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Discovery of a Novel Series of Tricyclic Oxadiazine 4a-Methyl Esters Based on Indoxacarb as Potential Sodium Channel Blocker/ Modulator insecticides

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ABSTRACT: Indoxacarb, a commercialized oxadiazine insecticide, nearly irreversibly blocks open/inactivated, but not resting sodium channels. The structure-activity relationships showed that the substituents at the position of the chiral atom in the oxadiazine ring is very important to the biological activity of oxadiazine insecticide. Here we synthesized a series of tricyclic oxadiazine 4a-methyl ester derivatives. The chiral atom in the oxadiazine ring has been epimerized and substituted with either pyrethric acid or cinnamic acid derivatives. Benzene ring in the tricyclic moiety was substituted with a chlorine, fluorine or bromine atom and nitrogen-linked benzene ring was substituted with a trifluoromethyl or trifluoromethoxy group. Toxicity of these compounds against *Spodoptera litura* F. was evaluated. Diastereoisomers of most toxic compounds J7 and J9 with pyrethric acid moiety were separated by flash column chromatography. The more polar diastereoisomers, J7-L-Rf and J9-L-Rf, and compounds J24 and J26 with cinnamic acid moiety exhibited highest insecticidal activities. We further used Monte Carlo energy minimizations to dock compound J7 and J24 in the NavMs-based homology model of the open cockroach sodium channel. In the low-energy binding modes, the compound interacted with residues in the inner pore and domain interfaces, which previously were proposed to contribute to receptors of pyrethroids and sodium channel blocker insecticides. Our results define compound J7 and J24 as a potentially useful optimized hit for the development of multiple sites sodium channel blocker and/or modulator.

KEYWORDS: indoxacarb derivatives; insecticidal activity; structure activity relationship (SAR); sodium channel; docking study

INTRODUCTION

With the growing demand for agricultural products for the rising global population, control of weeds, pathogens and insect pests remains a constant and critical need.[1] However, increasing resistance of insect pests to currently used insecticides limits the arsenal of pesticides suitable for pest control.[2] Therefore, development of new insecticides with novel modes of action is desirable.[3,4]

Indoxacarb (Figure 1), an oxadiazine insecticide, is the first commercialized pyrazoline–type sodium-channel blocker.[4] Metaflumizone (Figure 1), a semi–carbazone insecticide, is the first sodium channel blocker insecticide in the animal health market.[5] These compounds represent a class of sodium channel blocker insecticides (SCBIs) with favorable environmental and toxicological properties.[6] The molecular mechanisms of action and selective toxicity of these compounds have been studied.[6-9] Indoxacarb and metaflumizone cause a voltage–dependent, nearly irreversible block in the inactivated channels by selectively targeting recovery from the slow inactivation, thus preventing transition to the closed state after a prolonged membrane depolarization.[10,11] SCBIs bind at a receptor site in voltage–gated sodium channels, which overlaps with the binding site for local anesthetic/anticonvulsant and exhibit selective toxicity between pest insects and mammals.[12]

Voltage-gated sodium channels are transmembrane proteins that play key roles in the action potential initiation and propagation in excitable cells, including neurons. Following membrane depolarization, sodium channels open and permeate sodium ions into the cell, causing membrane depolarization. A few milliseconds after opening, the channels inactivate, the process playing an important role in the action potential termination. The pore-forming α1-subunit, which folds from a single polypeptide, has four homologous repeat domains. Every repeat domain contains six transmembrane segments (S1–S6) connected by intracellular and extracellular loops, including large extracellular membrane-reentering P-loops between S5 and S6. A P-loop has membrane-descending helix P1, membrane-ascending helix P2 and residues between P1-P2 that contribute to the selectivity filter. In each domain, segments S1–S4 form a voltage-sensing module, while S5, S6 and P-loop contribute a quarter to the pore module.

Mutational analysis and computational modeling suggest that SCBIs bind in the inner pore and

extend their trifluoromethoxy-phenyl moiety into the III/IV domain interface, while the common fragment C=N–NH–C=O chelates a sodium ion at the focus of P1 helices to form the energetically preferable 5–membered ring.[13-15] Another class of sodium-channel targeting insecticides, pyrethroids, promote the channel activation and inhibit inactivation, resulting in prolonged channel openings.[16,17] Pyrethroids bind to two analogous receptor sites on sodium channels, which are distinct from the receptor site of SCBIs.[18,19] Pyrethroids and SCBIs showed little cross-resistance in pest insects.[20,21]

Fragment–based drug discovery (FBDD) revolutionized development of new drugs. Many leads with dual/multi–target or novel mode of action were developed with FBDD.[22-26] Both pyrethroids and SCBIs affect sodium channel inactivation, but the action details are different. Pyrethroids inhibit fast inactivation, while SCBIs inhibit recovery from the fast and slow inactivation.

Cinnamic acid and its esters show diverse biological activities such as leishmanicidal, insecticidal, acaricidal and antimicrobial properties.[27-31] The wide ranges of biological applications have intrigued considerable attention of synthetic chemists to design and synthesize diverse cinnamic acid derivatives. [27,28]

In our previous work, we found that the presence of strong electron-withdrawing group in 5-position of the indanone ring of indoxacarb derivatives could enhance insecticidal activity and cockroach sodium channel variant (BgNav1-1a) inhibitory activity.[32] Based on these reports, a new series of tricyclic oxadiazine 4a-methyl ester derivatives were designed and synthesized by introducing the cinnamic or pyrethric acid moiety at the position of the chiral atom in the oxadiazine ring, and their insecticidal activities against *S. litura* F. were evaluated. The binding activities of compounds J7 and J24 into the sodium channel model were also studied by molecular docking investigations, which proposed structural models of sodium channel complexes with most potent compounds.

MATERIALS AND METHODS

Chemicals and instruments

Starting materials and reagents were all analytically or chemically pure. All anhydrous solvents reagents were dried by standard methods in advance. The melting points were determined on an YRT-3 melting point apparatus (P.I.T TIANJING UNVERSITY) without calibration. Yields were not optimized. NMR spectra were obtained on Bruker AV-600 instrument. Chemical shifts were expressed in parts per million (ppm) with TMS as internal standard. High-resolution mass spectra

(HRMS) of ultimate target compounds were obtain by Bruker maxis 4G ESI-Q-TOF. Data were reported as m/z. Analytical thin layer chromatography (TLC) was performed on silica gel GF254. Flash chromatography was performed with silica gel (200–300 mesh and 300–400 mesh).

Preparation of Compounds B–G. Compounds B–G were synthesized referring to the methods reported in the literature.[32] The melting point and ^{1}H NMR data were consistent with the literature.

General Methods for Synthesis of Compounds H1–H6. In an ice bath, a solution of compound G1-G6 (2 mmol, 1 eq) in anhydrous tetrahydrofuran (THF) (10 mL) was added dropwise to a suspension of $LiAlH_4$ (38 mg, 1 mmol, 1 eq) and anhydrous THF (5 mL) under argon. The TLC assay was supplemented with $LiAlH_4$ (18 mg, 0.5 mmol, 0.25 eq) until the reactant consumption was complete. Then, the mixture was stirred at room temperature for 2 h and adjusted pH to 2–3 with 1 M HCl. The organic layers were collected and washed with brine (3 × 30 mL), dried over $MgSO_4$, filtered and concentrated in vacuum for silica gel (200–300 mesh) column chromatography (petroleum ether/ethyl acetate= 2:1, v/v) to give the desired products H1–H6.

***7-chloro-4a-(hydroxymethyl)-N-(4-(trifluoromethyl)phenyl)-4a,5-dihydroindeno[1,2-e][1,3,4]oxadiazine-2(3H)-carboxamide* (H1).** ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.53 (s, 1H, NH), 7.68 (s, 1H, phenyl), 7.65 (d, J = 8.4 Hz, 2H, phenyl), 7.60 (d, J = 8.6 Hz, 2H, phenyl), 7.38 (d, J = 11.2 Hz, 2H, phenyl), 5.57 (d, J = 9.2 Hz, 1H, oxadiazine), 5.25 (d, J = 9.1 Hz, 1H, oxadiazine), 3.82 (d, J = 13.2 Hz, 1H, cyclopentane), 3.62 (d, J = 12.1 Hz, 1H, cyclopentane), 3.34 (d, J = 15.8 Hz, 1H, CH_2), 3.06 (d, J = 15.6 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 156.16 (CONH), 151.70 (oxadiazine-CN), 144.72 (phenyl-C), 140.99 (phenyl-C), 137.76 (phenyl-C), 132.35 (phenyl-C), 128.74 (phenyl-C), 126.55 (phenyl-C), 126.27 (phenyl-C), 125.42 (phenyl-C), 125.20 (CF_3), 123.30 (phenyl-C), 118.84 (phenyl-C), 81.45 (oxadiazine-C), 69.83 (oxadiazine-CH_2), 64.67 (CH_2OH), 38.46 (cyclopentane-CH_2).

***7-chloro-4a-(hydroxymethyl)-N-(4-(trifluoromethoxy)phenyl)-4a,5-dihydroindeno[1,2-e][1,3,4]oxadiazine-2(3H)-carboxamide* (H2).** ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.40 (s, 1H, NH), 7.60 (d, *J* = 8.2 Hz, 1H, phenyl), 7.52 (d, *J* = 9.0 Hz, 2H, phenyl), 7.33 (d, *J* = 8.2 Hz, 1H, phenyl), 7.31 (s, 1H, phenyl), 7.16 (d, *J* = 8.4 Hz, 2H, phenyl), 5.52 (d, *J* = 9.1 Hz, 1H, oxadiazine), 5.22 (dd, *J* = 9.1, 1.5 Hz, 1H, oxadiazine), 3.77 (d, *J* = 12.1 Hz, 1H, cyclopentane), 3.57 (d, *J* = 12.1 Hz, 1H, cyclopentane), 3.28 (dd, *J* = 15.8, 2.8 Hz, 1H, CH_2), 3.00 (d, *J* = 15.8 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 156.21 (CONH), 151.70 (oxadiazine-CN), 144.90 (phenyl-C), 137.72 (phenyl-C), 136.63 (phenyl-C), 132.60 (phenyl-C), 128.84 (phenyl-C), 126.63 (phenyl-

C), 122.81(phenyl-C), 121.90 (OCF_3), 120.82 (phenyl-C), 120.84 (phenyl-C), 81.62 (oxadiazine-C), 69.91 (oxadiazine-CH_2), 64.50 (CH_2OH), 38.52 (cyclopentane-CH_2)

7-bromo-4a-(hydroxymethyl)-N-(4-(trifluoromethyl)phenyl)-4a,5-dihydroindeno[1,2-e][1,3,4]oxadiazine-2(3H)-carboxamide **(H3).** ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.39 (s, 1H, NH), 7.58 (d, J = 9.2 Hz, 2H, phenyl), 7.55 (s, 1H, phenyl), 7.53 (d, J = 3.5 Hz, 2H, phenyl), 7.20 (d, J = 8.7 Hz, 2H, phenyl), 5.55 (d, J = 9.1 Hz, 1H, oxadiazine), 5.23 (d, J = 9.1 Hz, 1H, oxadiazine), 3.81 (d, J = 13.1 Hz, 1H, cyclopentane), 3.61 (d, J = 12.1 Hz, 1H, cyclopentane), 3.34 (d, J = 15.8 Hz, 1H, CH_2), 3.06 (d, J = 15.7 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 156.05 (CONH), 151.44 (oxadiazine-CN), 144.88 (phenyl-C), 136.48 (phenyl-C), 132.89 (phenyl-C), 131.55 (phenyl-C), 129.51 (phenyl-C), 125.95 (phenyl-C), 122.94 (phenyl-C), 121.79 (phenyl-C), 121.36 (CF_3), 120.59 (phenyl-C), 119.66 (phenyl-C), 81.38 (oxadiazine-C), 69.87 (oxadiazine-CH_2), 64.65 (CH_2OH), 38.39 (cyclopentane-CH_2).

7-bromo-4a-(hydroxymethyl)-N-(4-(trifluoromethoxy)phenyl)-4a,5-dihydroindeno[1,2-e][1,3,4]oxadiazine-2(3H)-carboxamide **(H4).** ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.42 (s, 1H, NH), 7.54 (d, J = 9.3 Hz, 2H, phenyl), 7.52 (s, 1H, phenyl), 7.50 (s, 2H, phenyl), 7.17 (d, J = 8.7 Hz, 2H, phenyl), 5.51 (d, J = 9.1 Hz, 1H, oxadiazine), 5.25 (d, J = 9.2 Hz, 1H, oxadiazine), 3.78 (d, J = 12.1 Hz, 1H, cyclopentane), 3.58 (d, J = 11.8 Hz, 1H, cyclopentane), 3.29 (d, J = 15.8 Hz, 1H, CH_2), 3.00 (d, J = 15.7 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 155.99 (CONH), 151.59 (oxadiazine-CN), 144.95 (phenyl-C), 136.43 (phenyl-C), 132.95 (phenyl-C), 131.49 (phenyl-C), 129.46 (phenyl-C), 125.87 (phenyl-C), 122.92 (phenyl-C), 121.75 (phenyl-C), 121.36(OCF_3), 121.09 (phenyl-C), 120.70 (phenyl-C), 81.43 (oxadiazine-C), 69.77 (oxadiazine-CH_2), 64.30 (CH_2OH), 38.38 (cyclopentane-CH_2).

7-fluoro-4a-(hydroxymethyl)-N-(4-(trifluoromethyl)phenyl)-4a,5-dihydroindeno-[1,2-e][1,3,4]oxadiazine-2(3H)-carboxamide **(H5).** ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.53 (s, 1H, NH), 7.68 (dd, *J* = 8.4, 5.1 Hz, 1H, phenyl), 7.64 (d, *J* = 8.6 Hz, 2H, phenyl), 7.57 (d, *J* = 8.6 Hz, 2H, phenyl), 7.08 (dt, *J* = 8.8, 2.0 Hz, 1H, phenyl), 7.04 (d, *J* = 8.3 Hz, 1H, phenyl), 5.55 (d, *J* = 9.1 Hz, 1H, oxadiazine 5.19 (d, *J* = 9.1 Hz, 1H, oxadiazine), 3.78 (dd, *J* = 12.1, 1.0 Hz, 1H, cyclopentane), 3.60 (d, *J* = 12.1 Hz, 1H, cyclopentane), 3.32 (d, *J* = 15.8 Hz, 1H, CH_2), 3.04 (d, *J* = 15.8 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.11 (CONH), 164.43 (oxadiazine-CN), 156.72 (phenyl-C), 151.50 (phenyl-C), 145.81 (phenyl-C), 141.22 (phenyl-C), 126.43 (phenyl-C), 125.50 (phenyl-C), 123.73 (phenyl-C), 123.41 (phenyl-C), 119.00 (CF_3), 116.13

(phenyl-C), 113.60 (phenyl-C), 81.71 (oxadiazine-C), 69.97 (oxadiazine-CH_2), 64.91 (CH_2OH), 38.73 (cyclopentane-CH_2).

7-fluoro-4a-(hydroxymethyl)-N-(4-(trifluoromethoxy)phenyl)-4a,5-dihydroindeno[1,2-e][1,3,4]oxadiazine-2(3H)-carboxamide **(H6).** ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.44 (s, 1H, NH), 7.65 (dd, J = 8.5, 5.0 Hz, 1H, phenyl), 7.51 (d, J = 8.9 Hz, 2H, phenyl), 7.14 (d, J = 8.6 Hz, 2H, phenyl), 7.04 (t, J = 8.7 Hz, 1H, phenyl), 7.00 (d, J = 8.1 Hz, 1H, phenyl), 5.51 (d, J = 9.1 Hz, 1H, oxadiazine), 5.21 (d, J = 9.1 Hz, 1H, oxadiazine), 3.76 (d, J = 12.0 Hz, 1H, cyclopentane), 3.55 (dd, J = 11.9, 6.3 Hz, 1H, cyclopentane), 3.28 (d, J = 15.8 Hz, 1H, CH_2), 2.98 (d, J = 15.8 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 165.81 (CONH), 164.14 (oxadiazine-CN), 156.27 (phenyl-C), 151.73 (phenyl-C), 145.77 (phenyl-C), 144.83 (phenyl-C), 136.52 (phenyl-C), 130.00 (phenyl-C), 123.45 (phenyl-C), 121.69 (phenyl-C), 120.68 (OCF_3), 115.89 (phenyl-C), 113.46 (phenyl-C), 81.60 (oxadiazine-C), 69.73 (oxadiazine-CH_2), 64.22 (CH_2OH), 38.80 (cyclopentane-CH_2).

General synthetic procedure for compounds J1–J34. In an ice bath, acyl chloride (3 mmol, 3 eq) was added to a solution of compound H (1 mmol, 1 eq), dimethylaminopyridine (DMAP), dry diisopropylethylamine (DIPEA) (0.42 mL, 3 mmol, 3 eq) in anhydrous THF (5 mL) under an argon atmosphere. After 2 h, the organic layers were collected and washed with ice-cold sodium hydroxide solution (3 × 30 mL), collected with ethyl acetate (3 × 15 mL) and dried over $MgSO_4$, filtered and concentrated in vacuum for silica gel (300–400 mesh) column chromatography (petroleum ether/ethyl acetate = 8:1, v/v) to give the desired products J1-J34.

