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Synthesis and herbicidal activity of phenyl-substituted benzoylpyrazoles

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Abstract: A novel series of substituted 3-phenyl benzoylpyrazoles were prepared and tested as potential grass herbicides. The targeted materials were prepared by three newly developed synthetic routes, which allowed a comprehensive study of the SAR (structure–activity relationships) of this series. The best combination of grass weed activity (*Avena fatua* L, *Setaria viridis* (L) Beauv and *Alopecurus myosuroides* Huds) and wheat selectivity was obtained with an alkoxy group in the 4-position of the phenyl ring. Activity was further enhanced by the presence of *tert*-butyl on the pyrazole and a methyl group at the C-2 position of the benzoyl moiety. The alkoxy-substituted 3-phenylbenzoylpyrazoles are a novel class of herbicides with potential utility for control of important grass weeds in cereals.

Keywords: herbicide; benzoylpyrazoles; hydroxyphenylpyruvate dioxygenase inhibitors

1 INTRODUCTION

The benzoylpyrazole area of chemistry represents a relatively new class of highly active, bleaching herbicides (Fig 1; **1**). The area, which was originally discovered by Sankyo, is exemplified by two commercial rice herbicides, pyrazolate[1] and pyrazoxyfen.[2] Each of these materials is a pro-drug for a common active ingredient, DTP,[1,3] a hydroxybenzoylpyrazole in which a 2,4-dichloro-substituted benzoyl is attached to a dimethyl-substituted hydroxypyrazole. The activity of these simple members of the series is rather modest and, as a result, their utility has been somewhat limited. The benzoylpyrazole area was greatly expanded when chemists at Nissan discovered that activity in the series is significantly enhanced with the presence of more complex electron-withdrawing substituents on the benzene ring (Fig 1).[4,5] They, and we,[6] have shown that certain members of this family of chemistry deliver an attractive combination of desirable attributes, including necrosis and plant death, activity against both grass and broadleaf weeds, phloem mobility, pre- and post-emergent application flexibility, selectivity in important crops and a relatively unexploited mode-of-action.

Benzoylpyrazoles are a subset of a larger class of 'diketone' herbicides[7] (Fig 1) which includes the benzoylcyclohexanediones, originally discovered by Stauffer and recently commercialized by Syngenta (originally Zeneca) in the form of sulcotrione[8] and mesotrione,[9] and the benzoylisoxazoles, typified by the Aventis herbicide, isoxaflutole.[10,11] In the latter case, a diketonitrile, formed by base-catalyzed opening of the isoxazole ring of isoxaflutole, has been shown to be the actual herbicidal species,[11,12] the isoxazole thus functioning as a pro-form for yet another class of diketones.[7] Bioactivity of these diketone herbicides results from an inhibition of 4-hydroxyphenylpyruvate dioxygenase (HPPD), the enzyme which catalyzes the formation of homogentisic acid.[7,12–15] In plants homogentisic acid is the precursor to important plant quinones such as the plastoquinones[16] which, in turn, function as cofactors in the biosynthesis of carotenoids.[14] The latter are essential for protection of the plant from light-induced radical degradation processes. Thus, it is believed that the inability of the treated plants to generate such quinones is responsible for the intense bleaching symptoms typically observed from these compounds. Ultimately plant death occurs through some type of radical-mediated event.[14]

Through structural comparisons and other observations, we, and others,[7] have concluded that the pharmacophore for the diketone series of HPPD inhibitors includes an electron-deficient enolizable β-dicarbonyl system, a lipophilic, electron-deficient benzene attached to one of these carbonyls, and an *ortho* substituent on the benzene ring. Structure–activity studies within the benzoylpyrazole series have shown that highest levels of overall herbicidal activity are attained when: (a) the nitrogen of the pyrazole (**1**, R; Fig 1) is substituted with a relatively small alkyl group; (b) the *ortho* substituent (X) on the benzene is a halogen or small alkyl; (c) there is a methyl sulfone

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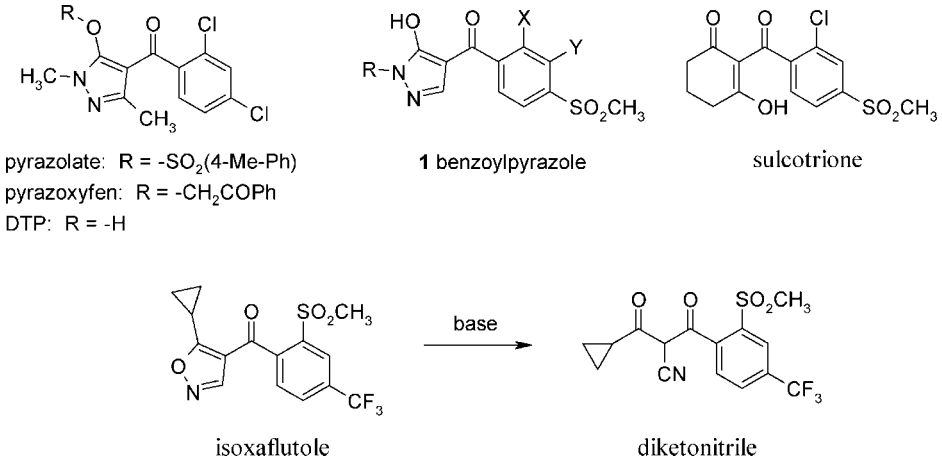


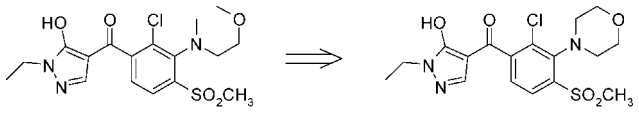
Figure 1. Representative examples of the diketone class of HPPD inhibitors.

attached at the C-4 position of the benzene. The most active compounds also contain a substituent at the *meta* position (Y) on the benzene, ie the benzene is 1,2,3,4-tetrasubstituted. However, it is difficult to draw any definitive conclusions concerning the optimal nature of the C-3 substituent on the benzoyl, as benzoylpyrazoles containing a wide variety of groups at C-3 (including alkyl, alkoxy, amine, carboxylate and sulfone) have exhibited very high levels of herbicidal activity.

During optimization of the 3-amino series of benzoylpyrazoles[6,17] we discovered that the addition of certain cyclic amines at the 3-position of the benzene, most notably morpholine, provided much better cool-season grass activity than their close acyclic amino analogs. For example, formation of a bond between the two methyl groups of the (methoxyethyl)-methylamino substituent on benzoylpyrazole **2**, to give morpholine **3a**, resulted in a significant (>10-fold) increase in activity against *Avena fatua* L (AVEFA, Table 1). However, despite extensive synthetic work in the cyclic amine series, none of the grass active analogs synthesized had the necessary levels of safety to relevant grass crops, such as wheat (*Triticum aestivum* L, TRZAS).

A priori, analogous cyclic or acyclic amino-substituted benzoylpyrazoles might not be expected to have significantly different physical (eg log*P*) or chemical (basicity, reactivity) properties. Thus, we suspected that the enhanced grass activity of the 3-morpholino benzoylpyrazoles, as compared to their acyclic analogs, was somehow related to the cyclic nature of the morpholine group. If this hypothesis were valid, then substitution of the morpholine with another cyclic moiety might yield compounds with similar high levels of cool-season grass activity. Conceptually, one of the simplest and most direct approaches to test this hypothesis was to replace the morpholine with an aromatic system, such as a phenyl (eg **4**). In the event, we discovered that certain 3-phenyl-subsituted benzoylpyrazoles provided outstanding control of important cool-season grass weeds with excellent selectivity to wheat. In this report, we describe the preparation of an extensive series of such phenyl-substituted benzoylpyrazoles (Fig 2) and their herbicidal properties.

