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Synthesis and selective cyclooxygenase-2 (COX-2) inhibitory activity of a series of novel bicyclic pyrazoles☆

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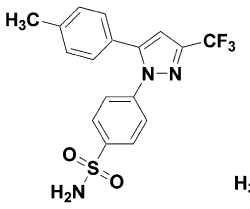
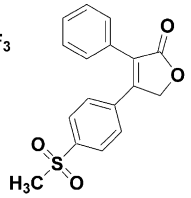
Abstract—Novel series of pyrazolo[5,1-*b*]1,3-oxazolidines, pyrazolo[5,1-*b*]1,3-oxazines and imidazolidino[1,2-*d*]pyrazoles were synthesized. These compounds were evaluated in vitro for their ability to inhibit cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) in human whole blood (HWB). Several of the compounds were found to be novel and selective COX-2 inhibitors, the most potent and selective being 1-(5-cyclohexyl (2H,3H-pyrazolo[5,1-*b*]-1,3-oxazolidin-6-yl)-4-(methylsulfonyl)benzene, **7a** (IC_{5o} for COX-1 > 100 μM; for COX-2 = 1.3 μM).

1. Introduction

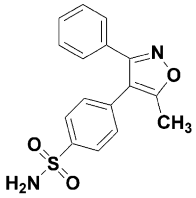
Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to treat acute or chronic inflammation and offer symptomatic pain relief.[1,2] Conventional NSAIDs act by non selective inhibition of cyclooxygenase (COX) enzymes, which catalyze the formation of prostaglandins (PGs) from arachidonic acid.[3–5] There are at least two main mammalian COX isoforms, COX-1 and COX-2.[6,7] Constitutive COX-1 has housekeeping functions, including low-level production of gastroprotective PGs, whereas COX-2 is induced in inflammatory cells and generates PGs that help mediate the inflammatory response. Adverse gastrointestinal (GI) side-effects of conventional NSAIDs largely reflect inhibition of COX-1 and the associated reduction in gastroprotection.[8–11] In contrast, selective COX-2 inhibitors such as Celecoxib,[12] Rofecoxib[13] and Valdecoxib[14] exert anti-inflammatory and analgesic activity in the clinic with markedly less GI toxicity than traditional NSAIDs.



Celecoxib

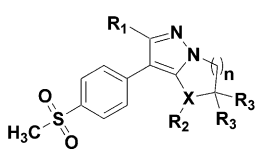


Rofecoxib



Valdecoxib

The improved GI tolerance of COX-2 selective inhibitors notwithstanding, there is evidence to suggest that COX-2 selective inhibitors may inhibit COX-1 and induce GI irritation or ulceration with long-term use or at higher doses.[15–18] Preclinical cardiovascular and renal liabilities of at least some COX-2 selective inhibitors have also been reported.[19] Thus there is still a need for new, selective COX-2 inhibitors with an improved safety profile.



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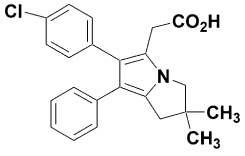

ML 3000

A search of the literature revealed very few reports of COX-2 selective inhibitors containing a bicyclic core.

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Two examples are the imidazo[1,2-*a*]-pyridines[20] and the pyrazolo[1,5-*b*]pyridazines[21] which contain a planar central unit. A slightly less rigid system can be found in the 2,3-dihydro-1H-pyrrolines as exemplified by ML 3000.[22–27] We now wish to report the synthesis and COX-2 selective inhibition of a series of novel bicyclic-pyrazole inhibitors. While this manuscript was in preparation, a patent[28] appeared covering this structural core, but the compounds reported herein have not been fully described or characterized.

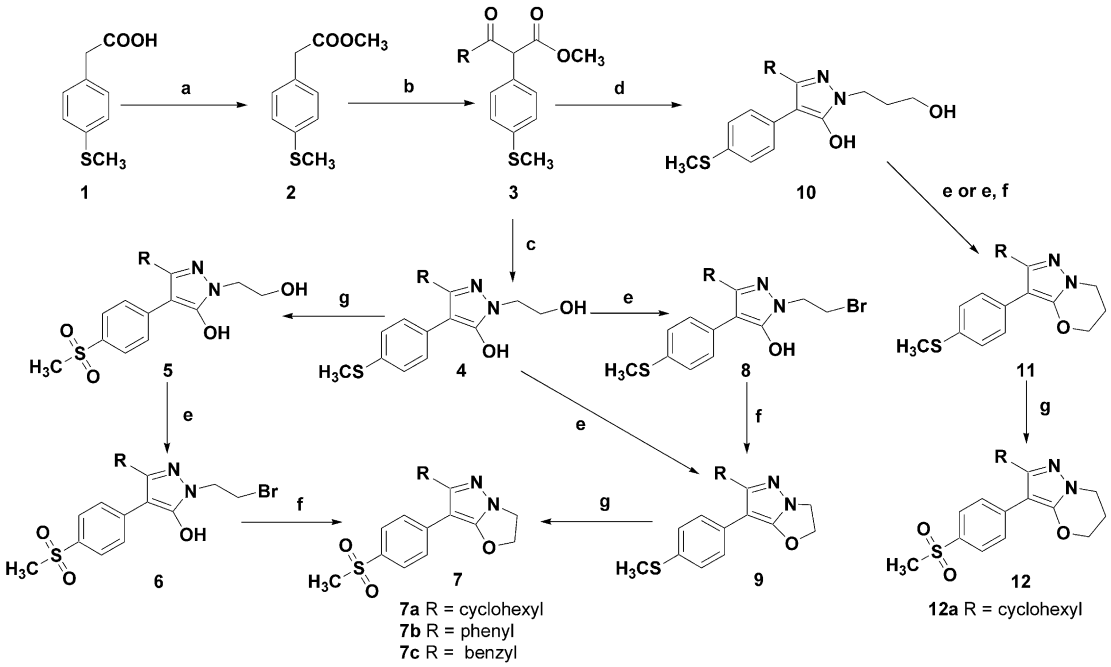
2. Chemistry

The general routes outlined in Schemes 1–3 were used to synthesize all compounds described herein. The key synthetic step for construction of the bicyclic-pyrazole core involves either basic or acidic cyclization of 2-hydroxyalkyl pyrazole intermediates (**4**, **10**, **18**, **26**).

As shown in Scheme 1, pyrazolo[5,1-*b*]1,3-oxazolidines **7a–c** and pyrazolo[5,1-*b*]1,3-oxazine **12** were obtained from commercially available 2-(4-methylthiophenyl)-acetic acid, **1**. This was converted into the corresponding methyl ester **2**, whose enolate, prepared using LiHMDS, reacted with acid chlorides to give the ketoesters **3** in high yield. This was condensed with hydrazinoalkanols[29] in glacial acetic acid at 100 °C to obtain 2-hydroxyalkyl substituted pyrazoles **4** and **10** in high yield. In most cases, 1,3,4-substituted pyrazoles (**4**, **10**) were formed exclusively. In those few cases where the 1,2,3-regioisomer was also formed as a minor by-product, it was readily removed by column chromatography followed by recrystallization. Bicyclic-pyrazoles **9** and **11** were obtained by bromination of **4** or **10** with CBr_4 and PPh_3 (or polymer supported PPh_3) followed by cyclization using K_2CO_3. In fact, minor quantities of **9** or **11** were formed during the bromination of **4** or **10**, indicating that cyclization was spontaneous but slow in the absence of base. Methyl sulfides **9** and **11** were oxidized to the sulfones (**7a–c**, **12a**) with Oxone® in high yield. Alternatively, **7a–c** could be synthesized from **4** by reversing the order of oxidation and cyclization (**4** to **5** to **6** to **7**). In this route however, the oxidation of **4** gave a low isolated yield due to the high polarity and insolubility of **5**.

