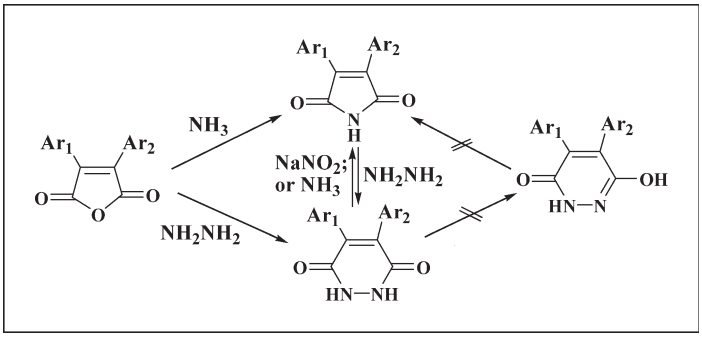
Hsiencheng Shih[1],[a]* Renshuay J. Shih,[b] and Dennis A. Carson[a]

[a]Department of Medicine, University of California, San Diego, La Jolla, California 92093
[b]Pharmatek Laboratories, 7730 Carroll Road, Suite 200, San Diego, California 92121
*E-mail: hsiencheng@sbcglobal.net

Received March 30, 2010
DOI 10.1002/jhet.631
Published online 19 July 2011 in Wiley Online Library (wileyonlinelibrary.com).

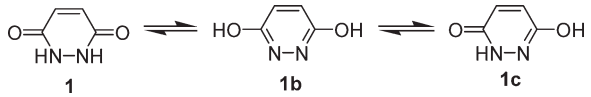


2,3-Diaryl-substituted maleic anhydrides were prepared by a modified one-pot synthesis of Perkin condensation using mixed sodium salts of arylglyoxylic acid and arylacetic acid with acetic anhydride in 1,4-dioxane. The treatment of these anhydrides with ammonium bicarbonate, or methanolic hydrazine, offered the corresponding 2,3-diaryl-substituted maleimides and maleic hydrazides (4,5-diaryl-substituted 1,2-dihydropyridazine-3,6-dione), respectively. Evidence obtained from NMR, UV, and mass spectra suggest that 2,3-diaryl-substituted maleic hydrazides do not exhibit monolactim forms. Ring contraction of the diaryl-substituted maleic hydrazide by nitrosation led to the formation of the corresponding maleimide. Interconversion between the corresponding maleic hydrazide and maleimide was observed following equilibrium reaction. Our experiment proposes that the chemistry of 2,3-diaryl-substituted maleic hydrazides rarely involves the function of ethylene moiety and resembles that of succinic hydrazine.

J. Heterocyclic Chem., **48**, 1243 (2011).

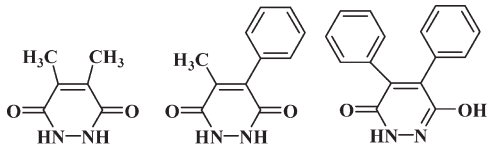
INTRODUCTION

Maleic hydrazide (1,2-dihydropyridazine-3,6-dione, **1**) is a well-known plant growth regulator [2] due to its ability to inhibit glycogen synthase [3]. The growth inhibiting activity of **1** has been demonstrated to be associated with its free radical intermediate, formed readily by oxidation [4]. Although analysis of **1** by NMR indicates that it favors the aromatic form of 3,6-dihydroxypyridazine **1b**, studies by ESR spectroscopy suggest it exists almost entirely in the monolactim form, 6-hydroxypyridazin-3(2*H*)-one, **1c** [4]. Due to the tautomeric isoforms, the relative acidity of the hydroxyl proton in maleic hydrazine offers beneficial properties in the design of bioactive compounds [5].



1 **1b** **1c**

Currently, only a few compounds of 2,3-disubstituted maleic hydrazides have been reported in literature and are suggested to favor specific monolactim forms. Of those reported, such as 2,3-dimethyl (**2**, mp 347–351°C) [6], 2-methyl-3-phenyl (**3**, mp 322–326°C) [7] and the notable monolactim form, 2,3-diphenyl maleic hydrazide (**4**, mp 350°C) [8], none have been previously characterized by NMR.



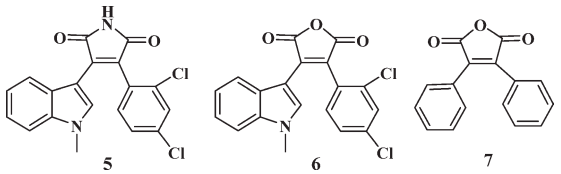
2 **3** **4**

Our research involved an interest in synthesizing a series of 2,3-diaryl substituted maleic hydrazides for their role as potential glycogen synthase kinase-3 inhibitors, as they potentially hold therapeutic benefits for treatments of Type II diabetes, neurodegenerative diseases such as Alzheimer's disease, and certain forms of cancer [9–11]. The current results of our research introduces novel information regarding the preparation and chemistry of 2,3-diaryl-substituted maleic hydrazides.

RESULTS AND DISCUSSION

It is well-known that one of the options for preparing maleimide is from the reaction of maleic anhydride with

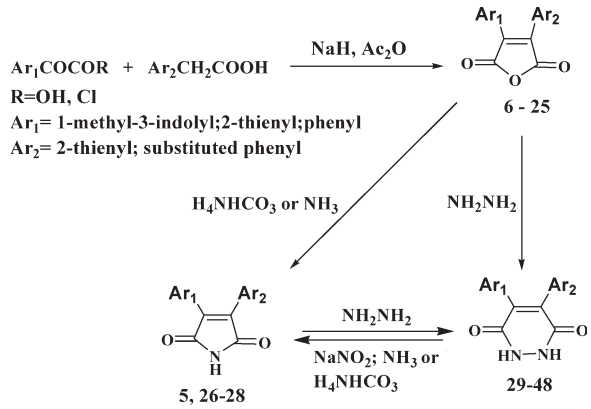
an amine [12]. Originally, we were interested in synthesizing a reference maleimide, **5** (SB216763) [10], for biological study from its corresponding anhydride, 2-(2,4-dichlorophenyl)-3-(1-methyl-3-indolyl)maleic anhydride, **6**. In 1992, Davis *et al*, reported the synthesis of a series of diaryl-substituted maleic anhydrides and maleimides [13]. However, in using their procedure, we were unable to isolate **6** from a small scale reaction (400 mg) of 1-methyl-3-indolylglyoxylyl chloride with 2,4-dichlorophenylacetic acid, using Et_3N as a base in dichloromethane [13]. The use of stronger bases such as sodium methoxide, potassium t-butoxide, and sodium hydride in THF at 60–100°C, did not increase the isolation of the desired product, **6**, in the same scale reaction.



