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The synthesis of pyrazole derivatives from hydrazone using Amberlyst A26 resin under ultrasonic radiation

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A B S T R A C T

Pyrazoles are highly versatile and find applications in various industries including chemicals, pharmaceuticals, polymers, medications, and agriculture. Pyrazoles and their analogues exhibit a range of biological activities, including anti-inflammatory, anti-tuberculosis, antibacterial, antifungal, anti-cancer, and anti-diabetic effects. In this context, this investigation focuses on the synthesis of pyrazoles containing heterocyclic components using Amberlite resin in reactions with ultrasonic irradiation. Synthesized pyrazoles containing heterocyclic components are intermediates of the apixaban API. Some pyrazole derivatives are key impurities of the apixaban API, which is synthesized by a multistep chemical conversion and has been reported previously. The use of the heterogeneous Amberlyst resin, which acts as a reusable catalyst and is gentle on reactions, allows for a more sustainable solution that reduces costs, accelerates reactions, and shortens reaction times. The procedures for using Amberlyst resin under ultrasonic irradiation to synthesize pyrazole derivatives are cost-effective, energy-efficient, and environmentally friendly for chemical synthesis and material preparation. They also simplify workups and produce quality and yields comparable to or better than existing methods.

1. Introduction

This research paper aims to synthesize pyrazole-form hydrazone derivatives using Amberlyst resin under ultrasound irradiation conditions. The chemical compound pyrazole is a ring with five members comprising two nitrogen. In 1883, Ludwig Knorr first discovered pyrazole [1]. In 1889, the first synthesis occurred in a five-membered ring containing two nitrogen atoms. This class of heterocycles is exceedingly powerful in numerous organic synthesis processes[2]. Many synthetic strategies and analogues have been reported in recent years, emphasizing their role in the research field and applications. The importance of analogues in therapeutic and pharmaceutical applications has also been well-documented [3-4]. In recent years, there has been a definition of pyrazole derivatives and novel bioactive compounds that are FDA-approved and commercially available for treatment[5] **(Fig. 1).** The synthesis of pyrazoles and their nitrogen derivatives is significant due to their utilization in various applications in medicinal chemistry[6-9]. Recently, researchers synthesized pyrazole-containing heterocycles and their various synthetic approaches, which is useful for many newcomers in their research[10-15].

In our current work, we used Amberlyst A26 resin under ultrasonic irradiation to efficiently synthesize specific pyrazoles from hydrazone derivatives. Hydrazone derivatives are important in chemical synthesis due to their distinct reactivity and unique structure [16]. Different chemical transformations can be utilized to synthesize pyrazole derivatives. Analysts use various starting materials for this synthesis, including 1,3-diketones, α β-unsaturated carbonyl compounds, alkynes, N, N-dimethyl enaminones, and vinyl ketones with a good leaving group. They use organic-inorganic bases and metal catalysts in the presence of common organic solvents [3-4]. Compound 3a, ethyl 1-(4-methoxyphenyl)-7a-morpholino-7-oxo-6-(4-(2-

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oxopiperidin-1-yl)phenyl)-3a,4,5,6,7,7a-hexahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate is an essential component in the synthesis of Apixaban[17]. Apixaban is prescribed by doctors to treat patients with atrial fibrillation for the prevention of stroke and systemic embolism, as well as for the treatment and prevention of thromboembolic disease [18-20]. Synthesis of Apixaban may involve a complex, multi-step process that includes several chemical steps. The patented synthesis of pyrazole derivatives from N-phenylvalerolactam and hydrazone derivatives utilizes organic bases and reagents [21]. Compound 3a was synthesized through a [3+2] cycloaddition process by Jian'an Jiang and Yafei Ji, resulting in a 70% yield [22]. The chemical compound 3i, a pyrazole derivative as described in the patent, was synthesized using triethylamine (TEA) and ethyl acetate as the solvent at a temperature between 75 to 80 °C. Afterwards, it underwent an aqueous HCl treatment, which resulted in an 85 % yield [23]. Furthermore, the same patent also details the chemical synthesis of compound 3h using iron metal, AlCl3, 5-CVC, and other components at high temperatures [23]. We have developed an efficient method for synthesizing pyrazole compounds 2b,3a, and 3h-j, which serve intermediate and compound 3b-g are key impurities of the Apixaban API. Several researchers employ sustainable techniques, such as microwaves and ultrasonic irradiation, to produce pyrazole derivatives in the presence of organic-inorganic bases, catalysts, and resin using organic solvents [24-30]. Due to the considerable decrease in turnaround times from days or hours to minutes, ultrasonic irradiation is currently utilized in medicinal chemistry and drug development processes [31]. The techniques are more affordable, offer superior reaction conversion, and require fewer workups. These qualities are important because they benefit society in many ways, such as minimizing wastewater pollution, avoiding harmful chemicals and environmental dangers, conserving energy, saving time, and preserving biological life [32-34].

