Design and Synthesis of Novel Sulfone-containing Pyrazolo[1,5-*a*]-pyrimidines and Pyrazolo[5,1-*d*][1,2,3,5]tetrazine-4(3*H*)-ones

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A series of novel sulfone-containing pyrazolo[1,5-*a*]pyrimidines (**2-3**) and pyrazolo[5,1-*d*][1,2,3,5]tetrazine-4(3*H*)-ones (**5a-5k**) were designed and efficiently synthesized, some of which have been identified as being potential rape inhibitors. These results widen the structural diversity of rape inhibitors and confirm the perspectives of further investigations in this area. Moreover, a plausible reaction mechanism is outlined.

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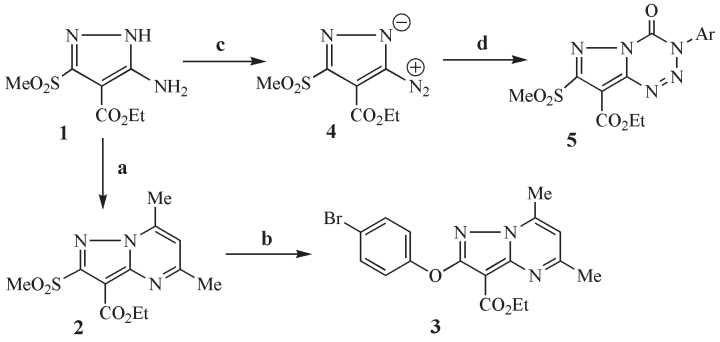
Heterocyclic nitrogen compounds and their fused analogs have attracted considerable attention because of their presence in numerous natural products [1-2] and their potential in various applications as pharmaceuticals and materials [3-4]. For example, indolo[1,2-*c*]benzo-[1,2,3]triazines exhibit antitumor and antimicrobial activity [5]. Pyrazolo[1,5-*a*]-1,3,5-triazines are portent, orally bioavailable CRF1 receptor antagonists [6]. Pyrazolo[1,5-*a*]pyrimidines are a new class of COX-2-selective inhibitors [7], and imidazo[5,1-*d*]-1,2,3,5-tetrazine-4(3*H*)-ones exhibit antitumour activity [8]. So it is attractive to discover novel heterocyclic nitrogen compounds possessing potential pharmaceutical activities and representing new chemical classes that operate by modes of action different from those already existing, which will consequently lack cross-resistance to chemicals currently used [9].

Moreover, a common method to vary the characteristic of interesting molecules is by the introduction of sulfone moiety. One may also use the sulfone moiety as a key intermediate to prepare certain compounds [10]. The sulfone nucleus is a key unit distributed in the plant kingdom [11] and possesses a broad spectrum of biological and pharmaceutical activities such as antitumor, anti-HIV and protein kinase inhibitors [12-14]. They are also widely used as important intermediates in organic synthesis due to the chemical versatility of the sulfone moiety [15]. For example, they can be eliminated to introduce a new bond into an organic molecule when appropriate [16]. Therefore the development of synthetic methods for sulfone-containing compounds has been an important field in both multistep synthetic chemistry and pharmaceutics.

As a result of these interesting properties, it is important to design and synthesize new sulfone-containing heterocyclic nitrogen compounds possessing potential pharmaceutical activities. So it is our interest to develop a facile method for introducing the sulfone moiety to heterocyclic nitrogen compounds and study their potential pharmaceutical activities. To the best of our knowledge, there are no reports involving the synthesis of sulfone-containing pyrazolo[1,5-*a*]pyrimidines and pyrazolo[5,1-*d*][1,2,3,5]-tetrazine-4(3*H*)-ones. Herein, we report our strategy for the synthesis of these sulfone-containing heterocyclic nitrogen compounds (**2**, **3** and **5a**-**5k**), which are illustrated in Scheme 1, and the results of their biological and pharmaceutical activities.

