Communication

Synthesis and Properties of Pentafluorosulfanyl Group (SF5)-Containing meta-Diamide Insecticides

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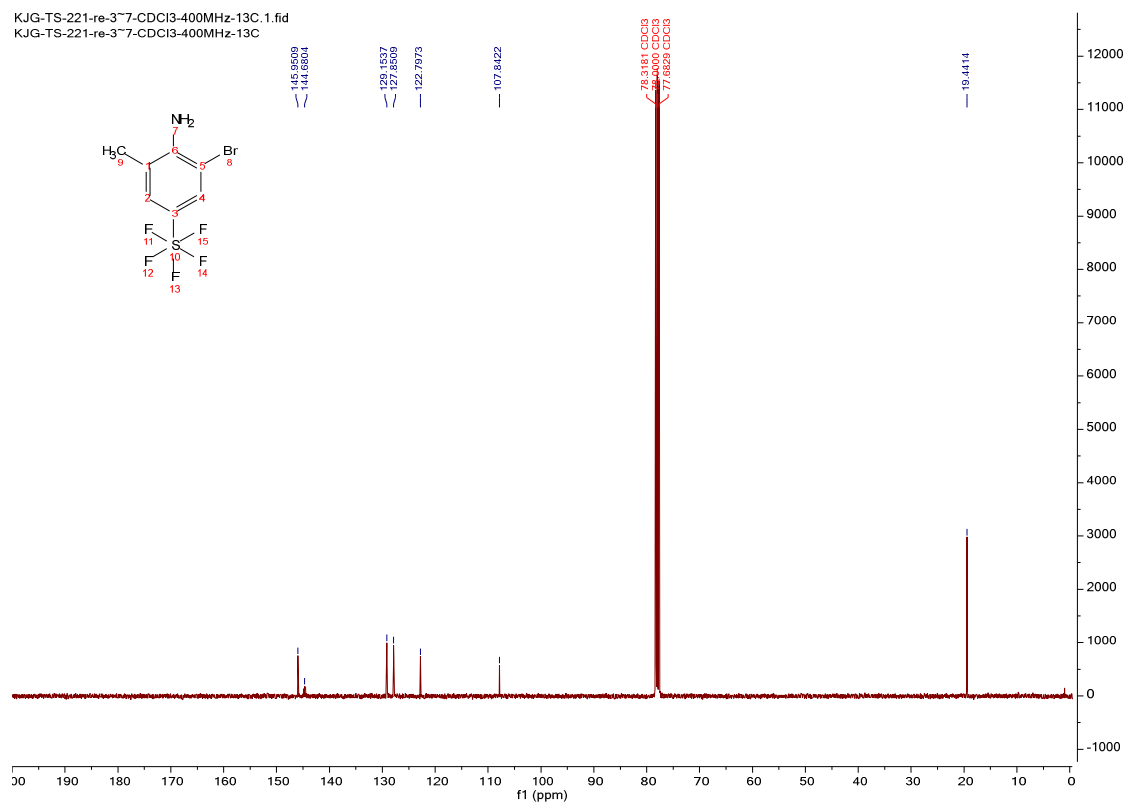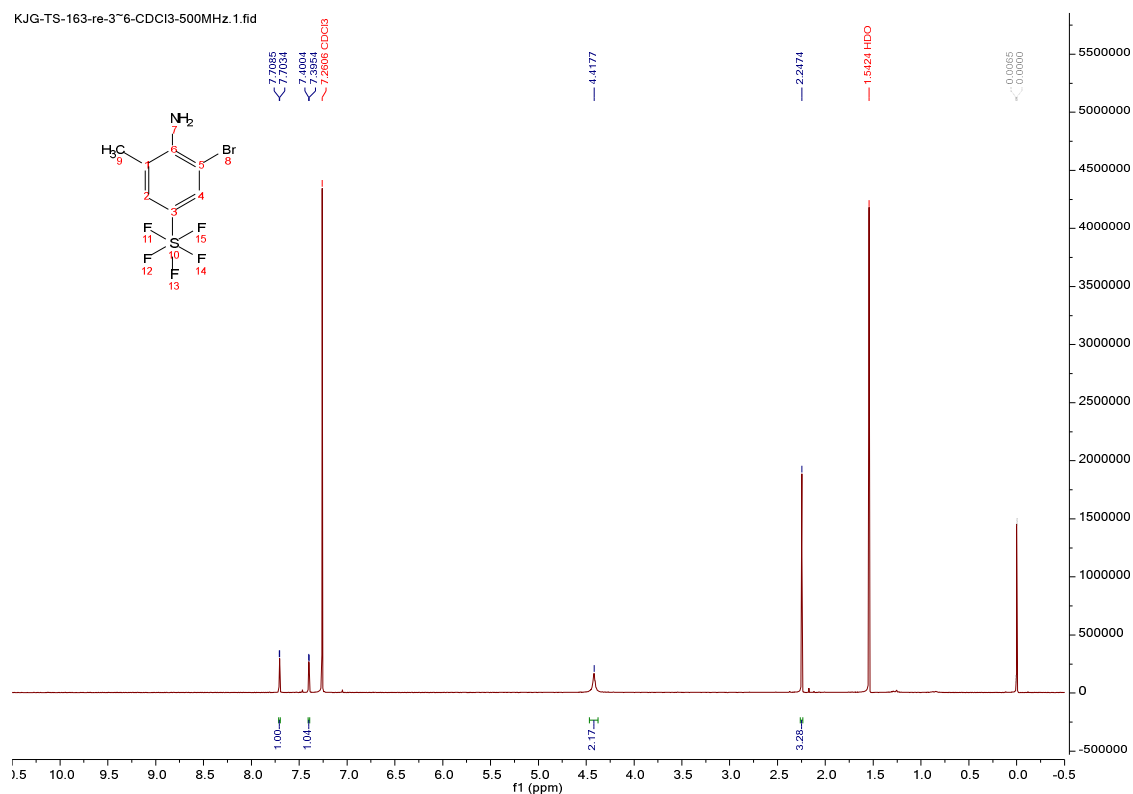
Supporting information (Supplementary Data)

Contents

¹H, ¹³C and ¹⁹F NMR spectroscopy of 1c.

KJG-TS-163-re-3~6-CDCl3-500MHz.1.fid

KJG-TS-221-re-3~7-CDCl3-400MHz-13C.1.fid
KJG-TS-221-re-3~7-CDCl3-400MHz-13C

2C-CDCl3-500MHz-19F.1.fid
2C-CDCl3-500MHz-19F

¹H, ¹³C and ¹⁹F NMR spectroscopy of 1d.

KJG-TS-169-2-CDCl3

KJG-TS-356-re-4-CDCl3-400MHz-13C.1.fid
KJG-TS-356-re-4-CDCl3-400MHz

2D-CDCl3-500MHz-19F.1.fid
2D-CDCl3-500MHz-19F

¹H, ¹³C and ¹⁹F NMR spectroscopy of 3.

KJG-TS-Benzoylation-DMSO-400MHz-13C.13.fid
KJG-TS-Benzoylation-DMSO-400MHz-13C

KJG-TS-Benzoylation-DMSO-500MHz-19F.1.fid
KJG-TS-Benzoylation-DMSO-500MHz-19F

¹H, ¹³C and ¹⁹F NMR spectroscopy of 4a.

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KJG-TS-363-Recry-CDCl3-500MHz

