Design and Synthesis of Novel Pyrazole-based Lp-PLA$_2$ Inhibitors

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A series of novel pyrazole-based lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$) inhibitors have been designed and synthetized by a variety of acetophenones via a 10-step convergent approach. The synthetic approach is carefully optimized, and an unsuccessful alternative route is also discussed. The *in vitro* biological activity reveals that all the synthesized compounds are potent Lp-PLA$_2$ inhibitors with compound **13b** being the most potent one (Lp-PLA$_2$, IC_{50}=1.5 nmol/L).

Keywords lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$), inhibitors, pyrazole, pyrimidone, design, synthesis

Introduction

Recent years, cardiovascular and cerebrovascular diseases have become a great threat to human health. Lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$) is an enzyme produced by inflamatory cell in the circulation and vascular intima, most of which (80%) binds to LDL (low density lipoprotein).[1] Kolodgie *et al.*[2] found Lp-PLA$_2$ strongly expressed in the necrotic core of coronary lesions, and thereafter scientists found more evidences that Lp-PLA$_2$ was closely related with atherogenesis diseases. Lp-PLA$_2$ hydrolyzes oxidized phospholipids in LDL, yielding lysophosphatidylcholine (lysoPC), and oxidized nonesterified fatty acids (NEFA), which are proposed to play an important role in initiating atherogenesis diseases.[3] Consequently, development of Lp-PLA$_2$ inhibitors is a promising way to prevent these diseases.

Lp-PLA$_2$ may be a complementary therapeutic target to the cardiovascular and cerebrovascular diseases,[4,5] and darapladib is a highlight among the inhibitors of Lp-PLA$_2$, which can make sustained inhibition of plasma Lp-PLA$_2$ activity in patients receiving intensive atorvastatin therapy. Changes in IL-6 and hs-CRP after 12 weeks of darapladib suggest a possible reduction in inflammatory burden.[6] Based on the structure of darapladib, we design and synthetize a series of novel pyrazole-based compounds **13a**—**13e** as Lp-PLA$_2$ inhibitors (Figure 1). As depicted in Figure 1, in the designed Lp-PLA$_2$ inhibitors we replace the central benzene ring in darapladib with a pyrazole ring, and in view of the steric volume of the designed pyrazole ring being slightly smaller than that of the initial benzene ring, we lengthen the tether below the pyrimidine nucleus by one atom while removing the carbonyl group in darapladib.

Experimental

Melting points were determined with an XT-4 microscopic melting point apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 AV or a Bruker 300 AV with DMSO-d_6 or $CDCl_3$ as solvent and TMS as internal standard. The HR-MS data were collected on an Agilent Q-TOF 6510 mass spectrometer using electrospray ionization (ESI) technique.

Synthesis of ethyl 3-(4-substitutedphenyl)-1*H*-pyrazole-5-carboxylate (**2a**—**2e**) was carried out according to the procedures reported earlier.[7,8] Synthesis of **12, 14** and darapladib was according to a procedure reported earlier.[9]

General procedure for the synthesis of ethyl 3-(4-substituted phenyl)-1*H*-pyrazole-5-carboxylate (2a—2e)

A 250-mL three-necked round-bottomed flask was charged with 120 mL of absolute ethanol and 3.6 g (0.16 mol) of sodium, and the mixture was mechanically stirred under nitrogen until all the sodium disappeared. The reaction mixture was cooled to room temperature, then was added 23 g (0.16 mol, 21 mL) of diethyl oxalate. The mixture thus obtained was stirred for another 10 min, followed by dropwise addition of 0.13 mol of

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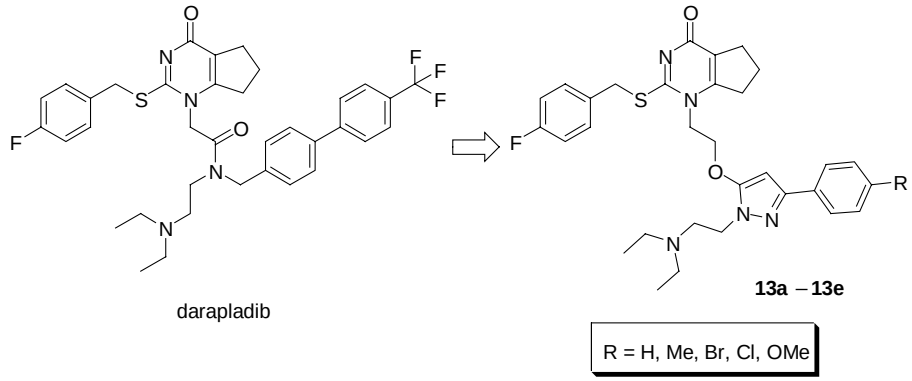


Figure 1 Structure of darapladib and designed Lp-PLA$_2$ inhibitors.

1a—**1e** through a pressure-equallizing funnel within 1.5 h. The resulting mixture was stirred for another 4 h before 9.3 g (0.16 mol) of acetic acid was added, followed by dropwise addition of 5.0 g (0.13 mol, 80%, 9.8 mL) of aqueous hydrazine hydrate, and the stirring was continued at room temperature overnight.

The reaction mixture was concentrated on a rotary evaporator to afford a reside, which was dissolved in 200 mL of dichloromethane. The organic solution thus obtained was washed successively with saturated brine and water, dried over sodium sulfate and evaporated on a rotary evaporator to yield the crude product as a white solid, which was recrystallized from ethyl acetate to afford the pure product as a white solid.

Ethyl 3-phenyl-1*H*-pyrazole-5-carboxylate (2a) White solid, yield 85%, m.p. 139—141 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.91 (br, 1H), 7.82—7.86 (m, 2H), 7.37—7.46 (m, 4H), 4.30 (q, J=7.2 Hz, 2H), 1.31 (t, J=7.2 Hz, 3H).

Ethyl 3-*p*-tolyl-1*H*-pyrazole-5-carboxylate (2b) White solid, yield 84%, m.p. 141—143 ℃.

Ethyl 3-(4-bromophenyl)-1*H*-pyrazole-5-carboxylate (2c) Yellow solid, yield 80%, m.p. 145—147 ℃.

Ethyl 3-(4-chlorophenyl)-1*H*-pyrazole-5-carboxylate (2d) White solid, yield 84%, m.p. 136—138 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 11.82 (br, 1H), 7.72 (d, J=8.4 Hz, 2H), 7.39 (d, J=8.4 Hz, 2H), 7.07 (s, 1H), 4.38 (q, J=7.2 Hz, 2H), 1.39 (t, J=7.2 Hz, 3H).

Ethyl 3-(4-methoxyphenyl)-1*H*-pyrazole-5-carboxylate (2e) White solid, yield 82%, m.p. 134—136 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 12.53 (br, s, 1H), 7.64 (d, J=8.7 Hz, 2H), 6.94 (s, 1H), 6.91 (d, J=8.7 Hz, 2H), 4.28 (q, J=7.2 Hz, 2H), 3.82 (s, 3H), 1.28 (t, J=7.2 Hz, 3H).

General procedure for the synthesis of ethyl 1-(2-bromoethyl)-3-*p*-substituted phenyl-1*H*-pyrazole-5-carboxylate (3a—3e)

A 250-mL round-bottomed flask was charged with the carboxylates **2a**—**2e** (0.10 mol), 1,2-dibromoethane (0.20 mol), potassium carbonate (0.40 mol), potassium iodide (5.0 mmol) and 120 mL of acetonitrile. The mixture was stirred for 10 min at room temperature, and then heated to reflux for 3 h. The reaction mixture was cooled to room temperature and filtered off, and filtrate was evaporated on a rotary evaporator to afford the crude product as an oil, which was purified by column chromatography to furnish the pure products **3a**—**3e** as whilte solids.

Ethyl 1-(2-bromoethyl)-3-phenyl-1*H*-pyrazole-5-carboxylate (3a) White solid, yield 88%, m.p. 89—90 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.86—7.88 (m, 2H), 7.32—7.44 (m, 4H), 4.95 (t, J=6.4 Hz, 2H), 4.33 (q, J=7.2 Hz, 2H), 3.89 (t, J=6.4 Hz, 2H), 1.33 (t, J=7.2 Hz, 2H); HR-MS (ESI-Q-TOF) calcd for $C_{14}H_{15}BrN_2O_2$ ($[M+H]^+$) 323.0395, found 323.0388.

