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SYNTHESIS AND ANTITUMOR ACTIVITY OF HETEROCYLIC AURONE AND ITS ANALOGUE INDANONE DERIVATIVES

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Abstract – Based on non-classical bioisosterism and the rule of alkene insertion, thirty-five heterocyclic aurones and its analogue indanones derivatives were designed and synthesized. They were evaluated for inhibitory activity against HELA, HT-29 and A549 and HepG2 human cancer cell lines. Among them, twenty-five compounds exhibited moderate to excellent antitumor activity. The minimum value of IC_{50} was 1.649±0.083 μM (compound **B1**). The SAR showed that aurone with B ring as aromatic heterocycles such as 4-bromothiophene, quinoline, carbazole and indanone derivatives and some or indanone were more potent than others. Besides, the introduction of acetylated glycosides was beneficial to the activity. Compounds **A1**, **B1**, **C5**, **C8**, **C10**, **C11**, **C12** and **D1** were promising antitumor agents. Among them, compounds molecular docking studies were performed between **B1**, **C8** and potential targets Aurora B (PBD: 2BFY). On the basis, the chemical and physical properties, as well as ADMET of active compounds were predicted and analyzed. And it showed that most of compounds had good pharmacokinetic profiles and high safety profiles.

INTRODUCTION

Tumors are one of the major diseases causing human mortality, caused by the long-term abnormal proliferation of tissue cells.[1] Tumor cells are not regulated by normal organism physiology and consume a lot of nutrients consumed by patients, which leads to dysfunction of organism and causes necrosis and

death patients. Tumor not only brings great pain to patients, but also brings heavy burden and serious harm to families and society.

Aurones are a subclass of flavonoids that have received attention because of their broad range of activities, including antitumor,[2-4] antibacterial,[5] anti-inflammatory[6] and antiviral activities.[7,8] However, the amount of aurones in nature is much smaller than flavones and chalcones etc., which greatly limits its research. According to the principle of bioelectronic equipartition, the oxygen atom in the nucleus of aurone (2-benzylidene-1-benzofuran-3(2*H*)-one) is transposed to the carbon atom to obtain the indanone structure (2-benzylidene-1-indanone). Aurones, indanones and their heterocycle substituted derivatives have attracted attention for their prominent antitumor activity, mainly focusing on the activity studies against colon, cervical, myeloid leukemia, lung, breast and liver cancers.[9-13] And some are regarded as promising antitumor leading compounds (Figure 1). However, reported aurones studies have a few limitations, such as high toxicity, poor metabolic properties, narrow antitumor spectrum, etc., and further in-depth studies are still needed.

Our previous work suggested that the compound **HJ-I** (Figure 1), obtained from *Coreopsis tinctoria*, had anti-hepatocarcinoma activity. The **HJ-1** was structurally modified to improve the antitumor activity (Figure 2), since the change from aurone to indanone was attempted.[14] The benzene ring of the B-ring was replaced by various aromatic heterocycle with a steric hindrance, and the hydroxyl group was modified to improve the lipid-water partition coefficient (Log P). In addition, the heterocyclic aurones containing acetylated glycosides were found to have the strongest antitumor activity, which deserved to be studied in depth.

