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Note

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Cross-Dehydrogenative Coupling of Azoles with *α*-Csp^3-H of Ethers and Thioethers Under Metal-free condition: Functionalization of H-N azoles *via* C-H activation

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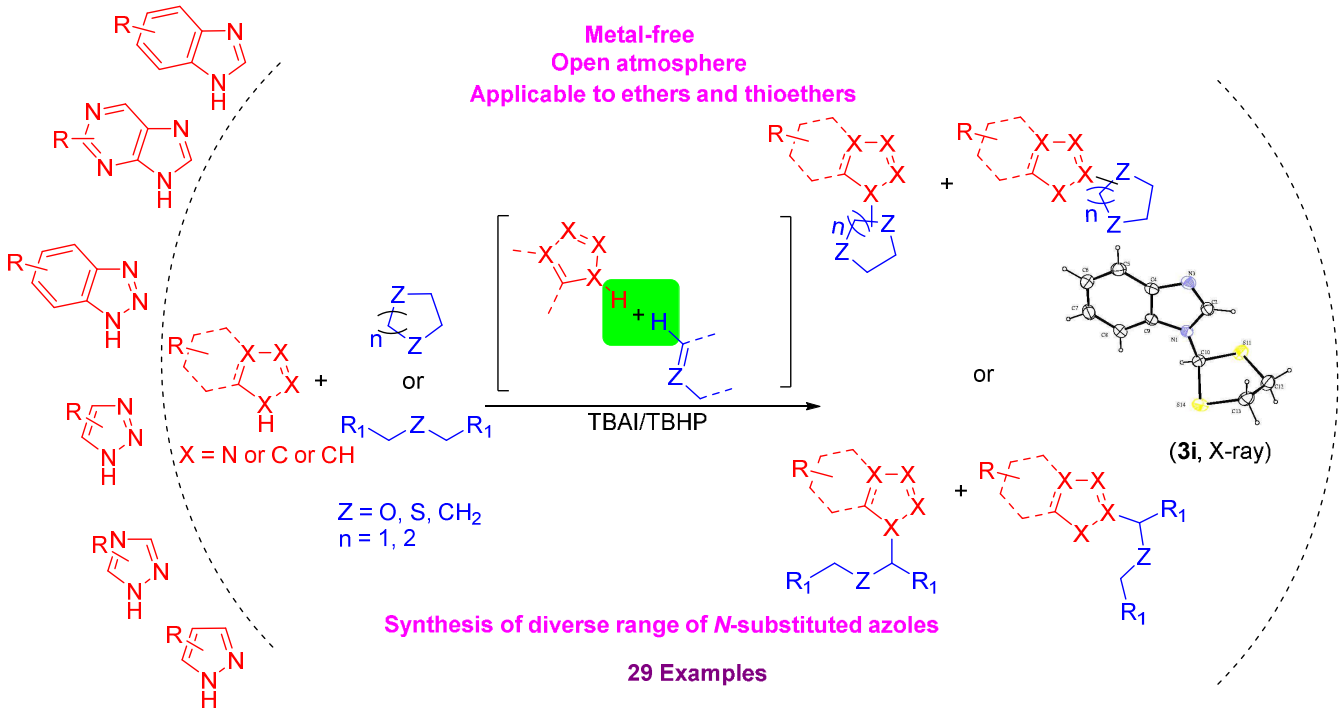

Abstract:

A metal-free and cross-dehydrogenative coupling method for the synthesis of *N*-substituted azoles has been developed. TBAI/TBHP system catalyzed the coupling of azoles with ethers and thioethers *via* α-Csp^3-H activation. Under optimized condition, diverse range of un/substituted azoles such as 1*H*-benzimidazole, 9*H*-purine, 1*H*-benzotriazole, 1*H*-1,2,3-triazole, 1*H*-1,2,4-triazole, 1*H*-pyrazole were successfully employed for coupling with various ethers and thioethers such as tetrahydrofuran, tetrahydropyran, 1,4-dioxane, diethylethers tetrahydrothiophene and 1,3-dithiolane.

N-Substituted azoles particularly *N*-alkylated azoles represent an important class of compounds because of their common occurrence in medicinally important products (some examples are given in Fig 1)[1] as well as their use as precursors for *N*-heterocyclic carbenes and ionic liquids.[2] In view the importance of *N*-substituted azoles, the development of new synthetic methods for the functionalization of azoles is of great interest. Traditionally, the *N*-alkylated azoles were synthesized by coupling azoles with electrophiles (Fig 2). These reactions normally require harsh conditions and often result in over alkylation.[3] In the last decade, there has been a great interest in the exploration and development of metal- and metal-free catalysed C-H bond activation/functionalization methods for the C-C, C-O and C-N bond.[4-6] In this direction, Pan S. *et al.* has applied Fe/TBHP catalyzed C–H activation strategy for the *N*-alkylation of azoles (as shown in Fig 2)[7] Moreover, in the recent years, metal-free organo-catalytic system such as tetrabutylammonium iodide (TBAI) / *tert*-butyl hydroperoxide (TBHP) has also been extensively explored for C-H activation/functionalization method.[8]

