Section A-Research paper

A new alternative synthesis methodof rivaroxabanas a potential anti-coagulant drug: *in silico* screening, and ADMET properties

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ABSTRACT

For the first-of-its-kind, we disclose a new alternative and improved synthesis of an anti-coagulant drug rivaroxaban with their *insilico* studies, physicochemical and ADMET properties. We developed the synthesis with an overall yield of 24%, and diminished reaction times. An alternative and inexpensive chemical urea, which formed oxalidinone ring in a cost-efficient method have been developed. Here, the drug was docked with protein targets (PDB: 2Q3G, 3CEN, and 4CRC) as anti-coagulant agent. Docking results along with physicochemical and pharmacokinetic properties have been evaluated and compared with commercially available drugs such as apixaban, dabigatran, and warfarin. All these analysisprovides insight into anti-coagulant properties of rivaroxabanand provide researchers to design and develop anti-coagulant therapeutic drugs. This synthetic protocol offers an economic, cost-effective, eco-friendly, high yielding, non-tedious, by-product-free, and impurity-free synthesis of rivaroxaban which enables direct isolation of API.

Keywords: Convergent synthesis, Rivaroxaban drug,*in silico* studies,physicochemical,pharmacokinetic properties

INTRODUCTION

Anti-coagulant treatment is an important in several clinical treatments. Rivaroxaban (Xarelto®) is an oral oxazolidinone-based anti-coagulant agent and it has rapid onset of action of the first and high bioavailability direct factor X_a(FX_a) inhibitor which was developed by Bayer and approved by United States Food and Drug Administration (USFDA) [1,2]. It is employed for the prevention of venous thromboembolism (VTE) in patients undergoing knee and hip replacement surgery. Furthermore, rivaroxaban is widely used for the treatment of several thromboembolic

diseases, deep venous thrombosis, angina pectoris, transitory ischemic attacks and peripheral arterial occlusive diseases [3,4].

The synthesis based upon the type of synthons were homochiral and can create a heterocyclic frame work [5], which encouraged us to synthesize rivaroxaban. First synthesis was reported by Alexander et al [3,4]In this synthesis, morpholin-3-one (**1**) was condensed with fluoro nitrobenzene (**2**) in the presence of a base sodium hydride and *N*-methyl pyrrolidine (NMP) to afford nitro morpholinone (**3**). The nitro group of (**3**) was reduced using palladium on carbon (Pd-C) and hydrogen in tetrahydrofuran (THF) to get 4-(4-aminophenyl)-3-morpholinone (**4**). The product (**4**) on condensation with 2-[(2*S*)-2-oxiranylmethyl]-1*H*-isoindole-1, 3(2*H*)-dione (**5**) in ethanol and water mixture gave amino alcohol (**6**). Cyclization of the obtained product (**6**) using *N*,*N*´-carbonyldiimidazole (CDI) in the presence of 4-dimethylaminopyridine (DMAP) in THF formed 2-({5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1*H*-isoindole-1,3(2*H*)-dione (**7**). Deprotection of (**7**) by methyl amine in ethanol followed by condensation formed the product (**8**) and it is further treated with 5-chlorothiophene-2-carbonyl chloride (**9**) in pyridine to obtain rivaroxaban (**10**) with an overall yield of 4.5% from the starting substrate **1** (**Scheme 1**).

The aforesaid process has various disadvantages such as excessive use of expensive starting materials, which generate large amount of by-products and makes the process economically and environmentally inefficient. Moreover, the process involves tedious work-up procedures, use of highly flammable, toxic, hazardous solvents making the procedure unsafe for API preparation, lowyield of each step (4.5%) makes the process less feasible for commercial production.

In the pursuit and continuation of our earlier reported efficient, facile protocols and biologically potent compounds [6-13],we herein disclose for the first time an eco-friendly, economic, cost-effective, high yield, by-product free, reduced reaction times, non-tedious and impurity-free synthesis of rivaroxaban which enables direct isolation of API. Rivaroxaban was accomplished with an overall yield of 24%. In addition, *in silico* molecular docking studies, physicochemical and pharmacokinetic properties of the synthesized Rivaroxaban drug has been evaluated.

EXPERIMENTAL

Materials and methods

All chemicals and solvents were commercial products and used without further purification. ^{1}H, ^{13}C NMR spectra were recorded using DMSO-d_6 at 400 and 100MHz, respectively. Chemical shifts (d) are given in parts per million (ppm) and coupling constants (*J*) in Hertz (Hz). Abbreviations used for ^{1}H NMR signals are: s = singlet, d = doublet, t = triplet, and m = multiplet.2D structures of all the drugs were drawn with the help of ChemDraw pro, Cambridge software. Physicochemical properties have been evaluated with the help of online available software, i.e., swissADME, pkCSM and molinspiration. SMILES have been generated with the help of swissADME for analyzing all physicochemical and pharmacokinetic properties. ADMET (absorption, distribution, metabolism, excretion and toxicity) have been evaluated with the help of pkCSM tool [14].All structures have been docked with anti-coagulant protein targets, present in PDB (Protein Data Bank) format. Three targets have been selected for docking evaluation PDB: 2Q3G, 3CEN and 4CRC.

General procedure for the synthesis of rivaxoraban (10)

In the first step, condensation of morpholin-3-one (**1**) with fluoro nitrobenzene (**2**) in the presence of a base sodium hydride and *N*-methyl pyrrolidine (NMP) was taken in a 500 mL round-bottomed flask obtained nitro morpholinone (**3**) with enhanced yields of 21% by use of toluene in 1h. Further, in the second step, the nitro group of (**3**) was reduced using palladium on carbon (Pd-C) and hydrogen in toluene to get 4-(4-aminophenyl)-3-morpholinone (**4**) in 6h. Subsequently, in the third step, 50 g of 4-(4-aminophenyl)morpholin-3-one (**4**) and 45 g of 2-(oxiran-2-ylmethyl)isoindoline-1, 3-dione (**5**) dissolved in toluene at reflux conditions yielded 2-(2-hydroxy-3-((4-(3-oxomorpholino) phenyl)amino)propyl) isoindoline-1, 3-dione (**6**) in 94% yields. The obtained off-white solid was again purified in water and dried. In the fourth step, 34.5 g of the obtained product (**6**), 50 g of urea and 22 g of potassium hydroxide was added into a 500 mL rb flask refluxed for 21 h gave 2-({5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1*H*-isoindole-1,3(2*H*)-dione (**7**) in 89% yields. After completion of the reaction, the reaction mixture was monitored by thin layer chromatography and the precipitate was filtered to obtain an off-white solid which was further purified in water. In the subsequent fifth step, 15 g of the product (**7**) was subjected for de-phthalation in 100 mL of 10% ammonia in

isopropyl alcohol (IPA) refluxed for 30 min. The reaction mass was filtered and the light brown product 4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one (**8**) was obtained. In the final step of the synthesis, 75 g of the product (**8**), 82 g of 5-chlorothiophene-2-carbonyl chloride (**9**), 45 g of potassium *tert*-butoxide dissolved in dimethylformamide at 0^{o}C for 30 min yielded rivaxoraban(**10**) in 91% yields.After completion of the reaction, 350 mL of water was added to quench the reaction and the obtained white product was purified in ethyl acetate to get high pure material (**10**) (Scheme 2).

2-(2-hydroxy-3-((4-(3-oxomorpholino) phenyl)amino)propyl) isoindoline-1, 3-dione (6)

^{1}H NMR (DMSO-d_6, 400 MHz, ppm): □ 7.81-7.88 (m, 4H), 7.03 (d, *J*= 6.3 Hz, 2H), 6.62 (d, *J*= 12.4 Hz, 2H), 5.66 (t, *J*= 9.3 Hz, 1H), 5.17 (d, *J*= 11.3 Hz, 1H), 3.98 (s, 2H), 3.91-3.93 (m, 1H), 3.65 (t, *J*= 7.6 Hz, 2H), 3.58-3.63 (m, 4H), 3.14-3.20 (m,1H), 3.02-3.05 (m, 1H).^{13}C NMR (DMSO-d_6, 100 MHz, ppm): □ 168.1, 165.7, 147.4, 134.2, 131.8, 130.3, 126.4, 112.9, 112.0, 67.7, 66.3, 63.5, 49.6, 47.4, 42.4.LC-MS: *m/z*397 $[M+2]^{+}$.

