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Catalyst-free synthesis of *N*-rich heterocycles via multi-component reactions

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ABSTRACT

Efficient and straightforward methods for the synthesis of 5-substituted 1*H*-tetrazoles via multi-component reaction of α-dicarbonyl compounds, 2,3-diaminomaleonitrile and sodium azide without any catalyst has been reported. These general protocols provide a wide variety of *N*-rich heterocyclic compounds (1*H*-tetrazole-5-yl) pyrazines and di(1*H*-tetrazole-5-yl) pyrazines, in good to excellent yields.

1. Introduction

One of the main challenges in medicinal chemistry is the design and synthesis of biologically active molecules. Multi-component reactions (MCRs), because of their productivity, simple procedures, convergence, facile execution, and atom economy,[1] are one of the best tools in the synthesis of diverse and complex compounds as well as small and drug like heterocycles.[2] In this context, tetrazole derivatives show interesting features that make them attractive for use in MCRs.

Tetrazoles are a class of heterocycles with a wide range of applications that are receiving considerable attention. This functional group has a role in coordination chemistry as ligands,[3] in materials science as specialty explosives and information recording systems, as good potential inhibitors and as intermediates in a variety of synthetic transformations. Moreover, the tetrazole groups have found use in pharmaceuticals as lipophilic spacers and carboxylic acid surrogates. Also the tetrazole ring appears in some well-known drugs.[4] Therefore, a number of methods have been reported for the preparation of tetrazoles.[5] One of the major synthetic routes to tetrazole formation is the [2+3] cycloaddition of an organonitrile and an azide salt.[6]

However, many of these protocols have some disadvantages, such as the use of toxic metals, strong Lewis acid, expensive reagents, low yield, harsh reaction conditions, water sensitivity, and the presence of hydrazoic acid, which is toxic and explosive. In addition, all of the known methods use organic solvents, in particular, dipolar aprotic solvents, such as DMF.[7,3b] Recently, Sharpless and co-workers reported an improved preparation of tetrazoles by the reaction of nitriles and NaN_3 in the presence of Zn (II) salts in water. In the case of sterically hindered aromatic or deactivated alkyl nitriles, high temperature (140–170 °C) and long reaction times are required.[8]

Thus, the development of a convenient and safe process for the preparation of new tetrazole derivatives is an interesting problem for investigation. Although limited number of isocyanide-based multi-component reactions have been reported for the synthesis of tetrazoles,[9] to the best of our knowledge, the synthesis of tetrazole fused heterocycles via diaminomaleonitrile-based multi-component reactions has not been reported yet.

Therefore, as part of our program aimed for the preparation of new heterocycles,[10] guided by observation that the presence of two or more different heterocyclic moieties in a molecule often enhances the biological profile remarkably, we investigated herein, an efficient synthesis of terazoles containing pyrazine moiety via diaminomaleonitrile-based multi-component reactions. We seek to replace the environmentally harmful solvents, i.e., DMF with dimethyl sulfoxide (DMSO) as an environmentally friendly solvent. According to the U.S. Food and Drug Administration (FDA) solvent classification based on their possible risk to human health, DMSO belong to class 3, which is defined as *solvent with low toxic potential* (solvent with low toxic potential to humans; no health-based exposure limit is needed).[11]

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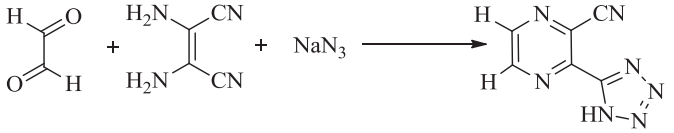
2. Results and discussion

The choice of an appropriate reaction medium is of crucial importance for successful synthesis. Initially, the three-component reaction of oxalaldehyde **1a**, 2,3-diaminomaleonitrile **2**, and sodium azide as a simple model substrate was investigated in different solvents without any catalyst (Table 1). The desired product was scarcely obtained in non-polar solvents (entries 8–10) and even methanol, ethanol, and water as a polar protic solvent failed to produce the desired product in good yield (entries 5–7). It was found that DMSO is the best solvent with respect to reaction yield (entry 2). We performed the model reaction using different quantities of reagents in DMSO (entries 1–3). The best result was obtained with a 1:1:1.5 ratio of oxalaldehyde **1a**, 2,3-diaminomaleonitrile **2**, and sodium azide.

