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Article

Construction of Spirooxindole Analogues Engrafted with Indole and Pyrazole Scaffolds as Acetylcholinesterase Inhibitors

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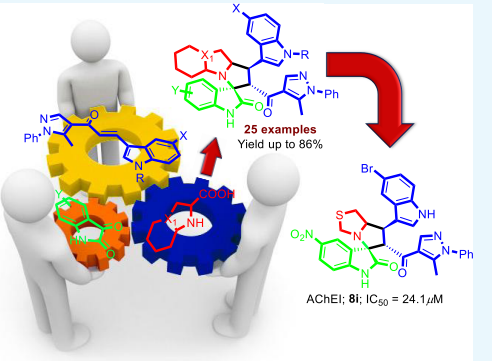
ABSTRACT: Twenty-five new hits of spirooxindole analogs **8a−y** engrafted with indole and pyrazole scaffolds were designed and constructed *via* a [3+2]-cycloaddition (32CA) reaction starting from three components: new chalcone-based indole and pyrazole scaffolds **5a−d**, substituted isatins **6a−c**, and secondary amines **7a−d**. The potency of the compounds were assessed in modulating cholinesterase (AChE) activity using Ellman's method. Compounds **8i** and **8y** showed the strongest acetylcholine esterase inhibition (AChEI) with IC_{50} values of 24.1 and 27.8 μM, respectively. Molecular docking was used to study their interaction with the active site of hAChE.



■ INTRODUCTION

Neurodegeneration is a key aspect of a large number of diseases that come under the umbrella of neurodegenerative disease. Of these different disorders, the most notable are Parkinson's disease, Huntington's disease, and Alzheimer's disease (AD). Alzheimer's disease (AD) symptoms are memory loss, impairment of cognitive functions, and dementia. AD involves two major neuropathological hallmarks causing neuronal dysfunctions and cell death: the presence of extracellular amyloid β-peptide (Aβ) deposits (senile plaques) and aggregates of the hyperphosphorylated tau protein (neurofibrillary tangles)[1] along with the tau hyperphosphorylation are the most proposed pathogenetic mechanisms,[2] and mitochondrial cascade hypothesis has attracted much interest recently.[3] Other much debatable AD hypotheses are the tau hypothesis,[4] cholesterol hypothesis,[5] inflammatory hypothesis,[6] oxidative stress hypothesis,[7] metal hypothesis,[8] vascular hypothesis,[9] and cell cycle hypothesis.[10] Up to date, rivastigmine, galantamine, and donepezil represent the only ChE inhibitors approved for AD treatment, differing in chemical structures and pharmacologic and pharmacokinetic profiles. To design and discover a new agent that might work as ChE inhibitors is a challenge.

Heterocycles having azoles as a core structure have been discovered for several applications.[11] Pyrazoles are one of the important heterocycles, which exhibited significant properties in material sciences,[12] agriculture development,[13] medicine,[14] and pharmacological applications.[15] Among pharmacological applications are antibiotic,[16] sensors,[17] pesticide,[18] antibacterial,[19] and antifungal activities.[20] On the other hand, several molecules engrafted with the pyrazole scaffold have shown high efficacy toward antiviral,[21] antitumor,[22] anti-inflammatory,[23] antioxidant,[24] and antidepressant activities.[25] Indeed, many drugs incorporated the pyrazole moiety employed for the treatment of metabolic disorder diseases such as Alzheimer's,[26] Parkinson's,[27] and neuroprotective,[28] which makes this pharmacophore very attractive for drug discovery. One representative example of advanced glycation inhibitors reported by Han et al. is that this agent is based on the pyrazole-5-carboxamide as a core structure.[29] However, Turkan et al. have reported substituted pyrazole derivatives, which have been discovered as potent cholinesterase inhibitors.[30]

Spirooxindoles exhibit a broad range of biological effects and are well-tolerated in biomedical applications.[31] Their applications use AChEs.[32] Kia et al. reported representative examples, including spirooxindoles engrafted with piperidine and pyrrolizine scaffolds, which are found to be beneficial for AChE (compound **III**; IC_{50} = 3.36 μM or 2.28 ± 0.07 μg/mL) (Figure 1),[32d] and another representative example based on mono- and *bis*-spiro-pyrrolidines, where the hit **IV** shows high efficacy against AChE with an IC_{50} value of 2.35 μM (Figure 1).[32f] Chigurupati et al. reported indolopyrazolines with the

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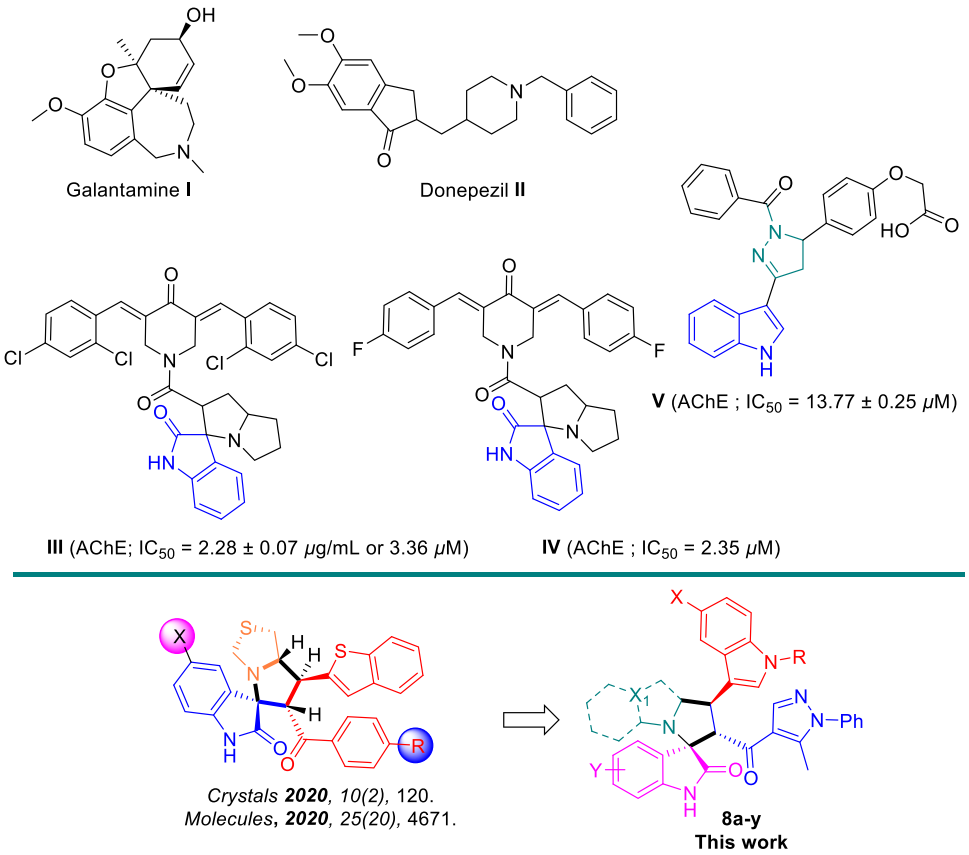
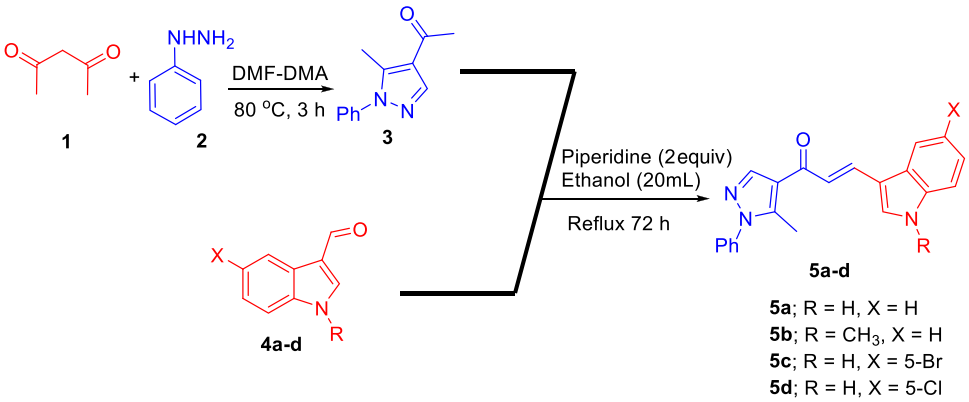


Figure 1. Significant acetylcholinesterase (AChE) inhibitory activity of representative spirooxindole analogues.

Scheme 1. Synthesis of the Chalcone Engrafted with Indole and Pyrazole Scaffolds 5a−d



high biochemical application against AChE inhibition (**V**; IC_{50} = 13.77 ± 0.25 lM), respectively.[33] Extending our recent efforts on the development of cholinesterase inhibition, Barakat et al. reported a new series of spirooxindoles engrafted with the benzo[*b*]thiophene scaffold, which were found to exhibit moderate potential against AD (Figure 1).[32h,34] The above reports inspired the investigation of several pharmacophores inside the rigid spirooxindole privileged structure, such as indole and pyrazole scaffolds, which might act as better AChE inhibitors.

Several progresses have been devoted toward the synthesis of spirooxindoles recently.[35] In between these approaches, the [3 + 2] cycloaddition reaction protocol was efficient and promising to afford the spirooxindole privileged structures with several stereogenic centers.[36]

In this paper, we described the [3 + 2] cycloaddition reaction approach for the synthesis of new spirooxindoles based on a new chalcone engrafted with indole and pyrazole motifs. Many substituted isatins and amino acids were also investigated. The biochemical potential of AChE was also studied.

■ RESULTS AND DISCUSSION

Synthesis of Spirooxindole Analogs 8a−y Engrafted with Indole and Pyrazole Scaffolds. The indole and pyrazole scaffolds as interesting pharmacophores are combined into the spirooxindole analogs for exploring the acetylcholinesterase (AChE) inhibitory activity. Initially, we synthesized the new chalcones **5a−d** by aldol condensation of acetylpyrazole and substituted indole-3-carbaldehyde in basic

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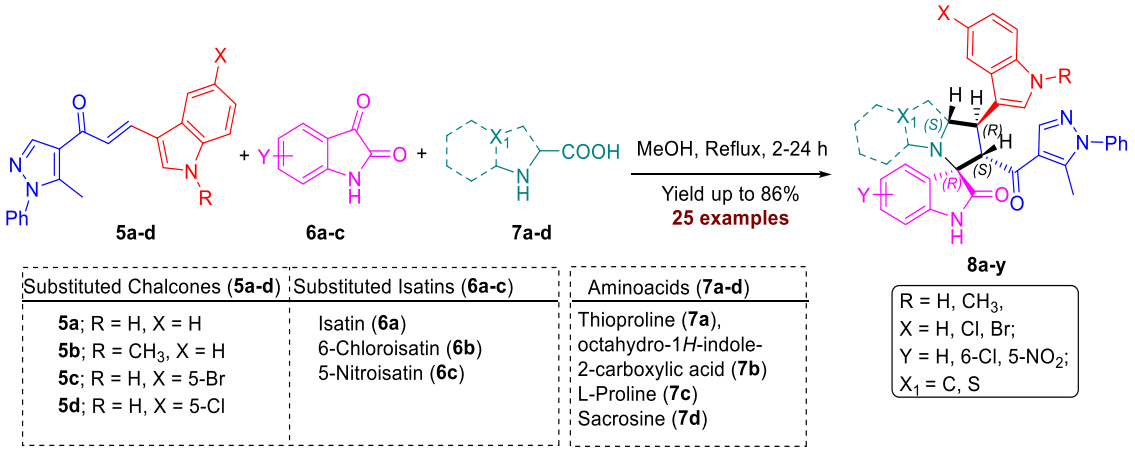
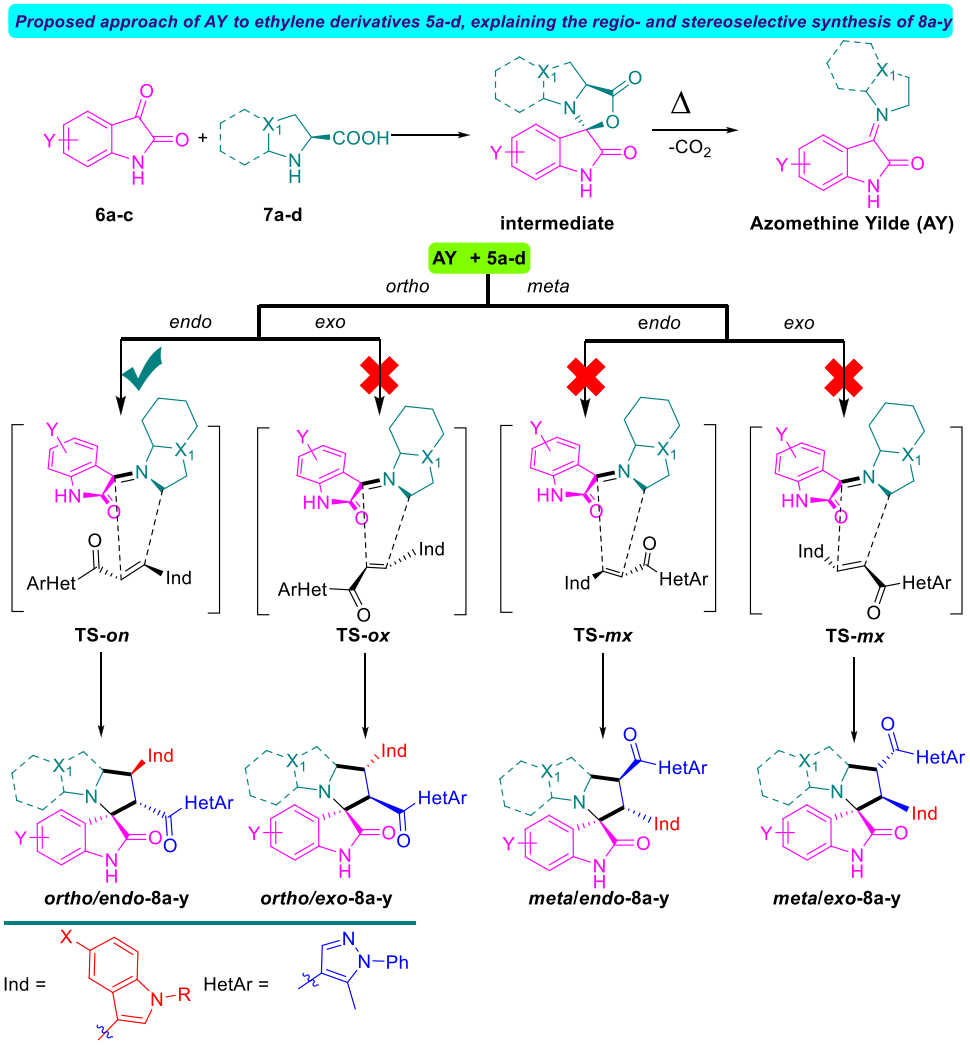
Scheme 2. Synthesis of the Spirooxindole Analogues Engrafted with Indole and Pyrazole Scaffolds 8a−y



Scheme 3. Proposed Approach for the [3 + 2] Cycloaddition Reaction, Explaining the Regio- and Diastereoselective Synthesis



condition under reflux for 72 h. The new chalcone-based indole and pyrazole scaffolds, which act as a synthon for the [3 + 2] cycloaddition (32CA) reaction, are depicted in Scheme 1. Subsequently, the new series of spirooxindole analogues tethered indole and pyrazole scaffolds were constructed *via* a one-pot multicomponent reaction approach[37] in MeOH under reflux conditions for 2−24 h (Scheme 2). Twenty-five examples were achieved by variation of many substituted isatins **6a−c** with different electronic effects (isatin **6a**; 6-chloroisatin **6b**; 5-nitroisatin **6c**) with four different amino acids **7a−d** (thioproline **7a**, octahydro-1*H*-indole-2-carboxylic acid **7b**; L-proline **7c**; sacrosine **7d**). The spirooxindole analogues engrafted with indole and pyrazole scaffolds were isolated in a single regio- and diastereoselective isomer in

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acceptable to excellent chemical yield up to 86%. The proposed mechanism, as shown in Scheme 3, proceeded *via* an *ortho/endo* 32CA approach.[38] The optical rotation of the synthesized compounds was measured, and the regio- and diastereoselectivity of the cycloadducts were confirmed. Single-crystal X-ray diffraction analysis of compound **8c** confirmed that our hypothesis belongs to the final stereoselectivity of the cycloadducts of the final compounds. The absolute configurations of products **8a−y** were assigned based on the obtained x-ray diffraction analysis as follows for the 4 stereogenic centers as *R*, *S*, *R*, *S*.

