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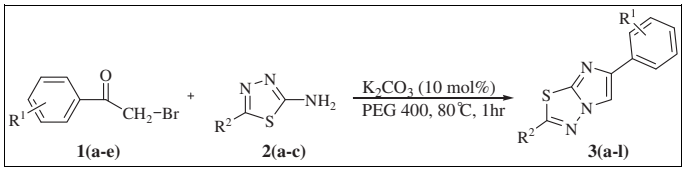

Polyethylene glycol (PEG) was found to be an inexpensive nontoxic and effective medium for the synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazoles in the presence of potassium carbonate as a green base in high yields. In addition, the solvent system can be recovered and reused, making this protocol economically and potentially viable.

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INTRODUCTION

Imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives have been of interest to the medicinal chemists for many years because of their anticancer [1], antitubercular [2], antibacterial [3], antifungal [4], anticonvulsant, analgesic [5], and antisecretory [6] activities. This has generated much interest in the synthesis of these compounds. The most common method of synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazoles is the reaction of 5-*R*-2-amino-1,3,4-thiadiazoles with α-halo ketones [7–9]. However, these reactions are performed in organic solvents at reflux temperatures giving only moderate yields; therefore, this synthetic methodology does not meet the requirement of green chemistry. Also, these methodologies do not provide the possibility of synthesizing a wide range of derivatives of imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives.

Regulatory pressure is increasingly focusing on the use, manufacture, and disposal of organic solvents, and thus, the development of nonhazardous alternatives (one of the several goals of green chemistry and engineering) is vitally important for the continued and sustainable development of the chemical enterprise.

Recently, polyethylene glycol (PEG) is found to be an interesting solvent system. It is being extensively used as a solvent in organic synthesis [10–14]. It has previously been suggested that PEGs could be used as complexing solvents of inorganic salts, to enhance the reactivity of the anion with the organic substrate [15]. In these systems, the anion could be brought into solution with higher reactivity.

In continuation of our studies in developing cheap and environmentally benign methodologies for organic synthesis [16–18], we report our finding that readily available K_2CO_3 as the base, in combination with an eco-friendly solvent PEG-400 is an extremely effective catalytic system for the synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazoles (Scheme 1).

RESULTS AND DISCUSSION

In a model reaction, we used phenacyl bromide **1a** (1 mmol) and 2-aminothiadiazole **2a** (1 mmol) as reactants with ethanol as solvent in the presence of inorganic base such as K_2CO_3 at 80°C and found that imidazo[2,1-*b*]-1,3,4-thiadiazole **3a** could be produced in 62% yield in 6 h (Entry 1, Table 1). To improve the yield and to optimize the reaction conditions, the same reaction was carried out in the presence of PEG-400 as environmentally friendly medium. A tremendous improvement was observed and the yield of **3a** was increased up to 92% after stirring the mixture at 80°C for only 1 h (Entry 5, Table 1). A plausible explanation for such an increase could be that PEGs can be regarded as open-chain crown ethers as they are able to form complexes with alkaline and alkaline-earth cations in protic and aprotic solvents [19]. Various other solvents were tried for the same reaction. The results have been summarized in Table 1.

Our next investigation into an effective synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazoles began with phenacyl bromide **1a** (1 mmol), 2-aminothiadiazole **2a** (1 mmol), and 10 mol % K_2CO_3 and an array of solvents combined with PEG 400. The choice of solvent has a significant impact on the efficiency of the reaction. When the reaction was carried out in PEG/DMSO, PEG/H_2O, and PEG/DMF at 80°C for 12 h scarcely afforded the corresponding imidazo[2,1-*b*]-1,3,4-thiadiazole. When PEG/C_2H_5OH, PEG/toluene, PEG/CH_3CN, or PEG/dioxane systems were used as solvents, the yields of the products were also very low. Evidently, the best solvent for the reaction was pure PEG, which produced 92% of imidazo[2,1-*b*]-1,3,4-thiadiazoles in only 1 h.

