атомної економії та структурної складності в сучасному органічному синтезі та медичній хімії. Особливу увагу приділено застосуванню цієї методології для синтезу систем тіопірано[2,3-d]тіазолу – гетероциклічних каркасів із доведеною або прогнозованою біологічною активністю. Розглянуто еволюцію умов проведення реакцій, використання каталітичних систем нового покоління, можливості мікрохвильової активації, а також перспективи інтеграції досліджуваних реакцій у багатокомпонентні, тандемні та доміно-послідовності. Обговорюються можливості застосування даних реакцій у дизайні біологічно активних молекул у контексті пошуку нових потенційних фармацевтичних агентів із протиепілептичною, протипухлинною та антимікробною активністю.

Ключові слова: доміно-реакції, гетеро-Дільса–Альдера, конденсація Кновенагеля, тіопіранотіазоли, гетероциклічні сполуки, фармакологічна активність.

KNOEVENAGEL–HETERO-DIELS–ALDER TANDEM AND DOMINO REACTIONS AS A PLATFORM FOR DESIGNING BIOLOGICALLY RELEVANT MOLECULES IN ORGANIC AND MEDICINAL CHEMISTRY: A REVIEW

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This article presents a critical analysis of the development of Knoevenagel–hetero-Diels–Alder domino and tandem reactions (KHDA) as an integrated synthetic strategy that provides a high level of atom economy and structural complexity in modern organic synthesis and medicinal chemistry. Particular attention is paid to the application of this methodology for the synthesis of thiopyrano[2,3-d]thiazole systems – heterocyclic frameworks with proven or predicted biological activity. The evolution of reaction conditions, the use of new generation catalytic systems, the possibilities of microwave activation, as well as the prospects for integrating the studied reactions into multicomponent, tandem and domino sequences are considered. The possibilities of using KHDA in the design of biologically active molecules are considered in the context of searching for new potential pharmaceutical agents with antiepileptic, antitumor and antimicrobial activity.

Keywords: domino reactions; hetero-Diels–Alder; Knoevenagel condensation; thiopyranothiazoles; heterocyclic compounds; pharmacological activity.

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