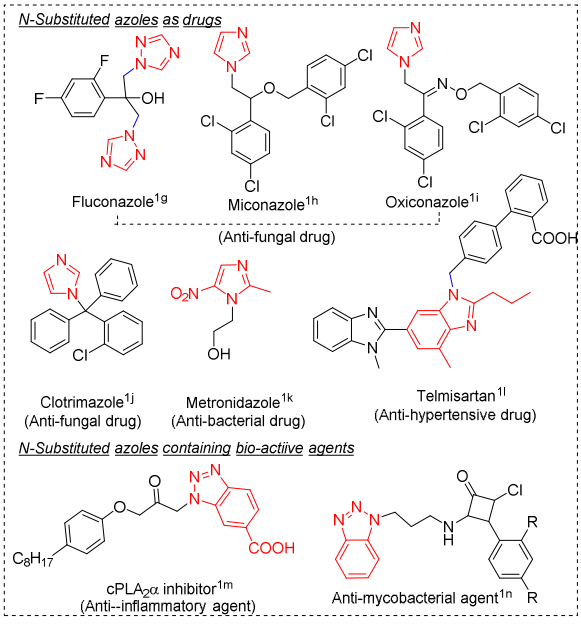

Fig 1. Medicinally important N-substituted azoles

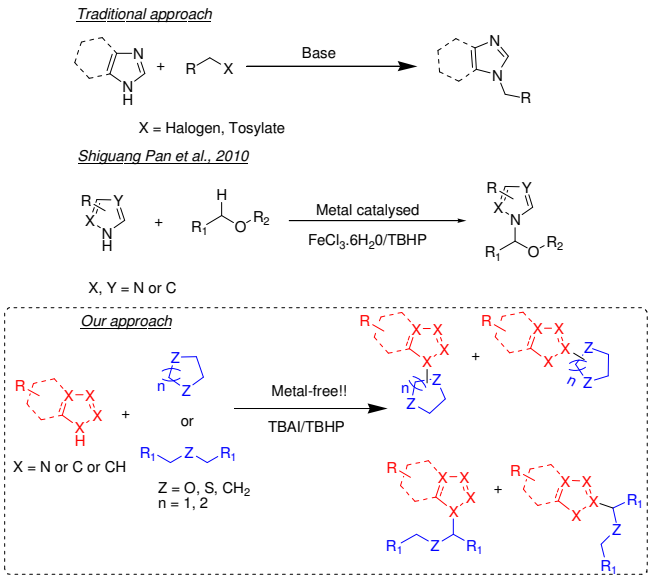

Fig 2. Previous and present approaches for the alkylation of N-azoles

In continuation to our interest towards the development of C-H activation/functionalization methods,[9] here we have developed a general and cross-dehydrogenative coupling (CDC) method for the coupling of azoles with α-Csp^3-H of ethers and thioethers under metal-free condition. Tetrabutylammonium iodide in presence of *tert*-butyl hydroperoxide (TBHP) was utilized for the activation of α-Csp^3-H of ethers and thioethers. The present method has wide applicability and successfully work with diverse un/substituted azoles such as 1*H*-benzimidazole, 9*H*-purine, 1*H*-benzotriazole, 1*H*-1,2,3-triazole, 1*H*-1,2,4-triazole and 1*H*-pyrazole.

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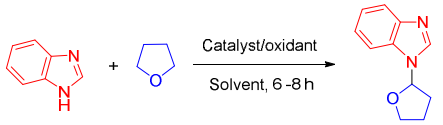
To optimize the reaction condition, 1*H*-benzimidazole **1** and tetrahydrofuran (THF) **2** were used as coupling partners and all the attempts towards reaction optimization studies are summarized in Table 1. In the first instance, 1*H*- benzimidazole on coupling with THF in the presence of 10 mol% of TBAI and two equivalent of 70% aq. TBHP in 1,2-dichloroethane (DCE) gave expected coupled product **3a** with 45% yield (Table 1, entry a) as confirmed by

NMR and MS spectroscopy. Increase in the amount of TBHP from 2 equivalents to 3.5 equivalents yielded 72% of coupled product **3a** (Table 1, entry b). Further increases in the amount of TBHP did not affect the formation of coupled product **3a** (Result not shown). Change in the amount of THF also effects the yield, wherein decreased in the amount of THF from 15 eq. → 5 eq. lowers the yield of **3a** from 72% to 60% (Table 1, entries c-d). When the reaction was performed in neat THF, no improvement has been noticed (Table 1, entry e). Change in the solvent from DCE to ethyl acetate (EtOAc) has also not shown any improvement (Table 1, entry f). Effect of temperature has also been studied and when the reaction was conducted at rt, coupled product **3a** was observed with 50% yield but the reaction took comparatively longer time (Table 1, entry g). Change in the source of iodide ions such as sodium iodide (NaI), potassium iodide (KI) also tried, but none of these conditions gave better results (Table 1, entries h-i). With molecular iodine (I_2), the expected coupled product **3a** was observed in only 55% yield (Table 1, entry j). In the absence of TBHP, no coupling was observed (Table 1, entry k). Based on the above results, the best coupling condition involved 15 equivalents of THF, 10 mol% of TBAI and 3.5 equivalents of TBHP using DCE as solvent at 80 ^{0}C.

Table 1. Optimization studies[a]



1 2 3a

Entry	Ether 2 (Eq.)	Catalyst	Oxidant (Eq.)[c]	Solvent	Temp. (°C)	Yield (%)[d]
a	THF (15)	TBAI (0.1)	TBHP (2)	DCE	80	45
b	THF (15)	TBAI (0.1)	TBHP (3.5)	DCE	80	72
c	THF (10)	TBAI (0.1)	TBHP (3.5)	DCE	80	70
d	THF (5)	TBAI (0.1)	TBHP (3.5)	DCE	80	60
e[b]	THF	TBAI (0.1)	TBHP (3.5)	-	80	70
f	THF (15)	TBAI (0.1)	TBHP (3.5)	EtOAc	80	70
g	THF (15)	TBAI (0.1)	TBHP (3.5)	DCE	rt	50
h	THF (15)	NaI (1)	TBHP (3.5)	DCE	80	65
i	THF (15)	KI (1)	TBHP (3.5)	DCE	80	65
j	THF (15)	I_2(1)	TBHP (3.5)	DCE	rt	55
k	THF (15)	TBAI (0.1)	-	DCE	80	0

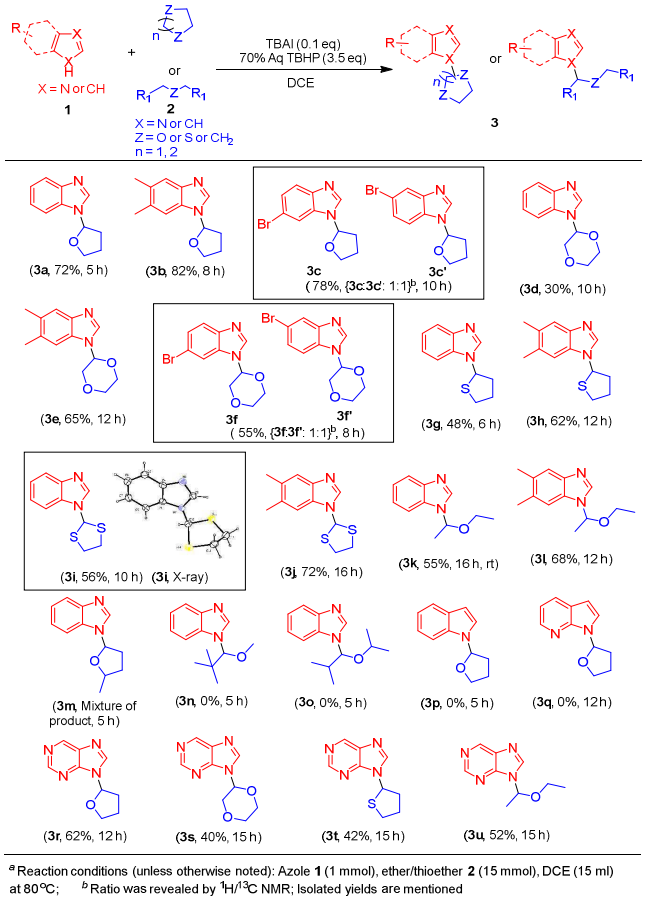
[a]**Reaction condition** (unless otherwise noted): All the reactions were performed with 1 mmol of azoles; [b]Performed using THF as solvent; [c]70% aq. TBHP; [d]Isolated yield

To know the generality of optimized condition, the coupling of various un/substituted 1*H*-benzimidazole with ethers and thioethers were also investigated and the results are given in Table 2. The presence of substitutions on 1*H*-benzimidazole greatly effects the formation of coupled products. The 5,6-dimethyl-1*H*-benzimidazole on coupling with THF gave corresponding coupled product **3b** with excellent 82% yield. 6-Bromo-1*H*-benzimidazole with THF gave mixture of un-separable regio-isomers **3c** and **3c'** with overall yield of 78%. 1*H*-Benzimidazole **1** underwent coupling with 1,4-dioxane and gave **3d** with 30% yield while on the other hand, 5,6-dimethyl-1*H*-benzimidazole coupled with 1,4-dioxane and gave corresponding **3e** with the yield of 65%. Similarly, 6-bromo-1*H*-benzimidazole when coupled 1,4-dioxane, gave unseparable mixture of regio-isomers **3f/3f'** with overall 55% yield.