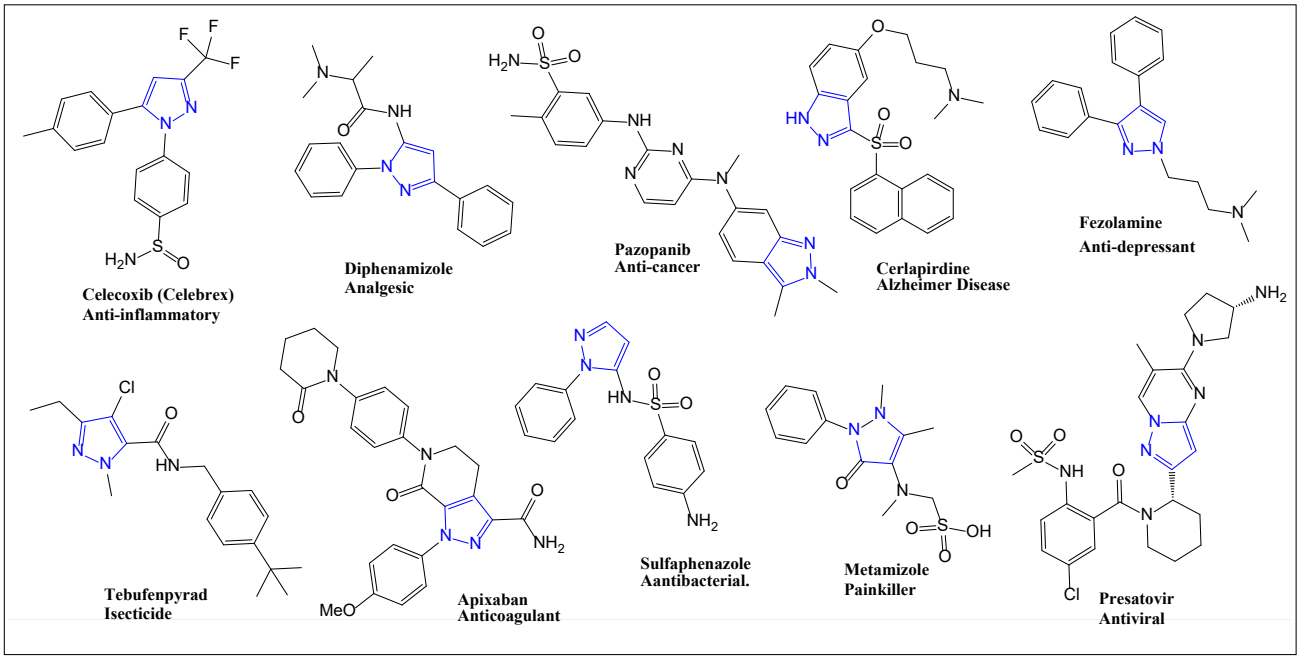


Fig. 1. Bio-active Pyrazole containing derivatives.

2. Results and Discussion

The study aims to investigate the synthesis of specific pyrazole analogues from N-phenylvalrolactam and hydrazone derivatives using Amberlyst resin under ultrasonic irradiation. Initially, several Amberlyst resins were screened for the reaction. Details are provided in **Table 1**.

Table 1: Screening some Amberlyst resin.

Sr No	Resin/Solvent	Condition	Time	Conversion
1	Amberlyst A21/Ethyl acetate	50-60°C	30-60 min	NA
2	Amberlite IRA-67/Ethyl acetate	50-60°C	30-60 min	NA
3	Amberlite IRA96/Ethyl acetate	50-60°C	30-60 min	NA
4	**Amberlyst A26/Ethyl acetate**	**50-60°C**	**30-60 min**	**55%**

In synthesizing compound 3a, rection through intermediate 2b is produced by using N-phenylvalrolactam and hydrazone derivatives in combination with Amberlyst A26 under ultrasonic irradiation. The nitrilimine of hydrazone is formed in the presence of Amberlyst resin, followed by a [3 + 2] cycloaddition process in the presence of ethanol. After filtering the Amberlyst A26 resin, the filtrate undergoes treatment with an acidic solution and ultrasonic radiation to convert compound 2b to compound 3a. This reaction succession is portrayed in **Fig. 2**.