Ethyl 1-(2-bromoethyl)-3-*p*-tolyl-1*H*-pyrazole-5-carboxylate (3b) White solid, yield 89%, m.p. 87—89 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.69 (d, J=8.1 Hz, 2H), 7.22 (d, J=8.1 Hz, 2H), 4.97 (t, J=7.1 Hz, 2H), 4.37 (q, J=7.2 Hz, 2H), 3.75 (t, J=7.1 Hz, 2H), 2.37 (s, 3H), 1.41 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 160.18, 151.26, 138.60. 134.20, 129.98, 129.92, 126.03, 108.62, 61.80, 52.84, 30.01, 21.79, 14.75; HR-MS (ESI-Q-TOF) calcd for $C_{15}H_{17}BrN_2O_2$ ($[M+H]^+$) 337.0551, found 337.0549.

Ethyl 1-(2-bromoethyl)-3-(4-bromophenyl)-1*H*-pyrazole-5-carboxylate (3c) White solid, yield 87%, m.p. 91—92 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.68 (d, J=8.7 Hz 2H), 7.53 (d, J=8.7 Hz, 2H), 7.13 (s, 1H), 4.98 (t, J=7.1 Hz, 2H), 4.38 (q, J=7.2 Hz, 2H), 3.76 (t, J=7.1 Hz, 2H), 1.42 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 159.50, 149.61, 134.07, 131.87, 131.31, 127.20, 122.24, 108.27, 61.42, 52.26, 29.37, 14.24; HR-MS (ESI-Q-TOF) calcd for $C_{14}H_{14}Br_2N_2O_2$ ($[M+H]^+$) 402.9480, found 402.9478.

Ethyl 1-(2-bromoethyl)-3-(4-chlorophenyl)-1*H*-pyrazole-5-carboxylate (3d) White solid, yield 87%, m.p. 90—91 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.89 (d, J=8.4 Hz, 2H), 7.48 (d, J=8.4 Hz, 2H), 7.42 (s, 1H), 4.94 (t, J=6.4 Hz, 2H), 4.33 (q, J=7.2 Hz, 2H), 3.88 (t, J=6.4 Hz, 2H), 1.33 (t, J=7.2 Hz, 3H); HR-MS (ESI-Q-TOF) calcd for $C_{14}H_{14}BrClN_2O_2$ ($[M+H]^+$) 357.0005, found 357.0008.

Ethyl 1-(2-bromoethyl)-3-(4-methoxyphenyl)-1*H*-

pyrazole-5-carboxylate (3e) White solid, yield 88%, m.p. 88—90 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.73 (d, J=9.0 Hz, 2H), 6.94 (d, J=9.0 Hz, 2H), 7.07 (s, 1H), 4.96 (t, J=7.1 Hz, 2H), 4.37 (q, J=7.2 Hz, 2H), 3.84 (s, 3H), 3.75 (t, J=7.1 Hz, 2H), 1.40 (t, J=7.2 Hz, 3H); HR-MS (ESI-Q-TOF) calcd for $C_{15}H_{17}BrN_2O_3$ ([M+H]$^+$) 353.0501, found 352.0507.

General procedure for the synthesis of ethyl 1-(2-(diethylamino)ethyl)-3-*p*-tolyl-1*H*-pyrazole-5-carboxylate (4a—4e)

A 250-mL round-bottomed flask was charged with the carboxylates **3a**—**3e** (0.080 mol), diethylamine (0.16 mol), potassium carbonate (0.40 mol), potassium iodide (5.0 mmol) and 120 mL of acetonitrile. The mixture was stirred for 10 min at room temperature, and then heated to reflux for 5 h. The reaction mixture was cooled to room temperature and filtered off, and the filtrate was concentrated on a rotary evaporator to afford the crude product as an oil, which was purified by column chromatography to produce **4a**—**4e** as colorless oils.

Ethyl 1-(2-(diethylamino)ethyl)-3-phenyl-1*H*-pyrazole-5-carboxylate (4a) Colorless oil, yield 81%, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.82—7.86 (m, 2H), 7.28—7.46 (m, 4H), 4.57 (t, J=6.8 Hz, 2H), 4.33 (q, J=7.2 Hz, 2H), 2.76 (t, J=6.8 Hz, 2H), 2.44 (q, J=7.2 Hz, 4H), 1.33 (t, J=7.2 Hz, 3H), 0.86 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{18}H_{25}N_3O_2$ ([M+H]$^+$) 316.2025, found 316.2027.

Ethyl 1-(2-(diethylamino)ethyl)-3-*p*-tolyl-1*H*-pyrazole-5-carboxylate (4b) Colorless oil, yield 79%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.69 (d, J=8.1 Hz, 2H), 7.20 (d, J=8.1 Hz, 2H), 7.06 (s, 1H), 4.68 (t, J=7.1 Hz, 2H), 4.35 (q, J=7.2 Hz, 2H), 2.90 (t, J=7.1 Hz, 2H), 2.59 (q, J=7.2 Hz, 4H), 2.36 (s, 3H), 1.39 (t, J=7.2 Hz, 3H), 1.00 (t, J=7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 160.32, 150.54, 138.18, 134.18, 130.44, 129.83, 125.96, 108.11, 61.44, 53.50, 50.12, 47.87, 21.76, 14.79, 12.59; HR-MS (ESI-Q-TOF) calcd for $C_{19}H_{27}N_3O_2$ ([M+H]$^+$) 330.2182, found 330.2186.

Ethyl 3-(4-bromophenyl)-1-(2-(diethylamino)ethyl)-1*H*-pyrazole-5-carboxylate (4c) Colorless oil, yield 79%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.80 (d, J=8.4 Hz, 2H), 7.59 (d, J=8.4 Hz, 2H), 7.33 (s, 1H), 4.57 (t, J=6.8 Hz, 2H), 4.32 (q, J=7.2 Hz, 2H), 2.76 (t, J=6.8 Hz, 2H), 2.43 (q, J=7.2 Hz, 4H), 1.32 (t, J=7.2 Hz, 3H), 0.84 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{18}H_{24}BrN_3O_2$ ([M+H]$^+$) 394.1130, found 394.1130.

Ethyl 3-(4-chlorophenyl)-1-(2-(diethylamino)ethyl)-1*H*-pyrazole-5-carboxylate (4d) Colorless oil, yield 80%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.73 (d, J=8.4 Hz, 2H), 7.39 (d, J=8.4 Hz, 2H), 7.06 (s, 1H), 4.67 (t, J=7.1 Hz, 2H), 4.37 (q, J=7.2 Hz, 2H), 2.91 (t, J=7.1 Hz, 2H), 2.58 (q, J=7.2 Hz, 4H), 1.42 (t, J=7.2 Hz, 3H), 0.98 (t, J=7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 160.08, 149.24, 134.43, 134.07, 131.76, 129.25, 127.25, 108.17, 61.49, 53.51, 50.31, 47.85, 14.75, 12.61; HR-MS (ESI-Q-TOF) calcd for $C_{18}H_{24}ClN_3O_2$ ([M+H]$^+$) 350.1635, found 350.1636.

Ethyl 1-(2-(diethylamino)ethyl)-3-(4-methoxyphenyl)-1*H*-pyrazole-5-carboxylate (4e) Colorless oil, yield 80%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.73 (d, J=9.0 Hz, 2H), 7.02 (s, 1H), 6.94 (d, J=9.0 Hz, 2H), 4.67 (t, J=7.1 Hz, 2H), 4.36 (q, J=7.2 Hz, 2H), 3.83 (s, 3H), 2.90 (t, J=7.2 Hz, 2H), 2.59 (q, J=7.1 Hz, 4H), 1.40 (t, J=7.2 Hz, 3H), 1.01 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{19}H_{27}N_3O_3$ ([M+H]$^+$) 346.2131, found 346.2131.

General procedure for the synthesis of (1-(2-(diethylamino)ethyl)-3-*p*-substituted phenyl-1*H*-pyrazol-5-yl)methanol (5a—5e)

A 250-mL round-bottomed flask was charged with the carboxylates **5a**—**5e** (0.060 mol) and 80 mL of dried THF, and the solution was stirred on an ice-water bath. Lithium aluminium hydride (0.040 mol) was added in portions. This reaction mixture was stirred for 1.0 h at room temperature and then 50 mL of water was added dropwise. The mixture thus obtained was extracted with 200 mL of dichloromethane in three portions, and the combined exacts were washed with saturated brine, dried over anhydrous sodium sulfate and concentrated on a rotary evaporator to yield **5a**—**5e** as colorless liquids.