Table 1. Comparison of the post-emergent cool-season grass activity of a C-3-morpholine substituted benzoylpyrazole *versus* its acyclic analog



2 **3a**

	AVEFA[a]	*ALOMY*[a]
Compound No	GR_{80} *(mg liter*$^{-1}$*)*[b]	
2	>31	>31
3a	2.6	8.0

[a] AVEFA = *Avena fatua*; ALOMY = *Alopecurus myosuroides*.
[b] Concentration which produced 80% visual injury.

2 EXPERIMENTAL

2.1 Synthesis

Three routes were devised for preparation of the 3-phenyl-substituted benzoylpyrazoles. A representative example of each is described in detail in Section 5. The method of preparation and melting point for each targeted product is included in the tables.

2.1.1 Phenyl-substituted benzoylpyrazoles—Method A

A general, one-step route (Fig 3) was used for preparation of most of the 3-phenyl-susbtituted benzoylpyrazole targets. This route proved to be ideal for analog synthesis as the phenyl group, along with its substituent, was introduced onto a common, advanced benzoylpyrazole intermediate (**11**) through Suzuki condensation[18] with an appropriately substituted phenylboronic acid. Optimal reaction conditions included a typical palladium–phosphine catalyst system with potassium carbonate as base in refluxing aqueous acetonitrile. In general, the reaction worked well with boronic acids that were substituted with electron-donating substituents; boronic acids containing only electron-withdrawing substituents tended to give lower yields. Many of the boronic acids used in

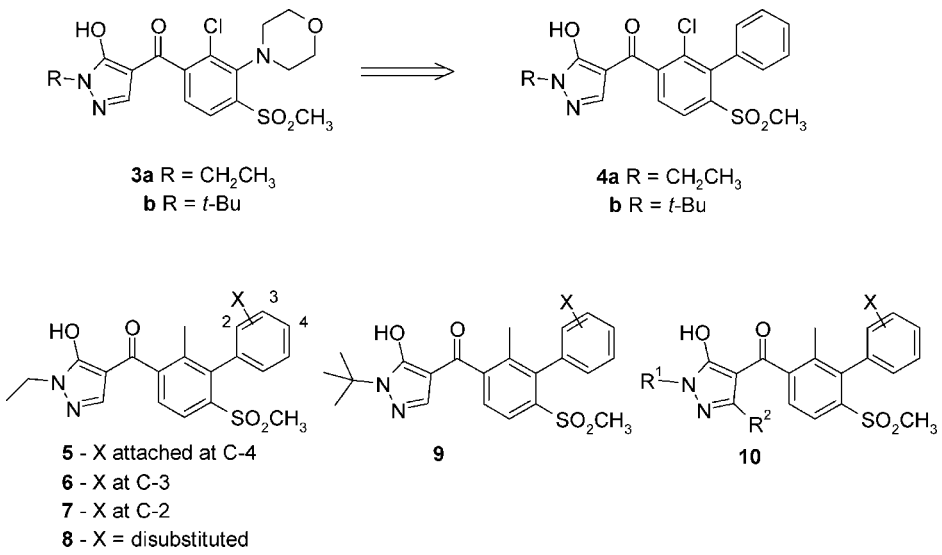


Figure 2. Compounds discussed in the text.

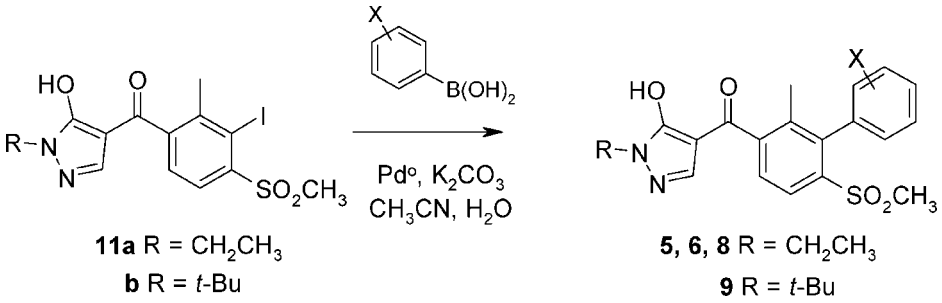


Figure 3. Method A for preparation of 3-phenylbenzoylpyrazoles.

this series were commercially available. The remaining phenylboronic acids were prepared in standard fashion by metallation of the corresponding bromobenzene followed by boronation with tri-isopropyl borate.[19]

2.1.2 Phenyl-substituted benzoylpyrazoles—Method B

The 3-iodo-substituted benzoic acid **12** was used in a second, related method for formation of phenyl-substituted benzoylpyrazoles. In this instance (Fig 4) the phenyl group was added by Suzuki condensation between the appropriate phenylboronic acid and the iodobenzoic acid **12**, and the benzoylpyrazole then formed in a subsequent series of transformations. This route was particularly useful for preparation of benzoylpyrazoles with non-standard (eg methyl or isopropyl) pyrazole substituents.

2.1.3 Synthesis of phenyl-substituted benzoylpyrazoles—Method C

Ortho-substituted phenylboronic acids failed to react, presumably for steric reasons, under typical Suzuki conditions with either iodobenzoylpyrazole **4** or iodobenzoic acid **5**. Attempts to overcome this limitation, using conditions reported for sterically encumbered Suzuki reaction partners,[20–22] likewise met with limited success. Thus, a separate route for preparation of the *ortho*-substituted 3-phenylbenzoylpyrazoles was devised in which the biphenyl moiety was formed at an early stage in the synthetic sequence (Fig 5)

*2.1.4 Intermediate 3-iodobenzoylpyrazoles **11** (for Method A) and 3-iodobenzoic acids **12** (for Method B)*

The requisite intermediate 3-iodobenzoylpyrazoles **11** and 3-iodobenzoic acid **12a** were prepared as illustrated in Fig 6.

2.2 Biological testing

Seeds were planted in 10-cm square pots filled with a high organic soil media, Metro mix 360. Plants were propagated under greenhouse conditions of 18 °C day and night temperature. Natural light was supplemented with greenhouse metal halide lamps to a

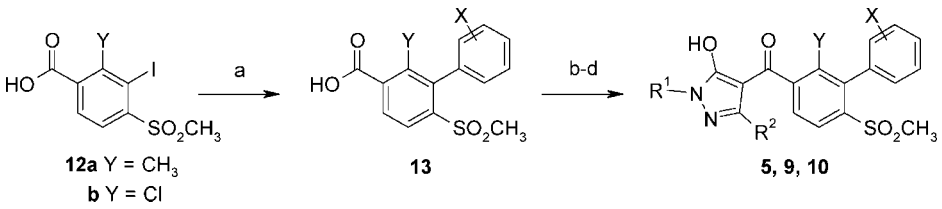


Figure 4. Method B for preparation of 3-phenylbenzoylpyrazoles. (a) X-PhB(OH)$_2$, Pd(OAc)$_2$, P(*o*-Tol)$_3$; (b) SOCl$_2$; (c) 1,3-dialkyl-5-hydroxypyrazole, NEt$_3$; (d) base, cat CN^-.