(7-chloro-2-((4-(trifluoromethyl)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate **(J1). J1-H-Rf(Higher Rf value compd)** Yield: 37.5%; white solid: mp 87–88 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.54 (s, 1H, NH), 7.68 (d, *J* = 8.6 Hz, 2H, phenyl), 7.64 – 7.58 (m, 3H, phenyl), 7.39 (d, *J* = 8.2 Hz, 1H, phenyl), 7.37 (s, 1H, phenyl), 6.16 (d, *J* = 9.0 Hz, 1H, vinyl), 5.58 (d, *J* = 9.5 Hz, 1H, oxadiazine), 5.43 (d, *J* = 9.5 Hz, 1H, oxadiazine), 4.52 (d, *J* = 13.2 Hz, 1H, cyclopentane), 4.10 (d, *J* = 12.3 Hz, 1H, cyclopentane), 3.33 (d, *J* = 15.8 Hz, 1H, CH_2), 3.12 (d, *J* = 15.8 Hz, 1H, CH_2), 2.05 (t, *J* = 8.7 Hz, 1H, cyclopropane), 1.78 (d, *J* = 8.5 Hz, 1H, cyclopropane), 1.24 (s, 3H, CH_3), 1.21 (s, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.75 (O=C-O), 152.87 (CONH), 151.14 (oxadiazine-CN), 144.85 (phenyl-C), 144.07 (phenyl-C), 137.46 (C=C), 132.77 (phenyl-C), 128.83 (C=C), 126.33 (phenyl-C), 124.39 (CF_3), 122.60

(phenyl-C), 121.82 (phenyl-C), 121.37 (phenyl-C), 121.14 (phenyl-C), 120.50 (phenyl-C), 119.66 (phenyl-C), 79.14 (oxadiazine-CN), 69.36 (oxadiazine-CH_2), 63.68 (CH_2OH), 39.33 (cyclopentane-CH_2), 33.03 (cyclopropane-C), 31.41 (cyclopropane-C), 29.70 (cyclopropane-$C(Me)_2$), 28.23 (CH_3), 28.09 (CH_3), 14.81. **J1-L-Rf (Lower Rf value compd)** Yield: 45.8%; white solid: mp 104–106 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.39 (d, *J* = 6.3 Hz, 1H, NH), 7.61 (dd, *J* = 12.1, 8.1 Hz, 1H, phenyl), 7.57 (dd, *J* = 9.0, 3.6 Hz, 2H, phenyl), 7.40 – 7.33 (m, 2H, phenyl), 7.20 (d, *J* = 8.6 Hz, 2H, phenyl), 5.57 – 5.52 (m, 1H, vinyl), 5.52 – 5.46 (m, 1H, oxadiazine), 5.46 – 5.40 (m, 1H, oxadiazine), 4.54 – 4.46 (m, 1H, cyclopentane), 4.19 – 4.10 (m, 1H, cyclopentane), 3.37 – 3.23 (m, 1H, CH_2), 3.12 (dd, *J* = 15.8, 4.0 Hz, 1H, CH_2), 2.19 (dt, *J* = 8.5, 4.9 Hz, 1H, cyclopropane), 1.53 (dd, *J* = 16.8, 5.3 Hz, 1H, cyclopropane), 1.25 (d, *J* = 3.7 Hz, 2H, CH_3), 1.21 (s, 1H, CH_3), 1.20 (s, 1H, CH_3), 1.15 (d, *J* = 3.0 Hz, 2H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.64 (O=C-O), 153.00 (CONH), 151.13 (oxadiazine-CN), 144.83 (phenyl-C), 143.93 (phenyl-C), 136.53 (C=C), 132.77 (phenyl-C), 132.66 (phenyl-C), 128.86 (C=C), 126.47 (phenyl-C), 126.27 (phenyl-C, 124.48 (CF_3), 122.73 (phenyl-C), 122.69 (phenyl-C), 122.59 (phenyl-C), 121.81 (phenyl-C), 120.50 (phenyl-C), 79.15 (oxadiazine-CN), 69.53 (oxadiazine-CH_2), 64.43 (CH_2O), 39.35 (cyclopentane-CH_2), 33.37(cyclopropane-C), 33.01(cyclopropane-C), 29.48 (cyclopropane-$C(Me)_2$), 28.20 (CH_3), 22.43 (CH_3), 19.97. HRMS (ESI-TOF) m/z: calcd for $C_{27}H_{23}F_3Cl_3N_3O_4$ $[M + CH_3CN]^+$ 654.0782; found 654.0763.

***7-chloro-2-((4-(trifluoromethoxy)phenyl)carbamoyl-2,5-tetrahydroindeno [1,2-e][1,3,4]oxadiazin-4a-yl)methyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylate* (J2). J2-H-Rf (Higher Rf value compd)** Yield: 35.5%; white solid: mp 130–131 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.37 (s, 1H, NH), 7.58 (d, J = 8.1 Hz, 1H, phenyl), 7.57–7.54 (m, 2H, phenyl), 7.36 (d, J = 8.2 Hz, 1H, phenyl), 7.35 (s, 1H, phenyl), 7.19 (d, J = 8.4 Hz, 2H, phenyl), 6.15 (d, J = 9.0 Hz, 1H, vinyl), 5.53 (d, J = 9.5 Hz, 1H, oxadiazine), 5.41 (d, J = 9.5 Hz, 1H, oxadiazine), 4.49 (dd, J = 12.3, 1.3 Hz, 1H, cyclopentane), 4.08 (d, J = 12.3 Hz, 1H, cyclopentane), 3.31 (d, J = 15.8 Hz, 1H, CH_2), 3.10 (d, J = 16.3 Hz, 1H, CH_2), 2.03 (t, J = 8.7 Hz, 1H, cyclopropane), 1.76 (d, J = 8.5 Hz, 1H, cyclopropane), 1.22 (s, 3H, CH_3), 1.20 (s, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.92 (O=C-O), 152.99 (CONH), 151.29 (oxadiazine-CN), 145.00 (phenyl-C), 144.99 (phenyl-C), 144.23 (phenyl-C), 137.62 (C=C), 136.69 (phenyl-C), 132.92 (phenyl-C), 128.99 (C=C), 126.49 (phenyl-C), 124.54 (CF_3), 122.77 (phenyl-C), 121.99 (phenyl-C), 121.28 (phenyl-C), 79.29 (oxadiazine-CN), 69.50 (oxadiazine-CH_2), 63.82 (CH_2O),

39.48 (cyclopentane-CH_2), 33.19 (cyclopropane-C), 31.56 (cyclopropane-C), 33.53 (cyclopropane-C(Me)$_2$), 28.38 (CH_3), 28.26 (CH_3), 14.95. **J2-L-Rf (Lower Rf value compd)** Yield: 53.6%; white solid: mp 85–86 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.37 (d, *J* = 6.2 Hz, 1H, NH), 7.59 (dd, *J* = 12.4, 8.1 Hz, 1H, phenyl), 7.56 (dd, *J* = 9.0, 3.7 Hz, 2H, phenyl), 7.38 – 7.33 (m, 2H, phenyl), 7.19 (d, *J* = 8.7 Hz, 2H, phenyl), 5.54 (dd, *J* = 8.2, 5.8 Hz, 1H, vinyl), 5.50 (dd, *J* = 15.2, 9.5 Hz, 1H, oxadiazine), 5.42 (dd, *J* = 11.9, 9.5 Hz, 1H, oxadiazine), 4.49 (dd, *J* = 14.8, 12.8 Hz, 1H, cyclopentane), 4.14 (dd, *J* = 12.3, 5.4 Hz, 1H, cyclopentane), 3.35 – 3.24 (m, 1H, CH_2), 3.11 (dd, *J* = 15.8, 3.9 Hz, 1H, CH_2), 2.17 (td, *J* = 8.8, 5.4 Hz, 1H, cyclopropane), 1.52 (dd, *J* = 16.4, 5.3 Hz, 1H, cyclopropane), 1.24 (d, *J* = 3.8 Hz, 3H, CH_3), 1.14 (d, *J* = 3.0 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 170.60 (O=C-O), 153.29 (CONH), 153.10 (oxadiazine-CN), 144.96 (phenyl-C), 144.26 (phenyl-C), 137.63 (C=C), 132.91 (phenyl-C), 132.80 (phenyl-C), 129.00 (phenyl-C), 128.95 (phenyl-C), 126.65 (CF_3), 126.61 (phenyl-C), 122.83 (phenyl-C), 122.73 (phenyl-C), 122.52 (phenyl-C), 121.96 (phenyl-C), 120.62 (phenyl-C), 79.38 (oxadiazine-CN), 69.54 (oxadiazine-CH_2), 64.13 (CH_2O), 39.51 (cyclopentane-CH_2), 34.36 (cyclopropane-C), 33.51 (cyclopropane-C), 33.50 (cyclopropane-C(Me)$_2$), 29.66 (CH_3), 29.61 (CH_3). HRMS (ESI-TOF) m/z: calcd for $C_{22}H_{20}F_3N_3O_7$ $[M + Na]^+$ 654.0548; found 654.0546.

***(7-bromo-2-((4-(trifluoromethyl)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate* (J3). J3-H-Rf (Higher Rf value compd)** Yield: 45.6%; white solid: mp 80–81 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.53 (d, J = 8.5 Hz, 1H, NH), 7.68 (dd, J = 8.7, 3.3 Hz, 2H, phenyl), 7.60 (d, J = 8.5 Hz, 2H, phenyl), 7.57 – 7.50 (m, 3H, phenyl), 6.15 (dd, J = 17.1, 9.0 Hz, 1H, vinyl), 5.58 (d, J = 9.8 Hz, 1H, oxadiazine), 5.57 – 5.52 (m, 1H, oxadiazine), 5.48 – 5.40 (m, 1H, cyclopentane), 4.52 (ddd, J = 12.4, 5.0, 1.4 Hz, 1H, cyclopentane), 4.18 – 4.07 (m, 1H, CH_2), 3.38 – 3.24 (m, 1H, CH_2), 3.16 – 3.09 (m, 1H, cyclopropane), 2.07 – 2.01 (m, 1H, cyclopropane), 1.78 (d, J = 9.8 Hz, 1H, CH_3), 1.27 – 1.25 (m, 2H, CH_3), 1.24 (s, 1H, CH_3), 1.22 – 1.20 (m, 2H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.74 (O=C-O), 153.03 (CONH), 150.86 (oxadiazine-CN), 144.11 (phenyl-C), 141.00 (phenyl-C), 137.57 (C=C), 132.68 (phenyl-C), 128.86 (C=C), 126.35 (phenyl-C), 126.30 (phenyl-C), 125.37 (phenyl-C), 125.10 (phenyl-C), 124.37 (CF_3), 122.65 (phenyl-C), 121.16 (phenyl-C), 118.76 (phenyl-C), 79.15 (oxadiazine-CN), 69.34 (oxadiazine-CH_2), 63.64 (CH_2O), 39.34 (cyclopentane-CH_2), 33.05 (cyclopropane-C), 31.41 (cyclopropane-C), 29.70 (CH_3), 28.23 (CH_3). **J3-L-Rf (Lower Rf value compd)** Yield: 29.4%;

white solid: mp 111–112 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.55 – 8.36 (m, 1H, NH), 7.67 (dd, *J* = 8.6, 3.4 Hz, 1H, phenyl), 7.60 – 7.55 (m, 2H, phenyl), 7.55 – 7.49 (m, 3H, phenyl), 7.19 (d, *J* = 8.8 Hz, 1H, phenyl), 5.53 (dd, *J* = 9.6, 3.0 Hz, 1H, vinyl), 5.41 (dd, *J* = 9.5, 3.7 Hz, 1H, oxadiazine), 4.57 – 4.48 (m, 1H, oxadiazine), 4.14 – 4.09 (m, 1H, cyclopentane), 3.32 (dd, *J* = 15.8, 3.8 Hz, 1H, cyclopentane), 3.11 (d, *J* = 15.9 Hz, 1H, CH_2), 2.17 (t, *J* = 9.0 Hz, 1H, CH_2), 1.91 (d, *J* = 8.3 Hz, 1H, cyclopropane), 1.77 (d, *J* = 8.5 Hz, 1H, cyclopropane), 1.27 (d, *J* = 5.9 Hz, 3H, CH_3), 1.26 (d, *J* = 5.2 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.43 (O=C-O), 153.12 (CONH), 151.14 (oxadiazine-CN), 144.07 (phenyl-C), 136.53 (C=C), 133.12 (phenyl-C), 131.75 (phenyl-C), 129.60 (C=C), 129.57 (phenyl-C), 129.27 (phenyl-C), 125.77 (phenyl-C), 122.88 (CF_3), 121.81 (phenyl-C), 120.46 (phenyl-C), 79.23 (oxadiazine-CN), 69.55 (oxadiazine-CH_2), 64.61 (CH_2O), 39.24 (cyclopentane-CH_2), 31.25 (cyclopropane-C), 29.70 (CH_3), 28.19 (CH_3). HRMS (ESI-TOF) m/z: calcd for $C_{27}H_{23}F_3B_rCl_2N_3O_4$ [M + Na] $^{+}$ 682.0093; found 682.0105.

***(7-bromo-2-((4-(trifluoromethyl)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate* (J4). J4-H-Rf (Higher Rf value compd)** Yield: 36.4%; white solid: mp 74–76 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.54 (s, 1H, NH), 7.68 (d, J = 8.6 Hz, 2H, phenyl), 7.64 – 7.58 (m, 3H, phenyl), 7.39 (d, J = 8.2 Hz, 1H, phenyl), 7.37 (s, 1H, phenyl), 6.16 (d, J = 9.0 Hz, 1H, vinyl), 5.58 (d, J = 9.5 Hz, 1H, oxadiazine), 5.43 (d, J = 9.5 Hz, 1H, oxadiazine), 4.52 (d, J = 13.2 Hz, 1H, cyclopentane), 4.10 (d, J = 12.3 Hz, 1H, cyclopentane 3.33 (d, J = 15.8 Hz, 1H, CH_2), 3.12 (d, J = 15.8 Hz, 1H, CH_2), 2.05 (t, J = 8.7 Hz, 1H, cyclopropane), 1.78 (d, J = 8.5 Hz, 1H, cyclopropane), 1.24 (s, 3H, CH_3), 1.21 (s, 3H, CH_3).^{13}C NMR (151 MHz, Chloroform-*d*) δ 170.40 (O=C-O), 152.96 (CONH) , 151.08 (oxadiazine-CN) , 144.77 (phenyl-C), 136.60 (C=C), 133.25 (phenyl-C) , 131.66 (phenyl-C) , 131.62 (phenyl-C) , 129.28 (phenyl-C) , 129.21 (C=C) , 126.55 (CF_3), 126.51 (phenyl-C) , 125.71 (phenyl-C), 124.52 (phenyl-C), 122.91 (phenyl-C), 122.87 (phenyl-C), 122.78 (phenyl-C) , 122.50 (CF_3) , 120.45 (phenyl-C), 79.25 (oxadiazine-CN), 69.30 (oxadiazine-CH_2), 64.39 (CH_2O), 39.25 (cyclopentane-CH_2), 34.23 (cyclopropane-C), 34.13 (cyclopropane-C), 29.48 (cyclopropane-$C(Me)_2$), 27.99 (CH_3), 22.39 (CH_3). **J4-L-Rf (Lower Rf value compd)** Yield: 48.8%; white solid: mp 112–113 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.53 (s, 1H, NH), 7.68 (d, *J* = 8.5 Hz, 2H, phenyl), 7.60 (d, *J* = 8.6 Hz, 2H, phenyl), 7.54 (d, *J* = 6.0 Hz, 3H, phenyl), 6.16 (d, *J* = 9.0 Hz, 1H, vinyl), 5.62 (d, *J* = 8.4 Hz, 1H, oxadiazine), 5.57 (d, *J* = 9.5 Hz,

1H, oxadiazine), 5.43 (d, *J* = 9.5 Hz, 1H, cyclopentane), 4.52 (d, *J* = 13.1 Hz, 1H, cyclopentane), 4.10 (d, *J* = 12.3 Hz, 1H, CH_2), 3.33 (d, *J* = 15.8 Hz, 1H, CH_2), 3.13 (d, *J* = 15.7 Hz, 1H, cyclopropane), 2.24 (dd, *J* = 8.4, 5.4 Hz, 1H, cyclopropane), 1.21 (s, 3H, CH_3), 1.20 (s, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.74 (O=C-O), 153.06 (CONH), 150.86 (oxadiazine-CN), 144.30 (phenyl-C), 140.99 (phenyl-C), 140.98 (phenyl-C), 131.71 (phenyl-C), 129.33 (C=C), 127.12 (phenyl-C), 126.30 (phenyl-C) , 125.84 (phenyl-C), 125.02 (phenyl-C) 124.36 (CF_3), 122.85 (phenyl-C), 118.78 (phenyl-C), 69.33 (oxadiazine-CH_2), 63.62 (CH_2O), 39.26 (cyclopentane-CH_2), 34.87 (cyclopropane-C), 33.05 (cyclopropane-C), 31.40 (cyclopropane-$C(Me)_2$), 28.23 (CH_3) , 28.13 (CH_3). HRMS (ESI-TOF) m/z: calcd for $C_{27}H_{23}F_3B_rCl_2N_3O_5$ [M + CH_3CN]$^+$ 714.0254; found 714.0224.

***7-fluoro-2-((4-(trifluoromethyl)phenyl)carbamoyl-2,5-tetrahydroindeno-[1,2-e][1,3,4]oxadiazin-4a-yl)methyl3-(2,2-dichlorovinyl)2,2-dimethylcyclopropane Carboxylate* (J5). J5-H-Rf (Higher Rf value compd)** Yield: 33.5%; white solid: mp 88–89 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.52 (s, 1H, NH), 7.69–7.64 (m, 3H, phenyl), 7.59 (d, J = 8.6 Hz, 2H, phenyl), 7.09 (dt, J = 8.6, 2.2 Hz, 1H, phenyl), 7.06 (d, J = 8.3 Hz, 1H, phenyl), 6.15 (d, J = 9.0 Hz, 1H, vinyl), 5.52 (d, J = 9.4 Hz, 1H, oxadiazine), 5.43 (d, J = 9.4 Hz, 1H, oxadiazine), 4.49 (dd, J = 12.3, 1.4 Hz, 1H, cyclopentane), 4.10 (d, J = 12.3 Hz, 1H, cyclopentane), 3.32 (d, J = 15.8 Hz, 1H, CH_2), 3.12 (d, J = 15.8 Hz, 1H, CH_2), 2.03 (t, J = 8.7 Hz, 1H, cyclopropane), 1.77 (d, J = 8.5 Hz, 1H, cyclopropane), 1.22 (s, 3H, CH_3), 1.19 (s, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.92 (O=C-O), 165.97 (phenyl-C), 164.30 (phenyl-C), 153.55 (CONH), 151.11 (oxadiazine-CN), 145.24 (phenyl-C), 141.23 (phenyl-C), 130.33 (C=C), 130.31 (C=C), 126.50 (phenyl-C), 126.47 (phenyl-C), 126.45 (phenyl-C), 126.42 (phenyl-C), 125.27 (phenyl-C), 124.55 (phenyl-C), 123.57 (CF_3), 123.51 (phenyl-C), 121.29 (phenyl-C), 118.90 (phenyl-C), 116.31 (phenyl-C), 79.36 (oxadiazine-CN), 69.50 (oxadiazine-CH_2), 63.87 (CH_2O), 39.67 (cyclopentane-CH_2), 33.18 (cyclopropane-C), 31.57 (cyclopropane-C), 28.37 (CH_3), 28.23 (CH_3). HRMS(ESI-TOF) m/z: calcd for $C_{22}H_{20}F_3N_3O_7$ [M + Na]$^+$ 622.0894; found 622.0908. **J5-L-Rf (Lower Rf value compd)** Yield: 54.6%; white solid: mp 100–102 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.51 (d, *J* = 7.3 Hz, 1H, NH), 7.68 (d, *J* = 7.9 Hz, 1H, phenyl), 7.66 (d, *J* = 2.9 Hz, 1H, phenyl), 7.65 (d, *J* = 6.7 Hz, 1H, phenyl), 7.58 (d, *J* = 8.6 Hz, 2H, phenyl), 7.09 (d, *J* = 4.1 Hz, 1H, phenyl), 7.06 (d, *J* = 8.2 Hz, 1H, phenyl), 5.53 (dd, *J* = 15.5, 8.3 Hz, 1H, vinyl), 5.51 – 5.46 (m, 1H, oxadiazine), 5.46 – 5.41 (m, 1H, oxadiazine), 4.49 (dd, *J* = 18.0, 12.3 Hz, 1H, cyclopentane), 4.15 (d, *J* = 12.2 Hz,

1H, cyclopentane), 3.31 (dd, *J* = 28.0, 15.8 Hz, 1H, CH_2), 3.13 (dd, *J* = 15.8, 5.1 Hz, 1H, CH_2), 2.17 (dt, *J* = 8.3, 5.4 Hz, 1H, cyclopropane), 1.52 (dd, *J* = 9.3, 5.3 Hz, 1H) , cyclopropane, 1.24 (d, *J* = 3.1 Hz, 3H, CH_3), 1.13 (d, *J* = 3.0 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 170.63 (O=C-O), 165.98 (phenyl-C), 165.94 (phenyl-C), 164.30 (phenyl-C), 164.28 (phenyl-C), 153.90 (phenyl-C), 153.61 (phenyl-C), 151.08 (oxadiazine-CN), 145.25 (phenyl-C), 145.19 (phenyl-C), 145.16 (phenyl-C), 145.10 (phenyl-C), 141.20 (phenyl-C), 130.32 (phenyl-C), 126.65 (CF_3), 126.49 (phenyl-C), 126.47 (phenyl-C), 126.44 (phenyl-C), 126.42 (phenyl-C), 125.47 (phenyl-C), 125.45 (phenyl-C), 125.26 (phenyl-C), 125.24 (phenyl-C), 123.66 (phenyl-C), 123.60 (phenyl-C), 79.38 (oxadiazine-CN), 69.54 (oxadiazine-CH_2), 64.66 (CH_2O), 39.68 (cyclopentane-CH_2), 34.31 (cyclopropane-C), 33.53 (cyclopropane-C), 29.67 (cyclopropane-$C(Me)_2$), 22.58 (CH_3), 20.11 (CH_3). HRMS (ESI-TOF) m/z: calcd for $C_{22}H_{20}F_3N_3O_7$ $[M + Na]^+$ 622.0894; found 622.0892.