5 6 7

In 1941, Koelsch and Wawzonek [12] investigated various routes for anhydride formations and reported an improved method of synthesizing diphenylmaleic anhydride, **7**. Their procedure involved a Perkin condensation of the sodium or potassium salt of benzoylformic acid with substituted phenylacetic acid in acetic anhydride. In 1990, Fields *et al*. [14] prepared several hundred grams of a series of diaryl-substituted maleic anhydrides in high yields by following Koelsch and Wawzonek's procedure with some modification. Using this modification, we were also able to obtain a 40% yield of **7,** while using a smaller scale reaction (250 mg of benzoylformic acid). Our analysis of the Perkin condensation, which refluxes the sodium or potassium salt of one acid with another acid in acetic anhydride, found that the mixed salts of both acids can be formed during the reaction. Accordingly, we developed a new modified one-pot synthesis by refluxing a mixture of benzoylformic acid (250 mg), phenylacetic acid (1.0 molar equiv), and NaH (2.5 molar equiv) in 1,4-dioxane for 30 min, followed by addition of an excess acetic anhydride (6 molar equiv) with continuous reflux overnight. As a result, our process granted a 69% yield of the desired product, **7**, without a need to prepare the sodium or potassium salt of arylglyoxylic or arylacetic acid in advance. It is important to note that 1-methyl-3-indolylglyoxylic acid and 2,4-dichlorophenylacetic acid are bulky compounds and will cause steric hindrance during the subsequent condensation reaction. With this limitation, however, we were able to obtain **6** in a yield of 11% using a small scale reaction (400 mg) by following this same procedure. This convenient modified one-pot procedure provided a yield up to 86% for a series

Scheme 1. Synthesis of diaryl-substituted maleic anhydrides, imides, and hydrazides.

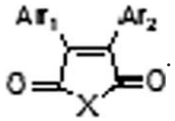


of 2,3-diaryl-substituted maleic anhydrides, **8–25** (Scheme 1; Table 1). We observed that the presence of electron withdrawing groups, such as NO_2 or Cl, may activate the α-hydrogen of arylacetic acid and then enhance condensation to increase the yield of product. The yields of resulting products were observed in the order of para- > meta- > ortho-substitution moieties of phenylacetic acid in small-scale synthesis.

Subsequently, the reference maleimides, **5** (SB216763) [10] and **26–28** (Scheme 1; Table 1), were prepared from the reaction of the corresponding maleic anhydrides with methanolic ammonium bicarbonate (6 equiv), or anhydrous ammonia in a steel bomb at 100°C. The NMR spectra of **5**, and **26–28** appeared very similar to those of the corresponding maleic anhydrides, **6–9**, except for the appearance of an imide proton peak around δ11.2 (Fig. 1). In 1970, Berry and Burawoy [8] reported the synthesis of 6-hydroxy-4,5-diphenylpyridazine-3(2*H*)-one, **4**, mp 350°C, a monolactim form of 2,3-diphenylmaleic hydrazide. They obtained this compound by heating **7** and hydrazine hydrochloride in dilute hydrochloride (5 mL) and water (60 mL), in a Carius tube at 185°C for 12 h. Unfortunately, their results did not include evidence of an NMR spectrum for characterization of the product. In our experiment, the treatment of **7** with anhydrous hydrazine (3 molar equiv) and methanol in a steel bomb at 100°C offered a product with a much lower melting point, 216–217°C. In accordance with similar NMR chemical shift patterns to **7**, except for a single peak near δ4.9 due to the protons of hydrazide (Fig. 1), we assigned the product as 2,3-diphenylmaleic hydrazide, **29**. This simple method permitted us to synthesize a series of diaryl-substituted maleic hydrazides, **30–48,** with good yields (Scheme 1; Table 1). The NMR spectra of **30–48** were also in excellent similarity with those of the corresponding maleic anhydrides with the exception of protons pertaining to hydrazides (Fig. 1).

Table 1

Synthesis of diaryl-substituted maleic anhydrides, imides, and hydrazides.



Product	Hetero Atom (X)	Ar_1	Ar_2	Yield%
5	NH	2,4-$Cl_2C_6H_3$	1-CH_3-3-indolyl	75[a]
6	O	2,4-$Cl_2C_6H_3$	1-CH_3-3-indolyl	11
7	O	C_6H_5	C_6H_5	67
8	O	C_6H_5	3,4-$(HC_3O)_2C_6H_3$	40
9	O	C_4H_3S	C_4H_3S	42
10	O	C_4H_3S	C_6H_5	86
11	O	C_4H_3S	2-ClC_6H_4	23
12	O	C_4H_3S	2-$CH_3OC_6H_4$	15
13	O	C_4H_3S	2-$CH_3C_6H_4$	14
14	O	C_4H_3S	2-$NO_2C_6H_4$	18
15	O	C_4H_3S	3-ClC_6H_4	52
16	O	C_4H_3S	3-$CH_3OC_6H_4$	40
17	O	C_4H_3S	3-$CH_3C_6H_4$	28
18	O	C_4H_3S	3-$NO_2C_6H_4$	35
19	O	C_4H_3S	3-ClC_6H_4	43
20	O	C_4H_3S	4-$CH_3OC_6H_4$	36
21	O	C_4H_3S	4-$CH_3C_6H_4$	36
22	O	C_4H_3S	4-$NO_2C_6H_4$	69
23	O	C_4H_3S	2,4-$Cl_2C_6H_3$	36
24	O	C_4H_3S	3,4-$(CH_3O)_2C_6H_3$	42
25	O	C_4H_3S	1-CH_3-3-indolyl	13
26	NH	C_6H_5	C_6H_5	95[a]
27	NH	C_6H_5	3,4-$(CH_3O)_2C_6H_3$	42[b]
28	NH	C_6H_3S	C_4H_3S	68[a]
29	NHNH	C_6H_5	C_6H_5	80
30	NHNH	2,4-$Cl_2C_6H_3$	1-CH_3-3-indolyl	75
31	NHNH	C_6H_5	3,4-$(CH_3O)_2C_6H_3$	72
32	NHNH	C_4H_3S	C_4H_3S	95
33	NHNH	C_4H_3S	C_6H_5	64
34	NHNH	C_4H_3S	2-ClC_6H_4	32
35	NHNH	C_4H_3S	2-$CH_3OC_6H_4$	64
36	NHNH	C_4H_3S	2-$CH_3C_6H_4$	95
37	NHNH	C_4H_3S	2-$NO_2C_6H_4$	54
38	NHNH	C_4H_3S	3-ClC_6H_4	48
39	NHNH	C_4H_3S	3-$CH_3OC_6H_4$	71
40	NHNH	C_4H_3S	3-$CH_3C_6H_4$	89
41	NHNH	C_4H_3S	3-$NO_2C_6H_4$	59
42	NHNH	C_4H_3S	3-ClC_6H_4	58
43	NHNH	C_4H_3S	4-$CH_3OC_6H_4$	95
44	NHNH	C_4H_3S	4-$CH_3C_6H_4$	72
45	NHNH	C_4H_3S	4-$NO_2C_6H_4$	94
46	NHNH	C_4H_3S	2,4-$Cl_2C_6H_3$	54
47	NHNH	C_4H_3S	3,4-$(CH_3O)_2C_6H_3$	44
48	NHNH	C_4H_3S	1-CH_3-3-indolyl	95

[a] Method B-1.
[b] Method B-2.