Imidazolidino[1,2-d]pyrazoles (**21**, **22**, **24**, **25**) were prepared as illustrated in Scheme 2. The ketonitrile intermediate **16** was prepared in three steps from commercially available 4-methylthiobenzyl alcohol **13**. Reaction of **13** with $SOCl_2$ gave **14** in 97% yield. Substitution of the chloride with NaCN gave the nitrile **15** which, upon acylation with cyclohexanecarbonyl chloride in the presence of LiHMDS, afforded ketonitrile **16**. This was condensed with 2-hydroxyethyl hydrazine in glacial acetic acid at 100 °C to give 5-amino-1(2-hydroxyethyl)pyrazole **17**. Mesylation of **17** afforded **18**, which was cyclized in the presence of K_2CO_3 at 60 °C for 3 days to give imidazolidino[1,2-*d*]pyrazole **19**. Oxidation of the sulfide group of **19** with Oxone® at room temperature gave a significant amount of *N*-oxide as a by-product together with the desired product **20**. When the reaction was repeated at 0 °C, *N*-oxide formation was greatly reduced. Acylation of **20** with acetic anhydride gave 4-acetylimidazolidino[1,2-*d*]pyrazole **21**. On the other hand, alkylation of **20** with methyl iodide and K_2CO_3 in DMF at room temperature gave *N*-methyl-imidazolidino [1,2-d]pyrazole **22**.

Incorporating an acid group into the molecule could be useful either to improve its solubility or to allow for further chemical modification. Therefore, imdazolidino[1,2-*d*]-



Scheme 1. (a) MeOH, c. H_2SO_4, rfx, 16 h; (b) LiHMDS, RCOCl, THF; (c) gl. acetic acid, $NH_2NH(CH_2)_2OH$, 100 °C, 1 h; (d) gl. acetic acid, $NH_2NH(CH_2)_3OH$, 100 °C, 1 h; (e) polymer supported-PPh_3, CBr_4, DMF, rt, 3 days or CBr_4, PPh_3, CH_2Cl_2, rt, 3 days; (f) K_2CO_3/DMF, rt, 1 h; (g) Oxone, MeOH/H_2O, rt.

pyrazolyl-2-acetic acid **25** (Scheme 2) was targeted. Compound **19** was alkylated with *tert*-butylbromoacetate in the presence of K_2CO_3 to give **23**, which was oxidized with Oxone® at 0 °C to give the sulfone **24**. Cleavage of the *tert*-butyl ester group in **24** afforded imidazolidino[1,2-*d*]pyrazolyl-2-acetic acid **25**.

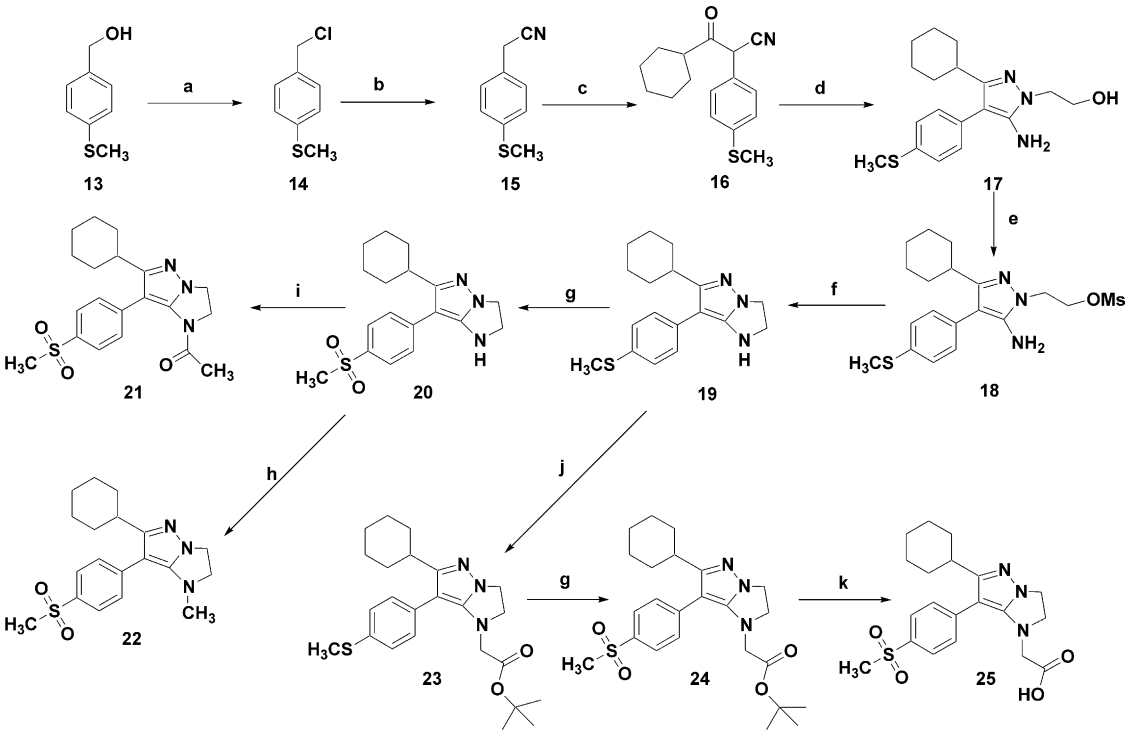
In order to incoporate a *gem* dimethyl group, as found in ML 3000, compound **28** was targeted and prepared as shown in Scheme 3. Ketoester **3a** was condensed with 1-hydrazino-2-methyl-2-propanol[30] in glacial acetic acid at 100 °C for 1 h to give the pyrazolediol **26**. This was subjected to cyclization under acidic conditions to provide the methyl sufide **27** along with unreacted **26**. Oxidation of methyl sulfide **27** with Oxone® gave the pyrazolo[5,1-*b*]1,3-oxazolidine **28**.

3. Results and discussion

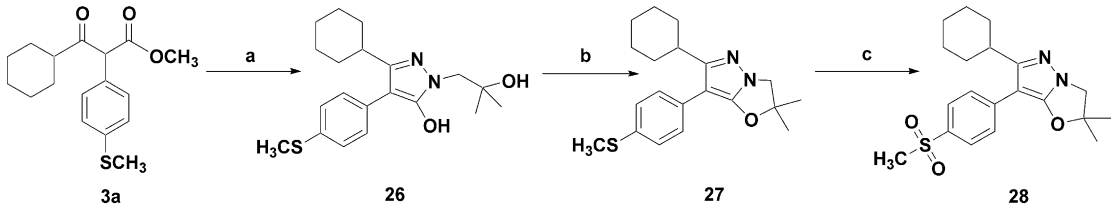
The compounds were tested for their ability to inhibit COX-1 and COX-2 isozymes in human whole blood (HWB).[31–32] For this initial in vitro screen, compounds were assayed against COX-1 at 100 μM and COX-2 at 10 μM and 1 μM (Table 1). For the most potent and selective COX-2 inhibitors, full IC_{50}'s were then determined (Table 2).

The results reported in Table 1 show that the substituent at the position 5 of the pyrazolo[5,1-*b*]oxazolidine is critically important. Having a cyclohexyl group, **7a** showed selective COX-2 inhibition (COX-2 inhibition: 90% at 10 μM and 25% at 1 μM; COX-1 inhibition: 25% at 100 μM). Replacement of the cyclohexyl group at position 5 of **7a** by a phenyl group enhanced COX-1 inhibitory activity slightly (COX-1 inhibition by **7b**: 40% at 100 μM) while leaving COX-2 activity unaffected. Surprisingly, substitution of a benzyl group at position 5, as in **7c**, resulted in complete loss of COX-1 and COX-2 activity. The COX inhibitory IC_{50}'s for **7a** (COX-1 > 100 μM; COX-2 1.3μM) confirmed the conclusion that **7a** is a highly potent and selective COX-2 inhibitor (Table 2).

On the basis of the COX-2 potency and selectivity demonstrated by pyrazolo[5,1-*b*]oxazolidine **7a**, this was

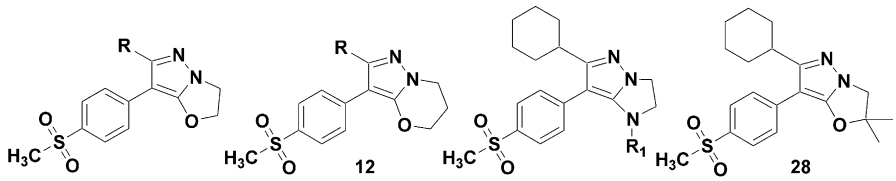


Scheme 2. (a) $SOCl_2$, toluene, rt, 30 min, 97%; (b) NaCN, DMSO, rt, 2 h, 89%; (c) cyclohexanecarbonyl chloride, LiHMDS, THF, −78 °C to rt, 67%; (d) gl. acetic acid, $NH_2NH(CH_2)_2OH$, 100 °C, 1 h, 64%; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min, 64%; (f) K_2CO_3, DMF, 60 °C, 3 days, 44%; (g) Oxone, MeOH, H_2O, 0 °C, 2 h; (h) MeI, K_2CO_3, rt, 7 days, 39%; (i) Ac_2O, DMAP, CH_2Cl_2, rt, 16 h, 36%; (j) *tert*-Butylbromoacetate, K_2CO_3, DMF, rt, 5d, 80%; (k) TFA, CH_2Cl_2, rt, 3 h, 69%.



