Parallel Synthesis of Bis-heterocyclic Isoxazolylmethyl- and Isoxazolinylmethylpyrazoles

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The solution-phase parallel synthesis of a 136-member library of isoxazol(in)e-CH_2-pyrazoles is described. X-ray crystallographic structure determination verified the regioselectivities of the *N*-alkylation and nitrile oxide 1,3-dipolar cycloaddition steps. The construction of these pharmaceutically relevant heterocycles on solid support under microwave irradiation is also demonstrated. The resulting library of drug-like compounds has been added to the National Institutes of Health repository (∼10 mg of each with ≥90% purity) for pilot-scale biomedical studies with bioassay data available at the National Center for Biotechnology Information PubChem database. A subset of these compounds has been broadly screened by Dow AgroSciences for herbicidal, fungicidal, and insecticidal activity.

Introduction

Heterocyclic scaffolds provide core structures for drugs as well as drug-like molecules and, because of this rich tradition, combinatorial heterocyclic chemistry and related parallel heterocyclic synthesis are recognized as important tools in lead generation, target validation, and lead optimization for drug discovery.[1] Recent reports describe libraries of derivatized heterocycles where the most active compounds are bis-heterocycles;[2] indeed, 14 of the top 50 prescription drugs in 2008 contain bis-heterocycles.[3] However, a literature survey revealed only three references to compounds containing an isoxazoline-CH_2-pyrazole core[4] and twelve references to compounds containing an isoxazole-CH_2-pyrazole core.[5] Despite this low profile, these bis-heterocycles exhibit broad biological activity[4,5] (see Figure 1). On the basis of these observations, it appeared worthwhile to develop practical and efficient methods to generate a diverse isoxazol(in)e-CH_2-pyrazole library (Figure 2) for high-throughput biological screening to identify potential drug candidates through the NIH pilot-scale biomedical studies program and the Dow AgroSciences Lead Generation program.

We have employed nitrile oxide 1,3-dipolar cycloadditions in "scaffold-directed" methods to construct various isoxazol(in)e libraries, including thiazolo[4,5-*e*]benzoisoxa-zoles,[6] dispiroisoxazolinopiperidinochromanones,[7] 4-(isoxazol-3-yl)pyrimidines,[8] 3-aryl-4,5-dihydroisoxazole-5-carboxamides,[9] 5-carbamoyl-3-sulfanylmethylisoxazole-4-carboxylic acids.[10] To continue these efforts, we report herein a novel 136-member isoxazol(in)e-CH_2-pyrazole library constructed via the key steps of pyrazole *N*-alkylation and nitrile oxide 1,3-dipolar cycloaddition. Parallel solution phase methods were employed for most of the work, but, to further increase the diversity of the library as well as to demonstrate the versatility of the synthetic route, resin-bound transformations under microwave irradiation were also employed. In contrast to current methods, these strategies accommodate the introduction of greater molecular diversity with the combinatorial matrices of building blocks, stereochemical isomers, and even molecular skeletons. A large number of structurally diverse isoxazol(in)e derivatives for drug development projects can be rapidly synthesized in good purity and high yield using these methods.

Results and Discussion

The requisite *N*-allylpyrazole derivatives **4** and **5** as well as *N*-propargylpyazoles **6** and **7** were readily prepared from acetophenones in two steps as shown in Scheme 1. Step one is a one-pot synthesis of pyrazole **3** starting from acetophenone **1** and diethyl oxalate followed by dehydrative condensation with hydrazine in the presence of acetic acid. This transformation proceeds at room temperature[11] and affords ethyl 3-aryl-1*H*-pyrazole-5-carboxylate **3** in excellent overall yield (85−87%). In step two, pyrazole **3** is converted into its *N*-allyl (**4** and **5**) or *N*-propargyl (**6** and **7**) derivative by alkylation with allyl bromide or propargyl bromide, respectively, in refluxing solvent.

A variety of bases and solvents were surveyed for the pyrazole *N*-alkylation step[12] and the results with two systems are shown in Table 1. In K_2CO_3/acetone,[12d] *N*-alkylation produces the 1,3-isomer (**5** or **7**) as the major product. In contrast, NaH/THF[12e] gives the 1,5-isomer (**4** or **6**) as the major product. However, in the reaction to form **6** with NaH/THF, significant allene formation was observed (propargyl → allene isomerization).[13] In an attempt to avoid this unwanted isomerization, pyrazole **3** was added first to the THF-suspended sodium hydride and, after pyrazole anion

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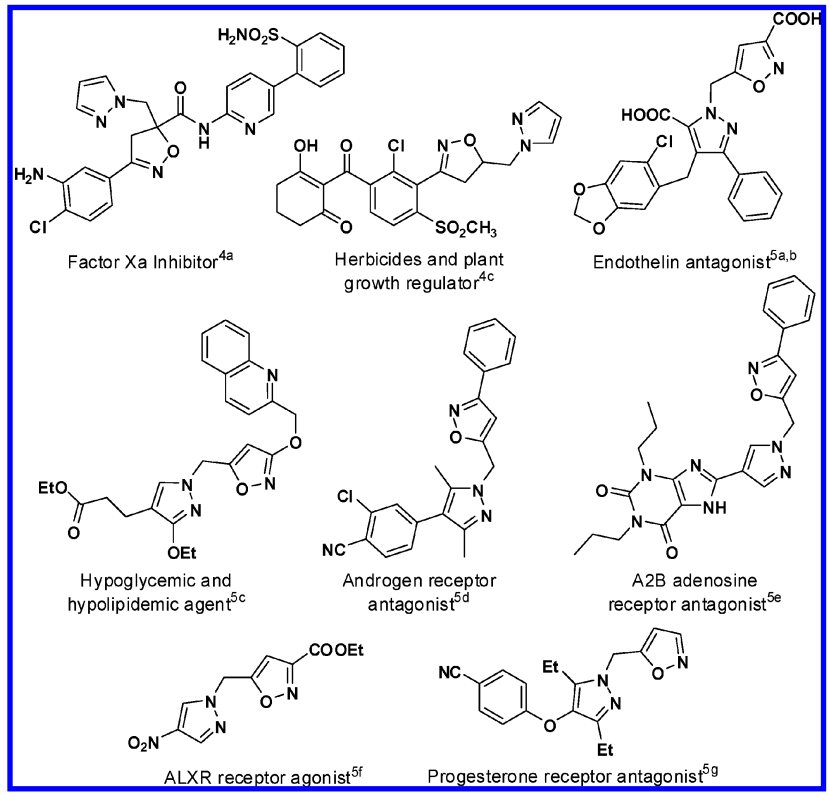