***(7-fluoro-2-((4-(trifluoromethoxy)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate* (J6). J6-H-Rf (Higher Rf value compd)** Yield: 33.2%; white solid: mp 144–146 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.43 – 8.36 (m, 1H, NH), 7.66 (ddd, *J* = 12.2, 8.4, 5.0 Hz, 1H, phenyl), 7.60 – 7.54 (m, 2H, phenyl), 7.22 – 7.17 (m, 2H, phenyl), 7.12 – 7.04 (m, 2H, phenyl), 5.57 – 5.48 (m, 1H, vinyl), 5.47 (d, *J* = 1.2 Hz, 1H, oxadiazine), 5.46 – 5.42 (m, 1H, oxadiazine), 4.56 – 4.43 (m, 1H, cyclopentane), 4.19 – 4.06 (m, 1H, cyclopentane), 3.34 (d, *J*=8.4Hz, 1H, CH_2), 3.13 (d, *J* = 5.3 Hz, 1H, CH_2), 2.04(dd, *J* = 11.0, 5.3 Hz, 1H, cyclopropane), 1.78(d, *J*=6.6Hz, 1H, cyclopropane) 1.25 (d, *J* = 3.5 Hz, 3H, CH_3), 1.19 (d, *J* = 2.3 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.75 (O=C-O), 165.77 (phenyl-C), 164.10 (phenyl-C), 153.30 (CONH), 151.24 (oxadiazine-CN), 145.04 (phenyl-C), 144.84 (phenyl-C), 136.59 (phenyl-C), 130.24 (C=C), 126.95 (phenyl-C), 124.41 (phenyl-C), 123.28 (CF_3), 121.78 (phenyl-C), 121.71 (phenyl-C), 121.13 (phenyl-C), 120.50 (phenyl-C), 116.10 (phenyl-C), 79.21 (oxadiazine-CN), 69.38 (oxadiazine-CH_2), 63.77 (CH_2O), 39.53 (cyclopentane-CH_2), 33.01 (cyclopropane-C), 31.43 (cyclopropane-C), 28.21 (CH_3), 22.42 (CH_3). **J6-L-Rf (Lower Rf value compd)** Yield: 38.6%; white solid: mp 120–122 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.53 (d, *J* = 7.5 Hz, 1H, NH), 7.71 – 7.66 (m, 3H, phenyl), 7.60 (d, *J* = 8.6 Hz, 2H, phenyl), 7.14 – 7.06 (m, 2H, phenyl), 5.58 – 5.52 (m, 1H, vinyl), 5.51 – 5.43 (m, 2H, oxadiazine), 4.50 (dd, *J* = 17.7, 12.3 Hz, 1H, cyclopentane), 4.16 (d, *J* = 12.3 Hz, 1H, cyclopentane), 3.32 (dd, *J* = 28.4, 15.8 Hz, 1H, CH_2),

3.14 (dd, J = 15.8, 5.1 Hz, 1H, CH_2), 2.21 – 2.16 (m, 1H, cyclopropane), 1.54 (dd, J = 9.2, 5.3 Hz, 1H, cyclopropane), 1.26 (d, J = 3.2 Hz, 3H, CH_3), 1.15 (d, J = 2.9 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 170.454 (O=C-O), 165.84 (phenyl-C), 164.16 (phenyl-C), 153.78 (CONH), 150.94 (oxadiazine-CN), 145.01 (phenyl-C), 130.07 (C=C), 126.44 (phenyl-C), 126.27 (phenyl-C), 125.11 (phenyl-C), 123.51 (CF_3), 122.56 (phenyl-C), 118.73 (phenyl-C), 116.20 (phenyl-C), 116.05 (phenyl-C), 113.44 (phenyl-C), 113.28 (phenyl-C) ， 79.33 (oxadiazine-CN), 69.41 (oxadiazine-CH_2), 64.54 (CH_2O), 39.56 (cyclopentane-CH_2), 34.26 (cyclopropane-C), 33.37 (cyclopropane-C), 29.48 (cyclopropane-C($Me)_2$), 22.44 (CH_3). HRMS(ESI-TOF) m/z: calcd for $C_{27}H_{23}Cl_2F_4N_3O_5$ [M + Na] $^+$ 616.1024; found 616.0997.

***(7-chloro-2-((4-(trifluoromethyl)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl-3-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2-dimethylcyclopropanecarboxylate*(J7). J7-H-Rf (Higher Rf value compd)** Yield: 23.5%; white solid: mp 133–134 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.53 (d, J = 10.6 Hz, 1H, NH), 7.67 (d, J = 8.4 Hz, 2H, phenyl), 7.59 (d, J = 6.1 Hz, 3H, phenyl), 7.36 (d, J = 12.0 Hz, 2H, phenyl), 6.82 (dd, J = 12.0, 9.8 Hz, 1H, vinyl), 5.53 (dd, J = 25.5, 9.4 Hz, 1H, oxadiazine), 5.44 (dd, J = 24.1, 9.8 Hz, 1H, oxadiazine), 4.52 (dd, J = 25.0, 12.3 Hz, 1H, cyclopentane), 4.13 (dd, J = 34.4, 12.3 Hz, 1H, cyclopentane), 3.29 (dd, J = 45.1, 15.8 Hz, 1H, CH_2), 3.11 (d, J = 15.8 Hz, 1H, CH_2), 2.17 (q, J = 9.0 Hz, 1H, cyclopropane), 1.92 (dd, J = 8.4, 3.6 Hz, 1H, cyclopropane), 1.27 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.49 (O=C-O), 153.09 (CONH), 150.86 (oxadiazine-CN), 144.28 (phenyl-C), 140.98 (phenyl-C), 133.07 (C=C), 131.71 (phenyl-C), 129.55 (phenyl-C), 129.52 (phenyl-C), 129.50 (=C-Cl), 129.47 (=C-Cl), 129.29 (phenyl-C), 126.32 (phenyl-C), 126.30 (phenyl-C), 126.27 (phenyl-C), 126.25 (phenyl-C), 125.85 (phenyl-C), 125.37 (CF_3), 125.09 (CF_3), 122.85 (phenyl-C), 118.80 (phenyl-C), 79.01 (oxadiazine-CN), 69.29 (oxadiazine-CH_2), 63.64 (CH_2O), 39.24 (cyclopentane-CH_2), 32.36 (cyclopropane-C), 31.25 (cyclopropane-C), 28.19 (CH_3), 14.75. **J7-L-Rf (Lower Rf value compd)** Yield: 32.4%; white solid: mp 115–117 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.51 (s, 1H, NH), 7.68 (d, J = 8.5 Hz, 2H, phenyl), 7.61 (d, J = 8.6 Hz, 2H, phenyl 7.55 (d, J = 8.1 Hz, 1H, phenyl), 7.19 (d, J = 8.4 Hz, 2H, phenyl), 5.58 (d, J = 9.6 Hz, 1H, vinyl), 5.32 (d, J = 9.5 Hz, 1H, oxadiazine), 4.54 (d, J = 12.3 Hz, 1H, oxadiazine), 4.02 (d, J = 12.4 Hz, 1H, cyclopentane), 3.21 (d, J = 15.8 Hz, 1H, cyclopentane), 3.10 (d, J = 10.5 Hz, 1H, CH_2), 3.07 (d, J = 15.8 Hz, 1H, CH_2), 2.24 (dd, J = 13.1, 6.6Hz, 1H, cyclopropane), 1.97(q, J=3.9Hz, 1H, cyclopropane), 1.01 (d, J = 6.5 Hz, 3H, CH_3),

0.68 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 172.89 (O=C-O), 152.53 (CONH), 150.81 (oxadiazine-CN), 143.95 (phenyl-C), 141.00 (phenyl-C), 137.50 (phenyl-C), 136.06 (phenyl-C), 133.41 (C=C), 132.64 (=C-Cl), 129.66 (=C-Cl), 128.85 (C=C), 128.75 (phenyl-C), 126.32 (CF_3), 126.31 (CF_3), 122.56 (phenyl-C), 118.77 (phenyl-C), 79.02 (oxadiazine-CN), 69.21 (oxadiazine-CH_2), 64.26 (CH_2O), 39.31 (cyclopentane-CH_2), 31.81 (cyclopropane-C), 29.70 (CH_3), 21.29 (CH_3), 19.98. HRMS (ESI-TOF) m/z: calcd for $C_{28}H_{23}Cl_2F_6N_3O_4$ $[M + H]^+$ 672.0862; found 672.0881.

***7-chloro-2-((4-(trifluoromethoxy)phenyl)carbamoyl-2,5-tetrahydroindeno [1,2-e][1,3,4]oxadiazin-4a-yl)methyl 2,2-dimethyl -3-(2,3,3,3-tetrafluoroprop-1-en-1-yl) cyclopropanecarboxylate* (J8). J8-H-Rf (Higher Rf value compd)** Yield: 38.5%; white solid: mp 125–126 °C; ^1H NMR (600 MHz, Chloroform-*d*) δ 8.37 (s, 1H, NH), 7.57(d, J = 8.1Hz, 1H, phenyl), 7.56–7.53 (m, 2H, phenyl), 7.36 (d, J = 8.2 Hz, 1H, phenyl), 7.34 (s, 1H, phenyl), 7.19 (d, J = 8.5 Hz, 2H, phenyl), 6.81 (d, J = 9.4 Hz, 1H, vinyl), 5.52 (d, J = 9.5 Hz, 1H, oxadiazine), 5.41 (d, J = 9.5 Hz, 1H, oxadiazine), 4.51 (dd, J = 12.2, 0.1 Hz, 1H, cyclopentane), 4.09 (d, J = 12.3 Hz, 1H, cyclopentane), 3.31(d, J = 15.8 Hz, 1H, CH_2), 3.10 (d, J = 16.0 Hz, 1H, CH_2), 2.16 (t, J = 8.8 Hz, 1H, cyclopropane), 1.90 (d, J = 8.3 Hz, 1H, cyclopropane), 1.26 (s, 3H, CH_3) , 1.25 (s, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.58 (O=C-O), 153.28 (CONH), 151.31 (oxadiazine-CN), 144.99 (phenyl-C), 144.02 (phenyl-C), 137.66 (C=C), 136.68 (phenyl-C), 132.80 (phenyl-C), 129.77 (phenyl-C), 129.74 (phenyl-C), 129.71 (phenyl-C), 129.68 (=C-Cl), 129.05 (=C-Cl), 126.45 (CF_3), 122.83 (CF_3), 121.95 (phenyl-C), 120.60 (phenyl-C), 79.45 (oxadiazine-CN), 69.72 (oxadiazine-CH_2), 64.80 (CH_2O), 39.46 (cyclopentane-CH_2), 32.55 (cyclopropane-C), 31.39 (cyclopropane-C), 29.25 (CH_3), 28.33 (CH_3), 14.90. HRMS (ESI-TOF) m/z: calcd for $C_{22}H_{20}F_3N_3O_7$ $[M + Na]^+$ 688.0811; found 688.0822. **J8-L-Rf (Lower Rf value compd)** Yield: 44.5%; white solid: mp 142–143 °C; ^1H NMR (600 MHz, Chloroform-*d*) δ 8.35 (s, 1H, NH), 7.57 (d, J = 8.2 Hz, 1H, phenyl), 7.56–7.54 (m, 2H, phenyl), 7.36 (d, J = 8.2 Hz, 1H, phenyl), 7.33 (s, 1H, phenyl), 7.19 (d, J = 8.3 Hz, 2H, phenyl), 6.79 (dd, J = 9.3, 0.8 Hz, 1H, vinyl), 5.47 (d, J = 9.4 Hz, 1H, oxadiazine), 5.45 (d, J = 9.4 Hz, 1H, oxadiazine), 4.47 (dd, J = 12.4, 1.1 Hz, 1H, cyclopentane), 4.14 (d, J = 12.3 Hz, 1H, cyclopentane 3.23 (d, J = 15.8 Hz, 1H, CH_2), 3.10 (d, J = 15.0 Hz, 1H, CH_2), 2.14 (t, J = 8.6 Hz, 1H, cyclopropane), 1.90 (d, J = 8.4 Hz, 1H, cyclopropane), 1.24 (s, 3H, CH_3), 1.23 (s, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.58 (O=C-O), 153.25 (CONH), 151.30 (oxadiazine-CN), 144.02 (phenyl-C), 137.65 (phenyl-C),

136.68 (C=C), 132.79 (C=C), 129.78 (phenyl-C), 129.75 (phenyl-C), 129.72 (phenyl-C), 129.69 (phenyl-C), 129.04 (phenyl-C), 126.44 (CF_3), 122.82 (CF_3), 121.95 (phenyl-C), 120.59 (phenyl-C), 79.44 (oxadiazine-CN), 69.70 (oxadiazine-CH_2), 64.77 (CH_2O), 39.44 (cyclopentane-CH_2), 32.53 (cyclopropane-C), 31.37 (cyclopropane-C), 28.32 (CH_3). HRMS (ESI-TOF) m/z: calcd for $C_{22}H_{20}F_3N_3O_7$ $[M + Na]^+$ 688.0811; found 688.0826.

(7-bromo-2-((4-(trifluoromethyl)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl-3-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2-dimethylcyclopropanecarboxylate **(J9). J9-H-Rf (Higher Rf value compd)** Yield: 27.6%; white solid: mp 145–147 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.52 (d, *J* = 10.0 Hz, 1H, NH), 7.67 (d, *J* = 8.3 Hz, 2H, phenyl), 7.60 (d, *J* = 7.6 Hz, 2H, phenyl), 7.55 – 7.50 (m, 3H, phenyl), 6.81 (dd, *J* = 11.9, 9.8 Hz, 1H, vinyl), 5.54 (dd, *J* = 25.4, 9.5 Hz, 1H, oxadiazine), 5.44 (dd, *J* = 24.8, 9.5 Hz, 1H, oxadiazine), 4.52 (dd, *J* = 25.0, 12.3 Hz, 1H, cyclopentane), 4.20 – 4.06 (m, 1H, cyclopentane), 3.29 (dd, *J* = 46.6, 15.8 Hz, 1H, CH_2), 3.13 (d, *J* = 15.8 Hz, 1H, CH_2), 2.17 (q, *J* = 9.0 Hz, 1H, cyclopropane), 1.92 (dd, *J* = 8.4, 3.6 Hz, 1H, cyclopropane), 1.27 (d, *J* = 3.8 Hz, 3H, CH_3), 1.25 (d, *J* = 3.0 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.69 (O=C-O), 152.95 (CONH), 151.54 (oxadiazine-CN), 146.23 (phenyl-C), 142.98 (phenyl-C), 133.83 (C=C), 131.99 (phenyl-C), 131.52 (phenyl-C), 129.54 (phenyl-C), 126.29 (phenyl-C), 125.83 (phenyl-C), 124.87 (phenyl-C), 124.14 (phenyl-C), 124.03 (CF_3), 123.43 (CF_3), 121.66 (phenyl-C), 119.98 (phenyl-C), 79.52 (oxadiazine-CN), 69.79 (oxadiazine-CH_2), 64.71 (CH_2O), 32.78 (cyclopropane-C), 30.68 (cyclopropane-C), 29.50 (CH_3), 27.47 (CH_3). **J9-L-Rf (Lower Rf value compd)** Yield: 45.3%; white solid: mp 155–157 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.36 (s, 1H, NH), 7.57 – 7.56 (m, 1H, phenyl), 7.56 (d, *J* = 2.1 Hz, 1H, phenyl), 7.53 (d, *J* = 1.7 Hz, 2H, phenyl), 7.52 (s, 1H, phenyl), 7.21 (s, 1H, phenyl), 7.20 (s, 1H, phenyl), 6.80(d, *J*=1.7Hz, 1H, vinyl), 5.49 (d, *J* = 9.4 Hz, 1H, oxadiazine), 5.46 (d, *J* = 9.4 Hz, 1H, oxadiazine), 4.48 (d, *J* = 12.9 Hz, 1H, cyclopentane), 4.16 (d, *J* = 12.3 Hz, 1H, cyclopentane), 3.25(d, *J*=15.8Hz, 1H, CH_2), 3.11(d, *J*=2.1Hz, 1H, CH_2), 2.16 (t, *J* = 8.9 Hz, 1H, cyclopropane), 1.92 (d, *J* = 8.4 Hz, 1H, cyclopropane), 1.26 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.43 (O=C-O), 153.12 (CONH), 151.14 (oxadiazine-CN), 144.83 (phenyl-C), 144.07 (phenyl-C), 136.53 (phenyl-C), 133.12 (C=C), 131.75 (C=C), 129.60 (phenyl-C), 129.27 (phenyl-C), 125.77 (phenyl-C), 124.48 (CF_3), 123.97 (CF_3), 122.88 (phenyl-C), 121.81 (phenyl-C), 120.46 (phenyl-C), 118.80 (phenyl-C), 79.23 (oxadiazine-CN), 69.55 (oxadiazine-CH_2), 64.61 (CH_2O), 39.24 (cyclopentane-

