Structure–Activity Relationships in a Series of Fungicidal Pyrazole Carboxanilides

John L. HUPPATZ, John N. PHILLIPS and Barbara WITRZENS

CSIRO, Division of Plant Industry, Canberra, A.C.T. 2601, Australia

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All possible 1-methylpyrazole carboxanilides and their mono- and dimethyl derivatives have been synthesised and assessed for their effectiveness in inhibiting the mycelial growth of *Rhizoctonia solani* and for the control of root rot disease caused by that organism in cotton seedlings. The structural requirements for activity are discussed and compared with previous assessments of general structure–activity relationships in carboxamide fungicides.

Since the discovery[1] of the systemic antifungal properties of carboxin (**I**) (5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide), similar activity has been demonstrated in numerous other carboxamides, including appropriately substituted benzene,[2] thiazole,[3] furan,[4,5] dihydropyran,[6] thiophene,[7] pyridine[8] and pyrazole derivatives.[9] A number of major studies of structure–activity relationships in compounds of this type have appeared in the literature[3,7,10] and attempts have been made to define the structural features necessary for activity.[3,10]

Pyrazole carboxamides (*e.g.*, **II**) have been shown to be potent fungicidal agents for the control of rusts and smuts[9] and to be particularly effective for the control of *Rhizoctonia solani* (Kühn) in cotton.[11] Although compounds related to (**II**) possess one of the essential elements[10] required for good activity, *viz.*, a methyl group ortho to a carboxanilide function, the effect on activity of locating these groups in other positions on the pyrazole nucleus was not known. Accordingly, a number of mono-, di- and trimethyl derivatives of pyrazole carboxanilide were synthesised and assessed for their fungicidal activity, both *in vitro* and *in vivo* against the soil pathogen, *R. solani*.

EXPERIMENTAL

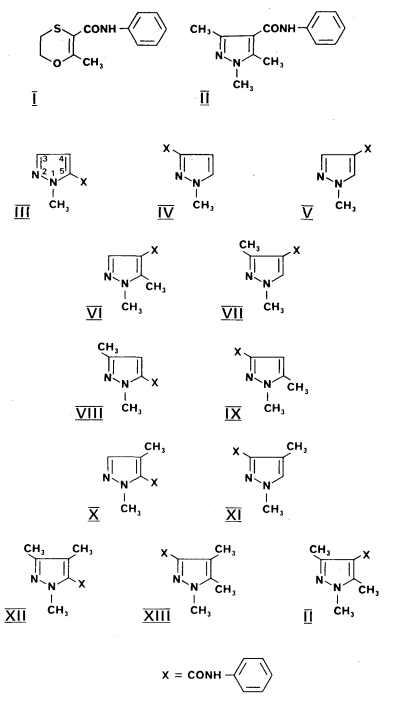
Synthesis of compounds. Melting points of all synthesised compounds are uncorrected. NMR spectra were recorded on a Varian A60 or a JEOL FX 90Q spectrometer using TMS as the internal standard and $CDCl_3$ as the solvent. Analyses were performed by the Australian Microanalytical Service, Melbourne.

N-Phenyl-1,3,5-trimethylpyrazole-4-carboxamide (**II**) has been described previously[9] and the synthesis of *N*-phenyl-1,5-dimethylpyrazole-4-carboxamide (**VI**) and the isomeric 1,3-dimethyl compound (**VII**) will be reported elsewhere.[12]

N-Phenyl-1-methylpyrazole-5-carboxamide (**III**) and the corresponding 3-carboxamide (**IV**) were prepared by conversion of the corresponding acids[13] to the acid chlorides, followed by treatment with aniline in the presence of pyridine. Ethyl 1-methylpyrazole-4-carboxylate[12] was similarly converted to the corresponding 4-carboxamide (**V**).

N-Phenyl-1,3-dimethylpyrazole-5-carboxamide (**VIII**) and the isomeric *N*-phenyl-1,5-dimethyl-3-carboxamide (**IX**) were also prepared *via* the corresponding acids.[12]

The synthesis of *N*-phenyl-1,4-dimethylpyrazole-5-carboxamide (**X**) and the corresponding 3-isomer (**XI**) commenced with ethyl 4-methylpyrazole-3(5)-carboxylate, prepared by treating ethyl crotonate with diazomethane followed by bromine oxidation of the pyrazoline.[14] This compound was methylated, the isomeric esters carefully purified and converted to the corresponding anilides *via* the acids and acid chlorides. Identification of the isomeric esters (and anilides) followed from their NMR spectra. The deshielding effect of the 5-COOEt group results in a downfield shift of the N–CH_3 signal in the spectrum of this isomer when compared with that of the pyrazole-3-carboxylate. This effect has been well docu-



mented in the published spectral data of pyrazole esters.[15]

