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Discovery, synthesis, and evaluation of *N*-substituted amino-2(5*H*)-oxazolones as novel insecticides activating nicotinic acetylcholine receptors

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ABSTRACT

N-Substituted amino-2(5*H*)-oxazolones **A** are a novel class of insecticides acting as nicotinic acetylcholine receptor (nAChR) agonists and show potent activity against hemipteran insect species. Here we report the discovery and preparation of this class of chemistry. Our efforts in SAR elucidation, biological activity evaluation, as well as mode-of-action studies are also presented.

Neonicotinoids are a modern class of insecticides initially discovered in the 1980's. They target the nicotinic acetylcholine receptor (nAChR) and act as competitive agonists for acetylcholine. Commercial neonicotinoids are small polar molecules. They have rather low logP_{ow} values (−0.64 to 1.26) and high water solubility (0.185–840 g/L at 20 °C). As a result of these physical properties, neonicotinoids have been used with a range of different application techniques to control sucking pest species. Since the first introduction of imidacloprid (**1**) into the global crop protection market in 1991, seven representative members of neonicotinoid insecticides have achieved a market value of $3640 million in 2011 and represented about 28.5% of the overall world insecticide sale in that same year (see Fig. 1).[1]

The rapid adoption of neonicotinoids, however, has resulted in increasing cases of neonicotinoid resistance among major pests targeted by this chemistry in recent years. There has been a renewed interest in searching for novel neonicotinoid insecticides to overcome resistance while maintaining attractive physical properties and biological profiles.[2,3]

In their search for novel neonicotinoid insecticides, researchers at Nippon Soda reported the *N*-substituted enaminolactones, such as **8**, as potent insecticides (see Fig. 2).[4] Inspired by the enaminolactones, we discovered a novel class of *N*-substituted amino-2(5*H*)-oxazolone insecticides **A** as potent nAChR agonists. Herein

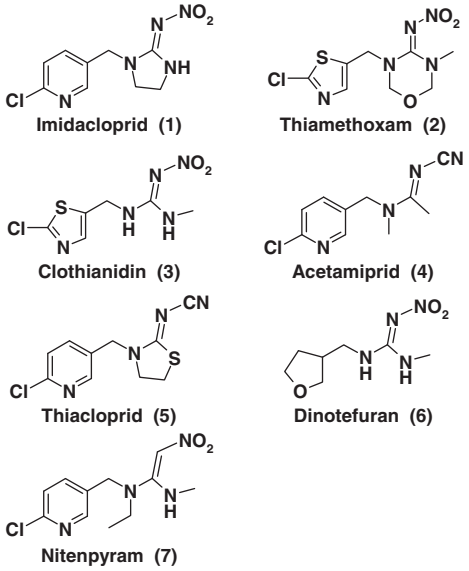

Figure 1. Neonicotinoid insecticides.

we describe our discovery of this novel class of compounds. Further studies in this area that resulted in the identification of exceptionally potent compounds such as **18a** will be presented as well.[5]

The compounds shown in Tables 1–3 were prepared as described in Schemes 1–5. 2-Aminopyrrolin-5-ones **13** (**13a** and

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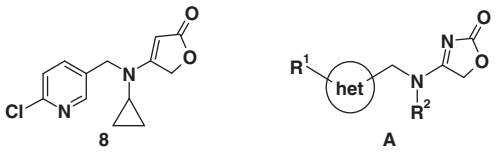
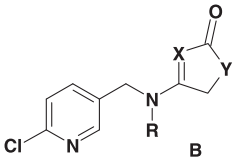


Figure 2. Novel amino heterocycle insecticides.

Table 1
Insecticidal potency of substituted amino-2(5*H*)-oxazolones and other heterocycle analogs[a]



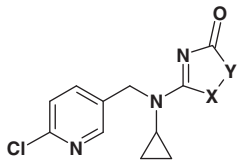
Entry	X	Y	R	GPA	CMA	CPH	PLH	WF
8	CH	O	*c*-Pr	2.1	0.2	0.6	0.6	52.6
33	CH	O	Me	2	0.5	2.1	9	70.7
13a	N	CH_2	*c*-Pr	57.6	<250	<250	>250	No data
13b	N	CH_2	Me	>250	35.3	<250	>250	No data
18a	N	O	*c*-Pr	3.6	3.2	0.9	3.5	108.8
18b	N	O	Me	4.7	0.5	6.8	<2	<250
Imidacloprid	—	—	—	0.2	0.8	0.3	0.8	20.2

Insect LC_{50} values (ppm) are shown for green peach aphid (*Myzus persicae* (Sulzer), GPA), cotton melon aphid (*Aphis gossypii* Glover, CMA), corn planthopper (*Peregrinus maidis* (ashmead), CPH), potato leafhopper (*Empoasca fabae* Harris, PLH), and sweetpotato whitefly (*Bemisia tabaci* (Gennadius), WF).

