Automated *de novo* drug design and Anti-coronavirus activity studies of 3CL^{pro} inhibitors

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Content

1. Figures, Schemes and Tables

1.1 Figures

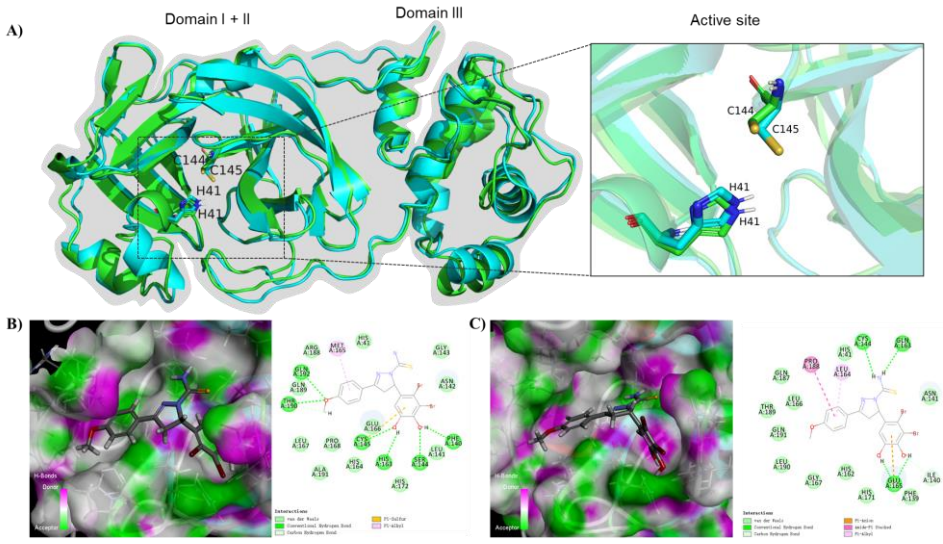
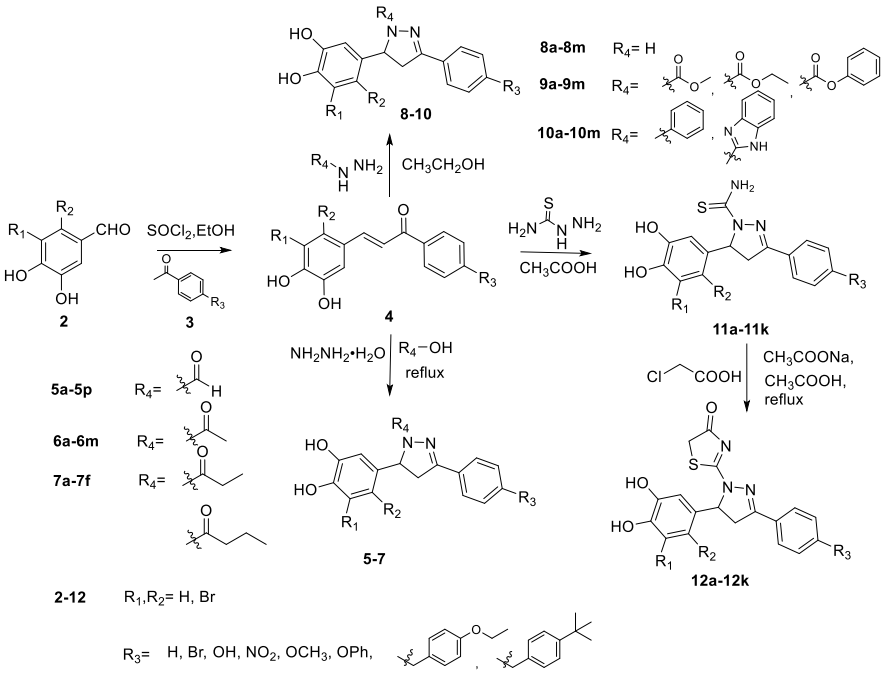


Figure S1. (A) The molecular structure of SARS-CoV-2 3CL^{pro} (PDB code 6y2g, blue) and PEDV 3CL^{pro} (PDB code 6l70, green). Cys145 (Cys144) and His41 are highlighted. (B) Docking result of **11b** with SARS-CoV-2 3CL^{pro} (PDB code 6w63). (C) Docking result of **11b** with PEDV 3CL^{pro} (PDB code 6l70). Hydrogen bond interactions are shown as green dashed lines.

Figure S2. (A) RT-PCR results of diarrhea diseased pigs. M is DNA Marker; Lanes 1-3 are TGEV, PEDV and PGAR, respectively. (B) Dead pigs in the control group. (C) Pigs with diarrhea in the IgY group. (D) The cured pigs in the **11b**-treated group.

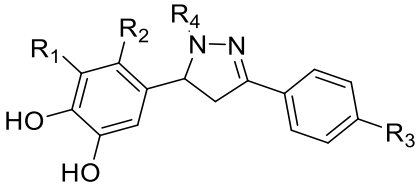
1.2 Schemes

Scheme S1. Synthesis of compounds **5-12**.

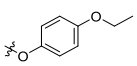
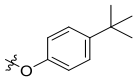


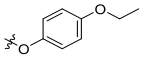
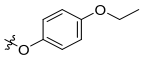
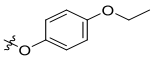
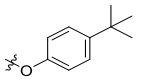
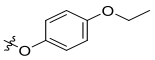
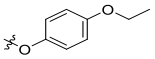
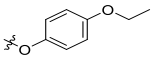
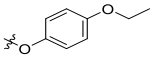
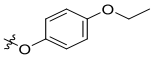
1.3 Tables

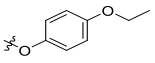
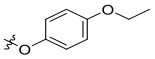
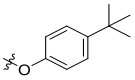
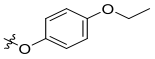
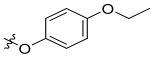
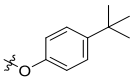
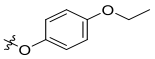
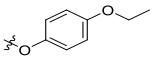
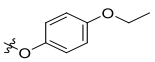
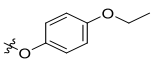
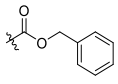
Table S1. Inhibition effect of pyrazoline (**5-12**) derivatives on SHP2 activities.

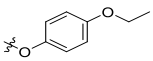
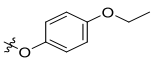
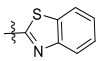
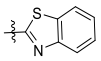
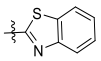
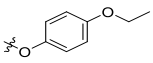
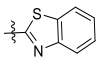
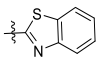
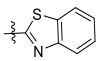
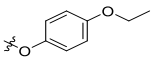
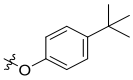
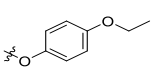
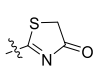
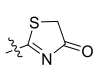
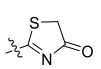


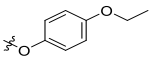
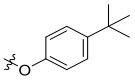
5-12

Compd.	R_1	R_2	R_3	R_4	SARS-Cov-2 IC_{50} (μM)	PEDV IC_{50} (μM)
5a	H	H	H	CHO	>10	>20
5b	H	H	-OCH_3	CHO	>10	>20
5c	H	H		CHO	>10	>20
5d	H	H		CHO	>10	>20
5e	H	H		CHO	>10	>20
5f	H	H	Br	CHO	>10	>20
5g	Br	Br	-OCH_3	CHO	>10	>20
5h	Br	Br	Br	CHO	>10	>20

5i	Br	Br	NO_2	CHO	>10	>20
5j	Br	Br		CHO	5.77±1.44	>20
5k	Br	Br	OH	CHO	>10	>20
5l	Br	H	H	CHO	>10	>20
5m	Br	H	$-OCH_3$	CHO	>10	>20
5n	Br	H	OH	CHO	>10	>20
5o	Br	H		CHO	8.45±0.52	>20
6a	H	H	OCH_3		>10	>20
6b	H	H			>10	>20
6c	H	H			>10	>20
6d	H	H			>30	3.17±0.56
6e	H	H			>10	>20
6f	H	H	Br		>10	>20
6g	Br	Br	$-OCH_3$		>10	>20
6h	Br	Br	H		>10	>20
6i	Br	Br	Br		>10	>20
6j	Br	H	H		>10	>20
6k	Br	H	$-OCH_3$		>10	>20
6l	Br	H			8.07±0.41	>20
6m	Br	Br			3.54±0.37	>20
7a	H	H			8.02±0.86	>20
7b	Br	Br			9.73±0.20	>20
7c	Br	Br	H		>30	>20
7d	Br	Br	Br		6.60±0.19	>20

7e	Br	Br	-OCH_3		>30	>20
7f	Br	Br			7.04±0.28	>20
8a	H	H	H	H	12.48±0.04	1.65±0.22
8b	Br	Br		H	1.07±0.03	>20
8c	H	H	Br	H	10.22±0.13	1.24±0.47
8d	H	H	-OCH_3	H	9.66±0.63	1.41±0.30
8e	H	H		H	>10	1.04±0.46
8f	H	H		H	7.02±0.58	2.12±0.50
8g	H	H		H	>10	2.49±0.30
8h	Br	Br	H	H	>10	>20
8i	Br	H		H	5.39±0.64	4.22±0.34
8j	Br	Br	-OCH_3	H	>10	1.24±0.69
8k	Br	H	H	H	>10	>20
8l	Br	H	-OCH_3	H	>10	1.65±0.82
9a	H	H	H		>10	4.73±0.04
9b	H	H			>10	>20
9c	H	H	Br		>10	>20
9d	H	H	-OCH_3		>10	>20
9e	H	H			>10	>20
9f	Br	H			8.79±0.08	>20
9g	H	H			>10	>20
9h	Br	Br	H		>10	>20
9i	Br	H	H		>10	>20
9j	Br	H	-OCH_3		>10	>20
9k	Br	Br			13.39±0.93	>20
9l	Br	Br			17.57±0.86	>20

10a	H	H	H		>30	>20
10b	Br	Br			12.77±0.21	>20
10c	Br	Br			7.61±0.46	>20
10d	H	H	H		>30	>20
10e	H	H	OH		8.08±0.62	6.02±0.15
10f	H	H			>30	>20
10g	Br	Br	H		3.85±0.28	>20
10h	Br	H	H		4.86±0.5	>20
11a	H	H	H		2.57±0.09	4.70±1.41
11b	Br	Br	-OCH_3		2.17±0.08	1.97±0.83
11c	H	H			3.17±0.04	2.34±0.35
11d	H	H	-OCH_3		>10	>20
11e	H	H			4.62±0.74	3.02±0.69
11f	H	H			1.78±0.2	2.04±0.51
11g	H	H	Br		9.14±0.4	>20
11h	Br	Br	H		>10	7.98±0.34
11i	Br	Br	Br		3.45±0.41	>20
11j	Br	H	H		>10	>20
11k	Br	H	-OCH_3		>10	>20
12a	Br	Br			1.92±0.04	>20
12b	H	H	H		>10	>20
12c	H	H	-OCH_3		3.38±0.46	>20

12d	H	H			9.27±0.81	>20
12e	H	H			>10	>20
12f	H	H			>10	>20
12g	H	H	Br		4.87±0.57	>20
12h	Br	Br	H		>10	>20
12i	Br	Br	Br		6.42±0.52	>20
12j	Br	H	H		>10	>20
12k	Br	H	-OCH_3		>10	>20

2. DeepRLADS and molecular generation

This paper presents a novel method for generating drug lead molecules based on actor-critic deep reinforcement learning model, ADMET evaluation and docking simulations-DeepRLADS, which is able to generate new compounds with multi-target properties by performing fragment replacement on an initial set of lead compounds. The specific steps will be described in detail below.

2.1 Fragment Combination Library Construction

The input data of the DeepRLADS method include two data sets, the lead compound molecular set and the virtual fragment combinatorial library. The lead compound molecular set contains 175 lead compounds with M^{pro} activity that were virtually screened from 969 lead compounds in our laboratory. The virtual fragment combinatorial library was constructed with 9823 M^{pro} inhibitors from the ChEMBL database. Molecules were splitted into fragments, such as ring structures, side chains, and linkers, using the open-source cheminformatics python software RDKit (Figure S3). The original ligation sites were recorded and saved for use in later assembly steps.

Fragments with more than 12 heavy atoms and fragments with four or more attachment points were discarded to reduce the complexity of the resulting molecules.

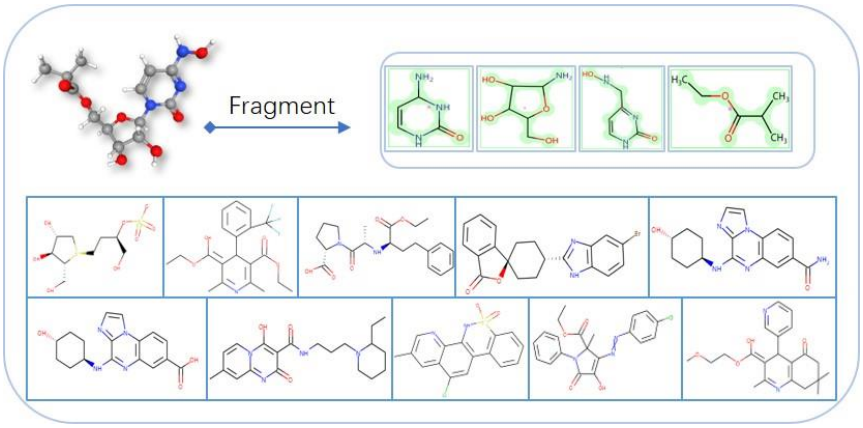


Figure S3. Fragment combination library

2.2 Fragment Encoding based on Similarity Calculations

The constructed fragment combinatorial library was subjected to data preprocessing by calculating the similarity and coding between fragments. The fragments were encoded as binary strings (a sequence of ones and zeros), so that similar fragments get similar encodings.

2.2.1 Fragment Similarity Calculations

Similarities between different molecular fragments were calculated by a combinatorial method of calculating chemical similarities. The measure of intermolecular similarity is the maximum common substructure similarity Tanimoto-MCS (TMCS):

$$\mathrm{TMCS}(M_1, M_2) = \frac{mcs(M_1,M_2)}{a(M_1)+a(M_2)-mcs(M_1,M_2)} \quad (1)$$

In formula 1, $\mathrm{TMCS}(\mathrm{M}_1, \mathrm{M}_2)$ is the number of atoms in the maximum common substructure of molecules M_1 and M_2. $\alpha(\mathrm{M}_1)$ and $\alpha(\mathrm{M}_2)$ are the number of atoms in molecule M_1 and M_2, respectively. TMCS works well for "drug-like" molecular comparisons, but not so well for small fragments. An improved Levenshtein Distance method, Damerau-Levenshtein Distance, was introduced and defined as:

$$DL_{S_1,S_2}(i,j) = \begin{cases} 0 & if(i=0)or(j=0) \\ DL(s_1, i-1, s_2, j-1)+1 & if(i,j>0)and\left(s_{1_i} \neq s_{2_j}\right) \\ max(DL(s_1,i,s_2,j-1), DL(s_1,i-1,s_2,j)\ if(i,j>0)and(s_{1_i} \neq s_{2_j}) \end{cases} \quad (2)$$

The similarity between two molecules M_1 and M_2 was measured with the corresponding SMILES representations S_1 and S_2, which is defined as:

$$\mathrm{Max}(\mathrm{TMCS}(M_1, M_2), \mathrm{DL}(S_1, S_2) \quad (3)$$

2.2.2 Fragments Encoding

A balanced binary tree was constructed based on similarity, on which all segments were encoded as binary strings. The encoding of each fragment was determined by the path from the root to the leaf where the fragment was stored. As shown in Figure S4, each branch to the left adds a one ("1") to the end of the encoding, and each branch to the right adds a zero ("0").

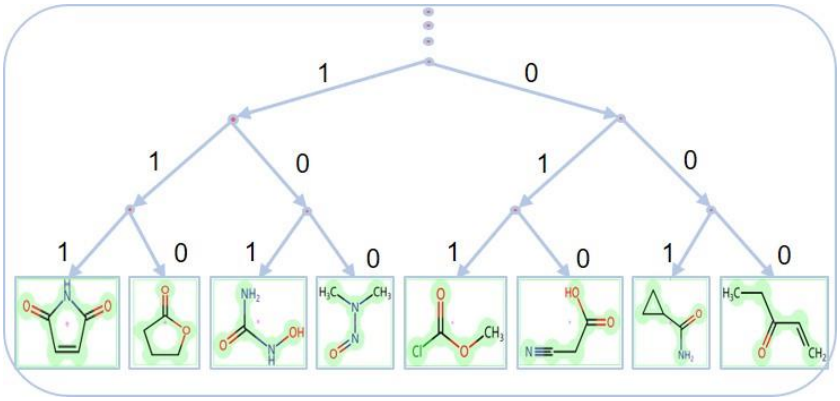


Figure S4. A subpart of the binary tree holding fragments

2.3 Generation of molecules

Preprocessed data were fed into the actor network structure of deep reinforcement learning, which is the core of the generative model of DeepRLADS method. Molecular generation was achieved by fragment replacement, which was represented by the exchange of codes representing fragments. Modifying a little at the end of the encoding will represent changes to very similar fragments, while changes at the beginning will represent changes to very different types of fragments. A series of compounds with a specific functional group structure can be generated by defining a specific leading

number of codes.

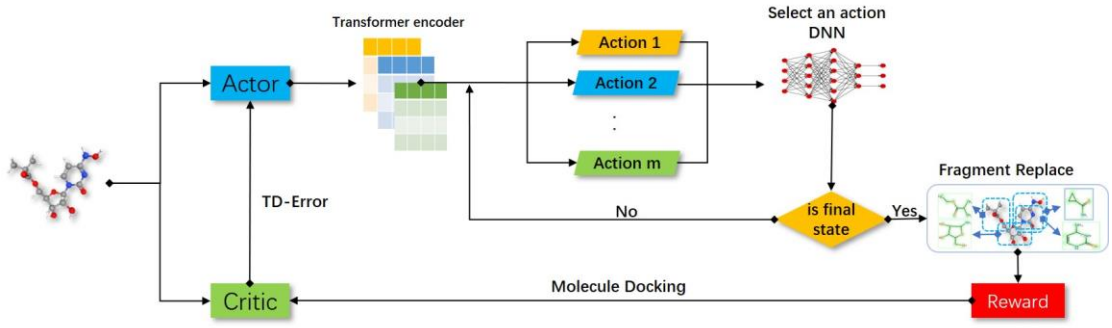


Figure S5. A model based on actor-critic deep reinforcement learning

As shown in Figure S5, the actor-critic deep reinforcement learning based model starts from a fragmented molecular state, the current state S. Actor module adopts the bidirectional transformer encoder mechanism and densenet to decide the way of fragment replacement, the action A_i. The generated molecule is scored with a reward module according to the new state S_i. The difference of the rewards between S_i and S, TD-Error, is checked by the critic module and then fed back to the actor module. The current state S is replaced by the optimized new state S_i, and the whole process is repeated a given number of times.

The positional information of the fragments in a molecule was introduced by actor network through the bidirectional transformer encoder mechanism and the densenet network. As the input of the transformer encoder network, the representation vector X of each fragment contains two parts: fragment encoding and fragment position encoding. The importance of the fragment was obtained by calculating the attention coefficient of the segment through the transformer encoder mechanism. Molecular-related property changes caused by fragment changes were vectorized by forward and backward transformer encoders. The probability distribution of a certain molecular property obtained by transformer was classified by densenet network (Figure S6).

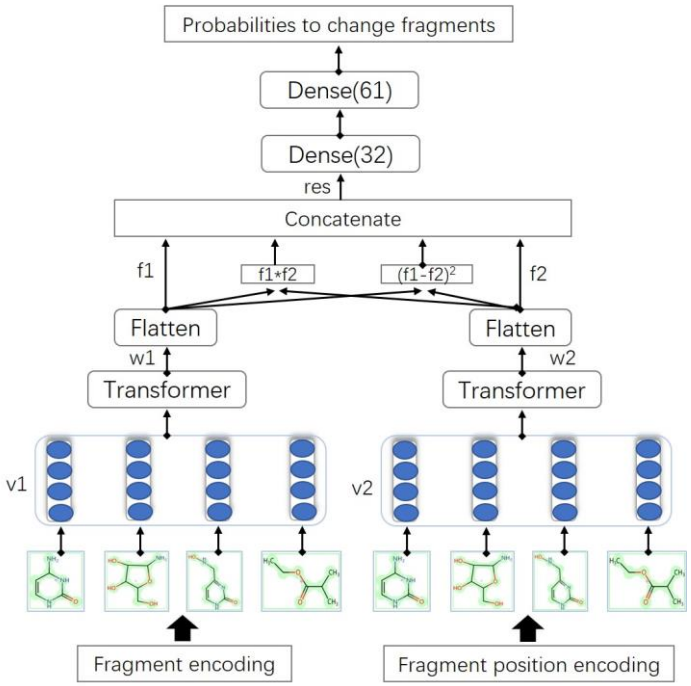


Figure S6. Actor network structure of deep reinforcement learning model

2.4 Evaluation and Optimization of Molecules

The evaluation and optimization of molecular properties were finally realized through the reward mechanism of reinforcement learning in the DeepRLADS method.