KJG-TS-363-Recry-13C-CDCl3-400MHz.1.fid
KJG-TS-363-Recry-13C-CDCl3-400MHz

Download/5A-CDCl3-500MHz-19F
1
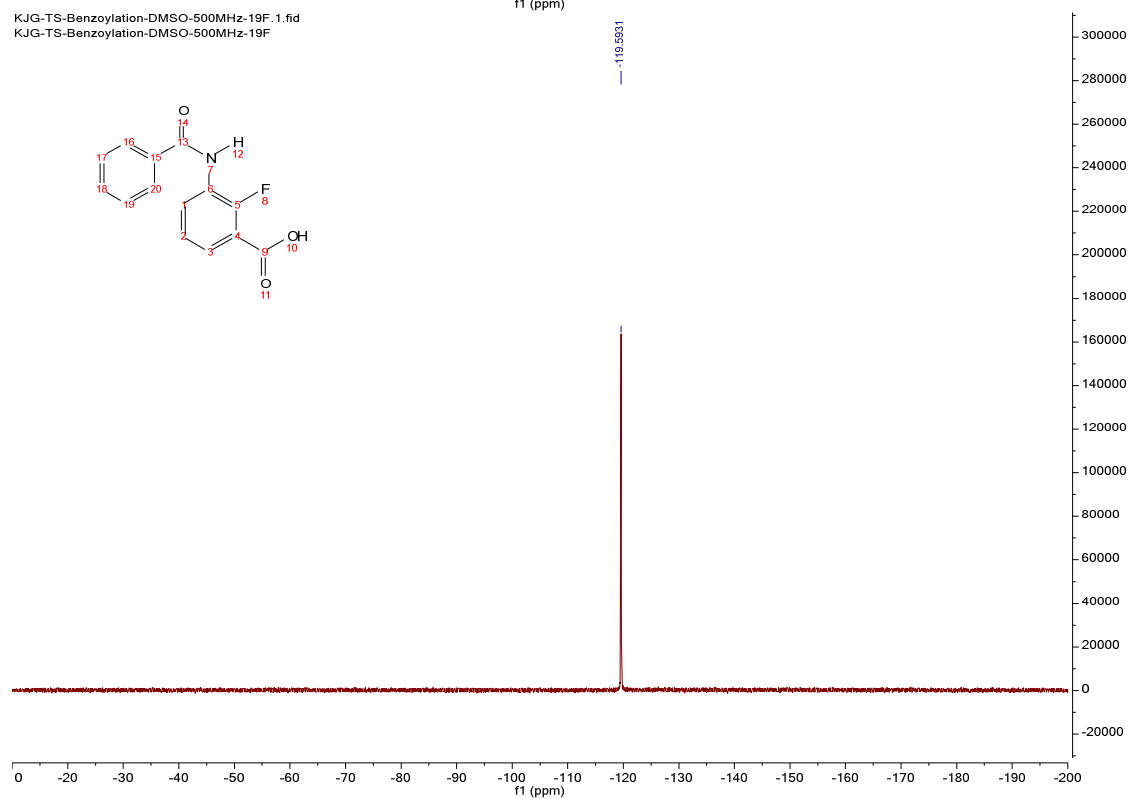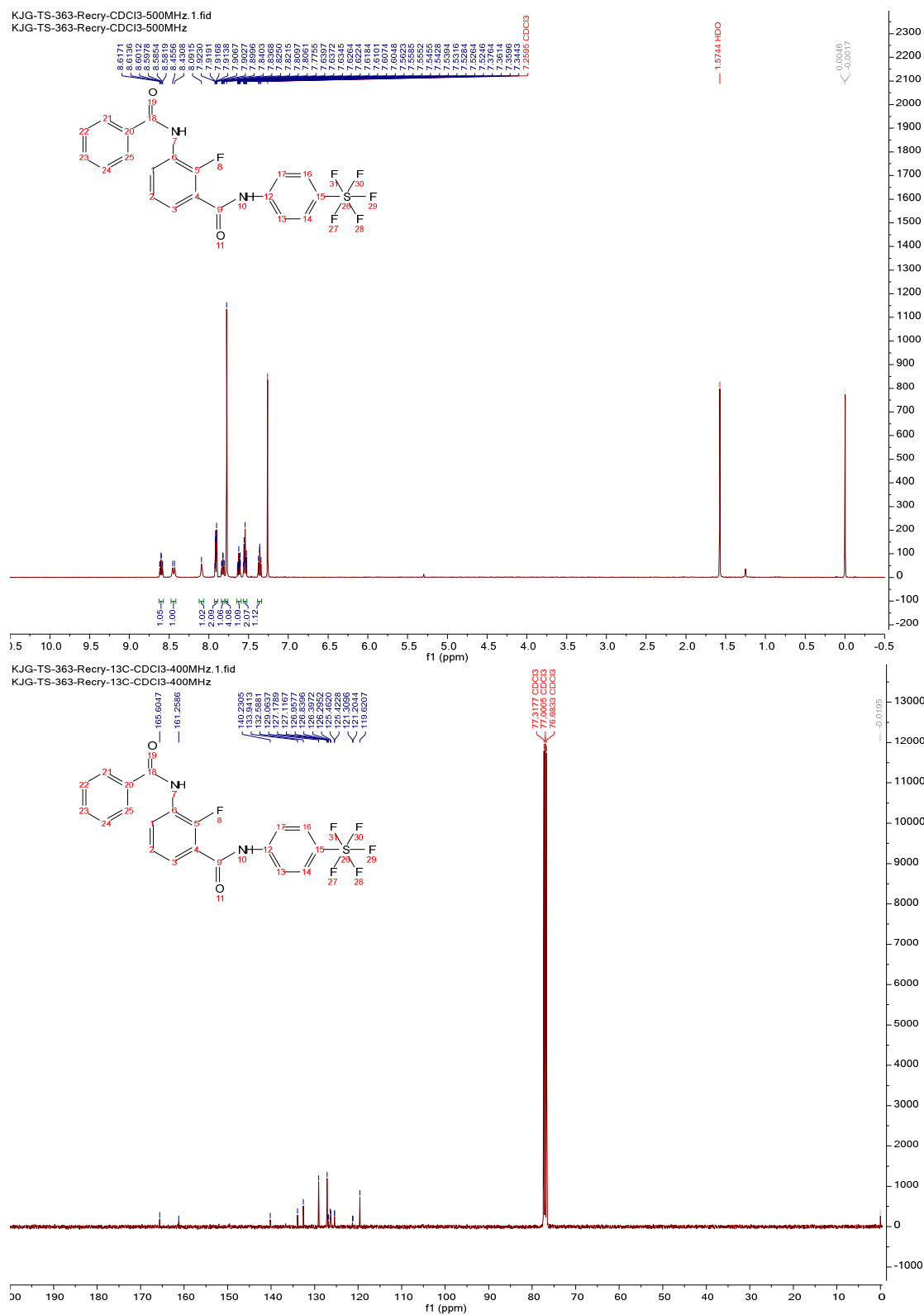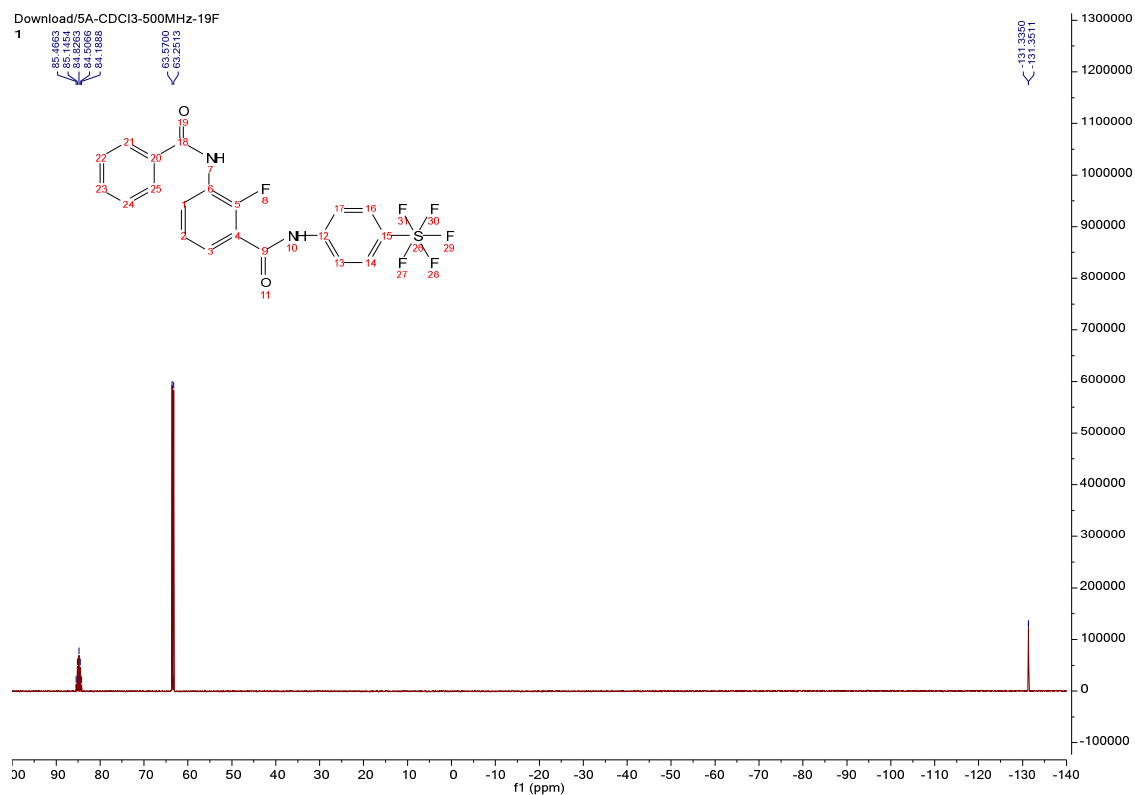
¹H, ¹³C and ¹⁹F NMR spectroscopy of 4b.

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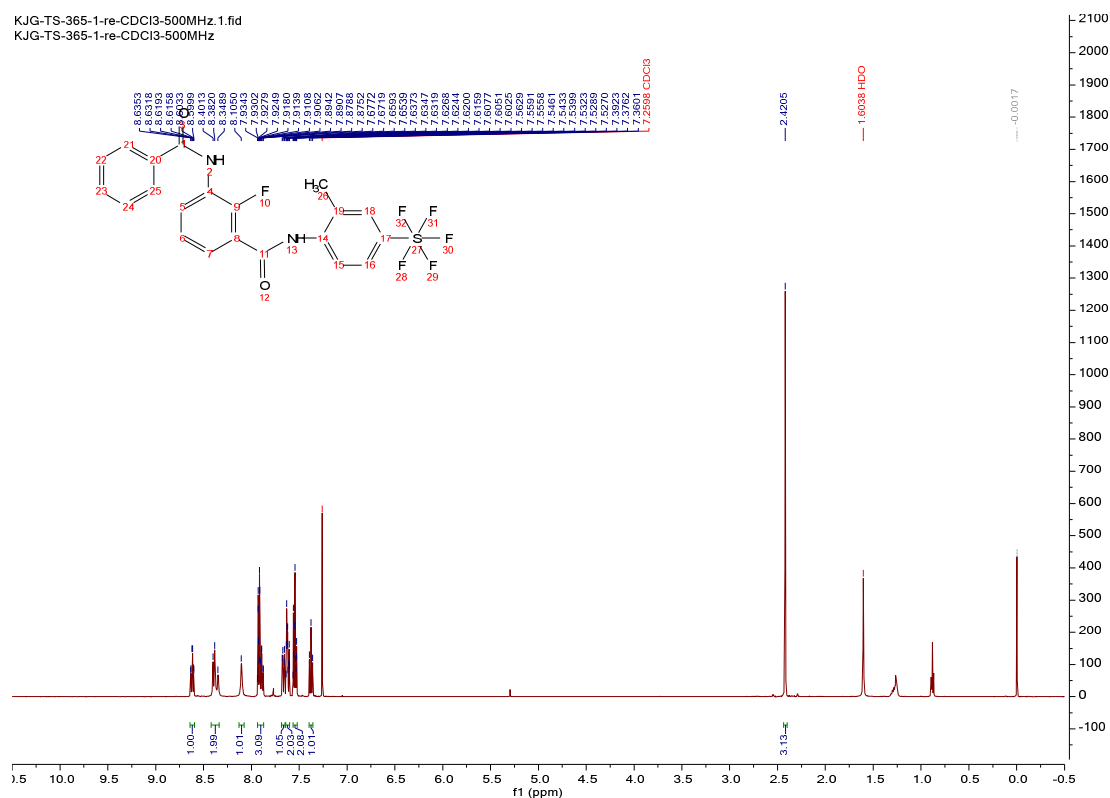
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KJG-TS-365-1-re-CDCl3-400MHz-13C

5B-CDCl3-500MHz-19F.1.fid
5B-CDCl3-500MHz-19F

¹H, ¹³C and ¹⁹F NMR spectroscopy of 4c.