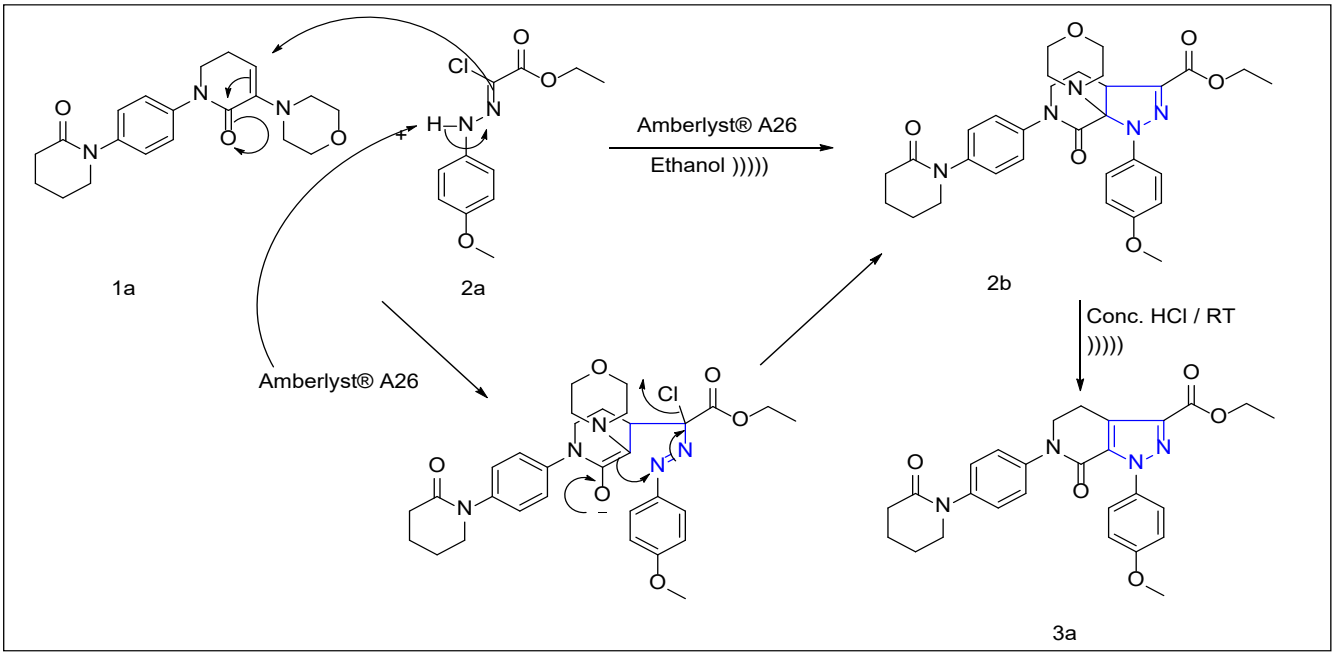


Fig. 2. Reaction sequence of pyrazole derivative (3a)

To find the optimal method for converting Compound 3a from N-phenylvalrolactum through a [3+2] cycloaddition, the study tested different organic solvents and Amberlyst A26 at various temperatures. Afterwards, de-morpholiniline was used in an aqueous HCl solution under ultrasonic irradiation at room temperature. The specific parameters can be found in **Table 2**.

Table 2. Optimizing the conditions for 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 (3a)

Sr No	Resin/Solvent	Condition	Time	Conversion
1	Amberlyst A26 /Ethyl acetate	50-60°C	30-60 min	55%
2	Amberlyst A26 /Ethyl acetate	25-35°C	30-60 min	<5%
3	Amberlyst A26 /Toluene	25-35°C	30-60 min	<10%
4	Amberlyst A26 /Toluene	50-60°C	30-60 min	65%
5	Amberlyst A26/MDC	25-35°C	30-60 min	54%
6	Amberlyst A26/THF	40-50°C	30-60 min	<10%
7	Amberlyst A26/Water	25-35°C	30-60 min	0%
8	Amberlyst A26/Ethanol	25-35°C	30-60 min	15 %
9	Amberlyst A26/ Neat	25-35°C	30-60 min	0 %
11	**Amberlyst A26/ Ethanol**	**50-60°C**	**30-60 min**	**89%**

Recent data shows that when Amberlyst A26 is used in ethanol at 50-60°C for synthesizing pyrazole derivatives, it leads to high conversion rates and reduced synthesis time. Compound 3a, identified as 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 with a mass m/z peak of 489, ^{1}H MNR, ^{13}C MNR spectroscopy and FT-IR data .

The results of the present study were compared with previously published research for the 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 via [3+2] cycloaddition from N-phenylvalrolactum and hydrazone using catalysts, conditions, times, and conversion, as listed in **Table 3**

Table 3. Comparison of current and earlier findings

Sr No	Condition	Time	Yield	Reference
1	TEA/ Ethyl Acetate/Reflux	6 h	67 %	21
2	TEA, KI/ Ethyl Acetate/ Reflux	6 h	75 %	22
3	TEA / Toluene /85-90°C	2 h	77 %	35
4	TEA, KI/ Ethyl Acetate/ Reflux	6 h	85 %	36
5	Na_2CO_3/ Acetone/ 45-50	3 h	85 %	37
6	**Amberlyst A26/ Ethanol/ 50-60**	**60 min**	**89 %**	**Current work**

We synthesized the pyrazole analogues 3b-j by using different hydrazone derivatives and N-phenylvalrolactum in a [3 + 2] cycloaddition process with Amberlyst A26 in ethanol at 50-60°C. The confirmation of the obtained derivatives was done using analytical tools such as mass m/z peak of 489, ^{1}H MNR, ^{13}C MNR spectroscopy and FT-IR.