435 CH_2), 32.40 (cyclopropane-C), 31.43 (cyclopropane-C), 30.19 (cyclopropane-C$(Me)_2$), 29.12
436 (CH_3), 28.19 (CH_3). HRMS (ESI-TOF) m/z: calcd for $C_{28}H_{23}BrClF_6N_3O_4$ $[M + Na]^+$ 716.0357;
437 found 716.0359.
438 ***(7-bromo-2-((4-(trifluoromethoxy)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-***
439 ***e][1,3,4]oxadiazin-4a-yl)methyl-3-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2-dimethyl-***
440 ***cyclopropanecarboxylate*** **(J10). J10-H-Rf (Higher Rf value compd)** Yield: 32.4%; white solid:
441 mp 127–128 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.59 (s, 1H, NH), 7.91 (d, J = 8.6 Hz, 2H,
442 phenyl), 7.75 (d, J = 8.1 Hz, 1H, phenyl), 7.68 (s, 2H, phenyl), 7.66 (s, 1H, phenyl), 7.65 (s, 1H,
443 phenyl), 6.88(d, J=8.6Hz, 1H, vinyl), 5.36 (d, J = 9.3 Hz, 1H, oxadiazine), 5.26 (d, J = 9.4 Hz, 1H,
444 oxadiazine), 4.35 (d, J = 12.4 Hz, 1H, cyclopentane), 4.31 (d, J = 12.4 Hz, 1H, cyclopentane), 3.30
445 (d, J = 16.0 Hz, 1H, CH_2), 3.12 (d, J = 15.9 Hz, 1H, CH_2), 2.18 (t, J = 8.8 Hz, 1H, cyclopropane),
446 2.08 (d, J = 8.3 Hz, 1H, cyclopropane), 1.17 (s, 3H, CH_3), 1.16 (s, 3H, CH_3). ^{13}C NMR (151 MHz,
447 DMSO-d_6) δ 169.72 (O=C-O), 153.82 (CONH), 151.63 (oxadiazine-CN), 145.37(phenyl-C),
448 133.60 (C=C), 132.03 (phenyl-C), 131.54 (phenyl-C), 129.57 (phenyl-C), 126.29 (phenyl-C),
449 124.87 (C=C), 124.13 (CF_3), 124.03 (CF_3), 123.41 (phenyl-C), 123.20 (phenyl-C), 121.82 (phenyl-
450 C), 121.66 (phenyl-C), 120.29 (phenyl-C), 119.49 (phenyl-C), 79.62 (oxadiazine-CN), 69.59
451 (oxadiazine-CH_2), 64.24 (CH_2O), 32.80 (cyclopropane-C), 30.68 (cyclopropane-C), 30.64
452 (cyclopropane-C), 29.41 (CH_3), 27.50 (CH_3). **J10-L-Rf (Lower Rf value compd)** Yield: 41.6%;
453 white solid: mp 138–140 °C; ^{1}H NMR (600 MHz, Chloroform-d) δ 8.37 (d, J = 10.2 Hz, 1H, NH),
454 7.57 (d, J = 9.1 Hz, 2H, phenyl), 7.55 – 7.51 (m, 3H, phenyl), 7.21 (d, J = 8.6 Hz, 2H, phenyl),
455 6.83 – 6.78 (m, 1H, vinyl), 5.56 – 5.48 (m, 1H, oxadiazine), 5.47 – 5.40 (m, 1H, oxadiazine), 4.51
456 (dd, J = 28.5, 12.3 Hz, 1H, cyclopentane), 4.13 (dd, J = 38.5, 12.3 Hz, 1H, cyclopentane), 3.29
457 (dd, J = 48.0, 15.8 Hz, 1H, CH_2), 3.13 (d, J = 15.8 Hz, 1H, CH_2), 2.17 (q, J = 9.2 Hz, 1H,
458 cyclopropane), 1.92 (dd, J = 8.4, 2.1 Hz, 1H, cyclopropane), 1.26 (s, 3H, CH_3), 1.25 (s, 3H, CH_3).
459 ^{13}C NMR (151 MHz, Chloroform-d) δ 169.44 (O=C-O), 153.07 (CONH), 151.12 (oxadiazine-
460 CN), 144.76 (phenyl-C), 136.58 (C=C), 133.13 (phenyl-C), 131.70 (phenyl-C), 129.69 (phenyl-
461 C), 129.66 (phenyl-C), 129.24 (C=C), 125.72 (CF_3), 122.86 (CF_3), 121.76 (phenyl-C), 121.37
462 (phenyl-C), 121.31 (phenyl-C), 120.43 (phenyl-C), 119.67 (phenyl-C), 119.51 (phenyl-C), 79.22
463 (oxadiazine-CN), 69.50 (oxadiazine-CH_2), 64.49 (CH_2O), 39.19 (cyclopentane-CH_2), 32.40
464 (cyclopropane-C), 31.22 (cyclopropane-C), 29.10 (CH_3), 28.11 (CH_3). HRMS(ESI-TOF) m/z:
465 calcd for $C_{28}H_{23}BrClF_6N_3O_5$ $[M + Na]^+$ 734.0286; found 734.0266.

***7-fluoro-2-((4-(trifluoromethyl)phenyl)carbamoyl-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl-3-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2-dimethyl-cyclopropanecarboxylate* (J11). J11-H-Rf (Higher Rf value compd)** Yield: 46.5%; white solid: mp 110–111 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.51 (s, 1H, NH), 7.67–7.63 (m, 3H, phenyl), 7.59 (d, J = 8.6 Hz, 2H, phenyl), 7.09 (td, J = 8.7, 2.3 Hz, 1H, phenyl), 7.06 (d, J = 8.2 Hz, 1H, phenyl), 6.81 (dd, J = 9.4, 0.7 Hz, 1H, vinyl), 5.50 (d, J = 9.4 Hz, 1H, oxadiazine), 5.43 (d, J = 9.4 Hz, 1H, oxadiazine), 4.50 (dd, J = 12.2, 1.3 Hz, 1H, cyclopentane), 4.11 (d, J = 12.3 Hz, 1H, cyclopentane), 3.33 (d, J = 15.8 Hz, 1H, CH_2), 3.12 (d, J = 15.8 Hz, 1H, CH_2), 2.15 (t, J = 8.6 Hz, 1H, cyclopropane), 1.90 (d, J = 8.3 Hz, 1H, cyclopropane), 1.26 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.69 (O=C-O), 165.98 (phenyl-C), 164.31 (phenyl-C), 153.55 (CONH), 151.10 (oxadiazine-CN), 145.22 (phenyl-C), 145.16 (phenyl-C), 141.19 (C=C), 130.26 (C=C), 129.70 (phenyl-C), 129.67 (phenyl-C), 129.64 (phenyl-C), 126.48 (phenyl-C), 126.45 (phenyl-C), 125.50 (phenyl-C), 125.28 (phenyl-C), 125.26 (phenyl-C), 123.57 (CF_3), 123.51 (CF_3), 122.38 (phenyl-C), 122.13 (phenyl-C), 121.41 (phenyl-C), 119.61 (phenyl-C), 118.90 (phenyl-C), 116.34 (phenyl-C), 79.30 (oxadiazine-C), 69.46 (oxadiazine-CH_2), 63.88 (CH_2O), 39.64 (cyclopentane-CH_2), 32.53 (cyclopropane-C), 31.40 (cyclopropane-C), 29.30 (cyclopropane-C(Me)$_2$), 28.35 (CH_3), 14.91. **J11-L-Rf (Lower Rf value compd)** Yield: 42.7%; white solid: mp 145–146 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.50 (s, 1H, NH), 7.66–7.63 (m, 3H, phenyl), 7.58 (d, J = 8.6 Hz, 2H, phenyl), 7.10 (td, J = 8.7, 2.2 Hz, 1H, phenyl), 7.05 (d, J = 8.3 Hz, 1H, phenyl), 6.79 (dd, J = 9.4, 0.8 Hz, 1H, vinyl), 5.47 (d, J = 9.3 Hz, 1H, oxadiazine), 5.45 (d, J = 9.4 Hz, 1H, oxadiazine), 4.48 (dd, J = 12.3, 1.1 Hz, 1H, cyclopentane), 4.15 (d, J = 12.2 Hz, 1H, cyclopentane), 3.24 (d, J = 15.9 Hz, 1H, CH_2), 3.12 (d, J = 15.8 Hz, 1H, CH_2), 2.13 (t, J = 8.6 Hz, 1H, cyclopropane), 1.90 (d, J = 8.4 Hz, 1H, cyclopropane), 1.24 (s, 3H, CH_3), 1.24 (s, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.60 (O=C-O), 165.98 (phenyl-C), 164.31 (phenyl-C), 153.78 (CONH), 151.13 (oxadiazine-CN), 145.00 (phenyl-C), 144.94 (phenyl-C), 141.21 (C=C), 130.22 (C=C), 129.78 (phenyl-C), 129.75 (phenyl-C), 129.72 (phenyl-C), 129.69 (phenyl-C), 126.48 (phenyl-C), 126.46 (CF_3), 125.47 (phenyl-C), 125.26 (phenyl-C), 123.65 (CF_3), 123.59 (CF_3), 122.40 (phenyl-C), 122.15 (phenyl-C), 121.43 (phenyl-C), 119.63 (phenyl-C), 116.40 (phenyl-C), 79.55 (oxadiazine-C), 69.71 (oxadiazine-CH_2), 64.88 (CH_2O), 39.64 (cyclopentane-CH_2), 32.56 (cyclopropane-C), 31.38 (cyclopropane-C), 29.25 (cyclopropane-

C(Me)$_2$), 28.34 (CH_3). HRMS (ESI-TOF) m/z: calcd for $C_{22}H_{20}F_3N_3O_7$ [M + Na] $^+$ 656.1158; found 656.1156.

(7-fluoro-2-((4-(trifluoromethoxy)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl-3-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2-dimethylcyclopropanecarboxylate **(J12). J12-H-Rf (Higher Rf value compd)** Yield: 28.4%; white solid: mp 160–161 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.39 (d, *J* = 11.0 Hz, 1H, NH), 7.65 (dd, *J* = 8.5, 4.9 Hz, 1H, phenyl), 7.56 (d, *J* = 9.0 Hz, 2H, phenyl), 7.20 (d, *J* = 8.6 Hz, 2H, phenyl), 7.10 (td, *J* = 8.6, 2.2 Hz, 1H, phenyl), 7.05 (d, *J* = 8.2 Hz, 1H, phenyl), 6.81 (dd, *J* = 9.5, 1.2 Hz, 1H, vinyl), 5.48 (d, *J* = 9.3 Hz, 1H, oxadiazine), 5.43 (d, *J* = 9.3 Hz, 1H, oxadiazine), 4.48 (d, *J* = 12.3 Hz, 1H, cyclopentane), 4.16 (d, *J* = 12.3 Hz, 1H, cyclopentane), 3.29 (dd, *J* = 47.7, 15.9 Hz, 1H, CH_2), 3.13 (d, *J* = 15.9 Hz, 1H, CH_2), 2.15 (t, *J* = 9.0 Hz, 1H, cyclopropane), 1.92 (d, *J* = 8.4 Hz, 1H, cyclopropane), 1.27 (s, 1H, CH_3), 1.26 (s, 1H, CH_3), 1.25 (s, 2H, CH_3), 1.25 (s, 2H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.54 (O=C-O), 153.24 (CONH), 151.22 (oxadiazine-CN), 144.82 (phenyl-C), 136.57 (C=C), 130.19 (phenyl-C), 129.58 (C=C), 123.36 (CF_3), 121.82 (CF_3), 121.74 (phenyl-C), 121.37 (phenyl-C), 121.27 (phenyl-C), 120.47 (phenyl-C), 119.67 (phenyl-C), 115.98 (phenyl-C), 79.15 (oxadiazine-CN), 69.33 (oxadiazine-CH_2), 63.77 (CH_2O), 39.49 (cyclopentane-CH_2), 32.39 (cyclopropane-C), 31.42 (cyclopropane-C), 30.19 (cyclopropane-C(Me)$_2$), 29.15 (CH_3), 28.19 (CH_3), 14.77. **J12-L-Rf (Lower Rf value compd)** Yield: 36.6%; white solid: mp 146–148 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.39 (d, *J* = 11.0 Hz, 1H, NH), 7.65 (dd, *J* = 8.5, 4.9 Hz, 1H, phenyl), 7.56 (d, *J* = 9.0 Hz, 2H, phenyl), 7.20 (d, *J* = 8.6 Hz, 2H, phenyl), 7.08 (dd, *J* = 32.4, 9.4 Hz, 2H, phenyl), 6.82 (t, *J* = 9.8 Hz, 1H, vinyl), 5.48 (d, *J* = 9.3 Hz, 1H, oxadiazine), 5.43 (d, *J* = 9.3 Hz, 1H, oxadiazine), 4.49 (dd, *J* = 18.5, 12.3 Hz, 1H, cyclopentane), 4.14 (dd, *J* = 27.8, 12.2 Hz, 1H, cyclopentane), 3.29 (dd, *J* = 47.7, 15.9 Hz, 1H, CH_2), 3.13 (d, *J* = 15.9 Hz, 1H, CH_2), 2.15 (t, *J* = 9.0 Hz, 1H, cyclopropane), 1.92 (d, *J* = 8.4 Hz, 1H, cyclopropane), 1.28 – 1.25 (m, 3H, CH_3), 1.25 (s, 3H, CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.43 (O=C-O), 153.63 (CONH), 150.97 (oxadiazine-CN), 144.79 (phenyl-C), 141.063 (phenyl-C), 130.05 (C=C), 129.57 (phenyl-C), 126.30 (C=C), 125.10 (phenyl-C), 123.49 (CF_3), 122.26 (CF_3), 122.01 (phenyl-C), 121.28 (phenyl-C), 118.72 (phenyl-C), 116.24 (phenyl-C), 79.40 (oxadiazine-CN), 69.56 (oxadiazine-CH_2), 64.73 (CH_2O), 39.52 (cyclopentane-CH_2), 32.41 (cyclopropane-C), 31.23 (cyclopropane-C), 29.09 (CH_3), 28.19 (CH_3). HRMS (ESI-TOF) m/z: calcd for $C_{28}H_{23}ClF_7N_3O_5$ [M + Na] $^+$ 672.1107; found 672.1083.

(7-chloro-2-((4-(trifluoromethyl)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl-2,2,3,3-tetramethylcyclopropanecarboxylate **(J13).** Yield: 76.8%; white solid: mp 98–99 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.40 (s, 1H, NH), 7.60 (d, *J* = 8.1 Hz, 1H, phenyl), 7.59 – 7.54 (m, 2H, phenyl), 7.38 – 7.33 (m, 2H, phenyl), 7.22 – 7.17 (m, 2H, phenyl), 5.55(d, *J*=6.5Hz, 1H, oxadiazine), 5.44(d, J=12.3Hz, 1H, oxadiazine), 4.45 (d, *J* = 13.0 Hz, 1H, cyclopentane), 4.10 (d, *J* = 12.3 Hz, 1H, cyclopentane), 3.31 (d, *J* = 15.8 Hz, 1H, CH_2), 3.10 (d, *J* = 15.7 Hz, 1H, CH_2), 1.20 (d, *J* = 6.5 Hz, 6H, CH_3), 1.14 (d, *J* = 3.7 Hz, 6H, CH_3) , 1.11(s, 1H, cyclopropane). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.17 (O=C-O), 153.14 (phenyl-C-cyclopentane), 151.16 (CONH), 144.77 (phenyl-C), 144.26 (phenyl-C), 137.29 (phenyl-C), 132.92 (phenyl-C), 128.70 (phenyl-C), 126.25 (CF_3), 122.59 (phenyl-C), 121.79 (phenyl-C), 121.37 (phenyl-C), 120.47 (phenyl-C), 119.67 (phenyl-C), 79.28 (oxadiazine-CN), 69.41 (oxadiazine-CH_2), 63.22 (CH_2O), 39.41 (cyclopentane-CH_2), 35.34 (cyclopropane-C), 31.08 (cyclopropane-C), 30.99 (cyclopropane-C$(Me)_2$), 29.70 (CH_3), 23.41 (CH_3), 23.37 (CH_3), 16.48 (CH_3), 16.46 (CH_3). HRMS(ESI-TOF) m/z: calcd for $C_{27}H_{27}ClF_3N_3O_4$ $[M + Na]^+$ 572.1534; found 572.1537.

7-chloro-2-((4-(trifluoromethoxy)phenyl)carbamoyl-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 2,2,3,3-tetramethylcyclopropanecarboxylate **(J14).** Yield: 64.6%; white solid: mp 134–135 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.38 (s, 1H, NH), 7.58 (d, J = 8.1 Hz, 1H, phenyl), 7.56–7.54 (m, 2H, phenyl), 7.34 (d, J = 8.2 Hz, 1H, phenyl), 7.33 (s, 1H, phenyl), 7.18 (d, J = 8.4 Hz, 2H, phenyl), 5.53 (d, J = 9.4 Hz, 1H, oxadiazine), 5.43 (d, J = 9.4 Hz, 1H, oxadiazine), 4.44 (dd, J = 12.3, 1.1 Hz, 1H, cyclopentane), 4.09 (d, J = 12.3 Hz, 1H, cyclopentane), 3.29 (d, J = 15.6 Hz, 1H, CH_2), 3.08 (d, J = 15.7 Hz, 1H, CH_2), 1.19 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.12 (s, 3H, CH_3) , 1.09(s, 1H, cyclopropane). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.30 (O=C-O), 153.27 (phenyl-C-cyclopentane), 151.28 (CONH), 144.91 (phenyl-C), 144.39 (phenyl-C), 137.43 (phenyl-C), 136.76 (phenyl-C), 133.06 (phenyl-C), 128.83 (phenyl-C), 126.38 (phenyl-C), 122.72 (CF_3), 121.91 (phenyl-C), 120.59 (phenyl-C), 79.41 (oxadiazine-CN), 69.55 (oxadiazine-CH_2), 63.36 (CH_2O), 39.54 (cyclopentane-CH_2), 35.47 (cyclopropane-C), 31.20 (cyclopropane-C), 31.12 (cyclopropane-C$(Me)_2$), 23.53 (CH_3), 23.49 (CH_3). HRMS (ESI-TOF) m/z: calcd for $C_{22}H_{20}F_3N_3O_7$ $[M + Na]^+$ 588.1484; found 588.1499.