Table 1
Model reaction, conditions, and yield[a]



1a **2** **3** **4a**

Entry	Conditions	NaN_3 (mmol)	Yield (%)
1	DMSO (100 °C)	1	63
2	DMSO (100 °C)	1.5	91
3	DMSO (100 °C)	2	90
4	DMF (100 °C)	1.5	84
5	H_2O (reflux)	1.5	43
6	MeOH (reflux)	1.5	Trace
7	EtOH (reflux)	1.5	Trace
8	Benzene (reflux)	1.5	Trace
9	Toluene (reflux)	1.5	Trace
10	$CHCl_3$ (reflux)	1.5	Trace

[a] Oxalaldehyde (1 mmol), diaminomaleonitrile (1 mmol). Reaction time=3 h.

To explore the scope and limitations of this reaction, the procedure was extended to various aliphatic and aromatic α-dicarbonyl compounds **1a**–**e** and corresponding (1*H*-tetrazole-5-yl) pyrazine-2-carbonitrile **3a**–**e** were synthesized in DMSO at 100 °C (Table 2). The reaction proceeded very cleanly in the absence of any catalyst. The catalyst-free reactions carried out in DMSO are safe, non-toxic, environmentally friendly, and inexpensive. The absence of catalyst for the reaction avoids the use of moisture-sensitive heavy metals, such as Lewis acids.

Mechanistically, the formation of products can be rationalized by initial formation of pyrazine-2,3-dicarbonitrile **4** by a condensation reaction of **1** and **2**. Subsequent [2+3] cycloaddition reaction of **4** with the sodium azide to afford product **3** (Scheme 1). To clarify the proposed mechanism, first, the pyrazine-2,3-dicarbonitrile **4a** was synthesized from condensation of **1a** and **2**, subsequently reaction of **4a** with sodium azide afforded corresponding product **3a**.

During our investigation on the synthesis of tetrazoles fused pyrazine, we found that increasing the reaction time and amount of the sodium azide afforded new tetrazoles, di(1*H*-tetrazole-5-yl) pyrazines **5a**–**g**, in good to excellent yields under same reaction conditions (Table 3).

Encouraged by these results, ninhydrin **6** was selected as dicarbonyl compound, the reactions proceeded very efficiently and led to the formation of the corresponding di(1*H*-tetrazole-5-yl)-9*H*-indeno[2,1-*b*]pyrazin-9-one **7** in 89% yield (Scheme 2).

Finally, selective synthesized compounds were screened for antimicrobial activity. The microorganisms used in this study were *Escherichia coli* ATCC 25922, *Pseudomonas aeruginusa* ATCC 85327, (Gram-negative bacteria), *Bacillus subtilis* ATCC 465, *Staphylococcus aureus* ATCC 25923 (Gram-positive bacteria), *Candida albicans* ATCC 10231, and *Saccharomyses cerevisiae* ATCC 9763 (fungi). The minimum inhibitory concentration (MIC) of the synthesized compounds determined by microdillution method[12] (Table 4). As can be seen from Table 4, good to improved antibacterial activity was observed for most of the compounds **5** against all species of Gram-positive and Gram-negative bacteria and fungi used in the study. Compounds **3** don't have any activity against all microorganisms used in this study.

3. Conclusion

In conclusion, an efficient, catalyst-free and convenient method for the preparation of tetrazoles containing pyrazine in DMSO is reported. To the best of our knowledge, it is the first example of a multi-component reaction to synthesis of these compounds. The present green synthesis shows attractive characteristics, such as one-pot conditions, short reaction times, easy work-up/purification and reduced waste production without using any catalyst or additive agent.

4. Experimental

4.1. General

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. ^1H and ^{13}C NMR spectra were obtained on solutions in DMSO-d_6. IR spectra were recorded using a BOMEM MB-Series. Elemental analyses were performed using a Heracus CHN–O-Rapid analyzer.

The chemicals used in this work were obtained from Fluka and Merck and were used without purification.