The UV absorption characteristics of diaryl-substituted maleic hydrazides are comparable to their corresponding maleic anhydrides and imides (Fig. 2) suggesting that they have similar chromophores.

Under further electron impact study, the strong characteristic peak of a molecular ion with the same mass in

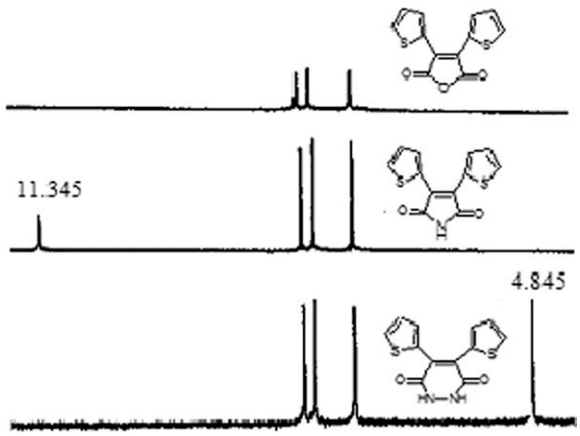


Figure 1. NMR spectra of the corresponding diaryl-substituted maleic anhydride, imide, and hydrazide.

the pattern of $[Ar_1{-}C{\equiv}C{-}Ar_2]^{+\bullet}$ was found in the mass spectra of the corresponding maleic anhydrides, imides, and hydrazides (Fig. 3). The identical $[Ar_1{-}C{\equiv}C{-}Ar_2]^{+\bullet}$ pattern seen in the ions are the result of cleavages between the diaryl-substituted ethylene moiety and the rest of the heterocycle with loss of

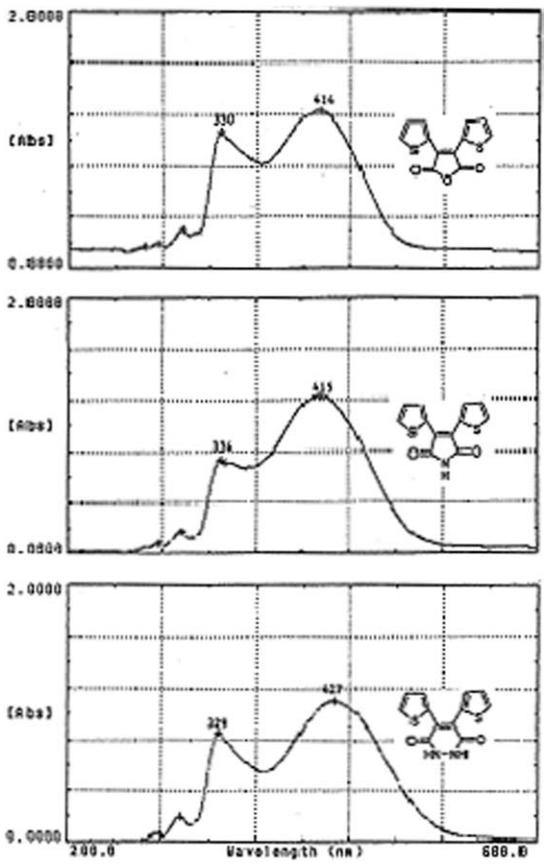


Figure 2. UV spectra of the corresponding diaryl-substituted maleic anhydride, imide, and hydrazide.

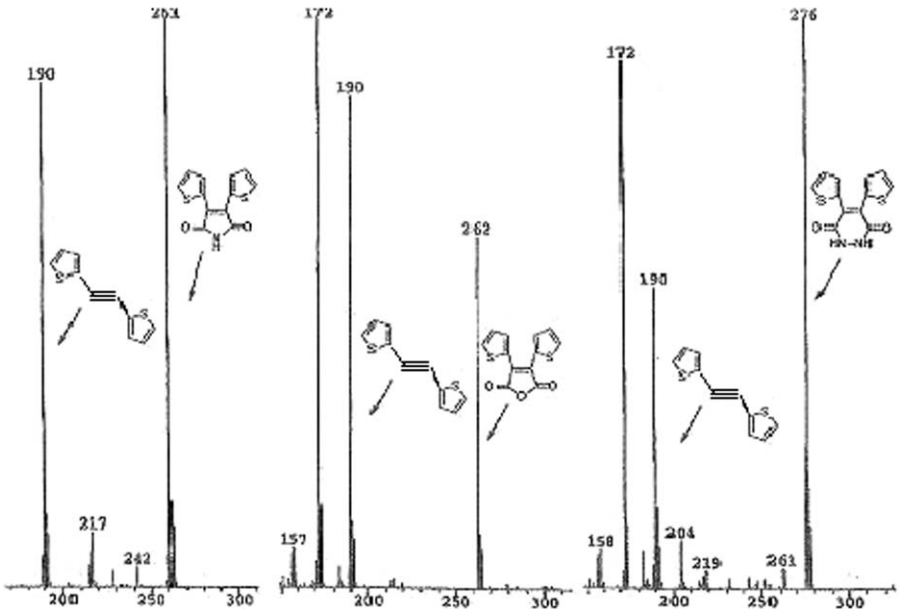


Figure 3. Mass spectra of the corresponding diaryl-substituted maleic anhydride, imide, and hydrazide.

$C_2O_3^{+\bullet}$,$C_2O_2NH^{+\bullet}$, and $C_2O_2N_2H_2^{+\bullet}$, in the aforementioned corresponding structures, respectively (Fig. 4). The data obtained from NMR, UV, and mass spectra for the corresponding maleic anhydrides, imides, and hydrazides, do not reveal information of hydroxyl group and suggest that the 2,3-diaryl-substituted maleic hydrazides do not demonstrate the monolactim form.

In addition to the previous information obtained from NMR, UV, and mass spectra, the melting point of **4** was significantly different from that of **29**. The variation in melting points may theoretically allow separation of both products if produced in the same reaction. Consequently, **4** and **29** should not be classified as tautomeric isomers, contrasting **1, 1b,** and **1c**. Furthermore, it is possible that a product of diphenyldiazoquinone, **49**, could be generated via further oxidation [15] of **29** during the reaction conditions used to generate **4** [8], which would be followed by hydration to form a di-monolactim bishydrazide [16], **50** (Scheme 2). The elemental analysis of this hypothesized compound, **50** (C, 73.0; H, 4.2; N, 10.6), closely follows the reported characteristic of **4** (C, 72.6; H, 4.6; N, 10.7) [8]. As a result, we deduce that **4** is not a monolactim form of **29,** but a bishydrazide, **50**.

In studying the chemical functions of diaryl-substituted maleic hydrazides, compounds **29–32** were treated with 1.2 equiv. of $NaNO_2$ with 30% HOAc in CH_2Cl_2 at room temperature, but did not result in the production of nitroso products. Instead, the chemical shift patterns of the products were in excellent agreement with those of the corresponding maleimides, **5**, and **26–28**. The proposed mechanism for this reaction suggests that the mono-nitroso hydrazine is formed initially by electrophilic attack of nitrosonium cation, which is then followed by the ring contraction and concomitant formation of the corresponding maleimides (Scheme 3).