2-({5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1*H*-isoindole-1,3(2*H*)-dione (7)

^{1}H NMR (DMSO-d_6, 400 MHz, ppm): □ 7.85-7.90 (m, 4H), 7.53 (d, *J*= 8.4 Hz, 2H), 7.42 (d, *J*= 12.0 Hz, 2H), 4.93-4.96 (m, 1H), 4.21 (t, *J*= 11.2 Hz, 3H), 3.89-3.98 (m, 5H), 3.72 (t, *J*= 10.2 Hz, 2H).^{13}C NMR (DMSO-d_6, 100 MHz, ppm):□ 167.7, 165.9, 153.8, 137.1, 136.3, 134.5, 131.4, 125.9, 123.2, 118.3, 70.0, 67.7, 63.4, 48.9, 47.4, 40.4.LC-MS: 422.1 $[M+H]^{+}$.

4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one(8)

^{1}H NMR (DMSO-d_6, 400 MHz, ppm):□ 7.62 (d, *J*= 7.2 Hz, 2H), 7.41 (d, *J*= 13.5 Hz, 2H), 4.63-5.12 (m, 1H), 4.20 (s, 2H), 3.98-4.18 (m, 2H), 3.93-3.97 (m, 1H), 3.71 (t, *J*= 13.2 Hz, 2H), 2.75-2.92 (m, 2H), 1.91 (s, 2H).^{13}C NMR (DMSO-d_6, 100 MHz, ppm): □ 165.9, 154.4, 136.7, 125.9, 118.1, 73.9, 67.7, 63.4, 49.0, 47.0, 44.1, 40.1, 39.9, 38.8.LC-MS: 292.2 $[M+H]^{+}$.

Rivaxoraban (10)

^{1}H NMR (DMSO-d_6, 400 MHz, ppm):□ 8.97 (t, *J*= 11.3 Hz, 1H), 7.73 (d, *J*= 7.6 Hz, 2H), 7.54 (d, *J*= 9.1 Hz, 2H), 7.43 (d, *J*= 12.4 Hz, 2H), 7.19 (d, *J*= 8.4 Hz, 1H), 4.76-4.91 (m, 1H), 4.11-4.22 (m, 3H), 3.97-4.09 (m, 2H), 3.85-3.95 (m, 1H), 3.74 (t, *J*= 9.2 Hz, 2H), 3.61 (t, *J*= 12.1 Hz, 2H).^{13}C NMR (DMSO-d_6, 100 MHz, ppm):□165.9, 160.8,154.0, 138.4, 137.0, 136.4, 133.2, 128.4, 125.9, 118.3, 71.3, 67.7, 63.4, 49.00, 47.41, 42.21, 40.12, 39.49, 39.28, 39.08, 38.87; LC-MS: 436.15 $[M+H]^{+}$.

RESULTS AND DISCUSSION

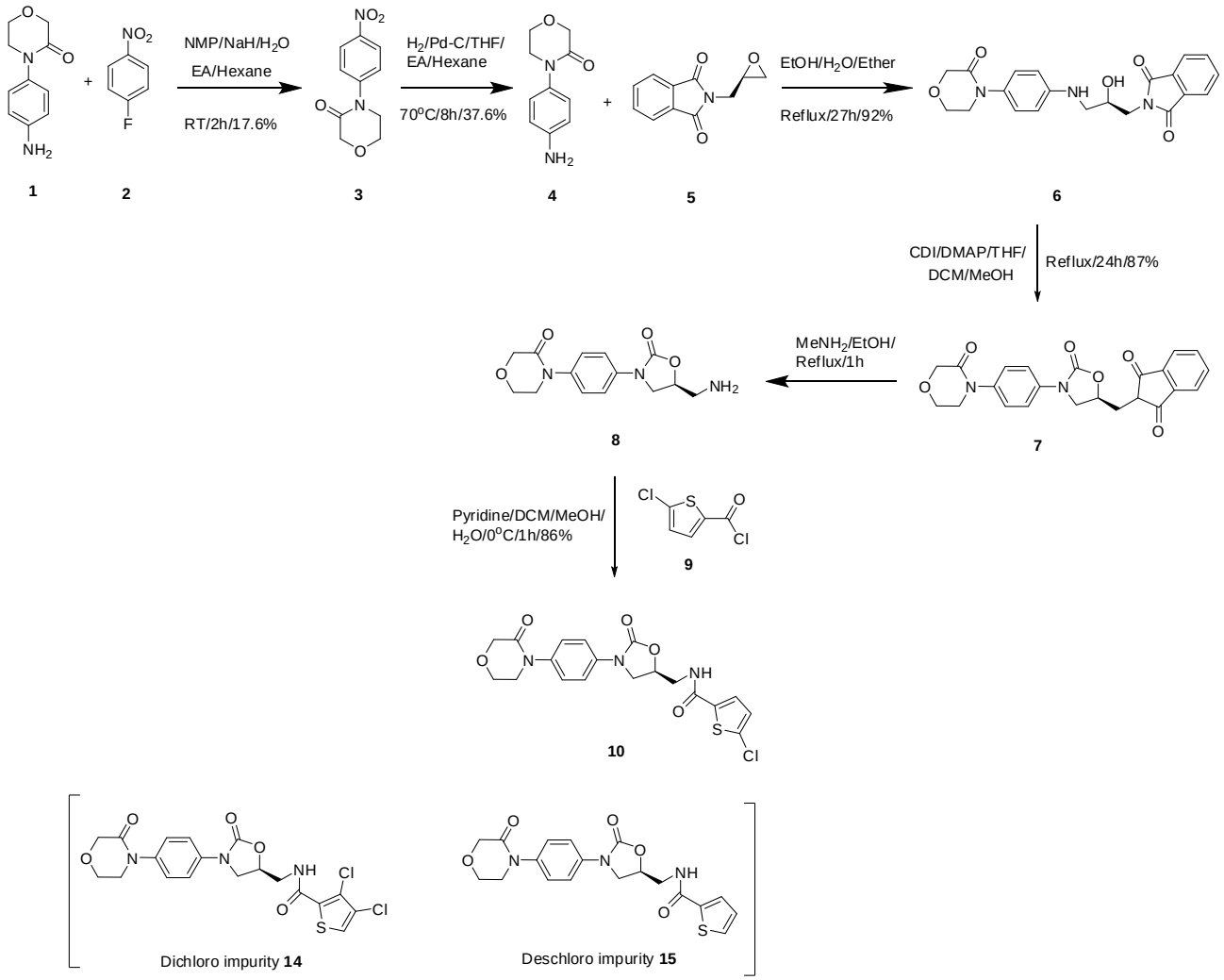
At the outset, for the synthesis of rivaxoraban, our focus was on reducing the use expensive starting substrates, toxic reagents, and hazardous solvents and designing an eco-friendly protocol without any by-products. In addition, we also aimed to improve the overall yield and to obtain the desired product in shorter reaction times which is important for API stage.

It was noted that in the reported method (Scheme 1) the use of CDI in step 4 produced some impurities. Therefore, an alternative to CDI is necessary. In such search, we found urea was the alternative reagent for the development process. Urea is 70 times cheaper than CDI which could express a big success for oxalidinone ring formation in a very cost efficient manner.