5C-CDCl3-500MHz-19F.1.fid
5C-CDCl3-500MHz-19F

¹H, ¹³C and ¹⁹F NMR spectroscopy of 4d.

KI-03066-re-re-re-Recry-CDCl3-500MHz.1.fid
KI-03066-re-re-re-Recry-CDCl3-500MHz

KI-03066-re-re-18-13C-400MHz.1.fid
KI-03066-re-re-18-13C-400MHz
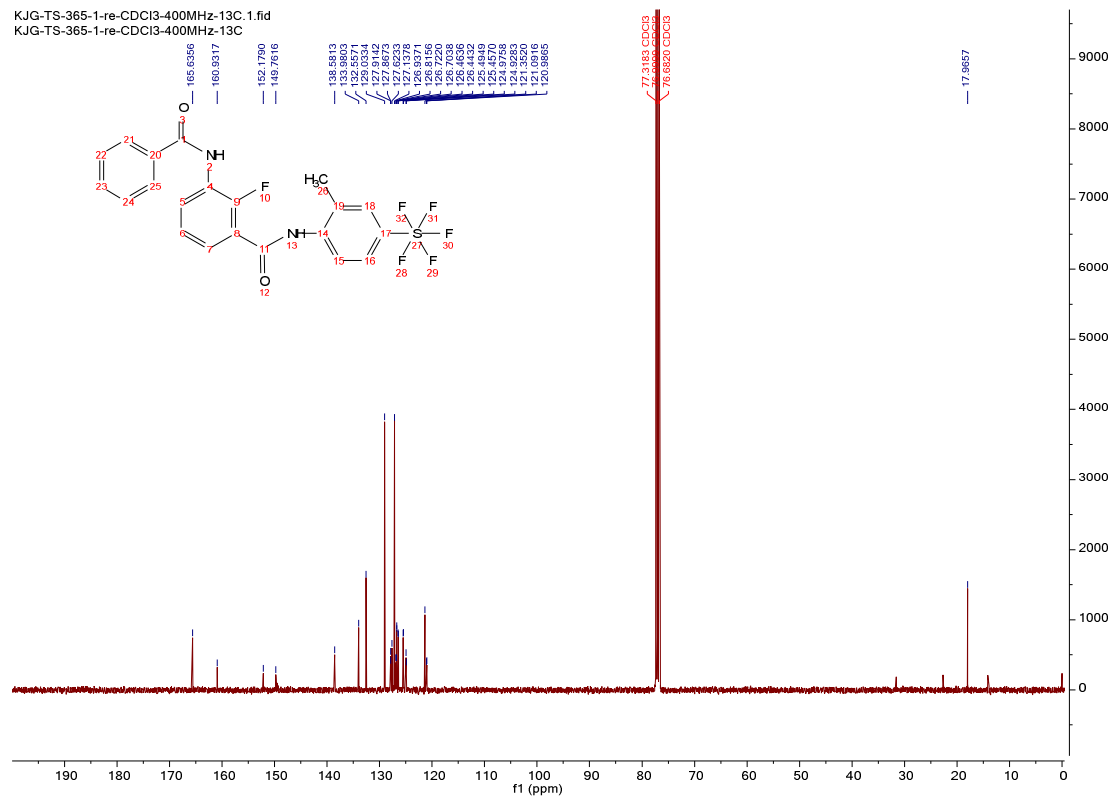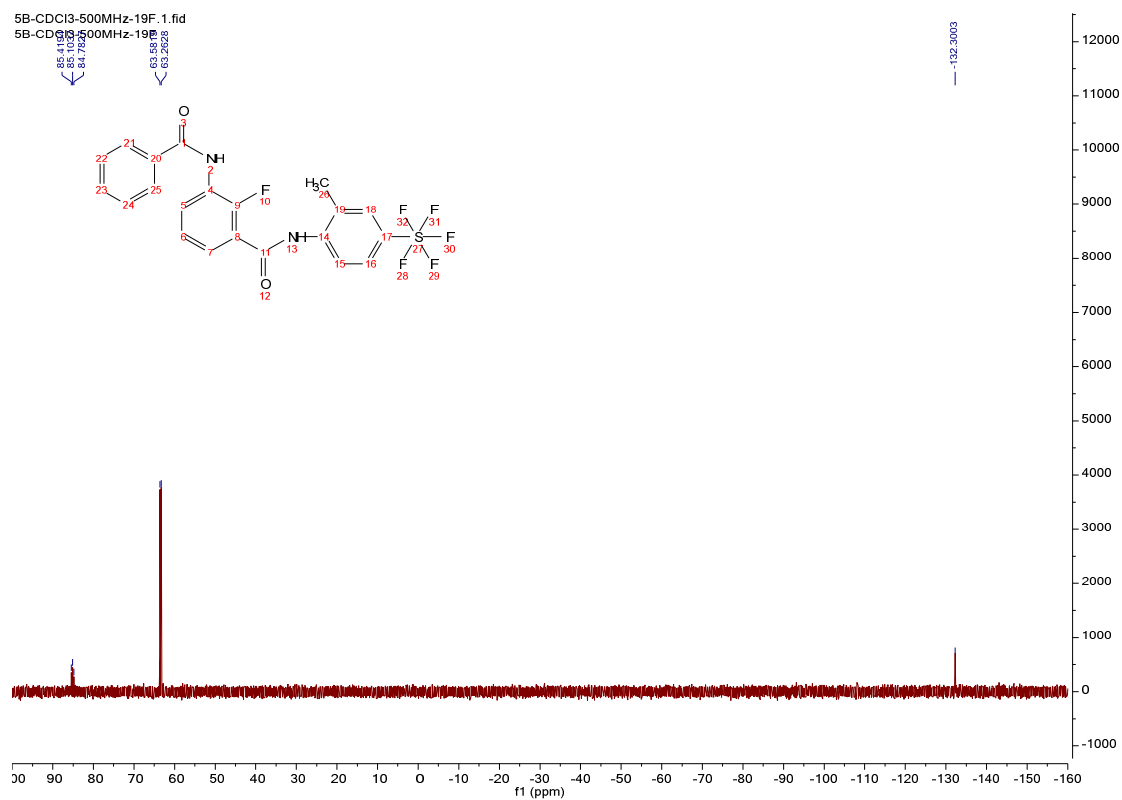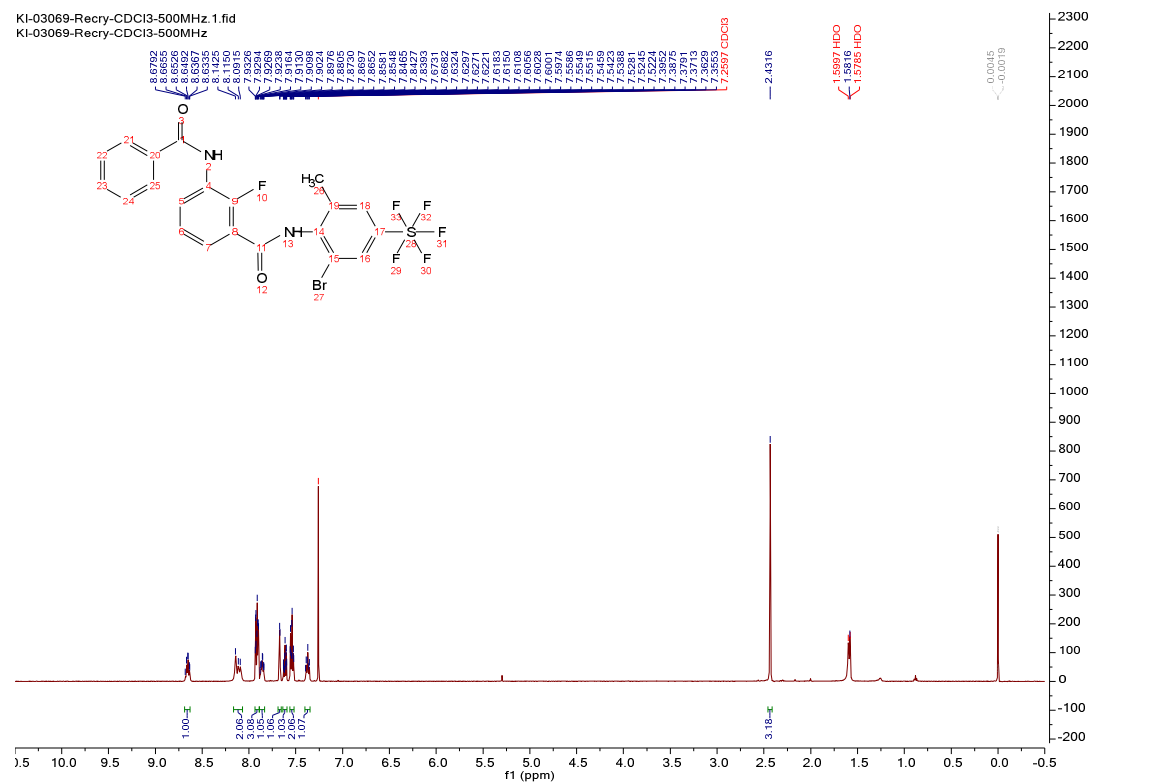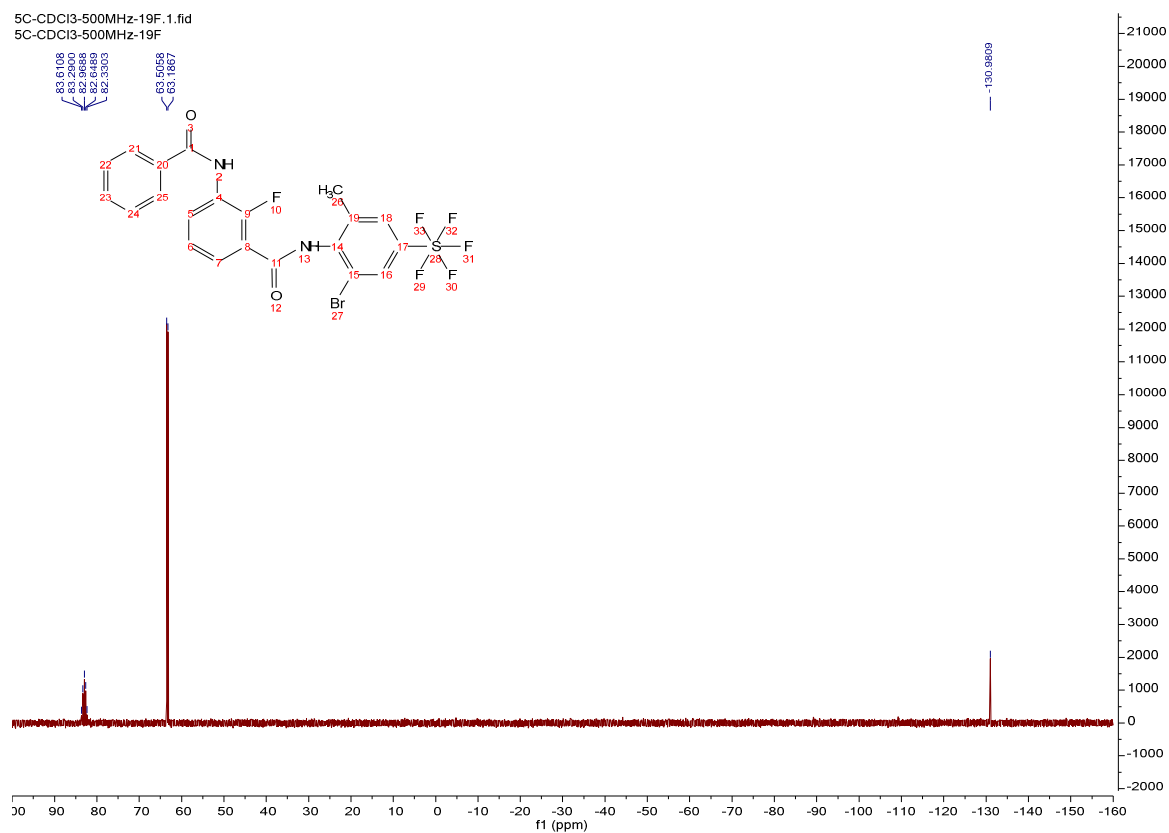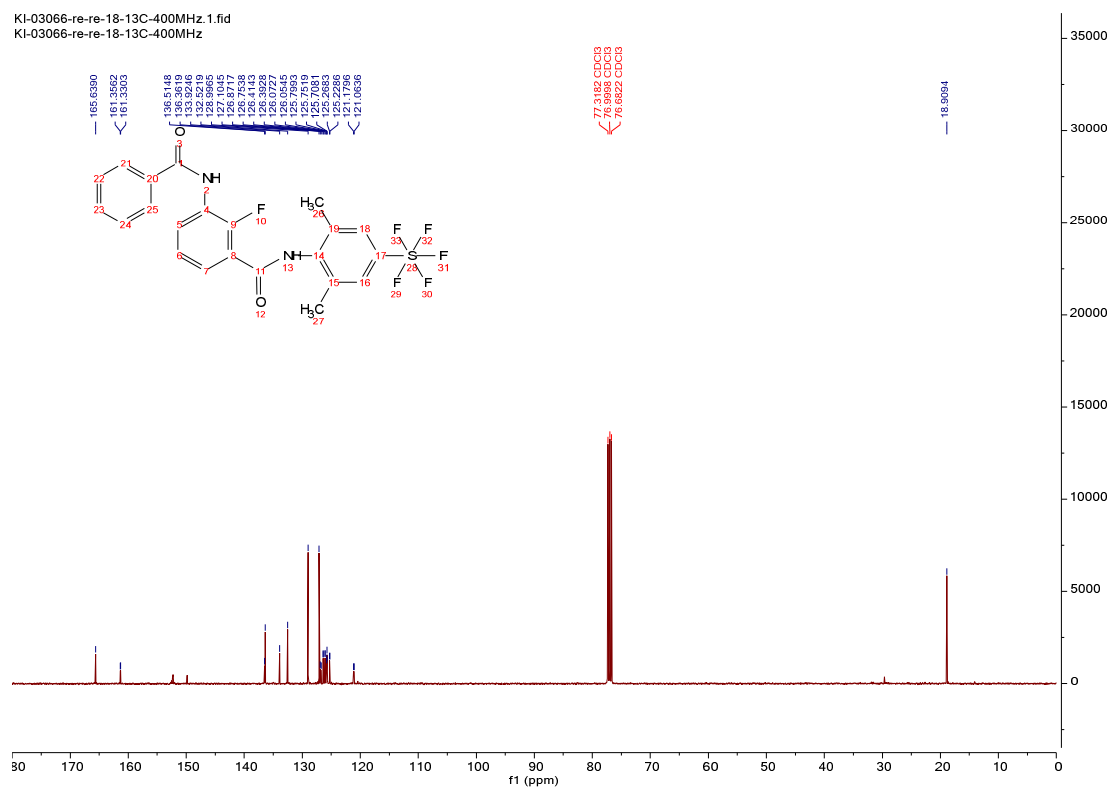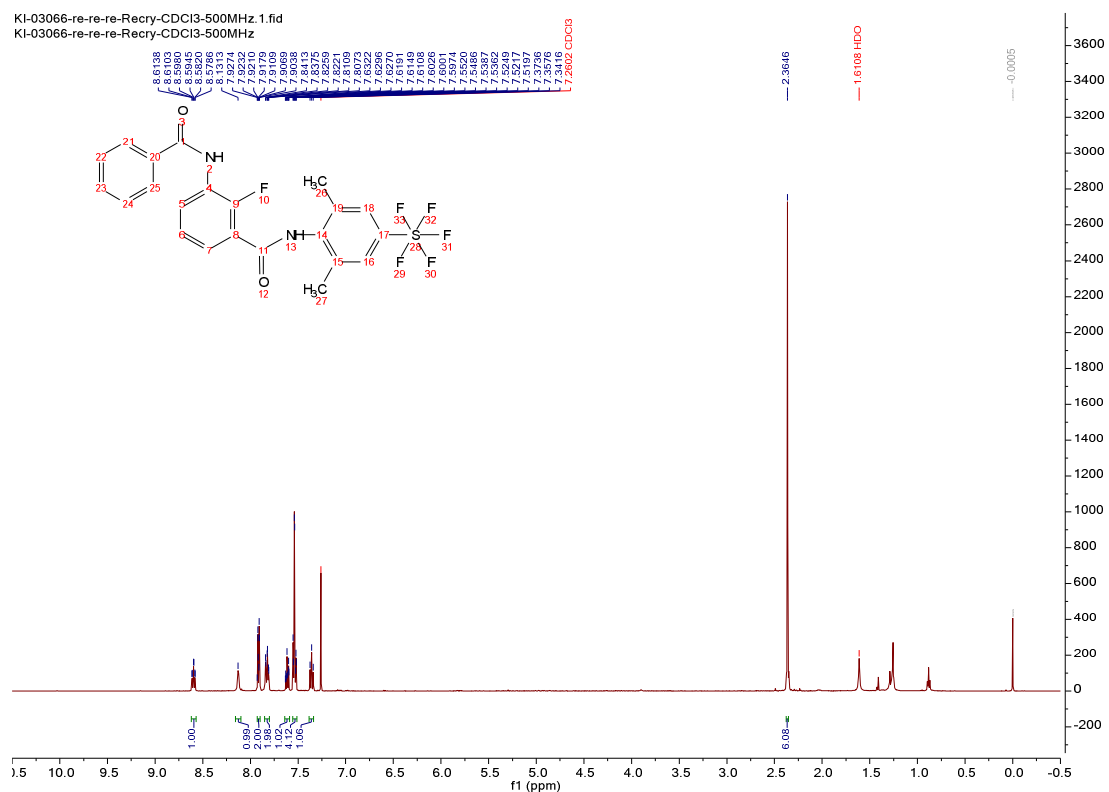
Table S1 and S2: Larvicidal activity against Plutella xylostella (4c and 4d)

The lavicidal activities of synthesized compounds were evaluated by the leaf-dip procedure. The aqueous solution of prepared compounds and Broflanilide in acetone (H$_2$O : acetone = 95 : 5) were sprayed to a cabbage leave placed on moistened filter paper (disc, diameter 8.8 cm) in petri dishes. After allowing to dry, the dishes were infested with 10 Plutella xylostella (third-instar). After 1, 2, 3, and 4 days, percentage of mortalities was evaluated. The treatments were replicated three times. For negative control, larvicidal activities were 0 % at each time. Ref. is Broflanilide as a positive control.

Table S1. Larvicidal activity depend on time.

