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Practical and Efficient Synthesis of 2-Thio-imidazole derivative - ZY12201: A Potent TGR5 Agonist

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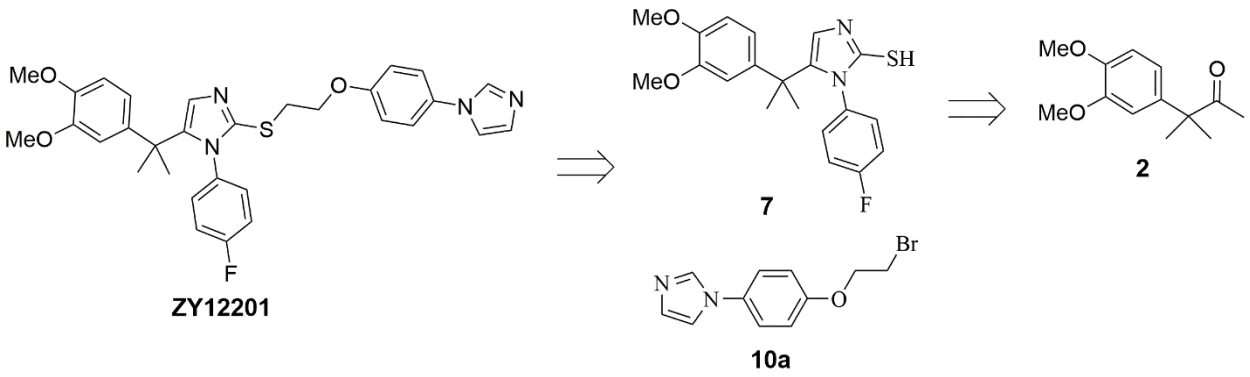
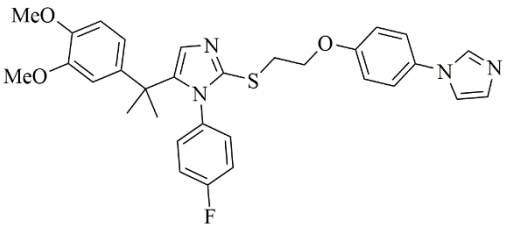


ABSTRACT: Early scalable process development for the synthesis of ZY12201, a novel TGR5 receptor agonist as potential clinical candidate is described. A practical, efficient and scalable synthetic route had provided ZY12201 in 7-steps and 32% overall yield. The key step involves an inexpensive acetic acid mediated cyclization of thiourea **6** for the construction of 2-thio-imidazole derivative **7**. In addition, an efficient process has been described for synthesis of advance intermediates **2** and **10a** that facilitated the synthesis of ZY12201. The developed process demonstrated cost effective, high yielding, kilogram scalable and environmentally friendly synthesis of ZY12201.This high yielding route enabled us to rapidly synthesize large quantities of ZY12201 in 99% purity to support *in vivo* and toxicity studies.



ZY12201

KEYWORDS: *TGR5, TGR5 agonist, type 2 diabetes, 2-thio imidazole, 1,2-dibromo ethane*.

▪ INTRODUCTION

Diabetes is increasing at an alarming rate with approximately more than 463 million people affected worldwide and the number of patients is expected to reach 700 million by the year 2045.[1] Diabetes caused at least USD 760 billion dollars in health expenditure in 2019, which is 10% of total spending on adults treatment. With the rising incidence of obesity, a major risk factor for the onset of type 2 diabetes, this metabolic disorder represents a major health concern and commonly termed as "Diabesity".[2] Although a range of anti-diabetic agents are available, still there is high unmet medical need.[3-5]

Takeda G-protein-coupled receptor 5 (TGR5), also known as GPR 131, or GPBAR1, is a bile acid G protein-coupled receptor primarily expressed in monocytes, macrophages, lung, spleen, intestinal tract and is activated by bile acids.[6,7] It has been suggested that bile acids induce glucagon-like peptide-1 (GLP-1) secretion from primary intestinal enteroendocrine cells by increasing intracellular cAMP levels *via* the TGR5 receptor.[8,9] Activation of TGR5 receptors in brown adipose tissue has been proposed to increase energy expenditure through the induction of type 2 iodothyronine deiodinase (D2).[10] Recent studies suggest that the activation of TGR5 in macrophages may play a key role in the pathogenesis of

atherosclerosis.[11] TGR5 is being investigated as an attractive therapeutic target for the treatment of obesity and its highly associated type 2 diabetes. Recently we have reported the identification of several novel TGR5 agonists,[12-13] including the discovery of 2-((2-(4-(1H-imidazol-1-yl)phenoxy)ethyl)thio)-5-(2-(3,4-dimethoxyphenyl)propan-2-yl)-1-(4-fluorophenyl)-1H-imidazole (ZY12201) as a potent, selective, orally bioavailable and efficacious TGR5 agonist (Fig. 1).[14] The 2-thio-imidazole derivative ZY12201 was found to be highly potent TGR5 agonist (hTGR5 EC_{50} = 57 pM, mTGR5 = 62 pM) with favorable pharmacokinetic profile. The compound was found to have excellent glucose lowering effects *in vivo* during an oral glucose tolerance test in DIO C57BL/6 mice with ED_{50} of 7.9 mg/kg and ED_{90} of 29.2 mg/kg. Thus, an efficient synthetic route was needed to cater large quantities of ZY12201 to support further preclinical studies including *in vivo* and toxicity studies.

