A Platinum Open Access Journal for Organic Chemistry

Paper

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2023** (viii) 202312151

An alternative synthetic strategy to construct apixaban analogues

Dattatray Gaikwad,[a] Rana Chatterjee,[b] Sujeet Gaware,[b] Achyuta Nanda Acharya,[*a] Rambabu Dandela[*b]

[a] *Department of Chemistry, Odisha University of Technology and Research (OUTR), Kalinga Nagar, Bhubaneswar-751003, Odisha, India*

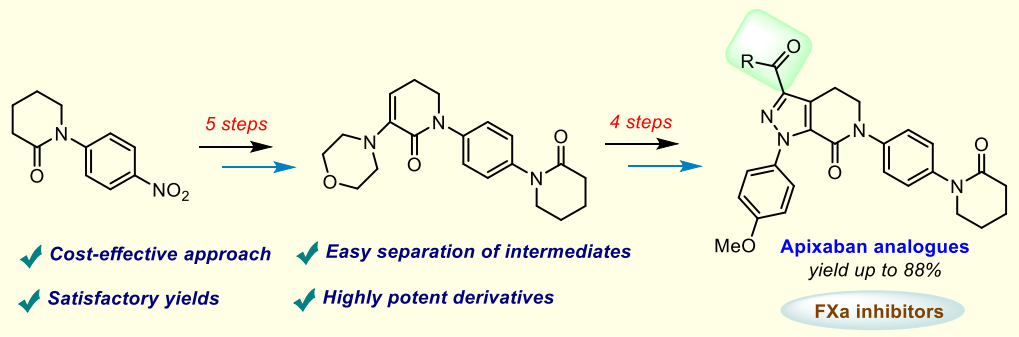
[b] *Department of Chemistry, Institute of Chemical Technology-Indian Oil Odisha Campus, IIT Kharagpur Extension Centre, Mouza Samantpuri, Bhubaneswar, Odisha-751013, India*

Email: r.dandela@iocb.ictmumbai.edu.in

Received 12-12-2023 **Accepted Manuscript** 06-27-2024 **Published on line** 07-07-2024

Abstract

An alternate synthetic approach has been described to access novel apixaban analogues. The present strategy offers a practical and cost-effective synthetic procedure to construct the privileged scaffold and its amide derivatives that may exhibit promising anticoagulant potency. Moreover, the method was performed by using less expensive reagents, easily achievable precursors, and fewer intermediary steps, providing a good yield of the desired substances.



Keywords: Apixaban, Cost-effective, Novel apixaban analogues, FXa inhibitors,

Introduction

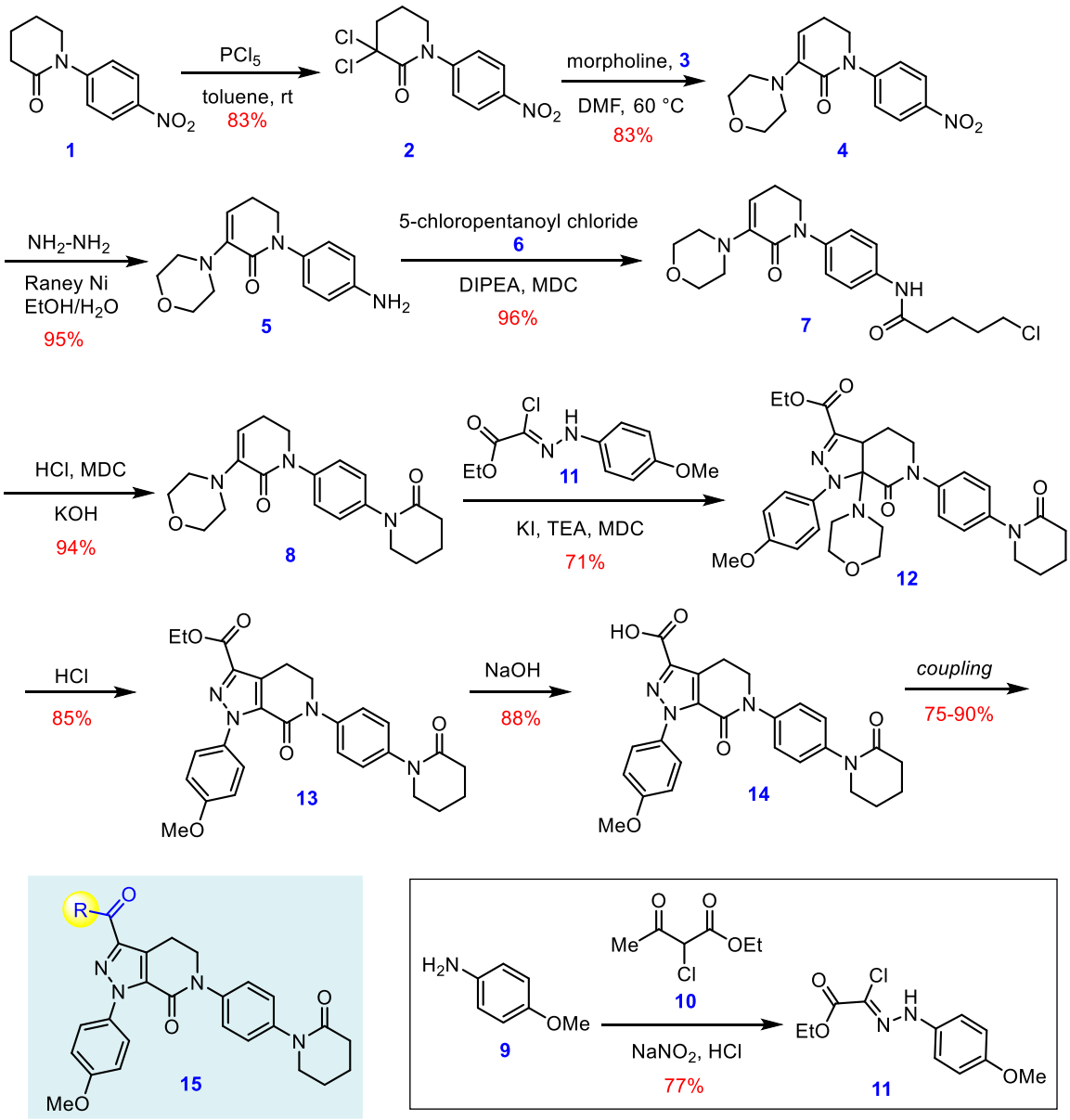
Heterocyclic compounds are recognized as a crucial component of medicinal chemistry. They are building blocks of many synthetic and natural biologically active substances.[1-9] In particular, fused pyrazole analogues have received huge attention due to exhibiting significant biological activity. For instance, Ruxolitinib was approved recently to treat myelofibrosis which causes anemia, fatigue, pain and swelling of the spleen.[10-12] It works mainly by blocking Janus kinase subtypes 1 and 2 associated with the disease. Crizotinib is known as the familiar small-molecule kinase inhibitor.[13-15] This active substance got approval for the purpose of treating patients with regionally advanced or metastatic non-small-cell lung cancer. Furthermore, another important substance Eltrombopag which is a c-mpl (TpoR) receptor agonist, has received clinical permission for thrombocytopenia (abnormally low platelet counts).[16-17] In this regard, another important pyrazole-containing analogue, Apixaban an anticoagulant that came with a lesser mortality rate than warfarin. This is the recommended course of treatment for atrial fibrillation patients to avoid strokes and a prevalent cardiac rhythm problem for the last few decades.[18-21] Noteworthily, Apixaban was released onto the market before the other two novel blood thinners, pradaxa and xarelto, but they were judged to be virtually identical. A previous clinical contender from Bristol-Myers Squibb was Razaxaban, a competitive oral direct factor Xa inhibitor. It could potentially be promoted as a remedy for deep vein thrombosis (DVT) and as a new-generation anticoagulant. Furthermore, it has demonstrated potential in the treatment of cancer, cerebrovascular ischemia, and acute coronary syndrome (ACS). Later, several structural modifications have been carried out to avoid the risky consequences. The results showed that the cyclization of the amide nitrogen to the pyrazole ring led to a class of bicyclic tetrahydropyrazolopyridinones having strong factor Xa-binding activity.[22-24] In addition, these potent compounds display significant factor Xa potency, enhanced selectivity, efficacy, and superior pharmacokinetic features.

Previously, several strategies have been developed for the preparation of apixaban. In the earlier of twenty-first century, a novel approach to synthesize 4,5-dihydro-pyrazolo[3,4-c]pyrid-2-ones and its derivatives was reported by Zhou et al.[25] Subsequently, in 2007, Pinto et al. disclosed an unique strategy to produce a highly potent 1-(4-methoxypheny)-7-oxo-6-(-4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (apixaban, BMS-562247) compounds showing a high level of fXa potency and a stronger pharmacokinetic balance.[26] Next, Shahbaz and the group reported a large-scale preparation of apixaban with a slight improvement in the process.[27] In the last decade, Liu et al. have reported novel apixaban and tetrahydropyrazolopyridone derivatives as FXa inhibitors with potent anticoagulant activity.[28-30] Recently, Satheesh et al. have reported the synthetic procedure and characterization of apixaban drug substance and also shown anticoagulant activity for treatment of venous thromboembolic disorders.[31] Last year, Chu and the group have developed a practical and efficient process for the preparation of the key intermediate of apixaban. They have started the experiment with 4-chloronitrobenzene and piperidine and after following eight-step procedure the targeted intermediate was produced.[32] However, these previous methods faced some major limitations such as expensive materials, extreme heating, tedious intermediate preparation, lower yields, harsh conditions etc. It is noteworthy that a convenient and cost-effective approach is still significant to develop these privileged scaffolds in terms of better yields, large-scale synthesis and inexpensive auxiliaries. In the continuation of our ongoing research, we are delighted to disclose an alternative synthetic strategy to achieve novel apixaban analogues that could lead to active pharmaceutical ingredients (API) in marketplaces. Herein, the reported method was started with cheap and easily accessible 4-methoxyaniline and ethyl 2-chloro-3-oxobutanoate, affording an improved yield. The process also avoids the use of Cu(I)-mediated low-yielding Ullmann coupling steps and demonstrates the practical application to

produce the required intermediates. Moreover, the current multi-step procedures were successfully executed using cost-effective and readily available materials, under mild conditions that led to good yields of the intermediates in each conversion.

