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A REVIEW OF THE EFFECTIVENESS AND USE OF PAIN RELIEF MEDICINE

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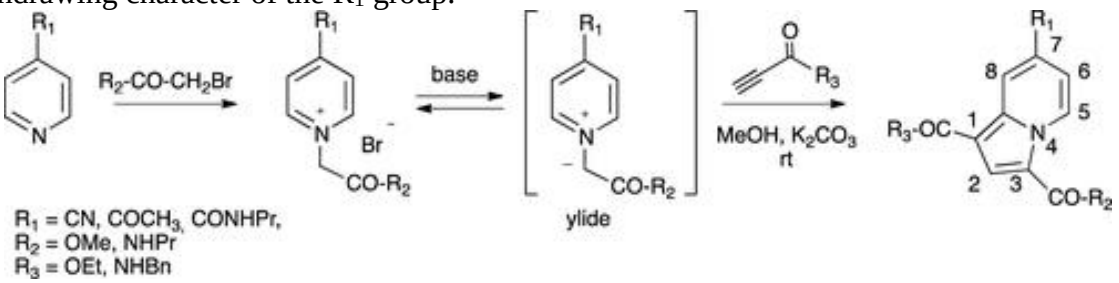
Abstract:
We describe the design and optimization of poly functional scaffolds based on a fluorescent indolizine core derivatized with various orthogonal groups (amines, esters, oximes, alkynes, etc.). To show one application as tools in biology, the scaffold was used to prepare drug−biotin conjugates that were then immobilized onto avidin-agarose for affinity chromatography. we report a synthetic protocol for the synthesis of carbamates by employing zinc chloride as a catalyst from carbamoyl chlorides and aromatic/aliphatic alcohols. The developed protocol successfully utilizes the gram-scale synthesis of the FDA-approved rivastigmine drug and its derivative .Synthesis of spiroindolo quinazolines via one-pot three-component condensation reactions of trypanothione, malononitrile or ethyl cyanoacetate, and nucleophiles was carried out in MeOH using triethylamine as the base catalyst under reflux conditions. This method has the advantages of short reaction time, excellent yields, and an easy work-up procedure.
Keywords: chromatography, ethyl cyanoacetate**,** malononitrile and trypanothione

Introduction:
The mechanisms involved in the development of chronic pain are varied and complex. Pain processes are plastic, and unrelieved pain may lead to changes in the neural structure involved in pain generation. Nociceptive pain announces the presence of a potentially damaging stimulus that occurs when noxious stimuli activate primary afferent neurons. Neuropathic pain is initiated or caused by a primary lesion or dysfunction in the nervous system resulting from trauma, infection, ischemia, cancer or other causes such as chemotherapy. The exact mechanisms involved in the pathophysiology of chronic pain are not well understood, but rapid and long-term changes are thought to occur in parts of the central nervous system that are involved in the transmission and modulation of pain following injury. Peripheral and central sensitization of sensory nerve fibers are the primary reasons for hypersensitivity to pain after injury and mainly occur in inflammatory and neuropathic pain. During these processes the sensation of pain is enhanced because of changes in the environment, the nerve fibers and modifications of the functional properties and the genetic programmer of primary and secondary afferent neurons. Response to drug treatment shows significant interindividual

variability and can lead to side effects. The neurobiological mechanisms that cause pain may account for the different types of pain observed. Identification of these mechanisms may allow us to move from an empirical therapeutic approach to one that it is specifically targeted at the mechanisms of the type of pain experienced by an individual patient.

Indolizine:Based Scaffolds as Efficient and Versatile Tools: Application to the Synthesis of Biotin-Tagged Antiangiogenic Drugs.

During the last decades, the development of orthogonal chemistries [i,ii] opened the way to the conception of molecular scaffolds decorated with orthogonal reactive groups (azide, alkyne, alkene, carbonyl, etc.) and their use for bioconjugations [iii-vii] . So far, there are a few heterocyclic platforms, [viii-ix] and none with intrinsic luminescent properties. In a previous work, we considered the use of pyridinium yielded alkyne cycloaddition forming indolizine as fluorogenic coupling methodology [x] . Indeed, bioactive indolizines are well-known as shown in Singh and Mmatli [xi], but new applications have emerged in the fields of fluorescent markers in biology, [xii] detection of organic compounds, [xiii] or material sciences [xiv] . Among the different synthetic strategies, we selected the two-step preparation of 1,3,7-trisubstituted indolizines (illustrated in Scheme1) from easily accessible reactants (pyridine, alkylating agent, and propionic ester or amide) and simple reaction conditions. The three partners of the reaction were thus optimized, and the study pointed to the importance of the electron-withdrawing character of the R_1 group.



