Original Article

CHARCTERIZATION, PRE-CLINICAL EVALUATION OF NOVEL OXADIAZOLE DERIVATIVES

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Abstract

The practice of medicinal chemistry is devoted to the discovery and development of new therapeutic agents for treating different diseases. Novel 7-Azaisatin, Oxazolone, Oxadiazole derivatives possess various pharmacological properties as per literature studies. The aim of this research work is to synthesize novel substituted 7-Azaisatin, Oxazolone, Oxadiazole by synthetic methodologies and to evaluate the biological activity.

The present study focuses to design "New 7-Azaisatin, Oxazolone, Oxadiazole Derivatives". Total 30 compounds were synthesized by three different schemes. The synthesized compounds were categorized into 7-azaisatin derivatives (VIIA-VIIL) ,Oxazolone derivatives (OXA01-OXA09),Oxadiazole (OXDO01-OXDO07). Reactions were carried out by reflexing at temp of 75°C-80°C and some at rt. Most of the reactions were completed in shorter times and products were obtained in good yields. The structure of synthesized compounds were established by IR,1H NMR,C NMR spectral studies.

The newly synthesized compounds were evaluated for their against different cancer cell lines by the standard MTT assay method. All the synthesized novel derivatives were found to be potent biological activities.

Keywords: 7-Azaisatin, Molecular docking, Oxazolone, Analgesic activity, Anti-inflammatory activity, Oxadiazole.

1. INTRODUCTION

Oxadiazoles are small five-membered heterocycles, composed of two carbon, one oxygen, and two nitrogen atoms, which attracted a lot of interest in different scientific disciplines: from medicine and agro chemistry to materials science.

Their aromatic flat surface is effective in the target binding, through π-stacking interactions, or to properly outdistance the substituents according to a specific orientation. Depending on nitrogen atoms position, oxadiazoles exist in four different regioisomeric forms 1,2,3-, 1,2,4-, 1,2,5-, and 1,3,4-oxadiazoles. [1]

Among the four isomers, 1,2,4- and 1,3,4-oxadiazoles frequently occur in a large series of drug-like molecules, including antiviral, antihypertensive, anti-diabetic anti-inflammatory, and analgesic, as well as anticancer compounds. Probably, this is a direct consequence of the orientation of the side chains (-R1 and -R2 in Figure 1), very similar for 1,2,4- and 1,3,4-oxadiazoles with respect to 1,2,3- and 1,2,5-oxadiazoles. Indeed, small bioactive molecules with resembling shapes usually show target-binding similarity that translates into the same biological effects . Moreover, their bioisosteric correspondence with ester and amide groups makes oxadiazoles an interesting synthetic alternative to avoid intrinsic molecular instability (e.g., due to hydrolysis reactions), guaranteeing different hydrogen-bonding potentials with the receptors .

The extensively use of this class of heterocyclic compounds in medicinal chemistry is confirmed by the presence of several commercially available drugs based on these interesting scaffolds. The reasons for their success lie in an efficient and simple synthesis, high versatility, giving rise to elevated structural diversity, and remarkable stability, a key feature for in vivo applications. Thanks to its structural nature, oxadiazoles easily interact with bio-targets establishing π-stacking interactions or forming strong hydrogen bonds.[3]

During the last decades, the design of new oxadiazole-based scaffolds accelerated in medicinal chemistry, bringing most of these compounds to the preclinical stage or, even, to commercialization. Among these, the most commercially available drugs are Oxolamine, a cough suppressant, Ataluren, indicated for the treatment of Duchenne muscular dystrophy and cystic fibrosis, Butalamine, a vasodilator, Proxazole, a drug for functional gastrointestinal disorders, Fasiplon, an anxiolytic drug, Raltegravir, an antiretroviral drug used to treat HIV which has been recently proposed as repurposing drug against SARS-COV-2 , as well as the antiviral Pleconaril selected for the SARS-COV-2 spike protein [4] (Figure 2). Equally well known is Zibotentan, an anticancer drug in late-stage clinical trials (www.ClinicalTrials.gov Identifier: NCT00554229), which is a candidate in development by AstraZeneca.

1.1 MINI REVIEW ON BIOLOGICAL ACTIVITY OF OXADIAZOLE DERIVATIVES

Among heterocyclic compounds, 1,3,4-oxadiazole has become an important synthase in development of new drugs[32-34]. Compounds containing 1,3,4-oxadiazole cores have a broad biological activity spectrum, including antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, anticancer, antidepressant, anticonvulsant, and anti-diabetic properties. The ability of 1,3,4-oxadiazole heterocyclic compounds to undergo various chemical reactions has made them important because of their privileged structure, which has an enormous biological potential.

1.2 bromo-2-(p-tolyl)-1H-benzo[d]imidazole:

Take clean and dry four necks 50 ml RBF.25mL EtOH taken by this RBF and a mixture of 5-bromo, O-phenyl diamine (1mol) and p-methyl benzoic acid (1.154mol) aldehyde (1.154mol) is introduced in an RBF.A Lew's acid catalyst gradually added above mixture .The total set up arranged on magnetic stirrer and continued the reaction at reflux for 4 hrs. The progress of the reaction was monitored by TLC (5:5- EtOH: n-hexane) and after completion of the reaction cooled at RT. The reaction mixture added with ice water and also addition with EtOAc as solvent .The reaction mixture was washed with Braine solution and separated the organic solvent and also distilled out. The compound get after purified by columns chromatography.

Pale yellow; Yield-91 %; m.p: 214-2160C; Rf: 0.45(EtOH: n-hexane: 5:5) ; IR(KBr, cm-1): 3448,3048,2945,1569,1512,1502,1485,698;1HNMR(400MHz,CDCl3)δppm: 11.496(s,1H,N-H),8.246(d,J=8.8Hz,Ar-H),7.717(s,1H,Ar-H),7.482-7.414(m,3H,Ar-H),1.176(s,3H,CH3); 13CNMR(100MHz,CDCl3):146.74,139.61,137.36,130.76,129.46,128.84,128.46,126.66, 119.08,117.44,115.64,24.78. LCMS (m/z): 288.22(M+2); Molecular formulae:C14H11Br N2; Elemental analysis: Calculated : C-58.56 ,H-3.86 ,N-9.76; Obtained : C-58.49 , H-3.84 , N- 9.83;

1.3 2-(5-bromo-2-(p-tolyl)-1H-benzo[d]imidazol-1-yl)-3-chloropropan-2-one:

5-bromo-2-(p-tolyl)-1H-benzo[d]imidazole is dissolved in 25mL of methylene dichloride in 50mLfour neck RBF and triethylamine was added .The slowly add the chloroacetyl chloride by using dropping funnel. The total mixture setup on the magnetic stirrer and continued the reaction for 5hrs at reflux. The progress of the reaction was monitored by TLC (5:5 = EtOH: n-hexane). After completion of the reaction, unconsumed chloroacetyl chloride can be evaporated and the crude was taken in a EtOAc and washed with saturated solution of sodium bi carbonate and separated the organic solvent. The organic solvent distilled off under vacuum distillation final compounds obtained.