[a] LC_{50} values were obtained for multiple test rates, each tested in replicate ($n \geqslant 3$). LC_{50} calculations were determined by Probit analysis using a maximum quasi-likelihood curve fitting algorithm.

13b) were the first set of molecules prepared and their synthesis is outlined in Scheme 1. Reaction between succinimide and silver nitrate under basic conditions produced silver succinimide **10**.[6]

Table 3
Insecticidal potency of substituted amino-2(5*H*)-oxazolones and other heterocycle analogs[a]



Entry	X	Y	GPA	CMA	CPH	PLH	WF
50	S	CH_2	67.1	150.5	>250	227.2	>250
51	O	CH_2	55.8	133.3	>250	<250	>250
52	$CHCH_3$	O	15.2	6.6	92.4	19.6	>250
53	CH_2	S	17.6	22.8	>250	48.7	>250
54	NH	NH	>250	>250	>250	>250	>250
55	NH	O	>250	>250	>250	79.7	>250
56	NMe	NH	>250	>250	>250	>250	>250
57	NMe	O	11.5	10.3	<250	22.1	122.7

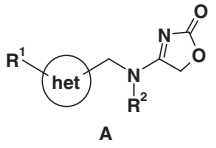
Insect LC_{50} values (ppm) are shown for green peach aphid (*Myzus persicae* (Sulzer), GPA), cotton melon aphid (*Aphis gossypii* Glover, CMA), corn planthopper (*Peregrinus maidis* (ashmead), CPH), potato leafhopper (*Empoasca fabae* Harris, PLH), and sweetpotato whitefly (*Bemisia tabaci* (Gennadius), WF).

[a] LC_{50} values were obtained for multiple test rates, each tested in replicate ($n \geqslant 3$). LC_{50} calculations were determined by Probit analysis using a maximum quasi-likelihood curve fitting algorithm.

Heating this compound in the dark and in the presence of iodoethane generated 2-ethoxypyrrolin-5-one **11**, which, in turn, reacted with secondary amines **12** to displace the ethoxy group and generate the desired 2-aminopyrrolin-5-ones **13** in good yields.[7]

4-Amino-2(5*H*)-oxazolones **18** (**18a** and **18b**) were prepared as described in Scheme 2. Cyclization of glycolamide **14** with diethyl carbonate in the presence of potassium *tert*-butoxide in methanol generated oxazolidinedione **15**.[8] The amide carbonyl group of dione **15** was then selectively converted into a thiocarbonyl group when treated with Lawesson Reagent. The conversion for this step

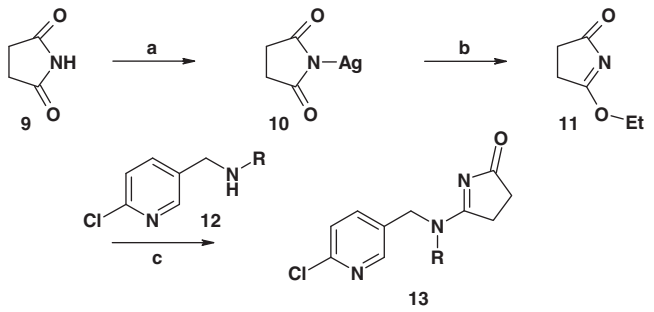
Table 2
Insecticidal potency of various substituted amino-2(5*H*)-oxazolones[a]