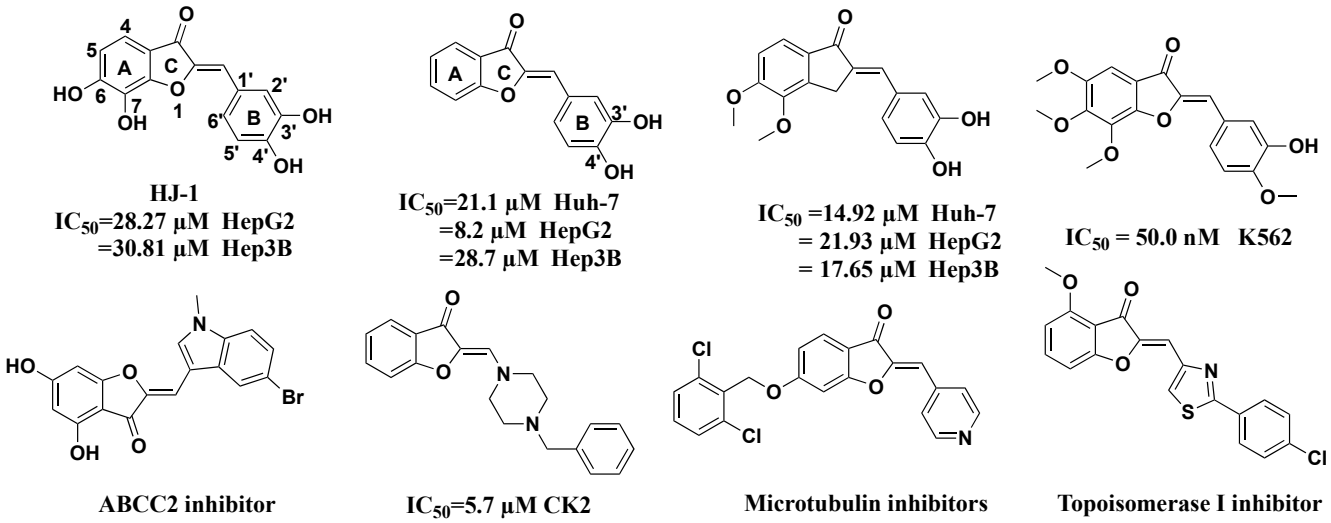

Figure 1. Anti-hepatoma activity of aurone and aurone analogues

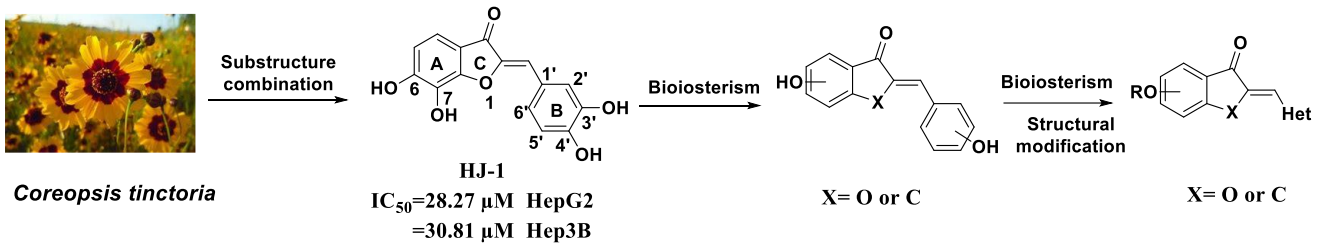

Figure 2. Design of aurone and indanone derivatives

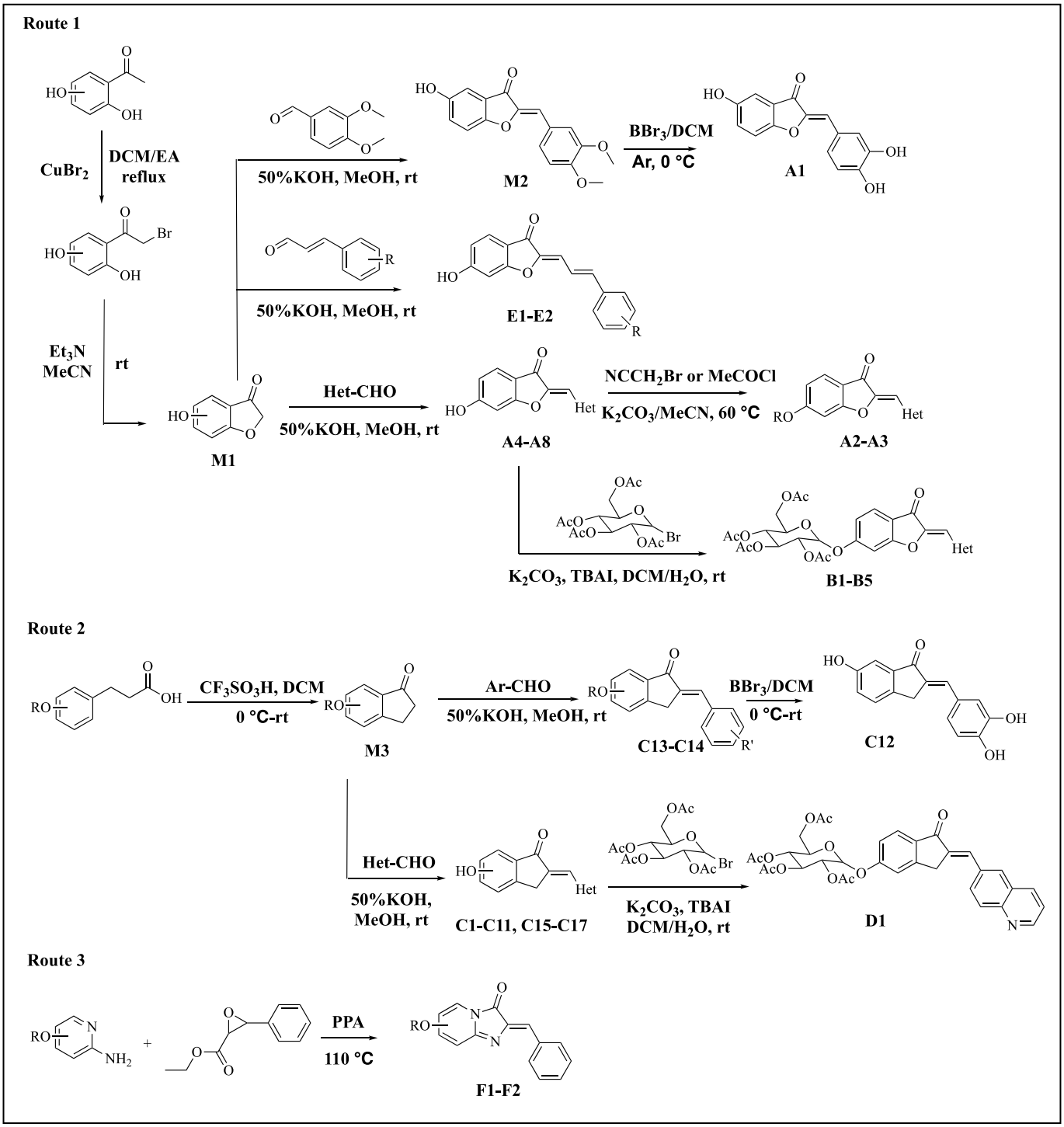

Figure 3. Synthetic routes of target compounds

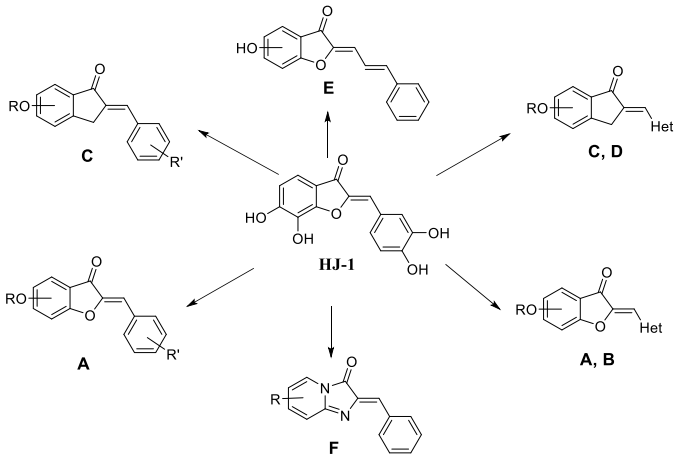

Figure 4. Synthesis of various backbones in the beginning of the research

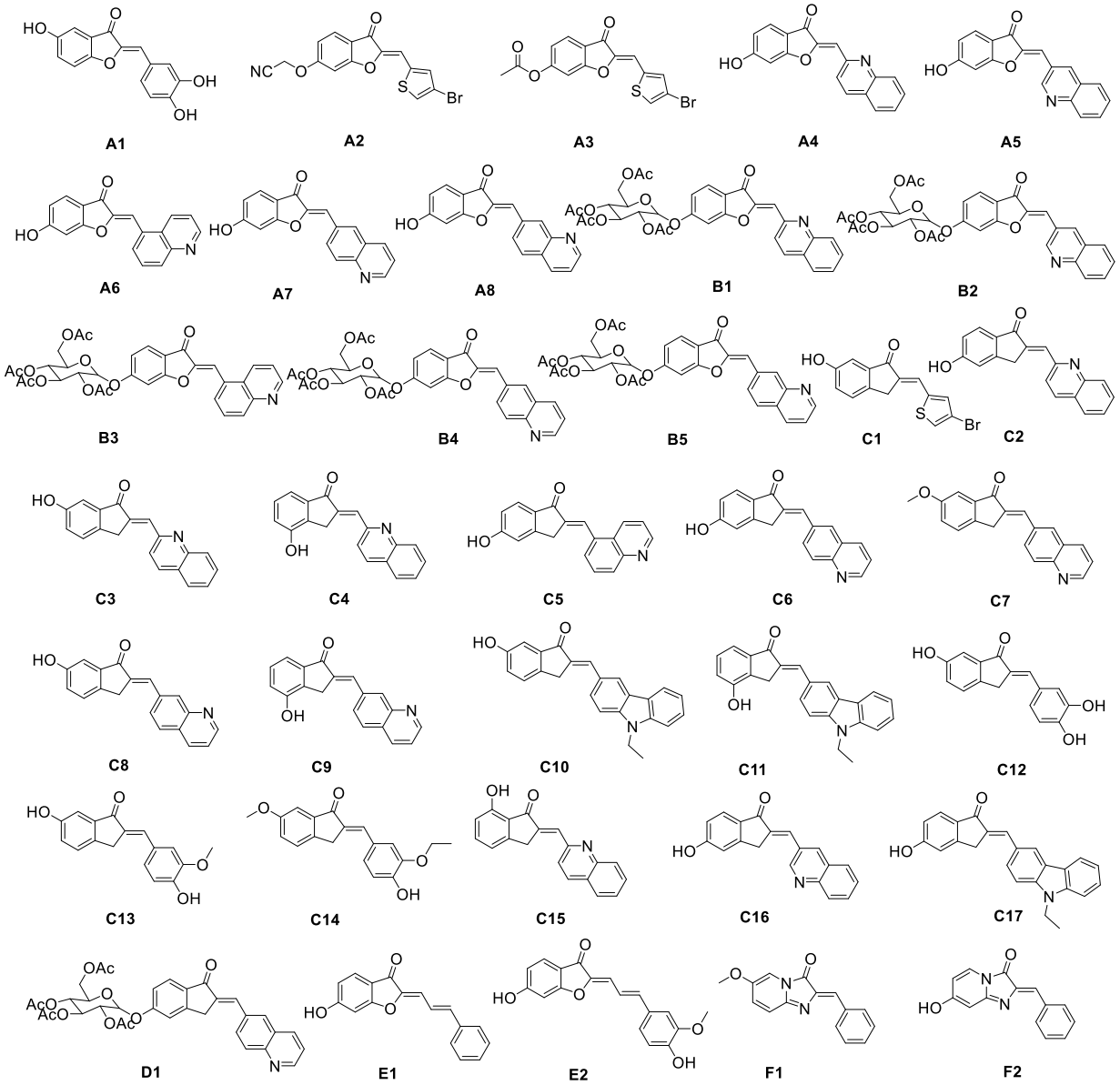

Figure 5. Structures of target compounds

RESULTS AND DISCUSSION

Synthesis. The aldol condensation reaction[15] was finally selected to construct the tricyclic skeletons of the aurone and indanone derivatives (Figure 3). For the synthesis of aurone derivatives, 2,4-dihydroxyacetophenone was used as the starting material to generate intermediate hydroxybenzofuran-3(2*H*)-one (**M1**) in the presence of copper bromide and triethylamine. Then, 6-hydroxybenzofuran-3(2*H*)-one was reacted with benzaldehyde, aromatic heterocyclic aldehyde or cinnamaldehyde containing substituents in the presence of 50% KOH solution using anhydrous methanol as solvent to produce the corresponding aurone and its derivatives (**M2**, **E1**-**E2**, **A4**-**A8**). The synthesis of indanone derivatives was based on phenylpropanoids, which first produced 2,3-dihydro-1*H*-inden-1-one (**M3**) containing substituents by intramolecular Friedel-Crafts acylation under the action of trifluoromethanesulfonic acid. Similar to the aurone derivatives, the intermediates (**M3**) underwent aldol condensation reaction to obtain the corresponding 2-arylidene-1-indanone derivatives (**C1**-**C17**). Some of the aurone and indanone products were demethylated in the presence of BBr_3 to get compound **A1** and **C12**. Also, some derivatives underwent nucleophilic substitution reactions with 2,3,4,6-tetraacetoxy-α-D-glucopyranosyl bromide, 2-bromoacetonitrile or acetyl chloride under alkalinity, producing corresponding target products (**A2**-**A3**, **B1**-**B5**, **D1**). All the structures of the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS analysis. Among these thirty-five compounds, twenty-seven were novel.

In the synthesis work, we tried a variety of methods to build the aurone skeleton, such as aldol condensation, metal catalysis, rearrangement reaction, etc. The aldol condensation stood out. In the experiment, it was found that the yield not only depended on the electronic effect of the raw material, but also closely related to the solubility of the product. The Cannizzaro reaction was the main side reaction that could be reduced by controlling lower temperatures, adding aldehydes drop-by-drop, and appropriately reducing the amount of base. For the glycosylation of hydroxyl groups, we used a two-phase solvent of water and dichloromethane. Potassium carbonate and tetrabutylammonium iodide acted as a base and tetrabutylammonium iodide as the phase transfer catalyst. The room temperature was essential for the specificity of the reaction to generate the desired product. In order to improve the reactivity, the amount of alkali could be appropriately increased. The synthetic route had mild conditions, high yield, few side reactions and simple post-treatment.

Antitumor Activity. In the beginning of structural modifications, we tried to synthesize various skeletons such as compounds **A1**, **B1**, **C1**, **C12**, **D1**, **E1**, **F1** (Figure 4, Figure 5). According to the activity evaluation, aurone and indanone derivatives were superior than others. Our previous studies indicated that the 6-hydroxyl group of aurone was required, while the position of hydroxyl group of indanone was flexible. Based on the non-classical bioisosterism, the B-ring of aurone was replaced by aromatic

heterocycles, such as thiophene, quinoline and carbazole, which resulted in a significant increase in antitumor activity. For structural diversity, the oxygen atom was substituted by carbon atom, and obtain indanone derivatives. In addition, modification on hydroxyl groups and introduction of acetylated glycosides were carried out to improve the membrane permeability.

The in vitro antitumor activity of the compounds was determined against HELA, HT-29, A549, HepG2 human cancer cell lines by MTT assay. Compounds with >50% inhibition at 50 μM were further assayed for median inhibition concentration (IC_{50}) (Table 1). Both the aurone and indanone derivatives had potent antitumor activity. The most active one was compound **B1**, with IC_{50} values of 2.202 ± 0.132 μM, 3.748 ± 0.417 μM and 1.649 ± 0.083 μM against HELA, HT-29 and A549 cells, respectively.

In the aspect of the SAR, the 3,4-dihydroxyphenyl on B ring was essential for the selectivity and activity against HELA cells (compounds **A1** and **C12**) in aurone and indanone skeletons. However, the activity was decreased when the hydroxyl group was alkylated. For heterocyclic aurone derivatives, compounds with a large steric hindrance aromatic heterocyclic ring, such as 2-quinoline or 4-bromothiophene were more potent. The activity was significantly enhanced when 6-hydroxyl group was modified by acetylated glycosylation (e.g. compounds **A4**-**A7** and **B1**-**B4**). An enlarged antitumor spectrum and slight decrease in activity were observed when 6-OH was acetylated or alkylated (compounds **A2** and **A3**). For indanone derivatives, the hydroxyl group on 5-, 6- or 4-position of A ring was beneficial to the activity. While 7-OH would lead to a loss in antitumor activity, probably due to intramolecular hydrogen bonding and low solubility. The activity was improved when the B ring was substituted with 2-quinoline, 5-quinoline, 6-quinoline, 7-quinoline, N-ethylcarbazole and 4-bromothiophene. Although the acetylated glycosides were introduced to of 6-OH of A ring, the effect of compounds **C8** and **D1** on cancer cells were comparable. The activity of quinoline indanone derivatives was similar to that of quinoline aurone glycoside (compounds **C6**, **C8**, **C10**-**C12** and **B1**-**B4**).

Overall, most of the indanone derivatives were more active than corresponding aurone derivatives (compounds **A4** and **C2**, **A6** and **C5**, **A7** and **C6**). The modification of the hydroxyl on A-ring of aurones and indanones with water-soluble groups seemed to be more reasonable. Heterocyclic aurone glycosides (compound **B1**-**B4**) and heterocyclic indanones (compound **C8**, **C10**, **C11** and **C12**) were promising classes of antitumor compounds that deserved further research.

