



Design, synthesis, and mechanism study of novel tetrahydroisoquinoline derivatives as antifungal agents

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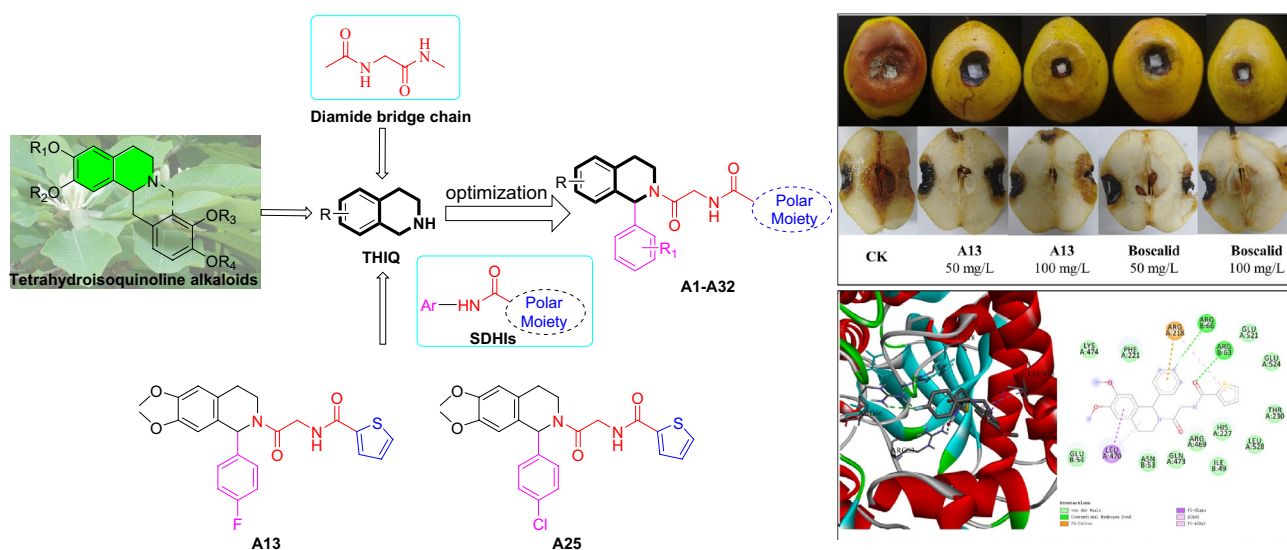
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Abstract

In screening for natural-derived fungicides, a series of 32 novel tetrahydroisoquinoline derivatives were designed and synthesized based on tetrahydroisoquinoline alkaloids. Their structures were verified by ¹H NMR, ¹³C NMR, HRMS, and single X-ray crystal diffraction analysis. Most of the target products exhibited medium to excellent antifungal activity against 6 phytopathogenic fungi in vitro at a concentration of 50 mg/L. Interestingly, compounds **A13** and **A25** with EC₅₀ values of 2.375 and 2.251 mg/L against *A. alternata* were similar to boscalid (EC₅₀ = 1.195 mg/L). The in vivo experiments revealed that **A13** presented 51.61 and 70.97% protection activities against *A. alternata* at the dosage of 50 and 100 mg/L, respectively, which were equal to that of boscalid (64.52 and 77.42%). SDH enzyme assays and molecular docking studies indicated that compound **A13** may act on SDH. In addition, the SEM analysis showed that compound **A13** could strongly damage the mycelium morphology. These results revealed that **A13** may be a promising lead compound for the development of natural-derived fungicides.

Graphic Abstract

A series of novel tetrahydroisoquinoline derivatives **A1–A32** were rationally designed and synthesized based on tetrahydroisoquinoline alkaloids.



Introduction

Phytopathogenic fungi are causing substantial harm to grain crops, resulting in diminished yield, compromised quality, and ultimately posing a threat to the worldwide food security [1]. Although chemical fungicides remain as the most effective and economical method for the control of fungal diseases at present [2], with the prolonged and massive irrational of traditional-chemicals have caused resistance, residual toxicity, and even environmental problems [3, 4]. Therefore, it was urgent to discover and develop novel biocompatibility antifungal agents to control plant diseases and ensure the agricultural production safety.

The natural-based/derived compounds have attracted increasing attention as potential candidates to develop “green” agrochemicals due to their extensive biological properties, multiple modes of action, and environment friendly [5]. Tetrahydroisoquinoline alkaloids (THIQs) are a kind of natural products with a common tetrahydroisoquinoline motif and widely exist in the Papaveraceae family and Rutaceae family [6, 7]. THIQs and their derivatives exhibit antibacterial, antitumor, antimalarial, anti-inflammatory, and influence on the activities of various important biological enzymes [8–10]. In addition, Tiwari et al. reported a series of 1-aryl-tetrahydroisoquinoline derivatives with antibacterial activity [11].

Amide is an important classic structural motif in agrochemicals and natural products, often serving as a linking bridge to introduce active pharmacophores for the development of novel pesticides [5]. Valine carbamate fungicides feature a double amide-bridge chain in their structure, which provides good environmental compatibility [12]. Succinate dehydrogenase inhibitors (SDHIs) have become the most rapidly growing type of agrochemical due to their powerful and broad-spectrum antifungal activities, which damaging the citric acid cycle and respiratory chain electron transmission in fungal mitochondria [13–15]. The structure of commercial SDHIs typically consists of three components: polar segment, hydrophobic core, and amide-bridge that binds them together. The three parts often modified by diversity models, which is beneficial in enhancing the antifungal action of bioactive carboxamide derivatives [16–18].

In our previous work, several isoquinoline compounds were designed and synthesized with antifungal activities [19, 20]. In order to further study isoquinoline derivatives’ activities and find novel natural-derived fungicidal candidates. A series of tetrahydroisoquinoline derivatives were designed via active fragment splicing strategy, and the common skeleton of tetrahydroisoquinoline alkaloids was

chosen as the “hydrophobic core,” introduced the double amide-bridge to bind “hydrophobic core” and polar moiety together (Fig. 1). Their antifungal activities against six plant pathogenic fungi were investigated. Compounds with excellent fungicidal activity were further tested in vivo against *A. alternata* on fragrant pears. In addition, enzymatic assays, scanning electron microscopy observations, molecular electrostatic potential, and molecular docking analysis were conducted.

Results and discussion

Chemistry

The synthetic route of the target compounds **A1–A32** as shown in Scheme 1. 2-(3',4'-Dimethoxyphenyl)ethylamine **1** reacts with appropriate aldehydes **2a–2h** in anhydrous toluene to form the schiff bases **3a–3h**. The intermediates **4a–4h** were obtained by intramolecular cyclization of **3** under trifluoroacetic acid. Then, **4a–4h** were condensed with Boc-glycine to obtain intermediates **5a–5h**. The Boc protective group was removed to obtain intermediates **6a–6h**, and then condensed with heterocyclic aryl chlorides **7a–7d** to obtain target compounds **A1–A32**.

The structures of the title compounds were identified by ^1H NMR, ^{13}C NMR, HRMS, and single-crystal X-ray diffraction. As **A5**, the ^1H NMR spectrum showed that the proton signals of the methylene groups at C3 and C4, the methoxy groups at C6 and C7, and most of the carbon atoms on the aromatic ring were splitted as two signals. It indicated this type of compounds exhibits steric isomerism, resulted in the splitting of proton signals at room temperature. The variable temperature nuclear magnetic resonance test results showed that the “doubled signals” gradually converged to a single signal when the test temperature increased to 120 °C (Fig. 2). In addition, **A5** was further identified by X-ray diffraction (Fig. 3). Based on the above details, the target compounds were confirmed as pure substance.

Antifungal activity

The in vitro antifungal activities of target compound **A1–A32** against six kinds of phytopathogenic fungi at a concentration of 50 mg/L are shown in Table 1. All the target compounds exhibited varying degrees of inhibition against the tested fungi. For *R. cerealis*, compounds **A30**, **A31**, and **A32** exceeded more than 70% antifungal activities, which are superior to the positive control boscalid (6.23%). Compound **A25** has an inhibitory rate of 67.25% against the *P. piricola*, which was comparable to the boscalid (66.56%), but lower than chlorothalonil (88.69%). In particular, compounds **A5**, **A9**, **A13**, **A21**,

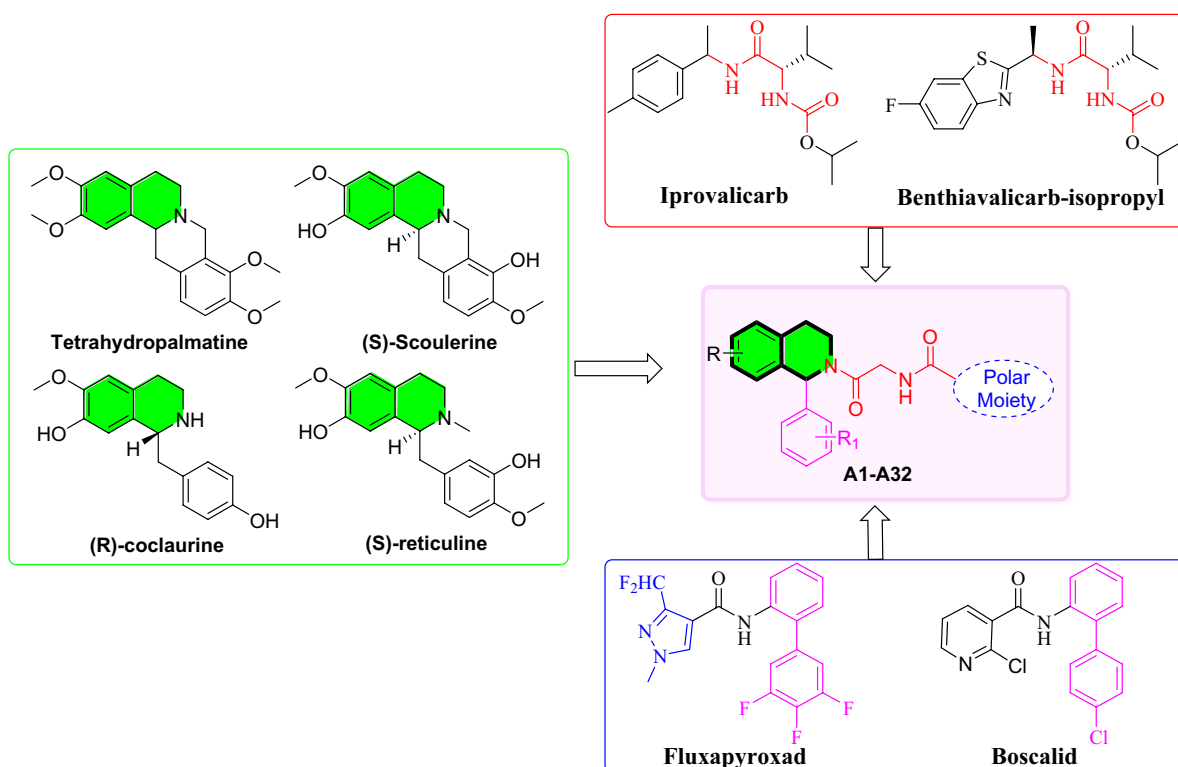
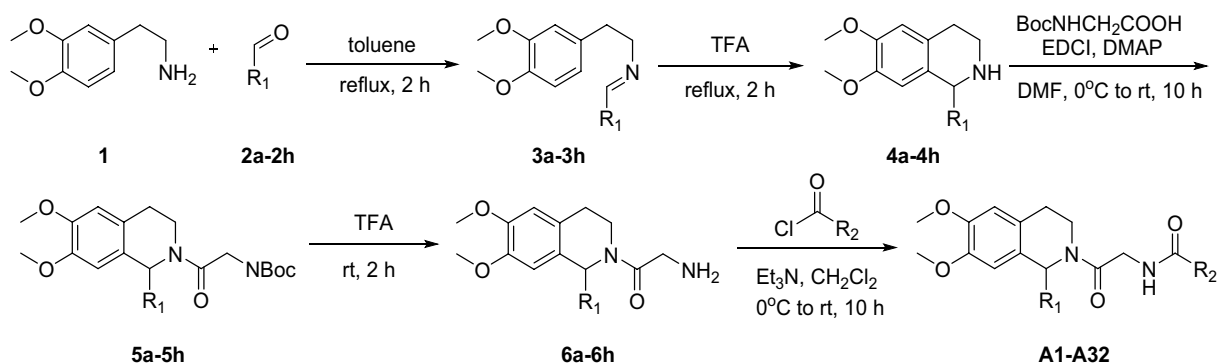


