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Synthesis and insecticidal activity of some nicotinic acid derivatives

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ABSTRACT

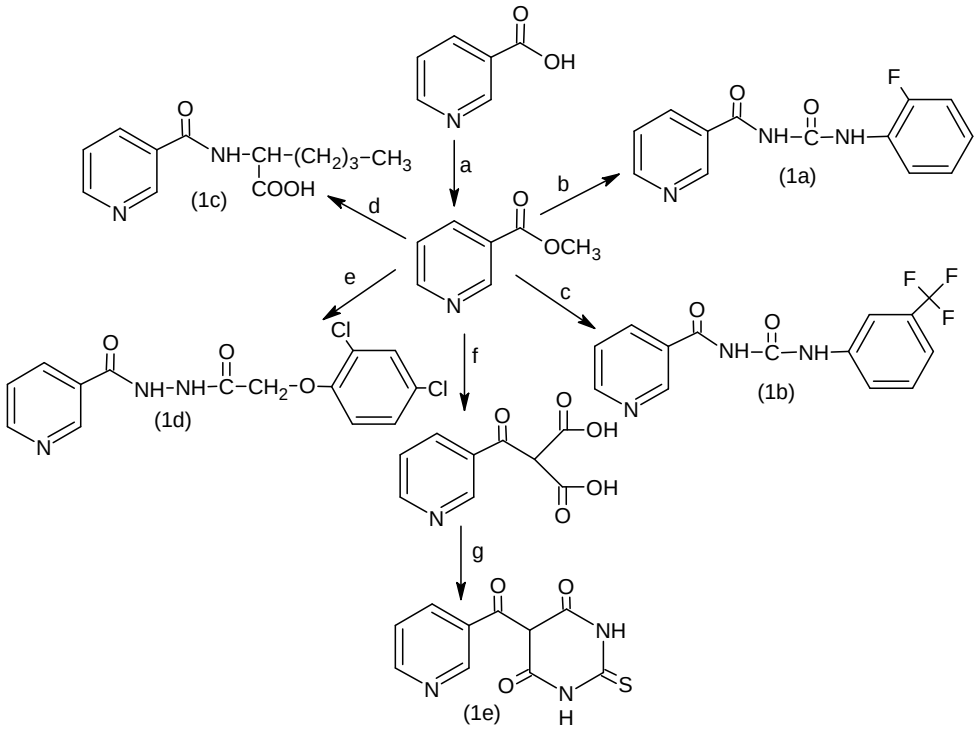
Nicotinic acid containing pyridine nucleus having side chain at third position gives the significant effect on toxicity to the insects. Therefore, we have reported the synthesis of some nicotinic acid derivatives and their insecticidal activities. The strategy employed for the synthesis of desired nicotinic acid derivatives involved esterification of nicotinic acid. The methyl nicotinate get derivatise by 2-Fluorophenyl urea, 3-trifluoro methylphenyl urea, DL-nor-leucine, 2, 4-dichlorophenoxy acetic acid hydrazone and diethyl malonate which are further reacted with thiourea to get corresponding condensed product (1a-e). Further methyl nicotinate react with hydrazine hydrate to form nicotinoyl hydrazine (2). This when condensed with substituted aryl aldehydes gave the corresponding arylidene derivatives (3a -e). The structures of these synthesized compounds are confirmed on the basis of IR, PMR and Mass spectral analysis. Most of them showed the promising activity against Green peach aphid, Myzus persicae (Sulzer), American bollworm, Helicoverpa armigera (Hubner) and stored grain pest, Maize weevil, Sitophiles zeamais (Motschulsky).

Keywords: Nicotinic acid, Esterification, Insecticidal activity.