Results and Discussion

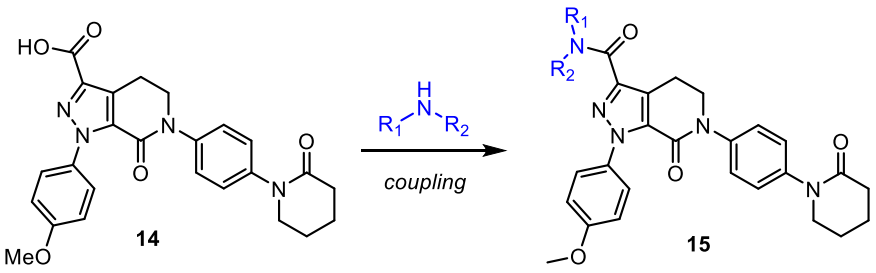
In order to synthesise the desired scaffold, a number of muti-step process have been performed under the standard conditions (Scheme 1). Initially, we have carried out the chlorination reaction of 1-(4-nitrophenyl)piperidin-2-one **1** with phosphorus pentachloride (PCl_5) to produce 3,3-dichloro-1-(4-nitrophenyl)piperidin-2-one **2** in 83% yield. In the next step, the dechlorinated product **2** underwent nucleophilic substitution and elimination with morpholine **3**, providing 3-morpholino-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one **4** in 75% yield. Subsequently, a catalytic reduction of nitro-substrate **4** with hydrazine hydrate and Raney nickel led to 1-(4-aminophenyl)-3-morpholino-5,6-dihydropyridin-2(1*H*)-one **5** in 95% yield. The amino phenyl intermediate **5** was then treated with a solution of 5-chlorovaleroyl chloride **6** (CVC) to obtain 5-chloro-N-(4-(5-morpholino-6-oxo-3,6-dihydropyridin-1(2*H*)-yl)phenyl)pentanamide **7** with an excellent yield of 96%. Later, the intramolecular cyclization of **7** afforded the product 3-morpholino-1-(4-(2-oxopiperidin-1-yl)phenyl)-5,6-dihydropyridin-2(1*H*)-one **8** with 94% yield. On the other side, a reaction of 4-methoxyaniline **9** and ethyl 2-chloroacetoacetate **10** was conducted in a solution of sodium nitrite and hydrochloric acid to form ethyl (Z)-2-chloro-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate **11** (yield 77%) as a useful synthon. Hereafter, the substrate **11** was used to react with intermediate **8** in the presence of triethylamine and KI to produce ethyl 1-(4-methoxyphenyl)-7a-morpholino-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-3a,4,5,6,7,7a-hexahydro-1*H*-pyrazolo[3,4-c]pyridine-3-carboxylate **12** in 71% yield. Then the acidic hydrolysis of resulting compound **12** and followed by recrystallization provided ethyl 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1*H* pyrazolo[3,4-c]pyridine-3-carboxylate **13** in 85% yield. Eventually, after ester hydrolysis with sodium hydroxide solution, **13** was converted to 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid **14** in 88% yield.



Scheme 1. An alternate route to access apixaban analogues.

In addition, we have synthesized a number of potential amide derivatives **15** *via* the acid-amine coupling reactions of the resulting compounds, **14** (Table 1). Herein, we carried out the coupling reactions using a number of aliphatic and aromatic amine that possess different functionalities and groups, providing the corresponding compounds **15a-s** in good to excellent yields (75-90%).

Table 1. Synthesis of amide derivatives from compound **14**[a,b]



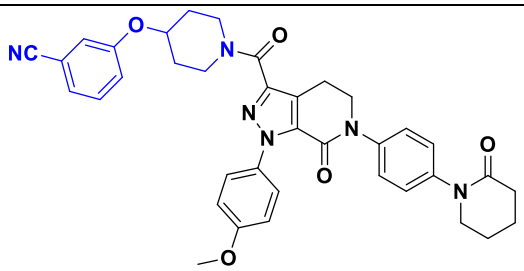
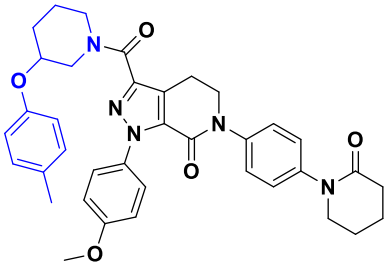
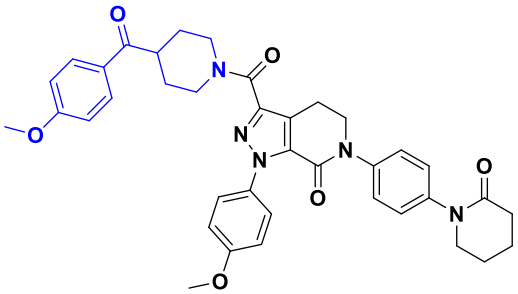
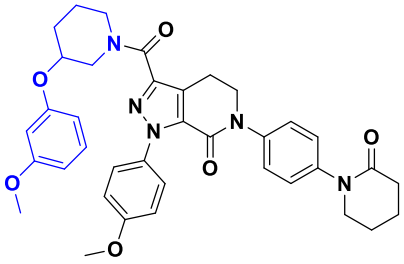
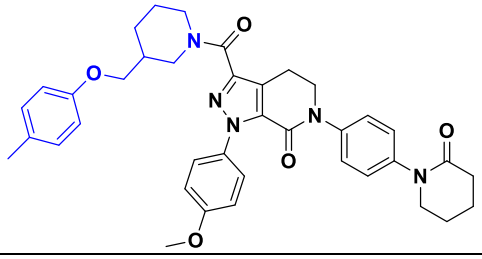
Sl. No.	Amide structure	Product	Yield (%)
1		**15a**	90
2		**15b**	86
3		**15c**	85
4		**15d**	82
5		**15e**	79

Table 1. Continued

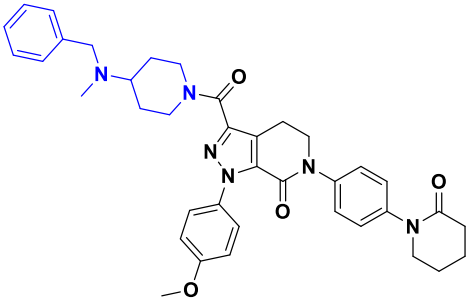
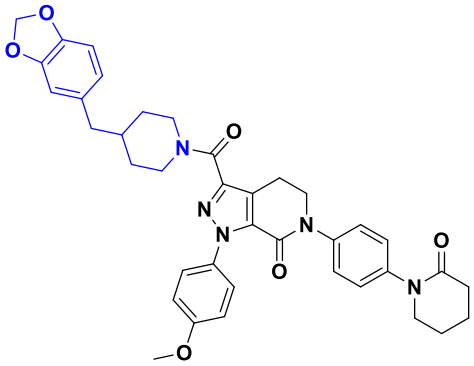
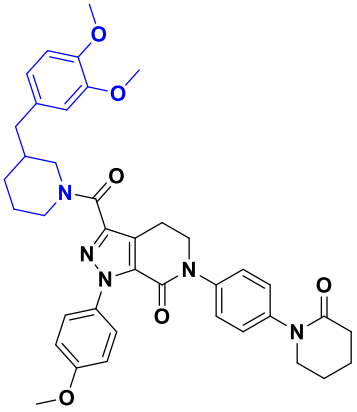
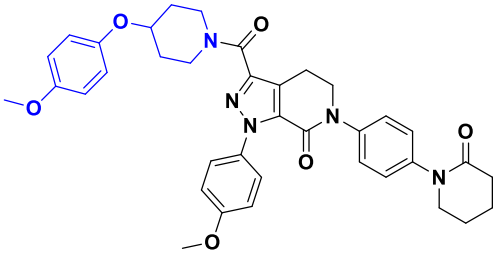
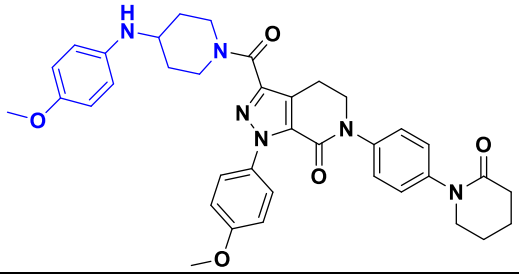
Sl. No.	Amide structure	Product	Yield (%)
6		**15f**	75
7		**15g**	78
8		**15h**	76
9		**15i**	80
10		**15j**	84