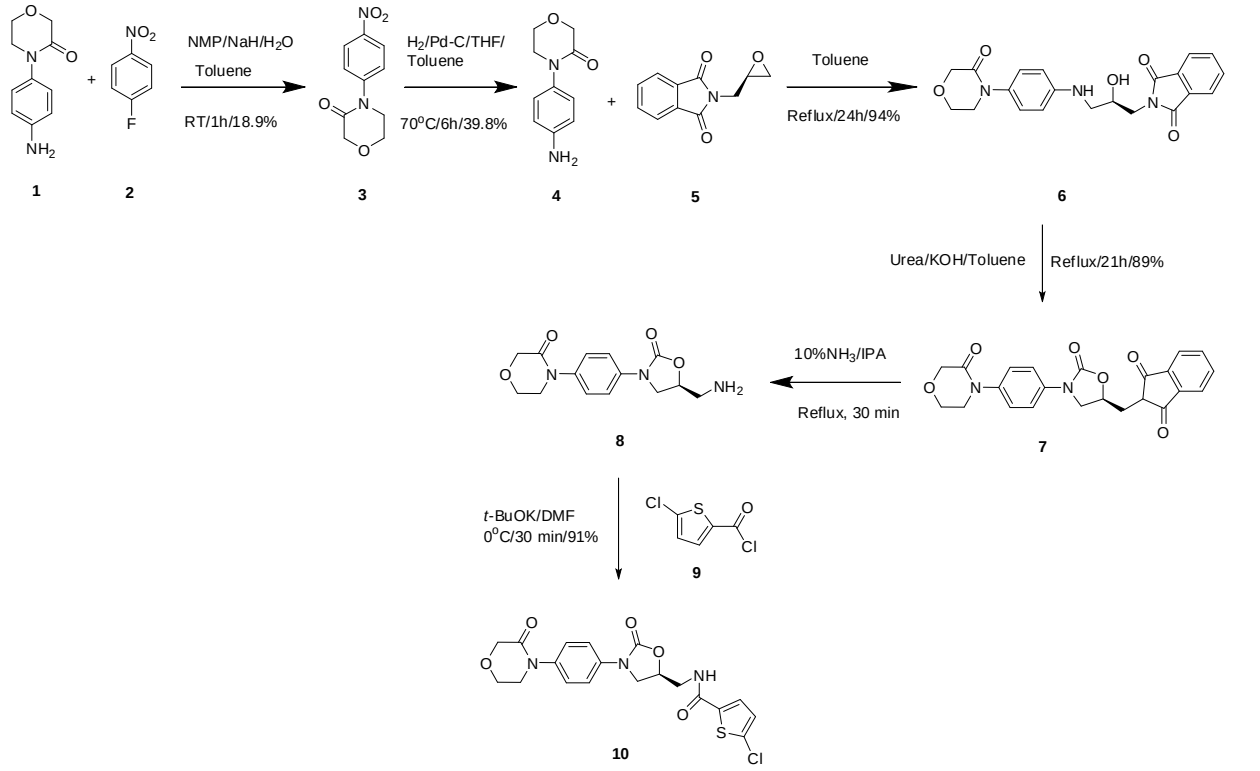
In the first step, condensation of morpholin-3-one (**1**) with fluoro nitrobenzene (**2**) in the presence of a base sodium hydride and *N*-methyl pyrrolidine (NMP) afforded (**3**) with enhanced yields of 21% by use of toluene in 1h. The nitro group of (**3**) was reduced using palladium on carbon (Pd-C) and hydrogen in toluene to get (**4**) in 6h. The intermediate (**6**) was synthesized starting from 4-(4-aminophenyl)morpholin-3-one (**4**) and 2-(oxiran-2-ylmethyl)isoindoline-1,3-dione (**5**) in a cost-effective manner with reduced usage of reagents and solvents. At reflux conditions using toluene as a solvent, we improved yields to 94% and completed the reaction in 24 h. Subsequently, we have used urea in KOH and toluene under reflux conditions. In this step, we obtained an improved yield of (**7**) 91% in 21h. A simple dephthalation of (**7**) with 10% ammonia in isopropyl alcohol for 30 min afforded (**8**). Finally, 5-chlorothiophene-2-carbonyl chloride (**9**) was reacted with the obtained product (**7**) in the presence of potassium *tert*-butoxide and DMF for 30 min to afford rivaxoraban (**10**) in 91% yields (Scheme 2). All these steps were successfully accomplished by improving the yields and also reduced the reaction times in each step. Urea proved to be a cost-efficient reagent and no side products obtained during this synthesis (Scheme 2).

Evaluations of physicochemical and pharmacokinetic properties are crucial for drug designing and development. Physicochemical properties depend on some key parameters, i.e., according to RO5 rule (Lipinski rule of five). These parameters are molecular weight, hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), number of rotational bonds (nRot), violations, topological surface area (TPSA), etc. For best physicochemical property, a drug should have MW ≤ 600, HBA ≤ 10, HBD ≤ 5, TPSA ≤ 150 Å2, nRot ≤ 10, MR ≤ 155, violations ≤ 4. When

Rivaxoraban was carried out for physicochemical properties (Table 2), it was found that it fulfils all the criteria of RO5. It showed zero violation and exhibited comparable results with marketed available drugs (Table 3). Rivaxoraban's physicochemical properties has been conferred via three tools, i.e., swissADME, pkCSM and molinspiration. Pharmacokinetic properties have been evaluated on the basis of certain parameters. These parameters should be Caco-2 cell permeability (log Papp in 10^{-6} cm/s > 0.09), Intestinal absorption (human) % Absorbed (> 30), VD_{SS} (human) {Numeric (log L/kg)} (Low if < - 0.15 and high. if > 0.45. Molecular docking has been done after analysing the physicochemical and pharmacokinetic properties. Molecular docking works as "lock & key" hypothesis, where protein targets act as lock and drug/ligand act as key. Molecular docking depends on preparation of ligand/drug and selection of targets (protein). We have prepared the drug with the help of MarvinSketch tool and cleaned in "CLEAN 2D" and "CLEAN 3D". Drug is saved in mol2 format after cleaning via MarvinSketch server. Protein (targets) have been downloaded in PDB (Protein Data Bank) format from rcsb.org. There are certain parameters of molecular docking on which it works, i.e., full fitness score, number of clusters, binding energy modes, Deltagligsolvolpol, hydrogen binding interactions, DeltaG etc. We evaluated the activity and affinity of Rivaxoraban drug along with three marketed drugs. All drugs have been docked with three anti-coagulant protein targets, i.e., PDB: 2Q3G, 3CEN and 4CRC. Rivaxoraban exhibited comparable results with marketed drugs on the basis of full fitness score and DeltaG value.



Scheme 1.Reported route for the synthesis of Rivaroxaban



Scheme 2.Alternativeapproach for the synthesis of anti-coagulant drug Rivaroxaban

Physicochemical, pharmacokinetic and docking studies of Rivaxoraban

Evaluation of physicochemical and pharmacokinetic properties are crucial for drug designing and development. Physicochemical properties depend on some key parameters, *i.e*., according to RO5 rule (Lipinski rule of five). These parameters are molecular weight, hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), number of rotational bonds (nRot), violations, and topological surface area (TPSA), etc. For best physicochemical property, a drug should have MW ≤ 600, HBA ≤ 10, HBD ≤ 5, TPSA ≤ 150 Å2, nRot ≤ 10, MR ≤ 155, violations ≤ 4. When Rivaxoraban drug was carried out for physicochemical properties (Table 2), it was found that it fulfils all the criteria of RO5. It shown zero violation and exhibited comparable results with commercially available drugs (Tables 1 and 3). Rivaxoraban's physicochemical properties have been conferred *via* three tools, i.e., swissADME, pkCSM and molinspiration. Pharmacokinetic properties have been evaluated on the basis of certain parameters. These parameters should be Caco-2 cell permeability (log Papp in 10^{-6} cm/s > 0.09), Intestinal absorption (human) % absorbed (> 30), VD_{SS} (human) {Numeric (log L/kg)} (Low if < - 0.15 and high. if > 0.45 (Tables 4 and 5). Molecular docking has been done after analyzing the physicochemical and

pharmacokinetic properties. Molecular docking works as 'lock & key' hypothesis, where protein targets act as lock and drug/ligand act as key. Molecular docking depends on preparation of ligand/drug and selection of target proteins. We have prepared the drug with the help of MarvinSketch tool and cleaned in "CLEAN 2D" and "CLEAN 3D". Drug was saved in mol2 format after cleaning *via*MarvinSketch server. Protein (targets) have been downloaded in PDB (Protein Data Bank) format from rcsb.org. There are certain parameters of molecular docking on which it works, i.e., full-fitness score, number of clusters, binding energy modes, deltagligsolvolpol, hydrogen binding interactions, and deltaG, etc. We evaluated the activity and affinity of Rivaxoraban drug (Figure 1) along with three above marketed drugs. All drugs have been docked with three anti-coagulant protein targets, i.e., PDB: 2Q3G, 3CEN and 4CRC (Tables 6 and 7).Rivaxoraban exhibited comparable results with marketed drugs on the basis of full-fitness score and deltaG value.[14]