INTRODUCTION

Nicotine is one of the oldest known plant origin insecticides, which possesses the remarkable insecticidal activity. Nicotine kills the insects rapidly within an hour causing the intensive tremors, convulsions and then paralysis. As early as 1746, the insecticidal activity of crude extract of tobacco leaves was used to control the insects. Metcalf has reported that 1.2 million pound of free nicotine was used in Agriculture in USA during 1944. Nicotine represents the class of "nicotinoids" with a unique mechanism of action. Nicotine mimics nAch and some of the nAchR types, has a direct interaction with the nAchR has been demonstrated and reported earlier. [1] Merger work has been done to co-relate the chemical structure with biological activity of nicotine and related compounds in mammals. However, much less attention has been devoted by their effects on insects. Therefore, the mechanism of action of nicotine and its derivatives is not primarily connected with anti-acetylcholine esterase activity. Detailed requirements by Yamamoto, lead to understand the structure activity relationship. Altering the position of side chain at the pyridine ring and the chain length between the 3-pyridyl and basic nitrogen had significant effect on toxicity. The secondary and tertiary amines were found to have insecticidal potency. Due to the high basicity of the second nitrogen in compare with pyridine nitrogen, the pyrrolidine or related nitrogen becomes protonated in a physiological medium at pH 7, in insect body. In this way, the molecule acquires the active form, which is able to compete with Ach on the receptor protein. With this view, nicotine or structurally related compounds are pre-insecticides enable to penetrate easily in to the body and the nervous tissue to the site of action. The protonation converts this pre-insecticide to the active form with the quaternary nitrogen, which is essential for the binding of the molecule to the anion site of the receptor. [2] Yamamoto, have reported the detail investigations on the structure

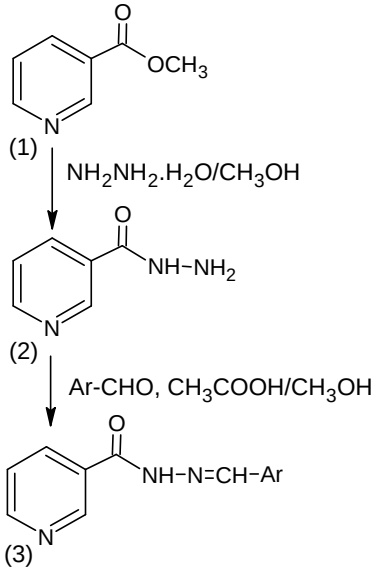
activity relationships of 26 synthetic nicotine analogues and to discover these compounds resembling acetylcholine in configuration and charge distribution toxic to several insect species. [3] Eldetrawi, thought that synthetic nicotinoids may effective as a future insecticides. Based on these lead, around 1984 chemists at Nihon Bayer, Japan synthesized the nitroguanidine, which was later called as imidacloprid [4-5] and its insecticidal activity was found Yamamoto, 10,000 folds higher than that of natural insecticide nicotine.



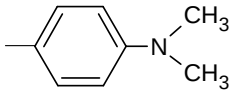
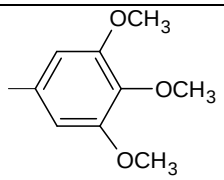
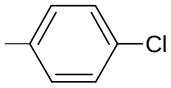
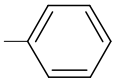
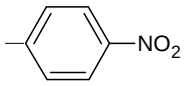
Scheme 1.

Reagents

(a) CH_3OH / H_2SO_4 , (b) 2-Fluro phenyl urea, CH_3COOH, CH_3OH, (c) 3-Trifluro methyl phenyl urea, CH_3COOH, CH_3OH, (d) DL-nor-leucine, CH_3COOH, CH_3OH, (e) 2,4-dicloro phenoxy acetic acid hydrazide, CH_3OH (f) Diethyl melonate, $NaOCH_3$, CH_3OH, (g) Thiourea, $NaOCH_3$, CH_3OH.



Scheme 2.

Compound No.	Substituents (Ar)
3a	
3b	
3c	
3d	
3e	

Further, the currently available insecticides acting on nicotinic acetylcholine receptors has no structural similarities with neo-nicotinoids and therefore, neo-nicotinoids has constitutes the compounds with a new mode of action. These are acute contact and stomach poisons with a trans-laminar activity and systemic properties. At the lower concentrations, these compounds act as an anti-feedent. [6] For this view, we have reported the synthesis and insecticidal activity of some nicotinic acid derivatives (Scheme 1 and Scheme 2).