(7-bromo-2-((4-(trifluoromethyl)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 2,2,3,3-tetramethylcyclopropanecarboxylate **(J15).** Yield:

67.7%; white solid: mp 80–81 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.44 (s, 1H, NH), 7.77 (d, J = 9.0 Hz, 2H, phenyl), 7.73 (d, J = 8.1 Hz, 1H, phenyl), 7.68 – 7.62 (m, 2H, phenyl), 7.32 (d, J = 8.7 Hz, 2H, phenyl), 5.38 (d, J = 9.2 Hz, 1H, oxadiazine), 5.29 (d, J = 9.3 Hz, 1H, oxadiazine), 4.34 (d, J = 12.3 Hz, 1H, cyclopentane), 4.21 (d, J = 12.3 Hz, 1H, cyclopentane), 3.26 (d, J = 16.0 Hz, 1H, CH_2), 3.09 (d, J = 15.9 Hz, 1H, CH_2), 1.10 (d, J = 13.7 Hz, 6H, CH_3), 1.04 (d, J = 8.8 Hz, 6H, CH_3) , 1.01(s, 1H, cyclopropane). ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.17 (O=C-O), 153.14 (phenyl-C-cyclopentane), 151.16 (CONH), 144.77 (phenyl-C), 144.26 (phenyl-C), 137.29 (phenyl-C), 136.62 (phenyl-C), 132.92 (phenyl-C), 128.70 (phenyl-C) 126.25(CF_3), 122.59 (phenyl-C), 121.79 (phenyl-C), 121.37 (phenyl-C), 120.47 (phenyl-C), 119.67 (phenyl-C), 79.28 (oxadiazine-CN), 69.41 (oxadiazine-CH_2), 63.22 (CH_2O), 39.41 (cyclopentane-CH_2), 35.34 (cyclopropane-C), 30.99 (cyclopropane-C), 23.37 (CH_3). HRMS(ESI-TOF) m/z: calcd for $C_{27}H_{27}BrF_3N_3O_4$ [M + Na] $^{+}$ 616.1029; found 616.1023.

(7-bromo-2-((4-(trifluoromethoxy)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 2,2,3,3-tetramethylcyclopropanecarboxylate **(J16).** Yield: 64.4%; white solid: mp 103–104 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.40 (s, 1H, NH), 7.65 (dd, J = 8.4, 5.1 Hz, 1H, phenyl), 7.57 (d, J = 9.0 Hz, 2H, phenyl), 7.20 (d, J = 8.6 Hz, 2H, phenyl), 7.12 – 7.04 (m, 2H, phenyl), 5.51 (d, J = 9.4 Hz, 1H, oxadiazine), 5.45 (d, J = 9.4 Hz, 1H, oxadiazine), 4.45 (d, J = 13.0 Hz, 1H, cyclopentane), 4.11 (d, J = 12.3 Hz, 1H, cyclopentane), 3.32 (d, J = 15.8 Hz, 1H, CH_2), 3.11 (d, J = 15.8 Hz, 1H, CH_2), 1.19 (s, 6H, CH_3), 1.14 (d, J = 4.7 Hz, 6H, CH_3), 1.02 (s, 1H, cyclopropane). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.18 (O=C-O), 165.74 (phenyl-C), 153.65 (phenyl-C-cyclopentane), 150.96 (CONH), 145.23 (phenyl-C), 144.45 (phenyl-C), 141.14 (phenyl-C), 130.32 (phenyl-C), 126.28 (phenyl-C), 125.13 (phenyl-C), 125.01 (phenyl-C), 123.37 (CF_3), 118.71 (phenyl-C), 116.02 (phenyl-C), 79.38 (oxadiazine-CN), 69.41 (oxadiazine-CH_2), 63.27 (CH_2O), 39.59 (cyclopentane-CH_2), 35.36 (cyclopropane-C), 31.06 (cyclopropane-C), 23.41 (CH_3). HRMS(ESI-TOF) m/z: calcd for $C_{27}H_{27}BrF_3N_3O_5$ [M + Na] $^{+}$ 632.0978; found 632.0965.

7-fluoro-2-((4-(trifluoromethyl)phenyl)carbamoyl-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 2,2,3,3-tetramethylcyclopropanecarboxylate **(J17).** Yield: 68.3%; white solid: mp 131–133 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.53 (s, 1H, NH), 7.67–7.64 (m, 3H, phenyl), 7.58 (d, J = 8.6 Hz, 2H, phenyl), 7.08 (td, J = 8.6, 2.1 Hz, 1H, phenyl), 7.05 (d, J = 8.3 Hz, 1H, phenyl), 5.51 (d, J = 9.4 Hz, 1H, oxadiazine), 5.45 (d, J = 9.4 Hz, 1H,

oxadiazine), 4.44 (dd, *J* = 12.3, 1.2 Hz, 1H, cyclopentane), 4.10 (d, *J* = 12.3 Hz, 1H, cyclopentane), 3.31 (d, *J* = 15.8 Hz, 1H, CH_2), 3.10 (d, *J* = 15.7 Hz, 1H, CH_2), 1.19 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.10 (s, 1H, cyclopropane). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.35 (O=C-O), 165.89 (phenyl-C-cyclopentane), 153.79 (phenyl-C), 151.11 (CONH), 145.38 (phenyl-C), 141.29 (phenyl-C), 130.46 (phenyl-C), 130.44 (phenyl-C), 126.46 (phenyl-C), 126.43 (phenyl-C), 126.41 (phenyl-C), 126.38 (CF_3), 125.37 (phenyl-C), 125.28 (phenyl-C), 125.15 (phenyl-C), 123.53 (phenyl-C), 123.4 (phenyl-C), 118.86 (phenyl-C), 116.17 (phenyl-C), 79.52 (oxadiazine-CN), 69.54 (oxadiazine-CH_2), 63.40 (CH_2O), 39.72 (cyclopentane-CH_2), 35.48 (cyclopropane-C), 31.22 (cyclopropane-C), 31.14 (cyclopropane-C$(Me)_2$), 23.55 (CH_3), 23.51 (CH_3). HRMS (ESI-TOF) m/z: calcd for $C_{22}H_20F_3N_3O_7$ $[M + Na]^+$ 556.1830; found 556.1836.

(7-fluoro-2-((4-(trifluoromethoxy)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl-2,2,3,3-tetramethylcyclopropanecarboxylate **(J18).** Yield: 58.0%; white solid: mp 108–109 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.55 (s, 1H, NH), 7.67 (t, *J* = 7.4 Hz, 3H, phenyl), 7.59 (d, *J* = 8.6 Hz, 2H, phenyl), 7.10 (td, *J* = 8.7, 2.0 Hz, 1H, phenyl), 7.06 (d, *J* = 8.3 Hz, 1H, phenyl), 5.53 (d, *J* = 9.4 Hz, 1H, oxadiazine), 5.46 (d, *J* = 9.4 Hz, 1H, oxadiazine), 4.46 (d, *J* = 12.3 Hz, 1H, cyclopentane), 4.12 (d, *J* = 12.3 Hz, 1H, cyclopentane), 3.32 (d, *J* = 15.8 Hz, 1H, CH_2), 3.12 (d, *J* = 15.8 Hz, 1H, CH_2), 1.20 (d, *J* = 5.2 Hz, 6H, CH_3), 1.14 (d, *J* = 6.8 Hz, 6H, CH_3) , 1.12 (s, 1H, cyclopropane). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.18 (O=C-O), 165.74 (phenyl-C-cyclopentane), 164.07 (phenyl-C), 153.65 (phenyl-C), 150.96 (CONH), 145.23 (phenyl-C), 144.45 (phenyl-C), 141.14 (phenyl-C), 130.32 (phenyl-C), 126.28 (CF_3), 125.22 (phenyl-C), 125.13 (phenyl-C), 125.01 (phenyl-C), 123.37 (CF_3), 123.31 (phenyl-C), 118.71 (phenyl-C), 116.02 (phenyl-C), 79.38 (oxadiazine-CN), 69.41 (oxadiazine-CH_2), 63.27 (CH_2O), 39.59 (cyclopentane-CH_2), 35.36 (cyclopropane-C), 31.06 (cyclopropane-C), 23.41 (CH_3). HRMS (ESI-TOF) m/z: calcd for $C_{27}H_{27}F_4N_3O_5$ $[M + Na]^+$ 572.1779; found 572.1762.

(7-chloro-2-((4-(trifluoromethyl)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 3-chloropropanoate **(J19).** Yield: 60.8%; white solid: mp 75–77 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.43 (s, 1H, NH), 7.76 (d, *J* = 2.0 Hz, 1H, phenyl), 7.76 – 7.73 (m, 2H, phenyl), 7.68 (s, 1H, phenyl), 7.65 (d, *J* = 8.2 Hz, 1H, phenyl), 7.32 (d, *J* = 8.7 Hz, 2H, phenyl), 6.20 (d, *J* = 16.0 Hz, 1H, oxadiazine), 6.09 (dd, *J* = 17.3, 10.4 Hz, 1H, oxadiazine), 5.92 (d, *J* = 10.3 Hz, 1H, cyclopentane), 5.39 (d, *J* = 9.3 Hz, 1H, cyclopentane), 5.30 (d, *J* = 9.3

Hz, 1H, CH_2), 4.51 (d, *J* = 12.3 Hz, 1H, CH_2), 4.24 (d, *J* = 12.3 Hz, 1H, CH_2), 3.13 (d, *J* = 16.0 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.52 (O=C-O), 153.27 (CONH), 151.54 (oxadiazine-CN), 145.03 (phenyl-C), 136.93 (phenyl-C), 133.29 (phenyl-C), 130.46 (phenyl-C), 128.89 (phenyl-C), 126.62 (phenyl-C), 123.87 (CF_3), 120.03 (phenyl-C), 119.99 (phenyl-C), 79.42 (oxadiazine-CN), 69.65 (oxadiazine-CH_2), 65.37 (CH_2O), 56.62 (C-Cl), 39.42 (cyclopentane-CH_2). HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{18}Cl_2F_3N_3O_4$ [M + H] $^+$ 502.0543; found 502.0539.

(7-bromo-2-((4-(trifluoromethyl)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 3-chloropropanoate **(J20).** Yield: 62.5%; white solid: mp 71–73 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.51 (s, 1H, NH), 7.67 (d, *J* = 8.5 Hz, 2H, phenyl), 7.60 (d, *J* = 8.5 Hz, 2H, phenyl), 7.57 (d, *J* = 8.7 Hz, 1H, phenyl), 7.53 (dd, *J* = 6.4, 1.8 Hz, 2H, phenyl), 6.34 (dd, *J* = 17.3, 1.2 Hz, 1H, oxadiazine), 6.09 (d, *J* = 10.5 Hz, 1H, oxadiazine), 5.86 (dd, *J* = 10.5, 1.2 Hz, 1H, cyclopentane), 5.54 (d, *J* = 9.5 Hz, 1H, cyclopentane), 5.44 (d, *J* = 9.5 Hz, 1H, CH_2), 4.59 (dd, *J* = 12.3, 1.3 Hz, 1H, CH_2), 4.18 (d, *J* = 12.3 Hz, 1H, CH_2), 1H), 3.17 – 3.12 (m, 1H, CH_2). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 172.52 (O=C-O), 153.27 (CONH), 151.54 (oxadiazine-CN), 145.03 (phenyl-C), 136.93 (phenyl-C), 136.18 (phenyl-C), 133.29 (phenyl-C), 130.46 (phenyl-C), 128.89 (phenyl-C), 128.82 (phenyl-C), 128.70 (phenyl-C), 126.62 (phenyl-C), 126.25 (phenyl-C), 123.87 (CF_3), 120.03 (phenyl-C), 119.99 (phenyl-C), 79.42 (oxadiazine-CN), 69.65 (oxadiazine-CH_2), 65.37 (CH_2O), 58.56 (C-Cl), 39.42 (cyclopentane-CH_2). HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{18}BrClF_3N_3O_4$ [M + H] $^+$ 546.0038; found 546.0035.

(7-bromo-2-((4-(trifluoromethoxy)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 3-chloropropanoate **(J21).** Yield: 63.3%; white solid: mp 69–70 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.45 (s, 1H, NH), 7.75 (dd, *J* = 8.5, 5.5 Hz, 3H, phenyl), 7.69 (s, 1H, phenyl), 7.66 (s, 1H, phenyl), 7.33 (d, *J* = 8.7 Hz, 2H, phenyl), 6.21 (dd, *J* = 17.3, 1.4 Hz, 1H, oxadiazine), 6.14 – 6.06 (m, 1H, oxadiazine), 5.93 (dd, *J* = 10.4, 1.4 Hz, 1H, cyclopentane), 5.39 (d, *J* = 9.3 Hz, 1H, cyclopentane), 5.30 (d, *J* = 9.3 Hz, 1H, CH_2), 4.52 (d, *J* = 12.3 Hz, 1H, CH_2), 4.24 (d, *J* = 12.3 Hz, 1H, CH_2), 3.13 (d, *J* = 15.9 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.52 (O=C-O), 152.98 (CONH), 151.69 (phenyl-C), 151.71 (oxadiazine-CN), 145.23 (phenyl-C), 138.42 (phenyl-C), 133.77 (phenyl-C), 132.44 (phenyl-C), 131.51 (phenyl-C), 130.49 (phenyl-C), 129.54 (phenyl-C), 128.91 (phenyl-C), 128.84 (phenyl-C), 124.83 (phenyl-C), 124.00 (CF_3), 121.86 (phenyl-C), 121.77 (phenyl-C), 121.70 (phenyl-C), 79.63

(oxadiazine-CN), 69.86 (oxadiazine-CH_2), 64.32 (CH_2O), 56.32 (C-Cl),39.42 (cyclopentane-CH_2),. HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{18}BrClF_3N_3O_5$ $[M + H]^+$ 561.9987; found 562.0013.

(7-bromo-2-((4-(trifluoromethoxy)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 3-chloropropanoate **(J22).** Yield: 58.8%; white solid: mp 101–102 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.38 (s, 1H, NH), 7.67 (dd, *J* = 8.4, 5.1 Hz, 1H, phenyl), 7.59 – 7.54 (m, 2H, phenyl), 7.22 – 7.18 (m, 2H, phenyl), 7.12 – 7.05 (m, 2H, phenyl), 6.33 (dd, *J* = 17.4, 1.2 Hz, 1H, oxadiazine), 6.07 (dd, *J* = 17.3, 10.5 Hz, 1H, oxadiazine), 5.85 (dd, *J* = 10.5, 1.2 Hz, 1H, cyclopentane), 5.46 (s, 1H, cyclopentane), 5.46 (s, 1H, CH_2), 4.56 (dd, *J* = 12.3, 1.3 Hz, 1H, CH_2), 4.20 (d, *J* = 12.2 Hz, 1H, CH_2), 3.16 (s, 1H, CH_2). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 165.29 (O=C-O), 153.32 (CONH), 151.21 (oxadiazine-CN), 145.03 (phenyl-C), 144.79 (phenyl-C), 132.01 (phenyl-C), 127.41 (CF_3), 123.43 (phenyl-C), 123.36 (CF_3), 121.78 (phenyl-C), 121.37 (phenyl-C), 120.51 (phenyl-C), 119.67 (phenyl-C), 116.10 (phenyl-C), 115.95 (phenyl-C), 113.37 (phenyl-C), 113.21 (phenyl-C), 79.22 (oxadiazine-CN), 69.45 (oxadiazine-CH_2), 64.29 (CH_2O), 39.58 (cyclopentane-CH_2). HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{18}ClF_4N_3O_5$ $[M + H]^+$ 502.0787; found 502.0811.

(7-chloro-2-((4-(trifluoromethoxy)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl cinnamate **(J23).** Yield: 56.5%; white solid: mp 133–135 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.60 (s, 1H, NH), 7.87 (dd, *J* = 10.9, 8.5 Hz, 3H, phenyl), 7.64 (d, *J* = 8.7 Hz, 2H, phenyl), 7.54 (t, *J* = 6.3 Hz, 4H, phenyl), 7.43 (d, *J* = 16.1 Hz, 1H, phenyl), 7.37 (t, *J* = 7.4 Hz, 1H, vinyl), 7.29 (t, *J* = 7.6 Hz, 2H, phenyl), 6.53 (d, *J* = 16.1 Hz, 1H, vinyl), 5.50 (d, *J* = 9.2 Hz, 1H, oxadiazine), 5.27 (d, *J* = 9.2 Hz, 1H, oxadiazine), 4.47 (d, *J* = 12.2 Hz, 1H, cyclopentane), 4.37 (d, *J* = 12.2 Hz, 1H, cyclopentane), 3.38 (d, *J* = 16.0 Hz, 1H, CH_2), 3.18 (d, *J* = 16.0 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.77 (O=C-O), 154.59 (CONH), 145.63 (oxadiazine-CN), 145.36 (=C-phenyl), 136.29 (phenyl-C), 134.07 (phenyl-C), 133.25 (phenyl-C), 131.04 (phenyl-C), 129.23 (phenyl-C), 128.76 (phenyl-C), 126.71 (phenyl-C), 126.21 (phenyl-C), 125.84 (phenyl-C), 124.01 (phenyl-C), 123.33 (CF_3), 119.86 (=CH), 117.65 (phenyl-C), 79.75 (oxadiazine-CN), 70.05 (oxadiazine-CH_2), 65.09 (CH_2O), 39.80 (cyclopentane-CH_2). HRMS (ESI-TOF) m/z: calcd for $C_{28}H_{21}ClF_3N_3O_4$ $[M + Na]^+$ 578.1165; found 578.1163.

(7-bromo-2-((4-(trifluoromethyl)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl cinnamate **(J24).** Yield: 57.6%; white solid: mp 154–155 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.51 (s, 1H, NH), 7.63 (d, *J* = 8.5 Hz, 2H, phenyl), 7.58 (d, *J* =

7.9 Hz, 1H, phenyl), 7.53 (dq, *J* = 5.9, 3.7, 2.9 Hz, 5H, phenyl), 7.44 – 7.39 (m, 2H, phenyl), 7.36 (s, 1H, vinyl), 7.34 – 7.28 (m, 2H, phenyl), 6.35 (d, *J* = 16.1 Hz, 1H, vinyl), 5.53 (s, 1H, oxadiazine), 5.47 (s, 1H, oxadiazine), 4.58 (d, *J* = 12.2 Hz, 1H, cyclopentane), 4.26 (d, *J* = 12.1 Hz, 1H, cyclopentane), 3.32 (d, *J* = 15.7 Hz, 1H, CH_2), 3.18 (s, 1H, CH_2). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.00 (O=C-O), 154.09 (CONH), 150.84 (oxadiazine-CN), 146.22 (=C-phenyl), 144.38 (phenyl-C), 140.98 (phenyl-C), 133.82 (phenyl-C), 131.74 (phenyl-C), 130.69 (phenyl-C), 129.34 (phenyl-C), 128.88 (phenyl-C), 128.20 (phenyl-C), 126.28 (phenyl-C), 126.25 (phenyl-C), 126.22 (phenyl-C), 126.20 (phenyl-C), 125.96 (phenyl-C), 125.31 (phenyl-C), 125.10 (phenyl-C), 123.00 (CF_3), 118.76 (=CH), 116.60 (phenyl-C), 79.31 (oxadiazine-CN), 69.69 (oxadiazine-CH_2), 64.66 (CH_2O), 39.43 (cyclopentane-CH_2). HRMS (ESI-TOF) m/z: calcd for $C_{28}H_{21}BrF_3N_3O_4$ [M + Na]$^+$ 622.0560; found 622.0549.