2. Characterisation:

Whitesolid;Yield-86%:m.p:256-2580C;Rf;0.45(EtOH:n-hexane-4:6);IR(KBr,cm-1):

3047,2978,2847,1745,1598,1543,1508,1478,1346,714;1HNMR(400MHz,CDCl3)δppm: 8.214(d,J=7.2Hz,2H,Ar-H),7.704(s,1H,Ar-H);7.518-7.428(m,4H,Ar-H),3.874(s2H,-CH2-), 2.248-1.849(m,2H,-CH2-),1.158(s,3H,-CH3),0.975(t,3H,-CH3);13CNMR(100MHz,CDCl3): 195.74,150.34,138.37,134.76,130.40,128.84,128.04,127.66,125.67,119.09,118.44,117.74, 60.76,33.61,22.46,11.72;LCMS(m/z):358.54(M+2);Molecularformulae:C18H17BrN2O; Elemental analysis:Calculated C-60.52,H- 4.80,N- 7.84; Obtained: C-60.45, H-4.78, N- 7. 88;

2.1 2-(5-bromo-2-(p-tolyl)-1H-benzo[d]imidazol-1-yl) acetohydrazide:

Take clean and dry the four neck 50mL RBF and poured 25 mL EtOH in a RBF. The 1-(5-bromo-2-(p-tolyl)-1H-benzo[d]imidazol-1-yl)-3-chloropropan-2-one was dissolved in EtOH and addition with hydrazine hydrate. The reaction mixture was continued for 6-7 hrs. The progress of the reaction was checked by TLC and after completion of the reaction and solvent can be removed. The final compound can be obtained.

Characterisation:

Whitesolid;Yield-84%:m.p:215-2170C;Rf;0.40(EtOH:n-hexane-6:4);IR(KBr,cm-1):3641, 3475,3054,2954,2889,1787,1594,1548,1507,1497,698;1HNMR(400MHz,CDCl3)δppm: 9.047(s,1H,NH);8.184(d,J=9.2Hz,2H,Ar-H),7.715(s,1H,Ar-H);7.504-7.412(m,4H,Ar-H), 3.854(s,2H,-CH2-),3.647(s,2H,-NH2),1.158(s,3H,-CH3);13CNMR(100MHz,CDCl3): 163.45,150.55,138.18,134.07,130.40,129.47,128.98,128.44,127.22,126.47,125.06,119.12,118.32,116.75,38.55,22.68.;LCMS(m/z):360.21(M+2);Molecularformulae:C16H15BrN4O; Elemental analysis: Calculated: C- 53.50,H- 4.21,N-15.60; Obtained: C-53.42, H-4.19, N-15.68;

2.2 Genera procedure of 2-((5-bromo-2-(p-tolyl)-1Hbenzo[d]imidazole-1-yl) methyl)-5-phenyl-1 3, 4-oxidiazole:

The mixture of 2-(5-bromo-2-(p-tolyl)-1H-benzo[d]imidazol-1-yl) acetohydrazide and substituted benzoic acid taken in 50mL RBF and slowly addition with POCl3 . The reaction mixtures was fitted on the magnetic stirrer and check the reaction and poured in ice cold water and addition of organic solvent .The crude was washed with a solution of NaHCO3 and get final product after purified by the chromatography. [6]

2.4 ((5-bromo-2-(p-tolyl)-1Hbenzo[d]imidazole-1-yl) methyl)-5-phenyl-1 3, 4-oxidiazole:

White solid; Yield: 87%; m.p-213-2150C: Rf -0.45(EtOH: n-hexane: 6:4); IR (KBr, cm-1):

3047,2972,2868,1601,1569,1528,1502,1486,696;1HNMR(400MHz,CDCl3)δppm:8.204(d, J=6.4Hz,2H,Ar-H),7.708(s,1H,Ar-H),7.498-7.272(m,7H,Ar-H),3.914(s,2H,-CH2-),1.164 (s,3H,-CH3);13CNMR(100MHz,CDCl3):163.62,161.09,149.66,138.84,130.09,129.78, 129.17, 128.91,128.08,127.64,127.15,126.44,125.39,119.14,118.07,117.84,50.35,22.66;LCMS(m/z):444.15(M+2);Molecularformula e:C23H17BrN4O;Elementalanalysis:Calculated:C-62.01,H-3.85,N-12.56; Obtained : C-61.95 , H-3.83 , N- 12.63;

2.3 2-((5-bromo-2-(p-tolyl)-1H benzo[d]imidazol-1-yl) methyl)-1, 3, 4-oxidiazol-2-yl)-2-ethoxyphenol:

Whitesolid;Yield:90%;m.p–208-2100C:Rf-0.45(EtOH:n-hexane6:4);IR(KBr,cm-1):3048, 2982,2844,1602,1572,1541,1513,1486,1149,715,647;1HNMR(400MHz,CDCl3)δppm: 9.173(s,1H,-OH);8.226(d,J=5.8Hz,2H,Ar-H),7.712(s,1H,Ar-H),7.513-7.275(m,7H,Ar-H), 3.942(s,2H,-CH2-),2.136-1.473(m,2H,-CH2-);1.189(s,3H,-CH3);0.947(t,3H,-CH3);1 3CNMR(100MHz,CDCl3):163.91,161.69,150.08,139.77,138.04,131.35,129.74,128.95, 128.53,128.12,127.36,126.36,12644,125.11,119.08,118.29,116.96,51.65,28.46,22.64,22.64,11.36.LCMS(m/z):506.31(M+2); Molecular formulae: C25H21BrN4O3; ElementalAnalaysis: Calculated: C- 59.42, H-4.19, N-11.09; Obtained: C- 59.35, H-4.17, N- 11.18; [10]

2.5 2-((5-bromo-2-(p-tolyl)-1hbenzo[d]imidazole-1-yl)methyl)-5-(4-methoxyphenyl)-1,3, 4-oxidiazole:

Whitesolid;Yield:92%m.p-221-2230C;Rf-0.45(EtOH:n-hexane:6:4);IR(KBr,cm-1):3061, 2956,2896,1602,,1567,1537,1501,1482,1184,704,636;1HNMR(400MHz,CDCl3)δppm: 8.124(d,J=7.8Hz,2H,Ar-H),7.886(d,J=9.2Hz,2H,Ar-H),7.677(s,1H,Ar-H),7.517-7.274 (m,6H,Ar-H),3.967(s,2H,-CH2-),3.616(s,3H,-OCH3),1.096(s,3H,-CH3),13CNMR(100MHz, CDCl3):162.76,160.37,149.14,139.23,130.84,129.56,128.67,128.39,128.02,127.64,126.18, 125.64,119.16,118.09,117.69,54.62,50.16,22.04;LCMS(m/z):476.16(M+2);Molecular formulae:C24H19BrN4O2;Elementalanalysis:Calculated:C-60.64,H-4.03 ,N-11.79; Obtained : C-60.58 , H-4.01 , N- 11.86;

2.6 2-((5-bromo-2-(p-tolyl)-1hbenzo[d]imidazole-1-yl) methyl)-5-(3,5-dichloro phenyl) -1,3,4-oxidiazole:

Whitesolid;Yield-88%:m.p-207-2090C:Rf-0.47(EtOH:n-hexane:5:5);IR(KBr,cm-1):3051, 2966,2884,1597,1552,1524,1501,1496,742,696;1HNMR(400MHz,CDCl3)δppm:8.226(d, J=7.0Hz,2H,Ar-H),7.792-7.596(m,3H,Ar-H),7.542(s,1H,Ar-H),7.461-7.354(m,4H,Ar-H), 3.946(s,2H,-CH2-),1.096(s,3H,-CH3);13CNMR(100MHz,CDCl3)δppm:163.87,161.08, 150.17,139.44,132.63,129.86,128.28,128.07,127.77,127.38,126.74,125.88,124.64,119.09,118.36,117.64,50.39,22.06;LCMS(m/z):513.44(M+H);Molecularormulae:C23H15BrCl2 N4O; Elemental analysis: Calculated: C-53.72, H-2.94, N-10.90; Obtained: C-53.65, H-2.92 , N-10.98;

2.8 2-((5-bromo-2-(p-tolyl)-1hbenzo[d]imidazole-1-yl)methyl)-5-(3,4,5-trimethoxy phenyl) -1,3,4-oxidiazole:

Whitesolid;Yield-92%;m.p-218-2200C:Rf-0.42(EtOH:n-hexane:4:6);IR(KBr,cm-1):3046, 2956,2897,1602,1574,1538,1510,1196,710,649;1HNMR(400MHz,CDCl3)δppm:8.118 (d,J=7.2HZ,2H,Ar-H),7.716(s,1H,Ar-H),7.467-7.289(m,6H,Ar-H),3.975(s,2H,-CH2-), 3.617(s,3H,-OCH3),3.567(s,3H,OCH3),1.015(s,3H,-CH3);13CNMR(100MHz,CDCl3): 163.09,160.76,150.37,145.66,139.11,135.09,129.17,128.69,128.06,127.74,126.68,125.19, 124.38,118.57,117.31,116.34,58.38,54.06,50.09,22.46.LCMS(m/z):536.11(m/z);Molecular formulae: C26H23BrN4O4; Elemental analysis: Calculated: C- 58.33, H-4.33, N-10.46; Obtained: C-58.25, H-4.31, N- 10.52;

2.7 2-((5-bromo-2-(p-tolyl)-1hbenzo[d]imidazole-1-yl) methyl)-5-(4,-nitro phenyl) -1,3,4-oxidiazole:

Whitesolid;Yield-86%;m.p-198-2000CRf-0.45(EtOH:n-hexane:6:4);IR(KBr,cm-1):3051, 2966,2872,1595,1547,1512,1496,714,684;1HNMR(400MHz,CDCl3)δppm:8.218(d,J=8.0 HZ,2H,Ar-H),8.065(d,J=6.4HZ,2H,Ar-H),,7.884(d,J=8.8HZ,2H,Ar-H),7.715(s,1H,Ar-H), 7.486-7.214(m,8H,Ar-H),4.125(s,1H,-CH2-),1.126(s,3H,-CH3);13CNMR (100MHz,CDCl3): 164.08,161.96,150.88,143.46,139.37,131.28,130.54,129.18,128.46,127.09,126.84,125.39, 118.92, 116.84,51.09,22.46;LCMS(m/z):491.14;Molecularformulae: C23 H16 Br N5 O3; Elemental analysis: Calculated: C- 56.34, H-3.29, N-14.28; Obtained: C-56.28, H-3.28, N- 14.34;

2.9 2-((5-bromo-2-(p-tolyl)-1Hbenzo[d]imidazol-1-yl)methyl)-1,3,4-oxidiazol-2-yl) benzonitrile.

Whitesolid;Yield:87%;m.p:Rf-0.45(EtOH:n-hexane:6:4); ;IR(KBr,cm-1):3049,2946,2877,2156,1601,1574,1538,1502,715,696;1HNMR (400MHz,CDCl3)δppm:8.134(d,J=8.0HZ,2H,Ar-H),7.810(s,1H,Ar-H),7.775-7.417(m,8H,Ar-H),2.830(s,1H,-CH2-),1.126(s,3H,-CH3).13CNMR(100MHz ,CDCl3):163.88,161.15,150.08, 139.74,131.19,130.03,129.49,128.94,128.26,127.52,126.45,125.37,124.68,119.09,117.64, 116.66,51.39,22.46.LCMS(m/z):471.24(M+2); Molecular formulae: C24 H16 BrN5O; Elemental analysis: Calculated: C-61.29 ,H-3.43 ,N-14.89; Obtained : C-61.22 , H- 3.42 , N-14.95;

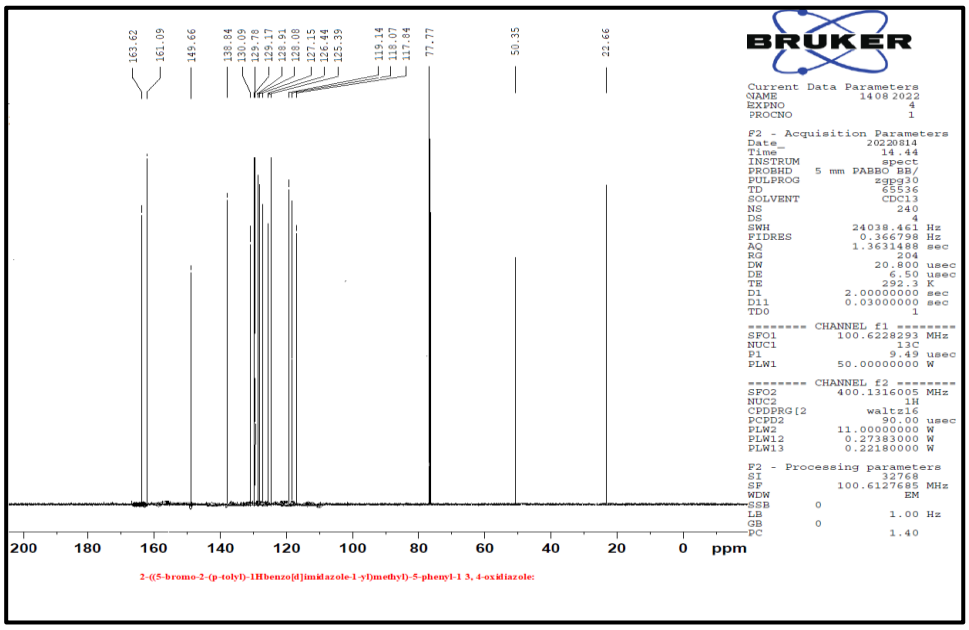


Figure 1: 2-((5-bromo-2-(p-tolyl)-1Hbenzo[d]imidazole-1-yl) methyl)-5-phenyl-1 3, 4-oxidiazole