Preparation of *N*-phenyl-1,3,4-trimethylpyrazole-5-carboxamide (**XII**) and the corresponding 3-carboxamide (**XIII**) utilised ethyl 3(5),4-dimethylpyrazole-5(3)-carboxylate as the starting material. This compound was obtained in low yield from ethyl hydrazinoacetate and diacetyl, *via* the corresponding hydrazone, using the method of Alemagna *et al.*[16] *N*-Alkylation produced the 1,3,4- and 1,4,5-trimethylpyrazoles in the ratio of approximately 2:3. The isomeric esters were efficiently separated by column chromatography and converted to the anilides (**XII**) and (**XIII**) after hydrolysis to the corresponding acids. Again, structural assignment followed from the NMR spectra of the compounds. The N–CH_3 signal in the spectrum of (**XII**) appeared downfield with respect to the corresponding signal in the spectrum of (**XIII**), indicating an acyl group at position 5 in the former compound.

Full experimental details are recorded below.

Preparation of compounds (**III**), (**IV**), (**V**), (**VIII**) *and* (**IX**). 1-Methylpyrazole-5-carboxylic acid[13] (1.5 g) was treated with thionyl chloride (5 ml) and the mixture heated under reflux for 2 hr. The excess thionyl chloride was removed *in vacuo* and a mixture of aniline (1.5 g) in pyridine (10 ml) was slowly added. The mixture was warmed on a steam-bath for 30 min, poured into water (100 ml) and the product extracted with chloroform (3 × 25 ml). The combined extracts were washed well with water, dried and evaporated. The residual oil was distilled *in vacuo* and *N-phenyl-1-methylpyrazole-5-carboxamide* (**III**) was obtained as a pale yellow oil (1.8 g, 90%), bp 169 ~ 170°C/0.5 mm, which solidified on standing, mp 85 ~ 87°C. NMR δ (J = Hz): 4.17 (3H, s), 6.64 (1H, d, J = 2.0), 7.04 ~ 7.72 (5H, arom.; 1H, C3), 8.45 (1H, br.s exchangeable). *Anal.* Found: C, 65.6; H, 5.5; N, 21.2. Calcd. for $C_{11}H_{11}N_3O$: C, 65.7; H, 5,5; N, 20.9%.

From the appropriate acids[12,13] the following anilides were similarly prepared. *N-Phenyl-1-methylpyrazole-3-carboxamide* (**IV**), colourless crystals from aqueous ethanol, mp 87 ~ 89°C. NMR δ (J = Hz): 3.92 (3H, s), 6.87 (1H, d, J = 2.2), 6.93 ~ 7.79 (5H, arom.; 1H, C5), 8.70 (1H, br.s, exchangeable). *Anal.* Found: C, 65.6; H, 5.5; N, 21.1. Calcd. for $C_{11}H_{11}N_3O$: C, 65.7; H, 5.5; N, 20.9%. *N-Phenyl-1-methylpyrazole-4-carboxamide* (**V**), colourless prisms from ethanol, mp 178 ~ 180°C. NMR δ 3.82 (3H, s), 7.06 ~ 7.79 (5H, arom.), 7.89 (2H, s, C-3 and C-5), 8.10 (1H, br.s, exchangeable). *Anal.* Found: C, 65.4; H, 5.4; N, 21.1. Calcd. for $C_{11}H_{11}N_3O$: C, 65.7; H, 5.5; N, 20.9%. *N*-Phenyl-1,3-dimethylpyrazole-5-carboxamide (**VIII**), colourless needles from ethyl acetate–petroleum ether (bp 40 ~ 60°C), mp 98 ~ 99°C. NMR δ: 2.22 (3H, s), 4.13 (3H, s), 6.44 (1H, s), 7.00 ~ 7.73 (5H, m, arom.), 8.27 (1H, br.s, exchangeable). *Anal.* Found: C, 67.0; H, 6.2; N, 19.4. Calcd. for $C_{12}H_{13}N_3O$: C, 66.9; H, 6.1; N, 19.5%. *N-Phenyl-1,5-dimethylpyrazole-3-carboxamide* (**IX**), colourless needles from aqueous ethanol, mp 142 ~ 144°C. NMR δ: 2.21 (3H, s), 3.80 (3H, s), 6.57 (1H, s), 6.87 ~ 7.83 (5H, m, arom., 1H exchangeable). *Anal.* Found: C, 66.8; H, 6.3; N, 19.6. Calcd. for $C_{12}H_{13}N_3O$: C, 66.9; H, 6.1; N, 19.5%.