2.4.1 ADMET-related Assessment in Reward Mechanism

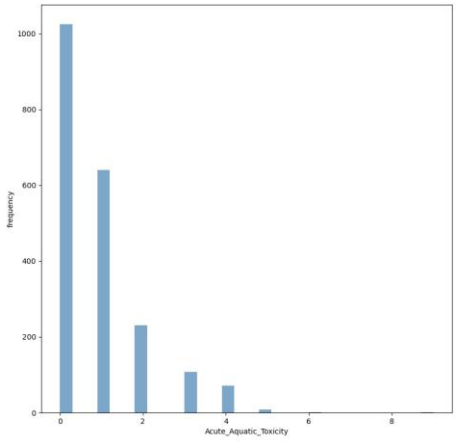
The ADMET-related assessment of virtual molecules was achieved through *in* silico prediction of physical chemistry, medicinal chemistry, absorption, distribution, metabolism, excretion and toxicity properties. First, possible toxic molecules were filtered out from the initially generated molecules via toxicity rules and toxicity substructures. Then, molecules with excellent ADME properties were screened out of those meeting the preliminary safety profile. Pharmacokinetic parameters mainly include physicochemical properties, medicinal chemistry properties, absorption, distribution, metabolism and excretion[1, 2]. All ADMET-related parameter ranges were mainly set by a statistical distribution of outcomes for 2086 existing drugs.

(1) Toxicities

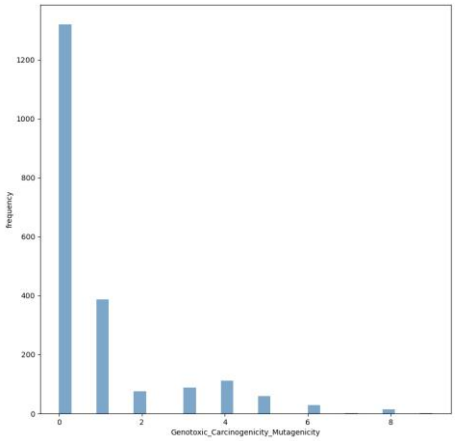
The prediction method was based on chemical similarity and the identification of

fragments that were over-represented in toxic compounds. In addition, by collecting protein-ligand-based pharmacophores (‘toxicophores’), this web server can also be used to predict possible toxicity target and shed light on the mechanisms that are involved in toxicity development.

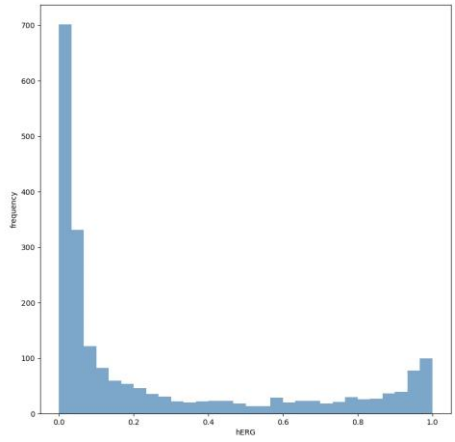
Acute Toxicity Acute toxicity describes the adverse effects of a substance that occur within a short period after dose or exposure and is an important indicator of the drug safety assessment[3]. The acute toxicity rule refers to molecules containing certain substructures that may cause acute toxicity during oral administration. Optimal: 0 or 1.



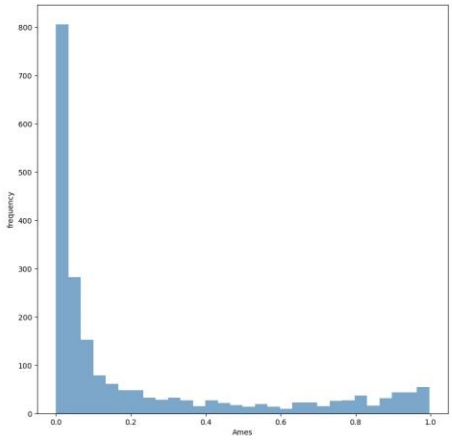
Genotoxicity Genotoxicity is an important factor in the pre-clinical toxicity tests of drug design. The mechanism of genotoxicity is complex, including inhibiting DNA synthesis by nucleotide analogues or base pair mismatch caused by macrocyclic organics embedding into the DNA helix. Genotoxicity Rule refers to molecules containing certain substructures that may cause carcinogenicity. Optimal: 0 or 1



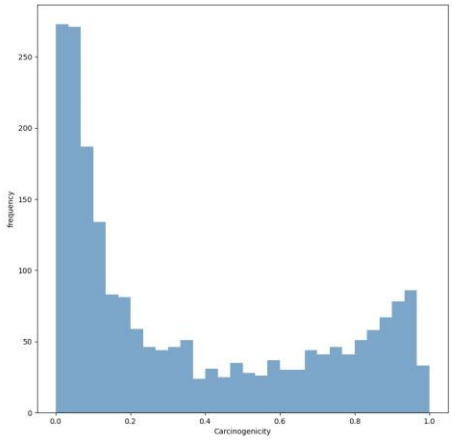
hERG toxicity Sudden death induced by a blockade of hERG K^+ channels (encoded by the hERG) is widely regarded as the predominant cause of drug-induced QT interval prolongation. There are some databases that have collected large amounts of hERG toxicity data, such as WOMBAT-PK and PubChem BioAssay[3]. In silico analysis of hERG toxicity can be performed based on a diverse range of drug structures that can cause hERG toxicity. The output value is the probability that the IC_{50} less than 10 μM, within the range of 0 to 1. Optimal: 0 to 0.2.



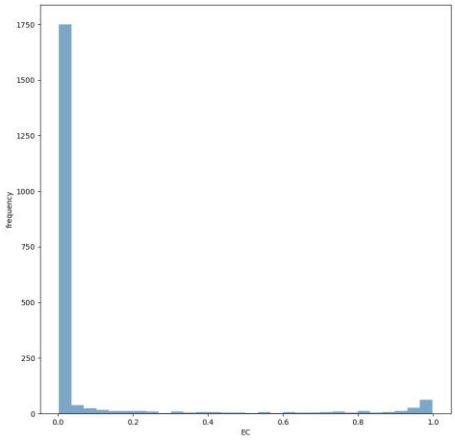
AMES Toxicity The Ames test for mutagenicity. The mutagenic effect has a close relationship with the carcinogenicity, and it is the most widely used assay for testing the mutagenicity of compounds. The output value is the probability of being toxic, within the range of 0 to 1. Optimal: 0-0.07.



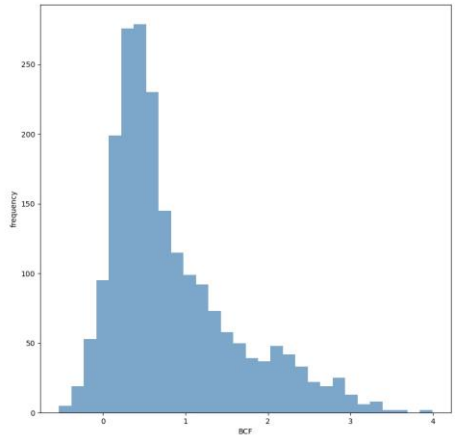
Carcinogencity The carcinogenic mechanism of chemicals may be due to their ability to damage the genome or disrupt cellular metabolic processes. The output value is the probability of being toxic, within the range of 0 to 1. Optimal: 0-0.3.



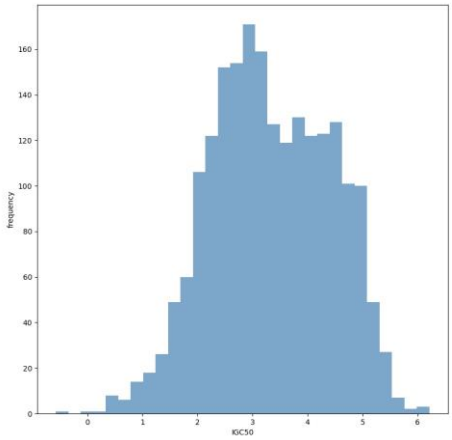
Eye Corrosion Assessing the eye irritation/corrosion (EI/EC) potential of a chemical. The output value is the probability of being toxic, within the range of 0 to 1. Optimal: 0-0.03.



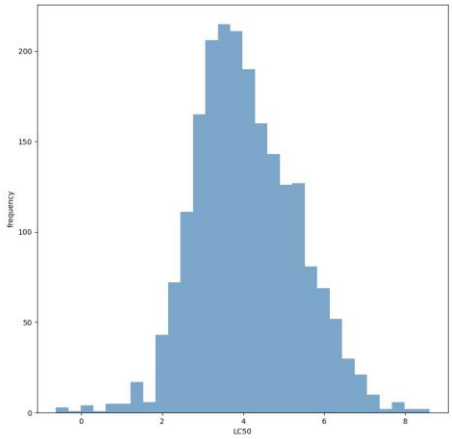
Bioconcentration Factor The bioconcentration factor BCF is defined as the ratio of the chemical concentration in biota as a result of absorption via the respiratory surface to that in water at steady state. The unit of BCF is log10(L/kg). Optimal: 0-1.



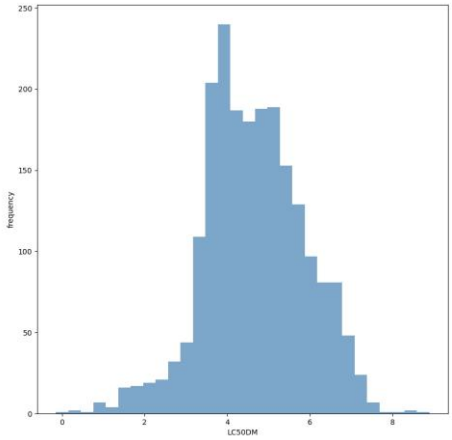
IGC_{50} 48 hour Tetrahymena pyriformis IGC50 (concentration of the test chemical in water in mg/L that causes 50% growth inhibition to Tetrahymena pyriformis after 48 hours). The unit of IGC50 is -log10[(mg/L)/(1000*MW)]. Optimal: 2-5.5



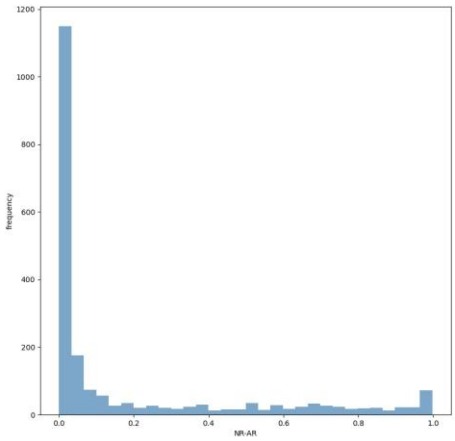
$LC_{50}FM$ 96 hour fathead minnow LC50 (concentration of the test chemical in water in mg/L that causes 50% of fathead minnow to die after 96 hours). The unit of LC50FM is -log10[(mg/L)/(1000*MW)]. Optimal: 2-6.5



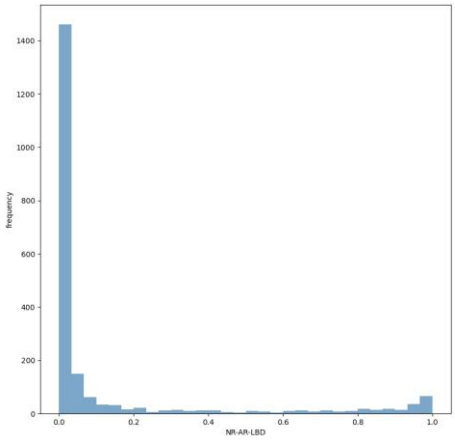
$LC_{50}DM$ 48 hour Daphnia magna LC50 (concentration of the test chemical in water in mg/L that causes 50% of Daphnia magna to die after 48 hours). The unit of LC50DM is -log10[(mg/L)/(1000*MW)]. Optimal: 3-7.



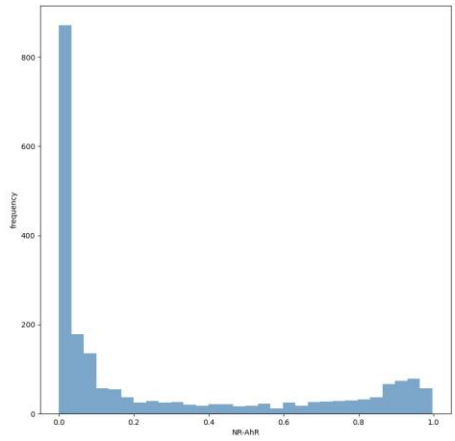
NR-AR Androgen receptor (AR), a nuclear hormone receptor, plays a critical role in AR-dependent prostate cancer. The output value is the probability of being AR agonists, within the range of 0 to 1. Optimal: 0-0.05.



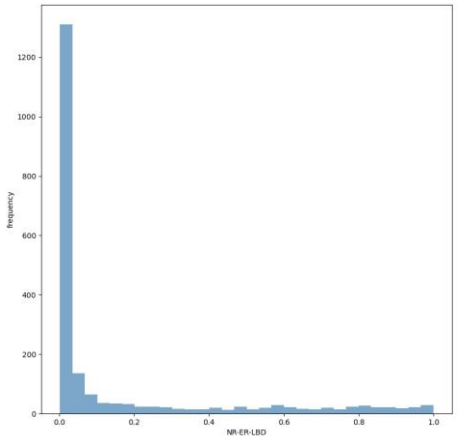
NR-AR-LBD Molecules that labeled 1 in this bioassay may bind to the LBD of androgen receptor. The output value is the probability of being actives, within the range of 0 to 1. Optimal: 0-0.05.



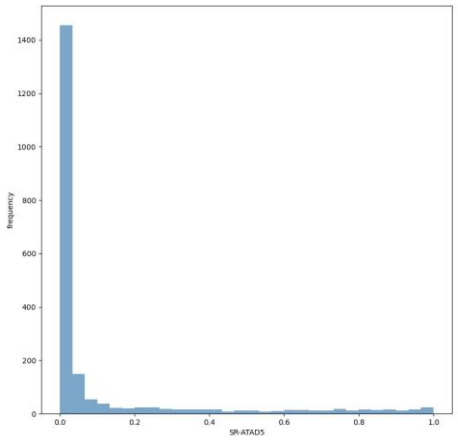
NR-Aromatase Endocrine disrupting chemicals (EDCs) interfere with the biosynthesis and normal functions of steroid hormones including estrogen and androgen in the body. The output value is the probability of being actives, within the range of 0 to 1. Optimal: 0-0.2.



NR-ER-LBD Estrogen receptor (ER), a nuclear hormone receptor, plays an important role in development, metabolic homeostasis and reproduction. Endocrine disrupting chemicals (EDCs) and their interactions with steroid hormone receptors like ER causes disruption of normal endocrine function. The output value is the probability of being actives within the range of 0 to 1. Optimal: 0-0.2.



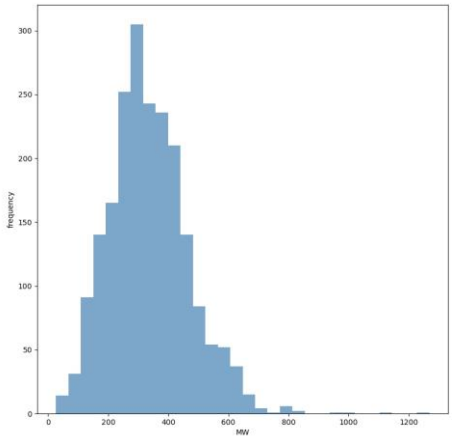
SR-ATAD5 ATPase family AAA domain-containing protein 5. Enhanced Level of Genome Instability Gene 1 (ELG1; human ATAD5) protein levels increase in response to various types of DNA damage. The output value is the probability of being actives within the range of 0 to 1. Optimal: 0-0.2



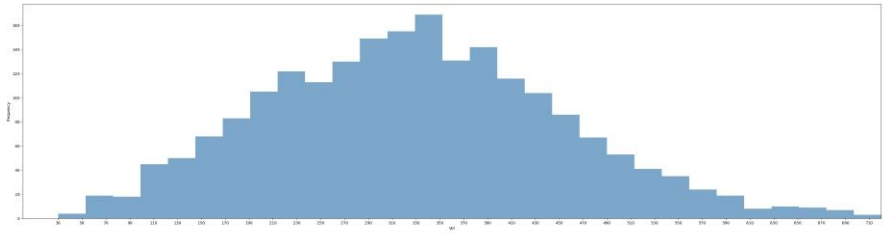
(2) Physicochemical properties

A number of structural properties closely relevant to drug-likeness was calculated , such as MW, volume, LogP, LogS, LogD, charge, nRot, nRing, flexibility, nHet, nHA, nHD, maxRing, TPSA, and stereo centers.

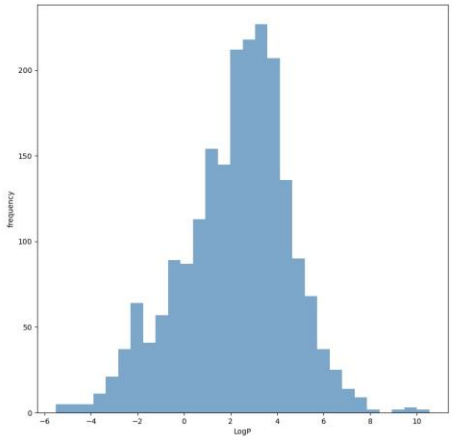
MW Molecular weight. The sum of the atomic weights in the molecule. Optimal: 200 to 500.



Volume Van der Waals volume. Optimal: 200 to 430

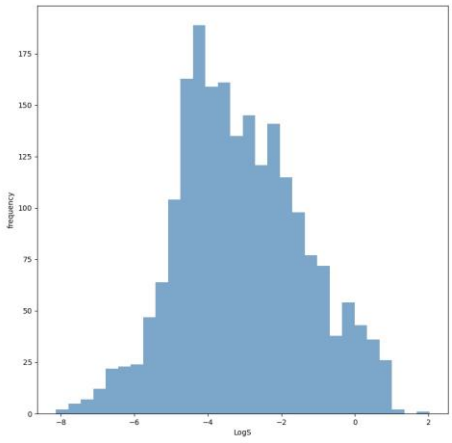


LogP The logarithm of the n-octanol/water distribution coefficient. Log P has a considerable effect on membrane permeability and also on hydrophobic binding to macromolecular protein targets, such as plasma proteins, transporters or metabolic enzymes. Optimal: 0 to 5.5.

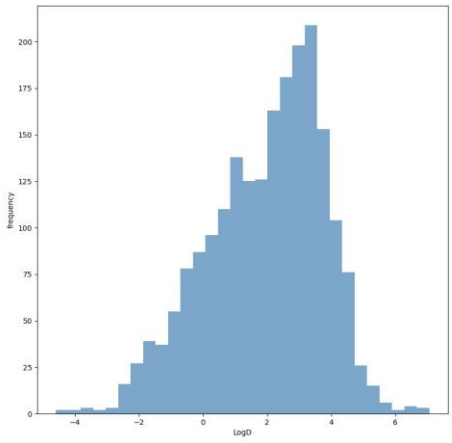


LogS The logarithm of aqueous solubility value (log mol/L). Aqueous solubility is one of the most important factors. To be absorbed, a drug must be soluble in water first and then have the opportunity to permeate across biological membranes. Optimal:

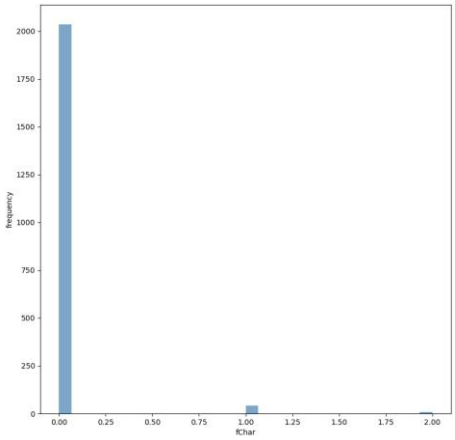
-4.7 to -2.



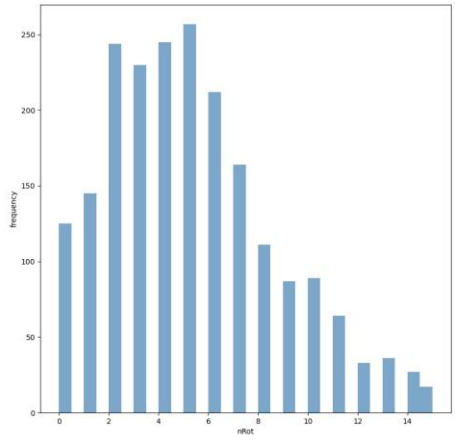
LogD The logarithm of the n-octanol/water distribution coefficients at pH=7.4. An eligible drug usually needs to keep a balance between lipophilicity and hydrophilicity to dissolve in the body fluid and penetrate the biomembrane effectively. Optimal: -1 to 4.5.