(7-bromo-2-((4-(trifluoromethoxy)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl cinnamate **(J25).** Yield: 54.5.8%; white solid: mp 196–197 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.37 (s, 1H, NH), 7.54 (d, *J* = 8.0 Hz, 1H, phenyl), 7.52 – 7.44 (m, 3H, phenyl), 7.40(s, 1H, phenyl), 7.38(s, 1H, vinyl), 7.34 (t, *J* = 7.4 Hz, 2H, phenyl), 7.32(d, *J*=7.2 Hz, 1H, phenyl), 7.30(m, 2H, phenyl), 7.17 (d, *J* = 8.7 Hz, 2H, phenyl), 6.37 (d, *J* = 16.0 Hz, 1H, vinyl), 5.54 (d, *J* = 9.3 Hz, 1H, oxadiazine), 5.47 (d, *J* = 9.3 Hz, 1H, oxadiazine), 4.59 (dd, *J* = 12.2, 1.1 Hz, 1H, cyclopentane), 4.28 (d, *J* = 12.2 Hz, 1H, cyclopentane), 3.33 (d, *J* = 15.8 Hz, 1H, CH_2), 3.22 – 3.15 (m, 1H, CH_2). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.04 (O=C-O), 153.78 (CONH), 151.13 (oxadiazine-CN), 146.19 (=C-phenyl), 144.79 (phenyl-C), 144.35 (phenyl-C), 136.50 (phenyl-C), 133.84 (phenyl-C), 133.10 (phenyl-C), 131.71 (phenyl-C), 130.68 (phenyl-C), 129.32 (phenyl-C), 128.88 (phenyl-C), 128.23 (phenyl-C), 127.99 (phenyl-C), 125.83 (phenyl-C), 122.96 (CF_3), 121.77 (phenyl-C), 120.52 (=CH), 116.63 (phenyl-C), 79.27 (oxadiazine-CN), 69.72 (oxadiazine-CH_2), 64.68 (CH_2O), 39.41 (cyclopentane-CH_2). HRMS (ESI-TOF) m/z: calcd for $C_{28}H_{21}BrF_3N_3O_5$ [M + Na]$^+$ 638.0299; found 638.0303.

(7-fluoro-2-((4-(trifluoromethoxy)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl cinnamate **(J26).** Yield: 56.8%; white solid: mp 191–192 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.43 (s, 1H, NH), 7.88 (dd, *J* = 8.5, 5.4 Hz, 1H, phenyl), 7.75 (m, 2H, phenyl), 7.56 (s, 1H, phenyl), 7.55 (s, 1H, phenyl), 7.46 (d, *J* = 16.1 Hz, 1H, phenyl), 7.39 (t, *J* = 7.4 Hz, 1H, phenyl), 7.36 – 7.33 (m, 1H, vinyl), 7.31 (s, 1H, phenyl), 7.30(s, 1H, phenyl), 7.29 (dd, *J* = 8.4, 2.7 Hz, 3H, phenyl), 6.53 (d, *J* = 16.1 Hz, 1H, vinyl), 5.49 (d, *J* = 9.1 Hz, 1H,

oxadiazine), 5.21 (d, J = 9.1 Hz, 1H, oxadiazine), 4.44 (d, J = 12.4 Hz, 1H, cyclopentane), 4.36 (d, J = 12.2 Hz, 1H, cyclopentane), 3.37 (d, J = 16.0 Hz, 1H, CH_2), 3.18 (d, J = 16.1 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.80 (O=C-O), 154.70 (CONH), 151.87 (oxadiazine-CN), 146.06 (=C-phenyl), 145.62 (phenyl-C), 143.80 (phenyl-C), 138.52 (phenyl-C), 134.09 (phenyl-C), 131.04 (phenyl-C), 130.72 (phenyl-C), 129.23 (phenyl-C), 128.76 (phenyl-C), 124.43 (CF_3), 121.81 (phenyl-C), 121.54 (phenyl-C), 117.69 (=CH), 116.14 (phenyl-C), 115.98 (phenyl-C), 79.88 (oxadiazine-CN), 70.04 (oxadiazine-CH_2), 65.22 (CH_2O), 39.86 (cyclopentane-CH_2). HRMS (ESI-TOF) m/z: calcd for $C_{28}H_{21}F_4N_3O_4$ $[M + Na]^+$ 578.1100; found 578.1111.

(7-chloro-2-((4-(trifluoromethyl)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 2-(thiophen-2-yl)acetate **(J27).** Yield: 65.8%; white solid: mp 109–111 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.58 (s, 1H, NH), 7.92 (d, J = 8.6 Hz, 2H, phenyl), 7.82 (d, J = 8.9 Hz, 1H, phenyl), 7.69 (s, 1H, phenyl), 7.67 (s, 1H, phenyl), 7.52 (s, 1H, phenyl), 7.38 (d, J = 5.1 Hz, 2H, CH_2), 6.95(s, 1H, phenyl), 6.94– 6.92 (m, 2H, thiophene), 6.89(s, 1H, thiophene), 5.37 (d, J = 9.4 Hz, 1H, oxadiazine), 5.33 (s, 1H, oxadiazine), 4.51 (d, J = 12.4 Hz, 1H, cyclopentane), 4.17 (d, J = 12.4 Hz, 1H, cyclopentane), 3.35 (s, 1H, CH_2), 3.09 (d, J = 16.0 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.14 (O=C-O), 152.92 (CONH), 151.53 (oxadiazine-CN), 145.10 (phenyl-C), 143.00 (thiophene-C-S), 136.61 (phenyl-C), 136.13 (phenyl-C), 135.18 (phenyl-C), 128.73 (phenyl-C), 127.58 (phenyl-C), 127.17 (phenyl-C), 127.16 (phenyl-C), 127.05 (phenyl-C), 126.68 (phenyl-C), 126.29 (thiophene-C), 126.27 (thiophene-C), 125.97 (phenyl-C), 125.84 (phenyl-C), 125.57 (phenyl-C), 124.04 (CF_3), 69.46 (oxadiazine-CH_2), 79.24 (oxadiazine-CN), 64.72 (CH_2O), 35.35 (cyclopentane-CH_2), 31.42 (CH_2). HRMS (ESI-TOF) m/z: calcd for $C_{25}H_{19}ClF_3N_3O_4S$ $[M + H]^+$ 550.0810; found 550.0788.

(7-bromo-2-((4-(trifluoromethyl)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 2-(thiophen-2-yl)acetate **(J28).** Yield: 77.6%; white solid: mp 119–120 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.57 (s, 1H, NH), 7.91 (d, J = 8.6 Hz, 2H, phenyl), 7.76 (d, J = 8.0 Hz, 1H, phenyl), 7.65 (dd, J = 21.3, 9.6 Hz, 4H, phenyl), 7.37 (dd, J = 4.9, 1.4 Hz, 2H, CH_2), 6.97 – 6.91 (m, 2H, thiophene), 6.88 (d, J = 3.2 Hz, 1H, thiophene), 5.38 – 5.32 (m, 2H, oxadiazine), 4.49 (d, J = 12.4 Hz, 1H, cyclopentane), 4.16 (d, J = 12.4 Hz, 1H, cyclopentane), 3.35 (s, 1H, CH_2), 3.08 (d, J = 16.0 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, DMSO-d_6) δ 170.80 (O=C-O), 153.08 (CONH), 151.53 (oxadiazine-CN), 145.29 (phenyl-C), 136.58 (phenyl-C), 135.13 (phenyl-C), 133.73 (phenyl-C), 131.52 (phenyl-C), 129.55 (phenyl-C), 127.56 (phenyl-C), 127.15 (phenyl-

C), 127.05 (phenyl-C), 126.27 (phenyl-C), 126.25 (phenyl-C), 126.22 (thiophene-C), 126.20 (thiophene-C), 125.91 (phenyl-C), 125.81 (phenyl-C), 125.52 (CF_3), 124.91 (phenyl-C), 124.17 (phenyl-C), 124.02 (thiophene-C), 79.41 (oxadiazine-CN), 69.47 (oxadiazine-CH_2), 64.84 (CH_2O), 35.35 (CH_2). HRMS (ESI-TOF) m/z: calcd for $C_{25}H_{19}BrF_3N_3O_4S$ $[M + H]^+$ 596.0258; found 596.0270.

(7-bromo-2-((4-(trifluoromethoxy)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 2-(thiophen-2-yl)acetate **(J29).** Yield: 63.6%; white solid: mp 98–100 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.43 (s, 1H, NH), 7.75 (dd, J = 19.8, 8.6 Hz, 3H, phenyl), 7.67 – 7.63 (m, 2H, phenyl), 7.39 (d, J = 5.0 Hz, 2H, phenyl), 7.34 (d, J = 8.5 Hz, 2H, CH_2), 7.32(m, 1H, thiophene), 6.99 – 6.93 (m, 2H, thiophene), 5.34 (d, J = 9.4 Hz, 1H, oxadiazine), 5.32 (d, J = 9.4 Hz, 1H, oxadiazine), 4.49 (dd, J = 12.4, 1.3 Hz, 1H, cyclopentane), 4.16 (d, J = 12.4 Hz, 1H, cyclopentane), 3.88 (s, 2H), 3.30 (d, J = 15.1 Hz, 1H, CH_2), 3.09 (d, J = 15.7 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.78 (O=C-O), 156.29 (CONH), 152.61 (oxadiazine-CN), 144.91 (phenyl-C), 144.15 (thiophene-C-S), 136.48 (phenyl-C), 134.22 (phenyl-C), 131.70 (phenyl-C), 129.32 (phenyl-C), 127.21 (phenyl-C), 127.13 (phenyl-C), 126.93 (phenyl-C), 126.91 (thiophene-C), 125.30 (thiophene-C), 125.28 (CF_3), 121.83 (phenyl-C), 121.80 (phenyl-C), 120.69 (phenyl-C), 120.58 (phenyl-C), 78.99 (oxadiazine-CN), 69.30 (oxadiazine-CH_2), 64.32 (CH_2O), 39.29 (cyclopentane-CH_2), 34.99 (CH_2). HRMS (ESI-TOF) m/z: calcd for $C_{25}H_{19}BrF_3N_3O_4S$ $[M + CH_3CN]^+$ 648.0284; found 648.0302.

(7-fluoro-2-((4-(trifluoromethoxy)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 2-(thiophen-2-yl)acetate **(J30).** Yield: 72.5%; white solid: mp 89–91 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.57 (s, 1H, NH), 7.91 (d, J = 8.5 Hz, 2H, phenyl), 7.76 (d, J = 8.0 Hz, 1H, phenyl), 7.71(d, J = 8.6 Hz, 2H, phenyl), 7.67 (d, J = 8.6 Hz, 2H, phenyl), 7.65 – 7.62 (m, 2H, CH_2), 7.37 (dq, J = 3.9, 1.4 Hz, 2H, thiophene), 6.89 – 6.87 (m, 1H, thiophene), 5.36 (d, J = 9.4 Hz, 1H, oxadiazine), 5.34 (d, J = 9.4 Hz, 1H, oxadiazine), 4.49 (dd, J = 12.4, 1.3 Hz, 1H, cyclopentane), 4.16 (d, J = 12.4 Hz, 1H, cyclopentane), 3.35 (s, 1H, CH_2), 3.08 (d, J = 15.9 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, DMSO-d_6) δ 170.21 (O=C-O), 165.31 (phenyl-C), 163.67 (phenyl-C), 153.23 (CONH), 151.79 (oxadiazine-CN), 145.77 (phenyl-C), 143.87 (thiophene-C-S), 138.50 (phenyl-C), 136.61 (phenyl-C), 135.19 (phenyl-C), 127.58 (phenyl-C), 127.17 (phenyl-C), 127.06 (phenyl-C), 125.98 (thiophene-C), 125.58 (thiophene-C), 124.43 (CF_3), 121.85 (phenyl-C), 121.68 (phenyl-C), 116.09 (phenyl-C), 115.93 (phenyl-C), 79.60 (oxadiazine-CN),

69.44 (oxadiazine-CH_2), 64.86 (CH_2O), 34.75 (cyclopentane-CH_2), 26.80 (CH_2). HRMS (ESI-TOF) m/z: calcd for $C_{25}H_19F_4N_3O_4S$ $[M + H]^+$ 550.1050; found 550.1054.

(7-chloro-2-((4-(trifluoromethyl)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 3-(3-(trifluoromethyl)phenyl)acrylate **(J31).** Yield: 78.6%; white solid: mp 187–189 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.36 (s, 1H, NH), 7.71 (d, *J* = 9.6 Hz, 2H, phenyl), 7.62 (d, *J* = 8.3 Hz, 1H, phenyl), 7.59 (s, 1H, phenyl), 7.57 (s, 1H, phenyl), 7.52 (d, *J* = 8.9 Hz, 2H, phenyl), 7.44 (t, *J* = 7.8 Hz, 1H, vinyl), 7.14 (d, *J* = 8.7 Hz, 2H, phenyl), 7.12 – 7.08 (m, 2H, phenyl), 6.44 (d, *J* = 16.1 Hz, 1H, vinyl), 5.57 (d, *J* = 9.2 Hz, 1H, oxadiazine), 5.40 (d, *J* = 9.2 Hz, 1H, oxadiazine), 4.61 (d, *J* = 12.1 Hz, 1H, cyclopentane), 4.29 (d, *J* = 12.1 Hz, 1H, cyclopentane), 3.34 (d, *J* = 15.9 Hz, 1H, CH_2), 3.23 – 3.17 (m, 1H, CH_2). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 165.45 (O=C-O), 154.15 (CONH), 150.83 (oxadiazine-CN), 144.24 (=C-phenyl), 144.15 (phenyl-C), 140.91 (phenyl-C), 137.75 (phenyl-C), 134.61 (phenyl-C), 132.48 (phenyl-C), 131.58 (phenyl-C), 131.37 (phenyl-C), 131.08 (phenyl-C), 129.45 (phenyl-C), 128.92 (phenyl-C), 127.04 (phenyl-C), 127.02 (phenyl-C), 126.39 (phenyl-C), 126.24 (phenyl-C), 126.22 (phenyl-C), 126.19 (phenyl-C), 124.75 (phenyl-C), 124.72 (phenyl-C), 123.27 (CF_3), 122.84 (CF_3), 118.38 (C=C), 79.39 (oxadiazine-CN), 69.70 (oxadiazine-CH_2), 64.78 (CH_2O), 39.46 (cyclopentane-CH_2). HRMS (ESI-TOF) m/z: calcd for $C_{29}H_{20}ClF_6N_3O_4$ $[M + Na]^+$ 646.0939; found 646.0949.

(7-bromo-2-((4-(trifluoromethyl)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 2-(3-(trifluoromethyl)phenyl)acetate **(J32).** Yield: 68.5%; white solid: mp 159–160 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.48 (s, 1H, NH), 7.70 (s, 1H, phenyl), 7.63 (s, 1H, phenyl), 7.61 (d, *J* = 5.2 Hz, 2H, phenyl), 7.59 (dd, *J* = 8.6, 5.3 Hz, 2H, phenyl), 7.56(m, 1H, phenyl), 7.55 – 7.53 (m, 3H, phenyl), 7.52 – 7.44 (m, 1H, vinyl), 7.42 (s, 1H, phenyl), 6.43 (d, *J* = 16.0 Hz, 1H, vinyl), 5.55 (d, *J* = 9.3 Hz, 1H, oxadiazine), 5.46 (d, *J* = 9.3 Hz, 1H, oxadiazine), 4.62 (d, *J* = 12.2 Hz, 1H, cyclopentane), 4.28 (d, *J* = 12.2 Hz, 1H, cyclopentane), 3.34 (d, *J* = 15.8 Hz, 1H, CH_2), 3.19 (d, *J* = 15.8 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 165.44 (O=C-O), 154.19 (CONH), 150.82 (oxadiazine-CN), 144.34 (=C-phenyl), 144.24 (phenyl-C), 140.91 (phenyl-C), 134.62 (phenyl-C), 132.94 (phenyl-C), 131.76 (phenyl-C), 131.59 (phenyl-C), 131.38 (phenyl-C), 131.10 (phenyl-C), 129.45 (phenyl-C), 129.36 (phenyl-C), 127.01 (phenyl-C), 126.24 (phenyl-C), 126.21 (phenyl-C), 126.19 (phenyl-C), 126.02 (phenyl-C), 125.12 (phenyl-C), 125.07 (phenyl-C), 124.74 (phenyl-C), 124.56 (CF_3), 123.02 (CF_3), 118.70 (C=C),

79.32 (oxadiazine-CN), 69.70 (oxadiazine-CH_2), 64.77 (CH_2O), 39.40 (cyclopentane-CH_2). HRMS (ESI-TOF) m/z: calcd for $C_{29}H_{20}BrF_6N_3O_4$ $[M + H]^+$ 668.3812; found 668.3805.

(7-bromo-2-((4-(trifluoromethoxy)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 3-(3-(trifluoromethyl)phenyl)acrylate **(J33).** Yield: 74.6%; white solid: mp 151–153 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.36 (s, 1H, NH), 7.70 (s, 1H, phenyl), 7.61 (t, *J* = 9.2 Hz, 2H, phenyl), 7.57 (d, *J* = 3.0 Hz, 1H, phenyl), 7.54 (s, 2H, phenyl), 7.52 (d, *J* = 9.0 Hz, 2H, phenyl), 7.46 (s, 1H, phenyl), 7.44 (t, *J* = 7.8 Hz, 1H, vinyl), 7.14 (d, *J* = 8.5 Hz, 2H, phenyl), 6.43 (d, *J* = 16.1 Hz, 1H, vinyl), 5.54 (d, *J* = 9.3 Hz, 1H, oxadiazine), 5.45 (d, *J* = 9.3 Hz, 1H, oxadiazine), 4.61 (d, *J* = 12.2 Hz, 1H, cyclopentane), 4.27 (d, *J* = 12.2 Hz, 1H, cyclopentane), 3.34 (d, *J* = 15.9 Hz, 1H, CH_2), 3.18 (d, *J* = 15.8 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 165.45 (O=C-O), 153.83 (CONH), 151.10 (oxadiazine-CN), 144.80 (=C-phenyl), 144.30 (phenyl-C), 144.22 (phenyl-C), 136.44 (phenyl-C), 134.64 (phenyl-C), 133.05 (phenyl-C), 131.73 (phenyl-C), 131.38 (phenyl-C), 131.15 (phenyl-C), 129.44 (phenyl-C), 129.34 (phenyl-C), 127.02 (phenyl-C), 126.99 (phenyl-C), 126.38 (phenyl-C), 125.89 (phenyl-C), 124.74 (phenyl-C), 124.71 (phenyl-C), 124.57 (CF_3), 122.97 (CF_3), 122.76 (phenyl-C), 121.75 (phenyl-C), 118.69 (C=C), 79.27 (oxadiazine-CN), 69.73 (oxadiazine-CH_2), 64.79 (CH_2O), 39.40 (cyclopentane-CH_2). HRMS (ESI-TOF) m/z: calcd for $C_{29}H_{20}BrF_6N_3O_5$ $[M + H]^+$684.3806; found 684.3792.

