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Short communication

Azide-enolate 1,3-dipolar cycloaddition in the synthesis of novel triazole-based miconazole analogues as promising antifungal agents

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ABSTRACT

Seven miconazole analogs involving 1,4,5-tri and 1,5-disubstituted triazole moieties were synthesized by azide-enolate 1,3-dipolar cycloaddition. The antifungal activity of these compounds was evaluated *in vitro* against four filamentous fungi, including *Aspergillus fumigatus*, *Trichosporon cutaneum*, *Rhizopus oryzae*, and *Mucor hiemalis* as well as three species of *Candida* spp. as yeast specimens. These pre-clinical studies suggest that compounds **4b**, **4d** and **7b** can be considered as drug candidates for future complementary biological studies due to their good/excellent antifungal activities.

1. Introduction

Miconazole is an azole-type drug with a broad spectrum of antifungal activity [1]. Due to the development of fungal resistance to this drug [2], the medicinal chemistry of anti-fungal agents has become an important field of study in organic synthesis [3]. To design new agents free of antibiotic resistance, the modification of functional groups in lead molecules has been an efficient strategy [4].

The triazole ring system, is a very well-recognized pharmacophore [5], this nitrogen heterocycle is prominent among U.S. FDA approved pharmaceuticals [6]. In particular, the 1,2,3-triazole core has been an increasingly important heterocycle with successful application in medicinal chemistry [7]. There are reports in literature about the biological activity of 1,2,3-triazole derivatives against cancer [8], malaria [9], tuberculosis [10], trypanosomiasis [11], leishmaniasis [12], HIV [13], influenza [14], dengue [15], pain (analgesic) [16], epilepsy [17], obesity [18], inflammation [19] and bacterial infection [20]. On the other hand, the study of 1,2,3-triazole scaffolds for the synthesis of antifungals [21], and particularly for miconazole analogs [22] has represented an ongoing and promising field of research in the last few years.

Cu-catalyzed azide-alkyne cycloaddition (CuAAC) represents the conventional method for obtaining 1,2,3-triazole moieties [23]. In recent years, azide-enolate 1,3-dipolar cycloaddition has emerged as a novel and potent tool for the synthetic approach to these valuable heterocycles [24]. Its application in medicinal chemistry has already been demonstrated [25].

We previously reported the antifungal activity of *benzyloxy* derivatives of miconazole [26]. As part of our ongoing research, we herein describe the synthesis/evaluation of *triazolic* analogs (1,4,5- and 1,5-substituted derivatives) that maintain the 1-(2-phenylethyl)imidazole core responsible for the biological activity of this compound [27] (Fig. 1).

2. Chemistry

From 2,4-dichlorobenzaldehyde **1** [Eq. (1)], the 1-(2,4-

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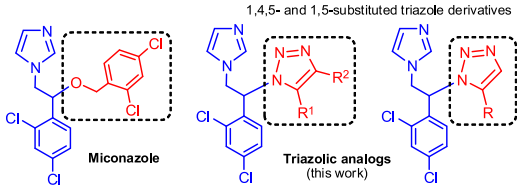
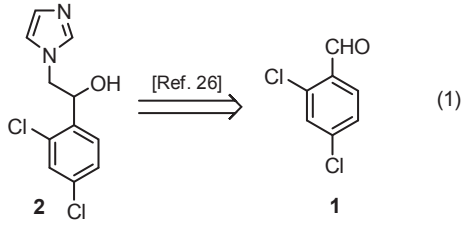
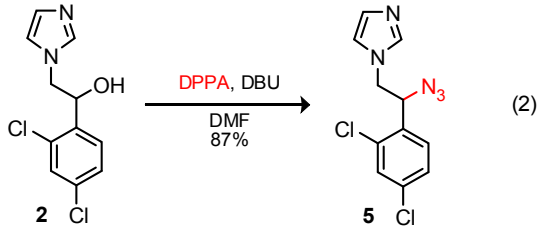


Fig. 1. Proposed triazolic analogs of miconazole.

dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol **2** (key precursor) was obtained in two steps according to our previous report [26]. Previously we published a novel method for preparing 1,4,5-trisubstituted 1,2,3-triazoles from benzylic alcohols *via* an azide-enolate 1,3-dipolar cycloaddition [28]. For this purpose we used diphenylphosphoryl azide (DPPA) as an azidating agent, followed by an efficient cycloaddition in the presence of active ketones. Miconazole analogs **4a**–**d** (1,4,5-trisubstituted derivatives) were synthesized in good yields (Table 1) by coupling acetylacetone **3a**, 2-benzoylacetophenone **3b**, benzoylacetonitrile **3c** and 1-(phenylsulfonyl)heptan-2-one **3d** under the aforementioned protocol.