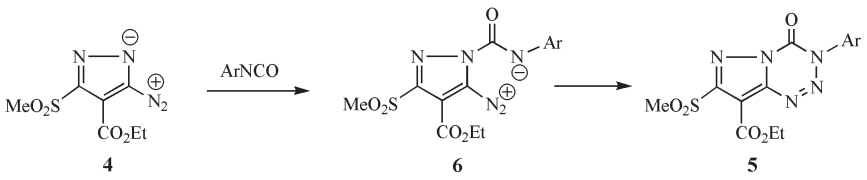
Scheme 1



Reaction conditions: **a** AcOH, H_2SO_4, pentane-2,4-dione, reflux; **b** toluene, 4-bromophenol, NaH, reflux; **c** (1) $NaNO_2$, HCl, -5°C; (2) Na_2CO_3; **d** CH_2Cl_2, aryl isocyanates.

Ar: **5a** = 4-FC_6H_4; **5b** = 2-FC_6H_4; **5c** = 3-ClC_6H_4; **5d** = 4-ClC_6H_4; **5e** = 2,4-$Cl_2C_6H_3$; **5f** = 4-CNC_6H_4; **5g** = 4-$NO_2C_6H_4$; **5h** = 2-$NO_2C_6H_4$; **5i** = 2-$CF_3C_6H_4$; **5j** = 4-$EtO_2CC_6H_4$. **5k** = H-C_6H_4

Scheme 2



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Proposed mechanism of the cycloaddition

Ethyl 5-amino-3-(methylsulfonyl)-1*H*-pyrazole-4-carboxylate (**1**) was easily prepared according to the reported method [17]. Since compound (**1**) has two strong electron-attracting groups, ethoxycarboryl and methylsulfonyl, the density of electron cloud in the 1 and 5-position is low and therefore the nucleophilic ability is weak. As a result, it is not easy to complete the condensation of compound (**1**) with pentane-2,4-dione under usual way. After screening various reaction conditions, we found that ethyl 5,7-dimethyl-2-(methylsulfonyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**2**) can be easily obtained by the condensation of compound (**1**) with pentane-2,4-dione in boiling acetic acid with the addition of two drops of concentrated vitriol. Since methylsulfonyl eliminates easily to introduce a new bond, ethyl 2-(4-bromophenoxy)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**3**) can be synthesized efficiently by the condensation of compound (**2**) with sodium 4-bromophenoxide in boiling toluene.

The diazotization of compound (**1**) using nitrous acid at -5 °C followed by neutralization with saturated aqueous sodium carbonate to give ethyl 5-diazo-3-(methylsulfonyl)-1*H*-pyrazole-4-carboxylate (**4**), and ethyl 3-aryl-3,4-dihydro-7-(methylsulfonyl)-4-oxopyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate (**5a**-**5k**) were obtained by the cycloaddition of compound (**4**) and aryl isocyanates.

Various aryl isocyanates were examined to investigate the scope and limitation of this cycloaddition. As Table 1 indicates, the yields were good when aryl isocyanates bearing weak electron-attracting groups such as halogen (entry 1-5) are used. Pure products were obtained *via* recrystallization from dichloromethane/diethyl ether. High yields were also obtained when using aryl isocyanates bearing strong electron-attracting groups such as ethoxycarboryl, nitro, cyano, *etc*. (entry 6-10). Pure products were obtained *via* recrystallization from DMSO/ethanol. When phenyl isocyanate was used, the yield decreased dramatically (entry 11). In this case pure products were obtained by flash chromatography on silica gel (200-300 mesh). The reaction failed to give any product at all when aryl isocyanates bearing electron-donating groups such as methoxy (entry 12) were used.

Table 1

Synthesis of Compounds **5** *via* Cycloaddition of Compound **4** with Aryl Isocyanates

Entry	Ar	Time (days)	**5**	m.p. (°C)	Yield (%)
1	4-FC_6H_4	7	**5a**	168-169	86
2	2-FC_6H_4	8	**5b**	152-153	82
3	3-ClC_6H_4	6	**5c**	162-163	89
4	4-ClC_6H_4	5	**5d**	178-179	93
5	2,4-$Cl_2C_6H_3$	3	**5e**	144-145	91
6	4-CNC_6H_4	0.5	**5f**	162-163	97
7	4-$NO_2C_6H_4$	0.5	**5g**	142-143	96
8	2-$NO_2C_6H_4$	1	**5h**	152-153	94
9	2-$CF_3C_6H_4$	1	**5i**	162-163	98
10	4-$EtO_2CC_6H_4$	0.5	**5j**	154-155	97
11	H-C_6H_4	10	**5k**	166-167	50
12	4-$MeOC_6H_4$	10			0