Fig. 1 Design strategy of target compounds **A1–A32**



A1 $R_1 = \text{H}$	$R_2 = \text{thiophenyl}$	A17 $R_1 = 2\text{-Cl-C}_6\text{H}_4$	$R_2 = \text{thiophenyl}$
A2 $R_1 = \text{H}$	$R_2 = 3\text{-(difluoromethyl)-1-methyl-1H-pyrazolyl}$	A18 $R_1 = 2\text{-Cl-C}_6\text{H}_4$	$R_2 = 3\text{-(difluoromethyl)-1-methyl-1H-pyrazolyl}$
A3 $R_1 = \text{H}$	$R_2 = 1\text{-methyl-3-(trifluoromethyl)-1H-pyrazolyl}$	A19 $R_1 = 2\text{-Cl-C}_6\text{H}_4$	$R_2 = 1\text{-methyl-3-(trifluoromethyl)-1H-pyrazolyl}$
A4 $R_1 = \text{H}$	$R_2 = 2\text{-methyl-4-(trifluoromethyl)thiazolyl}$	A20 $R_1 = 2\text{-Cl-C}_6\text{H}_4$	$R_2 = 2\text{-methyl-4-(trifluoromethyl)thiazolyl}$
A5 $R_1 = 2\text{-F-C}_6\text{H}_4$	$R_2 = \text{thiophenyl}$	A21 $R_1 = 3\text{-Cl-C}_6\text{H}_4$	$R_2 = \text{thiophenyl}$
A6 $R_1 = 2\text{-F-C}_6\text{H}_4$	$R_2 = 3\text{-(difluoromethyl)-1-methyl-1H-pyrazolyl}$	A22 $R_1 = 3\text{-Cl-C}_6\text{H}_4$	$R_2 = 3\text{-(difluoromethyl)-1-methyl-1H-pyrazolyl}$
A7 $R_1 = 2\text{-F-C}_6\text{H}_4$	$R_2 = 1\text{-methyl-3-(trifluoromethyl)-1H-pyrazolyl}$	A23 $R_1 = 3\text{-Cl-C}_6\text{H}_4$	$R_2 = 1\text{-methyl-3-(trifluoromethyl)-1H-pyrazolyl}$
A8 $R_1 = 2\text{-F-C}_6\text{H}_4$	$R_2 = 2\text{-methyl-4-(trifluoromethyl)thiazolyl}$	A24 $R_1 = 3\text{-Cl-C}_6\text{H}_4$	$R_2 = 2\text{-methyl-4-(trifluoromethyl)thiazolyl}$
A9 $R_1 = 3\text{-F-C}_6\text{H}_4$	$R_2 = \text{thiophenyl}$	A25 $R_1 = 4\text{-Cl-C}_6\text{H}_4$	$R_2 = \text{thiophenyl}$
A10 $R_1 = 3\text{-F-C}_6\text{H}_4$	$R_2 = 3\text{-(difluoromethyl)-1-methyl-1H-pyrazolyl}$	A26 $R_1 = 4\text{-Cl-C}_6\text{H}_4$	$R_2 = 3\text{-(difluoromethyl)-1-methyl-1H-pyrazolyl}$
A11 $R_1 = 3\text{-F-C}_6\text{H}_4$	$R_2 = 1\text{-methyl-3-(trifluoromethyl)-1H-pyrazolyl}$	A27 $R_1 = 4\text{-Cl-C}_6\text{H}_4$	$R_2 = 1\text{-methyl-3-(trifluoromethyl)-1H-pyrazolyl}$
A12 $R_1 = 3\text{-F-C}_6\text{H}_4$	$R_2 = 2\text{-methyl-4-(trifluoromethyl)thiazolyl}$	A28 $R_1 = 4\text{-Cl-C}_6\text{H}_4$	$R_2 = 2\text{-methyl-4-(trifluoromethyl)thiazolyl}$
A13 $R_1 = 4\text{-F-C}_6\text{H}_4$	$R_2 = \text{thiophenyl}$	A29 $R_1 = 2, 4\text{-Cl-C}_6\text{H}_4$	$R_2 = \text{thiophenyl}$
A14 $R_1 = 4\text{-F-C}_6\text{H}_4$	$R_2 = 3\text{-(difluoromethyl)-1-methyl-1H-pyrazolyl}$	A30 $R_1 = 2, 4\text{-Cl-C}_6\text{H}_4$	$R_2 = 3\text{-(difluoromethyl)-1-methyl-1H-pyrazolyl}$
A15 $R_1 = 4\text{-F-C}_6\text{H}_4$	$R_2 = 1\text{-methyl-3-(trifluoromethyl)-1H-pyrazolyl}$	A31 $R_1 = 2, 4\text{-Cl-C}_6\text{H}_4$	$R_2 = 1\text{-methyl-3-(trifluoromethyl)-1H-pyrazolyl}$
A16 $R_1 = 4\text{-F-C}_6\text{H}_4$	$R_2 = 2\text{-methyl-4-(trifluoromethyl)thiazolyl}$	A32 $R_1 = 2, 4\text{-Cl-C}_6\text{H}_4$	$R_2 = 2\text{-methyl-4-(trifluoromethyl)thiazolyl}$

Scheme 1 Synthetic route of title compounds **A1–A32**

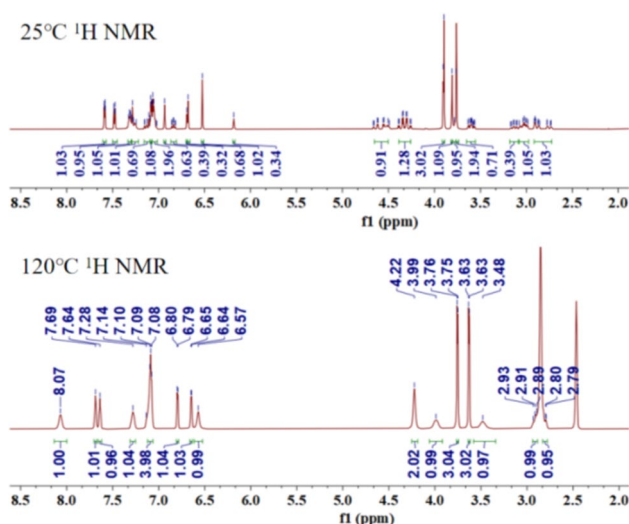


Fig. 2 ¹H NMR spectrum of A5

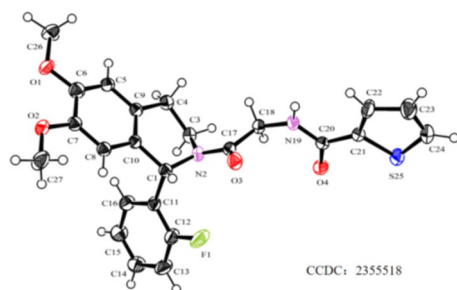


Fig. 3 X-ray crystal structure of A5

A25, **A28**, and **A32** all had over 70% inhibition rates against *A. alternata*. Among them, **A13** (90.81%) and **A25** (94.13%) were equal to boscalid (92.13%), and better than chlorothalonil (37.79%). Compared with boscalid, compounds **A13** and **A25** exhibited broader antifungal spectrum. Furthermore, the EC₅₀ value of **A13** (2.375 mg/L) and **A25** (2.251 mg/L) against *A. alternata* was equivalent to the positive control boscalid (1.195 mg/L) (Table 2).

According to the in vitro results, **A13** and **A25** were selected to evaluate in vivo against *A. alternata* on fragrant pears. As shown in Fig. 4 and Table 3, **A13** indicated effective protective activity at the concentration of 50 and 100 mg/L (51.613 and 70.968%), which was slightly better than **A25** (44.57 and 68.48%) and equal to boscalid (64.516 and 77.419%). Longitudinal section of the pear revealed that the decay caused by *A. alternata* not only expand on the surface of the pear but also spread into the interior of the pear.

Inhibitory effect of compound A13 on SDH

SDH is a key enzyme involved in mitochondrial respiration, and a crucial target of fungicides. To validate our synthesized tetrahydroisoquinoline derivatives whether act on SDH, an enzymatic assay of **A13** on SDH was conducted. As shown in Table 4, compound **A13** had favorable inhibitory activity against the SDH. It displayed regular dose-dependent trends and the inhibitory rate was over 90% at concentrations > 10 mg/L. Therefore, the results indicated that SDH may be a potential target of **A13**.

Structure–activity relationship

The bioassay results of in vitro and in vivo tests indicated that the "common" scaffold of tetrahydroisoquinoline served as a promising antifungal core. The substituents at the C1 position of tetrahydroisoquinoline core and the heterocyclic acid fragments were identified as significant factors on modulating antifungal activity. When the heterocyclic acid fragment remains consistent, compounds featuring aromatic ring at the C1 position demonstrated higher antifungal efficacy compared to others (**A1–A4** versus **A5–A32**). Notably, among the aryl-substituents, para-substituted phenyl exhibited higher antifungal inhibition than the meta- and ortho-substituted phenyl, mono-substituted compounds (**A5–A28**) displayed greater antifungal efficacy than multi-substituted compounds (**A29–A32**). Compare between **A13–A16** with **A25–A28**, revealed that when the R1 was identical, the antifungal potency of R2 followed as thiophenyl>thiazolyl>pyrazolyl. Compounds containing thiophenyl heterocyclic fragments displayed pronounced antifungal activities and broad-spectrum for various pathogenic fungi.

Molecular properties and drug-likeness evaluation

The fungicidal activity and the in silico interaction with the assumed target enzyme were greatly affected by the chemical structure. The physical and chemical properties of highly active compounds **A13** and **A25** were calculated. As shown in Table 5, the chemical structure of **A13** and **A25** meets the Lipinski rule and demonstrates good drug-likeness.