(1-(2-(Diethylamino)ethyl)-3-phenyl-1*H*-pyrazol-5-yl)methanol (5a) Colorless oil, yield 98%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.77—7.79 (m, 2H), 7.37—7.41 (m, 2H), 7.29—7.31 (m, 1H), 6.50 (s, 1H), 4.57 (s, 2H), 4.23—4.26 (m, 2H), 2.85—2.87 (m, 2H), 2.46 (q, J=7.2 Hz, 4H), 0.92 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{16}H_{23}N_3O$ ([M+H]$^+$) 274.1919, found 274.1923.

(1-(2-(Diethylamino)ethyl)-3-*p*-tolyl-1*H*-pyrazol-5-yl)methanol (5b) Colorless oil, yield 98%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.67 (d, J=8.1 Hz, 2H), 7.19 (d, J=8.1 Hz, 2H), 6.46 (s, 1H), 4.55 (s, 2H), 4.22—4.24 (m, 2H), 2.83—2.86 (m, 2H), 2.45 (q, J=7.2 Hz, 4H), 2.36 (s, 3H), 0.91 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{17}H_{25}N_3O$ ([M+H]$^+$) 288.2076, found 288.2076.

(3-(4-Bromophenyl)-1-(2-(diethylamino)ethyl)-1*H*-pyrazol-5-yl)methanol (5c) White solid, yield 98%, m.p. 56—57 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.71 (d, J=8.4 Hz, 2H), 7.55 (d, J=8.4 Hz, 2H), 6.66 (s, 1H), 4.51 (s, 2H), 4.13—4.17 (m, 2H), 2.75—2.78 (m, 2H), 2.45 (q, J=7.2 Hz, 4H), 0.88 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{16}H_{22}BrN_3O$ ([M+H]$^+$) 352.1024, found 352.1027.

(3-(4-Chlorophenyl)-1-(2-(diethylamino)ethyl)-1*H*-pyrazol-5-yl)methanol (5d) Colorless oil, yield 97%, ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.70 (d, J=8.1 Hz, 2H), 7.36 (d, J=8.1 Hz, 2H), 6.47 (s, 1H), 4.56 (s, 2H), 4.22—4.25 (m, 2H), 2.84—2.87 (m, 2H), 2.47 (q, J=7.2 Hz, 4H), 0.92 (t, J=7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75

MHz) δ: 150.28, 145.45, 133.75, 132.56, 129.20, 127.29, 103.32, 54.48, 54.32, 50.36, 49.39, 11.30; HR-MS (ESI-Q-TOF) calcd for $C_{16}H_{22}ClN_3O$ ($[M+H]^+$) 308.1530, found 308.1536.

(1-(2-(Diethylamino)ethyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)methanol (5e) White solid, yield 96%, m.p. 52—54 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.68 (d, J=8.8 Hz, 2H), 6.94 (d, J=8.8 Hz, 2H), 6.488 (s, 1H), 5.568 (Br, s, 1H), 4.509 (s, 2H), 4.14 (t, J=6.4 Hz, 2H), 3.766 (s, 3H), 2.78 (t, J=6.4 Hz, 2H), 2.47 (q, J=7.2 Hz, 4H), 0.89 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{17}H_{25}N_3O_2$ ($[M+H]^+$) 304.2025, found 304.2028.

General procedure for the synthesis of ethyl 2-((1-(2-(diethylamino)ethyl)-3-*p*-substituted phenyl-1*H*-pyrazol-5-yl)methoxy)acetate (6a, 6b, 6e)

A 250-mL round-bottomed flask was charged with the alcohols **5a**, **5b** or **5e** (0.060 mol) and 50 mL dried THF, and then 1.80 g (0.075 mol) sodium hydride was added slowly. The mixture thus obtained was stirred for 10 min under nitrogen prior to ethyl chloroacetate (0.18 mol) was added dropwise and then heated to reflux for 3 h. The mixture was cooled to room temperature prior to the dropwise addition of 50 mL water, and the resulting mixture was extracted with 250 mL of dichloromethane in three portions. The combined exacts were washed with saturated brine, dried over anhydrous sodium sulfate and concentrated on a rotary evaporator to give the crude products as yellow oils, which were purified by column chromatography to give the pure products **6a**, **6b**, **6e** as colorless oils.

Ethyl 2-((1-(2-(diethylamino)ethyl)-3-phenyl-1*H*-pyrazol-5-yl)methoxy)acetate (6a) Colorless oil, yield 11%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.76—7.79 (m, 2H), 7.28—7.40 (m, 3H), 6.51 (s, 1H), 4.73 (s, 2H), 4.33 (t, J=6.8 Hz, 2H), 4.23 (q, J=7.2 Hz 2H), 4.10 (s, 2H), 2.97 (t, J=6.8 Hz, 2H), 2.60 (q, J=7.2 Hz, 4H), 1.29 (t, J=7.2 Hz, 3H), 1.02 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{20}H_{29}N_3O_3$ ($[M+H]^+$) 360.2287, found 360.2285.

Ethyl 2-((1-(2-(diethylamino)ethyl)-3-*p*-tolyl-1*H*-pyrazol-5-yl)methoxy)acetate (6b) Colorless oil, yield 10%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.66 (d, J=8.1 Hz, 2H), 7.19 (d, J=8.1 Hz, 2H), 6.48 (s, 1H), 4.72 (s, 2H), 4.26 (t, J=6.8 Hz, 2H), 4.19 (q, J=7.2 Hz, 2H), 4.06 (s, 2H), 2.94 (t, J=6.8 Hz, 2H), 2.57 (q, J=7.2 Hz, 4H), 2.36 (s, 3H), 1.29 (t, J=7.2 Hz, 3H), 0.99 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{21}H_{31}N_3O_3$ ($[M+H]^+$) 374.2444, found 374.2445.

Ethyl 2-((1-(2-(diethylamino)ethyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)methoxy)acetate (6e) Colorless oil, yield 10%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.69 (d, J=9.0 Hz, 2H), 6.91 (d, J=9.0 Hz, 2H), 6.43 (s, 1H), 4.69 (s, 2H), 4.29 (t, J=6.6 Hz, 2H), 4.23 (q, J=7.2 Hz, 2H), 4.10 (s, 2H), 3.83 (s, 3H), 2.96 (t, J=6.6 Hz, 2H), 2.59 (q, J=7.2 Hz, 4H), 1.29 (t, J=7.2 Hz, 3H), 1.02 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{21}H_{31}N_3O_4$ ($[M+H]^+$) 390.2393, found 390.2386.

General procedure for the synthesis of *tert*-butyl 2-((1-(2-(diethylamino)ethyl)-3-phenyl-1*H*-pyrazol-5-yl)methoxy)acetate (7a—7e)

A 250-mL round-bottomed flask was charged with 150 mL of dried *t*-butanol and 4.80 g of potassium (0.12 mol), the mixture was stirred under nitrogen until all the potassium disappeared completely. The alcohols **5a**—**5e** (0.060 mol) were dissolved into 50 mL dried *t*-butanol and added dropwise to the solution of potassoium *t*-butoxide prepared above. The mixture thus obtained was stirred for 10 min and ethyl chloroacetate (0.18 mol) was added. The stirring was continued at reflux for an additional 3.0 h. The mixture was cooled to room temperature and concentrated on a rotary evaporator, followed by addition of 100 mL of water. The solution thus obtained was extracted with 250 mL of dichloromethane in three portions. The combined exacts were washed with saturated brine, dried over anhydrous sodium sulfate and concentrated on a rotary evaporator to give the crude products as red oils, which were purified by column chromatography to give the pure products **7a**—**7e** as colorless oils.

***tert*-Butyl 2-((1-(2-(diethylamino)ethyl)-3-phenyl-1*H*-pyrazol-5-yl)methoxy)acetate (7a)** Colorless oil, yield 54%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.76—7.79 (m, 2H), 7.28—7.40 (m, 3H), 6.50 (s, 1H), 4.72 (s, 2H), 4.29 (t, J=6.8 Hz, 2H), 3.98 (s, 2H), 2.92 (t, J=6.8 Hz, 2H), 2.56 (q, J=7.2 Hz, 4H), 1.48 (s, 9H), 0.99 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{22}H_{33}N_3O_3$ ($[M+H]^+$) 388.2600, found 388.2609.