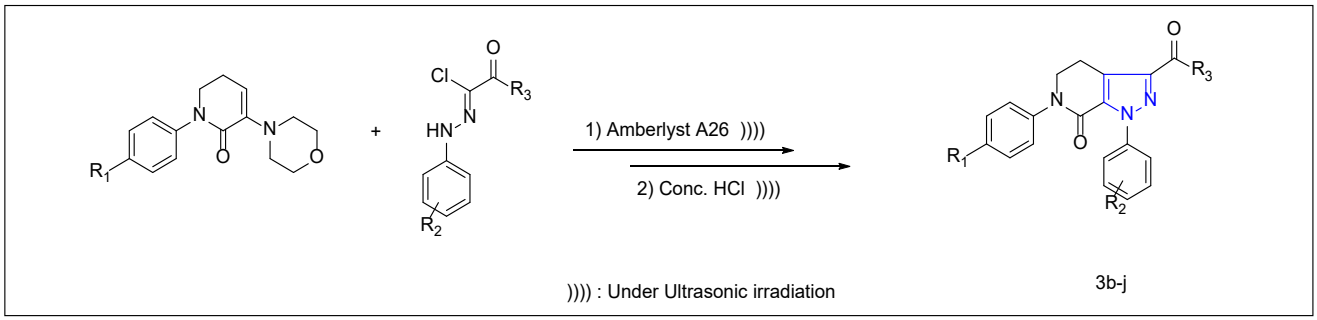
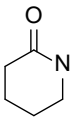
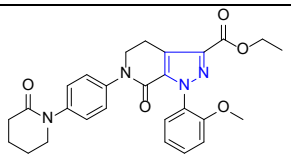
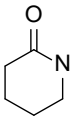
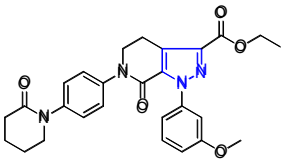
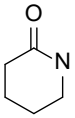
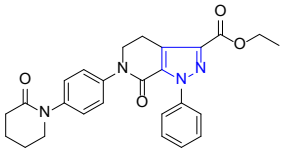
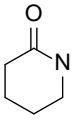
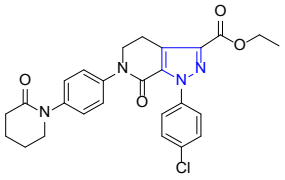
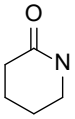
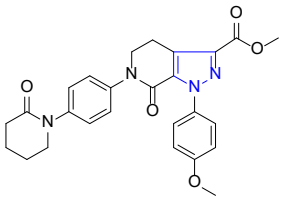
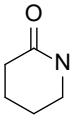
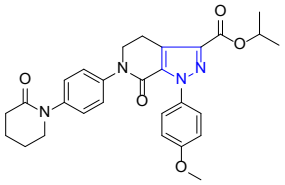
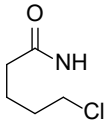
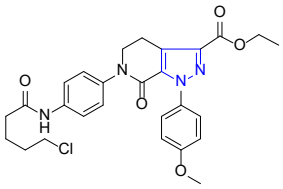
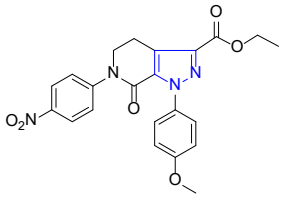
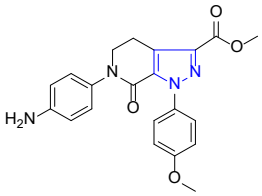


Fig. 3. General pathway for the preparation of some pyrazole derivatives

The general reaction scheme is presented in Figure 3, and the results are detailed in **Table 4**

Table 4. Synthesis of Compound 3b-j

Sr. No.	Comp (3b-j)	R1	R2	R3	Product
1	**3b**		ortho -OMe	-OEt	
2	**3c**		meta -OMe	-OEt	
3	**3d**		H	-OEt	
4	**3e**		para -Cl	-OEt	
5	**3f**		para -OMe	-OMe	
6	**3g**		para -OMe	-Isopropyl	

7	**3h**		para -OMe	-OEt	
8	**3i**	-NO2	para -OMe	-OEt	
9	**3j**	-NHBoc	para -OMe	-OMe	

3. Conclusions

In our study, we synthesized pyrazole derivatives using Amberlyst A26 resin under ultrasonic irradiation conditions, with ethanol as the solvent. This method allowed us to avoid using hazardous chemicals and multiple reagents, saving us time. We optimized the reaction conditions to achieve the best conversion of the desired product. Our investigation revealed that using Amberlyst A26 as the catalyst facilitated a cycloaddition reaction of [3 + 2] at a temperature range of 50-60°C in ethanol. After the reaction, we recovered the resin through filtration. Treating the filtrate with aqueous acid under ultrasonic irradiation effectively yielded the intended product. The pyrazole-containing heterocyclic derivatives synthesized effectively may serve as important intermediates and key impurities of the apixaban API. They are listed in Table 4 as compounds 3a-j. Our contemporary approach, utilizing Amberlyst A26 resin under ultrasonic irradiation, is noteworthy due to its properties as a heterogeneous catalyst, making it easy to handle and reusable. This approach also allows for easy workup, is environmentally friendly, reduces wastewater pollution, and contributes to maintaining biodiversity and the ecosystem.

Acknowledgements

The author expresses gratitude towards the principal and the chemistry department of Yogeshwari Mahavidyalaya, Ambajogai College, for their invaluable research support.