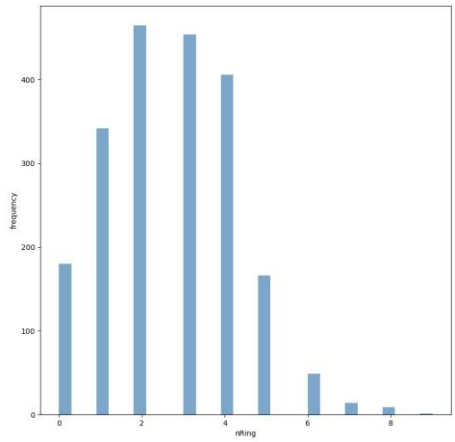
Charge Formal charge (fChar) is a useful thermodynamic parameter to modulate several key molecular properties. Optimal: 0



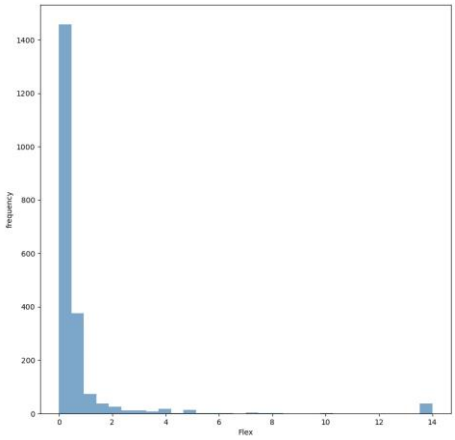
nRot Number of rotatable bonds. Optimal: 0 to 8



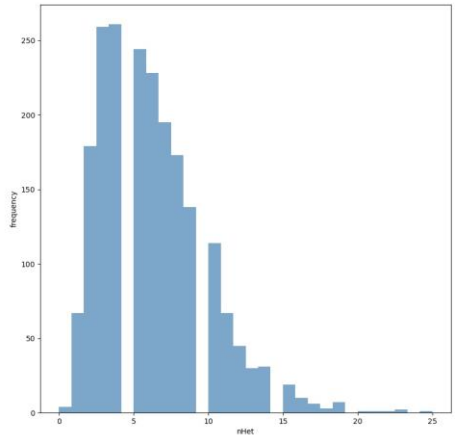
nRing Number of rings. Optimal: 0 to 5



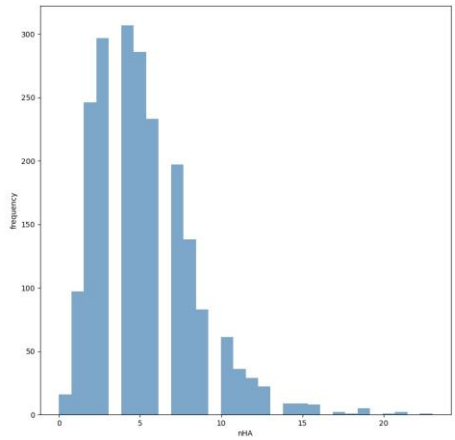
Flexibility Flexibility = nRot /nRig. Optimal: 0 to 1



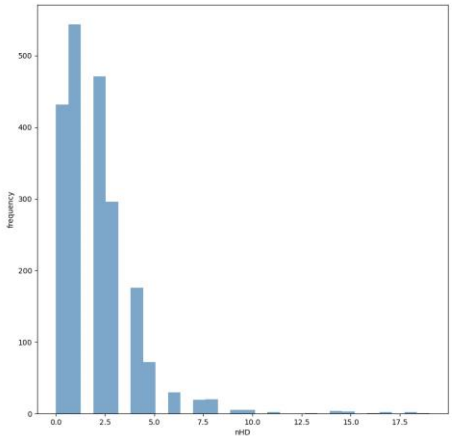
nHet Number of heteroatoms. Optimal: 1 to 11



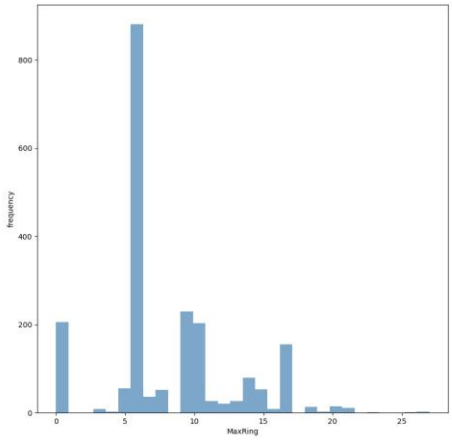
nHA Number of hydrogen bond acceptors. Optimal: 1-9



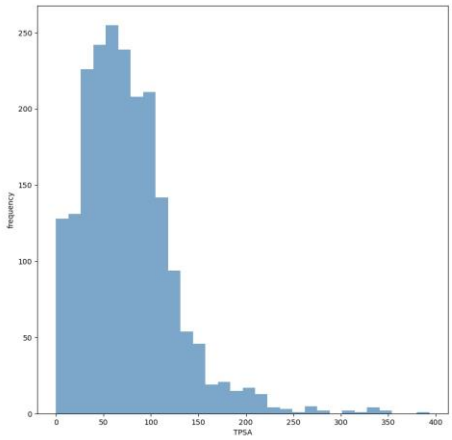
nHD Number of hydrogen bond donors. Optimal: 0 to 4



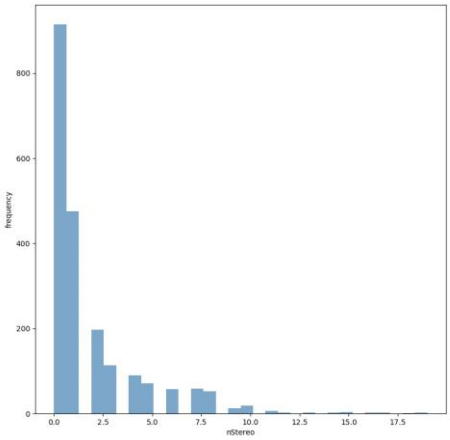
MaxRing Number of atoms in the biggest ring. Optimal: 6



TPSA Topological polar surface area. Sum of tabulated surface contributions of polar fragments. Optimal: 0 to 130



Stereo Centers Number of stereocenters. Optimal: 0 to 1

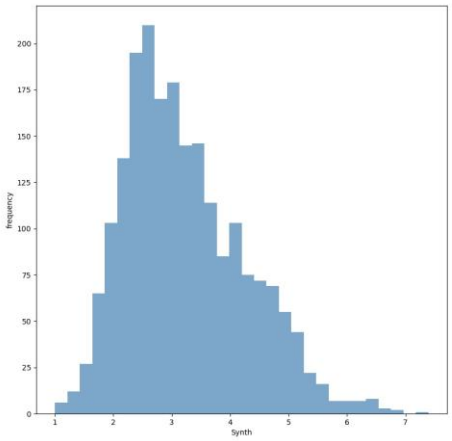


(3) Medicinal chemistry properties

Medicinal chemistry properties contains some quantitative measures to evaluate molecular druglikeness and synthetic feasibility, including MCE-18, SAscore, and NPscore.

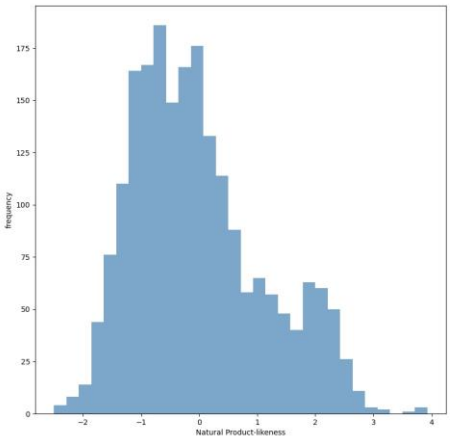
MCE-18 MCE-18 stands for medicinal chemistry evolution in 2018, and this measure can effectively score molecules by novelty in terms of their cumulative sp3 complexity[4]. Optimal: ⩾45 is considered a suitable value.

SAscore Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules, based on a combination of fragment contributions and a complexity penalty[5]. Optimal: 0 to 5, easy to synthesize.



NPscore Natural Product-likeness score can help to guide the design of new molecules toward interesting regions of chemical space which have been identified as

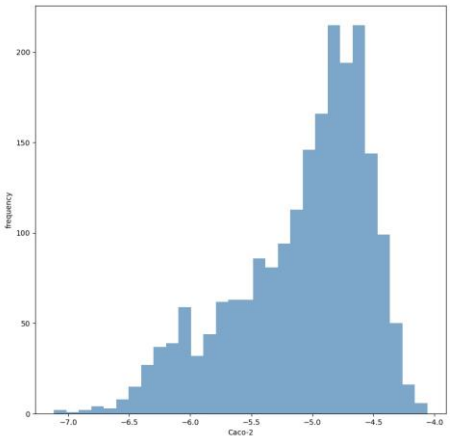
“bioactive regions” by natural evolution. Optimal: -1.5 to 1.



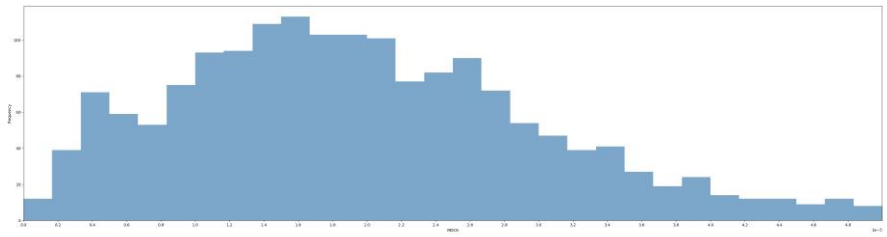
(4) Absorption

The ideal oral drug will be rapidly and completely absorbed from the alimentary canal. For any drug administered by the oral route, the relevant pharmacokinetic parameters of absorption are undoubtedly the most important.

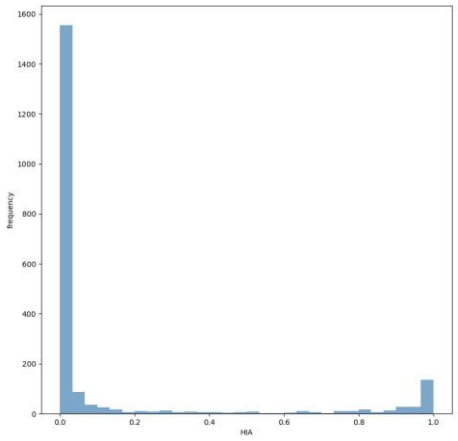
Caco-2 Permeability The human colon adenocarcinoma cell lines (Caco-2), as an alternative approach for the human intestinal epithelium, has been used to estimate in vivo drug permeability due to their morphological and functional similarities. The predicted Caco-2 permeability of a given compound is given as the log cm/s. Optimal: -5.3 to -4.5.



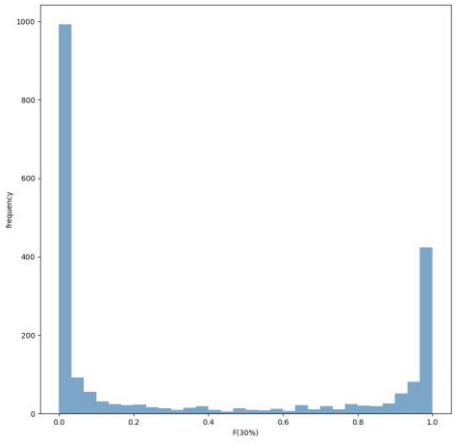
MDCK Permeability Madin-Darby Canine Kidney cells (MDCK) have been developed as an in vitro model for permeability screening. Optimal: >2 x 10^{-6} cm/s.



HIA Human intestinal absorption, as a key procedure of oral absorption, is one of the most influential ADME properties in the early stages of lead discovery and optimization. Category 1: HIA^{+}(HIA < 30%); Category 0: HIA^{-}(HIA < 30%)[1]. Optimal: 0 to 0.03, only for oral drug.



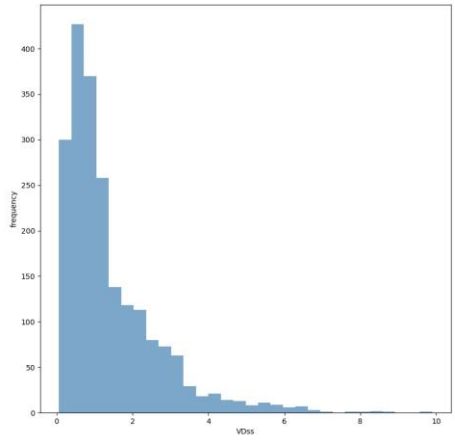
F30% The human oral bioavailability 30%. Molecules with a bioavailability ≥ 30% were classified as $F30\%^{-}$ (Category 0), while molecules with a bioavailability < 30% were classified as $F30\%^{+}$ (Category 1). The output value is the probability of being F30%+, within the range of 0 to 1. Optimal: 0 to 0.03, only for oral drug.



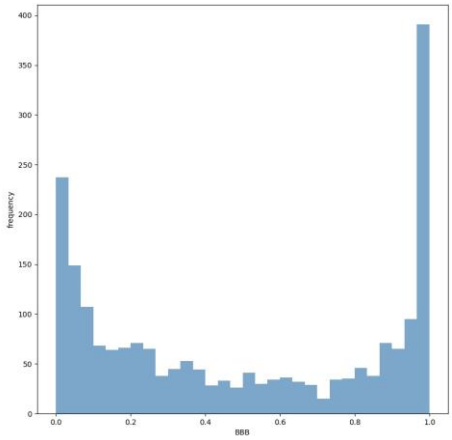
(5) Distribution

The ideal oral drug will find its way directly and specifically to its site of action.

VD Volume Distribution. The VD is a theoretical concept that connects the administered dose with the actual initial concentration present in the circulation and it is an important parameter to describe the in vivo distribution for drugs. The unit of predicted VD is L/kg. Optimal: 0 to 2.



BBB Penetration The blood–brain barrier (BBB) is the microvascular endothelial cell layer of the brain and plays a pivotal role in separating the brain from the blood. By contrast, for drugs with a peripheral target, little or no BBB penetration might be required in order to avoid CNS side effects. The unit of BBB penetration is cm/s. Optimal: 0 to 0.2 (peripheral target); 0.8 to 1 (brain target).



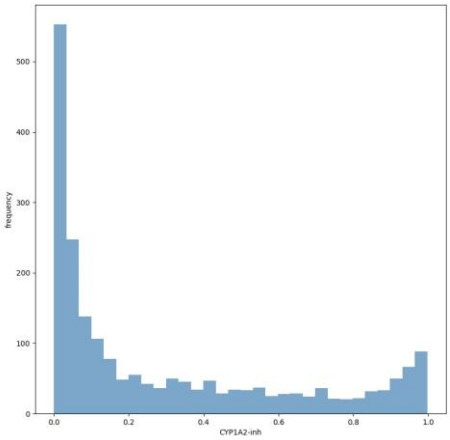
(6) Metabolism

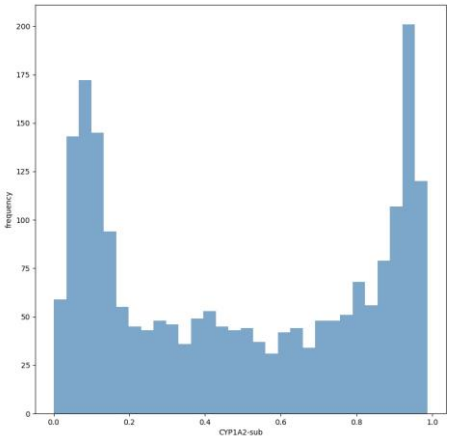
Elimination generally refers to the irreversible removal of a compound or its metabolite(s) from the body, primarily by two routes: metabolism and excretion. Metabolism prediction is a research priority in many areas, including pharmaceutical, food safety, and environmental studies. For the majority of drugs and NCEs, metabolism is the major pathway of elimination.

Drug metabolism can be divided into phases I and II; phase I involves oxidation, reduction, and hydrolysis, whereas phase II only involves conjugation, including methylation, sulphation, glutathione conjugation, and glycine conjugation. The human cytochrome P450 family (phase I enzymes) contains 57 isozymes and these isozymes metabolize approximately two-thirds of known drugs in human with 80% of this attribute to five isozymes—1A2, 3A4, 2C9, 2C19 and 2D6.

CYP 1A2 inhibitor Optimal: 0 to 0.1.

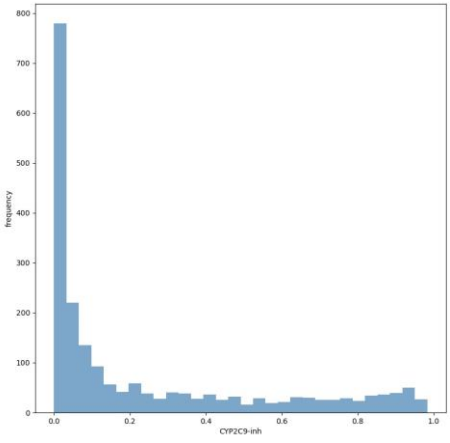
CYP 1A2 substrate Optimal: irregular.

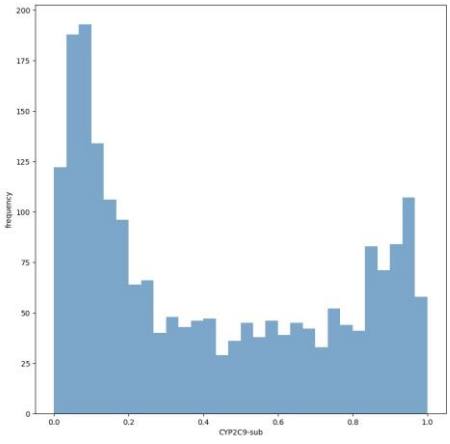




CYP 2C9 inhibitor Optimal: 0 to 0.1

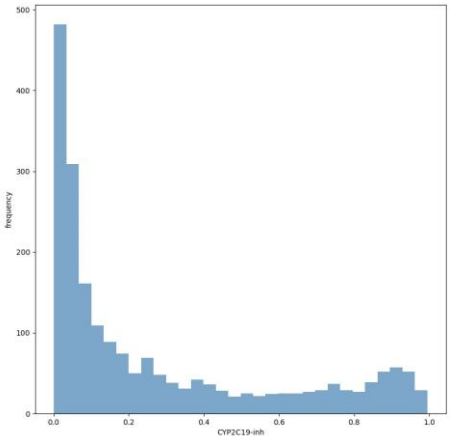
CYP 2C9 substrate Optimal: irregular.

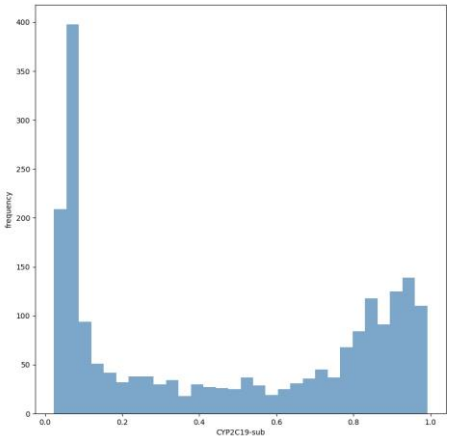




CYP 2C19 inhibitor Optimal: 0 to 0.1.

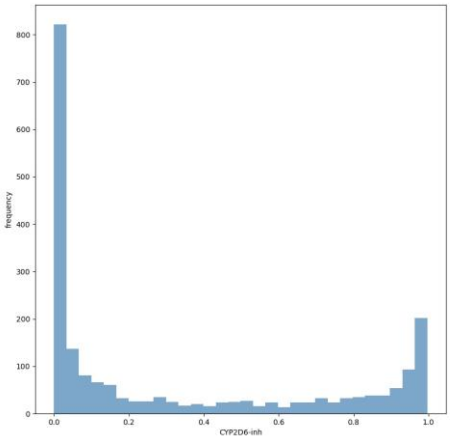
CYP 2C19 substrate Optimal: irregular.

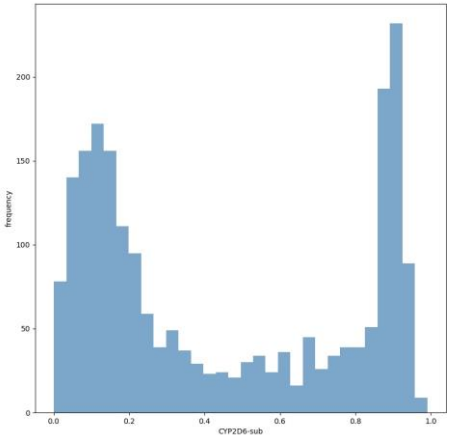




CYP 2D6 inhibitor Optimal: 0 to 0.1.

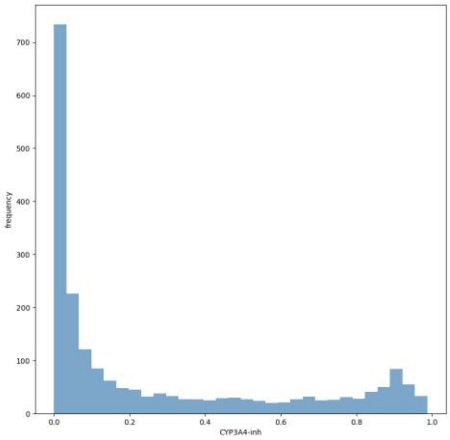
CYP 2D6 substrate Optimal: irregular.

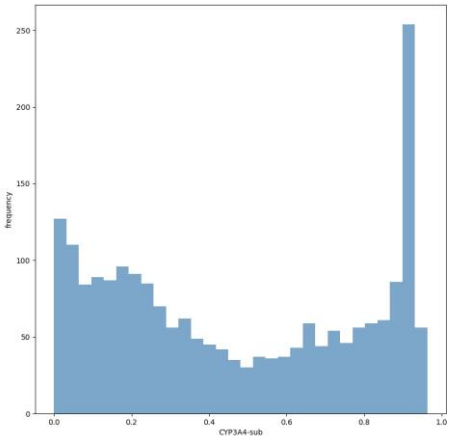




CYP 3A4 inhibitor Optimal: 0 to 0.1.

CYP 3A4 substrate irregular.

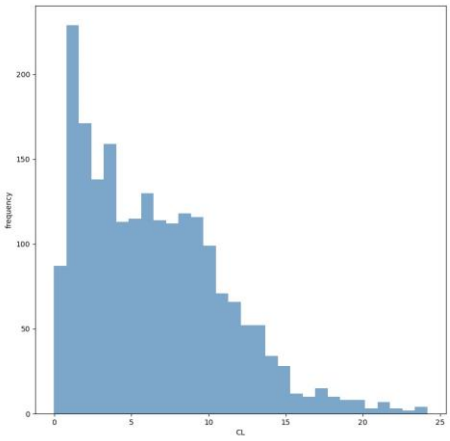




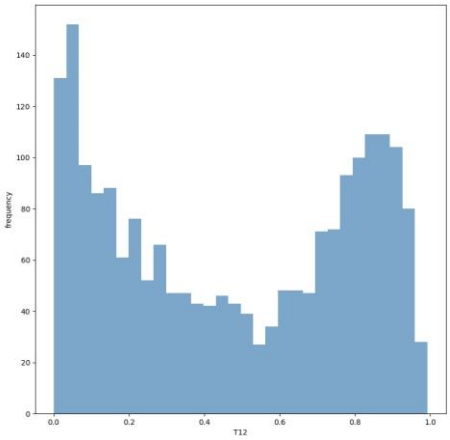
(7) Excretion

There are two major excretory routes for xenobiotics and their metabolites from the body: renal and biliary excretion.