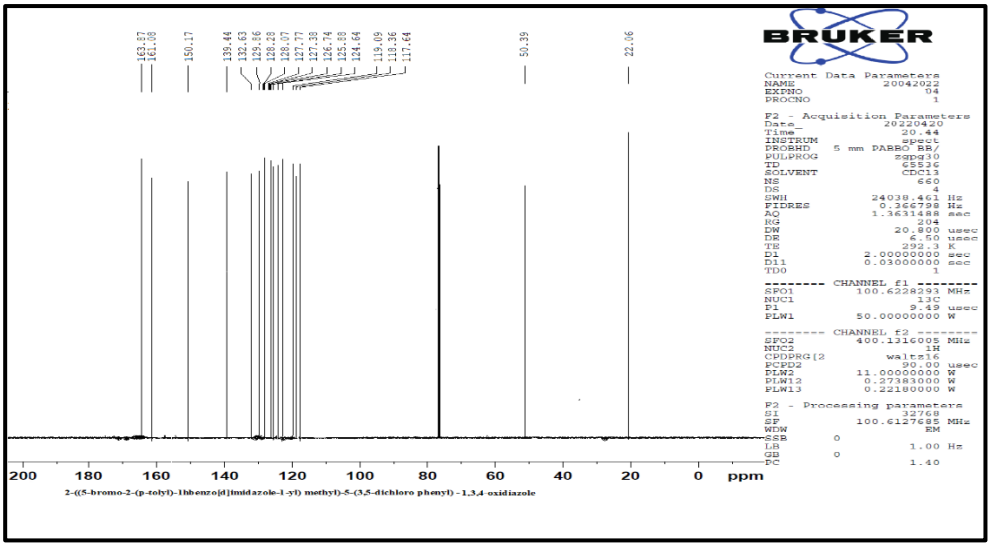


Figure 2: 2-((5-bromo-2-(p-tolyl)-1H benzo[d]imidazol-1-yl) methyl)-1, 3, 4-oxidiazol-2-yl)-2-ethoxyphenol

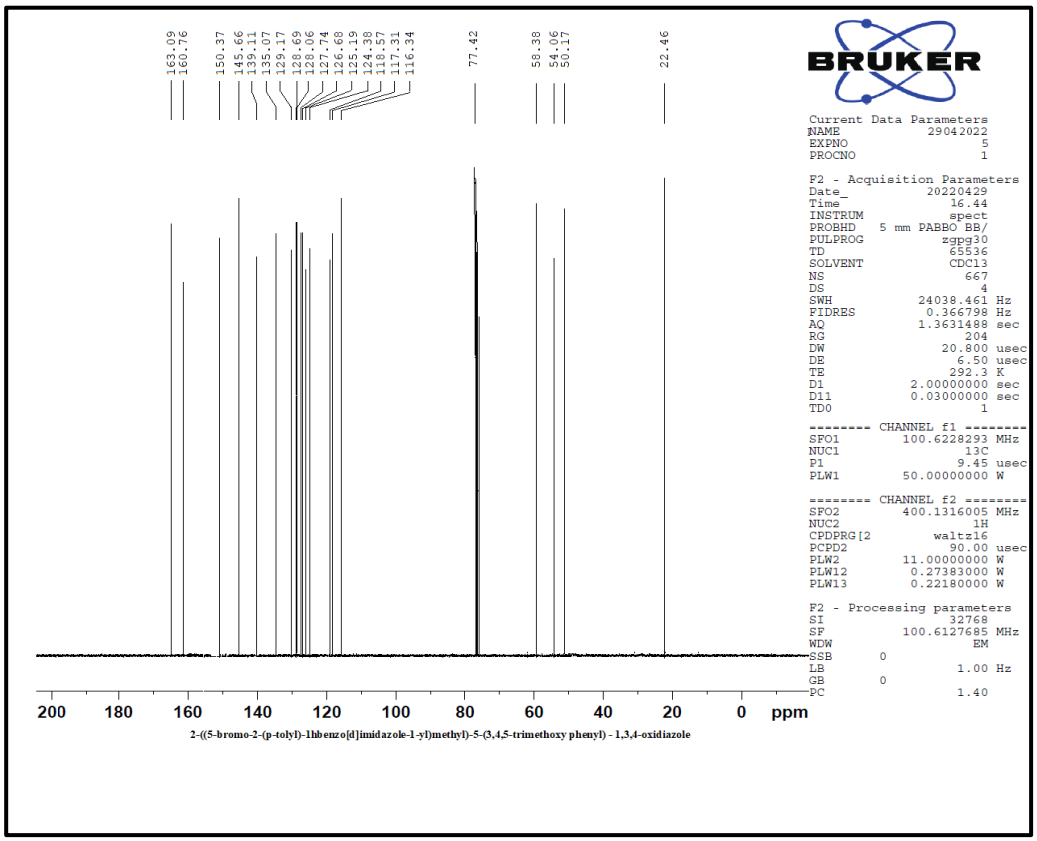


Figure 3: 2-((5-bromo-2-(p-tolyl)-1hbenzo[d]imidazole-1-yl)methyl)-5-(4-methoxyphenyl)-1,3, 4-oxidiazole

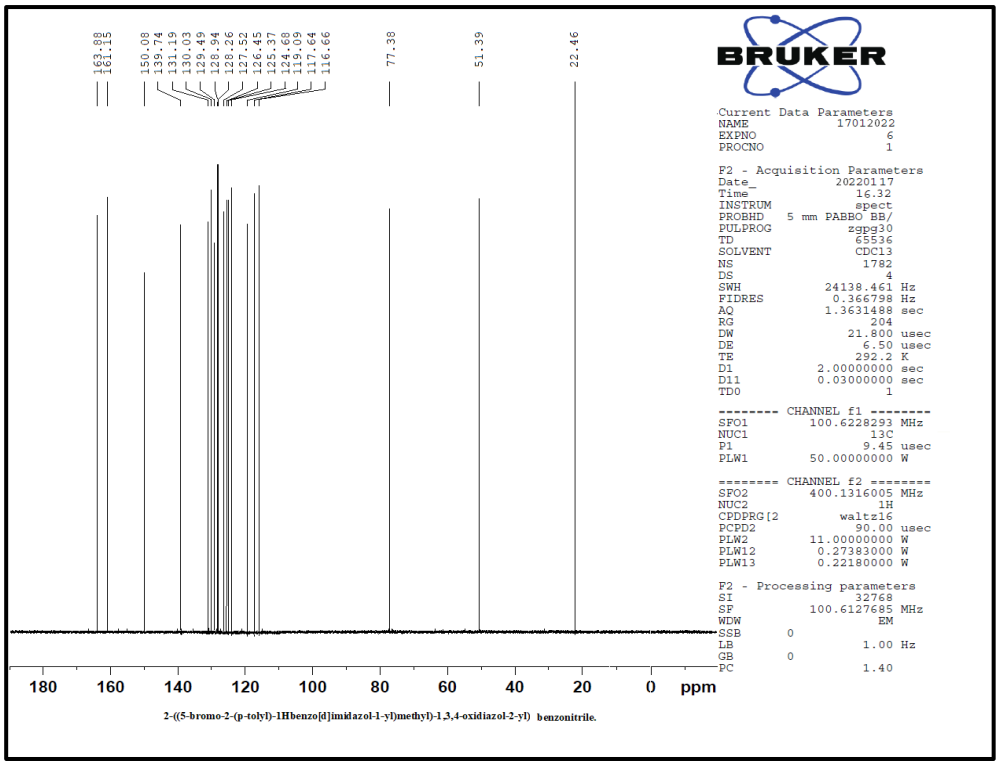


Figure 4: 2-((5-bromo-2-(p-tolyl)-1hbenzo[d]imidazole-1-yl) methyl)-5-(3,5-dichloro phenyl) -1,3,4-oxidiazole