Figure 1. Bioactive bis-heterocycles containing isoxazol(in)e-CH_2-pyrazole core.

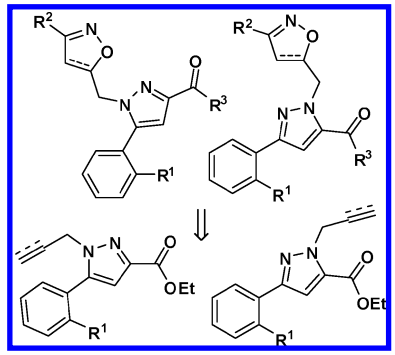
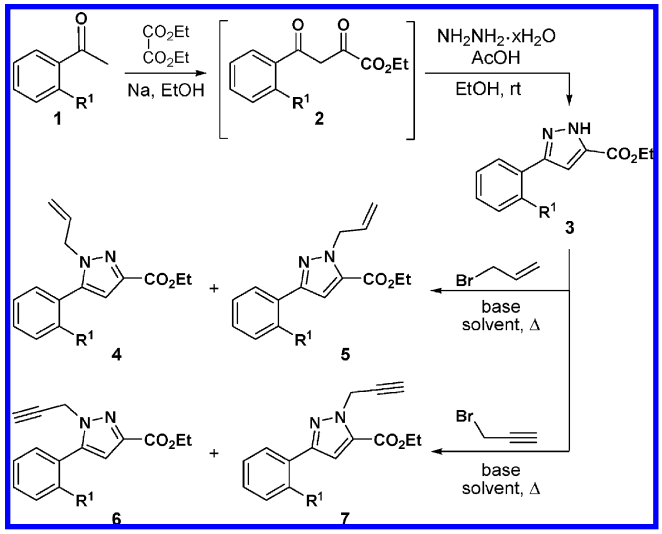


Figure 2. Isoxazol(in)e-CH_2-pyrazole libraries with four points of diversity.

Scheme 1. Synthesis of *N*-Allyl- and *N*-Propargylpyrazoles



formation was complete (30 min), the propargyl bromide was added. Even with this modification, treating **3**{*2*} (R^1 = Me) with NaH/THF followed by propargyl bromide at reflux gave allene product in 66% yield. Adding the propargyl bromide at room temperature and stirring for 16 h reduced allene formation (from 66% to 14%), and afforded **6**{*2*} in 37% yield and **7**{*2*} in 1% yield. No allene formation was observed in the K_2CO_3/acetone system.[14]

Table 1. *N*-Alkylation Regioselectivity with 3-Aryl-1*H*-pyrazole-5-carboxylate **3**

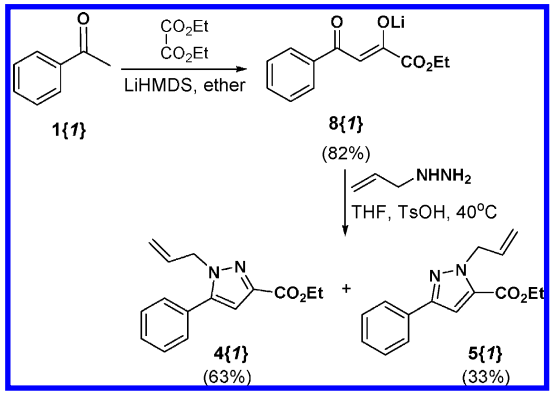
base/solvent	R^1	compd	yield(%)[a]	compd	yield(%)[a]
K_2CO_3/acetone/Δ	H	4{*1*}	15	5{*1*}	85
	Me	4{*2*}	6	5{*2*}	78
	H	6{*1*}	17	7{*1*}	81
	Me	6{*2*}	26	7{*2*}	70
NaH/THF/Δ	H	4{*1*}	86	5{*1*}	10
	Me	4{*2*}	90	5{*2*}	3
	H	6{*1*}	69	7{*1*}	11
	Me	6{*2*}	12	7{*2*}	5

[a] Yield of isolated product.

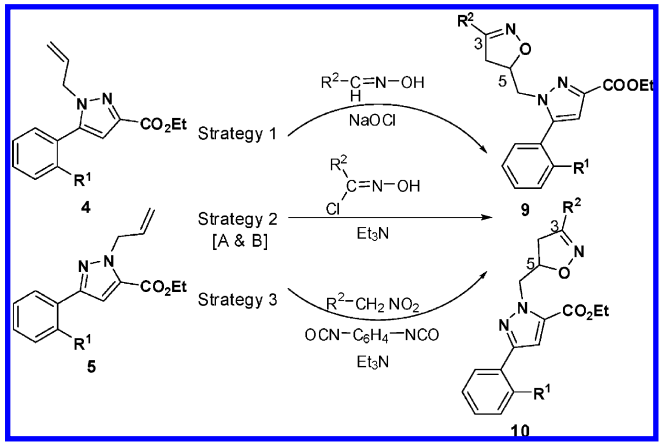
An alternative route[15] for the synthesis of *N*-allylpyrazole derivatives **4**{*1*} and **5**{*1*} was also investigated as depicted in Scheme 2. This route, which employs allylhydrazine in the 2,4-dioxo-4-arylbutanoate condensation reaction, directly delivers the *N*-substituted pyrazoles **4**{*1*} (1,5-isomer) and **5**{*1*} (1,3-isomer) in a 2:1 ratio, respectively. While operationally more direct, the reduced regioselectivity of this route makes it less attractive for library construction. X-ray crystallographic analysis of **6**{*1*} (see Figure 3) and subsequent comparative NMR analysis allowed us to unambiguously assign structures to all of the regioisomers represented by generic structures **4/5** and **6/7**.