Preparation of compounds (**X**) *and* (**XI**).

(i) Sodium (3.1 g) was dissolved in ethanol (150 ml) and ethyl 4-methylpyrazole-3(5)-carboxylate[14] (19 g) added. Methyl iodide (18.9 g) was then added dropwise and the mixture stirred overnight at room temperature. Most of the ethanol was removed *in vacuo*, water (250 ml) was added and the product extracted with chloroform (3 × 50 ml). The combined extracts were washed with water, dried and evaporated to yield a light brown oil (18.3 g), which was fractionally distilled *in vacuo*. *Ethyl 1,4-dimethylpyrazole-5-carboxylate* (6.2 g, 30%) was obtained as a colourless oil, bp 58 ~ 59°C/0.3 mm. NMR δ: 1.39 (3H, t), 2.25 (3H, s), 4.08 (3H, s), 4.34 (2H, q), 7.22 (1H, s). *Anal.* Found: C, 57.0; H, 7.1; N, 16.6. Calcd. for $C_8H_{12}N_2O_2$: C, 57.1; H, 7.2; N, 16.7%. *Ethyl 1,4-dimethylpyrazole-3-carboxylate* (9.3 g, 45%) was obtained as a colourless oil, bp 87 ~ 88°C/0.3 mm, which subsequently solidified, mp 50 ~ 52.5°C. NMR δ: 1.40 (3H, t), 2.28 (3H, s), 3.89 (3H, s), 4.36 (2H, q), 7.13 (1H, s). *Anal.* Found: C, 57.1; H, 7.0; N, 16.8. Calcd. for $C_8H_{12}N_2O_2$: C, 57.1; H, 7.2; N, 16.7%.

(ii) Ethyl 1,4-dimethylpyrazole-5-carboxylate was hydrolysed by boiling under reflux in an aqueous ethanolic sodium hydroxide solution (1 N) for 2 hr. *1,4-Dimethylpyrazole-5-carboxylic acid* was obtained in a 92% yield as colourless crystals from water, mp 169 ~ 170°C.

Anal. Found: C, 51.5; H, 5.5; N, 19.7. Calcd. for $C_6H_8N_2O_2$: C, 51.4; H, 5.7; N, 20.0%. The foregoing acid was converted to the corresponding anilide as described above. After crystallisation from aqueous ethanol, *N-phenyl-1,4-dimethylpyrazole-5-carboxamide* (**X**) was obtained in an 89% yield as colourless plates, mp 123~124°C. NMR ($CDCl_3$) δ: 2.32 (3H, s), 4.11 (3H, s), 7.03~7.68 (5H, m, arom.; 1H, C-3; 1H, NH). *Anal.* Found: C, 66.7; H, 6.1; N, 19.7. Calcd. for $C_{12}H_{13}N_3O$: C, 66.9; H, 6.1; N, 19.5%.

Similarly, *1,4-dimethylpyrazole-3-carboxylic acid* was obtained in a 90% yield as colourless needles from water, mp 171~173°C. *Anal.* Found: C, 51.2; H, 5.5; N, 19.8. Calcd. for $C_6H_8N_2O_2$: C, 51.4; H, 5.7; N, 20.0%. From the foregoing acid *N-phenyl-1,4-dimethylpyrazole-3-carboxamide* (**XI**) was obtained in an 85% yield as colourless needles from aqueous ethanol, mp 92~93°C. NMR δ: 2.31 (3H, s), 3.89 (3H, s), 6.82~7.77 (5H, m, arom.; 1H, 5-C), 8.62 (1H, br.s, exchangeable). *Anal.* Found: C, 66.7; H, 6.1; N, 19.4. $C_{12}H_{13}N_3O$ requires C, 66.9; H, 6.1; N, 19.5%.

Preparation of compounds (**XII**) *and* (**XIII**).

