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DESIGN, SYNTHESIS AND CHARACTERIZATION OF NOVEL DERIVATIVES OF APIXABAN AS AN INHIBITOR OF BLOOD COAGULATION

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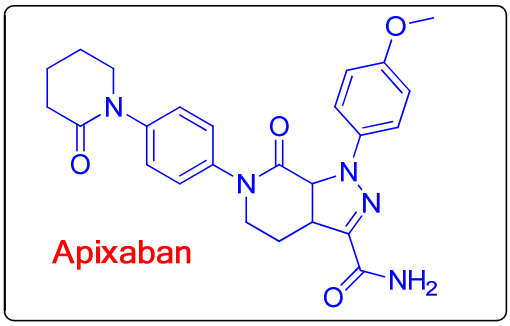
ABSTRACT:
The design and synthesis of a novel class of apixaban derivatives possessing theoxadiazole moiety, 1,2,4-triazole moiety and pyrazole moiety. All the synthesized compounds were obtained in better yields and by simple procedure.The newly synthesized compounds have been characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

KEY WORDS: Apixaban,Oxadiazole, 1,2,4-triazole, pyrazole, inhibitor of blood coagulation factorXa and synthesis.

INTRODUCTION:

Apixaban, a direct factor Xa inhibitor. It is a highly potent, selective, efficacious, and oral anticoagulantsin a late-stage clinical development.[I]It has the potential to reduce the generation of endogenous thrombin and indirectly decrease thrombin mediated platelet aggregation in vivo.[II]Thromboembolic are causes pathogenesis ofnumerous cardiovascular disorders,[III]acute coronary syndrome (ACS),[IV]ischemic stroke,[V]deep venous thrombosis (DVT), venous thromboembolism (VTE), and pulmonary embolism (PE).[VI]In clinical trials, it has shown predictable and consistent anticoagulation as well as promising safety and efficacy results for the treatment of these fatal disease.[VII]The structure-activity relationships (SARs) of apixaban was studied by Yong Wang et al.[VIII] According to this study the introducing of nitrogenous heterocyclic with carboxamido moiety gives a better activity of anticoagulation. There areseveral routes for the synthesis of apixaban have been reported, out of which we are considering a best and simple route that was developed by Jian'an Jiang &YafeiJi.[IX] In this they reduced multi steps, elimination of expensive chemicals, rare auxiliaries, and inefficient Ullmann reaction. Considering these advantage and requirement of apixaban drugs. Herein, we are

reporting some novel derivatives of apixabanpossessing oxadiazole moiety, 1,2,4-triazole moiety and pyrazole moiety which may give better efficient as compare to reported derivatives of factor Xa inhibitor.