4. Experimental

4.1. Materials and Methods

All the ingredients and materials used in this experiment were sourced from high-quality commercial suppliers. We used borosilicate glassware and a 6.5-liter ultrasonic bath for sonication. Silica gel was used for TLC analysis to monitor the progress and conversion of the product. The characteristics of each spot were visible under ultraviolet light. We used a Bruker 400 MHz spectrometer to record ^{1}H-NMR and ^{13}C-NMR spectra with TMS as the internal standard chemical shift defined as ppm. Additionally, all compound masses were analysed by mass spectrophotometer Shimadzu LCMS-8030, and the used MASS spectrum analysis.

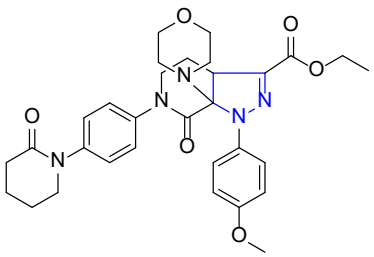
4.2. General pathway for the preparation of compound-3a

Please make a note of the following: In a dry test tube, 0.281 mmol of 3-Morpholino-1-[4-(2-oxo-1-piperidyl)phenyl]-5,6-dihydropyridin-2(1H)-one and 0.309 mmol of ethyl 2-chloro-2-(2-(4-methoxyphenyl)hydrazone) were combined with 20% of Amberlyst A26 and ethanol. The resulting mixture was then stirred under ultrasonic radiation at 50-60°C. It was confirmed that the starting material was absent on TLC (Solvent system MDC: Methanol, 95:5). The resin was recovered by filtration, and then 0.703 mmol of concentrated HCl was added to the filtrate and stirred again under ultrasonic radiation. Complete conversion of the intermediate to the product was confirmed on TLC (Solvent system MDC: Methanol, 95:5).

The resulting mixture was filtered in ice water and washed with water. The crude compounds were then recrystallised in alcohol.

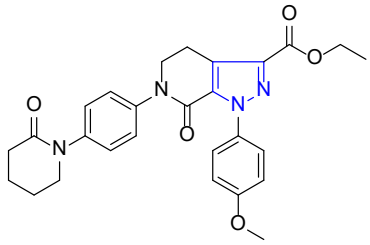
4.3 Physical and Spectral Data pyrazole derivative compound 2b, 3a-j

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 (2b)



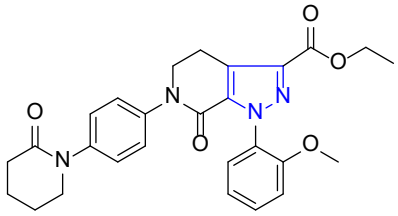
Yellow Solid, Melting Point:109-111°C, ^{1}H NMR (400 MHz, DMSO), δ(ppm): 7.57-7.55 (d, 2H, Ar-H), 7.16-7.14 (d, 2H, Ar-H), 6.88-6.85 (d, 4H, Ar-H), 4.30-4.21 (m, 2H, -CH_2), 4.01-3.99 (m, 1H, -CH), 3.71 (s, 3H, -CH_3), 3.67-3.59 (m, 4H, -CH_2), 3.55-3.39 (m, 4H, -CH_2), 2.54-2.49 (t, 2H, -CH_2), 2.42-2.39 (m, 2H, -CH_2), 2.35-2.32 9(t, 2H, -CH_2), 2.19-2.12 (m, 2H, -CH_2), 1.84-1.79 (m, 4H, -CH_2), 1.31-1.27 (t, 3H, -CH_3); ^{13}C NMR (400 MHz, DMSO) δ :168.81, 162.02, 161.18, 155.84, 141.64, 140.66, 137.78, 134.42, 126.52, 125.74, 120.81, 113.59, 89.11, 65.96, 60.65, 55.20, 50.70, 46.79, 44.58, 42.36, 32.52, 26.13, 22.93, 20.84, 14.17; FT-IR cm^{-1} (KBr):2905.41, 1699.58, 1637.49, 1507.00, 1422.92, 1250.82, 1238.62, 1096.06, 954.83; MS (ESI):m/z= 576.

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 (3a)



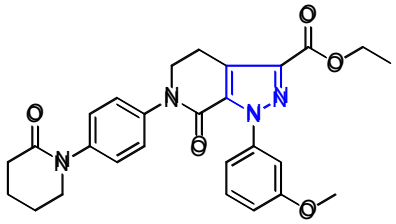
Light yellow solid, Melting Point:179-181°C, ^{1}H NMR (400 MHz, DMSO), δ(ppm):7.50-7.47 (d, 2H, Ar-H), 7.36-7.33 (d, 2H, Ar-H), 7.29-7.26 (d, 2H, Ar-H), 7.02-6.98 (d, 2H, Ar-H), 4.36-4.31 (q, 2H, -CH_2), 4.09-4.05 (t, 2H, -CH_2), 4.08 (s, 3H, -CH_3), 3.60-3.57 (t, 2H, -CH_2), 3.21-3.18 (t, 2H, -CH_2), 2.39-2.36 (t, 2H, -CH2), 1.86-1.82 (m, 4H, -CH_2), 1.34-1.31 (t, 3H, -CH_3); ^{13}C NMR (400 MHz, DMSO) δ:168.84, 161.38, 159.29, 156.36, 141.44, 139.65, 138.42, 132.99, 132.42, 126.78, 126.73, 126.33, 126.00, 113.45, 60.60, 55.47, 50.80, 50.68, 32.58, 22.99, 21.13, 20.89, 14.17; FT-IR cm^{-1} (KBr):2988.69, 1726.67, 1673.98, 1648.35, 1513.72, 1458.06, 1250.45, 1145.13, 1086.55; MS (ESI):m/z= 489[M+H]

