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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and enzyme inhibitory activities of some new pyrazole-based heterocyclic compounds

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Abstract Three tridentate *N,N*-bis(3,5-dimethylpyrazol-1-ylmethyl)-1-hydroxy-2-aminoethane (**2**), *N,N*-bis(3,5-dimethylpyrazol-1-ylmethyl)-cyclohexylamine (**3**) and 2-[bis (1,5-dimethyl-1*H*-pyrazol-3-ylmethyl)amino]ethan-1-ol (**4**) are synthesized and spectroscopically characterized together with 1-hydroxymethyl-3,5-dimethylpyrazole (**1**). These have been tested in inhibitory activities against various hyperactive enzymes like urease, β-glucuronidase, phosphodiesterase, α-chymotrypsin, acetylcholinesterase and butyrylcholinesterase. Compounds **1**, **2** and **3** were found to be selective inhibitors of urease. Compound **4** was found to be selective inhibitor of butyrylcholinesterase. The nature of the junction between pyrazoles cycles determined the activities of these tripods. While the tripods are inactive towards urease or glucuronidase, they turn to be selective towards butyrylcholinesterase.

Keywords Pyrazole · Tripod · Microwave · Enzyme inhibition · Acetylcholinesterase · α-Chymotrypsin · β-Glucuronidase · Butyrylcholinesterase · Phosphodiesterase · Urease

Introduction

Polypyrazolic ligands have diverse applications in pharmacology (Park *et al.*, 2005; Tewari and Mishra, 2001; Finn *et al.*, 2003; Yahyi *et al.*, 2010), biology (Radi *et al.*, 2010; Janus *et al.*, 1999; Pimerova and Voronina, 2001; Michon *et al.*, 1995; Bailey *et al.*, 1985), and catalysis (Sorrell *et al.*, 1984; Boussalah *et al.*, 2009) and electronics (Marzin *et al.*, 1987; Steel and Constable, 1990). They are also used in extraction, complexation and the transport of some alkaline and transition metals (Tarrago *et al.* 1988; Malek *et al.*, 2002, 2005a, b; Radi *et al.*, 2006; Malek and Radi, 2009).

A number of tripod pyrazolic ligands have been studied in our laboratory (Malek *et al.*, 2004, 2007; El Kodadi *et al.*, 2003, 2008; Attayibat *et al.*, 2010; Tebbji *et al.*, 2005; Bouabdallah *et al.*, 2007). These compounds were synthesized creating N–C–N or C–N–C junctions (Scheme 1). Their main feature is two sp^2 and sp^3 hybridized amine nitrogen atoms as donors. The three sites of complexation form a pyramidal complexing metal. Moreover, the nature of the lateral arm R can be modified according to intended application. Nevertheless, these tridentate compounds show a powerful complexing effect

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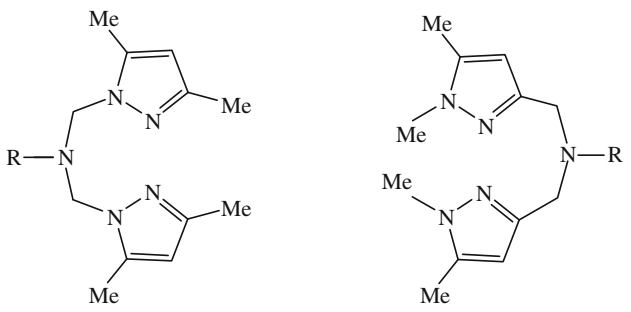
towards transition metals (Malek *et al.*, 2004, 2007; El Kodadi *et al.*, 2003; Attayibat *et al.*, 2010) and thus acquire catalytic action (El Kodadi *et al.*, 2008; Tebbji *et al.*, 2005; Bouabdallah *et al.*, 2007).

Recently, we studied the anticancer effects of two tridentate ligands against mastocytoma murine P815 cell line. Results showed that these tripods possess good cytotoxic activities against the cell line P815 (El Kodadi *et al.*, 2007; Bouabdallah *et al.*, 2006). Moreover, pyrazole diaryl derivatives, known as Celebrex, exhibit anti-inflammatory, analgesic and antipyretic activities in animal models (Millêtre-Berdardin *et al.*, 1995). The mechanism of action of Celebrex involves inhibition of the synthesis of prostaglandins through the inhibition of cyclooxygenase-2. It was also reported that Celebrex does not prevent the action of the isoenzyme cyclooxygenase-1. In the animal models of tumour, the Celebrex reduced the impact and multiplicity of tumours. Pyrazoles were also reported as potent inhibitors of the *Helicobacter pylori* dihydroorotate dehydrogenase (Haque *et al.*, 2002).