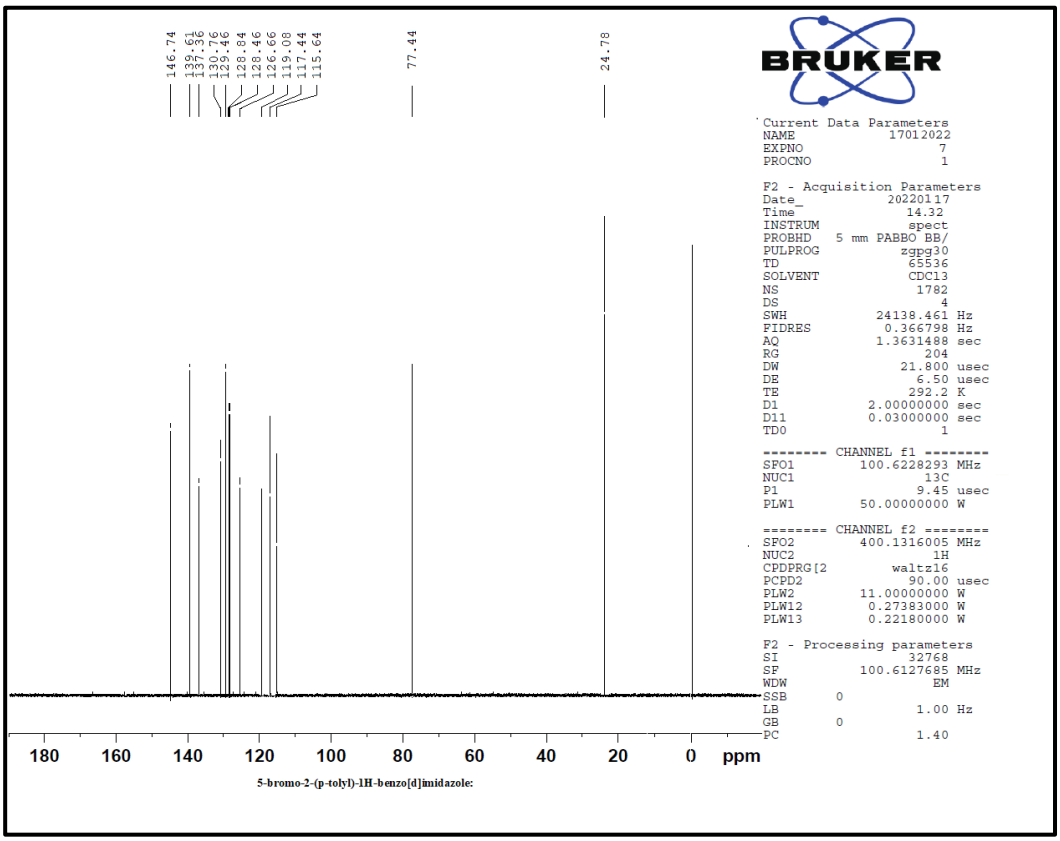


Figure 5: 2-((5-bromo-2-(p-tolyl)-1hbenzo[d]imidazole-1-yl)methyl)-5-(3,4,5-trimethoxy phenyl) -1,3,4-oxidiazole

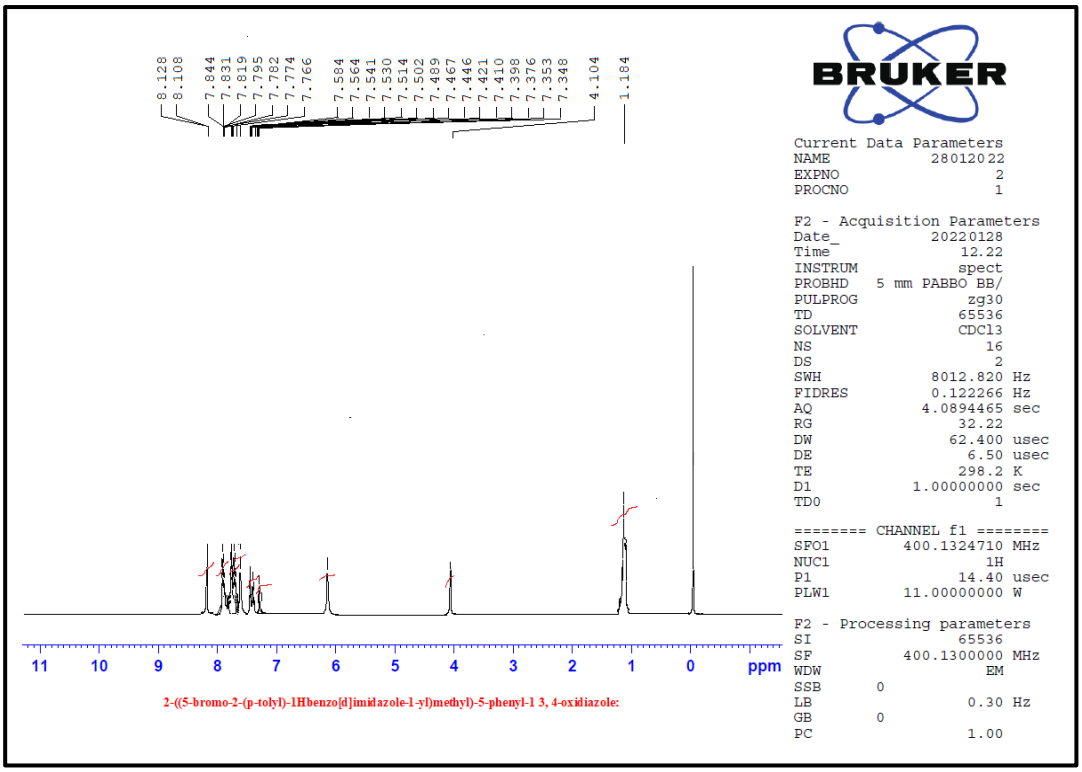


Figure 6: 2-((5-bromo-2-(p-tolyl)-1hbenzo[d]imidazole-1-yl) methyl)-5-(4,-nitro phenyl) -1,3,4-oxidiazole