Scheme 1. Two-Step Synthesis of Indolizines .

With these results in hand and to go further toward biochemical or biological applications, in this review decided to exploit the pre- and post-functionalization's of these 1, 3, 7-trisubstituted indolizines to design versatile multipodal scaffolds containing various orthogonal groups. As a proof of interest, the methodology was next applied to the synthesis of biotin–drug conjugates, very useful reactants for affinity chromatography. As a matter of fact, we recently described [xv] the synthesis and biological evaluation of a series of antiangiogenic molecules whose leader compound (COB223) is shown in Figure 1.

along with the inactive analogue COB236. COB223 inhibits the vascular endothelial growth factor (VEGF) signaling pathway downstream of Ras and upstream of extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation.

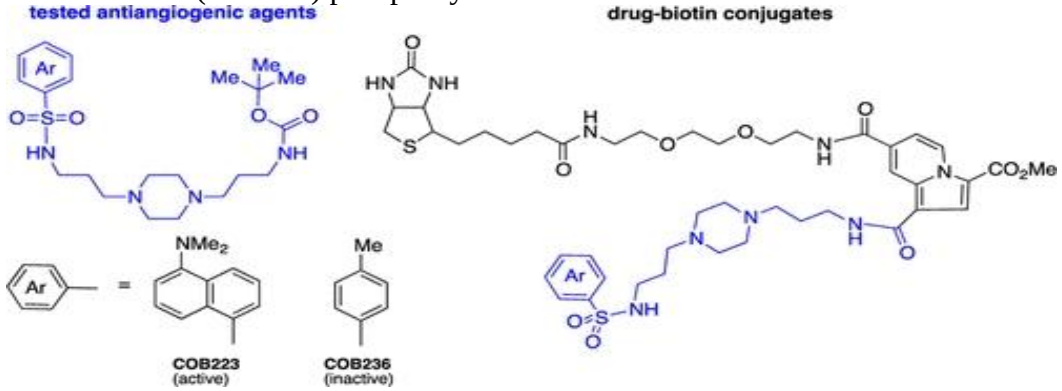
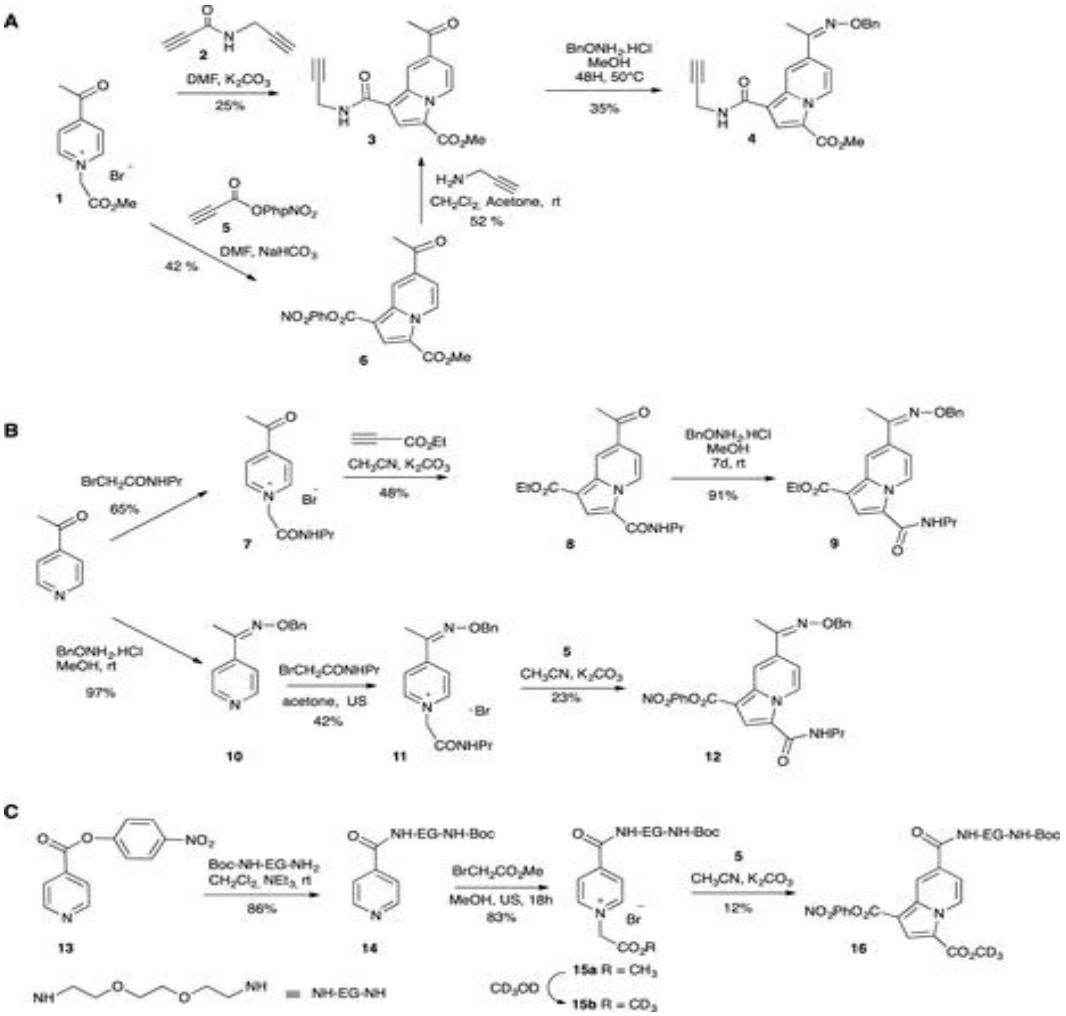