Scheme 3. (a) gl. acetic acid, $NH_2NHCH_2C(CH_3)_2OH$, 100 °C, 1 h; (b) neat phosphoric acd, 70 °C, 6 h; (c) Oxone, MeOH/H_2O, rt, 2 h.

Table 1. In vitro human whole blood COX-1 and COX-2 inhibition by bicyclic-pyrazole derivatives



7a R = cyclohexyl
7b R = phenyl
7c R = benzyl

12a R = cyclohexyl

20 R_1 = -H
21 R_1 = -$COCH_3$
22 R_1 = -CH_3
24 R_1 = -CH_2COO^tBu
25 R_1 = -CH_2COOH

			% Inhibition HWB[a]		
			COX-1	COX -2	
Compd	R	R_1	100 μM	10 μM	1 μM
7a	Cyclohexyl		25	90	25
7b	Phenyl		40	90	20
7c	Benzyl		0	0	0
12a	Cyclohexyl		35	25	10
20		–H	65	80	5
21		–$COCH_3$	20	10	0
22		–CH_3	0	38	0
24		–CH_2COO^tBu	50	55	55
25		–CH_2COOH	48	34	0
28			0	12.5	0
	Celecoxib		65[b]	100	50
	Rofecoxib		75	100	75

[a] Percent inhibition of COX-1 (100 μM) or COX-2 (10 and 1 μM) in human whole blood. Assays were performed in duplicate. Average % inhibition using blood from two donors (see Experimental).
[b] COX-inhibition at 30 μM Celecoxib.

selected for further modification (Table 1). Changing the bicyclic ring from five- to six-membered (to give pyrazolo[5,1-*b*]oxazine **12**) significantly compromised COX-2 potency (COX-2 inhibition: 25% at 10 μM and 10% at 1 μM). This loss of COX-2 inhibitory potency suggests that, in this series, a fused six-membered bicyclic ring is detrimental to COX-2 activity.

We next investigated substituting the oxygen in compound **7a** with a nitrogen atom. To this end, a series of imidazolidino[1,2-*d*]pyrazoles was synthesized (Scheme 2) and evaluated for COX inhibition (Table 1). Compound **20** showed good potency toward COX-2 at 10 μM, although with reduced COX-2 selectivity in comparison to **7a** (COX-2 inhibition by **20**: 80% at 10 μM and 5% at 1 μM; COX-1 inhibition: 65% at 100 μM). Additional substitution at the available nitrogen of **20**, specifically *N*-acylation (to give **21**) and *N*-methylation (to give **22**), reduced all COX inhibitory activity. Compound **24**, containing a bulky and hydrophobic *tert*-butyl ester, showed good, but seemingly concentration independent, COX-2 activity (COX-2 inhibition: 55% at both 10 μM and 1 μM) and moderate selectivity versus COX-1 (COX-1 inhibition: 50% at 100 μM) in comparison to **7a**. The acid **25** was found to be a less potent COX-2 inhibitor than **24**. In view of the greater activity of **24** over **25**, other ester and amide derivatives could be envisioned as rational attempts to enhance COX-2 inhibitor potency and selectivity. Finally, we explored the effect of substitution on the saturated ring of **7a**, since the potent and selective COX-2 inhibitor ML 3000 has a bicyclic ring system substituted with two methyl groups. Compound **28**, which appeared to mimic this feature, had however, almost zero activity indicating that other features of ML 3000 are important contributors to enzyme binding.

Table 2. IC_{50} Values of bicyclic-pyrazole, **7a** and some standard COX-2 inhibitors in human blood

	IC_{50} (μM)	
Compd	COX-1	COX-2
Celecoxib	14	1.2
Rofecoxib	40	0.3
ML3000[21]		0.21[a]
7a	>100	1.3

[a] IC_{50} value for inhibition of cyclooxygenases.[23]

4. Conclusion

Activation of a hydroxyalkyl group attached to the pyrazole nucleus followed by cyclization produced three new series of bicyclic-pyrazoles. Several compounds

were found to be selective COX-2 inhibitors, the most potent and selective being the pyrazolo[5,1-*b*]1,3-oxazolidine **7a** (IC_{50}'s for COX-1 > 100 μM; COX-2 1.3 μM). Although marginally less potent than celecoxib and rofecoxib (Table 1), identification of **7a** as a lead compound from such a small series of compounds is encouraging. Modification of **7a** may generate still more potent and selective inhibitors.

5. Experimental

5.1. COX-Inhibition—HWB assay

Fresh human blood, obtained by informed consent from non-fasted donors of either sex who had not taken asprin or any NSAID during the prior 14 days, was collected in sodium heparin (20 units/mL) and distributed in 1 mL aliquots per well of 24-well tissue culture plate. The plates were placed on a gently rotating platform shaker in a 5% CO_2 incubator at 37 °C for 15 min. Test compounds were dissolved and diluted in DMSO, and 1 μL of each dilution of the test compound was added per well in duplicate wells. To induce COX-2, lipopolysaccharide from *E. coli* (Sigma Chemical Co., St. Louis, MO) was added at 10 μg/mL to appropriate wells 15 min after the addition of the test compounds. To activate COX-1, the calcium ionophore A23187 (Sigma Chemical Co., St Louis, MO) was added to a final concentration of 25 μM to separate wells 4.75 h after the addition of the test compounds. At 30 min after A23187 addition or 5 h after LPS addition, all incubations were terminated. The blood samples were processed for thromboxane B_2 determination and assayed in duplicate by EIA (Cayman Chemical Co., Ann Arbor, MI).[31] COX inhibition data in the text and tables are derived from averages of two EIA determinations on each of duplicate blood sample from two donors.

5.2. General procedures

All reagents and anhydrous solvents were generally used as received from the commercial supplier. Reactions were routinely performed under a nitrogen atmosphere in oven-dried glassware. Melting points were determined with an electrothermal heating block (Mettler) and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. NMR spectra were recorded in $CDCl_3$ unless otherwise specified, and chemical shifts are reported relative to tetramethylsilane as an internal standard. Low-resolution mass spectra were obtained using atmospheric pressure-turbo ion spray ionization. Elemental analyses were performed by Robertson Microlit Laboratories Inc., Madison, NJ. Gravity and flash column chromatography were performed using EM Science silica gel 60 (230–400 mesh). Analytical TLC was performed on 250 μM pre-coated EM Science silica gel 60 F_{254} aluminum sheets. Preparative TLC was performed using 20×20 cm 1000 μM pre-coated silica gel plates (Whatman). Spots were visualized under 254 nm light or after staining with phosphomolybdate spray.

5.3. 1-(5-Cyclohexyl(2H,3H-pyrazolo[5,1-*b*]1,3-oxazolidin-6-yl)-4-(methylsulfonyl) benzene (7a)

5.3.1. Methyl 2-(4-methylthiophenyl)acetate (2). Concentrated sulfuric acid (1 mL) was added dropwise to a solution of 2-(4-methylthiophenyl)acetic acid **1** (5.0 g, 27.4 mmol) in MeOH (40 mL) at room temperature. The resultant mixture was heated at 50 °C for 16 h, cooled to room temperature and the solvent was evaporated. The residue was dissolved in EtOAc, washed with saturated $NaHCO_3$, dried over Na_2SO_4 and filtered. The filtrate was evaporated to give **2** (5.4 g, ~100%) as a viscous oil. ^1H NMR δ 7.18–7.26 (m, 4H), 3.69 (s, 3H), 3.58 (s, 2H), 2.47 (s, 3H). ^{13}C NMR δ 172.0, 137.4, 130.9, 129.8, 127.0, 52.1, 40.7, 16.0. MS *m*/*z* 197 (MH^+), 214 (MNH_4^+), 219 (MNa^+), 137 (M-$COOCH_3$). Anal. calcd ($C_{10}H_{12}O_2S$): C, 61.20; H, 6.16. Found: C, 60.79; H, 5.80.