With *N*-allylpyrazoles **4/5** and *N*-propargylpyrazoles **6/7** in hand, we turned to the construction of the isoxazoline and isoxazole rings. This transformation is typically accomplished by [3 + 2] cycloaddition of a nitrile oxide to the corre-

Scheme 2. Synthesis of *N*-Allylpyrazoles via Allylhydrazine



Scheme 3. Three Strategies for Isoxazoline Formation



sponding alkene and alkyne, respectively.[16] To minimize dipole dimerization, the nitrile oxide intermediate is typically generated in situ.

Three strategies were investigated for isoxazoline formation (Scheme 3). In the first, a modified Huisgen method[17] (Strategy 1) was employed. For instance, 4-chlorobenzaldehyde oxime was co-mixed with **4**{*1*} in DCM and treated with bleach at 0 °C. Under these conditions, partial chlorination of the pyrazole ring at C4 was observed, and the subsequent purification proved to be troublesome.[18] After separating by column chromatography on silica gel followed by preparative RP-HPLC, the desired product **9**{*1,1*} was obtained in 62% yield. Structural verification was accomplished by X-ray crystallographic analysis (see Figure 4).

To avoid unwanted chlorination at C4 of the pyrazole ring, a second cycloaddition method was explored (Scheme 3, Strategy 2). Adopting literature procedures,[19] aromatic hydroximoyl chloride, prepared from the corresponding oxime by treatment with *N*-chlorosuccinimide (1.1 equiv), was employed without prior purification in the 1,3-dipolar cycloaddition with allylpyrazole **4** (or **5**) in DCM in the presence of triethylamine (Strategy 2A). The desired cycloadduct was obtained in 57−60% yield. However, to our surprise, partial C4-chlorination of the pyrazole ring again occurred; apparently the consequence of unreacted NCS in the crude hydroximoyl chloride.[20] Therefore, it was deemed necessary to purify the aromatic hydroximoyl chloride by column chromatography prior to nitrile oxide formation. Applying purified hydroximoyl chloride (Strategy 2B) in the

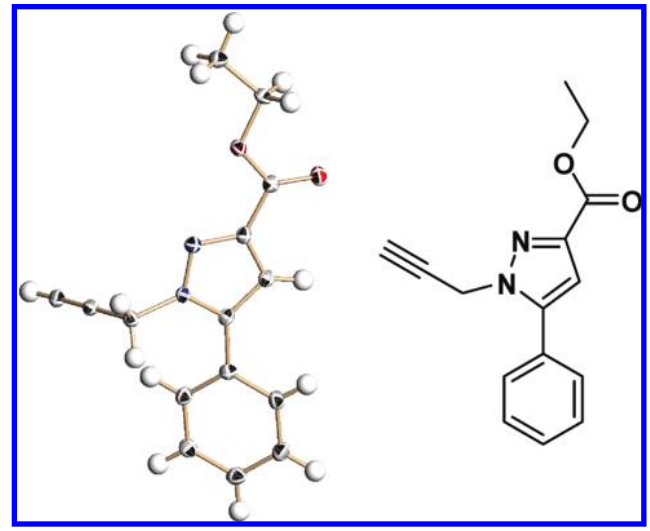


Figure 3. X-ray crystallographic structure of **6**{*1*}.

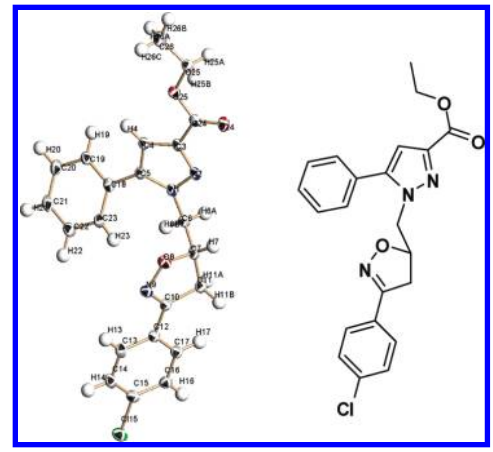


Figure 4. X-ray crystallographic structure of **9**{*1,1*}.

1,3-dipolar cycloaddition resulted in no chlorinated byproducts. The isolated yields of cycloadducts 1-(isoxazolin-5-yl)methyl-5-aryl-*1H*-pyrazole-3-carboxylate **9** and 1-(isoxazolin-5-yl)methyl-3-aryl-*1H*-pyrazole-5-carboxylate **10** were 72−89% (R^2 = aryl).