SEM analysis

SEM analysis of *A. alternata* was conducted to investigate microstructural variations in the mycelia. The untreated mycelia exhibited a relatively uniform, robust, and smooth appearance (Fig. 5a). In contrast, mycelia treated with compound **A13** at concentrations of 50 mg/L and 100 mg/L

Table 1 In vitro antifungal activity of target compounds **A1–A32** (50 mg/L, Inhibition rate $\pm$ Standard deviation %)

Compd	<i>R. cerealis</i>	<i>P. piricola</i>	<i>F. graminearum</i>	<i>C. lagenarium</i>	<i>B. Cinerea</i>	<i>A. alternata</i>
A1	24.20 $\pm$ 0.5	26.10 $\pm$ 0.0	6.50 $\pm$ 1.0	13.50 $\pm$ 0.5	10.90 $\pm$ 0.6	17.80 $\pm$ 0.3
A2	16.40 $\pm$ 0.3	20.80 $\pm$ 0.5	5.30 $\pm$ 0.0	6.00 $\pm$ 0.8	17.60 $\pm$ 0.3	13.23 $\pm$ 0.9
A3	14.50 $\pm$ 0.3	22.20 $\pm$ 0.6	11.70 $\pm$ 0.0	1.20 $\pm$ 1.3	5.50 $\pm$ 0.5	16.28 $\pm$ 1.6
A4	20.00 $\pm$ 0.3	16.40 $\pm$ 0.0	9.60 $\pm$ 0.3	7.62 $\pm$ 0.6	13.60 $\pm$ 0.3	21.34 $\pm$ 1.4
A5	46.94 $\pm$ 1.0	32.12 $\pm$ 0.3	17.26 $\pm$ 0.3	20.68 $\pm$ 0.0	23.11 $\pm$ 0.3	74.55 $\pm$ 1.3
A6	48.19 $\pm$ 0.5	33.74 $\pm$ 0.3	19.15 $\pm$ 0.5	19.41 $\pm$ 0.3	21.21 $\pm$ 0.0	6.98 $\pm$ 0.8
A7	50.56 $\pm$ 0.6	37.37 $\pm$ 0.5	24.82 $\pm$ 0.0	21.10 $\pm$ 0.5	27.27 $\pm$ 0.3	12.08 $\pm$ 0.5
A8	56.32 $\pm$ 0.8	30.32 $\pm$ 1.6	16.35 $\pm$ 1.3	18.69 $\pm$ 0.3	19.32 $\pm$ 0.7	60.49 $\pm$ 1.1
A9	26.45 $\pm$ 0.0	33.98 $\pm$ 0.5	15.67 $\pm$ 0.3	20.00 $\pm$ 0.3	11.79 $\pm$ 1.1	84.36 $\pm$ 0.0
A10	18.49 $\pm$ 0.8	1.47 $\pm$ 0.7	12.99 $\pm$ 0.0	4.80 $\pm$ 0.3	3.40 $\pm$ 0.5	13.33 $\pm$ 0.3
A11	18.49 $\pm$ 0.4	12.79 $\pm$ 0.3	17.51 $\pm$ 0.3	12.31 $\pm$ 0.5	1.66 $\pm$ 1.1	28.89 $\pm$ 0.0
A12	30.36 $\pm$ 0.8	26.79 $\pm$ 0.6	20.72 $\pm$ 1.1	14.68 $\pm$ 0.5	6.32 $\pm$ 0.7	65.79 $\pm$ 1.3
A13	65.57 $\pm$ 0.5	39.88 $\pm$ 0.0	18.89 $\pm$ 0.5	17.91 $\pm$ 0.1	3.21 $\pm$ 0.2	90.81 $\pm$ 1.0
A14	5.60 $\pm$ 0.2	21.43 $\pm$ 0.7	6.11 $\pm$ 0.2	4.48 $\pm$ 0.0	13.46 $\pm$ 0.2	12.12 $\pm$ 0.2
A15	3.24 $\pm$ 1.1	24.40 $\pm$ 0.3	2.78 $\pm$ 0.2	1.99 $\pm$ 0.0	19.23 $\pm$ 0.2	23.23 $\pm$ 0.5
A16	47.49 $\pm$ 0.5	30.95 $\pm$ 1.1	16.67 $\pm$ 0.2	19.90 $\pm$ 0.0	24.36 $\pm$ 0.2	63.64 $\pm$ 0.5
A17	20.63 $\pm$ 0.0	3.54 $\pm$ 0.5	8.73 $\pm$ 0.9	12.95 $\pm$ 1.1	5.86 $\pm$ 0.3	51.53 $\pm$ 0.5
A18	13.75 $\pm$ 0.7	6.56 $\pm$ 0.0	18.8 $\pm$ 0.2	12.46 $\pm$ 0.5	19.24 $\pm$ 0.7	3.43 $\pm$ 1.0
A19	21.9 $\pm$ 0.3	20.9 $\pm$ 0.3	17.7 $\pm$ 0.0	13.7 $\pm$ 0.7	31.2 $\pm$ 0.2	39.37 $\pm$ 0.2
A20	28.6 $\pm$ 0.0	8.3 $\pm$ 1.1	18.3 $\pm$ 0.5	22.4 $\pm$ 0.5	34.3 $\pm$ 0.5	50.23 $\pm$ 0.2
A21	39.00 $\pm$ 0.6	37.00 $\pm$ 0.2	25.00 $\pm$ 0.5	48.00 $\pm$ 0.5	29.00 $\pm$ 0.0	76.05 $\pm$ 0.0
A22	1.47 $\pm$ 0.3	28.57 $\pm$ 0.0	0.56 $\pm$ 0.2	5.97 $\pm$ 0.2	0.64 $\pm$ 1.0	6.06 $\pm$ 0.5
A23	12.68 $\pm$ 1.1	1.19 $\pm$ 0.5	1.67 $\pm$ 0.5	1.00 $\pm$ 0.2	10.90 $\pm$ 0.3	8.08 $\pm$ 0.0
A24	26.34 $\pm$ 1.6	13.64 $\pm$ 0.3	16.79 $\pm$ 1.1	34.16 $\pm$ 1.6	26.34 $\pm$ 1.9	61.23 $\pm$ 0.8
A25	66.77 $\pm$ 0.0	67.25 $\pm$ 0.2	17.00 $\pm$ 0.50	59.82 $\pm$ 0.0	51.56 $\pm$ 0.2	94.13 $\pm$ 0.0
A26	58.68 $\pm$ 0.3	33.31 $\pm$ 0.5	28.12 $\pm$ 0.29	38.00 $\pm$ 0.2	42.87 $\pm$ 1.2	62.89 $\pm$ 0.2
A27	64.35 $\pm$ 1.3	39.46 $\pm$ 0.5	28.85 $\pm$ 0.0	38.93 $\pm$ 1.1	51.15 $\pm$ 0.5	59.29 $\pm$ 1.1
A28	47.49 $\pm$ 0.0	13.69 $\pm$ 0.3	20.56 $\pm$ 0.29	25.87 $\pm$ 0.5	37.18 $\pm$ 1.0	73.69 $\pm$ 0.5
A29	15.69 $\pm$ 0.6	10.27 $\pm$ 0.2	14.41 $\pm$ 0.2	7.81 $\pm$ 0.5	14.29 $\pm$ 0.5	56.11 $\pm$ 0.0
A30	77.78 $\pm$ 0.3	47.47 $\pm$ 0.3	26.71 $\pm$ 0.5	38.40 $\pm$ 0.5	48.11 $\pm$ 0.0	56.03 $\pm$ 0.2
A31	73.61 $\pm$ 0.0	41.41 $\pm$ 1.1	33.81 $\pm$ 0.5	35.02 $\pm$ 0.3	50.38 $\pm$ 0.5	65.22 $\pm$ 0.2
A32	77.22 $\pm$ 0.3	47.88 $\pm$ 0.7	30.02 $\pm$ 0.2	36.71 $\pm$ 1.0	40.35 $\pm$ 0.2	72.81 $\pm$ 0.5
CH	95.56 $\pm$ 0.3	88.69 $\pm$ 0.6	82.51 $\pm$ 0.2	83.12 $\pm$ 0.0	75.2 $\pm$ 0.2	37.79 $\pm$ 0.2
Boscalid	6.23 $\pm$ 1.1	66.56 $\pm$ 0.6	13.59 $\pm$ 1.2	15.46 $\pm$ 0.3	40.49 $\pm$ 1.3	92.13 $\pm$ 1.6

CH Chlorothalonil, BS Boscalid

Table 2 EC₅₀ of **A13**, **A25** against *A. alternata*

Comp	95% confidence	EC ₅₀	Toxic regression equation	<i>r</i>
A13	0.698–4.335	2.375	$y = -0.65 + 1.65x$	0.985
A25	0.731–3.966	2.251	$y = -0.73 + 1.97x$	0.989
Boscalid	0.124–2.932	1.195	$y = -0.27 + 1.52x$	0.949

significant coarsening were observed, with twisted and broken hyphae and a shriveled surface (Fig. 5c, d). These findings indicated that compound **A13** induces substantial damage to the mycelia of *A. alternata*.

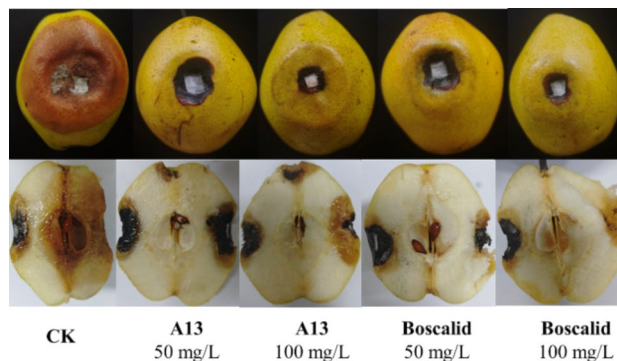
**Fig. 4** In vivo antifungal activity of compound **A13** against *A. alternata*

Table 3 In vivo antifungal inhibition of compounds **A13** and **A25** against *A. alternata*

Compd	Inhibition %	
	50 mg L ⁻¹	100 mg L ⁻¹
A13	51.613 ± 2.4	70.968 ± 1.9
A25	44.573 ± 2.2	68.483 ± 2.0
Boscalid	64.516 ± 1.6	77.419 ± 2.1

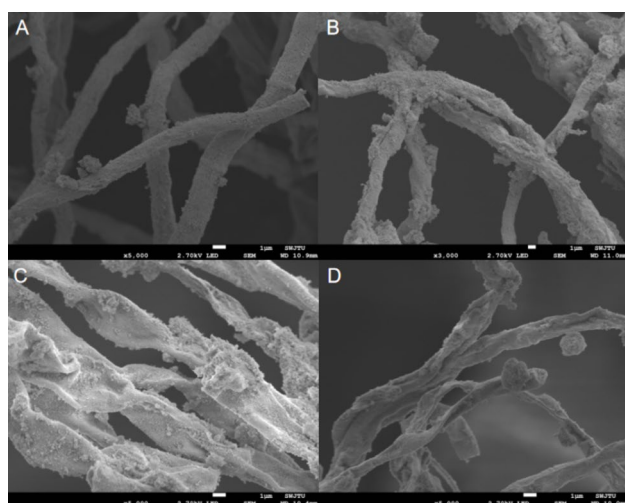
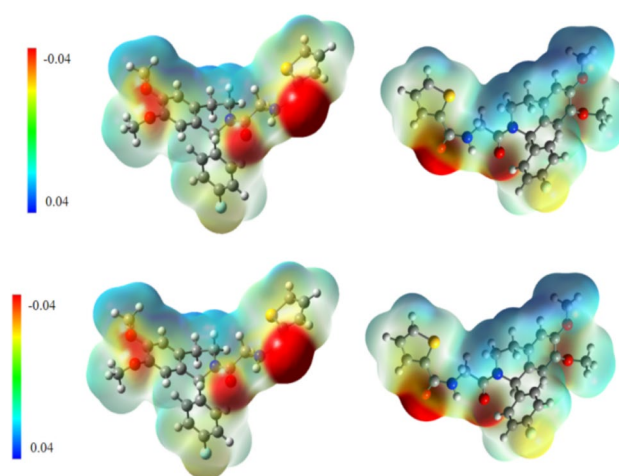
Table 4 Inhibitory activity of compound **A13** on SDH (%)

Comp	2 mg/L	5 mg/L	10 mg/L	20 mg/L
A13	43.2	71.4	90.7	95.6
Boscalid	81.2	94.5	100	100

Table 5 Lipinski properties of **A13** and **A25**

Compound	A13	A25
MW	454.52	470.89
LogP	3.34	3.83
nOHNH	1	1
nON	6	6
nRotb	6	6
DL	0.252	0.244

MW molecular weight; LogP octanol/water partition coefficient; nOHNH number of hydrogen bond acceptors; nON number of hydrogen bond donors; nRotb number of rotatable bonds; DL drug-likeness evaluation

**Fig. 5** SEM of the hyphae of *A. alternata*. **a** Negative control, **b** Boscalid with a concentration of 25 mg/L, **c** compound **A13** with a concentration of 25 mg/L, **d** compound **A13** with a concentration of 50 mg/L**Fig. 6** The molecular electrostatic potential of **A13**

Mechanism

Molecular electrostatic potential was an important factor for activity and provided a meaningful reference for uncovering the interaction modes of the drug with the target. As shown in Fig. 6, the positive region of compound **A13** is relatively weak, and the negative region located around the oxygen atoms of the tetrahydroisoquinoline ring at C6, C7 methoxy, and the bridge carboxyl group. This distribution suggests the potential for the formation of hydrogen bonds with the target enzyme.

