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Benzophenyl urea insecticides – useful and eco-friendly options for insect pest control

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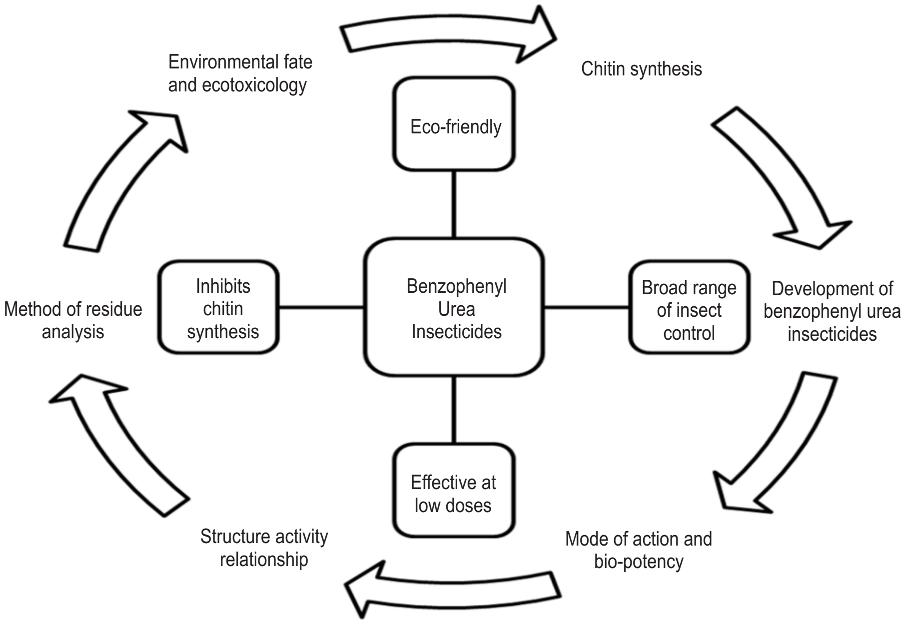
Abstract

Insecticides play a very important role in increasing production by protecting crops from destructive insect pests. But indiscriminate use of conventional and broad spectrum insecticides, leads to development of resistance, resurgence and environmental pollution. Therefore, it is necessary to select new, safe and less persistent products for ecofriendly and sustainable pest management. Benzophenyl urea based insecticides fit well in this aspect. These are basically inhibitors of the chitin synthesis in insects which make them strong candidate for the integrated pest management. Extensive research has been carried out on different aspects to assess the potentiality and environment friendliness of this group of insecticides. Thus, the aim of this review is to gather comprehensive information about benzophenyl urea insecticide related to its development, mode of action, bio-efficacy, environmental fate and eco-toxicity, which may be helpful for the researchers for future endeavour.



Key words: Benzophenyl urea, Chitin, Insecticide, Pest control, Toxicity

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Introduction

Research has been advanced during the last few years in search of novel compounds which can act as potent insecticides as the existing molecules (organophosphate, organochlorine, carbamate) were showing serious threats to the beneficial organisms, disturbing ecological balance. There was increasing demand for eco-friendly and target-specific insecticides that do not harm beneficial and non-target living organisms (Horowitz and Ishaaya, 2004, Bhattacharyya *et al.,* 2009). As a result, new chemistry compounds (e.g. thiamethoxam, flubendiamide, pyridalyl etc.) have been synthesized which are specific in action and safer than traditional ones towards natural enemies (Patra *et al.,* 2017, 2018; Barik *et al.,* 2010), thus new generation pesticides become vital component of Integrated Pest Management (IPM) programs (Casida and Quistad, 1998; Patra and Samanta, 2017, 2018).

Insect's chitin plays an important role in its growth, development and reproduction. Previously, a considerable number of chemically different group of insecticides were developed to inhibit the chitin synthesis (Muthukrishnan *et al.,* 2012). In order to inhibit biosynthesis of chitin, these products often cause unsuccessful molting and egg laying resulting into deformed cuticle. Moreover, some compounds have also shown to affect formation of peritrophic matrix and its function in the insect's intestine. Peritrophic matrix also plays an important role by providing a protective shield against attack by microorganisms in the insect's midgut (Hegedus *et al.,* 2009). Brief information about chitin and its formation can give some clues about how the idea of this insect control was evolved.

Chitin and its synthesis in insects: Chitin is basically a polymer of monosaccharide called N-acetylglucosamine linked by β-(1-4)-glycosidic bonds. It forms microfibrils of about 20 sugar chains that act as building blocks of insect cuticle. Chitin hydrolysis, in the presence of chitinase enzyme, produces glucosamine along with N-acetylglucosamine that shows the co-existence of former in the polymer unit. Although, NMR analysis of cuticle present in tobacco hornworm did not show the presence of glucosamine (Kramer *et al.,* 1995). As confirmed by X-Ray Diffraction analysis, chitin is mainly divided into three types, viz. α, β and γ chitin. In these forms, α chitin is predominantly found in chitinous cuticle where rests two are prevalent in cocoons (Kenchington, 1976; Peters, 1992). The major differences among three forms lie in the extent of hydration, unit cell size and chitin chain number in unit cell.