CL The clearance of a drug. Clearance is an important pharmacokinetic parameter. The unit of predicted CL penetration is ml/min/kg. Optimal: 0 to 10.



$T_{1/2}$ The half-life of a drug is a hybrid concept that involves clearance and volume of distribution, and it is arguably more appropriate to have reliable estimates of these two properties instead. Molecules with T1/2 > 3 were classified as $T1/2^-$ (Category 0), while molecules with T1/2 ≤ 3 were classified as $T1/2^+$ (Category 1). The output value is the probability of being $T1/2^+$, within the range of 0 to 1[1]. Optimal: irregular. The output value is the probability of having long half-life.



2.4.2 Vina@QNLM in Reward Mechanism

The biological activity prediction of molecules was realized by constructing classifiers and super large-scale molecular docking method. A two-stage parallel acceleration method Vina@QNLM was established to quickly and accurately calculate the affinity score between small molecules and specific targets. This improved method includes scheduling strategy based on MPI (Multi Point Interface) and acceleration method based on Sunway supercomputer. In order to quickly obtain the active docking data of these molecules, Vina@QNLM uses MPI to realize the docking of multiple target proteins and multiple ligands between different MPEs (Management Processing Elements). In Sunway supercomputer, each CG (Core Group) consists of one MPE and 64 CPEs (Computing Processing Element). Embedding protein target data into the grid can effectively reduce the time spent in docking calculation of the interaction. The optimal molecular conformation can be obtained quickly by performing the Monte Carlo search algorithm on 64 CPEs.

The actor of the reinforcement learning will be rewarded for each effective molecule generated. It will be highly rewarded for producing molecules that satisfy multi-objective properties. Through continuous iterative optimization, compounds with well properties and novel structures can be obtained.

3. Biological activity evaluation

3.1 Enzyme activity assays

3.1.1 Fluorescence resonance energy transfer (FRET) assay

SARS-CoV-2 and PEDV M^{pro} purification and enzymatic assays were performed as previously described with minor modifications [6, 7]. Proteins were purified using GST-glutathione affinity chromatography and cleaved with thrombin. The homogeneity of purified proteins was detected by the SDS-PAGE method. The enzymatic activity of M^{pro} was measured by continuous kinetic assays using a fluorescent labeled substrate MCA-AVLQ/SGFR-Lys (DNP)-Lys-NH2 (Apetide Co, Ltd, Shanghai, China). The fluorescence intensity was monitored by Microplate reader (SpectraMax®i3x, Molecular Devices, U.S.A.). The excitation and emission wavelengths were 320 and 405 nm, respectively. Experiments were performed in 99 μL buffer（50 mM Tris-HCl, pH 7.3, 1 mM EDTA）containing 196 nM M^{pro}, 2 μM substrate and 1μL desired concentration drugs. The candidate catechol-pyrazoline derivatives (**5-12**) were screened at the final concentration of 10 μM. The primary hits were confirmed at different concentration and the IC_{50} values were determined by GraphPad Prism6.

3.1.2 Surface plasmon resonance (SPR) assay

SPR interaction analyses were performed using a Biacore T200 optical biosensor. SPR measurements were carried out in phosphate buffer saline [0.1 M phosphate buffer with 27 mM KCl and 1.37 M NaCl 0.005% polysorbate 20 pH 7.4] containing 0.02% P20, and compounds stock solutions were diluted in the PBS-P20 buffer containing 5% DMSO. Data was collected with the Biacore control software version 2.0. Experiments were performed by monitoring the refractive index changes as a function of time under a constant flow rate of 10 μL/min. The relative amount of inhibitor bound to the $hPTP1B^{1-321}$ was determined by measuring the net increase in refractive index over time compared to the reference flow cell. There is an inline subtraction of reference surface during the run. This change is usually reported in response units (RU).

3.2 Cell studies

3.2.1 Antiviral Effects of Compounds in Cell Culture

Vero-E6 cells (ATCC, CRL-1586™) were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 10 mM HEPES, 0.1 mM non-essential amino acids, and 100 U/ml of penicillin-streptomycin. Cells were maintained in the incubator at 37 ℃ with 5% CO_2. The pre-seeded Vero E6 cells (5×10^4 cells/well) were pretreated with different concentrations of compounds (**11b** and **11f**) to be tested for 1 h, and SARS-CoV-2 and PEDV (MOI of 0.05) was added to infect them for 2 h. Then, the virus-compound mixture was removed, and the cells were further cultured with fresh bromophenol-pyrazoline compound-containing medium. After 24 hours, the cell supernatant was collected and the vRNA in the supernatant was subjected to qRT-PCR analysis. The 50% effective concentration (EC50) values were calculated using GraphPad Prism software 7.

3.2.2 PEDV titration and Immunofluorescence assay

Vero cells seeded into 96-well plates were cultured to 85-95% confluence. The cell monolayers were washed three times with PBS. Serial 10-fold dilutions of the collected supernatant were made between 10^{-1} to 10^{-8}. Volume of 100 μl to each dilution were then inoculated into five wells of the 96-well plate. The plates were then cultured for another 72 hours and checked by IFA analysis with a fluorescence microscope (TE2000U; Nikon). The dilution of the supernatant was titrated by $TCID_{50}$ assay and calculated based on the Reed-Muench method.

Cells were firstly fixed with 4% paraformaldehyde for 20 min and then permeabilized with 1% Triton X-100 for 10 min at room temperature. After blocking with 5% skim milk for 1 h, cells were incubated with mouse anti-PEDV-nucleocapsid monoclonal antibody (1:5000 dilution) for 1 h, followed by incubating with the Alexa Fluor 488 goat anti-mouse IgG antibody (1:500 dilution) (Thermo, USA) for another 1 h. The cells were finally observed with a fluorescence microscope (TE2000U; Nikon).

3.2.3 Cell cytotoxicity Assay

Human colon epithelial cell line NCM460 was purchased from the Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences (Shanghai, China). NCM460 cells were incubated in the medium with 10% fetal bovine serum (PAN, Adenbach, Bavaria, Germany) and 1% penicillin-streptomycin (Gibco-Invitrogen, Grand Island, NY, USA) under a humidified atmosphere of 5% CO_2 at 37 ℃. The inhibition rate of cell proliferation was detected by 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide (MTT, Solarbio, Beijing, China) assay. The suspension cells were inoculated in 96-well plates at the density of 5, 000 cells per well, and incubated with **11b** at indicated concentrations dissolved in DMSO for 72 h. Each well was incubated with MTT solution (5 mg/mL) at 37 ℃ for 4 h, DMSO was added and incubated overnight at 37 ℃. The absorbance at 570 nm was measured in a multimode reader (Berthold Technologies, Germany).

3.2.4 RNA extraction and quantitative PCR

Total RNA was extracted with RNAiso Plus (9109, Takara). Reverse transcription was performed with PrimeScript^{TM} RT reagent Kit (RR047A, Takara) with gDNA Eraser. Quantitative real-time PCR was performed on LightCycler®96 (Roche) using FastStart Essential DNA Green Master (35732800, Roche). Gene expression was normalized to the housekeeping gene GAPDH.

3.3 Animal studies

3.3.1 Animal challenge experiment

Two litters of 5-day-old neonatal pigs (15 piglets) that were confirmed negative for PEDV, TGEV, PDCoV, PRV, PRRSV, and PCV2 were transferred to an isolation room and fed milk. The piglets were randomly divided into three groups of five each, namely the control group, the PEDV group, and the PEDV+11b group. All pigs except the controls were orally infected with 1 ×105 TCID50 PEDV (GS2014-LJX) in 1.5 mL water per pig. After challenge exposures, piglets in the PEDV + **11b** group were orally

administered with **11b** at the dosage of 5 mg/kg body weight (dissolved in a liquid milk replacer) twice a day for three consecutive days, whereas the other two groups were given the same volume of liquid milk replacer. The occurrence of diarrhea, the body weight and the survival rate were monitored and recorded. The tissues (duodenum, jejunum, ileum, cecum, colon, rectum and spleen) were collected for pathological examination and viral load were analysis using qRT-PCR.

3.3.2 Pharmacokinetic studies

Plasma pharmacokinetics. Six SD rats with half males and half females were administered orally at a dose of 25 mg/kg. Blood samples were collected through saphenous vein at 0 min, 5 min, 15 min, 30 min, 1 h, 2 h, 4h, 6 h, 8h, and 24 h. All samples were centrifuged under 4000 rpm/min for 10 min at 4 ℃ and the plasma (supernatants) were collected and stored at -80 ℃ for future analysis. An aliquot of 50 μL each plasma sample was treated with 250 μL of ethyl acetate. The samples were centrifuged under 4000 rpm/min for 10 min and filtered through 0.2 μm membrane filters. The concentration of analytes in each sample were analyzed by LC/MS/MS. The plasma concentration-time data of compound **11b** were determined by a noncompartmental method using the Kinetica 2000 software package (version 3.0; InnaPhase Corp., Philadelphia, PA, USA) to derive pharmacokinetic parameters.

Tissue distribution. Twenty-four SD rats with half males and half females were equally divided into four groups and administered orally at a dose of 25 mg/kg. Large intestine and small intestine tissues were collected from sacrificed rats at 10 min, 15 min, 1 h, and 4 h, respectively. Tissues were broken and processed with ethyl acetate followed by quantitation against a standard curve (13.7–10000 nmol/L) prepared in blank plasma.

Feces and urine. Eighteen SD rats with half males and half females were equally divided into three groups and administered orally at a dose of 25 mg/kg. Urine and feces within 24 hours were collected in three sections (0-4 hours, 4-8 hours, 8-24 hours) at room temperature and stored frozen at -20 ℃. Urine and feces samples were processed with ethyl acetate followed by quantitation against a standard curve (13.7–10000

nmol/L) prepared in blank plasma. Percent excreted in urine and feces was calculated as the amount of analyte in the urine divided by the amount dosed.

3.3.3 Histopathologic and immunofluorescence analysis

The tissues were fixed in 4% paraformaldehyde in PBS and stored in 50% ethanol overnight, then fixed tissues were embedded in paraffin, sectioned, and stained with hematoxylin and eosin solution (H&E) according to the manufacturers' instructions. For immunofluorescence, samples were incubated with anti-PEDV-N antibody (1:500) for 30 min at 37 ℃. After three washes, samples were stained with goat secondary antibody and DAPI. Images were obtained using a fluorescent microscope.

3.3.4 Toxicological safety evaluation

In acute study, 18 healthy Kunming mice with half males and half females, 18-20 g of weight, were randomly divided into three groups (n=6). Three groups of mice were orally administered with single oral doses of vehicle (0.5% CMC-Na solution) and **11b** (1000 and 3000 mg/kg body wt.), respectively. Body weight, toxicity effect, general behavior and mortality of mice were recorded during the following 14 days.

In sub-acute toxicity assay, 30 healthy Kunming mice with half males and half females, 20-22 g of weight, were randomly divided into control group and two experimental groups. The mice of experimental groups were orally administered with 500 and 1500 mg/kg body wt $\cdot day^{-1}$ once a day for 28 days. All mice were observed for mortality, visual toxic effect, behavioral change and body weight daily. After 28 days of treatment, the mice were anaesthetized with isoflurane and killed by decapitation. The heart, liver, and kidney tissues were collected, and histologically analyzed by H&E staining.

At the completion of the studies, animals were euthanized by overdose of inhaled anesthesia followed by exsanguination.

4. Chemistry and Synthesis

All commercial reagents were purchased and used without further purification or

distillation unless otherwise stated. Melting points were measured on a Griffin apparatus and are uncorrected. NMR (^{1}H, ^{13}C) spectra were obtained with a Bruker AV-500 spectrometer with chemical shifts reported as parts per million (TMS as internal standard). The following abbreviations are used for the multiplicity of NMR signals: s= singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Column chromatography was performed on silica gel with 200-300 mesh. The high-resolution mass spectra (HRMS) were obtained on a HPLC-Q-Tof MS (Micro) spectrometer. Purity of all final products was determined by analytical HPLC to be >95%. The HPLC purity of compounds was measured with a normal phase HPLC column (XBridge C18, 4.6 ×150 mm, 5 μm) in conjunction with two diverse wavelength detection systems. Compounds were eluted using a gradient elution of 40/60 to 0/100 H_2O/CH_3OH over 30 min at a flow rate of 0.3 mL/min.

The catechol group of the series **1** is similar to the active bromophenol derivatives previously discovered by our group from red algae[8, 9], which provides inspiration for the design of synthetically processed compounds **5-12** (Scheme S1). Starting materials **2** and **3** were synthesized according to the reported methods[10]. Catechols **2** reacted with substituted acetophenones (**3**) under the action of $SOCl_2$ in ethanol to generate intermediate product chalcones (**4**). Intermediate **4** and hydrazine hydrate were refluxed in different liquid acids (formic acid, acetic acid, propionic acid, butyric acid) to obtain the target products **5-7**, respectively. The target product pyrazoline derivatives **8-10** were obtained by cyclization of the intermediate product **4** with different substituted hydrazines. In addition, intermediates **4** were reacted with thiosemicarbazide to obtain carbothioamides **11** in acetic acid under reflux. Carbothioamides were cyclized with chloroacetic acid in acetic acid under reflux to afford target products **12**.

General procedure for the preparation of 5-(3,4-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5a**).

To 3,4-dihydroxybenzaldehyde (1.38 g, 0.01 mol) dissolved in ethanol (20 mL) was added acetophenone (1.20 g, 0.01 mol). When complete solution was obtained, $SOCl_2$ (0.5 mL) was incrementally added, while stirring. The reaction mixture was stirred at room temperature for 24 h. 10 mL water was slowly added with rapid stirring

under ice-water bath. The precipitate was filtered off and washed with ethanol. (*E*)-3-(3,4-dihydroxyphenyl)-1-phenylprop-2-en-1-one was afforded as a yellow solid (1.71 g, 71.3 %).

To a mixed solution of 3 mL ethanol and 1 mL formic acid, (*E*)-3-(3,4-dihydroxyphenyl)-1-phenylprop-2-en-1-one (120 mg, 0.5 mmol) and hydrazine hydrate (200 mg, 85%) were added with stirring. This mixture was heated at reflux for 2 h. After cooling to ambient temperature, the precipitate was filtered off and washed with water. Recrystallization of the crude product yielded the desired product 5-(3,4-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5a**, 93 mg, 66.2 %).

^{1}H NMR (500 MHz, dmso) δ 8.93 (s, 1H), 8.84 (d, *J* = 4.5 Hz, 2H), 7.83 – 7.74 (m, 2H), 7.52 – 7.42 (m, 3H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.56 (d, *J* = 1.9 Hz, 1H), 6.49 (dd, *J* = 8.1, 1.9 Hz, 1H), 5.33 (dd, *J* = 11.6, 4.3 Hz, 1H), 3.83 (dd, *J* = 18.1, 11.7 Hz, 1H), 3.14 (dd, *J* = 18.1, 4.4 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 159.92 (s), 156.58 (s), 145.83 (s), 145.19 (s), 132.85 (s), 131.29 (s), 130.94 (s), 129.29 (s), 127.11 (s), 117.14 (s), 115.98 (s), 113.25 (s), 58.61 (s), 42.76 (s). HRMS [M-H]: $C_{16}H_{13}N_2O_3$, calcd for 281.09317, found 281.09296.

Compounds **5b-5o** were synthesized according to the synthetic method of compound **5a**.

5-(3,4-dihydroxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5b**)

^{1}H NMR (500 MHz, dmso) δ 8.91 (s, 1H), 8.81 (s, 2H), 7.71 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.56 (s, 1H), 6.48 (dd, *J* = 8.1, 1.7 Hz, 1H), 5.30 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.84 – 3.76 (m, 4H), 3.10 (dd, *J* = 18.0, 4.3 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 161.49 (s), 159.64 (s), 159.42 (s), 156.31 (s), 145.81 (s), 145.15 (s), 132.96 (s), 128.80 (s), 123.80 (s), 117.12 (s), 115.98 (s), 114.71 (s), 113.24 (s), 58.44 (s), 55.81 (s), 42.86 (s). HRMS [M-H]: $C_{17}H_{15}N_2O_4$, calcd for 311.10373, found 311.10361.

5-(3,4-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5c**)

^{1}H NMR (500 MHz, dmso) δ 8.92 (s, 1H), 8.84 (s, 1H), 8.82 (s, 1H), 7.74 (d, *J* =

8.7 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.95 (dd, *J* = 8.8, 5.3 Hz, 4H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 1.8 Hz, 1H), 6.47 (dd, *J* = 8.1, 1.8 Hz, 1H), 5.31 (dd, *J* = 11.5, 4.1 Hz, 1H), 4.03 – 3.98 (m, 2H), 3.78 (dd, *J* = 18.0, 11.6 Hz, 1H), 3.10 (dd, *J* = 18.0, 4.2 Hz, 1H), 1.31 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, dmso) δ 162.52 (s), 160.52 (s), 159.72 (s), 156.06 (s), 155.85 (s), 148.71 (s), 145.82 (s), 145.17 (s), 132.89 (s), 129.06 (s), 125.48 (s), 121.75 (s), 117.39 (s), 117.09 (s), 116.06 (d, *J* = 19.7 Hz), 113.22 (s), 63.83 (s), 59.83 (s), 42.84 (s), 15.13 (s). HRMS [M-H]: $C_{24}H_{21}N_2O_5$, calcd for 417.14560, found 417.14532.

3-(4-(4-(tert-butyl)phenoxy)phenyl)-5-(3,4-dihydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5d**)

^{1}H NMR (500 MHz, dmso) δ 8.91 (s, 1H), 8.82 (s, 2H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.01 (t, *J* = 8.7 Hz, 4H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 2.0 Hz, 1H), 6.48 (dd, *J* = 8.1, 2.0 Hz, 1H), 5.32 (dd, *J* = 11.5, 4.2 Hz, 1H), 3.80 (dd, *J* = 18.0, 11.6 Hz, 1H), 3.10 (dd, *J* = 18.0, 4.3 Hz, 1H), 1.28 (s, 9H). ^{13}C NMR (126 MHz, dmso) δ 159.75 (s), 159.59 (s), 156.03 (s), 153.61 (s), 147.10 (s), 145.82 (s), 145.18 (s), 132.88 (s), 129.11 (s), 127.34 (s), 125.98 (s), 119.48 (s), 118.30 (s), 117.10 (s), 115.99 (s), 113.24 (s), 58.56 (s), 42.86 (s), 34.59 (s), 31.68 (s). HRMS [M-H]: $C_{26}H_{25}N_2O_4$, calcd for 429.18197, found 429.18173.

5-(3,4-dihydroxyphenyl)-3-(4-phenoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5e**)

^{1}H NMR (500 MHz, dmso) δ 8.91 (s, 1H), 8.82 (s, 2H), 7.77 (d, *J* = 8.6 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.05 (dd, *J* = 16.7, 8.3 Hz, 4H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.56 (s, 1H), 6.48 (dd, *J* = 8.1, 1.4 Hz, 1H), 5.32 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.80 (dd, *J* = 18.0, 11.6 Hz, 1H), 3.11 (dd, *J* = 18.0, 4.2 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 161.99 (s), 159.79 (s), 156.08 (s), 145.81 (s), 145.16 (s), 132.88 (s), 130.68 (s), 129.14 (s), 126.21 (s), 124.72 (s), 119.88 (s), 118.58 (s), 117.14 (s), 115.99 (s), 113.24 (s), 58.58 (s), 42.83 (s). HRMS [M-H]: $C_{22}H_{17}N_2O_4$, calcd for 373.11938, found 373.11905.

3-(4-bromophenyl)-5-(3,4-dihydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5f**)

^{1}H NMR (500 MHz, dmso) δ 8.92 (s, 1H), 8.84 (d, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 2.0 Hz, 1H), 6.48 (dd, *J* = 8.1, 2.0 Hz, 1H), 5.34 (dd, *J* = 11.6, 4.4 Hz, 1H), 3.81 (dd, *J* = 18.1, 11.7 Hz, 1H), 3.13 (dd, *J* = 18.1, 4.6 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 160.00 (s), 155.71 (s), 145.83 (s), 145.23 (s), 132.71 (s), 132.28 (s), 130.54 (s), 129.05 (s), 124.32 (s), 117.16 (s), 116.00 (s), 113.31 (s), 58.83 (s), 42.62 (s). HRMS [M-H]: $C_{26}H_{12}BrN_2O_3$, calcd for 359.00368, found 359.00348.

5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5g**)

^{1}H NMR (600 MHz, DMSO) δ 10.06 (s, 1H), 9.62 (s, 1H), 8.93 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 6.55 (s, 1H), 5.63 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.94 – 3.88 (m, 1H), 3.80 (s, 3H), 3.05 (dd, *J* = 17.9, 4.4 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 161.64 (s), 159.79 (s), 156.53 (s), 146.09 (s), 144.58 (s), 132.31 (s), 128.95 (s), 123.56 (s), 114.74 (s), 114.08 (s), 112.44 (s), 59.62 (s), 55.85 (s), 42.14 (s). HRMS [M-H]: $C_{27}H_{14}Br_2N_2O_4$, calcd for 468.92271, found 468.92233.