(i) Ethyl 3(5),4-dimethylpyrazole-5(3)-carboxylate[16] (5 g) was methylated with methyl iodide in the presence of sodium ethoxide as described above. The crude product was chromatographed on a silica gel column (50 × 3 cm) using chloroform as the eluent. The first fractions gave *ethyl 1,3,4-trimethylpyrazole-5-carboxylate* (1.7 g, 31%) as a pale yellow oil. This compound was further purified by distillation *in vacuo*; bp 75~76°C/0.6 mm. NMR δ: 1.40 (3H, t), 2.21 (6H, s), 4.07 (3H, s), 4.39 (2H, q). *Anal.* Found: C, 59.1; H, 7.8; N, 15.6. Calcd. for $C_9H_{14}N_2O_2$: C, 59.3; H, 7.7; N, 15.4%. Succeeding fractions contained a pale yellow oil (0.4 g) which proved to be a mixture of the isomeric pyrazole esters. Subsequent fractions afforded *ethyl 1,4,5-trimethylpyrazole-3-carboxylate* as a pale yellow oil (3.0 g, 55%), which had bp 106~108°C/0.4 mm on distillation *in vacuo*. NMR δ: 1.40 (3H, t), 2.22 (6H, s), 3.85 (3H, s), 4.43 (2H, q). *Anal.* Found: C, 59.4; H, 7.7; N, 15.6. Calcd. for $C_9H_{14}N_2O_2$: C, 59.3; H, 7.7; N, 15.4%.

(ii) Ethyl 1,3,4-trimethylpyrazole-5-carboxylate was hydrolysed by boiling under reflux in aqueous ethanolic sodium hydroxide solution (1 N). The corresponding *acid* was obtained quantitatively and separated from water as a colourless solid, mp 182~183°C. *Anal.* Found: C, 54.8; H, 6.6; N, 18.1. Calcd for $C_7H_{10}N_2O_2$: C, 54.5; H, 6.5; N, 18.2%. *N-Phenyl-1,3,4-dimethylpyrazole-5-carboxamide* (**XII**) was obtained from the above acid in an 87% yield and had mp 183~184°C, after recrystallisation from ethanol. NMR δ: 2.21 (6H, s), 4.03 (3H, s), 7.17~7.83 (5H, m, arom.; 1H, NH). *Anal.* Found: C, 67.8; H, 6.6; N, 18.5. Calcd. for $C_{13}H_{15}N_3O$: C, 68.1; H, 6.6; N, 18.3%.

Similarly, ethyl 1,4,5-trimethylpyrazole-3-carboxylate was converted to the acid in a quantitative yield. The *acid* crystallised from water as colourless crystals, mp 209~211°C. *Anal.* Found: C, 54.5; H, 6.2; N, 18.0. Calcd. for $C_7H_{10}N_2O_2$: C, 54.5; H, 6.5; N, 18.2%. Treatment of the above acid in the usual way gave *N-phenyl-1,4,5-trimethylpyrazole-3-carboxamide* (**XIII**) as colourless prisms (88% yield), after crystallisation from ethanol, mp 127~128.5°C. NMR δ: 2.18 (3H, s), 2.30 (3H, s), 3.78 (3H, s), 7.10~7.93 (5H, m, arom.), 8.83 (H, br. s, exchangeable). *Anal.* Found: C, 67.8; H, 6.6; N, 18.6. Calcd. for $C_{13}H_{15}N_3O$: C, 68.1; H, 6.6; N, 18.3%.

Measurement of antifungal activity. The procedures described below are similar to those reported previously.[11]

a) *Inhibition of mycelial growth of R. solani.* Compounds were incorporated in the growth medium by the addition of 0.2 ml of an acetone solution of appropriate concentration to 20 ml of liquid sterilized potato dextrose agar (PDA) contained in an 8.5 cm Petri dish. The medium was cooled and inoculated with agar discs (0.7 sq cm) taken from the periphery of plate cultures of *R. solani*, isolated from infected cotton seedlings and incubated at 25°C. Treatments as well as untreated controls were replicated fivefold. The growth of the organisms was measured in terms of the mean diameter of the colony after 7 days, by which time the untreated controls had just covered the plate. The ratio of treated to untreated colony diameter was plotted against the molar concentration of the test

TABLE I. THE EFFECT OF PYRAZOLE CARBOXAMIDES ON THE MYCELIAL GROWTH OF *R. solani* AND ON ROOT ROT IN COTTON SEEDLINGS

Compound	ED_{50} (μM)[a]	Soil incorporation[b] % healthy plants
III	200	33e
IV	1600	19e
V	2500	15e
VI	2500	23e
VII	20	97ab
VIII	80	64d
IX	2500	19e
X	40	84bc
XI	320	28e
XII	40	75cd
XIII	2500	15e
II	8	100a
Carboxin (**I**)	0.4	100a
Uninoculated control		98
Inoculated control		0

[a] Molar concentration of the compound giving 50% inhibition of the mycelial growth of *R. solani* on PDA over 7 days.