Molecular docking simulations were performed to investigate the binding mechanism of compound **A13** with succinate dehydrogenase (SDH, PDB: 2FBW). The CDOCKER Interaction Energies of **A13** and boscalid were −8.4 and −8.3 kcal/mol, respectively. As illustrated in Fig. 7a, b, the isoquinoline ring of **A13** engages in a Pi-sigma interaction with Leu A470, while the aromatic ring at the C1 position and the thiophenyl ring form Pi-cation interactions with the Arg A218. Additionally, the fluorine atom on the phenyl ring and the oxygen atom of the amide bond establish hydrogen bonds with the arginine residue (Arg B63). Notably, compared to boscalid, compound **A13** exhibits a greater difference in binding sites and interaction modes with SDH. It provided a valuable reference for further modification of tetrahydroisoquinoline derivatives.

Conclusions

In summary, a series of 32 novel tetrahydroisoquinoline derivatives were designed, synthesized, and evaluated for their antifungal activities. The in vitro bioassay results showed that **A13** and **A25** exhibited effective antifungal activity against *A. alternata* as well as boscalid. The

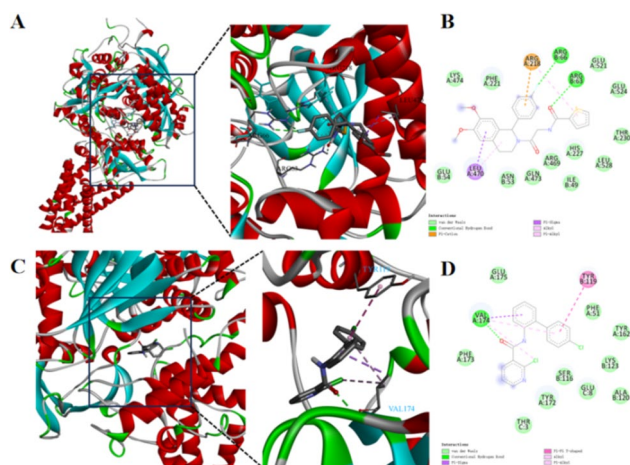


Fig. 7 Docking modes of compound **A13** and boscalid with SDH (2FBW). **a** 3D map of the binding mode of compound **A13** to SDH, **b** 2D map of the binding mode of compound **A13** to SDH, **c** 3D map of the binding mode of boscalid to SDH, **d** 2D map of the binding mode of compound boscalid to SDH

in vivo activities of **A13** and **A25** were investigated on pears and indicated that they can control *A. alternate* at the dosage of 50 and 100 mg/L. SDH enzyme inhibition, molecular docking, and molecular electrostatic potential studies further confirmed the crucial role of the tetrahydroisoquinoline scaffold in the predicted biological activity. These studies showed a new way to optimize the tetrahydroisoquinoline alkaloids and discover of natural-derived fungicides.

Experimental

Instruments and materials

The melting points were determined by RY-1G melting point meter. ^1H NMR spectra and ^{13}C NMR spectra were recorded on Bruker Avance NEO 400 using CDCl_3 , $\text{DMSO}-d_6$ as solvent and tetramethylsilane as the internal standard, and chemical shift values (δ) were given in parts per million (ppm). High-resolution mass spectrometry (HRMS) data were obtained on Xevo G2-S ToF Mass Spectrometer (Waters). The crystal structure was recorded by a Rigaku XtaLAB P200 diffractometer. Column chromatography silica gel H type (Qingdao Ocean Chemical Plant, 200–300 mesh) was used. Commercial reagents were analytically pure and used without further purification. All solvents were dried by standard methods in advance and distilled before use.

General synthetic procedure for target compounds **A1**–**A32**

The synthetic route of the target compound is shown in Scheme 1. 2-(3',4'-Dimethoxyphenyl)ethylamine **1** reacts with appropriate aldehydes **2a**–**2h** in anhydrous toluene to form the intermediate diazo compound **3a**–**3h**. The intermediate 1-substituted-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline compound **4a**–**4h** is obtained by intramolecular cyclization with trifluoroacetic acid [21]. Compound **4a**–**4h** was condensed with Boc-glycine to obtain intermediate **5a**–**5h**. Under acidic conditions, the Boc protective group was removed to obtain intermediate **6a**–**6h**, and then condensed with heterocyclic acid **7a**–**7d** amide to obtain target compounds **A1**–**A32** [22].

N-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)thiophene-2-carboxamide (A1): white solid, yield 94%, mp 113–115 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.55 (q, $J = 2.2$ Hz, 1H), 7.42 (d, $J = 5.0$ Hz, 1H), 7.34–7.30 (m, 1H), 7.02 (t, $J = 4.1$ Hz, 1H), 6.58 (d, $J = 8.0$ Hz, 2H), 4.64 (s, 1H), 4.49 (s, 1H), 4.26 (q, $J = 3.0$, 2.6 Hz, 2H), 3.82 (s, 1H), 3.81 (d, $J = 2.7$ Hz, 6H), 3.61 (td, $J = 6.0$, 2.0 Hz, 1H), 2.81 (3t, $J = 5.9$ Hz, 1H), 2.75 (t, $J = 6.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.88, 161.77 (161.74), 148.15 (148.31), 148.05, 138.55, 130.08, 128.40, 125.65 (126.52), 124.57 (123.41), 111.52 (111.80), 109.58 (109.21), 56.04, 56.03, 45.77, 44.21, 42.32, 41.93, 41.73, 40.29, 28.63, 27.79. HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_4\text{S} [\text{M} + \text{H}]^+$ 361.1222, found 361.1234.

3-(Difluoromethyl)-N-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-1-methyl-1H-pyrazole-4-carboxamide (A2): white solid, yield 96%, mp 78–80 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (s, 1H), 7.51 (d, $J = 5.3$ Hz, 1H), 7.00 (td, $^1J_{\text{CF}} = 54.2$, 3.9 Hz, 1H), 6.61 (s, 1H), 6.58 (d, $J = 5.8$ Hz, 1H), 4.64 (s, 1H), 4.50 (s, 1H), 4.25 (t, $J = 3.8$ Hz, 2H), 3.87 (s, 3H), 3.83 (d, $J = 2.2$ Hz, 3H), 3.82 (d, $J = 1.6$ Hz, 3H), 3.80 (s, 1H), 3.81–3.80 (m, 1H), 3.62 (t, $J = 5.9$ Hz, 1H), 2.82 (t, $J = 5.9$ Hz, 1H), 2.76 (t, $J = 6.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.97, 161.34 (d, $^4J_{\text{CF}} = 4.8$ Hz), 148.13 (148.30), 148.05 (148.02), 144.31 (t, $^2J_{\text{CF}} = 26.4$ Hz), 133.57 (d, $^4J_{\text{CF}} = 10.4$ Hz), 125.63 (126.56), 124.59 (123.38), 116.12, 111.79 (111.50), 110.62 (t, $^1J_{\text{CF}} = 234.9$ Hz), 109.57 (109.19), 56.02, 55.99, 45.77, 44.17, 42.33, 41.77, 41.53, 40.24, 39.40, 28.57, 27.75. HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{23}\text{F}_2\text{N}_4\text{O}_4 [\text{M} + \text{H}]^+$ 408.1609, found 408.1624.

N-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (A3): white solid, yield 95%, mp 90–92 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.94 (s, 1H), 7.41 (d, $J = 5.4$ Hz, 1H), 6.60 (s, 1H), 6.58 (d, $J = 6.9$ Hz, 1H), 4.63 (s, 1H), 4.49 (s, 1H), 4.24 (t, $J = 3.8$ Hz, 2H), 3.89 (s, 3H), 3.81 (dd, $J = 3.8$, 1.7 Hz, 6H), 3.79 (s, 1H), 3.61 (t, $J = 6.0$ Hz, 1H), 2.82 (t, $J = 6.0$ Hz, 1H), 2.75 (t, $J = 6.0$ Hz,

1H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.82, 160.37 (d, $^4J_{\text{CF}}=3.7$ Hz), 148.13 (148.31), 148.06 (148.02), 139.21 (dd, $^2J_{\text{CF}}=37.6$, 8.0 Hz), 134.58 (d, $^4J_{\text{CF}}=8.6$ Hz), 125.61 (126.55), 124.53 (123.34), 120.82 (d, $^1J_{\text{CF}}=269.3$ Hz), 116.57, 111.50 (111.79), 109.56 (109.19), 56.01, 55.97, 45.73, 44.16, 42.30, 41.90, 41.66, 40.26, 39.58, 28.54, 27.72. HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ 427.1593, found 427.1606.

N-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-2-methyl-4-(trifluoromethyl)thiazole-5-carboxamide (A4): white solid, yield 92%, mp 96–98 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.50 (d, $J=3.8$ Hz, 1H), 6.58 (d, $J=2.4$ Hz, 1H), 6.55 (d, $J=8.5$ Hz, 1H), 4.60 (s, 1H), 4.46 (s, 1H), 4.24 (t, $J=3.5$ Hz, 2H), 3.80 (s, 5H), 3.79 (d, $J=1.5$ Hz, 4H), 3.77 (d, $J=6.1$ Hz, 1H), 3.58 (t, $J=5.9$ Hz, 1H), 2.80 (t, $J=6.0$ Hz, 1H), 2.74 (t, $J=6.0$ Hz, 1H), 2.66 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 167.97 (168.01), 165.79 (d, $^4J_{\text{CF}}=6.5$ Hz), 158.57 (d, $^4J_{\text{CF}}=7.3$ Hz), 148.03 (148.21), 147.94 (147.90), 141.59–139.98 (m), 134.62–134.44 (m), 125.39 (126.41), 124.30 (123.02), 120.16 (q, $^1J_{\text{CF}}=272.0$ Hz), 111.25 (111.59), 109.30 (108.89), 55.98, 55.96, 55.94 (55.92), 45.70, 44.16, 42.52, 42.32, 42.25, 40.28, 28.52, 27.69, 19.11. HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{21}\text{F}_3\text{N}_3\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ 444.1205, found 444.1230.

N-(2-(1-(2-Fluorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)thiophene-2-carboxamide (A5): white solid, yield 89%, mp 126–128 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.59 (dd, $J=3.7$, 1.2 Hz, 1H), 7.48 (dd, $J=5.0$, 1.3 Hz, 1H), 7.32 (t, $J=3.7$ Hz, 1H), 7.29–7.23 (m, 1H), 7.15–7.09 (6.86–76.82) (m, 1H), 7.09–7.07 (m, 1H), 7.05 (dd, $J=6.1$, 3.4 Hz, 2H), 6.93 (6.69) (s, 1H), 6.68 (6.18) (s, 1H), 6.52 (s, 1H), 4.72–4.19 (m, 3H), 3.90 (d, $J=3.4$ Hz, 3H), 3.78 (s, 1H), 3.76 (3.81) (s, 3H), 2.92–2.69 (m, 1H), 3.66–3.07 (m, 1H), 3.01 (dt, $J=10.9$, 5.3 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.53 (167.24), 161.79 (161.97), 160.73 (d, $^1J_{\text{CF}}=249.4$ Hz), 148.50 (148.90), 148.10 (147.94), 138.53 (138.64), 130.77 (130.63), 130.06, 129.63 (129.54), 128.87 (128.73), 128.41, 127.58, 126.21 (126.00), 123.86 (124.05), 115.89 (d, $^2J_{\text{CF}}=22.1$ Hz), 111.73 (111.39), 110.89 (110.66), 56.00, 55.95, 51.27 (53.26), 41.88, 39.32 (36.76), 28.41 (27.16). HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{24}\text{FN}_2\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ 455.1441, found 455.1457.