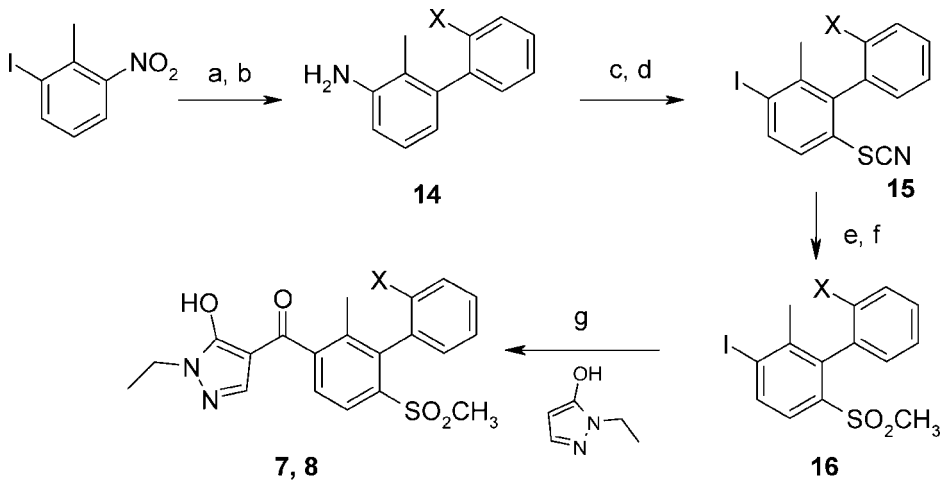


Figure 5. Method C for preparation of *ortho*-substituted 3-phenyl benzoylpyrazoles. (a) X—$PhB(OH)_2$, K_2CO_3, $Pd(OAc)_2$, P(*o*-Tol)$_3$, glyme–H_2O–EtOH, 80 °C (60–95%); (b) H_2, Pd(C), EtOH (90–95%); (c) KSCN, Br_2, MeOH–CH_2Cl_2, 0–5 °C (90–100%); (d) $NaNO_2$, HCl; KI, 5–10 °C, H_2O–CH_2Cl_2 (70–100%); (e) NaOMe, MeOH; MeI (80–95%); (f) MCPBA, CH_2Cl_2 (80–100%); (g) CO, Et_3N, $Pd(OAc)_2$, P(*o*-Tol)$_3$, CH_3CN, 115 °C (30–40%).

16-h day length. Plant material was overhead watered prior to spraying. Plant material ranged from 1.5 to 2.5 leaves at the time of treatment. After treatment, plants were returned to the greenhouse under the standard growing condition of 18 °C.

Samples of test chemicals were weighed into 25-ml glass vials. The amount weighed depended on the high rate in the test (eg 60 mg of test material was added to provide a rate of 512 g ha^{-1}). A concentrated stock solution was made by adding 2.2 ml of acetone + dimethyl sulfoxide (DMSO), (97 + 3 by volume) to the weighed sample. Most of the samples dissolved readily, but gentle warming or sonication was occasionally needed. Spray solutions were formulated at five rates with a high rate (x) and four half-fold dilutions ($1/2x$, $1/4x$, $1/8x$, and $1/16x$). The solutions were prepared by injecting aliquots of the stock solution into a mixture comprised of deionized water + acetone + isopropyl alcohol + DMSO + crop oil concentrate (COC) + Triton X-155 (38.8 + 48.5 + 10 + 1.5 + 1 + 0.02 by volume) to deliver 10 ml of spray solution. The solutions containing the highest concentration to be tested were prepared by diluting 1-ml aliquots of the stock solution with 9 ml of the mixture and lower concentrations were prepared accordingly. Solutions were applied with a mechanized track-sprayer operated at 3.2 km h^{-1} with a spray height of 51 cm and an application volume of 187 liter ha^{-1}.

Visual assessments of weed control and crop injury were made 3 weeks after application. In several tests, crop injury was evaluated 1 week after treatment since this tended to be the time when injury was at its highest level in the greenhouse. Plant injury was visually assessed on a scale of 0 to 100% with 0 equal to no injury and 100 equal to complete kill. Herbicidal data are reported as GR_{80}, the concentration that caused 80% visual injury to the weed or, in the case of wheat, as GR_{20}, the concentration which caused 20% injury.

3 RESULTS AND DISCUSSION

Two probe 3-phenylbenzoylpyrazoles (**4**), each containing a simple unsubstituted phenyl moiety, were prepared for comparison with the corresponding morpholine-substituted benzoylpyrazole lead compounds. In each instance, the only other structural variable was the pyrazole nitrogen substituent (ethyl or *tert*-butyl). This comparison (Table 2) clearly showed that the herbicidal activity of the two phenyl analogs against two key grass species, AVEFA and ALOMY (*Alopecurus myosuroides* Huds) was roughly equivalent to that of the corresponding cyclic amines, and verified our original proposal that the morpholine group could be replaced with other cyclic systems while still maintaining cool-season grass activity. Such a simple modification failed to deliver the desired improvement

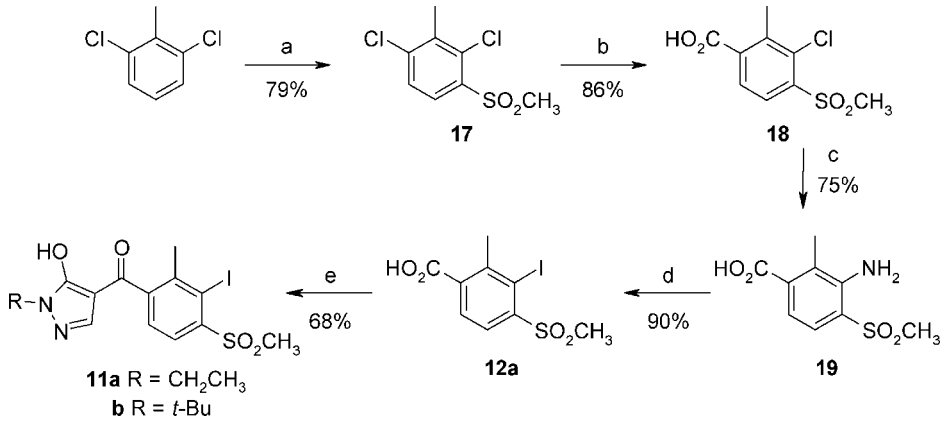
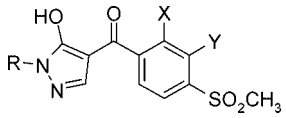


Figure 6. Preparation of the key intermediate iodobenzoylpyrazoles **11a** (for Method A) and iodobenzoic acid **12a** (for Method B). (a) $(CH_3SO_2)_2O$, cat Tf_2O, 120 °C; (b) CO, $NaHCO_3$, 10:1 *t*-BuOH:H_2O, $Pd(OAc)_2$, 1,4-bis(diphenylphosphino)butane, 125 °C; (c) NH_4OH, CuO, 180 °C; (d) 1. $NaNO_2$, H_2SO_4, 2. KI; (e) 1. $SOCl_2$, 2. 1-alkyl-5-hydroxypyrazole, NEt_3, 3. NEt_3, cat CN^-.

Table 2. Comparison of the post-emergence activity of 3-morpholino- *versus* 3-phenyl-substituted benzoylpyrazole



				TRZAS[a]	*AVEFA*[a]	*ALOMY*[a]
No	*X*	*Y*	*R*	GR_{20} (mg liter^{-1})[b]	GR_{80} (mg liter^{-1})[b]	
3a	Cl	4-Morpholine	CH_2CH_3	2.0	3.3	7.8
4a	Cl	Phenyl	CH_2CH_3	2.6	14	>250
3b	Cl	4-Morpholine	*tert*-Bu	<1	3.9	16
4b	Cl	Phenyl	*tert*-Bu	<1	3.9	12
5a	CH_3	Phenyl	CH_2CH_3	0.8	12	47

[a] TRZAS = wheat (*Triticum aestivum*); AVEFA = *Avena fatua*; ALOMY = *Alopecurus myosuroides*.
[b] Concentration which produced either 20% (GR_{20}) or 80% (GR_{80}) visual injury.

in selectivity to wheat. However, the literature is replete with examples of wheat herbicides whose selectivity to the crop results from differential oxidation in wheat (but not in the weeds) either directly on an aromatic ring (ring hydroxylation) or on an attached alkyl group.[23] Thus, modification of the phenyl ring substituent(s) was seen as a potential solution to the wheat selectivity issue.