***tert*-Butyl 2-((1-(2-(diethylamino)ethyl)-3-*p*-tolyl-1*H*-pyrazol-5-yl)methoxy)acetate (7b)** Colorless oil, yield 52%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.67 (d, J=8.1 Hz, 2H), 7.19 (d, J=8.1 Hz, 2H), 6.46 (s, 1H), 4.72 (s, 2H), 4.28 (t, J=6.8 Hz, 2H), 3.98 (s, 2H), 2.92 (t, J=6.8 Hz, 2H), 2.56 (q, J=7.2 Hz, 4H), 2.37 (s, 3H), 1.48 (s, 9H), 0.99 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{23}H_{36}N_3O_3$ ($[M+H]^+$) 402.2757, found 402.2764.

***tert*-Butyl 2-((3-(4-bromophenyl)-1-(2-(diethylamino)ethyl)-1*H*-pyrazol-5-yl)methoxy)acetate (7c)** Colorless oil, yield 54%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.65 (d, J=6.8 Hz, 2H), 7.49 (d, J=6.8 Hz, 2H), 6.47 (s, 1H), 4.70 (s, 2H), 4.28 (t, J=6.8 Hz, 2H), 3.98 (s, 2H), 2.91 (t, J=6.8 Hz, 2H), 2.55 (q, J=7.2 Hz, 4H), 1.48 (s, 9H), 0.98 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{22}H_{32}BrN_3O_3$ ($[M+H]^+$) 466.1705, found 466.1709.

***tert*-Butyl 2-((3-(4-chlorophenyl)-1-(2-(diethylamino)ethyl)-1*H*-pyrazol-5-yl)methoxy)acetate (7d)** Colorless oil, yield 55%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.70 (d, J=8.4 Hz, 2H), 7.29 (d, J=8.4 Hz, 2H), 6.48 (s, 1H), 4.70 (s, 2H), 4.29 (t, J=6.8 Hz, 2H), 3.98 (s, 2H), 2.92 (t, J=6.8 Hz, 2H), 2.56 (q, J=7.2 Hz, 4H), 1.48 (s, 9H), 0.99 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-

TOF) calcd for $C_{22}H_{32}ClN_3O_3$ ([M+H]$^+$) 422.2210, found 422.2218.

***tert*-Butyl 2-((1-(2-(diethylamino)ethyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)methoxy)acetate (7e)** Colorless oil, yield 55%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.70 (d, J=7.2 Hz, 2H), 6.92 (d, J=7.2 Hz, 2H), 6.42 (s, 1H), 4.70 (s, 2H), 4.27 (t, J=6.8 Hz, 2H), 3.97 (s, 2H), 3.83 (s, 3H), 2.91 (t, J=6.8 Hz, 2H), 2.55 (q, J=7.2 Hz, 4H), 1.48 (s, 9H), 0.99 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{23}H_{35}N_3O_4$ ([M+H]$^+$) 418.2706, found 418.2710.

General procedure for the synthesis of 2-((1-(2-(diethylamino)ethyl)-3-(4-substituted phenyl)-1*H*-pyrazol-5-yl)methoxy)ethanol (8a—8e)

A 250-mL round-bottomed flask was charged with the acetates **7a**—**7e** (0.030 mol) and 100 mL of dried THF, the solution thus obtained was stirred for 10 min on an ice-water bath. Lithium aluminium hydride (0.020 mol) was added in portions. The mixture was stirred for 1.0 h at room temperature and 50 mL of water was added dropwise under stirring. The mixture was extracted with 200 mL of dichloromethane in three portions, and the combined exacts were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator to yield **8a**—**8e** as colourless liquids.

2-((1-(2-(Diethylamino)ethyl)-3-phenyl-1*H*-pyrazol-5-yl)methoxy)ethanol (8a) Colorless oil, yield 98%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.75—7.77 (m, 2H), 7.27—7.39 (m, 3H), 6.68 (s, 1H), 4.63 (s, 2H), 4.17 (t, J=6.4 Hz, 2H), 3.75—3.77 (m, 2H), 3.70—3.73 (m, 2H), 2.81 (t, J=6.4 Hz, 2H), 2.48 (q, J=7.2 Hz, 4H), 0.91 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{18}H_{27}N_3O_2$ ([M+H]$^+$) 318.2182, found 318.2188.

2-((1-(2-(Diethylamino)ethyl)-3-*p*-tolyl-1*H*-pyrazol-5-yl)methoxy)ethanol (8b) Colorless oil, yield 97%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.64 (d, J=8.1 Hz, 2H), 7.17 (d, J=8.1 Hz, 2H), 6.43 (s, 1H), 4.61 (s, 2H), 4.28 (t, J=6.8 Hz, 2H), 3.70—3.73 (m, 2H), 3.66—3.68 (m, 2H), 2.89 (t, J=6.8 Hz, 2H), 2.46 (q, J=7.2 Hz, 4H), 2.37 (s, 3H), 1.00 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{19}H_{29}N_3O_2$ ([M+H]$^+$) 332.2338, found 332.2338.

2-((3-(4-Bromophenyl)-1-(2-(diethylamino)ethyl)-1*H*-pyrazol-5-yl)methoxy)ethanol (8c) Colorless oil, yield 98%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.69 (d, J=8.8 Hz, 2H), 7.34 (d, J=8.8 Hz, 2H), 6.44 (s, 1H), 4.61 (s, 2H), 4.29 (t, J=6.8 Hz, 2H), 3.71—3.74 (m, 2H), 3.65—3.68 (m, 2H), 2.92 (t, J=6.8 Hz, 2H), 2.53 (q, J=7.2 Hz, 4H), 1.01 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{18}H_{26}BrN_3O_2$ ([M+H]$^+$) 396.1287, found 396.1290.

2-((3-(4-Chlorophenyl)-1-(2-(diethylamino)ethyl)-1*H*-pyrazol-5-yl)methoxy)ethanol (8d) Colorless oil, yield 98%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.64 (d, J=8.4 Hz, 2H), 7.50 (d, J=8.4 Hz, 2H), 6.45 (s, 1H), 4.61 (s, 2H), 4.31 (t, J=6.8 Hz, 2H), 3.72—3.76 (m, 2H), 3.65—3.68 (m, 2H), 2.95 (t, J=6.8 Hz, 2H), 2.55 (q, J=7.2 Hz, 4H), 1.02 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{18}H_{26}ClN_3O_2$ ([M+H]$^+$) 352.1792, found 352.1795.

2-((1-(2-(Diethylamino)ethyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)methoxy)ethanol (8e) Colorless oil, yield 98%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.93—6.95, 7.67—7.69 (d, J=8.8 Hz, 2H), 6.57 (s, 1H), 4.57 (s, 2H), 4.13 (t, J=6.8 Hz, 2H), 3.77 (s, 3H) 3.52—3.54 (m, 2H), 3.46—3.48 (m, 2H), 2.76—2.80 (t, J=6.8 Hz, 2H), 2.49 (q, J=7.2 Hz, 4H), 0.92 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{19}H_{29}N_3O_3$ ([M+H]$^+$) 348.2287, found 348.2290.

General procedure for the synthesis of 2-((1-(2-(diethylamino)ethyl)-3-(4-substituted phenyl)-1*H*-pyrazol-5-yl)methoxy)ethyl methanesulfonate (9a—9e)

A 250-mL round-bottomed flask was charged with the compounds **8a**—**8e** (0.030 mol), triethylamine (0.060 mol) and 100 mL of dried dichloromethane. Methanesulfonyl chloride (0.030 mol) or 4-toluenesulfonyl chloride (0.030 mol) were added dropwise upon cooling. The mixture was stirred at room temperature for 1.0 h and concentrated on a rotary evaporator to give the crude products **9a**—**9e**, which were purified by column chromatography to give the pure products **9a**—**9e** as colorless oils.

2-((1-(2-(Diethylamino)ethyl)-3-phenyl-1*H*-pyrazol-5-yl)methoxy)ethyl methanesulfonate (9a) Colorless oil, yield 98%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.76—7.78 (m, 2H), 7.29—7.40 (m, 3H), 6.50 (s, 1H), 4.68 (s, 2H), 4.36—4.38 (m, 2H), 4.21—4.25 (m, J=6.8 Hz, 2H), 3.74—3.77 (m, 2H), 3.02 (s, 3H), 2.91 (t, J=6.8 Hz, 2H), 2.55 (q, J=7.2 Hz, 4H), 0.99 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{19}H_{29}N_3O_4S$ ([M+H]$^+$) 396.1957, found 396.1959.