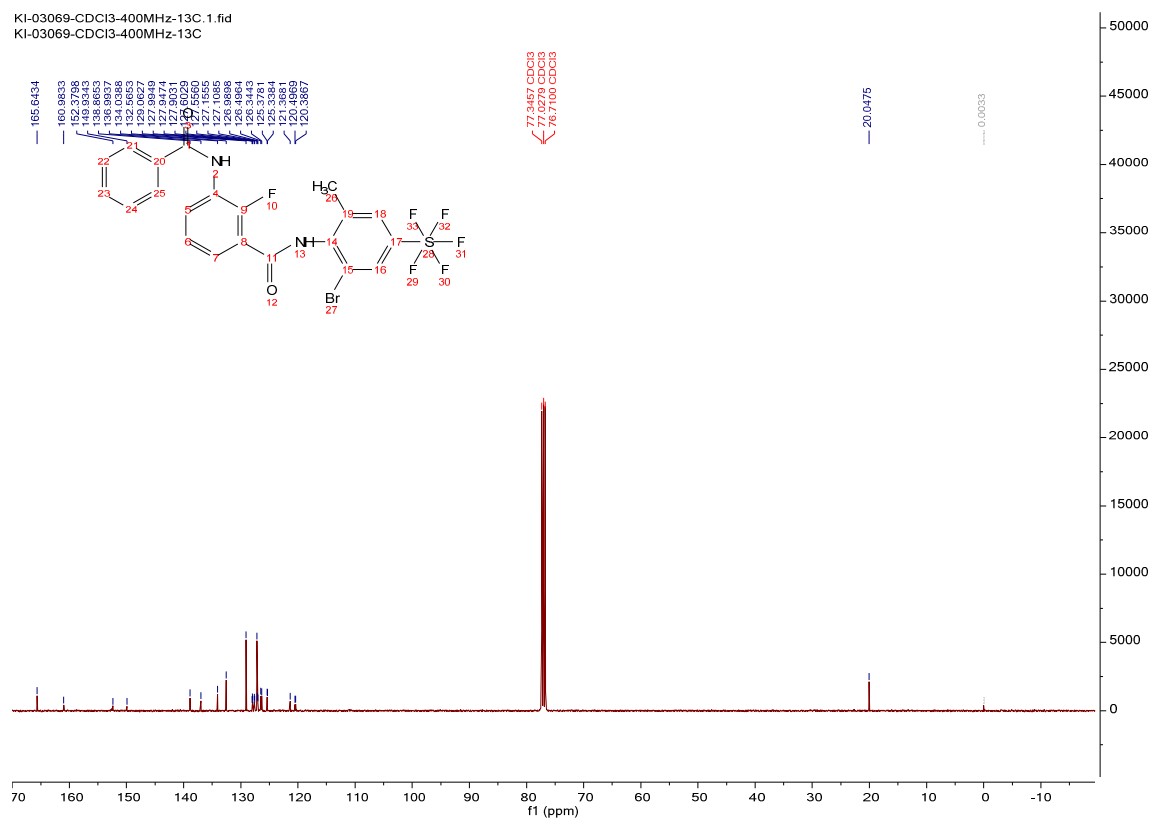| Entry	Compound	Concentration (ppm)	Against the 3rd Instar Larvae of *Plutella xylostella*			
			Larvicidal activity (%) at **24 h**			
			1	2	3	Average
1	**4c**	10	50.0	60.0	60.0	56.7
2	**4d**	10	0	10.0	20.0	10.0
3	Ref.	10	100	100	100	100.0

Entry	Compound	Concentration (ppm)	Against the 3rd Instar Larvae of *Plutella xylostella*			
			Larvicidal activity (%) at 48 h			
			1	2	3	Average
1	**4c**	10	90.0	90.0	90.0	90.0
2	**4d**	10	90.0	70.0	80.0	80.0
4	Ref.	10	100	100	100	100.0

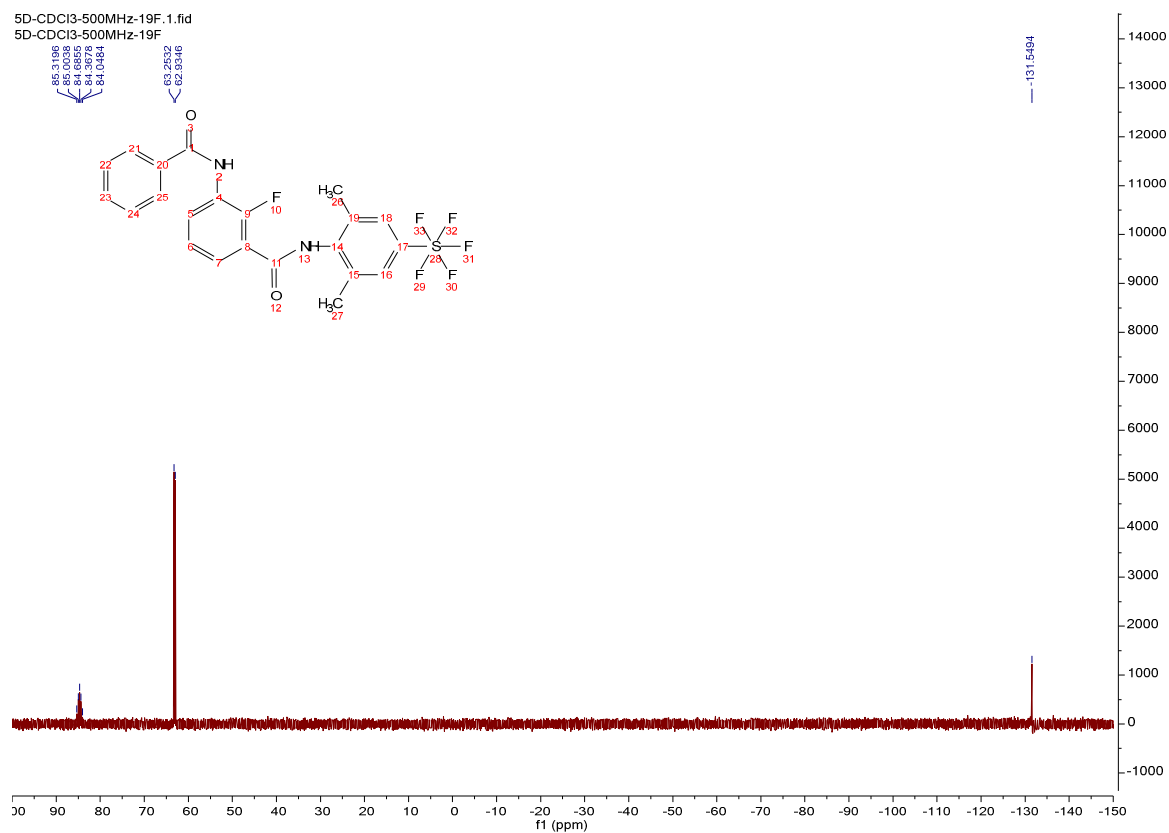| Entry	Compound	Concentration (ppm)	Against the 3rd Instar Larvae of *Plutella xylostella*			
			Larvicidal activity (%) at 72 h			
			1	2	3	Average
1	**4c**	10	90.0	90.0	90.0	90.0
2	**4d**	10	90.0	80.0	80.0	83.3
4	Ref.	10	100	100	100	100.0

Entry	Compound	Concentration (ppm)	Against the 3rd Instar Larvae of *Plutella xylostella*			
			Larvicidal activity (%) at 96 h			
			1	2	3	Average
1	**4c**	10	90.0	90.0	90.0	90.0
2	**4d**	10	90.0	90.0	80.0	86.7
4	Ref.	10	100	100	100	100.0

Table S2. Picture of eating area.

Entry	Compd	Pictures of eating area_ after 96 h (The 3rd instar stage larvae of *Spodoptera litura*)
1	**4c**	5–10 % eating
2	**4d**	0–5 % eating
3	Ref. positive control (Broflanilide)	0–5 % eating
4	Negative control	

pH-metric

Sample name: **KI-03066**	Experiment start time: **08/09/2020 07:26:11**
Assay name: **pH-metric medium logP**	Analyst:
Assay ID: **20I-08012**	Instrument ID: **T313101**
Filename: **D:\Data\Customer\20I-08012_KI-03066_pH-metric medium logP.t3r**	

Overall results

RMSD	0.168
Average ionic strength	0.156 M
Average temperature	25.0°C
Partition ratio	0.2833 : 1
Analyte concentration range	1430.9 µM to 1492.8 µM
Total points considered	30 of 44

Warnings and errors

Errors	None
Warnings	Sample concentration factor out of range

Four-Plus parameters

🔒	Alpha	0.072	08/09/2020 07:26:11	D:\Data\Customer\20I-07022_Blank standardisation.t3r
🔒	S	1.0038	08/09/2020 07:26:11	D:\Data\Customer\20I-07022_Blank standardisation.t3r
🔒	jH	0.4	08/09/2020 07:26:11	D:\Data\Customer\20I-07022_Blank standardisation.t3r
🔒	jOH	−0.3	08/09/2020 07:26:11	D:\Data\Customer\20I–07022_Blank standardisation.t3r

Titrants

🔒	0.50 M HCl	0.979835	08/09/2020 07:26:11	D:\Data\Customer\20I-07023_Blank standardisation.t3r
🔒	0.50 M KOH	1.004720	08/09/2020 07:26:11	D:\Data\Customer\20I-07020_KHP_Base standardisation using KHP.t3r

Sample

🔻	KI-03066 concentration factor	0.088
🔒	Acid pKa 1	11.00
🔒	Acid pKa 2	12.20
🔻	logP (neutral XH2)	4.68
🔻	logP (XH -)	6.11
🔻	logP (X 2-)	-3.45