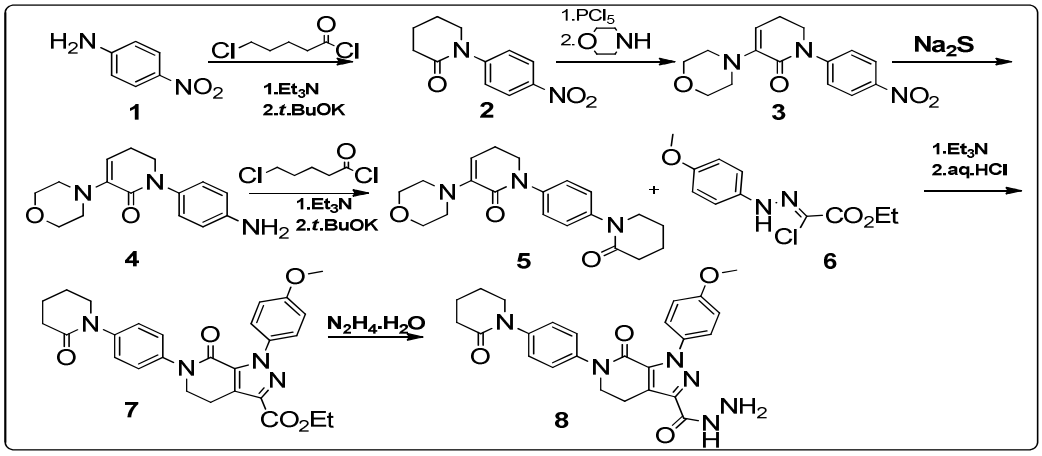
RESULTS AND DISCUSSION

The compound **8** was prepared (**Scheme I)** by six-step procedure, starting from 4-nitroaniline **1**. The 4-nitroaniline **1** was reacted with 4-chlorobutanoyl chloride using excess triethylamine as an acid scavenger in the acylation reaction and then potassium tert-butoxide as a strong condensing agent to provide compound **2**, it was further chlorinated with PCl_5 and substituted with morpholine to obtain compound **3**. Reduction of compound **3** with sodium sulfide[X, XI] gave the corresponding aniline **4**. In a similar manner, the second acylation and cyclization were carried out between **4** and 5-chlorobutanoyl chloride to obtain compound **5**. Then **6** was obtained separately by reaction with diazonium salt of4-methoxyaniline and ethyl-2- chloro-3-oxobutanoate. The [3+2] cycloaddition reaction of **5** with compound **6** in presence of excess triethylamine and a catalytic amount of potassium iodide under reflux (6 h), and obtained compound **7**.[IX] Finally, the compound **7** was treated with hydrazine hydrate to give compound **8** which was further derivatized to compounds **9-14 (Table I, Scheme II)**, respectively. Obtained products were purified by recrystallisation and structure elucidation carried out by using IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data.

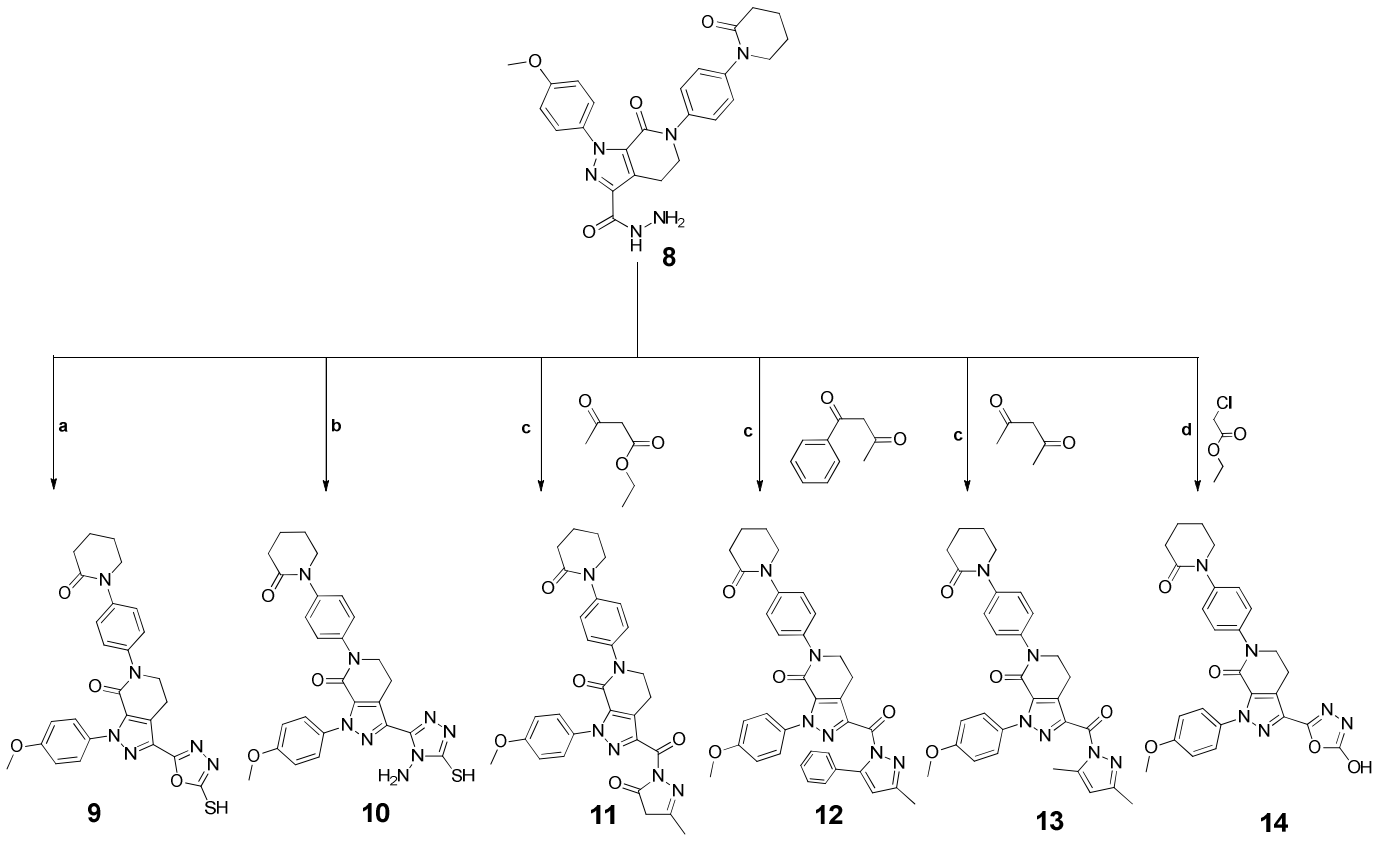
Table I: Physical Data of all synthesized Compounds.