Initial optimization of the 3-phenylbenzoylpyrazole series focused on varying the nature of the substituent on the phenyl ring while keeping the other benzoylpyrazole substituents constant. Thus, for consistency of data comparison, each of these initial examples contained an ethyl group on the nitrogen of the pyrazole, a methyl-sulfone at the 4-position of the benzoyl and a methyl group at the 2-position of the benzoyl (**5**–**8**, Fig 2). The latter was chosen over chlorine at C-2 for two reasons. First, a simple comparison between chlorine (**4a**) and methyl (**5a**) at C-2, using an unsubstituted phenyl at C-3, showed that the methyl-substituted derivative provided a higher level of herbicidal activity with little differentiation in level of wheat selectivity (Table 2). Second, compounds in the C-2 methyl series were typically synthetically more accessible than the corresponding chloro-substituted materials.

3.1 Structure-activity relationships of the phenyl substituent

The bulk of the analogs in the phenyl series were prepared with a substituent in the 4-position of the benzene (**5**, Table 3). This was, in part, a result of the ready availability of many of the key *para*-substituted phenylboronic acid intermediates. More important, however, was the discovery that certain *para* substituents on the benzene ring resulted in wheat-selective compounds in which grass weed activity was not compromised. Most notable was the excellent wheat selectivity and very good AVEFA activity seen with most members of the 4-alkoxy series (**5m**–**t**, Table 3). Unfortunately, most other materials with *para* substituents (including chlorine, alkyls, trifluoromethyl, or methyl-sulfone) were only weakly active, at best, on the grass weeds, while causing unacceptable damage to the wheat. Two other analogs in this series, 4-F (**5b**) and 4-CN (**5i**), provided fair to good activity on all the target weed species, but neither was selective to wheat. We concluded that the 4-alkoxy substituents were unique in their ability to combine attractive levels of grass activity with crop selectivity.

While a variety of substituents were prepared at the *meta* position of the phenyl group, the focus of this series was again directed towards alkoxy groups. However, most of these materials were, at best, weakly active against the grass weed targets (**6**, Table 4). Only two analogs, 3-fluoro (**6a**) and 3-isopropyl (**6e**), provided reasonable levels of activity against AVEFA, but in each case the crop selectivity was poor. Clearly, the trend for increased activity with alkoxy substituents was not replicated in the *meta*-alkoxy series.

Synthetic difficulties precluded an extensive survey of substituents on the *ortho* position of the phenyl group. Furthermore, of the few *ortho*-substituted materials that were prepared (Table 5), only **7d**, containing an *ortho*-methoxy substituent, resulted in a significant degree of crop selectivity, but at a substantial cost in grass activity.

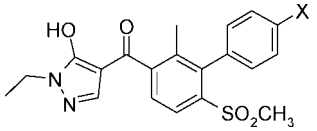
For synthetic reasons, only two 2,4-disubstituted analogs were prepared, both containing the preferred 4-methoxy substituent. Neither of these materials, however, demonstrated a significant level of activity at the rate of 256 g ha^{-1} (**8a**–**b**, Table 6).

The trend for excellent crop tolerance with a 4-methoxy substituent was evident in the corresponding 3,4-disubstituted (**8c**–**l**, Table 6) examples as well. Of these, the 3,4-dimethoxy-substituted 3-phenylbenzoylpyrazole (**8f**) provided the best combination of activity and selectivity, rivaling that of the corresponding C-4 mono-methoxy analog (**5m**). None of the remaining disubstituted analogs (**8m**–**p**) provided the requisite combination of grass activity and wheat selectivity.

3.2 Optimization of the pyrazole substituent

Earlier studies in the benzoylpyrazole series had shown that the nature of the alkyl substituent on the pyrazole nitrogen can have a significant affect on both herbi-

Table 3. Post-emergence activity of *para*-substituted 3-phenylbenzoylpyrazoles[a]



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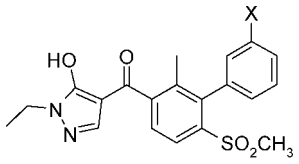
			TRZAS[b]	*AVEFA*[b]	*SETVI*[b]
No	*mp (°C)*	*X*	*GR_{20} (g ha^{-1})*[c]	*GR_{80} (g ha^{-1})*[c]	
5a	151–152	H	<8	12	>128
5b	195–197	F	<32	40	<32
5c	209–210	Cl	53	>128	93
5d	197–198	CH_3	25	>128	52
5e	167–169	CH_2CH_3	127	454	80
5f	155–156	i-Pr	217	463	<64
5g	179–181	$CH=CH_2$	>256	>256	>256
5h	155–156	CF_3	19	>128	24
5i	192–193	CN	<32	<32	108
5j	160–161	CO_2CH_3	>256	>256	>256
5k	232–233	SO_2CH_3	45	>256	203
5l	203–205	OH	>256	>256	>256
5m	147–148	OCH_3	>256	63	113
5n	164	OCH_2CH_3	>256	50	141
5o	133	O-i-Pr	>256	43	40
5p	Foam	$OCH_2CH=CH_2$	>256	50	139
5q	116–118	OCF_3	<32	118	40
5r	177–181	OCH_2CH_2F	>256	67	152
5s	140–142	OCH_2OCH_3	>256	<32	112
5t	144–146	$OCH_2CH_2OCH_3$	42	48	<32

[a] All materials were prepared by Method A except **5k** for which Method B was used.
[b] TRZAS = wheat (*Triticum aestivum*); AVEFA = *Avena fatua*; SETVI = *Setaria viridis*.
[c] Rate which produced either 20% (GR_{20}) or 80% (GR_{80}) visual injury in post-emergence greenhouse testing.

Table 4. Post-emergence activity of *meta*-substituted 3-phenylbenzoylpyrazoles[a]



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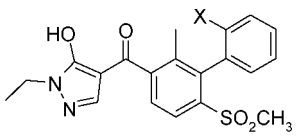
			TRZAS[b]	*AVEFA*[b]	*SETVI*[b]
No	*mp (°C)*	*X*	*GR_{20} (g ha^{-1})*[c]	*GR_{80} (g ha^{-1})*[c]	
5a		H	<8	12	>128
6a	185–187	F	<32	<32	40
6b	160–161	Cl	8	81	>128
6c	138–139	CH_3	>128	>128	83
6d	164–166	CH_2CH_3	<64	130	80
6e	176–178	i-Pr	<64	<64	80
6f	157	OCH_3	227	>256	>256
6g	151	OCH_2CH_3	>256	>256	>256
6h	165	O-i-Pr	>256	>256	>256
6i	Foam	$OCH_2CH=CH_2$	>256	>256	>256
6j	74–76	OCF_3	<32	95	64
6k	127–128	OCH_2OCH_3	46	219	>256
6l	166–168	$OCH_2OCH_2OCH_3$	<32	112	83

[a] All materials were prepared by Method A.
[b] TRZAS = wheat (*Triticum aestivum*); AVEFA = *Avena fatua*; SETVI = *Setaria viridis*.
[c] Rate which produced either 20% (GR_{20}) or 80% (GR_{80}) visual injury in post-emergence greenhouse testing.

Table 5. Post-emergence activity of *ortho*-substituted 3-phenylbenzoylpyrazoles[a]



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			TRZAS[b]	*AVEFA*[b]	*SETVI*[b]
No	*mp (°C)*	*X*	GR_{20} *(g ha^{-1})*[c]	GR_{80} *(g ha^{-1})*[c]	
5a		H	<8	12	>128
7a	176–177	F	<32	43	40
7b	173–175	Cl	<32	<32	124
7c	179–180	CH_3	<16	22	65
7d	181–182	OCH_3	152	66	199

[a] All materials were prepared by Method C.

[b] TRZAS = wheat (*Triticum aestivum*); AVEFA = *Avena fatua*; SETVI = *Setaria viridis*.