Table 1. Continued

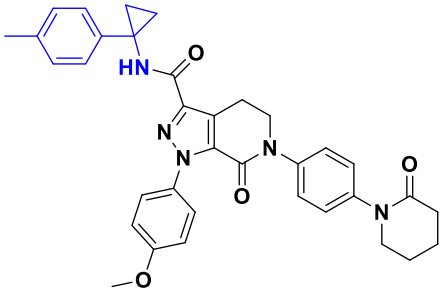
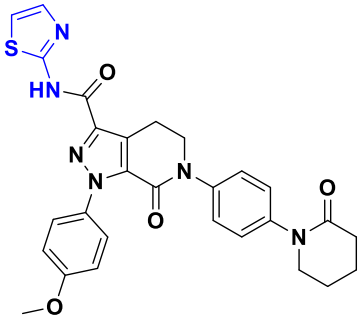
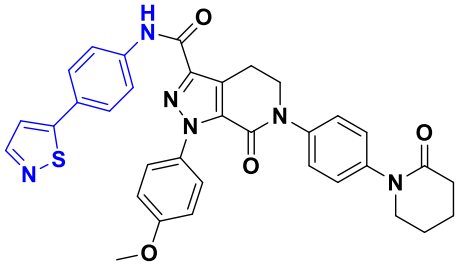
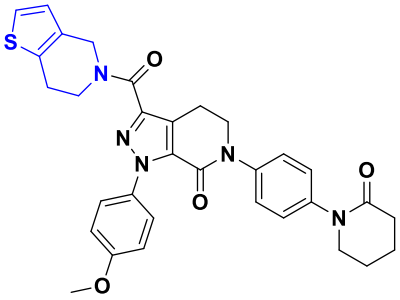
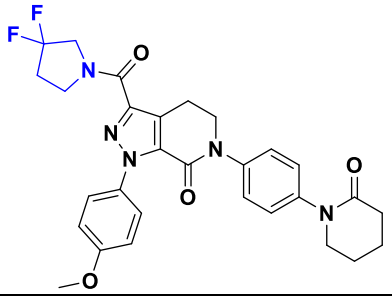
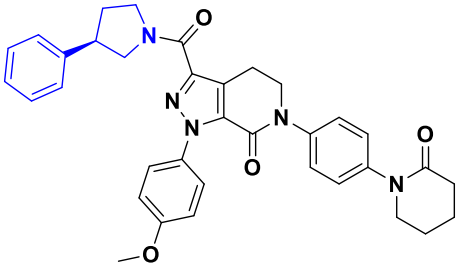
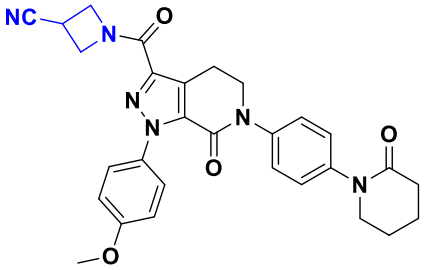
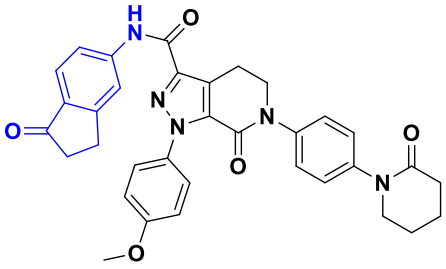
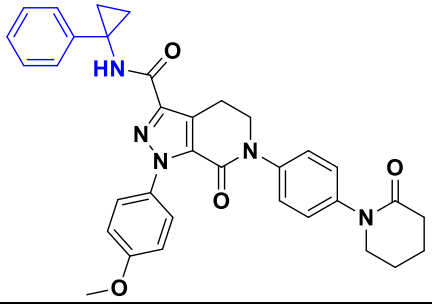
Sl. No.	Amide structure	Product	Yield (%)
11		**15k**	86
12		**15l**	88
13		**15m**	80
14		**15n**	82
15		**15o**	77

Table 1. Continued

Sl. No.	Amide structure	Product	Yield (%)
16		**15p**	81
17		**15q**	85
18		**15r**	78
19		**15s**	83

[a]Reaction conditions: **14** (1 mmol), DIPEA (3 equiv.), DMF (2 mL), rt. [b]Isolated yield

Conclusions

In summary, we have designed an alternative synthetic route to access a series of novel apixaban derivatives. The method demonstrates easily affordable multi-step procedures that involve less expensive and readily available reagents and catalyst, leading to the targeted apixaban analogues in good yields. Furthermore, the process was further investigated to prepare a number amide derivatives with different functionalities that could show interesting biological activity. In comparison to the other synthetic procedure, the present method avails a promising choice by avoiding the regeneration of the intermediates and excessive use of metal-catalysed coupling reaction.

Experimental Section

General Information.

All starting materials and commercial reagent were purchased from Alfa Aesar, Sigma Aldrich, Spectrochem, TCI. Thin Layer Chromatography plates were visualized by exposure to ultraviolet light (UV) with 254 nm of wavelength and then further analysed by using iodine chamber. Thin-layer chromatography was performed using pre-coated plates. Column chromatography was performed in 120 to 200 mesh size silica gel. The reactions were carried out in round bottom flask and sealed tube. Crude product was examined by SIMADZU GC-MS (Selected Ion Monitoring and all NMR spectra were recorded by Bruker Advanced 400 spectrometer (^{1}H at 400 MHz and ^{13}C at 100 MHz). Chemical shifts for ^{1}H NMR spectra have been reported in parts per million (ppm) from tetramethyl silane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Similarly,^{13}C NMR spectra have been reported in parts per million (ppm) from tetramethyl silane with the solvent as the internal standard ($CDCl_3$: δ 77.00 ppm). The ^{1}H NM Rand ^{13}C NMR of the known products were compared with literature reports.

Synthesis of 3,3-dichloro-1-(4-nitrophenyl) piperidin-2-one (2):[29] PCl_5 (212.5 g, 1.02 mol) was gradually added to a mixture of 1-(4-nitrophenyl) piperidin-2-one (**1**, 75 g, 0.340 mol) in toluene (225 mL) at 25-30° C. The resultant mixture was heated gently to 75-80° C. for 1 h and put in an ice bath (1 L), keeping the temperature around 10 °C. Following a one-hour stir at 0–5° C, the settled material was passed through filters by a suction device. The light-yellow substance had been dried in an air oven at 55°-60° C for 6-8 hrs, forming to yellow solid (83%, 81.7 g). ^{1}H NMR (500 MHz, DMSO) δ 8.28 (d, *J* = 8.1 Hz, 2H), 7.86 (d, *J* = 11.5 Hz, 2H), 3.8 (t, *J* = 11 Hz, 1H), 2.9 (t, *J* = 7.7 Hz, 2H), 2.16 (d, *J* = 5.5 Hz, 2H). ^{13}C NMR (500 MHz, DMSO) δ 162.89, 148.11, 145.41, 126.63, 124.23, 84.66, 50.76, 42.83, 20.34. *m/z* $(M + H)^+$ calc for $C_{11}H_{10}Cl_2N_2O_3$, 290.11; found 291.0.

Synthesis of 3-morpholino-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one (4):[29] After the drying, the product was dissolved in DMF (130 ml) and morpholine (130 ml) under refluxed conditions for 1 h. Then the reaction mixture has been cooled to 60° C, followed by addition of water to the reaction mass was completed at the same temperature. A yellow solid was obtained by filtering the resultant slurry under suction and then washing it with water. The solid was recrystallized from MeOH to get the required off-white solid. Yield: 85.73 g, 83.0%; MP 158-160° C. ^{1}H NMR (500 MHz, DMSO) δ 8.23 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 9.0 Hz, 2H), 5.811 (t, *J* = 8.5, 1H), 3.83 (t, *J* = 12.5 Hz, 2H), 3.64 (t, *J* = 11 Hz, 4H), 2.78 (t, *J* = 11 Hz, 4H), 2.49 (t, *J* = 12.5 Hz, 2H). ^{13}C NMR (500 MHz, DMSO) δ 160.59, 148.72, 143.74, 142.43, 125.18, 123.77, 116.38, 65.91, 49.98, 47.87, 22.70. *m/z* $(M + H)^+$ calc for $C_{15}H_{17}N_3O_4^+$ 304.32; found 304.4.

Synthesis of 1-(4-aminophenyl)-3-morpholino-5,6-dihydropyridin-2(1H)-one (5):[28] At about 60–65° C, hydrazine hydrate 80% (60 gm, 1.19 mol) was mixed drop by drop to the solution containing 3-morpholino-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one (50 gm, 0.16 mol), Raney nickel (1 gm, 2%) in EtOH (750 ml) with water (150 ml). After the addition is completed, stir for 30 minutes at the same temperature before cooling to room temperature. Thereafter, the reaction mass mixture was filtered through celite bed, followed by concentrating under vacuum and addition of EtOAc (100 ml). The resulting mass was then filtered off using a suction and dried in air oven to obtain the desired product as a cream coloured solid. Yield: 43 g; 95.55%. ^{1}H NMR (500 MHz, DMSO) δ 6.91 (d, *J* = 8.5 Hz, 2H), 6.53 (d, *J* = 8.5 Hz, 2H), 5.61 (s, 1H), 5.04 (bs, 2H), 3.63 (bs, 4H), 3.56 (bs, 2H), 2.78 (bs, 4H), 2.37 (bs, 2H). ^{13}C NMR (500 MHz, DMSO) δ 160.58, 146.70, 143.09, 131.94, 126.35, 126.35, 113.72, 113.51, 113.51, 65.94, 65.94, 49.90, 49.90, 48.91, 22.90. *m/z* $(M + H)^+$ calc for $C_{15}H_{19}N_3O_2^+$, 274.34; found 274.1.