5.3.2. Methyl 3-cyclohexyl-2-(4-methylthiophenyl)-3-oxopropanoate (3a). To a stirred solution of **2** (4.9 g, 25.0 mmol) in THF (50 mL) was added dropwise a solution of lithium bis(trimethylsilyl)amide (1 M solution in THF, 62.4 mL, 62.4 mmol) at −78 °C under nitrogen. The resulting solution was stirred at −78 °C for 10 min and then at room temperature for 1 h. The reaction mixture was cooled to −78 °C and cyclohexanecarbonyl chloride (5.49 g, 37.4 mmol) was added dropwise. The mixture was allowed to warm to 0 °C over 1 h and then stirred at 0 °C for 1 h. Saturated NH_4Cl was added and the organic layer was separated. The aqueous phase was extracted with EtOAc and the combined organic phases were washed with brine and dried over Na_2SO_4. The residue after filtration and evaporation of the solvent was chromatographed on silica gel eluted with 1:9 EtOAc:Hex to give **3a** (7.6 g, 99%) as a white crystalline solid. Mp 104–106 °C. ^1H NMR δ 13.12 (s, 1H), 7.20–7.26 (m, 2H), 7.03–7.09 (m, 2H), 3.68 (s, 3H), 2.52 (s, 3H), 2.10–2.16 (m, 1H), 1.55–1.72 (m, 7H), 1.02–1.20 (m, 3H). ^{13}C NMR δ 180.8, 173.5, 137.2, 131.8, 131.7, 126.2, 101.9, 51.9, 41.2, 29.5, 25.7, 15.7. MS *m*/*z* 307 (MH^+), 324 (MNH_4^+). Anal. calcd ($C_{17}H_{22}O_3S$): C, 66.64; H, 7.24; N, 10.46. Found: C, 66.61; H, 7.34; N, 10.39.

5.3.3. 3-Cyclohexyl-1-(2-hydroxyethyl)-4-(4-methylthiophenyl)pyrazol-5-ol (4a). A mixture of **3a** (5.52 g, 18.0 mmol) and 2-hydroxyethylhydrazine (6.17 g, 81.2 mmol) in glacial AcOH (24 mL) was heated at 100 °C for 1 h. The solvent was evaporated and dried under vacuum to give a pale yellow solid which was dissolved in 1:9 MeOH:CH_2Cl_2. To this solution, water was added and the resultant precipitate was filtered, washed with water and then hexane to give **4a** (2.75 g, 46%) as an off-white solid. Mp 204–205 °C. ^1H NMR (d_4-MeOH) δ 7.26–7.32 (m, 4H), 3.98 (t, $J = 5.7$ Hz, 2H), 3.80 (t, $J = 5.6$ Hz, 2H), 2.76–2.84 (m, 1H), 2.47 (s, 3H), 1.22–1.87 (m, 10H). ^{13}C NMR (d_4-MeOH) δ 152.8, 138.0, 130.8, 130.3, 127.7, 105.4, 60.9, 47.6, 37.1, 32.9, 27.4, 26.9, 15.9. MS *m*/*z* 333 (MH^+). Anal. calcd ($C_{18}H_{24}N_2O_2S$): C, 65.03; H, 7.28; N, 8.43; S, 9.64. Found: C, 64.80; H, 7.30; N, 8.30; S, 9.53.

5.3.4. 1-[3-Cyclohexyl-5-hydroxy-1-(2-hydroxyethyl)pyrazol-4-yl]-4-(methylsulfonyl) benzene (5a). To a solution of **4a** (316 mg, 0.95 mmol) in MeOH (18 mL) was added dropwise a solution of Oxone® (1.35 g, 2.20 mmol) in water (4 mL). The white suspension was stirred at room temperature for 30 min. The solid was filtered and washed with CH_2Cl_2. The filtrate was treated with water to give a white precipitate. The precipitate was filtered and washed with water and hexane to give **5a** (0.15 g, 43%) as a white solid. Mp 247–249 °C. ^{1}H NMR (d_4-MeOH) δ 7.96 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H), 4.02 (t, J = 5.6 Hz, 2H), 3.81 (t, J = 5.6 Hz, 2H), 3.13 (s, 3H), 2.84–2.96 (m, 1H), 1.20–1.95 (m, 10H). ^{13}C NMR ($CDCl_3$/d_4-MeOH) δ 152.7, 139.8, 138.7, 130.2, 128.3, 103.6, 60.7, 47.5, 44.6, 36.8, 32.7, 27.2, 26.6. MS m/z 365 (MH^+). Anal. calcd ($C_{18}H_{24}N_2O_4S$·1/2 mol H_2O): C, 57.89; H, 6.74; N, 7.50; S, 8.58. Found: C, 58.18; H, 6.54; N, 7.40; S, 8.40.

5.3.5. 1-[1-(2-bromoethyl)-3-cyclohexyl-5-hydroxypyrazol-4-yl]-4-(methylsulfonyl)benzene (6a). To a stirred solution of **5a** (140 mg, 0.38 mmol) and carbon tetrabromide (191 mg, 0.57 mmol) in CH_2Cl_2 (0.8 mL) at 0 °C under nitrogen was added a solution of triphenylphosphine (151 mg, 0.57 mmol) in CH_2Cl_2 (0.4 mL). The resultant orange solution was stirred at room temperature for 3 days. The residue after evaporation of the solvent was chromatographed on silica gel eluted with 0.5:9.5 MeOH: CH_2Cl_2 to give **6a** (152 mg, 93%) as a pale yellow foam. ^{1}H NMR δ 7.90 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H), 4.22 (t, J = 6.0 Hz, 2H), 3.66 (t, J = 5.9 Hz, 2H), 3.07 (s, 3H), 2.78–2.82 (m, 1H), 1.20–1.92 (m, 10H). MS m/z 427 / 429 (MH^+).

5.3.6. 1-(5-Cyclohexyl(2H,3H-pyrazolo[5,1-*b*]1,3-oxazolidin-6-yl)-4-(methylsulfonyl) benzene (7a). To a solution of **6a** (0.15 g, 0.35 mmol) in DMF (9 mL), K_2CO_3 (58 mg, 0.45 mmol) was added. The resultant mixture was stirred at room temperature for 3 h. The solid was filtered and the solvent was evaporated. The residue was extracted with EtOAc and the organic phase was washed with water, brine and then dried over Na_2SO_4 . The residue after filtration and evaporation of the solvent was chromatographed on silica gel eluted with 1:1 EtOAc:CH_2Cl_2 to give **7a** (75 mg, 62%) as a white solid. Mp 172–173 °C. ^{1}H NMR δ 7.94 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 5.15 (t, J = 7.7 Hz, 2H), 4.36 (t, J = 8.3 Hz, 2H), 3.10 (s, 3H), 2.80–2.92 (m, 1H), 1.25–2.05 (m, 10H). ^{13}C NMR δ 160.9, 157.4, 138.7, 136.7, 127.9, 127.2, 94.0, 75.7, 45.5, 44.8, 38.2, 32.7, 26.8, 26.2. MS m/z 347 (MH^+). Anal. calcd ($C_{18}H_{22}N_2O_3S$): C, 62.40; H, 6.40; N, 8.09. Found: C, 62.32; H, 6.30; N, 8.02.

5.4. 4-(Methylsulfonyl)-1-(5-phenyl(2H,3H-pyrazolo[5,1-*b*]1,3-oxazolidin-6-yl))benzene (7b)

5.4.1. Methyl 2-(4-methylthiophenyl)-3-oxo-3-phenylpropanoate (3b). To a stirred solution of **2** (6.0 g, 36.0 mmol) in THF (60 mL) was added dropwise a solution of lithium bis(trimethylsilyl)amide (1 M solution in THF, 76.5 mL, 76.5 mmol) at −78 °C under nitrogen. The resulting solution was stirred at −78 °C for 10 min and then at room temperature for 1 h. The reaction mixture was cooled to −78 °C, and benzoyl chloride (6.45 g, 45.9 mmol) was added dropwise. The mixture was allowed to warm to room temperature over 1 h and stirred at room temperature for 16 h. The mixture was cooled to 0 °C. To this solution, saturated NH_4Cl was added, and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine and dried over Na_2SO_4. The residue after filtration and evaporation of the solvent was recrystallized from CH_2Cl_2/Hex to give **3b** (7.97 g, 87%) as a pale yellow solid. Mp 82–83 °C. ^{1}H NMR δ 7.88–7.95 (m, 2H), 7.77–7.82 (m, 1H), 7.18–7.54 (m, 6H), 5.56 (s, 1H), 3.73 (s, 3H), 2.42 (s, 3H). MS m/z 301 (MH^+), 318 (MNH_4^+).