We also screened a range of other bases. Na_2CO_3, KOH, and NaOH were found to be effective in the reaction. $K_3PO_4.3H_2O$, KOAc, NaOAc, and Cs_2CO_3 led to acceptable moderate yields of the product, whereas Et_3N was

Scheme 1. Synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazoles.

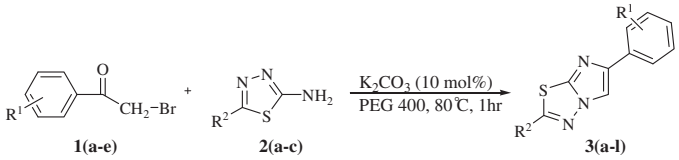

Table 1

Effect of solvents for the synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazoles.[a]

Entries	Solvents	Time (h)	Yield (%)[b]
1	Ethanol	6	62
2	Acetonitrile	6	62
3	Toluene	7	60
4	PEG 200	1	92
5	PEG 400	1	92
6	PEG 600	1	92

[a]Reaction conditions: phenacyl bromide **1a** (1 mmol), 2-aminothiadiazole **2a** (1 mmol); base: K_2CO_3 (10 mol %); temp: 80°C.
[b]Isolated yields.

completely inactive. Finally, K_2CO_3 proved to be the most effective base leading to 92% isolated yield in 1 h (Table 2).

The PEG/K_2CO_3 system was applied to a wide range of substrates to give the products with good to excellent yields (Table 3). A wide array of functional groups were tolerated in the reaction and were not affected by the system.

To check the eco-friendliness of PEG, we recycled PEG 400 for several times. The reaction proceeded cleanly with consistent results, although a weight loss of ~ 5% of PEG 400 was observed from cycle to cycle due to mechanical loss.

CONCLUSIONS

In conclusion, we have developed an effective catalytic system PEG 400/K_2CO_3 for the synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazoles. The methodology is simple, efficient, and environmentally friendly with simple work up. We could reuse our solvent system several times. All these characteristics of our protocol make the reaction quite suitable for scale up and commercialization.

Table 2

Effect of base on the synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazoles.[a]

Entries	Bases	Time (h)	Yield (%)[b]
1	K_2CO_3	1	92
2	$K_3PO_4.3H_2O$	9	77
3	KOAc	3	81
4	KOH	1.5	89
5	Na_2CO_3	1	92
6	$NaHCO_3$	11	62
7	NaOAc	3	79
8	NaOH	1.5	87
9	Cs_2CO_3	9	72
10	Et_3N	14	Trace

[a]Reaction conditions: phenacyl bromide **1a** (1 mmol), 2-aminothiadiazole **2a** (1 mmol); solvent: PEG 400 (1 mL); temp: 80°C.
[b]Isolated yields.

EXPERIMENTAL

Materials and methods. All chemicals were purchased from Sigma-Aldrich and were used as such. All reactions and purity of imidazo[2,1-*b*]-1,3,4-thiadiazoles were monitored by thin-layer chromatography (TLC) using aluminum plates coated with silica gel F_{254} plates; (Merck) using 20% ethyl acetate, 80% petroleum ether as an eluent. The spots were detected either under UV light or by placing in iodine chamber. Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer FTIR-1710 spectrophotometer using KBr as pastilles. ^{1}H-NMR were recorded on a Bruker spectrospin 300 MHz FT NMR system using TMS as an internal standard. Elemental analysis was performed on a Hereaus CHN rapid analyzer. The temperature of the reaction mixture was measured through a noncontact infrared mini gun thermometer (AZ minigun type, model 8868).