Sample graphs
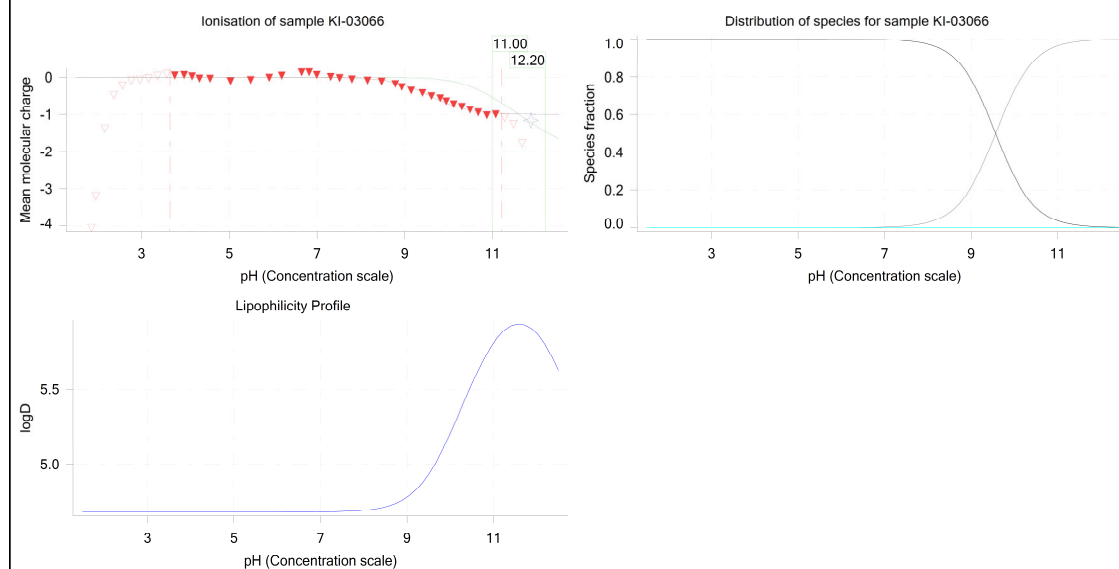
Ionisation of sample KI-03066

Distribution of species for sample KI-03066

Lipophilicity Profile

pH-metric

Sample name: **KI-03066** Experiment start time: **08/09/2020 07:26:11**
Assay name: **pH-metric medium logP** Analyst:
Assay ID: **20I-08012** Instrument ID: **T313101**
Filename: **D:\Data\Customer\20I-08012_KI-03066_pH-metric medium logP.t3r**

Sample logD and percent species

pH	KI-03066 logD	KI-03066 KI-03066H2	KI-03066 KI-03066H	KI-03066 KI-03066	KI-03066 KI-03066H2*	KI-03066 KI-03066H*	KI-03066 KI-03066*	Comment
1.000	4.68	0.01 %	0.00 %	0.00 %	99.99 %	0.00 %	0.00 %	
1.200	4.68	0.01 %	0.00 %	0.00 %	99.99 %	0.00 %	0.00 %	Stomach pH
2.000	4.68	0.01 %	0.00 %	0.00 %	99.99 %	0.00 %	0.00 %	
3.000	4.68	0.01 %	0.00 %	0.00 %	99.99 %	0.00 %	0.00 %	
4.000	4.68	0.01 %	0.00 %	0.00 %	99.99 %	0.00 %	0.00 %	
5.000	4.68	0.01 %	0.00 %	0.00 %	99.99 %	0.00 %	0.00 %	
6.000	4.68	0.01 %	0.00 %	0.00 %	99.97 %	0.03 %	0.00 %	
6.500	4.68	0.01 %	0.00 %	0.00 %	99.91 %	0.09 %	0.00 %	
7.000	4.68	0.01 %	0.00 %	0.00 %	99.72 %	0.27 %	0.00 %	
7.400	4.68	0.01 %	0.00 %	0.00 %	99.31 %	0.68 %	0.00 %	Blood pH
8.000	4.69	0.01 %	0.00 %	0.00 %	97.35 %	2.65 %	0.00 %	
9.000	4.78	0.01 %	0.00 %	0.00 %	78.62 %	21.37 %	0.00 %	
10.000	5.20	0.00 %	0.00 %	0.00 %	26.89 %	73.10 %	0.00 %	
11.000	5.81	0.00 %	0.00 %	0.00 %	3.55 %	96.45 %	0.00 %	
12.000	5.87	0.00 %	0.00 %	0.00 %	0.37 %	99.63 %	0.00 %	

Carbonate and acidity

Carbonate   0.138 mM
Acidity error 0.539 mM

Other graphs

pH-metric

Sample name:　**KI-03066**　　　　　　　　　　　　Experiment start time:　**08/09/2020 07:26:11**
Assay name:　**pH-metric medium logP**　　　　　　Analyst:
Assay ID:　　**20I-08012**　　　　　　　　　　　　Instrument ID:　　　**T313101**
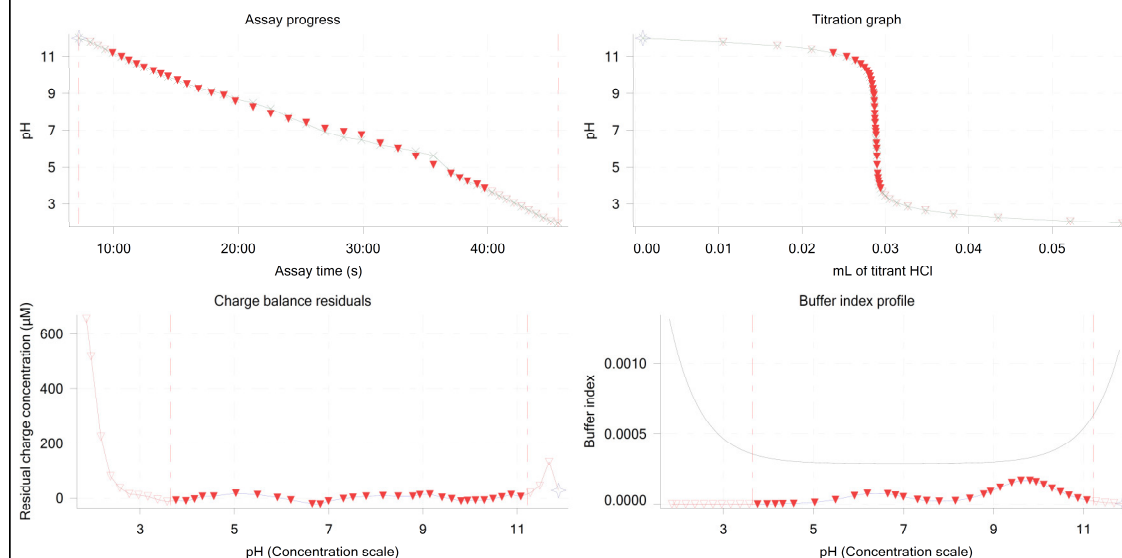Filename:　　**D:\Data\Customer\20I-08012_KI-03066_pH-metric medium logP.t3r**

Other graphs (continued)
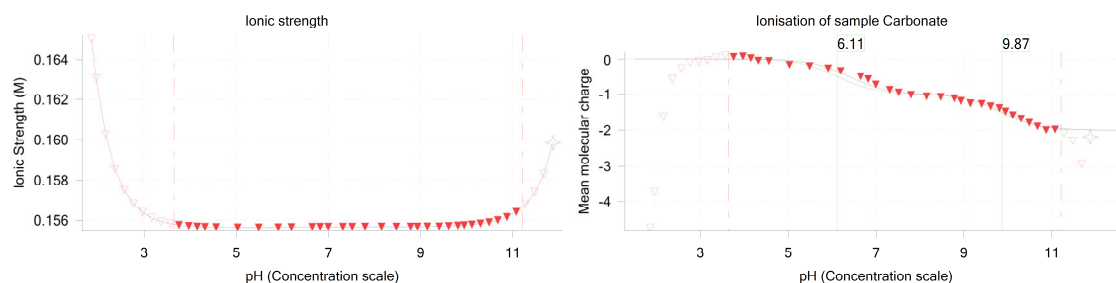
Figure S1. pH-metric Log P of compounds **4d** (KI-03066).

pH-metric

Sample name: **KI-ref-B**	Experiment start time: **08/09/2020 06:53:17**
Assay name: **pH-metric medium logP**	Analyst:
Assay ID: **20I-08011**	Instrument ID: **T313101**
Filename: **D:\Data\Customer\20I-08011_KI-ref-B_pH-metric medium logP.t3r**	

Overall results

RMSD	0.157
Average ionic strength	0.156 M
Average temperature	25.0°C
Partition ratio	0.2834 : 1
Analyte concentration range	1063.3 µM to 1110.3 µM
Total points considered	21 of 32

Warnings and errors

Errors	None
Warnings	Sample concentration factor out of range

Four-Plus parameters

🔒	Alpha	0.072	08/09/2020 06:53:17	D:\Data\Customer\20I-07022_Blank standardisation.t3r
🔒	S	1.0038	08/09/2020 06:53:17	D:\Data\Customer\20I-07022_Blank standardisation.t3r
🔒	jH	0.4	08/09/2020 06:53:17	D:\Data\Customer\20I-07022_Blank standardisation.t3r
🔒	jOH	-0.3	08/09/2020 06:53:17	D:\Data\Customer\20I-07022_Blank standardisation.t3r

Titrants

🔒	0.50 M HCl	0.979835	08/09/2020 06:53:17	D:\Data\Customer\20I-07023_Blank standardisation.t3r
🔒	0.50 M KOH	1.004720	08/09/2020 06:53:17	D:\Data\Customer\20I-07020_KHP_Base standardisation using KHP.t3r

Sample

🔻	KI-ref-B concentration factor	0.096
🔒	Acid pKa 1	10.30
🔻	logP (neutral XH)	4.22
🔻	logP (X -)	3.81