Ethyl 1-(2-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (3b).



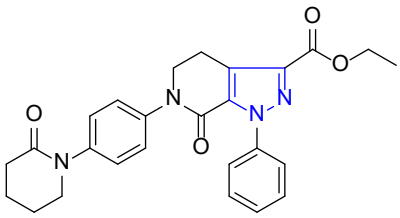
Yellow solid, Melting Point:147-150°C, ^{1}H NMR (400 MHz, DMSO), δ(ppm):7.49-7.44 (dd, 1H, Ar-H), 7.39-7.36 (dd, 1H, Ar-H), 7.32-7.30 (d, 2H, Ar-H), 7.27-7.25 (d, 2H, Ar-H), 7.17-7.15 (d, 1H, Ar-H), 7.06-7.02 (m, 1H, Ar-H), 4.36-4.30 (q, 2H, -CH_2), 4.06 (t, 2H, -CH_2), 3.71 (s, 3H, -CH_3), 3.58-3.56 (t, 2H, -CH_2), 3.22-3.19 (t, 2H, -CH_2), 2.39-2.36 (t, 2H, -CH_2), 1.84-1.81 (m, 4H, -CH_2), 1.34-1.30 (t, 3H, -CH_3); ^{13}C NMR (400 MHz, DMSO) δ:168.82, 161.35, 156.40, 154.06, 141.42, 139.50, 138.68, 134.39, 130.64, 128.72, 127.42, 126.40, 125.89, 125.47, 120.09, 112.25, 60.57, 55.80, 50.79, 32.56, 22.96, 20.91, 20.87, 14.16; FT-IR cm^{-1} (KBr):2931.09, 2882.74, 1712.94, 1642.96, 1504.53, 1456.80, 1304.97, 1246.39, 1140.53, 1088.55, 968.29; MS (ESI):m/z= 489[M+H].

Ethyl 1-(3-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (3c).



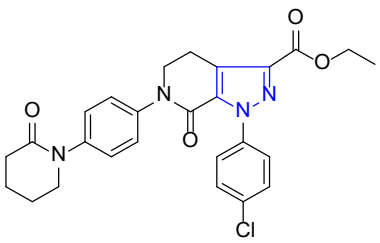
Yellow solid, Melting Point:163-165°C, ^{1}H NMR (400 MHz, DMSO), δ(ppm):7.34-7.32 (dd, 2H, Ar-H), 7.30-7.26 (d, 1H, Ar-H), 7.25-7.23 (dd, 2H, Ar-H), 7.12-7.08 (m, 2H, Ar-H), 4.47-4.42 (q, 2H, -CH_2), 4.14-4.10 (t, 2H, -CH_2), 3.79 (s, 3H, -CH_3), 3.58-3.57 (t, 2H, -CH_2), 3.32-3.28 (t, 2H, -CH_2), 2.55-2.52 (t, 2H, -CH_2), 1.93-1.91 (m, 4H, -CH_2), 1.44-1.40 (t, 3H, -CH_3); ^{13}C NMR (400 MHz, DMSO) δ:168.83, 161.31, 159.01, 156.20, 141.45, 140.26, 139.66, 138.76, 133.29, 129.22, 127.04, 126.37, 126.03, 117.68, 114.41, 111.43, 60.67, 55.52, 50.80, 50.69, 32.56, 22.97, 21.14, 20.87, 14.16; FT-IR cm^{-1} (KBr):2971.07, 1684.19, 1652.92, 1456.90, 1402.35, 1323.08, 1263.01, 1121.78, 1050.49, 984.47; MS (ESI):m/z= 489[M+H].

Ethyl 7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-1-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (3d).