EXPERIMENTAL SECTION

General: The nicotinic acid derivatives have been synthesized and their representative procedure is given below. These compounds were purified by column chromatography using silica gel and their yields were optimized. Melting points were measured and all compounds were tested on TLC having purity >98%. All the structures with their consistent assigned spectral data are given. FTIR spectra were obtained on a Perkin-Elmer FTIR 783 spectrometer. GCMS spectra were given by using QP2010 (Shimadzu) spectrometer. ^{1}H NMR spectra were obtained by Bruker Avance II (400 MHz) spectrometer.

Methyl pyridine-3-carboxylate (1): Reaction mixture containing 10 gm (0.5 mol.) nicotinic acid in 30 ml of methanol, 4 ml. Conc.H_2SO_4 was added and reaction mixture was get refluxed for about a 13 h; on a water bath. The whole reaction has to get cooled and neutralized with a solution of 10% sodium carbonate. The reaction has been completed and to be extracted with 20 ml chloroform.

The chloroform gets distilled out for the separation of white crystalline product [7-11] Yield (70%), M.P.38^{0}C.

N-[(2-Fluorophenyl)carbamoyl]pyridine-3-carboxamide (1a): Reaction mixture containing methyl nicotinate (0.05 mol.) and 2-Fluoro phenyl urea in methanol (15 ml), add 3 drops of glacial acetic acid, the reaction mixture was get refluxed on water bath for 5 h, cooled, to get solid product which was recrystallized by methanol. Yield (75%), M.P.177^{0}C. IR (KBr): 3425, 3321, 1655, 1625, 1600, 1553, 1361, 754 cm^{-1}; Mass (m/e): 239, 154, 112, 111, 91, 83, 64, 57, 44.

N-{[3-(Trifluoromethyl)phenyl]carbamoyl}pyridine-3-carboxamide (1b): Reaction mixture containing methyl nicotinate (0.05 mol.) and 3-(trifluoromethyl) phenyl urea in methanol (10 ml), add 3 drops of glacial acetic acid and refluxed by steam bath for 5 h. After completion of reaction, solvent were removed under vacuum. The solid product is recrystallized from methanol. Yield (70%), M.P.177^{0}C. IR (KBr): 3471, 3356, 3219, 1722, 1707, 1670, 1599, 1561, 1336, 1122 cm^{-1}. ^{1}H NMR δ (DMSO): 5.73(2H, s, NH), 6.85-8.19(8H, m, Ar-H and Py-H); Mass (m/e): 306(M^+), 244, 187, 168, 159, 145, 139, 132, 109, 90, 75, 69, 63.

2-[(Pyridin-3-ylcarbonyl)amino]hexanoic acid (1c): Reaction mixture containing Methyl nicotinate (0.05 mol.) and DL-nor leucine (0.05 mol.) in ethanol (10 ml), add 3 drops of glacial acetic acid, the reaction mixture was refluxed using water bath in a period of 5 h. After completion of reaction the mixture was cooled, to get a solid product, is recrystallized from ethanol. Yield (70%), M.P.200^{0}C. IR (KBr): 3458, 3197, 3061, 2716, 1774, 751, 1604, 1467, 1387, 1307, 1052, 1307, 715 cm^{-1}: Mass (m/e): 147, 104, 90, 70, 66, 50, 38.