Sample graphs
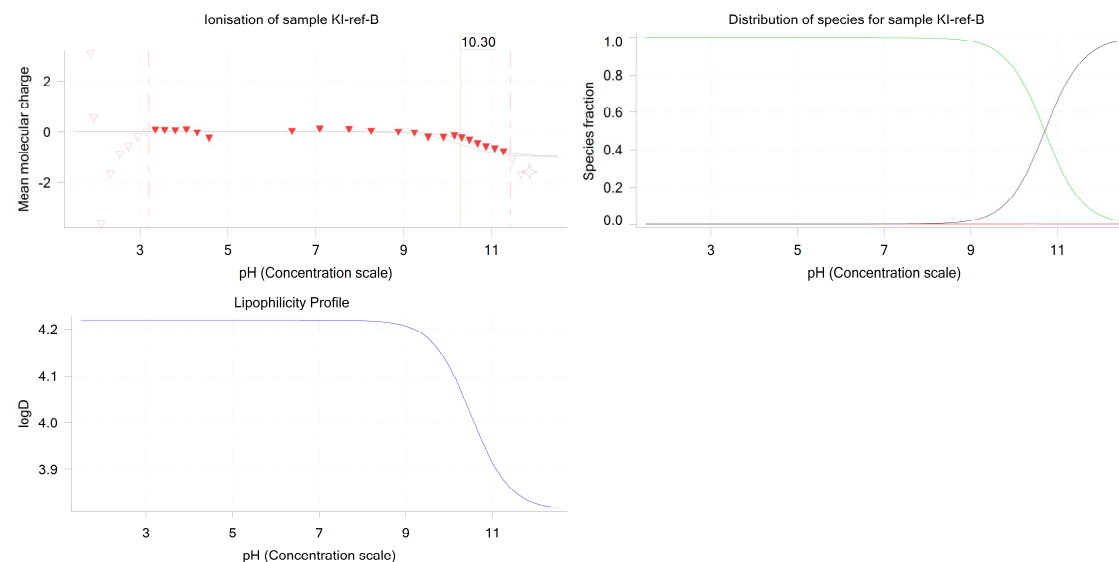
Ionisation of sample KI-ref-B

Distribution of species for sample KI-ref-B

Lipophilicity Profile

pH-metric

Sample name: **KI-ref-B** Experiment start time: **08/09/2020 06:53:17**
Assay name: **pH-metric medium logP** Analyst:
Assay ID: **20I-08011** Instrument ID: **T313101**
Filename: **D:\Data\Customer\20I-08011_KI-ref-B_pH-metric medium logP.t3r**

Sample logD and percent species

| pH	KI-ref-B logD	KI-ref-B KI-ref-BH	KI-ref-B KI-ref-B	KI-ref-B KI-ref-BH*	KI-ref-B KI-ref-B*	Comment
1.000	4.22	0.02 %	0.00 %	99.98 %	0.00 %	
1.200	4.22	0.02 %	0.00 %	99.98 %	0.00 %	Stomach pH
2.000	4.22	0.02 %	0.00 %	99.98 %	0.00 %	
3.000	4.22	0.02 %	0.00 %	99.98 %	0.00 %	
4.000	4.22	0.02 %	0.00 %	99.98 %	0.00 %	
5.000	4.22	0.02 %	0.00 %	99.98 %	0.00 %	
6.000	4.22	0.02 %	0.00 %	99.98 %	0.00 %	
6.500	4.22	0.02 %	0.00 %	99.97 %	0.01 %	
7.000	4.22	0.02 %	0.00 %	99.96 %	0.02 %	
7.400	4.22	0.02 %	0.00 %	99.93 %	0.05 %	Blood pH
8.000	4.22	0.02 %	0.00 %	99.78 %	0.20 %	
9.000	4.21	0.02 %	0.00 %	98.05 %	1.93 %	
10.000	4.12	0.02 %	0.01 %	83.54 %	16.43 %	
11.000	3.91	0.01 %	0.04 %	33.69 %	66.27 %	
12.000	3.83	0.00 %	0.05 %	4.83 %	95.11 %	

Carbonate and acidity

Carbonate   0.227 mM
Acidity error 0.763 mM

Other graphs
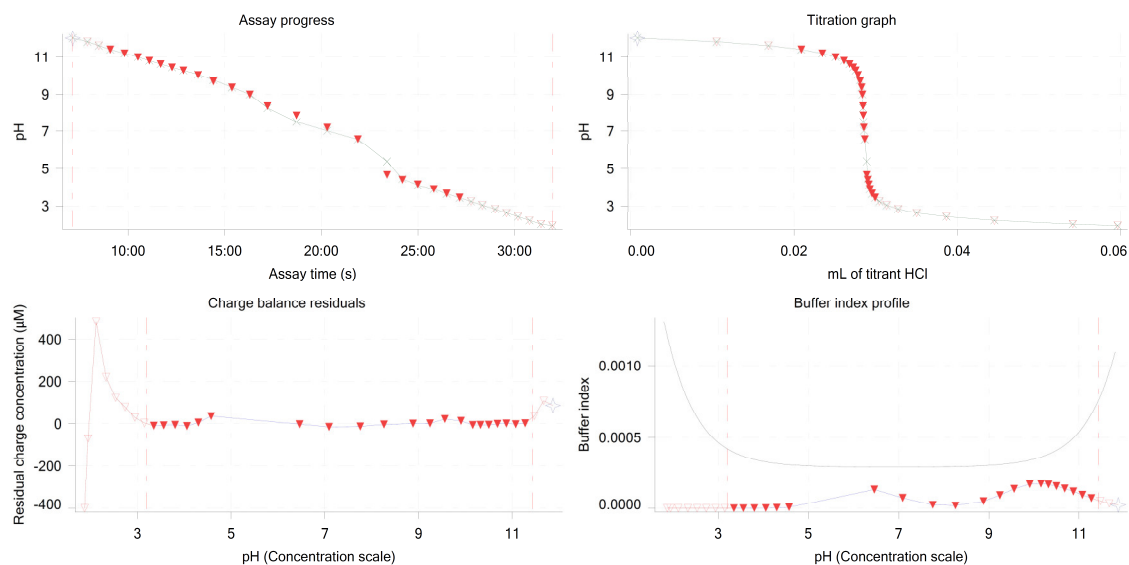
pH-metric

Sample name: **KI-ref-B**   Experiment start time: **08/09/2020 06:53:17**
Assay name: **pH-metric medium logP**   Analyst:
Assay ID: **20I-08011**   Instrument ID: **T313101**
Filename: **D:\Data\Customer\20I-08011_KI-ref-B_pH-metric medium logP.t3r**

Other graphs (continued)
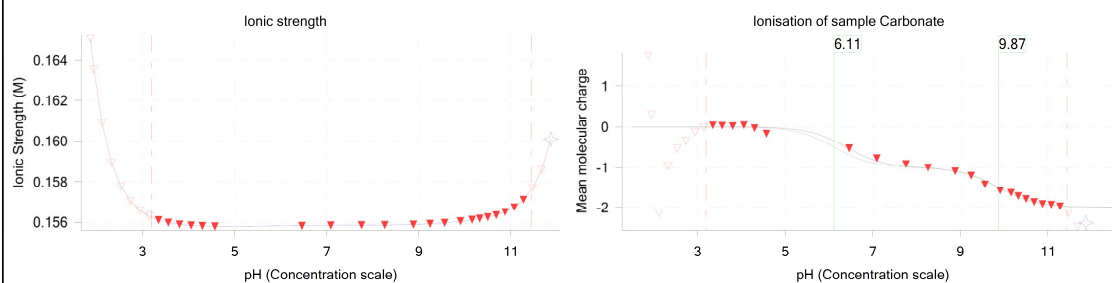
Figure S2. pH-metric Log P of Broflanilide.

Figure S3. Ion Channels assay of 4d (KI-03066) and Broflanilide

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Release Date: 24 Aug 2020

REPORT

Study Period │ 31 Jul 2020 – 21 Aug 2020

STUDY OBJECTIVE:

Client Name: KRICT
Compound Names: KI-03066, KI-Ref.B
Tested in Ion Channel GABAA α1/β3/γ2 & GlyRA1 Antagonist IonFlux Assays

STUDY INFORMATION:

- **Study code#: US034-0009484**

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SPONSOR INFORMATION	Name: Sung Joon Park, Ph.D. Company: KRICT Address: Gajeong-ro 141, Yuseong-gu Daejeon, 34114 Korea Phone Number: +82 42-860-7085 Email: sjunpark@krict.re.kr

INVESTIGATOR	Jennifer Wesley Eurofins Panlabs, Inc. Tel: (636) 362-7147 JenniferWesley@eurofins.com

TECHNICAL SUPPORT	Bryan Koci, M.S. Study Director, Eurofins Panlabs Tel: (636) 362-7006 BryanKoci@eurofins.com

STUDY APPROVAL	*I certify that this report accurately reflects all relevant data collected in this study.* *Jennifer Wesley, Associate Scientist*	*I certify that the results presented in this report were generated using materials and methods mentioned and that these results accurately reflect the raw data.* *Diane Werth, Senior Operations Manager* *Quality statement*

TABLE OF CONTENTS

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COMPOUND INFORMATION

Test compounds

Eurofins Compound I.D.	Client Compound I.D.	Client Reference I.D.	MW	MW + Salt	Weight received (mg)	Received condition
US034-0009484-1	KI-03066			488.45	3.1	Dry Powder
US034-0009484-2	KI-Ref.B			663.29	3.1	Dry Powder

Reference compounds

In each experiment and if applicable, the respective reference compounds were tested concurrently with the test compounds, and the data were compared with historical values determined at Eurofins. The experiment was accepted in accordance with Eurofins Standard Operating Procedure on assay validation.