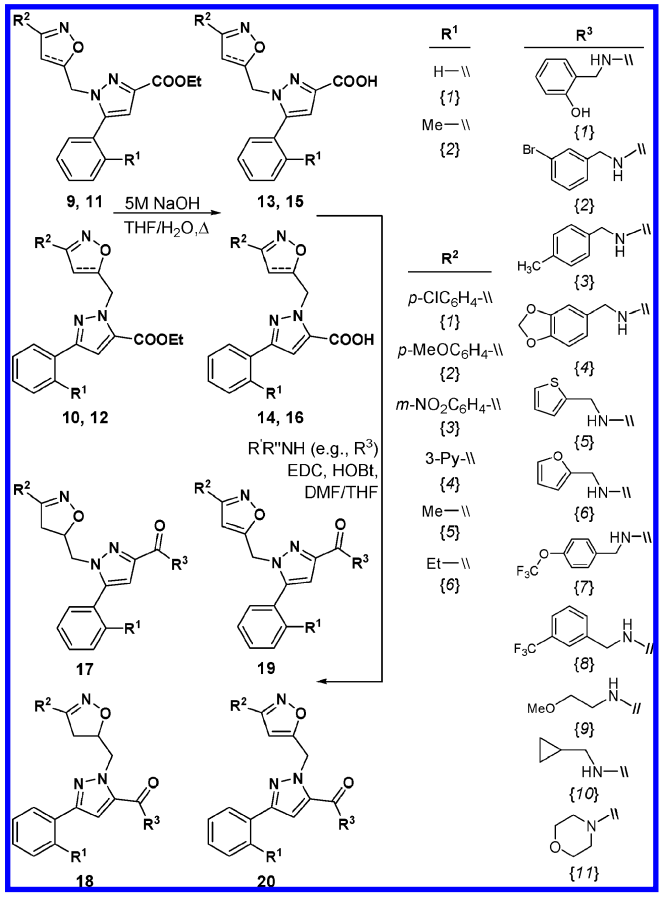
Since aliphatic hydroximoyl chlorides are known to be less stable and prone to dimerization,[21] the purification of aliphatic hydroximoyl chlorides is often not practical. Therefore, a modified Mukaiyama method (Strategy 3)[22] was utilized to synthesize isoxazoline-CH_2-pyrazole **9**{*1,5*} where R^2 is a methyl group. Catalytic triethylamine together with stoichiometric 1,4-diisocyanatobenzene were used to generate the nitrile oxide from nitroethane. Concomitant 1,3-dipolar cycloaddition delivered **9**{*1,5*} in excellent isolated yield (95%). This method was also employed to synthesize 1-(isoxazol-5-yl)methyl-5-aryl-1*H*-pyrazole-3-carboxylate **11** (61−97% yield) and 1-(isoxazol-5-yl)methyl-3-aryl-1*H*-pyrazole-5-carboxylate **12** (63−82% yield) from alkynes **6** and **7**, respectively.

It is of note that only one isoxazol(in)e regioisomer was obtained in all of these cycloadditions as confirmed by ^{1}H NMR. Moreover, X-ray crystallographic analysis of **9**{*1,1*} (Figure 4) established that the 1,3-dipolar cycloaddition reaction afforded the expected 3,5-disubstituted isoxazoline. By spectroscopic analogy, all of the reported 1,3-dipolar cycloadditions proceeded with complete regioselectivity,

Table 2. Nitrile Oxide Cycloadducts **9**, **10**, **11**, and **12**

compd	R^1	R^2	strategy	yield (%)	compd	R^1	R^2	strategy	yield (%)
9{*1,1*}	H	*p*-ClC_6H_4	1	62	**10**{*1,4*}	H	3-Py	1	52
9{*1,2*}	H	*p*-$MeOC_6H_4$	2A	57	**10**{*2,2*}	Me	*p*-$MeOC_6H_4$	2B	80
9{1,3}	H	*m*-$NO_2C_6H_4$	1	51	**10**{*2,4*}	Me	3-Py	1	68
9{1,3}	H	*m*-$NO_2C_6H_4$	2B	89	**11**{*1,5*}	H	Me	3	97
9{*1,4*}	H	3-Py	1	58	**11**{*1,6*}	H	Et	3	76
9{*1,5*}	H	Me	3	95	**11**{*2,5*}	Me	Me	3	73
9{*2,2*}	Me	*p*-$MeOC_6H_4$	2B	72	**11**{*2,6*}	Me	Et	3	61
9{*2,3*}	Me	*m*-$NO_2C_6H_4$	2B	78	**12**{*1,5*}	H	Me	3	82
9{*2,4*}	Me	3-Py	1	53	**12**{*1,6*}	H	Et	3	74
10{*1,2*}	H	*p*-$MeOC_6H_4$	2B	76	**12**{*2,5*}	Me	Me	3	74
10{*1,3*}	H	*m*-$NO_2C_6H_4$	1	67	**12**{*2,6*}	Me	Et	3	63

Scheme 4. Diversity Inputs and Preparation of Isoxazol(in)e-CH_2-pyrazole Libraries

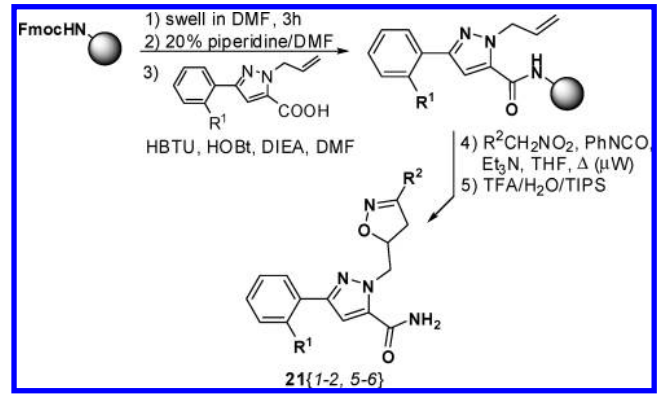


giving only the 3,5-disubstituted isoxazol(in)e. This regioselectivity is also consistent with similar results reported by others.[22,23] The nitrile oxide cycloaddition yields for all the scaffolds are summarized in Table 2.

It is notable that complete chlorination of the pyrazole at C4 can be achieved with sulfuryl chloride (2.1 equiv) in glacial acetic acid.[24] However, under these conditions, pyrazole chlorination of **9**−**12** is complicated by concomitant chlorination of the anisole (R^2 = *p*-$MeOC_6H_4$) and isoxazole rings.