3-(Difluoromethyl)-N-(2-(1-(2-fluorophenyl)-6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-1-methyl-1H-pyrazole-4-carboxamide (A6): white solid, yield 93%, mp 108–110 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.88 (d, $J=5.1$ Hz, 1H), 7.51 (d, $J=59.2$ Hz, 1H), 7.32–7.21 (m, 1H), 7.18–7.06 (6.85–6.79) (m, 1H), 7.02 (d, $J=130.6$ Hz, 1H), 7.02–6.96 (m, 2H), 6.91 (6.66) (d, $J=1.6$ Hz, 1H), 6.65 (6.14) (d, $J=3.3$ Hz, 1H), 6.48 (d, $J=2.3$ Hz, 1H), 4.65–4.10 (m, 2H), 3.88 (s, 3H), 3.87 (3.91) (s, 3H), 3.76 (s, 1H), 3.75 (3.77) (d, $J=18.2$ Hz,

3H), 3.61–3.05 (m, 1H), 3.00 (ddd, $J=16.7$, 10.7, 5.7 Hz, 1H), 2.90–2.63 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.05 (167.36), 161.60 (162.01), 160.77 (d, $^1J_{\text{CF}}=249.3$ Hz), 148.58 (148.94), 148.13 (147.97), 144.74 (d, $^2J_{\text{CF}}=30.0$ Hz), 132.94 (133.59), 130.82 (130.65), 129.56 (129.64), 128.87 (128.73), 127.43 (125.05), 126.17 (126.09), 123.86 (124.11), 115.96, 115.74, 111.44 (111.76), 110.94 (110.67), 110.28 (t, $^1J_{\text{CF}}=235.4$ Hz), 56.05, 56.00, 51.20 (53.28), 41.41, 39.45, 39.37 (37.76), 28.42 (27.18). HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{26}\text{F}_3\text{N}_4\text{O}_4$ $[\text{M} + \text{H}]^+$ 503.1906, found 502.3.1921.

N-(2-(1-(2-Fluorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (A7): white solid, yield 91%, mp 124–126 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.98 (s, 1H), 7.54 (dt, $J=116.5$, 4.3 Hz, 1H), 7.35–7.20 (m, 1H), 7.14–7.04 (6.85–6.81) (m, 1H), 7.02–6.96 (m, 2H), 6.93 (6.68) (s, 1H), 6.68 (6.15) (s, 1H), 6.50 (d, $J=2.4$ Hz, 1H), 4.64–4.16 (m, 2H), 3.89 (3.94) (s, 3H), 3.89 (s, 3H), 3.78–3.75 (m, 1H), 3.74 (3.79) (s, 3H), 3.64–3.09 (m, 1H), 3.01 (dq, $J=11.8$, 6.1, 5.6 Hz, 1H), 2.80 (dddd, $J=55.5$, 16.2, 4.4, 2.7 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.81 (167.10), 161.79 (161.67), 160.73 (d, $^1J_{\text{CF}}=248.9$ Hz), 148.55 (148.91), 148.10 (147.94), 139.71 (d, $^2J_{\text{CF}}=37.4$ Hz), 134.72, 134.11, 130.80 (130.61), 129.61 (129.53), 128.76 (128.62), 126.10 (126.02), 124.07, 123.81, 125.34–116.65 (m), 116.42 (116.80), 115.93 (115.71), 111.39 (111.73), 110.90 (110.62), 55.99, 55.94, 51.14 (53.24), 41.57, 39.57, 39.27 (36.70), 28.35 (27.11). HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{25}\text{F}_4\text{N}_4\text{O}_4$ $[\text{M} + \text{H}]^+$ 521.1812, found 521.1825.

N-(2-(1-(2-Fluorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-2-methyl-4-(trifluoromethyl)thiazole-5-carboxamide (A8): white solid, yield 93%, mp 119–121 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.46 (d, $J=4.0$ Hz, 1H), 7.24 (dddd, $J=13.7$, 8.6, 5.7, 1.8 Hz, 1H), 7.08 (6.81–6.77) (dd, $J=10.2$, 8.8 Hz, 1H), 7.05–6.93 (m, 2H), 6.86 (6.65) (s, 1H), 6.63 (6.09) (s, 1H), 6.47 (s, 1H), 4.26–4.25 (4.61–4.43) (m, 2H), 3.85 (d, $J=4.7$ Hz, 3H), 3.70 (3.75) (s, 2H), 3.67 (dd, $J=5.8$, 2.8 Hz, 1H), 3.54 (3.11–3.04) (ddd, $J=13.9$, 11.2, 4.5 Hz, 1H), 2.97 (ddd, $J=16.9$, 11.5, 5.7 Hz, 1H), 2.83 (2.72–2.71) (ddd, $J=15.8$, 4.5, 2.8 Hz, 1H), 2.68 (d, $J=1.5$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.86, 166.11, 165.35, 160.67 (dd, $^1J_{\text{CF}}=248.4$, 12.7 Hz), 158.57 (158.40), 148.45 (148.88), 148.02 (147.87), 140.95 (dd, $^2J_{\text{CF}}=36.5$, 27.4 Hz), 134.32 (134.81), 130.86 (130.72), 130.18 (129.67), 128.38 (127.59), 127.28 (125.95), 125.78 (124.65), 124.11 (123.81), 120.16 (d, $^1J_{\text{CF}}=277.3$ Hz), 116.02 (115.97), 115.80 (115.75), 111.21 (111.96), 110.69 (110.38), 55.94, 55.91, 53.17 (51.20), 42.44, 39.15 (36.61), 28.31, 27.09, 19.12. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{24}\text{F}_4\text{N}_3\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ 538.5376, found 538.5394.

N-(2-(1-(3-Fluorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)thiophene-2-carboxamide (A9): white solid, yield 87%, mp 106–108 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.58 (dt, $J=4.9$, 2.5 Hz, 1H), 7.44 (dd, $J=5.0$, 1.2 Hz, 1H), 7.36 (q, $J=4.0$ Hz, 1H), 7.22 (td, $J=8.0$, 5.9 Hz, 1H), 7.04 (dd, $J=5.0$, 3.7 Hz, 1H), 7.01 (d, $J=7.7$ Hz, 1H), 6.97–6.92 (m, 1H), 6.91 (dt, $J=9.8$, 2.1 Hz, 1H), 6.76 (6.62) (s, 1H), 6.66 (s, 1H), 6.50 (5.88) (s, 1H), 4.33–4.23 (4.52–4.42) (m, 2H), 3.87 (s, 3H), 3.75 (3.82) (s, 3H), 3.70 (ddd, $J=13.8$, 6.0, 3.0 Hz, 1H), 3.41 (ddd, $J=13.7$, 11.3, 4.4 Hz, 1H), 3.00–2.86 (m, 1H), 2.77 (dt, $J=16.2$, 3.9 Hz, 1H). ^{13}C NMR (150 MHz, CDCl_3) δ 166.75, 162.82 (d, $^1J_{\text{CF}}=246.6$ Hz), 161.82, 148.54 (148.88), 147.94 (147.75), 144.34 (144.29), 138.44 (138.36), 130.27, 129.95 (130.01), 128.50, 127.72, 126.13, 125.67, 124.29 (124.27), 115.74 (115.59), 114.83 (114.69), 111.20 (111.64), 111.04 (110.79), 56.04, 55.97, 55.13, 41.85, 38.81, 28.25. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{24}\text{FN}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 455.1441, found 455.1453. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 302.1215, Found: 302.1222.

3-(Difluoromethyl)-N-(2-(1-(3-fluorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-1-methyl-1H-pyrazole-4-carboxamide (A10): white solid, yield 93%, mp 110–112 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.93 (d, $J=4.1$ Hz, 1H), 7.54 (s, 1H), 7.07 (d, $J=47.8$ Hz, 1H), 7.02 (s, 1H), 7.00–6.88 (m, 2H), 6.80 (6.62) (s, 1H), 6.69 (s, 1H), 6.52 (5.87) (s, 1H), 4.29 (4.52–4.43) (d, $J=4.2$ Hz, 2H), 3.93 (s, 2H), 3.90 (d, $J=1.6$ Hz, 2H), 3.78 (3.85) (s, 3H), 3.70 (ddd, $J=13.8$, 5.9, 2.9 Hz, 1H), 3.43 (ddd, $J=13.8$, 11.2, 4.4 Hz, 1H), 2.98 (ddt, $J=19.5$, 13.9, 6.9 Hz, 1H), 2.80 (dt, $J=16.3$, 3.7 Hz, 1H). ^{13}C NMR (150 MHz, CDCl_3) δ 166.67, 162.80 (d, $^1J_{\text{CF}}=246.6$ Hz), 161.25, 148.54, 147.93, 144.29 (144.25), 133.80 (133.76), 129.94, 129.88, 126.06, 125.70, 124.26, 116.17, 115.65 (d, $^2J_{\text{CF}}=22.1$ Hz), 114.71 (d, $^2J_{\text{CF}}=21.2$ Hz), 112.50–110.69 (m), 111.18, 111.04, 56.02, 55.95, 55.02, 41.72, 39.54, 38.76, 28.18. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{26}\text{F}_3\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 503.5022, found 503.5046.

N-(2-(1-(3-Fluorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (A11): white solid, yield 88%, mp 122–124 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.94 (d, $J=1.4$ Hz, 1H), 7.35 (s, 1H), 7.31–7.20 (m, 1H), 7.02 (d, $J=7.7$ Hz, 1H), 6.97 (dd, $J=8.4$, 2.5 Hz, 1H), 6.94–6.88 (m, 1H), 6.79 (6.60) (s, 1H), 6.67 (s, 1H), 6.50 (5.84) (s, 1H), 4.27 (4.48–4.44) (d, $J=3.9$ Hz, 2H), 3.95 (s, 2H), 3.89 (s, 3H), 3.77 (3.84) (s, 3H), 3.68 (ddd, $J=13.6$, 6.1, 2.9 Hz, 1H), 3.41 (ddd, $J=13.7$, 11.3, 4.5 Hz, 1H), 2.97 (ddt, $J=17.2$, 11.9, 6.0 Hz, 1H), 2.84–2.73 (m, 1H). ^{13}C NMR (150 MHz, CDCl_3) δ 166.62, 162.90 (d, $^1J_{\text{CF}}=246.7$ Hz), 160.43, 148.64 (148.98), 148.04 (147.82), 144.33 (144.28), 139.26 (d, $^2J_{\text{CF}}=37.6$ Hz), 134.86, 130.03 (130.52), 126.11, 125.74, 124.38 (123.21),

120.91 (q, $^1J_{\text{CF}}=269.5$ Hz), 116.74, 115.83 (115.68), 114.91 (114.77), 111.26 (111.74), 111.11 (110.79), 56.11, 56.05, 55.13, 41.95, 39.86, 38.82, 28.26. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{25}\text{F}_4\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 521.1812, found 521.1836.