(7-fluoro-2-((4-(trifluoromethoxy)phenyl)carbamoyl)-2,5-tetrahydroindeno[1,2-e][1,3,4]oxadiazin-4a-yl)methyl 3-(3-(trifluoromethyl)phenyl)acrylate **(J34).** Yield: 73.4%; white solid: mp 178–180 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.36 (s, 1H**,** NH), 7.73 – 7.70 (m, 2H, phenyl), 7.64 – 7.61 (m, 1H, phenyl), 7.61 – 7.57 (m, 2H, phenyl), 7.53 – 7.50 (m, 2H, phenyl), 7.45 (d, *J* = 7.8 Hz, 1H, vinyl), 7.16 – 7.14 (m, 2H, phenyl), 7.13 – 7.08 (m, 2H, phenyl), 6.44 (d, *J* = 16.1 Hz, 1H, vinyl), 5.57 (d, *J* = 9.2 Hz, 1H, oxadiazine), 5.40 (d, *J* = 9.3 Hz, 1H, oxadiazine), 4.61 (dd, *J* = 12.1, 1.2 Hz, 1H, cyclopentane), 4.29 (d, *J* = 12.1 Hz, 1H, cyclopentane), 3.34 (d, *J* = 15.9 Hz, 1H, CH_2), 3.20 (d, *J* = 15.9 Hz, 1H, CH_2). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 165.49 (O=C-O), 154.35 (CONH), 144.20 (=C-phenyl), 136.51 (phenyl-C), 134.65 (phenyl-C), 131.59 (phenyl-C), 131.37 (phenyl-C), 131.10 (phenyl-C), 130.07 (phenyl-C), 129.44 (phenyl-C), 129.29 (phenyl-C), 127.00 (phenyl-C), 126.98 (phenyl-C), 124.77 (phenyl-C), 124.74 (phenyl-C), 124.72 (phenyl-C), 124.69 (phenyl-C), 124.47 (phenyl-C), 123.97 (CF_3), 123.56 (CF_3), 123.50 (phenyl-C), 121.75 (phenyl-C), 116.21 (C=C), 79.45 (oxadiazine-CN), 69.76 (oxadiazine-CH_2),

64.94 (CH_2O). 39.68 (cyclopentane-CH_2). HRMS (ESI-TOF) m/z: calcd for $C_{29}H_{20}F_7N_3O_5$ [M + H]$^+$ 623.4750; found 623.4735.

Assessment of Bioactivity on *Spodoptera litura* F. Larvae of *S. litura* F. were obtained from Guangzhou zhongda biological engineering co. LTD. and raised with artificial diet at 26 ± 1 °C and 75 ± 5% relative humidity under a photoperiod of 16:8 h (light/dark).

The toxicities of indoxacarb and its derivatives against the third-instar larvae of *S. litura* F. were determined by the artificial diet method.[32] The compounds were dissolved in acetone and then mixed with an artificial diet. The treated artificial diet was placed into Petri dishes (9 cm diameter) and allowed acetone to volatilize for 2–3 h. Then, 10 larvae were introduced into each dish. Acetone without test compound was used as the control. The treated larvae in Petri dishes were kept at 26 ± 1 °C, photoperiod in a climatic chamber with 75 ± 5% relative humidity with a 16:8 h (light/dark). All treatments were replicated five times. Mortalities were determined 48 h after treatment. The LC_{50} values were calculated by the SPSS software.

Molecular Modeling. We used our most recent model of the bumble bee sodium channel to build a model of the cockroach channel BgNav1-1 and dock ligands with pyrethric acid (J7) and cinnamic acid (J24) moieties.[33] The model is based on the X-ray structure of an open sodium channel NavMs.[34] The chiral atom in the five-membered ring had the same configuration as in our model with an indoxacarb derivative, DCJW.[13] Configuration of the chiral atoms in the dimethylcyclopropane ring was the same as in pyrethric acid.[35] Atom charges at compound J7 and J24 were calculated by Austin Model 1(AM1) method realized in Motif Finding by Preprocessing and Agglomerative Clustering (MOPAC).[36] We designate residues in the model by using a labeling scheme, which is universal for P-loop channels.[37] A label includes the domain number (1– 4), segment type (i, an inner helix S6; p, a P-loop, and o, an outer helix S5), and relative number of the residue in the segment (**Figure 2)**. Computations were performed using the facilities of the Shared Hierarchical Academic Research Computing Network (SHARCNET, www.sharcnet.ca/my/front/).

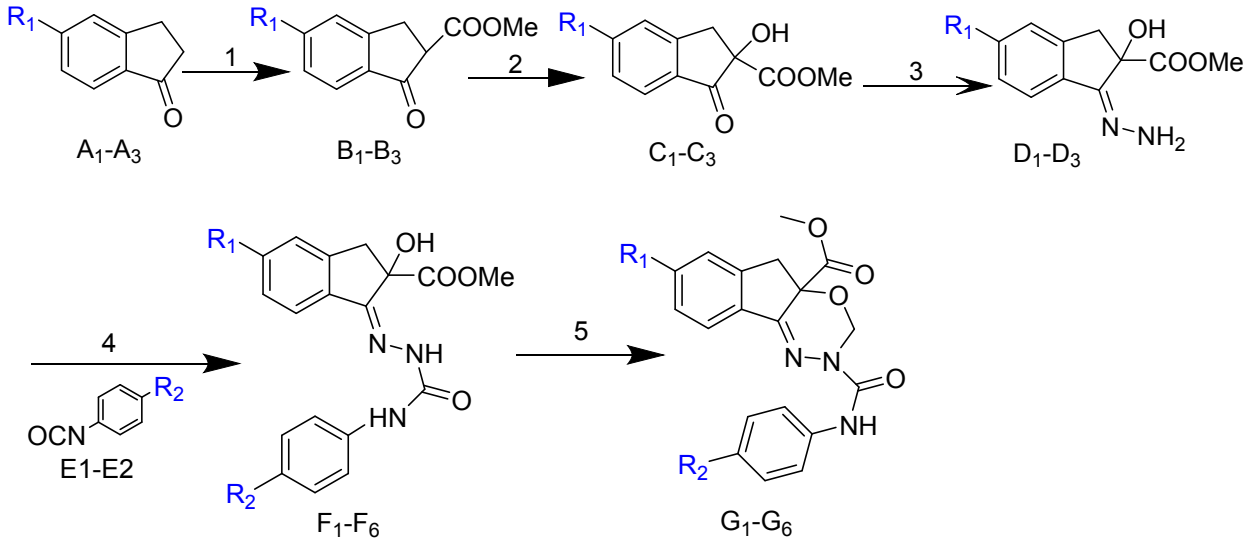
The ligand docking was performed with the Zimbabwe-Malawi- Mozambique (ZMM) program and Monte Carlo energy minimizations method (MCM) as described elsewhere.[38] The ligand was initially placed in the central cavity and its tricyclic moiety was oriented as in our model of DCJW-bound sodium channel.[13] Position, orientation and conformation of the ligand and the channel sidechain conformations were randomly sampled in the MCM protocol, but all degrees of freedom,

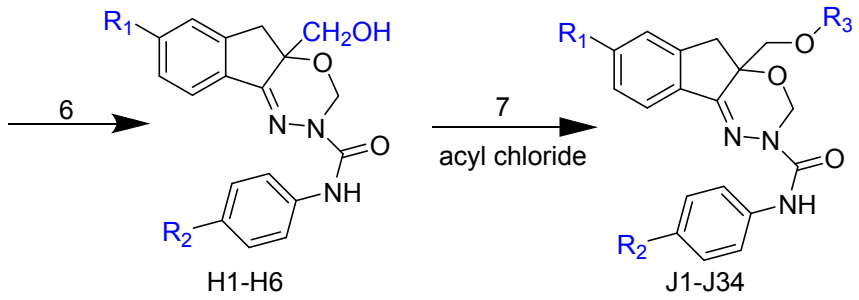
including translation of the sodium ion, backbone torsions and bond angles of the ligands and proline residues were energy minimized after each sampling.

RESULTS AND DISCUSSION

Chemistry. Indoxacarb analogs G1–G6 were synthesized as described in our previous work.[32] The ester group in G1–G6 was reduced with $LiAlH_4$ to yield alcohol intermediates H1–H6. These intermediates were synthesized by stirring indoxacarb analogs G1–G6 with dropwise a suspension of $LiAlH_4$ in anhydrous THF under argon. H1–H6 were treated with acyl chloride in DMAP and dry DIPEA in anhydrous THF under an argon atmosphere to give compounds J1–J34 **(Scheme 1)**. The TLC assay was supplemented with $LiAlH_4$ until the reactant consumption was complete. The NMR spectra of the key intermediates were obtained. We followed the same route employed in the synthesis of H1–H6. The latter were reacted with pyrethric acid chloride, cinnamoyl chloride and chloroacetyl chloride to give the title compounds J1–J34 (**Table 1**). These compounds were esterified with DMAP and dry DIPEA in anhydrous THF under an argon atmosphere and 0 ℃. After 2 hours, the reaction was quenched by anhydrous EtOH.

Due to compounds J1–J12 containing three chiral centers in alcohol and acid moieties, the two diastereomeric isomers, less polar isomers (J1-H-Rf to J12-H-Rf) and more polar isomers (J1-L-Rf to J12-L-Rf) showed different retention factor (Rf) values, were separated from each other by silica gel column chromatography (petroleum ether/ethyl acetate = 8:1, v/v).[39] The ^1H NMR, ^{13}C NMR and HRMS for all target compounds may be found in the supporting information.





Scheme 1. Synthesis of indoxacarb analogs J1–J34. Reagents and conditions: (1) DMC (dimethyl carbonate), NaH, t–BuOK; (2) Cinchonine, t–BuOOH, PhMe; (3) NH_2–$NH_2 \cdot H_2O$, CH_3COOH, MeOH; (4) THF; (5) $CH_2(OCH_3)_2$, P_2O_5, $ClCH_2CH_2Cl$; (6) $LiAlH_4$, THF; (7) DMAP, DIPEA, THF. Note: For indoxacarb, R_1=Cl and R_2=OCF_3 in G_1–G_6.

Insecticidal Activities and Structure–Activity Relationships (SAR). Preliminary larvicidal activities of compounds J1–J34 and indoxacarb (as control) against 3rd–instar larvae of *S. litura* F. were determined using an artificial diet method at the concentration of 50 μg/ml. High mortalities (63.33 – 100%) were observed for indoxacarb and compounds J7-L-Rf, J9-L-Rf, J21, J23, J24, and J26 and no to low mortalities for other forty compounds (**Table 2**)**.** In addition, we found that the insecticidal activity of J7-L-Rf and J9-L-Rf far exceeds that of J7-H-Rf and J9-H-Rf **(Table 2)**.

To explore structure–activity relationships of indoxacarb derivatives, we attached different substituents to the angular methoxycarbonyl position of indoxacarb by the methyl ester spacer arm (compounds J1–J34), indoxacarb and the six potent compounds, J7-L-Rf, J9-L-Rf, J21, J23, J24, and J26, were further tested to determine their LC_{50} values against *S. litura* F. in the artificial diet bioassay. **Table 3** shows toxicity of these compounds against *S. litura* F**.** Among these, J24 and J26 with substituent bromine and fluorine in the oxadiazine respectively, trifluoromethyl and trifluoromethoxy in the benzene ring and cinnamic acid in the angular methoxycarbonyl of oxadiazine of indoxacarb moiety are more potent than indoxacarb toxicity against *S. litura* F**.** Compounds J7-L-Rf and J9-L-Rf with substituent chlorine and bromine in the oxadiazine respectively, trifluoromethyl in the benzene ring, and pyrethric acid of cyhalothrin, tefluthrin or bifenfluthrin in the angular methoxycarbonyl of oxadiazine of indoxacarb moiety also had high insecticidal activities and compounds J21 and J23 with substituent bromine and chlorine in the oxadiazine, trifluoromethoxy and trifluoromethyl in the benzene ring, and chloroacetic acid and

cinnamic acid respectively in the angular methoxycarbonyl of oxadiazine of indoxacarb moiety exhibited moderate insecticidal activity on *S. litura* F. (**Table 3**).

Configuration of the indoxacarb carbon attached to methoxycarbonyl affects bioactivity, which resides almost exclusively in the S–enantiomer.[12] Studies of bioactivity and ecotoxicity of diastereomers and enantiomers of synthetic pyrethroids revealed the critical role of configuration of their chiral centers.[40-44] For example, the insecticidal activity of the *R, S, S* isomer, (*R, S*)-α-cyano-3-phenoxybenzyl (*S*)-2-(4-chlorophenyl)-isovalerate, of fenvalerate against the American cockroach was more than 36 times higher than that of the *R, S, R* isomer, (*R, S*)-α-cyano-3-phenoxybenzyl (*R*)-2-(4-chlorophenyl)-isovalerate.[43] In our current study, we demonstrated that the configuration of chiral carbons in indoxacarb derivatives also affects insecticidal activities. Thus, activities of the more polar diastereoisomers of J7 and J9 (J7-L-Rf and J9-L-Rf) was much higher than that of less polar diastereoisomers (J7-H-Rf and J9-H-Rf) (**Table 2**).

Docking Compound J7 and J24 into Homology Model of Insect Sodium Channel. An important feature of our previous models of sodium channel with DCJW and metaflumizone is presence of a sodium ion, which does not bind to the protein, but directly interacts with the ligands.[13] A completely hydrated sodium ion located at position Na_{III}, which does not bind to the channel residues, but would be accessible for interaction with the pore-bound ligands, is now seen in the X-ray structure a prokaryotic sodium channel NavMs.[45] In the NavMs-based homology model of the Nav1.4 sodium channel, a sodium ion at position Na_{III} is predicted to play a key role in attracting electronegative groups of various small-molecule ligands.[46] These include local anesthetics whose receptor site inside the pore overlaps with that of SCBIs.[14] In the current study we initially placed a sodium ion in position Na_{III} between four backbone carbonyls at the C-ends of P1 helices (T^{1p48}, C^{2p48}, T^{3p48} and T^{4p48}).

The lowest-energy complexes of the BgNav1-1 sodium channel with compound J7 is shown in **Figure 3**. The carbonyl oxygen in the amide group and trifluoromethyl substituted benzene ring are attracted by the sodium ion located at position Na_{III}. The central oxadiazine ring is close to the pore axis, while large terminal groups extend towards interfaces between repeat domains. The pyrethric acid moiety accepted an H-bond from N^{2i15} and interacted with many hydrophobic residues in helices IS6, IP1 and IIS6, including F^{1p44}, M^{1p47}, T^{1p48}, L^{1i18}, L^{1i21}, I^{1i22}, V^{2i11}, V^{2i12}, and L^{2i19}. Three of these (L^{1i18}, I^{1i22} and N^{2i15}) interact with deltamethrin in the model of the pyrethroid receptor site PyR2, which is based on the open potassium channel X-ray structure,[47] whereas V^{2i12}

947 and I^{1i22} interact with PyR-2 bound DDT.[48] Importantly, deltamethrin and DDT reach the PyR2
948 site from the lipid-exposed side of the I/II domain interface, while compound J7 reaches the four
949 residues in the PyR2 site from the inner-pore side of the same interface. The hydrophobic 5-
950 membered ring of J7 fused with the chlorine-substituted aromatic ring bind in the II/III domain
951 interface and enjoy hydrophobic interactions with L^{2o13}, L^{2p47}, C^{2p48}, V^{2i11}, V^{2i18}, L^{2i19}, F^{3p49}, I^{3i11}
952 and I^{3i12}. Two these (V^{2i18} and I^{3i12}) interact with deltamethrin in the PyR1 model [47] and four
953 residues (L^{2p47}, L^{2o13}, I^{3i12} and V^{2i18}) interact with tau-fluvalinate, which is bound in the PyR1 site
954 of the bumble bee sodium channel.[34] Importantly, while tau-fluvalinate reaches the PyR1 site from
955 the lipid-exposed side of the II/III domain interface, compound J7 reaches the four residues in the
956 PyR1 site from the inner-pore side of the same interface. The trifluoromethyl group of J7 binds
957 between helices IIIP1 and IVS6 and interacts with residues F^{4i15}, S^{4p49} and T^{3p48}.
958 The binding mode of compound J24 (**Figure 4**) general resembles that of J7, but has some
959 peculiarities. A common feature is location of the oxadiazine ring close to the pore axis, interaction
960 of the amide carbonyl oxygen with Na_{III}, binding of two large terminal moieties in domain
961 interfaces I/II and II/III where they interact with residues that contribute to the PyR1 and PyR2
962 receptor sites. However, the aromatic ring does not interact with Na_{III}. Specific list of ligand-
963 sensing residues overlaps with, but does not coincide with that for J7 (**Figures 3** and **4**).
964 It should be noted that, besides above-described lowest-energy binding modes of compounds J7
965 and J24, additional binding models with energies up to 7 kcal/mol from the apparent global minima
966 were found in our computations. In all these binding modes the oxadiazine ring binds inside the
967 pore and terminal moieties bind in domain interfaces. The homology models of the pseudo-
968 heteromeric eukaryotic sodium channels are not precise enough to favor particular binding modes
969 using only the ligand-channel energy. Further mutational, electrophysiological, and ligand-binding
970 experiments are necessary to refine the ligand-binding modes described in this study.
971 In general, we synthesized a series of tricyclic oxadiazine 4a-methyl ester derivatives containing
972 pyrethric acid or cinnamic acid ester moieties and explored relationships between structure and
973 biological activity. Several compounds exhibited excellent insecticidal activity against third–instar
974 larvae of *S. litura* F. These results open a new avenue towards developing new sodium channel
975 blocker and/or modulator insecticides. Computational docking of compounds J7 and J24 in the
976 homology models of the cockroach sodium channel predicts that the ligands bind in the inner pore
977 and their low-energy binding models generally resemble those that were previously proposed for

sodium-channel blocking insecticides, DCJW and metaflumizone. In particular, compound J7 and J24 interact with a sodium ion bound at the selectivity-filter region. The compound extends the terminal moieties into the I/II and II/III domain interfaces, reaching some residues that contribute to the pyrethroid receptor sites PyR1 and PyR2. Simultaneous interaction of the compounds with SCBI- and pyrethroid-sensing residues may explain their high toxicity.

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NOTES

The authors declare no competing financial interest.

Supplementary data

Supporting information may be found in the online version of this article: ^{1}H NMR, ^{13}C NMR and HRMS for all target compounds.