Compound	Target	Mode	Concentration(s) (μM)
GABA (EC_{80})	GABAA $\alpha1/\beta3/\gamma2$	Antagonist	8
Glycine (EC_{80})	GlyRA1	Antagonist	30
Bicuculline	GABAA $\alpha1/\beta3/\gamma2$	Antagonist	0.032, 0.16, 0.8, 4, 20, 100
Strychnine	GlyRA1	Antagonist	0.00001 0.0001, 0.001, 0.01, 0.1, 1

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SUMMARY

Ion Channels tested

Ligand-Gated Ion Channels: GABAA $\alpha1/\beta3/\gamma2$, GlyRA1

Study objective

Electrophysiological assays conducted to profile two (2) compounds for activities on the ion channel targets specified above using the IonFlux HT electrophysiological platform.

Measurements

Methods employed in this study have been developed and validated with reliability and reproducibility. Assays were performed under conditions described in the accompanying "Materials and Methods" section of this report

Where presented, IC_{50} values were determined by a non-linear, least squares regression analysis. Reference standards were run as an integral part of each assay to ensure the validity of the results obtained.

Significant results

Results showing an inhibition greater than 25% are considered to represent significant effects of test compounds and listed in the following tables with individual calculation results and calculable IC_{50}.

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EXPERIMENTAL RESULTS
Client Compound Data Tables

GABAA α1β3γ2

Compound ID	Client Compound ID	Concentration (µM)	% inhibition		
			n1	n2	mean
US034-0009484-1	KI-03066	0.3	6.97	5.10	6.03
US034-0009484-1	KI-03066	1	7.68	8.56	8.12
US034-0009484-1	KI-03066	3	11.24	11.15	11.19
US034-0009484-1	KI-03066	10	11.91	11.25	11.58
US034-0009484-1	KI-03066	30	17.92	21.88	19.90
US034-0009484-2	KI-Ref.B	0.3	8.47	7.29	7.88
US034-0009484-2	KI-Ref.B	1	13.71	8.91	11.31
US034-0009484-2	KI-Ref.B	3	14.83	14.80	14.82
US034-0009484-2	KI-Ref.B	10	7.26	6.69	6.98
US034-0009484-2	KI-Ref.B	30	7.53	9.75	8.64
Time-Matched Vehicle Control	GABA EC$_{80}$	8	10.18	6.23	8.20
Time-Matched Vehicle Control	GABA EC$_{80}$	8	8.99	11.66	10.33
Time-Matched Vehicle Control	GABA EC$_{80}$	8	10.63	14.04	12.34
Positive Reference Control	Bicuculline	0.032	10.10	5.90	8.00
Positive Reference Control	Bicuculline	0.16	23.88	22.01	22.94
Positive Reference Control	Bicuculline	0.8	36.81	36.53	36.67
Positive Reference Control	Bicuculline	4	82.09	82.02	82.06
Positive Reference Control	Bicuculline	20	96.98	97.42	97.20
Positive Reference Control	Bicuculline	100	98.90	99.03	98.97

GlyRA1

Compound ID	Client Compound ID	Concentration (µM)	% inhibition		
			n1	n2	mean
US034-0009484-1	KI-03066	0.3	-1.49	-10.64	-6.07
US034-0009484-1	KI-03066	1	-1.66	-9.41	-5.54
US034-0009484-1	KI-03066	3	-8.75	-2.91	-5.83
US034-0009484-1	KI-03066	10	0.39	1.50	0.95
US034-0009484-1	KI-03066	30	4.13	8.74	6.43
US034-0009484-2	KI-Ref.B	0.3	-8.14	-2.00	-5.07
US034-0009484-2	KI-Ref.B	1	-13.15	-3.04	-8.10
US034-0009484-2	KI-Ref.B	3	-0.52	7.84	3.66
US034-0009484-2	KI-Ref.B	10	6.33	1.52	3.93
US034-0009484-2	KI-Ref.B	30	-2.53	-1.99	-2.26
Time-Matched Vehicle Control	Glycine EC$_{80}$	30	-2.38	2.52	0.07
Time-Matched Vehicle Control	Glycine EC$_{80}$	30	2.58	-2.29	0.15
Time-Matched Vehicle Control	Glycine EC$_{80}$	30	3.98	-0.97	1.51
Positive Reference Control	Strychnine	0.00001	-0.97	4.95	1.99
Positive Reference Control	Strychnine	0.0001	25.64	15.98	20.81
Positive Reference Control	Strychnine	0.001	50.75	53.02	51.89
Positive Reference Control	Strychnine	0.01	99.06	99.29	99.17
Positive Reference Control	Strychnine	0.1	98.87	99.02	98.95
Positive Reference Control	Strychnine	1	99.91	99.82	99.87

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Estimated IC$_{50}$ Compound Summary Table

Compound	Target	Mode	Estimated IC$_{50}$ (µM)
KI-03066	GABAA α1/β3/γ2	Antagonist	>30
KI-Ref.B	GABAA α1/β3/γ2	Antagonist	>30
KI-03066	GlyRA1	Antagonist	>30
KI-Ref.B	GlyRA1	Antagonist	>30

REFERENCE COMPOUND RESULTS

Reference Compound Table

ITEM	Assay Name	Mode	Reference Compound	Estimated IC$_{50}$ (µM)
CYL8053IF2	GABAA (alpha1/beta3/gamma2) Human Ion Channel Cell Based Antagonist IonFlux Assay	Antagonist	Bicuculline	1.0
CYL8056IF2	GlyRA1 Human Glycine Ion Channel Cell Based Antagonist IonFlux Assay	Antagonist	Strychnine	0.00071

DATA CALCULATION AND ANALYSIS

CYL8053IF2 GABAA IonFlux HT Antagonist Assay

Peak inward currents in response to the GABA additions in the presence of a single concentration of compound were measured. All compound data have been normalized to the baseline peak current induced by addition of EC$_{80}$ GABA for 2 seconds:

$$Normalized\ Peak\ Current\ = \left(I^{Compound\ +\ GABA}/_{I\ GABA} \right)$$

Where *I (Compound + GABA)* is the peak current induced by addition of test compound + EC$_{80}$ GABA after 30 seconds incubation of test compound, *I GABA* is the baseline peak current induced by addition of EC$_{80}$ GABA.

All data were first exported to an Excel compatible data file and then analyzed using Graph Pad Prism software.

CYL8056IF2 GlyRA1 IonFlux HT Antagonist Assay

Peak inward currents in response to the Glycine additions in the presence of a single concentration of compound were measured. All compound data have been normalized to the baseline peak current induced by addition of EC$_{80}$ Glycine for 2 seconds:

$$Normalized\ Peak\ Current\ = \left(I^{Compound\ +\ Glycine}/_{I\ Glycine} \right)$$

Where *I (Compound + Glycine)* is the peak current induced by addition of test compound + EC$_{80}$ Glycine after 30 seconds incubation of test compound, *I Glycine* is the baseline peak current induced by addition of EC$_{80}$ Glycine.

All data were first exported to an Excel compatible data file and then analyzed using Graph Pad Prism software.

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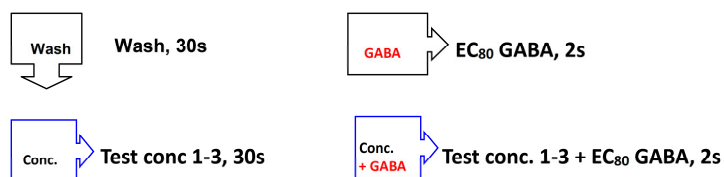
MATERIALS AND METHODS

IonFlux Protocols

CYL8053IF2 GABAA IonFlux HT Antagonist Assay

All recordings were obtained from a holding potential of -60 mV.

The compound addition sequence that was used for all additions was the same for all assays. One addition of the EC_{80} concentration of GABA was added to establish baseline response. Each test concentration of compound was applied for 30 seconds followed by the addition of EC_{80} GABA in the presence of the compound for 2 seconds. The process was repeated with the next ascending concentration of test compound, up to three (3) concentrations per experimental pattern.


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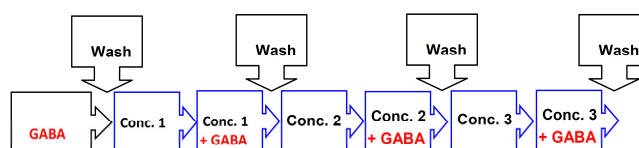
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CYL8056IF2 GlyRA1 IonFlux HT Antagonist Assay

All recordings were obtained from a holding potential of -60 mV.

The compound addition sequence that was used for all additions was the same for all assays. One addition of the EC_{80} concentration of Glycine was added to establish baseline response. Each test concentration of compound was applied for 30 seconds followed by the addition of EC_{80} Glycine in the presence of the compound for 2 seconds. The process was repeated with the next ascending concentration of test compound, up to three (3) concentrations per experimental pattern.
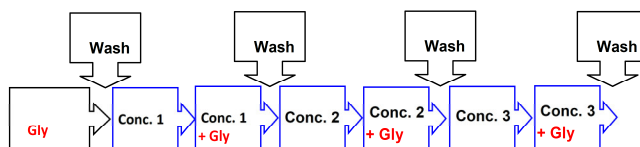
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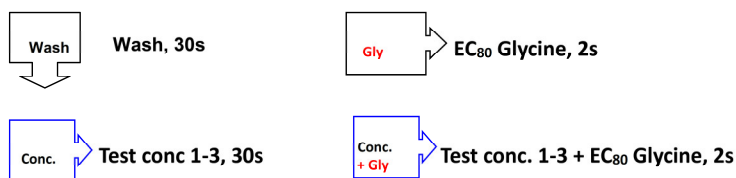
STORAGE AND RETENTION OF RECORDS

Documents generated during the performance of the study will be archived by Eurofins Discovery for a period of time after study completion (this period of time is dependent on each individual site policy). The access to the archives is restricted to authorized employees only.