Entry	R^1	het	R^2	GPA	CMA	CPH	PLH	WF
34	H	3-Pyridyl	*c*-Pr	>250	<250	<50	>250	>250
35	5-Br	3-Pyridyl	*c*-Pr	>250	>250	<250	>250	>250
36	6-F	3-Pyridyl	*c*-Pr	49.3	18.6	7.3	>250	>250
37	2,6-Cl_2	3-Pyridyl	*c*-Pr	>250	>250	>250	>250	>250
38	5,6-Cl_2	3-Pyridyl	*c*-Pr	5.4	10.9	59.2	<50	196.9
39	6-Br	3-Pyridyl	*c*-Pr	3.9	5.3	3	5.7	58.4
40	2-Cl	5-Thiazolyl	*c*-Pr	8.8	6.1	<2	<2	78.2
41	5-Me	2-Pyridazinyl	*c*-Pr	>250	>250	>250	>250	>250
42	1-Me	4-Pyrazolyl	*c*-Pr	>250	122.4	No data	70.7	>250
43	H	5-Pyrimidinyl	Me	>250	>250	>250	>250	>250
44	6-Cl	3-Pyridyl	Et	6.4	1.9	1.9	6	98.5
45	6-Cl	3-Pyridyl	*n*-Pr	55.1	45.4	<250	<250	>250
46	2-Cl	5-Thiazolyl	*c*-PrCH_2	>250	>250	>250	>250	>250
47	6-Cl	3-Pyridyl	*c*-Bu	>250	>250	>250	>250	>250
48	6-Cl	3-Pyridyl	OMe	>250	74.5	>250	>250	>250
49	6-Cl	3-Pyridyl	CHF_2CH_2	14.3	3.1	3.3	25.7	50

Insect LC_{50} values (ppm) are shown for green peach aphid (*Myzus persicae* (Sulzer), GPA), cotton melon aphid (*Aphis gossypii* Glover, CMA), corn planthopper (*Peregrinus maidis* (ashmead), CPH), potato leafhopper (*Empoasca fabae* Harris, PLH), and sweetpotato whitefly (*Bemisia tabaci* (Gennadius), WF).

[a] LC_{50} values were obtained for multiple test rates, each tested in replicate ($n \geqslant 3$). LC_{50} calculations were determined by Probit analysis using a maximum quasi-likelihood curve fitting algorithm.



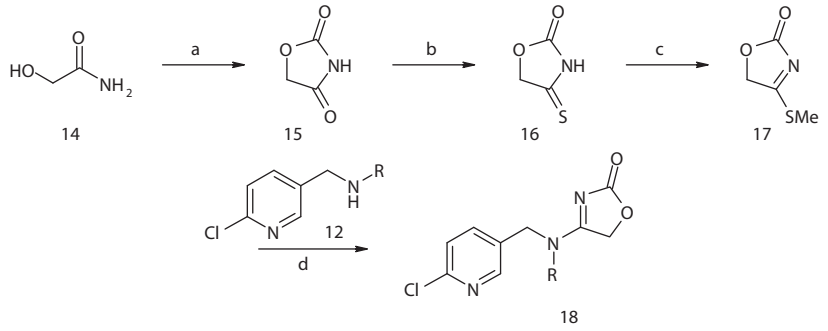
Scheme 1. Reagents and conditions: (a) $AgNO_3$, NaOEt, ethanol, DMSO, 25–5 °C, 88–94%; (b) EtI, chloroform, reflux in the dark, 30%; and (c) toluene, 110 °C, 60–85%.

was reasonably good, but separation of the product 4-thio-oxazolidine-2-one **16** from the reaction mixture turned out to be difficult and a careful crystallization was employed to isolate thioamide **16** in excellent purity. This thioamide was further converted into 4-methylsulfanyl-5*H*-oxazol-2-one **17** and subsequent displacement with required secondary amines provided desired product 4-amino-2(5*H*)-oxazolones **18** in excellent yields.

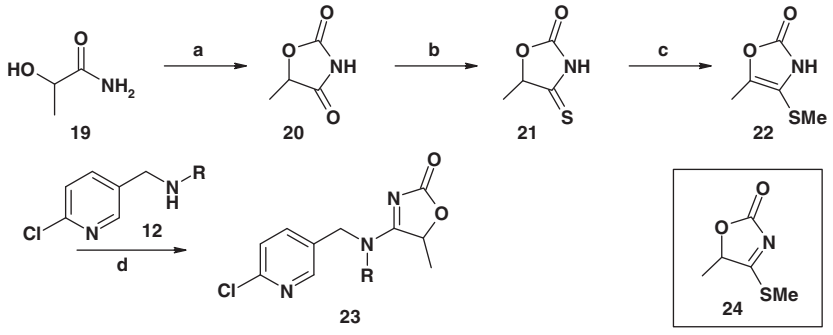
The corresponding 5-methyl oxazolone analogs of **18a** and **18b** were prepared in a similar way as outlined in Scheme 3. The desired intermediates oxazolidinedione **20** and subsequent thioamide **21** were prepared uneventfully. However, methylation of thioamide **21** generated the unexpected tautomer 5-methylsulfanyl-3*H*-oxazol-2-one **22** instead of 5-methylsulfanyl-5*H*-oxazol-2-one **24**.[9] Furthermore, there was no reaction between 3*H*-oxazol-2-one **22** and amines **12** when they were mixed and subjected to the same reaction conditions used for the formation of **18**. However, when a catalytic amount of acetic acid was added into the reaction mixture, the reaction took place and the desired 5-methyl-4-amino-2(5*H*)-oxazolones **23** were isolated in yields comparable to those from the reactions with the parent oxazol-2-one **17**.