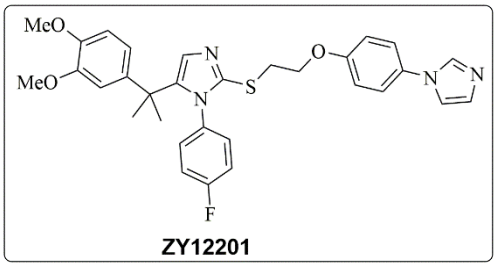
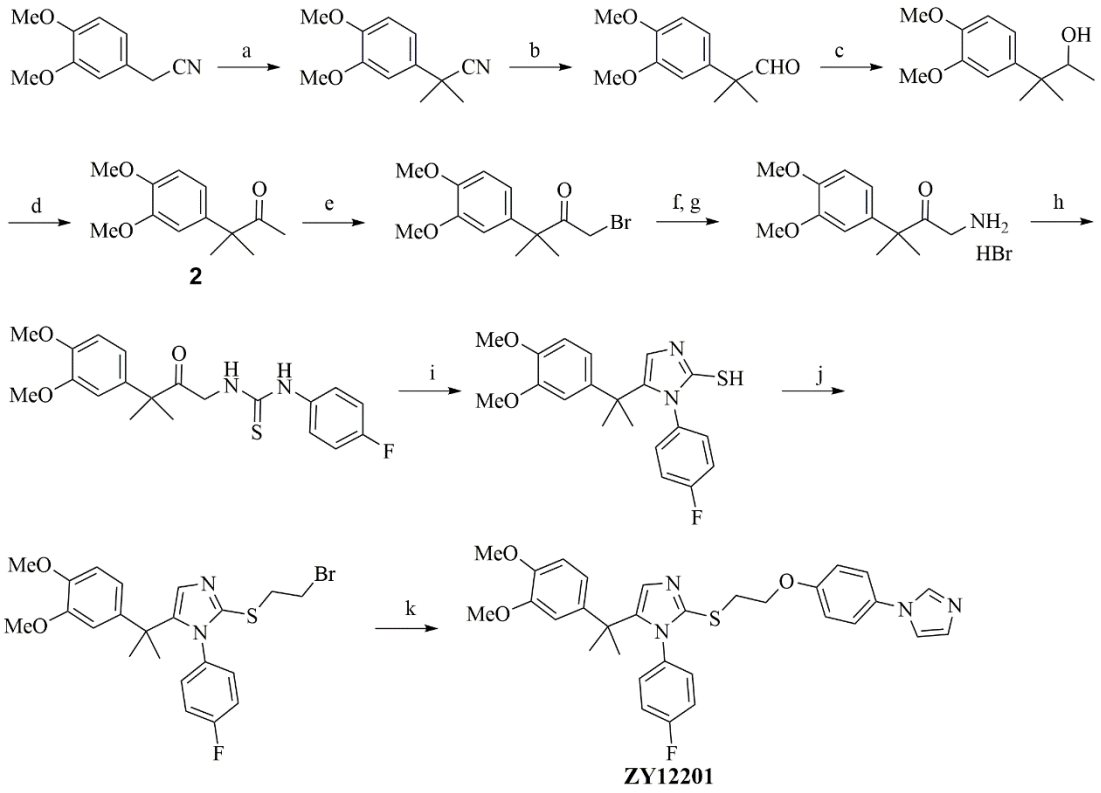


Figure 1. TGR5 receptor agonist.

Our original medicinal chemistry synthesis of ZY12201 (Scheme 1),[14-15] began with commercially available 2-(3,4-dimethoxyphenyl) acetonitrile. Key intermediate **2** was obtained from 2-(3,4-dimethoxyphenyl) acetonitrile via a 4-step sequence in 56% overall yield. Other synthetic routes of **2** involved harsh conditions, multi-step synthesis with cumbersome work up, difficult product isolation and unsatisfactory yields.[16] Moreover, the original approach involved high manufacturing costs due to the application of expensive raw materials and reagents. Loss of significant component of the API during column chromatographic purification also attributes to the higher costs. In addition, many of these reactions were not feasible on multi 100 g scale. Thus, further work on technical improvements to overcome the limitations was still a crucial experimental challenge. This report describes our synthetic and process chemistry efforts towards the development of a practical, efficient and scalable process for synthesis of TGR5 agonist ZY12201 to support preclinical studies.