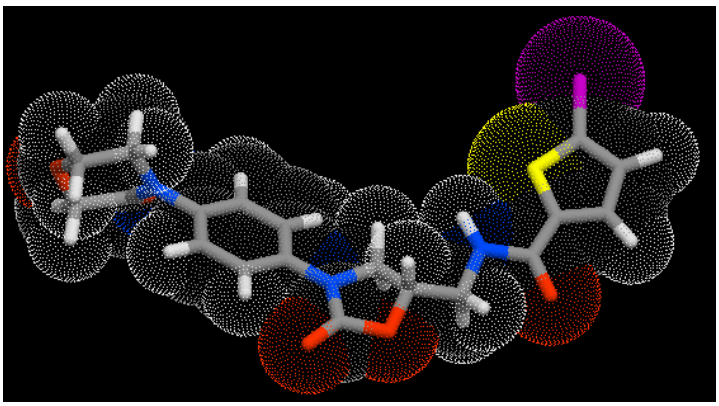


Figure 1: 3D molinspiration structure of Rivaxoraban(an anti-coagulant drug) in dotted form

CONCLUSION

In conclusion,an alternative and improved synthesis of an anti-coagulant drug rivaroxaban was developed by using inexpensive and readily available urea, which was the key step in the synthesis. This synthesis has several advantages such as economic, cost-effective, eco-friendly, overall yields of 24%, non-tedious work-up procedure, reduced reaction times, by-product free and impurity-free synthesis of rivaroxaban which enables direct isolation of API. In addition, *in silico* studies, physicochemical and pharmacokinetic properties were performed. Hence, the present protocol could also be helpful for investigating efficient synthesis of other new anti-coagulant drugs.

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Conflict of interest

The authors declare no conflict of interest.

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Table 1.Structures and IUPAC name of Rivaxoraban and marketed drugs

Drugs	IUPAC Name	Structure
Rivaxoraban	(S)-5-chloro-*N*-((2-oxo-3-(4-(3-oxomorpholino)phenyl)oxazolidin-5-yl)methyl)thiophene-2-carboxamide	
Apixaban	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	
Dabigatran	3-(2-(((4-carbamimidoylphenyl)amino)methyl)-1-methyl-N-(pyridin-2-yl)-1H-benzo[d]imidazole-5-carboxamido)propanoic acid	
Warfarin	4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one	

Table 2. Computed physicochemical properties of Rivaxoraban

Rivaxoraban			
	swissADME	**pkCSM**	**Molinspiration**
MW	435.88	435.88	435.89
nRot	6	5	5
HBA	5	6	1
HBD	1	1	8
TPSA	116.42	175.486	88.18
No. of violations	0	0	0

Table 3. Computed physicochemical properties of marketed anti-coagulant drugs

Marketed Drugs			
	Apixaban	**Dabigatran**	**Warfarin**
MW	459.50	471.51	308.33
nRot	5	10	4
HBA	5	6	4
HBD	1	4	1
TPSA	110.76	150.22	67.51
No. of violations	0	0	0

*M*W ≤ 600, Mlog*P* ≤ 5, Ali log *S* ≤ 0, HBA ≤ 10, HBD ≤ 5, TPSA ≤ 150 Å2, *n*Rot ≤ 10, MR ≤ 155

Table 4. Computed pharmacokinetic properties of Rivaxoraban and marketed drugs

Compound	**Caco2 permeability (logPappin 10-6cm/s)**	**Intestinal absorption (human) (%Absorbed)**	**VDss (human) (logL/kg)**	**Fraction unbound (human)**	**P-gp substrate (yes/No)**
Rivaxoraban	1.058	92.71	-0.564	0.014	No
Apixaban	0.894	97.65	-0.196	0	No
Dabigatran	-0.816	57.04	0.841	0	Yes
Warfarin	0.955	96.137	-0.137	0.075	No

Caco-2 cell permeability (log Papp in 10^{-6} cm/s > 0.09), Intestinal absorption (human) % Absorbed (> 30), VD_{SS}(human) {Numeric (log L/kg)} (Low if < - 0.15 and high. if > 0.45)

Table 5. Computed pharmacokinetic (toxicity) properties of Rivaxoraban and marketed drugs

Compound	Total Clearance	Renal OCT2 substrate	AMES toxicity	hERG I inhibitor	Oral Rat Acute Toxicity (LD50)	Oral Rat Chronic Toxicity (LOAEL)	Hepato-toxicity	Skin Sensitization
Rivaxoraban	0.29	Yes	No	No	2.465	1.173	Yes	No
Apixaban	0.283	No	No	No	2.689	1.275	Yes	No
Dabigatran	0.539	No	No	No	2.513	1.707	Yes	No
Warfarin	0.803	No	No	No	2.568	1.593	Yes	No

Table 6. Molecular docking data of Rivaxoraban docked with PDB: 2Q3G, 3CEN & 4CRC

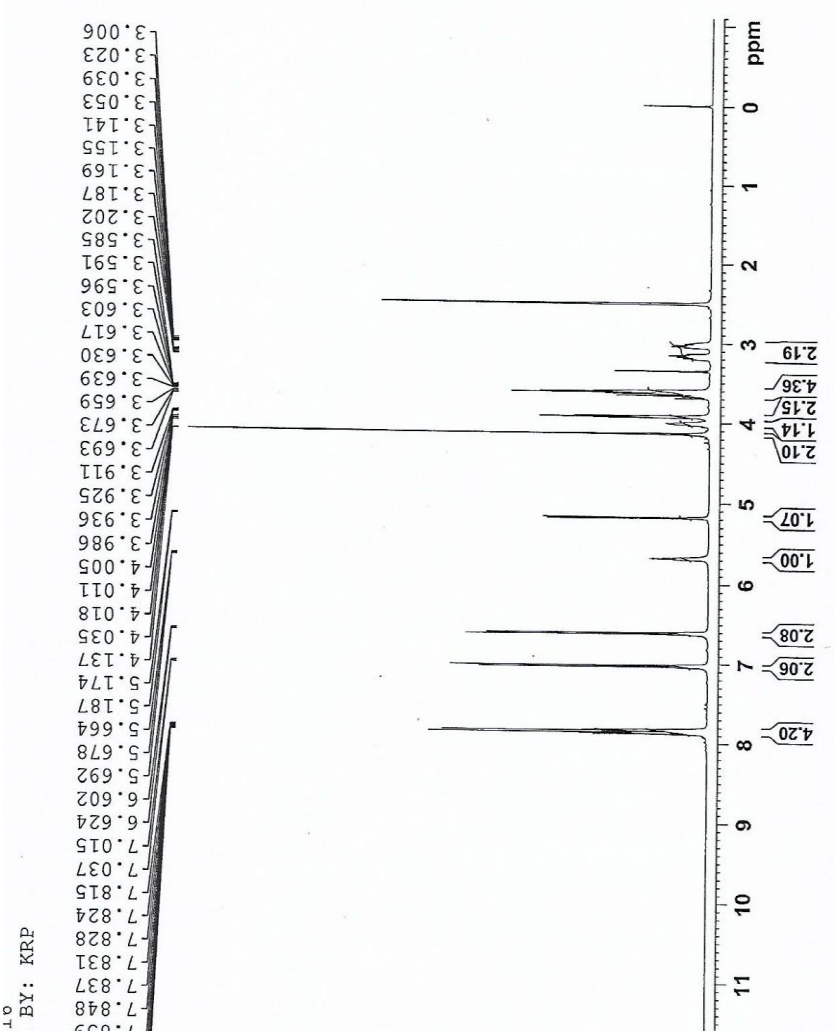
Rivaxoraban docked with PDB	No. of SwissDock clusters	Cluster rank	deltaG	Full fitness (kcal/mol)	Energy	H-Binding Interactions
PDB:2Q3G	0	0	-7.57	-3874.63	11.23	[1]. #0 GLU 523 HN-#1.1 LIG 1 O2 2.327 Å.
PDB:3CEN	0	0	-9.94	-1605.15	-4.58	[1]. #1.1 LIG 1 H16-#0 GLY 218 O 2.383 Å.
PDB:4CRC	1	4	-7.52	-1086.80	13	[1]. #0 GLY 193 HN-#1.13 LIG 1 O5 2.024 Å. [2]. #0 SER 195 HN-#1.13 LIG 1 O5 2.106 Å.

