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Ionic liquids with dual pesticidal function

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Ionic liquids with dual pesticidal function were obtained using cheap, well known and commonly employed fungicides and herbicides. High activity was maintained for both the fungicide (cation) and the herbicide (anion). The obtained salts are novel phytopharmaceuticals, which may be successfully used as an alternative to conventional pesticides.

Ionic liquids (ILs) with low (typically less than 100 °C) or no melting points and unique properties represent object of interest and studies of scientific and industrial communities.[1-3] In 2011, a new group of ILs called herbicidal ionic liquids (HILs) was described.[4] HILs are ionic, organic compounds with a melting temperature below 100 °C, with some of the ions manifesting herbicidal activity. These phytopharmaceuticals enrich the third generation of ILs (demonstrating targeted biological properties with selected physical and chemical properties).[5,6] HILs allow for a reduction of the herbicide dose per hectare, while controlling its toxicity (toxic phenoxy herbicides may become nontoxic as HILs[4]) and possessing unique physicochemical properties (thermal stability, low volatility). Reduced volatility of the described ILs contributes to their safer use by the operators and reduction of overall environmental impact of the employed herbicide.[7] Thanks to their multifunctionality, HILs do not overload the environment, as opposed to other commercial products, which represent mixtures of many different compounds. Use of HILs can decrease the non-profitable effects of chemical weed control. ILs with one herbicidal function (an anion containing herbicide)[4,7-9] as well as with dual herbicidal function (an anion containing the herbicide and a cation as a growth regulator)[10,11] were already described.

The use of chemicals in agriculture is a necessity when it comes to crop yields improvement or weed and pathogen control. New EU legislation regarding plant protection products aims to ensure a high standard of protection of both human and animal health and the environment. Since2014, EU Member States apply an integrated pest management, which gives priority to non-chemical methods wherever possible. The idea is to ensure the health of crop plants with the least possible disruption to environment.[12] But in practice, it is very difficult to achieve the proper level of field crop protection without the use of chemicals. However, it is important to reduce the risks associated with pesticide use. Therefore, low-risk plant protection products have a very important place in integrated pest management. For these reasons, various compounds are investigated in order to provide an alternative to conventional pesticides. In recent years, application of ILs has become an interesting and relevant suggestion.

The aim of this study was to synthesize ILs with dual pesticidal function, which contained a herbicide in the anion and a fungicide in the cation, as well as to evaluate their efficiency. The combination of a herbicide with a fungicide in a single salt was applied in order to improve and facilitate the protection of crop plants and to introduce a novel, promising solution to modern agriculture.

Tebuconazole-based salts (**1-4**) and propiconazole-based salts (**5-8**) were synthesized in acid-base reaction in methanol. Changes in pH of the reactive mixture were detected, ranging from 0.12 to 1.47 for salts **1-4** and from 0.12 to 1.23 for salts **5-8**. The most pronounced changes accompanied the synthesis of salts with MCPA and the least pronounced accompanied the synthesis with Dicamba, which reflected the power of the substrate acid (pKa for MCPA amounts to 3.07 and for Dicamba it is restricted to 1.97). The structures of cations and anions of obtained salts with herbicides (MCPA, MCPP, 2,4-D and Dicamba) were shown in Fig. 1.

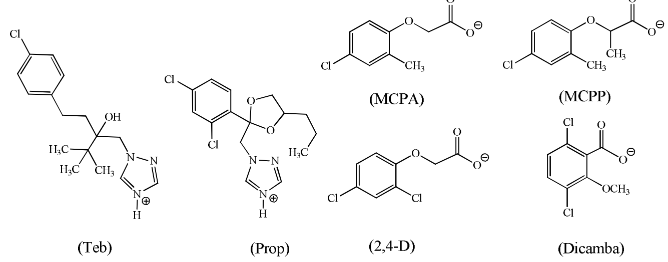

Fig. 1. Structures of cations and anions used for the synthesis of ILs with dual pesticidal function.

All of the salts obtained with very high yield were liquids at room temperature, except for **3**, which was a grease, hence new protic ILs were synthesized (Table 1). All ILs were stable in air as well as in contact with water and popular organic liquids. They were insoluble in hexane and water but they were fully soluble in chloroform, acetone, toluene, DMSO, ethyl acetate and low molecular weight alcohols. Even though the synthesized salts were insoluble in water, it was difficult to obtain an anhydrous salt, hence the compounds required drying at 60 °C in vacuum for 10 hours. Upon such treatment of synthesized ILs, the water content was found to be less than 500 ppm by colorimetric Karl-Fischer titration. The obtained liquids manifested various densities, which at the temperature of 20 °C varied within the range of 1.1943 to 1.3487 g mL^{-1} (Table 1). The density and viscosity values decreased with increase in temperature (as shown in ESI). The synthesized tebuconazole-based ILs at room temperature represented viscous liquids (**1** and **2**), a very dense liquid (**4**) or even grease (**3**). Propiconazole-based ILs manifested definitely lower viscosities, ranging from 25 to 17.5 Pa s and only **8** - [Prop][Dicamba] was a viscous liquid manifesting viscosity value of 92.3 Pa s (Table 1).