A plausible reaction mechanism is outlined in Scheme 2 according to the reported paper [18]. The cycloaddition of ethyl 5-diazo-3-(methylsulfonyl)-1*H*-pyrazole-4-carboxylate (**4**) to the electron deficient C=N double bond of various aryl isocyanates can be understood as a [7+2] cycloaddition consisting of a ring nitrogen acylation to a 1,9-dipole followed by intramolecular coupling.

The preliminary biological activity of these sulfone-containing heterocyclic nitrogen compounds was evaluated against barnyard grass and rape using a previously reported procedure [20]. All of the compounds possess some herbicide activity against rape with no activity against barnyard grass. For example, the herbicide activities of compound **5a** to compound **5e** against rape at 200 ppm are 54.3%, 66.5%, 52.7%, 52.8%, and 49.6% respectively, which were illustrated in Table 2.

Table 2

Bioassay Test of Compounds **5a-e** Against Rape

Compound	**5a**	**5b**	**5c**	**5d**	**5e**	**Atriazine**
Activity (%)	54.3	66.5	52.7	52.8	49.6	100

Due to the continuing evolution of herbicide resistance in agriculture, discovery of new herbicides such as potent

barnyard grass inhibitors is an important research objective. These results widen the structural diversity of anti-rape and confirm the perspectives of further investigations in this area. Further bioassay test, other biological and pharmaceutical activities test, structure modifications as well as synthetic applications of this new strategy are in progress in our laboratory.

EXPERIMENTAL

General Methods.

All reactions were performed using oven-dried glassware under a positive atmosphere of dry nitrogen. Common reagents and materials were purchased from commercial sources and purified by recrystallization or distillation. Analytical thin layer chromatography was performed with 0.2 mm coated commercial silica gel plates (Kiesselgel 60 GF_{254}). NMR spectra were measured on a Bruker XL-300 (^1H, 300 MHz and ^{13}C, 75 MHz) or Bruker AC-P200 (^1H, 200 MHz). Data for ^1H are reported as follows: chemical shift (δ ppm), number, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration and coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). Infrared (IR) spectra were recorded on a Shimadzu-435 spectrophotometer and are reported in terms of frequency of absorption (cm^{-1}). Elemental analyses were performed on Yanaco-CHN CORDER elementary analyzer. Mass spectra were obtained from VG ZAB-HS instrument. Melting points were measured on a Thomas-Hoover apparatus and were not corrected.

Preparation of Ethyl 5-Amino-3-(methylsulfonyl)-1*H*-pyrazole-4-carboxylate (**1**).

According to our previous method [18]. To a solution of ethyl 5-amino-3-(methylthio)-1*H*-pyrazole-4-carboxylate (10.05 g, 50 mmol) and $Na_2WO_4 \cdot 2H_2O$ (1.00 g, 3 mmol) in 40 ml acetic acid at 40 °C, 15 ml 30% hydrogen peroxide (H_2O_2) was added dropwise. After this dropping, the mixture was stirred at 55 °C and 15 ml 30% H_2O_2 was added slowly. Then the mixture was stirred vigorously at 70 °C until the reaction was completed as monitored by TLC (ethyl acetate, R_f (**1**) = 0.4.), the crude product was isolated by filtering and washed by ethanol to give pure white crystals in 74.3% yield; mp 223-224 °C; ^1H nmr (200 MHz, dimethylsulfoxide-d_6): δ 1.25 (t, 3H, CH_2-*CH_3*, *J* = 7.10 Hz), 3.27 (s, 3H, SO_2*CH_3*), 4.19 (q, 2H, *CH_2*-CH_3, *J* = 7.10 Hz), 6.41 (s, 1H, N-*H*).