Thiazolinone analogs **27** were prepared in a more straightforward way as shown in Scheme 4. Treatment of 2,4-thiazolidinedione **25** with phosphorus pentasulfide generated isorhodanine **26** in 68% yield.[10] When **26** was heated in ethanol in the presence of the required secondary amines **12**, desired thiazolinones **27** were isolated in modest yields.[11]

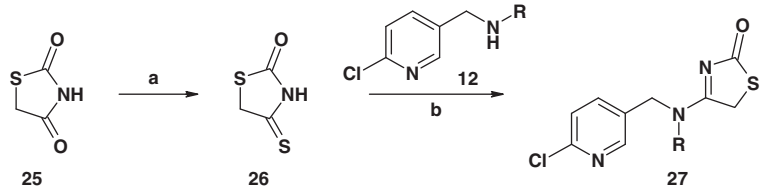
Besides the azolinone and thiazolinone five-membered ring systems, other five-membered ring systems were also prepared as



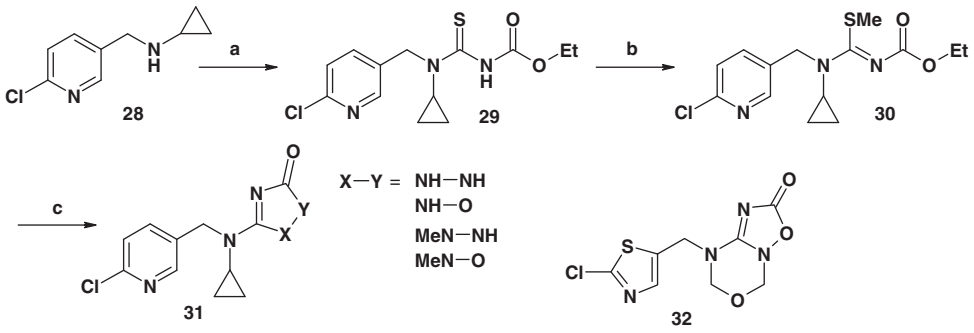
Scheme 2. Reagents and conditions: (a) $CO(OEt)_2$, KOBu-*t*, methanol, 80 °C, 44%; (b) Lawesson reagent, toluene, 110 °C; crystallization; (c) MeI, NaOAc, dichloromethane, 25 °C, 24% for two steps; and (d) chloroform, 61 °C, 85–90%.



Scheme 3. Reagents and conditions: (a) $CO(OEt)_2$, KOBu-*t*, methanol, 80 °C, 98%; (b) Lawesson reagent, toluene, 110 °C; (c) MeI, Hunig's base, dichloromethane, 25 °C, 98% for two steps; and (d) chloroform, acetic acid (0.3 equiv), 61 °C, 48–78%.



Scheme 4. Reagents and conditions: (a) P_2S_5, toluene, 110 °C, 68%; and (b) ethanol, 80 °C, 18%.



Scheme 5. Reagents and conditions: (a) $SCNCO_2Et$, chloroform, 23 °C, 97%; (b) NaH, MeI, THF, 23 °C, 92%; (c) hydroxylamines or hydrazines, 2-propanol, 82 °C, 33–35%.

outlined in Scheme 5. Reaction of secondary amine **28** with ethoxycarbonyl isothiocyanate provided intermediate thiourea **29** in quantitative yield. Alkylation of **29** with iodomethane in the presence of sodium hydride generated methylthiocarbamate **30** in excellent yield. This carbamate is a suitable substrate for the desired tandem double displacement and ring formation reactions. Therefore, treatment of carbamate **30** with hydrazine or hydroxylamine provided the expected cyclization product triazolinones or oxadiazolinones **31** in moderate yields.[12] The corresponding tied-back analogs, such as oxadiazolinones **32**, can be prepared in a similar way when the hydroxylamine group is tethered to the amine moiety in advance.