2-((1-(2-(Diethylamino)ethyl)-3-*p*-tolyl-1*H*-pyrazol-5-yl)methoxy)ethyl 4-methylbenzenesulfonate (9b) Colorless oil, yield 98%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.76 (d, J=8.1 Hz, 2H), 7.66 (d, J=8.1 Hz, 2H), 7.28 (d, J=7.8Hz, 2H), 7.19 (d, J=7.8 Hz, 2H), 6.39 (s, 1H), 4.56 (s, 2H), 4.15—4.18 (m, 2H), 4.14 (t, J=6.9 Hz, 2H), 3.62—3.65 (m, 2H), 2.85 (t, J=6.9 Hz, 2H), 2.51 (q, J=7.2 Hz, 4H), 2.39 (s, 3H), 2.35 (s, 3H), 0.96 (t, J=7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 150.73, 145.37, 139.79, 137.69, 133.40, 131.24, 130.32, 129.74, 128.41, 125.88, 104.30, 69.48, 67.77, 63.97, 53.84, 49.09, 48.16, 22.09, 21.72, 12.52; HR-MS (ESI-Q-TOF) calcd for $C_{26}H_{35}N_3O_4S$ ([M+H]$^+$) 486.2427, found 486.2426.

2-((3-(4-Bromophenyl)-1-(2-(diethylamino)ethyl)-1*H*-pyrazol-5-yl)methoxy)ethyl methanesulfonate (9c) Colorless oil, yield 97%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.64 (d, J=8.8 Hz, 2H), 7.39 (d, J=8.8 Hz, 2H), 6.47 (s, 1H), 4.66 (s, 2H), 4.36—4.38 (m, 2H), 4.20—4.25 (t, 2H, J=6.8 Hz), 3.74—3.77 (m, 2H), 3.02 (s, 3H), 2.92 (t, J=6.8 Hz, 2H), 2.56 (q, J=7.2 Hz, 4H), 0.98 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for

$C_{19}H_{28}BrN_3O_4S$ ($[M+H]^+$) 474.1062, found 474.1067.

2-((3-(4-Chlorophenyl)-1-(2-(diethylamino)ethyl)-1*H*-pyrazol-5-yl)methoxy)ethyl methanesulfonate (9d) Colorless oil, yield 97%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.70 (d, J=8.8 Hz, 2H), 7.35 (d, J=8.8 Hz, 2H), 6.47 (s, 1H), 4.67 (s, 2H), 4.36—4.38 (m, 2H), 4.20—4.24 (m, 2H, J=6.8 Hz), 3.75—3.77 (m, 2H), 3.02 (s, 3H), 2.92 (t, J=6.8 Hz, 2H), 2.56 (q, J=7.2 Hz, 4H), 0.99 (t, J = 7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{19}H_{28}ClN_3O_4S$ ($[M+H]^+$) 430.1567, found 430.1564.

2-((1-(2-(Diethylamino)ethyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)methoxy)ethyl methanesulfonate (9e) Colorless oil, yield 98%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.69 (d, J=8.8 Hz, 2H), 6.92 (d, J=8.8 Hz, 2H), 6.42 (s, 1H), 4.66 (s, 2H), 4.36—4.38 (m, 2H), 4.21—4.24 (m, J=6.8 Hz, 2H), 3.83 (s, 3H), 3.74—3.76 (m, 2H), 3.02 (s, 3H), 2.92 (t, J=6.8 Hz, 2H), 2.57 (q, J=7.2 Hz, 4H), 1.00 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{20}H_{31}N_3O_5S$ ($[M+H]^+$) 426.2063, found 426.2070.

General procedure for the synthesis of synthesis of 2-(4-fluorobenzylthio)-6,7-dihydro-1*H*-cyclopenta[*d*]-pyrimidin-4(5*H*)-one (12)

A 250-mL round-bottomed flask was charged with 120 mL of absolute ethanol and 3.50 g sodium (0.15 mol), and the mixture was stirred under nitrogen until the sodium disappeared. Subsequently, 9.0 g of thiourea (0.12 mol) was added, and the solution was stirred for 30 min. After 16.0 g of ethyl 2-oxocyclopentane carboxylate (0.096 mol) was added, the mixture thus obtained was heated to reflux for 2.0 h under nitrogen. On cooling, the reaction mixture was concentrated on a rotary evaporator, then 30 mL of water was added. The pH of the solution was adjusted to 5 using concentrated hydrochloric acid followed by precipitation of crude **11**, which were collected by suction filtration.

A 250-mL round-bottomed flask was charged with the crude compoud **11** (0.050 mol) and 100 mL of acetone. Potassium carbonate (0.10 mol), potassium iodide (5.0 mmol) and 4-flurobenzyl chloride (0.060 mol) were added, and the mixture was strirred for 10 min at room temperature and then heated to reflux for 1.0 h. On cooling, the solution was evaporated on a rotary evaporator and 50 mL water was added. The pH of the solution was adjusted to 7 using concentrated hydrochloric acid followed by precipitation of crude **12**, which was collected by suction filtration and recrystallized from ethyl acetate to afford the pure products as a white solid.

2-(4-Fluorobenzylthio)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidin-4(5*H*)-one (12) White solid, yield 38%, m.p. 209—210 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 12.49 (br, s, 1H), 7.46 (dd, J=8.4, 1.5 Hz, 2H), 7.14 (t, J=8.4, 8.4 Hz, 2H), 4.38 (s, 2H), 2.69 (t, J=7.5 Hz, 2H), 2.59 (t, J=7.2 Hz, 2H), 1.91—2.01 (m, J=7.2, 7.5 Hz, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 168.67, 162.94, 160.68, 159.71, (133.58, 133.54), (131.05, 130.95), 119.37, (115.29, 115.00), 34.20, 32.69, 26.66, 20.51.

General procedure for the synthesis of 2-(4-fluorobenzylthio)-1-(2-((1-(2-(diethylamino)ethyl)-3-*p*-tolyl-1*H*-pyrazol-5-yl)methoxy)ethyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidin-4(5*H*)-one (13a—13e)

A 250-mL round-bottomed flask was charged with the compound **12** (0.030 mol), compounds **9a**—**9e** (0.030 mol), potassium carbonate (0.10 mol), and 100 mL of DMF. The mixed solution was heated to 80 ℃ for 3.0 h and then cooled to room temperature. The reaction mixture was filtered off and the filtrate was diluted with 300 mL of dichloromethane and washed with 50 mL of water. The organic layer was dried over anhydrous sodium sulfate and concentrated on a rotary evaporator to afford the crude products **13a**—**13e** as colorless oils, which were purified by column chromatography to afford the pure products **13a**—**13e** as colorless oils. Compounds **13a** — **13e** (0.025 mol) and *L*-tartaric acid (0.025 mol) were dissovled in methanol, and the solution thus obtained was stirred for 0.5 h and then evaporated on a rotary evaporator to give the salts of **13a**—**13e** after washing with diethyl ether and drying *in vacuo* at room temperature to give the pure salts of **13a**—**13e** as white solid.

2-(4-Fluorobenzylthio)-1-(2-((1-(2-(diethylamino)-ethyl)-3-phenyl-1*H*-pyrazol-5-yl)methoxy)ethyl)-6,7-dihydro-1*H*-cyclopenta[d]pyrimidin-4(5*H*)-one (13a) Colorless oil, yield 92%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.75—7.77 (m, 2H), 7.35—7.40 (m, 4H), 7.28—7.30 (m, 1H), 6.94—6.98 (m, 2H), 6.47 (s, 1H), 4.65 (s, 2H), 4.50 (t, J=4.8 Hz, 2H), 4.34 (s, 2H), 4.22 (t, J=7.2 Hz, 2H), 3.77 (t, J=4.8 Hz, 2H), 2.85—2.91 (m, 4H), 2.78 (t, J=7.2 Hz, 2H), 2.53 (q, J=7.6 Hz, 4H), 2.05—2.11 (m, 2H), 0.99 (t, J=7.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.69, 168.54, 165.03, 163.06, 160.62, 150.17, 139.72, (133.71, 133.50), (130.36, 130.28), 128.53, 127.46, 125.46, 115.57, (115.30, 115.09), 103.95, 67.88, 65.26, 63.43, 53.30, 48.55, 47.61, 34.53, 34.06, 26.29, 21.82, 11.98; HR-MS (ESI-Q-TOF) calcd for $C_{32}H_{38}FN_5O_2S$ ($[M+H]^+$) 576.2808, found 576.2811.