Compounds	Melting point (^{o}C)	% of yield
9	240-242	93.7
10	178-180	87.5
11	180-182	72.2
12	138-140	61.3
13	135-137	71.4
14	144-146	95.1

REACTION SCHEME



Scheme: I



Reagents and conditions: a) CS_2 ,KOH/ EtOH,reflux, b) CS_2 ,KOH/ EtOH,reflux then add NH_2NH_2 reflux , c) AcOH/ EtOH, reflux, d)Ether/reflux.

Scheme: II

EXPERIMENTAL

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Bruker500 MHz,700 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

Synthesis ofIntermediate(7)[IX]:

Preparation of *1-(4-Nitrophenyl)piperidin-2-one***(2)**[I]

A solution of 5-chloropentanoyl chloride (64.5mL,77.5 g, 0.5mol) in tetrahydrofuran(THF, 100mL) was added below 5^{0}C to a solution of 4-nitroaniline**1**(55 g, 0.4mol) and triethylamine (112 mL, 0.8mol) in THF (250 mL). Mixture was stirred at room temperature under N_2 for 5 h. Potassium tert-butoxide(123.5 g, 1.1mol) was added to the reaction solution in batches below 5^{0}C during30 min and then stirred at room temperature for 2 h. Upon Completion of the reaction, mixture was concentrated under vacuum and poured into ice-cold water. The product was extracted by ethyl acetate.The combinedorganic phase was dried over anhydrous sodium sulfate and concentrated completelyto get a pale yellow solid**2**.

Yield: 76%, **mp:** 97–99 ^{0}C.

Preparation of *3-Morpholino-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one***(3)**[I]

Phosphorus pentachloride (90.4 g, 0.45mol) was slowly added to a solution of **2** (33 g, 0.15mol) in chloroform (200 mL) at room temperature. The resulting mixture was reflux for 3h, poured into ice water, and extracted with chloroform. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuum to dryness. The residue was dissolved in morpholine (100 mL) and refluxed for 1 h. The reaction mixture was cooled to room temperature and concentrated in vacuum. The resulting solid was poured in water, and the precipitate was filtered. The recrystallization of crude solid from ethyl acetate afforded **3** as a yellow solid. **Yield**: 72%,**mp**:158–160 ^{0}C.

Preparation of *1-(4-Aminophenyl)-3-morpholino-5,6-dihydropyridin-2(1H)-one* (**4**)[IX]

A solution of sodium sulfide nonahydrate (48 g, 0.2mol) in water (100 mL) wasadded to a solution of **3** (30.35 g, 0.1mol) in ethanol (300mL). The mixture was heatedto 50 ^{0}C and stirred for 4 h, cooled to room temperature, and concentrated in vacuum.The residue was added to ethyl acetate (150mL), heated to boiling, and filtered. Thefiltrate was concentrated in vacuum to dryness to yield **4** as a pale yellow solid. **Yield**: 82%,**mp:** 180–182 ^{0}C.