N-(2-(1-(3-Fluorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-2-methyl-4-(trifluoromethyl)thiazole-5-carboxamide (A12): white solid, yield 92%, mp 116–118 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.50 (s, 1H), 7.29–7.23 (m, 1H), 7.05–6.98 (m, 1H), 6.97 (dq, $J=8.3$, 4.9, 3.8 Hz, 1H), 6.91 (dq, $J=10.0$, 2.3 Hz, 1H), 6.78 (6.62) (d, $J=3.7$ Hz, 1H), 6.69 (d, $J=2.1$ Hz, 1H), 6.51 (5.82) (d, $J=1.6$ Hz, 1H), 4.29 (4.53–4.42) (dd, $J=4.0$, 2.0 Hz, 2H), 3.90 (d, $J=3.1$ Hz, 3H), 3.78 (3.85) (d, $J=2.6$ Hz, 3H), 3.74–3.63 (m, 1H), 3.43 (dddd, $J=13.7$, 11.4, 4.5, 2.1 Hz, 1H), 3.04–2.93 (m, 1H), 2.89–2.77 (m, 1H). ^{13}C NMR (150 MHz, CDCl_3) δ 168.17, 165.71, 162.86 (d, $^1J_{\text{CF}}=246.8$ Hz), 158.64, 148.64 (149), 148.04 (147.83), 144.17 (144.13), 141.19 (140.05), 134.59, 130.07 (130.02), 125.96, 125.59, 124.37, 123.04–117.21 (m), 115.80 (115.65), 114.94 (114.80), 111.22 (111.71), 110.06 (110.75), 56.07, 56.01, 55.17, 42.47, 38.79, 28.22, 19.28. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{24}\text{F}_4\text{N}_3\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 538.1424, found 538.1426.

N-(2-(1-(4-Fluorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)thiophene-2-carboxamide (A13): white solid, yield 91%, mp 144–146 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.61 (td, $J=4.0$, 2.1 Hz, 1H), 7.50 (dd, $J=5.0$, 1.1 Hz, 1H), 7.33–7.28 (m, 2H), 7.27–7.21 (m, 1H), 7.10 (dd, $J=5.0$, 3.7 Hz, 1H), 7.07–7.03 (m, 1H), 6.99 (ddd, $J=8.3$, 3.5, 1.5 Hz, 2H), 6.97–6.92 (m, 1H), 6.80 (5.90) (s, 1H), 6.69 (d, $J=2.8$ Hz, 1H), 6.52 (d, $J=12.1$ Hz, 1H), 4.32–4.30 (m, 2H), 3.91 (d, $J=1.4$ Hz, 3H), 3.78 (d, $J=6.0$ Hz, 3H), 3.75 (t, $J=3.1$ Hz, 1H), 3.51–3.36 (m, 1H), 2.98 (dtd, $J=17.4$, 11.4, 4.6 Hz, 1H), 2.86–2.77 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.63 (166.46), 162.82 (d, $^1J_{\text{CF}}=246.8$ Hz), 161.79, 148.55 (148.45), 147.95, 144.30 (144.23), 138.38, 130.45 (130.37), 130.24, 130.01 (129.93), 128.48, 127.69, 126.06, 125.64 (125.99), 124.28 (128.25), 115.77 (115.56), 115.42 (115.20), 114.87 (114.66), 111.19, 111.04, 56.03, 55.96, 55.12, 41.85, 38.76, 28.28. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{24}\text{F}_4\text{N}_3\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 454.1441, found 455.1456.

3-(Difluoromethyl)-N-(2-(1-(4-fluorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-1-methyl-1H-pyrazole-4-carboxamide (A14): white solid, yield 94%, mp 165–166 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.93 (d, $J=2.6$ Hz, 1H), 7.55 (d, $J=16.4$ Hz, 1H), 7.28–7.13 (m, 1H), 7.02 (dd, $J=6.7$, 3.1 Hz, 1H), 6.97 (dd, $J=8.6$, 2.4 Hz, 1H), 6.93 (ddd, $J=9.8$, 4.5, 2.5 Hz, 1H), 6.80 (5.87) (s, 1H), 6.68 (d, $J=4.8$ Hz, 1H), 6.50 (6.62–6.57) (d, $J=18.9$ Hz, 1H), 4.39–4.23 (m, 2H), 3.93 (d, $J=2.9$ Hz, 3H), 3.90 (d, $J=2.0$ Hz, 3H), 3.77 (3.84) (d, $J=9.3$ Hz, 3H), 3.70 (ddd, $J=13.9$, 6.0, 2.9 Hz, 1H),

3.42 (dddd, $J=20.6, 16.2, 11.6, 4.4$ Hz, 1H), 3.03–2.90 (m, 1H), 2.80 (dt, $J=16.4, 3.6$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.84 (166.62), 162.81 (d, $^1J_{\text{CF}}=246.6$ Hz), 161.30, 148.68, 148.06, 144.35 (144.29), 133.62, 130.38 (130.30), 129.82 (129.91), 126.15, 125.84, 124.18, 116.19, 115.67 (115.46), 115.30 (115.09), 114.73 (114.52), 111.41, 111.30, 109.55 (d, $^1J_{\text{CF}}=234.9$ Hz), 56.05, 55.97, 55.09, 41.65, 39.44, 38.85, 28.16, 26.89. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{26}\text{F}_3\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 503.1906, found 5003.1933.

***N*-(2-(1-(4-Fluorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (A15)**: white solid, yield 93%, mp 135–137 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.99–7.96 (m, 1H), 7.37 (d, $J=5.3$ Hz, 1H), 7.36–7.12 (m, 2H), 7.07–7.02 (m, 1H), 7.02–6.97 (m, 1H), 6.97–6.91 (m, 1H), 6.82 (5.85) (s, 1H), 6.69 (d, $J=2.9$ Hz, 1H), 6.51 (6.59) (d, $J=12.5$ Hz, 1H), 4.28 (4.48) (dd, $J=5.5, 3.9$ Hz, 2H), 3.98 (s, 3H), 3.91 (d, $J=1.6$ Hz, 3H), 3.78 (3.85) (d, $J=6.2$ Hz, 3H), 3.70 (ddd, $J=13.9, 5.9, 3.2$ Hz, 1H), 3.49–3.35 (m, 1H), 2.99 (ddt, $J=17.0, 11.6, 5.8$ Hz, 1H), 2.81 (ddd, $J=16.2, 4.4, 2.8$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.42, 162.79 (d, $^1J_{\text{CF}}=240.38$ Hz), 160.32, 148.56, 147.95, 144.24 (144.17), 134.81, 130.40, 129.98 (129.90), 126.00, 125.65, 124.30, 116.71, 115.78 (115.56), 115.38 (115.17), 114.85 (114.64), 111.18, 111.04, 56.02, 55.96, 55.03, 41.91, 39.78, 38.71, 28.17. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{25}\text{F}_4\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 521.1812, found 521.1826.

***N*-(2-(1-(4-Fluorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-2-methyl-4-(trifluoromethyl)thiazole-5-carboxamide (A16)**: white solid, yield 88%, mp 144–146 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.49 (q, $J=6.7, 4.2$ Hz, 1H), 7.36–7.11 (m, 1H), 7.06–7.01 (m, 1H), 7.01–6.94 (m, 1H), 6.92 (dt, $J=9.9, 2.1$ Hz, 1H), 6.79 (5.82) (s, 1H), 6.69 (d, $J=2.8$ Hz, 1H), 6.50 (d, $J=12.7$ Hz, 1H), 4.53–4.25 (m, 2H), 3.90 (d, $J=1.5$ Hz, 3H), 3.77 (d, $J=6.3$ Hz, 2H), 3.72–3.62 (m, 1H), 3.43 (dddd, $J=14.1, 11.2, 9.5, 4.5$ Hz, 1H), 2.97 (tdd, $J=16.8, 10.2, 5.8$ Hz, 1H), 2.86–2.77 (m, 1H), 2.77 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 168.11, 165.63, 162.81 (d, $^1J_{\text{CF}}=246.9$ Hz), 158.57, 148.59, 147.99, 144.12 (144.05), 141.02 (d, $^2J_{\text{CF}}=36.8$ Hz), 130.49 (130.41), 130.02 (129.94), 138.17–117.92 (m), 125.88, 125.53, 124.31 (124.28), 115.78 (115.56), 115.42 (115.21), 114.92 (114.71), 111.16, 111.00, 56.01, 55.95, 55.11, 42.41, 38.72, 28.16, 19.22. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{24}\text{F}_4\text{N}_5\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 538.1424, found 538.1443.

***N*-(2-(1-(2-Chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)thiophene-2-carboxamide (A17)**: white solid, yield 91%, mp 112–114 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J=3.7$ Hz, 1H), 7.43 (d, $J=5.5$ Hz, 1H), 7.40 (s, 1H), 7.35–7.30 (m, 1H), 7.21 (q, $J=7.4$ Hz, 1H), 7.13 (t,

$J=7.5$ Hz, 1H), 7.05–7.00 (m, 1H), 6.94 (d, $J=1.8$ Hz, 1H), 6.92 (6.18) (d, $J=1.7$ Hz, 1H), 6.66 (s, 1H), 6.54 (s, 1H), 4.62–4.18 (m, 2H), 3.86 (s, 3H), 3.73 (3.75) (s, 3H), 3.80–3.64 (m, 1H), 3.54 (dt, $J=14.0, 7.0$ Hz, 1H), 3.03 (ddd, $J=17.1, 11.4, 5.8$ Hz, 1H), 2.90–2.83 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.93, 161.78, 148.56, 148.14, 139.53, 138.54, 134.13, 130.80, 130.06, 128.97, 128.39, 127.57, 127.06, 126.66, 125.91, 111.83 (111.53), 110.89 (111.53), 55.95, 54.00, 41.90, 39.42, 28.45. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{24}\text{ClN}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 471.1145, found 471.1156.

***N*-(2-(1-(2-Chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide (A18)**: white solid, yield 92%, mp 116–118 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.87 (s, 1H), 7.61–7.58 (7.45) (m, 1H), 7.39 (7.44) (dd, $J=7.9, 1.4$ Hz, 1H), 7.27–7.18 (m, 1H), 7.18–7.08 (m, 1H), 7.09–6.97 (m, 1H), 6.92 (6.53) (s, 1H), 6.90 (dd, $J=7.9, 1.6$ Hz, 1H), 6.67 (d, $J=3.7$ Hz, 1H), 6.50 (6.16) (s, 1H), 4.25 (ddd, $J=99.6, 17.3, 4.4$ Hz, 1H), 3.88 (d, $J=8.4$ Hz, 3H), 3.85 (s, 2H), 3.74 (s, 1H), 3.73 (3.77) (s, 3H), 3.51 (3.19–3.14) (ddd, $J=14.0, 11.5, 4.4$ Hz, 1H), 3.04 (ddd, $J=17.0, 11.4, 5.8$ Hz, 1H), 2.93–2.65 (m, 1H). ^{13}C NMR (150 MHz, CDCl_3) δ 167.19 (168.39), 161.49 (161.09), 148.45 (148.72), 148.01 (147.84), 144.86 (t, $^2J_{\text{CF}}=25.6$ Hz), 139.38 (138.56), 134.14 (133.61), 132.82, 130.97, 130.04 (130.26), 129.01 (129.56), 126.63, 126.49 (127.09), 125.83 (125.70), 115.99, 111.29, 111.95–108.44 (m), 110.65, 55.92 (56.28), 53.88, 41.45 (42.03), 39.50, 39.30 (37.48), 28.41, 26.90 (27.15). HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{26}\text{ClF}_2\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 519.1611, found 519.1642.