Figure 1. Antiangiogenic agents and their biotin-tagged analogues.

7-acetyl- and 7-carboxamidoindolizines as potential multifunctional platforms. Various orthogonal groups (esters, amines, alkoxyamines, alkynes) were introduced at positions 1, 3, and 7 of the indolizine rings, by either pre- or post-functionalization to illustrate the variety of reactions that may be performed. The most suitable methodology was applied to the synthesis of two biotin-tagged antiangiogenic drugs. To evaluate the possible impact of the indolizine nucleus on drug–protein interaction, the biotin-tagged molecules were immobilized onto streptavidin agarose beads and used for affinity chromatography and subsequent proteomics analysis. The comparison of the data obtained using either the biologically active drug (COB223) or the inactive analogue (COB236) is discussed[xvi].

The indolizines shown in Scheme 2, contain three points of modification, each of them coming from one of the three reactants: R_1 from the pyridine, R_2 from the alkylating agent (halogen acetic ester or amide), and R_3 from the activated alkyne (propionic ester or amide). Two strategies were envisioned for the introduction of functional groups: either before cyclization (pre-functionalization) by synthesizing modified starting reactants, or after cyclization (more versatile post-functionalization). Choosing between the two approaches would mainly be dependent on the stability and orthogonality of the different functions, and on the efficiency of isolation and purification.

7-Acetyl Indolizine **3** was first evaluated as a potential tripodal scaffold Scheme 2A) with methyl ester and two "clickable" functions (alkyne and carbonyl) for further post-functionalization. The triple bond may either be introduced using the propiolic amide **2** as diplography [xvii] or via formation of the reactive para-nitrophenyl ester **5** [xviii] followed by substitution with propargylamine. Next, the reaction with alkoxyamines (illustrated by benzyloxyamine) yielded the corresponding oxime **4**.