Under optimized condition, un/substituted 1*H*-benzimidazole also underwent coupling with tetrahydrothiophene and gave corresponding coupled product with moderate to good yield. 1*H*-

Benzimidazole **1** when coupled with tetrahydrothiophene, corresponding coupled product **3g** was observed with 48% yield. 5,6-Dimethylbenzimidazole underwent coupling with tetrahydrothiophene and gave **3h** with 62% yield. Benzimidazole **1** also underwent coupling with 1,3-dithiolane and gave respective product **3i** with 56% yield. The structure of coupled product **3i [**1-(1, 3-dithiolan-2-yl)-1*H*-benzo[*d*]imidazole] was also confirmed with X-ray (details given in SI). 5,6-Dimethylbenzimidazole also underwent coupling with 1,3-dithiolane and gave **3j** with 72% yield. The optimized condition also worked with alicyclic ether such as diethyl ether and gave corresponding coupled product **3k** with 55% yield. Coupled product **3l** was formed with 68% yield in reaction between 5,6-dimethylbenzimidazole and diethyl ether. Substituted cyclic ether such as 2-methyltetrahydrofuran when tried, mixture of products was observed. Apart from diethyl ether, other alicyclic ether such as di-*iso*-propylether and *tert*-butylmethyl ether did not work under optimized condition. *N*-Heterocycles such as indole and 7-aza-indole also did not work under optimized condition. Interestingly when purine tried, coupling underwent and gave coupled product with good to moderate yields. Purine with THF, 1,4-dioxane, tetrahydrothiophene and diethyl ether gave corresponding coupled product **3r**, **3s**, **3t** and **3u** with 62%, 40%, 42% and 52% yields respectively. The electron-donating group containing 1*H*-benzimidazole gave comparatively better yield.

Table 2. Coupling of un/substituted azoles with ethers/thioethers

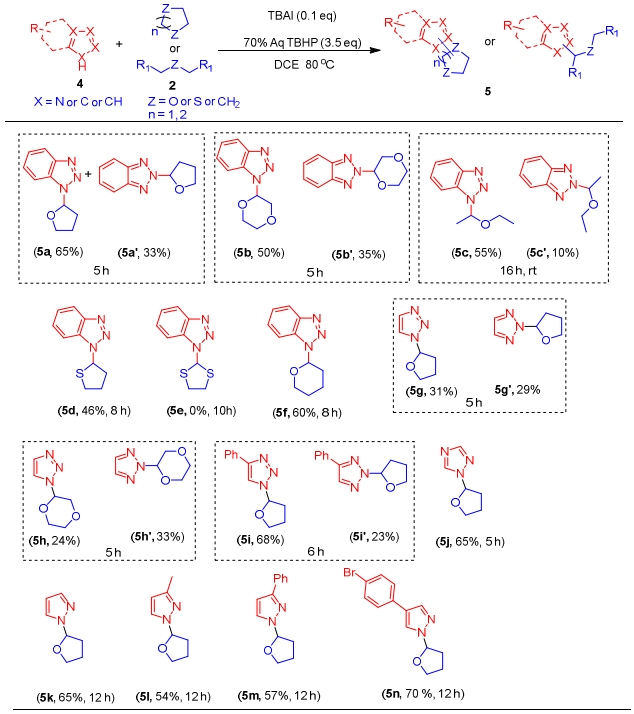


[a] Reaction conditions (unless otherwise noted): Azole **1** (1 mmol), ether/thioether **2** (15 mmol), DCE (15 ml) at 80°C; [b] Ratio was revealed by $^{1}H/^{13}C$ NMR; Isolated yields are mentioned

Next, we extended to other azoles such as 1*H*-1,2,3-benzotriazole, 1*H*-1,2,3-triazoles and the optimized method work efficiently and gave corresponding separable regio-isomeric mixture of coupled product with moderate to good yield (Table 3). 1*H*-1,2,3-Benzotriazole when treated with THF under optimized condition, mixture of separable regio-isomers **5a** and **5a'** was observed with 65% and 33% yields respectively. 1,4-Dioxane also underwent coupling smoothly and gave mixture of separable regio-isomers **5b** and **5b'** with 50% and 35% yields. Similarly, 1*H*-1,2,3-benzotriazole also underwent coupling with diethyl ether and gave a mixture of regio-isomer **5c** and **5c**', with 55% and 10% yield respectively. 1*H*-1,2,3-Benzotriazole also underwent coupling with tetrahydrothiopene and gave coupled product **5d** (with 46% yield) as major isolable regio-isomer. 1,3-Dithiolane did not work with benzotriazole while pyran coupled

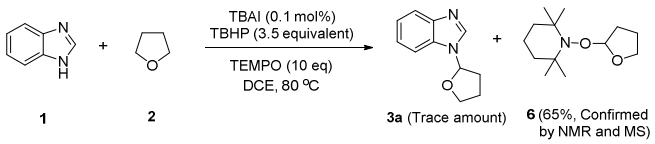
successfully and gave **5f** (with 60% yield) as major isolable regio-isomer. 1*H*-1,2,3-Triazole underwent coupling with THF and gave corresponding mixture of separable regio-isomers **5g** and **5g'** with 31 and 29% yield. Under optimized condition, 1*H*-1,2,3-triazole also coupled with 1,4-dioxane and mixture of regio-isomers **5h** and **5h'** with 24 and 33% yield were isolated. 4-Phenyl-1*H*-1,2,3-triazole when tried, also underwent coupling with THF and gave mixture of separable regio-isomers **5i** and **5i'** with 68 and 23% yield respectively. To our delight, optimized method also work with 1*H*-1,2,4-triazole and underwent coupling with THF and gave corresponding coupled product **5j** with 65% yield**.** 1*H*-Pyrazole when tried for coupling with THF under optimized condition, gave corresponding coupled product **5k** with 65% yield. 3-Methyl and 3-phenyl-1*H*-pyrazole also underwent coupling with THF and gave respective coupled product **5l** and **5m** with 54 and 57% yield respectively. 4-(Substituted phenyl)-1*H*-pyrazole also work under optimized method and gave coupled product **5n** with 70% yield.