Chitin is synthesized both in the epidermis and midgut of the insect. Inside the cuticle, chitin mainly exists as procuticle and that to much higher in endocuticle as compared to exocuticle, however, it is not found in epicuticle. Chitin is also an important part of peritrophic matrix (gut lining). Actual process involved in biosynthesis of chitin in insect is not so clear and apparently involves several genes (Fig. 1). The enzyme highly responsible for synthesis of chitin is chitin synthases (UDP-N-acetyl-Dglucosamine: chitin 4-β-Nacetylglucosaminyltransferase; EC 2.4.1.16) (Merzendorfer and Zimoch, 2003),which is difficult to assay. However, this biosynthetic pathway is considered almost similar to the Leloir pathway in microbes. The preliminary sugar required for chitin synthesis is fat body glycogen and the entire pathway can be subdivided into three parts. The first part sets of the reactions to form amino sugar GlcNAc. The second part involves reactions that produce UDP-GlcNAc. The third includes the formation of polymeric chitin (Muthukrishnan *et al.,* 2012). Any alteration in the bio-synthetic pathway by the foreign particle can inhibit chitin synthesis in insects and can cause lethal effects.

Benzophenyl urea insecticides–potent chitin synthesis inhibitor: Among the chitin synthesis inhibitors, the important compounds are benzophenylureas (BPUs). These are potent insecticides which regulate the growth of insects in somewhat negative way so that they can be controlled before causing any harm. Insect's endocuticle gets affected and loses its elasticity when exposed of these insecticides. BPUs are very selective in action and can be an important component of any IPM schedule. As higher animal and plants do not have chitin in their body structure, these BPUs are relatively safe to them. The global market share of BPU insecticides was reported as 3.6% in 2011 (Sun *et al.,* 2015) and the trend is increasing. In India, several compounds are registered by Central Insecticide Board & Registration Committee for use in agriculture, household and for public health as well (Table 1). These are very stable in crop environment and exert reproducible results in insects. Another advantage of using BPUs is that it has broad application because insects take longer time to molt (Table 2).

Development of benzophenyl urea insecticides: N-benzoyl-N'-phenyl urea have been found as basic moiety for potent chitin biosynthesis inhibitor (Post *et al.,* 1974), which causes unusual endocuticular deposition that leads to unsuccessful molting (Mulder and Gijswijt, 1973). Till date, almost 15 BPU insecticides (Fig. 2) have been commercialized after extensive research. Discovery of first commercial BPU insecticide, diflubenzuron, was carried out in an unplanned way. With the invention of powerful herbicides diuron and dichlobenil, a metabolite (DU19111), 1-(2,6-dichlorobenzoyl)-3-(3,4-dichlorophenyl)-urea, was synthesized, however, the compound showed insecticidal activity rather than possessing herbicidal action. This led to the synthesis of diflubenzuron, as an analogue of Du19111.

Besides agricultural use, this insecticide plays an important role in public hygiene as it is widely used for controlling mosquitos in Europe where neurotoxins are prohibited for use in mosquito breeding centre (Douris *et al.,* 2016). After the discovery of diflubenzuron, three more products namely chlorbenzuron, dichlorbenzuron and penfluoron had been developed with increased larvicidal action (Sun *et al.,* 2015).With a requirement for more potent and stronger BPUs, scientists have discovered chlorine and/or fluorine derivatives of BPUs, such as teflubenzuron (Clarke and Jewess, 1990). Another breakthrough had been made when researchers invented the compound triflumuron. It is considered as the second generation BPU

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insecticide, which is more potent ovicide and larvicide as compared to diflubenzuron. In the following years, a number of compounds like hexaflumuron as termiticide, novaluron, lufenuron, noviflumuron and bistrifluron have been identified and synthesized as powerful larvicides. Hexaflumuron (Komblas and Hunter, 1986), lufenuron (Schenker and Moyses, 1994), novaluron (Ishaaya et al., 1996) and noviflumuron (Sbragia *et al.,* 1998), containing α-fluoroalkoxy residue in the para position, are insecticides, especially very active against hymenoptera. They are more effective against different harmful insect pests as compared to diflubenzuron (Ishaaya, 1990). Bistrifluron is active against whitefly and lepidopteran insects (Kim *et al.,* 2000). Being non-toxic to vertebrates, triflumuron, hexaflumuron and lufenuron have wide application as veterinary as well as household insecticides to control animal and human pests such as fleas, mosquitos, ticks and cockroaches (Krämer and Schirmer, 2007). Effectiveness of lufenuron against okra shoot and fruit borer (Patra *et al.,* 2007) and brinjal shoot and fruit borer (Patra *et al.,* 2009) have been documented in several literatures. Investigation for third generation BPU insecticides has resulted in discovery of flufenoxuron.

This compound has an excellent control on eggs and nymphs of spider mites as well as larvae of some insect pests (Anderson *et al.,* 1986). These third generation BPU insecticides have shown increased topical activity as well as broad spectrum control. Flucycloxuron, the first BPU that controls rust mites (Scheltes *et al.,* 1988), was invented by Philip-Duphar B.V. Another compound, chlorfluazuron introduced in the market for