Preparation of *3-Morpholino-1-(4-(2-oxopiperidin-1-yl)phenyl)-5,6-dihydropyridin-2(1H)-one* (**5**)[IX]

A solution of 5-chloropentanoyl chloride (8 mL, 9.7 g, 63 mmol) in THF (50 mL) was added to a solution of **4** (13.6 g, 50mmol) and triethylamine (14mL, 100 mmol) in THF (250 mL) below 5 ^{0}C. The mixture was stirred at 50 ^{0}C under N_2 for 2 h. Potassium tert-butoxide (16.8 g, 150 mmol) was added to the reaction solution in batches below 5 ^{0}C during 30 min and then stirred at 50 ^{0}C for 8 h. The suspension was cooled to room temperature and concentrated in vacuum to

dryness. The residue was taken in water, stirred, and then filtered. The filter cake was washed withwater and dried to afford**5** as a white solid. **Yield**: 79%, **mp**: 204–206 ^{0}C.

Preparation of *(Z)-Ethyl 2-Chloro-2-(2-(4-methoxyphenyl)hydrazono)acetate***(6)**[IX]
Hydrochloric acid (35–36%, 9.3 mL, 300mmol) was added to a solution of 4-methoxyaniline (12.3 g, 100mmol) in water (60 mL) at -5 to 0^{0}C. A solution of sodium nitrite (8.3 g, 120mmol) in water (40 mL) was added to the mixture dropwise below 0 ^{0}C. Then, the reaction solution was stirred for 30 min at 0 ^{0}C, followed by the addition of sodium acetate (16.4 g, 200mmol) until pH 5–6. After that, a solution of ethyl-2-chloroacetoacetate (14 ml, 16.4 g, 100 mmol) in methanol (150 mL) was added dropwise to the reaction mixture at 0 to 5 ^{0}C. The resulting solution was stirred at room temperature for 4 h. Upon Completion of the reaction, mixture was concentrated under vacuum and poured into ice-cold water. The product was extracted by ethyl acetate. The combinedorganic phase was dried over anhydrous sodium sulfate and concentrated completely**.** The recrystallization of the crude product from ethyl acetate afforded **6** as a pale yellow solid. **Yield**: 68%, **mp**: 106-109 ^{0}C.

Preparation 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***(7)**[I]
Compound **5** (7.1 g, 20mmol), triethylamine (8.5 mL, 60mmol), and potassium iodide (0.32 g, 20 mmol) were added to a solution of **6** (5.65 g, 220mol) in ethyl acetate (200mL) at room temperature. The mixture was stirred for 6 h under reflux and then cooled to 0 ^{0}C. The resulting mixture was added dropwise with 4.0N hydrochloric acid (25 mL, 100mmol) and stirred at room temperature for 2 h. Upon Completion of the reaction, mixture was concentrated under vacuum and poured into ice-cold water. The product was extracted by ethyl acetate. The combinedorganic phase was dried over anhydrous sodium sulfate and concentrated completely. Recrystallization of the residue from ethyl acetate and drying in vacuum afforded **7** as a pale yellow solid. **Yield**: 75%, **mp** 120–124 ^{0}C.

Preparation of *1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-3a,4,5,6,7,7a-hexahydro-1H-pyrazolo[3,4-c]pyridine-3-carbohydrazide* **(8)**[VIII]
A solution of 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**7**(5 g, 10 mmol) in hydrazine hydrate (30mL) was stirred at 80°C for 3-4 hr. After completion of the reaction, the excess of hydrazine hydrate was distilled off. The crude solid wascollected, washed with water and recrystallizedfrom ethanol to give pale yellow solid **8**. **Yield**: 84%, **m.p**:168-170 ^{0}C.

Synthesis of apixaban derivatives (9-14)
Preparation of *3-(5-mercapto-1,3,4-oxadiazol-2-yl)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-5,6-dihydro-1H-pyrazolo[3,4-c]pyridin-7(4H)-one* **(9)**
A mixture of Hydrazide**8** (569 mg, 1.2 mmol) was dissolved in absolute ethanol (15 mL). Carbon disulfide (92 mg, 16.0mmol) was then added to the solution followed by the addition of a solution of potassium hydroxide (120mg, 19.0mmol) in water (5 mL). The reaction mixture was stirred at 50 ^{0}C for 4-5 hr. Evolution of hydrogen sulfide gas was observed during the reaction. The progress of the reaction was monitored by TLC. After completion of the reaction, excess of

ethanol was removed under reduced pressure. The mixture was diluted with distilled water (50 mL) and acidified with 4N hydrochloric acid to pH 2-3. The crude solid was collected, washed with ice cold water and recrystallized from ethanol to yield white solid**9**.