***N*-(2-(1-(2-Chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (A19)**: white solid, yield 91%, mp 118–120 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.92 (s, 1H), 7.49–7.38 (m, 2H), 7.22 (td, $J=7.9, 1.9$ Hz, 1H), 7.13 (t, $J=7.6$ Hz, 1H), 6.94 (6.53) (s, 1H), 6.90 (dd, $J=7.8, 1.7$ Hz, 1H), 6.68 (d, $J=3.5$ Hz, 1H), 6.52 (6.15) (s, 1H), 4.38–4.16 (4.59–4.40) (m, 2H), 3.96–3.89 (m, 3H), 3.88 (s, 3H), 3.74 (3.78) (s, 3H), 3.73–3.70 (m, 1H), 3.51 (3.20–3.15) (ddd, $J=14.1, 11.6, 4.5$ Hz, 1H), 3.05 (ddd, $J=17.2, 11.6, 5.8$ Hz, 1H), 2.93–2.66 (m, 1H). ^{13}C NMR (150 MHz, Chloroform-*d*) δ 166.84 (168.16), 160.40 (160.08), 148.51 (148.78), 148.05 (147.88), 139.26, 140.09–138.31 (m), 134.21 (134.84), 134.10 (133.62), 131.04, 130.08 (130.28), 129.04 (129.58), 126.59 (127.07), 125.81 (126.49), 123.89–117.55 (m), 116.54, 111.32 (111.67), 110.73 (110.27), 55.93, 53.87, 41.73 (42.23), 39.68, 39.19 (37.44), 28.38, 27.12. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{25}\text{ClF}_3\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 537.9442, found 537.9453.

***N*-(2-(1-(2-Chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-2-methyl-4-(trifluoromethyl)thiazole-5-carboxamide (A20)**: white

solid, yield 93%, mp 108–120 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.40 (t, $J=4.3$ Hz, 1H), 7.36 (d, $J=7.9$ Hz, 0H), 7.24–7.12 (m, 1H), 7.08 (t, $J=7.6$ Hz, 1H), 6.88 (6.50) (s, 1H), 6.85 (s, 1H), 6.63 (d, $J=4.4$ Hz, 1H), 6.48 (6.09) (s, 1H), 4.25 (4.60–4.30) (t, $J=4.6$ Hz, 2H), 3.82 (s, 3H), 3.70 (d, $J=11.2$ Hz, 3H), 3.67 (s, 1H), 3.53–3.41 (m, 1H), 2.98 (ddd, $J=17.3, 11.5, 6.1$ Hz, 1H), 2.87–2.78 (m, 1H), 2.65 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.74, 167.37, 165.79, 158.56, 148.61, 148.14, 141.10 (d, $^2J_{\text{CF}}=35.9$ Hz), 139.15, 134.16 (134.25, 130.94, 130.09, 129.60, 129.05, 127.11, 126.58 (126.49), 125.78 (125.61), 120.15 (d, $^1J_{\text{CF}}=272.4$ Hz), 111.50 (111.82), 110.89 (110.43), 55.92, 53.95, 42.54 (42.69), 39.20 (37.11), 28.35 (27.11), 19.03. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{24}\text{ClF}_3\text{N}_3\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 554.1128, found 554.1141.

N-(2-(1-(3-Chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)thiophene-2-carboxamide (A21): white solid, yield 90%, mp 128–130 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.61 (dd, $J=3.8, 1.3$ Hz, 1H), 7.48 (tt, $J=3.3, 1.3$ Hz, 1H), 7.34 (p, $J=3.9$ Hz, 1H), 7.29–7.19 (m, 3H), 7.17–7.10 (m, 1H), 7.07 (dt, $J=4.7, 3.6$ Hz, 1H), 6.78 (s, 1H), 6.69 (6.63) (s, 1H), 6.51 (5.89) (s, 1H), 4.31 (4.52–4.48) (t, $J=4.0$ Hz, 2H), 3.90 (d, $J=2.1$ Hz, 3H), 3.78 (3.85) (d, $J=1.9$ Hz, 3H), 3.73 (ddd, $J=14.2, 5.9, 2.9$ Hz, 1H), 3.49–3.37 (m, 1H), 2.99 (ddd, $J=16.9, 11.4, 5.8$ Hz, 1H), 2.81 (ddd, $J=16.3, 4.5, 2.6$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.77, 161.84, 148.63, 148.05, 143.86, 138.47, 134.53, 130.27, 129.79, 128.77, 128.53, 128.08, 127.74, 126.91, 126.17, 125.58, 111.30, 111.09, 56.10, 56.01, 55.18, 38.80, 28.30. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{24}\text{ClN}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 471.1145, found 471.1164.

N-(2-(1-(3-Chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide (A22): white solid, yield 92%, mp 136–138 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (s, 1H), 7.55 (dt, $J=4.8, 2.3$ Hz, 1H), 7.25–7.22 (m, 1H), 7.20 (d, $J=2.1$ Hz, 1H), 7.19 (d, $J=2.1$ Hz, 1H), 7.09 (dq, $J=7.1, 2.1$ Hz, 1H), 7.00 (t, $J=54.2$ Hz, 1H), 6.75 (6.58) (s, 1H), 6.66 (s, 1H), 6.47 (5.84) (s, 1H), 4.33–4.23 (4.46–4.42) (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.74 (3.82) (s, 3H), 3.68 (ddd, $J=13.9, 6.0, 2.8$ Hz, 1H), 3.40 (ddd, $J=13.8, 11.3, 4.4$ Hz, 1H), 2.95 (ddt, $J=16.5, 11.0, 5.5$ Hz, 1H), 2.77 (ddd, $J=16.1, 4.3, 2.8$ Hz, 1H). ^{13}C NMR (150 MHz, CDCl_3) δ 166.88, 161.33, 148.57, 147.97, 144.53–144.00 (m), 143.79, 134.41, 133.62, 129.70, 128.69, 127.97, 126.84, 126.10, 125.56, 116.09, 111.24, 111.03, 110.68 (t, $^1J_{\text{CF}}=234.7$ Hz), 56.03, 55.95, 55.05, 41.62, 39.51, 38.77, 28.17, 26.90. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{26}\text{ClF}_2\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 519.9358, found 519.9367.

N-(2-(1-(3-Chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (A23):

white solid, yield 91%, mp 110–112 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.94 (s, 1H), 7.35 (s, 1H), 7.25–7.21 (m, 2H), 7.19 (d, $J=2.1$ Hz, 1H), 6.78 (6.58) (s, 1H), 6.67 (s, 1H), 6.48 (5.81) (s, 1H), 4.27 (4.48–4.44) (d, $J=3.9$ Hz, 2H), 3.89 (s, 3H), 3.76 (3.84) (s, 3H), 3.67 (ddd, $J=13.9, 6.0, 2.8$ Hz, 1H), 3.40 (ddd, $J=13.9, 11.4, 4.4$ Hz, 1H), 2.97 (d, $J=5.5$ Hz, 1H), 2.79 (ddd, $J=16.2, 4.5, 2.7$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.54, 160.44, 148.69, 148.10, 143.84, 139.43, 134.94, 134.59, 129.86, 128.87, 128.17, 127.03, 126.13, 125.61, 122.28, 116.83, 111.31, 111.10, 56.16, 56.08, 55.14, 42.03, 39.91, 38.77, 28.30. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{25}\text{ClF}_3\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 537.1516, found 537.1542.

N-(2-(1-(3-Chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-2-methyl-4-(trifluoromethyl)thiazole-5-carboxamide (A24): white solid, yield 86%, mp 125–127 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.48 (s, 1H), 7.27 (7.31–7.30) (d, $J=1.8$ Hz, 1H), 7.25 (t, $J=7.6$ Hz, 1H), 7.21 (d, $J=1.8$ Hz, 1H), 7.14 (dt, $J=7.3, 1.7$ Hz, 1H), 6.79 (6.60) (s, 1H), 6.70 (s, 1H), 6.50 (5.80) (s, 1H), 4.30 (4.51–1.47) (d, $J=3.8$ Hz, 2H), 3.92 (s, 3H), 3.79 (3.87) (s, 3H), 3.67 (ddd, $J=13.9, 6.1, 2.8$ Hz, 1H), 3.44 (ddd, $J=13.8, 11.5, 4.4$ Hz, 1H), 3.05–2.99 (m, 1H), 2.83 (ddd, $J=16.3, 4.4, 2.7$ Hz, 1H), 2.76 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 168.12, 165.62, 158.57, 148.61, 148.03, 143.59, 141.05 (d, $^2J_{\text{CF}}=36.8$ Hz), 134.51, 129.77, 128.75, 128.12, 126.92, 125.87, 125.37, 120.17 (d, $^1J_{\text{CF}}=272.0$ Hz), 111.17, 110.95, 56.03, 55.96, 55.11, 42.43, 38.66, 28.18 (26.92), 19.24. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{24}\text{ClF}_3\text{N}_3\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 554.1128, found 554.1139.

N-(2-(1-(4-Chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)thiophene-2-carboxamide (A25): white solid, yield 87%, mp 123–125 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.61 (dd, $J=3.8, 1.2$ Hz, 1H), 7.49 (dd, $J=5.0, 1.2$ Hz, 1H), 7.32–7.30 (m, 1H), 7.27–7.25 (m, 2H), 7.21–7.16 (7.13–7.12) (m, 2H), 7.08 (dd, $J=5.0, 3.7$ Hz, 1H), 6.78 (6.60) (s, 1H), 6.69 (d, $J=2.8$ Hz, 1H), 6.49 (5.89) (s, 1H), 4.34–4.25 (4.51–4.50) (m, 2H), 3.90 (s, 3H), 3.77 (3.84) (s, 3H), 3.72 (ddd, $J=13.9, 5.8, 2.6$ Hz, 1H), 3.41 (ddd, $J=13.8, 11.5, 4.4$ Hz, 1H), 3.02–2.96 (m, 1H), 2.80 (ddd, $J=16.2, 4.2, 2.6$ Hz, 1H). ^{13}C NMR (150 MHz, CDCl_3) δ 166.66, 161.82, 148.52, 147.99, 140.35, 138.44, 133.75, 130.30, 130.12, 129.03 (128.89), 128.67, 128.52, 127.75, 126.11, 125.80, 111.20, 110.99, 56.05, 56.00, 55.00, 41.90 (42.15), 38.67 (37.64), 28.34 (27.12). HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{24}\text{ClN}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 471.1145, found 471.1167.

N-(2-(1-(4-Chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide (A26): white solid, yield 88%, mp 117–119 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (s, 1H), 7.50 (tt, $J=4.2, 2.1$ Hz, 1H), 7.28–7.22 (m, 1H), 7.21 (d, $J=2.1$ Hz, 1H), 7.12 (d,

$J=4.9$ Hz, 1H), 7.11–6.81 (m, 1H), 6.75 (s, 1H), 6.65 (s, 1H), 6.45 (s, 1H), 4.39–4.16 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.73 (s, 3H), 3.71–3.62 (m, 1H), 3.37 (ddd, $J=13.8$, 11.4, 4.4 Hz, 1H), 3.06–2.86 (m, 1H), 2.76 (ddd, $J=16.2$, 4.3, 2.6 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.66, 161.26, 148.48, 147.94, 144.13 (t, $^2J_{\text{CF}}=27.1$ Hz), 140.30, 133.78, 133.64, 130.05, 128.97 (128.91), 128.56, 126.04, 125.81, 116.12, 111.17, 110.87 (110.68), 113.56–108.20 (m), 110.68, 55.99, 55.94, 54.86, 41.70 (42.03), 39.52, 38.63 (37.52), 28.22 (27.05). HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{26}\text{ClF}_2\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 519.1611, found 519.1633.