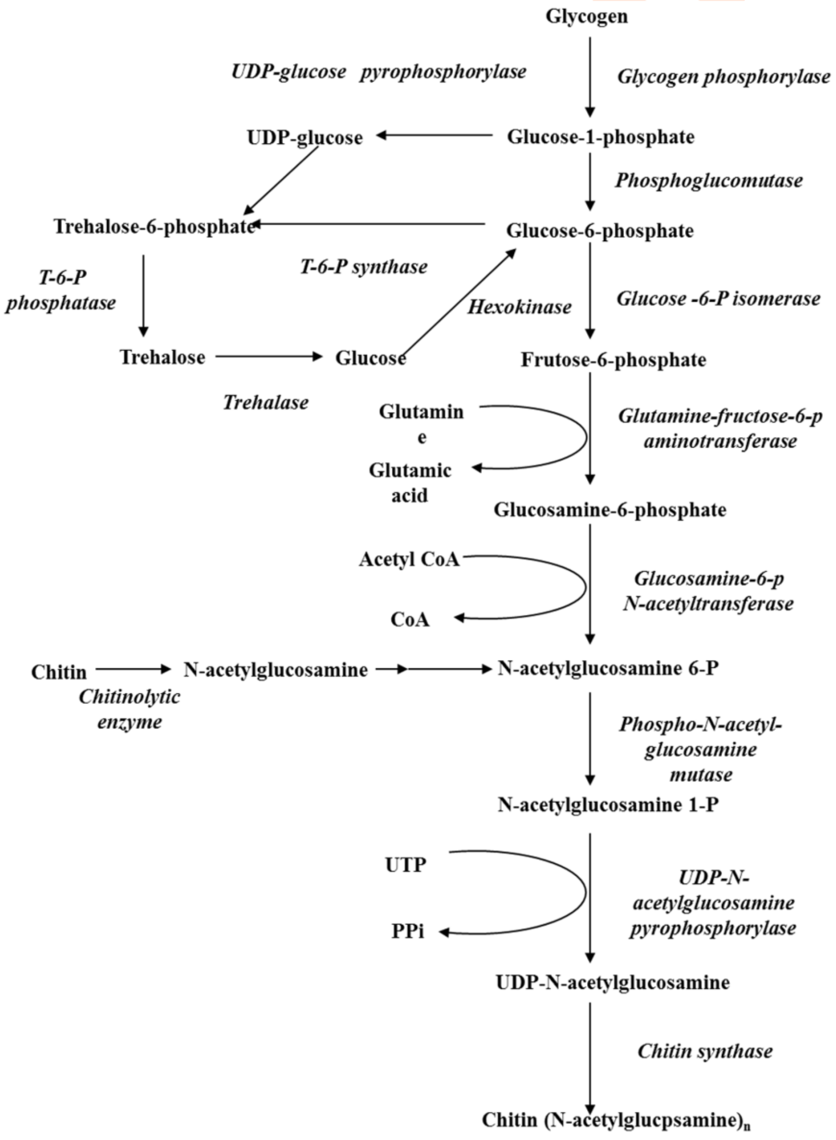

Fig. 1: Chitin biosynthetic pathway in insect (Merzendorfer and Zimoch, 2003).