We hereby report the synthesis of 1-hydroxymethyl-3,5-dimethylpyrazole (**1**), [*N,N*-bis(3,5-dimethylpyrazol-1-ylmethyl)-1-hydroxy-2-aminoethane] (**2**) and [*N,N*-bis(3,5-dimethylpyrazol-1-ylmethyl) cyclohexylamine (**3**), as well as a molecule with a tripod C–N–C junction, 2-[bis(1,5-dimethyl-1*H*-pyrazol-3-ylmethyl)amino]ethan-1-ol (**4**) and their inhibitory activities against various hyperactive enzymes such as urease, β-glucuronidase, phosphodiesterase, α-chymotrypsin, acetylcholinesterase and butyrylcholinesterase. Urease (urea amidohydrolase EC 3.5.1.5) is a nickel containing metalloenzyme which catalyzes the hydrolysis of urea to ammonia and carbon dioxide. It is an enzyme responsible for the use of urea as a nitrogen source. In plants, urease also acts as defense protein in systemic nitrogen transport pathways. Urease in organism is known to be one of the major causes of pathologies induced by *H. pylori*, thus allow them to survive at low pH of the stomach and, therefore, play an important role in the pathogenesis of gastric and peptic ulcers. Urease is also directly involved in the formation of kidney stones and contributes to the pathogenesis of urolithiasis, pyelonephritis, and hepatic encephalopathy, hepatic coma and urinary catheter encrustation (Rama *et al.*, 2010).



Scheme 1 Structures and junctions of bipyrazolic tripods

Acetylcholinesterase (AChE) (EC 3.1.1.7) is a key component of cholinergic brain synapses and neuromuscular junctions. The major biological role of the enzyme is the termination of impulse transmission by rapid hydrolysis of the cationic neurotransmitter acetylcholine (Tougu, 2001). According to the cholinergic hypothesis, memory impairments in patients with the senile dementia disease are due to a selective and irreversible deficiency in the cholinergic functions in brain (Perry, 1986). This serves as a rationale for the use of AChE inhibitors for the symptomatic treatment of Alzheimer's disease (AD) in its early stages. The role of butyrylcholinesterase (BChE) (EC 3.1.1.8) in normal ageing and brain diseases is still elusive. It has been found that BChE is found in significantly higher quantities in Alzheimer's plaques than in plaques of normal age related non-demented brains (Yu *et al.*, 1999).

The inhibitors of AChE and BChE help to enhance the efficiency of the remaining neurons (Trabace *et al.*, 2000). Due to the diverse functions of these enzymes, their inhibition by potent and specific compounds could provide an invaluable addition for treatment of infections.

Experimental

Techniques

The proton NMR spectra of the compounds (**1**–**4**) were recorded in $CDCl_3$ on a Bruker spectrometer (250 MHz), at room temperature. Chemical shifts are reported in parts per million (δ) using internal TMS standard. The IR spectra have been recorded, in film form, on a SHIMADZU FTIR 8400, between 4,000 and 600 cm^{-1} with a resolution of 4 cm^{-1}. The number of scans was 20 for each sample. Letters s, f, F and m indicate broadband, low, medium and heavy, respectively. Mass spectra were measured on a Platform II Micromass instrument (ESI^+, CH_3CN/H_2O: 50/50). Elemental analyses were performed by Microanalysis Central Service (CNRS). Melting points were determined on a Büchi–Totolli capillary apparatus and are uncorrected. Microwave-assisted synthesis were carried out using a Prolabo Maxidigest MX 350 focused monomode system (100% power = 300 W).

Reagents

The 3,5-dimethylpyrazole and 3-chloromethyl-1,5-dimethyl-1*H*-pyrazole were prepared according to the procedure described in the literature (Dvoretzky and Richter, 1950; Fifani *et al.*, 1977). The 37% formaldehyde solution, ethanolamine, cyclohexylamine, dichloromethane, ethyl

alcohol and ethyl acetate were all high quality reagents (Aldrich 99%).