5.4.2. 1-(2-Hydroxyethyl)-4-(4-methylthiophenyl)-3-phenylpyrazol-5-ol (4b). A mixture of **3b** (3.5 g, 11.7 mmol) and 2-hydroxyethylhydrazine (3.99 g, 52.4 mmol) in glacial AcOH (35 mL) was heated at 100 °C for 1 h. The solvent was evaporated to give a pale yellow oil which was dissolved in EtOAc. To this solution, water was added, the resultant precipitate was filtered and washed with water, hexane and then dried under vacuum to give **4b** (2.36 g, 62%) as a white solid. Mp 235–237 °C. ^{1}H NMR (DMSO-d_6) δ 7.14–7.36 (m, 9H), 4.02 (t, J = 6.2 Hz, 2H), 3.76 (t, J = 6.3 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 145.7, 135.1, 129.7, 129.5, 128.2, 127.6, 125.9, 101.5, 59.5, 48.4, 14.8. MS m/z 327 (MH^+), 349 (MNa^+). Anal. calcd ($C_{18}H_{18}N_2O_2S$): C, 66.23; H, 5.56; N, 8.58; S, 9.82. Found: C, 66.03; H, 5.57; N, 8.47; S, 9.82.

5.4.3. 1-(2-Bromoethyl)-4-(4-methylthiophenyl)-3-phenylpyrazol-5-ol (8b). To a stirred solution of **4b** (0.81 g, 2.48 mmol) in DMF (16 mL) was added polymer supported triphenylphosphine (1.65 g of resin, 3 mmol of P/g of resin, 5 mmol). The mixture was stirred at room temperature for 30 min under nitrogen. To this mixture, carbon tetrabromide (1 g, 2.98 mmol) was added portionwise. The resultant mixture was stirred at room temperature for 4 days. The solid was filtered and washed with EtOAc. The residue after evaporation of the solvent was dissolved in EtOAc/MeOH, washed with water, brine and then dried over Na_2SO_4. Filtration and evaporation of the solvent gave **8b** (0.76 g, 78%) as a pale yellow foam. ^{1}H NMR δ 7.15–7.42 (m, 9H), 4.34 (t, J = 6.5 Hz, 2H), 3.67 (t, J = 7.1 Hz, 2H), 2.47 (s, 3H). MS m/z 390/ 392 (MH^+).

5.4.4. 4-Methylthio-1-(5-phenyl(2H,3H-pyrazolo[5,1-*b*]1,3-oxazolidin-6-yl))benzene (9b). Compound **9b** was synthesized in a manner similar to the synthesis of **7a** using **8b** (0.47 g, 1.21 mmol) and K_2CO_3 (0.22 g, 1.56 mmol) in DMF (30 mL) to give **9b** (0.2 g, 54%) as a white foam. ^{1}H NMR δ 7.50–7.56 (m, 2H), 7.32–7.38 (m, 3H), 7.15–7.25 (m, 4H), 5.12 (t, J = 7.7 Hz, 2H), 4.40 (t, J = 8.3 Hz, 2H), 2.47 (s, 3H). ^{13}C NMR δ 157.1, 154.5, 135.6, 134.5, 128.8, 128.5, 128.4, 128.1, 127.0, 95.4, 75.4, 45.6, 16.2. MS m/z 309 (MH^+).

5.4.5. 4-(Methysulfonyl)-1-(5-phenyl(2H,3H-pyrazolo[5,1-*b*]1,3-oxazolidin-6 yl))benzene (7b). To a solution of **9b**

(0.22 g, 0.71 mmol) in MeOH (9 mL) was added dropwise a solution of Oxone® (0.88 g, 1.43 mmol) in water (3 mL). The white suspension was stirred at room temperature for 1 h. The solid was filtered and washed with CH_2Cl_2. The filtrate was diluted with CH_2Cl_2, and the layers were separated. The organic phase was washed with water and then dried over Na_2SO_4. The residue after filtration and evaporation of the solvent was recrystallized from CH_2Cl_2/EtOAc/Hex to give **7b** (0.23 g, 95%) as a white crystalline solid. Mp 194–195 °C. ^{1}H NMR δ 7.79 (d, J = 8.5 Hz, 2H), 7.35–7.52 (m, 7H), 5.20 (t, J = 7.8 Hz, 2H), 4.44 (t, J = 7.8 Hz, 2H), 3.04 (s, 3H). ^{13}C NMR δ 157.7, 154.9, 138.0, 137.0, 134.0, 128.8, 128.6, 128.6, 127.8, 127.6, 94.6, 75.9, 45.6, 44.7. MS m/z 341 (MH^+). Anal. calcd ($C_{18}H_{16}N_2O_3S$): C, 63.51; H, 4.74; N, 8.23; S, 9.42. Found: C, 63.26; H, 4.70; N, 8.14; S, 9.32.

5.5. 4-(Methylsulfonyl)-1-(5-benzyl(2H,3H-pyrazolo[5,1-*b*]1,3-oxazolidin-6-yl))benzene (7c)

5.5.1. Methyl 2-(4-methylthiophenyl)-3-oxo-4-phenylbutanoate (3c). Compound **3c** was synthesized in a manner similar to the synthesis of **3b** using **2** (8.39 g, 42.8 mmol), phenyl acetyl chloride (9.9 g, 64.2 mmol) and lithium bis(trimethylsilyl)amide (1 M solution in THF, 107 mL, 107 mmol) in THF (60 mL). The residue after filtration and evaporation of the solvent was chromatographed on silica gel eluted with 1:9 EtOAc:Hex to give a mixture of ketoenol tautomers, **3c** (10 g, 75%) as a colorless oil. MS m/z 315 (MH^+), 332 (MNH_4^+).

5.5.2. 1-(2-Hydroxyethyl)-4-(4-methylthiophenyl)-3-benzylpyrazol-5-ol (4c). A mixture of **3c** (4.89 g, 15.6 mmol) and 2-hydroxyethylhydrazine (5.33 g, 70.0 mmol) in glacial AcOH (35 mL) was heated at 100 °C for 1 h. The residue after evaporation of the solvent was chromatographed on silica gel eluting with 0.2:9.8 to 0.5:9.5 MeOH:CH_2Cl_2 to give **4c** (2 g, 38%) as a pale yellow solid. Mp 121–123 °C. ^{1}H NMR δ 7.00–7.26 (m, 9H), 3.75–3.85 (m, 4H), 3.60–3.75 (m, 2H), 2.41 (s, 3H). ^{13}C NMR δ 160.3, 145.5, 137.2, 136.5, 129.1, 128.8, 128.5, 128.5, 126.9, 126.7, 105.9, 61.0, 47.3, 32.1, 15.9. MS m/z 341 (MH^+). Anal. calcd ($C_{19}H_{20}N_2O_2S$·1/2 mol H_2O): 65.30; H, 6.05; N, 8.02. Found: C, 65.33; H, 5.88; N, 8.13.

5.5.3. 1-(2-Bromoethyl)-4-(4-methylthiophenyl)-3-benzylpyrazol-5-ol (8c). Compound **8c** was synthesized in a manner similar to the synthesis of **6a** using **4c** (1 g, 2.94 mmol), carbon tetrabromide (1.17 g, 3.53 mmol) and triphenylphosphine (0.93 g, 3.53 mmol) in CH_2Cl_2 to give **8c** (1.08 g, 91%) as a pale yellow foam. ^{1}H NMR δ 7.13–7.30 (m, 9H), 4.25 (bt, J = 6.4 Hz, 2H), 3.95 (s, 2H), 3.65 (bs, 1H), 3.62 (bt, J = 6.4 Hz, 2H), 2.47 (s, 3H). MS m/z 403/405 (MH^+).