Under hydrogenolysis using 10% palladium on carbon, these maleic hydrazide moieties remained intact, but the nitro group present on the phenyl ring were reduced to an amino group (δ4.77, 2H, NH; 5.74, 2H, NH_2). The steric interference of the diaryl substituents may play an important role in preventing the approach of hydrogen on the ethylene moiety. Treatment of these diaryl-substituted maleic hydrazides with methyl iodide in the presence of NaH offered mono or dialkyl maleic hydrazides as detected by mass spectra. These results indicate that the N—N bond of these compounds do not exhibit tautomerism as seen in pyridazine-3,6-diol, **1b**, or its monolatim form, **1c**, and are vulnerable to electrophiles, such as alkylating agents. Additionally, the

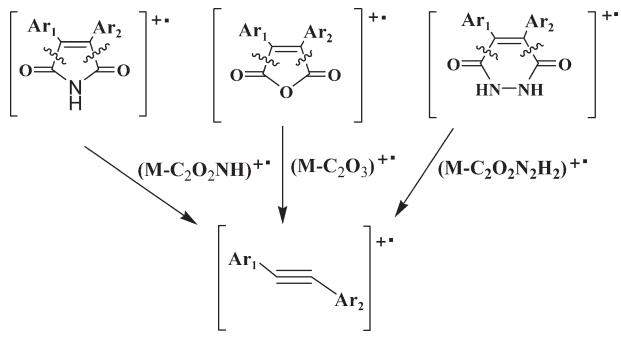
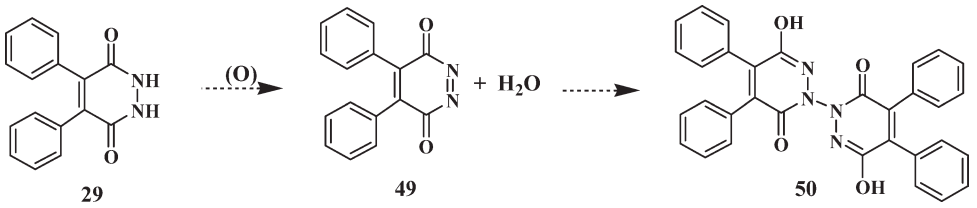


Figure 4. The pattern of molecular ions in the mass spectra of the corresponding maleic imides, anhydrides, and hydrazides.

Scheme 2. Proposed formation of hypothesized bishydrazide 50.



corresponding maleic hydrazides and maleimides are interconvertable in an equilibrium condition during the treatment of maleic hydrazide with methanolic ammonium bicarbonate, or vice versa in the treatment of maleimide with methanolic hydrazine at 60–100°C (Scheme 1). The intermediate was identified by mass spectroscopy as 2,3-diaryl-4-hydrazino-4-oxobut-2-enamide. These 2,3-diaryl-substituted maleic hydrazides have lower melting points than **4** and their solubility in dichloromethane make them highly nonpolar. The feasibility of ring-opening reactions induced by nucleophilic or electrophilic reagents should not involve the ethylene moiety function. We believe that the configurations seen in these heterocyclic compounds result from the steric repulsion and influence of strain between the two diaryl substituents, which force out planarity of the aromatic sextet.

In summary, the chemistry of 2,3-diaryl-substituted maleic hydrazides resembles that of succinic hydrazine. They react readily with oxidants, alkylating agents, other electrophiles, and nucleophiles. Currently, we are investigating further into the chemical and biological activities of diaryl-substituted maleic hydrazides.

EXPERIMENTAL

Melting points were taken on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR spectra were obtained from Varian 500-MHz. Mass spectra were recorded by a Hewlett-Packard 5890 GCMS instrument operated at 70 eV ionizing energy at the Mass Spectrometry Facility, University of California, Riverside, CA. A DB-5 capillary column was used for the sample introduction. All chemicals including 2-thiopheneglyoxylic acid (95%) were purchased from Aldrich Chemical Company and used without further purification.

General procedures. ***2,3-Diaryl-substituted maleic anhydrides (3,4-diarylfuran-2,5-dione).*** To a mixture of arylglyoxylic acid (200–400 mg,1 molar equiv) and arylacetic acid (1 molar equiv) in dry 1,4-dioxane (60 mL), NaH (2.5 molar equiv) was added and stirred at 100°C for 30 min. Acetic anhydride (5 molar equiv) was introduced dropwise to the resulting suspension with stirring overnight. After cooling, the reaction mixture was evaporated *in vacuo*. The residue was dissolved in ethyl acetate (50 mL) and washed twice with water. The organic phase was dried and evaporated. The residue was chromatographed on silica gel with a mixture of 30% hexane in dichloromethane to give desired product, or added small amount of methanol (20 mL) to yield solidified product.

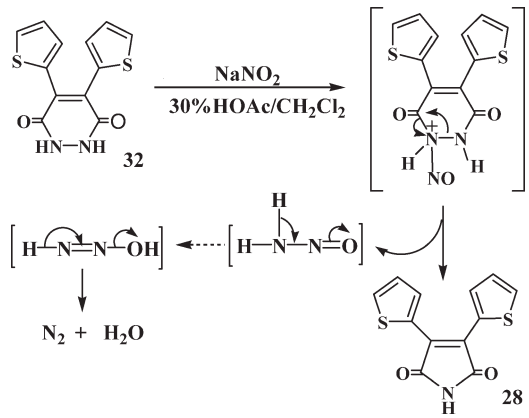
2,3-Diaryl-substituted maleimides (3,4-diaryl-1H-pyrrole-2,5-dione). A mixture of 2,3-diarylmaleic anhydride (200–400 mg, 1 molar equiv) and anhydrous ammonium bicarbonate (6 molar equiv), or saturated anhydrous NH_3 in methanol (40 mL), was heated overnight in a stainless steel bomb at 100°C. After cooling, the reaction mixture was evaporated, dissolved in EtOAc (50 mL) and washed with water. The organic phase was dried over anhydrous magnesium sulfate and evaporated. The residue was chromatographed on silica gel with a mixture of 1% acetone in dichloromethane to give the desired product.

$NaNO_2$ (1.2 equiv.) was added slowly to a mixture of 2,3-diaryl-substituted maleic hydrazine (20–100 mg) in 10 mL of 30% HOAc in CH_2Cl_2 with stirring at RT for 30 min to 1 h. The reaction mixture was evaporated. The residue in ethyl acetate (50 mL) was washed twice with water and dried over anhydrous $MgSO_4$ and then evaporated. The residue was chromatographed on silica gel with a mixture of 1% acetone in dichloromethane to give the product.