Preparation of Ethyl 5,7-Dimethyl-2-(methylsulfonyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (**2**).

The mixture of compound (**1**) (0.23 g, 1.0 mmol), pentane-2,4-dione (0.12 g, 1.2 mmol) and two drops of concentrated vitriol in 20 ml boiling acetic acid was stirred until the reaction was completed as monitored by TLC (ethyl acetate, R_f (**2**) = 0.2). The solution was washed with 10 ml water, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was washed by diethyl ether to give pure white solid in 84.1% yield; mp 154-155 °C; ^1H nmr (300MHz, dimethylsulfoxide-d_6): δ 1.32 (t, 3H, CH_2-*CH_3*, *J* = 7.09 Hz,), 2.60 (s, 3H, *CH_3*), 2.70 (s, 3H, *CH_3*), 3.50 (s, 3H, SO_2*CH_3*), 4.32 (q, 2H, *CH_2*-CH_3, *J* = 7.09 Hz), 7.30 (s, 1H, Ar-*H*) ; ^{13}C nmr (75MHz, dimethylsulfoxide-d_6): δ 164.88 (CO), 161.09, 154.69, 148.14, 147.51, 113.39, 100.40, 61.12 (*CH_2*-CH_3), 43.26 (SO_2*CH_3*), 25.27(*CH_3*), 16.79 (*CH_3*), 14.49 (CH_2-*CH_3*).

Anal. Calcd. For $C_{12}H_{15}N_3O_4S$: C, 48.47; H, 5.08; N, 14.13. Found: C, 48.42; H, 4.90; N, 14.25.

Preparation of Ethyl 2-(4-Bromophenoxy)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**3**).

The mixture of 4-bromophenol (0.61 g, 3.5 mmol), 85% sodium hydrid (0.12 g, 3.5 mmol) in 20 ml boiling toluene was stirred for 1 hour, and compound (**2**) (0.30 g, 1.0 mmol) was added. After the reaction was completed as monitored by TLC (ethyl acetate:petroleum ether = 4:1, v/v, R_f (**4**) = 0.8), the solution was cooled to room temperature. The crude product was collected by filtration and was washed by diethyl ether to give pure white solid in 71.8% yield; mp 179-180 °C; ir (potassium bromide): 3390, 3043, 2914, 1703 (CO), 1619, 1561, 1479, 1448, 1368, 1198, 1135, 1085, 830 cm^{-1}; ^1H nmr (200MHz, deuteriochloroform): δ 1.25 (t, 3H, *CH_2*-CH_3, *J* = 6.97Hz), 2.62 (s, 3H, *CH_3*), 2.66 (s, 3H, *CH_3*), 4.29 (q, 2H, *CH_2*-CH_3, *J* = 6.97 Hz), 7.10 (s, 1H, Ar-*H*) , 7.24 (d, 2H, Ar-*H*, *J* = 8.40 Hz) , 7.45 (d, 2H, Ar-*H*, *J* = 8.40 Hz).

Anal. Calcd. For $C_{17}H_{16}BrN_3O_3$: C, 52.32; H, 4.13; N, 10.77. Found: C, 52.25; H, 4.05; N, 10.75.

Preparation of Ethyl 5-Diazo-3-(methylsulfonyl)-1*H*-pyrazole-4-carboxylate (**4**).

To a solution of compound (**1**) (1.47 g, 6.3 mmol) and hydrochloric acid (1.52 g, 36.5%) in 10 ml ethanol at -5 °C, 10 ml 5 % aqueous sodium nitrite was added slowly. After the reaction was completed as monitored by TLC (ethyl acetate:petroleum ether = 1:2, v/v, R_f (**4**) = 0.6), 40 ml dichloromethane was added and then the mixture was neutralized with saturated aqueous sodium carbonate until Ph = 8. The organic layer was separated, and the aqueous solution was extracted with 40 ml dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent was removed *in vacuo*. The crude product was washed by diethyl ether to give pure pale crystals in 78.0% yield; mp 132-133 °C; ir (potassium bromide): 2967, 2236 (N≡N), 1703 (CO), 1523, 1324, 1162, 1088, 1020, 766 cm^{-1}; ^1H nmr (200MHz, deuteriochloroform): δ 1.39 (t, 3H, *CH_2*-CH_3, *J* = 7.12 Hz), 3.41 (s, 3H, SO_2*CH_3*), 4.41 (q, 2H, *CH_2*-CH_3, *J* = 7.12 Hz).