Recently [29] we reported a novel method for obtaining 1,5-disubstituted triazoles from azides by coupling them with β-keto-phosphonates. Therefore, we decided to begin with the synthesis of benzyl azide **5** [Eq. (2)] as a precursor. The azidation of benzyl alcohol **2** was achieved using DPPA and DBU in dry DMF with good yields [30]. The synthesis of alkyl (**7a** and **7b**) and aryl (**7c**) 1,5-disubstituted triazole derivatives was carried out *via* an azide-enolate 1,3-dipolar cycloaddition (Table 2).



An outstanding aspects for compounds **7a**–**c** is a singlet signal in the range δ 7.6–7.4 ppm (^{1}H NMR spectra) attributable to the triazolic hydrogen [Eq. (3)]. Likewise, for all final compounds, the hydrogens H^a, H^b and H^c on the imidazole moiety can be observed in the ranges δ 7.7–7.4, 7.0–6.9 and 6.9–6.6 ppm respectively.

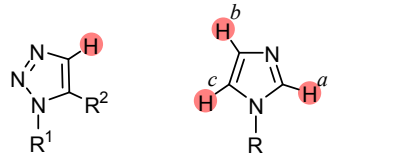
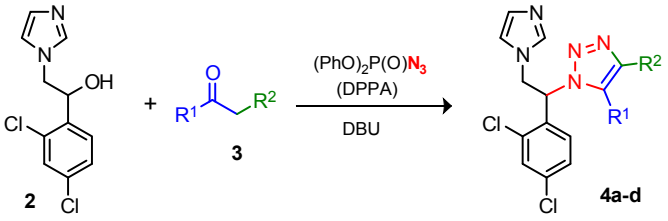


Table 1
Synthesis of 1,4,5-trisubstituted 1,2,3-triazole **4a**–**d** (miconazole analogs) from alcohol 2 by coupling with active ketones 3.



Entry[a]	Ketone	Triazole[b] (Yield%)[c]
1	**3a**: R^1 = CH_3, R^2 = $COCH_3$	**4a** (75%)
2	**3b**: R^1 = Ph, R^2 = COPh	**4b** (67%)
3	**3c**: R^1 = Ph, R^2 = CN	**4c** (63%)
4	**3d**: R^1 = $CH_3(CH_2)_4$–, R^2 = SO_2Ph	**4d** (78%)

[a] *Reaction conditions*: A mixture of compound **2** (1.0 eq), DPPA (1.1 eq), and DBU (2.0 eq) in DMF was stirred at r.t. for 3 h. Then **3** (1.0 eq) was added and the reaction continued at 60 °C for 3 h.
[b] Confirmed by ^{1}H NMR, ^{13}C NMR, and MS.
[c] Yields refer to chromatographically pure isolated compounds.

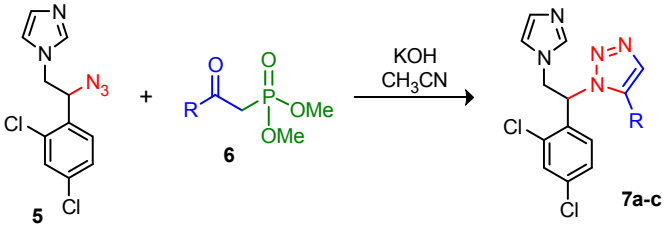
3. Microbiology

Compounds **4a-d** and **7a-c** were evaluated for their *in vitro* antifungal activity against four filamentous fungi (*Aspergillus fumigatus* ATCC-16907, *Trichosporon cutaneum* ATCC-28592, *Rhizopus oryzae* ATCC-10329 and *Mucor hiemalis* ATCC-8690) as well as three yeast specimens (*Candida utilis* ATCC-9226, *Candida albicans* ATCC-10231 and *Candida tropicalis* ATCC-13803).