The final step in isoxazol(in)e-CH_2-pyrazole library formation is ester to amide conversion. Direct methods, for example, treatment of **10**{*1,4*} with 2-methoxybenzyl-amine in EtOH at 80 °C under microwave irradiation, resulted in no amide formation as judged by LC-MS analysis. Therefore, an ester to acid to amide (Scheme 4) method was employed. The requisite acids were obtained in nearly quantitative yield

Scheme 5. Solid-Phase Variant-Synthesis of 1°-Amide **21**



by saponification of the corresponding esters (**9**, **10**, **11**, and **12**) with aqueous sodium hydroxide in THF. Subsequent acid → amide conversion with 11 amines employing EDC-mediated coupling conditions in solution phase[25] delivered the targeted amides in 87−99% crude yield and 85−98% crude purity. Purification by preparative HPLC delivered 10+ mg of each isoxazol(in)e-CH_2-pyrazole carboxamide. All compounds were characterized by analytical LC/MS to ensure purity (>90%), as well as to confirm compound identity. ^{1}H NMR analysis of 20 random members of the library confirmed their correct structures (see Experimental Section and Supporting Information). One hundred thirty-six isoxazol(in)e-CH_2-pyrazole carboxamides have been synthesized by this process.

With this solution-phase route in hand, we set out to demonstrate this chemistry on solid-phase. As outlined in Scheme 5, Rink-amide resin was swollen in DMF, and the Fmoc-amine deprotected with 20% piperidine. 1-Allyl-3-aryl-1*H*-pyrazole-5-carboxylic acid was coupled to the resulting Rink-amine resin, which was then divided into two pyrex vessels. A different commercially available nitroalkane was added to each, and 1,3-dipolar cycloaddition with a Mukaiyama-generated nitrile oxide was conducted under microwave irradiation at 80 °C for 45 min. Subsequent treatment of each vessel with TFA cleaved the targeted isoxazoline-CH_2-pyrazole compound from the resin as the unsubstituted amide [e.g., R-C(=O)NH_2; **21**{*1*−*2,5*−*6*}]. The overall yields for the four compounds prepared on solid-phase by this four-step method from Rink-amide resin ranged from 83−92%.

A common practice for lead generation libraries is to use Lipinski's rule-of-five[26] as a guideline for input design. This 140 compound library was designed using the concepts of Lipinski's rule-of-five in addition to Dow AgroSciences' in

house filters derived from Tice.[27] A subset of the library, 60 compounds from the **17**−**20** collection, was screened for herbicide, fungicide, and insecticide activity according to recently published protocols.[28] Unfortunately, none of the analogues demonstrated consequential biological activity across the three therapeutic areas. The lack of herbicide activity is perhaps not surprising, since none of these compounds have an acidic moiety, a feature common to most herbicides to impart phloem mobility. However, the lack of insecticidal and fungicidal activity was disappointing, and may, at least in part, be a reflection of the physical properties of the compounds. This may be related to the effects of poor physical properties on translocation, absorption, and metabolism, thus limiting the expression of in vivo biological activity. Therefore, 13 truncated analogues with a carboxylic acid moiety (Scheme 4, compounds **13**−**16**) were screened. These compounds exhibited weak herbicidal activity, and again no insecticidal activity or fungicidal activity was observed. Future efforts to reduce the lipophilicity of these isoxazol(in)e-CH_2-pyrazole derivatives will omit the aryl substituent on the pyrazole core as well as limit the survey to carboxylate derivatives in attempt to improve the physical/lead-like properties of these novel heterocycles.

Conclusions

In conclusion, a high-throughput, parallel, solution-phase route to biologically relevant isoxazol(in)e-CH_2-pyrazole bis-heterocycles has been developed. The regioselectivity outcomes of the pyrazole *N*-alkylation and nitrile oxide 1,3-dipolar cycloaddition steps were determined by X-ray crystallography. The methods can be extended to include microwave-assisted solid-phase methods, which proceed in good overall yield and within short reaction times. Using these methods on solid-phase in conjunction with one-bead/one-compound combinatorial strategies and high-throughput screening will allow large libraries to be synthesized and rapidly screened. The resulting isoxazol(in)e-CH_2-pyrazole amide library has been transferred to the NIH for pilot-scale biomedical studies with assay data being available via the PubChem database. A subset of this library was screened broadly by Dow AgroScience, but the majority of these compounds were inactive (herbicide, fungicide and insecticide HTS screens).

Experimental Section

General Procedures. All chemicals were purchased from commercial suppliers and used without further purification. Analytical thin layer chromatography was carried out on precoated plates (silica gel 60F254, 250 μm thickness) and visualized with UV light. Flash column chromatography was performed with silica gel 60 (230−400 mesh) or using CombiFlash on SiO_2. ^{1}H NMR spectra were recorded at 400 or 600 MHz at ambient temperature. ^{13}C NMR spectra were recorded at 100 or 150 MHz at ambient temperature. Chemical shifts are reported in parts per million relative to $CDCl_3$ (^{1}H, δ 7.26; ^{13}C, δ 77.26), CD_3OD (^{1}H, δ 3.31; ^{13}C, δ 49.00), or $(CD_3)_2SO$ (^{1}H, δ 2.50; ^{13}C, δ 39.52). Infrared spectra were recorded on a FTIR spectrophotometer (Mattson Genesis II). Melting points were determined with an EZMelt Automated Melting Point Apparatus (Stanford Research Systems). The specifications of the LC/MS are as follows: electrospray (+) ionization, mass range 150−1500 Da, 20 V cone voltage, and Xterra MS C18 column (2.1 mm × 50 mm × 3.5 ìm). The specifications on the preparative HPLC are as follows: 15 mL/min flow rate, Xterra MS C_{18} column (19 × 100 mm), and dual wavelength absorbance detector. In microwave mediated reactions, the temperature was maintained using Personal Chemistry Emrys Optimizer EXP microwave reactor, which heated the sealed samples to 80 °C in 25 s, and then maintained that temperature for the duration of the 45 min reaction. Concentration refers to rotary evaporation under reduced pressure. Rink Amide-MBHA resin (0.59 mmol/g loading, 100−200 mesh) was purchased from Tianjin Nankai Hecheng Sci & Tech. Co., Ltd., (batch number GRMH0808). After each solid-phase step, the resin was washed by sequential treatment with the following solvents: DMF (2 × 5 mL), H_2O (2 × 5 mL), CH_3OH (3 × 5 mL), and CH_2Cl_2 (5 × 5 mL).

