RSC Advances

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2025, **15**, 45619

Design and synthesis of novel spirocyclic oxindole based hybrid scaffolds: *in silico* docking approach towards therapeutic target exploration

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Received 22nd September 2025
Accepted 6th November 2025

DOI: 10.1039/d5ra07175e

rsc.li/rsc-advances

The isatin derivatives exhibit various pharmacological activities, including antihypertensive, anti-inflammatory, and ACE-inhibitory effects. The synthetic flexibility of isatin makes it valuable for synthesising various heterocycles, including pharmacologically potent spirocyclic derivatives. In this paper, an efficient procedure is employed for the synthesis of novel alkyne-appended spiro[indoline-3,3′-pyrrolizin]-2-one derivatives (**6–8**) as a potential anti-inflammatory agent predicted by molecular docking *via* a catalyst-free reaction from alkyne isatin, the starting material. Subsequently, these compounds were treated with the azide derivative of isatin to get the triazolated derivatives (**11–14**), which were further reacted with L-hydroxyproline in ethanol in the presence of $InCl_3$ as a catalyst to get the final products (**15–19**). Molecular docking studies of all the synthesised ligands were carried out to examine the interactions of the ligands with the active sites of the COX-2, a key enzyme in the inflammatory pathways responsible for prostaglandin synthesis. All the synthesised compounds have shown good binding affinity towards the targeted enzyme. Herein, compound **19** displayed the highest binding affinity, −10.3 kcal mol^{-1}, among all the synthesised compounds. Thus, the synthesised compound holds the potential to exhibit anti-inflammatory activity similar to that of celecoxib, the standard reference drug.

1. Introduction

Indoline (I), pyrrolizine (II), and oxindole (III) (Fig. 1) scaffolds are present in many natural products such as physostigmine,[1] senecionine,[2] and alstonisine[3] and are incorporated in drugs to show a diverse range of biological activities, such as antihypertensive, anticancer, anti-inflammatory and angiotensin-converting enzyme inhibitory effects.[4,5] Since they exhibit a wide variety of pharmacological activities,[6,7] there is a compelling need to design and synthesise novel derivatives of these heterocyclic compounds to further enhance their therapeutic potential.[8]

Oxindoles (III) are a class of heterocyclic[9] organic compounds that commonly exist as natural products of various plants and in the body fluids and tissues of mammals.[10,11] Baeyer and Knop reported the first oxindole synthesis in 1866. The oxindole-containing compounds illustrate a broad area of pharmacological activities, such as antimicrobial,[12] antiviral,[13] antitubercular,[14] antioxidative,[15] tyrosinase inhibitory,[16] anti-rheumatic arthritis,[17] *etc.* There are various commercially available drugs (Fig. 2) containing an oxindole core that are widely used and well accepted in the market.[18]

Due to the synthetic versatility of isatin (indole-2,3-dione, IV), it is used as a precursor for drug synthesis. It can also be utilised for the synthesis of various heterocyclic compounds, including indole and pyrrolidine derivatives.[19] The pharmacological activity of isatin derivatives is intriguing, and they are widely used as antifungal,[20] antiviral,[21] anticonvulsant,[22] antibacterial,[23] anti-Alzheimer,[24] antioxidant[25] and antimicrobial[26] therapeutics.

Pyrrolizines play an important role in the synthesis of numerous biologically active natural alkaloids. Due to their capacity to produce reactive pyrrolic metabolites that can bind to DNA and create cross-links, they are speculated to have anti-cancer activity. The [3 + 2] cycloaddition reaction, known as 1,3-dipolar cycloaddition, has become a potent method for creating five-membered heterocyclic molecules. For the [3 + 2] cycloaddition reactions, several 1,3-dipoles have been used, including

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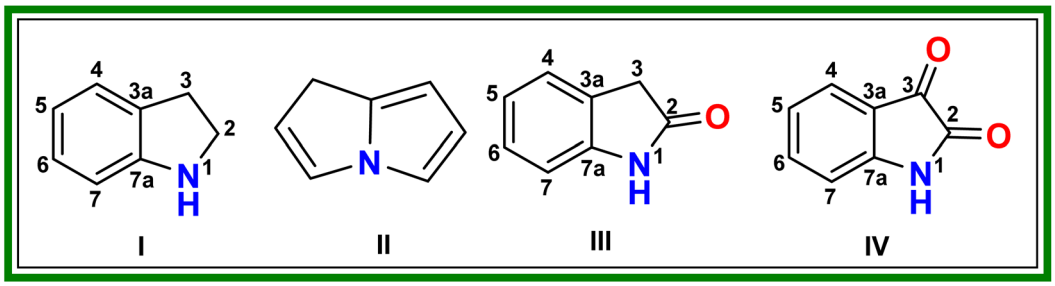


Fig. 1 Structures of indoline (I), pyrrolizine (II), oxindole (III) and isatin (IV).