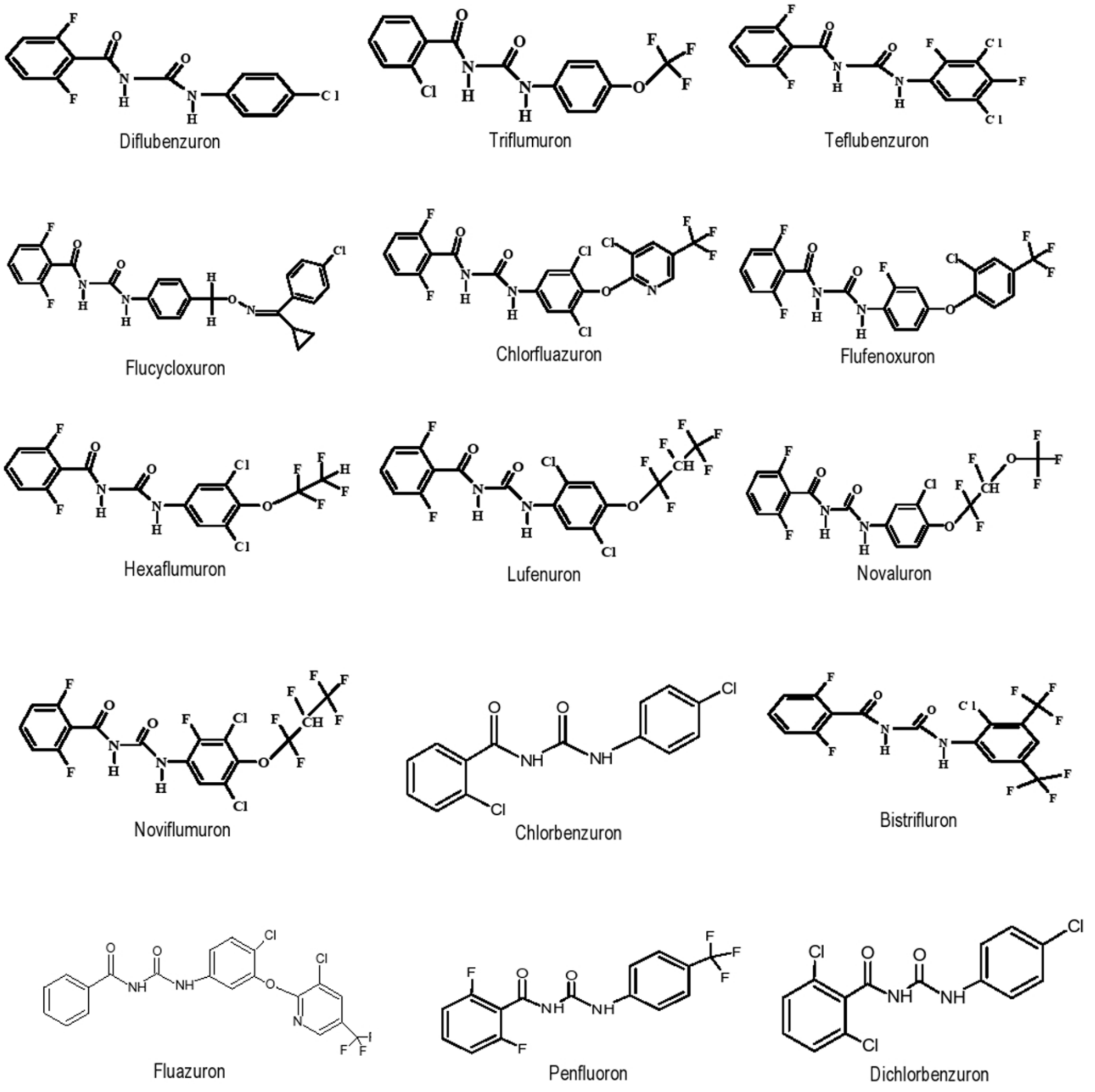

Fig. 2: Structures of BPU Insecticides.

controlling chewing insect, diamondback moth (*Plutella xylostella*), thrips and other pests on vegetables (Neumann and Guyer, 1987). This insecticide can also be applied on fruit and plantation crops. Recently, few BPUs are merged with photoswitchable azobenzene that would cause photoresponsive inhibition in chitin synthesis. The preparation can be activated upon irradiation with UV source and can show 2-fold and 6-fold increased activity against sulfonylurea receptors of German cockroach (*Blattella germanica*) and armyworm (*Mythimna separata*), respectively. It can open new avenues for the spatio-temporal management of harmful lepidopterans (Tian *et al.,* 2017).

Mode of action and potency in pest management: BPUs insecticides can selectively affect insect's larval stage by interrupting the molting process (Mulder and Gijswijt, 1973; Ishaaya and Casida, 1974). Upon ingestion, they produce toxic effects in the insects; even some compounds can suppress fecundity and can act as potent ovicide (Ishaaya and Horowitz,

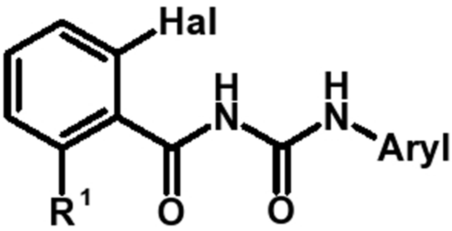

Fig. 3: General structure of N-benzoyl-N'-phenyl ureas (BPUs).

1998). It has been reported that diflubenzuron can significantly alter the composition of cuticle that is made of chitin-thus reducing the firmness and elasticity of insect's endocuticle (Grosscurt, 1978; Grosscurt and Anderson, 1980). The decreased level of chitin in the insect's cuticle is a strong evidence of inhibition of chitin bio-synthesis (Post *et al.,* 1974; Ishaaya and Casida, 1974; Hajjar and Casida, 1979; Van Eck, 1979). Chitin synthetase is not a mandatory site for inhibiting this synthesis as found in different studies. This theory is supported by the fact that BPU insecticides does not inhibit this enzyme externally (cell-free systems) (Cohen and Casida, 1980; Mayer *et al.,* 1981; Cohen, 1985).

Some studies indicate that there is a chance for BPU insecticides to affect insect's hormones, thereby disturbing the vital physiological processes like DNA synthesis (Mitlin *et al.,* 1977; DeLoach *et al.,* 1981; Soltani *et al.,* 1984), phenoloxidase and carbohydrase activities (Ishaaya and Casida, 1974; Ishaaya and Asher, 1977), or inhibit microsomal oxidase activity (Van Eck, 1979). Moreover, researchers have identified that BPU compounds can restrict incorporation of 20E-dependent GlcNAc into chitin (Mikołajczyk *et al.,* 1994; Oberlander and Silhacek, 1998). This significant outcome suggests that BPU compounds alter ecdysone-dependent biochemical sites, thereby inhibiting chitin. Diflubenzuron have shown promising results against *Aedes aegypti* (Marcombe *et al.,* 2011); *Culex pipiens* larvae (Cetin *et al.,* 2006); *Aedes albopictus* (Lau *et al.,* 2018); *Culex quinquefasciatus* Say (Sadanandane *et al.,* 2012); body louse (*Damalinia limbata*) of Angora goats (Fourie *et al.,* 1995).

It could be opted as an alternative against the chemicals to control larva and could be incorporated in the integrated vector control programmes in urban and rural areas (Msangi *et al.,* 2011). It is a promising agent for codling moth management programs in apple orchards (Anderson and Elliott, 1982); pear psylla, *Cacopsylla pyricola* (Emami, 2016); boll weevil, *Anthonomus grandis grandis* Boheman (Hopkins *et al.,* 1982); subterranean termite (Kalawate, 2012); looper complex, *Hyposidra* spp. in tea plantations (Basu Majumder *et al.,* 2012). It can be recommended for controlling of synanthropic flies in the feces of commercial egg laying chickens (Silva *et al.,* 2000). Chitin synthesis inhibitors (diflubenzuron, flufenoxuron, lufenuron, and triflumuron) have also shown good efficacy against stored grain insect pests (Kavallieratos *et al.,* 2012). Generally, the primary route of entry of BPU insecticides is ingestion, but novaluron can exhibit contact and translaminar property, thereby controlling whitefly (by contact action) and leafminer (by translaminar activity), in addition to larvae of lepidoptera and coleoptera (by ingestion) (Ishaaya *et al.,* 1996 & 2002). Novaluron has been found effective insecticide against *Helicoverpa armigera* (Shivanna *et al.,* 2012; Wavare *et al.,* 2008; Prasad and Rao, 2009); spotted bollworm, *Earias* spp (Singh *et al.,* 2009); *Spodoptera litura* Fab. (Krishna *et al.,* 2008); colorado potato beetle (Culter *et al.,* 2007); *Aedes albopictus* (Lau *et al.,* 2018); *Aedes aegypti* (Mulla *et al.,* 2003). It can be used for integrated livestock pest management program (Lohmeyer *et al.,* 2014).