3-(4-bromophenyl)-5-(2,3-dibromo-4,5-dihydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5h**)

^{1}H NMR (600 MHz, DMSO) δ 10.07 (s, 1H), 9.64 (s, 1H), 8.97 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 2H), 6.54 (s, 1H), 5.66 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.94 (dd, *J* = 17.9, 12.0 Hz, 1H), 3.10 (dd, *J* = 18.1, 4.1 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 160.18 (s), 156.02 (s), 146.09 (s), 144.63 (s), 132.33 (s), 130.32 (s), 129.18 (s), 124.55 (s), 112.43 (s), 59.97 (s), 41.92 (s). HRMS [M-H]: $C_{16}H_{10}Br_3N_2O_3$, calcd for 516.82266, found 516.82239.

5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5i**)

^{1}H NMR (600 MHz, DMSO) δ 10.08 (s, 1H), 9.66 (s, 1H), 9.04 (s, 1H), 8.30 (d, *J* = 8.5 Hz, 2H), 8.02 (d, *J* = 8.1 Hz, 2H), 6.55 (s, 1H), 5.77 – 5.66 (m, 1H), 4.02 (dd, *J* = 17.8, 12.1 Hz, 1H), 3.19 (dd, *J* = 18.0, 4.5 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 160.57 (s), 159.47 (s), 155.24 (s), 148.68 (s), 146.10 (s), 144.70 (s), 137.16 (s), 128.39 (s), 124.47 (s), 114.18 (s), 112.44 (s), 41.87 (s). HRMS [M-H]: $C_{16}H_{11}Br_2N_3O_5$, calcd

for 483.89722, found 483.89697.

5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5j**)

^{1}H NMR (600 MHz, DMSO) δ 8.94 (s, 1H), 7.75 (s, 1H), 7.74 (s, 1H), 7.04 (d, *J* = 8.9 Hz, 2H), 6.97 (dd, *J* = 13.6, 8.8 Hz, 4H), 6.53 (s, 1H), 5.63 (dd, *J* = 11.4, 3.8 Hz, 1H), 4.03 – 4.00 (m, 2H), 3.91 (dd, *J* = 17.8, 11.8 Hz, 1H), 3.04 (dd, *J* = 17.9, 4.3 Hz, 1H), 1.33 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 160.69 (s), 159.89 (s), 156.30 (s), 155.92 (s), 148.69 (s), 146.19 (s), 129.20 (s), 125.24 (s), 121.83 (s), 117.39 (s), 116.19 (s), 112.34 (s), 63.87 (s), 59.73 (s), 42.15 (s), 15.16 (s). HRMS [M-H]: $C_{24}H_{19}Br_2N_2O_5$, calcd for 574.96457, found 574.96405.

5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5k**)

^{1}H NMR (600 MHz, DMSO) δ 10.06 (s, 1H), 10.04 (s, 1H), 9.61 (s, 1H), 8.91 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.53 (s, 1H), 5.61 (dd, *J* = 11.5, 4.2 Hz, 1H), 3.88 (dd, *J* = 17.8, 11.6 Hz, 1H), 3.00 (dd, *J* = 17.9, 4.4 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 160.26 (s), 159.67 (s), 156.77 (s), 146.07 (s), 144.55 (s), 129.08 (s), 121.97 (s), 116.09 (s), 114.06 (s), 112.43 (s), 59.50 (s), 42.15 (s). HRMS [M-H]: $C_{16}H_{11}Br_2N_2O_4$, calcd for 454.90706, found 454.90706.

5-(3-bromo-4,5-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5l**)

^{1}H NMR (600 MHz, DMSO) δ 9.84 (s, 1H), 9.15 (s, 1H), 8.88 (s, 1H), 7.80 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.49 (overlap, 3H), 6.83 (s, 1H), 6.62 (s, 1H), 5.38 (dd, *J* = 11.6, 4.5 Hz, 1H), 3.85 (dd, *J* = 18.1, 11.7 Hz, 1H), 3.21 (dd, *J* = 18.2, 4.6 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 160.08 (s), 156.72 (s), 147.01 (s), 142.86 (s), 133.83 (s), 131.19 (s), 131.07 (s), 129.34 (s), 127.20 (s), 120.63 (s), 112.08 (s), 110.02 (s), 58.13 (s), 42.64 (s). HRMS [M-H]: $C_{16}H_{13}BrN_2O_3$, calcd for 359.00368, found 359.00345.

5-(3-bromo-4,5-dihydroxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5m**)

^{1}H NMR (600 MHz, DMSO) δ 9.84 (s, 1H), 9.14 (s, 1H), 8.84 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.04 – 7.02 (m, 2H), 6.81 (s, 1H), 6.61 (s, 1H), 5.34 (dd, *J* = 11.6, 4.4

Hz, 1H), 3.84 – 3.77 (overlap, 4H), 3.17 (dd, *J* = 18.0, 4.5 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 161.60 (s), 159.80 (s), 156.44 (s), 147.00 (s), 142.82 (s), 133.94 (s), 128.92 (s), 123.68 (s), 120.59 (s), 114.76 (s), 112.05 (s), 110.01 (s), 57.95 (s), 55.85 (s), 42.73 (s). HRMS [M-H]: $C_{17}H_{14}BrN_2O_4$, calcd for 389.01424, found 389.01404.

5-(3-bromo-4,5-dihydroxyphenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5n**)

^{1}H NMR (600 MHz, DMSO) δ 10.04 (s, 1H), 9.85 (s, 1H), 9.14 (s, 1H), 8.83 (s, 1H), 7.63 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.61 (d, *J* = 2.0 Hz, 1H), 5.33 (dd, *J* = 11.5, 4.3 Hz, 1H), 3.77 (dd, *J* = 18.0, 11.6 Hz, 1H), 3.13 (dd, *J* = 18.0, 4.4 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 160.21 (s), 159.67 (s), 156.67 (s), 147.00 (s), 142.79 (s), 134.01 (s), 129.04 (s), 122.10 (s), 120.60 (s), 116.11 (s), 112.02 (s), 110.00 (s), 57.84 (s), 42.74 (s). HRMS [M-H]: $C_{16}H_{12}BrN_2O_4$, calcd for 374.99859, found 374.99841.

5-(3-bromo-4,5-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**5o**)

^{1}H NMR (600 MHz, DMSO) δ 9.83 (s, 1H), 9.14 (s, 1H), 8.85 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.99 – 6.96 (overlap, 4H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.60 (d, *J* = 1.9 Hz, 1H), 5.35 (dd, *J* = 11.6, 4.4 Hz, 1H), 4.02 (q, *J* = 7.0 Hz, 2H), 3.80 (dd, *J* = 18.1, 11.7 Hz, 1H), 3.16 (dd, *J* = 18.1, 4.5 Hz, 1H), 1.33 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 160.63 (s), 159.89 (s), 156.20 (s), 155.90 (s), 148.74 (s), 147.00 (s), 142.83 (s), 133.87 (s), 129.17 (s), 125.37 (s), 121.79 (s), 120.56 (s), 117.45 (s), 116.20 (s), 112.06 (s), 110.02 (s), 63.88 (s), 58.04 (s), 42.73 (s), 15.16 (s). HRMS [M-H]: $C_{24}H_{20}BrN_2O_5$, calcd for 495.05611, found 495.05591.

General procedure for the preparation of 1-(5-(3,4-dihydroxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**6a**)

To an acetic acid (4 mL) solution of (*E*)-3-(3,4-dihydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (135 mg, 0.5 mmol) was added hydrazine hydrate (120 mg, 2mmol, 85% concentration) with stirring. This mixture was heated at reflux for 2 h. After cooling to ambient temperature, the precipitate was filtered off and washed with water. Recrystallization of the crude product yielded the desired product

1-(5-(3,4-dihydroxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**6a**, 116 mg, 71.2 %).

^{1}H NMR (500 MHz, dmso) δ 8.85 (s, 1H), 8.75 (s, 1H), 7.70 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.63 (d, *J* = 8.1 Hz, 1H), 6.52 (s, 1H), 6.43 (d, *J* = 6.8 Hz, 1H), 5.32 (dd, *J* = 11.5, 3.8 Hz, 1H), 3.78 (s, 3H), 3.71 (dd, *J* = 17.9, 11.6 Hz, 1H), 3.03 (dd, *J* = 17.9, 3.9 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (126 MHz, dmso) δ 167.30 (s), 161.31 (s), 154.41 (s), 145.70 (s), 144.88 (s), 134.05 (s), 128.67 (s), 124.19 (s), 116.85 (s), 115.92 (s), 114.65 (s), 113.09 (s), 59.31 (s), 55.78 (s), 42.66 (s), 22.21 (s). HRMS [M-H]: $C_{18}H_{17}N_2O_4$, calcd for 325.11938, found 325.11911.

Compounds **6b-6m** were synthesized according to the synthetic method of compound **6a**.

1-(5-(3,4-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**6b**)

^{1}H NMR (500 MHz, dmso) δ 8.87 (s, 1H), 8.77 (s, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.05 – 6.99 (m, 2H), 6.99 – 6.91 (m, 4H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 2.0 Hz, 1H), 6.42 (dd, *J* = 8.1, 2.0 Hz, 1H), 5.32 (dd, *J* = 11.6, 3.9 Hz, 1H), 4.00 (q, *J* = 6.9 Hz, 2H), 3.72 (dd, *J* = 17.9, 11.6 Hz, 1H), 3.02 (dd, *J* = 17.9, 4.0 Hz, 1H), 2.24 (s, 3H), 1.31 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, dmso) δ 167.39 (s), 160.23 (s), 155.76 (s), 154.16 (s), 148.86 (s), 145.70 (s), 144.90 (s), 133.97 (s), 128.93 (s), 125.93 (s), 121.59 (s), 117.50 (s), 116.83 (s), 116.12 (s), 115.92 (s), 113.06 (s), 63.83 (s), 59.40 (s), 42.65 (s), 22.21 (s), 15.13 (s). HRMS [M-H]: $C_{25}H_{23}N_2O_5$, calcd for 431.16125, found 431.16098.

1-(3-(4-(4-(tert-butyl)phenoxy)phenyl)-5-(3,4-dihydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**6c**)

^{1}H NMR (500 MHz, dmso) δ 8.85 (s, 1H), 8.75 (s, 1H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.51 (s, 1H), 6.43 (d, *J* = 8.2 Hz, 1H), 5.33 (dd, *J* = 11.5, 3.7 Hz, 1H), 3.76 – 3.70 (m, 1H), 3.03 (dd, *J* = 18.0, 4.0 Hz, 1H), 2.24 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (126 MHz, dmso) δ 167.42 (s), 159.27 (s), 154.12 (s), 153.78 (s), 146.96 (s), 145.70 (s), 144.91 (s), 133.96 (s), 128.98 (s), 127.31 (s), 126.46 (s), 119.27 (s), 118.46 (s), 116.83

(s), 115.93 (s), 113.08 (s), 59.44 (s), 31.69 (s), 22.21 (s). HRMS [M-H]: $C_{27}H_{27}N_2O_4$, calcd for 443.19763, found 443.19736.

1-(5-(3,4-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**6d**)

^{1}H NMR (500 MHz, dmso) δ 8.87 (s, 1H), 8.77 (s, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.05 – 6.99 (m, 2H), 6.99 – 6.91 (m, 4H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 2.0 Hz, 1H), 6.42 (dd, *J* = 8.1, 2.0 Hz, 1H), 5.32 (dd, *J* = 11.6, 3.9 Hz, 1H), 4.00 (q, *J* = 6.9 Hz, 2H), 3.72 (dd, *J* = 17.9, 11.6 Hz, 1H), 3.02 (dd, *J* = 17.9, 4.0 Hz, 1H), 2.24 (s, 3H), 1.31 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, dmso) δ 167.39 (s), 160.23 (s), 155.76 (s), 154.16 (s), 148.86 (s), 145.70 (s), 144.90 (s), 133.97 (s), 128.93 (s), 125.93 (s), 121.59 (s), 117.50 (s), 116.83 (s), 116.12 (s), 115.92 (s), 113.06 (s), 63.83 (s), 59.40 (s), 42.65 (s), 22.21 (s), 15.13 (s). HRMS [M-H]: $C_{25}H_{23}N_2O_5$, calcd for 431.16125, found 431.16098.

1-(5-(3,4-dihydroxyphenyl)-3-(4-phenoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**6e**)

^{1}H NMR (500 MHz, dmso) δ 8.86 (s, 1H), 8.76 (s, 1H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.05 (t, *J* = 9.0 Hz, 4H), 6.63 (d, *J* = 8.1 Hz, 1H), 6.52 (s, 1H), 6.45 – 6.41 (m, 1H), 5.34 (dd, *J* = 11.6, 3.8 Hz, 1H), 3.78 – 3.71 (m, 1H), 3.04 (dd, *J* = 17.9, 3.9 Hz, 1H), 2.25 (s, 3H). ^{13}C NMR (126 MHz, dmso) δ 167.44 (s), 158.98 (s), 156.25 (s), 154.09 (s), 145.71 (s), 144.92 (s), 133.96 (s), 130.65 (s), 129.01 (s), 126.70 (s), 124.58 (s), 119.68 (s), 118.73 (s), 116.85 (s), 115.94 (s), 113.09 (s), 59.47 (s), 42.64 (s), 22.21 (s). HRMS [M-H]: $C_{23}H_{19}N_2O_4$, calcd for 387.13503, found 387.13486.

1-(3-(4-bromophenyl)-5-(3,4-dihydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**6f**)

^{1}H NMR (500 MHz, dmso) δ 8.87 (s, 1H), 8.77 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 6.63 (d, *J* = 8.1 Hz, 1H), 6.52 (s, 1H), 6.43 (d, *J* = 8.1, 1H), 5.35 (dd, *J* = 11.7, 4.1 Hz, 1H), 3.74 (dd, *J* = 18.0, 11.8 Hz, 1H), 3.06 (dd, *J* = 18.0, 4.2 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (126 MHz, dmso) δ 167.66 (s), 153.70 (s), 145.71 (s), 144.96 (s), 133.80 (s), 132.22 (s), 130.91 (s), 128.94 (s), 124.01 (s), 116.87 (s), 115.95

(s), 113.13 (s), 59.70 (s), 42.40 (s), 22.23 (s). HRMS [M-H]: $C_{17}H_{14}BrN_2O_3$, calcd for 373.01933, found 373.01901.

1-(5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**6g**)

^{1}H NMR (600 MHz, DMSO) δ 9.99 (s, 1H), 9.55 (s, 1H), 7.72 – 7.70 (m, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.49 (s, 1H), 5.62 (dd, *J* = 11.5, 3.8 Hz, 1H), 3.88 – 3.82 (m, 1H), 3.80 (s, 3H), 2.98 (dd, *J* = 17.9, 4.2 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (151 MHz, DMSO) δ 167.51 (s), 161.47 (s), 154.68 (s), 145.99 (s), 144.32 (s), 133.35 (s), 128.83 (s), 123.91 (s), 114.68 (s), 114.01 (s), 112.22 (s), 60.60 (s), 55.83 (s), 41.91 (s), 22.14 (s). HRMS [M-H]: $C_{18}H_{15}Br_2N_2O_4$, calcd for 482.93836, found 482.93790.

1-(5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**6h**)

^{1}H NMR (600 MHz, DMSO) δ 9.99 (s, 1H), 9.57 (s, 1H), 7.80 – 7.77 (m, 2H), 7.46 (d, *J* = 6.4 Hz, 3H), 6.49 (s, 1H), 5.65 (dd, *J* = 11.5, 3.9 Hz, 1H), 3.92 – 3.86 (m, 1H), 3.02 (dd, *J* = 18.0, 4.2 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (151 MHz, DMSO) δ 167.79 (s), 154.93 (s), 146.01 (s), 144.35 (s), 133.23 (s), 131.41 (s), 130.89 (s), 129.26 (s), 127.14 (s), 114.04 (s), 112.22 (s), 60.76 (s), 41.81 (s), 22.16 (s). HRMS [M-H]: $C_{17}H_{13}Br_2N_2O_3$, calcd for 452.92779, found 452.92752.

1-(3-(4-bromophenyl)-5-(2,3-dibromo-4,5-dihydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**6i**)

^{1}H NMR (600 MHz, DMSO) δ 10.00 (s, 1H), 9.57 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.67 (s, 2H), 6.48 (s, 1H), 5.65 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.91 – 3.85 (m, 1H), 3.02 (dd, *J* = 18.0, 4.3 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (151 MHz, DMSO) δ 167.86 (s), 154.08 (s), 145.99 (s), 144.37 (s), 133.09 (s), 132.26 (s), 130.66 (s), 129.09 (s), 124.26 (s), 112.20 (s), 60.94 (s), 41.66 (s), 22.15 (s). HRMS [M-H]: $C_{17}H_{12}Br_3N_2O_3$, calcd for 530.83831, found 530.83801.

1-(5-(3-bromo-4,5-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**6j**)

^{1}H NMR (600 MHz, DMSO) δ 9.78 (s, 1H), 9.08 (s, 1H), 7.79 (d, *J* = 6.5, 2H), 7.48 – 7.46 (m, 3H), 6.77 (s, 1H), 6.57 (s, 1H), 5.37 (dd, *J* = 11.7, 4.3 Hz, 1H), 3.78

(dd, *J* = 18.1, 11.8 Hz, 1H), 3.13 (dd, *J* = 18.1, 4.3 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (151 MHz, DMSO) δ 167.79 (s), 154.79 (s), 146.92 (s), 142.60 (s), 134.93 (s), 131.54 (s), 130.82 (s), 129.28 (s), 127.11 (s), 120.39 (s), 111.94 (s), 109.99 (s), 59.05 (s), 42.43 (s), 22.23 (s). HRMS [M-H]: $C_{17}H_{14}BrN_2O_3$, calcd for 373.01933, found 373.01889.

1-(5-(3-bromo-4,5-dihydroxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**6k**)

^{1}H NMR (600 MHz, DMSO) δ 9.78 (s, 1H), 9.08 (s, 1H), 7.73 (d, *J* = 8.9 Hz, 2H), 7.02 (d, *J* = 8.9 Hz, 2H), 6.76 (s, 1H), 6.57 (s, 1H), 5.35 (dd, *J* = 11.6, 4.2 Hz, 1H), 3.81 (s, 3H), 3.74 (dd, *J* = 18.0, 11.7 Hz, 1H), 3.10 (dd, *J* = 18.0, 4.2 Hz, 1H), 2.27 (s, 3H). ^{13}C NMR (151 MHz, DMSO) δ 167.52 (s), 161.43 (s), 154.58 (s), 146.90 (s), 142.55 (s), 135.04 (s), 128.79 (s), 124.05 (s), 120.36 (s), 114.71 (s), 111.92 (s), 109.98 (s), 58.88 (s), 55.83 (s), 42.54 (s), 22.21 (s). HRMS [M-H]: $C_{18}H_{16}BrN_2O_4$, calcd for 403.02989, found 403.02936.

1-(5-(3-bromo-4,5-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**6l**)

^{1}H NMR (600 MHz, DMSO) δ 9.78 (s, 1H), 9.08 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 9.1 Hz, 2H), 6.98 (d, *J* = 9.1 Hz, 4H), 6.76 (s, 1H), 6.56 (s, 1H), 5.36 (dd, *J* = 11.7, 4.2 Hz, 1H), 4.02 (q, *J* = 7.0 Hz, 2H), 3.74 (dd, *J* = 18.0, 11.7 Hz, 1H), 3.09 (dd, *J* = 18.0, 4.2 Hz, 1H), 2.27 (s, 3H), 1.33 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 167.60 (s), 160.36 (s), 155.82 (s), 154.32 (s), 148.88 (s), 146.91 (s), 142.58 (s), 134.97 (s), 129.04 (s), 125.80 (s), 121.64 (s), 120.34 (s), 117.54 (s), 116.17 (s), 111.93 (s), 109.99 (s), 63.88 (s), 58.97 (s), 42.53 (s), 22.21 (s), 15.15 (s). HRMS [M-H]: $C_{25}H_{22}BrN_2O_5$, calcd for 509.07176, found 509.07132.

1-(5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**6m**)

^{1}H NMR (500 MHz, dmso) δ 9.97 (s, 1H), 9.54 (s, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 6.98 – 6.91 (m, 4H), 6.46 (s, 1H), 5.61 (d, *J* = 7.8 Hz, 1H), 4.05 – 3.98 (m, 2H), 3.89 – 3.82 (m, 1H), 2.98-2.93 (m, 1H), 2.31 (s, 3H), 1.31 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, dmso) δ 167.56 (s), 160.39 (s), 155.80 (s), 154.41 (s), 148.79 (s), 145.96 (s), 144.29 (s), 133.22 (s), 129.05 (s), 125.62 (s), 121.63 (s),

117.45 (s), 116.15 (s), 113.99 (s), 112.15 (s), 63.84 (s), 22.11 (s), 15.13 (s). HRMS [M-H]: $C_{25}H_{21}Br_2N_2O_5$, calcd for 588.98022, found 588.97986.

General procedure for the preparation of 1-(5-(3,4-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)propan-1-one (**7a**)

To a propionic acid (4 mL) solution of (*E*)-3-(3,4-dihydroxyphenyl)-1-(4-(4-ethoxyphenoxy)phenyl)prop-2-en-1-one (188 mg, 0.5 mmol) was added hydrazine hydrate (120 mg, 2mmol, 85% concentration) with stirring. This mixture was heated at reflux for 2 h. After cooling to ambient temperature, the precipitate was filtered off and washed with water. Recrystallization of the crude product yielded the desired product 1-(5-(3,4-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)propan-1-on (**7a**, 99 mg, 44.6 %).