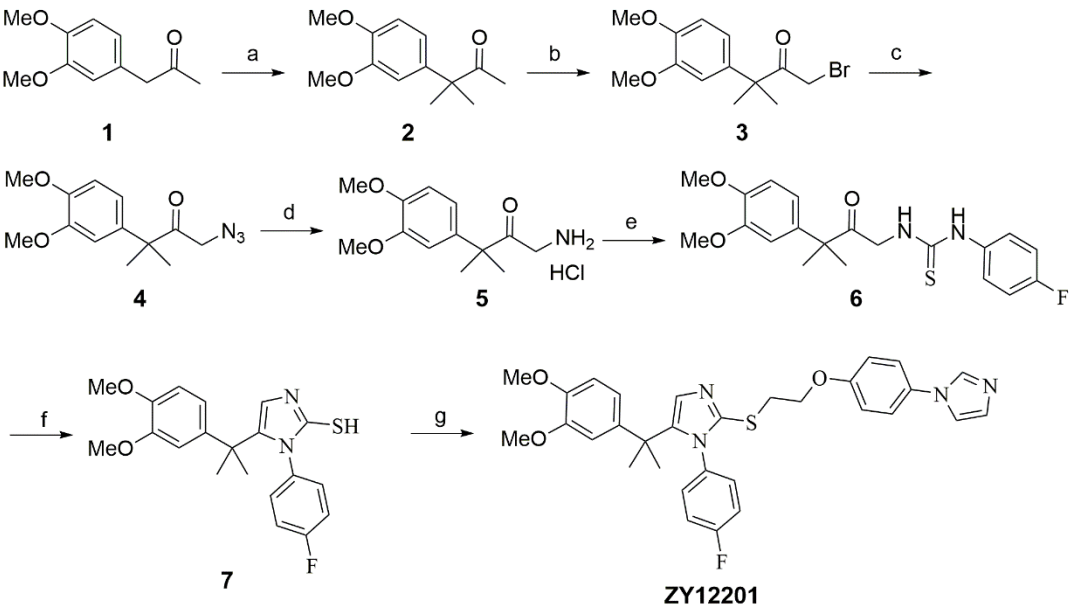


Scheme 1. Original synthesis of **ZY12201**. *Reagent and Conditions:* (a) MeI, NaH, THF, 0 ºC to r.t., 3 h, 93%; (b) DIBAL, Toluene, -78 ºC, 2 h, 93%; (c) MeMgBr, dry Et_2O, 0 ºC to r.t., 80%; (d) oxalyl chloride, DMSO, Et_3N, DCM, -78 ºC, 2 h, 82%; (e) Bu_4NBr_3, DCM, MeOH, 0 ºC to r.t., 7 h, 100%; (f) HMTA, DCM, r.t., 48 h; (g) EtOH, HCl, 80 ºC, 3 h; (h) 1-fluoro-4-isothiocyanatobenzene, Et_3N, DCM, 0 ºC to r.t., 1 h, 42%; (i) AcOH, 118 ºC, 3 h, 73%; (j) 1,2-dibromoethane, K_2CO_3, acetone, r.t., 2 h, 73%; (k) 4-(1H-imidazol-1-yl)phenol, K_2CO_3, DMF, 90 ºC, 5 h, 73%.

▪ RESULTS AND DISCUSSION

The optimized synthesis of ZY12201 began with an inexpensive commercially available 2-(3,4-dimethoxyphenyl)acetone (**1**) as depicted in Scheme 2. An efficient dimethylation of **1** using excess of methyl iodide afforded desired intermediate **2** in one-step with 93% yield, purified by filtration over short path of silica gel. Subsequently, alpha-bromination[17] of compound **2**, using tetrabutyl ammoniumtribromide afforded bromo compound **3**, on multi gram scale in quantitative yield. As shown in Scheme 1, **3** was directly converted into **5** using HMTA (hexamethylenetetramine) followed by treatment with hydrochloric acid. However, the reaction was generally low yielding and generated several unknown impurities which were difficult to remove, thus complicating the subsequent step. To circumvent difficulties associated with this reaction, **3** was first transformed to azide **4** which upon

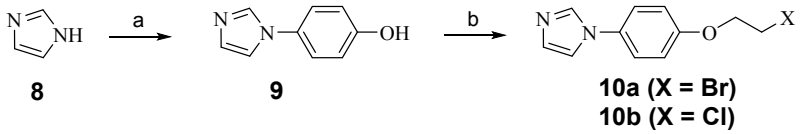
hydrogenation provided amine **5** as its corresponding hydrochloride salt. Importantly here, the solid product was filtered and washed with diisopropyl ether to provide **5** in high purity (93% by HPLC) and excellent yield (96%), on 120 g scale. We recommend appropriate safety measures, such as a closed delivery system, personal protective equipment and protective nitrile gloves should be used while handling sodium azide on a large scale.[18-19]



Scheme 2. Optimized synthesis of **ZY12201**. *Reagent and Conditions:* (a) MeI, NaH, dry THF, 0 ºC to r.t., 3 h, 93%; (b) Bu_4NBr_3, DCM, MeOH, 0 ºC to r.t., 7 h, 100%; (c) NaN_3, DMF, 0 ºC to r.t., 2 h, 94%; (d) Pd/C, H_2 (gas), HCl, MeOH, r.t., 45 h, 96%; (e) 1-fluoro-4-isothiocyanatobenzene, Et_3N, DCM, 0 ºC to r.t., 18 h, 61%; (f) AcOH, reflux, 3 h, 77%; (g) **10a**, K_2CO_3, acetone, r.t., 2 h, 80%.