Synthesis of 5-chloro-N-(4-(5-morpholino-6-oxo-3,6-dihydropyridin-1(2H)-yl) phenyl) pentanamide (7):[28] A dichloromethane (100 ml) solution of 5-chlorovaleroyl chloride (CVC, 82 gm, 0.5273 mol) was added to the suspension of 1-(4-aminophenyl)-3-morpholino-5,6-dihydropyridin-2(1H)-one (125 gm, 0.4573 mol), sodium hydroxide (22 gm, 0.55 mol), TBAB (3.75 gm) in CH_2Cl_2 (1150 ml) and water (49 ml) at 0-5 °C and stirred for 1 hrs. the mixture was slowly heated between 25 and 30° C, followed by 300 ml addition of water to the reaction mass and continued stirring for 10 min. After that, the organic layer was taken off and water (200 ml) was used to wash it, followed by drying over anhydrous sodium sulphate, and distilled at 50° C in an ambient condition to produce a residue. Then, the residue was purified by washing with EtOAc to afford pale yellow solid. Yield: 172 g, 96.08%. ^{1}H NMR (500 MHz, DMSO) δ 9.96 (bs, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 5.68 (s, 1H), 3.64-3.67 (m, 8H), 2.78 (bs, 4H), 2.41 (q, 4H), 2.34 (t, *J* = 12 Hz, 2H), 1.70-1.76 (m, 4H). ^{13}C NMR (500 MHz, DMSO) δ 170.80, 160.57, 142.87, 138.05, 136.79, 125.77, 125.77, 119.04, 119.04, 114.55, 65.95, 65.95, 49.96, 49.96, 48.47, 45.11, 35.39, 31.56, 22.87, 22.46. *m/z* (M + H)$^+$ calc for $C_{20}H_{26}ClN_3O_3^+$, 392.90; found 392.3.

Synthesis of 3-morpholino-1-(4-(2-oxopiperidin-1-yl)phenyl)-5,6-dihydropyridin-2(1H)-one (8):[28] A solution of 5-chlorovaleroyl chloride (CVC, 82 gm, 0.5273 mol) in CH_2Cl_2 (100 ml) was mixed to the suspension of product **7** (125 gm, 0.4573 mol) with sodium hydroxide (22 gm, 0.55 mol), TBAB (3.75 gm) dissolved in MDC (1150 ml) and water (49 ml) at 0-5° C and treated over 1 hr. After that, the resulting mixture was gently brought to room temp. and then the aq. solution of KOH (187 gm, 3.33 mol in 311 ml water) was poured slowly in 10-15 min and stirred for 8-10 hrs at same temperature. In subsequent, water (300 ml) was mixed to the reaction mass and continued stirring for 10 min. Then after, the organic layer was removed, and washed carefully with water (300 ml), followed by distillation 50° C generating a solid product. Next, the solid was recrystallized from EtOAc to produce the required solid, which had a buff colour. Yield: 153 gm, 94.27% Purity: 98+%; MP 204-206° C. ^{1}H NMR (500 MHz, DMSO) δ 7.32 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 5.71 (s, 1H), 3.71 (t, *J* = 12 Hz, 2H), 3.64 (bs, 4H), 3.59 (t, *J* = 12 Hz, 2H), 2.79 (bs, 4H), 2.43 (q, 2H), 2.38 (t, *J* = 12 Hz, 2H), 1.85 (m, 4H). ^{13}C NMR (500 MHz, DMSO) δ 168.85, 160.58, 142.82, 140.95, 140.77, 126.29, 126.29, 125.66, 125.66, 114.83, 65.95, 65.95, 50.85, 49.96, 49.96, 48.38, 32.57, 23.00, 22.87, 20.91. *m/z* (M + H)$^+$ calc for $C_{20}H_{25}N_3O_3^+$, 356.44; found 356.4.

Synthesis of ethyl (Z)-2-chloro-2-(2-(4-methoxyphenyl) hydrazono) acetate (11):[28] In this case, hydrochloric acid (35-36%, 60 ml, 0.6 mol) was firstly added to a solution of 4-methoxyaniline (24.6 g, 0.2 mol) in water (120 ml) at around -5 to 0 ℃ temperature. Then an aqueous (80 ml) solution of sodium nitrite (16.6 g, 0.24 mol) was poured to the mixture drop wise under low temperature, 0 ℃. Then, the reaction mixture was stirred for 30 min at 0℃., followed by the addition of sodium acetate (32.8 g, 0.40 mol) until pH 5-6. After that, a dropwise addition of ethyl 2-chloroacetoacetate (28 mL, 32.8 g, 0.2 mol) in MeOH (300 mL) took place with the temperature kept between 25 and 30 °C for four to six hours. It was then concentrated in vacuum at low pressure, and the resulting residue was dissolved in 200 ml of EtOAc and 100 mL of water, along with the organic layer was separated. In next, the aqueous phase was washed with water (2 x 100 ml) and brine (2 x 100 ml), dried over anhydrous sodium sulphate, filtered, and concentrated till residual stage. The pure product appeared as a pale yellow solid after the substance was recrystallized from EtOAc. Yield: 77%, 39.4 g. ^{1}H NMR (500 MHz, DMSO) δ 10.42 (bs, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 4.28 (q, 2H), 3.72 (s, 3H), 1.36-1.27 (t, *J* = 12 Hz, 3H). ^{13}C NMR (500 MHz, DMSO) δ 159.44, 155.64, 155.64, 136.27, 115.83, 114.50, 114.50, 112.22, 61.94, 55.22, 14.09. *m/z* (M + H)$^+$ calc for $C_{11}H_{13}ClN_2O_3^+$, 256.9; found 256.9.

Synthesis of ethyl 1-(4-methoxyphenyl)-7a-morpholino-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-3a,4,5,6,7,7a-hexahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (12):[33] 3-morpholino-1-(4-(2-oxopiperidin-1-yl)phenyl)-5,6-dihydropyridin-2(1H)-one (14.2 g, 0.04 mol), TEA (17 mL, 0.12 mol), and KI (0.64 g, 0.004

mol) were added to a solution of ethyl (Z)-2-chloro-2-(2-(4-methoxyphenyl) hydrazono) acetate (11.3 g, 0.044 mol) in MDC (80 mL) at room temperature. The mixture was stirred for 12-15 hrs at 42-45° C, the process was monitored by TLC. After performing the TLC, reaction mass directly taken for next step.
Brown oil, ^{1}H NMR (500 MHz, DMSO) δ 7.57 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.89-6.85 (m, 4H), 4.30-4.20 (m, 2H), 4.01 (d, 2H), 3.72 (s, 1H), 3.67-3.60 (m, 4H), 3.55-3.40 (m, 4H), 2.52-2.40 (m, 4H), 2.35 (t, *J* = 12 Hz, 2H), 2.23-2.12(m, 2H), 1.84-1.77 (m, 4H), 1.31-1.28 (t, *J* = 12 Hz 3H). ^{13}C NMR (500 MHz, DMSO) δ 168.82, 162.01, 161.18, 155.84, 141.63, 140.67, 137.77, 134.39, 126.53, 126.53, 125.75, 125.75, 120.81, 120.81, 113.59, 113.59, 89.14, 65.96, 65.96, 60.66, 55.72, 50.20, 46.79, 44.57, 44.57, 42.35, 32.52, 26.13, 22.93, 20.83, 14.18. *m/z* (M + H)$^+$ calc for $C_{31}H_{37}N_5O_6^+$, 576.67; found 576.4.

Synthesis of ethyl 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (13):[28] After getting reaction mass from **12** in hand, which is then directly introduced into a dry round bottom flask and cooled to around 0 °C. In the next step, 4.0N hydrochloric acid (50 mL, 0.02 mol) was added drop wise to the resulting mixture and stirred at room temperature for 2-4 hrs. Thereafter, the mixture was diluted with water (100 mL) to separate the organic layer. Meanwhile, the aqueous layer was extracted by using CH_2Cl_2 (50 mL). Subsequently, the mixture of organic extracts underwent brine (2x100 mL) washes before being dried off. After the recrystallization from EtOAc and the residue was vacuum-dried, a cream-colored solid was the result. Yield: 16.58 g, 85.00%. Purity: 99.5+%**.** ^{1}H NMR (500 MHz, DMSO) δ 7.50 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 9 Hz, 2H), 7.01 (d, *J* = 9 Hz, 2H), 4.35 (q, 2H), 4.10 (t, 2H), 3.81 (s, 3H), 3.60 (t, *J* = 11 Hz, 2H), 3.21 (t, *J* = 11 Hz, 2H), 2.41 (t, *J* = 12 Hz, 2H), 1.88-1.83 (m, 4H), 1.35-1.32 (t, *J* = 12 Hz 3H). ^{13}C NMR (500 MHz, DMSO) δ 162.50, 159.66, 156.94, 141.86, 140.19, 139.74, 133.34, 132.98, 127.27, 127.14, 127.14, 126.81, 126.81, 126.46, 126.46, 113.89, 113.89, 60.66, 55.92, 51.29, 51.21, 33.05, 23.45, 21.59, 21.36, 14.45. *m/z* (M + H)$^+$ calc for $C_{27}H_{28}N_4O_5^+$, 489.54; found 489.3.