CLSI standardized methods were adopted to carry out the microbiological tests. The M38-A microdilution method [31] was used to determine the sensitivity of filamentous fungi, and the M27-A3 method [32] for *Candida* yeasts.

The antifungal activity of compounds **4a**–**d** and **7a**–**c** was compared with itraconazole, a standard antifungal drug. The minimum inhibitory concentration (MIC) values of the compounds and standard drugs, expressed in micrograms per millilitre, were determined in 96-well plates by using RPMI 1640 medium buffered with MOPS (3-[N-morpholino]propane sulfonic acid; Sigma-Aldrich).

Table 2
Synthesis of 1,5-disubstituted 1,2,3-triazole **7a**–**c** (miconazole analogs) from azide 5 by coupling with β-ketophosphonates 6.



Entry[a]	Ketone	Triazole[b] (Yield%)[c]
1	**6a**: R = cyclohexyl	**7a** (64%)
2	**6b**: R = $CH_3(CH_2)_3C(CH_3)_2$–	**7b** (70%)
3	**6c**: R = *p*-(CH_3S)phenyl	**7c** (72%)

[a] *Reaction conditions*: A mixture of compound **5** (1.0 eq), **6** (1.0 eq), and KOH (3.0 eq), in CH_3CN was stirred at 60 °C for 5 h.
[b] Confirmed by ^{1}H NMR, ^{13}C NMR, and MS.
[c] Yields refer to chromatographically pure isolated compounds.

Table 3
In vitro antifungal activities of synthetized compounds (MIC, μg/mL).

Compound	Yeast fungi			Filamentous fungi			
	C. uti.	*C. alb.*	*C. trop.*	*A. fum.*	*T. cut.*	*R. ory.*	*M. hie*
4a	16	16	16	16	16	8	16
4b	16	0.03	0.06	16	16	8	16
4c	16	16	16	16	16	16	16
4d	0.25	0.06	0.06	2	0.12	0.5	0.25
7a	16	16	8	16	16	2	0.12
7b	2	0.03	0.03	0.5	8	8	16
7c	16	4	1	16	16	16	16
Standard[a]	0.06	0.03	0.03	0.25	1	0.5	1

Abbreviations: *C. uti., Candida utilis; C. alb., Candida albicans; C. trop., Candida tropicalis; A. fum., Aspergillus fumigatus; T. cut., Trichosporon cutaneum; R. ory., Rhizopus oryzae; M. hie., Mucor hiemalis.*
[a] Itraconazole.

Table 4
Determination of the sensitivity of yeast (according to document M27-A3): Susceptible (S), dose-dependent sensitive (SDD) and resistant (R).

Compound	*C. uti.*	*C. alb.*	*C. trop.*
4a	R	R	R
4b	R	S	S
4c	R	R	R
4d	SDD	S	S
7a	R	R	R
7b	R	S	S
7c	R	R	SDD
Standard[a]	S	S	S

[a] Itraconazole. Interpretive criteria: Breakpoints (MIC, μg/mL) = 0.12 [S], 0.25–0.5 [SDD], 1 [R].

4. Results and discussion

The antifungal activity of the evaluated compounds is summarized in Table 3. Compounds **4b**, **4d** and **7b** showed good activity against *C. albicans* and *C. tropicalis* (MIC 0.03–0.06 μg/mL) as compared to itraconazole (MIC 0.03 μg/mL). Such compounds proved to be 'sensitive'[1] according to the sensitivity parameters of document M27-A3 (Table 4). On the other hand, the antifungal screening of compound **4d** showed that it was either better than or comparable to itraconazole against filamentous fungi *T. cutaneum, R. oryzae,* and *M. hiemalis* (MIC 0.12 versus 1.0, 0.5 versus 0.5, and 0.25 versus 1.0 μg/mL respectively). Compound **7b** demonstrated moderate growth inhibition of *A. fumigatus* (MIC 0.5 μg/mL) compared with the standard drug (MIC 0.25 μg/mL). In contrast with the results observed for an aryl substituent, these outcomes clearly indicate that an alkyl group in the 5-substituted triazole promotes the biological activity of this type of compound. Additionally, substituent probably allows for a better interaction with the 14-α-demethylase ($P450_{14DM}$, CYP51) enzyme [33], leading to its selective inhibition and therefore the growth inhibition of the fungal cell.