General procedure for the synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazoles. In a 50-mL round-bottom flask, phenacyl bromide **1a** (0.1990 g, 1 mmol), 2-aminothiadiazole **2a** (0.1151 g, 1 mmol), and K_2CO_3 (0.0138 g, 10 mol %) in PEG 400 (1 mL)

Table 3

Synthesis of various imidazo[2,1-*b*]-1,3,4-thiadiazoles using PEG/K_2CO_3 system.[a]

Entries	R^2	R^1	Time (h)	M.P (°C)	Yield (%)[b]
3a	Me	H	1	135–137 [20]	92
3b	Me	*p*OMe	1	200–202 [21]	94
3c	Me	*p*Br	1.25	210–212 [21]	90
3d	Me	*o*Cl	1.25	169–171	90
3e	Me	*p*Me	1	158–160 [21]	93
3f	Ph	H	1	206–208 [20]	93
3g	Ph	*p*OMe	1	178–180	96
3h	Ph	*p*Br	1	220–222	94
3i	Ph	*o*Cl	1	154–156	92
3j	*m*BrPh	*p*Me	1.25	274–276	92
3k	*m*BrPh	H	1.25	144–146	94
3l	*m*BrPh	*p*OMe	1.25	260–262	93

[a]Reaction conditions: substituted phenacyl bromide **1(a-e)** (1 mmol), 2-nothiadiazole **2(a-c)** (1 mmol); base: K_2CO_3 (10 mol %); solvent: PEG 400 (1 mL); temp: 80°C.
[b]Isolated yields.

were mixed and stirred at 80°C. The progress of the reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was cooled with a dry ice-acetone bath to precipitate the PEG and extracted with ether (PEG being insoluble in ether). The ether layer was decanted, dried, and concentrated under reduced pressure. The product though seen as a single compound by TLC, was subjected to further purification by silica gel column chromatography using 15% ethyl acetate and 85% hexane as an eluent to yield the products **3**(**a**–**l**). The recovered PEG can be reused for consecutive runs. The structures of all the products were unambiguously established based on their spectral analysis (IR, ^{1}H-NMR, mass spectral and elemental analyses data).

Spectral data for the novel compounds. ***6-(2-Chloro-phenyl)-2-methyl-imidazo[2,1-b][1,3,4]thiadiazole (3d).*** Yellow solid; IR (KBr) ν_{max}: 2924, 1597, 1504, 1474, 1342 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.27 (s, 3H, CH_3), 7.94 (s, 1H, C_5-H imidazole), 7.30–7.62 (m, 4H, Ar-H); MS (EI): *m/z* calcd for $C_{11}H_8ClN_3S$: 249.01; found: 249.013; Anal. Calcd. for $C_{11}H_8ClN_3S$; C, 52.91; H, 3.23; N, 16.83. Found: C, 52.83; H, 3.19; N, 16.89.

6-(4-Methoxy-phenyl)-2-phenyl-imidazo[2,1-b][1,3,4]thiadiazole (3g). White solid; IR (KBr) ν_{max}: 2924, 1638, 1573, 1506, 1391, 1317 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.94–7.42 (m, 9H, Ar-H), 8.02 (s, 1H, C_5-H imidazole), 3.63 (s, 3H, -OCH_3); MS (EI): *m/z* calcd for $C_{17}H_{13}N_3OS$: 307.08; found: 307.078; Anal. Calcd. for $C_{17}H_{13}N_3OS$; C, 66.43; H, 4.26; N, 13.67; found: C, 66.51; H, 4.33; N, 13.59.

6-(4-Bromo-phenyl)-2-phenyl-imidazo[2,1-b][1,3,4]thiadiazole (3h). Light yellow solid; IR (KBr) ν_{max}: 2922, 1603, 1537, 1472, 1346 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34–7.67 (m, 9H, Ar-H), 8.01 (s, 1H, C_5-H imidazole); MS (EI): *m/z* calcd for $C_{16}H_{10}N_3BrS$: 354.98; found: 354.978; Anal. Calcd. for $C_{16}H_{11}N_3BrS$: C, 53.94; H, 2.83; N, 11.80; found: C, 53.99; H, 2.89; N, 11.72.