Synthesis of 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid (14):[30] 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid (10.0 g, 1 mol), taken into 50 ml water and 50 ml THF. To that added 2.2 g NaOH, dissolved in 10 ml water drop wise over 10 min. After completion of reaction in 4 h, THF distilled under vacuum. Added 100 ml EtOAc into aqueous reaction mass and added 50 mL water. Extracted and layer separated. The aqueous layer acidified with 10 ml 1 N HCl. Obtained precipitate were filtered and dried under vacuum at 50-55° C for 8 h. Yield: 7.8 g, 88%. Purity: 96%. ^{1}H NMR (500 MHz, DMSO) δ 13.18 (b hump, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 9 Hz, 2H), 7.00 (d, *J* = 9 Hz, 2H), 4.06 (t, 2H), 3.80 (s, 3H), 3.58 (t, *J* = 11 Hz, 2H), 3.19 (t, *J* = 11 Hz, 2H), 2.38 (t, *J* = 12 Hz, 2H), 1.84(m, 4H), ^{13}C NMR (500 MHz, DMSO) δ 162.50, 159.66, 156.94, 141.86, 140.19, 139.74, 133.34, 132.98, 127.27, 127.14, 127.14, 126.81, 126.81, 126.46, 126.46, 113.89, 113.89, 55.92, 51.29, 51.21, 33.05, 23.45, 21.67, 21.36. *m/z* (M + H)$^+$ calc for $C_{25}H_{24}N_4O_5^+$, 461.49; found 461.4.

Synthesis of amide derivatives (15): 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl) phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c] pyridine-3-carboxylic acid (**14**, 0.25 mol) was taken into 1-2 ml DMF. RM cooled to 10-15 ℃ and to that added substituted amine (1.1 eq., 0.47 mol) (series of amine from 1 to 19), DIPEA (0.22 ml, 3.0 eq., 1.2 mol). Mixture stirred at 25-30℃ for 3 h. On completion of reaction, mixture was diluted with 10 ml water, stirred for 2 h. Precipitate filtered and dried under vacuum at 50-55℃ for 8 h. Dried material recrystallized in DMF + Water (1:5 volume ratio) afford desired material in pure form. (Yield: 75-90%, Purity: 95-98%)

3-(4-(3-isocyanophenoxy)piperidine-1-carbonyl)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one(15a): Creamy solid (145 mg, MP: 176°C) ^{1}H NMR (500

MHz, CDCl3) δ 7.48 (d, *J* = 10 Hz, 2H), 7.41 (t, *J* = 20 Hz, 1H), 7.36 (d, *J* = 5 Hz, 2H), 7.29 (dd, *J* = 10 Hz, 3H), 7.19 (d, *J* = 10 Hz, 2H), 6.94 (d, *J* = 10 Hz, 2H), 4.68 (m, 1H), 4.28 (d, *J* = 5 Hz, 1H), 4.15 (t, *J* = 15 Hz, 3H), 3.98 (t, *J* = 11 Hz, 1H), 3.89 (t, *J* = 11 Hz, 1H), 3.83 (s, 3H), 3.62 (t, *J* = 7.7 Hz, 2H), 3.31 (m, 2H), 2.57 (m, 2H), 2.10 (m, 2H), 1.96 (m, 4H), 1.66 (m, 2H) ^{13}C NMR (500 MHz, CDCl3) δ 170.12, 161.87, 159.66, 157.41, 157.29, 142.01, 141.36, 140.00, 132.65, 132.42, 130.60, 127.08, 126.77, 126.67, 126.15, 124.85, 121.09, 118.83, 118.62, 113.66, 113.44, 72.36, 55.53, 51.61, 51.12, 43.55, 39.18, 32.86, 31.16, 30.22, 23.53, 21.50, 21.43. *m/z* $(M + H)^+$ calc for $C_{37}H_{36}N_6O_5^+$, 645.73; found 645.4.

1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-3-(3-(p-tolyloxy)piperidine-1-carbonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (15b): Off white solid (136 mg, MP: 122°C) ^{1}H NMR (500 MHz, CDCl3) δ 7.50 (d, *J* = 10 Hz, 1H), 7.41 (d, *J* = 10 Hz, 2H), 7.35 (d, *J* = 5 Hz, 2H), 7.29 (dd, *J* = 10 Hz, 2H), 7.12 (d, *J* = 10 Hz, 1H), 6.94 (d, *J* = 10 Hz, 2H), 6.89 (d, *J* = 10 Hz, 1H), 6.73 (d, *J* = 10 Hz, 1H), 4.62 (m, 1H), 4.28 (d, *J* = 5 Hz, 1H), 4.15 (t, *J* = 15 Hz, 3H), 3.98 (t, *J* = 11 Hz, 1H), 3.89 (t, *J* = 11 Hz, 1H), 3.83 (s, 3H), 3.62 (t, *J* = 7.7 Hz, 2H), 3.31 (m, 2H), 2.57 (m, 2H), 2.31 (s, 3H), 2.10 (m, 2H), 1.96 (m, 4H), 1.66 (m, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 170.23, 162.53, 159.67, 157.39, 154.87, 141.97, 141.33, 140.10, 132.67, 132.30, 130.37, 130.13, 129.81, 126.95, 126.80, 126.24, 116.14, 115.47, 113.64, 72.00, 71.63, 55.61, 55.54, 51.63, 51.14, 50.89, 47.44, 46.79, 43.58, 43.01, 40.53, 32.83, 30.54, 23.49, 22.50, 21.49, 21.30, 20.52, 18.58, 17.18, 12.49. *m/z* $(M + H)^+$ calc for $C_{37}H_{39}N_5O_5^+$, 634.75; found 634.3.

3-(4-(4-methoxybenzoyl)piperidine-1-carbonyl)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (15c): Pale brown solid (140 mg, MP: 205°C) ^{1}H NMR (500 MHz, CDCl3) δ 7.98 (d, *J* = 10 Hz, 2H), 7.49 (d, *J* = 10 Hz, 2H), 7.37 (d, *J* = 5 Hz, 2H), 7.29 (dd, *J* = 10 Hz, 2H), 6.98 (d, *J* = 10 Hz, 2H), 6.94 (d, *J* = 10 Hz, 2H), 4.93 (d, *J* = 5Hz, 1H), 4.76 (d, *J* = 15Hz, 1H), 4.14 (s, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.63 (s, 2H), 3.58 (dd, *J* = 7.7 Hz, 2H), 3.29 (m, 2H), 3.11 (m, 1H), 3.01 (s, 1H), 2.57 (m, 2H), 2.04 (m, 4H), 1.68 (m, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 200.24, 170.14, 163.61, 161.86, 159.60, 157.48, 142.19, 141.33, 140.07, 132.71, 132.32, 130.71, 130.60, 128.70, 126.94, 126.76, 126.69, 126.20, 114.17, 113.96, 113,64, 55.53, 51.62, 51.15, 46.63, 43.06, 42.13, 32.85, 29.24, 28.60, 23.52, 21.48, 21.42 *m/z* $(M + H)^+$ calc for $C_{38}H_{39}N_5O_6^+$, 662.76; found 662.6.

3-(3-(3-methoxyphenoxy)piperidine-1-carbonyl)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (15d): Off white Solid (133 mg, MP: 90°C) ^{1}H NMR (500 MHz, CDCl3) δ 7.50 (d, *J* = 5 Hz, 1H), 7.38(d, *J* = 5Hz, 2H), 7.35(d, *J* = 5 Hz, 2H), 7.29 (dd, *J* = 10 Hz, 2H), 7.26 (d, *J* = 10 Hz, 1H), 7.21 (m,1H), 6.95 (t, *J* = 10 Hz, 1H), 6.91(d, *J* = 5 Hz, 1H), 6.84(d, *J* = 10 Hz, 1H), 6.62(m,1H), 6.55(dd, *J* = 10Hz, 1H), 6.48(d, *J* = 10Hz, 1H), 6.42(d, *J* = 10Hz, 1H), 6.36(s, 1H), 4.35 (m, 2H), 4.12 (bm, 3H), 3.71 (s, 3H), 3.62 (s, 3H), 3.63 (s, 2H), 3.58 (dd, *J* = 7.7 Hz, 2H), 3.28 (m, 2H), 3.11 (m, 1H), 3.01 (s, 1H), 2.57 (m, 2H), 1.68 (m, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 170.19, 163.19, 162.69, 160.93, 158.54, 157.33, 141.88, 141.29, 140.12, 132.60, 132.22, 132.60, 132.22, 130.41, 130.06, 129.84, 126.94, 126.67, 126.19, 113.65, 113.58, 107.32, 106.42, 102.42, 71.44, 55.54, 55.22, 51.63, 51.01, 50.57, 43.07, 32.84, 30.32, 23.50, 21.29, 21.40, 21.28. *m/z* $(M + H)^+$ calc for $C_{37}H_{39}N_5O_6^+$, 650.75; found 650.5.

1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-3-(3-((p-tolyloxy)methyl)piperidine-1-carbonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (15e): Creamy solid (127 mg, MP: 152°C) ^{1}H NMR (500 MHz, CDCl3) δ 7.54 (d, *J* = 5 Hz, 2H), 7.49 (d, *J* = 10 Hz, 1H), 7.36(t, *J* = 5Hz, 3H), 7.28(t, *J* = 5 Hz, 4H), 7.10 (d, *J* = 10 Hz, 1H), 7.54(d, *J* = 5 Hz, 1H), 6.95-6.91 (m,3H), 6.84 (d, *J* = 10 Hz, 1H), 6.68(d, *J* = 10 Hz, 2H), 4.75 (dd, *J* = 15 Hz, 2H), 4.15 (d, *J* = 5 Hz, 3H), 3.95 (m, 2H), 3.83 (s, 3H), 3.45(m, 1 H), 3.28 (m, 2H), 3.15 (m, 1H), 2.58 (s, 3H), 2.29 (m, 2H), 2.23 (m, 1H), 1.92 (m, 2H), 1.86 (m, 2H), 1.53 (m, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 170.16, 162.24,159.60, 159.55, 157.47, 156.69, 142.42, 142.16, 141.28, 140.12, 132.78, 132.14, 130.01, 129.89, 126.75, 126.68, 126.18, 114.43, 114.18, 113.65, 70.26, 69.55, 55.52, 51.63, 51.01, 50.41, 47.94, 45.83, 43.40,

36.68, 32.85, 27.31, 25.65, 24.09, 23.51, 21.41, 21.25, 20.49. *m/z* (M + H)$^+$ calc for $C_{38}H_{41}N_5O_5^+$, 648.78; found 649.2.