Molecular Docking. Aurora B was found to be a very promising target for tumor. Molecular docking studies were performed by DS 2019 to analyze the interaction between the active derivatives (**B1** and **C8**) and Aurora B (PDB: 2BFY).[16] The docking energy values between **B1** and Aurora B was -34.0299 KJ/mol. The carbonyl group of benzofuranone formed a hydrogen bond with ALA173 (Figure 6). The other two hydrogen bonds were formed by the acetyl group on the glycoside interacting with LYS180 and GLU177. The acetyl group also had a hydrophobic interaction with ARG97. In addition, the benzene and

quinoline rings formed a large number of hydrophobic interactions with LEU99, PHE172, LYS103, VAL107, ALA120, LEU223 and LEU170, which enhanced the binding of the compound to the protein. Pi-cation interactions were formed by the quinoline ring with LYS122. As for compound **C8** (Figure 7), the 6-OH respectively formed hydrogen bonds with LYS122 and ASP234. The quinoline ring formed a large number of hydrophobic interactions with LEU99, VAL107, PRO174, and ALA173, which stabilized the protein-small molecule complex. In contrast **B1** and **C8**, the introduction of glycosides not only changed the physicochemical properties of the compounds, but also strengthened the interaction with the targets.

Chemical and Physical Properties. Since most antitumor drugs needed to penetrate membranes to reach their targets, it is crucial to investigate the effects of lipid solubility, polarity and membrane permeability of compounds. The data was from PubChem, ChemSpider, Reaxys, Zinc, ChemDraw, Swiss, etc.[17] (Table 2).

In the predicted compounds, CLogP indicated most of them had good lipid solubility. And most compounds met Lipinski's rule. The TPSA of compounds suggested that aurone and indanone derivatives had good membrane permeability, and the latter one was better, which was consistent with drug design ideas of bioisosterism. As for the potential toxicity of the compounds, CMR showed the predicted compounds were enough safe. However, the low solubility of various skeletal was unsatisfactory. Therefore, N-containing heterocycles such as piperidine, piperazine, pyridine, etc. or polar groups such as hydroxyl, carboxyl, trifluoromethyl, etc. would be introduced to promote solubility. Overall, the synthesized compounds showed excellent pharmacological and physicochemical properties, which deserved to be studied in depth.

ADMET Prediction. The ADMET properties of active compounds were further predicted to guide future structural design and optimization using DS 2019 software, and the results were shown in Table 3.

According to the results, the predicted absorption levels were all 0, indicating that the compounds were well absorbed. Most of the compounds had high plasma protein binding rates and might be adequately transported and maintained at more stable drug concentrations. The penetrant of most compounds was reasonable. Ames and NTP predictions showed that the vast majority of compounds were essentially free of potentially mutagenic and carcinogenic effects. Also, the TD50, LD50 and maximum tolerated dose predictions in rats demonstrated that the compounds had a high safety profile. Overall, the majority of compounds possessed good pharmacokinetic properties and were thought to be relatively safe based on ADMET predictions illustrated.

CONCLUSION

In summary, thirty-five compounds, including aurones and its analogues indanone derivatives, were designed and synthesized based on non-classical bioisosterism and the rule of alkene insertion. The inhibitory activities against HELA, HT-29, A549 and HepG2 human cancer cells were evaluated in vitro. Twenty-five compounds exhibited moderate to potent antitumor activity. The minimum value of IC_{50} was 1.649±0.083 μM (**B1**). The SAR study indicated that the antitumor activity was greatly enhanced when the B ring of aurone or indanone was replaced with aromatic heterocycles, such as 4-bromothiophene, quinoline, and carbazole. The introduction of glycosides significantly improved the activity of the compounds. Molecular docking studies showed the compounds interacted with the targets mainly through hydrogen bonds and hydrophobic interactions. The chemical and physical properties, as well as ADMET of active ones were predicted and analyzed. The results showed that most of them (**A1**, **B1**, **C5**, **C8**, **C10**, **C11**, **C12**, **D1**) had good druggability, pharmacokinetic profiles and high safety profiles, which might be developed as antitumor agents.

Table 1. IC_{50} of synthesized compounds against tumor cells [a]

Compound No.	HELA IC_{50} (μM)	HT-29 IC_{50} (μM)	A549 IC_{50} (μM)	HepG2 IC_{50} (μM)
A1	14.25±0.85	I.R. [b] ≤ 50%	I.R.≤50%	I.R.≤50%
A2	39.18±2.58	23.15±2.33	I.R.≤50%	66.60±6.72
A3	69.59±5.22	I.R.≤50%	I.R.≤50%	74.84±8.03
A4	I.R.≤50%	20.27±3.42	I.R.≤50%	I.R.≤50%
A5	I.R.≤50%	I.R.≤50%	I.R.≤50%	I.R.≤50%
A6	I.R.≤50%	I.R.≤50%	I.R.≤50%	I.R.≤50%
A7	I.R.≤50%	I.R.≤50%	I.R.≤50%	I.R.≤50%
A8	I.R.≤50%	I.R.≤50%	I.R.≤50%	I.R.≤50%
B1	**2.20±0.13**	**3.75±0.42**	**1.65±0.08**	I.R.≤50%
B2	11.45±0.83	17.16±1.19	**9.29±0.30**	I.R.≤50%
B3	I.R.≤50%	**2.23±0.21**	I.R.≤50%	I.R.≤50%
B4	26.80±2.37	**7.65±0.51**	**8.02±1.34**	I.R.≤50%
B5	I.R.≤50%	I.R.≤50%	I.R.≤50%	I.R.≤50%
C1	13.09±1.02	23.13±1.92	I.R.≤50%	I.R.≤50%
C2	22.12±0.36	I.R.≤50%	I.R.≤50%	I.R.≤50%
C3	38.37±2.34	29.27±2.49	I.R.≤50%	31.78±2.79
C4	44.38±3.91	I.R.≤50%	I.R.≤50%	54.85±3.97
C5	18.76±0.60	**5.29±0.25**	**8.93±1.17**	I.R.≤50%
C6	**7.88±0.57**	**8.89±0.74**	I.R.≤50%	I.R.≤50%
C7	22.85±1.59	I.R.≤50%	I.R.≤50%	I.R.≤50%
C8	**4.47±0.14**	I.R.≤50%	I.R.≤50%	I.R.≤50%

C9	45.97±2.98	27.18±3.15	I.R.≤50%	I.R.≤50%
C10	**6.77±0.43**	**6.15±0.43**	I.R.≤50%	49.94±3.01
C11	I.R.≤50%	**6.56±0.45**	I.R.≤50%	I.R.≤50%
C12	**8.39±0.64**	I.R.≤50%	I.R.≤50%	I.R.≤50%
C13	25.62±2.46	I.R.≤50%	I.R.≤50%	I.R.≤50%
C14	I.R.≤50%	48.36±5.01	I.R.≤50%	I.R.≤50%
C15	I.R.≤50%	I.R.≤50%	I.R.≤50%	I.R.≤50%
C16	I.R.≤50%	I.R.≤50%	I.R.≤50%	I.R.≤50%
C17	I.R.≤50%	I.R.≤50%	I.R.≤50%	I.R.≤50%
D1	**6.40±0.67**	**4.70±0.27**	15.99±0.12	I.R.≤50%
E1	44.32±3.90	I.R.≤50%	I.R.≤50%	40.65±3.41
E2	I.R.≤50%	I.R.≤50%	I.R.≤50%	I.R.≤50%
F1	66.83±7.35	I.R.≤50%	I.R.≤50%	I.R.≤50%
F2	I.R.≤50%	I.R.≤50%	I.R.≤50%	I.R.≤50%
DOX [c]	0.55±0.05	1.15±0.03	0.86±0.07	0.73±0.04

[a]: Compounds with antitumor activity are indicated by orange shading. The values of IC_{50} ≤10 μM are indicated in bold. [b]: I.R.: Inhibition Rate. [c]: DOX: doxorubicin, as the positive control drug.

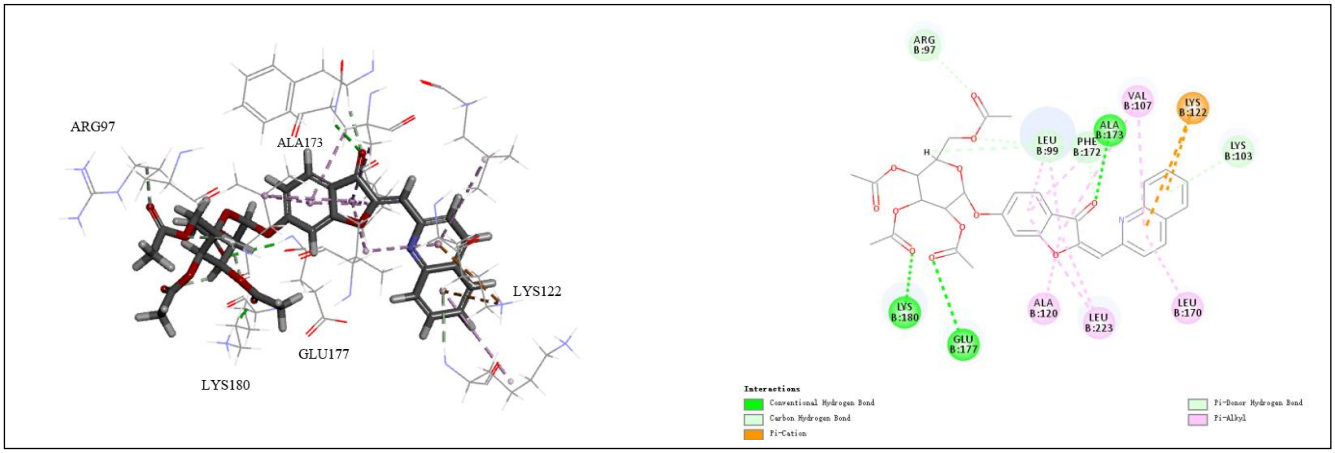

Figure 6. 3D and 2D patterns illustrating the docking mode and types of interaction with Aurora B for compound **B1**