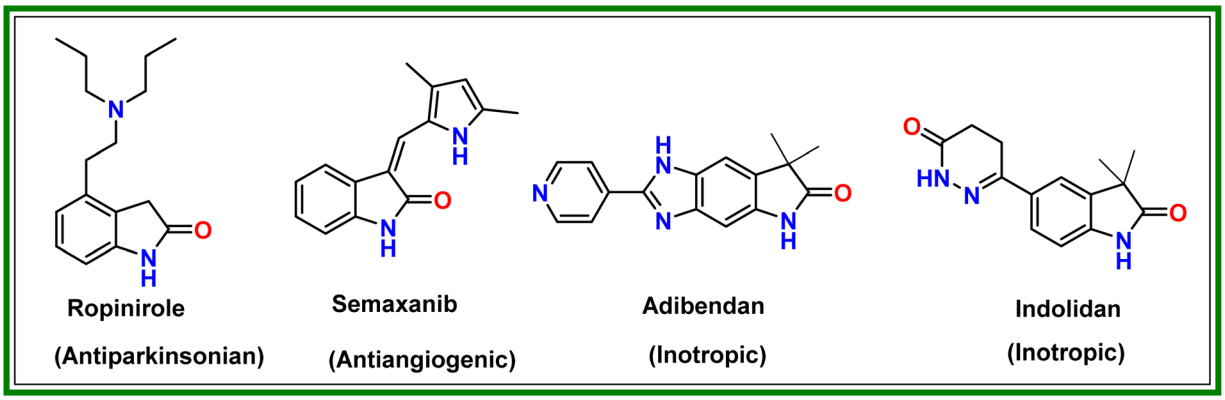


Fig. 2 Commercially available drugs containing the oxindole moiety.

nitrones, nitrile oxides, azides, azomethine imines, and azomethine ylides.[27] Among these, azomethine ylides have proven a crucial precursor for the synthesis of pyrrolizines (Fig. 3).

Spirocyclic compounds containing indoline scaffolds have significant pharmacological effects. Polycyclic rings fused at a central carbon atom are called spirocyclic compounds. The establishment of spiroheterocyclic compounds requires specific design strategies, as their synthesis has always been challenging for organic chemists.[28] The nomenclature for the spirocyclic compounds was first described by a German chemist, Adolf van Baeyer, in 1900. The unique features of spiroheterocycles related to their synthesis, isolation, stereochemistry and pharmacological effects have generated immense curiosity among chemists toward spiroheterocyclic scaffolds.[29] It is undeniable that the presence of a spiro carbon in a molecule causes structural stiffness, which has a significant impact on the biological activities. The interesting conformational features with the presence of chiral spiro carbon provide it an asymmetric characteristic attribute to its extremely diverse range of biological properties that comprises antifungal, anticancer, antidiabetic, antihypertensive, antibacterial, antidepressant, diuretic, antiviral, and anti-inflammatory activity.[30] Spirocyclic compounds are abundantly present in a variety of naturally occurring and biologically active substances.

The spirocyclic skeleton is also present in several terpenoids, alkaloids, insect pheromones, polyether antibiotics, and

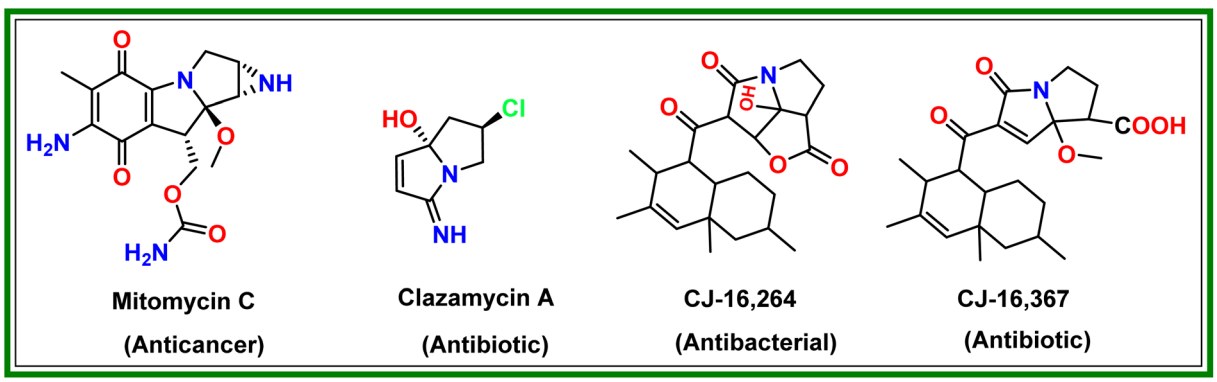


Fig. 3 Structures of commercially available drugs having pyrrolizines.