^{1}H NMR (500 MHz, dmso) δ 8.88 (s, 1H), 8.78 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.05 – 6.98 (m, 2H), 6.95 (d, *J* = 9.1 Hz, 4H), 6.63 (d, *J* = 8.1 Hz, 1H), 6.52 (d, *J* = 1.9 Hz, 1H), 6.43 (dd, *J* = 8.1, 1.8 Hz, 1H), 5.32 (dd, *J* = 11.6, 3.9 Hz, 1H), 3.99 (q, *J* = 6.9 Hz, 2H), 3.69 (dd, *J* = 17.9, 11.7 Hz, 1H), 3.01 (dd, *J* = 17.9, 4.0 Hz, 1H), 2.66 (qd, *J* = 7.6, 2.1 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.03 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, dmso) δ 170.73 (s), 160.19 (s), 155.75 (s), 153.99 (s), 148.88 (s), 145.72 (s), 144.89 (s), 134.10 (s), 128.89 (s), 126.01 (s), 121.56 (s), 117.51 (s), 116.80 (s), 116.10 (s), 115.94 (s), 113.04 (s), 63.83 (s), 59.49 (s), 42.44 (s), 27.37 (s), 15.12 (s), 9.50 (s). HRMS [M-H]: $C_{26}H_{25}N_2O_5$, calcd for 445.17690, found 445.17645.

Compounds **7b-7f** were synthesized according to the synthetic method of compound **7a**.

1-(5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)propan-1-one (**7b**)

^{1}H NMR (600 MHz, DMSO) δ 9.81 (s, 1H), 9.62 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.98 (m, 4H), 6.47 (s, 1H), 5.65-5.63 (m, 1H), 4.03-4.02 (m, 2H), 3.93-3.78 (m, 1H), 2.95 (t, *J* = 21.6 Hz, 1H), 2.12 (d, *J* = 7.4 Hz, 2H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.02 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 172.34 (s), 170.95 (s), 160.40 (s), 155.83 (s), 154.32 (s), 148.86 (s), 145.90 (s), 144.22 (s), 133.46 (s), 129.07 (s), 125.74 (s), 121.65 (s), 117.51 (s), 116.18 (s), 112.27 (s), 63.87 (s), 60.74 (s),

41.68 (s), 27.33 (s), 26.83 (s), 15.15 (s), 10.13 (s). HRMS [M-H]: $C_{26}H_{23}Br_2N_2O_5$, calcd for 602.99587, found 602.99530.

1-(5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)propan-1-one (**7c**)

^{1}H NMR (600 MHz, DMSO) δ 9.94 (s, 1H), 9.50 (s, 1H), 7.73 – 7.70 (m, 2H), 7.42 – 7.38 (m, 3H), 6.42 (s, 1H), 5.60 (dd, *J* = 11.6, 3.9 Hz, 1H), 3.82 (dd, *J* = 18.0, 11.8 Hz, 1H), 2.95 (dd, *J* = 18.0, 4.3 Hz, 1H), 2.75 – 2.67 (m, 2H), 1.05 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 171.13 (s), 154.80 (s), 133.45 (s), 131.49 (s), 130.85 (s), 129.27 (s), 127.12 (s), 112.31 (s), 41.58 (s), 27.36 (s), 9.51 (s). HRMS [M-H]: $C_{18}H_{15}Br_2N_2O_3$, calcd for 466.94344, found 466.94305.

1-(3-(4-bromophenyl)-5-(2,3-dibromo-4,5-dihydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)propan-1-one (**7d**)

^{1}H NMR (600 MHz, DMSO) δ 10.01 (s, 1H), 9.57 (s, 1H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 6.46 (s, 1H), 5.71 – 5.62 (m, 1H), 3.87 (dd, *J* = 18.0, 12.0 Hz, 1H), 3.02 (dd, *J* = 18.0, 4.2 Hz, 1H), 2.76 (m, 2H), 1.12 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 171.20 (s), 153.95 (s), 147.57 (s), 146.02 (s), 144.37 (s), 132.27 (s), 130.74 (s), 129.07 (s), 124.22 (s), 114.01 (s), 113.29 (s), 112.24 (s), 60.97 (s), 41.44 (s), 40.53 (s), 27.36 (s), 9.49 (s). HRMS [M-H]: $C_{18}H_{14}Br_3N_2O_3$, calcd for 544.85396, found 544.85345.

1-(5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)propan-1-one (**7e**)

^{1}H NMR (600 MHz, DMSO) δ 10.00 (s, 1H), 9.55 (s, 1H), 7.72 – 7.70 (m, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.47 (s, 1H), 5.63 (dd, *J* = 11.4, 3.5 Hz, 1H), 3.87 – 3.81 (m, 1H), 3.80 (s, 3H), 2.97 (dd, *J* = 17.9, 4.1 Hz, 1H), 2.78 – 2.73 (m, 2H), 1.11 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 170.85 (s), 161.44 (s), 154.55 (s), 146.01 (s), 144.31 (s), 133.50 (s), 128.81 (s), 128.76 (s), 123.99 (s), 114.68 (s), 113.97 (s), 112.26 (s), 60.62 (s), 55.83 (s), 41.68 (s), 27.34 (s), 9.53 (s). HRMS [M-H]: $C_{19}H_{17}Br_2N_2O_4$, calcd for 496.95401, found 496.95352.

1-(5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)butan-1-one (**7f**)

^{1}H NMR (600 MHz, DMSO) δ 9.93 (s, 1H), 9.49 (s, 1H), 7.68 (d, *J* = 8.8 Hz, 2H), 6.98 – 6.94 (m, 2H), 6.92 – 6.88 (m, 4H), 6.41 (s, 1H), 5.63 – 5.54 (m, 1H), 3.95 (q, *J* = 6.9 Hz, 2H), 3.77 (dd, *J* = 17.9, 11.9 Hz, 1H), 2.89 (dd, *J* = 17.9, 4.0 Hz, 1H), 2.65 (ddd, *J* = 27.5, 15.1, 7.6 Hz, 2H), 2.02 (t, *J* = 7.3 Hz, 1H), 1.57 (ddd, *J* = 14.6, 7.3, 3.8 Hz, 2H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 170.11 (s), 160.38 (s), 155.82 (s), 154.27 (s), 148.87 (s), 133.52 (s), 129.06 (s), 125.74 (s), 121.63 (s), 117.52 (s), 116.17 (s), 112.27 (s), 63.87 (s), 60.69 (s), 41.66 (s), 35.88 (s), 18.39 (s), 15.15 (s), 14.34 (s). HRMS [M-H]: $C_{27}H_{25}Br_2N_2O_5$, calcd for 617.01152, found 617.01129.

General procedure for the preparation of 4-(3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**8a**).

To an ethanol (3 mL) solution of (*E*)-3-(3,4-dihydroxyphenyl)-1-phenylprop-2-en-1-one (120 mg, 0.5 mmol) and hydrazine hydrate (200 mg, 85%) were added with stirring. This mixture was heated at reflux for 2 h. After cooling to ambient temperature, the precipitate was filtered off and washed with water. Recrystallization of the crude product yielded the desired product 4-(3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**8a**, 95 mg, 46.7%).

^{1}H NMR (500 MHz, dmso) δ 7.60 (d, *J* = 7.3 Hz, 2H), 7.35 (t, J = 7.3 Hz, 2H), 7.28 (t, J = 7.3 Hz, 1H), 6.74 (s, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.58 (d, *J* = 8.0, 1H), 4.64 (t, *J* = 9.8 Hz, 1H), 3.32 (m, 1H), 2.76 (m, 1H). ^{13}C NMR (126 MHz, dmso) δ 148.74 (s), 145.65 (s), 144.91 (s), 134.44 (s), 133.86 (s), 128.90 (s), 128.35 (s), 125.76 (s), 117.82 (s), 115.75 (s), 114.22 (s), 63.85 (s), 40.99 (s). HRMS [M-H]: $C_{15}H_{13}N_2O_2$, calcd for 253.09825, found 253.09785.

Compounds **8b-8l** were synthesized according to the synthetic method of compound **8a**.

3,4-dibromo-5-(3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**8b**)

^{1}H NMR (600 MHz, DMSO) δ 10.06 (s, 1H), 9.51 (s, 1H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.08 (s, 1H), 7.01 – 6.99 (m, 2H), 6.96 (dt, *J* = 4.7, 2.9 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.99 (t, *J* = 10.2 Hz, 1H), 4.01 (q, *J* = 6.9 Hz, 2H), 3.51 (m, 1H), 2.67 – 2.60

(m, 1H), 1.32 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 158.54 (s), 155.54 (s), 149.42 (s), 148.12 (s), 128.19 (s), 127.59 (s), 121.34 (s), 117.61 (s), 116.09 (s), 113.39 (s), 112.73 (s), 64.24 (s), 63.85 (s), 40.50 (s), 15.17 (s). HRMS [M-H]: $C_{23}H_{19}Br_2N_2O_4$, calcd for 546.96966, found 546.96942.

4-(3-(4-bromophenyl)-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**8c**)

^{1}H NMR (600 MHz, DMSO) δ 8.87 (s, 1H), 8.78 (s, 1H), 7.55 (overlap, 4H), 6.75 (d, *J* = 2.0 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.60 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.68 (m, 1H), 3.34 – 3.30 (overlap, 1H), 2.77 (dd, *J* = 16.3, 10.2 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 147.70 (s), 147.69 (s), 145.69 (s), 144.97 (s), 134.31 (s), 133.15 (s), 131.88 (s), 127.69 (s), 121.31 (s), 117.88 (s), 115.79 (s), 114.23 (s), 64.05 (s), 40.77 (s). HRMS [M-H]: $C_{15}H_{12}BrN_2O_2$, calcd for 331.00876, found 331.00851.

4-(3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**8d**)

^{1}H NMR (600 MHz, DMSO) δ 8.85 (s, 1H), 8.75 (s, 1H), 7.55 (d, *J* = 8.9 Hz, 2H), 7.17 (s, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.76 (s, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 4.61 (m, 1H), 3.77 (s, 3H), 3.31 (dd, *J* = 16.2, 10.5 Hz, 1H), 2.74 (dd, *J* = 16.2, 10.3 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 159.71 (s), 149.00 (s), 145.64 (s), 144.86 (s), 134.60 (s), 127.29 (s), 126.59 (s), 117.89 (s), 115.75 (s), 114.40 (s), 114.25 (s), 63.76 (s), 55.62 (s), 41.33 (s). HRMS [M-H]: $C_{16}H_{15}N_2O_3$, calcd for 283.10882, found 283.10861.

4-(3-(4-phenoxyphenyl)-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**8e**)

^{1}H NMR (600 MHz, DMSO) δ 7.65 – 7.61 (m, 2H), 7.43 – 7.38 (m, 2H), 7.32 (d, *J* = 2.5 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.07 – 7.02 (m, 2H), 7.02 – 6.98 (m, 2H), 6.76 (d, *J* = 2.1 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.60 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.67 – 4.63 (m, 1H), 3.32 (dd, *J* = 16.2, 10.6 Hz, 1H), 2.77 (dd, *J* = 16.2, 10.1 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 157.01 (s), 156.89 (s), 148.40 (s), 145.80 (s), 145.05 (s), 134.42 (s), 130.57 (s), 129.30 (s), 127.58 (s), 124.12 (s), 119.26 (s), 118.98 (s), 117.78 (s), 115.75 (s), 114.22 (s), 63.90 (s), 41.18 (s). HRMS [M-H]: $C_{21}H_{17}N_2O_3$, calcd for 345.12447, found 345.12418.

4-(3-(4-(4-(tert-butyl)phenoxy)phenyl)-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**8f**)

^{1}H NMR (600 MHz, DMSO) δ 8.86 (s, 1H), 8.76 (s, 1H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 6.99 – 6.96 (m, 4H), 6.76 (d, *J* = 1.9 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.60 (dd, *J* = 8.1, 1.9 Hz, 1H), 4.65 (t, *J* = 10.4 Hz, 1H), 3.31 (overlap, 1H), 2.76 (dd, *J* = 16.2, 10.1 Hz, 1H), 1.28 (s, 9H). ^{13}C NMR (151 MHz, DMSO) δ 157.39 (s), 154.39 (s), 146.52 (s), 145.66 (s), 144.91 (s), 134.48 (s), 129.01 (s), 127.55 (s), 127.23 (s), 118.92 (s), 118.65 (s), 117.86 (s), 115.76 (s), 114.23 (s), 63.85 (s), 41.22 (s), 34.55 (s), 31.73 (s). HRMS [M-H]: $C_{25}H_{25}N_2O_3$, calcd for 401.18707, found 401.18671.

4-(3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**8g**)

^{1}H NMR (600 MHz, DMSO) δ 7.60 – 7.57 (m, 2H), 7.27 (d, *J* = 2.9 Hz, 1H), 7.01 – 6.99 (m, 2H), 6.97 – 6.94 (m, 2H), 6.93 – 6.90 (m, 2H), 6.75 (d, *J* = 1.9 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.59 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.63 (td, *J* = 10.3, 2.7 Hz, 1H), 4.00 (q, *J* = 7.0 Hz, 2H), 3.31 (overlap, 1H), 2.75 (dd, *J* = 16.2, 10.1 Hz, 1H), 1.32 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 158.41 (s), 155.52 (s), 149.50 (s), 148.52 (s), 145.70 (s), 144.94 (s), 134.50 (s), 128.49 (s), 127.49 (s), 121.29 (s), 117.82 (s), 117.65 (s), 116.09 (s), 115.75 (s), 114.22 (s), 63.85 (s), 41.22 (s), 15.16 (s). HRMS [M-H]: $C_{23}H_{21}N_2O_4$, calcd for 389.15068, found 389.15039.

3,4-dibromo-5-(3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**8h**)

^{1}H NMR (600 MHz, DMSO) δ 7.61 (d, *J* = 7.3 Hz, 2H), 7.49 (br, 1H), 7.37 (dd, *J* = 10.5, 4.7 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 6.89 (s, 1H), 5.01 (t, *J* = 9.8 Hz, 1H), 3.46 (dd, *J* = 16.4, 10.9 Hz, 1H), 2.66 (dd, *J* = 16.4, 9.5 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 148.37 (s), 133.71 (s), 128.95 (s), 128.48 (s), 125.84 (s), 113.27 (s), 113.16 (s), 112.01 (s), 64.43 (s), 40.52 (s). HRMS [M-H]: $C_{15}H_{11}Br_2N_2O_2$, calcd for 410.91613, found 410.91693.

3-bromo-5-(3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**8i**)

^{1}H NMR (600 MHz, DMSO) δ 9.78 (s, 1H), 9.05 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.38 (s, 1H), 7.01 (d, *J* = 9.1 Hz, 2H), 6.96 (d, *J* = 9.1 Hz, 2H), 6.92 (overlap, 3H), 6.80 (s, 1H), 4.66 (t, *J* = 10.3 Hz, 1H), 4.01 (q, *J* = 7.0 Hz, 2H), 3.34 (dd, *J* = 16.3, 10.7 Hz, 1H), 2.76 (dd, *J* = 16.3, 9.9 Hz, 1H), 1.32 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz,

DMSO) δ 158.51 (s), 155.54 (s), 149.45 (s), 148.59 (s), 146.78 (s), 142.43 (s), 135.76 (s), 128.30 (s), 127.56 (s), 121.32 (s),117.63 (s), 116.09 (s), 113.06 (s), 109.87 (s), 63.86 (s), 63.13 (s), 41.25 (s), 15.16 (s). HRMS [M-H]: $C_{23}H_{20}BrN_2O_4$, calcd for 467.06119, found 467.06076.

3,4-dibromo-5-(3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**8j**)

^{1}H NMR (600 MHz, DMSO) δ 7.57 – 7.53 (m, 2H), 7.28 (s, 1H), 6.95 – 6.90 (overlap, 3H), 4.96 (t, *J* = 10.1 Hz, 1H), 3.77 (s, 3H), 3.44 (dd, *J* = 16.4, 10.7 Hz, 1H), 2.62 (dd, *J* = 16.4, 9.6 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 159.77 (s), 148.56 (s), 148.13 (s), 147.29 (s), 127.35 (s), 126.38 (s), 114.41 (s), 113.17 (s), 112.38 (s), 112.17 (s), 64.26 (s), 55.62 (s), 40.58 (s). HRMS [M-H]: $C_{16}H_{13}Br_2N_2O_4$, calcd for 440.92779, found 440.92743.

3-bromo-5-(3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**8k**)

^{1}H NMR (600 MHz, DMSO) δ 9.35 (br, 2H), 7.62 (d, *J* = 7.4 Hz, 2H), 7.49 (s, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 6.92 (s, 1H), 6.80 (s, 1H), 4.68 (t, *J* = 10.3 Hz, 1H), 3.39 (overlap, 1H), 2.79 (dd, *J* = 16.3, 10.0 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 148.87 (s), 146.81 (s), 142.48 (s), 135.72 (s), 133.73 (s), 128.96 (s), 128.50 (s), 125.85 (s), 121.23 (s), 113.06 (s), 109.87 (s), 63.17 (s), 41.05 (s). HRMS [M-H]: $C_{15}H_{12}BrN_2O_2$, calcd for 331.00876, found 331.00848.

3-bromo-5-(3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**8l**)

^{1}H NMR (600 MHz, DMSO) δ 7.55 (d, *J* = 8.9 Hz, 2H), 7.25 (s, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.87 (s, 1H), 6.75 (s, 1H), 4.62 (t, *J* = 10.3 Hz, 1H), 3.77 (s, 3H), 3.32 (dd, *J* = 16.3, 10.6 Hz, 1H), 2.74 (dd, *J* = 16.2, 10.1 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 159.76 (s), 149.05 (s), 147.33 (s), 143.21 (s), 135.13 (s), 127.33 (s), 126.46 (s), 120.85 (s), 114.42 (s), 113.02 (s), 109.77 (s), 63.16 (s), 55.63 (s), 41.31 (s). HRMS [M-H]: $C_{16}H_{14}BrN_2O_3$, calcd for 361.01933, found 361.01910.

General procedure for the preparation of methyl 5-(3,4-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (**9a**)

To an ethanol (4 mL) solution of (*E*)-3-(3,4-dihydroxyphenyl)-1-phenylprop-2-en-

1-one (120 mg, 0.5 mmol) was added 104 mg（1.0 mmol）methyl hydrazinecarboxylate with stirring. This mixture was heated at reflux for 4 h. After cooling to ambient temperature, the white solid that crystallized out of solution was filtered, washed with cold water and ethanol. Recrystallization of the crude product yielded the desired product methyl 5-(3,4-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (**9a**, 122 mg, 78.6%).

^{1}H NMR (500 MHz, dmso) δ 8.91 (s, 1H), 8.79 (s, 1H), 7.73 (dd, *J* = 6.1, 3.0 Hz, 2H), 7.44 (d, *J* = 2.3 Hz, 3H), 6.64 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.54 (s, 1H), 6.46 (d, *J* = 8.0 Hz, 1H), 5.24 (dd, *J* = 11.7, 4.2 Hz, 1H), 3.77 (dd, *J* = 17.8, 11.8 Hz, 1H), 3.62 (s, 3H), 3.07 (dd, *J* = 17.9, 4.3 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 160.66 (s), 154.15 (s), 152.93 (s), 145.82 (s), 145.12 (s), 140.49 (s), 137.37 (s), 134.10 (s), 131.74 (s), 130.51 (s), 129.20 (s), 126.99 (s), 116.93 (s), 116.00 (s), 112.93 (s), 61.06 (s), 52.90 (s), 42.64 (s). HRMS [M-H]: $C_{17}H_{15}N_2O_4$, calcd for 311.10373, found 311.10361.