5. Conclusion

In summary, azide-enolate 1,3-dipolar cycloaddition allowed for the synthesis of seven miconazole analogs with 1,4,5-tri and 1,5-disubstituted triazole moieties. The pre-clinical studies showed that compounds **4b**, **4d** and **7b** have a good scope against *C. albicans* and *C. tropicalis*. A broader spectrum of **4d** against filamentous fungi (*T. cutaneum, R. oryzae,* and *M. hiemalis*) has been demonstrated. Due to their good/excellent activity, these miconazole analogs can be considered as drug candidates for future complementary biological studies.

6. Experimental section

6.1. General

Flash column chromatography: SiO_2 60 (230–400 mesh). *TLC*: Silica-gel plates (SiO_2; 0.20-mm thickness); visualization with UV light at 254 nm *m.p.*: Fischer-Johns Scientific melting point apparatus; uncorrected. ^1H and ^{13}C-NMR spectra: Bruker Avance 300 MHz and Varian 500 MHz; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. *MS*: Shimadzu GCMS-QP2010 Plus; in *m*/*z* (rel. %).

6.2. Experimental procedures

6.2.1. 1-(1-(1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethanone **4a**

To a cold solution (0 °C) of benzylic alcohol **2** (0.35 g, 1.36 mmol) and diphenylphosphoryl azide (0.32 mL, 1.5 mmol) in anhydrous DMF (3.5 mL) was added DBU (0.4 mL, 2.72 mmol). The solution was stirred for 15 min at 0 °C under nitrogen atmosphere, and then brought to room temperature with continuous stirring for 3 h. At this time, TLC indicated the disappearance of the starting material. Acetylacetone **3a**, (0.14 mL, 1.36 mmol) was then added to the reaction mixture, which was stirred for 3 h at 60–70 °C. Brine (~40 mL) was added and then the reaction mixture was washed with EtOAc (3 × 10 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **4a** (0.37 g, 75%). R_f: 0.3 (DCM/MeOH 95/5). ^1H NMR: (500 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 1.7 Hz, 1Im-H), 7.33–7.26 (m, 3Ar–H), 7.01 (s, 1Im–H), 6.86 (s, 1Im–H), 6.03 (dd, *J* = 9.9, 4.0 Hz, 1H), 5.25 (dd, *J* = 14.7, 10.0 Hz, 1H), 4.62 (dd, *J* = 14.7, 3.9 Hz, 1H), 2.69 (s, 3H), 2.31 (s, 3H) ppm. ^{13}C NMR: (125 MHz, $CDCl_3$) δ = 193.91 (C=O), 143.86 (C), 137.94 (C–Cl), 136.42 (C), 133.09 (C), 131.03 (CH), 130.91 (C–Cl), 130.20 (CH), 129.94 (CH), 129.18 (CH), 128.78 (CH), 128.72 (CH), 59.52 (CH), 49.25 (CH_2), 27.77 (CH_3), 8.56 (Ar–CH_3) ppm. MS-EI$^+$ *m*/*z* (%): 364 [M^++1], 212 (100), 203 (45), 149 (63), 81 (20), 57 (19), 43 (83).