Crystal Structure Description. The X-ray structure of **8c** showing atom numbering and thermal ellipsoids drawn at a 30% probability level is shown in Figure 2. The structure

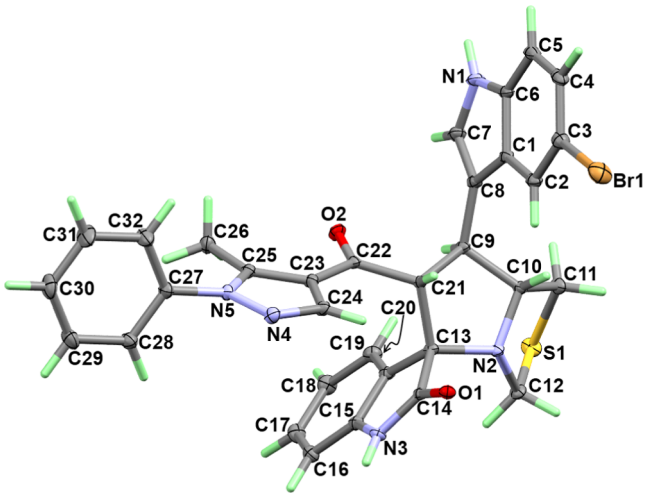

Figure 2. Atom numbering and thermal ellipsoids at a 30% probability level for **8c**.

agreed very well with the spectral analyses and revealed the presence of asymmetric centers at C9, C21, C10, and C13. The crystal data and structure refinement details are depicted in Table 1. The compound crystallized in the triclinic system and the $P\bar{1}$ space group with unit cell parameters of a = 12.71740(10) Å, b = 15.72830(10) Å, c = 19.3853(2) Å, and β = 105.9640(10)°. The unit cell volume is 3727.97(6) Å^3 with Z = 4. The asymmetric unit comprised one molecule and two chloroform molecules as the crystal solvent. The selected bond distances and angles are listed in Table S1 (Supporting Information).

The molecular packing in **8c** is controlled by strong N−H...O and N−H...N hydrogen bonds as well as weak C−−H...X interactions (X═Cl, Br, N, or O). The corresponding hydrogen bond parameters are listed in Table S2 (Supporting Information) and are shown in the left part of Figure 3. The hydrogen bond network is shown in the right part of the same figure.

Acetylcholine Esterase Inhibitory Activity. The ability of the synthesized compounds to inhibit acetylcholine esterase (AChE) was evaluated using Ellman's method.[39] Compounds **8i** and **8y** showed the strongest acetylcholine esterase inhibition (AChEI) with IC_{50} values of 24.1 and 27.8 μM, respectively.

Four Compounds; **8c**, **8d**, **8f**, **8h**, **8j**, **8w**, and **8x** showed moderate activity inhibitory activity (with $IC_{50} \leq 50$ μM). Compounds **8m**, **8o**, **8p**, **8q**, and **8s** had weak activity (with

Table 1. Crystal Data

	8c
CCDC	2105913
empirical formula	$C_{34}H_{28}BrCl_6N_5O_2S$
fw	863.28
temp (K)	120(2)
λ (Å)	1.54184
cryst syst	monoclinic
space group	$P21/n$
a (Å)	12.71740(10)
b (Å)	15.72830(10)
c (Å)	19.3853(2)
β (deg)	105.9640(10)
V (Å^3)	3727.97(6)
Z	4
ρ_{calc} (Mg/m^3)	1.538
μ (Mo Kα) (mm^{-1})	6.305
no. reflns.	38891
unique reflns.	7824
completeness to θ = 67.684°	100.0%
GOOF (F^2)	1.024
R_{int}	0.0352
R_1[a] ($I \geq 2\sigma$)	0.0354
wR_2[b] ($I \geq 2\sigma$)	0.0861

[a]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b]$wR_2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

IC_{50} values 65−90 μM), while compounds **8b**, **8e**, **8q**, **8k**, **8e**, **9r**, **8r**, **8t**, **8u**, and **8v** were in active with IC_{50} > 100 μM (Table 2).

Molecular Docking Study. Molecular docking has been used extensively to identify and explain the molecular mechanism of several lead compounds in drug discovery.[40] The software validation revealed that it was able to reproduce the experimental pose with root-mean-square deviation (RMSD) equal to 0.39 (Figure 4). Since *in vitro* enzyme inhibition showed that compounds **8i**, **8h**, and **8y** are the most active among the synthesized compounds with moderate inhibition activity, we used molecular docking to gain insights into the molecular interaction of the compound with the active site of hACHE.

In the context of the total energy required for binding, the cocrystallized ligand achieved much better binding affinity than the 3 compounds, yet their binding energy was found to be reasonable with respect to their moderate activity in the enzyme inhibition assay, as presented in Table 3. Post docking analysis showed that compound **8i** has different binding modes rather than compounds **8h** and **8y**, as the first one tends to bind in the middle of the gorge of hACHE. On the other hand, compounds **8h** and **8y** showed most of their interactions with amino acids located at the entrance of the gorge. For example, compound **8i** was able to interact with amino acids in diverse sites in the enzyme such as TRP-86 and TYR-337 in the anionic site, Ser-203 and HIS-447 in the catalytic site, PHE-295 and PHE-297 in the acyl binding site, and formed 2 hydrogen bonds with SER-125 and GLU-202, as depicted in Figure 5, these interactions are well reported to be important for achieving good inhibitory activity.[41]

On the other hand, compound **8y** showed interactions only with TYR-337 and PHE-295 from the anionic and acyl binding sites, respectively, but with less hydrophobic interaction than **8i**. Nevertheless, they were able to access the peripheral anionic site by interacting with amino acids, such as TYR-124,

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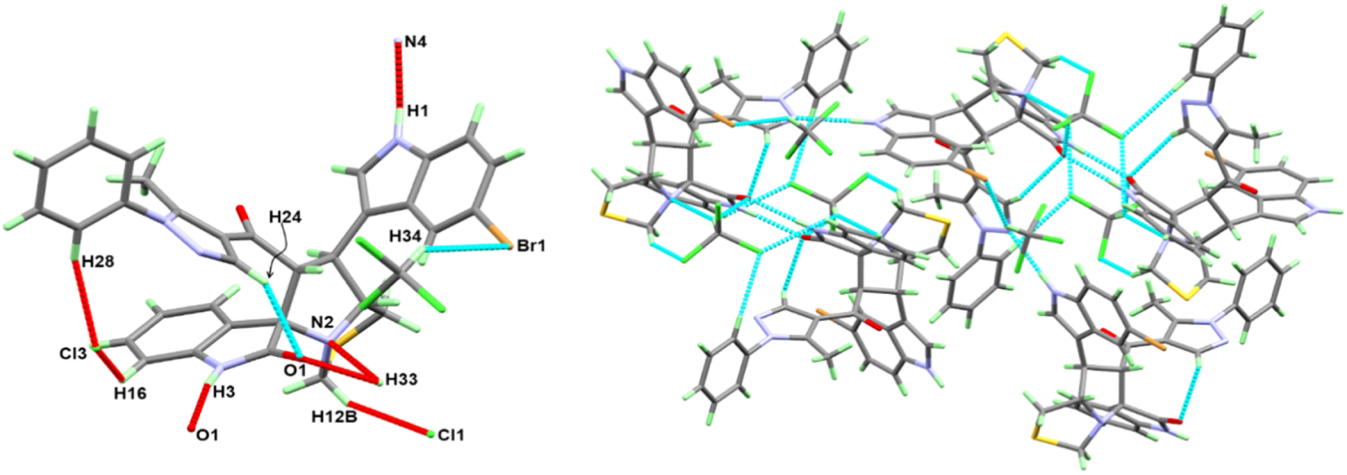

Figure 3. Hydrogen bond contacts (left) and packing of molecular units *via* hydrogen bonding interactions (right).

TRY-341, and TRP-286, as shown in Figures 6 and 7, which might explain their ability to achieve the moderate inhibitory effect as observed in the enzyme inhibition assay.

■ CONCLUSIONS

We summarized in this paper that we had synthesized 25 hits based on a spirooxindole scaffold engrafted with two other pharmacophores, including indole and pyrazole moieties. The results of the AChE assay show that compounds **8i** and **8y** show the strongest acetylcholine esterase inhibition (AChEI) with IC_{50} values of 24.1 and 27.8 μM, respectively. The AChE activity exhibited promising results, which make them candidates for further research.

■ EXPERIMENTAL SECTION

General information. Phenylhydrazine, acetylacetone, *N*,*N*-dimethylformamide-dimethyl acetal (DMF-DMA), Piperidine, and NaOH were purchased from Aldrich and used as received. All of the indole derivatives were purchased from Aldrich and used as is. All bases were used as received (in air) or dried under vacuum at 100 °C (under an inert atmosphere). All solvents were used as received when experiments were conducted in air. Flash chromatography was performed on 100−200 mesh silica gel. ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectra were recorded on JEOL-700 MHz spectrometers at ambient temperature in $CDCl_3$ & DMSO-d_6, which were purchased from Sigma-Aldrich. Chemical shifts (ppm) are referenced to the residual solvent peak. Coupling constants, *J*, are given in hertz. Abbreviations used in the designation of the signals: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, and m = multiplet. All melting points were measured on a Gallenkamp melting point apparatus in open glass capillaries and are uncorrected. IR Spectra were measured as KBr pellets on a Nicolet 6700 FT-IR spectrophotometer. Specific rotations were recorded in 'A KRÜSS Optronic GmbH P8000 polarimeter.

*Synthesis of 1-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)-ethanone (**3**).* *N*,*N*-Dimethylformamide-dimethyl acetal (DMF-DMA) (17.85 g, 0.15 mol) was added to acetylacetone **1** (0.1 mol) and stirred for 10 min at ambient temperature, followed by the addition of phenylhydrazine derivative **2** (0.1 mol), and the reaction mixture was heated at 70−80 °C for 24 h. The completion of the reaction was monitored by thin-layer chromatography (TLC) (20% EA/*n*-hexane). The reaction mixture was then allowed to cool and kept in a fridge for 24 h and a white solid precipitated out, which was isolated by simple filtration and washed with diethyl ether to afford pure white product **3** (5 g, 25 mmol, 25% yield). The MLs part was concentrated and purified using a column to afford another 6 g of pure white product **3** (30 mmol, 30%). The overall yield of acetyl-pyrazole-**3** (11.0 g, 55%).[42]

m.p.: 88−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.99 (s, 1H, pyrazole-H), 7.52−7.46 (m, 2H, Ar-H), 7.44 (d, *J* = 6.8 Hz, 1H, Ar-H), 7.41−7.36 (m, 2H, Ar-H), 2.56 (s, 3H, $COCH_3$), 2.47 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 193.56 (CO), 143.05, 141.97, 138.58, 129.36, 128.89, 125.61, 121.16, 28.75 ($COCH_3$), 12.44 (CH_3); IR (KBr, cm^{-1}): 3060, 3001, 1660, 1597, 1545, 1502, 1457, 1399, 1382, 1363, 1276, 1238, 1196, 1171, 1011, 937, 884, 866, 769, 718, 690, 662, 637, 558; [anal. calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99; found: C, 72.07; H, 6.01; N, 13.94]; LC/MS (ESI, *m*/*z*): found 201 $[M + H]^+$; exact mass 200.09 for $C_{12}H_{12}N_2O$. All of the analytical data are in accordance with the reported literature.[42]

*Synthesis of Chalcones (**5a−d**) from Acetyl-pyrazole (**3**) and Substituted Indole-3-Carboxyaldehyde (**4a−d**) (**GP1**).* Compound **3** (1 g, 5 mmol) and substituted indole-3-carboxyaldehyde **4a−d** (5 mmol) were dissolved in ethanol (20 mL) in a 100 mL round bottom flask. Piperidine (950 mg, 2 equiv) was added to the reaction mixture and refluxed at 80 °C 48−72 h. The completion of the reaction was monitored by TLC (30% EA/*n*-hexane). Then, the solid precipitated out, which was isolated by simple filtration and washed with ethanol to afford pure white/yellow product **5a−d** (70−80% yield).

*Synthesis of (E)-3-(1H-Indol-3-yl)-1-(5-methyl-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one (**5a**).* Following the general procedure (GP1), acetyl-pyrazole **3** (1.0 g, 5.0 mmol) and indole-3-carboxyaldehyde **4a** (0.87 g, 6.0 mmol) produce pyrazolenone-**5a** (yield 0.9 g, 55%); m.p.: 222−224; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = δ 11.85 (s, 1H, NH), 8.59 (s, 1H, Ar-H), 8.17−8.11 (m, 1H, Ar-H), 8.08 (s, 1H, Ar-H), 8.00 (d, *J* = 15.4 Hz, 1H, CH═CH), 7.58 (d, *J* = 4.3 Hz, 4H, Ar-H), 7.54−7.41 (m, 3H, Ar-H & CH═CH), 7.29−7.17 (m, 2H, Ar-H), 2.62 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = δ 184.19 (CO), 142.69, 141.53, 138.53, 137.47,

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Table 2. AChE Inhibitory Activity of the Synthesized Spirooxindole Analogues Engrafted with Indole and Pyrazole Scaffolds 8a−y

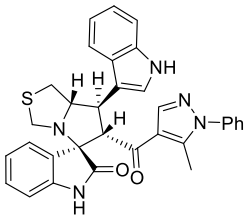
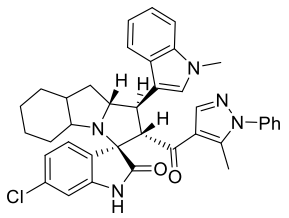
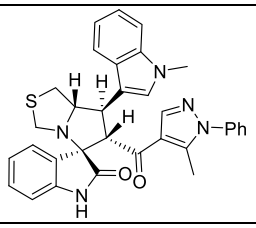
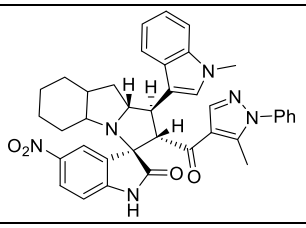
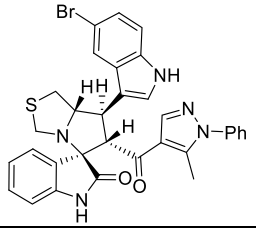
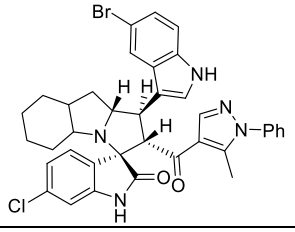
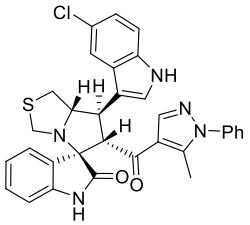
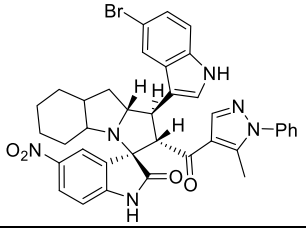
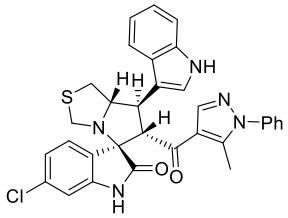
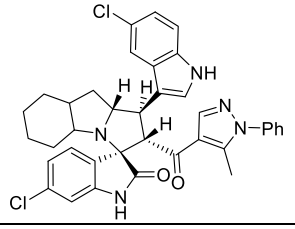
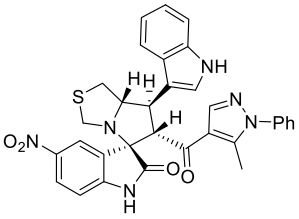
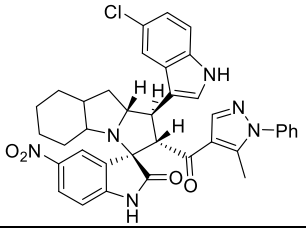
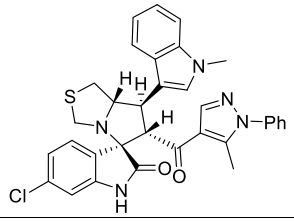
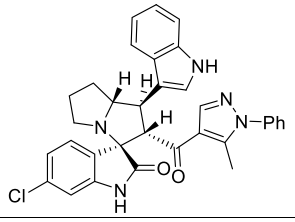
#	Chemical Structure	IC_{50} (μM)	#	Chemical Structure	IC_{50} (μM)
8a		57.1	**8n**		>100
8b		>100	**8o**		75.9
8c		41.2	**8p**		78.4
8d		36.5	**8q**		91.2
8e		>100	**8r**		>100
8f		33.4	**8s**		65.5
8g		>100	**8t**		>100