Anal. Calcd. For $C_7H_8N_4O_4S$: C, 34.42; H, 3.30; N, 22.94. Found: C, 34.20; H, 3.40; N, 22.94.

Preparation of Ethyl 3-Aryl-3,4-dihydro-7-(methylsulfonyl)-4-oxopyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate (**5a-5j**).

The mixture of 2 mmol aryl isocyanates and 2 mmol compound (**4**) in 5 ml dichloromethane was stirred at room temperature. After the reaction was completed as monitored by TLC (ethyl acetate:petroleum ether = 1:2, v/v, R_f (**4**) = 0.6.), the solvent was removed *in vacuo*. The crude product was recrystallized with DMSO/ethanol or dichloromethane/diethyl ether to give pure crystals (**5a-5j**)

Ethyl 3-(4-Fluorophenyl)-3,4-dihydro-7-(methylsulfonyl)-4-oxopyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate (**5a**).

This compound was obtained as white solids, mp 168-169 °C; ir (potassium bromide): 2959, 1778 (CO), 1725 (CO), 1566, 1330, 1152, 1051, 948 cm^{-1}; ^1H nmr (300MHz, deuteriochloro-

form): δ 1.45 (t, 3H, CH_2-CH_3, J = 6.85 Hz), 3.50 (s, 3H, SO_2CH_3), 4.52 (q, 2H, CH_2-CH_3, J = 6.85 Hz), 7.28~7.67 (m, 4H, Ar-*H*); ^{13}C nmr (75MHz, dimethylsulfoxide-d_6): δ 164.83 (CO), 162.91 (CO), 159.52, 145.14, 140.63, 139.42, 130.99, 130.17, 126.76, 112.56, 106.56, 61.82 (CH_2-CH_3), 41.19 (SO_2CH_3), 14.0 (CH_2-CH_3).

Anal. Calcd. For $C_{14}H_{12}FN_5O_5S$: C, 44.09; H, 3.17; N, 18.37. Found: C, 44.28; H, 3.34; N, 18.69.

Ethyl 3-(2-Fluorophenyl)-3,4-dihydro-7-(methylsulfonyl)-4-oxopyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate (**5b**).

This compound was obtained as white solids, mp 152-153 °C; ir (potassium bromide): 2933, 1778 (CO), 1723 (CO), 1575, 1322, 1188, 1050, 958 cm^{-1}; ^{1}H nmr (300MHz, deuteriochloroform): δ 1.46 (t, 3H, CH_2-CH_3, J = 7.13 Hz), 3.52 (s, 3H, SO_2CH_3), 4.54 (q, 2H, CH_2-CH_3, J = 7.13 Hz), 7.37 (t, 1H, Ar-*H*, J = 8.54 Hz), 7.41 (t, 1H, Ar-*H*, J = 7.92 Hz), 7.58-7.65 (m, 2H, Ar-*H*); ^{13}C nmr (75MHz, deuteriochloroform): δ 158.42 (CO), 157.34 (CO), 155.39, 145.01, 137.98, 133.09, 132.98, 128.81, 125.31, 125.26, 117.37, 117.12, 110.03, 63.08 (CH_2-CH_3), 42.73 (SO_2CH_3), 14.03 (CH_2-CH_3).

Anal. Calcd. For $C_{14}H_{12}FN_5O_5S$: C, 44.09; H, 3.17; N, 18.37. Found: C, 43.86; H, 3.04; N, 18.28.

Ethyl 3-(3-Chlorophenyl)-3,4-dihydro-7-(methylsulfonyl)-4-oxopyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate (**5c**).