[b] Compounds applied at 16 kg·ha^{-1} in the soil prior to sowing the cotton. Seedlings (10~12 day old) were inoculated with *R. solani* and assessed after 14 days. Values followed by the same letter are not significantly different ($p = 0.05$).

compound and the ED_{50} value determined. The results are recorded in Table I.

b) *Control of root rot caused by R. solani in cotton seedlings.* Each compound was dissolved in acetone and mixed with 40 ml of sand. The acetone was allowed to evaporate and the sand placed as a layer over soil in 10 cm pots to give an equivalent surface application rate of the compound of 16 kg ha^{-1}. Cotton seeds were sown in the sand layer and covered with 2 cm of soil. Each treatment, as well as untreated inoculated and untreated uninoculated controls, were replicated in 25 pots (4 plants per pot).

The inoculum was prepared by autoclaving 60 g of wheat seed with 120 ml of distilled water for 30 ~ 40 min. Three 1 cc pieces of agar covered with mycelium were added and the wheat seed incubated for 7 days at 25°C. A 3 g portion of this incubated mixture was blended with 1200 ml of distilled water and 50 ml of the resultant suspension was poured over the soil surface of a pot containing four 10 ~ 12 day old cotton seedlings. The mycelial inoculum was then covered with a thin layer of soil. Such inoculation led to infection at the base of the stem and seedlings began to wilt and collapse within 5 days. The level of disease control was assessed 14 days after inoculation in terms of the number of upright plants. This assay procedure also served as an indicator of the phytotoxicity of the compound. The results, recorded as the percentage of healthy plants in each treatment, are listed in Table I.

RESULTS AND DISCUSSION

Earlier investigations[9] of the antifungal activity of pyrazole analogues of carboxin revealed that maximum activity was associated with 1-methyl derivatives. Accordingly, all possible 1-methylpyrazole carboxanilides and their mono- and dimethyl derivatives form the basis of the present study. Table I records the effectiveness of these compounds in inhibiting the mycelial growth of *R. solani* and in controlling root rot caused by that organism in cotton seedlings.

The pyrazoles studied ranged from being very weak (ED_{50} approx. 2500 μM) to quite potent (ED_{50} 8 μM) inhibitors of the mycelial growth of *R. solani in vitro*. They also varied greatly in their ability to protect cotton seedlings from disease after inoculation with *R. solani*. However, there was a good correlation between their relative fungitoxicities *in vitro* and their chemotherapeutic activity *in vivo* when applied as a soil-incorporated treatment. Table I also records the values for carboxin under the same assay conditions. As previously noted,[11] carboxin was more effective *in vitro* than the best of the pyrazole derivatives (**II**), but of a similar order of activity in the control of *R. solani* in cotton seedlings.

Earlier studies of the relationship between molecular structure and fungicidal activity of carboxin and related compounds enabled certain structural features necessary for activity to be defined.[3,10] It was concluded that the optimum fungicidal activity in these compounds was associated with anilides derived from α,β-unsaturated acids with a methyl group on the β-carbon atom, *i.e.*, adjacent to the anilide function. Furthermore, it appeared desirable for the double bond to form part of a planar, aromatic system as in benzene, furan, thiazole, *etc.*, or be conjugated to an electron-releasing atom such as oxygen or sulphur as in dihydrooxathiin or dihydropyran derivatives.[10]

In agreement with these earlier studies, compounds **IV**, **V** and **IX**, which lacked a methyl group adjacent to the anilide function, were very weakly fungitoxic. Compounds **III**, **VII** and **VIII**, on the other hand, showed moderate to high fungitoxicity (ED_{50} 20 ~ 200 μM) even though they cannot be regarded formally as β-substituted, α,β-unsaturated acid anilides. Nevertheless, the anilide function in these compounds is flanked by a methyl group in position 3 in compound **VII** and position 1 in compounds **III** and **VIII**. The C_3–C_4 and N_1–C_5 bonds represent the longer of the carbon to carbon and carbon to nitrogen links in pyrazole itself (C_3–C_4 1.41; C_4–C_5 1.335; C_5–N_1 1.35; N_2–C_3 1.31 Å)[17] and are formally represented as single bonds. In contrast, all the active furan and thiophene carboxamide fungicides hitherto reported have the methyl and anilide groups occupying positions 2 and 3, *i.e.*, across the shorter of the carbon–carbon bonds in these nuclei (in furan, C_2–C_3 1.361; C_3–C_4 1.431; in thiophene C_2–C_3 1.370; C_3–C_4 1.423 Å).[17] Surprisingly, however, compound **VI**, the only pyrazole to possess an unambiguous configuration of methyl and anilide groups about the shorter C_4–C_5 bond, was virtually inactive *in vitro* and ineffective *in vivo*.