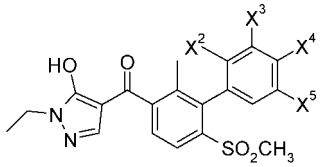
[c] Rate which produced either 20% (GR_{20}) or 80% (GR_{80}) visual injury in post-emergence greenhouse testing.

cidal activity and selectivity. In particular, we have noted that activity on certain grasses is sometimes improved with branched alkyl substitutions (isopropyl or *tert*-butyl) in comparison to the small straight-chain alkyls, methyl or ethyl. Initial studies in the unsubstituted 3-phenyl series showed a similar trend with the *N-tert*-butylpyrazole analog (**4b**, Table 2) providing improved grass weed activity relative to the corresponding *N*-ethylpyrazole (**4a**).

This observation elicited a study in which the pyrazole substituents were varied using one of the 'best' phenyl substituents (4-methoxy) from the survey described above. As can be seen from the results in Table 7, there was a clear trend for increased activity on grass weeds as the size of the *N*-alkyl substituent increased from methyl through *tert*-butyl. This correlation fails with *sec*-butyl substitution, where activity was nearly totally lost, suggesting that there is a limitation to the size of the substituent tolerated on the nitrogen of the pyrazole. In this limited series, there was no observed difference in the level of crop selectivity regardless of the nature of the *N*-alkyl substituent. An additional methyl substituent on the carbon of the pyrazole (**10d**–**e**) failed to offer any activity advantages. Furthermore, the combination of *C*-methyl and *N-tert*-butyl substituents on the pyrazole (**10e**) resulted in a significant decrease in wheat selectivity.

To explore further the effect of the *N*-pyrazole substituent upon activity and selectivity, a selection of phenyl substituents that had provided better levels of activity in the *N*-ethylpyrazole series were chosen, and the corresponding *N-tert*-butylpyrazole analogs prepared. Most of these *tert*-butyl-substituted materials provided very good levels of activity on the target weed species (Table 8) with the sole exception being the 3,4-dimethoxy-substituted analog (**9f**), which was nearly inactive. The superiority of a methyl group, as compared to chlorine, at C-2 on the benzoyl is clear in the comparison of both the activity and selectivity of **9a** *versus* the corresponding chloro analog, **9g**.

Table 6. Post-emergence activity of disubstituted 3-phenylbenzoylpyrazoles



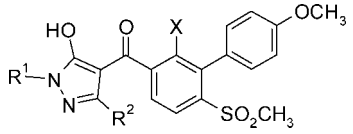
8

							TRZAS[a]	*AVEFA*[a]	*SETVI*[a]
No	*mp (°C)*	*Method*	X^2	X^3	X^4	X^5	GR_{20} *(g ha^{-1})*[b]	GR_{80} *(g ha^{-1})*[b]	
8a	151–152	C	F	—	OCH_3	—	>256	>256	>256
8b	155–157	C	Cl	—	OCH_3	—	>256	>256	>256
8c	152	A	—	F	OCH_3	—	>256	>256	192
8d	157	A	—	Cl	OCH_3	—	>256	>256	136
8e	160–161	A	—	CH_3	OCH_3	—	>256	88	>256
8f	192–194	A	—	OCH_3	OCH_3	—	>256	40	80
8g	128–130	A	—	Cl	F	—	<32	>256	>256
8h	217–219	A	—	Cl	Cl	—	67	>256	127
8i	208–210	A	—	Cl	CH_3	—	>256	>256	>256
8j	202–204	A	—	CH_3	Cl	—	>256	>256	129
8k	147–149	A	—	OCH_3	F	—	19	137	80
8l	199–205	A	—	OCH_3	Cl	—	105	>256	>256
8m	185–187	A	—	Cl	—	Cl	<16	256	132
8n	198–203	A	—	Cl	—	CH_3	>256	>256	97
8o	197–199	A	—	Cl	—	OCH_3	156	>256	>256
8p	204–205	A	—	CH_3	—	CH_3	>256	>256	183

[a] TRZAS = wheat (*Triticum aestivum*); AVEFA = *Avena fatua*; SETVI = *Setaria viridis*.

[b] Rate which produced either 20% (GR_{20}) or 80% (GR_{80}) visual injury in post-emergence greenhouse testing.

Table 7. Effect of pyrazole substitution on the postemergence activity of the 3-(4-methoxyphenyl)benzoylpyrazoles



						TRZAS[a]	AVEFA[a]	SETVI[a]	ALOMY[a]
No	mp (°C)	Method	X	R^1	R^2	GR_{20} (g ha^{-1})[b]		GR_{80} (g ha^{-1})[b]	
10a	211–213	B	CH_3	CH_3	—	>256	137	>256	>256
5m	147–148	A	CH_3	CH_2CH_3	—	>256	60	136	>256
10b	174–175	B	CH_3	i-Pr	—	>256	56	72	94
9a	167–168	A	CH_3	*tert*-Bu	—	>256	25	20	63
10c	177–179	B	CH_3	*sec*-Bu	—	>256	>256	<32	>256
10d	174–176	B	CH_3	CH_3	CH_3	>256	86	112	256
10e	201–204	B	CH_3	*tert*-Bu	CH_3	103	<16	55	214

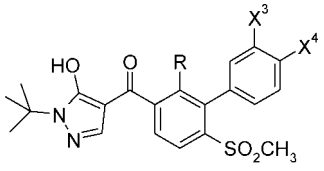
[a] TRZAS = wheat (*Triticum aestivum*); AVEFA = *Avena fatua*; SETVI = *Setaria viridis*; ALOMY = *Alopecurus myosuroides*.
[b] Rate which produced either 20% (GR_{20}) or 80% (GR_{80}) visual injury in post-emergence greenhouse testing.

In the optimization of any herbicide series, selecting the candidate with the best crop safety profile is a key factor in decision making. In the 3-phenylbenzoylpyrazole area, maximum crop injury on wheat was typically observed at 7–10 days after treatment in the greenhouse. Therefore, selection of the best candidates was made by comparison of a therapeutic index of crop safety to level of activity. This therapeutic index was defined as follows: the wheat GR_{20} at 7 days after treatment was divided by the AVEFA GR_{80} at 21 days after treatment. The SAR of the chemicals described above clearly indicated that molecules in the 4-alkoxyphenyl series coupled with an *N-tert*-butyl pyrazole substituent provided the best combination of activity and selectivity (Table 8). The top candidates in the alkoxy series were sorted using the described therapeutic index. Of these, the 4-methoxyphenyl analog (**9a**) provided the largest therapeutic index along with an activity level on the three target weed species that was superior to other candidate 4-alkoxy derivatives (Tables of 7 and 8). While the therapeutic indices for the corresponding ethoxy (**9b**) and methoxymethyl (**9e**) analogs are slightly inferior to the methoxy, they still have very good crop safety and provide a similar level of activity on target weed species.

4 CONCLUSIONS

A series of 3-phenyl-substituted benzoylpyrazoles were prepared as structural analogs of cool-season grass-active 3-morpholino benzoylpyrazoles. The targeted 3-phenylbenzoylpyrazoles were prepared by three newly developed synthetic routes which allowed both a comprehensive SAR study and optimization of the series against three important grass weeds in cereal

Table 8. Post-emergence activity of *N-tert*-butyl-3-phenylbenzoylpyrazoles



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						TRZAS[a]	AVEFA[a]	SETVI[a]	ALOMY[a]	
No	mp (°C)	Method	R	X^3	X^4	GR_{20} (g ha^{-1})[c]		GR_{80} (g ha^{-1})[c]		TI[b]
9a	174–175	A, B	CH_3		OCH_3	>256	25	20	63	>10.2
9b	110	A	CH_3		OCH_2CH_3	140	25	<16	55	5.6
9c	97	A	CH_3		O-i-Pr	63	28	19	84	2.3
9d	108–109	A	CH_3		$OCH_2CH=CH_2$	25	34	20	116	0.7
9e	138–140	A	CH_3		OCH_2OCH_3	156	20	30	65	7.8
9f	205–207	A	CH_3	OCH_3	OCH_3	126	>256	<32	>256	<0.5
9g	225–227	B	Cl		OCH_3	25	156	56	256	0.2
9h	187–188	B	CH_3		SO_2CH_3	<32	<32	<32	43	—

[a] TRZAS = wheat (*Triticum aestivum*); AVEFA = *Avena fatua*; SETVI = *Setaria viridis*; ALOMY = *Alopecurus myosuroides*.
[b] Therapeutic index: TRZAS GR_{20} divided by AVEFA GR_{80}.
[c] Rate which produced either 20% (GR_{20}) or 80% (GR_{80}) visual injury in post-emergence greenhouse testing.

crops: AVEFA, SETVI (*Setaria viridis* (L) Beauv) and ALOMY. Addition of certain substituents to the phenyl ring resulted in significant activity and spectrum improvements against the targeted grass weeds. In general, substitution at the *para* position on the benzene ring provided compounds with the best overall levels of activity, yet there was no clear relationship between this activity and the usual lipophilicity or electronic parameters associated with these substituents. Small substituents (eg F, CN) at any position delivered higher levels of activity. However, there were exceptions, as an isopropyl group provided one of the most active materials in the *meta* series (**6e**), yet the corresponding material with this substituent in the *para* position (**5f**) was nearly inactive. Disubstitution on the phenyl ring was detrimental to activity, regardless of the nature or location of the substituents.