This compound was obtained as white solids, mp 162-163 °C; ir (potassium bromide): 2930, 1787 (CO), 1729 (CO), 1578, 1319, 1150, 1059, 967 cm^{-1}; ^{1}H nmr (300MHz, dimethylsulfoxide-d_6): δ 1.36 (t, 3H, CH_2-CH_3, J = 6.87 Hz), 3.61 (s, 3H, SO_2CH_3), 4.45 (q, 2H, CH_2-CH_3, J = 6.87 Hz), 7.68-7.73 (m, 4H, Ar-*H*); ^{13}C nmr (75MHz, dimethylsulfoxide-d_6): δ 159.19 (CO), 155.74 (CO), 145.79, 139.80, 138.38, 133.87, 131.77, 130.80, 126.92, 125.98, 108.19, 68.82 (CH_2-CH_3), 43.24 (SO_2CH_3), 14.35 (CH_2-CH_3).

Anal. Calcd. For $C_{14}H_{12}ClN_5O_5S$: C, 42.27; H, 3.04; N, 17.61. Found: C, 42.29; H, 3.37; N, 17.94.

Ethyl 3-(4-Chlorophenyl)-3,4-dihydro-7-(methylsulfonyl)-4-oxopyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate (**5d**).

This compound was obtained as white solids, mp 178-179 °C; ir (potassium bromide): 2929, 1771 (CO), 1730 (CO), 1568, 1327, 1148, 1053, 950 cm^{-1}; ^{1}H nmr (300MHz, dimethylsulfoxide-d_6): δ 1.38 (t, 3H, CH_2-CH_3, J = 6.97 Hz), 3.49 (s, 3H, SO_2CH_3), 4.41 (q, 2H, CH_2-CH_3, J = 6.97 Hz), 7.69-7.76 (m, 4H, Ar-*H*); ^{13}C nmr (75MHz, dimethylsulfoxide-d_6): δ 163.39 (CO), 160.05 (CO), 145.70, 140.00, 136.32, 135.18, 129.97, 128.94, 106.97, 68.33 (CH_2-CH_3), 40.98 (SO_2CH_3), 14.49 (CH_2-CH_3).

Anal. Calcd. For $C_{14}H_{12}ClN_5O_5S$: C, 42.27; H, 3.04; N, 17.61. Found: C, 42.05; H, 2.97; N, 17.72.

Ehyl 3-(2,4-Dichlorophenyl)-3,4-dihydro-7-(methylsulfonyl)-4-oxopyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate (**5e**).

This compound was obtained as white solids, mp 144-145 °C; ir (potassium bromide): 2928, 1774 (CO), 1717 (CO), 1523, 1320, 1161, 1005, 959 cm^{-1}; ^{1}H nmr (200MHz, deuteriochloroform): δ 1.44 (t, 3H, CH_2-CH_3, J = 7.06 Hz), 3.51 (s, 3H, SO_2CH_3), 4.53 (q, 2H, CH_2-CH_3, J = 7.06 Hz), 7.51~7.67 (m, 3H, Ar-*H*); ^{13}C nmr (75MHz, dimethylsulfoxide-d_6): δ 158.62 (CO), 157.73 (CO), 150.99, 136.67, 132.88, 132.34, 130.22, 129.07, 120.87, 118.28, 108.60, 62.19 (CH_2-CH_3), 42.80 (SO_2CH_3), 13.52 (CH_2-CH_3).

Anal. Calcd. For $C_{14}H_{11}Cl_2N_5O_5S$: C, 38.90; H, 2.57; N, 16.20. Found: C, 38.87; H, 2.69; N, 15.84.

Ethyl 3-(4-Cyanophenyl)-3,4-dihydro-7-(methylsulfonyl)-4-oxopyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate (**5f**).

This compound was obtained as white solids, mp 162-163 °C; ir (potassium bromide): 2960, 1778 (CO), 1731 (CO), 1569, 1329, 1281, 1151, 1055, 958 cm^{-1}; ^{1}H nmr (300MHz, dimethylsulfoxide-d_6): δ 1.38 (t, 3H, CH_2-CH_3, J = 7.00 Hz), 3.62 (s, 3H, SO_2CH_3), 4.47 (q, 2H, CH_2-CH_3, J = 7.00 Hz), 7.91 (d, 2H, Ar-*H*, J = 8.31 Hz), 8.15 (d, 2H, Ar-*H*, J = 8.31 Hz); ^{13}C nmr (75MHz, dimethylsulfoxide-d_6): δ 159.14 (CO), 155.86 (CO), 145.73, 140.78, 139.69, 134.18, 127.79, 118.44, 113.38, 108.43, 62.87 (CH_2-CH_3), 43.22 (SO_2CH_3), 14.33 (CH_2-CH_3).