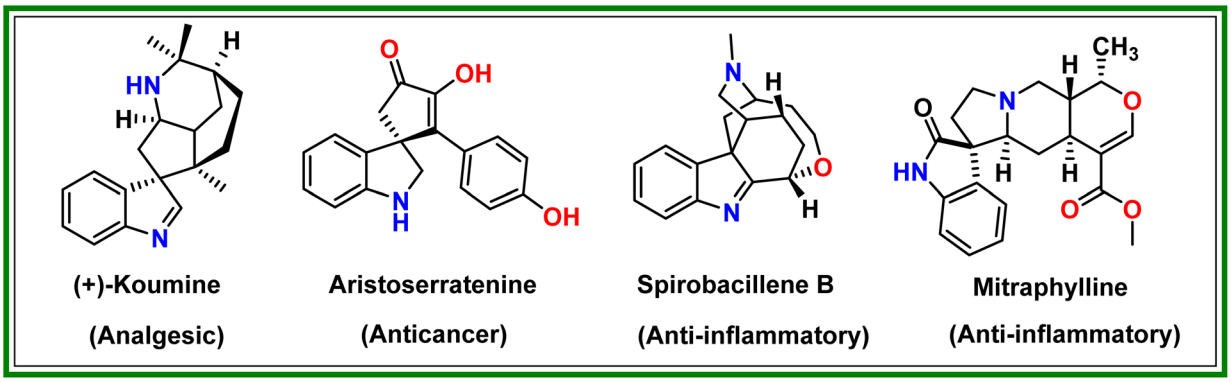


Fig. 4 Natural alkaloids containing the C3-spirocyclic indoline core structure.

natural products such as (+)-koumine,[31] aristoserratenine,[32] spirobacillene B,[33] and mitraphylline[34] (Fig. 4), which exhibit analgesic, anticancer, and anti-inflammatory activities, respectively. For this reason, heterocyclic scaffolds such as isatin, possessing prochiral centres that can be exploited for the generation of spiroheterocycles, are of great importance to synthetic organic chemists. The presence of a prochiral centre at the C-3 position of isatin makes it undoubtedly the most attractive moiety for the construction of a spiroheterocyclic framework possessing excellent biological activities.[35]

According to the literature review, previously reported methods for the synthesis of spiro compounds suffer from a number of drawbacks, including low yields, prolonged reaction times, expensive catalysts, time-consuming work-up procedures, and poor selectivity. These constraints limit their broader application in synthetic and medicinal chemistry.

In this regard, we have created a green, one-pot multicomponent reaction-based synthesis approach for new, densely substituted spirooxindole derivatives. This protocol not only eliminates the need for external catalysts but also simplifies the synthetic procedure under mild, environment-friendly conditions, resulting desired products in good yields. It is worth highlighting that this approach includes the integration of 1,2,3-triazole pharmacophores into the spirooxindole framework, thereby enhancing structural diversity and providing a versatile platform for further modification. Architectural components such as fused spirocyclic motif, isatin scaffold, and triazole integration are expected to collectively improve biological profiles through increased affinity toward biological targets.

Furthermore, inclusion of a biocompatible L-hydroxyproline unit into the triazole-spirooxindole framework shows a new structural feature that to the best of our knowledge rarely has been reported in literature previously. This incorporation is expected to enhance polarity and potential biological compatibility, providing a new hybrid for COX-2-targeted anti-inflammatory drug candidate.