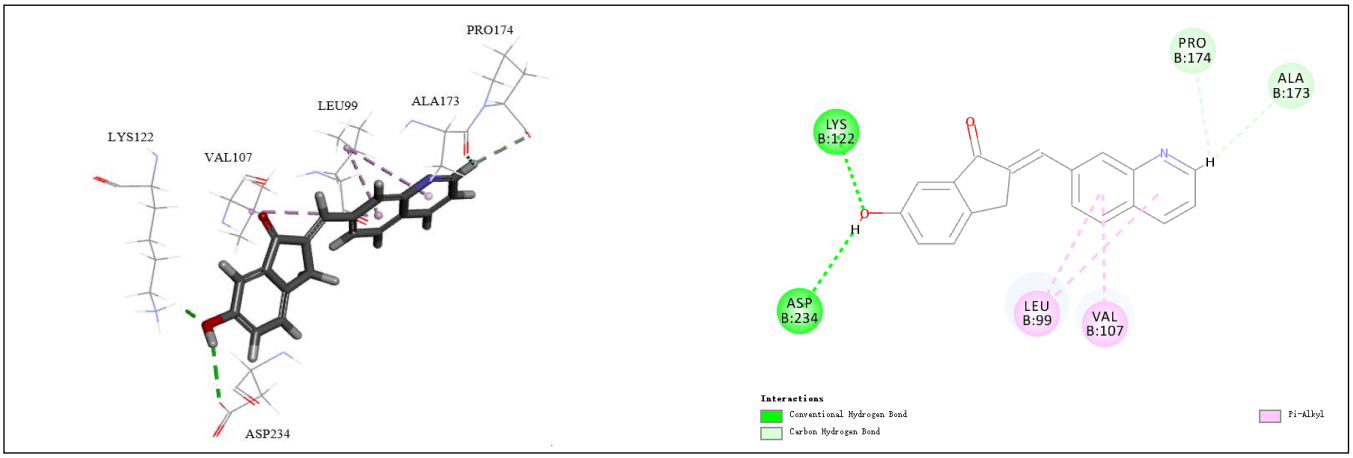

Figure 7. 3D and 2D patterns illustrating the docking mode and types of interaction with Aurora B for compound **C8**

Table 2. Some pharmaceutical properties and physical and chemical properties of compounds

Compound No.	CLogP[a]	Rule of 5 Violations[b]	TPSA (Å^2)[c]	CMR[d]	pKa[e]	CLogS[f]
HJ-1	1.25	0	107.2	7.4936	14.027	-3.197
A1	1.4	0	87.0	7.3405	7.874	-3.585
B1	1.76	1	162.3	15.5833	[g]	-6.492
C5	3.2	0	49.7	8.8219	8.726	-4.288
C8	3.2	0	49.7	8.8219	8.270	-4.255
C10	2.479	0	77.8	7.6512	8.314	-3.468
C11	4.28	0	40.5	11.0781	8.320	-6.345
C12	2.34	0	77.8	7.6512	13.657	-3.468
D1	2.28	1	153.1	16.046		-6.293

[a]: CLogP: calculated measured lipid-water partition coefficient (reflecting the lipid solubility, less than 5 is ideal); [b]: Rules of 5 Violation: items that violate Lipinski rules; [c]: TPSA: topological polar surface area, reflecting membrane permeability (TPSA > 140 Å^2: difficulty crossing cell membranes; TPSA>90 Å^2: difficulty crossing the blood-brain barrier); [d]: CMR: carcinogenic, mutagenic and toxic to reproduction (a large CMR usually means higher safety);[e]: pKa: dissociation constant; [f]: cLogS: solubility (-6 < LogS < -4: low water solubility; - 4 < LogS < -2: good water solubility. - 2 < LogS < 0: best water solubility); [g]: Blank means no relevant data were found.

Table 3. Prediction of ADMET properties of some compounds

Compound No.	Absorption level[a]	PPB[b]	BBB level[c]	CYP2D6[d]	Ames[e]	Rat oral TD_{50} (mg/kg)[f]	Rat oral LD_{50} (g/kg)[f]	Rat Maximum Tolerated Dose (Feed; g/kg body weight)	Rat NTP[g]
A1	0	false	4	false	M	20.3768	0.475708	0.0206022	NC
B1	0	false	1	false	NM	102.059	1.68121	0.274029	NC
C5	0	true	1	false	NM	38.664	0.150597	0.274029	NC
C10	0	false	2	false	NM	87.37	0.398067	0.735433	NC
D1	0	false	4	false	NM	51.5128	1.77887	0.83204	NC

[a]: Absorption level: 0-4 respectively means good absorption, moderate absorption, low absorption and very low absorption. [b]: PBB: plasma protein binding, Ture: PBB ≥90%; false: PBB <90%. [c]: BBB: blood-brain barrier. 0-4 respectively means very high penetrant (LogBBB≥0.7), high penetrant (0≤LogBBB<0.7), medium penetrant (-0.52≤LogBBB<0), low penetrant (LogBBB ≤ -0.52) and undefined penetrant. [d]: CYP2D6: inhibition of the CYP2D6 (closely related to drug interactions). Ture indicates CYP2D6 inhibitor. False indicates no CYP2D6 inhibition. [e]: Ames: Ames mutagenicity assay, to predict whether a compound is a mutagen or not, NM means not mutagenic. M means mutagenic. [f]: The rat oral TD_{50} and LD_{50}: median toxic dose (mg/Kg) and median lethal dose (g/Kg), respectively. [g]: NTP (national toxicology program): carcinogenicity of the compound in rats. Non-carcinogen (NC): probabilities less than 0.3. Carcinogen: probabilities greater than 0.7.

EXPERIMENTAL

General methods. All reagents and solvents (analytical grade) were obtained from Tansoole.com and Inno-Chem.com, without additional purification. The reaction progress was monitored using TLC (GF-254; Qingdao Haiyang Chemical Co., Ltd.) and ZF-20D black box UV analyzer. The products were purified by column chromatography using silica gel (100-200 mesh; Qingdao Haiyang Chemical Co., Ltd.). ^{1}H and ^{13}C NMR spectra were determined with the V ARIAN MR 400 and BRUKER AVANCE NEO 600 spectrometer with TMS as the internal standard. High resolution mass spectra (HRMS) were determined by AB SCIEX QSTAR Elite quadrupole time-of-flight mass spectrometer. Melting points were determined on a WRR-Y drug melting point apparatus.

General procedure for the synthesis of compounds A1-A8. Dissolve 2 mmol of copper bromide in 20 mL of EtOAc, heat and boil at 77 °C. Weigh 1 mmol of 2,5-dihydroxyacetophenone or 2,4-dihydroxyacetophenone dissolved in 20 mL of CH_2Cl_2 and add to the reaction system. The reaction solution was cooled to room temperature and filtered, and the filter cake was washed with EtOAc (3×20 mL). The filtrate was washed with water, saturated salt water, dried with anhydrous sodium sulfate, filtered, and spun dried under reduced pressure to obtain the crude intermediate 2-bromo-1-(2,4-dihydroxyphenyl)ethanone, which was directly put into the next reaction step without purification. Measure 3 mmol of triethylamine dissolved in 20 mL MeCN. Another intermediate was dissolved in 10 mL MeCN. Slowly add the reaction system with a constant pressure dropping funnel, stir for 5 h at room temperature. Remove MeCN under reduced pressure. The residue was washed with 30 mL of water, extracted with EtOAc (3×20 mL). The organic phase was washed with water, saturated salt water, dried with anhydrous sodium sulfate, filtered, spun dried under reduced pressure, using eluent. The organic phase was purified by silica gel column chromatography with PE: EA (10:1), and 5-hydroxybenzofuran-3(2*H*)-one or 6-hydroxybenzofuran-3(2*H*)-one was obtained. 1 mmol of 5- or 6-hydroxybenzofuran-3(2*H*)-one was dispersed in 5 mL of MeOH, to which 1 mL of 50% KOH solution was added. After stirring for 10 min at room temperature, the corresponding 1.2 mmol of benzaldehyde or aromatic heterocyclic aldehyde derivative was added to it, and the mixture was stirred at room temperature for 8-10 h. Monitor the reaction by TLC, and the MeOH was removed under reduced pressure after the reaction had finished. The reaction solution was diluted with 10 mL of hot water, and the pH was adjusted to 5-6 with dilute hydrochloric acid to obtain a solid precipitate, which was filtered and washed. The target compounds **A4-A8** were obtained after recrystallization in MeOH. Intermediate (*Z*)-2-(3,4-dimethoxybenzylidene)-5-hydroxybenzofuran-3(2*H*)-one (0.5 mmol) was dissolved in 5 mL of CH_2Cl_2, and 2 mmol of BBr_3 was added in anhydrous and argon atmosphere. After the reaction was monitored by TLC, a small amount of ice water was added and extracted with EtOAc. The organic phase was washed with water, dried with anhydrous sodium sulfate, filtered by extraction, spun dried and

purified by silica gel column chromatography (PE: EA=3:1) to obtain compounds **A1**. Intermediate (*Z*)-2-((4-bromothiophen-2-yl)methylene)-6-hydroxybenzofuran-3(2*H*)-one (0.5 mmol) was dissolved in 10 mL of MeCN. Then add 1.5 mmol potassium carbonate. After heating to 60 ℃, add 1 mmol of chloroacetonitrile or acetyl chloride and stir for 6-8 h. When TLC showed the end of the reaction, remove the solvent under reduced pressure. Add 30 mL of water to obtain the precipitate. Filter and wash the precipitate with water. The precipitate was recrystallized in EtOH to give compounds **A2-A3**.

(*Z*)-2-(3,4-Dihydroxybenzylidene)-5-hydroxybenzofuran-3(2*H*)-one (A1). Orange solid, yield 76%, mp 307.9-308.2 ℃. ^{1}H NMR (400 MHz, DMSO) δ 9.74 (s, 1H), 9.29 (s, 1H), 7.48 (s, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 8.3 Hz, 1H), 7.20 (dd, J = 8.8, 2.5 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.74 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 183.78, 159.23, 154.09, 148.81, 145.99, 145.90, 125.69, 125.40, 123.80, 122.09, 118.57, 116.46, 114.06, 113.85, 107.97. HRMS (ESI) *m/z*: calcd for $C_{15}H_9O_5$ $[M-H]^-$ 269.0455, found 269.0455.

(Z)-2-((2-((4-Bromothiophen-2-yl)methylene)-3-oxo-2,3-dihydrobenzofuran-6-yl)oxy)acetonitrile (A2). Light yellow solid, yield 71%, mp 272.7-272.7 ℃. ^{1}H NMR (400 MHz, DMSO) δ 8.04 (d, J = 1.5 Hz, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.72 (s, 1H), 7.33 (d, J = 2.2 Hz, 1H), 7.26 (s, 1H), 6.99 (d, J = 10.8 Hz, 1H), 5.38 (s, 2H). ^{13}C NMR (151 MHz, DMSO) δ 180.89, 166.97, 163.84, 145.92, 136.26, 134.76, 129.70, 125.93, 115.98, 115.80, 112.91, 110.22, 104.65, 98.45, 54.20. HRMS (ESI) *m/z*: calcd for $C_{15}H_8BrNO_3S$ $[M+H]^+$ 361.9481, found 361.9481.