Insecticidal activity of amino-2(5*H*)-oxazolones and other heterocyclic analogs is summarized in Tables 1–3. Test compounds were formulated using a solution containing 10% acetone, 90% water and 300 ppm of a non-ionic surfactant. The formulated compounds were sprayed on the foliage of plants at 2–5 rates and replicated three times. Efficacy was evaluated on the following test units: 12–15 day-old radish plant for green peach aphid (*Myzus persicae* (Sulzer) GPA), 6–7 day-old cotton plant for cotton melon aphid (*Aphis gossypii* (Glover), CMA), 3–4 day-old corn for corn planthopper (*Peregrinus maidis* (Ashmead) CPH), 5–6 day-old bean for potato leafhopper (*Empoasca fabae* (Harris) PLH), and 12–14 day-old cotton for sweetpotato whitefly (*Bemisia tabaci* (Gennadius) WF). Mortality was evaluated 6 days after application for all insects except for WF, which was evaluated 12 days after application. Insecticidal activity is reported as an LC_{50} (the lethal concentration required for 50% mortality) in ppm. In general, all compounds showed better control against aphid species and hopper species than whitefly.

Table 1 shows compounds initially prepared in comparison to Nippon Soda's enaminolactone compounds **8** and **33**. Both **8** and **33** are potent insecticides against all four hemipteran insect species tested (GPA, CMA, CPH, and PLH). Novel 2-aminopyrrolin-5-ones **13a** and **13b** displayed only weak levels of activity.

4-Amino-2(5*H*)-oxazolones **18a** and **18b**, on the other hand, showed potent insecticidal activity against all four hemipteran insect species tested (GPA, CMA, CPH, and PLH). This result illustrates that it is critical to maintain the ring oxygen atom so as to form an ester moiety, which may mimic the nitro group in imidacloprid (**1**). Although *N*-cyclopropyl enaminolactone **8** demonstrated overall higher levels of insecticidal activity than the corresponding *N*-methyl enaminolactone **33** when tested against CMA, CPH, PLH, and WF, this trend is not as clear for the 4-amino-2(5*H*)-oxazolones **18a** and **18b**.

Based on the activity of amino-2(5*H*)-oxazolones **18a** and **18b**, a series of analogs **A** containing different substitutions on the amino group was investigated (Table 2). Compounds **34** through **39** are analogs containing a *N*-3-pyridylmethyl group, unsubstituted, or substituted by one or two halogen atoms at different ring positions. All these analogs showed a reduction in activity, except 6-bromo-3-pyridylmethyl compound **39**, which provided insecticidal activity close to the corresponding 6-chloro analog (**18a**).

Compounds containing *N*-2-chloro-5-thiazolylmethyl groups (**40**) showed anticipated insecticidal activity similar to that of the *N*-6-chloro-3-pyridylmethyl analog (**18a**). Compounds containing other heterocycles, 2-pyridazinyl **41**, 4-pyrazolyl **42**, and pyrimidinyl **43** showed a significant reduction in activity.

The R_2 group attached to the amino nitrogen also played an important role on the insecticidal activity. Compounds containing a small alkyl group, methyl **18b**, ethyl **44**, cyclopropyl **18a**, showed highest activity. The 2,2-difluoroethyl compound **49**, showed less activity on GPA and PLH, while compounds containing larger alkyl groups, *n*-propyl **45**, cyclopropylmethyl **46**, as well as cyclobutyl **47**, showed a drastic loss of activity. However, the size of the substituent is not the only factor responsible for the insecticidal potency because the *N*-methoxy compound **48**, displayed only marginal activity on CMA with no activity on other species tested.

Finally, we explored a series of analogs which maintained the carbonyl amidine feature, while containing various heteroatoms or moieties to make up the five-membered heterocycle rings (Table 3). Most variations resulted in loss of activity, while compounds **52**, **53**, and **57** containing the lactone (or thio-lactone) function showed reasonably good activity on GPA and CMA.

The most potent analogs approached or were comparable to the activity of imidacloprid (Table 1). For GPA and CPH, **18a** was ~18-fold and 3-fold less potent than imidacloprid, respectively. For CMA, **18b** was 1.6-fold more potent than imidacloprid. Precise LC_{50} values were not obtained for **18b** and **40** on PLH, however both were <2 ppm whereas imidacloprid was determined to be 0.8 ppm. For WF, **49** was ~2.5-fold less potent than imidacloprid.