Anal. Calcd. For $C_{15}H_{12}N_6O_5S$: C, 46.39; H, 3.11; N, 21.64. Found: C, 46.18; H, 3.27; N, 21.75.

Ehyl 3,4-Dihydro-7-(methylsulfonyl)-3-(4-nitrophenyl)-4-oxopyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate (**5g**).

This compound was obtained as yellow solids, mp 142-143 °C; ir (potassium bromide): 2923, 1774 (CO), 1727 (CO), 1529, 1350, 1148, 1042, 951 cm^{-1}; ^{1}H nmr (200MHz, dimethylsulfoxide-d_6): δ 1.37 (t, 3H, CH_2-CH_3, J = 7.02 Hz), 3.62 (s, 3H, SO_2CH_3), 4.46 (q, 2H, CH_2-CH_3, J = 7.02 Hz), 7.95 (d, 2H, Ar-*H*, J = 8.39 Hz), 8.52 (d, 2H, Ar-*H*, J = 8.39 Hz); ^{13}C nmr (75MHz, dimethylsulfoxide-d_6): δ 159.14 (CO), 155.82 (CO), 148.41, 142.09, 139.70, 128.14, 125.37, 108.43, 62.87 (CH_2-CH_3), 43.23 (SO_2CH_3), 14.33 (CH_2-CH_3).

Anal. Calcd. For $C_{14}H_{12}N_6O_7S$: C, 41.18; H, 2.96; N, 20.58. Found: C, 40.93; H, 3.00; N, 20.58.

Ethyl 3,4-Dihydro-7-(methylsulfonyl)-3-(2-nitrophenyl)-4-oxopyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate (**5h**).

This compound was obtained as yellow solids, mp 152-153 °C; ir (potassium bromide): 2925, 1773 (CO), 1720 (CO), 1536, 1324, 1149, 1054, 956 cm^{-1}; ^{1}H nmr (200MHz, dimethylsulfoxide-d_6): δ 1.37 (t, 3H, CH_2-CH_3, J = 6.98 Hz), 3.61 (s, 3H, SO_2CH_3), 4.46 (q, 2H, CH_2-CH_3, J = 6.98 Hz), 7.91~8.42 (m, 4H, Ar-*H*); ^{13}C nmr (75MHz, dimethylsulfoxide-d_6): δ 163.76 (CO), 161.12 (CO), 149.50, 144.26, 140.95, 137.91, 135.73, 134.20, 131.31, 130.58, 114.17, 67.65 (CH_2-CH_3), 47.98 (SO_2CH_3), 19.09 (CH_2-CH_3).

Anal. Calcd. For $C_{14}H_{12}N_6O_7S$: C, 41.18; H, 2.96; N, 20.58. Found: C, 41.22; H, 3.06; N, 20.70.

Ethyl 3-(2-(Trifluoromethyl)phenyl)-3,4-dihydro-7-(methylsulfonyl)-4-oxopyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate (**5i**).

This compound was obtained as white solids, mp 162-163 °C; ir (potassium bromide): 2926, 1786 (CO), 1719 (CO), 1575, 1320, 1178, 1052, 955 cm^{-1}; ^{1}H nmr (300MHz, dimethylsulfoxide-d_6): δ 1.35 (t, 3H, CH_2-CH_3, J = 7.10 Hz), 3.59 (s, 3H, SO_2CH_3), 4.45 (q, 2H, CH_2-CH_3, J = 7.10 Hz), 7.93 (t, 2H, Ar-*H*, J = 8.08 Hz), 8.02 (d, 1H, Ar-*H*, J = 7.64 Hz), 8.09 (d, 1H, Ar-*H*, J = 8.07 Hz); ^{13}C nmr (75MHz, dimethylsulfoxide-d_6): δ 159.09 (CO), 156.09 (CO), 145.94, 139.79, 135.19, 134.08, 132.73, 131.35, 126.70, 109.40, 62.86 (CH_2-CH_3), 43.25 (SO_2CH_3), 14.36 (CH_2-CH_3).