2-(4-Fluorobenzylthio)-1-(2-((1-(2-(diethylamino)-ethyl)-3-*p*-tolyl-1*H*-pyrazol-5-yl)methoxy)ethyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidin-4(5*H*)-one (13b) Colorless oil, yield 91%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.65 (d, J=7.8 Hz, 2H), 7.34—7.38 (m, 2H), 7.18 (d, J=7.8 Hz, 2H), 6.92—6.98 (m, 2H), 6.43 (s, 1H), 4.64 (s, 2H), 4.50 (t, J=4.8 Hz, 2H), 4.33 (s, 2H), 4.23 (t, J=7.2 Hz, 2H), 3.76 (t, J=4.8 Hz, 2H), 2.84—2.92 (m, 4H), 2.77 (t, J=7.2 Hz, 2H), 2.53 (q, J=7.2 Hz, 4H), 2.355 (s, 3H), 2.02—2.12 (m, 2H), 0.99 (t, J=7.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 176.20, 169.10, 165.57, 164.01, 160.76, 150.78, 140.15, 137.66, (134.28, 134.23), (130.89, 130.78), 129.72, 125.90, (116.09, 115.84), 115.56, 104.26, 68.41, 65.78, 63.98, 53.83, 49.03, 48.15, 35.06, 34.58, 26.81, 22.34, 21.71, 12.49; HR-MS (ESI-Q-TOF) calcd for $C_{33}H_{40}FN_5O_2S$ ($[M+H]^+$) 590.2965, found 590.2964.

2-(4-Fluorobenzylthio)-1-(2-((3-(4-bromophenyl)-1-(2-(diethylamino)ethyl)-1*H*-pyrazol-5-yl)methoxy)-ethyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidin-4(5*H*)-one (13c) Colorless oil, yield 90%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.63 (d, J=6.8 Hz, 2H), 7.49 (d, J=6.8 Hz, 2H), 7.34—7.39 (m, 2H), 6.93—6.98 (m, 2H), 6.44 (s, 1H), 4.64 (s, 2H), 4.49 (t, J=4.8 Hz, 2H), 4.34 (s, 2H), 4.21 (t, J=7.2 Hz, 2H), 3.76 (t, J=4.8 Hz, 2H), 2.85—2.90 (m, 4H), 2.78 (t, J=7.2 Hz, 2H), 2.52 (q, J=7.2 Hz, 4H), 2.04—2.09 (m, 2H), 0.96 (t, J=7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.67, 168.57, 165.02, 163.06, 160.62, 149.08, 140.08, (133.70, 133.49), (130.34, 130.26), 128.49, 127.45, 125.45, 115.52, (115.26, 115.05), 103.93, 68.04, 65.23, 63.41, 53.13, 48.48, 47.57, 34.52, 34.04, 26.27, 21.79, 11.80; HR-MS (ESI-Q-TOF) calcd for $C_{32}H_{37}BrFN_5O_2S$ ([M+H]$^+$) 654.1914, found 654.1918.

2-(4-Fluorobenzylthio)-1-(2-((3-(4-chlorophenyl)-1-(2-(diethylamino)ethyl)-1*H*-pyrazol-5-yl)methoxy)-ethyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidin-4(5*H*)-one (13d) Colorless oil, yield 90%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.69 (d, J=6.8 Hz, 2H), 7.34—7.39 (m, 2H), 7.33 (d, J=6.8 Hz, 2H), 6.93—6.98 (m, 2H), 6.44 (s, 1H), 4.64 (s, 2H), 4.49 (t, J=4.8 Hz, 2H), 4.34 (s, 2H), 4.21 (t, J=7.2 Hz, 2H), 3.76 (t, J=4.8 Hz, 2H), 2.85—2.90 (m, 4H), 2.78 (t, J=7.2 Hz, 2H), 2.52 (q, J=7.2 Hz, 4H), 2.05—2.09 (m, 2H), 0.96 (t, J=7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.59, 168.51, 164.94, 162.99, 160.55, 148.93, 139.96, (133.68, 133.65), 132.03, (130.27, 130.20), 128.56, 126.62, 115.45, (115.19, 115.98), 103.73, 67.93, 65.14, 63.33, 53.21, 48.60, 47.55, 34.44, 33.98, 26.20, 21.72, 11.92; HR-MS (ESI-Q-TOF) calcd for $C_{32}H_{37}ClFN_5O_2S$ ([M+H]$^+$) 610.2419, found 610.2425.

2-(4-Fluorobenzylthio)-1-(2-((1-(2-(diethylamino)-ethyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)methoxy)ethyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidin-4(5*H*)-one (13e) Colorless oil, yield 92%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.69 (d, J=6.8 Hz, 2H), 7.34—7.39 (m, 2H), 6.93—6.98 (m, 2H), 6.92 (d, J=6.8 Hz, 2H), 6.39 (s, 1H), 4.64 (s, 2H), 4.48—4.51 (t, J=4.8 Hz, 2H), 4.34 (s, 2H), 4.20 (t, J=7.2 Hz, 2H), 3.83 (s, 3H), 3.76 (t, J=4.8 Hz, 2H), 2.85—2.90 (m, 4H), 2.78 (t, J=7.2 Hz, 2H), 2.53 (q, J=7.2 Hz, 4H), 2.05—2.09 (m, 2H), 0.96 (t, J=7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.22, 168.18, 164.66, 162.65, 160.21, 158.79, 149.54, 139.34, (133.48, 133.45), (130.01, 129.93), 126.28, 115.14, (114.86, 114.64), 113.53, 102.99, 67.55, 64.91, 63.04, 54.77, 52.90, 48.05, 47.23, 34.10, 33.66, 25.89, 21.38, 11.63; HR-MS (ESI-Q-TOF) calcd for $C_{33}H_{40}FN_5O_3S$ ([M+H]$^+$) 606.2914, found 606.2915.

2-(4-Fluorobenzylthio)-1-(2-hydroxyethyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidin-4(5*H*)-one (15) White solid, yield 86%, m.p. 97—99 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.36—7.41 (m, 2H), 6.94—7.00 (m, 2H), 4.48 (t, J=4.8 Hz, 2H), 4.35 (s, 2H), 3.93 (t, J=4.8 Hz, 2H), 2.90 (t, J=7.8 Hz, 2H), 2.80 (t, J=7.5 Hz, 2H), 2.05—2.15 (m, 2H); HR-MS (ESI-Q-TOF) calcd for $C_{16}H_{17}FN_2O_2S$ ([M+H]$^+$) 321.1073, found 321.1075.

2-(4-Fluorobenzylthio)-1-(2-chloroethyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidin-4(5*H*)-one (17) Colorless oil, yield 20%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.36—7.41 (m, 2H), 6.94—7.02 (m, 2H), 4.57 (t, J=6.0 Hz, 2H), 4.35 (s, 2H), 3.75 (t, J=6.0 Hz, 2H), 2.91 (t, J=7.8 Hz, 2H), 2.79 (t, J=7.5 Hz, 2H), 2.04—2.14 (m, 2H); HR-MS (ESI-Q-TOF) calcd for $C_{16}H_{16}ClFN_2O_1S$ ([M+H]$^+$) 339.0734, found 339.0742.

4-(4-Fluorobenzyl)-6-oxo-1,2,3,4,6,7,8,9-octahydrocyclopenta[*e*][1,3]thiazino[3,2-*a*]pyrimidin-4-ium-chloride (18) Colorless oil, yield 80%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.35—7.42 (m, 2H), 6.98—7.04 (m, 2H), 4.40 (s, 2H), 4.34 (t, J=7.2 Hz, 2H), 3.73 (t, J=7.2 Hz, 2H) 2.75—2.86 (m, 4H), 2.04—2.12 (m, 2H); HR-MS (ESI-Q-TOF) calcd for $C_{16}H_{16}ClFN_2OS$ ([M+H]$^+$) 339.0734, found 339.0743.