Table 3. Coupling of un/substituted azoles with ethers/thioethers



[a]**Reaction conditions** (unless otherwise noted): Azole **4** (1 mmol), ether/thioether **2** (15 mmol), DCE (15 ml) at 80 °C; Isolated yields are mentioned

To gain insight into the reaction mechanism involved for the coupling of azoles with ethers/thioethers, some experiments have been conducted. When the coupling of benzimidazole with THF in the presence of free-radical scavenger such as 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) was performed, the yield of the coupled product **3a** was decreased drastically and the formation of THF-TEMPO coupled product **6** was observed, confirming the involvement of free-radical pathway. Surprisingly, even in the presence of 10 equivalent of TEMPO, the formation of coupled product was not completely suppressed (Scheme 1) indicated the first formation of radical **2a** followed by immediate conversion into cation **2b** (as observed earlier)[7,8] which was attacked by azoles and gave *N*-alkylated product. Based on literature[7,8] and our experimental findings, the plausible mechanism might involved the radical/oxonium or thionium ion intermediacy and followed the path as depicted in Fig 3.



Scheme 1. Coupling in presence of free-radical scavenger

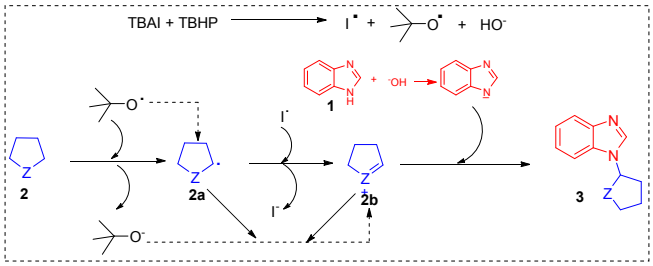


Fig 3. Plausible mechanism for the coupling of azoles with ethers/thioethers

In conclusion, we have developed a general, metal-free- TBAI /TBHP catalyzed method for the *N*-alkylation of azoles *via* α-Csp^3-H activation of ethers and thioethers. The optimized method works successfully with a diverse range of un/substituted azoles as well as ethers and thioethers. Moreover, the present method gives a diverse range of *N*-substituted azoles and can be explored for pharmacological applications as well as synthons/intermediates in organic synthesis.

Experimental section:

General Information:

^{1}H NMR, ^{13}C NMR, and DEPT were recorded on 400 MHz spectrometer using $CDCl_3$ solvent. Melting points were recorded on digital melting point apparatus. HRMS spectras were recorded UHD-Q-TOF HRMS machines. MALDI MS were recorded on MALDI-TOF mass spectrophotometer using 2,5-Dihydroxy benzoic acid/ α-Cyano-4-hydroxy cinnamic acid as matrix in acetonitrile: water containing 0.01% TFA. GC-MS was obtained by using GC-EI-Mass spectrophotometer. Three-dimensional X-ray intensity diffraction data for a block-shaped single crystal was recorded on *X-ray Diffractometer* having *CCD Camera.*

General procedure for the synthesis of compounds in Table 2:

1 mmol of azole **1** (1*H*-Benzimidazole, 5,6-dimethyl-1*H*-benzimidazole, 6-bromo-1*H*-benzimidazole and 9*H*-Purine), 15 mmol of ether/thiother **2**, 3.5 mmol of *tert*-butyl hydroperoxide (70% in water), and 0.01 mmol of tetrabutylammonium iodide (TBAI) was dissolved in 8 ml of DCE solvent. Reaction mixture was refluxed until consumption of starting material. After completion of reaction, solvent was evaporated from reaction mixture and extracted with ethyl acetate solvent. Product was purified by using 1% methanol and DCM solvent system on flash chromatography.

General procedure for the synthesis of compounds in Table 3:

1 mmol of azole **4** (1*H*-Benzotriazole, 1*H*-1,2,3-triazole, 1*H*-1,2,4-triazole, pyrazole) 15 mmol of ether/thioether **2**, 3.5 mmol of *tert*- butyl hydroperoxide (70% in water), and 0.01 mmol of tetrabutylammonium iodide was dissolved in 8 ml of DCE solvent. Reaction mixture was refluxed until consumption of starting material. After completion of reaction, solvent was evaporated from reaction mixture and extracted with ethyl acetate solvent. Product was purified by using 15% ethyl acetate and hexane solvent system on flash chromatography. (Note: We observed that 1*H*-1,2,3-triazole containing products underwent degradation on storage at room temperature).

Spectral data:

1-(Tetrahydrofuran-2-yl)-1*H*-benzo[*d*]imidazole[1] 3a (IIIM/724/1572/CN/18):

Colorless liquid; TLC $R_f = 0.5$ (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.85 – 7.75 (m, 1H), 7.50 – 7.42 (m, 1H), 7.36 – 7.25 (m, 2H), 6.19 (dd, J = 5.6, 4.0 Hz, 1H), 4.23– 4.17 (m, 1H), 4.10– 4.04 (m, 1H), 2.52– 2.44 (m, 2H), 2.19– 2.12 (m, 2H); ^{13}C

NMR (100.61 MHz, $CDCl_3$) δ 144.1, 140.2, 132.6, 123.1, 122.5, 120.3, 110.5, 86.0, 68.9, 31.8, 24.2; HRMS (ESI+) calcd. for $C_{11}H_{13}N_2O$: 189.1028 (M+ H), found 189.1028.

5,6-Dimethyl-1-(tetrahydrofuran-2-yl)-1*H*-benzo[*d*]imidazole 3b (IIIM/724/1572/CN/65):

Colorless liquid; TLC R_f = 0.6 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.55 (s, 1H), 7.23 (s, 1H), 6.14 (t, *J* = 4.7 Hz, 1H), 4.17 (dd, *J* = 14.7, 7.1 Hz, 1H), 4.05 (dd, *J* = 15.3, 7.7 Hz, 1H), 2.50 – 2.30 (m, 8H), 2.15 (dd, *J* = 14.3, 7.1 Hz, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 142.9, 139.5, 132.2, 131.3, 131.2, 120.3, 110.6, 85.9, 68.8, 31.7, 24.2, 20.5, 20.2; HRMS (ESI+) calcd. for $C_{13}H_{17}N_2O$: 217.1341 (M+ H), found 217.1349.

6-Bromo-1-(tetrahydrofuran-2-yl)-1*H*-benzo[*d*]imidazole 3c (IIIM/724/1572/CN/48)

& 5-bromo-1-(tetrahydrofuran-2-yl)-1*H*-benzo[*d*]imidazole 3c' (IIIM/724/1572/CN/48):

Ratio was calculated by ^{1}H and ^{13}C NMR. Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.91 (s, 0.47H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.33 (dd, *J* = 22.5, 8.5 Hz, 1.51H), 6.10 (dd, *J* = 5.8, 2.8 Hz, 1H), 4.19 – 4.09 (m, 1H), 4.08– 3.99 (m, 1H), 2.50 – 2.30 (m, 2H), 2.19 – 1.98 (m, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 141.2, 140.8, 126.1, 125.8, 123.0, 121.4, 116.4, 115.5, 113.7, 111.8, 86.1, 69.0, 31.8, 24.1; HRMS (ESI+) calcd. for $C_{11}H_{12}BrN_2O$: 267.0133 (M+ H), found 267.0139.