Compounds **9b-9l** were synthesized according to the synthetic method of compound **9a**.

methyl 5-(3,4-dihydroxyphenyl)-3-(4-phenoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carboxylate (**9b**)

^{1}H NMR (500 MHz, dmso) δ 8.91 (s, 1H), 8.79 (s, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.53 (s, 1H), 6.45 (d, *J* = 8.1 Hz, 1H), 5.23 (dd, *J* = 11.6, 4.1 Hz, 1H), 3.74 (dd, *J* = 17.8, 11.7 Hz, 1H), 3.61 (s, 3H), 3.04 (dd, *J* = 17.8, 4.2 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 158.94 (s), 156.19 (s), 153.60 (s), 152.91 (s), 145.81 (s), 145.11 (s), 134.12 (s), 130.67 (s), 128.99 (s), 126.72 (s), 124.63 (s), 119.82 (s), 118.60 (s), 116.90 (s), 116.01 (s), 112.91 (s), 61.04 (s), 52.86 (s), 42.73 (s). HRMS [M-H]: $C_{23}H_{19}N_2O_5$, calcd for 403.12994, found 403.12961.

methyl 3-(4-bromophenyl)-5-(3,4-dihydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carboxylate (**9c**)

^{1}H NMR (500 MHz, dmso) δ 8.91 (s, 1H), 8.80 (s, 1H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 2H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.53 (d, *J* = 2.0 Hz, 1H), 6.45 (dd, *J* = 8.1, 2.0 Hz, 1H), 5.25 (dd, *J* = 11.8, 4.5 Hz, 1H), 3.75 (dd, *J* = 17.9, 11.8 Hz, 1H),

3.61 (s, 3H), 3.06 (dd, *J* = 17.9, 4.5 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 153.27 (s), 152.89 (s), 145.82 (s), 145.15 (s), 133.95 (s), 132.19 (s), 130.98 (s), 128.94 (s), 123.84 (s), 116.94 (s), 116.01 (s), 112.96 (s), 61.29 (s), 52.96 (s), 42.48 (s). HRMS [M-H]: $C_{17}H_{14}BrN_2O_4$, calcd for 389.01424, found 389.01376.

methyl 5-(3,4-dihydroxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carboxylate (**9d**)

^{1}H NMR (500 MHz, dmso) δ 8.90 (s, 1H), 8.77 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.53 (d, *J* = 1.7 Hz, 1H), 6.45 (dd, *J* = 8.1, 1.8 Hz, 1H), 5.21 (dd, *J* = 11.6, 4.2 Hz, 1H), 3.78 (s, 3H), 3.72 (dd, *J* = 17.7, 11.7 Hz, 1H), 3.60 (s, 3H), 3.02 (dd, *J* = 17.8, 4.2 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 161.18 (s), 153.91 (s), 152.94 (s), 145.80 (s), 145.07 (s), 134.23 (s), 128.65 (s), 124.27 (s), 116.90 (s), 115.99 (s), 114.62 (s), 112.91 (s), 60.89 (s), 55.76 (s), 52.79 (s), 42.75 (s). HRMS [M-H]: $C_{18}H_{17}N_2O_5$, calcd for 341.14429, found 341.11395.

methyl 3-(4-(4-(tert-butyl)phenoxy)phenyl)-5-(3,4-dihydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carboxylate (**9e**)

^{1}H NMR (500 MHz, dmso) δ 8.90 (s, 1H), 8.78 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 5.9 Hz, 2H), 6.99 (d, *J* = 6.0 Hz, 2H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.53 (s, 1H), 6.45 (d, *J* = 8.1 Hz, 1H), 5.23 (dd, *J* = 11.7, 4.1 Hz, 1H), 3.74 (dd, *J* = 17.8, 11.8 Hz, 1H), 3.61 (s, 3H), 3.03 (dd, *J* = 17.7, 4.0 Hz, 1H), 1.27 (s, 9H). ^{13}C NMR (126 MHz, dmso) δ 159.22 (s), 153.63 (s), 152.91 (s), 147.00 (s), 145.81 (s), 145.10 (s), 134.14 (s), 128.96 (s), 127.32 (s), 126.48 (s), 119.40 (s), 118.32 (s), 116.89 (s), 116.00 (s), 61.01 (s), 52.85 (s), 42.75 (s), 34.58 (s), 31.69 (s). HRMS [M-H]: $C_{27}H_{27}N_2O_5$, calcd for 459.19255, found 459.19235.

methyl 5-(3-bromo-4,5-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazole-1-carboxylate (**9f**)

^{1}H NMR (600 MHz, DMSO) δ 9.83 (s, 1H), 9.12 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 2H), 6.99 – 6.95 (m, 4H), 6.78 (s, 1H), 6.58 (s, 1H), 5.26 (dd, *J* = 11.7, 4.4 Hz, 1H), 4.02 (q, *J* = 6.9 Hz, 2H), 3.75 (dd, *J* = 17.9, 11.8 Hz, 1H), 3.64 (s, 3H), 3.08 (dd, *J* = 17.9, 4.4 Hz, 1H), 1.33 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 160.31 (s), 156.13 (s), 155.85 (s), 153.82 (s), 152.93 (s), 148.83 (s), 147.01

(s), 142.74 (s), 135.14 (s), 131.16 (s), 129.02 (s), 125.84 (s), 122.11 (s), 121.75 (s), 120.35 (s), 117.43 (s), 116.64 (s), 116.24 (s), 111.70 (s), 110.01 (s), 63.87 (s), 60.49 (s), 53.01 (s), 15.16 (s). HRMS [M-H]: $C_{25}H_{22}BrN_2O_6$, calcd for 525.06667, found 525.06586.

methyl 5-(3,4-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazole-1-carboxylate (**9g**)

^{1}H NMR (500 MHz, dmso) δ 8.92 (s, 1H), 8.80 (s, 1H), 7.70 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.94 (dd, *J* = 11.4, 9.0 Hz, 4H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.53 (d, *J* = 1.6 Hz, 1H), 6.44 (dd, *J* = 8.1, 1.6 Hz, 1H), 5.22 (dd, *J* = 11.6, 4.1 Hz, 1H), 4.00 (q, *J* = 6.9 Hz, 2H), 3.72 (dd, *J* = 17.8, 11.7 Hz, 1H), 3.60 (s, 3H), 3.02 (dd, *J* = 17.8, 4.1 Hz, 1H), 1.31 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, dmso) δ 160.18 (s), 155.79 (s), 153.66 (s), 152.90 (s), 148.80 (s), 145.81 (s), 145.09 (s), 134.14 (s), 128.90 (s), 125.96 (s), 121.70 (s), 117.38 (s), 116.88 (s), 116.05 (d, *J* = 16.5 Hz), 112.88 (s), 63.83 (s), 60.97 (s), 52.84 (s), 42.73 (s), 15.13 (s). HRMS [M-H]: $C_{25}H_{23}N_2O_6$, calcd for 447.15616, found 447.15555.

methyl 5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (**9h**)

^{1}H NMR (600 MHz, DMSO) δ 10.07 (s, 1H), 9.61 (s, 1H), 7.76 – 7.73 (m, 2H), 7.47 – 7.43 (overlap, 3H), 6.57 (s, 1H), 5.62 (dd, *J* = 11.7, 4.2 Hz, 1H), 3.91 (dd, *J* = 17.8, 11.8 Hz, 1H), 3.69 (s, 3H), 3.02 (dd, *J* = 17.8, 4.2 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 154.49 (s), 152.88 (s), 146.13 (s), 144.51 (s), 133.62 (s), 131.48 (s), 130.74 (s), 129.24 (s), 127.12 (s), 114.04 (s), 112.18 (s), 111.24 (s), 62.17 (s), 53.26 (s). HRMS [M-H]: $C_{17}H_{13}Br_2N_2O_4$, calcd for 468.92271, found 468.92206.

methyl 5-(3-bromo-4,5-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (**9i**)

^{1}H NMR (600 MHz, DMSO) δ 9.83 (s, 1H), 9.13 (s, 1H), 7.75 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.46 (dd, *J* = 5.0, 1.6 Hz, 3H), 6.80 (s, 1H), 6.59 (s, 1H), 5.29 (dd, *J* = 11.8, 4.5 Hz, 1H), 3.79 (dd, *J* = 17.9, 11.8 Hz, 1H), 3.66 (s, 3H), 3.13 (dd, *J* = 17.9, 4.5 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 154.32 (s), 152.96 (s), 147.02 (s), 142.77 (s), 135.10 (s), 131.61 (s), 130.66 (s), 129.24 (s), 127.07 (s), 120.42 (s), 111.71 (s), 110.01 (s),

60.58 (s), 53.07 (s), 42.55 (s). HRMS [M-H]: $C_{17}H_{14}BrN_2O_4$, calcd for 389.01424, found 389.01370.

methyl 5-(3-bromo-4,5-dihydroxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carboxylate (**9j**)

^{1}H NMR (600 MHz, DMSO) δ 9.82 (s, 1H), 9.11 (s, 1H), 7.69 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 6.78 (s, 1H), 6.58 (s, 1H), 5.25 (dd, *J* = 11.7, 4.4 Hz, 1H), 3.80 (s, 3H), 3.74 (dd, *J* = 17.8, 11.7 Hz, 1H), 3.64 (s, 3H), 3.09 (dd, *J* = 17.9, 4.4 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 161.30 (s), 154.08 (s), 152.96 (s), 147.01 (s), 142.72 (s), 135.22 (s), 128.76 (s), 124.13 (s), 120.37 (s), 114.68 (s), 111.70 (s), 109.99 (s), 60.40 (s), 55.81 (s), 52.96 (s), 42.67 (s). HRMS [M-H]: $C_{18}H_{16}BrN_2O_5$, calcd for 419.02481, found 419.02444.

ethyl 5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazole-1-carboxylate (**9k**)

^{1}H NMR (600 MHz, DMSO) δ 10.08 (s, 1H), 9.59 (s, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.06 – 7.02 (m, 2H), 6.99 – 6.96 (m, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 6.57 (s, 1H), 5.63 – 5.56 (m, 1H), 4.11 (br, 2H), 4.02 (q, *J* = 6.9 Hz, 2H), 3.86 (dd, *J* = 17.7, 11.8 Hz, 1H), 2.98 (d, *J* = 16.0 Hz, 1H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.15 (br, 3H). ^{13}C NMR (151 MHz, DMSO) δ 160.32 (s), 155.85 (s), 153.78 (s), 148.81 (s), 146.16 (s), 144.45 (s), 129.03 (s), 125.77 (s), 121.74 (s), 117.40 (s), 116.17 (s), 113.91 (s), 112.18 (s), 63.87 (s), 62.10 (s), 61.73 (s), 41.98 (s), 15.16 (s), 14.98 (s). HRMS [M-H]: $C_{26}H_{23}Br_2N_2O_6$, calcd for 618.99079, found 618.99048.

benzyl 5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazole-1-carboxylate (**9l**)

^{1}H NMR (600 MHz, DMSO) δ 10.08 (s, 1H), 9.61 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.29 (s, 4H), 7.05 – 7.02 (m, 2H), 7.01 – 6.91 (overlap, 5H), 6.59 (s, 1H), 5.67 (s, 1H), 5.14 (br, 2H), 4.02 (q, *J* = 7.0 Hz, 2H), 3.88 (dd, *J* = 17.8, 11.9 Hz, 1H), 3.01 (d, *J* = 16.9 Hz, 1H), 1.33 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 160.39 (s), 155.86 (s), 154.16 (s), 148.79 (s), 144.58 (s), 129.11 (s), 128.76 (s), 128.26 (s), 125.70 (s), 121.76 (s), 117.41 (s), 116.18 (s), 112.23 (s), 63.87 (s), 62.24 (s), 42.16 (s), 15.16 (s). HRMS [M-H]: $C_{31}H_{25}Br_2N_2O_6$, calcd for 681.00644, found 681.00604.

General procedure for the preparation of 4-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**10a**)

To an ethanol (4 mL) solution of (*E*)-3-(3,4-dihydroxyphenyl)-1-phenylprop-2-en-1-one (120 mg, 0.5 mmol) was added 108 mg（1.0 mmol）phenylhydrazine with stirring. This mixture was heated at reflux for 4 h. After cooling to ambient temperature, the white solid that crystallized out of solution was filtered, washed with cold water and ethanol. Recrystallization of the crude product yielded the desired product 4-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**10a**, 95 mg, 57.9%).

^{1}H NMR (500 MHz, dmso) δ 8.90 (s, 1H), 8.81 (s, 1H), 7.72 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 7.9 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.68 (dd, *J* = 16.8, 7.7 Hz, 2H), 6.61 (s, 1H), 6.59 (d, *J* = 8.1 Hz, 1H), 5.25 (dd, *J* = 12.1, 6.3 Hz, 1H), 3.82 (dd, *J* = 17.4, 12.3 Hz, 1H), 3.04 (dd, *J* = 17.4, 6.3 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 147.47 (s), 146.08 (s), 145.08 (s), 144.76 (s), 133.95 (s), 132.88 (s), 129.21 (s), 129.08 (s), 129.02 (s), 126.05 (s), 118.83 (s), 117.27 (s), 116.25 (s), 113.35 (s), 113.13 (s), 63.38 (s), 43.47 (s). HRMS [M-H]: $C_{21}H_{17}N_2O_2$, calcd for 329.12955, found 329.12927.

Compounds **10b-10k** were synthesized according to the synthetic method of compound **10a**.

3,4-dibromo-5-(3-(4-(4-ethoxyphenoxy)phenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**10b**)

^{1}H NMR (500 MHz, dmso) δ 10.00 (s, 1H), 9.60 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.97 – 6.90 (m, 4H), 6.86 (d, *J* = 8.3 Hz, 2H), 6.72 (t, *J* = 7.0 Hz, 1H), 6.56 (s, 1H), 5.51-5.47 (m, 1H), 4.03-3.98 (m, 2H), 3.95-3.89 (m, 1H), 3.43-3.40 (m, 1H), 1.31 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, dmso) δ 159.17 (s), 155.62 (s), 149.17 (s), 147.56 (s), 146.19 (s), 144.61 (s), 144.28 (s), 129.55 (s), 128.02 (s), 126.97 (s), 121.44 (s), 119.04 (s), 117.63 (s), 116.10 (s), 112.82 (s), 112.31 (s), 63.83 (s), 56.47 (s), 42.33 (s), 15.14 (s). HRMS [M-H]: $C_{29}H_{23}Br_2N_2O_4$, calcd for 623.00096, found 623.00061.

5-(1-(benzo[d]thiazol-2-yl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazol-5-yl)-3,4-dibromobenzene-1,2-diol (**10c**)

^{1}H NMR (500 MHz, dmso) δ 9.99 (s, 1H), 9.61 (s, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 4H), 6.59 (s, 1H), 5.87 (dd, *J* = 11.3, 4.4 Hz, 1H), 4.11 (dd, *J* = 17.8, 11.8 Hz, 1H), 4.00 (q, *J* = 6.9 Hz, 2H), 3.16 (dd, *J* = 17.8, 4.5 Hz, 1H), 1.32 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, dmso) δ 162.73 (s), 160.40 (s), 155.83 (s), 154.16 (s), 152.60 (s), 148.74 (s), 145.88 (s), 144.56 (s), 131.42 (s), 128.99 (s), 125.20 (s), 121.70 (s), 119.92 (s), 117.51 (s), 116.14 (s), 112.32 (s), 64.37 (s), 63.84 (s), 43.35 (s), 15.14 (s). HRMS [M-H]: $C_{30}H_{22}Br_2N_3O_4S$, calcd for 679.96828, found 679.96796.

4-(1-(benzo[d]thiazol-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**10d**)

^{1}H NMR (500 MHz, dmso) δ 8.93 (s, 1H), 8.83 (s, 1H), 7.78 (dd, *J* = 7.0, 2.6 Hz, 3H), 7.47 (d, *J* = 5.4 Hz, 3H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.66 (dd, *J* = 10.1, 4.8 Hz, 2H), 6.58 (dd, *J* = 8.1, 1.5 Hz, 1H), 5.63 (dd, *J* = 11.7, 4.6 Hz, 1H), 4.00 (dd, *J* = 17.8, 11.8 Hz, 1H), 3.26 (dd, *J* = 17.9, 4.6 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 162.88 (s), 154.32 (s), 152.71 (s), 145.83 (s), 145.24 (s), 132.96 (s), 131.32 (d, *J* = 17.0 Hz), 130.66 (s), 129.33 (s), 126.93 (s), 126.28 (s), 122.17 (s), 121.68 (s), 119.79 (s), 117.26 (s), 116.11 (s), 113.25 (s), 63.42 (s), 44.05 (s). HRMS [M-H]: $C_{22}H_{16}N_3O_2S$, calcd for 386.09687, found 386.09647.

4-(1-(benzo[d]thiazol-2-yl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**10e**)

^{1}H NMR (500 MHz, dmso) δ 10.01 (s, 1H), 8.93 (s, 1H), 8.82 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.70 – 6.61 (m, 2H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.58 (dd, *J* = 11.5, 4.3 Hz, 1H), 3.93 (dd, *J* = 17.6, 11.6 Hz, 1H), 3.18 (dd, *J* = 17.7, 4.3 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 162.90 (s), 159.95 (s), 154.49 (s), 152.86 (s), 145.81 (s), 145.17 (s), 133.14 (s), 131.35 (s), 128.80 (s), 126.21 (s), 125.74 (s), 122.21 (s), 121.87 (s), 121.59 (s), 121.36 (s), 119.55 (s), 117.24 (s), 116.14 (s), 116.10 (s), 113.21 (s), 63.09 (s), 44.25 (s). HRMS [M-H]: $C_{22}H_{16}N_3O_3S$, calcd for 403.10744, found 403.10715.

4-(1-(benzo[d]thiazol-2-yl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazol-5-yl)benzene-1,2-diol (**10f**)

^{1}H NMR (500 MHz, dmso) δ 8.93 (s, 1H), 8.83 (s, 1H), 7.76 (dd, *J* = 7.7, 5.6 Hz, 3H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 7.05 – 7.02 (m, 2H), 6.97 (t, *J* = 8.1 Hz, 4H), 6.65 (dd, *J* = 13.9, 4.8 Hz, 2H), 6.57 (dd, *J* = 8.1, 1.6 Hz, 1H), 5.61 (dd, *J* = 11.6, 4.5 Hz, 1H), 4.04 – 3.98 (m, 2H), 3.98 – 3.91 (m, 1H), 3.21 (dd, *J* = 17.8, 4.5 Hz, 1H), 1.31 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, dmso) δ 162.86 (s), 160.26 (s), 155.80 (s), 153.89 (s), 152.76 (s), 148.83 (s), 145.83 (s), 145.21 (s), 133.00 (s), 131.36 (s), 128.87 (s), 126.25 (s), 125.52 (s), 121.65 (s), 119.69 (s), 117.58 (s), 117.22 (s), 116.13 (s), 113.22 (s), 63.84 (s), 63.32 (s), 44.18 (s), 15.14 (s). HRMS [M-H]: $C_{30}H_{24}N_3O_4S$, calcd for 522.14930, found 522.14886.

5-(1-(benzo[d]thiazol-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)-3,4-dibromobenzene-1,2-diol (**10g**)

^{1}H NMR (600 MHz, DMSO) δ 10.01 (s, 1H), 9.62 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.80 (m, 2H), 7.50 – 7.47 (m, 4H), 7.28 (dd, *J* = 11.2, 4.1 Hz, 1H), 7.17 – 7.13 (m, 1H), 6.63 (s, 1H), 5.92 (dd, *J* = 11.6, 4.6 Hz, 1H), 4.17 (dd, *J* = 17.7, 11.9 Hz, 1H), 3.23 (dd, *J* = 17.8, 4.7 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 162.81 (s), 154.65 (s), 152.59 (s), 145.94 (s), 144.62 (s), 132.45 (s), 131.49 (s), 131.02 (s), 130.86 (s), 129.37 (s), 127.05 (s), 126.44 (s), 122.45 (s), 121.83 (s), 120.06 (s), 114.29 (s), 112.40 (s), 64.49 (s), 43.26 (s). HRMS [M-H]: $C_{22}H_{14}Br_2N_3O_2S$, calcd for 543.92313, found 543.91522.

5-(1-(benzo[d]thiazol-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)-3-bromobenzene-1,2-diol (**10h**)

^{1}H NMR (600 MHz, DMSO) δ 9.82 (s, 1H), 9.14 (s, 1H), 7.84 – 7.80 (overlap, 3H), 7.52 – 7.49 (overlap, 3H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.15 – 7.11 (m, 1H), 6.94 (s, 1H), 6.68 (s, 1H), 5.68 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.03 (dd, *J* = 17.9, 11.8 Hz, 1H), 3.31 (d, *J* = 4.9 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 162.95 (s), 154.53 (s), 152.64 (s), 146.99 (s), 142.87 (s), 133.98 (s), 131.16 (s), 130.80 (s), 129.39 (s), 127.04 (s), 126.40 (s), 122.35 (s), 121.79 (s), 120.72 (s), 119.92 (s), 112.02 (s), 110.14 (s), 62.90 (s), 43.98 (s). HRMS [M-H]: $C_{22}H_{15}BrN_3O_2S$, calcd for 464.00738, found 464.0093.

General procedure for the preparation of 5-(3,4-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (**11a**)

To an acetic acid (4 mL) solution of (*E*)-3-(3,4-dihydroxyphenyl)-1-phenylprop-2-en-1-one (120 mg, 0.5 mmol) were added 54.6 mg（0.6 mmol）thiosemicarbazide and two drops of concentrated hydrochloric acid with stirring. This mixture was heated at reflux for 4 h. After cooling to ambient temperature, 2 mL water was slowly added with rapid stirring under ice-water bath. The white solid that crystallized out of solution was filtered, washed with cold water and ethanol. Recrystallization of the crude product yielded the desired product 5-(3,4-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (**11a**, 75 mg, 48.2 %).

^{1}H NMR (500 MHz, dmso) δ 8.85 (s, 1H), 8.73 (s, 1H), 7.95 (s, 1H), 7.89 – 7.84 (m, 2H), 7.81 (s, 1H), 7.43 (dd, *J* = 10.1, 5.1 Hz, 3H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 1.6 Hz, 1H), 6.41 (dd, *J* = 8.1, 1.7 Hz, 1H), 5.72 (dd, *J* = 11.2, 2.8 Hz, 1H), 3.80 (dd, *J* = 17.9, 11.3 Hz, 1H), 3.07 (dd, *J* = 17.9, 2.9 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 176.38 (s), 155.44 (s), 145.57 (s), 144.72 (s), 134.50 (s), 131.47 (s), 130.93 (s), 129.13 (s), 127.51 (s), 116.83 (s), 115.88 (s), 112.99 (s), 62.95 (s), 42.91 (s). HRMS [M-H]: $C_{16}H_{14}N_3O_2S$, calcd for 312.08112, found 312.08081.

Compounds **11b-11l** were synthesized according to the synthetic method of compound **11a**.

5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**11b**)

^{1}H NMR (600 MHz, DMSO) δ 10.02 (s, 1H), 9.48 (s, 1H), 8.08 (s, 1H), 7.91 (s, 1H), 7.82 (d, *J* = 8.7 Hz, 2H), 7.02 – 6.98 (m, 2H), 6.43 (s, 1H), 6.01 (d, *J* = 10.9 Hz, 1H), 3.89 (dd, *J* = 17.9, 11.4 Hz, 1H), 3.80 (d, *J* = 1.1 Hz, 3H), 3.00 (dd, *J* = 17.9, 3.2 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 175.98 (s), 161.70 (s), 155.51 (s), 145.89 (s), 144.15 (s), 134.18 (s), 129.41 (s), 123.71 (s), 114.60 (s), 113.87 (s), 111.91 (s), 111.39 (s), 64.20 (s), 55.87 (s), 41.99 (s). HRMS [M-H]: $C_{17}H_{14}Br_2N_3O_3S$, calcd for 499.91076, found 499.91046.