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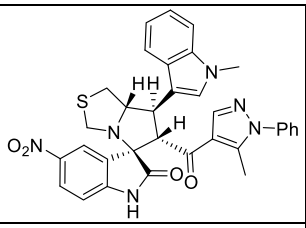
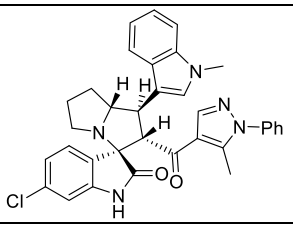
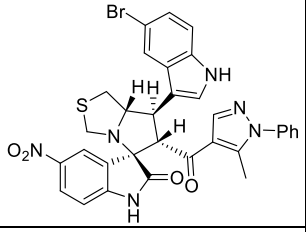
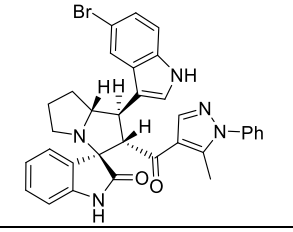
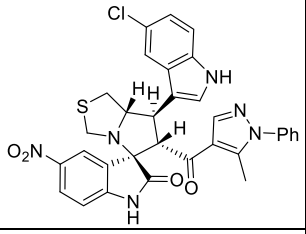
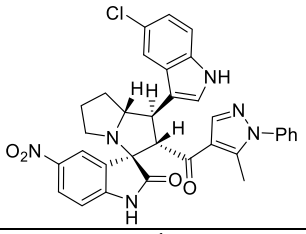
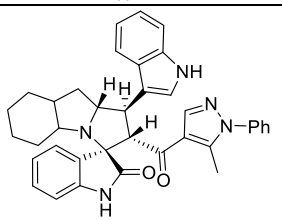
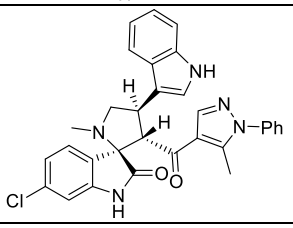
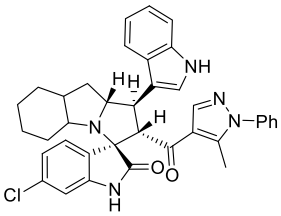
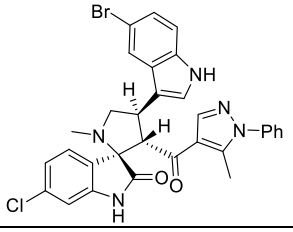
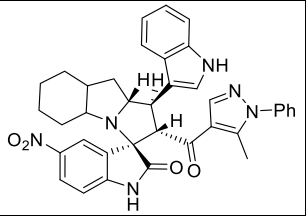
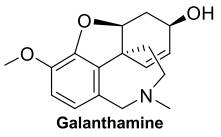
Table 2. continued

8h		31.3	**8u**		>100
8i		24.1	**8v**		>100
8j		36.8	**8w**		47.7
8k		>100	**8x**		39.5
8l		>100	**8y**		27.8
8m		80.3	STD	 Galanthamine	1.2

136.61, 132.48, 129.30, 128.56, 125.41, 125.20, 122.58, 121.61, 121.00, 120.51, 118.15, 112.55, 112.33, 12.20 ($\underline{C}H_3$); IR (KBr, cm^{-1}) ν_{max} = 3158, 3106, 3047, 2877, 1649, 1638, 1581, 1521, 1502, 1453, 1384, 1347, 1279, 1255, 1229, 1217, 1190, 1140, 1115, 1072, 1064, 1036, 1034, 1004, 974, 945, 893, 879, 852, 834, 762, 734, 714, 696, 656, 641, 603, 593, 558, 507; LC/MS (ESI, m/z): 328.2 $[M + H]^+$, exact mass 327.14 for $C_{21}H_{17}N_3O$.

*Synthesis of (E)-1-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)-3-(1-methyl-1H-indol-3-yl)prop-2-en-1-one (**5b**).* Following the general procedure (GP1), acetyl-pyrazole **3** (1.0 g, 5.0 mmol) and indole-1-methyl-3-carboxyaldehyde **4b** (0.95 g, 6.0 mmol) produce pyrazolenone-**5b** (yield 1.0 g, 56%); m.p.: 182−183; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = δ 8.58 (s, 1H, Ar-$\underline{H}$), 8.15 (d, J = 7.8 Hz, 1H, Ar-$\underline{H}$), 8.04 (s, 1H, Ar-$\underline{H}$), 7.95 (d, J = 15.5 Hz, 1H, C$\underline{H}$═CH), 7.58 (d, J = 4.4 Hz, 3H, Ar-$\underline{H}$), 7.57−7.49 (m, 3H, Ar-$\underline{H}$), 7.46 (d, J = 15.5 Hz, 1H, CH═C$\underline{H}$), 7.33−7.25 (m, 2H, Ar-$\underline{H}$), 3.85 (s, 3H, C$\underline{H}_3$), 2.62 (s, 3H, C$\underline{H}_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = δ 184.09 ($\underline{C}$O), 142.71, 141.53, 141.49, 138.51, 137.93, 135.98, 135.89, 129.30, 128.56, 125.63, 125.40, 122.66, 121.59, 121.26, 120.67, 120.61, 118.17, 118.10, 111.56, 110.75, 110.66, 32.97 ($\underline{C}H_3$), 12.15 ($\underline{C}H_3$); IR (KBr, cm^{-1}) ν_{max} = 3108, 3045, 1643, 1569, 1524, 1501, 1472, 1464, 1386, 1373, 1341, 1281, 1259, 1219, 1187, 1178, 1157, 1132, 1075, 1039, 1003, 937, 855, 841, 821, 771, 751, 699, 681, 654, 540; LC/MS (ESI, m/z): found 342.2 $[M + H]^+$, exact mass 341.15 for $C_{22}H_{19}N_3O$.

*Synthesis of (E)-3-(5-Bromo-1H-indol-3-yl)-1-(5-methyl-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one (**5c**).* Following the general procedure (GP1), acetyl-pyrazole **3** (1.0 g, 5.0 mmol)

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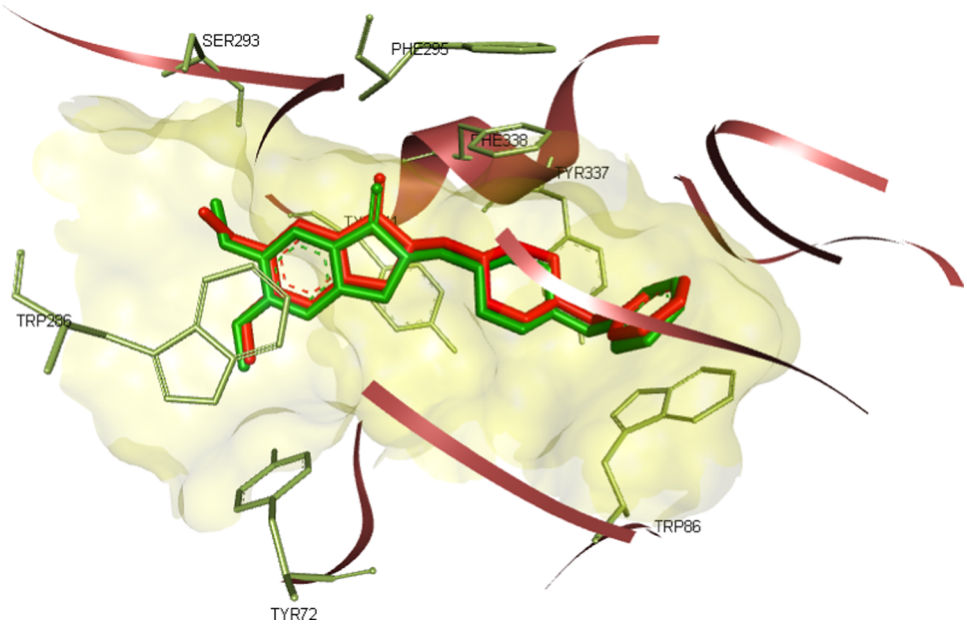

Figure 4. Donepezil (Red) docked in the active site of ACHE (4EY7) and overlaid with cocrystallized ligand (Green) RMSD = 0.39.

Table 3. Binding Energy of Compound Docked in the Binding Site of the hACHE Active Site[a]

	compound	total energy	VDW	H-bond
1.	**8i**	−127.335	−121.335	−6
2.	**8y**	−126.589	−118.253	−8.336
3.	**8h**	−123.962	−118.983	−4.979
4.	cocrystallized ligand	−149.55	−139.4	−10.15

[a]VDW = Van der Waals force and H-Bond = Hydrogen bond.

and 5-bromoindole-3-carboxyaldehyde **4c** (1.34 g, 6.0 mmol) produce pyrazolenone-**5c** (yield 0.85 g, 42%); m.p.: 214−215; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = δ 12.02 (s, 1H, N<u>H</u>), 8.63 (s, 1H, Ar-<u>H</u>), 8.26 (d, J = 1.9 Hz, 1H, Ar-<u>H</u>), 8.14 (s, 1H, Ar-<u>H</u>), 7.95 (d, J = 15.5 Hz, 1H, C<u>H</u>═CH), 7.60−7.55 (m, 4H, Ar-<u>H</u> + CH═C<u>H</u>), 7.53−7.49 (m, 1H, Ar-<u>H</u>), 7.46 (d, J = 3.9 Hz, 1H, Ar-<u>H</u>), 7.45 (d, J = 3.1 Hz, 1H, Ar-<u>H</u>), 7.35 (dd, J = 8.6, 1.9 Hz, 1H, Ar-<u>H</u>), 2.61 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = δ 184.22 (<u>C</u>O), 142.77, 141.76, 138.50, 136.07, 135.67, 132.99, 129.30, 128.56, 127.02, 125.39, 125.18, 122.39, 121.52, 119.03, 114.25, 113.74, 112.17, 12.19 (<u>C</u>H$_3$); IR (KBr, cm^{-1}) ν_{max} = 3153, 3077, 3030, 2934, 2900, 1643, 1559, 1500, 1454, 1433, 1394, 1370, 1299, 1273, 1243, 1223, 1182, 1136, 1095, 1038, 1022, 1007, 956, 938, 881, 851, 824, 789, 758, 689, 660, 636, 609, 554; LC/MS (ESI, m/z): found 406.6 [M($_{79}$Br) + H]$^+$, 408.1 [M($_{81}$Br) + H]$^+$; exact mass 405.05 for $C_{21}H_{16}BrN_3O$.

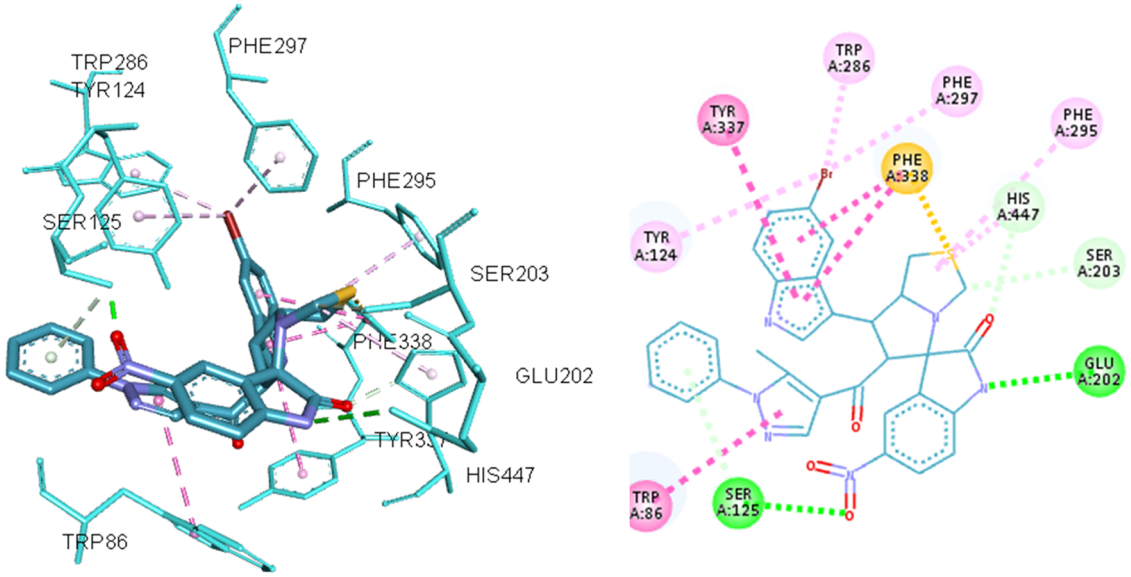

Figure 5. 8i docked in the active site of ACHE (4EY7) and corresponding two-dimensional (2D) presentation. The H-bond is represented by green dotted lines, hydrophobic interactions are represented by magenta dotted lines, and Pi-sulfur interaction is represented by orange dotted lines.

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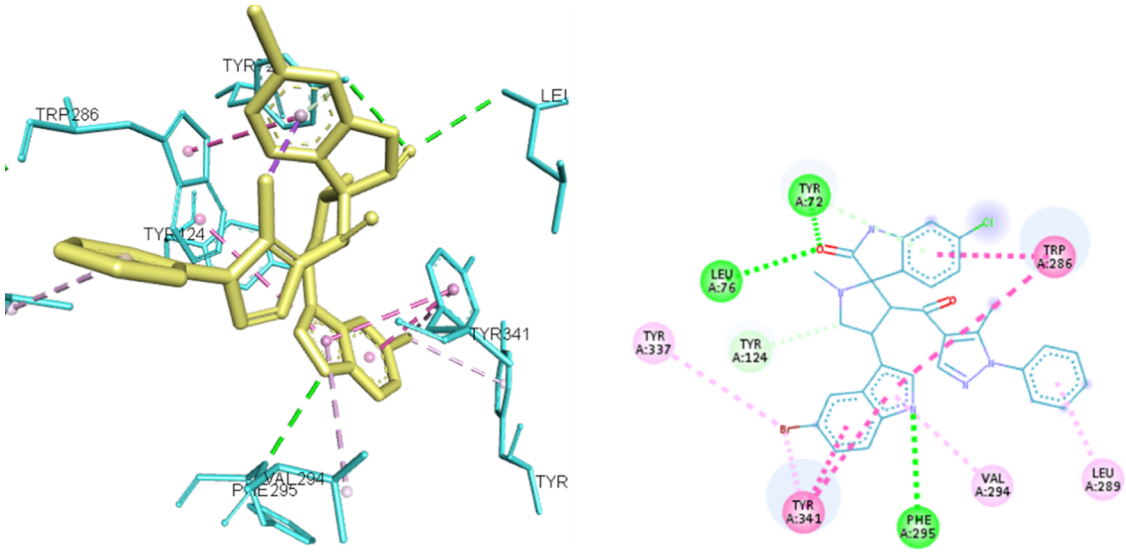

Figure 6. 8y docked in the active site of ACHE (4EY7) and corresponding 2D presentation. The H-bond is represented by green dotted lines, hydrophobic interactions are represented by magenta dotted lines, and Pi-sulfur interaction is represented by orange dotted lines.

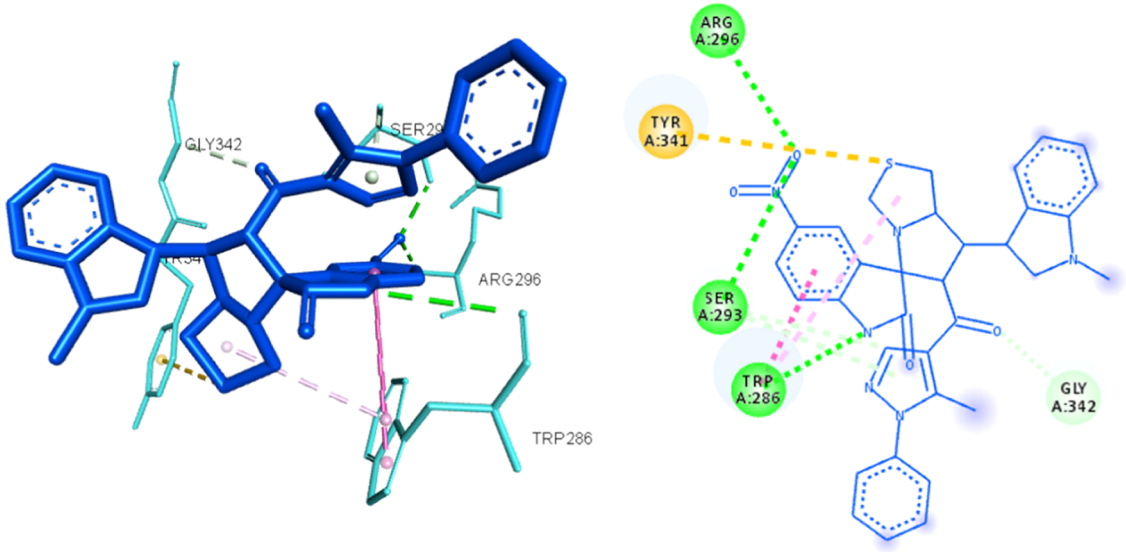

Figure 7. 8h docked in the active site of ACHE (4EY7) and corresponding 2D presentation. The H-bond is represented by green dotted lines, hydrophobic interactions are represented by magenta dotted lines, and Pi-sulfur interaction is represented by orange dotted lines.