1-(1,4-Dioxan-2-yl)-1*H*-benzo[*d*]imidazole 3d (IIIM/724/1572/CN/27):[10]

Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.75 (d, *J* = 6.0 Hz, 1H), 7.44 (d, *J* = 5.6 Hz, 1H), 7.29 – 7.18 (m, 2H), 5.63 (s, 1H), 4.07 (d, *J* = 4.6 Hz, 2H), 3.88 – 3.59 (m, 4H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 143.2, 141.4, 133.1, 123.6, 122.9, 120.3, 110.6, 78.5, 67.9, 66.4, 63.4; HRMS (ESI+) calcd. for $C_{11}H_{13}N_2O_2$: 205.0977 (M+ H), found 205.0978.

1-(1,4-Dioxan-2-yl)-5,6-dimethyl-1*H*-benzo[*d*]imidazole 3e (IIIM/724/1572/CN/67):

Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.57 (s, 1H), 7.28 (s, 1H), 5.65 (t, *J* = 3.6 Hz, 1H), 4.45 (t, *J* = 6.1 Hz, 1H), 4.24 – 4.06 (m, 1H), 3.97 – 3.75 (m, 4H), 2.38 (d, *J* = 7.3 Hz, 6H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 142.5, 140.8, 132.7, 131.7, 131.4, 120.3, 110.7, 78.5, 68.1, 66.4, 63.4, 20.5, 20.2; HRMS (ESI+) calcd. for $C_{13}H_{17}N_2O_2$: 233.1290 (M+ H), found 233.1293.

6-Bromo-1-(1,4-dioxan-2-yl)-1*H*-benzo[*d*]imidazole 3f (IIIM/724/1572/CN/61)

and 5-bromo-1-(1,4-dioxan-2-yl)-1*H*-benzo[*d*]imidazole 3f' (IIIM/724/1572/CN/61):

Ratio was calculated by ^{1}H and ^{13}C NMR. Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 1H), 7.90 (s, 0.46H), 7.66 – 7.57 (m, 1H), 7.35 (d, *J* = 4.8 Hz, 1.30H), 5.66 – 5.55 (m, 1H), 4.15 – 3.99 (m, 2H), 3.89 – 3.63 (m, 4H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 142.6, 142.2, 126.5, 126.2, 123.3, 121.7, 116.8, 115.8, 113.9, 111.9, 78.5, 67.8, 66.4, 63.1; HRMS (ESI+) calcd. for $C_{11}H_{12}BrN_2O_2$: 283.0082 (M+ H), found 283.0084.

1-(Tetrahydrothiophen-2-yl)-1*H*-benzo[*d*]imidazole 3g (IIIM/724/1572/CN/23):

Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.40 (d, *J* = 6.9 Hz, 1H), 7.28 – 7.09 (m, 2H), 6.00 (s, 1H), 3.29 – 3.16 (m, 1H), 2.97 (dd, *J* = 16.0, 9.3 Hz, 1H), 2.39–2.15 (m, 4H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 144.3, 141.8, 133.3, 122.9, 122.5, 120.5, 110.0, 63.0, 38.2, 33.0, 28.7; HRMS (ESI+) calcd. for $C_{11}H_{13}N_2S$: 205.0799 (M+ H), found 205.0797.

5,6-Dimethyl-1-(tetrahydrothiophen-2-yl)-1*H*-benzo[d]imidazole 3h(IIIM/724/1572/CN/68):

Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.48 (s, 1H), 7.14 (s, 1H), 5.99 – 5.87 (m, 1H), 3.22 (dd, *J* = 10.2, 6.2 Hz, 1H), 2.96 (dd, *J* = 16.0, 9.2 Hz, 1H), 2.41 – 2.23 (m, 8H), 2.22 – 2.08 (m, 1H), 2.06 – 1.89 (m, 1H); ^{13}C NMR

(100.61 MHz, $CDCl_3$) δ 142.1, 140.0, 131.0, 130.8, 130.3, 119.5, 109.1, 61.9, 37.1, 31.9, 27.6, 19.6, 19.2; HRMS (ESI+) calcd. for $C_{13}H_{17}N_2S$: 233.1112 (M+ H), found 233.1128.

1-(1, 3-Dithiolan-2-yl)-1*H*-benzo[*d*]imidazole 3i (IIIM/724/1572/CN/38):

White solid; M.pt. 110 ^{0}C; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.73 (dd, *J* = 6.6, 2.0 Hz, 1H), 7.42 (dd, *J* = 6.6, 1.9 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.00 (s, 1H), 3.54 – 3.32 (m, 4H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 144.5, 141.4, 132.8, 123.3, 122.9, 120.6, 110.4, 65.8, 39.5; HRMS (ESI+) calcd. for $C_{10}H_{11}N_2S_2$: 223.0364 (M+ H), found 223.0368.

1-(1,3-Dithiolan-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazole 3j (IIIM/724/1572/CN/69):

White solid; M.pt. 135 ^{0}C; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.54 (s, 1H), 7.24 (s, 1H), 7.01 (s, 1H), 3.58 – 3.40 (m, 4H), 2.39 (d, *J* = 16.5 Hz, 6H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 143.1, 140.7, 132.5, 131.8, 131.6, 120.6, 110.5, 65.8, 39.5, 20.6, 20.2; HRMS (ESI+) calcd. for $C_{12}H_{15}N_2S_2$: 251.0677 (M+ H), found 251.0694.

1-(1-Ethoxyethyl)-1*H*-benzo[*d*]imidazole 3k (IIIM/724/1572/CN/20)[7]:

(Note: Reaction with ethers was carried out at room temperature with longer reaction time) Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.78 (dd, *J* = 5.3, 2.9 Hz, 1H), 7.60 – 7.49 (m, 1H), 7.27 (dd, *J* = 5.8, 2.9 Hz, 2H), 5.68 (q, *J* = 5.9 Hz, 1H), 3.45– 3.35 (m, 1H), 3.31 – 3.18 (m, 1H), 1.73 (d, *J* = 6.0 Hz, 3H), 1.10 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 142.8, 140.0, 131.3, 122.2, 121.6, 119.2, 110.0, 82.2, 63.0, 21.1, 13.7; HRMS (ESI+) calcd. for $C_{11}H_{15}N_2O$: 191.1184 (M+ H), found 191.1185.