Preparation of *3-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-5,6-dihydro-1H-pyrazolo[3,4-c]pyridin-7(4H)-one* **(10)**
A mixture of 3-(5-mercapto-1,3,4-oxadiazol-2-yl)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-5,6-dihydro-1*H*-pyrazolo[3,4-c]pyridin-7(4*H*)-one**9** (474 mg, 1.0mmol) and 80%hydrazine hydrate (0.5 mL, 10mmol) in absolute ethanol (15 mL) were refluxed for 5 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent and excess hydrazine hydrate were removed under reduced pressure. The residue was washed with ice cold water and recrystallized from ethanol to yield white solid**10**.

Preparation of *1-(4-methoxyphenyl)-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbonyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-5,6-dihydro-1H-pyrazolo[3,4-c]pyridin-7(4H)-one* **(11)**
A mixture of Hydrazide **8 (**569 mg, 1.2 mmol) and ethylacetoacetate (170 mg, 1.3 mmol) in ethanol (15 ml) add a few drop of acetic acid as a catalyst refluxed for 4 h. The progress of the reaction was monitored by TLC. Upon completion, reaction mass was cooled, light yellow solid thus obtained was filtered to yield**11**.

Preparation of *1-(4-methoxyphenyl)-3-(3-methyl-5-phenyl-1H-pyrazole-1-carbonyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-5,6-dihydro-1H-pyrazolo[3,4-c]pyridin-7(4H)-one* **(12)**
A mixture of Hydrazide **8 (**569 mg, 1.2 mmol) and benzylacetone (210mg, 1.3 mmol) in ethanol (15 ml) add a few drop of acetic acid as a catalyst refluxed for 4 h. The progress of the reaction was monitored by TLC. Upon completion, reaction mass was cooled, light yellow solid thus obtained was filtered to yield **12**.

Preparation of *3-(3,5-dimethyl-1H-pyrazole-1-carbonyl)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-5,6-dihydro-1H-pyrazolo[3,4-c]pyridin-7(4H)-one* **(13)**
A mixture of Hydrazide **8 (**569 mg, 1.2 mmol) and acetylacetone (130 mg, 1.3 mmol) in ethanol (15 ml) add a few drop of acetic acid as a catalyst refluxed for 4 h. The progress of the reaction was monitored by TLC. Upon completion, reaction mass was cooled, light yellow solid thus obtained was filtered to yield **13**.
Preparation of *3-(5-hydroxy-1,3,4-oxadiazol-2-yl)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-5,6-dihydro-1H-pyrazolo[3,4-c]pyridin-7(4H)-one* **(14)**
A mixture of Hydrazide **8 (**569 mg, 1.2 mmol) and ethylchloroformate (136 mg, 1.3 mmol) in diethylether was refluxed for 5 h. The progress of the reaction was monitored by TLC. After completion of the reaction, excess solvent were removed under reduced pressure, to obtained light yellow solid **14**.

Selected SpectralData:
3-(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-5,6-dihydro-1*H*-pyrazolo[3,4-c]pyridin-7(4*H*)-one (9)

Yield: 87.5%, **m.p**.:178-180; **IR (cm-1)**:3448 and 3298 (N-H), 1669 (C=N), 1614 (C=O), 1334 and 1254 (C-N stretching), 1024 (C-O); **^{1}H NMR ($CDCl_3$, δ/ ppm)**:1.23 (m, *J*=6 Hz , 2H, CH_2), 1.86 (m, *J*=5 Hz, 2H, CH_2),2.39 (t, *J*=7 Hz, 2H, CH_2),3.20 (t, *J*=7 Hz, 2H, CH_2),3.60 (t, *J*=7 Hz2H, -CH_2), 3.81(s, 3H, -OCH_3), 4.09(t, *J*=7 Hz, 2H, CH_2), 5.95(s, 2H, NH_2), 7.01-7.55 (m, 8H, Ar-H),14.06 (s, 1H, -SH)
^{13}C NMR ($CDCl_3$, δ/ ppm):15.12, 26.01, 26.21, 28.11, 37.71, 55.94, 60.61, 116.63, 118.60, 129.61, 131.16, 131.47, 131.80, 137.61, 139.70, 144.84, 146.57, 148.79, 161.58, 164.30, 170.37, 173.98.**LCMS; m/z**: 530.60; **Anal.Calcd for** $C_{26}H_{26}N_8O_3$: C, 58.85; H, 4.94; N, 21.12%. **Found:** C, 58.45; H, 5.02; N, 20.89%.