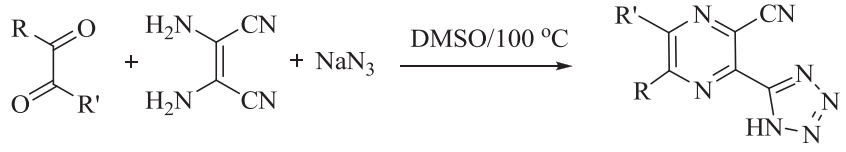
*4.1.1. Typical procedure for the preparation of 3-(1H-tetrazole-5-yl) pyrazine-2-carbonitrile (**3a**).* A mixture of oxalaldehyde (1 mmol), 2,3-diaminomaleonitrile (1 mmol), and sodium azide (1.5 mmol) in DMSO (2 mL) was stirred at 100 °C for 3 h. After completion of the reaction confirmed by TLC (eluent: EtOAc/*n*-hexane, 1:1), the solvent was removed. To the residue was added 10 mL of 2 N HCl with vigorous stirring causing the 3-(1*H*-tetrazole-5-yl) pyrazine-2-carbonitrile **3a** as cream powder (0.16 g, yield 91%). Mp 178–180 °C; [found: C, 41.55; H, 1.68; N, 56.54. $C_6H_3N_7$ requires C, 41.62; H, 1.75; N, 56.63%]; R_f (EtOAc/*n*-hexane, 1:1) 0.45; ν_{max} (KBr): 3401, 2128, 1673, 1540 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.73 (1H, s, CH), 8.94 (1H, s, CH); δ_C (75 MHz, DMSO-d_6) 117.2, 126.4, 143.9, 147.9, 148.1, 158.0; MS, *m*/*z*: 173 (M^+).

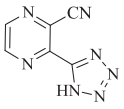
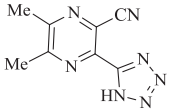
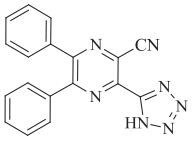
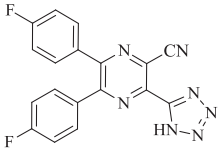
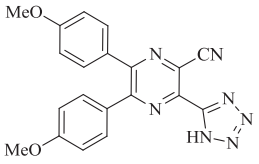
*4.1.2. 5,6-Dimethyl-3-(1H-tetrazole-5-yl)pyrazine-2-carbonitrile (**3b**).* Cream powder (0.17 g, yield 83%). Mp 199–201 °C; [found: C, 47.66; H, 3.59; N, 48.81. $C_8H_7N_7$ requires C, 47.76; H, 3.51; N, 48.73%]; R_f (EtOAc/*n*-hexane, 1:1) 0.41; ν_{max} (KBr): 3426, 2230, 1600, 1549 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.63 (3H, s, CH_3), 2.69 (3H, s, CH_3); δ_C (75 MHz, DMSO-d_6) 22.2, 22.7, 116.0, 123.9, 139.4, 153.0, 156.3, 157.8; MS, *m*/*z*: 201 (M^+).

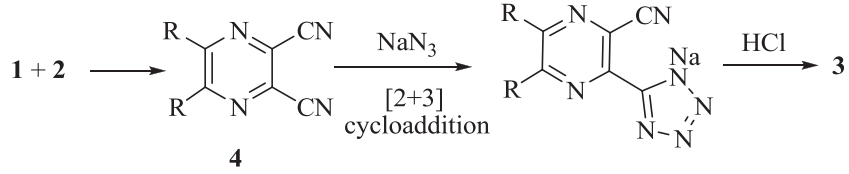
*4.1.3. 5,6-Diphenyl-3-(1H-tetrazole-5-yl)pyrazine-2-carbonitrile (**3c**).* Light yellow powder (0.28 g, yield 88%) mp 163–165 °C; [found: C, 66.53; H, 3.35; N, 30.20. $C_{18}H_{11}N_7$ requires C, 66.45; H, 3.41; N, 30.14%]; R_f (EtOAc/*n*-hexane, 1:1) 0.43; ν_{max} (KBr): 3425, 2237, 1524, 1448 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.40–7.62 (10H, m, H–Ar); δ_C (75 MHz, DMSO-d_6) 115.9, 124.4, 128.8, 128.9, 130, 130.4, 130.7, 136.5, 136.6, 139.7, 153.2, 153.5, 154.3; MS, *m*/*z*: 325 (M^+).

*4.1.4. 5,6-Bis(4-fluorophenyl)-3-(1H-tetrazole-5-yl)pyrazine-2-carbonitrile (**3d**).* Cream powder (0.29 g, yield 81%). Mp

Table 2
Synthesis of (1*H*-tetrazole-5-yl) pyrazine-2-carbonitrile **3**.