6-(2-Chloro-phenyl)-2-phenyl-imidazo[2,1-b][1,3,4]thiadiazole (3i). Creamy white solid; IR (KBr) ν_{max}: 2922, 1614, 1560, 1479, 1337 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.27–7.66 (m, 9H, Ar-H), 8.01 (s, 1H, C_5-H imidazole); MS (EI): *m/z* calcd for $C_{16}H_{10}ClN_3S$: 311.03; found: 311.029; Anal. Calcd. for $C_{16}H_{10}ClN_3S$: C, 61.64; H, 3.23; N, 13.48; found C, 61.72; H, 3.19; N, 13.50.

2-(3-Bromo-phenyl)-6-(p-tolyl)-imidazo[2,1-b][1,3,4]thiadiazole (3j). White solid; IR (KBr) ν_{max}: 2922, 1598, 1510, 1482, 1327 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.23 (s, 3H, CH_3), 7.25–7.57 (m, 8H, Ar-H), 7.99 (s, 1H, C_5-H imidazole); MS (EI): *m/z* calcd for $C_{17}H_{12}BrN_3S$: 368.99; found: 368.992; Anal. Calcd. for $C_{17}H_{12}BrN_3S$: C, 55.14; H, 3.27; N, 11.35; found C, 55.21; H, 3.19; N, 11.42.

2-(3-Bromo-phenyl)-6-phenyl-imidazo[2,1-b][1,3,4]thiadiazole (3k). Light brown solid; IR (KBr) ν_{max}: 2924, 1673, 1592, 1537, 1492, 1346 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.28–7.62 (m, 9H, Ar-H), 8.10 (s, 1H, C_5-H imidazole); MS (EI): *m/z* calcd for $C_{16}H_{10}BrN_3S$: 354.98; found: 354.977; Anal. Calcd. for $C_{16}H_{10}BrN_3S$; C, 53.94; H, 2.83; N, 11.80; found C, 53.89; H, 2.75; N, 11.87.

2-(3-Bromo-phenyl)-6-(4-methoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazole (3l). Yellow solid; IR (KBr) ν_{max}: 2924, 1676, 1587, 1534, 1468, 1344 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.62 (s, 3H, OMe), 7.01–7.69 (m, 8H, Ar-H), 8.02 (s, 1H, C_5-H imidazole); MS (EI): *m/z* calcd for $C_{17}H_{12}BrN_3OS$: 384.99; found: 384.987; Anal. Calcd. for $C_{17}H_{12}BrN_3OS$; C, 52.86; H, 3.13; N, 10.88; found C, 52.72; H, 3.21; N, 10.92.

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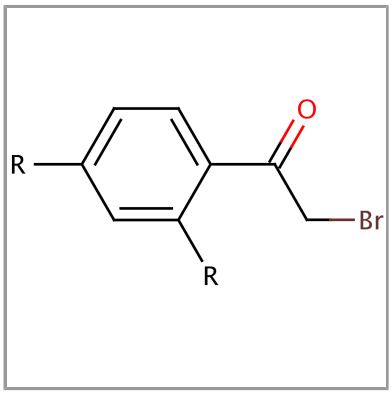

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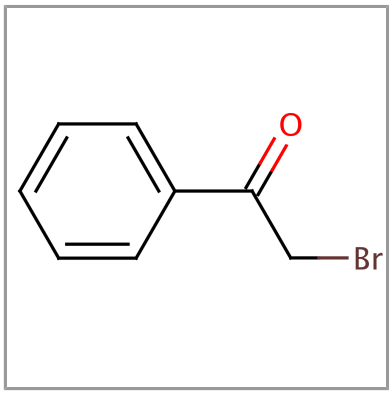