1-(4-methoxyphenyl)-3-(3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-1-carbonyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-5,6-dihydro-1*H*-pyrazolo[3,4-c]pyridin-7(4*H*)-one(11)
Yield: 72.2%, **m.p**:180-182 ^{0}C; **IR (cm-1):**1669 (C=N), 1614 (C=O), 1334 and 1254 (C-N), 1024 (C-O); **^{1}H NMR ($CDCl_3$, δ/ ppm)**: 1.20(m, 2H, CH_2), 1.28 (m , *J*=6 Hz , 2H, CH_2), 1.93(s, 3H, -CH_3), 2.22 (s, 2H, CH_2)2.55 (t, *J*=7.7 Hz, 2H, CH_2), 3.42 (t, *J*=6.3 Hz, 2H, CH_2), 3.81(s, 3H, -OCH_3), 4.11 (t, *J*=7 Hz 2H, -CH_2), 4.18(t, *J*=7 Hz, 2H, CH_2), 6.91-7.49(m, 8H, Ar-H),
^{13}C NMR ($CDCl_3$, δ/ ppm): 8.89, 15.92, 18.24, 27.55, 39.19, 45.93, 46.30, 50.27, 55.86, 108.35, 108.46, 120.93, 121.49, 121.59, 127.16, 128.22, 134.64, 134.90, 136.19, 145.34, 151.93, 152.40, 154.67, 164.41, 164.86**. LCMS; m/z**: 540.21; **Anal.Calcd for** $C_{29}H_{28}N_6O_5$: C, 64.43; H, 5.22; N, 15.55 % **Found:** C, 64.05; H, 5.23; N, 15.27%

3-(5-hydroxy-1,3,4-oxadiazol-2-yl)-1-(4-methoxyphenyl)-6-(4-(2-oxopiperidin-1-yl)phenyl)-5,6-dihydro-1H-pyrazolo[3,4-c]pyridin-7(4H)-one (14)
Yield: 95.1%, **m.p**:144-146 ^{0}C;**IR (cm-1):**3275 (O-H),1669 (C=N), 1614 (C=O), 1334 and 1254 (C-N stretching), 1024 (C-O); **^{1}H NMR (DMSO-d6, δ/ ppm**1.22 (m , *J*=6 Hz , 2H, CH_2), 1.85 (m, *J*=5 Hz, 2H, CH_2), 2.40 (t, *J*=6.5 Hz, 2H, CH_2), 3.25 (t, *J*=6.5 Hz, 2H, CH_2), 3.61 (t, *J*=7 Hz 2H, -CH_2), 3.81(s, 3H, -OCH_3), 4.09(t, *J*=6.9 Hz, 2H, CH_2), 7.01-7.55 (m, 8H, Ar-H), 10.19(s, 1H, OH), **^{13}C NMR (DMSO-d6, δ/ ppm)**:15.04, 21.34, 23.45, 33.05, 51.29, 55.97, 60.97, 113.89, 126.49, 126.79, 127.29, 132.74, 132.93, 133.41, 138.79, 140.22, 140.33, 141.88, 156.77, 156.96, 159.69, 169.35.**LCMS; m/z:**500.51**Anal.Calcd for** $C_{26}H_{24}N_6O_5$: C, 62.39; H, 4.83; N, 16.79% **Found:**C, 62.42; H, 4.05, N, 17.09 %.

CONCLUSION

In summary, we have synthesized a series of novel apixaban derivatives that containing the oxadiazole, 1,2,4-triazole and pyrazole moieties (**9-14**). These compounds were obtained in simple and mild condition. All the newly synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, Mass and elemental analysis.

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