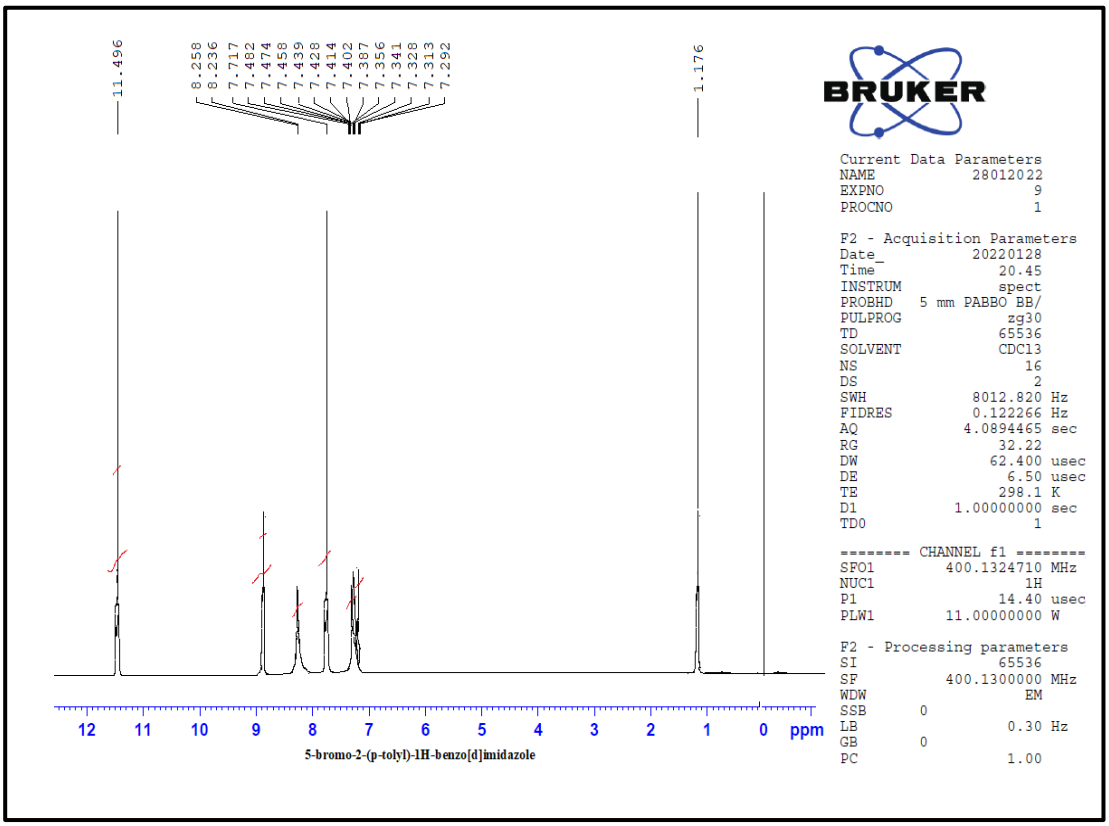
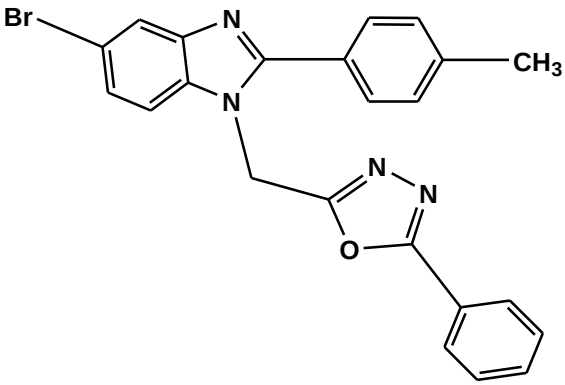
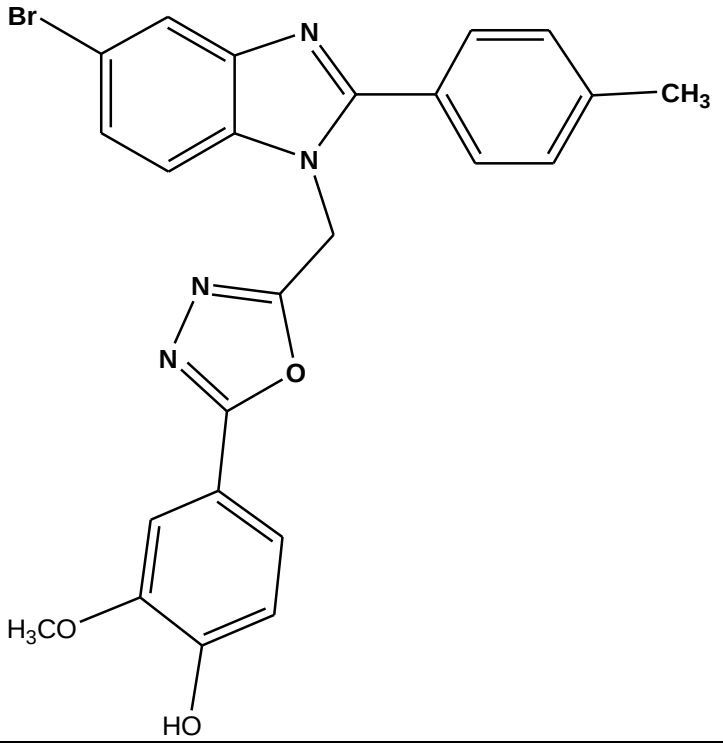
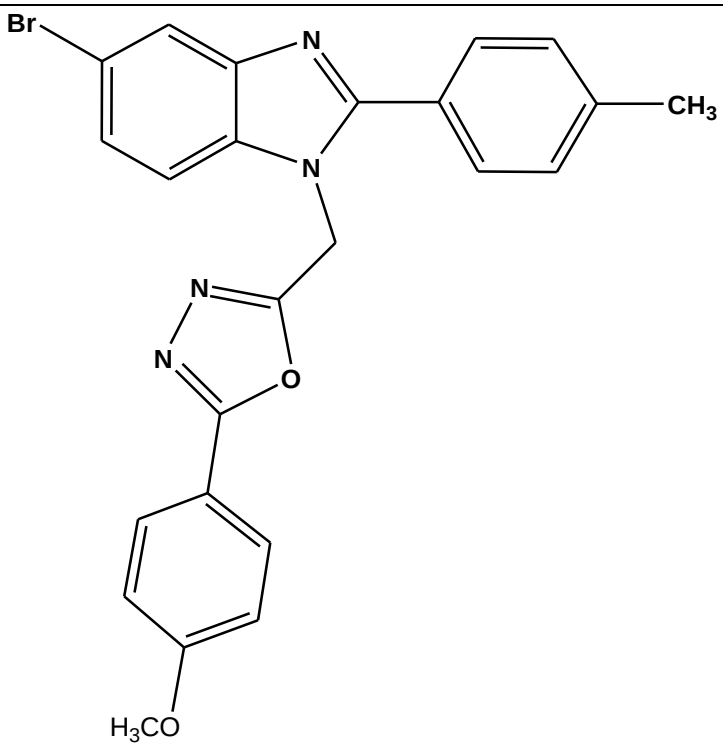
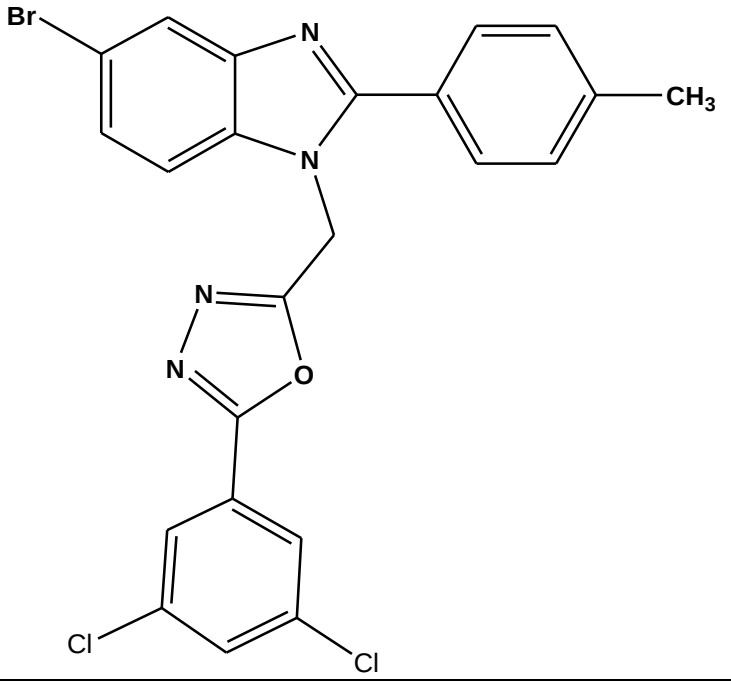
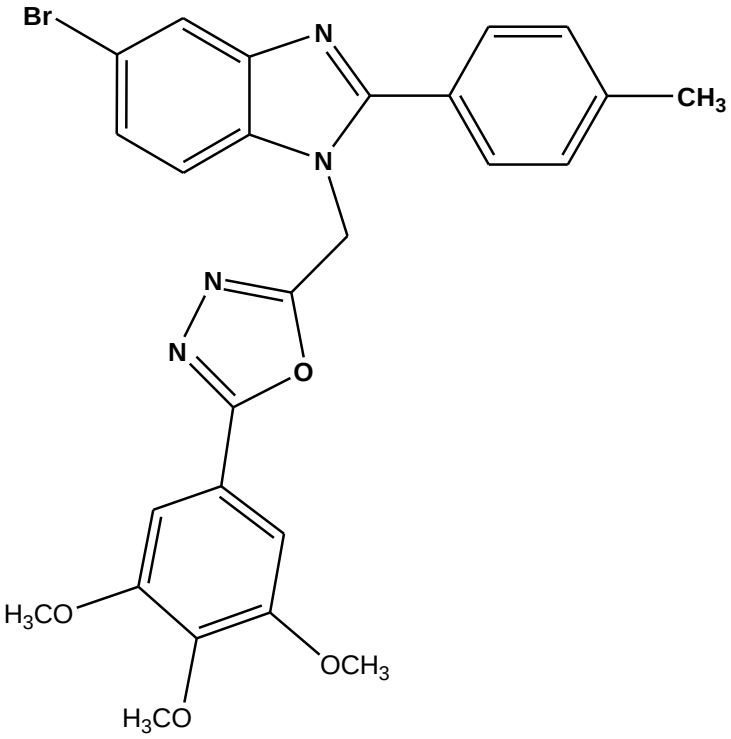