Novaluron was found to be safer to the predatory coccinellids (Wagh *et al.,* 2017) and its mix formulation with other insecticides demonstrated good efficacy against *Helicoverpa armigera* (Das *et al.,* 2015; Lalruatsangi *et al.,* 2018), *Plutella xylostella* (Patra *et al.,* 2015) and *Leucinodes orbonalis* (Sharma, 2010;Mahata et al., 2014). Lufenuron proved its efficacy against *Spodoptera litura* (Islam, 2015); thrips, *Scirtothrips dorsalis* Hood and pod borer, *Spodoptera litura* Fab. on chillies (Ahmed and Prasad, 2009); *Bactrocera oleae* (Moustafa *et al.,* 2009). It can be used as a potential product for pest management in mills, warehouses and food storage facilities (Yasir *et al.,* 2019). Hexaflumuron have shown excellent termiticidal efficacy against workers of *Reticuliter messantonensis* (Rasib and Wright, 2018). The target segment of BPU insecticides is primarily the larvae of insects, which produces chitin at the time of molting (Ghanim and Ishaaya, 2010). Moreover, benzophenyl ureas inhibit peritrophic matrix formation, which safeguards the midgut epithelium from several harmful agents (Soltani *et al.,* 1984; Clarke *et al.,* 1977; Becker, 1978). This inhibition can be correlated with the reduction in chitin content which ultimately alters the structure and functions of insect's cuticle (Post *et al.,* 1974; Van Eck, 1979; Hajjar and Casida, 1978). Moreover, the bio-potency of compound depends mainly on the basic structural moiety of itself.

Structure Activity Relationships (SAR): In earlier stages of research, there was little scope to modify the substituents at N-benzoyl moiety (Fig. 3) for improved activity. Substitution at ortho position can only make the compound insecticidally active. This substituent (R^1) can be CH_3, OC_2H_5, or OCF_3 to retain the potency the compound. But, practically, all commercialized compounds have ortho-halogen substitution and the order of insecticidal and/or acaricidal activity can be depicted as (Hal, R^1): 2,6-F_2> 2-Cl, 6H > 2,6- Cl_2> 2-F, 6H.

In case of N'-arylamino moiety, the scope of substitution is usually broadened. However, SAR studies have demonstrated that substitution with electron-withdrawing groups like halogen, halogenoalkyl, α-fluoroalkoxy or halogenated pyridin-2-yl can produce optimum effects. Generally, fluorine occupies the para position of the moiety of these BPUs to get additional stability and extended spectrum of use (especially mites). Some fluorinated substituents like F_2HC-F_2C-O, F_3C, FHC-F_2C-O are mainly found as substituents (Krämer and Schirmer, 2007). So far the

Table 1: Registered BPU in India for different uses (Anonymous, 2019)

Agricultural use

Name of the insecticide	Crop	Target pests	a.i (g)	Dosages/ha Formulation (g ml^{-1})	Dilution in Water (L)	Waiting Period (d)
Chlorfluazuron 5.4% EC	Cabbage	Diamond back moth, Tobacco leaf eating caterpillar	75	1500	500	7
	Cotton	American bollworm, Tobacco leaf eating caterpillar	75-100	1500-2000	500	10
Diflubenzuron 25% WP	Cotton	Tobacco Caterpillar,	75-87.5	300-350	500-1000	-
		Bollworms	75	300	500-1000	-
Flufenoxuron 10% DC	Rose	Mites	50	500	500-1000	6
	Cabbage	Diamond backmoth	30	600	500	14
	Cauliflower	Diamond backmoth	30	600	500	5
Lufenuron 5.4% EC	Pigeon pea	Pod borer, podfly	30	600	500-1000	65
	Cotton	American bollworm	30	600	500-750	48
	Black gram	Pod borer	30	600	500	10
	Chilli	Fruit borer	30	600	500	5
	Cotton	American Bollworm	100	1000	500-1000	40
	Cabbage	Diamond back moth	75	750	500-1000	5
	Tomato	Fruit borer	75	750	500-1000	1-3
Novaluron 10% EC	Chilli	Fruit borer, Tobacco Caterpillar	33.5	375	500	3
	Bengal gram	Pod borer	75	750	500	7
Novaluron 8.8% SC	Cotton	American boll worm, Tobacco caterpillar	100	1000	500-1000	20

Public health use

Name of the insecticide	Name of the pest	Habitat/place of application	a.i. (mg m^{-2})	Formulation (g)
Diflubenzuron 2% GR.	Mosquito larvae	Water bodies (Cess pits, Drains, & Disused wells and pools)	1.25 – 3.0 kg ha^{-1}	-
Novaluron 10%EC	An. Stephensi An. Aegypti	Clean surface water	30	0.03ml m^{-2}
		Polluted surface water	60	0.06 ml m^{-2}
	Culex quinquefasciatus and An. Subpictus			