1-(1-Ethoxyethyl)-5,6-dimethyl-1*H*-benzo[*d*]imidazole 3l (IIIM/724/1572/CN/66):

Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.49 (s, 1H), 7.27 (s, 1H), 5.52 (q, *J* = 6.0 Hz, 1H), 3.35 (dd, *J* = 15.7, 7.3 Hz, 1H), 3.23

(dd, *J* = 15.1, 7.8 Hz, 1H), 2.30 (d, *J* = 8.1 Hz, 6H), 1.69 (d, *J* = 6.0 Hz, 3H), 1.08 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 142.8, 140.3, 132.2, 131.4, 131.0, 120.3, 111.1, 82.9, 63.9, 22.1, 20.5, 20.2, 14.8; HRMS (ESI+) calcd. for $C_{13}H_{19}N_2O$: 219.1497 (M+ H), found 219.1505.

9-(Tetrahydrofuran-2-yl)-9*H*-purine 3r (IIIM/724/1572/CN/53):

Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.99 (s, 1H), 8.23 (s, 1H), 6.40 (dd, *J* = 6.2, 2.9 Hz, 1H), 4.32 (dd, *J* = 14.3, 7.0 Hz, 1H), 4.11 (dd, *J* = 15.4, 7.6 Hz, 1H), 2.73 – 2.46 (m, 2H), 2.27 – 2.11 (m, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 152.3, 150.5, 148.5, 143.4, 134.7, 85.9, 69.9, 32.3, 24.3; HRMS (ESI+) calcd. for $C_9H_{11}N_4O$: 191.0933 (M+ H), found 191.0927.

9-(1,4-dioxan-2-yl)-9*H*-purine 3s (IIIM/724/1572/CN/58):

Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.95 (s, 1H), 8.46 (s, 1H), 6.05 – 5.94 (m, 1H), 4.15 (dd, *J* = 11.8, 1.3 Hz, 1H), 4.06 (dd, *J* = 12.0, 5.7 Hz, 1H), 3.91– 3.81 (m, 4H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 152.9, 151.0, 148.8, 143.7, 133.8, 77.2, 68.3, 66.2, 64.3; HRMS (ESI+) calcd. for $C_9H_{11}N_4O_2$: 207.0882 (M+ H), found 207.0878.

9-(Tetrahydrothiophen-2-yl)-9*H*-purine 3t (IIIM/724/1572/CN/59):

Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.93 (s, 1H), 8.45 (s, 1H), 6.37 – 6.21 (m, 1H), 3.31– 3.26 (m, 1H), 3.03 – 2.97 (m, 1H), 2.41 – 2.32 (m, 2H), 2.31 – 2.15 (m, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 152.4, 150.9, 148.7, 144.5, 134.9, 62.0, 38.9, 33.3, 28.7; HRMS (ESI+) calcd. for $C_9H_{11}N_4S$: 207.0704 (M+ H), found 207.0696.

9-(1-Ethoxyethyl)-9*H*-purine 3u (IIIM/724/1572/CN/62):

Colorless liquid; TLC $R_f = 0.5$ (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.92 (s, 1H), 8.26 (s, 1H), 6.00 (q, *J* = 6.0 Hz, 1H), 3.56 – 3.39 (m, 1H), 3.35 – 3.19 (m, 1H), 1.74 (d, *J* = 6.0 Hz, 3H), 1.11 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 152.7, 151.1, 148.7, 142.7, 134.0, 80.8, 64.8, 22.4, 14.7; HRMS (ESI+) calcd. for $C_9H_{13}N_4O$: 193.1089 (M+ H), found 193.1088.

1-(Tetrahydrofuran-2-yl)-1*H*-benzo[*d*][1,2,3]triazole 5a (IIIM/724/1572/CN/21(a)):[10]

Colorless liquid; TLC $R_f = 0.4$ (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 6.44 (dd, *J* = 6.5, 1.6 Hz, 1H), 4.10 – 3.88 (m, 2H), 3.20 – 3.10 (m, 1H), 2.57– 2.47 (m, 1H), 2.32 – 2.43(m, 1H), 2.19 – 2.04 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 146.2, 132.8, 127.5, 124.1, 119.7, 110.4, 87.9, 69.2, 30.8, 24.3; HRMS (ESI+) calcd. for $C_{10}H_{12}N_3O$: 190.0980 (M+ H), found 190.0856; MALDI TOF MS: calcd for $C_{10}H_{12}N_3O$ $(M+H)^+$ 190.0980, found 190.0971.

2-(Tetrahydrofuran-2-yl)-2*H*-benzo[*d*][1,2,3]triazole 5a' (IIIM/724/1572/CN/21(b)) :

Colorless liquid; TLC $R_f = 0.8$ (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 6.4, 2.9 Hz, 2H), 7.38 (dd, *J* = 6.5, 2.8 Hz, 2H), 6.60 (d, *J* = 4.8 Hz, 1H), 4.33 (dd, *J* = 14.0, 7.4 Hz, 1H), 4.13 (dd, *J* = 14.3, 7.4 Hz, 1H), 2.77– 2.54 (m, 1H), 2.54– 2.45 (m, 2H), 2.17 – 2.09 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 144.2, 126.6, 118.4, 94.1, 70.2, 32.3, 24.3; HRMS (ESI+) calcd. for $C_{10}H_{12}N_3O$: 190.0980 (M+ H), found 190.0854; MALDI TOF MS: calcd for $C_{10}H_{12}N_3O$ $(M+H)^+$ 190.0980, found 190.0997.

1-(1,4-Dioxan-2-yl)-1*H*-benzo[*d*][1,2,3]triazole 5b (IIIM/724/1572/CN/29(a)):[10]

White solid; M.pt. 85 ^{0}C; TLC $R_f = 0.4$ (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 6.10 (dd, *J* = 7.2, 2.8 Hz, 1H), 4.54 (dd, *J* = 11.8, 7.3 Hz, 1H), 4.24 (dd, *J* = 11.9, 2.7 Hz,

1H), 4.03 – 3.80 (m, 4H); ^{13}C NMR (100.16 MHz, $CDCl_3$) δ146.0, 132.5, 127.9, 124.4, 120.1, 110.6, 82.0, 67.3, 65.9, 65.3; HRMS (ESI+) calcd. for $C_{10}H_{12}N_3O_2$: 206.0930 (M+ H), found 206.0925.

2-(1,4-Dioxan-2-yl)-2*H*-benzo[*d*][1,2,3]triazole 5b' (IIIM/724/1572/CN/29(b)):

White solid; M.pt. 85 ^{0}C; TLC R_f = 0.8 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.42 (dd, *J* = 6.6, 3.0 Hz, 2H), 6.12 (dd, *J* = 6.4, 2.8 Hz, 1H), 4.52 (dd, *J* = 11.9, 6.5 Hz, 1H), 4.22 (dd, *J* = 11.9, 2.7 Hz, 1H), 4.15 – 4.07 (m, 1H), 4.05 – 3.94 (m, 1H), 3.90 (t, *J* = 3.0 Hz, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ144.3, 127.1, 118.6, 86.4, 67.6, 65.7, 65.2; HRMS (ESI+) calcd. for $C_{10}H_{12}N_3O_2$: 206.0930 (M+ H), found 206.0932.