General Procedure for *N*-Alkylation in NaH/THF System: Ethyl 1-allyl-5-phenyl-1*H*-pyrazole-3-carboxylate (4{*1*}) and ethyl 1-allyl-3-phenyl-1*H*-pyrazole-5-carboxylate (5{*1*}). Ethyl 3-phenyl-1*H*-pyrazole-5-carboxylate **3**{*1*} (638 mg, 2.95 mmol) was added to NaH (60% dispersion in mineral oil; 144 mg, 3.54 mmol) in anhydrous THF (70 mL) and refluxed for 30 min. Allyl bromide (535 mg, 4.43 mmol) was added, and the resulting solution refluxed for a further 6 h. The reaction was monitored by TLC and was determined to be completely converted to product. The mixture was cooled to room temperature, and water (100 mL) was added. The product was extracted with Et_2O (2 × 75 mL), dried ($MgSO_4$), filtered, and evaporated to dryness. The crude oil was purified by CombiFlash on silica gel with eluent hexane/EtOAc, 2:1. The first eluted is ethyl 1-allyl-3-phenyl-1*H*-pyrazole-5-carboxylate (**5**{*1*}) (pale-yellow oil, 75 mg, 10% yield): IR (neat) 3063, 2942, 2984, 1719, 1607, 1539, 1505, 1450, 1431, 1368, 1253, 1204, 1084, 990, 917, 759, 692 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81−7.83 (m, 2H), 7.40−7.42 (m, 2H), 7.31−7.34 (m, 1H), 7.16 (s, 1H), 6.04−6.11 (m, 1H), 5.23−5.24 (m, 2H), 5.20 (dq, J = 10.2, 1.2 Hz, 1H), 5.13 (dq, J = 17.4, 1.2 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.8, 150.4, 133.7, 133.6, 132.8, 128.9, 128.3, 125.9, 117.6, 108.5, 61.3, 54.4, 14.5; ESIMS *m*/*z* 257.13 $(M + H)^+$; Purity was determined to be 96% by HPLC analysis on the basis of absorption at 214 nm. The second eluted is ethyl 1-allyl-5-phenyl-1*H*-pyrazole-3-carboxylate (**4**{*1*}) (pale-yellow oil, 651 mg, 86% yield). IR (neat) 3134, 3063, 2983, 2937, 1714, 1606, 1469, 1446, 1424, 1380, 1243, 1204, 1100, 1027, 992, 922, 761, 699 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24−7.29 (m,5H), 6.69 (s, 1H), 5.80−5.86 (m, 1H), 5.03 (dd, J = 10.2, 1.2 Hz, 1H), 4.81(dd, J = 17.4, 1.2 Hz, 1H), 4.65−4.67 (m, 2H), 4.25 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.7, 145.4, 143.4, 133.2, 129.8, 129.3, 129.1, 129.0, 118.2, 109.2, 61.2, 53.0, 14.7; ESIMS *m*/*z* 257.13 $(M + H)^+$; Purity was determined to be 100% by HPLC analysis on the basis of absorption at 214 nm.

General Procedure for *N*-Alkylation in K_2CO_3/MeCOMe System: Ethyl 5-phenyl-1-(prop-2-ynyl)-1*H*-pyrazole-3-carboxylate (6{*1*}) and ethyl 3-phenyl-1-(prop-2-ynyl)-1*H*-pyrazole-5-carboxylate (7{*1*}). To a solution of ethyl 3-phenyl-1*H*-pyrazole-5-carboxylate **3**{*1*} (3.9 g, 18 mmol) in acetone (75 mL) was added K_2CO_3 (7.6 g, 54 mmol) and propargyl bromide solution (80 wt % in toluene) (5.4 g, 36 mmol). The reaction mixture was heated to 70 °C for 6.5 h. The reaction mixture was cooled, and the solvent was removed to give a crude residue. The residue was taken into EtOAc, and filtered to remove undissolved particles. The filtrate was dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude solid was purified by CombiFlash on silica gel with eluent hexane/EtOAc, 2:1. The first eluted is ethyl 3-phenyl-1-(prop-2-ynyl)-1*H*-pyrazole-5-carboxylate (**7**{*1*}) (off-white solid, 3.7 g, 81% yield): mp 83−84 °C; IR (neat) 3216, 3134, 3063, 2990, 2942, 2119, 1717, 1542, 1507, 1470, 1454, 1430, 1369, 1317, 1294, 1262, 1204, 1094, 959, 943, 773, 756, 695 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.79−7.80 (m, 2H), 7.34−7.37 (m, 2H), 7.26−7.28 (m, 1H), 7.11 (s, 1H), 5.35 (d, $J = 3.0$ Hz, 2H), 4.30 (q, $J = 7.2$ Hz, 2H), 2.42 (t, $J = 3.0$ Hz, 1H), 1.32 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5, 150.8, 133.5, 132.4, 128.9, 128.5, 125.8, 108.7, 78.2, 73.6, 61.5, 41.8, 14.4; ESIMS *m*/*z* 255.10 $(M + H)^+$; Purity was determined to be 100% by HPLC analysis on the basis of absorption at 214 nm. The second eluted is ethyl 5-phenyl-1-(prop-2-ynyl)-1*H*-pyrazole-3-carboxylate (**6**{*1*}) (off-white solid, 754 mg, 17% yield): mp 102−103 °C; IR (neat) 3227, 3149, 3069, 2984, 2941, 2119, 1711, 1475, 1449, 1419, 1372, 1341, 1312, 1256, 1218, 1167, 1109, 1026, 1000, 946, 838, 822, 781, 755, 721, 686 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.24−7.34 (m, 5H), 6.65 (s, 1H), 4.76 (d, $J = 2.4$ Hz, 2H), 4.19 (q, $J = 7.2$ Hz, 2H), 2.34 (t, $J = 2.4$ Hz, 1H), 1.19 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.1, 145.2, 143.6, 129.4, 129.1, 129.0, 128.8, 109.1, 77.6, 74.8, 61.1, 40.7, 14.5; ESIMS *m*/*z* 255.10 $(M + H)^+$; Purity was determined to be 94% by HPLC analysis on the basis of absorption at 214 nm.