Anal. Calcd. For $C_{15}H_{12}F_3N_5O_5S$: C, 41.77; H, 2.80; N, 16.24. Found: C, 41.55; H, 2.77; N, 16.17.

Ethyl 3-(4-(Ethoxycarbonyl)phenyl)-3,4-dihydro-7-(methylsulfonyl)-4-oxopyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate (**5j**).

This compound was obtained as white solids, mp 154-155 °C; ir (potassium bromide): 2933, 1780 (CO), 1726 (CO), 1563, 1329, 1281, 1150, 1054, 966 cm^{-1}; ^1H nmr (300MHz, dimethylsulfoxide-d_6 and deuteriochloroform): δ 1.36 (t, 3H, CH_2-CH_3, J = 7.00 Hz), 1.38 (t, 3H, CH_2-CH_3, J = 7.02 Hz), 3.51 (s, 3H, SO_2CH_3), 4.35 (q, 2H, CH_2-CH_3, J = 7.00 Hz), 4.44 (q, 2H, CH_2-CH_3, J = 7.02 Hz), 7.78 (d, 2H, Ar-*H*, J = 8.40 Hz), 8.17 (d, 2H, Ar-*H*, J = 8.40 Hz); ^{13}C nmr (75MHz, dimethylsulfoxide-d_6 and deuteriochloroform): δ 165.08 (CO), 158.98 (CO), 155.90, 145.66, 140.74, 139.48, 131.69, 130.50, 126.71, 108.39, 62.54 (CH_2-CH_3), 61.45 (CH_2-CH_3), 43.13 (SO_2CH_3), 14.47 (CH_2-CH_3), 14.23 (CH_2-CH_3).

Anal. Calcd. For $C_{17}H_{17}N_5O_7S$: C, 46.89; H, 3.94; N, 16.08. Found: C, 46.72; H, 3.86; N, 15.93.

Preparation of Ethyl 3,4-Dihydro-7-(methylsulfonyl)-4-oxo-3-phenylpyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate (**5k**).

The mixture of 2 mmol phenyl isocyanate and 2 mmol compound (**4**) in 5 ml dichloromethane was stirred at room temperature. After the reaction was completed as monitored by TLC (ethyl acetate:petroleum ether = 1:2 v/v, R_f = 0.8.), the solvent was removed *in vacuo*. The white product was isolated by flash chromatography on silica gel (200-300 mesh) with ethyl acetate:petroleum ether (33:67, v/v), R_f = 0.8. mp 166-167 °C; ir (potassium bromide): 3043, 2932, 1790 (CO), 1728 (CO), 1558, 1435, 1330, 1150, 1111, 1064, 951 cm^{-1}; ^1H nmr (300MHz, dimethylsulfoxide-d_6 and deuteriochloroform): δ 1.45 (t, 3H, CH_2-CH_3, J = 7.12 Hz), 3.52 (s, 3H, SO_2CH_3), 4.49 (q, 2H, CH_2-CH_3, J = 7.12 Hz), 7.60-7.70 (m, 5H, Ar-*H*); ^{13}C nmr (75MHz, dimethylsulfoxide-d_6 and deuteriochloroform): δ 163.60 (CO), 160.94 (CO), 150.29, 144.01, 141.67, 135.03, 134.23, 131.10, 113.31, 67.33 (CH_2-CH_3), 47.70 (SO_2CH_3), 18.87 (CH_2-CH_3); ms (EI): m/z 363 (M^+), 335, 290, 119, 91, 44, 29.

Anal. Calcd. For $C_{14}H_{13}N_5O_5S$: C, 46.28; H, 3.61; N, 19.27. Found: C, 45.99; H, 3.58; N, 19.29.

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