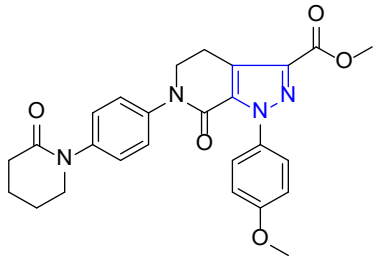
Off White solid, Melting Point:208-210°C, ^{1}H NMR (400 MHz, DMSO), δ(ppm):7.56-7.53 (dd, 2H, Ar-H), 7.42-7.36 (m, 3H, Ar-H), 7.33-7.31 (dd, 2H, Ar-H), 7.25-7.22 (dd, 2H, Ar-H), 4.47-4.42 (q, 2H, -CH_2), 4.13-4.10, (t, 2H, -CH_2), 3.59-3.56 (t, 2H, -CH_2), 3.32-3.29 (t, 2H, -CH_2), 2.55-2.52 (t, 2H, -CH_2), 1.92-1.90 (m, 4H, -CH_2), 1.43-1.40 (t, 3H, -CH_3); ^{13}C NMR (400 MHz, DMSO) δ:168.83, 161.32, 156.27, 141.46, 139.63, 139.26, 138.84, 133.16, 128.72, 128.40, 127.11, 126.37, 126.03, 125.41, 60.68, 50.81, 50.68, 32.57, 22.98, 21.13, 20.89, 14.17; FT-IR cm^{-1} (KBr):2938.15, 1695.19, 1678.12, 1504.64, 1438.25, 1370.42, 1303.39, 1255.26, 1143.72, 1013.88, 979.98; MS (ESI):m/z= 459 [M+H].

Ethyl 1-(4-chlorophenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (3e)



Pale yellow solid, Melting Point:194-196°C, ^{1}H NMR (400 MHz, DMSO), δ(ppm):7.65-7.62 (dd, 2H, Ar-H), 7.56-7.53 (dd, 2H, Ar-H), 7.37-7.34 (dd, 2H, Ar-H), 7.29-7.27 (dd, 2H, Ar-H), 4.37-4.32 (q, 2H, -CH_2), 4.10-4.07 (t, 2H, -CH_2), 3.60-3.57 (t, 2H, -CH_2), 3.22-3.19 (t, 2H, -CH_2), 2.40-2.36 (t, 2H, -CH_2), 1.88-1.82 (m 4H, -CH_2), 1.34-1.31 (t, 3H, -CH_3); ^{13}C NMR (400 MHz, DMSO) δ:168.84, 161.23, 156.29, 141.51, 139.54, 139.13, 138.00, 133.33, 133.21, 128.43, 127.21, 126.39, 126.01, 60.75, 50.81, 50.69, 32.57, 22.98, 21.11, 20.90, 14.16; FT-IR cm^{-1} (KBr):2948.70, 1708.93, 1640.84, 1500.60, 1447.73, 1309.43, 1247.81, 1138.56, 1087.88, 833.50, 780.90; MS (ESI):m/z= 493 [M+H].

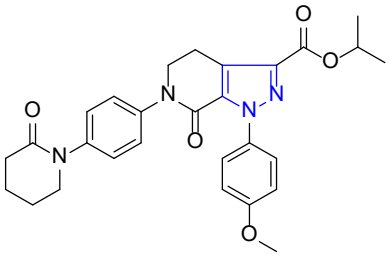
Methyl 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (3f).



Off white solid, Melting Point:139-141°C, ^{1}H NMR (400 MHz, DMSO), δ(ppm):7.46-7.43 (dd, 2H, Ar-H), 7.33-7.30 (dd, 2H, Ar-H), 7.25-7.22 (dd, 2H, Ar-H), 6.91-6.88 (dd, 2H, Ar-H), 4.13-4.09 Hz, (t, -CH_2), 3.96, (s, 3H, -CH_3), 3.79 (s, 3H, -

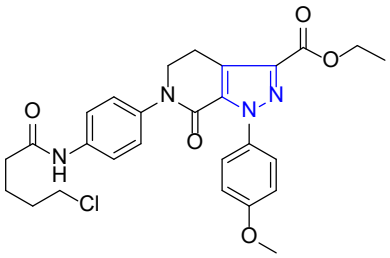
CH_3), 3.59-3.56 (t, 2H, -CH_2), 2.32-2.28 (t, 2H, -CH_2), 2.54-2.52 (t, 2H, -CH_2), 1.94-1.88 (m, 4H, -CH_2); ^{13}C NMR (400 MHz, $CDCl_3$) δ:170.07, 162.43, 159.85, 157.11, 141.40, 139.80, 138.67, 133.02, 132.42, 126.95, 126.87, 126.74, 126.14, 113.56, 55.45, 52.11, 51.55, 50.93, 32.19, 23.46, 21.40, 21.36; FT-IR cm^{-1} (KBr):2945.45, 1728.40, 1659.66, 1511.99, 1453.42, 1374.01, 1281.80, 1136.45, 829.50; MS (ESI):m/z=475[M+H].

Isopropyl 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 (3g).