2. Methodology

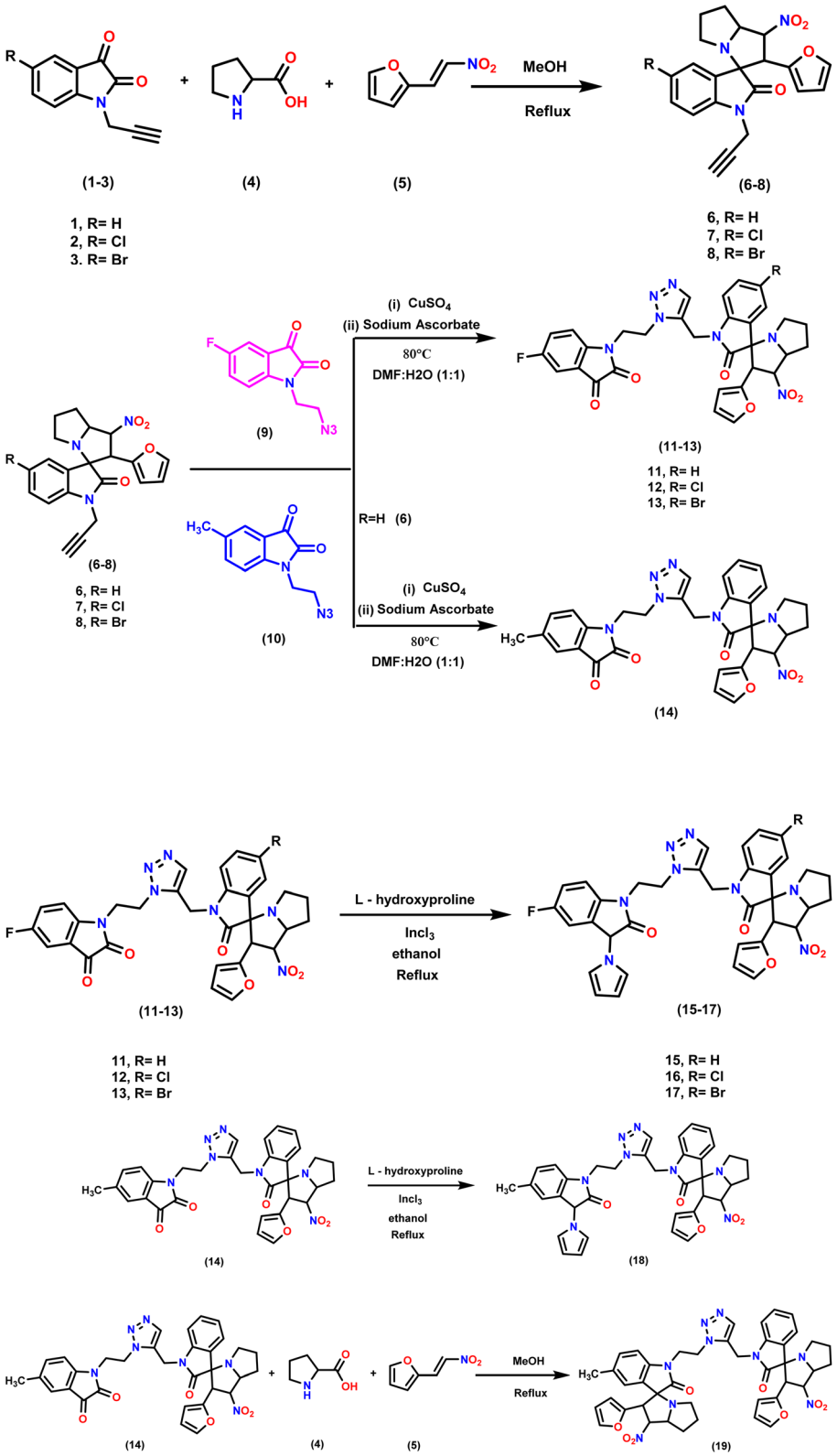
2.1 Materials and instrumentation

All the reagents (analytical grade) were purchased from Spectrochem Pvt. and used for synthesis without further purification. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at room temperature in deuterated DMSO-d_6 on JEOL, ECX-400P Spectrometer USA at 400 MHz and 100 MHz respectively. KBr disks were used to record the FTIR data on a SHIMADZU. Chemical shifts, coupling constants, and absorption frequency data have been indicated in terms of δ (ppm), J (Hz), and ν (cm^{-1}), respectively. Mass spectrometry measurements were obtained on a 6530 Accurate-Mass Q-TOF LC/MS spectrometer.

2.1.1 General procedure for the synthesis of compounds 6–8. A facile and efficient synthesis of the alkyne derivatives **6–8** of 2′-(furan-2-yl)-1′-nitro-1-(prop-2-yn-1-yl)-1′,2′,5′,6′,7′,7*a*′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one were achieved by three-component condensation of alkyne derivative of isatin **1–3** (1 mmol), proline (**4**) (1 mmol) and (*E*)-2-(2-nitrovinyl)furan (**5**) (1 mmol) in methanol under reflux condition for 2 h and the pure product were purified *via* silica gel chromatography (100–200 mesh size) by using hexane and ethyl acetate (70 : 30) as a solvent system to give 90–98% yield.

2.1.2 General procedure for the synthesis of compounds 11–13 and 14. The compounds **11–13** & **14** were synthesised by optimisation of alkyne derivative of spiroindolines **6–8** (1 mmol) with azide derivative of isatin **9** & **10** (1.2 mmol) in the presence of $CuSO_4$ (0.2 mmol) and sodium ascorbate (0.4 mmol) in DMF for 20 min. The completion of the reaction was checked by TLC. The resulting reaction mixture was poured onto 30 mL of ice-water and then extracted with chloroform (3 × 30 mL). The combined extracts were washed with brine solution, dried over anhydrous sodium sulphate, filtered and then concentrated at reduced pressure under vacuum, resulting in the isolation of the crude product. The crude product was further purified *via* silica gel chromatography (100–200 mesh size) to give desired compounds **11–13** and **14**, in 78–88% yields.

2.1.3 General procedure for the synthesis of compounds 15–17 and 18. Compound **11** in a round-bottom flask (1 mmol) was refluxed with L-hydroxyproline (1.2 mmol) in the presence of $InCl_3$ as Lewis acid catalyst in ethanol for 2–3 h. The completion of the reaction was checked by TLC. The resulting reaction mixture solvent was evaporated at rotavapour, then extracted with chloroform (3 × 30 mL). The combined extracts were washed with brine solution, dried over anhydrous sodium sulphate, filtered and then concentrated at reduced pressure under vacuum, resulting in the isolation of the crude product.