2,3-Diaryl-substituted maleic hydrazides (4,5-Diaryl-1,2-dihydropyridazine-3,6-dione). A mixture of 2,3-diarylmaleic anhydride (200–400 mg, 1 molar equiv) and anhydrous hydrazine (3 molar equiv) in methanol (50 mL) was heated in a stainless steel bomb at 100°C overnight. After cooling, the resulting crystals were collected. The remaining solution was evaporated. The residue was chromatographed on silica gel with a mixture of 2% acetone in dichloromethane to give another crop of product.

3-(2,4-Dichlorophenyl)-4-(1-methyl-1H-indol-3-yl)-1H-pyrrole-2,5-dione (SB216763) (5) [10,17]. Mp 195–197°C; MS m/z, 370 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H, CH_3), 6.32 (d, 1H, C4H), 6.78 (t, 1H, C6H), 7.12 (t, 1H, C5H), 7.35–7.50 (m, 3H, C7H, C′5H, & C′6H), 7.71 (s, 1H, C′3H), 8.09 (s, 1H, C2H), 11.17 (s, 1H, NH).

Scheme 3. The proposed mechanism for the conversion of diaryl-substituted maleic hydrazide to imide.



3-(2,4-Dichlorophenyl)-4-(1-methyl-1H-indol-3-yl)furan-2,5-dione (6) [17] Mp 163–165°C; ^{1}H NMR (DMSO-d_6) δ 6.33 (d, 1H, C4H), 6.83 (t, 1H, C6H), 7.19 (t, 1H, C5H), 7.48 (d, 1H, C7H), 7.50–7.56 (m, 2H, C′5H, C′6H), 7.80 (s, 1H, C′3H), 8.29 (s, 1H, C2H).

3,4-Diphenylfuran-2,5-dione (7) [18] Mp 148–150°C; MS m/z, 250 (M^+); ^{1}H NMR (DMSO-d_6) δ 7.40–7.50 (m, 10 H, phenyl protons).

3-(3,4-Dimethoxyphenyl)-4-phenylfuran-2,5-dione (8) [14]. Mp 111–113°C; MS m/z, 310 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.46 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 6.92 (s, 1H, C′2H), 7.04 (d, 1H, C′5H), 7.18 (d, 1H, C′6H), 7.42-7.50 (m, 5H, phenyl protons).

3,4-Di-2-thienylfuran-2,5-dione (9) [14] Mp 110-113°C; MS m/z, 262 (M^+); ^{1}H NMR (DMSO-d_6) δ 7.27 (t, 2H, C4H), 7.82 (d, 2H, C5H), 7.98 (d, 2H, C3H).

3-Phenyl-4-(2-thienyl)furan-2,5-dione (10) [14]. Mp 145-147 °C; MS m/z, 256 (M^+); ^{1}H NMR (DMSO-d_6) δ 7.19 (t, 1H, C4-H), 7.50–7.60 (m, 5H, phenyl protons), 7.73 (d, 1H, C5H), 7.91 (d, 1H, C3H).

3-(2-Chlorophenyl)-4-(2-thienyl)furan-2,5-dione (11). Mp 118-119 °C; MS m/z, 290 (M^+); ^{1}H NMR (DMSO-d_6) δ 7.23 (t, 1H, C4H), 7.52-7.58 (m, 2H, C′4H, C′6H), 7.63 (t, 1H, C′5H), 7.70-7.74 (m, 2H, C3′H, C5H), 7.98 (d, 1H, C3H); Anal. Calcd. for $C_{14}H_7ClO_3S$: C, 57.84; H, 2.43; S, 11.03. Found: C, 58.23; H, 2.82; S, 10.84.

3-(2-Methoxyphenyl)-4-(2-thienyl)furan-2,5-dione (12). Mp 125–126°C; MS m/z, 286 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.70 (s, 3H, CH_3O), 7.13 (t, 1H, C4H), 7.15-7.23 (m, 2H, C′3H, C′5H), 7.37 (d, C′6H), 7.56 (t, 1H, C′4H), 7.71 (d, 1H, C5H), 7.93 (d, 1H, C3H); Anal. Calcd. for $C_{15}H_{10}O_4S$: C, 62.93; H, 3.52. Found: C, 62.56; H, 3.85.

3-(2-Methylphenyl)-4-(2-thienyl)furan-2,5-dione (13). Mp 109–110°C; MS m/z, 270 (M^+); ^{1}H NMR (DMSO-d_6) δ 2.14 (s, 3H, CH_3), 7.19 (t, 1H, C4H), 7.31-7.48 (m, 4H, C′3H, C′4H, C′5H, C′6H), 7.62 (d, 1H, C5H), 7.92 (d, 1H, C3H); Anal. Calcd. for $C_{15}H_{10}O_3S$: C, 66.65; H, 3.73. Found: C, 66.41; H, 4.14.

3-(2-Nitrophenyl)-4-(2-thienyl)furan-2,5-dione (14). Mp 144–145°C; MS m/z, 301 (M^+), ^{1}H NMR (DMSO-d_6) δ 7.22 (t, 1H, C4H), 7.72 (d, 1H, C5H), 7.75 (d, 1H, C′6H), 7.92 (t, 1H, C′4H), 7.98 (d, 1H, C3H), 8.01 (t, 1H, C′5H), 8.42 (d, 1H, C′3H); Anal. Calcd. for $C_{14}H_7NO_5S$: C, 55.81; H, 2.34; N, 4.65. Found: C, 55.44; H, 2.10; N, 4.60.

3-(3-Chlorophenyl)-4-(2-thienyl)furan-2,5-dione (15). Mp 90–91°C; MS m/z, 290 (M+); 1H NMR (DMSO-d_6) δ 7.21 (t, 1H, C4H), 7.49 (d, 1H, C′4H), 7.58–7.77 (m, 3H, C′2H, C′5H, C′6H), 7.76 (d, C5H), 7.95 (d, 1H, C3H); Anal. Calcd. for $C_{14}H_7ClO_3S$: C, 57.84; H, 2.43. Found: C, 57.98; H, 2.34.

3-(3-Methoxyphenyl)-4-(2-thienyl)furan-2,5-dione (16). Mp 99–100°C; MS m/z, 286 (M+); ^{1}H NMR (DMSO-d_6) δ 3.76 (s, 3H, CH_3O), 7.07–7.09 (m, 2H, C′2H, C′4H), 7.11-7.14 (m, 1H, C′6H), 7.20 (t, 1H, C4H), 7.48 (t, 1H, C′5H), 7.76 (d, 1H, C5H), 7.92 (d, 1H, C3H); Anal. Calcd. for $C_{15}H_{10}O_4S$.0.1Hexane: C, 62.77; H, 3.97. Found: C, 62.94; H, 4.05.

3-(3-Methylphenyl)-4-(2-thienyl)furan-2,5-dione (17). Mp 105–106°C; MS m/z, 270 (M^+); ^{1}H NMR (DMSO-d_6) δ 2.35 (s, 3H, CH_3), 7.19 (t, 1H, C4H), 7.30 (d, 1H, C′4H), 7.32 (s, 1H, C′2H), 7.37 (d, 1H, C′6H), 7.44 (t, 1H, C′5H), 7.75 (d, 1H, C5H), 7.90 (d, 1H, C3H); Anal. Calcd. for $C_{15}H_{10}O_3S$: C, 66.65; H, 3.73. Found: C, 66.60; H, 3.97.