Household use

Name of the insecticide	Name of the pests	Habitat	Dosage	Dilution in water
Diflubenzuron 2% Tablets	Mosquitoes Larvae	Unused Coolers Clean surface water,	0.5-1.0 ppm 25-50 g a.i ha^{-1}	½ -1 Tablet in 40 L water
Diflubenzuron 25% WP	Mosquitoes Larvae	Polluted surface water	50-100 g a.i ha^{-1}	-
		Sewage pits, soak pits, latrines, septic tanks.	1 mg a.i. l^{-1}	
	House fly maggots	In poultry manure Garbage, Filth & dumping areas	5.0 g 10 m^{-2}	5 l water 10 m^{-2}

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benzophenyl urea insecticides are commercialized, the only compound is triflumuron which is not typically 2,6-difluoro substituted (Hammann and Sirrenberg, 1980). It has been found beneficial when pseudohalogenic trifluoromethoxy group is attached to the 4-position of N'-arylamino moiety as it results into stronger insecticidal action coupled with a pronounced feeding

Table 2: Activity spectrum of some important BPU insecticides(Merzendorfer, 2013)

Compound	Target pests	Remarks
Diflubenzuron	Highly effective in controlling holometabolous pests. Excellent control against lepidopteran larvae such as tobacco caterpillar, bollworm etc. Can control of maggots of fly and mosquito.	Not so effective against mites (Peleg and Gothilf, 1981) and aphids (Mulder and Gijswijt, 1973).
Triflumuron	Can control wide range of insects like flea larvae, mosquito, lice, silverfish, cockroach etc.	Can moderately control soft bodied scale insects (Darvas, 1997).
Chlorfluazuron	Highly effective against lepidopteran larvae like diamond back moth, tobacco caterpillar, bollworm etc.	Found some action against aphids (Ammar *et al.,* 1986).
Teflubenzuron	Effective against caterpillars, white fly, leaf miner, beetles etc.	Found some action against soft scales (Eisa *et al.,* 1991).
Hexaflumuron	Active against hompteran insects	Can act as potent termiticide (Sajap *et al.,* 2000).
Novaluron	Highly effective against American bollworm, diamond back moth, fruit borer, tobacco caterpillar etc.	Having rain fastness property, can be effective against Aedes aegypti (Farnesi *et al.,* 2012).
Flufenoxuron	Exclusive control of phytophagous mites	Makes Nuclear Polyhedrosis Virus (NPV) ineffective in silkworm (Arakawa *et al.,* 2002).
Lufenuron	Effective against pod fly, American bollworm, diamond back moth etc.	Can be adopted in veterinary flea control programme, having some antifungal activity (Ben-Ziony and Arzi, 2000).

and contact activity against chewing pests like fall armyworm (*Spodoptera frugiperda*) and coleopteran pests such as mustard leaf beetle, *Phaedon cochleariae* (Krämer and Schirmer, 2007). Another important hypothesis formulated by the scientists is that benzophenyl urea structurally resembles to sulphonyl urea. It is believed that these insecticides can alter the activity of potassium channel and also calcium transport. Due to this phenomenon, secretion of necessary protein for cuticle and PM formation gets interrupted (Merzendorfer, 2013).

Detection of BPUs residues: It is important to estimate the residues of benzyl phenyl urea in various environmental substrates to assess the persistence and toxic effects of the compounds, if any (Patra *et al.,* 2020). For which, several methods have been published in different literatures about the identification and quantification of benzophenyl urea residues in various environmental components. Most of them suggest to use Liquid Chromatography (LC) technique to detect these compounds. High Performance Liquid Chromatography coupled with Mass Spectrometry (HPLC-MS) can even detect the trace levels of BPU residues in crop, soil and water samples. Likewise, a HPLC enabled with photodiode array detector was used for identification of 4 chitin synthesis inhibitors such as flufenoxuron, teflubenzuron, diflubenzuron and chlorfluazuron in beef samples (Sasamoto *et al.,* 1995). The mixture of hexane:acetone (2:1) was used as extracting solvent. The extract was subjected to liquid-liquid partitioning using acetonitrile and hexane, succeeded by column clean up with Bond Elut silica. Separation was done on a Wakosil-II $5C_{18}$ HG column (4.6 mm i.d. x 250 mm) with mixture of acetonitrile: water (5:2) as the mobile solvent. These four compounds were detected at 250 nm and 260 nm wavelength. The average recoveries of these analytes, spiked in beef samples at 0.2 $\mu g\ g^{-1}$ level, were found in between 82.9-96.7%.

In another study, liquid chromatography technique, combined with diode array detector, was used to estimate the residues of BPU insecticides namely diflubenzuron, triflumuron, lufenuron, teflubenzuron, hexaflumuron, flufenoxuron, chlorfluazuron and flucycloxuron in cucumber, apple, chinese cabbage and mushroom (Hiemstra *et al.,* 1999). The samples

Table 3: Environmental fate of some BPU insecticides (Lewis *et al.,* 2016)