The assays described in this study were all based on contact sprays. The neonicotinoid class of chemistry is also known for possessing physical properties that allow uptake into plants via systemic delivery, either through soil treatment or seed treatment.[13] As such, a preliminary study using a soil application of either **18a** or **18b** resulted in activity against GPA that was comparable to the foliar application of these compounds.

Table 4
Comparative potency of nAChR agents at displacing ^{3}H-imidacloprid in GPA membrane preparations

Compounds	IC_{50} (nM)	95% Confidence interval	
		Lower	Upper
18a	310	244	392
40	1115	811	1532
Imidacloprid	3	2	4
Thiacloprid	3	2	4
Dinotefuran	13,300	11,655	15,162
Sulfoxaflor[a]	473	374	598

[a] For the structure of sulfoxaflor, see Ref. 2c.

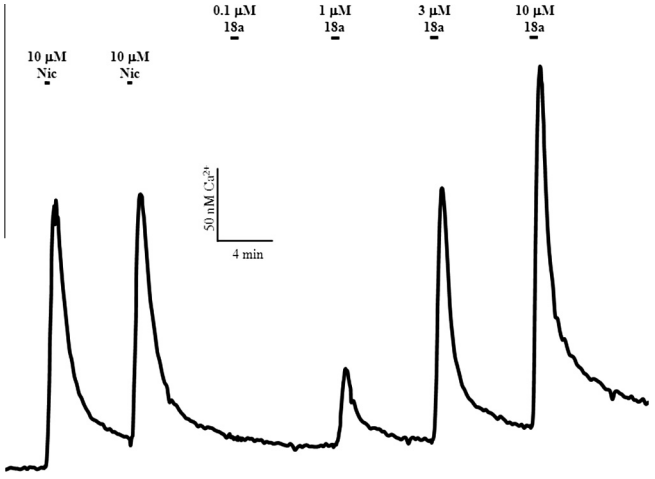


Figure 3. Typical Ca^{2+} mobilization trace of *P. americana* embryonic neurons showing nAChR agonist-induced response with nicotine (NIC) and **18a**. Neurons were continuously perfused with saline and test compounds applied during the periods shown with the solid bar. Compound **18a** stimulated nAChR activation with an EC_{50} value of 3.4 μM.

As the target of the *N*-substituted amino-2(5*H*)-oxazolones was expected to be nAChRs, ^{3}H-imidacloprid displacement studies were conducted using GPA membranes. Studies were conducted using a radioligand concentration approximately equal to the K_d value of the high affinity binding site for ^{3}H-IMI (2.5 nM). The concentration for test compounds ranged from 0.01 to 1000 nM in 10-fold dilution steps. In this assay the buffer, protein and test compound were allowed to incubate together for 10 min prior to addition of ^{3}H-imidacloprid. Following a 60-min incubation at room temperature assay tubes were quenched with 5 ml of ice cold buffer and stored on ice. The tubes were filtered through Whatman GF/C filters which were washed twice with cold buffer, placed in scintillation vials and read on a scintillation counter. As shown in Table 4, **18a** displaced ^{3}H-imidacloprid with a 100-fold lower potency than imidacloprid itself. This result is consistent with reduced potency of **18a** versus imidacloprid in the GPA bioassay. A second oxazolone analog, **40**, was less potent, with an IC_{50} value of 1.1 μM compared to 310 nM for **18a**.

To determine the functional action on insect nAChRs, **18a** was tested on cultured embryonic neurons from the American cockroach, *Periplaneta americana*. Neurons were loaded with the Ca^{2+}-sensitive fluoroprobe, Fura-2 AM, as previously described and nAChR-induced activation of intracellular Ca^{2+} influx monitored.[14,15] In this assay **18a** induced Ca^{2+} mobilization indicative of nAChR agonism (Fig. 3) with EC_{50} values of 3.4, 0.9 and 0.4 μM, obtained for **18a**, nicotine and imidacloprid, respectively.

In summary, *N*-substituted amino-2(5*H*)-oxazolones **A** have been discovered as a new class of nAChR agonists. This class of compounds showed potent activity against several sucking pest species. Compounds such as **18a** and **18b** show potential utility for combatting insect damage in the field.

References and notes

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