Treatment of amine **5** with 1-fluoro-4-isothiocyanatobenzene provided thiourea derivative **6**. The thiourea formation step suffered from variable yields (<40-60%) and incomplete conversion, often stalling at 40-55% conversion. During the optimization of this reaction, we varied amount of 1-fluoro-4-isothiocyanatobenzene and the reaction conditions. Charging additional reagent (1-fluoro-4-isothiocyanato benzene) or base (triethyl amine) did not improve conversion, and solvent switch from dichloromethane to acetone resulted in low yield with concomitant formation of black polymeric material. Interestingly, lower equimolar concentration of regent still gave high product yield with extended reaction time (1.0 equivalent of 1-fluoro-4-isothiocyanatobenzene, 18 h, 61% of **6**). The key step in our synthetic route was the cyclization of thiourea (**6**) using inexpensive acetic acid for the construction of imidazole skeleton.[20] Treatment of thiourea (**6**) in boiling acetic acid led to the facile cyclization which afforded 2-thio imidazole derivative **7**. The workup protocol and purification process were optimized; the reaction

mixture was cooled to room temperature and slowly poured onto ice-water with gentle stirring, instead of directly using ice with vigorous stirring. The slow addition of the reaction mixture onto ice minimizes the exotherm of the quench, thus minimizing product decomposition. The mixture was extracted with ethyl acetate and washed with saturated sodium bicarbonate solution and brine to afford crude compound as brown solid. Reprecipitation of the crude product with solvents like ethyl acetate and *n*-hexane resulted compound **7** with an improved yield of 77% and in high chemical purity (98% by HPLC).



Scheme 3. Synthesis of Compound **10**. *Reagent and Conditions:* (a) 4-bromo phenol, CuI, Cs_2CO_3, DMF, 110°C, 48 h, 67%; (b) 1,2-dihalogenethane, K_2CO_3, MeCN, 65°C, 24 h, (84% for **10a**; 60% for **10b**).

Table 1: Optimization of the alkylation reaction: Effects of increasing amount of 1,2-dibromoethane on the preparation of compound **10a**.

Entry	1,2-dibromoethane (equivalents)	10a, %Yield
1	4	40
2	20	64
3	40	84
4	80	78

The initial[14] synthesis of ZY12201, used the alkylation of **7** with 1,2-dibromo ethane. This route was particularly designed to explore SAR, as this compound serves as an excellent intermediate for synthesizing a wide variety of analogues. However, this reaction was found to be low yielding on large scale with formation of many uncharacterized impurities. Due to the poor results obtained, we next decided to examine the alkylation of 4-(1H-imidazol-1-yl)phenol (**9**) with 1,2-dibromo ethane to give intermediate **10a**. A highly effectual synthesis of novel intermediate **10a** was needed to accomplish the synthesis of ZY12201. Towards this end, various experimental conditions were explored. Commercially available imidazole (**8**) was converted to 4-(1H-imidazol-1-yl)phenol (**9**) on large scale using Buchwald-Hartwig[21] conditions. Phenol (**9**) was transformed to bromo intermediate **10a** using 1,2-dibromo ethane in the presence of potassium carbonate (Scheme 3). Gratifyingly, when the amount of 1,2-dibromo ethane was increased to 40 equivalents, the yield was improved from 40% to 84% (Table 1, entries 1-3), but further increase of 1,2-dibromo ethane did not improve the yield (entry 4). Having key intermediates **7** and **10a** in hand, finally alkylation of **7** with **10a** provided ZY12201 in excellent yield and high chemical

purity. Alternatively, alkylation of **7** with chloro derivative **10b** was also investigated, which afforded the final compound in best yield of 55% (using 20 equivalents of **10b**), on gram scale. However, this reaction for synthesis of ZY12201 was not feasible on large scale due to formation of many uncharacterized impurities. The structure of ZY12201 has been unequivocally confirmed by the X-ray crystal structure determination (Fig. 2). Additionally, the procedure opens up the way to an efficient and scalable synthesis of wide range 2-thio-imidazole analogues for structure–activity studies.