(*Z*)-2-((4-Bromothiophen-2-yl)methylene)-3-oxo-2,3-dihydrobenzofuran-6-yl acetate (A3). Light yellow solid, yield 62%, mp 262.9-263.3 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 9.0 Hz, 2H), 7.19 (s, 1H), 7.02 (s, 1H), 6.97 (d, J = 9.2 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.56, 168.55, 166.44, 157.56, 146.49, 136.51, 134.64, 128.56, 125.73, 119.69, 117.98, 111.56, 107.05, 105.58, 21.35. HRMS (ESI) *m/z*: calcd for $C_{15}H_9BrO_4S$ $[M+H]^+$ 364.9478, found 364.9475.

(*Z*)-6-Hydroxy-2-(quinolin-2-ylmethylene)benzofuran-3(2*H*)-one (A4). Yellow solid, yield 91%, mp 289.1-289.5 ℃. ^{1}H NMR (400 MHz, DMSO) δ 11.58 (s, 1H), 8.66 (d, J = 8.7 Hz, 1H), 8.37 (d, J = 8.7 Hz, 1H), 8.12 (d, J = 8.5 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.93 – 7.83 (m, 1H), 7.71 (t, J = 7.5 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 6.90 (s, 1H), 6.89 (d, J = 1.8 Hz, 1H), 6.76 (dd, J = 8.5, 1.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 181.60, 168.82, 167.89, 151.20, 151.07, 145.40, 139.81, 131.98, 128.64, 128.57, 127.46, 127.00, 126.92, 123.09, 114.08, 112.37, 107.09, 99.41. HRMS (ESI) *m/z*: calcd for $C_{15}H_{12}NO_3$ $[M+H]^+$ 290.0812, found 290.0810.

(*Z*)-6-Hydroxy-2-(quinolin-3-ylmethylene)benzofuran-3(2*H*)-one (A5). Yellow solid, yield 71%, mp 273.3-273.9 ℃. ^{1}H NMR (400 MHz, DMSO) δ 9.50 (d, J = 1.7 Hz, 1H), 9.28 (s, 1H), 9.28 (s, 1H), 8.30 (d, J = 8.2 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.00 (t, J = 7.7 Hz, 1H), 7.83 (t, J = 7.6 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.05 (s, 1H), 6.94 (d, J = 1.7 Hz, 1H), 6.78 (dd, J = 8.5, 1.6 Hz, 1H). ^{13}C NMR (101 MHz,

DMSO) δ 181.36, 168.54, 167.68, 149.72, 149.01, 142.69, 141.11, 133.77, 129.85, 129.46, 128.39, 126.88, 126.64, 124.38, 113.98, 112.64, 105.38, 99.39. HRMS (ESI) *m/z*: calcd for $C_{15}H_{12}NO_3$ $[M+H]^+$ 290.0812, found 290.0812.

(*Z*)-6-Hydroxy-2-(quinolin-5-ylmethylene)benzofuran-3(2*H*)-one (A6). Light yellow solid, yield 77%, mp 312.4-312.8 ℃. ^{1}H NMR (400 MHz, DMSO) δ 8.97 (d, J = 3.2 Hz, 1H), 8.75 (d, J = 8.5 Hz, 1H), 8.40 (d, J = 7.3 Hz, 1H), 8.10 (d, J = 8.3 Hz, 1H), 7.90 (t, J = 7.9 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.63 (dd, J = 8.6, 4.0 Hz, 1H), 7.42 (s, 1H), 6.79 (s, 1H), 6.74 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 181.65, 168.60, 167.25, 151.21, 149.13, 148.29, 132.52, 131.19, 130.03, 129.73, 129.15, 127.16, 126.64, 122.53, 113.67, 113.11, 104.93, 99.17. HRMS (ESI) *m/z*: calcd for $C_{15}H_{12}NO_3$ $[M+H]^+$ 290.0812, found 290.0811.

(*Z*)-6-Hydroxy-2-(quinolin-6-ylmethylene)benzofuran-3(2*H*)-one (A7). Yellow solid, yield 84%, mp 298.2-298.4 ℃. ^{1}H NMR (400 MHz, DMSO) δ 11.51 (s, 1H), 9.02 (s, 1H), 8.58 (s, 2H), 8.39 (s, 1H), 8.18 (s, 1H), 7.70 (s, 1H), 7.65 (s, 1H), 6.96 (s, 1H), 6.92 (s, 1H), 6.78 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 181.77, 168.49, 167.43, 150.61, 145.64, 148.64, 139.32, 132.57, 131.77, 131.52, 128.53, 128.09, 126.50, 122.74, 113.78, 112.90, 109.43, 99.20. HRMS (ESI) *m/z*: calcd for $C_{15}H_{12}NO_3$ $[M+H]^+$ 290.0812, found 290.0810.

(*Z*)-6-Hydroxy-2-(quinolin-7-ylmethylene)benzofuran-3(2*H*)-one (A8). Light yellow solid, yield 78%, mp 321.9-322.3 ℃. ^{1}H NMR (400 MHz, DMSO) δ 11.38 (s, 1H), 9.00 (s, 1H), 8.57 (s, 1H), 8.49 (d, J = 7.9 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 3.8 Hz, 1H), 7.60 (d, J = 8.6 Hz, 1H), 6.93 (s, 1H), 6.83 (s, 1H), 6.72 (d, J = 8.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 181.67, 168.50, 167.42, 149.35, 143.69, 140.61, 135.64, 129.96, 129.46, 128.63, 127.93, 126.61, 122.82, 113.79, 112.78, 108.99, 99.14. HRMS (ESI) *m/z*: calcd for $C_{15}H_{12}NO_3$ $[M+H]^+$ 290.0812, found 290.0812.

General procedure for the synthesis of compounds B1-B5. Take compounds **A1-A4** (0.5 mmol) and dissolve in 10 mL of CH_2Cl_2. Add 1 mmol of 2,3,4,6-tetraacetoxy-α-D-glucopyranosyl bromide, stir for 5 min, add 3 mmol of potassium carbonate and 0.1 mmol of tetrabutylammonium iodide, then add 7.5 mL of water and wrap the reaction vial with aluminum foil. After stirring for 72 h at room temperature and TLC showed that the reaction was finished, 30 mL of water was added to the reaction vial and extracted with CH_2Cl_2. The organic phase was washed with water, dried with anhydrous sodium sulfate, filtered by extraction, spun dried, and purified by silica gel column chromatography (PE: EA=5:1) to obtain compounds **B1-B5**.

(2*R*,3*R*,4*S*,5*R*)-2-(Acetoxymethyl)-6-(((*Z*)-3-oxo-2-(quinolin-2-ylmethylene)-2,3-dihydrobenzofuran-6-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (B1). Yellow solid, yield 65%, mp 189.9-190.2 ℃. ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.20 (s, 2H), 8.16 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 7.1 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 6.8 Hz, 1H), 7.18 (s, 1H), 6.94 (s, 1H), 6.82 (d, J = 8.2

Hz, 1H), 5.34 (d, *J* = 8.2 Hz, 1H), 5.32 (s, 1H), 5.29 (d, *J* = 7.1 Hz, 1H), 5.18 (t, *J* = 8.8 Hz, 1H), 4.29 (d, *J* = 4.6 Hz, 1H), 4.23 (d, *J* = 11.7 Hz, 1H), 4.00 (s, 1H), 2.19 – 1.83 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 182.73, 170.51, 170.21, 169.47, 169.31, 168.09, 164.11, 151.77, 149.80, 147.66, 137.13, 130.56, 129.09, 127.93, 127.60, 127.37, 126.38, 123.04, 116.43, 113.70, 111.45, 100.62, 98.32, 72.58, 72.55, 71.02, 68.17, 61.98, 20.78, 20.73, 20.69. HRMS (ESI) *m/z*: calcd for $C_{32}H_{30}NO_{12}$ $[M+H]^+$ 620.1763, found 620.1762.

(2*R*,3*R*,4*S*,5*R*)-2-(Acetoxymethyl)-6-(((*Z*)-3-oxo-2-(quinolin-3-ylmethylene)-2,3-dihydrobenzofuran-6-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (B2). Yellow solid, yield 62%, mp 211.1-211.5 °C. ^{1}H NMR (400 MHz,$CDCl_3$) *δ* 9.34 (s, 1H), 8.64 (s, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 7.4 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 6.94 (s, 1H), 6.94 (s, 1H), 6.82 (dt, *J* = 37.9, 19.0 Hz, 1H), 5.38 – 5.29 (m, 2H), 5.27 (t, *J* = 7.0 Hz, 1H), 5.18 (t, *J* = 9.2 Hz, 1H), 4.37 – 4.26 (m, 1H), 4.21 (d, *J* = 10.7 Hz, 1H), 4.08 – 3.91 (m, 1H), 2.08 (s, 3H), 2.06 (d, *J* = 3.1 Hz, 3H), 2.05 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 182.40, 170.39, 170.10, 169.33, 169.15, 167.76, 163.92, 151.09, 148.71, 146.60, 138.81, 131.29, 128.63, 128.41, 127.82, 127.75, 126.27, 125.83, 116.50, 113.60, 108.33, 100.29, 98.09, 72.43, 70.88, 67.98, 61.79, 60.91, 20.66, 20.58, 20.55. HRMS (ESI) *m/z*: calcd for $C_{32}H_{30}NO_{12}$ $[M+H]^+$ 620.1763, found 620.1763.

(2*R*,3*R*,4*S*,5*R*)-2-(Acetoxymethyl)-6-(((*Z*)-3-oxo-2-(quinolin-5-ylmethylene)-2,3-dihydrobenzofuran-6-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (B3). White solid, yield 69%, mp 219.3-219.6 °C. ^{1}H NMR (400 MHz,$CDCl_3$) *δ* 9.06 – 8.95 (m, 1H), 8.79 (d, *J* = 8.5 Hz, 1H), 8.49 (d, *J* = 7.4 Hz, 1H), 8.37 (d, *J* = 8.6 Hz, 1H), 7.89 (t, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.64 (dd, *J* = 8.6, 4.4 Hz, 1H), 7.51 (s, 1H), 6.93 (d, *J* = 1.9 Hz, 1H), 6.87 (dd, *J* = 8.5, 1.9 Hz, 1H), 5.37 – 5.30 (m, 2H), 5.27 – 5.23 (m, 1H), 5.21 – 5.15 (m, 1H), 4.27 (d, *J* = 5.5 Hz, 1H), 4.24 (d, *J* = 2.4 Hz, 1H), 4.03 – 3.91 (m, 1H), 2.08 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 182.61, 170.36, 170.12, 169.34, 169.15, 167.98, 163.98, 149.00, 148.24, 134.80, 130.96, 130.67, 129.03, 127.55, 126.37, 121.65, 116.53, 113.65, 105.44, 100.36, 98.16, 72.45, 72.39, 70.88, 68.00, 61.84, 20.60, 20.57, 20.54. HRMS (ESI) *m/z*: calcd for $C_{32}H_{30}NO_{12}$ $[M+H]^+$ 620.1763, found 620.1763.