Table 1. Prepared tebuconazole (**1-4**) and propiconazole-based salts (**5-8**).

Salt	Cation	Anion	Yield [%]	Density [a] [g mL^{-1}]	Viscosity [a] [Pa s]	Refractive index [a]
1	Teb	MCPA	99	1.2155	93.7	1.5487
2	Teb	MCPP	99	1.1943	95.6	1.5424
3	Teb	2,4-D	99	-	-	-
4	Teb	Dicamba	99	1.2690	658	1.5545
5	Prop	MCPA	99	1.2933	21.1	1.5490
6	Prop	MCPP	99	1.2689	17.4	1.5425
7	Prop	2,4-D	99	1.3487	24.9	1.5555
8	Prop	Dicamba	99	1.3419	92.3	1.5523

[a] at 20 °C.

The data presented in Table 2 show that the synthesised ILs were thermally stable. They manifested glass transition temperatures ranging from 3 to -17 °C. Their characteristic trait involved absence of a melting point. Decomposition temperatures were diverse and changed in the range of 174 – 259 °C for $T_{onset5\%}$ and 270 – 339 °C for $T_{onset50\%}$. In general, propiconazole-based ILs proved to be more thermally stable than tebuconazole-based ILs. Only ILs with the Dicamba anion manifested two steps of decomposition for **4** (272/262°C) and for **8** (276/272 °C). While decomposition of the two ILs exhibited an endothermic character, it was preceded by an exothermic effect for **4** (3.4 kJ mol^{-1}) and for **8** (2 kJ mol^{-1}). Decomposition temperatures for tebuconazole amounted to 302 °C for $T_{onset5\%}$ and 364 °C for $T_{onset50\%}$, while those for propiconazole amounted to 265 °C for $T_{onset5\%}$ and 322 °C for $T_{onset50\%}$, with marked differences from values established for the **1-8** ILs. In addition, tebuconazole manifested no glass transition temperature and for propiconazole the temperature amounted to -24 °C.

Tebuconazole-based ILs **1-4** showed fungistatic activity against *F. culmorum* and *M. nivale*. In all cases, significant differences were detected in the inhibition of mycelial growth between tested ILs and the control.

Table 2. Thermal transitions and decomposition temperatures [a] of synthesized ILs.

IL	T_g [b]	$T_{onset5\%}$ [c]	$T_{onset50\%}$ [d]
1	-8	174	275
2	-2	200	270
3	3	204	290
4	2	218	272/262[e]
5	-16	259	339
6	-15	245	338
7	-17	239	326
8	-7	193	276/272[e]

[a] in °C, [b] glass transition temperature, [c] decomposition temperature with mass loss 5%, [d] decomposition temperature with mass loss 50%, [e] second step of thermal decomposition.

Minimum mycelium growth was recorded only for *M. nivale* in the case of **2** and **4** as well as in Tebu 250 EW (concentration of 10 ppm). In other cases, the inhibition of mycelial growth reached 100%. Propiconazole-based ILs **5-8** strongly inhibited growth of *F. culmorum*, *M. nivale*, *B. cinerea* and *S. sclerotiorum* mycelia. In all cases, the inhibition of mycelial growth was statistically significant as compared to control. A minimum mycelial growth of the examined fungi was found after the application of ILs and fungicide Bumper 250 EC at the concentration of 10 ppm. The fungus least sensitive to ILs proved to be *S. sclerotiorum* (data shown in ESI).

All the obtained ILs **1**-**8** were tested under greenhouse and field conditions. The efficiency of these ILs against the weeds was compared to effects of appropriate commercial herbicides. In order to facilitate the determination of differences in herbicidal activity, the tested ILs were applied at doses, which did not cause a complete destruction of the plants (sub-lethal doses). Greenhouse studies showed that the effectiveness of ILs with dual pesticidal function against weeds depended on the type of anion and weed species.

Efficiency of tebuconazole-based ILs against two weed species was shown in Table 3. The best results against white mustard control were obtained after spraying with **1**, but in case of common lambsquarters the best efficiency was demonstrated by **2**. In most cases, ILs with dual pesticidal function were more effective against weeds compared to the commercial herbicides (Table 3).