Figure 7: 2-((5-bromo-2-(p-tolyl)-1Hbenzo[d]imidazol-1-yl)methyl)-1,3,4-oxidiazol-2-yl) benzo nitrile

Table 1: Structures of Oxadiazole derivatives

OXD01	

OXD02	
OXD03	

OXD04	
OXD05	

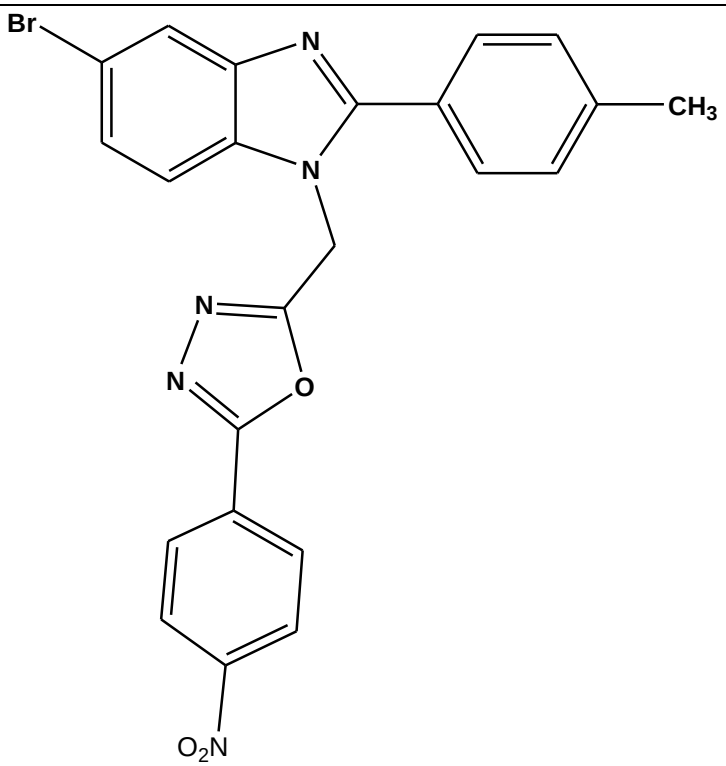
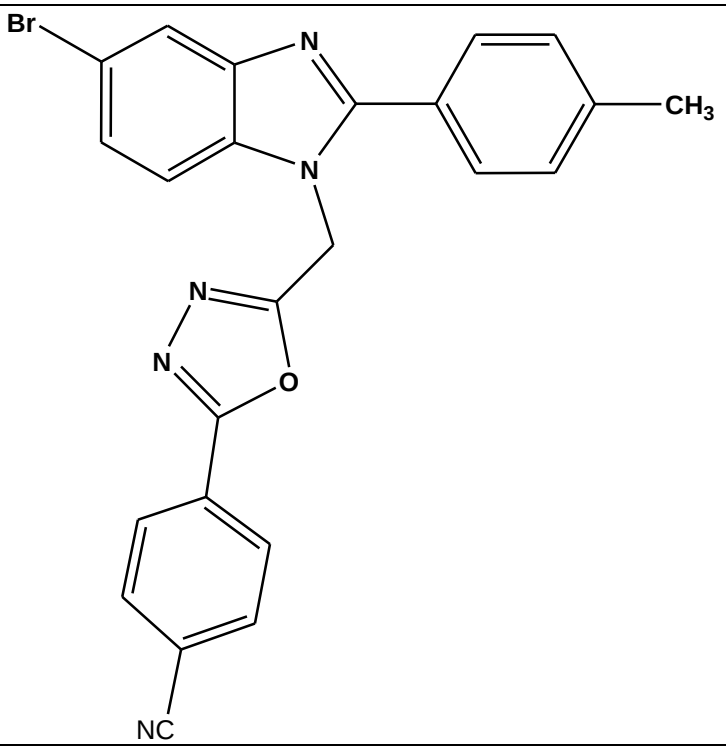
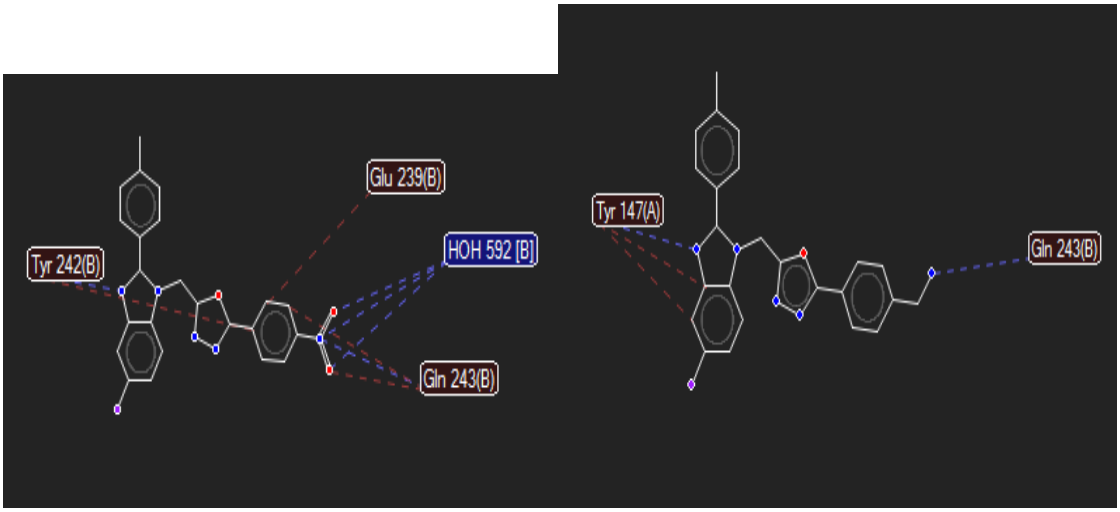
OXD06	
OXD07	