*Synthesis of (E)-3-(5-Chloro-1H-indol-3-yl)-1-(5-methyl-1-phenyl-1H-pyrazol-4-yl) prop-2-en-1-one (**5d**).* Following the general procedure (GP1), acetyl-pyrazole **3** (1.0 g, 5.0 mmol) and 5-chloroindole-3-carboxyaldehyde **4d** (1.07 g, 6.0 mmol) produce pyrazolenone-**5d** (yield 0.9 g, 50%); m.p.: 237−238; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = δ 11.95 (bs, 1H, N<u>H</u>), 8.65 (s, 1H, Ar-<u>H</u>), 8.20−8.05 (m, 2H, Ar-<u>H</u>), 7.95 (d, J = 15.4 Hz, 1H, C<u>H</u>═CH), 7.57 (d, J = 4.4 Hz, 4H, Ar-<u>H</u>), 7.50 (dd, J = 8.7, 4.6 Hz, 2H, Ar-<u>H</u>), 7.46 (d, J = 15.7 Hz, 1H, CH═C<u>H</u>), 7.23 (dd, J = 8.2, 2.1 Hz, 1H, Ar-<u>H</u>), 2.61 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = δ 184.24 (<u>C</u>O), 142.78, 141.80, 138.52, 135.86, 135.76, 133.34, 129.30, 128.56, 126.35, 125.73, 125.40, 122.60, 121.53, 119.55, 118.92, 113.81, 112.30, 12.19 (<u>C</u>H$_3$); IR (KBr, cm^{-1}) ν_{max} = 3107, 2896, 1648, 1637, 1576, 1518, 1500, 1453, 1395, 1383, 1373, 1314, 1251, 1212, 1142, 1123, 1072, 1047, 1005, 973, 944, 897, 863, 837, 794, 765, 740, 697, 651, 643, 609, 594, 575; LC/MS (ESI, m/z): found 362.1 [M($_{35}$Cl) + H]$^+$, 364.1 [M($_{37}$Cl) + H]$^+$; exact mass 361.09 for $C_{21}H_{16}ClN_3O$.

Synthesis of Spirooxindole Derivatives 8a−y. *General Procedure (**GP2**).* Chalcones **5a−d** (0.25 mmol), isatin derivatives **6a−c** (0.25 mmol), and amino acids **7a−d** (1.5 equiv, 0.37 mmol) were dissolved in methanol (20 mL), and the reaction mixture was refluxed for 2−4 h. Finally, the products were isolated by flash column chromatography, using 1−3% MeOH/DCM to afford pyrazole spirooxindole **8a−y**.

*(3R,6′S,7′R,7a′S)-7′-(1H-Indol-3-yl)-6′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-1′,6′,7′,7a′-tetrahydro-3′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one (**8a**).* Following the general procedure (GP2), chalcone **5a** (82 mg, 0.25 mmol), isatin **6a** (37 mg, 0.25 mmol), and thioproline **7a** (50 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8a**; yield (85 mg, 62%); m.p.: 138−139 °C; $[\alpha]_D^{25}$ =

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−16.19° (c 0.13, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$) δ (ppm) = 8.59 (s, 1H, N<u>H</u>), 8.33 (s, 1H, N<u>H</u>), 8.10 (d, *J* = 7.1 Hz, 1H, Ar-<u>H</u>), 7.92 (s, 1H, Ar-<u>H</u>), 7.72 (d, *J* = 7.6 Hz, 1H, Ar-<u>H</u>), 7.40−7.33 (m, 4H, Ar-<u>H</u>), 7.28 (d, *J* = 2.5 Hz, 1H, Ar-<u>H</u>), 7.20−7.17 (m, 2H, Ar-<u>H</u>), 7.17−7.14 (m, 3H, Ar-<u>H</u>), 7.04−7.01 (m, 1H, Ar-<u>H</u>), 6.64 (d, *J* = 7.7 Hz, 1H, Ar-<u>H</u>), 4.79 (d, *J* = 11.8 Hz, 1H, C<u>H</u>CO), 4.66−4.61 (m, 1H, NC<u>H</u>), 4.25 (dd, *J* = 11.8, 9.7 Hz, 1H, NCHC<u>H</u>), 3.94 (d, *J* = 10.5 Hz, 1H, NC<u>H</u>$_2$), 3.61 (d, *J* = 10.5 Hz, 1H, NC<u>H</u>$_2$), 3.11−3.03 (m, 2H, SC<u>H</u>$_2$), 1.92 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (176 MHz, $CDCl_3$) δ (ppm) = 191.09 (<u>C</u>O), 180.75 (<u>C</u>O), 143.50, 141.28, 141.03, 138.31, 136.74, 129.76, 129.29, 129.15, 128.88, 126.46, 125.47, 124.08, 123.02, 122.28, 122.27, 121.00, 119.93, 119.84, 113.65, 111.58, 109.65, 75.12, 73.75, 63.86, 55.16, 43.58, 37.41, 11.75 (<u>C</u>H$_3$); IR (KBr, cm^{-1}) ν_{max} = 3288, 3058, 2921, 1733, 1722, 1717, 1699, 1694, 1682, 1674, 1668, 1661, 1652, 1619, 1615, 1597, 1538, 1532, 1504, 1470, 1456, 1393, 1337, 1222, 1119, 935, 875, 807, 749, 695; [anal. calcd. for $C_{32}H_{27}N_5O_2S$: C, 70.44; H, 4.99; N, 12.83; found: C, 70.31; H, 5.05; N, 12.91]; LC/MS (ESI, *m*/*z*): found 546.4 [M + H]$^+$, exact mass 545.19 for $C_{32}H_{27}N_5O_2S$.

(3R,6′S,7′R,7a′S)-6′-(5-Methyl-1-phenyl-1H-pyrazole-4-carbonyl)-7′-(1-methyl-1H-indol-3-yl)-1′,6′,7′,7a′-tetrahydro-3′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one ***(8b)***. Following the general procedure (GP2), chalcone **5b** (85 mg, 0.25 mmol), isatin **6a** (37 mg, 0.25 mmol), and thioproline **7a** (50 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8b**; yield (101 mg, 72%); m.p.: 186−187 °C; $[\alpha]_D^{25}$ = −12.53° (c 0.13, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$) δ (ppm) = 8.80 (s, 1H, N<u>H</u>), 8.09 (d, *J* = 7.24 Hz, 1H, Ar-<u>H</u>), 7.92 (s, 1H, Ar-<u>H</u>), 7.72 (d, *J* = 7.63 Hz, 1H, Ar-<u>H</u>), 7.39−7.35 (m, 3H, Ar-<u>H</u>), 7.29 (ddd, *J* = 8.1, 1.4, 0.7 Hz, 1H, Ar-<u>H</u>), 7.25 (dd, *J* = 6.9, 1.3 Hz, 1H, Ar-<u>H</u>), 7.21 (dd, *J* = 5.0, 1.4 Hz, 1H, Ar-<u>H</u>), 7.19 (s, 1H, Ar-<u>H</u>), 7.19−7.16 (m, 2H, Ar-<u>H</u>), 7.16−7.12 (m, 2H, Ar-<u>H</u>), 7.03 (td, *J* = 7.6, 1.1 Hz, 1H, Ar-<u>H</u>), 6.65 (d, *J* = 7.73 Hz, 1H, Ar-<u>H</u>), 4.77 (d, *J* = 11.8 Hz, 1H, C<u>H</u>CO), 4.67−4.61 (m, 1H, NC<u>H</u>), 4.22 (dd, *J* = 11.8, 9.8 Hz, 1H, NCHC<u>H</u>), 3.94 (d, *J* = 10.6 Hz, 1H, NC<u>H</u>$_2$), 3.74 (s, 3H, C<u>H</u>$_3$), 3.61 (d, *J* = 10.5 Hz, 1H, NC<u>H</u>$_2$), 3.07 (d, *J* = 4.3 Hz, 2H, SC<u>H</u>$_2$), 1.92 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (176 MHz, $CDCl_3$) δ (ppm) = 191.09 (<u>C</u>O), 180.96 (<u>C</u>O), 143.43, 141.25, 141.21, 138.27, 137.40, 129.70, 129.23, 129.03, 128.81, 127.60, 126.88, 125.45, 124.02, 122.13, 121.80, 120.97, 119.90, 119.38, 112.03, 109.75, 109.58, 75.20, 73.86, 63.89, 55.20, 43.45, 37.35, 32.80 (<u>C</u>H$_3$), 11.67 (<u>C</u>H$_3$); IR (KBr, cm^{-1}) ν_{max} = 3237, 2923, 1738, 1733, 1722, 1699, 1694, 1682, 1674, 1668, 1661, 1652, 1645, 1634, 1622, 1615, 1597, 1557, 1538, 1532, 1505, 1470, 1456, 1398, 1329, 1229, 1180, 1156, 1115, 1069, 1013, 934, 801, 741, 695; [anal. calcd. for $C_{33}H_{29}N_5O_2S$: C, 70.82; H, 5.22; N, 12.51; found: C, 71.01; H, 5.15; N, 12.39]; LC/MS (ESI, *m*/*z*): found 560.4 [M + H]$^+$, exact mass 559.14 for $C_{33}H_{29}N_5O_2S$.

(3R,6′S,7′R,7a′S)-7′-(5-Bromo-1H-indol-3-yl)-6′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-1′,6′,7′,7a′-tetrahydro-3′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one ***(8c)***. Following the general procedure (GP2), chalcone **5c** (102 mg, 0.25 mmol), isatin **6a** (37 mg, 0.25 mmol), and thioproline **7a** (50 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8c**; yield (59 mg, 38%); m.p.: 180−181 °C; $[\alpha]_D^{25}$ = −12.53° (c 0.11, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$) δ (ppm) = 9.05 (s, 1H, N<u>H</u>), 8.66 (s, 1H, N<u>H</u>), 8.18 (s, 1H, Ar-<u>H</u>), 7.98 (s, 1H, Ar-<u>H</u>), 7.69 (d, *J* = 7.5 Hz, 1H, Ar-<u>H</u>), 7.38−7.35 (m, 4H, Ar-<u>H</u>), 7.20−7.18 (m, 1H, Ar-<u>H</u>), 7.15−7.13 (m, 2H, Ar-<u>H</u>), 7.03 (d, *J* = 7.6 Hz, 1H, Ar-<u>H</u>), 6.62 (d, *J* = 7.7 Hz, 1H, Ar-<u>H</u>), 4.63 (d, *J* = 11.6 Hz, 1H, C<u>H</u>CO), 4.50−4.49 (ddd, *J* = 9.4, 6.2, 2.5 Hz, 1H, NC<u>H</u>), 4.21 (m, 1H, NCHC<u>H</u>), 3.92 (d, *J* = 10.4 Hz, 1H, NC<u>H</u>$_2$), 3.60 (d, *J* = 10.4 Hz, 1H, NC<u>H</u>$_2$), 3.08−3.04 (m, 1H, SC<u>H</u>$_2$), 3.03−3.98 (m, 1H, SC<u>H</u>$_2$), 1.91 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (176 MHz, $CDCl_3$) δ (ppm) = 191.02 (<u>C</u>O), 180.91 (<u>C</u>O), 143.59, 141.14, 138.23, 135.18, 129.84, 129.33, 128.96, 128.58, 127.75, 127.12, 125.47, 125.19, 124.00, 123.78, 122.33, 122.04, 120.91, 113.74, 113.18, 113.03, 109.80, 75.06, 74.25, 65.41, 54.90, 42.63, 37.28, 11.70 (<u>C</u>H$_3$); IR (KBr, cm^{-1}) ν_{max} = 3273, 2924, 1721, 1668, 1617, 1597, 1537, 1503, 1470, 1455, 1396, 1331, 1283, 1223, 1179, 1099, 934, 884, 807, 795, 762, 752, 694, 656, 604; [anal. calcd. for $C_{32}H_{26}BrN_5O_2S$: C, 61.54; H, 4.20; N, 11.21; found: C, 61.43; H, 4.35; N, 11.27]; LC/MS (ESI, *m*/*z*): found 624.7 [M($_{79}$Br) + H]$^+$, 626.1 [M($_{81}$Br) + H]$^+$; exact mass 623.10 for $C_{32}H_{26}BrN_5O_2S$.

(3R,6′S,7′R,7a′S)-7′-(5-Chloro-1H-indol-3-yl)-6′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-1′,6′,7′,7a′-tetrahydro-3′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one ***(8d)***. Following the general procedure (GP2), chalcone **5d** (91 mg, 0.25 mmol), isatin **6a** (37 mg, 0.25 mmol), and thioproline **7a** (50 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8d**; yield (76 mg, 52%); m.p.: 210−212 °C; $[\alpha]_D^{25}$ = −12.03° (c 0.11, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$) δ (ppm) = 8.61 (s, 1H, N<u>H</u>), 8.38 (s, 1H, N<u>H</u>), 8.00 (s, 1H, Ar-<u>H</u>), 7.86 (s, 1H, Ar-<u>H</u>), 7.64 (d, *J* = 7.6 Hz, 1H, Ar-<u>H</u>), 7.33 (dd, *J* = 10.7, 7.0 Hz, 3H, Ar-<u>H</u>), 7.23−7.18 (m, 2H, Ar-<u>H</u>), 7.09 (dd, *J* = 15.4, 8.3 Hz, 4H, Ar-<u>H</u>), 7.00−6.96 (m, 1H, Ar-<u>H</u>), 6.60 (d, *J* = 7.8 Hz, 1H, Ar-<u>H</u>), 4.58 (d, *J* = 11.6 Hz, 1H, C<u>H</u>CO), 4.50−4.42 (m, 1H, NC<u>H</u>), 4.16 (t, *J* = 10.6 Hz, 1H, NCHC<u>H</u>), 3.88 (d, *J* = 10.4 Hz, 1H, NC<u>H</u>$_2$), 3.55 (d, *J* = 10.4 Hz, 1H, NC<u>H</u>$_2$), 3.06−2.94 (m, 2H, SC<u>H</u>$_2$), 1.86 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (176 MHz, $CDCl_3$) δ (ppm) = 190.95 (<u>C</u>O), 180.78 (<u>C</u>O), 143.60, 141.17, 141.01, 138.27, 134.95, 129.88, 129.35, 129.06, 128.97, 127.87, 125.71, 125.50, 124.00, 122.75, 122.40, 120.91, 119.13, 113.90, 112.54, 109.76, 74.12, 64.53, 54.95, 42.77, 37.30, 11.72 (<u>C</u>H$_3$); IR (KBr, cm^{-1}) ν_{max} = 3284, 2926, 1720, 1668, 1652, 1616, 1597, 1538, 1504, 1470, 1397, 1329, 1283, 1268, 1223, 1180, 1103, 934, 893, 806, 796, 763, 752, 694, 683, 658, 605; [anal. calcd. for $C_{32}H_{26}ClN_5O_2S$: C, 66.26; H, 4.52; N, 12.07; found: C, 66.14; H, 4.63; N, 12.15]; LC/MS (ESI, *m*/*z*): found 580.6 [M($_{35}$Cl) + H]$^+$, 582.3 [M($_{37}$Cl) + H]$^+$; exact mass 579.15 for $C_{32}H_{26}ClN_5O_2S$.

(3R,6′S,7′R,7a′S)-6-Chloro-7′-(1H-indol-3-yl)-6′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-3′,6′,7′,7a′-tetrahydro-1′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one ***(8e)***. Following the general procedure (GP2), chalcone **5a** (82 mg, 0.25 mmol), 6-chloroisatin **6b** (46 mg, 0.25 mmol), and thioproline **7a** (50 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8e**; yield (44 mg, 30%); m.p.: 188−190 °C; $[\alpha]_D^{25}$ = −18.78° (c 0.11, MeOH); ^{1}H NMR (700 MHz, DMSO-d_6): δ (ppm) = 11.00 (s, 1H, N<u>H</u>), 10.68 (s, 1H, N<u>H</u>), 7.87 (d, *J* = 7.8 Hz, 1H, Ar-<u>H</u>), 7.84 (d, *J* = 2.5 Hz, 1H, Ar-<u>H</u>), 7.54 (d, *J* = 8.2 Hz, 1H, Ar-<u>H</u>), 7.51−7.45 (m, 4H, Ar-

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H), 7.38−7.32 (m, 3H, Ar-H), 7.11−7.06 (m, 2H, Ar-H), 7.04 (d, J = 8.2 Hz, 1H, Ar-H), 6.67 (s, 1H, Ar-H), 4.73 (d, J = 11.8 Hz, 1H, CHCO), 4.33−4.29 (m, 1H, NCH), 4.13−4.09 (m, 1H, NCHCH), 3.78 (d, J = 10.3 Hz, 1H, $NCH_{2(a)}$), 3.43 (d, J = 8.2 Hz, 1H, $NCH_{2(b)}$), 3.07−2.99 (m, 2H, SCH_2), 1.92 (s, 3H, CH_3); ^{13}C NMR (176 MHz, DMSO-d_6): δ (ppm) =190.34 (CO), 178.87 (CO), 143.68, 142.64, 140.80, 137.91, 136.59, 133.90, 129.93, 129.31, 128.87, 128.07, 126.65, 126.45, 126.21, 125.26, 123.43, 122.45, 121.19, 120.54, 118.77, 112.02, 109.44, 73.87, 73.77, 62.86, 54.93, 53.92, 43.19, 36.70, 11.22 (CH_3); IR (KBr, cm^{-1}) ν_{max} = 3295, 2928, 1723, 1717, 1699, 1668, 1645, 1615, 1598, 1538, 1533, 1504, 1483, 1456, 1398, 1379, 1338, 1325, 1282, 1244, 1224, 1183, 1125, 1096, 1072, 926, 852, 811, 764, 743, 694, 658, 594, 529; [anal. calcd. for $C_{32}H_{26}ClN_5O_2S$: C, 66.26; H, 4.52; N, 12.07; found: C, 66.12; H, 4.67; N, 12.22]; LC/MS (ESI, m/z): found 580.5 [M($_{35}$Cl) + H]$^+$, 582.3 [M($_{37}$Cl) + H]$^+$; exact mass 579.15 for $C_{32}H_{26}ClN_5O_2S$.