General Procedure for Isoxazoline Synthesis (Strategy 2B): Ethyl 1-((3-(3-nitrophenyl)-4,5-dihydroisoxazol-5-yl)methyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (9{*1,3*}). Compound **4**{*1*} (317 mg, 1.24 mmol) and *N*-hydroxy-3-nitrobenzimidoyl chloride (purified via flash column chromatography on silica gel with 20% EtOAc in hexane, 372 mg, 1.85 mmol) were dissolved in DCM (5 mL) in 25 mL round-bottom flask, and the reaction mixture was cooled to 0 °C and placed under nitrogen. Triethylamine (513 μL, 3.72 mmol) was added to the reaction mixture via syringe. The reaction mixture was allowed to warm to room temperature and vigorously stirred overnight. After washing with water, the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by CombiFlash on silica gel with eluent hexane/EtOAc in gradient to give the product **9**{*1,3*} as pale-yellow solid (461 mg, 89% yield): mp 108−109 °C; IR (neat) 3073, 2995, 2938, 2162, 1733, 1526, 1479, 1458, 1443, 1391, 1350, 1246, 1205, 1112, 1034, 923, 889, 760, 739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.36 (t, $J = 1.8$ Hz, 1H), 8.24− 8.26 (m, 1H), 7.96−7.98 (m, 1H), 7.57 (t, $J = 7.8$ Hz, 1H), 7.43−7.49 (m, 5H), 6.83 (s, 1H), 5.26−5.31 (m, 1H), 4.37 (q, $J = 7.2$ Hz, 2H), 4.35−4.46 (m, 2H), 3.40−3.49 (m, 2H), 1.37 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.4, 155.3, 148.6, 146.7, 143.9, 132.5, 131.0, 130.0, 129.7, 129.6, 129.4, 129.2, 125.0, 121.9, 109.5, 80.0, 61.4, 52.4, 38.1, 14.6; ESIMS *m*/*z* 421.18 $(M + H)^+$; Purity was determined to be 100% by HPLC analysis on the basis of absorption at 214 nm.

General Procedure for Isoxazol(in)e Synthesis (Strategy 3): Ethyl 1-((3-methylisoxazol-5-yl)methyl)-3-phenyl-1*H*-pyrazole-5-carboxylate (12{*1,5*}). 1,4-Phenylene diisocyanate (1.92 g, 12 mmol) was added to **7**{*1*} (1.02 g, 4 mmol) in dry THF (53 mL). Triethylamine (1.67 mL, 12 mmol) was added to the reaction mixture, and this was heated to 45 °C. Nitroethane (862 μL, 12 mmol) was added in syringe pump over a period of 6−8 h, and then the reaction was heated an additional 2 h. The reaction was quenched with water (24 mL) and allowed to stir at room temperature for 1 h. 1,4-Phenylene diisocyanate was removed by filtration over Celite (washing several times with ethyl acetate), and the filtrate was then concentrated and subjected to flash column chromatography (Combiflash, silica gel, hexane/EtOAc in gradient) to afford **12**{*1,5*} as white solid (1.02 g, 82% yield): mp 66−67 °C; IR (neat) 3124, 3058, 2900, 2937, 2901, 1711, 1610, 1544, 1509, 1471, 1454, 1432, 1385, 1360, 1324, 1269, 1205, 1094, 1018, 1004, 957, 886, 828, 797, 782, 760, 747, 689 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.79−7.81 (m, 2H), 7.39−7.41 (m, 2H), 7.31−7.34 (m, 1H), 7.18 (s, 1H), 5.92 (s, 1H), 5.89 (s, 2H), 4.36 (q, $J = 7.2$ Hz, 2H), 2.23 (s, 3H), 1.38 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 160.1, 159.6, 151.3, 134.0, 132.3, 128.9, 128.6, 125.9, 109.0, 103.7, 61.7, 47.4, 14.4, 11.6; ESIMS *m*/*z* 312.12 $(M + H)^+$; Purity was determined to be 98% by HPLC analysis on the basis of absorption at 214 nm.

General Procedure for Solution-Phase Synthesis of Isoxazol(in)e-CH_2-Pyrazole Amides: *N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-((3-(4-methoxyphenyl)-4,5-dihydro isoxazol-5-yl)methyl)-5-phenyl-1*H*-pyrazole-3-carboxamide (17{*1,2,4*}). To a solution of compound **9**{*1,2*} (989 mg, 2.44 mmol) in THF/water (1:1, 20 mL) was added 5 M NaOH (1 mL). The reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was allowed to cool to room temperature. The THF was removed in vacuo, and the remaining aqueous layer was acidified by 2 M HCl to pH 2. The precipitate formed was filtered, washed with water and pentane, and dried in vacuum to give **13**{*1,2*} as a white solid (918 mg, 99% yield): mp 196−197 °C; IR (neat) 2946, 2367, 1725, 1607, 1515, 1445, 1424, 1359, 1253, 1176, 1042, 1013, 826, 786, 766, 698 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 7.52−7.55 (m, 4H), 7.41−7.47 (m, 3H), 6.92−6.94 (m, 2H), 6.74 (s, 1H), 5.14−5.18 (m, 1H), 4.35 (dd, $J = 14.4$, 7.2 Hz, 1H), 4.25 (dd, $J = 14.4$, 5.4 Hz, 1H), 3.82 (s, 3H), 3.47 (dd, $J = 16.8$, 10.2 Hz, 1H), 3.35 (dd, $J = 16.8$, 5.4 Hz, 1H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$) δ 164.2, 161.4, 157.1, 145.7, 130.2, 129.8, 129.5, 129.4, 128.9, 122.1, 114.9, 108.9, 105.0, 79.3, 56.0, 52.9, 38.6; ESIMS *m*/*z* 378.20 $(M + H)^+$; Purity was determined to be 100% by HPLC analysis on the basis of absorption at 214 nm.