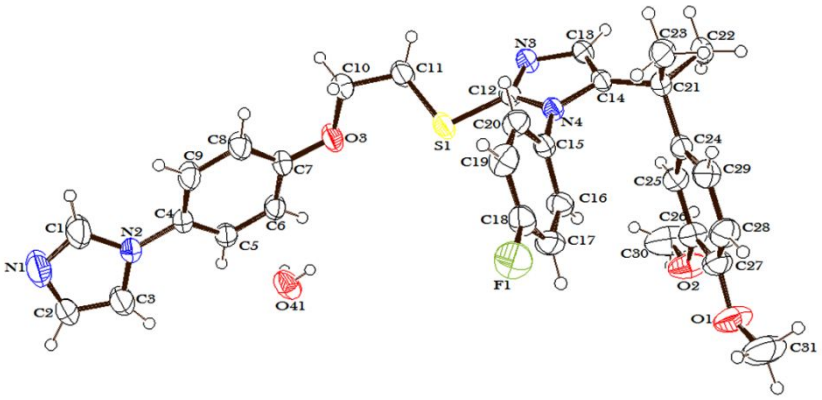


Figure 2. Single crystal X-ray analysis of 2-((2-(4-(1H-imidazol-1-yl)phenoxy)ethyl)thio)-5-(2-(3,4-dimethoxyphenyl)propan-2-yl)-1-(4-fluorophenyl)-1H-imidazole (**ZY12201**).

Compared with the reported synthesis, our optimized sequence was shortened from 11 steps to 7 steps, and the overall yield was significantly improved from 9% to 32%, on multi gram scale. Key to success of this approach was the identification of an efficient and practical synthesis of intermediates **2** and **10a** as well as the removal of column chromatography purification of several advanced intermediates.

▪ CONCLUSION

In conclusion, an efficient and scalable synthesis of a potent, selective and orally bioavailable TGR5 agonist ZY12201 has been described. The process involves an inexpensive acetic acid mediated cyclization of thiourea (**6**) to the corresponding 2-thio imidazole derivative (**7**), as a key step. A highly practical and convenient process was found for synthesis of advance intermediates **2** and **10a** that facilitated the synthesis of ZY12201. The original 11-step synthesis of ZY12201 was replaced by a robust 7-step route affording the target in 32% yield. Major highlights of our practical and scalable process includes higher overall yield, simplified reaction workup; and no usage of chromatography which resulted in huge reduction in the total solvent consumption, considering as an important parameter for green

chemistry Taken together, we have developed a process that is cost effective, environment friendly and commercially viable synthesis of TGR5 agonist ZY12201, leading to extensive prospects in industrial applications.

▪ EXPERIMENTAL SECTION

General Methods. Melting points were recorded on a scientific melting point apparatus and are uncorrected. IR spectra were recorded as neat (for oils) or on KBr pellet (for solid) on FT-IR 8300 Shimadzu and are reported in wavenumbers ν (cm^{-1}). NMR spectra were measured on a Varian Unity 400 (^1H at 400 MHz, ^{13}C at 100 MHz), magnetic resonance spectrometer. Spectra were taken in the indicated solvent at ambient temperature. Chemical shifts (δ) are given in parts per million (ppm) with tetramethylsilane as an internal standard. Multiplicities are recorded as follows: s = singlet, d = doublet, t = triplet, q = quartet, br = broad. Coupling constants (J values) are given in Hz. Mass spectra were recorded on Perkin-Elmer Sciex API 3000. ESI-Q-TOF-MS measurements were performed with a micrOTOF-Q II (Bruker Daltonics) mass spectrometer. HPLC analysis were carried out at λ_{max} 220 nm using column ODS C-18, 150 mm x 4.6 mm x 4 μm on AGILENT 1100 series. Reactions were monitored using thin layer silica gel chromatography (TLC) using 0.25 mm silica gel 60F plates from Merck. Plates were visualized by treatment with UV, acidic *p*-anisaldehyde stain or $KMnO_4$ stain with gentle heating. Products were purified by column chromatography using silica gel 100-200 mesh and the solvent systems indicated. All reactions involving air or moisture sensitive compounds were performed under nitrogen atmosphere in flame dried glassware. Solvents used for reactions were purified according to standard procedures. Starting reagents were purchased from commercial suppliers and used without further purification unless otherwise specified. All yields are reported before correction for compound purity.

3-(3,4-dimethoxyphenyl)-3-methylbutan-2-one (**2**): A 500 mL, four-neck, round-bottom flask equipped with a mechanical stirrer and thermometer pocket was charged with THF (160 mL) and cooled externally to -5-0 ^oC under nitrogen atmosphere. Sodium hydride (9.88 g, 0.247 mol, 50-55% in mineral oil) was added portion wise followed by addition of 1-(3,4-dimethoxyphenyl)propan-2-one (20 g, 0.103 mol) at 0 ^oC and stirred at 0-5 ^oC for 30 minutes. Methyl iodide (43.85 g, 19.3 mL, 0.309 mol) was added drop wise at 0 ^oC over a period of 1 h. The reaction mixture was warmed to room temperature and stirred for 2 h then dumped onto ice water (200 mL) at 0-5 ^oC. The reaction mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with 5% Na_2SO_3 solution (3 x 50 mL), water (2 x 100 mL) and brine (1 x 200 mL), treated with activated charcoal (2 g) and filtered through HyFlo

SuperCel. The filtrate was concentrated *in vacuo* to afford crude product (~ 28 g). The crude product was purified by filtration over short path of silica gel using 6% ethyl acetate/*n*-hexane as eluent to furnish compound **2** (21.3 g, 93%) as an oil.