It would seem from a consideration of all the available data that the activity of carboxamide fungicides, at least those incorporating heterocyclic nuclei, is not particularly sensitive to the nature or length of the bond separating the methyl and anilide groups, and that other factors may play a more important role. In particular, the lack of activity of compound **VI** may be due to steric factors, since the methyl group adjacent to the anilide function in this compound is itself flanked by a second methyl group at position 1, which may interfere with the ability of the molecule to interact with the receptor site. A similar explanation may also account for the lack of activity of compound **XIII** (ED_{50} 2500 μM) compared with that of compound **XI** (ED_{50} 320 μM).

In compounds **II**, **X** and **XII**, methyl groups flank the anilide function on both sides and hence two possible methyl-anilide configurations could be responsible for their fungitoxicity. The 3-methyl-4-anilide configuration would appear to be the more significant in compound **II** (ED_{50} 8 μM) since it is comparably active to compound **VII** (ED_{50} 20 μM) but quite different from compound **VI** (ED_{50} 2500 μM), which has the alternative 5-methyl-4-anilide arrangement. However, the configurations responsible for the activities of compounds **X** and **XII** (ED_{50} 40 μM) are less obvious, although the fact that they possess activity comparable to that of compound **VIII** (ED_{50} 80 μM) suggests the involvement of the 1-methyl-5-anilide arrangement, which is common to all three derivatives. Moreover, the alternative 4-methyl-5-anilide configuration is unlikely to be important, especially in respect of compound **XII** where the 4-methyl group is flanked by a second methyl substituent, a situation which appears to be unfavourable for activity (see above).

The simplest pyrazole derivative having a 1-methyl-5-anilide arrangement, compound **III**, is only moderately fungitoxic, but the introduction of additional methyl groups into the 3 and/or 4 position enhances activity (ED_{50} values for **III**, **VIII**, **X** and **XII**, respectively: 200, 80, 40 and 40 μM). That a slight change in electron distribution in the pyrazole ring occurs with the addition of a methyl group is apparent from the change in the *N*-methyl resonance peak in the NMR spectra of the compounds (δ 4.17, 4.13, 4.11 and 4.03 for compounds **III**, **VIII**, **X** and **XII** respectively). The shift to a lower magnetic field in the position of the *N*-methyl resonance has been attributed to a higher positive charge density at N-1.[13] In these compounds, this would result in an increased negative character of the amide carbonyl. Since upfield shifts correlate well with enhanced fungitoxicity, it would seem that the more electron-rich the carbonyl function becomes, the greater is the fungicidal activity of the pyrazole derivative. A similar explanation may also account for the higher activity of compound **II** (ED_{50} 8 μM; $\delta_{N\text{-}CH_3}$ 3.73) when compared with compound **VII** (ED_{50} 20 μM; $\delta_{N\text{-}CH_3}$ 3.78) and of compound **VII** when compared with its isomer **XI** (ED_{50} 320 μM; $\delta_{N\text{-}CH_3}$ 3.89).

The importance of an electron rich carbonyl function in determining fungitoxicity may be further illustrated by the enhanced activity against the growth of *Ustilago maydis* and *Rhizoctonia solani* reported[7] for *N*-phenyl-5-amino-3-methylthiophene-2-carboxamide (ED_{50} 0.10 μM—*U. maydis* and 2.8 μM—*R. solani*) when compared with its 4-amino isomer ($ED_{50} > 100$ μM for both organisms). The electron-donating amino function is formally conjugated to the carbonyl moiety only in the case of the 5-amino derivative.

Most of the pyrazole derivatives show no phytotoxicity towards cotton at the rate used in the *in vivo* assay. However, compounds **III** and **X**, both of which are moderately active, and compounds **V** and **VI**, which are virtually inactive against *R. solani*, cause damage to the foliage of the cotton plants when applied in the soil at the time of sowing. It is possible that this phytotoxic effect may be related to an unsubstituted position (C3) adjacent to the methine nitrogen, since this structural feature is common to all four phytotoxic compounds but is not present in the remaining pyrazole derivatives tested.

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