The above-obtained free acid (65 mg, 0.17 mmol) was dissolved in DMF (0.7 mL) and THF (1.5 mL). *N*-hydroxybenzotriazole (35 mg, 0.26 mmol), triethylamine (36.4 μL, 0.26 mmol), and *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (50 mg, 0.66 mmol) were added. After the solution was stirred at room temperature for 30 min, benzo[*d*][1,3]dioxol-5-ylmethanamine (79 mg, 0.52 mmol) was added, and the reaction was stirring for 24 h. The resulting reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were washed with aq. sodium bicarbonate, water, 1 M aq. HCl, and brine, dried over sodium sulfate, filtered, and concentrated to give the crude material. Purification by preparative HPLC delivered **17**{*1,2,4*} as a white solid (64 mg, 74% yield): mp 103−104 °C; IR (neat) 3409, 3316, 3063, 2921, 2835, 1661, 1608, 1536, 1516, 1502, 1487, 1442, 1358, 1250, 1177, 1039, 910, 867, 831, 764, 730, 701 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ7.50−7.53 (m, 2H), 7.40−7.49 (m, 5H), 7.10 (brs, NH, 1H), 6.88−6.90 (m, 3H), 6.86 (s, 1H), 6.77−6.82 (m, 2H), 5.95 (s, 2H), 5.13−5.17 (m, 1H), 4.54 (dd, J = 14.4, 6.0 Hz, 1H), 4.48 (dd, J = 14.4, 5.4 Hz, 1H), 4.35 (dd, J = 13.8, 6.0 Hz, 1H), 4.16 (dd, J = 13.8, 6.0 Hz, 1H), 3.83 (s, 3H), 3.37 (dd, J = 16.2, 10.2 Hz, 1H), 3.17 (dd, J = 16.2, 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.0, 161.5, 156.3, 148.1, 147.2, 146.9, 146.4, 132.5, 129.7, 129.5, 129.4, 129.2, 128.5, 121.7, 121.4, 114.4, 108.7, 108.5, 107.4, 101.3, 78.7, 55.6, 52.4, 43.2, 38.8; ESIMS *m/z* 511.25 $(M + H)^+$; Purity was determined to be 98% by HPLC analysis on the basis of absorption at 214 nm.

General Procedure for Solid-Phase Synthesis of Isoxazoline-CH_2-Pyrazole Amide: 1-((3-Methyl-4,5-dihydroisoxazol-5-yl)methyl)-3-*o*-tolyl-1*H*-pyrazole-5-carboxamide (21{*2,5*}). Rink amide resin (375 mg, 0.19 mmol) was swollen in DMF (5 mL) for 3 h, followed by treatment with 20% piperidine in DMF (5 mL) for 20 min. After washing and a positive Kaiser test,[29] 1-allyl-3-*o*-tolyl-1*H*-pyrazole-5-carboxylic acid (137 mg, 0.57 mmol) was coupled using 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (215 mg, 0.57 mmol), *N*-hydroxybenzotriazole hydrate (76 mg, 0.57 mmol), and diisopropylethylamine (98 μL, 0.57 mmol) in DMF (5 mL). After shaking for 10 h, the resin was washed, followed by a negative Kaiser test. The resin was split into two pyrex vessels (∼188 mg each) with one of the pyrex vessel receiving nitroethane (103.2 μL, 1.44 mmol), phenyl isocyanate (313.2 μL, 2.88 mmol), and triethylamine (7.2 μL) in THF (2 mL). The reaction mixture was submitted to microwave irradiation at 80 °C for 45 min. The resin was then washed with DMF, THF, and ether, vacuum-dried, and cleaved with 5 mL of TFA/triisopropylsilane/H_2O (95%/2.5%/2.5%) for 2 h. After this crude reaction product was drained and collected, the cleavage was repeated for an additional 2 h with fresh cleavage reagents. The combined crude cleavages were concentrated to a minimal volume to afford crude **21**{*2,5*}. Purification by preparative HPLC, gave **21**{*2,5*} as a white solid (24 mg, 85% overall yield from Rink resin): mp 44−45 °C; IR (neat) 3335, 3190, 2952, 2922, 1673, 1611, 1535, 1502, 1455, 1434, 1385, 1331, 1169, 959, 764, 729 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.50−7.51 (m, 1H), 7.23−7.28 (m, 3H), 6.73 (s, 1H), 6.42 (brs, NH_2, 1H), 5.88 (brs, NH_2, 1H), 5.05−5.09 (m, 1H), 4.69−4.75 (m, 2H), 3.06−3.07 (m, 2H), 2.47 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.0, 155.8, 151.1, 136.5, 136.0, 132.0, 130.9, 129.1, 128.2, 126.0, 108.0, 78.4, 53.3, 41.6, 21.2, 13.0; ESI-MS *m/z* 299.08 $(M + H)^+$. Purity was determined to be 98% by HPLC analysis on the basis of absorption at 214 nm.

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Supporting Information Available. Detailed synthetic experimental procedures, spectroscopic data, and X-ray crystallography data. This material is available free of charge via the Internet at http://pubs.acs.org.

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