6.2.2. (1-(1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-5-phenyl-1H-1,2,3-triazol-4-yl)(phenyl)methanone **4b**

Following the synthetic procedure for **4a**, compound **2** (0.35 g, 1.36 mmol) and **3b** (0.305 g, 1.36 mmol) were coupled in the presence of diphenylphosphoryl azide (0.32 mL, 1.5 mmol) and DBU (0.4 mL, 2.72 mmol). The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **4b** (0.445 g, 67%). R_f: 0.35 (DCM/MeOH 95/5). ^1H NMR: (500 MHz, $CDCl_3$) δ = 8.28–8.20 (m, 2Ar–H), 7.73 (d, *J* = 8.5 Hz, 1Im–H), 7.64–7.56 (m, 1Ar–H), 7.53–7.32 (m, 8Ar–H), 7.01 (s, 1Im–H), 6.87–6.80 (m, 2Ar–H), 6.71 (s, 1Im–H), 5.98 (dd, *J* = 10.6, 3.7 Hz, 1H), 5.18 (dd, *J* = 14.6, 10.6 Hz, 1H), 4.48 (dd, *J* = 14.6, 3.8 Hz, 1H) ppm. ^{13}C NMR: (125 MHz, $CDCl_3$) δ = 185.81 (C=O), 143.73 (C), 143.37 (C–Cl), 137.31 (C), 136.77 (C), 136.23 (C), 133.23 (C), 132.93 (C–Cl), 131.34 (CH), 130.57 (2CH), 130.40 (CH), 130.13 (C), 129.89 (CH), 129.59 (CH), 129.57 (CH), 129.39 (CH), 129.35 (2CH), 128.92 (2CH), 128.58 (CH), 128.28 (2CH), 60.02 (CH), 49.84 (CH_2) ppm. MS-EI$^+$ *m*/*z* (%): 487 [M^+], 105 [$C_7H_5O^\bullet$] (100), 84 (25), 77 [$C_6H_5^\bullet$] (61), 43 (47).

[1] 'S', 'SDD' and 'R' are represented by standardized values (breakpoints) used to appreciate the clinical value of the *in vitro* antifungal testing result and predicting the response of patients infected. Sensitivity is dependent on achieving the maximum dosages in plasma (breakpoints) to obtain optimal response. For itraconazole, an MIC within the susceptible-dose dependent (SDD) range indicates the need for plasma concentrations 0.25–0.5 μg/mL for an optimal response. Actual breakpoints are described in Table 4 (See Ref. [32b]).

*6.2.3. 1-(1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-5-phenyl-1H-1,2,3-triazole-4-carbonitrile **4c***

Following the synthetic procedure for **4a**, compound **2** (0.35 g, 1.36 mmol) and **3c** (0.197 g, 1.36 mmol) were coupled in the presence of diphenylphosphoryl azide (0.32 mL, 1.5 mmol) and DBU (0.4 mL, 2.72 mmol). The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **4c** (0.35 g, 63%). R_f: 0.3 (DCM/MeOH 95/5). ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 7.68 (d, J = 8.5 Hz, 1Ar–H), 7.59–7.55 (m, 1Ar–H), 7.52–7.47 (m, 3Ar–H), 7.39 (dd, J = 8.5, 2.1 Hz, 1Ar–H), 7.34 (s, 1Ar–H), 7.01 (s, 1Ar–H), 6.95–6.90 (m, 2Ar–H), 6.64 (s, 1Ar–H), 6.07 (dd, J = 10.5, 3.7 Hz, 1H), 5.13 (dd, J = 14.7, 10.5 Hz, 1H), 4.52 (dd, J = 14.7, 3.8 Hz, 1H) ppm. ^{13}C NMR: (125 MHz, $CDCl_3$) δ = 145.35 (C), 136.76 (C–Cl), 132.92 (C), 131.73 (CH), 130.57 (C), 130.23 (C–Cl), 130.15 (CH), 129.79 (2CH), 129.59 (CH), 129.43 (CH), 128.83 (CH), 128.75 (2CH), 124.73 (CH), 121.97 (CH), 120.89 (C), 111.21 (C≡N), 60.97 (CH), 49.99 (CH_2) ppm. MS-EI$^+$ m/z (%): 409 [M^+], 373 (20), 299 (30), 229 (31), 203 (100), 149 (36), 81 (85).