2-(5-((4-Fluorobenzyloxy)methyl)-3-(4-chlorophenyl)-1*H*-pyrazol-1-yl)-*N*,*N*-diethylethanamine (19) Colorless oil, yield 95%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.68—7.72 (m, 2H), 7.32—7.36 (m, 2H), 7.24—7.28 (m, 2H), 6.97—7.24 (m, 2H), 6.34 (s, 1H), 4.16 (t, J=6.6 Hz, 2H), 3.69 (s, 2H), 3.66 (s, 2H), 2.87 (t, J=6.6 Hz, 2H), 2.51 (q, J=7.2 Hz, 4H), 0.96 (t, J=7.2 Hz, 6H); HR-MS (ESI-Q-TOF) calcd for $C_{13}H_{27}ClFN_3O$ ([M+H]$^+$) 416.1905, found 416.1917.

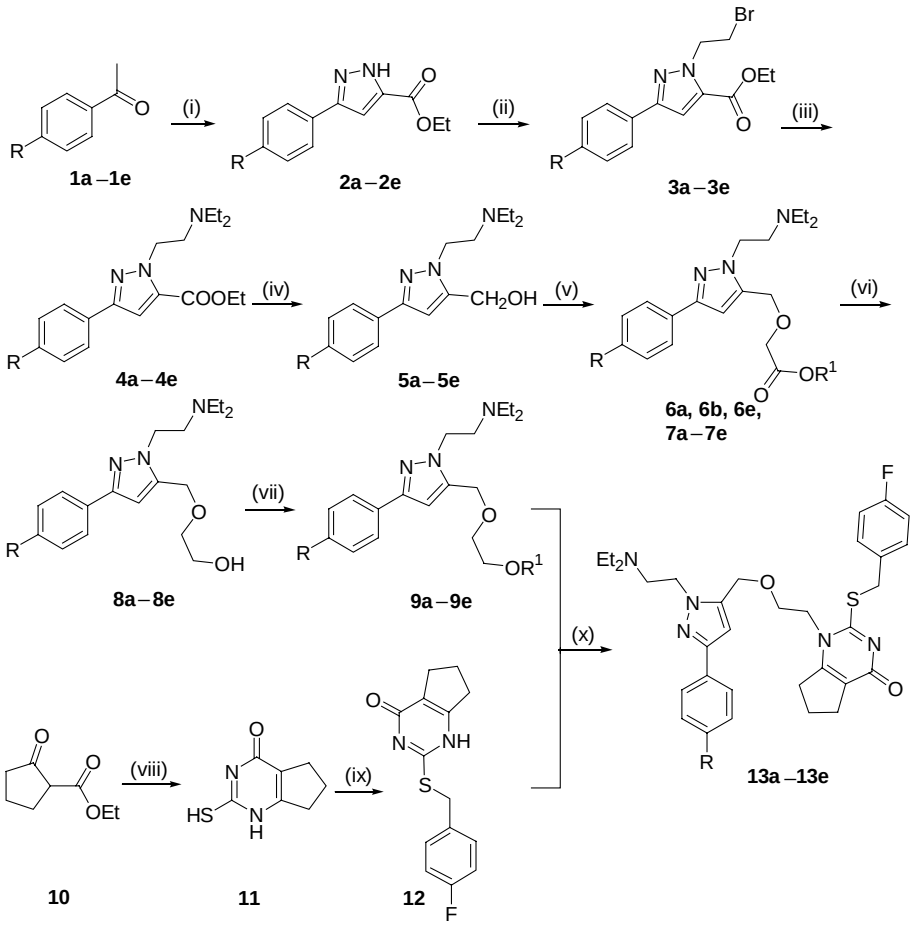
Results and discussion

The synthetic route to target compounds **13a**—**13e** is outlined in Scheme 1. Commercially available acetophenones **1a**—**1e** reacted with diethyl oxalate in the presence of EtONa in EtOH to give the intermediates ethyl 2,4-dioxo-4-(*p*-substitutedphenyl)butanoates, which was then reacted with N_2H_4•H_2O to aford the pyrazolecarboxylates **2a**—**2e**. Treatment of **2a**—**2e** with $BrCH_2CH_2Br$ in the presence of K_2CO_3 as base and KI as catalyst in refluxing MeCN produced **3a**—**3e**, which were sequentially treated with Et_2NH in the presence of K_2CO_3 and KI in refluxing MeCN to yield **4a**—**4e**. **4a**—**4e** were reduced with $LiAlH_4$ in dried THF at 0—5 ℃ to furnish alcohols **5a**—**5e**.

The conversion of **5a**—**5e** to **6** and **7** was intensively investigated, and the products and corresponding yields were summarized in Table 1. Noteworthy was that **7a**—**7e** were isolated as *t*-butyl esters arising from transesterification. As can be seen from Table 1, the conditions 3 and 4 were most preferred albeit with only modest conversions (54%—55%), whereas conditions 1, 2 and 5 gave unsatisfactory results with no or only marginal conversions (0—11%).

Synthesis of the sulfonates **9a**—**9e** was prepared by two steps as shown in Scheme 1. The esters **6** and **7** were reduced by the $LiAlH_4$ in THF, and the alcohols **8a**—**8e** thus obtained were converted to the corresponding sulfonates **9a**—**9e** with MsCl or TsCl in the presence of Et_3N in CH_2Cl_2 at room temperature.

Scheme 1 Synthetic route to the title compounds **13a**—**13e**



1a, R = H, **1b**, R = CH_3, **1c**, R = Br, **1d**, R = Cl, **1e**, R = CH_3O
2a, R = H, **2b**, R = CH_3, **2c**, R = Br, **2d**, R = Cl, **2e**, R = CH_3O
3a, R = H, **3b**, R = CH_3, **3c**, R = Br, **3d**, R = Cl, **3e**, R = CH_3O
4a, R = H, **4b**, R = CH_3, **4c**, R = Br, **4d**, R = Cl, **4e**, R = CH_3O
5a, R = H, **5b**, R = CH_3, **5c**, R = Br, **5d**, R = Cl, **5e**, R = CH_3O
6a, R = H, R^1 = Et, **6b**, R = CH_3, R^1 = Et, **6e**, R = CH_3O, R^1 = Et
7a, R = H, R^1 = $C(CH_3)_3$, **7b**, R = CH_3, R^1 = $C(CH_3)_3$, **7c**, R = Br, R^1 = $C(CH_3)_3$, **7d**, R = Cl, R^1 = $C(CH_3)_3$,
7e, R = CH_3O, R^1 = $C(CH_3)_3$,
8a, R = H, **8b**, R = CH_3, **8c**, R = Br, **8d**, R = Cl, **8e**, R = CH_3O,
9a, R = H, R^1 =Ms, **9b**, R= CH_3, R^1 = Ts, **9c**, R = Br, R^1 = Ms, **9d**, R = Cl, R^1 = Ms, **9e**, R = CH_3O R^1 = Ms,
13a, R = H, **13b**, R = CH_3, **13c**, R = Br, **13d**, R = Cl, **13e**, R = CH_3O

Reagents and conditions: (i) $(COOEt)_2$/EtONa, EtOH, r.t.; then AcOH, N_2H_4; (ii) $BrCH_2CH_2Br/K_2CO_3$/KI, CH_3CN, reflux; (iii) $HN(Et)_2$/ K_2CO_3/KI, CH_3CN, reflux; (iv) $LiAlH_4$, THF, ice bath to r.t.; (v) NaH/$ClCH_2COOEt$, THF, reflux or *t*-BuOK/$ClCH_2COOEt$, *t*-BuOH, reflux; (vi) $LiAlH_4$, THF, ice bath to r.t.; (vii) (MsCl or TsCl)/NEt_3, CH_2Cl_2, r.t.; (viii) EtONa/$CS(NH_2)_2$, EtOH, reflux; (ix) K_2CO_3/KI/ 4-fluorobenzyl chloride, acetone, reflux; (x) K_2CO_3, DMF, 80 °C

Reaction of commercially available ethyl 2-oxocyclopentanecarboxylate **10** and thiourea in the presence of EtONa in EtOH gave rise to the thiouracil derivative **11**, which was in turn alkylated with 4-fluorobenzyl chloride to yield thioether **12** in refluxing acetone in presence of K_2CO_3 and KI.

Finally, coupling of compounds **9a**—**9e** and compound **12** was effective to give the targets **13a**—**13e** on treatment of a mixture of **9** and **12** with K_2CO_3 in DMF at 80 ℃. The target compounds **13a**—**13e** were converted to *L*-tartaric acid salts thereof.