Table 7. Molecular docking data of marketed drugs docked with PDB: 2Q3G, 3CEN & 4CRC.

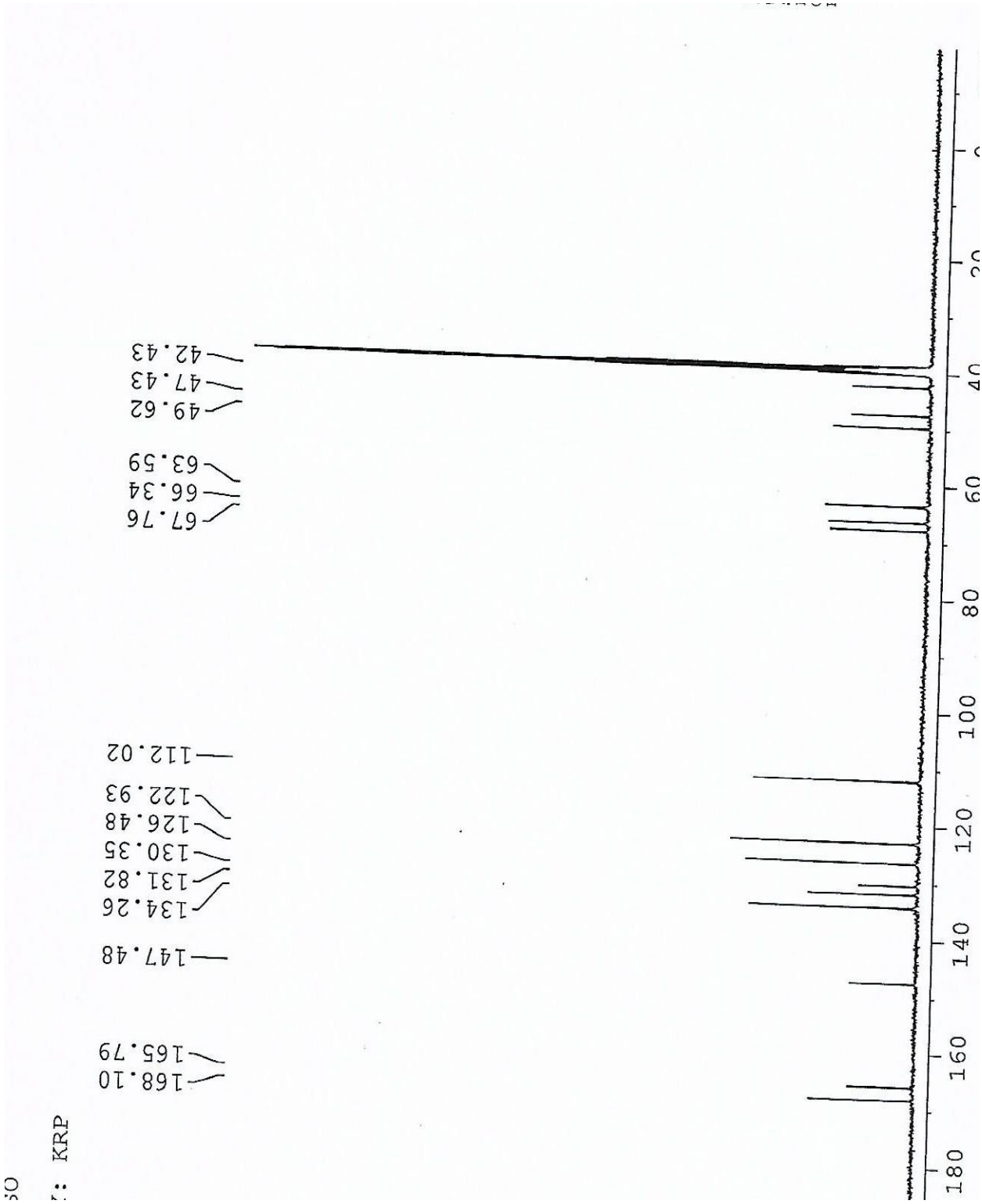
Marketed Drug: Apixaban						
Marketed Drugs docked with PDB	**No. of SwissDock clusters**	**Cluster rank**	**deltaG**	**Full fitness (kcal/mol)**	**Energy**	**H-Binding Interactions**
PDB:2Q3G	0	0	-7.12	-3848.35	43.51	[1]. #1.1 LIG 1 H24-#0 ASP 671 0 2.223 Å.
PDB:3CEN	0	0	-9.35	-1575.48	33.23	[1]. #0 GLY 216 HN-#1.1 LIG 1 O2 2.246 Å.
PDB:4CRC	22	0	-7.66	-1134.57	34	[1]. #1.133 LIG 1 H25-#0 LEU 162 O 2.422 Å. [2]. #1.133 LIG 1 H18-#0 VAL 132 O 2.164 Å.
Marketed Drug: Dabigatran						
Marketed Drugs docked with PDB	**No. of SwissDock clusters**	**Cluster rank**	**deltaG**	**Fullfitness (kcal/mol)**	**Energy**	**H-Binding Interactions**
PDB:2Q3G	23	1	-7.70	-3915.88	28.36	[1]. #1.188 LIG 1 H23-#0 LEU 420 O 2.119 Å. [2]. #1.188 LIG 1 H23-#0 LEU 420 O 2.069 Å. [3]. #1.188 LIG 1 H24-#0 ALA 399 O 1.942 Å.
PDB:3CEN	24	2	-7.51	-1633.91	32.74	[1]. #1.150 LIG 1 H23-#0 GLU 97 O 2.091 Å. [2]. #1.150 LIG 1 H25-#0 GLU 97 O 2.425 Å.
PDB:4CRC	13	2	-6.87	-1128.33	40.78	[1]. #1.98 LIG 1 H25-#0 LEU 162 O 2.418 Å. [2]. #1.98 LIG 1

						H18-#0 VAL 132 O 2.261 Å.
Marketed Drug:Warfarin						
Marketed Drugs docked with PDB	**No. of SwissDock clusters**	**Cluster rank**	**deltaG**	**Full fitness (kcal/mol)**	**Energy**	**H-Binding Interactions**
PDB:2Q3G	7	3	-6.46	-3863.30	24.01	[1]. #0 VAL 401 HN-#1.66 LIG 1 O3 2.128 Å.
PDB:3CEN	1	0	-7.48	-1587.59	20.87	[1]. #0 GLY 218 HN-#1.11 LIG 1 O2 2.169 Å.
PDB:4CRC	0	0	-9.49	-1145.96	16.43	[1]. #1.1 LIG 1 H9-#0 LEU 39 O 1.850 Å.