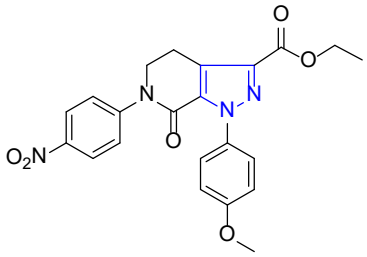
Yellow solid, Melting Point:166-169°C, ^{1}H NMR (400 MHz, DMSO), δ(ppm):7.51-7.46 (dd, 2H, Ar-H), 7.35-7.33 (dd, 2H, Ar-H), 7.28-7.26 (dd, 2H, Ar-H), 7.02-6.99 (dd, 2H, Ar-H), 5.20-5.14 (m, 1H, -CH), 4.09-4.05 (t, 2H, -CH_2), 3.80 (s, 3H, -CH_3), 3.60-3.57 (t, 2H, -CH_2), 3.21-3.18 (t, 2H, -CH_2), 2.39-2.18 (t, 2H, -CH_2), 1.84-1.82 (m, 4H, -CH_2) 1.34-1.32 (d, 6H, -CH_3); ^{13}C NMR (400 MHz, DMSO) δ:168.84, 161.38, 159.28, 156.36, 141.44, 139.66, 138.41, 133.00, 132.41, 126.79, 126.74, 126.36, 126.02, 113.45, 60.61, 55.47, 50.82, 50.69, 32.57, 22.99, 21.13, 20.90, 14.18; FT-IR cm^{-1} (KBr):2946.25, 1723.62, 1648.10, 1511.86, 1456.12, 1375.07, 1250.36, 1144.49; MS (ESI):m/z= 503 [M+H].

Ethyl 6-(4-(5-chloropentanamido)phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (3h).



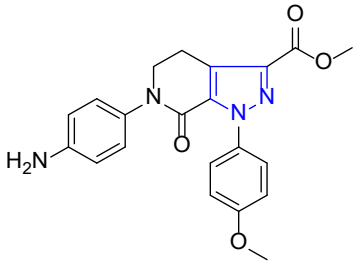
Light Yellow solid, Melting Point:163-165°C, ^{1}H NMR (400 MHz, DMSO), δ(ppm):9.97 (s, 1H, -NH) 7.59-7.57 (dd, 2H, Ar-H), 7.49-7.46 (dd, 2H, Ar-H), 7.27-7.25 (dd, 2H, Ar-H), 4.36-4.30 (q, 2H, -CH_2), 4.04-4.01 (t, 2H, -CH_2), 3.80 (s, 3H, -CH_3), 3.67-3.64 (t, 2H, -CH_2), 3.20-3.16 (t, 2H, -CH_2), 2.35-2.32 (t, 2H, -CH_2), 1.77-1.70 (m, 4H, -CH_2) 1.34-1.30 (t, 3H, -CH_3); ^{13}C NMR (400 MHz, DMSO) δ:170.83, 161.38, 159.27, 156.31, 138.36, 137.22, 136.88, 133.08, 132.44, 126.77, 126.66, 126.08, 119.04, 113.43, 60.58, 55.46, 50.77, 45.08, 35.37, 31.54, 22.41, 21.09, 14.16; FT-IR cm^{-1} (KBr):3297.88, 2948.63,1710.35, 1664.99, 1512.67, 1465.89, 1306.01, 1251.59, 1139.58, 1024.00, 829.01, 741.28; MS (ESI):m/z= 525.

Ethyl 1-(4-methoxyphenyl)-6-(4-nitrophenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (3i)



Light brown solid, Melting Point:159-161°C, ^{1}H NMR (400 MHz, DMSO), δ(ppm):8.22-8.20 (dd, 2H, Ar-H), 7.51-7.49 (dd, 2H, Ar-H), 7.45-7.43 (dd, 2H, Ar-H), 6.93-6.91 (dd, 2H, Ar-H) 4.84-4.43 (q, 2H, -CH_2), 4.20-4.17 (t, 2H, -CH_2), 3.81 (s, 3H, -CH_3), 3.38-3.34 (t, 2H, -CH_2), 1.44-1.40 (t, 3H, -CH_3); ^{13}C NMR (400 MHz, DMSO) δ:161.45, 159.23, 156.35, 147.17, 138.31, 133.34, 132.51, 130.58, 126.79, 126.61, 126.45, 113.49, 113.39, 60.55, 55.47, 51.20, 21.12, 14.18; FT-IR cm^{-1} (KBr):2983.86, 1711.01, 1664.41, 1512.41, 1439.84, 1319.70, 124785, 1136.25, 1027.40; MS (ESI):m/z= 437 [M+H].

Methyl 6-(4-aminophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (3j)



Yellow solid, Melting Point:151-154°C, ^{1}H NMR (400 MHz, DMSO), δ(ppm):7.42-7.39 (dd, 2H, Ar-H), 7.04-7.01 (dd, 2H, Ar-H), 6.96-6.92 (dd, 2H, Ar-H), 6.50-6.48 (dd, 2H, Ar-H) 3.88-3.85 (t, 2H, -CH_2), 3.78 (s, 3H, -CH_3), 3.13-3.10 (t, 2H, -CH_2), 2.65 (s, 3H, -CH_3); ^{13}C NMR (400 MHz, DMSO) δ:162.96, 159.14, 156.47, 147.13, 139.17, 133.23, 132.61, 130.66, 126.73, 126.60, 126.45, 113.49, 113.37, 55.45, 54.92, 51.27, 21.20; FT-IR cm^{-1} (KBr):3321.88, 2944.34, 2832.62, 1661.09, 1513.48, 1418.03, 1251.31, 1115.04; MS (ESI):m/z= 393[M+H].

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