N'-(phenoxyacetyl)pyridine-3-carbohydrazide (1d): Reaction mixture containing Methyl nicotinate (0.05 mol.) and 0.05 mole of 2, 4- dichloro phenoxyacetic acid hydrazine in 15 ml methanol, was refluxed on a steam bath for 6 h, cooled to get crystalline product. Yield (65%), M.P.145^{0}C. IR (KBr): 3318, 3217, 3102, 3039, 2922, 2852, 1672, 1642, 1500, 1480, 1436, 1270, 762 cm^{-1}; ^{1}H NMR δ (DMSO): 2.59(3H, s, OCH_3), 3.85(3H, s, OCH_3), 3.91(3H, s, OCH_3), 6.95-7.38 (6H, m, Ar-H and Py-H), 9.15(1H, s, NCH), 11.80(1H, s, CONH); Mass (m/e): 336(M^+), 274, 241, 239, 175, 145, 113, 111, 85, 71, 56, 42.

5-(Pyridin-3-ylcarbonyl)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (1e): The mixture containing methyl nicotinate (0.05 mol.) and diethyl malonate (0.05 mol.) add 10 ml, methanol with a pinch of $NaOCH_3$, the reaction was refluxed by water bath for about a 5 h. The solvent was removed to get diester (A), which was used, as such for further reaction with thiourea. The diester (A) (0.05 mol.) and thiourea (0.05 mol.) get refluxed on a water bath for 5-6 h, cooled and concentrated to crystalline product which was purified from ethanol. Yield, (85%), M.P.168^{0}C. IR (KBr): 3380, 3277, 3178, 1619, 1473, 1413 cm^{-1}; Mass (m/e): 249(M^+), 217, 134, 132, 130, 99, 97, 95, 94, 62, 60, 47.

Pyridine-3-carbohydrazide (2): Methyl nicotinate (0.1 mol.) was react with hydrazine hydrate (0.1 mol.) in methanol (10 ml.) is refluxed on water bath at 70^{0}C for 1 h, then cooled and the solvent was removed under reduced pressure to get solid, which was purified by recrystallization from ethanol [12], Yield (75%).

Nicotinoyl hydrazones (3_{a-e}): The mixture of nicotinoyl hydrazide (0.05 mol.) and aromatic aldehyde (0.05 mol.) was refluxed in methanol (10 ml) for 5 h, using a catalytic amount of acetic acid. After the completion of reaction, the mixture was cooled, and the separated product was filtered, dried and recrystallized from ethanol to get different hydrazones. [13] (3_{a-e})

Similarly, the compounds were prepared and their yield, M.P. and spectral data are given below:
N'-[4-(Diaminomethyl)benzylidene]pyridine-3-carbohydrazide (3_a): Yield (80%), M.P.132^{0}C. IR (KBr) : 3437, 3190, 3033, 1663, 1601, 1523, 1365 cm^{-1}; ^{1}H NMR δ (DMSO): 3.03(6H, s, 2xCH_3), 6.64-8.73(8H, m, Ar-H and Py-H), 9.13(1H, s, NCH), 11.52(1H, s, CONH); Mass (m/e): 268(M^+), 162, 146, 132, 118, 106, 91, 78, 65, 51.
N'-(3,4,5-Trimethoxybenzylidene)pyridine-3-carbohydrazide (3_b): Yield (80%), M.P.200^{0}C. IR (KBr): 3434, 3184, 2994, 2986, 2860, 1641,1577, 1127 cm^{-1}; ^{1}H NMR δ (DMSO): 2.59(3H, s, OCH_3), 3.85(3H, s, OCH_3), 3.91(3H, s, OCH_3), 7.02-8.75(6H, m, Ar-H and Py-H), 9.15(1H, s, NCH), 11.80(1H, s, CONH); Mass (m/e): 315(M^+), 193, 178, 163, 150, 135, 118, 106, 78, 66, 51.

N'-(4-Chlorobenzylidene)pyridine-3-carbohydrazide (3_c): Yield (70%), M.P.175^{0}C. IR (KBr): 3258, 2923, 1686, 1660, 592, 1282 cm^{-1}; Mass (m/e): 259(M^+), 224, 148, 137, 122, 106, 89, 78, 65, 51.
N'-Benzylidenepyridine-3-carbohydrazide (3_d): Yield (75%), M.P.130^{0}C. IR (KBr): 3196, 3028, 1656, 1589, 542, 1282 cm^{-1}; ^{1}H NMR δ (DMSO): 7.44-8.75(10H, m, Ar-H and Py-H), 9.16(1H, s, NCH), 11.85(1H, s, CONH); Mass (m/e): 225(M^+), 148, 122, 106, 89, 78, 65, 51.