*(3R,6′S,7′R,7a′S)-7′-(1H-Indol-3-yl)-6′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-5-nitro-1′,6′,7′,7a′-tetrahydro-3′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one (**8f**).* Following the general procedure (GP2), chalcone **5a** (82 mg, 0.25 mmol), 5-nitroisatin **6c** (48 mg, 0.25 mmol), and thioproline **7a** (50 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield yellow solid compound **8f**; yield (49 mg, 33%); m.p.: 213−214 °C; $[\alpha]_D^{25}$ = −36.24° (c 0.15, MeOH); ^{1}H NMR (700 MHz, DMSO-d_6) δ (ppm) = 11.26 (s, 1H, NH), 11.04 (s, 1H, NH), 8.46 (s, 1H, Ar-H), 8.17 (d, J = 8.2 Hz, 1H, Ar-H), 7.89−7.84 (m, 2H, Ar-H), 7.55 (s, 1H, Ar-H), 7.50−7.47 (m, 2H, Ar-H), 7.46 (d, J = 7.5 Hz, 1H, Ar-H), 7.36 (d, J = 6.9 Hz, 1H, Ar-H), 7.32−7.30 (m, 2H, Ar-H), 7.09−7.10 (m, 2H, Ar-H), 6.88 (d, J = 8.6 Hz, 1H, Ar-H), 4.79 (d, J = 12.0 Hz, 1H, CHCO), 4.41−4.36 (m, 1H, NCH), 4.14−4.09 (m, 1H, NCHCH), 3.80 (d, J = 10.8 Hz, 1H, $NCH_{2(a)}$), 3.50 (d, J = 10.8 Hz, 1H, $NCH_{2(b)}$), 3.08 (t, J = 3.6 Hz, 2H, SCH_2), 1.86 (s, 3H, CH_3); ^{13}C NMR (176 MHz, DMSO-d_6) δ (ppm) = 190.24 (CO), 179.44 (CO), 148.63, 142.79, 141.34, 140.76, 137.81, 136.64, 129.34, 128.93, 128.08, 126.92, 126.46, 126.07, 125.26, 124.34, 123.83, 121.25, 120.47, 118.89, 118.54, 111.42, 109.90, 74.15, 73.58, 62.93, 54.48, 43.59, 36.77, 11.25 (CH_3); IR (KBr, cm^{-1}) ν_{max} = 3252, 2924, 2853, 1736, 1729, 1665, 1652, 1626, 1598, 1526, 1504, 1478, 1455, 1398, 1338, 1300, 1248, 1223, 1198, 1180, 1124, 1098, 1069, 932, 907, 828, 807, 763, 743, 694, 557; [anal. calcd. for $C_{32}H_{26}N_6O_4S$: C, 65.07; H, 4.44; N, 14.23; found: C, 64.91; H, 4.56; N, 14.04]; LC/MS (ESI, m/z): found 591.7 [M + H], exact mass 590.17 for $C_{32}H_{26}N_6O_4S$.

*(3R,6′S,7′R,7a′S)-6-Chloro-6′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-7′-(1-methyl-1H-indol-3-yl)-1′,6′,7′,7a′-tetrahydro-3′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one (**8g**).* Following the general procedure (GP2), chalcone **5b** (85 mg, 0.25 mmol), 6-chloroisatin **6b** (46 mg, 0.25 mmol), and thioproline **7a** (50 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8g**; yield (55 mg, 37%); m.p.: 164−165 °C; $[\alpha]_D^{25}$ = −41.94° (c 0.12, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$) δ (ppm) = 9.23 (s, 1H, NH), 8.07 (d, J = 7.9 Hz, 1H, Ar-H), 7.94 (s, 1H, Ar-H), 7.64 (d, J = 8.1 Hz, 1H, Ar-H), 7.40 (d, J = 6.2 Hz, 2H, Ar-H), 7.36 (s, 1H, Ar-H), 7.29 (d, J = 8.2 Hz, 1H, Ar-H), 7.25−7.22 (m, 1H, Ar-H), 7.21−7.18 (m, 2H, Ar-H), 7.16 (d, J = 8.1 Hz, 2H, Ar-H), 7.00 (d, J = 8.1 Hz, 1H, Ar-H), 6.51 (s, 1H, Ar-H), 4.75 (d, J = 11.8 Hz, 1H, CHCO), 4.63−4.60 (m, 1H, NCH), 4.21−4.15 (m, 1H, NCHCH), 3.93 (d, J = 10.6 Hz, 1H, $NCH_{2(a)}$), 3.74 (s, 3H, NCH_3), 3.56 (d, J = 10.7 Hz, 1H, $NCH_{2(b)}$), 3.09−3.02 (m, 2H, SCH_2), 1.99 (s, 3H, CH_3); ^{13}C NMR (176 MHz, $CDCl_3$) δ (ppm) = 190.90 (CO), 180.77 (CO), 143.66, 141.19, 138.14, 137.42, 135.36, 130.05, 129.39, 129.11, 128.65, 127.59, 127.10, 126.86, 125.53, 122.49, 121.90, 120.90, 119.84, 119.50, 111.84, 110.17, 109.63, 74.78, 73.80, 63.95, 55.17, 43.58, 37.44, 32.85 (NCH_3), 11.71 (CH_3); IR (KBr, cm^{-1}) ν_{max} = 3234, 2922, 2849, 1733, 1717, 1699, 1667, 1652, 1612, 1598, 1544, 1537, 1532, 1503, 1483, 1454, 1401, 1377, 1327, 1261, 1223, 1182, 157, 1123, 1071, 1012, 925, 808, 765, 738, 694, 612, 529; [anal. calcd. for $C_{33}H_{28}ClN_5O_2S$: C, 66.71; H, 4.75; N, 11.79; found: C, 66.85; H, 4.62; N, 12.03]; LC/MS (ESI, m/z): found 594.5 [M($_{35}$Cl) + H]$^+$, 596.0 [M($_{37}$Cl) + H]$^+$; exact mass 593.17 for $C_{33}H_{28}ClN_5O_2S$.

*(3R,6′S,7′R,7a′S)-6′-(5-Methyl-1-phenyl-1H-pyrazole-4-carbonyl)-7′-(1-methyl-1H-indol-3-yl)-5-nitro-3′,6′,7′,7a′-tetrahydro-1′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one (**8h**).* Following the general procedure (GP2), chalcone **5b** (85 mg, 0.25 mmol), 5-nitroisatin **6c** (48 mg, 0.25 mmol), and thioproline **7a** (50 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 16 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield yellow solid compound **8h**; yield (41 mg, 27%); m.p.: 172−173 °C; $[\alpha]_D^{25}$ = −22.87° (c 0.13, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$) δ (ppm) = 9.78 (s, 1H, NH), 8.73 (s, 1H, Ar-H), 8.14 (dd, J = 27.8, 8.4 Hz, 2H, Ar-H), 7.99 (s, 1H, Ar-H), 7.47−7.41 (m, 3H, Ar-H), 7.40 (d, J = 4.3 Hz, 1H, Ar-H), 7.35 (d, J = 8.2 Hz, 1H, Ar-H), 7.30 (d, J = 8.2 Hz, 1H, Ar-H), 7.23−7.19 (m, 1H, Ar-H), 7.16 (dd, J = 6.7, 3.1 Hz, 2H, Ar-H), 6.69 (d, J = 9.2 Hz, 1H, Ar-H), 4.89 (d, J = 11.5 Hz, 1H CHCO), 4.73 (m, 1H NCH), 4.30 (t, J = 10.7 Hz, 1H, NCHCH), 3.99 (d, J = 10.4 Hz, 1H, $NCH_{2(a)}$), 3.79 (s, 3H, CH_3), 3.51 (d, J = 10.5 Hz, 1H, $NCH_{2(b)}$), 3.16 (d, J = 4.4 Hz, 2H, SCH_2), 2.01 (s, 3H, CH_3); ^{13}C NMR (176 MHz, $CDCl_3$) δ (ppm) = 190.04 (CO), 180.99 (CO), 146.95, 143.91, 142.89, 141.14, 137.92, 137.52, 129.47, 129.26, 128.66, 128.04, 127.74, 127.12, 126.55, 125.38, 125.06, 124.92, 121.96, 120.90, 119.75, 111.02, 109.77, 73.37, 63.71, 55.11, 44.29, 37.47, 32.86 (CH_3), 11.86 (CH_3); IR (KBr, cm^{-1}) ν_{max} = 3208, 2926, 2859, 1736, 1716, 1699, 1682, 1678, 1668, 1652, 1622, 1615, 1598, 1524, 1504, 1475, 1455, 1404, 1337, 1221, 1177, 1123, 1103, 932, 833, 805, 765, 741, 694, 556; [anal. calcd. for $C_{33}H_{28}N_6O_4S$: C, 65.55; H, 4.67; N, 13.90; found: C, 65.67; H, 4.81; N, 14.04]; LC/MS (ESI, m/z): found 605.6 [M + H], exact mass 604.19 for $C_{33}H_{28}N_6O_4S$.

*(3R,6′S,7′R,7a′S)-7′-(5-Bromo-1H-indol-3-yl)-6′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-5-nitro-3′,6′,7′,7a′-tetrahydro-1′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one (**8i**).* Following the general procedure (GP2), chalcone **5c** (102 mg, 0.25 mmol), 5-nitroisatin **6c** (48 mg, 0.25 mmol), and thioproline **7a** (50 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 16 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield yellow solid compound **8i**; yield (82 mg, 49%); m.p.: 250−251 °C; $[\alpha]_D^{25}$ = −126.29° (c 0.19, MeOH); ^{1}H NMR (700 MHz, DMSO-d_6) δ (ppm) = 11.30 (d, J = 2.6 Hz, 1H, NH), 11.25 (s, 1H, NH), 8.45 (d, J = 2.4 Hz, 1H, Ar-H), 8.17 (dd, J = 8.6, 2.4 Hz, 1H, Ar-H), 7.98 (d, J = 1.9 Hz, 1H, Ar-H), 7.84 (s, 1H, Ar-H), 7.67 (d, J = 2.6 Hz, 1H, Ar-H), 7.51−7.48 (m, 2H, Ar-H), 7.48−7.45 (m, 1H, Ar-H), 7.35−7.31 (m, 3H, Ar-H), 7.21

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(dd, J = 8.5, 1.9 Hz, 1H, Ar-H), 6.87 (d, J = 8.6 Hz, 1H, Ar-H), 4.67 (d, J = 11.9 Hz, 1H, CHCO), 4.37−4.33 (m, 1H, NCH), 4.10 (dd, J = 11.8, 9.5 Hz, 1H, NCHCH), 3.79 (d, J = 10.7 Hz, 1H, $NCH_{2(a)}$), 3.50 (d, J = 10.6 Hz, 1H, $NCH_{2(b)}$), 3.09−3.04 (m, 2H, SCH_2), 1.86 (s, 3H, CH_3); ^{13}C NMR (176 MHz, DMSO-d_6) δ (ppm) = 190.22 (CO), 179.25 (CO), 148.59, 142.75, 141.34, 140.74, 137.77, 135.16, 129.31, 128.90, 128.07, 126.90, 125.42, 125.21, 124.29, 123.85, 123.69, 120.73, 120.38, 113.84, 111.50, 111.42, 109.86, 73.95, 73.48, 63.46, 54.14, 42.83, 36.56, 11.21 (CH_3); IR (KBr, cm^{-1}) ν_{max} = 3383, 3101, 2855, 1747, 1729, 1649, 1622, 1598, 1530, 1504, 1463, 1454, 1412, 1337, 1290, 1253, 1222, 1199, 1173, 1097, 933, 880, 830, 799, 753, 693, 607; [anal. calcd. for $C_{32}H_{25}BrN_6O_4S$: C, 57.40; H, 3.76; N, 12.55; found: C, 57.36; H, 3.84; N, 12.59]; LC/MS (ESI, m/z): found 669.6 [M($_{79}$Br) + H]$^+$, 671.5 [M($_{81}$Br) + H]$^+$; exact mass 668.08 for $C_{32}H_{25}BrN_6O_4S$.

*(3R,6′S,7′R,7a′S)-7′-(5-Chloro-1H-indol-3-yl)-6′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-5-nitro-3′,6′,7′,7a′-tetrahydro-1′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one (**8j**).* Following the general procedure (GP2), chalcone **5d** (91 mg, 0.25 mmol), 5-nitroisatin **6c** (48 mg, 0.25 mmol), and thioproline **7a** (50 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield yellow solid compound **8j**; yield (53 mg, 40%); m.p.: 196−197 °C; $[\alpha]_D^{25}$ = −53.73° (c 0.10, MeOH); ^{1}H NMR (700 MHz, DMSO-d_6) δ (ppm) = 11.30 (s, 1H, NH), 11.27 (s, 1H, NH), 8.46 (s, 1H, Ar-H), 8.18 (d, J = 8.6 Hz, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 7.69 (s, 1H, Ar-H), 7.53−7.46 (m, 2H, Ar-H), 7.48 (d, J = 5.5 Hz, 1H, Ar-H), 7.39 (d, J = 8.6 Hz, 1H, Ar-H), 7.34−7.31 (m, 3H, Ar-H), 7.12 (d, J = 8.6 Hz, 1H, Ar-H), 6.88 (d, J = 8.7 Hz, 1H, Ar-H), 4.68 (d, J = 11.7 Hz, 1H, CHCO), 4.39−4.35 (m, 1H, NCH), 4.12 (t, J = 12.1 Hz, 1H, NCHCH), 3.80 (d, J = 10.9 Hz, 1H, $NCH_{2(a)}$), 3.51 (d, J = 10.9 Hz, 1H, $NCH_{2(b)}$), 3.11−3.05 (m, 2H, SCH_2), 1.87 (s, 3H, CH_3); ^{13}C NMR (176 MHz, DMSO-d_6) δ (ppm) = 190.27 (CO), 179.33 (CO), 148.63, 142.79, 141.39, 140.77, 137.80, 134.98, 129.35, 128.94, 127.38, 126.94, 126.66, 126.45, 125.62, 124.33, 123.50, 121.22, 120.41, 117.74, 113.42, 111.62, 109.90, 74.00, 73.49, 62.93, 54.94, 42.87, 36.62, 11.23 (CH_3); IR (KBr, cm^{-1}) ν_{max} = 3344, 3270, 2932, 2861, 1725, 1657, 1623, 1598, 1530, 1503, 1477, 1454, 1339, 1296, 1224, 1180, 1101, 931, 892, 797, 764, 693, 614, 553; [Anal. Calcd. for $C_{32}H_{25}ClN_6O_4S$: C, 61.49; H, 4.03; N, 13.44; found: C, 61.35; H, 3.91; N, 13.62]; LC/MS (ESI, m/z): found 625.8 [M ($_{35}$Cl) + H]$^+$, 627.2 [M ($_{37}$Cl) + H]$^+$; exact mass 624.13 for $C_{32}H_{25}ClN_6O_4S$.