The most interesting observation from the SAR study of the phenyl substituent was the excellent combination of grass activity and crop selectivity seen by most members of the *para*-alkoxy series. The nature of the alkoxy substituent did not seem critical for grass weed activity yet smaller alkoxy groups tended to provide better levels of crop selectivity. Once again, the superior biological properties associated with the *para*-alkoxy series did not translate to alkoxy substituents at other positions on the benzene ring. Likewise, the favorable activity/selectivity combination of the *para*-alkoxy series appears to be unique to those materials that contain a C-2 methyl group (and not a chlorine) on the benzoyl portion of the molecule.

In contrast to the confused SAR of the phenyl series, there was a very clear trend for increased grass weed activity as the pyrazole substituent was varied from *N*-methyl through *N*-*tert*-butyl. In addition, and much to our delight, there were no significant differences in the level of crop selectivity across this series of *N*-alkyl substituents. This remarkable wheat selectivity of the branched 1′-alkylpyrazoles was truly an astonishing observation, as it coincided with a significant increase in grass weed activity! An additional methyl substituent, on the 3′-carbon of the pyrazole, failed to offer any activity or selectivity advantages.

In summary, the *para*-alkoxy-substituted 3-phenyl-2-methyl-4-(methylsulfonyl)-benzoylpyrazoles are a novel class of HPPD-inhibiting herbicides with potential utility for control of important grass weeds in cereals.

5 SYNTHETIC METHODS

5.1 Phenyl-substituted benzoylpyrazoles—Method A

*5.1.1 1-(1,1-Dimethylethyl)-5-hydroxy-4-(3-(4-(methoxymethoxy)phenyl)-2-methyl-4-(methylsulfonyl)-benzoyl)pyrazole (Fig 3, **9e**)*

A mixture prepared from **11b** (1.39 g; 3 mmol), 4-(methoxymethoxy)phenylboronic acid (0.66 g; 3.6 mm), potassium carbonate (2.07 g; 15 mmol), $Pd(OAc)_2$ (34 mg; 0.15 mmol), tri-*o*-tolylphosphine (137 mg; 0.45 mmol), acetonitrile (25 ml) and water (6 ml) was stirred at reflux under nitrogen for 1 h. The mixture was cooled, diluted with water, and washed with diethyl ether. The aqueous layer was made acidic with hydrochloric acid (3 M) and the resulting mixture extracted twice with dichloromethane. The combined organic layers were washed with water, dried over anhydrous sodium sulfate, and evaporated to leave an oil. The oil was taken up in diethyl ether + hexane, decanted from some insoluble material and allowed to stand to give **9e** (1.09 g; 77%) as golden crystals; mp 139–141 °C; ^{1}H NMR ($CDCl_3$): δ 8.20 (d, 1H, J = 8 Hz), 7.58 (d, 1H, J = 8 Hz), 7.26 (s, 1H), 7.23 (d, 2H, J = 9 Hz), 7.15 (d, 2H, J = 9 Hz), 5.25 (s, 2H), 3.54 (s, 3H), 2.67 (s, 3H), 2.08 (s, 3H), 1.66 (s, 9H); calc for $C_{24}H_{28}N_2O_6S$: C, 61.00; H, 5.97; N, 5.93; found: C, 60.65; H, 6.07; N, 5.80.

5.2 Phenyl-substituted benzoylpyrazoles—Method B

*5.2.1 2-Methyl-3-(4-methoxyphenyl)-4-(methylsulfonyl)benzoic acid (Fig 4, **13**, X = 4-OCH_3, Y = CH_3)*

A mixture was prepared under nitrogen comprising **12a** (11.9 g; 35 mmol), 4-methoxyphenylboronic acid (6.91 g; 45.5 mmol), potassium carbonate (24.2 g; 175 mmol), $Pd(OAc)_2$ (0.39 g; 1.75 mmol), tri-*o*-tolylphosphine (1.07 g; 3.5 mmol), diglyme (150 ml) and water (15 ml). The mixture was stirred at 95 °C for 12 h, cooled to room temperature, diluted with water, and washed twice with diethyl ether. The aqueous layer was made acidic with hydrochloric acid (3 M) and then extracted three times with ethyl acetate. The ethyl acetate layers were combined and evaporated to leave a dark oily residue. The oil was taken up in aqueous sodium hydroxide (1 M), treated with activated charcoal, and then filtered through Celite. The filtrates were made acidic with hydrochloric acid (3 M) and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and evaporated to leave a solid which was recrystallized from toluene to give **13** (X = 4-OCH_3, Y = CH_3; 9.37 g; 84%) as colorless crystals; mp 178–180 °C; ^{1}H NMR ($CDCl_3$): δ 8.19 (d, 1H, J = 8 Hz), 8.08 (d, 1H, J = 8 Hz), 7.21 (d, 2H, J = 9 Hz), 7.03 (d, 2H, J = 9 Hz), 3.88 (s, 3H), 2.62 (s, 3H), 2.28 (s, 3H); calc for $C_{16}H_{16}O_5S$: C, 59.99; H, 5.03; S, 10.01; found: C, 59.10; H, 5.01; S, 10.08.

*5.2.2 1-(1,1-Dimethylethyl)-5-hydroxy-4-(3-(4-(methoxy)phenyl)-2-methyl-4-(methylsulfonyl)benzoyl)-pyrazole (Fig 3, **9a**)*

A mixture of **13** (X = 4-OCH_3, Y = CH_3; 12.2 g; 38 mmol), thionyl chloride (10 ml) and 1,2-dichloroethane (75 ml) was stirred at reflux for 3 h (gas evolution), cooled and evaporated to dryness. Toluene (50 ml) was added and the mixture again evaporated to dryness. The resulting yellow oil was dissolved in dichloromethane (20 ml) and added dropwise to a cold (5 °C) solution prepared from 1-*tert*-butyl-5-hydroxy-

pyrazole (6.39 g; 45.6 mmol), triethylamine (4.61 g; 45.6 mmol) and dichloromethane (150 ml). The mixture was allowed to warm to ambient temperature and then washed with cold hydrochloric acid (0.5 M), cold potassium carbonate solution (50 g liter^{-1}), dried over anhydrous magnesium sulfate, and evaporated to leave an oil.