% purity: 97.73% (HPLC); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.47 (s, 6H), 1.93 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 6.70 (s, 1H), 6.84 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.26, 25.41, 52.11, 55.99, 56.05, 109.63, 111.34, 119.05, 136.72, 148.12, 149.19, 211.48; IR (KBr): ν = 770, 810, 1028, 1258, 1466, 1516, 1589, 1705, 2835, 2936, 2972 cm^{-1}; ESI-MS (*m/z*): 223.0 $[M + H]^+$.

1-bromo-3-(3,4-dimethoxyphenyl)-3-methylbutan-2-one (**3**): To a solution of compound **2** (117 g, 0.526 mol) in dichloromethane (1.17 L) and methanol (0.585 L) was added tetra butyl ammonium tribromide (269 g, 0.557 mol) in one portion at 0 °C. The mixture was stirred for 2 h at 0 °C, then warmed to room temperature and stirred for 16 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate (1.17 L), and washed with water (2 x 1.17 L), 1M HCl (0.585 L), and brine (1.17 L). The organic layer was dried over sodium sulphate, filtered and concentrated *in vacuo* to afford a light brown color oil which was triturated with *n*-hexane to afford **3** (158.4 g, 100%).

% purity: 85.97% (HPLC); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.54 (s, 6H), 3.87 (s, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 6.68 (d, J = 2.0 Hz, 1H), 6.82 – 6.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.47, 32.01, 51.91, 55.98, 56.05, 109.49, 111.52, 119.08, 135.09, 148.51, 149.39, 204.13; IR ($CHCl_3$): ν = 762, 1026, 1216, 1258, 1518, 1591, 1724, 2839, 2976, 3021 cm^{-1}.

1-azido-3-(3,4-dimethoxyphenyl)-3-methylbutan-2-one (4): To a solution of compound **3** (139 g, 0.462 mol) in DMF (417 mL) was added sodium azide (39 g, 0.6 mol) in one portion at 0 °C and stirred for 30 minutes. The mixture was then warmed to room temperature and stirred for 2 h. The reaction mixture was dumped onto water (2.5 L) and stirred for 15 minutes. The mixture was extracted with ethyl acetate (3 x 1.4 L). The combined organic layer was washed with water (1.4 L) and brine (1.4 L), treated with activated charcoal and filtered through HyFlo SuperCel. The filtrate was concentrated *in vacuo* to afford **4** (138 g, 94%) as an oil which was used in next reaction without further purification. *(We recommend appropriate safety measures, such as a closed delivery system, personal protective equipment and protective nitrile gloves should be used while handling sodium azide on a large scale.)*

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.45 (s, 6H), 3.70 (s, 3H), 3.74 (s, 3H), 4.05 (s, 2H), 6.75 – 6.82 (m, 2H), 6.96 (d, J = 7.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 24.67, 50.10, 53.19, 55.43, 55.47,110.03, 111.84, 118.22, 134.95, 147.92, 148.76, 207.63.

1-amino-3-(3,4-dimethoxyphenyl)-3-methylbutan-2-one hydrochloride (5): To a solution of compound **4** (121.5 g, 0.461 mol) in methanol (2.43 L) was added concentrated hydrochloric acid (69.2 mL, 0.85 mol) and 10% palladium on activated charcoal (50% moisture) (1.6 mol%) at room temperature. The reaction mixture was flushed with hydrogen gas and was stirred at room temperature under hydrogen gas atmosphere for 45 h. After completion of reaction, filtered through HyFlo SuperCel, and concentrated *in vacuo* to afford crude product. Diisopropyl ether (2.43 L) was added to the crude product and the solid mixture was stirred for 1 h at room temperature. The solid product was filtered *in vacuo* and washed with diisopropyl ether (3 x 500 mL). The product was dried for 1 h to yield **5** (121 g, 96%) as a pale yellow solid.

% purity: 92.82% (HPLC); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.47 (s, 6H), 3.75 (s, 3H), 3.76 (s, 3H), 3.77 (s, 2H), 6.78 (d, J = 2.4 Hz, 1H), 6.84 – 6.96 (m, 2H), 8.2 (br s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 24.92, 43.39, 49.78, 55.55, 55.58, 110.36, 111.85, 118.33, 134.88, 148.01, 148.77, 206.28; ESI-MS (*m/z*): 238.1 $[M + H]^+$.

1-(3-(3,4-dimethoxyphenyl)-3-methyl-2-oxobutyl)-3-(4-fluorophenyl)thiouea (6): To a solution of **5** (49 g, 0.179 mol) in dichloromethane (490 mL) was added triethylamine (54.3 g, 74.8 mL, 0.537 mol) at 0 ^{o}C under nitrogen atmosphere. A solution of 1-fluoro-4-isothiocyanato benzene (27.4 g, 0.179 mol) in dichloromethane (190 mL) was added using dropping funnel to the reaction mixture at 0 ^{o}C under stirring. The cooling bath was removed and the mixture was stirred at room temperature for 18 h. Reaction mixture was diluted with dichloromethane (490 mL) and quenched with water (350 mL). Organic layer was separated and washed with water (3 x 350 mL) and dried over sodium sulfate, filtered and concentrated *in vacuo* to afford crude compound as light brown solid. The crude solid was stirred with diisopropyl ether (490 mL) at room temperature for 16 h. The solid product was filtered and dried *in vacuo* to afford compound **6** (42.6 g, 61%) as pale yellow solid.