As shown in Scheme 3, an unsuccessful alternative synthetic route to the title compound has ever been attempted, in which compound **16** was initially expected to react with **5a**—**5e** to give the title compounds **13a**—**13e**. Compound **12** was successfully converted to compound **15** in two steps. Unfortunately, treatment of compound **15** with MsCl in the presence of Et_3N in CH_2Cl_2 produced cyclic sulfonium **18** as a single product, instead of the expected mesylate **16**. This outcome may be attributable to the powerful nucleophilicity of the sulfur atom, which displaced the mesyloxy group in

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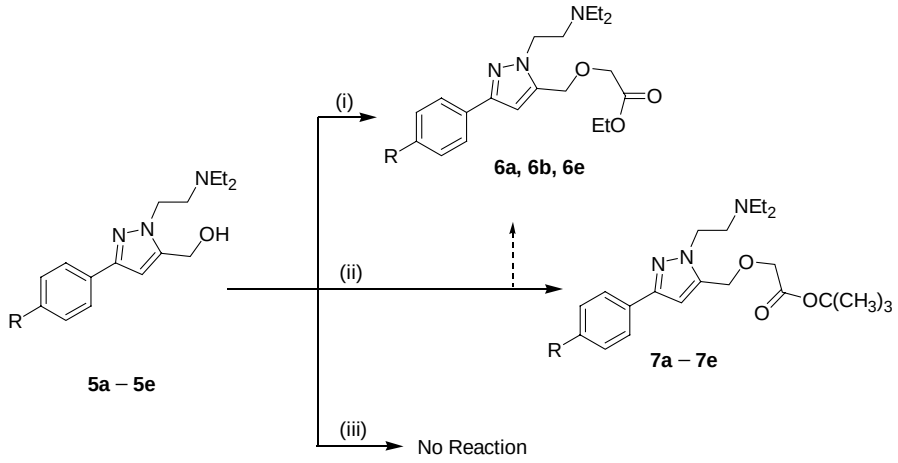
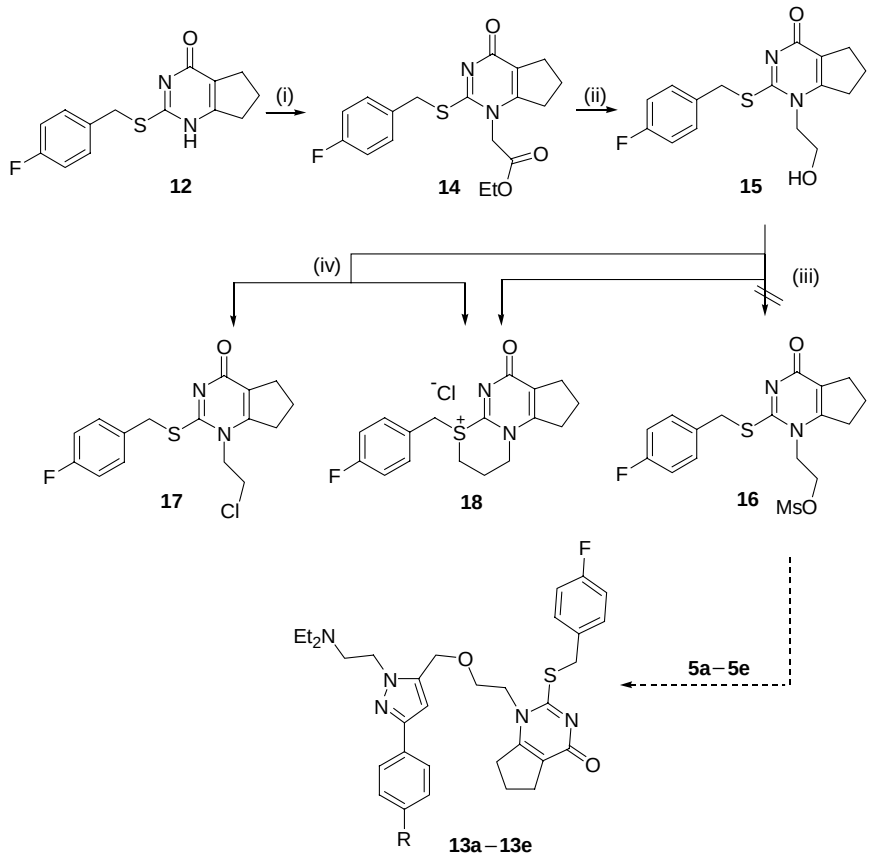
Scheme 2 Synthetic route to the carboxylates **6a**—**6b**, **6e**, **7a**—**7e**



Reagents and conditions: (i) NaH/ClCH$_2$COOEt, THF, reflux; (ii) ClCH$_2$COOEt/*t*-BuOK/*t*-BuOH, reflux; (iii) K$_2$CO$_3$/KI/ClCH$_2$COOEt, DMF, 80 ^{o}C

Scheme 3 An unsuccessful alternative route to the title compounds



Reagents and conditions: (i) K$_2$CO$_3$/KI/ClCH$_2$COOEt, CH$_3$CN, reflux; (ii) LiAlH$_4$, THF, ice bath to r.t.; (iii) MsCl/Et$_3$N, CH$_2$Cl$_2$, r.t; (iv) SOCl$_2$, reflux

16 by SN$_2$ pathway. Also, compound **15** reacted with thionyl chloride at reflux to give a mixture of **17** and **18** in a steady ratio of 1∶4, and the formation of the cyclic sulfonium **18** herein was obviously due to the identical reason as described above.

The Lp-PLA$_2$ inhibitory activities of **13a**—**13e** were determined according to a well-established method,[10,11] which are summarized in Table 2.

As can be learned from Table 2, all the synthesized compounds **13a**—**13e** were potent Lp-PLA$_2$ inhibitors, with all IC$_{50}$ being no more than 10 nmol•L^{-1}. Substituents in *para*-position can enhance the potency, as can be seen from the fact that the IC$_{50}$ for **13a** is larger than those of **13b**—**13e**, and the methyl group is most

Table 1 Formation of **6** and **7** under different conditions[a]

	R=H	R=CH_3	R=Cl	R=CH_3O
Condition 1	**5a** 89%	**5b** 90%	—	**5e** 90%
	6a 11%	**6b** 10%		**6e** 10%
Condition 2	**5a** 89%	**5b** 90%	—	**5e** 90%
	6a 11%	**6b** 10%		**6e** 10%
Condition 3	**5a** 46%	**5b** 48%	**5d** 45%	**5e** 45%
	7a 54%	**7b** 52%	**7d** 55%	**7e** 55%
Condition 4	**5a** 46%	**5b** 48%	**5d** 45%	**5e** 45%
	7a 54%	**7b** 52%	**7d** 55%	**7e** 55%
Condition 5	**5a** 100%	**5b** 100%	**5d** 100%	**5e** 100%

[a] Condition 1: NaH (1.5 equiv.)/$ClCH_2CO_2Et$ (2.0 equiv.), THF, reflux; Condition 2: NaH (2.0 equiv)/$ClCH_2CO_2Et$ (3.0 equiv.), THF, reflux; Condition 3: *t*-BuOK (1.5 equiv.)/$ClCH_2CO_2Et$ (2.0 equiv.)/*t*-BuOH, reflux; Condition 4: *t*-BuOK (2.0 equiv.)/$ClCH_2CO_2Et$ (3.0 equiv.)/*t*-BuOH, reflux; Condition 5: K_2CO_3 (3.0 equiv.)/KI (0.05 equiv.)/$ClCH_2CO_2Et$ (2.0 equiv.)/DMF, 80 ℃.

Table 2 The inhibitory activities (IC_{50}) of **13a**—**13e**

Compound	**13a**	**13b**	**13c**	**13d**	**13e**
IC_{50}/(nmol•L^{-1})	10.0	1.5	3.6	5.7	7.7

preferred one with **13b** being the most potent one (1.5 nmol•L^{-1}).

In clonclusion, 5 Lp-PLA_2 inhibitors were designed and synthesized by a convergent 10-step procedure, and *in vitro* evaluation demonstrated that all the prepared compounds **13a**—**13e** showed potent Lp-PLA_2 inhibitory activities with compound **13b** being the most potent one (IC_{50}=1.5 nmol•L^{-1}). An unsuccessful alternative synthetic route was also discussed, providing useful insight into the synthesis and structural nature of this class of compounds.

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