*(1′R,2′S,3R,9a′R)-1′-(1H-Indol-3-yl)-2′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-1′,2′,4a′,5′,6′,7′,8′,8a′,9′,9a′-decahydrospiro[indoline-3,3′-pyrrolo[1,2-a]indol]-2-one (**8k**).* Following the general procedure (GP2), chalcone **5a** (82 mg, 0.25 mmol), isatin **6a** (37 mg, 0.25 mmol), and octahydro-1*H*-indole-2-carboxylic acid **7b** (64 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8k**; yield (125 mg, 86%); m.p.: 200−201 °C; $[\alpha]_D^{25}$ = −18.76° (c 0.12, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$) δ (ppm) = 8.33 (s, 1H, NH), 8.04 (d, J = 1.2 Hz, 1H, Ar-H), 8.04−8.02 (m, 1H, Ar-H), 7.95 (s, 1H, NH), 7.42 (d, J = 7.4 Hz, 1H, Ar-H), 7.40−7.34 (m, 3H, Ar-H), 7.33−7.29 (m, 1H, Ar-H), 7.20−7.14 (m, 5H, Ar-H), 7.13−7.09 (m, 1H, Ar-H), 7.06−7.02 (m, 1H, Ar-H), 6.57 (d, J = 7.7 Hz, 1H, Ar-H), 4.96 (d, J = 11.9 Hz, 1H, CHCO), 4.57−4.52 (m, 1H, NCH), 4.20 (dd, J = 12.0, 10.0 Hz, 1H, NCHCH), 3.27 (q, J = 3.8 Hz, 1H, NCH), 2.19−2.14 (m, 1H, NCHCH), 1.93 (s, 3H, CH_3), 1.85−1.78 (m, 2H, CH_2), 1.59−1.44 (m, 4H, CH_2), 1.20−1.15 (m, 1H, CH_2), 1.07−1.01 (m, 1H, CH_2), 1.01−0.95 (m, 2H, CH_2); ^{13}C NMR (176 MHz, $CDCl_3$) δ (ppm) = 191.46 (CO), 181.76 (CO), 143.42, 141.62, 140.65, 138.43, 136.60, 129.25, 128.94, 128.74, 128.53, 127.06, 125.41, 125.10, 121.99, 121.78, 121.74, 121.26, 120.04, 119.48, 114.40, 111.35, 109.61, 72.74, 70.23, 66.94, 57.75, 45.57, 41.98, 38.40, 28.59, 27.78, 24.86, 20.13, 11.88 (CH_3); IR (KBr, cm^{-1}) ν_{max} = 3291, 2926, 2854, 1716, 1699, 1694, 1683, 1668, 1660, 1652, 1617, 1597, 1557, 1538, 1505, 1475, 1456, 1398, 1373, 1330, 1221, 1179, 1099, 1011, 934, 870, 790, 741, 694; [anal. calcd. for $C_{37}H_{35}N_5O_2$: C, 76.40; H, 6.06; N, 12.04; found: C, 76.28; H, 6.14; N, 12.11]; LC/MS (ESI, m/z): found 582.5 [M + H]$^+$, exact mass 581.28 for $C_{37}H_{35}N_5O_2$.

*(1′R,2′S,3R,9a′R)-6-Chloro-1′-(1H-indol-3-yl)-2′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-1′,2′,4a′,5′,6′,7′,8′,8a′,9′,9a′-decahydrospiro[indoline-3,3′-pyrrolo[1,2-a]indol]-2-one (**8l**).* Following the general procedure (GP2), chalcone **5a** (82 mg, 0.25 mmol), 6-chloroisatin **6b** (46 mg, 0.25 mmol), and octahydro-1*H*-indole-2-carboxylic acid **7b** (64 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8l**; yield (131 mg, 85%); m.p.: 205−206 °C; $[\alpha]_D^{25}$ = −20.56° (c 0.11, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$) δ (ppm) = 8.55 (s, 1H, NH), 8.32 (s, 1H, NH), 8.10 (d, J = 2.8 Hz, 1H, Ar-H), 8.00 (d, J = 7.6 Hz, 1H, Ar-H), 7.42−7.38 (m, 3H, Ar-H), 7.32 (d, J = 8.4 Hz, 2H, Ar-H), 7.19−7.11 (m, 5H, Ar-H), 7.01 (d, J = 8.0 Hz, 1H, Ar-H), 6.41 (d, J = 2.3 Hz, 1H, Ar-H), 4.96 (d, J = 12.0 Hz, 1H, CHCO), 4.56−4.52 (m, 1H, NCH), 4.15 (dd, J = 12.0, 10.0 Hz, 1H, NCHCH), 3.22 (q, J = 3.8 Hz, 1H, NCH), 2.19−2.14 (m, 1H, NCHCH), 2.00 (s, 3H, CH_3), 1.82−1.76 (m, 2H, CH_2), 1.59−1.55 (m, 1H, CH_2), 1.54−1.46 (m, 3H, CH_2), 1.20−1.16 (m, 1H, CH_2), 1.07−0.96 (m, 3H, CH_2); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 191.36 (CO), 181.77 (CO), 143.61, 142.07, 141.60, 138.28, 136.59, 134.55, 129.39, 129.03, 128.68, 126.99, 125.46, 123.59, 122.06, 121.81, 121.56, 121.16, 119.95, 119.55, 114.15, 111.40, 110.13, 72.39, 70.19, 67.06, 57.81, 45.69, 41.98, 38.35, 28.65, 27.77, 24.81, 20.14, 11.86 (CH_3); IR (KBr, cm^{-1}) ν_{max} = 3298, 2926, 2851, 1725, 1668, 1652, 1614, 1598, 1538, 1532, 1504, 1484, 1455, 1447, 1398, 1373, 1323, 1284, 1243, 1222, 1179, 1130, 1072, 1011, 937, 924, 869, 795, 764, 741, 694, 660, 597, 584, 524; [anal. calcd. for $C_{37}H_{34}ClN_5O_2$: C, 72.12; H, 5.56; N, 11.37; found: C, 71.96; H, 5.63; N, 11.28]; LC/MS (ESI, m/z): found 616.6 [M($_{35}$Cl) + H]$^+$, 618.3 [M($_{37}$Cl) + H]$^+$; exact mass 615.24 for $C_{37}H_{34}ClN_5O_2$.

*(1′R,2′S,3R,9a′R)-1′-(1H-Indol-3-yl)-2′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-5-nitro-1′,2′,4a′,5′,6′,7′,8′,8a′,9′,9a′-decahydrospiro[indoline-3,3′-pyrrolo[1,2-a]indol]-2-one (**8m**).* Following the general procedure (GP2), chalcone **5a** (82 mg, 0.25 mmol), 5-nitroisatin **6c** (48 mg, 0.25 mmol), and octahydro-1*H*-indole-2-carboxylic acid **7b** (64 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 4 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield yellow solid compound **8m**; yield (103 mg, 66%); m.p.: 210−211 °C; $[\alpha]_D^{25}$ = −15.63° (c 0.13, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$) δ (ppm) = 9.19 (s, 1H, NH), 8.27−8.22 (m, 2H, Ar-H), 8.11 (s, 1H, NH), 8.06 (d, J = 8.6 Hz, 1H, Ar-H),

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8.02 (d, J = 7.9 Hz, 1H, Ar-H), 7.42−7.37 (m, 3H, Ar-H), 7.34 (d, J = 7.0 Hz, 1H, Ar-H), 7.20 (s, 1H, Ar-H), 7.18−7.14 (m, 2H, Ar-H), 7.10 (d, J = 7.5 Hz, 2H, Ar-H), 6.42 (d, J = 8.7 Hz, 1H, Ar-H), 5.03 (d, J = 12.0 Hz, 1H, CHCO), 4.63−4.58 (m, 1H, NCH), 4.21 (t, J = 11.0 Hz, 1H, NCHCH), 3.24 (q, J = 3.7 Hz, 1H, NCH), 2.23−2.18 (m, 1H, NCHCH), 1.95 (s, 3H, CH_3), 1.90−1.86 (m, 1H, CH_2), 1.84−1.81 (m, 1H, CH_2), 1.61−1.56 (m, 1H, CH_2), 1.53−1.46 (m, 3H, CH_2), 1.22−1.17 (m, 1H, CH_2), 1.08−0.98 (m, 2H, CH_2), 0.93−0.89 (m, 1H, CH_2); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 190.53 (CO), 182.11 (CO), 146.67, 143.82, 142.71, 141.51, 138.12, 136.64, 129.48, 129.20, 127.14, 126.80, 126.02, 125.38, 123.96, 122.21, 121.96, 121.13, 120.02, 119.71, 113.58, 111.43, 109.26, 72.52, 70.05, 67.02, 57.95, 46.02, 42.11, 38.27, 28.56, 27.72, 24.77, 20.05, 11.95 (CH_3); IR (KBr, cm^{-1}) ν_{max} = 3341, 2926, 2854, 1733, 1668, 1653, 1623, 1598, 1533, 1503, 1477, 1455, 1397, 1338, 1221, 1178, 1125, 1096, 1072, 1011, 930, 833, 764, 742, 695, 660, 555; [anal. calcd. for $C_{37}H_{34}N_6O_4$: C, 70.91; H, 5.47; N, 13.41; found: C, 71.06; H, 5.39; N, 13.49]; LC/MS (ESI, m/z): found 627.5 [M + H]$^+$; exact mass 626.26 for $C_{37}H_{34}N_6O_4$.

*(1′R,2′S,3R,9a′R)-6-Chloro-2′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-1′-(1-methyl-1H-indol-3-yl)-1′,2′,4a′,5′,6′,7′,8′,8a′,9′,9a′-decahydrospiro[indoline-3,3′-pyrrolo[1,2-a]indol]-2-one (**8n**).* Following the general procedure (GP2), chalcone **5b** (85 mg, 0.25 mmol), 6-chloroisatin **6b** (46 mg, 0.25 mmol), and octahydro-1*H*-indole-2-carboxylic acid **7b** (64 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8n**; yield (134 mg, 85%); m.p.: 172−173 °C; $[\alpha]_D^{25}$ = −19.29° (c 0.10, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$) δ (ppm) = 8.06 (s, 1H, NH), 8.01 (d, J = 7.9 Hz, 1H, Ar-H), 7.44−7.40 (m, 3H, Ar-H), 7.31 (d, J = 8.0 Hz, 1H, Ar-H), 7.27 (s, 1H, Ar-H), 7.23−7.20 (m, 1H, Ar-H), 7.17 (d, J = 7.7 Hz, 3H, Ar-H), 7.10 (s, 1H, Ar-H), 7.02 (d, J = 8.0 Hz, 1H, Ar-H), 6.43 (s, 1H, Ar-H), 4.93 (d, J = 12.0 Hz, 1H, CHCO), 4.56−4.52 (m, 1H, NCH), 4.16−4.11 (m, 1H, NCHCH), 3.73 (s, 3H, NCH_3), 3.23 (q, J = 3.8 Hz, 1H, NCH), 2.20−2.15 (m, 1H, NCHCH), 2.02 (s, 3H, CH_3), 1.84−1.79 (m, 2H, CH_2), 1.60−1.56 (m, 1H, CH_2), 1.55−1.48 (m, 3H, CH_2), 1.21−1.17 (m, 1H, CH_2), 1.08−0.96 (m, 3H, CH_2); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 191.30 (CO), 181.64 (CO), 143.59, 142.02, 141.57, 138.33, 137.27, 134.52, 129.38, 128.99, 127.44, 127.12, 126.40, 125.46, 123.59, 121.66, 121.56, 121.16, 120.13, 119.09, 112.69, 110.05, 109.36, 72.29, 70.32, 67.20, 57.79, 45.60, 42.00, 38.38, 32.83 (NCH_3), 28.64, 27.78, 24.84, 20.11, 11.88 (CH_3); IR (KBr, cm^{-1}) ν_{max} = 3057, 2926, 2849, 1733, 1668, 1652, 1615, 1538, 1532, 1504, 1484, 1455, 1404, 1373, 1328, 1282, 1224, 1179, 1130, 1071, 1012, 935, 924, 869, 796, 764, 740, 694; [anal. calcd. for $C_{38}H_{36}ClN_5O_2$: C, 72.43; H, 5.76; N, 11.11; found: C, 72.52; H, 5.71; N, 11.03]; LC/MS (ESI, m/z): found 630.6 [M($_{35}$Cl) + H]$^+$, 632.3 [M($_{37}$Cl) + H]$^+$; exact mass 629.26 for $C_{38}H_{36}ClN_5O_2$.

*(1′R,2′S,3R,9a′R)-2′-(5-Methyl-1-phenyl-1H-pyrazole-4-carbonyl)-1′-(1-methyl-1H-indol-3-yl)-5-nitro-1′,2′,4a′,5′,6′,7′,8′,8a′,9′,9a′-decahydrospiro[indoline-3,3′-pyrrolo[1,2-a]indol]-2-one (**8o**).* Following the general procedure (GP2), chalcone **5b** (85 mg, 0.25 mmol), 5-nitroisatin **6c** (48 mg, 0.25 mmol), and octahydro-1*H*-indole-2-carboxylic acid **7b** (64 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 4 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield yellow solid compound **8o**; yield (119 mg, 74%); m.p.: 185−186 °C; $[\alpha]_D^{25}$ = −32.74° (c 0.14, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$) δ (ppm) = 11.03 (s, 1H, NH), 8.16 (d, J = 7.6 Hz, 2H, Ar-H), 7.98 (s, 1H, Ar-H), 7.86 (d, J = 7.9 Hz, 1H, Ar-H), 7.52−7.50 (m, 2H, Ar-H), 7.49−7.45 (m, 2H, Ar-H), 7.38−7.33 (m, 3H, Ar-H), 7.16−7.13 (m, 1H, Ar-H), 7.10−7.07 (m, 1H, Ar-H), 6.85 (d, J = 9.1 Hz, 1H, Ar-H), 4.92 (d, J = 12.1 Hz, 1H, CHCO), 4.25−4.12 (m, 1H, NCH), 4.13 (dd, J = 12.1, 9.9 Hz, 1H, NCHCH), 3.71 (s, 3H, NCH_3), 3.22 (q, J = 3.5 Hz, 1H, NCH), 2.19−2.13 (m, 1H, NCHCH), 2.05−1.99 (m, 1H, CH_2), 1.81 (s, 3H, CH_3), 1.65−1.61 (m, 1H, CH_2), 1.55−1.50 (m, 1H, CH_2), 1.48−1.43 (m, 1H, CH_2), 1.39−1.27 (m, 2H, CH_2), 1.15−1.10 (m, 1H, CH_2), 1.04−0.97 (m, 1H, CH_2), 0.96−0.90 (m, 1H, CH_2), 0.80−0.74 (m, 1H, CH_2); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 190.37 (CO), 181.03 (CO), 148.21, 142.53, 141.42, 141.08, 137.89, 136.71, 129.31, 128.82, 128.03, 127.10, 126.54, 126.41, 125.20, 125.07, 123.11, 121.17, 120.49, 119.19, 118.56, 111.66, 109.68, 71.51, 70.53, 66.16, 56.87, 44.37, 41.52, 37.53, 32.33 (NCH_3), 27.69, 27.27, 24.37, 19.27, 11.08 (CH_3); IR (KBr, cm^{-1}) ν_{max} = 3056, 2927, 2854, 1738, 1733, 1716, 1699, 1694, 1682, 1674, 1668, 1661, 1652, 1645, 1634, 1622, 1615, 1598, 1557, 1538, 1524, 1519, 1505, 1475, 1464, 1456, 1436, 1427, 1398, 1373, 1338, 1223, 1178, 1127, 1072, 1011, 930, 833, 795; [anal. calcd. for $C_{38}H_{36}N_6O_4$: C, 71.23; H, 5.66; N, 13.12; found: C, 71.31; H, 5.74; N, 13.27]; LC/MS (ESI, m/z): found 641.5 [M + H]$^+$; exact mass 640.26 for $C_{38}H_{36}N_6O_4$.

*(1′R,2′S,3R,9a′R)-1′-(5-Bromo-1H-indol-3-yl)-6-chloro-2′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-1′,2′,4a′,5′,6′,7′,8′,8a′,9′,9a′-decahydrospiro[indoline-3,3′-pyrrolo[1,2-a]indol]-2-one (**8p**).* Following the general procedure (GP2), chalcone **5c** (102 mg, 0.25 mmol), 6-chloroisatin **6b** (46 mg, 0.25 mmol), and octahydro-1*H*-indole-2-carboxylic acid **7b** (64 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8p**; yield (155 mg, 89%); m.p.: 199−200 °C; $[\alpha]_D^{25}$ = −26.47° (c 0.12, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$) δ (ppm) = 8.72 (s, 1H, NH), 8.63 (s, 1H, NH), 8.12 (s, 1H, Ar-H), 8.05 (s, 1H, Ar-H), 7.43−7.39 (m, 3H, Ar-H), 7.31 (d, J = 8.0 Hz, 1H, Ar-H), 7.23 (d, J = 1.5 Hz, 2H, Ar-H), 7.15−7.12 (m, 2H, Ar-H), 7.11 (d, J = 2.5 Hz, 1H, Ar-H), 7.02 (dd, J = 8.0, 1.9 Hz, 1H, Ar-H), 6.35 (s, 1H, Ar-H), 4.79 (d, J = 12.0 Hz, 1H, CHCO), 4.38−4.33 (m, 1H, NCH), 4.09 (dd, J = 12.1, 10.1 Hz, 1H, NCHCH), 3.21 (q, J = 3.7 Hz, 1H, NCH), 2.22−2.17 (m, 1H, NCHCH), 1.98 (s, 3H, CH_3), 1.85−1.78 (m, 2H, CH_2), 1.60−1.56 (m, 1H, CH_2), 1.54−1.45 (m, 3H, CH_2), 1.22−1.17 (m, 1H, CH_2), 1.09−0.97 (m, 3H, CH_2); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 191.05 (CO), 181.83 (CO), 143.75, 142.03, 141.48, 138.22, 135.08, 134.65, 129.46, 129.36, 129.17, 129.15, 128.70, 127.14, 125.45, 125.03, 123.42, 122.38, 122.12, 121.67, 121.05, 114.32, 112.87, 110.15, 72.37, 70.86, 67.65, 57.77, 44.84, 41.96, 38.35, 28.57, 27.77, 24.77, 20.11, 11.80 (CH_3); IR (KBr, cm^{-1}) ν_{max} = 3273, 2926, 2853, 1733, 1699, 1674, 1652, 1615, 1557, 1538, 1532, 1504, 1483, 1456, 1398, 1373, 1322, 1278, 1220, 1179, 1130, 1102, 1072, 936, 932, 884, 869, 797, 765, 693, 670, 595, 525; [anal. calcd. for $C_{37}H_{33}BrClN_5O_2$: C, 63.94; H, 4.79; N, 10.08; found: C, 64.09; H, 4.86; N, 10.13]; LC/MS (ESI, m/z): found 695.0 [M($_{35}$Cl/$_{79}$Br) + H]$^+$, 696.3 [M($_{37}$Cl/$_{81}$Br) + H]$^+$, 698.1 [M($_{37}$Cl + $_{81}$Br) + H]$^+$; exact mass 693.15 for $C_{37}H_{33}BrClN_5O_2$.