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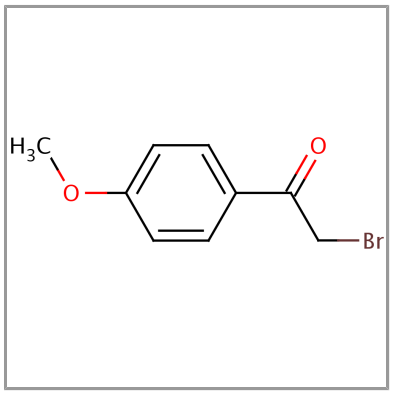

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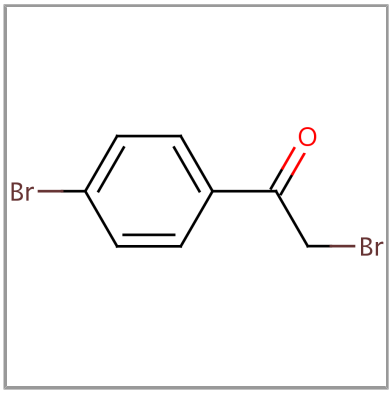

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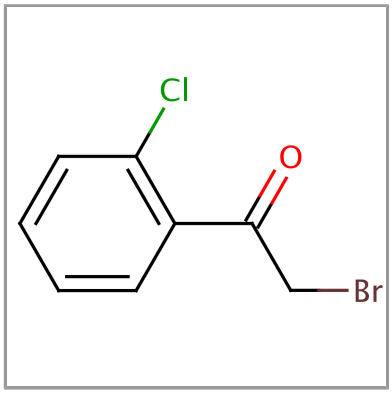

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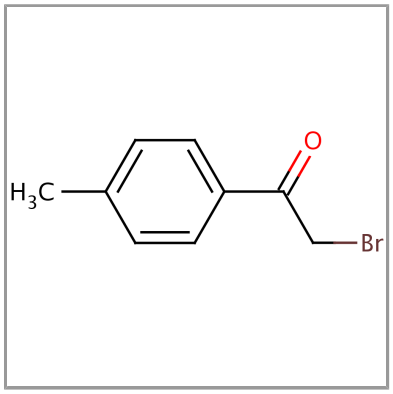

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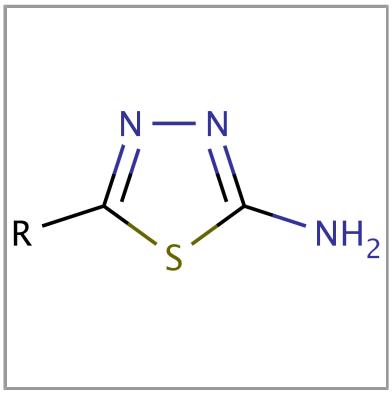

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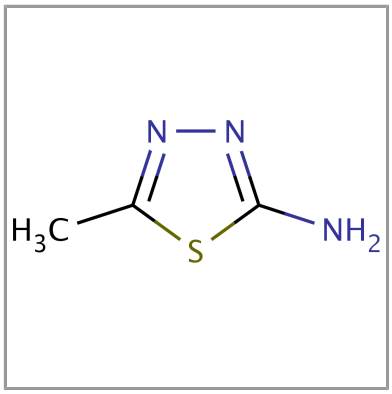

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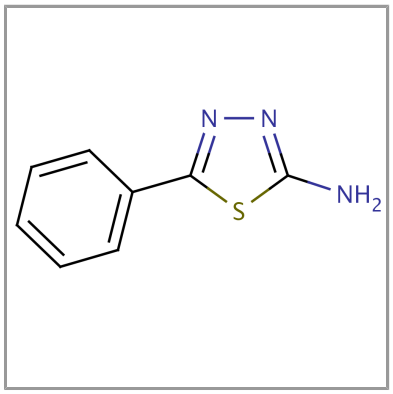