(2*R*,3*R*,4*S*,5*R*)-2-(Acetoxymethyl)-6-(((*Z*)-3-oxo-2-(quinolin-6-ylmethylene)-2,3-dihydrobenzofuran-6-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (B4). Light yellow solid, yield 60%, mp 197.9-198.1 °C. ^{1}H NMR (400 MHz,$CDCl_3$) *δ* 8.96 (s, 1H), 8.40 (d, *J* = 7.6 Hz, 1H), 8.36 (s, 2H), 8.28 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.58 (s, 1H), 6.95 (s, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 5.39 – 5.29 (m, 2H), 5.26 (d, *J* = 6.8 Hz, 1H), 5.18 (t, *J* = 9.2 Hz, 1H), 4.29 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.22 (d, *J* = 11.9 Hz, 1H), 4.00 (d, *J* = 6.2 Hz, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 182.68, 170.34, 170.09, 169.33, 169.14, 167.81, 163.89, 149.04, 148.39, 139.21, 132.63, 131.86, 131.21, 128.48, 127.85, 126.23, 121.80, 116.51, 113.52, 110.63, 100.34, 98.13, 72.43, 70.90, 68.02, 61.86, 20.64,

20.59, 20.55. HRMS (ESI) *m/z*: calcd for $C_{32}H_{30}NO_{12}$ $[M+H]^+$ 620.1763, found 620.1760.

(2*R*,3*R*,4*S*,5*R*)-2-(Acetoxymethyl)-6-(((*Z*)-3-oxo-2-(quinolin-7-ylmethylene)-2,3-dihydrobenzofuran-6-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (B5). Yellow solid, yield 63%, mp 204.7-205.0 °C. ^{1}H NMR (600 MHz,$CDCl_3$) δ 8.97 (d, J = 4.1 Hz, 1H), 8.80 (s, 1H), 8.20 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.54 – 7.40 (m, 1H), 7.02 (s, 1H), 7.01 (s, 1H), 6.85 (d, J = 8.4 Hz, 1H), 5.40 – 5.31 (m, 2H), 5.30 – 5.24 (m, 1H), 5.22 (t, J = 9.2 Hz, 1H), 4.35 (dd, J = 12.4, 5.4 Hz, 1H), 4.31 – 4.24 (m, 1H), 4.03 (dd, J = 8.9, 4.7 Hz, 1H), 2.12 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 182.97, 170.56, 170.21, 169.41, 169.23, 168.06, 163.90, 150.97, 148.52, 147.87, 136.16, 133.58, 132.28, 128.97, 128.77, 128.31, 126.19, 122.06, 116.63, 113.83, 111.53, 100.00, 98.20, 72.53, 72.50, 70.88, 67.93, 61.78, 20.75, 20.64, 20.61. HRMS (ESI) *m/z*: calcd for $C_{32}H_{30}NO_{12}$ $[M+H]^+$ 620.1763, found 620.1761.

General procedure for the synthesis of compounds C1-C17 and **D1.** Dissolve 10 mmol of hydroxy-substituted or methoxy-substituted phenylpropionic acid in 25 mL of CH_2Cl_2 and slowly add 100 mmol of trifluoromethanesulfonic acid under ice bath conditions. Stir for 2 h at room temperature. And the reaction was detected as complete by TLC. The reaction solution was poured into 60 mL of ice water and extracted with CH_2Cl_2 (3×30 mL). The organic phase was washed with water, saturated salt water, dried with anhydrous sodium sulfate, filtered by extraction and spun dried under reduced pressure. The residue was purified by silica gel column chromatography (the eluent was PE: EA, 20: 1) to obtain the corresponding intermediate, containing hydroxyl/methoxy-substituted 2,3-dihydro-1*H*-inden-1-one. 1 mmol of 4-hydroxy/5-hydroxy/6-hydroxy/6-methoxy-2,3-dihydro-1*H*-indenone was dispersed in 5 mL of MeOH, to which 1 mL of 50% KOH solution was added. After stirring for 10 min at room temperature, the corresponding 1.2 mmol of benzaldehyde or aromatic heterocyclic aldehyde derivative was added to the mixture and the mixture was stirred at room temperature overnight. The reaction solution was diluted with 10 mL of hot water and the pH was adjusted to 5-6 with dilute hydrochloric acid to obtain a solid precipitate. The precipitate was filtered and washed, and the target compounds **C1-C11** and **C13-C17** were obtained after recrystallization in MeOH. Compound **C13** (0.5 mmol) was dissolved in 5 mL of CH_2Cl_2, and 2 mmol of BBr_3 was added in anhydrous and argon atmosphere. After the reaction was monitored by TLC, a small amount of ice water was added and extracted with EtOAc. The organic phase was washed with water, dried with anhydrous sodium sulfate, filtered by extraction, spun dried and purified by silica gel column chromatography (PE: EA=3:1) to obtain compounds **C12**. Compound **C6** (0.5 mmol) was dissolved in 10 mL of MeCN. Then add 1.5 mmol potassium carbonate. After heating to 60 °C, add 1 mmol of chloroacetonitrile or acetyl chloride and stir for 6-8 h. After TLC showed the end of the reaction, remove the solvent under reduced pressure. Add 30 mL of water to obtain the precipitate. Filter and wash the precipitate with water. The precipitate was recrystallized in EtOH to give compound

D1.

(*E*)-2-((4-Bromothiophen-2-yl)methylene)-6-hydroxy-2,3-dihydro-1*H*-inden-1-one (C1). Light yellow solid, yield 84%, mp 265.8-266.3 °C. ^{1}H NMR (400 MHz, DMSO) δ 9.89 (s, 1H), 8.00 (s, 1H), 7.66 (s, 2H), 7.48 (d, J = 8.3 Hz, 1H), 7.16 – 7.10 (m, 1H), 7.06 (t, J = 4.5 Hz, 1H), 3.80 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 193.02, 157.70, 140.93, 140.34, 139.15, 135.62, 135.13, 129.10, 127.96, 124.41, 123.97, 110.90, 108.60, 31.30. HRMS (ESI) *m/z*: calcd for $C_{14}H_{10}BrO_2S$ $[M+H]^+$ 320.9579, found 320.9577.

(*E*)-5-Hydroxy-2-(quinolin-2-ylmethylene)-2,3-dihydro-1*H*-inden-1-one (C2). Yellow solid, yield 76%, mp 298.5-298.9 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.73 (s, 1H), 8.43 (d, J = 8.5 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.78 (t, J = 7.7 Hz, 1H), 7.62 (dd, J = 17.7, 8.1 Hz, 2H), 7.54 (s, 1H), 6.98 (s, 1H), 6.85 (dd, J = 8.4, 1.9 Hz, 1H), 4.26 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 193.32, 157.81, 150.23, 141.27, 139.87, 138.57, 133.11, 129.76, 129.22, 129.04, 128.98, 128.27, 128.16, 128.09, 127.85, 124.43, 108.82, 31.49. HRMS (ESI) *m/z*: calcd for $C_{19}H_{14}NO_2$ $[M+H]^+$ 288.1019, found 288.1017.

(*E*)-6-Hydroxy-2-(quinolin-2-ylmethylene)-2,3-dihydro-1*H*-inden-1-one (C3). Yellow solid, yield 74%, mp 320.7-321.1 °C. ^{1}H NMR (600 MHz, DMSO) δ 9.90 (s, 1H), 8.44 (d, J = 8.3 Hz, 1H), 8.11 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 7.82 (t, J = 7.4 Hz, 1H), 7.65 (d, J = 9.1 Hz, 2H), 7.54 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.12 (s, 1H), 4.28 (s, 2H). ^{13}C NMR (151 MHz, DMSO) δ 193.76, 157.18, 154.52, 147.80, 141.93, 141.09, 138.39, 136.75, 130.54, 130.16, 129.41, 127.86, 127.63, 127.44, 126.96, 124.24, 123.94, 108.22, 32.20. HRMS (ESI) *m/z*: calcd for $C_{19}H_{14}NO_2$ $[M+H]^+$ 288.1019, found 288.1019.

(*E*)-6-Hydroxy-2-(quinolin-2-ylmethylene)-2,3-dihydro-1*H*-inden-1-one (C4). Yellow solid, yield 74%, mp 320.7-321.1 °C. ^{1}H NMR (400 MHz, DMSO) δ 9.90 (s, 1H), 8.44 (d, J = 8.3 Hz, 1H), 8.11 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 7.82 (t, J = 7.4 Hz, 1H), 7.65 (d, J = 9.1 Hz, 2H), 7.54 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.12 (s, 1H), 4.28 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 193.76, 157.18, 154.52, 147.80, 141.93, 141.09, 138.39, 136.75, 130.54, 130.16, 129.41, 127.86, 127.63, 127.44, 126.96, 124.24, 123.94, 108.22, 32.20. HRMS (ESI) *m/z*: calcd for $C_{19}H_{14}NO_2$ $[M+H]^+$ 288.1019, found 288.1019.

(*E*)-5-Hydroxy-2-(quinolin-5-ylmethylene)-2,3-dihydro-1*H*-inden-1-one (C5). Yellow solid, yield 78%, mp 306.6-306.9 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 9.24 (d, J = 4.2 Hz, 1H), 9.16 (d, J = 8.4 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 7.3 Hz, 1H), 8.13 (d, J = 10.1 Hz, 1H), 8.11 (s, 1H), 7.97 (dd, J = 8.3, 4.8 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 6.96 (s, 1H), 6.91 (d, J = 8.2 Hz, 1H), 3.99 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 190.76, 164.29, 153.40, 148.50, 140.23, 133.07, 131.30, 129.24, 128.55, 127.11, 126.67, 126.16, 125.31, 122.22, 116.40, 111.96, 31.43. HRMS (ESI) *m/z*: calcd for $C_{19}H_{14}NO_2$

$[M+H]^+$ 288.1019, found 288.1015.

(*E*)-5-Hydroxy-2-(quinolin-6-ylmethylene)-2,3-dihydro-1*H*-inden-1-one (C6). Yellow solid, yield 73%, mp 311.2-311.4 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.87 (s, 2H), 9.18 – 9.03 (m, 3H), 8.90 (d, J = 8.2 Hz, 3H), 8.45 (s, 3H), 8.23 (q, J = 9.0 Hz, 6H), 7.87 (dd, J = 8.3, 4.9 Hz, 3H), 7.56 (d, J = 8.4 Hz, 3H), 7.44 (s, 3H), 6.96 (s, 3H), 6.84 (dd, J = 8.4, 1.6 Hz, 3H), 4.03 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 191.29, 164.75, 153.33, 147.88, 143.27, 141.40, 138.89, 135.43, 134.29, 130.78, 129.35, 129.27, 128.79, 126.30, 124.54, 122.82, 116.76, 112.22, 32.16. HRMS (ESI) *m/z*: calcd for $C_{19}H_{14}NO_2$ $[M+H]^+$ 288.1019, found 288.1019.