3-(4-(benzyl(methyl)amino)piperidine-1-carbonyl)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (15f): Creamy solid (121 mg, MP: 158°C) ^{1}H NMR (500 MHz, CDCl3) δ 7.49 (d, *J* = 10 Hz, 2H), 7.35 (bm, 5H), 7.27(bm, 4H), 6.95(d, *J* = 5 Hz, 2H), 4.97 (d, *J* = 15 Hz, 1H), 4.82 (d, *J* = 10 Hz, 1H), 4.13 (m, 3H), 3.83 (s, 3H), 3.68(bs, 2H), 3.62(bs, 2H), 3.28 (t, *J* = 10 Hz, 2H), 3.17(m, 1H), 2.85-2.77(m, 2H), 2.56 (t, *J* = 10 Hz, 2H), 2.26 (s, 3H), 1.96 (m, 5H), 1.71-1.67(m, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 170.22, 161.77, 159.65, 157.49, 142.22, 141.32, 140.11, 132.70, 132.31, 131.65, 128.95, 127.34, 126.85, 126.80, 126.75, 113.66, 77.29, 77.04, 76.79, 60.65, 57.77, 55.54, 51.64, 51.14, 46.49, 42.07, 37.50, 32.83, 28.79, 27.61, 23.49, 21.45, 21.39. *m/z* (M + H)$^+$ calc for $C_{38}H_{42}N_6O_4^+$, 647.79; found 647.6.

3-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperidine-1-carbonyl)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (15g): off white solid (128 mg, MP: 168°C) ^{1}H NMR (500 MHz, CDCl3) δ 7.48 (d, *J* = 5 Hz, 2H), 7.36 (d, *J* = 10 Hz, 2H), 7.29(d, *J* = 5 Hz, 1H), 7.27 (d, *J* = 10 Hz, 2H), 6.94(d, *J* = 10 Hz, 2H), 6.77(d, *J* = 10 Hz, 1H), 6.67(s, 1H), 6.61(d, *J* = 10 Hz, 1H), 5.95(s,1H), 4.83 (d, *J* = 10 Hz, 1H), 4.75 (d, *J* = 15 Hz, 1H), 4.13 (t, *J* = 10 Hz, 2H), 3.84 (s, 3H), 3.62(bs, 2H), 3.29(bs, 2H), 3.24 (m, 1H), 2.76(t, *J* = 15 Hz, 1H), 2.58 (d, *J* = 10 Hz, 2H), 2.51 (d, *J* = 10 Hz, 2H), 1.95 (bs, 2H), 1.81 (d, *J* = 5 Hz, 2H), 1.71(d, *J* = 5 Hz , 2H), 1.66(bs,1H), 1.32 (m, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 170.12, 161.81, 159.59, 157.49, 147.55, 145.78, 142.43, 141.31, 140.06, 133.84, 132.71, 132.26, 126.74, 126.71, 126.64, 126.17, 121.90, 113.64, 109.37, 108.07, 100.82, 77.29, 77.04, 76.78, 55.53, 51.62, 51.14, 47.42, 42.84, 42.67, 38.55, 32.86, 32.80, 31.86, 23.53, 21.43. *m/z* (M + H)$^+$ calc for $C_{38}H_{39}N_5O_6^+$, 662.76; found 662.7.

3-(3-(3,4-dimethoxybenzyl)piperidine-1-carbonyl)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (15h): Pale brown solid (128 mg, MP: 112°C) ^{1}H NMR (500 MHz, CDCl3) δ 7.48 (d, *J* = 5 Hz, 1H), 7.36 (dd, *J* = 10 Hz, 3H), 7.29(t, *J* = 10 Hz, 1H), 7.27 (d, *J* = 5 Hz, 1H), 6.93(d, *J* = 10 Hz, 2H), 6.83(d, *J* = 10 Hz, 1H), 6.74(bs, 1H), 6.64(bs, 1H), 4.68 (d, *J* = 10 Hz, 1H), 4.61 (m, 1H), 4.14-4.10 (m, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.62(bs, 2H), 3.24(m, 2H), 2.9(m, 2H), 2.70(m,1H), 2.57 (bs, 2H), 2.51 (bs, 1H), 1.95 (bs, 4H), 1.76 (bs, 2H), 1.58(m, 1H), 1.36(m,1H), 1.29 (m, 1H). ^{13}C NMR (500 MHz, CDCl3) δ 170.21, 162.01, 161.88, 159.58, 157.53, 148.82, 147.37, 142.48, 142.31, 141.32, 140.11, 132.72, 132.63, 132.18, 132.13, 132.07, 126.80, 126.70, 126.57, 126.24, 121.08, 120.73, 113.62, 113.58, 112.25, 111.13, 110.97, 77.32, 77.06, 76.81, 55.88, 55.79, 55.52, 55.44, 52.99, 51.63, 51.12, 48.46, 48.02, 43.41, 39.99, 39.79, 38.63, 38.05, 32.83, 31.16, 30.66, 26.07, 24.88, 23.49, 21.40. *m/z* (M + H)$^+$ calc for $C_{39}H_{43}N_5O_6^+$, 678.80; found 678.3.

1-(4-methoxyphenyl)-3-(4-((4-methoxyphenyl)amino)piperidine-1-carbonyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (15i): Off white solid (129 mg, MP: 170°C) ^{1}H NMR (500 MHz, CDCl3) δ 7.48 (d, *J* = 5 Hz, 2H), 7.36 (d, *J* = 10 Hz, 2H), 7.28(dd, *J* = 10 Hz, 2H), 6.94 (d, *J* = 10 Hz, 2H), 6.82(d, *J* = 5 Hz, 2H), 6.67(d, *J* = 5 Hz, 2H), 4.82 (d, *J* = 15 Hz, 1H), 4.66 (d, *J* = 15 Hz, 1H), 4.14(d, *J* = 5 Hz, 2H), 3.83 (s, 3H), 3.78 (s, 3H), 3.62(bs, 2H), 3.49(bs, 1H), 3.36(m, 1H), 3.28 (bs, 2H), 3.03 (bs, 1H), 2.57 (m, 2H), 2.16 (t, *J* = 10 Hz, 2H), 1.96(m, 4H), 1.49-1.42 (m, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 170.21, 164.92, 161.88, 159.67, 142.16, 141.42, 140.13, 132.71, 132.30, 126.95, 126.86, 126.79, 126.45, 115.03, 113.66, 55.80, 55.55, 51.62, 51.08, 45.92, 41.49, 36.24, 32.78, 23.45, 21.40, 21.35. *m/z* (M + H)$^+$ calc for $C_{37}H_{40}N_6O_5^+$, 649.76; found 649.5.

3-(4-(4-methoxyphenoxy)piperidine-1-carbonyl)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (15j): White solid (136 mg, MP: 188°C) ^{1}H NMR (500 MHz, CDCl3) δ 7.48 (d, *J* = 5 Hz, 2H), 7.36 (d, *J* = 10 Hz, 2H), 7.28(dd, *J* = 10 Hz, 2H), 6.94 (d, *J* = 5 Hz, 2H), 6.91(d, *J* = 10 Hz, 2H), 6.84(d, *J* = 10 Hz, 2H), 4.50 (bs, 1H), 4.28 (m, 1H), 4.25(t, *J* = 10 Hz, 2H), 4.05(m, 1H), 3.98 (m, 1H),

3.83 (s, 3H), 3.79 (s, 3H), 3.62(bs, 2H), 3.28(m, 2H), 2.58(d, *J* = 5 Hz, 2H), 2.04(m,1H), 1.95 (m, 4H), 1.73 (bs, 2H), 1.8(bs, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 170.23, 161.91, 159.62, 157.46, 154.32, 150.99, 142.16, 141.30, 140.06, 132.67, 132.34, 130.66, 126.89, 126.76, 126.67, 126.18, 117.89, 114.76, 113.65, 77.29, 77.04, 76.79, 72.91, 55.72, 55.53, 51.63, 51.15, 50.86, 43.76, 39.34, 32.81, 31.48, 30.48, 23.50, 21.45, 21.40. *m/z* (M + H)$^+$ calc for $C_{37}H_{39}N_5O_6^+$, 650.75; found 650.5.