*6.2.4. 1-(1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-5-pentyl-4-(phenylsulfonyl)-1H-1,2,3-triazole **4d***

Following the synthetic procedure for **4a**, compound **2** (0.35 g, 1.36 mmol) and **3d** (0.346 g, 1.36 mmol) were coupled in the presence of diphenylphosphoryl azide (0.32 mL, 1.5 mmol) and DBU (0.4 mL, 2.72 mmol). The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **4d** (0.54 g, 78%). R_f: 0.4 (DCM/MeOH 9/1). ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 8.07–8.01 (m, 2Ar–H), 7.68–7.63 (m, 1Im–H), 7.60–7.54 (m, 2Ar–H), 7.51 (dd, J = 1.6, 0.8 Hz, 1Ar–H), 7.39 (s, 1H), 7.31–7.29 (m, 2Ar–H), 6.92 (s, 1Im–H), 6.70 (s, 1Im–H), 6.03 (dd, J = 9.7, 4.2 Hz, 1H), 5.15 (dd, J = 14.7, 9.7 Hz, 1H), 4.56 (dd, J = 14.9, 4.3 Hz, 1H), 2.88–2.68 (m, 2H), 1.23–1.09 (m, 6H), 0.78 (t, J = 6.9 Hz, 3H) ppm. ^{13}C NMR: (125 MHz, $CDCl_3$) δ = 145.12 (C–Cl), 141.44 (C), 140.43 (C), 137.25 (C), 136.62 (C), 134.00 (C), 132.82 (CH), 130.90 (C–Cl), 129.91 (CH), 129.35 (2CH), 129.21 (CH), 128.91 (CH), 128.79 (CH), 127.90 (2CH), 118.76 (CH), 60.31 (CH), 49.52 (CH_2), 31.29 (CH_2), 28.49 (CH_2), 22.50 (CH_2), 22.02 (CH_2), 13.70 (CH_3) ppm. MS-EI$^+$ m/z (%): 518 [M^+], 376 (13), 280 (19), 203 (64), 172 (36), 159 (37), 149 (49), 125 (58), 77 (100), 41 (49).

*6.2.5. 1-(2-Azido-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole **5***

To a cold solution (0 °C) of benzylic alcohol **2** (1.5 g, 5.83 mmol) and diphenylphosphoryl azide (1.25 mL, 5.83 mmol) in anhydrous DMF (13.0 mL), was added DBU (0.872 mL, 5.83 mmol). The solution was stirred for 15 min at 0 °C under nitrogen atmosphere, and then brought to room temperature with continuous stirring for 3 h. Brine (~100 mL) was added to the reaction mixture and washed with EtOAc (3 × 30 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **5** (1.43 g, 87%). R_f: 0.4 (DCM/MeOH 95/5). ^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.46 (d, J = 2.0 Hz, 1Im–H), 7.38–7.20 (m, 3Ar–H), 7.05 (s, 1Im–H), 6.91 (s, 1Im–H), 5.26 (dd, J = 7.6, 3.5 Hz, 1H), 4.22 (dd, J = 14.4, 3.5 Hz, 1H), 4.01 (dd, J = 14.4, 7.6 Hz, 1H) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$) δ = 137.62 (C–Cl), 135.46 (C), 133.03 (CH), 132.32 (C–Cl), 129.81 (CH), 129.68 (CH), 128.81 (CH), 128.14 (CH), 119.45 (CH), 62.65 (CH–N_3), 50.51 (CH_2) ppm.

*6.2.6. 5-Cyclohexyl-1-(1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-1H-1,2,3-triazole **7a***

To a solution of benzyl azide **5** (0.35 g, 1.24 mmol) and β-ketophosphonate **6a** (0.29 g, 1.24 mmol) in acetonitrile grade reagent (3.5 mL) was added potassium hydroxide (0.2 g, 3.73 mmol). The solution was stirred for 5 h at 60 °C. Brine (~40 mL) was added to the reaction mixture and washed with EtOAc (3 × 30 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **7a** (0.31 g, 64%). R_f: 0.3 (DCM/MeOH 95/5). ^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.50 (d, J = 2.0 Hz, 1Im–H), 7.45 (s, 1Ar–H), 7.42 (s, 1Ar–H), 7.31–7.29 (m, 2Ar–H), 6.96 (s, 1Im–H), 6.76 (s, 1Im–H), 6.03 (dd, J = 9.9, 3.9 Hz, 1H), 5.22 (dd, J = 14.5, 9.9 Hz, 1H), 4.55 (dd, J = 14.5, 3.9 Hz, 1H), 2.64–2.50 (m, 1H), 1.90–1.47 (m, 5H), 1.43–1.01 (m, 5H) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$) δ = 143.80 (C–Cl), 135.94 (C), 132.75 (C), 132.19 (CH), 131.23 (C–Cl), 129.80 (CH), 129.67 (CH), 129.58 (CH), 128.64 (CH), 122.56 (CH), 118.99 (CH), 59.41 (CH), 51.56 (CH_2), 33.22 (CH), 32.37 ($2CH_2$), 25.71 (CH), 25.44 ($2CH_2$) ppm.