3-(3-Nitrophenyl)-4-(2-thienyl)furan-2,5-dione (18). Mp 141-143 °C; ^{1}H NMR (DMSO-d_6) δ 7.22 (t, 1H, C4H), 7.77 (d, 1H, C5H), 7.89 (t, 1H, C5′H), 7.94–7.99 (m, 2H, C3H, C′6H), 8.41 (s, 1H, C′2H), 8.42 (d, 1H, C′4H); Anal. Calcd. for $C_{14}H_7NO_5S$: C, 55.81; H, 2.34; N, 4.65. Found: C, 55.86; H, 2.35; N, 4.57.

3-(4-Chlorophenyl)-4-(2-thienyl)furan-2,5-dione (19). Mp 124–126°C; MS m/z, 290 (M^+); ^{1}H NMR (DMSO-d_6) δ 7.20 (t, 1H, C4H), 7.55 (d, 2H, C′2H, C′6H), 7.64 (d, 2H, C′3H, C′5H), 7.75 (d, 1H, C5H), 7.93 (d, 1H, C3H); Anal. Calcd. for $C_{14}H_7ClO_3S$: C, 57.84; H, 2.43. Found: C, 57.52; H, 2.51.

3-(4-Methoxyphenyl)-4-(2-thienyl)furan-2,5-dione (20). Mp 124–126°C; MS m/z, 286 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H, CH_3O), 7.10 (d, 2H, C′3H, C′5H), 7.19 (t, 1H, C4H), 7.50 (d, 2H, C′2H, C′6H), 7.76 (d,1H, C5H), 7.89 (d, 1H, C3H); Anal. Calcd. for $C_{15}H_{10}O_4S$.0.2H_2O: C, 62.14; H, 3.62. Found: C, 61.84; H, 3.52.

3-(4-Methylphenyl)-4-(2-thienyl)furan-2,5-dione (21). Mp 139–140°C; MS m/z, 270 (M^+); ^{1}H NMR (DMSO-d_6) δ 2.39 (s, 3H, CH_3), 7.19 (t, 1H, C4H), 7.36 (d, 2H, C3′H, C′5H), 7.42 (d, 2H, C′2H, C′6H), 7.45 (d, C5H), 7.90 (d, 1H, C3H); Anal. Calcd. for $C_{15}H_{10}O_3S$.0.1 H_2O: C, 66.21; H, 3.78. Found: C, 66.18; H, 3.47.

3-(4-Nitrophenyl)-4-(2-thienyl)furan-2,5-dione (22). Mp 143–144°C; MS m/z, 301 (M^+); 1H NMR (DMSO-d_6) δ 7.22 (t, 1H, C4H), 7.73 (d, 1H, C5H), 7.81 (d, 2H, C′2H, C′6H), 7.97 (d, 1H, C3H), 8.41 (d, 2H, C′3H, C′5H); Anal. Calcd. for $C_{14}H_7NO_5S$: C, 55.81; H, 2.34; N, 4.65. Found: C, 55.80; H, 2.16; N, 4.64.

3-(2,4-Dichlorophenyl)-4-(2-thienyl)furan-2,5-dione (23). Mp 140–141°C; MS m/z, 324 (M^+); ^{1}H NMR (DMSO-d_6) δ 7.25 (t, 1H, C4H), 7.57 (d, 1H, C′5H), 7.69 (d, 1H, C′6H), 7.76 (d, 1H, C5H, 7.94 (d, 1H, C3H), 8.01 (s, 1H, C′3H); Anal. Calcd. for $C_{14}H_6Cl_2O_3S$: C, 51.71; H. 1.86. Found: C, 51.55; H, 2.08.

3-(3,4-Dimethoxyphenyl)-4-(2-thienyl)furan-2,5-dione (24). Mp 184–185°C; MS m/z, 316 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.69 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 7.11 (s,1H, C′2H), 7.14 (bs, 2H, C′5H, C′6H), 7.2 (t,1H, C4H), 7.81 (d,1H, C5H), 7.89 (d,1H, C3H); Anal. Calcd. for $C_{16}H_{12}O_5S$: C, 60.75; H, 3.82. Found: C, 60.40; H, 3.54.

3-(1-Methyl-1H-indol-3-yl)-4-(2-thienyl)furan-2,5-dione (25) [13]. Mp 122–124°C; ^{1}H NMR (DMSO-d_6) δ 3.94 (s, 3H, CH_3), 6.75 (d, 1H, C′4H), 6.70 (t, 1H, C′6H), 7.11 (t, 1H, C4H), 7.24 (t, 1H, C′5H), 7.31 (d, 1H, C5H), 7.59 (d, 1H, C′7H), 7.85 (d, 1H, C3H), 8.08 (s,1H, C′2H).

3,4-Diphenyl-1H-pyrrole-2,5-dione (26) [19]. Mp 214–216°C; ^{1}H NMR (DMSO-d_6,) δ 7.36 (m, phenyl), 11.21 (NH).

3-(3,4-Dimethoxyphenyl-4-phenyl-)-1H-pyrrole-2,5-dione (27). Mp 207–208°C; MS m/z, 309 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.46 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 6.87 (s, 1H, C′2H), 6.95 (d, 1H, C′5H), 7.07 (d, 1H, C′6H), 7.32–7.42 (m, 5H, phenyl protons), 11.4 (s, 1H, NH), Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N4.53. Found: C, 70.09; H, 5.13; N, 4.31.

3,4-Di-2-thienyl-1H-pyrrole-2,5-dione (28). Mp 200–202°C; MS m/z, 261 (M^+); ^{1}H NMR (DMSO-d_6) δ 7.19 (t, 2H, C4H), 7.71 (d, 2H, C5H), 7.87 (d, 2H, C3H), 11.35 (s, 1H, NH); Anal. Calcd. for $C_{12}H_7NO_2S_2$.0.1H_2O: C, 54.80; H, 2.76; N, 5.33. Found: C, 54.78; H, 3.09; N, 5.34.

4,5-Diphenyl-1,2-dihydropyridazine-3,6-dione (29). Mp 216–217°C; MS m/z, 264 (M^+); ^{1}H NMR (DMSO-d_6) δ 4.87

(s, 2H, NH), 7.26–7.43 (m, 10H, phenyl protons); Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.67. Found: C, 72.37; H, 4.98; N, 10.67.

4-(2,4-Dichlorophenyl)-5-(1-methyl-1H-indol-3-yl)-1,2-dihydropyridazine-3,6-dione (30). Mp 256–258°C; MS m/z, 385 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H, CH_3), 4.89 (s, 2H, NH), 6.33 (d, 1H, C4H), 6.77 (t, 1H, C6H).7.13 (t, 1H, C5H), 7.37 (d, 1H, C7H), 7.39-7.49 (m, 2H, C′5H, C′6H), 7.72 (s, 1H, C′3H), 8.13 (s, 1H, C2H); Anal. Calcd. for $C_{19}H_{13}N_3Cl_2O_2$: C, 59.09; H, 3.39; N, 10.88. Found: C, 58.83; H, 3.46; N, 10.53.