The oil prepared above was dissolved in acetonitrile (75 ml) and powdered, anhydrous potassium carbonate (7.88 g; 57 mmol) was added followed by acetone cyanohydrin (0.5 ml). The resulting mixture was stirred overnight, concentrated with a rotary evaporator, and the residue partitioned between water and ether. The aqueous phase was treated with activated carbon, filtered through Celite, made acidic with hydrochloric acid (3 M), and then extracted three times with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and evaporated. The resulting oil was crystallized from ethanol to give **9a** (10.9 g; 65%) as off-white crystals; mp 174–175 °C; ^{1}H NMR ($CDCl_3$): δ 8.20 (d, 1H, $\mathcal{J}$ = 8 Hz), 7.57 (d, 1H, $\mathcal{J}$ = 8 Hz), 7.26 (s, 1H), 7.24 (d, 2H, $\mathcal{J}$ = 9 Hz), 7.02 (d, 2H, $\mathcal{J}$ = 9 Hz), 3.88 (s, 3H), 2.66 (s, 3H), 2.08 (s, 3H), 1.66 (s, 9H); calc for $C_{23}H_{26}N_2O_5S$: C, 62.43; H, 5.92; N, 6.33; S, 7.24; found: C, 62.34; H, 5.94; N, 6.25; S, 7.32.

5.3 Phenyl-substituted benzoylpyrazoles—Method C

5.3.1 2′-Fluoro-2-methyl-3-nitrobiphenyl (Fig 5)

A mixture of palladium acetate (260 mg; 1.1 mmol), tri-*o*-tolylphosphine (1.0 g; 3.4 mmol) and glyme (70 ml) was stirred for 5 min under nitrogen. Then 2-iodo-6-nitrotoluene (10 g; 38 mmol) was added and the mixture stirred for 10 min. Finally, a solution of 2-fluorophenylboronic acid (5.3 g; 38 mmol) in ethanol (30 ml) was added followed by a solution of potassium carbonate (26 g; 190 mmol) in water (50 ml) and the mixture warmed at reflux for 20 h under nitrogen. The resulting mixture was cooled, diluted with water and extracted three times with diethyl ether. The organic layers were filtered, washed with brine, dried and evaporated. The residue was chromatographed on silica with hexane + dichloromethane (9 + 1 by volume) to give 2′-fluoro-2-methyl-3-nitrobiphenyl (6.9 g; 97%) as a colorless solid; mp 77–79 °C; ^{1}H NMR ($CDCl_3$): δ 7.1–7.8 (m, 7H), 2.32 (s, 3H); calc for $C_{13}H_{10}FNO_2$: C, 67.53; H, 4.36; N, 6.06; found: C, 67.21; H, 4.46; N, 5.82.

*5.3.2 2′-Fluoro-2-methylbiphenyl-3-ylamine (Fig 5, **14**)*

A mixture of 2′-fluoro-2-methyl-3-nitrobiphenyl (6.4 g; 28 mmol), 5% Pd/C (1 g), ethanol (100 ml) and toluene (75 ml) was hydrogenated at 275–345 kPa for 17 h at 25 °C on a Parr apparatus. The resulting mixture was filtered and the solvents were evaporated to give **14** (5.3 g; 94%) as a tan solid; ^{1}H NMR ($CDCl_3$): δ 6.7–7.3 (m, 7H), 3.65 (br s, 2H), 1.99 (s, 3H).

5.3.3 2′-Fluoro-2-methyl-6-thiocyanatobiphenyl-3-ylamine (Fig 5)

A solution prepared from **14** (5.1 g; 26 mmol) and potassium thiocyanate (8.3 g; 86 mmol) in methanol (50 ml) was cooled to 0–5 °C and bromine (4.5 g; 28 mmol) was added dropwise with stirring. After 2 h a few ml of saturated sodium hydrogen sulfite solution were added and the mixture then diluted with water, extracted twice with dichloromethane, and the combined organic phases washed with water and brine, dried over anhydrous sodium sulfate and evaporated to give 2′-fluoro-2-methyl-6-thiocyanatobiphenyl-3-ylamine (6.4 g; 95%) as an oil which was used without further purification; ^{1}H NMR ($CDCl_3$): δ 6.8–7.5 (m, 6H), 3.96 (s, 2H), 1.89 (s, 3H).

*5.3.4 2′-Fluoro-3-iodo-2-methyl-6-thiocyanatobiphenyl (Fig 5, **15**)*

A solution of 2′-fluoro-2-methyl-6-thiocyanatobiphenyl-3-ylamine (6.1 g; 24 mmol) in dichloromethane (50 ml) was cooled to 5 °C and chilled concentrated hydrochloric acid (150 ml) was added. The mixture was vigorously stirred and treated in portions with a solution of sodium nitrite (2.4 g; 35 mmol) in water (10 ml) while keeping the temperature below 0 °C. After 25 min the mixture was poured slowly in portions into a stirred mixture of potassium iodide (5.8 g; 35 mmol), water (150 ml) and dichloromethane (100 ml). After 30 min, saturated sodium hydrogen sulfite solution was added and the organic phase separated, washed with water and brine, dried over anhydrous sodium sulfate and evaporated to give iodide **15** (8.6 g; 97%) as a tan solid; ^{1}H NMR ($CDCl_3$): δ 7.1–8.0 (m, 6H), 2.23 (s, 3H).

5.3.5 2′-Fluoro-3-iodo-2-methyl-6-methylthiobiphenyl (Fig 5)

A mixture of **15** (8.4 g; 23 mmol) in methanol (100 ml) was treated with sodium methoxide (2.5 g; 46 mmol). After 1.5 h the mixture was cooled in an ice-bath and treated dropwise with a solution of methyl iodide (3.6 ml; 58 mmol) in methanol (10 ml). After 30 min further sodium methoxide (1.5 g) was added and the mixture stirred for an additional 20 min. The resulting mixture was diluted with water (200 ml), extracted with dichloromethane (2 × 200 ml) and the combined organic layers washed with brine, dried over anhydrous sodium sulfate and evaporated to give 2′-fluoro-3-iodo-2-methyl-6-methylthiobiphenyl (6.8 g; 82%) as an oil; ^{1}H NMR ($CDCl_3$): δ 6.8–7.8 (m, 6H), 2.33 (s, 3H), 2.17 (s, 3H).

*5.3.6 2′-Fluoro-3-iodo-2-methyl-6-methylsulfonylbiphenyl (Fig 5, **16**)*

A solution of 2′-fluoro-3-iodo-2-methyl-6-methylthiobiphenyl (6.8 g; 19 mmol) in dichloromethane (200 ml) was cooled in an ice-bath and treated in portions with 60% 3-chloroperoxy benzoic acid (MCPBA) (16.5 g; 58 mmol). The mixture was allowed to warm to 25 °C, stirred for 18 h, and then

treated with saturated sodium hydrogen sulfite to destroy the excess oxidant. The organic phase was separated, washed to neutrality with aqueous sodium hydrogen carbonate and then with water (twice) and brine, dried over anhydrous sodium sulfate, and the solvent evaporated to give **16** (7.7 g; 100%) as a colorless solid; mp 116–117 °C; ^{1}H NMR ($CDCl_3$): δ 7.2–8.1 (m, 6H), 2.74 (s, 3H), 2.22 (s, 3H); calc for $C_{14}H_{12}FINO_2S$: C, 43.09; H, 3.10; S, 8.22; found: C, 43.41; H, 3.15; S, 8.09.

5.3.7 1-Ethyl-4-(-3-(2-fluorophenyl)-2-methyl-4-(methylsulfonyl)benzoyl)-5-hydroxypyrazole (Fig 5, ***7a****)*
A mixture was prepared from **16** (1.7 g; 4.4 mmol), 1-ethyl-5-hydroxypyrazole (1.5 g; 13 mmol), triethylamine (2.1 ml; 15 mmol), $Pd(OAc)_2$ (50 mg; 0.22 mmol) and tri-*o*-tolylphosphine (200 mg; 0.66 mmol) in acetonitrile (20 ml) in a 45-ml Hastelloy-C pressure reactor. The reactor was purged and pressurized with carbon monoxide to 2000 kPa and then warmed at 115 °C for 19 h. The mixture was cooled, diluted with water, washed twice with diethyl ether, made acidic with hydrochloric acid (6 M) and extracted twice with dichloromethane. The combined organic extracts were washed with water, dried over anhydrous sodium sulfate and evaporated. The residue was recrystallized from ethanol to give **7a** (550 mg; 31%) as a yellow solid; mp 176–177 °C; ^{1}H NMR ($CDCl_3$): δ 7.2–8.2 (m, 7H), 4.09 (q, 2H, J=7.3 Hz), 2.80 (s, 3H), 2.08 (s, 3H), 1.47 (t, 3H, J=7.3 Hz); calc for $C_{20}H_{19}FN_2O_4S$: C, 59.69; H, 4.76; S, 6.96; found: C, 59.23; H, 4.73; S, 7.82.