*6.2.7. 1-(1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-5-(2-methylhexan-2-yl)-1H-1,2,3-triazole **7b***

Following the synthetic procedure for **7a**, compound **5** (0.35 g, 1.24 mmol) and **6b** (0.311 g, 1.24 mmol) were coupled in the presence of KOH (0.2 g, 3.73 mmol). The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **7b** (0.35 g, 70%). R_f: 0.3 (DCM/MeOH 9/1). ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 7.54–7.53 (m, 1Im–H), 7.44 (s, 1Ar–H), 7.28–7.27 (m, 1Ar–H), 7.27–7.25 (m, 2Ar–H), 6.96 (s, 1Im–H), 6.78 (s, 1Im–H), 6.23 (dd, J = 10.6, 3.0 Hz, 1H), 5.29 (dd, J = 14.6, 10.6 Hz, 1H), 4.50 (dd, J = 14.6, 3.0 Hz, 1H), 1.37–1.21 (m, 2H), 1.10 (s, 3H), 1.03 (s, 3H), 0.97–0.82 (m, 2H), 0.75–0.64 (m, 1H), 0.61–0.54 (m, 3H), 0.43–0.31 (m, 1H) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$) δ = 145.93 (C–Cl), 137.33 (C), 135.81 (CH), 133.29 (CH), 132.53 (C–Cl), 132.26 (CH), 130.90 (C), 129.73 (CH), 129.50 (CH), 128.45 (CH), 118.89 (CH), 62.20 (CH), 49.80 (CH_2), 41.07 (CH_2), 33.47 (C), 27.77 (CH_3), 27.67 (CH_3), 26.73 (CH_2), 22.76 (CH_2), 13.65 (CH_3) ppm. MS-EI$^+$ m/z (%): 406 [M^+], 296 (11), 240 (28), 203 (53), 172 (25), 159 (33), 124 (34), 81 (45), 57 (100), 41 (71).

*6.2.8. 1-(1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-5-(4-(methylthio)phenyl)-1H-1,2,3-triazole **7c***

Following the synthetic procedure for **7a**, compound **5** (0.35 g, 1.24 mmol) and **6c** (0.341 g, 1.24 mmol) were coupled in the presence of KOH (0.2 g, 3.73 mmol). The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **7c** (0.385 g, 72%). R_f: 0.3 (DCM/MeOH 9/1). ^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.69 (m, 1Im–H), 7.68 (s, 1Ar–H), 7.47 (d, J = 2.1 Hz, 2Ar–H), 7.36–7.19 (m, 4Ar–H), 6.96 (s, 1Im–H), 6.75 (d, J = 8.4 Hz, 2Ar–H), 6.64 (s, 1Im–H), 6.01 (dd, J = 10.5, 3.5 Hz, 1H), 5.15 (dd, J = 14.5, 10.5 Hz, 1H), 4.48 (dd, J = 14.5, 3.6 Hz, 1H), 2.49 (s, 3H) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$) δ = 141.81 (C), 139.43 (C–Cl), 136.05 (C–S), 133.21 (C), 132.72 (CH), 131.83 (CH), 130.91 (C–Cl), 129.83 (CH), 129.77 (C), 129.40 (CH), 128.94 (2CH), 128.79 (CH), 128.55 (CH), 126.14 (2CH), 118.83 (CH), 59.98 (CH), 50.20 (CH_2), 15.05 (CH_3) ppm.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2016.02.013

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