5-(3,4-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**11c**)

^{1}H NMR (500 MHz, dmso) δ 8.85 (s, 1H), 8.73 (s, 1H), 7.89 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.74 (s, 1H), 7.06 – 6.98 (m, 2H), 6.94 (dd, *J* = 11.0, 9.0 Hz, 4H), 6.61 (d, *J* = 8.1 Hz, 1H), 6.47 (d, *J* = 2.0 Hz, 1H), 6.39 (dd, *J* = 8.1, 2.0 Hz, 1H), 5.70 (dd, *J* = 11.1, 2.8 Hz, 1H), 4.00 (q, *J* = 6.9 Hz, 2H), 3.76 (dd, *J* = 17.9, 11.2 Hz, 1H), 3.02 (dd, *J* = 17.8, 2.9 Hz, 1H), 1.31 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, dmso) δ 176.11 (s), 160.51 (s), 155.79 (s), 155.04 (s), 148.78 (s), 145.55 (s), 144.70 (s), 134.49 (s), 129.47 (s), 125.69 (s), 121.64 (s), 117.36 (s), 116.80 (s), 116.12 (s), 115.86 (s), 112.97 (s), 63.83 (s), 62.89 (s), 43.01 (s), 15.13 (s). HRMS [M-H]: $C_{24}H_{22}N_3O_4S$, calcd for 448.13365, found 448.13315.

5-(3,4-dihydroxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**11d**)

^{1}H NMR (500 MHz, dmso) δ 8.83 (s, 1H), 8.70 (s, 1H), 7.84 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.71 (s, 1H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.48 (s, 1H), 6.40 (d, *J* = 8.1 Hz, 1H), 5.72 – 5.68 (m, 1H), 3.79 (s, 3H), 3.78 – 3.70 (m, 1H), 3.04 (dd, *J* = 17.8, 2.4 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 176.00 (s), 172.44 (s), 161.58 (s), 155.39 (s), 145.55 (s), 144.68 (s), 134.56 (s), 129.25 (s), 123.93 (s), 116.84 (s), 115.86 (s), 114.59 (s), 113.02 (s), 62.80 (s), 55.82 (s), 43.03 (s). HRMS [M-H]: $C_{17}H_{16}N_3O_3S$, calcd for 342.09179, found 342.09122.

5-(3,4-dihydroxyphenyl)-3-(4-phenoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**11e**)

^{1}H NMR (500 MHz, dmso) δ 8.84 (s, 1H), 8.72 (s, 1H), 7.90 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.77 (s, 1H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.49 (s, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 5.72 (d, *J* = 10.9 Hz, 1H), 3.78 (dd, *J* = 17.8, 11.3 Hz, 1H), 3.04 (d, *J* = 17.7 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 176.21 (s), 159.25 (s), 156.18 (s), 154.95 (s), 145.57 (s), 144.72 (s), 134.49 (s), 130.66 (s), 129.55 (s), 126.47 (s), 124.63 (s), 119.73 (s), 118.59 (s), 116.82 (s), 115.88 (s), 113.00 (s), 62.95 (s), 43.02 (s). HRMS [M-H]: $C_{22}H_{18}N_3O_3S$, calcd for 404.10744, found 404.10672.

3-(4-(4-(tert-butyl)phenoxy)phenyl)-5-(3,4-dihydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**11f**)

^{1}H NMR (500 MHz, dmso) δ 8.84 (s, 1H), 8.71 (s, 1H), 7.90 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.75 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 6.99 (t, *J* = 7.8 Hz, 4H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.48 (s, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 5.71 (d, *J* = 11.1 Hz, 1H), 3.77 (dd, *J* = 17.8, 11.2 Hz, 1H), 3.03 (d, *J* = 17.8 Hz, 1H), 1.27 (s, 9H). ^{13}C NMR (126 MHz, dmso) δ 176.18 (s), 159.54 (s), 154.98 (s), 153.72 (s), 147.00 (s), 145.57 (s), 144.71 (s), 134.49 (s), 129.51 (s), 127.31 (s), 126.22 (s), 119.31 (s), 118.33 (s), 116.80 (s), 115.87 (s), 112.99 (s), 62.92 (s), 43.02 (s), 34.58 (s), 31.68 (s). HRMS [M-H]: $C_{26}H_{26}N_3O_3S$, calcd for 460.17004, found 460.16956.

3-(4-bromophenyl)-5-(3,4-dihydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**11g**)

^{1}H NMR (500 MHz, dmso) δ 8.84 (s, 1H), 8.72 (s, 1H), 7.97 (s, 1H), 7.87 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.48 (d, *J* = 1.9 Hz, 1H), 6.40 (dd, *J* = 8.1, 2.0 Hz, 1H), 5.73 (dd, *J* = 11.3, 3.0 Hz, 1H), 3.78 (dd, *J* = 18.0, 11.3 Hz, 1H), 3.06 (dd, *J* = 18.0, 3.1 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 176.53 (s), 154.41 (s), 145.58 (s), 144.75 (s), 134.40 (s), 132.12 (s), 130.78 (s), 129.42 (s), 124.35 (s), 116.83 (s), 115.89 (s), 113.00 (s), 63.15 (s), 42.77 (s). HRMS [M-H]: $C_{16}H_{13}BrN_3O_2S$, calcd for 389.99173, found 389.99127.

5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (**11h**)

^{1}H NMR (600 MHz, DMSO) δ 10.02 (s, 1H), 9.50 (s, 1H), 8.17 (s, 1H), 8.01 (s, 1H), 7.89 – 7.87 (m, 2H), 7.47 – 7.43 (m, 3H), 6.43 (s, 1H), 6.04 (d, *J* = 9.3 Hz, 1H), 3.94 (dd, *J* = 18.0, 11.5 Hz, 1H), 3.04 (dd, *J* = 18.0, 3.1 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 176.36 (s), 155.62 (s), 145.91 (s), 144.17 (s), 134.11 (s), 131.27 (s), 131.09 (s), 129.14 (s), 127.64 (s), 113.88 (s), 111.90 (s), 111.36 (s), 64.33 (s), 41.87 (s). HRMS [M-H]: $C_{16}H_{12}Br_2N_3O_2S$, calcd for 469.90020, found 469.89948.

3-(4-bromophenyl)-5-(2,3-dibromo-4,5-dihydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**11i**)

^{1}H NMR (600 MHz, DMSO) δ 10.02 (s, 1H), 9.50 (s, 1H), 8.19 (s, 1H), 8.07 (s, 1H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 6.41 (s, 1H), 6.05 – 6.01 (m, 1H), 3.92 (dd, *J* = 18.0, 11.5 Hz, 1H), 3.03 (dd, *J* = 18.0, 3.3 Hz, 1H). ^{13}C NMR (151

MHz, DMSO) δ 176.48 (s), 154.65 (s), 145.91 (s), 144.19 (s), 134.00 (s), 132.13 (s), 130.58 (s), 129.57 (s), 124.54 (s), 113.90 (s), 111.87 (s), 111.34 (s), 64.50 (s), 41.73 (s). HRMS [M-H]: $C_{16}H_{11}Br_3N_3O_2S$, calcd for 547.81071, found 547.81012.

5-(3-bromo-4,5-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (**11j**)

^{1}H NMR (600 MHz, DMSO) δ 9.76 (s, 1H), 9.03 (s, 1H), 8.04 (s, 1H), 7.89-7.88 (m, 3H), 7.49-7.45 (m, 3H), 6.71 (d, *J* = 2.0 Hz, 1H), 6.54 (d, *J* = 2.0 Hz, 1H), 5.75 (dd, *J* = 11.3, 3.2 Hz, 1H), 3.82 (dd, *J* = 18.0, 11.4 Hz, 1H), 3.14 (dd, *J* = 18.0, 3.3 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 176.46 (s), 155.50 (s), 146.81 (s), 142.36 (s), 135.55 (s), 131.38 (s), 131.05 (s), 129.18 (s), 127.61 (s), 120.13 (s), 111.87 (s), 109.97 (s), 62.54 (s), 42.81 (s). HRMS [M-H]: $C_{16}H_{13}BrN_3O_2S$, calcd for 389.99173, found 389.99121.

5-(3-bromo-4,5-dihydroxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**11k**)

^{1}H NMR (600 MHz, DMSO) δ 9.76 (s, 1H), 9.02 (s, 1H), 7.94 (s, 1H), 7.83 – 7.81 (m, 2H), 7.81 (d, *J* = 5.9 Hz, 1H), 7.02 – 7.00 (m, 2H), 6.70 (d, *J* = 2.0 Hz, 1H), 6.53 (d, *J* = 2.0 Hz, 1H), 5.72 (dd, *J* = 11.2, 3.1 Hz, 1H), 3.81 – 3.75 (overlap, 4H), 3.10 (dd, *J* = 17.9, 3.2 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 176.05 (s), 161.69 (s), 155.43 (s), 146.79 (s), 142.32 (s), 135.62 (s), 129.37 (s), 123.82 (s), 120.11 (s), 114.65 (s), 111.90 (s), 109.95 (s), 62.38 (s), 55.87 (s), 42.93 (s). HRMS [M-H]: $C_{17}H_{15}BrN_3O_3S$, calcd for 420.00230, found 420.00174.

General procedure for the preparation of 2-(5-(3,4-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**12a**)

5-(3,4-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (167 mg, 0.5 mmol) was dissolved in acetic acid (10 ml). Chloroacetic acid (57 mg, 0.6 mmol) and sodium acetate (49.2 mg, 0.6 mmol) were successively added. The mixture was refluxed for 4 h. After cooling to room temperature, 1 mL water was slowly added with rapid stirring under an ice-water bath. After standing for 1 h, the white solid that crystallized out of solution was filtered, washed with cold water and ethanol. Recrystallization of the crude product yielded the desired product 2-(5-(3,4-

dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**12a**, 73 mg, 41.2%).

^{1}H NMR (500 MHz, dmso) δ 8.98 (s, 1H), 8.90 (s, 1H), 7.87 – 7.80 (m, 2H), 7.58 – 7.46 (m, 3H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 2.0 Hz, 1H), 6.49 (dd, *J* = 8.1, 2.0 Hz, 1H), 5.58 (dd, *J* = 11.1, 3.6 Hz, 1H), 4.02 (dd, *J* = 18.2, 11.2 Hz, 1H), 3.90 (s, 2H), 3.35 (dd, *J* = 18.3, 3.6 Hz, 1H). ^{13}C NMR (126 MHz, dmso) δ 187.31 (s), 177.61 (s), 161.06 (s), 145.88 (s), 145.58 (s), 131.94 (s), 131.85 (s), 130.30 (s), 129.47 (s), 127.70 (s), 117.32 (s), 116.10 (s), 113.19 (s), 63.95 (s), 43.86 (s), 39.16 (s). HRMS [M-H]: $C_{18}H_{14}N_3O_3S$, calcd for 352.07614, found 352.07550.

Compounds **12b-12k** were synthesized according to the synthetic method of compound **12a**.

2-(5-(2,3-dibromo-4,5-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**12b**)

^{1}H NMR (600 MHz, DMSO) δ 10.11 (s, 1H), 9.70 (s, 1H), 7.84 – 7.79 (m, 2H), 7.08 – 7.04 (m, 2H), 7.03 – 6.98 (m, 4H), 6.45 (s, 1H), 5.88 (d, *J* = 7.9 Hz, 1H), 4.25 – 4.10 (m, 1H), 4.04 – 4.01 (m, 2H), 4.01 – 3.95 (m, 2H), 3.26 (overlap, 1H), 1.34 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 187.18 (s), 177.61 (s), 161.42 (s), 160.48 (s), 156.00 (s), 148.51 (s), 144.84 (s), 129.90 (s), 124.21 (s), 121.86 (s), 117.49 (s), 116.22 (s), 112.29 (s), 63.89 (s), 60.24 (s), 43.28 (s), 39.43 (s), 15.15 (s). HRMS [M-H]: $C_{26}H_{20}Br_2N_3O_5S$, calcd for 645.94754, found 645.94720.

2-(5-(3,4-dihydroxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**12c**)

^{1}H NMR (500 MHz, dmso) δ 8.98 (s, 1H), 8.89 (s, 1H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 1.9 Hz, 1H), 6.48 (dd, *J* = 8.1, 2.0 Hz, 1H), 5.55 (dd, *J* = 11.0, 3.4 Hz, 1H), 3.97 (dd, *J* = 18.1, 11.1 Hz, 1H), 3.88 (s, 2H), 3.81 (s, 3H), 3.33-3.29 (overlap, 1H). ^{13}C NMR (126 MHz, dmso) δ 187.22 (s), 177.05 (s), 162.30 (s), 160.79 (s), 145.87 (s), 145.54 (s), 131.93 (s), 129.56 (s), 122.74 (s), 117.28 (s), 116.09 (s), 114.92 (s), 113.15 (s), 63.81 (s), 55.93 (s), 43.91 (s), 39.13 (s). HRMS [M-H]: $C_{19}H_{16}N_3O_4S$, calcd for 382.08670, found 382.08636.

2-(5-(3,4-dihydroxyphenyl)-3-(4-phenoxyphenyl)-4,5-dihydro-1H-pyrazol-1-

yl)thiazol-4(5H)-one (**12d**)

^{1}H NMR (500 MHz, dmso) δ 8.98 (s, 1H), 8.91 (s, 1H), 7.84 (d, *J* = 8.6 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.09 (dd, *J* = 7.9, 6.4 Hz, 4H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.55 (s, 1H), 6.49 (dd, *J* = 8.1, 1.6 Hz, 1H), 5.57 (dd, *J* = 11.0, 3.3 Hz, 1H), 4.00 (dd, *J* = 18.2, 11.1 Hz, 1H), 3.89 (s, 2H), 3.34-3.30 (overlap, 1H). ^{13}C NMR (126 MHz, dmso) δ 187.26 (s), 177.33 (s), 160.48 (s), 160.12 (s), 155.88 (s), 145.88 (s), 145.57 (s), 131.86 (s), 130.73 (s), 129.88 (s), 125.12 (s), 124.89 (s), 119.98 (s), 118.66 (s), 117.28 (s), 116.10 (s), 113.16 (s), 63.93 (s), 43.92 (s), 39.16 (s). HRMS [M-H]: $C_{24}H_{18}N_3O_4S$, calcd for 444.10235, found 444.10181.

2-(5-(3,4-dihydroxyphenyl)-3-(4-(4-ethoxyphenoxy)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**12e**)

^{1}H NMR (500 MHz, dmso) δ 8.98 (s, 1H), 8.91 (s, 1H), 7.80 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 8.9 Hz, 2H), 6.98 (dd, *J* = 12.2, 8.9 Hz, 4H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 1.7 Hz, 1H), 6.48 (dd, *J* = 8.1, 1.8 Hz, 1H), 5.56 (dd, *J* = 11.0, 3.4 Hz, 1H), 4.03-3.95 (overlap, 3H), 3.88 (s, 2H), 3.32 – 3.27 (overlap, 1H), 1.31 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, dmso) δ 187.24 (s), 177.25 (s), 161.30 (s), 160.53 (s), 155.94 (s), 148.54 (s), 145.88 (s), 145.56 (s), 131.88 (s), 129.80 (s), 124.41 (s), 121.78 (s), 117.51 (s), 117.27 (s), 116.18 (s), 116.10 (s), 113.15 (s), 63.88 (s), 63.86 (s), 43.92 (s), 39.15 (s), 15.13 (s). HRMS [M-H]: $C_{26}H_{22}N_3O_5S$, calcd for 488.12856, found 488.12784.

2-(3-(4-(4-(tert-butyl)phenoxy)phenyl)-5-(3,4-dihydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**12f**)

^{1}H NMR (500 MHz, dmso) δ 8.98 (s, 1H), 8.90 (s, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.46 – 7.42 (m, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 7.03 – 7.00 (m, 2H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 2.1 Hz, 1H), 6.48 (dd, *J* = 8.1, 2.1 Hz, 1H), 5.57 (dd, *J* = 11.0, 3.5 Hz, 1H), 4.02 – 3.96 (m, 1H), 3.89 (s, 2H), 3.33-3.28 (overlap, 1H), 1.28 (s, 9H). ^{13}C NMR (126 MHz, dmso) δ 187.25 (s), 177.30 (s), 160.49 (s), 160.41 (s), 153.42 (s), 147.27 (s), 145.88 (s), 145.57 (s), 131.87 (s), 129.84 (s), 127.38 (s), 124.89 (s), 119.55 (s), 118.39 (s), 117.27 (s), 116.10 (s), 113.16 (s), 63.91 (s), 43.93 (s), 39.15 (s), 34.61 (s), 31.68 (s). HRMS [M-H]: $C_{28}H_{26}N_3O_4S$, calcd for 500.16495, found 500.16452.

2-(3-(4-bromophenyl)-5-(3,4-dihydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-

yl)thiazol-4(5H)-one (**12g**)

^{1}H NMR (500 MHz, dmso) δ 8.98 (s, 1H), 8.92 (s, 1H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 2.0 Hz, 1H), 6.49 (dd, *J* = 8.1, 2.1 Hz, 1H), 5.59 (dd, *J* = 11.2, 3.7 Hz, 1H), 4.01 (dd, *J* = 18.3, 11.2 Hz, 1H), 3.91 (s, 2H), 3.37-3.32 (overlap, 1H). ^{13}C NMR (126 MHz, dmso) δ 187.34 (s), 177.76 (s), 160.17 (s), 145.88 (s), 145.60 (s), 132.50 (s), 131.74 (s), 129.59 (s), 129.53 (s), 125.48 (s), 117.33 (s), 116.11 (s), 113.23 (s), 64.13 (s), 43.73 (s), 39.21 (s). HRMS [M-H]: $C_{18}H_{13}BrN_3O_3S$, calcd for 429.98665, found 429.98630.

5-(1-(benzo[d]thiazol-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)-3,4-dibromobenzene-1,2-diol (**12h**)

^{1}H NMR (600 MHz, DMSO) δ 10.01 (s, 1H), 9.62 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.80 (m, 2H), 7.50 – 7.47 (m, 4H), 7.28 (dd, *J* = 11.2, 4.1 Hz, 1H), 7.17 – 7.13 (m, 1H), 6.63 (s, 1H), 5.92 (dd, *J* = 11.6, 4.6 Hz, 1H), 4.17 (dd, *J* = 17.7, 11.9 Hz, 1H), 3.23 (dd, *J* = 17.8, 4.7 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 162.81 (s), 154.65 (s), 152.59 (s), 145.94 (s), 144.62 (s), 132.45 (s), 131.49 (s), 131.02 (s), 130.86 (s), 129.37 (s), 127.05 (s), 126.44 (s), 122.45 (s), 121.83 (s), 120.06 (s), 114.29 (s), 112.40 (s), 64.49 (s), 43.26 (s). HRMS [M-H]: $C_{22}H_{14}Br_2N_3O_2S$, calcd for 543.89511, found 543.89313.

2-(3-(4-bromophenyl)-5-(2,3-dibromo-4,5-dihydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**12i**)

^{1}H NMR (600 MHz, DMSO) δ 10.09 (s, 1H), 9.69 (s, 1H), 7.78 – 7.76 (m, 2H), 7.73 – 7.71 (m, 2H), 6.44 (s, 1H), 5.90 (d, *J* = 7.7 Hz, 1H), 4.14 (dd, *J* = 17.6, 11.6 Hz, 1H), 4.00 (s, 2H), 3.30 (overlap, 1H). ^{13}C NMR (151 MHz, DMSO) δ 187.26 (s), 178.10 (s), 160.21 (s), 146.09 (s), 144.88 (s), 132.54 (s), 129.69 (s), 129.36 (s), 125.63 (s), 112.30 (s), 65.19 (s), 43.11 (s). HRMS [M-H]: $C_{18}H_{11}Br_3N_3O_3S$, calcd for 587.80563, found 587.80493.

2-(5-(3-bromo-4,5-dihydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**12j**)

^{1}H NMR (600 MHz, DMSO) δ 9.94 (s, 1H), 9.26 (s, 1H), 7.85 (d, *J* = 7.0 Hz, 2H), 7.57 – 7.51 (m, 3H), 6.84 (d, *J* = 2.0 Hz, 1H), 6.61 (d, *J* = 2.0 Hz, 1H), 5.62 (dd, *J* = 11.2, 3.9 Hz, 1H), 4.04 (dd, *J* = 18.3, 11.2 Hz, 1H), 3.95 (d, *J* = 1.4 Hz, 2H), 3.42 (dd,

J = 18.3, 3.9 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 187.36 (s), 177.80 (s), 161.11 (s), 147.03 (s), 143.21 (s), 132.88 (s), 132.04 (s), 130.23 (s), 129.51 (s), 127.79 (s), 120.77 (s), 112.08 (s), 110.09 (s), 63.37 (s), 43.81 (s), 39.27 (s). HRMS [M-H]: $C_{18}H_{13}BrN_3O_3S$, calcd for 429.98665, found 429.98611.

2-(5-(3-bromo-4,5-dihydroxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**12k**)

^{1}H NMR (600 MHz, DMSO) δ 9.89 (s, 1H), 9.21 (s, 1H), 7.81 – 7.78 (m, 2H), 7.08 – 7.06 (m, 2H), 6.83 (d, *J* = 2.0 Hz, 1H), 6.58 (d, *J* = 2.1 Hz, 1H), 5.59 (dd, *J* = 11.1, 3.7 Hz, 1H), 3.99 (dd, *J* = 18.2, 11.2 Hz, 1H), 3.92 (d, *J* = 1.4 Hz, 2H), 3.83 (s, 3H), 3.38 (dd, *J* = 18.2, 3.8 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 187.25 (s), 177.24 (s), 162.40 (s), 160.84 (s), 147.02 (s), 143.19 (s), 132.96 (s), 129.66 (s), 122.67 (s), 120.75 (s), 114.97 (s), 111.90 (s), 110.05 (s), 63.22 (s), 55.98 (s), 43.83 (s), 39.23 (s). HRMS [M-H]: $C_{19}H_{15}BrN_3O_4S$, calcd for 459.99721, found 459.99685.

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