Product	Time (h)	Yield (%)
 **3a**	3	91
 **3b**	3.5	83
 **3c**	3	88
 **3d**	3.5	81
 **3e**	3.5	78



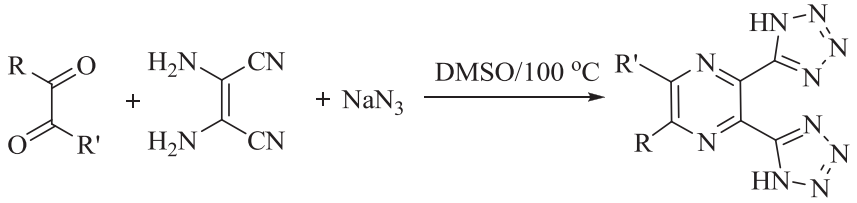
Scheme 1. Proposed mechanism of the reaction.

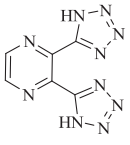
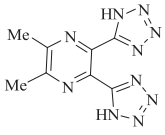
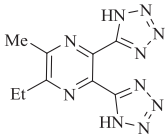
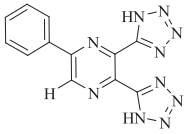
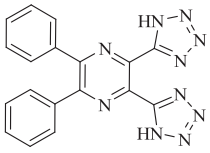
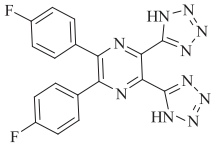
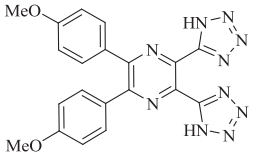
130–132 °C; [found: C, 59.73; H, 2.45; N, 27.08. $C_{18}H_9F_2N_7$ requires C, 66.45; H, 3.41; N, 30.14%]; R_f (EtOAc/*n*-hexane, 1:1) 0.51; ν_{max} (KBr): 3442, 2237, 1606, 1498 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.29 (4H, m, H–Ar), 7.54 (2H, m, H–Ar), 7.66 (2H, m, H–Ar); δ_C (75 MHz, DMSO-d_6) 116.3, 124.3, 132.4, 132.5, 132.8, 132.9, 133, 139.5, 152.6, 152.9, 153.4, 161.8, 162; MS, *m*/*z*: 361 (M^+).

*4.1.5. 5,6-Bis(4-methoxyphenyl)-3-(1H-tetrazole-5-yl)pyrazine-2-carbonitrile (**3e**).* Yellow powder (0.30 g, yield 78%). Mp 124–126 °C; [found: C, 62.45; H, 3.99; N, 25.51. $C_{20}H_{15}N_7O_2$ requires C, 62.33; H, 3.92; N, 25.44%.]; R_f (EtOAc/*n*-hexane, 1:1) 0.47; ν_{max} (KBr): 3469, 2225, 1606, 1549 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.79 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 6.97–7.63 (8H, m, H–Ar); δ_C (75 MHz, DMSO-d_6) 55.7, 55.8, 114.4, 114.5, 116.1, 123.3, 128.8, 129, 131.5, 131.7, 132, 138.7, 152.7, 153.4, 161, 161.4; MS, *m*/*z*: 385 (M^+).

*4.1.6. Typical procedure for the preparation of 2,3-di(1H-tetrazole-5-yl)pyrazine (**5a**).* A mixture of oxalaldehyde (1 mmol) 2,3-diaminomaleonitrile (1 mmol), sodium azide (3 mmol) in DMSO (2 mL) was stirred at 100 °C for 6 h. After completion of the reaction