5.6. 4-Methylthio-1-(5-benzyl(2H,3H-pyrazolo[5,1-*b*]1,3-oxazolidin-6-yl))benzene (9c)

The compound **9c** was synthesized in a manner similar to the synthesis of **7a** using **8c** (1.1 g, 2.7 mmol) and K_2CO_3 (0.49 g, 3.53 mmol) in DMF (10 mL). The residue after evaporation of the solvent was chromatographed on silica gel eluted with 1:1:2 EtOAc:Hex:CH_2Cl_2 to give **9c** (0.34 g) contaminated with triphenylphosphine as a white foam which was used for the next step without further purification. MS m/z 323 (MH^+).

5.6.1. 4-(Methysulfonyl)-1-(5-benzyl(2H,3H-pyrazolo[5,1-*b*]1,3-oxazolidin-6-yl))benzene (7c). Compound **7c** was synthesized in a manner similar to the synthesis of **7b** using **9c** (0.34 g, 1.06 mmol) in MeOH (13 mL) and Oxone® (1.29 g, 2.1 mmol) in water (4 mL). The residue after filtration and evaporation of the solvent was chromatographed on silica gel eluted with 1:1:2 EtOAc:Hex:CH_2Cl_2 to give **7c** (70 mg, 19%) as a white solid. Mp 169–170 °C. ^{1}H NMR δ 7.81 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 7.19–7.30 (m, 5H), 5.17 (t, J = 7.8 Hz, 2H), 4.38 (t, J = 7.7 Hz, 2H), 4.15 (s, 2H), 3.01 (s, 3H). ^{13}C NMR δ 157.7, 154.0, 138.7, 138.0, 136.6, 128.7, 128.5, 127.8, 126.8, 126.6, 95.2, 75.8, 45.5, 44.7, 35.6. MS m/z 355 (MH^+). Anal. calcd ($C_{19}H_{18}N_2O_3S$): C, 64.39; H, 5.12; N, 7.90; S, 9.05. Found: 64.41; H, 5.07; N, 7.84; S, 8.99.

5.7. 1-(2-Cyclohexyl(5H,6H,7H-pyrazolo[5,1-*b*]1,3-oxazaperhydroin-3-yl))-4-(methylsulfonyl)benzene, (12a)

5.7.1. 3-Cyclohexyl-1-(3-hydroxypropyl)-4-(4-methylthiophenyl)pyrazol-5-ol (10). A mixture of **3a** (1.4 g, 4.6 mmol) and 3-hydroxypropylhydrazine[29] (1.85 g, 20.6 mmol) in glacial AcOH (10 mL) was heated at 100 °C for 1 h. The resultant solution was cooled to room temperature, neutralized with saturated $NaHCO_3$ and extracted with 9:1 CH_2Cl_2/MeOH. The combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was chromatographed on silica gel eluted with MeOH:CH_2Cl_2 to give **10** (0.85 g, 52%) as an oil. ^{1}H NMR (DMSO-d_6) δ 7.20–7.50 (m, 4H), 3.90–4.10 (m, 2H), 3.40–3.70 (m, 2H), 2.80–3.00 (m, 1H), 2.45 (s, 3H), 1.20–2.20 (m, 12H). MS m/z 361 (MH^+).

5.7.2. 1-(2-Cyclohexyl(5H,6H,7H-pyrazolo[5,1-*b*]1,3-oxazaperhydroin-3-yl))-4-methylthiobenzene, (11). To a stirred solution of **10** (0.8 g, 2.3 mmol) in DMF (20 mL) was added polymer supported triphenylphosphine (1.54 g of resin, 3 mmol of P/g of resin, 4.6 mmol). The mixture was stirred at room temperature for 30 min under nitrogen. To this mixture, carbon tetrabromide (0.92 g, 2.8 mmol) was added portionwise. The resultant mixture was stirred at room temperature for 5 days. The solid was filtered and washed with EtOAc. The residue after evaporation of the solvent was diluted with 9:1 $CHCl_3$:MeOH washed with water, brine and then dried over Na_2SO_4. The residue after filtration and evaporation of the solvent was chromatographed on silica gel eluted with 9:1 CH_2Cl_2:MeOH to give **11** (0.4 g, 53%). ^{1}H NMR δ 7.19–7.42 (m, 4H), 3.80–4.02 (m, 4H), 2.72–2.85 (m, 1H), 2.52–2.69 (m, 2H), 2.41 (s, 3H), 1.20–2.05 (m, 10H). MS m/z 329 (MH^+).

5.7.3. 1-(2-Cyclohexyl(5H,6H,7H-pyrazolo[5,1-*b*]1,3-oxazaperhydroin-3-yl))-4-(methylsulfonyl)benzene, (12a). Compound **12a** was synthesized in a manner similar to the synthesis of **7b** using **11** (50 mg, 0.15 mmol) in

MeOH (2 mL) and Oxone® (0.19 g, 0.3 mmol) in water (1 mL). The residue after workup was chromatographed on silica gel eluted with 1:9 MeOH:CH_2Cl_2 to give **12a** (30 mg, 55%) as a white solid. Mp 145–148 °C. ^{1}H NMR δ 7.97 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 3.80–4.05 (m, 4H), 3.10 (s, 3H), 2.75–2.93 (m, 1H), 2.60–2.75 (m, 2H); 1.20–2.05 (m, 10H). ^{13}C NMR δ 159.8, 148.9, 138.8, 137.4, 129.6, 127.4, 108.4, 46.7, 44.6, 40.6, 36.2, 31.1, 27.4, 26.2, 25.7. MS m/z 361 (MH^+). Anal. calcd ($C_{19}H_{24}N_2O_3S$·1/4 mol H_2O): C, 62.52; H, 6.77; N, 7.67. Found: C, 62.27; H, 6.76; N, 7.57.

5.8. 1-(2-Cyclohexylimidazolidino[1,2-*d*]pyrazol-3-yl)-4-(methylsulfonyl)benzene (20)

5.8.1. 1-(Chloromethyl)-4-methylthiobenzene (14). To a solution of 4-methylthiobenzyl alcohol **13** (8.5 g, 55.1 mmol) in toluene (85 mL) was added dropwise neat thionyl chloride (4.82 mL, 7.87 g, 66.1 mmol) at room temperature. The resultant pale yellow solution was stirred at room temperature for 30 min, and brine was added. The organic phase was separated, washed with brine, dried over Na_2SO_4 and filtered. The solvent was evaporated to give **14** (9.2 g, 97%) as a viscous oil. ^{1}H NMR δ 7.20–7.35 (m, 4H), 4.56 (s, 2H), 2.49 (s, 3H). ^{13}C NMR δ 139.3, 134.3, 129.2, 126.7, 46.1, 15.8.

5.8.2. 2-(4-Methylthiophenyl)ethanenitrile (15). To a stirred suspension of sodium cyanide (3.15 g, 64.2 mmol) in DMSO (15 mL) was added dropwise a solution of **14** (9.2 g, 53.4 mmol) in DMSO (5 mL). The resultant mixture was stirred at room temperature for 2 h to give a pale yellow solution. Saturated NaCl was added, and the crude reaction mixture was extracted with EtOAc. The combined organic phases were washed with saturated NaCl, dried over Na_2SO_4 and filtered. The solvent was evaporated to give **15** (7.74 g, 89%) as a pale yellow solid. Mp 35–36 °C. ^{1}H NMR δ 7.20–7.30 (m, 4H), 3.69 (s, 2H), 2.47 (s, 3H). ^{13}C NMR δ 138.8, 128.4, 127.1, 126.6, 117.9, 23.2, 15.8.

5.8.3. 3-Cyclohexyl-2-(4-methylthiophenyl)-3-oxopropanenitrile (16). To a stirred solution of **15** (4.0 g, 24.5 mmol) in THF (95 mL) was added dropwise a solution of lithium bis(trimethylsilyl)amide (1 M solution in THF, 61.3 mL, 61.3 mmol) at −78 °C under nitrogen. The resulting solution was stirred at −78 °C for 10 min and then at room temperature for 1 h. The reaction mixture was cooled to −78 °C, and cyclohexanecarbonyl chloride (5.40 g, 36.8 mmol) was added dropwise. The mixture was allowed to warm to 0 °C over 1 h and stirred at 0 °C for 1.5 h. Saturated NH_4Cl was added, and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine and dried over Na_2SO_4. The residue after filtration and evaporation of the solvent was chromatographed on silica gel eluted with 1:5 to 1:3 to 1:1 EtOAc:Hex to give **16** (4.48 g, 67%) as a pale yellow solid. Mp 64–65 °C. ^{1}H NMR δ 7.20–7.38 (m, 4H), 4.75 (bs, 1H), 2.57–2.68 (m, 1H), 2.48 (s, 3H), 1.10–1.80 (m, 10H). ^{13}C NMR ($CDCl_3$/d_4-MeOH) δ 201.9, 140.5, 128.5, 127.7, 126.9, 126.0, 116.5, 29.0, 28.5, 25.3, 25.0, 15.2. MS m/z 274 (MH^+), 291 (MNH_4^+). Anal. calcd ($C_{16}H_{19}NOS$): C, 70.29; H, 7.01; N, 5.12. Found: C, 70.41; H, 7.08; N, 4.90.