Scheme 1 Schematic route for the synthesis of novel indoline-based hybrid scaffolds.

The crude product was further purified *via* silica gel chromatography (100–200 mesh size) to give the desired hybrid **15** in 68% yield. Similarly, compounds **16–18** were obtained starting from compounds **12–14.**

2.1.4 General procedure for the synthesis of compounds 19. Compound 2′-(furan-2-yl)-1-((1-(2-(2′-(furan-2-yl)-5-methyl-1′-nitro-2-oxo-1′,2′,5′,6′,7′,7*a*′-hexahydrospiro[indoline-3,3′-pyrrolizin]-1-yl)ethyl)-1*H*-1,2,3-triazol-5-yl)methyl)-1′-nitro-

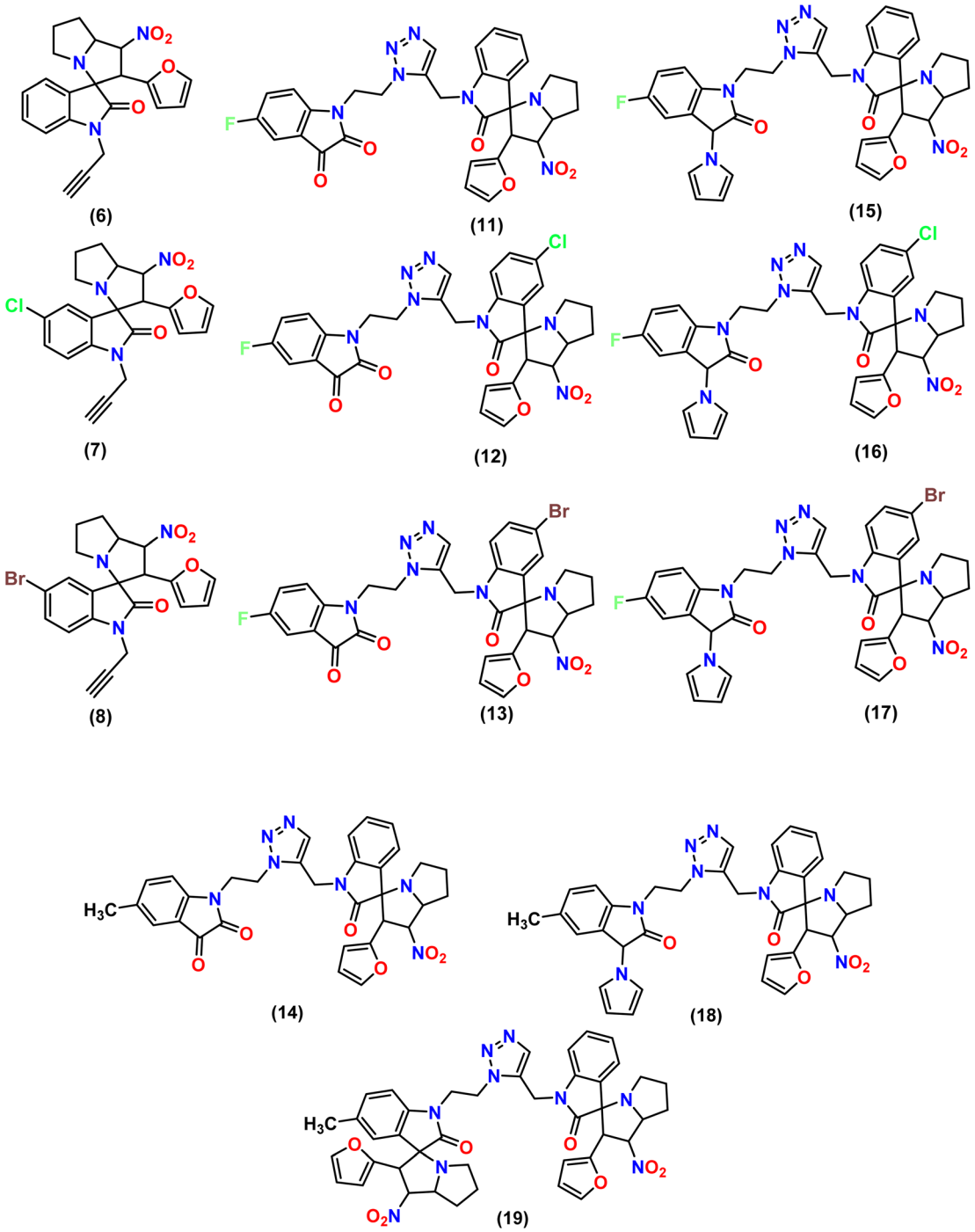


Fig. 5 Structures of newer synthesised spiroindoline derivatives **6–8** & **11–19**.