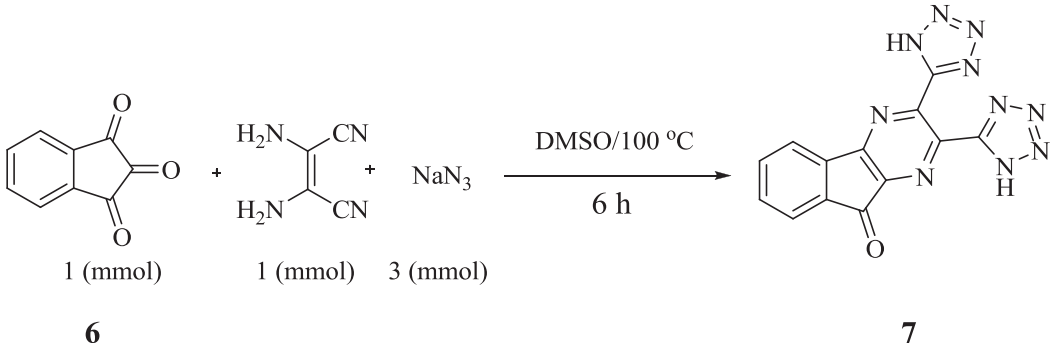
Table 3
Synthesis of di(1*H*-tetrazole-5-yl) pyrazines **5**



Product	Time (h)	Yield (%)
 **5a**	6	93
 **5b**	6.5	81
 **5c**	6.5	83
 **5d**	6	85
 **5e**	6.5	92
 **5f**	7.5	81
 **5g**	7.5	88

confirmed by TLC (eluent: EtOAc/*n*-hexane, 1:1), the solvent was evaporated under reduced pressure. To the participate was added 20 mL of 2 N HCl with vigorous stirring causing the 2,3-di(1*H*-tetrazole-5-yl) pyrazine to precipitate. The precipitate was filtered and dried in a drying oven to furnish the 2,3-di(1*H*-tetrazole-5-yl) **5a** as white powder (0.20 g, yield 93%). Mp 257–259 °C; [found: C, 33.25; H, 1.82; N, 64.73. $C_6H_4N_{10}$ requires C, 33.34; H, 1.87; N, 64.80%.]; R_f (EtOAc/*n*-hexane, 1:1) 0.56; ν_{max} (KBr): 3469, 2225, 1606, 1549 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.79 (3H, s, OCH_3), 39.09 (2H, s, H–Ar); δ_C (75 MHz, DMSO-d_6) 140.2, 146.5, 153.7; MS, *m*/*z*: 216 (M^+).

*4.1.7. 2,3-Dimethyl-5,6-di(1H-tetrazole-5-yl) pyrazine (**5b**).* Cream powder (0.20 g, yield 81%). Mp 230–232 °C; [found: C, 39.22; H, 3.23; N, 57.27. $C_8H_8N_{10}$ requires C, 39.34; H, 3.30; N, 57.35%.]; R_f (EtOAc/*n*-hexane, 1:1) 0.51; ν_{max} (KBr): 3425, 1631, 1543 cm^{-1}; δ_H



Scheme 2. Synthesis of di(1*H*-tetrazole-5-yl)-indenopyrazin **6**.

Table 4
MIC (μg/ml) values of products

Microorganisms	Products								
	5a	**5b**	**5e**	**5f**	**5g**	**3a**	**3b**	**3c**	**3e**
Bacillus subtilis	*	64	128	64	64	*	*	*	*
Staphylococcus aureus	32	*	32	64	256	*	*	*	*
Escherichia coli	*	128	*	*	128	*	*	*	*
Pseudomonas aeruginosa	32	32	64	*	*	*	*	*	*
Candida albicans	32	32	32	32	32	*	*	*	*
Saccharomyses cerevisiae	32	32	32	32	64	*	*	*	*

*Not Active.

(300 MHz, DMSO-d_6) 2.69 (6H, s, $2CH_3$); δ_C (75 MHz, DMSO-d_6) 22.2, 136.4, 153.6, 155.6; MS, *m*/*z*: 244 (M^+).

*4.1.8. 2-Ethyl-3-methyl-5,6-di(1H-tetrazole-5-yl)pyrazine (**5c**).* White powder (0.21 g, yield 83%). Mp 199–201 °C; [found: C, 41.73; H, 3.97; N, 54.29. $C_9H_{10}N_{10}$ requires C, 41.86; H, 3.90; N, 54.24%.]; R_f (EtOAc/*n*-hexane, 1:1) 0.45; ν_{max} (KBr): 3456, 1568, 1500 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.31 (3H, t, *J* 7.1 Hz, CH_3), 2.72 (3H, s, CH_3), 3.02 (2H, q, *J* 7.1 Hz, CH_2); δ_C (75 MHz, DMSO-d_6) 11.6, 21.8, 27.6, 136.2, 136.5, 153.4, 153.5, 155, 159.1; MS, *m*/*z*: 258 (M^+).