N'-(4-nitrobenzylidene)pyridine-3-carbohydrazide (3e): Yield (70%), M.P.250^{0}C. IR (KBr): 2924, 2853, 1595, 1518, 1103 cm^{-1}; ^{1}H NMR δ (DMSO): 7.47-8.77(8H, m, Ar-H and Py-H), 9.16(1H, s, NCH), 12.16(1H, s, CONH).

Insecticidal bio-assay: All the treatments were done at a room temperature and treated insects were cultured at 28^{o}C in laboratory for the process of bioassay, it was replicated thrice and recorded the percent mortality data. [14]

Myzus persicae: The process of bioassay was performed by residual dry film technique [15] by preparing the different concentrations of synthesized organic compounds at 100, 300, and 500 mg litre^{-1} in acetone. The solutions were then applied separately in the Petri-plate at the rate of 0.5 ml each on the upper and lower plate

and allowed to dry to get thin film of residue on both the inner sides of Petri-plates. The aphids collected from the tobacco plants are multiplied on livestock in laboratory and second instars aphids were transferred in to a batch of 30 insects on each plate. A period of 24, 48 and 72 h after treatment, the percent mortality data was recorded and presented in Table 1.

Table 1. Percent nymphal mortality of M. persicae.

Compd. No.	% Mortality in h after treatment.								
	24			48			72		
	Dose1ml/treatment in mg litre^{-1}			Dose1ml/treatment in mg litre^{-1}			Dose1ml/treatment in mg litre^{-1}		
	100	300	500	100	300	500	100	300	500
1a	83.0	53.0	53.0	93.0	70.0	80.0	100.0	80.0	93.0
1b	10.0	13.0	17.0	43.0	37.0	43.0	50.0	47.0	53.0
1c	47.0	40.0	17.0	87.0	63.0	60.0	97.0	77.0	77.0
1d	43.0	20.0	50.0	67.0	30.0	67.0	80.0	37.0	80.0
1e	47.0	43.0	30.0	60.0	70.0	53.0	77.0	87.0	63.0
3a	33.0	30.0	50.0	53.0	37.0	67.0	57.0	47.0	83.0
3b	17.0	50.0	33.0	40.0	57.0	50.0	53.0	60.0	57.0
3c	33.0	43.0	20.0	43.0	53.0	37.0	50.0	67.0	50.0
3d	27.0	50.0	37.0	33.0	67.0	40.0	53.0	90.0	47.0
3e	17.0	33.0	57.0	37.0	80.0	73.0	43.0	87.0	87.0
Imidacloprid	67.0	73.0	93.0	90.0	77.0	100.0	100.0	97.0	100.0
Acetone	10.0	00.0	00.0	20.0	00.0	00.0	30.0	00.0	00.0

Helicoverpa armigera: The third instars larva of H. armigera was collected from the field of chickpea (Cicer arietinum) in the month of November - December. The cannibalism is a behavior of larval individuals due to which the larvae were kept in separate container. [16] The test compounds get diluted in acetone at a concentration of 100, 300 and 500 mg litre^{-1}. These 1 ml diluted compounds of each concentration were then applied to socked chickpea, dried it and fed to a batch of 10 larval individuals along with control treated with acetone. After an interval of 48, 96 and 144 h of treatment, the number of individuals going to shrink and immobilized due to test chemicals have been listed in percent moribund larval data in Table 2.

Sitophilus zeamais: The adult stage of S. zeamais is collected from the maize storage godwon. The test compounds get diluted in acetone at a concentration of 100, 300 and 500 mg litre^{-1}. These 1ml diluted compounds of each concentrations were then applied to a moist sorghum grain (Sorghum vulgar), dried it and fed to a batch of 50 adult individuals along with the control of acetone. A period of 8 and 16 days after treatment, the percent mortality data has been counted and presented in Table 3.