1′,2′,5′,6′,7′,7*a*′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**19**) was obtained by three-component condensation of compound **14** (1 mmol), proline (**4**) (1 mmol) and (*E*)-2-(2-nitrovinyl)furan (**5**) (1 mmol) in methanol under reflux condition for 2 h. The compound was separated *via* silica gel chromatography (100–200 mesh size) by using hexane and ethyl acetate (20 : 80) as a solvent system to give a desired 70% yield, a higher proportion of hexane and ethyl acetate (20 : 80) was used for purification of compound **19** due to its higher polarity, resulting from multiple nitro and triazole functionalities, which caused poor elution with less polar solvent system used for compound **6–8** (Scheme 1 and Fig. 5).

2.2 Molecular docking studies

The binding-energy parameters for the protein and ligand molecules are calculated in the current work using AutoDock Vina, using pdbqt files of the compounds. The semi-empirical approach is used by the AutoDock Vina software. Each

synthesised compound's binding-energy values were determined against the active site of the target protein, taken into consideration for the investigation. In order to create schematic diagrams of the interactions between protein–ligand complexes, the graphical programme Ligplot+ was utilised. Molecular visualizations and 3D interaction diagrams were generated using BIOVIA Discovery Studio Visualizer.

3. Result and discussion

3.1 Chemistry

The methodology used for the synthesis of novel indoline-based hybrids **6–19** was established through a sequential multistep approach. Alkyne derivatives of spirooxinole cores **6–8** were synthesised *via* a three-component reaction using alkyne-functionalized isatin derivative **1–3**, proline (**4**), and (*E*)-2-(2-nitrovinyl)furan (**5**) as the precursor in methanol. These spirooxindoles were then tethered with azide-functionalised isatin **9–10** *via* Cu-catalysed 1,3-dipolar cycloaddition click reaction, leading to triazole tethered indoline scaffolds **11–14**. Further, these compounds were reacted with L-hydroxyproline in the presence of a Lewis acid in ethanol, yielding respective hydroxproline tethered hybrids **15–18**. A one-pot multicomponent reaction involving compound **14** with proline (**4**) and (*E*)-2-(2-nitrovinyl)furan (**5**) in methanol gave compound **19** in good yield. The structure of all the synthesised compounds was confirmed by standard spectroscopic techniques, including Fourier-transform infrared (FT-IR), Nuclear Magnetic Resonance (^{1}H NMR and ^{13}C NMR), and High-Resolution Mass Spectrometry (HRMS).

In the ^{1}H NMR spectra of synthesised triazole appended indoline scaffold, a characteristic peak at δ 7.78–δ 7.85 as a sharp singlet signifying the presence of the triazole ring proton. Another significant singlet between δ 5.83–δ 5.95 ppm corresponds to 1 proton of H–C (tertiary) at the C-3 position of the isatin ring substituted with a pyrrole moiety. The methylene proton of the pyrrolizine ring appeared as a triplet at δ 2.56–δ 2.59 ppm. The ^{13}C spectra of this compound confirm the presence of a characteristic peak of amide carbonyl (C=O) group at δ 173.90–174.82 ppm, and the peaks appearing at δ 24.50–25.68 ppm attribute to methylene carbons of the pyrrolizine ring. These characteristic peaks confirm the successful formation of triazole tethered indoline–pyrrolizine scaffolds. Additionally, the high-resolution mass spectrometry (HRMS) data of all synthesised compounds showed $(M + H)^+$ peak satisfying the observed mass; compound **14** displayed an $(M + H)^+$ ion at 741.15, validating the calculated mass of 741.15.