4-(3,4-Dimethoxyphenyl)-5-phenyl-1,2-dihydropyridazine-3,6-dione (31). Mp 171–173°C; MS m/z, 324 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.46 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.84 (s, 2H, NH), 6.86 (s, 1H, C′2H), 6.98 (d, 1H, C′5H), 7.10 (d, 1H, C′6H), 7.3-7.5 (m, 5H, phenyl protons); Anal. Calcd. for $C_{18}H_{16}N_2O_2.0.25\ H_2O$: C, 65.73; H, 5.06; N, 8.52. Found: C, 65.85; H, 5.18; N, 8.64.

4,5-Di-2-thienyl-1,2-dihydropyridazine-3,6-dione (32). Mp 194–196°C; MS m/z, 276 (M^+); ^{1}H NMR (DMSO-d_6) δ 4.85 (s, 2H, NH), 7.21 (t, 2H, 2C4H), 7.73 (d, 2H, 2C5H), 7.88 (d, 2H, 2C3H); Anal. Calcd. for $C_{12}H_8N_2O_2S_2$: C, 52.16; H, 2.92; N, 10.14; S, 23.2. Found: C, 51.96; H, 3.30; N, 10.23; S, 22.82.

4-Phenyl-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (33). Mp 194–196°C; MS m/z, 270 (M^+); ^{1}H NMR (DMSO-d_6) δ 4.85 (s, 2H, NH), 7.11 (t, 1H, C4—H), 7.43–7.46 (m, 2H, C′3H, C′5H), 7.48–7.53 (m, 3H, C′2H, C′4H, C′6H), 7.63 (d, 1H, C5H), 7.79 (d, 1H, C3H); Anal. Calcd. for $C_{14}H_{10}N_2O_2S.0.2\ H_2O$: C, 61.39; H, 3.83; N, 10.23. Found: C, 61.49; H, 4.15; N, 10.48.

4-(2-Chlorophenyl)-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (34). Mp 194–195°C; MS m/z, 304 (M^+); ^{1}H NMR (DMSO-d_6) δ 4.93 (s, 2H, NH), 7.14 (t, 1H, C4H), 7.45-7.52 (m, 2H, C′4H, C′6H), 7.54–7.61 (m, C′3H, C′5H), 7.67 (d, 1H, C5H), 7.83 (d, 1H, C3H), Anal. Calcd. for $C_{14}H_9ClN_2O_2S$: C, 55.26; H, 2.98; N, 9.21. Found: C, 55.13; H, 3.29; N, 9.30.

4-(2-Methoxyphenyl)-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (35). Mp 139–140°C; MS m/z, 300 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.66 (s, 3H, CH_3O), 4.86 (s, 2H, NH), 7.08 (t, 1H, C′5H), 7.11 (t, 1H, C4H), 7.17 (d, 1H, C′3H), 7.25 (d, 1H, C′6H), 7.50 (t, C′4H), 7.60 (d, C5H), 7.77 (d, 1H, C3H); Anal. Calcd. for $C_{15}H_{12}N_2O_3S$: C, 59.98; H, 4.07; N, 9.33. Found: C, 59.62; H, 4.27; N, 9.38.

4-(2-Methylphenyl)-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (36). Mp 187–188; MS m/z, 284 (M^+); ^{1}H NMR (DMSO-d_6) δ 2.14 (s, 3H, CH_3), 4.85 (s, 2H, NH), 7.11 (t, 1H, C4H), 7.23 (d, 1H, C′3H), 7.33 (t, 1H, C′4H), 7.38 (d, 1H, C′6H), 7.41 (t, 1H, C′5H), 7.51 (d, 1H, C5H), 7.77 (d,1H, C3H); Anal. Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.40; H, 4.24; N, 9.91.

4-(2-Nitrophenyl)-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (37). Mp 195–196°C; MS m/z, 315 (M^+); ^{1}H NMR (DMSO-d_6) δ 4.97 (s, 2H, NH), 7.14 (t, 1H, C4H), 7.62 (d, 1H, C5H), 7.70(d, 1H, C′6H), 7.82–7.86 (m, 2H, C′4H, C3H), 7.93 (t, 1H, C′5H), 8.35 (d, 1H, C′3H); Anal. Calcd. for $C_{14}H_9N_3O_4S$: C, 53.33; H, 2.87; N, 13.33. Found: C, 53.20; H, 3.01; N, 13.50.

4-(3-Chlorophenyl)-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (38). Mp 142–144°C; MS m/z, 304 (M^+); ^{1}H NMR (DMSO-d_6) δ 7.14 (t, 1H, C4H), 7.42 (d, 1H, C′6H), 7.5–7.6 (m, 3H, C′2H, C′4H, C′5H), 7.66 (d, 1H, C5H), 7.82 (d, 1H, C3H); Anal. Calcd. $C_{14}H_9ClN_2O_2S$: C, 55.26; H, 2.98; N, 9.21. Found: C, 55.49; H, 3.37; N, 9.34.

4-(3-Methoxyphenyl)-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (39). Mp 142–144°C; MS m/z, 300 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.74 (s, 3H CH_3O), 4.85 (s, 2H, NH), 6.99 (s, 1H, C′2H), 7.0 (d, 1H, C′4H), 7.06 (d, 1H, C′6H), 7.11 (t, 1H, C4H), 7.42 (t, 1H, C′5H), 7.65 (d, 1H, C5H), 7.79 (d, 1H, C3H); Anal. Calcd. for $C_{15}H_{12}N_2O_3S$: C, 59.99; H, 4.03; N, 9.33. Found: C, 60.04; H, 4.15; N, 9.46.

4-(3-Methylphenyl)-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (40). Mp 176–177°C; MS m/z, 284 (M^+); ^{1}H NMR (DMSO-d_6) δ 2.33 (s, 3H, CH_3), δ 4.86 (s, 2H, NH), 7.11 (d, 1H, C4H), 7.20–7.25 (m, 3H, C′2H, C′4H, C′5H), 7.30 (d, 1H, C′6H), 7.64 (d, 1H, C5H), 7.77 (d, 1H, C3H); Anal. Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.11, H, 4.54; N, 9.99.

4-(3-Nitrophenyl)-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (41). Mp 176–178°C; MS m/z, 315 (M^+); ^{1}H NMR (DMSO-d_6) δ 4.90 (s, 2H, NH), 7.15 (d, 1H, C4H), 7.67 (d, 1H, C5H), 7.80–7.84 (m, 2H, C3H, C′5H), 7.93 (d, 1H, C′6H), 8.32–8.38 (m, 2H, C′2H, C′4H); Anal. Calcd. for $C_{14}H_9N_3O_4S$: C, 53.33; H, 2.88; N, 13.33. Found: C, 53.37; H, 2.79; N, 13.07.