N-(2-(1-(4-Chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (A27): white solid, yield 93%, mp 114–116 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.96 (7.53) (s, 1H), 7.37 (s, 1H), 7.32–7.24 (m, 2H), 7.21–7.05 (m, 2H), 6.79 (6.57) (s, 1H), 6.69 (d, $J=3.9$ Hz, 1H), 6.48 (5.84) (s, 1H), 4.27 (4.53–4.42) (dd, $J=4.0$, 2.2 Hz, 2H), 3.97 (d, $J=3.4$ Hz, 4H), 3.90 (s, 3H), 3.77 (s, 3H), 3.68 (ddd, $J=13.8$, 6.0, 2.7 Hz, 1H), 3.40 (ddd, $J=13.8$, 11.5, 4.4 Hz, 1H), 2.99 (ddt, $J=19.1$, 13.1, 7.0 Hz, 1H), 2.80 (ddd, $J=16.2$, 4.3, 2.6 Hz, 1H). ^{13}C NMR (150 MHz, CDCl_3) δ 166.42, 160.31, 148.49, 147.95, 140.23, 139.10 (q, $^2J_{\text{CF}}=37.7$ Hz), 134.79, 133.69, 130.71, 130.07, 128.97 (128.95), 128.59, 125.99, 125.75, 120.82 (d, $^1J_{\text{CF}}=269.3$ Hz), 116.64, 111.14, 110.92, 55.99, 55.94, 54.86, 41.87, 39.76, 38.57, 28.22. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{25}\text{ClF}_3\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 537.1516, found 537.1528.

N-(2-(1-(4-Chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-2-methyl-4-(trifluoromethyl)thiazole-5-carboxamide (A28): white solid, yield 85%, mp 129–131 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.47–7.43 (m, 1H), 7.33–7.22 (m, 2H), 7.17 (s, 1H), 7.16–7.06 (m, 1H), 6.76 (6.55) (s, 1H), 6.67 (s, 1H), 6.46 (5.78) (s, 1H), 4.26 (4.50–4.43) (d, $J=3.9$ Hz, 2H), 3.88 (s, 3H), 3.75 (3.82) (s, 3H), 3.72–3.60 (m, 1H), 3.39 (ddd, $J=13.8$, 11.6, 4.4 Hz, 1H), 2.98 (ddd, $J=16.8$, 11.4, 5.7 Hz, 1H), 2.79 (ddd, $J=16.2$, 4.4, 2.6 Hz, 1H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 168.25, 165.66, 158.67, 148.66, 148.14, 141.12 (d, $^2J_{\text{CF}}=36.9$ Hz), 140.21, 134.69, 133.92, 130.21, 129.14, 129.03, 128.76, 125.95, 125.75, 120.28 (d, $^1J_{\text{CF}}=272.1$ Hz), 111.25, 111.04, 56.11, 56.06, 55.06, 42.54, 38.66, 28.34, 19.34. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{24}\text{ClF}_3\text{N}_3\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 554.1128 found 554.1154.

N-(2-(1-(2,4-Dichlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)thiophene-2-carboxamide (A29): white solid, yield 92%, mp 111–113 °C; ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 8.69 (t, $J=5.9$ Hz, 1H), 7.82–7.79 (m, 1H), 7.77–7.72 (m, 1H), 7.62 (d, $J=2.2$ Hz, 1H), 7.33 (dd, $J=8.4$, 2.2 Hz, 1H), 7.17–7.13 (m, 1H), 6.97 (d, $J=8.4$ Hz, 1H), 6.85 (s, 1H), 6.68 (s, 1H), 6.63 (s, 1H), 4.32 (dd, $J=16.9$, 6.2 Hz, 1H), 4.12 (dd, $J=16.8$, 5.6 Hz, 1H), 3.90 (dd, $J=11.3$, 7.0 Hz,

1H), 3.76 (s, 3H), 3.60 (s, 2H), 3.41 (ddd, $J=14.4$, 10.7, 4.5 Hz, 1H), 2.98 (ddd, $J=16.4$, 10.6, 5.7 Hz, 1H), 2.86 (dt, $J=16.6$, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 168.30, 161.81, 148.59, 147.94, 140.06, 139.99, 134.46, 133.11, 132.31, 131.35, 129.48, 128.83, 128.41, 127.64, 127.22, 126.56, 112.48, 111.25, 56.01, 55.95, 53.27, 41.40, 28.35. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{23}\text{Cl}_2\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 505.0756, found 505.0783.

N-(2-(1-(2,4-Dichlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide (A30): white solid, yield 89%, mp 133–135 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, $J=4.5$ Hz, 1H), 7.45 (d, $J=6.1$ Hz, 1H), 7.41 (d, $J=2.1$ Hz, 1H), 7.11 (ddd, $^1J_{\text{CF}}=17.2$, 8.4, 2.2 Hz, 1H), 7.02 (t, $J=54.2$ Hz, 1H), 6.86 (6.65) (s, 1H), 6.80 (d, $J=8.4$ Hz, 1H), 6.65 (6.46) (s, 1H), 6.45 (6.07) (s, 1H), 4.36–4.12 (4.57) (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.76 (s, 1H), 3.73 (s, 3H), 3.02 (ddd, $J=17.0$, 7.7, 4.0 Hz, 1H), 2.84 (ddd, $J=16.3$, 4.5, 2.3 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.23, 161.41, 148.72, 148.24, 144.68, 138.24, 134.87, 134.19, 132.98, 131.71, 129.81, 126.91, 126.08, 125.86, 116.06, 111.54, 110.69, 110.35, 55.97, 55.95, 53.49, 41.55, 39.42, 28.38, 26.89. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{25}\text{Cl}_2\text{F}_2\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 553.1221, found 553.1243.

N-(2-(1-(2,4-Dichlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (A31): white solid, yield 93%, mp 120–122 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.92 (s, 1H), 7.46 (dd, $J=19.5$, 2.1 Hz, 1H), 7.38 (d, $J=4.2$ Hz, 1H), 7.14 (ddd, $J=16.4$, 8.4, 2.2 Hz, 1H), 6.89 (6.08) (s, 1H), 6.83 (d, $J=8.5$ Hz, 1H), 6.68 (d, $J=4.3$ Hz, 1H), 6.48 (s, 1H), 4.46–4.17 (m, 2H), 3.94 (d, $J=9.8$ Hz, 4H), 3.89 (s, 3H), 3.75 (3.79) (s, 3H), 3.74–3.71 (m, 1H), 3.46 (ddd, $J=14.1$, 11.6, 4.5 Hz, 1H), 3.05 (ddt, $J=17.4$, 11.5, 6.7 Hz, 1H), 2.86 (ddd, $J=16.4$, 4.5, 2.2 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.01, 160.39, 148.74, 148.25, 138.14, 134.89, 134.24, 134.12, 131.76, 129.84, 126.90, 126.05, 125.83, 120.75 (d, $^1J_{\text{CF}}=269.6$ Hz), 116.54, 111.54, 110.70, 55.97, 55.95, 53.48, 41.74, 39.61, 39.31, 28.36, 26.89. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{24}\text{Cl}_2\text{F}_3\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 571.1127, found 571.1141.

N-(2-(1-(2,4-Dichlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-2-methyl-4-(trifluoromethyl)thiazole-5-carboxamide (A32): white solid, yield 88%, mp 115–117 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.48 (d, $J=27.3$ Hz, 1H), 7.41 (d, $J=21.8$ Hz, 1H), 7.16 (dd, $J=23.2$, 8.5 Hz, 1H), 6.91 (6.69) (s, 1H), 6.83 (d, $J=8.3$ Hz, 1H), 6.68 (s, 1H), 6.48 (6.06) (s, 1H), 4.32 (4.70–4.37) (d, $J=3.9$ Hz, 2H), 3.90 (s, 3H), 3.76 (3.80) (s, 3H), 3.75–3.69 (m, 1H), 3.47 (td, $J=14.4$, 13.1, 4.5 Hz, 1H), 3.13–3.00 (m, 1H), 2.90–2.85 (m, 1H), 2.75 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 167.96, 165.77, 158.63, 148.68,

148.18, 137.70, 134.99, 134.44, 134.24, 131.95 (132.07), 129.97 (130.11), 127.43, 126.90, 125.85, 125.60, 120.12 (d, $^1J_{\text{CF}} = 270.8$ Hz), 111.33 (111.74), 110.49 (109.98), 55.95, 53.46, 42.46 (42.75), 39.10 (37.35), 28.32 (26.91), 19.22. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{23}\text{Cl}_2\text{F}_3\text{N}_3\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ 588.0738, found 588.0743.

X-ray diffraction

Compound **A5** was recrystallized by slow evaporation from a solution of tetrahydrofuran to afford a single crystal suitable for X-ray crystallography for structure validation. A crystal structure was performed on a Rigaku XtaLAB P200 diffractometer. The crystal was kept at 138.15 K during data collection. Using Olex2 [23], the structure was solved with the SHELXT [24] structure solution program using Intrinsic Phasing and refined with the SHELXL [25] refinement package using Least Squares minimisation. Optimization of thermal ellipsoid diagram of crystal is done by ORTEP-3 [26]. The crystallographic data of **A5** can be downloaded from the CCDC and the Supporting Information.

Antifungal activity assay

The in vitro activity of the target compounds **A1–A32** against *Rhizoctonia cerealis*, *Physalospora piricola*, *Fusarium graminearum*, *Colletotrichum lagenarium* *Botrytis Cinerea*, and *Alternaria alternata* were tested at 50 mg/L by mycelial growth rate method [27, 28]. Chlorothalonil and boscalid were used as positive controls. The in vivo fungicidal activity against *Alternaria alternata* was evaluated at 50 mg/L and 100 mg/L on fragrant Pear. Boscalid as the positive control. Drugs showing excellent activity at 50 mg/L concentration were tested for in vitro inhibitory activity at concentrations of 100, 50, 25, 12.5, and 6.25 mg/L and their EC_{50} values were calculated.

Enzymatic assay

Experiments were performed as described previously with modification [29]. Compound **A13** was selected for evaluation, with Boscalid, a well-known SDHI, serving as the positive control. *A. alternata* was chosen as the fungal test organism. The activity of SDH was tested by using an enzyme activity detection kit (Bioss Antibodies Co., Ltd., China).

Calculation of molecular properties and drug-likeness evaluation

Molinspiration was used to calculate the main physical and chemical properties of the target compounds, such as the relative molecular weight, LogP (octanol/water partition

coefficient), number of hydrogen bond donors and acceptors, and number of rotatable bonds [30]. ADMET lap was used to calculate the drug-likeness of the target compounds [31].

Molecular electrostatic potential analysis

Compound **A13** was selected for the molecular electrostatic potential analysis by density functional theory (DFT) method via Gaussian 09. The optimization of molecular conformation was carried out by the B3LYP method at 6-31G(d,p) level, and electrostatic potential calculation was based on the optimized structure [32].

Molecular docking

Molecular docking simulation was performed by the CDOCKER module on AutoDock Vina1.1.2. The structures of the chose molecular was optimized and manually docked into the active site in porcine heart mitochondrial SDH from the RCSB Protein Data Bank (PDB ID: 2FBW). The crystal structure of SDH, compound **A13**, and positive control boscalid were treated according to standard procedures [33–35]. Protein receptor was converted and saved into pdbqt after the addition of hydrogen atoms and Kollman charges (4.0). For **A13**, Gasteiger charges (− 0.03) were added and saved in pdbqt format. The molecular docking grid was generated around the active site residues, which was identified as center_x: 21.325, center_y: 32.09, and center_z: 24.106 with dimensions size_x: 68.0, size_y: 118.0, and size_z: 74.0. The molecular docking results were analyzed and displayed by PyMol 2.5. Final visualization was achieved using Discovery Studio software.

SEM analysis

Mycelial morphology was made using scanning electron microscopy (SEM) technology according to previously reported methods [36]. The *A. alternata* mycelial cakes were cut from a PDA medium containing compound **A13** (including 0.1% DMSO) at a 25 mg/L concentration. The mycelial cakes containing the same amount of DMSO were used as blank controls. Following the treatment according to the literature procedure, the mycelial morphology was observed under the scanning electron microscope.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11030-024-11012-6>.

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Author contribution W. Chen, and Y. Chen conceived and designed the study; Y. Chen, Y.X. Jin, L.Y. Wang, W.X. Wang and H.P. Zhou performed the experiments, analyzed the data for all compounds; W. Chen and Y. Chen co-wrote the paper.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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