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*(1′R,2′S,3R,9a′R)-1′-(5-Bromo-1H-indol-3-yl)-6-chloro-2′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-1′,2′,4a′,5′,6′,7′,8′,8a′,9′,9a′-decahydrospiro[indoline-3,3′-pyrrolo[1,2-a]indol]-2-one (**8q**).* Following the general procedure (GP2), chalcone **5c** (102 mg, 0.25 mmol), 5-nitroisatin **6c** (48 mg, 0.25 mmol), and octahydro-1*H*-indole-2-carboxylic acid **7b** (64 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 4 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield yellow solid compound **8q**; yield (120 mg, 68%); m.p.: 190−199 °C; $[\alpha]_D^{25}$ = −167.95° (c 0.10, MeOH); ^{1}H NMR (700 MHz, DMSO-d_6): δ (ppm) = 11.17 (d, *J* = 2.7 Hz, 1H, N<u>H</u>), 11.01 (s, 1H, N<u>H</u>), 8.26 (d, *J* = 2.3 Hz, 1H, Ar-<u>H</u>), 8.15 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-<u>H</u>), 8.04 (s, 1H, Ar-<u>H</u>), 8.03 (d, *J* = 1.9 Hz, 1H, Ar-<u>H</u>), 7.57 (d, *J* = 2.6 Hz, 1H, Ar-<u>H</u>), 7.53−7.50 (m, 2H, Ar-<u>H</u>), 7.48−7.45 (m, 1H, Ar-<u>H</u>), 7.36 (d, *J* = 7.1 Hz, 2H, Ar-<u>H</u>), 7.29 (d, *J* = 8.6 Hz, 1H, Ar-<u>H</u>), 7.18 (dd, *J* = 8.5, 1.9 Hz, 1H, Ar-<u>H</u>), 6.84 (d, *J* = 8.6 Hz, 1H, Ar-<u>H</u>), 4.88 (d, *J* = 12.0 Hz, 1H, C<u>H</u>CO), 4.17−4.11 (m, 2H, NC<u>H</u> + NCHC<u>H</u>), 3.23 (q, *J* = 3.4 Hz, 1H, NC<u>H</u>), 2.18−2.10 (m, 2H NCHC<u>H</u>$_2$), 1.81 (s, 3H, C<u>H</u>$_3$), 1.63−1.58 (m, 1H, C<u>H</u>$_2$), 1.54−150 (m, 1H, C<u>H</u>$_2$), 1.49−1.45 (m, 1H, C<u>H</u>$_2$), 1.38−1.28 (m, 2H, C<u>H</u>$_2$), 1.15−1.10 (m, 1H, C<u>H</u>$_2$), 1.03−0.97 (m, 1H, C<u>H</u>$_2$), 0.96−0.90 (m, 1H, C<u>H</u>$_2$), 0.77−0.72 (m, 1H, C<u>H</u>$_2$); ^{13}C NMR (176 MHz, DMSO-d_6): δ (ppm) = 190.50 (<u>C</u>O), 180.99 (<u>C</u>O), 148.17, 142.49, 141.54, 141.20, 137.91, 134.91, 129.31, 128.92, 128.81, 128.03, 126.51, 126.40, 125.20, 125.06, 123.62, 123.52, 123.33, 121.21, 120.55, 113.43, 112.57, 111.14, 109.61, 71.50, 70.72, 66.35, 56.77, 43.80, 41.56, 37.06, 27.65, 27.29, 24.42, 19.25, 11.08 (<u>C</u>H$_3$); IR (KBr, cm^{-1}) ν_{max} = 3363, 2930, 2854, 1734, 1762, 1621, 1599, 1528, 1503, 1478, 1454, 1398, 1337, 1221, 1178, 1126, 1098, 1081, 928, 884, 866, 831, 795, 765, 753, 693, 659, 598, 553; [anal. calcd. for $C_{37}H_{33}BrN_6O_4$: C, 63.94; H, 4.79; N, 10.08; found: C, 64.09; H, 4.86; N, 10.13]; LC/MS (ESI, *m*/*z*): found 705.8 [M($_{79}$Br) + H]$^+$, 707.5 [M($_{81}$Br) + H]$^+$, exact mass 704.17 for $C_{37}H_{33}BrN_6O_4$.

*(1′R,2′S,3R,9a′R)-6-Chloro-1′-(5-chloro-1H-indol-3-yl)-2′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-1′,2′,4a′,5′,6′,7′,8′,8a′,9′,9a′-decahydrospiro[indoline-3,3′-pyrrolo[1,2-a]indol]-2-one (**8r**).* Following the general procedure (GP2), chalcone **5d** (91 mg, 0.25 mmol), 6-chloroisatin **6b** (46 mg, 0.25 mmol), and octahydro-1*H*-indole-2-carboxylic acid **7b** (64 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8r**; yield (148 mg, 91%); m.p.: 168−169 °C; $[\alpha]_D^{25}$ = −121.51° (c 0.12, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$) δ (ppm) = 8.77 (d, *J* = 11.7 Hz, 1H, N<u>H</u>), 8.63 (s, 1H, N<u>H</u>), 8.13 (d, *J* = 2.0 Hz, 1H, Ar-<u>H</u>), 7.91 (d, *J* = 2.0 Hz, 1H, Ar-<u>H</u>), 7.45−7.39 (m, 3H, Ar-<u>H</u>), 7.31 (d, *J* = 8.0 Hz, 1H, Ar-<u>H</u>), 7.28−7.26 (m, 1H, Ar-<u>H</u>), 7.15−7.12 (m, 3H, Ar-<u>H</u>), 7.11 (dd, *J* = 8.6, 2.0 Hz, 1H, Ar-<u>H</u>), 7.02 (dd, *J* = 8.0, 1.9 Hz, 1H, Ar-<u>H</u>), 6.35 (s, 1H, Ar-<u>H</u>), 4.81 (d, *J* = 12.0 Hz, 1H, C<u>H</u>CO), 4.39−4.36 (m, 1H, NC<u>H</u>), 4.10 (dd, *J* = 11.9, 10.0 Hz, 1H, NCHC<u>H</u>), 3.22 (q, *J* = 3.7 Hz, 1H, NC<u>H</u>), 2.19−2.14 (m, 1H, NCHC<u>H</u>), 1.99 (s, 3H), 1.83−1.76 (m, 2H, C<u>H</u>$_2$), 1.58−1.53 (m, 1H, C<u>H</u>$_2$), 1.52−1.44 (m, 3H, C<u>H</u>$_2$), 1.19−1.15 (m, 1H, C<u>H</u>$_2$), 1.07−0.95 (m, 3H, C<u>H</u>$_2$); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 191.10 (<u>C</u>O), 181.85 (<u>C</u>O), 143.75, 142.06, 141.49, 138.22, 134.82, 134.65, 129.46, 129.16, 128.69, 128.47, 127.14, 125.45, 123.43, 122.60, 122.47, 121.65, 121.05, 119.07, 114.34, 112.48, 110.16, 72.39, 70.79, 67.65, 57.78, 44.90, 41.96, 38.35, 28.58, 27.77, 24.77, 20.12, 11.79 (<u>C</u>H$_3$); IR (KBr, cm^{-1}) ν_{max} = 3287,2925, 2854, 1723, 1661, 1652, 1615, 1538, 1533, 1504, 1484, 1398, 1373, 1320, 1277, 1221, 1178, 1131, 1104, 1072, 736, 926, 893, 869, 796, 763, 694, 606, 525; [anal. calcd. for $C_{37}H_{33}Cl_2N_5O_2$: C, 68.31; H, 5.11; N, 10.76; found: C, 68.25; H, 5.07; N, 10.84]; LC/MS (ESI, *m*/*z*): found 650.8 [M($_{35}$Cl) + H]$^+$, 652.0 [M($_{37}$Cl) + H]$^+$, 654.0 [M($_{37}$Cl + $_{37}$Cl) + H]$^+$; exact mass 649.2 for $C_{37}H_{33}Cl_2N_5O_2$.

*(1′R,2′S,3R,9a′R)-1′-(5-Chloro-1H-indol-3-yl)-2′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-5-nitro-1′,2′,4a′,5′,6′,7′,8′,8a′,9′,9a′-decahydrospiro[indoline-3,3′-pyrrolo[1,2-a]indol]-2-one (**8s**).* Following the general procedure (GP2), chalcone **5d** (91 mg, 0.25 mmol), 5-nitroisatin **6c** (48 mg, 0.25 mmol), and octahydro-1*H*-indole-2-carboxylic acid **7b** (64 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 4 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield yellow solid compound **8s**; yield (132 mg, 80%); m.p.: 172−173 °C; $[\alpha]_D^{25}$ = −11.15° (c 0.10, MeOH); ^{1}H NMR (700 MHz, DMSO-d_6): δ (ppm) = 11.15 (d, *J* = 2.6 Hz, 1H, N<u>H</u>), 11.01 (s, 1H, N<u>H</u>), 8.25 (d, *J* = 2.3 Hz, 1H, Ar-<u>H</u>), 8.15 (dd, *J* = 8.6, 2.3 Hz, 1H, Ar-<u>H</u>), 8.03 (s, 1H, Ar-<u>H</u>), 7.89 (d, *J* = 2.1 Hz, 1H, Ar-<u>H</u>), 7.58 (d, *J* = 2.5 Hz, 1H, Ar-<u>H</u>), 7.53−7.49 (m, 2H, Ar-<u>H</u>), 7.49−7.45 (m, 1H, Ar-<u>H</u>), 7.38−7.35 (m, 2H, Ar-<u>H</u>), 7.33 (d, *J* = 8.6 Hz, 1H, Ar-<u>H</u>), 7.07 (dd, *J* = 8.6, 2.0 Hz, 1H, Ar-<u>H</u>), 6.84 (d, *J* = 8.6 Hz, 1H, Ar-<u>H</u>), 4.88 (d, *J* = 12.0 Hz, 1H, C<u>H</u>CO), 4.15 (m, 2H, NC<u>H</u> + NCHC<u>H</u>), 3.23 (q, *J* = 3.4 Hz, 1H, NC<u>H</u>), 2.19−2.09 (m, 2H, C<u>H</u>$_2$), 1.81 (s, 3H, C<u>H</u>$_3$), 1.62−1.59 (m, 1H, C<u>H</u>$_2$), 1.55−1.50 (m, 1H, C<u>H</u>$_2$), 1.49−1.44 (m, 1H, C<u>H</u>$_2$), 1.39−1.27 (m, 2H, C<u>H</u>$_2$), 1.14−1.10 (m, 1H, C<u>H</u>$_2$), 1.03−0.97 (m, 1H, C<u>H</u>$_2$), 0.97−0.91 (m, 1H, C<u>H</u>$_2$), 0.77−0.72 (m, 1H, C<u>H</u>$_2$); ^{13}C NMR (176 MHz, DMSO-d_6): δ (ppm) = 190.50 (<u>C</u>O), 180.99 (<u>C</u>O), 148.17, 142.49, 141.53, 141.20, 137.91, 134.69, 129.31, 128.81, 128.18, 128.03, 126.51, 126.40, 125.20, 123.81, 123.15, 121.00, 120.54, 118.20, 112.96, 112.64, 109.61, 71.51, 70.67, 66.34, 56.78, 43.83, 41.56, 37.09, 27.65, 27.29, 24.42, 19.25, 11.07 (<u>C</u>H$_3$); IR (KBr, cm^{-1}) ν_{max} = 3349, 2928, 2853, 1732, 1661, 1623, 1598, 1537, 1525, 1504, 1455, 1398, 1337, 1220, 1178, 1128, 1099, 1078, 931, 892, 867, 833, 798, 766, 755, 694, 552; [anal. calcd. for $C_{37}H_{33}ClN_6O_4$: C, 67.22; H, 5.03; N, 12.71; found: C, 67.34; H, 12.63; N, 12.56]; LC/MS (ESI, *m*/*z*): found 661.6 [M($_{35}$Cl) + H]$^+$, 663.3 [M($_{37}$Cl) + H]$^+$, exact mass 660.23 for $C_{37}H_{33}ClN_6O_4$.

*(1′R,2′S,3R,7a′R)-6-Chloro-1′-(1H-indol-3-yl)-2′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**8t**).* Following the general procedure (GP2), chalcone **5a** (82 mg, 0.25 mmol), 6-chloroisatin **6b** (46 mg, 0.25 mmol), and L-proline **7c** (43 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8t**; yield (103 mg, 73%); m.p.: 165−166 °C; $[\alpha]_D^{25}$ = −32.67° (c 0.12, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 9.13 (s, 1H, N<u>H</u>), 8.33 (s, 1H, N<u>H</u>), 8.09−8.04 (m, 1H, Ar-<u>H</u>), 7.93 (s, 1H, Ar-<u>H</u>), 7.41−7.35 (m, 3H, Ar-<u>H</u>), 7.32−7.30 (m, 1H, Ar-<u>H</u>), 7.29 (d, *J* = 8.1 Hz, 1H, Ar-<u>H</u>), 7.23 (d, *J* = 2.4 Hz, 1H, Ar-<u>H</u>), 7.19−7.13 (m, 4H, Ar-<u>H</u>), 6.99 (dd, *J* = 8.0, 1.9 Hz, 1H, Ar-<u>H</u>), 6.63 (d, *J* = 1.9 Hz, 1H, Ar-<u>H</u>), 4.89 (d, *J* = 11.4 Hz, 1H, C<u>H</u>CO), 4.49−4.46 (m, 1H, NC<u>H</u>), 4.19 (dd, *J* = 11.5, 9.9 Hz, 1H, NCHC<u>H</u>), 2.80−2.75 (m, 1H, NC<u>H</u>$_{2(a)}$), 2.70−2.66 (m, 1H, NC<u>H</u>$_{2(b)}$), 2.09 (s, 3H, C<u>H</u>$_3$), 2.06−2.02 (m, 1H, C<u>H</u>$_2$), 1.97−1.91 (m, 1H C<u>H</u>$_2$), 1.90−1.85

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(m, 1H C$\underline{H}_2$), 1.79−1.73 (m, 1H C$\underline{H}_2$); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) =191.91 ($\underline{C}$O), 181.47 ($\underline{C}$O), 143.56, 142.53, 141.27, 138.24, 136.68, 134.93, 129.33, 128.97, 128.86, 126.77, 125.58, 124.44, 122.32, 122.10, 121.88, 121.27, 119.90, 119.67, 114.21, 111.44, 110.70, 73.77, 70.74, 65.90, 48.38, 44.74, 31.06, 27.28, 12.00 ($\underline{C}H_3$); IR (KBr, cm^{-1}) ν_{max} = 3273, 3056, 2962, 2867, 1733, 1661, 1653, 1613, 1536, 1531, 1502, 1486, 1453, 1396, 1324, 1285, 1244, 1222, 1185, 1131, 1072, 936, 922, 813, 794, 763, 741, 694, 526; [anal. calcd. for $C_{33}H_{28}ClN_5O_2$: C, 70.52; H, 5.02; N, 12.46; found: C, 70.66; H, 4.91; N, 12.53]; LC/MS (ESI, m/z): found 562.4 [M($_{35}$Cl) + H]$^+$, 564.1 [M($_{37}$Cl) + H]$^+$; exact mass 561.19 for $C_{33}H_{28}ClN_5O_2$.