4-(4-Chlorophenyl)-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (42). Mp 158–159°C; MS m/z, 304 (M^+); ^{1}H NMR (DMSO-d_6) δ 4.86 (s, 2H, NH), 7.16 (t, 1H, C4H), 7.49 (d, 2H, C′2H, C′6H), 7.59 (d, 2H, C′3H, C′5H), 7.66 (d, 1H, C5H), 7.81 (d, 1H, C3H); Anal. Calcd. for $C_{14}H_9N_2ClO_2S.0.2H_2O$: C, 54.53; H, 3.07; N, 9.08. Found: C, 54.43; H, 3.02; N, 9.00.

4-(4-Methoxyphenyl)-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (43). Mp 153–156°C; MS m/z, 300 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H, CH_3O), 4.83 (s, 2H, NH), 7.06 (d, 2H, C′3H, C′5H), 7.12 (t, 1H, C4H), 7.42 (d, 2H, C′2H, C′6H), 7.66 (d, 1H, C5H), 7.77 (d, 1H, C3H); Anal. Calcd. for $C_{15}H_{12}N_2O_3S$: C, 59.98; H, 4.04; N, 9.33. Found: C, 59.76; H, 4.30; N, 9.36.

4-(4-Methylphenyl)-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (44). Mp 173–175°C; MS m/z, 284 (M^+); ^{1}H NMR (DMSO-d_6) δ 2.37 (s, 3H, CH_3), 7.10 (t, 1H, C4H), 7.30–7.50 (q, 4H, C′2H, C′3H, C′5H, C′′6H), 7.64 (d, 1H, C5H), 7.77 (d, 1H, C3H); Anal. Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.63; H, 4.60; N, 9.71.

4-(4-Nitrophenyl)-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (45). Mp 209–210°C; MS m/z, 315 (M^+); ^{1}H NMR (DMSO-d_6,) δ 4.90 (s, 2H, NH), 7.14 (t, 1H, C4H), 7.63 (d, 1H, C5H), 7.72 (d, 2H, C2′H, C′6H), 7.85 (d, 1H, C3H), 8.37 (d, 2H, C′3H, C′5H); Anal. Calcd. for $C_{14}H_9N_3O_4S$: C, 53.33; H, 2.87; N, 13.33. Found: C, 52.98; H, 3.19; N, 13.42.

4-(2,4-Dichlorophenyl)-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (46). Mp 173–175°C; MS m/z, 338 (M^+); ^{1}H NMR (DMSO-d_6) δ 4.93 (s, 2H, NH), 7.17 (t, 1H, C—4H), 7.52 (d, 1H, C′5H), 7.62 (d, 1H, C′6H), 7.64 (d, 1H, C5H), 7.85 (d, 1H, 3H), 7.88 (s, 1H, C′3H); Anal. Calcd. for $C_{14}H_8N_2Cl_2O_2S$: C, 49.57; H, 2.38; N, 8.26. Found: C, 49.56; H, 2.53; N, 8.17.

4-(3,4-Dimethoxyphenyl)-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (47). Mp 182–184°C; MS m/z, 330 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.67 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.83 (s, 2H, NH), 7.0–7.1 (m, 3H, C′2H, C′5H, C′6H), 7.2 (t, 1H, C4H), 7.81 (d, 1H, C5H), 7.89 (d, 1H, C3H); Anal. Calcd. for

$C_{16}H_{14}N_2O_4S$: C, 58.17; H, 4.27; N, 8.48. Found: C, 57.81; H, 4.22; N, 8.37.

4-(1-Methyl-1H-indol-3-yl)-5-(2-thienyl)-1,2-dihydropyridazine-3,6-dione (48). Mp 210–212°C; MS m/z, 323 (M^+); ^{1}H NMR (DMSO-d_6) δ 4.83 (s, 2H, NH), 6.69 (d, 1H, C′4H), 6.95 (t, 1H, C′6H), 7.03 (t, 1H, C4H), 7.17–7.24 (m, 2H, C′7H, C5H), 7.55 (d, 1H, C′5H), 7.71 (d, 1H, C3H), 7.93 (s, 1H, C2′H); Anal. Calcd. for $C_{17}H_{13}N_3O_2S$: C, 63.54; H, 4.38; N, 12.72; S, 9.65. Found: C, 63.14; H, 4.05; N, 12.99; S, 9.92.

Acknowledgment. An abstract of this article was presented at the 41st ACS Western Regional Meeting (October 9–13, 2007).

REFERENCES AND NOTES

[1] Present address: Quadstar International Corporation, 1250 W. Monte, Mesa, AZ 85202.

[2] Audus, L. J. Plant Growth Substances, 2nd ed.; Hill: London, 1959.

[3] Ozkan, A.; Yanikolu, A. J Appl Entomol 1999, 123, 211.

[4] Holton, D. M.; Hoyle, P. M.; Murphy, D. Tetrahedron Lett 1979, 30, 2821.

[5] Greenwood, J. R; Capper, H. R.; Allan, R. D.; Johnston, G. A. R. J Chem 1988, 1, Article 21.

[6] Horning, R. H.; Amstutz, E. D. J Org Chem 1955, 20, 707.

[7] Bly, R. K.; Zoli, E. C.; Moore, J. A. J Org Chem 1964, 29, 2128.

[8] Berry, R. W. R.; Burawoy, R. A. J Chem Soc C 1970, 1316.

[9] Cross, D. A.; Culbert, A. A.; Chalmers, K. A.; Facci, L.; Skaper, S. D. J Neurochem 2001, 77, 94.

[10] Meijer, L.; Flajolet, M.; Greengard, P. Trends Pharmacol Sci 2004, 25, 241.

[11] Gurwitz, D.; Eldar-Finkelman, H. Drug Discov Today 2001, 6, 1072.

[12] Koelsch, C. F.; Wawzonek, S. J Org Chem 1941, 6, 684.

[13] Davis, P. D.; Hill, C. H.; Lawtom, G.; Nixon, J. S.; Wilkinson, S. E.; Hurst, S. A.; Keech, E.; Turner, S. J Med Chem 1992, 35, 177.

[14] Fields, E. K.; Behrend, S. J.; Meyerson, S.; Winzenburg, M. L.; Ortega, B. R.; Hall, K Jr. J Org Chem 1990, 55, 5165.

[15] Clement, R. A. J Org Chem 1960, 25, 1724.

[16] Kealy, T. J Am Chem Soc 1962, 84, 996.

[17] Coghan, M. P.; Fenwick, A. E.; Haigh, D.; Holder, J. C.; Ife, R. J.; Reith, A. R.; Smith, D. G.; Ward, R.W. (2000) WO 200021927-A2 (cited reference for SB216763, but no data recorded).

[18] Heller, G. Annalen 1908, 358, 355.

[19] Davis, P. D.; Bit, R. A. Tetrahedron Lett 1990, 31, 5201.