(*E*)-6-Methoxy-2-(quinolin-6-ylmethylene)-2,3-dihydro-1*H*-inden-1-one (C7). Yellow solid, yield 78%, mp 297.3-297.7 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.95 – 8.81 (m, 2H), 8.35 (d, J = 8.2 Hz, 2H), 8.24 (s, 2H), 8.05 (dd, J = 10.4, 7.0 Hz, 5H), 7.67 (s, 2H), 7.59 – 7.46 (m, 4H), 7.29 – 7.17 (m, 4H), 4.10 (s, 4H), 3.82 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 192.79, 159.03, 150.97, 147.42, 142.06, 138.35, 136.51,136.44, 133.00, 131.82, 130.77, 130.32, 129.19, 127.78, 126.88, 123.20, 121.61, 105.41, 55.16, 31.15. HRMS (ESI) *m/z*: calcd for $C_{20}H_{16}NO_2$ $[M+H]^+$ 302.1176, found 302.1174.

(*E*)-6-Hydroxy-2-(quinolin-7-ylmethylene)-2,3-dihydro-1*H*-inden-1-one (C8). Yellow solid, yield 66%, mp 337.9-338.2 °C. ^{1}H NMR (400 MHz, DMSO) δ 9.88 (s, 1H), 8.96 (s, 1H), 8.41 (s, 1H), 8.58 (s, 1H), 8.28 (d, J = 7.7 Hz, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.71 (d, J = 8.9 Hz, 2H), 7.65 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 3.9 Hz, 1H), 7.51 – 7.48 (m, 1H), 7.27 (t, J = 7.4 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.11 (s, 1H), 4.47 (q, J = 6.8 Hz, 2H), 4.10 (s, 2H), 1.33 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 193.68, 157.65, 151.84, 148.06, 141.41, 138.79, 138.18, 136.49, 136.18, 132.21, 131.88, 129.13, 128.72, 128.31, 127.99, 124.08, 122.81, 108.63, 31.70. HRMS (ESI) *m/z*: calcd for $C_{19}H_{14}NO_2$ $[M+H]^+$ 288.1019, found 288.1017.

(*E*)-4-Hydroxy-2-(quinolin-7-ylmethylene)-2,3-dihydro-1*H*-inden-1-one (C9). Light yellow solid, yield 94%, mp 306.4-306.8 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.87 (dd, J = 4.1, 1.6 Hz, 1H), 8.39 (s, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.96 (s, 2H), 7.67 (s, 1H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.13 – 7.05 (m, 1H), 7.04 (d, J = 7.3 Hz, 1H), 4.08 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 194.86, 160.40, 151.70, 148.05, 138.83, 138.20,138.14, 136.68, 136.03, 131.77, 131.68, 129.39, 128.99, 128.55, 128.18, 122.62, 122.20, 110.76, 30.16. HRMS (ESI) *m/z*: calcd for $C_{19}H_{14}NO_2$ $[M+H]^+$ 288.1019, found 288.1016.

(*E*)-2-((9-Ethyl-9*H*-carbazol-3-yl)methylene)-6-hydroxy-2,3-dihydro-1*H*-inden-1-one (C10). Orange solid, yield 73%, mp 287.1-287.6 °C. ^{1}H NMR (400 MHz, DMSO) δ 9.82 (s, 1H), 8.58 (s, 2H), 8.28 (d, J = 7.7 Hz, 2H), 7.87 (d, J = 8.6 Hz, 2H), 7.71 (d, J = 8.9 Hz, 4H), 7.65 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 3.9 Hz, 2H), 7.51 – 7.45 (m, 2H), 7.27 (t, J = 7.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.11 (s, 2H), 4.47 (q, J = 6.8 Hz, 4H), 4.10 (s, 4H), 1.33 (t, J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 193.63, 157.53,

141.09, 140.70, 140.51, 139.41, 134.60, 133.31, 129.24, 127.75, 126.78, 126.33, 124.07, 123.38, 123.26, 122.63, 121.23, 119.89, 110.10, 109.98, 108.56, 37.61, 31.85, 14.17. HRMS (ESI) *m/z*: calcd for $C_{24}H_{20}NO_2$ $[M+H]^+$ 354.1489, found 354.1487.

(*E*)-2-((9-Ethyl-9*H*-carbazol-3-yl)methylene)-4-hydroxy-2,3-dihydro-1*H*-inden-1-one (C11). Yellow solid, yield 78%, mp 283.9-284.3 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.08 (s, 1H), 8.60 (s, 2H), 8.27 (d, *J* = 7.7 Hz, 2H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 9.0 Hz, 4H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.30 (dt, *J* = 17.1, 7.4 Hz, 6H), 7.12 (d, *J* = 7.4 Hz, 2H), 4.49 (q, *J* = 7.0 Hz, 4H), 4.05 (s, 4H), 1.34 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 193.44, 154.72, 140.32, 140.09, 139.40, 136.10, 134.58, 134.56, 131.86, 128.93, 128.67, 126.38, 125.87, 123.82, 122.81, 122.19, 120.73, 120.06, 119.50, 114.06, 109.73, 109.60, 37.20, 29.29, 13.76. HRMS (ESI) *m/z*: calcd for $C_{24}H_{20}NO_2$ $[M+H]^+$ 354.1489, found 354.1485.

(*E*)-2-(3,4-Dihydroxybenzylidene)-6-hydroxy-2,3-dihydro-1*H*-inden-1-one (C12). Brown solid, yield 60%, mp 244.0-244.4 °C. ^{1}H NMR (500 MHz, DMSO) δ 9.80 (s, 1H), 9.65 (s, 1H), 9.26 (s, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.33 (s, 1H), 7.20 (d, *J* = 2.0 Hz, 1H), 7.11 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.09 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 3.89 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 193.22, 157.11, 147.98, 145.62, 140.43, 138.93, 133.41, 132.38, 127.35, 126.50, 124.22, 122.93, 117.44, 116.05, 108.09, 31.28. HRMS (ESI) *m/z*: calcd for $C_{16}H_{13}O_4$ $[M+H]^+$ 269.0808, found 269.0802.

(*E*)-6-Hydroxy-2-(4-Hydroxy-3-methoxybenzylidene)-2,3-dihydro-1*H*-inden-1-one (C13). Yellow solid, yield 77%, mp 231.9-232.2 °C. ^{1}H NMR (600 MHz, DMSO) δ 9.81 (s, 1H), 9.74 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.43 (s, 1H), 7.32 (d, *J* = 1.5 Hz, 1H), 7.25 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.12 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.06 (d, *J* = 2.3 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 3.96 (s, 1H), 3.86 (s, 1H). ^{13}C NMR (151 MHz, DMSO) δ 193.25, 157.10, 148.88, 147.81, 140.55, 138.87, 133.36, 132.73, 127.35, 126.51, 124.97, 122.99, 115.95, 114.65, 108.09, 55.66, 31.11. HRMS (ESI) *m/z*: calcd for $C_{17}H_{15}O_4$ $[M+H]^+$ 283.0965, found 283.0961.

(*E*)-2-(3-Ethoxy-4-hydroxybenzylidene)-6-methoxy-2,3-dihydro-1*H*-inden-1-one (C14). Yellow solid, yield 70%, mp 216.7-217.0 °C. ^{1}H NMR (600 MHz, DMSO) δ 9.67 (s, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.46 (s, 1H), 7.32 (s, 1H), 7.30 – 7.24 (m, 2H), 7.23 (s, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 4.12 (q, *J* = 6.9 Hz, 2H), 3.98 (s, 2H), 3.83 (s, 3H), 1.38 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 193.07, 159.11, 149.23, 146.97, 142.35, 138.87, 133.72, 132.43, 127.44, 126.43, 125.10, 122.95, 116.03, 115.88, 105.50, 63.90, 55.48, 31.16, 14.72. HRMS (ESI) *m/z*: calcd for $C_{19}H_{19}O_4$ $[M+H]^+$ 311.3565, found 311.3563.

(*E*)-7-Hydroxy-2-(quinolin-2-ylmethylene)-2,3-dihydro-1*H*-inden-1-one (C15). Light yellow solid, yield 81%, mp 207.5-208.0 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.14 (s, 1H), 9.04 (d, *J* = 3.8 Hz, 1H), 8.87 (s, 1H), 8.45 (d, *J* = 8.2 Hz, 1H), 8.26 (d, *J* = 7.2 Hz, 1H), 8.09 (d, *J* = 8.1 Hz, 1H), 7.75 (t, *J* = 7.7

Hz, 1H), 7.65 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 4.13 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 193.09, 157.41, 151.66, 150.77, 146.68, 137.18, 137.06, 136.88, 133.06, 130.43,130.33, 128.54, 127.46, 126.92, 124.39, 122.44, 117.12, 114.74, 32.28. HRMS (ESI) *m/z*: calcd for $C_{19}H_{14}NO_2$ $[M+H]^+$ 288.1019, found 288.1015.

(*E*)-5-Hydroxy-2-(quinolin-3-ylmethylene)-2,3-dihydro-1*H*-inden-1-one (C16). Yellow solid, yield 77%, mp 286.8-287.4 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.98 – 10.71 (m, 1H), 9.38 (s, 1H), 9.04 (s, 1H), 8.23 (dd, *J* = 25.3, 8.3 Hz, 2H), 7.96 (t, *J* = 7.6 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.73 – 7.56 (m, 2H), 7.04 (s, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 4.22 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 191.28, 164.84, 153.58, 150.77, 139.75, 132.67, 129.63, 129.41, 129.32, 128.75, 128.22, 126.90, 126.57, 116.85, 112.34, 32.17. HRMS (ESI) *m/z*: calcd for $C_{19}H_{14}NO_2$ $[M+H]^+$ 288.1019, found 288.1017.