% purity: 95.90% (HPLC); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.53 (s, 6H), 3.85 (s, 3H), 3.86 (s, 3H), 4.38 (d, J = 4.4 Hz, 2H), 6.70 (s, 2H), 6.83 (s, 2H), 7.12 – 7.17 (m, 2H), 7.21 – 7.26 (m, 2H), 7.84 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.41, 50.25, 50.88, 56.03, 56.16, 109.64, 111.54, 117.20, 117.83, 118.45, 127.57, 127.66, 134.91, 148.59, 149.36, 180.53, 208.43; IR (KBr): ν = 800, 1040, 1215, 1258, 1510, 1545, 1726, 2926, 2965, 3167, 3333, 3433 cm^{-1}; ESI-MS (*m/z*) (%): 391.1 (100%) $[M + H]^+$.

5-(2-(3,4-dimethoxyphenyl)propan-2-yl)-1-(4-fluorophenyl)-1*H*-imidazole-2-thiol (7). A mixture of **6** (80 g, 0.204 mol) and acetic acid (800 mL) was heated at reflux temperature for 3 h. The reaction mixture was cooled to room temperature and poured onto ice-water (4000 mL) with gentle stirring. The mixture was extracted with ethyl acetate (2 x 1.12 L). The combined organic layer was washed with saturated

sodium bicarbonate solution (3 x 1.12 L) and brine (1.12 L). The organic layer was dried over sodium sulphate, filtered and concentrated *in vacuo* to afford crude compound as brown solid. The crude solid was stirred with 20% ethyl acetate/*n*-hexane (560 mL) at room temperature for 16 h. The solid product was filtered and dried *in vacuo* to afford compound (**7)** (59 g, 77%) as off-white solid.

% purity: 97.91% (HPLC); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.44 (s, 6H), 3.75 (s, 3H), 3.87 (s, 3H), 6.45 – 6.48 (m, 2H), 6.58 – 6.62 (m, 2H), 6.67 (d, J = 8.0 Hz, 1H), 6.79 (s, 1H), 6.87 (t, J = 8.8 Hz, 2H), 12.01 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 29.29, 38.07, 56.02, 56.10, 109.61, 110.93, 111.27, 111.85, 115.67, 118.48, 131.61, 132.69, 138.21, 140.34, 147.91, 148.85, 162.38 (d, $J_{C,F}$ = 248 Hz); IR (KBr): v = 797, 1026, 1215, 1265, 1512, 1599, 2720, 2835, 2932, 3051, 3464 cm^{-1}; ESI-MS (*m/z*) (%): 373.1 (100%) $[M + H]^+$.

4-(1*H*-imidazol-1-yl)phenol (9). In a 5 L glass assembly (equipped with a condenser and a thermometer pocket) was charged DMF (1.4 L), 1*H*-imidazol (82 g, 1.20 mol), 4-bromophenol (250 g, 1.445 mol), copper iodide (45.86 g, 0.241 mol) and cesium carbonate (784.9 g, 2.409 mol) at a room temperature. The mixture was heated at 100-110 °C and stirred for 48 h. The mixture was cooled to room temperature. The reaction mixture was diluted with mixture of ethyl acetate and methanol (1:1) (3 L) and filtered through HyFlo SuperCel. The filtrate was concentrated *in vacuo* to afford brown colour oily mass. The oily mass was stirred with 1N HCl solution (2.5 L) for 15 minutes, then mixture was extracted by ethyl acetate (3 x 1 L). The aqueous layer was basified with saturated sodium bicarbonate solution. The precipitated product was filtered, washed with water and dried *in vacuo* to afford crude compound (~ 200 g). The crude solid was stirred with acetonitrile (200 mL) for 30 minutes at room temperature. The solid product was filtered and dried *in vacuo* to afford titled compound **9** (130 g, 67%) as white solid.

% purity: 99.23% (GC); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.86 - 6.90 (m, 2H), 7.08 (s, 1H), 7.39 - 7.43 (m, 2H), 7.58 (s, 1H), 8.08 (s, 1H), 9.80 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 116.0, 118.0, 122.0, 129.0, 129.4, 137.0, 156.4; ESI-MS (*m/z*): 161.0 $[M + H]^+$.