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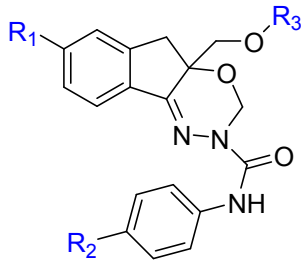
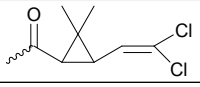
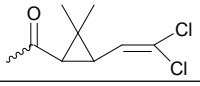
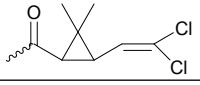
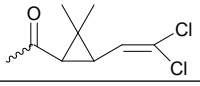
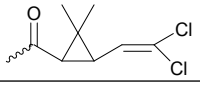
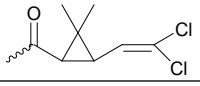
Table 1. the structures of target compounds J1-J34



J1-J34

Compd.	R_1	R_2	R_3
J1	Cl	CF_3	
J2	Cl	OCF_3	
J3	Br	CF_3	
J4	Br	OCF_3	
J5	F	CF_3	
J6	F	OCF_3	
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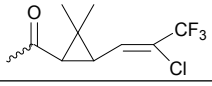
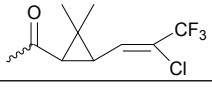
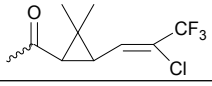
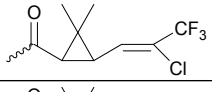
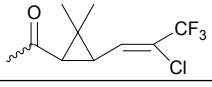
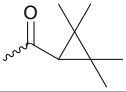
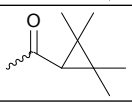
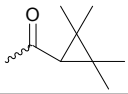
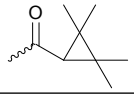
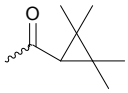
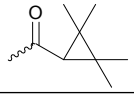
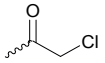
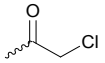
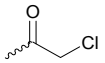
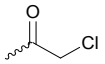
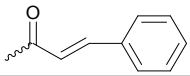
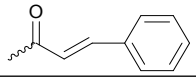
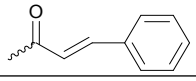
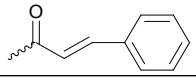
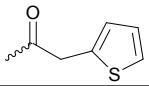
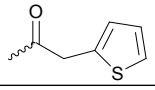
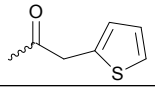
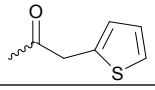
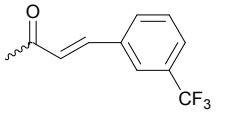
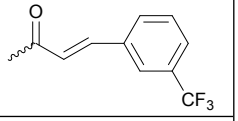
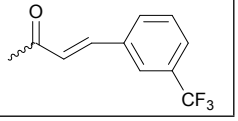
J8	Cl	OCF_3	
J9	Br	CF_3	
J10	Br	OCF_3	
J11	F	CF_3	
J12	F	OCF_3	
J13	Cl	CF_3	
J14	Cl	OCF_3	

J15	Br	CF_3	
J16	Br	OCF_3	
J17	F	CF_3	
J18	F	OCF_3	
J19	Cl	CF_3	
J20	Br	CF_3	
J21	Br	OCF_3	
J22	F	OCF_3	
J23	Cl	CF_3	
J24	Br	CF_3	
J25	Br	OCF_3	
J26	F	OCF_3	
J27	Cl	CF_3	
J28	Br	CF_3	
J29	Br	OCF_3	
J30	F	OCF_3	
J31	Cl	CF_3	
J32	Br	CF_3	
J33	Br	OCF_3	

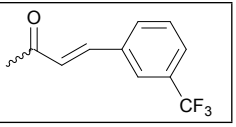
J34	F	OCF_3	

Table 2. Forty–eight hours effect of indoxacarb and compounds against third–instar larvae of *Spodoptera litura* F.

Compd.	Mortality (%)*
J1-H-Rf	23.33±0.33 g**
J1-L-Rf	0.00±0.00 l
J2-H-Rf	13.33±6.67 i
J2-L-Rf	0.00±0.00 l
J3-H-Rf	0.00±0.00 l
J3-L-Rf	0.00±0.00 l
J4-H-Rf	0.00±0.00 l
J4-L-Rf	0.00±0.00 l
J5-H-Rf	0.00±0.00 l
J5-L-Rf	3.33±0.33k
J6-H-Rf	0.00±0.00 l
J6-L-Rf	0.00±0.00 l
J7-H-Rf	0.00±0.00 l
J7-L-Rf	93.33±0.33 b
J8-H-Rf	16.67±3.33 h
J8-L-Rf	3.33±0.33 k
J9-H-Rf	0.00±0.00 l
J9-L-Rf	76.67±0.67 c
J10-H-Rf	0.00±0.00 l
J10-L-Rf	33.33±0.89 f
J11-H-Rf	16.67±3.33 h
J11-L-Rf	3.33±0.33 k
J12-H-Rf	0.00±0.00 l
J12-L-Rf	33.33±0.58 f
J13	10.00±0.58 i
J14	3.33±0.33 k
J15	0.00±0.00 l
J16	0.00±0.00 l
J17	3.33±0.33 k
J18	33.33±0.33 f
J19	16.67±0.33 h
J20	0.00±0.00 l
J21	63.33±0.33 d

J22	20.00±0.58 h
J23	63.33±0.89 d
J24	100.00±0.00 a
J25	43.33±0.33 e
J26	100.00±0.00 a
J27	10.00±0.58 i
J28	20.00±0.00 h
J29	23.33±0.33 h
J30	40.00±0.00 e
J31	3.33±0.33 k
J32	6.20±0.58 j
J33	0.00±0.00 l
J34	0.00±0.00 l
Indoxacarb	100.00±0.00 a
CK	0.00±0.00 l

*Test concentration is 50 μg/ml.

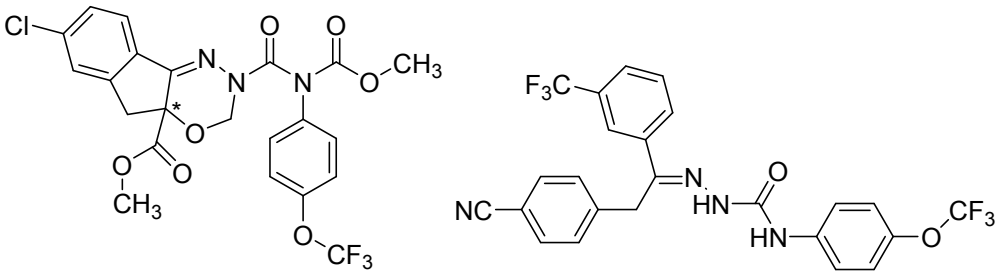
** Data followed by the same letter in a column are not significantly different at 5% level by Duncan's Multiple Range Test (DMRT).

Table 3. Larvicidal activity of indoxacarb derivatives against third-instar larvae of *Spodoptera litura* F.

Compd.	LC_{50}* (μg/ml) (95% CI†)	Slope±SE	Chi-Square (χ^2)	R
J7-L-Rf	6.37 (4.71-10.10)	5.735±0.334	0.225	0.993
J9-L-Rf	6.84(5.26-8.86)	6.830±0.311	2.609	0.965
J21	16.70(11.78-26.93)	5.218±0.275	0.409	0.977
J23	11.99(8.59-17.38)	5.571±0.274	0.171	0.953
J24	1.99(1.36-2.59)	5.168±0.437	0.987	0.951
J26	2.77(2.12-3.51)	5.777±0.434	2.938	0.963
Indoxacarb	4.54(3.17-6.38)	5.562±0.274	0.898	0.950

* LC_{50}: concentration required to kill 50%.

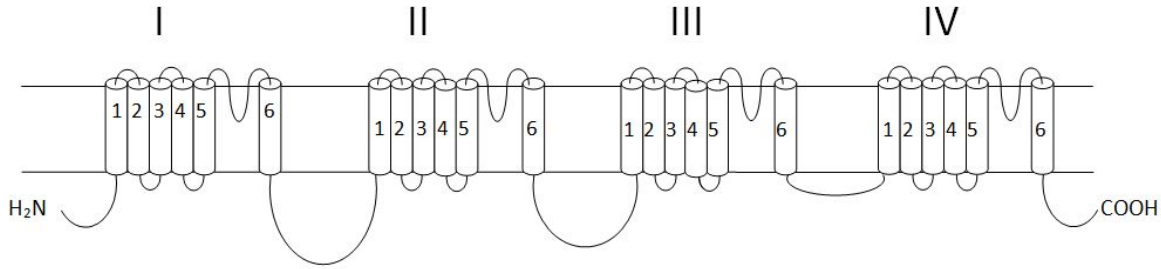
†CI: confidence interval.



Indoxacarb metaflumizone

Figure 1. Structures of indoxacarb and metaflumizone. Chiral centers are marked with asterisks.

A



B

Domain	Residue #	o1	o11	o21	
IS5	265	ESVKNLRDVI	ILTMFSLSVF	ALMGLQIYM	
IIS5	902	RTVGALGNLT	FVLCIIIFIF	AVMGMQLFG	
IIIS5	1397	QAIPSIFNVL	LVCLIFWLIF	AIMGVQLFA	
IVS5	1715	MSLPALFNIC	LLLFLVMFIF	AIFGMSFFM	
		p33	p41	p51	
IP	300	CIKNFWAF	LSAFRLMTQD	YWENLYQL	
IIP	937	VERFPHSF	MIVFRVLCGE	WIESMWDC	
IIIP	1436	STTLSKAY	LCLFQVATFK	GWIQIMND	
IVP	1750	GLDDVQSM	ILLFQMSTSA	GWDGVLDG	
		i1	i11	i21	i31
IS6	402	PWHMLFFIVI	IFLGSFYLVN	LILAIVAMSY	DELQKKA
IIS6	981	WSCIPFFLAT	VVIGNLVVLN	LFLALLLSNF	GSSNLSA
IIIS6	1506	IYMYLYFVFF	IIFGSFFTLN	LFIGVIIDNF	NEQKKKA
IVS6	1806	TVGLAFLLSY	LVISFLIVIN	MYIAVILENY	SQATEDV

Figure 2. **A**, Topology of alpga-1 subunit of sodium channels. **B,** Pore domain residues in cockroach sodium channel BgNav1-1. Position of a residue is designated by a symbol, which

identifies a segment, and a relative position of the residue in the segment. Symbols "o", "p" and "i", represent, respectively, the outer helix, the P-loop, and the inner helix.

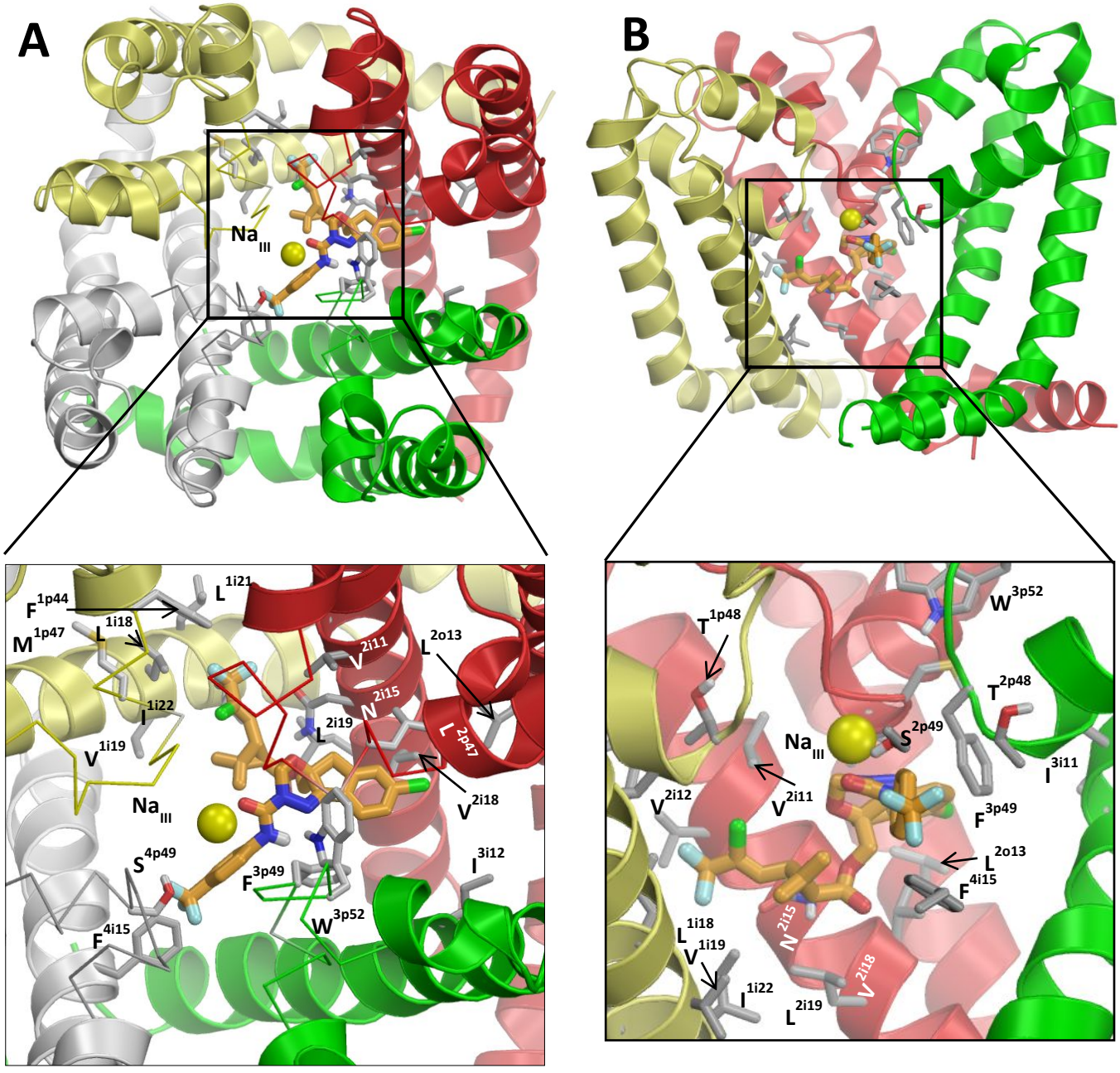


Figure 3. Extracellular (**A**) and membrane (**B**) views of compound J7 in the pore module of the open sodium channel BgNav1-1. Domains I, II, III and IV are yellow, red, green and gray, respectively. For clarity, P-loops are shown as C^{α} tracing at **A**, and domain IV is removed at **B**. The ligand is shown by thick sticks with orange carbons, and ligand-sensing residues with 5 Å

from the ligand as thin sticks with gray carbons. A sodium ion at the focus of P1 helices is shown by a yellow sphere.

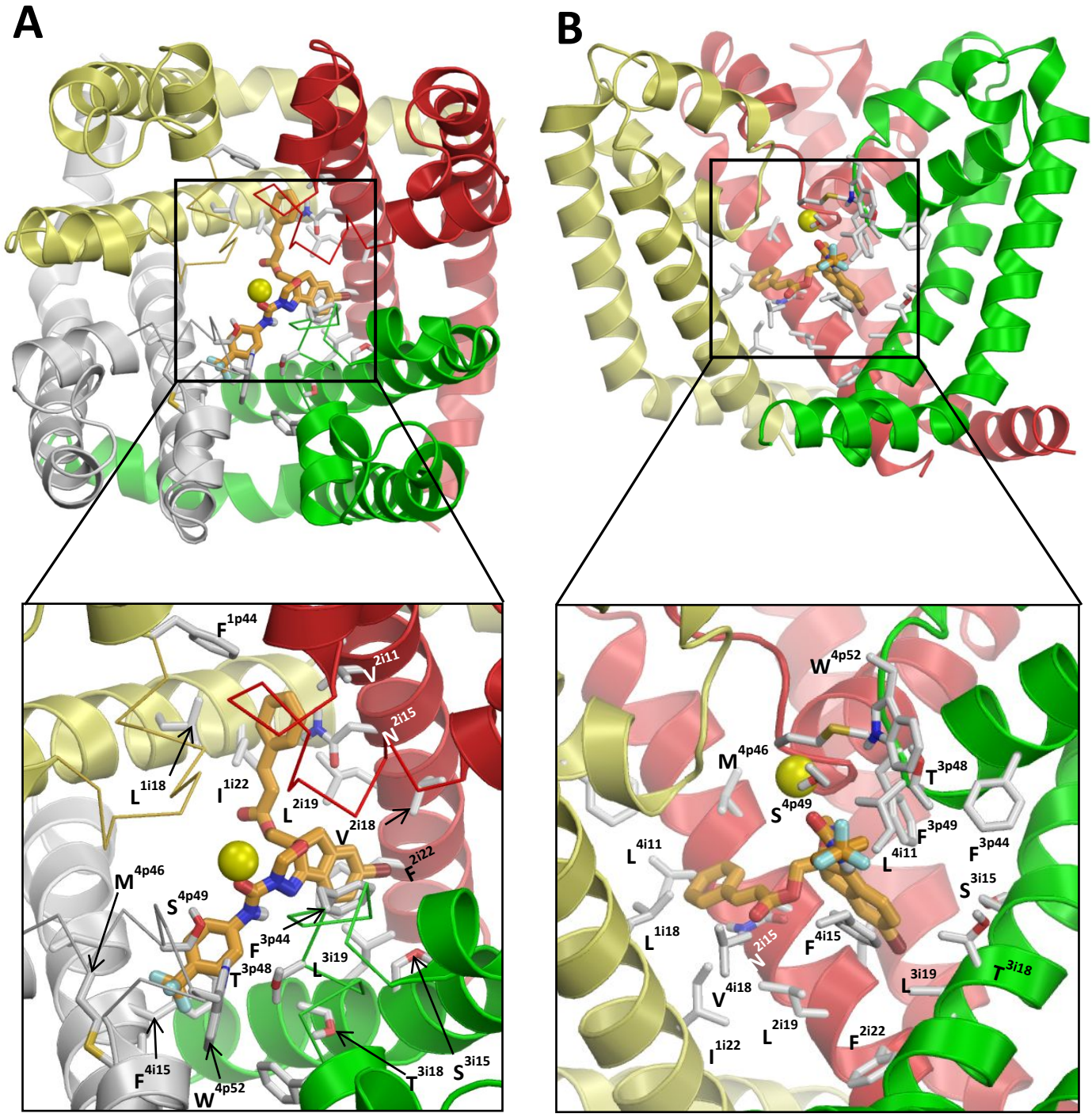


Figure 4. Extracellular (**A**) and membrane (**B**) views of compound J24 in the pore module of the open sodium channel BgNav1-1. Domains I, II, III and IV are yellow, red, green and gray, respectively. For clarity, P-loops are shown as C^{α} tracing at **A**, and domain IV is removed at **B**.

1181 The ligand is shown by thick sticks with orange carbons, and ligand-sensing residues with 5 Å
1182 from the ligand as thin sticks with gray carbons. A sodium ion at the focus of P1 helices is shown
1183 by a yellow sphere.