*(1′R,2′S,3R,7a′R)-6-Chloro-2′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-1′-(1-methyl-1H-indol-3-yl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**8u**).* Following the general procedure (GP2), chalcone **5b** (85 mg, 0.25 mmol), 6-chloroisatin **6b** (46 mg, 0.25 mmol), and L-proline **7c** (43 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8u**; yield (124 mg, 87%); m.p.: 150−151 °C; $[\alpha]_D^{25}$ = −23.35° (c 0.11, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 9.02 (s, 1H, N$\underline{H}$), 8.07 (d, J = 7.9 Hz, 1H, Ar-$\underline{H}$), 7.89 (s, 1H, Ar-$\underline{H}$), 7.41−7.35 (m, 3H, Ar-$\underline{H}$), 7.30−7.26 (m, 2H, Ar-$\underline{H}$), 7.23−7.20 (m, 1H, Ar-$\underline{H}$), 7.17 (dd, J = 16.0, 7.6 Hz, 3H, Ar-$\underline{H}$), 7.13 (s, 1H, Ar-$\underline{H}$), 6.99 (dd, J = 8.0, 1.9 Hz, 1H, Ar-$\underline{H}$), 6.65 (d, J = 1.9 Hz, 1H, Ar-$\underline{H}$), 4.85 (d, J = 11.5 Hz, 1H, C$\underline{H}$CO), 4.50−4.45 (m, 1H, NC$\underline{H}$), 4.16 (dd, J = 11.5, 10.0 Hz, 1H, NCHC$\underline{H}$), 3.73 (s, 3H, NC$\underline{H}_3$), 2.82−2.76 (m, 1H, NC$\underline{H}_{2(a)}$), 2.70−2.65 (m, 1H, NC$\underline{H}_{2(b)}$), 2.09 (s, 3H, C$\underline{H}_3$), 2.07−2.01 (m, 1H, C$\underline{H}_2$), 1.98−1.92 (m, 1H, C$\underline{H}_2$), 1.90−1.86 (m, 1H, C$\underline{H}_2$), 1.78−1.73 (m, 1H, C$\underline{H}_2$); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 191.89 ($\underline{C}$O), 181.46 ($\underline{C}$O), 143.51, 142.51, 141.24, 138.29, 137.38, 134.91, 129.32, 128.93, 128.86, 127.21, 126.92, 125.58, 124.47, 121.86, 121.71, 121.29, 120.07, 119.21, 112.71, 110.64, 109.44, 73.67, 70.80, 66.02, 48.43, 44.66, 32.82 (N$\underline{C}H_3$), 30.96, 27.19, 12.01 ($\underline{C}H_3$); IR (KBr, cm^{-1}) ν_{max} = 3216, 3058, 2958, 2872, 1733, 1662, 1614, 1536, 1503, 1484, 1455, 1398, 1326, 1285, 1227, 1184, 1130, 1172, 1012, 935, 922, 815, 795, 765, 740, 694; [anal. calcd. for $C_{34}H_{30}ClN_5O_2$: C, 70.89; H, 5.25; N, 12.16; found: C, 71.11; H, 5.16; N, 12.01]; LC/MS (ESI, m/z): found 576.5 [M($_{35}$Cl) + H]$^+$, 578.2 [M($_{37}$Cl) + H]$^+$; exact mass 575.21 for $C_{34}H_{30}ClN_5O_2$.

*(1′R,2′S,3R,7a′R)-1′-(5-Bromo-1H-indol-3-yl)-2′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**8v**).* Following the general procedure (GP2), chalcone **5c** (102 mg, 0.25 mmol), isatin **6a** (37 mg, 0.25 mmol), and L-proline **7c** (43 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8v**; yield (136 mg, 90%); m.p.: 178−179 °C; $[\alpha]_D^{25}$ = −37.86° (c 0.10, MeOH); ^{1}H NMR (700 MHz, DMSO-d_6) δ (ppm) = 11.16 (s, 1H, N$\underline{H}$), 10.35 (s, 1H, N$\underline{H}$), 8.10 (s, 1H, Ar-$\underline{H}$), 7.85 (d, J = 3.0 Hz, 1H, Ar-$\underline{H}$), 7.51−7.46 (m, 3H, Ar-$\underline{H}$), 7.44 (d, J = 9.1 Hz, 1H, Ar-$\underline{H}$), 7.39 (d, J = 7.9 Hz, 1H, Ar-$\underline{H}$), 7.34−7.29 (m, 3H, Ar-$\underline{H}$), 7.19 (d, J = 10.5 Hz, 1H, Ar-$\underline{H}$), 7.14−7.10 (m, 1H, Ar-$\underline{H}$), 6.98−6.94 (m, 1H, Ar-$\underline{H}$), 6.65 (d, J = 10.3 Hz, 1H, Ar-$\underline{H}$), 4.68 (d, J = 11.7 Hz, 1H, C$\underline{H}$CO), 4.09 (t, J = 12.0 Hz, 1H, NCHC$\underline{H}$), 4.05−4.01 (m, 1H, NC$\underline{H}$), 2.62−2.57 (m, 1H, NC$\underline{H}_{2(a)}$), 2.39−2.35 (m, 1H, NC$\underline{H}_{2(b)}$), 1.94−1.90 (m, 1H, C$\underline{H}_2$), 1.89 (s, 3H, C$\underline{H}_3$), 1.87−1.84 (m, 1H, C$\underline{H}_2$), 1.80−1.75 (m, 1H, C$\underline{H}_2$), 1.75−1.69 (m, 1H, C$\underline{H}_2$); ^{13}C NMR (176 MHz, DMSO-d_6) δ (ppm) = 191.33 ($\underline{C}$O), 179.87 ($\underline{C}$O), 142.37, 141.96, 140.86, 138.03, 135.10, 129.29, 129.08, 128.74, 128.70, 127.85, 125.27, 125.23, 123.96, 123.53, 121.32, 120.99, 120.78, 113.57, 113.33, 111.21, 109.43, 73.20, 71.04, 65.39, 47.42, 43.25, 30.49, 27.08, 11.21 ($\underline{C}H_3$); IR (KBr, cm^{-1}) ν_{max} = 3270, 2958, 2928, 2869, 1717, 1662, 1653, 1616, 1597, 1538, 1504, 1470, 1457, 1397, 1330, 1268, 1221, 1190, 1104, 936, 884, 793, 754, 694, 678, 659, 610; [anal. calcd. for $C_{33}H_{28}BrN_5O_2$: C, 65.35; H, 4.65; N, 11.55; found: C, 65.24; H, 4.77; N, 11.49]; LC/MS (ESI, m/z): found 606.7 [M($_{79}$Br) + H]$^+$, 608.4 [M($_{81}$Br) + H]$^+$; exact mass 605.14 for $C_{33}H_{28}BrN_5O_2$.

*(1′R,2′S,3R,7a′R)-1′-(5-Chloro-1H-indol-3-yl)-2′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-5-nitro-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**8w**).* Following the general procedure (GP2), chalcone **5d** (91 mg, 0.25 mmol), 5-nitroisatin **6c** (48 mg, 0.25 mmol), and L-proline **7c** (43 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 6 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield yellow solid compound **8w**; yield (74 mg, 49%); m.p.: 225−226 °C; $[\alpha]_D^{25}$ = −67.91° (c 0.13, MeOH); ^{1}H NMR (700 MHz, DMSO-d_6) δ (ppm) = 11.18 (s, 1H, N$\underline{H}$), 11.16 (s, 1H, N$\underline{H}$), 8.14 (dd, J = 8.6, 2.3 Hz, 1H, Ar-$\underline{H}$), 8.12 (d, J = 2.3 Hz, 1H, Ar-$\underline{H}$), 7.93 (d, J = 2.1 Hz, 1H, Ar-$\underline{H}$), 7.84 (s, 1H), 7.55 (d, J = 2.5 Hz, 1H, Ar-$\underline{H}$), 7.51−7.48 (m, 2H, Ar-$\underline{H}$), 7.47−7.44 (m, 1H, Ar-$\underline{H}$), 7.36 (d, J = 8.6 Hz, 1H, Ar-$\underline{H}$), 7.31 (d, J = 8.6 Hz, 2H, Ar-$\underline{H}$), 7.08 (dd, J = 8.6, 2.0 Hz, 1H, Ar-$\underline{H}$), 6.88 (d, J = 8.6 Hz, 1H, Ar-$\underline{H}$), 4.75 (d, J = 11.4 Hz, 1H, C$\underline{H}$CO), 4.15−4.09 (m, 2H, NC$\underline{H}$ + NCHC$\underline{H}$), 2.70−2.65 (m, 1H, NC$\underline{H}_{2(a)}$), 2.46−2.42 (m, 1H, NC$\underline{H}_{2(b)}$), 1.99−1.94 (m, 1H, C$\underline{H}_2$), 1.92 (s, 3H, C$\underline{H}_3$) 1.90−1.88 (m, 1H, C$\underline{H}_2$), 1.84−1.76 (m, 2H, C$\underline{H}_2$); ^{13}C NMR (176 MHz, DMSO-d_6) δ (ppm) = 191.15 ($\underline{C}$O), 180.27 ($\underline{C}$O), 148.48, 142.63, 141.67, 140.69, 137.82, 134.92, 129.30, 128.86, 127.70, 126.56, 126.22, 125.19, 124.53, 123.23, 122.78, 121.03, 120.59, 118.14, 113.15, 112.52, 109.86, 72.44, 70.67, 65.39, 47.41, 43.52, 30.02, 27.09, 11.21 ($\underline{C}H_3$); IR (KBr, cm^{-1}) ν_{max} = 3408, 3378, 3111, 3058, 2973, 2861, 2836, 1748, 1645, 1622, 1598, 1525, 1503, 1479, 1455, 1417, 1392, 1373, 1338, 1293, 1253, 1221, 1188, 1174, 1137, 1100, 1076, 986, 938, 930, 887, 860, 850, 832, 798, 763, 755, 694, 655, 610, 554; [anal. calcd. for $C_{33}H_{27}ClN_6O_4$: C, 65.29; H, 4.48; N, 13.84; found: C, 65.39; H, 4.56; N, 13.87]; LC/MS (ESI, m/z): found 607.5 [M ($_{35}$Cl) + H]$^+$, 609.2 [M ($_{35}$Cl) + H]$^+$; exact mass 606.18 for $C_{33}H_{27}ClN_6O_4$.

*(2′R,3′S,4′R)-6-Chloro-4′-(1H-indol-3-yl)-1′-methyl-3′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)spiro[indoline-3,2′-pyrrolidin]-2-one (**8x**).* Following the general procedure (GP2), chalcone **5a** (82 mg, 0.25 mmol), 6-chloroisatin **6b** (46 mg, 0.25 mmol), and sacrosine **7d** (34 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8x**; yield (48 mg, 35%); m.p.: 140−141 °C; $[\alpha]_D^{25}$ = −19.37° (c 0.10, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 8.51 (s, 1H, N$\underline{H}$), 8.19 (s, 1H, N$\underline{H}$), 8.08 (d, J = 9.5 Hz, 1H, Ar-$\underline{H}$), 7.73 (s, 1H, Ar-$\underline{H}$), 7.45−7.38 (m, 3H, Ar-$\underline{H}$), 7.33−7.30 (m, 1H, Ar-$\underline{H}$), 7.26 (d, J = 1.2 Hz, 1H, Ar-$\underline{H}$), 7.20−7.14 (m, 5H, Ar-$\underline{H}$), 6.92 (dd, J = 8.0, 1.9 Hz, 1H, Ar-$\underline{H}$), 6.49 (d, J = 1.8 Hz, 1H, Ar-$\underline{H}$), 4.80−4.73 (m, 1H, NCH$_2$C$\underline{H}$), 4.45 (d, J = 9.6 Hz, 1H, C$\underline{H}$CO), 3.86−3.81 (m, 1H, NC$\underline{H}_{2(a)}$), 3.49−3.45

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(m, 1H, NC$\underline{H}_{2(b)}$), 2.29 (s, 3H, NC$\underline{H}_3$), 2.17 (s, 3H, C$\underline{H}_3$); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 192.45 ($\underline{C}$O), 180.34 ($\underline{C}$O), 143.46, 142.23, 140.55, 138.20, 136.60, 134.48, 129.44, 129.18, 127.71, 126.87, 126.77, 125.71, 122.53, 122.21, 122.16, 121.44, 120.04, 119.75, 115.62, 111.30, 109.77, 73.69, 64.47, 59.54, 35.99, 35.30 (N$\underline{C}$H$_3$), 11.91 ($\underline{C}$H$_3$); IR (KBr, cm^{-1}) ν_{max} = 3278, 3072, 2934, 2826, 2797, 1726, 1666, 1654, 1612, 1597, 1534, 1503, 1485, 1552, 1398, 1322, 1284, 1240, 1216, 1179, 1119, 1094, 1069, 936, 910, 882, 814, 798, 766, 718, 693, 592; [anal. calcd. for $C_{31}H_{26}ClN_5O_2$: C, 69.46; H, 4.89; N, 13.07; found: C, 69.31; H, 4.97; N, 12.93]; LC/MS (ESI, m/z): found 536.4 [M($_{35}$Cl) + H]$^+$, 538.2 [M($_{37}$Cl) + H]$^+$; exact mass 535.18 for $C_{31}H_{26}ClN_5O_2$.

*(2′R,3′S,4′R)-4′-(5-Bromo-1H-indol-3-yl)-6-chloro-1′-methyl-3′-(5-methyl-1-phenyl-1H-pyrazole-4-carbonyl)-spiro[indoline-3,2′-pyrrolidin]-2-one (**8y**).* Following the general procedure (GP2), chalcone **5c** (102 mg, 0.25 mmol), 6-chloroisatin **6b** (46 mg, 0.25 mmol), and sacrosine **7d** (34 mg, 0.37 mmol) in methanol (20 mL) were refluxed for 3 h and purified by column chromatography 100−200 mesh silica gel and MeOH/CH_2Cl_2 (3:97) to yield light yellow solid compound **8y**; yield (73 mg, 47%); m.p.: 158−159 °C; $[\alpha]_D^{25}$ = −35.63° (c 0.12, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$): δ (ppm) = 8.99 (s, 1H, N$\underline{H}$), 8.42 (s, 1H, N$\underline{H}$), 8.18 (s, 1H, Ar-$\underline{H}$), 7.77 (s, 1H, Ar-$\underline{H}$), 7.44−7.38 (m, 3H, Ar-$\underline{H}$), 7.22 (dd, J = 8.7, 2.0 Hz, 2H, Ar-$\underline{H}$), 7.18−7.11 (m, 4H, Ar-$\underline{H}$), 6.92 (dd, J = 8.0, 1.8 Hz, 1H, Ar-$\underline{H}$), 6.54 (d, J = 1.8 Hz, 1H, Ar-$\underline{H}$), 4.70 (q, J = 9.8 Hz, 1H, NCH$_2$C$\underline{H}$), 4.36 (d, J = 9.4 Hz, 1H, C$\underline{H}$CO), 3.75 (t, J = 9.5 Hz, 1H, NC$\underline{H}_{2(a)}$), 3.46 (t, J = 9.5 Hz, 1H, NC$\underline{H}_{2(b)}$), 2.27 (s, 3H, NC$\underline{H}_3$), 2.19 (s, 3H, C$\underline{H}_3$); ^{13}C NMR (176 MHz, $CDCl_3$): δ (ppm) = 192.35 ($\underline{C}$O), 180.67 ($\underline{C}$O), 143.63, 142.34, 140.51, 138.14, 135.16, 134.58, 129.47, 129.24, 128.70, 127.64, 126.53, 125.71, 125.00, 123.27, 122.55, 122.51, 121.38, 115.62, 113.00, 112.75, 110.02, 73.75, 64.57, 59.54, 35.58, 35.26 (N$\underline{C}$H$_3$), 11.93 ($\underline{C}$H$_3$); IR (KBr, cm^{-1}) ν_{max} = 3276, 3071, 2936, 2843, 2795, 1722, 1668, 1652, 1613, 1598, 1537, 1504, 1484, 1554, 1397, 1321, 1280, 1244, 1219, 1181, 1115, 1096, 1068, 938, 916, 883, 813, 793, 765, 714, 694, 593; [anal. calcd. for $C_{31}H_{25}BrClN_5O_2$: C, 60.55; H, 4.10; N, 11.39; found: C, 60.41; H, 4.15; N, 11.47]; LC/MS (ESI, m/z): found 614.8 [M($_{35}$Cl/$_{79}$Br) + H]$^+$, 616.1 [M($_{37}$Cl/$_{81}$Br) + H]$^+$, 618.0 [M($_{37}$Cl + $_{81}$Br) + H]$^+$, exact mass 613.09 for $C_{31}H_{25}BrClN_5O_2$.

Acetylcholine Esterase (AChE) Inhibitory Assay (AChEI). AChEI activity was measured using Ellman's method as previously described and provided in the Supporting Information.[39b,c]

Molecular Docking Study. The protocol for the molecular docking study to investigate the binding mode of the most active compounds are provided in the Supporting Information.[43]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c03978.

AChE assay; molecular docking study protocol; copies of NMR and MS spectrum; and also X-ray single-crystal analysis of compound **8c** (PDF)

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Notes

The authors declare no competing financial interest.

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