1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-N-(1-(p-tolyl)cyclopropyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (15k): Off white solid (126 mg, MP: 115°C) ^{1}H NMR (400 MHz, DMSO) δ 9.10 (s, 1H), 7.56 (t, *J* = 8Hz, 2H), 7.38(t, *J* = 8Hz, 2H), 7.34 (t, *J* = 8 Hz, 2H), 7.18 (dd, *J* = 8 Hz, 2H), 7.12(dd, *J* = 8 Hz, 2H), 7.03(d, *J* = 8 Hz, 2H), 4.06 (t, *J* = 12Hz, 2H), 3.84(s, 3H), 3.64 (bs, 2H), 3.15 (t, *J* = 8 Hz, 2H), 2.38 (t, *J* = 8 Hz, 2H), 2.25 (s, 3H), 1.85 (t, *J* = 8 Hz, 4H), 1.36(t, *J* = 8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 168.83, 161.71, 141.39, 141.36, 140.42, 139.76, 132.54, 128.52, 126.30, 125.15, 125.09, 113.36, 55.48, 53.60, 50.81, 33.78, 32.59, 22.99, 20.94, 20.89, 20.51, 17.53, 16.73. *m/z* (M + H)$^+$ calc for $C_{35}H_{35}N_5O_4^+$, 590.70; found 590.3.

1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-N-(thiazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (15l): White solid (119 mg, MP: 270°C) ^{1}H NMR (400 MHz, DMSO) δ 7.65(d, *J* = 8Hz, 2H), 7.57 (d, *J* = 8 Hz, 1H), 7.38(d, *J* = 8Hz, 2H), 7.30(d, *J* = 8 Hz, 3H), 7.03(d, *J* = 8 Hz, 2H), 4.11(t, *J* = 12 Hz, 2H), 3.82(s, 3H), 3.61 (t, *J* = 12 Hz, 2H), 3.39(t, *J* = 8 Hz, 2H), 2.39(t, *J* = 8 Hz, 2H), 1.85(t, *J* = 8 Hz, 4H). . *m/z* (M + H) calc for $C_{28}H_{26}N_6O_4S^+$, 543.61; found 542.9.

N-(4-(isothiazol-5-yl)phenyl)-1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (15m): Creamy solid (123 mg, MP: 180°C) ^{1}H NMR (400 MHz, DMSO) δ 10.53 (s, 1H), 8.59(d, *J* = 8Hz, 1H), 8.00 (d, *J* = 8 Hz, 2H), 7.76(d, *J* = 8Hz, 2H), 7.59(d, *J* = 8 Hz, 3H), 7.38(d, *J* = 8 Hz, 2H), 7.30(d, *J* = 8 Hz, 2H), 7.04(d, *J* = 8 Hz, 2H), 4.11(bs, 2H), 3.83(s, 3H), 3.61 (t, *J* = 12 Hz, 2H), 3.30(t, *J* = 8 Hz, 2H), 2.40(t, *J* = 8 Hz, 2H), 1.87(t, *J* = 8 Hz, 4H). *m/z* (M + H)$^+$ calc for $C_{34}H_{30}N_6O_4S^+$, 619.71; found 619.4.

1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridine-5-carbonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (15n): Pale brown solid (119 mg, MP: 155°C) ^{1}H NMR (400 MHz, DMSO) δ 7.55(d, *J* = 12 Hz, 2H), 7.38 (d, *J* = 8 Hz, 2H), 7.36(d, *J* = 8Hz, 2H), 7.35(d, *J* = 12 Hz, 1H), 7.01(d, *J* = 8 Hz, 2H), 6.98(d, *J* = 8 Hz, 1H), 4.18(d, *J* = 8 Hz, 1H), 4.08(bs, 2H), 4.06 (d, *J* = 12Hz, 2H), 3.81 (s, 3H), 3.36-3.58 (dd, 2H), 3.13(t, *J* = 8 Hz, 2H), 2.94(t, *J* = 12 Hz, 3H), 2.83(m, 1H), 2.51(d, *J* = 8 Hz, 2H), 1.85 (t, *J* = 4Hz, 4H). ^{13}C NMR (100 MHz, DMSO) δ 169.32, 162.20, 159.56, 157.05, 141.27, 140.27, 133.01, 132.56, 127.21, 127.09, 126.81, 126.50, 125.92, 124.27, 113.94, 55.94, 51.30, 45.10, 43.18, 33.07, 26.07, 21.32. *m/z* (M + H)$^+$ calc for $C_{32}H_{31}N_5O_4S^+$, 582.69; found 582.2.

3-(3,3-difluoropyrrolidine-1-carbonyl)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (15o): Brown solid (105 mg, MP: 215°C) ^{1}H NMR (400 MHz, DMSO) δ 7.56 (t, *J* = 8Hz, 2H), 7.42(t, *J* = 8Hz, 2H), 7.38 (dd, *J* = 8 Hz, 2H), 7.03(d, *J* = 8 Hz, 2H), 4.38 (t, *J* = 12Hz, 1H), 4.19 (t, *J* = 8 Hz, 1H), 4.08 (t, *J* = 12 Hz, 2H), 3.95 (m, 1H), 3.78 (dd, *J* = 8 Hz, 4H), 3.61 (t, *J* = 8 Hz, 2H), 3.21 (t, *J* = 12Hz, 2H), 2.35 (t, *J* = 8 Hz, 2H), 1.84 (t, *J* = 8 Hz, 4H). *m/z* (M + H)$^+$ calc for $C_{29}H_{29}F_2N_5O_4^+$, 550.58; found 550.3.

(R)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-3-(3-phenylpyrrolidine-1-carbonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one(15p) : White solid (118 mg, MP: 190°C) ^{1}H NMR (400 MHz, DMSO) δ 7.56 (t, *J* = 8Hz, 2H), 7.42(t, *J* = 8Hz, 2H), 7.38 (dd, *J* = 8 Hz, 3H), 7.33(d, *J* = 8Hz, 2H), 7.31(d, *J* = 8 Hz, 2H), 7.03(d, *J* = 8 Hz, 2H), 4.41-4.23(m, 1H), 4.08 (t, *J* = 8 Hz, 2H), 3.81(s, 3H), 3.61 (t, *J* = 12 Hz, 2H), 3.42(t, *J* = 8 Hz, 2H), 3.21(t, *J* = 8 Hz, 2H), 2.38(t, *J* = 8 Hz, 2H), 2.33(m, 1H), 2.15(m, 1H), 1.85(bs, 4H). ^{13}C NMR (100 MHz,

DMSO) δ 168.83, 142.32, 141.37, 128.53, 128.51, 127.24, 127.12, 126.32, 126.00, 113.46, 55.41, 50.81, 46.43, 44.21, 41.41, 32.58, 22.99, 2.27, 20.89. *m/z* (M + H)$^+$ calc for $C_{35}H_{35}N_5O_4^+$, 590.70; found 590.2.

1-(1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carbonyl)azetidine-3-carbonitrile (15q) : Pale brown solid (111 mg, MP: 162°C) ^{1}H NMR (400 MHz, DMSO) δ 8.81 (t, *J* = 12 Hz, 1H), 7.52 (d, *J* = 8 Hz, 2H), 7.36(d, *J* = 12 Hz, 2H), 7.28(d, *J* = 8 Hz, 2H), 7.01(d, *J* = 8 Hz, 2H), 4.08(d, *J* = 8 Hz, 2H), 3.81 (s, 3H), 3.36-3.58 (m, 5H), 3.23(d, *J* = 8 Hz, 2H), 2.86(m, 1H), 2.40(d, *J* = 8 Hz, 2H), 1.86 (t, *J* = 4Hz, 4H). *m/z* (M + H)$^+$ calc for $C_{29}H_{28}N_6O_4$+, 525.58; found 525.4.

1-(4-methoxyphenyl)-7-oxo-N-(1-oxo-2,3-dihydro-1H-inden-5-yl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (15r) : Pale brown solid (114 mg, MP: 203°C) ^{1}H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.19 (s, 1H), 7.85(d, *J* = 8Hz, 1H), 7.61 (dd, *J* = 8 Hz, 3H), 7.38(d, *J* = 8Hz, 2H), 7.33(d, *J* = 8 Hz, 3H), 7.03(d, *J* = 8 Hz, 2H), 4.11(t, *J* = 12 Hz, 2H), 3.82(s, 3H), 3.61 (t, *J* = 12 Hz, 2H), 3.33(t, *J* = 8 Hz, 2H), 3.15(t, *J* = 8 Hz, 2H), 2.62(t, *J* = 8 Hz, 2H). 2.42(t, *J* = 8 Hz, 2H), 1.85(bs, 2H), 1.24(bs, 1H), 1.12(t, *J* = 8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 204.77, 168.84, 160.38, 159.32, 156.52, 156.44, 144.37, 141.43, 133.39, 132.42, 132.09, 127.02, 126.32, 126.00, 125.95, 123.60, 119.49, 116.96, 113.42, 55.51, 50.81, 36.00, 32.58, 25.49, 22.99, 15.15. *m/z* (M + H)$^+$ calc for $C_{34}H_{31}N_5O_5^+$, 590.65; found 590.3.

1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-N-(1-phenylcyclopropyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (15s) : White solid (119 mg, MP: 108°C) ^{1}H NMR (400 MHz, DMSO) δ 8.19 (d, *J* = 8Hz, 1H), 7.85(d, *J* = 8Hz, 1H), 7.61 (dd, *J* = 8 Hz, 3H), 7.38(d, *J* = 8Hz, 2H), 7.33(d, *J* = 8 Hz, 3H), 7.03(d, *J* = 8 Hz, 2H), 4.11(t, *J* = 12 Hz, 2H), 3.82(s, 3H), 3.61 (t, *J* = 12 Hz, 2H), 3.33(t, *J* = 8 Hz, 2H), 3.15(t, *J* = 8 Hz, 2H), 2.62(t, *J* = 8 Hz, 2H). 2.42(t, *J* = 8 Hz, 2H), 1.85(bs, 3H), 1.24(bs, 1H), 1.12(t, *J* = 8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 168.84, 161.80, 159.18, 143.45, 141.36, 133.03, 132.55, 128.38, 127.99, 126.95, 126.35, 125.97, 125.60, 124.97, 124.09, 113.37, 55.48, 50.90, 50.82, 33.95, 32.59, 22.99, 20.89, 19.10, 17.94. *m/z* (M + H)$^+$ calc for $C_{34}H_{33}N_5O_4^+$, 576.76; found 576.5.