Compound	Soil degradation DT_{50} (d)	Aqueous photolysis DT_{50} (d) at pH 7	Aqueous hydrolysis DT50 (d) at 20°C and pH 7	Soil adsorption and mobility
Diflubenzuron	3 (non-persistent)	80 (stable)	96 (moderately persistent)	Non mobile
Triflumuron	22 (non-persistent)	32.8 (stable)	Stable	No to slightly mobile
Teflubenzuron	92 (moderately persistent)	10 (moderately fast)	Stable	Non mobile
Flucycloxuron	208 (persistent)	18 (slow)	28 (non-persistent)	Non mobile
Chlorfluazuron	90 (moderately persistent)	stable	Stable	Non mobile
Hexaflumuron	57 (moderately persistent)	6.3 (moderately fast)	Stable	Non mobile
Lufenuron	16.3 (non-persistent)	0.5 (fast)	Stable	Non mobile
Novaluron	72 (moderately persistent)	stableis	Stable	Non mobile
Noviflumuron	250 (persistent)	-	Stable	Non mobile
Bistrifluron	80.5 (moderately persistent)	10 (moderately fast)	stable	Non mobile
Flufenoxuron	42 (moderately persistent)	6 (moderately fast)	267 (persistent)	Non-mobile

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Table 4: Eco-toxicological information about few BPU insecticides (Lewis *et al.,* 2016)

		Acute toxicity							
Compound	Bio-concentration factor (l kg^{-1})	Mammals-Acute oral Ld$_{50}$ (mg kg^{-1})	Birds-Acute Ld$_{50}$ (mg kg^{-1})	Fish-Acute 96 h Lc$_{50}$ (mg l^{-1})	Aquatic invertebrates – Acute 48 hour EC$_{50}$ (mg l^{-1})	Aquatic plants– Acute 7 day EC$_{50}$, biomass (mg l^{-1})	Algae– Acute 72 hour EC$_{50}$, growth (mg l^{-1})	Honeybee Oral acute Ld$_{50}$ (µg bee^{-1})	Earthworms-Acute 14 day Lc$_{50}$ (mg kg^{-1})
Diflubenzuron	320 (threshold for concern)	>4640 (low)	>5000 (low)	>0.13 (moderate)	0.0026 (high)	> 0.19 (moderate)	20 (low)	>9.1 (moderate)	>500 (moderate)
Triflumuron	612 (threshold for concern)	>5000 (low)	561 (moderate)	>0.021 (high)	0.0016 (high)	-	>0.025 (moderate)	>226 (low)	>500 (moderate)
Teflubenzuron	640 (threshold for concern)	>5038 (low)	>2250 (low)	>0.0065 (high)	0.0028 (high)	-	>0.02 (moderate)	72 (moderate)	>500 (moderate)
Flucycloxuron	-	>5000 (low)	>2000 (low)	>100 (low)	>0.0002 (high)	-	>0.002 (high)	-	1000 (moderate)
Chlorfluazuron	-	>8500 (low)	>2510 (low)	>300 (low)	0.000908 (high)	-	-	>100 (low)	>1000 (low)
Hexaflumuron	4700 (threshold for concern)	>5000 (low)	2000 (moderate)	100 (moderate)	0.0001 (high)	-	3.2 (moderate)	0.1 (high)	880 (moderate)
Lufenuron	5300 (high potential)	>2000 (low)	2000 (moderate)	>29 (moderate)	0.0013 (high)	-	8.8 (moderate)	>197 (low)	>500 (moderate)
Novaluron	2091 (threshold for concern)	>5000 (low)	>2000 (low)	>1.0 (moderate)	0.058 (high)	0.075 (moderate)	9.68 (moderate)	>100 (moderate)	>1000 (low)
Noviflumuron	-	>5000 (low)	>2000 (low)	1.8 (low)	3.11 (moderate)	-	-	-	>10000 (low)
Bistrifluron	2414 (threshold for concern)	>5000 (low)	>2250 (low)	>0.5 (moderate)	>1.2 (moderate)	-	-	-	>1000 (low)
Fluazuron	-	>5000 (low)	>2000 (low)	15 (moderate)	0.0006 (high)	-	27.9 (low)	-	1000 (moderate)
Chlorbenzuron	-	>10000 (low)	>5000 (low)	126.8 (low)	-	-	-	>17 (moderate)	-
Flufenoxuron	700500 (high potential)	>3000 (low)	>2000 (low)	>0.0049 (high)	0.000043 (high)	-	5.11 (moderate)	>109.1 (low)	>500 (moderate)

were extracted using acetone followed by partitioning with mixture of dichloromethane and petroleum ether. LC separations were performed on a reversed-phase column, with acetonitrile-water gradient as mobile phase. Compounds were detected at 260 nm in photo diode array detector, with producing full spectra for further confirmation. Recovery and repeatability studies were performed at single spiking level for all the compounds, except flucycloxuron. The detection limits varied from 20 to 50 µg kg^{-1} for all the compounds examined irrespective of the matrices. A GC-MS based method was also documented to confirm BPU residues and their metabolites using ion-trap detector. Another HPLC based method has been developed to analyse few BPU molecules such as diflubenzuron, teflubenzuron, triflumuron, flufenoxuron and lufenuron in the samples of grape and processed wine (Miliadis *et al.,* 1999). Solid phase extraction has been carried out using silica sorbent to clean up the sample after extraction with ethyl acetate. The detection was done in UV Photo Diode Array (PDA) and the recovery of the method was quite satisfactory.