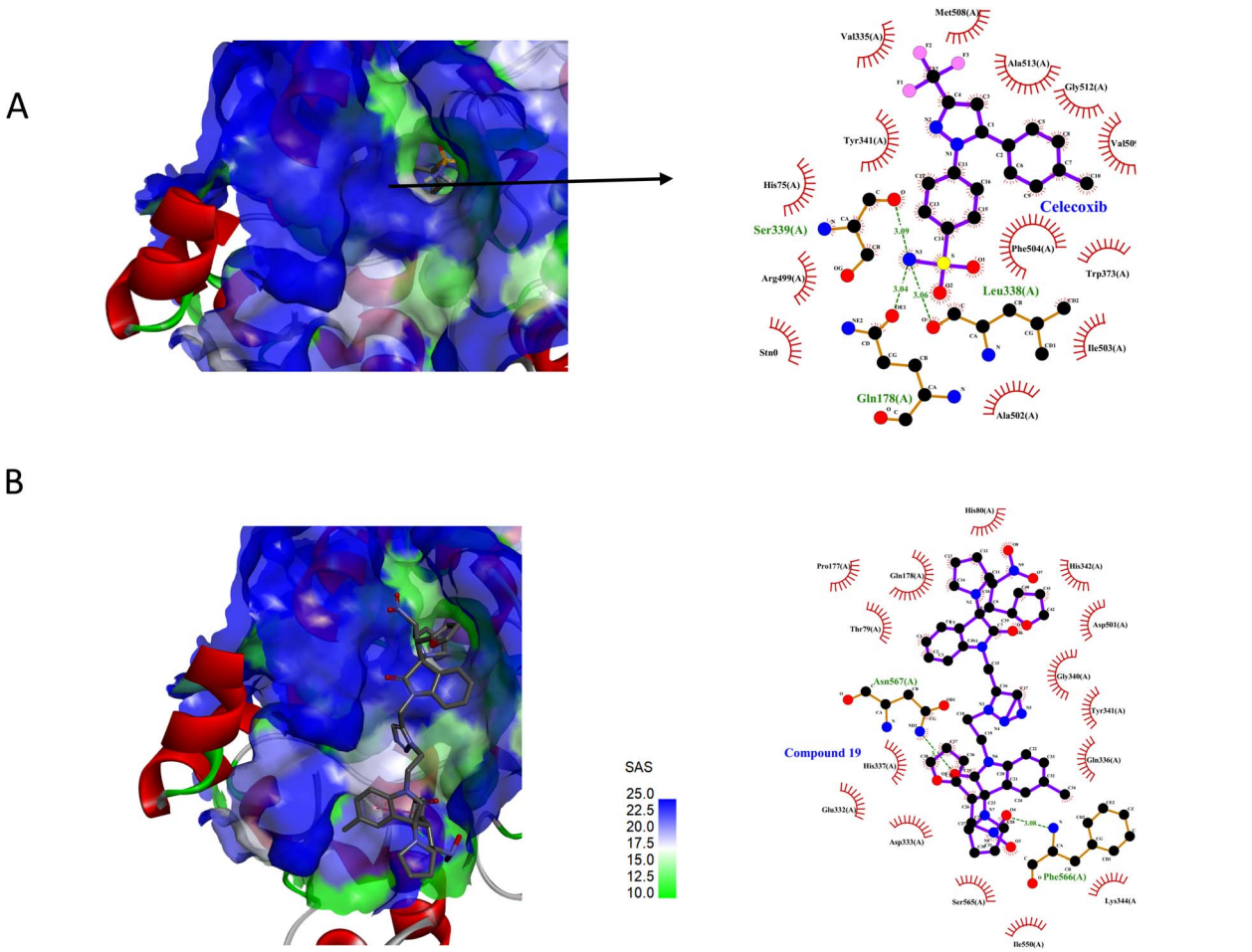


Fig. 6 3D and 2D images of (A) celecoxib and (B) compound **19** with the target protein cyclooxygenase (COX-2).

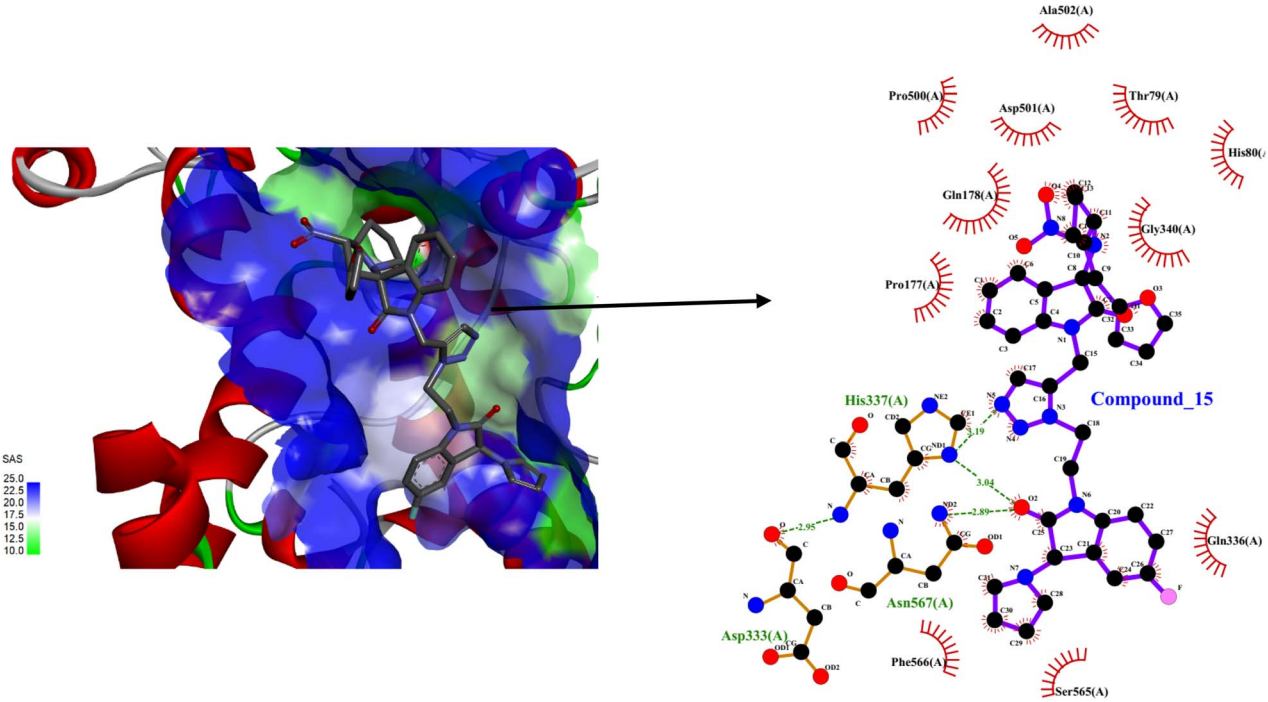


Fig. 7 3D and 2D images of compound **15** with target protein cyclooxygenase (COX-2).