Table 3. Efficiency of ILs **1**-**8** on weed species under greenhouse conditions.

Treatments	Fresh weight reduction [a]	
	White mustard	Common lambsquarters
1	45	17
2	19	21
3	19	10
4	23	16
5	41	31
6	13	24
7	34	16
8	26	22
MCPA[b]	25	16
2,4-D[c]	40	0
Dicamba[c]	13	23

[a] in %, [b] sodium/potassium salt, [c] dimethylammonium salt.

Similar results were obtained after application of propiconazole-based ILs, as shown in Table 3. The highest efficiency was manifested by **5**. Two tebuconazole-based ILs **1** and **3** were tested in the field. The investigations were carried out in the winter wheat, also using sub-lethal doses of herbicides. This experiment confirmed the previously observed results in the greenhouse, that the studied ILs with dual pesticidal function were generally more effective in comparison to the corresponding commercial herbicides (Table 4). It should also be noted that the tested ILs caused no damage to the winter wheat plants.

Table 4. Comparison of weed control by tebuconazole-base ILs **1, 3** and commercial herbicides under field conditions [a].

Treatments	Cornflower		Shepherd's purse	
	2 WAT [b]	4 WAT [c]	2 WAT [b]	4 WAT [c]
1	38	0	46	51
3	38	0	50	58
MCPA [d]	23	0	50	10
2,4-D [e]	34	13	0	40

[a] in %, [b] two weeks, [c] four weeks, [d] sodium/potassium salt, [e] dimethyl-ammonium salt, 2 WAT – two Weeks After Treatment, 4 WAT – four Weeks After Treatment.

Low concentrations of herbicides were used during the field studies (170 g of the active substance per 1 ha) in order to determine the difference between the biological activity of the studied compounds more easily. For this reason cornflower managed to overcome the damage caused by the herbicides and its further growth continued unhindered. The effect of 2,4-D on sheperd's purse plants was slower compared to other substances, which is why the effects were observed after more than two weeks upon application.
The results of the biodegradation tests for the studied ILs as well as the precursor compounds were presented in Table 5. The highest overall biodegradability was observed for samples containing tebuconazole and propiconazole (95 and 72%, respectively), whereas the biodegradation efficiency in samples containing herbicides (MCPA, MCPP, 2,4-D and Dicamba) was notably lower (in the range of 15-25%).

Table 5. Biodegradability of the studied ILs and the precursors.

Compound	Biodegradation efficiency [a]	
	Cation	Anion
1	88 ± 4	0 ± 0
2	89 ± 4	0 ± 1
3	94 ± 3	0 ± 0
4	100 ± 5	44 ± 2
5	58 ± 3	3 ± 0
6	68 ± 3	0.5 ± 0
7	65 ± 3	0 ± 1
8	56 ± 2	40 ± 2
Tebuconazole	95 ± 2	-
Propiconazole	72 ± 3	-
MCPA (sodium/potassium salt)	-	16 ± 1
MCPP (sodium/potassium salt)	-	24 ± 2
2,4-D (dimethylammonium salt)	-	20 ± 1
Dicamba (dimethylmmonium salt)	-	21 ± 1

[a] in %.

The biodegradability of tebuconazole as a cation in the studied ILs varied depending on the herbicidal anion used. The biodegradation efficiency was slightly lower for **1** and **2** (88 and 89%, respectively), unchanged for **3** (94%) and higher for **4** (100%) compared to the parental compound. On the other hand, the biodegradability of propiconazole as a cation in the studied ILs was lower in all samples, regardless of the anion used. The lowest value was observed for **8** - [Prop][Dicamba] (56%), while the highest value was obtained for **6** - [Prop][MCPP] (68%). In most cases the biodegradability of the herbicides as anions in the studied ILs was either completely inhibited (0% for **1**-**3** and **7**) or notably diminished (3 and 1% for ILs **5** and **6**, respectively). The exceptional **4** – [Teb][Dicamba] and **8** – [Prop][Dicamba] were the only ILs with enhanced biodegradability of the herbicide and both contained Dicamba as the anion. The susceptibility of the anion to biodegradation processes was increased by a factor of 2 (44 and 40% for **4** and **8**, respectively).
To summarize, the obtained ionic liquids with dual pesticidal functions exhibited excellent properties. Evaluation of fungicidal and herbicidal activities revealed that several of the synthesized salts can be a better tool in plant protection compared to commercially available agents. Additionally, certain modifications of the chemical structure may result in improved biodegradability of ILs, making them more environmentally friendly alternatives to commonly used pesticides. This study demonstrated that the synthesized ILs are novel and promising phytopharmaceuticals, which may be valuable for the development of next-generation crop protection agents.

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Notes and references

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