A multi-residue analysis method was developed to detect 17 pesticides including some BPUs (methabenzthiazuron, inabenfide, diclomezine, dimethomorph, cumyluron, acibenzolar-S-methyl, diamuron, diflubenzuron, tebufenozide, etobenzanid, hexaflumuron, pencycuron, teflubenzuron, lufenuron, pentoxazone, flufenoxuron, chlorfuazuron) in various agricultural commodities were detected by using LC/MS. The method was standardized for different matrices like rice, potato and orange by spiking the compounds at 0.1µg g^{-1} level. The samples were subjected to solvent extraction using acetonitrile followed by clean-up with primary and secondary amine (PSA) sorbent and elution with mixture of acetone and hexane (1:1) as eluting solvent. Compounds were detected using atmospheric pressure chemical ionization (APCI) techniques enabled with both positive and negative ion modes in the mass spectrometer (Okihashi *et al.,* 2002). The method was validated with acceptable accuracy and precision as the mean recoveries of the compounds usually ranged between 70 to 98% and the relative standard deviations (RSD) values were usually around 10% irrespective of the

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substrate. This finding has endorsed the suitability of the method to analyze trace levels of the pesticides in the selected matrices by using LC/MS with APCI.

In another experiment, LC system with Electro-Spray Ionisation (ESI) in both positive and negative mode was used for evaluating degradation pathway of diflubenzuron and hexaflumuron in water samples (Yang *et al.,* 2006). On the basis of product ion fragmentation pattern, authors confirmed the identity of both the analytes. The method developed was found accurate, precise, good linearity with lower detection limits. Recently, QuEChERS (Quick, Easy, Cheap, Effective, Rugged and Safe) method is getting popularity in residue analysis for having several advantages over conventional methods (Lehotay, 2011). Analysts are frequently adopting this method with suitable modification. Likewise, a method was developed to determine chlorfluazuron residues in cabbage using HPLC enabled with PDA (Ganguly *et al.,* 2017). Here, ChemElut (Agilent) sorbent was used to separate the analyte from the co-extractives. The LOD (limit of detection) and LOQ (Limit of Quantification) values were recorded as 0.05 and 0.10 $\mu g\ g^{-1}$ respectively. Here, analyte separation was achieved using a Chromatopak C18 column (250X4.6 mm; Peerless Basic) with mixture of methanol and water (95:5, v/v) solvent as mobile phase.

Environmental fate: By following different methods as mentioned above, scientists across the globe have been monitoring BPU residues in environmental substrates and several publications are available. Based on these findings, it can be concluded that BPUs are comparatively safer insecticides than the conventional organochlorine and organophosphate. Most of these compounds show low to moderate persistency in environment (Table 3) (Lewis *et al.,* 2016). Degradation of insecticides largely depends upon both biotic (micro & macro flora) and abiotic factors (soil, water, temperature, solar energy etc.). Any changes in these factors may cause wide variation in degradation pattern of the compounds. For example, chlorfluazuron is found to be dissipated at faster rate in alkaline pH as compared to acidic and neutral pH (Ganguly *et al.,* 2016a). Half-life value of different BPU insecticides varies from days to months depending upon the chemical structure and exposure to the factors mentioned earlier. Likewise, degradation of diflubenzuron is very fast as compared to noviflumuron, which generally takes 250 days.

The major pathway for quick dissipation of diflubenzuron is mediated through biotic processes whereas noviflumuron strongly binds to the soil colloids, solubilize less in water resulting less degradable. In case of chlorfluazuron, the half-life values ranged between 12-26 days in different soils (Ganguly *et al.,* 2016b). Upon degradation, these can produce toxic and non-toxic metabolites as well. For example, photo-degradation and hydrolysis of diflubenzuron may produce metabolites like 2,6-diflurobenzamide, 4-chloroaniline, N-methyl-4-chloroaniline and 4-chloroacetanilide, of which last three compounds are considered as mutagens (Rodrıguez *et al.,* 1999); Mobility in soil is very restricted for almost all the compounds.

Eco-toxicology: BPU insecticides, in general, are safe to mammals as of acute toxicity is concerned (Table 4) (Lewis *et al.,* 2016). Because of these low toxicity levels and also for higher bio-potency, BPU insecticides are the automatic choices for IPM (Morais *et al.,* 2011). These compounds can inhibit chitin formation in several orders of insect pests, but, do not possess any significant effects on the microbes and beneficial insects as well (Merzendorfer, 2013). But, in aquatic environment, the scenario is somewhat not so much encouraging. Bio-concentration is the process by which the concentration of a compound is increased within an aquatic organism for which the source is only water. Bio-concentration factor ($l\ kg^{-1}$) is at threshold limit almost for all BPU compounds except lufenuron where it exceeds the limit. Majority of the compounds show moderate to high acute toxicity to the fish and aquatic invertebrate. In case of honey bee and earthworm, most of the compounds have shown low to moderate toxicity except hexaflumuron which shows high toxicity towards honey bee.

BPU insecticides were developed and intended to affect biochemical sites that is present only in the target arthropods but not in non-target organisms. Based on these developments they are called "low risk" insecticides, showing less negative effect on the environment making them important element in IPM. Using as a partner with 'knock down' insecticides in tank mix, BPUs can control the pests more successfully. It is better to use BPUs 7-10 days after adulticide application when populations of adult insects are more in the field. Although BPUs insecticides provide greater benefits in crop protection, comparatively much safer than older molecules like organophosphates, carbamates etc., there are now growing concern that these molecules can negatively affect aquatic organisms. According to US EPA, diflubenzuron inhibits growth and reproduction of freshwater invertebrates, affecting their survival and also hampers the reproduction of marine/estuarine invertebrates (Anonymous, 1997). Investigation has been going on to find much safer, more potent benzoyl urea based molecules. But, for the time being, we need careful handling of existing molecules so as to avoid faulty application without leaving harmful residues in the environment.

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