3.2 Molecular docking evaluation

Molecular docking studies of all the synthesised spiro-heterocycles **6–19** were carried out to evaluate the interactions of the compounds with the active sites of the enzymes. The amino acids present in cyclooxygenase (COX-2),[36] an activated enzyme that catalyses the conversion of arachidonic acid to pro-inflammatory prostaglandins,[37] were examined to analyse their particular binding patterns (PDB ID: 3LN1).[38] High negative values of binding energy indicate that these compounds could interact more strongly with the target protein. The binding interactions of compounds with the targeted enzyme are shown in Fig. 6 and 7. The majority of the compounds displayed hydrogen bonding and hydrophobic interactions (Table 1). All the synthesised compounds have shown good binding affinity towards the targeted enzyme. Compounds **19** and **15** displayed the highest binding affinity, −10.3 kcal mol^{-1}, among all the synthesised compounds (Table 1). The oxygen atom present in the nitro group of hybrid **19** is involved in hydrogen bonding with the amino acid residue Phe566 (A). The oxygen atom of the (C-2) carbonyl group present in isatin is also showing a hydrogen bonding interaction with Asn567 (A). Celcoxib forms hydrogen bonds within the canonical COX-2 active pocket while compound **19** shows interaction with the residues in a spatially separate cavity close to the binding cavity of celecoxib. Despite occupying different binding sites, the similar docking energies (celecoxib = −12.4 kcal mol^{-1}; compound **19** = −10.2 kcal mol^{-1}) indicate that both complexes achieve an energetically stable binding mode. Furthermore, various

Table 1 Information on docking score against target protein (3LN1) and amino acid residues involved in hydrogen bonding

Ligand	Binding energy with protein 3LN1	Amino acid residues involved in hydrogen bonding
6	−7.1	No H-bonding
7	−6.8	His337(A), Ser565(A), Asn567(A)
8	−6.9	His337(A), Ser565(A), Asn567(A)
11	−9.2	His337(A)
12	−9.2	His337(A)
13	−9.3	His337(A), Ser565(A), Asn567(A)
14	−9.3	His337(A), Ser565(A), Asn567(A)
15	−9.8	Asp333(A), Asn567(A), His337(A)
16	−9.2	His337(A)
17	−9.4	Gln336(A)
18	−9.5	Gln178(A), His337(A), Ser565(A), Asn567(A)
19	−10.2	Phe566(A), Asn567(A)
Celecoxib	−12.4	Gln178(A), Leu338(A), Ser339(A)

appropriate hydrophobic interactions also exist between the ligand and the target proteins.

4. Conclusion

In view of diverse biological applications of the spirooxindole framework, a green, multicomponent reaction was employed to design and synthesise a series of novel spiro[indoline-3,3′-pyrrolizin]-2-one derivatives. The distinguishing features of this procedure are partly catalyst-free reaction conditions, good yields and operational simplicity. Furthermore, molecular docking studies of all the synthesised ligands **6–19** were carried out to examine the interactions of the compounds with the active sites of the enzymes COX-2, a key enzyme in inflammatory pathways, revealed consistently strong binding affinity towards the targeted enzyme, and compound **19** displayed the highest binding affinity, −10.2 kcal mol^{-1}, among all the synthesised compounds. Synergistic structural features, such as a fused spiro core, triazole linkage, and isatin moiety, contributed to enhancing the binding affinity. Collectively, these studies reveal that the synthesised molecule, particularly compound **19**, shows docking affinity for anti-inflammatory properties similar to standard drug celecoxib & further modification in the target molecule could provide a strong foundation for *in vitro* validation. Prospective studies will focus on the experimental validation of *in silico* studies through the *in vitro* COX-2 inhibition assays, anti-inflammatory screening on cell lines and cytotoxicity evaluation to check the safety and selectivity. The promising docking result of compound **19** lays a strong foundation for further biological assessment.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

All the data supporting the findings of this study have been fully incorporated into the supplementary information file (SI) provided along with the submission. Supplementary information is available. See DOI: **https://doi.org/10.1039/d5ra07175e**.

Acknowledgements

R. K. U. is thankful to the Council of Scientific and Industrial Research (CSIR) for the financial assistance as Senior Research Fellowship. All the authors acknowledge the Institute of Eminence (IoE), Department of Chemistry, University of Delhi, University Science Instrumentation Centre (USIC), and Council of Scientific and Industrial Research (CSIR), for providing research and characterisation facilities.

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