Acknowledgements

Rambabu Dandela thanks DST-SERB for Ramanujan fellowship (SB/S2/RJN-075/2016), Core research grant (CRG/2018/000782) and ICT-IOC start-up grant. The authors acknowledge ICT-IOC Bhubaneswar for providing necessary support.

Supplementary Material

Copies of the ^{1}H and ^{13}C NMR spectra of all compounds are given in the supplementary material a file associated with this manuscript

References

1. Komarova, E. S.; Makarov, V. A.; Granik, V. G.; Párkányi C. *J. Heterocyclic Chem*. **2012**, *49*, 969. https://doi.org/10.1002/jhet.986
2. Dolzhenko, A.; Dolzhenko, A.; Chui, W. *Heterocycles* **2008**, *75*, 1575-1622. http://hdl.handle.net/20.500.11937/41716

3. Al-Mulla, A. *Der Pharma Chemica* **2017**, *9*, 141-147. https://www.researchgate.net/profile/Abbas-Almulla/publication/318745179_ISSN_0975-413X_CODEN_USA_PCHHAX_A_Review_Biological_Importance_of_Heterocyclic_Compounds/links/597b15e2a6fdcc61bb406e2e/ISSN-0975-413X-CODEN-USA-PCHHAX-A-Review-Biological-Importance-of-Heterocyclic-Compounds.pdf
4. Kamble, O.; Chatterjee, R.; Dandela, R.; Shinde, S. *Tetrahedron* **2022**, *120*, 132893. https://doi.org/10.1016/j.tet.2022.132893
5. Hammouda, M. M.; Gaffer, H. E.; Elattar, K. M. *RSC Med. Chem*. **2022**, *13*, 1150-1196. https://doi.org/10.1039/D2MD00192F
6. Kumar, V.; Kaur, K.; Gupta, G. K.; Sharma, A. K. *Eur. J. Med. Chem*. **2013**, *69*, 735-753. https://doi.org/10.1016/j.ejmech.2013.08.053
7. Chatterjee, R.; Bhukta, S.; Angajala, K. K.; Dandela, R. *Org. Biomol. Chem*. **2023**, *21*, 5419-5423. https://doi.org/10.1039/D3OB00625E
8. Devi Priya, D.; Nandhakumar, M.; Mohana Roopan, S. *Synth. Commun.* **2020**, *50*, 3535-3562. https://doi.org/10.1080/00397911.2020.1805468
9. Bhukta, S.; Chatterjee, R.; R. Dandela, *Synthesis* **2023**, *55*, 846-856. https://doi.org/10.1055/a-1960-0042
10. Harrison, C.; Kiladjian, J. J.; Al-Ali, H. K.; Gisslinger, H .; Waltzman, R.; Stalbovskaya, V.; McQuitty, M.; Hunter, D. S.; Levy, R.; Knoops, L.; Cervantes, F. *N. Engl. J. Med*. **2012**, *366*, 787-798. https://doi.org/10.1056/NEJMoa1110556
11. Plosker, G. L. *Drugs* **2015**, *75*, 297-308. https://doi.org/10.1007/s40265-015-0351-8
12. Roskoski Jr., R. *Pharmacol. Res.* **2022**, *183*, 106362. https://doi.org/10.1016/j.phrs.2022.106362
13. Shaw, A. T.; Yasothan, U.; Kirkpatrick. P. *Nat. Rev. Drug Discov.* **2011**, *10*, 897-898. https://doi.org/10.1038/nrd3600
14. Wu, P.; Nielsen, T. E.; Clausen, M. H. *Trends Pharmacol. Sci.* **2015**, *36*, 422-439. https://doi.org/10.1016/j.tips.2015.04.005
15. Larkins, E.; Blumenthal, G. M.; Chen, H.; He, K.; Agarwal, R.; Gieser, G.; Stephens, O.; Zahalka, E.; Ringgold, K.; Helms, W.; Shord, S. *Clin. Cancer Res*. **2016**, *22*, 5171-5176. https://doi.org/10.1158/1078-0432.CCR-16-1293
16. Stasi, R. *Expert Opin. Drug. Discov*. **2009**, *4*, 85-93. https://doi.org/10.1517/17460440802642484
17. Yoshida, H.; Yamada, H.; Nogami, W.; Dohi, K.; Kurino-Yamada, T.; Sugiyama, K.; Takahashi, K.; Gahara, Y.; Kitaura, M.; Hasegawa, M.; Oshima, I. *Exp. Hematol*. **2018**, *59*, 30-39. https://doi.org/10.1016/j.exphem.2017.12.005
18. Byon, W.; Garonzik, S.; Boyd, R. A.; Frost, C. E. *Clin. Pharmacokinet.* **2019**, *58*, 1265-1279. https://doi.org/10.1007/s40262-019-00775-z
19. Granger, C. B.; Alexander, J. H.; McMurray, J. J.; Lopes, R. D.; Hylek, E. M.; Hanna, M.; Al-Khalidi, H. R.; Ansell, J.; Atar, D.; Avezum, A.; M. C. Bahit, *N. Engl. J. Med*. **2011**, *365*, 981-992. https://doi.org/10.1056/nejmoa1107039
20. Wong, P. C.; Pinto, D. J. P.; Zhang, D. *J. Thromb. Thrombolysis* **2011**, *31*, 478-492. https://doi.org/10.1007/s11239-011-0551-3

21. Carrier, M.; Abou-Nassar, K.; Mallick, R.; Tagalakis, V.; Shivakumar, S.; Schattner, A.; Kuruvilla, P.; Hill, D.; Spadafora, S.; Marquis, K.; Trinkaus, M. 2019. *N. Engl. J. Med*. **2019**, *380*, 711-719. https://doi.org/10.1056/NEJMoa1814468
22. Pinto, D. J. P.; Wong, P. C.; Knabb, R. M.; Wexler, R. R. Casehistory: eliquis (apixaban), a potent and selective inhibitorof coagulation factor Xa for the prevention and treatmentof thrombotic diseases. In *Annual Reports in Medicinal Chemistry* **2012**, Vol. *47*. M.C. Desai, Ed.: 123–141. Burlington: Academic Press. https://doi.org/10.1016/B978-0-12-396492-2.00009-6
23. Wu, Y.-J. Heterocycles and medicine: a survey of theheterocyclic drugs approved by the U.S. FDA from 2000 to Present. In Progress in *Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Ed.; Elsevier, **2012**; Chapter 1, *24*, 1−53. https://doi.org/10.1016/B978-0-08-096807-0.00001-4
24. Hanna, M. S.; Mohan, P.; Knabb, R.; Gupta, E.; Frost, C.; Lawrence, J. H. *Ann. N. Y. Acad. Sci.* **2014**, *1329*, 93-106. https://doi.org/10.1111/nyas.12567
25. Zhou, J. C.; Oh, L. M.; Ma, P.; Li, H. Y. Synthesis of 4,5-dihydro-pyrazolo[3,4-c]pyrid-2-ones. WO Patent 2003/0 49681, June 19, **2003**.
26. Pinto, D. J. P.; Orwat, M. J.; Koch, S.; Rossi, K. A.; Alexander, R. S.; Smallwood, A.; Wong, P. C.; Rendina, A. R.; Luettgen, J. M.; Knabb, R. M.; He, K.; Xin, B. M.; Wexler, R. R.; Lam, P. Y. S. *J. Med. Chem*. **2007**, *50*, 5339–5356. https://doi.org/10.1021/jm070245n
27. Gant, T. G.; Shahbaz, M. Pyrazole carboxamide inhibitors of factor Xa. WO Patent 2010/030983, March 18, **2010**
28. Jiang, J.; Ji, Y. *Synth. Commun*. **2013**, *43*, 72-79. https://doi.org/10.1080/00397911.2011.591956
29. Wang, Y.; Sun, X.; Yang, D.; Guo, Z.; Fan, X.; Nie, M.; Zhang, F.; Liu, Y.; Li, Y.; Wang, Y.; Gong, P. *Bioorganic Med. Chem. Lett.* **2016**, *24*, 5646-5661. https://doi.org/10.1016/j.bmc.2016.09.024
30. Sun, X.; Hong, Z.; Liu, M.; Guo, S.; Yang, D.; Wang, Y.; Lan, T.; Gao, L.; Qi, H.; Gong, P.; Liu, Y. *Bioorganic Med. Chem. Lett.* **2017**, *25*, 2800-2810. https://doi.org/10.1016/j.bmc.2017.03.055
31. Satheesh, D. ; Sreenivasulu, B.; Reddy, B.S.; Reddy, U.R.; Saladi, J.C.; Gupta, P.B.; Reddy, A.S.K.; Aegurla, B.; Basavaiah, K., *J. Heterocycl. Chem*. **2022**, *59*, 1736-1741.
32. Dong, W.; Gong, T.; Liu, C.; Lin, J.; Jia, Q.; Chu, C., *Monatsh. Chem*. **2024**, *155*, 99-104.
33. Current Patent Assignee: OPTIMUS DRUGS P - US2017/313695, **2017**, A1