1-(1-Ethoxyethyl)-1*H*-benzo[*d*][1,2,3]triazole (5c) (IIIM/724/1572/CN/22(a)):

Colorless liquid; TLC R_f = 0.5 (30 %EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.3 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 6.19 (q, *J* = 6.1 Hz, 1H), 3.55- 3.40 (m, 1H), 3.24 – 3.10 (m, 1H), 1.79 (d, *J* = 6.1 Hz, 3H), 1.06 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 146.8, 131.1, 127.4, 124.1, 120.0, 111.1, 87.0, 64.3, 21.1, 14.7; HRMS (ESI+) calcd. for $C_{10}H_{14}N_3O$: 192.1137 (M+ H), found 192.1009; GC-MS(EI) *m/z* (relative intensity) 192.2 (M^+, 2.1), 176.3 (4.65), 147.4 (100), 119.5 (53.98), 91.3 (88.3), 64.4 (37.04), 45.4 (77.61).

2-(1-Ethoxyethyl)-2*H*-benzo[*d*][1,2,3]triazole 5c' (IIIM/724/1572/CN/22 (b)):

Colorless liquid; TLC R_f = 0.8 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.9, 2.4 Hz, 2H), 7.33 (dd, *J* = 6.0, 2.3 Hz, 2H), 6.00 (q, *J* = 5.8 Hz, 1H), 3.59 – 3.42 (m, 1H), 3.36 – 3.17 (m, 1H), 1.85 (d, *J* = 5.9 Hz, 3H), 1.09 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 144.1, 126.7, 118.5, 91.5, 65.1, 21.5, 14.6; HRMS (ESI+) calcd. for $C_{10}H_{14}N_3O$:

192.1137 (M+ H), found 192.1009; GC-MS(EI) *m/z* (relative intensity) 192.2 (M^+, 2.2), 176.3 (5.7), 147.4 (100), 119.4 (68.2), 91.3 (86.6), 77.3 (33.54), 64.4 (41).

1-(Tetrahydrothiophen-2-yl)-1*H*-benzo[*d*][1,2,3]triazole 5d (IIIM/724/1572/CN/24):

Colorless liquid; TLC $R_f = 0.5$ (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 6.44 – 6.35 (m, 1H), 3.31 – 3.20 (m, 1H), 3.13 – 2.99 (m, 1H), 2.94 – 2.84 (m, 1H), 2.57 – 2.36 (m, 2H), 2.32 – 2.22 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 146.4, 132.1, 127.1, 123.9, 120.3, 110.3, 65.9, 37.1, 33.8, 29.9; HRMS (ESI+) calcd. for $C_{10}H_{12}N_3S$: 206.0752 (M+ H), found 206.0621; MALDI TOF MS: calcd for $C_{10}H_{11}N_3S$ $(M+H)^+$ 206.0752, found 206.0724.

1-(Tetrahydro-2H-pyran-2-yl)-1*H*-benzo[*d*][1,2,3]triazole 5f (IIIM/724/1582/CN/01):

Colorless liquid; TLC $R_f = 0.4$ (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 6.05 (dd, *J* = 8.2, 2.8 Hz, 1H), 3.96 (dd, *J* = 11.6, 4.4 Hz, 1H), 3.86 – 3.72 (m, 1H), 2.71 – 2.56 (m, 1H), 2.29 – 2.11 (m, 2H), 1.87 – 1.68 (m, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 146.2, 132.5, 127.4, 124.1, 119.8, 111.1, 85.6, 66.8, 29.2, 24.9, 21.4; HRMS (ESI+) calcd. for $C_{11}H_{13}N_3O$: 204.1137 (M+ H), found 204.1002; MALDI TOF MS: calcd for $C_{11}H_{13}N_3O$ $(M+H)^+$ 204.1137, found 204.1145.

1-(Tetrahydrofuran-2-yl)-1*H*-1, 2, 3-triazole 5g (IIIM/724/1572/CN/30(a)):

Colorless liquid; TLC $R_f = 0.3$ (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 2H), 6.25 (d, *J* = 6.5 Hz, 1H), 4.18 – 3.99 (m, 2H), 2.80 – 2.65 (m, 1H), 2.50– 2.40 (m, 1H), 2.16– 2.09 (m, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 133.6, 122.0, 89.4, 69.6, 32.2, 23.8; HRMS (ESI+) calcd. for $C_6H_{10}N_3O$: 140.0824 (M+ H), found 140.0771.

2-(Tetrahydrofuran-2-yl)-2*H*-1, 2, 3-triazole 5g' (IIIM/724/1572/CN/30(b)):

Colorless liquid; TLC $R_f = 0.7$ (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 2H), 6.39 – 6.26 (m, 1H), 4.16 (dd, *J* = 13.9, 7.4 Hz, 1H), 4.04 (dd, *J* = 13.9, 7.6 Hz, 1H), 2.72 – 2.56 (m, 1H), 2.45 – 2.36 (m, 2H), 2.20 – 2.01 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 134.5, 92.1, 69.5, 31.3, 24.4; HRMS (ESI+) calcd. for $C_6H_{10}N_3O$: 140.0824 (M+ H), found 140.0815; MALDI TOF MS: calcd for $C_6H_9N_3O$ $(M+H)^+$ 140.0824, found 140.0839.

1-(1,4-Dioxan-2-yl)-1*H*-1,2,3-triazole 5h (IIIM/724/1572/CN/31(a)):

Colorless liquid; TLC $R_f = 0.3$ (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.70 (s, 1H), 5.84 (s, 1H), 4.12 (dd, *J* = 11.9, 2.0 Hz, 1H), 4.01 (dd, *J* = 11.9, 5.9 Hz, 1H), 3.91 – 3.67 (m, 4H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 133.7, 122.7, 81.8, 68.2, 66.0, 64.3; HRMS (ESI+) calcd. for $C_6H_{10}N_3O_2$: 156.0773 (M+ H), found 156.0764.

2-(1,4-Dioxan-2-yl)-2*H*-1,2,3-triazole 5h' (IIIM/724/1572/CN/31 (b)):

Colorless liquid; TLC $R_f = 0.7$ (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 2H), 5.78 (dd, *J* = 7.1, 2.6 Hz, 1H), 4.27 (dd, *J* = 11.7, 7.3 Hz, 1H), 4.03 (dd, *J* = 11.8, 2.5 Hz, 1H), 3.95 – 3.84 (m, 2H), 3.80 – 3.70 (m, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 135.2, 84.8, 67.5, 65.8, 65.4; HRMS (ESI+) calcd. for $C_6H_{10}N_3O_2$: 156.0773 (M+ H), found 156.0764.