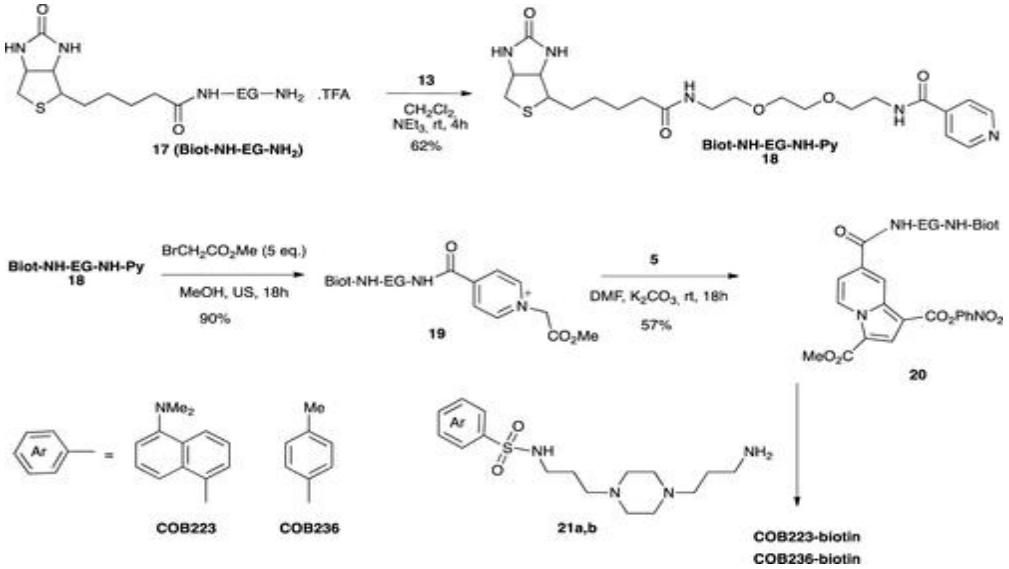


Scheme 2: Different Strategies of Formation and Modulation of Tripodal Core. Amine Containing Reactants were Introduced at Positions 1 (Part A), 3 (Part B) or 7 (Part C) of the Indolizine Ring

this first example, the amino group (i.e., propargylamine) was introduced at position 1 of the indolizine ring; however, it was also valuable to link amino groups to other positions. Indolizines **8**, **9**, and **12** contain the amino groups (illustrated by propylamine, see Scheme 2B) at position 3. To do so, the corresponding 2-bromo-N-propylacetamide was used as alkylating agent in the preparation of the pyridinium salt (**7** or **11**) [xii] . Two strategies were then evaluated. To form the indolizine **8**, the rather stable ethyl ester was introduced at position 1 by reacting ethyl propionate with **7**. The oxime bond was later formed to give **9**. In the case of indolizine **12** bearing reactive para-nitrophenyl ester, the oxime bond was formed in excellent yield at an earlier stage, i.e., before alkylation with the 2-bromo-N-propylacetamide and cyclization with the para-nitrophenyl propionate **5**. Lastly, the amino group (exemplified by the mono-Boc-protected 2,2′-(ethylendioxy)bis(ethylamine), often used as linker in the synthesis of bioconjugates), was introduced at position 7 of the indolizine ring. As drawn in Scheme 2C, isonicotinic amide **14** was prepared from the activated ester **13** [xix] and mono-Boc-protected 2,2′-(ethylendioxy)bis(ethylamine). Alkylation with the ethyl 2-bromoacetate gave the pyridinium salt **15a**. To highlight the high reactivity of ester at position 1 of pyridinium salts, due to the presence of the positive charge at *β*-position, a transesterification was realized in CD_3OD at room temperature (rt) with the formation of the deuterated analogue **15b**. The deuterated indolizine **16** was then obtained by cyclization of **15b** with the

reactive propionate **5** as described above. We thus formed a reactive scaffold containing two esters of different stabilities, and a Boc-protected amine that can easily be released by trifluoroacetic acid (TFA) treatment.

The latter approach was chosen to prepare the two biotin-tagged COB223 and COB236. Indeed, direct binding of biotin to the molecule was precluded due to limited access of the drug by the target protein during affinity chromatography, and to overcome this problem, ethylene glycol (EG) linker such as in Biot-NH-EG-NH_2 (Scheme 3) was added.. The site of functionalization of the active drug by the biotin was another key point to examine. As reported earlier, [xvii] the structure–activity relationships pointed to the importance of both the dansel chromophore and the polyamine linker for the antiangiogenic properties. We therefore chose to modify the Boc group of COB223 and COB236. As depicted in Scheme3 , the drugs were introduced at the last step to limit tedious purification steps. The key intermediate, Biot-NH-EG-NH-Py **18**, was prepared from Biot-NH-EG-NH_2**17** [xix] by reaction with the reactive para-nitrophenyl isonicotinic ester **13**. Alkylation with methyl 2-bromoacetate in acetone gave the corresponding pyridinium bromide **19** in excellent yield. This intermediate was stable at room temperature for extended period. Cyclization with para-nitrophenyl propionate **5** in dimethylformamide (DMF) in the presence of K_2CO_3 gave the indolizine **20** in reasonable yield. Due to the reactivity of the para-nitrophenyl ester, the next step was performed without further purification. The nucleophilic substitution by the primary amines of **21a,b**, issued from the Boc deprotection of COB223 or COB236, yielded the corresponding biotin-tagged molecules.