5.4 Intermediate 3-iodobenzoylpyrazoles 11 (for Method A) and 3-iodobenzoic acids 12 (for Method B)

5.4.1 2,6-Dichloro-3-(methylsulfonyl)toluene (Fig 6, ***17****)*[24]
A mixture of thionyl chloride (240 g; 2.0 mol) and methanesulfonic acid (480 g; 5.0 mol) was warmed at reflux for 1 h. At this point the reaction temperature had increased to 120 °C and the initial gas evolution had ceased. After cooling to 50 °C, 2,6-dichlorotoluene (161 g; 1.0 mol) and trifluoromethanesulfonic acid (10 g; 67 mmol) were added and the mixture warmed at 120 °C for 5 h. After cooling to 50 °C, the mixture was poured into ice water (2 liter) and the resulting precipitate taken up in dichloromethane. The aqueous layer was separated and washed twice with dichloromethane. The combined organic layers were washed with water, twice with sodium hydroxide solution (2 M), dried over anhydrous sodium sulfate and evaporated. The resulting solid was recrystallized from ethanol to give **17** (188 g; 79%) as a tan solid; mp 123–124 °C; ^{1}H NMR ($CDCl_3$): δ 7.95 (d, 1H, J=8 Hz), 7.48 (d, 1H, J=8 Hz), 3.28 (s, 3H), 2.58 (s, 3H); calc for $C_8H_8Cl_2O_2S$: C, 40.18; H, 3.37; S, 13.41; found: C, 40.40; H, 3.38; S, 13.02.

5.4.2 3-Chloro-2-methyl-4-(methylsulfonyl)benzoic acid (Fig 6, ***18****)*
A mixture of **17** (62 g; 0.26 mol), sodium hydrogen carbonate (66 g; 0.78 mol), $Pd(OAc)_2$ (1.75 g; 7.8 mmol), 1,4-bis(diphenylphosphino)butane (6.7 g; 16 mmol), and de-aerated *tert*-butanol + water (10 + 1 by volume; 500 ml) was prepared in a 1-liter Hastelloy C pressure reactor. The mixture was purged and pressurized with carbon monoxide to 2000 kPa, and warmed at 125 °C for 20 h. After cooling, the thick mixture was diluted with water to dissolve most of the solids and filtered through Celite. The solids were washed twice with sodium hydroxide solution (2 M) and the combined filtrates extracted three times with toluene. The aqueous layer was made acidic with concentrated hydrochloric acid, and the resulting precipitate collected by filtration, washed well with water, and dried to give **18** (55 g; 86%) as colorless crystals; mp 196–197 °C; ^{1}H NMR (d_6-DMSO): δ 7.98 (d, 1H, J=8 Hz), 7.84 (d, 1H, J=8 Hz), 3.40 (s, 3H), 2.55 (s, 3H); calc for $C_9H_9ClO_4S$: C, 43.47; H, 3.65; S, 12.89; found: C, 43.65; H, 3.67; S, 12.68.

5.4.3 3-Amino-2-methyl-4-(methylsulfonyl)benzoic acid (Fig 6, ***19****)*
A mixture of **18** (79 g; 320 mmol), copper(II) oxide (1.0 g; 12.6 mmol) and concentrated aqueous ammonia (500 ml) was warmed in a pressure reactor at 180 °C for 17 h. The resulting dark mixture was evaporated and the residue made acidic with hydrochloric acid (2 M) and then extracted with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to leave a solid. The solid was triturated with hexane and dried to leave **19** (50.0 g; 68%) as a tan solid; mp 199–201 °C; ^{1}H NMR (d_6-DMSO): δ 13.25 (s, 1H), 7.50 (d, 1H, J=8 Hz), 6.92 (d, 1H, J=8 Hz), 5.97 (s, 2H), 3.12 (s, 3H), 2.22 (s, 3H); calc for $C_9H_{11}NO_4S$: C, 47.15; H, 4.84; N, 6.11; found: C, 47.08; H, 4.77; N, 5.98.

5.4.4 3-Iodo-2-methyl-4-(methylsulfonyl)benzoic acid (Fig 6, ***12a****)*
A solution was prepared by dissolving **19** (74 g; 320 mmol) in warm (50 °C) sulfuric acid (18 M; 500 ml). The solution was cooled to 0–5 °C to produce a slurry and the mixture treated dropwise over 20 min with a solution prepared of sodium nitrite (26.7 g; 387 mmol) in water (70 ml). The resulting yellow solution was stirred at 5 °C for 30 min and then added in portions over 15 min to a stirred warm (45 °C) solution of potassium iodide (166 g; 1.0 mole) in water (1 liter). When addition was complete, the mixture was warmed at 80 °C for 20–30 min, cooled to 25 °C and the resulting solid collected by filtration, washed well with water, and dried to leave **12a** (99 g; 90%) as a colorless solid; mp 193 °C; ^{1}H NMR (d_6-DMSO): δ 13.80 (s, 1H), 7.98 (d, 1H, J=8 Hz), 7.80 (d, 1H, J=8 Hz), 3.40 (s, 3H), 2.62 (s, 3H); calc for $C_9H_9IO_4S$: C, 31.78; H, 2.67; S, 9.40; found: C, 31.79; H, 2.67; S, 9.25.

*5.4.5 1-Ethyl-5-hydroxy 4-(3-iodo-2-methyl-4-(methylsulfonyl)benzoyl)pyrazole (Fig 6, **11a**)*

A mixture of **12a** (62.1 g; 182 mmol) and thionyl chloride (20 ml; 270 mmol) in 1,2-dichloroethane (300 ml) was stirred at reflux for 3 h. The solvent was evaporated and the resulting acid chloride dissolved in dichloromethane (100 ml) and this solution added dropwise to an ice-cold solution prepared from 1-ethyl-5-hydroxypyrazole (24.7 g; 220 mmol) and triethylamine (22.3 g; 220 mmol) in dichloromethane (200 ml). The reaction mixture was allowed to warm to 25 °C and then washed with hydrochloric acid (0.5 M). The organic phase was separated and washed with potassium carbonate solution (50 g liter^{-1}), dried over anhydrous magnesium sulfate and evaporated to give 84 g of crude product. This material was slurried in acetonitrile (400 ml), treated with powdered, anhydrous sodium hydrogen carbonate (37.7 g; 270 mmol) and acetone cyanohydrin (1 ml), and stirred overnight. The mixture was then concentrated under vacuum and the residue dissolved in water, washed with diethyl ether and acidified with hydrochloric acid (3 M). The resulting mixture was extracted three times with dichloromethane, the combined organic layers dried over anhydrous magnesium sulfate and evaporated to leave a gum. This material was crystallized from ethanol to give **11a** (63.3 g; 68%) as a yellow crystalline solid; mp 84–87 °C; ^{1}H NMR ($CDCl_3$): δ 8.21 (d, 1H, J = 8 Hz), 7.55 (d, 1H, J = 8 Hz), 7.32 (s, 1H), 4.10 (q, 2H, J = 7 Hz), 3.38 (s, 3H), 2.62 (s, 3H), 1.46 (t, 3H, J = 7 Hz); calc for $C_{14}H_{15}IN_2O_4S$: C, 38.70; H, 3.48; N, 6.45; S, 7.38; found: C, 39.50; H, 3.54; N, 6.44; S, 7.49.

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