Table 2: Docking results of anti-inflammatory activity

compound	Mol Dock Score	Rerank Score	H Bond
Active ligand CEL_701[A]	**-159.04**	**-125.482**	**-4.45805**
Indomethacin	-77.9236	-52.934	0
OXD01	-87.058	-53.2344	0
OXD02	-95.893	-70.5461	-4.6064
OXD03	-94.039	-67.6783	-1.839
OXD04	-105.95	-67.9098	-2.5
OXD05	-72.9188	-15.7893	-4.2084
OXD06	-108.912	-77.36	-2.8287
OXD07	-102.829	-71.259	-5.00

The overall obtained mole docking scores should between -77.00 to –103.00 kcal/mol. Moldock scores of ligand -159.04 kcal/mol. We found our docking results scores are within the rage mentioned above. Oxadiazole derivatives core containing compound OXD-6 and OXD-7 exhibited binding scores are -179 k.cal/mol (Table 2).



*Blue color indication hydrogen bonds, Green color indication electrostatic interactions, Red color indication steric interactions

Oxadiazole derivatives of compounds OXD-5, OXD-6 and OXD-7 showed more interactions between hydrogen bond and steric interaction than remaining Oxadiazole derivatives (Table below).

Table 3: Docking results of anti-inflammatory activity

Compound	Steric Interaction	Hydrogen Bond
Indomethacin	Try 242 (B)	HOH 529 (B)
OXD01	Leu 238(B), Glu 239 (B)	-
OXD02	Asn 144 (A)	Asn 144 (A)

OXD03	Asn 144 (A)	Gln243 (A)
OXD04	Leu 238 (B)	Asn 144 (A)
OXD05	Phe 220 (A)	Asn 144 (A), Ser 146 (A)
OXD06	Tyr 242 (B), Glu 239 (B), Glu 243 (B)	HOH 592 (B), Tyr 242 (B)
OXD07	Glu 243 (B), Try 147 (A),	Try 147 (A), Glu 243(B)

3. SUMMARY

The ever-growing interest in this class of compounds is forcing scientists to develop new, efficient and environmentally friendly methods of synthesis. One of the latest synthetic approaches is the application of mechanochemistry. These techniques (grinding or milling) are a powerful strategy for the rapid, clean, and solvent-free synthesis of many biologically active compounds [168]. These reactions are usually performed in a mixer ball mill or mortar grinder and are of great value due to the possibility of reducing or completely eliminating the use of solvents, enhancing the conversion of substrates or even obtaining products that were unavailable with the previously used methods [169]. In addition, in many cases, the use of the above techniques allows for a significant reduction of reaction time and saving of synthesis costs. In the future the synthetic strategy may contribute in obtaining many new drug candidates, including very promising derivatives based on 1,2,4-oxadiazole scaffold. The newly synthesized compounds were evaluated for their different cancer cell lines by the standard MTT assay method. All the synthesized novel derivatives were found to be potent biological activities.

REFERENCES

1. Jing-Ping Liou, Kuo-Shun Hsu, Ching-Chuan Kuo, Chi-Yen Chang, Jang Yang Chang, " A novel oral indoline sulfonamide agent, J30, exhibits potent activity against human cancer cells in vitro and in vivo through the disruption of microtubule". JPET;2007;107:126680.
2. Periyasamy Selvam, Narayanan Muruges h, Mark and avel Chandra mohan, Robert W Sidwell, Miles K Wandersee and Donald F Smee. "Antiviral Chemistry & Chemotherapy , Anti-influenza activities of isatin derivatives". Int. Medical Press.2006.
3. Ping, Dun, De Sheng YU, Fang QIN, Lin FANG, " Synthesis and In Vitro Antiviral Activities of Some New 2-Aryl thiomethyl-4- tertiary aminomethyl substituted Derivatives of 6-Bromo-3- ethoxycarbonyl-5- Hydroxyl indoles". Chinese Chemical Letters.2004;15(1):19-22 .
4. Michel Frederich, Monique Tits, Luc Angenot, "Potential antimalarial activity of indole alkaloids", Trans. Roy. Soc. Trop. Med. and Hyg.2008; 102:11-19
5. Sudhakar G, Kadam V.D, Bayya S., Pranitha G., and Jagadeesh, B., Org. Lett.2011;130: 5452
6. Wurst J.M, Verano A.L, and Tan D.S, Org. Lett.2012;14:4442
7. Tosi G, Zironi, F, Caselli, E, Forni, A, and Prati F, Synthesis.2004; p:1625.
8. Shvaika, Osnovi sintezu likars'kikh rechovin (Principles of Synthesis of Medicines), Donets'k: Skhidnii Vidavn. Dim, 2002.
9. Assaf G, Cansell G, Critcher D, Field S., Hayes S., Mathew S, and Pettman A., Tetrahedron Lett.2010;51:5048.
10. Wong E.H.F, Sonders, M.S., Amara, S.G., Tinholt, P.M., Piercey, M.F.P., Hoffmann, W.P., Hyslop, D.K., Franklin, S., Porsolt, R.D., Bon- signori, A., Carfagna, N., and McArthur, R.A., Biol. Psych.2000;47: vol. 47, p. 818.
11. Aparicio, D.M., Terán, J.L., Gnecco, D., Galindo, A., Juárez, J.R., Orea, M.L., and Mendoza, A., Tetrahedron: Asymmetry, 2009:2764.
12. Hanlon S.P., Camattari, A., Abad, S., Glieder, A., Kittelmann, M., Lütz, S., Wirz, B., and Winkler, M., Chem. Commun. 2012;48:6001