Scheme 3: Synthetic Pathway for the Biotin-Tagged Compounds

Carbamates (urethanes) are conventional scaffolds in agricultural, pharmaceutical, and material science due to their diverse activities[xx]. Carbamate plays a key function in polyurethane polymers, which are often used in synthetic fibers, surface coatings, adhesives, foams, and composites in the manufacturing of paints[xxi]. Extensive application of carbamate compounds began in 1959 when the first carbamate pesticide "carbaryl" was approved in the United States[xxii] Figure 2

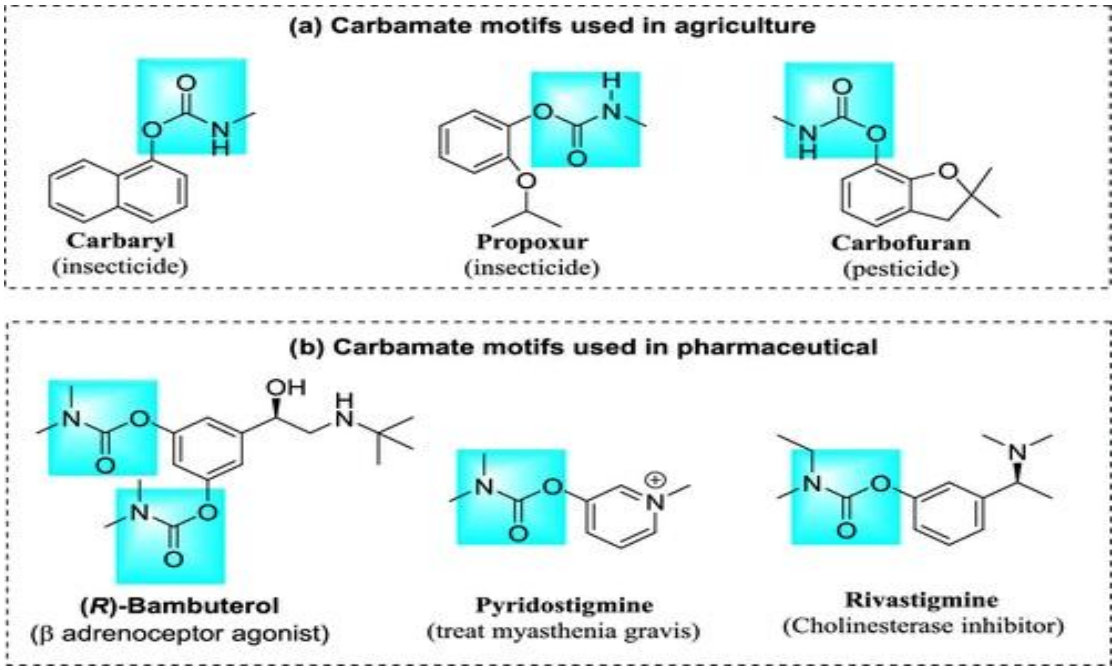
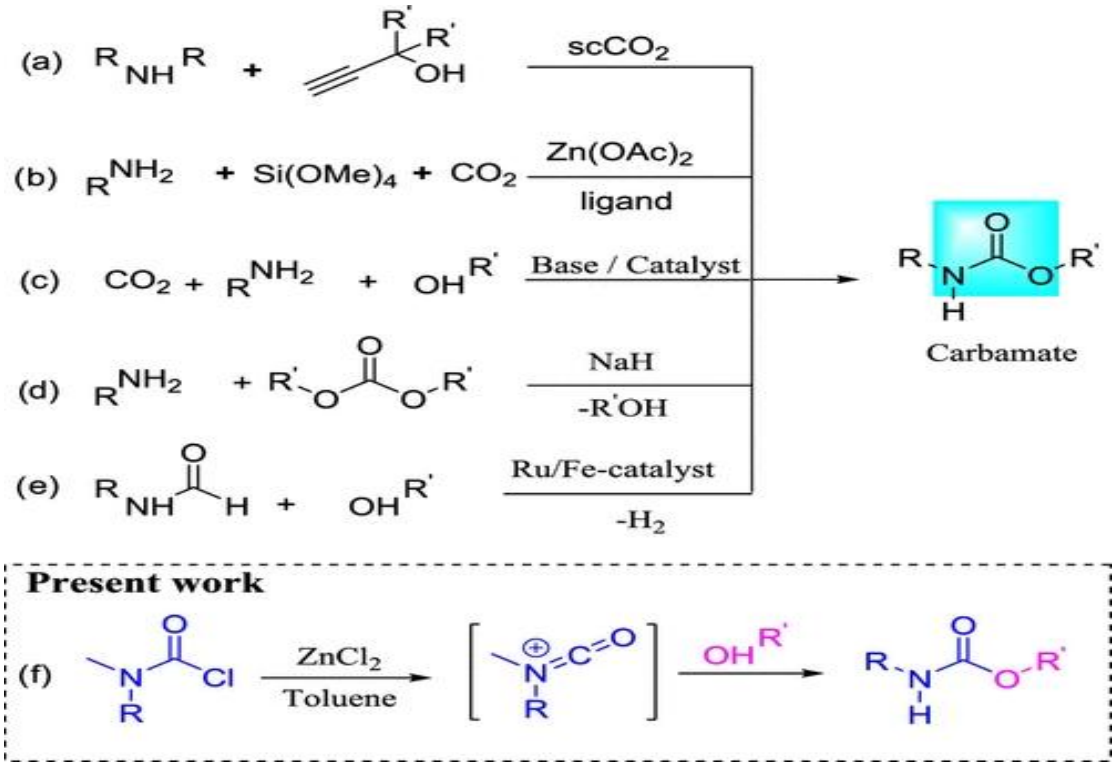