Table 2. Percent moribund larvae of H. armigera.

Compd. No.	% Moribund larvae in days after treatment.								
	2			4			6		
	Dose1ml/treatment in mg litre-1			Dose1ml/treatment in mg litre-1			Dose1ml/treatment in mg litre-1		
	100	300	500	100	300	500	100	300	500
1a	00.0	00.0	00.0	10.0	00.0	10.0	100.0	90.0	100.0
1b	10.0	20.0	0.00	10.0	20.0	20.0	80.0	90.0	80.0
1c	00.0	10.0	20.0	00.0	30.0	50.0	80.0	100.0	100.0
1d	40.0	00.0	00.0	50.0	20.0	10.0	90.0	80.0	50.0
1e	00.0	00.0	10.0	10.0	20.0	10.0	90.0	90.0	60.0
3a	00.0	40.0	10.0	10.0	50.0	10.0	60.0	60.0	50.0
3b	10.0	00.0	40.0	10.0	10.0	50.0	70.0	90.0	70.0
3c	00.0	00.0	00.0	30.0	10.0	10.0	90.0	80.0	80.0
3d	30.0	00.0	00.0	50.0	00.0	00.0	90.0	50.0	70.0
3e	10.0	00.0	20.0	20.0	00.0	40.0	80.0	80.0	100
Imidacloprid	40.0	10.0	10.0	40.0	20.0	50.0.	90.0	100.0	90.0
Acetone	10.0	20.0	00.0	10.0	20.0	00.0	10.0	20.0	00.0

RESULTS AND DISCUSSION

Myzus persicae: Dry film technique is use to performed bioassay process with the synthesized compounds showed more than 50% mortality and as compared to standard compound imidacloprid. The compounds imidacloprid > 1a > 1c > 1e > 3e > 1d > 3a > 3d > 3b > 3c > 1b > control (acetone) exhibited moderate to good activity against tobacco aphid M. persicae.

Helicoverpa armigera: The process of bioassay of synthesized compounds was performed on H. armigera, along with standard compound imidacloprid and control of the solvent acetone. The treatment of these compounds showed moderate to good insecticidal activity, the compounds imidacloprid > 1c > 1a > 3e > 1b ≡ 3c > 1e > 3b > 1d > 3d > 3a > control (acetone) exhibited promising activity, hence can be recommend as the lead compounds for controlling Heliothis.

Sitophilus zeamais: Synthesized compounds showed moderate insecticidal activity as compared with standard insecticide imidacloprid. In a series these compounds imidacloprid > 3d > 3c > 3b > 1c > 1b > 1e > 3e > 3a > 1d > 1a > control (acetone) showed good activity against stored grain pest S. zeamais. Hence, these compounds can be recommended as the pest control agents for stored grain pests.

Table 3. Percent mortality of adult S. zeamais.

Compd. No.	% Mortality in days after treatment.					
	8			16		
	Dose 1ml/treatment in mg litre-1			Dose 1ml/treatment in mg litre-1		
	100	300	500	100	300	500
1a	26.0	12.0	52.0	48.0	16.0	64.0
1b	50.0	22.0	22.0	72.0	36.0	40.0
1c	16.0	32.0	33.0	46.0	48.0	64.0
1d	12.0	40.0	30.0	28.0	40.0	66.0
1e	30.0	34.0	34.0	56.0	44.0	54.0
3a	16.0	18.0	56.0	30.0	40.0	72.0
3b	52.0	34.0	44.0	58.0	50.0	64.0
3c	16.0	56.0	54.0	22.0	78.0	74.0
3d	34.0	54.0	56.0	58.0	70.0	72.0
3e	14.0	30.0	32.0	38.0	60.0	48.0
Imidacloprid	44.0	68.0	82.0	60.0	68.0	88.0
Acetone	20.0	26.0	22.0	34.0	34.0	32.0

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