Synthesis of the 1-hydroxymethyl-3, 5-dimethylpyrazole (**1**)

20 g (0.208 mol) of 3,5-dimethylpyrazole, in 20 ml of ethyl alcohol and 25 ml of formaldehyde solution 35% were introduced in a beaker. The mixture was maintained under agitation at room temperature for 12 h. The concentrate solvent was thus reduced to half, after which ice was added. Deposited precipitate was washed with water and dried under pressure. Finally, a white solid was recuperated in 80% (21 g) yield with following characteristics:

MP: 106–108°C (CH_2Cl_2); ^{1}H-NMR: (δ) : 2.15 (s, 3H, CH_3); 2.30 (s, 3H, CH_3); 4.80 (s, 1H, OH); 5.45 (s, 2H, CH_2); 5.90 (s, 1H, Hpz). *m/z* : 127 $[M + 1]^+$ (FAB > 0); Anal. Calc. for $C_6H_{10}N_2O$: C: 57.14; H: 7.93; N: 22.22; Found: C: 57.41; H: 7.68; N: 22.04;

Synthesis of [*N,N*-bis(3,5-dimethylpyrazol-1-ylmethyl) -1-hydroxy-2-aminoethane] (**2**)

A mixture of 1-hydroxymethyl-3,5-dimethylpyrazole (3.78 g, 30 mmol) and ethanolamine (0.92 g, 15 mmol) was introduced into a Pyrex tube, which was then placed in a microwave reactor and irradiated with microwaves (60 W) in the absence of solvent for 20 min. The reaction mixture was extracted with dichloromethane and washed with water to eliminate the residual ethanolamine. The organic solution was dried under reduced pressure. The resulting solid was crystallized from ethyl acetate to obtain white crystals (3.8 g, 92%); MP: 81–83°C (ethyl acetate); ^{1}H-NMR (δ): 2.20 (s, 6H); 2.25 (s, 6H, CH_3); 2.95 (t, 2H, $J = 5.4$ Hz, N-CH_2); 3.65 (t, 2H, $J = 5.4$ Hz, CH_2OH); 4.95 (s, 4H, CH_2–N), 5.80 (s, 2H, Hpz); IR (cm^{-1}): 3259 (l, –OH); 2923 (m, =CH); 2858 (f, –CH); 1548 (f, C=C); 1457 (f, –C=N–); 1365 (m); 1333 (m); 1294(F); 1245(m); 1175 (F, –C–OH); 1135(f); 1070 (f); 797(m); 784(m); 736(m); *m/z*: 278 $[M + 1]^+$ (FAB > 0); Anal. Calc. for $C_{14}H_{23}N_5O$: C: 60.65, H: 8.30, N: 25.27; Found: C: 60.25, H: 8.06, N: 25.07.

Synthesis of [*N,N*-bis(3,5-dimethylpyrazol-1-ylmethyl) -cyclohexylamine (**3**)

In similar procedure, the title compound was obtained as solid crystals, with a yield of 87% (4.1 g).

MP: 95–97°C (ethyl acetate); ^{1}H NMR (δ): 1.10–1.80 (m, 10H, CH_2 cyclohexyl); 2.10 (s, 6H, CH_3); 2.25 (s, 6H, CH_3); 2.60 (s, 1H, N–CH cyclohexyl); 4.80 (s, 4H, –CH_2–N); 5.75 (s, 2H, Hpz); IR (cm^{-1}): 3125 (m, =CH); 2928(f, –CH); 2875(f, –CH); 1650 (m, –C=C–); 1556 (f); 1464 (f, –C=N–); 1310 (m); 1260(m); 1190(m); 1095(F); 970(f); 890(f); 870(f); 776(m); 636 (m); *m/z* : 316 $[M + 1]^+$ (FAB > 0); Anal. calc. for $C_{18}H_{29}N_5$: C: 68.57; H: 9.20; N: 22.22%; Found: C: 69.12; H: 8.82; N: 21.72%.

Synthesis of 2-[bis(1,5-dimethyl-1*H*-pyrazol-3-ylmethyl) amino]ethan-1-ol (**4**)

To acetonitrile (150 ml) containing 3-chloromethyl-1,5-dimethylpyrazole (2.96 g, 20.5 mmol) and sodium carbonate (8.64 g, 80 mmol) was added slowly (0.62 g, 10.2 mmol) with ethanolamine in 50 ml of acetonitrile. The mixture was stirred under reflux for 5 h. The solid material was filtered and the filtrate was concentrated under reduced pressure. The residue was purified on alumina using 97/3 CH_2Cl_2/MeOH as eluant to obtain an 80% yield (2.26 g).