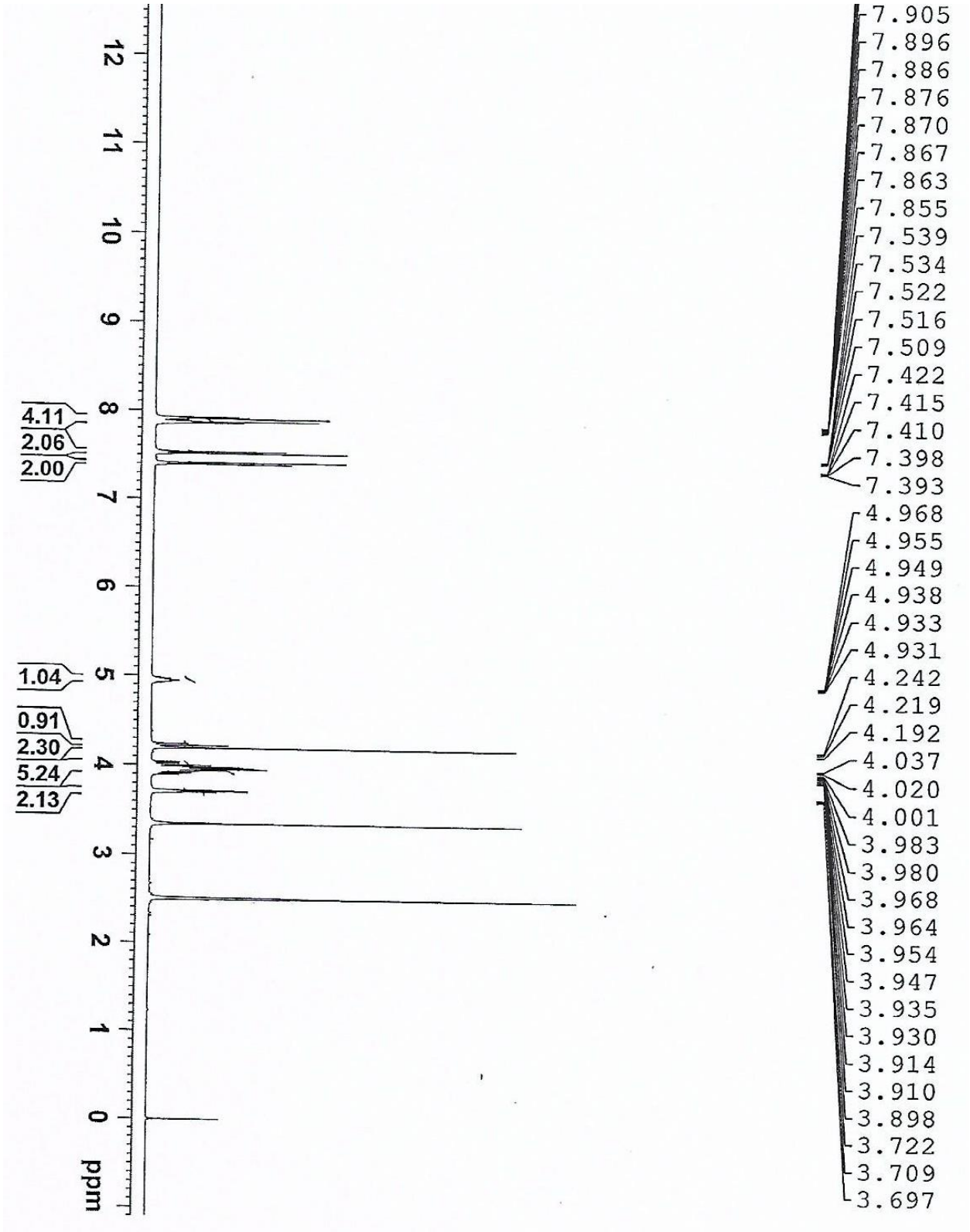
Supplementary information



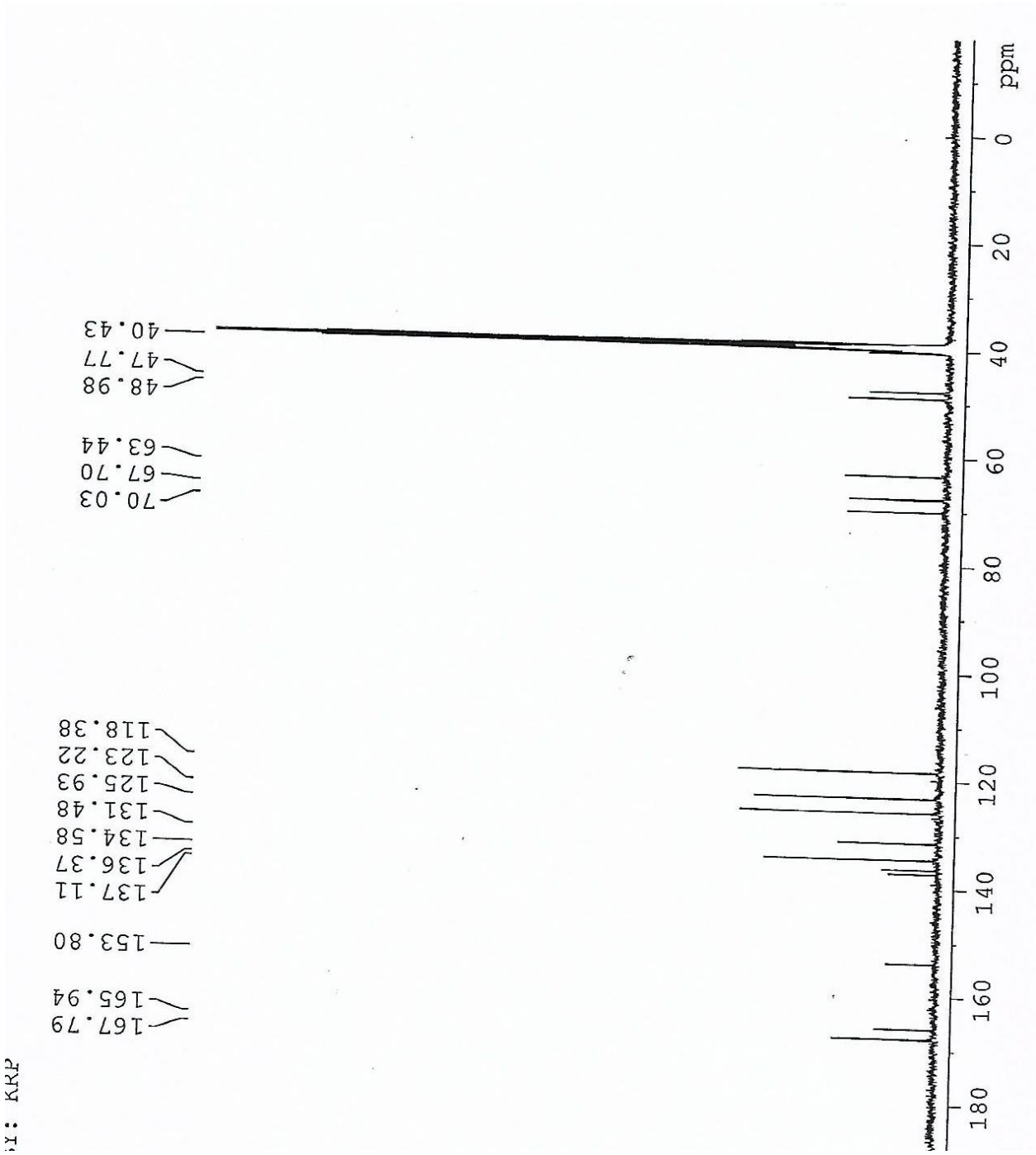
^{1}H NMR 2-(2-hydroxy-3-((4-(3-oxomorpholino) phenyl) amino) propyl) isoindoline-1, 3-dione **(6)**