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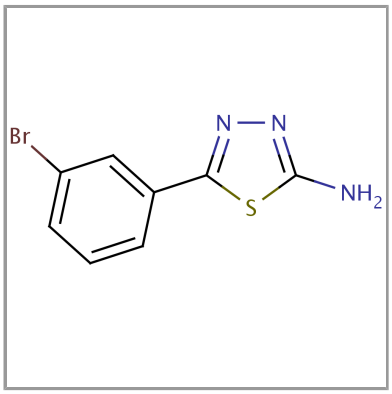

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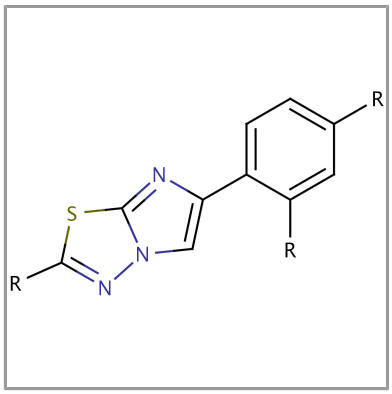

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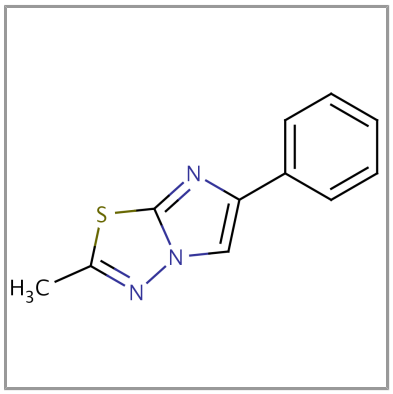

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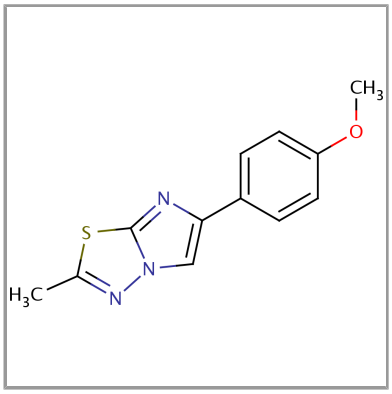

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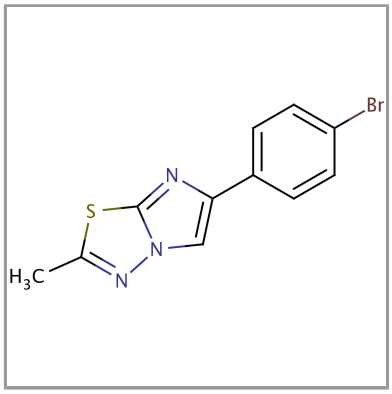

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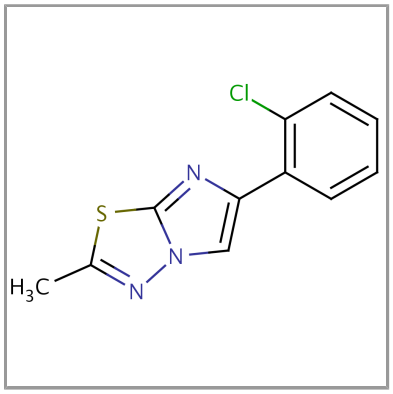

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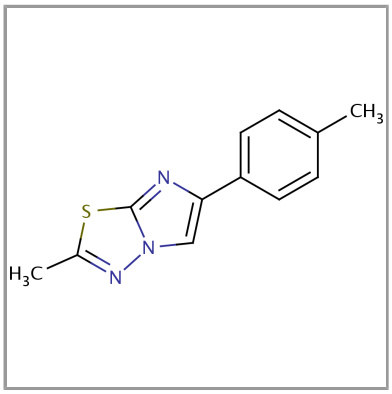