General procedure for synthesis of compound (10a-b)

To a stirred solution of 4-(1*H*-imidazol-1-yl)phenol (**9**) (25 g, 0.156 mol) in acetonitrile (300 mL) was added potassium carbonate (108 g, 0.780 mol) in one portion at room temperature. The mixture was stirred for 15 minutes at room temperature. A solution of 1,2-dihalo ethane (0.624 mol, 4 eq.) in acetonitrile (30 mL) was added dropwise and stirred the reaction mixture at 60-65 °C for 24 h. The mixture was cooled to 25-30 °C, filtered and concentrated *in vacuo* to afford oily mass. The oily mass was stirred with 1N HCl (350 mL) for 15 minutes and then mixture was extracted by ethyl acetate (3 x 100 mL). The aqueous layer was basified with 2N NaOH solution. The aqueous layer was extracted by diethyl

ether (3 x 200 mL) and washed by brine solution (100 mL). The organic layer was concentrated *in vacuo* to afford compound **(10a-b)** as oil.

1-(4-(2-bromoethoxy)phenyl)-1*H*-imidazole (10a). The compound **10a** was synthesized following the general procedure described for compound (10a-b), using 40 equivalents of 1,2-dibromo ethane. The compound **10a** was obtained as a dark brown oil (35 g, 84% yield) which was used for next reaction without any further purification. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.81 (t, J = 5.6 Hz, 2H), 4.36 (t, J = 5.6 Hz, 2H), 7.06 – 7.08 (m, 1H), 7.09-7.11 (m, 2H), 7.53 - 7.57 (m, 2H), 7.64 – 7.65 (t, J = 1.2 Hz, 1H), 8.13 (d, J = 0.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 31.39, 68.11, 115.90, 118.84, 121.99, 129.57, 131.31, 135.51, 156.64; ESI-MS (*m/z*): 268.9 $[M + H]^+$.

1-(4-(2-chloroethoxy)phenyl)-1*H*-imidazole (10b). The compound **10b** was synthesized following the above general procedure described for compound (10a-b). The compound **10b** was obtained as a dark brown oil (21 g, 60% yield). % purity: 87.44% (HPLC); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.83 (t, J = 5.6 Hz, 2H), 4.26 (t, J = 5.6 Hz, 2H), 6.98 - 7.02 (m, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.28 – 7.32 (m, 2H), 7.76 (d, J = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 41.82, 68.43, 115.78, 118.70, 123.23, 130.14, 131.31, 135.80, 157.53; ESI-MS (*m/z*): 223.0 $[M + H]^+$.

2-((2-(4-(1H-imidazol-1-yl)phenoxy)ethyl)thio)-5-(2-(3,4-dimethoxyphenyl)propan-2-yl)-1-(4-fluoro phenyl)-1H-imidazole (**ZY12201**). A mixture of compound **7** (9 g, 0.024 mol), 1-(4-(2-bromoethoxy)phenyl)-1H-imidazole (**10a**) (12.9 g, 0.048 mol), potassium carbonate (10.0 g, 0.072 mol) in acetone (100 mL) was stirred at room temperature for 2 h. Reaction mixture was diluted with acetone (90 mL), filtered and concentrated *in vacuo* to afford crude product (~19.5 g). The crude product was purified by a short column chromatography over silica gel with 1-3% methanol/chloroform as eluent to furnish compound ZY12201 (11.95 g, 80%) as white solid.

White powder; mp: 108 ºC; % purity: 99.57%; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.49 (s, 6H), 3.42 (t, J = 6.4 Hz, 2H), 3.72 (s, 3H), 3.84 (s, 3H), 4.27 (t, J = 6.4 Hz, 2H), 6.49 – 6.55 (m, 4H), 6.64 (d, J = 8.8 Hz, 1H), 6.80 - 6.85 (m, 2H), 6.98 – 7.00 (m, 2H), 7.15 (s, 1H), 7.18 – 7.20 (m, 2H), 7.27 – 7.29 (m, 2H), 7.77 (br s, 1H); ^{13}C NMR and DEPT (100 MHz, DMSO-d_6): δ = 29.61 (CH_3), 31.54 (CH_2), 38.12 (C), 55.99 (CH_3), 56.05 (CH_3), 67.17 (CH_2), 109.96 (CH), 110.83 (CH), 115.38 (CH), 115.61 (CH), 115.75 (CH), 118.45 (CH), 118.84 (CH), 123.22 (CH), 125.99 (CH), 130.01 (C), 130.97 (CH), 131.06 (C), 132.07 (C), 139.89 (C), 143.37 (C), 144.18 (C), 147.58 (C), 148.70 (C), 157.89 (C), 162.49 (C) (d, $J_{C,F}$ = 248 Hz); MS (EI): *m/z* (%) = 559.1 (100%) $(M)^+$, 560.5 $(M+H)^+$; ESI-Q-TOF-MS: *m/z* $[M+H]^+$ calcd for $[C_{31}H_{31}FN_4O_3S + H]^+$: 559.2134; found: 559.2244; IR (KBr): v = 3495, 3367, 3063, 2931, 2829, 1602,

1462 cm^{-1}; Anal. Calcd for $C_{31}H_{31}FN_4O_3S$: C, 66.68; H, 5.59; N, 10.02; S, 5.73. Found: C, 66.48; H, 5.95; N, 9.73; S, 5.66.

▪ ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge via the Internet at http://pubs.acs.org

Spectral data and X-Ray data file

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Notes

The authors declare no competing financial interest.

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