(*E*)-5-Hydroxy-2-(quinolin-8-ylmethylene)-2,3-dihydro-1*H*-inden-1-one (C17). Orange solid, yield 76%, mp 294.3-294.7 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.58 (s, 1H), 8.57 (s, 1H), 8.30 (d, *J* = 7.7 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 3.0 Hz, 1H), 7.65 (s, 1H), 7.64 (s, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.03 (s, 1H), 6.88 (dd, *J* = 8.3, 1.7 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 4.14 (s, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 181.57, 168.02, 166.75, 153.34, 146.41, 140.61, 140.50, 133.08, 129.58, 126.81, 126.11, 124.43, 123.27, 123.18, 122.53, 121.09, 119.99, 113.60, 113.37, 112.86, 110.20, 110.04, 99.15, 37.63, 32.48, 14.17. HRMS (ESI) *m/z*: calcd for $C_{24}H_{20}NO_2$ $[M+H]^+$ 354.1489, found 354.1489.

(2*R*,3*R*,4*S*,5*R*)-2-(Acetoxymethyl)-6-(((*E*)-1-oxo-2-(quinolin-6-ylmethylene)-2,3-dihydro-1*H*-inden-5-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (D1). Light yellow solid, yield 52%, mp 264.0-264.6 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.93 (s, 2H), 8.20 (d, *J* = 6.7 Hz, 2H), 8.14 (d, *J* = 7.7 Hz, 2H), 8.04 (s, 2H), 7.98 (d, *J* = 7.2 Hz, 2H), 7.86 (d, *J* = 7.4 Hz, 2H), 7.76 (s, 2H), 7.44 (s, 2H), 7.18 (d, *J* = 73.1 Hz, 3H), 7.02 (d, *J* = 6.7 Hz, 2H), 5.31 (s, 4H), 5.23 (s, 2H), 5.19 (d, *J* = 7.8 Hz, 2H), 4.29 (d, *J* = 7.0 Hz, 2H), 4.19 (d, *J* = 11.6 Hz, 2H), 4.09 (s, 4H), 3.93 (s, 2H), 2.04 (d, *J* = 8.4 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.39, 170.41, 170.13, 169.30, 169.17, 161.85, 151.94, 151.39, 148.11, 136.58, 135.80, 133.66, 133.26, 132.53, 131.09, 130.24, 130.00, 128.27, 126.33, 121.86, 116.73, 113.38, 98.25, 72.48, 72.24, 72.01, 68.05, 61.80, 32.44, 20.63, 20.55. HRMS (ESI) *m/z*: calcd for $C_{33}H_{32}NO_{11}$ $[M+H]^+$ 618.1970 found 618.1966.

General procedure for the synthesis of compounds E1-E2. 1 mmol of 6-hydroxybenzofuran-3(2*H*)-one was dispersed in 5 mL of MeOH, to which 1 mL of 50% KOH solution was added. After stirring for 10 min at room temperature, the corresponding 1.2 mmol of cinnamaldehyde or 4-hydroxy-3-methoxycinnamaldehyde was added to the mixture and the mixture was stirred overnight at room temperature. After the reaction was shown by TLC, MeOH was removed under reduced pressure and 10 mL of hot water was added to the reaction solution to dilute it. The pH was adjusted to 5-6 with

dilute hydrochloric acid to obtain a solid precipitate. Filter and wash the precipitate. And the corresponding compounds **E1-E2** were obtained after recrystallization in MeOH.

(*Z*)-6-Hydroxy-2-((*E*)-3-phenylallylidene)benzofuran-3(2*H*)-one (E1). Light yellow solid, yield 61%, mp 234.8-235.5 °C. ^{1}H NMR (400 MHz, DMSO) δ 7.63 (s, 1H), 7.61 (s, 1H), 7.47 (dd, J = 8.5, 2.0 Hz, 1H), 7.41 (s, 1H), 7.37 (s, 1H), 7.34 (d, J = 7.0 Hz, 1H), 7.27 (dd, J = 15.7, 11.2 Hz, 1H), 7.15 (d, J = 15.7 Hz, 1H), 6.58 (d, J = 11.2 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 6.51 (d, J = 8.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 179.91, 171.41, 168.27, 148.98, 139.83, 136.70, 129.35, 129.32, 127.60, 125.88, 120.94, 115.05, 111.63, 110.81, 98.68. HRMS (ESI) *m/z*: calcd for $C_{17}H_{13}O_3$ $[M+H]^+$ 265.0859, found 265.0854.

(*Z*)-6-Hydroxy-2-((*E*)-3-(4-hydroxy-3-methoxyphenyl)allylidene)benzofuran-3(2*H*)-one (E2). Orange solid, yield 87%, mp 249.4–250.0 °C. ^{1}H NMR (500 MHz, DMSO) δ 9.81 (s, 1H), 9.50 (s, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.26 (d, J = 1.8 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.12 – 7.10 (m, 1H), 7.09 (d, J = 6.4 Hz, 1H), 7.06 (d, J = 2.9 Hz, 1H), 7.04 (d, J = 4.0 Hz, 1H), 7.04 (d, J = 2.3 Hz, 1H), 6.80 (t, J = 5.6 Hz, 1H), 3.85 (s, 1H), 3.78 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 192.53, 157.06, 148.39, 147.97, 142.60, 140.10, 139.90, 135.61, 133.32, 128.01, 127.38, 122.94, 122.03, 122.01, 115.67, 110.47, 107.99, 55.71, 29.41. HRMS (ESI) *m/z*: calcd for $C_{19}H_{17}O_4$ $[M+H]^+$ 309.1121, found 309.1119.

General procedure for the synthesis of compounds F1-F2. Add 2 mmol of 5-methoxy-2-aminopyridine or 4-hydroxy-2-aminopyridine to 6 mL polyphosphoric acid and raise the temperature to 80 °C. Add 2 mmol 3-phenyloxiranoate ethyl ester under stirring and raise the temperature to 110 °C. After TLC showed complete reaction, add 30 mL of ice water and adjust the pH to 6-7 with KOH solution. The organic phase was extracted with CH_2Cl_2, washed with water, dried with anhydrous sodium sulfate, filtered by extraction, spun dried and purified by silica gel column chromatography (PE: EA=5:1) to obtain compounds **F1-F2**.

(*Z*)-2-Benzylidene-6-methoxyimidazo[1,2-*a*]pyridin-3(2*H*)-one (F1). Red solid, yield 49%, mp 166.3-167.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.19 (s, 1H), 7.45 (d, J = 6.8 Hz, 1H), 7.42 (s, 1H), 7.39 (d, J = 7.0 Hz, 1H), 7.32 (s, 1H), 7.06 (d, J = 1.9 Hz, 1H), 7.02 – 6.96 (m, 1H), 6.91 (d, J = 10.0 Hz, 1H), 3.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.74, 155.19, 146.42, 139.45, 134.78, 134.57, 132.67, 130.51, 129.64, 128.82, 119.72, 104.08, 55.99. HRMS (ESI) *m/z*: calcd for $C_{15}H_{13}N_2O_2$ $[M+H]^+$ 253.0972 found 253.0970.

(*Z*)-2-Benzylidene-7-hydroxyimidazo[1,2-*a*]pyridin-3(2*H*)-one (F2). Red solid, yield 53%, mp 166.3-167.4 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.16 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 7.5 Hz, 2H), 7.52 (t, J = 7.4 Hz, 2H), 7.47 (d, J = 7.2 Hz, 1H), 7.00 (s, 1H), 6.42 (d, J = 6.7 Hz, 1H), 6.31 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 176.40, 160.07, 151.38, 132.31, 130.50, 130.43, 130.14, 129.16, 129.11, 128.79, 124.76, 117.16, 112.61, 92.74. HRMS (ESI) *m/z*: calcd for $C_{14}H_{11}N_2O_2$ $[M+H]^+$ 239.0815 found 239.0810.

Antitumor activity. The screening models for antitumor activity were HELA cervical cancer cells, HT-

29 colon cancer cells, A549 lung cancer cells, and HepG2 liver cancer cells from the cell bank of Chinese Academy of Sciences. The samples were lysed with DMSO (50 μM) and stored at low temperature. Cell viability was detected by MTT assay. Cells in logarithmic growth phase were aspirated from the culture medium, washed once with PBS and trypsin digested. The cells were gently blown, counted, and inoculated in 96-well plates (100 μL/well) at the corresponding cell density and incubated overnight. Add compounds (20 μL/well), set a concentration gradient for each compound, and set 3 replicate wells for each concentration, CO_2 incubator (37 °C) for 48 h. After incubation at 37 °C for 2 h, the medium was removed and 150 μL DMSO was added. The optical absorption (OD) at 570 nm was measured using an MB enzyme standard. Inhibition rate = (OD value of control group experiment group)/(OD value of control group-OD value of blank group). The IC_{50} values were obtained by non-linear fitting of sample activity and sample concentration, and the software used for the calculation was Graphpad Prism 8.

Molecular docking. Molecular docking studies were performed using Discovery studio 2019. PDB format files of MetRS and PBP proteins were retrieved from RCSB (https://www.rcsb.org/). Water molecules and inorganic ions were removed. Prepare the proteins for processing (Tools - Macromolecules - Prepare Protein - Clean Protein; Tools - Macromolecules - Prepare Protein - Prepare Protein - Run). Find binding site in receptor cavities (Tools - Receptor Ligand Interactions - Define and Edit Binding Site - From Receptor Cavities). Save the processed protein as the sdf file. Save the ligand molecules (synthesized compounds) as sdf files. Perform structural optimization of the ligand molecules (Tools - Small Molecules - Minimize Ligands - Full Minimization). Use the CDOCKER module of DS for molecular docking (Tools - Receptor Ligand Interactions - Dock ligands - CDOCKER) and visualization and analysis of the results.

Chemical and physical properties. CLogP was from ChemSpider (https://www.chemspider.com/, from labnetwork) and reaxys database (https://www.reaxys.com/). Rule of 5 violations was from ChemSpider, Pubchem (https://zinc.docking.org/) and Zinc (https://zinc.docking.org/). TPSA, CMR, pKa and CLogS were from ChemDraw professional 2017 and Swiss (https://www.molecular-modelling.ch/swiss-drug-design.html).

ADMET prediction. BIOVIA DS 2019 software was used to perform the ADMET prediction. For ADMET prediction, import the small molecule compound file, and in the tool browser, expand Small Molecules - Calculate Molecular Properties. Click on ADMET Descriptors, and in the dialog box, select pk - test: All in Input Ligands to select all small molecules. Select the default settings for ADMET Descriptors parameters. Click Run. After finishing the job, double click Job Explorer to open the Report page. For Toxicity Prediction (TOPKAT), import the small molecule compound file. In the tool browser, expand Small Molecules - ADMET. Double-click Toxicity Prediction (TOPKAT) to open the parameter browser. Select ligand: Visible in Input Ligands, and select the small molecule compound file. Open the

Models dialog box and select the toxicological model to be tested. Set Detailed Report to Ture. Click Run. Open the Report page and click Detailed Report.

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