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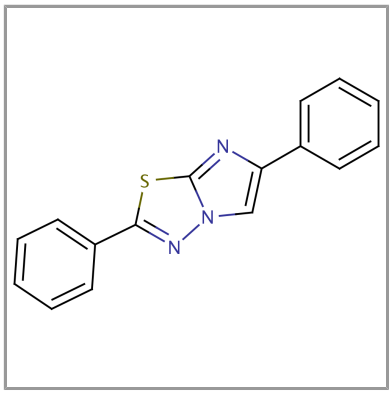

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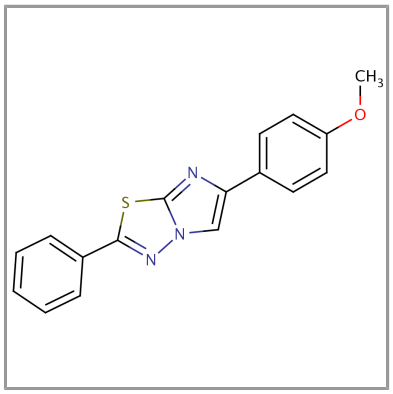

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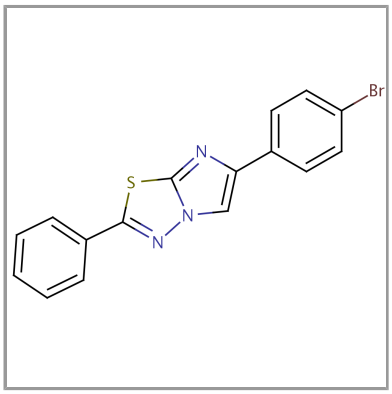
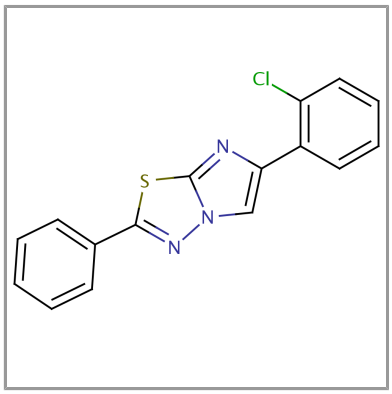


Compound Details Structure Search

3i



Compound Details Structure Search

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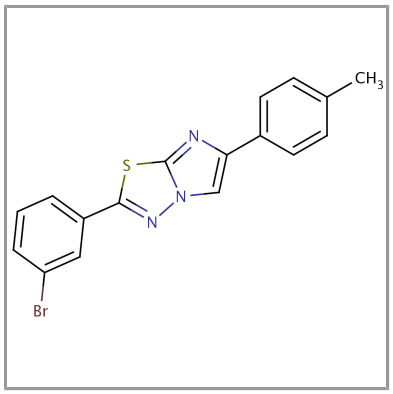

Compound Details Structure Search

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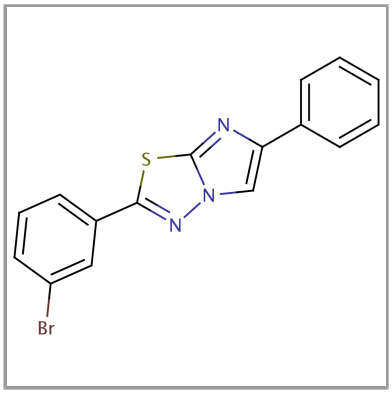
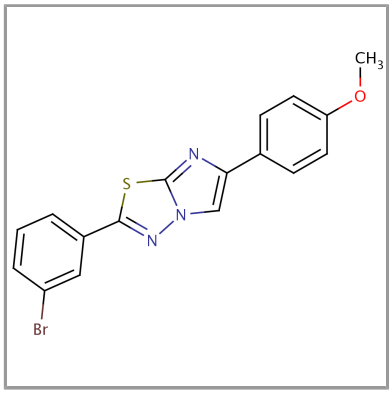


Compound Details Structure Search

3l



Compound Details Structure Search