Figure 2. Examples of commercially available carbamate molecules.

Carbaryl is utilized as an alternative to organophosphate insecticides [xxiii] and propoxur is commonly used to manage domestic pests [xxiv] .Pesticides like carbofuran are employed in the cultivation of maize, rice, and cotton crops. [xxv] FDA-approved carbamate-containing drug molecules, such as (R)-bambuterol, have the potential to be used in the treatment of cognitive decline and post-traumatic stress disorder (PTSD), [xxvi] while pyridostigmine is commonly used to treat myasthenia gravis [xxvii] . On the other hand, rivastigmine acts as an acetylcholinesterase (AChE) inhibitor. [xxviii]

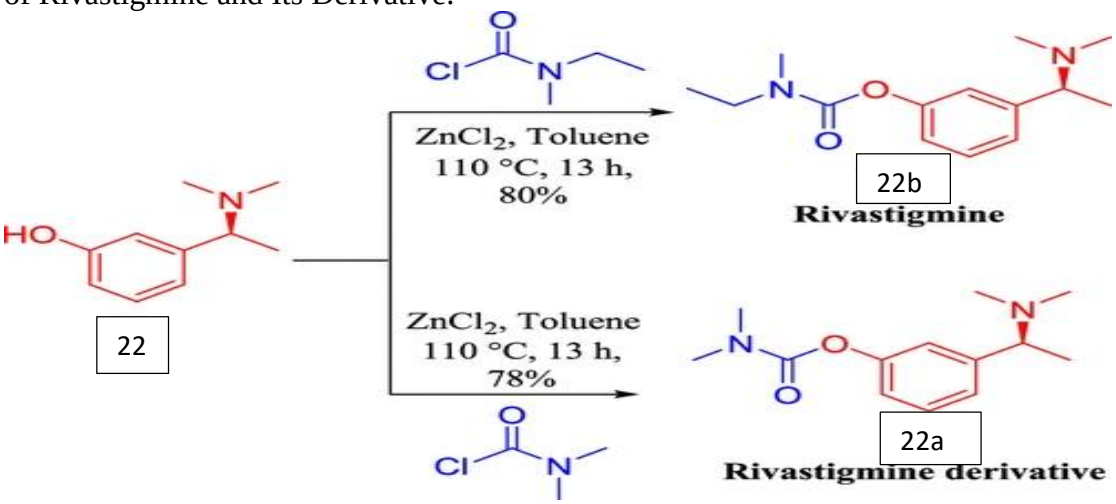
in literature revealed that carbamate synthesis can be accomplished using a variety of synthetic methods [xxix] .In most of these methods, carbamate synthesis is executed by the direct use of hazardous starting materials such as isocyanates, [xxx] phosgene, or carbon monoxide.