5.8.4. 2-[5-Amino-3-cyclohexyl-4-(4-methylthiophenyl)pyrazolyl]ethan-1-ol (17). A mixture of **16** (2.89 g, 10.6 mmol) and 2-hydroxyethylhydrazine (3.63 g, 47.6 mmol) in glacial AcOH (12 mL) was heated at 100 °C for 1 h. The residue after evaporation of the solvent was chromatographed on silica gel eluted with 1:10 MeOH:CH_2Cl_2 to give **17** (2.25 g, 64%) as a white solid. Mp 108–110 °C. ^{1}H NMR δ 7.16–7.40 (m, 4H), 3.95–4.15 (m, 4H), 3.75 (bs, 2H), 2.51–2.62 (m, 1H), 2.52 (s, 3H), 2.10 (bs, 1H), 1.15–1.95 (m, 10H). ^{13}C NMR δ 149.0, 137.5, 130.9, 125.4, 124.5, 122.0, 98.4, 57.0, 44.0, 31.1, 27.6, 21.5, 20.9, 10.7. MS m/z 332 (MH^+). Anal. calcd ($C_{18}H_{25}N_3OS$): C, 65.22; H, 7.60; N, 12.68. Found: 64.82; H, 7.50; N, 12.47.

5.8.5. 2-[5-Amino-3-cyclohexyl-4-(4-methylthiophenyl)-pyrazolyl]ethyl methylsulfonate (18). To a stirred solution of **17** (1.32 g, 3.98 mmol) and triethylamine (0.83 mL, 0.67 g, 5.97 mmol) in CH_2Cl_2 (20 mL) at 0 °C under nitrogen, was added dropwise methanesulfonyl chloride (0.46 g, 0.31 mL, 3.98 mmol). The mixture was stirred at 0 °C for 10 min. Water was added, and the layers were separated. The organic phase was washed with water and dried over Na_2SO_4. The residue after filtration and evaporation of the solvent was chromatographed on silica gel eluted with 1:1 EtOAc:Hex to give **18** (1.04 g, 64%) as a colorless oil. ^{1}H NMR δ 7.31 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 4.60 (t, J = 4.9 Hz, 2H), 4.31 (t, J = 4.9 Hz, 2H), 3.63 (bs, 2H), 2.84 (s, 3H), 2.45–2.65 (m, 1H), 2.50 (s, 3H), 1.15–1.85 (m, 10H). ^{13}C NMR δ 155.6, 143.1, 136.9, 130.7, 130.2, 127.6, 104.9, 69.6, 46.9, 37.4, 36.8, 33.4, 27.1, 26.5, 16.4. MS m/z 410 (MH^+).

5.8.6. 1-(2-Cyclohexylimidazolidino[1,2-*d*]pyrazol-3-yl)-4-methylthiobenzene (19). Potassium carbonate (1.01 g, 7.33 mmol) was added to a solution of **18** (1.0 g, 2.44 mmol) in DMF (30 mL). The resultant mixture was stirred at room temperature for 1 h and at 60 °C for 16 h. The solid was filtered and the solvent was evaporated. Ethyl acetate was added, and the organic phase washed with water and dried over Na_2SO_4. The residue after filtration and evaporation of the solvent was chromatographed on silica gel eluted with 1:1 EtOAc:Hex to 0.1:1:1 MeOH:EtOAc:Hex to give **19** (0.34 g, 44%) as a pale brown solid. Mp 128–130 °C. ^{1}H NMR δ 7.20–7.35 (m, 4H), 4.12–4.25 (m, 2H), 3.90–4.05 (m, 2H), 3.70 (bs, 1H), 2.65–2.80 (m, 1H), 2.50 (s, 3H), 1.48–2.00 (m, 7H), 1.20–1.43 (m, 3H). ^{13}C NMR δ 160.3, 150.9, 134.9, 131.2, 128.0, 127.5, 98.3, 49.2, 46.2, 37.3, 33.2, 26.9, 26.3, 16.3. MS m/z 314 (MH^+). Anal. calcd ($C_{18}H_{23}N_3S$·1/4 mol H_2O): C, 67.99; H, 7.45; N, 13.22. Found: C, 68.27; H, 7.19; N, 13.07.

5.8.7. 1-(2-Cyclohexylimidazolidino[1,2-*d*]pyrazol-3-yl)-4-(methylsulfonyl)benzene (20). To a solution of **19** (100 mg, 0.32 mmol) in MeOH (3 mL) was added dropwise a solution of Oxone® (294 mg, 0.47 mmol) in water (0.6 mL) at 0 °C. The white suspension was stirred at 0 °C for 2 h. The solid was filtered and washed with CH_2Cl_2.

The filtrate was diluted with CH_2Cl_2, and the layers were separated. The organic phase was washed with water and dried over Na_2SO_4. The residue after filtration and evaporation of the solvent was chromatographed on silica gel eluted with 0.1:1:1 MeOH/EtOAc/Hex to give **20** (60 mg, 54%) as a white foam. Mp 57 °C. ^{1}H NMR δ 7.84 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 4.32 (bs, 1H), 4.16 (t, J = 7.3 Hz, 2H), 4.00 (t, J = 7.3 Hz, 2H), 3.05 (s, 3H), 2.78 (tt, J = 3.1 Hz and 11.8 Hz, 1H), 1.45–2.00 (m, 7H), 1.15–1.42 (m, 3H). ^{13}C NMR δ 154.8, 146.6, 135.2, 130.8, 122.6, 121.9, 92.1, 43.9, 40.8, 39.4, 32.2, 27.7, 21.5, 20.9. MS m/z 346 (MH^+). Anal. calcd ($C_{18}H_{23}N_3O_2S$·1/4 mol H_2O): C, 61.77; H, 6.77; N, 12.00. Found: C, 61.70; H, 6.81; N, 11.81.

5.8.8. 4-Acetyl-2-cyclohexyl-3-[4-(methylsulfonyl)phenyl]-imidazolidino[1,2-*d*]pyrazole (21). To a solution of **20** (70 mg, 0.2 mmol) and DMAP (24.7 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) was added dropwise acetic anhydride (38 μL, 41.4 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 24 h. The residue after evaporation of the solvent was dissolved in EtOAc, washed with 0.1 N HCl, water, dried over Na_2SO_4, filtered and evaporated. The crude material was recrystallized from CH_2Cl_2/EtOAc/Hex to give **21** (28 mg, 36%) as a white solid. Mp 198–199 °C. ^{1}H NMR (DMSO-d_6) δ 7.80–8.04 (m, 2H), 7.29–7.52 (m, 2H), 4.48–4.62 (bs, 2H), 4.22–4.48 (bs, 2H), 3.11 (s, 3H), 2.28–2.48 (m, 1H), 1.91–2.28 (m, 1H), 1.40–1.87 (m, 9H), 1.08–1.37 (m, 3H). ^{13}C NMR (DMSO-d_6 at 373 K) δ 166.2, 159.5, 142.3, 140.3, 139.3, 131.8, 126.2, 102.4, 51.3, 45.2, 44.4, 36.9, 33.1, 26.5, 26.2, 22.7. MS m/z 388 (MH^+), 405 (MNH_4^+). Anal. calcd ($C_{20}H_{25}N_3O_3S$): C, 61.99; H, 6.50; N, 10.84. Found: C, 61.76; H, 6.22; N, 10.68.