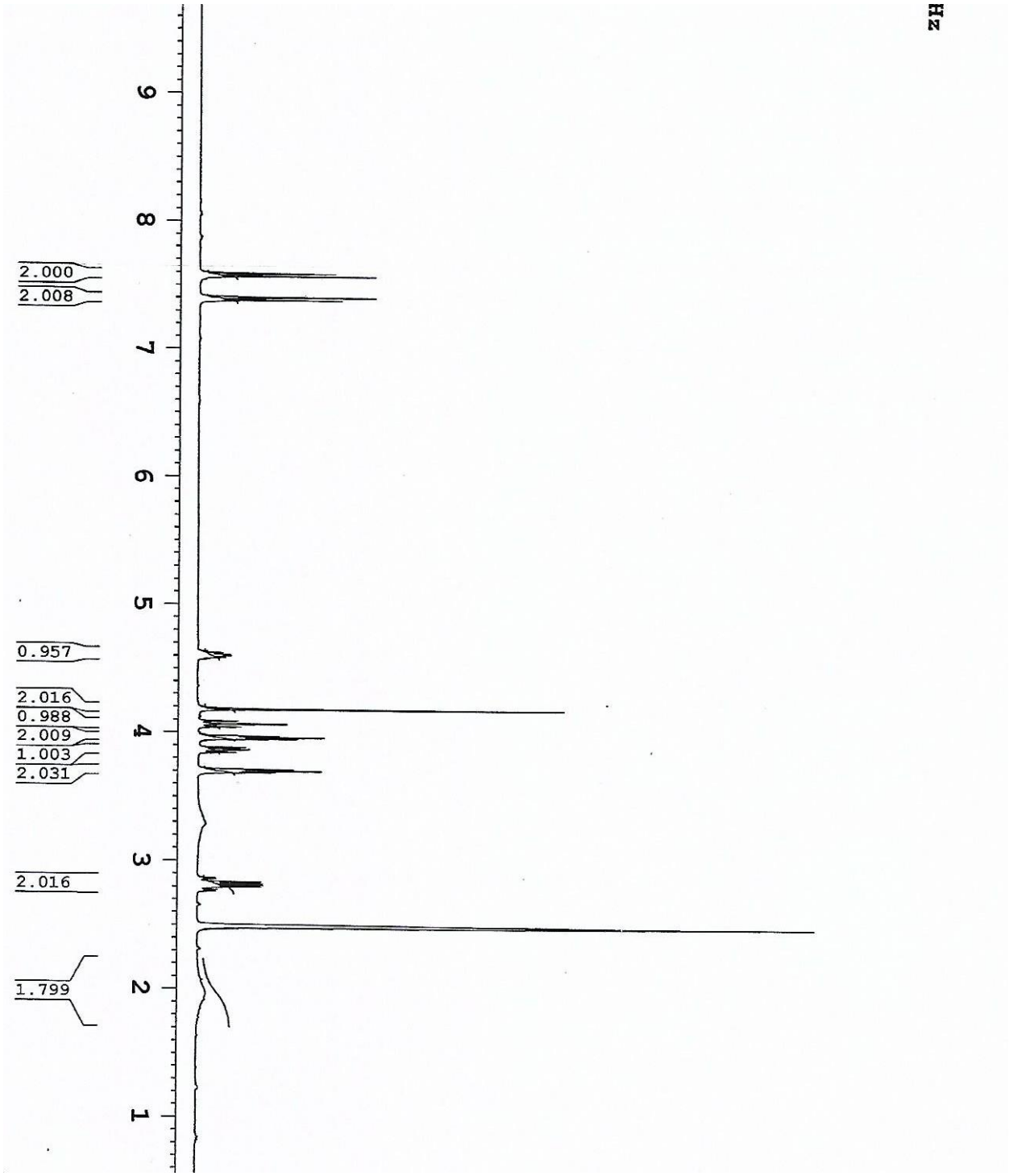
^{13}C NMR 2-(2-hydroxy-3-((4-(3-oxomorpholino) phenyl) amino) propyl) isoindoline-1,3-dione **(6)**



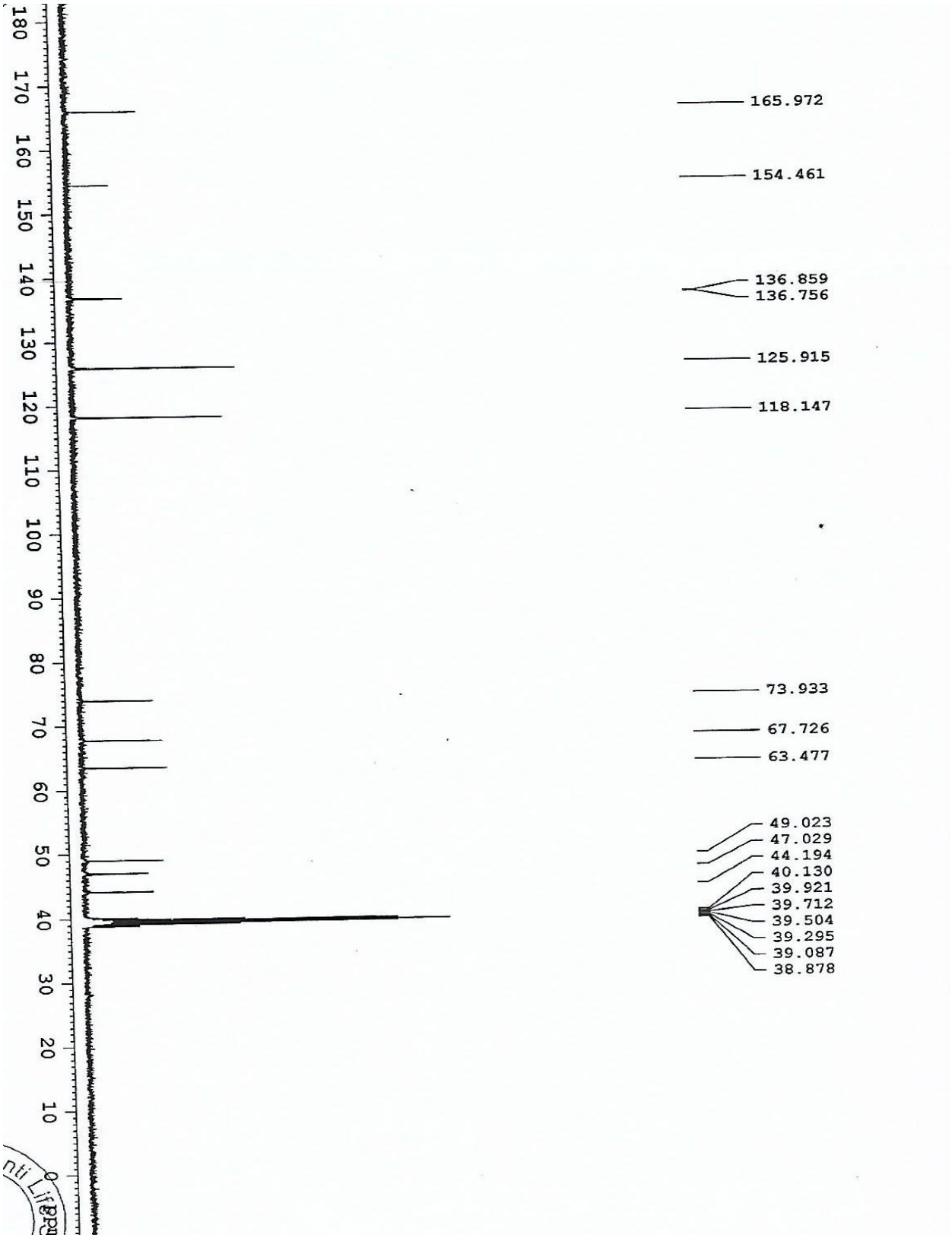
^{1}H NMR 2-((2-oxo-3-(4-(3-oxomorpholino) phenyl) oxazolidin-5-yl) methyl) isoindoline-1, 3-dione **(7)**