In this context, a few contemporary synthetic methods of carbamate synthesis have been illustrated in Scheme 4.



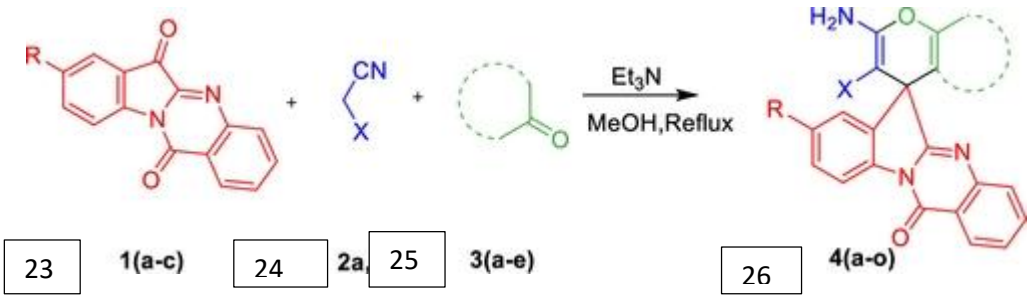
Scheme 4. Existing Synthetic Strategies of Carbamates[a]

The developed synthetic protocol was successfully employed for the synthesis of the FDA-approved drug rivastigmine and its derivative Scheme 5. Carbamate synthesis (**22b**) was accomplished using carbamoyl chloride in the presence of various bases or catalysts [xxxi] .The enantiomerically enriched scaffold (S)-3-(1-(dimethylamino)ethyl)phenol (**22**) [xxxii] was treated with *N*-ethyl,*N*-methyl carbamoyl chloride at 110 °C for 13 h to isolate an 80% yield of the rivastigmine (**22b**) [xxxiii] drug molecule with 91.23% ee. Rivastigmine derivative **22a** [xxxiv] synthesis was achieved via the treatment of phenol **22** with N,N-dimethyl carbamoyl chloride at 110 °C for 13 h to isolate 78% yield with 97.44% Scheme 4. Synthesis of Rivastigmine and Its Derivative.



Scheme 5.

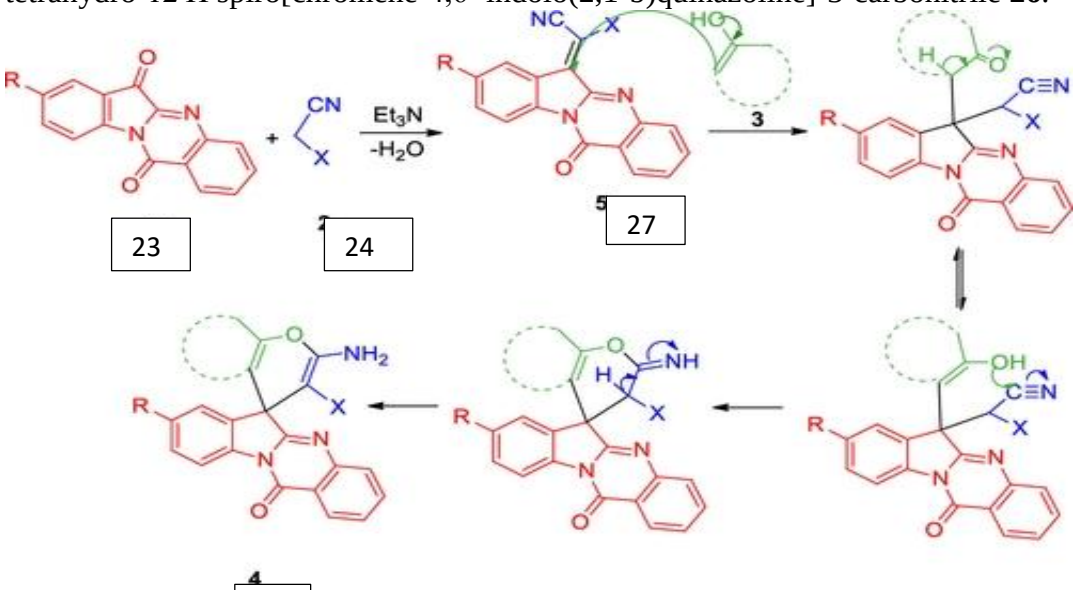
in this review, we are reporting herewith a facile and efficient one-pot synthesis of functionalized spiro indoloquinazoline compounds **26** involving a three-component condensation reaction catalyzed by triethylamine using the substrates trypanothione **23**, an active methylene compound **24**, and a nucleophile **25** carried out in MeOH using triethylamine as the base catalyst under reflux conditions[xxxv] Scheme 6.