MP: 64–66°C (CH_2Cl_2/EtOH); ^{1}H NMR (δ): 2.21 (s, 6H, CH_3); 2.66 (t, 2H, $J = 5{,}1$ Hz, N–CH_2); 3.55 (t, 2H, $J = 5{,}1$ Hz, CH_2OH); 3.65 (s, 4H, CH_2–N); 3.70 (s, 6H, N–CH_3); 5.95 (s, 2H, Hpz); IR (cm^{-1}): 3380 (l, –OH); 2980 (m, =CH); 1680(f, –C=C–); 1460 (f, –C=N–); 1400 (m); 1300(m); (F, –C–OH); 1140(f); 1070(f); 1040(f); 990(f); 800(m). *m/z*: 278 $[M + 1]^+$ (FAB > 0) Anal. Calc. for $C_{14}H_{23}N_5O$: C: 60.65, H: 8.30; N: 25.27; Found: C: 60.02; H: 7.98; N: 25.85.

Urease inhibition assay

Reaction mixtures comprising one unit of urease enzyme (*Jack bean*) solution, and 55 µl of buffers containing 100 mM urea were incubated with 5 µl of test compound (0.5 mM concentration) at 30°C for 15 min in 96-well plates. Urease activity was determined by measuring ammonia production using the indophenol method. Briefly, 45 µl of phenol reagent and 70 µl of alkali reagent were added to each well. The increasing absorbance at 630 nm was measured after 50 min, using a microplate reader. All reactions were performed in triplicate in a final volume of 200 µl. The results (change in absorbance per min) were processed by using SoftMax Pro software (Khan *et al.*, 2010).

Cholinesterase inhibition assay

AChE and BChE inhibiting activities were measured by the spectrophotometric method by using acetylthiocholine iodide and butyrylthiocholine chloride as substrates. The reaction mixture contained 130 µl of (100 mM) sodium phosphate buffer (pH 8.0), 20 µl of DTNB, 10 µl of tested compound solution and 20 µl of AChE or BChE solution, which were mixed and incubated for 15 min at 25°C. The reaction was then initiated by the addition of 20 µl

acetylthiocholine or butyrylthiocholine, respectively. The hydrolysis of acetylthiocholine and butyrylthiocholine were monitored at a wavelength of 412 nm (15 min). Absolute ethanol, which becomes 5% in the reaction mixture, was used as solvent for test compounds and the standard inhibitor. All the reactions were performed in triplicate in 96-well microplate using SpectraMax Plus 384 (Ellman *et al.*, 1961).

α-Chymotrypsin inhibition assay

Enzyme and substrate both are prepared in Tris–HCl buffer pH 7.6. Chymotrypsin 12 U/ml, was preincubated with test compounds, which was prepared in final concentration of 7% DMSO, for 25 min at 30°C. The 0.4 mM substrate, *N*-succinyl-phenylalanine-*p*-nitroanilide, was added to start the enzyme reaction. The absorbance of released *p*-nitroaniline was continuously monitored at 410 nm using a microplate reader, SpectraMax M2 (Molecular Device, CA, USA) until a significant colour change was observed (Cannell *et al.*, 1988).

Assay for β-glucuronidase

β-Glucuronidase inhibitory activity was evaluated in 0.1 M acetate buffer pH 8.8. The buffer, various concentrations of test compounds and enzyme were incubated at 37°C for 30 min. Then, the 96-well plates were read on SpectraMax plus 384 (Molecular Devices, CA, USA) at 405 nm after the addition of 0.4 mM *p*-nitrophenyl-β-D-glucuronide (Riaz *et al.*, 2003).

Phosphodiesterase inhibition assay

Snake venom phosphodiesterase activity was performed in 33 mM Tris–HCl buffer with 30 mM Mg-acetate buffer pH 8.8. The buffer, various concentrations of test compounds, and enzyme (0.742 mU/well) were incubated at 37°C for 30 min. The plates were read on a multiplate reader, SpectraMax plus 384 (Molecular Devices, CA, USA) at 410 nm after the addition of 0.33 mM bis-(*p*-nitropheny1) phosphate (Mamillapalli *et al.*, 1998).