4-Phenyl-1-(tetrahydrofuran-2-yl)-1*H*-1,2,3-triazole 5i (IIIM/724/1572/CN/39 (a)):

Colorless liquid; TLC $R_f = 0.3$ (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.70 (d, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 6.26 – 6.19 (m, 1H), 4.09 (dd, *J* = 14.3, 7.4 Hz, 1H), 3.94 (dd, *J* = 14.1, 7.4 Hz, 1H), 2.63 – 2.52 (m, 1H), 2.41 – 2.22 (m, 2H), 2.03 – 1.88 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 148.0, 131.4, 130.3, 128.8, 128.5, 126.0, 92.3, 69.5, 31.3, 24.5; HRMS (ESI+) calcd. for $C_{12}H_{14}N_3O$: 216.1137 (M+ H), found 216.1134.

4-Phenyl-2-(tetrahydrofuran-2-yl)-2*H*-1, 2, 3-triazole 5i' (IIIM/724/1572/CN/39 (b)):

Colorless liquid; TLC $R_f = 0.7$ (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.75 – 7.69 (m, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 6.29 – 6.23 (m, 1H), 4.13 (dd, *J* = 14.4, 7.3 Hz, 1H), 3.99 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.68 – 2.56 (m, 1H), 2.45 – 2.27 (m, 2H), 2.10 – 1.96 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 148.0, 131.4, 130.3, 128.8, 128.5, 126.0, 92.3, 69.5, 31.3, 24.4; HRMS (ESI+) calcd. for $C_{12}H_{14}N_3O$: 216.1137 (M+ H), found 216.1132; MALDI TOF MS: calcd for $C_{12}H_{13}N_3O$ $(M+H)^+$ 216.1137, found 216.1156.

4-(Tetrahydrofuran-2-yl)-4*H*-1,2,4-triazole[1] 5j (IIIM/724/1572/CN/34):

Colorless liquid; TLC $R_f = 0.4$ (50% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.97 (s, 1H), 6.12 – 6.02 (m, 1H), 4.18 (dd, *J* = 13.4, 8.0 Hz, 1H), 4.04 (dd, *J* = 15.4, 7.6 Hz, 1H), 2.60 – 2.53 (m, 1H), 2.43– 2.33 (m, 1H), 2.21 – 1.99 (m, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 151.7, 142.1, 88.9, 69.6, 32.2, 23.5; HRMS (ESI+) calcd. for $C_6H_{10}N_3O$: 140.0824 (M+ H), found 140.0829.

1-(Tetrahydrofuran-2-yl)-1*H*-pyrazole 5k (IIIM/724/1572/CN/47) :

Colorless liquid; TLC $R_f = 0.4$ (20% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 2H), 6.20 (s, 1H), 5.93 (d, *J* = 6.3 Hz, 1H), 4.05 (dd, *J* = 14.1, 7.6 Hz, 1H), 3.91 (dd, *J* = 14.8, 7.4 Hz, 1H), 2.58 – 2.45 (m, 1H), 2.34 – 2.22 (m, 1H), 2.18 – 2.04 (m, 1H), 2.01 – 1.93 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 139.8, 128.0, 105.6, 90.0, 69.1, 31.7, 24.4; HRMS (ESI+) calcd. for $C_7H_{10}N_2O$: 139.0871 (M+ H), found 139.0859.

3-Methyl-1-(tetrahydrofuran-2-yl)-1*H*-pyrazole 5l (IIIM/724/1572/CN/50):

Colorless liquid; TLC $R_f = 0.4$ (20% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 5.97 (s, 1H), 5.89 – 5.79 (m, 1H), 4.05 (dd, *J* = 14.3, 7.0 Hz, 1H), 3.89 (dd, *J* = 14.5, 7.2 Hz, 1H), 2.56 – 2.41 (m, 1H), 2.34 – 2.16 (m, 4H), 2.14 – 2.03 (m, 1H), 2.01 – 1.91 (m, 1H);

^{13}C-NMR (100.61 MHz, $CDCl_3$) δ 149.2, 128.6, 105.4, 89.8, 69.0, 31.6, 24.5, 13.5; HRMS (ESI+) calcd. for $C_8H_{13}N_2O$: 153.1028 (M+ H), found 153.1025.

3-Phenyl-1-(tetrahydrofuran-2-yl)-1*H*-pyrazole 5m (IIIM/724/1572/CN/44):

Colorless liquid; TLC R_f = 0.4 (20% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.4 Hz, 2H), 7.51 (d, *J* = 1.9 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.21 (dd, *J* = 14.3, 6.8 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 5.96 (dd, *J* = 6.3, 1.8 Hz, 1H), 4.11 (dd, *J* = 13.6, 7.8 Hz, 1H), 3.94 (dd, *J* = 15.0, 7.4 Hz, 1H), 2.65 – 2.51 (m, 1H), 2.33 – 2.23 (m, 1H), 2.21 – 2.09 (m, 1H), 2.02 – 1.94 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 151.7, 133.6, 129.1, 128.5, 127.4, 125.7, 102.9, 90.3, 69.2, 31.9, 24.3; HRMS (ESI+) calcd. for $C_{13}H_{15}N_2O$: 215.1184 (M+ H), found 215.1198.

4-(4-Bromophenyl)-1-(tetrahydrofuran-2-yl)-1*H*-pyrazole (5n) (IIIM/724/1572/CN/37):

Colorless liquid; TLC R_f = 0.4 (20% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 4.1 Hz, 2H), 7.61 (s, 1H), 7.53 (d, *J* = 7.0 Hz, 2H), 6.57 (d, *J* = 1.3 Hz, 1H), 6.05 (d, *J* = 5.2 Hz, 1H), 4.20 (dd, *J* = 12.5, 7.0 Hz, 1H), 4.04 (dd, *J* = 14.2, 7.0 Hz, 1H), 2.74 – 2.62 (m, 1H), 2.43 – 2.34 (m, 1H), 2.32 – 2.18 (m, 1H), 2.10 – 2.01(m, 1H); ^{13}C-NMR (100.61 MHz, $CDCl_3$) δ 150.7, 132.6, 131.6, 129.3, 127.2, 121.4, 102.8, 90.3, 69.4, 32.0, 24.3; HRMS (ESI+) calcd. for $C_{13}H_{14}BrN_2O$: 293.0290 (M+ H), found 293.0287.

2, 2, 6, 6-Tetramethyl-1-((tetrahydrofuran-2-yl)oxy)piperidine 6 (IIIM/724/1572/CN/55):

Colorless liquid; TLC R_f = 0.8 (5% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (d, *J* = 4.5 Hz, 1H), 3.84 – 3.69 (m, 2H), 2.00 – 1.78 (m, 4H), 1.40 (d, *J* = 6.5 Hz, 6H), 1.20 – 0.87 (m, 12H); ^{13}C-NMR (100.61 MHz, $CDCl_3$) δ 109.5, 66.6, 60.1, 58.6, 40.0, 39.6, 33.8, 33.3, 31.2, 23.8, 20.4, 20.0, 17.2; HRMS (ESI+) calcd. for $C_{13}H_{26}NO_2$: 228.1964 (M+ H), found 228.1961.

Supporting Information

Copies of NMRs and MS spectra along with XRD analysis details. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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