Scheme 6.

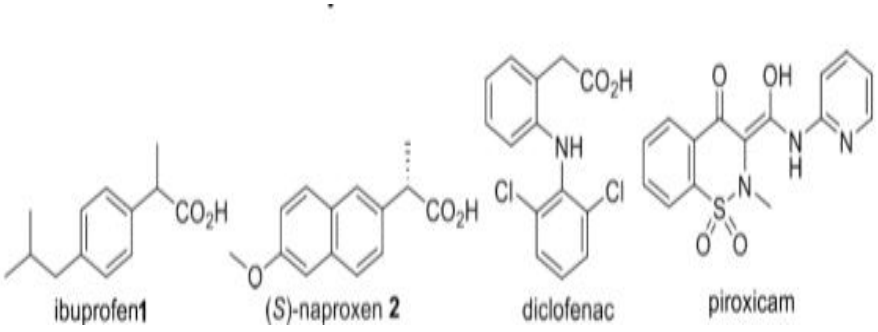
Even when the reaction was carried out in MeOH under catalyst-free conditions, only dicyanomethylene derivative **27** was obtained in 93% yield. When the above-mentioned reaction was carried out with various catalysts such as montmorillonite-K10 clay, I_2, and Amberlite IRA-400 Cl in MeOH under reflux conditions too, only **27**was obtained . When the reaction of trypanothione **23**, malononitrile **24,** and dimedone **25** in MeOH and the presence of the Et_3N catalyst under reflux conditions was carried out, **26** was obtained as the major product and **27** as a minor product as shown in scheme 7.

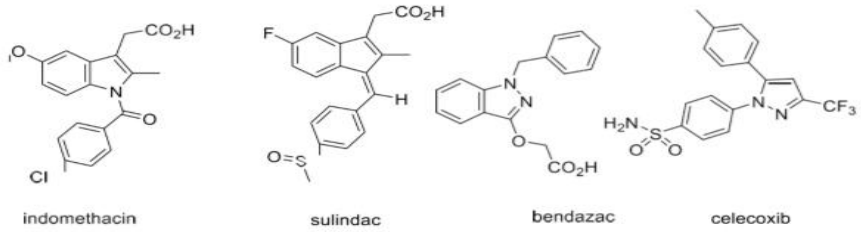
In the first step of the reaction, possibly the Knoevenagel reaction between trypanothione **23** and malononitrile **24** leads to the formation of dicyanomethylene derivative **27**. The subsequent hydroxide-promoted Michael addition of cyclic 1,3-diketone **25** to **27** results in electron-deficient 2-amino-7,7-dimethyl-5,12′-dioxo-5,6,7,8-tetrahydro-12′H spiro[chromene-4,6′-indolo(2,1-b)quinazoline]-3-carbonitrile **26**.



Sche[illegible] Plausible Mechanism for the Formation of Compound **26**

In addition, it was prescribed more than 2.4 million times in the USA in 2018 [xxxvi] and was the most prescribed NSAID in that year. The second most prescribed NSAID was naproxen, which was developed in the 1970s. Considering that both ibuprofen and naproxen can be purchased without a prescription, it is believed that their medicinal benefits have significantly improved patients' lives.





Conclusion

Pain relief medicines remain a cornerstone in the management of both acute and chronic pain. This review highlights the wide range of options available—from over-the-counter analgesics to prescription-strength medications—each with its own benefits, limitations, and appropriate use cases. While many pain relievers are effective when used correctly, they also carry potential risks, particularly with long-term or inappropriate use. It is crucial for both patients and healthcare providers to consider factors such as the type of pain, duration of treatment, and individual health conditions when selecting a pain relief medication. Responsible use, guided by medical advice, ensures that these medicines can provide effective relief while minimizing side effects and long-term complications. Ultimately, the appropriate use of pain relief medicine can significantly improve quality of life, making it an essential component of modern medical care.

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