Results and discussion

The basic precursor for the synthesis of *N,N*-bis(3, 5-dimethylpyrazol-1-ylmethyl)-1-hydroxy-2-aminoethane (**2**) and *N,N*-bis(3,5-dimethylpyrazol-1-ylmethyl)-cyclohexylamine (**3**) is 1-hydroxymethyl-3,5-dimethylpyrazole (**1**). The later was obtained by condensation of a formaldehyde solution on 3,5-dimethylpyrazole (Scheme 2) according to the procedure described in the literature (Dvoretzky and Richter, 1950).

Compound **2** was obtained by reacting the precursor **1** with commercially available ethanolamine in the ratio 2:1. The mixture was placed for 20 min in a microwave reactor and irradiated with microwaves (60 W) in the absence of any solvent; it yielded the product (**2**) in excellent yield (92%). Compound **3** was prepared in a 75% yield through a similar procedure by reacting cyclohexylamine with the synthon (**1**).

The route that we used to prepare the target ligand (**4**) is shown in Scheme 3. The process involves tree steps of the precursor 3-chloromethyl-1,5-dimethylpyrazole (Fifani *et al.*, 1977) that possesses a good leaving group. Scheme 3 summarizes the preparation process of the title compound. Compound **4** was obtained in a 80% yield by reacting the chloro derivative with 2-aminoethanol in a ratio of 2:1 under reflux condition using sodium carbonate as base. The compounds **2–4** were characterized by ^{1}H NMR, FTIR, elemental analyses and mass spectrometry.