*4.1.9. 5-Phenyl-2,3-di(1H-tetrazole-5-yl)pyrazine (**5d**).* White powder (0.25 g, yield 85%). Mp 194–196 °C; [found: C, 49.40; H, 2.82; N, 47.85.$C_{12}H_8N_{10}$ requires C, 49.32; H, 2.76; N, 47.93%.]; R_f (EtOAc/*n*-hexane, 1:1) 0.53; ν_{max} (KBr): 3545, 1543, 1435 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.59–7.62 (3H, m, H–Ar), 8.25–8.40 (2H, m, H–Ar), 9.65–9.71 (1H, m, H–Ar); δ_C (75 MHz, DMSO-d_6) 129.6, 129.8, 131.9, 132.1, 133.8, 134.3, 137.9, 139.2, 140.5, 143.4, 145.0, 152.5; MS, *m*/*z*: 292 (M^+).

*4.1.10. 2,3-Diphenyl-5,6-di(1H-tetrazole-5-yl)pyrazine (**5e**).* Cream powder (0.34 g, yield 92%). Mp 257–259 °C; [found: C, 58.59; H, 3.23; N, 38.10. $C_{18}H_{12}N_{10}$ requires C, 58.69; H, 3.28; N, 38.03%.]; R_f (EtOAc/*n*-hexane, 1:1) 0.45; ν_{max} (KBr): 3538, 1543, 1454 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.40–7.42 (6H, m, H–Ar), 7.60–7.62 (4H, m, H–Ar); δ_C (75 MHz, DMSO-d_6) 128.8, 130.2, 130.3, 136.7, 137.0, 152.9, 153.6; MS, *m*/*z*: 368 (M^+).

*4.1.11. 2,3-Bis(4-fluorophenyl)-5,6-di(1H-tetrazole-5-yl)pyrazine (**5f**).* Cream powder (0.33 g, yield 81%). Mp 207–209 °C; [found: C, 53.54; H, 2.44; N, 34.71. $C_{18}H_{10}F_2N_{10}$ requires C, 53.47; H, 2.49; N, 34.64%.]; R_f (EtOAc/*n*-hexane, 1:1) 0.51; ν_{max} (KBr): 3538, 1543, 1454 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.26–7.32 (4H, m, H–Ar), 7.64–7.69 (4H, m, H–Ar); δ_C (75 MHz, DMSO-d_6) 132.5, 132.7, 132.8, 133.3, 133.4, 152.0, 153.6; MS, *m*/*z*: 404 (M^+).

*4.1.12. 2,3-Bis(4-methoxyphenyl)-5,6-di(1H-tetrazole-5-yl) pyrazine (**5g**).* Cream powder (0.38 g, yield 88%). Mp 210–212 °C; [found: C, 56.19; H, 3.67; N, 32.60. $C_{20}H_{16}N_{10}O_2$ requires C, 56.07; H, 3.76; N, 32.69%.]; R_f (EtOAc/*n*-hexane, 1:1) 0.48; ν_{max} (KBr): 3538, 1543, 1454 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.78 (6H, s, OMe), 6.99 (4H, d, *J* 8.1 Hz, H–Ar), 7.47–7.60 (4H, m, H–Ar); δ_C (75 MHz, DMSO-d_6) 55.7, 114.4, 129.4, 131.5, 131.7, 132.0, 151.8, 160.9; MS, *m*/*z*: 428 (M^+).

*4.1.13. 2,3-Di(1H-tetrazole-5-yl)-9H-indeno[2,1-b]pyrazin-9-one (**7**).* Yellow powder (0.28 g, yield 89%). Mp 256–258 °C; [found: C, 48.95; H, 1.96; N, 43.94. $C_{13}H_6N_{10}O$ requires C, 49.06; H, 1.90; N, 44.01%.]; R_f (EtOAc/*n*-hexane, 1:1) 0.52; ν_{max} (KBr): 3440, 1735, 1601, 1570 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.71–7.76 (1H, m, H–Ar), 7.85–7.92 (2H, m, H–Ar), 8.00–8.03 (1H, m, H–Ar); δ_C (75 MHz, DMSO-d_6) 123.1, 125.1, 133.8, 135.6, 137.3, 139.3, 139.6, 141.4, 149.7, 154.0, 154.3, 160.1, 188.6; MS, *m*/*z*: 318 (M^+).

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