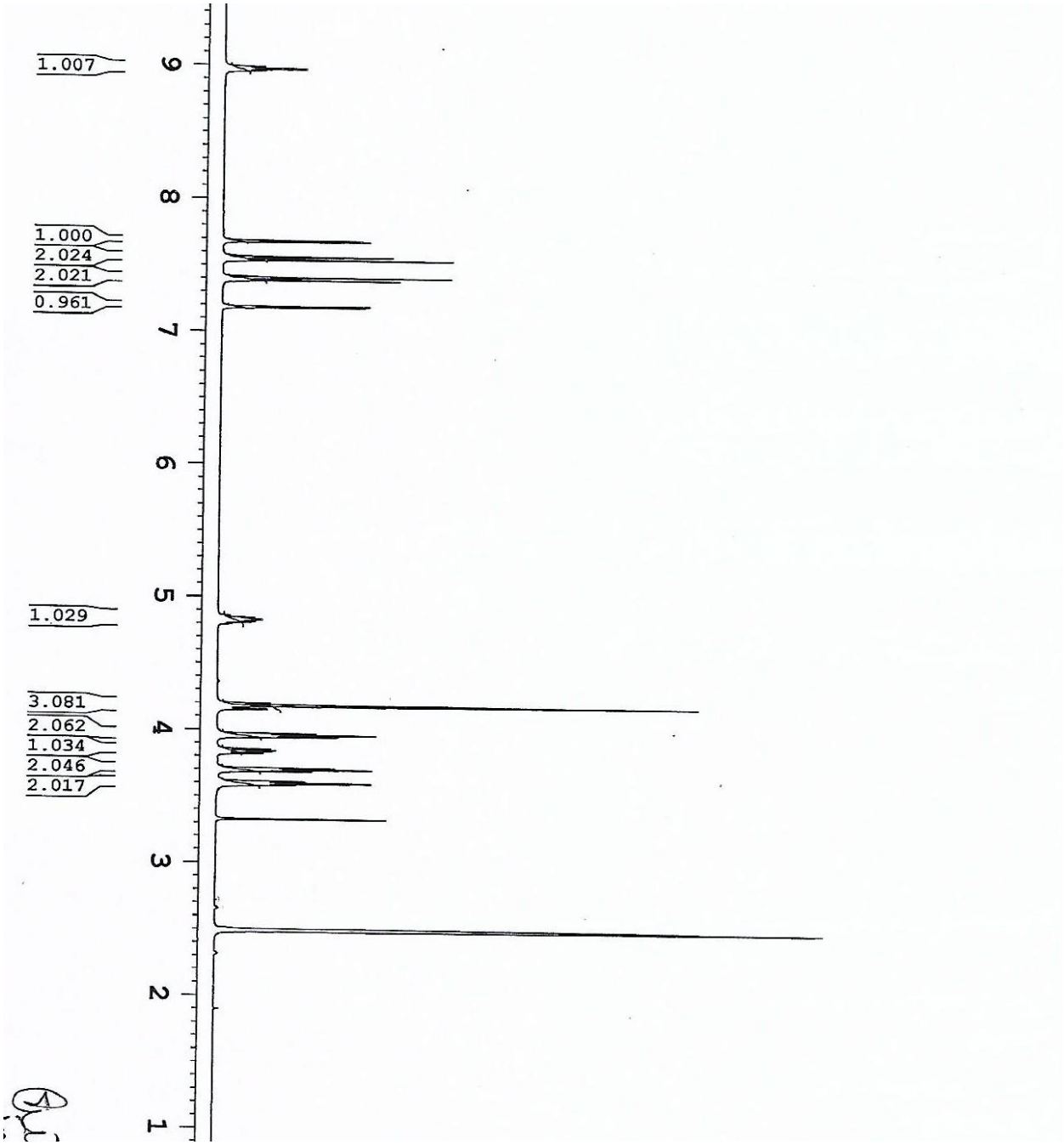
^{13}C NMR 2-((2-oxo-3-(4-(3-oxomorpholino) phenyl) oxazolidin-5-yl) methyl) isoindoline-1, 3-dione **(7)**



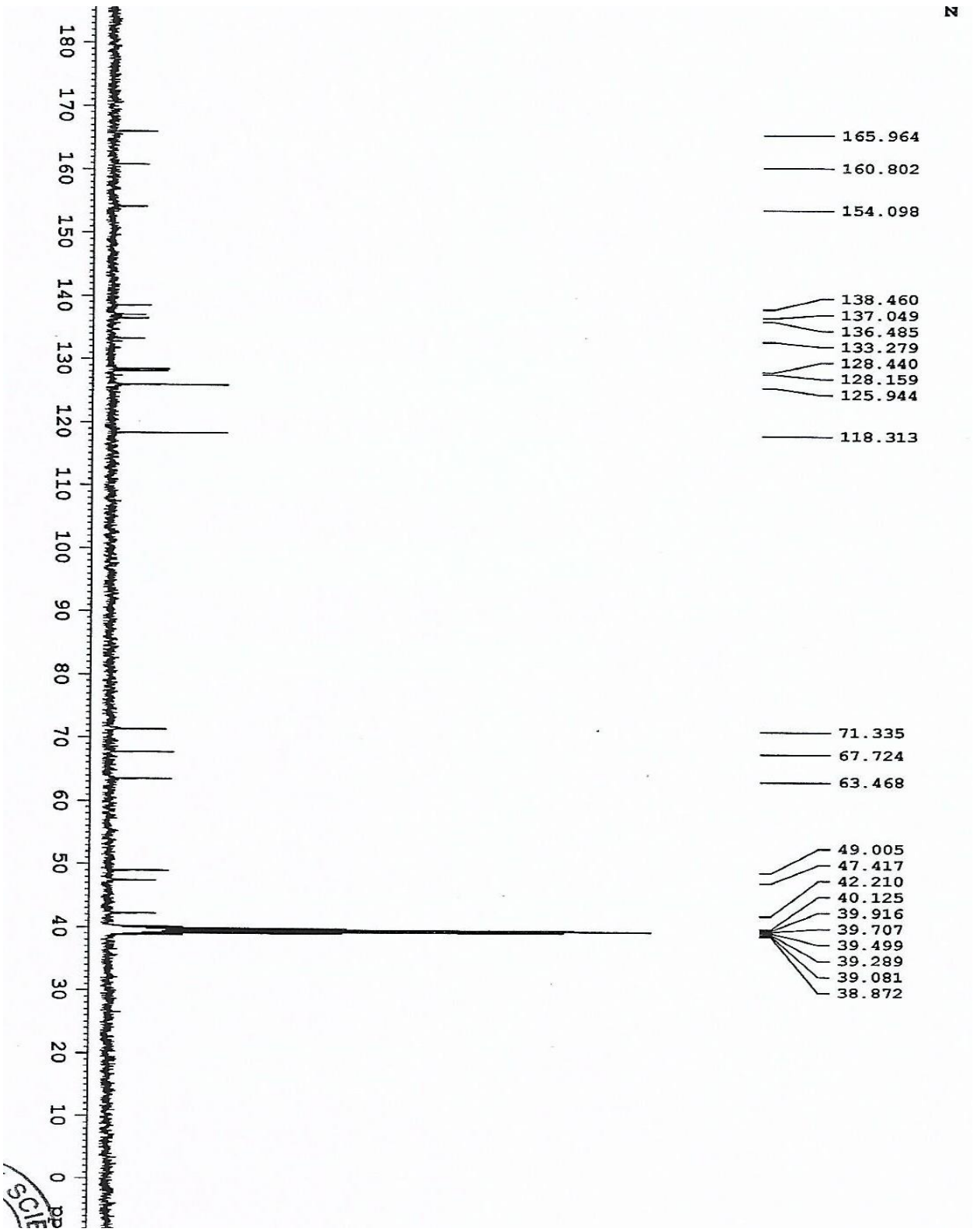
^{1}H NMR 4-(4-(5-(amino methyl)-2-oxooxazolidin-3-yl) phenyl) morpholin-3-one **(8)**



^{13}C NMR 4-(4-(5-(amino methyl)-2-oxooxazolidin-3-yl) phenyl) morpholin-3-one **(8)**



^{1}H NMR 5-chloro-n-((2-oxo-3-(4-(3-oxomorpholino) phenyl) oxazolidin-5-yl) methyl) thiophene-2-carboxamide **(10)**



^{13}C NMR of 5-chloro-n-((2-oxo-3-(4-(3-oxomorpholino) phenyl) oxazolidin-5-yl) methyl) thiophene-2-carboxamide **(10)**