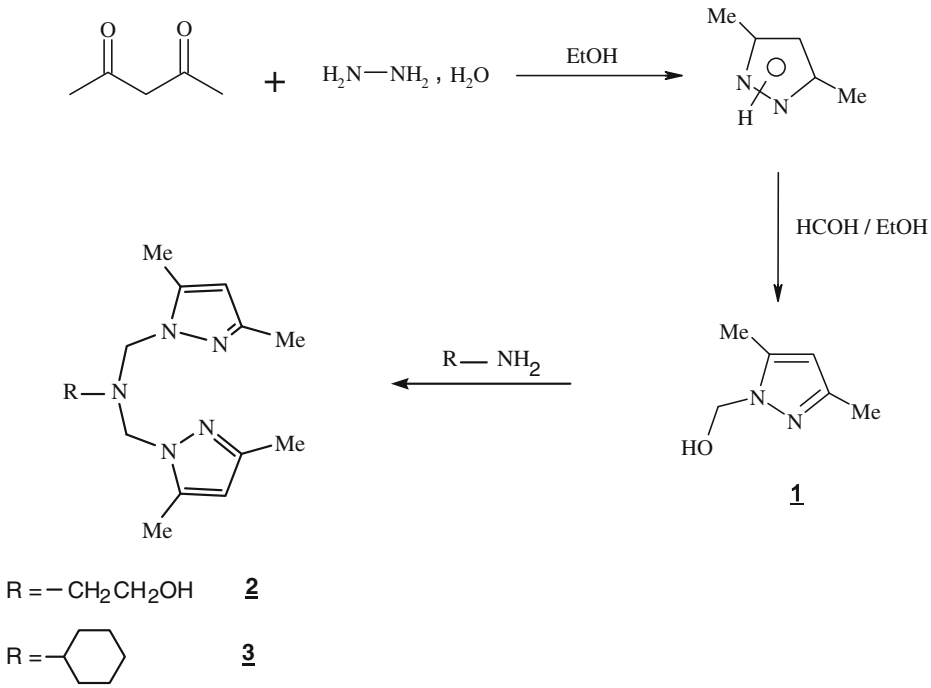
Enzyme inhibitory activities

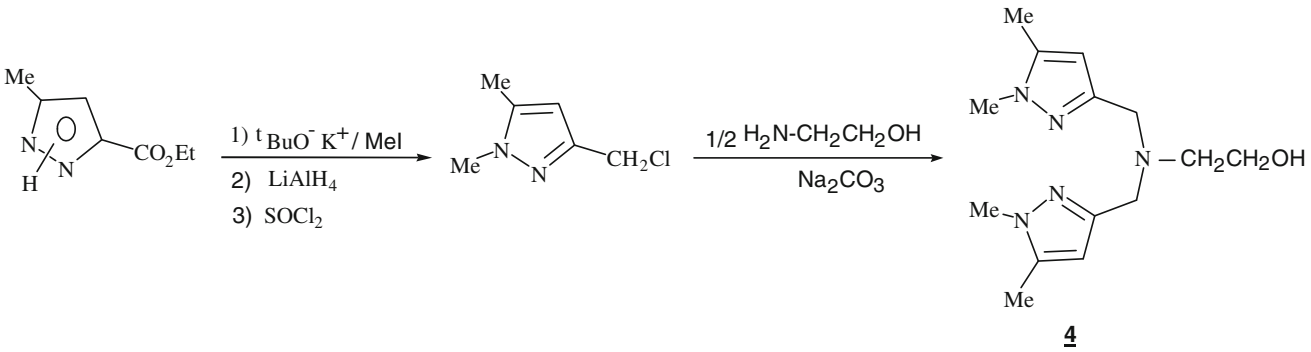
Enzyme inhibition is active area of research in drugs development. Here, we have synthesized two series of pyrazoles tripods **2–4**, which differ only from the junction between pyrazoles. To check their potential, we subjected these derivatives to various hyperactive enzymes inhibition assays against urease, β-glucuronidase, phosphodiesterase, α-chymotrypsin, acetylcholinesterase and butyrylcholinesterase. Both these series showed significant activity against urease and butyrylcholinesterase enzymes.

Compound **1** is a pyrazole found to be a selective inhibitor of urease. After its dimerization, the urease activity enhanced by twofold. The tripod **2** was also found to be selective for the inhibitor of urease, while the tripod **3** is found to be a weak inhibitor of β-glucuronidase. This activity is probably due to the cyclohexyl arm held by the lateral chain, which may have hydrophobic interaction with the active site. Its inhibition of urease is ten times higher than its activity against β-glucuronidase. The nature of the lateral arm has no influence on the activity of these tripods towards the urease, but it can inhibit other enzymes.

The tripod **4**, differing from the tripod **2** by the nature of the junction linking the two pyrazoles, acts selectively towards butyrylcholinesterase. It is however inactive towards the urease and other enzymes. It probably interacts with the active site of the butyrylcholinesterase. Results of the assay are presented in Table 1. The inhibition activities of these tripods depend on the nature of the junction between the pyrazoles.

Scheme 2 Process for preparing tridentate compounds **2** and **3**





Scheme 3 Preparation steps of compound **4**

Table 1 Enzymes inhibitory activities of compounds **1–4**

Compound code	$IC_{50} \pm$ SEM (μM)					
	α-Chymotrypsin	Phosphodiesterase	Urease	Acetylcholinesterase	Butyrylcholinesterase	β-Glucuronidase
1	NA	NA	94.3 ± 0.47	NA	NA	NA
2	NA	NA	44.66 ± 0.03	NA	NA	NA
3	NA	NA	43.46 ± 0.02	NA	NA	456.6 ± 1.36
4	NA	NA	NA	NA	68 ± 0.0025	NA
Standard	Chymostatin	EDTA	Thiourea	Galanthamine	Galanthamine	D-Saccharic acid 1,4-lactone
	5.7 ± 0.13	74 ± 1.25	21 ± 0.011	0.5 ± 0.01	0.17 ± 0.01	48.4 ± 1.25

NA not active, % of inhibition is less than 50% at 500 μM; *SEM* standard error of mean

Conclusions

Three tripods were synthesized from the substrate 1-hydroxymethyl-3,5-dimethylpyrazole. This concerns *N, N*-bis(3,5-dimethylpyrazol-1-ylmethyl)-1-hydroxy-2-aminoethane, *N,N*-bis(3,5-dimethylpyrazol-1-ylmethyl)-cyclohexylamine and 2-[bis(1,5-dimethyl-1*H*-pyrazol-3-ylmethyl) amino]ethan-1-ol. Their structures were characterized by ^{1}H NMR, FTIR, elemental analyses and mass spectrometry. Compounds **1**, **2** and **3** were found to be selective inhibitors of urease, while compound **4** is of butyrylcholinesterase. The nature of the junction between pyrazoles cycles seems to determine the activities of these tripods. While the tripods are inactive towards urease or glucuronidase, they turn to be selective towards butyrylcholinesterase.

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