5.8.9. 1-(6-Cyclohexyl-1-methylimidazolidino[1,2-d]pyrazol-7-yl)-4-(methylsulfonyl) benzene (22). A mixture of **20** (25 mg, 0.07 mmol), methyl iodide (4.5 μL, 10.3 mg, 0.07 mol) and K_2CO_3 (10 mg, 0.07 mmol) in DMF (0.4 mL) was stirred at room temperature for 7 days. The solvent was evaporated. The residue was chromatographed using preparative layer chromatography eluted with 1:1 EtOAc:Hex to give **22** (10.2 mg, 39%). Mp 138–140 °C. ^{1}H NMR δ 7.93 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 4.16 (t, J = 7.4 Hz, 2H), 3.73 (t, J = 7.3 Hz, 2H), 3.10 (s, 3H), 2.57 (s, 3H), 2.41–2.57 (m, 1H); 1.15–1.90 (m, 10H). MS m/z 360 (MH^+).

5.9. *tert*-Butyl 2-{2-cyclohexyl-3-[4-(methylsulfonyl)phenyl]-imidazolidino[1,2-*d*]pyrazol-4-yl}acetate (24)

5.9.1. *tert*-Butyl 2-[2-cyclohexyl-3-(4-methylthiophenyl)-imidazolidino[1,2-*d*]pyrazol-4-yl]acetate (23). Compound **19** (0.22 g, 0.7 mmol) was dissolved in DMF (5 mL) and K_2CO_3 (0.19 g, 1.4 mmol) added followed by *tert*-butylbromoacetate (0.16 mL, 0.21 g, 1.1 mmol). The resulting solution was stirred at room temperature for 5 days, diluted with a large volume of EtOAc, washed with water, dried over Na_2SO_4, filtered and evaporated. The residue was chromatographed on silica gel eluted with 1:1 EtOAc:CH_2Cl_2 to give **23** (0.24 g, 80%) as an oil. ^{1}H NMR δ 7.21–7.27 (m, 2H), 7.12–7.21 (m, 2H), 4.19 (t, J = 7.4 Hz, 2H), 3.91 (t, J = 8.4 Hz, 2H), 3.57 (s, 2H), 2.51 (s, 3H), 2.42–2.64 (m, 1H), 1.42–1.95 (m, 7H), 1.39 (s, 9H), 1.12–1.32 (m, 3H). ^{13}C NMR δ 168.7, 160.8, 150.6, 136.0, 130.4, 129.9, 126.7, 97.9, 81.8, 55.4, 51.3, 45.8, 36.8, 33.2, 28.1, 26.8, 26.2, 16.0. MS m/z 428 (MH^+).

5.9.2. *tert*-Butyl 2-{2-cyclohexyl-3-[4-(methylsulfonyl)-phenyl]imidazolidino[1,2-*d*]pyrazol-4-yl}acetate (24). To a solution of **23** (70 mg, 0.16 mmol) in MeOH (1.5 mL) was added dropwise a solution of Oxone® (150 mg, 0.25 mmol) in water (0.4 mL) at 0 °C. The white suspension was stirred at 0 °C for 6 h. The solid was filtered and washed with CH_2Cl_2. The filtrate was diluted with CH_2Cl_2 and the layers were separated. The organic phase was washed with water, 5% $NaHCO_3$, dried over Na_2SO_4 and filtered. The residue after evaporation of the solvent was chromatographed on silica gel eluted with 1:1 EtOAc:CH_2Cl_2 to give **24** (68 mg, 90%) as a white foam. Mp 56–58 °C. ^{1}H NMR δ 7.91 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 4.22 (t, J = 7.5 Hz, 2H), 3.95 (t, J = 7.4 Hz, 2H), 3.56 (s, 2H), 3.10 (s, 3H), 2.42–2.62 (m, 1H), 1.50–1.95 (m, 7H), 1.36 (s, 9H), 1.10–1.30 (m, 3H). ^{13}C NMR δ 168.5, 160.5, 151.1, 139.6, 137.7, 130.0, 127.6, 97.1, 82.2, 55.7, 51.4, 45.9, 44.7, 36.9, 33.2, 28.1, 26.8, 26.2. MS m/z 460 (MH^+).

5.9.3. 2-{6-Cyclohexyl-7-[4-(methylsulfonyl)phenyl]-imidazolidino[1,2-*d*]pyrazolyl}acetic acid (25). To a solution of **24** (0.14 g, 0.3 mmol) in CH_2Cl_2 (1 mL) was added dropwise TFA (1 mL) at room temperature. The mixture was stirred at room temperature for 3 h. The solvent was evaporated. The residue was chromatographed on silica gel eluted with 0.1:1:1 MeOH:EtOA:Hex to 2:8 MeOH:CH_2Cl_2 to give **25** (84 mg, 69%) as an off-white solid. Mp 83 °C. ^{1}H NMR δ 7.93 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 4.24 (t, J = 7.5 Hz, 2H), 3.98 (t, J = 7.7 Hz, 2H), 3.71 (s, 2H), 3.10 (s, 3H), 2.47–2.57 (m, 1H), 1.67–1.82 (m, 4H), 1.40–1.60 (m, 2H); 1.10–1.32 (m, 4H). ^{13}C NMR δ 160.6, 151.3, 152.0, 138.1, 130.2, 127.8, 127.5, 97.4, 55.7, 50.6, 46.0, 44.7, 36.8, 33.0, 26.7, 26.1. MS m/z 404 (MH^+). LCMS (100%).

5.10. 1-(6-Cyclohexyl-2,2-dimethyl(3H-pyrazolo[5,1-*b*]1,3-oxazolidin-7-yl))-4-(methylsulfonyl)benzene (28)

5.10.1. 3-Cyclohexyl-1-(2-hydroxy-2-methylpropyl)-4-(4-methylthiophenyl)pyrazol-5-ol (26). A mixture of **3a** (0.25 g, 0.82 mmol) and 1-hydrazino-2-methyl-2-propanol[30] (0.38 g, 3.7 mmol) in glacial AcOH (3 mL) was heated at 95 °C for 5 h. The solvent was evaporated. The residue was recrystallized from $CHCl_3$/Hex to give **26** (0.2 g, 68%) as a white solid. MS m/z 361 (MH^+).

5.10.2. 1-(6-Cyclohexyl-2,2-dimethyl(3H-pyrazolo[5,1-*b*]1,3-oxazolidin-7-yl))-4-methylthiobenzene (27). A solution of **26** (0.16 g, 0.44 mmol) in neat phosphoric acid (1 mL) was heated at 70 °C for 6 h. The reaction mixture was diluted with CH_2Cl_2, and cooled to 0 °C. Saturated $NaHCO_3$ was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, the combined

organic phase was washed with saturated $NaHCO_3$ and dried over Na_2SO_4. The residue after filtration and evaporation of the solvent was chromatographed on silica gel eluted with 1:1 EtOAc:Hex to give **27** (50 mg, 33%) as an oil. ^1H NMR δ 7.15–7.32 (m, 4H), 4.03 (s, 2H), 2.70–2.88 (m, 1H), 2.49 (s, 3H), 1.65 (s, 6H), 1.22–1.95 (m, 10H). ^{13}C NMR δ 160.3, 155.6, 134.9, 130.0, 127.8, 127.5, 94.6, 76.7, 57.3, 37.8, 32.9, 27.8, 26.9, 26.4, 16.5. MS *m*/*z* 343 (MH^+).

5.10.3. 1-(6-Cyclohexyl-2,2-dimethyl(3H-pyrazolo[5,1-*b*][1,3-oxazolidin-7-yl))-4-(methylsulfonyl)benzene (28). To a solution of **27** (30 mg, 0.09 mmol) in MeOH (1.1 mL) was added dropwise a solution of Oxone® (0.11 g, 0.18 mmol) in water (0.3 mL). The white suspension was stirred at room temperature for 1 h. The solid was filtered, and washed with CH_2Cl_2. The filtrate was diluted with CH_2Cl_2, and the layers were separated. The organic phase was washed with water and then dried over Na_2SO_4. The residue after filtration and evaporation of the solvent was chromatographed on silica gel eluted with 0.1:1:1 MeOH:EtOAc:Hex to give **28** (18 mg, 55%) as a white solid. Mp 210 °C with dec. ^1H NMR δ 7.91 (d, $J=8.6$ Hz, 2H), 7.58 (d, $J=8.6$ Hz, 2H), 4.06 (s, 2H), 3.06 (s, 3H), 2.73–2.81 (m, 1H), 1.69 (s, 6H), 1.10–2.05 (m, 10H). MS *m*/*z* 375 (MH^+). LCMS (97.6%).

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